Synthesis of *N*-Heterocycles and Their Reactive Precursors via Novel Pd/Cu-Catalyzed One-Pot Sequences

Kumulative Dissertation

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Erklärung

Die hier vorgelegte Dissertation habe ich eigenständig und ohne unerlaubte Hilfe angefertigt. Die Dissertation wurde in der vorgelegten oder in ähnlicher Form noch bei keiner anderen Institution eingereicht. Ich habe bisher keine erfolglosen Promotionsversuche unternommen.

Düsseldorf, den 12.09.2011 _____

(Eugen Merkul)

Die vorliegende Arbeit wurde in der Zeit von Juli 2006 bis Dezember 2006 am Organisch-Chemischen Institut der Ruprecht-Karls-Universität Heidelberg und von Januar 2007 bis Juli 2011 am Institut für Organische Chemie und Makromolekulare Chemie der Heinrich-Heine-Universität Düsseldorf unter der Leitung von Prof. Dr. T. J. J. Müller angefertigt.

To my beautiful wife Kateryna with love and gratitude

Il semble que la perfection soit atteinte non quand il n’y a plus rien à ajouter, mais quand il n’y a plus rien à retrancher.

(Vollkommenheit entsteht offensichtlich nicht dann, wenn man nichts mehr hinzuzufügen hat, sondern wenn man nichts mehr wegnehmen kann.)

{A designer knows he has achieved perfection not when there is nothing left to add, but when there is nothing left to take away.}

Antoine de Saint-Exupéry,
Terre des Hommes (Wind, Sand und Sterne) {Wind, Sand and Stars}

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This cumulative dissertation is based on the following published papers (in the reverse chronological order):

Publications

8. “Catalytic syntheses of *N*-heterocyclic ynones and ynediones by in situ activation of carboxylic acids with oxalyl chloride”, Christina Boersch, Eugen Merkul, Thomas J. J. Müller, *Angew. Chem. Int. Ed*. **2011**, 10.1002/anie.201103296, published online.

7. “One-pot synthesis of diazine-bridged bisindoles and concise synthesis of marine alkaloid hyrtinadine A”, Boris O. A. Tasch, Eugen Merkul, Thomas J. J. Müller, *Eur. J. Org. Chem*. **2011**, 4532-4535.

6. “Rapid preparation of triazolyl substituted NH-heterocyclic kinase inhibitors via one-pot Sonogashira coupling–TMS-deprotection–CuAAC sequence”, Eugen Merkul, Fabian Klukas, Dieter Dorsch, Ulrich Grädler, Hartmut E. Greiner, Thomas J. J. Müller, *Org. Biomol. Chem.* **2011**, *9*, 5129-5136.

5. “Rapid synthesis of bis(hetero)aryls by one-pot Masuda borylation – Suzuki coupling sequence and its application to concise total syntheses of meridianins A and G”, Eugen Merkul, Elisabeth Schäfer, Thomas J. J. Müller, *Org. Biomol. Chem.* **2011**, *9*, 3139-3141.

4. “Dreikomponentensynthese von Indionen durch eine Glyoxylierungs-Stephens-Castro-Kupplungssequenz”, Eugen Merkul, Janis Dohe, Charlotte Gers, Frank Rominger, Thomas J. J. Müller, *Angew. Chem.* **2011**, *123*, 3023-3026; “Three-component synthesis of ynediones by a glyoxylation/Stephens–Castro coupling sequence” *Angew. Chem. Int. Ed.* **2011**, *50*, 2966-2969.

3. “Consecutive one-pot Sonogashira-Glaser coupling sequence – direct preparation of symmetrical diynes by sequential Pd/Cu-catalysis”, Eugen Merkul, Dominik Urselmann, Thomas J. J. Müller, *Eur. J. Org. Chem.* **2011**, 238-242.

2. “Consecutive three-component synthesis of ynones by decarbonylative Sonogashira coupling”, Eugen Merkul, Thomas Oeser, Thomas J. J. Müller, *Chem. Eur. J*. **2009**, *15*, 5006-5011.

1. “Three-component synthesis of *N*-Boc-4-iodopyrroles and sequential one-pot alkynylation”, Eugen Merkul, Christina Boersch, Walter Frank, Thomas J. J. Müller, *Org. Lett*. **2009**, *11*, 2269-2272.

Additionally, following publications, which are not part of this thesis, appeared while it was in progress:

4. “One-pot four-component synthesis of pyrimidyl and pyrazolyl substituted azulenes via glyoxylation – decarbonylative alkynylation – cyclocondensation sequences”, Charlotte F. Gers, Julia Rosellen, Eugen Merkul, Thomas J. J. Müller, *Beilstein J. Org. Chem.* **2011**, *7*, 1173-1181.

3. “New three-component glyoxylation-decarbonylative Stille coupling sequence to acyl heterocycles under mild conditions”, Boris O. A. Tasch, Eugen Merkul, Walter Frank, Thomas J. J. Müller, *Synthesis* **2010**, 2139-2146.

2. “2-Oxazol-5-ylethanones by consecutive three-component amidation-coupling-cycloisomerization (ACCI) sequence”, Eugen Merkul, Oliver Grotkopp, Thomas J. J. Müller, *Synthesis* **2009**, 502-507.

1. “A new consecutive three-component oxazole synthesis by an amidation-coupling-cycloisomerization (ACCI) sequence”, Eugen Merkul, Thomas J. J. Müller, *Chem. Commun*. **2006**, 4817-4819.

Additionaly, following patents have been filed while this work was in progress and contain some methods or substances which resulted from this thesis (however, these results are not part of this thesis in the first line):

Patent Applications

5. “3-([1,2,3]Triazol-4-yl)pyrrolo[2,3-*b*]pyridine derivatives as PDK1 inhibitors and their preparation and use in the treatment of tumors”, Dieter Dorsch, Margarita Wucherer-Plietker, Thomas J. J. Müller, Eugen Merkul, *PCT Int. Appl*. **2010**, WO 2010127754 A1 20101111; *Ger. Offen*. **2010**, DE 102009019962 A1 20101111.

4. “Preparation of 3-(4-pyridinyl)-1*H*-pyrrolo[2,3-*b*]pyridines as anti-tumor agents”, Dieter Dorsch, Christian Sirrenberg, Thomas J. J. Müller, Eugen Merkul, Ger. Offen. **2009**, DE 102008025751 A1 20091203.

3. “Preparation of 4-pyrrolo[2,3-*c*]pyridin-3-yl)-pyrimidin-2-ylamines as antitumor agents”, Dieter Dorsch, Christian Sirrenberg, Thomas J. J. Müller, Eugen Merkul, (Merck Patent GmbH, Germany), *PCT Int. Appl.* **2009**, WO 2009092431 A1 20090730.

2. “4-(Pyrrolopyridinyl)pyrimidin-2-ylamine derivatives as cell proliferation inhibitors, their preparation, pharmaceutical compositions, and use as antitumor agents”, Dieter Dorsch, Christian Sirrenberg, Thomas J. J. Müller, Eugen Merkul, *Ger. Offen*. **2008**, DE 102007008419 A1 20080828; *PCT Int. Appl*. **2008**, WO 2008101587 A1 20080828.

1. “Preparation of pyrrolopyridinylpyrimidinylamines as inhibitors of cell proliferation”, Dieter Dorsch, Margarita Wuchrer, Lars Burgdorf, Christian Sirrenberg, Thomas J. J. Müller, Eugen Merkul, *Ger. Offen*. **2008**, DE 102007028515 A1 20081224; Dieter Dorsch, Margarita Wuchrer, Lars Burgdorf, Christian Sirrenberg, Christina Esdar, Thomas J. J. Müller, Eugen Merkul, *PCT Int. Appl*. **2008**, WO 2008155000 A1 20081224.

Three additional patents have been registered: DE 102010049877.7 (01.11.**2010**), DE 102011008352.9 (12.01.**2011**), and DE 102011009961.1 (01.02.**2011**).

Additionally, parts of this thesis have been presented in form of oral and poster contributions:

Oral Presentations

4. “Efficient construction of heterocycles and biologically active molecules by Pd/Cu-catalyzed one-pot strategies”, Eugen Merkul, Thomas J. J. Müller, Forum *GDCh-Wissenschaftsforum Chemie 2011* September 4-7 **2011**. Bremen, Germany.

3. “Efficient construction of heterocycles and biologically active molecules by Pd/Cu-catalyzed one-pot strategies”, Eugen Merkul, Thomas J. J. Müller, Conference *15th Annual Green Chemistry & Engineering Conference + 5th International Conference on Green and Sustainable Chemistry* June 21-23 **2011**. Washington DC, USA.

2. “Oxalyl chloride as a new versatile reagent in carbonylative cross-coupling reactions”, Eugen Merkul, Janis Dohe, Thomas J. J. Müller, Congress *3th European Chemistry Congress “Chemistry - the Creative Force” (3rd EuCheMS 2010)* August 29-September 2 **2010**. Nürnberg, Germany.

1. “Efficient construction of (hetero)aryl substituted (aza)indoles by Pd-catalyzed multi-component reactions”, Eugen Merkul, Dieter Dorsch, Thomas J. J. Müller, Conference *4th International Conference on Multicomponent Reactions and Related Chemistry (MCR 2009)* Mai 24-28 **2009**. Ekaterinburg, Russia.

Poster Presentations

6. “One-pot Masuda borylation – Suzuki coupling sequence for the efficient construction of biologically active compounds and natural products”, Eugen Merkul, Dieter Dorsch, Christian Sirrenberg, Per Hillertz, Elisabeth Schäfer, Thomas J. J. Müller, *17th Lecture Conference of Liebig-Vereinigung for Organic Chemistry (ORCHEM 2010)* September 13-15 **2010**. Weimar, Germany.

5. “One-pot Masuda borylation – Suzuki coupling sequence for the efficient construction of biologically active compounds and natural products”, Eugen Merkul, Dieter Dorsch, Christian Sirrenberg, Per Hillertz, Thomas J. J. Müller, Gordon Research Conference (GRC) *High Throughput Chemistry and Chemical Biology* June 20-25 **2010**. Les Diablerets, Switzerland.

4. “New glyoxylation – Sonogashira and glyoxylation – Stephens-Castro sequences for the efficient construction of alkynones and alkynediones”, Eugen Merkul, Janis Dohe, Thomas J. J. Müller, Forum *Heidelberg Forum of Molecular Catalysis (HFMC 2009)* November 6 **2009**. Heidelberg, Germany.

3. “Efficient construction of (aza)indolyl ynones by Pd/Cu-catalyzed multi-component reactions”, Eugen Merkul, Dieter Dorsch, Thomas J. J. Müller, Conference *4th International Conference on Multicomponent Reactions and Related Chemistry (MCR 2009)* Mai 24-28 **2009**. Ekaterinburg, Russia.

2. “One-pot Masuda – Suzuki sequence for the construction of heteroaryl substituted 7-azaindoles as bioactive compounds”, Eugen Merkul, Dieter Dorsch, Per Hillertz, Christian Sirrenberg, Thomas J. J. Müller, Conference *Frontiers in Medicinal Chemistry (FMC)* March 15-18 **2009**. Heidelberg, Germany.

1. “Oxalyl chloride as a new surrogate for carbon monoxide in one-pot syntheses of ynones”, Eugen Merkul, Thomas J. J. Müller, Congress *2nd EuCheMS Chemistry Congress* September 16-20 **2008**. Torino, Italy.

Zusammenfassung

Heterocyclen finden sich in einer Vielzahl von Natur-, Wirk- und Effektstoffen und ihre Herstellung nimmt einen Kernbereich der Organischen Chemie ein. Effiziente Synthesen von Heterocyclen sind deshalb von außerordentlich großer Bedeutung.

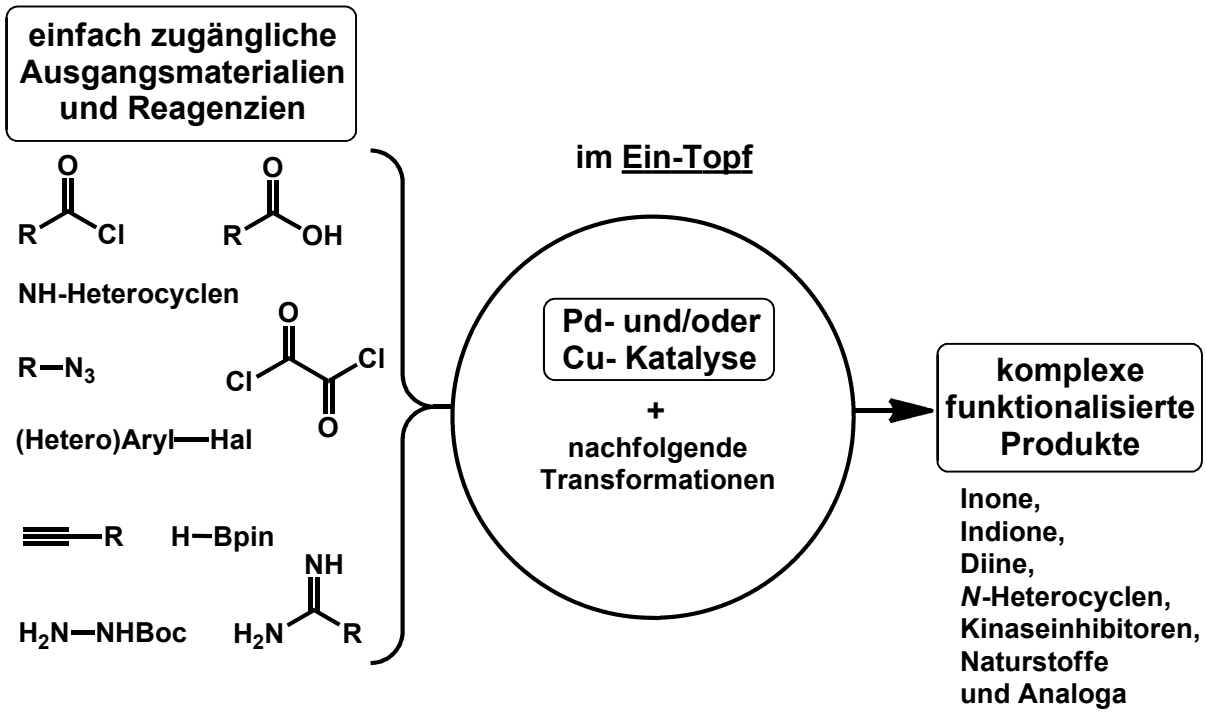
Das Ziel dieser Dissertationsarbeit war die Entwicklung neuer Ein-Topf-Reaktionen auf Basis der Palladium- und/oder Kupferkatalyse zur effizienten Darstellung von ausgewählten Heterocyclen oder ihrer Vorstufen. Ausgehend von einfachen Bausteinen und mittels einfacher Katalysatorsysteme sollten mithilfe dieser Methoden diverse funktionale Moleküle aufgebaut werden.

Im Rahmen dieser Arbeit konnten daher folgende Ziele erreicht werden:

1) Die Entwicklung einer Dreikomponentensynthese von schwer zugänglichen 2,4-disubstituierten Pyrrolen auf der Basis der Sonogashira-Kupplung.[399]
2) Die Konzeption und methodische Etablierung einer Pseudo-Vierkomponenten-Synthese von 1,4-di(hetero)arylsubstituierten 1,3-Diinen durch eine Sequenz aus der Sonogashira-Alkinylierung und nachfolgender Glaser-Homokupplung.[161]
3) Die Etablierung einer decarbonylierenden Alkinylierung heteroaromatischer Glyoxalylchloride als neue Variante der Sonogashira-Kupplung. Auf dieser Basis gelang eine konzeptuell neuartige Dreikomponentensynthese von Inonen, wichtigen Bausteinen in der Synthese vieler Heterocyclenklassen.[355]
4) Die Konzeption und methodische Etablierung einer neuen Dreikomponentensynthese heterocyclischer Indione durch Verknüpfung von Glyoxylierung und nachfolgender katalytischer Stephens-Castro-Alkinylierung im Ein-Topf-Verfahren. Da Indione bisher weitgehend unerforscht sind, konnten hier am Beispiel der selektiven Synthese von 5-Acylpyrazolen das synthetische Potenzial dieser reaktiven Zwischenprodukte illustriert werden.[303]
5) *N*-Heteroaromatische Carbonsäuren und α-Oxocarbonsäuren können mittels einer in situ-Aktivierung mit Oxalylchlorid den Alkinylierungen nach Sonogashira oder Stephens-Castro zugeführt werden und gestatten erstmals die effiziente Transformation schwieriger *N*-heterocyclischer Substrate.[91]

6) Mit der sequenziell Pd-katalysierten Masuda-Borylierung–Suzuki-Kupplungs-Synthese konnte eine direkte und effiziente Strategie zur Synthese von 3-(hetero)arylsubstituierten (Aza)Indolen und 2,4-di(hetero)arylsubstituierten Pyrrolen im Ein-Topf-Verfahren etabliert werden. Neben der Synthese von 7-Azaindolderivaten als Variolin B-Analoga konnte die Methode auf symmetrische heterocyclisch verbrückte Bisindole und kurze Totalsynthesen der marinen Alkaloide Meridianin G, Meridianin A[464] und Hyrtinadin A[481] übertragen werden. Mit den erhaltenen Verbindungen wurden in Kooperation mit Merck Serono, Darmstadt, biologische Tests an menschlichen Krebszelllinien und an einer Vielzahl von Kinasen durchgeführt. Damit eignet sich diese Methode als rascher, effizienter Zugang zu biologisch aktiven Leitstrukturen.
7) Die Konzeption und methodische Etablierung einer Dreikomponenten-Sequenz aus Sonogashira-Kupplung und nachfolgender Azid-Alkin-Cycloaddition (“Click”-Reaktion) zur Herstellung von (aza)indolylsubstituierten Triazolen. Mit dieser Methode gelang die Findung einer neuen Leitstruktur für selektive PDK1-Inhibitoren.[227]

Schema 1 fasst das grundlegende Prinzip dieser Dissertation zusammen:



Schema1. Das grundlegende Konzept dieser Dissertation: einfache Grundbausteine + einfache Katalysatoren = komplexe funktionalisierte Zielstrukturen.

Alle vorgestellten Ein-Topf-Synthesen sind unter milden Bedingungen durchführbar und breit in ihrem Substratspektrum. Sie sind präparativ einfach anwendbar, gehen von einfachen Startmaterialien aus und benutzen einfache Katalysatorsysteme. Darüber hinaus wird die synthetische Vielseitigkeit von Oxalylchlorid als Reagenz in katalytischen Kupplungen zur Einführung des C_1-Carbonylsynthons (“Kohlenmonoxid-Surrogat”) erstmals erfolgreich demonstriert.

Abstract

Heterocycles are found in a plethora of natural products and active ingredients and their preparation touches the very core of Organic Synthesis. Therefore, efficient syntheses of heterocycles are of paramount importance.

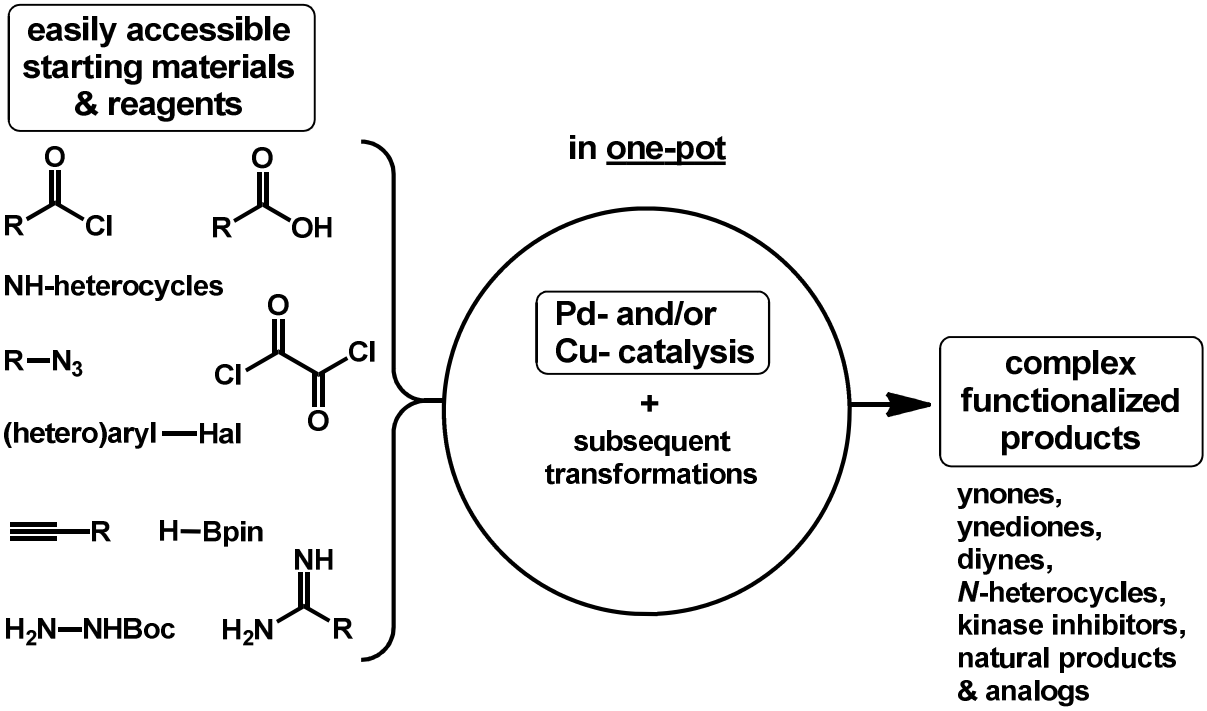
The goal of this thesis was the development of novel one-pot reactions based on palladium- and/or copper-catalysis for the efficient synthesis of heterocycles or their precursors. Starting from simple building blocks and using simple catalyst systems, diverse functional molecules should be prepared by these methodologies.

In the context of this work following goals were accomplished:

1) Development of a three-component synthesis of difficult-to-access 2,4-disubstituted pyrroles based on Sonogashira coupling.[399]
2) Conception and methodological establishment of a pseudo-four-component synthesis of 1,4-di(hetero)aryl substituted 1,3-diynes via sequential Sonogashira alkynylation–Glaser homocoupling.[161]
3) Establishment of a decarbonylative alkynylation of heteroaromatic glyoxylyl chlorides as a new variation of Sonogashira coupling. On this basis a conceptually novel three-component synthesis of ynones, which are important building blocks in many heterocycle syntheses, was devised.[355]
4) Conception and methodological establishment of a novel three-component synthesis of heterocyclic ynediones via catenation of glyoxylation and subsequent catalytic Stephens-Castro alkynylation in a one-pot fashion. Because the chemistry of ynediones is scarcely explored, the selective synthesis of 5-acyl pyrazoles was chosen to exemplify the synthetic potential of these reactive intermediates.[303]
5) *N*-Heteroaromatic carboxylic acids and α-oxo carboxylic acids can be in situ activated with oxalyl chloride for Sonogashira or Stephens-Castro alkynylations and allow for the first time an efficient transformation of notoriously difficult *N*-heterocyclic substrates.[91]

6) The sequentially Pd-catalyzed Masuda borylation–Suzuki coupling synthesis, which was established as a one-pot process, offers a direct and efficient strategy for the synthesis of 3-(hetero)aryl substituted (aza)indoles and 2,4-di(hetero)aryl substituted pyrroles. Besides the synthesis of 7-azaindole derivatives as analogs of variolin B this methodology was transposed to the preparation of symmetrical heterocycle-bridged bisindoles and to concise total syntheses of the marine alkaloids meridianin G, meridianin A,[464] and hyrtinadine A.[481] The obtained compounds were biologically evaluated in collaboration with Merck Serono, Darmstadt, on human cancer cell lines and on a broad panel of kinases, emphasizing that this methodology opens a rapid and efficient access to biologically active lead structures.
7) Conception and methodological establishment of a three-component Sonogashira coupling–azide-alkyne cycloaddition (“Click” reaction) sequence for the preparation of (aza)indolyl substituted triazoles. By this methodology a new lead structure for selective PDK1 inhibitors was found.[227]

Scheme 1 summarizes the basic principle of this thesis:



Scheme 1. Basic concept of this thesis: simple building blocks + simple catalysts = complex functionalized chemical targets.

All presented one-pot syntheses can be conducted under mild reaction conditions and are broad with respect to the substrate range. They are preparatively very simple, start from simple reactants and utilize simple catalyst systems. Moreover, the synthetic versatility of oxalyl chloride as a reagent in catalytic couplings for the introduction of the C_1-carbonyl synthon (“surrogate for carbon monoxide”) is successfully demonstrated for the first time.

Table of Contents

Abbreviations

[ ]	catalytic amount
A2780	ovarian tumor cell line; ECACC 93112519
Abl	Abelson (tyrosin kinase)
Ac	acetyl
acac	acetylacetonate
Ad	1-adamantyl
AGC	cAMP-dependent protein kinase/protein kinase G/protein kinase C
^{t}Am	*tert*-amyl (*tert*-pentyl)
API	active pharmaceutical ingredient
aq.	aqueous
Asc	ascorbate
atm	atmosphere(s)
ATP	adenosine-5'-triphosphate
[bmim]PF_6	1-butyl-3-methylimidazolium hexafluorophosphate
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
bp	boiling point
Bpin	pinacol boronate, pinacolborane
B_2pin_2	bis(pinacolato)diboron
BrettPhos	2-(dicyclohexylphosphino)-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl
Bu	butyl
°C	degrees Celsius
calcd	calculated
cAMP	3'-5'-cyclic adenosine monophosphate (cyclic AMP)
CDK	cyclin-dependent kinase
CK1	casein kinase 1
CML	chronic myeloid leukemia
CoA	coenzyme A
COD	1,5-cyclooctadiene
Cp	cyclopentadienyl

Cp*	pentamethyl cyclopentadienyl
CuAAC	Cu-catalyzed Azide – Alkyne Cycloaddition
Cy	cyclohexyl
CyDMEDA	*trans-N,N'*-dimethyl-1,2-cyclohexanediamine
d	day(s) or molecular orbital ("diffuse")
D	Dalton
Δ	thermal conditions
dabco	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DPPA	diphenylphosphoryl azide
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
DCM	dichloromethane
DCS	di(*N*-succinimidyl)carbonate
DEPT	Distortionless Enhancement by Polarization Transfer
DIPA	diisopropylamine
DIPEA	diisopropylethylamine (*Hünig's* base)
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMEDA	*N*,*N*'-dimethylethylenediamine
DMF	*N*,*N*-dimethylformamide
DMF-DMA	*N*,*N*-dimethylformamide dimethyl acetal
DMPU	*N*,*N*'-dimethylpropyleneurea
dppp	1,3-bis(diphenylphosphino)propane
dtbpy	2,6-di-*tert*-butylpyridine
(*E*)	"entgegen", configuration of double bond according to *E/Z* notation
ECACC	European Collection of Cell Culture
ED	effective dose
EDG	electron donating group
EI	Electron Impact Ionization

equiv(s)	equivalent(s)
Et	ethyl
EWG	electron withdrawing group
F_6-acac	1,1,1,5,5,5-hexafluoroacetylacetonate
FG	leaving group
g	gram(s)
GSK-3	glycogen synthase kinase 3
Gu	guanidine
h	hour(s)
Hal	halide
HE	hexanes
HCT116	colon tumor cell line; ATCC CCL-247
HIV	human immunodeficiency virus
HMG-CoA	3-hydroxy-3-methyl-glutaryl-CoA reductase
i	iso
IC_{50}	half maximal inhibitory concentration
IR	infrared (spectroscopy)
J	coupling constant
K_i	inhibition constant of a drug
L	ligand or liter(s)
M	metal
m	*meta*
MAP	mitogen-activated protein
MCM-41	Mobil Composition of Matter No. 41
MCR	multicomponent reaction
Me	methyl
MEM	methoxyethoxymethyl
min	minute(s)
MOM	methoxymethyl
Mp	melting point
MS	mass spectrometry or molecular sieves
μW	microwave
n	normal (linear, not branched)

NHC	*N*-heterocyclic carbene
NMP	*N*-methylpyrrolidone
NMR	Nuclear Magnetic Resonance (spectroscopy)
NPs	nanoparticles
Nu	nucleophile
o	*ortho*
p	*para*
π	aromatic system
PA-Ph	1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phosphaadamantane
Pd/C	palladium on charcoal
PDK1	3-phosphoinositide-dependent protein kinase-1
PE	petroleum ether (boiling range 40-60 °C)
pH	pondus Hydrogenii
Piv	pivaloyl
Ph	phenyl
phen	1,10-phenanthroline
PMB	*p*-methoxybenzyl
po	peroral
ppm	parts per million
Pr	propyl
PTK	protein tyrosine kinase
PTSA	*p*-toluenesulfonic acid
psi	pound per square inch; 1 psi = 0.068948 bar
Py	pyridine
rt	room temperature
RT	reverse transcriptase
RuAAC	Ru-catalyzed Azide-Alkyne Cycloaddition
RuPhos	2-(dicyclohexylphosphino)-2',6'-diisopropoxy-1,1'-biphenyl
(*S*)	absolute configuration according to RS-system
SAR	structure-activity relationship
sc	supercritical
SMR	structure-metabolism relationship
stoich.	stoichiometric amount

t	*tert*
TBAF	tetra-*n*-butylammonium fluoride
TBTA	tris(benzyltriazolyl)methyl amine
Tf	trifluoromethanesulfonyl (triflyl)
TFA	trifluoroacetate
Th	thienyl
THF	tetrahydrofuran
THP	tetrahydropyran-2-yl
TIPS	triisopropylsilyl
TLC	Thin Layer Chromatography
TMEDA	*N*,*N*,*N'*,*N'*-tetramethyl-1,2-ethylenediamine
TMHD	2,2,6,6-tetramethyl-3,5-heptanedionate
TMS	trimethylsilyl
TMSA	trimethylsilylacetylene
Tol	methylphenyl
Ts	4-toluenesulfonyl (tosyl)
vs	versus
W	watt
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos	2-(dicyclohexylphosphino)-2',4',6'-triisopropyl-1,1'-biphenyl
X-ray	X-radiation
(*Z*)	"zusammen", configuration of double bond according to *E/Z* notation

Introduction

Catalysis

Catalysis is one of the main principles of modern synthetic methodologies and is a key technology to achieve objectives of sustainable (green) chemistry.[1] The most important domain of metal-catalysis is the direct carbon-carbon bond coupling,[2] which has been considered to be the main goal for organic chemists for many decades. With the formulation of the concept of “click chemistry”, the alternative philosophy of making carbon-heteroatom bonds[3] in an easy way is now strongly in development, with catalysis again playing the central role.

Heterocycles

Heterocyclic chemistry is one of the most important topics in synthetic organic chemistry that covers a wide variety of potent molecules. The prevalent number of drugs contains heterocyclic moieties. Efficient syntheses of heterocycles are therefore of paramount importance for pharmaceutical industry. In particular, nitrogen containing heterocycles are structural constituents of many bioactive natural products, medicinally important compounds, and organic materials. Moreover, natural products containing heterocycles often possess unprecedented structures, which represent considerable synthetical challenges for organic chemists and encourage their creativity.

Concept of the ideal synthesis

Contemporary requirements for new synthetic methods go far beyond the traditional quests for chemo-, regio-, and stereoselectivity and include additional factors such as:

- Use of simple and readily available starting materials
- Experimental simplicity
- Favorable economic factors, including the cost of raw materials, human resources, and energy
- Low environmental impact: minimization of waste and *Trost's* atom economy[4]
- Concepts of step economy (*Wender* and *Baran*),[5] redox economy (*Baran* and *Hoffmann*),[6] and recently introduced pot economy (*Clarke*)[7]
- Synthetic elegance

These and other requirements are expressed in the concept of the "ideal" synthesis (Figure 1),[8] which is an ideal goal that certainly can only be approached asymptotically but which can still serve as a useful guideline for development of new synthetic methods.

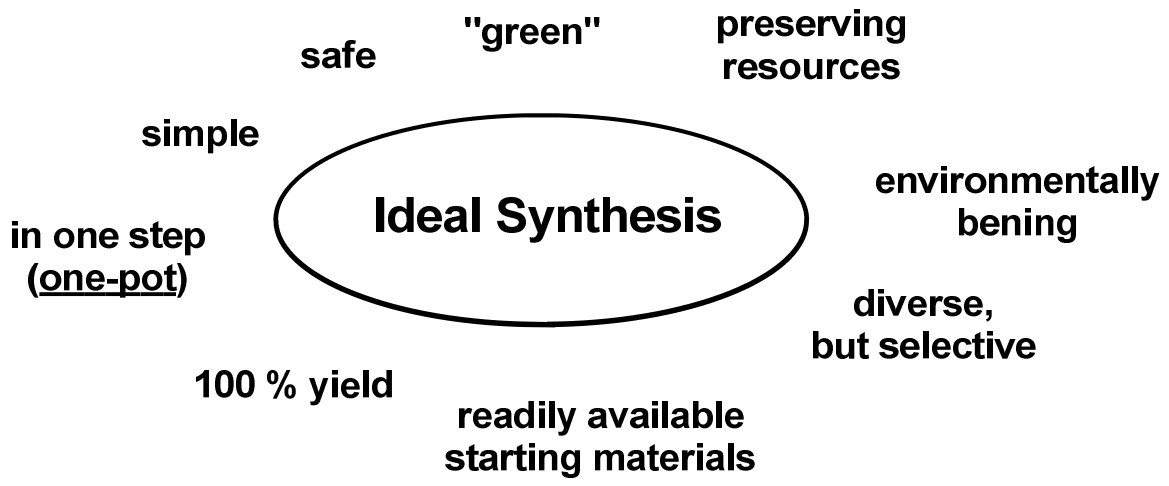


Figure 1. The ideal synthesis – showing the way (adapted from [55]).

One-pot and multicomponent reactions

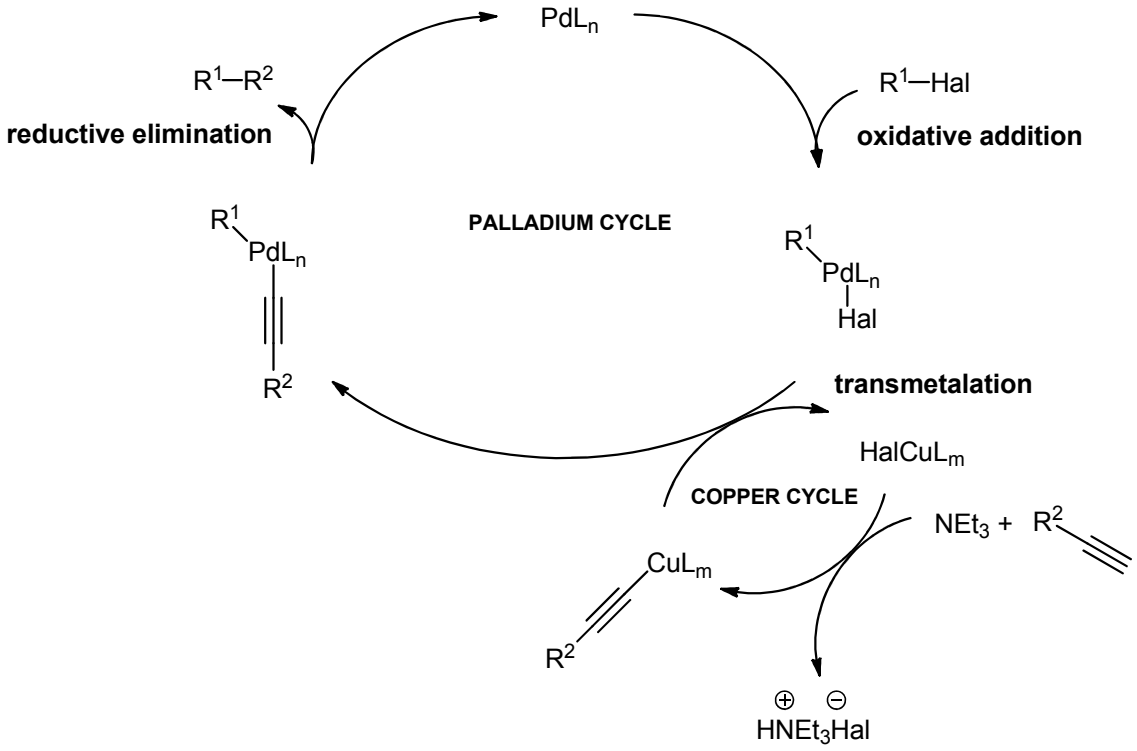
Nature with its chemistry going through cascade catalysis and multistep conversions in “one-pot” (living cells) provides concepts of high value for designing sustainable organic syntheses, which already have found applications on pilot or industrial scale.[9] From a practical aspect, one-pot reactions can accelerate the search for pharmaceuticals.[10]

“For this reason, development of processes that allow creation of several bonds in a single operation has become one of the most attractive scientific challenges. Multi-component reactions (MCRs) can be defined as convergent chemical processes where three or more reagents are combined in such a way that the final product retains significant portions of all starting materials”.[385a] MCRs can be successfully implemented in the synthesis of diverse heterocycles. “For a long time multicomponent syntheses of heterocycles have been a domain of classical carbonyl condensation chemistry, with isocyanide-based *Ugi* chemistry being still prevalent in this area of research.[11] However, the advent and rapid evolution of transition metal catalysis not only has revolutionized strategies in heterocyclic synthesis by uni- and bimolecular transformations but the past decade has also witnessed the rapid development of transition metal catalysis in new MCRs. Transition metal catalysis, and especially sequential catalysis, with palladium occupying a dominant but not monopolistic position”,[12],[13],[14] offers numerous possibilities to develop new MCRs due to the mild reaction conditions and generality of scope, favorable features that are shared by many cross-couplings.[15],[16]

Pd- and Cu-catalysis

Palladium and copper are the most widely used late transition metals with numerous applications in organic synthesis.

Pd- and Cu-assisted methods often work in a complementary fashion, giving for example different chemoselectivities. On the other hand, the combination of these two metals in a cooperative way plays a key role in some important transformations. The most prominent example is the *Sonogashira-Hagihara* cross-coupling where two catalytic cycles coexist, cooperate, and interlock with each other (Scheme 2).



Scheme 2. Pd and Cu cycles in the proposed mechanistic rationale for the *Sonogashira* coupling.

Natural products

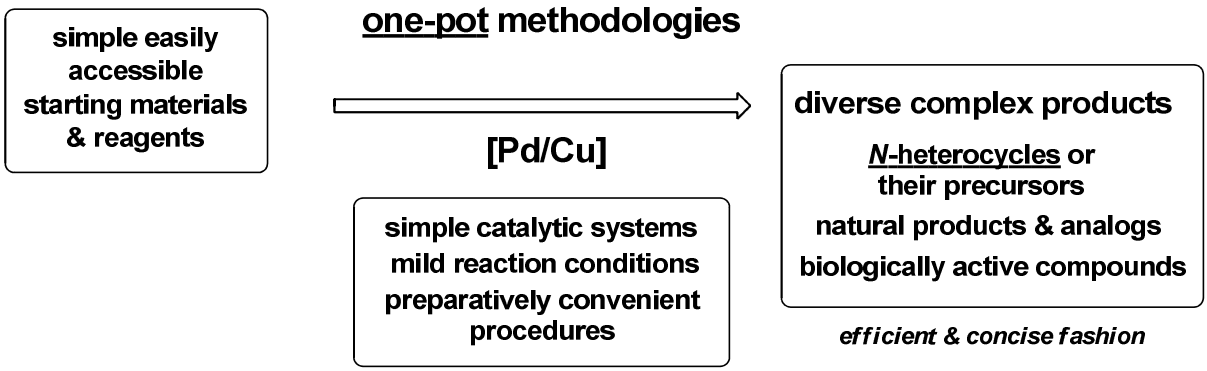
“Natural products are the richest source of small molecules that bind to proteins with high specificity thanks to millions of years of evolution”.[107] Hence, “medicine and natural products have been closely linked for thousands of years by the use of traditional medicine and natural poisons. It has been estimated that over half the drugs currently used for the treatment of cancer are either natural products or drugs derived from them. Even today, in the century of combinatorial chemistry, secondary metabolites of plants, fungi, marine organisms, and microorganisms are an important source for the development of new drugs.[17] Approximately 50 % of drugs introduced to the market are derived directly or indirectly from small molecules of natural origin”.[401]

Kinase inhibitors

Protein kinases catalyze the phosphorylation of serine, threonine, tyrosine, and histidine residues in proteins.[18] Reversible phosphorylation is one of the major modes of cellular signal transduction and plays a regulatory role in most metabolic pathways. Hence, virtually every aspect of cellular physiology, such as cell growth, metabolism, differentiation, and apoptosis, is inherently linked to the proper functioning of these enzymes. Abberant regulation of kinase activity has been implicated in many diseases including cancer. Hence, kinases are among the most promising drug targets.[19] Frequently, kinase inhibitors are small molecules suitable for development and preparation in chemical laboratories on a big scale. For this reason, small heterocyclic molecules play an immensely important role in oncology,[20] and investigations of new strategies for kinase inhibitor design remains an active area of research with direct relevance to drug development. Currently, it is estimated that approximately one-third of the drug discovery programs target protein kinases.[21] For medicinal chemists, protein kinases represent a goldmine of design opportunities.

1 Goal of This Work

The goal of this work was to develop novel one-pot Pd and/or Cu-catalyzed reaction sequences for the efficient construction of heterocycles or their immediate precursors. The reactions should be mild, preparatively convenient, and allow to synthesize biologically active heterocyclic molecules for biological studies as well as natural products in a concise sequential or consecutive fashion starting from easily accessible materials and using simple catalysts (Scheme 3).

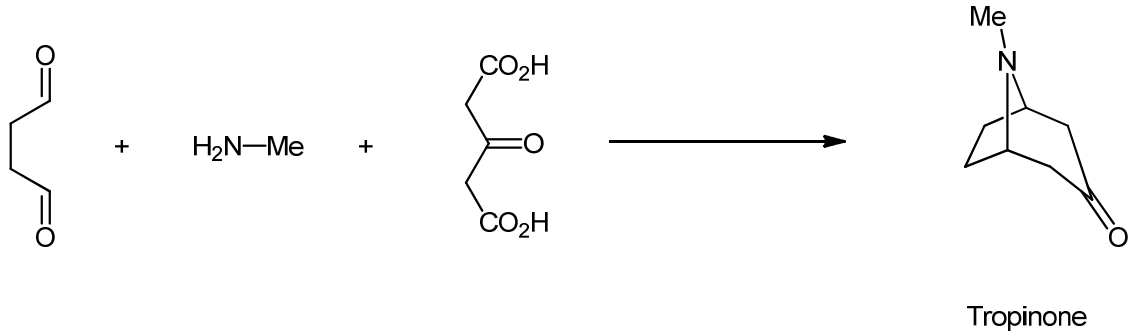


Scheme 3. Basic concept for the development of novel Pd/Cu-catalyzed sequences.

2 General Part – Literature Overview

2.1 Multicomponent Reactions and Sequential Catalysis

"One of the major research endeavors in synthetic chemistry over the past decades is the exploration of synthetic methods that maximize atom utilization".[70] "By generating structural complexity in a single step from three or more reactants, MCRs make it possible to synthesize target compounds with greater efficiency and atom economy. The history of such reactions can be traced back to the mid-19th century when *Strecker* first produced α-aminonitriles from the condensation of aldehydes with ammonia and hydrogen cyanide".[26a] An exceptionally beautiful first example for the utility of a MCR in the total synthesis of natural products is the tropinone synthesis by *Robinson*, published in 1917 (Scheme 4).[22]



Scheme 4. First total synthesis of natural product tropinone via MCR.

"Recently, academic chemists have revitalized their interest in MCRs.[23] In part, pharmaceutical industry has fueled this resurgence because of the growing need to assemble libraries of structurally complex substances for evaluation as lead compounds in drug discovery and development programs.[24],[32] The application of MCRs, however, remains limited by the relatively small number of traditionally proved reactions"[26a] such as *Strecker* (1850), *Hantzsch* (1882), *Biginelli* (1891), *Mannich* (1912), *Passerini* (1921), and *Ugi* (1959).[25] Not surprising, therefore, is the recent development of novel logic-based strategies for the engineering of new MCRs.[26]

In terms of classification, “domino reactions are regarded as sequences of uni- and bimolecular elementary reactions that proceed without isolation or workup of intermediates as a consequence of the reactive functionality that has been formed in the previous step. Besides uni- and bimolecular domino reactions that are generally referred to as “domino reactions”,[27] the third class is called multimolecular domino reactions or multicomponent reactions (MCRs). Whereas uni- and bimolecular domino reactions inevitably cause a significant increase in the degree of molecular complexity, MCRs inherently lead to an increase in molecular diversity.[28] Therefore, MCRs bear some significant advantages over uni- and bimolecular domino reactions. Besides the facile accessibility and high diversity of starting materials, multicomponent syntheses promise high convergence and enormous exploratory potential. In addition to a purist standpoint, where all ingredients of MCRs have to be present from the very beginning of the process (MCRs in a domino fashion), nowadays sequential (subsequent addition of reagents in a well defined order without changing the conditions) and consecutive (subsequent addition of reagents with changing the conditions) one-pot reactions are counted as well in the class of MCRs”[55] (Figure 2).

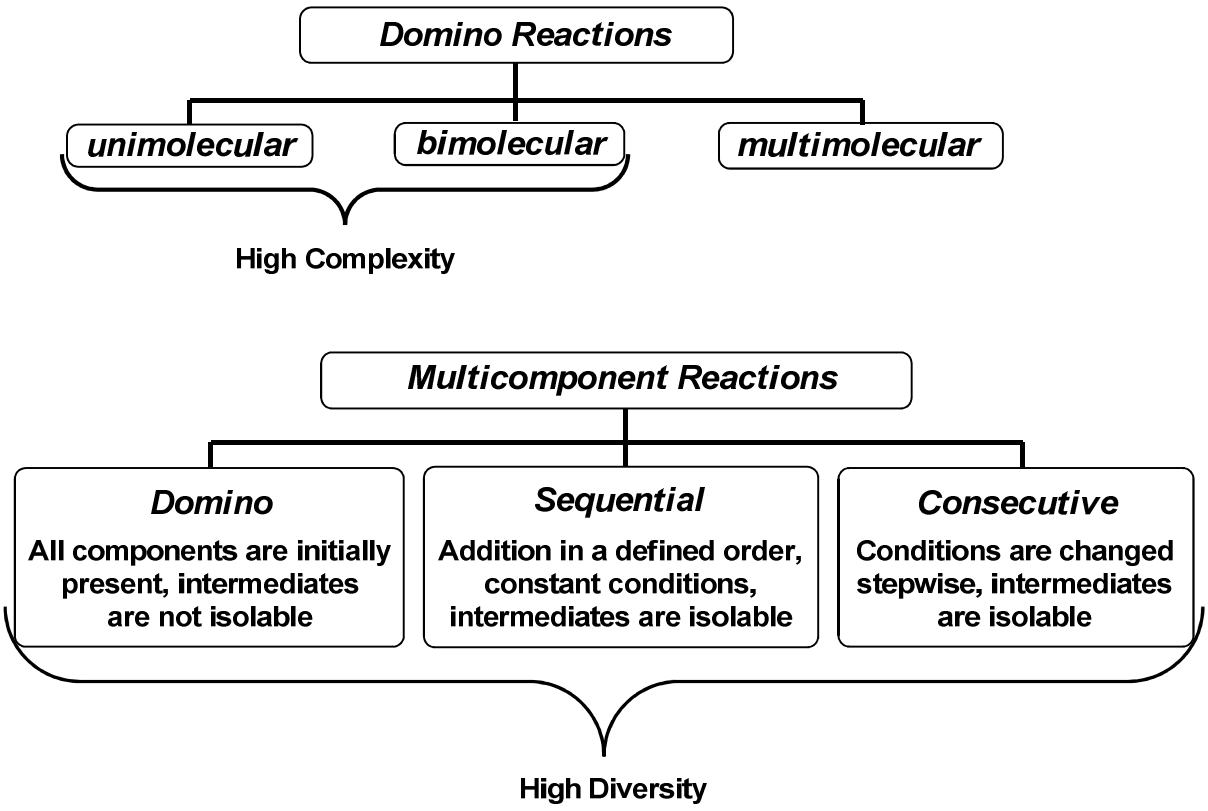


Figure 2. Multicomponent and domino reactions (adapted from [55]).

Sequential catalysis is defined as a combination of identical, related, or significantly different[29] (metal)-catalyzed processes that occur in a sequential or consecutive fashion in the same reaction vessel without addition of further amounts of catalyst to the reaction media.[13] *Fogg* and *dos Santos* provided a classification review on one-pot catalytic processes involving sequential elaboration of an organic substrate via multiple catalytic transformations with the focus on tandem catalysis.[30] Cooperative multicatalyst systems for one-pot organic transformation are also of high interest, with Pd and Cu-catalyzed *Sonogashira* coupling being one of the most prominent examples.[31]

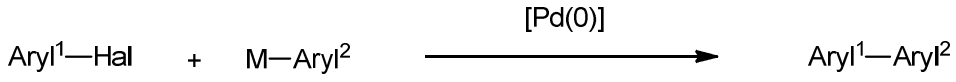
"Multicomponent and sequential one-pot processes address very fundamental principles of synthetic efficiency[32] and reaction design and they are steadily gaining a considerable and increasing academic, economic, and ecological interest".[293] According to the basic principles of MCRs the products of consecutive transformations should preferentially contain substantial fragments of all starting materials, thus providing a high degree of atom-efficiency (or atom economy,[4] defined as the number of atoms of the reactants which can be found in the product).

MCRs belong to highly sophisticated tools in the repertoire of an organic chemist. They are masterpieces and require intelligent reaction design and a judicious choice of propriate reaction conditions to combine different transformations into a one-pot process. Hence, it is not surprising that the separate steps of a reaction sequence have to be efficient by themselves to give an efficient and clean one-pot transformation. Otherwise, undesired byproducts will accumulate leading to a loss of efficiency and product purity. However, one-pot reactions are frequently more than just a clever combination of already known methods. They can include the generation of unstable intermediates, thus leading to higher product yields than the corresponding separated reactions. An even more sophisticated situation occurs if a byproduct generated during the first reaction promotes the second reaction in the same sequence. In the framework of this thesis both cases were experienced during the design of new one-pot reactions.

2.2 Cross-Coupling Reactions

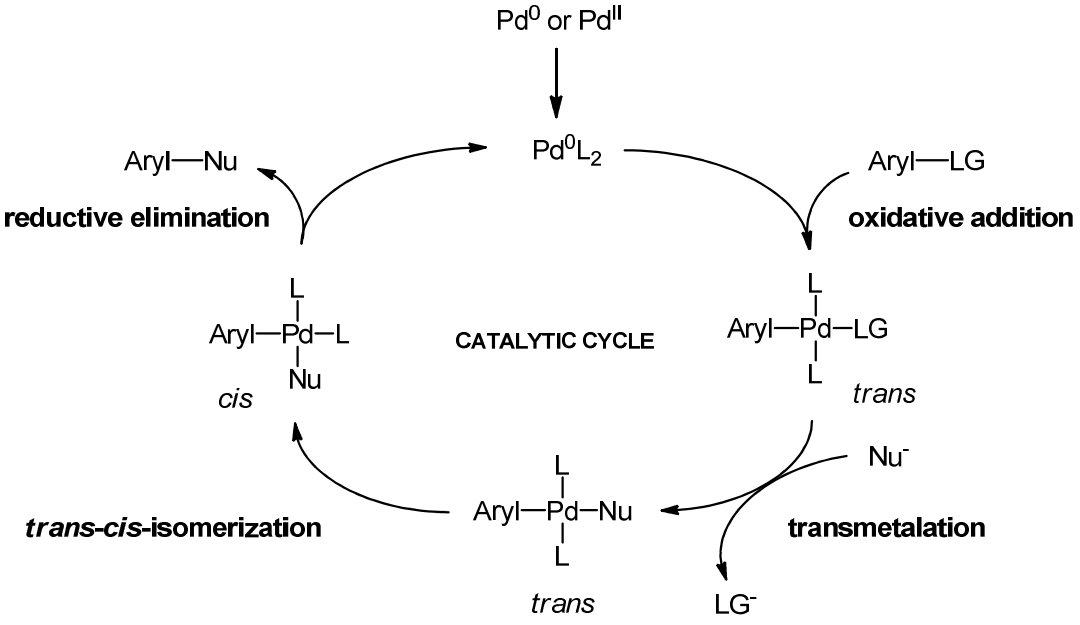
Transition metal-catalyzed cross-coupling is recognized as one of the most powerful C–C bond-forming reactions.[2] "Cross-coupling is a generic term used to denote a σ-bond metathesis reaction between a nucleophilic and an electrophilic reagent, and thus can be regarded as a generalization of nucleophilic substitution. Coupling reactions take place only in the presence of a catalyst".[42d]

The Pd-catalyzed coupling of aryl halides or their synthetic equivalents with aryl metals is very often employed in the synthesis of biaryl molecules,[33] whose scaffolds can be found in a wide range of important compounds including pharmaceuticals,[34] natural products, and functional organic materials (Scheme 5).



Scheme 5. Pd-catalyzed cross-coupling reactions for the synthesis of biaryls.

"The role of the catalyst is generally believed to take part in successive oxidative addition, transmetalation, and reductive elimination reactions"[42d] (Scheme 6).



Scheme 6. A simplified representation of the proposed general mechanism for Pd-catalyzed cross-coupling reactions using monodentate ligands.

Cross-coupling reactions have found numerous applications in the synthesis of biologically active molecules, heterocycles,[35] and total synthesis of natural products,[36] and have become a standard tool for the synthetic chemist.

Halides are the most frequently used electrophilic partners in coupling reactions. Following the dissociation energies of the sp^2-C–Hal bonds (272, 339, and 402 kJ mol^{-1} at 298 K for PhI, PhBr, and PhCl, respectively), aryl iodides are by far more reactive than bromides and chlorides. In recent years, “the acquisition of the ability to utilize inexpensive aryl chlorides has been of particular interest in the cross-coupling research arena.[37] However, by far the largest application of cross-coupling chemistry occurs in the medicinal and discovery groups of pharmaceutical companies and in academic laboratories. For the vast majority of these cases the scope, experimental ease, and reliability of a method is much more important than whether aryl chlorides can be used rather than aryl bromides or aryl iodides”.[195d]

Although the vast majority of synthetic methods is typically exemplified with simple aryl substrates, heterocyclic,[35] especially *N*-heterocyclic, substrates have remained demanding and challenging for the method development and, therefore, have been far less investigated. Heteroaromatics tend to be good ligands for transition metals, hence substrate and/or product inhibition are quite common. Moreover, free amino and alcohols groups often poison the metal catalyst via ligation or act as nucleophiles and need protection (Ts, Boc, Bn, Ac). Cross-coupling with heteroarenes is therefore highly topical and rapidly developing area of research. Just recently, methods of coupling two heteroarenes were reviewed, emphasizing the importance of this issue.[38]

2.3 Pd/Cu-Catalyzed Reactions

Pd reagents have decisively changed the synthetic strategies, especially of natural products, and altered even the way of thinking of organic chemists. They contributed to a change in synthetic schemes from previously linear to currently convergent strategies. “Today, cross-coupling is so closely associated with palladium catalysis that both terms are often regarded as inseparable parts of an idiom”.[42d] The element palladium possesses several unique features that render it highly suitable for cross-couplings:

- “The middle atom size (second transition metal row) between that of Ni and Pt leads to a moderate stability of Pd-complexes. They are more stable than the Ni-, but more reactive than Pt-complexes, thus being synthetically highly useful. There are sufficient coordination sites for catalytic reactions.
- Pd prefers two oxidation states: 0 and +II. The change between these two states is very facile, so that Pd is perfectly suited for performing oxidative addition and reductive elimination steps. The active species can be easily regenerated, closing the catalyst cycle. There is little tendency toward one electron radical processes.
- Pd is a late transition metal and realizes d^{10} and d^8 complexes. In connection with its medium size, the high number of electrons makes it “soft”. It possesses high affinity to unpolar π-systems such as alkynes, alkenes, arenes, as well as “soft” phosphane ligands.
- High electronegativity (2.2 according to *Pauling* electronegativity scale; C: 2.5). The unpolar C–Pd bonds display low reactivity toward polar functionalities, unlike polar organolithium or organomagnesium compounds. Therefore, Pd-catalyzed reactions are highly tolerant to functional groups. A very important exception are acyl halides, which are very reactive toward palladium and are extensively used as substrates”[39] (vide infra).

Pd is capable of absorbing large amounts of hydrogen gas, which led to one of its earliest chemical applications as a hydrogenation catalyst. In the last decades, many

synthetic transformations have been developed that use palladium compounds, such as carbon-carbon and carbon-heteroatom coupling reactions: *Buchwald-Hartwig*, *Heck-Mizoroki*, *Kumada-Corriu*, *Negishi*, *Nozaki-Hiyama*, *Sonogashira-Hagihara*, *Stille-Migita*, *Suzuki-Miyaura*, and *Tsuji-Trost*. An extremely important domain of Pd-catalysis are carbonylative reactions, which allow the introduction of the most important functionality, the carbonyl group.[40] All these reactions are gaining increasing popularity as they are generally tolerant to a wide range of functional groups and can therefore be applied to complicated advanced molecules.

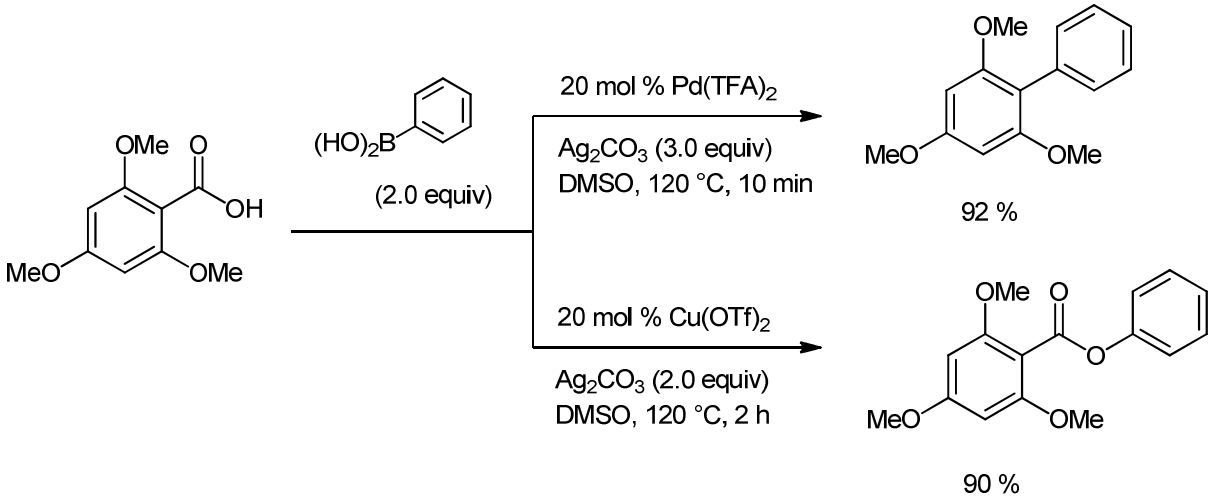
Cu-catalyzed transformations belong to the basic processes in the organic chemistry. Indeed, copper was the ancestor of palladium in the cross-coupling domain. “Classical *Ullmann* chemistry has been known for a full century and served well for C–N, C–S, C–O, and some other bond formation reactions. Moreover, C–C bond formation has been the priority domain of organocuprate chemistry. However, after the discovery and with the dramatic development of the Pd-catalyzed cross-coupling methodologies, Cu-mediated transformations became far less important and have fallen into oblivion. A critical point was the discovery and fast development of the Pd-catalyzed amination, known as *Buchwald-Hartwig* chemistry, which conquered the last stronghold of Cu – the synthesis of arylamines in which the classical *Ullmann* and *Goldberg* reactions had kept an exclusive and unshakable position”.[41] However, Cu possesses several very attractive features making it extremely versatile:

- “The most important feature of Cu is an easy accessability of four oxidation states from 0 to +III. Most likely, the cross-coupling catalytic cycle with Cu is operated by +I/+III oxidation states.
- Accessibility of odd-electron states in Cu, implying that Cu can take part in redox single-electron transfer processes.
- Cu is much cheaper than Pd. Despite of that, industrial processes need to be catalytic in Cu.
- *N*- or *O*-ligands required for the Cu-catalysis are usually cheap and easily accessible. Many of them are common analytical or general purpose reagents.
- Cu shows wide tolerance to functional groups and double bonds”.[41]

For these reasons, in the past years there has been a true renaissance of the Cu-chemistry, and a plenty of very exciting novel reactions were discovered and continue to appear in the literature.[42],[43]

Pd- and Cu-catalysis can be applied complementarily, for instance in arylations to give regioisomeric products. *Buchwald* reported an orthogonal catalyst system for the chemoselective *O*- and *N*-arylation of aminophenols, using CuI/picolinic acid or CyDMEDA and Pd/BrettPhos, respectively.[44] In the same group an orthogonal catalytic system for the chemoselective *C*- and *N*-arylation of oxindoles has been developed using Pd/XPhos or RuPhos and CuI/CyDMEDA, respectively.[45]

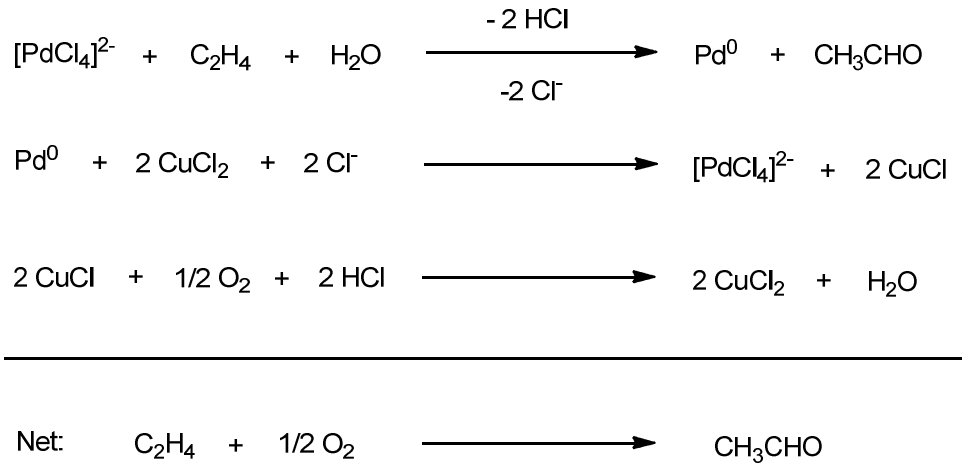
An interesting orthogonal system has been developed for arylation of aromatic carboxylic acids with boronic acids.[46] Under Pd-catalysis, biaryls were obtained, whereas the Cu-catalyst gives rise to the formation of carboxylic esters (Scheme 7).



Scheme 7. Orthogonal catalyst systems for arylation of aromatic acids.

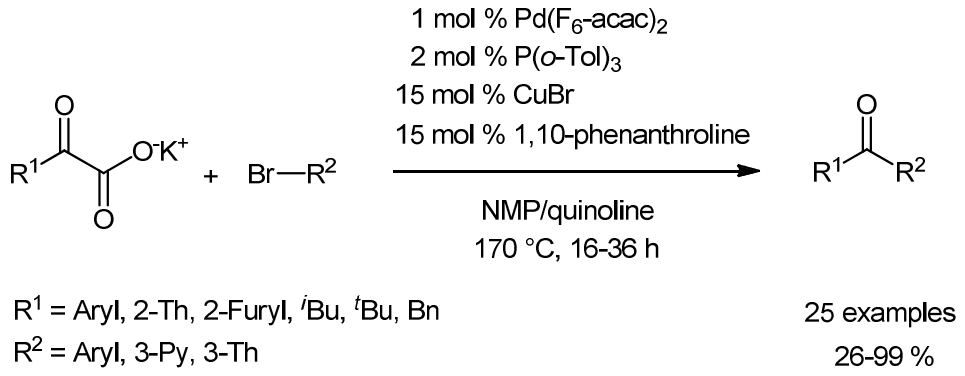
Palladium and copper can also work cooperatively in a variety of important transformations.

Cu is widely used to accelerate the reoxidation of Pd(0) to Pd(II) with O_2 as in the industrially important *Wacker* process for the aerobic oxidation of alkenes to aldehydes (Scheme 8).[47]



Scheme 8. Individual reactions of the *Wacker* process (scheme taken from [47a]).

Both Pd and Cu were required in the decarboxylative cross-coupling of α-oxocarboxylates and aryl bromides reported by *Gooßen* (Scheme 9).[48] The method is applicable to the synthesis of simple biaryl ketones.



Scheme 9. Decarboxylative cross-coupling according to *Gooßen*.

The postulated mechanism consists of Pd- and Cu-catalytic cycles, Cu being responsible for the decarboxylation of the Cu glyoxylate and transmetalation of the aroyl

residue to Pd. However, for practical applications high reaction temperatures and prolonged reaction times are less favorable. Moreover, many additives and rigorously dried solvents are indispensable.

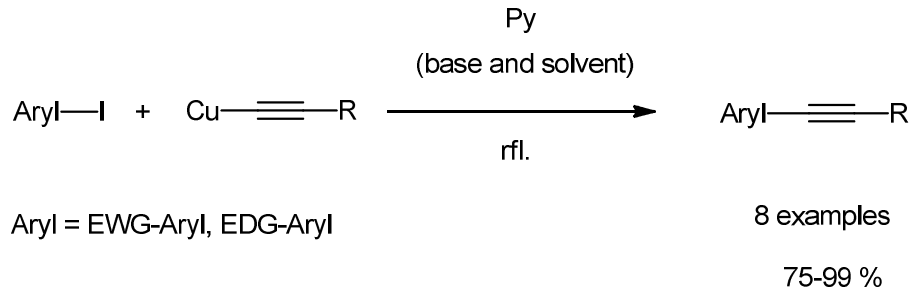
Similarly, both metals were used for the synthesis of biaryls via catalytic decarboxylative coupling of acids with aryl bromides according to *Gooßen*.[49] Later, the same group reported a decarboxylative coupling of carboxylate salts with triflates,[50] tosylates[51] and aryl chlorides,[52] a microvawe-assisted coupling of carboxylates with aryl bromides,[53] as well as a one-pot three-component synthesis of azomethines from α-oxo-carboxylates, amines, and aryl bromides.[54]

The most prominent example of Pd and Cu working in a cooperative fashion is the bimetallic *Sonogashira-Hagihara* cross-coupling, which will be discussed below in chapter *2.3.2 Sonogashira-Hagihara coupling*. In *Müller's* group Pd/Cu-catalyzed alkyne activation has been extensively used as an entry to diverse heterocycles (vide infra).[55]

Both metals have been shown to be essential also in the related alkyne homocoupling, where Cu is believed to possess a dual role, first being utilized to mediate the alkynyl transfer to Pd(II), and second in the reoxidation of Pd(0) to Pd(II).[144b] This reaction will be discussed in chapter *2.3.4 Glaser-type acetylene couplings*.

2.3.1 *Stephens-Castro* coupling

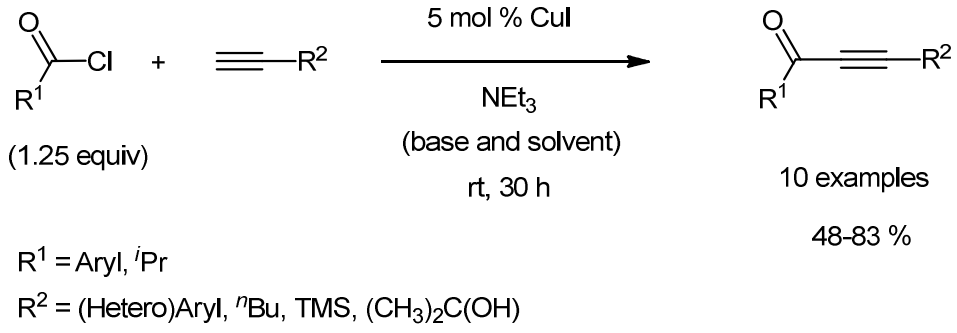
In 1963, *Stephens* and *Castro* disclosed that diarylacetylenes can be produced in good yields upon treatment of aryl iodides with copper(I) acetylides in refluxing pyridine (Scheme 10).[56]



Scheme 10. *Stephens-Castro* coupling.

Although the initial reaction conditions were quite harsh requiring refluxing pyridine and stoichiometric amounts of potentially explosive acetylides, this finding paved the way for the further development of alkynylations based on cross-coupling methodologies. Later, catalytic variants ("copper-only *Sonogashira* coupling") and milder conditions have been developed rendering the reaction more general.[57]

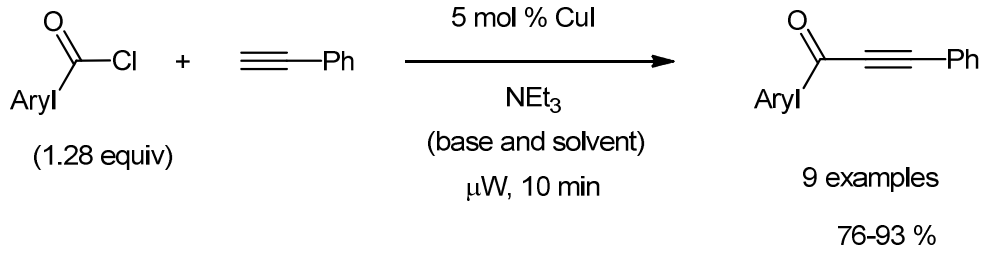
The reaction is also suitable for the preparation of ynones (for the detailed discussion on ynones, see chapter *2.6.1. Syntheses and reactivity of ynones*). In 1999, *Kundu* described a catalytic *Stephens-Castro* coupling of aromatic acid halides with terminal alkynes (Scheme 11). Triethylamine was used as a base and solvent.[58]



Scheme 11. Catalytic *Stephens-Castro* coupling of acid chlorides.

No diyne byproducts, which are usually formed in Pd-catalyzed reactions of terminal alkynes (vide infra), have been observed.

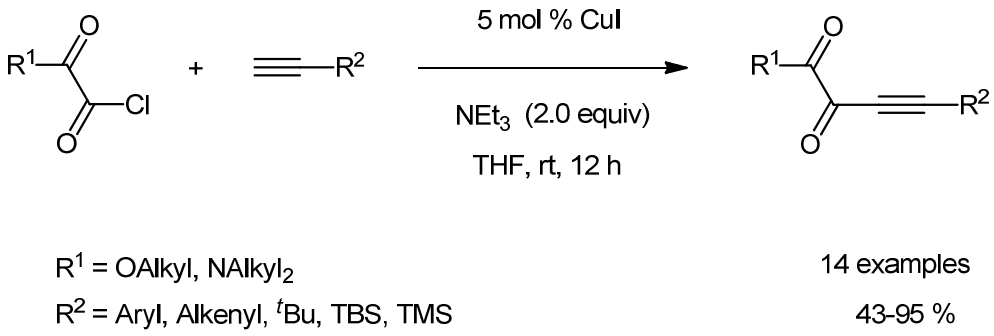
A microwave-assisted coupling of acid chlorides appeared in 2001 (Scheme 12).[59]



Scheme 12. Microwave-assisted synthesis of ynones.

The first carbonylative *Stephens-Castro* coupling of aryl iodides with alkynes using $Cu(TMHD)_2$ as a catalyst and triethylamine as a base was described in 2008 and proceeded at 90 °C and under 20 atm of CO pressure.[60] Simple aromatic ynones were obtained in moderate to good yields.

In 2003, a mild catalytic *Stephens-Castro* coupling of monooxalyl chlorides was reported (Scheme 13).[61] Here, triethylamine was used in slight excess.

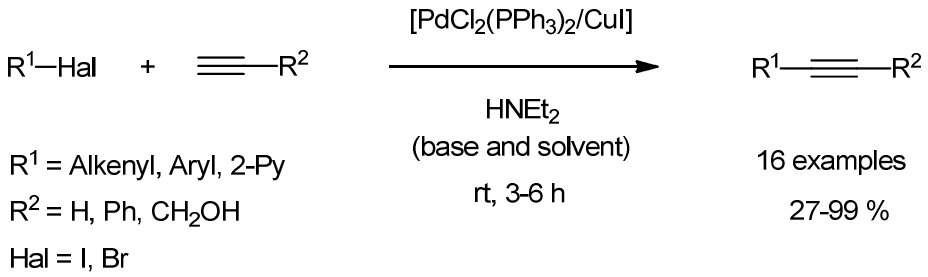


Scheme 13. Catalytic *Stephens-Castro* coupling of monooxalyl chlorides.

The reaction was highly suitable for the synthesis of 2-oxo-3-butynoates and 2-oxo-3-butynoamides. However, prior to this work this direct approach has been neither extended into a one-pot protocol nor applied to the functionalization of heterocycles. The potential of ynediones as versatile building blocks has not been explored to a proper extend.

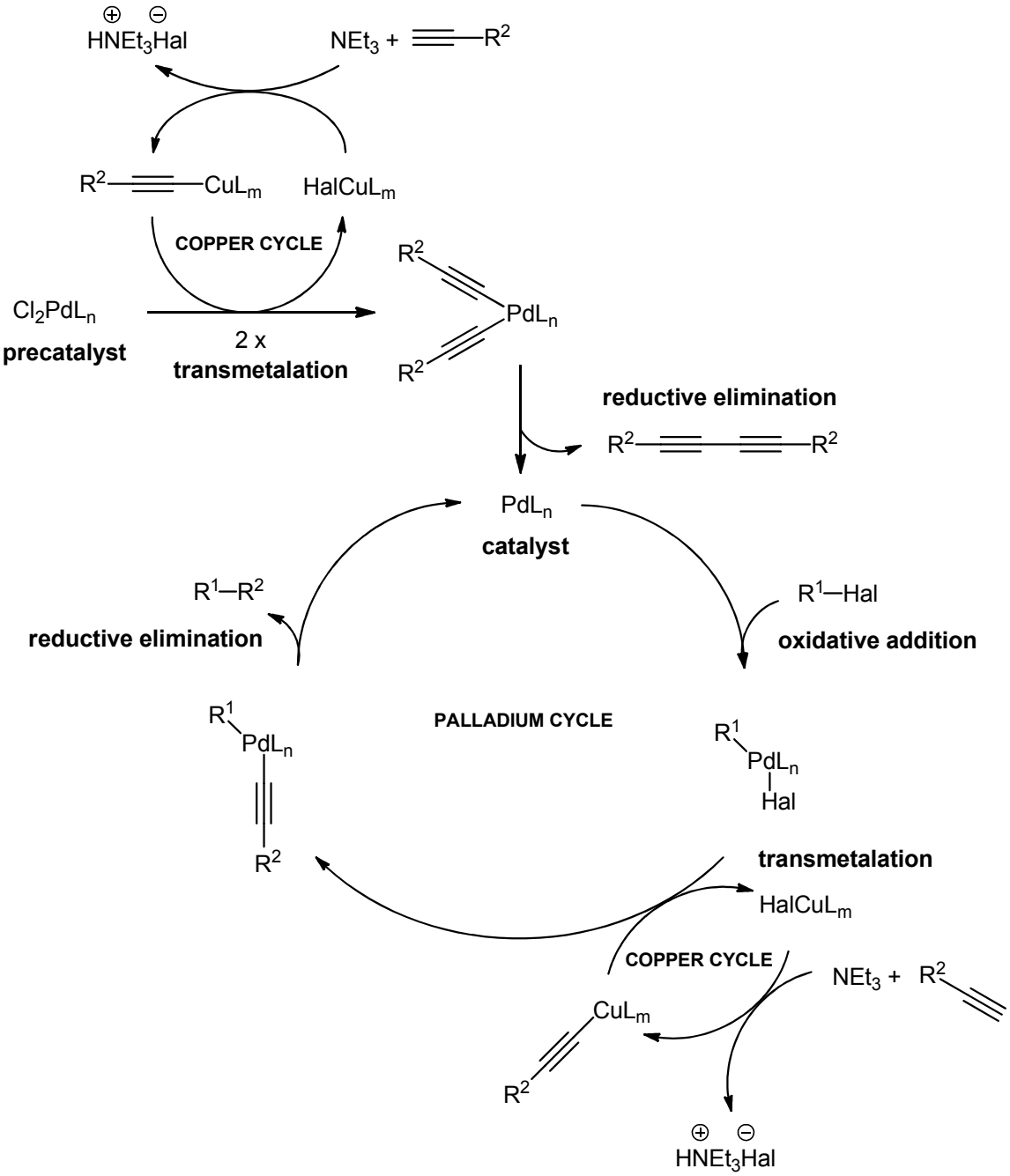
2.3.2 *Sonogashira-Hagihara* coupling

Soon after the pioneering report by *Stephens* and *Castro*, in 1975 *Sonogashira* demonstrated that terminal alkynes react smoothly with bromoalkenes, iodoarenes, and bromopyridines in the presence of catalytic amounts of bis(triphenylphosphane)palladium dichloride and cuprous iodide in diethylamine at room temperature (Scheme 14).[62]



Scheme 14. *Sonogashira* coupling.

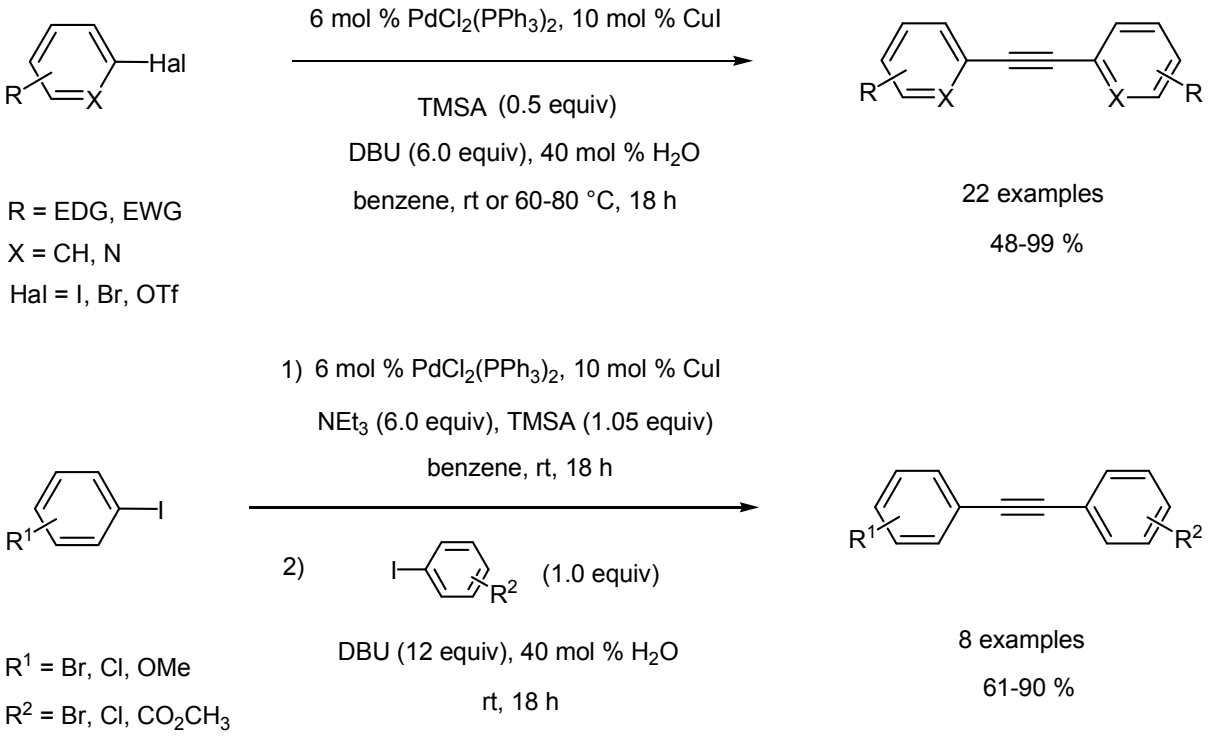
The authors proved that CuI was essential for the reaction to proceed under very mild conditions and proposed a mechanism which involved the generation of an active Pd(0)-species and of the crucial Pd(II)-alkynyl complex via a Cu-acetylide formed by the assistance of Cu(I) and the amine base (Scheme 15). Although the main features of the Pd catalytic cycle have been established, the Cu catalytic cycle is still poorly understood.



Scheme 15. General mechanistic rational for *Sonogashira* coupling with triethylamine as a base.

It should be mentioned that in the same year *Cassar*[63] and *Heck*[64] reported their catalytic systems based on Pd(0) and Pd(II) triphenylphosphane complexes. However, the Cu-cocatalyzed mild method of *Sonogashira* turned out to be more practical.[65]

In order to synthesize an unsymmetrical tolane, the *Sonogashira* coupling of aryl halides with trimethylsilylacetylene can be performed to provide TMS-protected alkynes, which have to be protodesilylated to obtain terminal alkynes that in turn can be coupled with another aryl halide to obtain the desired tolane. This stepwise procedure is tedious, thus the one-pot *sila-Sonogashira* coupling has been introduced by *Mori* and later generalized by *Brisbois* and *Grieco* in 2002 (Scheme 16).[66] Symmetrical and unsymmetrical tolanes are obtained in good yields.



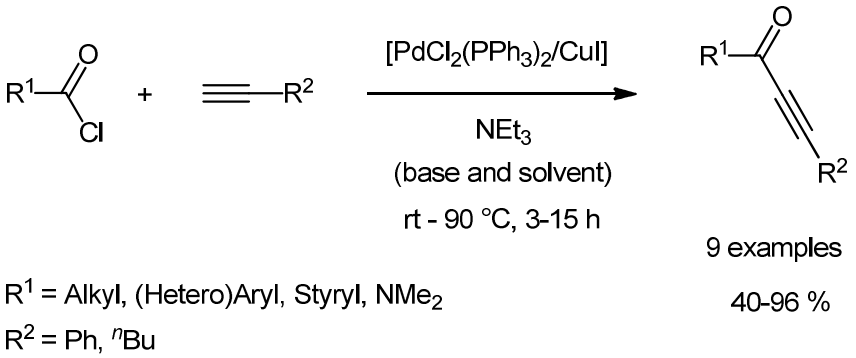
Scheme 16. *Sila-Sonogashira* coupling for the preparation of symmetrical and unsymmetrical tolanes.

Eventually, a recent one-pot procedure described the synthesis of unsymmetrical diarylalkynes via coupling of two different aryl halides and TMSA. The TMS-alkyne formed after the first coupling step is deprotected with aq. KOH and coupled again without additional Pd/Cu-catalysts.[67]

In the arena of alkyne chemistry, the *Sonogashira* coupling is one of the most significant developments over the past 35 years.[68] The *Sonogashira* reaction possesses several features that render it one of the most efficient and reliable C–C cross coupling reactions:

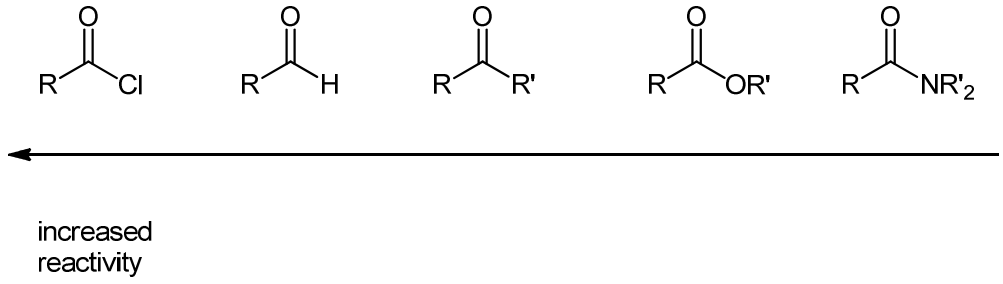
- The reaction is very general and includes (hetero)aryl or vinyl halides as electrophiles and terminal alkyl, alkenyl, (hetero)aryl, and silyl substituted alkynes or acetylene as nucleophiles.
- The catalysts are readily available. Cu(I)-sources are typically CuI or CuBr; typical Pd(II)-precatalysts are $PdCl_2(PPh_3)_2$ or $Pd(PPh_3)_4$.
- A base is required. Typically, amine bases are used, often as solvents.
- Solvents do not need to be rigorously dried (but deoxygenation is required!).
- A wide functional group tolerance. Therefore, useful in the synthesis of natural products and active pharmaceutical ingredients (APIs). However, 1-alkynes containing an EWG directly attached to the ethynyl carbon atom hardly react with aryl halides.
- Mild reaction conditions with reactions typically proceeding at room temperature or slightly above. At higher temperatures, alkynes are prone to undergo side reactions.
- Cu-acetylides are catalytically generated in situ.
- Good scaleability of the process.

In 1977, *Sonogashira* and *Hagihara* reported a coupling of acid chlorides with terminal alkynes to form ynones, a useful class of synthetic intermediates (Scheme 17).[69] Both coupling partners were used in exactly stoichiometrical amounts.



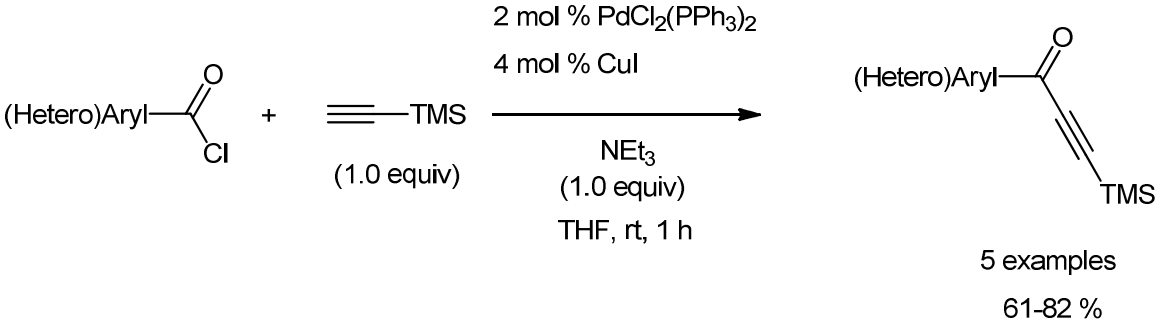
Scheme 17. *Sonogashira* coupling of acid chlorides.

The reactivity of acid chlorides toward alkyne addition is more pronounced as compared to other carbonyl compounds, thus making them attractive substrates for alkynylations (Scheme 18).[70]



Scheme 18. Reactivity of carbonyl compounds toward alkynylation.

Under classical conditions, the amine base is used as a solvent in large excess. In 2003, a useful modification of *Sonogashira* coupling of acid chlorides with terminal alkynes was introduced by *Müller* using exactly one equivalent of triethylamine as a base (Scheme 19).[71],[72] This amount is stoichiometrically required and is consumed by scaveging the hydrogen chloride formed during the reaction.



Scheme 19. *Modified Sonogashira* coupling using exactly one equivalent of triethylamine.

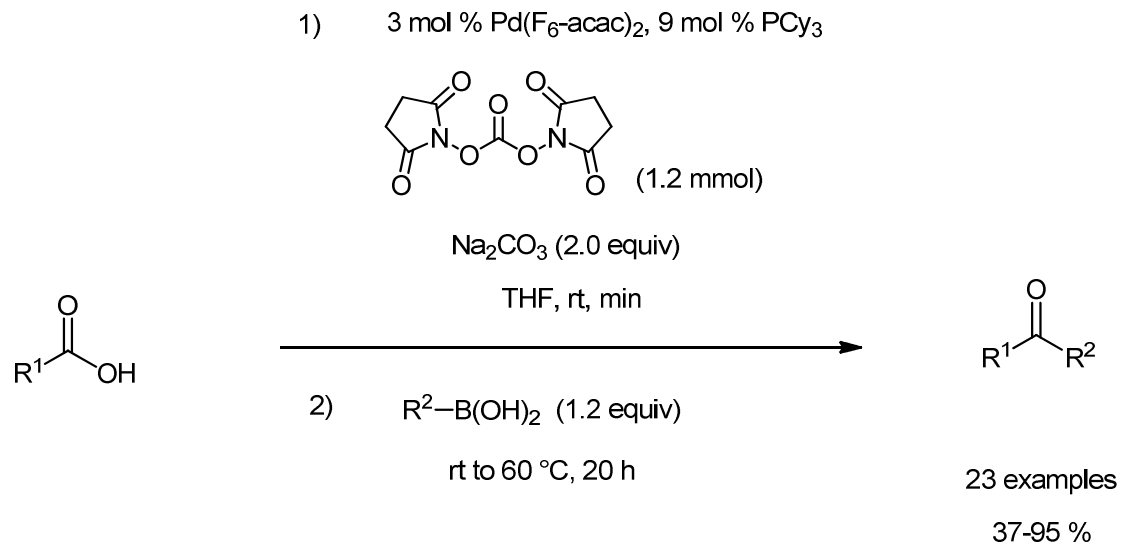
This subtle modification has the significant advantage of milder reaction conditions. The ynones formed under essentially neutral conditions can be now converted to a huge variety of *O*-, *S*-, and *N*-heterocycles in diverse one-pot reactions (see discussion in chapter *2.6.1 Synthesis and reactivity of ynones*).

A number of other conditions has been reported utilizing the reactivity of acid chlorides toward alkynes in *Sonogashira* reactions: (1) very efficient copper-free coupling

using phosphane-free oxime-derived palladacycle and triethylamine as a base, according to *Nájera*;[73] (2) coupling in water as solvent using a catalytic amount of sodium lauryl sulfate as a surfactant and K_2CO_3 as a base;[74] (3) recyclable nanosized MCM-41 anchored palladium bipyridyl complex-catalyzed coupling with very low catalyst loadings;[75] and (4) recyclable polystyrene-supported Pd(0)-complex under copper- and solvent-free conditions,[76] only to mention a few.

Certainly, the major limitation of using acid chlorides as substrates for metal-catalyzed cross-coupling reactions is the inherent need for protection of reactive functionalities such as OH and NH_2 groups. Moreover, acid chlorides are not always commercially available and have to be prepared from the corresponding acids. For that reason, an interesting alternative is the utilization of carboxylic acids,[77] which are readily available, stable, and easy-to-handle compounds, representing very attractive substrates for cross-couplings. These methodologies proceed mostly with a decarboxylative outcome. The first herald was a Cu-catalyzed biaryl synthesis reported in 1966 by *Nilsson*.[78] However, this approach was "reinvented" by *Myers*[79] and became very popular only in recent years.[80],[81] α-Oxo-acids are also known to undergo decarboxylative cross-couplings under Pd-[82] and Pd/Cu-catalysis.[48],[54] Although the initially drastic conditions[83] have mellowed, the major inherent disadvantage of these methods is the loss of the precious carbonyl group – a circumstance that frequently gives rise to the formation of products which are of little interest from the synthetical point of view and can be made by numerous other methods. However, there are notable exceptions working also with 5-ring electron rich heterocyclic substrates such as thiazole, oxazole, and pyrrole carboxylic acids.[84] In one report, a nicotinic acid derivative was coupled under decarboxylative conditions.[85] Further, indole carboxylic acids could be arylated via Pd-catalyzed decarboxylations.[86] Ultimately, a protodecarbonylation reaction, catalyzed by Ag_2CO_3/AcOH, is broadly applicable with diverse heterocyclic acids including pyridine carboxylic acids.[87]

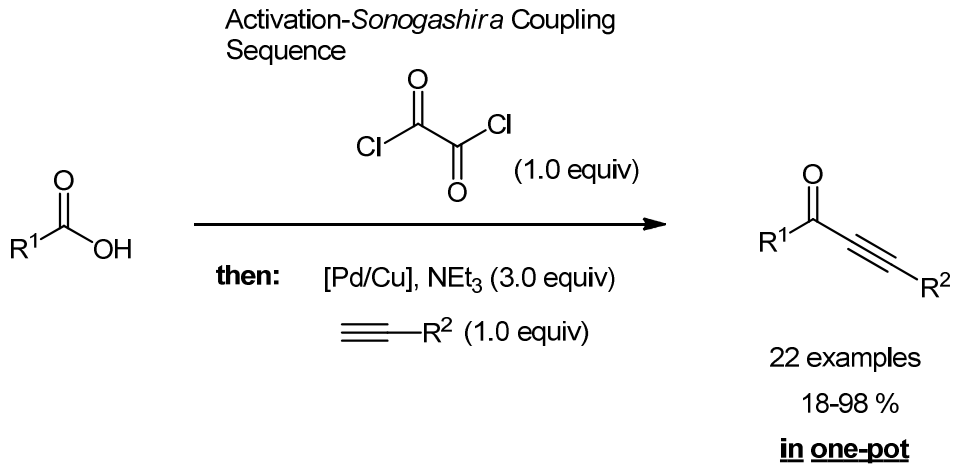
In situ activation of acids in metal-catalyzed cross-couplings in analogy to methods applied in the peptide synthesis has been described by *Gooßen*. As activators, DCS (Scheme 20),[88] Piv_2O,[89],[250] $(MeOCO)_2O$,[90] and Boc_2O[251] have been utilized. However, generally no *N*-heterocyclic carboxylic acids have been used as substrates. The activators were applied in excess (1.2-3.0 equivs), and the method required special ligands and additives.



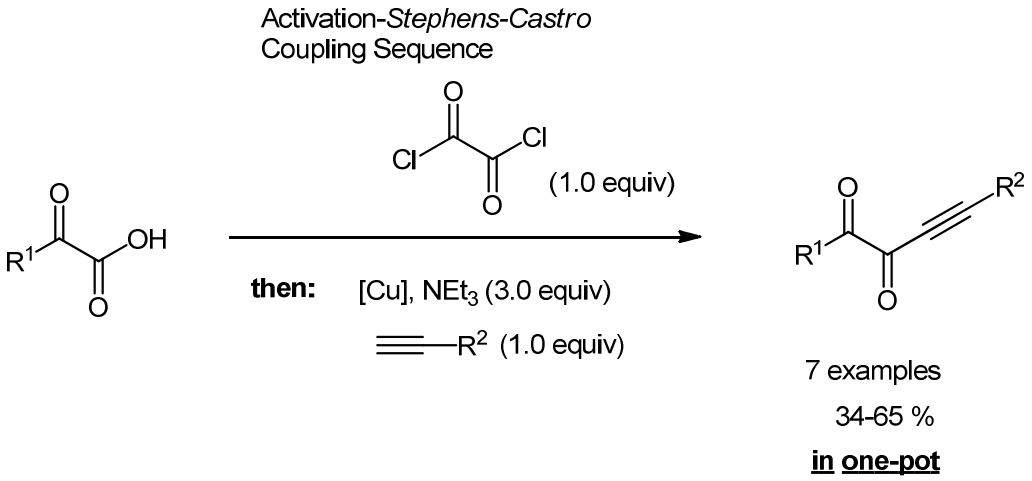
Scheme 20. In situ activation of carboxylic acids with DCS as an activator.

In conclusion, prior to this work carboxylic acids have never been used in alkynylations. Since many heterocyclic acids but not the corresponding chlorides are commercially available, a method to produce ynones from acids would beneficially complement already existing methods for the generation of ynones. Additionally, oxalyl chloride has never been used as an activator of carboxylic acids in metal-catalyzed cross-couplings (for a discussion, see chapter *2.7 Oxalyl chloride in organic synthesis*).

In the framework of this thesis, the synthetic utility of oxalyl chloride was exploited in novel activation – alkynylation sequences in collaboration with M. Sc. Christina Boersch, who performed the experimental work. Heterocyclic carboxylic acids and α-oxo-carboxylic acids could be efficiently converted to the corresponding acid chlorides via clean reaction with oxalyl chloride. The resulting acid chlorides were reacted in a one-pot fashion with alkynes under *Sonogashira* or catalytic *Stephens-Castro* coupling conditions giving rise to the formation of ynones and ynediones (Scheme 21 and Scheme 22).[91] Astonishingly, a wide variety of *N*-heterocyclic acids could be successfully brought to reaction, although *N*-heterocycles are notoriously difficult substrates in cross-couplings.

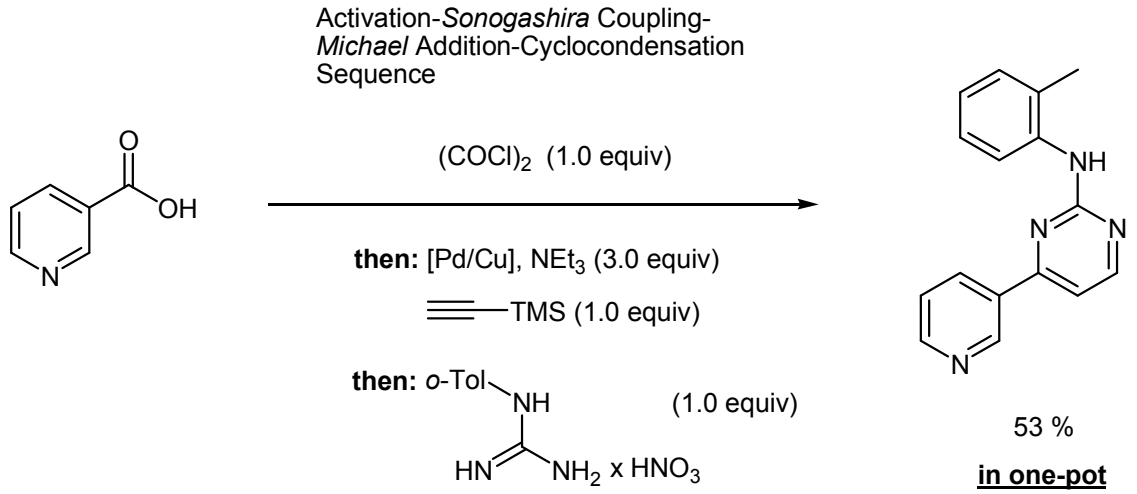


Scheme 21. One-pot synthesis of ynones from carboxylic acids.[91]



Scheme 22. One-pot synthesis of ynediones from α-oxo-carboxylic acids.[91]

This strategy represents a novel approach to ynones and ynediones using standard catalytic systems without need for exotic ligands or additives. Upon addition of guanidinium salts, a one-pot three-component synthesis of pyrimidines is feasible as illustrated by a concise one-pot preparation of the pharmacophore of the blockbuster drugs imatinib and nilotinib,[486],[494] both acting as tyrosine kinase inhibitors to combat cancer (Scheme 23).[91]



Scheme 23. One-pot synthesis of the pharmacophore of Gleevec® and Tasigna®.[91]

This approach represents the most concise synthesis of this highly important structural motif (for a discussion, see chapter *2.11 Kinases and kinase inhibitors*).

These results are part of this cumulative dissertation (**publication 3.1**).

2.3.3 Carbonylative *Sonogashira* coupling

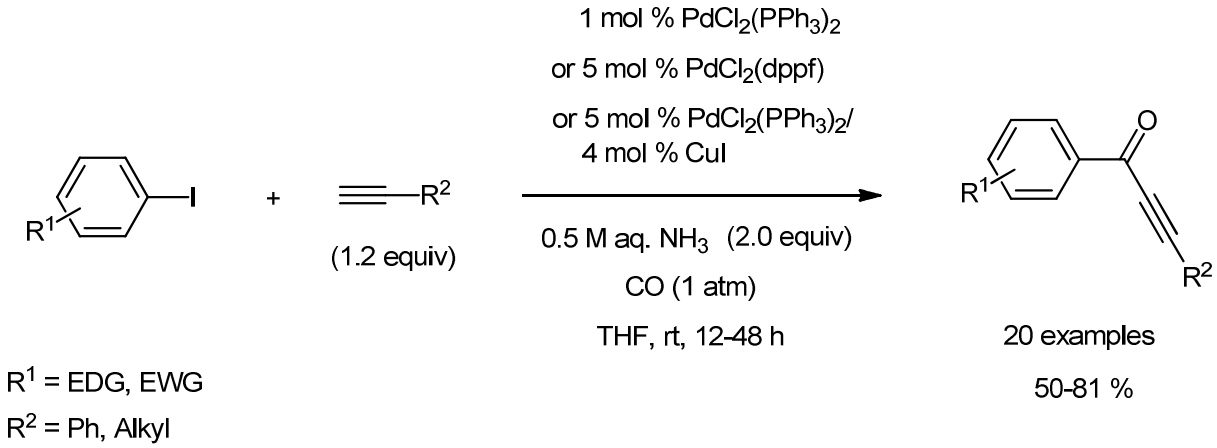
Given the case that acid chlorides are not readily available, another useful modification, such as carbonylative *Sonogashira* coupling, can be envisioned for the construction of ynones. Carbonylative alkynylation is recognized as the coupling of halides with terminal acetylenes in the presence of carbon monoxide. This transformation is a very useful approach and attracts much attention. However, high reaction temperatures and pressure of carbon monoxide are necessary in order to achieve selective carbonylative coupling.[92] For example, in a recent synthesis of the quinolone key substructure of the protease inhibitor BILN 2061 via carbonylative *Sonogashira* coupling, the reaction was run at 120 °C under 250 psi CO.[93] *Nicolaou* utilized the carbonylative *Sonogashira* coupling in the total synthesis of the natural product biyouyanagin A, working at 100 °C under 200 psi CO.[94] Several syntheses of heterocycles via carbonylative *Sonogashira* coupling have been reported. Flavons and chromones[95] as well as 4-quinolones[96] were prepared by *Kalinin* from *o*-iodophenols and *o*-iodoanilines, respectively (120 °C/20 atm CO). Simultaneously, *Torii* reported similar approaches to 4-pyridone-3-carboxylic esters (90 °C/40 atm CO),[97] 4-dialkylaminoquinolines (70 °C/10 kg cm^{-2} CO),[98] as well as 4-quinolone-3-carboxylic esters[99] and 4-quinolones[100] (120 °C/20 kg cm^{-2} CO).[101] A further example is the synthesis of (*E*)-3-arylidene-5-aryl-2-(3*H*)-furanones, performed at 110-120 °C and under 300-1200 psi CO pressure.[102]

Not surprisingly, attempts have been made to find milder conditions. For instance, a reaction under normal pressure of carbon monoxide but with a twofold excess of relatively precious aryl iodides can be applied.[103] A mild (30 °C/1 atm CO) Pd/Cu-catalyzed carbonylative coupling of iodonium salt was achieved, with a drawback of using rather precious starting materials.[104] For the coupling of vinyl triflates, a mild carbonylative alkynylation (60 °C/1 atm CO) using $Pd(OAc)_2$/dppp/NEt_3 system has been described as early as in 1991.[105] At the same time, the same authors performed studies on Pd-catalyzed carbonylative coupling of 2-hydroxyaryl iodides with ethynylarenes at 60 °C under 1 atm of CO pressure.[106] In this work, however, mixtures of flavones and (*Z*)-aurones were generally obtained.

In recent years, several mild procedures for carbonylative alkynylations of aryl iodides have been developed which allow couplings at ambient temperatures and pressure of carbon monoxide.

First report by *Yang* in this direction appeared in 2000 and described synthesis of flavones[107] at 40-45 °C under a balloon pressure of CO using $PdCl_2(PPh_3)_2$-thiourea-dppp complex.

The carbonylative *Sonogashira* coupling under mild conditions was generalized by *Mori* in 2003 (Scheme 24).[108]



Scheme 24. Carbonylative *Sonogashira* coupling according to *Mori*.

The authors claimed that aqueous ammonia as a base was superior to triethylamine and decisive for the carbonylative outcome of the reaction. The choice of the catalytic system depends on the electronic nature of substituents on the iodide and on the alkyne. The formation of the noncarbonylated product could be suppressed; only in some cases the byproduct was formed in 1-7 % yield. However, the method was demonstrated to proceed only with simple substrates.

Later, this approach was extended by the same group for a one-pot construction of pyrazoles and isoxazoles.[109]

In 2005, a Pd-catalyzed copper-free carbonylative alkynylation of aryl iodides for the synthesis of ynones and flavones in water as a solvent under ambient temperature and CO pressure was reported by *Yang*.[110]

Also in 2005, we used a mild carbonylative *Sonogashira* coupling as a key step in the total synthesis of natural products meridianins and a variolin B analog.[448] The synthesis of the key ynone structures has been performed at room temperature and using 1 atm of carbon monoxide and was particularly well suited for *N*-Boc protected 3-iodo (aza)indoles as substrates (see discussion in chapter *2.10.1.1 Meridianins*).

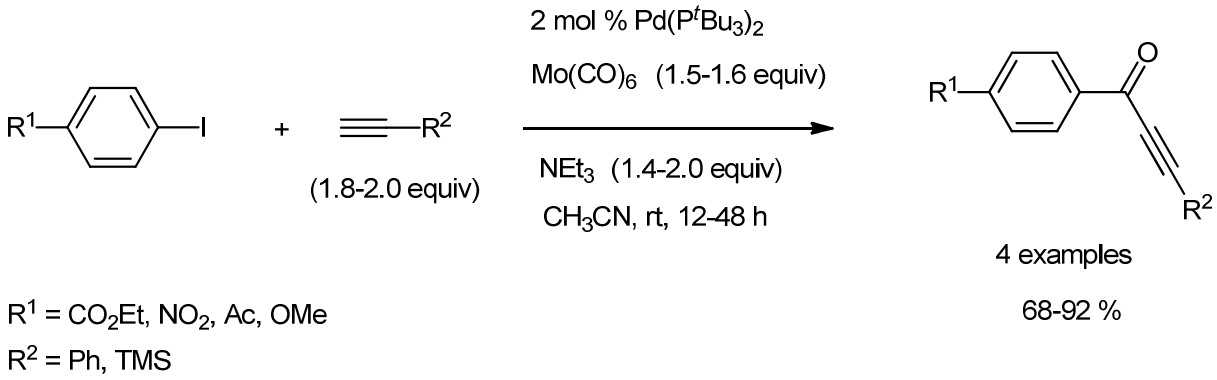
Ultimately, in 2009 *Capretta* presented an access to flavones via microwave-assisted one-pot three- and four-component carbonylative sequences working at 1 atm of CO.[111] PA-Ph was shown to be an effective ligand in these transformations.

However, these examples rather represent exceptions since newer reports continue to work under high temperatures and pressures of carbon monoxide: (1) coupling in an ionic liquid [bmim]PF_6 using $PdCl_2(PPh_3)_2/NEt_3$ (120 °C/20 atm CO);[112] (2) magnetically separable and recoverable heterogeneous catalyst Pd/Fe_3O_4 (130 °C/2.0 MPa CO);[113] (3) synthesis of alkyl alkynyl ketones using $PdCl_2(PPh_3)_2/NEt_3$ under photoirradiation conditions (500 W xenon lamp, Pyrex/45 atm CO);[114] (4) coupling of aryl bromides using $[(cinnamyl)PdCl]_2/BuPAd_2/K_2CO_3$ (100 °C/10 bar CO);[115] and (5) coupling of aryl triflates using $[(cinnamyl)PdCl]_2$/Xantphos/NEt_3 (110 °C/10 bar CO).[116] Obviously, the success of the selective carbonylative alkynylation without formation of the direct coupling product is strongly substrate dependent and remains matter of careful optimization. Additionally, it should be noted that all methods reported deal with rather simple substrates such as aryl iodides and aryl alkynes; no complex or *N*-heterocyclic halides and alkynes have been utilized.

In general, a palladium-catalyzed reaction in the presence of carbon monoxide[40] proceeds slower than under an inert atmosphere since CO serves as a strong ligand with electron withdrawing characteristics. Certainly, long reaction times are a significant drawback of carbonylative methods. Furthermore, the success of the carbonylative reactions using carbon monoxide is strongly dependent on the solubility or diffusion of the gas into the bulk, which can be cotrolled by the pressure of CO (however, increasing CO pressure causes additional coordination to the catalytic intermediates slowing down the reaction) and/or the surface area-to-volume ratio,[117] causing reproducibility and scaleability problems. Moreover, since carbon monoxide is a highly toxic gas,[118] which has no smell, color, or taste, special equipment is required for safety reasons. Moreover, synthetic organic chemists are reluctant to use high-pressure equipment. Thus, attempts have been made to replace it with other CO

sources (see discussion in chapter <u>2.5 Oxalyl chloride in organic synthesis</u>). A prominent CO surrogate is molybdenum hexacarbonyl $Mo(CO)_6$, which is utilized quite frequently.

An example of its use is the procedure described by *Kondo* in 2007 (Scheme 25).[119] Aryl iodides could be reacted, and P^tBu_3 was essential for smooth conversion and facilitated the formation of ynones rather then the direct *Sonogashira* coupling products.



Scheme 25. Carbonylative alkynylation using $Mo(CO)_6$ as a CO source.

A similar approach was used by *Stonehouse* in one-pot syntheses of pyrazoles and pyrimidines.[120]

Despite its nontoxicity and nonproblematic handling, $Mo(CO)_6$ as a CO source has one significant disadvantage of being typically used in large excess, rendering such processes not economical considering the high costs of this reagent.

In conclusion, the *Sonogashira* reaction with its numerous modifications has established itself as one of the most powerful and popular synthetic methods for the synthesis of substituted alkynes.[121] It is technically simple, efficient, high yielding, and tolerant toward a wide variety of functional groups. However, couplings of aryl bromides[122] and especially chlorides,[37],[123] as well as tosylates and mesylates[124] are not efficient with the standard catalytic system, and higher temperatures lead to alkyne side reactions. For this reason, improvements are still necessary, and the *Sonogashira* coupling remains an active research domain.[125] New catalyst systems

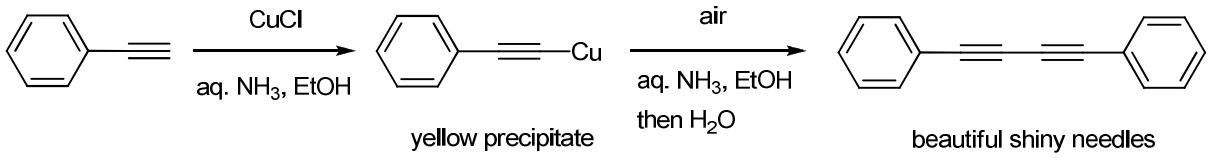
and ligands are being developing, and numerous metal complexes have been reported to catalyze the C(sp)–C(sp^2) coupling.[126] Due to the generality and mild reaction conditions, *Sonogashira* coupling is highly suitable for designing various one-pot sequences containing this transformation.[127]

“It appears from the recent literature on applications of the *Sonogashira* coupling in organic synthesis that the synthetic community is hesitant to apply the new highly efficient Pd catalysts that have been developed. Still, a very significant proportion of *Sonogashira* coupling reactions are carried out with the classical catalysts such as $PdCl_2(PPh_3)_2$ and $Pd(PPh_3)_4$ and aryl iodides as substrates. Although a catalyst loading in the 1-5 mol % range may be required, with typical yields of around 75 %, the transformation relies on an established protocol. Copper-only procedures (catalytic *Stephens-Castro* coupling) with aryl iodide substrates are already competitive with Pd-catalyzed reactions. From a practical point of view, the simplicity of the copper-only catalytic systems is a strong argument in favor of their application in organic synthesis, whereas Pd-based *Sonogashira* catalysts are characterized by their outstanding efficiency.”[126a]

Finally, the reaction is fraught with a limitation, in that it often results in considerable yields of the homocoupling product (*Glaser*-type or *Hay* product). This aspect will be discussed in chapter *2.3.4 Glaser-type acetylene couplings*.

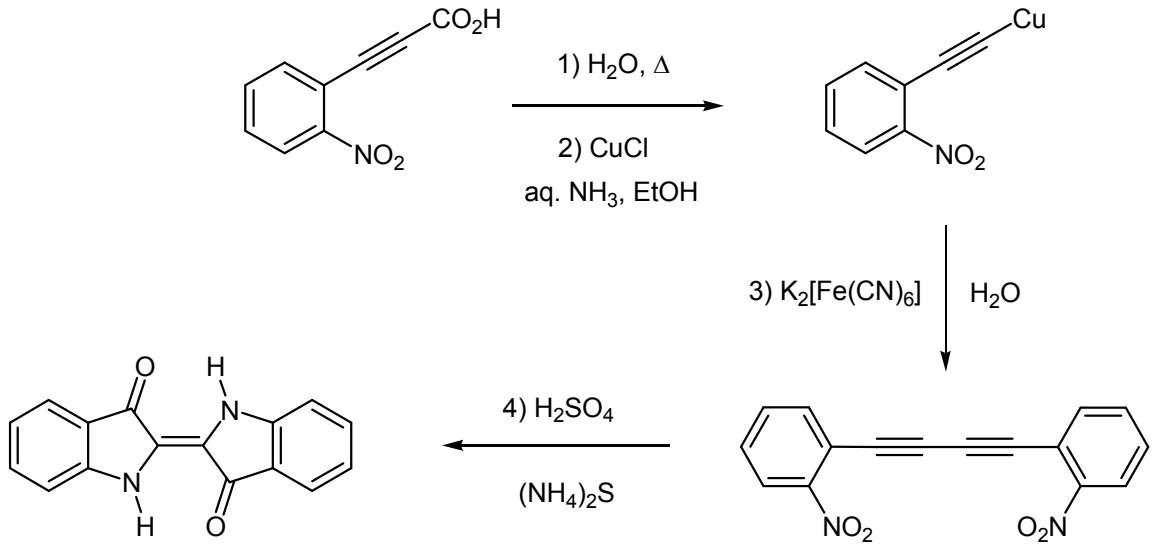
2.3.4 *Glaser*-type acetylene couplings

The synthetic studies of 1,3-disubstituted diyne derivatives via the homocoupling reaction of terminal alkynes has an extremely long history. As early as in 1869, *Glaser* made the observation that the alcoholic solution of copper phenylacetylide undergoes smooth homocoupling in the presence of aqueous ammonia when exposed to air (Scheme 26).[128]



Scheme 26. *Glaser* coupling.

Baeyer provided an early demonstration of the synthetic utility of the method in his 1882 synthesis of indigo (Scheme 27).[129] In this synthesis, potassium ferricyanide was used as an oxidizing agent.



Scheme 27. *Baeyer* synthesis of indigo.

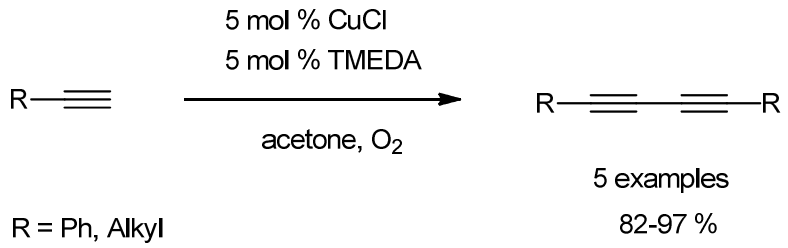
Nevertheless, the original *Glaser* reaction had a significant drawback of need for isolating potentially explosive copper acetylides, which was often tedious in view of the poor crystallization properties of most copper salts.

Therefore, many groups have modified and improved the reaction to obtain useful approaches to symmetrical and unsymmetrical butadiynes. Acetylene couplings as well as their synthetic applications were comprehensively reviewed by *Diederich* in 2000.[130]

Particularly important was the observation of *Zalkind* and *Aizikovich* in 1937 that tertiary alkynols coupled directly in the presence of CuCl and NH_4Cl to afford the corresponding diacetylene dicarbinols. The possibility of forming the copper(I) acetylide in situ paved the way for intensive investigations of the factors influencing the oxidative coupling of various substituted acetylenes, such as the proportion of copper(I) salt, oxidizing agent, pH, time, temperature, solvent, and character of the alkyne, which ultimately led to improved convenience and scope of the reaction and to industrial applications.

In 1956, *Eglinton* and *Galbraith* introduced the copper(II) mediated coupling in methanolic pyridine using an excess of $Cu(OAc)_2$, which turned out to be very useful in the preparation of unsaturated macrocycles.[131]

Another milestone in the evolution of oxidative acetylene coupling was reported in 1962 by *Hay*. In this important modification a Cu(I)-salt was used in the presence of an amine such as pyridine[132] or the bidentate ligand TMEDA[133] that promoted facile homocoupling of terminal acetylenes at room temperature in the presence of oxygen (Scheme 28). The modification provided better solubility of the reactive Cu(I)-species and allowed mild conditions, high efficiency, and catalytic amounts of Cu(I) and amine to be realized.

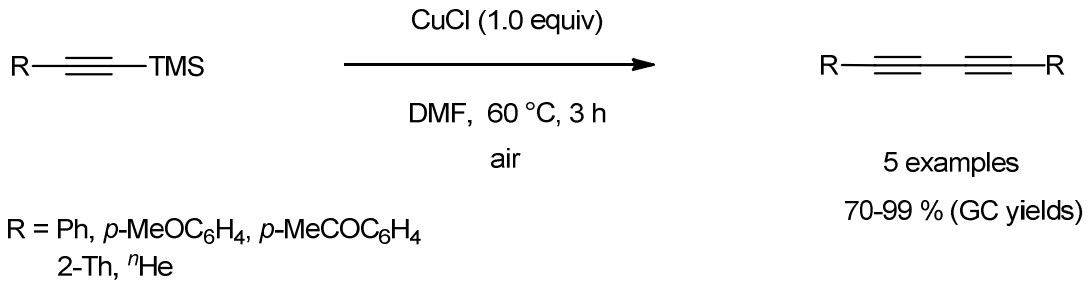


Scheme 28. *Hay* coupling.

The Cu-mediated homocouplings described above and the heterocoupling conditions according to *Cadiot–Chodkiewitz*, utilizing coupling of terminal acetylenes with 1-bromoalkynes,[134] still remain popular, and new Cu-promoted methods continue to

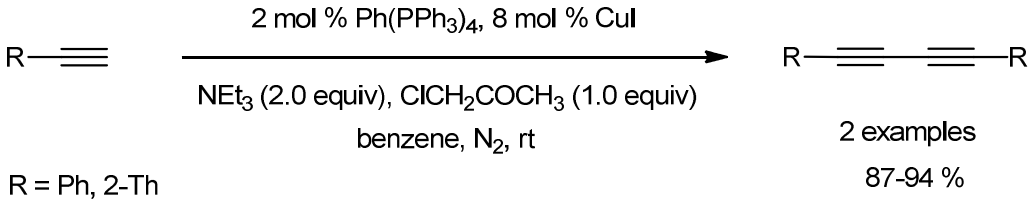
appear.[135] Just recently, a comprehensive investigation of the influence of bases and ligands on the outcome of the Cu(I)-catalyzed oxidative homocoupling of terminal alkynes to 1,4-disubstituted 1,3-diynes using oxygen as an oxidant (i.e. *Glaser-Hay* coupling) was performed by *Beifuss*.[136]

Instead of terminal alkynes alkynylsilanes can be coupled in a *sila* modification introduced by *Mori* (Scheme 29).[137] The method allows preparation of symmetrical and unsymmetrical 1,3-butadiynes. Nevertheless, the method was not extended into a one-pot alkynylation – oxidative dimerization sequence and still requires alkynylsilanes as starting materials.[138] A further drawback is the need for a stoichiometric amount of CuCl.



Scheme 29. Coupling of TMS-alkynes to symmetrical diynes.

Palladium is also a competent metal for acetylene couplings. An early observation was the formation of symmetrical diynes in the course of *Sonogashira* coupling.[62] In 1985, *Rossi* optimized this process as a homocoupling for terminal acetylenes (Scheme 30).[139] (Hetero)aryl substituted alkynes are excellent substrates for this reaction.[139],[140]



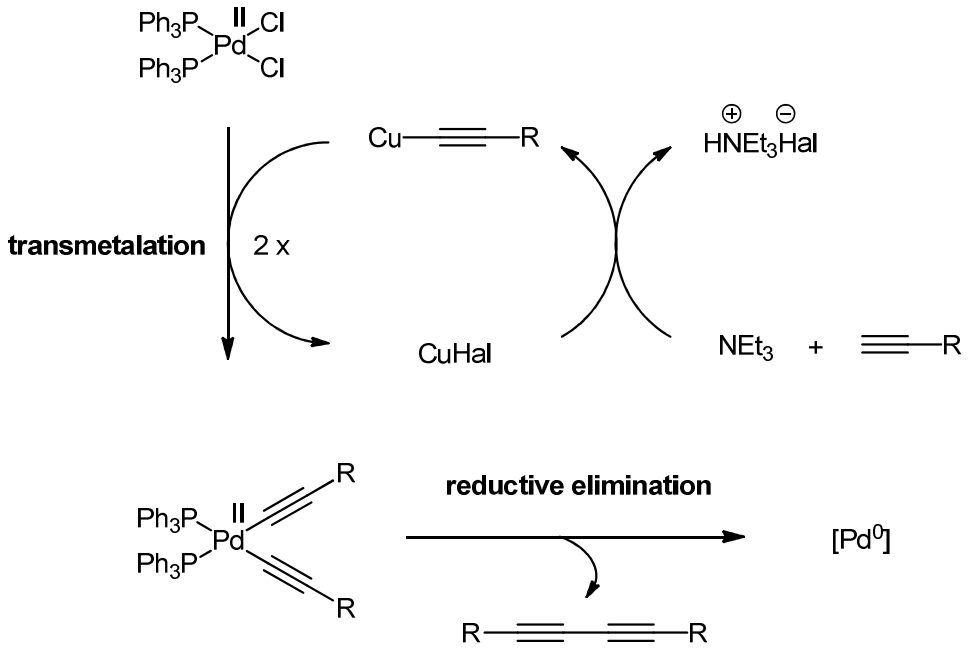
Scheme 30. Pd/Cu-catalyzed synthesis of diynes.

Pd(0) alone can be used in the presence of allyl bromide and phase transfer catalysts.[141] Another modification using $PdCl_2(PPh_3)_2$/CuI as a catalytic system, $^iPr_2NH$

as a base, and iodine as an oxidizing agent was reported by *Burton*.[142] Several new reports stem from the last decade: (1) room temperature coupling using $PdCl_2(PPh_3)_2$/CuI/$^iPr_2NH$ and ethyl bromoacetate as an initiator;[143] (2) efficient room temperature diyne synthesis "using standard *Sonogashira* conditions", i.e. $PdCl_2(PPh_3)_2$/PPh_3/CuI/NEt_3;[144] (3) amine- and phosphine-free Pd(II)/Cu(I)-catalyzed homocoupling with NaOAc as a base and Me_3NO as an oxidant;[145] (4) NHC-Pd(II)/Cu(I)-catalyzed homocoupling;[146] and (5) ligand- and base-free low-loading Pd/C-CuI-catalyzed homocoupling.[147]

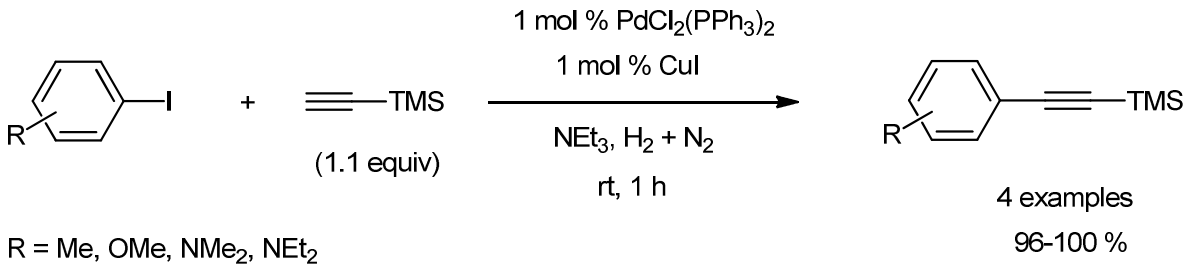
Some reports dealing with studies on both *Glaser* and *Sonogashira* reactions under similar conditions deserve a special mention. *Nájera* described in 2003 an efficient low-catalyst homocoupling catalyzed by oxime-derived palladacycle and CuI with pyrrolidine as a base and air as an oxidant.[148] Under very similar conditions, *Sonogashira* coupling (palladacycle/Bu_4NOAc) and *sila-Sonogashira* coupling (palladacycle/CuI/pyrrolidine) were also effective. In 2005 *Li* published a study dealing with a catalytic system which was very effective in both *Glaser*-type ($Pd(OAc)_2$/CuI/DABCO/O_2) homocoupling and *Sonogashira* coupling ($Pd(OAc)_2$/DABCO/O_2) reactions.[149] A report by *Wu* in 2007 delt with cyclopalladated ferrocenylimine/CuI/KOAc/O_2 as a catalytic system for the homocoupling. A similar palladacycle in the presence of Bu_4NBr and KOAc was also applied for *Sonogashira* couplings.[150] Despite all these reports described almost identical conditions for both alkyne couplings, no combination of these reactions in a one-pot transformation has been attempted.

The two processes are very closely related indeed. A similar Pd/Cu-catalyzed *Glaser*-type homocoupling is believed to be responsible for the generation of the catalytically active Pd(0) species at the beginning of the *Sonogashira* reaction.[62],[139] But the same process also leads to the unwanted alkyne dimerization, which is a known "plague" of the *Sonogashira* cross-coupling (Scheme 31).



Scheme 31. Mechanistic rationale for the formation of a symmetrical diyne along with the generation of the catalytically active palladium(0) species.

To avoid the diyne formation, even special strategies such as coupling under a hydrogen and nitrogen atmosphere have been developed (Scheme 32).[151] The method allowed to suppress the homocoupling and less than 2 % of diynes were formed.

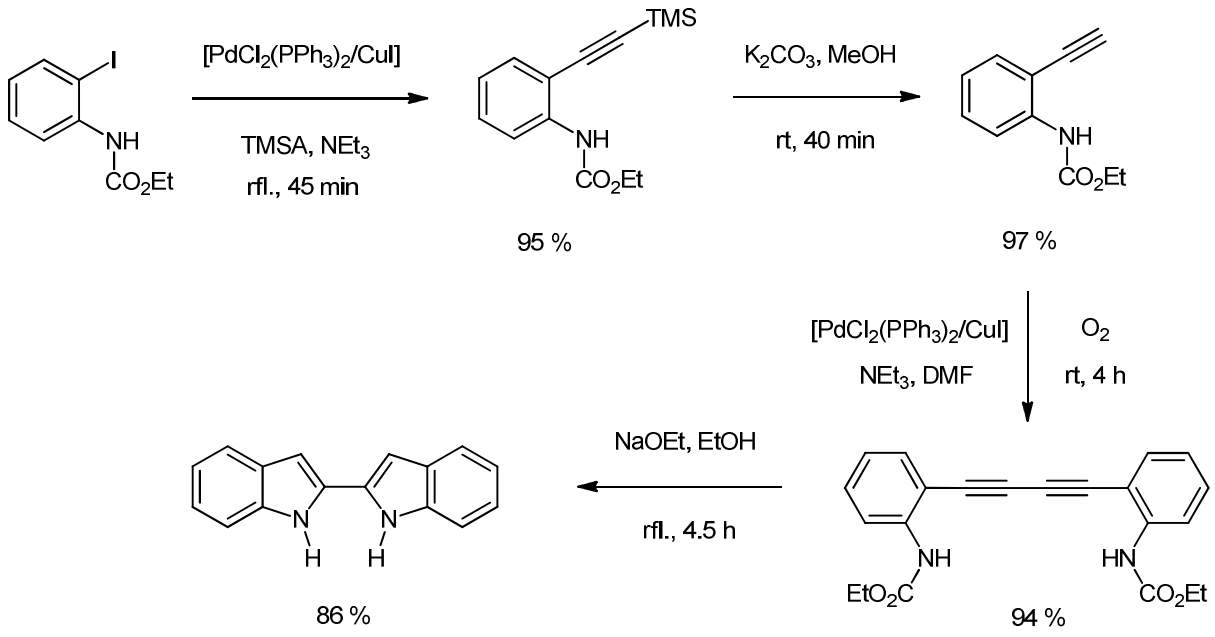


Scheme 32. *Sonogashira* reaction with diminished homocoupling.

Just very recently, a click-reagent version of the *Sonogashira* coupling, i.e. coupling using Cu(II)/NaAsc system, has been introduced with no or dramatically reduced homocoupling.[152]

However, prior to this work no attempts have been undertaken to make use of this obstacle and to combine *Sonogashira* and *Glaser* couplings into a one-pot procedure to synthesize diynes using the same catalytic system.

Diynes and higher polyynes are frequently found in natural products making up more than 1000 isolated compounds with two or more conjugated triple bonds.[153] Symmetrical 1,3-butadiynes can be used for the construction of chalcogene heterocycles such as thiophenes and selenophenes,[154] nitrogen heterocycles such as pyridines and pyrroles,[155] 3,3'-disubstituted 2,2'-biindoles,[156] as well as the indolo[2,3-*a*]carbazole ring system,[157] which is present in several biologically active molecules such as arcyriaflavin A and the potent antitumor agent rebeccamycin. A representative example of the utility of 1,4-di(hetero)aryl-1,3-butadiynes in the organic synthesis is the preparation of 2,2'-bisindole, which requires a linear stepwise approach (Scheme 33).[158]

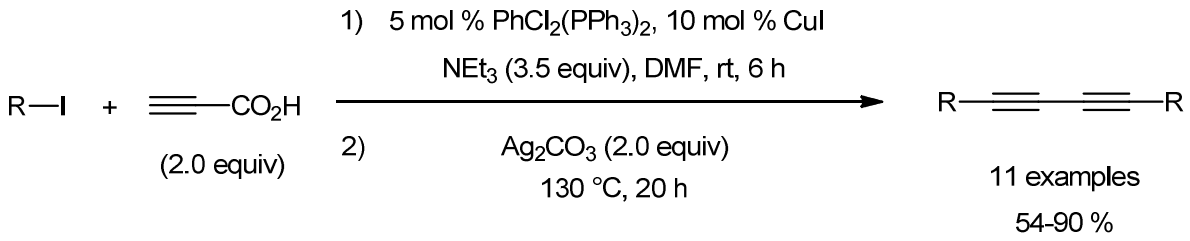


Scheme 33. Synthesis of 2,2'-bisindole via 1,3-diyne.

Typically, although the same catalytic system and the same base are required, the synthesis of the key diyne was performed in separate steps rather than in a one-pot procedure.

In conclusion, prior to this work no one-pot sequentially catalyzed method of synthesis of symmetrical 1,3-diynes starting directly from (hetero)aryl halides was known. However, just recently, two one-pot syntheses appeared in the literature starting from aryl iodides. In the first method, *Kim* described a Pd/Cu-catalyzed approach relying

on coupling of iodoarenes and propiolic acid via *Sonogashira* reaction followed by a Pd-catalyzed decarboxylative homocoupling (Scheme 34).[159]

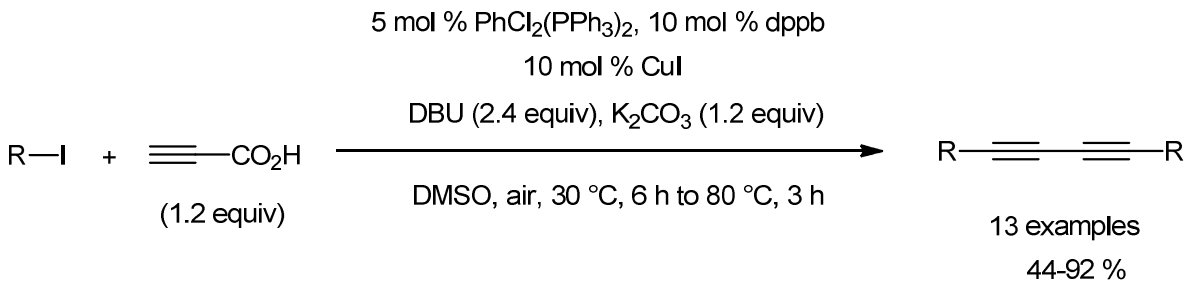


R = Ph, EDG-Aryl, EWG-Aryl, 2-Th, 3-Py

Scheme 34. *Kim's* one-pot synthesis of 1,3-diynes via *Sonogashira* coupling – decarboxylative homocoupling.

The major disadvantages of this procedure are the use of silver carbonate as a stoichiometric oxidant and the formation of 1-10 % of the corresponding tolane as a byproduct giving inseparable mixtures with the desired product.

The second method also works under Pd/Cu-catalysis and uses K_2CO_3 instead of Ag_2CO_3 (Scheme 35).[160]

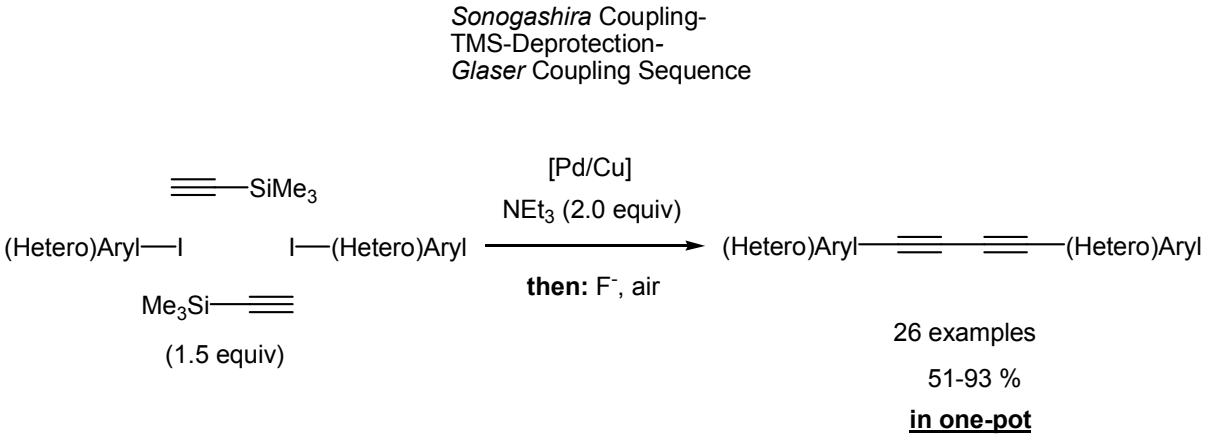


R = Ph, EDG-Aryl, EWG-Aryl, 2-Th, 3-Py

Scheme 35. *Lee's* one-pot synthesis of 1,3-diynes via *Sonogashira* coupling – decarboxylative homocoupling.

This procedure resembles the preceding precisely in scope and shares the same disadvantage of producing 4-33 % of the corresponding tolane.

In the framework of this thesis, two catalytic alkyne coupling reactions have been combined in the sense of a consecutive sequentially Pd/Cu-catalyzed process to furnish a novel one-pot pseudo-four-component synthesis of a broad variety of symmetrically substituted 1,4-di(hetero)aryl-1,3-butadiynes in good to excellent yields starting from easily available (hetero)aryl iodides and using air oxygen as an oxidant (Scheme 36).[161] Pd and Cu species as well as triethylamine as a base are essential for both couplings, which proceed with higher efficiency if performed in a one-pot sequence. The synthetic procedure is extremely simple to carry out, works for a variety of electronically different heterocyclic iodides and tolerates many functional groups including free hydroxy and amino groups.

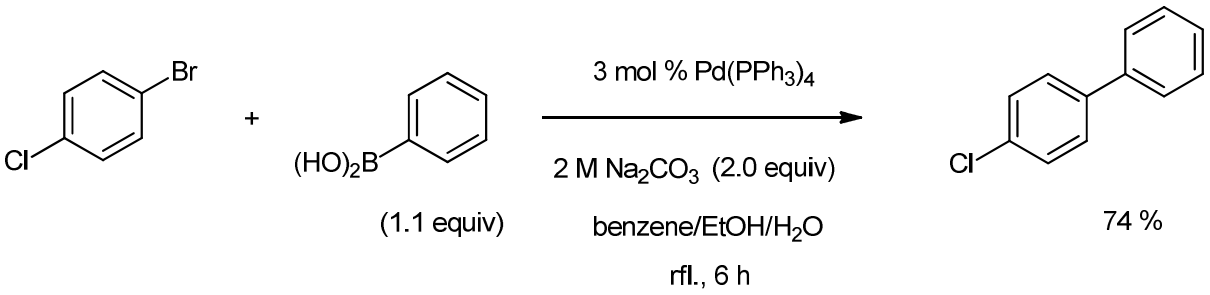


Scheme 36. One-pot synthesis of symmetrical diynes.[161]

These results are part of this cumulative dissertation (**publication 3.2**).

2.3.5 *Suzuki-Miyaura* coupling

In 1981, *Suzuki* and *Miyaura* described a palladium-catalyzed coupling of aryl halides or pseudo halides with arylboronic acids (Scheme 37).[162] The decisive breakthrough was achieved by the addition of a base, which is essential for this reaction.[163]



Scheme 37. *Suzuki-Miyaura* coupling (representative example).

The *Suzuki* coupling reaction has established itself as a powerful and general method for the formation of C–C bonds,[164] especially those involving sp^2-hybridized centers. The reaction is extremely popular in the synthetic community for the synthesis of biaryl compounds where it usually involves the Pd(0)-mediated linking of an aryl halide with an arylboronic acid or arylboronic ester.[165]

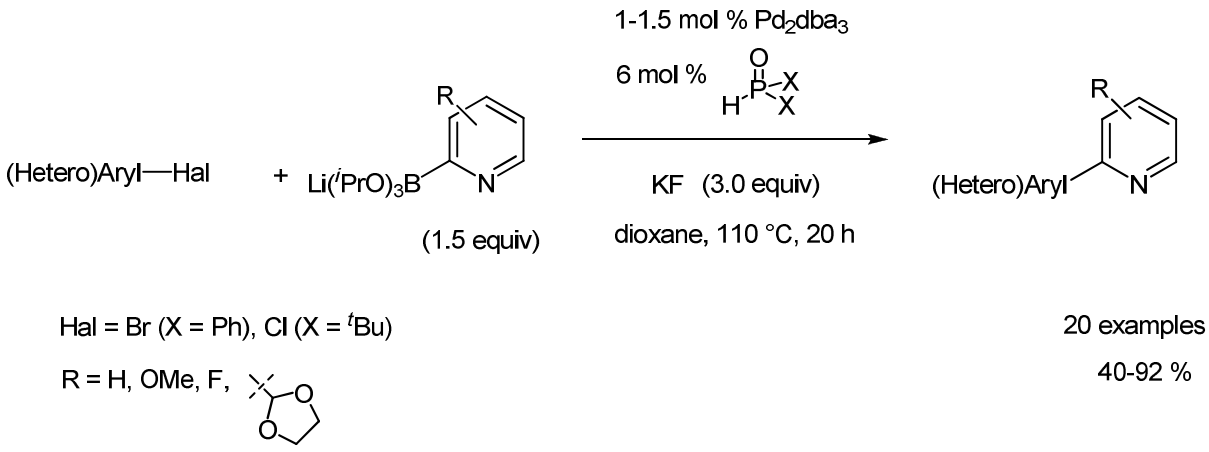
There are several significant advantages of this methodology:

- Mild reaction conditions and extreme versatility allowing the coupling of a wide range of carbons in aryl, alkenyl, alkyl, and alkynyl groups under a wide variety of conditions.
- High efficiency and reliability.
- Wide applicability and functional group tolerance, hence the reaction is highly suitable for designing one-pot methodologies.
- The coupling is stereo- and regioselective and is little affected by steric hindrance.
- No stoichiometric amounts of heavy metals are required.

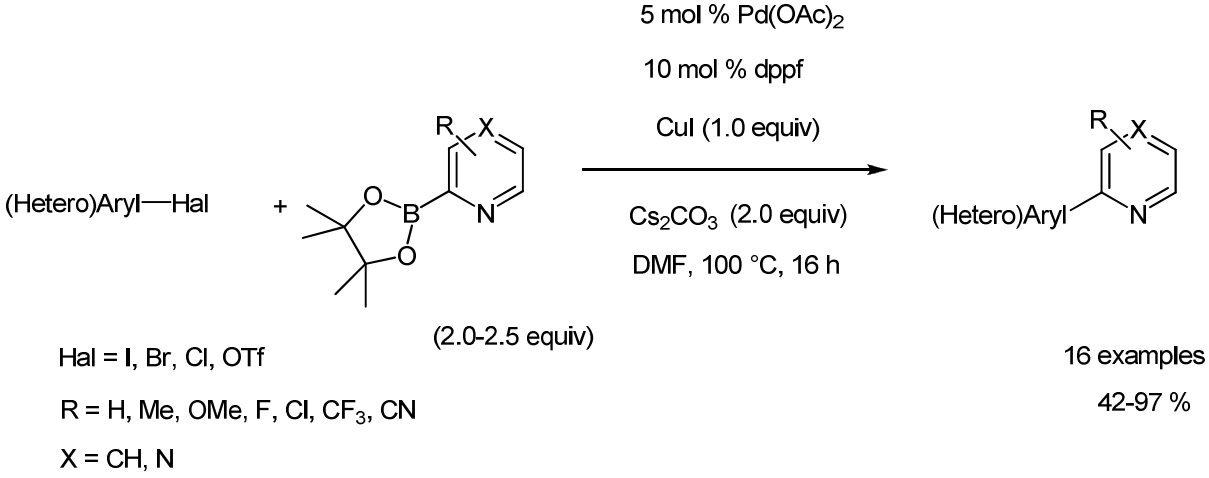
- Boronate reagents as well as byproducts are nontoxic, usually stable, and environmentally safe (in contrast, organostannanes used in the *Stille* coupling are toxic).
- The inorganic byproducts are easily removed from the reaction mixture, making the reaction suitable for industrial processes.

Although this method is well established, improvements are still necessary, promoting development of new and efficient rationally developed catalyst and ligand systems.[166] Heteroaromatic substrates deserve a special attention due to their importance in many areas of research and difficulties associated with their couplings.[167] The cross-coupling reactions of such substrates are generally considered to be problematic because these substrates can bind to the metal center and deactivate the catalyst. In the past, heteroaryl halides with heteroatom substituents bearing labile atoms such as OH and NH_2 were generally found to be unsuitable coupling partners. Further investigations are currently directed toward strategies for orthogonal functionalization of complex molecules, especially devising new sophisticated boron reagents.[168] On the other hand, normally used boronate reagents are frequently expensive and difficult to access. Furthermore, coupling of electron deficient arylboronic acids or arylboronates, especially those bearing an α-nitrogen atom, is a real challenge. The difficulty can be attributed to several factors: electron deficient heteroaryl boron derivatives undergo transmetalation at a relatively slow rate, and these reagents rapidly decompose by a protodeborylation pathway.

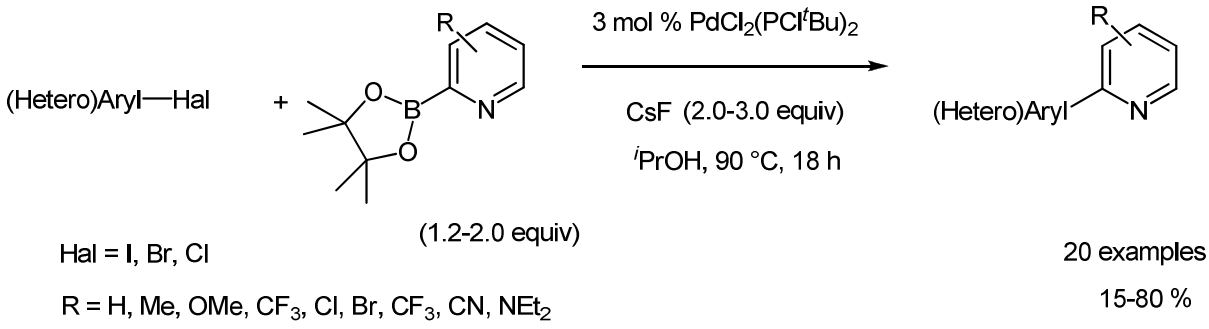
For this reason, several strategies directed to solve this problem have recently been described (Scheme 38,[169] Scheme 39,[170] and Scheme 40[171]).



Scheme 38. Strategy described by *Buchwald*.



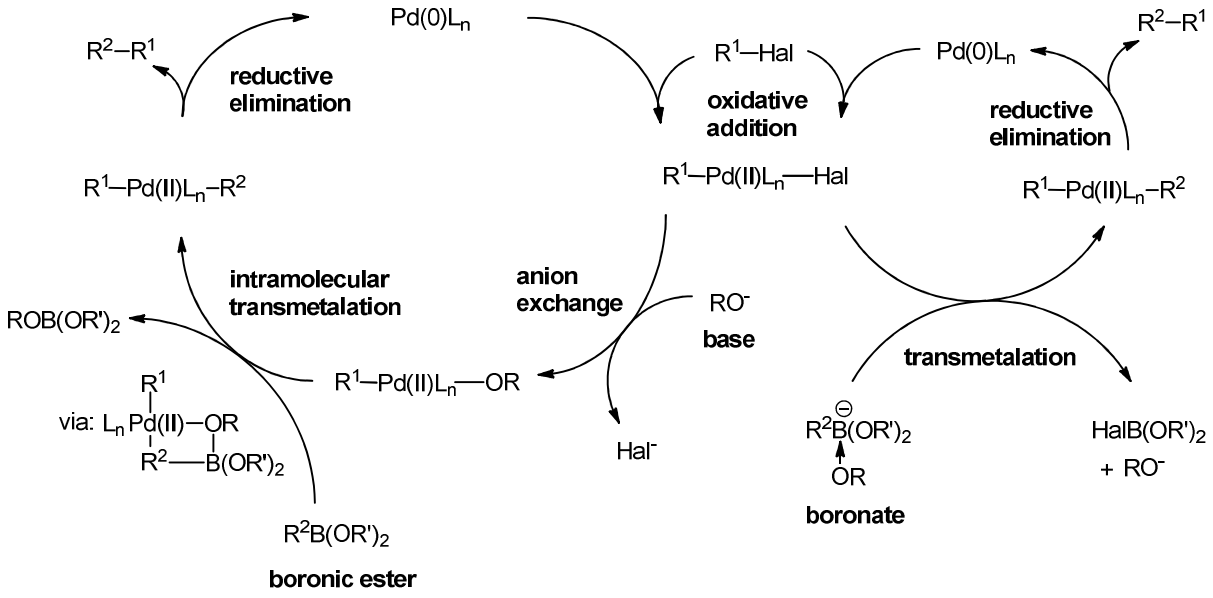
Scheme 39. Strategy described by *Deng* and *Paone*.



Scheme 40. Strategy described by *Li* and *Shen*.

However, all these strategies have a common disadvantage: the need for an excess of the precious boronate or boronic ester component.

“The mechanism of the *Suzuki* coupling is known to be complex in its details, and the oxidative addition, transmetalation, and reductive elimination steps have all been reported to be rate-determining in certain cases”[172] (Scheme 41).



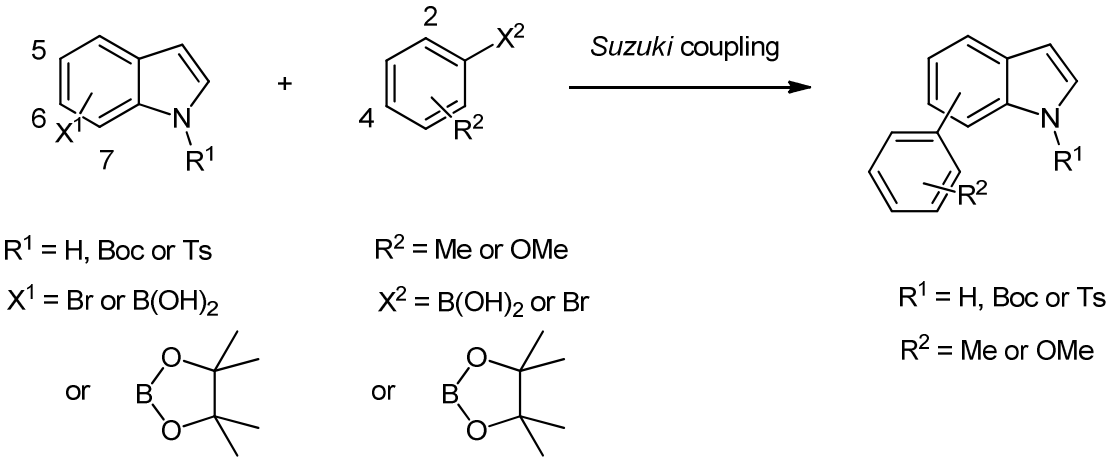
Scheme 41. Proposed mechanistic rationales for the *Suzuki* reaction.

“The reaction is still not fully understood and much remains to be clarified. The base is crucial for the transmetalation that can proceed inter- or intramolecularly. The choice of arylboron reagent may profoundly affect the outcome of a given coupling reaction, particularly since it usually determines the selection of other key reaction parameters such as solvent, base, and palladium(0) source. In contemporary practice, *Suzuki* couplings often employ widely differing reaction chemistries depending on whether arylboronic acids or arylboronate esters are used as reagents.

All other factors being equal, best results are usually obtained when the aryl halide coupling partner is electron deficient and the arylboron partner electron rich, a situation that favors oxidative addition and transmetalation, respectively. However, with complex, polyfunctionalized substrates it may not always be easy to judge which ring should be which component. Alternatively, tactical considerations may require a particular coupling reaction be carried out with the coupling partner roles inverted with

respect to those that are a priori desirable. The outcome of a given coupling may be significantly affected by the assignment of partner roles".[172]

A study on *Suzuki* coupling involving indoles revealed some interesting points.[172] 5-, 6-, or 7-Bromo indoles were coupled with arylboronic acids or pinacol esters, then the partner roles were swaped (Scheme 42).



Scheme 42. Study on the *Suzuki* coupling involving indoles.

The yields of the *Suzuki* coupling depended on:

- Whether arylboronic acids or arylpinacolboronate esters were used.
- Whether the heterocycle was the aryl halide or the arylboron coupling partner.
- Whether the heterocycle was protected or not, which provides a means of modulating the electronic character of the heterocycle.

A careful selection of the arylboron reagent, of the coupling partner roles, and of the protective groups was essential to ensuring optimum results in these *Suzuki* couplings. This study is very instructive also for coupling of other heterocycles since it gives an impression how the influences of different factors can affect the outcome of the *Suzuki* coupling reaction.

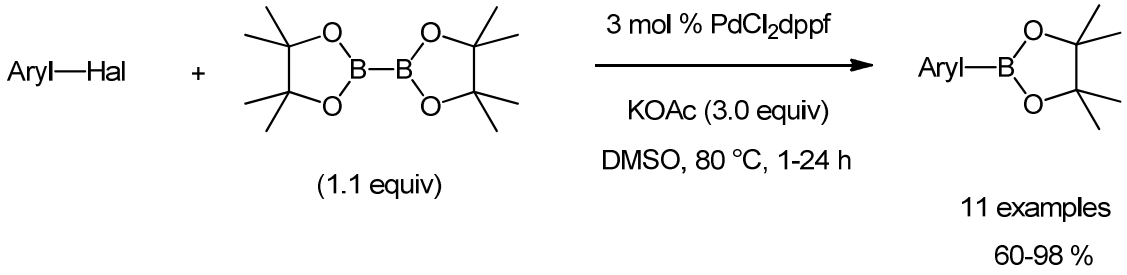
In 2010, *Suzuki*, *Heck*, and *Negishi* were awarded with the Nobel Prize in recognition of the enormous utility of Pd-catalyzed cross-coupling methodologies developed by these researchers, among others.[173]

2.3.6 *Miyaura* and *Masuda* borylations

The main limitation of the *Suzuki-Miyaura* reaction is the accessibility of the boronic acids or esters used as the nucleophilic partner. They are expensive and only a limited number of them are commercially available. The other issue is their sensitivity toward air and moisture as well as chromatographic instability. Classically, boronates are prepared by the transmetalation of Li- or Mg-organyls with borone compounds that contain good leaving groups such as halogen or alkoxy groups. These approaches suffer from functional group intolerance.

Among boronic species, pinacolboronic esters are the most convenient nucleophilic coupling partners in *Suzuki* cross-couplings because they are generally stable to air, moisture, and temperature and are much more amenable to chromatographic purification and spectroscopic characterization.

In 1995, *Miyaura* described a Pd-catalyzed coupling reaction between bispinacolatodiboron with halo arenes to give a direct procedure for preparation of arylboronic esters (Scheme 43).[174]



Scheme 43. *Miyaura* borylation.

As in the case of the *Suzuki* coupling, a suitable base is also essential for this borylation. Potassium acetate was found to be the best base, which did not promote the undesired *Suzuki* coupling reaction of starting halide with the formed boronic ester. The reaction is accelerated in polar solvents. Among Pd-precatalysts, $PdCl_2$dppf gave the best results. The reaction was found to proceed more efficiently with electron withdrawing substituents on aryl halide; iodides performed better than bromides. Various functional groups are tolerated including polar functionalities incompatible with *Grignard* or lithium reagents (ester, ketones, cyano groups).

The key step in the mechanism is believed to be the transmetalation between bispinacolatodiboron and acetoxopalladium(II) intermediate formed by the ligand exchange with acetoxy anion (Figure 3).

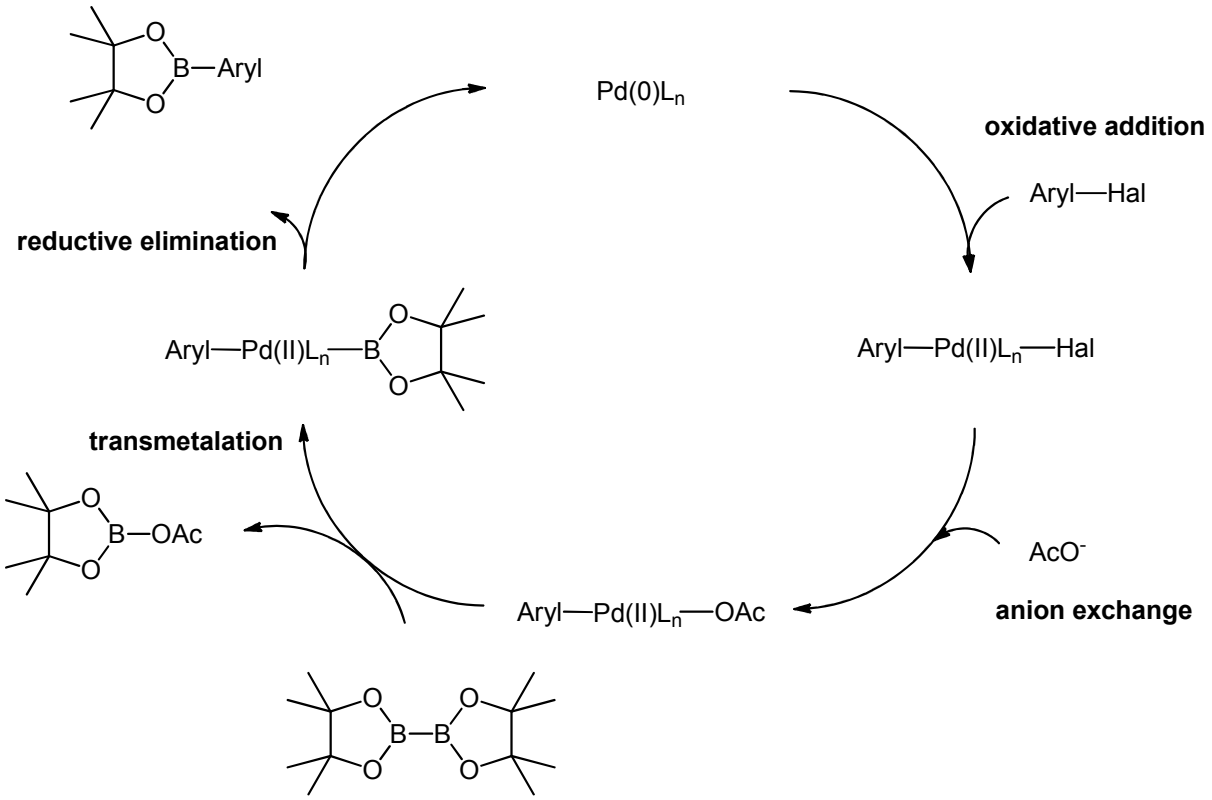
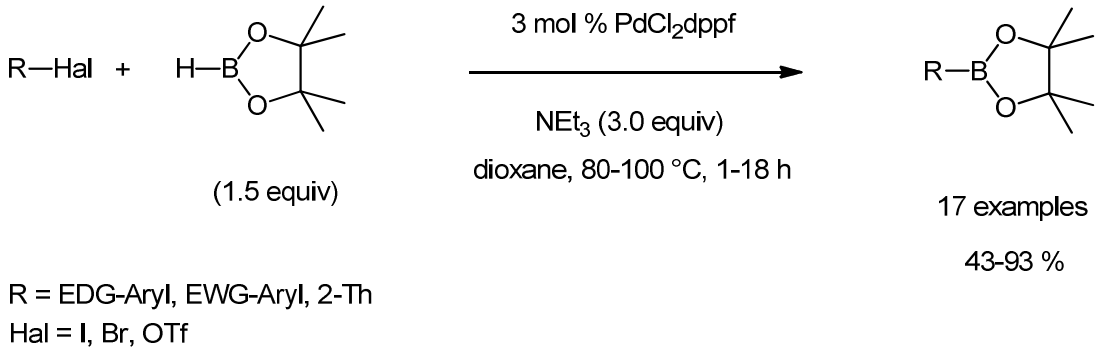


Figure 3. Proposed mechanism of the *Miyaura* borylation.

The main advantage of bispinacolatodiboron as a source of boron nucleophile is its thermal stability and insensitivity toward air, making it easy to handle.

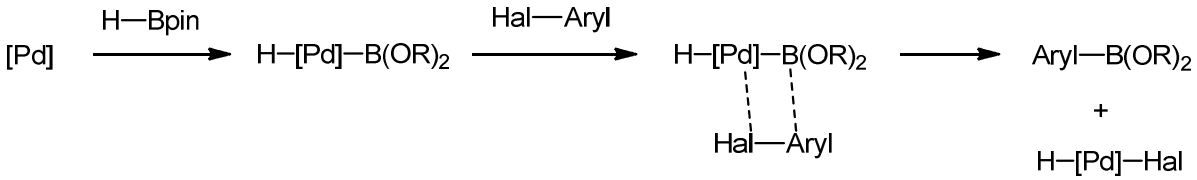
In 1997, *Masuda* reported a further improvement of this procedure using the cheaper pinacolborane.[175] The reaction now became highly elegant and atom economical (Scheme 44).[176]



Scheme 44. *Masuda* borylation.

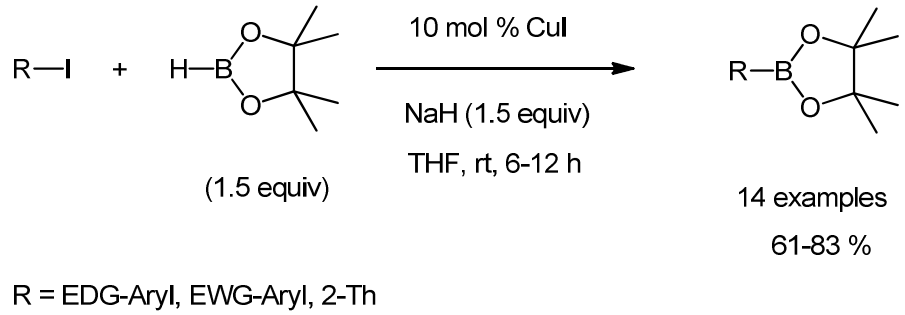
Aryl iodides gave the best yields. Only two heteroaromatic substrates have been investigated. Since pinacolborane tolerates various functional groups (ketone, ester, cyano, carbamate, and others), this borylation is broadly applicable. The typical by-product of this reaction is the dehalogenative hydrogenation as a result of the behavior of pinacolborane as a hydride donor. Triethylamine is the base of choice, allowing to minimize the reduction. The authors pointed out that the reaction was efficiently catalyzed by the palladium(II)-complexes having two equivalents of phosphane ligands such as $PdCl_2$dppf and $PdCl_2(PPh_3)_2$, and additional phosphane ligand retarded the reaction. Very low yield was observed for $Pd(PPh_3)_4$ as a catalyst. The solvent does not play an important role; however, polar solvents such as DMF cause low yields.

The reaction works best with electron rich halides, thus indicating that the mechanism should be different from the usual mechanism of cross-coupling reactions, which would start with the oxidative addition of the aryl halide on the Pd(0) species, followed by a transmetalation of boryl anion generated by deprotonation of pinacolborane with triethylamine, and concluded by a reductive elimination (however, at present this mechanism can not be ruled out). The mechanism could be rationalized to proceed via the first oxidative addition of pinacolborane to the Pd(0)-catalyst, followed by σ-bond metathesis between a B–Pd and a C–Hal bond (Scheme 45).



Scheme 45. Mechanistic rationale of *Masuda* borylation.

In 2006, a Cu(I)-catalyzed borylation of aryl iodides was reported using pinacolborane and NaH as a base (Scheme 46).[177]



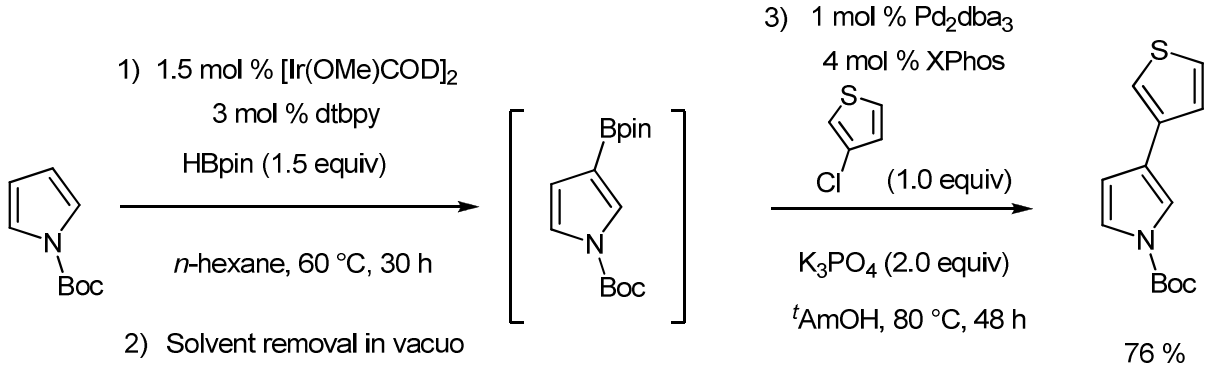
Scheme 46. Cu(I)-catalyzed borylation of aryl iodides.

An interesting borylation procedure was described by *Maleczka Jr.* and *Smith III* in 2009 for Boc-protected heterocycles.[178] This Ir-catalyzed borylation allows to introduce the pinacolboronate group directly involving C–H bond activation (Scheme 47).

Scheme 47. Ir-catalyzed borylation of *N*-Boc heterocycles.

Thus, pyrroles, indoles, azaindoles, and pyrazole can be selectively functionalized at C-H positions β to the nitrogen atom. The Boc protective group was shown to be eas-

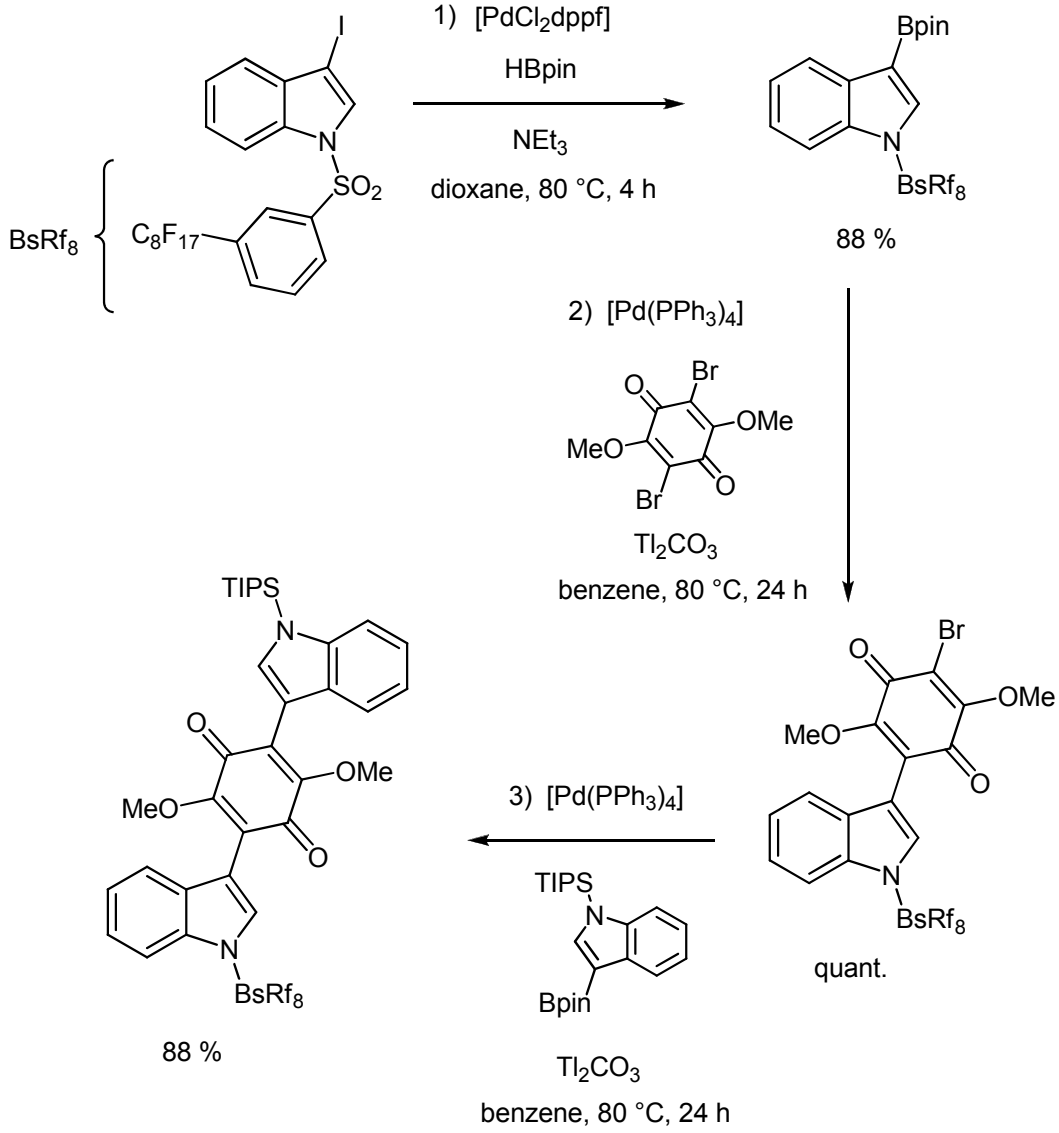
ily removed by thermal deprotection (except for 7-azaindole products); however, a temperature of 180 °C was required. In one case the possibility of performing the subsequent *Suzuki* coupling reaction in one-pot procedure has been demonstrated. However, the Pd-precatalyst and XPhos as a ligand had to be added; moreover, solvents used in the borylation step had to be removed and replaced by a solvent appropriate for the *Suzuki* coupling step (Scheme 48).



Scheme 48. An example of the Ir-catalyzed borylation – Pd-catalyzed *Suzuki* coupling reaction.

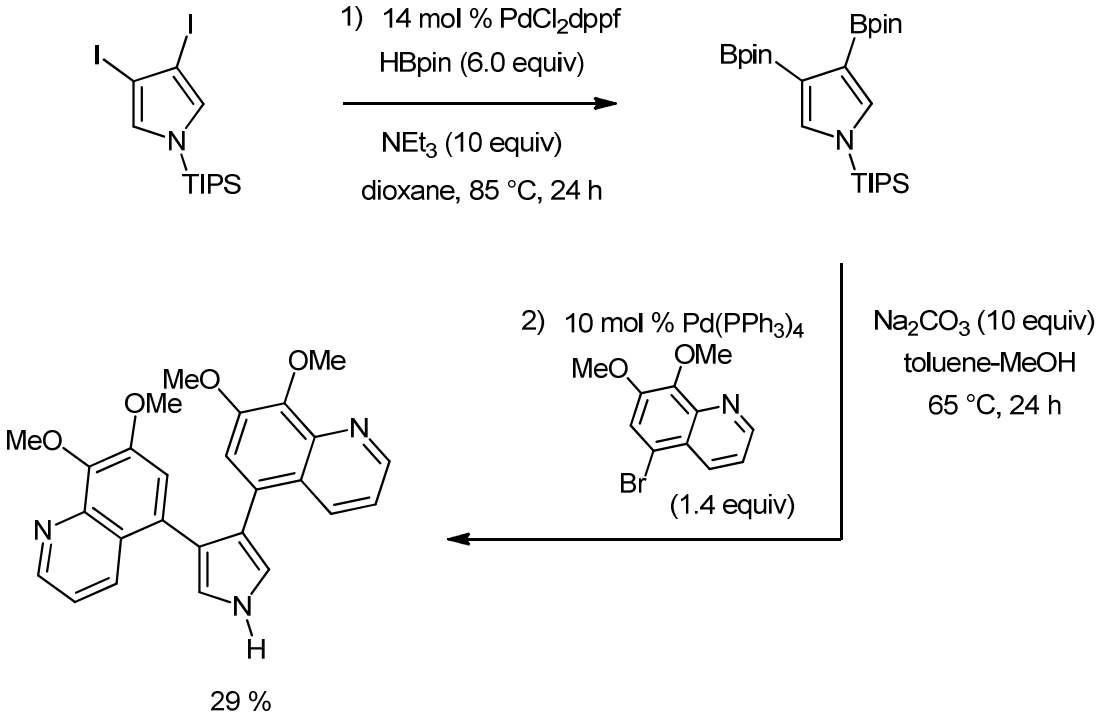
Despite the obvious utility of this methodology, the borylation has to be performed in a glovebox, which is not very practical.

An example for the construction of heterocycle-linked bisindole compounds using *Masuda* borylation and *Suzuki* coupling includes separate reaction steps and two different Pd-precatalysts (Scheme 49).[179]



Scheme 49. Synthesis of bisindole compounds using *Masuda* borylation and *Suzuki* coupling as separate steps.

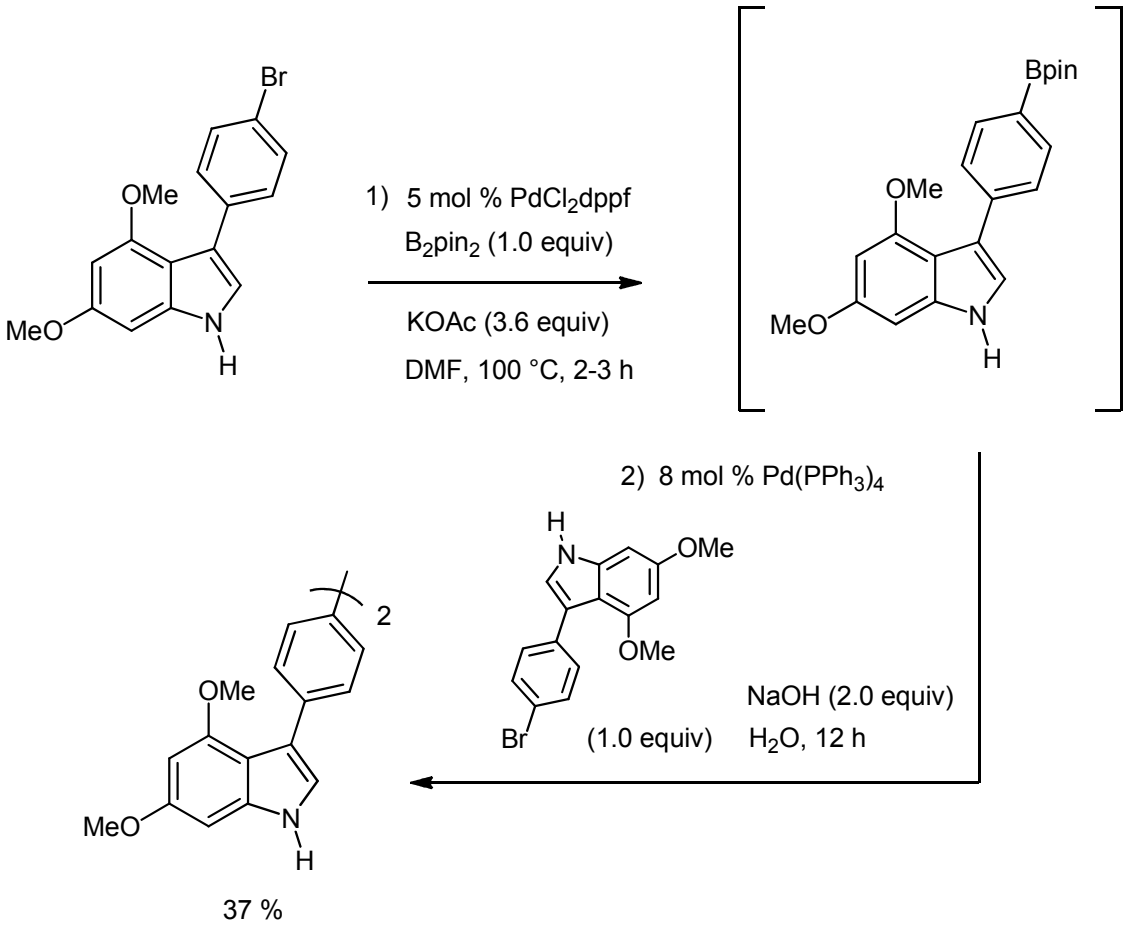
The same strategy was applied in the synthesis of a 3,4-disubsituted pyrrole as the pivotal subtarget toward the cytotoxic marine natural alkaloid halitulin (Scheme 50).[180]



Scheme 50. Synthesis of a substituted pyrrole using *Masuda* borylation and *Suzuki* coupling as separate steps.

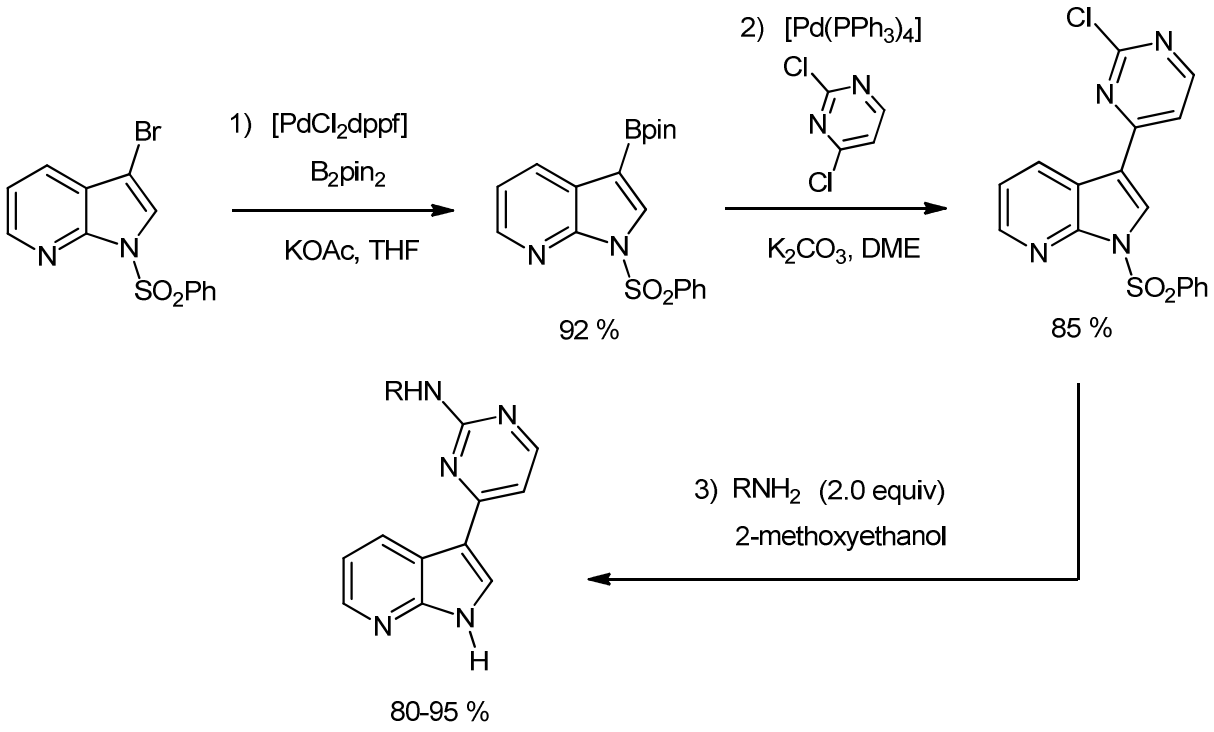
Since both the *Miyaura* and *Masuda* borylations are Pd-catalyzed reactions, it lies at hand to combine both reactions in a one-pot process to avoid the isolation of the intermediate pinacol boronic esters. This approach considerably improves the utility of the *Suzuki* coupling, since it allows to connect directly two organic halides that are broadly available. Moreover, time and materials needed for the isolation of arylboronate intermediates, are saved. In order to carry out the two steps in one-pot effectively, the boronate ester formation needs to be clean and proceed with complete conversion. The same holds true for the subsequent *Suzuki* coupling. Thus, a judicious selection of reaction conditions, such as catalyst, solvent, base, reaction temperature, and protective groups (where appropriate) is very essential for the success of this endeavor.

An example of a one-pot *Miyaura* borylation – *Suzuki* coiupling sequence is the recent synthesis of some bisindoles, bibenzofurans and biflavones (Scheme 51).[181] It should be noted that two different Pd-catalysts, $PdCl_2dppf$ and $Pd(PPh_3)_4$, are required and only symmetrical biheteroaryls could be prepared.



Scheme 51. Synthesis of bridged bisindoles via *Miyaura* borylation – *Suzuki* coupling sequence.

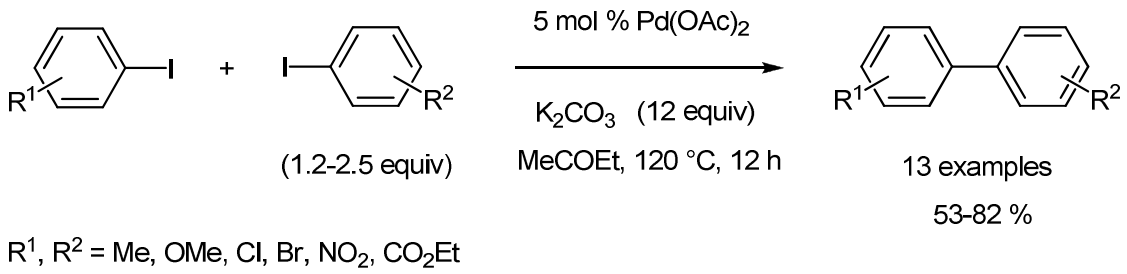
Huang reported on synthesis of 7-azaindolyl pyrimidines related to compounds prepared in the presented work. In this case, *Miyaura* borylation and *Suzuki* coupling have been performed in two separate steps, and two different Pd-precatalysts have been utilized (Scheme 52).[182] Interestingly, the authors underlined that the protection of 7-azaindole with phenylsulfonyl group was critical for the success of the reaction, and unprotected or Boc protected 7-azaindole failed to give the desired product. Phenylsulfonyl group remained uncleaved after the *Suzuki* coupling step, thus two equivalents of the amine had to be used (cleavage of the $PhSO_2$ group consumed one equivalent of the amine reagent).



Scheme 52. Synthesis of 7-azaindolyl pyrimidines according to *Huang*.

The biological activity of the obtained compounds will be discussed in chapter *2.10.1.3 Meriolins*.

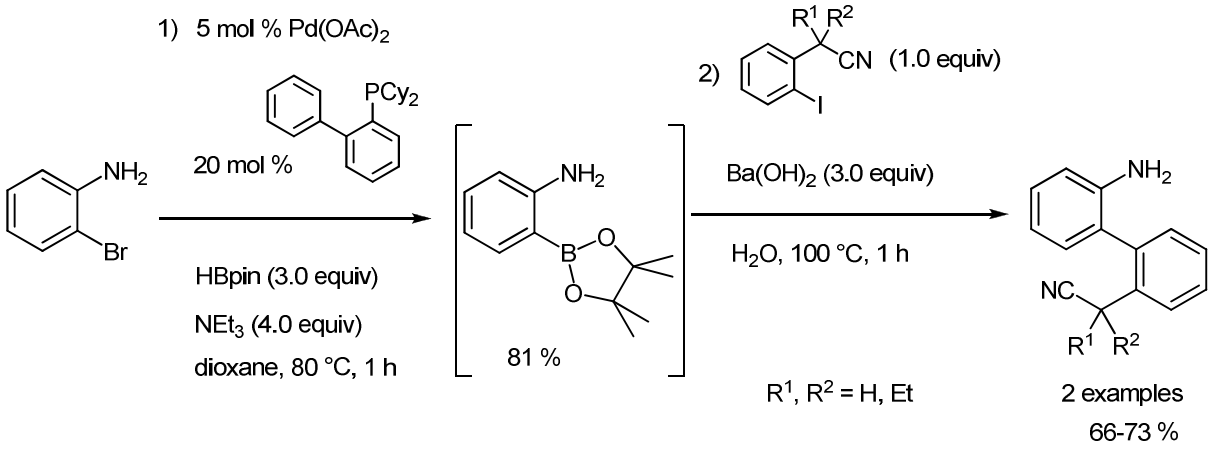
The idea of reacting two (hetero)aromatic halides to form a biaryl compound directly in a one-pot sence is very attractive because of the easy availability of halides. The direct coupling of two aryl iodides has precedence; however, the method suffers from intristic selectivity problems if unsymmetric biaryl synthesis is attempted (Scheme 53).[183] Hence, the reactivity difference between two iodo arenes and their employed ratios are crucial for the selectivity. One component is used in excess, which represents a serious limitation of this approach.



Scheme 53. Pd(II)-catalyzed coupling of aryl iodides to unsymmetrical biaryls.

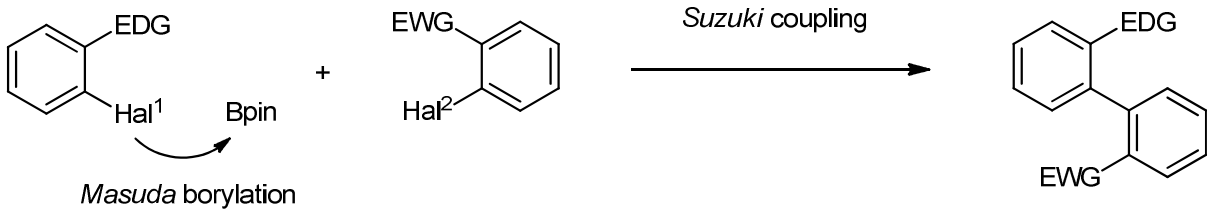
Another strategy is to prefix the umpolung of one electrophilic component (aryl iodide) in situ and perform the coupling upon addition of a second electrophilic component without isolation of the intermediate. There are several reports on successful implementation of the *Masuda* borylation using pinacolborane in combination with the *Suzuki* coupling in a one-pot manner.

This approach was pioneered by *Baudoin* in 2000 in the course of investigations toward the total synthesis of the antimitotic (-)-rhazinilam (Scheme 54).[184] The focus of this work was placed on the investigation of the *Masuda* borylation of *ortho*-substituted bromides, whereas the subsequent *Suzuki* coupling was only described for very few examples of special biphenyls. No heterocyclic halides were used. The sequence also required the *Buchwald* biphenyl ligand. With $Pd(PPh_3)_4$ as a catalyst, 0 % yield was obtained (5 mol % $Pd(PPh_3)_4$, 100 °C, 14 h).



Scheme 54. *Masuda* borylation – *Suzuki* coupling sequence according to *Baudoin*.

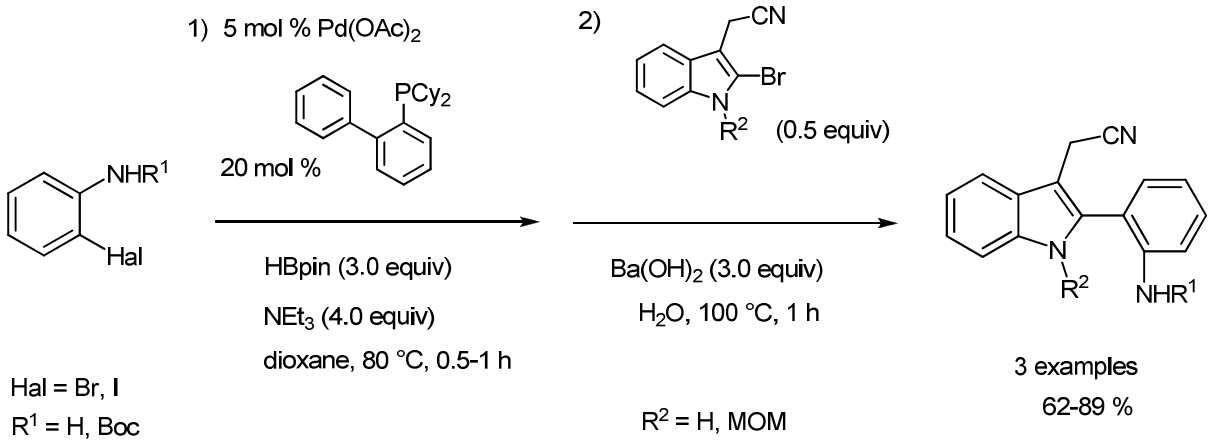
The authors figured out that the choice of the borylation and cross-coupling component depends on the nature of the substituents present on the aromatic ring (Scheme 55).



Scheme 55. Electronic requirements for the *Masuda* borylation – *Suzuki* coupling step according to *Baudoin*.

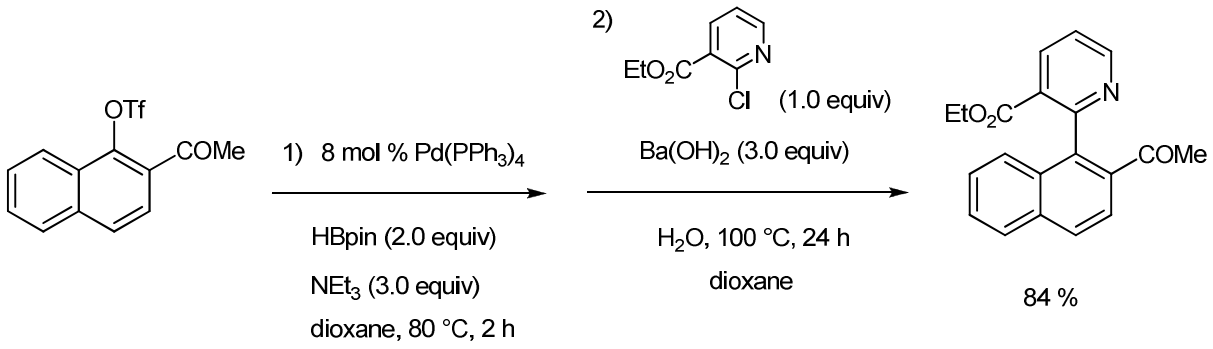
Thus, the borylation should be performed on the component that bears an electron rich group (EDG) and the coupling of the resulting boronate with the component bearing an electron poor group (EWG). The reason may be that electron rich boronates are more reactive in the transmetalation step, and the electron deficient halides in the oxidative addition step of the *Suzuki* coupling.

Using this strategy, special 2-phenylindoles as possible intermediates in the synthesis of paullone, have been prepared (Scheme 56).[185] Here, 2-bromoindoles were used as heterocyclic components. However, a two-fold excess of the halide, which was supposed to be borylated, was used in order to achieve good yields, thus making the reaction less efficient.



Scheme 56. *Masuda* borylation – *Suzuki* coupling sequence in the synthesis of intermediates toward paullone.

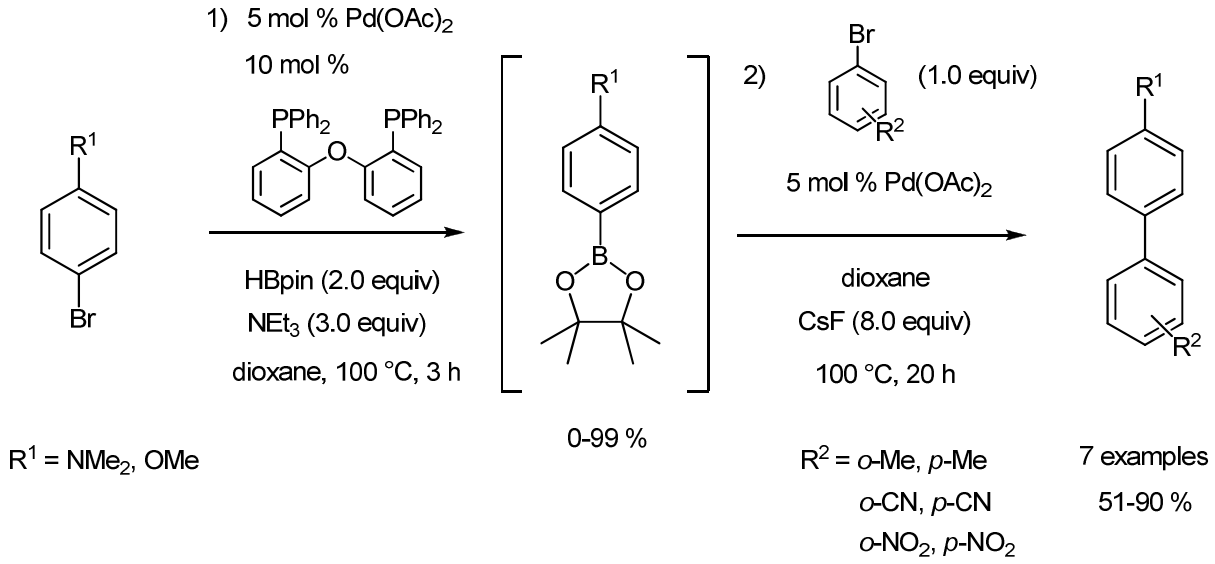
In 2003, *Levacher* presented a one-pot *Masuda* borylation – *Suzuki* coupling sequence for the synthesis of a special 2-naphthylpyridine required for the investigations on a bicyclic lactam construction (Scheme 57).[186]



Scheme 57. Preparation of a 2-naphthylpyridine via *Masuda* borylation – *Suzuki* coupling sequence according to *Levacher*.

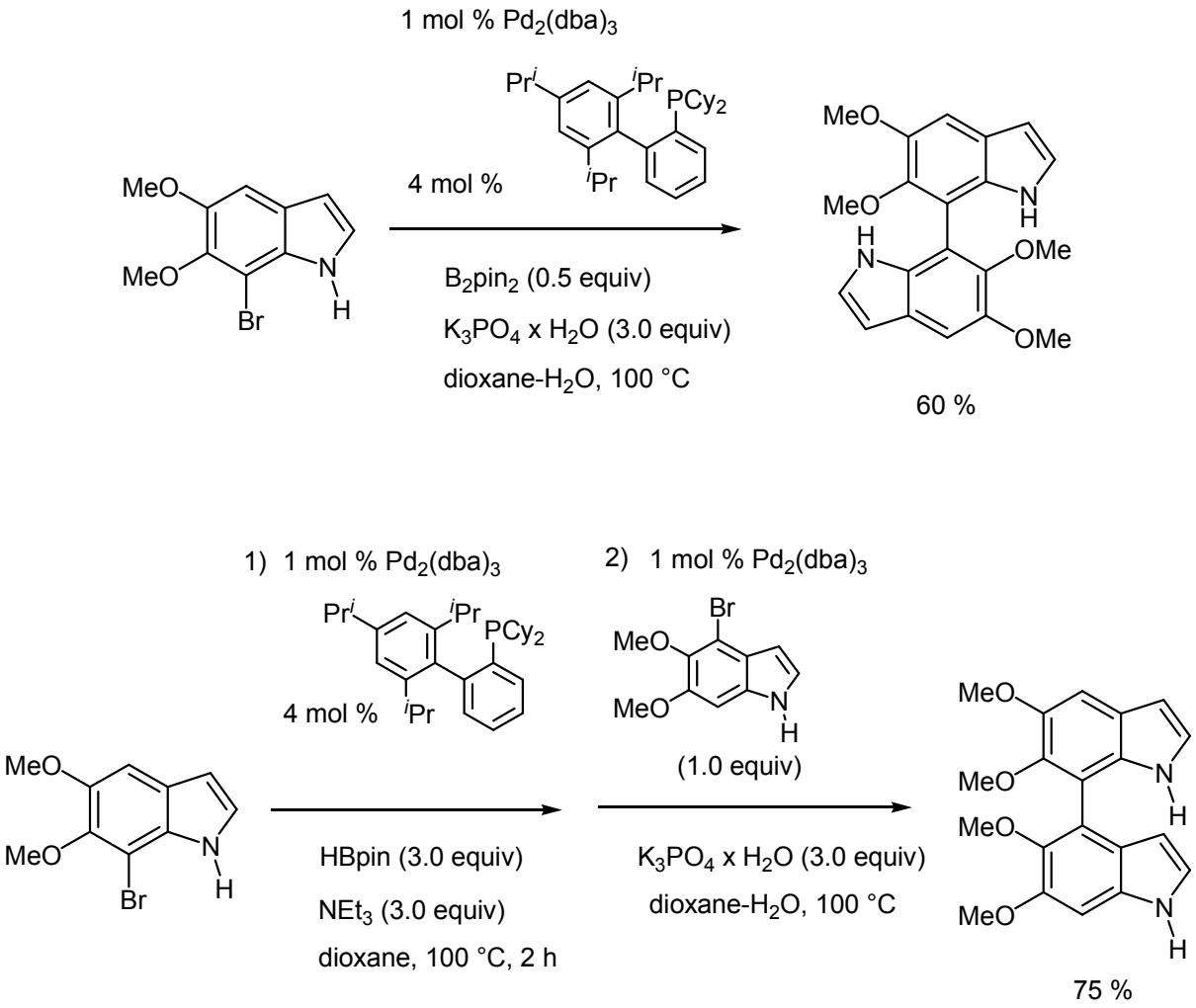
Although this sequence worked well for the synthesis of a heterocyclic product, these conditions have not been extended to other substrates and no generalization has been undertaken.

Colobert described in 2004 another sequence for the preparation of biaryls (Scheme 58).[187] Again, only few examples of rather simple biaryls have been presented, and no heterocyclic halides have been investigated. The sequence worked with DPEphos as a ligand, and a second charge of the precatalyst $Pd(OAc)_2$ had to be added in the *Suzuki* coupling step.



Scheme 58. *Masuda* borylation – *Suzuki* coupling sequence according to *Colobert*.

Eventually, in 2006 *Huleatt* and *Chai* reported the synthesis of a broad range of homo- and heterobisindoles using XPhos as a ligand.[188] The dimerization of bromoindoles was performed using the *Miyaura* borylation – *Suzuki* coupling procedure, whereas unsymmetrical bisindoles have been prepared by the *Masuda* borylation – *Suzuki* coupling sequence (Scheme 59). In the latter sequence, the authors observed precipitation of palladium during the borylation step, thus the addition of a second batch of Pd(0) was necessary in the second step. The bromo indoles used as starting materials were either unprotected or protected with the electron donating Bn group.



Scheme 59. Synthesis of bisindoles according to *Huleatt* and *Chai*.

In summary, prior to this work no general method for coupling of two heterocyclic halides via umpolung of one component with pinacolborane resulting in a *Masuda* borylation – *Suzuki* coupling sequence and using simple catalytic system was known.

2.4 Cu(I)-Catalyzed Reactions and Azide–Alkyne Cycloaddition (CuAAC)

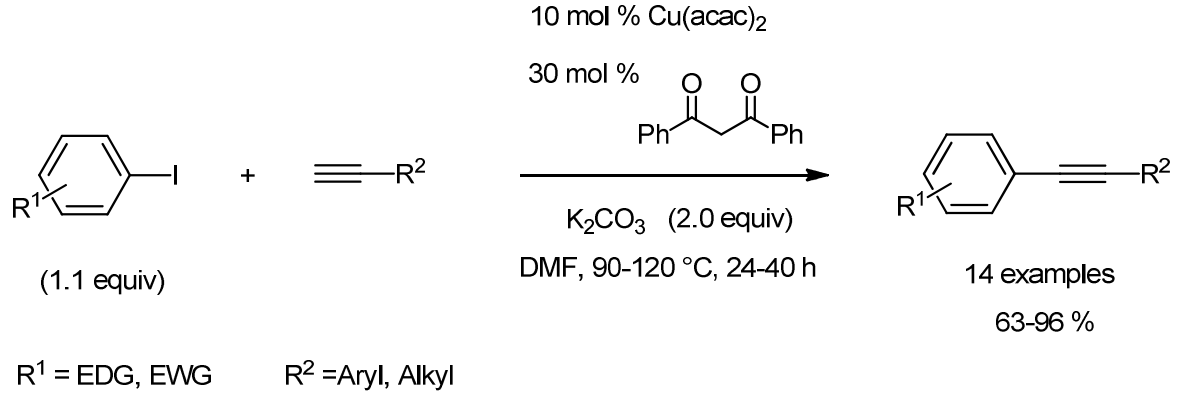
2.4.1 Cu(I) catalysis

The copper-mediated *Ullmann* biaryl synthesis,[189] arylation of amines, phenols (*Ullmann* condensations),[190] amides, carbamates (*Ullmann-Goldberg* condensations),[191] and activated methylene compounds (*Ullmann-Hurtley* condensations)[192] are well-documented methods that were discovered several decades prior to palladium and nickel-catalyzed procedures. Such copper-mediated coupling reactions have found numerous industrial applications. However, until 2000 the synthetic scope of the *Ullmann*-type coupling reactions was restricted because of the often harsh reaction conditions, a limited range of suitable substrates, and the only moderate yields obtained. The condensations were usually conducted in high-boiling polar solvents such as NMP, nitrobenzene, or DMF, at temperatures as high as 210 °C, often with stoichiometric amounts of copper reagents and usually with activated aryl halides.

In 2001, two research groups achieved important breakthroughs with the discovery of versatile and very efficient new Cu/ligand systems for the formation of C–C, C–N, and C–O bonds that enabled the use of only catalytic amounts of metal under much milder conditions (90-110 °C).[193] In the past few years, a plenty of novel exciting Cu-catalyzed reactions appeared in the literature, leading to a spectacular renaissance of this metal in organic synthesis.[42],[43] Recent examples of Cu-catalyzed processes cover an extremely wide range of very distinct transformations, making copper the metal of choice for numerous useful processes such as *Ullmann*-type couplings,[43],[194] *N*-arylations of NH-heterocycles,[195] halogen exchange,[196] cyanations,[197] diverse syntheses of heterocycles,[198],[199] trifluoromethylations,[200] and C–H activations,[201],[202] only to mention a few.

CuI is a widely utilized source of catalytically active Cu(I) species, although numerous other salts and complexes are currently in use.

As an example for the utility of Cu(I)-catalysis in modern organic chemistry, a Pd-free *Sonogashira*-type reaction under mild conditions using a nonexpensive 1,3-dicarbonyl ligand by *Monnier* and *Taillefer* should be mentioned (Scheme 60).[203] Although a Cu(II) salt is used as a precatalyst, the catalytic active species is assumed to be Cu(I).



Scheme 60. Pd-free *Sonogashira*-type coupling.

Further examples of these copper-only procedures were already discussed in chapter *2.3.1 Stephens-Castro coupling*.

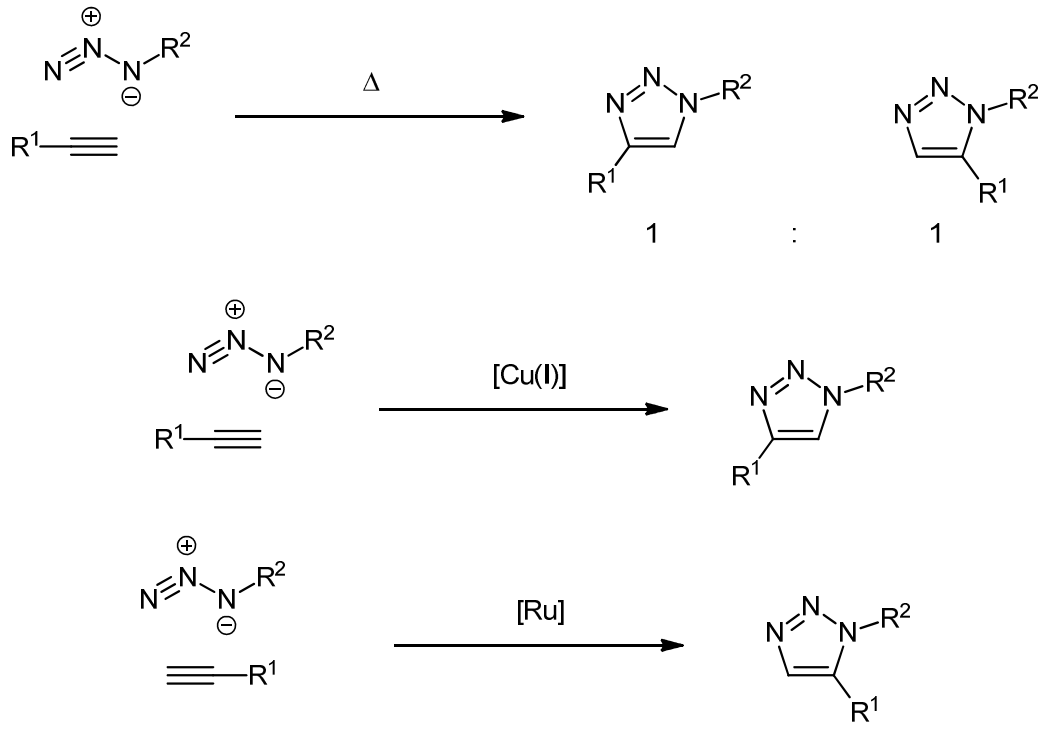
2.4.2 CuAAC

Probably the most exciting Cu-catalyzed reaction developed in the last decade is the azide-alkyne cycloaddition reaction (CuAAC).[204] This transformation belongs to and is meanwhile the premier example of “click” reactions, the term coined by *Sharpless* in 2001 and defined as “a set of powerful, highly reliable, and selective reactions for the rapid synthesis of useful new compounds and combinatorial libraries through heteroatom links (C–X–C)”.[205],[206] 1,4-Disubstituted 1,2,3-triazoles, which are the exclusive products of this transformation, are electron poor 5-membered heterocycles, which possess several properties rendering them interesting structural elements in medicinal chemistry,[207] drug discovery,[208] bioconjugate chemistry,[209] as well as in polymer and material science:

- Triazoles are among the most metabolically stable heterocycles as revealed by SMR studies.[210] They are stable to acid and base hydrolysis and reductive and oxidative conditions, even at high temperature, indicative of a high aromatic stabilization.
- Triazoles are rigid linking units and peptidomimetics with the distance of 5.1 Å between N-1 and N-3 compared with 3.9 Å found in peptides.[211] Unlike peptides, they are not susceptible to hydrolytic cleavage.
- Triazoles possess a large dipole moment (4.8–5.6 Debye) and are able to participate actively in hydrogen bond formation as well as in dipole-dipole and π-stacking interactions. Thus, they can interact productively with biological molecules, as well as with organic and inorganic surfaces and materials.

The crucial observation was made independently by the groups of *Sharpless* and *Meldal* in 2002,[212] who described the acceleration of the *Huisgen* 1,3-dipolar cycloaddition[213] by a factor up to 10^7 if the reaction was catalyzed by Cu(I). Moreover, 1,4-disubstituted 1,2,3-triazoles were exclusively formed rather than a statistical mixture of two possible isomers, which is obtained thermally. More recently, Ru complexes have been shown to give 4,5-disubstituted 1,2,3-triazoles,[214] but the reaction

has to be further developed to obtain such a broad scope and convenience comparable to CuAAC (Scheme 61).



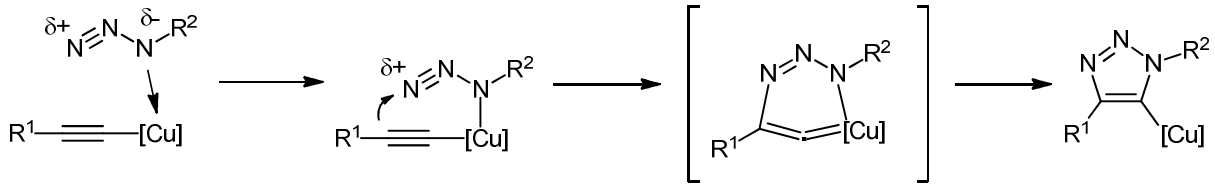
Scheme 61. Regioselectivities of the thermal 1,3-dipolar cycloaddition, CuAAC, and RuAAC.

This remarkable transformation is accompanied by several extremely attractive features:

- CuAAC is a very straightforward way for making covalent connections between building blocks containing various functional groups and is conceptually (but not mechanistically) simple.
- The reaction is extremely user friendly and can often be carried out under aerobic atmosphere, without need for dry solvents, and at ambient temperature or slightly above (25–70 °C). The products are frequently obtained as crystalline solids, which can be isolated by simple filtration without chromatographical purification.[215]
- CuAAC proceeds in high yields (often > 95 %) and with 100 % atom economy. Little or no byproducts (e.g. diynes via the *Glaser* homocoupling) are formed.

- The reaction proceeds under very mild conditions in most organic solvents. It is not sensitive to water and tolerates a wide range of pH values.
- The source of Cu(I) can be very different: (1) Cu(I)-salts such as CuI; (2) Cu(II) salts such as $CuSO_4$, accompanied by a reducing reagent such as sodium ascorbate; or (3) Cu(II) and Cu(0), often simply copper wire, furnishing Cu(I) via synproportionation. Typically, about 0.25–2 mol % of Cu(I) catalyst are used.
- No sophisticated additives or ligands are typically required, although TBTA[216] as a ligand and triethylammonium chloride as an additive[217] have been shown to promote the reaction. However, 1–5 equivalents of a base are usually used to generate the Cu(I)-acetylide in organic solvents.
- 1,4-Disubstituted triazoles are formed regiospecifically.
- The reaction tolerates most functional groups including unprotected alcohols, carboxylic acids, and amino groups, which makes protective groups futile in many cases. Therefore, CuAAC is highly reliable and became very popular in the synthetic community within a very short time. Not tolerated are electron deficient or strained double bonds, free thiols, and electron deficient nitriles.
- The reaction is usually insensitive to steric shielding effects.
- Both alkynes and azides are high in chemical potential energy, and their fusion to triazoles is an irreversible process with a strong thermodynamic driving force of > 45 kcal mol^{-1} (by contrast, equilibrium aldol reactions are energetically favored by less than 3 kcal mol^{-1}). However, alkynes and azides are kinetically stable, and this stability is responsible for a slow uncatalyzed cycloaddition.
- Alkynes and azides can be easily introduced into organic molecules and are inert toward many reaction conditions such as nucleophiles, electrophiles, and solvents. The azide is a rare example of a 1,3-dipole to have these qualities. Both alkynes and azides are small, incapable of significant hydrogen bonding, and relatively nonpolar functionalities. Thus, they are essentially unreactive toward biological molecules.

"The key C–N bond-forming event takes place between the nucleophilic, vinylidene-like β-carbon atom of copper(I) acetylide and the electrophilic terminal nitrogen atom of the coordinated organic azide (Scheme 62). [Cu] is either a single-metal center CuL_n or a di-/oligonuclear cluster Cu_mL_n".[204b]



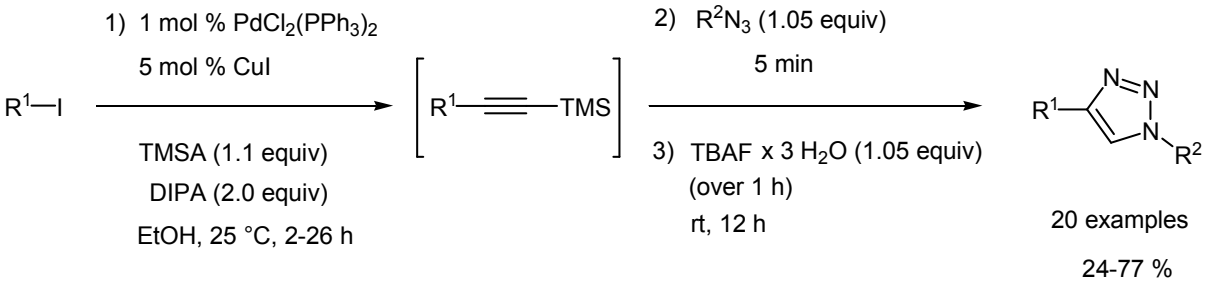
Scheme 62. Simplified representation of the C–N bond-forming step of the CuAAC.

Interestingly, other metals known to catalyze various transformations of alkynes have not so far yielded effective catalysts for the conversion of azides and terminal alkynes to 1,4-triazoles. The unique catalytic function of Cu(I) may be explained by the fortuitous combination of its ability to engage terminal alkynes in both σ- and π-interactions and the rapid exchange of ligands in its coordination sphere. When an organic azide is a ligand, the synergistic nucleophilic activation of the alkyne and electrophilic activation of the azide drives the formation of the first C–N bond.

Besides aiming to improve the biocompatibility of the method, recent efforts in the field of CuAAC have focused on one-pot multicomponent reactions based on the in situ generation of the azide component,[218] in situ utilization of TMS-acetylenes,[219] or the direct Cu(I)-catalyzed C–H-bond arylation of the obtained triazoles.[220] The attraction of these approaches is the minimization of time-consuming workup and purification protocols. Additionally, handling of potentially explosive organic azides is avoided. However, despite the obvious similarity of the *Sonogashira* coupling and CuAAC in terms of reaction conditions, Cu-acetylides being the putative essential intermediates[221] and Cu(I) the catalytically active species in both reactions, no attempts have been made to combine the two reactions into a one-pot procedure until recently.

Eventually, when this thesis was in progress, two reports appeared in the literature describing essentially the same one-pot approach based on the *Sonogashira* coupling of halides with trimethylsilylacetylene, followed by in situ deprotection of the

TMS group and CuAAC upon addition of an azide. In 2009, *Novák* reported a sequential *Sonogashira* coupling – CuAAC reaction starting from simple aryl and heteroaryl iodides (Scheme 63).[222]

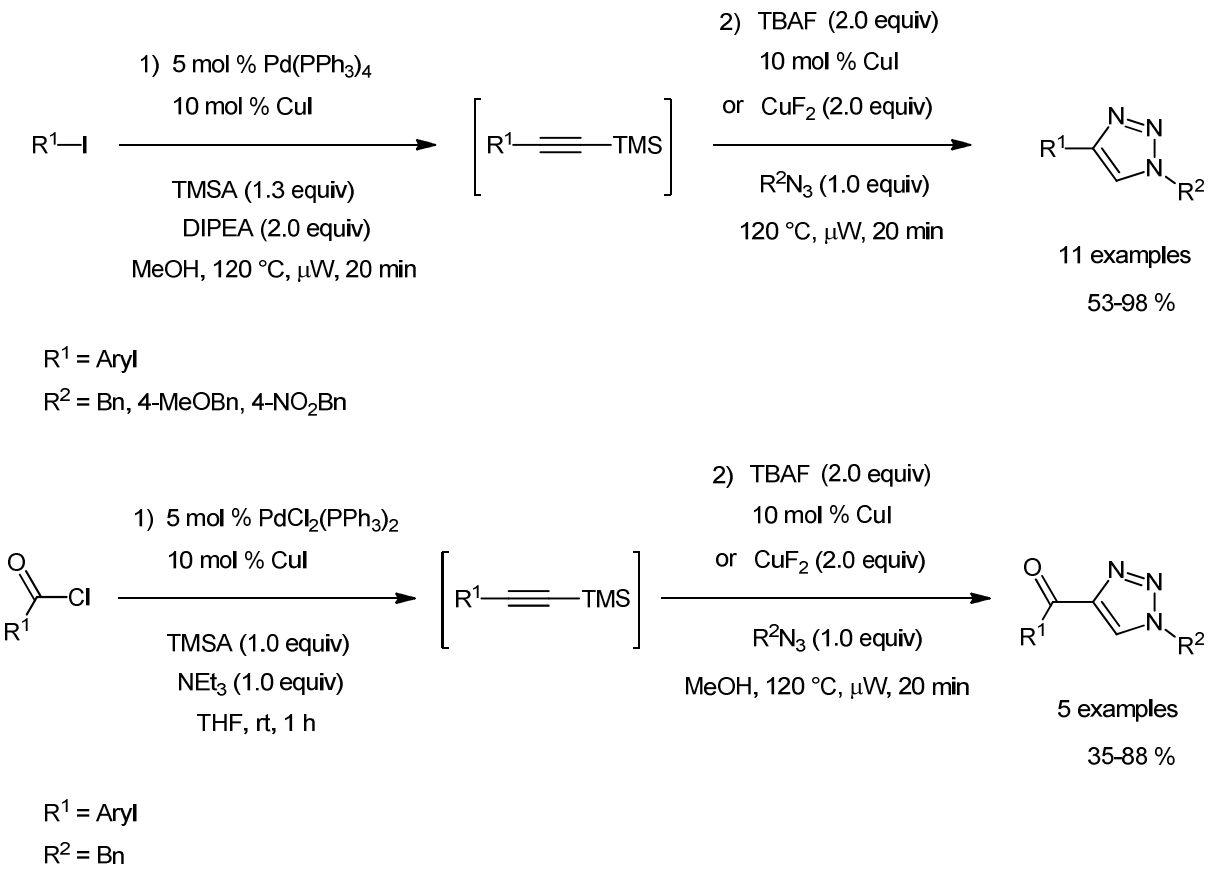


R^1 = Aryl, 2-Th, 3-Py, 4-Py

R^2 = Bn, CH_2SPh, Alkyl, Ad

Scheme 63. One-pot *Sonogashira* coupling – CuAAC sequence according to *Novák*.

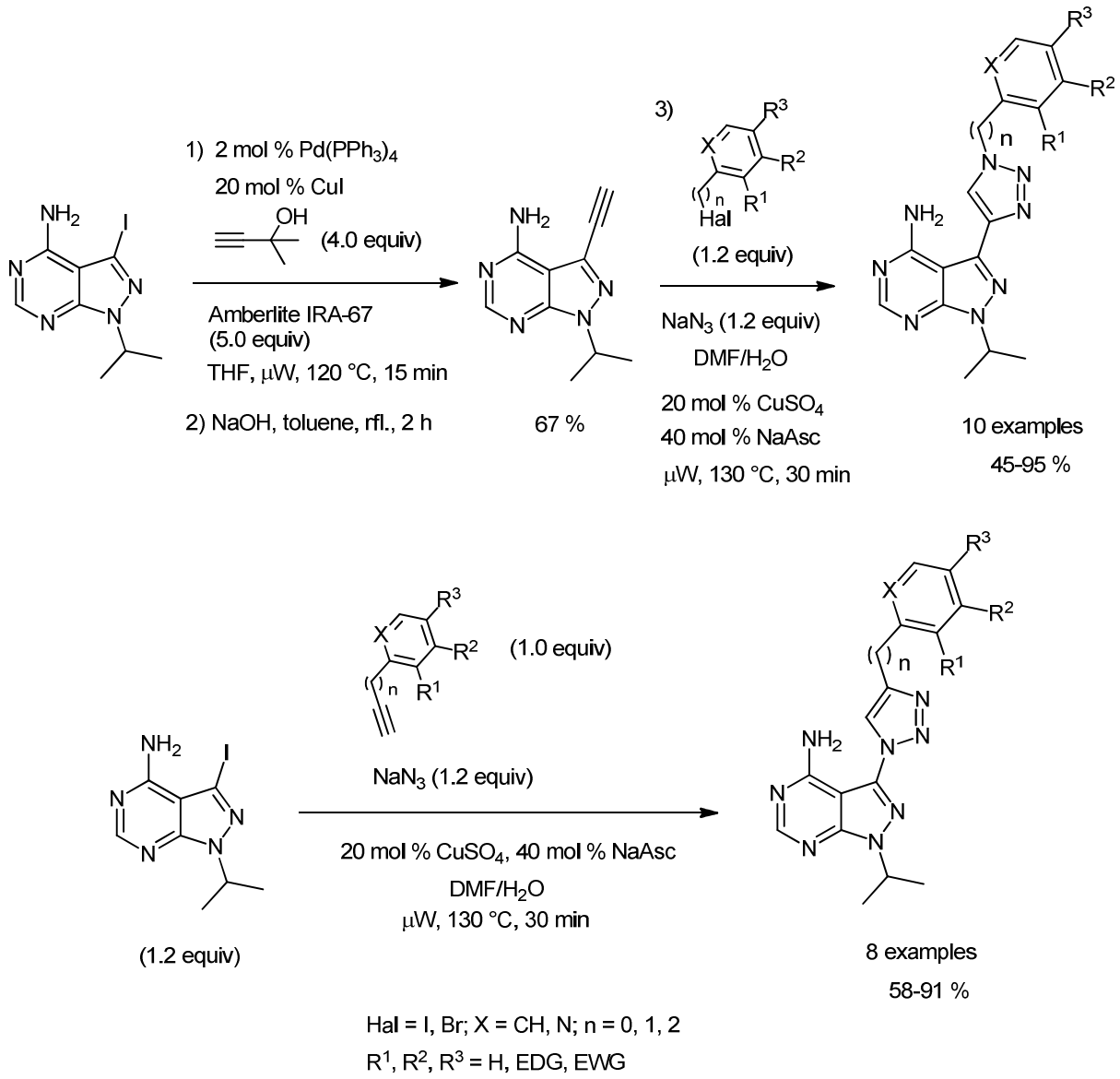
In 2010, another very similar microwave assisted approach was reported by *Boons* (Scheme 64).[223] The new aspect of this synthesis was the possibility to react acid chlorides to yield 4-acyl triazoles. It should be noted, however, that in this approach a second charge of CuI had to be added in the second step and the total loading of 20 mol % catalyst was considerably high. Alternatively, CuF_2 was used, however in excess (2.0 equivs). Moreover, the CuAAC was performed at 120 °C. This can cause problems if less stable azides are used as starting materials.



Scheme 64. One-pot *Sonogashira* coupling – CuAAC sequence according to *Boons*.

Ultimately, just recently *Kolarovič* presented a one-pot three-component synthesis of 1,4-disubstituted 1,2,3-triazoles using aryl iodides and alkynoic acids that proceeded via decarboxylation.[224] In addition to the accesibility issue of alkynoic acids, no heterocyclic iodides or propynoic acids have been applied.

CuAAC has already been used in several approaches to synthesize kinase inhibitors,[225] for instance in a recent synthesis of 3-triazolyl substituted pyrazolo[3,4-*d*]pyrimidines (Scheme 65).[226] Typically, the *Sonogashira* coupling for the preparation of the terminal alkyne and the CuAAC for the construction of triazole are performed in separate steps using two different Cu(I)-catalysts.

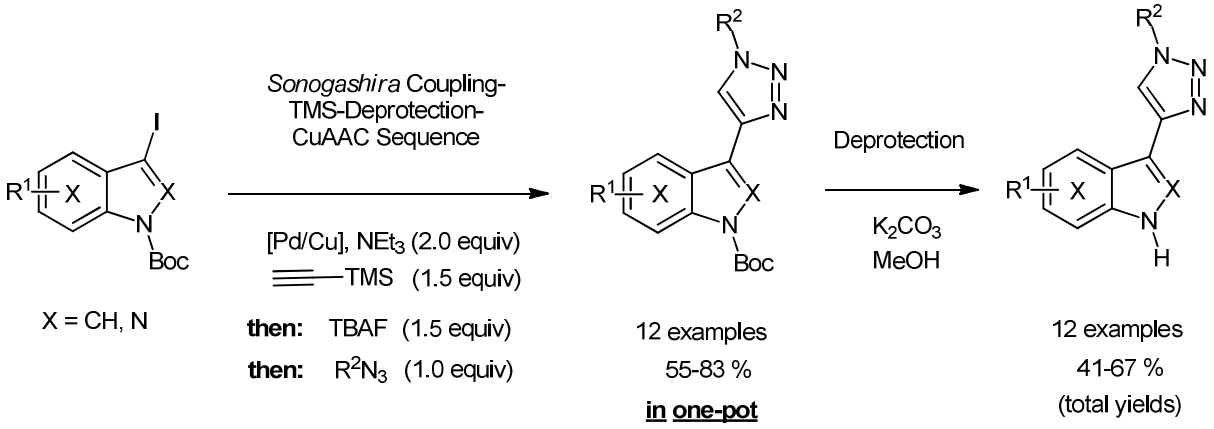


Scheme 65. Preparation of 3-triazolyl substituted pyrazolo[3,4-*d*]pyrimidines for the evaluation of their kinase inhibitory activity.

Two compounds showed activity toward the PfPK7 kinase of *Plasmodium falciparum* (IC_{50} values in 10-20 μM range), the organism responsible for the most virulent form of malaria.

In conclusion, prior to this work no synthesis of 3-triazolyl substituted indole and its aza analogs and investigations of their kinase inhibitory activity have been reported.

In the framework of this thesis, a very general one-pot three-component synthesis of NH-heterocyclic triazoles has been developed (Scheme 66).[227] *N*-Boc iodo NH-heterocycles were reacted with trimethylsilylacetylene, the corresponding TMS-alkynes were deprotected and converted to *N*-Boc protected triazolyl heterocycles via Cu-catalyzed azide-alkyne cycloaddition (CuAAC), all in a one-pot fashion. After mild deprotection, the final products were obtained in fair yields. The strategy was found to be applicable for indole and virtually all indole isosters such as azaindoles, as well as indazole, deazapurines, and diazaindole. Some other heterocycles such as pyrrole and pyrazole could be reacted as well.



Scheme 66. One-pot synthesis of indolyl triazoles by a *Sonogashira* coupling – TMS-deprotection – CuAAC sequence with subsequent deprotection.[227]

7-Azaindolyl triazole was found to be a submicromolar inhibitor of the kinase PDK1,[228] a target of high relevance for oncology (Figure 4). This compound became a new lead structure and was used for the synthesis of further analogs.[229] An X-ray structure analysis of this compound in PDK1 revealed the detailed binding mode of the molecule in the kinase. Interestingly, an isomeric compound differing only in the permutation of substituents on N-1 and C-4 atoms and following in the dipole moment of the triazole unit showed no activity on the kinase PDK1 (Figure 4).[227]

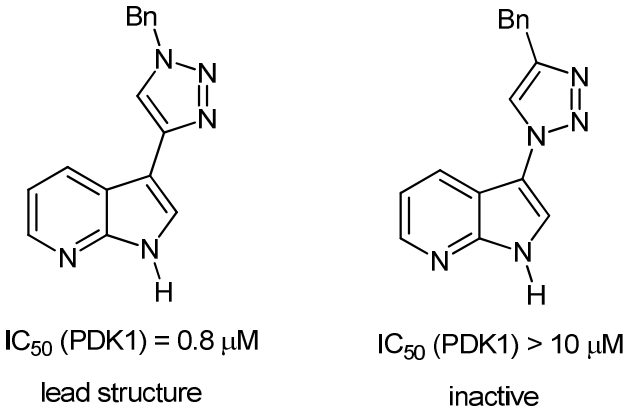


Figure 4. Comparison of PDK1 inhibitory activities of two isomeric 3-triazolyl 7-azaindoles.[227]

The strategy could be easily extended to four-component sequences with in situ *N*-Boc-protection of the NH-heterocyclic halide or in situ generation of azide via halide-azide exchange demonstrating high flexibility of this methodology.

These results are part of this cumulative dissertation (**publication 3.3**).

2.5 Decarbonylations

Carbonylations[40] and decarbonylations[230] belong to the most important elementary reactions occurring in the coordination sphere of a metal and constitute the very "heart" of the organometallic chemistry. The process of carbon monoxide insertion, i.e. the migratory insertion, is reversible depending on the pressure of carbon monoxide and temperature. The opposite process is a decarbonylation, i.e. the migratory deinsertion or extrusion.

In 1965, *Tsuji* and *Ohno* described a decarbonylation of aldehydes with stoichiometric amounts of *Wilkinson's* catalyst $RhCl(PPh_3)_3$.[231] This Rh-mediated transformation is now well known as *Tsuji-Wilkinson* decarbonylation of aldehydes (Scheme 67).[232]

$$RCHO + RhCl(PPh_3)_3 \longrightarrow RH + RhCl(CO)(PPh_3)_2 + PPh_3$$

Scheme 67. *Tsuji-Wilkinson* decarbonylation of aldehydes.

The formation of the very stable carbonyl complex *trans*-$[RhCl(CO)(PPh_3)_2]$ prevents catalysis by Rh around room temperature. Only at temperatures above 200 °C the complex $RhCl(CO)(PPh_3)_2$ becomes a catalyst.[233] *Tsuji* and *Ohno* immediately realized the immense synthetic potential of decarbonylative methods as they postulated that "decarbonylation reactions would be very useful in organic chemistry if they can be carried out smoothly under mild conditions".[233a]

Although later the reaction has been made catalytic in rhodium[234] and can proceed even at room temperature,[234b] still many current applications in total synthesis use *Wilkinson's* catalyst in stoichiometric amounts or even in a slight excess.[235] In order to realize the efficient decarbonylation of aldehydes, elevated reaction temperatures (typically > 160 °C) are indispensable. The other possibility is to use an associated chemical scavenger of the evolved CO, i.e. by an accompanying carbonylation reaction[339] or by addition of DPPA.[234b] CO is a strong ligand and can therefore be a catalyst poison.

Over the past years, a plenty of decarbonylation methods have been developed which utilize various substrates such as acyl halides, cyanides, phosphonates, silanes, stannanes, anhydrides, esters, thioesters, imides, aldehydes, ketones, 1,2-

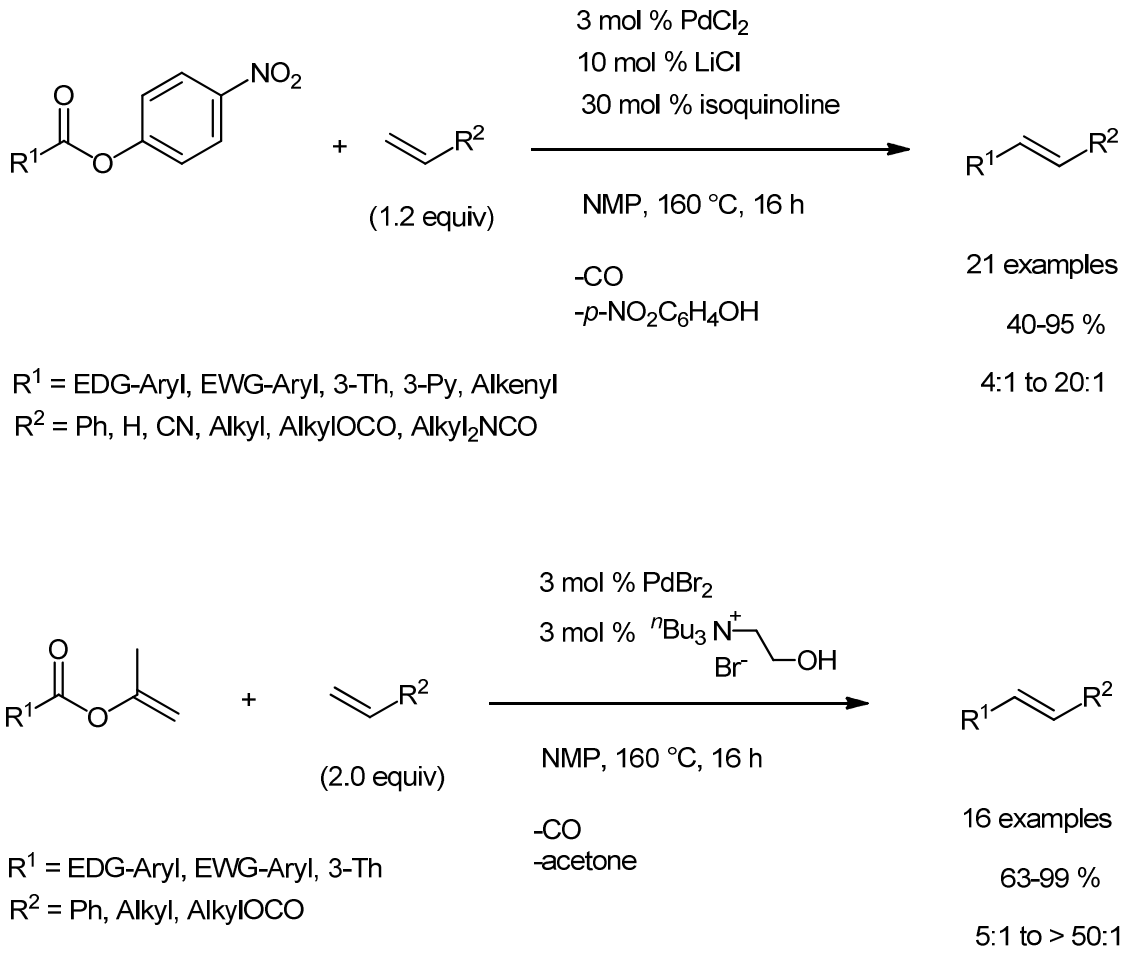
diketones, and others, catalyzed by transition metals such as Rh, Ni, Cu, Ru, Pd, Ir, Pt.[236]

A decarbonylation event is often coupled with a concomitant carbonylative reaction proceeding as a tandem process[348]-[353] (for a discussion, see chapter *2.7 Oxalyl chloride in organic synthesis*) or with a cross-coupling reaction. Biaryls have been prepared from carboxylic anhydrides, which serve as synthetic equivalents of halides, and from triaryl boroxines via Rh-catalyzed decarbonylative *Suzuki* coupling.[237] Despite harsh reaction conditions (160 °C, 8 h), the nondecarbonylated byproduct is also formed in substantial amounts.

Acid chlorides are also suitable substrates for metal-catalyzed decarbonylative transformations. In fact, *Ohno* and *Tsuji* first described decarbonylations of acyl halides using stoichiometric amounts of *Wilkinson's* catalyst at rt-180 °C or catalytic amounts of $RhCl(CO)(PPh_3)_2$ at 190-250 °C to form olefins or the corresponding halides depending on the acyl halide used.[233a,c] Notably, the Rh acyl complexes formed via an irreversible oxidative addition of acyl halides were stable and could be isolated and characterized. Almost simultaneously, *Blum* reported decarbonylation of aroyl chlorides to aryl chlorides under similar conditions.[238] To date, decarbonylations of acid chlorides are known to proceed with Rh,[239] Ir,[240] and Pd.[241]

For the first time a Pd-catalyzed decarbonylation of aldehydes was disclosed as a side reaction of the *Rosenmund* reduction.[242] Later, in 1960 *Hawthorn* and *Wilt* described a preparative procedure operating with 5 % Pd/C at 179-250 °C.[243] Interestingly, although a Pd-catalyzed decarbonylation of acid chlorides and aldehydes, which proceeded at 180-220 °C with Pd/C or $PdCl_2$ as a catalyst, was described by *Ohno* and *Tsuji* in the same year as the *Tsuji-Wilkinson* decarbonylation reaction,[244] it has not received a synthetic utility comparable to the latter process. In contrary, Pd-catalyzed decarbonylations received much less attention. Besides decarbonylation of aroyl chlorides under extremely high temperature (360 °C)[245] and decarbonylative carbostannylation of alkynes with acylstannanes catalyzed by Pd/C,[246] salt-free decarbonylative *Heck* reactions using anhydrides as substrates were known.[247] However, reaction conditions are harsh (NMP, 140-190 °C, 90-180 min).

In the last decade, *Gooßen* revitalized this strategy and reported salt-free *Heck* olefinations of *p*-nitrophenyl esters[248] and enol esters,[249] which however still proceed under harsh reaction conditions (160 °C, 16 h) in NMP as a solvent (Scheme 68).



Scheme 68. Decarbonylative *Heck* olefinations.

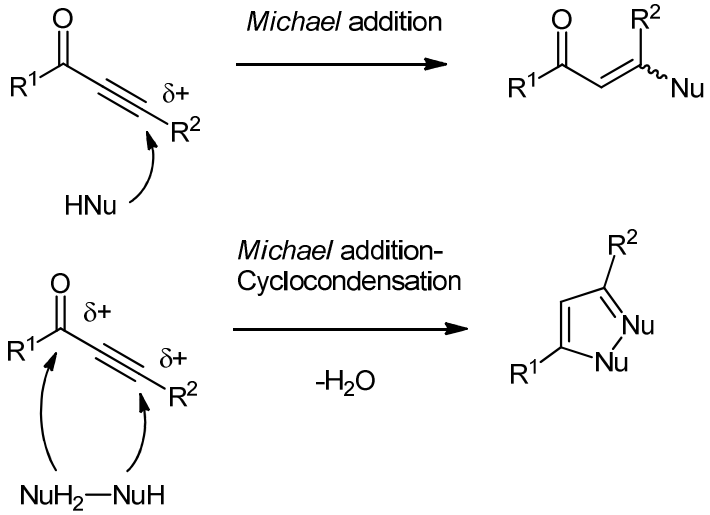
Other examples involve the in situ generation of acid anhydrides starting from aliphatic carboxylic acids. The activation can proceed with Piv_2O[250] or Boc_2O.[251] The mixed anhydrides are then decarbonylated under Pd-catalysis to give olefins. The reactions proceed at 110-120 °C for 16 h and use 2-3 equivs of anhydrides as activators.

In conclusion, prior to this work no decarbonylative alkynylation methods were known. A minor amount (4 %) of a decarbonylated product was detected by an attempt to perform the *Sonogashira* coupling with methyloxalylchloride, along with 4 % of the nondecarbonylated product.[252]

2.6 Ynones and Ynediones as Valuable Synthetic Building Blocks

2.6.1 Synthesis and reactivity of ynones

α,β-Acetylenic carbonyl compounds (propargyl ketones, ynones)[253] are of great interest because they represent very useful synthetic intermediates,[254] especially for the preparation of natural products [255],[285],[256],[448] and of a huge number of heterocyclic molecules.[257] The main feature of ynones is the presence of two electrophilic centers: the carbon atom of the carbonyl group and the β-carbon atom of the triple bond, which is activated toward *Michael* addition. As a consequence, ynones react with nucleophiles via *Michael* addition and with binucleophiles via *Michael* addition – cyclocondensation reactions. This reactivity has been extensively used in numerous syntheses of a wide range of important heterocycles (Scheme 69).[253]



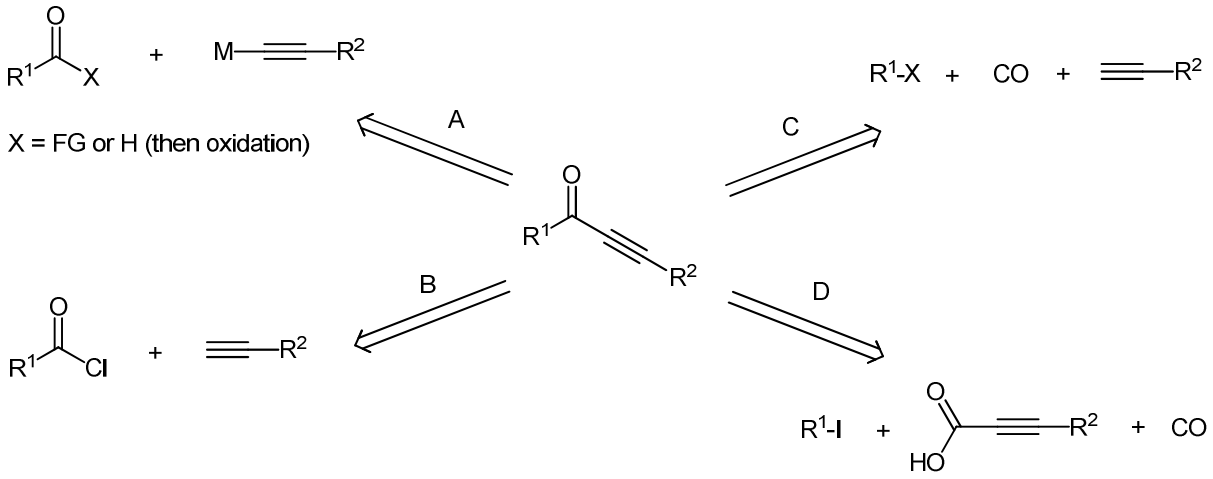
Scheme 69. Reactivity of ynones.

Ynones as versatile three-carbon building blocks can be easily converted to 5, 6-, and 7-ring *N*-, *O*-, and *S*-heterocycles such as pyrroles,[258] pyrrolin-4-ones,[259] indoles,[260] furans,[261] bifurans,[262] furanones,[263] oxazoles,[264] thiophenes,[265] pyrazoles,[266] pyrazolo[1,5-*a*]pyridines,[267] triazoles,[268] isoxazoles,[269] indolizines, pyrones,[270] chromones,[271] pyrimidines,[272] pyridazines, pyridopyrimidines, pyridines (*Bohlmann-Rahtz* synthesis),[273] pyridinones, quinolines,[274] naphthyridines,[275] ben-

zonaphthyridinones,[276] 4-oxo-indeno[1,2-*b*]pyrroles,[277] benzoheterozepines, and some others. In a very recent approach, a phosphane-mediated construction of 1,4-oxazepines and 1,3-oxazines from ynones and 2-azido alcohols was described.[278]

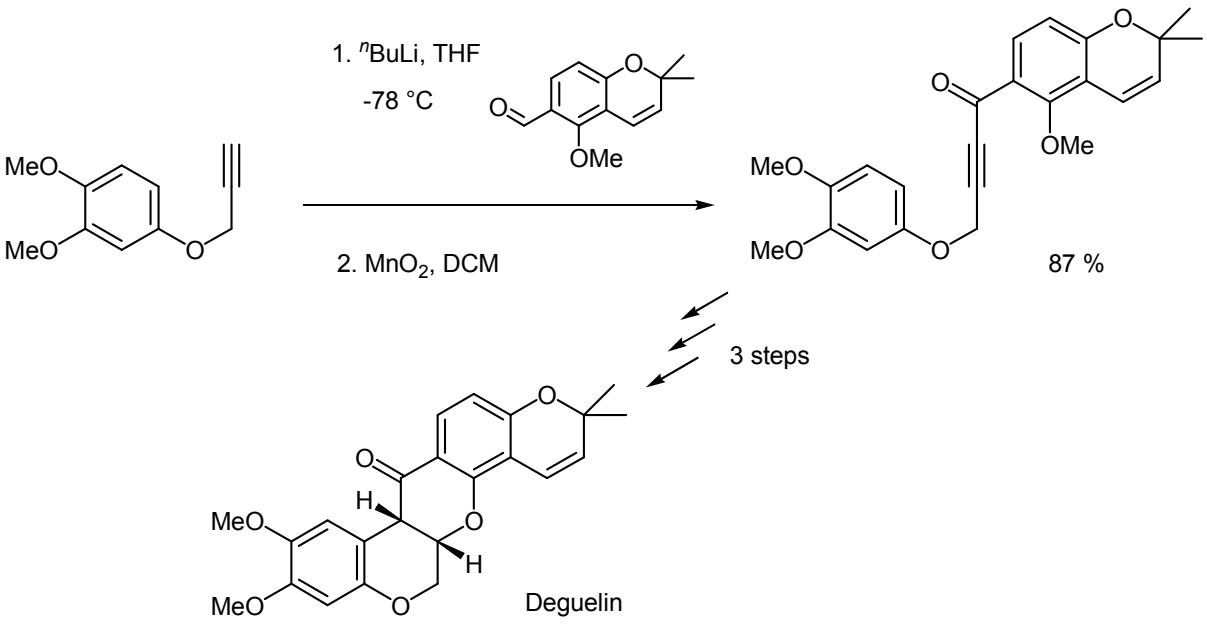
Besides their useful synthetic potential, ynones can possess interesting biological properties in their own right. *Kundu* reported uracil and its corresponding nucleosides substituted at C-5 by an acetylenic ketone functionality displaying promising cytotoxic activity against CCRF-CEM human lymphoblastoid cells and L1210 mouse leukemia cells in culture. These compounds were also shown to be inhibitors of thymidylate synthase, an essential enzyme needed for cellular multiplication processes.[279] As a further example, diphenylpropynone derivatives have been recently synthesized for in vivo use to image β-amyloid (Aβ) plaques in the brain of patients with *Alzheimer's* disease. Binding experiments in vitro revealed high affinity for Aβ (1-42) aggregates at a K_i value ranging from 6 to 326 nM.[280]

Not surprisingly, a considerable effort has been devoted to the development of efficient and general syntheses of ynones (Scheme 70).[281]



Scheme 70. Synthetic approaches toward ynones.

Classical approaches toward ynones (Scheme 70, path A) are mainly based on the reaction of organometallic acetylides with carboxylic acid derivatives such as acid chlorides,[282] *Weinreb* amides or morpholides,[283] or with aldehydes followed by oxidation of the formed propargyl alcohols.[284] An illustration of this strategy, which is still often used, is the synthesis of a chemopreventive agent (±)-deguelin with a quite complex ynone as a key intermediate (Scheme 71).[285]

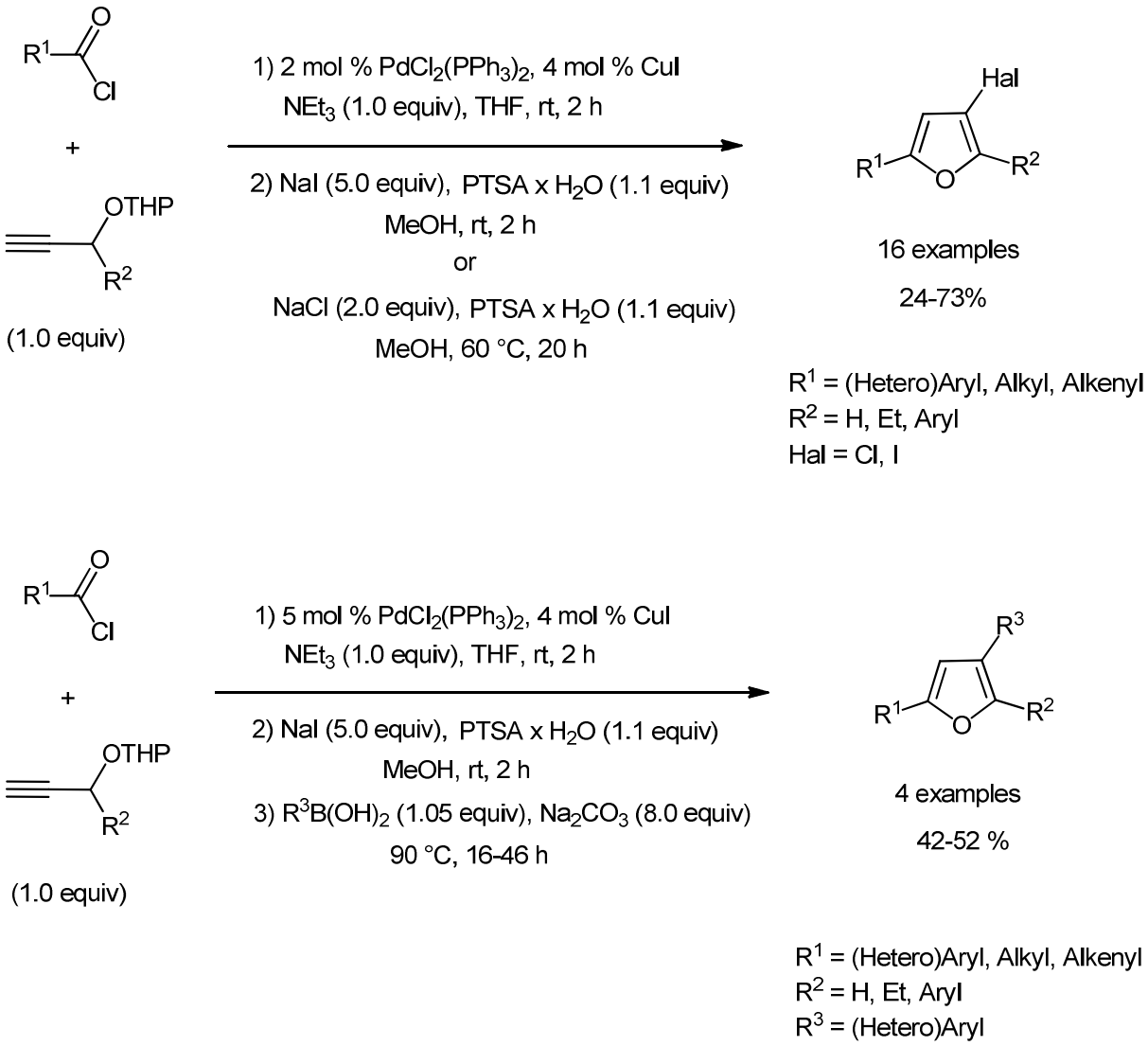


Scheme 71. Synthesis of (±)-deguelin via an ynone as a key intermediate.

In recent years, numerous catalytic approaches by direct reactions of acid chlorides with terminal alkynes appeared, which are more elegant, efficient, and atom economical (Scheme 70, path B; for a discussion, see chapter *2.3.2 Sonogashira-Hagihara coupling*). From a synthetic point of view, Pd and/or Cu are the most practical transition metals for these transformations.

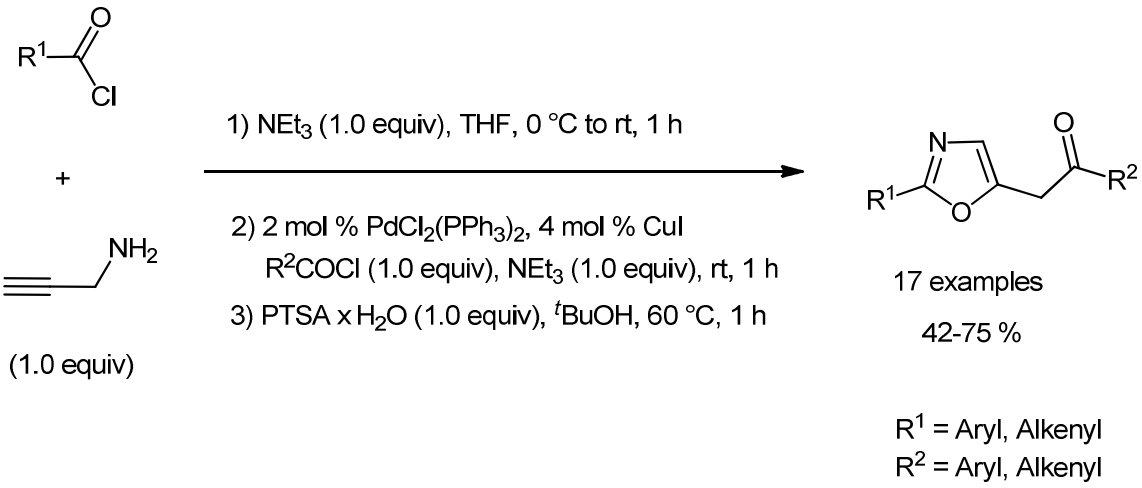
However, the most interesting and efficient syntheses of heterocycles involve the in situ generation of ynones with the subsequent conversion to diverse heterocycles in a one-pot sense.[286],[287] In *Müller's* group, syntheses of diverse heterocycles such as furans,[297] oxazoles,[298] pyrazoles,[288] isoxazoles,[289] pyrimidines,[290] indolizines,[291] quinolines,[292] tetrahydro-β-carbolines,[293] 4*H*-thiochromen-4-ones,[294] 1,5-benzodiazepines,[295] and 1,5-benzothiazepines[296] have been developed on the basis of the *Sonogashira* coupling.

In 2005, we reported a new one-pot synthesis of 2,5-disubstituted 3-halo furans via a three-component one-pot reaction. In the first reaction step acid chlorides were coupled with THP-protected propargyl alcohol in the sense of the *modified Sonogashira* coupling. The intermediate ynone was then converted to the furan in the course of *Michael* addition – deprotection – cyclocondensation sequence.[297] The iodo furans could be isolated or transformed into 3-aryl substituted furans by an additional *Suzuki* coupling step, still in a one-pot fashion (Scheme 72).



Scheme 72. One-pot synthesis of 3-halo and 3-aryl furans.

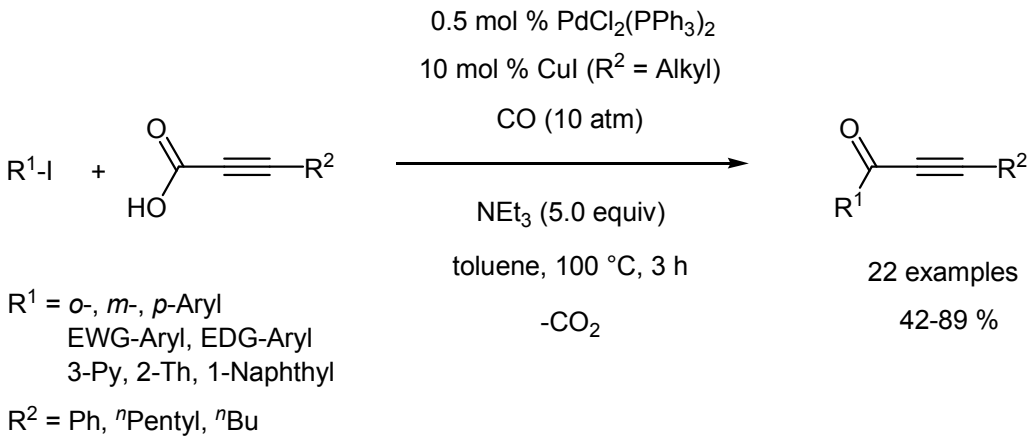
In 2006, we described the formation of 2,5-disubstituted oxazoles in the course of acylation of the propargyl amine with an acid chloride, the *modified Sonogashira* coupling of the resulting amide with another equivalent of an acid chloride, and an acid-mediated cycloisomerization sequence (Scheme 73).[298] Again, an ynone was the key intermediate in this synthesis.



Scheme 73. One-pot synthesis of oxazoles.

The carbonylative alkynylation (Scheme 70, path C; for a discussion, see chapter *2.3.3 Carbonylative Sonogashira coupling*) is a highly convergent approach and an increasingly popular tool for the construction of ynones. In 2005, we published the first application of this method in the synthesis of natural products meridianins, a class of marine indole alkaloids (for a discussion, see chapter *2.10.1.1 Meridianins*). The major drawback of carbonylative alkynylations is the preparative nuisance associated with toxic carbon monoxide.

Recently, a new approach (Scheme 70, path D) was demonstrated utilizing propynoic acids as substrates (Scheme 74).[299] However, the practical limitation is the accessibility of the starting materials.

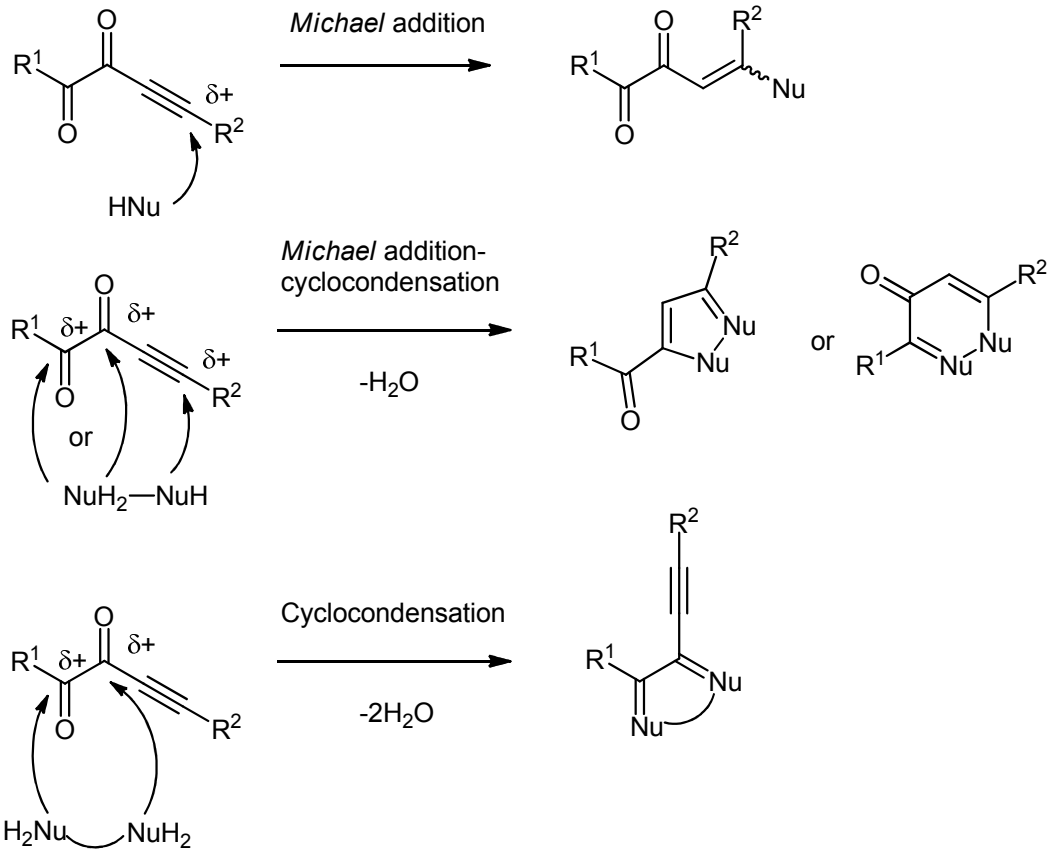


Scheme 74. Carbonylative alkynylation of (hetero)aryl iodides via decarboxylative coupling with alkynyl carboxylic acids.

Despite numerous syntheses of ynones bearing simple aryl substituents have been reported, only a very limited number of *N*-heterocyclic examples exists.[300],[448] Prior to this thesis, no general and broadly applicable method for obtaining these potentially highly requested building blocks was known.

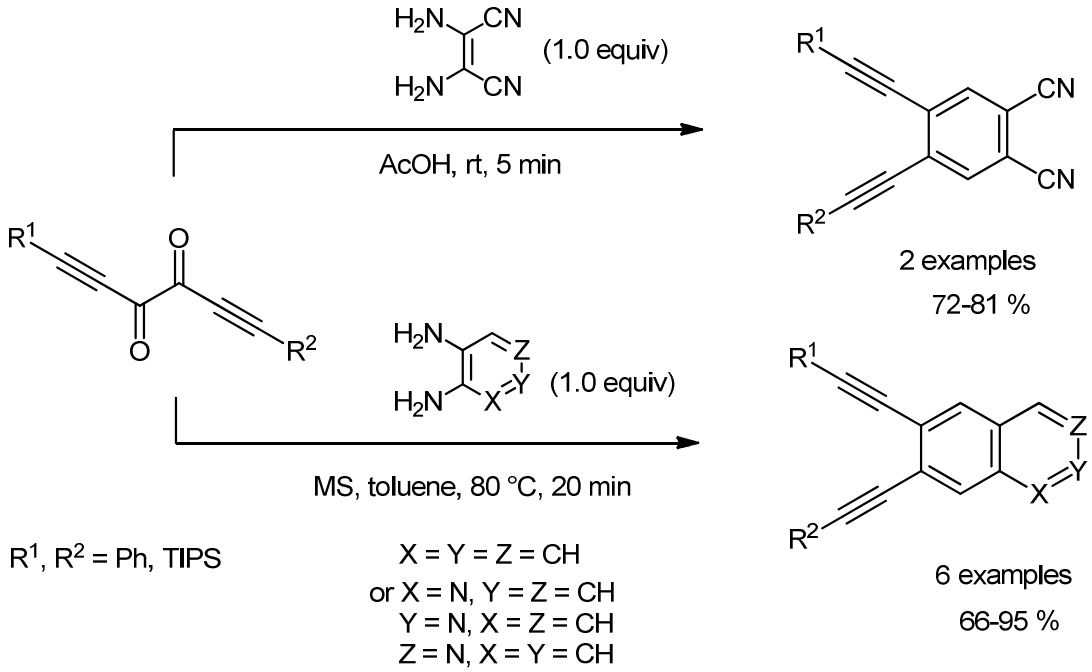
2.6.2 Synthesis and reactivity of ynediones

The chemistry of ynones is well explored, and many approaches exist toward this structural motif (for a discussion, see chapter *2.6.1 Synthesis and reactivity of ynones*). On the other hand, ynediones are very difficult to access, and therefore only little attention has been paid to them as building blocks in organic synthesis. However, ynediones possess an additional carbonyl group and therefore a 1,2-diketone motif, which makes them very promising structural elements in diversity oriented synthesis of various classes of heterocycles (Scheme 75).



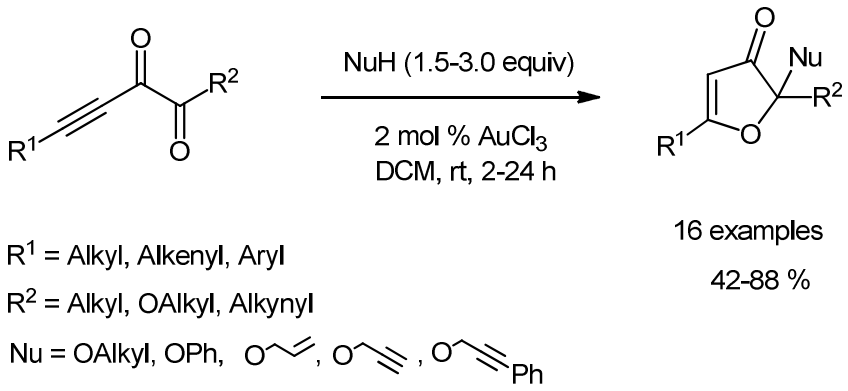
Scheme 75. Some modes of potential reactivity of ynediones.

The 1,2-diketone functionality of diynediones has been used in the synthesis of *ortho*-dialkynyl (hetero)cycles via cyclocondensations with diaminomaleic acid dinitrile or (hetero)aromatic *ortho*-diamines (Scheme 76).[301]



Scheme 76. Preparation of *ortho*-dialkynyl (hetero)arenes from diynediones.

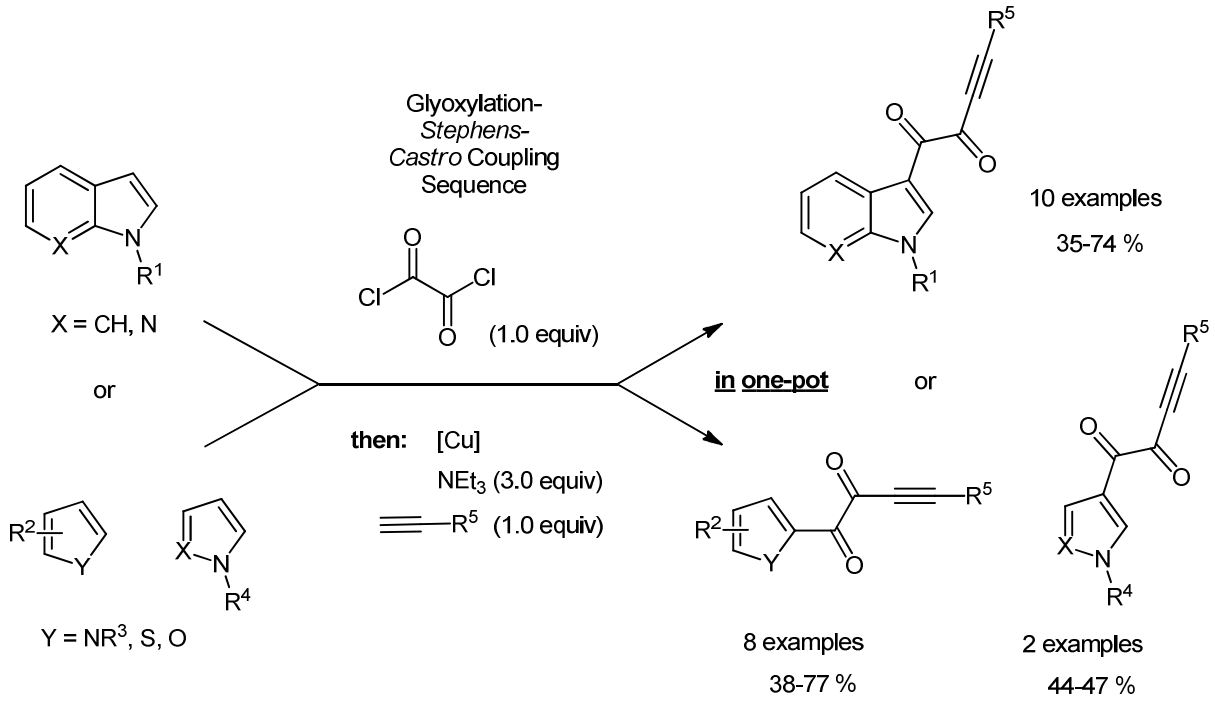
A rare example of a synthetic application of ynediones is a Au(III)-catalyzed reaction with nucleophiles (used in excess) followed by cyclization to form furanones (Scheme 77).[302]



Scheme 77. Au(III)-catalyzed synthesis of furanones from ynediones.

This reactivity was not adressed in the investigations described in this thesis. In conclusion, prior to this thesis neither general accesses to ynediones have been described nor the reactivity of ynediones has been thoroughly investigated.

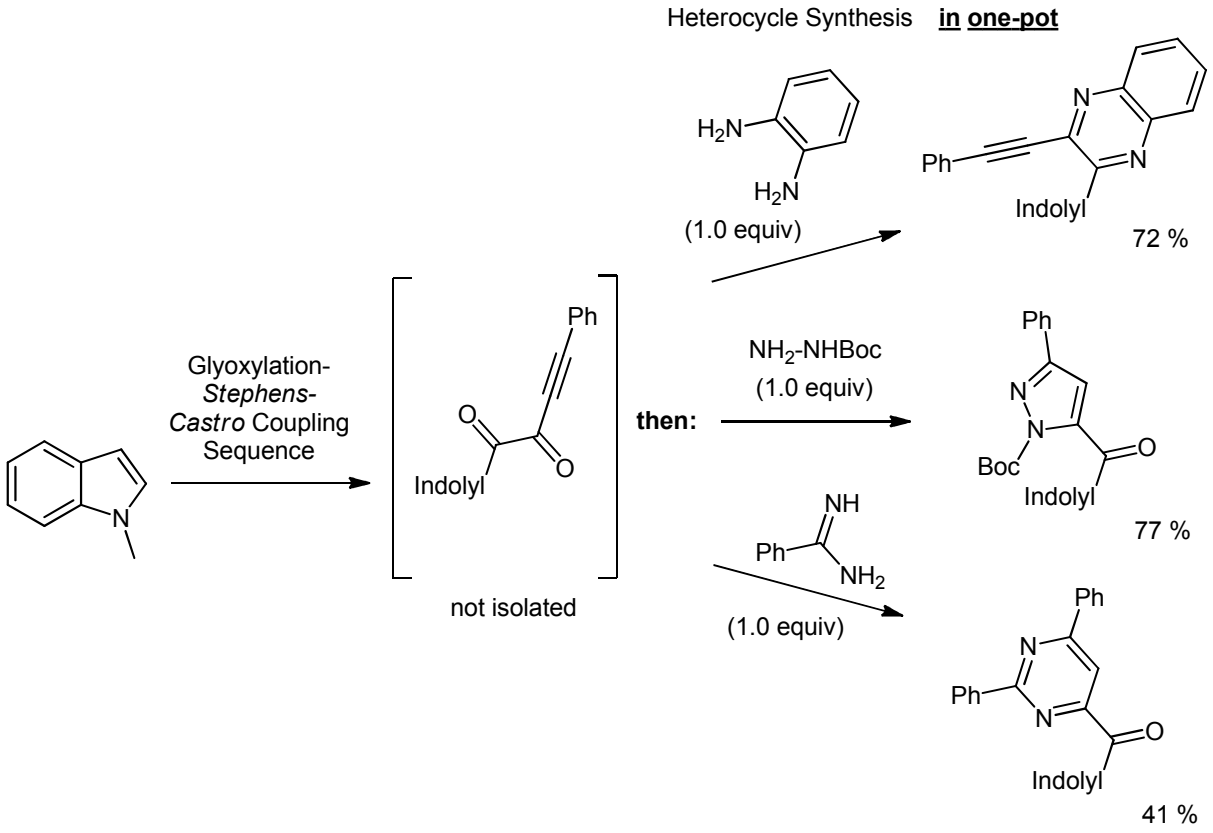
In the framework of this thesis, by omitting Pd responsible for the decarbonylative outcome of the *Sonogashira* coupling of glyoxylyl chlorides,[355] ynediones as novel useful synthetic intermediates can be obtained in a mild, concise, and straightforward fashion (Scheme 78).[303]



Scheme 78. One-pot synthesis of ynediones as valuable synthetic building blocks.[303]

The sequence is not restricted to indoles and 7-azaindole but could also be successfully extended to other electron rich heterocycles such as pyrroles, pyrazoles, thiophenes, and furans. No exotic ligand or additives are required, and the sequence gives a direct access to ynediones, whose synthetic potential has yet to be disclosed.

As an illustration of the versatility of the obtained ynediones in the synthesis of heterocyclic compounds, 5- and 6-membered *N*-heterocycles could be constructed via novel four-component syntheses (Scheme 79).[303] An unprecedented strategy toward selective and convenient synthesis of 5-acylpyrazoles was disclosed.



Scheme 79. One-pot syntheses of diverse heterocycles using ynediones as intermediates.[303]

Diverse heterocycles are obtained in an atom economical fashion since all reactants are used in strictly equimolar amounts.

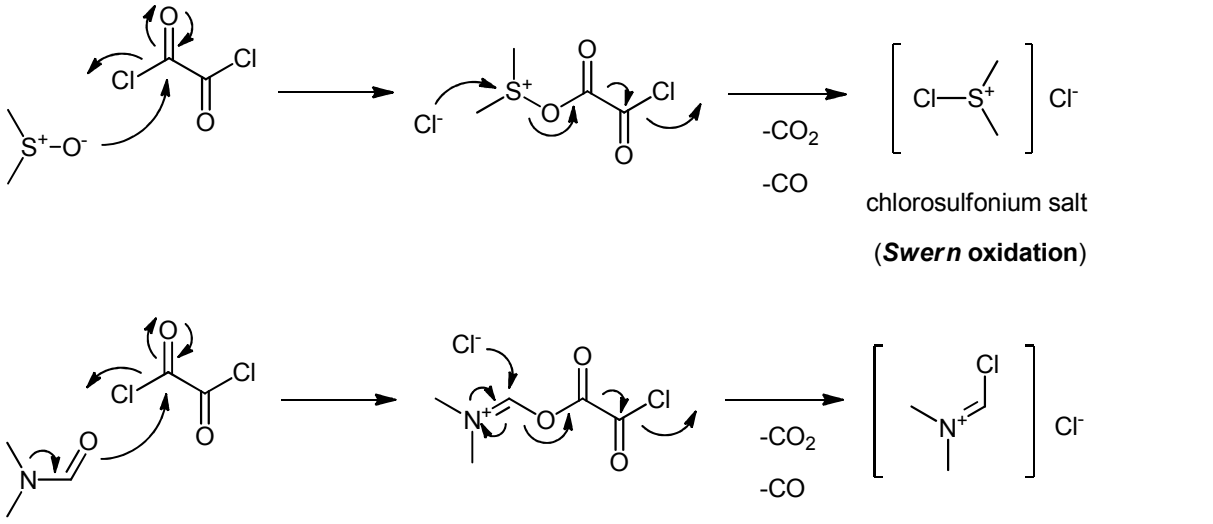
These results are part of this cumulative dissertation (**publication 3.4**).

2.7 Oxalyl Chloride in Organic Synthesis

Development of novel processes involving small molecules is a tremendously important area of research in synthetic organic chemistry. Oxalyl chloride[304] is an extremely versatile and extensively used C_2 reagent in the organic synthesis. Despite being a very reactive biselectrophile, it can be handled conveniently in the laboratory without the need for special equipment and can be simply transferred to the reaction flask via syringes in the air atmosphere.

As a donor of two carbonyl groups, oxalyl chloride has found applications in reactions with binucleophiles such as silyl enol ethers and 1,3-bis-silyl enol ethers to form various oxygen heterocycles,[305] in a synthesis of 5-oxo-2,5-dihydro-1*H*-pyrroles,[306] or in an approach to *N*-methylisatins.[307]

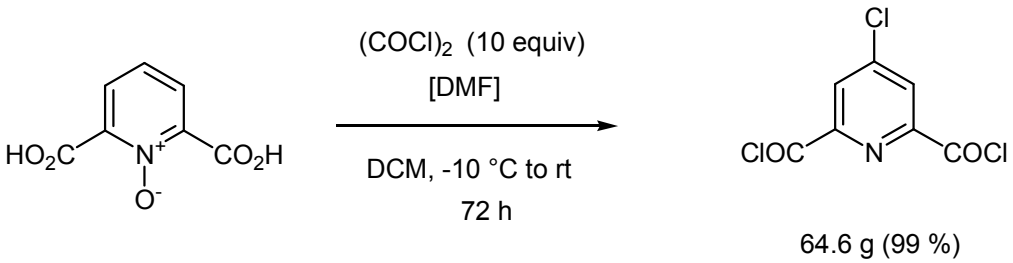
Moreover, oxalyl chloride is a reagent of choice in several important transformations such as *Swern* oxidation and *Vilsmeier-Haack* formylation. In these reactions oxalyl chloride readily decomposes to generate an active species, which is required for the key step (Scheme 80).



Scheme 80. Generation of active species in the *Swern* oxidation and *Vilsmeier-Haack* formylation reactions.

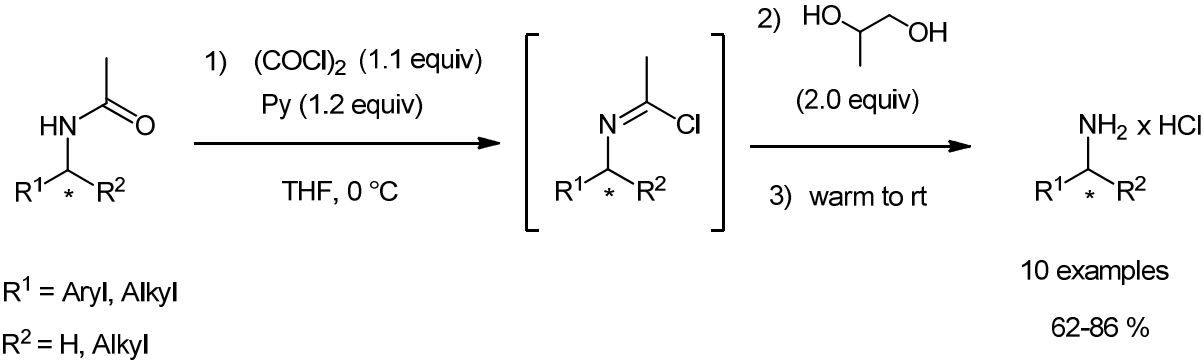
Since only volatile byproducts are formed (CO and CO_2), the reactions are generally very clean. This offers opportunities for designing efficient one-pot reactions.

In a large-scale preparation of a useful building block 4-chloropyridine-2,6-dicarbonyl dichloride, oxalyl chloride was crucial to achieve an excellent yield of the desired product (Scheme 81).[308]



Scheme 81. Deoxygenative chlorination of a pyridine *N*-oxide with oxalyl chloride.

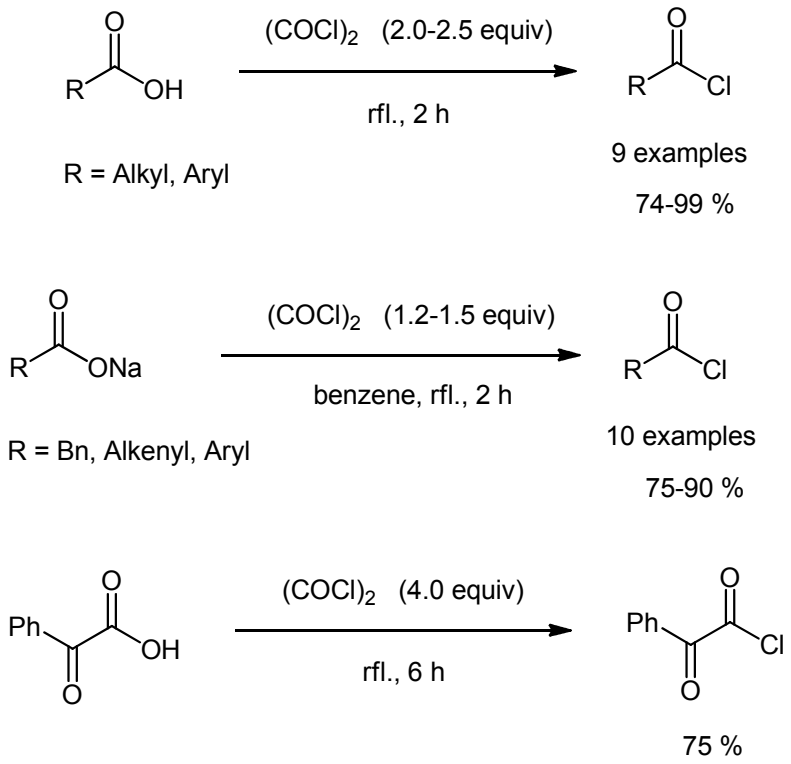
Amides can be reacted with oxalyl chlorides to give imidoyl chlorides. Recently, this reaction could be used in a deprotection of secondary acetamides (Scheme 82).[309] The reaction conditions are mild enough to allow for a deprotection without epimerization of the amino center.



Scheme 82. Deprotection of secondary acetamides using oxalyl chloride.

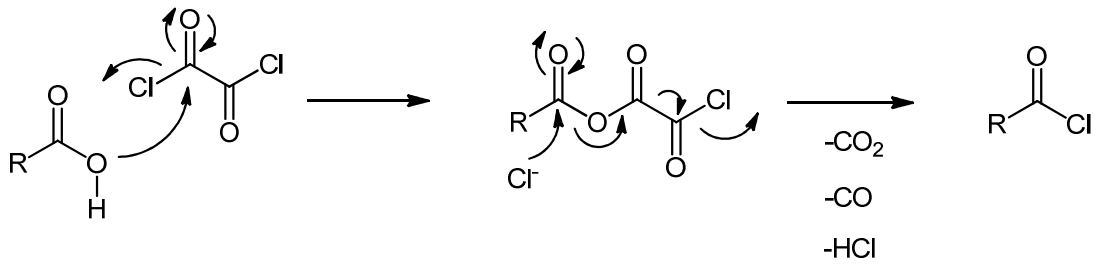
In another recent application, in situ formed imidoyl chlorides are utilized in a one-pot synthesis of 2-imidazolines via reaction with aziridines.[310]

Oxalyl chloride can be used as a reagent for the preparation of carboxylic acid chlorides from carboxylic acids or their salts (Scheme 83).[311] Usually, an excess of oxalyl chloride is used, especially in the case of the phenylglyoxylic acid.[312]



Scheme 83. Preparation of carboxylic acid chlorides from carboxylic acids using oxalyl chloride.

Again, only gaseous byproducts are formed during this clean reaction (Scheme 84). DMF is often applied as a catalyst to activate oxalyl chloride via formation of the *Vilsmeier* reagent (Scheme 83).[313]

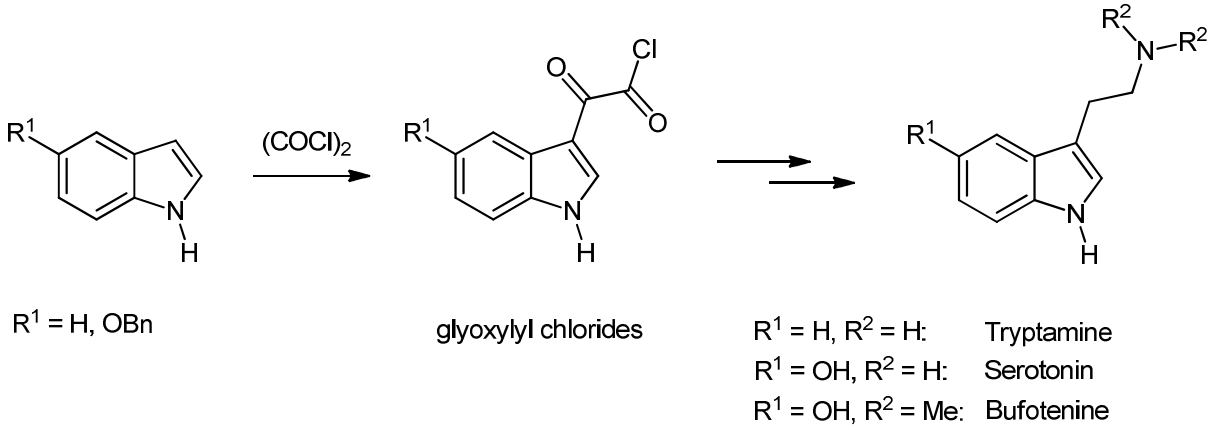


Scheme 84. Mechanism of the chlorodehydration of carboxylic acids.

Just recently, this in situ activation of aliphatic carboxylic acids was used in a *Barton* reductive decarboxylation using chloroform as a solvent and as a hydrogen atom donor.[314] Similarly, phosphine oxide reacts with oxalyl chloride to form the chlorophosphonium salt, again releasing only gaseous CO and CO_2 as byproducts, and can be

used as a catalyst in dichlorination of epoxides under *Appel* conditions.[315] Another interesting recent application is the synthesis of 2,3,4,5-tetramethoxybenzoyl chloride, which was reported to be a constituent of the fruiting body of the fungus *Antrodia camphorata*, in order to prove the correctness of the structure assignment of the natural product.[316]

In 1954, *Speeter* and *Anthony* reported an ingenious reaction of oxalyl chloride with indoles to give glyoxylyl chlorides in a very smooth way (Scheme 85).[317] The reaction belongs to the *Friedel-Crafts*-type acylations, thus electron rich unprotected or EDG-protected indoles are suitable substrates. The reaction conditions are very mild, proceeding typically in ethereal solvents at 0 °C or room temperature without need for *Lewis* acid assistance. The reaction has been developed to gain an efficient access to tryptamine derivatives.

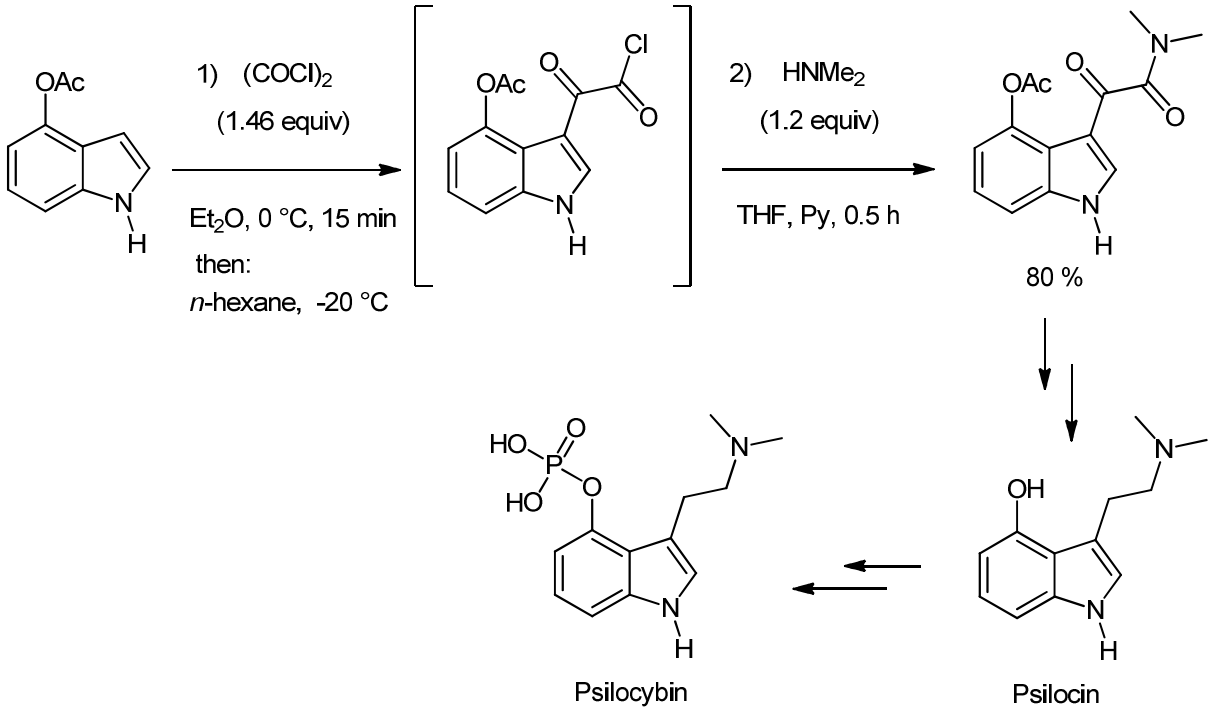


Scheme 85. The *Speeter-Anthony* reaction of indoles with oxalyl chloride.

Glyoxylyl chlorides are obtained as beautiful bright yellow or orange crystalline solids in very high yields. They can be isolated, but are typically immediately used due to the limited stability to storage. In most cases, oxalyl chloride is used in excess (1.2-3.0 equivs) and is removed after the reaction is complete.

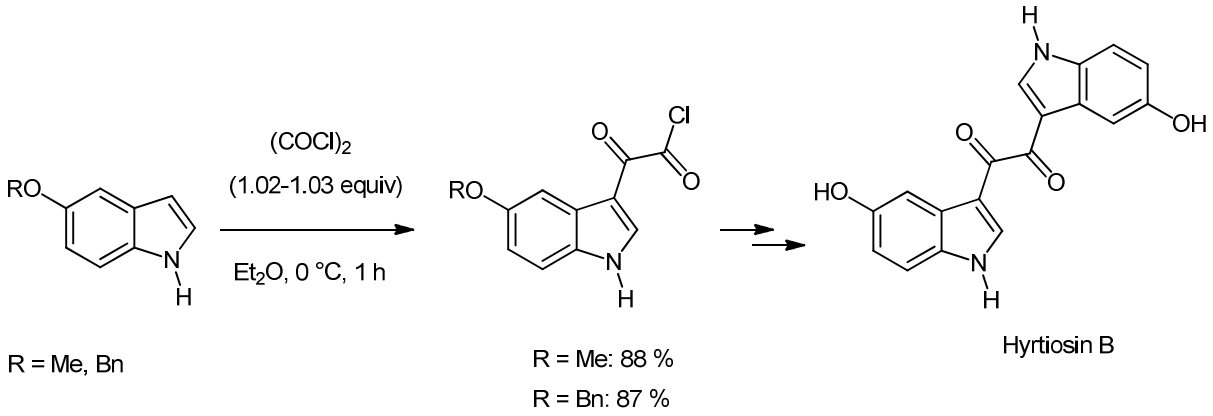
The reaction has been found to be very general for indoles and tolerates many functional groups including OMe, OBn, OAc, Alkyl, Aryl, Cl, F, OCF_3, and other functionalities at C-2, C-4, C-5, C-6, and C-7. This reaction has found numerous applications in the synthesis of natural products and biologically active molecules.[318] In the most cases, it is used in the beginning of a synthesis.

A typical example is the synthesis of psilocin and psilocybin, two principal hallucinogenic constituents of “magic mushrooms” (Scheme 86).[319]



Scheme 86. Synthesis of psilocin and psilocybin using the *Speeter-Anthony* reaction.

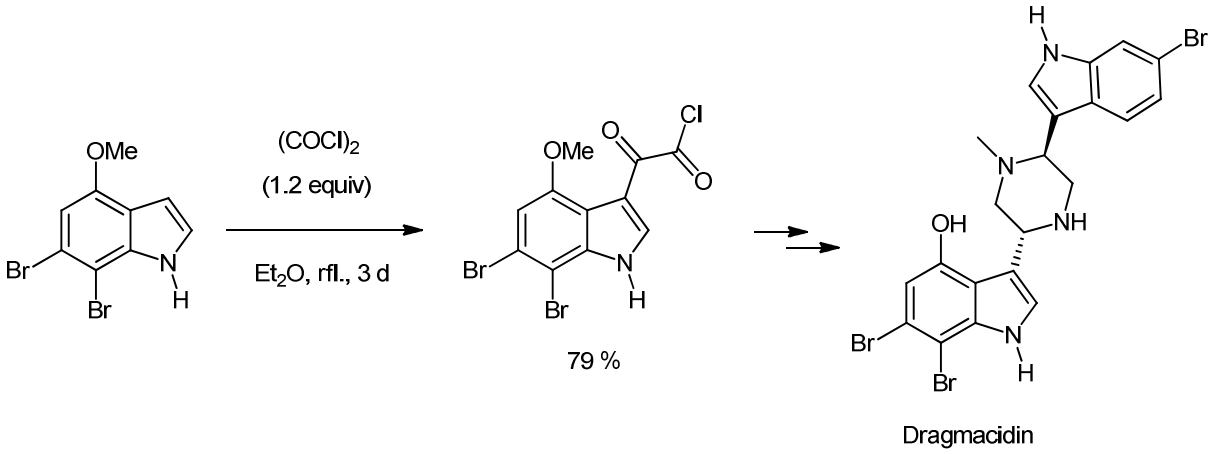
The marine natural product hytriosin B, a bisindole alkaloid isolated from the Okinawan marine sponge *Hyrtios erecta*, has been synthesized using the glyoxylation of 5-methoxy- or 5-benzyloxyindole (Scheme 87).[320]



Scheme 87. Glyoxylation in the synthesis of hyrtiosin B.

A similar strategy has been applied for the synthesis of coscinamides A and B, indolyl enamides isolated from the marine sponge *Coscinoderma* sp..[321]

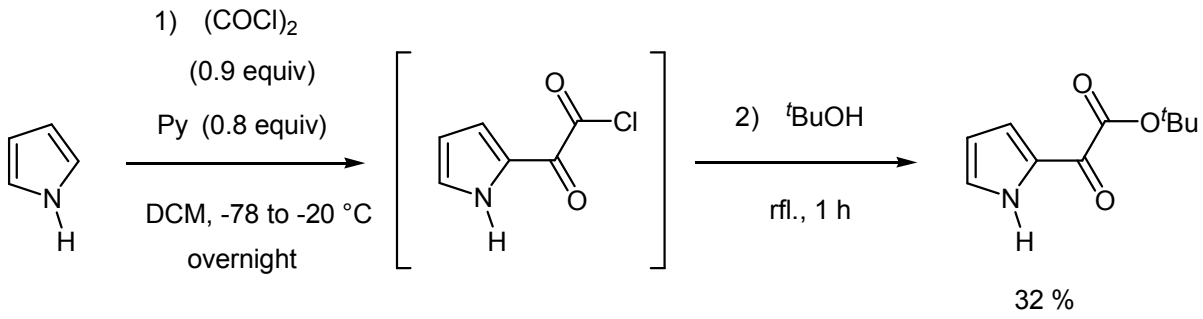
Another cytotoxic marine bisindole alkaloid (±)-dragmacidin from the deep water sponge *Dragmacidin* sp. has been synthesized using the glyoxylation reaction (Scheme 88).[322]



Scheme 88. Glyoxylation in the synthesis of (±)-dragmacidin.

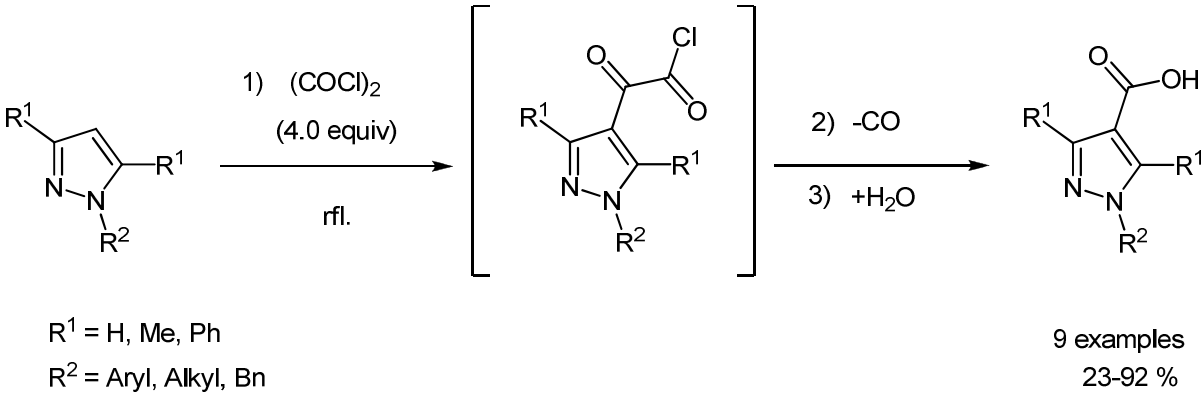
Examples of glyoxylation reactions of substrates other than indole are rare. The 3-position of azaindoles is known to be inert in comparison to that of indole as a consequence of the electron deficient nature of the pyridine moiety, which reduces the overall nucleophilicity of the heterocyclic system. This is further complicated by the potential of oxalyl chloride, which is typically used in excess, to acylate the pyridine nitrogen atom. For that reason, the reaction of 7-azaindole with oxalyl chloride in Et_2O was unproductive, while indole, under the same conditions, provided the corresponding 3-glyoxylated product in an excellent yield.[323] Benzyl protected 7-azaindoles, however, have been shown to react with oxalyl chloride in a similar way as indoles, but the reflux temperature was needed due to the diminished π-nucleophilicity of 7-azaindole compared to indole.[324]

Pyrrolyl glyoxylyl chloride has been used as intermediate in the synthesis of the corresponding ester in a rather low yield (Scheme 89).[325]



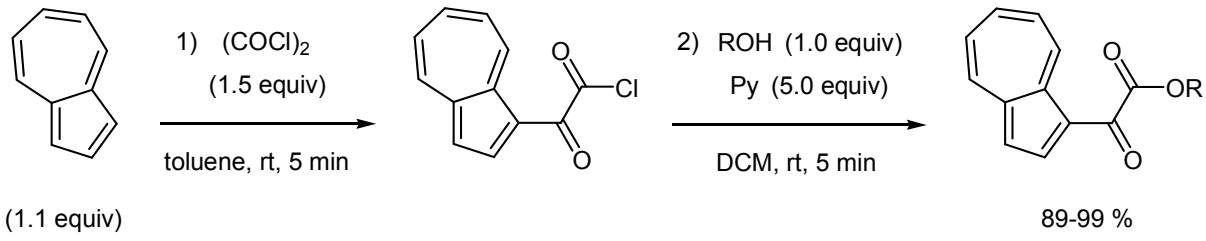
Scheme 89. Glyoxylation of pyrrole.

An interesting method has been described for the preparation of pyrazole-4-carboxylic acids (Scheme 90).[326] The reaction of pyrazoles with an excess of oxalyl chloride led to decarbonylation of the intermediate glyoxylyl chlorides.



Scheme 90. Glyoxylation of pyrazoles.

The hydrocarbon azulene was reacted with oxalyl chloride to form the corresponding glyoxylyl chloride. After trapping with an alcohol, a new colored azulen-1-yl-oxo-acetyl (Az) protective group was introduced, which is useful in the sugar chemistry (Scheme 91).[327]

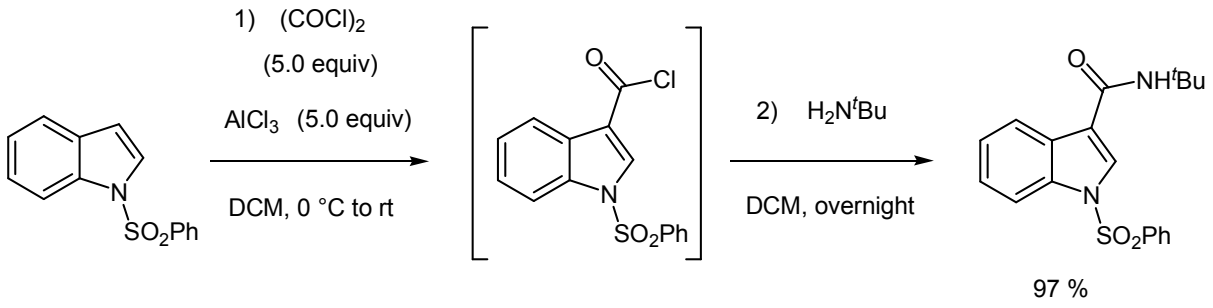


Scheme 91. Reaction of azulene with oxalyl chloride.

Very soon after the discovery of *Speeter* and *Anthony*, an attempt was undertaken to perform a decarbonylative reaction of the 3-indoleglyoxylyl chloride.[328] However, thermal decomposition in tetrachloroethane at 115-120 °C yielded only 16-23 % of the corresponding 3-indole carbonyl chloride along with polymeric amide arising from selfamidation.

Moreover, a facile decarbonylation of Pd(II)-alkyloxalyl complexes at room temperature in solution has been described to give the corresponding alkyloxycarbonyl complexes. Interestingly, by addition of phosphane ligands, the decarbonylation was retarded or even inhibited.[329] In contrary, the Pt(II)-alkyloxalyl complexes are stable at room temperature in solution. Despite these findings, no preparatively useful method utilizing metal-catalyzed decarbonylative reaction of glyoxylyl chlorides has been described so far.

Ultimately, oxalyl chloride can be used as a CO donor in combination with *Lewis* acids. *Gribble* demonstrated that $(COCl)_2/AlCl_3$ can be used as synthetic equivalent of phosgene in reaction with *N*-$PhSO_2$ protected indole (Scheme 92).[330] However, a large excess of both reagents had to be used.

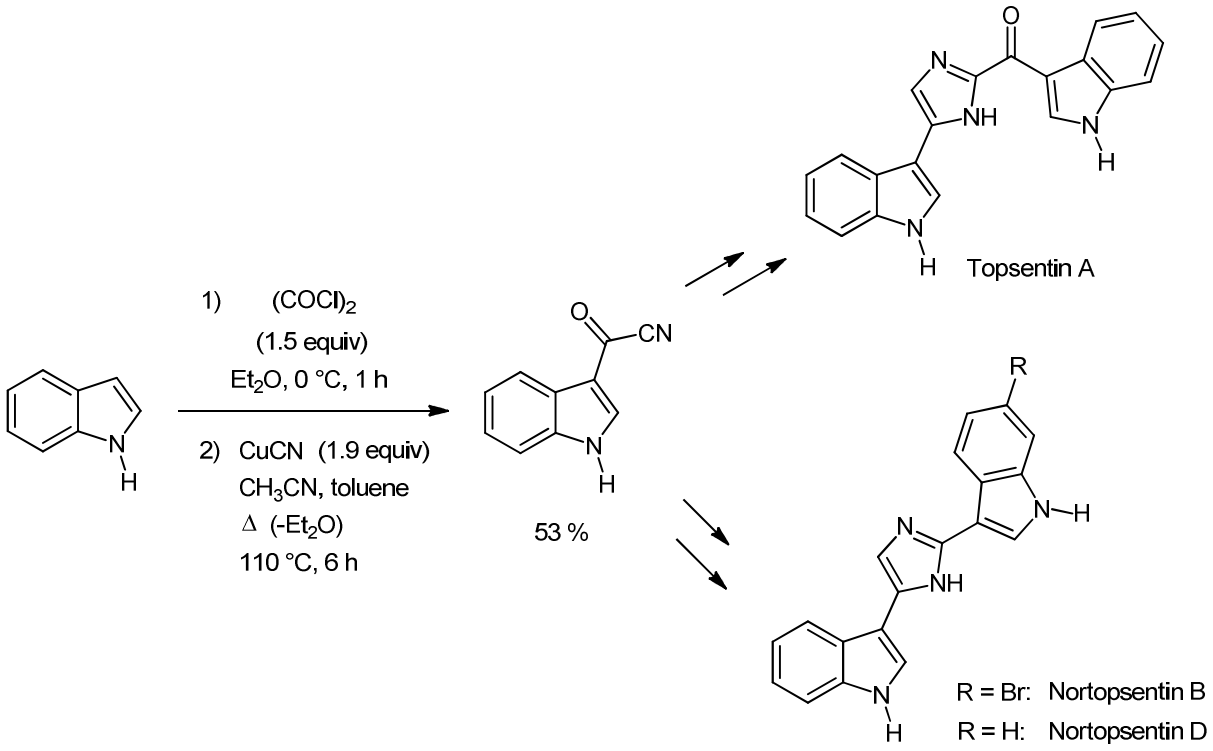


Scheme 92. $(COCl)_2/AlCl_3$ as a synthetic equivalent of $COCl_2$.

Consequently, metal salts tend to promote the decarbonylation. For example, a decarbonylation was observed when a mixed alkynylalane was coupled with oxalyl chloride.[282a] The corresponding diynone was obtained in a preparatively useful yield. This behavior of oxalyl chloride is typical of reactions under *Friedel-Crafts* conditions.

Furthermore, a copper-mediated decarbonylation of indolyl glyoxylyl chloride has also been described to deliver an acyl cyanide,[331] which was used in the synthesis of bisindole alkaloids (nor)topsentins (Scheme 93).[332] An excess of oxalyl chloride

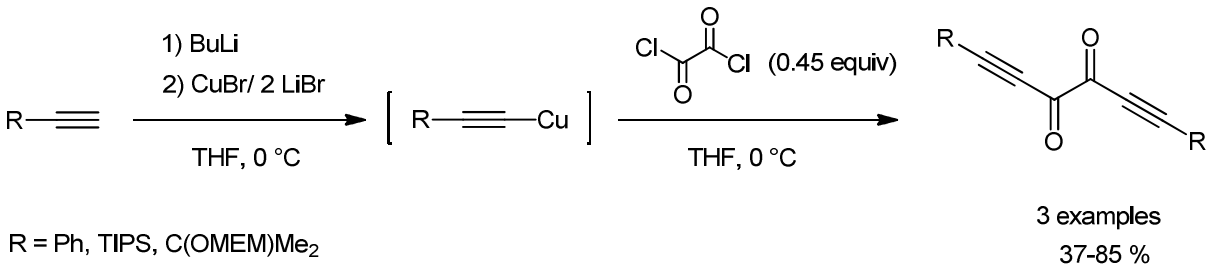
and copper cyanide had to be used and the decarbonylation proceeded at elevated temperatures.



Scheme 93. Cu-mediated decarbonylative cyanation of the indolyl glyoxylyl chloride.

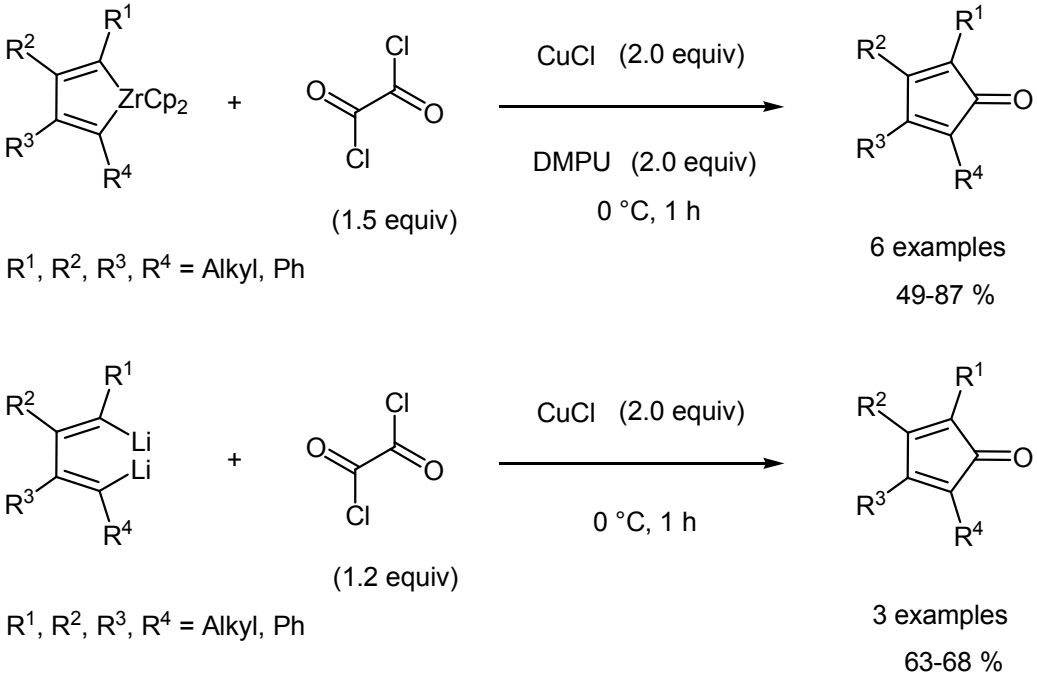
Despite the fact that glyoxylyl chlorides are very reactive and potentially very useful electrophilic components in cross-coupling reactions, prior to this work no attempts have been made to investigate this reactivity.

Interestingly, although oxalyl chloride is a very “carbonyl group rich” compound, it has found little attention in catalytic carbonylative reactions. Stoichiometric reactions of two equivalents of organometallic compounds, such as *Grignard* reagents, organolithium, organotin, or organocopper compounds, with oxalyl chlorides to give 1,2-diorgano-1,2-diones are more common.[333] A representative example is the preparation of symmetrical diynediones used in the synthesis of (hetero)arenes as already discussed in chapter *2.6.2 Synthesis and reactivity of ynediones* (Scheme 94).[301]



Scheme 94. Synthesis of symmetrical diynediones.

One report appeared in the literature, where oxalyl chloride was used as a one carbonyl donor (Scheme 95).[334] However, copper was applied in a stoichiometric rather than catalytic amount. Moreover, oxalyl chloride had to be used in excess.



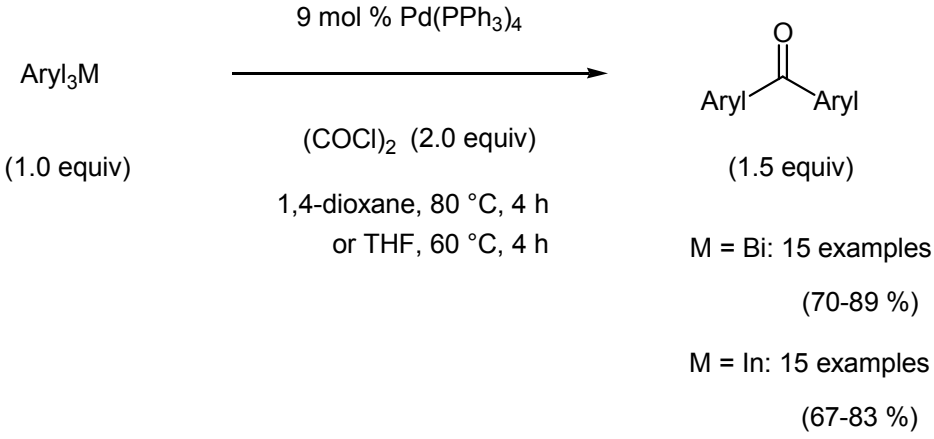
Scheme 95. Synthesis of cyclopentadienones using oxalyl chloride as a CO donor and stoichiometric amount of Cu(I).

Later, the same group developed a Cu(I)-catalyzed approach to cycopentenones by a reaction of zirconacyclopentenes with oxalyl chloride, which served as a C_1 synthon.[335]

In 1979, *Stille* made the observation that acetone was produced in 10 % yield in the reaction of oxalyl chloride with tetramethyltin under Pd-catalysis.[336] The assumption

was made that unreactive Pd carbonyl complexes were formed resulting in a low yield of the decarbonylated product. As a consequence, the utilization of oxalyl chloride in this direction was not further investigated.

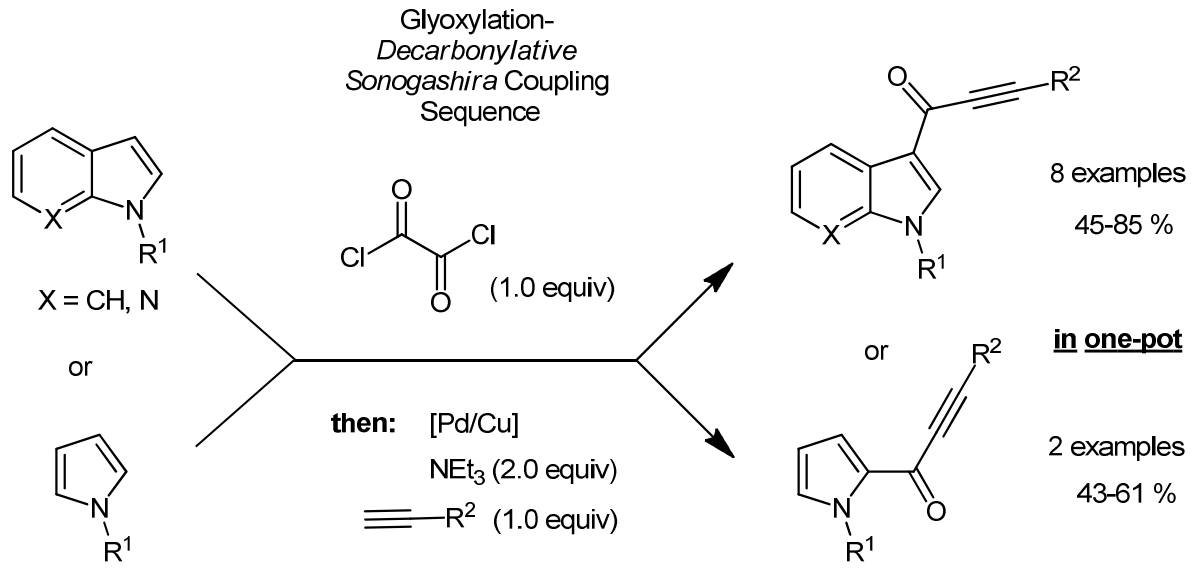
Very recently, in 2010 oxalyl chloride has been reported to serve as a C_1 carbonyl synthon in carbonylations of triarylbismuth and triarylindium nucleophiles under palladium catalysis.[337] Symmetrical ketones with simple aryl substituents can be obtained in moderate to good yields (Scheme 96). However, this method can hardly become synthetically useful due to the need for bismuth or indium organyls as starting materials. Moreover, oxalyl chloride is used in excess.



Scheme 96. Synthesis of symmetrical ketones from triarylbismuth and –indium organometallics.

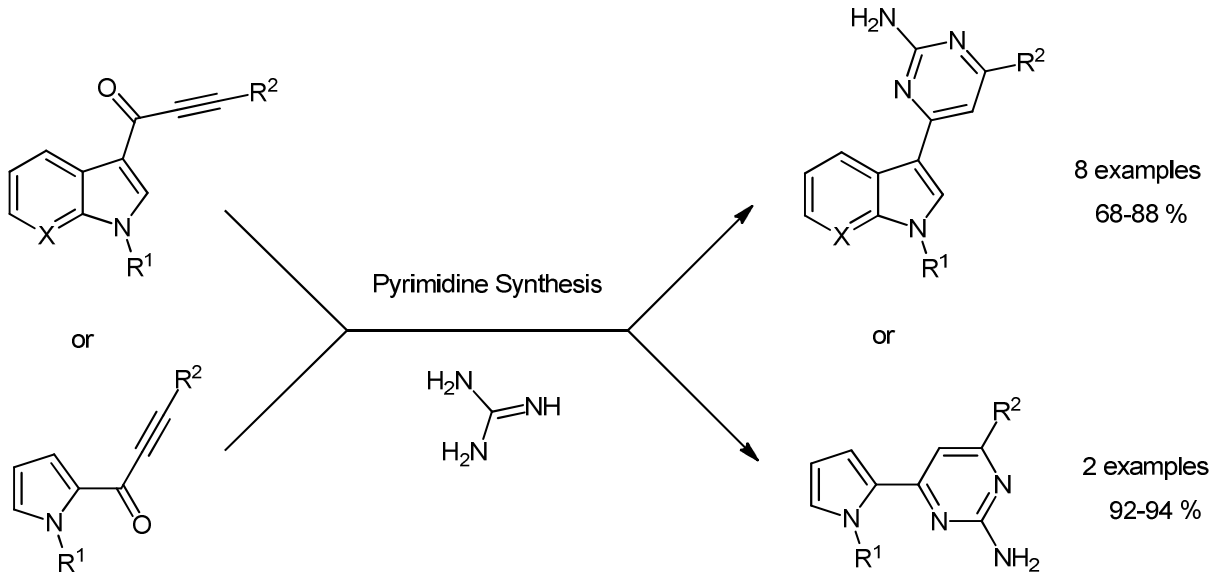
In conclusion, many reagents have been described as CO surrogates in carbonylative reactions[338],[339] including metal carbonyls, especially the nontoxic $Mo(CO)_6$,[119],[120],[340] carbamoylsilanes and –stannanes,[341] DMF,[342] DMF/$POCl_3$,[343] formic acid,[344] acetic formic anhydride,[345] Ac_2O/HOOLi,[346] chloroform/KOH,[347] methyl and 2-pyridylmethyl formates,[348] benzyl formate,[349] ammonium formate,[350] formaldehyde,[351] benzaldehydes,[352] and cinnamaldehyde.[353] However, the “carbonyl group rich” oxalyl chloride has found undeserved little attention. In spite of that, it possesses an enormous synthetic potential and its utility as a C_1 synthon and as a surrogate for the malicious toxic gas phosgene[354] (bp 8 °C) and for the toxic gas carbon monoxide in cross-coupling reactions should be explored more intensively.

In the framework of this thesis, it was shown that decarbonylative carbonylation by a consecutive glyoxylation of electron rich heterocycles such as indoles, 7-azaindole, or pyrroles with oxalyl chloride and subsequent Pd/Cu-catalyzed decarbonylative alkynylation with terminal alkynes furnishes alkynones in fair yields under mild conditions (Scheme 97).[355] The sequence works under standard *Sonogashira* coupling conditions ($PdCl_2(PPh_3)_2$/CuI/NEt_3) without need for exotic ligands or additives. No reagent excess is needed as well. The unprecedented decarbonylative alkynylation is a new modification of the *Sonogashira-Hagihara* coupling procedure.



Scheme 97. One-pot synthesis of ynones via glyoxylation – decarbonylative *Sonogashira* coupling sequence.[355]

As an illustration for the utility of the obtained ynones in the heterocycle synthesis, 4-(indol-3-yl)- and 4-(7-azaindol-3-yl)-2-amino pyrimidines, derivatives of the natural products meridianins and their 7-azaindole analogs meriolins, can be readily obtained in one step (Scheme 98).[355]



Scheme 98. Implementation of ynones in the synthesis of 2-amino pyrimidines.[355]

These results are part of this cumulative dissertation (**publication 3.5**).

2.8 *N*-Heterocycles

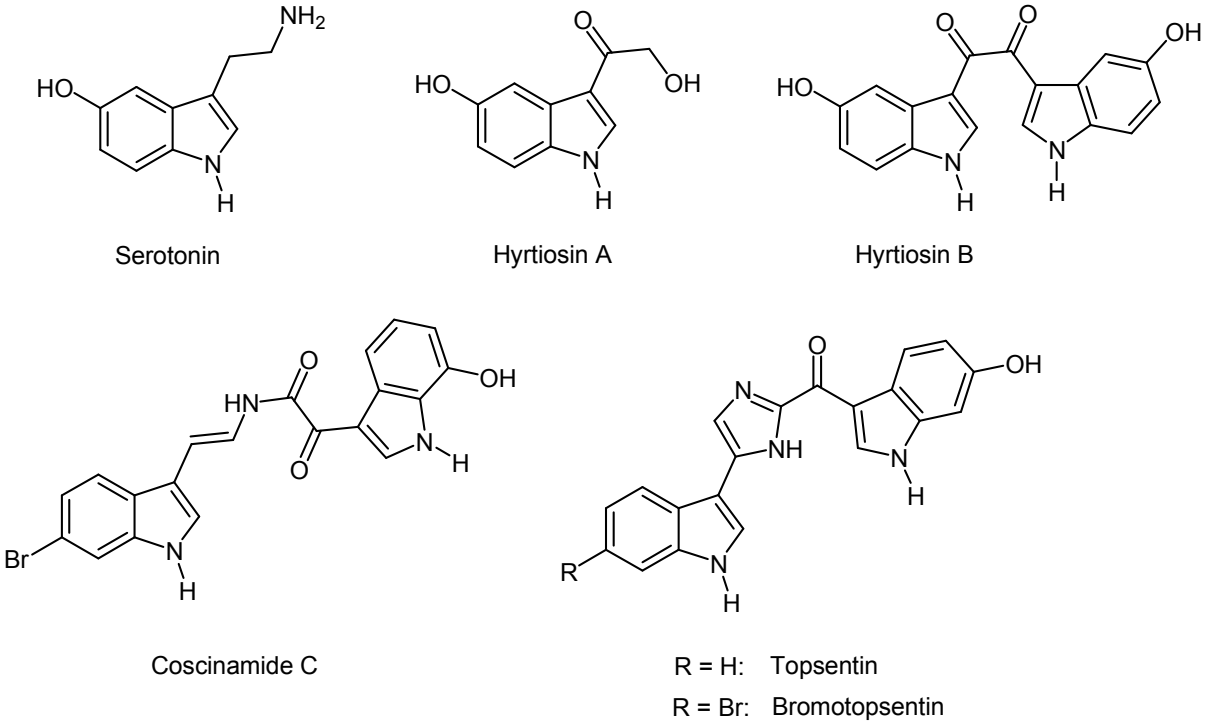
Nitrogen-heterocyclic frameworks are ubiquitous in natural products, pharmaceuticals, organic materials, and numerous functional molecules. Especially, small “drug-like” heterocycles are predominant building blocks in medicinal chemistry.[20] Privileged scaffolds, the term coined by *Evans* in 1988,[356] are dominated by heterocyclic motifs, especially by *N*-heterocycles.[357]

Despite numerous available methods, there is an ongoing search for simple and straightforward routes to heterocycles. Among new synthetic approaches to this compounds, many transition metal-catalyzed syntheses continue to appear.[358]

MCRs offer a plenty of possibilities to design novel heterocycle syntheses. Besides domino MCRs that are purely based on organometallic catalysis the sequential and consecutive combination with condensation, addition, and cycloaddition steps opens a vast playground for the invention of new sequences and strategies in heterocyclic synthesis[15],[359] or with heterocycles as substrates.[360]

2.8.1 Indoles

The indole scaffold represents one of the most important privileged structures since it is capable of binding to multiple receptors with high affinity.[34] Favorable features rendering indole an outstanding privileged structure are discussed in a recent review by *Fraga*.[361] Indole is broadly widespread in nature[362],[460] and pharmaceutically relevant compounds.[402] Selected examples of natural products with hydroxylated indole units are displayed in Scheme 99. Further representatives, especially those bearing heteroaryl substituents at C-3 position of an indole, will be discussed in chapter *2.10 Indole alkaloids*.

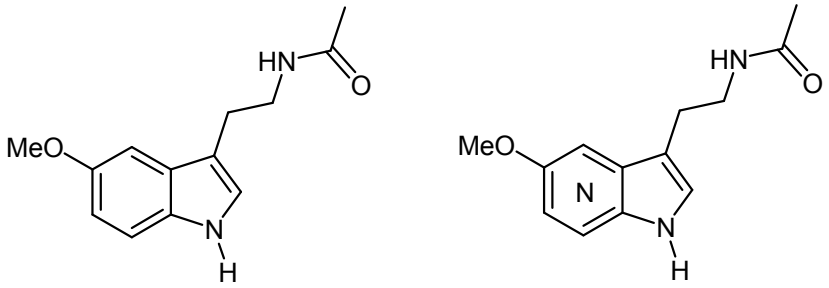


Scheme 99. Hydroxylated indole – a frequent structural motif in alkaloids.

Not suprisingly, the synthesis and functionalization of indoles has been the object of research for over 100 years and for many generations of researchers. Today, this scaffold continues to attract considerable interest of synthetic chemists, and numerous metal-catalyzed approaches continue to be developed, with Pd-catalyzed reactions such as *Larock* and *Cacchi* indole syntheses being the most popular methodologies.[363]

2.8.2 Indole bioisosters

Besides indoles, their aza analogs, i.e. indazole and azaindoles, play an increasingly important role as scaffolds for biologically active molecules. The azaindole and indazole moieties differ only by the presence of an additional nitrogen atom, and thus exhibit an excellent potential as bioisosters[364] of the indole ring system. Although considerably less frequent in nature, they constitute essential subunits in many pharmaceutically important compounds, and have been very valuable for synthetic and medicinal chemists. “Indazole is a relatively seldom used but effective pharmacophore in medicinal chemistry as illustrated by its applications in pharmaceutical agents in fields as diverse as CNS disorders (granisetron), antiinflammatory area (bendazac and benzydamine), oncology (lonidamine), and HIV protease inhibition (SE063)”.[373b] Azaindoles represent an extremely rich source of potentially active molecules with numerous possibilities for the preparation of analogs with different and unexpected behavior and improved drug properties such as metabolic stability, solubility, and oral bioavailability.[365] As early as in 1955, 7-azagramine, 7-azascatole, and 7-azatryptophan were prepared as aza analogs of the alkaloid gramine, the fragrance scatole, and the amino acid tryptophan.[366] More recently, azaindole analogs of melatonin, the key neurotransmitter in the CNS, have been prepared (Scheme 100).[367]



Scheme 100. Melatonin and its 7-azaindole analogs.

7-Azaindole is of particular interest because of its pronounced ability to bind to the hinge region of kinases via its H-donor/H-acceptor motif, thus mimicking purine (i.e. the pyrimidine portion of ATP).[182],[374],[368],[372] Consequently, the chemistry of 7-azaindole increased tremendously in the last decade leading to a wide variety of new synthetic methods for the preparation of derivatives for use in medicinal chemistry. Synthesis, reactivity, and biologically active derivatives of this interesting heterocycle were recently reviewed.[369] Similarly, 7-deazapurine[370] and pyrazolo[1,2-*b*]pyridine[371] are important structural motifs found in a wide range of biological niches. In contrast, 4,7-diazaindole core structure is a new promising scaffold that will certainly lead to many interesting derivatives in the near future.

Also in biologically active indole bioisosters, aromatic and heterocyclic substituents at C-3 position are very common (Figure 5).[182],[369],[372]

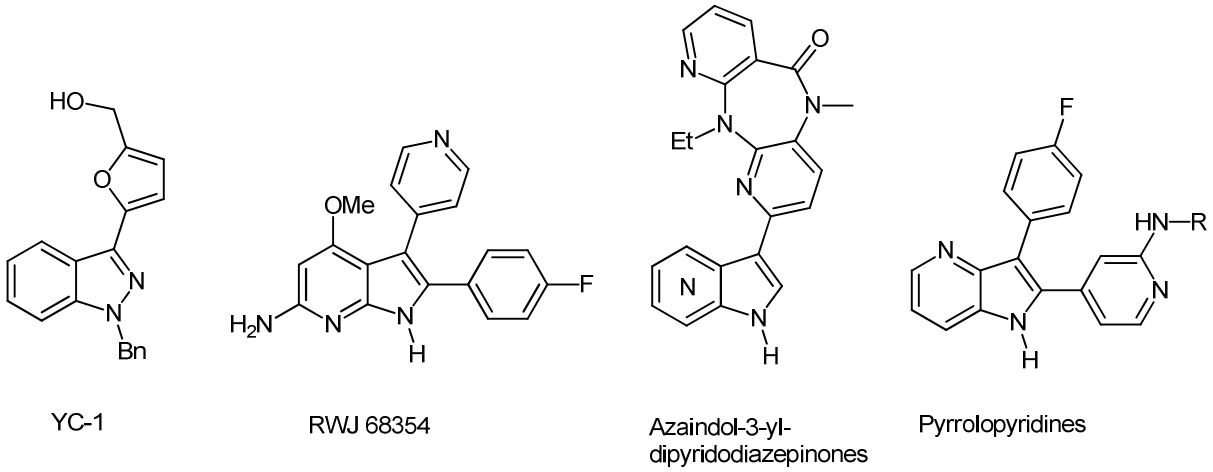


Figure 5. Indole bioisosters with (hetero)aryl substituents at C-3.

For example, the 3-furylindazole YC-1 is a potent inhibitor of platelet aggregation.[373] RWJ 68354 is a strong, selective, and orally active inhibitor of p38 kinase in vitro (IC_{50} = 9 nM) and in vivo (ED_{50} < 10 mg/kg po).[374] Azaindol-3-yl-dipyridodiazepinones are analogs of nevirapine (i.e. viramune, non-nucleoside inhibitor of reverse transcriptase (RT)) that have been investigated as inhibitors of wild-type RT as well as its mutants but were not further pursued due to their high toxicity. These compounds showed different activities dependent on the presence and position of an additional nitrogen atom in the indole moiety.[375] 3-(4-Fluorophenyl)-2-(pyridine-4-yl)-1*H*-pyrrolo[3,2-*b*]pyridine is the core structure of p38 MAP kinase in-

hibitors with R = (S)-2-hydroxypropyl being a potent, selective, and orally bioavailable inhibitor.[376]

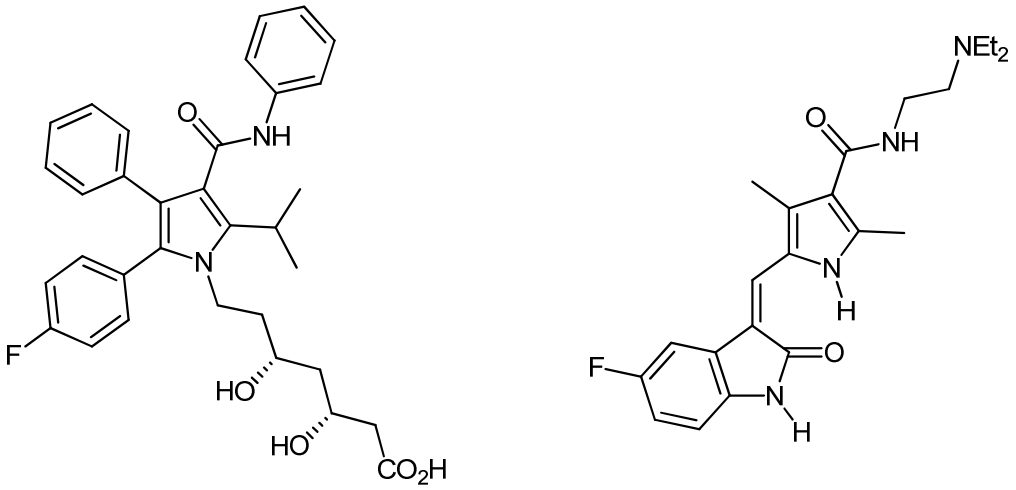
The development of further biologically active compounds with indole bioisosters as core structures is an extraordinarily active area of research in the medicinal chemistry.

2.9 Syntheses of Pyrroles

Pyrroles are among most prominent 5-membered heterocycles since they constitute important classes of natural products and synthetic pharmaceuticals.

The pyrrole nucleus is widespread in nature and is the key structural fragment of heme, vitamin B_{12}, chlorophyll, and cytochromes – tetrapyrrole pigments essential for life. Moreover, numerous secondary metabolites produced mainly by marine organisms and bacteria contain pyrrole.[377]

Many substituted pyrroles show important biological activities. A very prominent example of a pyrrole containing drug is the cholesterol lowering agent atorvastatin, world's largest selling pharmaceutical (2008 sales of US$: 12.4 billion). The "blockbuster" was developed by *Pfizer* and functions by binding to the active site of HMG-CoA reductase, thus inhibiting the enzyme (Figure 6). Sunitinib is a multiple inhibitor of receptor tyrosine kinases and is used clinically against GIST and renal cell cancinoma (Figure 6).



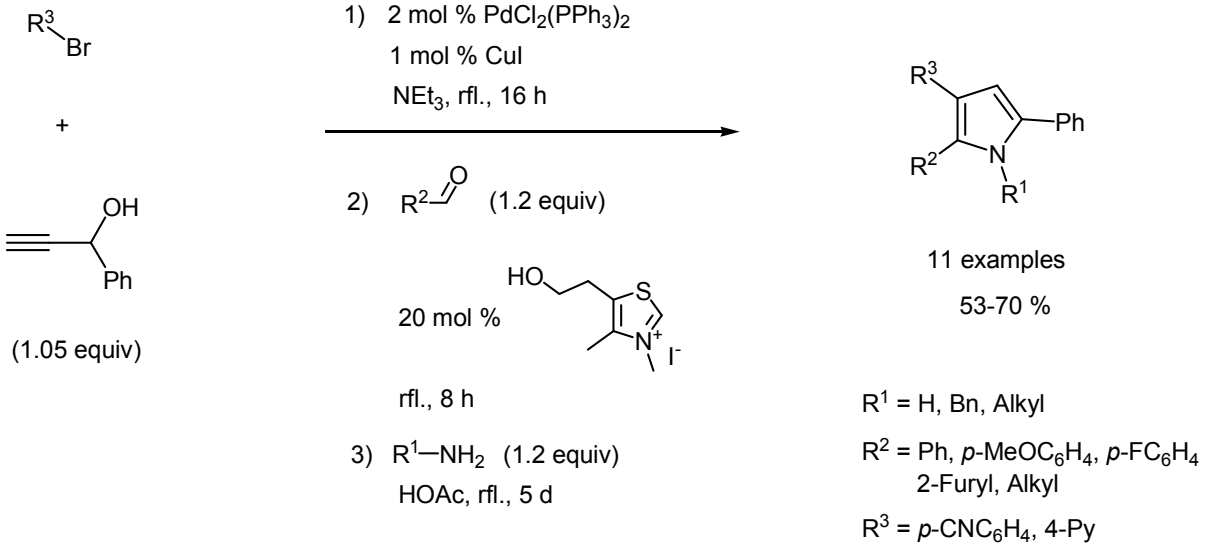
Atorvastatin Sunitinib

Figure 6. Structures of pyrrole-containing drugs atorvastatin (Lipitor®) and sunitinib.

Classical methods for the preparation of pyrroles include *Knorr*,[378] *Paal-Knorr*,[379],[380] *Hantzsch*,[381] and *Piloty-Robinson*[382] condensation reactions. How-

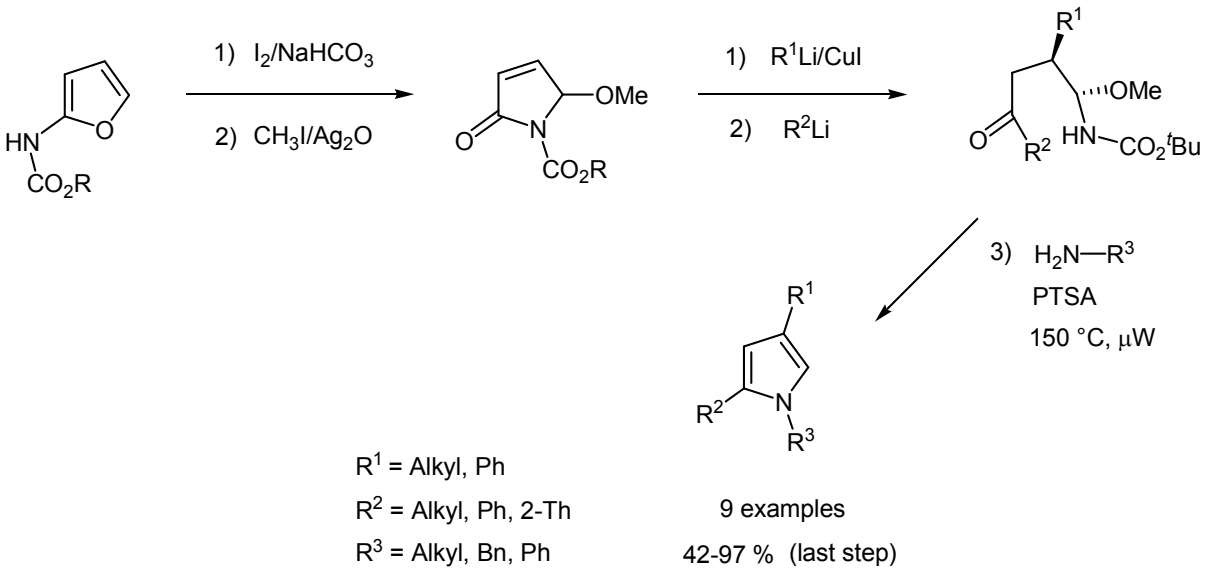
ever, these methods have some limitations with respect to harsh reaction conditions, as well as the regioselectivity and substitution patterns that can be assembled.

Therefore, the development of new pyrrole syntheses and synthetic strategies has remained an ongoing challenge,[383] and numerous syntheses continue to appear.[384] In particular, one-pot and multicomponent approaches have inevitably become increasingly important due to their elegance and practicability.[385],[386] For example, a four-component synthesis of 2,3,5-trisubstituted and 1,2,3,5-tetrasubstituted pyrroles was reported by *Müller*, which combined cross-coupling methodology (*Sonogashira* reaction) with classical condensation (*Paal-Knorr* pyrrole synthesis) chemistry (Scheme 101).[387]



Scheme 101. The *Sonogashira* coupling – isomerization – *Stetter* – *Paal-Knorr* sequence for the preparation of tri- and tetrasubstituted pyrroles.

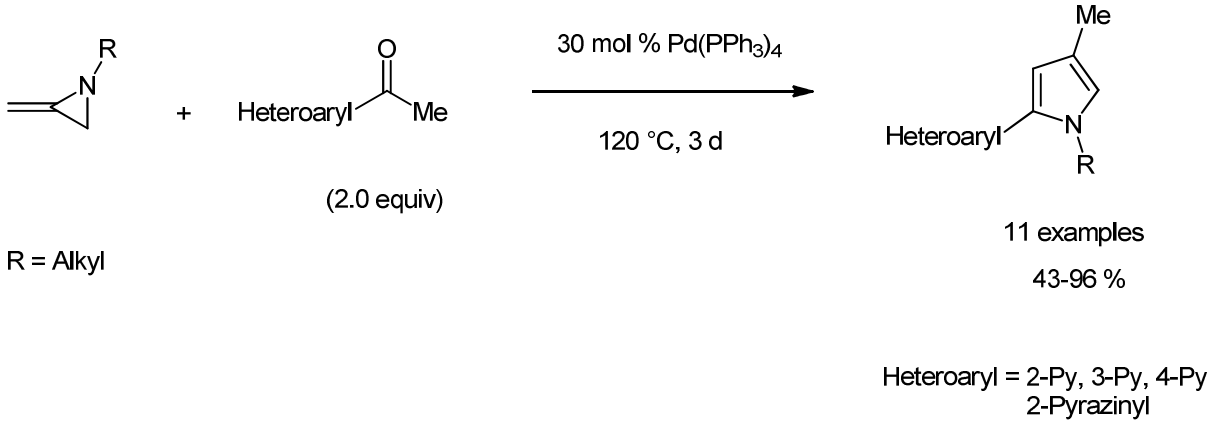
In contrast to a great number of approaches giving the classical *Paal-Knorr* products, the quest for mild synthetic methods for compounds with unusual substitution patterns such as 2,4-disubstituted pyrroles has turned out to be not trivial.[388],[258] The difficulty to obtain this substitution pattern can be illustrated by a rather complicated approach via rearrangement of 2-furanyl carbamates developed by *Padwa* (Scheme 102).[389] The synthesis requires multiple steps to accomplish the task.



Scheme 102. Synthesis of 2,4-disubstituted pyrroles by *Padwa*.

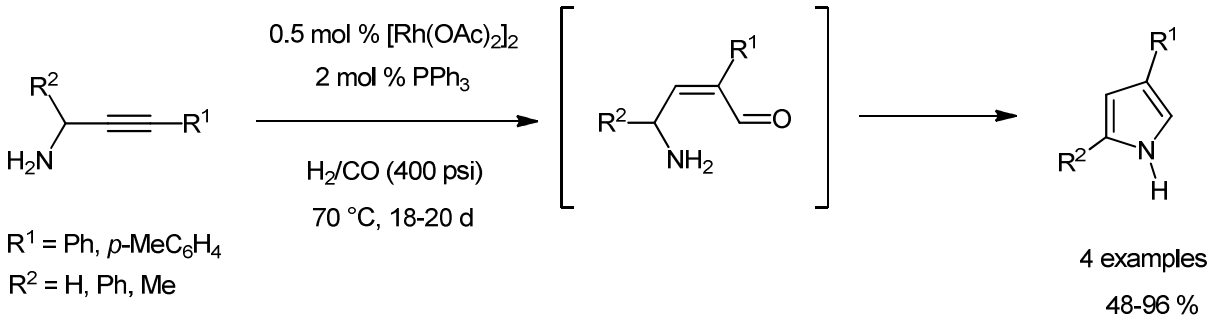
Interestingly, as early as in 1981 a Pd(II)-catalyzed pyrrole synthesis from 1-amino-3-alkyn-2-ols, which are obtained from the corresponding alkynones via addition of highly toxic TMSCN on the carbonyl group and subsequent reduction with $LiAlH_4$, was described by *Utimoto*.[390] The rather tedious preparation of the starting materials is a strong limitation of this method.

A rare example of a strategy toward 2,4-substituted pyrroles bearing *N*-heterocyclic substituents has been presented by *Yamamoto* in 2004 (Scheme 103).[391] However, the substituent at C-4 of the pyrrole is strictly limited to be methyl and the acetyl *N*-heterocycle has to be used in excess in order to obtain good yields.



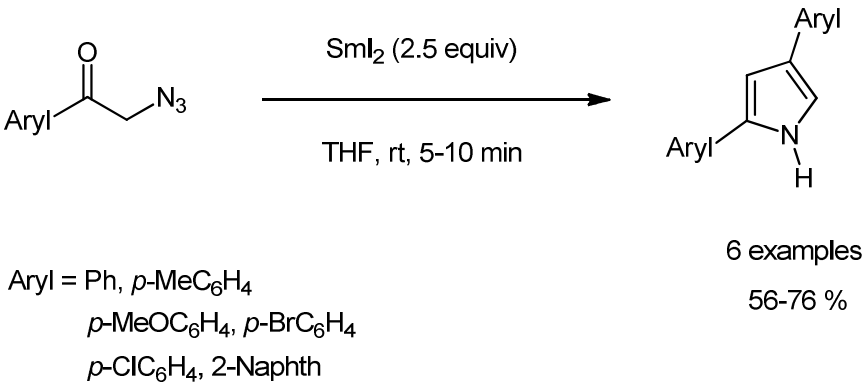
Scheme 103. Synthesis of 2-heteroaryl substituted 4-methyl pyrroles by *Yamamoto*.

Although many approaches exist toward 3-(hetero)aryl substituted indoles, there are only a few leading to the structurally related 2,4-diaryl substituted pyrroles.[392] For example, 2,4-disubstituted pyrroles with aryl substituents at the β-position could be obtained by a Rh-catalyzed hydroformylation of propargyl amines (Scheme 104).[393]



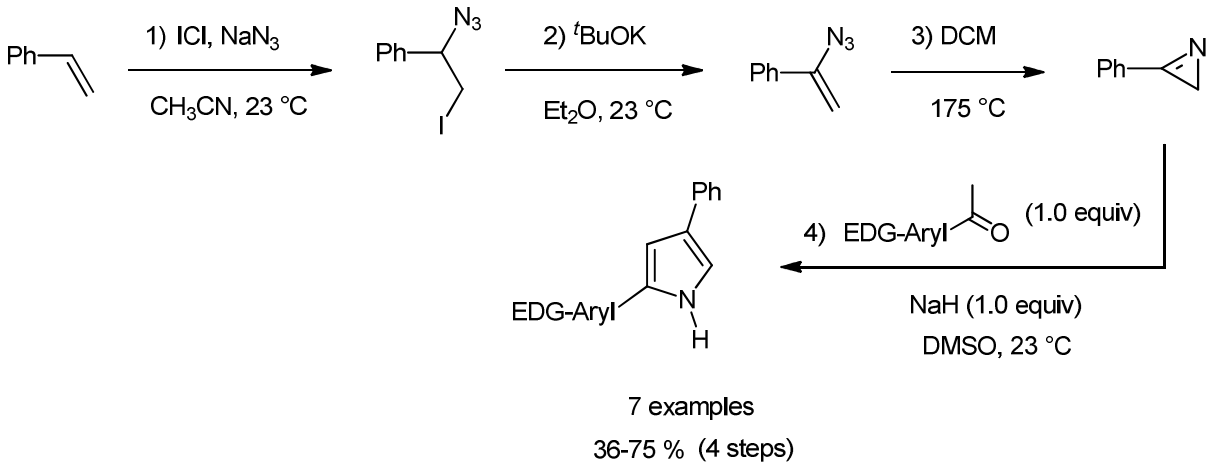
Scheme 104. Pyrroles via Rh-catalyzed reaction of propargyl amines with H_2/CO.

A Sm(II)-mediated synthesis of 2,4-diaryl pyrroles from phenacyl azides with a quite complex mechanistic rationale was described in 2002 (Scheme 105).[394] Besides the need for the preparation of azides as starting materials and for an excess of the *Kagan's* reagent, this synthesis is strongly limited to give pyrroles bearing two identical aryl substituents.



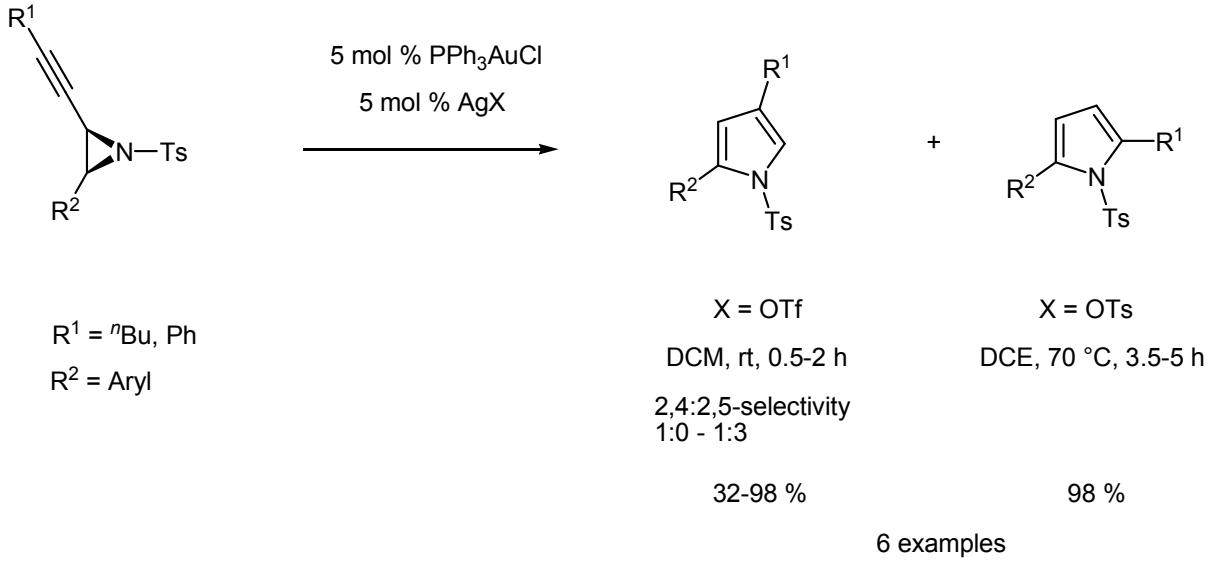
Scheme 105. SmI_2-mediated synthesis of 2,4-diarylpyrroles.

In 2006, *Carreira* described a synthesis of 2,4-diaryl pyrroles via a four-step synthesis from an alkene proceeding though an azirine as a key intermediate (Scheme 106).[395] Using this method pyrroles with an electron rich 2-aryl substituent and phenyl substituent on C-4 of the pyrrole can be obtained in moderate yields.



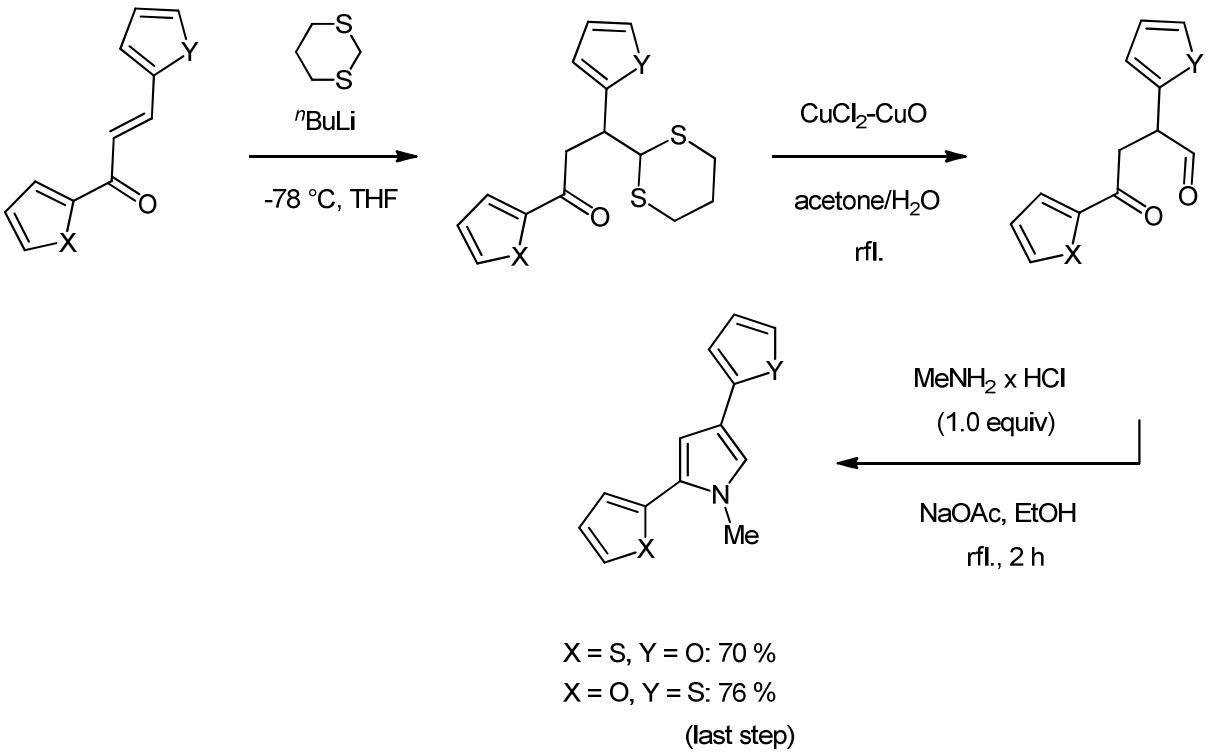
Scheme 106. Synthesis of 2,4-diaryl pyrroles according to *Carreira*.

Recently, a Au(I)-catalyzed synthesis of 2,4-diaryl pyrroles from alkynyl aziridines was reported by *Davies* (Scheme 107).[396] However, the starting materials are not readily available, and the formation of the desired products is accompanied by the formation of the corresponding 2,5-disubstituted pendants, even under the optimized reaction conditions.



Scheme 107. Au(I)-catalyzed synthesis of 2,4-diaryl pyrroles by *Davies*.

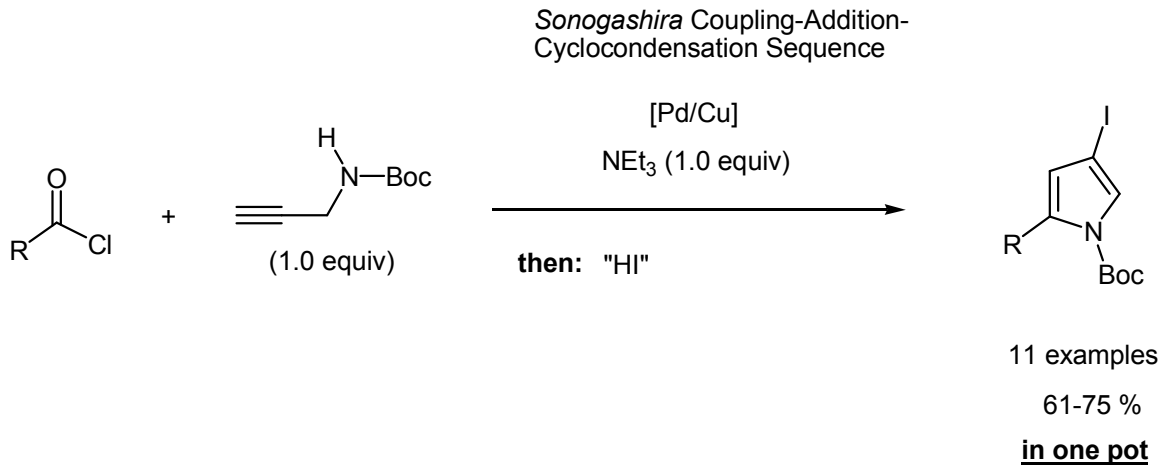
2,4-Diheteroaryl substituted pyrroles are even less common. Chalcones were shown to be used in an approach delivering only two examples of pyrroles bearing 2-furyl and 2-thienyl substituents (Scheme 108).[397]



Scheme 108. Preparation of 2,4-diheteroaryl substituted pyrroles from chalcones.

In conclusion, prior to this work there were no general and practically useful methods for the construction of 2,4-di(hetero)aryl pyrroles, especially those bearing *N*-heterocyclic moieties. Nevertheless, this substitution pattern could represent an yet underexplored class of biologically active compounds.[398]

In the framework of this thesis, (hetero)aryl, alkenyl, and selected alkyl substituted acid chlorides can be efficiently coupled with *N*-Boc protected propargyl amine to produce ynones, which are converted in a one-pot fashion into 2-substituted 4-iodo *N*-Boc pyrroles, valuable synthetic building blocks (Scheme 109).[399]



Scheme 109. One-pot synthesis of 2,4-disubstituted pyrroles.[399]

Upon addition of a further alkyne, a second *Sonogashira* coupling could be carried out still in a one-pot fashion. This sequentially Pd/Cu-catalyzed process represents a very mild, preparatively simple, and efficient entry to 2,4-disubstituted *N*-Boc pyrroles, which represent a rare substitution pattern. The obtained 2-substituted 4-iodo *N*-Boc pyrroles were shown to be excellent substrates for a borylation – coupling sequence, also developed in the course of this work, to give 2,4-di(hetero)aryl pyrroles.[464]

These results are part of this cumulative dissertation (**publication 3.6**).

2.10 Indole Alkaloids

“The marine environment, covering 70 % of the earth’s surface and 95 % of its tropical biosphere, represents 34 of the 36 phyla of life and provides a fascinating variety of biodiversity exceeding that of the terrestrial environment. Not surprising is that marine organisms produce an unprecedented molecular diversity by the incorporation of elements like bromine that are not readily available to terrestrial species. Partially responsible for the unique secondary metabolism of marine life are the ecological pressures in the marine ecosystem including significant competition for space, deterrence of predation, and a high level of symbiosis between different species. Due to the biogenetic origin, marine organism secondary metabolites possess a number of structural differences as compared to terrestrial natural products. In addition, marine organisms are not closely related to their terrestrial counterparts. Over 12,000 compounds from marine invertebrates, algae, and microorganisms have been discovered by a relative few marine research groups”.[400]

Marine organisms represent one of the most promising sources of bioactive molecules.[401],[402] “They produce natural products from a variety of structural classes exhibiting activity against numerous disease targets. Historically, marine natural products have largely been explored as anticancer agents. The indole alkaloids are a class of marine natural products that show unique promise in the development of new drug leads. A variety of marine sources including sponges, tunicates, red algae, acorn worms, and symbiotic bacteria have been shown to generate indole alkaloids, which represent the largest number and most complicated of marine alkaloids (1/4 of total alkaloids). Alkaloids obtained from marine organisms frequently possess novel frameworks, while in other cases terrestrially related compounds clearly exist. Their structure elucidation, chemical modification, stereochemistry, synthesis, and pharmacology have received a considerable interdisciplinary attention from areas of research other than chemistry and include pharmacology, physiology, and medicine. Specific biological activities of indole alkaloids include cytotoxic, antiviral, antimicrobial, antiparasitic, antiinflammatory, serotonin antagonistic, Ca^{2+}-releasing, calmodulin antagonistic, antitopoisomerase-I, and other pharmacological activities”.[400]

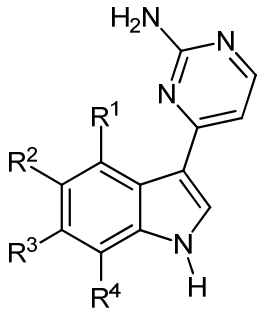
Total synthesis of natural products and especially of indole alkaloids remains a tremendously important area of chemical research. It is still the ultimative prove of correct structure determination as has been recently demonstrated by *Baker* who reassigned the structures of psammopemmins (for a discussion, see chapter *2.10.1.5 Other 3-heteroaryl substituted indole alkaloids*). Moreover, total synthesis is the only economically and ecologically bearable alternative to the isolation of natural products from their natural sources. For instance, there was not enough material available from the natural source to allow a full investigation of biological properties of variolin B. The combination of “high cost and difficulties of accessing the sponge *Kirkpatrickia varialosa* from Antarctica with the 1991 Madrid Protocol to the Antarctic treaty, which prohibits any person from removing flora and fauna from the region without the authorization of the government and which came into force in 1998, limits the possibility of obtaining more variolin B from its natural source”.[459] As a consequence, there has been significant interest in the synthesis of variolin B and related compounds, so that access to these interesting materials could be restored and full biological studies could be carried out. Finally, total synthesis remains the touchstone of new synthetic methods and gives the inspiration for the development of novel elegant and efficient synthetic routes.

2.10.1 Meridianins, variolins, and related compounds

Numerous biologically active indole alkaloids have been discovered. Among them, 3-substituted indoles constitute a huge structural class of compounds with remarkable biological activity. The substituent in 3-position is frequently another heterocyclic ring: imidazole (nortopsentins[403] and topsentins[404]); imidazolone;[405],[406] imidazoline (discodermindoles,[407] spongotines,[408] trachycladindoles[409]); maleimide (didemnimides[410]); oxazole (diazonamides,[411] martefragin A,[412] almazoles,[413] pimprinine,[414] and labradorins[415]); oxazoline (JBIR-34 and JBIR-35);[416] pyrrole (chromopyrrolic acid,[417] lynamicins[418]); pyrrolinone (violacein[419]); thiazole (camalexins[420], BE-10988[421]); oxazinone (oxazinins[422]); oxadiazinone (alboinon[423]); benzoxazinone (cephalandole A[424]); piperazine and (dihydro)pyrazine (dragmacidins,[425] hamacanthins[426]); pyrimidine (hyrtinadine A,[479] meridianins,[432],[433]); tetrahydropyrimidine (aplicyanins[477]); azepine (hyrtiazepine[427]); isoquinolinequinone (mensouramycin D[428]); β-carboline (eudistomin U,[429] hyrtioerectine A[430]); and another indole.[431]

2.10.1.1 Meridianins

"To date, more than 18,000 compounds have been reported from marine sources. However, only about 300 marine natural products originate from organisms collected in Antarctic habitats. Thus, cold-water marine habitats represent a source of natural products that has yet to be fully explored".[446] A class of indole alkaloids are meridianins A-E (Figure 7),[432] isolated and identified first in 1998 by the group of *Palermo* from the tunicate *Aplidium meridianum* (*Ascidiae*, *Polyclinidae* family), collected at a depth of 100 m in the vicinity of the South Georgia Islands (South Atlantic). This Antarctic tunicate, first described by *Sluiter* in 1906, has various coloration, often forming green or gray colonies.



Meridianins

A: R^1 = OH; R^2 = R^3 = R^4 = H
B: R^1 = OH; R^2 = R^4 = H; R^3 = Br
C: R^1 = R^3 = R^4 = H; R^2 = Br
D: R^1 = R^2 = R^4 = H; R^3 = Br
E: R^1 = OH; R^2 = R^3 = H; R^4 = Br
F: R^1 = R^4 = H; R^2 = R^3 = Br
G: R^1 = R^2 = R^3 = R^4 = H

Figure 7. Structures of meridianins.

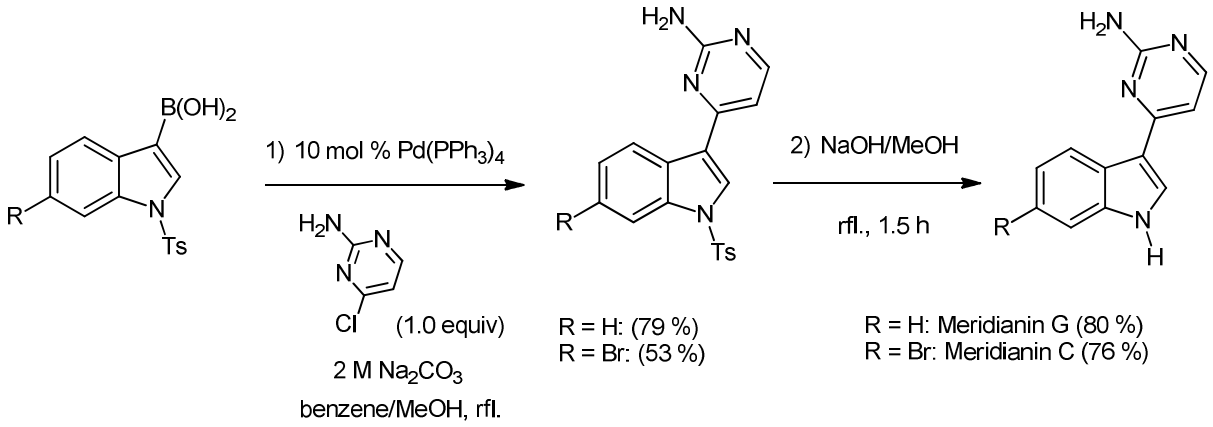
Later, the same group identified two further compounds, meridianins F and G, from a sample of another population of *Aplidium meridianum*.[433] Just recently, meridianins A, B, C, and E have been isolated from the Antarctic tunicate *Synoicum* sp.[476]

All compounds possess a brominated and/or hydroxylated indole core structure connected with a 2-amino pyrimidine substituent through a C-3/C-4' linkage. Only the simplest member of this family, meridianin G, has no substituents on the indole nucleus.

These alkaloids are cytotoxic toward cancer cell lines and inhibit protein kinases such as cyclin dependent kinases (CDKs), glycogen synthase kinase-3, cyclic nucleotide dependent kinases, and casein kinase 1. Meridianins display moderate cytotoxicity toward LMM3 (murine mammary adenocarcinoma cell line) and human cancer cell lines with IC_{50} values in low micromolar range. Certainly, exhibiting micromolar inhibi-

tion of protein kinases meridianins constitute a new scaffold, from which more potent and selective inhibitors can be designed. Meridianins penetrate into cells and interfere with the activity of kinases which are responsible for cell division and apoptosis.[434] The structure-activity studies show analogies with ATP-competitive CDK inhibitors.The “isomeridianins”, bearing the 2-amino pyrimidine substituent at the C-2-position of indole, are biologically inactive, which underlines the importance of the C-3 substitution.[434],[435]

The first synthesis of meridianins was reported in 2000 by *Jiang*.[436] The key step was the *Suzuki* coupling of 3-indolyl boronic acids with 2-amino-4-chloropyrimidine (Scheme 110). The boronic acids had to be prepared from the corresponding bromides via bromine-lithium exchange with ^{t}BuLi at -78 °C followed by the reaction of the indolyllithium reagents with trimethoxyborane and aqueous workup. After the *Suzuki* coupling step, the Ts protective group remained uncleaved and had to be removed in a separate step.



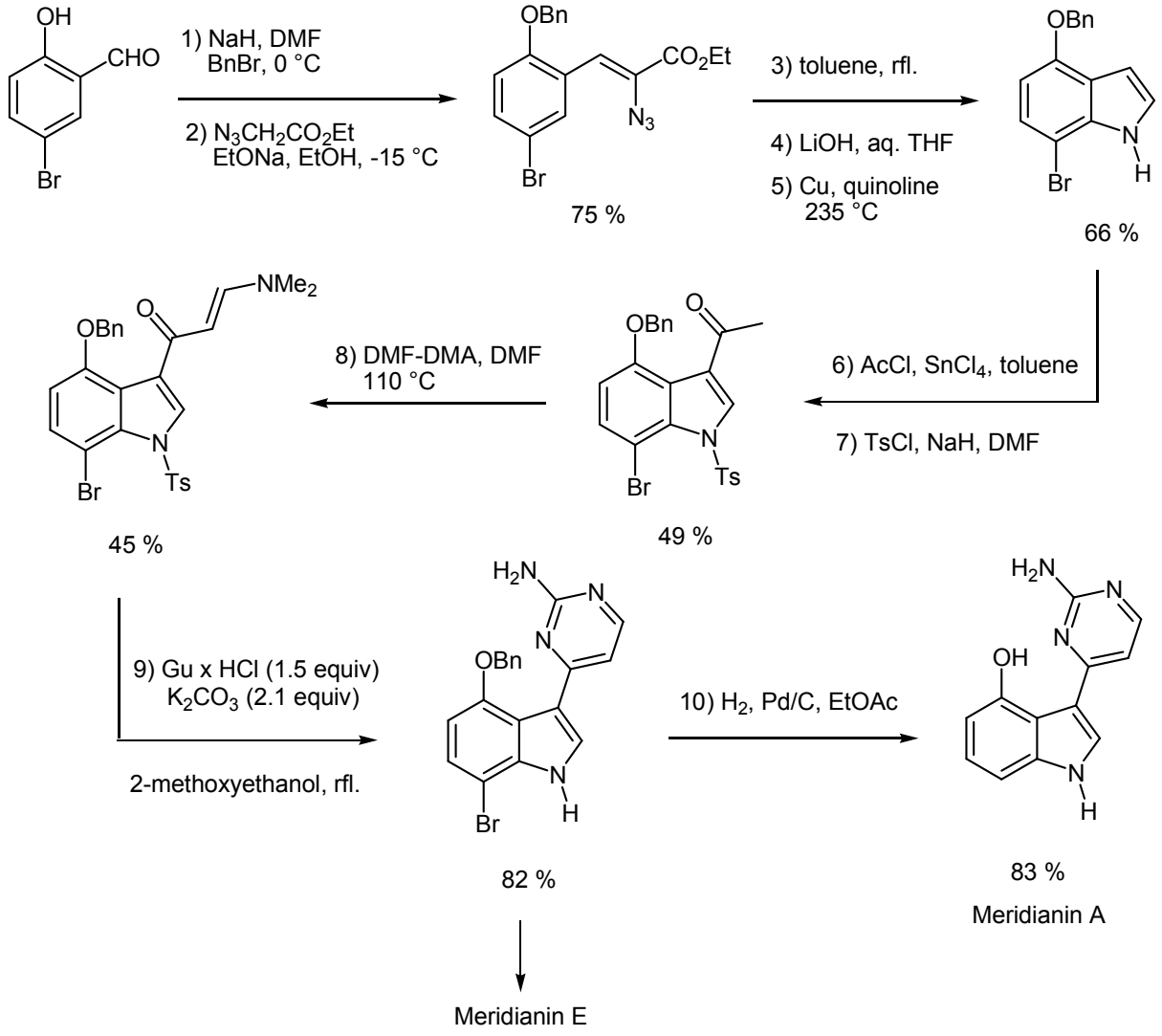
Scheme 110. Synthesis of meridianins according to *Jiang*.

In the meantime, several groups have reported syntheses of meridianins and their analogs as well as biological activities of these compounds: (1) synthesis of meridianins A-E via reaction of β-enaminones with guanidinium salts by *Fresneda* and *Molina* in 2001;[437] (2) preparation of *N*-alkylated derivatives using the approach of *Fresneda* and *Molina*;[438] (3) synthesis of derivatives with aryl substitution at C-5’[439] and their in vitro antiproliferative activities;[440] (4) synthesis of indolyluracils;[441] (5) derivatives via alkenylation of indoles with α-oxo ketene dithioacetals;[442] (6) new antimalarial agents via reaction of chalcones with guanidinium salts;[443] and (7) me-

ridianins C and G with analogs via one-pot indolization of nitrosoarenes.[444] Syntheses of meridianins have been reviewed.[445],[459]

An intriguing issue is the biological role of meridianins. “Tunicates are subject to little predation, and this is often attributed to chemical compounds”.[446] Meridianins from Antarctic colonial ascidians *Aplidium meridianum* and *Aplidium falklandicum* have been shown to serve as chemical defence against predation.[446] Crude extracts as well as isolated meridianins were tested for ecological activity against sympatric generalist predator, the Antarctic sea star *Odontaster validus*. The experiments showed significant feeding repellance. However, none of the isolated meridianins showed activity in laboratory assays against cosmopolitan bacteria and yeasts.

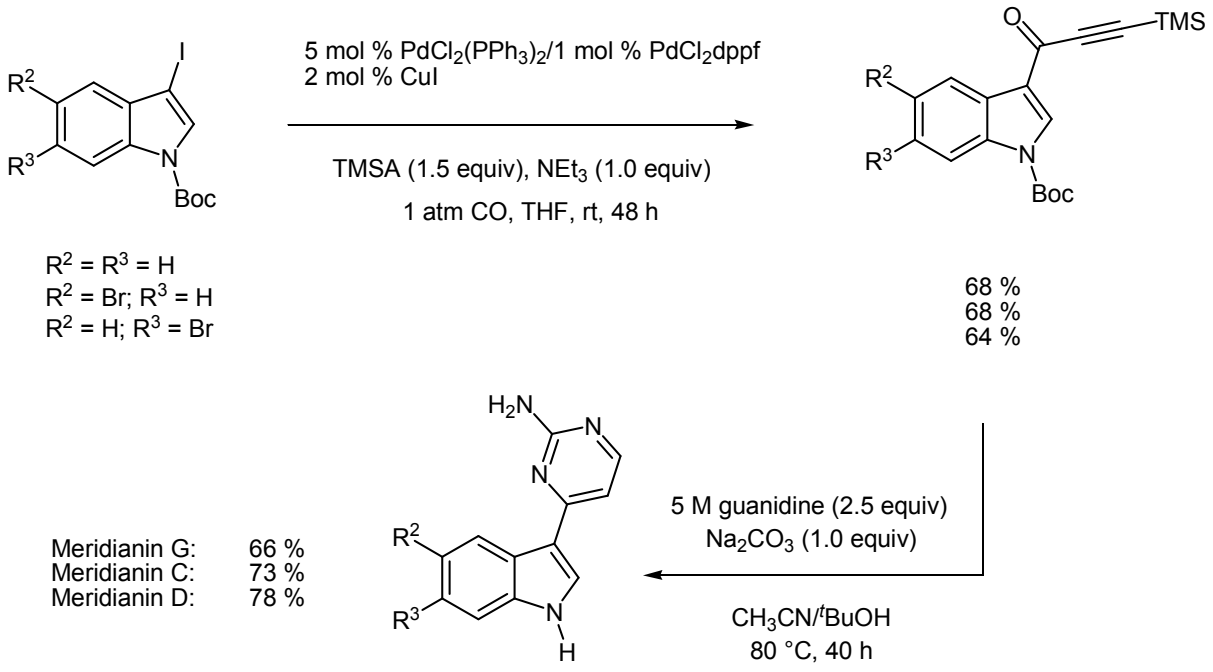
Prior to this investigations, a sole total synthesis of meridianin A was reported by *Molina* and *Fresneda* in 2001 (Scheme 111).[447]



Scheme 111. Synthesis of meridianin A according to *Molina* and *Fresneda*.

The natural product (19 mg) was obtained in 7 % total yield over 10 linear steps via a β-enaminone as a key intermediate (*Bredereck* pyrimidine synthesis). This synthesis can hardly be regarded as a useful approach since the objective was not to prepare meridianin A in a targeted fashion, but rather to prepare a common precursor for both meridianins A and E. Therefore, no efficient synthesis of this natural product was known prior to the presented work.

In 2005, we reported a short and elegant synthesis of several meridianins and a simplified variolin B analog (Scheme 112),[448] which was later called meriolin 1.[463] The key step was the carbonylative *Sonogashira* coupling of *N*-Boc 3-iodo (7-aza)indoles, which proceeded under mild conditions. The coupling was performed under ambient pressure of carbon monoxide at room temperature. It is worth mentioning that triethylamine was used as a base in the carbonylative *Sonogashira* step, whereas aqueous ammonia,[108] used in the procedure described by *Mori*, failed in our hands to give the desired products.



Scheme 112. Synthesis of meridianins by the carbonylative *Sonogashira* coupling as a key step.

The desired products were obtained in four steps and 28-41 % overall yields from the commercially available indoles. This total synthesis represents the first application of the carbonylative alkynylation in the synthesis of natural products.

Regarding the biological activity of the natural meridianins, kinase inhibition tests of the synthesized compounds have been performed revealing moderate micromolar activities. However, meridianins display only modest antiproliferative activities.

The synthesis and the biological activity of the 7-azaindole analog (meriolin 1), prepared by the same approach, will be discussed in chapter *2.10.1.3 Meriolins*.

2.10.1.2 Variolins

Meridianins show structural similarities with the alkaloid family of variolins, which have been extracted in 1994 from the rare and difficult-to-access red Antarctic sponge *Kirkpatrickia varialosa* by *Blunt* and *Munro* and have been shown to possess antitumor and antiviral activities (Figure 8).[449] The isolated compounds included variolin A, variolin B, *N*-3'-methyl tetrahydrovariolin B, and variolin D, the latter of which was reported to be an artifact of the extraction process produced by aerial oxidation of the variolins.

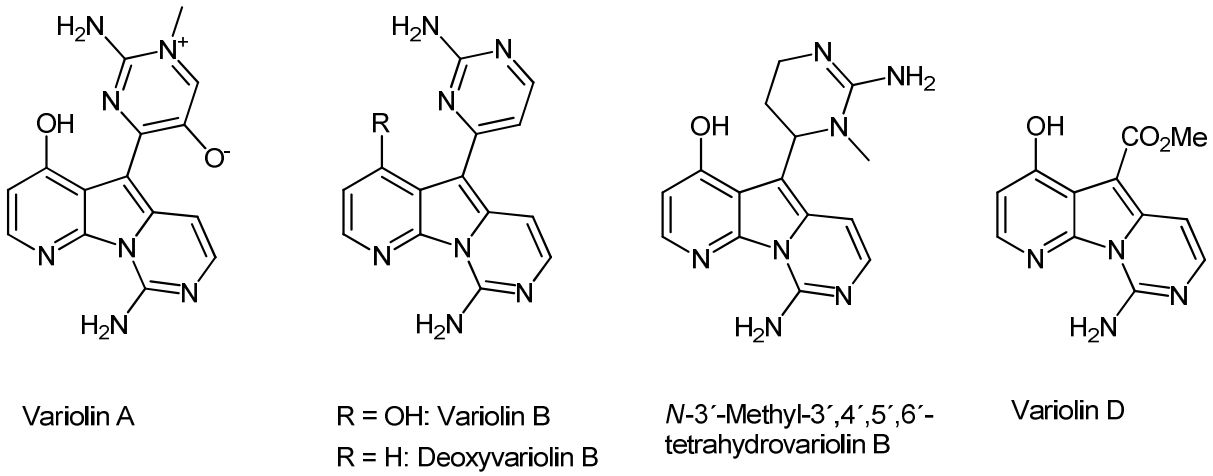


Figure 8. Structures of variolins.

Strikingly, variolin B possesses the same heterocyclic substituent on C-5 of the tricycles as meridianins on C-3 of the indole core.

Variolins are the first example of either terrestrial or marine natural products with a fused tricyclic pyrido[3',2':4,5]pyrrolo[1,2-*c*]pyrimidine heteroaromatic core. This unprecedented tricyclic skeleton has made variolins an interesting class of alkaloids from both structural and biogenetic points of view. Preliminary investigations established that variolin B displayed the highest biological activity, whereas variolin D was inactive in all assays, again indicating the importance of the 2-amino pyrimidine ring. Variolin B inhibited the growth of P388 murine leukemia tumor cell line in micromolar concentrations (IC_{50} value of 210 ng/mL) and was a very fast inducer of apoptosis. Moreover, it was active against *Herpes Simplex* type I and polio virus but inactive

against a range of bacteria and fungi. Further investigations have been hampered by a lack of material.

Therefore, there has been considerable interest in the synthesis of variolins due to the novelty of their structures, not to mention their biological properties and low natural occurrence. Several groups have reported syntheses of the variolin core[450] as well as synthetic manipulations on the core.[451]

To date, four total syntheses of variolin B have been reported in the literature: (1) the first successful total synthesis via tandem deoxygenation and cyclization of a triarylmethanol was reported by *Morris* in 2001, elegantly taking advantage of a hidden symmetry element in the molecule;[452] (2) *Molina* and *Fresneda* used a sequential approach with the *Bredereck* synthesis of the 2-amino pyrimidine ring;[453] *Álvarez* and *Joule* reported an approach based on the *Stille* coupling of the iodo tricycle with the pyridylstannane to introduce the C-5 substituent;[454] and finally *Vaquero* used Pd-mediated C–C, C–O, and C–N couplings to install substituents on a trihalo substituted tricyclic core.[455] Preparation of the synthetic deoxyvariolin B, which showed higher stability and solubility compared to the natural product, has also been described.[456],[452b],[454b] Syntheses and biological evaluation of simplified bicyclic analogs as well as of various derivatives such as 7-isovariolin B having the 2-amino pyrimidine ring at C-7 instead of C-5 and derivatives with the 2-amino pyrimidine at both positions have been reported as well.[457],[453b] However, none of the derivatives has shown improved activity compared to the natural product.

In different human cancer cell lines variolin B and deoxyvariolin B inhibited colony formation, caused cell cycle perturbations, and induced apoptosis at concentrations ranging from 0.1 to 2 μM. They prevent the cells from entering S phase, blocking cells in G1, and cause accumulation already evident 4 h after the beginning of treatment. Although intercalation of deoxyvariolin B in DNA has been demonstrated, neither variolin B nor deoxyvariolin B produce detectable breaks in DNA. In vitro biochemical assays also demonstrated that deoxyvariolin B is not a topoisomerase I or II poison. Instead, variolin B was identified as a potent inhibitor of all CDKs in micromolar concentrations, whereas deoxyvariolin B was 5- to 10-fold less potent. Both are a new class of CDK inhibitors that activate apoptosis in a *p*53-independent fashion, and thus they may be effective against tumors with *p*53 mutations or deletions.[458]

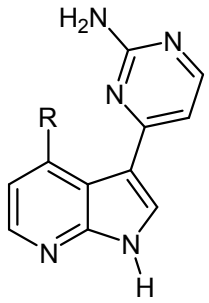
Additionally, variolin B was found to be the most potent inhibitor of CK1, a significant therapeutic target in both *Alzheimer's* disease and cancer.

In conclusion, the unique heterocyclic framework of variolins has emerged as a new scaffold for the design of new inhibitors of CDKs. Indeed, the Spanish pharmaceutical company *PharmaMar* has been investigating the potential of variolin B and its analogs as antitumor agents.

Isolation, structure determination, synthesis, and biological activity of variolins and related compounds such as meridianins and meriolins have been recently comprehensively reviewed by *Morris* in 2009[459] and by *Januário* in 2010.[460] An earlier review on syntheses of variolins and bicyclic analogs was provided by *Álvarez* in 2004.[461]

2.10.1.3 Meriolins

Through a combination of the common features of meridianins and variolins, a new class of 7-azaindole containing analogs known as meriolins has been designed. Due to the 7-azaindole core with its pronounced inherent ability to bind to the hinge region of kinases, these compounds are predestined for investigations as kinase inhibitors.[372],[374] The first synthesis of the simplest member of this class was performed by *Molina* and *Fresneda* in 2001,[447] followed by our synthesis in 2005.[448] Later, *Meijer* reported a comprehensive study on synthesis, kinase inhibitory activity, cellular effects, and structure of a CDK2/cyclin A/meriolin complex, and coined the term "meriolins" to describe these hybride structures (Figure 9).[462],[463]

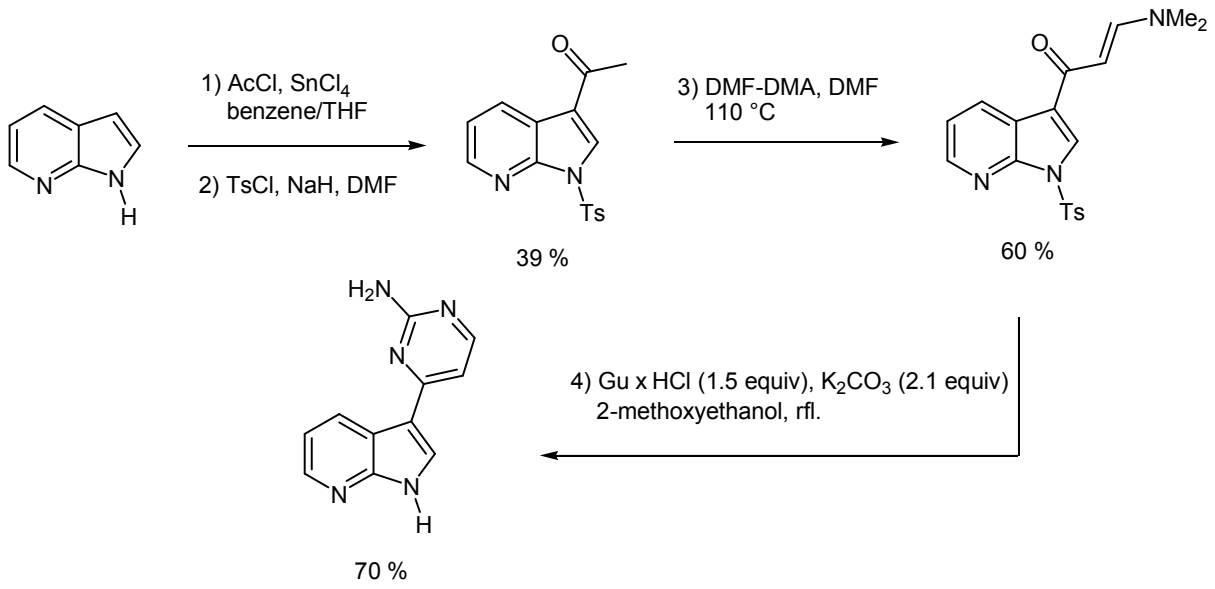


Meriolins

1: R = H
2: R = OH
3: R = OMe
7: R = $O(CH_2)_2OMe$
10: R = Cl

Figure 9. Some members of the meriolin family.

The above mentioned synthesis by *Molina* and *Fresneda* relies on the same synthetic strategy as used for the synthesis of meridianin A. The desired product was obtained in 4 linear steps and 16 % total yield (Scheme 113).[447] The major drawback of this synthesis is the difficult *Friedel-Crafts* acylation of 7-azaindole resulting in the poor yield of 3-acetyl 7-azaindole.



Scheme 113. Synthesis of meriolin 1 according to *Molina* and *Fresneda*.

Meriolins display enhanced specificity toward CDKs (from 32 kinases tested), with marked potency on CDK2 and CDK9. Indeed, meriolins have proved to be even more potent CDK inhibitors than variolin B. This class of compounds also exhibits better antiproliferative and proapoptotic properties in human tumor cell cultures compared with their "inspirational parent" molecules, meridianins and variolins. SAR studies complemented with the crystal structure have provided some clarification on the action mechanisms of these molecules on their CDK target. Meriolin 3 and variolin B bind within the ATP binding site of the kinase, but in different orientations and via different binding modes, as could be determined by the X-ray crystallography. Meriolins induce cell death at submicromolecular concentrations in all cell lines tested, with the noticeable exception of normal fibroblasts, which were rather resistant. Moreover, meriolin 3 potently inhibits tumor growth in two mouse xenograft cancer models, namely, *Ewing's* sarcoma and LS174T colorectal carcinoma. Meriolins thus constitute a new CDK inhibitory scaffold with promising antitumor activity, derived from molecules initially isolated from marine organisms.

Huang reported the synthesis of 7-azaindolyl pyrimidines with substituents on the amino group (described in chapter *2.3.6 Miyaura and Masuda borylations*) (Figure 10).[182]

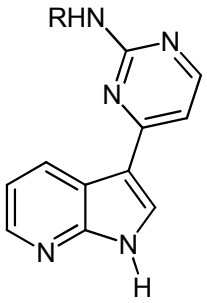
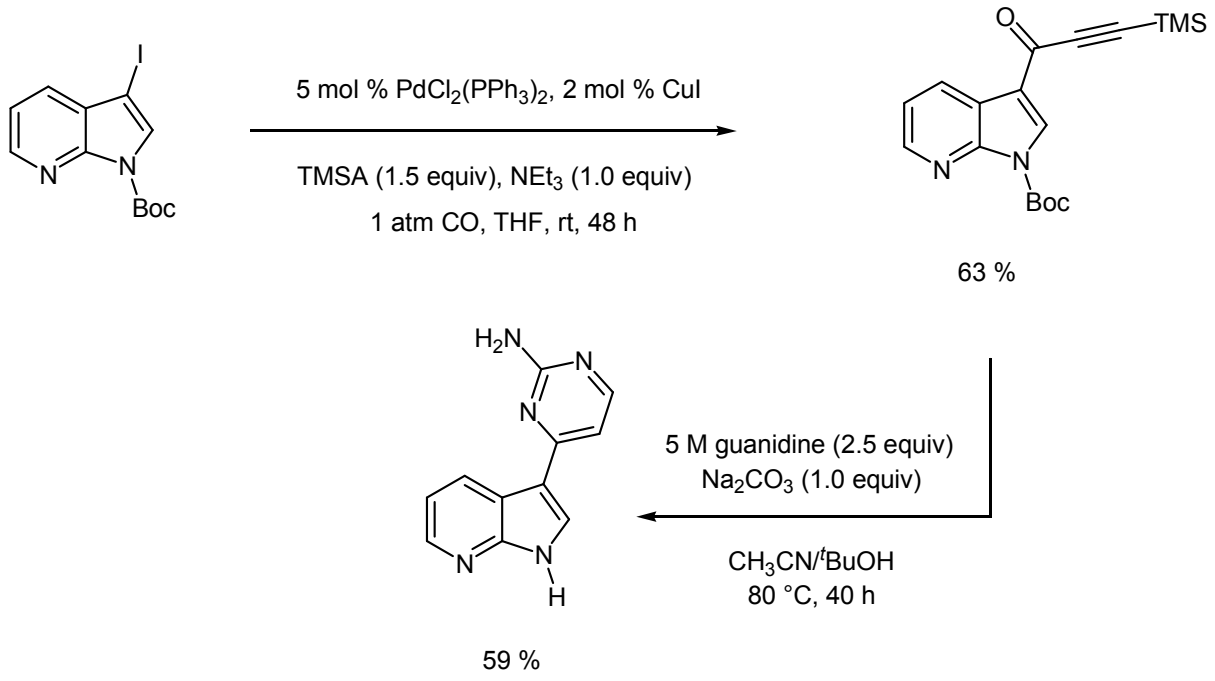


Figure 10. Structure of the meriolin analogs synthesized by *Huang*.

Some of the obtained compounds were shown to be very potent CDK1 inhibitors (IC_{50} value of 3 nM for R = *o*-MeC_6H_4), and exhibited high antiproliferation activity on the HeLa (cervical carcinoma) cell line (IC_{50} value of 28 nM for the same compound). The unsubstituted nitrogen atom of the indole nucleus was found to be essential for both CDK1 and antiproliferation activity. When screened against a panel of 100 kinases with 2 mM of ATP, the above mentioned compound displayed > 50 % inhibition of 61 kinases, and > 80 % inhibition of 33 kinases in the panel, thus representing a family of very potent multikinase inhibitors.

Our synthesis was based on the carbonylative *Sonogashira* coupling as described in chapter *2.10.1.1 Meridianins* (Scheme 114).[448] The desired product was obtained in 4 steps and 25 % total yield from the commercially available 7-azaindole.

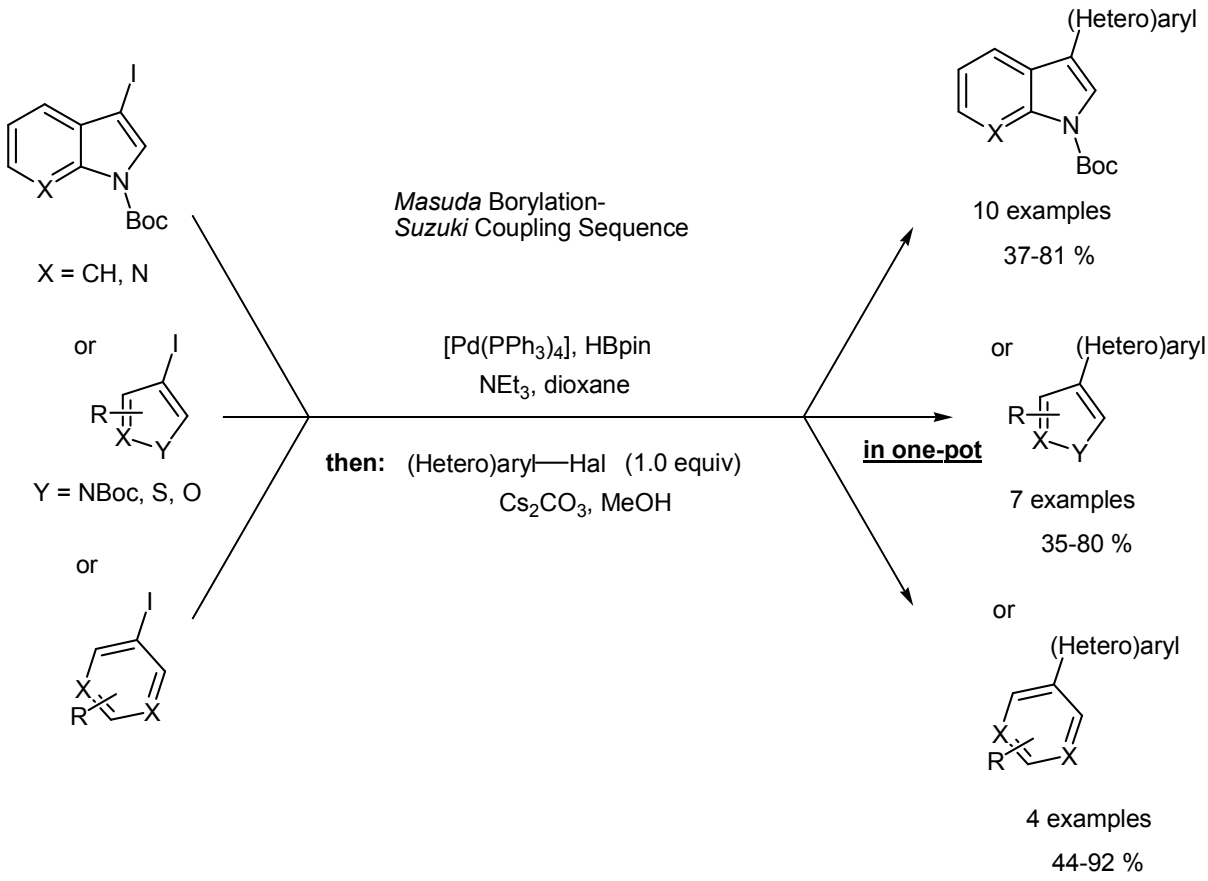


Scheme 114. Synthesis of meriolin 1 according to *Müller*.

The compound was tested against a panel of 121 kinases displaying an inhibitory activity of > 50 % on 25 and > 90 % on 4 kinases at a concentration of 1 μM. Moreover, a significant improvement of antiproliferative activity on cancer cell lines was determined. In contrast to meridianin G diplaying essentially no activity, meriolin 1 showed a sub-μM activity on HCT116 and A2780 cancer cell lines with IC_{50} values of 0.18 μM and 0.14 μM, respectively.

In conclusion, meriolins display better antiproliferative and proapoptotic properties in human tumor cell cultures than their parent natural products, as determined by us and others, and therefore represent a very promising 7-azaindole based scaffold for development of potent kinase inhibitors.

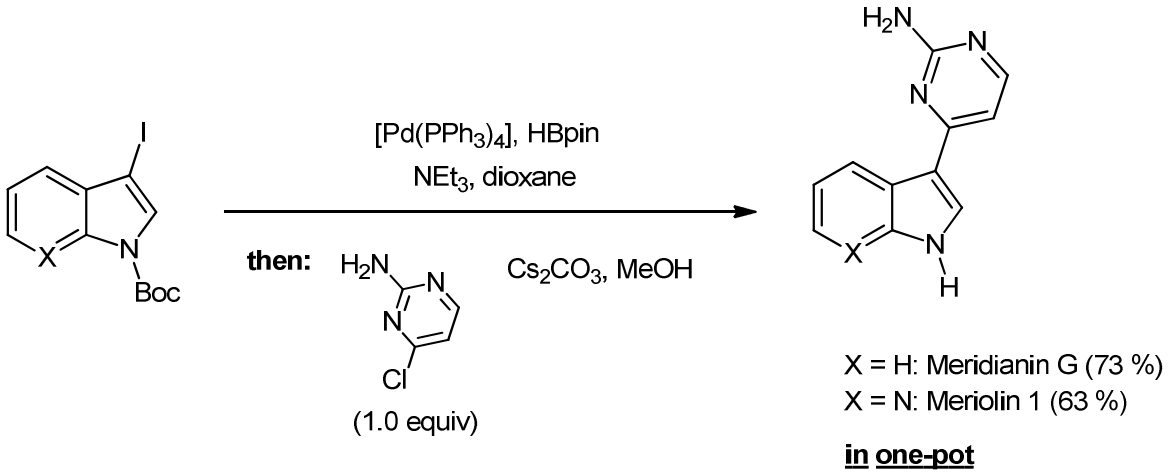
In the framework of this thesis, a practical *Masuda* borylation – *Suzuki* coupling sequence was developed for the direct preparation of (7-aza)indoles bearing diverse 5- and 6-membered aryl and heteroaryl substituents starting from the corresponding iodides (Scheme 115).[464]



Scheme 115. One-pot synthesis of (hetero)aryl substituted heterocycles.[464]

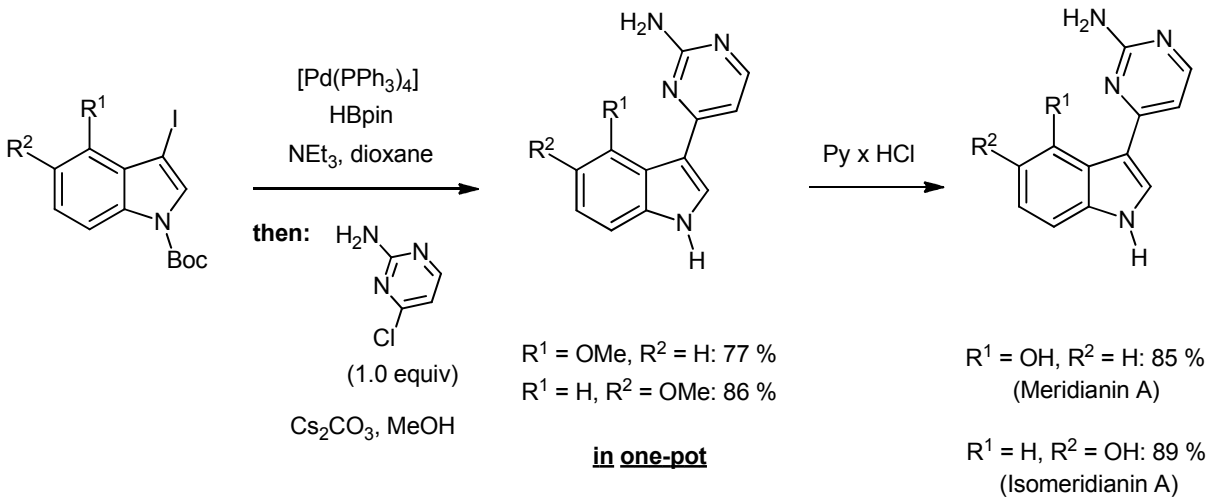
Besides iodo indoles and 7-azaindoles, iodo pyrroles[399] were found to be excellent substrates to furnish 2,4-di(hetero)aryl pyrroles as a rare substitution pattern. Other electron rich (hetero)aryls could be reacted as well, and the scope of this sequence is remarkable. Even free hydroxy and amino groups as well as notoriously difficult 2-amino pyridine and pyrimidine motifs on both substrate and (hetero)aryl halide are well tolerated.

An an illustration of the utility of the developed sequence, concise total syntheses of marine natural products meridianin G, meridianin A, as well as of the variolin B analog, meriolin 1, were performed (Scheme 116 and Scheme 117).[464] This strategy represents the most efficient and convenient approach to these alkaloids.



Scheme 116. Total syntheses of meridianin G and meriolin 1.[464]

Again, a single commercially available Pd-precatalyst has been used for both couplings. No exotic ligands or additives were required.



Scheme 117. Total syntheses of meridianin A and isomeridianin A.[464],[481]

Meridianin A was prepared in 65 % total yield, representing the first targeted synthesis of this natural product. In a similar way, literature unknown isomeridianin A bearing the hydroxy group at C-5 was prepared in 77 % total yield.

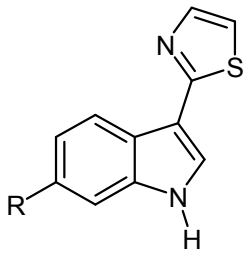
Whereas the precursor to meridianin A, *O*-Me-meridianin A, was essentially inactive in the viability and kinase inhibition assays (> 50 % inhibition of 3 from 102 kinases at a concentration of 1 μM), the natural product displayed a micromolar activity on the A2780 (ovarian tumor) cancer cell line (IC_{50} = 3.9 μM).

In contrary, isomeridianin A and its precursor, *O*-Me-isomeridianin A, were only weak kinase inhibitors (> 50 % inhibition of 8 and 7 from 110 kinases at a concentration of 1 μM, respectively) and showed no essential activity on the cancer cell lines tested (A2780 and HCT116 (colon tumor)).

These results are part of this cumulative dissertation (**publication 3.7**).

2.10.1.4 Camalexins

Two indole phytoalexins, camalexin and methoxycamalexin, were isolated for the first time in 1991 from *Camelina sativa* leaves.[465] These compounds are fungitoxic to *Alternaria brassicae* and are produced after exposure and in response to this fungus. Later, the compounds were found to possess antitumor activity as well. They bear a thiazol-2-yl substituent at C-3 of the indole core (Figure 11).

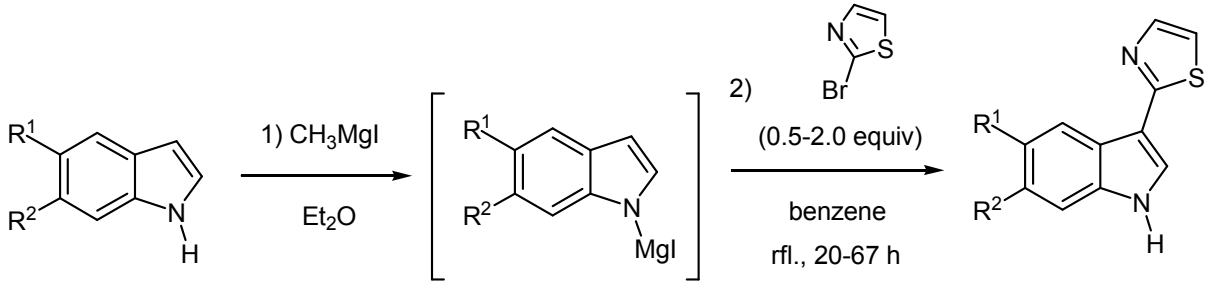


R = H: Camalexin
R = OMe: Methoxycamalexin

Figure 11. Structures of camalexin and methoxycamalexin.

The main phytoalexin camalexin attracted considerable interest, and extensive studies dealing with its biosynthesis[466] and biological role have been undertaken.[467]

The synthesis of camalexins and an analog, 5-methoxycamalexin, by an organometallic approach was reported in 1992 by *Ayer* (Scheme 118).[468]



$R^1 = R^2 = H$: Camalexin	76 %
$R^1 = H$; $R^2 = OMe$: Methoxycamalexin	77 %
$R^1 = OMe$; $R^2 = H$: 5-Methoxycamalexin	98 %

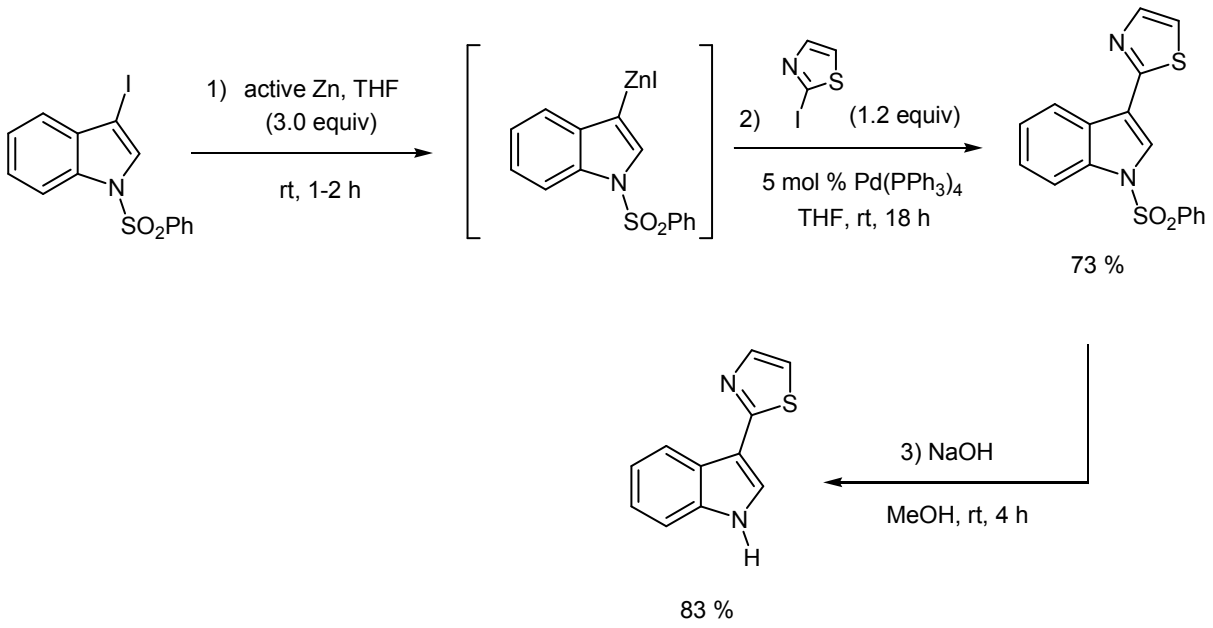
Scheme 118. Synthesis of camalexins by an organometallic approach.

The reaction is well suitable for the preparation of natural products but has a limitation of functional group intolerance typical for organometallic approaches, which may be an obstacle for the preparation of further analogs.

The biological activity of camalexin is not restricted to microorganisms and plants. The natural product and some analogs, prepared according to *Ayer's* method, were tested on the human breast cancer cell line SKBr3 with camalexin showing an IC_{50} value of 2.7 μM.[469]

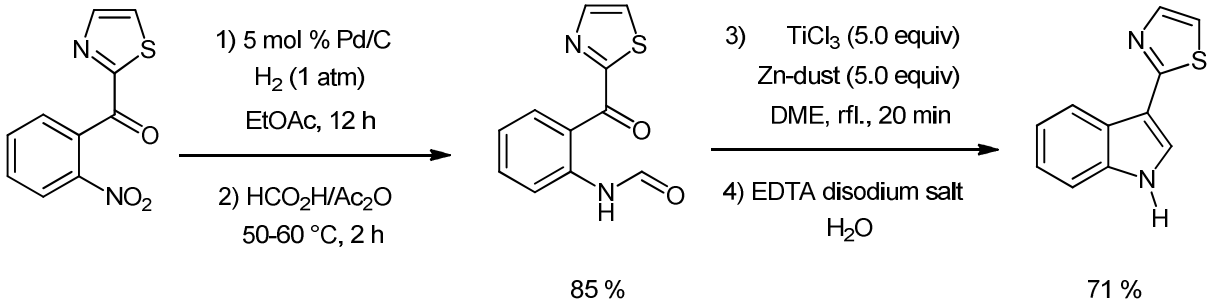
Analogs of camalexin such as 1-methylcamalexin, 5-methyl-, and 5-fluorocamalexin were prepared according to *Ayer's* method, and studies concerning detoxification and antifungal activity of these compunds were performed.[470] 5-Fluorocamalexin was found to be the best designer phytoalexin against fungus *Rhizoctonia solani* due to a slow metabolisation.

Another organometallic approach was described by *Sakamoto* using active Zn to produce indolylzinc iodide as the key intermediate that was coupled with 2-iodothiazole in a *Negishi* coupling to give camalexin in 2 steps and 61 % total yield (Scheme 119).[471] The method has a drawback of relatively tedious preparation of the active Zn reagent.



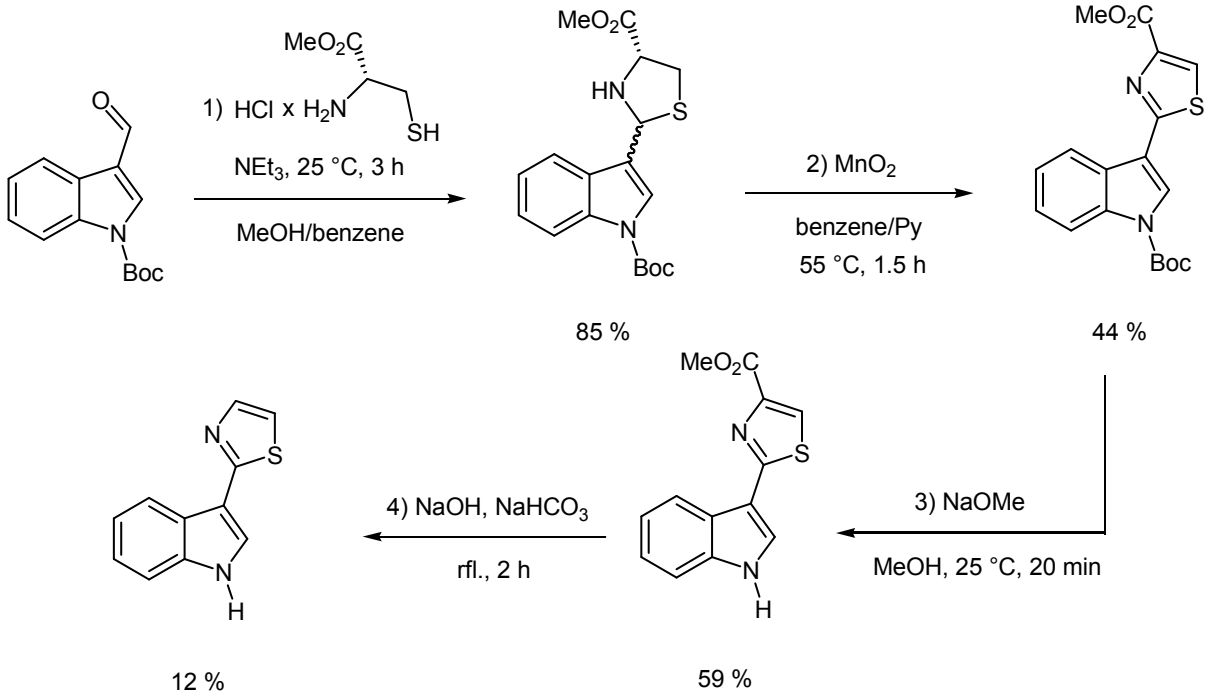
Scheme 119. Synthesis of camalexin according to *Sakamoto*.

A short synthetic route to camalexin was presented by *Fürstner* in 1995 based on a low-valent titanium induced reductive coupling of an oxo-amide, currently known as *Fürstner* indole synthesis (Scheme 120).[472] This synthesis gave the desired product in 61 % yield and is suitable for the synthesis of C-2 substituted analogs.



Scheme 120. Synthesis of camalexin according to *Fürstner*.

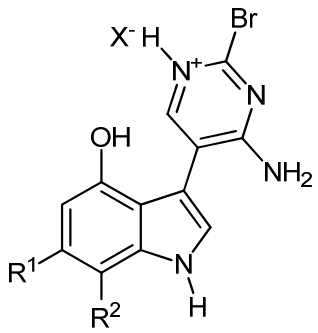
A biomimetic approach according to the proposed biosynthetic scheme was demonstrated in 2001 by *Dzurilla* (Scheme 121).[473] This synthesis gave only 10 mg of substance, which corresponds to 2.6 % total yield.



Scheme 121. Biomimetic synthesis of camalexin.

2-Aryl and 2-alkyl substituted camalexin derivatives were prepared using the Pd-catalyzed *Cacchi* indole synthesis.[474] However, no extensive SAR studies of camalexin analogs have been conducted yet.

Psammopemmins were described in 1992 by *Capon* to represent an unusual group of natural products isolated as an amine salt from an Antarctic marine sponge *Psammopemma* sp. (Figure 12).[475] Three structurally related compounds designated psammopemmins A–C have been assigned. Unfortunately, a recent study of *Baker*, who also performed the first total synthesis of the proposed psammopemmin A, revealed the incorrect structure assignment in the original report.[476] According to the comparison of NMR data of meridianin A with the reported data of psammopemmin A, the molecules are identical.

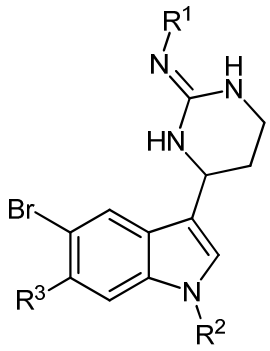


Psammopemmins

A: $R^1 = R^2 = H$
B: $R^1 = H$; $R^2 = Br$
C: $R^1 = Br$; $R^2 = H$

Figure 12. Erroneously assigned structures of psammopemmins.

A new family of indole alkaloids was recently isolated from the Antarctic tunicate *Aplidium cyaneum* by *Reyes* (Figure 13).[477] The aplicyanins A–F contain a bromoindole nucleus and a 6-tetrahydropyrimidine substituent at C-3. The aplicyanins share a common 3-(pyrimid-4-yl)indole structure with meridianins and variolins. The tetrahydropyrimidine system of the aplicyanins has a stereocenter at C-4', in contrast to the planar pyrimidine ring of the meridianins.



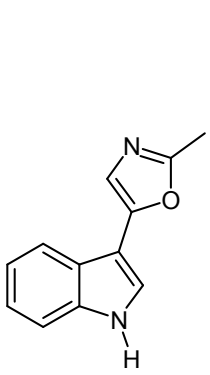
Aplicyanins

A: $R^1 = R^2 = R^3 =$ H
B: R^1 = Ac; $R^2 = R^3$ = H
C: R^1 = H; R^2 = OMe; R^3 = H
D: R^1 = Ac; R^2 = OMe; R^3 = H
E: R^1 = H; R^2 = OMe; R^3 = Br
F: R^1 = Ac; R^2 = OMe; R^3 = Br

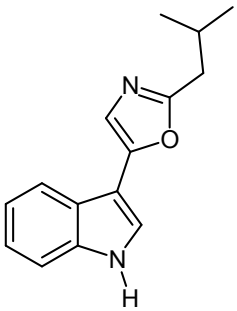
Figure 13. Structures of aplicyanins.

Aplicyanins B, D, and F have been found to possess significant cytotoxic and antimitotic activities, with IC_{50} values in the low to sub-μM range.

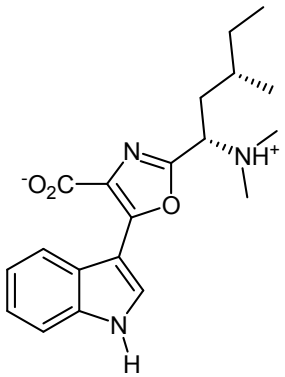
Indoles with 5-membered heterocyclic substituents at C-3 represent another widespread group of natural products. Some representatives are depicted in Figure 14.



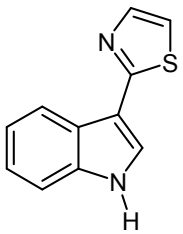
Pimprinine



Labradorin 1

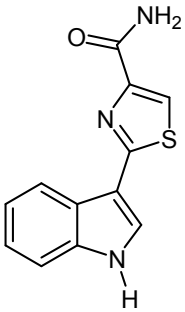


Martefragin A



Camalexin

(see chapter *2.10.1.4 Camalexins*)



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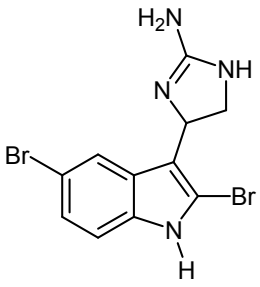
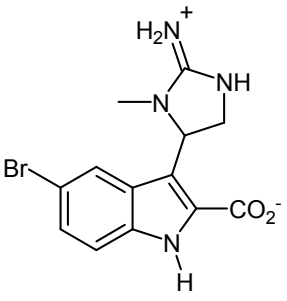
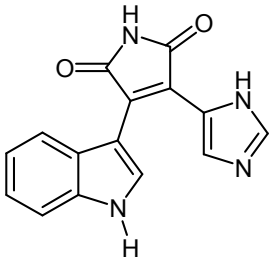


Discodermindole



Trachycladindole A



Didemnimide A

Figure 14. Natural products with 5-membered heterocycles at C-3 of an indole.

2.10.2 Marine bisindole alkaloids

Certain bisindole alkaloids possess unique structures with a 5- or 6-membered central ring which is shared by two indole units (Figure 15). These compounds display a broad spectrum of biological activities.[478]

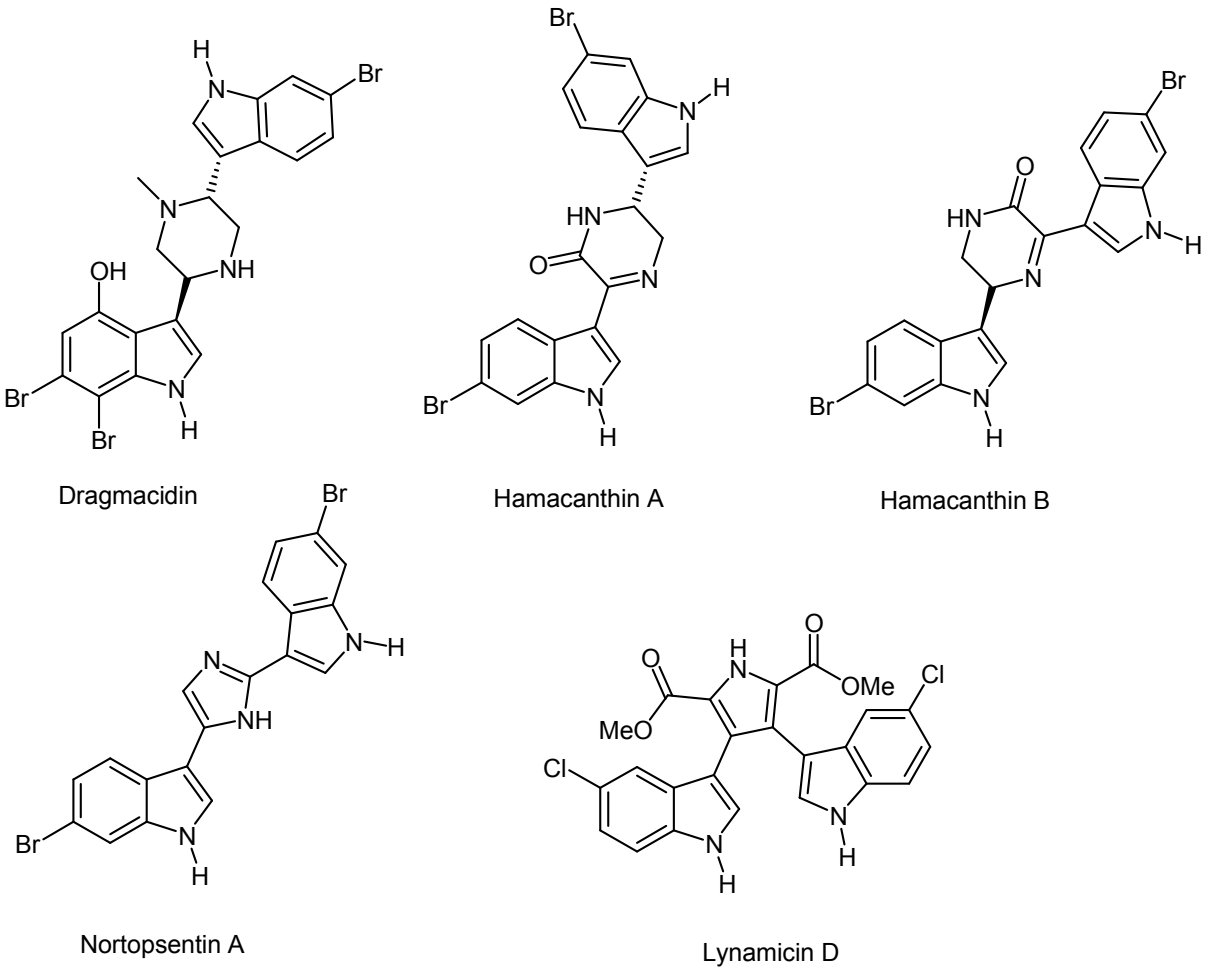
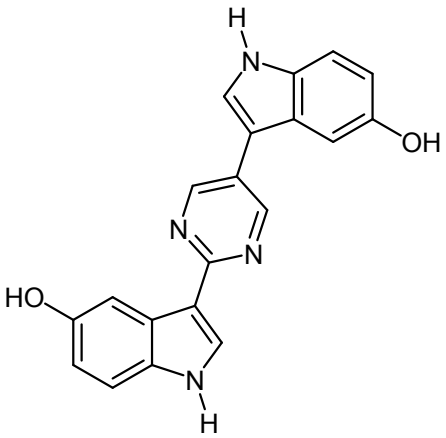


Figure 15. Structures of naturally occuring bisindole alkaloids (representative examples).

In 2007, *Kobayashi* reported the isolation and structural elucidation of the new bisindole alkaloid hyrtinadine A (Figure 16).[479]

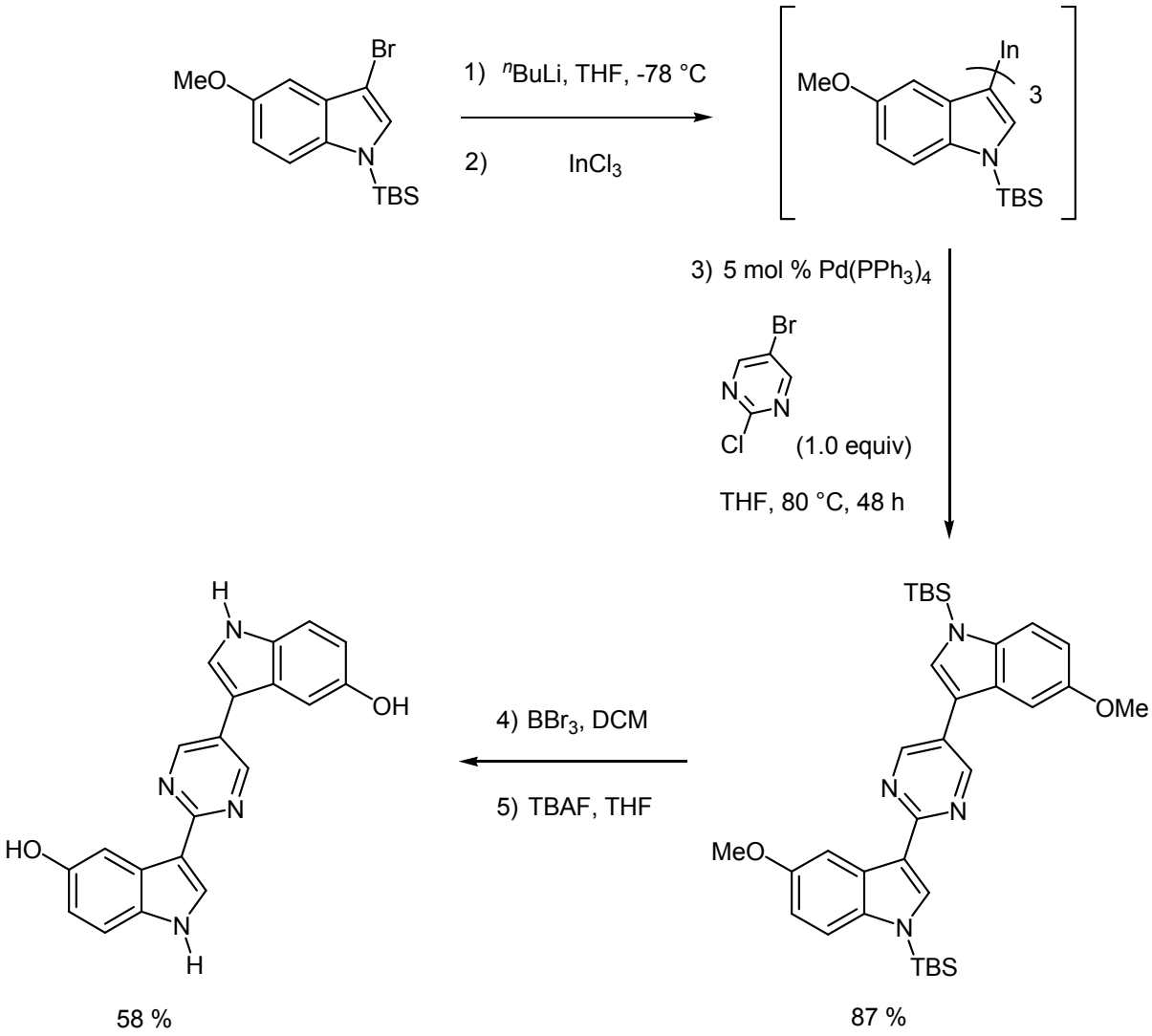


Hyrtinadine A

Figure 16. Structure of hyrtinadine A.

The compound was isolated from an Okinawan marine sponge *Hyrtios* sp. and contains two 5-hydroxyindole moieties connected by a 2,5-pyrimidyl ring. This structural element is unprecedented. It is worth mentioning that only 1 mg of this alkaloid could be obtained from 1.13 kg (!) sponge (wet weight), which corresponds to 0.0046 % yield. Hyrtinadine A exhibited cytotoxicity against murine leukemia L1210 cells (IC_{50} = 1 μg/mL) and human epidermoid carcinoma KB cells (IC_{50} = 3 μg/mL) in vitro.

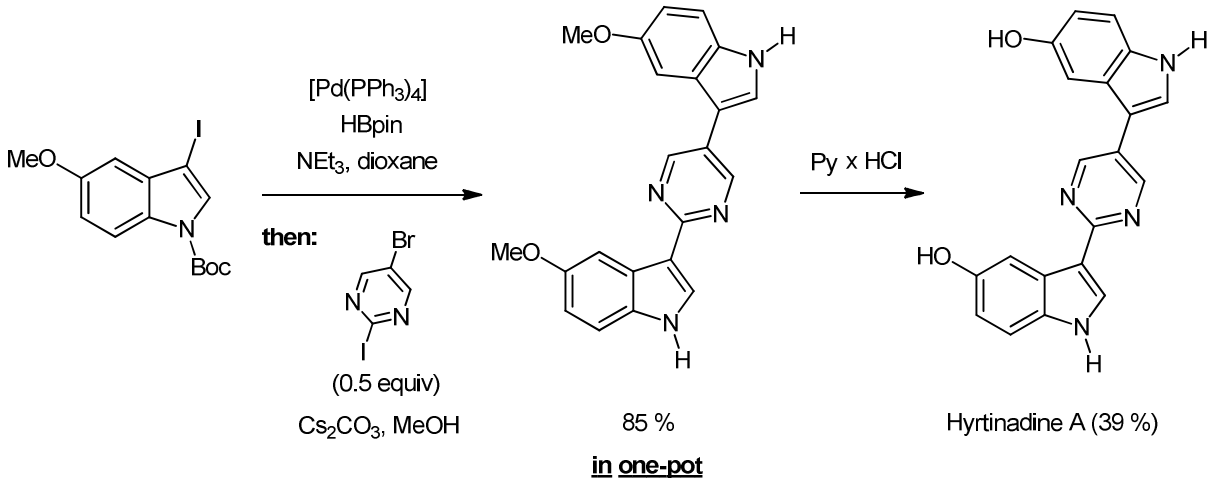
The sole total synthesis of hyrtinadine A, desribed in 2008 by *Sestelo* and *Sarandeses*, was achieved by a two-fold cross-coupling reaction between a tris(3-indolyl)indium reagent and 5-bromo-2-chloropyrimidine as a key step (Scheme 122).[480]



Scheme 122. Total synthesis of hyrtinadine A via Pd-catalyzed coupling of an organoindium compound.

The starting material was prepared in a one-pot procedure and 90 % yield from the commercially available 5-methoxyindole by *N*-silylation with TBSCl, followed by bromination with NBS at a low temperature. The natural product was obtained in 46 % overall yield (31 mg were prepared). Despite the elegance and novelty of the key step, the major drawback of this synthesis is the reqiured excess of the core indolylindium reagent, which has to be prepared and which is therefore a precious compound. In terms of the concept of atom economy, the key step is not efficient.

In the framework of this thesis, the developed *Masuda* borylation – *Suzuki* coupling sequence[464] working with a simple catalytic system could be successfully applied for a concise one-pot synthesis of heteroaryl brigded (aza)indoles as demonstrated for the total synthesis of the marine natural product hyrtinadine A (Scheme 123).[481]



Scheme 123. Total synthesis of hyrtinadine A.[481]

Although hyrtinadine A was found to be essentially inactive in viability assays and in kinase assays (> 50 % inhibition of 3 from 121 kinases at a concentration of 1 μM), its synthetic precursor, *O,O'*-dimethyl hyrtinadine A, possessed an antiproliferative activity in a low micromolar range in assays with two cancer cell lines (IC_{50} (HCT116) = 3.7 μM; IC_{50} (A2780) = 4.5 μM). However, none of the 110 kinases tested were inhibited, indicating that the cytotoxic activity is presumably not correlated to the kinase inhibition activity of these compounds.

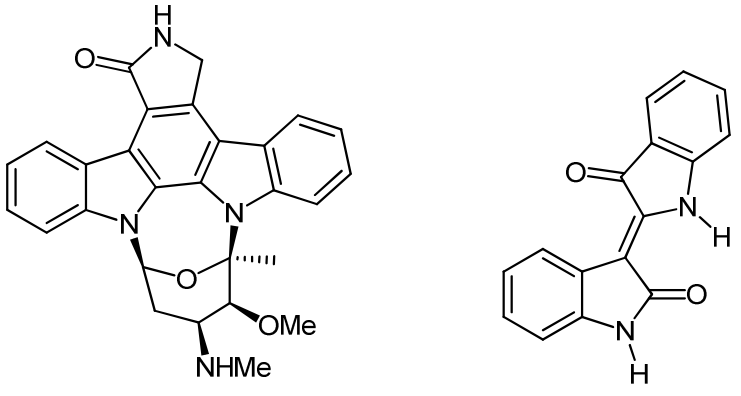
These results are part of this cumulative dissertation (**publication 3.8**).

2.11 Kinases and kinase inhibitors

The human genome encodes some 518 protein kinases (human kinome), which constitute one of the largest protein families in humans. The majority of small-molecule kinase inhibitors target the ATP-binding site of the enzymes.[482] The ATP-binding site in protein kinases, placed between the two lobes of the kinase fold and called the hinge region, is highly conserved, and therefore, the development of highly ATP-competitive kinase inhibitors is a difficult task. Moreover, these inhibitors usually lack selectivity. However, there are regions within the binding cleft that are not occupied by ATP, and these regions (hydrophobic pockets) show a higher degree of structural diversity between members of the kinase family than the ATP-binding regions. This provides opportunities for the discovery or design of selective and small molecule ATP-competitive inhibitors.[483],[484]

Although a few kinase inhibitors such as staurosporine (Figure 17), a natural indolo[2,3-α]carbazole alkaloid originally isolated in 1977 from *Streptomyces staurosporeus*, are unselective, many display a definite specificity profile, but all inhibit several kinases. Multitarget inhibitors may find appropriate medicinal use because they are less likely to allow resistance to develop.

Interestingly, certain indirubin dyes, which are the active ingredients in an ancient Chinese herbal remedy that has been used for centuries to treat diseases such as cancer, are potent CDK inhibitors (Figure 17).[485]



Staurosporine Indirubin

Figure 17. Structures of the multikinase inhibitor staurosporine and of CDK inhibitor indirubin, an isomer of indigo.

The anticancer drug Gleevec® (imatinib mesylate, Glivec®)[486] is one of the most interesting developments in the pharmaceutical industry in the last two decades. It is a 2-phenylamino pyrimidine[487] containing drug and belongs to the class of kinase inhibitors (Figure 18). The drug was developed by *Novartis* and is indicated for the treatment of chronic myeloid leukaemia (CML) and gastrointestinal stromal tumors (GISTs).

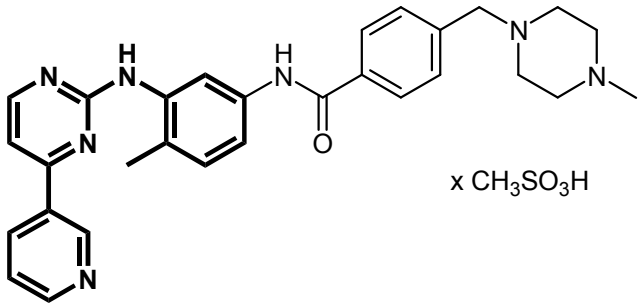


Figure 18. Structure of imatinib mesylate (gleevec). The pharmacophore is drawn in bold.

Gleevec, which was approved for clinical use in May 2001, is the first important drug to be developed by targeting a protein kinase specifically. Gleevec does not attack all proliferating cells, but blocks selectively the ATP-binding site of Bcr-Abl tyrosin kinase protein, which is a constitutively active fusion protein version of the protein kinase c-Abl and plays the key role in the occurrence of CML. The structure-activity-relationship shows the phenylamino pyrimidine unit to be essential for the biological activity. Further substituents enhance the selectivity and bioavailability. The impact of imatinib on the field of cancer therapy has been dramatic and can not be overestimated. As the first successful targeted drug to treat cancer, imatinib opened the era of molecular targeted therapy and established a model for the development of future drugs.

The compound has been rationally designed, in contrast to another kinase inhibitor drug sorafenib (Nexavar®, *Bayer*), which has been developed by a combinatorial approach (Figure 19).[488],[489] This compound inhibits Raf kinase, a key mediator of signal-transduction pathways from cell surface receptors to the cell nucleus.

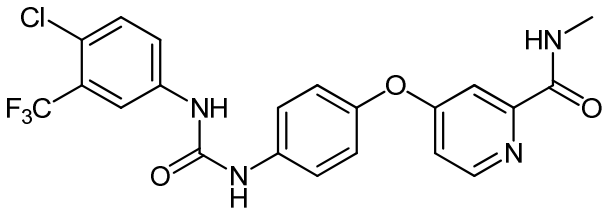
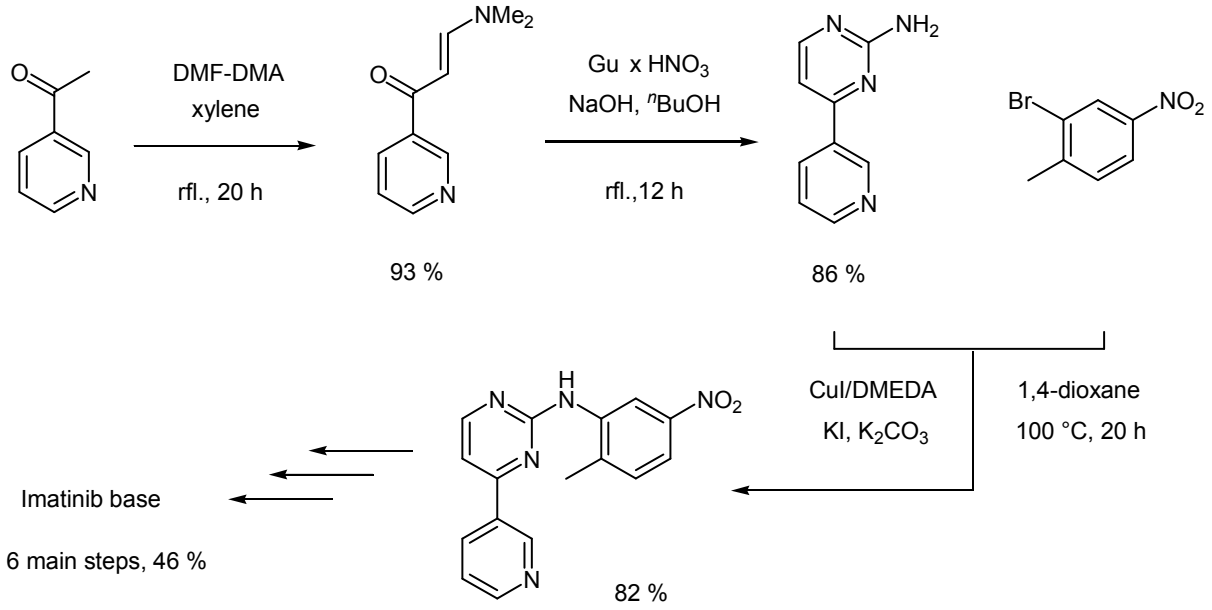


Figure 19. Structure of sorafenib (nexavar).

Due to the outstanding properties of imatinib, there has been an enormous interest in improvements of its synthesis.[490] In 2008, imatinib and its analogs were reported to be prepared in an improved procedure using a Cu-catalyzed *Ullmann*-type coupling as a key step to synthesize the pharmacophore. The amino pyrimidine intermediate, however, was prepared by the reaction of β-enaminone and guanidine nitrate in a classical stepwise fashion (Scheme 124).[491]



Scheme 124. Improved synthetic route to imatinib and its analogs.

In 2010, *Lu* presented a new synthesis of imatinib using a stepwise preparation of the key phenylamino pyrimidine intermediate via reaction of the enaminone with thiourea, followed by a nucleophilic aromatic substitution of the 2-(methylthio)pyrimidine with an aniline derivative. However, this approach required even more steps to construct the pharmacophore.[492] Also in 2010, *Ley* reported a concise flow-based synthesis of imatinib. Despite obvious advantages of this convergent approach, the pharma-

cophore is still built up via *Buchwald-Hartwig* amination using a large excess (4 equivs) of 4-(pyridine-3-yl)pyrimidine-2-amine for the ultimate construction of the phenylamino pyrimidine motif.[493]

Nilotinib[494] (Tasigna®, *Novartis*) posesses the same and bafetinib[495] a very similar pharmacophore as imitinib. They belong to the “second generation” inhibitors of Bcr-Abl for the treatment of imatinib-resistant CML (Figure 20).[496]

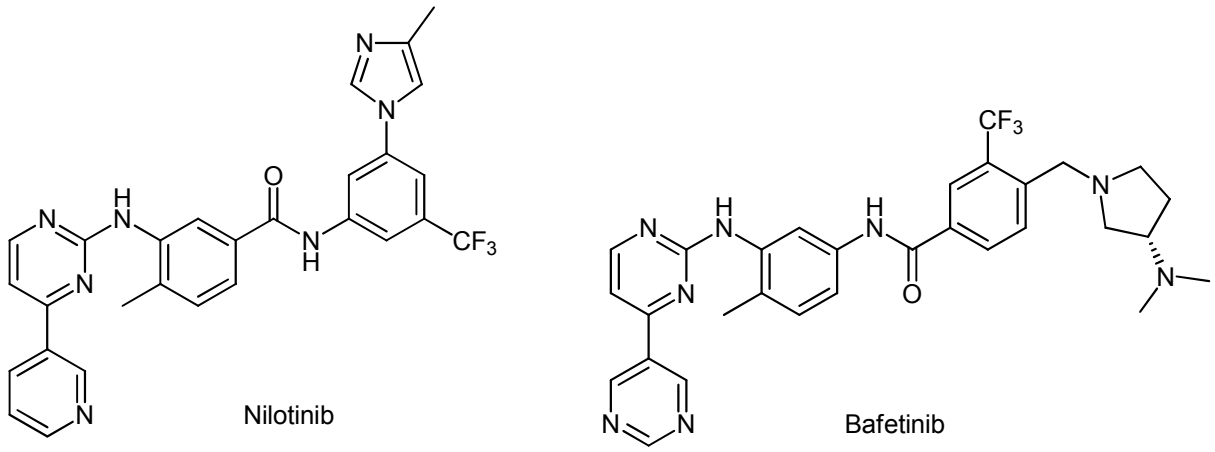


Figure 20. Kinase inhibitors as drugs.

It is worth mentioning that imatinib, sorafenib, and other kinase inhibitors which reached the market have been developed as selective inhibitors but turned out to be inhibitors of at least several kinases, which can also display cooperative effects.[484] For example, besides being a relatively specific inhibitor of Bcr-Abl, gleevec also inhibits the c-kit and PDGF-receptor tyrosin kinases with similar potency. It has been undergoing clinical trials for the treatment of gastrointestinal stromal tumors and other cancers in which c-kit or PDGF-receptor signalling is disregulated. Therefore, although achieving high selectivity is possible, it can often be an advantage to simultaneously inhibit several therapeutically relevant and complementary kinases at the same time (selectivity profile rather than absolute selectivity).[497] Thus, developing oligokinase inhibitors that inhibit a range of protein kinases is a valid approach.

To summarize, prior to this work the pharmacophore of imitinib and nilotinib had to be prepared in several steps rather than in a one-pot manner.

3 General Part – Publications

Publications relevant for this cumulative dissertation are enrolled and the estimated contributions are discussed.

Complete publication manuscripts with supporting information including characterization of all compounds can be found in the appendix.

3.1 Catalytic syntheses of *N*-heterocyclic ynones and ynediones by in situ activation of carboxylic acids with oxalyl chloride

Christina Boersch, Eugen Merkul, Thomas J. J. Müller, *Angew. Chem. Int. Ed.* **2011**, published online, 10.1002/anie.201103296.

Contribution

In the framework of this thesis, I developed the idea to establish this method, performed first orienting experiments that demonstrated its feasibility, was involved in the planning of the experiments, contributed to the writing of the first draft of the manuscript, assisted in the compilation of the supporting information, and was involved in the discussions. The experimental work was performed by M. Sc. Christina Boersch.

My contribution as a co-author of this paper is approximately 20 %.

3.2 Consecutive one-pot Sonogashira-Glaser coupling sequence – direct preparation of symmetrical diynes by sequential Pd/Cu-catalysis

Eugen Merkul, Dominik Urselmann, Thomas J. J. Müller, *Eur. J. Org. Chem.* **2011**, 238-242. DOI: 10.1002/ejoc.201001472.

Contribution

In the framework of this thesis, I developed the idea to work out this reaction as a preparative method, planned the experiments and performed approximately 55 % of the experimental work including the optimization. The remaining examples were prepared by Dipl.-Chem. Dominik Urselmann. I compiled the supporting information, contributed to the writing of the first draft of the manuscript, and was involved in the discussions.

My contribution as a co-author of this paper is approximately 70 %.

3.3 Rapid preparation of triazolyl substituted NH-heterocyclic kinase inhibitors via one-pot Sonogashira coupling–TMS-deprotection–CuAAC sequence

Eugen Merkul, Fabian Klukas, Dieter Dorsch, Ulrich Grädler, Hartmut E. Greiner, Thomas J. J. Müller, *Org. Biomol. Chem.* **2011**, *9*, 5129-5136. DOI: 10.1039/C1OB05586K.

Contribution

In the framework of this thesis, I developed the idea to establish this method, planned the experiments and performed most of the experimental and optimization work. Several examples and the optimization of one sequence were performed by Fabian Klukas in the course of his organic chemistry research practicum under my guidance. I wrote the first draft of the manuscript, compiled the supporting information, and was involved in the discussions. Dr. Dieter Dorsch and Dr. Hartmut Greiner were responsible for the biological evaluation of the compounds and the discussion of the obtained data. Dr. Ulrich Grädler performed the X-ray structure analysis of the complex of the compound **8f** with the kinase PDK1 and discussed the crystallographic data.

My contribution as a co-author of this paper is approximately 80 %.

3.4 Three-component synthesis of ynediones by a glyoxylation/Stephens-Castro coupling sequence

Eugen Merkul, Janis Dohe, Charlotte Gers, Frank Rominger, Thomas J. J. Müller, *Angew. Chem.* **2011**, *123*, 3023-3026; DOI: 10.1002/ange.201007194; *Angew. Chem. Int. Ed.* **2011**, *50*, 2966-2969; DOI: 10.1002/anie.201007194.

Contribution

In the framework of this thesis, I developed the idea to establish this method, planned the experiments, performed approximately 50 % of the experimental work and parts of the optimization studies. The remaining examples and additional optimization trials were performed by Janis Dohe in the course of his bachelor thesis and by B. Sc. Charlotte Gers in the course of her master thesis, both under my guidance. I wrote the first draft of the manuscript, compiled the supporting information, and was involved in the discussions. Dr. Frank Rominger performed the X-ray structure analysis.

My contribution as a co-author of this paper is approximately 80 %.

3.5 Consecutive three-component synthesis of ynones by decarbonylative Sonogashira coupling

Eugen Merkul, Thomas Oeser, Thomas J. J. Müller, *Chem. Eur. J*. **2009**, *15*, 5006-5011. DOI: 10.1002/chem.200900119.

Contribution

In the framework of this thesis, I developed the idea to establish this method, planned the experiments, performed the experimental work, compiled the supporting information, wrote the first draft of the manuscript, and was involved in the discussions. Dr. Thomas Oeser performed the X-ray structure analysis.

My contribution as a co-author of this paper is approximately 95 %.

3.6 Three-component synthesis of *N*-Boc-4-iodopyrroles and sequential one-pot alkynylation

Eugen Merkul, Christina Boersch, Walter Frank, Thomas J. J. Müller, *Org. Lett*. **2009**, *11*, 2269-2272. DOI: 10.1021/ol900581a.

Contribution

In the framework of this thesis, I developed the idea to establish this method, planned the experiments, and performed approximately 55 % of the experimental work including the optimization. The remaining examples were prepared by Christina Boersch in the course of her bachelor thesis under my guidance. I wrote the first draft of the manuscript, compiled the supporting information, and was involved in the discussions. The X-ray structure analysis was performed by Prof. Dr. Walter Frank.

My contribution as a co-author of this paper is approximately 80 %.

3.7 Rapid synthesis of bis(hetero)aryls by one-pot Masuda borylation – Suzuki coupling sequence and its application to concise total syntheses of meridianins A and G

Eugen Merkul, Elisabeth Schäfer, Thomas J. J. Müller, *Org. Biomol. Chem.* **2011**, *9*, 3139-3141. DOI: 10.1039/clob05310h.

Contribution

In the framework of this thesis, I developed the idea to adapt this one-pot method to our synthetic problem, planned the experiments and performed most of the experimental work including the optimization. The total synthesis of meridianin A was performed by Elisabeth Schäfer in the course of her organic chemistry internship under my guidance. I wrote the first draft of the manuscript, compiled the supporting information, and was involved in the discussions.

My contribution as a co-author of this paper is approximately 95 %.

3.8 One-pot synthesis of diazine-bridged bisindoles and concise synthesis of marine alkaloid hyrtinadine A

Boris O. A. Tasch, Eugen Merkul, Thomas J. J. Müller, *Eur. J. Org. Chem*. **2011**, 4532-4535. 10.1002/ejoc.201100680.

Contribution

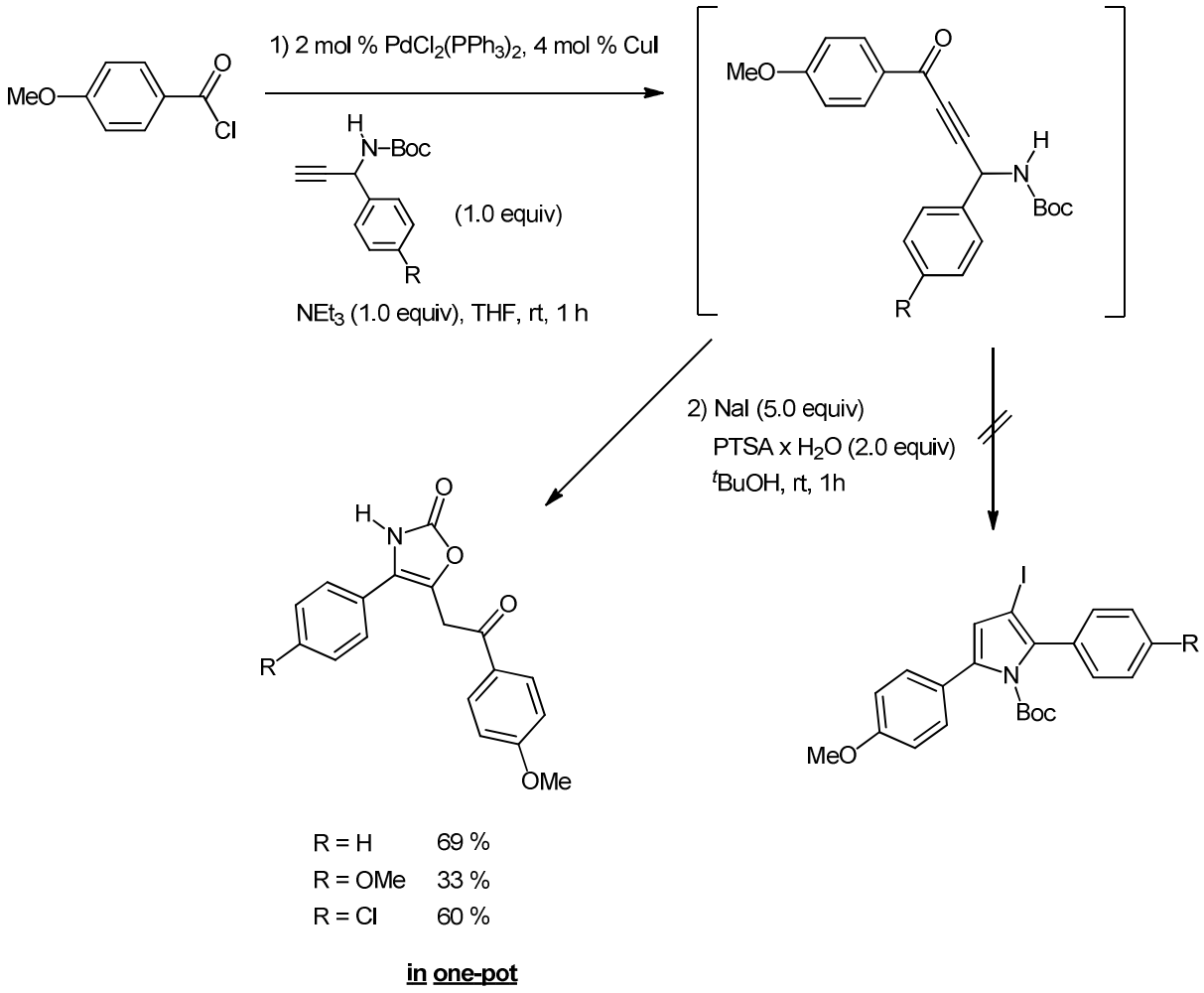
In the framework of this thesis, I developed the idea to perform this synthesis, planned the experiments and performed approximately 50 % of the experimental work including the initial total synthesis of the natural product hyrtinadine A. The remaining examples were prepared by Dipl.-Chem. Boris Tasch and he improved the yield in the last step of the synthesis of hyrtinadine A. I contributed in parts to the writing of the first draft of the manuscript, to the compilation of the supporting information, and was involved in discussions.

My contribution as a co-author of this paper is approximately 70 %.

4 General Part – Outlook

4.1 Oxazol-2-ones

When the synthesis of 2,5-disubstituted 4-iodo pyrroles in analogy to the presented one-pot three-component synthesis of 2-(hetero)aryl 4-iodo pyrroles was attempted, unexpectedly 4,5-disubstituted oxazol-2-ones were obtained in moderate yields.[498] Remarkably, no pyrrole byproducts could be detected, indicating a high selectivity of this process (Scheme 125).



Scheme 125. Unexpected selective formation of oxazol-2-ones.

In one case, the structure was also confirmed by an X-ray structure analysis (Figure 21). The compound forms an unsymmetrical dimer via intermolecular H-bonding between the two conformers.

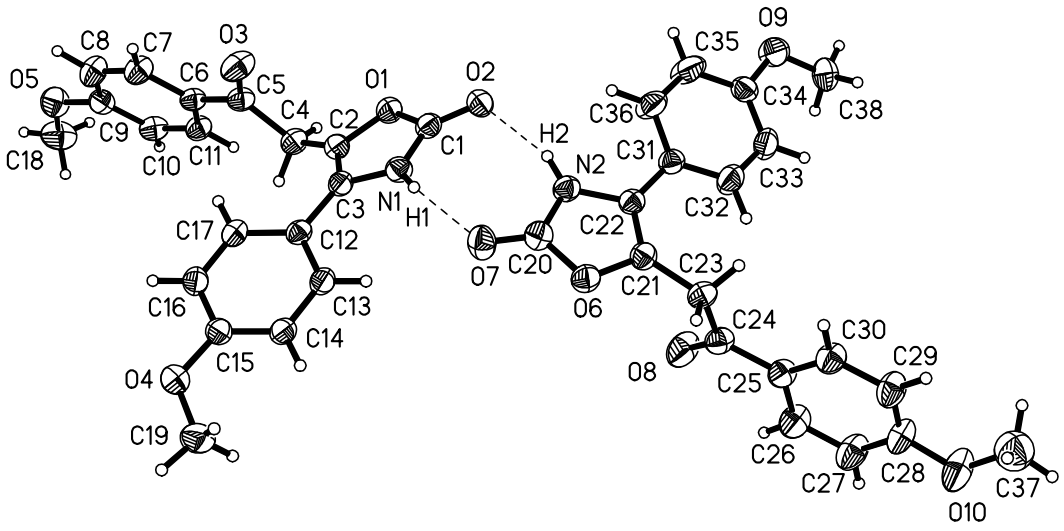


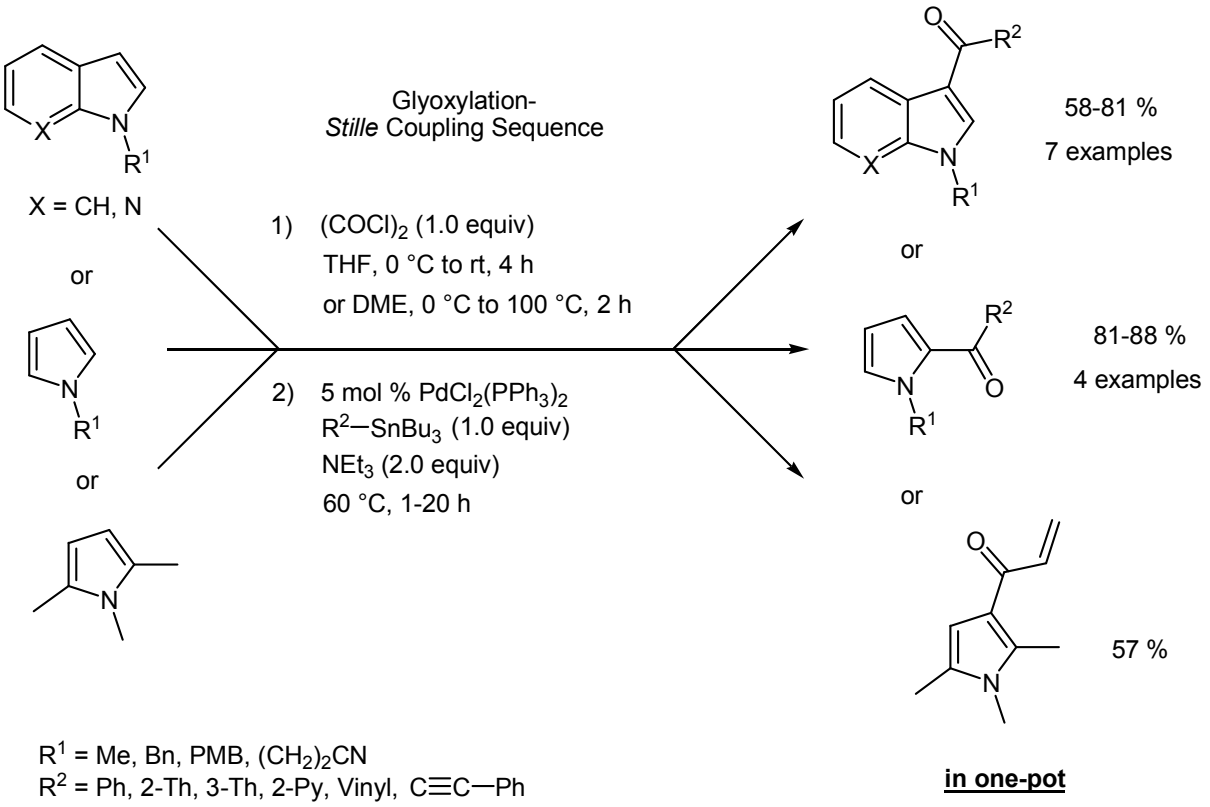
Figure 21. X-Ray structure analysis of 5-[2-(4-methoxyphenyl)-2-oxo-ethyl]-4-(4-methoxyphenyl)-3*H*-oxazol-2-one (performed by Prof. Dr. Walter Frank).

This new synthesis of oxazolones via coupling – isomerization should be further investigated to unravel substitution effects leading to the selective formation of oxazolones over pyrroles.

4.2 Glyoxylation – cross-coupling sequences

The developed strategy based on the glyoxylation of electron rich heterocycles with oxalyl chloride as a surrogate for carbon monoxide followed by metal-catalyzed coupling reactions such as *Sonogashira* or *Castro* couplings has the potential to be further developed in two directions: the one-pot synthesis of diverse heterocycles and the implementation of further cross-coupling reactions as part of new sequences.

As an illustration, in 2010 we reported a new synthesis of ketones by a glyoxylation – decarbonylative *Stille* coupling sequence as another example of decarbonylative reaction of glyoxylyl chlorides proceeding in a one-pot fashion (Scheme 126).[499]

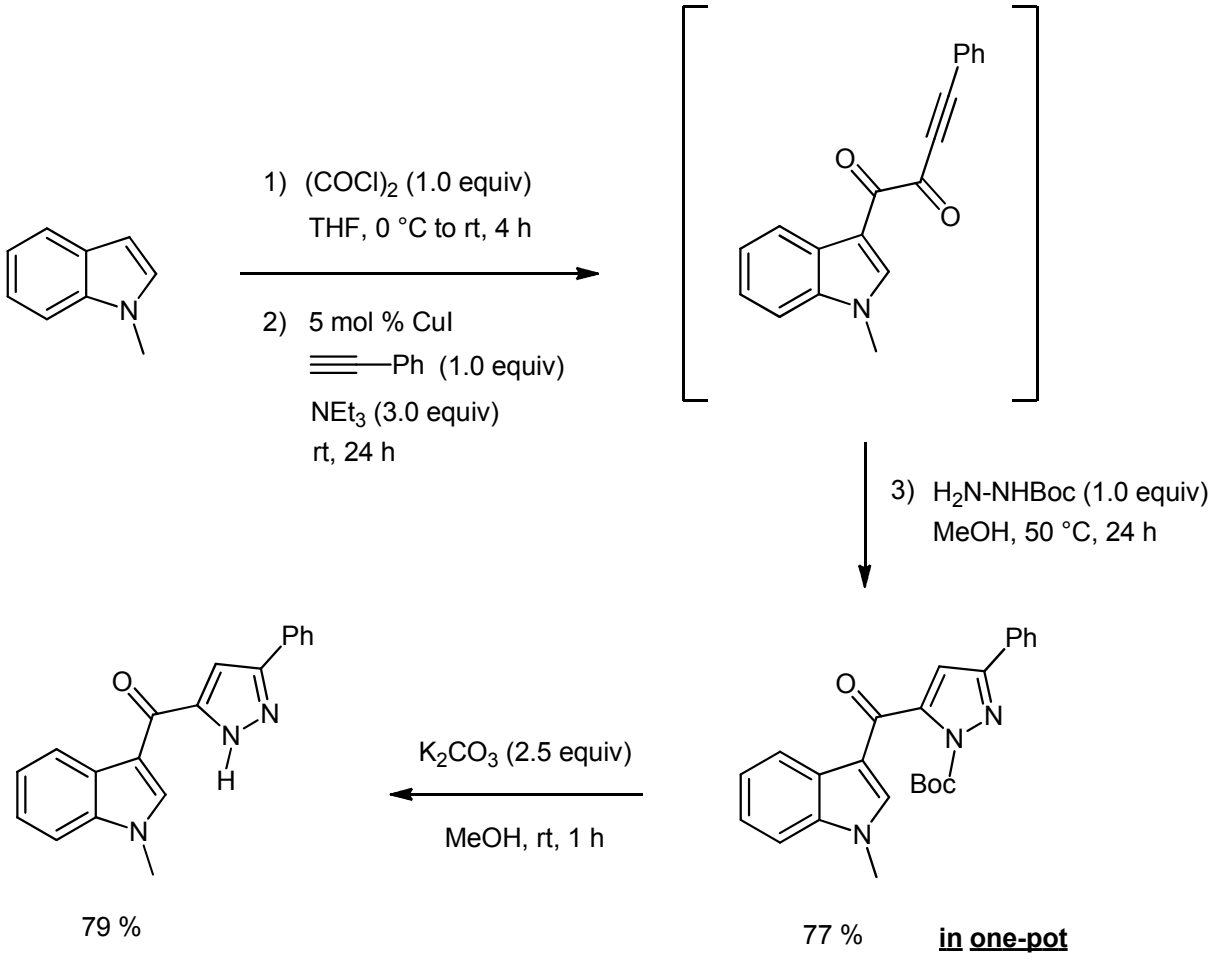


Scheme 126. Glyoxylation – *Stille* coupling sequence for the preparation of ketones.

Further sequences based on the glyoxylation – cross-coupling strategy can be conceived.

4.3 5-Acyl pyrazoles

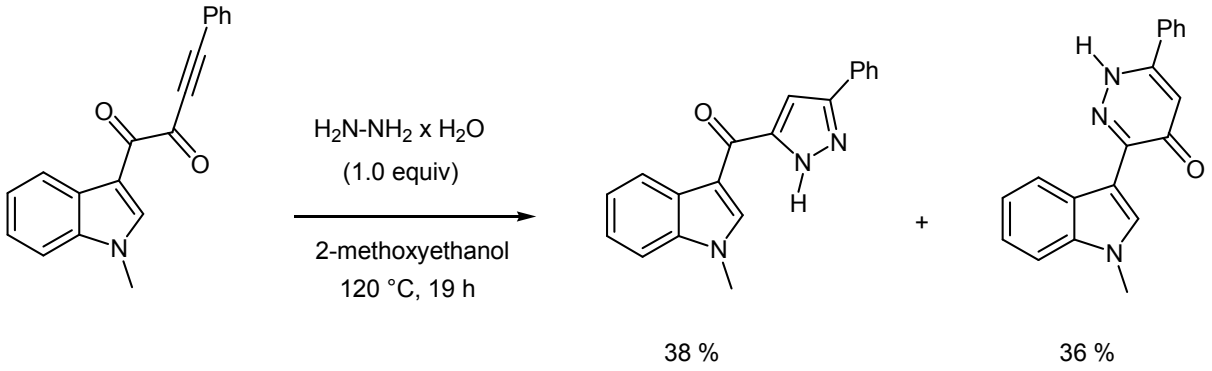
The disclosed access to ynediones via glyoxylation – *Stephens-Castro* alkynylation opens numerous possibilities for designing one-pot syntheses of heterocycles that are difficult to access in a conventional way. The best example is a novel strategy toward a selective synthesis of 5-acyl pyrazoles discovered in the scope of this work (Scheme 127).



Scheme 127. Selective formation of an indoloyl pyrazole using Boc hydrazine as a key reagent.

After the ynedione was formed in the course of the glyoxylation – *Stephens-Castro* coupling sequence, one equivalent of the Boc-protected hydrazine (*tert*-butyl carbazate) as an easy-to-handle, nontoxic, and safe reagent was added, furnishing the *N*-Boc protected indoloyl pyrazole in a good yield. After a smooth deprotection, the in-

doloyl pyrazole can be obtained in 61 % overall yield. No formation of the corresponding indolyl pyridazinone was observed. In contrary, the reaction of the same ynedione with hydrazine hydrate gave a statistical mixture of the acyl pyrazole (5-membered ring) with the corresponding pyridazinone (6-membered ring) (Scheme 128).



Scheme 128. Mixture of indoloyl pyrazole and indolyl pyridazinone by reaction of indolyl ynedione with hydrazine hydrate.

For the pyridazinone compound, an X-ray structure analysis confirmed the correct structural assignment (Figure 22). Dotted lines indicate intermolecular H-bonding between the molecules.

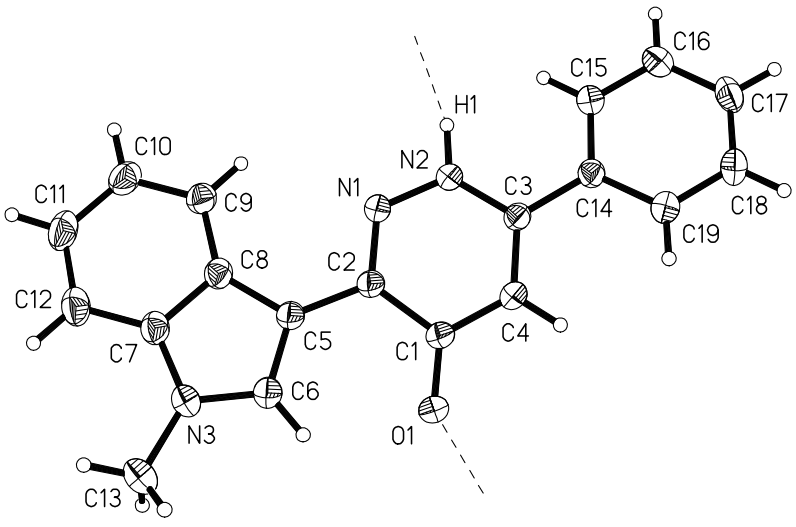
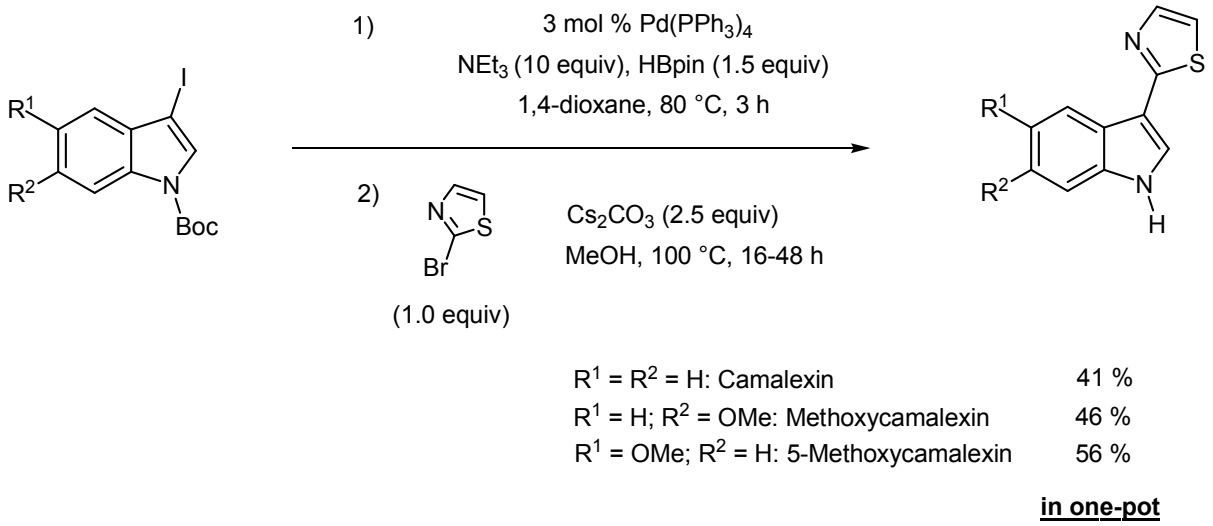


Figure 22. X-Ray structure analysis of 3-(1-methyl-1*H*-indol-3-yl)-6-phenylpyridazin-4(1*H*)-one (performed by Prof. Dr. Walter Frank).

Since pyrazoles as metabolically stable compounds represent one of the most widely used classes of 5-membered heterocycles in medicinal chemistry, this unprecedented strategy toward 3(5)-aryl-5(3)-aroyl pyrazoles,[500] to which no preparatively useful general synthetic approaches exist to date, may turn out to be very useful in the synthesis of pharmaceutically important molecules. This strategy is now under investigation.

4.4 Camalexins

The developed *Masuda* borylation – *Suzuki* coupling sequence works efficiently for the installation of 6-membered nitrogen heterocycles on (aza)indoles, pyrroles, and some other heterocycles. However, the sequence is by far less efficient in the case of 5-membered heterocyclic halides. Nevertheless, camalexin, methoxycamalexin, and 5-methoxycamalexin could be prepared in moderate yields using the standard procedure (Scheme 129).



Scheme 129. Synthesis of camalexins by the developed *Masuda* borylation – *Suzuki* coupling sequence.

The prepared camalexins were tested on two cancer cell lines and on a broad panel of kinases. Camalexin showed inhibition of the ovarian tumor cell line A2780 (IC_{50} = 3.6 μM) but inhibited none of the 103 kinases tested.

Prospective investigations could be focused on preparation of further analogs of these natural products and other derivatives with 5-membered heterocyclic rings at C-3 of indoles and related systems.

5 References

[1] For reviews, see: a) “Catalysis as an important tool of green chemistry” I. P. Beletskaya, L. M. Kustov, *Russ. Chem. Rev.* **2010**, *79*, 441-461; b) “Catalysis and sustainable (green) chemistry” G. Centi, S. Perathoner, *Catal. Today* **2003**, *77*, 287-297.

[2] *“Metal-Catalyzed Cross-Coupling Reactions”*, 2nd ed. (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**.

[3] *“Catalyzed Carbon-Heteroatom Bond Formation”*, (Ed.: A. K. Yudin), Wiley-VCH, Weinheim, **2011**.

[4] For the concept of atom economy, see: a) B. M. Trost, *Science* **1991**, *254*, 1471-1477; b) B. M. Trost, *Angew. Chem.* **1995**, *107*, 285-307; *Angew. Chem. Int. Ed.* **1995**, *34*, 259-281.

[5] a) T. Gaich, P. S. Baran, *J. Org. Chem.* **2010**, *75*, 4657-4673; b) T. Newhouse, P. S. Baran, R. W. Hoffmann, *Chem. Soc. Rev.* **2009**, *38*, 3010-3021; c) P. A. Wender, V. A. Verma, T. J. Paxton, T. H. Pillow, *Acc. Chem. Res.* **2008**, *41*, 40-49.

[6] N. Z. Burns, P. S. Baran, R. W. Hoffmann, *Angew. Chem.* **2009**, *121*, 2896-2910; *Angew. Chem. Int. Ed.* **2009**, *48*, 2854-2867.

[7] P. A. Clarke, S. Santos, W. H. C. Martin, *Green Chem.* **2007**, *9*, 438-440.

[8] For the concept of ideal synthesis, see: a) P. A. Wender, S. T. Handy, D. L. Wright, *Chem. Ind.* **1997**, 765-769; b) P. A. Wender, F. C. Bi, G. G. Gamber, F. Gosselin, R. D. Hubbard, M. J. C. Scanio, R. Sun, T. J. Williams, L. Zhang, *Pure Appl. Chem.* **2002**, *74*, 25-31; c) T. Gaich, P. S. Baran, *J. Org. Chem.* **2010**, *75*, 4657-4673.

[9] A. Bruggink, R. Schoevaart, T. Kieboom, *Org. Proc. Res. Dev.* **2003**, *7*, 622-640.

[10] C. Vaxelaire, P. Winter, M. Christmann, *Angew. Chem.* **2011**, *123*, 3685-3687; *Angew. Chem. Int. Ed.* **2011**, *50*, 3605-3607.

[11] For reviews, see: a) A. V. Ivachtchenko, Y. A. Ivanenkov, V. M. Kysil, M. Y. Krasavin, A. P. Ilyin, *Russ. Chem. Rev.* **2010**, *79*, 787-817; b) J. D. Sunderhaus, S. F. Martin, *Chem. Eur. J.* **2009**, *15*, 1300-1308; c) C. Hulme, J. Dietrich, *Mol. Diversity*

2009, *13*, 195-207; d) A. Dömling, *Chem. Rev.* **2006**, *106*, 17-89; e) J. Zhu, *Eur. J. Org. Chem.* **2003**, 1133-1144.

[12] Adapted from “Multi-component syntheses of heterocycles by transition-metal catalysis” D. M. D’Souza, T. J. J. Müller, *Chem. Soc. Rev.* **2007**, *36*, 1095-1108.

[13] “Sequentially palladium-catalyzed processes” T. J. J. Müller, *Top. Organomet. Chem.* **2006**, *19*, 149-205.

[14] “Pd-assisted multicomponent synthesis of heterocycles” G. Balme, E. Bossharth, N. Monteiro, *Eur. J. Org. Chem.* **2003**, 4101-4111.

[15] “Multi-component syntheses of heterocycles by transition-metal catalysis” D. M. D’Souza, T. J. J. Müller, *Chem. Soc. Rev.* **2007**, *36*, 1095-1108.

[16] “Metal-catalyzed one-step synthesis: towards direct alternatives to multistep heterocycle and amino acid derivative formation” B. A. Arndtsen, *Chem. Eur. J.* **2009**, *15*, 302-313.

[17] a) “Strategies for efficient lead structure discovery from natural products” J. M. Rollinger, T. Langer, H. Stuppner, *Curr. Med. Chem.* **2006**, *13*, 1491-1507; b) “The role of natural product chemistry in drug discovery” M. S. Butler, *J. Nat. Prod.* **2004**, *67*, 2141-2153.

[18] “Kinetic and catalytic mechanisms of protein kinases” J. A. Adams, *Chem. Rev.* **2001**, *101*, 2271-2290.

[19] “Protein kinases – the major drug targets of the twenty-first century?” P. Cohen, *Nat. Rev.* **2002**, *1*, 309-315.

[20] For general reviews, see: a) *Small Molecules in Oncology* (Ed.: U. M. Martens), Springer, Berlin Heidelberg, **2010**; b) “Protein kinase inhibitors in drug discovery” K. Parang, G. Sun in *Drug Discovery Handbook* (Ed.: S. C. Gad), Wiley, New Jersey, **2005**, Chapter 26.

[21] H. Weinmann, R. Metternich, *ChemBioChem* **2005**, *6*, 455-459.

[22] R. Robinson, *J. Chem. Soc.* **1917**, 762-768.

[23] “Sequential one-pot combination of multi-component and multi-catalysis cascade reactions: an emerging technology in organic synthesis” D. B. Ramachary, S. Jain, *Org. Biomol. Chem.* **2011**, *9*, 1277-1300.

[24] C. Hulme, V. Gore, *Curr. Med. Chem.* **2003**, *10*, 51-80.

[25] A. Dömling, I. Ugi, *Angew. Chem.* **2000**, *112*, 3300-3344; *Angew. Chem. Int. Ed.* **2000**, *39*, 3168-3210.

[26] a) B. Ganem, *Acc. Chem. Res.* **2009**, *42*, 463-472; b) L. Weber, K. Illgen, M. Almstetter, *Synlett* **1999**, 366-374.

[27] K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem.* **2006**, *118*, 7292-7344; *Angew. Chem. Int. Ed.* **2006**, *45*, 7134-7186.

[28] “Diversity-oriented syntheses of functional π-systems by multicomponent and domino reactions” T. J. J. Müller, D. M. D’Souza, *Pure Appl. Chem.* **2008**, *80*, 609-620.

[29] A. Ajamian, J. L. Gleason, *Angew. Chem.* **2004**, *116*, 3842-3848; *Angew. Chem. Int. Ed.* **2004**, *43*, 3754-3760.

[30] D. E. Fogg, E. N. dos Santos, *Coord. Chem. Rev.* **2004**, *248*, 2365-2379.

[31] J. M. Lee, Y. Na, H. Han, S. Chang, *Chem. Soc. Rev.* **2004**, *33*, 302-312.

[32] H. Bienaymé, C. Hulme, G. Oddon, P. Schmitt, *Chem. Eur. J.* **2000**, *6*, 3321-3329.

[33] For general reviews, see: a) “Aryl-aryl bond formation by transition-metal-catalyzed direct arylation” D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174-238; b) “Palladium-catalyzed direct arylation of simple arenes in synthesis of biaryl molecules” L. C. Campeau, K. Fagnou, *Chem. Commun.* **2006**, 1253-1264; c) “Aryl-aryl bond formation one century after the discovery of the Ullmann reaction” J. Hassan, M. Sévignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359-1469.

[34] For reviews on bicyclic privileged structures, see: a) D. A. Horton, G. T. Bourne, M. L. Smythe, *Chem. Rev.* **2003**, *103*, 893-930; b) P. J. Hajduk, M. Bures, J. Praestgaard, S. W. Fesik, *J. Med. Chem.* **2000**, *43*, 3443-3447.

[35] “Practical aspects of carbon–carbon cross-coupling reactions using heteroarenes” V. F. Slagt, A. H. M. de Vries, J. G. de Vries, R. M. Kellogg, *Org. Process Res. Dev.* **2010**, *14*, 30-47.

[36] “Palladium-catalyzed cross-coupling reactions in total synthesis” K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem.* **2005**, *117*, 4516-4563; *Angew. Chem. Int. Ed.* **2005**, *44*, 4442-4489.

[37] For a review, see: A. F. Littke, G. C. Fu, *Angew. Chem.* **2002**, *114*, 4350-4386; *Angew. Chem. Int. Ed.* **2002**, *41*, 4176-4211.

[38] “Recent progress in coupling of two heteroarenes” D. Zhao, J. You, C. Hu, *Chem. Eur. J.* **2011**, *17*, 5466-5492.

[39] Adapted from “Palladium-katalysierte Kreuzkupplungen” M. Gaab, Seminarvortrag zum Anorganisch-Chemischen Fortgeschrittenenpraktikum **2004**, Heidelberg.

[40] For reviews on palladium-catalyzed carbonylations, see: a) R. Grigg, S. P. Mutton, *Tetrahedron* **2010**, *66*, 5515-5548; b) A. Brennführer, H. Neumann, M. Beller, *Angew. Chem.* **2009**, *48*, 4114-4133; *Angew. Chem. Int. Ed.* **2009**, *121*, 4176-4196; c) C. F. J. Barnard, *Organometallics* **2008**, *27*, 5402-5422.

[41] Adapted from “Copper in cross-coupling reactions. The post-Ullmann chemistry” I. P. Beletskaya, A. V. Cheprakov, *Coord. Chem. Rev.* **2004**, *248*, 2337-2364.

[42] For recent reviews, see: a) “Copper-catalyzed coupling reactions” H. Rao, H. Fu, *Synlett* **2011**, 745-769; b) “Catalytic C–C, C–N, and C–O Ullmann-type coupling reactions” F. Monnier, M. Taillefer, *Angew. Chem.* **2009**, *121*, 7088-7105; *Angew. Chem. Int. Ed.* **2009**, *48*, 6954-6971; c) “Copper-mediated coupling reactions and their applications in natural products and designed biomolecules synthesis” G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, *108*, 3054-3131; d) “Copper in cross-coupling reactions. The post-Ullmann chemistry” I. P. Beletskaya, A. V. Cheprakov, *Coord. Chem. Rev.* **2004**, *248*, 2337-2364; e) “Modern synthetic methods for copper-mediated C(aryl)–O, C(aryl)–N, and C(aryl)–S bond formation” S. V. Ley, A. W. Thomas, *Angew. Chem.* **2003**, *115*, 5558-5607; *Angew. Chem. Int. Ed.* **2003**, *42*, 5400-5449; f) “Renaissance of Ullmann and Goldberg reactions – progress in copper cata-

lyzed C–N-, C–O- and C–S-coupling“ K. Kunz, U. Scholz, D. Ganzer, *Synlett* **2003**, 2428-2439.

[43] For recent developments in Ullmann-type coupling reactions, see: a) H.-J. Xu, Y.-F. Liang, Z.-Y. Cai, H.-X. Qi, C.-Y. Yang, Y.-S. Feng, *J. Org. Chem.* **2011**, *76*, 2296-2300; b) D. Ma, Q. Cai, *Acc. Chem. Res.* **2008**, *41*, 1450-1460. For a recent highlight, see: c) F. Monnier, M. Taillefer, *Angew. Chem.* **2008**, *120*, 3140-3143; *Angew. Chem. Int. Ed.* **2008**, *47*, 3096-3099, and references therein.

[44] D. Maiti, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 17423-17429.

[45] R. A. Altman, A. M. Hyde, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2008**, *130*, 9613-9620.

[46] J.-J. Dai, J.-H. Liu, D.-F. Luo, L. Liu, *Chem. Commun.* **2011**, *47*, 677-679.

[47] a) J. A. Keith, P. M. Henry, *Angew. Chem.* **2009**, *121*, 9200-9212; *Angew. Chem. Int. Ed.* **2009**, *48*, 9038-9049; b) J. Smidt, W. Hafner, R. Jira, R. Sieber, J. Sedlmeier, A. Sabel, *Angew. Chem.* **1962**, *74*, 93-102; *Angew. Chem. Int. Ed.* **1962**, *1*, 80-88; c) J. Smidt, W. Hafner, R. Jira, J. Sedlmeier, R. Sieber, R. Rüttinger, H. Kojer, *Angew. Chem.* **1959**, *71*, 176-182.

[48] L. J. Gooßen, F. Rudolphi, C. Oppel, N. Rodríguez, *Angew. Chem.* **2008**, *120*, 3085-3088; *Angew. Chem. Int. Ed.* **2008**, *47*, 3043-3045.

[49] L. J. Gooßen, G. Deng, L. M. Levy, *Science* **2006**, *313*, 662-664.

[50] L. J. Gooßen, N. Rodríguez, C. Linder, *J. Am. Chem. Soc.* **2008**, *130*, 15248-15249.

[51] L. J. Gooßen, N. Rodríguez, P. P. Lange, C. Linder, *Angew. Chem.* **2010**, *122*, 1129-1132; *Angew. Chem. Int. Ed.* **2010**, *49*, 1111-1114.

[52] L. J. Gooßen, B. Zimmermann, T. Knauber, *Angew. Chem.* **2008**, *120*, 7211-7214; *Angew. Chem. Int. Ed.* **2008**, *47*, 7103-7106.

[53] L. J. Gooßen, B. Zimmermann, C. Linder, N. Rodríguez, P. P. Lange, J. Hartung, *Adv. Synth. Catal.* **2009**, *351*, 2667-2674.

[54] F. Rudolphi, B. Song, L. J. Gooßen, *Adv. Synth. Catal.* **2011**, *353*, 337-342.

[55] “Palladium-copper catalyzed alkyne activation as an entry to multicomponent syntheses of heterocycles” T. J. J. Müller, *Top. Heterocycl. Chem.* **2010**, *25*, 25-94.

[56] Seminal publications: a) C. E. Castro, R. D. Stephens, *J. Org. Chem.* **1963**, *28*, 2163-2163; b) R. D. Stephens, C. E. Castro, *J. Org. Chem.* **1963**, *28*, 3313-3315.

[57] CuI/PPh_3 catalytic system: a) K. Okuro, M. Furuune, M. Miura, M. Nomura, *Tetrahedron Lett.* **1992**, *33*, 5363-5364; b) K. Okuro, M. Furuune, M. Enna, M. Miura, M. Nomura, *J. Org. Chem.* **1993**, *58*, 4716-4721; CuI/8-hydroxyquinoline catalytic system: c) M. Wu, J. Mao, J. Guo, S. Ji, *Eur. J. Org. Chem.* **2008**, 4050-4054, see also references therein for further catalytic systems.

[58] C. Chowdhury, N. G. Kundu, *Tetrahedron* **1999**, *55*, 7011-7016, and references therein.

[59] J.-X. Wang, B. Wei, Y. Hu, Z. Liu, Y. Fu, *Synth. Commun.* **2001**, *31*, 3527-3532.

[60] P. J. Tambade, Y. P. Patil, N. S. Nandurkar, B. M. Bhanage, *Synlett* **2008**, 886-888.

[61] M. Guo, D. Li, Z. Zhang, *J. Org. Chem.* **2003**, *68*, 10172-10174.

[62] Seminal publication: “A convenient synthesis of acetylenes: catalytic substitution of acetylenic hydrogen with bromoalkenes, iodoarenes, and bromopyridines” K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, *50*, 4467-4470.

[63] Seminal publication: L. Cassar, *J. Organomet. Chem.* **1975**, *93*, 253-257.

[64] Seminal publication: H. A. Dieck, F. R. Heck, *J. Organomet. Chem.* **1975**, *93*, 259-263.

[65] Mini account “Development of Pd–Cu catalyzed cross-coupling of terminal acetylenes with sp^2-carbon halides” K. Sonogashira, *J. Organomet. Chem.* **2002**, *653*, 46-49.

[66] M. J. Mio, L. C. Kopel, J. B. Braun, T. L. Gadzikwa, K. L. Hull, R. G. Brisbois, C. J. Markworth, P. A. Grieco, *Org. Lett.* **2002**, *4*, 3199-3202.

[67] R. Severin, J. Reimer, S. Doye, *J. Org. Chem.* **2010**, *75*, 3518-3521.

[68] For general reviews, see: a) “The Sonogashira Coupling Reaction” H. Plenio, A. Datta in *“Handbook of C-H Transformations, Applications in Organic Synthesis”*, Ed.: G. Dyker, Wiley-VCH, Weinheim, **2005**, 45-53; b) “Cross-Coupling Reactions to sp Carbon Atoms” J. A. Marsden, M. M. Haley in *“Metal-Catalyzed Cross-Coupling Reactions”*, 2nd ed. (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**, 319-345; c) “Cross-coupling Reactions to sp Carbon Atoms” K. Sonogashira in *“Metal-Catalyzed Cross-Coupling Reactions”*, Eds.: F. Diederich, P. J. Stang, Wiley-VCH, Weinheim, **1998**, 203-229.

[69] Y. Tohda, K. Sonogashira, N. Hagihara, *Synthesis* **1977**, 777-778.

[70] C.-J. Li, *Acc. Chem. Res.* **2010**, *43*, 581-590.

[71] a) “New entry to a three-component pyrimidine synthesis by TMS-ynones via Sonogashira coupling” A. Karpov, T. J. J. Müller, *Org. Lett.* **2003**, *5*, 3451-3454; b) D. M. D’Souza, T. J. J. Müller, *Nat. Prot.* **2008**, *3*, 1660-1665.

[72] For similar methods that appeared later, see: a) S. S. Palimkar, P. H. Kumar, N. R. Jogdand, T. Daniel, R. J. Lahoti, K. V. Srinivasan, *Tetrahedron Lett.* **2006**, *47*, 5527-5530; b) R. J. Cox, D. J. Ritson, T. A. Dane, J. Berge, J. P. H. Charmant, A. Kantacha, *Chem. Commun.* **2005**, 1037-1039.

[73] D. A. Alonso, C. Nájera, M. C. Pacheco, *J. Org. Chem.* **2004**, *69*, 1615-1619.

[74] L. Chen, C.-J. Li, *Org. Lett.* **2004**, *6*, 3151-3153.

[75] J.-Y. Chen, T.-C. Lin, S.-C. Chen, A.-J. Chen, C.-Y. Mou, F.-Y. Tsai, *Tetrahedron* **2009**, *65*, 10134-10141, see references therein for further examples.

[76] M. Bakherad, A. Keivanloo, B. Bahramian, S. Jajarmi, *Synlett* **2011**, 311-314.

[77] For recent reviews, see: a) “Carboxylic acids as substrates in homogeneous catalysis” L. J. Gooßen, N. Rodríguez, K. Gooßen, *Angew. Chem.* **2008**, *120*, 3144-3164; *Angew. Chem. Int. Ed.* **2008**, *47*, 3100-3120; b) “New catalytic transformations of carboxylic acids” L. J. Gooßen, K. Gooßen, N. Rodríguez, M. Blanchot, C. Linder, B. Zimmermann, *Pure Appl. Chem.* **2008**, *80*, 1725-1733.

[78] M. Nilsson, *Acta Chem. Scand.* **1966**, *20*, 423-426.

[79] a) D. Tanaka, S. P. Romeril, A. G. Myers, *J. Am. Chem. Soc.* **2005**, *127*, 10323-10333; b) D. Tanaka, A. G. Myers, *Org. Lett.* **2004**, *6*, 433-436; c) A. G. Myers, D. Tanaka, M. R. Mannion, *J. Am. Chem. Soc.* **2002**, *124*, 11250-11251.

[80] a) "Biaryl forming involving carbon-based leaving groups: why not?" S. M. Bonesi, M. Fagnoni, A. Albini, *Angew. Chem.* **2008**, *120*, 10172-10175; *Angew. Chem. Int. Ed.* **2008**, *47*, 10022-10025; b) "New approaches for decarboxylative biaryl coupling" O. Baudoin, *Angew. Chem.* **2007**, *119*, 1395-1397; *Angew. Chem. Int. Ed.* **2007**, *46*, 1373-1375.

[81] For recent examples, see: a) S. Mochida, K. Hirano, T. Satoh, M. Miura, *J. Org. Lett.* **2011**, *76*, 3024-3033; b) J. Wang, Z. Cui, Y. Zhang, H. Li, L.-M. Wu, Z. Liu, *Org. Biomol. Chem.* **2011**, *9*, 663-666; c) L. J. Gooßen, N. Rodríguez, P. P. Lange, C. Linder, *Angew. Chem.* **2010**, *122*, 1129-1132; *Angew. Chem. Int. Ed.* **2010**, *49*, 1111-1114; d) R. Shang, Z.-W. Yang, Y. Wang, S.-L. Zhang, L. Liu, *J. Am. Chem. Soc.* **2010**, *132*, 14391-14393; e) S. Mochida, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2010**, *12*, 5776-5779; f) Z. Fu, S. Huang, W. Su, M. Hong, *Org. Lett.* **2010**, *12*, 4992-4995; g) K. Xie, Z. Yang, X. Zhou, X. Li, S. Wang, Z. Tan, X. An, C.-C. Guo, *Org. Lett.* **2010**, *12*, 1564-1567; h) F. A. Arroyave, J. R. Reynolds, *Org. Lett.* **2010**, *12*, 1328-1331; i) R. Shang, Q. Xu, Y.-Y. Jiang, Y. Wang, L. Liu, *Org. Lett.* **2010**, *12*, 1000-1003; j) Z.-M. Sun, J. Zhang, P. Zhao, *Org. Lett.* **2010**, *12*, 992-995; k) M. Yamashita, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2010**, *12*, 592-595; l) R. Shang, Y. Fu, J.-B. Li, S.-L. Zhang, Q.-X. Guo, L. Liu, *J. Am. Chem. Soc.* **2009**, *131*, 5738-5739; m) C. Wang, I. Piel, F. Glorius, *J. Am. Chem. Soc.* **2009**, *131*, 4194-4195; n) J. Cornella, P. Lu, I. Larrosa, *Org. Lett.* **2009**, *11*, 5506-5509; o) J. Moon, M. Jang, S. Lee, *J. Org. Chem.* **2009**, *74*, 1403-1406; p) J. Moon, M. Jeong, H. Nam, J. Ju, J. H. Moon, H. M. Jung, S. Lee, *Org. Lett.* **2008**, *10*, 945-948; q) J.-M. Becht, C. Catala, C. Le Drian, A. Wagner, *Org. Lett.* **2007**, *9*, 1781-1783.

[82] a) M. Li, H. Ge, *Org. Lett.* **2010**, *12*, 3464-3467; b) M. Li, C. Wang, H. Ge, *Org. Lett.* **2011**, *13*, 2062-2064.

[83] L. J. Gooßen, N. Rodríguez, B. Melzer, C. Linder, G. Deng, L. M. Levy, *J. Am. Chem. Soc.* **2007**, *129*, 4824-4833.

[84] a) F. Zhang, M. F. Greaney, *Org. Lett.* **2010**, *12*, 4745-4747; b) F. Zhang, M. F. Greaney, *Angew. Chem.* **2010**, *122*, 2828-2831; *Angew. Chem. Int. Ed.* **2010**, *49*, 2768-2771; c) F. Bilodeau, M.-C. Brochu, N. Guimond, K. H. Thesen, P. Forgione, *J. Org. Chem.* **2010**, *75*, 1550-1560; d) P. Forgione, M.-C. Brochu, M. St-Onge, K. H. Thesen, M. D. Bailey, F. Bilodeau, *J. Am. Chem. Soc.* **2006**, *128*, 11350-11351.

[85] J. Lindh, P. J. R. Sjöberg, M. Larhed, *Angew. Chem.* **2010**, *122*, 7899-7903; *Angew. Chem. Int. Ed.* **2010**, *49*, 7733-7737.

[86] a) J. Zhou, P. Hu, M. Zhang, S. Huang, M. Wang, W. Su, *Chem. Eur. J.* **2010**, *16*, 5876-5881; b) M. Miyasaka, A. Fukushima, T. Satoh, K. Hirano, M. Miura, *Chem. Eur. J.* **2009**, *15*, 3674-3677.

[87] P. Lu, C. Sanchez, J. Cornella, I. Larossa, *Org. Lett.* **2009**, *11*, 5710-5713.

[88] L. J. Gooßen, K. Ghosh, *Chem. Commun.* **2001**, 2084-2085.

[89] a) L. J. Gooßen, K. Ghosh, *Chem. Commun.* **2002**, 836-837 (Pd-catalyzed reduction to aldehydes); b) L. J. Gooßen, K. Ghosh, *Angew. Chem.* **2001**, *113*, 3566-3568; *Angew. Chem. Int. Ed.* **2001**, *40*, 3458-3460.

[90] L. J. Gooßen, L. Winkel, A. Döhring, K. Ghosh, J. Peatzold, *Synlett* **2002**, 1237-1240.

[91] “Catalytic syntheses of *N*-heterocyclic ynones and ynediones by in situ activation of carboxylic acids with oxalyl chloride”, C. Boersch, E. Merkul, T. J. J. Müller, *Angew. Chem. Int. Ed.* **2011**, 10.1002/anie.201103296, published online.

[92] For some examples, see: a) A. Fusano, T. Fukuyama, S. Nishitani, T. Inouye, I. Ryu, *Org. Lett.* **2010**, *12*, 2410-2413; b) J. Liu, J. Chen, C. Xia, *J. Catal.* **2008**, *253*, 50-56; c) M. T. Rahman, T. Fukuyama, N. Kamata, M. Sato, I. Ryu, *Chem. Commun.* **2006**, 2236-2238; d) B. C. Bishop, K. M. J. Brands, A. D. Gibb, D. J. Kennedy, *Synthesis* **2004**, 43-52; e) L. Delaude, A. M. Masdeu, H. Alper, *Synthesis* **1994**, 1149-1151; f) T. Kobayashi, M. Tanaka, *J. Chem. Soc., Chem. Commun.* **1981**, 333-334.

[93] N. Haddad, J. Tan, V. Farina, *J. Org. Chem.* **2006**, *71*, 5031-5034.

[94] K. C. Nicolaou, D. Sarlah, D. M. Shaw, *Angew. Chem.* **2007**, *119*, 4792-4795; *Angew. Chem. Int. Ed.* **2007**, *46*, 4708-4711.

[95] V. N. Kalinin, M. V. Shostakovsky, A. B. Ponomaryov, *Tetrahedron Lett.* **1990**, *31*, 4073-4076.

[96] V. N. Kalinin, M. V. Shostakovsky, A. B. Ponomaryov, *Tetrahedron Lett.* **1992**, *33*, 373-376.

[97] S. Torii, L. H. Xu, H. Okumoto, *Synlett* **1991**, 695-696.

[98] S. Torii, L. H. Xu, M. Sadakane, H. Okumoto, *Synlett* **1992**, 513-514.

[99] S. Torii, H. Okumoto, L. H. Xu, *Tetrahedron Lett.* **1990**, *31*, 7175-7178.

[100] S. Torii, H. Okumoto, L. H. Xu, *Tetrahedron Lett.* **1991**, *32*, 237-240.

[101] S. Torii, H. Okumoto, L. H. Xu, M. Sadakane, M. V. Shostakovsky, A. B. Ponomaryov, V. N. Kalinin, *Tetrahedron* **1993**, *49*, 6773-6784.

[102] Y. Huang, H. Alper, *J. Org. Chem.* **1991**, *56*, 4534-4536.

[103] A. Arcadi, S. Cacchi, F. Marinelli, P. Pace, G. Sanzi, *Synlett* **1995**, 823-824.

[104] S.-K. Kang, K.-H. Lim, P.-S. Ho, W.-Y. Kim, *Synthesis* **1997**, 874-876.

[105] P. G. Ciattini, E. Morera, G. Ortar, *Tetrahedron Lett.* **1991**, *32*, 6449-6452.

[106] P. G. Ciattini, E. Morera, G. Ortar, S. S. Rossi, *Tetrahedron* **1991**, *47*, 6449-6456.

[107] H. Miao, Z. Yang, *Org. Lett.* **2000**, *2*, 1765-1768.

[108] “Carbonylative Sonogashira coupling of terminal alkynes with aqueous ammonia” M. S. M. Ahmed, A. Mori, *Org. Lett.* **2003**, *5*, 3057-3060.

[109] M. S. M. Ahmed, K. Kobayashi, A. Mori, *Org. Lett.* **2005**, *7*, 4487-4489.

[110] B. Liang, M. Huang, Z. You, Z. Xiong, K. Lu, R. Fathi, J. Chen, Z. Yang, *J. Org. Chem.* **2005**, *70*, 6097-6100.

[111] E. Awuah, A. Capretta, *Org. Lett.* **2009**, *11*, 3210-3213.

[112] T. Fukuyama, R. Yamaura, I. Ryu, *Can. J. Chem.* **2005**, *83*, 711-715.

[113] J. Liu, X. Peng, W. Sun, Y. Zhao, C. Xia, *Org. Lett.* **2008**, *10*, 3933-3936.

[114] A. Fusano, T. Fukuyama, S. Nishitani, T. Inouye, I. Ryu, *Org. Lett.* **2010**, *12*, 2410-2413.

[115] X.-F. Wu, H. Neumann, M. Beller, *Chem. Eur. J.* **2010**, *16*, 12104-12107.

[116] X.-F. Wu, B. Sundararaju, H. Neumann, P. H. Dixneuf, M. Beller, *Chem. Eur. J.* **2011**, *17*, 106-110.

[117] M. T. Rahman, T. Fukuyama, N. Kamata, M. Sato, I. Ryu, *Chem. Commun.* **2006**, 2236-2238.

[118] "Carbon monoxide intoxication: an updated review" L. D. Prockop, R. I. Chichkova, *J. Neurol. Sci.* **2007**, *262*, 122-130.

[119] M. Iizuka, Y. Kondo, *Eur. J. Org. Chem.* **2007**, 5180-5182.

[120] J. P. Stonehouse, D. S. Chekmarev, N. V. Ivanova, S. Lang, G. Pairaudeau, N. Smith, M. J. Stocks, S. I. Sviridov, L. M. Utkina, *Synlett* **2008**, 100-104.

[121] For reviews on *Sonogashira* coupling and related alkynylations, see: a) "The Sonogashira reaction: a booming methodology in synthetic organic chemistry" R. Chinchilla, C. Nájera, *Chem. Rev.* **2007**, *107*, 874-922; b) "Palladium-based catalytic systems for the synthesis of conjugated enynes by Sonogashira reactions and related alkynylations", H. Doucet, J.-C. Hierso, *Angew. Chem.* **2007**, *119*, 850-888; *Angew. Chem. Int. Ed.* **2007**, *46*, 834-871, and references therein; c) "Palladium- and/or copper-mediated cross-coupling reactions between 1-alkynes and vinyl, aryl, 1-alkynyl, 1,2-propadienyl, propargyl and allylic halides or related compounds. A review" R. Rossi, A. Carpita, F. Bellina, *Org. Prep. Proc. Int.* **1995**, *27*, 127-160.

[122] a) C. Torborg, A. Zapf, M. Beller, *ChemSusChem* **2008**, *1*, 91-96, and references therein; b) T. Hundertmark, A. F. Littke, S. L. Buchwald, G. C. Fu, *Org. Lett.* **2000**, *2*, 1729-1231; c) V. P. W. Böhm, W. A. Herrmann, *Eur. J. Org. Chem.* **2000**, 3679-3681; d) S. Thorand, N. Krause, *J. Org. Chem.* **1998**, *63*, 8551-8553.

[123] a) C. Torborg, J. Huang, T. Schulz, B. Schäffner, A. Zapf, A. Spannenberg, A. Börner, M. Beller, *Chem. Eur. J.* **2009**, *15*, 1329-1336, and references therein; b) A. Komáromi, Z. Novák, *Chem. Commun.* **2008**, 4968-4970; c) C. Yi, R. Hua, *J. Org. Chem.* **2006**, *71*, 2535-2537; d) D. Gelman, S. L. Buchwald, *Angew. Chem.* **2003**,

115, 6175-6178; *Angew. Chem. Int. Ed.* **2003**, *42*, 5993-5996; e) A. Köllhofer, T. Pullmann, H. Plenio, *Angew. Chem.* **2003**, *115*, 1086-1088; *Angew. Chem. Int. Ed.* **2003**, *42*, 1056-1058.

[124] P. Y. Choy, W. K. Chow, C. M. So, C. P. Lau, F. Y. Kwong, *Chem. Eur. J.* **2010**, *16*, 9982-9985.

[125] R. R. Tykwinski, *Angew. Chem.* **2003**, *115*, 1604-1606; *Angew. Chem. Int. Ed.* **2003**, *42*, 1566-1568.

[126] For a recent highlight on catalysts for the *Sonogashira* coupling, see: a) H. Plenio, *Angew. Chem.* **2008**, *120*, 7060-7063; *Angew. Chem. Int. Ed.* **2008**, *47*, 6954-6956. For new ligands, see: b) C. A. Fleckenstein, H. Plenio, *Chem. Eur. J.* **2007**, *13*, 2701-2716.

[127] For a review on one-pot syntheses of diarylalkynes, see: A. Nagy, Z. Novák, A. Kotschy, *J. Organomet. Chem.* **2005**, *690*, 4453-4461.

[128] C. Glaser, *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422-424.

[129] A. Baeyer, *Ber. Dtsch. Chem. Ges.* **1882**, *15*, 50-56.

[130] “Acetylenic coupling: a powerful tool in molecular construction” P. Siemsen, R. C. Livingston, F. Diederich, *Angew. Chem.* **2000**, *112*, 2740-2767; *Angew. Chem. Int. Ed.* **2000**, *39*, 2632-2657.

[131] a) G. Eglinton, A. R. Galbraith, *J. Chem. Soc.* **1959**, 889-896; modification using MeCN as a solvent: b) R. Berscheid, F. Vögtle, *Synthesis* **1992**, 58-62.

[132] A. S. Hay, *J. Org. Chem.* **1960**, *25*, 1275-1276.

[133] A. S. Hay, *J. Org. Chem.* **1962**, *27*, 3320-3321.

[134] General review: “Glaser Homocoupling and the Cadiot-Chodkiewicz Hetero-coupling Reaction” P. Siemsen, B. Felber in *“Handbook of C-H Transformations, Applications in Organic Synthesis”*, Ed.: G. Dyker, Wiley-VCH, Weinheim, **2005**, 53-62.

[135] Environmentally bening solvent: a) A. Kusuda, X.-H. Xu, X. Wang, E. Tokunaga, N. Shibata, *Green Chem.* **2011**, *13*, 843-846; CuNPs-promoted homocoupling: b) F. Nador, L. Fortunato, Y. Moglie, C. Vitale, G. Radivoy, *Synthesis* **2009**, 4027-4031;

CuCl/TMEDA/O_2 in [bmim]PF_6: c) J. S. Yadav, B. V. S. Reddy, K. B. Reddy, K. U. Gayathri, A. R. Prasad, *Tetrahedron Lett.* **2003**, *44*, 6493-6496; microwave enhanced solvent-free coupling: d) G. W. Kabalka, L. Wang, R. M. Pagni, *Synlett* **2001**, 108-110; homocoupling in scCO_2: e) J. Li, H. Jiang, *Chem. Commun.* **1999**, 2369-2370.

[136] S. Adimurthy, C. C. Malakar, U. Beifuss, *J. Org. Chem.* **2009**, *74*, 5648-5651.

[137] Y. Nishihara, K. Ikegashira, K. Hirabayashi, J.-i. Ando, A. Mori, T. Hiyama, *J. Org. Chem.* **2000**, *65*, 1780-1787.

[138] For further similar approaches, see: a) H. Yoshida, Y. Yamaryo, J. Ohshita, A. Kunai, *Chem. Commun.* **2003**, 1510-1511; b) M. A. Heuft, S. K. Collins, G. P. A. Yap, A. G. Fallis, *Org. Lett.* **2001**, *3*, 2883-2886.

[139] R. Rossi, A. Carpita, C. Bigelli, *Tetrahedron Lett.* **1985**, *26*, 523-526.

[140] D. H. Cho, J. H. Lee, B. H. Kim, *J. Org. Chem.* **1999**, *64*, 8048-8050.

[141] M. Vlassa, I. Ciocan-Tarta, F. Mărgineanu, I. Oprean, *Tetrahedron* **1996**, *52*, 1337-1342.

[142] Q. Liu, D.J. Burton, *Tetrahedron Lett.* **1997**, *38*, 4371-4374.

[143] A. Lei, M. Srivastava, X. Zhang, *J. Org. Chem.* **2002**, *67*, 1969-1971.

[144] a) I. J. S. Fairlamb, P. S. Bäuerlein, L. R. Marrison, J. M. Dickinson, *Chem. Commun.* **2003**, 632-633; b) A. S. Batsanov, J. C. Collings, I. J. S. Fairlamb, J. P. Holland, J. A. K. Howard, Z. Lin, T. B. Marder, A. C. Parsons, R. M. Ward, J. Zhu, *J. Org. Chem.* **2005**, *70*, 703-706.

[145] J.-H. Li, Y. Liang, X.-D. Zhang, *Tetrahedron* **2005**, *61*, 1903-1907.

[146] M. Shi, H.-x. Qian, *Appl. Organomet. Chem.* **2006**, *20*, 771-774.

[147] T. Kurita, M. Abe, T. Maegawa, Y. Monguchi, H. Sajiki, *Synlett* **2007**, 2521-2524.

[148] D. A. Alonso, C. Nájera, M. C. Pacheco, *Adv. Synth. Catal.* **2003**, *345*, 1146-1158.

[149] J.-H. Li, Y. Liang, Y.-X. Xie, *J. Org. Chem.* **2005**, *70*, 4393-4396.

[150] F. Yang, X. Cui, Y.-n. Li, J. Zhang, G.-r. Ren, Y. Wu, *Tetrahedron* **2007**, *63*, 1963-1969.

[151] A. Elangovan, Y.-H. Wang, T.-I. Ho, *Org. Lett.* **2003**, *5*, 1841-1844.

[152] S. S. Bag, R. Kundu, M. Das, *J. Org. Chem.* **2011**, *76*, 2332-2337.

[153] For a review, see: A. L. K. Shi Shun, R. R. Tykwinski, *Angew. Chem.* **2006**, *118*, 1050-1073; *Angew. Chem. Int. Ed.* **2006**, *45*, 1034-1057, and references therein.

[154] T. Okamoto, K. Kudoh, A. Wakamiya, S. Yamaguchi, *Org. Lett.* **2005**, *7*, 5301-5304.

[155] a) A. J. Chalk, *Tetrahedron Lett.* **1972**, *33*, 3487-3490; b) K. E. Schulte, J. Reisch, H. Walker, *Chem. Ber.* **1965**, *98*, 98-103.

[156] G. Abbiati, A. Arcadi, E. Beccalli, G. Bianchi, F. Marinelli, E. Rossi, *Tetrahedron* **2006**, *62*, 3033-3039.

[157] M. G. Saulnier, D. B. Frennesson, M. S. Deshpande, D. M. Vyas, *Tetrahedron Lett.* **1995**, *36*, 7841-7844.

[158] K. Shin, K. Ogasawara, *Synlett* **1995**, 859-860.

[159] J. Park, E. Park, A. Kim, S.-A. Park, Y. Lee, K.-W. Chi, Y. H. Jung, I. S. Kim, *J. Org. Chem.* **2011**, *76*, 2214-2219.

[160] Y. Kim, A. Park, K. Park, S. Lee, *Tetrahedron Lett.* **2011**, *52*, 1766-1769.

[161] “Consecutive one-pot Sonogashira-Glaser coupling sequence – direct preparation of symmetrical diynes by sequential Pd/Cu catalysis” E. Merkul, D. Urselmann, T. J. J. Müller, *Eur. J. Org. Chem.* **2011**, 238-242.

[162] Seminal publication: “The palladium-catalyzed cross-coupling reaction of phenylboronic acid with haloarenes in the presence of bases” N. Miyaura, T. Yanagi, A. Suzuki, *Synth. Commun.* **1981**, *11*, 513-519.

[163] For a 40th anniversary article, see: a) “Carbon-carbon bonding made easy” A. Suzuki, *Chem. Commun.* **2005**, 4759-4763. For a historical note, see: b) N. Miyaura, *J. Organomet. Chem.* **2002**, *653*, 54-57.

[164] For general reviews, see: a) “Metal-Catalyzed Cross-Coupling Reactions of Organoboron Compounds with Organic Halides” N. Miyaura in *“Metal-Catalyzed Cross-Coupling Reactions”*, 2nd ed. (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**, 41-123; b) “Coupling of Aryl and Alkyl Halides with Organoboron Reagents (Suzuki Reaction)” A. Zapf in *“Transition Metals for Organic Synthesis”*, 2nd ed. (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **2004**, 211-229.

[165] For selected reviews, see: a) S. Kotha, K. Lahiri, D. Kashinath, *Tetrahedron* **2002**, *58*, 9633-9695; b) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457-2483.

[166] a) T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685-4696; b) M. Miura, *Angew. Chem.* **2004**, *116*, 2251-2253; *Angew. Chem. Int. Ed.* **2004**, *43*, 2201-2203; c) F. Bellina, A. Carpita, R. Rossi, *Synthesis* **2004**, 2419-2440.

[167] A. S. Guram, X. Wang, E. E. Bunel, M. M. Faul, R. D. Larsen, M. J. Martinelli, *J. Org. Chem.* **2007**, *72*, 5104-5112.

[168] a) H. Bonin, R. Leuma-Yona, B. Marchiori, P. Demonchaux, E. Gras, *Tetrahedron Lett.* **2011**, *52*, 1132-1135; b) M. Tobisu, N. Chatani, *Angew. Chem.* **2009**, *121*, 3617-3620; *Angew. Chem. Int. Ed.* **2009**, *48*, 3565-3568.

[169] K. L. Billingsley, S. L. Buchwald, *Angew. Chem.* **2008**, *120*, 4773-4776; *Angew. Chem. Int. Ed.* **2008**, *47*, 4695-4698.

[170] J. Z. Deng, D. V. Paone, A. T. Ginnetti, H. Kurihara, S. D. Dreher, S. A. Weissman, S. R. Stauffer, C. S. Burgey, *Org. Lett.* **2009**, *11*, 345-347.

[171] D. X. Yang, S. L. Colletti, K. Wu, M. Song, G. Y. Li, H. C. Shen, *Org. Lett.* **2009**, *11*, 381-384.

[172] M. Prieto, E. Zurita, E. Rosa, L. Muñoz, P. Lloyd-Williams, E. Giralt, *J. Org. Chem.* **2004**, *69*, 6812-6820.

[173] X.-F. Wu, P. Anbarasan, H. Neumann, M. Beller, *Angew. Chem.* **2010**, *122*, 9231-9234; *Angew. Chem. Int. Ed.* **2010**, *49*, 9047-9050.

[174] T. Ishiyama, M. Murata, N. Miyaura, *J. Org. Chem.* **1995**, *60*, 7508-7510.

[175] C. E. Tucker, J. Davidson, P. Knochel, *J. Org. Lett.* **1992**, *57*, 3482-3485.

[176] Seminal publications: a) “Novel palladium(0)-catalyzed coupling reaction of dialkoxyborane with aryl halides: convenient synthetic route to arylboronates” M. Murata, S. Watanabe, Y. Masuda, *J. Org. Chem.* **1997**, *62*, 6458-6459; b) “Palladium-catalyzed borylation of aryl halides or triflates with dialkoxyborane: a novel and facile synthetic route to arylboronates” M. Murata, T. Oyama, S. Watanabe, Y. Masuda, *J. Org. Chem.* **2000**, *65*, 164-168.

[177] W. Zhu, D. Ma, *Org. Lett.* **2006**, *8*, 261-263.

[178] V. A. Kallepalli, F. Shi, S. Paul, E. N. Onyeozili, R. E. Maleczka Jr., M. R. Smith III, *J. Org. Chem.* **2009**, *74*, 9199-9201.

[179] T. Kasahara, Y. Kondo, *Chem. Commun.* **2006**, 891-893.

[180] M. G. Banwell, A. M. Bray, A. J. Edwards, D. J. Wong, *J. Chem. Soc., Perkin Trans. 1* **2002**, 1340-1343.

[181] M. Deodhar, D. StC. Black, D. S.-H. Chan, N. Kumar, *Heterocycles* **2010**, *80*, 1267-1274.

[182] S. Huang, R. Li, P. J. Connolly, S. Emanuel, S. A. Middleton, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4818-4821.

[183] L. Wang, W. Lu, *Org. Lett.* **2009**, *11*, 1079-1082.

[184] O. Baudoin, D. Guénard, F. Guéritte, *J. Org. Chem.* **2000**, *65*, 9268-9271.

[185] O. Baudoin, M. Cesario, D. Guénard, F. Guéritte, *J. Org. Chem.* **2002**, *67*, 1199-1207.

[186] M. Penhoat, V. Levacher, G. Dupas, *J. Org. Chem.* **2003**, *68*, 9517-9520.

[187] P.-E. Broutin, I. Čerňa, M. Campaniello, F. Leroux, F. Colobert, *Org. Lett.* **2004**, *6*, 4419-4422.

[188] H. A. Duong, S. Chua, P. B. Huleatt, C. L. L. Chai, *J. Org. Chem.* **2008**, *73*, 9177-9180.

[189] Seminal publication: F. Ullmann, J. Bielecki, *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 2174-2185.

[190] Seminal publications: a) F. Ullmann, *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382-2384; b) F. Ullmann, *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 853-854; c) F. Ullmann, P. Sponagel, *Ber. Dtsch. Chem. Ges.* **1905**, *38*, 2211-2212.

[191] Seminal publication: I. Goldberg, *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 1691-1692.

[192] Seminal publication: W. R. H. Hurtley, *J. Chem. Soc.* **1929**, 1870-1873.

[193] a) P. P. Cellier, H.-J. Cristau, J.-F. Spindler, M. Taillefer, US 2003/0171593; b) M. Taillefer, H.-J. Cristau, P. P. Cellier, US 2005/0234239; c) S. L. Buchwald, A. Klapars, J. C. Antilla, G. E. Job, M. Wolter, F. Y. Kwong, G. Nordmann, E. J. Hennessy, WO 02/085838.

[194] For selected examples, see: a) J. Jiao, X.-R. Zhang, N.-H. Chang, J. Wang, J.-F. Wei, X.-Y. Shi, Z.-G. Chen, *J. Org. Chem.* **2011**, *76*, 1180-1183; b) Z.-J. Liu, J.-P. Vors, E. R. F. Gesing, C. Bolm, *Adv. Synth. Catal.* **2010**, *352*, 3158-3162; c) D. Maiti, S. L. Buchwald, *J. Org. Chem.* **2010**, *75*, 1791-1794; d) Y. Monguchi, T. Maejima, S. Mori, T. Maegawa, H. Sajiki, *Chem. Eur. J.* **2010**, *16*, 7372-7375; e) Z.-J. Liu, J.-P. Vors, E. R. F. Gesing, C. Bolm, *Adv. Synth. Catal.* **2010**, *352*, 3158-3162; f) J. Kim, S. Chang, *Chem. Commun.* **2008**, 3052-3054; g) A. Shafir, P. A. Lichtor, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 3490-3491; h) Y. Liu, Y. Bai, J. Zhang, Y. Li, J. Jiao, X. Qi, *Eur. J. Org. Chem.* **2007**, 6084-6088; i) K. Okano, H. Tokuyama, T. Fukuyama, *Org. Lett.* **2003**, *5*, 4987-4990; j) D. Ma, Q. Cai, H. Zhang, *Org. Lett.* **2003**, *5*, 2453-2455; k) G. E. Job, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 3703-3706; l) A. Klapars, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 7421-7428; m) A. Klapars, J. C. Antilla, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, *123*, 7727-7729.

[195] For selected examples, see: a) K. Swapna, S. N. Murthy, Y. V. D. Nageswar, *Eur. J. Org. Chem.* **2010**, 6678-6684; b) R. A. Altman, E. D. Koval, S. L. Buchwald, *J. Org. Chem.* **2007**, *72*, 6190-6199; c) J. C. Antilla, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 11684-11688; d) A. Klapars, J. C. Antilla, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, *123*, 7727-7729.

[196] A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 14844-14845.

[197] a) T. Schareina, A. Zapf, W. Mägerlein, N. Müller, M. Beller, *Chem. Eur. J.* **2007**, *13*, 6249-6254; b) H.-J. Cristau, A. Ouali, J.-F. Spindler, M. Taillefer, *Chem. Eur. J.*

2005, *11*, 2483-2492; c) T. Schareina, A. Zapf, M. Beller, *Tetrahedron Lett.* **2005**, *46*, 2585-2588; d) I. P. Beletskaya, A. S. Sigeev, A. S. Peregudov, P. V. Petrovskii, *J. Organomet. Chem.* **2004**, *689*, 3810-3812; e) J. Zanon, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 2890-2891.

[198] For a review, see: a) S. R. Chemler, P. H. Fuller, *Chem. Soc. Rev.* **2007**, *36*, 1153-1160. For selected examples, see: b) Q. Liao, L. Zhang, S. Li, C. Xi, *Org. Lett.* **2011**, *13*, 228-231; c) J. Peng, M. Ye, C. Zong, F. Hu, L. Feng, X. Wang, Y. Wang, C. Chen, *J. Org. Chem.* **2011**, *76*, 716-719; d) R. Martín, C. H. Larsen, A. Cuenca, S. L. Buchwald, *Org. Lett.* **2007**, *9*, 3379-3382; e) M. Rodríguez Rivero, S. L. Buchwald, *Org. Lett.* **2007**, *9*, 973-976; f) X. Yuan, X. Xu, X. Zhou, J. Yuan, L. Mai, Y. Li, *J. Org. Chem.* **2007**, *72*, 1510-1513; g) R. Martín, M. Rodríguez Rivero, S. L. Buchwald, *Angew. Chem.* **2006**, *118*, 7237-7240; *Angew. Chem. Int. Ed.* **2006**, *45*, 7079-7082.

[199] For selected examples, see: a) S. Cacchi, G. Fabrizi, A. Goggiamani, *Org. Biomol. Chem.* **2011**, *9*, 641-652; b) B.-X. Tang, R.-J. Song, C.-Y. Wu, Y. Liu, M.-B. Zhou, W. T. Wei, G.-B. Deng, D.-L. Yin, J.-H. Li, *J. Am. Chem. Soc.* **2010**, *132*, 8900-8902; c) R. Bernini, G. Fabrizi, A. Sferrazza, S. Cacchi, *Angew. Chem.* **2009**, *121*, 8222-8225; *Angew. Chem. Int. Ed.* **2009**, *48*, 8078-8081; d) S. Ueda, H. Nagasawa, *Angew. Chem.* **2008**, *120*, 6511-6513; *Angew. Chem. Int. Ed.* **2008**, *47*, 6411-6413; d) G. Brasche, S. L. Buchwald, *Angew. Chem.* **2008**, *120*, 1958-1960; *Angew. Chem. Int. Ed.* **2008**, *47*, 1932-1934; e) T. V. Hansen, P. Wu, V. V. Fokin, *J. Org. Chem.* **2005**, *70*, 7761-7764.

[200] a) T. Knauber, F. Arikan, G.-V. Röschenthaler, L. J. Gooßen, *Chem. Eur. J.* **2011**, *17*, 2689-2697; b) T. Liu, Q. Shen, *Org. Lett.* **2011**, *13*, 2342-2345; c) T. D. Senecal, A. T. Parsons, S. L. Buchwald, *J. Org. Chem.* **2011**, *76*, 1174-1176; d) M. Oishi, H. Kondo, H. Amii, *Chem. Commun.* **2009**, 1909-1911.

[201] For a recent review, see: O. Daugulis, H.-Q. Do, D. Shabashov, *Acc. Chem. Res.* **2009**, *42*, 1074-1086.

[202] For selected examples, see: a) M. Rueping, N. Tolstoluzhsky, *Org. Lett.* **2011**, *13*, 1095-1097; b) J. J. Neumann, M. Suri, F. Glorius, *Angew. Chem.* **2010**, *122*, 7957-7961; *Angew. Chem. Int. Ed.* **2010**, *49*, 7790-7794; c) H.-Q. Do, O. Daugulis, *J.*

Am. Chem. Soc. **2009**, *131*, 17052-17053; d) H.-Q. Do, O. Daugulis, *J. Am. Chem. Soc.* **2007**, *129*, 12404-12405.

[203] F. Monnier, F. Turtaut, L. Duroure, M. Taillefer, *Org. Lett.* **2008**, *10*, 3203-3206.

[204] For reviews, see: a) "New Reactions of Copper Acetylides: Catalytic Dipolar Cycloadditions and Beyond" V. V. Fokin in *"Catalyzed Carbon-Heteroatom Bond Formation"*, (Ed.: A. K. Yudin), Wiley-VCH, Weinheim, **2011**; b) J. E. Hein, V. V. Fokin, *Chem. Soc. Rev.* **2010**, *39*, 1302-1315; c) C. Spiteri, J. E. Moses, *Angew. Chem.* **2010**, *122*, 33-36; *Angew. Chem. Int. Ed.* **2010**, *49*, 31-33; d) M. Meldal, C. W. Tornøe, *Chem. Rev.* **2008**, *108*, 2952-3015; e) P. Wu, V. V. Fokin, *Aldrichimica Acta* **2007**, *40*, 7-17; f) V. D. Bock, H. Hiemstra, J. H. van Maarseveen, *Eur. J. Org. Chem.* **2006**, 51-68; g) W. H. Binder, C. Kluger, *Curr. Org. Chem.* **2006**, *10*, 1791-1815.

[205] For the philosophy of click chemistry, see: a) M. G. Finn, V. V. Fokin, *Chem. Soc. Rev.* **2010**, *39*, 1231-1232; b) C. J. Hawker, V. V. Fokin, M. G. Finn, K. B. Sharpless, *Aust. J. Chem.* **2007**, *60*, 381-383; c) "Click chemistry: diverse chemical function from a few good reactions" H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem.* **2001**, *113*, 2056-2075; *Angew. Chem. Int. Ed.* **2001**, *40*, 2004-2021.

[206] For recent reviews on click chemistry, see: a) G. Frank, A. K. Kakkar, *Chem. Soc. Rev.* **2010**, *39*, 1536-1544; b) J. E. Moses, A. D. Moorhouse, *Chem. Soc. Rev.* **2007**, *36*, 1249-1262; c) M. V. Gil, M. J. Arévalo, Ó. López, *Synthesis* **2007**, 1589-1620.

[207] For a review, see: G. C. Tron, T. Pirali, R. A. Billington, P. L. Canonico, G. Sorba, A. A. Genazzani, *Med. Res. Rev.* **2008**, *28*, 278-308.

[208] a) W.-T. Li, W. H. Wu, C.-H. Tang, R. Tai, S.-T. Chen, *ACS Comb. Sci.* **2011**, *13*, 72-78, and references therein; b) S. K. Mamidyala, M. G. Finn, *Chem. Soc. Rev.* **2010**, *39*, 1252-1261; c) K. A. Kalesh, K. Liu, S. Q. Yao, *Org. Biomol. Chem.* **2009**, *7*, 5129-5136; d) A. D. Moorhouse, J. E. Moses, *ChemMedChem* **2008**, *3*, 715-723; e) K. B. Sharpless, R. Manetsch, *Expert Opin. Drug Discovery* **2006**, *1*, 525-538; f) H. C. Kolb, K. B. Sharpless, *Drug Discov. Today* **2003**, *8*, 1128-1137.

[209] Q. Wang, T. R. Chan, R. Hilgraf, V. V. Fokin, K. B. Sharpless, M. G. Finn, *J. Am. Chem. Soc.* **2003**, *125*, 3192-3193.

[210] D. K. Dalvie, A. S. Kalgutkar, S. C. Khojasteh-Bakht, R. S. Obach, J. P. O'Donnell, *Chem. Res. Toxicol.* **2002**, *15*, 269-299.

[211] Y. L. Angell, K. Burgess, *Chem. Soc. Rev.* **2007**, *36*, 1674-1689.

[212] For seminal publications, see: a) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem.* **2002**, *114*, 2708-2711; *Angew. Chem. Int. Ed.* **2002**, *41*, 2596-2599; b) C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057-3064.

[213] R. Huisgen, *Angew. Chem.* **1963**, *75*, 604-637.

[214] L. Zhang, X. Chen, P. Xue, H. H. Y. Sun, I. D. Williams, K. B. Sharpless, V. V. Fokin, G. Jia, *J. Am. Chem. Soc.* **2005**, *127*, 15998-15999.

[215] W. D. Sharpless, P. Wu, T. V. Hansen, J. G. Lindberg, *J. Chem. Educ.* **2005**, *82*, 1833-1836.

[216] T. R. Chan, R. Hilgraf, K. B. Sharpless, V. V. Fokin, *Org. Lett.* **2004**, *6*, 2853-2855.

[217] H. A. Orgueira, D. Fokas, Y. Isome, P. C.-M. Chan, C. M. Baldino, *Tetrahedron Lett.* **2005**, *46*, 2911-2914.

[218] a) F. Alonso, Y. Moglie, G. Rodivoy, M. Yus, *Adv. Synth. Catal.* **2010**, *352*, 3208-3214; b) D. Kumar, V. B. Reddy, *Synthesis* **2010**, 1687-1691; c) Y. Huang, G. L. Gard, J. M. Shreeve, *Tetrahedron Lett.* **2010**, *51*, 6951-6954; d) L. S. Campbell-Verduyn, W. Szymański, C. P. Postema, R. A. Dierckx, P. H. Elsinga, D. B. Janssen, B. L. Feringa, *Chem. Commun.* **2010**, *46*, 898-900; e) C.-T. Lee, S. Huang, B. H. Lipshutz, *Adv. Synth. Catal.* **2009**, *351*, 3139-3142; f) S. Maisonneuve, J. Xie, *Synlett* **2009**, 2977-2981, and references therein; g) K. Odlo, E. A. Høydahl, T. V. Hansen, *Tetrahedron Lett.* **2007**, *48*, 2097-2099; h) J. Andersen, S. Bolvig, X. Liang, *Synlett* **2005**, 2941-2947; i) K. Kacprzak, *Synlett* **2005**, 943-946; j) P. Appukkuttan, W. Dehaen, V. V. Fokin, E. van der Eycken, *Org. Lett.* **2004**, *6*, 4223-4225; k) A. K. Feldman, B. Colasson, V. V. Fokin, *Org. Lett.* **2004**, *6*, 3897-3899.

[219] F. Cuevas, A. I. Oliva, M. A. Pericàs, *Synlett* **2010**, 1873-1877, and references therein.

[220] L. Ackermann, H. K. Potukuchi, D. Landsberg, R. Viante, *Org. Lett.* **2008**, *10*, 3081-3084.

[221] For an indirect evidence for the in situ formation of copper acetylides during Sonogashira coupling, see: P. Bertus, F. Fecourt, C. Bauder, P. Pale, *New J. Chem.* **2004**, *28*, 12-14.

[222] K. Lörincz, P. Kele, Z. Novák, *Synthesis* **2009**, 3527-3532.

[223] F. Friscourt, G.-J. Boons, *Org. Lett.* **2010**, *12*, 4936-4939.

[224] A. Kolarovič, M. Schnürch, M. D. Mihovilovic, *J. Org. Chem.* **2011**, *76*, 2613-2618.

[225] For selected examples, see: a) L. Le Corre, A.-L. Girard, J. Aubertin, F. Radvanyi, C. Benoist-Lasselin, A. Jonquoy, E. Mugniery, L. Legeai-Mallet, P. Busca, Y. Le Merrer, *Org. Biomol. Chem.* **2010**, *8*, 2164-2173; b) K. A. Kalesh, K. Liu, S. Q. Yao, *Org. Biomol. Chem.* **2009**, *7*, 5129-5136; c) P. Dinér, T. Andersson, J. Kjellén, K. Elbing, S. Hohmann, M. Grøtli, *Org. Biomol. Chem.* **2009**, *33*, 1010-1016.

[226] M. Klein, P. Dinér, D. Dorin-Semblat, C. Doerig, M. Grøtli, *Org. Biomol. Chem.* **2009**, *7*, 3421-3429.

[227] “Rapid preparation of triazolyl substituted NH-heterocyclic kinase inhibitors via one-pot Sonogashira coupling–TMS-deprotection–CuAAC sequence” E. Merkul, F. Klukas, D. Dorsch, C. Sirrenberg, U. Grädler, H. E. Greiner, T. J. J. Müller, *Org. Biomol. Chem.* **2011**, *9*, 5129-5136.

[228] a) “PDK1: the major transducer of PI 3-kinase actions” J. R. Bayascas, *Curr. Top. Microbiol. Immunol.* **2010**, *346*, 9-29; b) “PDK1, the master regulator of AGC kinase signal transduction” A. Mora, D. Komander, D. M. F. van Aalten, D. R. Alessi, *Sem. Cell Dev. Biol.* **2004**, *15*, 161-170.

[229] D. Dorsch, M. Wucherer-Plietker, T. J. J. Müller, E. Merkul, *PCT Int. Appl.* **2010**, WO 2010127754 A1 20101111; D. Dorsch, M. Wucherer-Plietker, T. J. J. Müller, E. Merkul, *Ger. Offen.* **2010**, DE 102009019962 A1 20101111.

[230] “Decarbonylation reactions using transition metal compounds” J. Tsuji, K. Ohno, *Synthesis* **1969**, 157-169.

[231] Seminal publication: J. Tsuji, K. Ohno, *Tetrahedron Lett.* **1965**, *6*, 3969-3971.

[232] Mechanism of the *Tsuji-Wilkinson* decarbonylation: P. Fristrup, M. Kreis, A. Palmelund, P.-O. Norrby, R. Madsen, *J. Am. Chem. Soc.* **2008**, *130*, 5206-5215.

[233] a) K. Ohno, J. Tsuji, *J. Am. Chem. Soc.* **1968**, *90*, 99-107; b) J. Tsuji, K. Ohno, *Tetrahedron Lett.* **1967**, *8*, 2173-2176; c) J. Tsuji, K. Ohno, *Tetrahedron Lett.* **1966**, *7*, 4713-4716.

[234] a) [RhCl(dppp)$_2$], generated in situ from $RhCl_3$ x $3H_2O$ and dppp: M. Kreis, A. Palmelund, L. Bunch, R. Madsen, *Adv. Synth. Catal.* **2006**, *348*, 2148-2154; b) [RhCl(PPh_3)$_3$]/stoich. DPPA: J. M. O'Connor, J. Ma, *J. Org. Chem.* **1992**, *57*, 5075-5077; c) [RhCl(dppp)$_2$]: D. H. Doughty, L. H. Pignolet, *J. Am. Chem. Soc.* **1978**, *100*, 7083-7085.

[235] a) A. Padwa, H. Zhang, *J. Org. Chem.* **2007**, *72*, 2570-2582; b) J. P. Malerich, T. J. Maimone, G. I. Elliott, D. Trauner, *J. Am. Chem. Soc.* **2005**, *127*, 6276-6283; c) C.-m. Zeng, M. Han, D. F. Covey, *J. Org. Chem.* **2000**, *65*, 2264-2266; d) F. E. Ziegler, M. Belema, *J. Org. Chem.* **1997**, *62*, 1083-1094; e) M. Tanaka, T. Ohshima, H. Mitsuhashi, M. Maruno, T. Wakamatsu, *Tetrahedron* **1995**, *51*, 11693-11702.

[236] For selected examples, see: a) T. Inami, Y. Baba, T. Kurahashi, S. Matsubara, *Org. Lett.* **2011**, *13*, 1912-1915; b) Y. Kajita, T. Kurahashi, S. Matsubara, *J. Am. Chem. Soc.* **2008**, *130*, 17226-17227; c) Y. Kajita, S. Matsubara, T. Kurahashi, *J. Am. Chem. Soc.* **2008**, *130*, 6058-6059; d) T. Iwai, T. Fujihara, Y. Tsuji, *Chem. Commun.* **2008**, 6215-6217; e) F. Yamashita, H. Kuniyasu, J. Terao, N. Kambe, *Org. Lett.* **2008**, *10*, 101-104; f) T. C. Fessard, S. P. Andrews, H. Motoyoshi, E. M. Carreira, *Angew. Chem.* **2007**, *119*, 9492-9495; *Angew. Chem. Int. Ed.* **2007**, *46*, 9331-9334; g) D. V. Gribkov, S. J. Pastine, M. Schnürch, D. Sames, *J. Am. Chem. Soc.* **2007**, *129*, 11750-11755; h) R. N. Monrad, R. Madsen, *J. Org. Chem.* **2007**, *72*, 9782-9785; i) S. Matsubara, Y. Yokota, K. Oshima, *Org. Lett.* **2004**, *6*, 2071-2073; j) T. Tatamidani, K. Yokota, F. Kakiuchi, N. Chatani, *J. Org. Chem.* **2004**, *69*, 5615-5621; k) E. M. O'Brien, E. A. Bercot, T. Rovis, *J. Am. Chem. Soc.* **2003**, *125*, 10498-10499; l) N. Chatani, Y. Ie, F. Kakiuchi, S. Murai, *J. Am. Chem. Soc.* **1999**, *121*, 8645-8646; m) M. Murakami, H. Amii, Y. Ito, *Nature* **1994**, *370*, 540-541; n) S.-I. Murahashi, T. Naota, N.

Nakajima, *J. Org. Chem.* **1986**, *51*, 898-901; o) J. Blum, H. Rosenman, E. D. Bergmann, *J. Org. Chem.* **1968**, *33*, 1928-1930.

[237] L. J. Gooßen, J. Paetzold, *Adv. Synth. Catal.* **2004**, *346*, 1665-1668.

[238] a) J. Blum, *Tetrahedron Lett.* **1966**, *7*, 1605-1608; b) J. Blum, E. Oppenheimer, E. D. Bergmann, *J. Am. Chem. Soc.* **1967**, *89*, 2338-2341.

[239] K. Kokubo, K. Matsumasa, M. Miura, M. Nomura, *J. Org. Chem.* **1996**, *61*, 6941-6946.

[240] T. Yasukawa, T. Satoh, M. Miura, M. Nomura, *J. Am. Chem. Soc.* **2002**, *124*, 12680-12681.

[241] For some exceptional examples, see: a) T. Kashiwabara, M. Tanaka, *Organometallics* **2006**, *25*, 4648-4652; b) Y. Obora, Y. Tsuji, T. Kawamura, *J. Am. Chem. Soc.* **1995**, *117*, 9814-9821; c) Y. Obora, Y. Tsuji, T. Kawamura, *J. Am. Chem. Soc.* **1993**, *115*, 10414-10415.

[242] C. A. Rojahn, A. Seitz, *Liebigs Ann. Chem.* **1924**, *437*, 297-308.

[243] J. O. Hawthorne, M. H. Wilt, *J. Org. Chem.* **1960**, *25*, 2215-2216.

[244] a) J. Tsuji, K. Ohno, T. Kajimoto, *Tetrahedron Lett.* **1965**, *6*, 4565-4568; b) J. Tsuji, K. Ohno, *J. Am. Chem. Soc.* **1968**, *90*, 94-98.

[245] J. W. Verbicky, Jr., B. A. Dellacoletta, L. Williams, *Tetrahedron Lett.* **1982**, *23*, 371-372.

[246] Y. Nakao, J. Satoh, E. Shirakawa, T. Hiyama, *Angew. Chem.* **2006**, *118*, 2329-2332; *Angew. Chem. Int. Ed.* **2006**, *45*, 2271-2274.

[247] M. S. Stephan, A. J. J. M. Teunissen, G. K. M. Verzijl, J. G. de Vries, *Angew. Chem.* **1998**, *110*, 668-690; *Angew. Chem. Int. Ed.* **1998**, *37*, 662-664.

[248] L. J. Gooßen, J. Paetzold, *Angew. Chem.* **2002**, *114*, 1285-1289; *Angew. Chem. Int. Ed.* **2002**, *41*, 1237-1241.

[249] L. J. Gooßen, J. Paetzold, *Angew. Chem.* **2004**, *116*, 1115-1118; *Angew. Chem. Int. Ed.* **2004**, *43*, 1095-1098.

[250] L. J. Gooßen, N. Rodríguez, *Chem. Commun.* **2004**, 724-725.

[251] L. J. Gooßen, J. Paetzold, L. Winkel, *Synlett* **2002**, 1721-1723.

[252] R. J. Cox, D. J. Ritson, T. A. Dane, J. Berge, J. P. H. Charmant, A. Kantacha, *Chem. Commun.* **2005**, 1037-1039.

[253] For synthetic approaches to ynones, see: a) A. Nelson, "Product Class 7: Ynones" in *Science of Synthesis*; Georg Thieme Verlag, Stuttgart, **2005**, Vol. 26, pp. 971-979, and references therein.

[254] For a review, see: R. L. Bol'shedvorskaya, L. I. Vereshchagin, *Russ. Chem. Rev.* **1973**, *42*, 225-240.

[255] L. F. Tietze, R. Reddy Singidi, K. M. Gericke, H. Böckemeier, H. Laatsch, *Eur. J. Org. Chem.* **2007**, 5875-5878.

[256] Numerous examples of the utilization of *Bohlmann-Rahtz* pyridine synthesis in the natural product chemistry are given in M. C. Bagley, C. Glover, E. A. Merritt, *Synlett* **2007**, 2459-2482.

[257] See references in M. C. Bagley, D. D. Hughes, M. C. Lubinu, E. A. Merritt, P. H. Taylor, N. C. O. Tomkinson, *QSAR Comb. Sci.* **2004**, *23*, 859-867.

[258] T. Masquelin, D. Obrecht, *Synthesis* **1995**, 276-284.

[259] N. Gouault, M. Le Roch, C. Cornée, M. David, P. Uriac, *J. Org. Chem.* **2009**, *74*, 5614-5617.

[260] T. Sakamoto, T. Nagano, Y. Kondo, H. Yamanaka, *Synthesis* **1990**, 215-218.

[261] D. Obrecht, *Helv. Chim. Acta* **1989**, *72*, 447-456, also preparation of flavones and chromones.

[262] A. Jeevanandam, K. Narkunan, Y.-C. Ling, *J. Org. Chem.* **2001**, *66*, 6014-6020.

[263] B. G. Van den Hoven, B. El Ali, H. Alper, *J. Org. Chem.* **2000**, *65*, 4131-4137.

[264] P. Wipf, Y. Aoyama, T. E. Benedum, *Org. Lett.* **2004**, *6*, 3593-3595.

[265] a) D. Obrecht, F. Gerber, D. Sprenger, T. Masquelin, *Helv. Chim. Acta* **1997**, *80*, 531-537; b) T. Masquelin, D. Obrecht, *Tetrahedron Lett.* **1994**, *35*, 9387-9390.

[266] a) J. P. Waldo, S. Mehta, R. C. Larock, *J. Org. Chem.* **2008**, *73*, 6666-6670; b) B. C. Bishop, K. M. J. Brands, A. D. Gibb, D. J. Kennedy, *Synthesis* **2004**, 43-52, and references therein.

[267] H.-C. Wu, L.-C. Hwang, M.-J. Wu, *Org. Biomol. Chem.* **2011**, *9*, 670-672.

[268] J. Li, Y. Zhang, D. Wang, W. Wang, T. Gao, L. Wang, J. Li, G. Huang, B. Chen, *Synlett* **2010**, 1617-1622.

[269] J. P. Waldo, R. C. Larock, *J. Org. Chem.* **2007**, *72*, 9643-9647.

[270] I. Hachiya, H. Shibuya, M. Shimizu, *Tetrahedron Lett.* **2003**, *44*, 2061-2063.

[271] J. Renault, Z. Qian, P. Uriac, N. Gouault, *Tetrahedron Lett.* **2011**, *52*, 2476-2479.

[272] a) P. Bannwarth, A. Valleix, D. Grée, R. Grée, *J. Org. Chem.* **2009**, *74*, 4646-4649; b) M. C. Bagley, D. D. Hughes, M. C. Lubinu, E. A. Merritt, P. H. Taylor, N. C. O. Tomkinson, *QSAR Comb. Sci.* **2004**, *23*, 859-867, and references therein.

[273] For a review, see: a) M. C. Bagley, C. Glover, E. A. Merritt, *Synlett* **2007**, 2459-2482. Seminal publication: b) F. Bohlmann, D. Rahtz, *Chem. Ber.* **1957**, *90*, 2265-2272.

[274] a) A. Arcadi, M. Aschi, F. Marinelli, M. Verdecchia, *Tetrahedron* **2008**, *64*, 5354-5361; b) T. Masquelin, D. Obrecht, *Tetrahedron* **1997**, *53*, 641-646.

[275] G. Abbiati, A. Arcadi, F. Marinelli, E. Rossi, *Synthesis* **2002**, 1912-1916.

[276] G. A. Suárez-Ortiz, P. Sharma, M. Amézquita-Valencia, I. Arellano, A. Cabrera, N. Rosas, *Tetrahedron Lett.* **2011**, *52*, 1641-1643.

[277] Q. Cai, F. Zhou, T. Xu, L. Fu, K. Ding, *Org. Lett.* **2011**, *13*, 340-343.

[278] C. François-Endelmond, T. Carlin, P. Thuery, O. Loreau, F. Taran, *Org. Lett.* **2010**, *12*, 40-42.

[279] a) N. G. Kundu, B. Das, C. P. Spears, A. Majumdar, S.-I. Kang, *J. Med. Chem.* **1990**, *33*, 1975-1979; b) N. G. Kundu, S. K. Dasgupta, *J. Chem. Soc., Perkin Trans. 1* **1993**, 2657-2663; c) N. G. Kundu, J. S. Mahanty, C. P. Spears, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1497-1502.

[280] M. Ono, H. Watanabe, R. Watanabe, M. Haratake, M. Nakayama, H. Saji, *Bio-org. Med. Chem. Lett.* **2011**, *21*, 117-120.

[281] See references in D. A. Alonso, C. Nájera, M. C. Pacheco, *J. Org. Chem.* **2004**, *69*, 1615-1619.

[282] For an example, see: B. Wang, M. Bonin, L. Micouin, *J. Org. Chem.* **2005**, *70*, 6126-6128 (aluminium acetylides).

[283] a) S. J. Yim, C. H. Kwon, D. K. An, *Tetrahedron Lett.* **2007**, *48*, 5393-5395; b) M. M. Jackson, C. Leverett, J. F. Toczko, J. C. Roberts, *J. Org. Chem.* **2002**, *67*, 5032-5035.

[284] Y. Maeda, N. Kakiuchi, S. Matsumura, T. Nishimura, T. Kawamura, S. Uemura, *J. Org. Chem.* **2002**, *67*, 6718-6724.

[285] S. J. Pastine, D. Sames, *Org. Lett.* **2003**, *5*, 4053-4055.

[286] For reviews, see: a) B. Willy, T. J. J. Müller, *Curr. Org. Chem.* **2009**, *13*, 1777-1790; b) B. Willy, T. J. J. Müller, *ARKIVOC* **2008**, 195-208; c) T. J. J. Müller, *Chimica Oggi-Chemistry Today* **2007**, *25*, 70-78.

[287] For selected examples, see: a) J. Li, D. Wang, Y. Zhang, J. Li, B. Chen, *Org. Lett.* **2009**, *11*, 3024-3027 (1,2,3-triazoles); b) H.-L. Liu, H.-F. Jiang, M. Zhang, W.-J. Yao, Q.-H. Zhu, Z. Tang, *Tetrahedron Lett.* **2008**, *49*, 3805-3809 (pyrazoles); c) S. S. Palimkar, R. J. Lahoti, K. V. Srinivasan, *Green Chem.* **2007**, *9*, 146-152 (benzo[*b*][1,4]diazepines); d) K. Y. Lee, M. J. Lee, J. N. Kim, *Tetrahedron* **2005**, *61*, 8705-8710 (furans); e) M. C. Bagley, D. D. Hughes, H. M. Sabo, P. H. Taylor, X. Xiong, *Synlett* **2003**, 1443-1446 (pyridines and pyrimidines).

[288] a) B. Willy, T. J. J. Müller, *Org. Lett.* **2011**, *13*, 2082-2085; b) B. Willy, T. J. J. Müller, *Eur. J. Org. Chem.* **2008**, 4157-4168.

[289] B. Willy, F. Rominger, T. J. J. Müller, *Synthesis* **2008**, 293-303.

[290] a) A. S. Karpov, T. J. J. Müller, *Org. Lett.* **2003**, *5*, 3451-3454; b) A. S. Karpov, T. J. J. Müller, *Synthesis* **2003**, 2815-2826.

[291] A. V. Rotaru, I. D. Druta, T. Oeser, T. J. J. Müller, *Helv. Chim. Acta* **2005**, *88*, 1798-1812.

[292] S. Rotzoll, B. Willy, J. Schönhaber, F. Rominger, T. J. J. Müller, *Eur. J. Org. Chem.* **2010**, 3516-3524.

[293] A. S. Karpov, T. Oeser, T. J. J. Müller, *Chem. Commun.* **2004**, 1502-1503.

[294] B. Willy, T. J. J. Müller, *Synlett* **2009**, 1255-1260.

[295] B. Willy, T. Dallos, F. Rominger, J. Schönhaber, T. J. J. Müller, *Eur. J. Org. Chem.* **2008**, 4796-4805.

[296] B. Willy, T. J. J. Müller, *Mol. Diversity* **2010**, *14*, 443-453.

[297] a) “A novel one-pot three-component synthesis of 3-halofurans and sequential Suzuki coupling” A. S. Karpov, E. Merkul, T. Oeser, T. J. J. Müller, *Chem. Commun.* **2005**, 2581-2583; b) A. S. Karpov, E. Merkul, T. Oeser, T. J. J. Müller, *Eur. J. Org. Chem.* **2006**, 2991-3000.

[298] a) “A new consecutive three-component oxazole synthesis by an amidation – coupling – cycloisomerization (ACCI) sequence” E. Merkul, T. J. J. Müller, *Chem. Commun.* **2006**, 4817-4819; b) E. Merkul, O. Grotkopp, T. J. J. Müller, *Synthesis* **2009**, 502-507.

[299] A. Park, K. Park, Y. Kim, S. Lee, *Org. Lett.* **2011**, *13*, 944-947.

[300] a) C. François-Endelmond, T. Carlin, P. Thuery, O. Loreau, F. Taran, *Org. Lett.* **2010**, *12*, 40-42 (2 examples); b) B. Willy, W. Frank, T. J. J. Müller, *Org. Biomol. Chem.* **2010**, *8*, 90-95 (1 example); c) F. C. Fuchs, G. A. Eller, W. Holzer, *Molecules* **2009**, *14*, 3814-3832 (3 examples); d) A. S. Karpov, T. J. J. Müller, *Synthesis* **2003**, 2815-2826 (2 examples).

[301] R. Faust, C. Weber, *Tetrahedron* **1997**, *53*, 14655-14670.

[302] Y. Liu, M. Liu, S. Guo, H. Tu, Y. Zhou, H. Gao, *Org. Lett.* **2006**, *8*, 3445-3448.

[303] “Dreikomponentensynthese von Indionen durch eine Glyoxylierungs-Stephens-Castro-Kupplungssequenz”, E. Merkul, J. Dohe, C. Gers, F. Rominger, T. J. J. Müller, *Angew. Chem.* **2011**, *123*, 3023-3026; “Three-component synthesis of ynediones by a glyoxylation/Stephens–Castro coupling sequence” *Angew. Chem. Int. Ed.* **2011**, *50*, 2966-2969.

[304] D. R. da Rocha, *Synlett* **2007**, 1172-1173.

[305] a) P. Langer, *Synlett* **2006**, 3369-3381; b) P. Langer, *Synthesis* **2002**, 441-459.

[306] I. Yavari, S. Souri, *Synlett* **2008**, 1208-1210.

[307] Y. Cheng, H.-L. Ye, Y.-H. Zhan, O. Meth-Cohn, *Synthesis* **2001**, 904-908.

[308] K. Mitsui, J. R. Parquette, *Synthesis* **2009**, 713-714.

[309] S. G. Koenig, C. P. Vandenbossche, H. Zhao, P. Mousaw, S. P. Singh, R. P. Bakale, *Org. Lett.* **2009**, *11*, 433-436.

[310] M. R. Kuszpit, W. D. Wulff, J. J. Tepe, *J. Org. Chem.* **2011**, *76*, 2913-2919.

[311] R. Adams, L. H. Ulich, *J. Am. Chem. Soc.* **1920**, *42*, 599-611.

[312] M. S. Kharasch, H. C. Brown, *J. Am. Chem. Soc.* **1942**, *64*, 325-332.

[313] P. A. Stadler, *Helv. Chim. Acta* **1978**, *61*, 1675-1681.

[314] E. J. Ko, G. P. Savage, C. M. Williams, J. Tsanaktsidis, *Org. Lett.* **2011**, *13*, 1944-1947.

[315] R. M. Denton, X. Tang, A. Przeslak, *Org. Lett.* **2010**, *12*, 4678-4681.

[316] K. A. Punch, E. L. Ghisalberti, M. J. Piggott, *J. Nat. Prod.* **2011**, *74*, 1348-1350.

[317] M. E. Speeter, W. C. Anthony, *J. Am. Chem. Soc.* **1954**, *76*, 6208-6210.

[318] For selected examples, see: a) M. J. Thompson, V. Borsenberger, J. C. Louth, K. E. Judd, B. Chen, *J. Med. Chem.* **2009**, *52*, 7503-7511; b) J. B. Blair, D. Kurrasch-Orbaugh, D. Marona-Lewicka, M. G. Cumbay, V. J. Watts, E. L. Barker, D. E. Nichols, *J. Med. Chem.* **2000**, *43*, 4701-4710.

[319] O. Shirota, W. Hakamata, Y. Goda, *J. Nat. Prod.* **2003**, *66*, 885-887.

[320] J. Bergman, T. Janosik, A.-L. Johnsson, *Synthesis* **1999**, 580-582.

[321] Y. Ma, K. Yakushijin, F. Miyake, D. Horne, *Tetrahedron Lett.* **2009**, *50*, 4343-4345.

[322] B. Jiang, J. M. Smallheer, C. Amaral-Ly, M. A. Wuonola, *J. Org. Chem.* **1994**, *59*, 6823-6827.

[323] Z. Zhang, Z. Yang, H. Wong, J. Zhu, N. A. Meanwell, J. F. Kadow, T. Wang, *J. Org. Chem.* **2002**, *67*, 6226-6227.

[324] N. Hoefgen, U. Egerland, T. Kronbach, D. Marx, S. Szelenyi, H. Kuss, E. Polymeropoulos, *PCT Int. Appl*. **2002**, WO2002034747.

[325] T. L. Gilchrist, A. Lemos, C. J. Ottaway, *J. Chem. Soc., Perkin Trans. 1* **1997**, 3005-3012.

[326] C. I. Chiriac, *Synthesis* **1986**, 753-755.

[327] M. S. M. Timmer, B. L. Stocker, P. T. Northcote, B. A. Burkett, *Tetrahedron Lett.* **2009**, *50*, 7199-7204.

[328] P. E. Peterson, J. P. Wolf III, C. Niemann, *J. Org. Chem*. **1958**, *23*, 303-304.

[329] E. D. Dobrzynski, R. J. Angelici, *Inorg. Chem*. **1975**, *14*, 59-63.

[330] D. M. Ketcha, G. W. Gribble, *J. Org. Chem.* **1985**, *50*, 5451-5457.

[331] I. T. Hogan, M. Sainsbury, *Tetrahedron* **1984**, *40*, 681-682.

[332] F. Y. Miyake, K. Yakushijin, D. A. Horne, *Org. Lett.* **2000**, *2*, 2121-2123.

[333] T. Kashiwabara, M. Tanaka, *J. Org. Chem.* **2009**, *74*, 3958-3961.

[334] C. Chen, C. Xi, Y. Jiang, X. Hong, *J. Am. Chem. Soc.* **2005**, *127*, 8024-8025.

[335] C. Chen, Y. Liu, C. Xi, *Tetrahedron Lett.* **2009**, *50*, 5434-5436.

[336] D. Milstein, J. K. Stille, *J. Org. Lett.* **1979**, *44*, 1613-1618.

[337] M. L. N. Rao, V. Venkatesh, P. Dasgupta, *Tetrahedron Lett.* **2010**, *51*, 4975-4980.

[338] For a minireview, see: “Evolution of carbonylation catalysis: no need for carbon monoxide” T. Morimoto, K. Kakiuchi, *Angew. Chem.* **2004**, *116*, 5698-5706; *Angew. Chem. Int. Ed.* **2004**, *43*, 5580-5588.

[339] T. Morimoto, M. Fujioka, K. Fuji, K. Tsutsumi, K. Kakiuchi, *Pure Appl. Chem.* **2008**, *80*, 1079-1087.

[340] a) P. Appukkuttan, L. Axelsson, E. Van der Eycken, M. Larhed, *Tetrahedron Lett.* **2008**, *49*, 5625-5628; b) K. M. Brummond, D. P. Curran, B. Mitasev, S. Fischer, *J. Org. Chem.* **2005**, *70*, 1745-1753; c) K. Yamazaki, Y. Kondo, *J. Comb. Chem.* **2004**, *6*, 121-125; d) J. Wannberg, M. Larhed, *J. Org. Chem.* **2003**, *68*, 5750-5753; e) N.-F. K. Kaiser, A. Hallberg, M. Larhed, *J. Comb. Chem.* **2002**, *4*, 109-111.

[341] a) R. F. Cunico, B. C. Maity, *Org. Lett.* **2003**, *5*, 4947-4949; b) R. F. Cunico, B. C. Maity, *Org. Lett.* **2002**, *4*, 4357-4359; c) C. M. Lindsay, D. A. Widdowson, *J. Chem. Soc., Perkin Trans. 1* **1988**, 569-573.

[342] Y. Wan, M. Alterman, M. Larhed, A. Hallberg, *J. Org. Chem.* **2002**, *67*, 6232-6235.

[343] K. Hosoi, K. Nozaki, T. Hiyama, *Org. Lett.* **2002**, *4*, 2849-2851.

[344] a) J.-P. Simonato, *J. Mol. Catal. A* **2003**, *197*, 61-64; b) J.-P. Simonato, T. Walter, P. Métivier, *J. Mol. Catal. A* **2001**, *171*, 91-94.

[345] S. Cacchi, G. Fabrizi, A. Goggiamani, *J. Comb. Chem.* **2004**, *6*, 692-694.

[346] a) S. Cacchi, C. L. Cotet, G. Fabrizi, G. Forte, A. Goggiamani, L. Martín, S. Martínez, E. Molins, M. Moreno-Mañas, F. Petrucci, A. Roig, A. Vallribera, *Tetrahedron* **2007**, *63*, 2519-2523; b) P. Berger, A. Bessmernykh, J.-C. Caille, S. Mignonac, *Synthesis* **2006**, 3106-3110; c) S. Cacchi, G. Fabrizi, A. Goggiamani, *Org. Lett.* **2003**, *5*, 4269-4272.

[347] V. V. Grushin, H. Alper, *Organometallics* **1993**, *12*, 3846-3850.

[348] a) K. H. Park, S. U. Son, Y. K. Chung, *Chem. Commun.* **2003**, 1898-1899; b) S. Ko, C. Lee, M.-G. Choi, Y. Na, S. Chang, *J. Org. Chem.* **2003**, *68*, 1607-1610.

[349] H. W. Lee, A. S. C. Chan, F. Y. Kwong, *Chem. Commun.* **2007**, 2633-2635.

[350] H. Tatamidani, K. Yokota, F. Kakiuchi, N. Chatani, *J. Org. Chem.* **2004**, *69*, 5615-5621.

[351] a) K. Fuji, T. Morimoto, K. Tsutsumi, K. Kakiuchi, *Tetrahedron Lett.* **2004**, *45*, 9163-9166; b) K. Fuji, T. Morimoto, K. Tsutsumi, K. Kakiuchi, *Angew. Chem.* **2003**, *115*, 2511-2513; *Angew. Chem. Int. Ed.* **2003**, *42*, 2409-2411.

[352] T. Morimoto, K. Fuji, K. Tsutsumi, K. Kakiuchi, *J. Am. Chem. Soc.* **2002**, *124*, 3806-3807.

[353] a) T. Shibata, N. Toshida, K. Takagi, *Org. Lett.* **2002**, *4*, 1619-1621; b) T. Shibata, N. Toshida, K. Takagi, *J. Org. Chem.* **2002**, *67*, 7446-7450.

[354] For a recently developed process for the safe production of phosgene from triphosgene, see: H. Eckert, J. Auerweck, *Org. Process Res. Dev.* **2010**, *14*, 1501-1505.

[355] "Consecutive three-component synthesis of ynones by decarbonylative Sonogashira coupling" E. Merkul, T. Oeser, T. J. J. Müller, *Chem. Eur. J.* **2009**, *15*, 5006-5011.

[356] B. E. Evans, K. E. Rittle, M. G. Bock, R. M. DiPardo, R. M. Freidinger, W. L. Whitter, G. F. Lundell, D. F. Veber, P. S. Anderson, R. S. L. Chang, V. J. Lotti, D. J. Cerino, T. B. Chen, P. J. Kling, K. A. Kunkel, J. P. Springer, J. Hirshfield, *J. Med. Chem.* **1988**, *31*, 2235-2246.

[357] "Privileged scaffolds for library design and drug discovery" M. E. Welsch, S. A. Snyder, B. R. Stockwell, *Curr. Opin. Chem. Biol.* **2010**, *14*, 347-361.

[358] For reviews, see: a) "Construction of nitrogen-containing heterocycles by C-H bond functionalization" P. Thansandote, M. Lautens, *Chem. Eur. J.* **2009**, *15*, 5874-5883; b) "Coinage metal-assisted synthesis of heterocycles" N. T. Patil, Y. Yamamoto, *Chem. Rev.* **2008**, *108*, 3395-3442; c) "Synthesis of heterocycles via palladium-catalyzed oxidative addition" G. Zeni, R. C. Larock, *Chem. Rev.* **2006**, *106*, 4644-4680; d) "Synthesis of heterocycles via palladium π-olefin and π-alkyne chemistry" G. Zeni, R. C. Larock, *Chem. Rev.* **2004**, *104*, 2285-2309; e) "Transition-metal-catalyzed reactions in heterocyclic synthesis" I. Nakamura, Y. Yamamoto, *Chem. Rev.* **2004**, *104*, 2127-2198; f) "Synthesis of aromatic heterocycles" T. L. Gilchrist, *J. Chem. Soc., Perkin Trans. 1* **1999**, 2849-2866.

[359] For recent reviews, see: a) N. Isambert, M. del Mar Sanchez Duque, J.-C. Plaquevent, Y. Génisson, J. Rodriguez, T. Constantieux, *Chem. Soc. Rev.* **2011**, *40*, 1347-1357; b) R. V. A. Orru, M. de Greef, *Synthesis* **2003**, 1471-1499.

[360] For a recent review, see: N. Isambert, R. Lavilla, *Chem. Eur. J.* **2008**, *14*, 8444-8454.

[361] “From nature to drug discovery: the indole scaffold as a ‘privileged structure’” F. R. de Sá Alves, E. J. Barreiro, C. A. M. Fraga, *Mini-Rev. Med. Chem.* **2009**, *9*, 782-793.

[362] For a recent review, see: M. Ishikura, K. Yamada, T. Abe, *Nat. Prod. Rep.* **2010**, *27*, 1630-1680.

[363] For recent reviews on synthesis and functionalization of indoles, see: a) “Catalytic functionalization of indoles in a new dimension” M. Bandini, A. Eichholzer, *Angew. Chem.* **2009**, *121*, 9786-9824; *Angew. Chem. Int. Ed.* **2009**, *48*, 9608-9644; b) “Transition metal-catalysed, direct and site-selective N1-, C2- or C3-arylation of the indole nucleus: 20 years of improvements” L. Joucla, L. Djakovitch, *Adv. Synth. Catal.* **2009**, *351*, 673-714; c) “Catalytic synthesis of indoles from alkynes” K. Krüger, A. Tillack, M. Beller, *Adv. Synth. Catal.* **2008**, *350*, 2153-2167; d) “Practical methodologies for the synthesis of indoles” G. R. Humphrey, J. T. Kuethe, *Chem. Rev.* **2006**, *106*, 2875-2911; e) “Synthesis and functionalization of indoles through palladium-catalyzed reactions” S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *105*, 2873-2920; f) “The aminopalladation/reductive elimination domino reaction in the construction of functionalized indole rings” G. Battistuzzi, S. Cacchi, G. Fabrizi, *Eur. J. Org. Chem.* **2002**, 2671-2681.

[364] For a recent review on the role of bioisosterism in rational drug design, see: L. M. Lima, E. J. Barreiro, *Curr. Med. Chem.* **2005**, *12*, 23-49.

[365] Y.-S. Tung, M. S. Coumar, Y.-S. Wu, H.-Y. Shiao, J.-Y. Chang, J.-P. Liou, P. Shukla, C.-W. Chang, C.-Y. Chang, C.-C. Kuo, T.-K. Yeh, C.-Y. Lin, J.-S. Wu, S.-Y. Wu, C.-C. Liao, H.-P. Hsieh, *J. Med. Chem.* **2011**, *54*, 3076-3080.

[366] M. M. Robison, B. L. Robison, *J. Am. Chem. Soc.* **1955**, *77*, 457-460.

[367] D. Mazeas, G. Guillaumet, M.-C. Viaud, *Heterocycles* **1999**, *50*, 1065-1080.

[368] For selected recent examples, see: a) N. D. Adams, J. L. Adams, J. L. Burgess, A. M. Chaudhari, R. A. Copeland, C. A. Donatelli, D. H. Drewry, K. E. Fisher, T. Hamajima, M. A. Hardwicke, W. F. Huffman, K. K. Koretke-Brown, Z. V. Lai, O. B.

McDonald, H. Nakamura, K. A. Newlander, C. A. Oleykowski, C. A. Parrish, D. R. Patrick, R. Plant, M. A. Sarpong, K. Sasaki, S. J. Schmidt, D. J. Silva, D. Sutton, J. Tang, C. S. Thompson, P. J. Tummino, J. C. Wang, H. Xiang, J. Yang, D. Dhanak, *J. Med. Chem.* **2010**, *53*, 3973-4001; b) J. R. Medina, S. W. Grant, J. M. Axten, W. H. Miller, C. A. Donatelli, M. A. Hardwicke, C. A. Oleykowski, Q. Liao, R. Plant, H. Xiang, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2552-2555; c) T. Wang, M. W. Ledeboer, J. P. Duffy, A. C. Pierce, H. J. Zuccola, E. Block, D. Shlyakter, J. K. Hogan, Y. L. Bennani, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 153-156; d) A. Ermoli, A. Bargiotti, M. G. Brasca, A. Ciavoletta, N. Colombo, G. Fachin, A. Isacchi, M. Menichincheri, A. Molinari, A. Montagnoli, A. Pillan, S. Rainoldi, F. R. Sirtori, F. Sola, S. Thieffine, M. Tibolla, B. Valsasina, D. Volpi, C. Santocanale, E. Vanotti, *J. Med. Chem.* **2009**, *52*, 4380-4390; e) J. Kempson, J. Guo, J. Das, R. V. Moquin, S. H. Spergel, S. H. Watterson, C. M. Langevine, A. J. Dyckman, M. Pattoli, J. R. Burke, X. X. Yang, K. M. Gillooly, K. W. McIntyre, L. Chen, J. H. Dodd, M. McKinnon, J. C. Barrish, W. J. Pitts, *Biiorg. Med. Chem. Lett.* **2009**, *19*, 2646-2649; f) J. Liddle, P. Bamborough, M. D. Barker, S. Campos, R. P. C. Cousins, G. J. Cutler, H. Hobbs, D. S. Holmes, C. Ioannou, G. W. Mellor, M. A. Morse, J. J. Payne, J. M. Pritchard, K. J. Smith, D. T. Tape, C. Whitworth, R. A. Williamson, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2504-2508; g) M. A. Seefeld, M. B. Rouse, K. C. McNulty, L. Sun, J. Wang, D. S. Yamashita, J. I. Luengo, S. Y. Zhang, E. A. Minthorn, N. O. Concha, D. A. Heerding, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2244-2248; h) H. Schirok, R. Kast, S. Figueroa-Pérez, S. Bennabi, M. J. Gnoth, A. Feurer, H. Heckroth, M. Thutewohl, H. Paulsen, A. Knorr, J. Hütter, M. Lobell, K. Münter, V. Geiß, H. Ehmke, D. Lang, M. Radtke, J. Mittendorf, J.-P. Stasch, *ChemMedChem* **2008**, *3*, 1893-1904; i) J. Tang, T. Hamajima, M. Nakano, H. Sato, S. H. Dickerson, K. E. Lackey, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4610-4614.

[369] For some examples from the patent literature, see: F. Popowycz, S. Routier, B. Joseph, J.-Y. Mérour, *Tetrahedron* **2007**, *63*, 1031-1064.

[370] a) M. Missbach, E. Altmann, L. Widler, M. Šuša, E. Buchdunger, H. Mett, T. Meyer, J. Green, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 945-949; b) J. Witherington, V. Bordas, S. L. Garland, D. M. B. Hickey, R. J. Ife, J. Liddle, M. Saunders, D. G. Smith, R. W. Ward, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1577-1580.

[371] S. Huang, R. Lin, Y. Yu, Y. Lu, P. J. Connolly, G. Chiu, S. Li, S. L. Emanuel, S. A. Middleton, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1243-1245.

[372] For selected recent examples of 3-(hetero)aryl substituted 7-azaindoles as kinase inhibitors, see: a) S. Hong, S. Lee, B. Kim, H. Lee, S.-S. Hong, S. Hong, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7212-7215; b) M. Hammond, D. G. Washburn, T. H. Hoang, S. Manns, J. S. Frazee, H. Nakamura, J. R. Patterson, W. Trizna, C. Wu, L. M. Azzarano, R. Nagilla, M. Nord, R. Trejo, M. S. Head, B. Zhao, A. M. Smallwood, K. Hightower, N. J. Laping, C. G. Schnackenberg, S. K. Thompson, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4441-4445; c) H.-C. Zhang, H. Ye, B. R. Conway, C. K. Derian, M. F. Addo, G.-H. Kuo, L. R. Hecker, D. R. Croll, J. Li, L. Westover, J. Z. Xu, R. Look, K. T. Demarest, P. Andrade-Gordon, B. P. Damiano, B. E. Maryanoff, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3245-3250.

[373] a) V. G. Kharitonov, V. S. Sharma, D. Magde, D. Koesling, *Biochemistry* **1999**, *38*, 10699-10706; b) V. Collot, P. Dallemagne, P. R. Bovy, S. Rault, *Tetrahedron* **1999**, *55*, 6917-6922.

[374] a) J. R. Henry, K. C. Rupert, J. H. Dodd, I. J. Turchi, S. A. Wadsworth, D. E. Cavender, B. Fahmy, G. C. Olini, J. E. Davis, J. Lee Pellegrino-Gensey, P. H. Schafer, J. J. Siekierka, *J. Med. Chem.* **1998**, *41*, 4196-4198; b) J. R. Henry, K. C. Rupert, J. H. Dodd, I. J. Turchi, S. A. Wadsworth, D. E. Cavender, P. H. Schafer, J. J. Siekierka, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3335-3340; c) J. R. Henry, J. H. Dodd, *Tetrahedron Lett.* **1998**, *39*, 8763-8764.

[375] T. A. Kelly, D. W. McNeil, J. M. Rose, E. David, C.-K. Shih, P. M. Grob, *J. Med. Chem.* **1997**, *40*, 2430-2433.

[376] A. Trejo, H. Arzeno, M. Browner, S. Chanda, S. Cheng, D. D. Comer, S. A. Dalrymple, P. Dunten, J. Lafargue, B. Lovejoy, J. Freire-Moar, J. Lim, J. Mcintosh, J. Miller, E. Papp, D. Reuter, R. Roberts, F. Sanpablo, J. Saunders, K. Song, A. Villasenor, S. D. Warren, M. Welch, P. Weller, P. E. Whiteley, L. Zeng, D. M. Goldstein, *J. Med. Chem.* **2003**, *46*, 4702-4713.

[377] For a recent review, see: H. Fan, J. Peng, M. T. Hamann, J.-F. Hu, *Chem. Rev.* **2008**, *108*, 264-287.

[378] Seminal publication: L. Knorr, *Ann.* **1886**, *236*, 290-332.

[379] Seminal publications: a) L. Knorr, *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 299-311; b) C. Paal, *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 367-371.

[380] Recent examples: a) N. Azizi, A. Khajeh-Amiri, H. Ghafuri, M. Bolourtchian, M. R. Saidi, *Synlett* **2009**, *14*, 2245-2248; b) B. K. Banik, S. Samajdar, I. Banik, *J. Org. Chem.* **2004**, *69*, 213-216. Investigation of the mechanism: c) V. Amarnath, D. C. Anthony, K. Amarnath, W. M. Valentine, L. A. Wetterau, D. G. Graham, *J. Org. Chem.* **1991**, *56*, 6924-6931.

[381] Seminal publication: A. Hantzsch, *Chem. Ber.* **1890**, *23*, 1474-1476.

[382] Seminal publications: a) O. Piloty, *Ber.* **1910**, *43*, 489-498; b) G. M. Robinson, R. Robinson, *J. Chem. Soc. Trans.* **1918**, *113*, 639-645.

[383] a) “The synthesis of highly functionalized pyrroles: a challenge in regioselectivity and chemical reactivity” C. Schmuck, D. Rupprecht, *Synthesis* **2007**, 3095-3110; b) “Recent advances in the synthesis of pyrroles” V. F. Ferreira, M. C. B. V. de Souza, A. C. Cunha, L. O. R. Pereira, M. L. G. Ferreira, *Org. Prep. Proc. Int.* **2001**, 33, 411-454.

[384] For selected recent examples, see: a) M. Yoshida, S. Easmin, M. Al-Amin, Y. Hirai, K. Shishido, *Tetrahedron* **2011**, *67*, 3194-3200; b) D. R. Stuart, P. Alsabeh, M. Kuhn, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 18326-18339; c) S. Rakshit, F. W. Patureau, F. Glorius, *J. Am. Chem. Soc.* **2010**, *132*, 9585-9587; d) M. Rueping, A. Parra, *Org. Lett.* **2010**, *12*, 5281-5283; e) R. Saijo, Y. Hagimoto, M. Kawase, *Org. Lett.* **2010**, *12*, 4776-4779; f) E. Benedetti, G. Lemière, L.-L. Chapellet, A. Penoni, G. Palmisano, M. Malacria, J.-P. Goddard, L. Fensterbank, *Org. Lett.* **2010**, *12*, 4396-4399; g) T. J. Donohoe, N. J. Race, J. F. Bower, C. K. A. Callens, *Org. Lett.* **2010**, *12*, 4094-4097; h) S. Kramer, J. L. H. Madsen, M. Rottländer, T. Skrydstrup, *Org. Lett.* **2010**, *12*, 2758-2761; i) A. Saito, T. Konishi, Y. Hanzawa, *Org. Lett.* **2010**, *12*, 372-374; j) W. Liu, H. Jiang, L. Huang, *Org. Lett.* **2010**, *12*, 312-315; k) S. Ngwerume, J. E. Camp, *J. Org. Chem.* **2010**, *75*, 6271-6274; l) R.-L. Yan, J. Luo, C.-X. Wang, C.-W. Ma, G.-S. Huang, Y.-M. Liang, *J. Org. Chem.* **2010**, *75*, 5395-5397; m) X. Du, X. Xie, Y. Liu, *J. Org. Chem.* **2010**, *75*, 510-513; n) I. Deb, D. Seidel, *Tetrahedron Lett.* **2010**, *51*, 2945-2947; o) A. Mizuno, H. Kusama, N. Iwasawa, *Angew. Chem.* **2009**, *121*,

8468-8470; *Angew. Chem. Int. Ed.* **2009**, *48*, 8318-8320; p) T. Miura, M. Yamauchi, M. Murakami, *Chem. Commun.* **2009**, 1470-1471; q) H. M. Peng, J. Zhao, X. Li, *Adv. Synth. Catal.* **2009**, *351*, 1371-1377; r) M. Egi, K. Azechi, S. Akai, *Org. Lett.* **2009**, *11*, 5002-5005; s) D. Cież, *Org. Lett.* **2009**, *11*, 4282-4285; t) X. Zhao, E. Zhang, Y.-Q. Tu, Y.-Q. Zhang, D.-Y. Yuan, K. Cao, C.-A. Fan, F.-M. Zhang, *Org. Lett.* **2009**, *11*, 4002-4004; u) M. Blangetti, A. Deagostino, C. Prandi, S. Tabasso, P. Venturello, *Org. Lett.* **2009**, *11*, 3914-3917; v) L. Ackermann, R. Sandmann, L. T. Kaspar, *Org. Lett.* **2009**, *11*, 2031-2034; w) I. Bergner, C. Wiebe, N. Meyer, T. Opatz, *J. Org. Chem.* **2009**, *74*, 8243-8253; x) W. R. Dolbier, Jr., Z. Zheng, *J. Org. Chem.* **2009**, *74*, 5626-5628; y) R. Bhattacharya, A. K. Atta, D. Dey, T. Pathak, *J. Org. Chem.* **2009**, *74*, 669-674; z) M. Yoshida, M. Al-Amin, K. Shishido, *Synthesis* **2009**, 2454-2466; aa) X. Yuan, X. Xu, X. Zhou, J. Yuan, L. Mai, Y. Li, *J. Org. Chem.* **2007**, *72*, 1510-1513; bb) B. Ramanathan, A. J. Keith, D. Armstrong, A. L. Odom, *Org. Lett.* **2004**, *6*, 2957-2960. For numerous further examples, see references in cc) E. Merkul, C. Boersch, W. Frank, T. J. J. Müller, *Org. Lett.* **2009**, *11*, 2269-2272.

[385] For a recent review, see: a) “Multicomponent reactions for the synthesis of pyrroles” V. Estévez, M. Villacampa, J. C. Menéndez, *Chem. Soc. Rev.* **2010**, *39*, 4402-4421. For a highlight, see: b) G. Balme, *Angew. Chem.* **2004**, *116*, 6396-6399; *Angew. Chem. Int. Ed.* **2004**, *43*, 6238-6241.

[386] For recent examples, see: a) B. M. Trost, J.-P. Lumb, J. M. Azzarelli, *J. Am. Chem. Soc.* **2011**, *133*, 740-743; b) L. V. Frolova, N. M. Evdokimov, K. Hayden, I. Malik, S. Rogelj, A. Kornienko, I. V. Magedov, *Org. Lett.* **2011**, *13*, 1118-1121; c) S. Lamandé-Langle, M. Abarbri, J. Thibonnet, A. Duchêne, J.-L. Parrain, *Chem. Commun.* **2010**, *46*, 5157-5159; d) A. Herath, N. D. P. Cosford, *Org. Lett.* **2010**, *12*, 5182-5185; e) M. S. T. Morin, D. J. St-Cyr, B. A. Arndtsen, *Org. Lett.* **2010**, *12*, 4916-4919; f) Q. Li, A. Fan, Z. Lu, Y. Cui, W. Lin, Y. Jia, *Org. Lett.* **2010**, *12*, 4066-4069; g) D. J. St-Cyr, M. S. T. Morin, F. Bélanger-Gariépy, B. A. Arndtsen, E. H. Krenske, K. N. Houk, *J. Org. Chem.* **2010**, *75*, 4261-4273; h) S. Maiti, S. Biswas, U. Jana, *J. Org. Chem.* **2010**, *75*, 1674-1683; i) X.-t. Liu, L. Hao, M. Lin, L. Chen, Z.-p. Zhan, *Org. Biomol. Chem.* **2010**, *8*, 3064-3072; j) B. Das, G. C. Reddy, P. Balasubramanyam, B. Veeranjaneyulu, *Synthesis* **2010**, 1625-1628; k) V. Cadierno, J. Gimeno, N. Nebra, *J. Heterocycl. Chem.* **2010**, *47*, 233-236; l) Y. Lu, X. Fu, H. Chen, X. Du, X. Jia, Y. Liu,

Adv. Synth. Catal. **2009**, *351*, 129-134; m) I. R. Baxendale, C. D. Buckle, S. V. Ley, L. Tamborini, *Synthesis* **2009**, 1485-1493; n) I. Yavari, E. Kowsari, *Mol. Diversity* **2009**, *13*, 519-528. For older examples, see references in o) E. Merkul, C. Boersch, W. Frank, T. J. J. Müller, *Org. Lett.* **2009**, *11*, 2269-2272.

[387] a) R. U. Braun, K. Zeitler, T. J. J. Müller, *Org. Lett.* **2001**, *3*, 3297-3300; b) R. U. Braun, T. J. J. Müller, *Synthesis* **2004**, *14*, 2391-2406.

[388] For some selected examples, see: a) H.-Y. Wang, D. S. Mueller, R. M. Sachwani, H. N. Londino, L. L. Anderson, *Org. Lett.* **2010**, *12*, 2290-2293; b) J.-H. Mirebeau, M. Haddad, M. Henry-Ellinger, G. Jaouen, J. Louvel, F. Le Bideau, *J. Org. Chem.* **2009**, *74*, 8890-8892, and references therein; c) W. S. Bremner, M. G. Organ, *J. Comb. Chem.* **2008**, *10*, 142-147; d) N. Zanatta, J. M. F. M. Schneider, P. H. Schneider, A. D. Wouters, H. G. Bonacorso, M. A. P. Martins, L. A. Wessjohann, *J. Org. Chem.* **2006**, *71*, 6996-6998.

[389] S. Kiren, X. Hong, C. A. Leverett, A. Padwa, *Org. Lett.* **2009**, *11*, 1233-1235.

[390] K. Utimoto, H. Miwa, H. Nozaki, *Tetrahedron Lett.* **1981**, *22*, 4277-4278.

[391] A. I. Siriwardana, K. K. A. D. S. Kathriarachchi, I. Nakamura, I. D. Gridnev, Y. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 13898-13899.

[392] For older examples, see: a) A. Padwa, R. Gruber, D. Pashayan, *J. Org. Chem.* **1968**, *33*, 454-455; b) L. W. Deady, *Tetrahedron* **1967**, *23*, 3505-3509; c) S. Sato, H. Kato, M. Ohta, *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2936-2938; d) C. F. H. Allen, C. V. Wilson, *Org. Synth.* **1955**, *Coll. Vol. 3*, p. 358; *Org. Synth.* **1947**, *Vol. 27*, p. 33.

[393] E. M. Campi, G. D. Fallon, W. R. Jackson, Y. Nilsson, *Aust. J. Chem.* **1992**, *45*, 1167-1178.

[394] X. Fan, Y. Zhang, *Tetrahedron Lett.* **2002**, *43*, 1863-1865.

[395] W. Zhao, E. M. Carreira, *Chem. Eur. J.* **2006**, *12*, 7254-7263.

[396] P. W. Davies, N. Martin, *Org. Lett.* **2009**, *11*, 2293-2296.

[397] A. Rámila, J. Plumet, E. Camacho, *Heterocycles* **1997**, *45*, 2425-2430.

[398] For 2,4-disubstituted pyrroles as dopamine D4 receptor partial agonists, see: M. Bergauer, H. Hübner, P. Gmeiner, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1937-1940.

[399] “Three-component synthesis of *N*-Boc-4-iodopyrroles and sequential one-pot alkynylation” E. Merkul, C. Boersch, W. Frank, T. J. J. Müller, *Org. Lett.* **2009**, *11*, 2269-2272.

[400] “Indole alkaloid marine natural products: as established source of cancer drug leads with considerable promise for the control of parasitic, neurological and other diseases” W. Gul, M. T. Hamann, *Life Sci.* **2005**, *78*, 442-453.

[401] “Marine compounds for the therapeutic treatment of neurological disorders” D. Alonso, A. Castro, A. Martinez, *Expert Opin. Ther. Patents* **2005**, *15*, 1377-1386.

[402] “Marine indole alkaloids: potential new drug leads for the control of depression and anxiety” A. J. Kochanowska-Karamyan, M. T. Hamann, *Chem. Rev.* **2010**, *110*, 4489-4497.

[403] J. Sakemi, H. H. Sun, *J. Org. Chem.* **1991**, *56*, 4304-4307.

[404] a) J. Shin, Y. Seo, K. W. Cho, J.-R. Rho, C. J. Sim, *J. Nat. Prod.* **1999**, *62*, 647-649; b) L. M. Murray, T. K. Lim, J. N. A. Hooper, R. J. Capon, *Aust. J. Chem.* **1995**, *48*, 2053-2058, and references therein; c) K. Bartik, J.-C. Braekman, D. Daloze, C. Stoller, J. Huysecom, G. Vandevyver, R. Ottinger, *Can. J. Chem.* **1987**, *65*, 2118-2121.

[405] M. Guyot, M. Meyer, *Tetrahedron Lett.* **1986**, *27*, 2621-2622.

[406] A. Loukaci, M. Guyot, A. Chiaroni, C. Riche, *J. Nat. Prod.* **1998**, *61*, 519-522.

[407] a) H. H. Sun, J. Sakemi, *J. Org. Chem.* **1991**, *56*, 4307-4308; b) J. Cohen, G. K. Paul, S. P. Gunasekera, R. E. Longley, S. A. Pomponi, *Pharm. Biol.* **2004**, *42*, 59-61.

[408] S. Tsujii, K. L. Rinehart, S. P. Gunasekera, Y. Kashman, S. S. Cross, M. S. Lui, S. A. Pomponi, M. C. Diaz, *J. Org. Chem.* **1988**, *53*, 5446-5453.

[409] R. J. Capon, C. Peng, C. Dooms, *Org. Biomol. Chem.* **2008**, *6*, 2765-2771.

[410] H. C. Vervoort, S. E. Richards-Gross, W. Fenical, A. Y. Lee, J. Clardy, *J. Org. Chem.* **1997**, *62*, 1486-1490.

[411] N. Lindquist, W. Fenical, G. D. Van Duyne, J. Clardy, *J. Am. Chem. Soc.* **1991**, *113*, 2303-2304.

[412] S. Takahashi, T. Matsunaga, C. Hasegawa, H. Saito, D. Fujita, F. Kiuchi, Y. Tsuda, *Chem. Pharm. Bull.* **1998**, *46*, 1527-1529.

[413] a) G. Guella, I. Mancini, I. N'Diaye, F. Pietra, *Helv. Chim. Acta* **1994**, *77*, 1999-2006; b) F. Miyake, M. Hashimoto, S. Tonsiengsom, K. Yakushijin, D. A. Horne, *Tetrahedron* **2010**, *66*, 4888-4893.

[414] B. S. Joshi, W. I. Taylor, D. S. Bhate, S. S. Karmarkar, *Tetrahedron* **1963**, *19*, 1437-1439.

[415] G. R. Pettit, J. C. Knight, D. L. Herald, R. Davenport, R. K. Pettit, B. E. Tucker, J. M. Schmidt, *J. Nat. Prod.* **2002**, *65*, 1793-1797.

[416] K. Motohashi, M. Takagi, K. Shin-ya, *J. Nat. Prod.* **2010**, *73*, 226-228.

[417] T. Hoshino, Y. Kojima, T. Hayashi, T. Uchiyama, K. Kaneko, *Biosci. Biotechnol. Biochem.* **1993**, *57*, 775-781.

[418] K. A. McArthur, S. S. Mitchell, G. Tsueng, A. Rheingold, D. J. White, J. Grodberg, K. S. Lam, B. C. M. Potts, *J. Nat. Prod.* **2008**, *71*, 1732-1737.

[419] N. Durán, G. Z. Justo, C. V. Ferreira, P. S. Melo, L. Cordi, D. Martins, *Biotechnol. Appl. Biochem.* **2007**, *48*, 127-133.

[420] L. M. Browne, K. L. Conn, W. A. Ayer, J. P. Tewari, *Tetrahedron* **1991**, *47*, 3909-3914.

[421] a) H. Oka, T. Yoshinari, T. Murai, K. Kawamura, F. Satoh, K. Funaishi, A. Okura, H. Suda, M. Okanishi, Y. Shizuri, *J. Antibiot.* **1991**, *44*, 486-491; b) H. Suda, K. Matsunaga, S. Yamamura, Y. Shizuri, *Tetrahedron Lett.* **1991**, *32*, 2791-2792.

[422] P. Ciminiello, C. Dell'Aversano, E. Fattorusso, M. Forino, L. Grauso, F. U. Santelia, L. Tartaglione, V. I. Moutsos, E. N. Pitsinos, E. A. Couladouros, *Eur. J. Org. Chem.* **2007**, 5434-5439, and references therein.

[423] T. Bergmann, D. Schories, B. Steffan, *Tetrahedron* **1997**, *53*, 2055-2060.

[424] a) J. J. Mason, J. Bergman, T. Janosik, *J. Nat. Prod.* **2008**, *71*, 1447-1450; b) P.-L. Wu, Y.-L. Hsu, C.-W. Jao, *J. Nat. Prod.* **2006**, *69*, 1467-1470.

[425] a) R. J. Capon, F. Rooney, L. M. Murray, E. Collins, A. T. R. Sim, J. A. P. Rostas, M. S. Butler, A. R. Carroll, *J. Nat. Prod.* **1998**, *61*, 660-662; b) A. E. Wright, S. A. Pomponi, S. S. Cross, P. McCarthy, *J. Org. Chem.* **1992**, *57*, 4772-4775; c) S. A. Morris, R. J. Andersen, *Tetrahedron Lett.* **1990**, *46*, 715-720; d) S. Kohmoto, Y. Kashman, O. J. McConnell, K. L. Rinehart, Jr., A. Wright, F. Koehn, *J. Org. Chem.* **1988**, *53*, 3116-3118.

[426] a) B. Bao, Q. Sun, X. Yao, J. Hong, C.-O. Lee, H. Y. Cho, J. H. Jung, *J. Nat. Prod.* **2007**, *70*, 2-8; b) B. Bao, Q. Sun, X. Yao, J. Hong, C.-O. Lee, C. J. Sim, K. S. Im, J. H. Jung, *J. Nat. Prod.* **2005**, *68*, 711-715; c) K.-B. Oh, W. Mar, S. Kim, J.-Y. Kim, M.-N. Oh, J.-G. Kim, D. Shin, C. J. Sim, J. Shin, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4927-4931; d) A. Casapullo, G. Bifulco, I. Bruno, R. Riccio, *J. Nat. Prod.* **2000**, *63*, 447-451; e) S. P. Gunasekera, P. J. McCarthy, M. Kelly-Borges, *J. Nat. Prod.* **1994**, *57*, 1437-1441.

[427] P. Sauleau, M.-T. Martin, M.-E. T. H. Dau, D. T. A. Youssef, M.-L. Bourguet-Kondracki, *J. Nat. Prod.* **2006**, *69*, 1676-1679.

[428] U. W. Hawas, M. Shaaban, K. A. Shaaban, M. Speitling, A. Maier, G. Kelter, H. H. Fiebig, M. Meiners, E. Helmke, H. Laatsch, *J. Nat. Prod.* **2009**, *72*, 2120-2124.

[429] A. Badre, A. Boulanger, E. Abou-Mansour, B. Banaigs, G. Combaut, C. Francisco, *J. Nat. Prod.* **1994**, *57*, 528-533.

[430] D. T. A. Youssef, *J. Nat. Prod.* **2005**, *68*, 1416-1419.

[431] a) H. Su, Z. H. Yuan, J. Li, S. J. Guo, L. P. Deng, L. J. Han, X. B. Zhu, D. Y. Shi, *Chin. Chem. Lett.* **2009**, *20*, 456-458; b) A. A. El-Gamal, W.-L. Wang, C.-Y. Duh, *J. Nat. Prod.* **2005**, *68*, 815-817; c) N. K. Kubota, H. Iwamoto, Y. Fukazawa, Y. Uchio, *Heterocycles* **2005**, *65*, 2675-2682.

[432] L. Hernández Franco, E. Bal de Kier Joffé, L. Puricelli, M. Tatian, A. M. Seldes, J. A. Palermo, *J. Nat. Prod.* **1998**, *61*, 1130-1132.

[433] A. M. Seldes, M. F. R. Brasco, L. Hernández Franco, J. A. Palermo, *Nat. Prod. Res.* **2007**, *21*, 555-563.

[434] M. Gompel, M. Leost, E. Bal de Kier Joffé, L. Puricelli, L. Hernández Franco, J. Palermo, L. Meijer, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1703-1707.

[435] a) L. Hernández Franco, J. A. Palermo, *Chem. Pharm. Bull.* **2003**, *51*, 975-977; b) A. Seggio, G. Priem, F. Chevallier, F. Mongin, *Synthesis* **2009**, 3617-3632.

[436] B. Jiang, C.-g. Yang, *Heterocycles* **2000**, *53*, 1489-1498.

[437] a) P. M. Fresneda, P. Molina, J. A. Bleda, *Tetrahedron* **2001**, *57*, 2355-2363. See also an earlier study: b) P. M. Fresneda, P. Molina, S. Delgado, J. A. Bleda, *Tetrahedron Lett.* **2000**, *41*, 4777-4780.

[438] G. Simon, H. Couthon-Gourves, J.-P. Haelters, B. Corbel, N. Kervarec, F. Michaud, L. Meijer, *J. Heterocycl. Chem.* **2007**, *44*, 793-801.

[439] a) E. Rossignol, A. Youssef, P. Moreau, M. Prudhomme, F. Anizon, *Tetrahedron* **2007**, *63*, 10169-10176; b) R. Akue-Gedu, E. Debiton, Y. Ferandin, L. Meijer, M. Prudhomme, F. Anizon, P. Moreau, *Bioorg. Med. Chem.* **2009**, *17*, 4420-4424.

[440] E. Rossignol, E. Debiton, D. Fabbro, P. Moreau, M. Prudhomme, F. Anizon, *Anti-Cancer Drugs* **2008**, *19*, 789-792.

[441] Z. Časar, D. Bevk, J. Svete, B. Stanovnik, *Tetrahedron* **2005**, *61*, 7508-7519.

[442] H. Yu, Z. Yu, *Angew. Chem.* **2009**, *121*, 2973-2977; *Angew. Chem. Int. Ed.* **2009**, *48*, 2929-2933.

[443] A. Agarwal, K. Srivastava, S. K. Puri, P. M. S. Chauhan, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3133-3136.

[444] F. Tibiletti, M. Simonetti, K. M. Nicholas, G. Palmisano, M. Parravicini, F. Imbesi, S. Tollari, A. Penoni, *Tetrahedron* **2010**, *66*, 1280-1288.

[445] B. Stanovnik, J. Svete, *Mini-Rev. Org. Chem.* **2005**, *2*, 211-224.

[446] L. Núñez-Pons, R. Forestieri, R. M. Nieto, M. Varela, M. Nappo, J. Rodríguez, C. Jiménez, F. Castelluccio, M. Carbone, A. Ramos-Espla, M. Gavagnin, C. Avila, *Polar Biol.* **2010**, *33*, 1319-1329.

[447] “Synthesis of the indole alkaloids meridianins from the tunicate *Aplidium meridianum*” P. M. Fresneda, P. Molina, J. A. Bleda, *Tetrahedron* **2001**, *57*, 2355-2363.

[448] “Concise syntheses of meridianins by carbonylative alkynylation and a four-component pyrimidine synthesis” A. S. Karpov, E. Merkul, F. Rominger, T. J. J. Müller, *Angew. Chem.* **2005**, *117*, 7112-7117; *Angew. Chem. Int. Ed.* **2005**, *44*, 6951-6956.

[449] a) N. B. Perry, L. Ettouati, M. Litaudon, J. W. Blunt, M. H. G. Munro, S. Parkin, H. Hope, *Tetrahedron* **1994**, *50*, 3987-3992; b) G. Trimurtulu, D. J. Faulkner, N. B. Perry, L. Ettouati, M. Litaudon, J. W. Blunt, M. H. G. Munro, G. B. Jameson, *Tetrahedron* **1994**, *50*, 3993-4000.

[450] a) J. Mendiola, A. Baeza, J. Alvarez-Builla, J. J. Vaquero, *J. Org. Chem.* **2004**, *69*, 4974-4983; b) R. J. Anderson, J. C. Morris, *Tetrahedron Lett.* **2001**, *42*, 311-313; c) J. Mendiola, J. M. Minguez, J. Alvarez-Builla, J. J. Vaquero, *Org. Lett.* **2000**, *2*, 3253-3256; d) P. M. Fresneda, P. Molina, S. Delgado, J. A. Bleda, *Tetrahedron Lett.* **2000**, *41*, 4777-4780.

[451] A. Baeza, C. Burgos, J. Alvarez-Builla, J. J. Vaquero, *Tetrahedron Lett.* **2007**, *48*, 2597-2601.

[452] a) R. J. Anderson, J. C. Morris, *Tetrahedron Lett.* **2001**, *42*, 8697-8699; b) R. J. Anderson, J. B. Hill, J. C. Morris, *J. Org. Chem.* **2005**, *70*, 6204-6212.

[453] a) P. Molina, P. M. Fresneda, S. Delgado, J. A. Bleda, *Tetrahedron Lett.* **2002**, *43*, 1005-1007; b) P. Molina, P. M. Fresneda, S. Delgado, *J. Org. Chem.* **2003**, *68*, 489-499.

[454] a) A. Ahaidar, D. Fernández, O. Pérez, G. Danelón, C. Cuevas, I. Manzanares, F. Albericio, J. A. Joule, M. Álvarez, *Tetrahedron Lett.* **2003**, *44*, 6191-6194; b) A. Ahaidar, D. Fernández, G. Danelón, C. Cuevas, I. Manzanares, F. Albericio, J. A. Joule, M. Álvarez, *J. Org. Chem.* **2003**, *68*, 10020-10029.

[455] A. Baeza, J. Mendiola, C. Burgos, J. Alvarez-Builla, J. J. Vaquero, *Tetrahedron Lett.* **2008**, *49*, 4073-4077.

[456] M. Álvarez, D. Fernández, J. A. Joule, *Tetrahedron Lett.* **2001**, *42*, 315-317.

[457] P. M. Fresneda, S. Delgado, A. Francesch, I. Manzanares, C. Cuevas, P. Molina, *J. Med. Chem.* **2006**, *49*, 1217-1221.

[458] M. Simone, E. Erba, G. Damia, F. Vikhanskaya, A. M. Di Francesco, R. Riccardi, C. Bailly, C. Cuevas, J. M. Fernandez Sousa-Faro, M. D'Incalci, *Eur. J. Cancer* **2005**, *41*, 2366-2377.

[459] "Variolins and related alkaloids" S. R. Walker, E. J. Carter, B. C. Huff, J. C. Morris, *Chem. Rev.* **2009**, *109*, 3080-3098.

[460] "Halogenated indole alkaloids from marine invertebrates" P. M. Pauletti, L. S. Cintra, C. G. Braguine, A. A. S. Filho, M. L. A. Silva, W. R. Cunha, A. H. Januário, *Mar. Drugs* **2010**, *8*, 1526-1549.

[461] D. Fernández, A. Ahaidar, G. Danelón, P. Cironi, M. Marfil, O. Pérez, C. Cuevas, F. Albericio, J. A. Joule, M. Álvarez, *Monatsh. Chem.* **2004**, *135*, 615-627.

[462] "Meriolins, a new class of cell death-inducing kinase inhibitors with enhanced selectivity for cyclin-dependent kinases" K. Bettayeb, O. M. Tirado, S. Marionneau-Lambot, Y. Ferandin, O. Lozach, J. C. Morris, S. Mateo-Lozano, P. Drueckes, C. Schächtele, M. H. G. Kubbutat, F. Liger, B. Marquet, B. Joseph, A. Echalier, J. A. Endicott, V. Notario, L. Meijer, *Cancer Res.* **2007**, *67*, 8325-8334.

[463] A. Echalier, K. Bettayeb, Y. Ferandin, O. Lozach, M. Clément, A. Valette, F. Liger, B. Marquet, J. C. Morris, J. A. Endicott, B. Joseph, L. Meijer, *J. Med. Chem.* **2008**, *51*, 737-751.

[464] "Rapid synthesis of bis(hetero)aryls by one-pot Masuda borylation – Suzuki coupling sequence and its application to concise total syntheses of meridianins A and G", E. Merkul, E. Schäfer, T. J. J. Müller, *Org. Biomol. Chem.* **2011**, *9*, 3139-3141.

[465] L. M. Browne, K. L. Conn, W. A. Ayer, J. P. Tewari, *Tetrahedron* **1991**, *47*, 3909-3914.

[466] a) R. Schuhegger, T. Rauhut, E. Glawischnig, *J. Plant Physiol.* **2007**, *164*, 636-644; b) R. Schuhegger, M. Nafisi, M. Mansourova, B. L. Petersen, C. E. Olsen, A. Svatoš, B. A. Halkier, E. Glawischnig, *Plant Physiol.* **2006**, *141*, 1248-1254.

[467] For a review, see: E. Glawischnig, *Phytochemistry* **2007**, *68*, 401-406.

[468] W. A. Ayer, P. A. Craw, Y.-t. Ma, S. Miao, *Tetrahedron* **1992**, *48*, 2919-2924.

[469] C. J. Moody, J. R. A. Roffey, M. A. Stephens, I. J. Stratford, *Anti-Cancer Drugs* **1997**, *8*, 489-499.

[470] M. S. C. Pedras, J. Liu, *Org. Biomol. Chem.* **2004**, *2*, 1070-1076.

[471] T. Sakamoto, Y. Kondo, N. Takazawa, H. Yamanaka, *J. Chem. Soc., Perkin Trans. 1* **1996**, 1927-1934.

[472] A. Fürstner, A. Ernst, *Tetrahedron* **1995**, *51*, 773-786.

[473] M. Dzurilla, P. Kutschy, J. Zaletova, M. Ruzinsky, V. Kovacik, *Molecules* **2001**, *6*, 716-720.

[474] a) S. Cacchi, G. Fabrizi, L. M. Parisi, *Synthesis* **2004**, 1889-1894; b) S. Cacchi, G. Fabrizi, D. Lamba, F. Marinelli, L. M. Parisi, *Synthesis* **2003**, 728-734.

[475] M. S. Butler, R. J. Capon, C. C. Lu, *Aust. J. Chem.* **1992**, *45*, 1871-1877.

[476] M. D. Lebar, B. J. Baker, *Aust. J. Chem.* **2010**, *63*, 862-866.

[477] F. Reyes, R. Fernández, A. Rodríguez, A. Francesch, S. Taboada, C. Ávila, C. Cuevas, *Tetrahedron* **2008**, *64*, 5119-5123.

[478] L. Gupta, A. Talwar, P. M. S. Chauhan, *Curr. Med. Chem.* **2007**, *14*, 1789-1803.

[479] T. Endo, M. Tsuda, J. Fromont, J. Kobayashi, *J. Nat. Prod.* **2007**, *70*, 423-424.

[480] Á. Mosquera, R. Riveiros, J. P. Sestelo, L. A. Sarandeses, *Org. Lett.* **2008**, *10*, 3745-3748.

[481] “One-pot synthesis of diazine-bridged bisindoles and concise synthesis of marine alkaloid hyrtinadine A” B. O. A. Tasch, E. Merkul, T. J. J. Müller, manuscript submitted for *Eur. J. Org. Chem.* **2011**, 4532-4535.

[482] “ATP site-directed competitive and irreversible inhibitors of protein kinases” C. García-Echeverría, P. Traxler, D. B. Evans, *Med. Res. Rev.* **2000**, *20*, 28-57.

[483] a) V. Birault, C. J. Harris, J. Le, M. Lipkin, R. Nerella, A. Stevens, *Curr. Med. Chem.* **2006**, *13*, 1735-1748; b) M. E. M. Noble, J. A. Endicott, L. N. Johnson, *Sci-*

ence **2004**, *303*, 1800-1805; c) M. Cherry, D. H. Williams, *Curr. Med. Chem.* **2004**, *11*, 663-673; d) I. Muegge, I. J. Enyedy, *Curr. Med. Chem.* **2004**, *11*, 693-707.

[484] “Molecular recognition of protein kinase binding pockets for design of potent and selective kinase inhibitors” J. J.-L. Liao, *J. Med. Chem.* **2007**, *50*, 1-16.

[485] R. Hoessel, S. Leclerc, J. A. Endicott, M. E. M. Nobel, A. Lawrie, P. Tunnah, M. Leost, E. Damiens, D. Marie, D. Marko, E. Niederberger, W. Tang, G. Eisenbrand, L. Meijer, *Nature Cell Biol.* **1999**, *1*, 60-67.

[486] a) M. Deininger, E. Buchdunger, B. J. Druker, *Blood* **2005**, *105*, 2640-2653; b) J. Zimmermann, *Nachr. Chem.* **2002**, *50*, 1084-1094; c) J. Zimmermann, E. Buchdunger, H. Mett, T. Meyer, N. B. Lydon, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 187-192; d) J. Zimmermann, E. Buchdunger, H. Mett, T. Meyer, N. B. Lydon, P. Traxler, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1221-1226.

[487] For selected examples of 4-substituted 2-amino pyrimidines as pharmacophores in kinase inhibitors, see: a) P. S. Humphries, J. A. Lafontaine, C. S. Agree, D. Alexander, P. Chen, Q.-Q. T. Do, L. Y. Li, E. A. Lunney, R. J. Rajapakse, K. Siegel, S. L. Timofeevski, T. Wang, D. M. Wilhite, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2099-2102; b) H.-H. Ha, J. S. Kim, B. M. Kim, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 653-656; c) K. L. Stevens, D. K. Jung, M. J. Alberti, J. G. Badiang, G. E. Peckham, J. M. Veal, M. Cheung, P. A. Harris, S. D. Chamberlain, M. R. Peel, *Org. Lett.* **2005**, *7*, 4753-4756; d) F. X. Tavares, J. A. Boucheron, S. H. Dickerson, R. J. Griffin, F. Preugschat, S. A. Thomson, T. Y. Wang, H.-Q. Zhou, *J. Med. Chem.* **2004**, *47*, 4716-4730.

[488] D. Strumberg, *Drugs Today* **2005**, *41*, 773-784.

[489] For a scaleable synthesis of sorafenib, see: D. Bankston, J. Dumas, R. Natero, B. Riedl, M.-K. Monahan, R. Sibley, *Org. Process Res. Dev.* **2002**, *6*, 777-781.

[490] For a microwave-assisted solid-phase synthesis, see: F. Leonetti, C. Capaldi, A. Carotti, *Tetrahedron Lett.* **2007**, *48*, 3455-3458. For further references, see: H. Liu, W. Xia, Y. Luo, W. Lu, *Monatsh. Chem.* **2010**, *141*, 907-911.

[491] Y.-F. Liu, C.-L. Wang, Y.-J. Bai, N. Han, J.-P. Jiao, X.-L. Qi, *Org. Process Res. Dev.* **2008**, *12*, 490-495.

[492] H. Liu, W. Xia, Y. Luo, W. Lu, *Monatsh. Chem.* **2010**, *141*, 907-911.

[493] M. D. Hopkin, I. R. Baxendale, S. V. Ley, *Chem. Commun.* **2010**, *46*, 2450-2452.

[494] E. Weisberg, P. W. Manley, W. Breitenstein, J. Brüggen, S. W. Cowan-Jacob, A. Ray, B. Huntly, D. Fabbro, G. Fendrich, E. Hall-Meyers, A. L. Kung, J. Mestan, G. Q. Daley, L. Callahan, L. Catley, C. Cavazza, A. Mohammed, D. Neuberg, R. D. Wright, D. G. Gilliland, J. D. Griffin, *Cancer Cell* **2005**, *7*, 129-141.

[495] A. Yokota, S. Kimura, S. Masuda, E. Ashihara, J. Kuroda, K. Sato, Y. Kamitsuji, E. Kawata, Y. Deguchi, Y. Urasaki, Y. Terui, M. Ruthardt, T. Ueda, K. Hatake, K.-i. Inui, T. Maekawa, *Blood* **2007**, *109*, 306-314.

[496] E. Weisberg, P. W. Manley, S. W. Cowan-Jacob, A. Hochhaus, J. D. Griffin, *Nat. Rev.* **2007**, *7*, 345-358.

[497] C. Kung, K. M. Shokat, *ChemBioChem* **2005**, *6*, 523-526.

[498] “Multikomponentensynthese von Pyrrolen auf Basis der Kupplung von Propargylamiden” C. Boersch, Bachelorarbeit **2008**, Düsseldorf.

[499] “New three-component glyoxylation – decarbonylative Stille coupling sequence to acyl heterocycles under mild conditions” B. O. A. Tasch, E. Merkul, W. Frank, T. J. J. Müller, *Synthesis* **2010**, 2139-2146.

[500] For a synthesis via addition of diazaridines to dibenzoylacetylene, see: H. W. Heine, T. R. Hoye, P. G. Williard, R. C. Hoye, *J. Org. Chem.* **1973**, *38*, 2984-2988.

Appendix

Genius is one percent inspiration and ninety–nine percent perspiration.

Thomas Alva Edison

“Catalytic syntheses of *N*-heterocyclic ynones and ynediones by in situ activation of carboxylic acids with oxalyl chloride”, Christina Boersch, Eugen Merkul, Thomas J. J. Müller, *Angew. Chem. Int. Ed.* **2011**, published online, 10.1002/anie.201103296.

One-Pot Reactions

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Catalytic Syntheses of N-Heterocyclic Ynones and Ynediones by In Situ Activation of Carboxylic Acids with Oxalyl Chloride**

*Christina Boersch, Eugen Merkul, and Thomas J. J. Müller**

Dedicated to Professor Kenkichi Sonogashira on the occasion of his 80th birthday

Ynones are highly reactive Michael systems and can be smoothly reacted with various mono- and binucleophiles in addition and addition–cyclocondensation processes. Consequently, they have received considerable attention as valuable building blocks in heterocycle[1] and natural-product[2] synthesis. Ynediones contain a 1,2-dione motif and are even more densely functionalized electrophiles, thus enabling a more multifaceted transformation profile towards heterocycles.[3,4] Despite their auspicious synthetic potential, ynediones have remained scarcely explored owing to a lack of a general and practical preparative access.[5] Therefore, a direct, simple, and efficient route to this class of compounds would be highly desirable.

Aryl-substituted ynones can be easily prepared by stoichiometric or catalytic acylation of organometallic reagents, especially by Sonogashira coupling.[6,7] However, an essential limitation of this methodology to date is the lack of an efficient method for the preparation of ynones with N-heterocyclic substituents.[8,9] N-Heteroarenes are pervasive in numerous natural products[10] and in biologically active agents in medicinal chemistry, and the quest for nitrogen-containing building blocks is enormous. However, the often observed low reactivity in cross-coupling reactions resulting from substrate or product inhibition by coordination to transition metals[11] has fostered the necessity to develop a convincing and robust methodology for breaking this bottleneck. For instance, pyridine or quinoline carboxylic acid chlorides, which are highly interesting building blocks in medicinal chemistry, are often not readily available and thus, their transformation to ynones under modified Sonogashira coupling conditions[12] was not considered to be practical. On the other hand, N-heterocyclic carboxylic acids are the immediate precursors of acid chlorides. Therefore, a one-pot access to ynones starting directly from carboxylic acids could overcome the shortcomings of acid chloride preparation and isolation, and a valuable, conceptually new synthetic tool for ynone preparation could evolve.

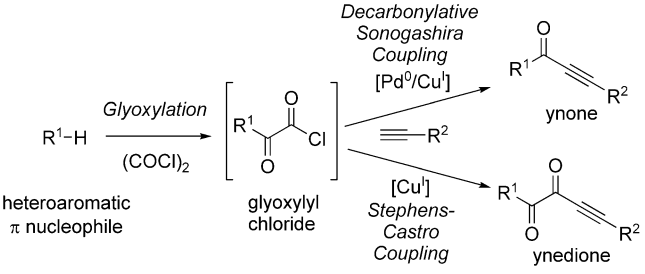
Aromatic carboxylic acids have received considerable attention as aryl-nucleophile precursors in metal-catalyzed cross-couplings,[13] which in most cases proceed under decarboxylation.[14,15] Cross-couplings of carboxylic acids using an excess of anhydrides or carbonates for activation allow for the carbonyl group to be maintained but result in the formation of simple alkyl and aryl ketones.[16]

At the same time, the activation of carboxylic acids with oxalyl chloride is a widespread, mild, and clean method for the preparation of acid chlorides, which produces only gaseous by-products (carbon monoxide, carbon dioxide, and hydrogen chloride).[17] Thus, an in situ conversion of carboxylic acids to acid chlorides using oxalyl chloride followed by alkyne coupling in a one-pot fashion can be considered as an activation–alkynylation sequence to ynones and ynediones. To our knowledge this straightforward alkynylation methodology is unprecedented to date.

Recently, we disclosed conceptually novel approaches to ynones and ynediones initiated by glyoxylation of electron-rich heteroaromatic π nucleophiles with oxalyl chloride and subsequent alkyne coupling. The Pd/Cu-catalyzed decarbonylative Sonogashira coupling gives rise to the formation of ynones,[9] whereas the Cu-catalyzed Stephens–Castro coupling maintains both carbonyl groups and results in the generation of ynediones (Scheme 1).[4]

Inspired by the alkynylation of in situ generated glyoxylyl chlorides, we set out to design one-pot activation–alkynylation sequences that either start from α-keto carboxylic acids **1** and apply Castro conditions for the synthesis of ynediones **3** or from carboxylic acids **4** using Sonogashira conditions for the generation of ynones **5** (Scheme 2), especially addressing notoriously difficult transformations of N-heterocyclic carboxylic acids.

For the optimization of the activation–alkynylation sequence phenylglyoxylic acid (**1a**) and phenylacetylene



Scheme 1. One-pot three-component glyoxylation–alkynylation syntheses of ynones and ynediones.

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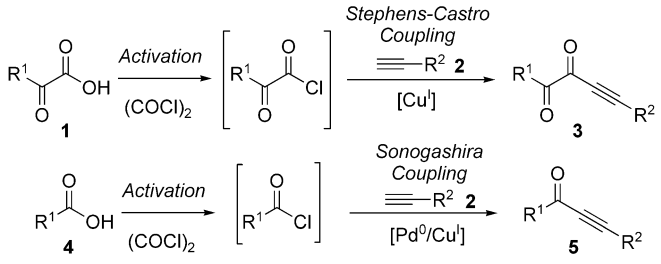
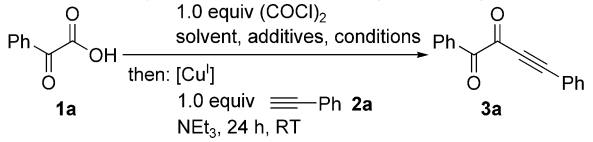


Scheme 2. Conceptual access to ynediones and ynones by sequential activation–alkynylation.

(**2a**) were chosen as model substrates furnishing 1,4-diphenylbut-3-yne-1,2-dione (**3a**; Table 1). Different ethereal solvents were examined and parameters such as temperature, reaction time, order of reagent addition, and amount of CuI were modified (for experimental details and full optimization, see the Supporting Information).

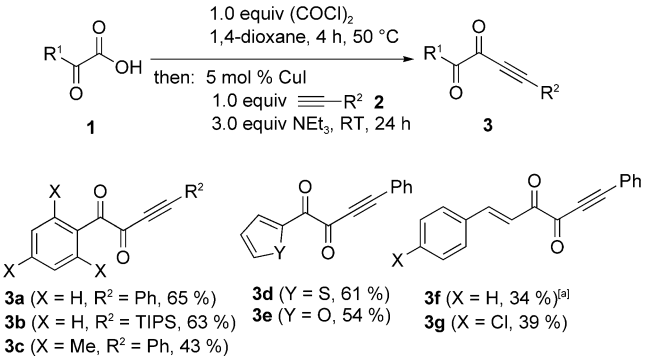
Table 1: Selected optimization trials for the synthesis of ynedione **3a**.



Entry	First reaction step[a]	Second reaction step	Yield [%][b]
1	1.0 equiv NEt_3, THF	5 mol% CuI, 2.0 equiv NEt_3	39
2	THF	5 mol% CuI, 3.0 equiv NEt_3	43
3	**1,4-dioxane**	**5 mol% CuI, 3.0 equiv NEt_3**	**65**
4	1,4-dioxane/DMF[c]	5 mol% CuI, 3.0 equiv NEt_3	51
5	1,4-dioxane	2 mol% CuI, 3.0 equiv NEt_3	47
6	1,4-dioxane	10 mol% CuI, 3.0 equiv NEt_3	64

[a] Reaction temperature: 50°C, reaction time: 4 h. [b] Yield of isolated product on a 2.0 mmol scale. [c] Addition of 2 mol% *N*,*N*-dimethylformamide.

The addition of triethylamine in the first step for deprotonation of the carboxylic acid in the chlorination step or scavenging the generated hydrogen chloride is not necessary (Table 1, entries 1 and 2). The most significant increase of the yield of isolated product from 43 to 65% was observed upon changing the solvent from THF to 1,4-dioxane (entry 3). It is known that 1,4-dioxane and oxalyl chloride form oligomeric complex chains of alternating 1,4-dioxane and oxalyl chloride molecules by coordination of the oxygen atoms of 1,4-dioxane to the chlorine atoms of oxalyl chloride.[18] Presumably, the enhanced reactivity is caused by an activation of the reagent by destabilization of the chlorine–carbon bond of oxalyl chloride. We also attempted to exploit the known catalytic effect of DMF on the chlorination with oxalyl chloride by addition of 2 mol% of DMF; however, the obtained yield was lower (entry 4). The variation of the CuI loading in the alkynylation step from 2 to 10 mol% revealed an optimum with 5 mol% of the catalyst (entries 3, 5, and 6). These optimized conditions were successfully applied to one-pot syntheses of several ynediones **3**, which were obtained in moderate to good yields (Scheme 3).[19]



Scheme 3.
One-pot synthesis of ynediones **3** by an activation–Stephens–Castro alkynylation sequence. All reactions were carried out on a 2.00 mmol scale [c(**1**) = 0.2 M] and yields refer to isolated and purified compounds. [a] The potassium carboxylate was used as a substrate. Ph = phenyl, TIPS = triisopropylsilyl, Me = methyl.

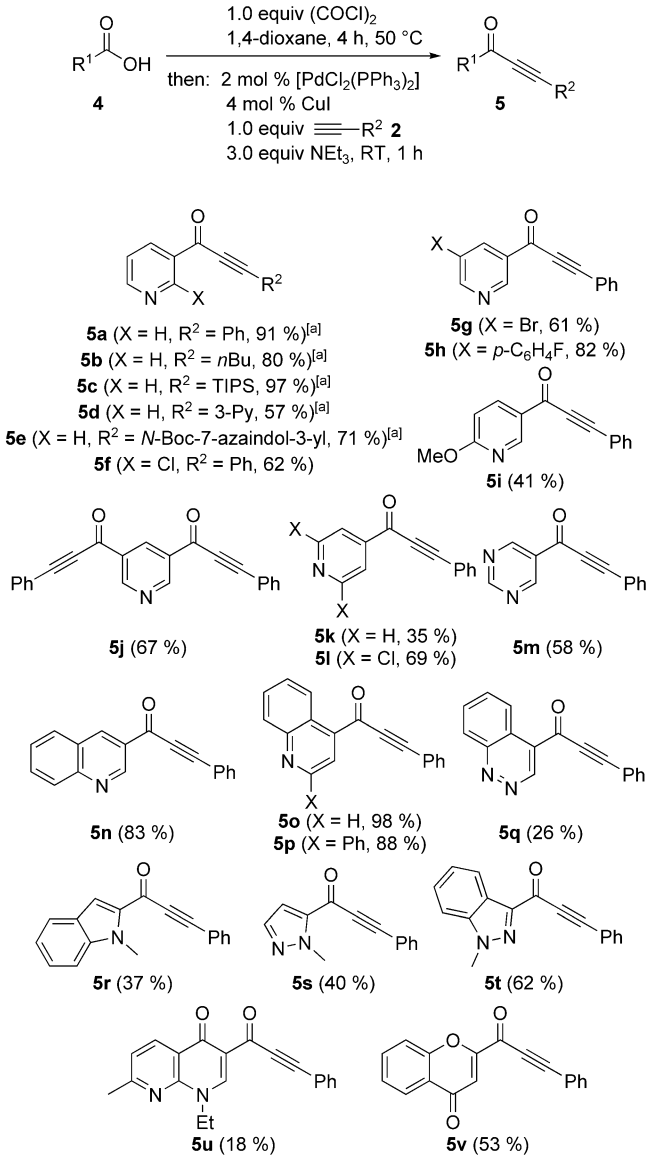
With this new and mild activation–Stephens–Castro alkynylation sequence it was possible to prepare aryl (**3a–c**), heteroaryl (**3d,e**), and alkenyl ynediones (**3f,g**) in moderate to good yields starting directly from α-keto carboxylic acids **1** or their carboxylates. This novel, valuable sequence convincingly complements the glyoxylation–Stephen–Castro coupling sequence,[4] because electron-neutral and even sterically hindered substrates (see formation of **3c**) can be transformed uneventfully.

Likewise, the one-pot in situ activation–alkynylation scenario was transposed to carboxylic acids **4** in the presence of 2 mol% [$PdCl_2(PPh_3)_2$] and 4 mol% CuI as a catalyst system, leading to the successful formation of ynones **5** in moderate to excellent yields (Scheme 4).[19] Expectedly, the reaction times under Sonogashira conditions are considerably shorter, and complete conversion was achieved after only 1 h at room temperature.

The activation–Sonogashira alkynylation sequence starting from heterocyclic carboxylic acids and carboxylates **4** furnishes a broad variety of the corresponding ynones **5**. Most remarkably, Sonogashira coupling of commercially available pyridine-3-carbonyl chloride hydrochloride (Merck KGaA) to give ynone **5a** under identical reaction conditions failed completely, even if the reason for this strange observation is yet unknown.

For sodium nicotinate (**4a**) it was demonstrated that the variation of the alkyne **2** was feasible. Besides phenylacetylene, 1-hexyne, and TIPS-acetylene, also N-heterocyclic alkynes can be efficiently coupled to yield highly functionalized building blocks (see formation of **5d,e**). The example of the ynone **5e** shows that even the highly labile Boc protective group on the 7-azaindolyl moiety is preserved.

Substituents in 2-, 5-, and 6- as well as in 2,6-positions of the pyridine core are well tolerated (**5f–i** and **5l**). Bromine in 3-position of pyridine (**5g**) remains untouched under these gentle conditions, ready for addressing this ynone in further functionalizations. It could also be shown that dinicotinic acid can be activated and coupled to give a bis(ynone) (**5j**) in a good yield. In addition to pyridine-containing carboxylic acids, this method can be well applied to convert a whole



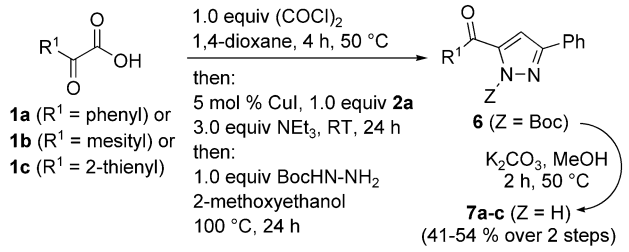
Scheme 4.
One-pot synthesis of ynones **5** by an activation–Sonogashira alkynylation sequence. All reactions were carried out on a 2.00 mmol scale [c(**4**) = 0.2 M] and yields refer to isolated and purified compounds. [a] The sodium carboxylate was used as a substrate. *n*Bu = *n*-butyl, Py = pyridyl, Boc = *tert*-butyloxycarbonyl.

variety of 6-membered N-heterocyclic carboxylic acids, such as isonicotine, pyrimidine, quinoline, and cinnoline carboxylic acid (see formation of **5k**–**q**). Also azoles such as indole, pyrazole, and indazole carboxylic acids can be successfully carried through the sequence (see formation of **5r**–**t**).

It is noteworthy that the indazole derivative **5t** is accessible neither by the carbonylative Sonogashira coupling[2] nor by the glyoxylation–decarbonylative alkynylation sequence.[9] Therefore, it is quite remarkable that there is no limitation with respect to the electronic nature of the substrates. Electron-poor (**5a**–**q**) as well as electron-rich (**5r**–**t**) ynones are accessible. Interestingly, the antimicrobial nalidixic acid[20] (**4p**) can also be functionalized (**5u**) as well as a chromone carboxylic acid (**4q**) to give a chromenyl ynone (**5v**), now opening access to heterocyclic derivatives of flavones.

Both activation–alkynylation sequences for the preparation of ynediones **3** and ynones **5** are preparatively very simple, mild, and straightforward to perform. In particular, they open an entry to derivatives that are not accessible or difficult or expensive to access with known methods. Carboxylic acids are easily available, stable, and generally nontoxic compounds. Moreover, oxalyl chloride is a liquid which can be conveniently handled. Both sequences use simple standard catalyst systems. Neither exotic ligands nor additives are required, and the alkynylation steps proceed smoothly at room temperature. Finally, all reactants and reagents are used in strictly equimolar amounts without the need for excess reagents.

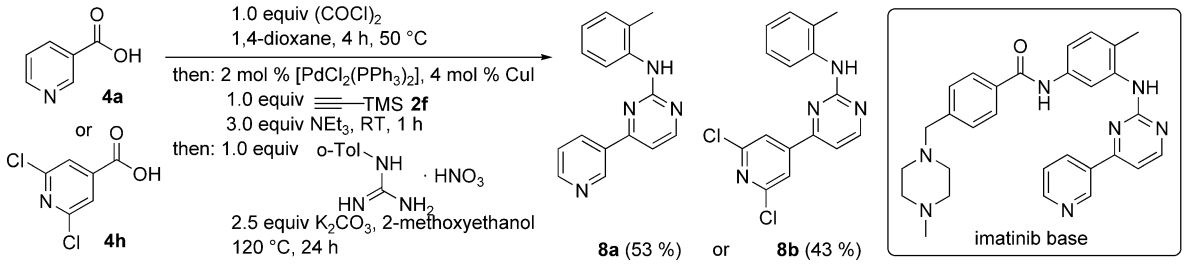
As an illustration of the applicability of ynediones and ynones as intermediates, one-pot three-component heterocycle syntheses of *N*-Boc-5-acylpyrazoles **6** and 2-aminopyrimidines **8** were conceived. In a consecutive three-component fashion the in situ generated ynediones **3** can be selectively transformed to *N*-Boc-protected 5-acylpyrazoles **6** with *N*-Boc-hydrazine. After deprotection, the 5-acylpyrazoles **7a**–**c** are isolated as analytically pure products (Scheme 5).



Scheme 5. One-pot three-component access to 5-acylpyrazoles **6**.

Likewise, the cyclocondensation of *o*-tolyl guanidinium nitrate with the in situ generated trimethylsilyl (TMS) ynones concludes the one-pot three-component synthesis of 2-*o*-tolylaminopyrimidines **8** (Scheme 6). 4-(3-Pyridyl)-2-*o*-tolylaminopyrimidine (**8a**) is the pharmacophore of the blockbuster drugs imatinib (Gleevec)[21] and nilotinib (Tasigna),[22] both acting as tyrosine kinase inhibitors in cancer chemotherapy. This new sequence allows the rapid assembly of the phenylaminopyrimidine scaffold in a one-pot fashion using simple and cheap starting materials, whereas other known procedures take two or more steps and use more elaborate precursors.[23] Most remarkably, the analogue **8b** possesses two activated chlorine atoms that have remained untouched, again emphasizing the high compatibility with other functionalities and the mild reaction conditions of the presented methodology.

In conclusion, we have developed new one-pot activation–alkynylation sequences starting from α-keto carboxylic acids or carboxylic acids as versatile and efficient approaches to ynediones and N-heterocyclic ynones, respectively. The one-pot three-component syntheses of 5-acylpyrazoles and 2-*o*-tolylaminopyrimidines illustrate the implementation of this



Scheme 6. One-pot three-component synthesis of 4-pyridyl-2-*o*-tolylaminopyrimidines **8**. Tol = tolyl.

highly efficient methodology in multicomponent syntheses of pharmaceutically important heterocycles. Further methodological studies are currently underway.

Experimental Section

3a: Phenylglyoxylic acid (**1a**, 306 mg, 2.00 mmol) in dry 1,4-dioxane (10 mL) was placed under argon atmosphere in a screw-cap Schlenk vessel with septum. Argon was passed through the solution for 5 min. Then, oxalyl chloride (0.18 mL, 2.00 mmol) was added dropwise to the reaction mixture at room temperature (water bath). The mixture was stirred for 4 h at 50 °C in a preheated oil bath and then cooled to room temperature. CuI (20 mg, 0.10 mmol), phenylacetylene (**2a**, 0.23 mL, 2.00 mmol), and dry triethylamine (0.84 mL, 6.00 mmol) were successively added to the mixture, and stirring at room temperature was continued for 24 h. After complete conversion, water (10 mL) was added and the mixture was extracted with dichloromethane. The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuum the residue was adsorbed on Celite and purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 50:1; $R_f = 0.14$) to give the analytically pure 1,4-diphenylbut-3-yne-1,2-dione (**3a**, 302 mg, 65 %) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta =$ 7.39–7.43 (m, 2H), 7.48–7.56 (m, 3H), 7.63–7.70 (m, 3H), 8.07–8.10 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 87.0$ (C_{quat}), 99.1 (C_{quat}), 119.1 (C_{quat}), 128.7 (CH), 128.9 (CH), 130.5 (CH), 131.5 (C_{quat}), 131.7 (CH), 133.6 (CH), 134.9 (CH), 178.5 (C_{quat}), 188.4 ppm (C_{quat}); elemental analysis calcd (%) for $C_{16}H_{10}O_2$ (234.3): C 82.04, H 4.30; found: C 82.13, H 4.31.

5o: Quinoline-4-carboxylic acid (**4k**, 357 mg, 2.00 mmol) in dry 1,4-dioxane (10 mL) was placed under argon atmosphere in a screw-cap Schlenk vessel with septum. Argon was passed through the solution for 5 min. Then, oxalyl chloride (0.18 mL, 2.00 mmol) was added dropwise to the reaction mixture at room temperature (water bath). The mixture was stirred for 4 h at 50 °C in a preheated oil bath and was cooled to room temperature. [$PdCl_2(PPh_3)_2$] (28 mg, 0.04 mmol), CuI (15 mg, 0.08 mmol), phenylacetylene (**2a**, 0.23 mL, 2.00 mmol), and dry triethylamine (0.84 mL, 6.00 mmol) were successively added to the mixture and stirring at room temperature was continued for 1 h. After complete conversion, water (10 mL) was added, and the mixture was extracted with dichloromethane. The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuum the residue was adsorbed on Celite and purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 6:1, $R_f = 0.22$) to give the analytically pure 3-phenyl-1-(quinolin-4-yl)prop-2-yn-1-one (**5o**, 505 mg, 98 %) as a pale brown solid. M.p. 93 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta =$ 7.38–7.56 (m, 3H), 7.65–7.76 (m, 3H), 7.76–7.85 (m, 1H), 8.16–8.28 (m, 2H), 8.93–9.02 (m, 1H), 9.12–9.19 ppm (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 88.4$ (C_{quat}), 94.1 (C_{quat}), 119.9 (C_{quat}), 124.3 (C_{quat}), 124.4 (CH), 125.9 (CH), 129.1 (CH), 129.4 (CH), 130.3 (CH), 130.4 (CH), 131.6 (CH), 133.6 (CH), 139.9 (C_{quat}), 149.6 (C_{quat}), 150.3 (CH), 179.3 ppm (C_{quat}); elemental analysis calcd. (%) for $C_{18}H_{11}NO$ (257.3): C 84.03, H 4.31, N 5.44; found: C 83.86, H 4.40, N 5.51.

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[1] For selected reviews on alkynones in heterocycle syntheses, see: a) T. J. J. Müller, *Top. Heterocycl. Chem.* **2010**, *25*, 25–94; b) M. C. Bagley, C. Glover, E. A. Merritt, *Synlett* **2007**, 2459–2482; c) R. L. Bol'shedvorskaya, L. I. Vereshchagin, *Russ. Chem. Rev.* **1973**, *42*, 225–240, and references therein.

[2] For the synthesis of marine alkaloids meridianins, see: A. S. Karpov, E. Merkul, F. Rominger, T. J. J. Müller, *Angew. Chem.* **2005**, *117*, 7112–7117; *Angew. Chem. Int. Ed.* **2005**, *44*, 6951–6956.

[3] For the Au^{III}-catalyzed synthesis of furanones, see: Y. Liu, M. Liu, S. Guo, H. Tu, Y. Zhou, H. Gao, *Org. Lett.* **2006**, *8*, 3445–3448.

[4] For a recently reported glyoxylation–Stephens–Castro coupling sequence and four-component syntheses of heterocycles, see: E. Merkul, J. Dohe, C. Gers, F. Rominger, T. J. J. Müller, *Angew. Chem.* **2011**, *123*, 3023–3026; *Angew. Chem. Int. Ed.* **2011**, *50*, 2966–2969.

[5] a) For a cross-coupling reaction of phenylglyoxylyl chloride with tributylstannylphenylacetylene, see: T. Kashiwabara, M. Tanaka, *J. Org. Chem.* **2009**, *74*, 3958–3961; b) for a synthesis starting from benzotriazolyl alkynes, see: A. R. Katritzky, Z. Wang, H. Lang, D. Feng, *J. Org. Chem.* **1997**, *62*, 4125–4130; c) for electrochemical syntheses, see: M. Cariou, J. Simonet, *J. Chem. Soc. Chem. Commun.* **1990**, 445–446; M. Cariou, *Tetrahedron* **1991**, *47*, 799–808; d) for a transition metal-catalyzed synthesis, see: S. Ahmad, J. Iqbal, *J. Chem. Soc. Chem. Commun.* **1987**, 692–693; e) for a four-step synthesis, see: J. Leyendecker, U. Niewöhner, W. Steglich, *Tetrahedron Lett.* **1983**, *24*, 2375–2378.

[6] a) For coupling of acid chlorides, see: Y. Tohda, K. Sonogashira, N. Hagihara, *Synthesis* **1977**, 777–778; b) for a carbonylative coupling, see e.g.: M. S. M. Ahmed, A. Mori, *Org. Lett.* **2003**, *5*, 3057–3060.

[7] For reviews, see: a) R. Grigg, S. P. Mutton, *Tetrahedron* **2010**, *66*, 5515–5548; b) A. Brennführer, H. Neumann, M. Beller, *Angew. Chem.* **2009**, *121*, 4176–4196; *Angew. Chem. Int. Ed.* **2009**, *48*, 4114–4133.

[8] a) C. François-Endelmond, T. Carlin, P. Thuery, O. Loreau, F. Taran, *Org. Lett.* **2010**, *12*, 40–42; b) F. C. Fuchs, G. A. Eller, W. Holzer, *Molecules* **2009**, *14*, 3814–3832; c) B. Willy, W. Frank, T. J. J. Müller, *Org. Biomol. Chem.* **2010**, *8*, 90–95.

[9] E. Merkul, T. Oeser, T. J. J. Müller, *Chem. Eur. J.* **2009**, *15*, 5006–5011.

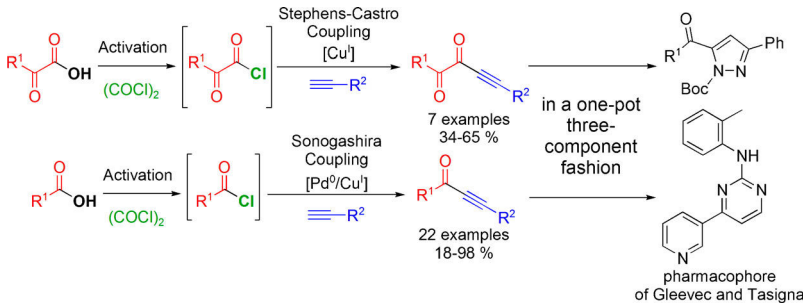
[10] a) M. Ishikura, K. Yamada, T. Abe, *Nat. Prod. Rep.* **2010**, *27*, 1630 – 1680; b) D. O'Hagan, *Nat. Prod. Rep.* **2000**, *17*, 435 – 446; c) J. P. Michael, *Nat. Prod. Rep.* **2008**, *25*, 166 – 187.
[11] V. F. Slagt, A. H. M. de Vries, J. G. de Vries, R. M. Kellogg, *Org. Process Res. Dev.* **2010**, *14*, 30 – 47.
[12] A. S. Karpov, T. J. J. Müller, *Org. Lett.* **2003**, *5*, 3451 – 3454.
[13] For reviews on carboxylic acids in homogenous catalysis, see: a) L. J. Gooßen, N. Rodríguez, K. Gooßen, *Angew. Chem.* **2008**, *120*, 3144 – 3164; *Angew. Chem. Int. Ed.* **2008**, *47*, 3100 – 3120; b) L. J. Gooßen, K. Gooßen, N. Rodríguez, M. Blanchot, C. Linder, B. Zimmermann, *Pure Appl. Chem.* **2008**, *80*, 1725 – 1733.
[14] For selected recent examples of decarboxylative cross-couplings starting from carboxylic acids, see: a) F. Zhang, M. F. Greaney, *Org. Lett.* **2010**, *12*, 4745 – 4747; b) K. Xie, Z. Yang, X. Zhou, X. Li, S. Wang, Z. Tan, X. An, C.-C. Guo, *Org. Lett.* **2010**, *12*, 1564 – 1567; c) F. Bilodeau, M.-C. Brochu, N. Guimond, K. H. Thesen, P. Forgione, *J. Org. Chem.* **2010**, *75*, 1550 – 1560; d) L. J. Gooßen, N. Rodríguez, P. P. Lange, C. Linder, *Angew. Chem.* **2010**, *122*, 1129 – 1132; *Angew. Chem. Int. Ed.* **2010**, *49*, 1111 – 1114; e) J.-J. Dai, J.-H. Liu, D.-F. Luo, L. Liu, *Chem. Commun.* **2011**, *47*, 677 – 679.
[15] For recent examples of decarboxylative cross-couplings starting from α-keto carboxylic acids and derivatives, see: a) F. Rudolphi, B. Song, L. J. Gooßen, *Adv. Synth. Catal.* **2011**, *353*, 337 – 342; b) M. Li, C. Wang, H. Ge, *Org. Lett.* **2011**, *13*, 2062 – 2064; c) M. Li, H. Ge, *Org. Lett.* **2010**, *12*, 3464 – 3467; d) L. J. Gooßen, F. Rudolphi, C. Oppel, N. Rodríguez, *Angew. Chem.* **2008**, *120*, 3085 – 3088; *Angew. Chem. Int. Ed.* **2008**, *47*, 3043 – 3045.
[16] For non-decarboxylative cross-couplings starting from carboxylic acids, see: a) L. J. Gooßen, K. Ghosh, *Angew. Chem.* **2001**, *113*, 3566 – 3568; *Angew. Chem. Int. Ed.* **2001**, *40*, 3458 – 3460; b) L. J. Gooßen, K. Ghosh, *Chem. Commun.* **2001**, 2084 – 2085; c) L. J. Gooßen, L. Winkel, A. Döhring, K. Gosh, J. Paetzold, *Synlett* **2002**, 1237 – 1240.
[17] a) For chlorination of alkyl and aryl carboxylic acids, see: R. Adams, L. H. Ulich, *J. Am. Chem. Soc.* **1920**, *42*, 599 – 611; b) for chlorination of α-keto carboxylic acids, see: M. S. Kharasch, H. C. Brown, *J. Am. Chem. Soc.* **1942**, *64*, 325 – 332.
[18] a) G. A. Varvoglis, *Ber. Dtsch. Chem. Ges. B* **1938**, *71*, 32 – 34; b) B. E. Damm, O. Hassel, C. Rømming, *Acta Chem. Scand.* **1965**, *19*, 1159 – 1165.
[19] All assigned structures were unambiguously supported by NMR spectroscopy, mass spectrometry, and combustion analysis.
[20] For a general review on quinolones, see: A. M. Emmerson, A. M. Jones, *J. Antimicrob. Chemother.* **2003**, *51*, 13 – 20.
[21] a) B. J. Druker, S. Tamura, E. Buchdunger, S. Ohno, G. M. Segal, S. Fanning, J. Zimmermann, N. B. Lydon, *Nat. Med.* **1996**, *2*, 561 – 566; b) for a review on imatinib, see: C. F. Waller in *Small Molecules in Oncology* (Ed.: U. M. Martens), Springer, Berlin, **2010**, pp. 3 – 20.
[22] a) E. Weisberg et al., *Cancer Cell* **2005**, *7*, 129 – 141, see the Supporting Information; b) for a review on nilotinib, see: A. Quintás-Cardama, T. D. Kim, V. Cataldo, P. Le Coutre in *Small Molecules in Oncology* (Ed.: U. M. Martens), Springer, Berlin, **2010**, pp. 103 – 117; c) for a review on second-generation inhibitors, see: E. Weisberg, P. W. Manley, S. W. Cowan-Jacob, A. Hochhaus, J. D. Griffin, *Nat. Rev. Cancer* **2007**, *7*, 345 – 356.
[23] For recent syntheses, see: H. Liu, W. Xia, Y. Lou, W. Lu, *Monatsh. Chem.* **2010**, *141*, 907 – 911, and references therein.

Communications

One-Pot Reactions

C. Boersch, E. Merkul,
T. J. J. Müller* ——————— ■■■■–■■■■

Catalytic Syntheses of N-Heterocyclic Ynones and Ynediones by In Situ Activation of Carboxylic Acids with Oxalyl Chloride



Breaking the bottleneck: α-Keto carboxylic acids and N-heterocyclic carboxylic acids are activated in situ with oxalyl chloride and subsequently catalytically alkynylated to furnish ynediones and N-heterocyclic ynones very efficiently in a one-pot fashion. 5-Acylpyrazoles and 2-phenylaminopyrimidines, potentially interesting for pharmaceutical applications, are readily synthesized in concise one-pot, three-component syntheses.

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Supporting Information

69451 Weinheim, Germany

Catalytic Syntheses of N-Heterocyclic Ynones and Ynediones by In Situ Activation of Carboxylic Acids with Oxalyl Chloride**

*Christina Boersch, Eugen Merkul, and Thomas J. J. Müller**

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1 General considerations

All cross coupling reactions were carried out in oven-dried Schlenk glassware using septa and syringes under nitrogen or argon atmosphere. 1,4-Dioxane was dried using *MBraun* system MB-SPS-800 and triethylamine was refluxed under argon over ketyl sodium, distilled and stored in a Schlenk flask over potassium hydroxide pellets under argon atmosphere.

Commercial grade reagents were used as supplied without further purification and were purchased from *ABCR GmBH & Co. KG, Acros Organics*, *Alfa Aesar GmbH & Co. KG, Fluka AG*, *Maybridge, Merck KGaA*, Darmstadt, and *Sigma-Aldrich Chemie GmbH*.

The content of palladium (4 μg/g) in copper(I) iodide was determined in the laboratory Elementaranalytik of *Merck Serono*, Darmstadt.

The purification of pyrazoles was performed on silica gel 60 M (0.04-0.063 mm) from *Fluka Analytical* using flash technique and under pressure of 2 bar. The purification of alkynediones and alkynones was performed on Biotage SP-1 system using cartridges filled with ca. 340 g silica gel 60 (0.015-0.040 mm) from *Merck KGaA*, Darmstadt. The crude mixtures were adsorbed on Celite® 545 (0.02-0.10 mm) from *Merck Serono*, Darmstadt before chromatographic purification.

The reaction progress was monitored qualitatively using TLC Silica gel 60 F_{254} 20 x 20 cm aluminium sheets obtained from *Merck KGaA*, Darmstadt. The spots were detected with UV light at 254 nm and using aqueous potassium permanganate solution.

^{1}H-, ^{13}C-, and 135-DEPT-^{13}C-NMR spectra were recorded on Bruker Advanced DRX 500, Bruker Advanced DRX 200 and Bruker AVIII-300. $CDCl_3$ and DMSO-d_6 were used as deuterated solvents. TMS was used as reference (δ = 0.0) or the resonances of the solvents were locked as internal standards ($CDCl_3$: ^{1}H δ 7.26, ^{13}C δ 77.4; DMSO-d_6: ^{1}H δ 2.50, ^{13}C δ 39.5). The multiplicities of signals were abbreviated as follows:

s: singlet; d: doublet; dd: doublet of doublets; dt: doublet of triplets; ddd: doublet of doublets of doublets; t: triplet; tt: triplet of triplets; q: quartet; quin: quintet; sext: sextet; m: multiplet and br: broad signal. The type of carbon atoms was determined on the basis of 135-DEPT-NMR spectra. For the description of the ^{13}C-NMR spectra

primary carbon atoms are abbreviated with CH_3, secondary carbon atoms with CH_2, tertiary carbon atoms with CH and quaternary carbon atoms with C_{quat}.

EI mass spectra were measured on Finnigan MAT 8200 spectrometer.

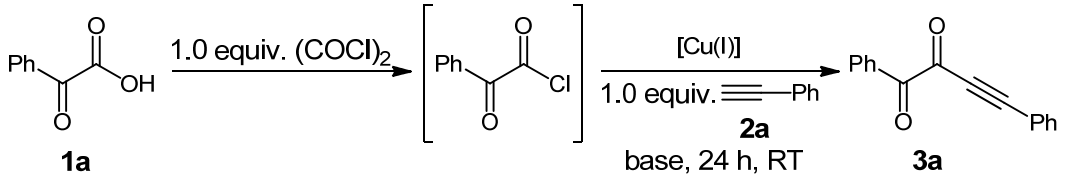
IR spectra were obtained on Bruker Vector 22 FT-IR, where the solids were measured as potassium bromide pellets and oils as films on potassium bromide plates or on Shimadzu IRAffinity-1 which works with the attenuated total reflection (ATR) method. The intensity of signals is abbreviated as follows: s (strong), m (medium) and w (weak).

The melting points (uncorrected) were measured on Reichert Thermovar.

Combustion analyses were carried out on Perkin Elmer Series II Analyser 2400 in the micro analytical laboratory of Institut für Pharmazeutische und Medizinische Chemie der Heinrich-Heine-Universität Düsseldorf.

2 Optimization studies

For optimization of the activation-alkynylation sequence the following model reaction has been chosen (Scheme 1).



Scheme 1. Model reaction for the optimization.

The reaction was carried out on a 2.00 mmol scale. The yields refer to the isolated and pure product **3a**. The optimization steps are summarized (Table 1).

Table 1. Optimization of the activation-alkynylation sequence.

Entry	1st Reaction step				2nd Reaction step		Yield ynedione **3a**
	NEt_3	Solvent	T	t	NEt_3	[CuI]	
1	1.0 equiv.[a]	THF	0 °C → RT	4 h	2.0 equivs.	5 mol %	28 %
2	1.0 equiv.[b]	THF	0 °C → RT	4 h	2.0 equivs.	5 mol %	23 %
3	1.0 equiv.[b]	THF	0 °C → 50 °C	4 h	2.0 equivs.	5 mol %	39 %
4	-	THF	0 °C → 50 °C	4 h	3.0 equivs.	5 mol %	43 %
5	-	THF	0 °C → 50 °C	4 h	3.0 equivs.	10 mol %	27 %
6	-	THF	0 °C → 50 °C	1 h	3.0 equivs.	5 mol %	36 %
7	-	THF	0 °C → 50 °C	4 h	3.0 equivs.[c]	5 mol %	n. i.
8	-	1,4-dioxane	RT → 100 °C	4 h	3.0 equivs.	5 mol %	59 %

Table 1 (continuation).

Entry	1st Reaction step				2nd Reaction step		Yield ynedione **3a**
	NEt_3	Solvent	T	t	NEt_3	[CuI]	
9	-	DMF	0 °C → 80 °C	4 h	3.0 equivs.	5 mol %	39 %
10	-	diglyme[d]	0 °C → 120 °C	4 h	3.0 equivs.	5 mol %	n. i.
11	-	1,4-dioxane	RT → 100 °C	4 h	3.0 equivs.	2 mol %	44 %
12	-	1,4-dioxane	RT → 100 °C	1 h	3.0 equivs.	5 mol %	56 %
13	-	1,4-dioxane	RT → 50 °C	4 h	3.0 equivs.	5 mol %	65 %[e]
14	-	1,4-dioxane 2 mol % DMF	RT → 50 °C	4 h	3.0 equivs.	5 mol %	51 %
15	-	1,4-dioxane	RT → 50 °C	2 h	3.0 equivs.	5 mol %	59 %
16	-	1,4-dioxane	RT	4 h	3.0 equivs.	5 mol %	56 %
17	-	1,4-dioxane	RT	3 h	3.0 equivs.	5 mol %	63 %
18	-	1,4-dioxane	RT → 50 °C	4 h	3.0 equivs.	2 mol %	47 %
19	-	1,4-dioxane	RT → 50 °C	4 h	3.0 equivs.	10 mol %	64 %
20	1.0 equiv.[b]	1,4-dioxane	RT → 50 °C	4 h	2.0 equivs.	5 mol %	59 %
21	-	1,4-dioxane	RT → 50 °C	24 h	3.0 equivs.	5 mol %	49 %

[a] Addition of oxalyl chloride, then addition of NEt_3

[b] Addition of NEt_3, then addition of oxalyl chloride

[c] *Hünig's* base (*N*,*N*-diisopropylethylamine) was used instead of NEt_3

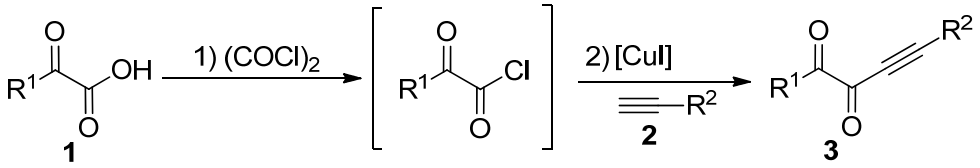
[d] 1-Methoxy-2-(2-methoxyethoxy)ethane

[e] On a 5.00 mmol scale, 61 % yield was optained

n. i.: not isolated

3 Preparation of ynediones 3

3.1 General procedure



2.00 mmol of glyoxylic acid **1** in dry 1,4-dioxane (10 mL) were placed under argon atmosphere in a screw-cap Schlenk vessel with septum and degassed with argon. Then, oxalyl chloride (0.18 mL, 2.00 mmol, 1.00 equiv.) was added dropwise to the reaction mixture at room temperature (water bath). The mixture was stirred for 4 h at 50 °C in a preheated oil bath and was allowed to come to room temperature. CuI (20 mg, 0.10 mmol, 5 mol %), alkyne **2** (2.00 mmol, 1.00 equiv.) and dry triethylamine (0.84 mL, 6.00 mmol, 3.00 equivs.) were successively added to the mixture and stirring at room temperature was continued for 24 h. After complete conversion (product monitored by TLC) water (10 mL) was added and the mixture was extracted with dichloromethane (4 x 10 mL, monitored by TLC). The combined organic layers were dried with anhydrous sodium sulfate and the desiccant was removed by filtration. After removal of the solvents in vacuum the residue was adsorbed on Celite® and purified chromatographically (Biotage SP-1 apparatus, 100 g SNAP cartridge) on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl acetate to give ynediones **3**.

The experimental details for the synthesis of ynediones **3** are given in Table 2.

Table 2. Experimental details for the synthesis of ynediones 3.

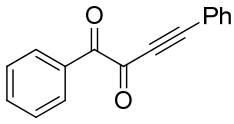
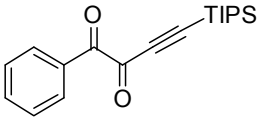
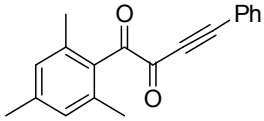
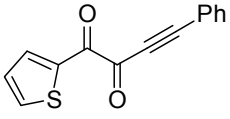
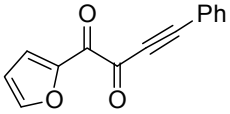
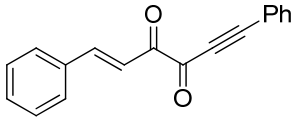
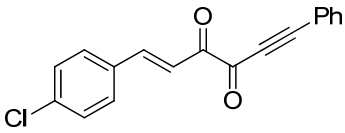
Entry	Glyoxylic acid **1** (2.00 mmol)	Alkyne **2** (2.00 mmol)	Ynedione **3** (isolated yield)	Chromatographic purification R_f (eluent)
1	Phenylglyoxylic acid (*Merck*) **1a** 306 mg	Phenyl-acetylene **2a** (*Merck*) 0.23 mL	 **3a** 302 mg (1.29 mmol) 65 %	PE/EtOAc = 50:1 R_f (PE/EtOAc = 50:1) = 0.14
2	**1a** 306 mg	Tiisopropylsilyl-acetylene **2b** (*Fluka*) 0.45 mL	 **3b** 396 mg (1.26 mmol) 63 %	PE/EtOAc = 100:1 R_f (PE/EtOAc = 100:1) = 0.19
3	Mesiylglyoxylic acid (*ABCR*) **1b** 388 mg	**2a** 0.23 mL	 **3c** 237 mg (0.86 mmol) 43%	PE/EtOAc = 50:1 R_f (PE/EtOAc = 50:1) = 0.36
4	2-Thiophenyl glyoxylic acid (*Alpha Aesar*) **1c** 319 mg	**2a** 0.23 mL	 **3d** 293 mg (1.22 mmol) 61 %	PE/EtOAc = 50:1 R_f (PE/EtOAc = 50:1) = 0.15

Table 2 (continuation).

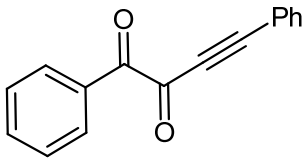
Entry	Glyoxylic acid **1** (2.00 mmol)	Alkyne **2** (2.00 mmol)	Ynedione **3** (isolated yield)	Chromatographic purification R_f (eluent)
5	2-Furanyl glyoxylic acid (*Sigma Aldrich*) **1d** 289 mg	**2a** 0.23 mL	 **3e** 244 mg (1.09 mmol) 54 %	PE/EtOAc = 10:1 R_f (PE/EtOAc = 10:1) = 0.27
6	(*E*)-Benzylidene glyoxylic acid potassium salt **1e**[a] 429 mg	**2a** 0.23 mL	 **3f** 175 mg (0.67 mmol) 34 %	PE/EtOAc = 50:1 R_f (PE/EtOAc = 50:1) = 0.14
7	(*E*)-*p*-Chloro-benzylidene glyoxylic acid **1f**[b] 421 mg	**2a** 0.23 mL	 **3g** 228 mg (0.77 mmol) 39 %	PE/EtOAc = 50:1 R_f (PE/EtOAc = 50:1) = 0.18

[a] The potassium salt was prepared according to the literature procedure: C. Allais, T. Constantieux, J. Rodriguez, *Synthesis* **2009**, *15*, 2523-2530. 2.00 equivs. of triethylamine in the 2nd reaction step were used.

[b] The potassium salt was prepared according to the literature procedure: C. Allais, T. Constantieux, J. Rodriguez, *Synthesis* **2009**, *15*, 2523-2530. The free acid was obtained after acidifying with hydrochlorid acid..

3.2 Spectroscopic data of compounds 3a-g

3.2.1 1,4-Diphenylbut-3-yne-1,2-dione (3a)



$C_{16}H_{10}O_2$

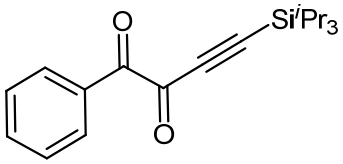
234.25

302 mg (1.29 mmol, 65 % yield) as a yellow oil. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.33-7.47 (m, 2 H), 7.47-7.59 (m, 3 H), 7.61-7.74 (m, 3 H), 8.00-8.21 (m, 2 H). ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 87.4 (C_{quat}), 99.5 (C_{quat}), 119.5 (C_{quat}), 129.1 (CH), 129.3 (CH), 130.9 (CH), 131.9 (C_{quat}), 132.1 (CH), 134.0 (CH), 135.3 (CH), 178.9 (C_{quat}), 188.8 (C_{quat}). EI + MS (*m/z* (%)): 234 (M^+, 0.4), 206 ($(M-CO)^+$, 3), 178 ($(M-C_2O_2)^+$, 31), 129 ($C_9H_5O^+$, 71), 106 (7), 105 ($C_7H_5O^+$, 100), 85 (11), 77 ($C_6H_5^+$, 38), 75 (11), 71 (15), 57 (13). IR (film): $\tilde{\nu}$ 3065 (w) cm^{-1}, 2927 (w), 2593 (w), 2361 (w), 2191 (s), 1656 (s), 1595 (m), 1489 (w), 1449 (m), 1249 (m), 1182 (w), 1108 (s), 1025 (w), 1000 (w), 924 (m), 816 (w), 778 (m), 759 (m), 738 (m), 685 (s), 611 (w), 538 (w). Anal. calcd. for $C_{16}H_{10}O_2$ (234.3): C 82.04, H 4.30. Found: C 82.13, H 4.31.

Data reported in the literature: Y. C.-T. Chen, J.-Q. Kao, S. B. Salunke, Y.-H. Lin, *Org. Lett.* **2011**, *13*, 26-29.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41 (t, *J* = 7.74 Hz, 2 H), 7.46-7.55 (m, 3 H), 7.64-7.69 (m, 3 H), 8.08 (d, *J* = 7.74 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 87.05, 99.14, 119.24, 128.73, 128.92, 130.50, 131.66, 133.63, 134.86, 178.53, 188.43. MS (EI, 70 eV): 234 (M^+, 27), 129 (44), 105 (100). R_f(EtOAc/hexanes = 1:15) = 0.37.

3.2.2 1-Phenyl-4-[tris(propan-2-yl)silyl]but-3-yne-1,2-dione (3b)

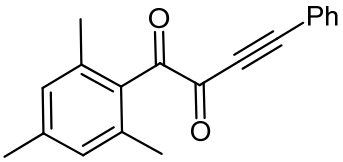


$C_{19}C_{26}O_2Si$

314.49

396 mg (1.26 mmol, 63 % yield) as a yellow oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.06-1.19 (m, 21 H), 7.44-7.54 (m, 2 H), 7.59-7.68 (m, 1 H), 7.98-8.06 (m, 2 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 11.2 (CH), 18.7 (CH_3), 102.8 (C_{quat}), 106.5 (C_{quat}), 129.1 (CH), 130.6 (CH), 131.8 (C_{quat}), 135.1 (CH), 178.4 (C_{quat}), 188.5 (C_{quat}). EI + MS (*m/z* (%)): 286 ((M-CO)$^+$, 0.1), 258 ((M-C_2O_2)$^+$, 0.4), 271 ((M-C_3H_7)$^+$, 3), 243 ((M-C_3H_7-CO)$^+$, 3), 106 (8), 106 (7), 105 ($C_7H_5O^+$, 100), 77 ($C_6H_5^+$, 16). IR (ATR): $\tilde{\nu}$ 2945 (w) cm^{-1}, 2666 (w), 2145 (w),1665 (s), 1597 (w), 1462 (w), 1450 (w), 1385 (w), 1319 (w), 1279 (w), 1125 (s), 1072 (w),1018 (w), 999 (w), 916 (s), 881 (s), 812 (w), 756 (w), 733 (m), 681 (s), 662 (s). Anal. calcd. for $C_{19}H_{26}O_2Si$ (314.5): C 72.56, H 8.33. Found: C 72.20, H 8.62.

3.2.3 4-Phenyl-1-(2,4,6-trimethylphenyl)but-3-yne-1,2-dione (3c)

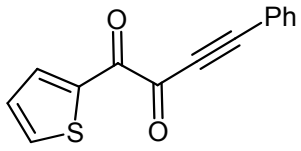


$C_{19}H_{16}O_2$

276.33

237 mg (0.86 mmol, 43 % yield) as a yellow oil. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 2.26 (s, 6 H), 2.32 (s, 3 H), 6.91 (s, 2 H), 7.39-7.48 (m, 2 H), 7.50-7.58 (m, 1 H), 7.60-7.73 (m, 2 H). ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 20.4 (CH_3), 21.6 (CH_3), 86.8 (C_{quat}), 99.8 (C_{quat}), 119.6 (C_{quat}), 129.1 (CH), 129.3 (CH), 132.0 (CH), 132.6 (C_{quat}), 134.1 (CH), 136.6 (C_{quat}), 141.4 (C_{quat}), 177.1 (C_{quat}), 194.8 (C_{quat}). EI + MS (*m/z* (%)): 276 (M^+, 0.2), 220 ($(M-C_2O_2)^+$, 1), 148 (12), 147 ($C_{10}H_{11}O^+$, 100), 129 ($C_9H_5O^+$, 6), 119 ($C_9H_{11}^+$, 24), 57 (10). IR (film): $\tilde{\nu}$ 3299 (w) cm^{-1}, 2923 (m), 2561 (w), 2181 (s), 1661 (s), 1610 (m), 1489 (m), 1444 (m), 1379 (m), 1295 (w), 1234 (w), 1101 (m), 1027 (m), 959 (m), 905 (s), 853 (m), 760 (m), 687 (m), 611 (m), 543 (m). Anal. calcd. for $C_{19}H_{16}O_2$ (276.3): C 82.58, H 5.84. Found: C 82.60, H 5.98.

3.2.4 4-Phenyl-1-(thiophen-2-yl)but-3-yne-1,2-dione (3d)

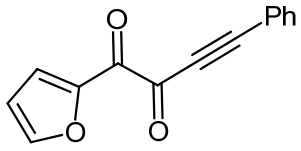


$C_{14}H_8O_2S$

240.28

293 mg (1.22 mmol, 61 % yield) as a yellow solid. Mp 84 °C. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.15-7.25 (m, 1 H), 7.35-7.46 (m, 2 H), 7.47-7.58 (m, 1 H), 7.62-7.75 (m, 2 H), 7.79-7.92 (m, 1 H), 8.13-8.25 (m, 1 H). ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 87.2 (C_{quat}), 99.6 (C_{quat}), 119.6 (C_{quat}), 129.1 (CH), 132.0 (CH), 134.1 (CH), 137.5 (C_{quat}), 137.9 (CH), 138.2 (CH), 176.5 (C_{quat}), 178.9 (C_{quat}). EI + MS (*m/z* (%)): 240 (M^+, 2), 212 ($(M-CO)^+$, 11), 184 ($(M-C_2O_2)^+$, 31), 130 (10), 129 ($C_9H_5O^+$, 100), 111 ($C_5H_3OS^+$, 97), 83 ($C_4H_3S^+$, 9), 75 (12). IR (KBr): $\tilde{\nu}$ 2181 (s) cm^{-1}, 1650 (s), 1592 (m), 1501 (m), 1487 (m), 1443 (w), 1405 (m), 1363 (m), 1298 (w), 1248 (m), 1111 (m), 1072 (w), 1040 (m), 909 (m), 858 (m), 763 (m), 732 (s), 684 (m), 624 (w), 567 (w), 540 (w). Anal. calcd. for $C_{14}H_8O_2S$ (240.3): C 69.98, H 3.36. Found: C 69.79, H 3.34.

3.2.5 1-(Furan-2-yl)-4-phenylbut-3-yne-1,2-dione (3e)

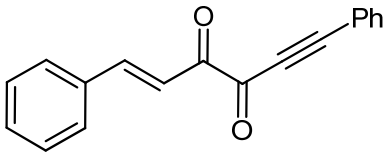


$C_{14}H_8O_3$

224.21

244 mg (1.09 mmol, 54 % yield) as a yellow solid. Mp 84 °C. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 6.59-6.69 (m, 1 H), 7.35-7.48 (m, 2 H), 7.49-7.54 (m, 1 H), 7.63-7.73 (m, 2 H), 7.74-7.78 (m, 1 H), 7.78-7.82 (m, 1 H). ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 87.1 (C_{quat}), 99.5 (C_{quat}), 113.5 (CH), 119.6 (C_{quat}), 125.5 (CH), 129.1 (CH), 132.0 (CH), 134.1 (CH), 148.1 (C_{quat}), 150.0 (CH), 173.8 (C_{quat}), 175.9 (C_{quat}). EI + MS (*m/z* (%)): 224 (M^+, 0.1), 196 ($(M\text{-}CO)^+$, 7), 168 ($(M\text{-}C_2O_2)^+$, 15), 130 (10), 129 ($C_9H_5O^+$, 100), 95 ($C_5H_3O_2^+$, 15). IR (KBr): $\tilde{\nu}$ 3117 (m) cm^{-1}, 2191 (s), 1654 (s), 1596 (m), 1552 (m), 1489 (w), 1459 (s), 1367 (m), 1323 (m), 1272 (m), 1186 (w), 1129 (s), 1084 (m), 1030 (s), 999 (w), 950 (s), 892 (s), 757 (s), 685 (s), 591 (m), 538 (m), 515 (w). Anal. calcd. for $C_{14}H_8O_3$ (224.2): C 75.00, H 3.60. Found: C 74.82, H 3.68.

3.2.6 (1*E*)-1,6-Diphenylhex-1-en-5-yne-3,4-dione (3f)



$C_{18}H_{12}O_2$

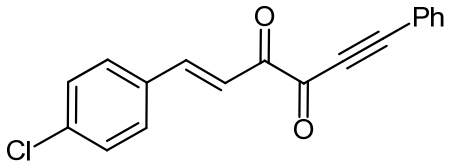
260.29

170 mg (0.65 mmol, 34 % yield) as a yellow solid. Mp 104 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.37-7.57 (m, 7 H), 7.63-7.75 (m, 4 H), 7.93 (d, *J* = 16.1 Hz, 1 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 87.0 (C_{quat}), 99.4 (C_{quat}), 118.2 (CH), 119.8 (C_{quat}), 129.1 (CH), 129.4 (CH), 131.9 (CH), 132.0 (CH), 134.1 (CH), 134.6 (C_{quat}), 148.9 (CH), 177.4 (C_{quat}), 184.8 (C_{quat}). EI + MS (*m/z* (%)): 260 (M^+, 2), 232 ($(M-CO)^+$, 2), 204 ($(M-C_2O_2)^+$, 3), 132 (10), 131 ($(M-C_9H_5O)^+$, 100), 129 ($C_9H_5O^+$, 33), 103 ($C_8H_7^+$, 28), 77 ($C_6H_5^+$, 12). IR (KBr): ṽ 2200 (m) cm^{-1}, 1719 (w), 1701 (w), 1685 (m), 1654 (s), 1608 (s), 1572 (m), 1561 (m), 1544 (m), 1509 (w), 1490 (w), 1459 (w), 1440 (m), 1273 (w), 1180 (w), 1033 (m), 1011 (m), 993 (s), 736 (s), 681 (m), 566 (w), 540 (w). Anal. calcd. for $C_{18}H_{12}O_2$ (260.3): C 83.06, H 4.65. Found: C 82.90, H 4.70.

Data reported in the literature: A. R. Katritzky, Z. Wang, H. Lang, D. Feng, *J. Org. Chem.* **1997**, *62*, 4125-4130.

*O*btained as yellow needles, yield 85%, mp 103-105 °C; ^{1}H NMR δ7.41-7.60 (m, 7 H), 7.62-7.82 (m, 4 H), 7.94 (d, 1 H, *J* 16.2 Hz); ^{13}C NMR δ 86.6, 99.0, 118.0, 119.4, 128.7, 129.0, 131.5, 131.6, 133.7, 134.2, 148.5, 177.1, 184.5. Anal. Calcd. for $C_{18}H_{12}O_2$: C, 83.06; H, 4.65. Found: C, 83.20; H, 4.64.

3.2.7 (1*E*)-1-(4-Chlorophenyl)-6-phenylhex-1-en-5-yne-3,4-dione (3g)



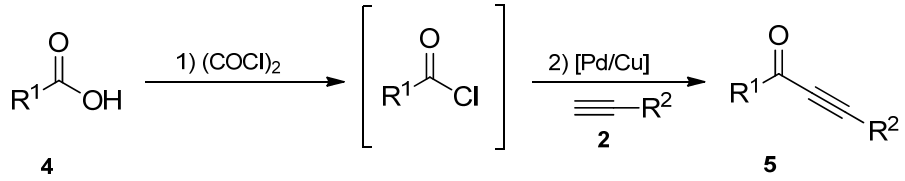
$C_{18}H_{11}ClO_2$

294.73

170 mg (0.65 mmol, 39 % yield) as a yellow solid. Mp 144 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.34-7.55 (m, 6 H), 7.56-7.63 (m, 2 H), 7.66-7.73 (m, 2 H), 7.86 (d, *J* = 16.1 Hz, 1 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 86.9 (C_{quat}), 99.7 (C_{quat}), 118.6 (CH), 119.7 (C_{quat}), 129.1 (CH), 129.8 (CH), 130.5 (CH), 132.0 (CH), 133.1 (C_{quat}), 134.1 (CH), 138.0 (C_{quat}), 147.2 (CH), 177.2 (C_{quat}), 184.6 (C_{quat}). EI + MS (*m/z* (%)): 296 ($M(^{37}Cl)^+$, 1), 294 ($M(^{35}Cl)^+$, 4), 265 (($M(^{35}Cl)$-CO-H)$^+$, 5), 259 ((M-Cl)$^+$, 7), 167 (($M(^{37}Cl)$-C_9H_5O+2H)$^+$, 33), 166 (9), 165 (($M(^{35}Cl)$-C_9H_5O+2H)$^+$, 100), 139 ($C_8H_6{}^{37}Cl^+$, 6), 137 ($C_8H_6{}^{35}Cl^+$, 19), 129 ($C_9H_5O^+$, 77), 102 ($C_8H_6{}^+$, 17), 101 (18), 75 (13), 43 (24), 40 (10). IR (ATR): $\tilde{\nu}$ 2195 (m) cm^{-1}, 1682 (w), 1649 (w), 1630 (m), 1614 (m), 1595 (m), 1568 (m), 1489 (m), 1443 (w), 1368 (w), 1290 (m), 1209 (w), 1175 (m), 1146 (w), 1119 (w), 1026 (w), 1011 (m), 995 (w), 988 (w), 957 (m), 785 (m), 750 (s), 685 (s), 658 (w). Anal. calcd. for $C_{18}H_{11}ClO_2$ (294.7): C 73.35, H 3.76. Found: C 73.36, H 3.81.

4 Preparation of heterocyclic ynones 5

4.1 General procedure



4 2 5

2.00 mmol of carboxylic acid **4** in dry 1,4-dioxane (10 mL) were placed under argon atmosphere in a dry screw-cap Schlenk vessel with septum and degassed with argon. Then, oxalyl chloride (0.18 mL, 2.00 mmol, 1.00 equiv.) was added dropwise to the reaction mixture at room temperature (water bath). The mixture was stirred for 4 h at 50 °C in a preheated oil bath and was allowed to come to room temperature. $PdCl_2(PPh_3)_2$ (28 mg, 0.04 mmol, 2 mol %), CuI (15 mg, 0.08 mmol, 4 mol %), alkyne **2** (2.00 mmol, 1.00 equiv.), and dry triethylamine (0.84 mL, 6.00 mmol, 3.00 equivs.) were successively added to the mixture and stirring at room temperature was continued for 1 h. After complete conversion (product monitored by TLC) water (10 mL) was added and the mixture was extracted with dichloromethane (4 x 10 mL, monitored by TLC). The combined organic layers were dried with anhydrous sodium sulfate and the desiccant was removed by filtration. After removal of the solvents in vacuum the residue was adsorbed on Celite® and purified chromatographically (Biotage SP-1 apparatus, 100 g SNAP cartridge) on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl acetate to give ynones **5**.

The experimental details for the synthesis of ynones **5** are given in Table 3.

Table 3. Experimental details for the synthesis of ynones 5.

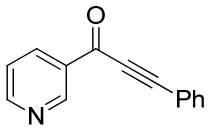
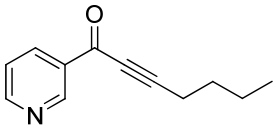
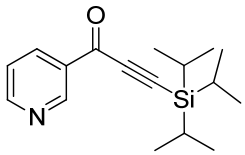
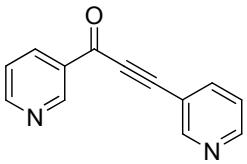
Entry	Carboxylic acid **4** (2.00 mmol)	Alkyne **2** (2.00 mmol)	Ynone **5** (isolated yield)	Chromatographic purification R_f (eluent)
1	3-Pyridyl carboxylic acid sodium salt (*ABCR*) **4a**[a] 296 mg	Phenylacetylene (*Merck*) **2a** 0.23 mL	 **5a** 377 mg (1.82 mmol) 91 %	PE/EtOAc = 3:1 R_f (PE/EtOAc = 3:1) = 0.25
2	**4a**[a] 296 mg	1-Hexyne (*Acros Organics*) **2c** 0.24 mL	 **5b** 299 mg (1.60 mmol) 80 %	PE/EtOAc = 5:1 R_f (PE/EtOAc = 5:1) = 0.33
3	**4a**[a] 296 mg	Ethynyltriiso-propylsilane (*Fluka*) **2b** 0.45 mL	 **5c** 558 mg (1.94 mmol) 97 %	PE/EtOAc = 15:1 R_f (PE/EtOAc = 15:1) = 0.24
4	**4a**[a] 296 mg	3-Ethynylpyridine (*Sigma Aldrich*) **2d** 210 mg	 **5d** 238 mg (1.14 mmol) 57 %	PE/EtOAc = 1:1 R_f (PE/EtOAc = 1:1) = 0.06

Table 3 (Continuation).

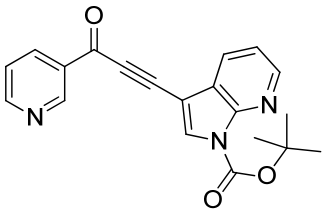
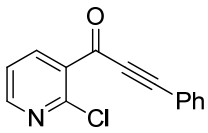
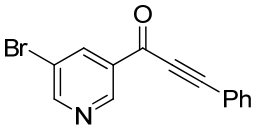
Entry	Carboxylic acid **4** (2.00 mmol)	Alkyne **2** (2.00 mmol)	Ynone **5** (isolated yield)	Chromatographic purification R_f (eluent)
5	**4a**[a] 296 mg	*tert*-Butyl 3-ethynylpyrrolo[2,3-*b*]pyridine-1-carboxylate[b] **2e** 485 mg	 **5e** 491 mg (1.41 mmol) 71 %	PE/EtOAc= 1:1 R_f (PE/EtOAc = 1:1) = 0.06
6	2-Chloro-nicotinic acid[c] **4b** 315 mg	**2a** 0.23 mL	 **5f** 297 mg (1.23 mmol) 62 %	PE/EtOAc= 7:1 R_f (PE/EtOAc = 7:1) = 0.16
7	5-Bromo-nicotinic acid[c] **4c** 404 mg	**2a** 0.23 mL	 **5g** 349 mg (1.22 mmol) 61 %	PE/EtOAc = 20:1 R_f (PE/EtOAc = 20:1) = 0.16

Table 3 (Continuation).

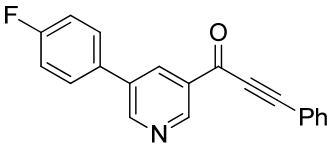
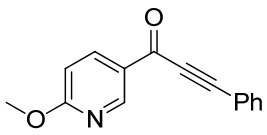
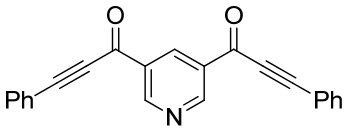
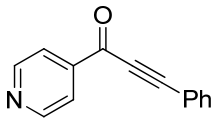
Entry	Carboxylic acid **4** (2.00 mmol)	Alkyne **2** (2.00 mmol)	Ynone **5** (isolated yield)	Chromatographic purification R_f (eluent)
8	5-(4-Fluoro-phenyl)-nicotinic acid[c] **4d** 434 mg	**2a** 0.23 mL	 **5h** 495 mg (1.64 mmol) 82 %	PE/EtOAc = 4:1 R_f (PE/EtOAc = 4:1) = 0.25
9	6-Methoxy-nicotinic acid (*Matrix Scientific*) **4e** 313 mg	**2a** 0.23 mL	 **5i** 197 mg (0.83 mmol) 41 %	PE/EtOAc = 25:1 R_f (PE/EtOAc = 25:1) = 0.13
10	Dinicotinic acid (*Alfa Aesar*) **4f** 341 mg	**2a** 0.23 mL	 **5j** 449 mg (1.34 mmol) 67 %[d]	PE/EtOAc = 6:1 R_f (PE/EtOAc = 6:1) = 0.30
11	Isonicotinic acid (*Sigma Aldrich*) **4g** 249 mg	**2a** 0.23 mL	 **5k** 143 mg (0.69 mmol) 35 %	PE/EtOAc = 2:1 R_f (PE/EtOAc = 2:1) = 0.35

Table 3 (Continuation).

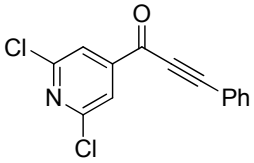
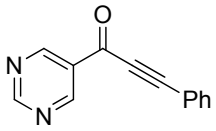
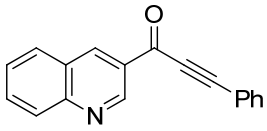
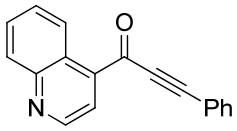
Entry	Carboxylic acid **4** (2.00 mmol)	Alkyne **2** (2.00 mmol)	Ynone **5** (isolated yield)	Chromatographic purification R_f (eluent)
12	2,6-Dichloro-isonicotinic acid (*ABCR*) **4h** 396 mg	**2a** 0.23 mL	 **5l** 379 mg (1.37 mmol) 69 %	PE/EtOAc = 50:1 R_f (PE/EtOAc = 50:1) = 0.19
13	Pyrimidine-5-carboxylic acid[c] **4i** 248 mg	**2a** 0.23 mL	 **5m** 242 mg (1.16 mmol) 58 %	PE/EtOAc = 4:1 R_f (PE/EtOAc = 4:1) = 0.20
14	Quinoline-3-carboxylic acid (*Alfa Aesar*) **4j** 353 mg	**2a** 0.23 mL	 **5n** 425 mg (1.65 mmol) 83 %	PE/EtOAc = 6:1 R_f (PE/EtOAc = 6:1) = 0.24
15	Quinoline-4-carboxylic acid (*Maybridge*) **4k** 357 mg	**2a** 0.23 mL	 **5o** 505 mg (1.98 mmol) 98 %	PE/EtOAc = 6:1 R_f (PE/EtOAc = 6:1) = 0.22

Table 3 (Continuation).

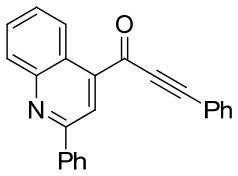
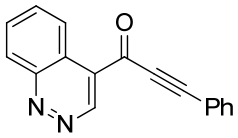
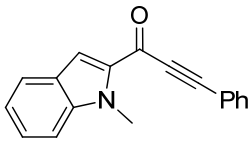
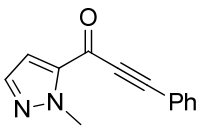
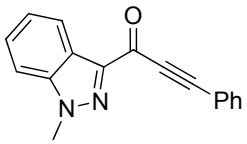
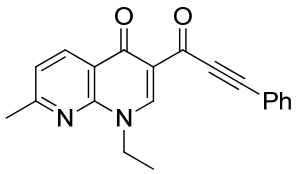
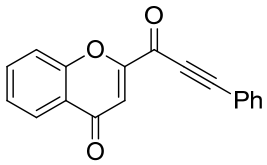
Entry	Carboxylic acid **4** (2.00 mmol)	Alkyne **2** (2.00 mmol)	Ynone **5** (isolated yield)	Chromatographic purification R_f (eluent)
16	2-Phenyl-quinoline-4-carboxylic acid[c] **4l** 499 mg	**2a** 0.23 mL	 **5p** 584 mg (1.75 mmol) 88 %	PE/EtOAc = 25:1 R_f (PE/EtOAc = 25:1) = 0.20
17	Cinnoline-4-carboxylic acid (*Sigma Aldrich*) **4m** 359 mg	**2a** 0.23 mL	 **5q** 134 mg (0.52 mmol) 26 %	PE/EtOAc = 4:1 R_f (PE/EtOAc = 4:1) = 0.21
18	1-Methylindole-2-carboxylic acid (*Acros Organics*) **4n** 350 mg	**2a** 0.23 mL	 **5r** 190 mg (0.73 mmol) 37 %	PE/EtOAc = 30:1 R_f (PE/EtOAc = 30:1) = 0.19
19	2-Methyl-pyrazole-3-carboxylic acid (*ABCR*) **4o** 363 mg	**2a** 0.23 mL	 **5s** 168 mg (0.80 mmol) 40 %	PE/EtOAc = 20:1 R_f (PE/EtOAc = 20:1) = 0.09

Table 3 (Continuation).

Entry	Carboxylic acid **4** (2.00 mmol)	Alkyne **2** (2.00 mmol)	Ynone **5** (isolated yield)	Chromatographic purification R_f (eluent)
20	1-Methyl-indazole-3-carboxylic acid (*Alfa Aesar*) **4p** 363 mg	**2a** 0.23 mL	 **5t** 325 mg (1.25 mmol) 62 %	PE/EtOAc = 5:1 R_f (PE/EtOAc = 5:1) = 0.18
21	Nalidixic acid (*Sigma Aldrich*) **4q** 464 mg	**2a** 0.23 mL	 **5u** 117 mg (0.37 mmol) 18 %	PE/EtOAc = 3:1 R_f (PE/EtOAc = 3:1) = 0.07
22	4-Oxo-chromene-2-carboxylic acid (*Acros Organics*) **4r** 392 mg	**2a** 0.23 mL	 **5v** 470 mg (1.06 mmol) 53%	PE/EtOAc = 6:1 R_f (PE/EtOAc = 6:1) = 0.22

[a] 2.00 equivs. of triethylamine in the 2nd reaction step

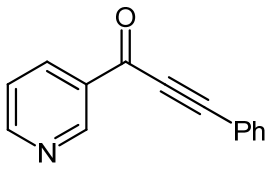
[b] The alkyne **2e** was prepared by Sonogashira coupling of *tert*-butyl 3-iodopyrrolo[2,3-*b*]pyridine-1-carboxylate with trimethylsilylacetylene. The trimethylsilyl group was removed by adding tetra-*n*-butylammonium fluoride solution (1 M in THF, *Aldrich*).

[c] The carboxylic acid was prepared in the laboratories of *Merck Serono KGaA*, Darmstadt.

[d] Differing from the general procedure 0.36 mL (4.00 mmol, 2.00 equivs.) of $(COCl)_2$, 56 mg $PdCl_2(PPh_3)_2$ (0.08 mmol, 4 mol %), 30 mg CuI (0.16 mmol, 8 mol %), 0.46 mL (4.00 mmol, 2.00 equivs.) of phenylacetylene **2a**, and 1.65 mL (12.0 mmol, 6.00 equivs.) of triethylamine were used.

4.2 Spectroscopic data of compounds 5a-u

4.2.1 3-Phenyl-1-(pyridin-3-yl)prop-2-yn-1-one (5a)



$C_{14}H_9NO$

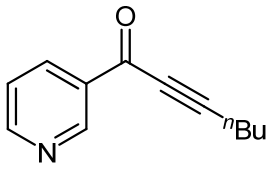
207.23

377 mg (1.82 mmol, 91 % yield) as a pale brown solid. Mp 73 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.40-7.60 (m, 4 H), 7.65-7.74 (m, 2 H), 8.34-8.48 (m, 1 H), 8.80-8.88 (m, 1 H), 9.40-9.47 (m, 1 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 86.6 (C_{quat}), 95.1 (C_{quat}), 119.9 (C_{quat}), 123.9 (CH), 129.1 (CH), 131.6 (CH), 132.5 (C_{quat}), 133.6 (CH), 136.6 (CH), 151.7 (CH), 154.5 (CH), 176.7 (C_{quat}). EI + MS (*m/z* (%)): 208 ($(M+H)^+$, 7), 207 (M^+, 46), 206 (12), 179 ($(M-CO)^+$, 29), 178 ($(M-CO-H)^+$, 14), 130 (10), 129 ($C_9H_5O^+$, 100), 101 ($C_8H_5^+$, 8), 75 (12). IR (KBr): $\tilde{\nu}$ 3063 (w) cm^{-1}, (w), 2200 (s), 1650 (s), 1584 (s), 1488 (m), 1443 (m), 1421 (s), 1328 (s), 1304 (s), 1215 (s), 1193 (m), 1156 (w), 1115 (m), 1080 (w), 1044 (s), 1030 (m), 1014 (m), 995 (s), 918 (w), 838 (w), 820 (w), 756 (s), 719 (s), 694 (m), 684 (s), 636 (m), 616 (m), 533 (m). Anal. calcd. for $C_{14}H_9NO$ (207.2): C 81.14, H 4.38, N 6.76. Found: C 80.94, H 4.53, N 6.59.

Data reported in the literature: J. P. Waldo, R. C. Larock, *J. Org. Chem.* **2007**, *72*, 9643-9647.

Mp 73-75 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.42-7.54 (m, 4 H), 7.69-7.71 (dd, *J* = 8.2, 1.4 Hz, 2 H), 8.42-8.45 (m, 1 H), 8.84-8.86 (dd, *J* = 4.8, 1.6 Hz, 1 H), 9.45 (t, *J* = 0.8, 1 H). ^{13}C-NMR δ 86.4, 94.8, 119.6, 123.7, 128.9, 131.4, 132.3, 133.4, 136.3, 151.5, 154.3, 176.5. HRMS Calcd. for $C_{14}H_9NO$: 207.0684; Found: 207.0689.

4.2.2 1-(Pyridin-3-yl)hept-2-yn-1-one (5b)

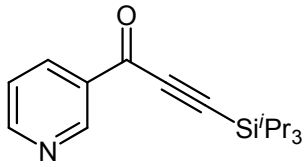


$C_{12}H_{13}NO$

187.24

274 mg (1.46 mmol, 73 % yield) as an orange oil. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 0.93 (t, *J* = 7.3 Hz, 3 H), 1.47 (sext, *J* = 7.6 Hz, 2 H), 1.64 (quin, *J* = 7.3 Hz, 2 H), 2.50 (t, *J* = 7.3 Hz, 2 H), 7.40 (ddd, *J* = 8.2 Hz, *J* = 5.0 Hz, *J* = 0.5 Hz, 1 H), 8.31 (dt, *J* = 7.9 Hz, *J* = 1.9 Hz, 1 H), 8.77 (dd, *J* = 4.7 Hz, *J* = 1.6 Hz, 1 H), 9.30 (d, *J* = 1.6 Hz, 1 H). ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 13.8 (CH_3), 19.2 (CH_2), 22.4 (CH_2), 30.0 (CH_2), 79.5 (C_{quat}), 99.0 (C_{quat}), 123.7 (CH), 132.5 (C_{quat}), 136.5 (CH), 151.8 (CH), 154.3 (CH), 176.9 (C_{quat}). EI + MS (*m/z* (%)): 187 (M^+, 5), 186 (20), 172 ($(M-CH_3)^+$, 10), 159 ($(M-CO)^+$, 23), 158 ($(M-CO-H)^+$, 49), 146 (29), 145 ($(M-CO-CH_3+H)^+$, 100), 144 ($(M-CO-CH_3)^+$, 14), 131 (14), 130 ($(M-CO-C_2H_5)^+$, 22), 117 (18), 116 ($(M-CO-C_3H_7)^+$, 9), 109 ($(M-C_5H_4N)^+$, 42), 106 (62), 90 (10), 89 (11), 79 ($C_5H_5N^+$, 50), 78 ($C_5H_4N^+$, 40), 77 (11), 53 (16), 51 (19), 43 (10), 41 (13). IR (ATR): $\tilde{\nu}$ 2959 (w) cm^{-1}, 2934 (w), 2872 (w), 2251 (w), 2203 (m), 1645 (s), 1584 (s), 1572 (w), 1464 (w), 1416 (m), 1327 (w), 1267 (s), 1234 (w), 1194 (w), 1125 (w), 1084 (w), 1024 (w), 984 (w), 961 (w), 910 (m), 845 (w), 826 (w), 721 (s), 698 (m), 625 (w). Anal. calcd. for $C_{12}H_{13}NO$ (187.2): C 76.98, H 7.00, N 7.48. Found: C 77.15, H 7.18, N 7.18.

4.2.3 1-(Pyridin-3-yl)-3-[tris(propan-2-yl)silyl]prop-2-yn-1-one (5c)

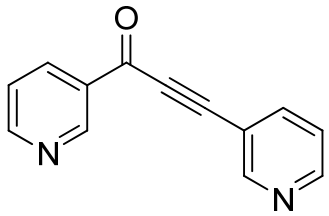


$C_{17}H_{25}NOSi$

287.47

558 mg (1.94 mmol, 97 % yield) as a colorless oil. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.11-1.22 (m, 21 H), 7.36-7.50 (m, 1 H), 8.36 (dt, *J* = 8.0 Hz, *J* = 2.0 Hz, 1 H), 8.80 (dd, *J* = 4.8 Hz, *J* = 1.7 Hz, 1 H), 9.32-9.44 (m, 1 H). ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 11.4 (CH), 18.9 (CH_3), 100.5 (C_{quat}), 102.5 (C_{quat}), 123.8 (CH), 132.4 (C_{quat}), 136.5 (CH), 151.7 (CH), 154.4 (CH), 176.2 (C_{quat}). EI + MS (*m/z* (%)): 287 (M^+, 2), 245 (21), 244 ((M-C_3H_7)$^+$, 100), 217 (9), 216 ((M-CO-C_3H_7)$^+$, 45), 202 ((M-C_6H_{13})$^+$, 17), 189 (13), 188 (77), 173 ((M-CO-C_6H_{13})$^+$, 23), 160 ((M-C_9H_{19})$^+$, 13), 158 (11), 156 (11), 142 (10), 130 (M-Si(C_3H_7)$_3$)$^+$, 9), 106 (24), 78 ($C_5H_4N^+$, 21), 75 (11). IR (ATR): $\tilde{\nu}$ 2943 (w) cm^{-1}, 2866 (w), 2149 (w), 1647 (s), 1584 (m), 1460 (w), 1418 (m), 1248 (s), 1192 (w), 1107 (w), 1076 (w), 1051 (s), 1009 (s), 920 (w), 881 (m), 824 (w), 785 (m), 715 (s), 677 (s), 660 (s), 602 (s). Anal. calcd. for $C_{17}H_{25}NOSi$ (287.5): C 71.03, H 8.77, N 4.87. Found: C 70.94, H 8.53, N 4.73.

4.2.4 Bis(pyridin-3-yl)prop-2-yn-1-one (5d)

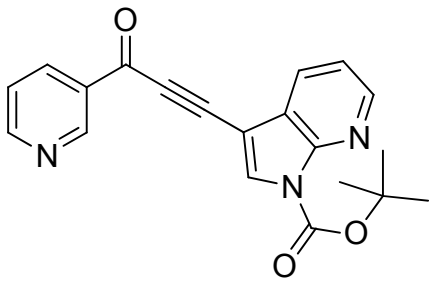


$C_{13}H_8N_2O$

208.22

238 mg (1.14 mmol, 57 % yield) as a pale brown solid. Mp 131 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.35-7.42 (m, 1 H), 7.44-7.50 (m, 1 H), 7.96 (dt, *J* = 7.9 Hz, *J* = 1.9 Hz, 1 H), 8.40 (dt, *J* = 8.0 Hz, *J* = 2.0 Hz, 1 H), 8.70 (dd, *J* = 4.9 Hz, *J* = 1.7 Hz, 1 H), 8.84 (dd, *J* = 4.8 Hz, *J* = 1.7 Hz, 1 H), 8.87-8.93 (m, 1 H), 9.34-9.45 (m, 1 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 89.0 (C_{quat}), 90.8 (C_{quat}), 117.3 (C_{quat}), 123.7 (CH), 124.0 (CH), 132.2 (C_{quat}), 136.6 (CH), 140.4 (CH), 151.5 (CH), 151.8 (CH), 153.8 (CH), 154.9 (CH), 176.3 (C_{quat}). EI + MS (*m/z* (%)): 208 (M^+, 65), 207 (19), 180 ($(M\text{-}CO)^+$, 33), 179 (22), 131 (9), 130 ($(M\text{-}C_5H_4N)^+$, 100), 102 (17), 77 (14), 75 (13), 74 (10), 51 (11). IR (ATR): $\tilde{\nu}$ 2203 (m) cm^{-1}, 1641 (s), 1582 (s), 1479 (m), 1422 (w), 1410 (m), 1329 (m), 1302 (s), 1323 (m), 1192 (m), 1121 (m), 1080 (w), 1047 (w), 1026 (m), 1007 (s), 826 (w), 802 (m), 719 (s), 694 (s), 642 (m). Anal. calcd. for $C_{13}H_8N_2O$ (208.2): C 74.99, H 3.87, N 13.45. Found: C 74.97, H 4.12, N 13.27.

4.2.5 *tert*-Butyl 3-[3-oxo-3-(pyridin-3-yl)prop-1-yn-1-yl]-1*H*-pyrrolo[2,3-*b*]-pyridine-1-carboxylate (5e)

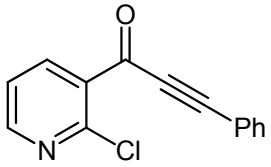


$C_{20}H_{17}N_3O_3$

347.37

491 mg (1.41 mmol, 71 % yield) as a pale brown solid. Mp 148 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.69 (s, 9 H), 7.35 (dd, *J* = 7.8 Hz, *J* = 4.8 Hz, 1 H), 7.49 (dd, *J* = 7.9 Hz, *J* = 4.8 Hz, 1 H), 8.13 (dd, *J* = 7.8 Hz, *J* = 1.5 Hz, 1 H), 8.19 (s, 1 H), 8.43 (dt, *J* = 8.0 Hz, *J* = 1.9 Hz, 1 H), 8.61 (dd, *J* = 4.8 Hz, *J* = 1.6 Hz, 1 H), 8.85 (dd, *J* = 4.8 Hz, *J* = 1.6 Hz, 1 H), 9.39-9.58 (m, 1 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 28.4 (CH_3), 86.2 (C_{quat}), 87.7 (C_{quat}), 91.1 (C_{quat}), 97.9 (C_{quat}), 120.1 (CH), 122.9 (C_{quat}), 124.0 (CH), 129.1 (CH), 132.5 (CH), 134.6 (CH), 136.4 (C_{quat}), 147.0 (C_{quat}), 147.3 (CH), 147.9 (C_{quat}), 151.8 (CH), 154.6 (CH), 176.2 (C_{quat}). EI + MS (*m/z* (%)): 347 (M^+, 2), 248 (17), 247 ((M-$C_5H_9O_2$+H)$^+$, 100), 246 ((M-$C_5H_9O_2$)$^+$, 67), 219 ((M-$C_5H_9O_2$-CO)$^+$, 52), 218 (19), 19 (12), 191 (10), 170 (11), 169 ((M-$C_5H_9O_2$-C_5H_4N)$^+$, 99), 164 (13), 141 (44), 114 (30), 110 (11), 88 (10), 87 (15), 78 ($C_5H_4N^+$, 12), 57 ($C_4H_9^+$, 66), 56 (15), 51 (10), 44 (14), 41 (26), 39 (12). IR (ATR): $\tilde{\nu}$ 2195 (m) cm^{-1}, 1765 (s), 1634 (s), 1584 (w), 1541 (m), 1477 (w), 1412 (m), 1365 (m), 1333 (m), 1296 (s), 1246 (s), 1233 (m), 1182 (m), 1148 (s), 1140 (s), 1096 (m), 1057 (m), 1034 (m), 980 (m), 854 (w), 775 (s), 748 (w), 719 (s), 696 (m), 646 (s), 629 (m), 617 (m). Anal. calcd. for $C_{20}H_{17}N_3O_3$ (347.4): C 69.15, H 4.93, N 12.10. Found: C 69.01, H 5.14, N 12.14.

4.2.6 1-(2-Chloropyridin-3-yl)-3-phenylprop-2-yn-1-one (5f)



$C_{14}H_8ClNO$

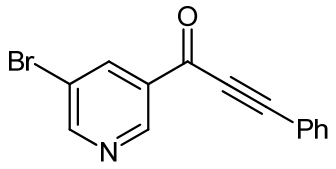
241.67

297 mg (1.23 mmol, 62 % yield) as a pale brown solid. Mp 72 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.37-7.46 (m, 3 H), 7.47-7.55 (m, 1 H), 7.61-7.70 (m, 2 H), 8.34 (dd, *J* = 7.1 Hz, *J* = 2.0 Hz, 1 H), 8.56 (dd, *J* = 4.8 Hz, *J* = 2.0 Hz, 1 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 88.3 (C_{quat}), 96.1 (C_{quat}), 120.0 (C_{quat}), 122.8 (CH), 129.2 (CH), 131.7 (CH), 133.0 (C_{quat}), 133.6 (CH), 141.1 (CH), 149.9 (C_{quat}), 152.7 (CH), 175.9 (C_{quat}). EI + MS (*m/z* (%)): 243 (($M(^{37}Cl)$)$^+$, 7), 241 (($M(^{35}Cl)$)$^+$, 21), 215 (($M(^{37}Cl)$-CO)$^+$, 6), 213 (($M(^{35}Cl)$-CO)$^+$, 17), 178 ((M-CO-Cl)$^+$, 6), 130 (10), 129 ($C_9H_5O^+$, 100), 75 (11). IR (ATR): ṽ 2195 (m) cm^{-1}, 1634 (s), 1572 (m), 1489 (w), 1443 (w), 1400 (m), 1312 (m), 1260 (w), 1088 (s), 1065 (m), 1028 (w), 1015 (m), 995 (m), 822 (m), 750 (s), 710 (m), 681 (s), 658 (m), 627 (m), 619 (m). Anal. calcd. for $C_{14}H_8ClNO$ (241.7): C 69.58, H 3.34, N 5.80. Found: C 69.33, H 3.55, N 5.54.

Data reported in the literature: F. C. Fuchs, G. A. Eller, W. Holzer, *Molecules* **2009**, *14*, 3815-3832.

Yellowish-brown crystals, mp 69–71 °C (MeOH); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.56 (dd, ^{3}J(H5,H6) = 4.7 Hz, ^{4}J = 1.9 Hz, 1H, H-6), 8.34 (dd, ^{3}J = 7.7 Hz, ^{4}J = 1.9 Hz, 1H, H-4), 7.65 (m, 2H, Ph H-2,6), 7.51 (m, 1H, Ph H-4), 7.42 (m, 3H, H-5, Ph H-3,5); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 175.5 (C=O, ^{3}J(CO,H4) = 5.3 Hz), 152.3 (C-6, ^{1}J(C6,H6) = 183.7 Hz, ^{2}J(C6,H5) = 3.8 Hz, ^{3}J(C6,H4) = 8.2 Hz), 149.5 (C-2, ^{3}J(C2,H4) = 8.8 Hz, ^{3}J(C2,H6) = 13.8 Hz, ^{4}J(C2,H5) = 1.5Hz), 140.7 (C-4, ^{1}J(C4,H4) = 166.2 Hz, ^{2}J(C4,H5) = 1.9 Hz, ^{3}J(C4,H6) = 6.7 Hz), 132.6 (C-3), 133.2 (Ph C-2,6), 131.3 (Ph C-4), 128.8 (Ph C-3,5), 122.4 (C-5, ^{1}J(C5,H5) = 168.2 Hz, ^{2}J(C5,H6) = 8.2 Hz), 119.5 (Ph C-1, ^{3}J(Ph C1,Ph H3,5) = 8.6 Hz, ^{4}J(Ph C1,Ph H4) = 1.4 Hz), 95.7 (COC≡C, ^{3}J(C,Ph H2,6) = 5.3 Hz), 87.9 (COC≡C); ^{15}N-NMR (50 MHz): δ −70.3 (N-1); IR: 2199 (C≡C), 1636 (C=O) cm^{-1}; MS *m/z* (%): 243/241 (M^+, 6/15), 215/213 ($[M - C{=}O]^+$, 6/21), 129 ($[COC{\equiv}CC_6H_5]^+$, 100), 101 ($[C{\equiv}CC_6H_5]^+$, 13). Calcd. for $C_{14}H_8ClNO$: C, 69.58; H, 3.34; N, 5.80. Found: C, 69.59; H, 3.16; N, 5.67.

4.2.7 1-(5-Bromopyridin-3-yl)-3-phenylprop-2-yn-1-one (5g)

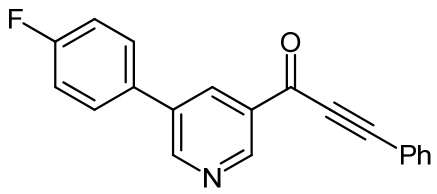


$C_{14}H_8BrNO$

286.12

349 mg (1.22 mmol, 61 % yield) as a pale brown solid. Mp 127 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.31-7.58 (m, 3 H), 7.59-7.86 (m, 2 H), 8.53 (t, *J* = 2.1 Hz, 1 H), 8.89 (d, *J* = 2.3 Hz, 1 H), 9.33 (d, *J* = 1.8 Hz, 1 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 86.4 (C_{quat}), 96.0 (C_{quat}), 119.6 (C_{quat}), 121.5 (C_{quat}), 129.2 (CH), 131.9 (CH), 133.7 (CH), 138.9 (CH), 149.6 (CH), 155.6 (CH), 175.3 (C_{quat}). EI + MS (*m/z* (%)): 287 ($M(^{81}Br)^+$, 40), 286 (11), 285 ($M(^{79}Br)^+$, 40), 259 ($(M(^{81}Br)-CO)^+$, 16), 257 ($(M(^{79}Br)-CO)^+$, 15), 206 ($(M-Br)^+$, 3), 130 (10), 129 ($C_9H_5O^+$, 100), 101 ($C_8H_5^+$, 6), 77 ($C_6H_5^+$, 3), 75 (11). IR (ATR): $\tilde{\nu}$ 2201 (m) cm^{-1}, 1628 (m), 1570 (w), 1489 (w), 1416 (m), 1290 (m), 1213 (m), 1153 (m), 1140 (w), 1092 (w), 1040 (m), 1013 (m), 964 (w), 928 (w), 905 (w), 839 (m), 764 (s), 739 (s), 685 (s), 660 (m), 619 (m). Anal. calcd. for $C_{14}H_8BrNO$ (286.1): C 58.77, H 2.82, N 4.90. Found: C 58.99, H 2.95, N 4.69.

4.2.8 1-[5-(4-Fluorophenyl)pyridin-3-yl]-3-phenylprop-2-yn-1-one (5h)

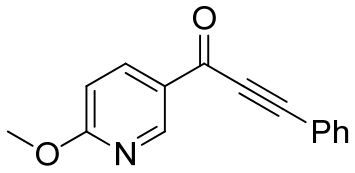


$C_{20}H_{12}FNO$

301.31

495 mg (1.64 mmol, 82 % yield) as a bright yellow solid. Mp 136 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.21-7.34 (m, 2 H), 7.45-7.61 (m, 3 H), 7.62-7.71 (m, 2 H), 7.72-7.84 (m, 2 H), 8.59 (t, *J* = 2.1 Hz, 1 H), 9.03-9.12 (m, 1 H), 9.42-9.50 (m, 1 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 86.8 (C_{quat}), 95.4 (C_{quat}), 116.8 (d, *J* = 21.8 Hz, CH), 119.8 (C_{quat}), 129.2 (CH), 129.4 (d, *J* = 8.3 Hz, CH), 131.7 (CH), 132.6 (C_{quat}), 133.0 (d, *J* = 3.3 Hz, C_{quat}), 133.7 (CH), 134.2 (CH), 136.2 (C_{quat}), 150.5 (CH), 152.8 (CH), 163.7 (d, *J* = 249.1 Hz, C_{quat}), 176.6 (C_{quat}). EI + MS (*m/z* (%)): 302 (11), 301 (M^+, 52), 300 (6), 273 ($(M-CO)^+$, 26), 272 (10), 130 (10), 129 ($C_9H_5O^+$, 100), 75 (8). IR (ATR): ṽ 2197 (m) cm^{-1}, 1638 (m), 1605 (w), 1585 (w), 1566 (w), 1512 (m), 1489 (w), 1445 (m), 1431 (m), 1329 (w), 1308 (m), 1271 (m), 1225 (m), 1198 (m), 1155 (m), 1099 (w), 1072 (m), 1018 (m), 995 (m), 860 (w), 833 (s), 812 (m), 758 (s), 745 (s), 702 (m), 685 (s), 673 (m), 617 (m). Anal. calcd. for $C_{20}H_{12}FNO$ (301.3): C 79.72, H 4.01, N 4.65. Found: C 79.51, H 3.92, N 4.59.

4.2.9 1-(6-Methoxypyridin-3-yl)-3-phenylprop-2-yn-1-one (5i)

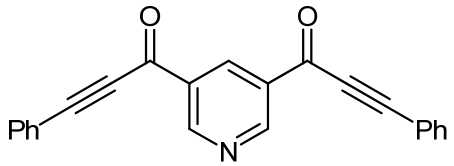


$C_{15}H_{11}NO_2$

237.25

197 mg (0.83 mmol, 41 % yield) as a colorless solid. Mp 86 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 4.04 (s, 3 H), 6.83 (d, *J* = 8.7 Hz, 1 H), 7.36-7.54 (m, 3 H), 7.63-7.72 (m, 2 H), 8.29 (dd, *J* = 8.7 Hz, *J* = 2.4 Hz, 1 H), 9.09 (d, *J* = 2.3 Hz, 1 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 54.6 (CH_3), 86.7 (C_{quat}), 93.6 (C_{quat}), 111.7 (CH), 120.3 (C_{quat}), 127.5 (C_{quat}), 129.1 (CH), 131.3 (CH), 133.5 (CH), 138.8 (CH), 152.1 (CH), 167.8 (C_{quat}), 175.8 (C_{quat}). EI + MS (*m/z* (%)): 238 (16), 237 (M^+, 100), 236 (76), 209 (10), 208 ($(M\text{-}CO)^+$, 39), 207 (14), 180 (23), 178 ($(M\text{-}C_5H_4N\text{+}H)^+$, 10), 139 (14), 130 (7), 129 ($C_9H_5O^+$, 68), 75 (13). IR (ATR): ṽ 2195 (s) cm^{-1}, 1632 (s), 1597 (s), 1560 (m), 1495 (m), 1375 (s), 1300 (m), 1285 (s), 1213 (m), 1117 (m), 1032 (m), 1022 (m), 1007 (s), 993 (m), 939 (w), 912 (w), 833 (s), 787 (w), 772 (s), 750 (s), 706 (m), 679 (s), 625 (m), 615 (s). Anal. calcd. for $C_{15}H_{11}NO_2$ (237.3): C 75.94, H 4.67, N 5.90. Found: C 76.00, H 4.83, N 5.81.

4.2.10 3-Phenyl-1-[5-(3-phenylprop-2-ynoyl)pyridin-3-yl]prop-2-yn-1-one (5j)

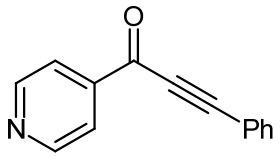


$C_{23}H_{13}NO_2$

335.35

449 mg (1.34 mmol, 67 % yield) as a yellow solid. Mp 153 °C. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.35 (tt, *J* = 7.5 Hz, *J* = 1.1 Hz, 2 H), 7.39-7.44 (m, 4 H), 7.68-7.72 (m, 4 H), 9.16 (t, *J* = 2.1 Hz, 1 H), 9.60 (d, *J* = 2.1 Hz, 2 H). ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 86.5 (C_{quat}), 96.2 (C_{quat}), 119.6 (C_{quat}), 129.2 (CH), 131.9 (CH), 132.4 (C_{quat}), 133.7 (CH), 137.4 (CH), 155.0 (CH), 175.6 (C_{quat}). EI + MS (*m/z* (%)): 336 (8), 335 (M^+, 29), 334 (3), 307 ($(M\text{-}CO)^+$, 4), 280 ($(M\text{-}C_2O_2\text{+}H)^+$, 1), 279 ($(M\text{-}C_2O_2)^+$, 6), 130 (9), 129 ($C_9H_5O^+$, 100). IR (ATR): $\tilde{\nu}$ 3028 (w) cm^{-1}, 2922 (w), 2851 (w), 2199 (m), 2174 (w), 1732 (w), 1636 (s), 1582 (m), 1441 (w), 1423 (w), 1279 (m), 1240 (w), 1165 (m), 1067 (m), 1018 (w), 918 (w), 872 (w), 791 (w), 752 (s), 729 (s), 700 (s), 632 (m), 617 (m). Anal. calcd. for $C_{23}H_{13}NO_2$ (335.4): C 82.37, H 3.91, N 4.18. Found: C 82.61, H 4.18, N 4.08.

4.2.11 3-Phenyl-1-(pyridin-4-yl)prop-2-yn-1-one (5k)



$C_{14}H_9NO$

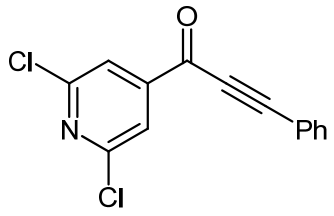
207.23

143 mg (0.69 mmol, 35 % yield) as a pale brown solid. Mp 81 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.40-7.56 (m, 3 H), 7.66-7.74 (m, 2 H), 7.95-8.02 (m, 2 H), 8.84-8.90 (m, 2 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 86.7 (C_{quat}), 95.4 (C_{quat}), 119.7 (C_{quat}), 122.3 (CH), 129.2 (CH), 131.7 (CH), 133.6 (CH), 142.8 (C_{quat}), 151.2 (CH), 177.2 (C_{quat}). EI + MS (*m/z* (%)): 207 (M^+, 27), 179 ($(M-CO)^+$, 10), 130 (10), 129 ($C_9H_5O^+$, 100), 101 ($C_8H_5^+$, 6), 75 (8). IR (KBr): $\tilde{\nu}$ 2197 (s) cm^{-1}, 1645 (s), 1555 (m), 1491 (w), 1449 (w), 1404 (m), 1324 (m), 1290 (m), 1218 (m), 1200 (m), 1058 (w), 1035 (m), 995 (m), 839 (m), 760 (s), 745 (m), 686 (s), 627 (m), 535 (m). Anal. calcd. for $C_{14}H_9NO$ (207.2): C 81.14, H 4.38, N 6.76. Found: C 80.92, H 4.58, N 6.87.

Data reported in the literature: R. Erenler, M. Uno, T. V. Goud, J.-F. Biellmann, *J. Chem. Res.* **2009**, *7*, 459-464.

UV (CH_2Cl_2): λ_{max} (ε) 233 (9300), 301 (7200). IR (CH_2Cl_2): 1264, 1421, 1551, 1604, 1650, 1961 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (m, 2H), 7.48 (m, 1H), 7.66 (m, 2H), 7.96 (d, *J* = 5.8 Hz, 2H), 8.83 (d, *J* = 5.8 Hz, 2H), ^{13}C NMR (100 MHz, $CDCl_3$): δ 86.2, 95.2, 119.3, 122.1, 128.8, 131.4, 133.3, 142.5, 150.6, 176.7. MS (FAB^+): *m/z* 208 $[M + H]^+$. Anal. Calcd for $C_{14}H_9NO$ (207.2): C, 81.14; H, 4.38; N, 6.76. Found: C, 81.02; H, 4.42; N, 6.69%.

4.2.12 1-(2,6-Dichloropyridin-4-yl)-3-phenylprop-2-yn-1-one (5l)

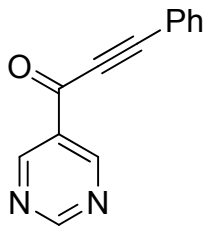


$C_{14}H_7Cl_2NO$

276.12

379 mg (1.37 mmol, 69 % yield) as a pale yellow solid. Mp 121 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.43-7.51 (m, 2 H), 7.52-7.60 (m, 1 H), 7.67-7.74 (m, 2 H), 7.92 (s, 2 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 86.3 (C_{quat}), 97.1 (C_{quat}), 119.2 (C_{quat}), 122.3 (CH), 129.2 (CH), 132.3 (CH), 133.9 (CH), 147.8 (C_{quat}), 152.2 (C_{quat}), 174.0 (C_{quat}). EI + MS (*m/z* (%)): 279 (M(^{37}Cl^{37}Cl)$^+$, 2), 277 (M(^{37}Cl^{35}Cl)$^+$, 7), 275 (M(^{35}Cl^{35}Cl)$^+$, 13), 251 ((M(^{37}Cl^{37}Cl)-CO)$^+$, 0.4), 249 ((M(^{37}Cl^{35}Cl)-CO)$^+$, 3), 247 ((M(^{35}Cl^{35}Cl)-CO)$^+$, 5), 130 (10), 129 ($C_9H_5O^+$, 100), 101 ($C_8H_5^+$, 5), 75 (9). IR (ATR): $\tilde{\nu}$ 2197 (m) cm^{-1}, 1643 (s), 1578 (w), 1541 (m), 1489 (w), 1443 (w), 1406 (w), 1350 (m), 1296 (s), 1283 (m), 1211 (s), 1175 (w), 1153 (m), 1105 (m), 1074 (w), 1053 (m), 1022 (w), 937 (w), 883 (m), 858 (w), 806 (m), 762 (s), 735 (s), 691 (s), 637 (s). Anal. calcd. for $C_{14}H_7Cl_2NO$ (276.1): C 60.90, H 2.56, N 5.07. Found: C 61.07, H 2.84, N 4.96.

4.2.13 3-Phenyl-1-(pyrimidin-5-yl)prop-2-yn-1-one (5m)

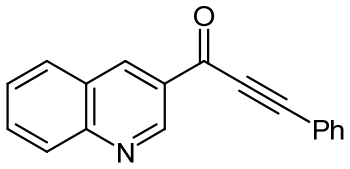


$C_{13}H_8N_2O$

208.22

242 mg (1.16 mmol, 58 % yield) as a pale yellow solid. Mp 99 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.40-7.49 (m, 2 H), 7.50-7.58 (m, 1 H), 7.66-7.74 (m, 2 H), 9.08-9.83 (m, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 86.1 (C_{quat}), 96.7 (C_{quat}), 119.4 (C_{quat}), 129.3 (CH), 130.1 (C_{quat}), 132.1 (CH), 133.8 (CH), 158.1 (CH), 162.1 (CH), 174.8 (C_{quat}). EI + MS (*m/z* (%)): 208 (M^+, 43), 207 (28), 181 ($(M\text{-}CO+H)^+$, 12), 180 ($(M\text{-}CO)^+$, 21), 153 (11), 130 (10), 129 ($C_9H_5O^+$, 100), 126 (24), 101 ($C_8H_5^+$, 8), 75 (12). IR (ATR): $\tilde{\nu}$ 2197 (m) cm^{-1}, 1632 (s), 1574 (s), 1557 (m), 1487 (w), 1433 (m), 1408 (m), 1348 (w), 1300 (m), 1221 (m), 1196 (m), 1113 (m), 1043 (m), 1009 (m), 993 (m), 925 (w), 827 (w), 764 (s), 731 (s), 712 (m), 689 (s), 632 (s), 621 (m). Anal. calcd. for $C_{13}H_8N_2O$ (208.2): C 74.99, H 3.87, N 13.45. Found: C 74.99, H 4.07, N 13.21.

4.2.14 3-Phenyl-1-(quinolin-3-yl)prop-2-yn-1-one (5n)

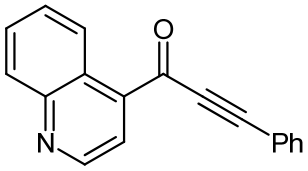


$C_{18}H_{11}NO$

257.29

302 mg (1.18 mmol, 59 % yield) as a pale brown solid. Mp 125 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.40-7.58 (m, 3 H), 7.62-7.70 (m, 1 H), 7.70-7.78 (m, 2 H), 7.84-7.93 (m, 1 H), 8.02 (d, *J* = 8.0 Hz, 1 H), 8.21 (d, *J* = 8.2 Hz, 1 H), 8.97 (s, 1 H), 9.62-9.68 (m, 1 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 86.6 (C_{quat}), 95.1 (C_{quat}), 112.0 (C_{quat}), 127.1 (C_{quat}), 128.2 (CH), 129.2 (CH), 129.7 (C_{quat}), 129.8 (CH), 130.0 (CH), 131.6 (CH), 133.0 (CH), 133.6 (CH), 139.5 (CH), 149.9 (CH), 150.3 (C_{quat}), 176.6 (C_{quat}). EI + MS (*m/z* (%)): 258 (18), 257 (M^+, 91), 256 (31), 229 ($(M-CO)^+$, 41), 228 (26), 155 (10), 130 (10), 129 ($C_9H_5O^+$, 100), 128 ($C_9H_6N^+$, 9), 127 (15), 114 (23), 101 ($C_8H_5^+$, 27), 75 (18), 43 (13). IR (ATR): $\tilde{\nu}$ 2195 (w) cm^{-1}, 1651 (m), 1609 (m), 1585 (m), 1568 (m), 1487 (m), 1443 (w), 1410 (w), 1287 (w), 1271 (w), 1180 (w), 1086 (w), 1007 (m), 986 (s), 951 (w), 897 (w), 822 (m), 772 (m), 750 (s), 687 (s), 646 (w). Anal. calcd. for $C_{18}H_{11}NO$ (257.3): C 84.03, H 4.31, N 5.44. Found: C 83.94, H 4.28, N 5.41.

4.2.15 3-Phenyl-1-(quinolin-4-yl)prop-2-yn-1-one (5o)



$C_{18}H_{11}NO$

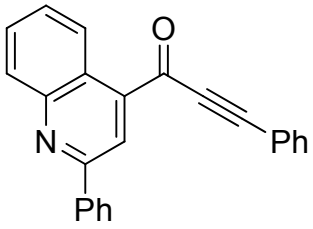
257.29

354 mg (1.37 mmol, 69 % yield) as a pale brown solid. Mp 93 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.38-7.56 (m, 3 H), 7.65-7.76 (m, 3 H), 7.76-7.85 (m, 1 H), 8.16-8.28 (m, 2 H), 8.98 (d, *J* = 9.0 Hz, 1 H), 9.16 (d, *J* = 9.2 Hz, 1 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 88.4 (C_{quat}), 94.1 (C_{quat}), 119.9 (C_{quat}), 124.3 (C_{quat}), 124.4 (CH), 125.9 (CH), 129.1 (CH), 129.4 (CH), 130.3 (CH), 130.4 (CH), 131.6 (CH), 133.6 (CH), 139.9 (C_{quat}), 149.6 (C_{quat}), 150.3 (CH), 179.3 (C_{quat}). EI + MS (*m/z* (%)): 258 (13), 257 (M^+, 74), 256 (49), 229 ($(M-CO)^+$, 31), 228 (36), 202 (33), 201 (14), 200 (11), 130 (10), 129 ($C_9H_5O^+$, 100), 114 (18), 101 ($C_8H_5^+$, 26), 100 (12), 75 (22). IR (KBr): $\tilde{\nu}$ 3045 (w) cm^{-1}, 2199 (s), 1638 (s), 1578 (m), 1506 (m), 1492 (m), 1460 (m), 1443 (m), 1349 (w), 1288 (s), 1210 (w), 1162 (m), 1141 (w), 1108 (s), 1069 (m), 963 (m), 930 (w), 878 (w), 858 (m), 789 (m), 774 (s), 759 (s), 688 (s), 629 (m), 620 (m), 570 (w), 538 (m), 514 (w). Anal. calcd. for $C_{18}H_{11}NO$ (257.3): C 84.03, H 4.31, N 5.44. Found: C 83.86, H 4.40, N 5.51.

Data reported in the literature: R. Erenler, M. Uno, T. V. Goud, J.-F. Biellmann, *J. Chem. Res.* **2009**, *7*, 459-464.

UV (CH_2Cl_2): λ_{max} (ε) 230 (25200), 309 (13200). IR (CH_2Cl_2): 1605, 2354, 3679 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.47 (m, 2H), 7.50 (m, 1H), 7.69-7.74 (m, 3H), 7.78-7.83 (m, 1H), 8.21 (d, *J* = 8.5 Hz, 1H), 8.25 (d, *J* = 4.4 Hz, 1H), 8.98 (d, *J* = 8.5 Hz, 1H), 9.15 (d, *J* = 4.4 Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$): δ 88.2, 93.8, 119.7, 124.1, 125.7, 128.9, 129.1, 130.2, 131.4, 133.3, 139.7, 149.4, 150.1, 179.1. MS (FAB^+): *m/z* 258 $[M+H]^+$. Anal. Calcd for $C_{18}H_{11}NO$: C, 84.03; H, 4.31; N, 5.44. Found: C, 84.11; H, 4.23; N, 5.49%.

4.2.16 3-Phenyl-1-(2-phenylquinolin-4-yl)prop-2-yn-1-one (5p)

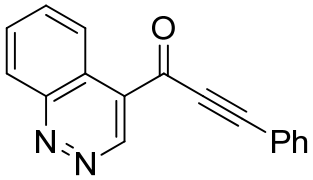


$C_{24}H_{15}NO$

333.38

584 mg (1.75 mmol, 88 % yield) as a yellow solid. Mp 101 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.41-7.63 (m, 6 H), 7.64-7.75 (m, 3 H), 7.77-7.84 (m, 1 H), 8.22-8.30 (m, 3 H), 8.72 (s, 1 H), 8.95 (dd, *J* = 8.5 Hz, *J* = 0.9 Hz, 1 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 88.6 (C_{quat}), 94.2 (C_{quat}), 120.0 (C_{quat}), 122.6 (CH), 123.3 (C_{quat}), 125.7 (CH), 127.8 (CH), 129.0 (CH), 129.2 (CH), 129.5 (CH), 130.2 (CH), 130.6 (CH), 130.7 (CH), 131.7 (CH), 133.7 (CH), 139.2 (C_{quat}), 141.0 (C_{quat}), 149.8 (C_{quat}), 157.2 (C_{quat}), 179.6 (C_{quat}). EI + MS (*m/z* (%)): 334 (29), 333 (M^+, 100), 332 (38), 305 ($(M-CO)^+$, 38), 304 (89), 303 (11), 256 ($(M-C_6H_5)^+$, 5), 203 (12), 202 (47), 152 (11), 151 (11), 130 (5), 129 ($C_9H_5O^+$, 47). IR (ATR): ṽ 2922 (w) cm^{-1}, 2197 (m), 1645 (m), 1580 (w), 1543 (w), 1491 (m), 1443 (w), 1333 (m), 1288 (m), 1269 (m), 1236 (m), 1219 (m), 1163 (m), 1139 (m), 1101 (s), 1063 (w), 1026 (w), 999 (w), 951 (m), 887 (w), 757 (s), 756 (s), 731 (m), 685 (s), 667 (m), 629 (m), 617 (m). Anal. calcd. for $C_{24}H_{15}NO$ (333.4): C 86.46, H 4.54, N 4.20. Found: C 86.35, H 4.75, N 4.11.

4.2.17 1-(Cinnolin-4-yl)-3-phenylprop-2-yn-1-one (5q)

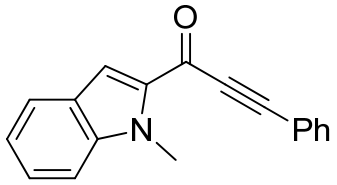


$C_{17}H_{10}N_2O$

258.27

134 mg (0.52 mmol, 26 % yield) as a yellow solid. Mp 131 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.41-7.60 (m, 3 H), 7.70-7.79 (m, 2 H), 7.91-8.01 (m, 2 H), 8.63-8.74 (m, 1 H), 9.01-9.10 (m, 1 H), 10.04 (s, 1 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 87.9 (C_{quat}), 95.6 (C_{quat}), 119.5 (C_{quat}), 121.9 (C_{quat}), 125.1 (CH), 126.0 (C_{quat}), 129.3 (CH), 131.1 (CH), 131.5 (CH), 132.1 (CH), 133.9 (CH), 134.6 (CH), 145.5 (CH), 152.1 (C_{quat}), 178.4 (C_{quat}). EI + MS (*m/z* (%)): 259 (7), 258 (M^+, 39), 230 $(M\text{-}CO)^+$, 2), 202 (12), 130 (10), 129 ($C_9H_5O^+$, 100), 101 (10), 75 (11). IR (ATR): $\tilde{\nu}$ 3057 (w) cm^{-1}, 2201 (m), 1632 (m), 1522 (w), 1497 (w), 1443 (w), 1377 (w), 1302 (m), 1182 (w), 1163 (m), 1115 (m), 1061 (m), 980 (w), 930 (w), 777 (s), 750 (s), 685 (s), 633 (m). Anal. calcd. for $C_{17}H_{10}N_2O$ (258.3): C 79.06, H 3.90, N 10.85. Found: C 78.92, H 4.00, N 10.83.

4.2.18 1-(1-Methyl-1*H*-indol-2-yl)-3-phenylprop-2-yn-1-one (5r)

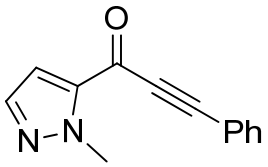


$C_{18}H_{13}NO$

259.30

190 mg (0.73 mmol, 37 % yield) as a yellow solid. Mp 97 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 4.13 (s, 3 H), 7.12-7.24 (m, 1 H), 7.32-7.56 (m, 5 H), 7.60-7.83 (m, 4 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 32.5 (CH_3), 88.3 (C_{quat}), 90.0 (C_{quat}), 110.8 (CH), 116.8 (CH), 120.8 (C_{quat}), 121.4 (CH), 123.7 (CH), 126.3 (C_{quat}), 127.2 (CH), 129.0 (CH), 130.9 (CH), 133.3 (CH), 136.5 (C_{quat}), 141.4 (C_{quat}), 170.0 (C_{quat}). EI + MS (*m/z* (%)): 260 (19), 259 (M^+, 100), 258 (47), 231 ($(M-CO)^+$, 19), 230 (79), 201 (11), 182 (17), 154 (20), 143 (18), 142 (18), 130 (6), 129 ($C_9H_5O^+$, 28), 128 (14), 116 (14), 115 ($(M-C_9H_5O-CH_3)^+$, 41), 102 (10), 101 ($C_8H_5^+$, 11), 89 (16). IR (ATR): $\tilde{\nu}$ 2197 (m) cm^{-1}, 1603 (s), 1506 (m), 1466 (m), 1423 (m), 1395 (m), 1273 (m), 1186 (m), 1146 (w), 1128 (s), 1096 (w), 1028 (m), 1015 (m), 993 (s), 818 (w), 756 (s), 737 (s), 685 (s), 644 (m). Anal. calcd. for $C_{18}H_{13}NO$ (259.3): C 83.37, H 5.05, N 5.40. Found: C 83.38, H 5.28, N 5.30.

4.2.19 1-(1-Methyl-1*H*-pyrazol-5-yl)-3-phenylprop-2-yn-1-one (5s)



$C_{13}H_{10}N_2O$

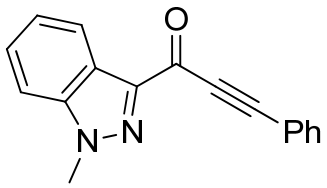
210.23

168 mg (0.80 mmol, 40 % yield) as a pale yellow solid. Mp 107 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 4.21 (s, 3 H), 7.13 (d, *J* = 2.1 Hz, 1 H), 7.36-7.55 (m, 4 H), 7.60-7.68 (m, 2 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 40.5 (CH_3), 87.7 (C_{quat}), 91.8 (C_{quat}), 115.2 (CH), 120.1 (C_{quat}), 129.1 (CH), 131.4 (CH), 133.4 (CH), 138.3 (CH), 139.9 (C_{quat}), 167.4 (C_{quat}). EI + MS (*m/z* (%)): 211 (3), 210 (M^+, 25), 209 (47), 182 ($(M\text{-}CO)^+$, 6), 181 (8), 154 (23), 130 (3), 129 ($C_9H_5O^+$, 25). IR (ATR): $\tilde{\nu}$ 2199 (m) cm^{-1}, 1643 (s), 1503 (m), 1489 (w), 1462 (m), 1441 (m), 1422 (m), 1395 (w), 1314 (m), 1296 (m), 1269 (m), 1209 (m), 1157 (w), 1069 (m), 1024 (w), 982 (s), 926 (m), 806 (m), 791 (m), 762 (s), 745 (3), 719 (m), 689 (s), 637 (m). Anal. calcd. for $C_{13}H_{10}N_2O$ (210.2): C 74.27, H 4.79, N 13.33. Found: C 74.00, H 4.94, N 13.33.

Data reported in the literature: M. S. Shvartsberg, G. Fedenok, *Russ. Chem. Bull.* **1991**, *39*, 1906-1910.

Mp. 76.5-77.5 °C, Anal. calcd.: C 74.06, H 4.61, N 13.44. Found: C 74.27, H 4.79, N 13.44. ^{1}H NMR: δ 4.08 (s, 3H, CH_3), 6.73 (d, 1H, C^4H), 7.59 (d, 1H, C^3H), 7.53-7.57 and 8.12-8.22 (m, 5H, Ph).

4.2.20 1-(1-Methyl-1*H*-indazol-3-yl)-3-phenylprop-2-yn-1-one (5t)

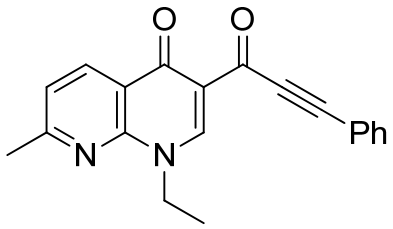


$C_{17}H_{12}N_2O$

260.29

325 mg (1.25 mmol, 62 % yield) as a pale brown solid. Mp 83 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 4.22 (s, 3 H), 7.32-7.52 (m, 6 H), 7.70-7.78 (m, 2 H), 8.40 (dt, *J* = 8.1 Hz, *J* = 1.0 Hz, 1 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 37.0 (CH_3), 88.1 (C_{quat}), 92.1 (C_{quat}), 109.8 (CH), 120.9 (C_{quat}), 122.9 (CH), 123.4 (C_{quat}), 124.4 (CH), 127.6 (CH), 128.9 (CH), 130.9 (CH), 133.5 (CH), 141.6 (C_{quat}), 143.2 (C_{quat}), 172.6 (C_{quat}). EI + MS (*m/z* (%)): 261 (18), 260 (M^+, 90), 233 ($(M-CO+H)^+$, 14), 232 ($(M-CO)^+$, 82), 231 (48), 130 (11), 129 ($C_9H_5O^+$, 100), 116 ($C_7H_4N_2^+$, 22), 101 ($C_8H_5^+$, 15), 94 (17), 93 (29), 77 (10), 75 (18). IR (ATR): $\tilde{\nu}$ 2195 (w) cm^{-1}, 1607 (m), 1474 (m), 1443 (w), 1423 (m), 1391 (m), 1304 (m), 1275 (w), 1242 (m), 1150 (m), 1084 (s), 1042 (m), 1005 (w), 961 (m), 799 (m), 777 (s), 746 (s), 691 (s), 644 (m), 629 (s). Anal. calcd. for $C_{17}H_{12}N_2O$ (260.3): C 78.44, H 4.65, N 10.76. Found: C 78.22, H 4.56, N 10.88.

4.2.21 1-Ethyl-7-methyl-3-(3-phenylprop-2-ynoyl)-1,4-dihydro-1,8-naphthyridin-4-one (5u)

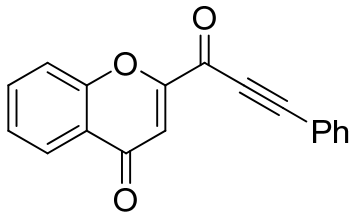


$C_{20}H_{16}N_2O_2$

316.35

117 mg (0.37 mmol, 18 % yield) as a yellow-brown solid. Mp 169 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.52 (t, *J* = 7.2 Hz, 3 H), 2.67 (s, 3 H), 4.52 (q, *J* = 7.2 Hz, 2 H), 7.29 (s, 1 H), 7.34-7.48 (m, 3 H), 7.70-7.81 (m, 2 H), 8.66-8.72 (m, 1 H), 8.72-8.75 (m, 1 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 15.6 (CH_3), 25.7 (CH_3), 47.3 (CH_2), 90.0 (C_{quat}), 94.2 (C_{quat}), 119.8 (C_{quat}), 121.3 (C_{quat}), 121.9 (CH), 122.5 (C_{quat}), 128.8 (CH), 130.8 (CH), 133.7 (CH), 137.2 (CH), 149.1 (CH), 163.3 (C_{quat}), 174.3 (C_{quat}), 175.4 (C_{quat}). EI + MS (*m/z* (%)): 317 (23), 316 (M^+, 100), 315 (5), 288 ($(M\text{-}CO)^+$, 25), 287 (19), 273 ($(M\text{-}CO\text{-}CH_3)^+$, 22), 261 (11), 260 (57), 259 (21), 245 (16), 232 (15), 231 (11), 144 (14), 129 ($C_9H_5O^+$, 14). IR (ATR): ṽ 2193 (m) cm^{-1}, 1641 (s), 1614 (m), 1591 (s), 1568 (m), 1531 (s), 1489 (m), 1439 (s), 1369 (m), 1337 (s), 1300 (m), 1263 (m), 1252 (m), 1221 (m), 1173 (s), 1157 (m), 1115 (s), 1061 (s), 1042 (s), 997 (m), 930 (m), 791 (s), 770 (s), 748 (s), 691 (s), 656 (s), 619 (m). Anal. calcd. for $C_{20}H_{16}N_2O_2$ (316.4): C 75.93, H 5.10, N 8.86. Found: C 75.82, H 5.31, N 8.64.

4.2.22 2-(3-Phenylprop-2-ynoyl)-4*H*-chromen-4-one (5v)



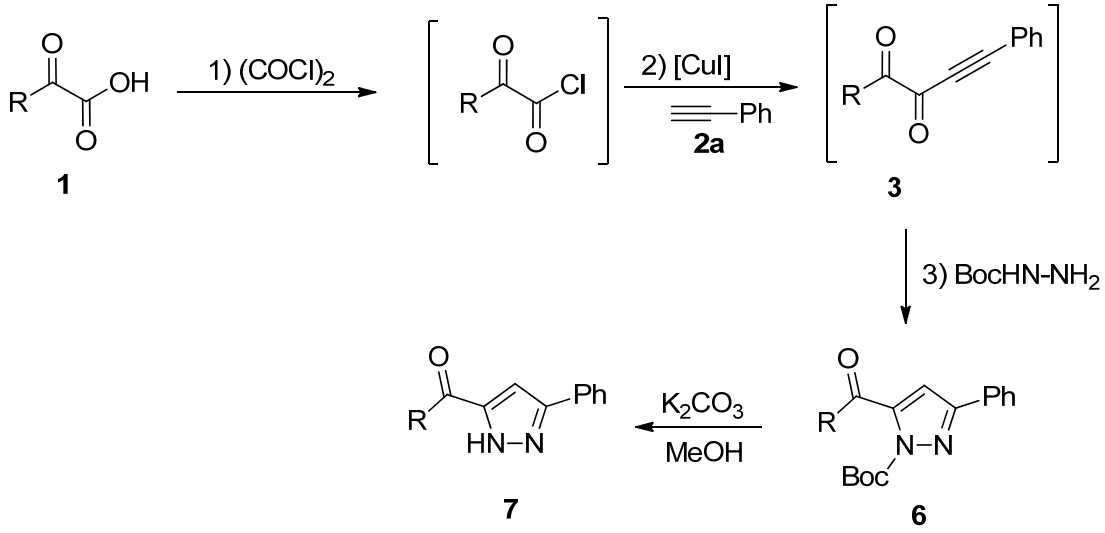
$C_{18}H_{10}O_3$

274.27

470 mg (1.06 mmol, 53 % yield) as a yellow solid. Mp 153 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.34 (s, 1 H), 7.42-7.59 (m, 4 H), 7.62-7.81 (m, 4 H), 8.22 (dd, *J* = 8.0 Hz, *J* = 1.7 Hz, 1 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 81.1 (C_{quat}), 97.0 (C_{quat}), 116.1 (CH), 119.2 (C_{quat}), 119.3 (CH), 125.0 (C_{quat}), 126.2 (CH), 126.5 (CH), 129.3 (CH), 132.3 (CH), 133.9 (CH), 135.5 (CH), 156.1 (C_{quat}), 156.8 (C_{quat}), 171.2 (C_{quat}), 179.1 (C_{quat}). EI + MS (*m/z* (%)): 276 (2), 275 (4), 274 (M^+, 15), 246 ($(M\text{-}CO)^+$, 10), 130 (9), 129 ($C_9H_5O^+$, 100), 75 (7). IR (ATR): $\tilde{\nu}$ 2922 (w) cm^{-1}, 2851 (w), 2193 (m), 1641 (s), 1614 (m), 1570 (w), 1462 (m), 1443 (w), 1396 (m), 1335 (w), 1308 (m), 1271 (m), 1219 (w), 1180 (w), 1121 (s), 1049 (s), 997 (m), 961 (w), 930 (w), 856 (m), 777 (m), 752 (s), 685 (s), 671 (m). Anal. calcd. for $C_{18}H_{10}O_3$ (274.3): C 78.82, H 3.67. Found: C 78.71, H 3.76.

5 Preparation of 2-acylpyrazoles 7

5.1 General procedure



2.00 mmol of glyoxylic acid **1** in dry 1,4-dioxane (10 mL) were placed under argon atmosphere in a dry screw-cap Schlenk vessel with septum and degassed with argon. Then, oxalyl chloride (0.18 mL, 2.00 mmol, 1.00 equiv.) was added dropwise to the reaction mixture at room temperature (water bath). The mixture was stirred for 4 h at 50 °C in a preheated oil bath and was allowed to come to room temperature. CuI (20 mg, 0.10 mmol, 5 mol %), phenylacetylene (**2a**) (0.23 mL, 2.00 mmol, 1.00 equiv.), and dry triethylamine (0.84 mL, 6.00 mmol, 3.00 equivs.) were successively added to the mixture and stirring at room temperature was continued for 24 h. Afterwards, *tert*-butyl carbazate (267 mg, 2.00 mmol, 1.00 equiv.) and 2 mL of 2-methoxyethanol were added. This mixture was stirred for 24 h at 100 °C (preheated oil bath). After complete conversion (product monitored by TLC) water (10 mL) was added and the mixture was extracted with dichloromethane (4 x 10 mL, monitored by TLC). The combined organic layers were dried with anhydrous sodium sulfate and the desiccant was removed by filtration. After removal of the solvents in vacuum the residue was adsorbed on Celite® and purified chromatographically on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl acetate to give the *N*-Boc protected acylpyrazoles **6** as pale brown solids which were used as obtained in the subsequent step.

For deprotection the *N*-Boc protected acylpyrazoles **6** were dissolved in methanol (0.2 M), 2.5 equivs. of potassium carbonate were added, and the mixture was stirred for 2 h at 50 °C (preheated oil bath). After complete deprotection (monitored by TLC) the mixture was adsorbed on Celite® and chromatographed on silica gel with dichloromethane (DCM)/methanol/aqueous ammonia to give 2-acylpyrazoles **7**.

The experimental details for the synthesis of the 2-acylpyrazoles **7** are given in Table 4.

Table 4. Experimental details for the synthesis of 2-acylpyrazoles 7.

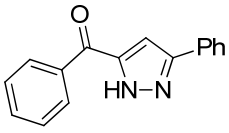
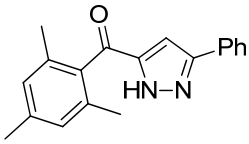
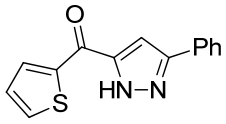
Entry	Glyoxylic acid **1** (2.00 mmol)	2-Acylpyrazole **7** (isolated yield)	Chromatographic purification
1	Phenylglyoxylic acid (*Merck*) **1a** 306 mg	 **7a** 201 mg (0.81 mmol) 41 %	DCM/methanol/aqueous ammonia = 100:1:1
2	Mesiylglyoxylic acid (*ABCR*) **1b** 388 mg	 **7b** 232 mg (0.80 mmol) 41 %	DCM/methanol/aqueous ammonia = 100:1:1

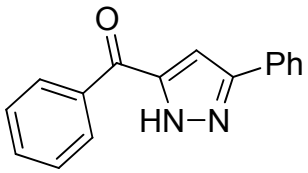
Table 4 (Continuation).

Entry	Glyoxylic acid **1** (2.00 mmol)	2-Acylpyrazole **7** (isolated yield)	Chromatographic purification
3	2-Thiophenyl glyoxylic acid (*Alpha Aesar*) **1c** 319 mg	 **7c** 256 mg (1.08 mmol) 54 %	DCM/methanol/aqueous ammonia = 100:1:1[a]

[a] Additionally purified by dissolving in hydrogen chloride solution in ethanol (1.25 M, *Fluka*).

5.2 Spectroscopic data of compounds 7a-c

5.2.1 5-Benzoyl-3-phenyl-1*H*-pyrazole (7a)



$C_{16}H_{12}N_2O$

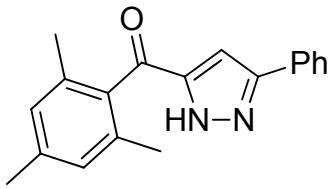
248.28

201 mg (0.81 mmol, 41 % yield) as a colorless solid. Mp 167-170 °C. ^{1}H-NMR (DMSO-d_6, 200 MHz, 100 °C): δ 6.71-6.81 (m, 1 H), 6.85-7.25 (m, 6 H), 7.33-7.44 (m, 2 H), 7.52-7.88 (m, 2 H), 13.2 (brs, NH). EI + MS (*m/z* (%)): 249 (19), 248 (M^+, 100), 247 (3), 220 (11), 219 (13), 191 (10), 171 ((M-C_6H_5)$^+$, 14), 149 (10), 114 (13), 105 ($C_7H_5O^+$, 58), 77 ($C_6H_5^+$, 50), 71 (13), 57 (12). IR (KBr): $\tilde{\nu}$ 3223 (m) cm^{-1}, 1719 (w), 1636 (s), 1573 (m), 1492 (w), 1466 (m), 1397 (m), 1277 (m), 1257 (m), 1183 (m), 1065 (w), 1025 (w), 960 (w), 901 (m), 831 (m), 798 (m), 764 (m), 729 (s), 686 (m), 512 (w). Anal. calcd. for $C_{16}H_{12}N_2O$ (248.3): C 77.40, H 4.87, N 11.28. Found: C 77.20, H 5.04, N 11.06.

Data reported in the literature: S. Ito, A. Kakehi, K. Okada, *Heterocycles* **1999**, *51*, 2949-2960.

Mp 174-175 °C. ^{1}H NMR ($CDCl_3$): δ 14.01 (bs, NH), multipletts near 7-8 ppm due to aromatic protons are omitted. IR (KBr): $\tilde{\nu}$ 3221 cm^{-1} (NH), 1636 (C=O), 1397, 1256 (pyrazole ring). Anal. calcd.: C 77.40, H 4.87, N 11.28. Found: C 77.31, H 4.84, N 11.44.

5.2.2 3-Phenyl-5-[(2,4,6-trimethylphenyl)carbonyl]-1*H*-pyrazole (7b)

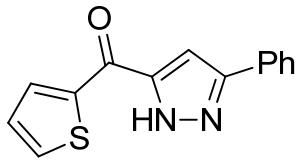


$C_{19}H_{18}N_2O$

290.36

232 mg (0.80 mmol, 41 % yield) as a colorless solid. Mp 71 °C. ^{1}H-NMR (DMSO-d_6, 200 MHz, 100 °C): δ 1.65 (s, 6 H), 1.85 (s, 3 H), 6.47 (s, 2 H), 6.54 (s, 1 H), 6.80-7.12 (m, 3 H), 7.27-7.41 (m, 2 H), 13.2 (brs, NH). EI + MS (*m/z* (%)): 291 (19), 290 (M^+, 100), 289 (30), 273 (21), 262 ($(M\text{-}CO)^+$, 23), 261 (24), 247 (14), 187 (17), 172 (17), 158 (22), 157 (15), 147 ($C_{10}H_{11}O^+$, 20), 146 (24), 145 (12), 144 (26), 119 ($C_9H_{11}^+$, 26), 117 (18), 116 (15), 115 (24), 104 (16), 103 (13), 91 (36), 77 ($C_6H_5^+$, 25), 43 (14). IR (KBr): $\tilde{\nu}$ 1661 (m) cm^{-1}, 1611 (w), 1462 (m), 1429 (m), 1398 (m), 1375 (m), 1273 (w), 1242 (m), 1177 (m), 1142 (w), 1061 (w), 1032 (w), 1016 (w), 961 (w), 953 (w), 883 (s), 849 (m), 829 (m), 762 (s), 739 (m), 691 (s), 627 (m). Anal. calcd. for $C_{19}H_{18}N_2O$ (290.4): C 78.59, H 6.25, N 9.65. Found: C 78.53, H 6.44, N 9.41.

5.2.3 3-Phenyl-5-[(thiophen-2-yl)carbonyl]-1*H*-pyrazole (7c)



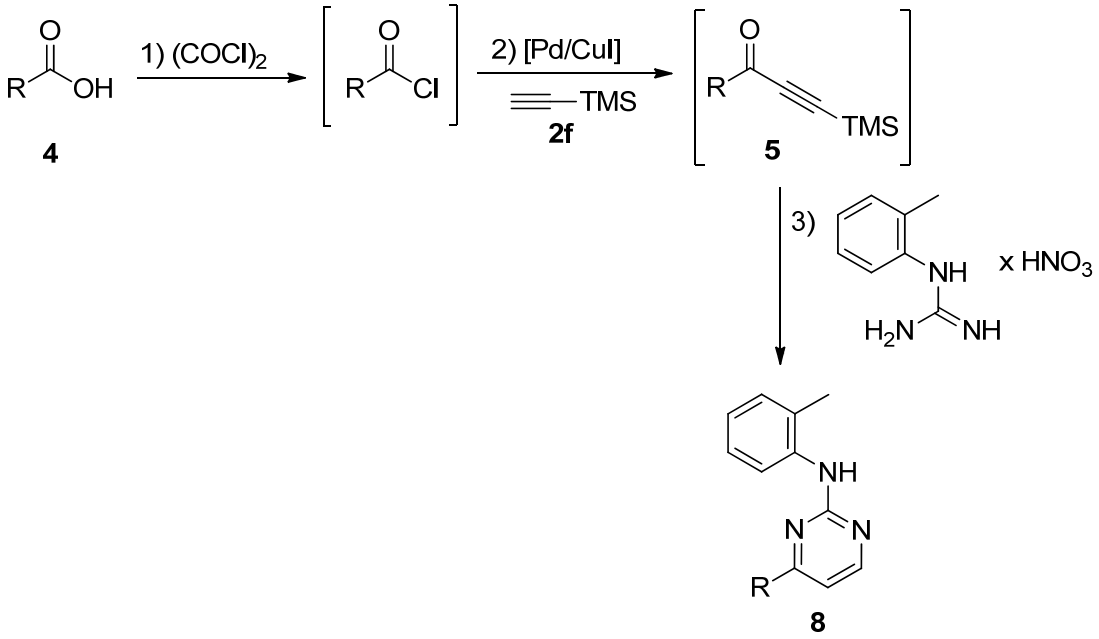
$C_{14}H_{10}N_2OS$

254.31

256 mg (1.08 mmol, 54 % yield) as a colorless solid. Mp 187 °C. ^{1}H-NMR (DMSO-d_6, 200 MHz, 100 °C): δ 6.63-6.87 (m, 2 H), 6.87-7.06 (m, 3 H), 7.27-7.42 (m, 2 H), 7.42-7.58 (m, 1 H), 7.91 (brs, 1 H), 13.30 (brs, 1 H). EI + MS (*m/z* (%)): 256 (6), 255 (17), 254 (M^+, 100), 253 (8), 226 ($(M\text{-}CO)^+$, 7), 225 (6), 171 (15), 123 (11), 115 (13), 114 (49), 113 (10), 111 ($C_5H_3OS^+$, 90), 83 ($C_4H_3S^+$, 12), 77 ($C_6H_5^+$, 10). IR (ATR): $\tilde{\nu}$ 3204 (w) cm^{-1}, 2980 (w), 2361 (w), 1603 (m), 1516 (w), 1472 (w), 1396 (w), 1258 (w), 1192 (w), 1155 (w), 997 (w), 961 (w), 914 (w), 858 (w), 820 (s), 772 (m), 756 (s), 716 (s), 680 (s), 673 (m), 642 (w), 617 (w). Anal. calcd. for $C_{14}H_{10}N_2OS$ (254.3): C 66.12, H 3.96, N 11.02. Found: C 65.89, H 4.13, N 11.27.

6 Preparation of 2-phenylaminopyrimidines 8

6.1 General procedure

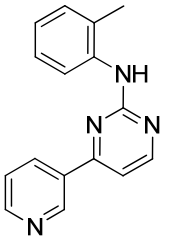
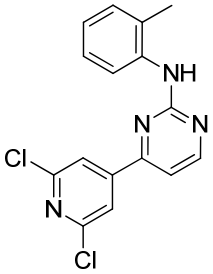


2.00 mmol of carboxylic acid **1** in dry 1,4-dioxane (10 mL) were placed under argon atmosphere in a dry screw-cap Schlenk vessel with septum and degassed with argon. Then, oxalyl chloride (0.18 mL, 2.00 mmol, 1.00 equiv.) was added dropwise to the reaction mixture at room temperature (water bath). The mixture was stirred for 4 h at 50 °C in a preheated oil bath and was allowed to come to room temperature. $PdCl_2(PPh_3)_2$ (28 mg, 0.04 mmol, 2 mol %), CuI (15 mg, 0.08 mmol, 4 mol %), trimethylsilylacetylene (*ABCR*) (**2f**) (0.27 mL, 2.00 mmol, 1.00 equiv.), and dry triethylamine (0.84 mL, 6.00 mmol, 3.00 equivs.) were successively added to the mixture and stirring at room temperature was continued for 1 h. Afterwards, 1-(2-methylphenyl)guanidinium nitrate[a] (424 mg, 2.00 mmol, 1.00 equiv.), potassium carbonate (698 mg, 5.00 mmol, 2.50 equivs.), and 2 mL of 2-methoxyethanol were added. This mixture was stirred for 24 h at 120 °C (preheated oil bath). After complete conversion the residue was adsorbed on Celite® and purified chromatographically on silica gel with dichloromethane/methanol/aqueous ammonia to give 2-phenylaminopyrimidines **8** as analytically pure compounds.

[a] 1-(2-Methylphenyl)guanidinium nitrate was prepared according to the literature procedure: F. X. Tavares, J. A. Boucheron, S. H. Dickerson, R. J. Griffin, F. Preugschat, S. A. Thomson, T. Y. Wang, H.-Q. Zhou, *J. Med. Chem.* **2004**, *47*, 4716-4730.

The experimental details for the synthesis of 2-phenylaminopyrimidines **8** are given in Table 5.

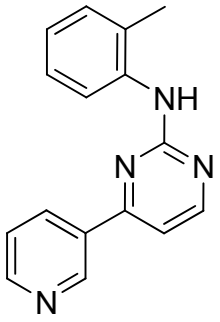
Table 5. Experimental details for the synthesis of 2-phenylaminopyrimidines 8.

Entry	Carboxylic acid **4** (2.00 mmol)	2-Phenylamino-pyrimidine **8** (isolated yield)	Chromatographic purification
1	3-Pyridyl carboxylic acid sodium salt (*ABCR*) **4a**[a] 296 mg	 **8a** 279 mg (1.06 mmol) 53 %[a]	DCM/methanol/aqueous ammonia = 100:1:1
2	2,6-Dichloro-isonicotinic acid (*ABCR*) **4h** 396 mg	 **8b** 282 mg (0.85 mmol) 41 %	DCM/methanol/aqueous ammonia = 100:1:1

[a] 2.00 equivs. of triethylamine in the 2nd reaction step

6.2 Spectroscopic data of compounds 8a-b

6.2.1 *N*-(2-Methylphenyl)-4-(pyridin-3-yl)pyrimidin-2-amine (8a)



$C_{16}H_{14}N_4$

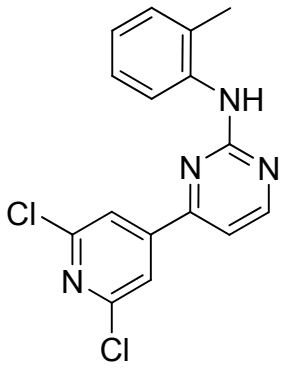
262.31

279 mg (1.06 mmol, 53 % yield) as an orange solid. Mp 84 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.36 (s, 3 H), 7.01-7.12 (m, 2 H), 7.14 (d, *J* = 5.2 Hz, 1 H), 7.20-7.32 (m, 2 H), 7.36-7.44 (m, 1 H), 8.07 (d, *J* = 8.1 Hz, 1 H), 8.29-8.37 (m, 1 H), 8.49 (d, *J* = 5.2 Hz, 1 H), 8.67-8.74 (m, 1 H), 9.23-9.29 (m, 1 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 18.5 (CH_3), 108.4 (CH), 122.3 (CH), 124.0 (CH), 124.2 (CH), 127.0 (CH), 129.2 (C_{quat}), 130.9 (CH), 133.0 (C_{quat}), 134.8 (CH), 137.6 (C_{quat}), 148.9 (CH), 151.8 (CH), 159.5 (CH), 161.2 (C_{quat}), 162.9 (C_{quat}). EI + MS (*m/z* (%)): 263 (12), 262 (M^+, 66), 261 (49), 248 (18), 247 ($(M\text{-}CH_3\text{-}H)^+$, 100), 246 (21), 130 (11). IR (ATR): $\tilde{\nu}$ 1591 (m) cm^{-1}, 1557 (s), 1530 (m), 1483 (m), 1445 (s), 1373 (m), 1333 (m), 1319 (m), 1287 (m), 1240 (m), 1196 (m), 1140 (w), 1120 (w), 1107 (w), 1080 (w), 1024 (m), 989 (w), 935 (w), 853 (w), 791 (s), 748 (s), 718 (s), 702 (s), 642 (s), 613 (m). Anal. calcd. for $C_{16}H_{14}N_4$ (262.3): C 73.26, H 5.38, N 21.36. Found: C 73.19, H 5.60, N 21.16.

Data reported in the literature: M. G. Bursavich, S. Lombardi, A. M. Gilbert, *Org. Lett.* **2005**, *7*, 4113-4116.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.26 (s, 3 H), 7.19-7.26 (m, 2 H), 7.41 (d, *J*=5.2 Hz, 1 H), 7.52-7.57 (m, 2 H), 8.38-8.42 (m, 1 H), 8.50 (d, *J*=5.0 Hz, 1 H), 8.70 (dd, *J*=4.8, 1.8 Hz, 1 H), 8.94 (s, 1 H), 9.25 (dd, *J*=2.3, 0.7 Hz, 1 H). MS (ESI) *m/z* 263.1.

6.2.2 4-(2,6-Dichloropyridin-4-yl)-*N*-(2-methylphenyl)pyrimidin-2-amine (8b)

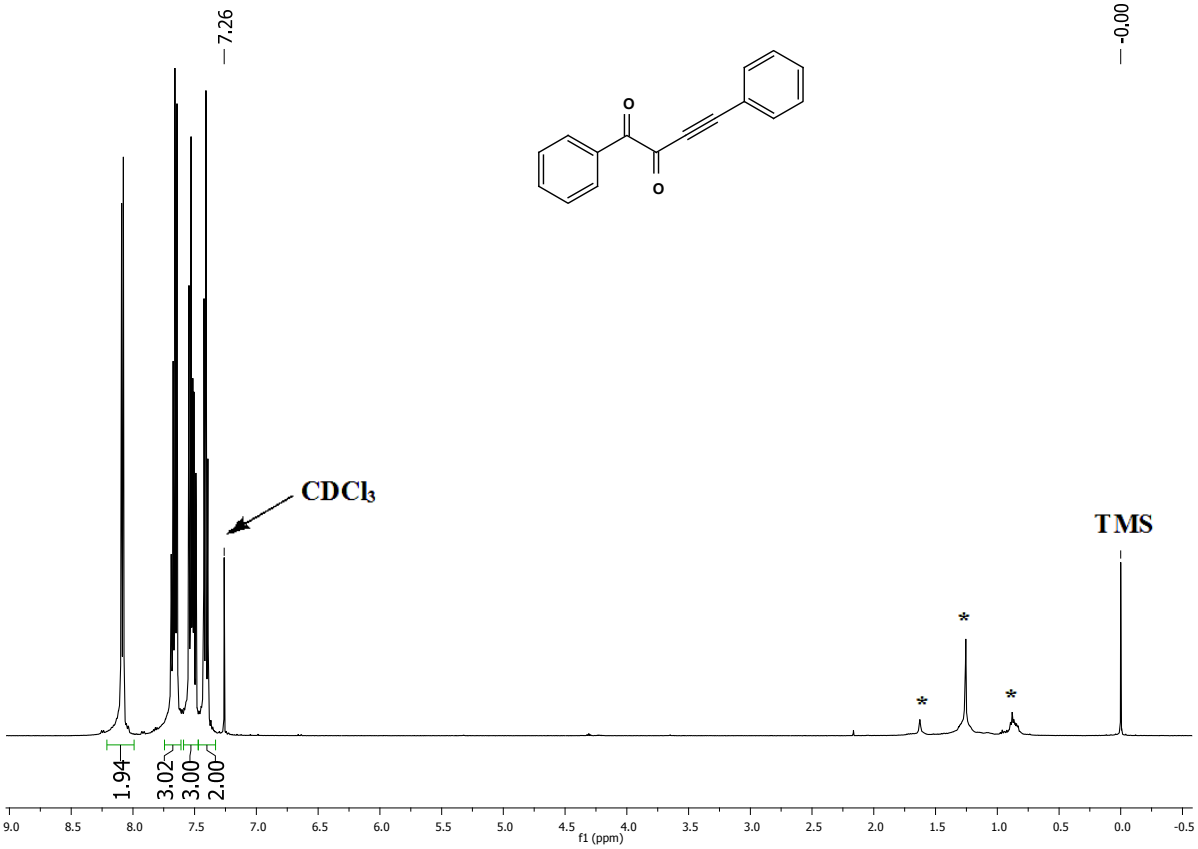


$C_{16}H_{12}Cl_2N_4$

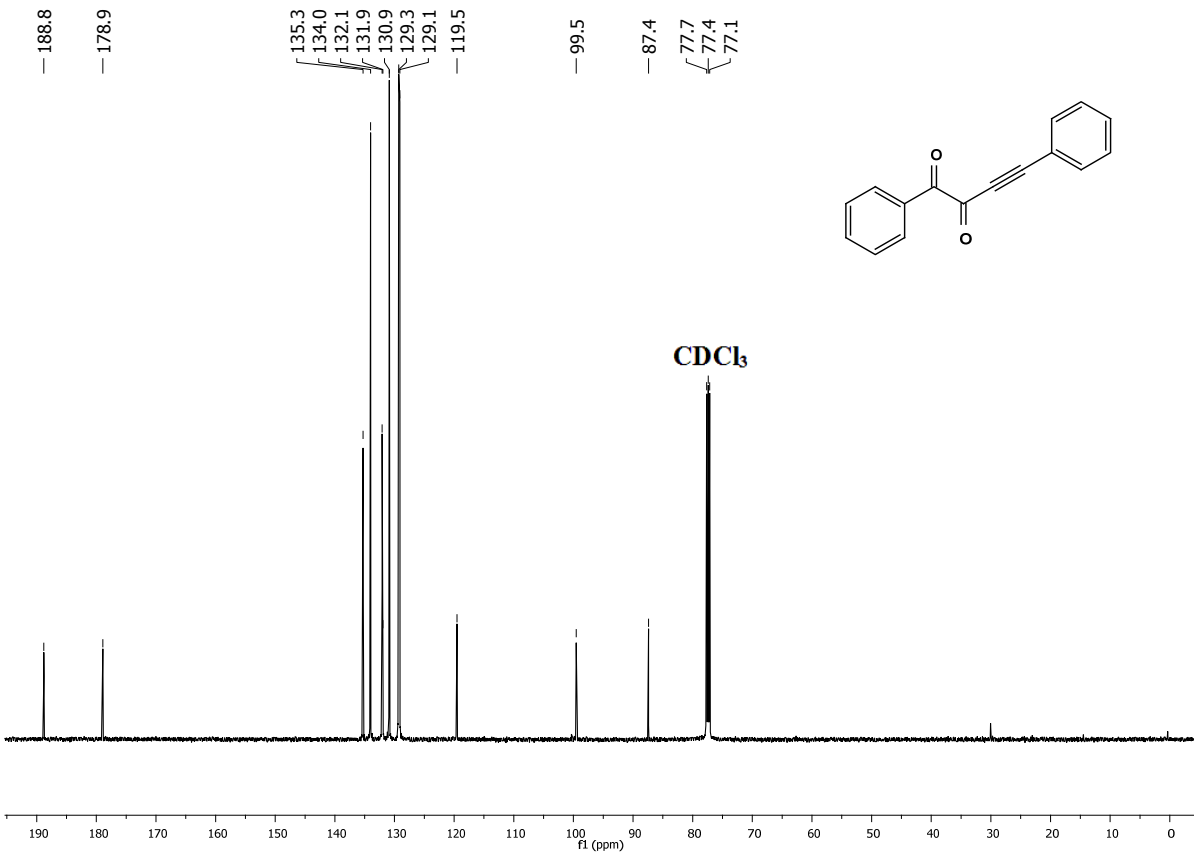
331.20

282 mg (0.85 mmol, 43 % yield) as a yellow solid. Mp 155 °C. ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 2.25 (s, 3 H), 7.05-7.15 (m, 1 H), 7.15-7.30 (m, 2 H), 7.45-7.60 (m, 2 H), 8.13 (s, 2 H), 8.59 (m, 1 H), 9.12 (s, 1 H). ^{13}C-NMR (DMSO, 75 MHz): δ 18.1 (CH_3), 108.3 (CH), 120.7 (CH), 124.8 (CH), 125.2 (CH), 125.9 (CH), 130.3 (CH), 132.5 (C_{quat}), 137.5 (C_{quat}), 150.2 (C_{quat}), 150.5 (C_{quat}), 158.5 (C_{quat}), 160.4 (CH), 161.2 (C_{quat}). EI + MS (*m/z* (%)): 333 (($M(^{37}Cl^{37}Cl)$-H)$^+$, 12), 332 ($M(^{37}Cl^{35}Cl)^+$, 39), 331 (($M(^{37}Cl^{35}Cl)$-H)$^+$, 37), 330 ($M(^{35}Cl^{35}Cl)^+$, 61), 329 (($M(^{35}Cl^{35}Cl)$-H)$^+$, 45), 319 (($M(^{37}Cl^{37}Cl)$-CH_3)$^+$, 11), 318 (($M(^{37}Cl^{37}Cl)$-CH_3-H)$^+$, 14), 317 (($M(^{37}Cl^{35}Cl)$-CH_3)$^+$, 64), 316 (($M(^{37}Cl^{35}Cl)$-CH_3-H)$^+$, 33), 315 (($M(^{35}Cl^{35}Cl)$-CH_3)$^+$, 100), 314 (($M(^{35}Cl^{35}Cl)$-CH_3-H)$^+$, 24), 165 (10), 164 (11), 132 (14), 130 (10), 129 (15), 116 (16), 106 ($C_7H_8N^+$, 17), 104 (12), 91 ($C_7H_7^+$, 16), 89 (12), 77 ($C_6H_5^+$, 17), 65 ($C_5H_5^+$, 13), 43 (13). IR (ATR): $\tilde{\nu}$ 2920 (w) cm^{-1}, 1601 (w), 1570 (w), 1528 (w), 1487 (w), 1452 (s), 1400 (m), 1373 (m), 1354 (m), 1321 (w), 1285 (w), 1271 (w), 1252 (m), 1238 (m), 1196 (w), 1171 (m), 1146 (s), 1111 (w), 1049 (w), 1020 (w), 874 (m), 793 (s), 741 (s), 714 (m), 689 (m), 652 (m), 615 (w). Anal. calcd. for $C_{16}H_{12}Cl_2N_4$ (331.2): C 58.02, H 3.65, N 16.92. Found: C 57.80, H 3.77, N 16.75.

7 ^{1}H- and ^{13}C-NMR Spectra of compounds 3a-g

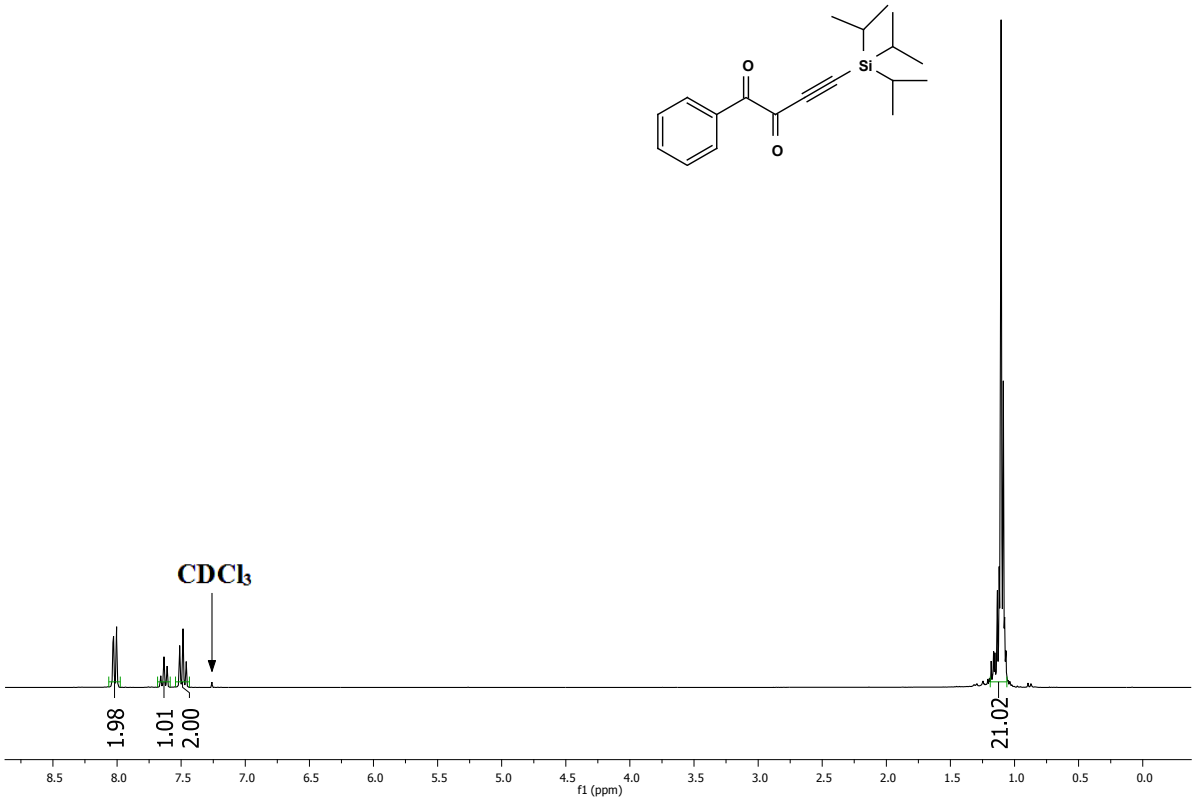


^{1}H-NMR (500 MHz) of **3a** (30 mg) in $CDCl_3$ at 295 K (δ in ppm). *Impurities from residual solvents.

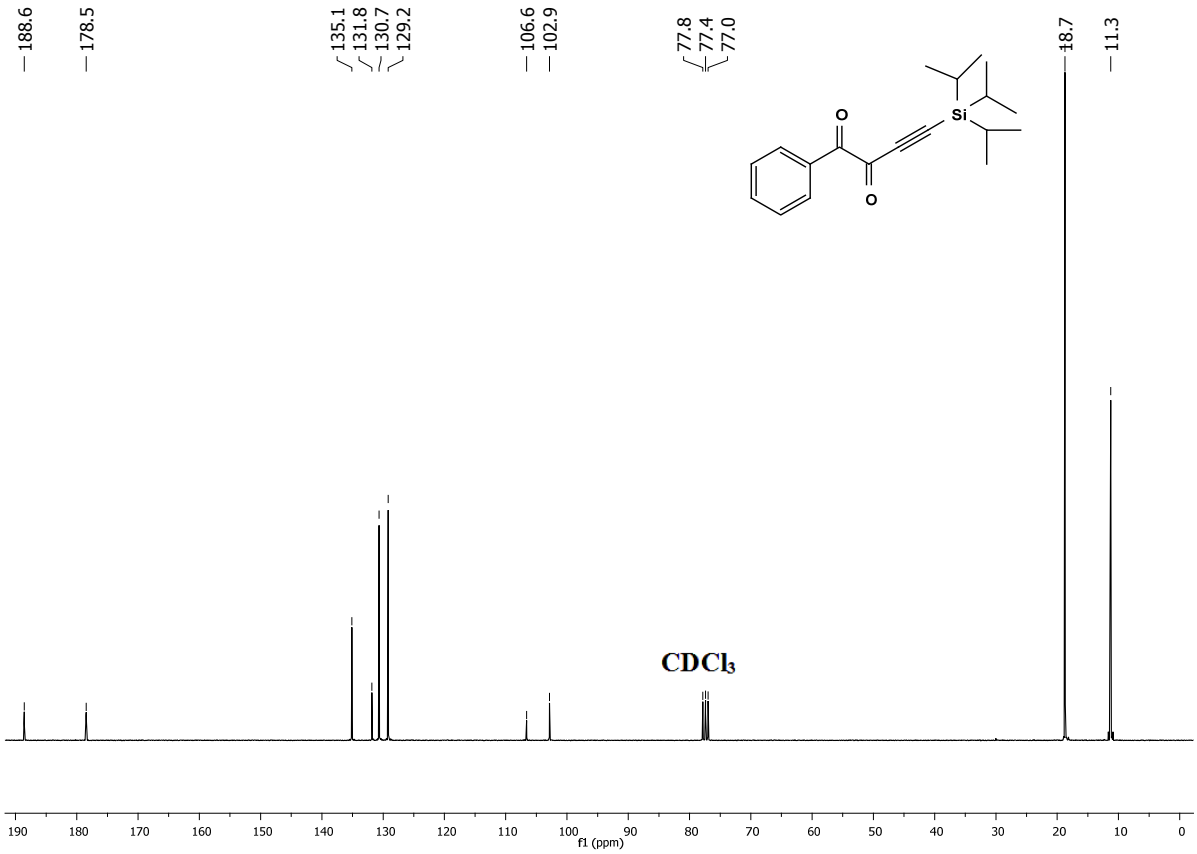


^{13}C-NMR (125 MHz) of **3a** (30 mg) in $CDCl_3$ at 295 K (δ in ppm).

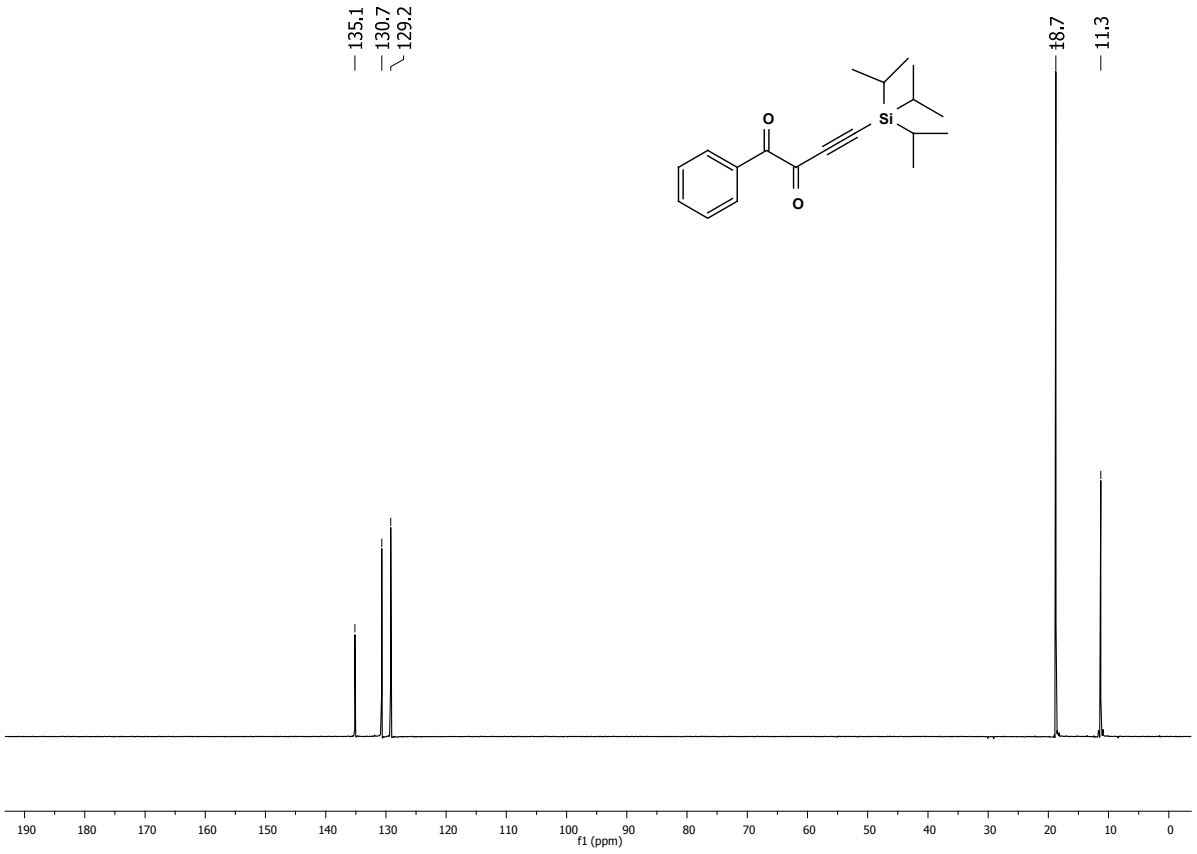
^{13}C-DEPT 135-NMR (125 MHz) of **3a** (30 mg) in $CDCl_3$ at 295 K (δ in ppm).



^{1}H-NMR (300 MHz) of **3b** (30 mg) in $CDCl_3$ at 295 K (δ in ppm).

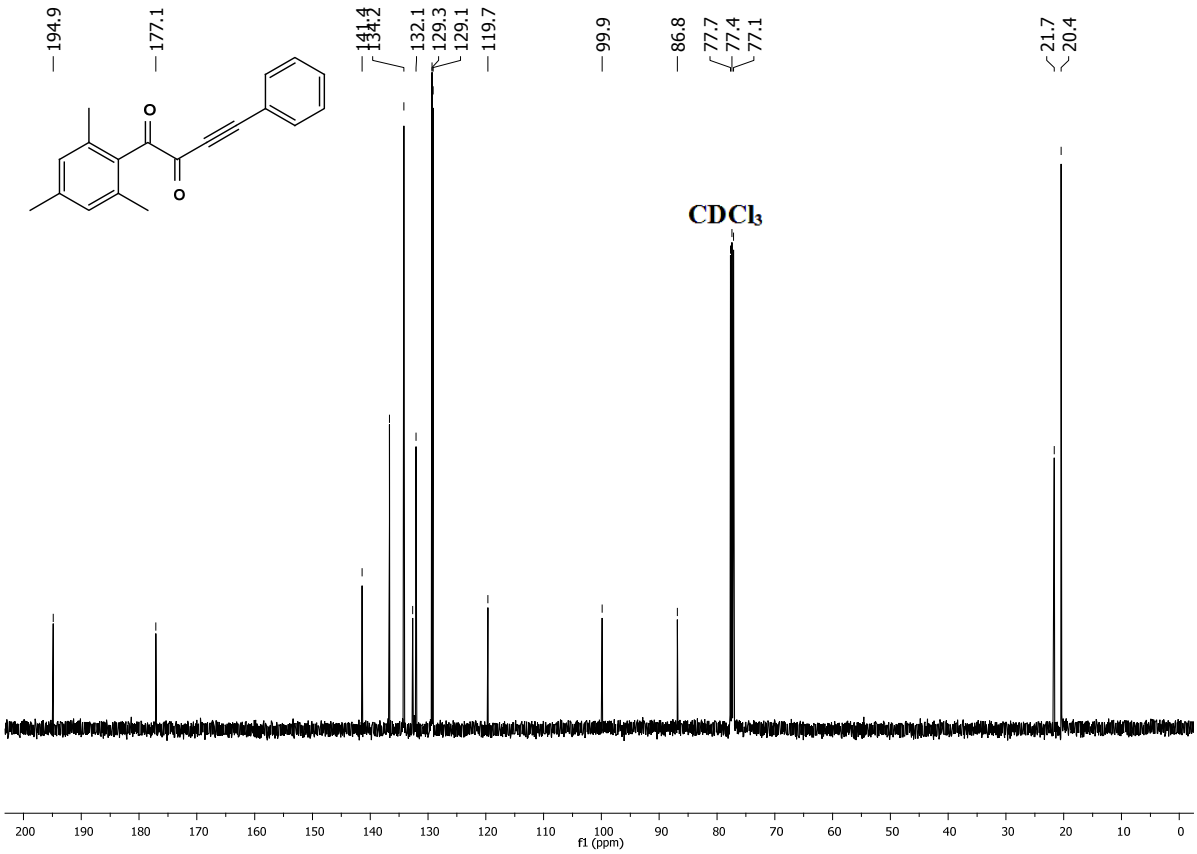


^{13}C-NMR (75 MHz) of **3b** (30 mg) in $CDCl_3$ at 295 K (δ in ppm).

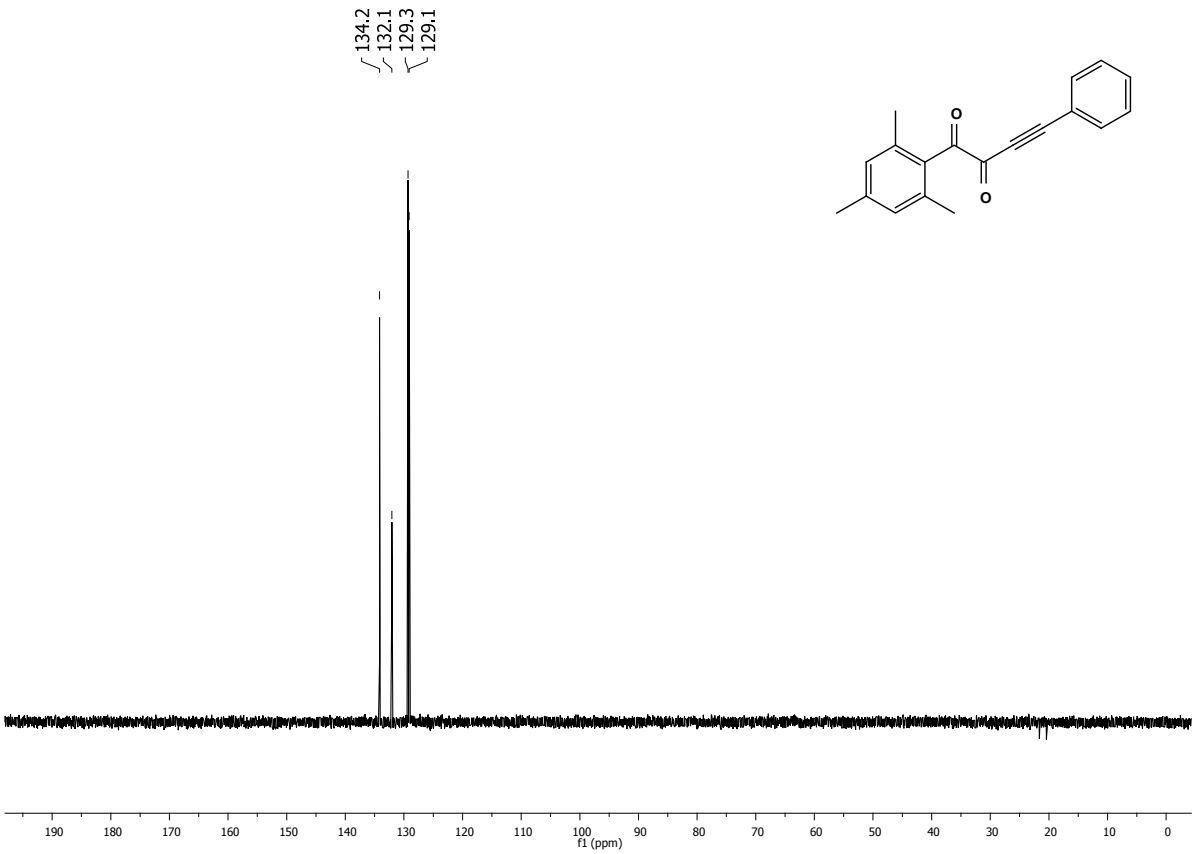


^{13}C-DEPT 135-NMR (75 MHz) of **3b** (30 mg) in $CDCl_3$ at 295 K (δ in ppm).

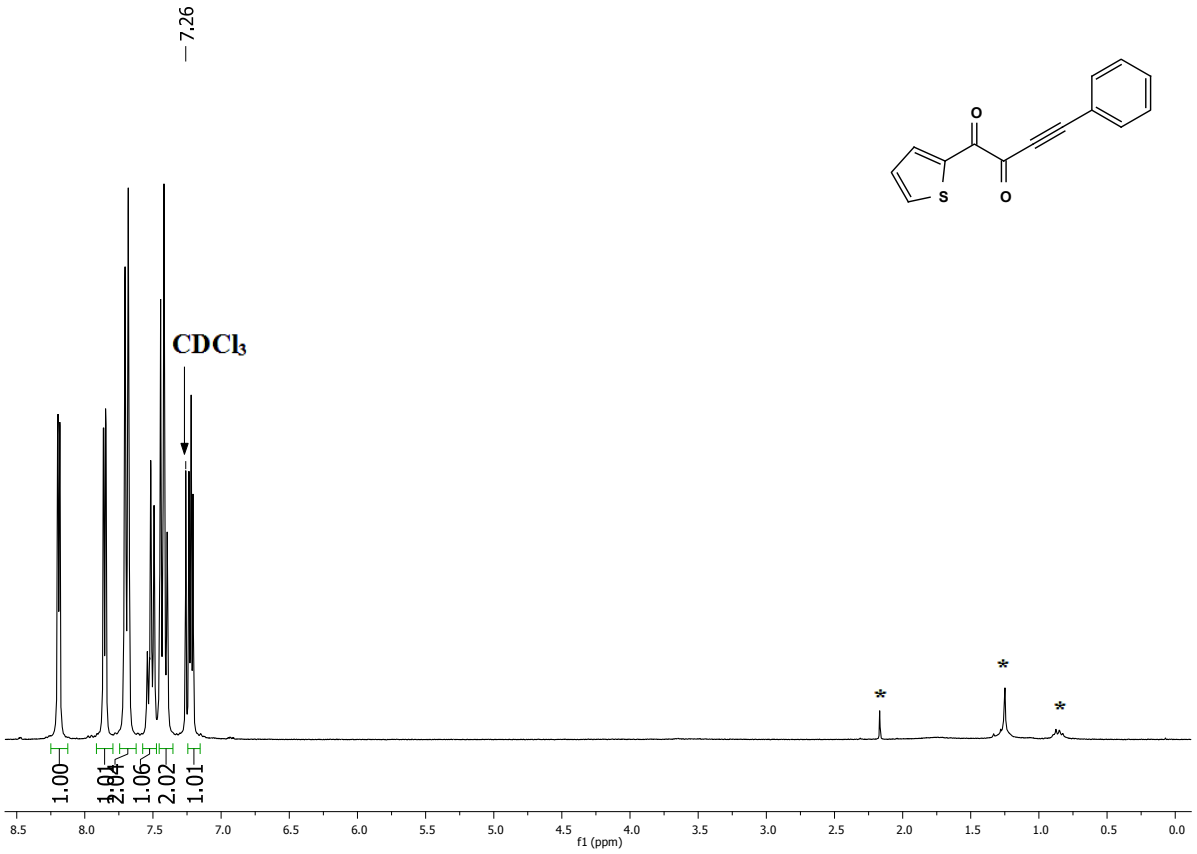
^{1}H-NMR (500 MHz) of **3c** (30 mg) in $CDCl_3$ at 296 K (δ in ppm).



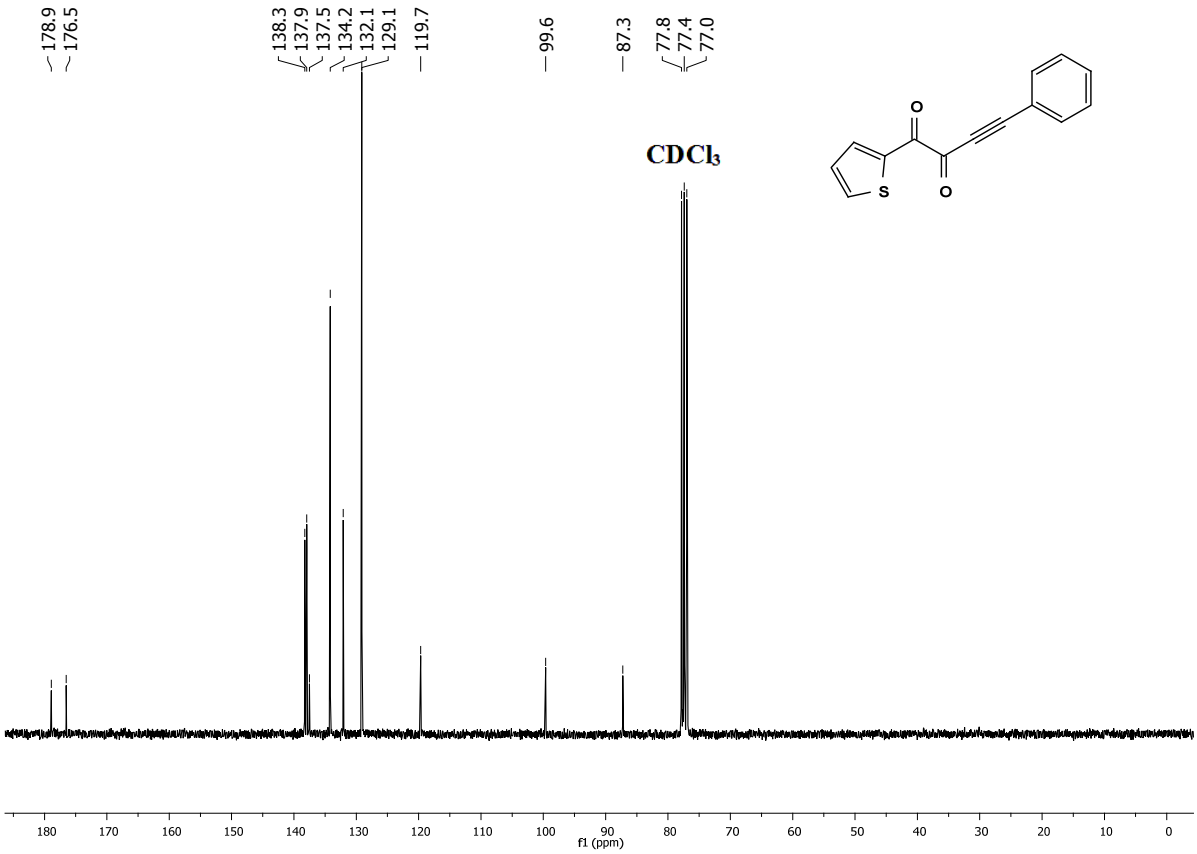
^{13}C-NMR (125 MHz) of **3c** (30 mg) in $CDCl_3$ at 296 K (δ in ppm).



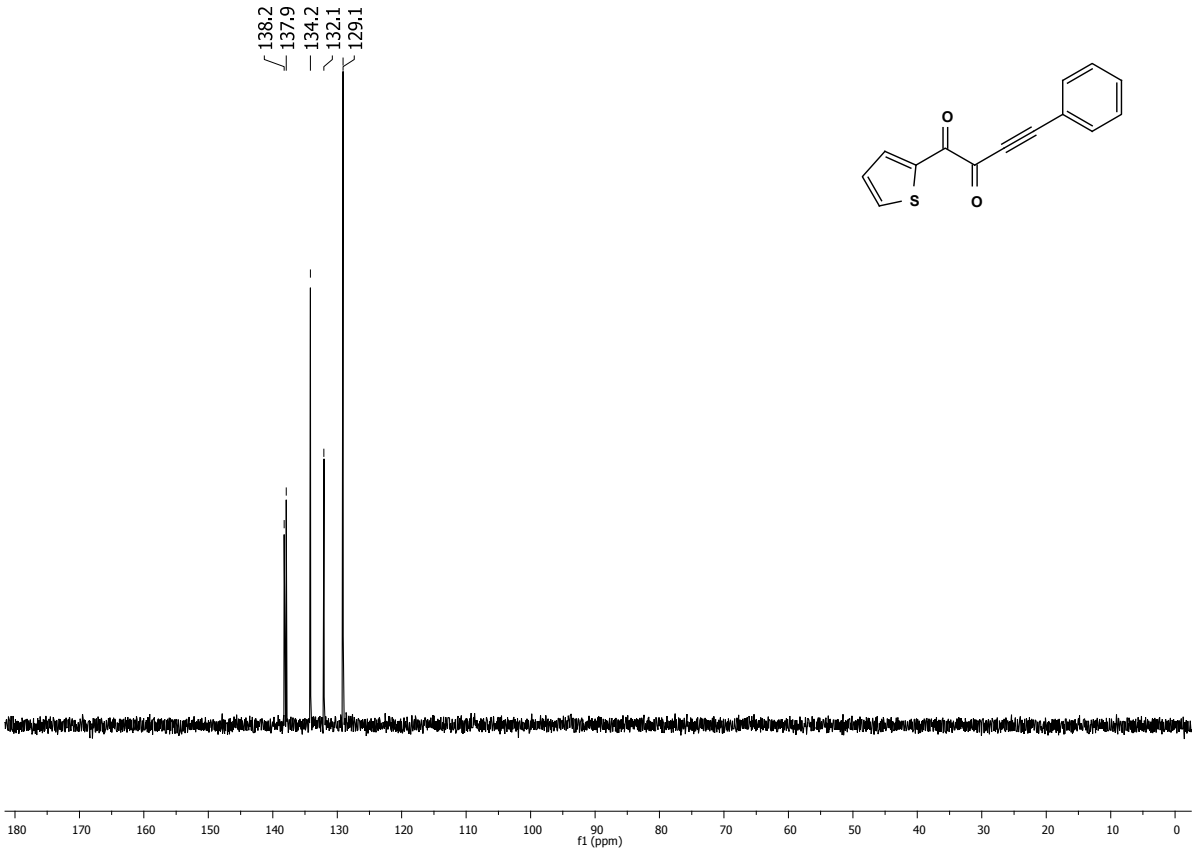
^{13}C-DEPT 135-NMR (125 MHz) of **3c** (30 mg) in $CDCl_3$ at 296 K (δ in ppm).



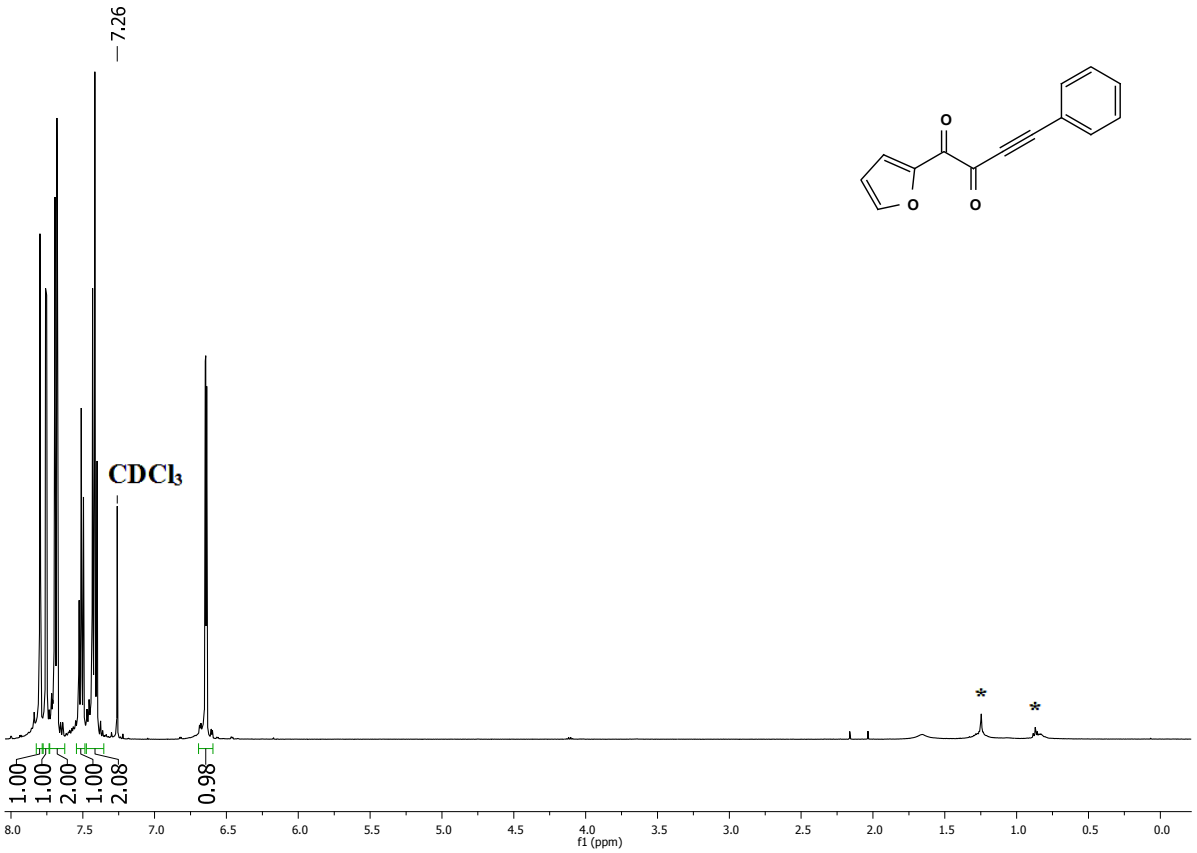
^{1}H-NMR (300 MHz) of **3d** (30 mg) in $CDCl_3$ at 294 K (δ in ppm). *Impurities from residual solvents.



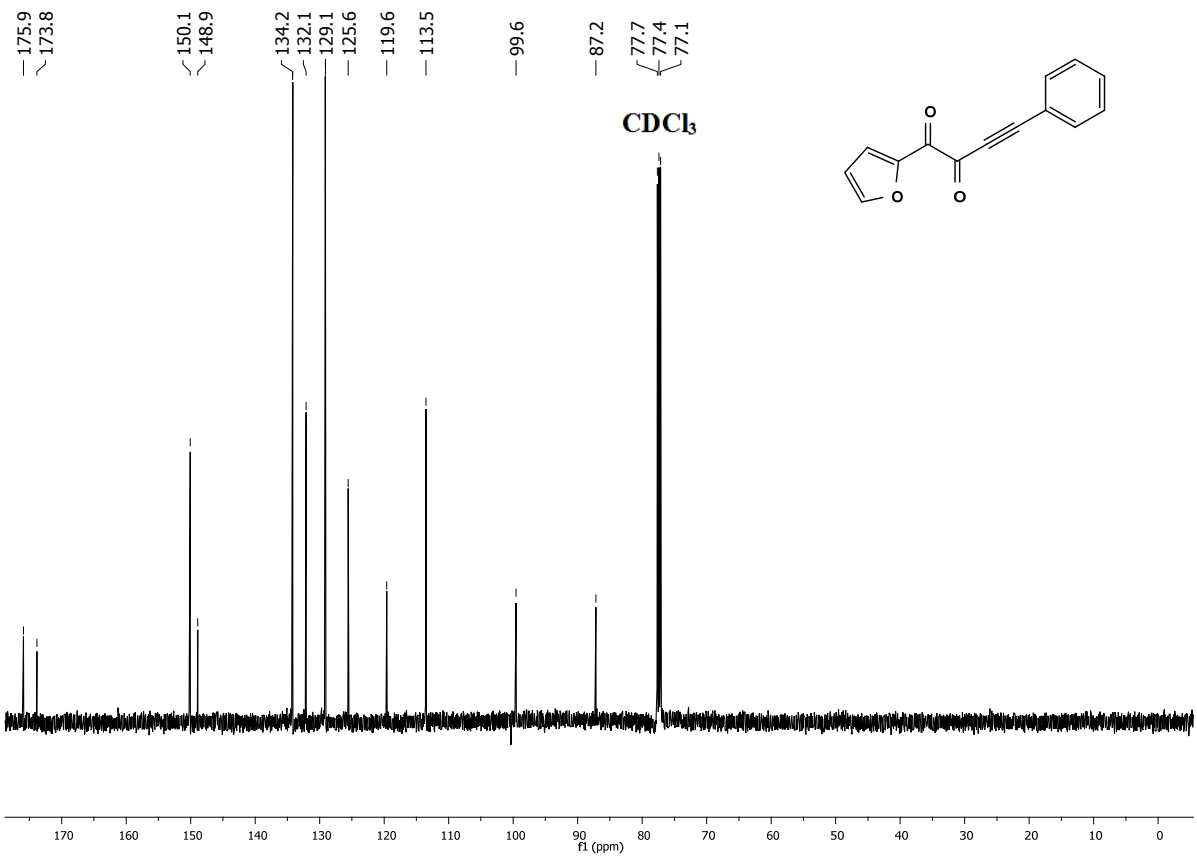
^{13}C-NMR (75 MHz) of **3d** (30 mg) in $CDCl_3$ at 295 K (δ in ppm).



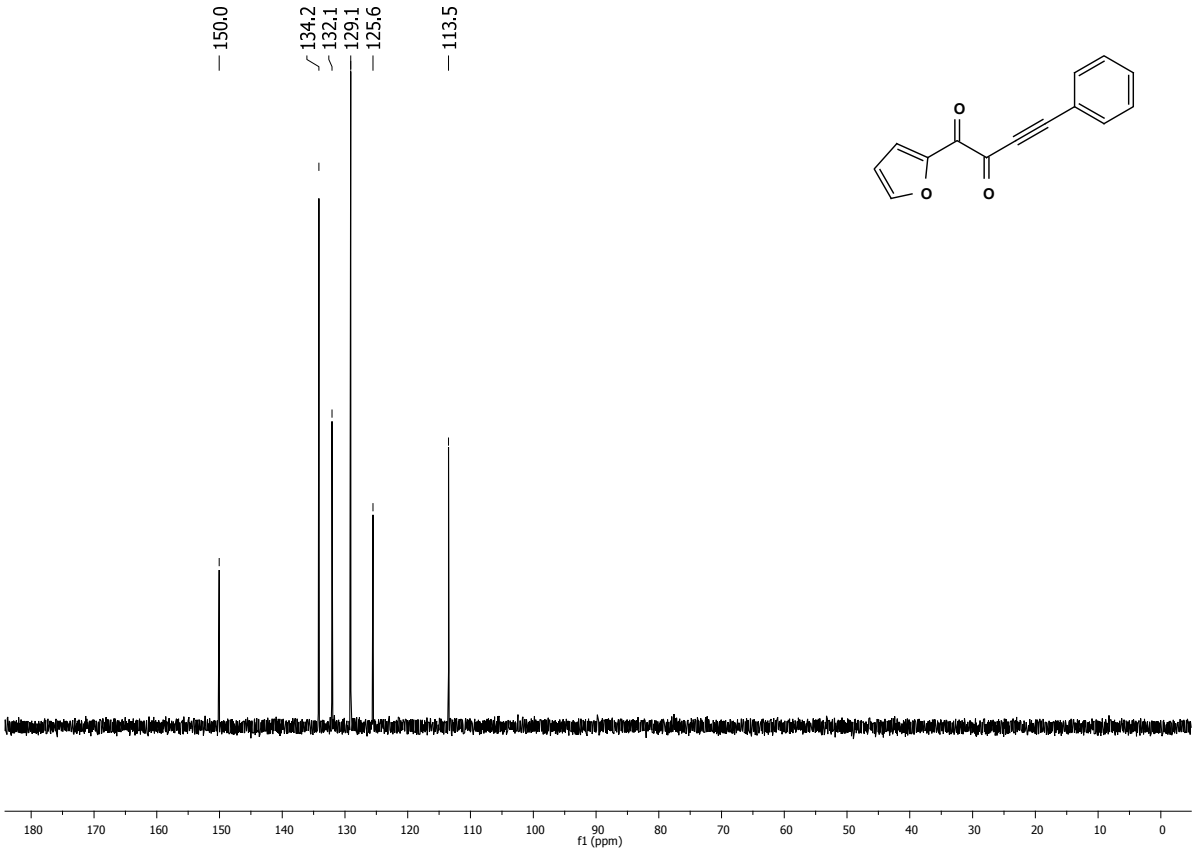
^{13}C-DEPT 135-NMR (75 MHz) of **3d** (30 mg) in $CDCl_3$ at 296 K (δ in ppm).



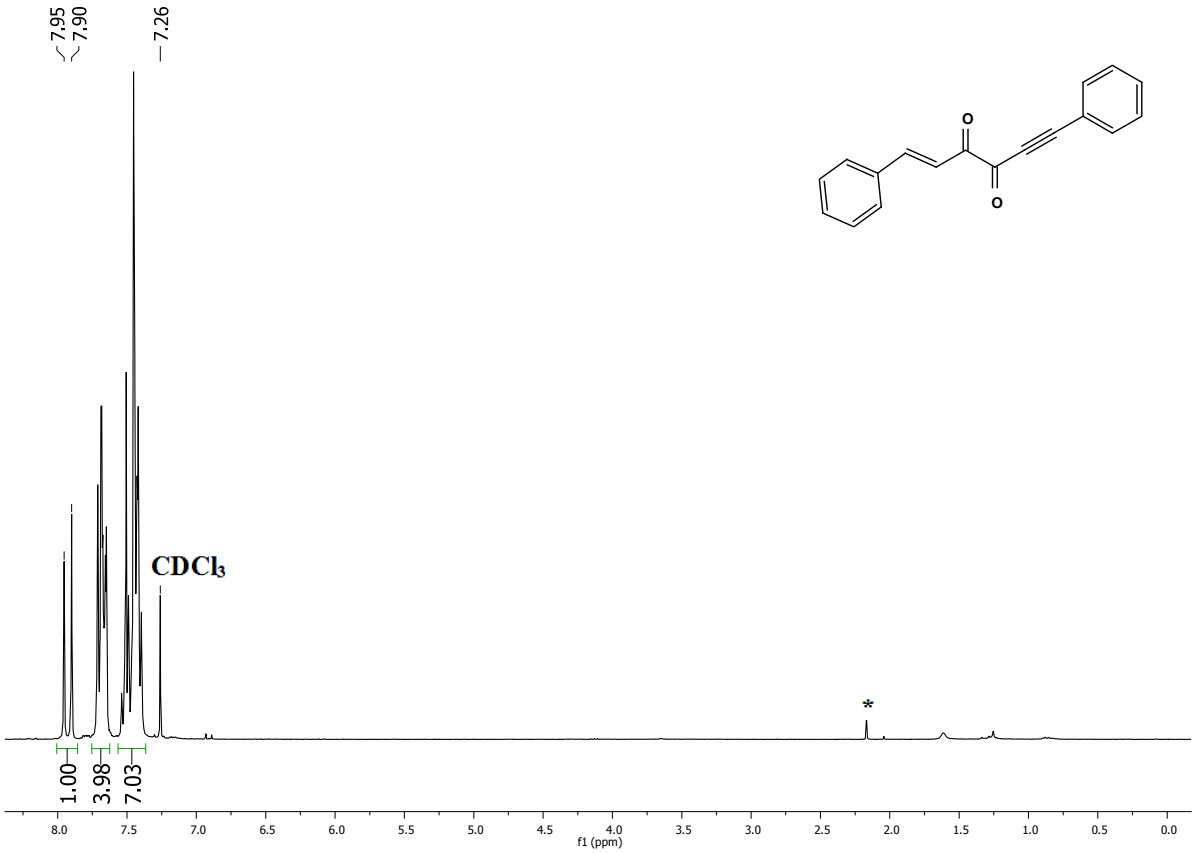
^{1}H-NMR (500 MHz) of **3e** (30 mg) in $CDCl_3$ at 297 K (δ in ppm). *Impurities from residual solvents.



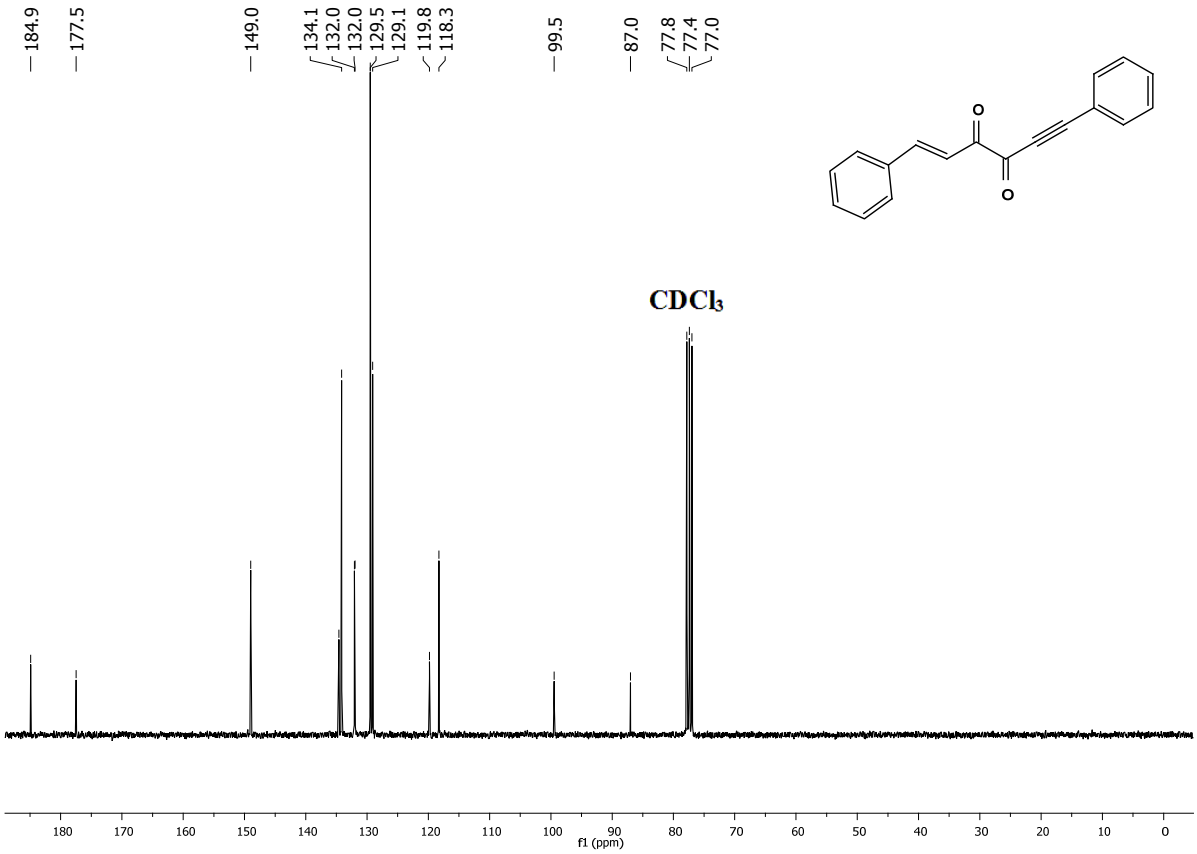
^{13}C-NMR (125 MHz) of **3e** (30 mg) in $CDCl_3$ at 297 K (δ in ppm).



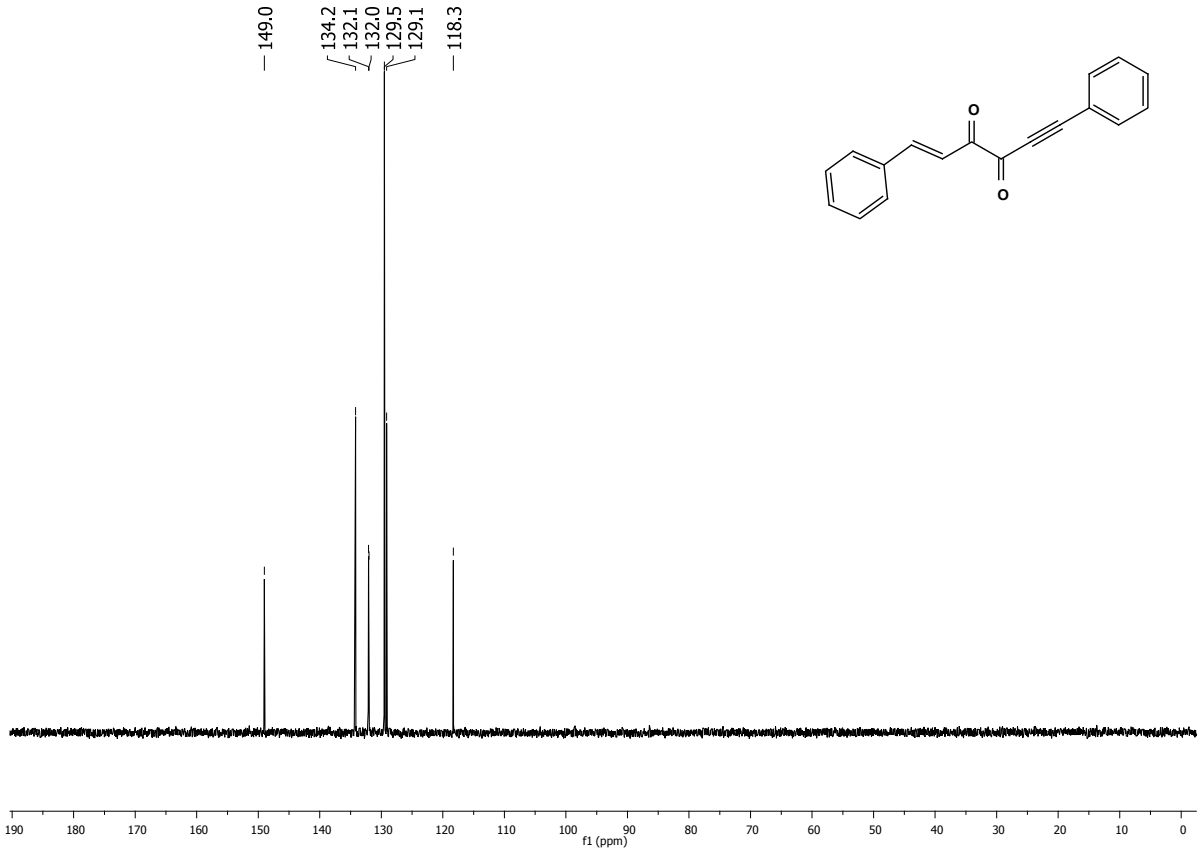
^{13}C-DEPT 135-NMR (125 MHz) of **3e** (30 mg) in $CDCl_3$ at 297 K (δ in ppm).



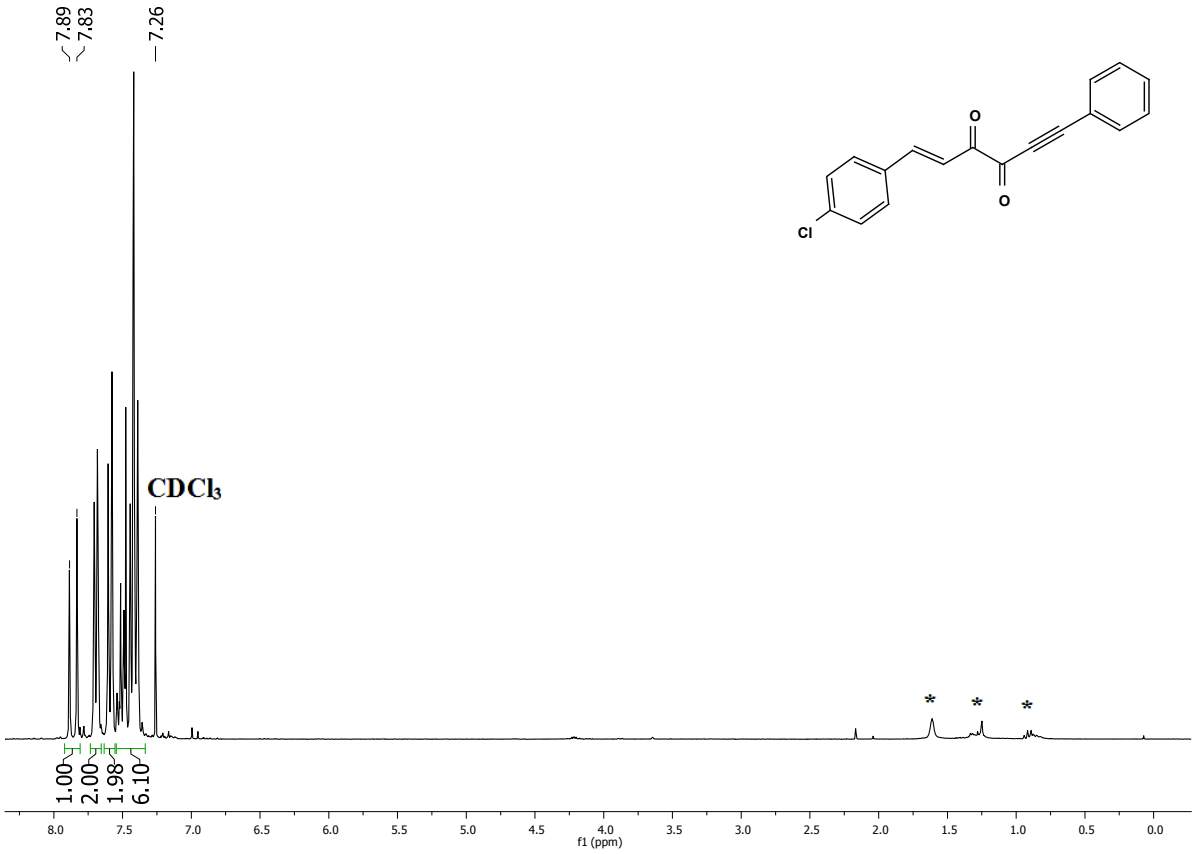
^{1}H-NMR (300 MHz) of **3f** (30 mg) in $CDCl_3$ at 295 K (δ in ppm). *Impurities from residual solvents.



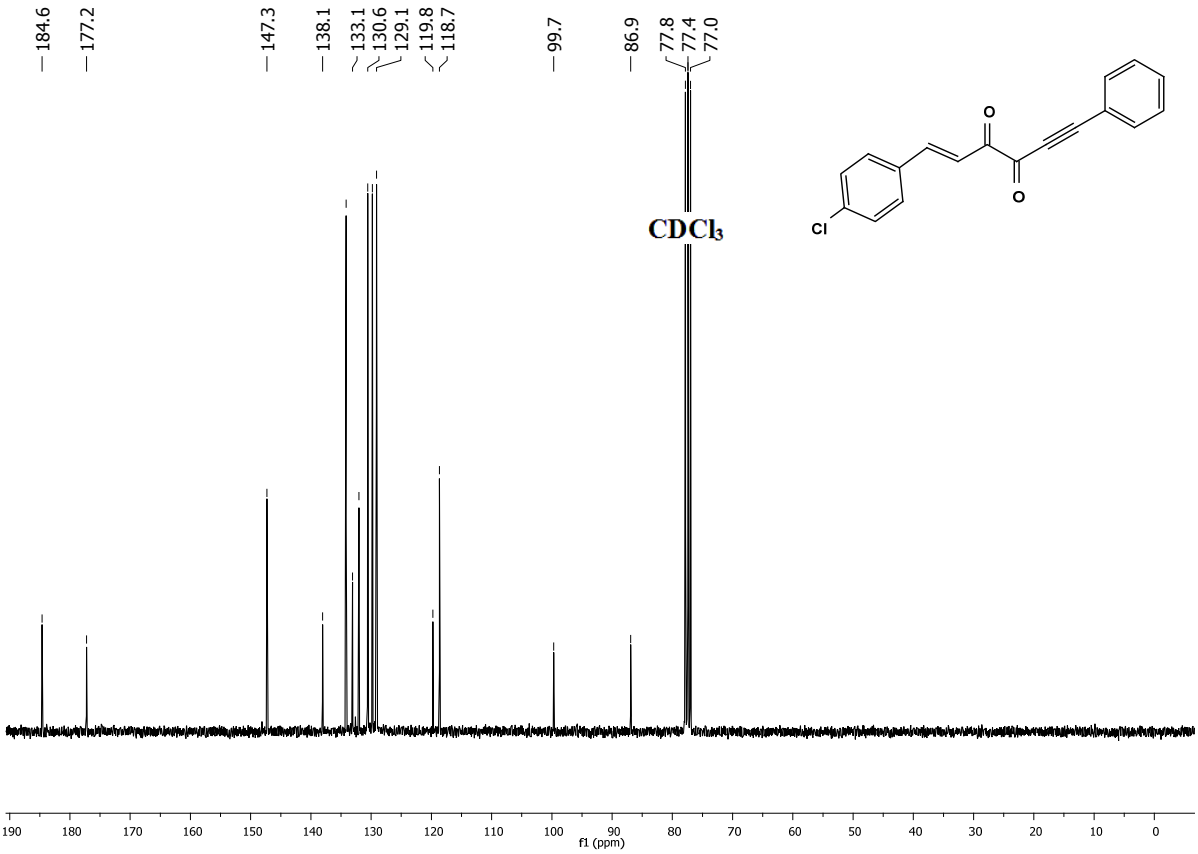
^{13}C-NMR (75 MHz) of **3f** (30 mg) in $CDCl_3$ at 295 K (δ in ppm).



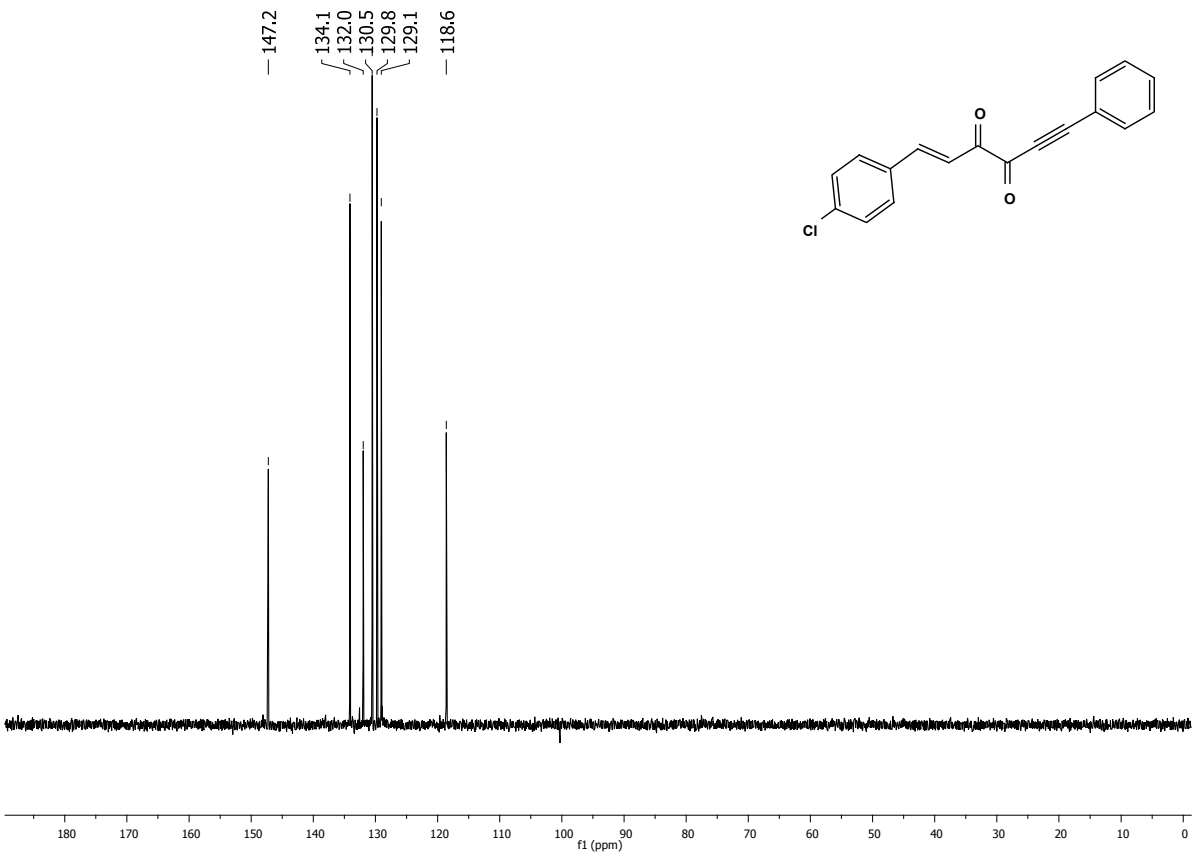
^{13}C-DEPT 135-NMR (75 MHz) of **3f** (30 mg) in $CDCl_3$ at 295 K (δ in ppm).



^{1}H-NMR (300 MHz) of **3g** (30 mg) in $CDCl_3$ at 295 K (δ in ppm). *Impurities from residual solvents.

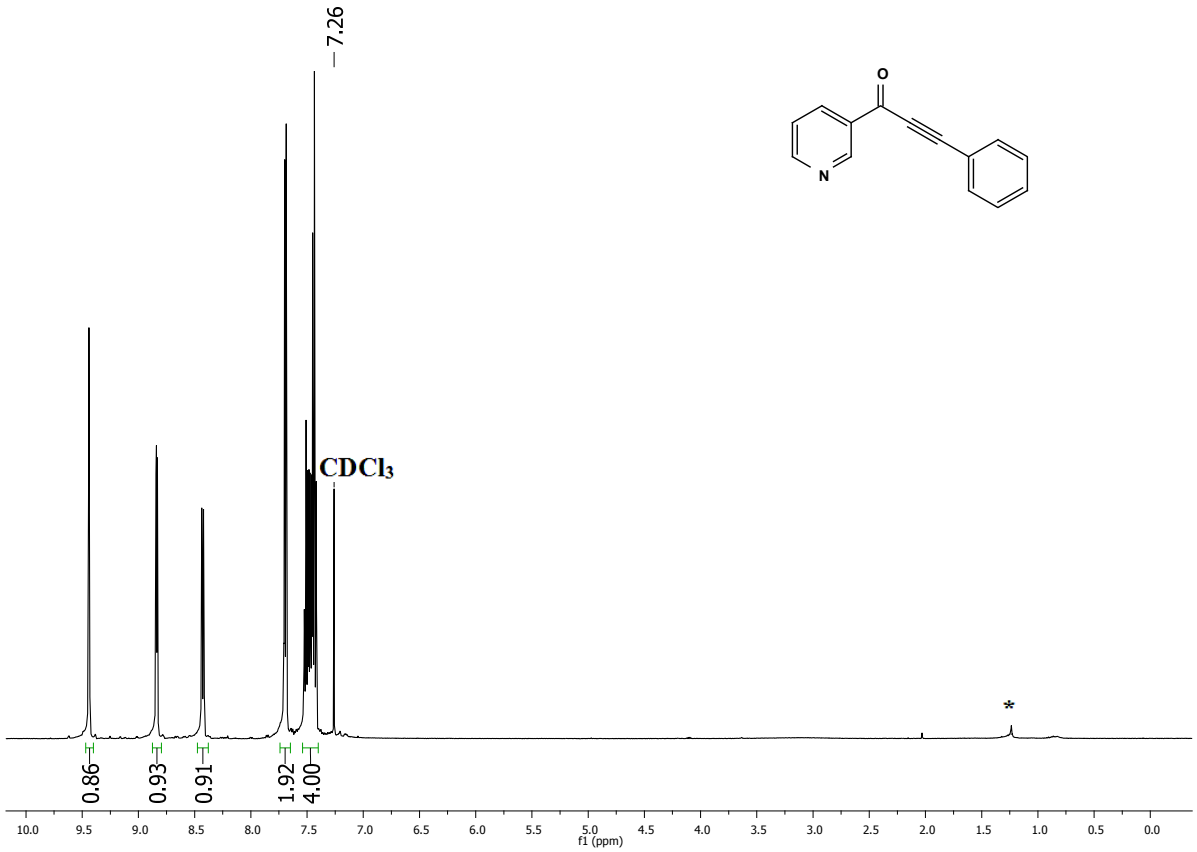


^{13}C-NMR (75 MHz) of **3g** (30 mg) in $CDCl_3$ at 296 K (δ in ppm).

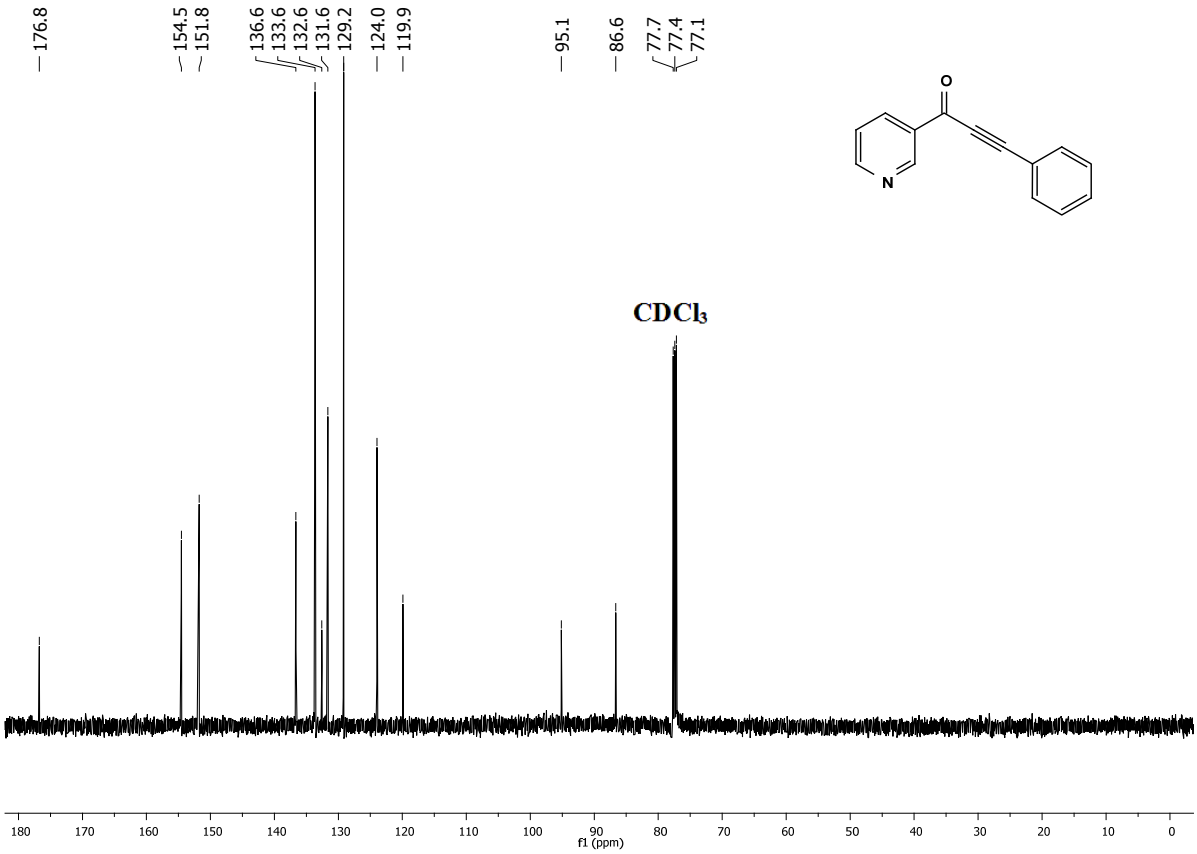


^{13}C-DEPT 135-NMR (75 MHz) of **3g** (30 mg) in $CDCl_3$ at 295 K (δ in ppm).

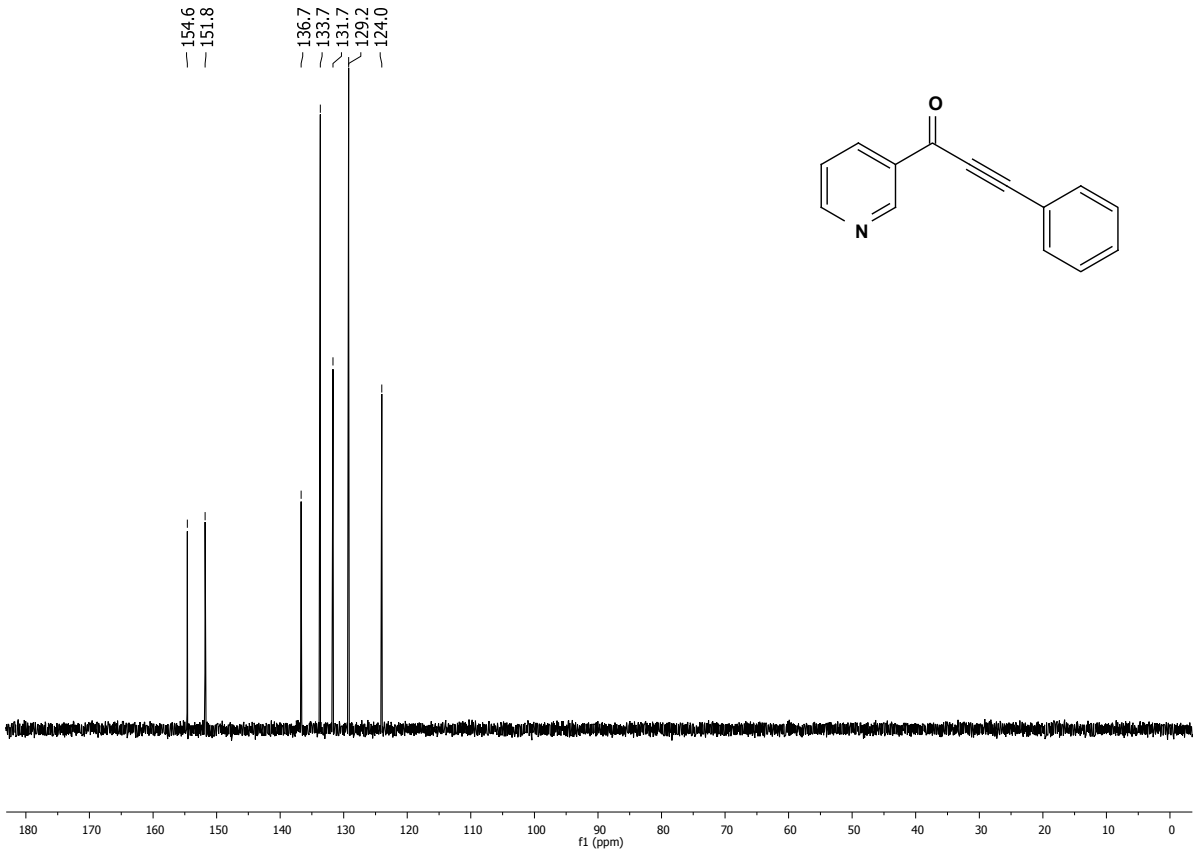
8 ^{1}H- and ^{13}C-NMR Spectra of compounds 5a-u



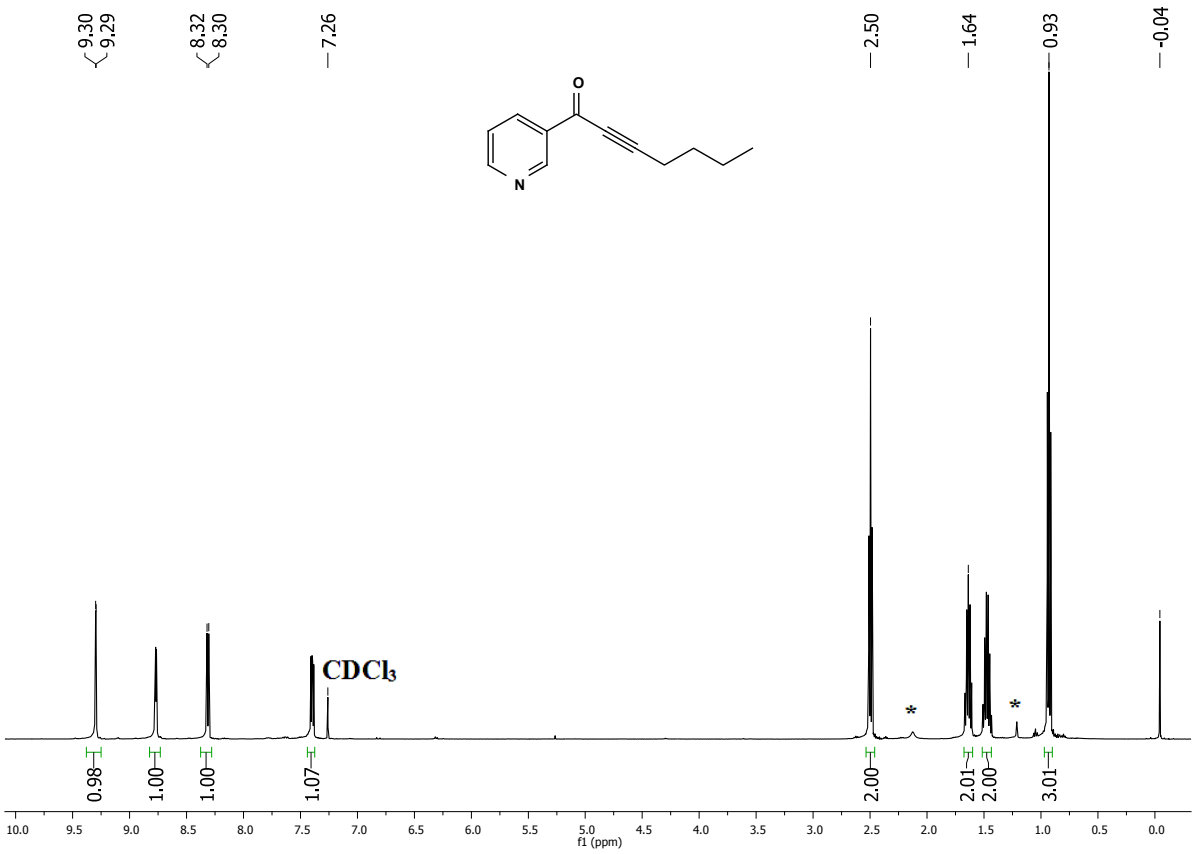
^{1}H-NMR (500 MHz) of **5a** (30 mg) in $CDCl_3$ at 296 K (δ in ppm). *Impurities from residual solvents.



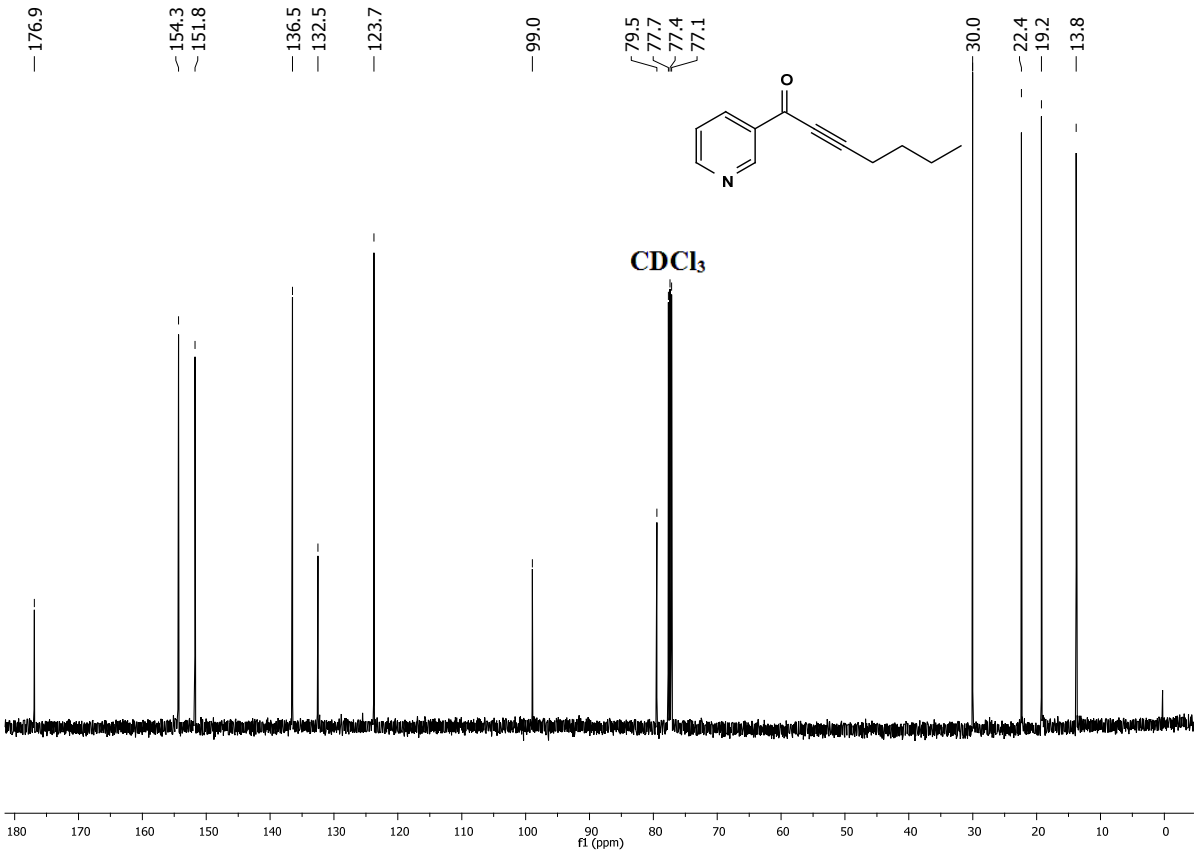
^{13}C-NMR (125 MHz) of **5a** (30 mg) in $CDCl_3$ at 296 K (δ in ppm).



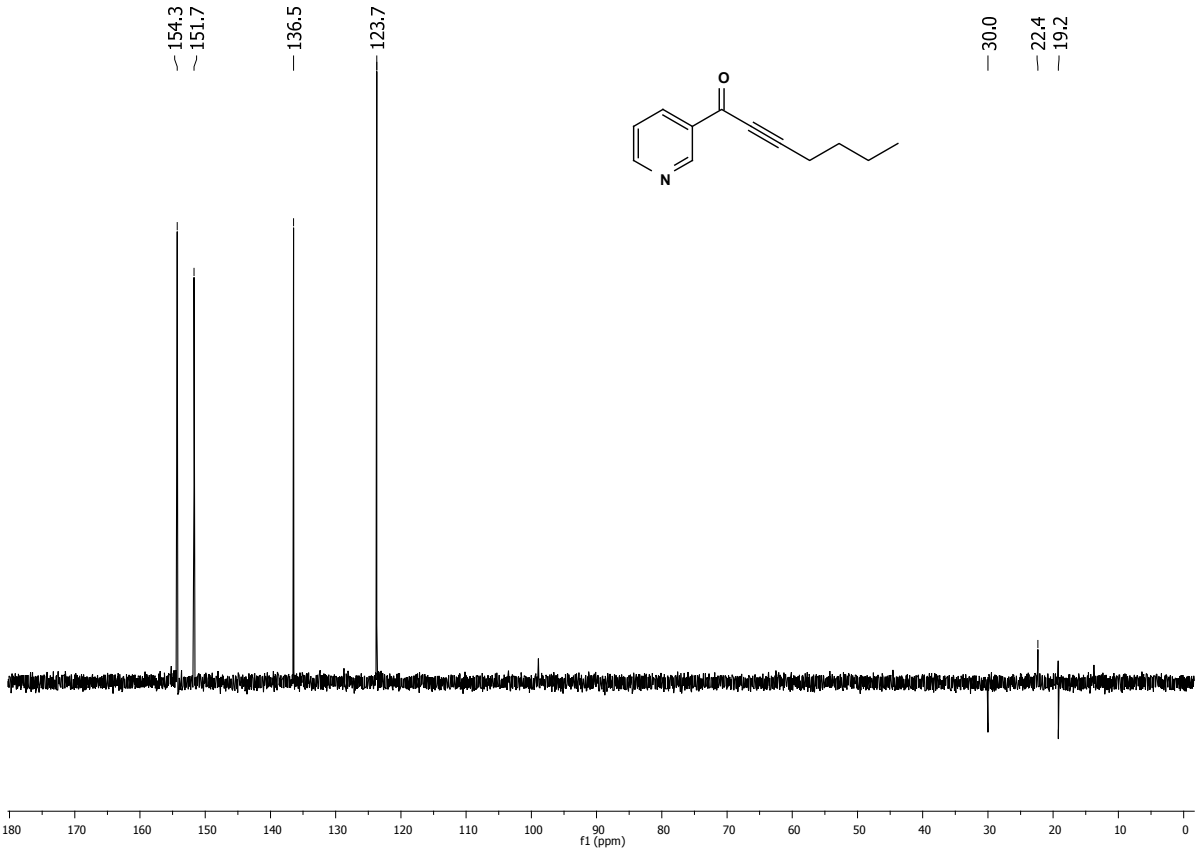
^{13}C-DEPT 135-NMR (125 MHz) of **5a** (30 mg) in $CDCl_3$ at 296 K (δ in ppm).



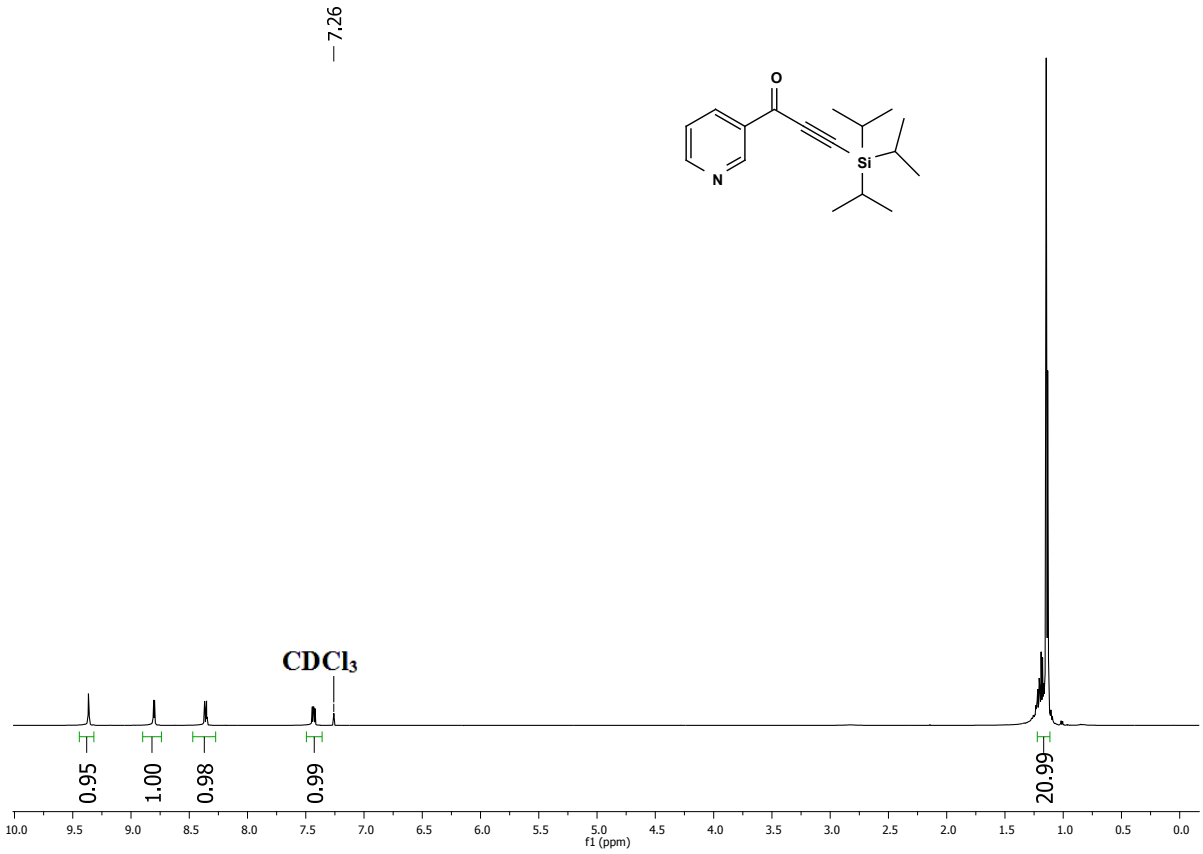
^{1}H-NMR (500 MHz) of **5b** (30 mg) in $CDCl_3$ at 299 K (δ in ppm). *Impurities from residual solvents.



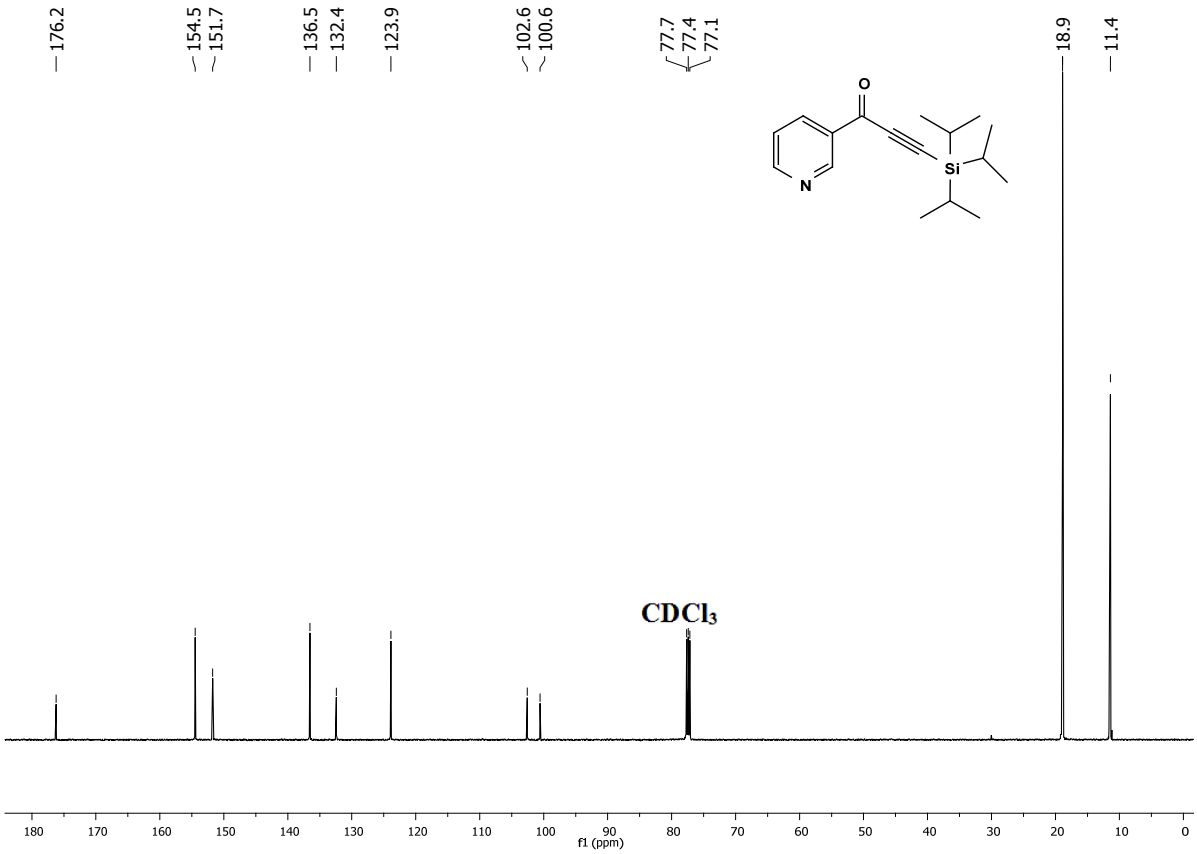
^{13}C-NMR (125 MHz) of **5b** (30 mg) in $CDCl_3$ at 299 K (δ in ppm).



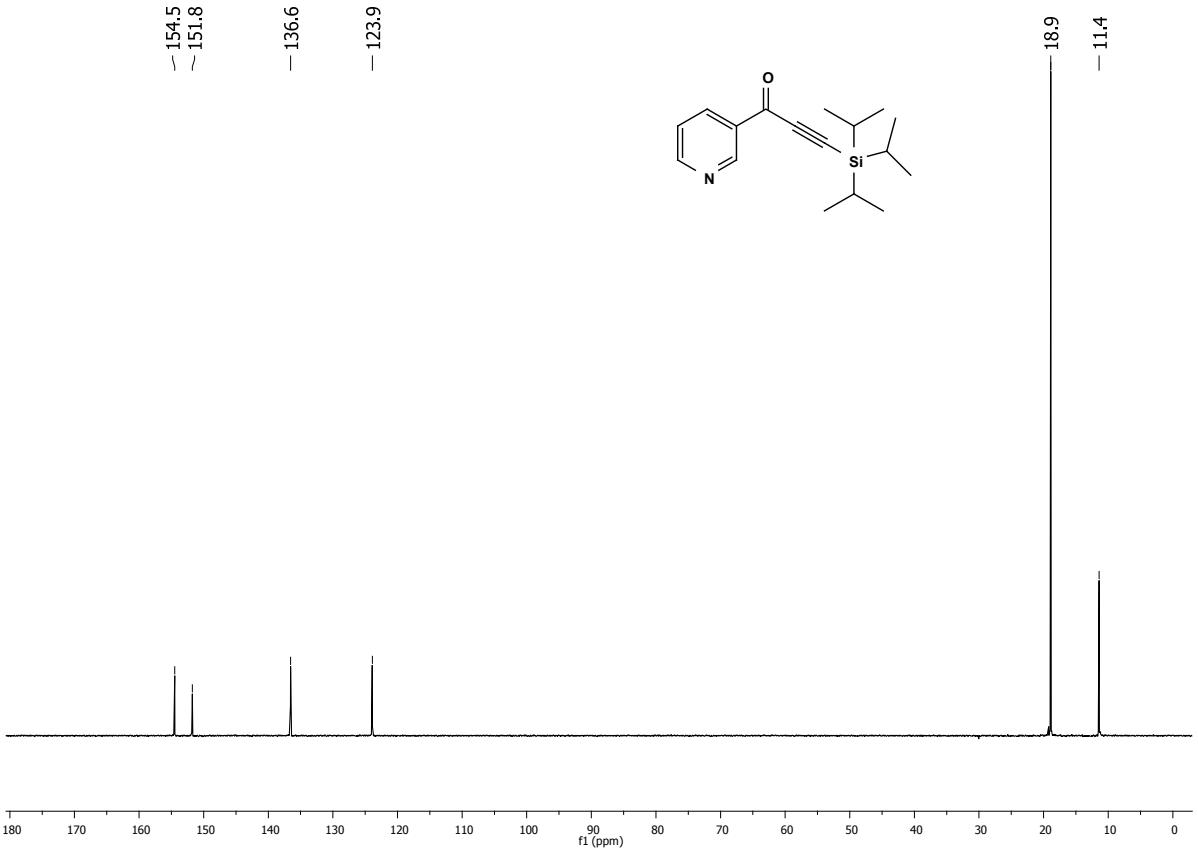
^{13}C-DEPT 135-NMR (125 MHz) of **5b** (30 mg) in $CDCl_3$ at 299 K (δ in ppm).



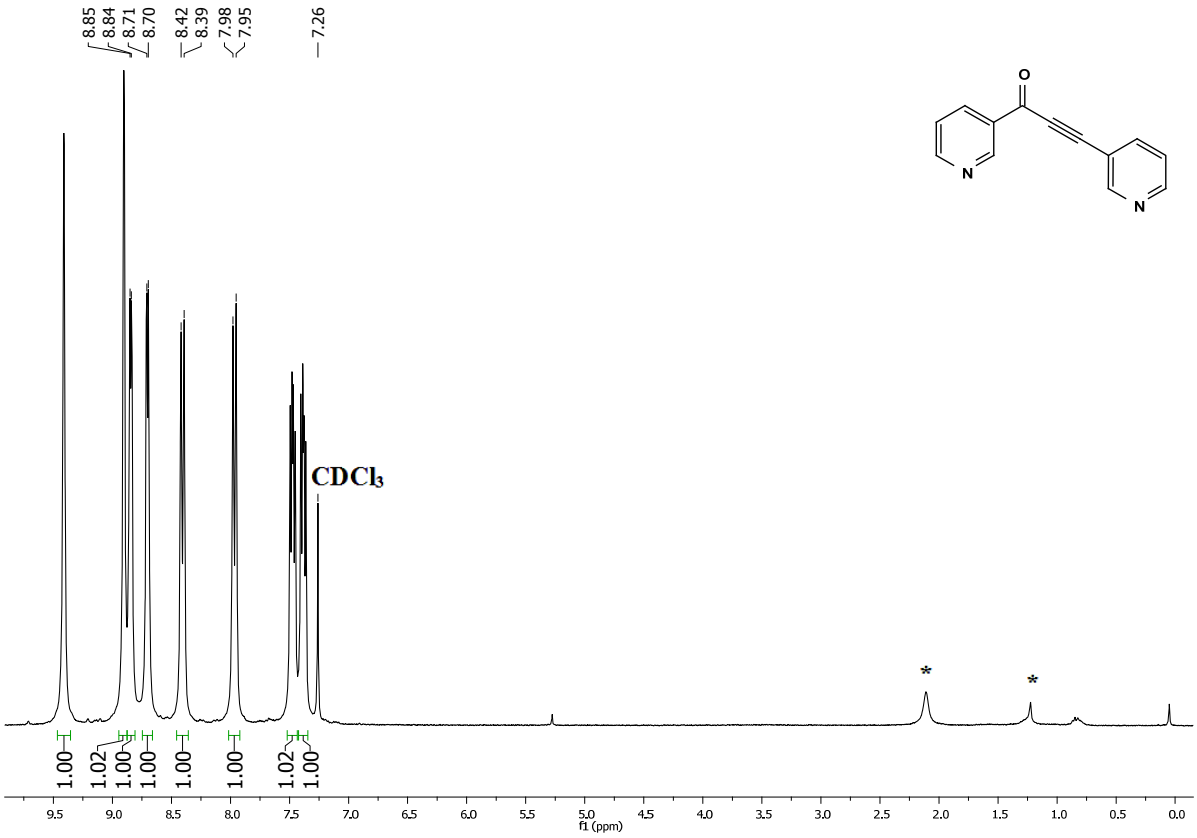
^{1}H-NMR (300 MHz) of **5c** (30 mg) in $CDCl_3$ at 298 K (δ in ppm).



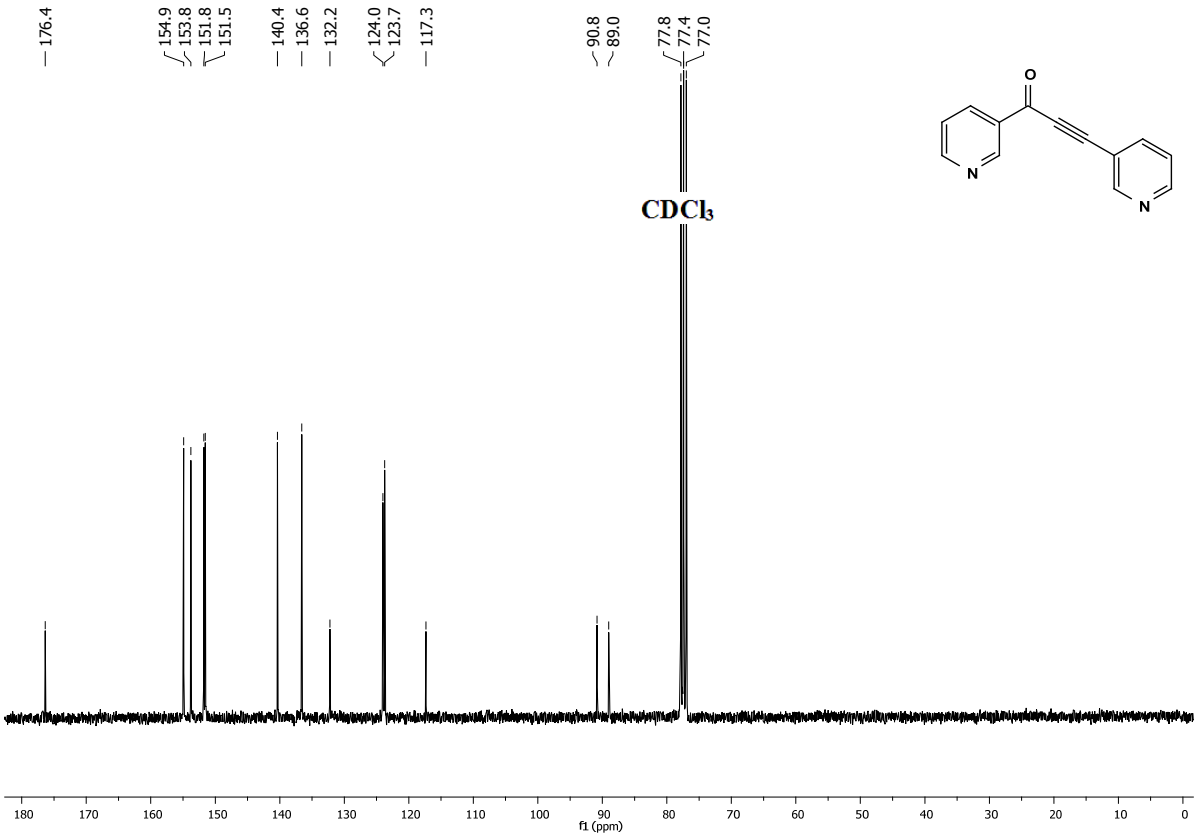
^{13}C-NMR (75 MHz) of **5c** (30 mg) in $CDCl_3$ at 298 K (δ in ppm).



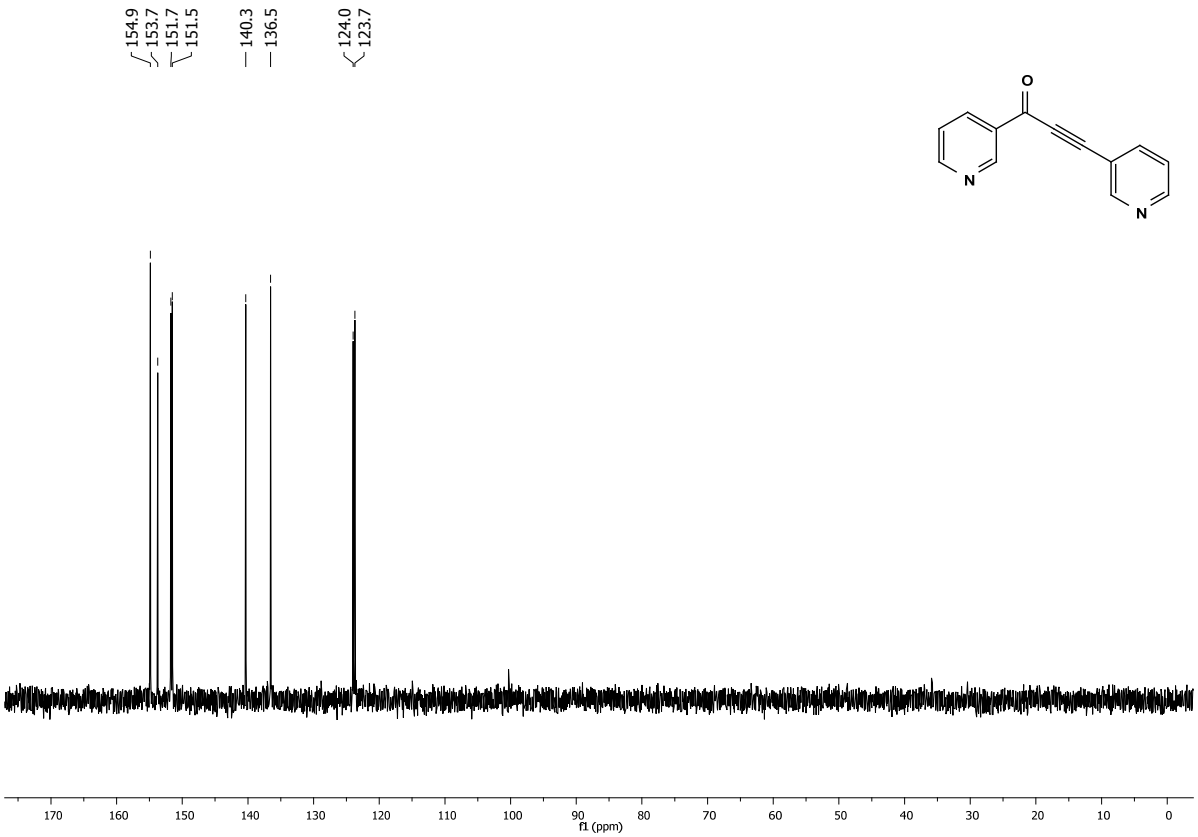
^{13}C-DEPT 135-NMR (75 MHz) of **5c** (30 mg) in $CDCl_3$ at 298 K (δ in ppm).



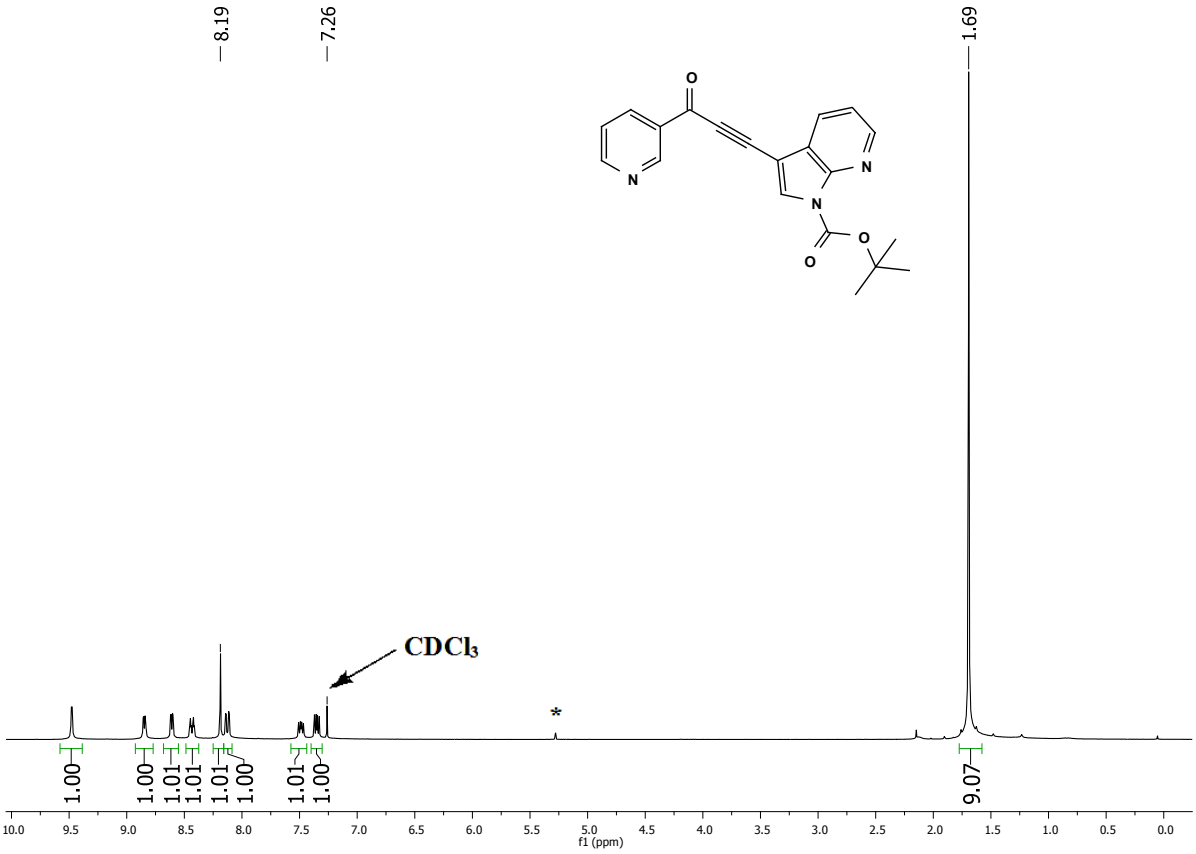
^{1}H-NMR (300 MHz) of **5d** (30 mg) in $CDCl_3$ at 298 K (δ in ppm). *Impurities from residual solvents.



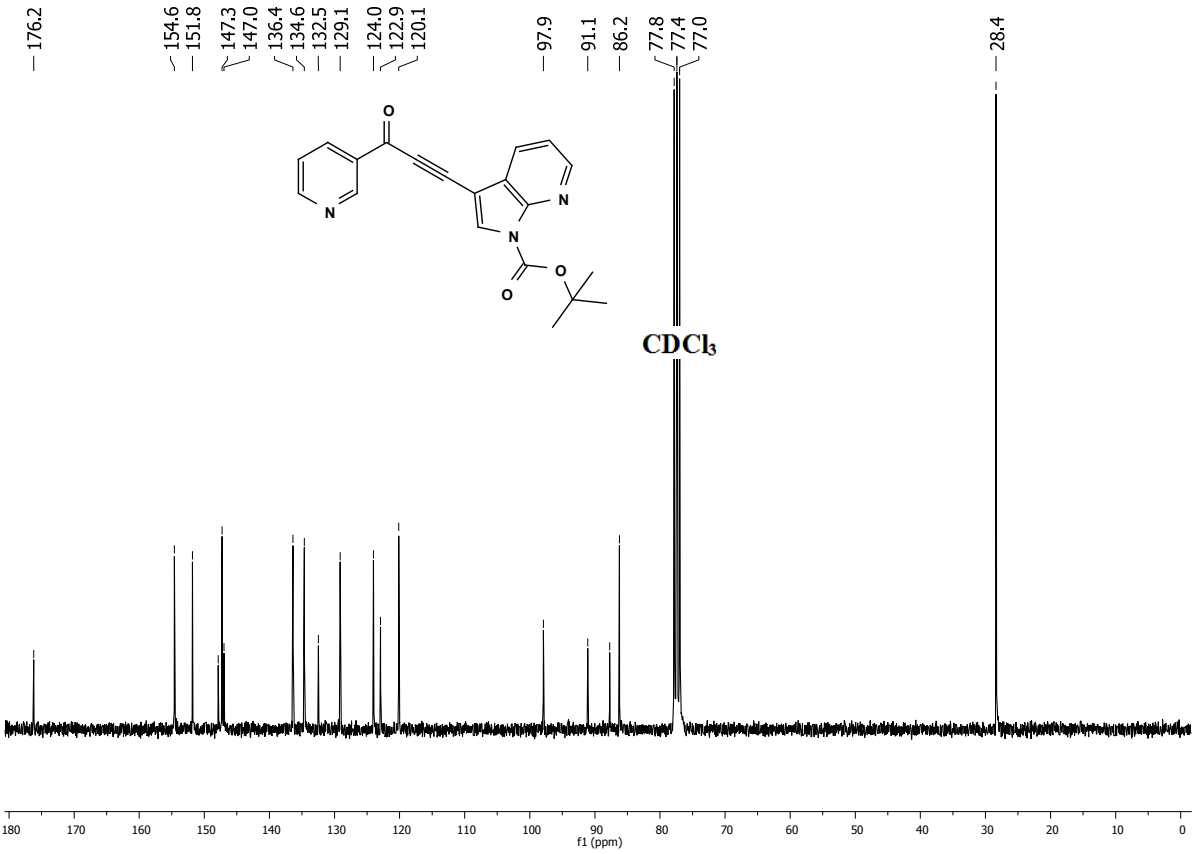
^{13}C-NMR (75 MHz) of **5d** (30 mg) in $CDCl_3$ at 298 K (δ in ppm).



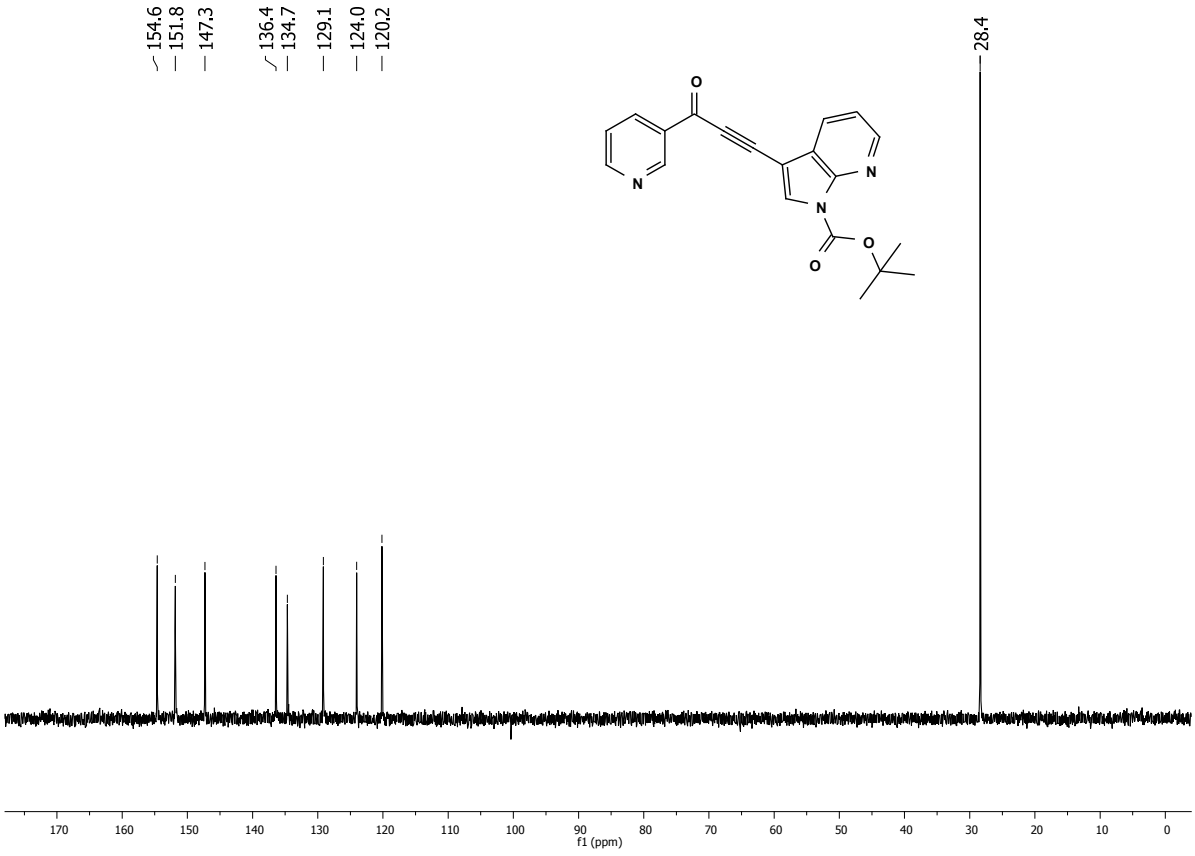
^{13}C-DEPT 135-NMR (75 MHz) of **5d** (30 mg) in $CDCl_3$ at 298 K (δ in ppm).



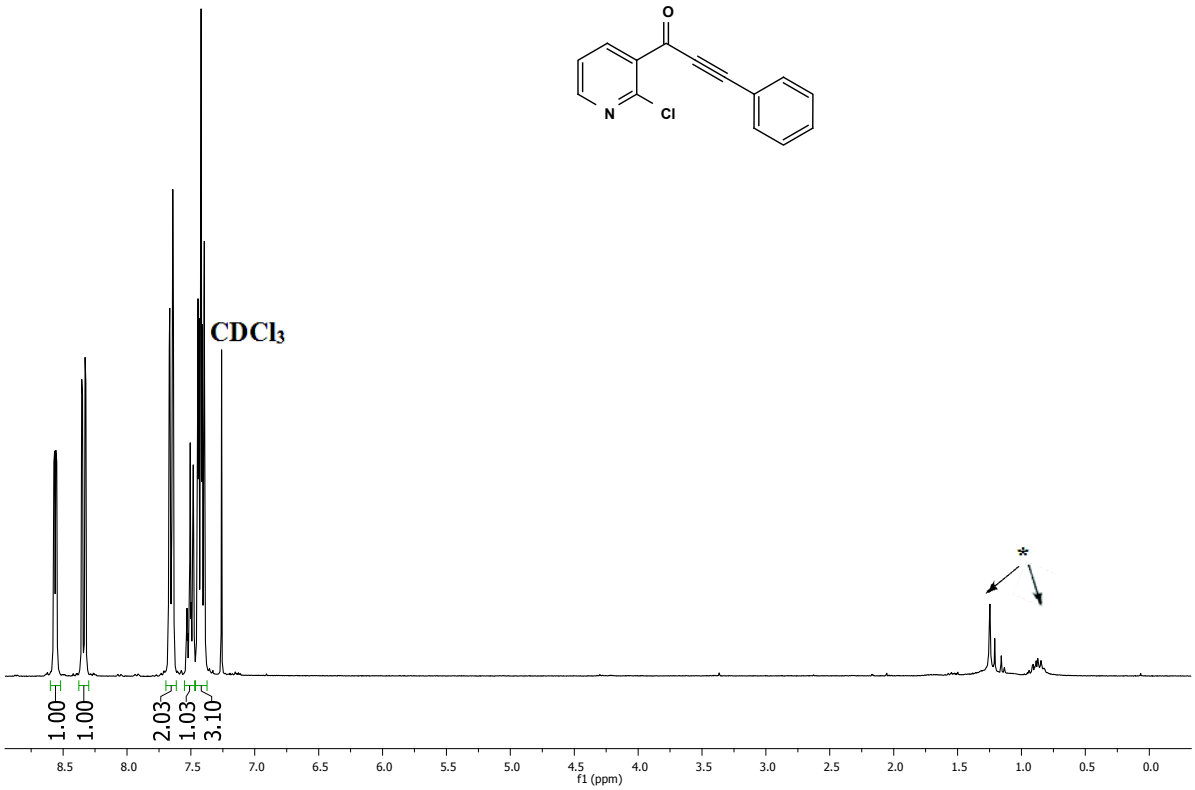
^{1}H-NMR (300 MHz) of **5e** (30 mg) in $CDCl_3$ at 298 K (δ in ppm). *Impurities from residual solvents.



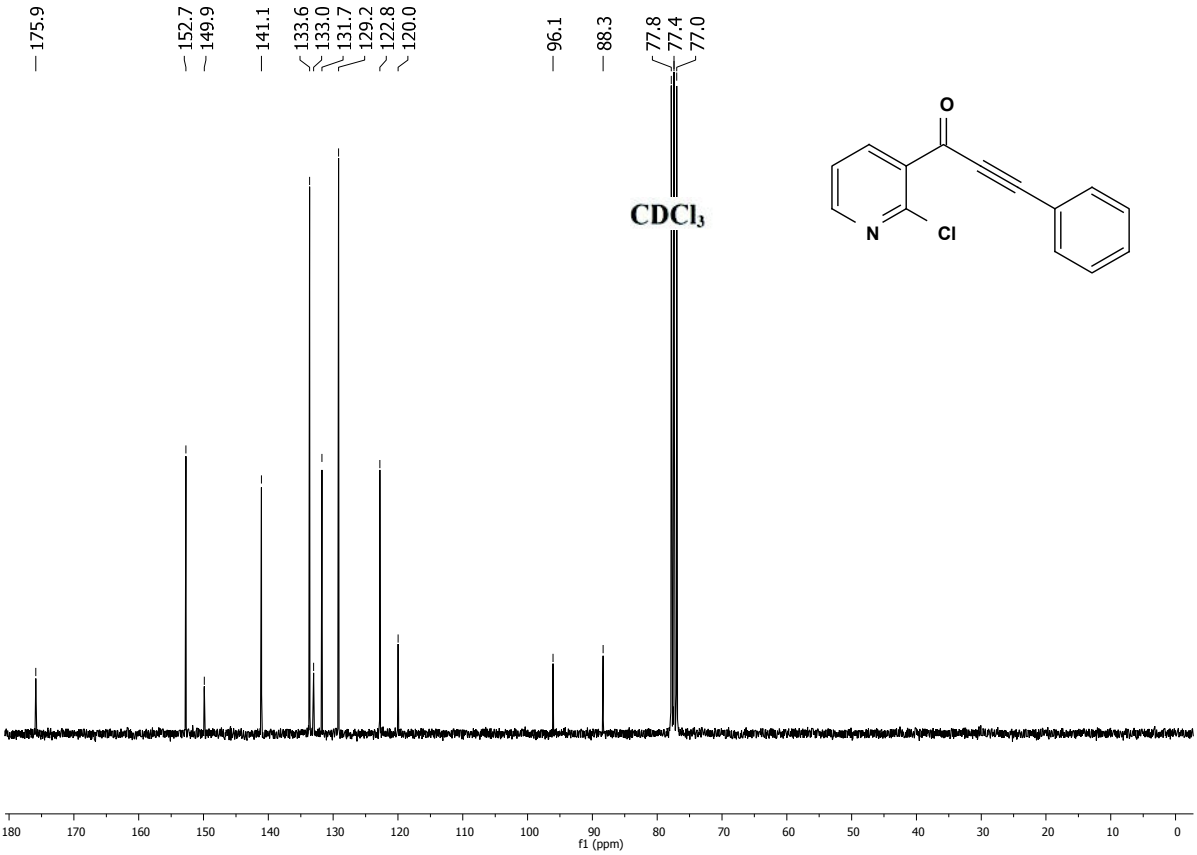
^{13}C-NMR (75 MHz) of **5e** (30 mg) in $CDCl_3$ at 298 K (δ in ppm).



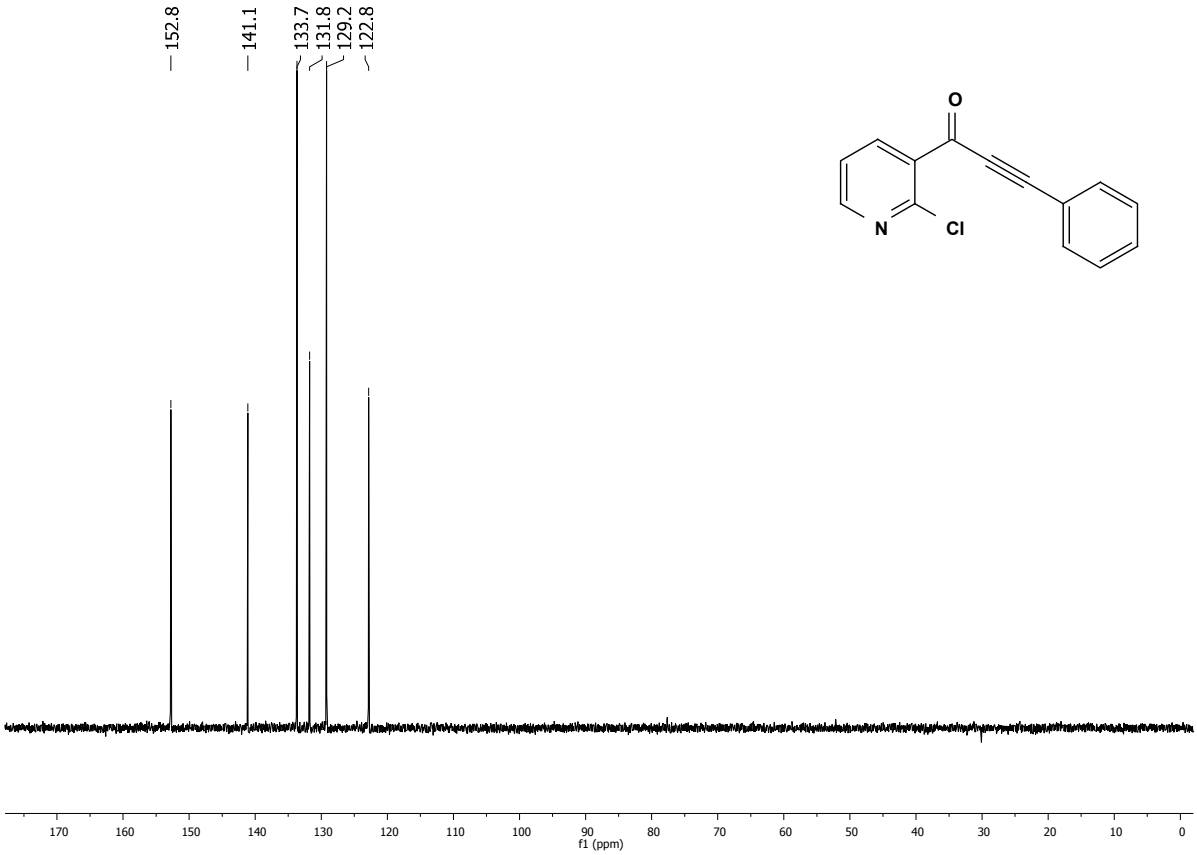
^{13}C-DEPT 135-NMR (75 MHz) of **5e** (30 mg) in $CDCl_3$ at 298 K (δ in ppm).



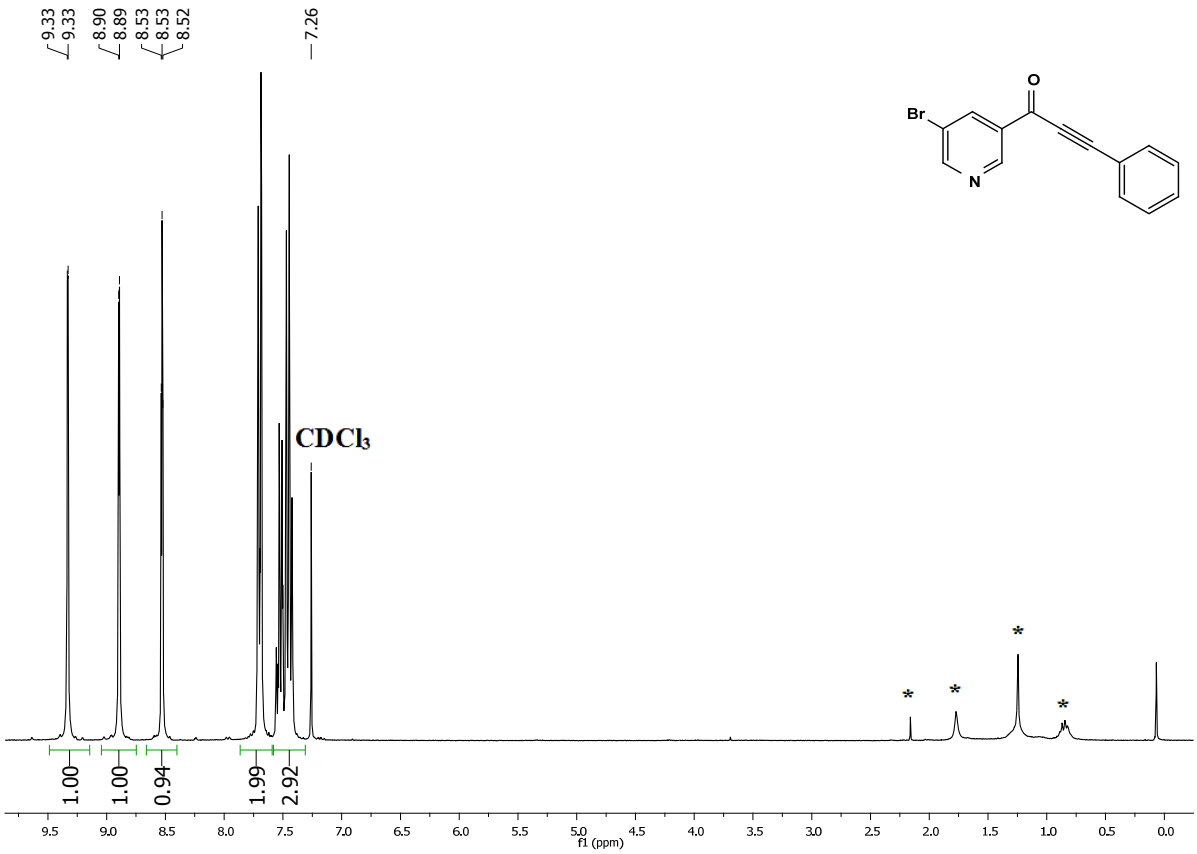
^{1}H-NMR (300 MHz) of **5f** (30 mg) in $CDCl_3$ at 298 K (δ in ppm). *Impurities from residual solvents.



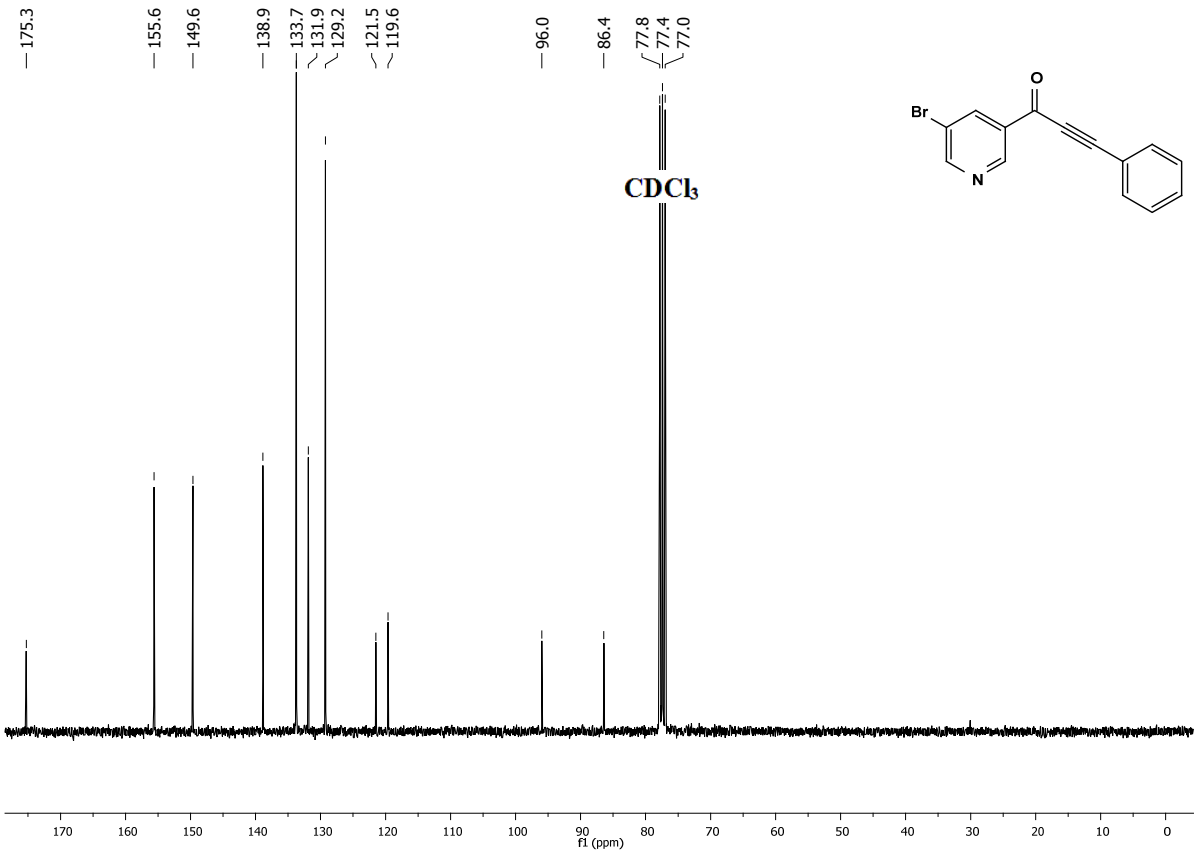
^{13}C-NMR (75 MHz) of **5f** (30 mg) in $CDCl_3$ at 298 K (δ in ppm).



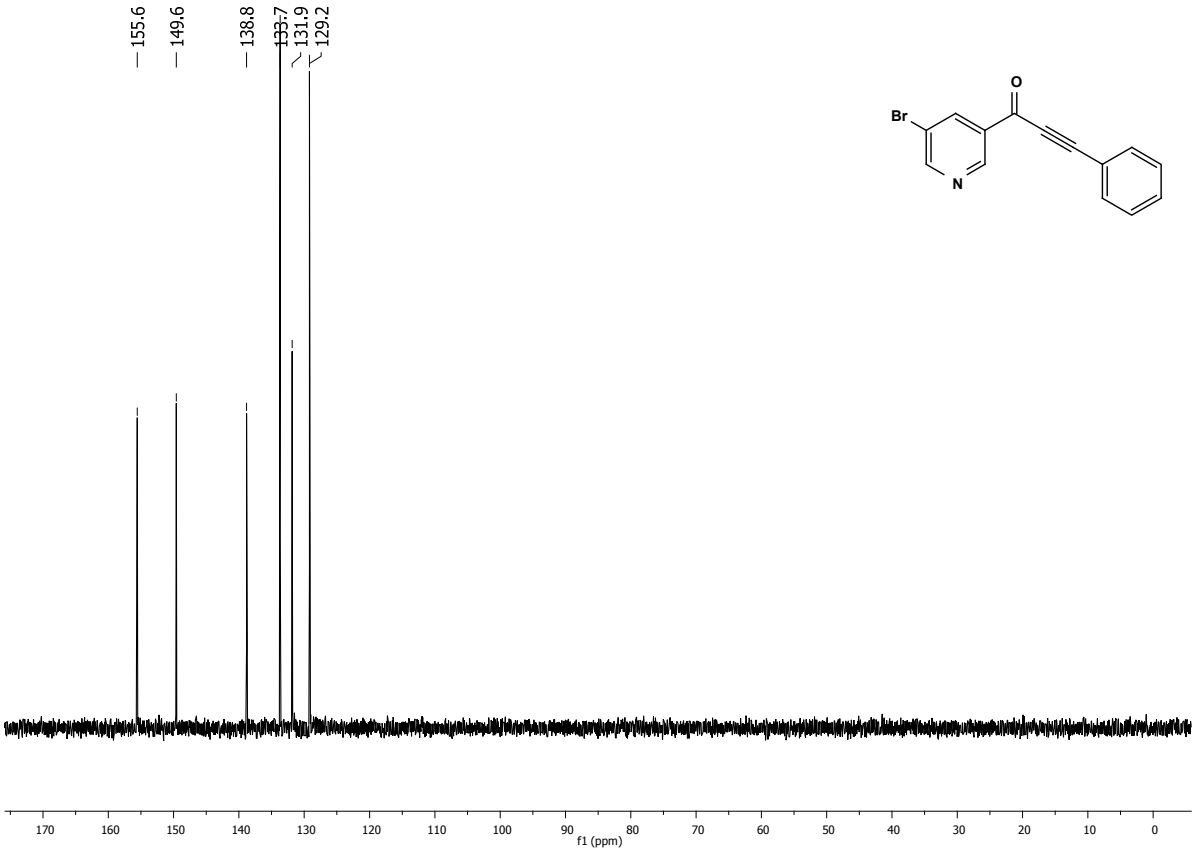
^{13}C-DEPT 135-NMR (75 MHz) of **5f** (30 mg) in $CDCl_3$ at 298 K (δ in ppm).



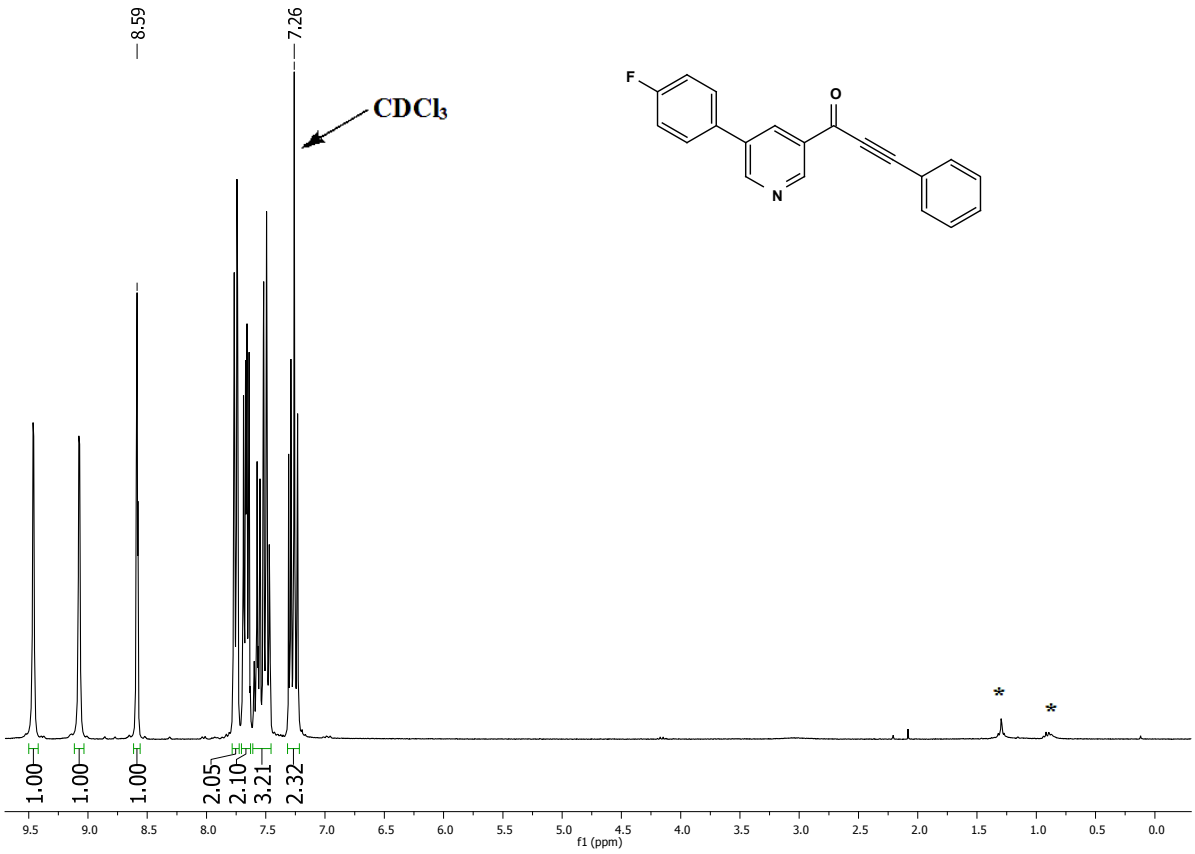
^{1}H-NMR (300 MHz) of **5g** (30 mg) in $CDCl_3$ at 298 K (δ in ppm). *Impurities from residual solvents.



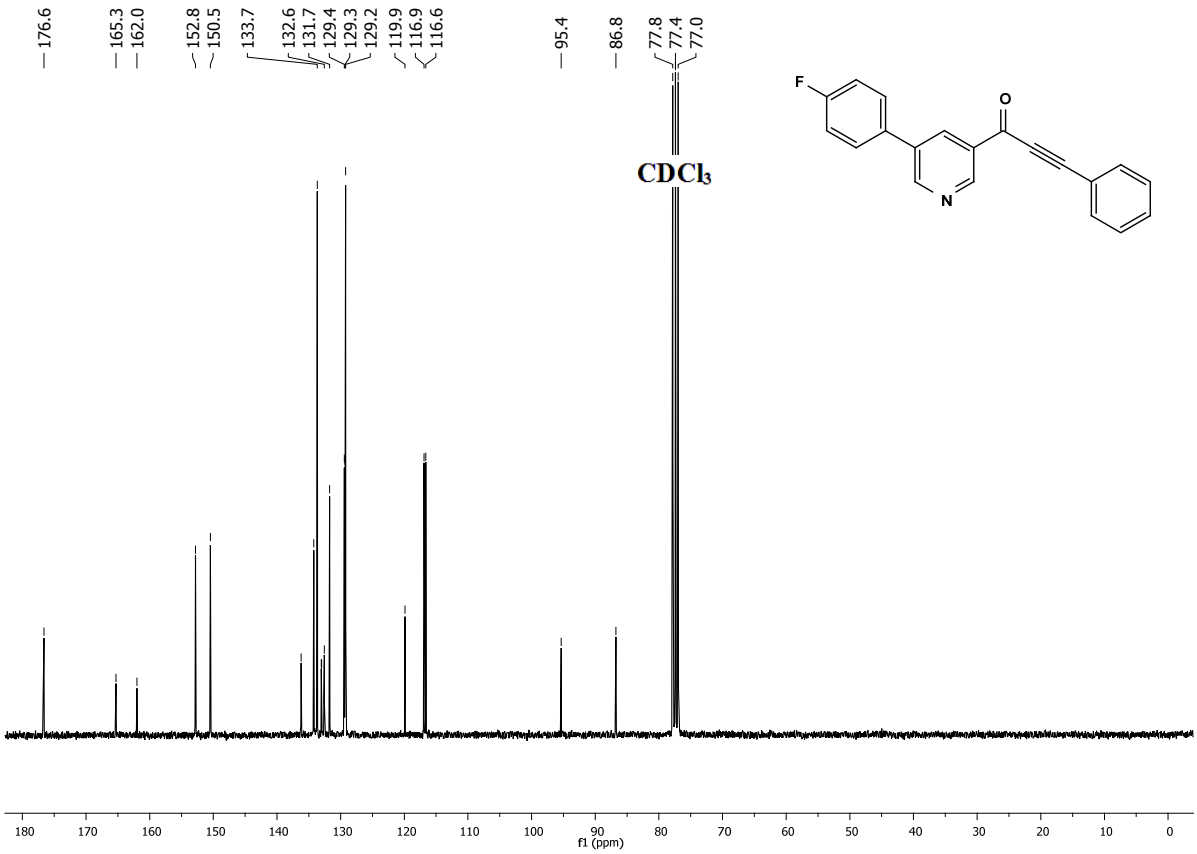
^{13}C-NMR (75 MHz) of **5g** (30 mg) in $CDCl_3$ at 298 K (δ in ppm).



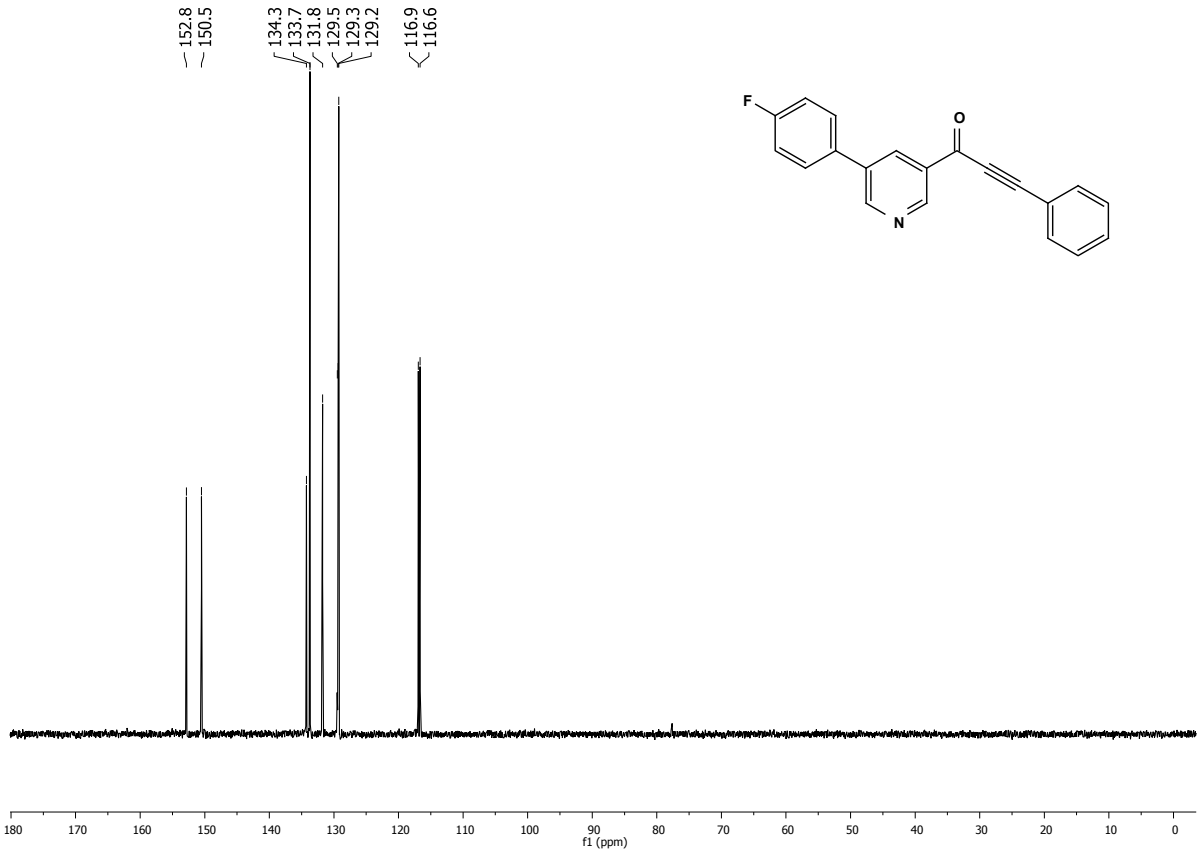
^{13}C-DEPT 135-NMR (75 MHz) of **5g** (30 mg) in $CDCl_3$ at 298 K (δ in ppm).



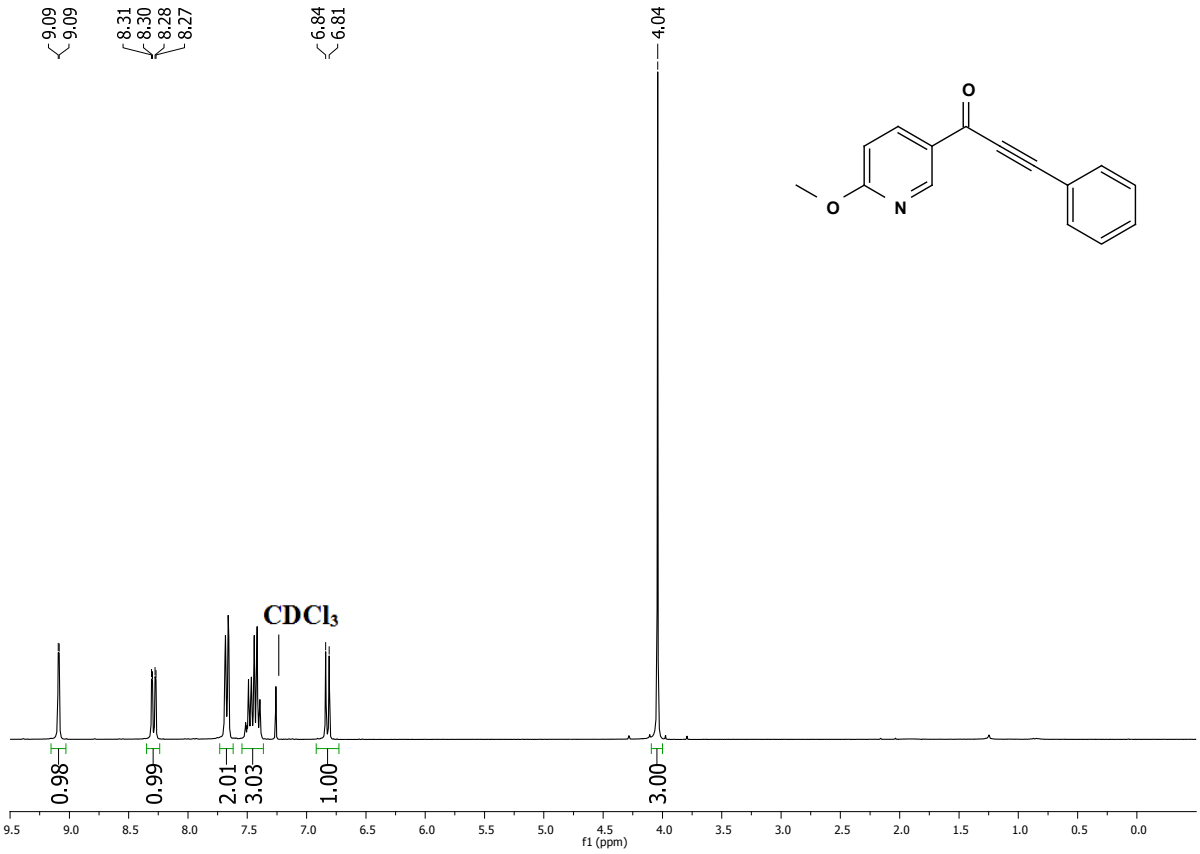
^{1}H-NMR (300 MHz) of **5h** (30 mg) in $CDCl_3$ at 298 K (δ in ppm). *Impurities from residual solvents.



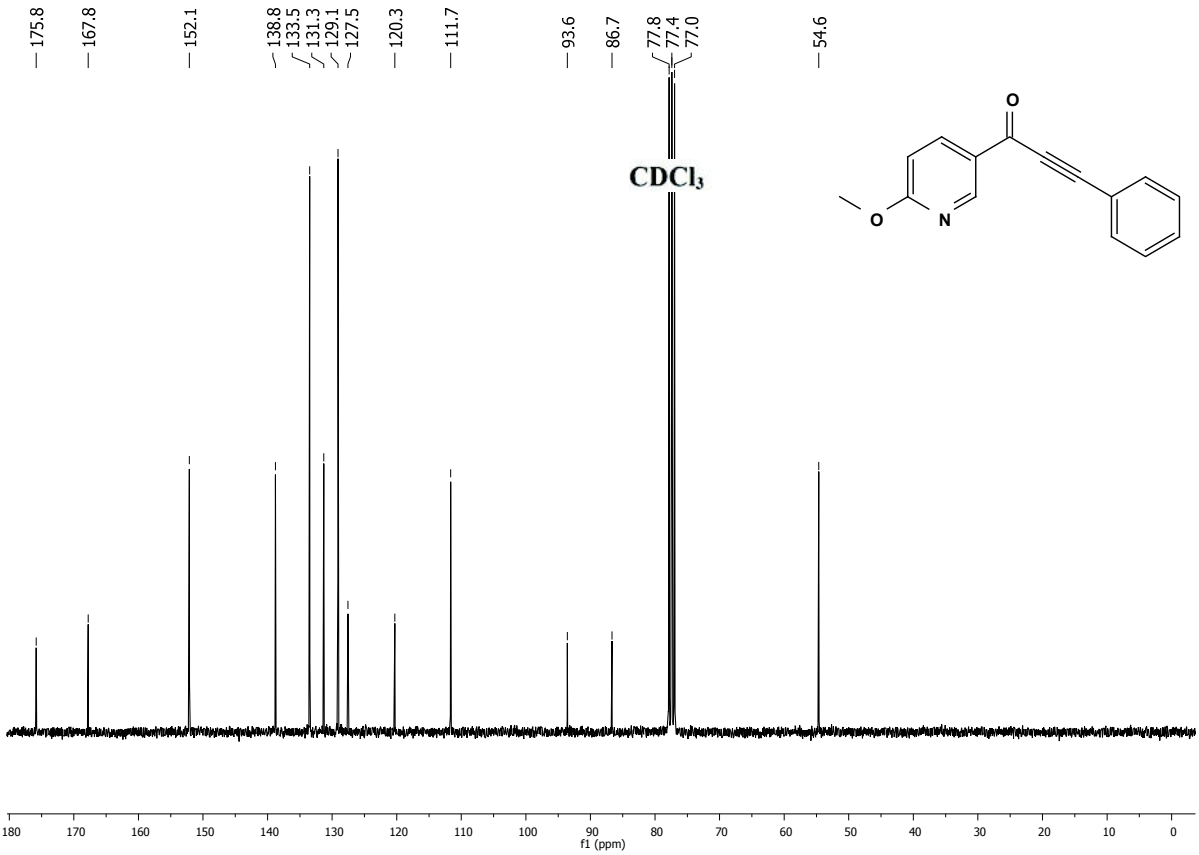
^{13}C-NMR (75 MHz) of **5h** (30 mg) in $CDCl_3$ at 298 K (δ in ppm).



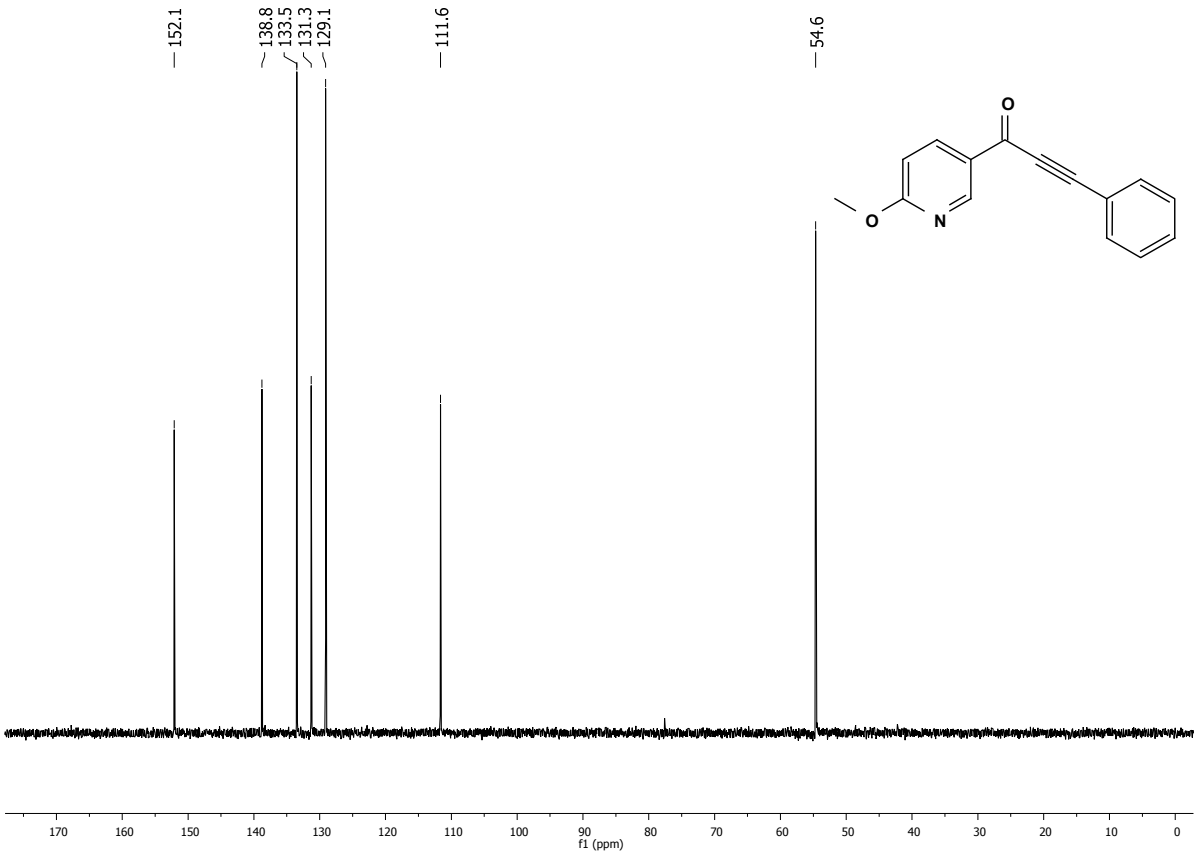
^{13}C-DEPT 135-NMR (75 MHz) of **5h** (30 mg) in $CDCl_3$ at 298 K (δ in ppm).



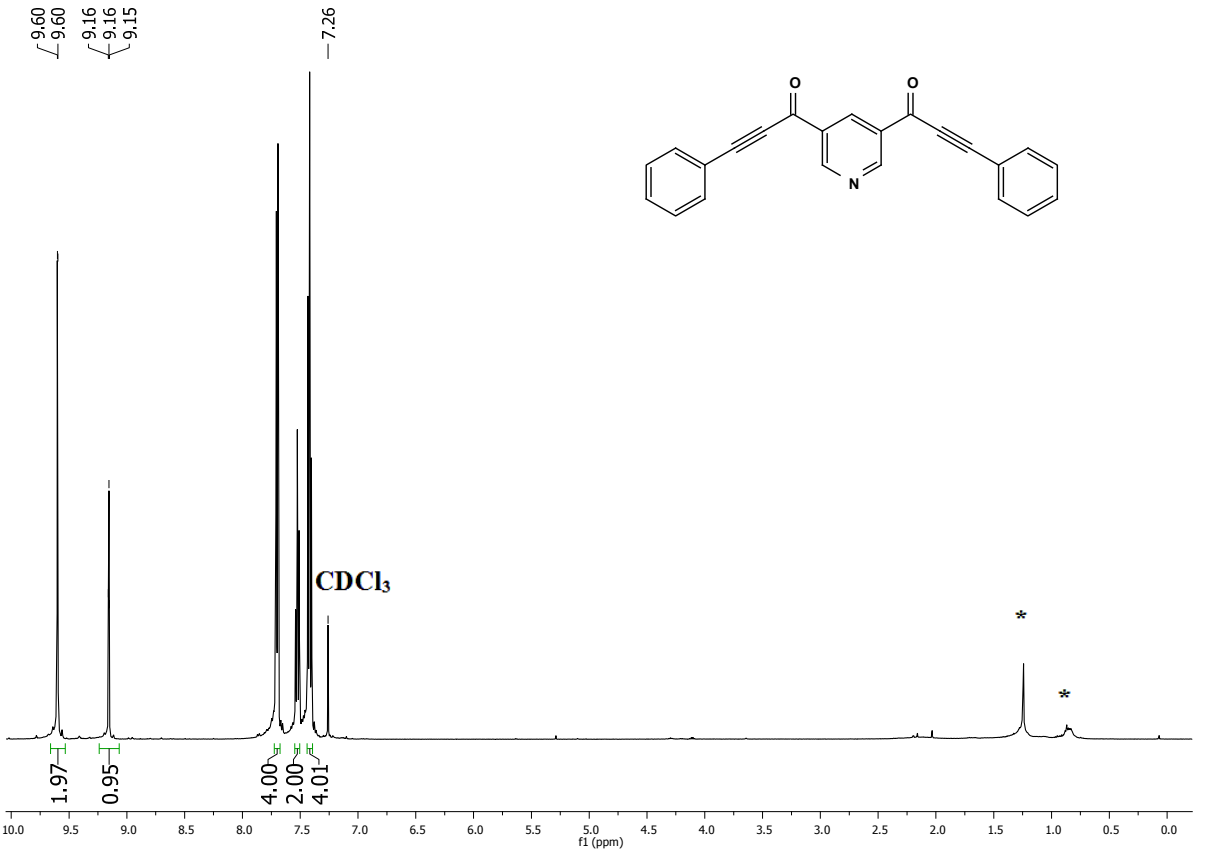
^{1}H-NMR (300 MHz) of **5i** (30 mg) in $CDCl_3$ at 298 K (δ in ppm).



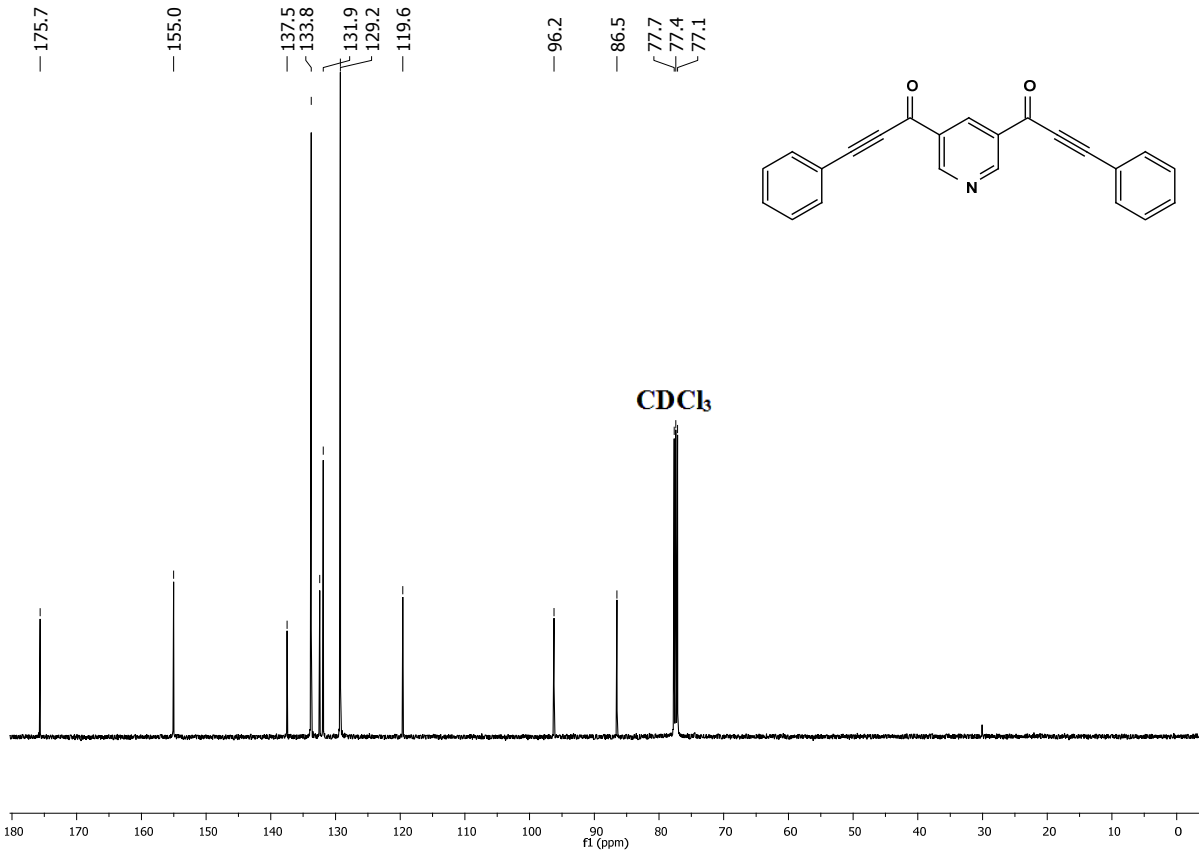
^{13}C-NMR (75 MHz) of **5i** (30 mg) in $CDCl_3$ at 298 K (δ in ppm).



^{13}C-DEPT 135-NMR (75 MHz) of **5i** (30 mg) in $CDCl_3$ at 298 K (δ in ppm).

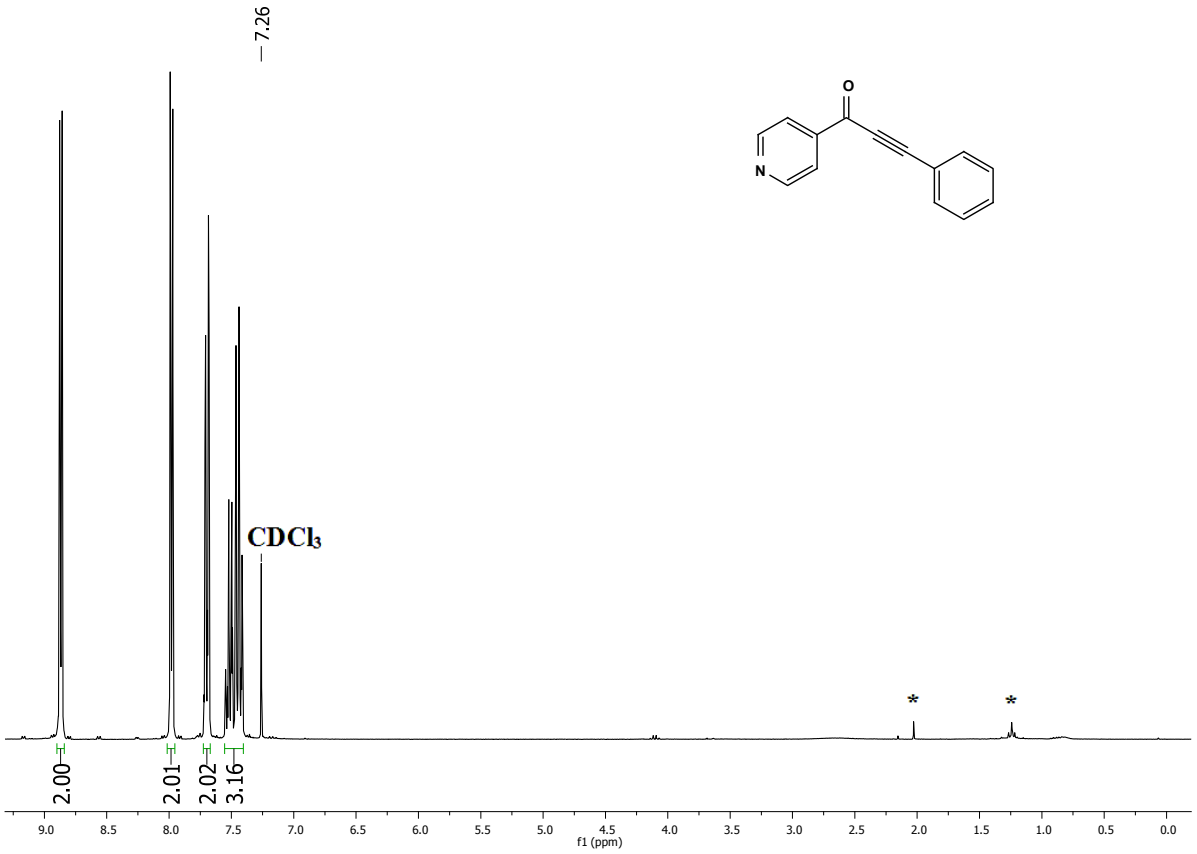


^{1}H-NMR (500 MHz) of **5j** (30 mg) in $CDCl_3$ at 298 K (δ in ppm). *Impurities from residual solvents.

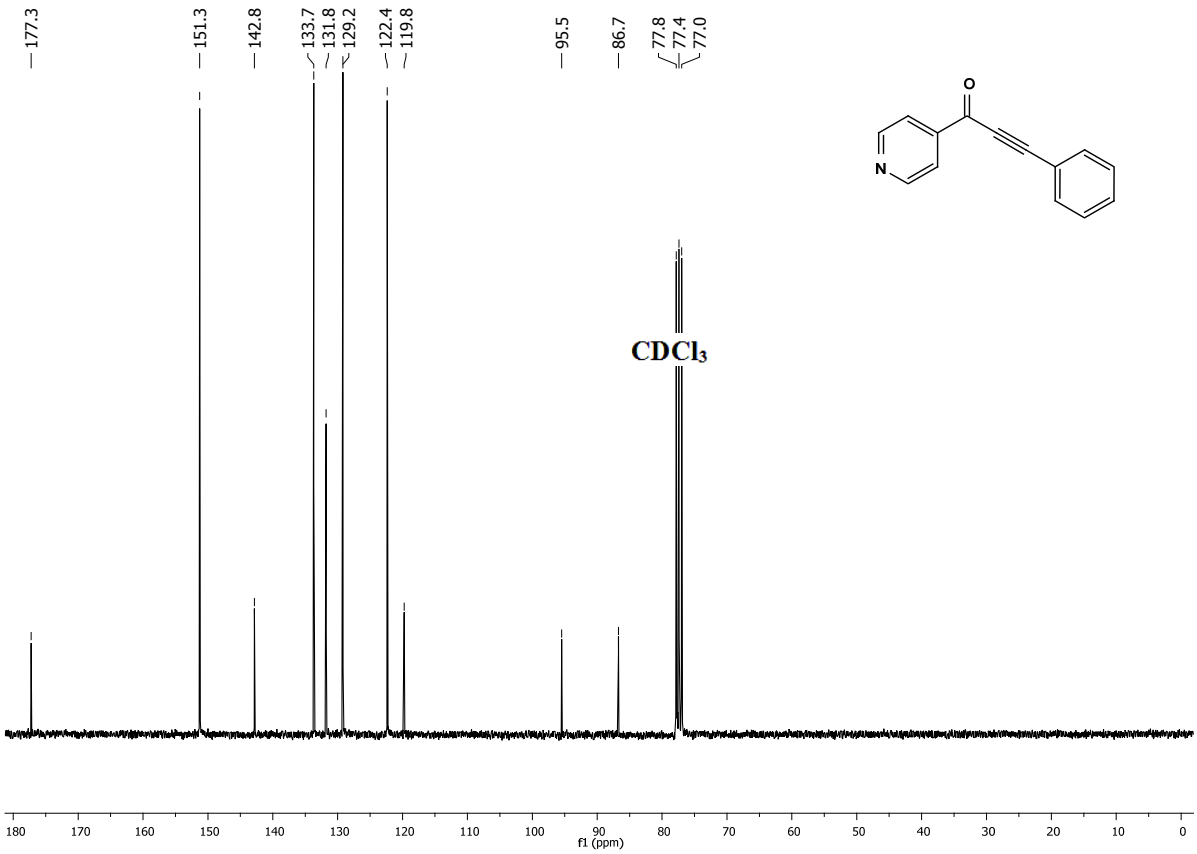


^{13}C-NMR (125 MHz) of **5j** (30 mg) in $CDCl_3$ at 298 K (δ in ppm).

^{13}C-DEPT 135-NMR (125 MHz) of **5j** (30 mg) in $CDCl_3$ at 298 K (δ in ppm).

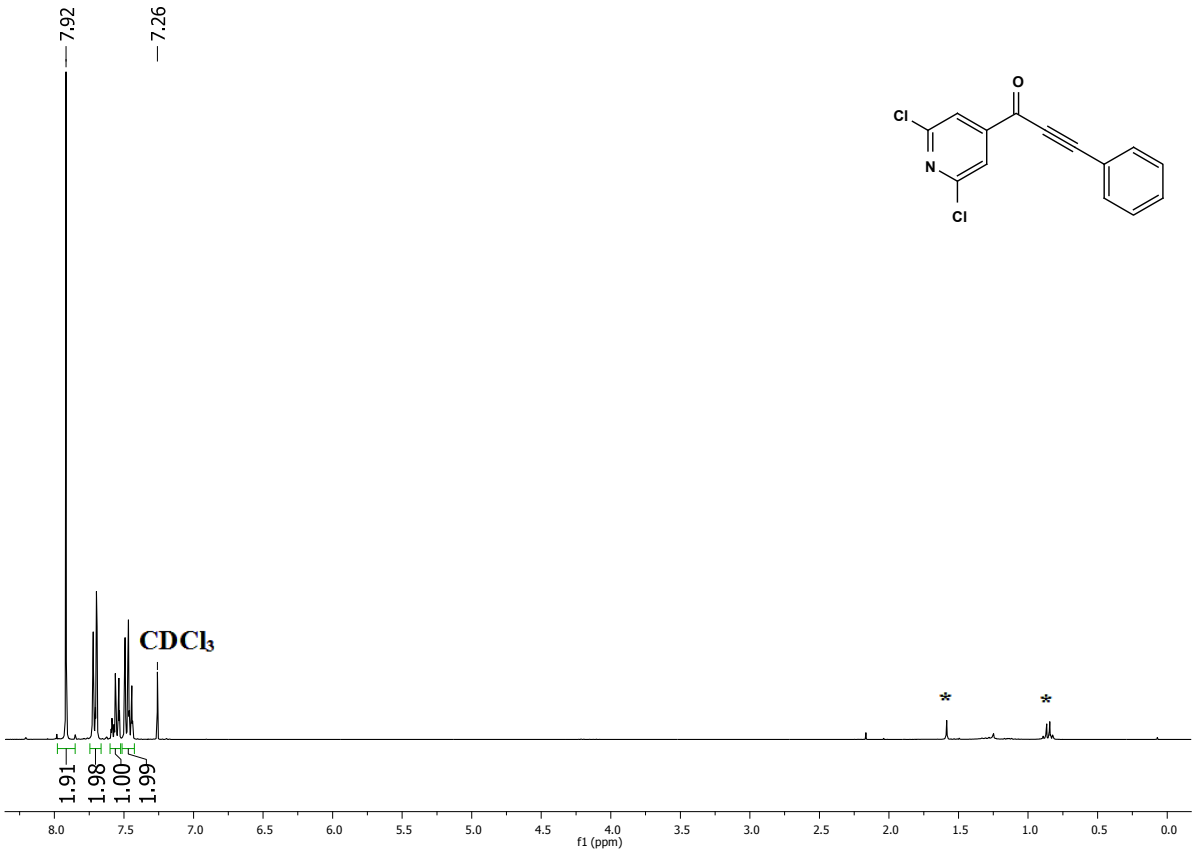


^{1}H-NMR (300 MHz) of **5k** (30 mg) in $CDCl_3$ at 297 K (δ in ppm). *Impurities from residual solvents.

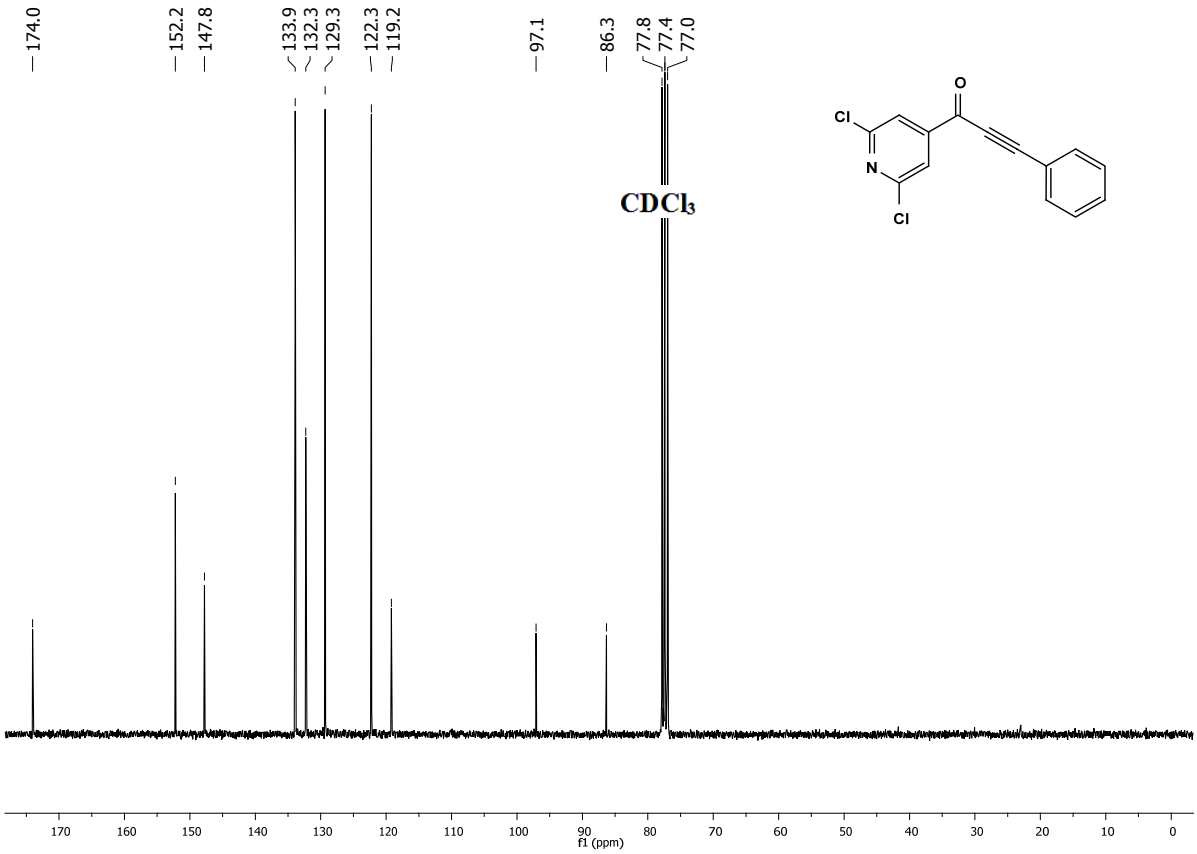


^{13}C-NMR (75 MHz) of **5k** (30 mg) in $CDCl_3$ at 297 K (δ in ppm).

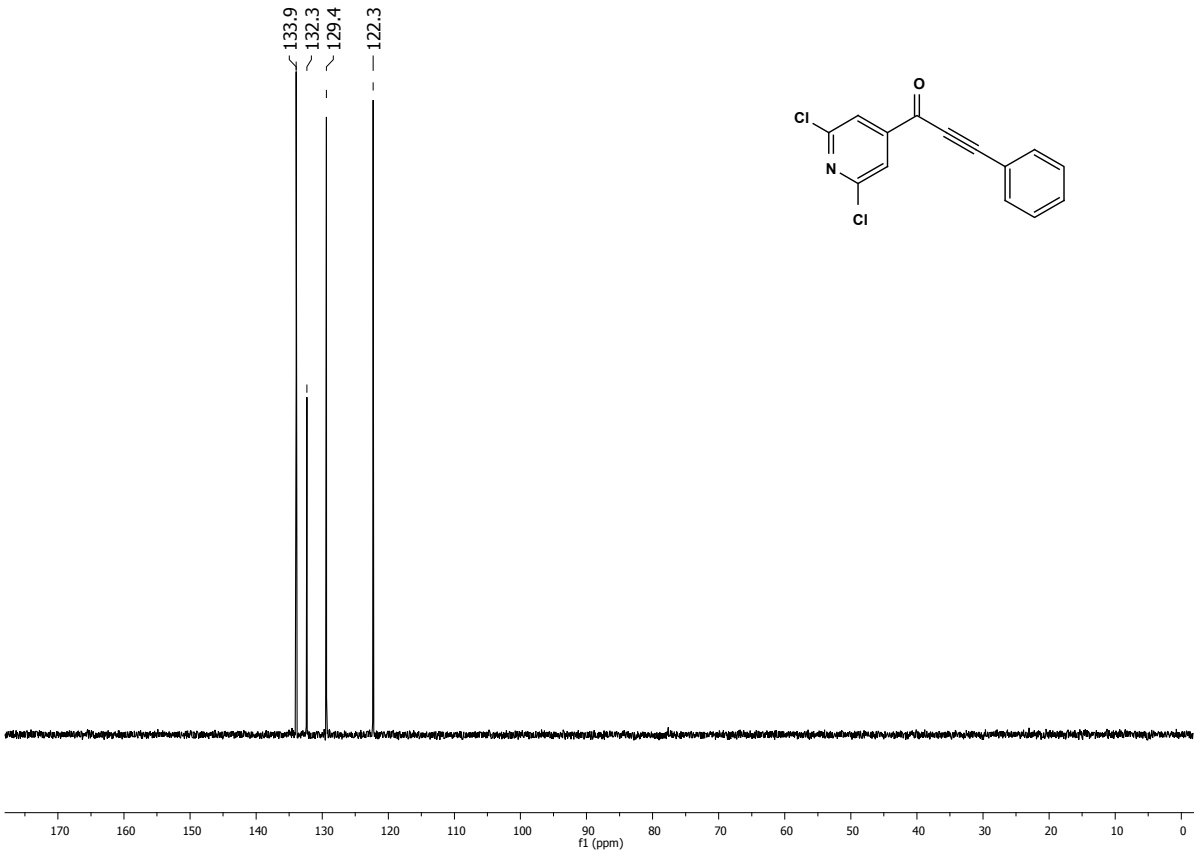
^{13}C-DEPT 135-NMR (75 MHz) of **5k** (30 mg) in $CDCl_3$ at 297 K (δ in ppm).



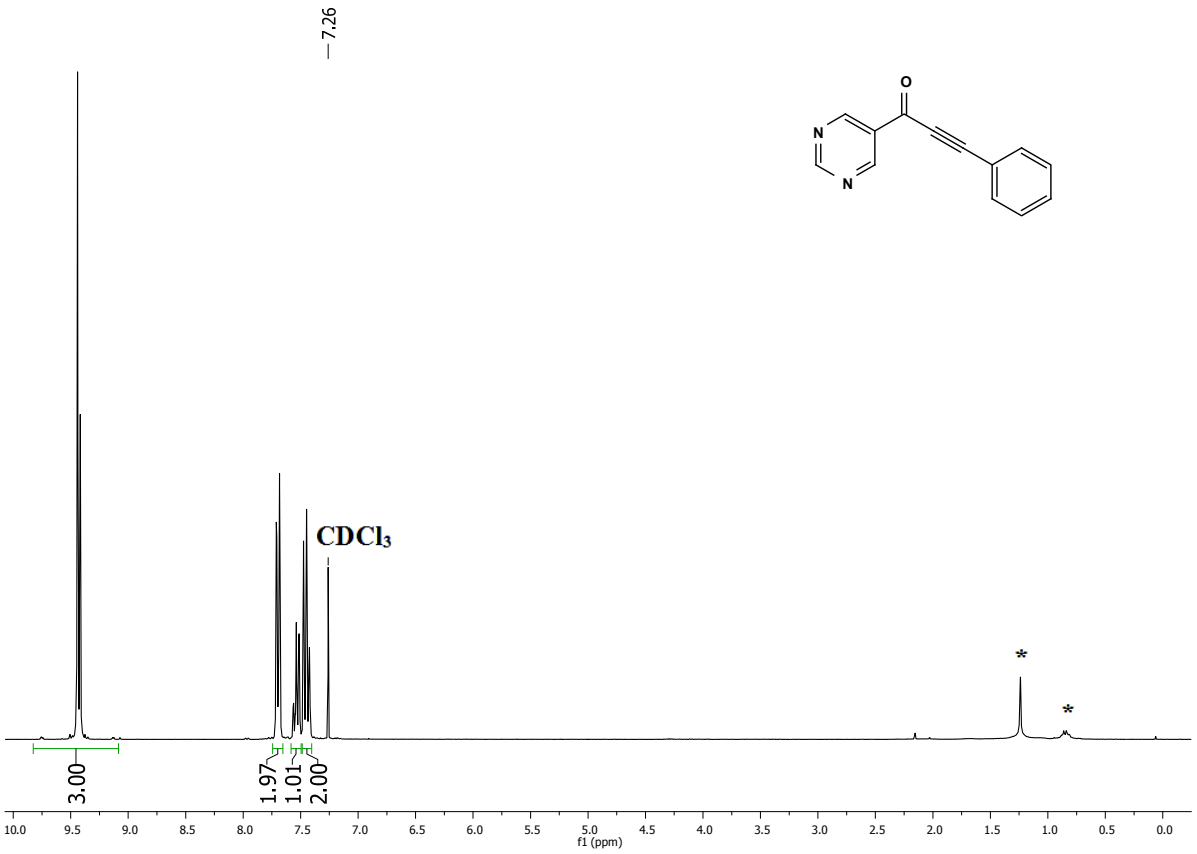
^{1}H-NMR (300 MHz) of **5l** (30 mg) in $CDCl_3$ at 298 K (δ in ppm). *Impurities from residual solvents.



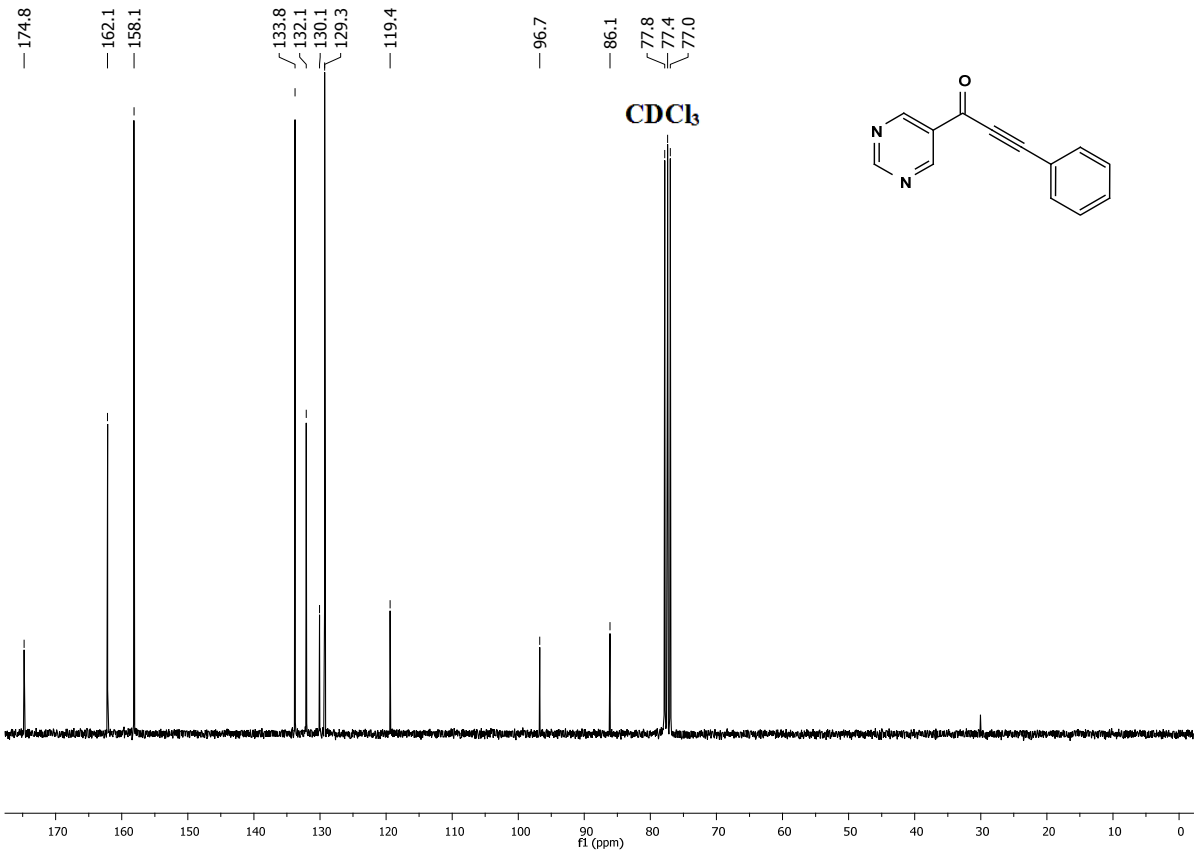
^{13}C-NMR (75 MHz) of **5l** (30 mg) in $CDCl_3$ at 298 K (δ in ppm).



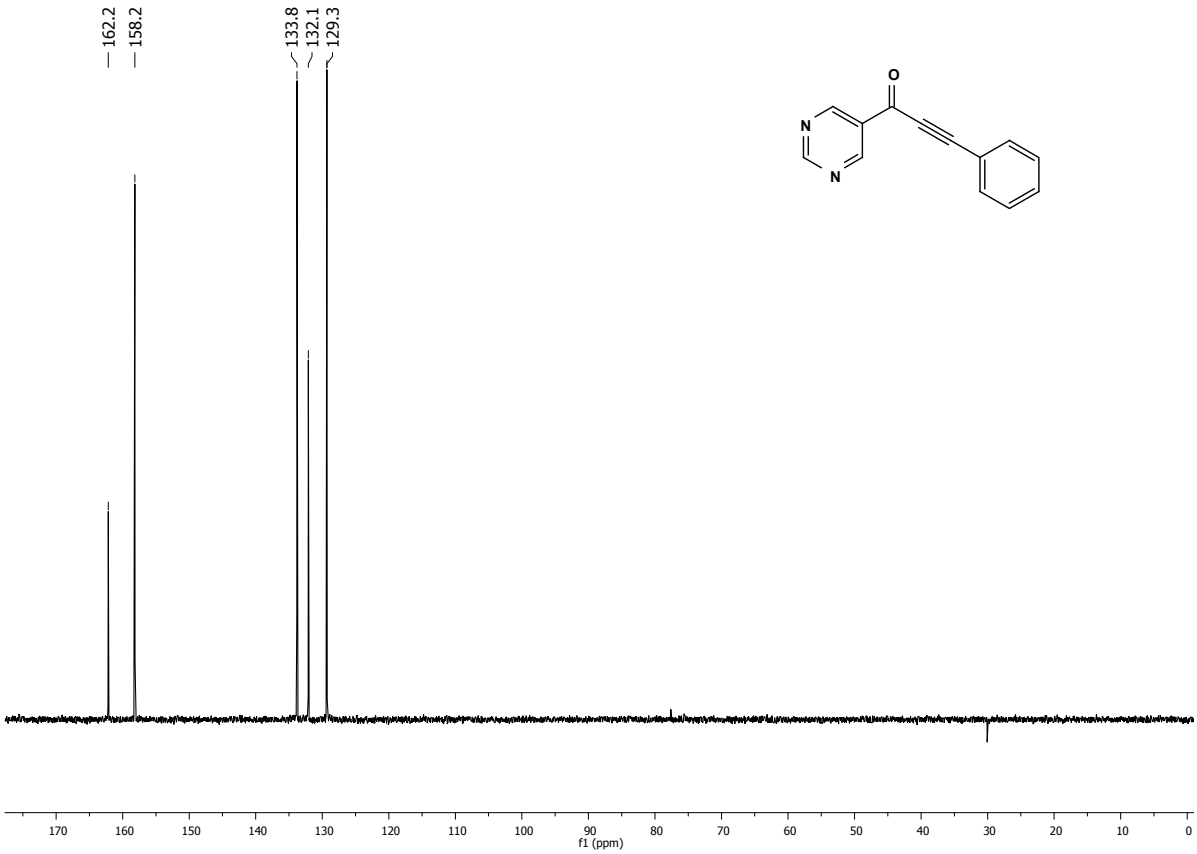
^{13}C-DEPT 135-NMR (75 MHz) of **5l** (30 mg) in $CDCl_3$ at 298 K (δ in ppm).



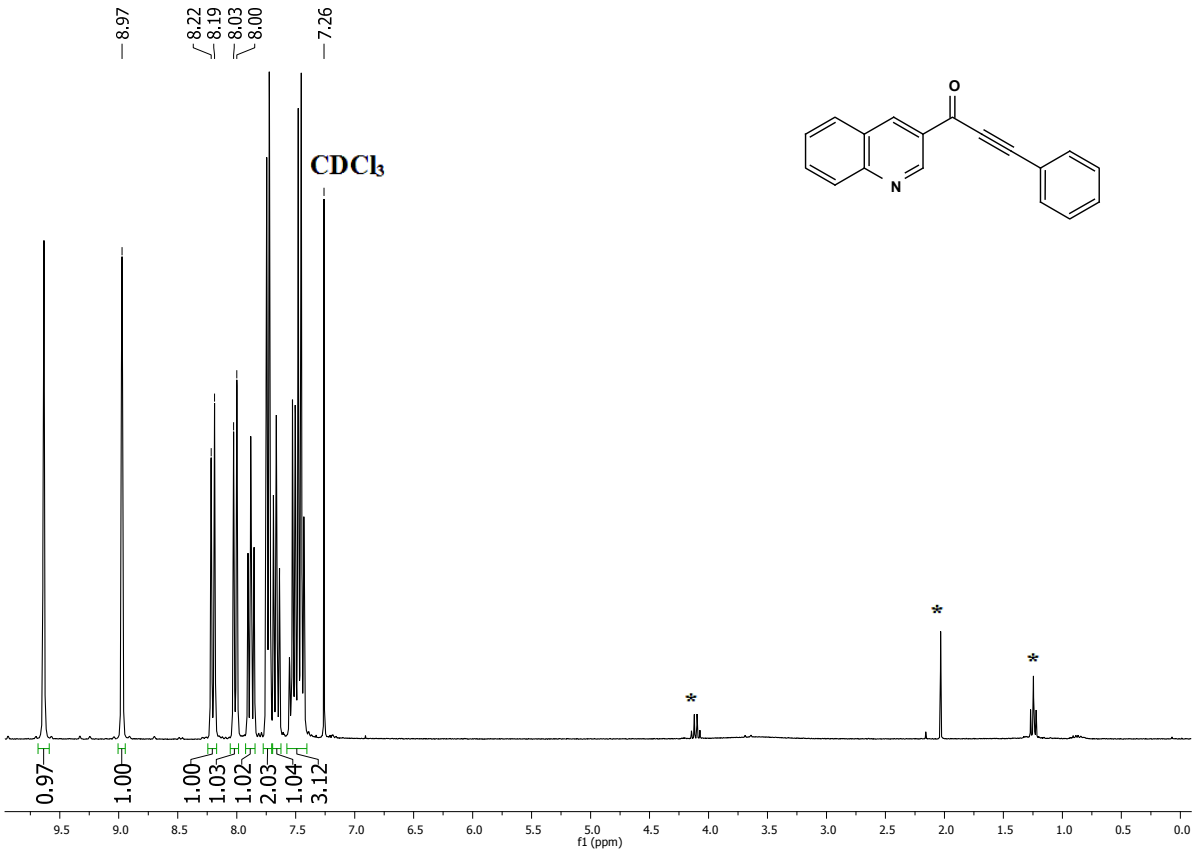
^{1}H-NMR (300 MHz) of **5m** (30 mg) in $CDCl_3$ at 298 K (δ in ppm). *Impurities from residual solvents.



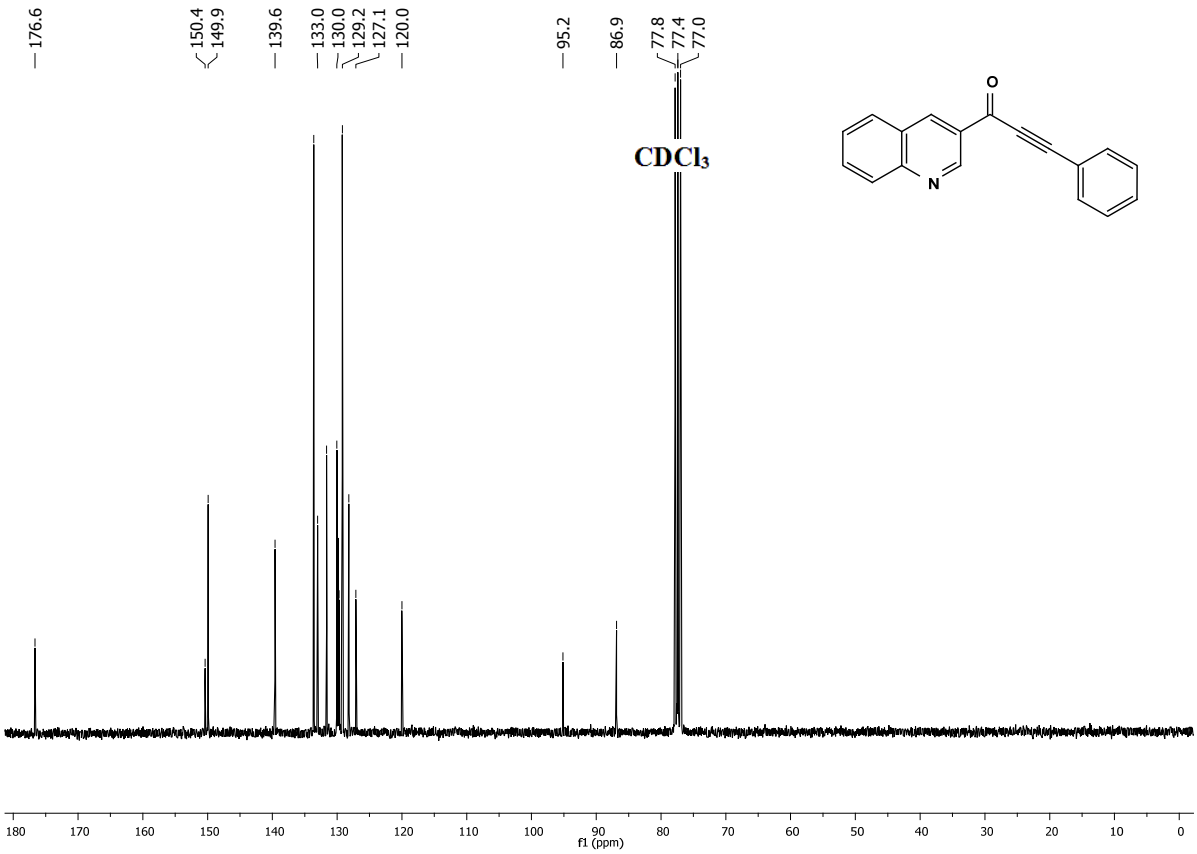
^{13}C-NMR (75 MHz) of **5m** (30 mg) in $CDCl_3$ at 298 K (δ in ppm).



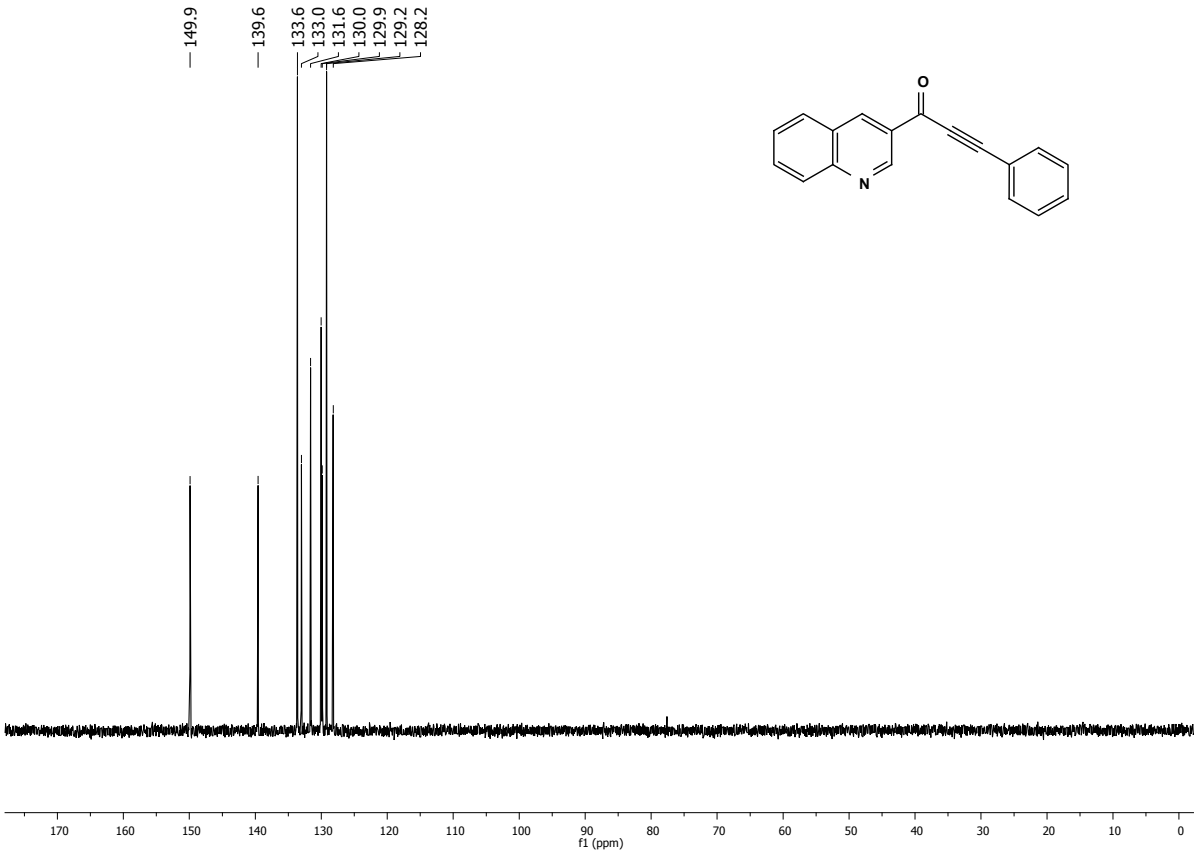
^{13}C-DEPT 135-NMR (75 MHz) of **5m** (30 mg) in $CDCl_3$ at 298 K (δ in ppm).



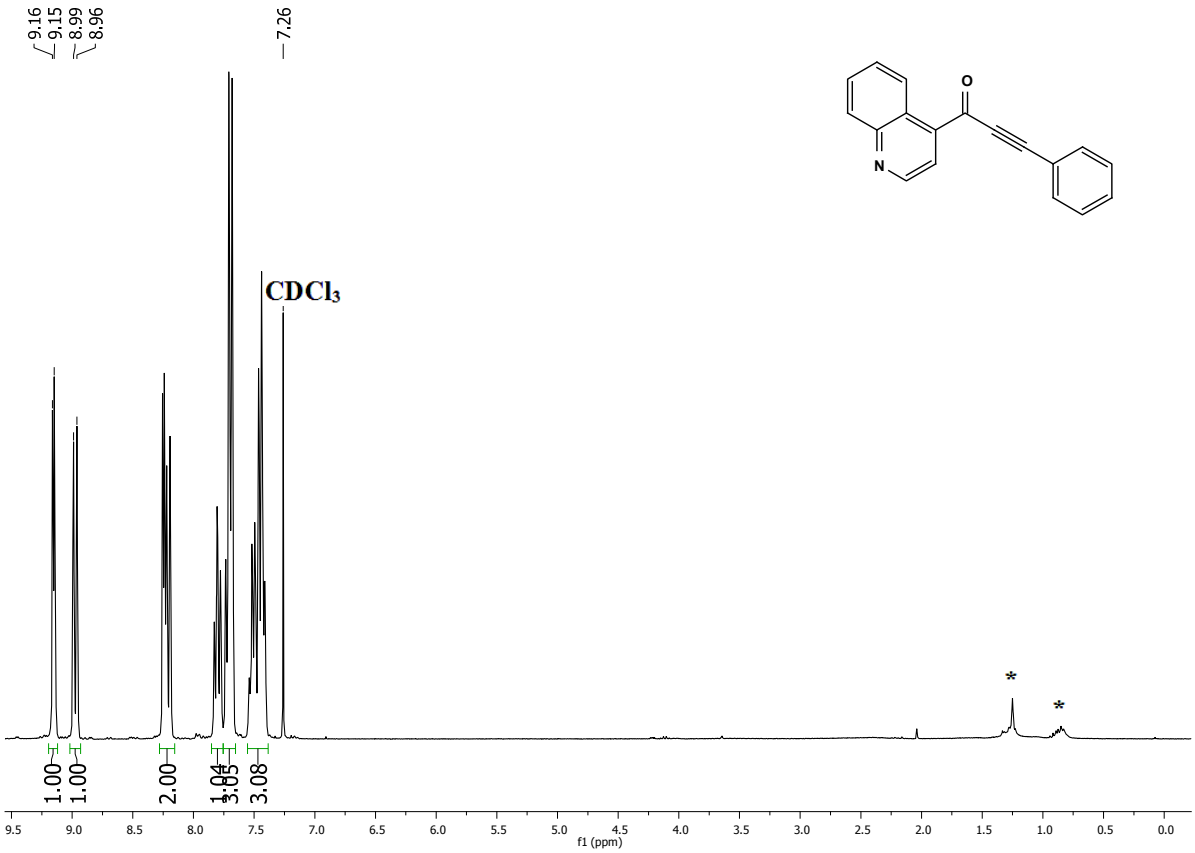
^{1}H-NMR (300 MHz) of **5n** (30 mg) in $CDCl_3$ at 295 K (δ in ppm). *Impurities from residual solvents.



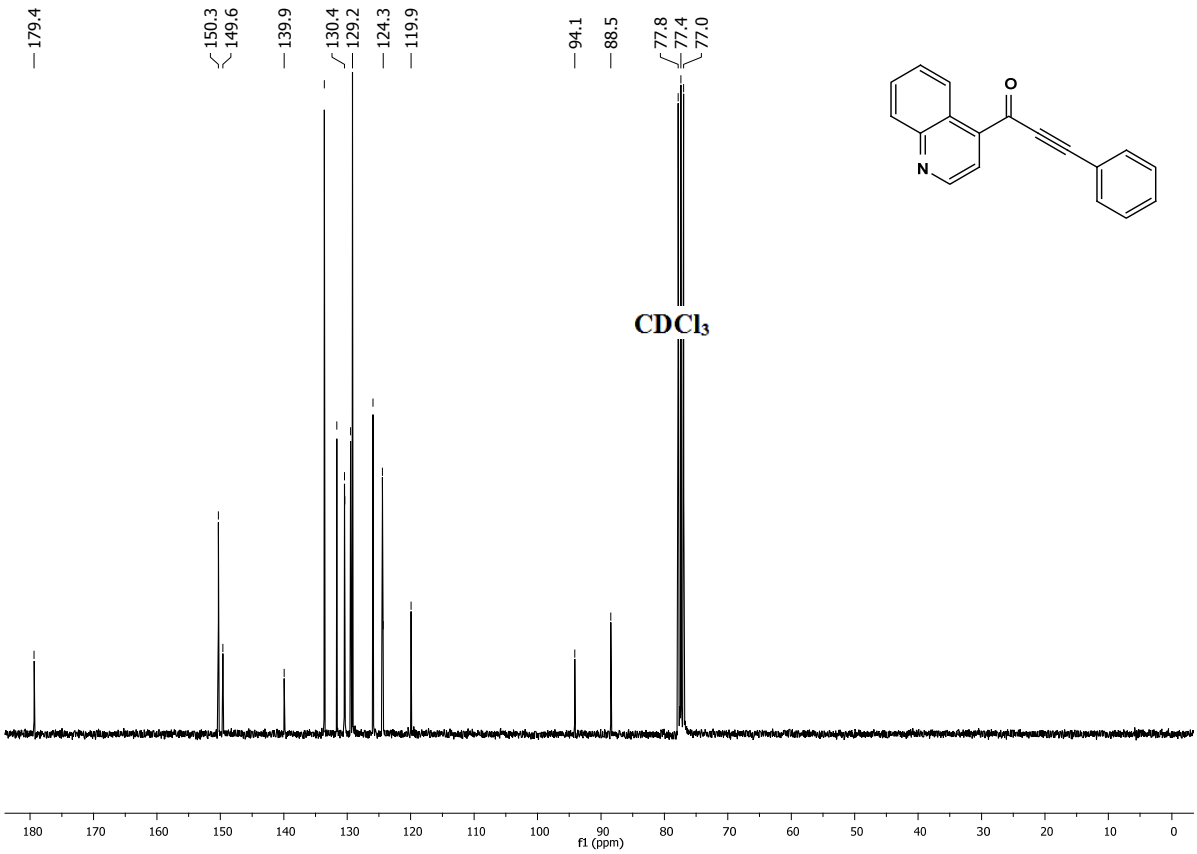
^{13}C-NMR (75 MHz) of **5n** (30 mg) in $CDCl_3$ at 295 K (δ in ppm).



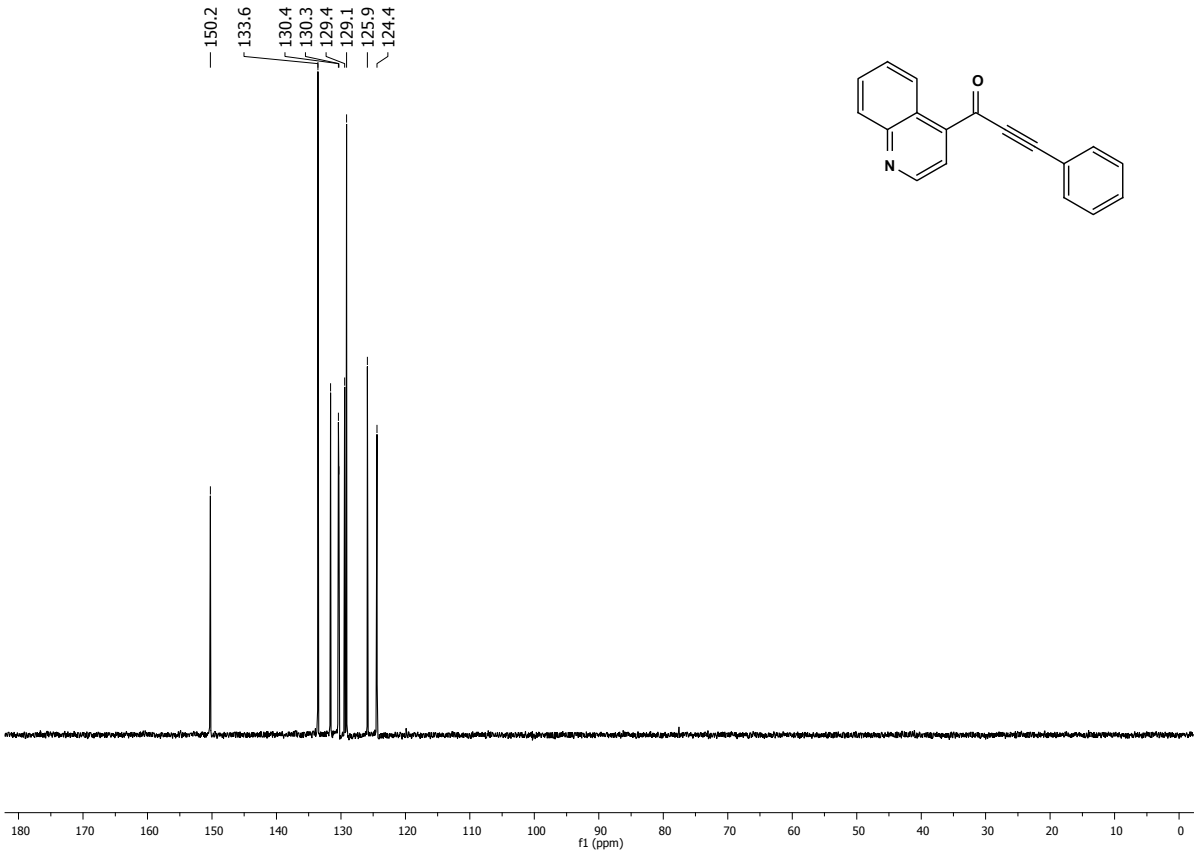
^{13}C-DEPT 135-NMR (75 MHz) of **5n** (30 mg) in $CDCl_3$ at 296 K (δ in ppm).



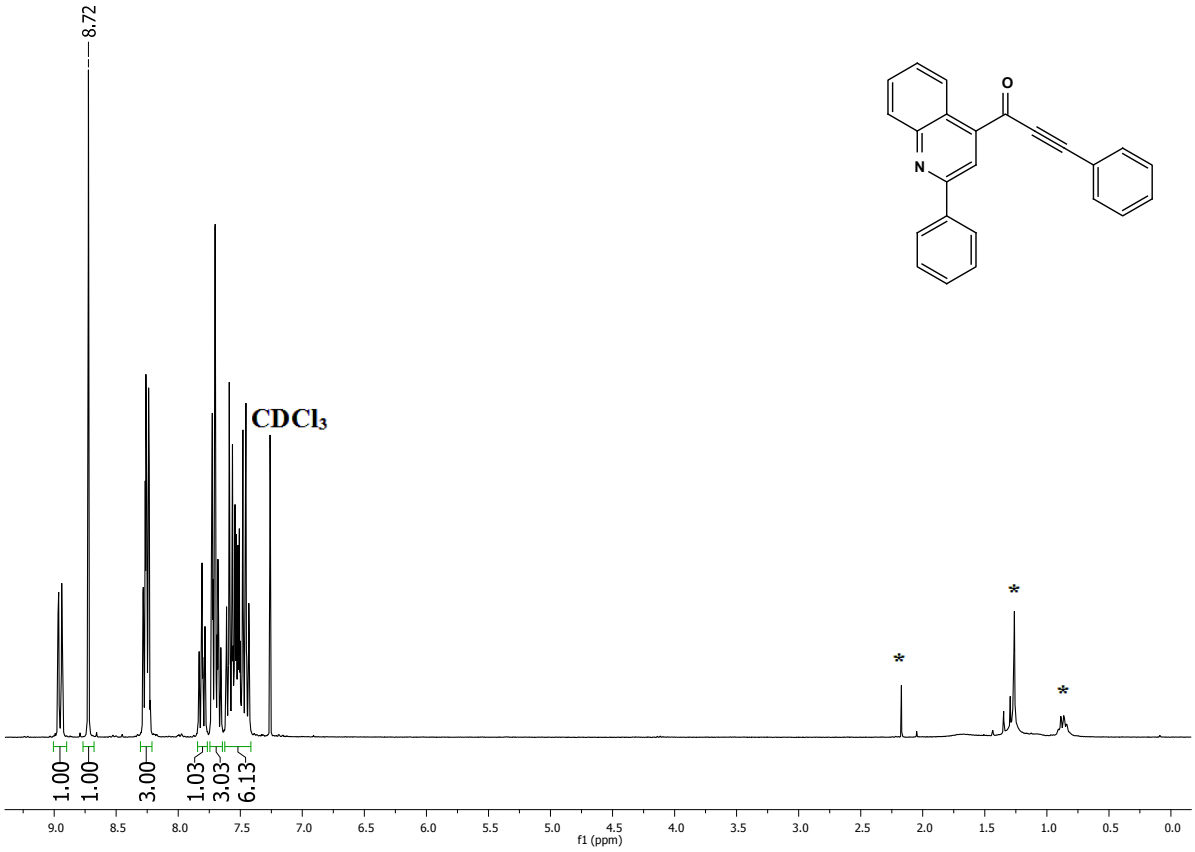
^{1}H-NMR (300 MHz) of **5o** (30 mg) in $CDCl_3$ at 296 K (δ in ppm). *Impurities from residual solvents.



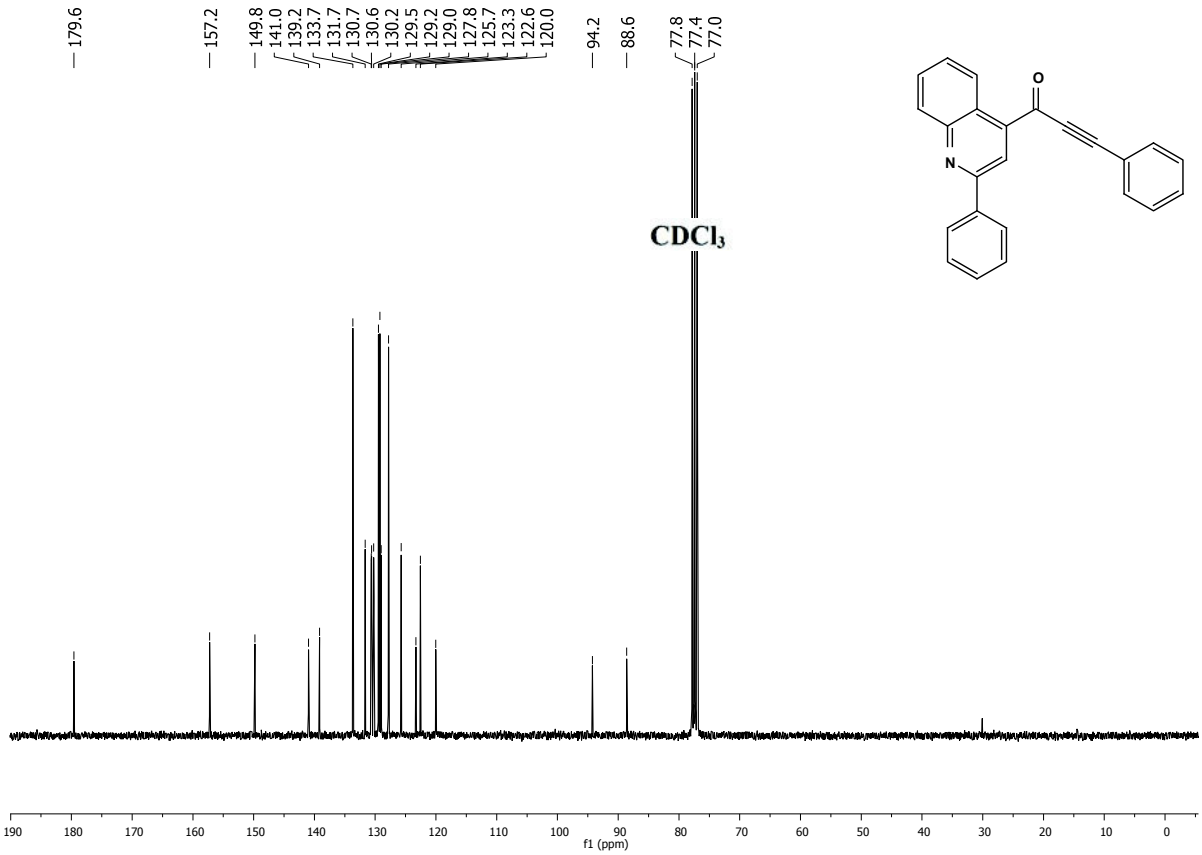
^{13}C-NMR (75 MHz) of **5o** (30 mg) in $CDCl_3$ at 297 K (δ in ppm).



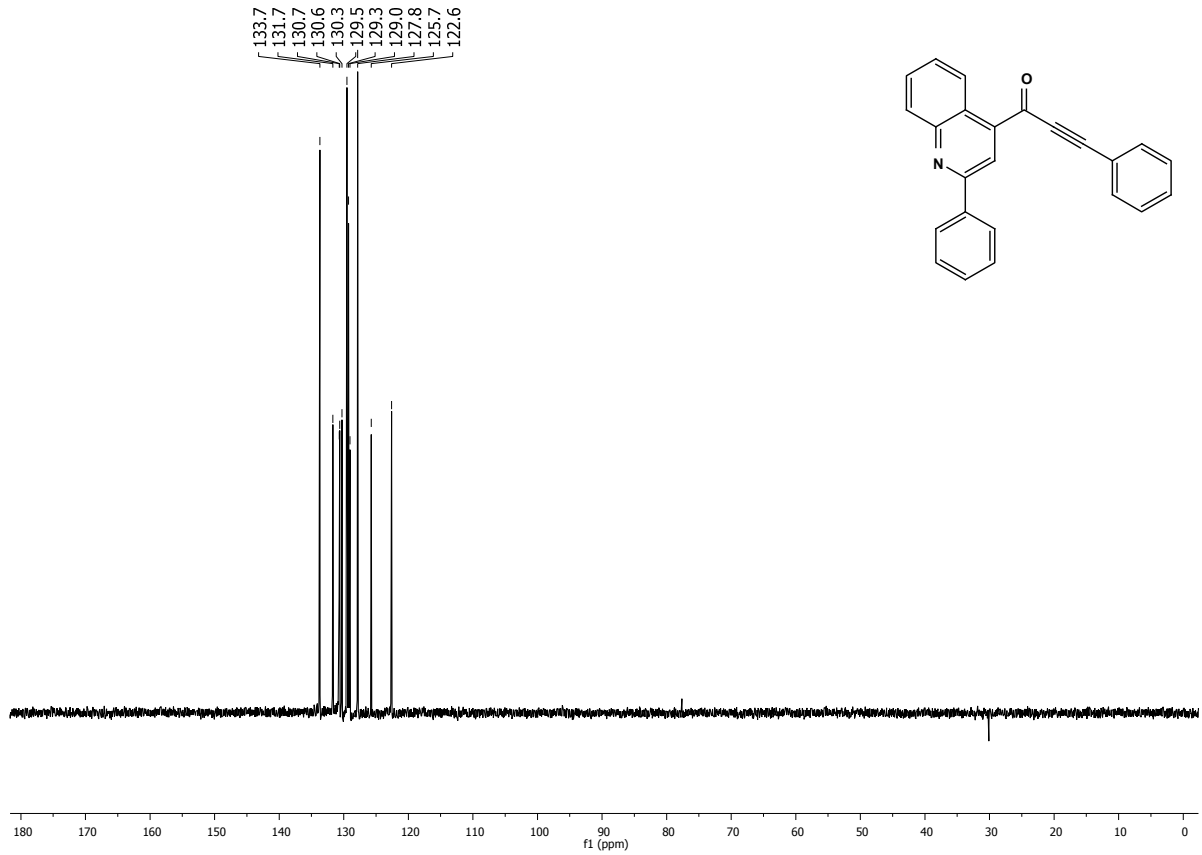
^{13}C-DEPT 135-NMR (75 MHz) of **5o** (30 mg) in $CDCl_3$ at 297 K (δ in ppm).



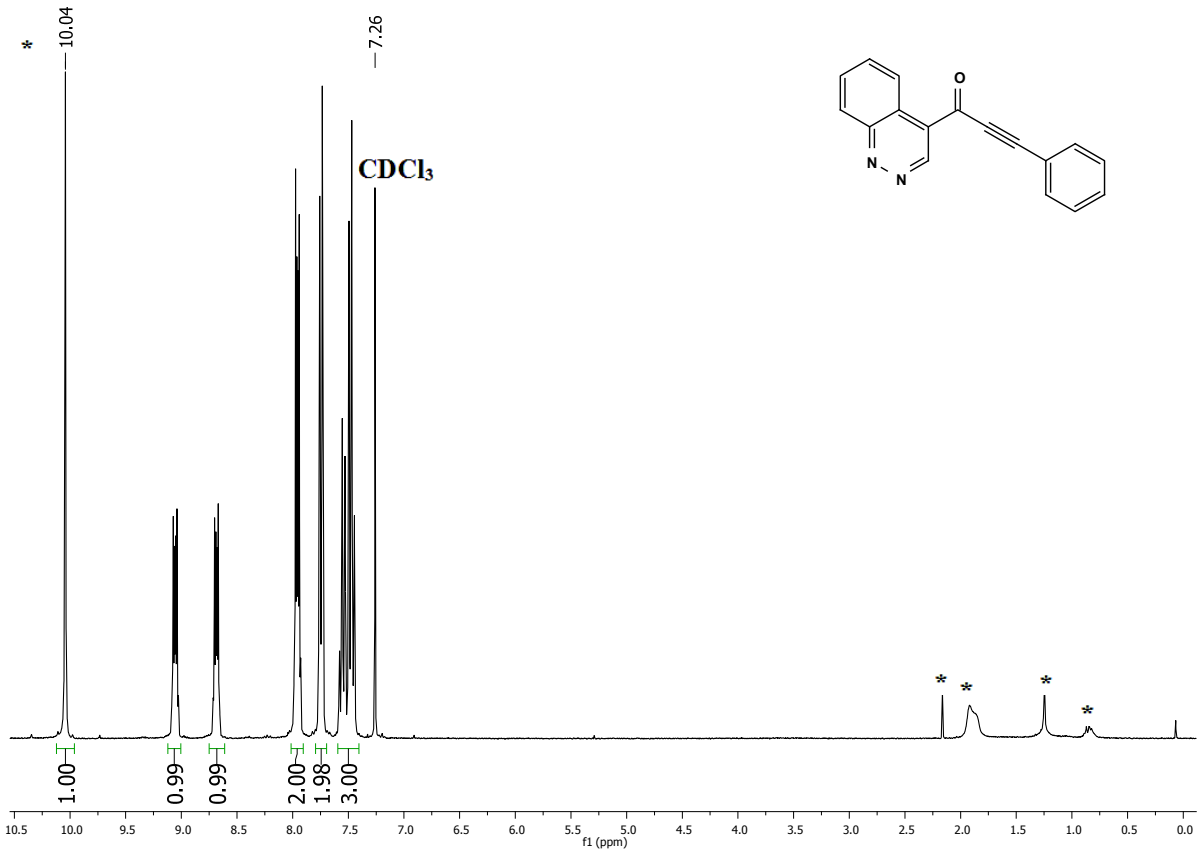
^{1}H-NMR (300 MHz) of **5p** (30 mg) in $CDCl_3$ at 298 K (δ in ppm). *Impurities from residual solvents.



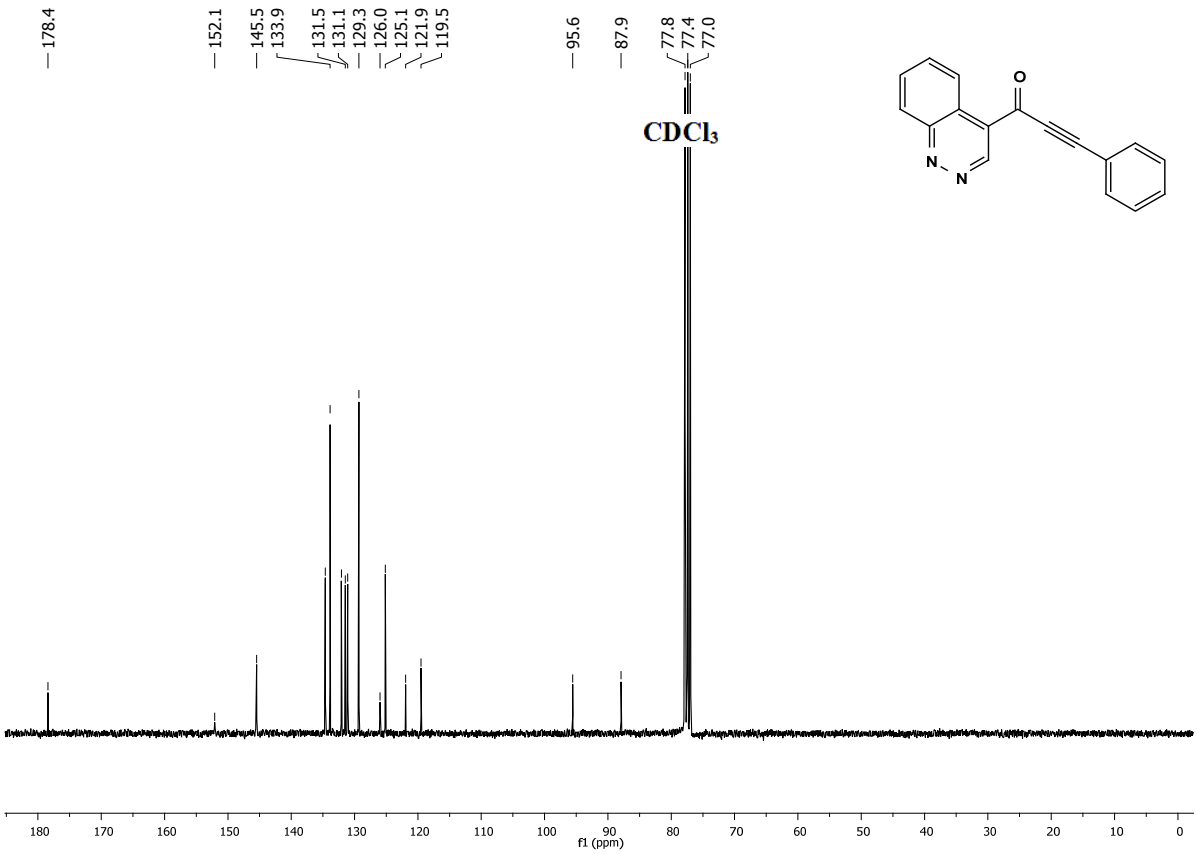
^{13}C-NMR (75 MHz) of **5p** (30 mg) in $CDCl_3$ at 298 K (δ in ppm).



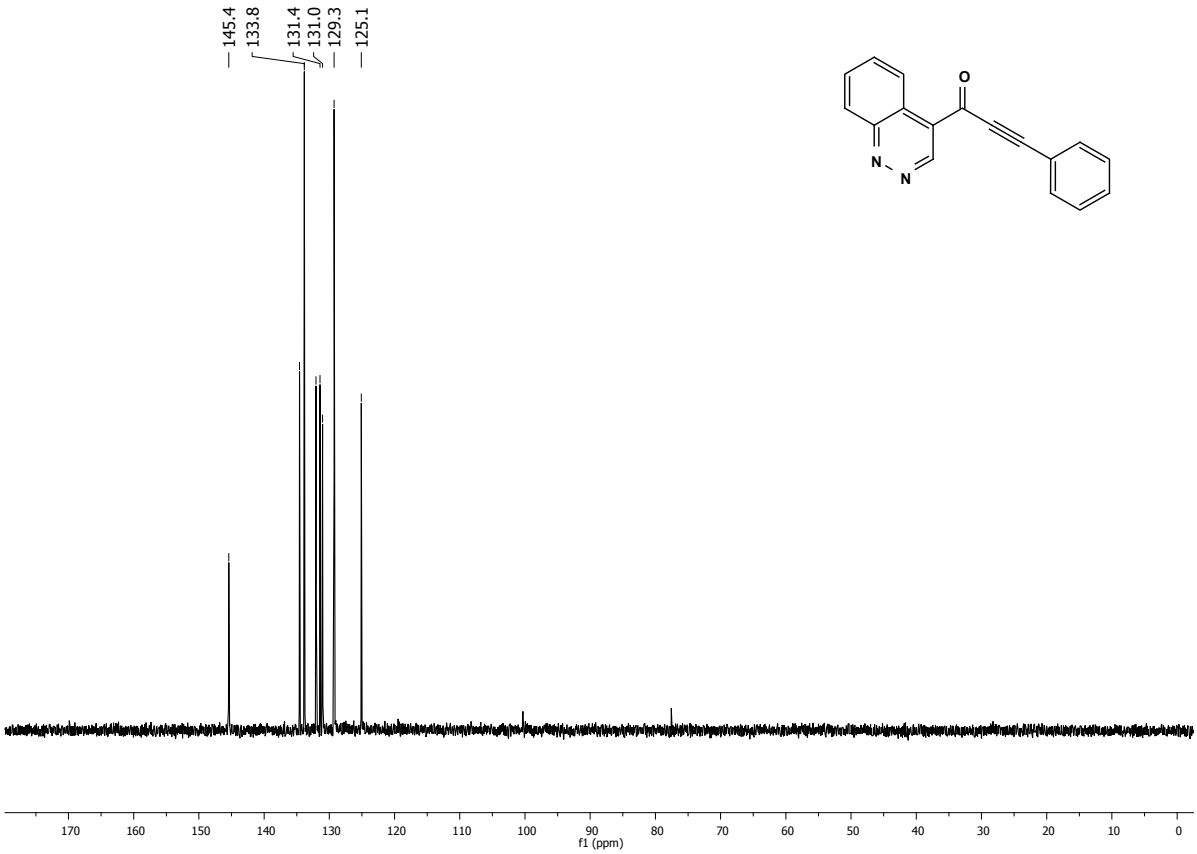
^{13}C-DEPT 135-NMR (75 MHz) of **5p** (30 mg) in $CDCl_3$ at 298 K (δ in ppm).



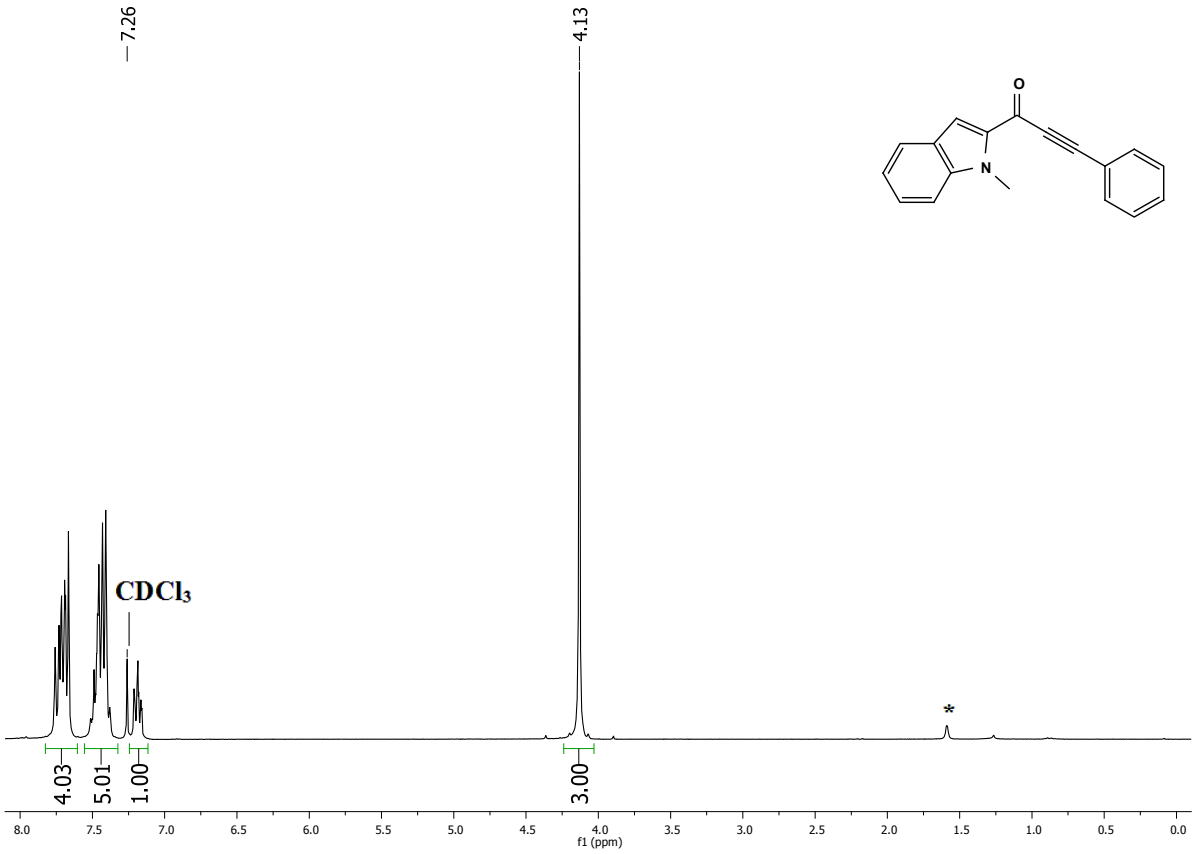
^{1}H-NMR (300 MHz) of **5q** (30 mg) in $CDCl_3$ at 298 K (δ in ppm). *Impurities from residual solvents.



^{13}C-NMR (75 MHz) of **5q** (30 mg) in $CDCl_3$ at 298 K (δ in ppm).



^{13}C-DEPT 135-NMR (75 MHz) of **5q** (30 mg) in $CDCl_3$ at 298 K (δ in ppm).



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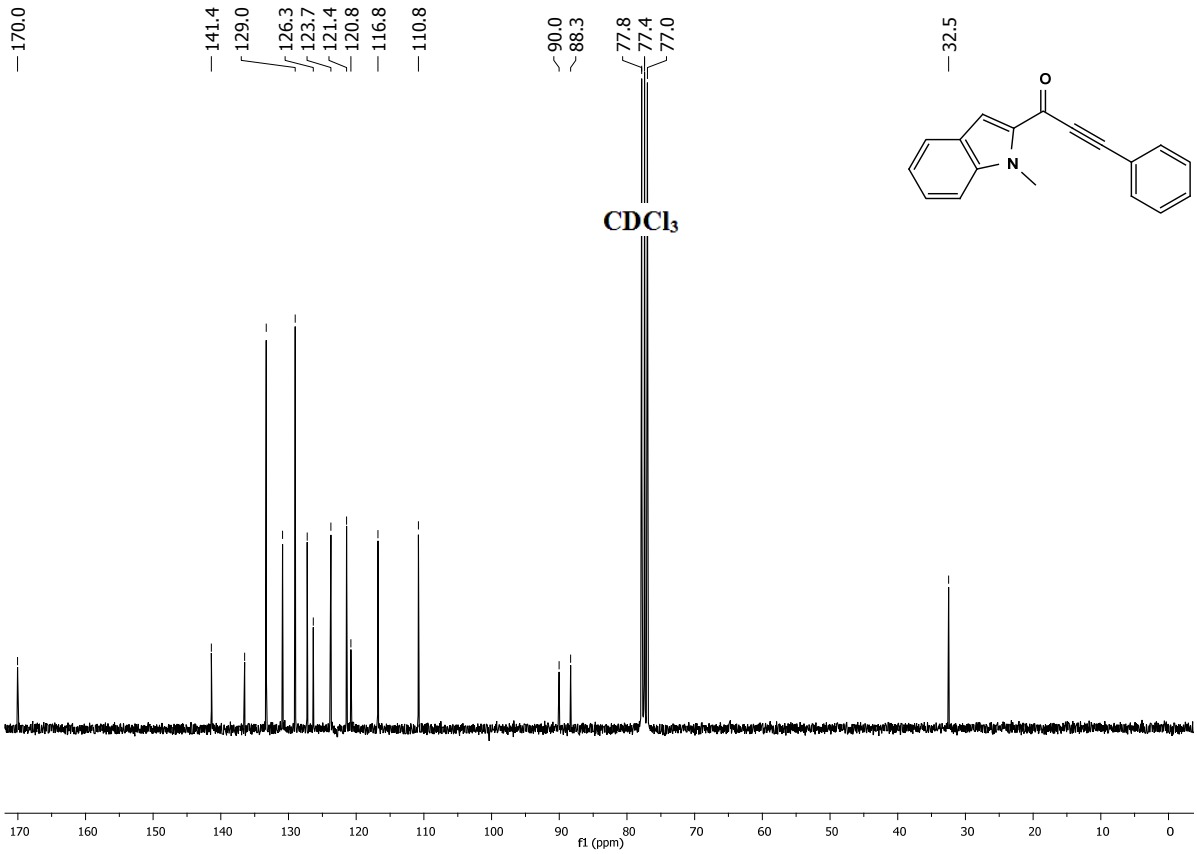

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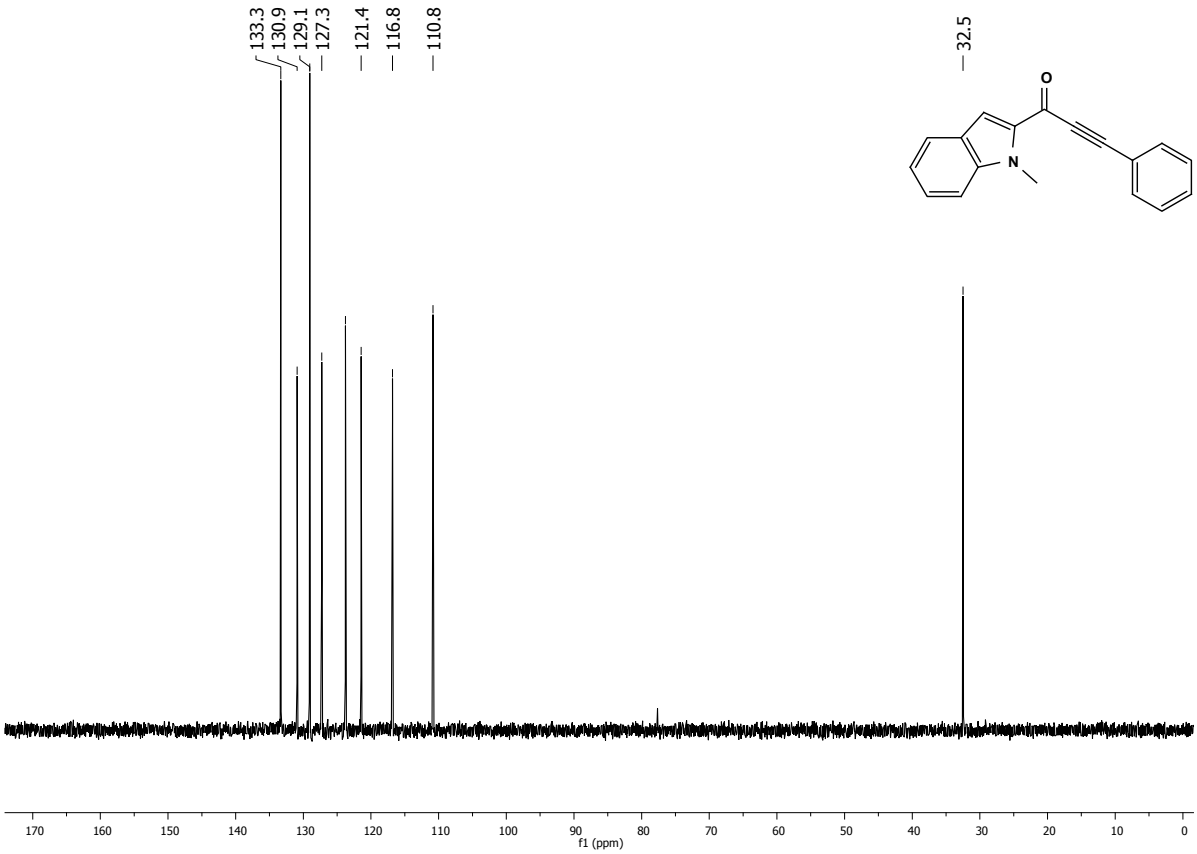

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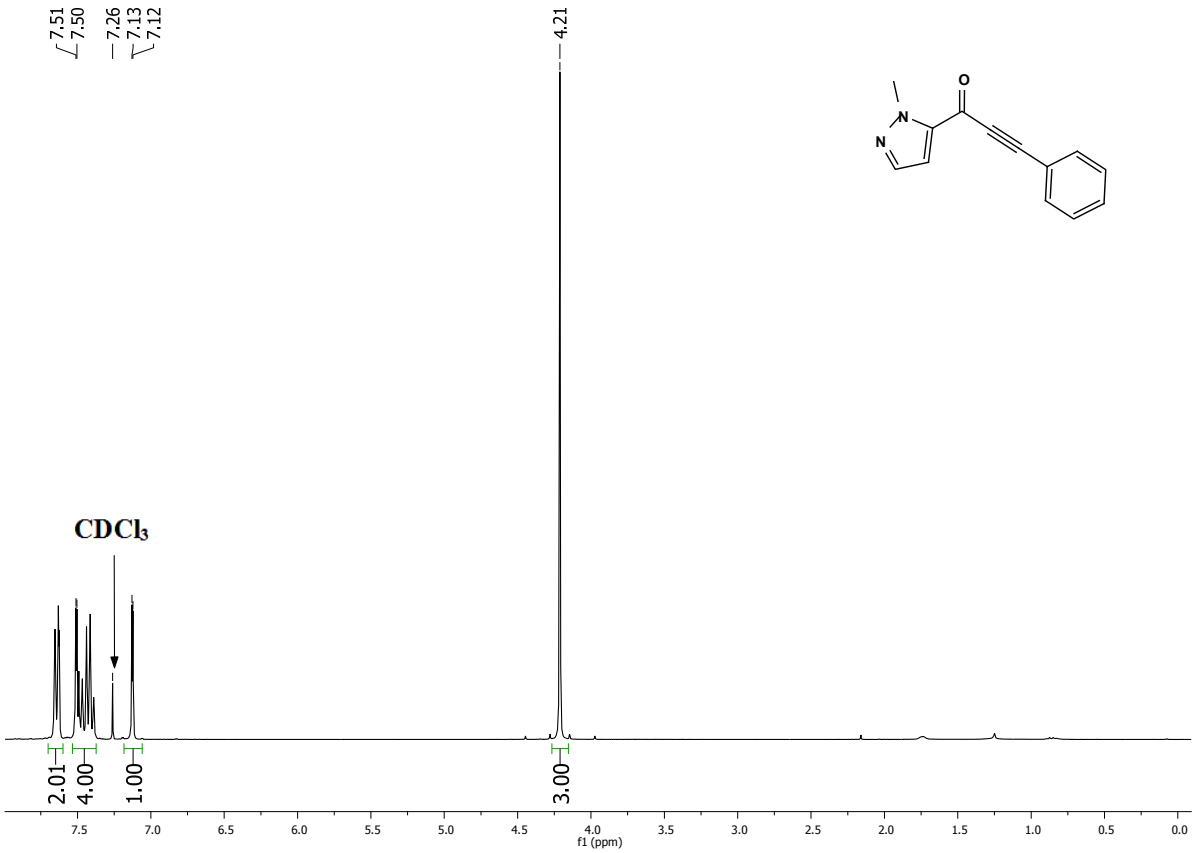

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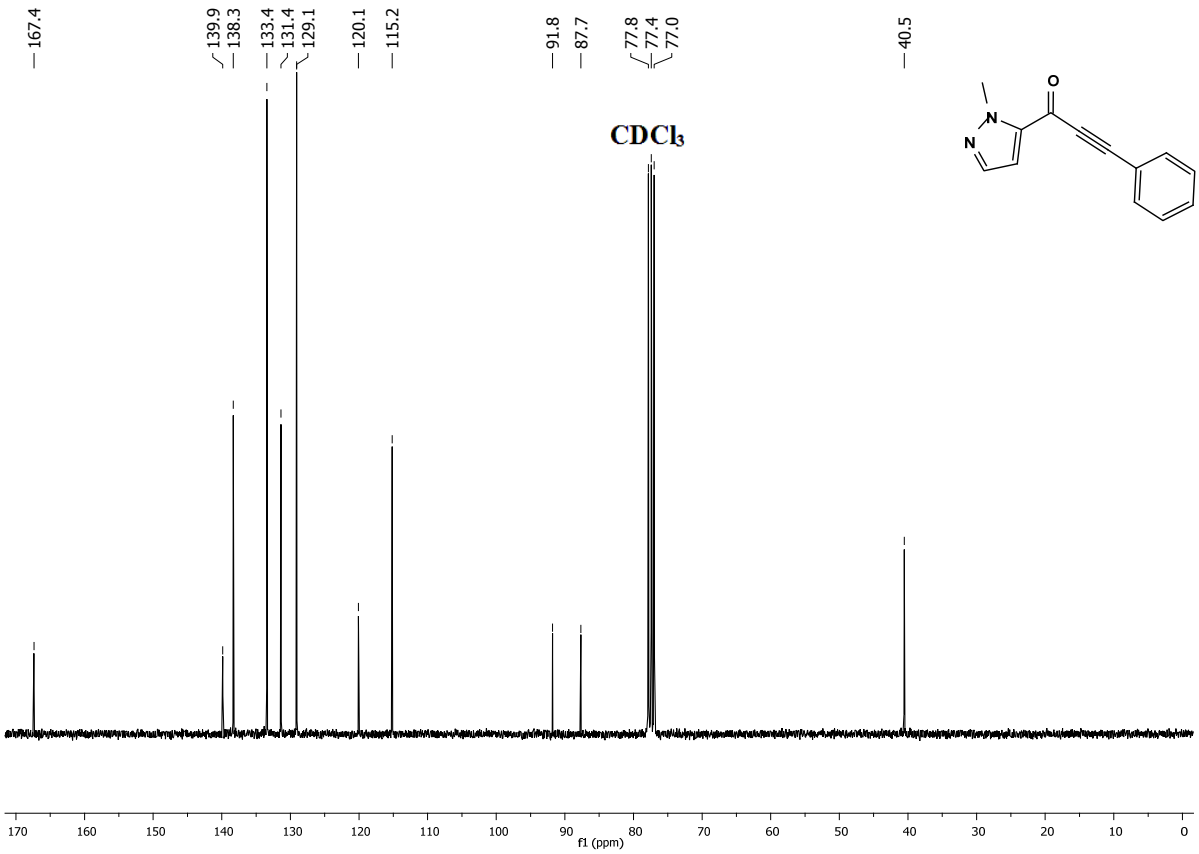

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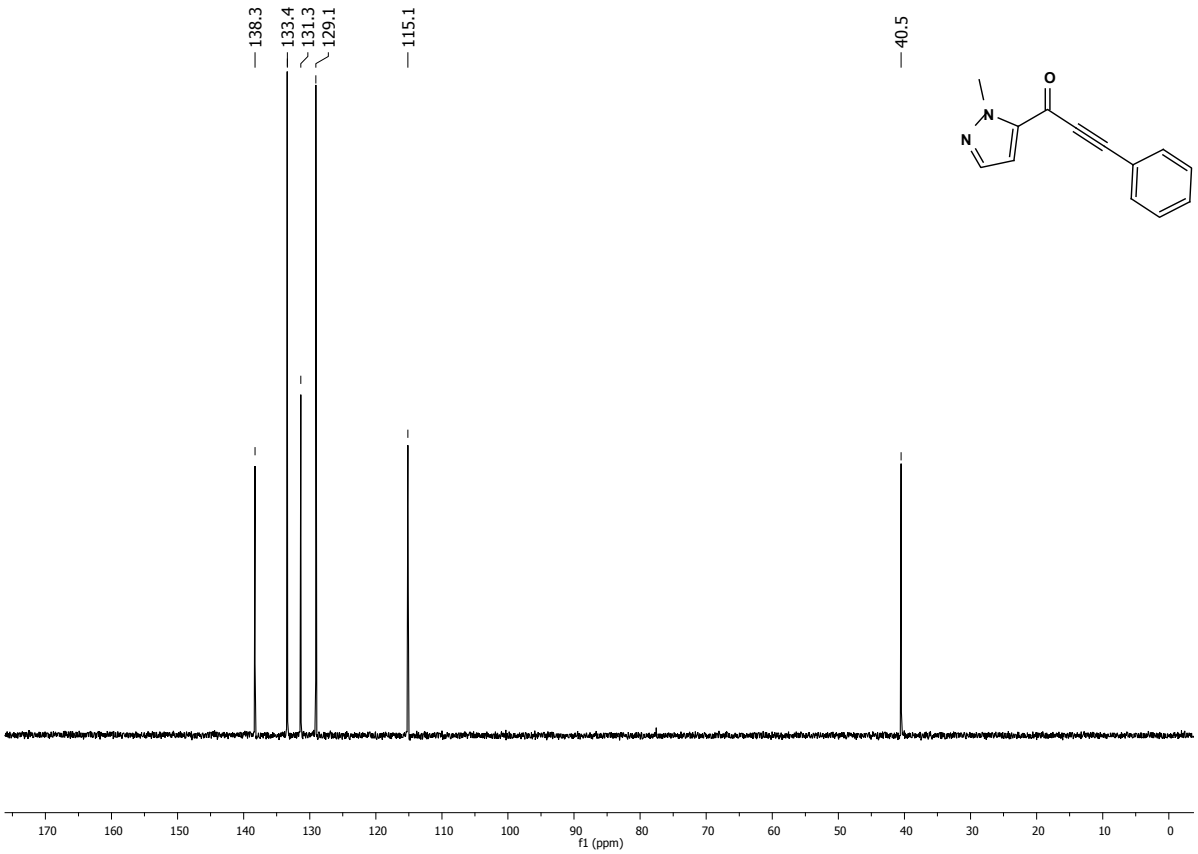

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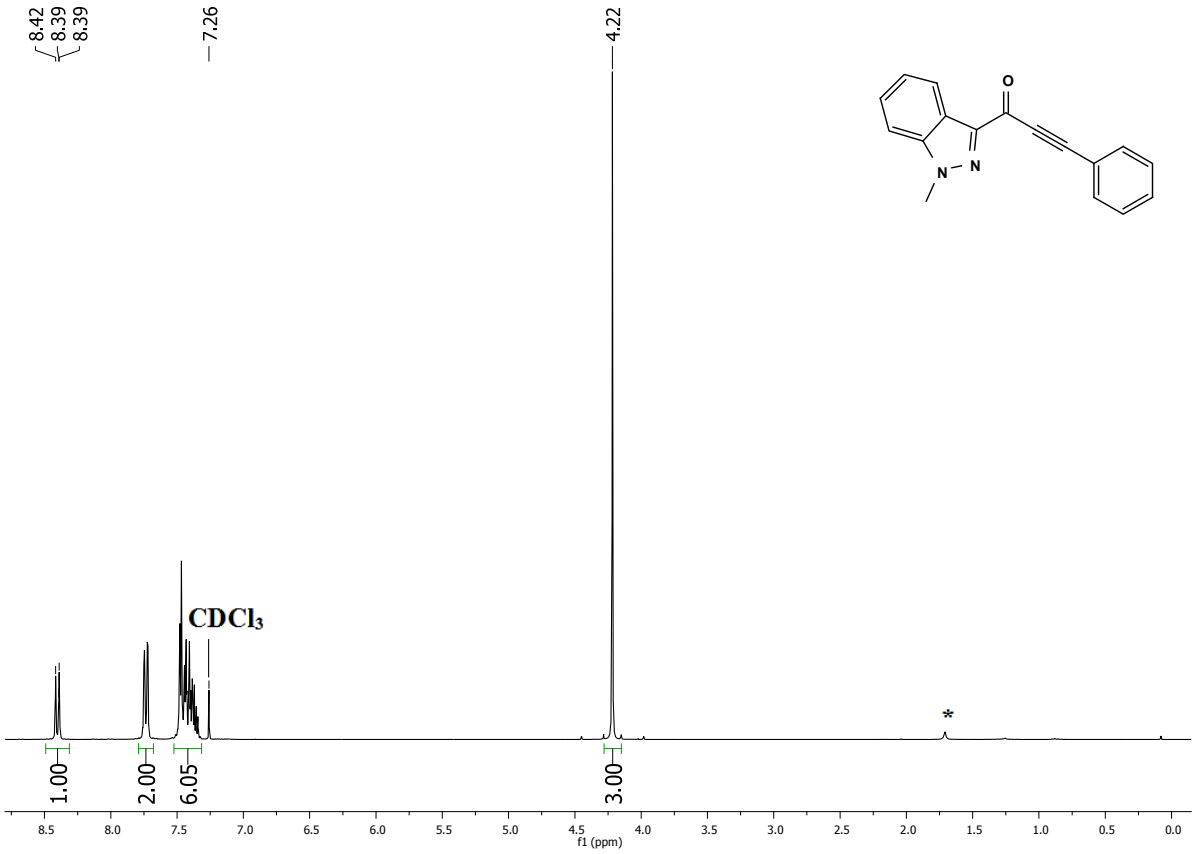
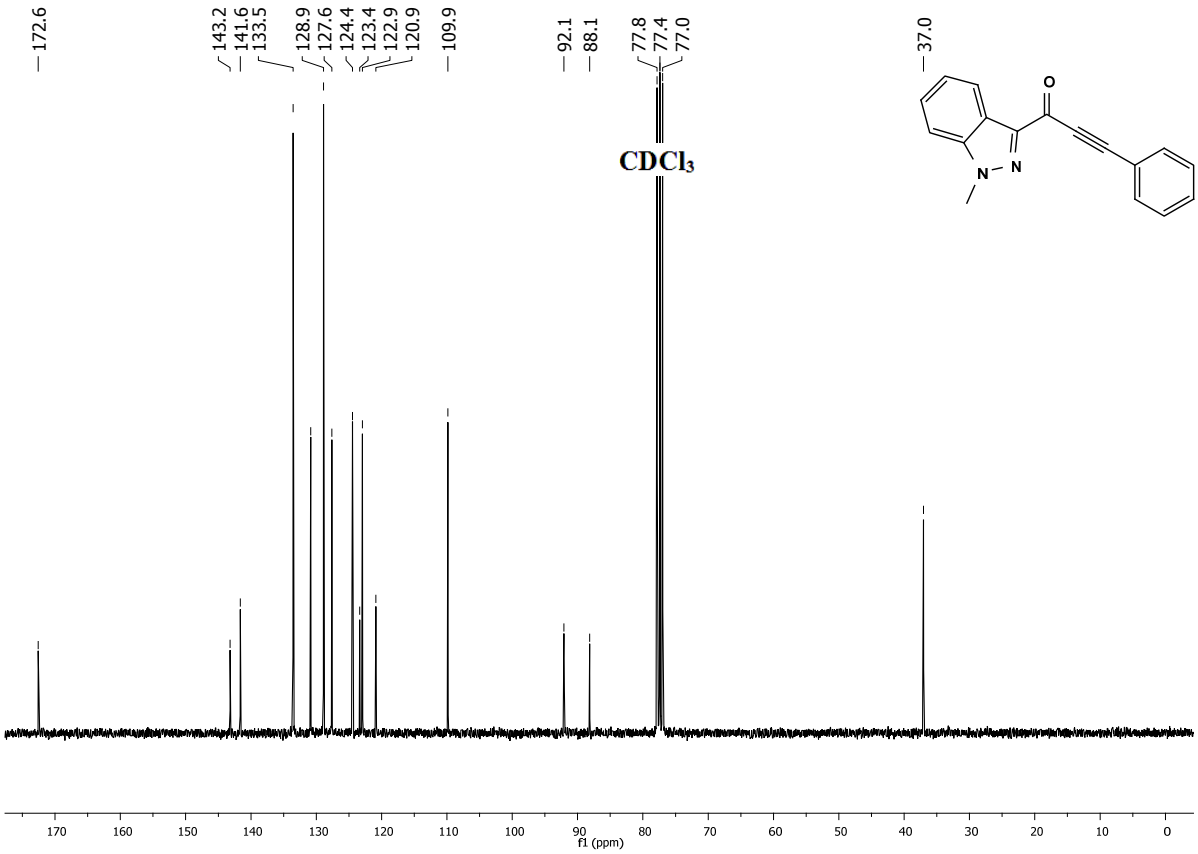


^{1}H-NMR (300 MHz) of **5t** (30 mg) in $CDCl_3$ at 298 K (δ in ppm). *Impurities from residual solvents.



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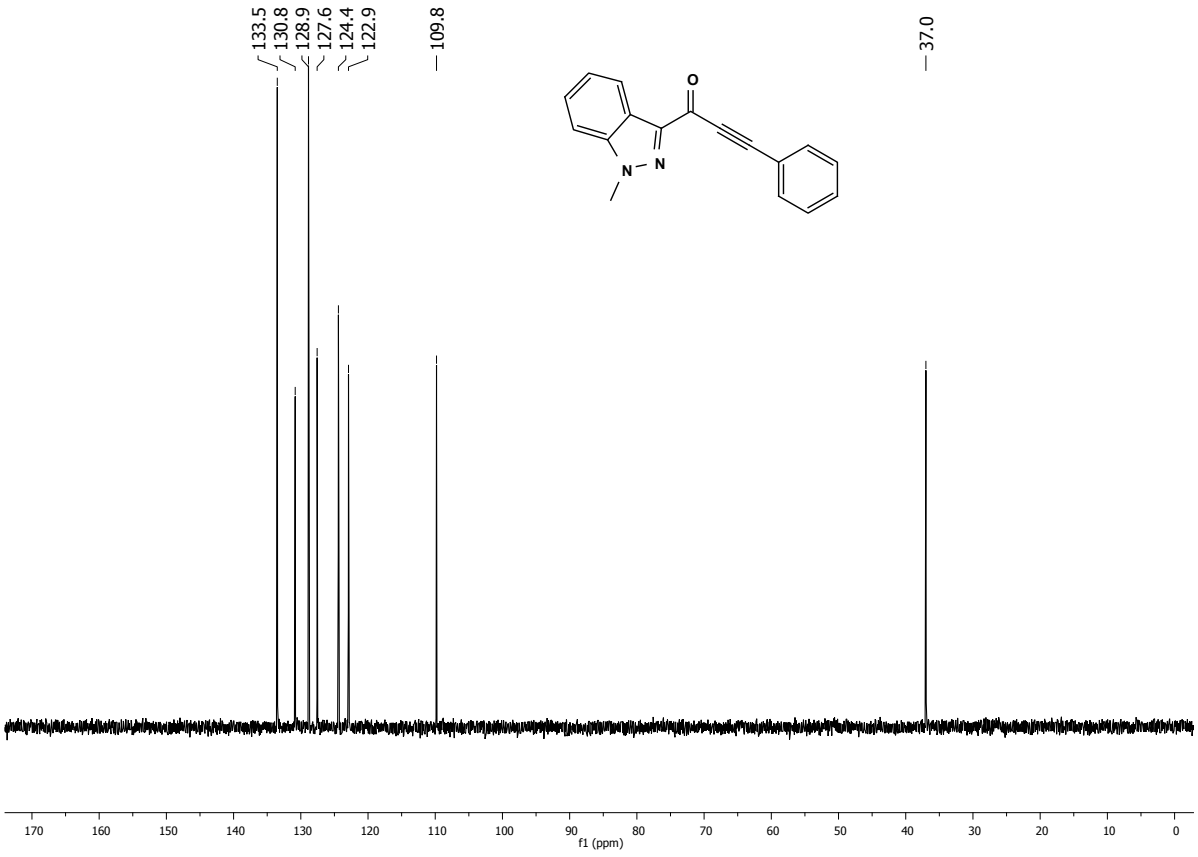

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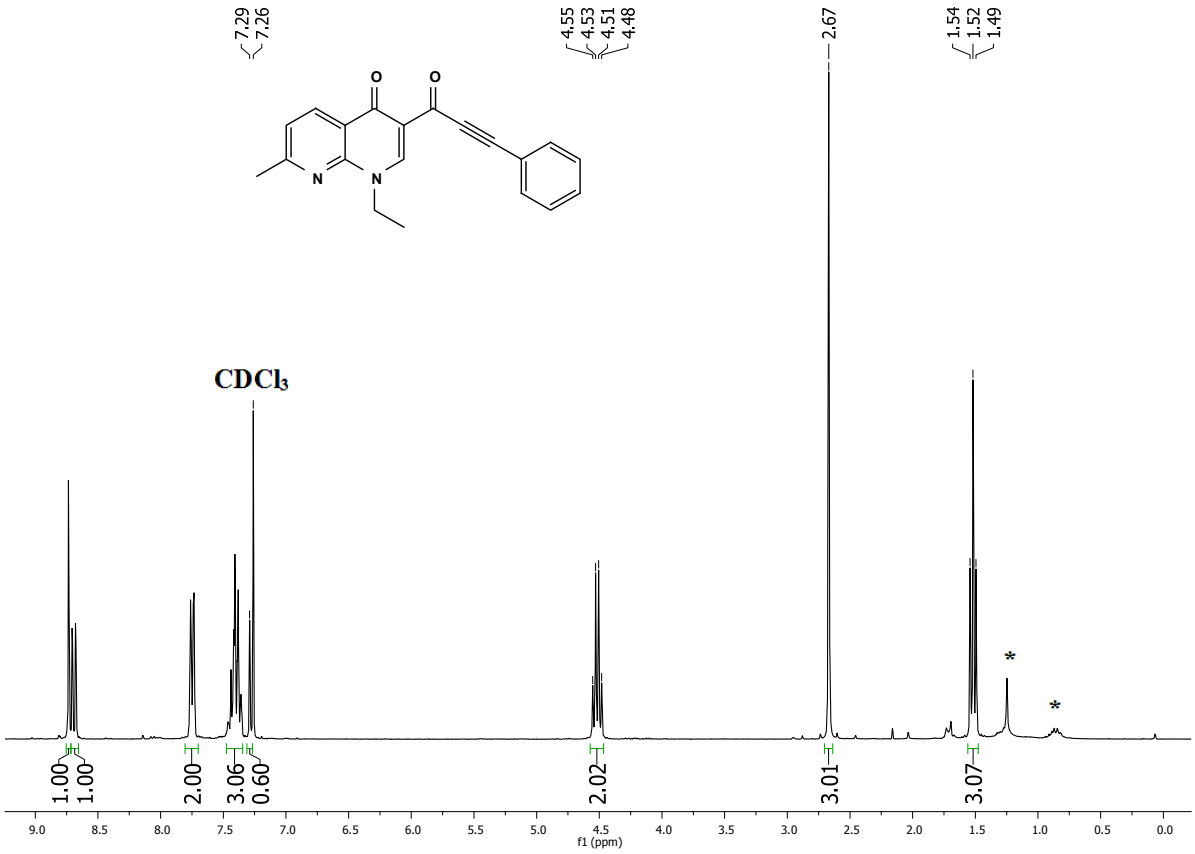

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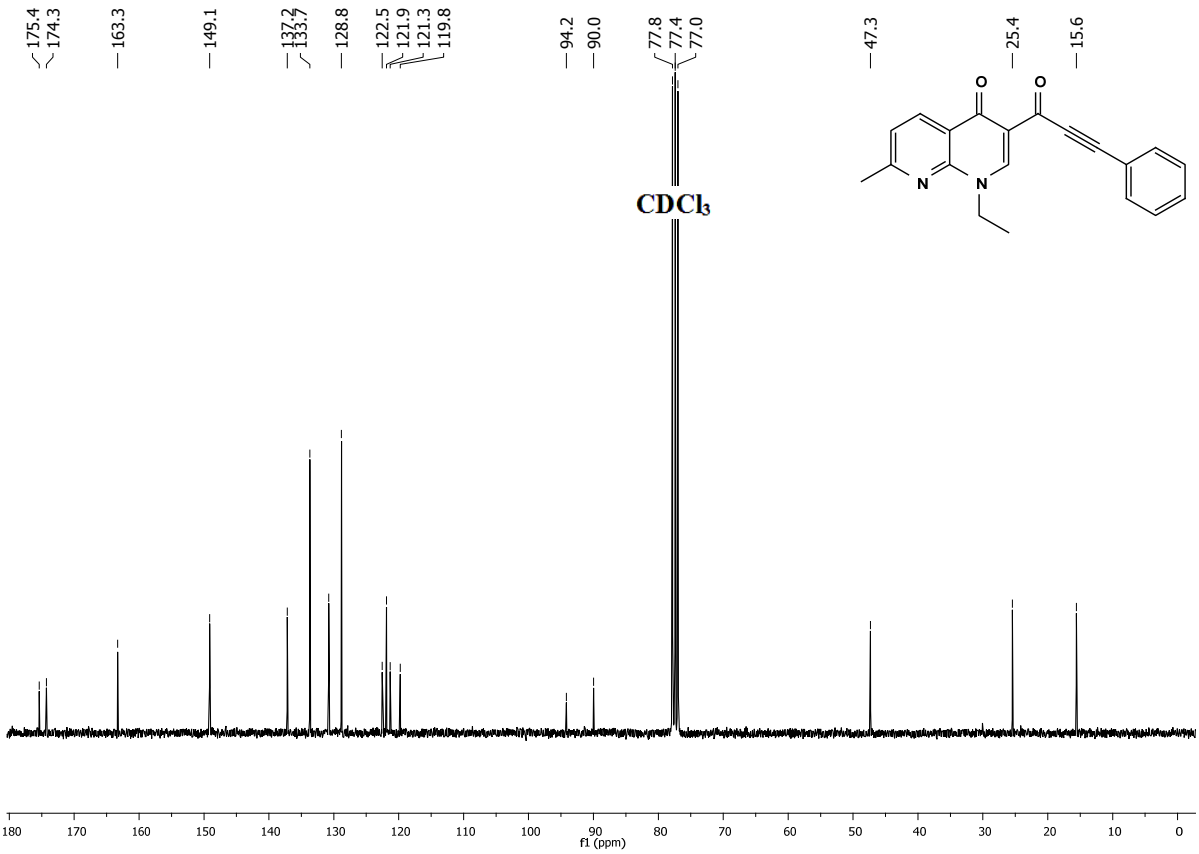

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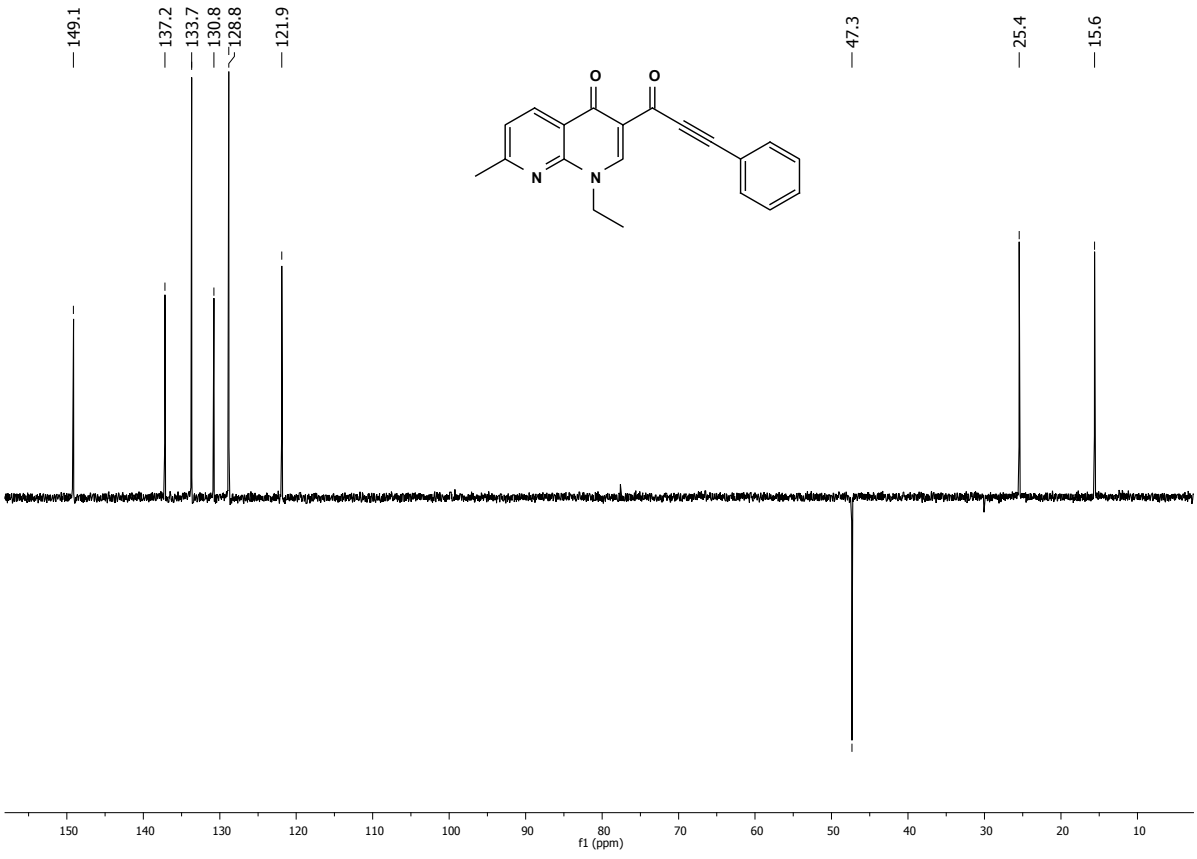

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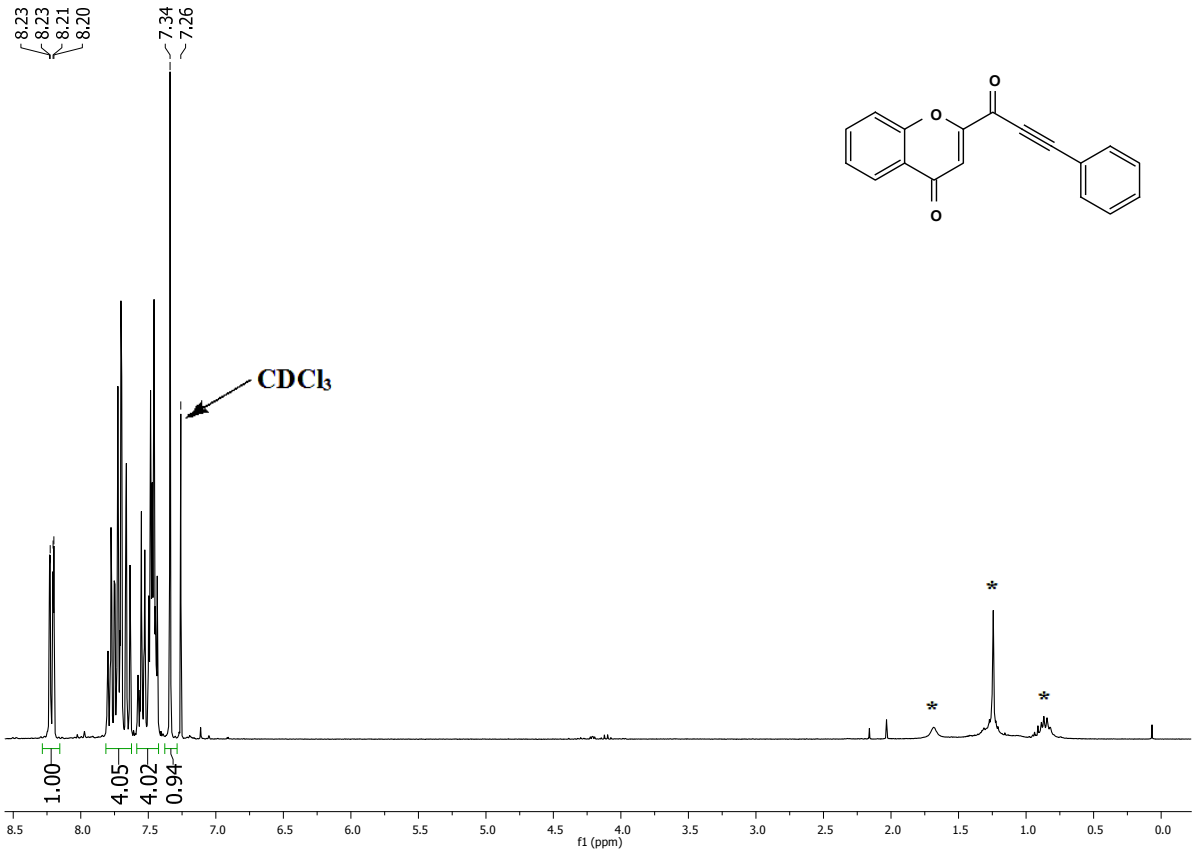

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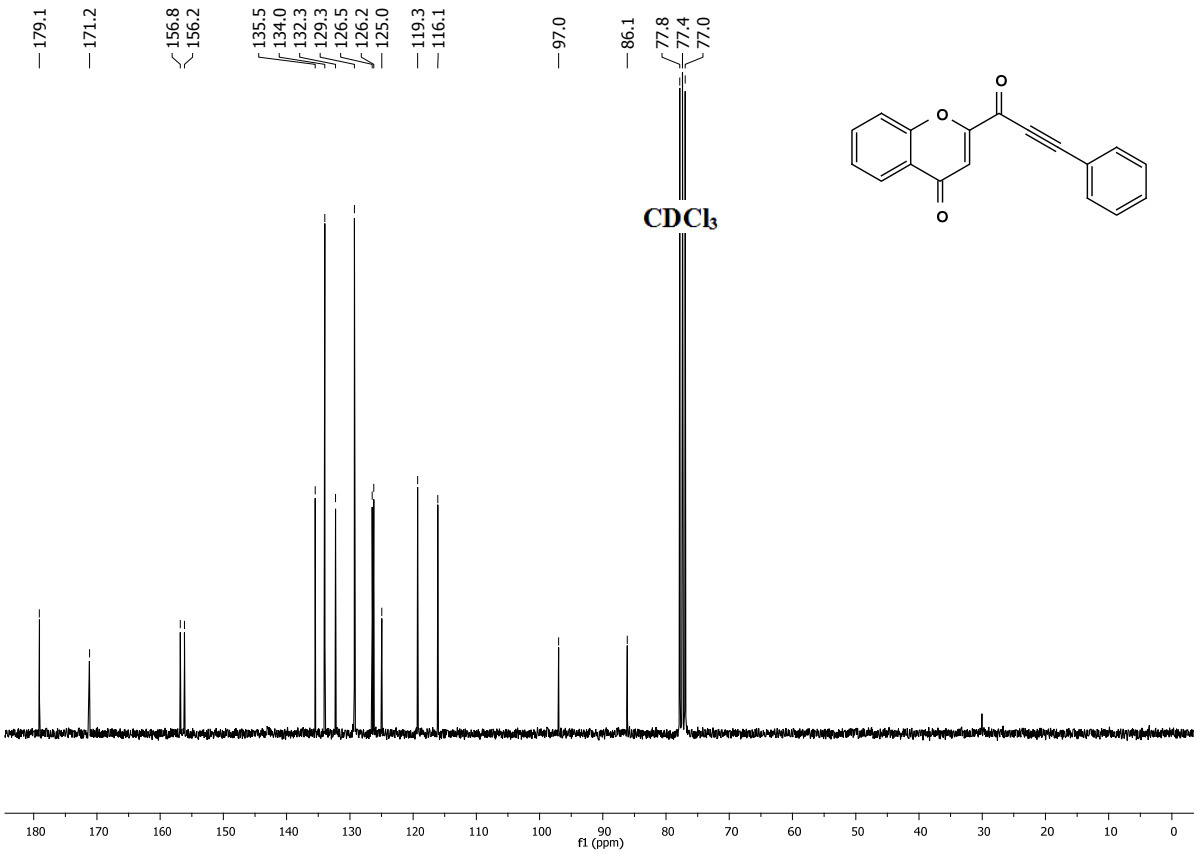

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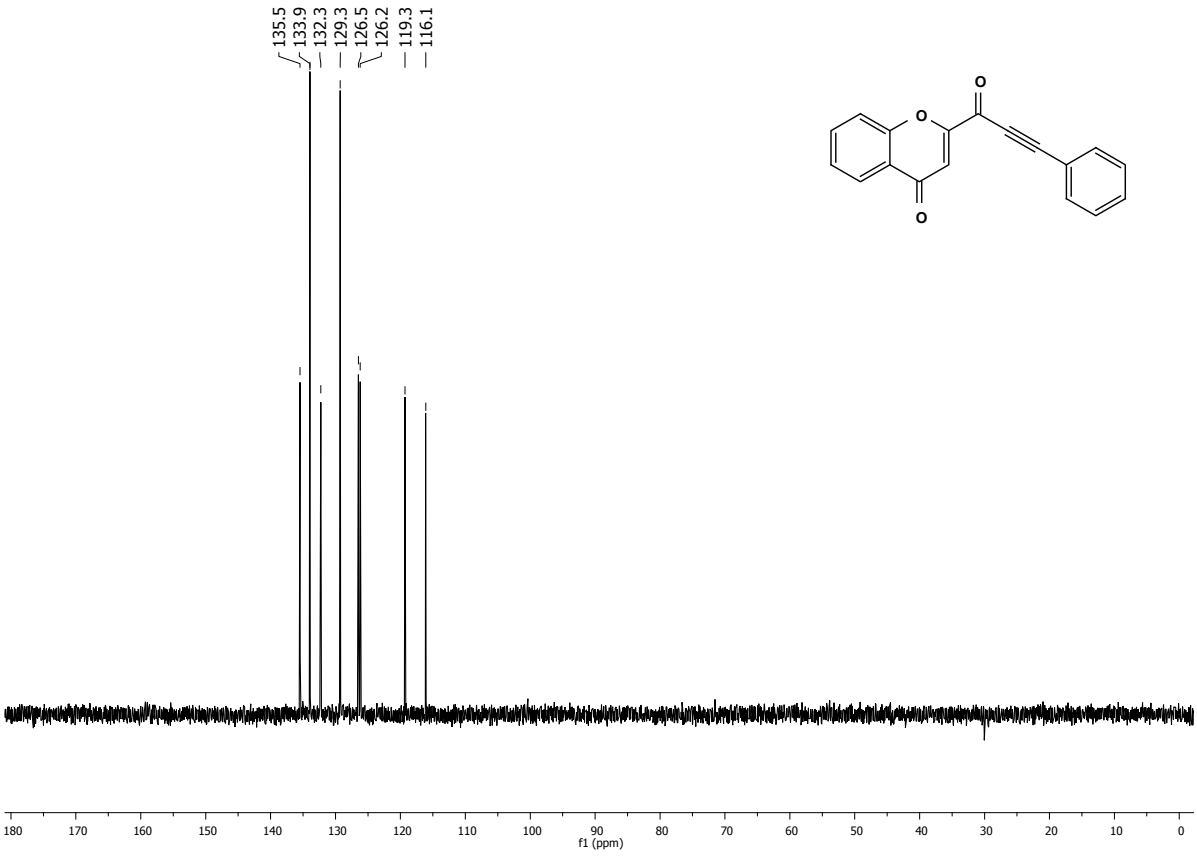
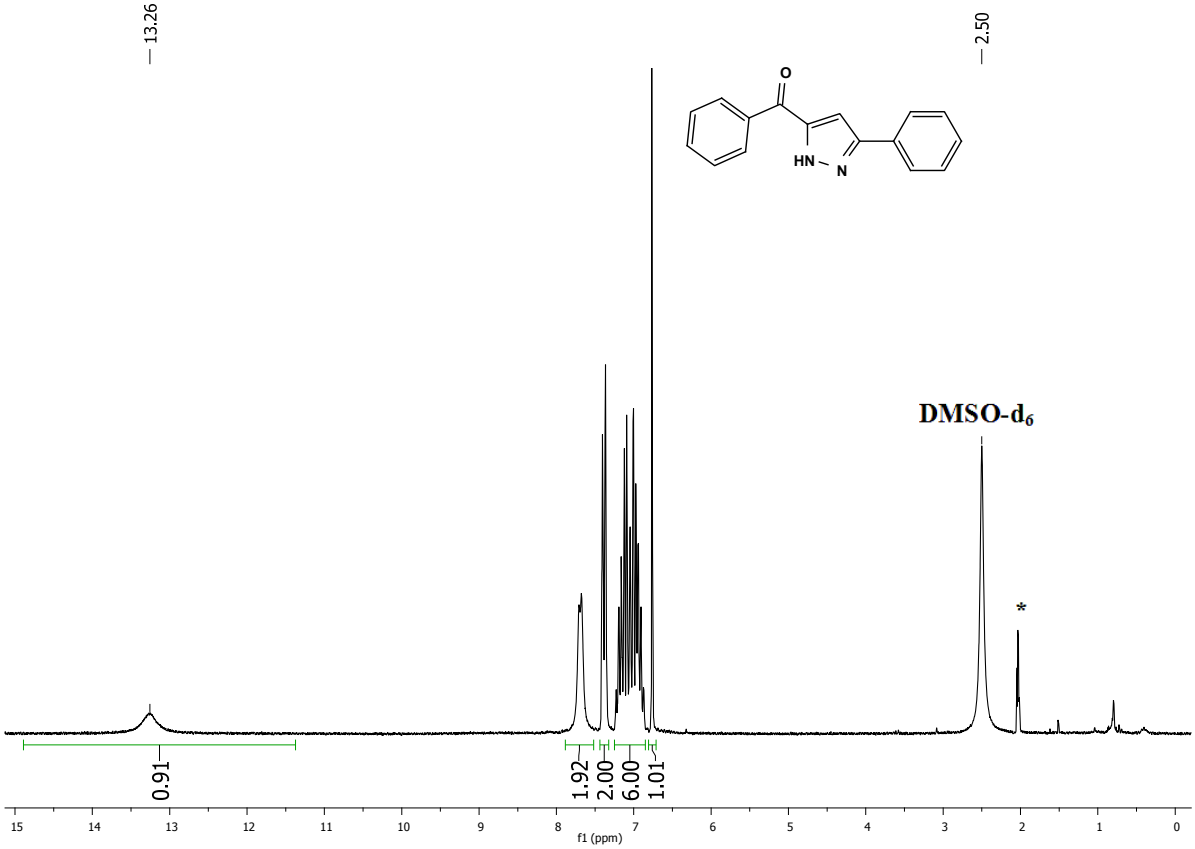
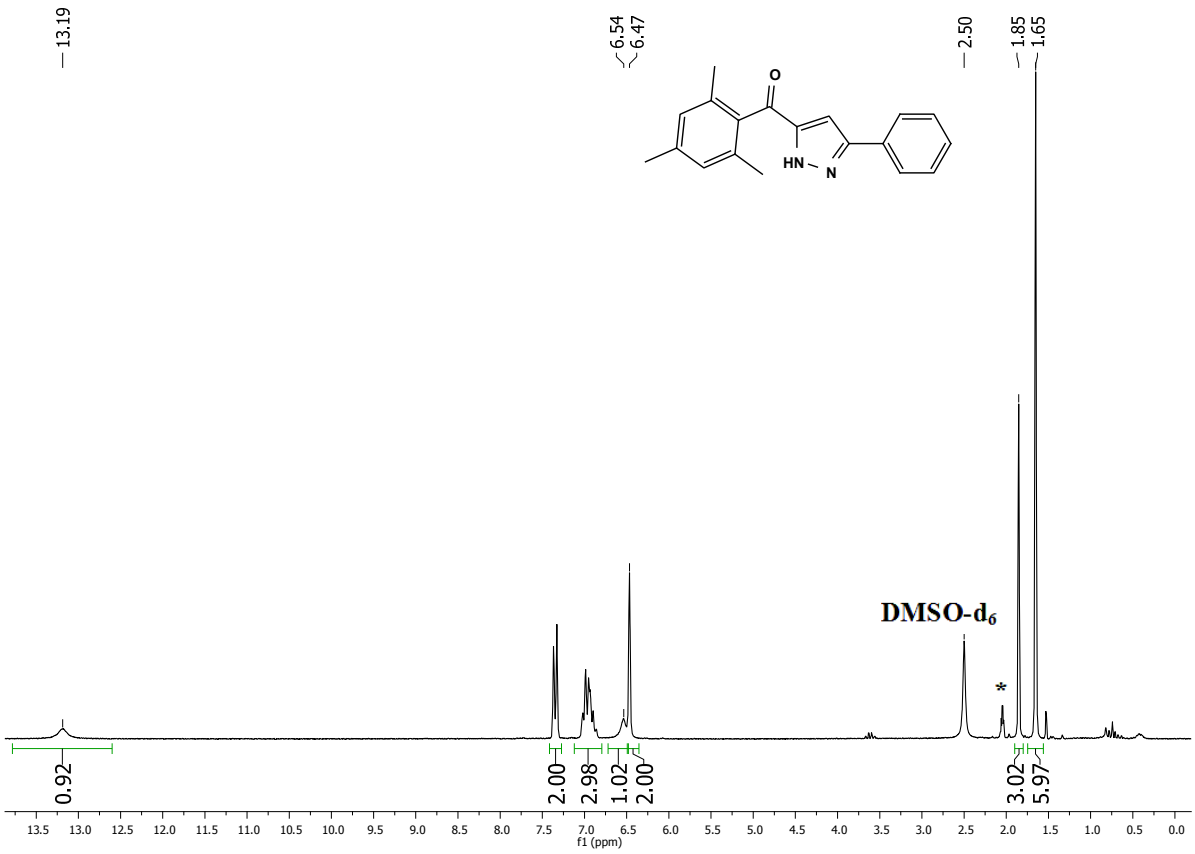


^{13}C-DEPT 135-NMR (75 MHz) of **5v** (30 mg) in $CDCl_3$ at 298 K (δ in ppm).

9 ^{1}H- and ^{13}C-NMR Spectra of compounds 7a-c



^{1}H-NMR (200 MHz) of **7a** (30 mg) in DMSO-d_6 at 373 K (δ in ppm). *Impurities from residual solvents.



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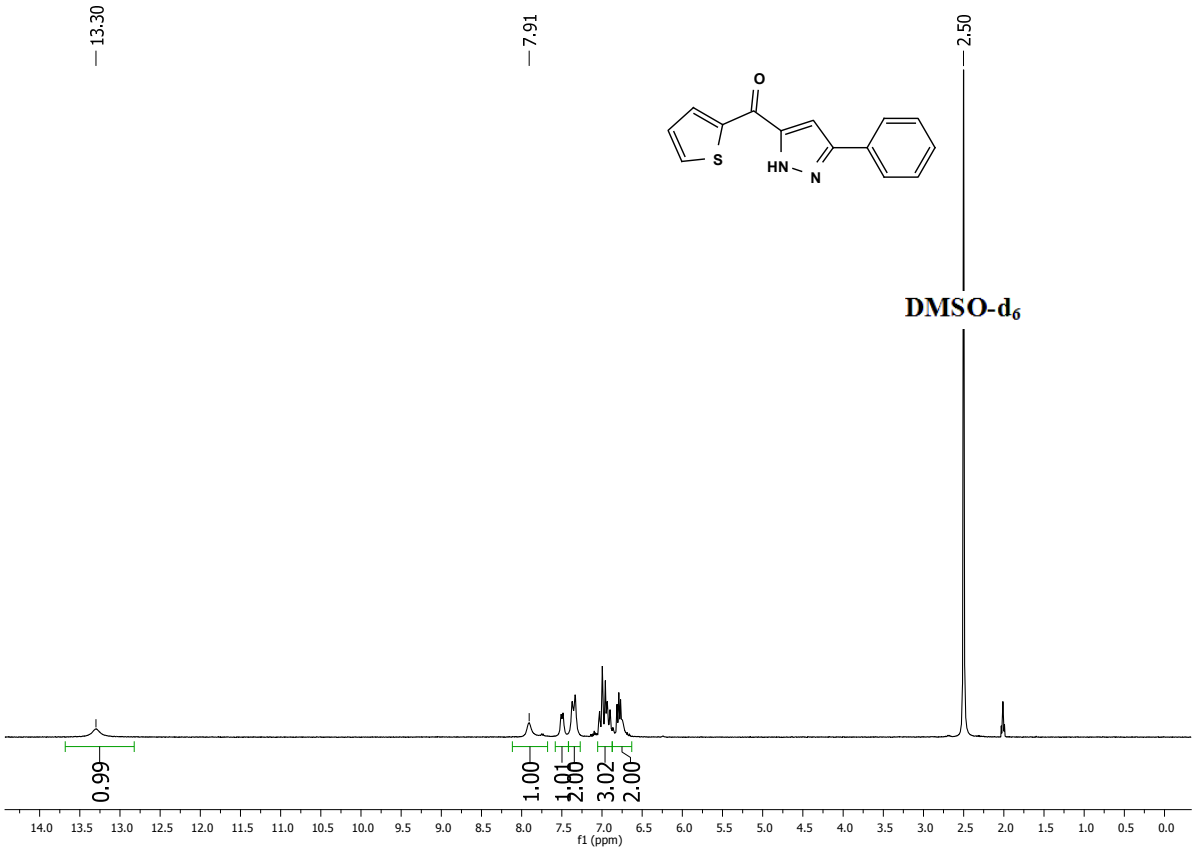
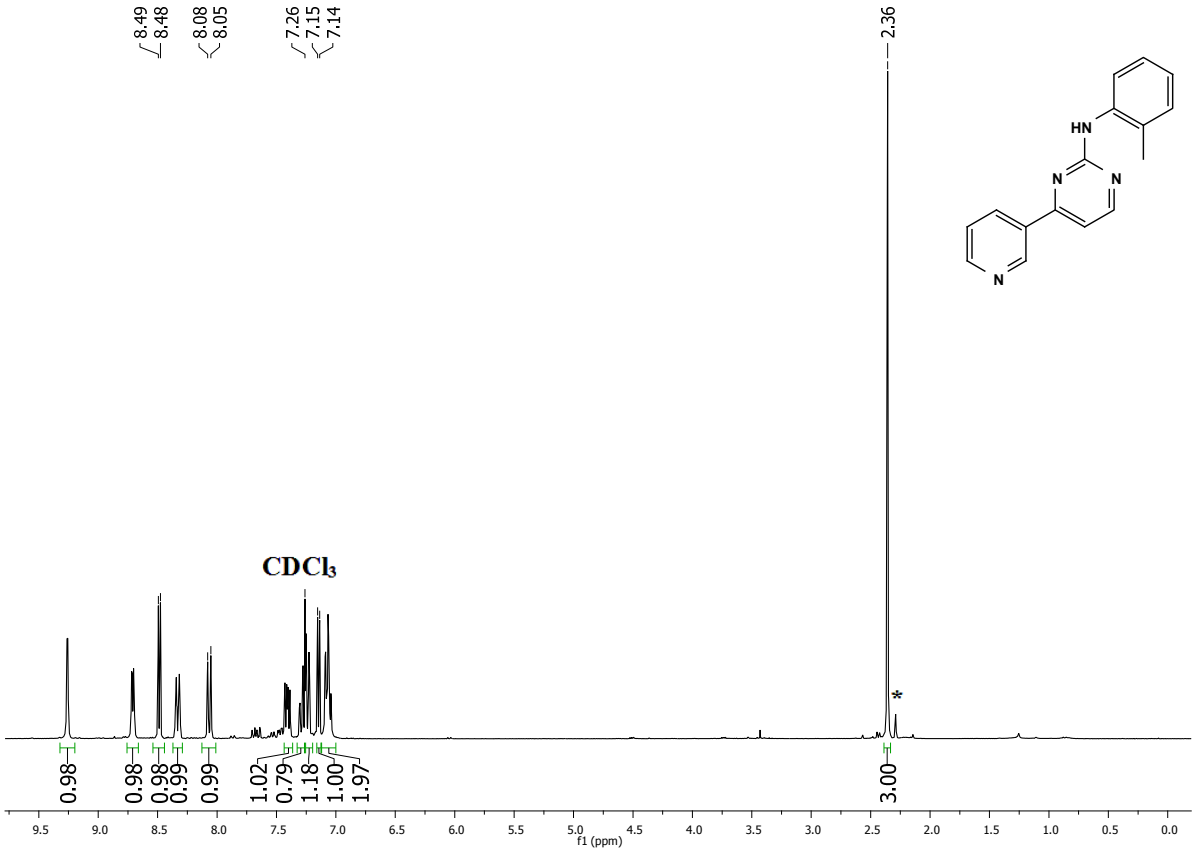


^{1}H-NMR (200 MHz) of **7c** (30 mg) in DMSO-d_6 at 373 K (δ in ppm).

10 ^{1}H- and ^{13}C-NMR Spectra of compounds 8a-b



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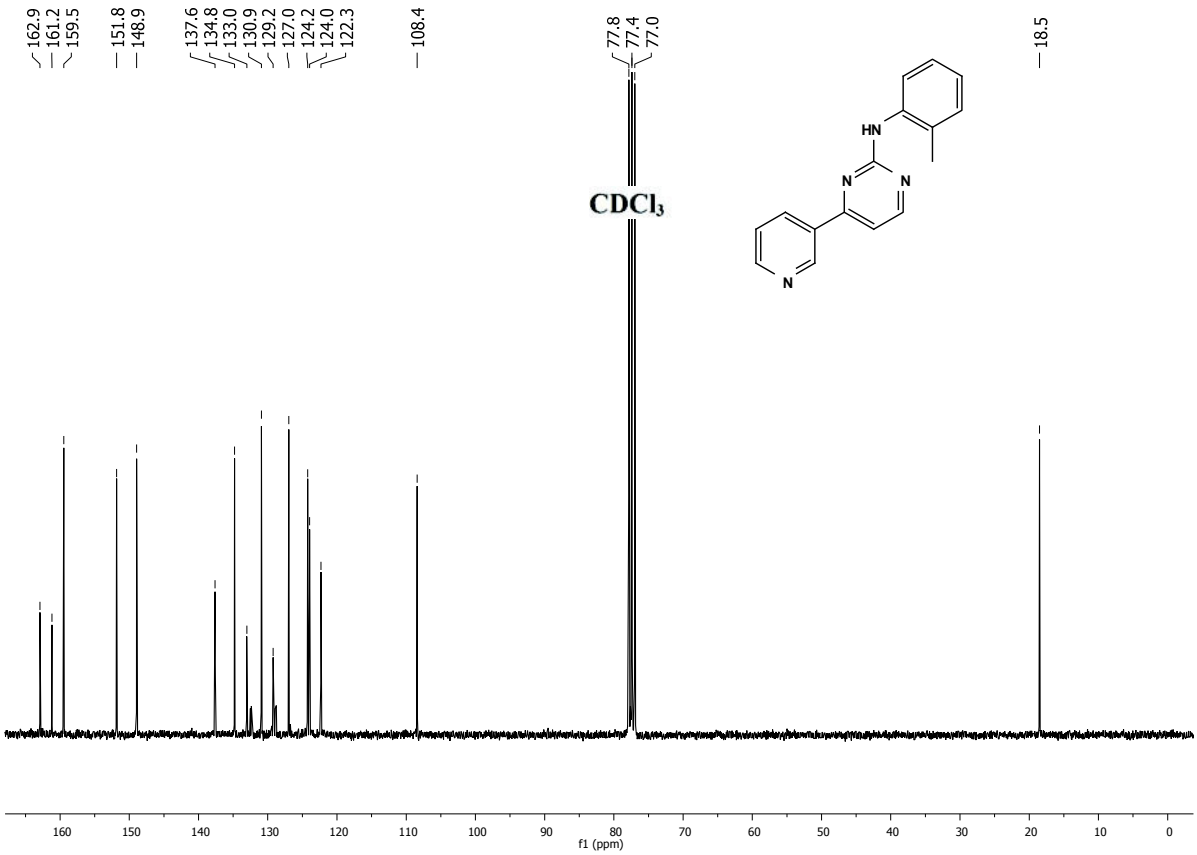

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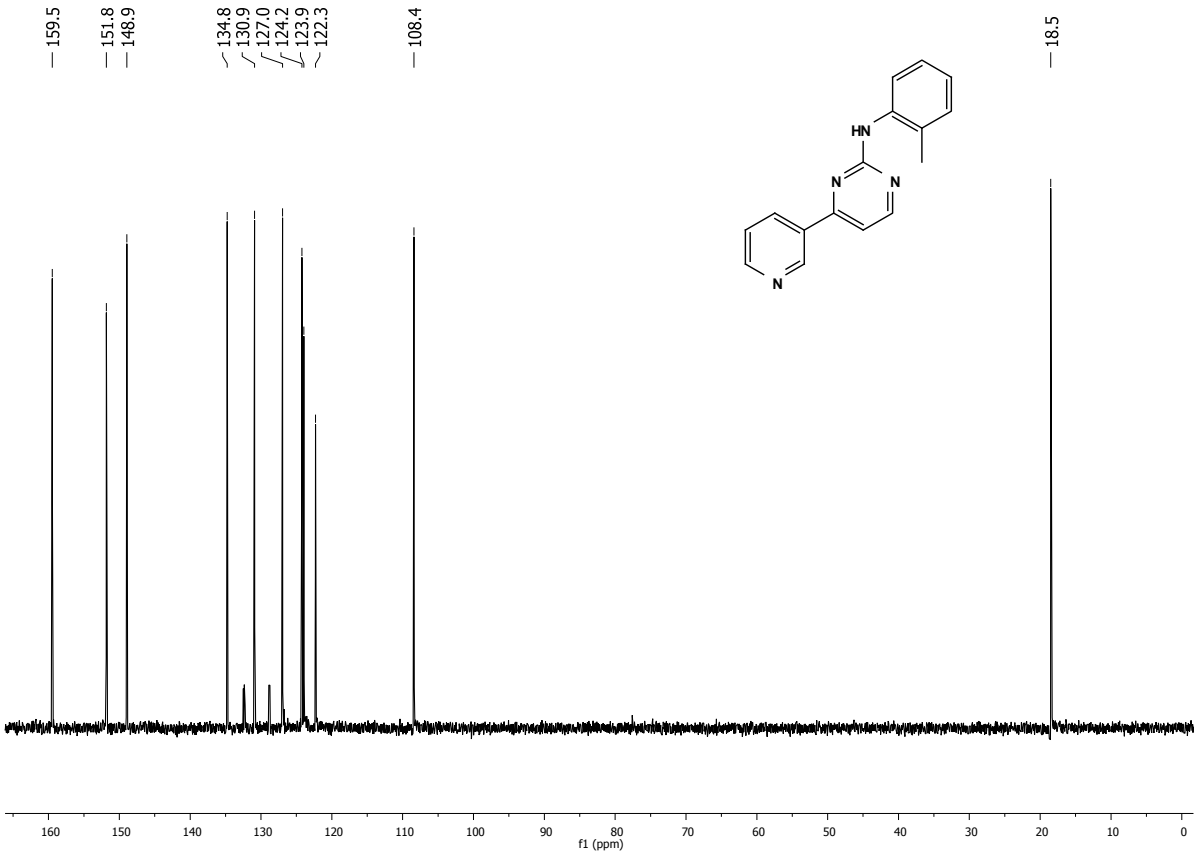

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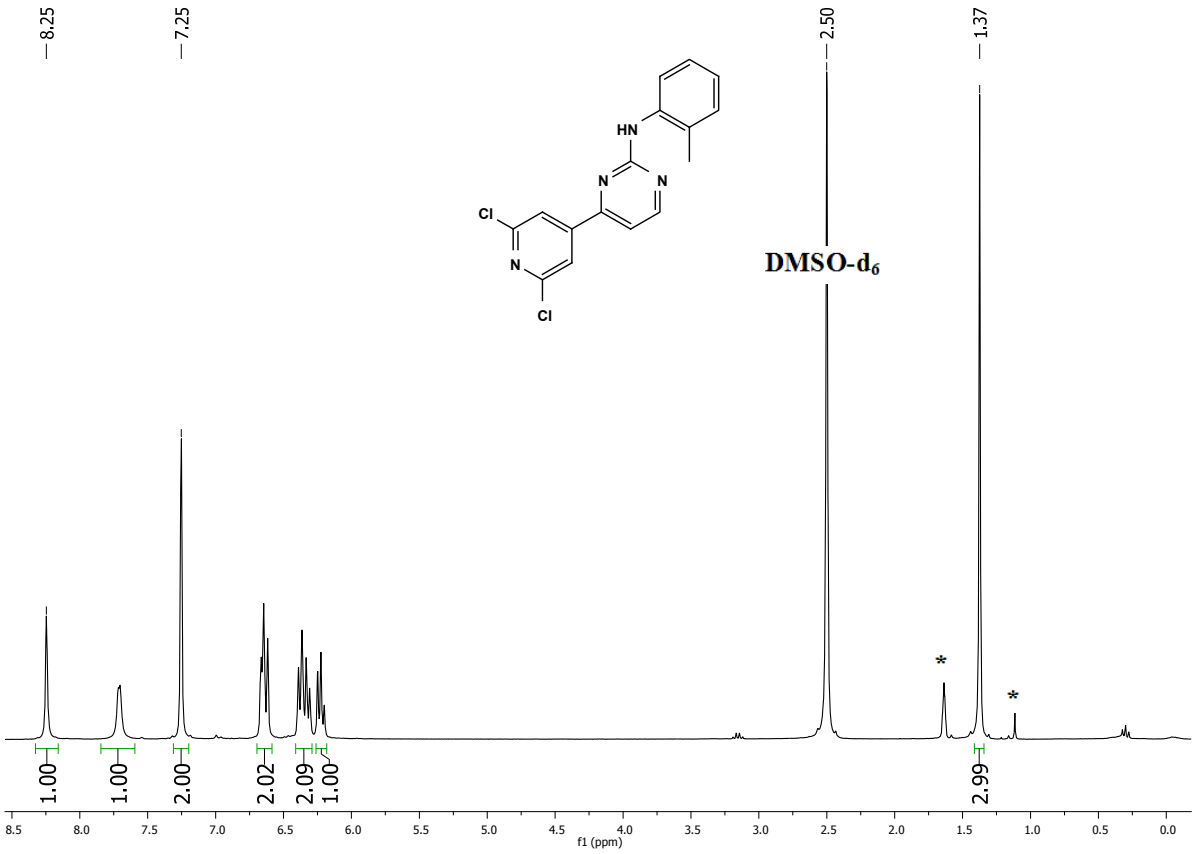

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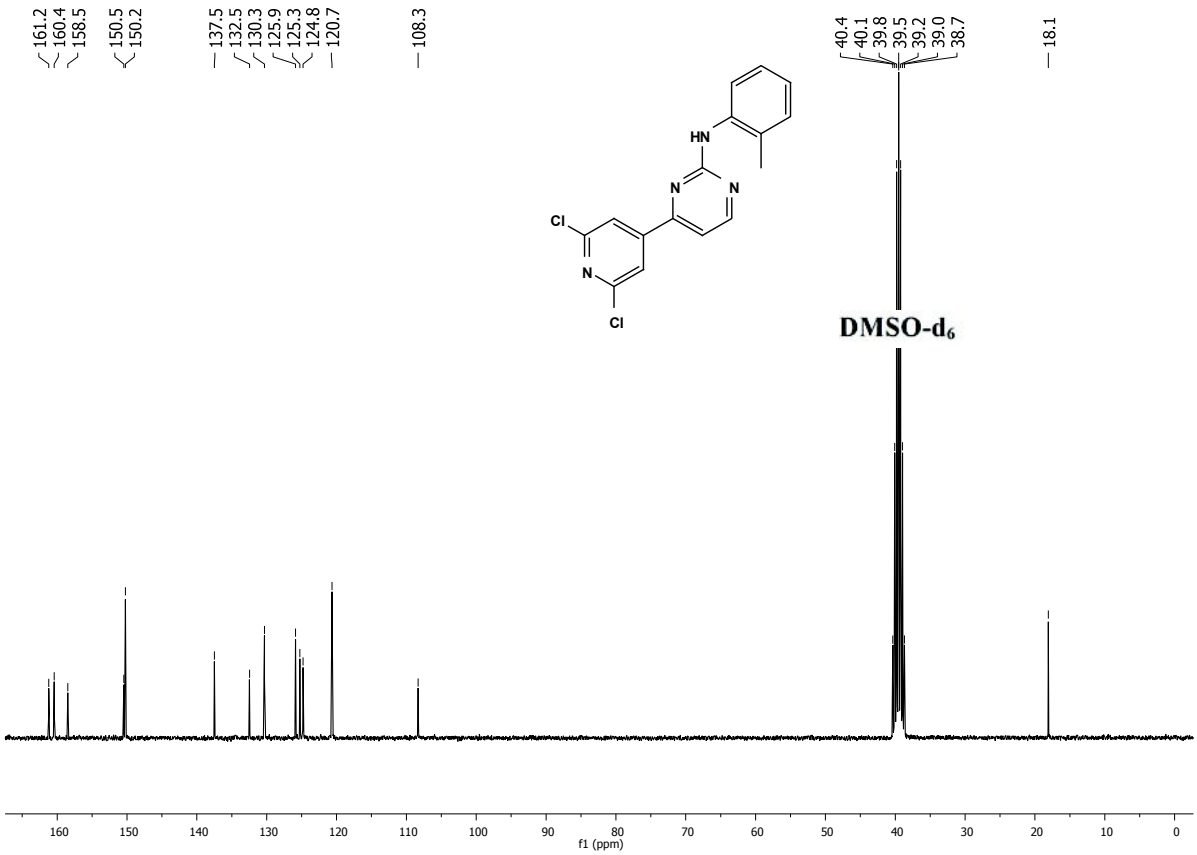

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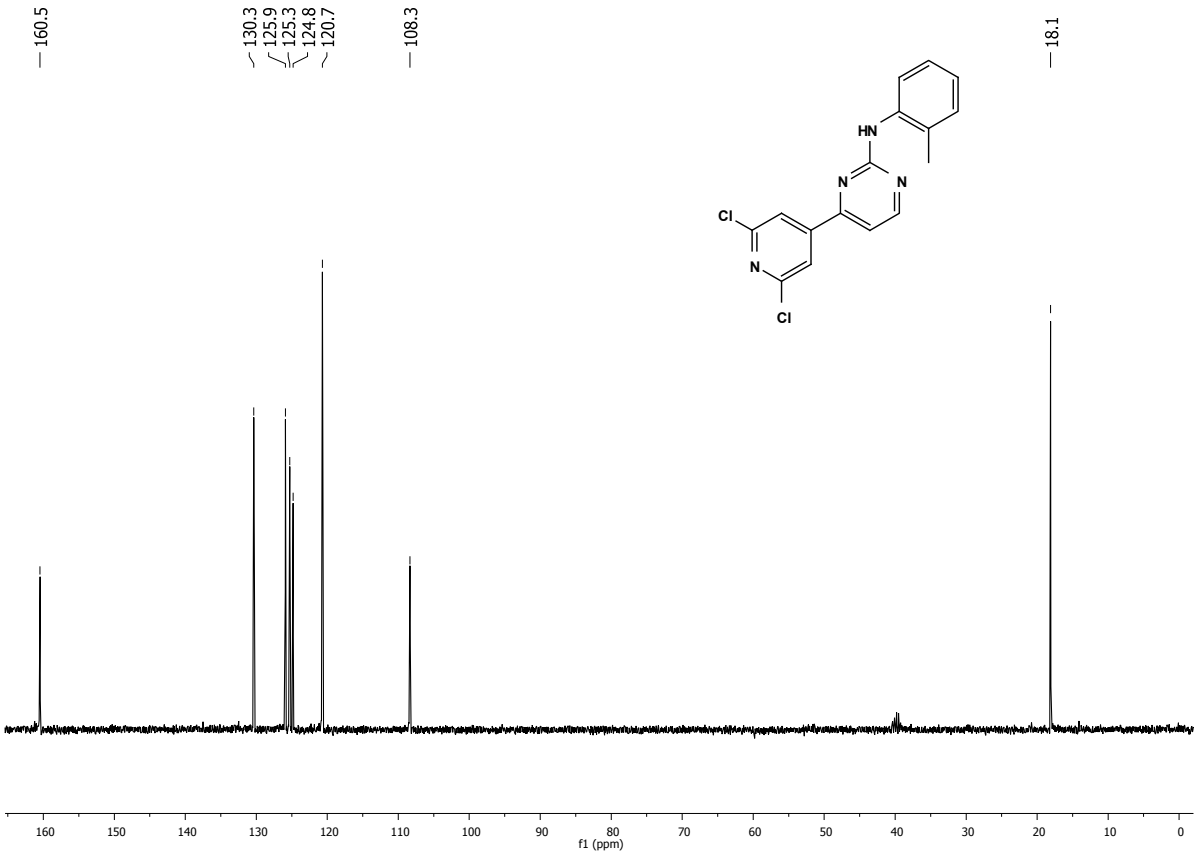

^{13}C-DEPT 135-NMR (75 MHz) of **8b** (30 mg) in DMSO-d_6 at 298 K (δ in ppm).

11 Full Reference

[22] a) E. Weisberg, P. W. Manley, W. Breitenstein, J. Brüggen, S. W. Cowan-Jacob, A. Ray, B. Huntly, D. Fabbro, G. Fendrich, E. Hall-Meyers, A. L. Kung, J. Mestan, G. Q. Daley, L. Callahan, L. Catley, C. Cavazza, A. Mohammed, D. Neuberg, R. D. Wright, D. G. Gilliland, J. D. Griffin, *Cancer Cell* **2005**, *7*, 129-141.

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Consecutive One-Pot Sonogashira–Glaser Coupling Sequence – Direct Preparation of Symmetrical Diynes by Sequential Pd/Cu Catalysis

Eugen Merkul,[a] Dominik Urselmann,[a] and Thomas J. J. Müller*[a]

Dedicated to Prof. Dr. Henning Hopf on the occasion of his 70th birthday

Keywords: Alkynes / C–C coupling / Copper / Multicomponent reactions / Palladium

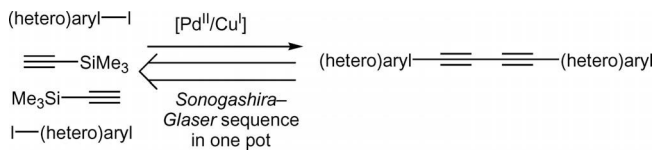
Sonogashira coupling and the catalytic Glaser coupling are both catalyzed by the Pd–Cu complex couple and can be concatenated to a consecutive sequentially Pd/Cu-catalyzed process in a one-pot fashion, and air oxygen serves as the only oxidant in the second step. In a pseudo-four-component synthesis, a broad variety of symmetrically substituted 1,4-bis(hetero)aryl-1,3-butadiynes are obtained in good to excellent yields. Interestingly, the presence of iodide ions has been found to be advantageous over other halides to trigger the Pd/Cu-catalyzed Glaser step, and Pd and Cu species, as well as triethylamine as a base, are prerequisite for both couplings, which proceed with higher efficiency if performed in a one-pot sequence.

Introduction

1,4-Disubstituted 1,3-butadiynes are recurring building blocks in natural products and analogues,[1] molecular electronic devices,[2] or optical materials[3] and serve as intermediates in the synthesis of a variety of heterocycles.[4] Traditionally, copper(I)- or copper(II)-catalyzed Glaser,[5] Eglinton,[6] or Hay[7] coupling reactions and their numerous modifications[8] utilizing terminal alkynes as substrates are applied for the synthesis of symmetrical 1,3-diynes. Even more efficient transformations rely on catalytic systems consisting of combined palladium(0) or palladium(II) and copper(I) sources.[9] Recently, a ligand-, palladium-, amine- and even oxidant-free procedure, which uses copper nanoparticles as a catalyst, has been reported.[8a] Despite numerous efficient strategies developed for Glaser-type acetylene dimerizations,[10] the major drawback of utilizing terminal alkynes as substrates is their sensitivity towards polymerization and their occasionally tedious purification. Moreover, some of the terminal alkynes proved to be quite unstable, which limits their shelf life and complicates their synthesis. Therefore, a synthetic route that avoids the isolation of these compounds would be highly desirable.

In the past years some methodologies for the preparation of 1,3-butadiynes starting from alkynyltrifluoroborates,[11a] alkynylboronates,[11b] or alkynylsilanes[11c–11e] have been published. Although these transformations avoid the use of free terminal alkynes, they still require the application of sophisticated organoboron or organosilicon substrates.

A reliable, quick and general approach to generate terminal alkynes starting from easily available (hetero)aryl halides employs the Pd/Cu-cocatalyzed Sonogashira–Hagihara cross coupling, followed by subsequent deprotection.[12] Since this catalytic system matches with the conditions of the Glaser-type couplings mentioned above,[9] the development of a sequentially catalyzed route for the synthesis of 1,4-disubstituted 1,3-butadiynes utilizing the same catalyst couple for alkynylation and oxidative coupling lies at hand (Scheme 1). The isolation of intermediate terminal alkynes becomes dispensable. To the best of our knowledge, this obvious and straightforward concept has never been realized.



Scheme 1. Concept of a Sonogashira–Glaser coupling sequence.

Concatenating the Sonogashira and the Glaser coupling reactions into a one-pot sequence is especially advantageous from an economical point of view but also because of practical considerations. Herein, we report a sequence of a Pd/Cu-cocatalyzed Sonogashira coupling of iodo arenes with trimethylsilylacetylene (TMSA), followed by in-situ cleavage of the silyl protective group and subsequent Glaser-type homocoupling of the generated terminal alkynes

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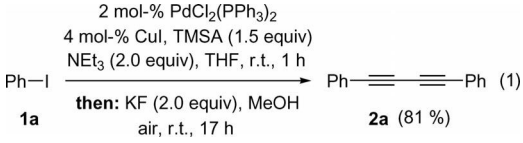
to form symmetrical 1,4-disubstituted 1,3-butadiynes under aerobic conditions in a one-pot fashion. This resulting sequence represents another unique showcase for sequentially Pd/Cu-catalyzed processes.[13]

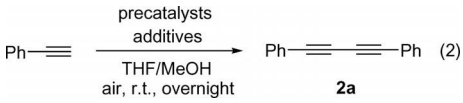
Results and Discussion

At the outset of our investigations, we reacted iodobenzene (**1a**) with TMSA (1.5 equiv.) under standard Sonogashira conditions [$PdCl_2(PPh_3)_2$, CuI, and NEt_3 as a base][14] to form trimethyl(phenylethynyl)silane in a smooth reaction within 1 h at ambient temperature. After the reaction vessel was opened, potassium fluoride and methanol were added to cleave the TMS protective group. Simultaneously, upon subjecting to aerobic atmosphere and further stirring at room temperature, the Glaser-type coupling proceeded smoothly. The desired 1,4-diphenylbuta-1,3-diyne (**2a**) was isolated in 81% yield [Equation (1)].



(1)

To gain insight into the mode of action of the catalytic system in the final Glaser coupling step, we subjected commercially available phenylacetylene to different combinations of precatalysts and additives used for the entire sequence to form the diyne **2a** in a single step [Equation (2), Table 1].



(2)

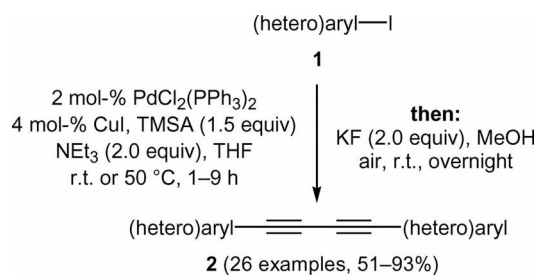
Table 1. Influence of precatalysts and additives in the Glaser-type coupling step.[a]

Entry	Conditions	Time [h]	Yield of **2a** [%][b]
1	no additives	24	58
2	no $PdCl_2(PPh_3)_2$, no additives	25	8
3	no CuI, no additives	25	36
4	1.0 equiv. KF	26	82
5	1.0 equiv. NH_4Cl	26	86
6	1.0 equiv. NaBr	26	92
7	1.0 equiv. NaI	26	95
8	1.0 equiv. NaI, no NEt_3	26	5
9	1.0 equiv. NaI, no CuI	26	41
10	1.0 equiv. NaI, no $PdCl_2(PPh_3)_2$	26	7

[a] All reactions were carried out on a 2-mmol scale with 2 mol-% $PdCl_2(PPh_3)_2$, 4 mol-% CuI, and NEt_3 (1.0 equiv.) in a mixture of THF (5 mL) and methanol (5 mL). The mixture was stirred at room temperature for the indicated time. The conditions were varied or adjusted by additives as indicated. [b] Yield of isolated and purified compound **2a**.

Whilst use of Cu^I iodide as a single catalyst gave only very low amounts of the desired compound **2a** (Entry 2), application of the palladium precatalyst led to the formation of an increased amount of diyne **2a** (Entry 3). Upon combination of both precatalysts, a slight increase in the isolated yield of product **2a** could be observed (Entry 1). Another experiment, which uses 2 mol-% $PdCl_2(PPh_3)_2$, 4 mol-% CuI, and 1.5 equiv. KF starting from commercially available trimethyl(phenylethynyl)silane, gave 55% of diyne **2a** within 28 h of reaction time. This implies that no fluorosilanate complexes are involved in the transmetalation step. Surprisingly, the yields of the Glaser coupling step alone were much lower than those from the complete sequence, which additionally includes Sonogashira and deprotection steps. Bearing in mind that the apparent difference between the conditions applied in the sequence and in the separated Glaser coupling step is the generation of 1 equiv. triethylammonium iodide in the Sonogashira coupling step, we scrutinized the influence of halide anions on the Glaser coupling step. Thus, upon addition of 1.0 equiv. potassium fluoride, the yield of the isolated diyne **2a** increased dramatically relative to the yield obtained without additives (Entries 1 and 4). Furthermore, the yield continuously increased from fluoride (82%) through chloride (86%) and bromide (92%) to iodide (95%) (Entries 4–7). To the best of our knowledge, the effect of halide anions on the Glaser coupling has neither been observed nor investigated. Although the reason for this behavior is not clear at this stage, the high yield obtained by the addition of iodide may explain the high efficiency of the developed sequence, since ammonium iodide generated in the Sonogashira step could promote the Glaser coupling step. Moreover, this preliminary investigation shows that the catalytic system $PdCl_2(PPh_3)_2$/CuI/NEt_3 is essential for both Sonogashira and Glaser coupling reactions to proceed efficiently, since the absence of one of these components diminishes the yield dramatically (Entries 8–10). These findings clearly emphasize the benefits of combining Sonogashira and Glaser couplings into a one-pot sequence.

The presented sequence is preparatively strikingly simple and utilizes commercially available and stable reagents and precatalysts without fancy ligands or additives. The use of air as an oxidant additionally supports the sustainable aspect of the method (Scheme 2). With these mild conditions for the sequence in hand, the substrate scope was examined and a novel pseudo-four-component synthesis of symmetrical 1,3-butadiynes **2** was established (Figure 1). All reactions were carried out on a 2-mmol scale with respect to (hetero)aryl iodide **1**. The structures of compounds **2** were unambiguously supported by combustion analysis, NMR spectroscopy, and mass spectrometry.



Scheme 2. Optimized Sonogashira–Glaser coupling sequence for the synthesis of 1,4-bis(hetero)aryl-1,3-butadiynes **2**.

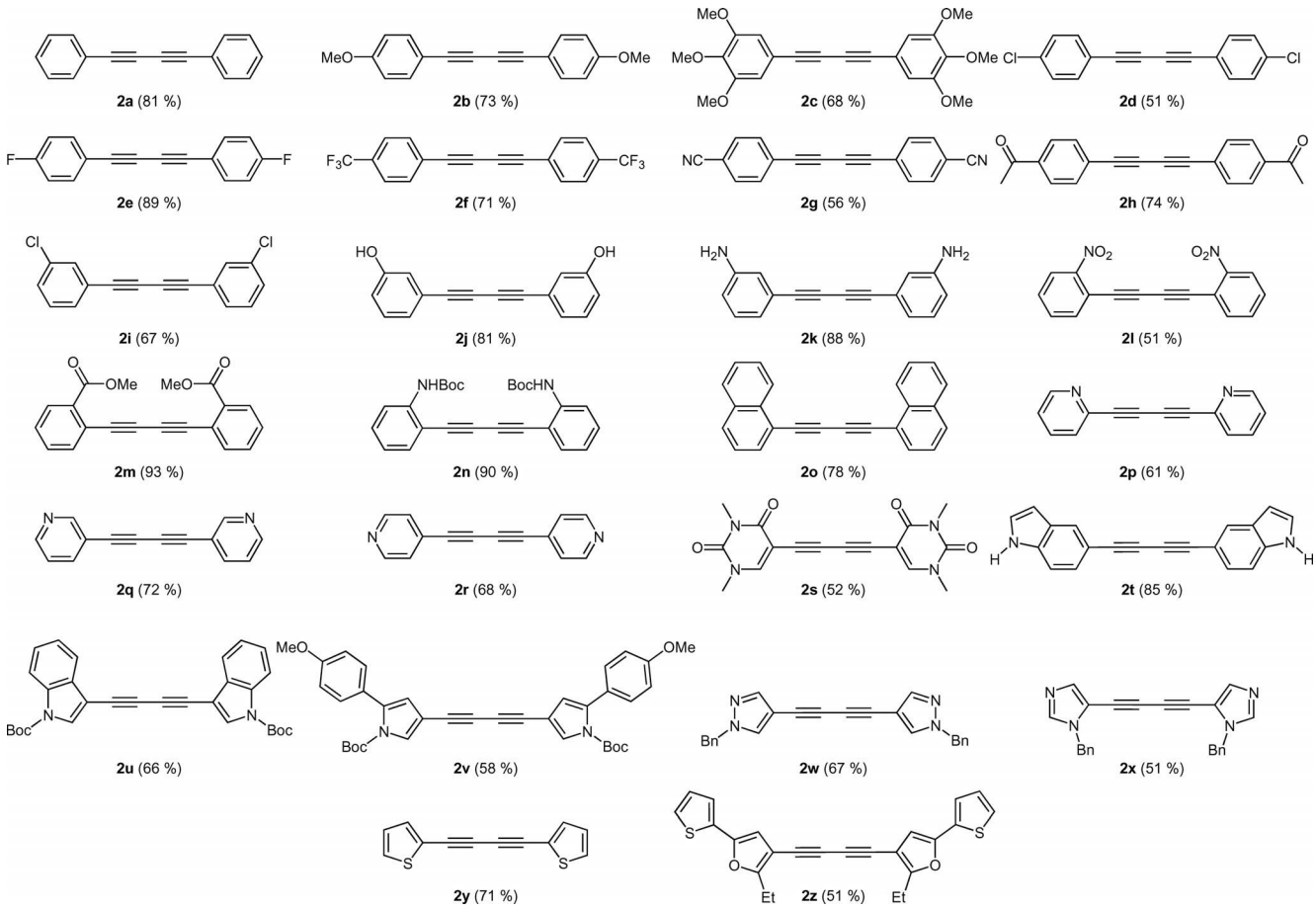
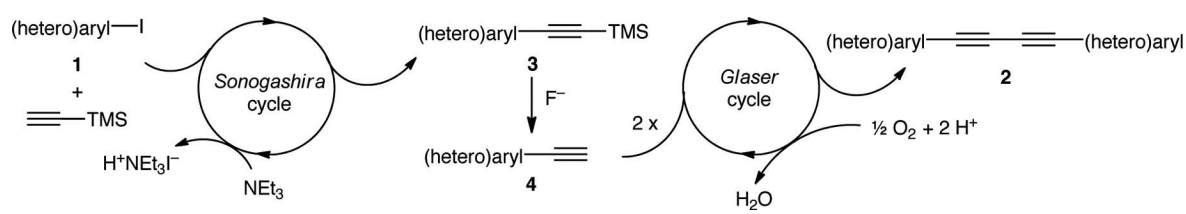


Figure 1. Synthesized diynes **2** (isolated yields). Me = methyl, Boc = *tert*-butoxycarbonyl, Bn = benzyl, Et = ethyl.

The substituent pattern of the obtained 1,4-bis(hetero)-aryl-1,3-butadiynes **2** (Figure 1) clearly supports that the precursor (hetero)aryl halides **1** can be electroneutral, electron rich, as well as electron poor. Substituents in the *ortho*-, *meta*- and *para* position, as well as the higher-substituted trimethoxyphenyl group or the dimethyluracil derivative, are tolerated. Overall, a large variety of functional groups in the (hetero)aryl iodides **1**, such as halides, nitro, cyano, ester, amide, carbamate, urea, and, even unprotected hydroxy and amino groups, can be carried through the sequence without difficulties. The functional group tolerance and the possibility to react different types of electronically diverse six- and five-membered heterocyclic iodides are remarkable for such a simple sequence. In most cases, the isolated target compounds **2** are stable crystalline solids that can be conveniently purified by column chromatography or recrystallization. The crude reaction mixtures obtained by the described sequence showed no notable amounts of by-products in the TLC in nearly all examples mentioned above. Thus, isolation of the desired 1,3-butadyines **2** turned out to be remarkably quick and easy. It should be noted that the reaction times (see Supporting Information, Table S2) are not optimized and might be considerably shorter than indicated. The yields of the isolated diynes **2** are fair to excellent regardless of the electronic nature or substituent pattern of the applied iodides. The whole sequence is performed at ambient temperature. Indeed, many applications in medicinal chemistry and material science can be envisioned.

By considering the results obtained from our preliminary studies (vide supra), the mechanistic rationale of this Sonogashira–Glaser coupling sequence can be outlined as follows (Scheme 3). In the Sonogashira cycle, driven by the catalytic Pd^0/Cu^I pair, the cross-coupling of (hetero)aryl io-



Scheme 3. Mechanistic sketch of the consecutive one-pot Sonogashira–Glaser coupling sequence.

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dide **1** and TMSA furnishes the TMS-protected (hetero)aryl alkyne **3**, which is deprotected with fluoride to give the corresponding terminal alkyne **4**. Alkyne **4** (2 equiv.) now enters the Glaser cycle, which is triggered by the catalytic Pd^{II}/Cu^{I} pair. Cu^{I} ions are involved in transmetalation to Pd^{II}, and thus a dialkynyl Pd^{II} complex is generated, which furnishes the desired 1,3-butadiyne **2** upon reductive elimination. Moreover, Cu^{I} is readily oxidized to Cu^{II} by atmospheric oxygen. In analogy to the Wacker oxidation,[15] an intercepting Cu^{I}/Cu^{II} cycle fueled by oxygen is ultimately responsible for reoxidizing Pd^{0} back to Pd^{II}. Interestingly, the same mechanism that leads to the unwanted by-product of the Sonogashira coupling in the initial activation step[16] now becomes the modus operandi to form the desired diynes **2**.

Conclusions

In conclusion, we have disclosed a general, efficient and economical sequentially Pd/Cu-catalyzed one-pot reaction for transforming (hetero)aryl iodides into symmetrical 1,4-disubstituted 1,3-butadiynes. The commercially available or easily accessible starting materials,[17] the wide range of tolerated functional groups, and the simplicity of the described sequence render it a practical method for routine applications. Methodological extension to aryl bromides and chlorides as substrates and studies taking advantage of the versatility of 1,3-butadiynes in a variety of catalytic and non-catalytic conversions are currently under investigation.

Experimental Section

Synthesis of 2m: A mixture of methyl 2-iodobenzoate (**1m**) (535 mg, 2.00 mmol), $PdCl_2(PPh_3)_2$ (28 mg, 0.04 mmol, 2 mol-%) and CuI (16 mg, 0.08 mmol, 4 mol-%) was dissolved in dry degassed THF (5.00 mL) in a screw-cap Schlenk vessel with septum. After addition of TMSA (0.43 mL, 3.00 mmol) and dry triethylamine (0.55 mL, 4.00 mmol), the solution was stirred at room temperature (water bath) for 1 h until complete conversion (monitored by TLC). KF (236 mg, 4.00 mmol) and methanol (5.00 mL) were then added, and the reaction mixture was stirred in air (the reaction vessel was opened) for 22 h. After completion of the reaction, as indicated by TLC, the mixture was filtered and adsorbed on Celite®, and after removal of the solvents in vacuo, the residue was purified by column chromatography on silica gel by using petroleum ether (boiling range 40–60 °C)/ethyl acetate = 10:1 (R_f = 0.15) to give, after drying in vacuo, 1,4-bis(2-methylbenzoyl)buta-1,3-diyne (**2m**) (296 mg; 93%) as a yellow oil. Upon suspension in *n*-pentane, sonication in ultrasound bath, filtration and drying in vacuo, an analytically pure yellow solid was obtained. M.p. 59–60 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.97 (s, 6 H), 7.40–7.44 (m, 2 H), 7.48–7.52 (m, 2 H), 7.65–7.69 (m, 2 H), 7.97–8.00 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 52.4 (CH_3), 78.9 (C_{quat}), 81.5 (C_{quat}), 122.5 (C_{quat}), 128.8 (CH), 130.6 (CH), 131.8 (CH), 132.7 (C_{quat}), 135.2 (CH), 166.1 (C_{quat}) ppm. EI-MS (70 eV): *m*/*z* (%) = 318 $[M]^+$ (46), 303 $[M - CH_3]^+$ (32), 285 (61), 275 (25), 272 (28), 259 $[M - C_2H_3O_2]^+$ (74), 258 (34), 257 (40), 204 (28), 202 $[C_{16}H_{10}]^+$ (49), 200 $[C_{16}H_8]^+$ (25), 189 (35), 188 (31), 187 (60), 176 (41), 144 (100), 133 (25), 127 (32), 114 (37), 105 (27), 101 (35), 100 (51), 88 (48), 87 (35). $C_{20}H_{14}O_4$ (318.3): C 75.46, H 4.43; found C 75.22, H 4.70.

Supporting Information (see footnote on the first page of this article): Experimental procedures and spectroscopic data for the compounds prepared are presented.

Acknowledgments

The authors cordially thank Merck Serono KGaA, Darmstadt for the financial support of this research.

[1] a) A. L. K. Shi Shun, R. R. Tykwinski, *Angew. Chem.* **2006**, *118*, 1050–1073; *Angew. Chem. Int. Ed.* **2006**, *45*, 1034–1057; b) W. N. Setzer, D. M. Moriarity, *Chem. Pharm. Bull.* **2000**, *48*, 1776–1777; c) T. R. Hoye, P. R. Chanson, *Tetrahedron Lett.* **1993**, *34*, 5043–5046; d) A. B. Holmes, A. B. Tabor, R. Baker, *J. Chem. Soc. Perkin Trans. 1* **1991**, 3307–3313; e) L. Crombie, A. J. W. Hobbs, M. A. Horsham, R. J. Blade, *Tetrahedron Lett.* **1987**, *28*, 4875–4878; f) A. B. Holmes, C. L. D. Jennings-White, D. A. Kendrick, *J. Chem. Soc., Chem. Commun.* **1983**, 415–417.

[2] C. Fouquey, J.-M. Lehn, J. Malthête, *J. Chem. Soc., Chem. Commun.* **1987**, 1424–1426.

[3] a) T. Kitamura, C. H. Lee, Y. Taniguchi, Y. Fujiwara, *J. Am. Chem. Soc.* **1997**, *119*, 619–620; b) D. R. Kanis, M. A. Ratner, T. J. Marks, *Chem. Rev.* **1994**, *94*, 195–242.

[4] a) V. Lavallo, G. D. Frey, B. Donnadieu, M. Soleilhavoup, G. Bertrand, *Angew. Chem.* **2008**, *120*, 5302–5306; *Angew. Chem. Int. Ed.* **2008**, *47*, 5224–5228; b) T. Okitsu, D. Nakazawa, R. Taniguchi, A. Wada, *Org. Lett.* **2008**, *10*, 4967–4970; c) T. Matsuda, S. Kadowaki, M. Murakami, *Chem. Commun.* **2007**, 2627–2629; d) G. Abbiati, A. Arcadi, E. Beccalli, G. Bianchi, F. Marinelli, E. Rossi, *Tetrahedron* **2006**, *62*, 3033–3039; e) C. Koradin, W. Dohle, A. L. Rodriguez, B. Schmid, P. Knochel, *Tetrahedron* **2003**, *59*, 1571–1587; f) K. Shin, K. Ogasawara, *Synlett* **1995**, 859–860; g) F. Freeman, H. Lu, Q. Zeng, *J. Org. Chem.* **1994**, *59*, 4350–4354.

[5] a) S. Adimurthy, C. C. Malakar, U. Beifuss, *J. Org. Chem.* **2009**, *74*, 5648–5651; b) C. Glaser, *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422–424.

[6] G. Eglinton, A. R. Galbraith, *J. Chem. Soc.* **1959**, 889–896.

[7] a) L. Fomina, B. Vazquez, E. Tkachouk, S. Fomine, *Tetrahedron* **2002**, *58*, 6741–6747; b) A. S. Hay, *J. Org. Chem.* **1962**, *27*, 3320–3321.

[8] a) F. Nador, L. Fortunato, Y. Moglie, C. Vitale, G. Radivoy, *Synthesis* **2009**, 4027–4031; b) J. Li, H. Jiang, *Chem. Commun.* **1999**, 2369–2370.

[9] a) S.-N. Chen, W.-Y. Wu, F.-Y. Tsai, *Green Chem.* **2009**, *11*, 269–274; b) F. Yang, X. Cui, Y.-n. Li, J. Zhang, G.-r. Ren, Y. Wu, *Tetrahedron* **2007**, *63*, 1963–1969; c) M. Shi, H.-X. Qian, *Appl. Organomet. Chem.* **2006**, *20*, 771–774; d) A. S. Batsanov, J. C. Collings, I. J. S. Fairlamb, J. P. Holland, J. A. K. Howard, Z. Lin, T. B. Marder, A. C. Parsons, R. M. Ward, J. Zhu, *J. Org. Chem.* **2005**, *70*, 703–706; e) J.-H. Li, Y. Liang, X.-D. Zhang, *Tetrahedron* **2005**, *61*, 1903–1907; f) J.-H. Li, Y. Liang, Y.-X. Xie, *J. Org. Chem.* **2005**, *70*, 4393–4396; g) I. J. S. Fairlamb, P. S. Bäuerlein, L. R. Marrison, J. M. Dickinson, *Chem. Commun.* **2003**, 632–633; h) A. Lei, M. Srivastava, X. Zhang, *J. Org. Chem.* **2002**, *67*, 1969–1971; i) Q. Liu, D. J. Burton, *Tetrahedron Lett.* **1997**, *38*, 4371–4374; j) R. Rossi, A. Carpita, C. Bigelli, *Tetrahedron Lett.* **1985**, *26*, 523–526.

[10] For a review on acetylenic couplings, see: P. Siemsen, R. C. Livingston, F. Diederich, *Angew. Chem.* **2000**, *112*, 2740–2767; *Angew. Chem. Int. Ed.* **2000**, *39*, 2632–2657.

[11] a) M. W. Paixão, M. Weber, A. L. Braga, J. B. de Azeredo, A. M. Deobald, H. A. Stefani, *Tetrahedron Lett.* **2008**, *49*, 2366–2370; b) Y. Nishihara, M. Okamoto, Y. Inoue, M. Miyazaki, M. Miyasaka, K. Takagi, *Tetrahedron Lett.* **2005**, *46*, 8661–8664; c) M. A. Heuft, S. K. Collins, G. P. A. Yap, A. G.

Fallis, *Org. Lett.* **2001**, *3*, 2883–2886; d) Y. Nishihara, K. Ikegashira, A. Mori, T. Hiyama, *Tetrahedron Lett.* **1998**, *39*, 4075–4078; e) K. Ikegashira, Y. Nishihara, K. Hirabayashi, A. Mori, T. Hiyama, *Chem. Commun.* **1997**, 1039–1040.
[12] S. Takahashi, Y. Kuroyama, K. Sonogashira, N. Hagihara, *Synthesis* **1980**, 627–630.
[13] T. J. J. Müller, *Top. Organomet. Chem.* **2006**, *19*, 149–205.
[14] Although numerous precatalysts have been described for the Sonogashira-type reactions, this standard catalytic system is still by far the most-widely used one. For a recent review, see: R. Chinchilla, C. Nájera, *Chem. Rev.* **2007**, *107*, 874–922.
[15] J. Tsuji, H. Nagashima, H. Nemoto, *Org. Synth.* **1990**, *7*, 137–139.
[16] The formation of diynes is a well-known "plague" of the Sonogashira coupling. For a strategy to diminish homocoupling in Sonogashira coupling reactions, see: A. Elangovan, Y.-H. Wang, T.-I. Ho, *Org. Lett.* **2003**, *5*, 1841–1844.
[17] For the one-pot synthesis of **1z**, see: a) A. S. Karpov, E. Merkul, T. Oeser, T. J. J. Müller, *Chem. Commun.* **2005**, 2581–2583; b) A. S. Karpov, E. Merkul, T. Oeser, T. J. J. Müller, *Eur. J. Org. Chem.* **2006**, 2991–3000. For the one-pot synthesis of **1v**, see: c) E. Merkul, C. Boersch, W. Frank, T. J. J. Müller, *Org. Lett.* **2009**, *11*, 2269–2272.

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SUPPORTING INFORMATION

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Title: Consecutive One-Pot Sonogashira□Glaser Coupling Sequence □Direct Preparation of Symmetrical Diynes by Sequential Pd/Cu Catalysis
Author(s): Eugen Merkul, Dominik Urselmann, Thomas J. J. Müller*

Table of Contents

1. General Considerations

All cross coupling reactions were carried out in oven-dried Schlenk glassware using septa and syringes under nitrogen or argon atmosphere. THF was dried using *MBraun* system MB-SPS-800, and triethylamine was refluxed under argon over ketyl sodium, distilled and stored in a Schlenk flask over potassium hydroxide pellets under argon atmosphere.

tert-Butyl 3-iodo-1*H*-indole-1-carboxylate (**1u**)[1] and *tert*-butyl 4-iodo-2-(4-methoxy-phenyl)-1*H*-pyrrole-1-carboxylate (**1v**)[2], 1-benzyl-5-iodo-1*H*-imidazole (**1x**)[3] and 2-ethyl-3-iodo-5-(thiophen-2-yl)furan (**1z**)[4] were prepared according to the literature procedures. Commercial grade reagents were used as supplied without further purification and were purchased from *Sigma-Aldrich Chemie GmbH*, *Fluka AG*, *ABCR GmBH & Co. KG, Alfa Aesar GmbH & Co. KG*, *Riedel-de Haën, EGA-Chemie-Gesellschaft,* and *Merck Serono KGaA*. Trimethylsilylacetylene (TMSA) and potassium fluoride were obtained from *Merck Serono KGaA*.

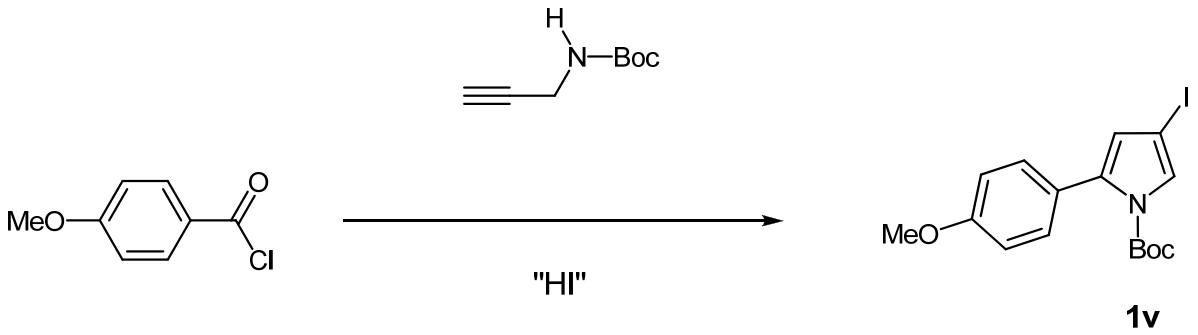
The purification of products was performed on silica gel 60 (0.015-0.040 mm) from *Merck Serono KGaA* Darmstadt using flash technique and under pressure of 2 bar. The crude mixtures were adsorbed on Celite® 545 (0.02-0.10 mm) from *Merck Serono KGaA* Darmstadt before chromatographic purification.

The reaction progress was monitored qualitatively using TLC Silica gel 60 F_{254} 5 x 7.5 cm aluminium sheets obtained by *Merck Serono KGaA* Darmstadt. The spots were detected with UV light at 254 nm and using aqueous potassium permanganate solution.

^{1}H, ^{13}C, and 135-DEPT NMR spectra were recorded on Bruker DRX 500 spectrometer. $CDCl_3$ and DMSO-d_6 were used as deuterated solvents. TMS was used as reference (δ = 0.0) or the resonances of the solvents were locked as internal standards ($CDCl_3$: ^{1}H δ 7.24, ^{13}C δ 77.2; DMSO-d_6: ^{1}H δ 2.50, ^{13}C δ 39.5). The multiplicities of signals were abbreviated as follows: s: singlet; d: doublet; t: triplet; dd: doublet of doublets, ddd: doublet of doublets of doublets, dt: doublet of triplets, td: triplet of doublets, q: quartet, m: multiplet and br: broad signal. The type of carbon atoms was determined on the basis of 135-DEPT NMR spectra. EI mass spectra were measured on Finnigan MAT 8200 spectrometer. IR spectra were obtained on Bruker Vector 22 FT-IR. The solids were measured as KBr pellets and oils as films on KBr plates. The intensity of signals is abbreviated as follows: s (strong), m (medium) and w (weak). The melting points (uncorrected) were measured on Reichert-Jung Thermovar. Combustion analyses were carried out on Perkin Elmer Series II Analyser 2400 in the microanalytical laboratory of Institut für Pharmazeutische und Medizinische Chemie der Heinrich-Heine-Universität Düsseldorf.

2. Preparation of Starting Materials

2.1. Preparation of tert-butyl 4-iodo-2-(4-methoxyphenyl)-1H-pyrrole-1-carboxylate (1v)[2]

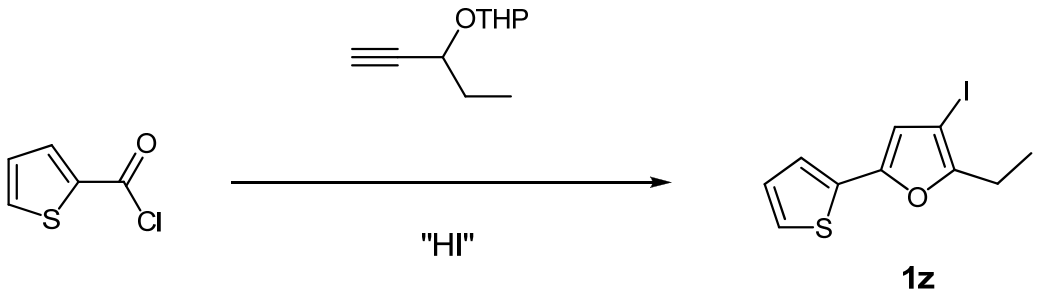


1v

$PdCl_2(PPh_3)_2$ (425 mg, 0.60 mmol, 2 mol %) and CuI (233 mg, 1.20 mmol, 4 mol %) were placed under argon atmosphere in a screw-cap vessel, which was then dried with a heat gun and cooled to the room temperature (water bath). Then, 150 mL of dry THF were added and the mixture was degassed with argon. Dry triethylamine (4.16 mL, 30.0 mmol), 4-methoxybenzoyl chloride (5.28 g, 30.0 mmol), and *tert*-butyl prop-2-ynylcarbamate (4.66 g, 30.0 mmol) were successively added to the mixture which was stirred at room temperature for 1 h (monitored by TLC). Then, sodium iodide (22.7 g, 150 mmol), toluene-4-sulfonic acid monohydrate (11.6 g, 60.0 mmol) and 30 ml of *tert*-butanol were successively added to the mixture which was stirred at room temperature for 1 h (monitored by TLC). The reaction mixture was diluted with 300 mL brine, the phases were separated and the aqueous phase was extracted with dichloromethane (3 x 150 mL). The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuo the residue was absorbed onto Celite® and chromatographed on silica gel with petrolether (boiling range 40-60 °C)/ethyl acetate (PE-EE = 100:1) to give 9.23 g (23.1 mmol, 77 % yield) of the desired product (**1v**) as a colorless solid.

"Three-component synthesis of *N*-Boc-4-iodopyrroles and sequential one-pot alkynylation" E. Merkul, C. Boersch, W. Frank, T. J. J. Müller, *Org. Lett.* **2009**, *11*, 2269-2272.

2.2. Preparation of 2-ethyl-3-iodo-5-(thiophen-2-yl)furan (1z)[4]



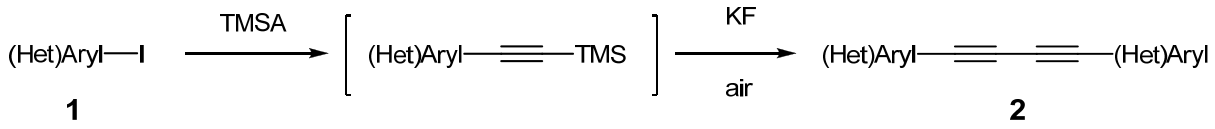
$PdCl_2(PPh_3)_2$ (142 mg, 0.20 mmol, 2 mol %) and CuI (78 mg, 0.40 mmol, 4 mol %) were placed under argon atmosphere in a screw-cap vessel, which was then dried with a heat gun and cooled to the room temperature (water bath). Then, 50 mL of dry THF were added and the mixture was degassed with argon. Dry triethylamine (1.39 mL, 10.0 mmol), thiophene-2-carbonyl chloride (1.50 g, 10.0 mmol), and tetrahydro-2-(pent-1-yn-3-yloxy)-2*H*-pyran (4.66 g, 10.0 mmol) were successively added to the mixture which was stirred at room temperature for 2 h (monitored by TLC). Then, sodium iodide (7.57 g, 50.0 mmol), toluene-4-sulfonic acid monohydrate (2.14 g, 11.0 mmol) and 30 ml of methanol were successively added to the mixture which was stirred at room temperature for 2 h (monitored by TLC). After removal of the solvents in vacuo the residue was absorbed onto Celite® and chromatographed on silica gel with petrolether (boiling range 40-60 °C)/ethyl acetate (PE-EE = 10:1) to give 2.72 g (8.93 mmol, 89 % yield) of the desired product (**1z**) as an orange oil.

“A novel one-pot three-component synthesis of 3-halofurans and sequential Suzuki coupling“ A. S. Karpov, E. Merkul, T. Oeser, T. J. J. Müller, *Chem. Commun.* **2005**, 2581-2583.

“One-pot three-component synthesis of 3-halofurans and 3-chloro-4-iodofurans” A. S. Karpov, E. Merkul, T. Oeser, T. J. J. Müller, *Eur. J. Org. Chem.* **2006**, 2991-3000.

3. *Sonogashira-Glaser* Coupling Sequence

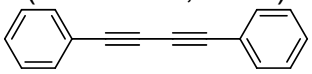
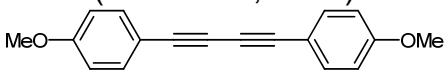
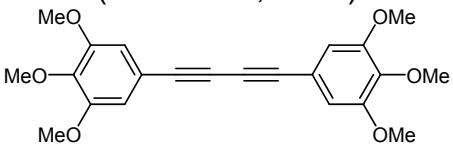
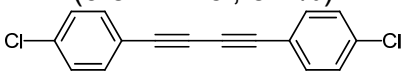
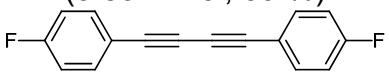
3.1. General Procedure



A mixture of (hetero)aryl iodide **1** (2.00 mmol), $PdCl_2(PPh_3)_2$ (28 mg, 0.04 mmol, 2 mol %) and CuI (16 mg, 0.08 mmol, 4 mol %) was dissolved in degassed THF (5.00-10.0 mL) in a dry screw-cap Schlenk vessel with septum. After addition of trimethylsilylacetylene (0.43 mL, 3.00 mmol) and dry triethylamine (0.55 mL, 4.00 mmol) the solution was stirred at room temperature (water bath) until the complete conversion (monitored by TLC). Then, KF (236 mg, 4.00 mmol) and methanol (5.00 mL) were added subsequently and the reaction mixture was stirred under air atmosphere (the reaction vessel was opened) overnight at room temperature (water bath) or 50 °C (for compounds **2v**, **2w**, **2x** and **2z** in a preheated oil bath). After completion of the reaction, as indicated by TLC, the mixture was filtered (for compounds purified chromatographically; scarcely soluble **2s** was transferred directly into a flask and adsorbed onto Celite® for chromatographic purification) or diluted with THF and filtered through neutral aluminium oxide (for compounds purified by recrystallisation). After removal of the solvents in vacuo the residue was either absorbed onto Celite® and purified by column chromatography on silica gel using petrolether (boiling range 40-60 °C)/ethyl acetate or it was purified by recrystallisation from the appropriate solvent to give the analytically pure diynes **2**.

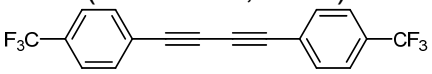
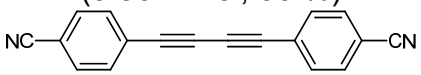
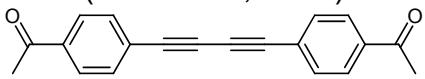
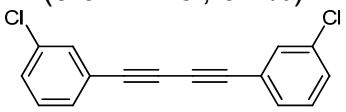
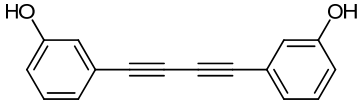
The experimental details are depicted in *Table 1*.

Table 1. *Experimental details for the synthesis of diynes* ***2****.*

Entry	(Hetero)Aryl iodide **1**	Diyne **2** (isolated yield %)[a]	Chromatographic purification R_f (eluent) or recrystallisation (solvent)
1	412 mg (2.00 mmol) 1-Iodo-benzene (*Merck*) **1a**	Pale yellow solid 157 mg (0.78 mmol, 78 %)  **2a**	PE (eluent) R_f (PE) : 0.44 Recrystallisation from *n*-pentane
		Pale brown needles 163 mg (0.81 mmol, 81 %) **2a**	^{i}PrOH/H_2O (solvents)
2	468 mg (2.00 mmol) 1-Iodo-4-methoxy-benzene (*Merck*) **1b**	Yellow crystals 191 mg (0.73 mmol, 73 %)  **2b**	^{i}PrOH (solvent)
3	600 mg (2.00 mmol) 5-Iodo-1,2,3-trimethoxy-benzene (*Alfa Aesar*) **1c**	Pale yellow solid 259 mg (0.68 mmol, 68 %)  **2c**	DCM (eluent) R_f (DCM) : 0.24
4	477 mg (2.00 mmol) 1-Iodo-4-chloro-benzene (*ABCR*) **1d**	Colorless solid 137 mg (0.51 mmol, 51 %)  **2d**	EE (solvent)
5	444 mg (2.00 mmol) 1-Fluoro-4-iodobenzene (*ABCR*) **1e**	Colorless crystals 212 mg (0.89 mmol, 89 %)  **2e**	PE (eluent) R_f (PE) : 0.50

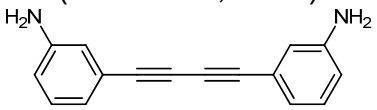
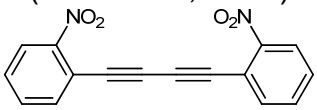
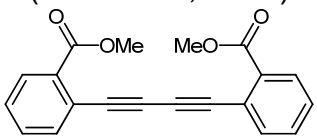
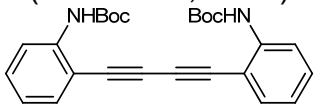
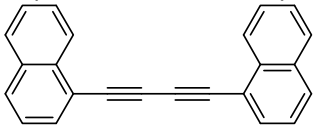
[a] The yield refers to 1.00 mmol of (hetero)aryl iodide **1**.

Table 1 (continuation). *Experimental details for the synthesis of diynes* ***2****.*

Entry	(Hetero)Aryl iodide **1**	Diyne **2** (isolated yield %)[a]	Chromatographic purification R_f (eluent) or recrystallisation (solvent)
6	544 mg (2.00 mmol) 1-(Trifluoro-methyl)-4-iodobenzene (*Alfa Aesar*) **1f**	Colorless solid 241 mg (0.71 mmol, 71 %)  **2f**	PE (eluent) R_f (PE) : 0.64
7	458 mg (2.00 mmol) 4-Iodo-benzonitrile (*ABCR*) **1g**	Pale brown crystals 141 mg (0.56 mmol, 56 %)  **2g**	EE (solvent)
8	502 mg (2.00 mmol) 1-(4-Iodo-phenyl)-ethanone (*Alfa Aesar*) **1h**	Blue solid 211 mg (0.74 mmol, 74 %)  **2h**	PE-EE = 5:1 R_f (PE-EE = 5:1) : 0.23
9	477 mg (2.00 mmol) 1-Iodo-3-chloro-benzene (*ABCR*) **1i**	Pale yellow crystals 183 mg (0.67 mmol, 67 %)  **2i**	PE (eluent) R_f (PE) : 0.61
10	449 mg (2.00 mmol) 3-Iodophenol (*Alfa Aesar*) **1j**	Pale beige solid 189 mg (0.81 mmol, 81 %)  **2j**	DCM-MeOH-NH_3 = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1

[a] The yield refers to 1.00 mmol of (hetero)aryl iodide **1**.

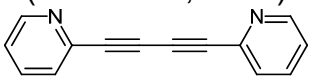
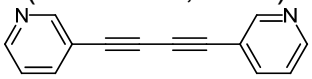
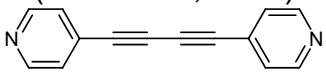
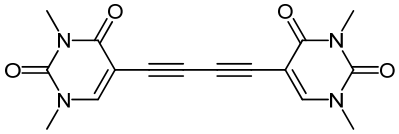
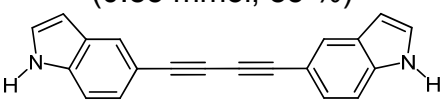
Table 1 (continuation). *Experimental details for the synthesis of diynes* ***2****.*

Entry	(Hetero)Aryl iodide **1**	Diyne **2** (isolated yield %)[a]	Chromatographic purification R_f (eluent) or recrystallisation (solvent)
11	447 mg (2.00 mmol) 3-Iodo-benzenamine (*Merck*) **1k**	Pale yellow solid[b] 204 mg (0.88 mmol, 88 %)  **2k**	PE-EE = 2:1 → 1:1 R_f (PE-EE = 2:1) : 0.14 Suspended in 1.25 *M* HCl in EtOH[b] (*Fluka*)
12	498 mg (2.00 mmol) 1-Iodo-2-nitrobenzene (*ABCR*) **1l**	Yellow solid 150 mg (0.51 mmol, 51 %)  **2l**	DCM (solvent)
13	535 mg (2.00 mmol) Methyl 2-iodobenzoate (*ABCR*) **1m**	Yellow solid 296 mg (0.93 mmol, 93 %)  **2m**	PE-EE = 10:1 R_f (PE-EE = 10:1) : 0.16
14	658 mg (2.00 mmol) *tert*-Butyl 2-iodophenyl-carbamate (*Aldrich*) **1n**	Yellow solid 387 mg (0.90 mmol, 90 %)  **2n**	PE-EE = 20:1 R_f (PE-EE = 20:1) : 0.32
15	519 mg (2.00 mmol) 1-Iodo-naphthalene (*Alfa Aesar*) **1o**	Yellow solid 235 mg (0.78 mmol, 78 %)  **2o**	PE (eluent) R_f (PE) : 0.21

[a] The yield refers to 1.00 mmol of (hetero)aryl iodide **1**.

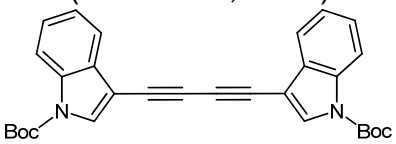
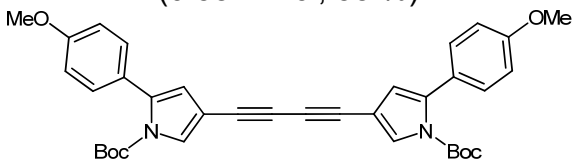
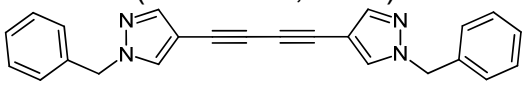
[b] The solid was unstable as a free base. It was characterized as the corresponding dihydrochloride.

Table 1 (continuation). *Experimental details for the synthesis of diynes* ***2****.*

Entry	(Hetero)Aryl iodide **1**	Diyne **2** (isolated yield %)[a]	Chromatographic purification R_f (eluent) or recrystallisation (solvent)
16	410 mg (2.00 mmol) 2-Iodopyridine (*ABCR*) **1p**	Colorless solid 124 mg (0.61 mmol, 61 %)  **2p**	PE-EE = 1:1 R_f (PE-EE = 1:1) : 0.38
17	410 mg (2.00 mmol) 3-Iodopyridine (*EGA*) **1q**	Colorless solid 148 mg (0.72 mmol, 72 %)  **2q**	PE-EE = 1:1 R_f (PE-EE = 1:1) : 0.31
18	410 mg (2.00 mmol) 4-Iodopyridine (*ABCR*) **1r**	Colorless solid 139 mg (0.68 mmol, 68 %)  **2r**	DCM-MeOH-NH_3 = 100:2:1 R_f (PE-EE = 1:1) : 0.18
19	537 mg (2.00 mmol) 5-Iodo-1,3-dimethyl-pyrimidine-2,4(1*H*,3*H*)-dione (5-Iodo-1,3-dimethyl-uracil) (*Aldrich*) **1s**	Yellow solid 170 mg (0.52 mmol, 52 %)  **2s**	DCM-MeOH-NH_3 = 100:1:1
20	496 mg (2.00 mmol) 5-Iodo-1*H*-indole (*ABCR*) **1t**	Brown solid 238 mg (0.85 mmol, 85 %)  **2t**	PE-EE = 3:1 R_f (PE-EE = 2:1) : 0.20

[a] The yield refers to 1.00 mmol of (hetero)aryl iodide **1**.

Table 1 (continuation). *Experimental details for the synthesis of diynes* ***2****.*

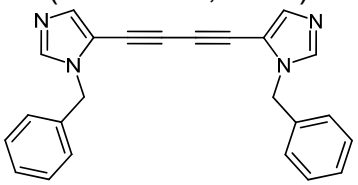
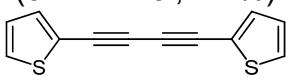
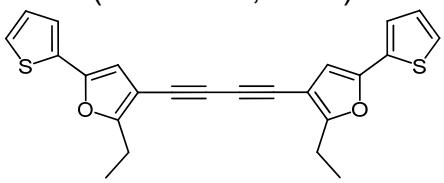
Entry	(Hetero)Aryl iodide **1**	Diyne **2** (isolated yield %)[a]	Chromatographic purification R_f (eluent) or recrystallisation (solvent)
21	686 mg (2.00 mmol) *tert*-Butyl 3-iodo-1*H*-indole-1-carboxylate[b] **1u**	Pale yellow solid 315 mg (0.66 mmol, 66 %)  **2u**	PE-EE = 50:1 R_f (PE-EE = 50:1) : 0.15 Crystallisation in *n*-pentane
22	798 mg (2.00 mmol) *tert*-Butyl 4-iodo-2-(4-methoxy-phenyl)-1*H*-pyrrole-1-carboxylate[c] **1v**	Pale yellow solid 341 mg (0.58 mmol, 58 %)  **2v**	PE-EE = 10:1 R_f (PE-EE = 10:1) : 0.15
23	568 mg (2.00 mmol) 1-Benzyl-4-iodo-1*H*-pyrazole (*Aldrich*) **1w**	Yellow solid 244 mg (0.67 mmol, 67 %)  **2w**	PE-EE = 3:1 R_f (PE-EE = 3:1) : 0.30

[a] The yield refers to 1.00 mmol of (hetero)aryl iodide **1**.

[b] B. Witulski, N. Buschmann, U. Bergsträßer, *Tetrahedron* **2000**, *56*, 8473-8480.

[c] E. Merkul, C. Boersch, W. Frank, T. J. J. Müller, *Org. Lett.* **2009**, *11*, 2269-2272.

Table 1 (continuation). *Experimental details for the synthesis of diynes* ***2****.*

Entry	(Hetero)Aryl iodide **1**	Diyne **2** (isolated yield %)[a]	Chromatographic purification R_f (eluent) or recrystallisation (solvent)
24	568 mg (2.00 mmol) 1-Benzyl-5-iodo-1*H*-imidazole[b] **1x**	Colorless solid[c] 183 mg (0.51 mmol, 51 %)  **2x**	DCM-MeOH-NH_3 = 100:1:1 Suspended in 1.25 *M* HCl in EtOH[c] (*Fluka*)
25	420 mg (2.00 mmol) 2-Iodothiophene (*Aldrich*) **1y**	Pale brown solid 151 mg (0.71 mmol, 71 %)  **2y**	PE (eluent) R_f (PE) : 0.48
26	608 mg (2.00 mmol) 2-Ethyl-3-iodo-5-(thiophen-2-yl)furan[d] **1z**	Yellow solid 204 mg (0.51 mmol, 51 %)  **2z**	PE □ PE-EE = 100:1 R_f (PE) : 0.17

[a] The yield refers to 1.00 mmol of (hetero)aryl iodide **1**.

[b] **1x** was obtained along with isomeric 1-benzyl-4-iodo-1*H*-imidazole as a separable mixture from 4(5)-iodo-1*H*-imidazole according to a procedure described for the synthesis of 1-benzyl 4-iodo-1*H*-pyrazole from 4-iodo-1*H*-pyrazole: W. Holzer, I. Pöcher, *J. Het. Chem.* **1995**, *32*, 189-194. For a similar procedure and characterisation of both isomers, see: C. J. Lovely, H. Du, R. Sivappa, M. R. Bhandari, Y. He, H. V. R. Dias, *J. Org. Chem.* **2007**, *72*, 3741-3749.

[c] The compound was characterized as its dihydrochloride salt.

[d] A. S. Karpov, E. Merkul, T. Oeser, T. J. J. Müller, *Chem. Commun.* **2005**, 2581-2583; A. S. Karpov, E. Merkul, T. Oeser, T. J. J. Müller, *Eur. J. Org. Chem.* **2006**, 2991-3000.

Table 2. *Reaction times[a] in the synthesis of diynes* ***2****.*

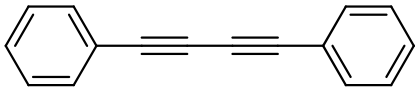
Diyne **2**	*Sonogashira* coupling step	Deprotection/ *Glaser* coupling step	Diyne **2**	*Sonogashira* coupling step	Deprotection/ *Glaser* coupling step
2a	1 h	18 h	**2o**	1 h	16 h
	1 h	17 h			
2b	3 h	16 h	**2p**	3 h	16 h
2c	1 h	18 h	**2q**	3 h	16 h
2d	2 h	17 h	**2r**	3 h	16 h
2e	2 h	17 h	**2s**	1 h	15 h
2f	2 h	17 h	**2t**	1 h	27 h
2g	2 h	17 h	**2u**	1.5 h	73 h
2h	1 h	19 h	**2v**	2 h	25 h[b]
2i	2 h	17 h	**2w**	1 h	22 h[b]
2j	1 h	16 h	**2x**	9 h	16 h[b]
2k	1 h	24 h	**2y**	2 h	17 h
2l	2 h	17 h	**2z**	1 h	52 h[b]
2m	1 h	22 h			
2n	1 h	24 h			

[a] The reaction times for both steps are not optimized. The actual reaction times might be much shorter than indicated.

[b] The deprotection-Glaser coupling step was performed at 50 °C.

3.2 Spectroscopic Data of Compounds 2a-2aa

3.2.1. 1,4-Diphenylbuta-1,3-diyne (2a)



$C_{16}H_{10}$

202.25

157 mg (0.78 mmol, 78 % yield) as a pale yellow solid. Mp 82-85 °C (*n*-pentane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.28-7.40 (m, 6 H), 7.46-7.56 (m, 4 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 74.1 (C_{quat}), 81.8 (C_{quat}), 122.0 (C_{quat}), 128.7 (CH), 129.4 (CH), 132.7 (CH). EI + MS (*m/z* (%)): 203 (17), 202 (M^+, 100), 201 ($(M-H)^+$, 11), 200 (23), 101 ($C_8H_5^+$, 19), 88 (13). IR (KBr): $\tilde{\nu}$ 3049 (w) cm^{-1}, 2148 (w), 1655 (w), 1638 (w), 1483 (w), 1439 (w), 1067 (w), 1024 (w), 915 (w), 755 (s), 685 (s), 524 (m). Anal. calcd for $C_{16}H_{10}$ (202.3) : C 95.02, H 4.98. Found: C 94.96, H 5.10.

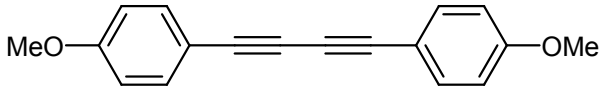
Alternatively, the product can be isolated by crystallisation from ^{i}PrOH/H_2O as pale brown needles (163 mg; 0.81 mmol, 81 % yield). Mp 84-86 °C (^{i}PrOH/H_2O).

Product from the studies concerning the influence of halide anions upon the *Glaser* coupling step (*Table 1* in manuscript) was obtained as a colorless solid. Mp 83-86 °C.

Data reported in the literature: S.-N. Chen, W.-Y. Wu, F.-Y. Tsai, *Green Chem.* **2009**, *11*, 269-274.

White solid. Mp 86-87 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.31-7.35 (m, 6 H), 7.53 (d, *J* = 7.3 Hz, 4 H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 73.9, 81.0, 121.8, 128.4, 129.1, 132.5.

3.2.2. 1,4-Bis(4-methoxyphenyl)buta-1,3-diyne (2b)



$C_{18}H_{14}O_2$

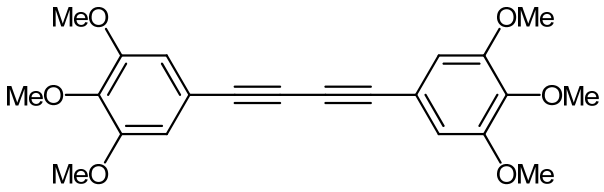
262.30

191 mg (0.73 mmol, 73 % yield) as yellow crystals. Mp 142 °C (^{i}PrOH). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.80 (s, 6 H), 7.80-7.87 (m, 4 H), 7.41-7.47 (m, 4 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 55.6 (CH_3), 73.2 (C_{quat}), 81.4 (C_{quat}), 114.3 (C_{quat}), 114.4 (CH), 134.3 (CH), 160.4 (C_{quat}). EI + MS (*m/z* (%)): 263 (19), 262 (M^+, 100), 248 (10), 247 ($(M-CH_3)^+$, 51), 219 (13), 176 (16), 149 (12), 131 (23), 111 (14), 109 (13), 99 (10), 97 (20), 95 (14), 85 (18), 83 (17), 81 (13), 71 (25), 69 (15), 57 (27), 55 (14), 43 (12). IR (KBr): $\tilde{\nu}$ 3003 (w) cm^{-1}, 2975 (w), 2936 (w), 2841 (w), 2138 (w), 1599 (s), 1561 (w), 1504 (s), 1461 (m), 1439 (w), 1294 (s), 1256 (s), 1182 (w), 1168 (s), 1108 (w), 1028 (m), 842 (m), 821 (m), 691 (w), 538 (w). Anal. calcd for $C_{18}H_{14}O_2$ (262.3) : C 82.42, H 5.38. Found: C 82.58, H 5.57.

Data reported in the literature: S.-N. Chen, W.-Y. Wu, F.-Y. Tsai, *Green Chem.* **2009**, *11*, 269-274.

White solid. Mp 141-142 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.82 (s, 6 H), 6.85 (d, *J* = 8.7 Hz, 4 H), 7.46 (d, *J* = 8.7 Hz, 4 H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 55.3, 73.0, 81.2, 113.9, 114.1, 134.0, 160.2.

3.2.3. 1,4-Bis(3,4,5-trimethoxyphenyl)buta-1,3-diyne (2c)

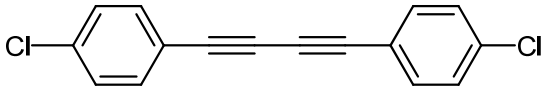


$C_{22}H_{22}O_6$

382.41

259 mg (0.68 mmol, 68 % yield) as a pale yellow solid. Mp 199-201 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.86 (s, 12 H), 3.87 (s, 6 H), 6.76 (s, 4 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 56.1 (CH_3), 61.0 (CH_3), 73.0 (C_{quat}), 81.6 (C_{quat}), 109.6 (CH), 116.5 (C_{quat}), 139.8 (C_{quat}), 153.0 (C_{quat}). EI + MS (*m/z* (%)): 382 (M^+, 5), 279 (7), 167 (34), 150 (12), 149 ($C_8H_5O_3^+$, 100), 113 (11), 95 (10), 94 (98), 84 (12), 83 (14), 71 (27), 70 (17), 69 (11), 57 (28), 55 (15), 43 (14). IR (KBr): $\tilde{\nu}$ 3014 (w) cm^{-1}, 2941 (w), 2838 (w), 2143 (w), 1573 (s), 1504 (s), 1464 (m), 1436 (w), 1410 (s), 1331 (s), 1236 (s), 1186 (w), 1128 (s), 993 (s), 963 (w), 887 (m), 821 (m), 774 (w), 739 (w), 675 (w), 624 (w), 564 (w), 526 (w). Anal. calcd for $C_{22}H_{22}O_6$ (382.4) : C 69.10, H 5.80. Found: C 68.96, H 5.73.

3.2.4. 1,4-Bis(4-chlorophenyl)buta-1,3-diyne (2d)



$C_{16}H_8Cl_2$

271.14

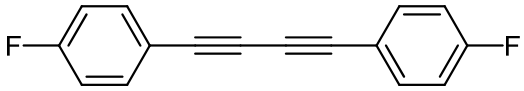
137 mg (0.51 mmol, 51 % yield) as a colorless solid. Mp 253 °C (dec., ethyl acetate). EI + MS (*m/z* (%)): 274 (M($^{37}Cl^{37}Cl$)$^+$, 11), 272 (M($^{37}Cl^{35}Cl$)$^+$, 64), 270 (M($^{35}Cl^{35}Cl$)$^+$, 100), 236 (14), 200 (26), 71 (23). IR (KBr): $\tilde{\nu}$ 1890 (w) cm^{-1}, 1639 (w), 1587 (w), 1544 (w), 1509 (w), 1485 (s), 1466 (m), 1396 (m), 1095 (s), 1013 (m), 823 (s), 592 (w), 521 (m). Anal. calcd for $C_{16}H_8Cl_2$ (271.1) : C 70.88, H 2.97. Found: C 71.09, H 2.85.

After being dried, the substance was found to be insoluble in the usual deuterated solvents. No NMR spectra could be obtained.

Data reported in the literature: W. Yin, C. He, M. Chen, H. Zhang, A. Lei, *Org. Lett*. **2009**, *11*, 709-712.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.32 (d, *J* = 8.1 Hz, 4 H), 7.46 (d, *J* = 8.1 Hz, 4 H). Very insoluble in common organic solvents.

3.2.5. 1,4-Bis(4-fluorophenyl)buta-1,3-diyne (2e)



$C_{16}H_8F_2$

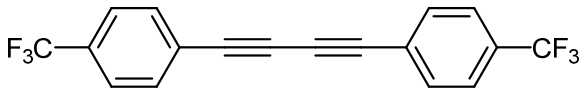
238.23

212 mg (0.89 mmol, 89 % yield) as colorless crystals. Mp 187-188 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.00-7.06 (m, 4 H), 7.46-7.52 (m, 4 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 73.7 (C_{quat}), 80.6 (C_{quat}), 116.1 (d, *J* = 22.2 Hz, CH), 118.0 (d, *J* = 3.6 Hz, C_{quat}), 134.8 (d, *J* = 8.6 Hz, CH), 163.3 (d, *J* = 251.7 Hz, C_{quat}). EI + MS (*m/z* (%)): 239 (26), 238 (M^+, 100), 236 (17), 119 (22). IR (KBr): $\tilde{\nu}$ 2143 (w) cm^{-1}, 1888 (w), 1639 (w), 1596 (s), 1502 (s), 1404 (w), 1275 (w), 1228 (s), 1159 (s), 1094 (m), 1013 (w), 829 (s), 697 (m), 525 (s). Anal. calcd for $C_{16}H_8F_2$ (238.2) : C 80.67, H 3.38. Found: C 80.53, H 3.61.

Data reported in the literature: S.-N. Chen, W.-Y. Wu, F.-Y. Tsai, *Green Chem.* **2009**, *11*, 269-274.

White solid. Mp 187-189 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.04 (dd, *J* = 8.6 Hz, *J* = 8.6 Hz, 4 H), 7.51 (dd, *J* = 8.6 Hz, *J* = 2.2 Hz, 4 H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 73.6, 80.4, 115.9 (d, *J* = 22.2 Hz), 117.9 (d, *J* = 3.8 Hz), 134.5 (d, *J* = 8.4 Hz), 163.0 (d, *J* = 250.3 Hz).

3.2.6. 1,4-Bis(4-(trifluoromethyl)phenyl)buta-1,3-diyne (2f)



$C_{18}H_8F_6$

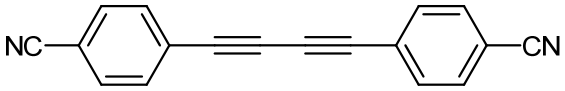
338.25

241 mg (0.71 mmol, 71 % yield) as a colorless solid. Mp 163 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.56-7.66 (m, 8 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 75.8 (C_{quat}), 81.2 (C_{quat}), 123.9 (q, J = 272.3 Hz, C_{quat}), 125.4-125.5 (m, C_{quat}), 125.7 (q, J = 3.7 Hz, CH), 131.3 (q, J = 32.9 Hz, C_{quat}), 133.0 (CH). EI + MS (*m/z* (%)): 339 (19), 338 (M^+, 100), 319 (14), 143 (12), 119 (12). IR (KBr): $\tilde{\nu}$ 2219 (w) cm^{-1}, 1925 (w), 1802 (w), 1611 (m), 1561 (w), 1408 (m), 1318 (s), 1234 (w), 1177 (s), 1134 (s), 1107 (s), 1065 (s), 1015 (m), 841 (s), 734 (m), 596 (m), 551 (w), 522 (w). Anal. calcd for $C_{18}H_8F_6$ (338.3) : C 63.92, H 2.38. Found: C 63.70, H 2.56.

Data reported in the literature: J.-H. Li, Y. Liang, X.-D. Zhang, *Tetrahedron* **2005**, *61*, 1903-1907.

White solid. Mp 166-168 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62 (d, J = 8.4 Hz, 4 H), 7.65 (d, J = 8.4 Hz, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 75.6, 81.0, 122.3, 125.0, 125.2, 125.4, 125.5, 130.9, 131.2, 132.8. MS (*m/z* (%)): 338 (M^+, 100).

3.2.7. 1,4-Bis(4-cyanophenyl)buta-1,3-diyne (2g)



$C_{18}H_8N_2$

252.27

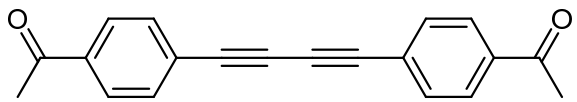
141 mg (0.56 mmol, 56 % yield) as pale brown crystals. Mp 292 °C (dec., ethyl acetate). EI + MS (*m/z* (%)): 253 (20), 252 (M^+, 100). IR (KBr): $\tilde{\nu}$ 3092 (w) cm^{-1}, 2227 (s), 1689 (w), 1599 (w), 1546 (w), 1493 (m), 1404 (m), 1269 (w), 1172 (w), 1104 (w), 1014 (w), 840 (s), 826 (s), 652 (w), 553 (s). Anal. calcd for $C_{18}H_8N_2$ (252.3) : C 85.70, H 3.20, N 11.10. Found: C 85.64, H 3.28, N 11.15.

After being dried, the substance was found to be insoluble in the usual deuterated solvents. No NMR spectra could be obtained.

Data reported in the literature: V. Kumar, A. Chipeleme, K. Chibale, *Eur. J. Org. Chem*. **2008**, *1*, 43-46.

Light brown solid. Mp 183-185 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.48-7.51 (d, *J* = 8.6 Hz, 4 H), 7.60-7.63 (d, *J* = 8.8 Hz, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 74.6, 76.9, 112.3, 115.7, 127.0, 131.8, 133.0. MS (*m/z* (%)): 252 (M^+). Anal. calcd for $C_{18}H_8N_2$ (252.3) : C 85.70, H 3.20, N 11.10. Found: C 85.89, H 2.98, N 11.13.

3.2.8. 1,4-Bis(4-acetylphenyl)buta-1,3-diyne (2h)



$C_{20}H_{14}O_2$

286.32

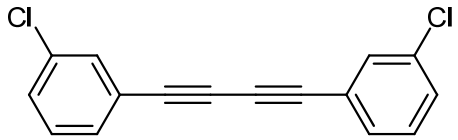
211 mg (0.74 mmol, 74 % yield) as a blue solid. Mp 172-174 °C. EI + MS (*m/z* (%)): 287 (14), 286 (M^+, 64), 272 (21), 271 ($(M-CH_3)^+$, 100), 243 ($(M-C_2H_3O)^+$, 11), 228 ($(M-C_3H_6O)^+$, 24), 200 ($(M-C_4H_6O_2)^+$, 23), 199 (10), 149 (12), 128 ($C_9H_4O^+$, 26), 114 (15), 100 (12), 94 (11), 43 ($C_2H_3O^+$, 15). IR (KBr): $\tilde{\nu}$ 1668 (s) cm^{-1}, 1598 (m), 1402 (w), 1364 (w), 1285 (w), 1264 (m), 1180 (w), 962 (w), 835 (m), 652 (w), 595 (w). Anal. calcd for $C_{20}H_{14}O_2$ (286.3) : C 83.90, H 4.93. Found: C 84.03, H 4.66.

After being dried, the substance was found to be insoluble in the usual deuterated solvents. No NMR spectra could be obtained.

Data reported in the literature: S.-N. Chen, W.-Y. Wu, F.-Y. Tsai, *Green Chem.* **2009**, *11*, 269-274.

Blue solid. Mp 178-180 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.62 (s, 6 H), 7.62 (d, *J* = 8.3 Hz, 4 H), 7.94 (d, *J* = 8.3 Hz, 4 H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 26.6, 76.5, 81.9, 126.1, 128.2, 132.6, 137.0, 196.8. HRMS calcd for $C_{20}H_{14}O_2$, 286.0994; found, 286.0998.

3.2.9. 1,4-Bis(3-chlorophenyl)buta-1,3-diyne (2i)



$C_{16}H_8Cl_2$

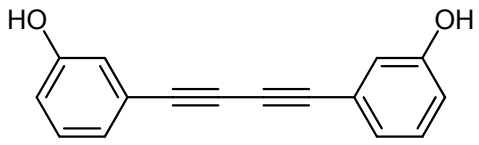
271.14

183 mg (0.67 mmol, 67 % yield) as pale yellow crystals. Mp 73 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.19-7.24 (m, 2 H), 7.29-7.33 (m, 2 H), 7.34-7.38 (m, 2 H), 7.44-7.47 (m, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 74.9 (C_{quat}), 80.8 (C_{quat}), 123.5 (C_{quat}), 129.9 (CH), 130.9 (CH), 132.5 (CH), 134.6 (C_{quat}). EI + MS (*m/z* (%)): 274 (M(^{37}Cl^{37}Cl)$^+$, 10), 273 (11), 272 (M(^{37}Cl^{35}Cl)$^+$, 66), 271 (17), 270 (M(^{35}Cl^{35}Cl)$^+$, 100), 243 (24), 217 (16), 200 (38), 199 (11), 135 (14), 100 (17), 99 (12), 85 (12), 71 (13). IR (KBr): $\tilde{\nu}$ 1584 (m) cm^{-1}, 1557 (m), 1471 (m), 1454 (m), 1402 (m), 1202 (w), 1165 (w), 1094 (m), 1077 (m), 907 (w), 890 (s), 854 (m), 793 (s), 683 (s), 523 (w). Anal. calcd for $C_{16}H_8Cl_2$ (271.1) : C 70.88, H 2.97. Found: C 70.84, H 2.95.

Data reported in the literature: K. Kamata, S. Yamaguchi, M. Kotani, K. Yamaguchi, N. Mizuno, *Angew. Chem. Int. Ed.* **2008**, *47*, 2407-2410.

^{1}H NMR ($CDCl_3$, 270 MHz): δ 7.18-7.26 (m, 2 H), 7.28-7.36 (m, 4 H), 7.44-7.46 (m, 2 H). ^{13}C NMR ($CDCl_3$, 67.8 MHz): δ 75.2, 81.0, 123.7, 130.2, 131.1, 132.7, 134.8. EI + MS (*m/z* (%)): 274 (11), 273 (12), 272 (64), 271 (M$^+$, 18), 270 (100), 200 (31).

3.2.10. 3-(4-(3-Hydroxyphenyl)buta-1,3-diynyl)phenol (2j)

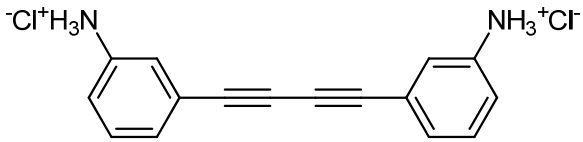


$C_{16}H_{10}O_2$

234.25

189 mg (0.81 mmol, 81 % yield) as a pale beige solid. Mp 200 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 6.90 (dd, *J* = 8.2 Hz, *J* = 1.9 Hz, 2 H), 6.94-6.96 (m, 2 H), 7.02-7.05 (m, 2 H), 7.24 (t, *J* = 7.9 Hz, 2 H), 9.86 (s, 2 H, O<u>H</u>). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 72.9 (C_{quat}), 81.8 (C_{quat}), 117.6 (CH), 118.5 (CH), 121.2 (C_{quat}), 123.2 (CH), 130.1 (CH), 157.4 (C_{quat}). EI + MS (*m/z* (%)): 235 (17), 234 (M^+, 100), 176 (13), 149 (11), 117 ($C_8H_5O^+$, 9). IR (KBr): $\tilde{\nu}$ 3224 (s) cm^{-1}, 1603 (w), 1590 (s), 1448 (s), 1364 (w), 1308 (w), 1262 (m), 1244 (m), 1149 (m), 1081 (w), 997 (w), 932 (m), 856 (m), 785 (s), 721 (w), 680 (s), 563 (w), 527 (w). Anal. calcd for $C_{16}H_{10}O_2$ (234.3) : C 82.04, H 4.30. Found: C 82.15, H 4.33.

3.2.11. 3-(4-(3-Aminophenyl)buta-1,3-diynyl)benzenamine dihydrochloride (2k)



$C_{16}H_{14}Cl_2N_2$

305.20

204 mg (0.88 mmol, 88 % yield) as a pale brown solid (free base). For characterisation, it was suspended in 1.25 *M* HCl in EtOH, stirred at the room temperature, filtered and washed with *n*-pentane. Pale brown solid. Mp 150-155 °C. EI + MS (*m/z* (%)): 233 (19), 232 ((M-2 HCl)$^+$, 100), 116 ($C_8H_6N^+$, 11). IR (KBr): $\tilde{\nu}$ 3054 (m) cm^{-1}, 2878 (s), 2551 (m), 1590 (w), 1561 (m), 1516 (m), 1481 (w), 1440 (w), 1098 (w), 1074 (w), 998 (w), 917 (w), 889 (w), 795 (s), 681 (s), 531 (m). Anal. calcd for $C_{16}H_{14}Cl_2N_2$ (305.2) : C 62.97, H 4.62, N 9.18. Found: C 62.79, H 4.59, N 9.13.

The dihydrochloride was found to be insoluble in the usual deuterated solvents. No NMR spectra could be obtained.

Data reported in the literature for the free base: L. Yin, J. Liebscher, *Synthesis* **2005**, 131-135.

Grey-green solid. Mp 124-125 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.70 (br s, 4 H), 6.69 (m, 2 H), 6.81 (t, *J* = 1.9 Hz, 2 H), 6.93 (dt, *J* = 7.5 Hz, *J* = 1.2 Hz, 2 H), 7.11 (t, *J* = 7.9 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 73.4, 81.7, 116.3, 118.4, 122.4, 123.0, 129.4, 146.3. Anal. calcd for $C_{16}H_{12}N_2$ (232.3) : C 82.73, H 5.21, N 12.06. Found: C 82.84, H 5.40, N 12.01.

3.2.12. 1,4-Bis(2-nitrophenyl)buta-1,3-diyne (2l)

$C_{16}H_8N_2O_4$

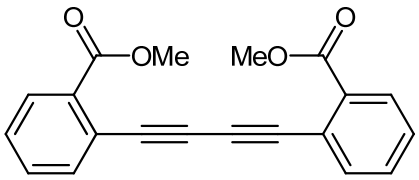
292.25

150 mg (0.51 mmol, 51 % yield) as a yellow solid. Mp 204 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.53 (t, *J* = 7.8 Hz, 2 H), 7.63 (t, *J* = 7.6 Hz, 2 H), 7.76 (d, *J* = 7.7 Hz, 2 H), 8.13 (d, *J* = 8.2 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 79.4 (C_{quat}), 81.1 (C_{quat}), 100.2 (C_{quat}), 117.5 (C_{quat}), 125.3 (CH), 130.1 (CH), 133.4 (CH), 136.2 (CH). MALDI MS (*m/z* (%)): 292.4 (M^+). IR (KBr): $\tilde{\nu}$ 3105 (w) cm^{-1}, 2850 (w), 1836 (w), 1602 (m), 1564 (m), 1518 (s), 1474 (m), 1437 (m), 1381 (w), 1340 (s), 1301 (m), 1254 (m), 1207 (w), 1143 (m), 1080 (m), 991 (w), 957 (w), 858 (s), 781 (s), 739 (s), 687 (s), 660 (s). Anal. calcd for $C_{16}H_8N_2O_4$ (292.3) : C 65.76, H 2.76, N 9.59. Found: C 65.61, H 2.88, N 9.36.

Data reported in the literature: V. Kumar, A. Chipeleme, K. Chibale, *Eur. J. Org. Chem*. **2008**, *1*, 43-46.

Dark brown solid. Mp 204-205 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.19-7.54 (m, 2 H), 7.59-7.63 (dt, *J* = 7.7 Hz, *J* = 1.3 Hz, 2 H), 7.39-7.76 (dd, *J* = 7.7 Hz, *J* = 1.5 Hz, 2 H), 8.10-8.13 (dd, *J* = 8.2 Hz, *J* = 1.2 Hz, 2 H). MS (*m/z* (%)): 292 (M^+). Anal. calcd for $C_{16}H_8N_2O_4$ (292.3) : C 65.76, H 2.76, N 9.59. Found: C 65.55, H 2.65, N 9.03.

3.2.13. 1,4-Bis(2-methylbenzoyl)buta-1,3-diyne (2m)

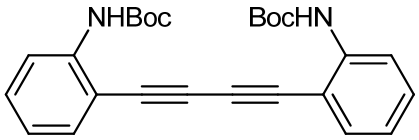


$C_{20}H_{14}O_4$

318.32

296 mg (0.93 mmol, 93 % yield) as a yellow oil. Suspending in *n*-pentane, sonication in ultrasound bath, filtration and drying gave a yellow solid. Mp 59-60 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.97 (s, 6 H), 7.40-7.44 (m, 2 H), 7.48-7.52 (m, 2 H), 7.65-7.69 (m, 2 H), 7.97-8.00 (m, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 52.4 (CH_3), 78.9 (C_{quat}), 81.5 (C_{quat}), 122.5 (C_{quat}), 128.8 (CH), 130.6 (CH), 131.8 (CH), 132.7 (C_{quat}), 135.2 (CH), 166.1 (C_{quat}). EI + MS (*m/z* (%)): 318 (M^+, 46), 303 ($(M-CH_3)^+$, 32), 285 (61), 275 (25), 272 (28), 259 ($(M-C_2H_3O_2)^+$, 74), 258 (34), 257 (40), 204 (28), 202 ($C_{16}H_{10}^+$, 49), 200 ($C_{16}H_8^+$, 25), 189 (35), 188 (31), 187 (60), 176 (41), 144 (100), 133 (25), 127 (32), 114 (37), 105 (27), 101 (35), 100 (51), 88 (48), 87 (35). IR (KBr): $\tilde{\nu}$ 3011 (w) cm^{-1}, 2961 (w), 1715 (s), 1593 (w), 1562 (w), 1479 (w), 1442 (m), 1426 (w), 1294 (s), 1251 (m), 1185 (w), 1124 (m), 1088 (w), 1044 (w), 956 (w), 839 (w), 798 (w), 774 (w), 751 (s), 696 (m), 656 (w), 573 (w), 539 (w). Anal. calcd for $C_{20}H_{14}O_4$ (318.3) : C 75.46, H 4.43. Found: C 75.22, H 4.70.

3.2.14. 1,4-Bis(2-*tert*-butyl carbamoylphenyl)buta-1,3-diyne (2n)

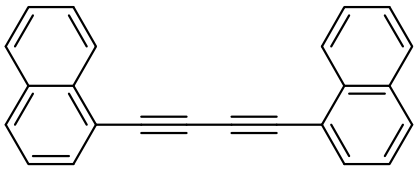


$C_{26}H_{28}N_2O_4$

432.51

387 mg (0.90 mmol, 90 % yield) as a yellow solid (purification by suspending in *n*-pentane and sonication in ultrasound bath). Mp 134 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.56 (s, 18 H), 6.98 (td, *J* = 7.6 Hz, *J* = 0.9 Hz, 2 H), 7.20 (s, 2 H, NH), 7.33-7.38 (m, 2 H), 7.48 (dd, *J* = 7.6 Hz, *J* = 1.3 Hz, 2 H), 8.17 (d, *J* = 8.5 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 28.3 (CH_3), 78.9 (C_{quat}), 79.7 (C_{quat}), 81.2 (C_{quat}), 109.4 (C_{quat}), 118.0 (CH), 122.3 (CH), 130.9 (CH), 133.2 (CH), 141.1 (C_{quat}), 152.3 (C_{quat}). EI + MS (*m/z* (%)): 432 (M^+, 1), 332 ((M-$C_5H_9O_2$)$^+$, 5), 302 (17), 285 (10), 284 (50), 276 (23), 259 (12), 258 (42), 233 (16), 232 ((M-$C_{10}H_{18}O_4$)$^+$, 92), 231 ((M-$C_{10}H_{19}O_4$)$^+$, 100), 230 ((M-$C_{10}H_{20}O_4$)$^+$, 16), 229 (51), 228 (12), 204 (38), 203 (14), 201 (12), 146 (12), 102 (13), 101 (11), 89 (14), 88 (14), 59 (27), 57 ($C_4H_9^+$, 50), 56 (13), 44 (CO_2^+, 12), 41 (25). IR (KBr): $\tilde{\nu}$ 3408 (w) cm^{-1}, 2979 (w), 2933 (w), 2146 (w), 1735 (s), 1578 (m), 1516 (s), 1446 (m), 1393 (w), 1368 (w), 1305 (m), 1280 (w), 1232 (m), 1155 (s), 1051 (w), 1024 (w), 945 (w), 899 (w), 836 (w), 754 (m), 578 (w), 550 (w). Anal. calcd for $C_{26}H_{28}N_2O_4$ (432.5) : C 72.20, H 6.53, N 6.48. Found: C 72.18, H 6.69, N 6.48.

3.2.15. 1,4-Di(naphthalen-1-yl)buta-1,3-diyne (2o)



$C_{24}H_{14}$

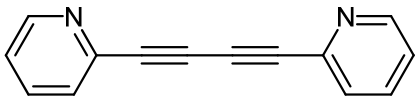
302.37

235 mg (0.78 mmol, 78 % yield) as a yellow solid. Mp 175-177 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.43-7.48 (m, 2 H), 7.52-7.57 (m, 2 H), 7.60-7.65 (m, 2 H), 7.81-7.84 (m, 2 H), 7.85-7.90 (m, 4 H), 8.42 (d, *J* = 8.5 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 78.7 (C_{quat}), 81.0 (C_{quat}), 119.5 (C_{quat}), 125.2 (CH), 126.1 (CH), 126.7 (CH), 127.2 (CH), 128.5 (CH), 129.8 (CH), 132.1 (CH), 133.1 (C_{quat}), 133.9 (C_{quat}). EI + MS (*m/z* (%)): 303 (19), 302 (M^+, 74), 300 (30), 167 (28), 151 ($C_{12}H_7^+$, 17), 150 (32), 149 (100), 94 (21), 71 (19), 70 (13), 57 (15). IR (KBr): $\tilde{\nu}$ 3055 (w) cm^{-1}, 2137 (w), 1812 (w), 1638 (w), 1584 (w), 1504 (w), 1390 (m), 1332 (w), 1267 (w), 1155 (w), 1012 (w), 905 (w), 862 (w), 796 (s), 769 (s), 694 (w), 561 (w). Anal. calcd for $C_{24}H_{14}$ (302.4) : C 95.33, H 4.67. Found: C 95.22, H 4.44.

Data reported in the literature: S.-N. Chen, W.-Y. Wu, F.-Y. Tsai, *Green Chem.* **2009**, *11*, 269-274.

Yellow solid. Mp 177-180 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.43-7.68 (m, 6 H), 7.82-7.92 (m, 6 H), 8.44 (d, *J* = 8.0 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 78.7, 81.0, 119.5, 125.2, 126.1, 126.7, 127.2, 128.4, 129.7, 132.0, 133.1, 133.9.

3.2.16. 2-(4-(Pyridin-2-yl)buta-1,3-diynyl)pyridine (2p)



$C_{14}H_8N_2$

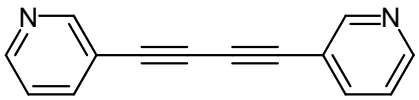
204.23

124 mg (0.61 mmol, 61 % yield) as a colorless solid. Mp 119 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.25-7.30 (m, 2 H), 7.53 (d, *J* = 7.8 Hz, 2 H), 7.67 (td, *J* = 7.7 Hz, *J* = 1.6 Hz, 2 H), 8.60 (d, *J* = 4.8 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 73.4 (C_{quat}), 81.1 (C_{quat}), 124.0 (CH), 128.6 (CH), 136.4 (CH), 142.1 (C_{quat}), 150.6 (CH). EI + MS (*m/z* (%)): 205 (18), 204 (M^+, 100), 203 ($(M-H)^+$, 21), 177 (10), 176 (10), 151 (12). IR (KBr): $\tilde{\nu}$ 1655 (m) cm^{-1}, 1638 (m), 1577 (m), 1561 (m), 1544 (w), 1459 (m), 1425 (m), 1240 (w), 1047 (w), 987 (w), 887 (w), 774 (s), 734 (m), 629 (w), 532 (w). Anal. calcd for $C_{14}H_8N_2$ (204.2) : C 82.33, H 3.95, N 13.72. Found: C 82.35, H 3.94, N 13.50.

Data reported in the literature: S. Adimurthy, C. C. Malakar, U. Beifuss, *J. Org. Chem.* **2009**, *74*, 5648-5651.

Pale yellow crystalline solid. Mp 121-122 °C. ^{1}H NMR ($CDCl_3$): δ 8.63 (br d, *J* = 4.7 Hz, 2 H), 7.70 (dt, *J* = 1.7 Hz, 7.7 2 H), 7.56 (br dt, *J* = 1.0 Hz, 7.9 Hz, 2 H), 7.31 (ddd, *J* = 1.2 Hz, 4.8 Hz, 7.6 Hz, 2 H). ^{13}C NMR ($CDCl_3$): δ 150.3, 141.8, 136.2, 128.4, 123.8, 80.8, 73.3. MS (EI, 70 eV): *m/z* (%): 204 (M+, 100), 176 (14), 152 (9), 99 (9), 50 (15). IR (ATR): $\tilde{\nu}$ = 1560 cm^{-1}, 1424, 1230, 990, 770, 733. Anal. calcd for $C_{14}H_8N_2$ (204.2) : C 82.33, H 3.95, N 13.72. Found: C 82.11, H 4.08, N 13.63.

3.2.17. 3-(4-(Pyridin-3-yl)buta-1,3-diynyl)pyridine (2q)



$C_{14}H_8N_2$

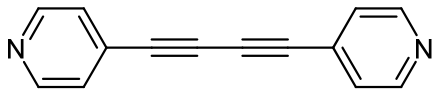
204.23

148 mg (0.72 mmol, 72 % yield) as a colorless solid. Mp 153 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.28 (dd, *J* = 7.9 Hz, *J* = 4.9 Hz, 2 H), 7.80 (dt, *J* = 7.9 Hz, *J* = 1.8 Hz, 2 H), 8.58 (dd, *J* = 4.9 Hz, *J* = 1.5 Hz, 2 H), 8.75 (d, *J* = 1.6 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 76.9 (C_{quat}), 79.3 (C_{quat}), 119.1 (C_{quat}), 123.3 (CH), 139.7 (CH), 149.6 (CH), 153.2 (CH). EI + MS (*m/z* (%)): 205 (17), 204 (M^+, 100), 203 ($(M-H)^+$, 12), 151 (17), 98 (12). IR (KBr): $\tilde{\nu}$ 3054 (w) cm^{-1}, 3006 (w), 2150 (w), 1638 (w), 1579 (m), 1560 (m), 1474 (m), 1413 (s), 1329 (m), 1189 (m), 1121 (w), 1065 (w), 1038 (m), 1022 (s), 957 (w), 804 (s), 699 (s), 626 (m), 515 (m). Anal. calcd for $C_{14}H_8N_2$ (204.2) : C 82.33, H 3.95, N 13.72. Found: C 82.11, H 3.66, N 13.46.

Data reported in the literature: F. Yang, X. Cui, Y.-n. Li, J. Zhang, G.-r. Ren, Y. Wu, *Tetrahedron* **2007**, *63*, 1963-1969.

White solid. Mp 144-146 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34 (t, *J* = 4.8 Hz, 2 H), 7.86 (d, *J* = 8.0 Hz, 2 H), 8.62 (d, *J* = 4.0 Hz, 2 H), 8.79 (s, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 79.1, 119.1, 123.3, 139.9, 149.0, 152.7.

3.2.18. 4-(4-(Pyridin-4-yl)buta-1,3-diynyl)pyridine (2r)



$C_{14}H_8N_2$

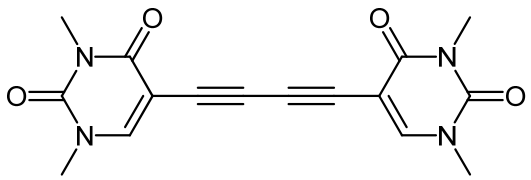
204.23

139 mg (0.68 mmol, 68 % yield) as a colorless solid. Mp 206 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.31 (dd, *J* = 4.5 Hz, *J* = 1.5 Hz, 4 H), 8.57 (dd, *J* = 4.5 Hz, *J* = 1.5 Hz, 4 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 77.4 (C_{quat}), 80.4 (C_{quat}), 126.3 (CH), 129.6 (C_{quat}), 150.2 (CH). EI + MS (*m/z* (%)): 205 (16), 204 (M^+, 100), 203 ($(M-H)^+$, 11), 177 (11), 151 (12). IR (KBr): $\tilde{\nu}$ 3026 (w) cm^{-1}, 1671 (w), 1584 (s), 1538 (m), 1486 (w), 1398 (m), 1217 (w), 1062 (w), 987 (w), 815 (s), 778 (s), 671 (w), 542 (m), 513 (w). Anal. calcd for $C_{14}H_8N_2$ (204.2) : C 82.33, H 3.95, N 13.72. Found: C 82.30, H 4.02, N 13.49.

Data reported in the literature: J. Gonzalo Rodríguez, R. Martín-Villamil, F. H. Cano, I. Fonseca, *J. Chem. Soc., Perkin Trans. 1* **1997**, 709-714.

Brown solid. Mp 198-201 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.41 (d, *J* = 7.2 Hz, 4 H), 8.67 (br s, 4 H). ^{13}C NMR ($CDCl_3$, 200 MHz): δ 76.9, 79.9, 125.7, 128.9, 149.6. MS (*m/z* (%)): 204 (M^+, 100), 177 (13), 151 (14), 124 (6). IR (nujol): $\tilde{\nu}$ 1580 cm^{-1}, 980, 810.

3.2.19. 5-(4-(1,2,3,4-Tetrahydro-1,3-dimethyl-2,4-dioxopyrimidin-5-yl)buta-1,3-diynyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (2s)



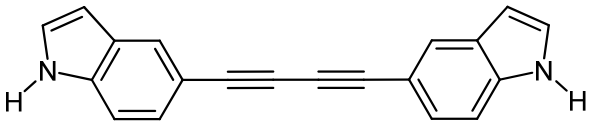
$C_{16}H_{14}N_4O_4$

326.31

170 mg (0.52 mmol, 52 % yield) as a yellow solid. Mp 319-321 °C. EI + MS (*m/z* (%)): 327 (20), 326 (M^+, 100), 228 (58), 212 (11), 200 (34), 156 (19), 155 (11), 143 (18), 115 (22), 114 (14), 86 (13), 84 (13). IR (KBr): $\tilde{\nu}$ 3061 (w) cm^{-1}, 2952 (w), 2152 (w), 1704 (s), 1655 (s), 1620 (m), 1451 (m), 1392 (w), 1343 (m), 1263 (w), 1177 (w), 1077 (m), 930 (w), 764 (w), 752 (m), 553 (w). Anal. calcd for $C_{16}H_{14}N_4O_4$ (326.3) : C 58.89, H 4.32, N 17.17. Found: C 58.65, H 4.42, N 17.10.

The compound was not sufficiently soluble in DMSO-d_6 to obtain NMR spectra.

3.2.20. 5-(4-(1*H*-Indol-5-yl)buta-1,3-diynyl)-1*H*-indole (2t)

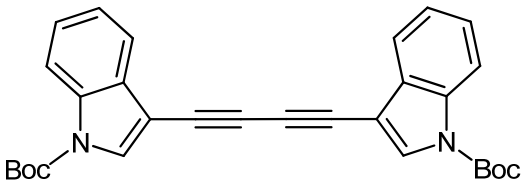


$C_{20}H_{12}O_2$

280.32

238 mg (0.85 mmol, 85 % yield) as a yellow solid. Suspending in dichloromethane, sonication in ultrasound bath, filtration and drying gave a brown solid. Mp 250 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 6.48-6.51 (m, 2 H), 7.29 (dd, *J* = 8.2 Hz, *J* = 1.6 Hz, 2 H), 7.43-7.47 (m, 4 H), 7.85-7.86 (m, 2 H), 11.41 (s, 2 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 71.8 (C_{quat}), 83.0 (C_{quat}), 101.5 (CH), 110.7 (C_{quat}), 112.0 (CH), 124.9 (CH), 125.1 (CH), 127.0 (CH), 127.5 (C_{quat}), 136.0 (C_{quat}). EI + MS (*m/z* (%)): 281 (22), 280 (M^+, 100), 279 (10), 251 (6), 140 ($C_{10}H_6N^+$, 20), 125 (10). IR (KBr): $\tilde{\nu}$ 3399 (s) cm^{-1}, 2146 (w), 1719 (w), 1655 (w), 1609 (w), 1561 (w), 1543 (w), 1509 (w), 1460 (m), 1412 (m), 1342 (w), 1310 (w), 1093 (w), 896 (w), 881 (w), 813 (m), 764 (w), 729 (m), 603 (m), 506 (m). Anal. calcd for $C_{20}H_{12}O_2$ (280.3) : C 85.69, H 4.31, N 9.99. Found: C 85.80, H 4.07, N 10.00.

3.2.21. *tert*-Butyl 3-(4-(1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl)buta-1,3-diynyl)-1*H*-indole-1-carboxylate (2u)

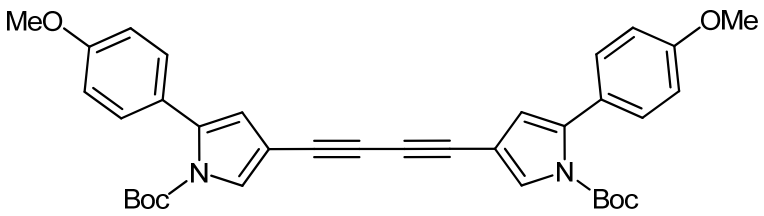


$C_{30}H_{28}N_2O_4$

480.55

315 mg (0.66 mmol, 66 % yield) as a yellow oil. Upon crystallisation in *n*-pentane, a pale yellow solid was obtained. Mp 120-121 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.68 (s, 18 H), 7.30-7.35 (m, 2 H), 7.35-7.40 (m, 2 H), 7.73-7.76 (m, 2 H), 7.89 (s, 2 H), 8.15 (d, *J* = 7.9 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 28.1 (CH_3), 74.1 (C_{quat}), 77.4 (C_{quat}), 84.6 (C_{quat}), 102.1 (C_{quat}), 115.3 (CH), 120.2 (CH), 123.4 (CH), 125.4 (CH), 130.4 (C_{quat}), 131.1 (CH), 134.5 (C_{quat}), 148.8 (C_{quat}). EI + MS (*m/z* (%)): 480 (M^+, 2), 368 ($C_{22}H_{12}N_2O_4^+$, 10), 324 ($C_{21}H_{12}N_2O_2^+$, 7), 280 ($C_{20}H_{12}N_2^+$, 40), 279 (10), 140 ($C_{10}H_7N^+$, 10), 57 ($C_4H_9^+$, 27), 56 (64), 55 (28), 44 (CO_2^+, 100), 43 (27), 42 (16), 41 (82). IR (KBr): $\tilde{\nu}$ 3158 (w) cm^{-1}, 2974 (w), 2149 (w), 1724 (s), 1616 (w), 1544 (m), 1475 (m), 1453 (s), 1369 (s), 1305 (m), 1288 (m), 1260 (m), 1226 (s), 1156 (s), 1106 (m), 1087 (m), 1053 (m), 1014 (w), 938 (w), 857 (w), 810 (w), 744 (m), 613 (w), 579 (w), 503 (w). Anal. calcd for $C_{30}H_{28}N_2O_4$ (480.6) : C 74.98, H 5.87, N 5.83. Found: C 75.15, H 5.93, N 5.80.

3.2.22. *tert*-Butyl 2-(4-methoxyphenyl)-4-(4-(2-(4-methoxyphenyl))-1-(*tert*-butoxycarbonyl)-1*H*-pyrrol-3-yl)buta-1,3-diynyl)-1*H*-pyrrole-1-carboxylate (2v)

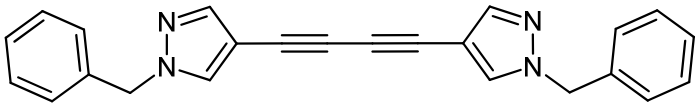


$C_{36}H_{36}N_2O_6$

592.68

341 mg (0.58 mmol, 58 % yield) as a pale yellow solid. Mp 143-145 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.39 (s, 18 H), 3.82 (s, 6 H), 6.21 (d, *J* = 1.9 Hz, 2 H), 6.87-6.91 (m, 4 H), 7.23-7.26 (m, 4 H), 7.57 (d, *J* = 1.9 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 27.6 (CH_3), 55.2 (CH_3), 74.2 (C_{quat}), 75.2 (C_{quat}), 84.4 (C_{quat}), 105.5 (C_{quat}), 113.1 (CH), 116.3 (CH), 125.5 (C_{quat}), 127.5 (CH), 130.5 (CH), 135.1 (C_{quat}), 148.3 (C_{quat}), 159.3 (C_{quat}). EI + MS (*m/z* (%)): 592 (M^+, 0.2), 392 ($C_{26}H_{20}N_2O_2^+$, 6), 310 (3), 197 (4), 57 ($C_4H_9^+$, 14), 56 (77), 55 (31), 44 (CO_2^+, 94), 41 (100). IR (KBr): $\tilde{\nu}$ 3147 (w) cm^{-1}, 2981 (w), 2836 (w), 2150 (w), 1742 (s), 1614 (w), 1571 (w), 1524 (w), 1488 (s), 1361 (s), 1331 (s), 1287 (m), 1249 (s), 1205 (w), 1177 (m), 1151 (s), 1108 (w), 1035 (w), 991 (w), 847 (m), 766 (w), 608 (w). Anal. calcd for $C_{36}H_{36}N_2O_6$ (592.7) : C 72.95, H 6.12, N 4.73. Found: C 72.70, H 6.05, N 4.75.

3.2.23. 1-Benzyl-4-(4-(1-benzyl-1*H*-pyrazol-4-yl)buta-1,3-diynyl)-1*H*-pyrazole (2w)

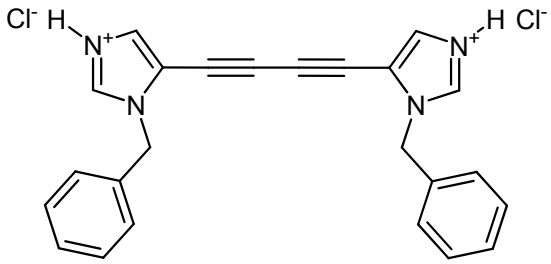


$C_{24}H_{18}N_4$

362.43

244 mg (0.67 mmol, 67 % yield) as a yellow solid. Mp 182-184 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.26 (s, 4 H), 7.19-7.23 (m, 4 H), 7.29-7.37 (m, 6 H), 7.53 (s, 2 H), 7.66 (s, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 56.3 (CH_2), 72.5 (C_{quat}), 74.8 (C_{quat}), 102.4 (C_{quat}), 127.9 (CH), 128.4 (CH), 129.0 (CH), 133.3 (CH), 135.4 (C_{quat}), 143.1 (CH). EI + MS (*m/z* (%)): 363 (14), 362 (M^+, 47), 271 ($(M-C_7H_7)^+$, 5), 91 ($C_7H_7^+$, 100), 65 ($C_5H_5^+$, 8). IR (KBr): $\tilde{\nu}$ 3103 (w) cm^{-1}, 2147 (m), 1638 (w), 1536 (s), 1493 (w), 1451 (m), 1435 (m), 1373 (s), 1343 (m), 1200 (w), 1162 (m), 1076 (m), 1005 (m), 988 (m), 856 (s), 820 (w), 721 (s), 695 (m), 656 (w), 632 (m), 586 (w). Anal. calcd for $C_{24}H_{18}N_4$ (362.4) : C 79.54, H 5.01, N 15.46. Found: C 79.40, H 4.94, N 15.27.

3.2.24. 1-Benzyl-5-(4-(1-benzyl-1*H*-imidazol-5-yl)buta-1,3-diynyl)-1*H*-imidazole dihydrochloride (2x)



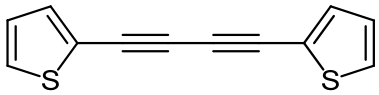
$C_{24}H_{20}Cl_2N_4$

435.35

183 mg (0.51 mmol, 51 % yield) as a colorless solid (free base). For characterisation, it was suspended in 1.25 *M* HCl in EtOH, stirred at the room temperature, filtered and washed with *n*-pentane. Colorless solid. Mp 160-162 °C. EI + MS (*m/z* (%)): 362 ((M-2 HCl)$^+$, 4), 277 (14), 158 ($C_{10}H_{10}N_2^+$, 44), 91 ($C_7H_7^+$, 100), 65 ($C_5H_5^+$, 8). IR (KBr): $\tilde{\nu}$ 3445 (w) cm^{-1}, 3131 (m), 3088 (m), 3029 (w), 2974 (w), 2639 (w), 2332 (s), 1904 (m), 1638 (w), 1572 (w), 1497 (w), 1458 (w), 1437 (w), 1395 (w), 1377 (w), 1306 (s), 1262 (w), 1188 (m), 1098 (w), 971 (w), 898 (m), 866 (m), 819 (m), 727 (s), 695 (w), 625 (m), 520 (w). Anal. calcd for $C_{24}H_{20}Cl_2N_4$ (435.4) : C 66.21, H 4.63, N 12.87. Found: C 65.95, H 4.61, N 12.85.

The dihydrochloride was found to be insoluble in the usual deuterated solvents. No NMR spectra could be obtained.

3.2.25. 2-(4-(Thiophen-2-yl)buta-1,3-diynyl)thiophene (2y)



$C_{12}H_6S_2$

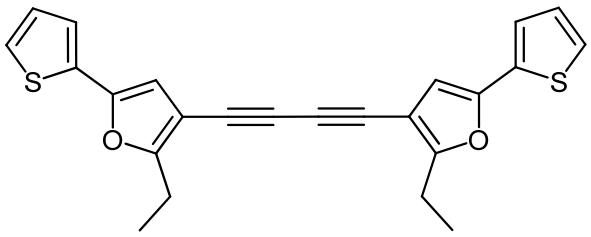
214.31

151 mg (0.71 mmol, 71 % yield) as a pale brown solid. Mp 86-88 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.98 (dd, *J* = 5.1 Hz, *J* = 3.7 Hz, 2 H), 7.31 (dd, *J* = 5.1 Hz, *J* = 1.1 Hz, 2 H), 7.33 (dd, *J* = 3.7 Hz, *J* = 1.1 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 76.8 (C_{quat}), 78.0 (C_{quat}), 122.1 (C_{quat}), 127.4 (CH), 129.1 (CH), 134.6 (CH). EI + MS (*m/z* (%)): 216 (10), 215 (15), 214 (M^+, 100), 170 (19). IR (KBr): $\tilde{\nu}$ 3104 (w) cm^{-1}, 2140 (m), 1655 (w), 1544 (w), 1408 (m), 1368 (w), 1226 (m), 1208 (w), 1148 (m), 1130 (m), 1080 (w), 1038 (w), 836 (s), 711 (s), 569 (w), 508 (m). Anal. calcd for $C_{12}H_6S_2$ (214.3) : C 67.25, H 2.82. Found: C 67.02, H 2.94.

Data reported in the literature: Y. Nishihara, K. Ikegashira, K. Hirabayashi, J.-i. Ando, A. Mori, T. Hiyama, *J. Org. Chem.* **2000**, *65*, 1780-1787.

Light sensitive pale yellow solid. Mp 92-93 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.00 (dd, *J* = 5.1 Hz, *J* = 3.7 Hz, 2 H), 7.32 (dd, *J* = 5.1 Hz, *J* = 1.2 Hz, 2 H), 7.34 (dd, *J* = 3.7 Hz, *J* = 1.2 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 76.6, 77.8, 122.0, 127.2, 128.9, 134.4. IR (neat): $\tilde{\nu}$ 3106 cm^{-1}, 2141, 1408, 714. Anal. calcd for $C_{12}H_6S_2$ (214.3) : C 67.25, H 2.82. Found: C 67.12, H 2.69.

3.2.26. 2-Ethyl-3-(4-(2-ethyl-5-(thiophen-2-yl)furan-3-yl)buta-1,3-diynyl)-5-(thiophen-2-yl)furan (2z)

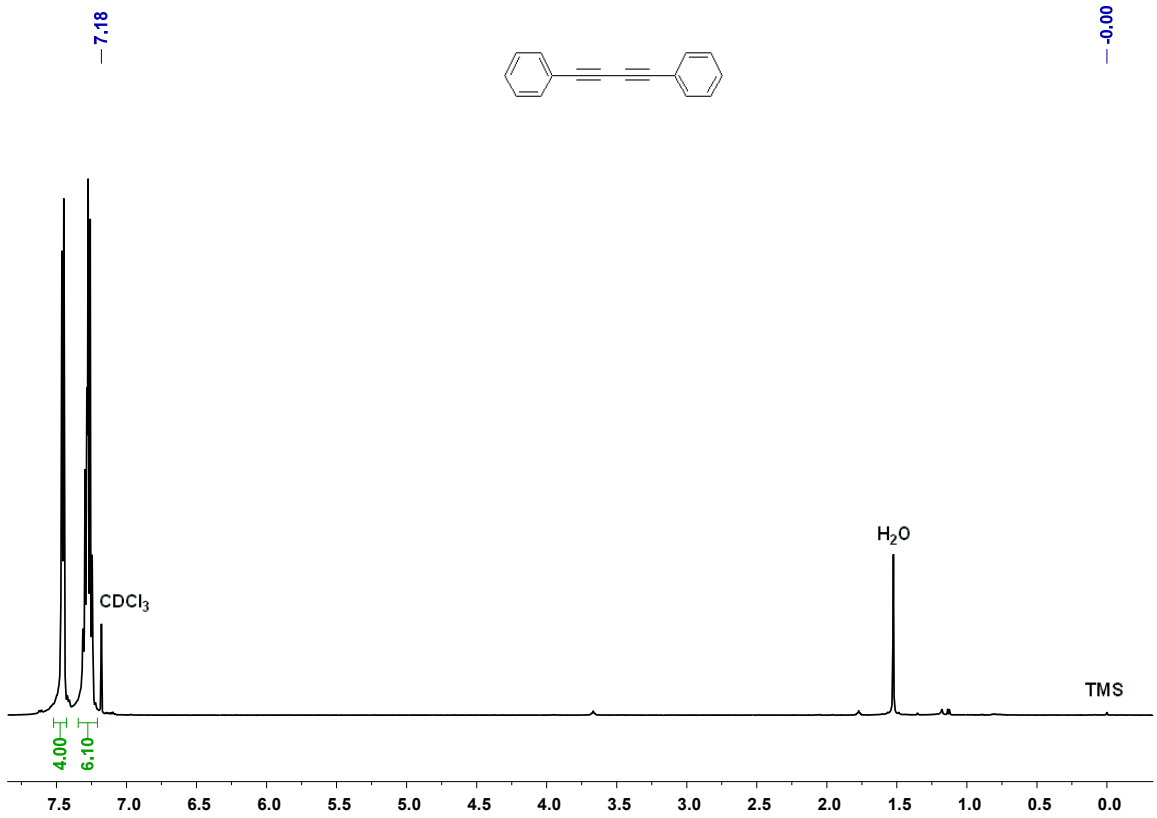


$C_{24}H_{18}O_2S_2$

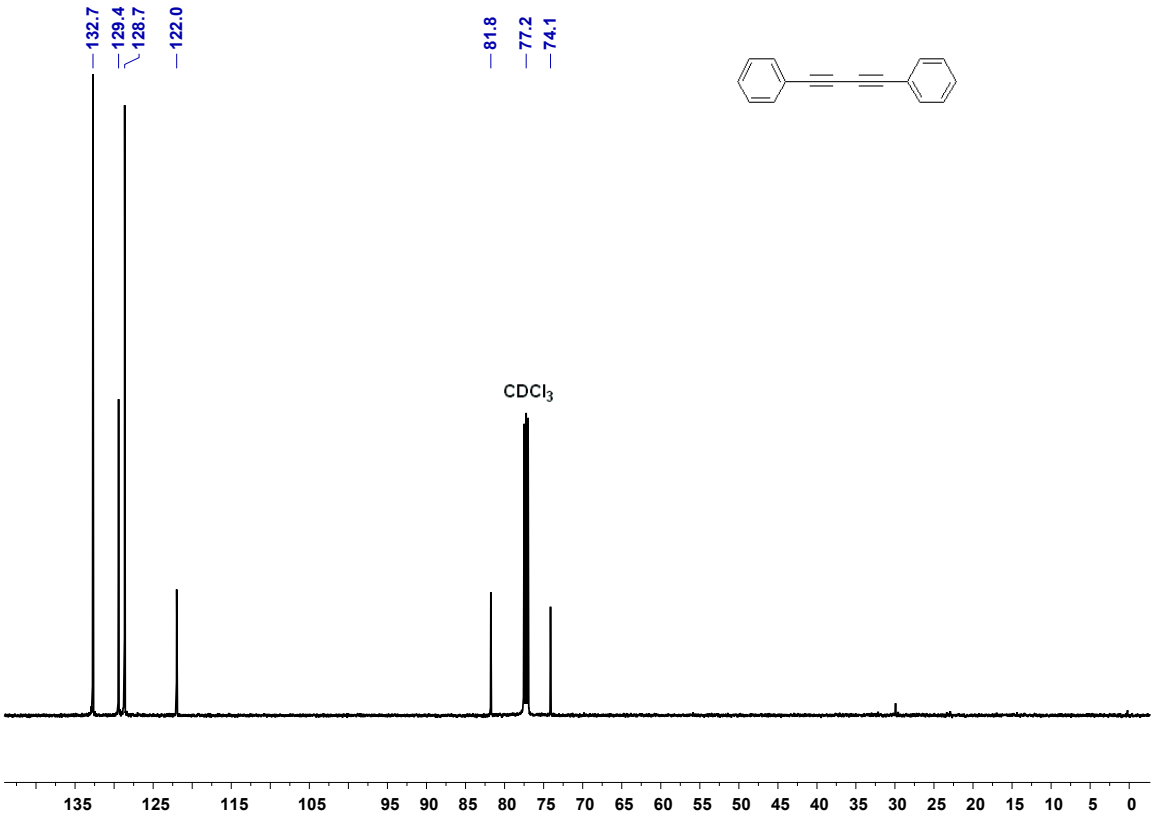
402.53

204 mg (0.51 mmol, 51 % yield) as a yellow solid. Mp 122 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.32 (t, *J* = 7.6 Hz, 6 H), 2.84 (q, *J* = 7.6 Hz, 4 H), 6.46 (s, 2 H), 7.01-7.04 (m, 2 H), 7.21-7.24 (m, 4 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 12.4 (CH_3), 21.1 (CH_2), 73.7 (C_{quat}), 76.8 (C_{quat}), 103.3 (C_{quat}), 107.4 (CH), 122.9 (CH), 124.4 (CH), 127.6 (CH), 132.8 (C_{quat}), 147.3 (C_{quat}), 163.2 (C_{quat}). EI + MS (*m/z* (%)): 404 (14), 403 (28), 402 (M^+, 100), 389 (12), 388 (25), 387 ($(M\text{-}CH_3)^+$, 98), 201 ($C_{12}H_{10}OS^+$, 12), 193 (18), 187 (19), 186 ($C_{11}H_6OS^+$, 66), 135 (20), 111 (43), 43 (11). IR (KBr): $\tilde{\nu}$ 2973 (w) cm^{-1}, 2933 (m), 2143 (w), 1655 (m), 1638 (m), 1561 (m), 1543 (w), 1509 (w), 1450 (w), 1422 (w), 1376 (w), 1251 (w), 1203 (m), 1114 (w), 1050 (s), 1037 (m), 996 (w), 895 (w), 849 (m), 819 (w), 785 (s), 689 (s), 635 (w), 579 (m). Anal. calcd for $C_{24}H_{18}O_2S_2$ (402.5) : C 71.61, H 4.51. Found: C 71.65, H 4.46.

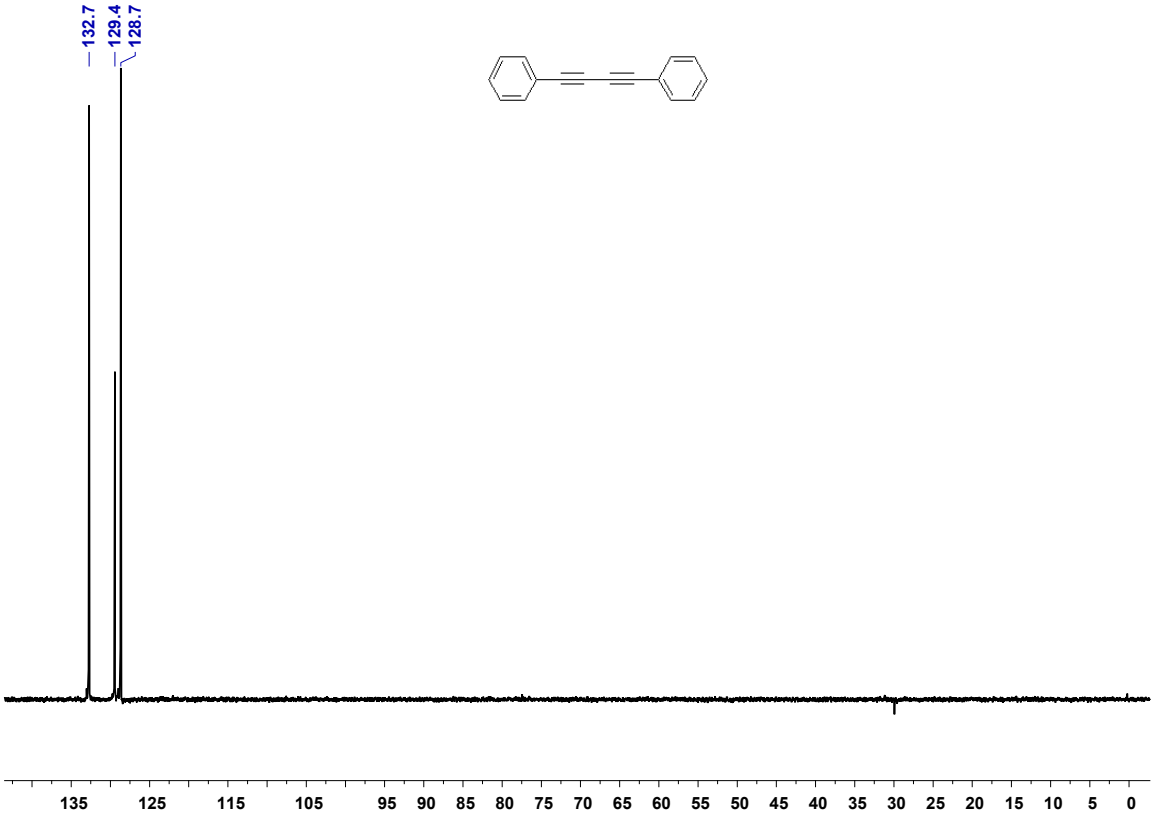
4. ^{1}H and ^{13}C NMR Spectra of Compounds 2a-2z



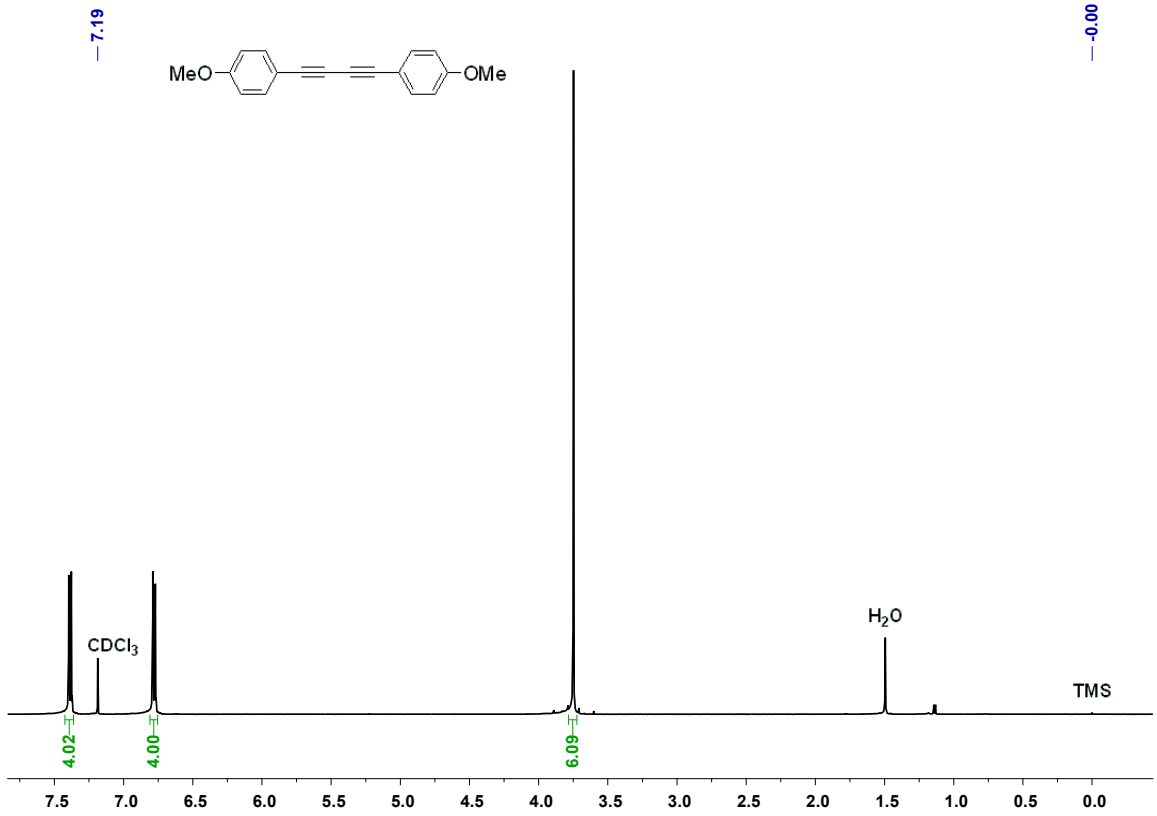
^{1}H NMR of **2a** in $CDCl_3$ at 298 K (δ in ppm).



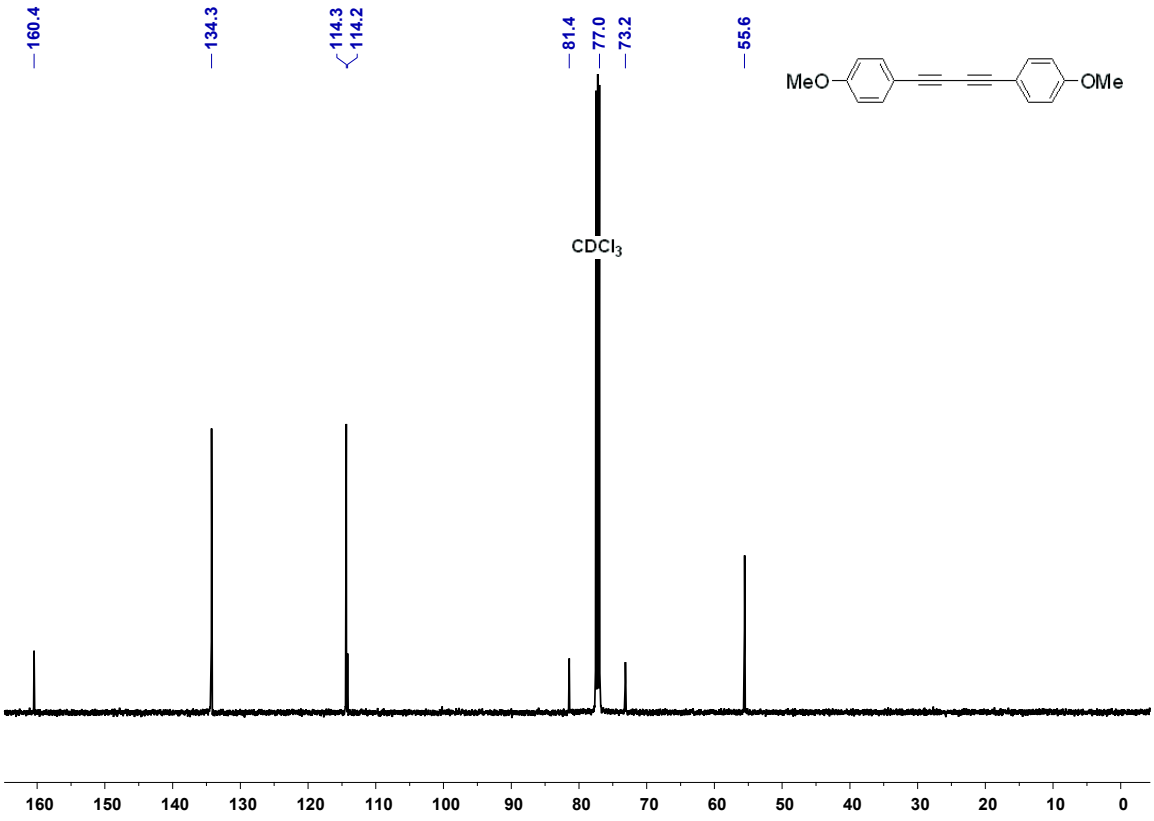
^{13}C NMR of **2a** in $CDCl_3$ at 296 K (δ in ppm).



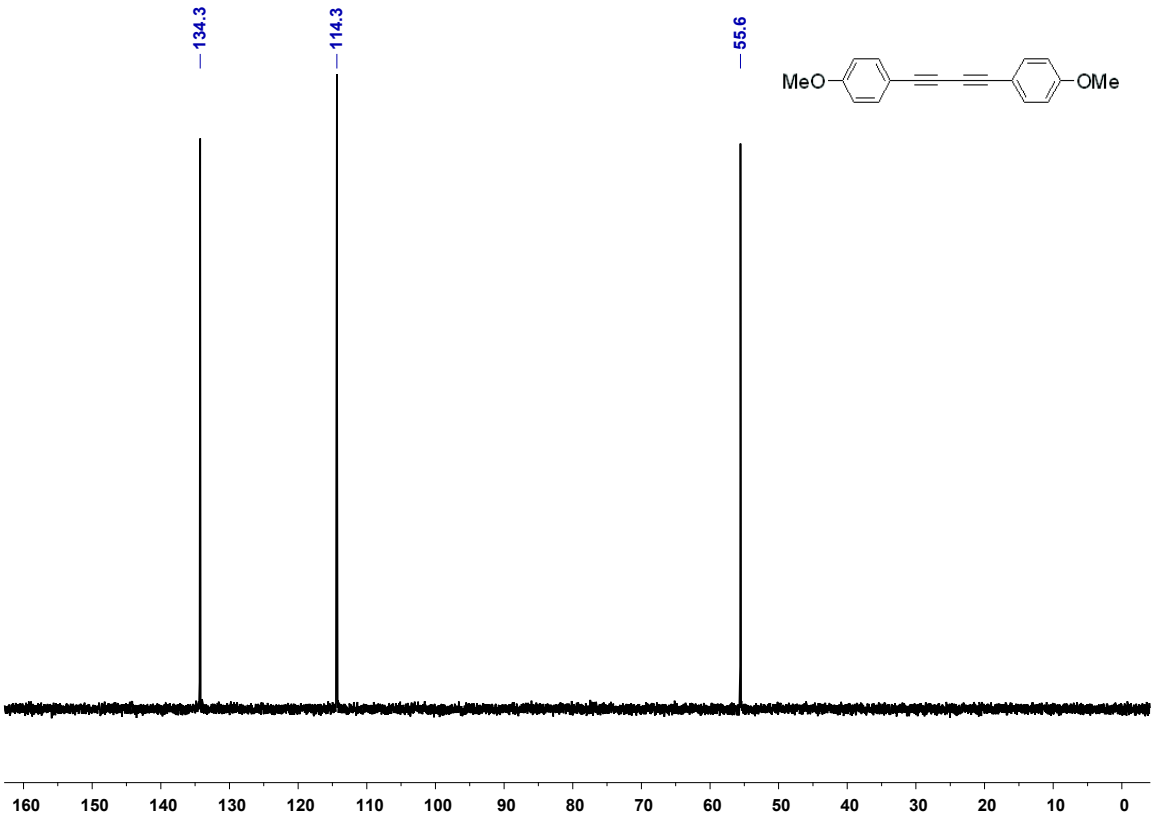
^{13}C DEPT 135-NMR of **2a** in $CDCl_3$ at 296 K (δ in ppm).



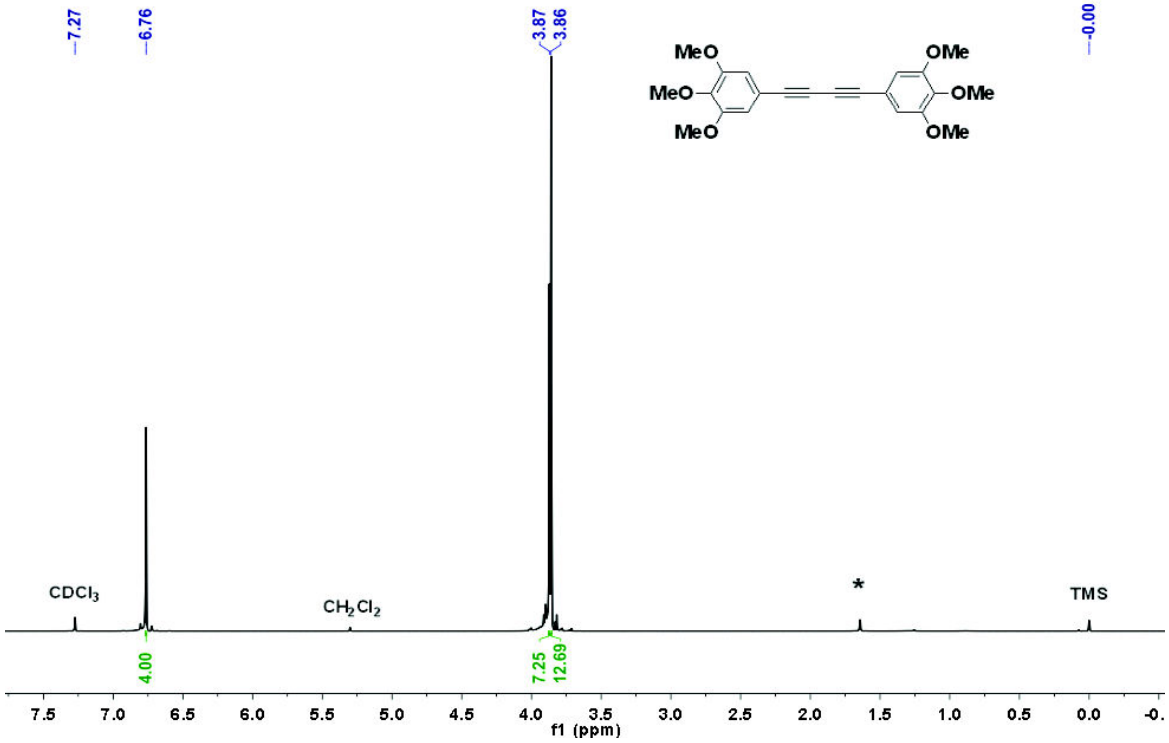
^{1}H NMR of **2b** in $CDCl_3$ at 296 K (δ in ppm).



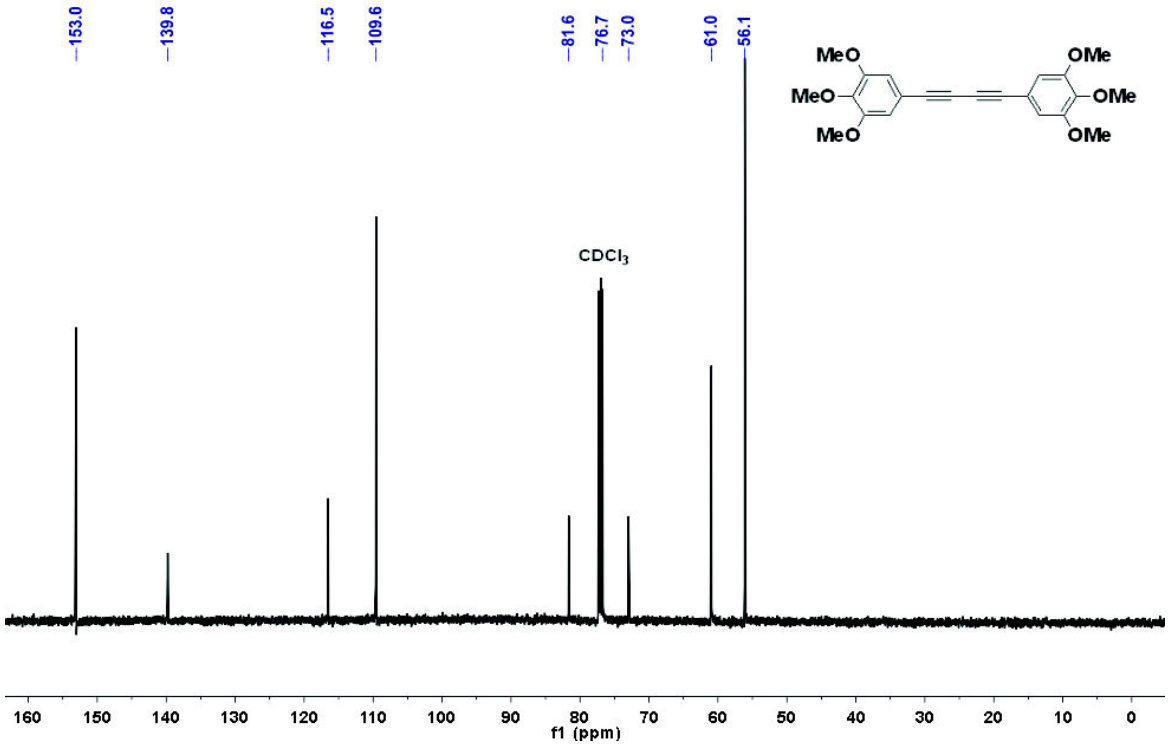
^{13}C NMR of **2b** in $CDCl_3$ at 298 K (δ in ppm).



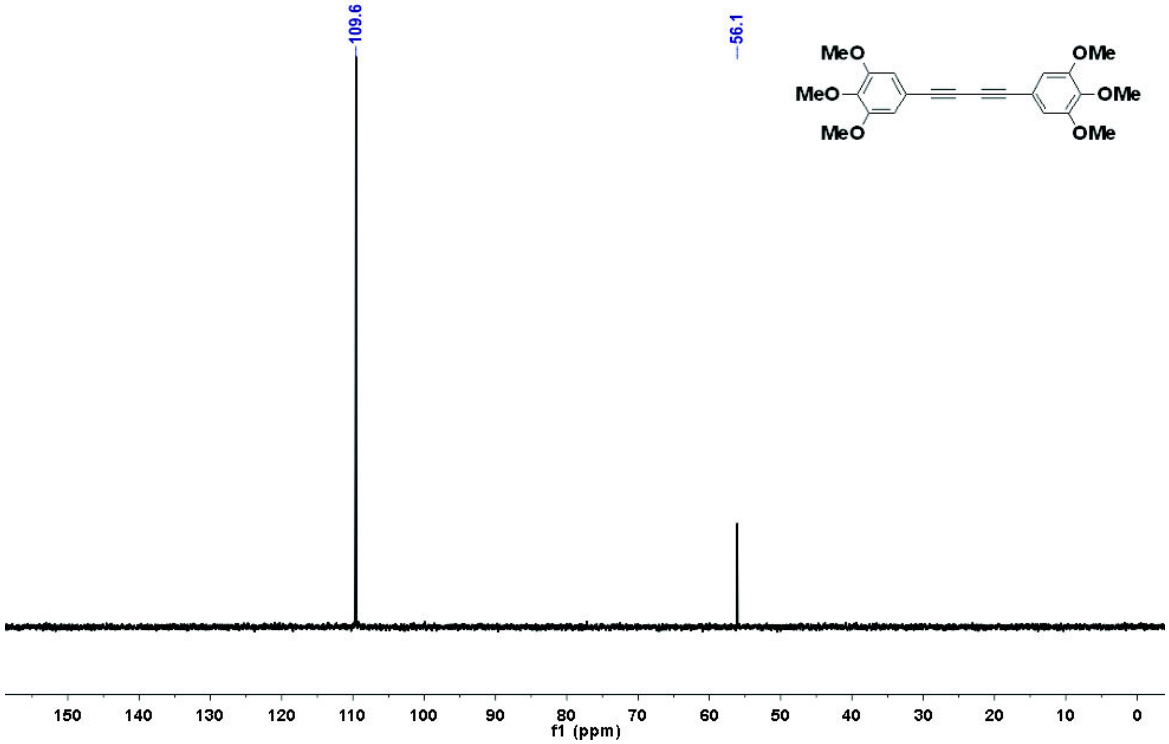
^{13}C DEPT 135-NMR of **2b** in $CDCl_3$ at 298 K (δ in ppm).



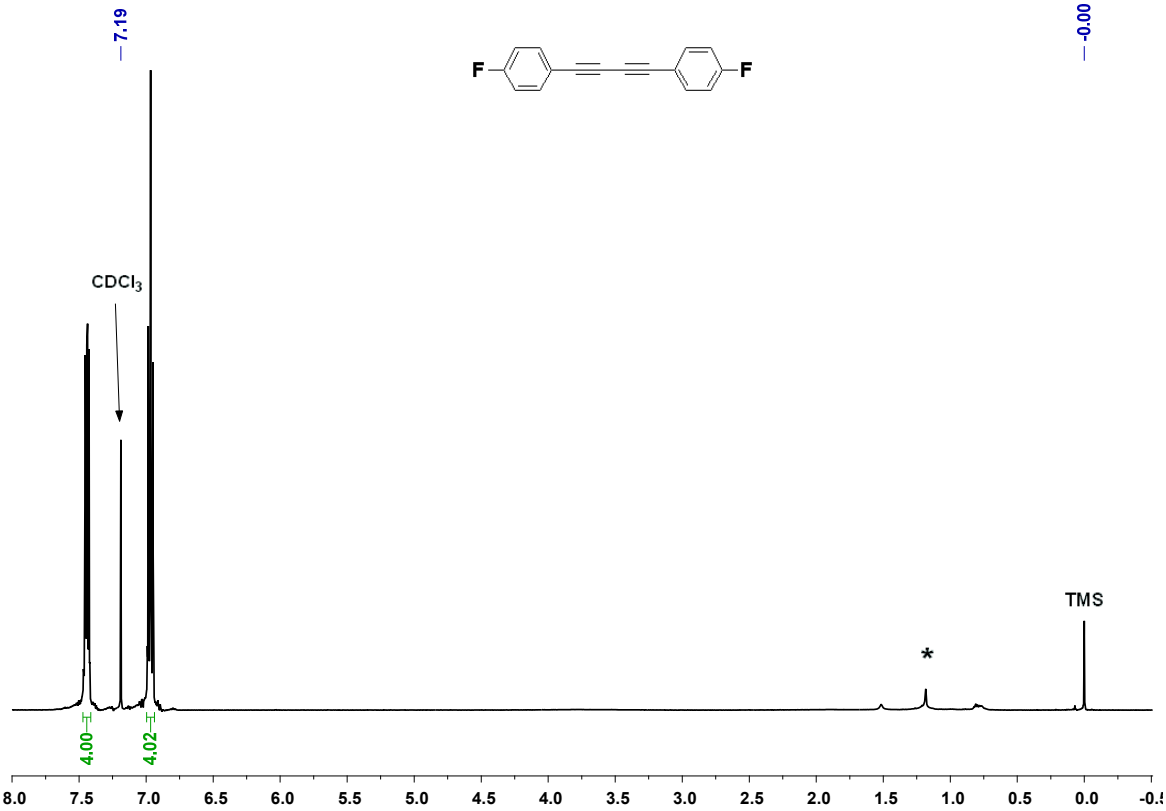
^{1}H NMR of **2c** in $CDCl_3$ at 296 K (δ in ppm). *Impurities from residual solvents.



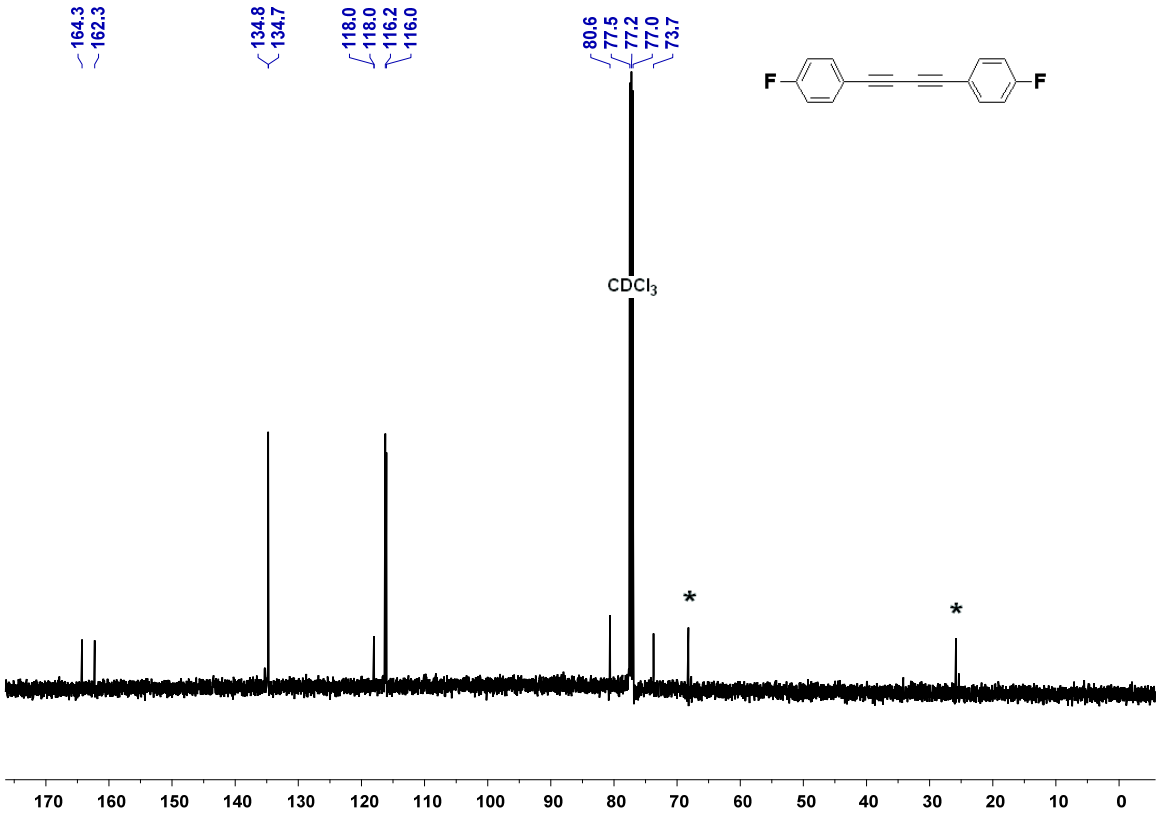
^{13}C NMR of **2c** in $CDCl_3$ at 296 K (δ in ppm).



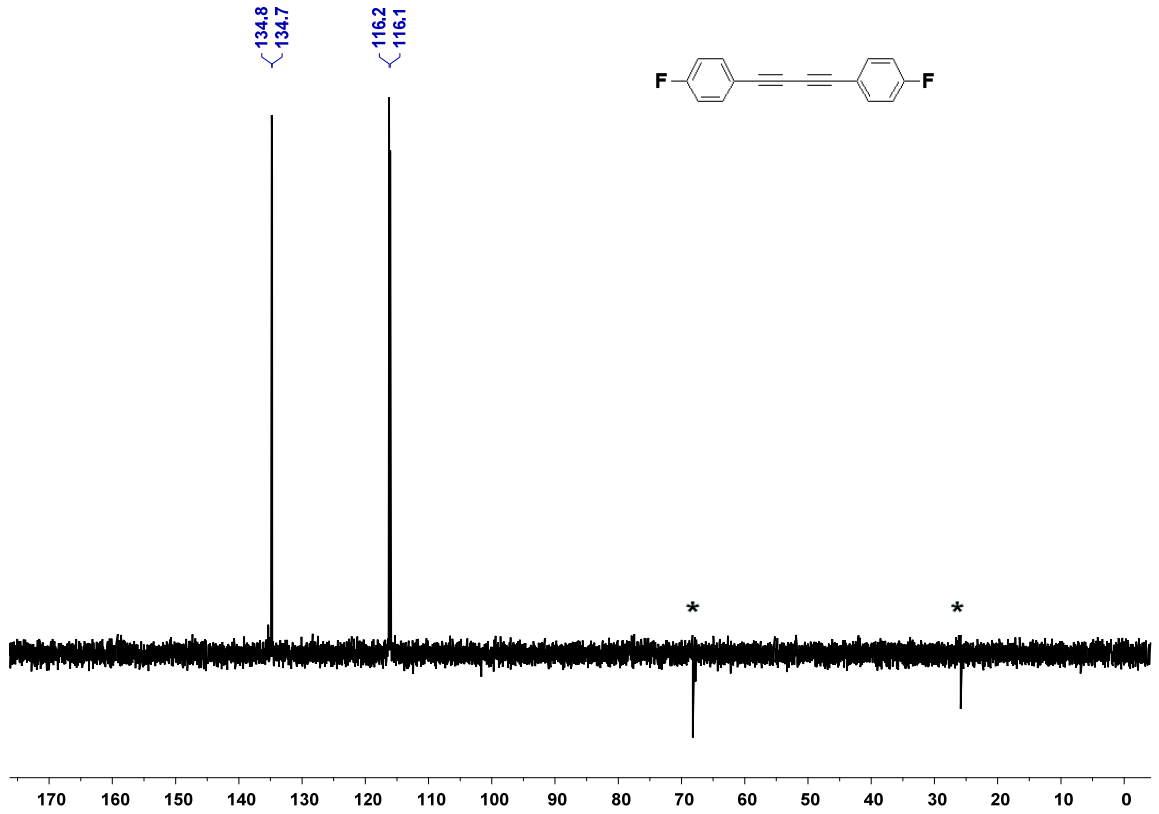
^{13}C DEPT 135-NMR of **2c** in $CDCl_3$ at 296 K (δ in ppm).



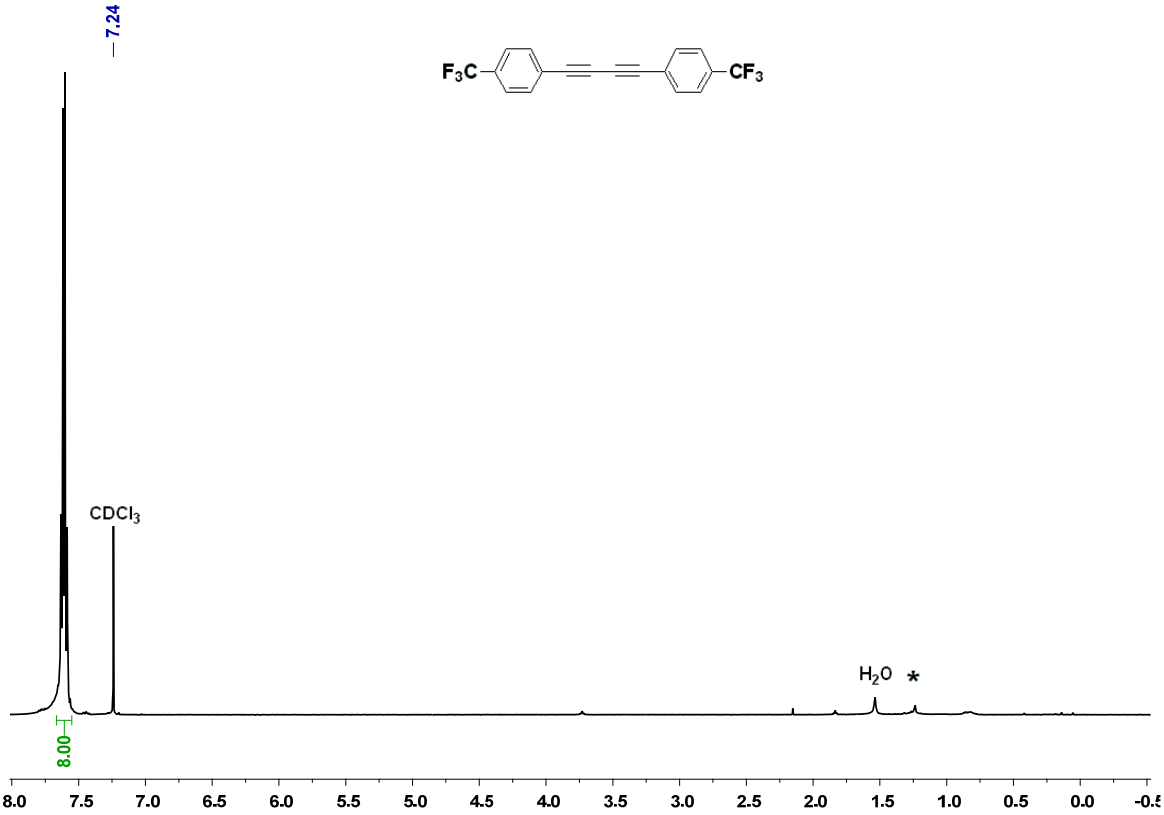
^{1}H NMR of **2e** in $CDCl_3$ at 298 K (δ in ppm). *Impurities from residual solvents.



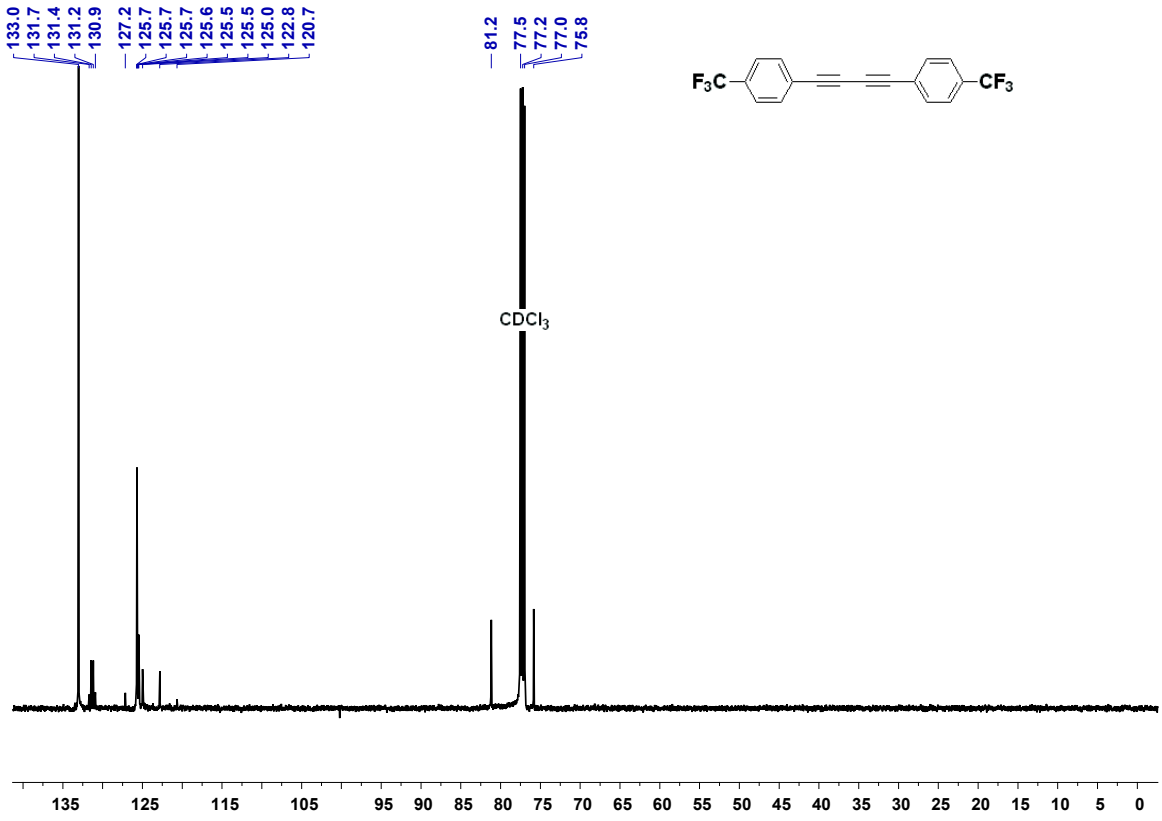
^{13}C NMR of **2e** in $CDCl_3$ at 297 K (δ in ppm). *Impurities from residual solvents.



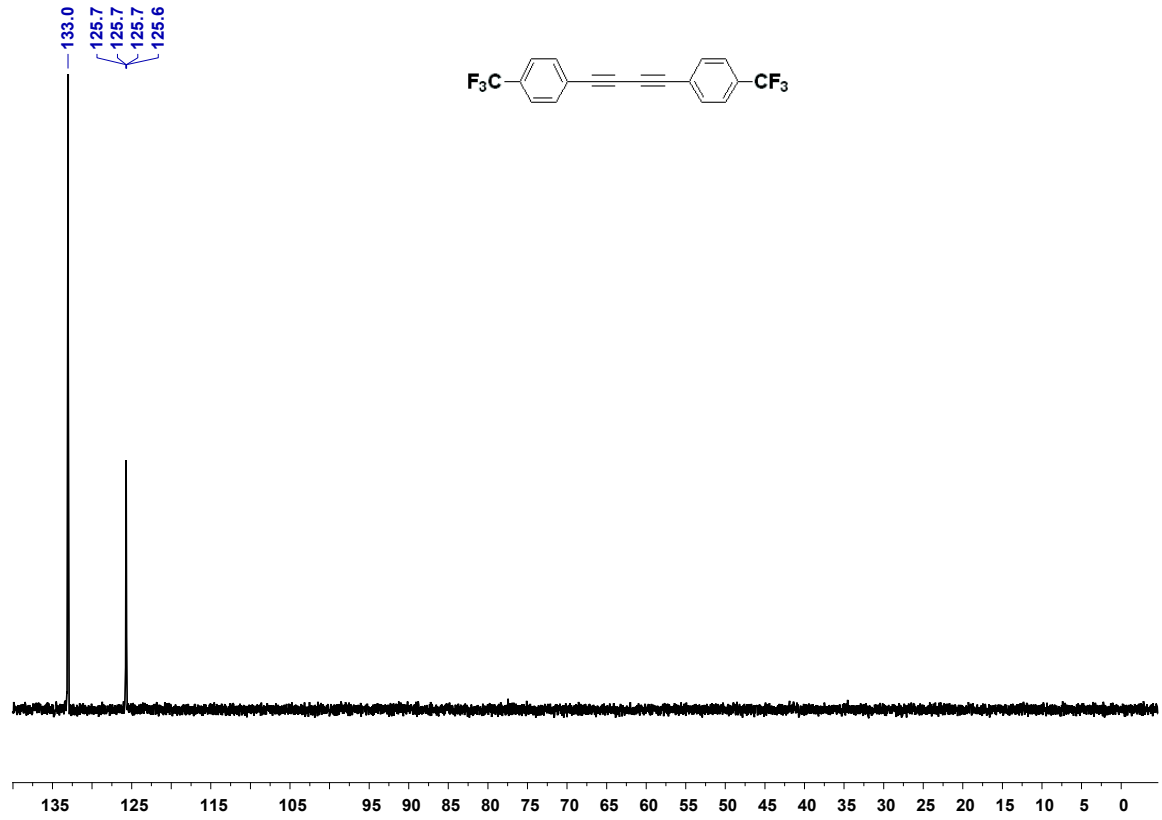
^{13}C DEPT 135-NMR of **2e** in $CDCl_3$ at 297 K (δ in ppm). *Impurities from residual solvents.



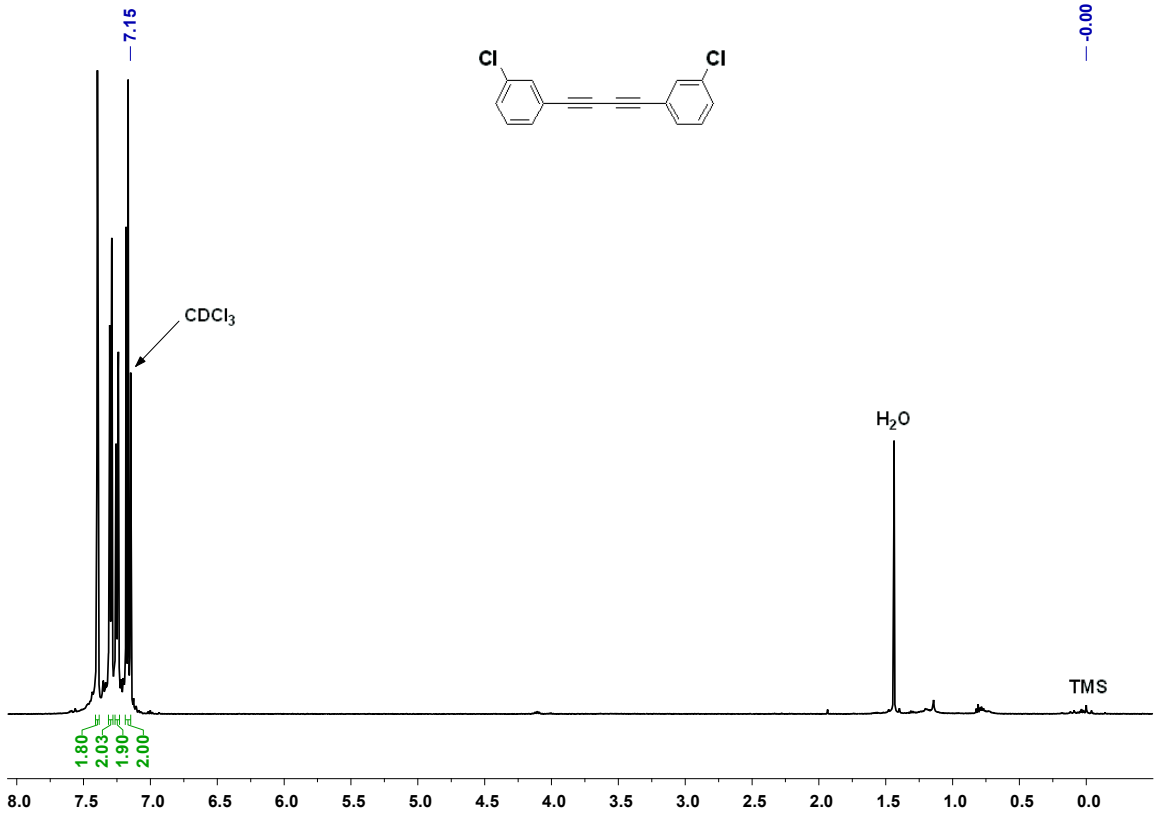
^{1}H NMR of **2f** in $CDCl_3$ at 296 K (δ in ppm). *Impurities from residual solvents.



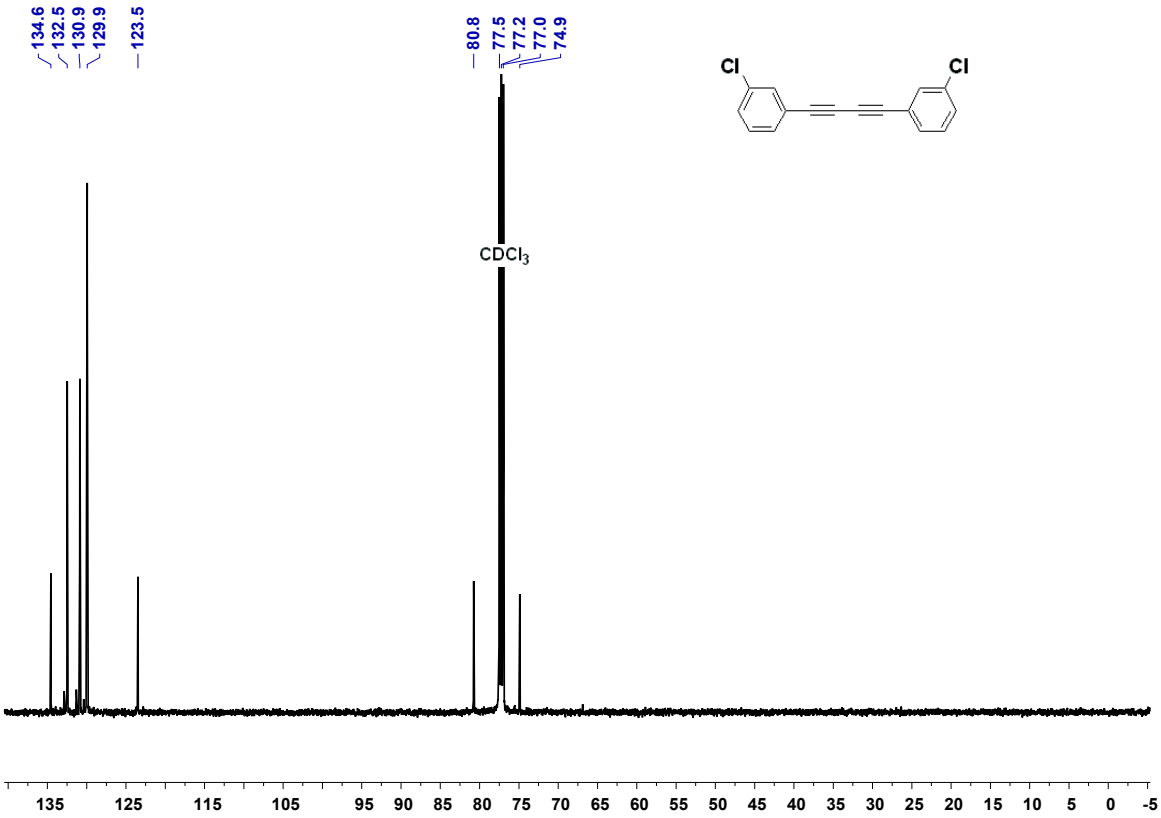
^{13}C NMR of **2f** in $CDCl_3$ at 296 K (δ in ppm).



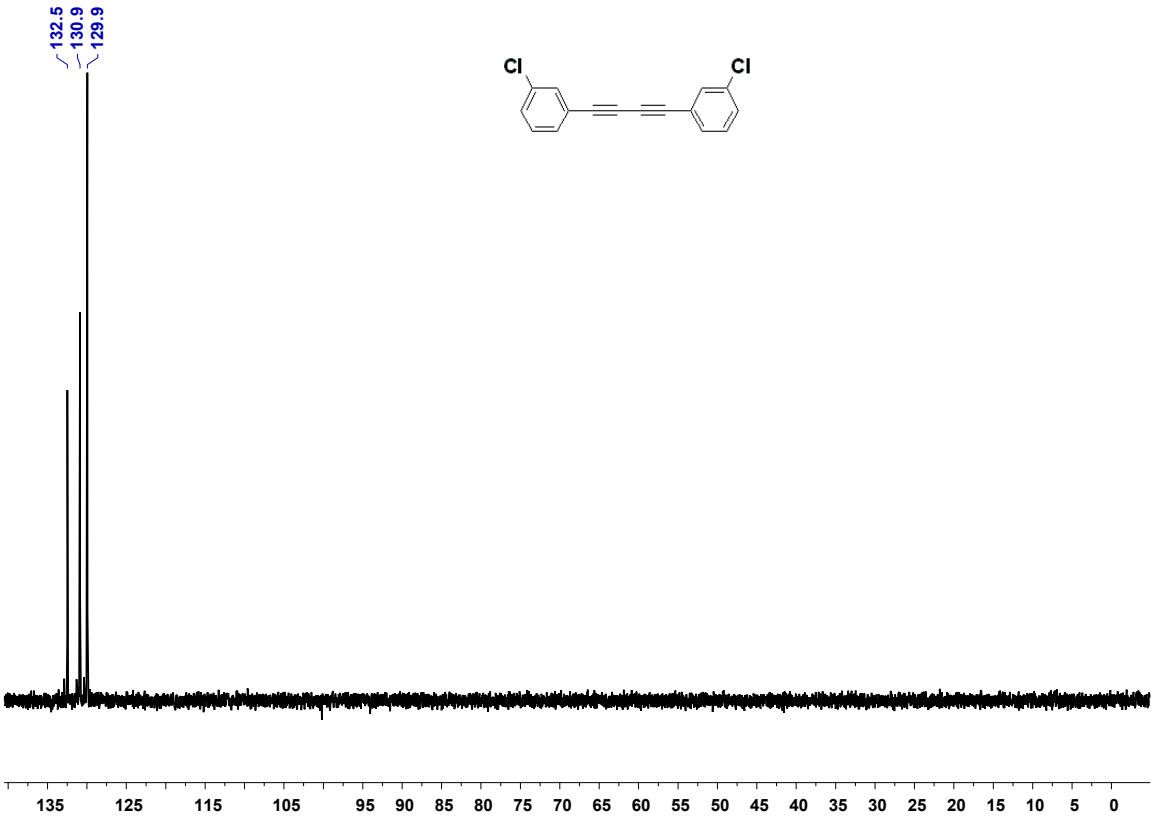
^{13}C DEPT 135-NMR of **2f** in $CDCl_3$ at 297 K (δ in ppm).



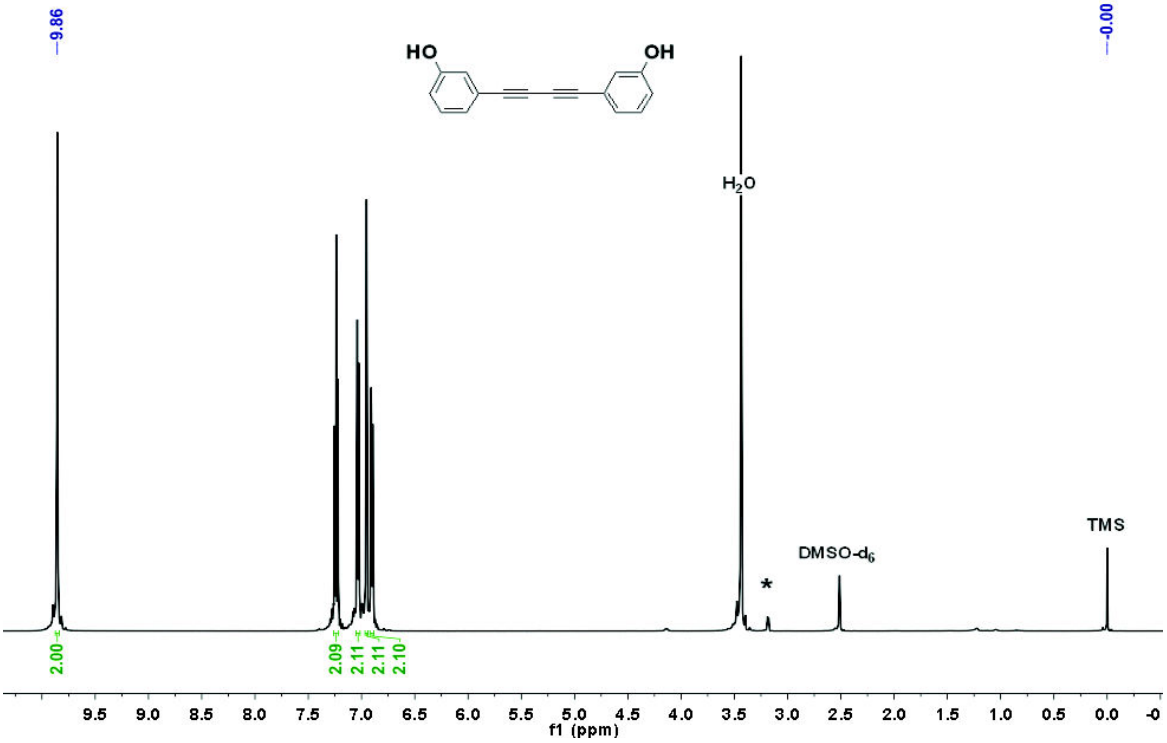
^{1}H NMR of **2i** in $CDCl_3$ at 298 K (δ in ppm).



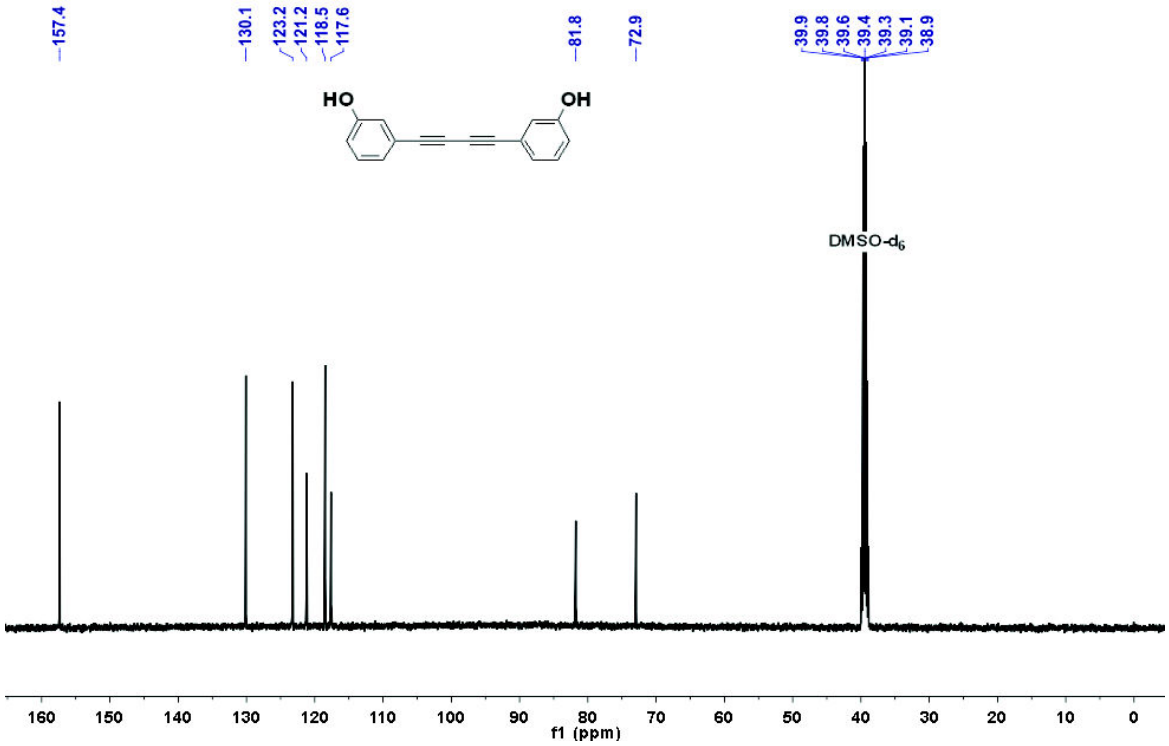
^{13}C NMR of **2i** in $CDCl_3$ at 298 K (δ in ppm).



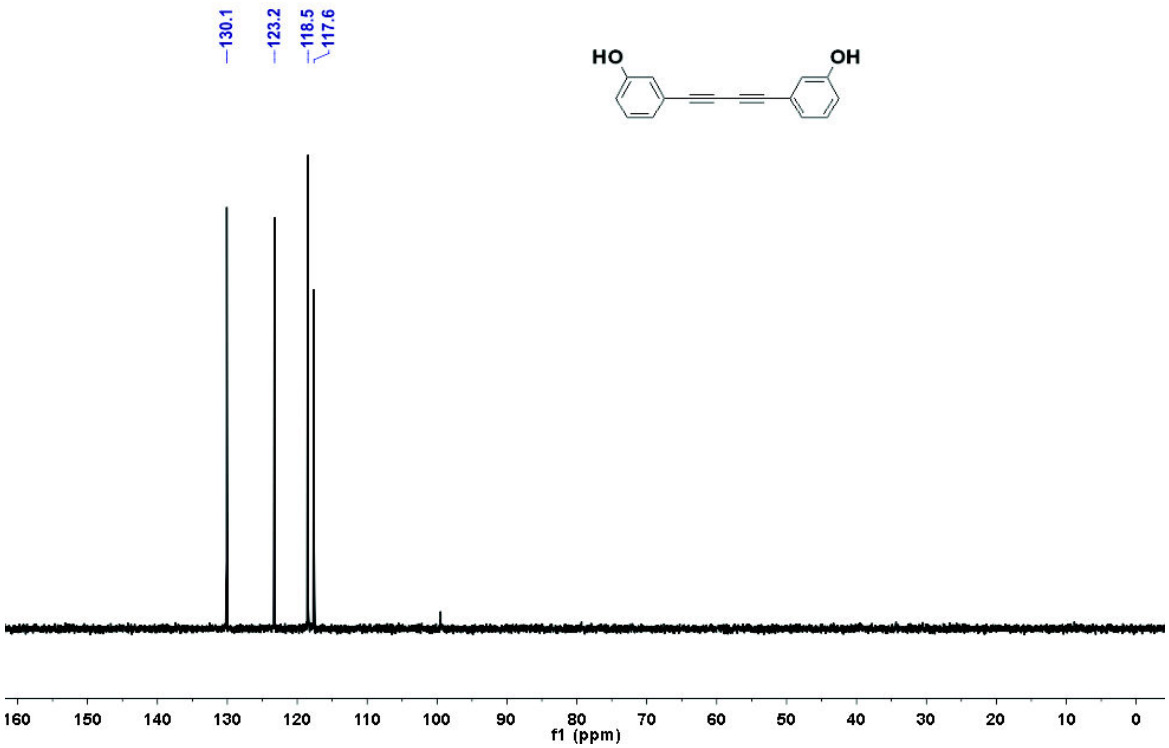
^{13}C DEPT 135-NMR of **2i** in $CDCl_3$ at 298 K (δ in ppm).



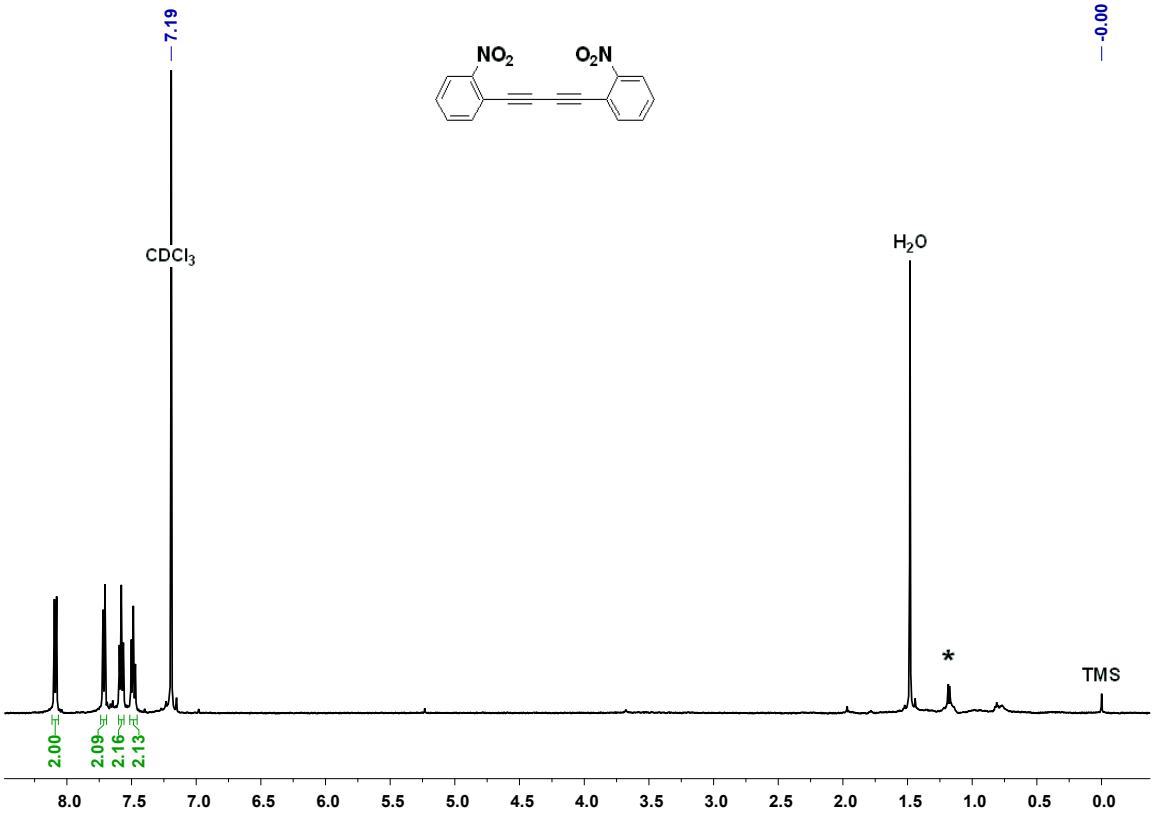
^{1}H NMR of **2j** in $CDCl_3$ at 296 K (δ in ppm). *Impurities from residual solvents.



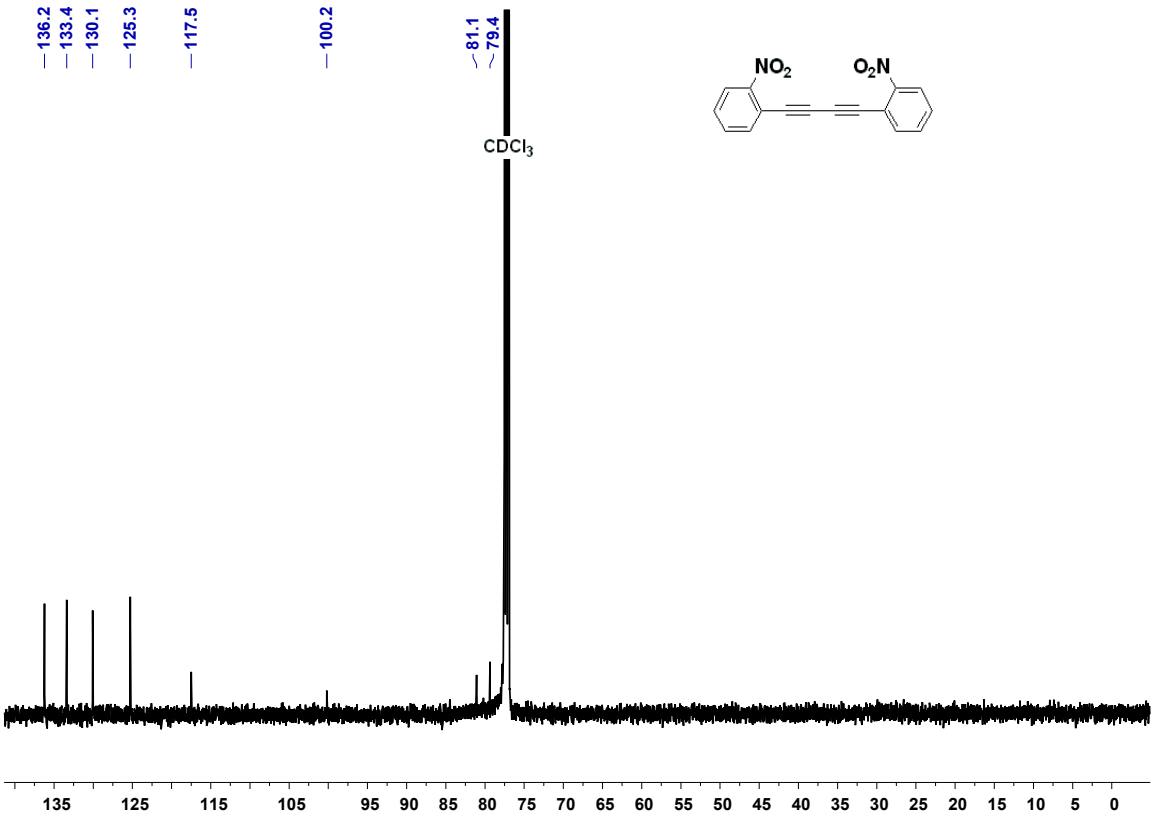
^{13}C NMR of **2j** in $CDCl_3$ at 296 K (δ in ppm).



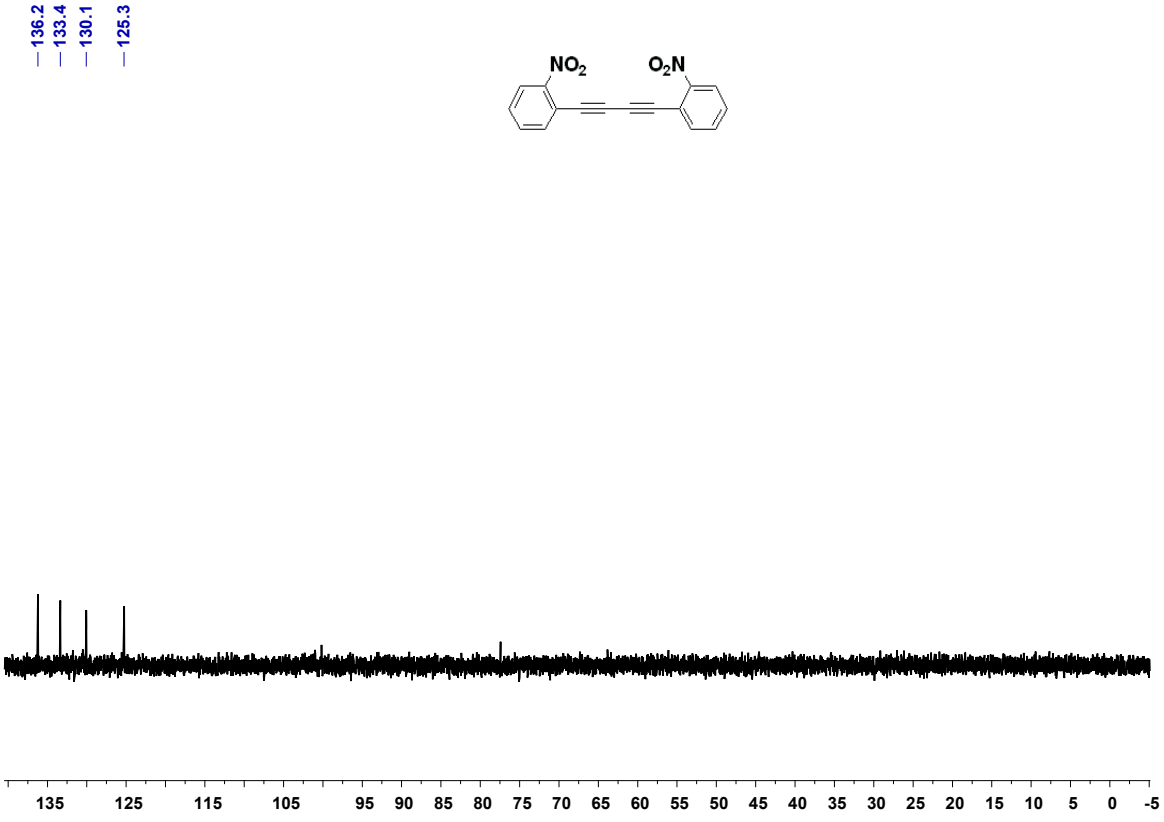
^{13}C DEPT 135-NMR of **2j** in $CDCl_3$ at 296 K (δ in ppm).



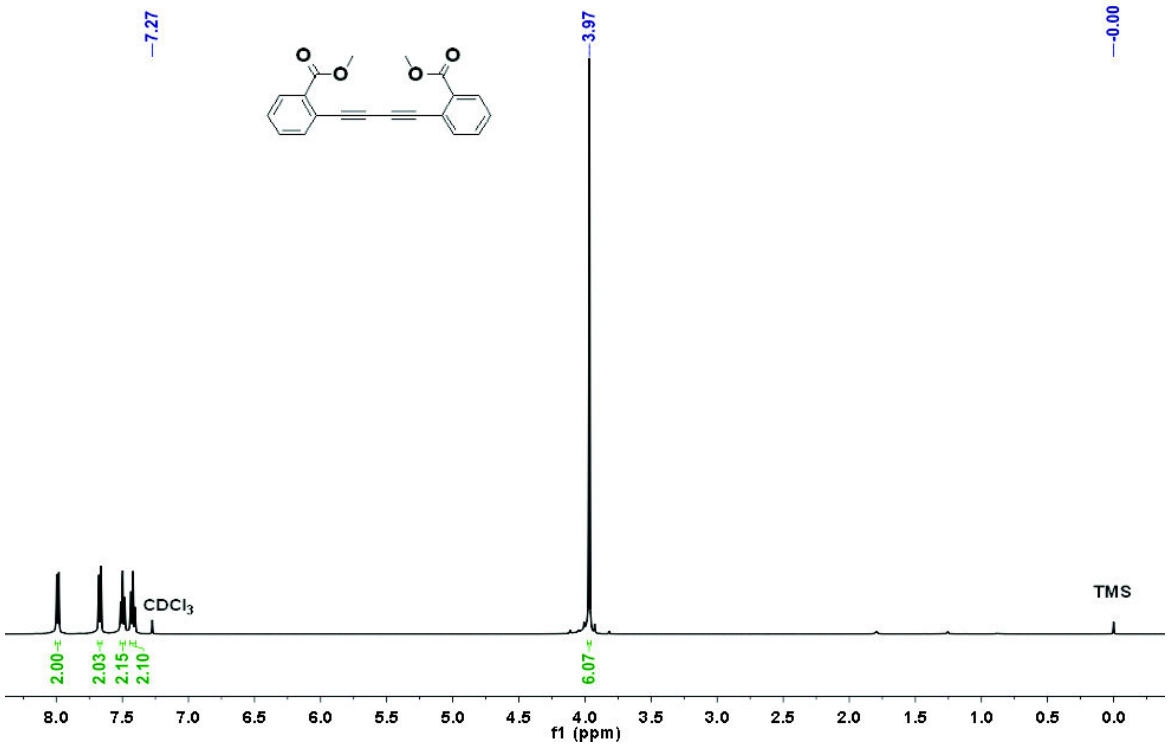
^{1}H NMR of **2l** in $CDCl_3$ at 295 K (δ in ppm). *Impurities from residual solvents.



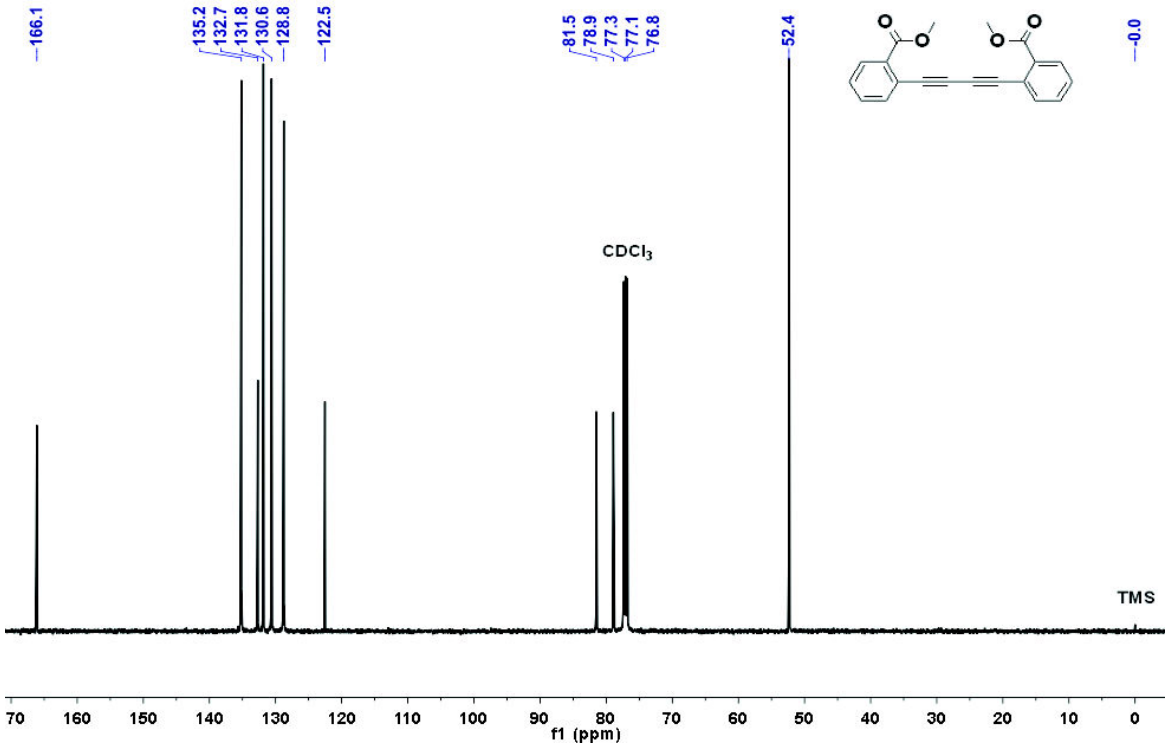
^{13}C NMR of **2l** in $CDCl_3$ at 296 K (δ in ppm).



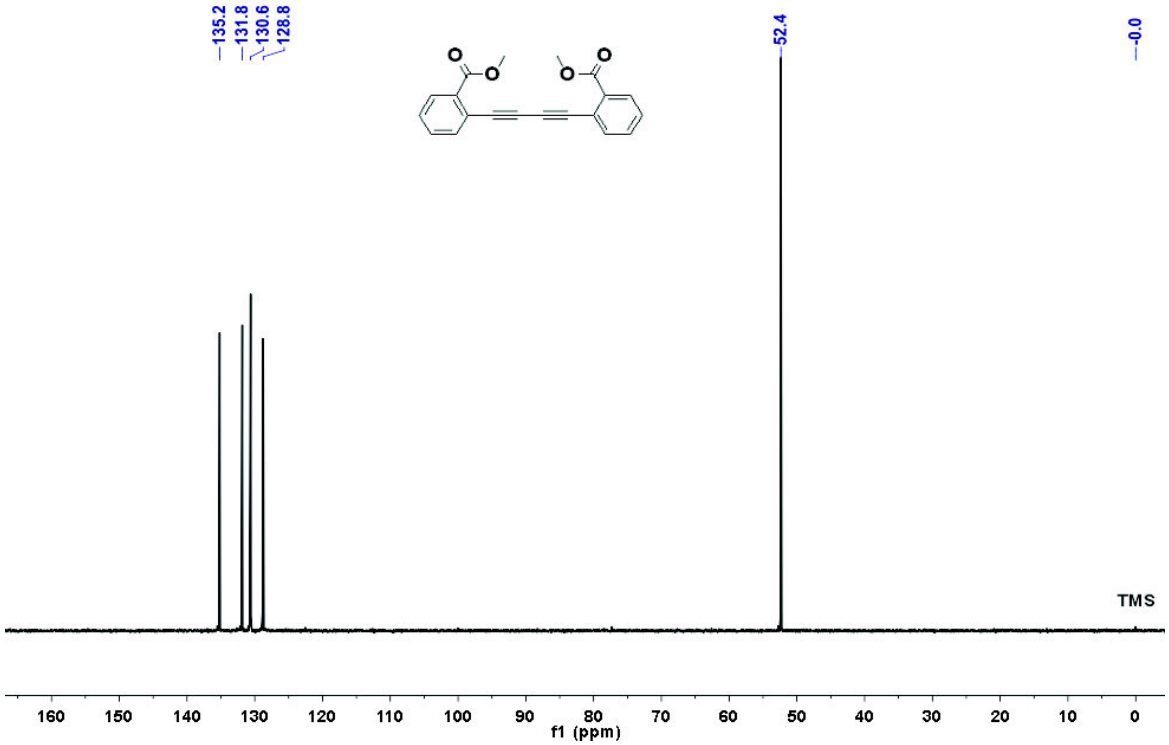
^{13}C DEPT 135-NMR of **2l** in $CDCl_3$ at 296 K (δ in ppm).



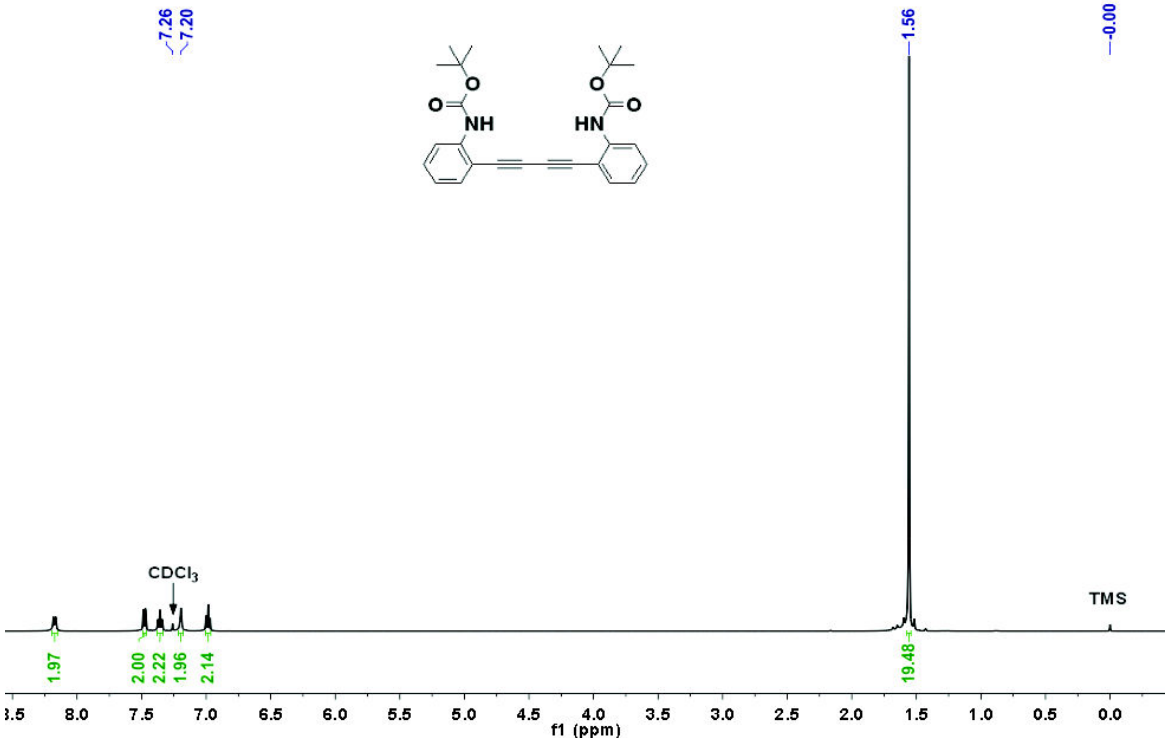
^{1}H NMR of **2m** in $CDCl_3$ at 296 K (δ in ppm).



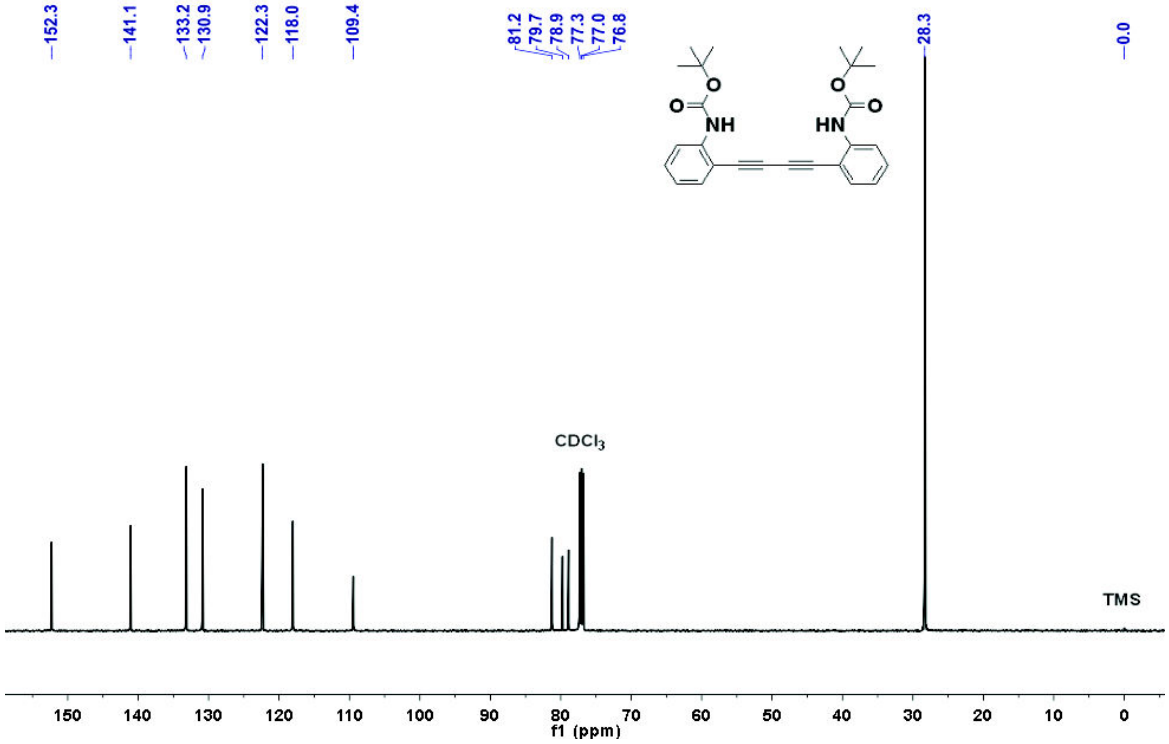
^{13}C NMR of **2m** in $CDCl_3$ at 297 K (δ in ppm).



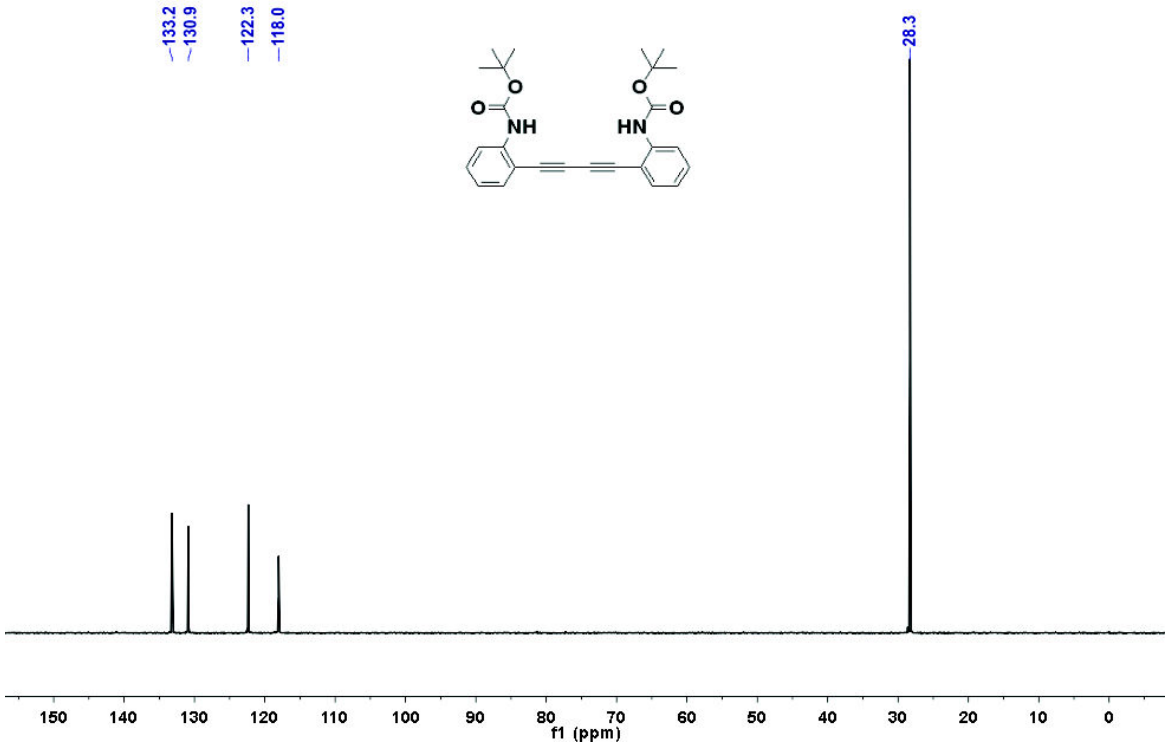
^{13}C DEPT 135-NMR of **2m** in $CDCl_3$ at 296 K (δ in ppm).



^{1}H NMR of **2n** in $CDCl_3$ at 296 K (δ in ppm).



^{13}C NMR of **2n** in $CDCl_3$ at 296 K (δ in ppm).



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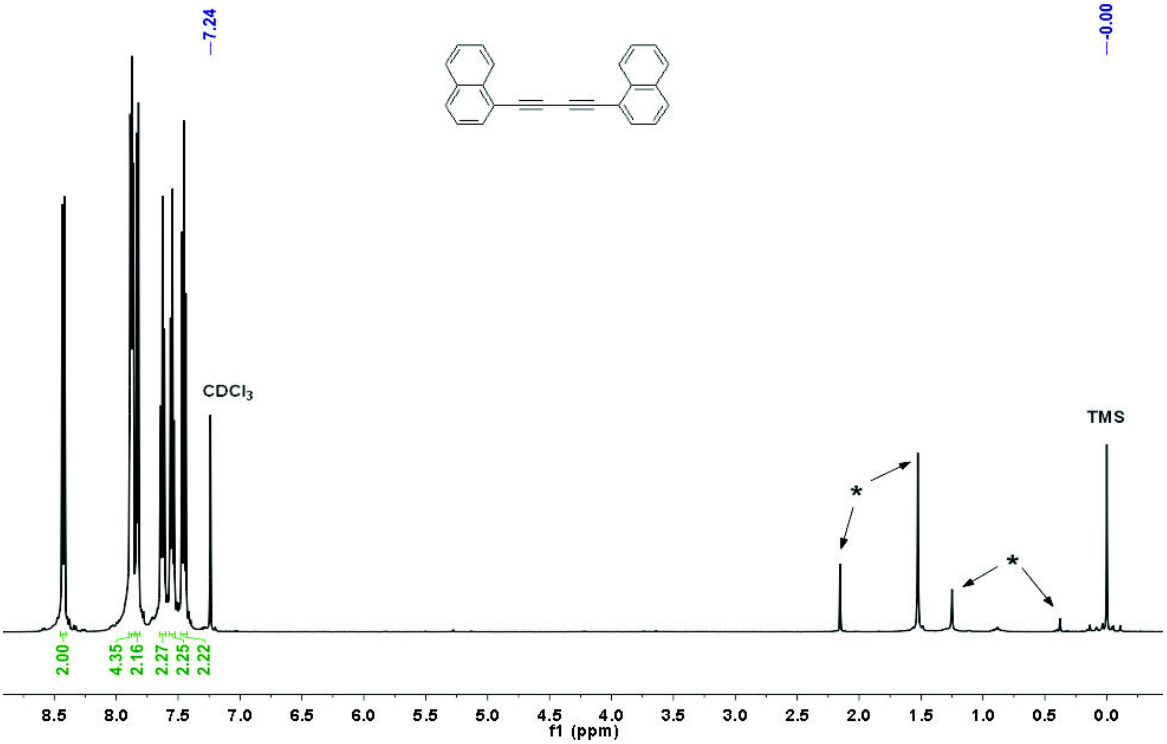
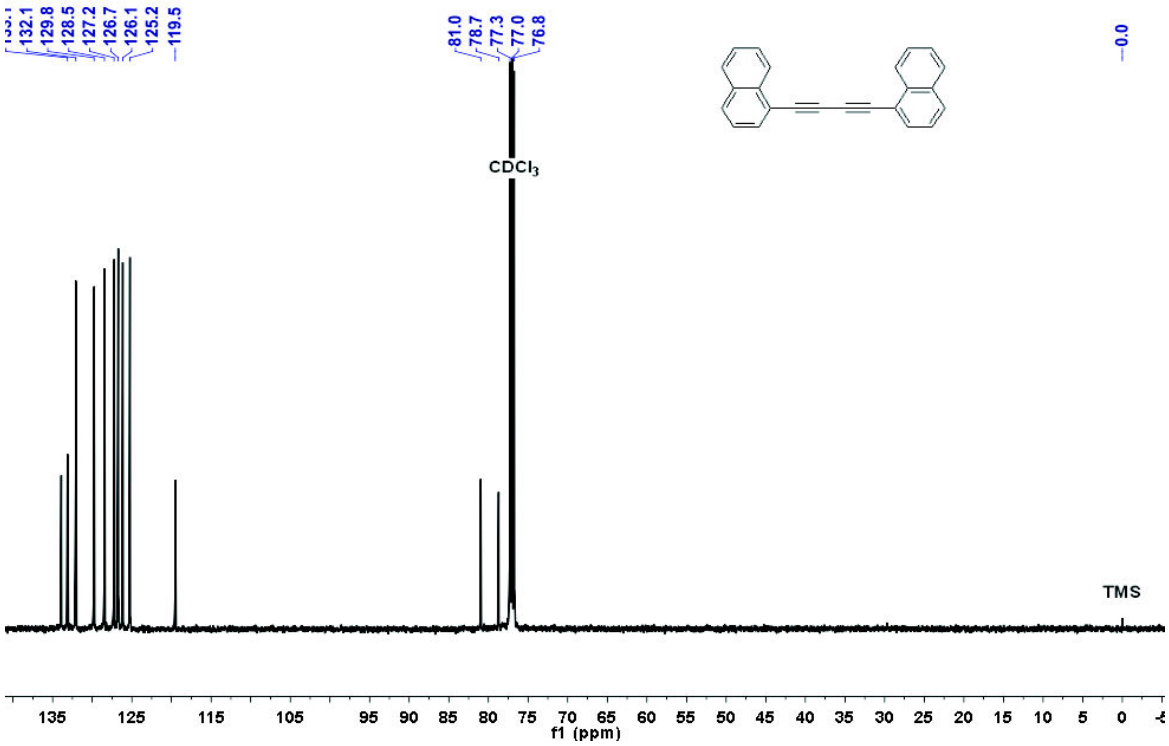


^{1}H NMR of **2o** in $CDCl_3$ at 298 K (δ in ppm). *Impurities from residual solvents.



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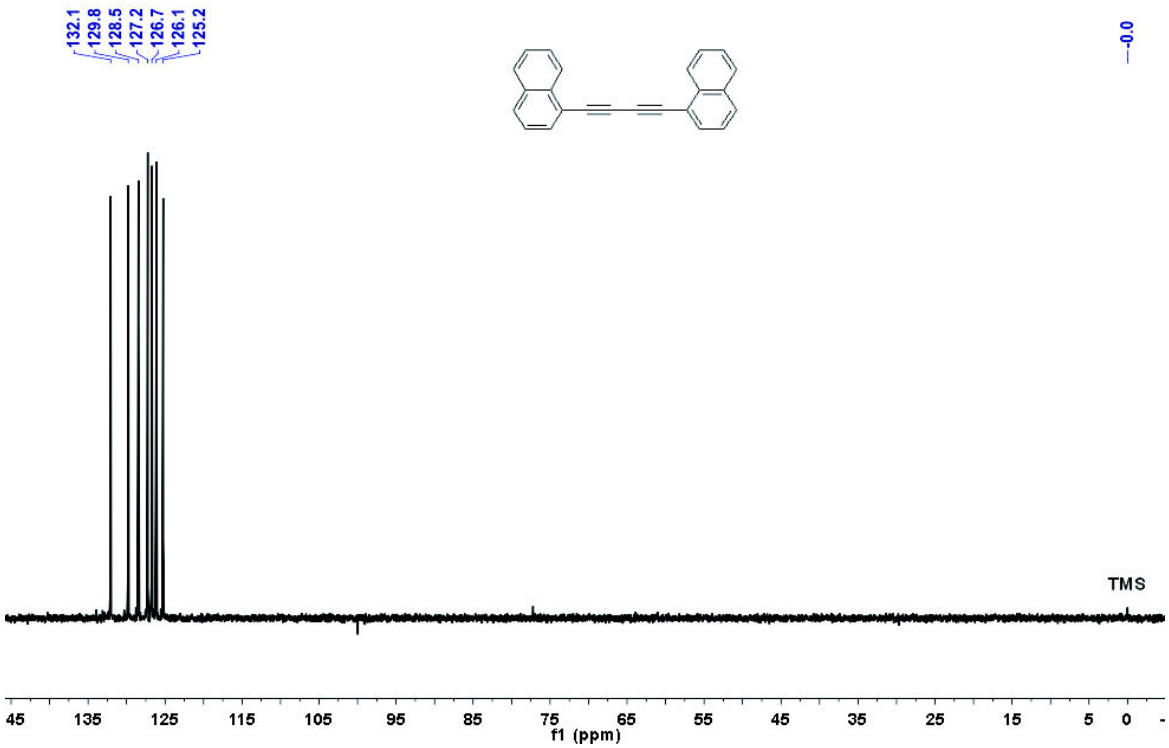

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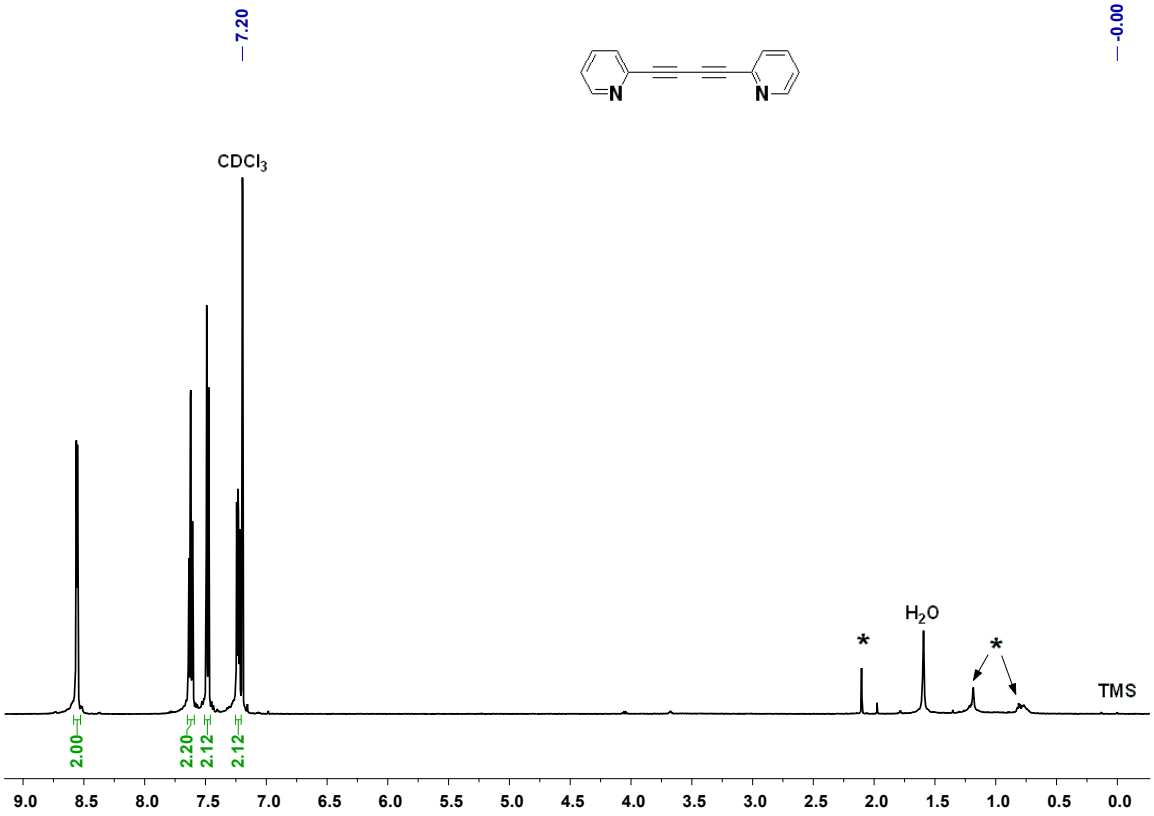

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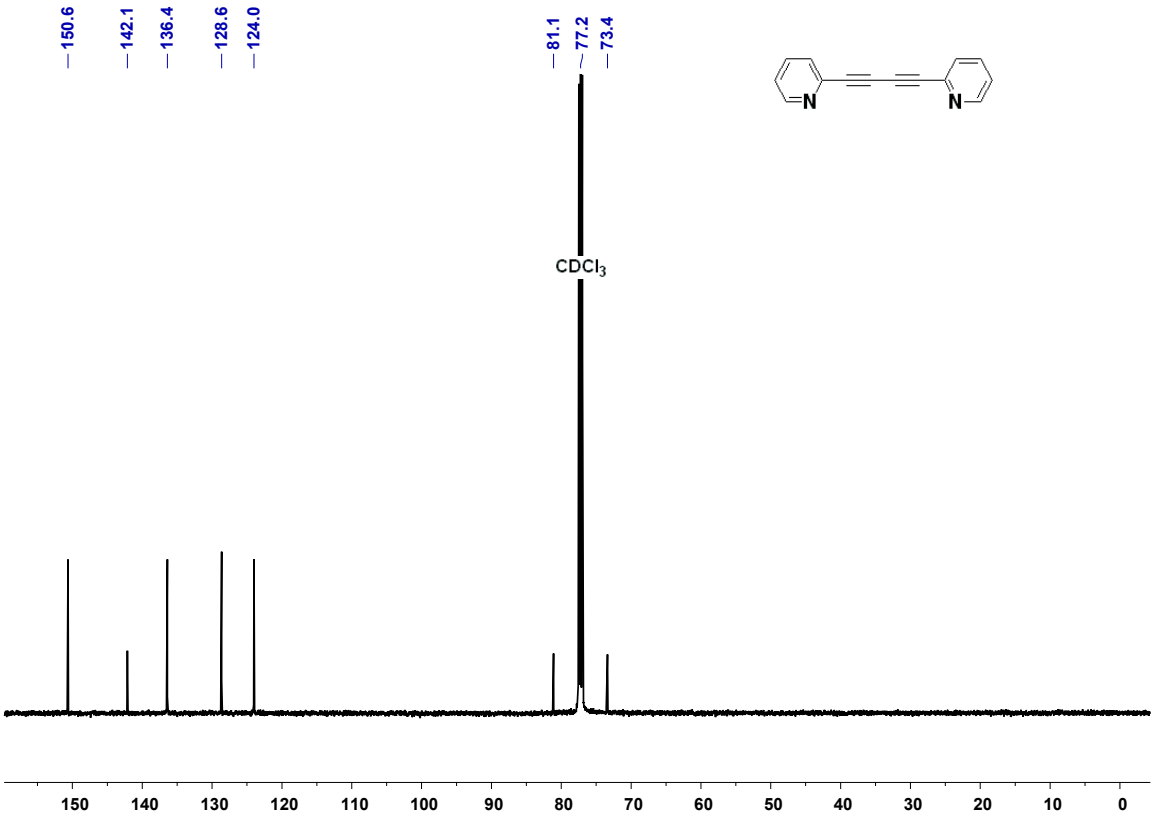

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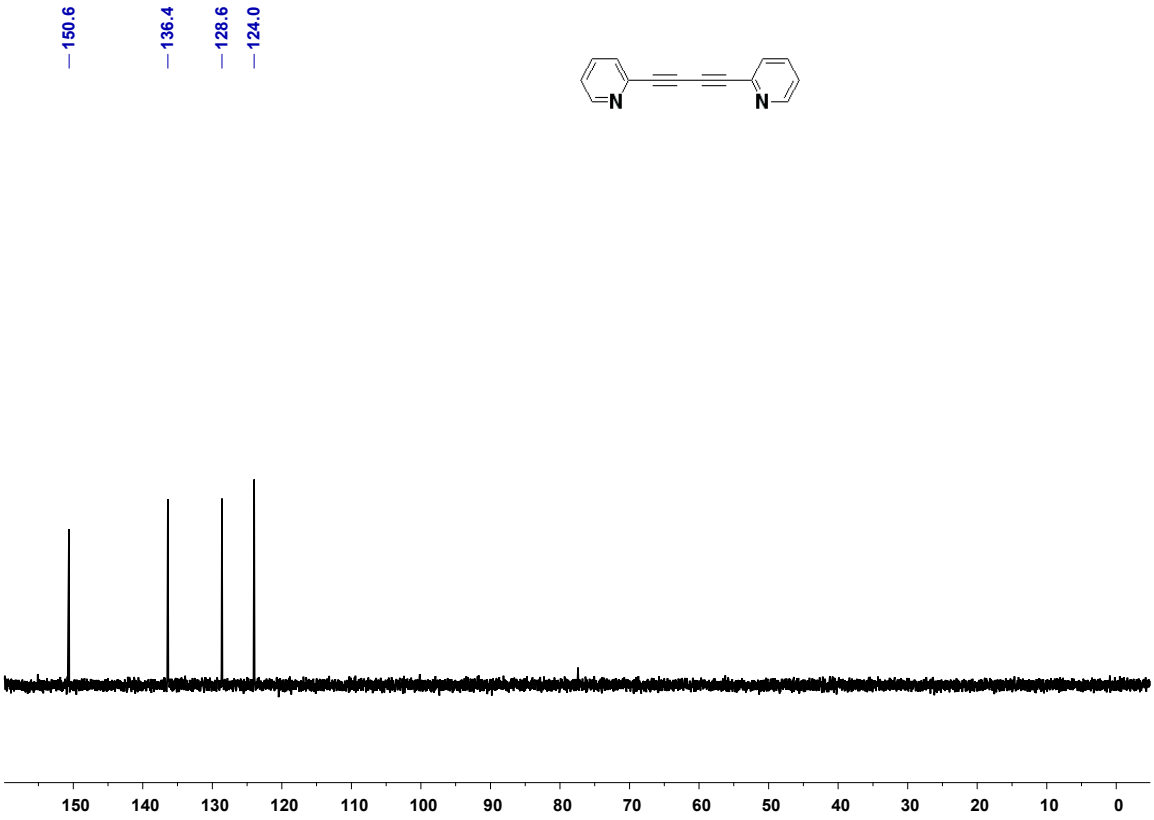

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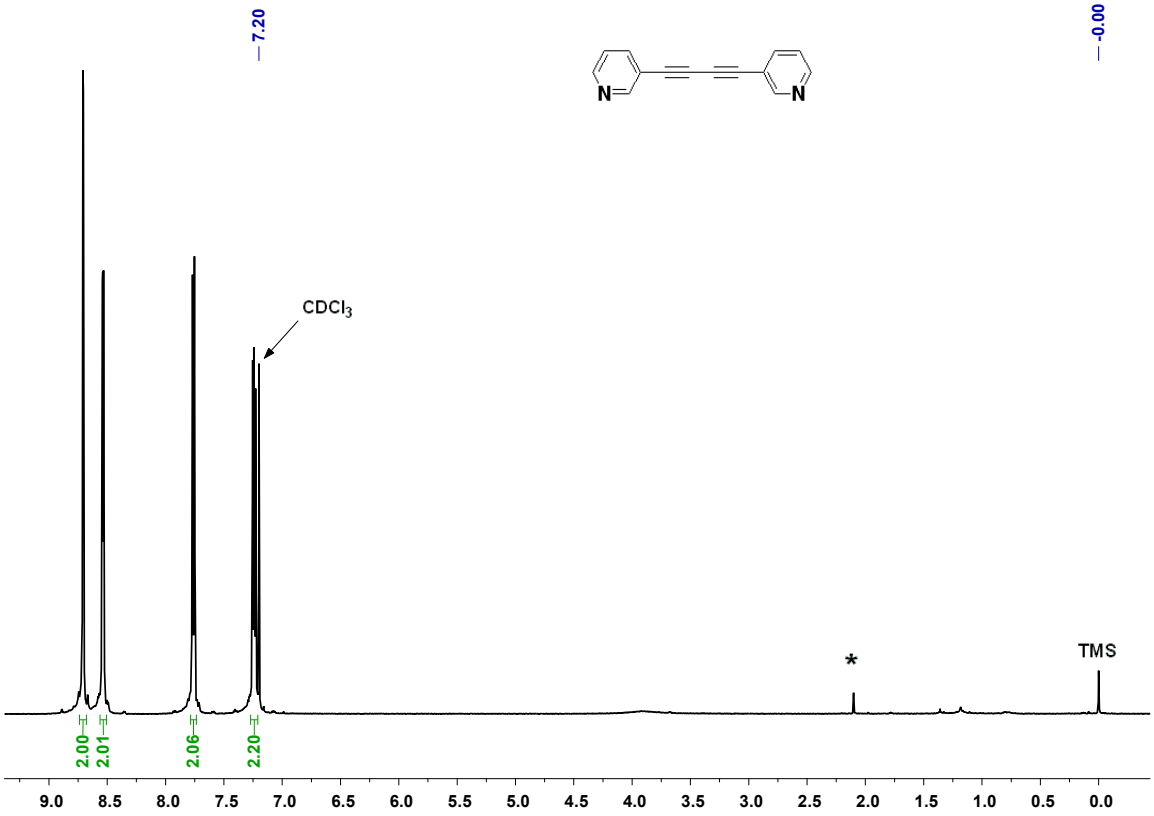

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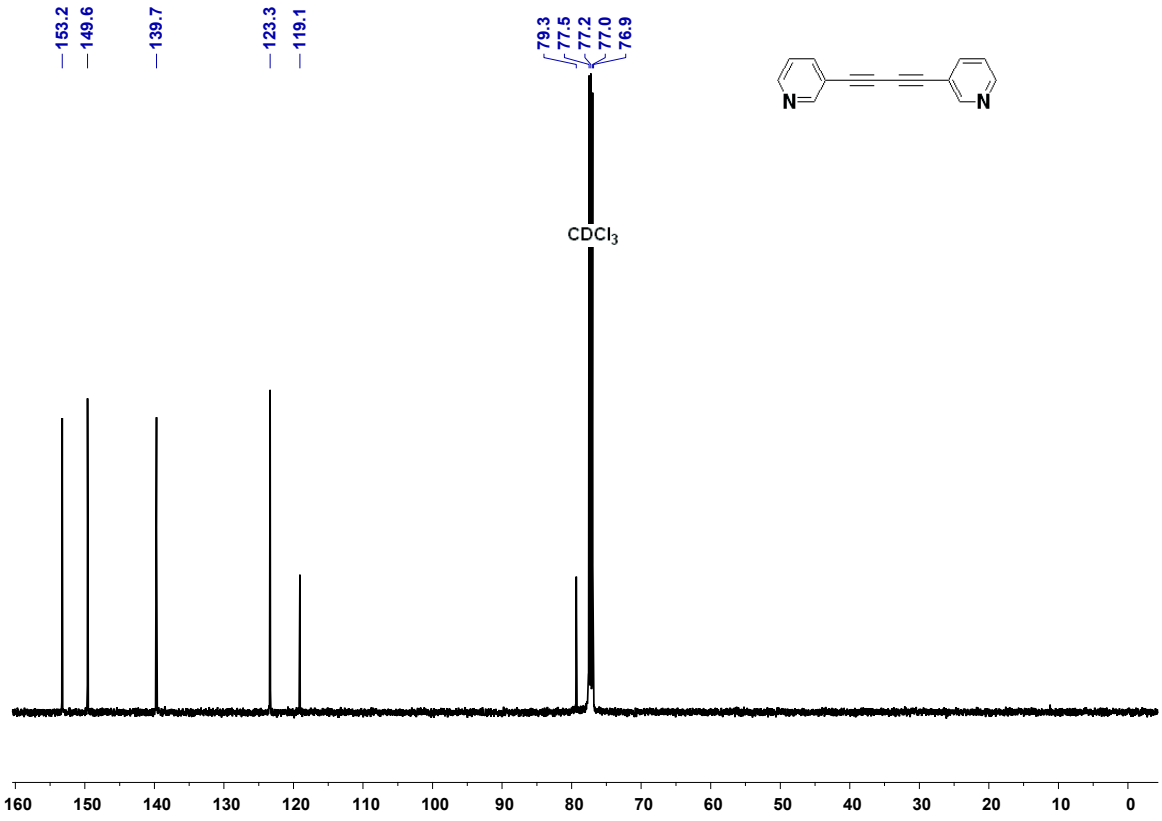

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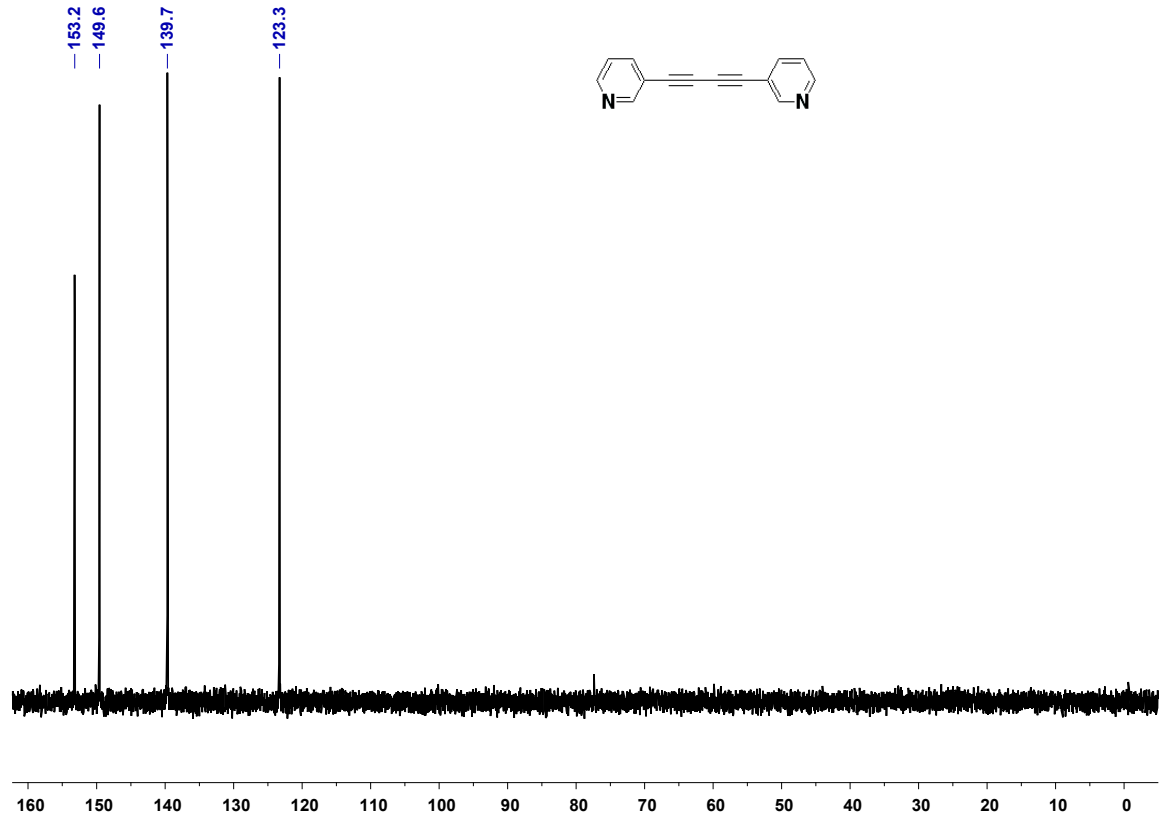

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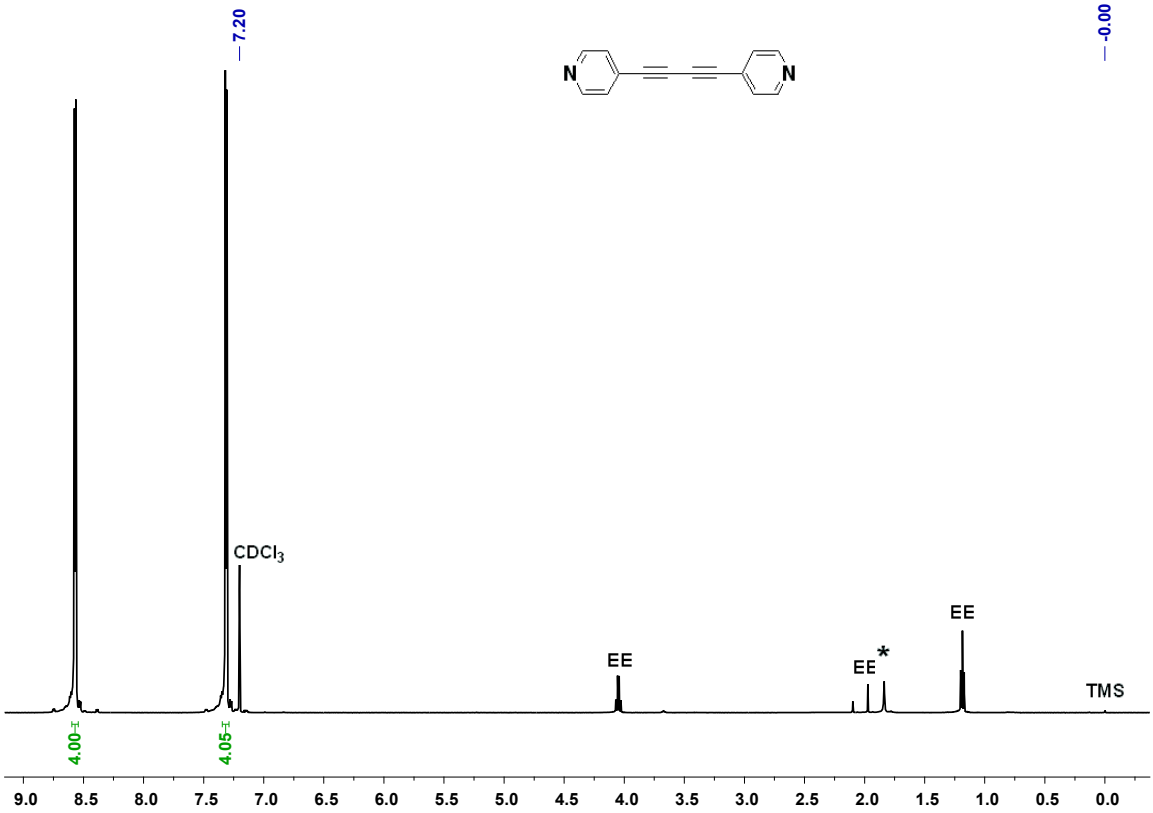

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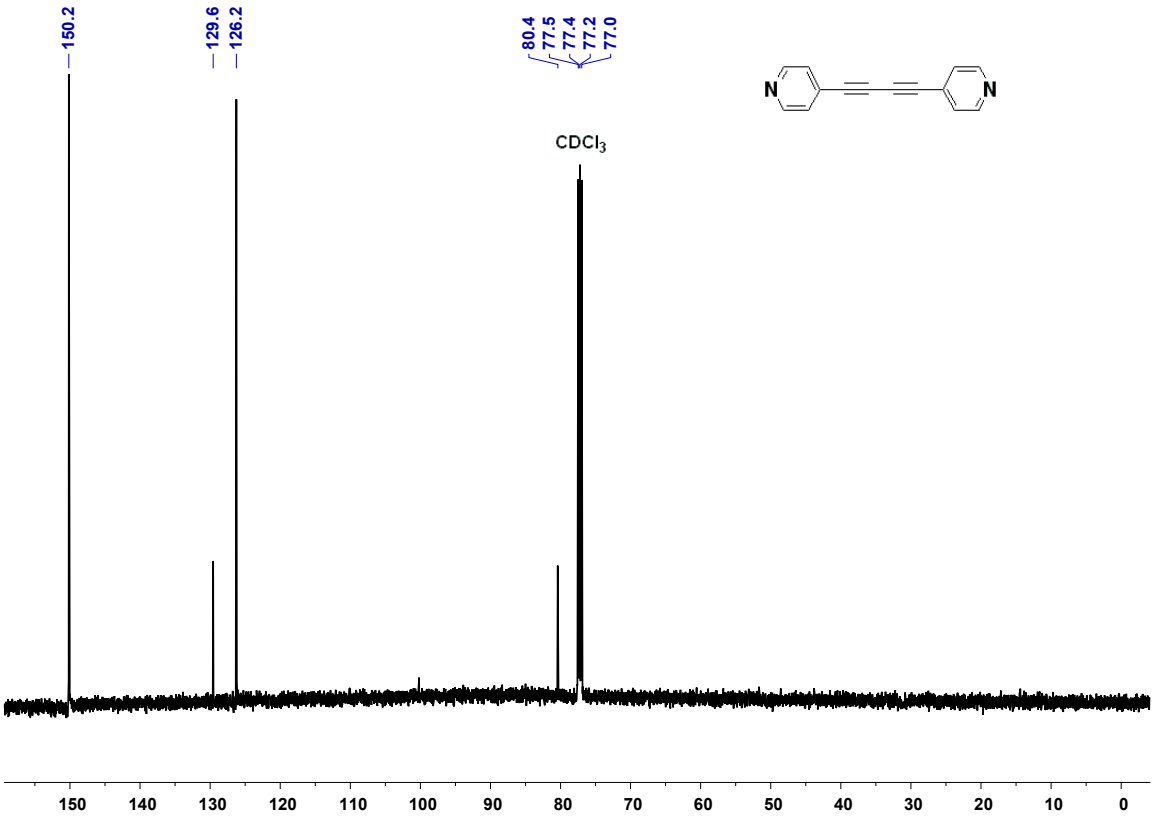
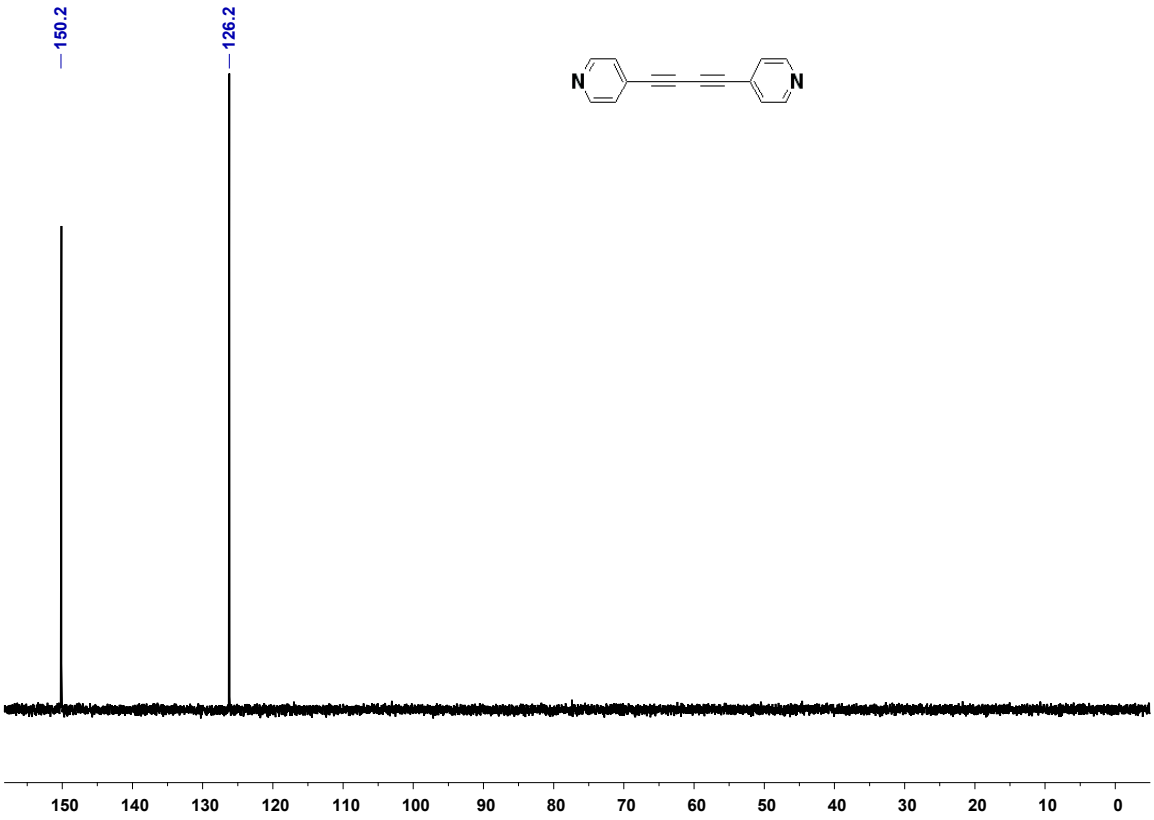


^{13}C NMR of **2r** in $CDCl_3$ at 298 K (δ in ppm).



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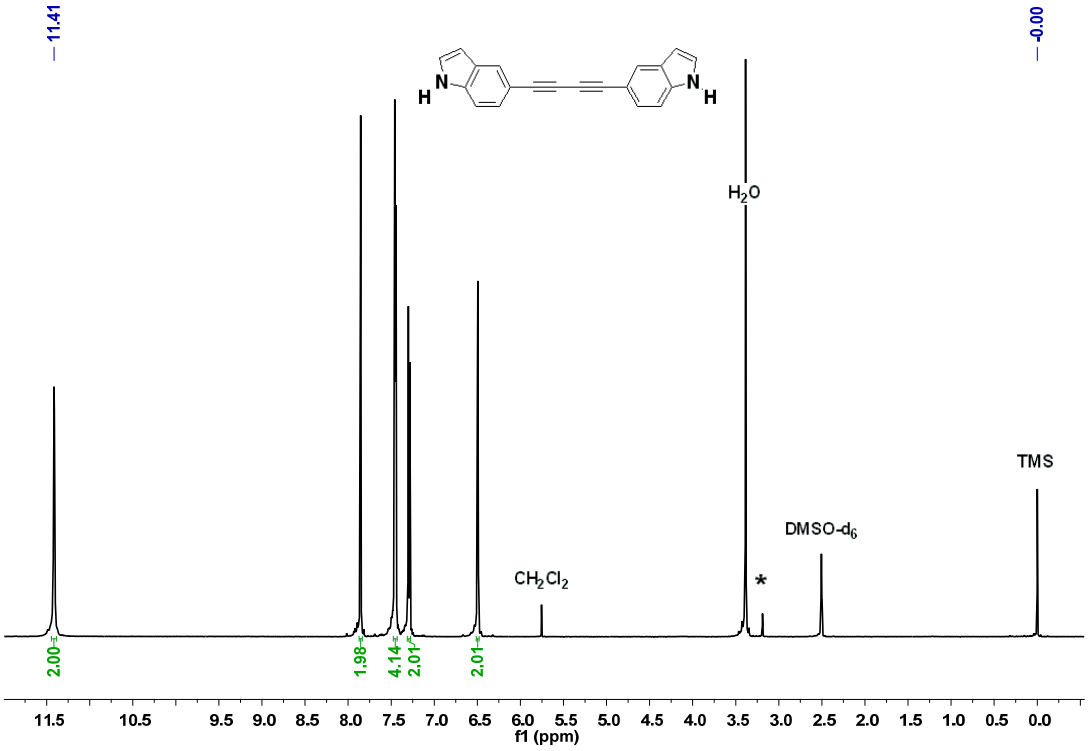
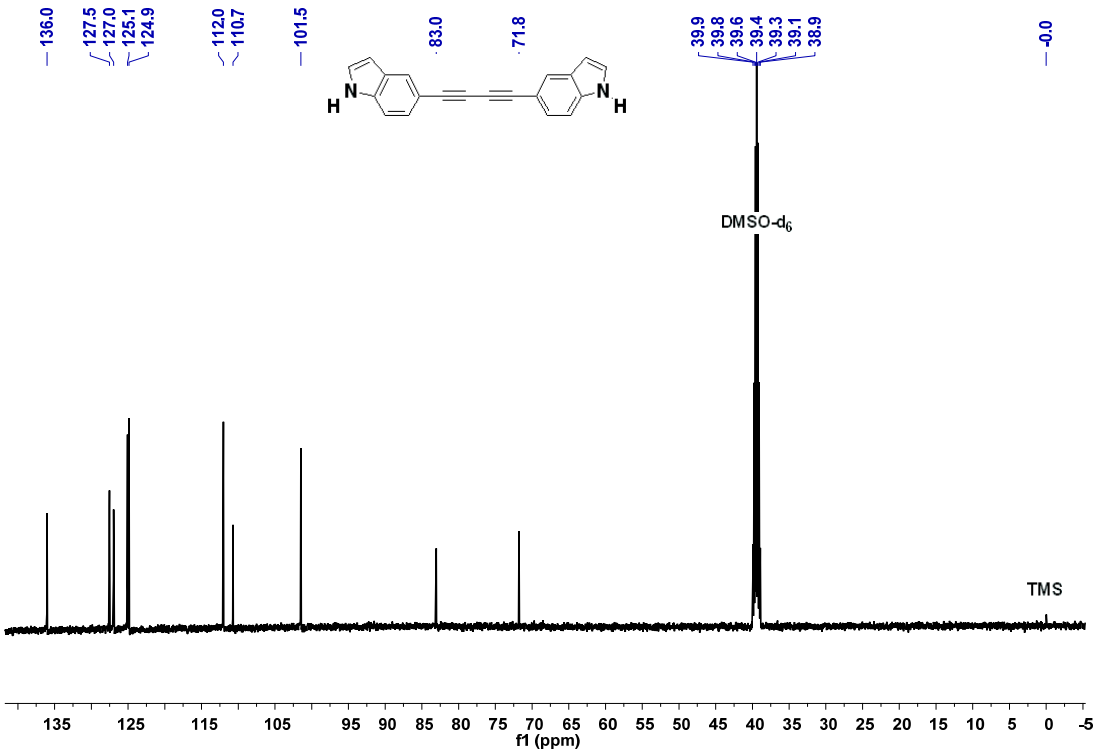


^{1}H NMR of **2t** in $CDCl_3$ at 299 K (δ in ppm). *Impurities from residual solvents.



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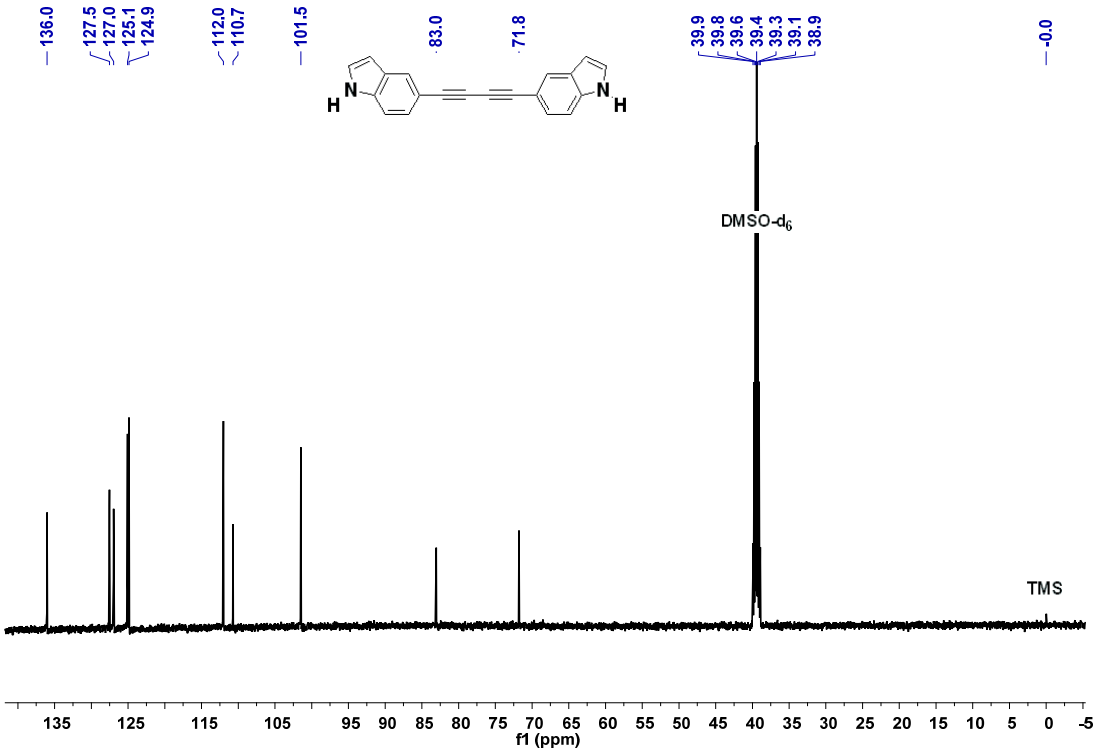

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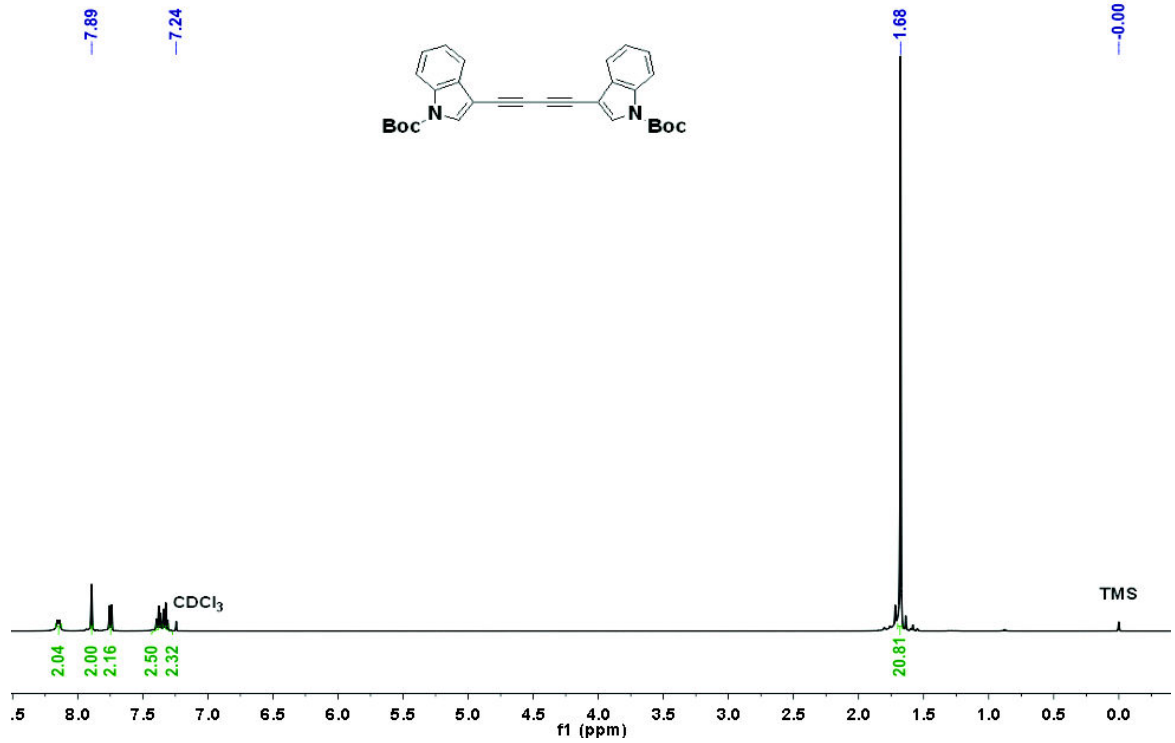
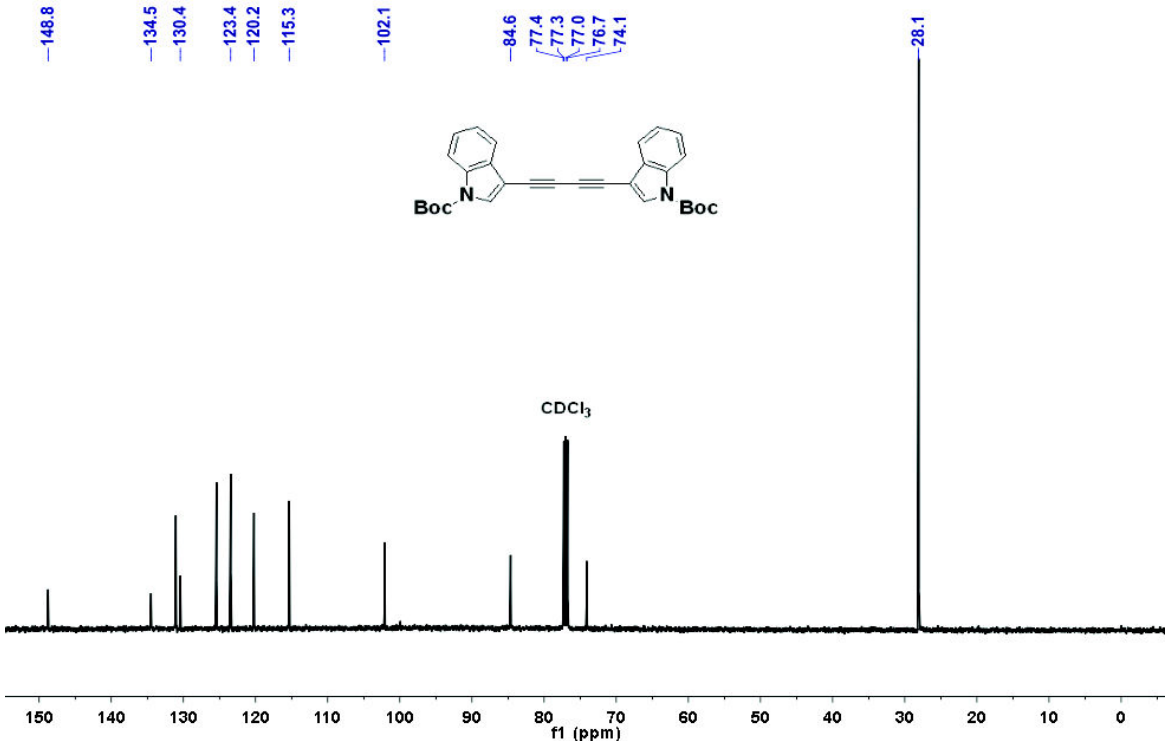
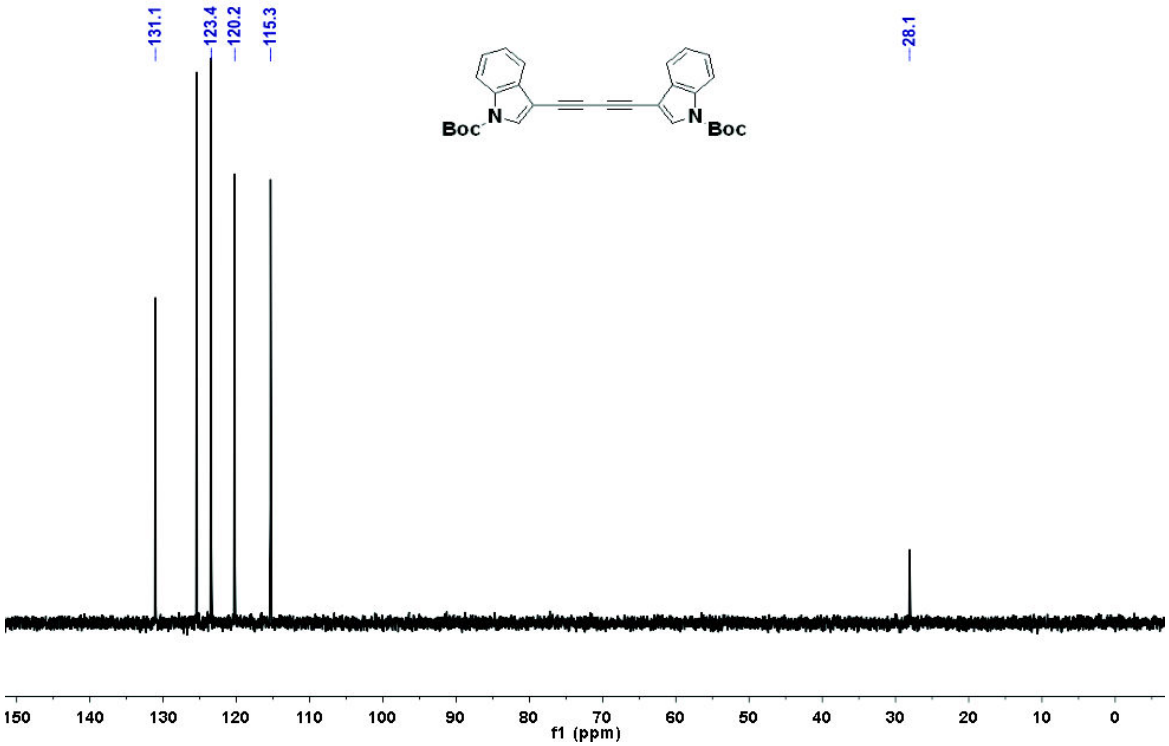


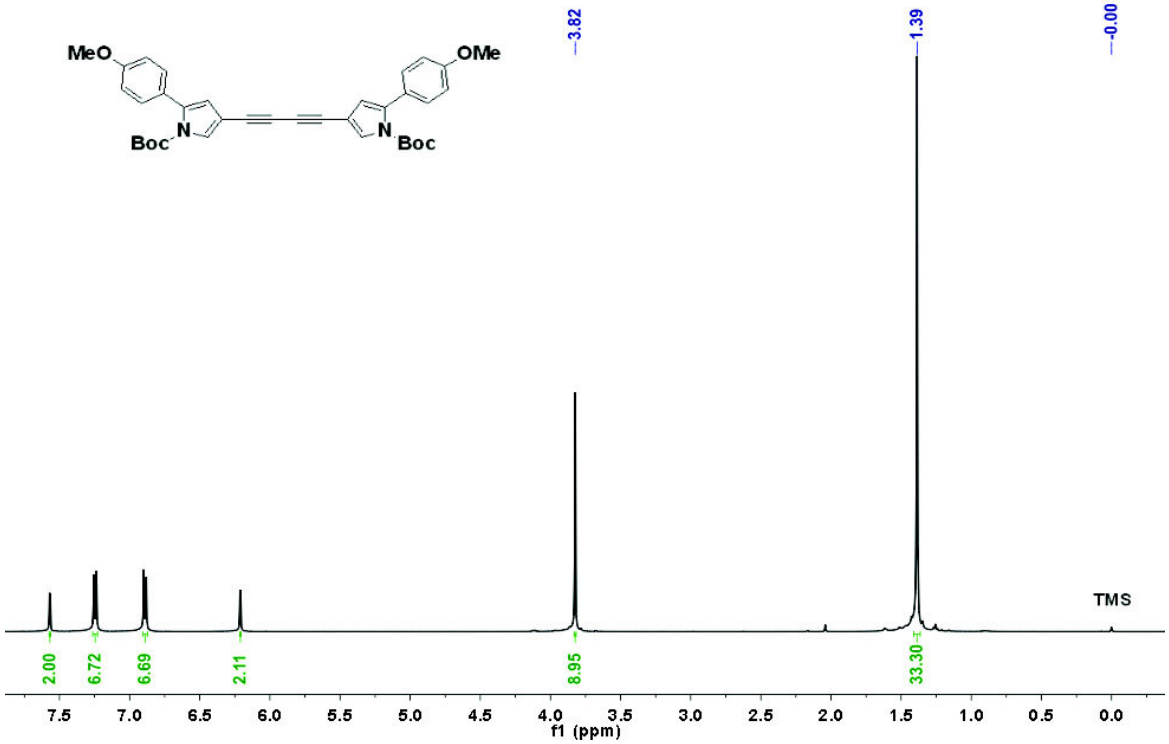
^{1}H NMR of **2u** in $CDCl_3$ at 296 K (δ in ppm).



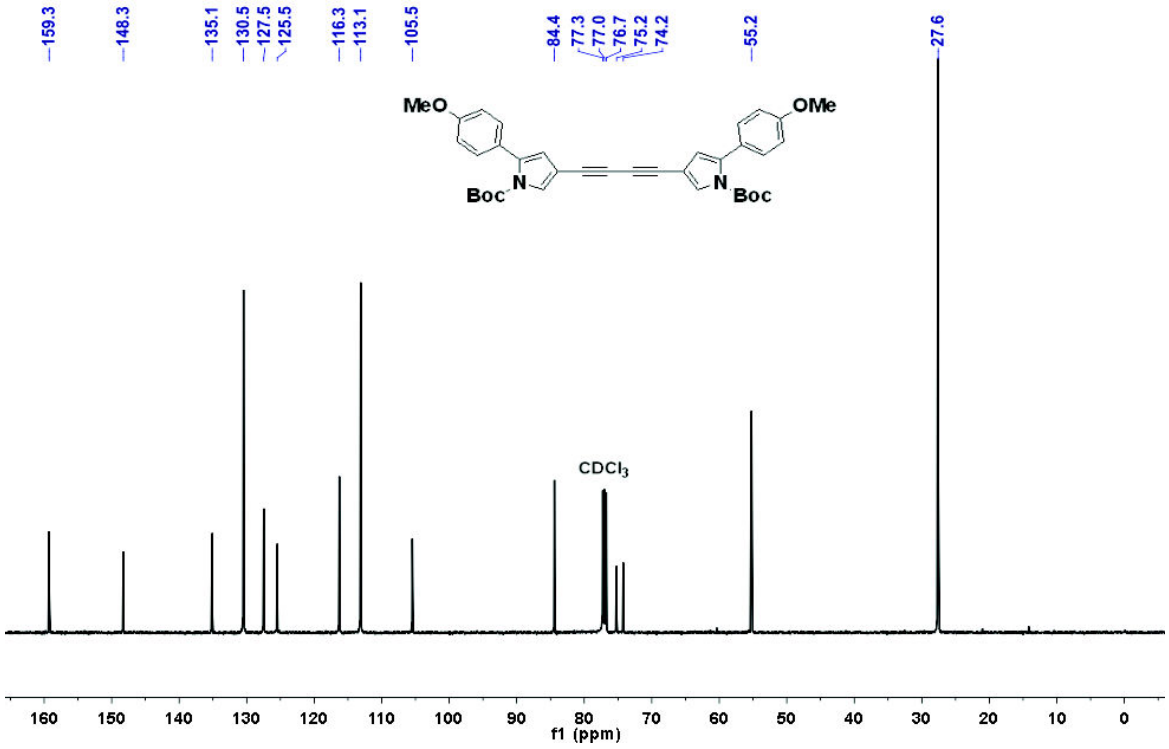
^{13}C NMR of **2u** in $CDCl_3$ at 296 K (δ in ppm).



^{13}C DEPT 135-NMR of **2u** in $CDCl_3$ at 296 K (δ in ppm).



^{1}H NMR of **2v** in $CDCl_3$ at 297 K (δ in ppm).



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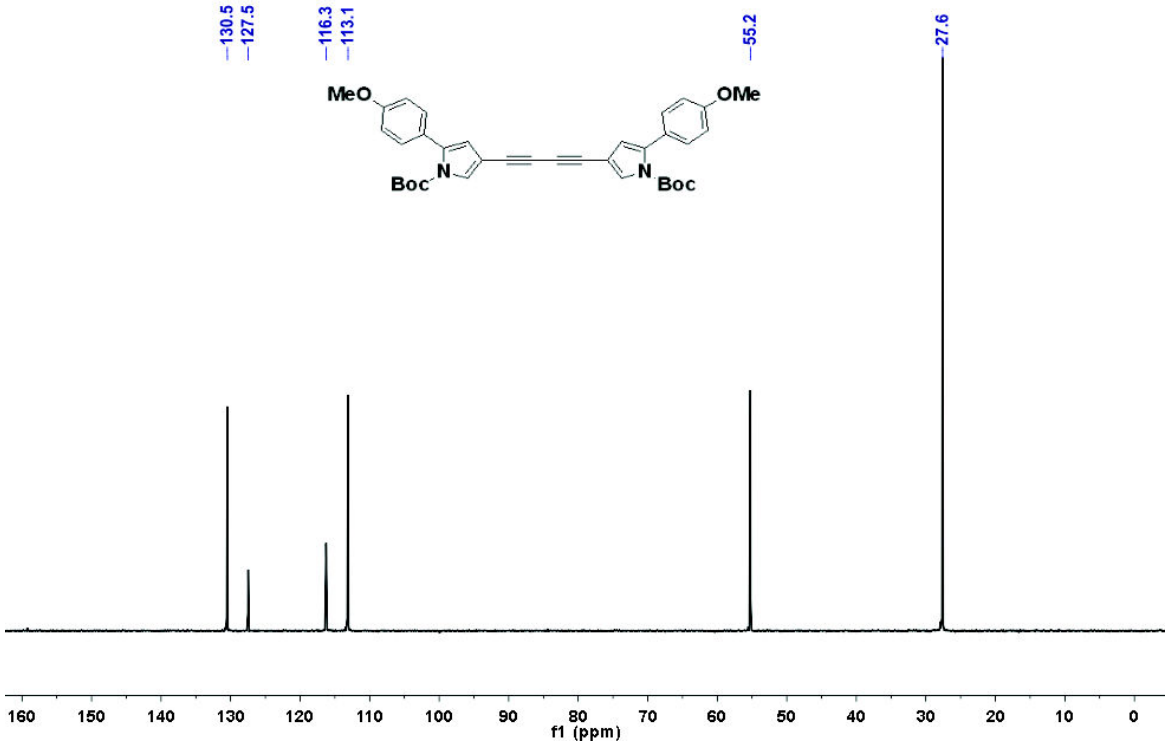

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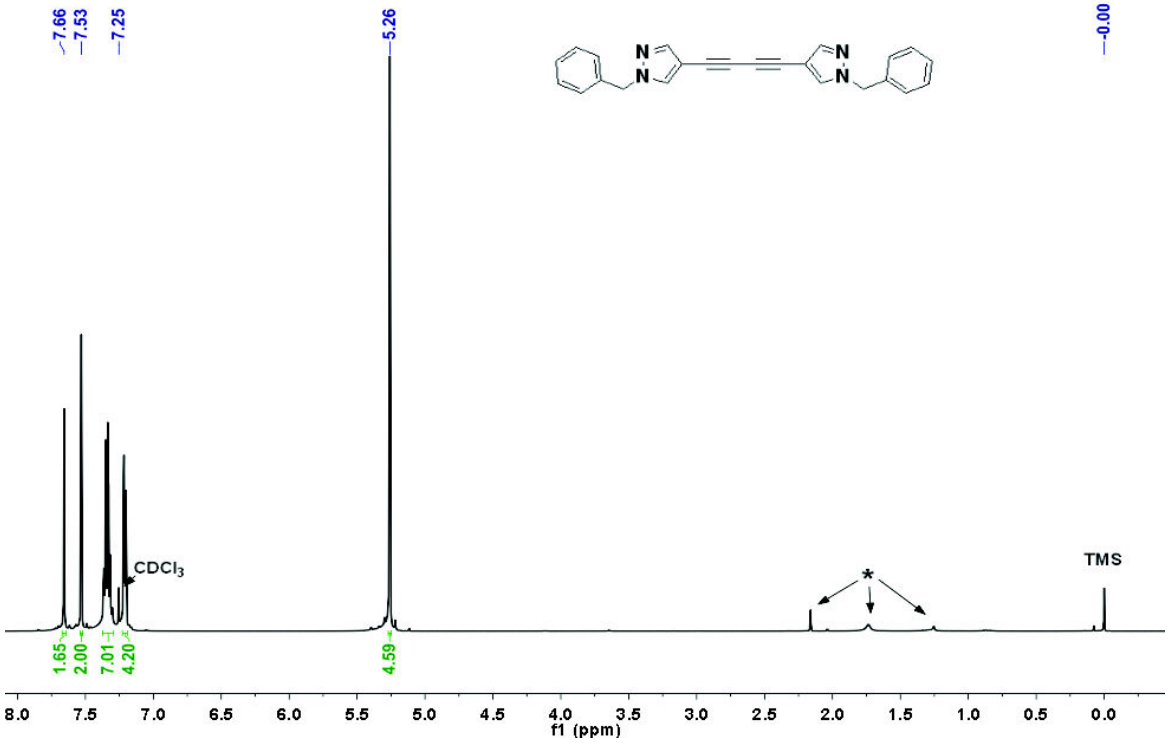
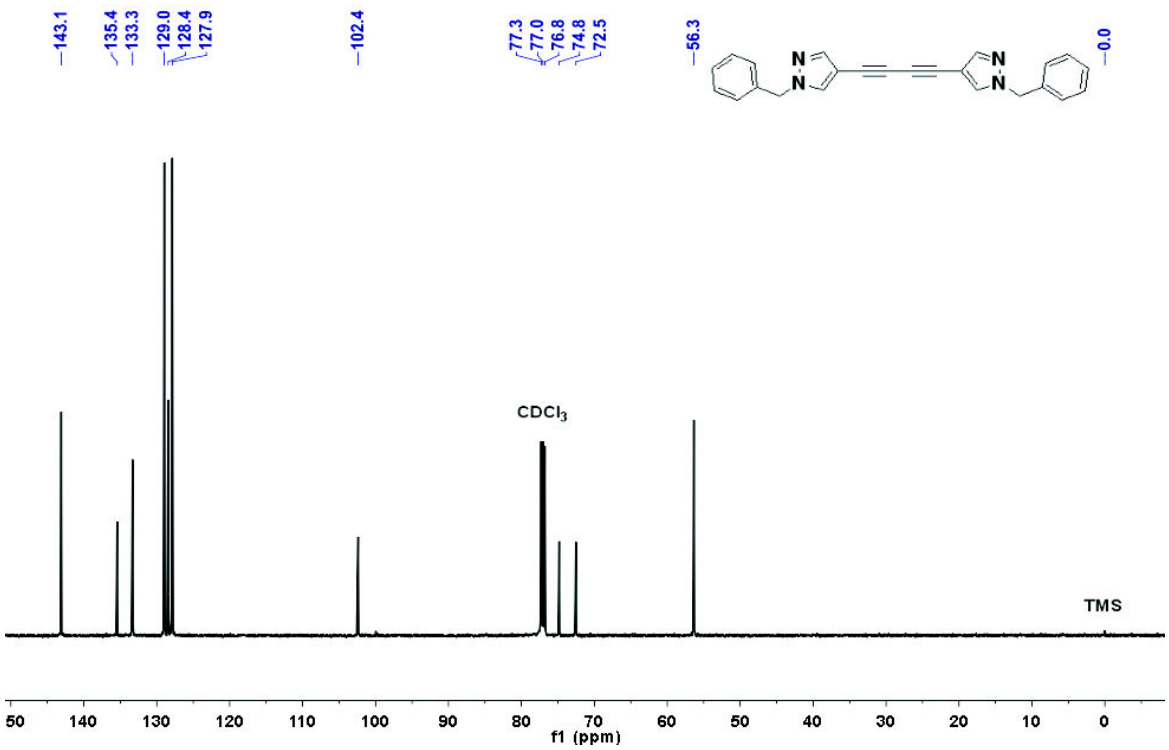


^{1}H NMR of **2w** in $CDCl_3$ at 297 K (δ in ppm). *Impurities from residual solvents.



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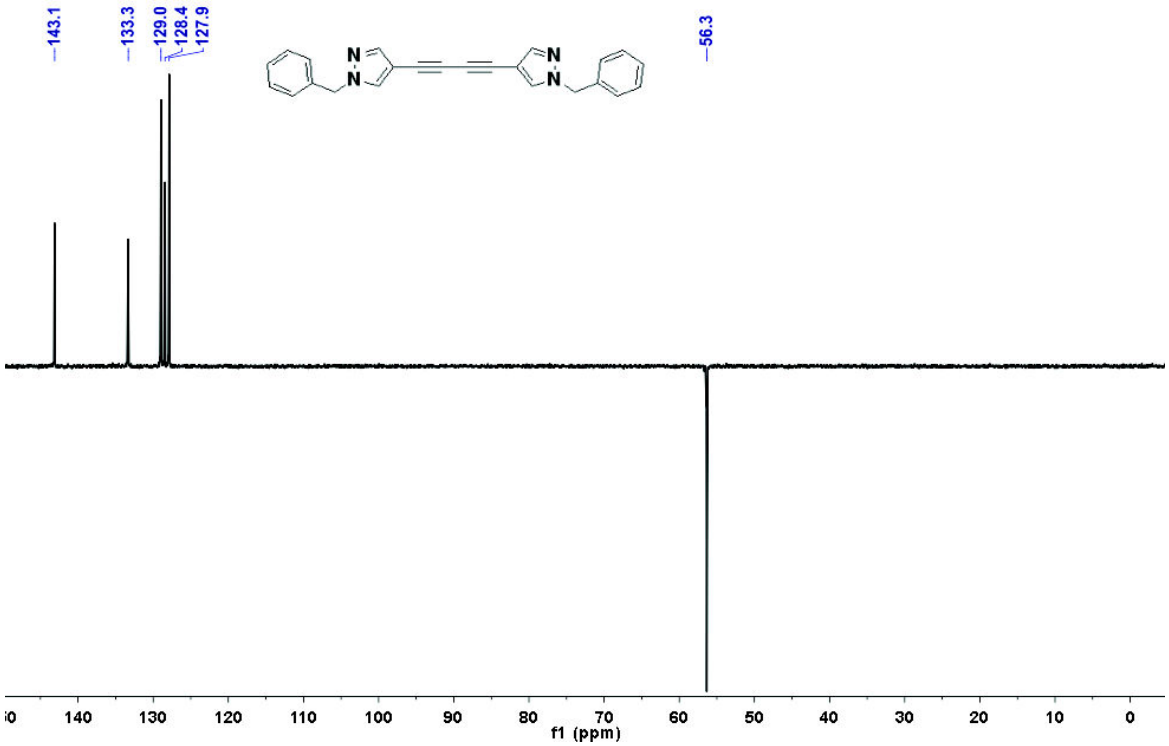

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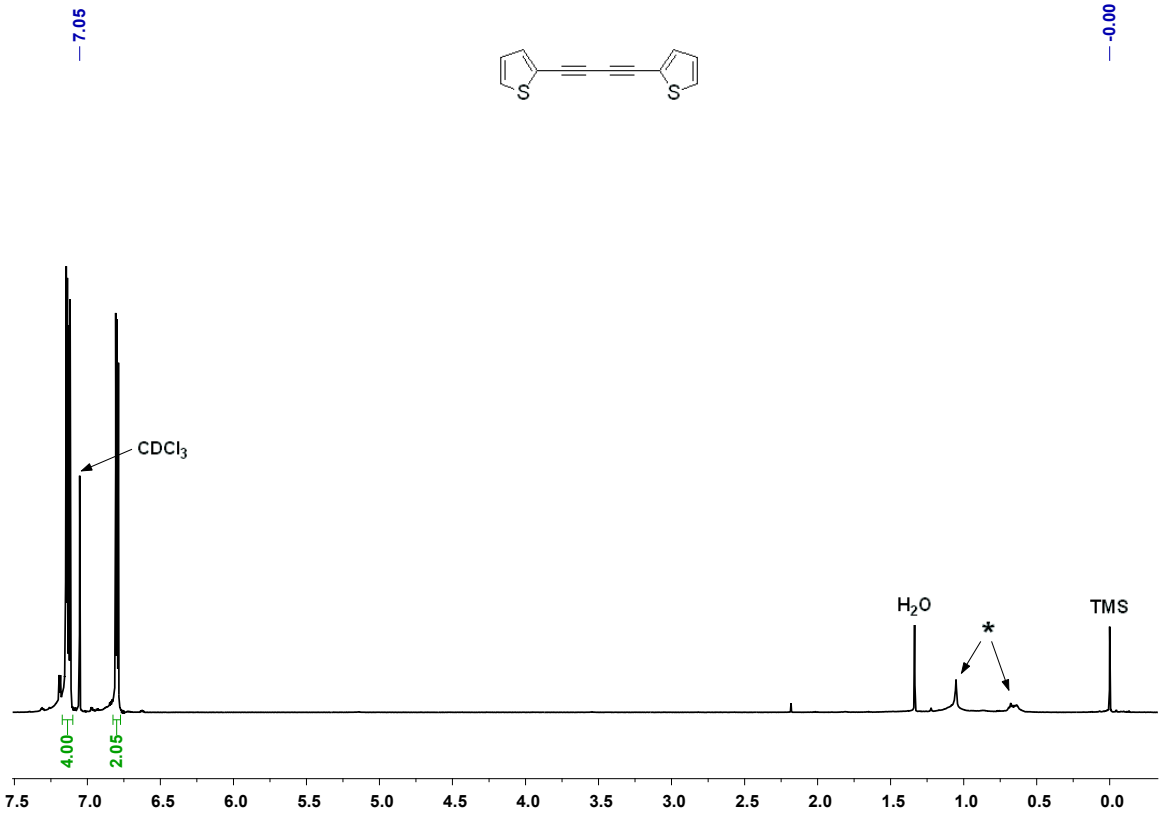
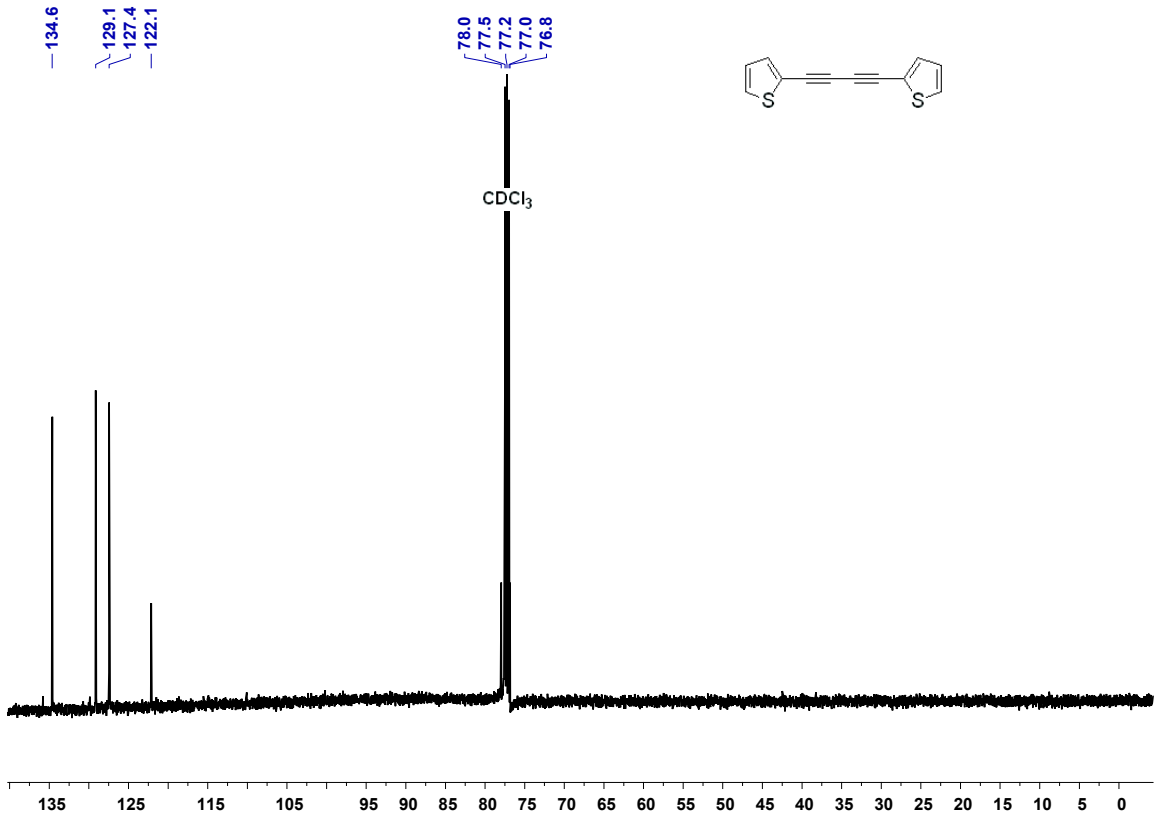
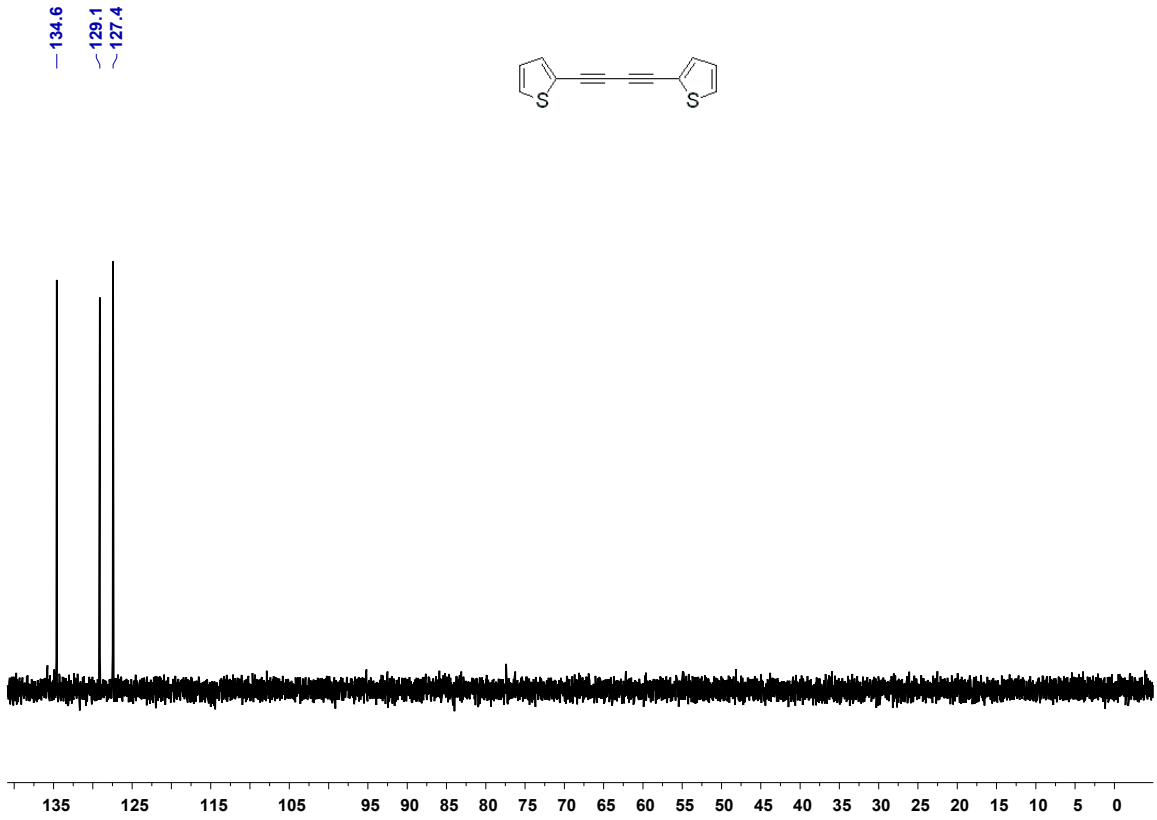


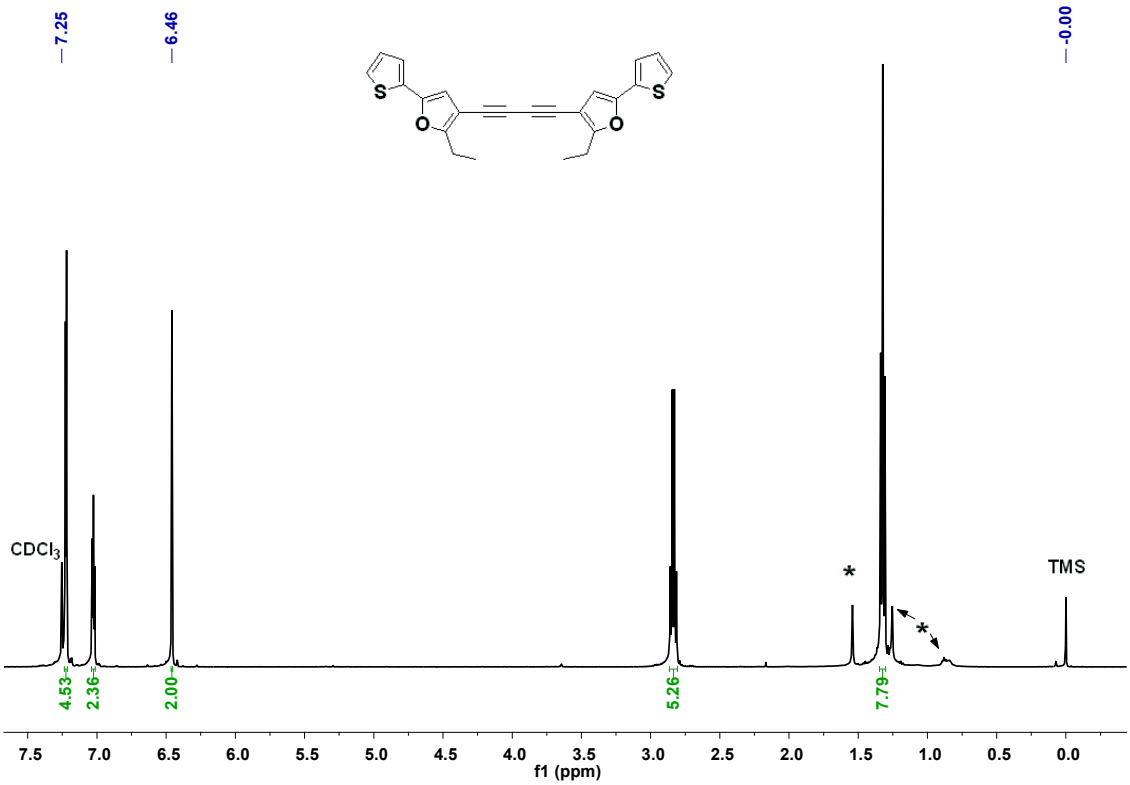
^{1}H NMR of **2y** in $CDCl_3$ at 298 K (δ in ppm). *Impurities from residual solvents.



^{13}C NMR of **2y** in $CDCl_3$ at 297 K (δ in ppm).



^{13}C DEPT 135-NMR of **2y** in $CDCl_3$ at 297 K (δ in ppm).



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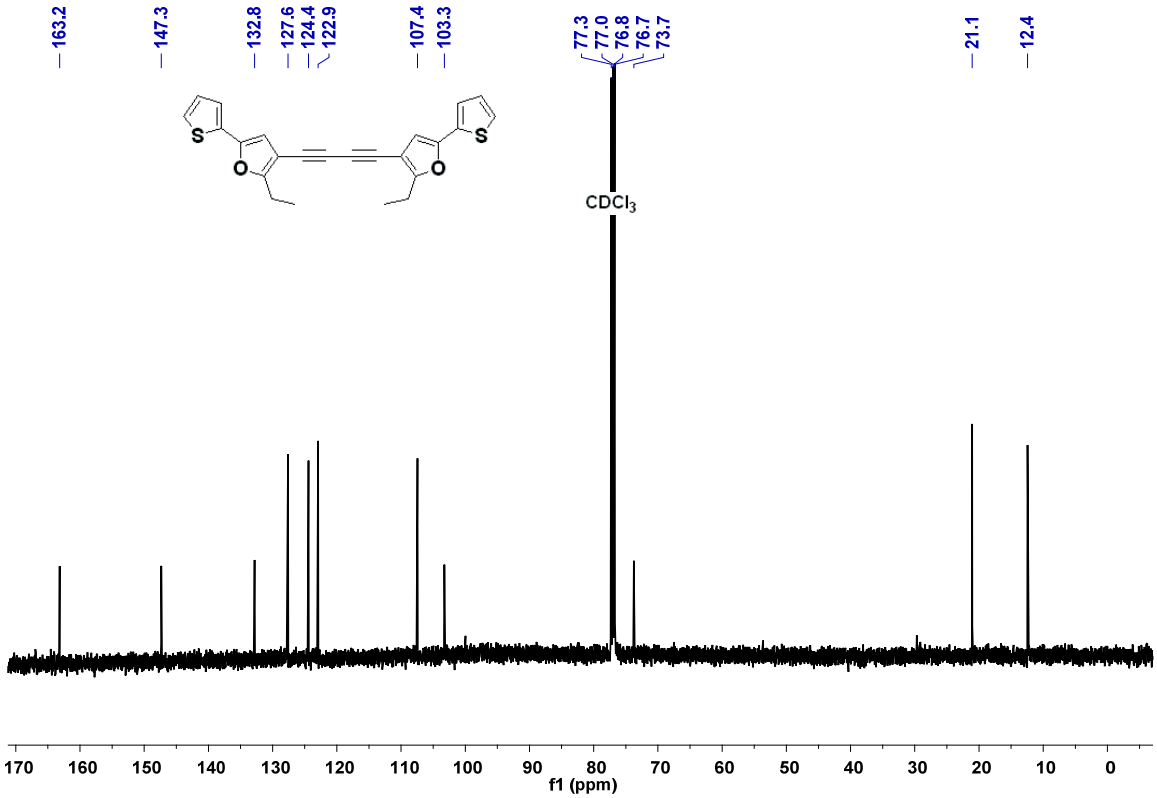
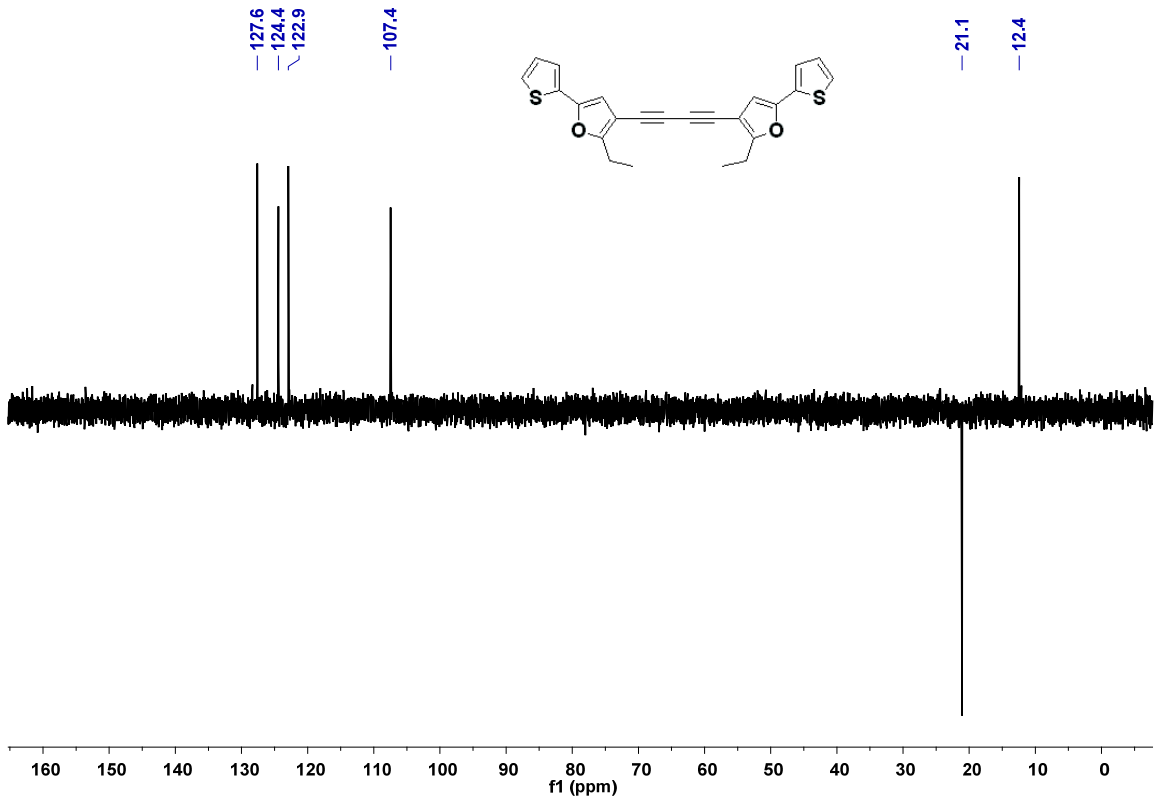


^{13}C NMR of **2z** in $CDCl_3$ at 299 K (δ in ppm).



^{13}C DEPT 135-NMR of **2z** in $CDCl_3$ at 299 K (δ in ppm).

5. References

[1] B. Witulski, N. Buschmann, U. Bergsträßer, *Tetrahedron* **2000**, *56*, 8473-8480.

[2] E. Merkul, C. Boersch, W. Frank, T. J. J. Müller, *Org. Lett.* **2009**, *11*, 2269-2272.

[3] W. Holzer, I. Pöcher, *J. Het. Chem.* **1995**, *32*, 189-194; C. J. Lovely, H. Du, R. Sivappa, M. R. Bhandari, Y. He, H. V. R. Dias, *J. Org. Chem.* **2007**, *72*, 3741-3749.

[4] A. S. Karpov, E. Merkul, T. Oeser, T. J. J. Müller, *Chem. Commun.* **2005**, 2581-2583; A. S. Karpov, E. Merkul, T. Oeser, T. J. J. Müller, *Eur. J. Org. Chem.* **2006**, 2991-3000.

“Rapid preparation of triazolyl substituted NH-heterocyclic kinase inhibitors via one-pot Sonogashira coupling–TMS-deprotection–CuAAC sequence”, Eugen Merkul, Fabian Klukas, Dieter Dorsch, Ulrich Grädler, Hartmut E. Greiner, Thomas J. J. Müller, *Org. Biomol. Chem.* **2011**, *9*, 5129-5136. DOI: 10.1039/C1OB05586K.

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PAPER

Rapid preparation of triazolyl substituted NH-heterocyclic kinase inhibitors *via* one-pot Sonogashira coupling–TMS-deprotection–CuAAC sequence†‡

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The one-pot, three-component Sonogashira coupling–TMS-deprotection–CuAAC ("click") sequence is the key reaction for the rapid synthesis of triazolyl substituted *N*-Boc protected NH-heterocycles, such as indole, indazole, 4-, 5-, 6-, and 7-azaindoles, 4,7-diazaindole, 7-deazapurines, pyrrole, pyrazole, and imidazole. Subsequently, the protective group was readily removed to give the corresponding triazolyl derivatives of these tremendously important NH-heterocycles. All compounds have been tested in a broad panel of kinase assays. Several compounds, **8f**, **8h**, **8k**, and **8l**, have been shown to inhibit the kinase PDK1, a target with high oncology relevance, and thus they are promising lead structures for the development of more active derivatives. The X-ray structure analysis of compound **8f** in complex with PDK1 has revealed the detailed binding mode of the molecule in the kinase.

Introduction

Indoles represent one of the most prominent privileged structures[1] because they are widespread in nature[2] and pharmaceutically relevant compounds.[3] Among them, indoles bearing 5- and 6-membered heterocycles as substituents in the 3-position represent a conspicuously frequently occurring substitution pattern. In particular, the heterocyclic ring found in natural products or their bioactive analogues can be pyrimidine (meridianins,[4] hyrtinadine A[5]), tetrahydropyrimidine (aplicyanins[6]), piperazine and (dihydro)pyrazine (dragmacidins,[7] hamacanthins[8]), oxazinone (oxazinins[9]), oxadiazinone (alboinon[10]), imidazole (nortopsentins,[11] topsentins[12]), imidazolone,[13,14] oxazole (diazonamides,[15] martefragin A,[16] almazoles,[17] pimprinine,[18] and labradorins[19]), thiazole (camalexins,[20] BE-10988[21]), imidazoline (spongotines,[22] discodermindoles,[23] trachycladindoles[24]), oxazoline,[25] maleimide (didemnimides[26]), isoquinolinequinone (mensouramycin D[27]), β-carboline (eudistomin U,[28] hyrtioerectine A[29]), pyrrole (chromopyrrolic acid,[30] lynamicins[31]), pyrrolinone (violacein[32]), or another indole.[33] Besides indoles, their aza analogues, *i.e.* indazole and azaindoles, apparently play an increasingly important role as scaffolds for biologically active molecules.[34] In particular, 7-azaindoles are predestined to be promising scaffolds for investigations as kinase inhibitors due to their pronounced ability to bind to the hinge region of kinases.[35] Again, heterocyclic substituents at the C-3 position are very common. The most prominent examples are the marine natural products variolins[36] and the simplified synthetic analogues of variolin B, *i.e.* the meriolins[37] (Fig. 1).

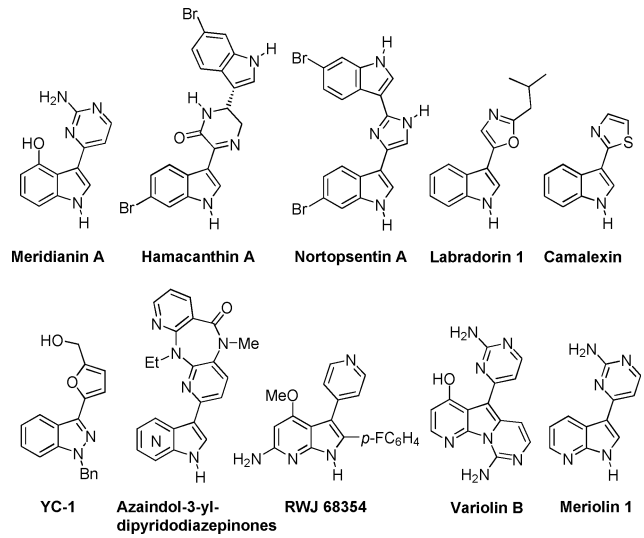

Fig. 1 Biologically active (aza)indoles with 5- and 6-membered heterocycles at C-3 (corresponds to C-5 in variolin B).

Recently, we reported a practical approach to indoles and 7-azaindoles substituted with azines *via* a one-pot Masuda borylation–Suzuki coupling sequence.[38] Using this approach,

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[b]*Merck Serono Research & Development, Merck KGaA, D-64271, Darmstadt, Germany*

† Dedicated to Prof. K. Barry Sharpless on the occasion of his 70th birthday.

‡ Electronic supplementary information (ESI) available: experimental procedures and analytical data of compounds **1a–l**, **1n**, **8a–s**, **9a–b**, **10**, and **11**. See DOI: 10.1039/c1ob05586k

concise total syntheses of meridianins A and G could be realized. Previously, we synthesized some members of the meridianin family and a 7-azaindole analogue of variolin B (later called meriolin 1),[37] using a carbonylative Sonogashira coupling as a key step.[39] In these compounds, as well as in variolin B, the key structural feature responsible for the observed biological activity is the 2-aminopyrimidine ring at C-3, even though meridianins, meriolins, and variolins bind differently to the hinge region of kinases.[37,40] Notably, isomeridianins,[41] possessing the 2-aminopyrimidine moiety at C-2, and variolin D, lacking a heterocycle substituent at C-5, are not biologically active.

Surprisingly, triazolyl substituted indoles have hardly been explored,[42] although the 1,2,3-triazole ring as an electron-poor metabolically stable[43] 5-membered heterocyclic substituent has attracted considerable attention in bioconjugate chemistry, medicinal chemistry, and drug discovery.[44] In addition to its function as a convenient linker,[45] 1,4-disubstituted 1,2,3-triazole is a peptidomimetic,[46] has a large dipole moment and is an H-acceptor over N-2 and N-3 atoms. Here, we report a diversity-oriented synthetic concept to access 3-triazolyl-substituted (aza)indole scaffolds in a one-pot fashion. In addition, the potential of the title compounds as kinase inhibitors[47,48] and cytostatics is explored.

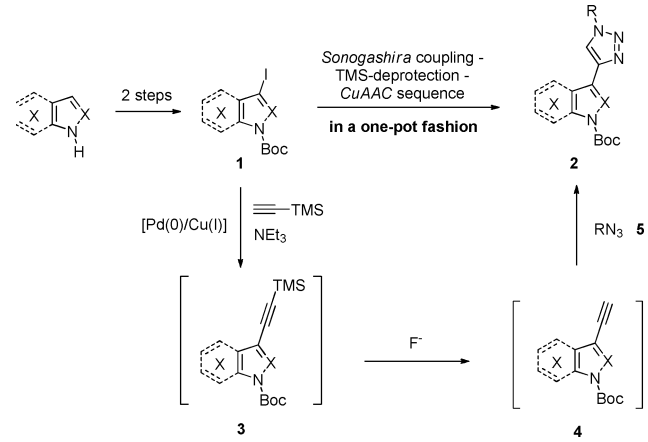
Results and discussion

The Sonogashira coupling–TMS-deprotection–CuAAC sequence

The Sonogashira–Hagihara cross-coupling[49] is among the most reliable C–C bond forming reactions and has become the method of choice for the construction of internal alkynes from (hetero)aryl halides and terminal alkynes.[50] Upon coupling halides with trimethylsilylacetylene (TMSA), TMS-protected alkynes are formed, which can be easily deprotected to give (hetero)aromatic terminal alkynes.[51] The latter are perfectly suited for the copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC),[52,53] the most remarkable Cu(I)-catalyzed process developed in the last decade. The transformation belongs to click-type reactions,[54] which proceed with a high degree of atom economy.[55] This process is also very reliable, mild, general, and highly tolerant to diverse functional groups. All these features render this reaction highly practical.[56] In the past, many efforts have been made to develop one-pot methodologies based upon the *in situ* generation of the azide component,[57] the *in situ* utilization of TMS-acetylenes,[58] or the direct sequential Cu(I)-catalyzed C–H-bond arylation of the obtained triazoles.[59] Surprisingly, only little attention has been paid to the *in situ* construction of terminal alkynes.[60]

As a continuation of our program directed to develop new one-pot multi-component reactions initiated by metal-catalyzed cross-coupling as an entry for the synthesis of heterocycles[61,62] we envisioned the possibility of performing Sonogashira coupling and CuAAC in a one-pot fashion. Coupling of *N*-Boc protected 3-iodo NH-heterocycles **1** with TMSA would furnish the intermediate TMS-protected heterocyclic alkynes **3**, which after *in situ* deprotection would give terminal alkynes **4**, the starting material to accomplish CuAAC with an azide **5**, resulting in another Cu(I)-catalyzed reaction. It was hoped the strategy would give direct access to triazoles **2** in the sense of sequential catalysis (Scheme 1).

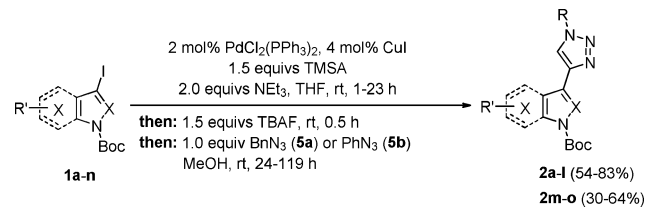
Boc (*tert*-butoxycarbonyl) is one of the cheapest and most frequently used nitrogen protective groups.[63] Either it can be



Scheme 1 Synthetic concept for triazolyl *N*-Boc protected heterocycles (X = CH or N; R = alkyl or aryl, may be generated *in situ*).

easily introduced on the nitrogen atoms of 5-membered NH-heterocycles[64] or it can be installed directly in the course of their synthesis.[65,66] If not further required, this group can be removed easily and cleanly under various conditions.[67] Previously, we have demonstrated the enormous utility and versatility of 3-iodo *N*-Boc protected indoles, 7-azaindoles, and pyrroles as easily accessible synthetic building blocks.[38,39,66]

The Sonogashira coupling of iodo *N*-Boc NH-heterocycles[68] **1** with TMSA proceeded smoothly under standard Sonogashira conditions ($PdCl_2(PPh_3)_2$/CuI/NEt_3).[69] The obtained TMS-alkynes were not isolated but directly deprotected with TBAF and subsequently reacted with one equivalent of the commercially available and stable benzyl azide (**5a**) to furnish *N*-Boc 3-triazolyl (aza)indoles **2a–l** and azoles **2m–o** in a one-pot fashion (Scheme 2). The yields were very similar for (aza)indoles and pyrrole regardless of the number and position of nitrogen atoms.

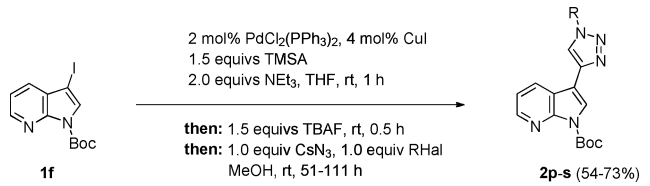


Scheme 2 Sonogashira coupling–TMS-deprotection–CuAAC sequence for the synthesis of *N*-Boc 3-triazolyl (aza)indoles **2a–l** and azoles **2m–o** (X = CH or N; R = Bn, Ph; R′ = Me, OMe, $O(CH_2)_2OMe$, *p*-$MeOC_6H_4$).

No further addition of CuI was required in the CuAAC step. The reaction progress can be conveniently monitored by TLC and the steps cleanly proceed as "spot-to-spot" reactions without noticeable amounts of byproducts. No Glaser-type homodimerization products[70] were detected because the CuAAC reaction was performed under an argon atmosphere. It is worth mentioning that the electron-withdrawing Boc protective group renders the (aza)indolyl iodides **1** stable to storage,[71] whereas the unprotected iodides are frequently sensitive to light and temperature and therefore inconvenient to handle.[72] Moreover, the Sonogashira coupling is greatly facilitated, or even becomes feasible, due to the diminished electron density of these heterocycles.

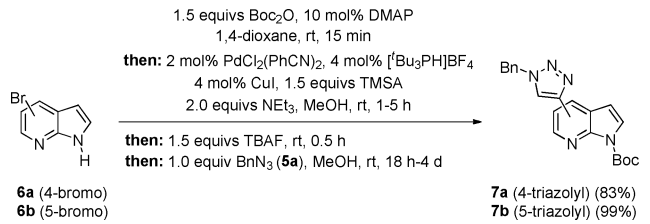
For the synthesis of triazoles with different substituents on the N-1 atom of the triazole moiety, the sequence was extended

to a four-component reaction with *N*-Boc protected 3-iodo 7-azaindole (**1f**) as a substrate. This sequence additionally includes the *in situ* generation of the azide **5** *via* nucleophilic substitution of a halide with caesium azide (Scheme 3). Hence, not only electronically diverse benzyl substituents (**2p** and **2q**), and even α-phenylethyl substituents (**2s**), but also the homobenzyl group can be introduced with a comparable yield (**2r**).



Scheme 3 Four-component Sonogashira coupling–TMS-deprotection–Finkelstein-type reaction–CuAAC sequence for the synthesis of *N*-Boc protected triazolyl 7-azaindoles **2p–s** (R = alkyl; Hal = Br, Cl).

For 4- and 5-bromo 7-azaindoles (**6a** and **6b**), which are commercially available and stable compounds, a four-component Boc-protection–Sonogashira coupling–TMS-deprotection–CuAAC sequence was developed to give *N*-Boc protected 4- and 5-triazolyl azaindoles (**7a** and **7b**) in very good yields (Scheme 4). The Sonogashira coupling was performed at room temperature using Fu's catalytic system.[73]

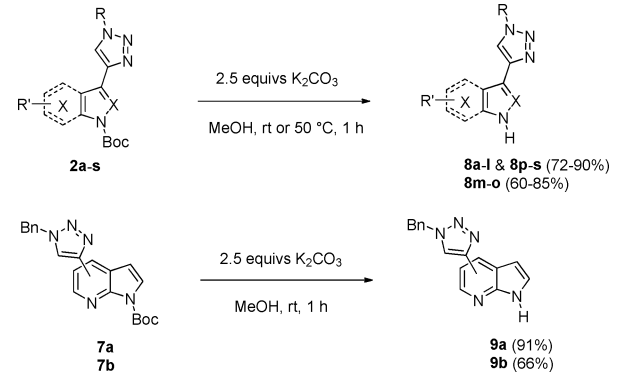


Scheme 4 Boc-protection–Sonogashira coupling–TMS-deprotection–CuAAC sequence for the synthesis of *N*-Boc 4- and 5-triazolyl 7-azaindoles **7a** and **7b**.

The possibility to easily adopt the whole synthesis to a specific substrate and a flexible incorporation of additional steps into the sequence is an additional advantage of this one-pot methodology.

The obtained *N*-Boc protected triazolyl NH-heterocycles **2** and **7** were readily deprotected under extremely mild conditions using potassium carbonate in methanol at room temperature or slightly above (Scheme 5). It should be mentioned that although the Boc protective group could be removed after the completed sequence in a one-pot fashion, we preferred to perform the Boc-deprotection in a separate step to ensure the high purity of the final products **8** and **9** (as determined by HT-LC-MS analysis, the UV purity was 99.9–100% for all presented compounds). The content of Pd and Cu in compound **8f** was determined to be $< 1\ \mu g\ g^{-1}$ (< 3 ppm) and $< 2\ \mu g\ g^{-1}$ (< 9 ppm), respectively. Thus, no additional removal of these heavy metals is required.[74]

The scope of the presented methodology includes indole (**8a**) and its bioisosters[75] such as indazole (**8b**), all azaindoles (**8c–i**, **8p–s**, and **9**), diazaindole (**8j**), deazapurines (**8k–l**), as well as pyrrole (**8m**), pyrazole (**8n**), and imidazole (**8o**) (Fig. 2).



Scheme 5 Deprotection of *N*-Boc 3-triazolyl heterocycles **2** and **7** to 3-triazolyl NH-heterocycles **8** and **9** (X = CH or N; R = Me, OMe, $O(CH_2)_2OMe$, *p*-$MeOC_6H_4$; R′ = Ph, homobenzyl, Bn, or benzyl derivatives).

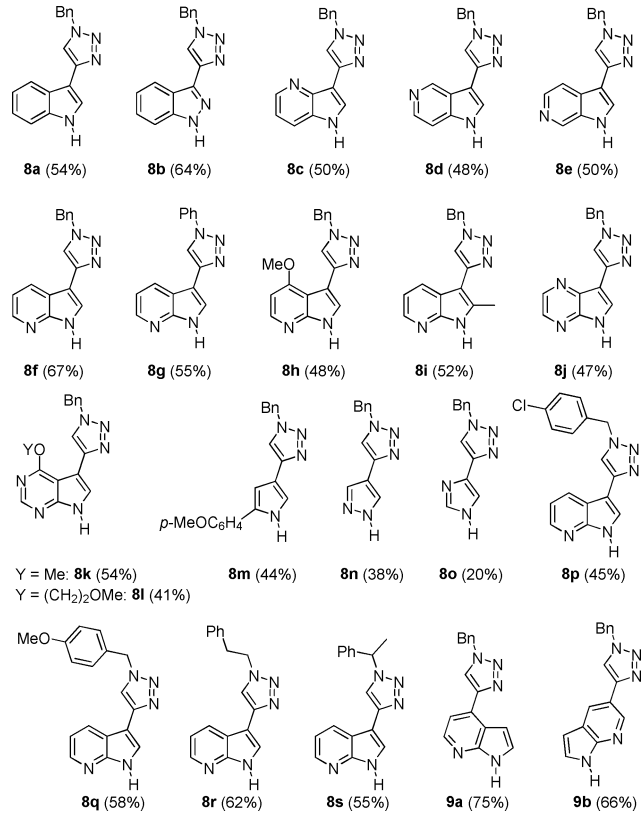


Fig. 2 Scope of the synthetic strategy towards triazolyl NH-heterocycles **8** and **9** (isolated yields over two steps).

The yields are fair to good and are very similar for all indole analogues **8a–l**. They are little affected by the position and number of additional nitrogen atoms, which is not self-evident (according to personal observations experienced with other coupling reactions of these substrates) and emphasizes the synthetic power gained from the combination of two very general methods, Sonogashira coupling and CuAAC. Only the azoles **8n** and **8o** gave poor yields due to the increased lability of the Boc protective group in the corresponding starting materials. Moreover, with *tert*-butyl 4-iodo-1*H*-imidazole-1-carboxylate (**1n**) the Sonogashira coupling proceeded very sluggishly and required

15 d reaction time. The structures of the obtained triazoles **8** and **9** were unambiguously supported by NMR spectroscopy, mass spectrometry, and combustion analysis, and later by an X-ray structure analysis of compound **8f**, cocrystallized with kinase PDK1 (*vide infra*).

The sequences are very straightforward and preparatively extremely simple to perform. Generally, all steps proceed at room temperature, which is especially important if less stable azides are to be used. However, they can even be generated *in situ* with comparable efficiency. It should be noted that while these studies were in progress two reports appeared in the literature which described the same synthetic approach with simple aryl iodides.[76] However, we used this strategy to synthesize triazolyl NH-heterocycles, which are more sophisticated chemical targets and show promising biological activity, thus illustrating the synthetic utility of this practical synthesis. Since a variety of diverse NH-heterocycles, which are of paramount importance in many areas of research, can be decorated with triazoles in a very straightforward fashion, the sequence is quite general. Starting from these small lead structures, more potent derivatives can be readily developed using this synthetic approach.

Biological data

All compounds **8** and **9** were tested for inhibition of a broad panel of kinases at the Division of Signal Transduction Therapy (DSTT) at the University of Dundee, UK. The compounds were screened against 95–121 kinases at a concentration of 1 μM. In addition, for all compounds, IC_{50} values for the inhibition of the kinase PDK1, a target of high relevance for oncology,[77] were determined. The results for compounds that showed submicromolar activity on at least one kinase are summarized in Table 1.

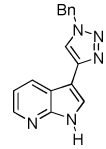
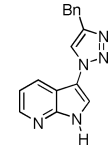
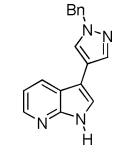
For the compounds described here, a hydrogen donor/acceptor pattern of the 7-azaindole core that can interact with the hinge region of kinases, is a prerequisite for kinase inhibitory activity. All compounds in this table possess such a pattern whereas the great majority of the inactive compounds **8a**, **8c**, **8d**, **8e**, **8m**, **8n**, and **8o**, lack this peculiar structural feature. In particular, compounds with a benzyltriazole group in the 3-position of a 7-azaindole-like template turned out to be broad kinase inhibitors with **8h**, **8k**, and **8l** having the broadest activity. In contrast, compounds **9a** and **9b**, which possess a benzyltriazole substituent at C-4 and C-5 of the 7-azaindole, are much less active, thus emphasizing the importance of C-3 substitution. Furthermore, substitution at C-2 or a nitrogen atom in the *para*-position to N-7 of the 7-azaindole seem to reduce the biological activity of compounds **8i** and **8j**.

Table 1 Biological data of selected compounds **8** and **9**

	Number of kinases with >50% inhibition @ 1 μM/number of kinases tested	IC_{50}[PDK1] (μM)
8b	4/121	>10
8f	22/121	0.8
8g	10/120	5.2
8h	48/95	0.1
8i	2/120	2.3
8j	11/95	4.9
8k	54/120	0.2
8l	60/102	0.3
8p	15/95	1.8
8q	3/121	>10
8r	17/121	>10
8s	11/120	1.1
9a	12/110	7.9
9b	4/110	>10

IC_{50}: concentration inhibiting kinase activity or reducing cell proliferation by 50%.

Table 2 Comparison of IC_{50} values of PDK1 inhibition between isomeric 3-triazolyl 7-azaindole compounds **8f** and **10**, as well as 3-pyrazolyl 7-azaindole **11**

PDK1 inhibition/IC_{50} (μM)		
		
8f	**10**	**11**
0.8	>10	2.6

For determining whether the triazole unit is merely a linker or possesses an additional function, an analogue of compound **8f** was prepared *via* the recently reported Masuda borylation–Suzuki coupling sequence.[38] This compound bears a pyrazole moiety instead of a triazole. Interestingly, the triazole unit seems to be important for the biological activity, since the pyrazole compound **11** was significantly less active with an IC_{50} value of 2.6 μM for PDK1 compared with 0.8 μM for the triazole **8f**. Therefore, triazole does not simply seem to be a linker, as in many applications of this heterocycle, but rather displays a pharmacophore character. However, even more exciting was the observation that the isomeric compound **10**,[78] differing from **8f** only in the permutation of substituents on N-1 and C-4 of the triazole unit, showed no activity on kinases, including PDK1 (Table 2).

X-ray structure of 8f in complex with PDK1

For further characterization of the binding mode, compound **8f** was soaked in crystals of the kinase domain of PDK1. Broad kinase activity of triazole derivatives is related to PDK1 activity (Table 1), which suggests that the binding mode in this kinase may be representative for several other kinases. The crystal structure was solved at 1.7 Å (Table 3) and reveals the detailed binding mode of **8f** within the ATP-binding site (Fig. 3).

Compound **8f** shows two canonical hydrogen bonds to the hinge region, an H-bond donor contact from azaindole N-1 to Ser160, and an H-bond acceptor contact from azaindole N-7 to Ala162. The triazole nitrogen atoms are also involved in hydrogen bonding interactions: N-3 to the Thr222 side chain (which may explain the lower activity of the pyrazole **11**) and N-2 to a water molecule. This water molecule is also in the H-bond distance to the catalytic amino acids Lys111 and Asp223. The molecule binds in an overall bent conformation with the benzyl group forming hydrophobic interactions with the glycine-rich region (GC-loop). The reason for the inactivity of compound **10**, which is a bioisostere of compound **8f** and differs only in the relative position of the substituents on N-1 and C-4 of the triazole unit and consequently in the dipole moment

Table 3 Crystallographic data of compound **8f**

PDB ID	**3RCJ**
Total number of reflections collected	110193
Number of unique reflections	33266
Space group	*C*2
Cell dimensions *a*, *b*, *c* (Å)	148.87, 44.39, 47.10
Cell dimensions α, β, γ (°)	90, 101.01, 90
R_{merge} overall, highest resolution shell (%)	55.4, 7.2
I/σ overall, highest resolution shell	20.58, 2.81
Completeness (%)	99.0
Redundancy	3.31
Resolution range used in refinement (Å)	70–1.7
Number of unique reflections used in refinement	33266
R_{factor} (%)	19.8
R_{free} (%)	21.7
Number of molecules per asymmetric unit	1
Number of ligands per asymmetric unit	1
Number of protein atoms	2278
Number of ligand atoms	21
Number of water molecules	162

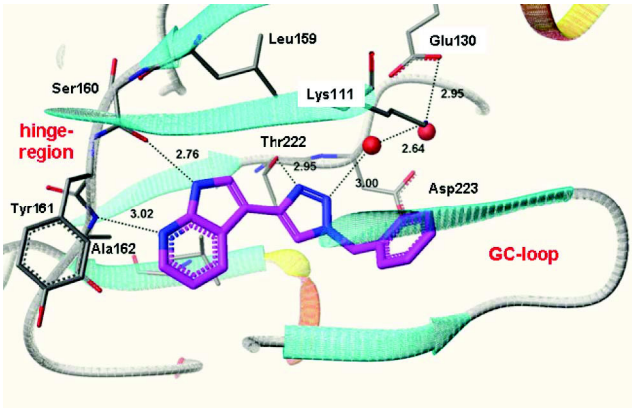


Fig. 3 X-ray structure of the complex of **8f** with PDK1 at 1.7 Å resolution. The 7-azaindole ring forms H-bonds to the hinge region (Ser160 & Ala162); two of the triazole N-atoms form H-bonds to Thr222 and a water molecule. The benzyl ring is oriented towards the GC-loop.

of the molecule, cannot be deduced from this X-ray structure and still remains obscure.

Conclusions

A practical and preparatively simple one-pot three-component Sonogashira coupling–TMS-deprotection–CuAAC sequence was developed to synthetically access a variety of triazolyl NH-heterocycles **8** and **9** in high purity and a very concise fashion. The sequence works very reliably for substrates with nitrogen atoms in different positions of various indole isosters, arising from the robustness, the versatility, and the generality of both Sonogashira coupling and CuAAC. The title compounds were tested for inhibition of a broad panel of kinases to reveal their kinase inhibitory activities. Compounds **8f**, **8h**, **8k**, and **8l** were found to inhibit PDK1 kinase with IC_{50} values below 1 μM. The X-ray structure analysis of compound **8f** in complex with PDK1 reveals the importance of the benzyl substituent for the binding. The phenyl and homobenzyl derivatives **8g** and **8r** were considerably less active, indicating a suboptimal position of their aromatic rings for favorable interaction towards the GC-loop compared with the benzyl substituent in **8f**. Since all synthesized compounds are small molecules, more potent analogues can be envisioned by derivatization, which can be achieved easily with the presented method.

Experimental

Synthesis of 3-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (8f)

(Compound **2f**): $PdCl_2(PPh_3)_2$ (71 mg, 0.10 mmol, 2 mol%) and CuI (39 mg, 0.20 mmol, 4 mol%) were placed in a dry screw-cap Schlenk vessel with a septum. Then, *tert*-butyl 3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (**1f**) (1.72 g, 5.00 mmol) was added in 25 mL of dry tetrahydrofuran under an argon atmosphere and the reaction mixture was degassed with argon. After that, trimethylsilylacetylene (1.08 mL, 7.50 mmol, 1.50 equiv.) and dry triethylamine (1.39 mL, 10.0 mmol, 2.00 equiv.) were added and the mixture was stirred at room temperature (in a water bath) for 1 h until the complete consumption of the starting material (monitored by TLC). Then, 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (7.50 mL, 1.50 mmol, 1.50 equiv.) was added dropwise and the mixture was stirred at room temperature for 0.5 h until the deprotection was complete (monitored by TLC). After that, benzyl azide (**5a**) (679 mg, 5.00 mmol, 1.00 equiv.) in 5 mL of dry methanol was added and the mixture was stirred at room temperature for 40 h until the complete conversion to the product (monitored by TLC). After removal of the solvents *in vacuo* the residue was absorbed onto Celite® and purified chromatographically on silica gel with petroleum ether (boiling range 40–60 °C)–ethyl acetate PE–EtOAc = 2 : 1 (R_f (PE–EtOAc = 2 : 1): 0.20) to give 1.56 g (4.15 mmol, 83%) *tert*-butyl 3-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (**2f**) as a yellow foam. The obtained compound was deprotected without characterization and further purification.

(Compound **8f**): *tert*-Butyl 3-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (**2f**) (1.56 g, 4.15 mmol) was placed in 21 mL of methanol. Then, potassium carbonate (1.45 g, 10.4 mmol, 2.50 equiv.) was added and the mixture was stirred at room temperature (in a water bath) for 1 h (monitored by TLC). A precipitate formed after a few min. The mixture was adsorbed on Celite® and purified chromatographically on silica gel with dichloromethane–methanol–aqueous ammonia DCM–MeOH–NH_3 = 100 : 1 : 1 → 100 : 2 : 1 → 100 : 3 : 1 (stepwise gradient). After drying *in vacuo* overnight, 930 mg (3.38 mmol, 81%) of a pale yellow solid were obtained. The product was additionally purified by suspension in dichloromethane, sonication in ultrasonic bath for 0.5 h, filtration and drying *in vacuo* at 70 °C overnight to obtain the analytically pure 3-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (**8f**) as a colorless solid. UV purity (HT-LC-MS): 100%. M.p. 234–237 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 5.66 (s, 2 H), 7.17 (dd, J = 7.9 Hz, J = 4.7 Hz, 1 H), 7.32–7.43 (m, 5 H), 7.92 (d, J = 2.5 Hz, 1 H), 8.29 (dd, J = 4.7 Hz, J = 1.6 Hz, 1 H), 8.44 (dd, J = 7.9 Hz, J = 1.6 Hz, 1 H), 8.54 (s, 1 H), 11.9 (br, 1 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ (ppm) 52.8 (CH_2), 105.0 (C_{quat}), 115.9 (CH), 116.9 (C_{quat}), 119.8 (CH), 123.2 (CH), 127.8 (CH), 128.1 (CH), 128.3 (CH), 128.7 (CH), 136.1 (C_{quat}), 142.4 (C_{quat}), 143.1 (CH), 148.5

(C_{quat}). EI + MS (m/z (%)): 275 (M^+, 100), 248 (13), 247 (74), 246 (87), 220 (11), 219 (35), 170 (15), 156 (24), 142 (10), 129 (17), 91 ($C_7H_7^+$, 19), 44 (19). IR (KBr): $\tilde{\nu}$ 1584 (s) cm^{-1}, 1458 (m), 1420 (m), 1220 (m), 941 (m), 799 (m), 771 (s), 722 (s). Anal. calcd for $C_{16}H_{13}N_5$ (275.3): C 69.80, H 4.76, N 25.44. Found: C 69.71, H 5.02, N 25.44.

PDK1 biochemical kinase assay

The PDK1 (3-phosphoinositide-dependent protein kinase-1) assay was carried out in 384-well streptavidin-coated FlashPlates (PerkinElmer). 3.4 nM His6-PDK1(Δ1-50), 400 nM biotinylated PDKtide (Biotin-βA-βA-KTFCGTPEYLAPEVRREPRILS-EEEQEMFRDFDYIADWC), and 4 μM ATP (spiked with 0.25 μCi ^{33}P-ATP per well) were incubated in a total volume of 50 μL (50 mM TRIS, 10 mM magnesium acetate, 0.1% mercaptoethanol, 0.02% Brij35, 0.1% bovine serum albumin, pH 7.5) with or without test compound (7–10 concentrations) for 60 min at 30 °C. The reaction was stopped by the addition of 25 μL 200 mM EDTA. After 30 min at room temperature the liquid was removed and each well washed three times with 100 μL 0.9% sodium chloride solution. Nonspecific reaction was determined in the presence of 100 nM staurosporine. Radioactivity was measured in a Topcount (PerkinElmer). Results (IC_{50} values) were calculated with *e.g.* AssayExplorer (Symyx).

DSTT kinase assays

The kinase assays[79] were carried out at room temperature. Compounds were pre-incubated in the presence of the enzyme and peptide/protein substrate for 5 min before initiation of the reaction by adding ATP. Assays were incubated at room temperature before termination by the addition of 5 μL orthophosphoric acid. The assay plates were then harvested onto P81 Unifilter Plates (wash buffer was 50 mM orthophosphoric acid) and dried in air. The dry Unifilter plates were then sealed on the addition of MicroScint O and were counted in Packard Topcount NXT scintillation counters.

Cocrystallization of compound 8f with PDK1 and X-ray structure determination

Crystallization of PDK1 was performed as previously described[80] and crystals were used for soaking with compound **8f**. X-Ray diffraction data were collected at the PXIII beamline equipped with a Pilatus detector at the Paul Scherrer Institut in Villingen, Switzerland. With the detector set at 270 mm, data were collected in 720 contiguous 0.25° oscillation images at 1 Å wavelength. The data for compound **8f** extends to 1.7 Å resolution, has an R_{merge} of 7.2% and 3.31-fold multiplicity. The structure was refined using CNX (Accelrys Inc.) to an R_{factor} of 19.8%.

Acknowledgements

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Notes and references

1 For a review on indole scaffold as a privileged structure, see: F. R. de Sá Alves, E. J. Barreiro and C. A. M. Fraga, *Mini-Rev. Med. Chem.*, 2009, **9**, 782; For a general review on bicyclic privileged structures, see: D. A. Horton, G. T. Bourne and M. L. Smythe, *Chem. Rev.*, 2003, **103**, 893; For a comprehensive listing of privileged scaffolds, see: M. E. Welsch, S. A. Snyder and B. R. Stockwell, *Curr. Opin. Chem. Biol.*, 2010, **14**, 347.
2 For a recent review on halogenated marine indole alkaloids, see: P. M. Pauletti, L. S. Cintra, C. G. Braguine, A. A. S. Filho, M. L. A. Silva, W. R. Cunha and A. H. Januário, *Mar. Drugs*, 2010, **8**, 1526.
3 For recent reviews on indole alkaloid marine natural products as a source of drug leads, see: A. J. Kochanowska-Karamyan and M. T. Hamann, *Chem. Rev.*, 2010, **110**, 4489; W. Gul and M. T. Hamann, *Life Sci.*, 2005, **78**, 442; For a recent review on anticancer properties of indole compounds, see: A. Ahmad, W. A. Sakr and K. M. W. Rahman, *Curr. Drug Targets*, 2010, **11**, 652.
4 M. D. Lebar and B. J. Baker, *Aust. J. Chem.*, 2010, **63**, 862 (note authors' claim that the compound isolated from *Psammopemma* sp. as described in M. S. Butler, R. J. Capon and C. C. Lu, *Aust. J. Chem.*, 1992, **45**, 1871, is meridianin A and not psammopemmin A, which apparently does not exist); A. M. Seldes, M. F. R. Brasco, L. Hernández Franco and J. A. Palermo, *Nat. Prod. Res.*, 2007, **21**, 555; L. Hernández Franco, E. Bal de Kier Joffé, L. Puricelli, M. Tatian, A. M. Seldes and J. A. Palermo, *J. Nat. Prod.*, 1998, **61**, 1130.
5 T. Endo, M. Tsuda, J. Fromont and J. Kobayashi, *J. Nat. Prod.*, 2007, **70**, 423.
6 F. Reyes, R. Fernández, A. Rodríguez, A. Francesch, S. Taboada, C. Ávila and C. Cuevas, *Tetrahedron*, 2008, **64**, 5119.
7 R. J. Capon, F. Rooney, L. M. Murray, E. Collins, A. T. R. Sim, J. A. P. Rostas, M. S. Butler and A. R. Carroll, *J. Nat. Prod.*, 1998, **61**, 660; A. E. Wright, S. A. Pomponi, S. S. Cross and P. McCarthy, *J. Org. Chem.*, 1992, **57**, 4772; S. A. Morris and R. J. Andersen, *Tetrahedron Lett.*, 1990, **46**, 715; S. Kohmoto, Y. Kashman, O. J. McConnell, K. L. Rinehart, Jr., A. Wright and F. Koehn, *J. Org. Chem.*, 1988, **53**, 3116.
8 B. Bao, Q. Sun, X. Yao, J. Hong, C.-O. Lee, H. Y. Cho and J. H. Jung, *J. Nat. Prod.*, 2007, **70**, 2; B. Bao, Q. Sun, X. Yao, J. Hong, C.-O. Lee, C. J. Sim, K. S. Im and J. H. Jung, *J. Nat. Prod.*, 2005, **68**, 711; K.-B. Oh, W. Mar, S. Kim, J.-Y. Kim, M.-N. Oh, J.-G. Kim, D. Shin, C. J. Sim and J. Shin, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 4927; A. Casapullo, G. Bifulco, I. Bruno and R. Riccio, *J. Nat. Prod.*, 2000, **63**, 447; S. P. Gunasekera, P. J. McCarthy and M. Kelly-Borges, *J. Nat. Prod.*, 1994, **57**, 1437.
9 P. Ciminiello, C. Dell'Aversano, E. Fattorusso, M. Forino, L. Grauso, F. U. Santelia, L. Tartaglione, V. I. Moutsos, E. N. Pitsinos and E. A. Couladouros, *Eur. J. Org. Chem.*, 2007, 5434, and references therein.
10 T. Bergmann, D. Schories and B. Steffan, *Tetrahedron*, 1997, **53**, 2055.
11 S. Sakemi and H. H. Sun, *J. Org. Chem.*, 1991, **56**, 4304.
12 J. Shin, Y. Seo, K. W. Cho, J.-R. Rho and C. J. Sim, *J. Nat. Prod.*, 1999, **62**, 647; L. M. Murray, T. K. Lim, J. N. A. Hooper and R. J. Capon, *Aust. J. Chem.*, 1995, **48**, 2053, and references therein; K. Bartik, J.-C. Braekman, D. Daloze, C. Stoller, J. Huysecom, G. Vandevyver and R. Ottinger, *Can. J. Chem.*, 1987, **65**, 2118.
13 M. Guyot and M. Meyer, *Tetrahedron Lett.*, 1986, **27**, 2621.
14 A. Loukaci, M. Guyot, A. Chiaroni and C. Rieche, *J. Nat. Prod.*, 1998, **61**, 519.
15 N. Lindquist, W. Fenical, G. D. Van Duyne and J. Clardy, *J. Am. Chem. Soc.*, 1991, **113**, 2303.
16 S. Takahashi, T. Matsunaga, C. Hasegawa, H. Saito, D. Fujita, F. Kiuchi and Y. Tsuda, *Chem. Pharm. Bull.*, 1998, **46**, 1527.
17 G. Guella, I. Mancini, I. N'Diaye and F. Pietra, *Helv. Chim. Acta*, 1994, **77**, 1999; F. Miyake, M. Hashimoto, S. Tonsiengsom, K. Yakushijin and D. A. Horne, *Tetrahedron*, 2010, **66**, 4888.
18 B. S. Joshi, W. I. Taylor, D. S. Bhate and S. S. Karmarkar, *Tetrahedron*, 1963, **19**, 1437.
19 G. R. Pettit, J. C. Knight, D. L. Herald, R. Davenport, R. K. Pettit, B. E. Tucker and J. M. Schmidt, *J. Nat. Prod.*, 2002, **65**, 1793.
20 L. M. Browne, K. L. Conn, W. A. Ayer and J. P. Tewari, *Tetrahedron*, 1991, **47**, 3909.
21 H. Oka, T. Yoshinari, T. Murai, K. Kawamura, F. Satoh, K. Funaishi, A. Okura, H. Suda, M. Okanishi and Y. Shizuri, *J. Antibiot.*, 1991, **44**, 486; H. Suda, K. Matsunaga, S. Yamamura and Y. Shizuri, *Tetrahedron Lett.*, 1991, **32**, 2791.

22 S. Tsujii, K. L. Rinehart, S. P. Gunasekera, Y. Kashman, S. S. Cross, M. S. Lui, S. A. Pomponi and M. C. Diaz, *J. Org. Chem.*, 1988, **53**, 5446.
23 H. H. Sun and S. Sakemi, *J. Org. Chem.*, 1991, **56**, 4307; J. Cohen, G. K. Paul, S. P. Gunasekera, R. E. Longley and S. A. Pomponi, *Pharm. Biol.*, 2004, **42**, 59.
24 R. J. Capon, C. Peng and C. Dooms, *Org. Biomol. Chem.*, 2008, **6**, 2765.
25 K. Motohashi, M. Takagi and K. Shin-ya, *J. Nat. Prod.*, 2010, **73**, 226.
26 H. C. Vervoort, S. E. Richards-Gross, W. Fenical, A. Y. Lee and J. Clardy, *J. Org. Chem.*, 1997, **62**, 1486.
27 U. W. Hawas, M. Shaaban, K. A. Shaaban, M. Speitling, A. Maier, G. Kelter, H. H. Fiebig, M. Meiners, E. Helmke and H. Laatsch, *J. Nat. Prod.*, 2009, **72**, 2120.
28 A. Badre, A. Boulanger, E. Abou-Mansour, B. Banaigs, G. Combaut and C. Francisco, *J. Nat. Prod.*, 1994, **57**, 528.
29 D. T. A. Youssef, *J. Nat. Prod.*, 2005, **68**, 1416.
30 T. Hoshino, Y. Kojima, T. Hayashi, T. Uchiyama and K. Kaneko, *Biosci., Biotechnol., Biochem.*, 1993, **57**, 775.
31 K. A. McArthur, S. S. Mitchell, G. Tsueng, A. Rheingold, D. J. White, J. Grodberg, K. S. Lam and B. C. M. Potts, *J. Nat. Prod.*, 2008, **71**, 1732.
32 N. Durán, G. Z. Justo, C. V. Ferreira, P. S. Melo, L. Cordi and D. Martins, *Biotechnol. Appl. Biochem.*, 2007, **48**, 127.
33 N. K. Kubota, H. Iwamoto, Y. Fukazawa and Y. Uchio, *Heterocycles*, 2005, **65**, 2675; A. A. El-Gamal, W.-L. Wang and C.-Y. Duh, *J. Nat. Prod.*, 2005, **68**, 815.
34 For YC-1, see: K. W. Hering, J. D. Artz, W. H. Pearson and M. A. Marletta, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 618; J.-C. Lien, F.-Y. Lee, L.-J. Huang, S.-L. Pan, J.-H. Guh, C.-M. Teng and S.-C. Kuo, *J. Med. Chem.*, 2002, **45**, 4947; F.-Y. Lee, J.-C. Lien, L.-J. Huang, T.-M. Huang, S.-C. Tsai, C.-M. Teng, C.-C. Wu, F.-C. Cheng and S.-C. Kuo, *J. Med. Chem.*, 2001, **44**, 3746; For azaindol-3-yl-dipyridodiazepinones, see: T. A. Kelly, D. W. McNeil, J. M. Rose, E. David, C.-K. Shih and P. M. Grob, *J. Med. Chem.*, 1997, **40**, 2430.
35 For selected examples of kinase inhibitors with (hetero)aryl substituents at C-3, see: S. Hong, S. Lee, B. Kim, H. Lee, S.-S. Hong and S. Hong, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 7212; M. Hammond, D. G. Washburn, T. H. Hoang, S. Manns, J. S. Frazee, H. Nakamura, J. R. Patterson, W. Trizna, C. Wu, L. M. Azzarano, R. Nagilla, M. Nord, R. Trejo, M. S. Head, B. Zhao, A. M. Smallwood, K. Hightower, N. J. Laping, C. G. Schnackenberg and S. K. Thompson, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 4441; S. Huang, R. Li, P. J. Connolly, S. Emanuel and S. A. Middleton, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 4818; H.-C. Zhang, H. Ye, B. R. Conway, C. K. Derian, M. F. Addo, G.-H. Kuo, L. R. Hecker, D. R. Croll, J. Li, L. Westover, J. Z. Xu, R. Look, K. T. Demarest, P. Andrade-Gordon, B. P. Damiano and B. E. Maryanoff, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 3245; For RWJ 68354, see: J. R. Henry, K. C. Rupert, J. H. Dodd, I. J. Turchi, S. A. Wadsworth, D. E. Cavender, B. Fahmy, G. C. Olini, J. E. Davis, J. Lee Pellegrino-Gensey, P. H. Schafer and J. J. Siekierka, *J. Med. Chem.*, 1998, **41**, 4196; J. R. Henry, K. C. Rupert, J. H. Dodd, I. J. Turchi, S. A. Wadsworth, D. E. Cavender, P. H. Schafer and J. J. Siekierka, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 3335.
36 N. B. Perry, L. Ettouati, M. Litaudon, J. W. Blunt, M. H. G. Munro, S. Parkin and H. Hope, *Tetrahedron*, 1994, **50**, 3987; G. Trimurtulu, D. J. Faulkner, N. B. Perry, L. Ettouati, M. Litaudon, J. W. Blunt, M. H. G. Munro and G. B. Jameson, *Tetrahedron*, 1994, **50**, 3993; For a recent review on variolins and related alkaloids, see: S. R. Walker, E. J. Carter, B. C. Huff and J. C. Morris, *Chem. Rev.*, 2009, **109**, 3080.
37 A. Echalier, K. Bettayeb, Y. Ferandin, O. Lozach, M. Clément, A. Valette, F. Liger, B. Marquet, J. C. Morris, J. A. Endicott, B. Joseph and L. Meijer, *J. Med. Chem.*, 2008, **51**, 737; K. Bettayeb, O. M. Tirado, S. Marionneau-Lambot, Y. Ferandin, O. Lozach, J. C. Morris, S. Mateo-Lozano, P. Drueckes, C. Schächtele, M. H. G. Kubbutat, F. Liger, B. Marquet, B. Joseph, A. Echalier, J. A. Endicott, V. Notario and L. Meijer, *Cancer Res.*, 2007, **67**, 8325.
38 E. Merkul, E. Schäfer and T. J. J. Müller, *Org. Biomol. Chem.*, 2011, **9**, 3139.
39 A. S. Karpov, E. Merkul, F. Rominger and T. J. J. Müller, *Angew. Chem., Int. Ed.*, 2005, **44**, 6951.
40 According to an X-ray structure analysis of meridianin C and meriolin 1 in the kinase TGFβ, which will be published elsewhere.
41 A. Seggio, G. Priem, F. Chevallier and F. Mongin, *Synthesis*, 2009, 3617; M. Gompel, M. Leost, E. Bal de Kier Joffé, L. Puricelli, L. Hernández Franco, J. Palermo and L. Meijer, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 1703; L. Hernández Franco and J. A. Palermo, *Chem. Pharm. Bull.*, 2003, **51**, 975.
42 For triazole as a linking element in an indole salicylic acid based library, see: X. Zhang, Y. He, S. Liu, Z. Yu, Z.-X. Jiang, Z. Yang, Y. Dong, S. C. Nabinger, L. Wu, A. M. Gunawan, L. Wang, R. J. Chan and Z.-Y. Zhang, *J. Med. Chem.*, 2010, **53**, 2482.
43 D. K. Dalvie, A. S. Kalgutkar, S. C. Khojasteh-Bakht, R. S. Obach and J. P. O'Donnell, *Chem. Res. Toxicol.*, 2002, **15**, 269.
44 W.-T. Li, W.-H. Wu, C.-H. Tang, R. Tai and S.-T. Chen, *ACS Comb. Sci.*, 2011, **13**, 72, and references therein; S. K. Mamidyala and M. G. Finn, *Chem. Soc. Rev.*, 2010, **39**, 1252; K. A. Kalesh, K. Liu and S. Q. Yao, *Org. Biomol. Chem.*, 2009, **7**, 5129; G. C. Tron, T. Pirali, R. A. Billington, P. L. Canonico, G. Sorba and A. A. Genazzani, *Med. Res. Rev.*, 2008, **28**, 278; A. D. Moorhouse and J. E. Moses, *ChemMedChem*, 2008, **3**, 715; A. Dondoni, *Chem.–Asian J.*, 2007, **2**, 700; K. B. Sharpless and R. Manetsch, *Expert Opin. Drug Discovery*, 2006, **1**, 525; H. C. Kolb and K. B. Sharpless, *Drug Discovery Today*, 2003, **8**, 1128; R. Breinbauer and M. Köhn, *ChemBioChem*, 2003, **4**, 1147.
45 J.-F. Lutz, *Angew. Chem., Int. Ed.*, 2007, **46**, 1018.
46 Y. L. Angell and K. Burgess, *Chem. Soc. Rev.*, 2007, **36**, 1674.
47 D. Dorsch, M. Wucherer-Plietker, T. J. J. Müller and E. Merkul, *PCT Int. Appl.* 2010, WO 2010127754 A1 20101111; D. Dorsch, M. Wucherer-Plietker, T. J. J. Müller and E. Merkul, *Ger. Offen.* 2010, DE 102009019962 A1 20101111.
48 For a recent synthesis of kinase inhibitors based on 3-triazolyl substituted pyrazolo[3,4-*d*]pyrimidines, see: M. Klein, P. Dinér, D. Dorin-Semblat, C. Doerig and M. Grøtli, *Org. Biomol. Chem.*, 2009, **7**, 3421.
49 For seminal publications, see: K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 1975, **16**, 4467; Y. Tohda, K. Sonogashira and N. Hagihara, *Synthesis*, 1977, 777.
50 For recent reviews, see: R. Chinchilla and C. Nájera, *Chem. Rev.*, 2007, **107**, 874; H. Doucet and J.-C. Hierso, *Angew. Chem., Int. Ed.*, 2007, **46**, 834; For general reviews, see: H. Plenio and A. Datta, in *Handbook of C-H Transformations*, Wiley, Weinheim, 2005, ch. 1.2; J. A. Marsden and M. M. Haley, in *Metal-Catalyzed Cross-Coupling Reactions*, Wiley, Weinheim, 2nd edn, 2004, ch. 6; K. Sonogashira, in *Metal-Catalyzed Cross-Coupling Reactions*, Wiley, Weinheim, 1998, ch. 5.
51 S. Takahashi, Y. Kuroyama, K. Sonogashira and N. Hagihara, *Synthesis*, 1980, 627.
52 For seminal publications on CuAAC, see: V. V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2002, **41**, 2596; C. W. Tornøe, C. Christensen and M. Meldal, *J. Org. Chem.*, 2002, **67**, 3057.
53 For recent reviews on CuAAC, see: V. V. Fokin, in *Catalyzed Carbon-Heteroatom Bond Formation*, Wiley, Weinheim, 2011, ch. 7; J. E. Hein and V. V. Fokin, *Chem. Soc. Rev.*, 2010, **39**, 1302; C. Spiteri and J. E. Moses, *Angew. Chem. Int. Ed.*, 2010, **49**, 31; M. Meldal and C. W. Tornøe, *Chem. Rev.*, 2008, **108**, 2952; P. Wu and V. V. Fokin, *Aldrichimica Acta*, 2007, **40**, 7; V. D. Bock, H. Hiemstra and J. H. van Maarseveen, *Eur. J. Org. Chem.*, 2006, 51; W. H. Binder and C. Kluger, *Curr. Org. Chem.*, 2006, **10**, 1791.
54 For the philosophy of click chemistry, see: M. G. Finn and V. V. Fokin, *Chem. Soc. Rev.*, 2010, **39**, 1231; C. J. Hawker, V. V. Fokin, M. G. Finn and K. B. Sharpless, *Aust. J. Chem.*, 2007, **60**, 381; H. C. Kolb, M. G. Finn and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2001, **40**, 2004; For recent reviews on click chemistry, see: G. Franc and A. K. Kakkar, *Chem. Soc. Rev.*, 2010, **39**, 1536; J. E. Moses and A. D. Moorhouse, *Chem. Soc. Rev.*, 2007, **36**, 1249; M. V. Gil, M. J. Arévalo and Ó. López, *Synthesis*, 2007, 1589.
55 For the concept of atom economy, see: B. M. Trost, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 259; B. M. Trost, *Science*, 1991, **254**, 1471.
56 W. D. Sharpless, P. Wu, T. V. Hansen and J. G. Lindberg, *J. Chem. Educ.*, 2005, **82**, 1833.
57 F. Alonso, Y. Moglie, G. Rodivoy and M. Yus, *Adv. Synth. Catal.*, 2010, **352**, 3208; D. Kumar and V. B. Reddy, *Synthesis*, 2010, 1687; L. S. Campbell-Verduyn, W. Szymański, C. P. Postema, R. A. Dierckx, P. H. Elsinga, D. B. Janssen and B. L. Feringa, *Chem. Commun.*, 2010, **46**, 898; Y. Huang, G. L. Gard and J. M. Shreeve, *Tetrahedron Lett.*, 2010, **51**, 6951; V. Bénéteau, A. Olmos, T. Boningari, J. Sommer and P. Pale, *Tetrahedron Lett.*, 2010, **51**, 3673; C.-T. Lee, S. Huang and B. H. Lipshutz, *Adv. Synth. Catal.*, 2009, **351**, 3139; S. Maisonneuve and J. Xie, *Synlett*, 2009, 2977, and references therein; K. Odlo, E. A. Høydahl and T. V. Hansen, *Tetrahedron Lett.*, 2007, **48**, 2097; J. Andersen, S. Bolvig and X. Liang, *Synlett*, 2005, 2941; K. Kacprzak, *Synlett*, 2005,

943; P. Appukkuttan, W. Dehaen, V. V. Fokin and E. Van der Eycken, *Org. Lett.*, 2004, **6**, 4223; A. K. Feldman, B. Colasson and V. V. Fokin, *Org. Lett.*, 2004, **6**, 3897.
58 F. Cuevas, A. I. Oliva and M. A. Pericàs, *Synlett*, 2010, 1873, and references therein.
59 L. Ackermann, H. K. Potukuchi, D. Landsberg and R. Viante, *Org. Lett.*, 2008, **10**, 3081.
60 I. R. Baxendale, S. V. Ley, A. C. Mansfield and C. D. Smith, *Angew. Chem., Int. Ed.*, 2009, **48**, 4017; D. Luvino, C. Amalric, M. Smietana and J.-J. Vasseur, *Synlett*, 2007, 3037.
61 For recent reviews, see: T. J. J. Müller, *Top. Heterocycl. Chem.*, 2010, **25**, 25; B. Willy and T. J. J. Müller, *Curr. Org. Chem.*, 2009, **13**, 1777; B. Willy and T. J. J. Müller, *ARKIVOC*, 2008, **Part I**, 195; D. M. D'Souza and T. J. J. Müller, *Chem. Soc. Rev.*, 2007, **36**, 1095.
62 For selected examples of syntheses of other 5-membered heterocycles, see: A. S. Karpov, E. Merkul, T. Oeser and T. J. J. Müller, *Eur. J. Org. Chem.*, 2006, 2991; A. S. Karpov, E. Merkul, T. Oeser and T. J. J. Müller, *Chem. Commun.*, 2005, 2581 (furans); E. Merkul and T. J. J. Müller, *Chem. Commun.*, 2006, 4817; E. Merkul, O. Grotkopp and T. J. J. Müller, *Synthesis*, 2009, 502 (oxazoles); B. Willy and T. J. J. Müller, *Eur. J. Org. Chem.*, 2008, 4157 (pyrazoles); B. Willy, F. Rominger and T. J. J. Müller, *Synthesis*, 2008, 293 (isoxazoles).
63 P. G. M. Wuts and T. W. Greene, in *Green's Protective Groups in Organic Synthesis*, Wiley, New York, 4th edn, 2007, ch. 7.
64 Boc_2O/CsF method: N. Inahashi, A. Matsumiya and T. Sato, *Synlett*, 2008, 294; for the standard protocol (Boc_2O/DMAP), see: L. Grehn and U. Ragnarsson, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 296.
65 For some examples, see: J. J. Richards and C. Melander, *J. Org. Chem.*, 2008, **73**, 5191; R. Martín, C. H. Larsen, A. Cuenca and S. L. Buchwald, *Org. Lett.*, 2007, **9**, 3379; M. R. Rivero and S. L. Buchwald, *Org. Lett.*, 2007, **9**, 973; Y.-Q. Fang, J. Yuen and M. Lautens, *J. Org. Chem.*, 2007, **72**, 5152; R. Martín, M. R. Rivero and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2006, **45**, 7079; F. S. Al-Hajjar and S. S. Sabri, *J. Heterocyclic Chem.*, 1986, **23**, 727.
66 For a one-pot synthesis of 2-substituted *N*-Boc 4-iodo pyrroles, see: E. Merkul, C. Boersch, W. Frank and T. J. J. Müller, *Org. Lett.*, 2009, **11**, 2269.
67 Cleavage with boiling water: J. Wang, Y.-L. Liang and J. Qu, *Chem. Commun.*, 2009, 5144; cleavage with fluorinated alcohols: J. Choy, S. Jaime-Figueroa, L. Jiang and P. Wagner, *Synth. Commun.*, 2008, **38**, 3840; cleavage with NaOMe/dry MeOH: K. Ravinder, A. V. Reddy, K. C. Mahesh, M. Narasimhulu and Y. Venkateswarlu, *Synth. Commun.*, 2007, 281; cleavage with aqueous K_2CO_3/MeOH under reflux: M. Chakrabarty, T. Kundu and Y. Harigaya, *Synth. Commun.*, 2006, **36**, 2069, see also references therein; cleavage using TBAF: U. Jacquemard, V. Bénéteau, M. Lefoix, S. Routier, J.-Y. Mérour and G. Coudert, *Tetrahedron*, 2004, **60**, 10039; thermolytic cleavage: V. H. Rawal and M. P. Cava, *Tetrahedron Lett.*, 1985, **26**, 6141.
68 Compounds **1a**, **1d–k**, and **1n** were prepared as described in: B. Witulski, N. Buschmann and U. Bergsträßer, *Tetrahedron*, 2000, **56**, 8473.
69 Although numerous efficient catalytic systems have been described for the Sonogashira-type alkynylations, this standard catalytic system is still by far the most widely used one: H. Plenio, *Angew. Chem., Int. Ed.*, 2008, **47**, 6954; R. R. Tykwinski, *Angew. Chem., Int. Ed.*, 2003, **42**, 1566.
70 E. Merkul, D. Urselmann and T. J. J. Müller, *Eur. J. Org. Chem.*, 2011, 238.
71 *N*-Boc protected 3-iodo (aza)indoles and 4-iodo pyrroles are storable for years in the refrigerator under an argon atmosphere without decomposition.
72 3-Iodo (aza)indoles can be prepared in large quantities without need for argon atmosphere, but they should be promptly protected with Boc to avoid decomposition and for convenient handling and storage.
73 M. R. Netherton and G. C. Fu, *Org. Lett.*, 2001, **3**, 4295; T. Hundertmark, A. F. Littke, S. L. Buchwald and G. C. Fu, *Org. Lett.*, 2000, **2**, 1729.
74 For some strategies developed to remove Pd from pharmaceutically active ingredients, see a review: C. E. Garrett and K. Prasad, *Adv. Synth. Catal.*, 2004, **346**, 889.
75 For a recent review on the role of bioisosterism in rational drug design, see: L. M. Lima and E. J. Barreiro, *Curr. Med. Chem.*, 2005, **12**, 23.
76 F. Friscourt and G.-J. Boons, *Org. Lett.*, 2010, **12**, 4936; K. Lörincz, P. Kele and Z. Novák, *Synthesis*, 2009, 3527.
77 J. R. Bayascas, *Curr. Top. Microbiol. Immunol.*, 2010, **346**, 9; A. Mora, D. Komander, D. M. F. van Aalten and D. R. Alessi, *Sem. Cell Dev. Biol.*, 2004, **15**, 161.
78 J. Andersen, S. Bolvig and X. Liang, *Synlett*, 2005, 2941.
79 J. Bain, L. Plater, M. Elliott, N. Shpiro, C. J. Hastie, H. McLauchlan, J. Klevernic, J. S. C. Arthur, D. R. Alessi and P. Cohen, *Biochem. J.*, 2007, **408**, 297; J. Bain, H. McLauchlan, M. Elliott and P. Cohen, *Biochem. J.*, 2003, **371**, 199.
80 V. Hindie, A. Stroba, H. Zhang, L. A. Lopez-Garcia, L. Idrissova, S. Zeuzem, D. Hirschberg, F. Schaeffer, T. J. D. Jørgensen, M. Engel, P. M. Alzari and R. M. Biondi, *Nat. Chem. Biol.*, 2009, **5**, 758.

Electronic Supplementary Material (ESI) for Organic and Biomolecular Chemistry

Rapid preparation of triazolyl substituted NH-heterocyclic kinase inhibitors via one-pot Sonogashira coupling□TMS-deprotection□CuAAC sequence**

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Supporting Information

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1. General Considerations

All cross coupling reactions were carried out in oven-dried Schlenk glassware using septa and syringes under nitrogen or argon atmosphere. THF and 1,4-dioxane were dried using *MBraun* system MB-SPS-800, and triethylamine was refluxed under argon atmosphere over ketyl sodium, distilled and stored in a Schlenk flask over potassium hydroxide pellets under argon atmosphere. Dry methanol was purchased from *Sigma-Aldrich Chemie GmbH*.

7-, 6-, and 5-Azaindoles were obtained commercially from *Biosynth*. 4-Azaindole, 4-chloro-7-azaindole, and 4-chloro-deazapurine were synthesized in laboratories of *Merck Serono*, Darmstadt. 4,7-Diazaindole and 2-methyl-7-azaindole were obtained from *Ark Pharm, Inc.* 4(5)-Iodo-1*H*-imidazole and *tert*-butyl 4-iodo-1*H*-pyrazole-1-carboxylate (**1m**) were purchased from *ABCR GmBH & Co.* 4-Bromo-7-azaindole (**6a**) and 5-bromo-7-azaindole (**6b**) were obtained from *Sigma-Aldrich Chemie GmbH.*

Trimethylsilylacetylene was obtained from *Sigma-Aldrich Chemie GmbH.* Tetrabutylammonium fluoride (1 M in THF) was obtained from *Sigma-Aldrich Chemie GmbH*. Benzyl azide (**5a**) was obtained from *ABCR GmBH & Co*. Azidobenzene solution (~ 0.5 M in *tert*-butylmethylether) was obtained from *Sigma-Aldrich Chemie GmbH*. Cesium azide was obtained from *Sigma-Aldrich Chemie GmbH*. Cp*RuCl(PPh_3)$_2$ was obtained from *ABCR GmBH & Co*.

Commercial grade reagents were used as supplied without further purification and were purchased from *Acros Organics*, *Sigma-Aldrich Chemie GmbH*, *Fluka AG*, *ABCR GmBH & Co. KG, AppliChem,* and *Merck KGaA*.

The purification of products was performed on silica gel 60 (0.015-0.040 mm) from *Merck KGaA* using flash technique and under pressure of 2 bar. The crude mixtures were adsorbed on Celite 545 (0.02-0.10 mm) from *Merck KGaA* before chromatographic purification.

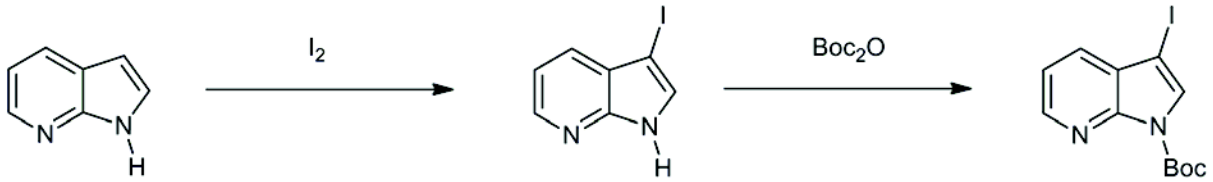
The reaction progress was monitored qualitatively using TLC Silica gel 60 F_{254} 5 x 7.5 cm aluminium sheets obtained by *Merck KGaA*. The spots were detected with UV light at 254 nm and using aqueous potassium permanganate solution.

^{1}H, ^{13}C, and 135-DEPT NMR spectra were recorded on Bruker DRX 500 spectrometer. $CDCl_3$ and DMSO-d_6 were used as deuterated solvents. TMS was used as reference (δ = 0.0) or the resonances of the solvents were locked as internal standards ($CDCl_3$: ^{1}H δ 7.26, ^{13}C δ 77.0; DMSO-d_6: ^{1}H δ 2.50, ^{13}C δ 39.4). The multiplicities of signals were abbreviated as follows: s: singlet; d: doublet; t: triplet; dd: doublet of doublets, q: quartet, m: multiplet and br: broad signal. The type of carbon atoms was determined on the basis of 135-DEPT NMR spectra.

EI mass spectra were measured on Finnigan MAT 8200 spectrometer. IR spectra were obtained on Bruker Vector 22 FT-IR. The solids were measured as KBr pellets and oils as films on KBr plates. The intensity of signals is abbreviated as follows: s (strong), m (medium) and w (weak). The melting points (uncorrected) were measured on Reichert-Jung Thermovar. Combustion analyses were carried out on Perkin Elmer Series II Analyser 2400 in the microanalytical laboratory of Institut für Pharmazeutische und Medizinische Chemie der Heinrich-Heine-Universität Düsseldorf. HT-LC-MS spectra were measured in the Molecule Analytics laboratory of Central Analytical Services, *Merck KGaA* Darmstadt. The content of Pd and Cu in the compound **8f** was determined in the Element Analytics laboratory of Central Analytical Services, *Merck KGaA* Darmstadt.

2. Preparation of Starting Materials 1a-l and 1n

2.1. Preparation of N-Boc 3-iodo (aza)indoles 1a, 1d-k, and 1n (shown for tert-butyl 3-iodo-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (1f))[1]



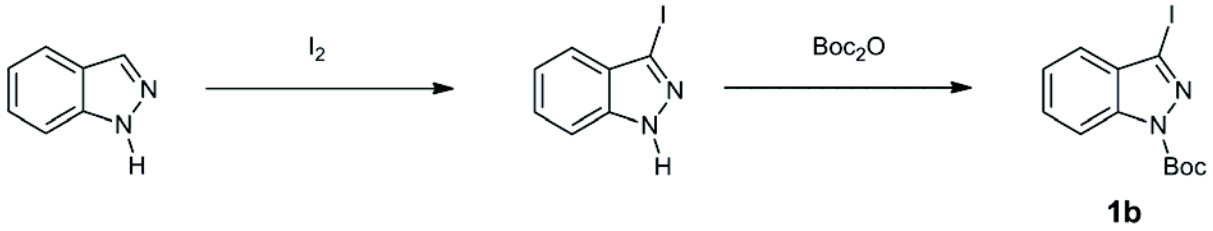
1f

A solution of iodine (25.7 g, 101 mmol, 1.01 equiv) in 180 mL of DMF was dropped to the solution of 7-azaindole (12.1 g, 100 mmol) and potassium hydroxide (16.5 g, 250 mmol, 2.50 equiv) in 180 mL of DMF at room temperature and the mixture was stirred for 45 min. The reaction mixture was then poured on 1 L ice water containing 1 % ammonia and 0.2 % sodium disulfite. The precipitate was filtered, washed with ice water and dried in vacuo to obtain 23.7 g (97.2 mmol, 97 % yield) of a yellow solid.
The obtained iodide was used without further purification in the next step. It was suspended in 180 mL of dichloromethane, 4-dimethylaminopyridine (1.21 g, 9.72 mmol, 10 mol %) was added and di-*tert*-butyl dicarbonate (32.8 g, 146 mmol, 1.50 equiv), dissolved in 180 mL of dichloromethane, was added dropwise over 30 min. The mixture was stirred for 30 min at room temperature, washed with 200 mL of 0.1 N HCl, and the aqueous phase was extracted with dichloromethane (2 x 100 mL). The combined organic layers were dried with sodium sulphate, the solvents were removed under reduced pressure and the residue was adsorbed onto Celite® and purified chromatographically on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl acetate (PE-EtOAc = 20:1, R_f (PE-EtOAc = 20:1): 0.14) to give 31.6 g (91.8 mmol, 94 % yield; 92 % total yield over two steps) of *tert*-butyl 3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (**1f**) as an orange oil, which solidifies upon storage in refrigerator.

Compounds **1a**, **1d**-**e**, **1g**-**k**, and **1n** were obtained analogously.

The experimental details are depicted in ***Table 1***.

2.2. Preparation of tert-butyl 3-iodo-1H-indazole-1-carboxylate (1b)

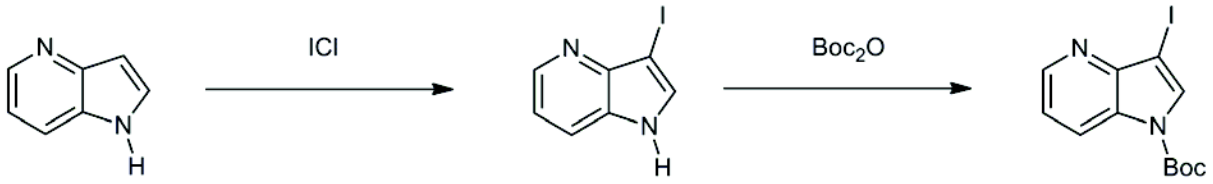


1b

A solution of iodine (13.8 g, 54.3 mmol, 2.00 equiv) in 50 mL of DMF was dropped to the solution of 1*H*-indazole (3.34 g, 27.1 mmol) and potassium hydroxide (5.70 g, 102 mmol, 3.76 equiv) in 50 mL of DMF at room temperature and the mixture was stirred for 4 h. The reaction mixture was then poured onto 200 mL of saturated sodium silfite solution and extracted with diethylether (2 x 50 mL). The combined organic layers were washed with water and brine and dried with sodium sulphate. After the solvents were removed under reduced pressure, 6.09 g (24.9 mmol, 92 % yield) of a yellow solid were obtained.

The obtained iodide was used without further purification for the next step. 3-Iodo-1*H*-indazole (5.09 g, 20.9 mmol) was dissolved in 100 mL of dichloromethane, then triethylamine (27.2 mL, 196 mmol, 9.39 equiv) and 4-dimethylaminopyridine (261 mg, 2.09 mmol, 10 mol %) were added, and di-*tert*-butyl dicarbonate (14.1 g, 62.6 mmol, 3.00 equiv), dissolved in 50 mL of dichloromethane, was slowly added dropwise. The mixture was stirred for 4 h at room temperature, washed with saturated sodium sulfite solution (3 x 20 mL), dried with sodium sulphate, and the solvents were removed under reduced pressure. The residue was adsorbed onto Celite® and purified chromatographically on basic Alox with petroleum ether (boiling range 40-60 °C)/ethyl acetate (PE-EtOAc = 20:1, R_f (PE-EtOAc = 20:1): 0.31) to give 6.26 g (18.2 mmol, 87 % yield; 80 % total yield over two steps) of *tert*-butyl 3-iodo-1*H*-indazole-1-carboxylate (**1b**) as a pale yellow solid.

2.3. Preparation of tert-butyl 3-iodo-1H-pyrrolo[3,2-b]pyridine-1-carboxylate (1c)[2]



1c

4-Azaindole (11.8 g, 100 mmol) was dissolved in 200 mL of pyridine and the solution was cooled with an ice bath. Then, 220 mL of a 0.5 M solution of iodomonochloride (17.9 g, 110 mmol, 1.10 equiv) in dichloromethane was added over 5 min. After 15 min the cooling bath was removed, and after another 30 min the solution was diluted with 2 L of ethyl acetate. The mixture was washed successively with 1 N HCL and 1 N NaOH, dried with sodium sulphate, and the solvents were removed in vacuo. The residue was dried in vacuo to give 18.3 g (75.0 mmol, 75 %) of an orange solid.

The obtained iodide was used without further purification for the next step. 3-Iodo-1*H*-pyrrolo[3,2-*b*]pyridine (1.82 g, 7.45 mmol) was dissolved in 30 mL of dichloromethane, then triethylamine (6.62 mL, 47.8 mmol, 6.41 equiv) and 4-dimethylaminopyridine (91 mg, 0.75 mmol, 10 mol %) were added, and di-*tert*-butyl dicarbonate (3.25 g, 14.9 mmol, 2.00 equiv), dissolved in 25 mL of dichloromethane, was slowly added dropwise. The mixture was stirred for 4 h at room temperature, washed with saturated sodium sulfite solution (2 x 20 mL), dried with sodium sulphate, and the solvents were removed under reduced pressure. The residue was adsorbed onto Celite® and purified chromatographically on neutral Alox with petroleum ether (boiling range 40-60 °C)/ethyl acetate (PE-EtOAc = 5:1, R_f (PE-EtOAc = 5:1): 0.41) to give 1.88 g (5.45 mmol, 73 % yield; 55 % total yield over two steps) of *tert*-butyl 3-iodo-1*H*-pyrrolo[3,2-*b*]pyridine-1-carboxylate (**1c**) as a colorless solid.

Table 1. *Experimental details for the synthesis of N-Boc 3-iodo (aza)indoles* ***1a-k*** *and N-Boc 4-iodo imidazole* ***1n****.*

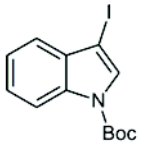
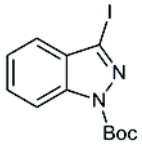
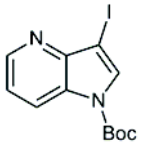
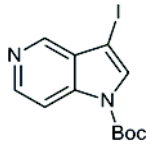
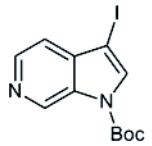
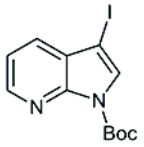
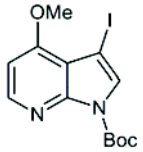
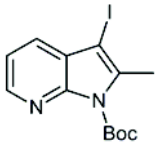
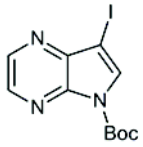
Entry	(Aza)Indole	3-Iodo (aza)indole	*N*-Boc 3-Iodo (aza)indole **1** (isolated yield %)	Chromatographic purification (eluent) R_f (eluent)
1	20.0 g (171 mmol) 1*H*-Indole (*Acros*)	Yellow solid 32.8 g (135 mmol, 79 %) For Boc-protection: 10.0 g (41.1 mmol)	Brown oil 11.3 g (32.9 mmol, 80 %) Total yield: 63 %  **1a**	PE-EtOAc = 50:1 R_f (PE-EtOAc = 50:1): 0.38
2	3.34 g (27.1 mmol) 1*H*-Indazole (*ABCR*)	Yellow solid 6.09 g (24.9 mmol, 92 %) For Boc-protection: 5.09 g (20.9 mmol)	Colorless solid 6.26 g (18.2 mmol, 87 %) Total yield: 80 %  **1b**	PE-EtOAc = 20:1 R_f (PE-EtOAc = 20:1): 0.31
3	11.8 g (100 mmol) 1*H*-Pyrrolo[3,2-*b*]pyridine (4-Azaindole) (*Biosynth*)	Orange solid 18.3 g (75.0 mmol, 75 %) For Boc-protection: 1.82 g (7.45 mmol)	Colorless solid 1.88 g (5.45 mmol, 73 %) Total yield: 55 %  **1c**	PE-EtOAc = 5:1 R_f (PE-EtOAc = 5:1): 0.41

Table 1 (continuation). *Experimental details for the synthesis of N-Boc 3-iodo (aza)indoles* ***1a-k*** *and N-Boc 4-iodo imidazole* ***1n****.*

Entry	Azaindole	3-Iodo azaindole	*N*-Boc 3-Iodo azaindole **1** (isolated yield %)	Chromatographic purification (eluent) R_f (eluent)
4	1.00 g (8.47 mmol) 1*H*-Pyrrolo[3,2-*c*]pyridine (5-Azaindole) (*Biosynth*)	Pale yellow solid 1.50 g (6.14 mmol, 73 %)	Colorless solid 1.85 g (5.36 mmol, 87 %) Total yield: 64 %  **1d**	PE-EtOAc = 2:1 R_f (PE-EtOAc = 2:1): 0.37
5	5.00 g (42.3 mmol) 1*H*-Pyrrolo[2,3-*c*]pyridine (6-Azaindole) (*Biosynth*)	Yellow solid 8.10 g (33.2 mmol, 78 %) For Boc-protection: 7.11 g (29.1 mmol)	Pale yellow solid 7.52 g (21.9 mmol, 75 %) Total yield: 59 %  **1e**	PE-EtOAc = 2:1 R_f (PE-EtOAc = 2:1): 0.36
6	12.1 g (100 mmol) 1*H*-Pyrrolo[2,3-*b*]pyridine (7-Azaindole) (*ABCR*)	Yellow solid 23.7 g (97.2 mmol, 97 %)	Yellow-orange oil[a] 31.6 g (91.8 mmol, 94 %) Total yield: 92 %  **1f**	PE-EtOAc = 20:1 R_f (PE-EtOAc = 20:1): 0.14

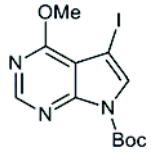
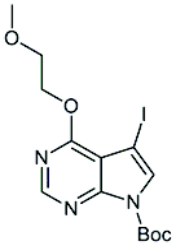
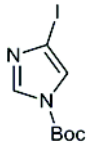
[a] Solidifies upon storage in refrigerator.

Table 1 (continuation). *Experimental details for the synthesis of N-Boc 3-iodo (aza)indoles* ***1a-k*** *and N-Boc 4-iodo imidazole* ***1n****.*

Entry	Azaindole	3-Iodo azaindole	*N*-Boc 3-Iodo azaindole **1** (isolated yield %)	Chromatographic purification (eluent) R_f (eluent)
7	284 mg (1.92 mmol) 4-Methoxy-1*H*-pyrrolo[2,3-*b*]pyridine[a]	Yellow solid 420 mg (1.53 mmol, 80 %) For Boc-protection: 385 mg (1.40 mmol)	Colorless solid 428 mg (1.14 mmol, 82 %) Total yield: 65 %  **1g**	PE-EtOAc = 1:1 R_f (PE-EtOAc = 1:1): 0.51
8	2.50 g (18.0 mmol) 2-Methyl-1*H*-pyrrolo[2,3-*b*]pyridine (*Ark Pharm*)	Beige solid 4.33 g (16.8 mmol, 93 %) For Boc-protection: 4.25 g (16.5 mmol)	Yellow oil[b] 5.58 g (15.6 mmol, 95 %) Total yield: 88 %  **1h**	PE-EtOAc = 20:1 → 15:1 R_f (PE-EtOAc = 15:1): 0.44
9	1.25 g (10.0 mmol) 5*H*-Pyrrolo[2,3-*b*]pyrazine (4,7-Diaza-indole) (*Ark Pharm*)	Yellow solid 2.00 g (8.18 mmol, 82 %) For Boc-protection: 1.96 g (7.99 mmol)	Pale yellow solid 2.53 g (7.33 mmol, 92 %) Total yield: 75 %  **1i**	PE-EtOAc = 5:1 R_f (PE-EtOAc = 5:1): 0.31

[a] Preparation from 4-chloro-1*H*-pyrrolo[2,3-*b*]pyridine is described in S. Benoit, S. Gingras, N. Soundararajan, PCT Int. Appl. 2003, WO 2003082289 A1 20031009. The beige solid was obtained in 78 % yield.
[b] Solidifies upon storage in refrigerator.

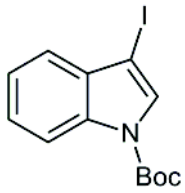
Table 1 (continuation). *Experimental details for the synthesis of N-Boc 3-iodo (aza)indoles* ***1a-k*** *and N-Boc 4-iodo imidazole* ***1n****.*

Entry	Azaindole	3-Iodo azaindole	*N*-Boc 3-Iodo azaindole **1** (isolated yield %)	Chromatographic purification (eluent) R_f (eluent)
10	611 mg (4.10 mmol) 4-Methoxy-7*H*-pyrrolo[2,3-*d*]pyrimidine[a]	Pale yellow solid 897 mg (3.26 mmol, 80 %)	Colorless solid 1.12 g (2.98 mmol, 91 %) Total yield: 73 %  **1j**	PE-EtOAc = 5:1 R_f (PE-EtOAc = 5:1): 0.38
11	966 mg (5.00 mmol) 4-(2-Methoxyethoxy)-7*H*-pyrrolo[2,3-*d*]pyrimidine[b]	Pale yellow solid 1.33 g (4.15 mmol, 83 %) For Boc-protection: 1.26 g (3.95 mmol)	Pale yellow oil 1.55 g (3.70 mmol, 94 %) Total yield: 78 %  **1k**	PE-EtOAc = 5:1 → 4:1 R_f (PE-EtOAc = 5:1): 0.22
12		2.06 g (10.0 mmol) 4(5)-Iodo-1*H*-imidazole (*ABCR*)	Yellow oil 2.71 g (9.23 mmol, 92 %)[c]  **1n**	PE-EtOAc = 20:1 R_f (PE-EtOAc = 20:1): 0.16

[a] Preparation from 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine as described for 4-methoxy-7-azaindole in S. Benoit, S. Gingras, N. Soundararajan, PCT Int. Appl. 2003, WO 2003082289 A1 20031009. The colorless solid was obtained in 76 % yield.
[b] Preparation from 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine upon refluxing with 2.5 equivs of Cs_2CO_3 in 2-methoxyethanol (*c* = 0.2 M) as a colorless solid in 85 % yield.
[c] The isomer, *tert*-butyl 5-iodo-1*H*-imidazole-1-carboxylate, was obtained along with **1n** as a yellow solid in 4 % yield (123 mg, 0.42 mmol).

2.4. Spectroscopic data of compounds 1a-k and 1n

2.4.1. tert-Butyl 3-iodo-1*H*-indole-1-carboxylate (1a)



$C_{13}H_{14}INO_2$

343.16

11.3 g (32.9 mmol, 63 % yield over two steps) as a pale brown oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.66 (s, 9 H), 7.28-7.32 (m, 1 H), 7.33-7.36 (m, 1 H), 7.36-7.40 (m, 1 H), 7.72 (s, 1 H), 8.12 (d, *J* = 7.3 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 28.1 (CH_3), 65.4 (C_{quat}), 84.2 (C_{quat}), 115.0 (CH), 121.4 (CH), 123.3 (CH), 125.3 (CH), 130.0 (CH), 132.0 (C_{quat}), 134.8 (C_{quat}), 148.6 (C_{quat}). EI + MS (*m/z* (%)): 343 (M^+, 14), 287 ($(M-C_4H_9+H)^+$, 59), 270 ($(M-C_4H_9O+H)^+$, 6), 243 ($(M-C_5H_9O_2+H)^+$, 79), 116 ($C_8H_6N^+$, 30), 115 ($C_8H_5N^+$, 22), 88 (10), 57 ($C_4H_9^+$, 100), 41 (13). Anal. calcd for $C_{13}H_{14}INO_2$ (343.2): C 45.50, H 4.11, N 4.08. Found: C 45.24, H 4.30, N 3.89.

Data reported in the literature:

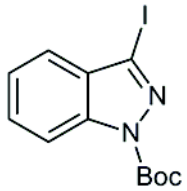
B. Witulski, N. Buschmann, U. Bergsträßer, *Tetrahedron* **2000**, *56*, 8473-8480.

Colorless solid (*n*-pentane). Mp 36-40 °C. ^{1}H NMR (400 MHz): δ 1.68 (s, 9 H), 7.29-7.43 (m, 3 H), 7.73 (s, 1 H), 8.13 (d, *J* = 8.1 Hz, 1 H). ^{13}C NMR (100 MHz): δ 28.1 (q), 65.4 (s), 115.1 (d), 121.5 (d), 123.3 (d), 125.3 (d), 130.1 (d), 132.1 (s), 134.9 (s), 148.7 (s). EI + MS (*m/z* (%)): 343 (M^+, 69), 287 (100), 270 (13), 243 (98), 116 (28), 57 (98). Anal. calcd for $C_{13}H_{14}INO_2$ (343.2): C 45.50, H 4.11, N 4.08. Found: C 45.37, H 3.66, N 3.96.

T. A. Kelly, D. W. McNeil, J. M. Rose, E. David, C.-K. Shih, P. M. Grob, *J. Med. Chem*. **1997**, *40*, 2430-2433.

^{1}H NMR ($CDCl_3$): δ 1.69 (s, 9 H), 7.20-7.41 (m, 3 H), 7.72 (s, 1 H), 8.15 (d, *J* = 5.0 Hz, 1 H).

2.4.2. tert-Butyl 3-iodo-1*H*-indazole-1-carboxylate (1b)



$C_{12}H_{13}IN_2O_2$

344.15

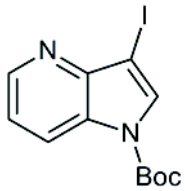
6.26 g (18.2 mmol, 80 % yield over two steps) as a colorless solid. Mp 117 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.73 (s, 9 H), 7.34-7.39 (m, 1 H), 7.47-7.51 (m, 1 H), 7.56-7.61 (m, 1 H), 8.11 (d, *J* = 8.5 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 28.1 (CH_3), 85.4 (C_{quat}), 102.9 (C_{quat}), 114.5 (CH), 121.9 (CH), 124.1 (CH), 129.9 (CH), 130.1 (C_{quat}), 139.5 (C_{quat}), 148.3 (C_{quat}). EI + MS (*m/z* (%)): 344 (M^+, 21), 244 ((M-C_4H_9+H-CO_2)$^+$, 100), 117 ($C_7H_5N_2^+$, 13), 58 (11), 57 ($C_4H_9^+$, 61), 43 (14). Anal. calcd for $C_{12}H_{13}IN_2O_2$ (344.2): C 41.88, H 3.81, N 8.14. Found: C 42.11, H 4.03, N 8.01.

Data reported in the literature:

J. Vazquez, S. K. De, L.-H. Chen, M. Riel-Mehan, A. Emdadi, J. Cellitti, J. L. Stebbins, M. F. Rega, M. Pellecchia, *J. Med. Chem.* **2008**, *51*, 3460-3465.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.72 (s, 9 H), 7.37 (t, *J* = 8.1 Hz, 1 H), 7.49 (d, *J* = 8.1 Hz, 1 H), 7.58 (t, *J* = 7.5 Hz, 1 H), 8.11 (d, *J* = 8.7 Hz, 1 H). MS (*m/z*): 367 (M+Na)$^+$, 345 (M+H)$^+$, 310, 289, 244, 124, 74, 56. HRMS calcd for $C_{12}H_{14}IN_2O_2$ (M+H): 345.0100. Found 345.0095.

2.4.3. tert-Butyl 3-iodo-1*H*-pyrrolo[3,2-*b*]pyridine-1-carboxylate (1c)

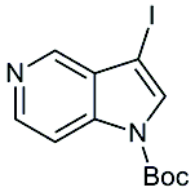


$C_{12}H_{13}IN_2O_2$

344.15

1.88 g (5.45 mmol, 55 % yield over two steps) as a colorless solid. Mp 125 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.68 (s, 9 H), 7.30 (dd, *J* = 8.5 Hz, *J* = 4.7 Hz, 1 H), 7.98 (s, 1 H), 8.4 (br, 1 H), 8.62 (dd, *J* = 4.7 Hz, *J* = 1.6 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 28.1 (CH_3), 67.7 (C_{quat}), 85.2 (C_{quat}), 119.9 (CH), 122.6 (CH), 128.3 (C_{quat}), 132.8 (CH), 146.4 (CH), 147.9 (C_{quat}), 148.2 (C_{quat}). EI + MS (*m/z* (%)): 344 (M^+, 33), 288 ($(M-C_4H_9+H)^+$, 85), 244 ($(M-C_4H_9+H-CO_2)^+$, 81), 57 ($C_4H_9^+$, 100). Anal. calcd for $C_{12}H_{13}IN_2O_2$ (344.2): C 41.88, H 3.81, N 8.14. Found: C 42.04, H 4.06, N 8.04.

2.4.4. tert-Butyl 3-iodo-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (1d)



$C_{12}H_{13}IN_2O_2$

344.15

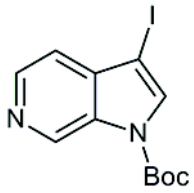
1.85 g (5.36 mmol, 64 % yield over two steps) as a colorless solid. Mp 119 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.68 (s, 9 H), 7.73 (s, 1 H), 7.95 (br, 1 H), 8.54 (d, *J* = 5.7 Hz, 1 H), 8.71 (s, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 28.0 (CH_3), 62.1 (C_{quat}), 85.5 (C_{quat}), 109.5 (CH), 128.1 (C_{quat}), 130.8 (CH), 139.7 (C_{quat}), 144.5 (CH), 145.1 (CH), 148.0 (C_{quat}). EI + MS (*m/z* (%)): 344 (M^+, 11), 288 ((M-C_4H_9+H)$^+$, 36), 244 ((M-C_4H_9+H-CO_2)$^+$, 65), 117 ($C_7H_5N_2^+$, 15), 116 ($C_7H_4N_2^+$, 7), 57 ($C_4H_9^+$, 100), 41 (13). Anal. calcd for $C_{12}H_{13}IN_2O_2$ (344.2): C 41.88, H 3.81, N 8.14. Found: C 42.13, H 3.82, N 8.13.

Data reported in the literature:

M. Lefoix, J.-P. Daillant, S. Routier, J.-Y. Mérour, I. Gillaizeau, G. Coudert, *Synthesis* **2005**, 3581-3588.

White solid. R_f (PE-EtOAc = 6:4): 0.3. Mp 127-128 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.68 (s, 9 H, $C(CH_3)_3$), 7.73 (s, 1 H, H-2), 7.95 (dd, *J* = 5.7 Hz, *J* = 0.9 Hz, 1 H, H-6), 8.55 (d, *J* = 5.7 Hz, 1 H, H-7), 8.71 (d, *J* = 0.9 Hz, 1 H, H-4). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 28.2 ($C(CH_3)_3$), 62.2 (C-I), 85.7 ($C(CH_3)_3$), 109.7 (CH-6), 128.3 (C_{quat}), 131.0 (CH-2), 139.8 (C_{quat}), 144.6 (CH-4), 145.1 (CH-7), 148.2 (*t*-BuOOC). EI + MS (*m/z* (%)): 345 (MH^+, 92), 289 ((MH-*t*-Bu)$^+$, 100), 245 ((MH-Boc)$^+$, 29). IR (KBr): $\tilde{\nu}$ 2982 cm^{-1}, 1746, 1168. HRMS (EI) *m/z* calcd for $C_{12}H_{13}IN_2O_2$: 344.00218; found: 344.0021.

2.4.5. tert-Butyl 3-iodo-1*H*-pyrrolo[2,3-*c*]pyridine-1-carboxylate (1e)

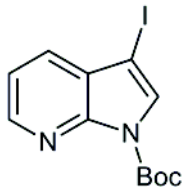


$C_{12}H_{13}IN_2O_2$

344.15

7.52 g (21.9 mmol, 59 % yield over two steps) as a pale yellow solid. Mp 149-150 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.70 (s, 9 H), 7.38 (d, *J* = 5.4 Hz, 1 H), 7.90 (s, 1 H), 8.51 (d, *J* = 5.4 Hz, 1 H), 9.37 (s, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 28.0 (CH_3), 63.4 (C_{quat}), 85.9 (C_{quat}), 115.8 (CH), 131.8 (C_{quat}), 133.5 (CH), 136.8 (CH), 138.3 (C_{quat}), 141.8 (CH), 147.7 (C_{quat}). EI + MS (*m/z* (%)): 344 (M^+, 13), 288 ($(M-C_4H_9+H)^+$, 27), 244 ($(M-C_4H_9+H-CO_2)^+$, 100), 117 ($C_7H_5N_2^+$, 22), 116 ($C_7H_4N_2^+$, 11), 90 (10), 57 ($C_4H_9^+$, 100), 41 (13). Anal. calcd for $C_{12}H_{13}IN_2O_2$ (344.2): C 41.88, H 3.81, N 8.14. Found: C 42.13, H 3.93, N 8.01.

2.4.6. tert-Butyl 3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (1f)



$C_{12}H_{13}IN_2O_2$

344.15

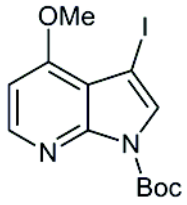
31.6 g (91.8 mmol, 92 % yield over two steps) as a yellow oil (solidified upon storage in refrigerator). Mp 79 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.66 (s, 9 H), 7.22 (dd, *J* = 7.9 Hz, *J* = 4.7 Hz, 1 H), 7.61 (dd, *J* = 7.9 Hz, *J* = 1.6 Hz, 1 H), 7.78 (s, 1 H), 8.50 (dd, *J* = 4.7 Hz, *J* = 1.6 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 27.4 (CH_3), 61.3 (C_{quat}), 83.8 (C_{quat}), 118.5 (CH), 124.3 (C_{quat}), 128.9 (CH), 129.9 (CH), 145.3 (CH), 146.0 (C_{quat}), 146.6 (C_{quat}). EI + MS (*m/z* (%)): 344 (M^+, 4), 245 (8), 244 ((M-$C_5H_9O_2$+H)$^+$, 100), 117 ($C_7H_5N_2^+$, 23), 116 ($C_7H_4N_2^+$, 10), 90 (10), 57 ($C_4H_9^+$, 26).

Data reported in the literature:

T. A. Kelly, D. W. McNeil, J. M. Rose, E. David, C.-K. Shih, P. M. Grob, *J. Med. Chem*. **1997**, *40*, 2430-2433.

^{1}H NMR ($CDCl_3$): δ 1.70 (s, 9 H), 7.28 (dd, *J* = 8.5 Hz, 1 H), 7.72 (dd, *J* = 8.1 Hz, 1 H), 7.80 (s, 1 H), 8.49 (dd, *J* = 5.1 Hz, 1 H).

2.4.7. tert-Butyl 3-iodo-4-methoxy-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (1g)

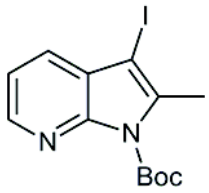


$C_{13}H_{15}IN_2O_3$

374.17

428 mg (1.14 mmol, 65 % yield over two steps) as a colorless solid. Mp 122 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.65 (s, 9 H), 3.99 (s, 3 H), 6.67 (d, J = 5.7 Hz, 1 H), 7.63 (s, 1 H), 8.40 (d, J = 5.7 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 28.0 (CH_3), 54.6 (C_{quat}), 55.5 (CH_3), 84.6 (C_{quat}), 101.0 (CH), 112.8 (C_{quat}), 129.7 (CH), 146.8 (C_{quat}), 147.8 (CH), 149.0 (C_{quat}), 160.1 (C_{quat}). EI + MS (*m/z* (%)): 374 (M^+, 5), 301 ((M-$C_4H_9O)^+$, 2), 274 ((M-$C_5H_9O_2$+H)$^+$, 61), 273 ((M-$C_5H_9O_2$)$^+$, 13), 259 ((M-$C_5H_9O_2$+H-CH_3)$^+$, 9), 243 ((M-$C_5H_9O_2$+H-OCH_3)$^+$, 2), 231 ((M-I-CH_3)$^+$, 8), 131 ($C_7H_3N_2O^+$, 15), 117 ($C_7H_5N_2^+$, 18), 116 ($C_7H_4N_2^+$, 21), 77 (11), 57 ($C_4H_9^+$, 100), 43 ($C_2H_3O^+$, 12), 41 ($C_2H_3N^+$, 53), 39 ($C_3H_3^+$, 13). Anal. calcd for $C_{13}H_{15}IN_2O_3$ (374.2): C 41.73, H 4.04, N 7.49. Found: C 41.89, H 3.91, N 7.23.

2.4.8. tert-Butyl 3-iodo-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (1h)

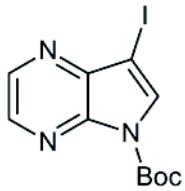


$C_{13}H_{15}IN_2O_2$

358.17

5.58 g (15.6 mmol, 88 % yield over two steps) as a yellow oil (solidified upon storage in refrigerator). Mp 47 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.69 (s, 9 H), 2.69 (s, 3 H), 7.21 (dd, *J* = 7.9 Hz, *J* = 4.7 Hz, 1 H), 7.61 (dd, *J* = 7.9 Hz, *J* = 1.9 Hz, 1 H), 8.43 (dd, *J* = 5.0 Hz, *J* = 1.6 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 17.9 (CH_3), 28.1 (CH_3), 67.1 (C_{quat}), 84.8 (C_{quat}), 119.1 (CH), 124.4 (C_{quat}), 128.7 (CH), 138.3 (C_{quat}), 145.0 (CH), 148.1 (C_{quat}), 148.8 (C_{quat}). EI + MS (*m/z* (%)): 358 (M^+, 19), 285 ($(M-C_4H_9O)^+$, 4), 258 ($(M-C_5H_9O_2+H)^+$, 100), 158 ($(M-C_4H_9O-I)^+$, 2), 131 ($C_8H_7N_2^+$, 13), 57 ($C_4H_9^+$, 55), 41 ($C_2H_3N^+$, 11). Anal. calcd for $C_{13}H_{15}IN_2O_2$ (358.2): C 43.59, H 4.22, N 7.82. Found: C 43.59, H 4.45, N 7.63.

2.4.9. tert-Butyl 7-iodo-5*H*-pyrrolo[2,3-*b*]pyrazine-5-carboxylate (1i)

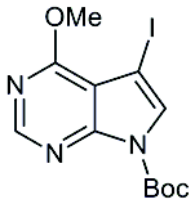


$C_{11}H_{12}IN_3O_2$

345.14

2.53 g (7.33 mmol, 75 % yield over two steps) as a pale yellow solid. Mp 128 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.69 (s, 9 H), 8.12 (s, 1 H), 8.46 (d, J = 2.5 Hz, 1 H), 8.60 (d, J = 2.5 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 28.0 (CH_3), 64.2 (C_{quat}), 85.8 (C_{quat}), 134.4 (CH), 139.8 (CH), 141.1 (C_{quat}), 141.3 (CH), 141.8 (C_{quat}), 146.4 (C_{quat}). EI + MS (*m/z* (%)): 345 (M^+, 23), 245 ((M-C_4H_9+H-CO_2)$^+$, 100), 57 ($C_4H_9^+$, 85), 41 (13). Anal. calcd for $C_{11}H_{12}IN_3O_2$ (345.1): C 38.28, H 3.50, N 12.17. Found: C 38.31, H 3.62, N 12.11.

2.4.10. tert-Butyl 5-iodo-4-methoxy-7*H*-pyrrolo[2,3-*d*]pyrimidine-7-carboxylate (1j)

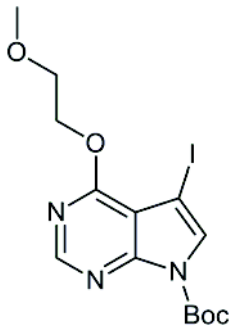


$C_{12}H_{14}IN_3O_3$

375.16

1.12 g (2.98 mmol, 73 % yield over two steps) as a colorless solid. Mp 98-99 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.67 (s, 9 H), 4.15 (s, 3 H), 7.63 (s, 1 H), 8.65 (s, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 27.9 (CH_3), 53.9 (CH_3), 54.9 (C_{quat}), 85.6 (C_{quat}), 109.1 (C_{quat}), 129.4 (CH), 146.2 (C_{quat}), 152.4 (C_{quat}), 153.6 (CH), 163.1 (C_{quat}). EI + MS (*m/z* (%)): 375 (M^+, 7), 276 (9), 275 ($(M-C_5H_9O_2+H)^+$, 100), 274 ($(M-C_5H_9O_2)^+$, 15), 246 (10), 234 (10), 148 ($C_7H_6N_3O^+$, 7), 118 ($C_6H_4N_3^+$, 8), 57 ($C_4H_9^+$, 50). Anal. calcd for $C_{12}H_{14}IN_3O_3$ (375.2): C 38.42, H 3.76, N 11.20. Found: C 38.46, H 3.85, N 11.32.

2.4.11. *tert*-Butyl 4-(2-methoxyethoxy)-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine-7-carboxylate (1k)

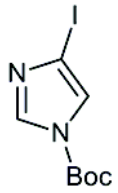


$C_{14}H_{18}IN_3O_4$

419.21

1.55 g (3.70 mmol, 78 % yield over two steps) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.67 (s, 9 H), 3.49 (s, 3 H), 3.84-3.88 (m, 2 H), 4.67-4.71 (m, 2 H), 7.62 (s, 1 H), 8.62 (s, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 27.9 (CH_3), 55.1 (C_{quat}), 59.3 (CH_3), 66.0 (CH_2), 70.4 (CH_2), 85.6 (C_{quat}), 109.0 (C_{quat}), 129.4 (CH), 146.2 (C_{quat}), 152.5 (C_{quat}), 153.5 (CH), 162.6 (C_{quat}). EI + MS (*m/z* (%)): 419 (M^+, 1), 319 ((M-$C_5H_9O_2$+H)$^+$, 3), 261 ($C_6H_4IN_3O^+$, 6), 88 (13), 70 (13), 61 (16), 45 ($C_2H_5O^+$, 15), 43 (100). Anal. calcd for $C_{14}H_{18}IN_3O_4$ (419.2): C 40.11, H 4.33, N 10.02. Found: C 40.41, H 4.55, N 9.81.

2.4.12. tert-Butyl 4-iodo-1*H*-imidazole-1-carboxylate (1n)

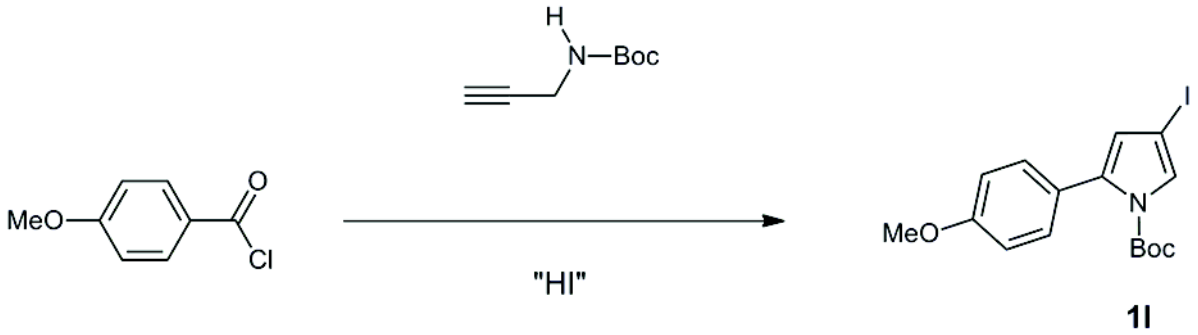


$C_8H_{11}IN_2O_2$

294.09

2.71 g (9.23 mmol, 92 % yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.62 (s, 9 H), 7.47 (d, *J* = 1.3 Hz, 1 H), 7.95 (d, *J* = 1.3 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 27.8 (CH_3), 84.3 (C_{quat}), 86.5 (C_{quat}), 122.8 (CH), 138.1 (CH), 145.7 (C_{quat}). EI + MS (*m/z* (%)): 295 (8), 294 (M^+, 62), 238 ($(M-C_4H_9+H)^+$, 12), 221 ($(M-C_4H_9O)^+$, 28), 194 ($(M-C_5H_9O_2+H)^+$, 64), 166 ($(M-I+H)^+$, 18), 59 (10), 58 (19), 57 ($C_4H_9^+$, 100), 41 (64). Anal. calcd for $C_8H_{11}IN_2O_2$ (294.1): C 32.67, H 3.77, N 9.53. Found: C 32.95, H 4.07, N 9.35.

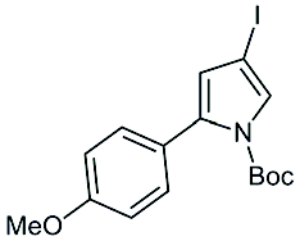
2.5. Preparation of tert-butyl 4-iodo-2-(4-methoxy-phenyl)-1H-pyrrole-1-carboxylate (1l)[3]



1l

$PdCl_2(PPh_3)_2$ (425 mg, 0.60 mmol, 2 mol %) and CuI (233 mg, 1.20 mmol, 4 mol %) were placed under argon atmosphere in a dry screw-cap vessel. Then, 150 mL of dry THF were added and the mixture was degassed with argon. Dry triethylamine (4.16 mL, 30.0 mmol, 1.00 equiv), 4-methoxybenzoyl chloride (5.28 g, 30.0 mmol), and *tert*-butyl prop-2-ynylcarbamate (4.66 g, 30.0 mmol, 1.00 equiv) were successively added to the mixture which was stirred at room temperature for 1 h (monitored by TLC). Then, sodium iodide (22.7 g, 150 mmol, 5.00 equiv), toluene-4-sulfonic acid monohydrate (11.6 g, 60.0 mmol, 2.00 equiv) and 30 ml of *tert*-butanol were successively added to the mixture which was stirred at room temperature for 1 h (monitored by TLC). The reaction mixture was diluted with 300 mL brine, the phases were separated and the aqueous phase was extracted with dichloromethane (3 x 150 mL). The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuo the residue was absorbed onto Celite® and purified chromatographically on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl acetate (PE-EtOAc = 100:1) to give 9.23 g (23.1 mmol, 77 % yield) of the desired product (**1l**) as a colorless solid.

tert-Butyl 4-iodo-2-(4-methoxyphenyl)-1_H_-pyrrole-1-carboxylate (1l)



$C_{16}H_{18}INO_3$

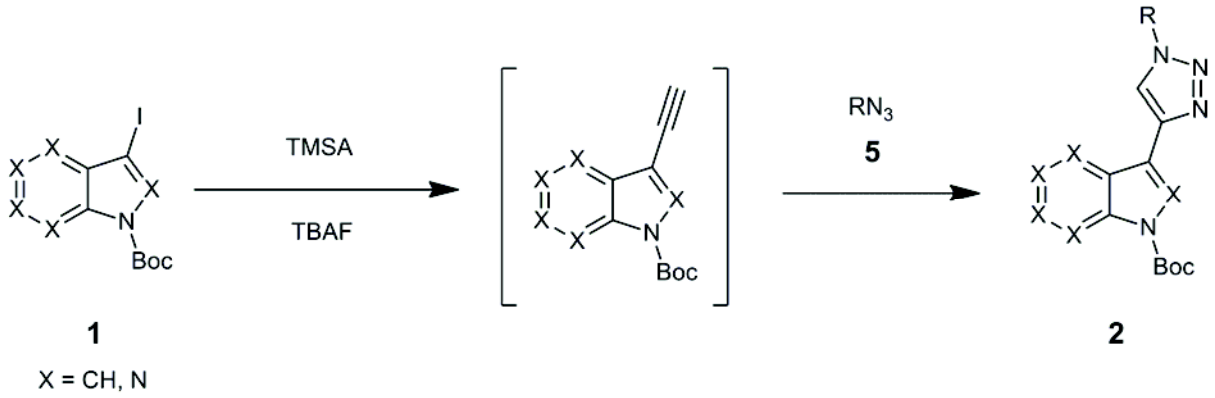
399.22

1.46 g (3.66 mmol, 73 % yield) as a colorless solid. Mp 71-72 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.39 (s, 9 H), 3.82 (s, 3 H), 6.20 (d, J = 1.9 Hz, 1 H), 6.88 (d, J = 8.8 Hz, 1 H), 7.24 (d, J = 8.8 Hz, 1 H), 7.39 (d, J = 1.9 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 27.6 (CH_3), 55.3 (CH_3), 64.4 (C_{quat}), 84.2 (C_{quat}), 113.1 (CH), 120.3 (CH), 125.3 (C_{quat}), 126.7 (CH), 130.4 (CH), 136.5 (C_{quat}), 147.9 (C_{quat}), 159.3 (C_{quat}). EI + MS (*m/z* (%)): 399 (M^+, 3), 343 ($(M-C_4H_9+H)^+$, 11), 299 ($(M-C_5H_9O_2+H)^+$, 16), 298 ($(M-C_5H_9O_2)^+$, 13), 171 ($(M-C_5H_9O_2-I)^+$, 6), 156 (12), 128 (11), 57 ($C_4H_9^+$, 100), 41 (34). IR (KBr): $\tilde{\nu}$ 3145 (m) cm^{-1}, 2986 (m), 2934 (w), 2832 (w), 1734 (s), 1609 (m), 1576 (w), 1557 (w), 1511 (s), 1476 (m), 1460 (m), 1435 (w), 1370 (s), 1337 (s), 1293 (s), 1251 (s), 1180 (s), 1151 (s), 1108 (m), 1032 (s), 985 (m), 904 (m), 847 (s), 833 (m), 808 (s), 771 (m), 675 (w), 629 (w), 615 (w), 594 (m), 528 (w), 511 (w). Anal. calcd for $C_{16}H_{18}INO_3$ (399.2): C 48.14, H 4.54, N 3.51. Found: C 48.36, H 4.37, N 3.34.

3 Multicomponent Syntheses of Triazolyl Substituted *N*-Boc protected *NH*-Heterocycles 2a-s

3.1. Three-component Sonogashira coupling □ TMS-deprotection □ CuAAC sequence

3.1.1. General procedure for the preparation of compounds 2a-o



1

X = CH, N

2

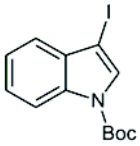
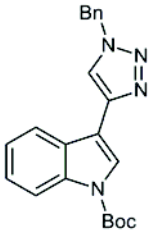
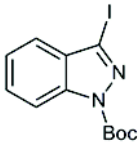
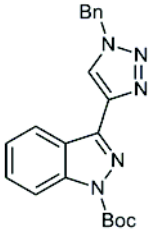
$PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol, 2 mol %) and CuI (8 mg, 0.04 mmol, 4 mol %) were placed in a dry screw-cap Schlenk vessel with septum. Then, 1.00 mmol of *N*-Boc iodo *NH*-heterocycle **1** was added in 5 mL of dry tetrahydrofuran under argon atmosphere and the reaction mixture was degassed with argon. After that, trimethylsilylacetylene (0.21 mL, 1.50 mmol, 1.50 equiv) and dry triethylamine (0.28 mL, 2.00 mmol, 2.00 equiv) were added and the mixture was stirred at room temperature (water bath) until the complete consumption of the starting material (monitored by TLC). Then, 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (1.50 mL, 1.50 mmol, 1.50 equiv) was added dropwise and the mixture was stirred at room temperature for 0.5 h until the deprotection was complete (monitored by TLC). After that, benzyl azide (**5a**) (136 mg, 1.00 mmol, 1.00 equiv) in 1 mL of dry methanol* was added and the mixture was stirred at room temperature until the complete conversion to the product (monitored by TLC). After removal of the solvents in vacuo the residue was absorbed onto Celite® and purified chromatographically on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl

acetate to give the *N*-Boc protected triazoles **2**. The obtained compounds were not characterized but directly deprotected in the next step.

* For the synthesis of compound **2g** 2 mL of phenyl azide solution (~ 0.5 *M* in TBME) (**5b**) (1.00 mmol, 1.00 equiv) were added, followed by the addition of 1 mL of dry methanol.

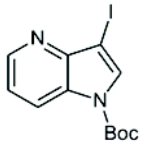
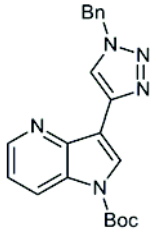
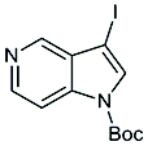
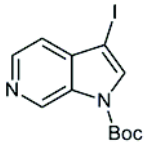
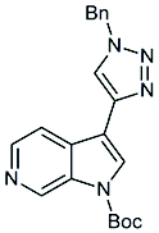
The experimental details are depicted in ***Table 1***.

Table 1. Experimental details of the three-component *Sonogashira*-CuAAC sequence for the synthesis of *N*-Boc protected (aza)indolyl triazoles **2a**-**b**.

Entry	*N*-Boc iodo *NH*-heterocycle **1**	Reaction time[a] 1st step 2nd step	*N*-Boc protected (aza)indolyl triazole **2**	Chromatographic purification (eluent) R_f (eluent)
1	343 mg (1.00 mmol)  **1a**	1 h 4 d	Beige-yellow solid 280 mg (0.75 mmol, 75 %)  **2a**	PE-EtOAc = 5:1
2	688 mg (2.00 mmol)  **1b**	2 h 24 h	Pale beige solid 538 mg (1.43 mmol, 72 %)  **2b**	PE-EtOAc = 5:1 R_f (PE-EtOAc = 5:1) = 0.13

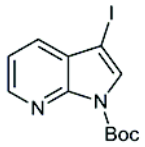
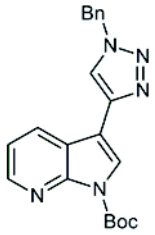
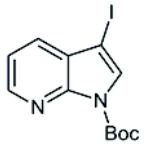
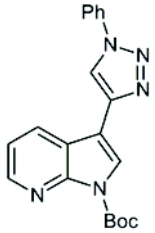
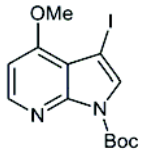
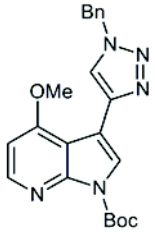
[a] The reaction times are not optimized and might be shorter than indicated.

Table 1 (continuation). Experimental details of the three-component *Sonogashira*-CuAAC sequence for the synthesis of *N*-Boc protected (aza)indolyl triazoles **2c**-**e**.

Entry	*N*-Boc iodo *NH*-heterocycle **1**	Reaction time[a] 1st step 2nd step	*N*-Boc protected (aza)indolyl triazole **2**	Chromatographic purification (eluent)
3	344 mg (1.00 mmol)  **1c**	1 h 3 d	Pale yellow solid 230 mg (0.61 mmol, 61 %)  **2c**	PE-EtOAc = 3:1
4	344 mg (1.00 mmol)  **1d**	1 h 24 h	Colorless solid 207 mg (0.55 mmol, 55 %)  **2d**	PE-EtOAc = 1:1
5	344 mg (1.00 mmol)  **1e**	1 h 24 h	Pale yellow oil 218 mg (0.58 mmol, 58 %)  **2e**	PE-EtOAc = 1:1

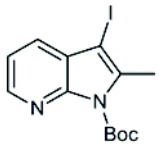
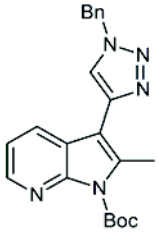
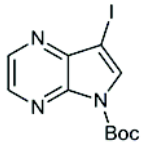
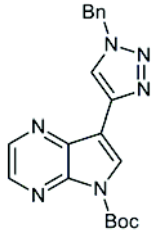
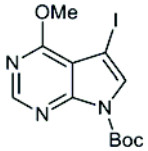
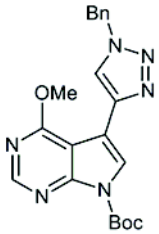
[a] The reaction times are not optimized and might be shorter than indicated.

Table 1 (continuation). Experimental details of the three-component *Sonogashira*-CuAAC sequence for the synthesis of *N*-Boc protected (aza)indolyl triazoles **2f**-**h**.

Entry	*N*-Boc iodo *NH*-heterocycle **1**	Reaction time[a] 1st step 2nd step	*N*-Boc protected (aza)indolyl triazole **2**	Chromatographic purification (eluent) R_f (eluent)
6	1.72 g (5.00 mmol)  **1f**	1 h 40 h	Yellow foam 1.56 g (4.15 mmol, 83 %)[b]  **2f**	PE-EtOAc = 2:1 R_f (PE-EtOAc = 2:1): 0.20
7	344 mg (1.00 mmol)  **1f**	1 h 66 h	Yellow foam 254 mg (0.70 mmol, 70 %)  **2g**	PE-EtOAc = 3:1
8	374 mg (1.00 mmol)  **1g**	1 h 64 h	Pale yellow solid 219 mg (0.54 mmol, 54 %)  **2h**	PE-EtOAc = 1:1 → 1:2

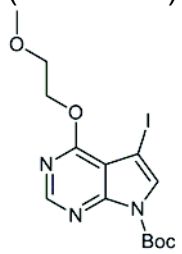
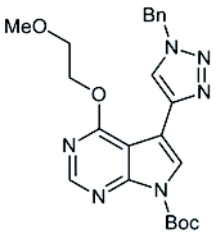
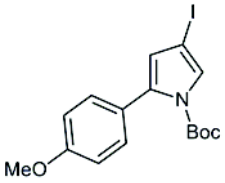
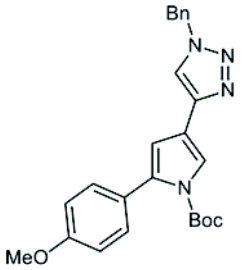
[a] The reaction times are not optimized and might be shorter than indicated.
[b] On a 1.00 mmol scale, 295 mg (0.79 mmol, 79 % yield) of a yellow foam were obtained.

Table 1 (continuation). Experimental details of the three-component *Sonogashira*-CuAAC sequence for the synthesis of *N*-Boc protected (aza)indolyl triazoles **2i**-**k**.

Entry	*N*-Boc iodo *NH*-heterocycle **1**	Reaction time[a] 1st step 2nd step	*N*-Boc protected (aza)indolyl triazole **2**	Chromatographic purification (eluent)
9	716 mg (2.00 mmol)  **1h**	23 h 119 h	Pale yellow solid 462 mg (1.19 mmol, 59 %)  **2i**	PE-EtOAc = 3:1
10	345 mg (1.00 mmol)  **1i**	1 h 48 h	Colorless solid 211 mg (0.56 mmol, 56 %)  **2j**	PE-EtOAc = 2:1
11	375 mg (1.00 mmol)  **1j**	1 h 72 h	Yellow solid 297 mg (0.73 mmol, 73 %)  **2k**	PE-EtOAc = 1:1

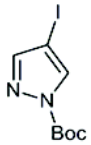
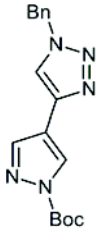
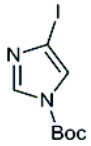
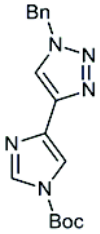
[a] The reaction times are not optimized and might be shorter than indicated.

Table 1 (continuation). Experimental details of the three-component *Sonogashira*-CuAAC sequence for the synthesis of *N*-Boc protected (aza)indolyl triazole **2l** and pyrrolyl triazole **2m**.

Entry	*N*-Boc iodo *NH*-heterocycle **1**	Reaction time[a] 1st step 2nd step	*N*-Boc protected (aza)indolyl or pyrrolyl triazole **2**	Chromatographic purification (eluent)
12	720 mg (1.72 mmol)  **1k**	1 h 87 h	Pale yellow foam 341 mg (0.97 mmol, 57 %)  **2l**	PE-EtOAc = 1:1
13	399 mg (1.00 mmol)  **1l**	2 h 115 h	Yellow oil 224 mg (0.52 mmol, 52 %)  **2m**	PE-EtOAc = 3:1

[a] The reaction times are not optimized and might be shorter than indicated.

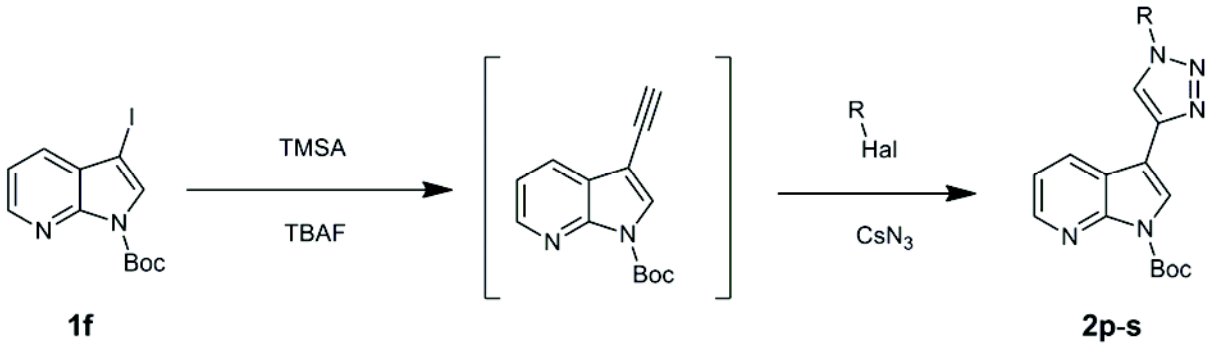
Table 1 (continuation). Experimental details of the three-component *Sonogashira*-CuAAC sequence for the synthesis of *N*-Boc protected azolyl triazoles **2n**-**o**.

Entry	*N*-Boc iodo *NH*-heterocycle **1**	Reaction time[a] 1st step 2nd step	*N*-Boc protected azolyl triazole **2**	Chromatographic purification (eluent)
14	294 mg (1.00 mmol) *tert*-Butyl 4-iodo-1*H*-pyrazole-1-carboxylate (*ABCR*)  **1m**	3 h 63 h	Yellow-orange oil 208 mg (0.64 mmol, 64 %)  **2n**	PE-EtOAc = 1:1
15	294 mg (1.00 mmol)  **1n**	15 d 23 h	Yellow oil 99 mg (0.30 mmol, 30 %)  **2o**	PE-EtOAc = 1:1

[a] The reaction times are not optimized and might be shorter than indicated.

3.2. Four-component Sonogashira coupling □ TMS-deprotection □ Azide-Halide exchange □ CuAAC sequence

3.2.1. General procedure for the preparation of compounds 2p-s

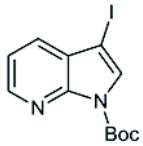
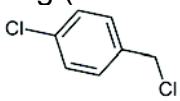
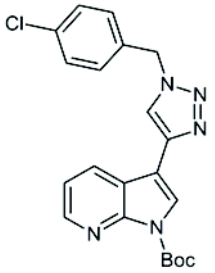
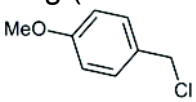
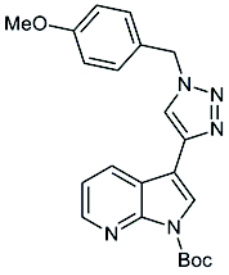


1f **2p-s**

$PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol, 2 mol %) and CuI (8 mg, 0.04 mmol, 4 mol %) were placed in a dry screw-cap Schlenk vessel with septum. Then, *tert*-butyl 3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (**1f**) (344 mg, 1.00 mmol) was added in 5 mL of dry tetrahydrofuran under argon atmosphere and the reaction mixture was degassed with argon. After that, trimethylsilylacetylene (0.21 mL, 1.50 mmol, 1.50 equiv) and dry triethylamine (0.28 mL, 2.00 mmol, 2.00 equiv) were added and the mixture was stirred at room temperature (water bath) until the complete consumption of the starting material (monitored by TLC). Then, 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (1.50 mL, 1.50 mmol, 1.50 equiv) was added dropwise and the mixture was stirred at room temperature for 0.5 h until the deprotection was complete (monitored by TLC). After that, cesium azide (175 mg, 1.00 mmol, 1.00 equiv) and an organic halide (1.00 mmol, 1.00 equiv) in 1 mL of dry methanol were added and the mixture was stirred at room temperature until the complete conversion to the product (monitored by TLC). After removal of the solvents in vacuo the residue was absorbed onto Celite® and purified chromatographically on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl acetate to give the *N*-Boc protected 7-azaindolyl triazoles **2p**-**s**. The obtained compounds were not characterized but used as obtained in the subsequent deprotection step.

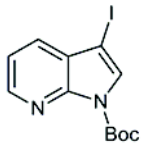
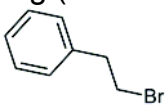
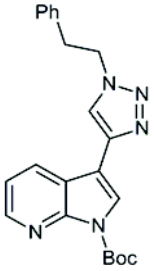
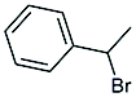
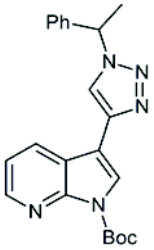
The experimental details are depicted in ***Table 3***.

Table 3. Experimental details of the four-component *Sonogashira* coupling – TMS-deprotection – azide-halide exchange – CuAAC sequence for the synthesis of indolyl triazoles **2p**-**s**.

Entry	*N*-Boc 3-iodo 7-azaindole **1f** In situ generated azide **5**	Reaction time[a] 1st step 2nd step	*N*-Boc protected 7-azaindolyl triazole **2**	Chromatographic purification (eluent)
1	688 mg (2.00 mmol)  **1f** 350 mg (2.00 mmol) CsN_3 (*Aldrich*) 322 mg (2.00 mmol)  (*Merck*) **5c**	1 h 51 h	Pale yellow solid 444 mg (1.08 mmol, 54 %)  **2p**	PE-EtOAc = 2:1
2	344 mg (1.00 mmol) **1f** 175 mg (1.00 mmol) CsN_3 163 mg (1.00 mmol)  (*ABCR*) **5d**	1 h 72 h	Yellow foam 295 mg (0.73 mmol, 73 %)  **2q**	PE-EtOAc = 2:1

[a] The reaction times are not optimized and might be shorter than indicated.

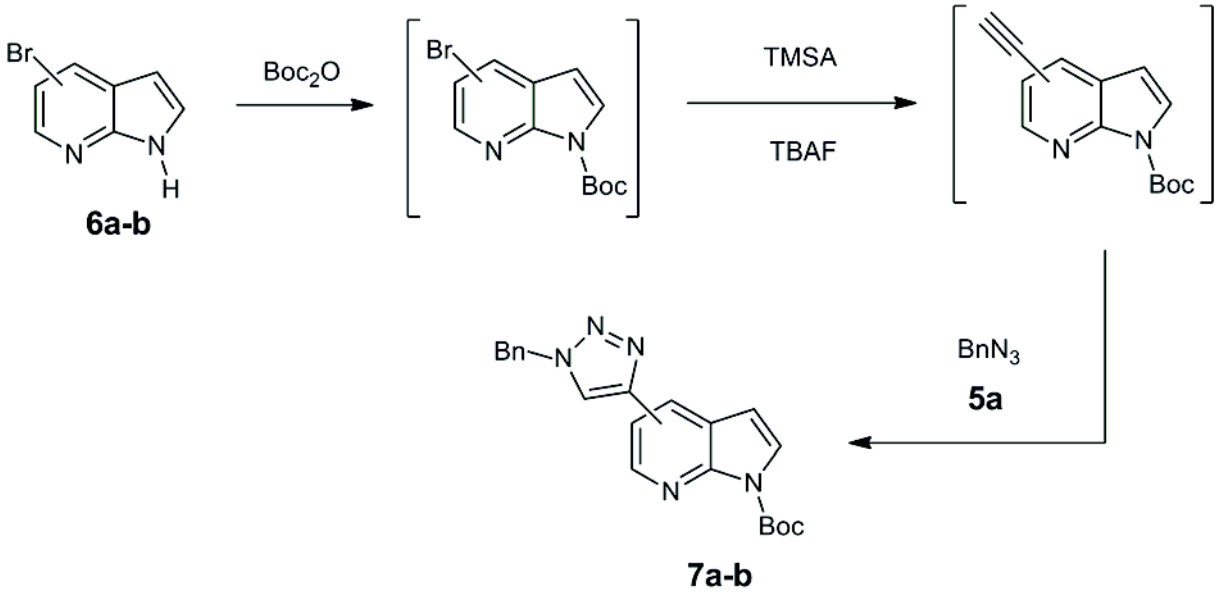
Table 3. Experimental details of the three-component *Sonogashira*-CuAAC sequence for the synthesis of indolyl triazoles **2p**-**s**.

Entry	*N*-Boc 3-iodo 7-azaindole **1** In situ generated azide **5**	Reaction time[a] 1st step 2nd step	*N*-Boc protected 7-azaindolyl triazole **2**	Chromatographic purification (eluent)
3	344 mg (1.00 mmol)  **1f** 175 mg (1.00 mmol) CsN_3 (*Aldrich*) 189 mg (1.00 mmol)  (*Merck*) **5e**	1 h 111 h	Yellow oil 269 mg (0.69 mmol, 69 %)  **2r**	PE-EtOAc = 2:1
4	344 mg (1.00 mmol) **1f** 175 mg (1.00 mmol) CsN_3 (*Aldrich*) 191 mg (1.00 mmol)  (*ABCR*) **5f**	1 h 64 h	Yellow oil 250 mg (0.64 mmol, 64 %)  **2s**	PE-EtOAc = 2:1

[a] The reaction times are not optimized and might be shorter than indicated.

3.3. Four-component Boc-protection Sonogashira coupling TMS-deprotection CuAAC sequence

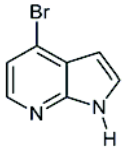
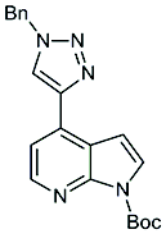
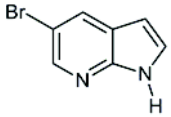
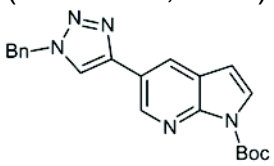
3.3.1. General procedure for the preparation of compounds 7a-b



1.00 mmol of a bromo-7-azaindole **6** was placed under argon atmosphere in a dry screw-cap Schlenk vessel with septum. Then, di-*tert*-butyl dicarbonate (338 mg, 1.50 mmol, 1.50 equiv) in 1 mL of dry 1,4-dioxane and 4-dimethylaminopyridine (12 mg, 0.10 mmol, 10 mol %) were added under argon atmosphere and the reaction mixture was stirred at room temperature (water bath) for 15 min until the complete consumption of the starting material (evolution of a gas ceased, monitored by TLC). After that, 1 mL of dry methanol was added and the mixture was degassed with argon. Then, $PdCl_2(PhCN)_2$ (8 mg, 0.02 mmol, 2 mol %), $[^tBu_3PH]BF_4$ (12 mg, 0.04 mmol, 4 mol %), CuI (8 mg, 0.04 mmol, 4 mol %), trimethylsilylacetylene (0.21 mL, 1.50 mmol, 1.50 equiv), and dry triethylamine (0.28 mL, 2.00 mmol, 2.00 equiv) were added subsequently and the mixture was stirred at room temperature until the complete consumption of the starting material (monitored by TLC). Then, 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (1.50 mL, 1.50 mmol, 1.50 equiv) was added dropwise and the mixture was stirred at room temperature for 0.5 h until the deprotection was complete (monitored by TLC). After that, benzyl azide (**5a**) (136 mg, 1.00 mmol, 1.00 equiv) in 1 mL of dry methanol was added and the mixture was stirred at room temperature until the complete conversion to the product (monitored by TLC). After removal of the solvents in vacuo the residue was absorbed onto Celite® and purified chromatographically on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl acetate to give the *N*-Boc protected 7-azaindolyl triazole **7**. The obtained compound was not characterized but used as obtained in the subsequent deprotection step.

The experimental details are depicted in ***Table 4***.

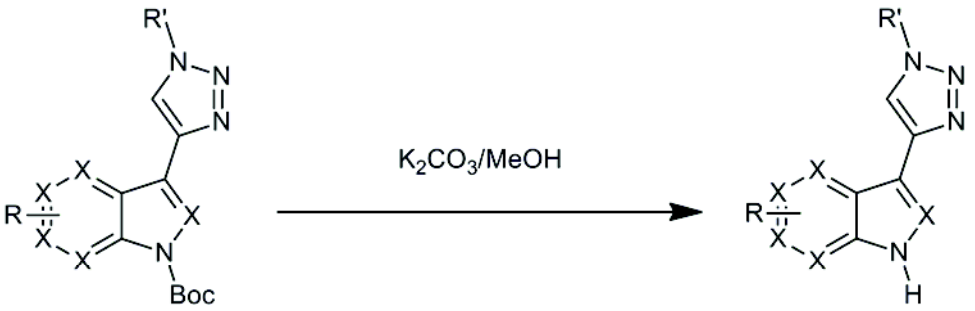
Table 4. Experimental details for the four-component Boc-protection – *Sonogashira* coupling – TMS-deprotection – CuAAC sequence for the synthesis of *N*-Boc protected 7-azaindolyl triazoles **7a**-**b**.

Entry	Bromo-7-azaindole **6**	Reaction time[a] 2nd step[b] 3rd step[c]	*N*-Boc protected 7-azaindolyl triazole **7** (isolated yield %)	Chromatographic purification (eluent)
1	205 mg (1.00 mmol)  (4-Bromo-7-azaindole) (*Aldrich*) **6a**	1 h 18 h	Yellow oil 311 mg (0.83 mmol, 83 %)  **7a**	PE-EtOAc = 1:1
2	203 mg (1.00 mmol)  (5-Bromo-7-azaindole) (*Aldrich*) **6b**	5 h 4 d	Yellow oil 373 mg (0.99 mmol, 99 %)  **7b**	PE-EtOAc = 2:1

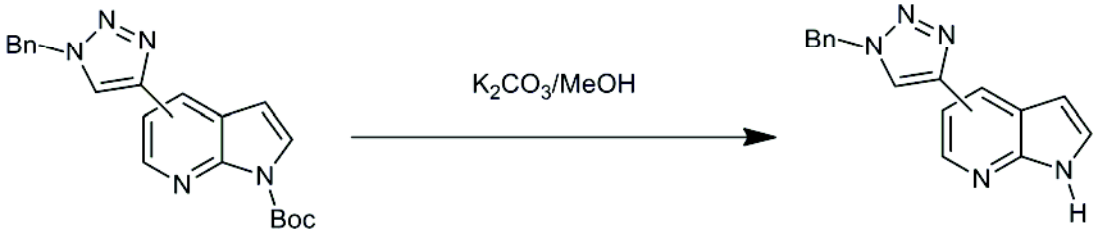
[a] The reaction times are not optimized and might be shorter than indicated.
[b] 2nd step: Sonogashira coupling with TMSA.
[c] 3rd step: CuAAC with benzyl azide (**5a**).

4. Deprotection of *N*-Boc Protected Triazolyl *NH*-Heterocycles

4.1. General procedure for the preparation of compounds 8a-s and 9a-b



2a-s **8a-s**



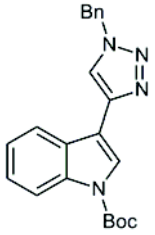
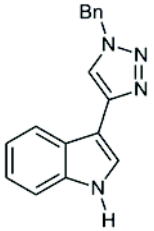
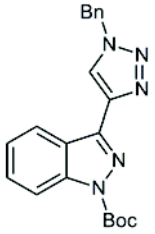
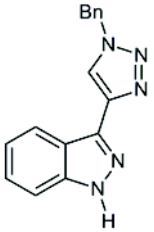
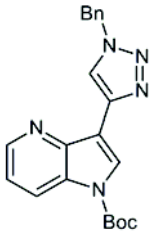
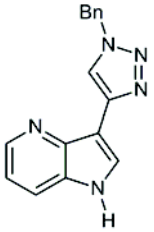
7a-b **9a-b**

N-Boc protected triazolyl heterocycle **2** or **7** was placed in methanol (c = 0.2 M). Then, 2.50 equiv of potassium carbonate were added and the mixture was stirred at room temperature (water bath) or 50 °C (for compounds **2a** and **2i**, preheated oil bath) for 1 h* (monitored by TLC). Frequently, a precipitate was formed. The mixture was adsorbed on Celite® and purified chromatographically on silica gel with dichloromethane-methanol-aqueous ammonia. After drying in vacuo at 70 °C overnight, analytically pure triazoles **8** or **9** were obtained. The products can be further purified by suspension in dichloromethane and sonication in ultrasound bath for 0.5-1 h, filtration and drying in vacuo at 70 °C overnight.

* 5 h for compound **2m**.

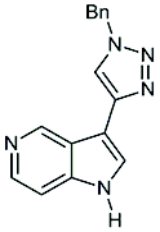
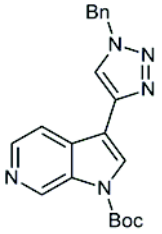
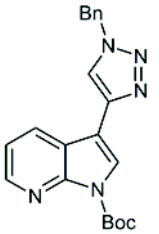
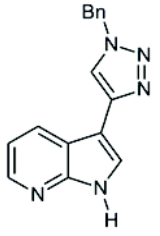
The experimental details are given in ***Table 5***, ***Table 6***, and ***Table 7***.

Table 5. Experimental details for the deprotection of *N*-Boc (aza)indolyl triazoles **8a-c**.

Entry	*N*-Boc protected (aza)indolyl triazole **2**	(Aza)indolyl triazole **8** (isolated yield %)	Chromatographic purification (eluent) UV purity
1	280 mg (0.75 mmol)  **2a**	Pale yellow solid[a] 147 mg (0.54 mmol, 72 %) Total yield: 54 %  **8a**	$DCM-MeOH-NH_3$ = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 HT-LC-MS: 100 %
2	404 mg (1.08 mmol)  **2b**	Colorless solid 264 mg (0.96 mmol, 89 %) Total yield: 64 %  **8b**	$DCM-MeOH-NH_3$ = 100:1:1 HT-LC-MS: 100 %[b]
3	230 mg (0.61 mmol)  **2c**	Colorless solid 137 mg (0.50 mmol, 81 %) Total yield: 50 %  **8c**	$DCM-MeOH-NH_3$ = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 HT-LC-MS: 100 %

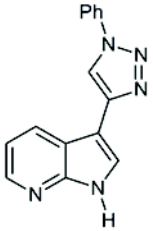
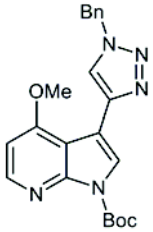
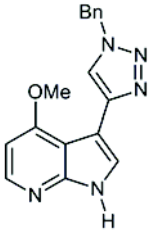
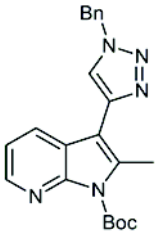
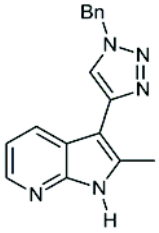
[a] Deprotection was performed at 50 °C for 1 h.
[b] Additionally purified by suspension in DCM and sonication in ultrasound bath.

Table 5 (continuation). Experimental details for the deprotection of *N*-Boc (aza)indolyl triazoles **8d**-**f**.

Entry	*N*-Boc protected (aza)indolyl triazole **2**	(Aza)indolyl triazole **8** (isolated yield %)	Chromatographic purification (eluent) UV purity
4	149 mg (0.40 mmol)  **2d**	Colorless solid 95 mg (0.35 mmol, 86 %) Total yield: 48 %  **8d**	$DCM-MeOH-NH_3$ = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 → 100:6:1 → 100:7:1 HT-LC-MS: 100 %[a]
5	149 mg (0.40 mmol)  **2e**	Pale yellow solid 93 mg (0.34 mmol, 85 %) Total yield: 50 %  **8e**	$DCM-MeOH-NH_3$ = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 → 100:6:1 → 100:7:1 HT-LC-MS: 99.9 %[a]
6	1.56 g (4.15 mmol)  **2f**	Colorless solid 930 mg (3.38 mmol, 81 %) Total yield: 67 %[b]  **8f**	$DCM-MeOH-NH_3$ = 100:1:1 → 100:2:1 → 100:3:1 HT-LC-MS: 100 %[a]

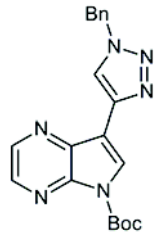
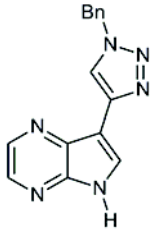
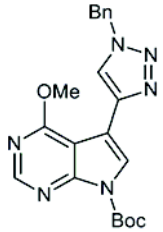
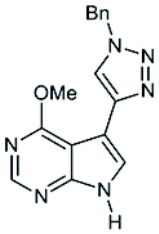
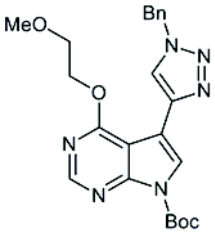
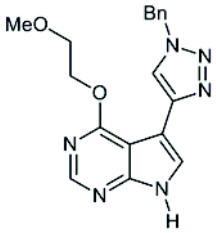
[a] Additionally purified by suspension in DCM and sonication in ultrasound bath.
[b] On a 1.00 mmol scale, 179 mg (0.65 mmol, 65 % yield over two steps) were obtained as a colorless solid.

Table 5 (continuation). Experimental details for the deprotection of *N*-Boc (aza)indolyl triazoles **8g-i**.

Entry	*N*-Boc protected (aza)indolyl triazole **2**	(Aza)indolyl triazole **8** (isolated yield %)	Chromatographic purification (eluent) UV purity
7	254 mg (0.70 mmol)  **2g**	Yellow solid 143 mg (0.55 mmol, 78 %) Total yield: 55 %  **8g**	$DCM-MeOH-NH_3$ = 100:1:1 → 100:2:1 → 100:3:1 HT-LC-MS: 100 %
8	162 mg (0.40 mmol)  **2h**	Yellow solid 109 mg (0.36 mmol, 89 %) Total yield: 48 %  **8h**	$DCM-MeOH-NH_3$ = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 → 100:6:1 HT-LC-MS: 100 %[a]
9	462 mg (1.19 mmol)  **2i**	Colorless solid[b] 300 mg (1.04 mmol, 87 %) Total yield: 52 %  **8i**	$DCM-MeOH-NH_3$ = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 HT-LC-MS: 100 %

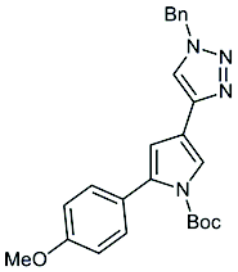
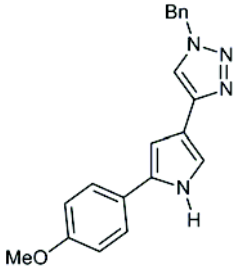
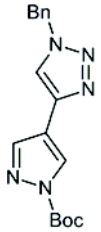
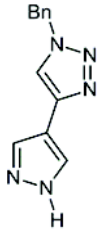
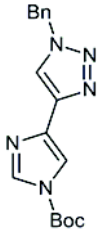
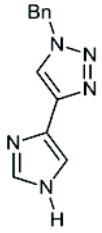
[a] Additionally purified by suspension in DCM and sonication in ultrasound bath.
[b] Deprotection was performed at 50 °C for 1 h.

Table 5 (continuation). Experimental details for the deprotection of *N*-Boc (aza)indolyl triazoles **8j**-**l**.

Entry	*N*-Boc protected (aza)indolyl triazole **2**	(Aza)ndolyl triazole **8** (isolated yield %)	Chromatographic purification (eluent) UV purity
10	152 mg (0.40 mmol)  **2j**	Colorless solid 93 mg (0.34 mmol, 83 %) Total yield: 47 %  **8j**	$DCM-MeOH-NH_3$ = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1→ 100:6:1 HT-LC-MS: 100 %
11	297 mg (0.73 mmol)  **2k**	Colorless solid 165 mg (0.54 mmol, 74 %) Total yield: 54 %  **8k**	$DCM-MeOH-NH_3$ = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 HT-LC-MS: 100 %
12	197 mg (0.56 mmol)  **2l**	Colorless solid 141 mg (0.40 mmol, 72 %) Total yield: 41 %  **8l**	$DCM-MeOH-NH_3$ = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 HT-LC-MS: 100 %[a]

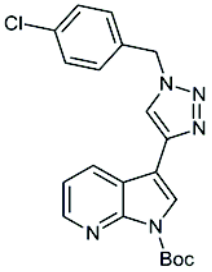
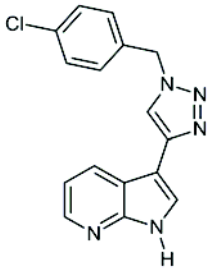
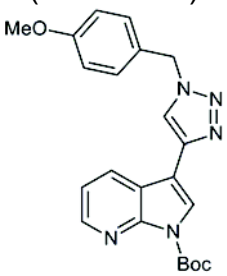
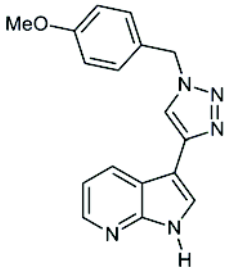
[a] Additionally purified by suspension in DCM and sonication in ultrasound bath.

Table 5 (continuation). Experimental details for the deprotection of *N*-Boc azolyl triazoles **8m**-**o**.

Entry	*N*-Boc protected azolyl triazole **2**	Azolyl triazole **8** (isolated yield %)	Chromatographic purification (eluent) UV purity
13	224 mg (0.52 mmol)  **2m**	Pale yellow solid[a] 147 mg (0.44 mmol, 85 %) Total yield: 44 %  **8m**	$DCM-MeOH-NH_3$ = 100:1:1 HT-LC-MS: 100 %
14	208 mg (0.64 mmol)  **2n**	Colorless solid 86 mg (0.38 mmol, 60 %) Total yield: 38 %  **8n**	$DCM-MeOH-NH_3$ = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 → 100:6:1 → 100:7:1 HT-LC-MS: 100 %
15	99 mg (0.30 mmol)  **2o**	Colorless solid 46 mg (0.20 mmol, 68 %) Total yield: 20 %  **8o**	$DCM-MeOH-NH_3$ = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 → 100:6:1 → 100:7:1 HT-LC-MS: 100 %

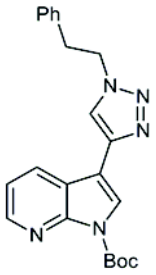
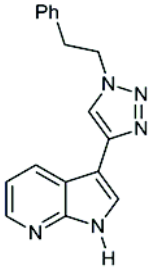
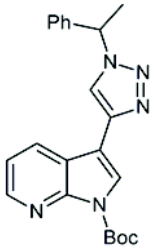
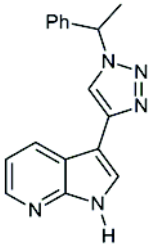
[a] Deprotection was performed at room temperature for 5 h.

Table 6. Experimental details for the deprotection of *N*-Boc 7-azaindolyl triazoles **8p-q**.

Entry	*N*-Boc protected 7-azaindolyl triazole **2**	7-Azaindolyl triazole **8** (isolated yield %)	Chromatographic purification (eluent) UV purity
16	347 mg (0.85 mmol)  **2p**	Colorless solid 218 mg (0.70 mmol, 83 %) Total yield: 45 %  **8p**	DCM-MeOH-NH_3 = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 → 100:6:1 → 100:7:1 HT-LC-MS: 100 %[a]
17	295 mg (0.73 mmol)  **2q**	Colorless solid 179 mg (0.58 mmol, 80 %) Total yield: 58 %  **8q**	DCM-MeOH-NH_3 = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 HT-LC-MS: 100 %[a]

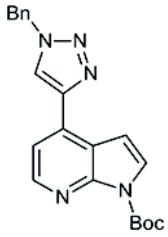
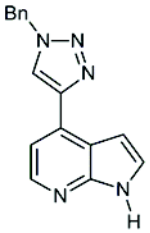
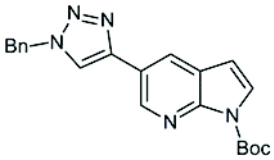
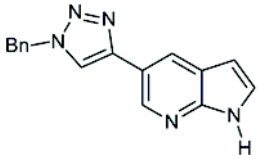
[a] Additionally purified by suspension in DCM and sonication in ultrasound bath.

Table 6 (continuation). Experimental details for the deprotection of *N*-Boc 7-azaindolyl triazoles **8r**-**s**.

Entry	*N*-Boc protected 7-azaindolyl triazole **2**	7-Azaindolyl triazole **8** (isolated yield %)	Chromatographic purification (eluent) UV purity
18	269 mg (0.69 mmol)  **2r**	Colorless solid 179 mg (0.62 mmol, 90 %) Total yield: 62 %  **8r**	DCM-MeOH-NH_3 = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 → 100:6:1 → 100:7:1 HT-LC-MS: 100 %[a]
19	250 mg (0.64 mmol)  **2s**	Pale yellow solid 160 mg (0.55 mmol, 86 %) Total yield: 55 %  **8s**	DCM-MeOH-NH_3 = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 HT-LC-MS: 100 %[a]

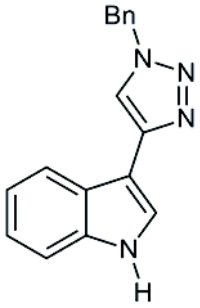
[a] Additionally purified by suspension in DCM and sonication in ultrasound bath.

Table 7. Experimental details for the Boc-deprotection of 7-azaindolyl triazoles **9a**-**b**.

Entry	*N*-Boc protected 7-azaindolyl triazole **7**	7-Azaindolyl triazole **9** (isolated yield %)	Chromatographic purification (eluent) UV purity
20	311 mg (0.83 mmol)  **7a**	Colorless solid 207 mg (0.75 mmol, 91 %) Total yield: 75 %  **9a**	$DCM-MeOH-NH_3$ = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 HT-LC-MS: 100 %
21	373 mg (0.99 mmol)  **7b**	Colorless solid 182 mg (0.66 mmol, 66 %) Total yield: 66 %  **9b**	$DCM-MeOH-NH_3$ = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 HT-LC-MS: 100 %

4.2. Spectroscopic data of compounds 8a-s and 9a-b

4.2.1. 3-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-1*H*-indole (8a)

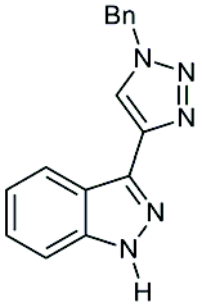


$C_{17}H_{14}N_4$

274.32

147 mg (0.54 mmol, 54 % yield over two steps) as a pale yellow solid. Mp 171 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 5.64 (s, 2 H), 7.08-7.12 (m, 1 H), 7.13-7.18 (m, 1 H), 7.31-7.36 (m, 1 H), 7.36-7.41 (m, 4 H), 7.42-7.45 (m, 1 H), 7.79 (d, *J* = 2.5 Hz, 1 H), 8.03 (d, *J* = 7.9 Hz, 1 H), 8.49 (s, 1 H), 11.3 (br, 1 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 52.8 (CH_2), 106.1 (C_{quat}), 111.8 (CH), 119.5 (CH), 119.6 (CH), 119.9 (CH), 121.6 (CH), 123.1 (CH), 124.6 (C_{quat}), 127.9 (CH), 128.1 (CH), 128.8 (CH), 136.3 (C_{quat}), 136.3 (C_{quat}), 142.9 (C_{quat}). EI + MS (*m/z* (%)): 275 (9), 274 (M^+, 44), 246 (47), 245 (100), 219 (11), 218 (50), 217 (16), 169 ($C_{10}H_7N_3^+$, 31), 155 (46), 129 (10), 128 (43), 127 (10), 117 (16), 115 (12), 101 (26), 91 ($C_7H_7^+$, 43), 77 ($C_6H_5^+$, 14), 65 ($C_5H_5^+$, 12). IR (KBr): $\tilde{\nu}$ 3397 (s) cm^{-1}, 1624 (w), 1601 (w), 1497 (w), 1456 (m), 1337 (w), 1221 (m), 1099 (w), 1053 (w), 939 (w), 776 (w), 749 (m), 727 (m), 586 (w), 522 (w). Anal. calcd for $C_{17}H_{14}N_4$ (274.3): C 74.43, H 5.14, N 20.42. Found: C 74.31, H 4.91, N 20.36.

4.2.2. 3-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-1*H*-indazole (8b)

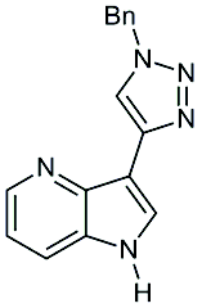


$C_{16}H_{13}N_5$

275.31

264 mg (0.96 mmol, 64 % yield over two steps) as a colorless solid. Further purified by suspension in DCM and sonication in ultrasound bath. Mp 164 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 5.70 (s, 2 H), 7.19-7.23 (m, 1 H), 7.31-7.43 (m, 6 H), 7.55-7.59 (m, 1 H), 8.29 (d, *J* = 8.2 Hz, 1 H), 8.69 (d, *J* = 0.9 Hz, 1 H), 13.24 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 52.9 (CH_2), 110.2 (CH), 120.2 (C_{quat}), 120.9 (CH), 121.4 (CH), 121.7 (CH), 126.4 (CH), 127.9 (CH), 128.1 (CH), 128.7 (CH), 136.0 (C_{quat}), 136.1 (C_{quat}), 140.9 (C_{quat}), 142.2 (C_{quat}). EI + MS (*m/z* (%)): 275 (M^+, 79), 246 ($(M-HN_2)^+$, 84), 219 (16), 156 ($C_9H_6N_3^+$, 79), 102 (21), 91 ($C_7H_7^+$, 100), 65 ($C_5H_5^+$, 20). IR (KBr): $\tilde{\nu}$ 3181 (s) cm^{-1}, 1624 (w), 1597 (w), 1497 (w), 1478 (w), 1457 (m), 1431 (w), 1348 (m), 1299 (w), 1241 (m), 1228 (w), 1217 (w), 1152 (w), 1133 (w), 1098 (w), 1062 (m), 1046 (w), 1003 (w), 965 (w), 904 (w), 819 (w), 773 (w), 750 (s), 715 (s), 584 (w). Anal. calcd for $C_{16}H_{13}N_5$ (275.3): C 69.80, H 4.76, N 25.44. Found: C 69.68, H 4.63, N 25.50.

4.2.3. 3-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-1*H*-pyrrolo[3,2-*b*]pyridine (8c)

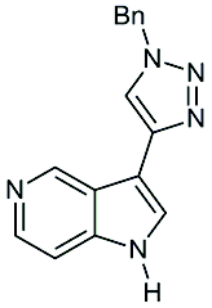


$C_{16}H_{13}N_5$

275.31

137 mg (0.50 mmol, 50 % yield over two steps) as a colorless solid. Mp 246 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 5.69 (s, 2 H), 7.18 (dd, *J* = 8.2 Hz, *J* = 4.7 Hz, 1 H), 7.30-7.36 (m, 1 H), 7.36-7.41 (m, 4 H), 7.83 (dd, *J* = 8.2 Hz, *J* = 1.3 Hz, 1 H), 8.1 (br, 1 H), 8.40 (dd, *J* = 4.7 Hz, *J* = 1.3 Hz, 1 H), 8.61 (s, 1 H), 11.6 (br, 1 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 52.7 (CH_2), 106.5 (C_{quat}), 116.9 (CH), 119.1 (CH), 120.5 (CH), 125.6 (CH), 128.0 (CH), 128.1 (CH), 128.8 (CH), 129.0 (C_{quat}), 136.4 (C_{quat}), 140.9 (C_{quat}), 142.5 (C_{quat}), 142.8 (CH). EI + MS (*m/z* (%)): 275 (M^+, 21), 247 (20), 246 ($(M-HN_2)^+$, 100), 219 (19), 156 ($C_9H_6N_3^+$, 76), 149 (23), 143 (20), 129 (26), 102 (16), 97 (11), 91 ($C_7H_7^+$, 46), 89 (13), 85 (11), 84 (14), 83 (11), 77 ($C_6H_5^+$, 15), 71 (14), 69 (10), 65 ($C_5H_5^+$, 11), 57 (18), 55 (11), 43 (13). IR (KBr): $\tilde{\nu}$ 3163 (s) cm^{-1}, 3047 (m), 1628 (s), 1561 (w), 1497 (w), 1457 (w), 1413 (s), 1362 (m), 1335 (w), 1314 (w), 1277 (w), 1221 (w), 1200 (w), 1123 (w), 1106 (w), 1085 (w), 1051 (s), 943 (w), 889 (w), 776 (s), 718 (s), 697 (w), 613 (w), 580 (w), 508 (w). Anal. calcd for $C_{16}H_{13}N_5$ (275.3): C 69.80, H 4.76, N 25.44. Found: C 69.85, H 4.94, N 25.34.

4.2.4. 3-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine (8d)

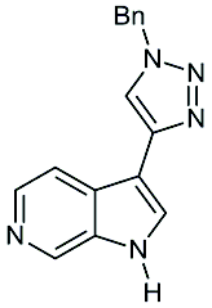


$C_{16}H_{13}N_5$

275.31

95 mg (0.35 mmol, 48 % yield over two steps) as a colorless solid. Mp 195 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 5.66 (s, 2 H), 7.31-7.37 (m, 1 H), 7.37-7.41 (m, 4 H), 7.43 (d, *J* = 5.7 Hz, *J* = 0.6 Hz, 1 H), 7.89 (s, 1 H), 8.24 (d, *J* = 5.7 Hz, 1 H), 8.60 (s, 1 H), 9.33 (s, 1 H), 11.7 (br, 1 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 52.9 (CH_2), 106.0 (C_{quat}), 107.0 (CH), 120.3 (CH), 121.7 (C_{quat}), 124.0 (CH), 127.9 (CH), 128.1 (CH), 128.7 (CH), 136.1 (C_{quat}), 139.7 (C_{quat}), 140.5 (CH), 141.9 (C_{quat}), 143.0 (CH). EI + MS (*m/z* (%)): 276 (19), 275 (M^+, 100), 248 (14), 247 (86), 246 ($(M\text{-}HN_2)^+$, 87), 220 (19), 219 (53), 170 (27), 156 ($C_9H_6N_3^+$, 61), 129 (38), 102 (13), 91 ($C_7H_7^+$, 99), 75 (13), 65 ($C_5H_5^+$, 22). IR (KBr): $\tilde{\nu}$ 3088 (s) cm^{-1}, 2975 (s), 2694 (s), 1627 (s), 1597 (s), 1578 (s), 1494 (w), 1464 (s), 1341 (m), 1299 (w), 1244 (m), 1212 (m), 1167 (w), 1117 (w), 1053 (m), 1026 (m), 938 (w), 901 (w), 854 (w), 806 (m), 769 (w), 716 (s), 693 (m), 650 (w), 631 (w), 596 (w), 505 (w). Anal. calcd for $C_{16}H_{13}N_5$ (275.3): C 69.80, H 4.76, N 25.44. Found: C 69.85, H 4.77, N 25.31.

4.2.5. 3-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-1*H*-pyrrolo[2,3-*c*]pyridine (8e)

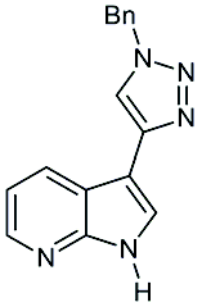


$C_{16}H_{13}N_5$

275.31

93 mg (0.34 mmol, 50 % yield over two steps) as a pale yellow solid. Further purified by suspension in DCM and sonication in ultrasound bath. Mp 226 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 5.66 (s, 2 H), 7.31-7.42 (m, 5 H), 7.98 (d, *J* = 5.4 Hz, 1 H), 8.03 (s, 1 H), 8.20 (d, *J* = 5.4 Hz, 1 H), 8.55 (s, 1 H), 8.80 (s, 1 H), 11.8 (br, 1 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 52.9 (CH_2), 105.9 (C_{quat}), 114.6 (CH), 120.0 (CH), 126.9 (CH), 127.9 (CH), 128.1 (CH), 128.8 (CH), 128.8 (C_{quat}), 133.5 (C_{quat}), 134.8 (CH), 136.2 (C_{quat}), 138.3 (CH), 142.0 (C_{quat}). EI + MS (*m/z* (%)): 276 (7), 275 (M^+, 34), 247 (47), 246 ($(M-HN_2)^+$, 100), 220 (14), 219 (55), 170 (28), 156 ($C_9H_6N_3^+$, 50), 129 (39), 102 (21), 91 ($C_7H_7^+$, 68), 75 (13), 65 ($C_5H_5^+$, 18). IR (KBr): $\tilde{\nu}$ 3068 (m) cm^{-1}, 2901 (m), 1655 (w), 1628 (m), 1560 (w), 1543 (w), 1499 (m), 1459 (s), 1340 (w), 1296 (w), 1225 (s), 1173 (w), 1125 (m), 1061 (m), 1041 (m), 1028 (m), 887 (w), 810 (m), 722 (m), 711 (w), 670 (w), 596 (w). Anal. calcd for $C_{16}H_{13}N_5$ (275.3): C 69.80, H 4.76, N 25.44. Found: C 69.88, H 4.96, N 25.24.

4.2.6. 3-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (8f)

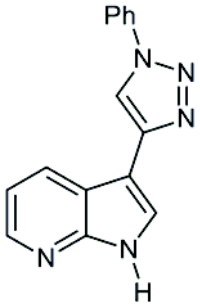


$C_{16}H_{13}N_5$

275.31

930 mg (3.38 mmol, 67 % yield over two steps) as a pale yellow solid. After suspension in dichloromethane, sonication in ultrasonic bath, filtration, and drying, a colorless solid was obtained. Mp 234-237 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 5.66 (s, 2 H), 7.17 (dd, *J* = 7.9 Hz, *J* = 4.7 Hz, 1 H), 7.32-7.43 (m, 5 H), 7.92 (d, *J* = 2.5 Hz, 1 H), 8.29 (dd, *J* = 4.7 Hz, *J* = 1.6 Hz, 1 H), 8.44 (dd, *J* = 7.9 Hz, *J* = 1.6 Hz, 1 H), 8.54 (s, 1 H), 11.9 (br, 1 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 52.8 (CH_2), 105.0 (C_{quat}), 115.9 (CH), 116.9 (C_{quat}), 119.8 (CH), 123.2 (CH), 127.8 (CH), 128.1 (CH), 128.3 (CH), 128.7 (CH), 136.1 (C_{quat}), 142.4 (C_{quat}), 143.1 (CH), 148.5 (C_{quat}). EI + MS (*m/z* (%)): 275 (M^+, 100), 248 (13), 247 (74), 246 (87), 220 (11), 219 (35), 170 (15), 156 (24), 142 (10), 129 (17), 91 ($C_7H_7^+$, 19), 44 (19). IR (KBr): $\tilde{\nu}$ 3133 (w) cm^{-1}, 1655 (w), 1626 (w), 1584 (s), 1498 (w), 1458 (m), 1420 (m), 1327 (w), 1286 (w), 1220 (m), 1130 (w), 1111 (w), 1058 (w), 941 (m), 897 (w), 799 (m), 771 (s), 722 (s), 587 (w). Anal. calcd for $C_{16}H_{13}N_5$ (275.3): C 69.80, H 4.76, N 25.44. Found: C 69.71, H 5.02, N 25.44.

4.2.7. 3-(1-Phenyl-1*H*-1,2,3-triazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (8g)



$C_{15}H_{11}N_5$

261.28

143 mg (0.55 mmol, 55 % yield over two steps) as a yellow solid. Mp 260 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.23 (dd, *J* = 7.9 Hz, *J* = 4.7 Hz, 1 H), 7.50-7.55 (m, 1 H), 7.63-7.68 (m, 2 H), 8.01-8.04 (m, 3 H), 8.34 (dd, *J* = 4.4 Hz, *J* = 0.9 Hz, 1 H), 8.58 (d, *J* = 7.9 Hz, 1 H), 9.18 (s, 1 H), 12.0 (br, 1 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 104.6 (C_{quat}), 116.1 (CH), 116.9 (C_{quat}), 117.5 (CH), 119.9 (CH), 123.6 (CH), 128.3 (CH), 128.4 (CH), 129.8 (CH), 136.7 (C_{quat}), 142.9 (C_{quat}), 143.3 (CH), 148.6 (C_{quat}). EI + MS (*m/z* (%)): 261 (M^+, 11), 234 (14), 233 ($C_5H_{11}N_3^+$, 88), 232 (100), 205 (31), 156 (43), 130 (15), 129 (15), 103 (29), 102 (19), 77 ($C_6H_5^+$, 13), 76 (11), 51 ($C_4H_3^+$, 10). IR (KBr): $\tilde{\nu}$ 3440 (s) cm^{-1}, 3080 (s), 2924 (w), 2852 (w), 1656 (w), 1623 (w), 1585 (s), 1545 (w), 1495 (m), 1460 (w), 1423 (s), 1322 (m), 1281 (m), 1236 (w), 1215 (m), 1157 (w), 1129 (w), 1113 (w), 1074 (w), 1044 (s), 993 (w), 933 (w), 895 (w), 832 (w), 799 (m), 757 (s), 692 (s), 647 (w), 626 (w), 584 (s), 538 (w), 518 (w). Anal. calcd for $C_{15}H_{11}N_5$ (261.3): C 68.95, H 4.24, N 26.80. Found: C 68.71, H 4.43, N 26.90.

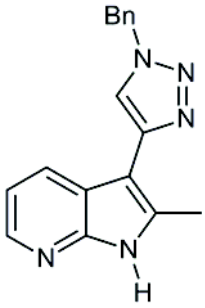
4.2.8. 3-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-4-methoxy-1*H*-pyrrolo[2,3-*b*]pyridine (8h)

$C_{17}H_{15}N_5O$

305.33

109 mg (0.36 mmol, 48 % yield over two steps) as a yellow solid. Mp 253-258 °C (dec.). ^{1}H NMR (DMSO-d$_6$, 500 MHz): δ 3.92 (s, 3 H), 5.65 (s, 2 H), 6.68 (d, *J* = 5.4 Hz, 1 H), 7.32-7.43 (m, 5 H), 7.74 (d, *J* = 2.2 Hz, 1 H), 8.12 (d, *J* = 5.4 Hz, 1 H), 8.24 (s, 1 H), 11.8 (br, 1 H, NH). ^{13}C NMR (DMSO-d$_6$, 125 MHz): δ 52.6 (CH_2), 55.3 (CH_3), 98.2 (CH), 104.7 (C_{quat}), 106.4 (C_{quat}), 121.5 (CH), 122.1 (CH), 127.9 (CH), 128.1 (CH), 128.7 (CH), 136.4 (C_{quat}), 142.0 (C_{quat}), 145.2 (CH), 150.3 (C_{quat}), 159.6 (C_{quat}). EI + MS (*m/z* (%)): 306 (21), 305 (M^+, 100), 278 (17), 277 (83), 276 (86), 262 (27), 261 (11), 250 (12), 249 (38), 234 (10), 200 (16), 186 (31), 159 (14), 156 (18), 131 (12), 129 (11), 91 ($C_7H_7^+$, 58), 65 ($C_5H_5^+$, 12). IR (KBr): $\tilde{\nu}$ 3091 (w) cm^{-1}, 3007 (w), 2940 (w), 2842 (w), 1578 (s), 1512 (w), 1498 (w), 1459 (w), 1430 (w), 1410 (w), 1321 (m), 1308 (m), 1279 (m), 1222 (w), 1150 (w), 1098 (m), 1051 (w), 974 (w), 939 (w), 852 (w), 801 (m), 726 (m), 653 (w). Anal. calcd for $C_{17}H_{15}N_5O$ (305.3): C 66.87, H 4.95, N 22.94. Found: C 66.74, H 5.15, N 22.96.

4.2.9. 3-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (8i)

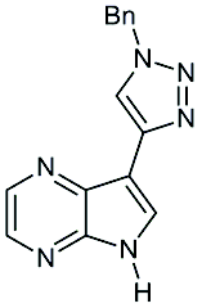


$C_{17}H_{15}N_5$

289.33

300 mg (1.04 mmol, 52 % yield over two steps) as a colorless solid. Mp 263 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 2.63 (s, 3 H), 5.67 (s, 2 H), 7.10 (dd, *J* = 7.9 Hz, *J* = 4.7 Hz, 1 H), 7.32-7.37 (m, 1 H), 7.38-7.41 (m, 4 H), 8.18 (dd, *J* = 4.7 Hz, *J* = 1.3 Hz, 1 H), 8.28 (dd, *J* = 7.6 Hz, *J* = 0.9 Hz, 1 H), 8.51 (s, 1 H), 11.8 (br, 1 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 13.0 (CH_3), 52.8 (CH_2), 101.0 (C_{quat}), 115.7 (CH), 118.5 (C_{quat}), 120.4 (CH), 126.9 (CH), 127.8 (CH), 128.0 (CH), 128.7 (CH), 134.1 (C_{quat}), 136.2 (C_{quat}), 141.8 (CH), 142.2 (C_{quat}), 147.8 (C_{quat}). EI + MS (*m/z* (%)): 289 (M^+, 64), 262 (18), 261 ($(M-N_2)^+$, 100), 260 (45), 246 (54), 233 (45), 232 (25), 231 (18), 219 (35), 184 (54), 170 (71), 157 (17), 156 (38), 155 (37), 143 (23), 132 (24), 131 (17), 130 (17), 129 (14), 116 (15), 103 (15), 102 (43), 91 ($C_7H_7^+$, 55), 65 ($C_5H_5^+$, 17). IR (KBr): $\tilde{\nu}$ 3425 (m) cm^{-1}, 3103 (w), 3035 (w), 2921 (w), 2850 (w), 1625 (w), 1585 (s), 1527 (m), 1494 (w), 1457 (m), 1417 (s), 1390 (w), 1279 (s), 1217 (s), 1138 (w), 1117 (w), 1070 (m), 1046 (w), 969 (w), 931 (s), 824 (w), 796 (m), 771 (s), 715 (s), 693 (w), 673 (m), 650 (w), 582 (w). Anal. calcd for $C_{17}H_{15}N_5$ (289.3): C 70.57, H 5.23, N 24.21. Found: C 70.33, H 5.20, N 24.25.

4.2.10. 7-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-5*H*-pyrrolo[2,3-*b*]pyrazine (8j)

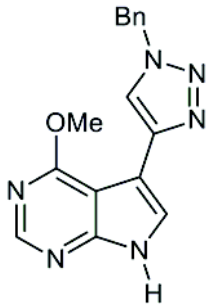


$C_{15}H_{12}N_6$

276.30

93 mg (0.34 mmol, 47 % yield over two steps) as a colorless solid. Mp 248-249 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 5.70 (s, 2 H), 7.31-7.37 (m, 1 H), 7.37-7.41 (m, 4 H), 8.31-8.35 (m, 2 H), 8.47 (d, J = 2.5 Hz, 1 H), 8.59 (s, 1 H), 12.3 (br, 1 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 52.7 (CH_2), 105.4 (C_{quat}), 120.8 (CH), 127.1 (CH), 127.9 (CH), 128.1 (CH), 128.7 (CH), 135.6 (C_{quat}), 136.2 (C_{quat}), 137.5 (CH), 138.3 (CH), 139.8 (C_{quat}), 141.7 (C_{quat}). EI + MS (*m/z* (%)): 276 (M^+, 50), 248 ($(M-N_2)^+$, 44), 247 ($(M-HN_2)^+$, 100), 220 (14), 157 ($C_8H_5N_4^+$, 48), 130 (12), 91 ($C_7H_7^+$, 39), 65 ($C_5H_5^+$, 8). IR (KBr): $\tilde{\nu}$ 3151 (s) cm^{-1}, 1632 (m), 1590 (m), 1544 (w), 1492 (m), 1456 (s), 1409 (m), 1364 (m), 1336 (s), 1221 (s), 1180 (m), 1119 (m), 1054 (m), 1038 (m), 944 (m), 908 (w), 849 (w), 799 (m), 721 (s), 694 (w), 673 (w), 628 (w), 586 (m), 540 (w). Anal. calcd for $C_{15}H_{12}N_6$ (276.3): C 65.21, H 4.38, N 30.42. Found: C 65.00, H 4.68, N 30.35.

4.2.11. 5-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-4-methoxy-7*H*-pyrrolo[2,3-*d*]pyrimidine (8k)

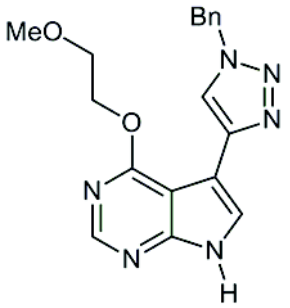


$C_{16}H_{14}N_6O$

306.32

165 mg (0.54 mmol, 54 % yield over two steps) as a colorless solid. Mp 249 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 4.07 (s, 3 H), 5.70 (s, 2 H), 7.34-7.45 (m, 5 H), 7.84 (s, 1 H), 8.38 (s, 1 H), 8.42 (s, 1 H), 12.3 (br, 1 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 52.6 (CH_2), 53.4 (CH_3), 101.4 (C_{quat}), 105.1 (C_{quat}), 121.4 (CH), 122.1 (CH), 127.9 (CH), 128.0 (CH), 128.7 (CH), 136.2 (C_{quat}), 141.0 (C_{quat}), 150.7 (CH), 152.7 (C_{quat}), 162.3 (C_{quat}). EI + MS (*m/z* (%)): 307 (7), 306 (M^+, 32), 278 ($(M-N_2)^+$, 54), 277 (90), 250 (26), 201 (13), 187 (46), 146 (14), 132 (12), 130 (22), 103 (14), 91 ($C_7H_7^+$, 100), 65 ($C_5H_5^+$, 20), 42 (11). IR (KBr): $\tilde{\nu}$ 3449 (w) cm^{-1}, 3084 (w), 2969 (w), 2923 (w), 2851 (w), 1581 (s), 1566 (s), 1476 (m), 1455 (m), 1433 (m), 1406 (w), 1376 (w), 1312 (s), 1219 (w), 1143 (w), 1091 (m), 1049 (m), 1031 (w), 962 (w), 936 (w), 880 (m), 851 (w), 798 (w), 771 (w), 720 (w), 691 (w), 671 (w), 633 (w), 575 (w). Anal. calcd for $C_{16}H_{14}N_6O$ (306.3): C 62.74, H 4.61, N 27.44. Found: C 62.78, H 4.53, N 27.67.

4.2.12. 4-(2-Methoxyethoxy)-5-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (8l)

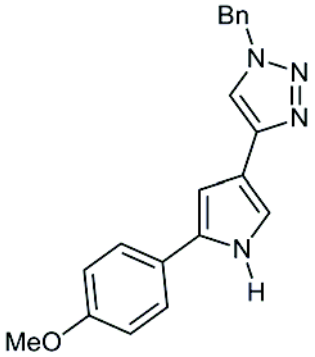


$C_{18}H_{18}N_6O_2$

350.37

141 mg (0.40 mmol, 41 % yield over two steps) as a colorless solid. Mp 240 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 3.23 (s, 3 H), 3.68-3.71 (m, 2 H), 4.57-4.60 (m, 2 H), 5.65 (s, 2 H), 7.29-7.36 (m, 3 H), 7.37-7.42 (m, 2 H), 7.85 (s, 1 H), 8.37 (s, 1 H), 8.43 (s, 1 H), 12.3 (br, 1 H, N<u>H</u>). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 52.9 (CH_2), 57.9 (CH_3), 64.7 (CH_2), 69.8 (CH_2), 101.3 (C_{quat}), 105.2 (C_{quat}), 121.5 (CH), 122.1 (CH), 127.4 (CH), 128.0 (CH), 128.8 (CH), 136.2 (C_{quat}), 141.3 (C_{quat}), 150.7 (CH), 152.8 (C_{quat}), 161.8 (C_{quat}). EI + MS (*m/z* (%)): 351 (24), 350 (M^+, 97), 322 (18), 321 (46), 264 (39), 263 (100), 236 (20), 231 (13), 201 (18), 173 (15), 161 (12), 148 (19), 146 (18), 111 (15), 109 (10), 97 (21), 95 (14), 91 ($C_7H_7^+$, 97), 85 (17), 83 (20), 81 (12), 71 (24), 69 (22), 65 ($C_5H_5^+$, 12), 59 (14), 57 (36), 55 (17), 43 (22). IR (KBr): $\tilde{\nu}$ 1578 (s) cm^{-1}, 1446 (m), 1321 (m), 1207 (w), 1143 (w), 1091 (m), 1028 (w), 905 (w), 721 (m), 629 (w). Anal. calcd for $C_{18}H_{18}N_6O_2$ (350.4): C 61.70, H 5.18, N 23.99. Found: C 61.59, H 5.22, N 24.10.

4.2.13. 1-Benzyl-4-(5-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)-1*H*-1,2,3-triazole (8m)

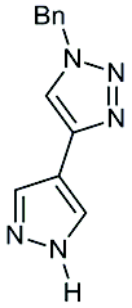


$C_{20}H_{18}N_4O$

330.38

147 mg (0.44 mmol, 44 % yield over two steps) as a pale yellow solid. Mp 238 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 3.76 (s, 3 H), 5.60 (s, 2 H), 6.70-6.72 (m, 1 H), 6.93-6.97 (m, 2 H), 7.18-7.20 (m, 1 H), 7.32-7.36 (m, 3 H), 7.37-7.41 (m, 2 H), 7.56-7.60 (m, 2 H), 8.16 (s, 1 H), 11.3 (br, 1 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 52.7 (CH_2), 55.0 (CH_3), 102.3 (CH), 114.1 (CH), 115.2 (C_{quat}), 115.8 (CH), 119.1 (CH), 124.7 (CH), 125.4 (C_{quat}), 127.8 (CH), 128.0 (CH), 128.7 (CH), 131.9 (C_{quat}), 136.2 (C_{quat}), 143.7 (C_{quat}), 157.5 (C_{quat}). EI + MS (*m/z* (%)): 331 (16), 330 (M^+, 66), 302 (40), 301 (100), 286 (11), 274 (34), 258 (12), 225 (11), 211 (36), 184 (21), 169 (13), 168 (17), 167 (13), 141 (10), 140 (12), 134 (23), 91 ($C_7H_7^+$, 48), 65 ($C_5H_5^+$, 10). IR (KBr): $\tilde{\nu}$ 3429 (s) cm^{-1}, 1655 (w), 1638 (w), 1560 (w), 1543 (w), 1501 (m), 1458 (w), 1290 (w), 1256 (m), 1051 (m), 1022 (m), 835 (m), 798 (m), 718 (m), 548 (m). Anal. calcd for $C_{20}H_{18}N_4O$ (330.4): C 72.71, H 5.49, N 16.96. Found: C 72.45, H 5.68, N 17.08.

4.2.14. 1-Benzyl-4-(1*H*-pyrazol-4-yl)-1*H*-1,2,3-triazole (8n)

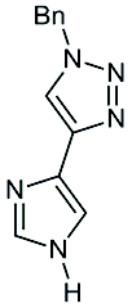


$C_{12}H_{11}N_5$

225.25

86 mg (0.38 mmol, 38 % yield over two steps) as a colorless solid. Mp 218 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 5.60 (s, 2 H), 7.31-7.35 (m, 3 H), 7.36-7.41 (m, 2 H), 7.7-8.2 (br, 2 H), 8.25 (s, 1 H), 13.0 (br, 1 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 52.8 (CH_2), 111.8 (C_{quat}), 120.2 (CH), 127.9 (CH), 128.1 (CH), 128.8 (CH), 136.0 (C_{quat}), 140.6 (C_{quat}). EI + MS (*m/z* (%)): 225 (M^+, 18), 196 ($(M-HN_2)^+$, 72), 169 (27), 167 (10), 143 (16), 106 ($C_7H_8N^+$, 96), 104 (10), 91 ($C_7H_7^+$, 100), 79 ($C_4H_3N_2^+$, 15), 65 ($C_5H_5^+$, 24), 51 ($C_4H_3^+$, 10). IR (KBr): $\tilde{\nu}$ 3122 (s) cm^{-1}, 3064 (m), 2952 (m), 2878 (m), 1630 (m), 1544 (w), 1496 (w), 1458 (m), 1390 (w), 1360 (m), 1270 (w), 1215 (m), 1142 (w), 1111 (w), 1077 (w), 1049 (m), 1018 (w), 965 (w), 934 (m), 885 (m), 830 (s), 812 (s), 717 (s), 707 (s), 669 (w), 650 (w), 624 (m), 590 (w). Anal. calcd for $C_{12}H_{11}N_5$ (225.3): C 63.99, H 4.92, N 31.09. Found: C 63.75, H 5.05, N 31.10.

4.2.15. 1-Benzyl-4-(1*H*-imidazol-4-yl)-1*H*-1,2,3-triazole (8o)

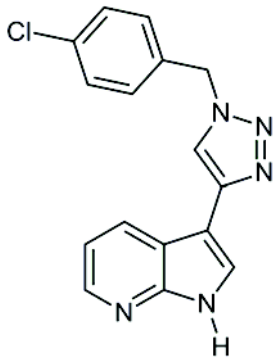


$C_{12}H_{11}N_5$

225.25

46 mg (0.20 mmol, 20 % yield over two steps) as a colorless solid. Mp 188 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 5.62 (s, 2 H), 7.29-7.41 (m, 5 H), 7.5 (br, 1 H), 7.70 (s, 1 H), 8.2 (br, 1 H), 12.2 & 12.7 (br, 1 H, NH). EI + MS (*m/z* (%)): 225 (M^+, 30), 197 ($(M-N_2)^+$, 18), 196 ($(M-HN_2)^+$, 100), 169 (37), 149 (13), 143 (10), 142 (12), 120 (16), 115 (11), 106 ($C_7H_8N^+$, 86), 105 (11), 93 (11), 92 (18), 91 ($C_7H_7^+$, 90), 85 (10), 77 ($C_6H_5^+$, 18), 71 (12), 65 ($C_5H_5^+$, 25), 57 (13), 55 (10), 52 ($C_4H_4^+$, 11), 44 (10), 43 (10), 41 (11). IR (KBr): $\tilde{\nu}$ 3113 (s) cm^{-1}, 3032 (m), 2925 (m), 2832 (m), 1655 (w), 1625 (m), 1535 (m), 1498 (w), 1458 (s), 1354 (w), 1215 (s), 1162 (w), 1121 (w), 1097 (w), 1054 (w), 1016 (w), 945 (s), 833 (m), 787 (w), 715 (s), 693 (m), 660 (w), 627 (w), 583 (w). Anal. calcd for $C_{12}H_{11}N_5$ (225.3): C 63.99, H 4.92, N 31.09. Found: C 64.08, H 5.08, N 30.85.

4.2.16. 3-(1-(4-Chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (8p)

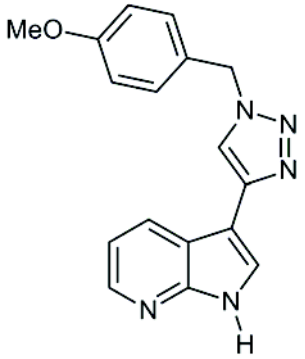


$C_{16}H_{12}ClN_5$

309.75

218 mg (0.70 mmol, 45 % yield over two steps) as a colorless solid. Mp 225 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 5.67 (s, 2 H), 7.18 (dd, *J* = 7.9 Hz, *J* = 4.7 Hz, 1 H), 7.38-7.43 (m, 2 H), 7.45-7.50 (m, 2 H), 7.92 (d, *J* = 2.2 Hz, 1 H), 8.29 (d, *J* = 4.4 Hz, 1 H), 8.44 (d, *J* = 7.9 Hz, 1 H), 8.53 (s, 1 H), 11.9 (br, 1 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 52.0 (CH_2), 104.9 (C_{quat}), 115.9 (CH), 116.9 (C_{quat}), 119.8 (CH), 123.3 (CH), 128.2 (CH), 128.7 (CH), 129.8 (CH), 132.8 (C_{quat}), 135.1 (C_{quat}), 142.4 (C_{quat}), 143.1 (CH), 148.5 (C_{quat}). EI + MS (*m/z* (%)): 311 ($M(^{37}Cl)^+$, 26), 310 (14), 309 ($M(^{35}Cl)^+$, 80), 283 (27), 282 (44), 281 (75), 280 (100), 253 (20), 246 (20), 219 (16), 218 (19), 170 (26), 156 (54), 129 (35), 127 (15), 125 (45), 118 (11), 102 (18), 89 (17), 57 (12), 44 (24). IR (KBr): $\tilde{\nu}$ 3139 (m) cm^{-1}, 2895 (w), 1625 (w), 1584 (s), 1493 (s), 1418 (m), 1326 (w), 1286 (w), 1222 (w), 1130 (w), 1091 (w), 1054 (w), 1016 (w), 941 (w), 897 (w), 801 (m), 771 (s), 653 (w), 619 (w), 586 (w). Anal. calcd for $C_{16}H_{12}ClN_5$ (309.8): C 62.04, H 3.90, N 22.61. Found: C 61.92, H 3.90, N 22.54.

4.2.17. 3-(1-(4-Methoxybenzyl)-1*H*-1,2,3-triazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (8q)

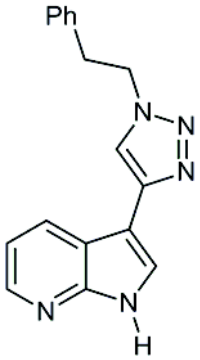


$C_{17}H_{15}N_5O$

305.33

179 mg (0.58 mmol, 58 % yield over two steps) as a pale yellow solid. After suspension in dichloromethane, sonication in ultrasonic bath, filtration, and drying, a colorless solid was obtained. Mp 185 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 3.74 (s, 3 H), 5.57 (s, 2 H), 6.94-6.97 (m, 2 H), 7.17 (dd, *J* = 7.9 Hz, *J* = 4.7 Hz, 1 H), 7.34-7.38 (m, 2 H), 7.90 (d, *J* = 2.5 Hz, 1 H), 8.28 (dd, *J* = 4.7 Hz, *J* = 1.6 Hz, 1 H), 8.44 (dd, *J* = 7.9 Hz, *J* = 1.3 Hz, 1 H), 8.48 (s, 1 H), 11.9 (br, 1 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 52.4 (CH_2), 55.0 (CH_3), 105.0 (C_{quat}), 114.0 (CH), 115.9 (CH), 116.9 (C_{quat}), 119.4 (CH), 123.2 (CH), 128.0 (C_{quat}), 128.2 (CH), 129.5 (CH), 142.3 (C_{quat}), 143.1 (CH), 148.5 (C_{quat}), 159.0 (C_{quat}). EI + MS (*m/z* (%)): 306 (7), 305 (M^+, 36), 277 ((M-N_2)$^+$, 43), 276 (72), 249 (19), 170 (18), 156 (40), 129 (36), 122 (11), 121 ($C_8H_9O^+$, 100), 103 (10), 102 (13), 91 ($C_7H_7^+$, 13), 78 ($C_6H_6^+$, 19), 77 ($C_6H_5^+$, 20). IR (KBr): $\tilde{\nu}$ 3447 (m) cm^{-1}, 3424 (m), 3136 (w), 2903 (w), 1612 (w), 1584 (m), 1514 (s), 1462 (w), 1419 (m), 1335 (w), 1281 (w), 1249 (s), 1211 (w), 1180 (w), 1127 (w), 1033 (m), 938 (w), 896 (w), 827 (w), 798 (w), 764 (s), 697 (w), 618 (w), 588 (w), 552 (w). Anal. calcd for $C_{17}H_{15}N_5O$ (305.3): C 66.87, H 4.95, N 22.94. Found: C 66.68, H 5.20, N 23.03.

4.2.18. 3-(1-Phenethyl-1*H*-1,2,3-triazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (8r)

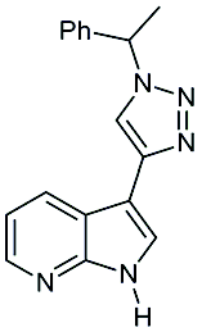


$C_{17}H_{15}N_5$

289.33

179 mg (0.62 mmol, 62 % yield over two steps) as a colorless solid. Mp 228 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 3.26 (t, *J* = 7.3 Hz, 2 H), 4.68 (t, *J* = 7.3 Hz, 2 H), 7.18 (dd, *J* = 7.9 Hz, *J* = 4.4 Hz, 1 H), 7.20-7.32 (m, 5 H), 7.89 (d, *J* = 2.2 Hz, 1 H), 8.30 (dd, *J* = 4.4 Hz, *J* = 1.6 Hz, 1 H), 8.40 (dd, *J* = 7.9 Hz, *J* = 1.6 Hz, 1 H), 8.44 (s, 1 H), 11.9 (br, 1 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 35.5 (CH_2), 50.4 (CH_2), 105.1 (C_{quat}), 115.9 (CH), 116.9 (C_{quat}), 119.6 (CH), 123.0 (CH), 126.5 (CH), 128.1 (CH), 128.3 (CH), 128.6 (CH), 137.6 (C_{quat}), 141.7 (C_{quat}), 143.1 (CH), 148.5 (C_{quat}). EI + MS (*m/z* (%)): 289 (M^+, 40), 261 ($(M-N_2)^+$, 13), 260 (13), 234 (16), 233 (36), 171 (12), 170 (100), 157 (15), 156 (18), 144 (11), 143 (80), 142 (28), 132 (12), 131 (20), 130 (14), 129 (13), 116 (20), 115 (18), 105 ($C_8H_9^+$, 24), 103 (17), 91 ($C_7H_7^+$, 12), 79 (15), 77 ($C_6H_5^+$, 18). IR (KBr): $\tilde{\nu}$ 3449 (w) cm^{-1}, 3089 (m), 3064 (m), 3028 (w), 2932 (w), 2893 (w), 1624 (w), 1584 (s), 1495 (m), 1455 (m), 1416 (s), 1320 (w), 1283 (m), 1218 (m), 1134 (w), 1112 (w), 1058 (w), 1030 (m), 942 (w), 898 (w), 842 (w), 793 (m), 770 (s), 730 (s), 698 (s), 629 (w), 585 (w). Anal. calcd for $C_{17}H_{15}N_5$ (289.3): C 70.57, H 5.23, N 24.21. Found: C 70.47, H 5.40, N 24.25.

4.2.19. 3-(1-(1-Phenylethyl)-1*H*-1,2,3-triazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin (8s)

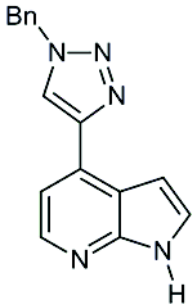


$C_{17}H_{15}N_5$

289.33

160 mg (0.55 mmol, 55 % yield over two steps) as a pale yellow solid. Mp 184 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.96 (d, *J* = 7.3 Hz, 3 H), 6.00 (q, *J* = 7.3 Hz, 1 H), 7.18 (dd, *J* = 7.9 Hz, *J* = 4.7 Hz, 1 H), 7.30-7.35 (m, 1 H), 7.37-7.40 (m, 4 H), 7.91 (d, *J* = 2.5 Hz, 1 H), 8.29 (dd, *J* = 4.4 Hz, *J* = 1.6 Hz, 1 H), 8.48 (dd, *J* = 7.9 Hz, *J* = 1.3 Hz, 1 H), 8.62 (s, 1 H), 11.9 (br, 1 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 21.0 (CH_3), 59.2 (CH), 105.1 (C_{quat}), 115.9 (CH), 116.9 (C_{quat}), 118.3 (CH), 123.2 (CH), 126.2 (CH), 127.9 (CH), 128.3 (CH), 128.7 (CH), 141.2 (C_{quat}), 142.1 (C_{quat}), 143.1 (CH), 148.5 (C_{quat}). EI + MS (*m/z* (%)): 290 (6), 289 (M^+, 30), 260 (13), 247 (19), 246 (100), 219 (12), 156 (47), 143 (11), 129 (35), 105 ($C_8H_9^+$, 34), 103 (17), 102 (12), 79 (13), 77 ($C_6H_5^+$, 17). IR (KBr): $\tilde{\nu}$ 3457 (w) cm^{-1}, 3120 (m), 3080 (m), 2927 (m), 2874 (m), 1623 (w), 1586 (s), 1495 (w), 1458 (m), 1420 (m), 1383 (w), 1333 (m), 1302 (w), 1279 (m), 1234 (w), 1211 (m), 1196 (m), 1136 (m), 1109 (w), 1058 (w), 1040 (w), 1023 (w), 982 (w), 937 (m), 896 (w), 824 (m), 793 (w), 770 (s), 722 (w), 694 (m), 648 (w), 624 (w), 584 (m), 544 (w), 526 (w). Anal. calcd for $C_{17}H_{15}N_5$ (289.3): C 70.57, H 5.23, N 24.21. Found: C 70.30, H 5.42, N 24.01.

4.2.20. 4-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (9a)

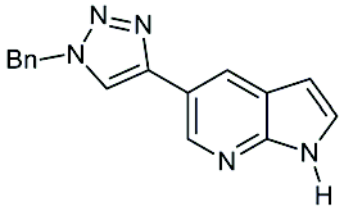


$C_{16}H_{13}N_5$

275.31

207 mg (0.75 mmol, 75 % yield over two steps) as a colorless solid. Mp 200 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 5.73 (s, 2 H), 7.00-7.03 (m, 1 H), 7.33-7.44 (m, 5 H), 7.58-7.61 (m, 2 H), 8.29 (dd, *J* = 5.0 Hz, *J* = 0.6 Hz, 1 H), 9.03 (d, *J* = 0.9 Hz, 1 H), 11.8 (br, 1 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 53.0 (CH_2), 100.1 (CH), 111.6 (CH), 115.5 (C_{quat}), 123.8 (CH), 126.5 (CH), 127.9 (CH), 128.1 (CH), 128.7 (CH), 129.3 (C_{quat}), 135.9 (C_{quat}), 142.6 (CH), 144.8 (C_{quat}), 149.4 (C_{quat}). EI + MS (*m/z* (%)): 276 (10), 275 (M^+, 48), 247 (14), 246 (64), 219 (14), 170 (10), 157 (11), 156 (100), 149 (20), 130 (14), 129 (30), 109 (10), 102 (10), 91 ($C_7H_7^+$, 98), 85 (11), 71 (13), 65 ($C_5H_5^+$, 14), 57 (14). IR (KBr): $\tilde{\nu}$ 3128 (m) cm^{-1}, 2869 (m), 1604 (s), 1543 (w), 1498 (m), 1458 (m), 1391 (w), 1333 (s), 1226 (w), 1050 (m), 897 (w), 824 (s), 723 (m), 645 (w), 601 (w). Anal. calcd for $C_{16}H_{13}N_5$ (275.3): C 69.80, H 4.76, N 25.44. Found: C 69.58, H 4.83, N 25.58.

4.2.21. 5-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (9b)

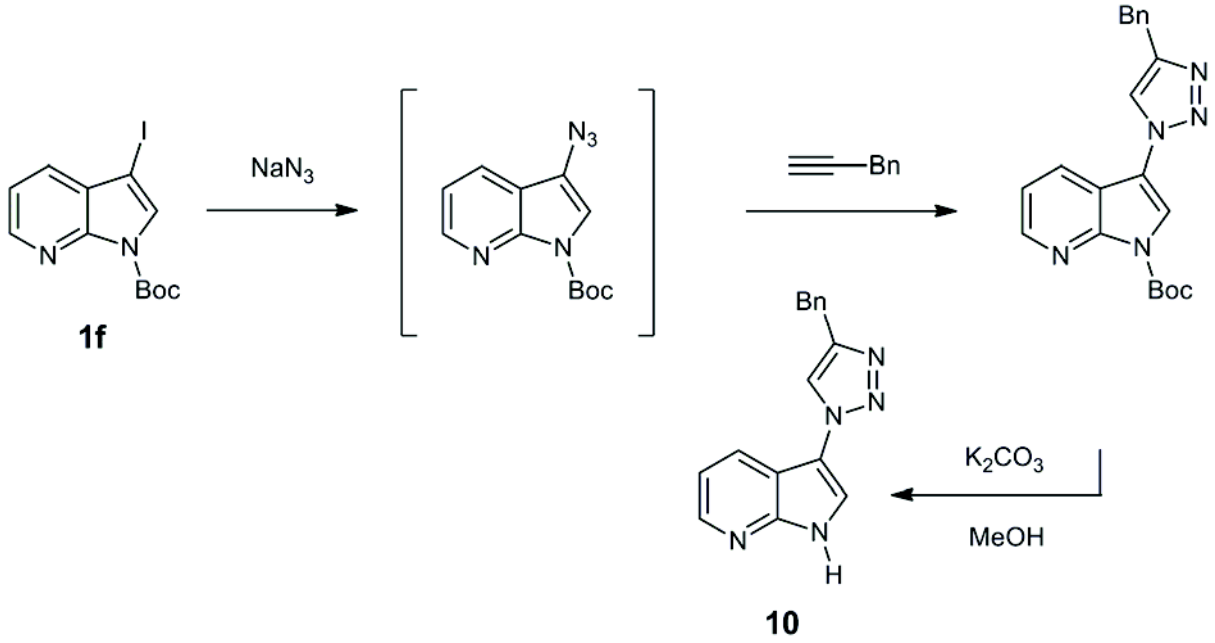


$C_{16}H_{13}N_5$

275.31

182 mg (0.66 mmol, 66 % yield over two steps) as a colorless solid. Mp 210 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 5.65 (s, 2 H), 6.50 (dd, *J* = 3.5 Hz, *J* = 1.9 Hz, 1 H), 7.32-7.43 (m, 5 H), 7.49-7.51 (m, 1 H), 8.38 (d, *J* = 1.9 Hz, 1 H), 8.64 (s, 1 H), 8.71 (d, *J* = 1.9 Hz, 1 H), 11.7 (br, 1 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 53.1 (CH_2), 100.2 (CH), 118.9 (C_{quat}), 119.5 (C_{quat}), 120.8 (CH), 124.6 (CH), 127.0 (CH), 128.0 (CH), 128.2 (CH), 128.8 (CH), 136.0 (C_{quat}), 140.4 (CH), 145.7 (C_{quat}), 148.2 (C_{quat}). EI + MS (*m/z* (%)): 276 (6), 275 (M^+, 28), 247 (23), 246 (100), 219 (25), 170 (22), 156 (68), 129 (39), 91 ($C_7H_7^+$, 58), 65 ($C_5H_5^+$, 11). IR (KBr): $\tilde{\nu}$ 3125 (m) cm^{-1}, 1608 (w), 1585 (w), 1497 (w), 1454 (w), 1435 (w), 1407 (m), 1340 (m), 1314 (w), 1298 (w), 1228 (w), 1214 (w), 1069 (w), 1051 (w), 919 (w), 905 (w), 805 (m), 781 (w), 734 (s), 693 (w), 621 (w), 505 (w). Anal. calcd for $C_{16}H_{13}N_5$ (275.3): C 69.80, H 4.76, N 25.44. Found: C 69.95, H 4.64, N 25.48.

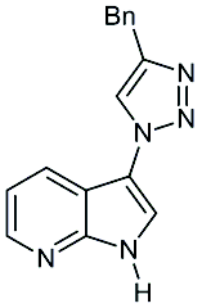
5. Preparation of 3-(4-Benzyl-1*H*-1,2,3-triazol-1-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (10) by the One-Pot Synthesis of 1-Aryl 1,2,3-Triazoles from Aryl Halides and Terminal Alkynes in the Presence of Sodium Azide[4]



Copper(I) iodide (39 mg, 0.20 mmol, 10 mol %) was placed under argon atmosphere in a dry screw-cap vessel with septum. Then, *tert*-butyl 3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (**1f**) (688 mg, 2.00 mmol) in 5 mL of dimethylsulfoxide and 1mL of water was added and the mixture was degassed with argon. Sodium azide (138 mg, 2.10 mmol, 1.05 equiv), sodium ascorbate (40 mg, 0.20 mmol, 10 mol %), benzylacetylene (0.26 mL, 2.00 mmol, 1.00 equiv), and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.22 mL, 0.30 mmol, 0.15 equiv) were successively added to the mixture which was stirred at room temperature (water bath) for 112 h (monitored by TLC, but the reaction did not go to completion). Then, the mixture was diluted with 10 mL of water, extracted with 10 mL of dichloromethane, the organic phase was washed with water (3 x 10 mL), dried with sodium sulphate, and filtered. The solvents were removed in vacuo and the residue was absorbed onto Celite® and purified chromatographically on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl acetate (PE-EtOAc = 5:1). After drying in vacuo, 105 mg (0.28 mmol, 14 % yield) of a yellow oil were obtained.

The obtained oil was dissolved in 1.4 mL of methanol, potassium carbonate (98 mg, 0.70 mmol, 2.50 equiv) was added, and the mixture was stirred at room temperature for 1 h. Then, the solvent was removed in vacuo and the residue was absorbed onto Celite® and purified chromatographically on silica gel with dichloromethane-methanol-aqueous ammonia DCM-MeOH-NH_3 = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 (stepwise gradient). After drying in vacuo at 70 °C overnight, 3-(1-benzyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (**10**) (49 mg, 0.18 mmol, 64 % yield) was obtained as a colorless solid.

3-(4-Benzyl-1*H*-1,2,3-triazol-1-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (10)

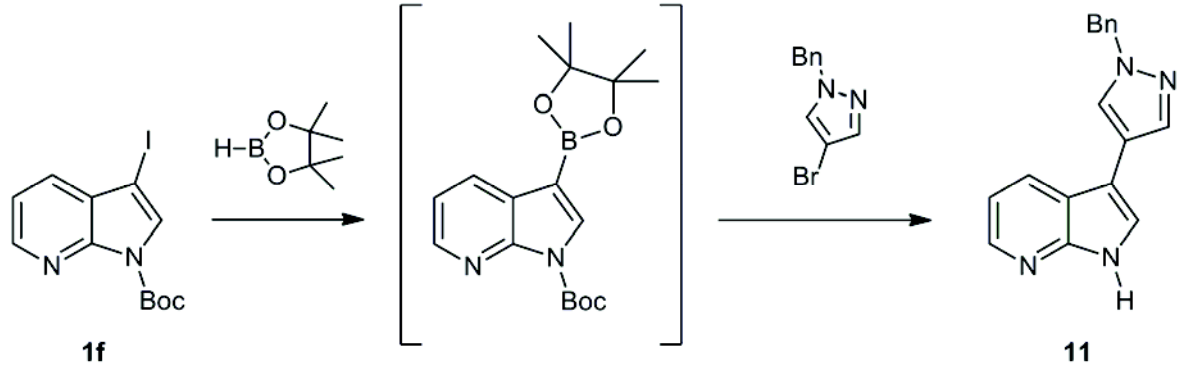


$C_{16}H_{13}N_5$

275.31

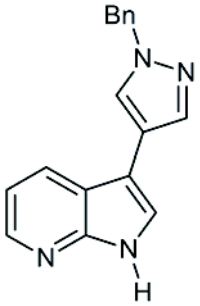
49 mg (9 % yield over two steps) as a colorless solid. Mp 177 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 4.11 (s, 2 H), 7.21-7.26 (m, 2 H), 7.30-7.35 (m, 4 H), 8.11 (d, *J* = 2.8 Hz, 1 H), 8.30 (dd, *J* = 7.9 Hz, *J* = 1.6 Hz, 1 H), 8.37 (dd, *J* = 4.4 Hz, *J* = 1.6 Hz, 1 H), 8.46 (s, 1 H), 12.2 (br, 1 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 31.1 (CH_2), 112.2 (C_{quat}), 113.6 (C_{quat}), 116.7 (CH), 117.6 (CH), 121.4 (CH), 126.1 (CH), 127.5 (CH), 128.4 (CH), 128.5 (CH), 139.3 (C_{quat}), 144.3 (CH), 146.1 (C_{quat}), 146.4 (C_{quat}). EI + MS (*m/z* (%)): 275 (M^+, 1), 247 ($(M-N_2)^+$, 37), 246 (100), 170 (27), 144 (32), 143 (44), 132 (16), 128 (10), 117 (15), 116 (11), 115 (14), 104 (37), 103 (15), 91 ($C_7H_7^+$, 18), 90 (15), 78 (10), 77 ($C_6H_5^+$, 14), 65 ($C_5H_5^+$, 5). IR (KBr): $\tilde{\nu}$ 3447 (s) cm^{-1}, 3421 (s), 3144 (w), 3108 (w), 3025 (w), 2920 (w), 2821 (w), 1655 (m), 1613 (s), 1586 (m), 1563 (w), 1515 (w), 1494 (m), 1436 (m), 1409 (s), 1377 (m), 1341 (w), 1288 (s), 1206 (s), 1136 (m), 1103 (m), 1073 (w), 1049 (s), 1021 (w), 947 (m), 895 (m), 830 (w), 790 (m), 766 (s), 721 (s), 691 (m), 665 (w), 616 (w), 586 (m), 531 (w). Anal. calcd for $C_{16}H_{13}N_5$ (275.3): C 69.80, H 4.76, N 25.44. Found: C 69.63, H 4.96, N 25.20.

6. Preparation of 3-(1-Benzyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (11) by the *Masuda* Borylation □ *Suzuki* Coupling Sequence[5]



Tetrakis(triphenylphosphane)-palladium(0) (35 mg, 0.03 mmol, 3 mol %) and *tert*-butyl 3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (**1f**) (344 mg, 1.00 mmol) were placed under argon atmosphere in a dry screw-cap vessel with septum. Then, 5 mL of dry dioxane were added and the mixture was degassed with argon. Dry triethylamine (1.39 mL, 10.0 mmol, 10.0 equiv), and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.22 mL, 1.50 mmol, 1.50 equiv) were successively added to the mixture which was stirred at 80 °C (preheated oil bath) for 3 h (monitored by TLC). Then, after cooling to room temperature (water bath), 5 mL of dry methanol, 1-benzyl-4-bromo-1*H*-pyrazole (237 mg 1.00 mmol, 1.00 equiv), and cesium carbonate (823 mg, 2.50 mmol, 2.50 equiv) were successively added and the mixture was stirred at 100 °C (preheated oil bath) for 24 h. Then, after cooling to room temperature (water bath) the solvents were removed in vacuo and the residue was absorbed onto Celite® and purified chromatographically on silica gel with dichloromethane-methanol-aqueous ammonia DCM-MeOH-NH_3 = 100:1:1. After drying in vacuo at 70 °C overnight, 3-(1-benzyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (**11**) was obtained as a yellow solid. Recrystallization from dichloromethane/*n*-pentane gave a colorless solid.

3-(1-Benzyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (11)

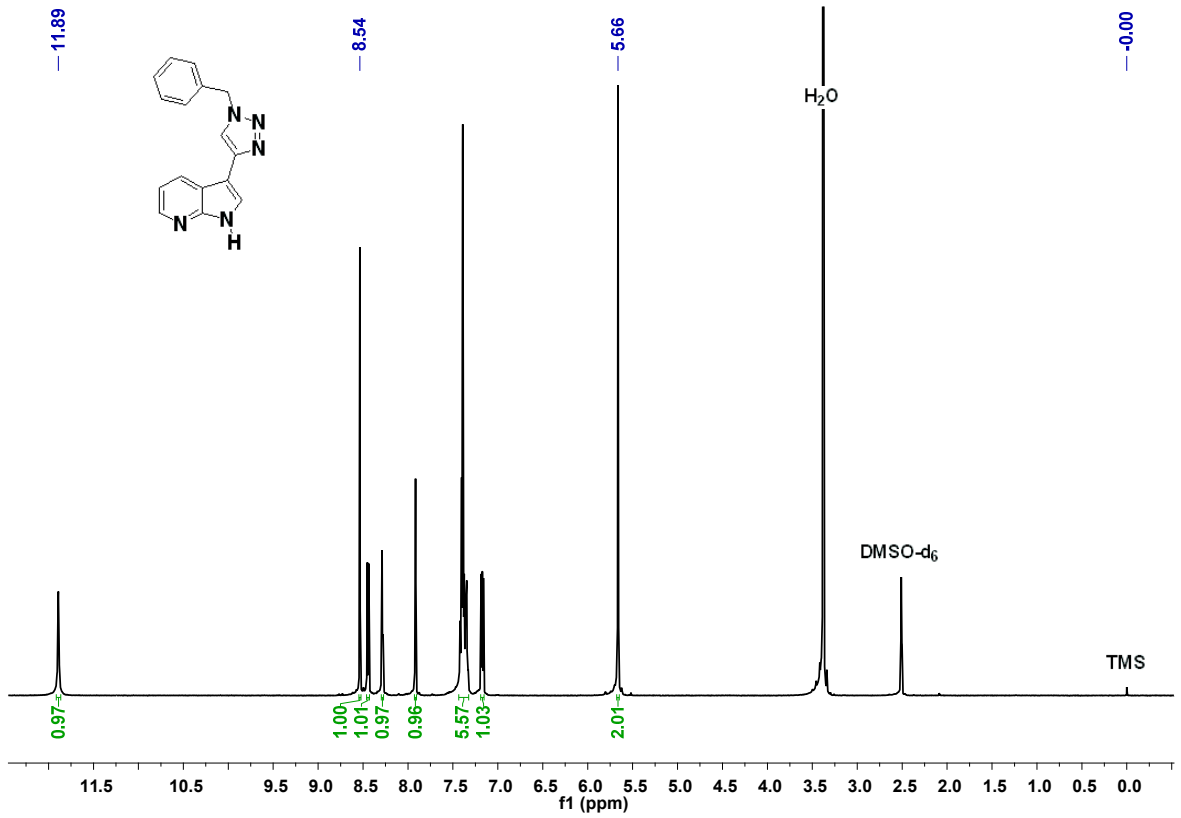


$C_{17}H_{14}N_4$

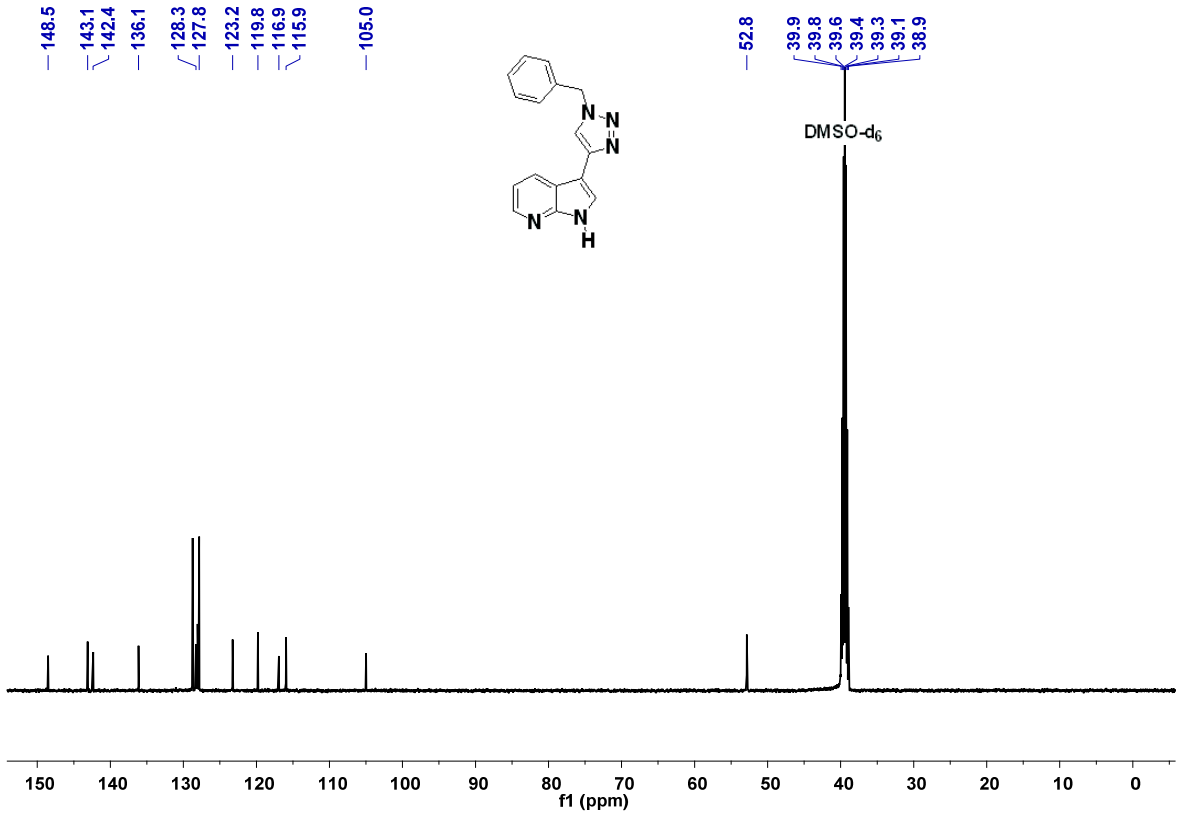
274.32

41 mg (0.15 mmol, 15 % yield) as a colorless solid (dichloromethane/*n*-pentane). Mp 198 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 5.37 (s, 2 H), 7.12 (dd, *J* = 7.9 Hz, *J* = 4.4 Hz, 1 H), 7.26-7.32 (m, 3 H), 7.33-7.38 (m, 2 H), 7.71 (d, *J* = 2.5 Hz, 1 H), 7.90 (s, 1 H), 8.21 (dd, *J* = 7.9 Hz, *J* = 1.3 Hz, 1 H), 8.24 (dd, *J* = 4.4 Hz, *J* = 1.3 Hz, 1 H), 8.29 (s, 1 H), 11.7 (br, 1 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 54.8 (CH_2), 106.2 (C_{quat}), 115.4 (CH), 115.6 (C_{quat}), 117.2 (C_{quat}), 121.9 (CH), 126.3 (CH), 127.4 (CH), 127.5 (CH), 127.5 (CH), 128.5 (CH), 136.5 (CH), 137.7 (C_{quat}), 142.7 (CH), 148.6 (C_{quat}). EI + MS (*m/z* (%)): 275 (26), 274 (M^+, 100), 273 ($(M-H)^+$, 10), 183 ($C_{10}H_7N_4^+$, 9), 142 ($C_9H_6N_2^+$, 7), 91 ($C_7H_7^+$, 51), 65 ($C_5H_5^+$, 6). IR (KBr): $\tilde{\nu}$ 3449 (w) cm^{-1}, 3103 (m), 3027 (m), 2819 (m), 1655 (w), 1579 (m), 1492 (m), 1459 (w), 1421 (s), 1337 (w), 1288 (m), 1229 (w), 1196 (w), 1149 (w), 1130 (w), 1110 (w), 989 (m), 918 (w), 897 (w), 857 (m), 822 (w), 793 (w), 763 (s), 719 (s), 695 (w), 665 (w), 650 (w), 614 (w), 587 (w), 532 (w). Anal. calcd for $C_{17}H_{14}N_4$ (274.3): C 74.43, H 5.14, N 20.42. Found: C 74.41, H 5.22, N 20.27.

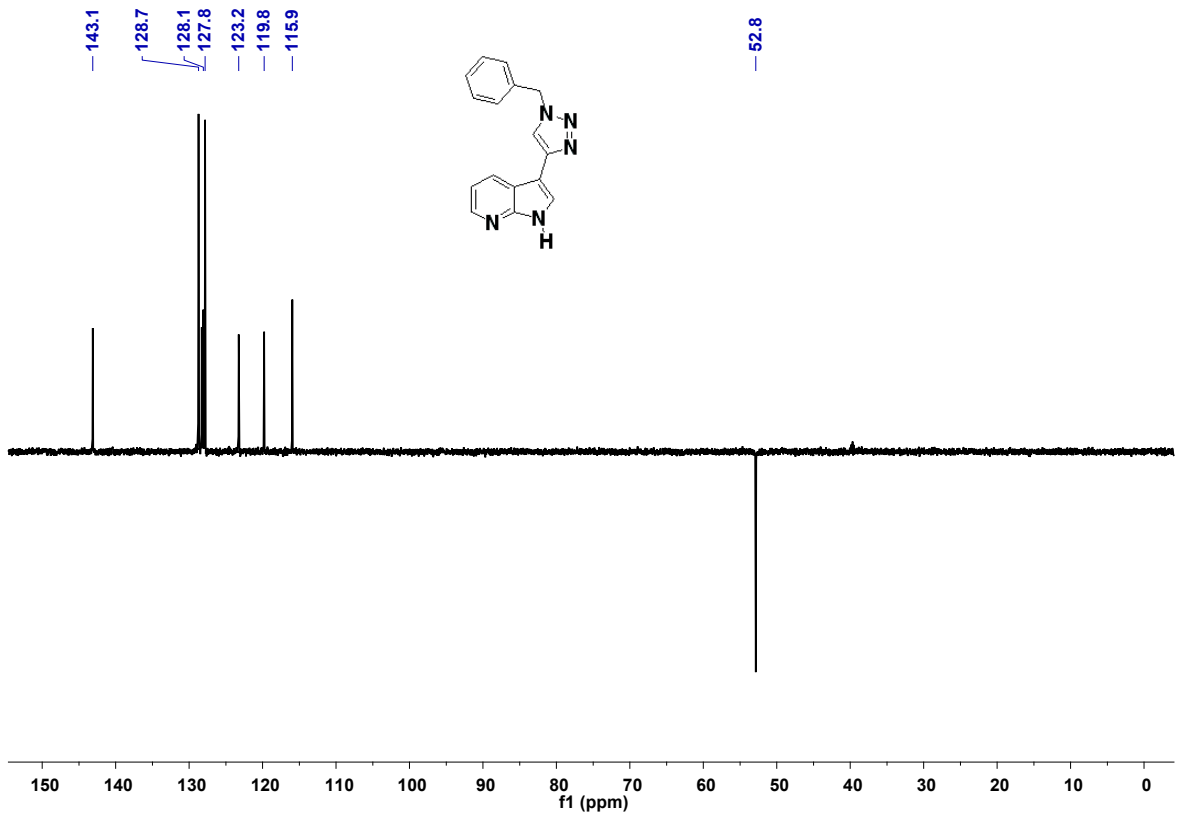
7. ^{1}H and ^{13}C NMR Spectra of Compounds 8f, 8g, 8r, 9a, 10, and 11



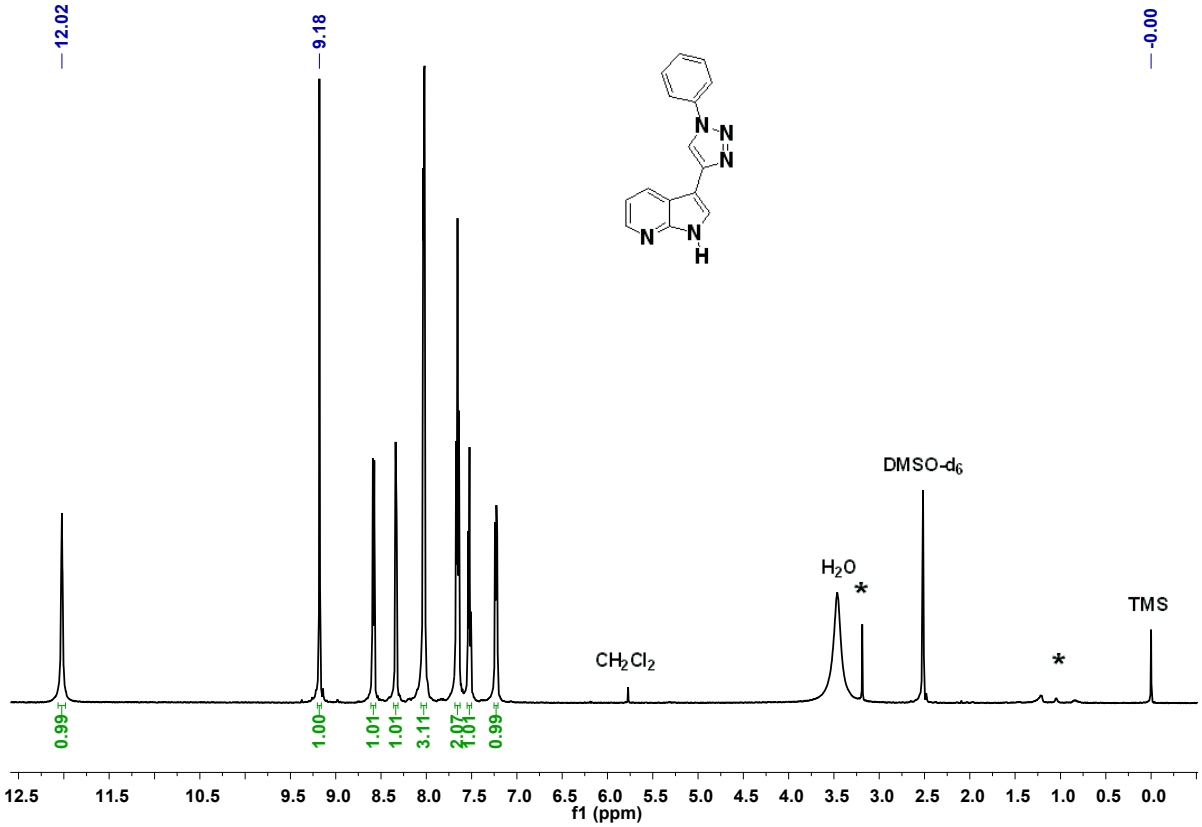
^{1}H NMR of **8f** (15 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).



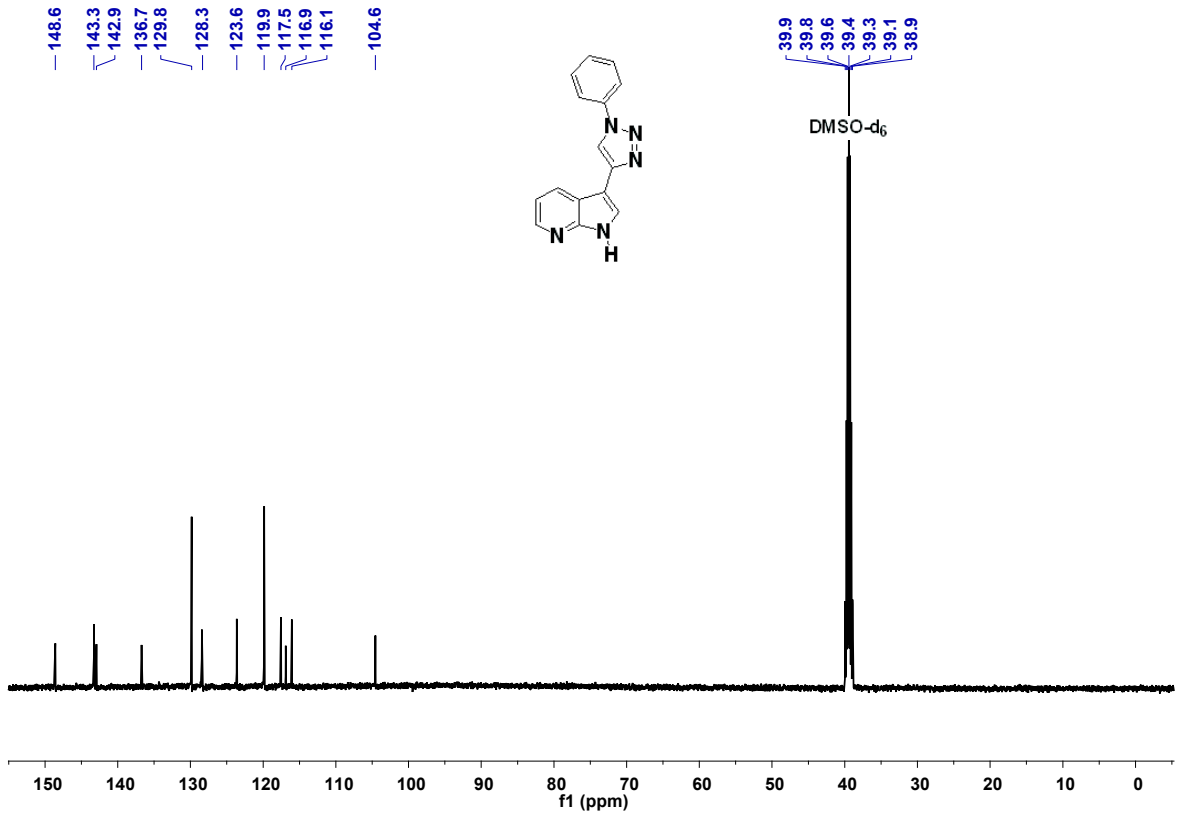
^{13}C NMR of **8f** (15 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).



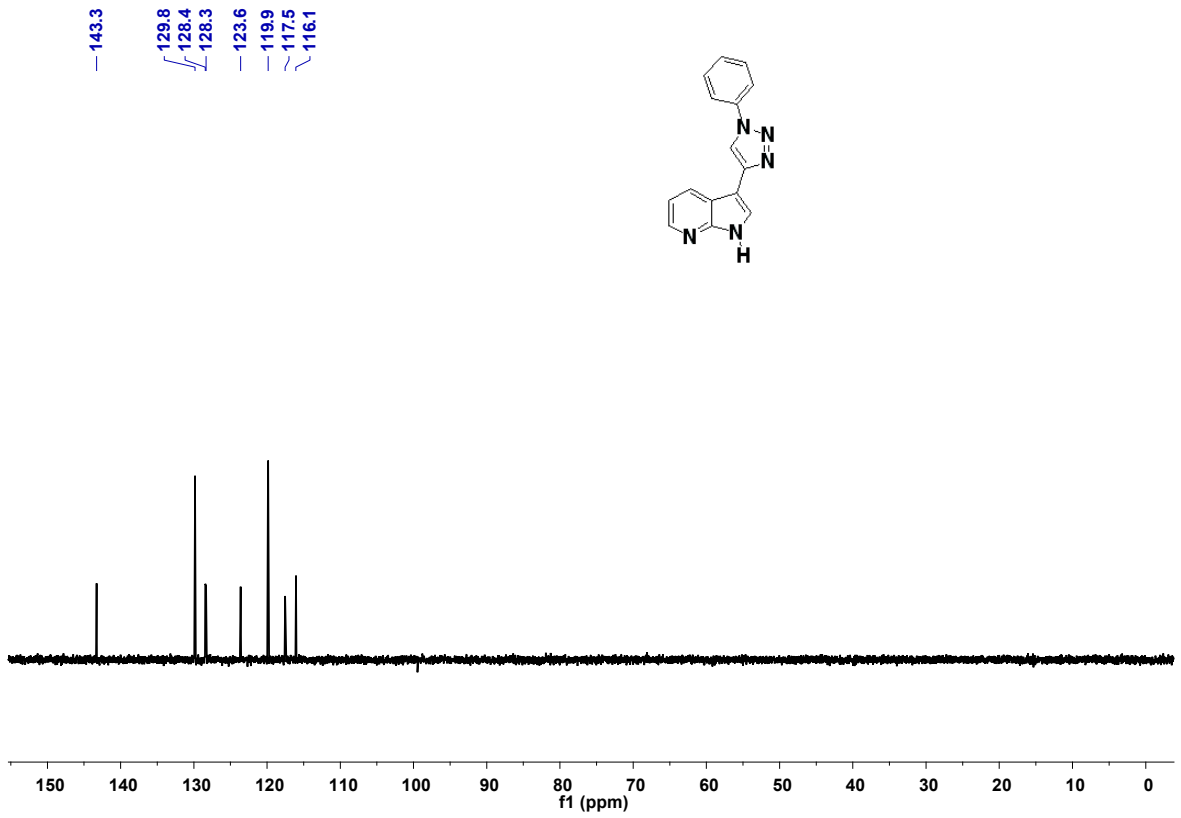
^{13}C DEPT 135-NMR of **8f** (15 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).



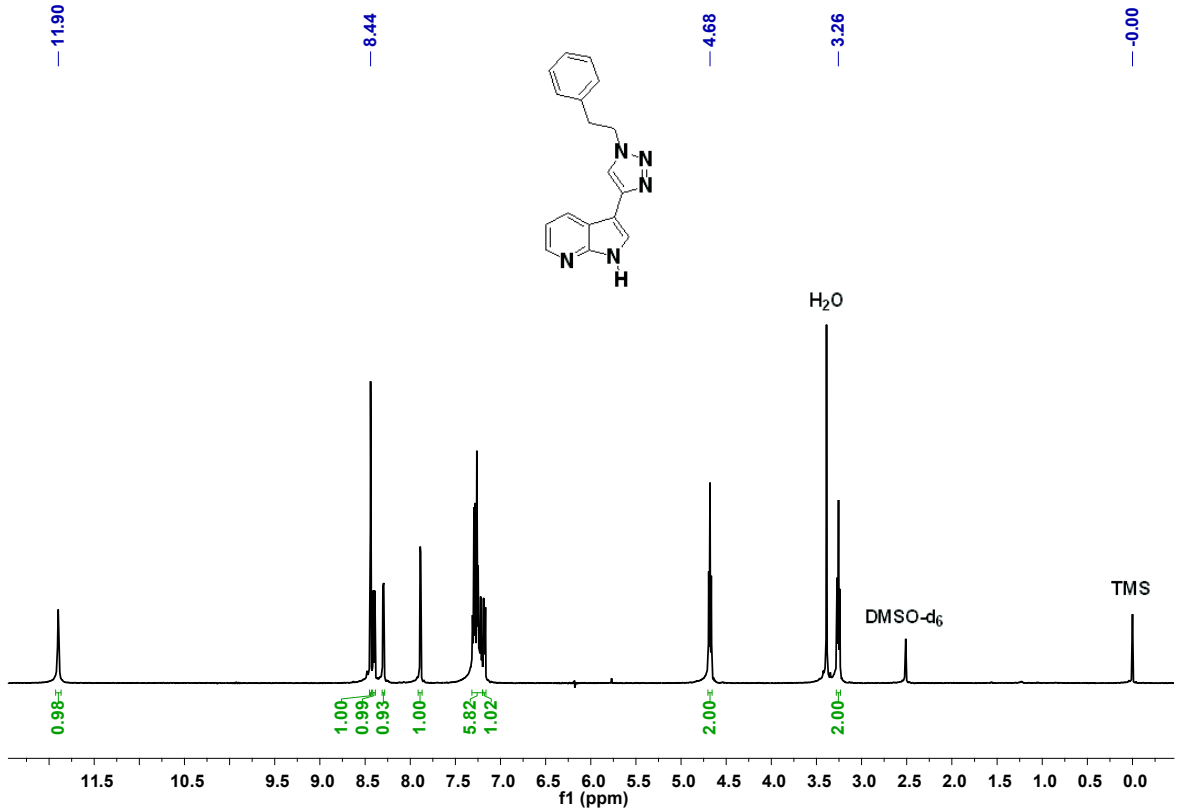
^{1}H NMR of **8g** (20 mg) in 0.7 mL DMSO-d_6 at 297 K (δ in ppm). *Impurities from residual solvents.



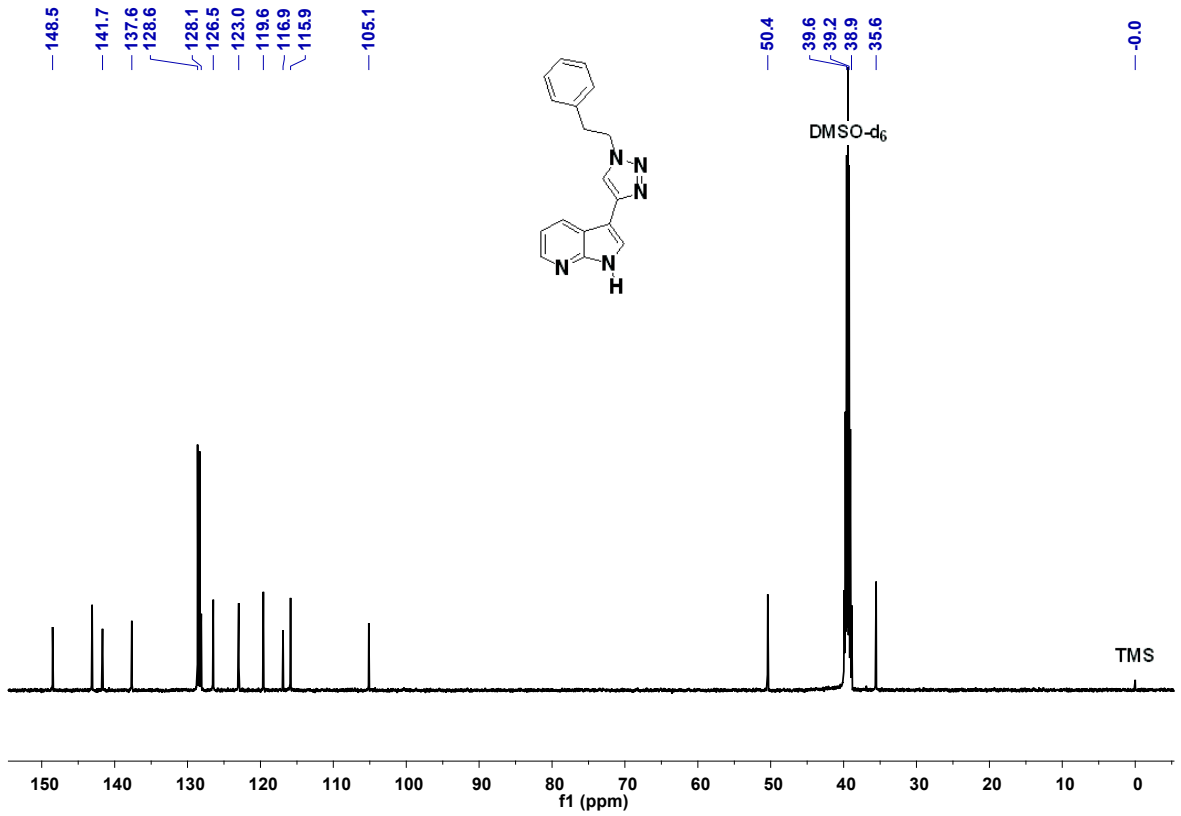
^{13}C NMR of **8g** (20 mg) in 0.7 mL DMSO-d_6 at 297 K (δ in ppm).



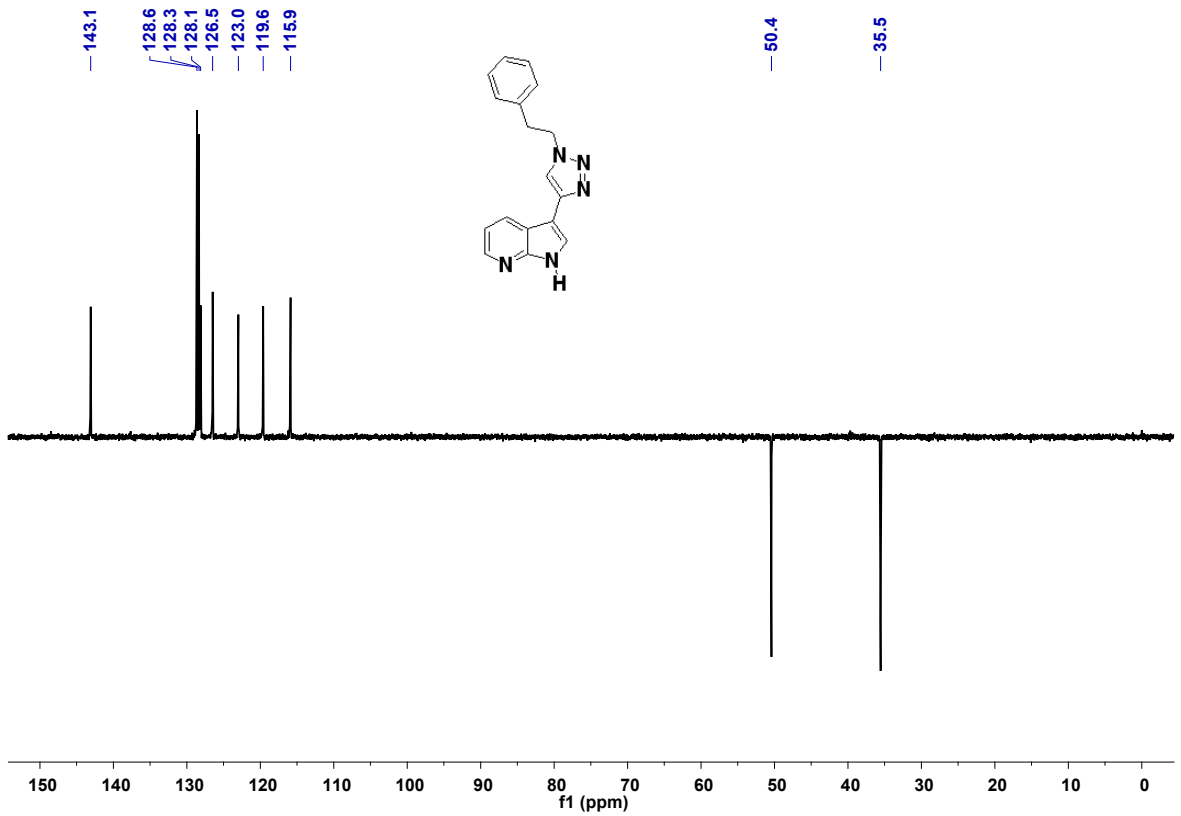
^{13}C DEPT 135-NMR of **8g** (20 mg) in 0.7 mL DMSO-d_6 at 297 K (δ in ppm).



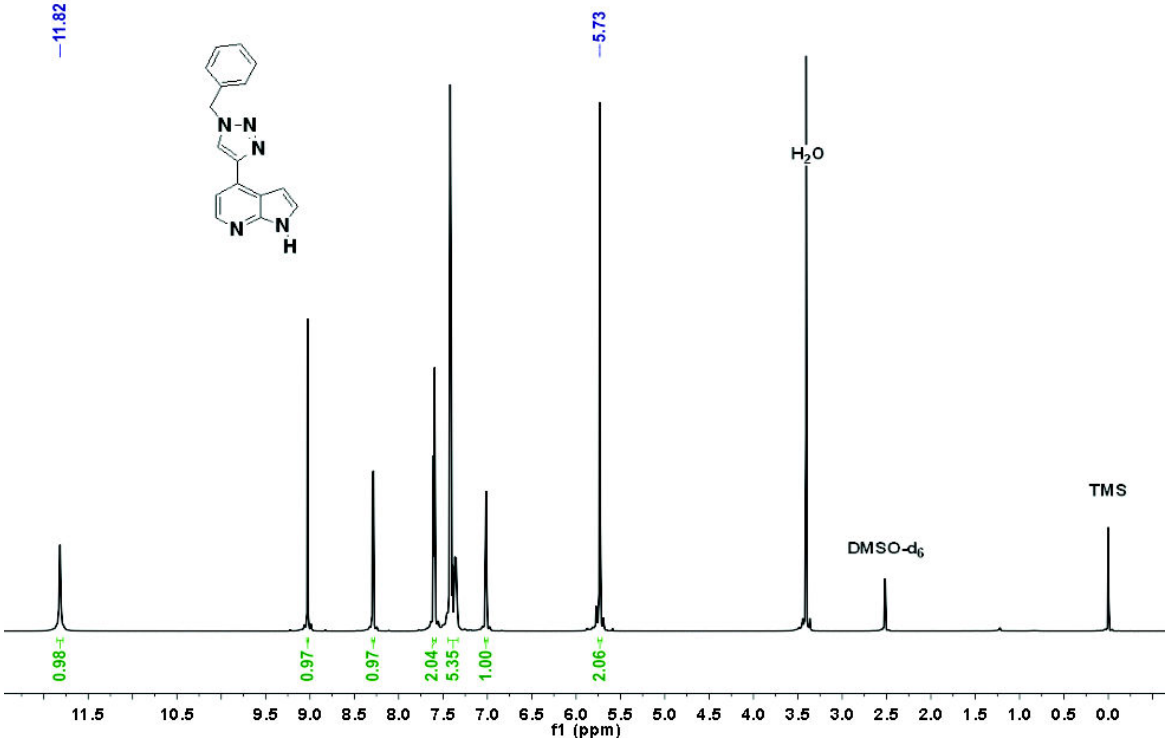
^{1}H NMR of **8r** (20 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).



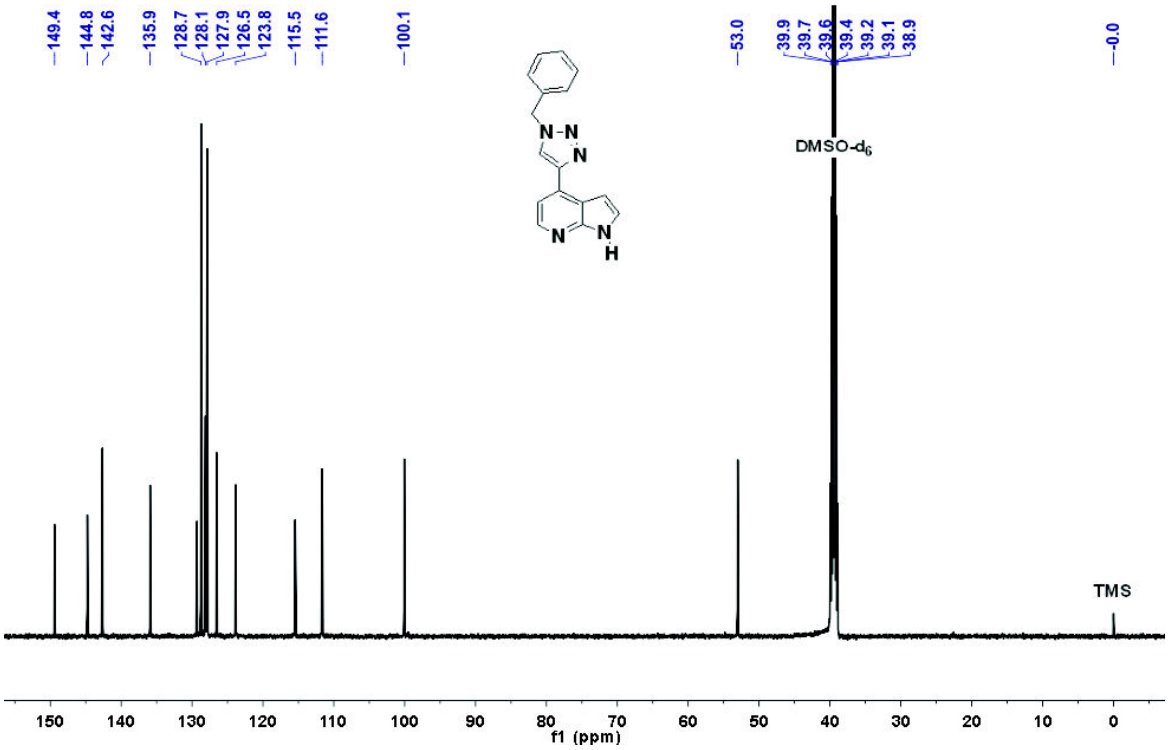
^{13}C NMR of **8r** (20 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).



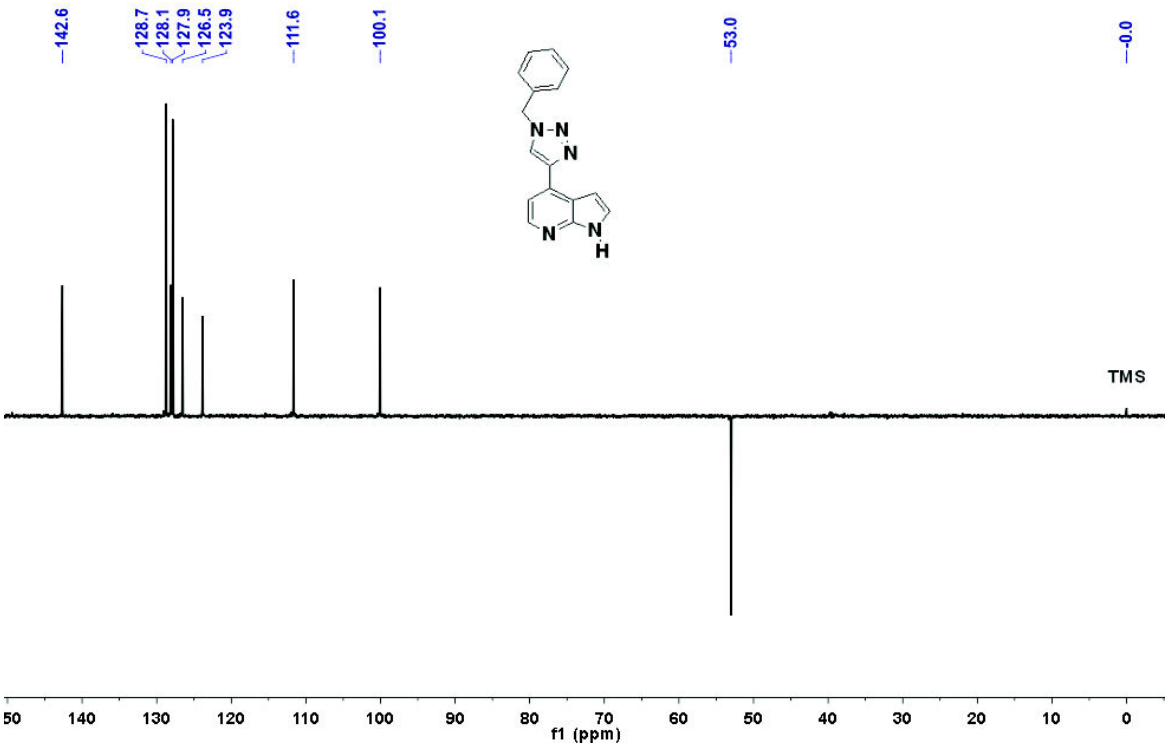
^{13}C DEPT 135-NMR of **8r** (20 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).



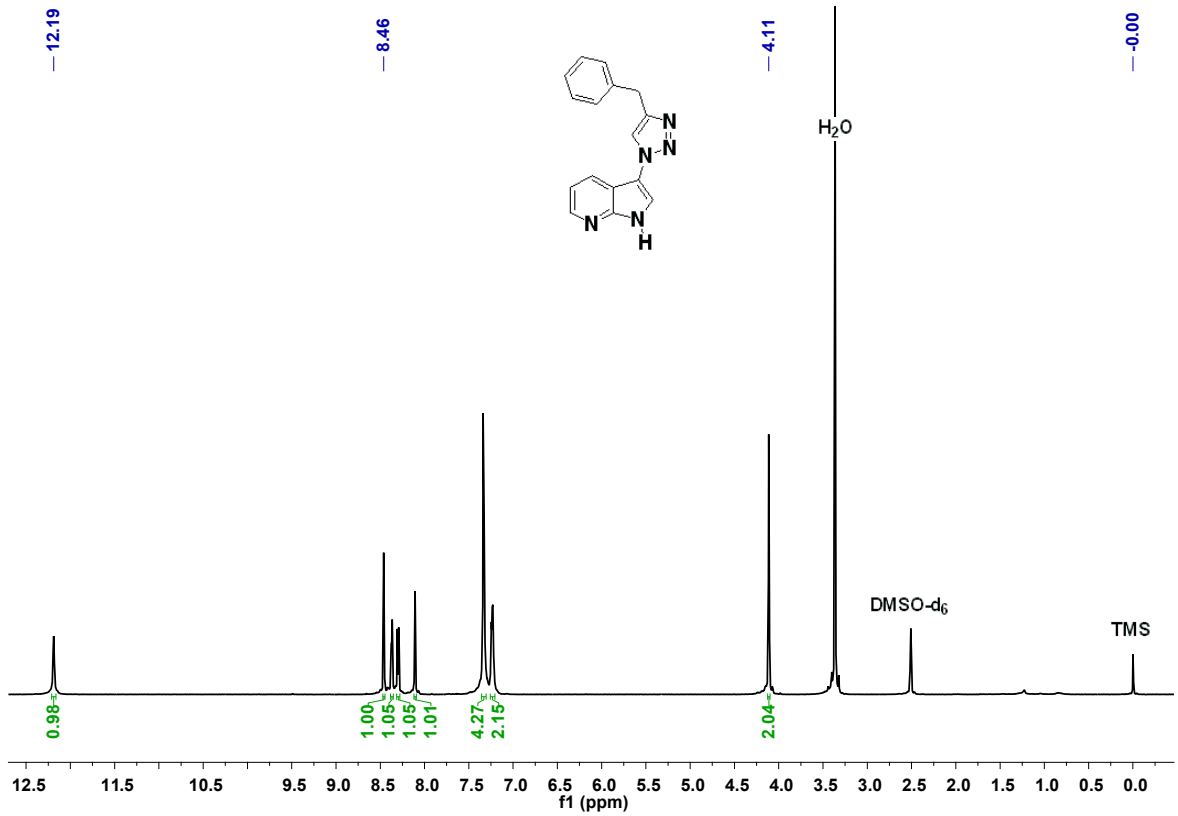
^{1}H NMR of **9a** (15 mg) in 0.7 mL DMSO-d_6 at 295 K (δ in ppm).



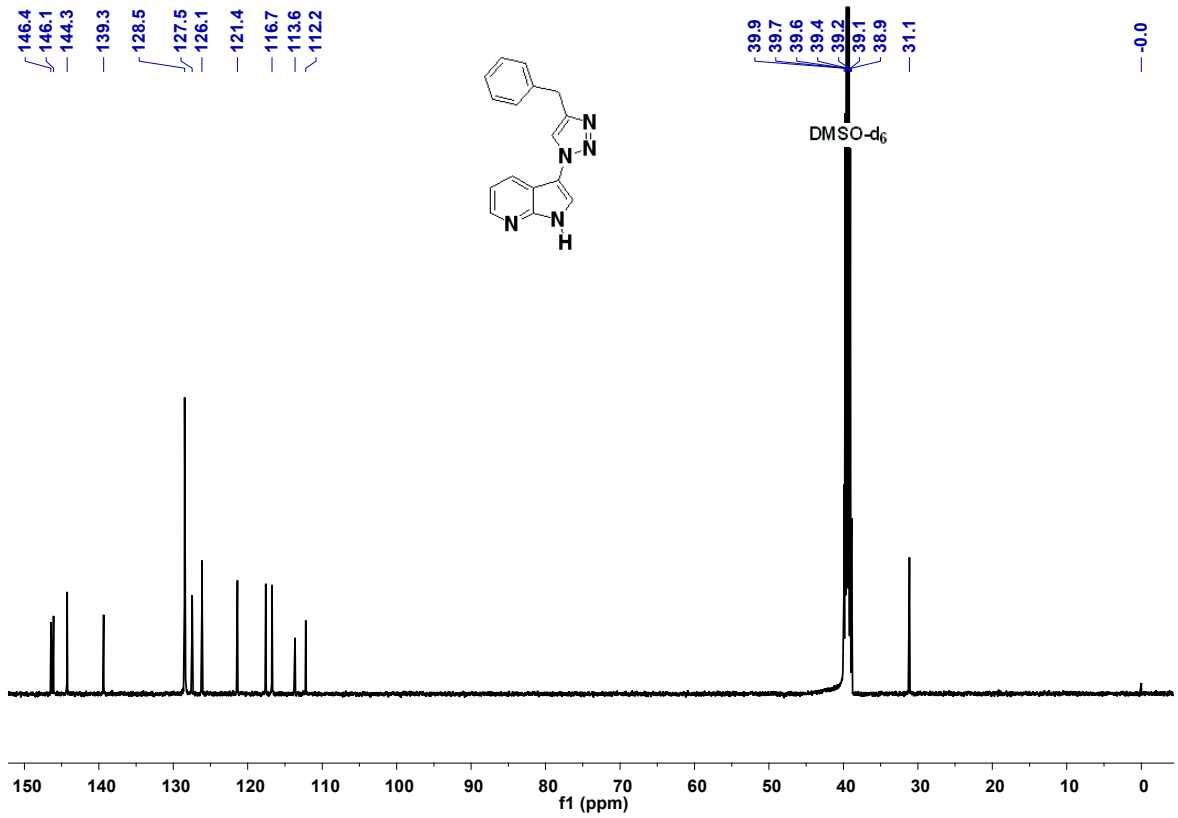
^{13}C NMR of **9a** (15 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).



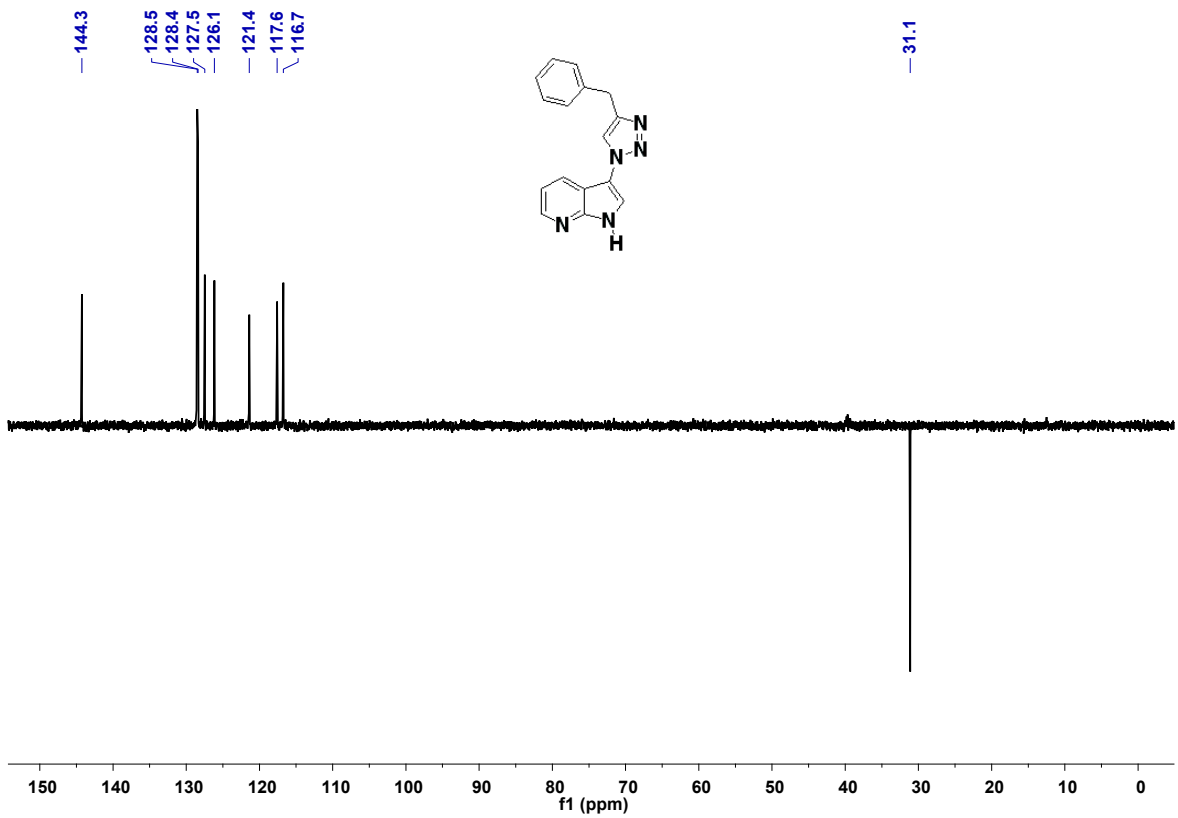
^{13}C DEPT 135-NMR of **9a** (15 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).



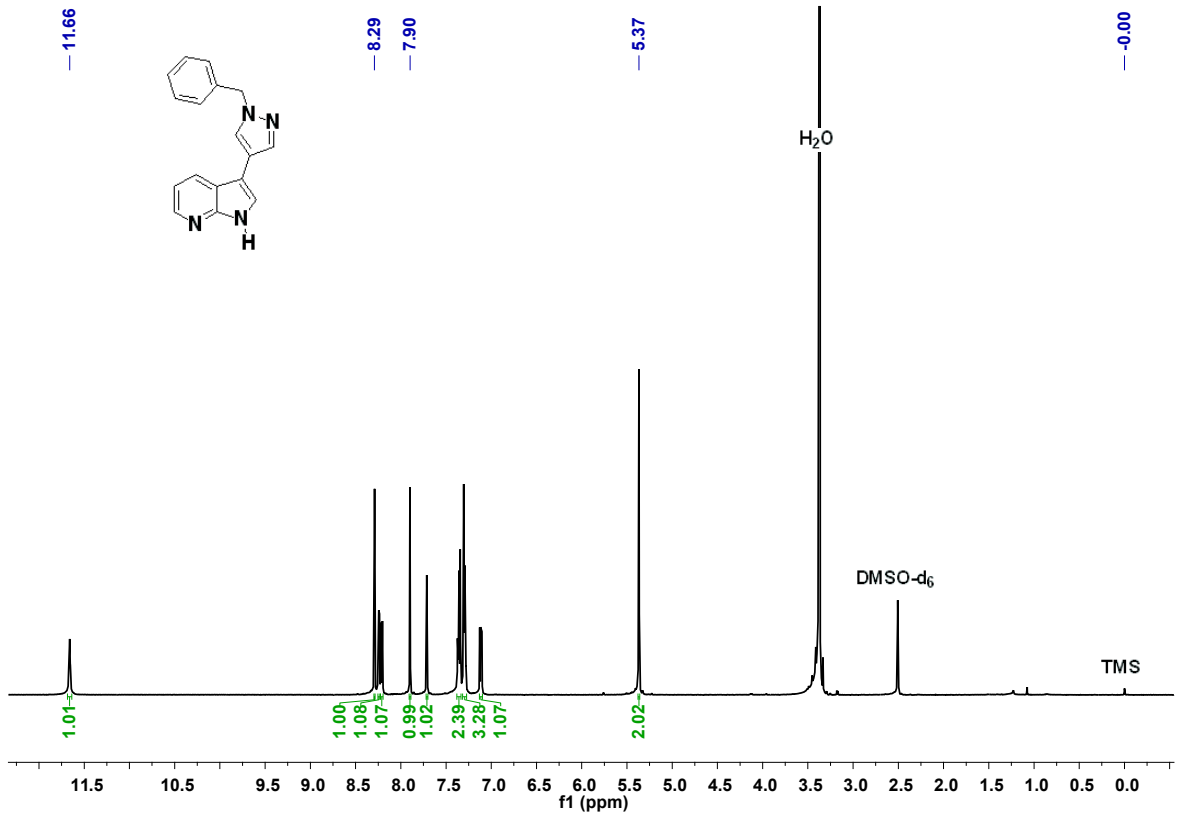
^{1}H NMR of **10** (15 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).



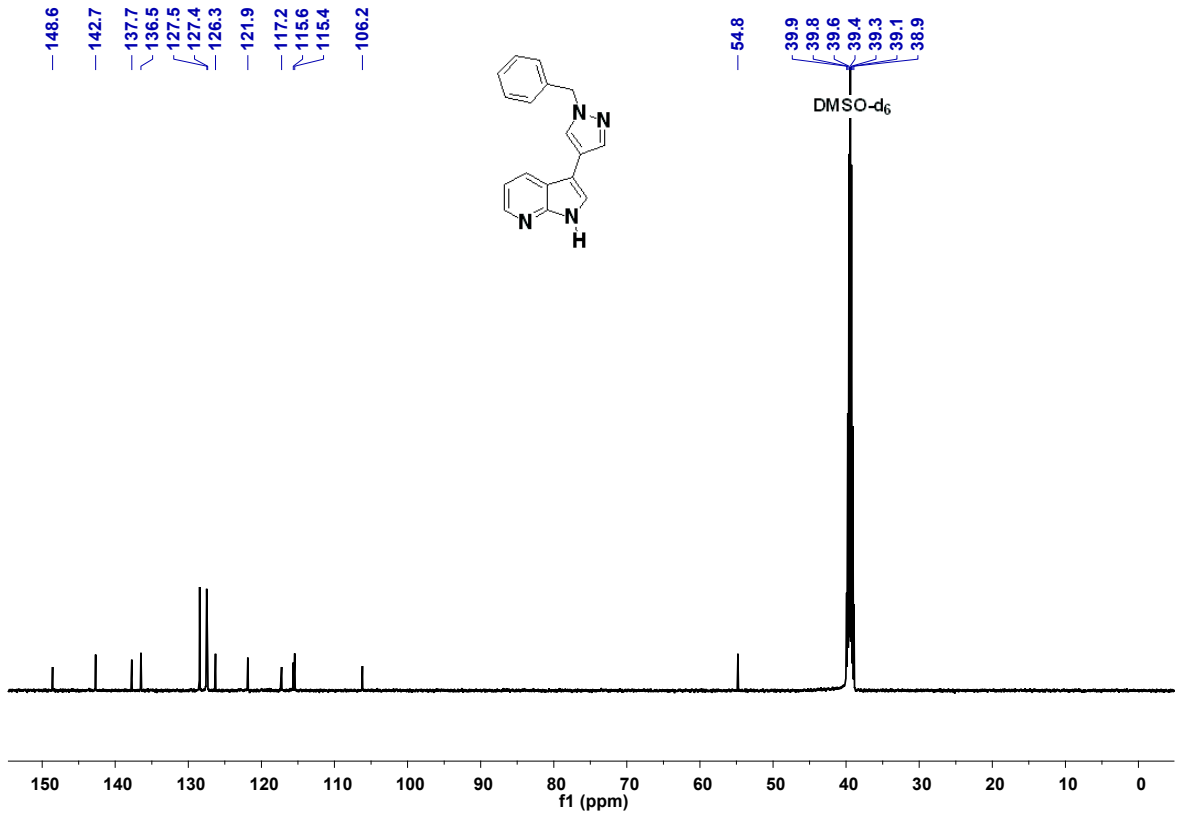
^{13}C NMR of **10** (15 mg) in 0.7 mL DMSO-d_6 at 297 K (δ in ppm).



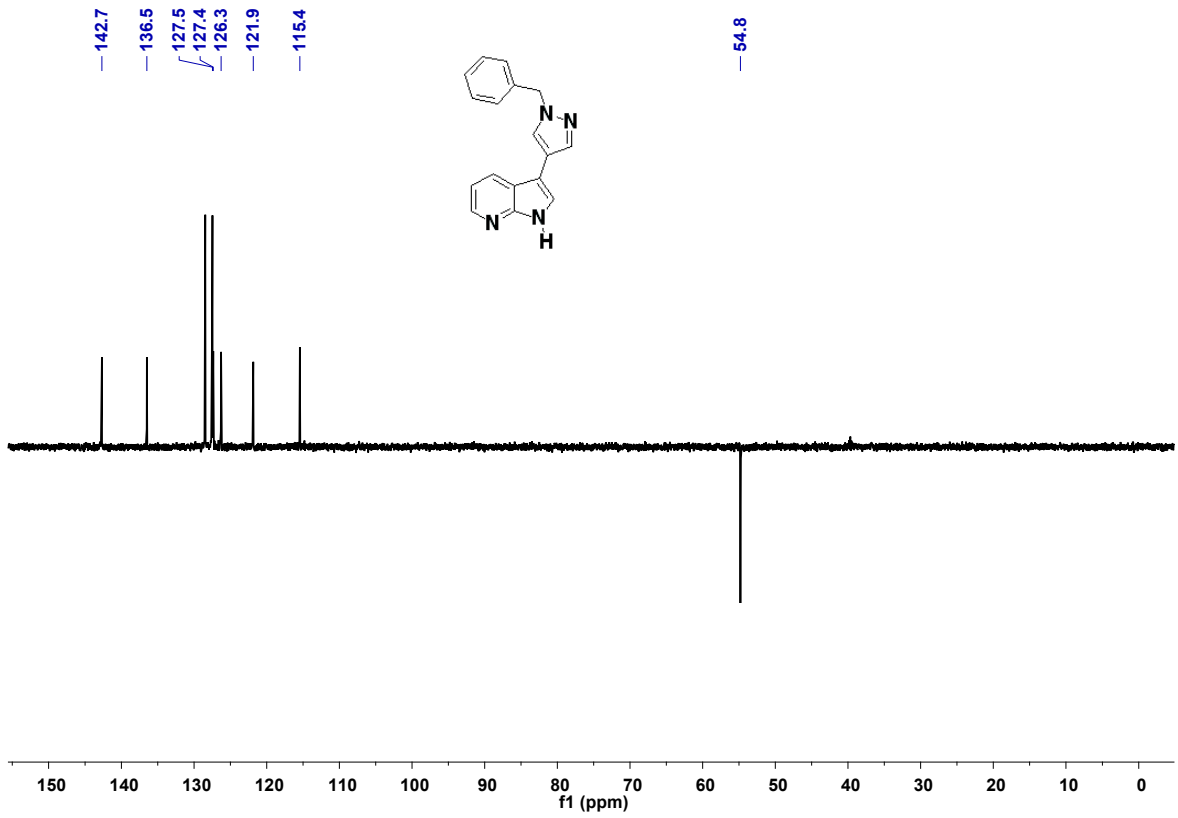
^{13}C DEPT 135-NMR of **10** (15 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).



^{1}H NMR of **11** (15 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).



^{13}C NMR of **11** (15 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).

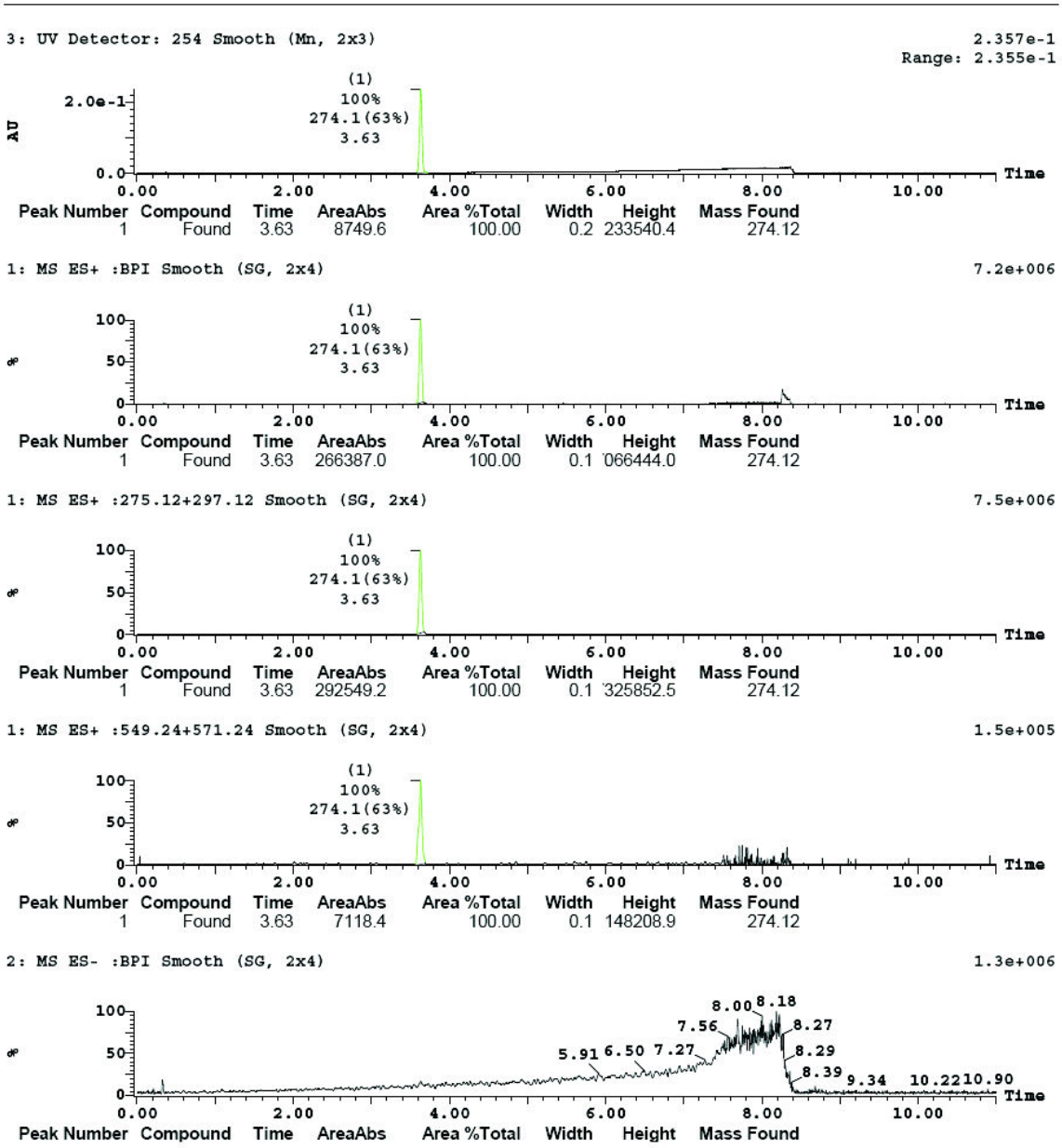


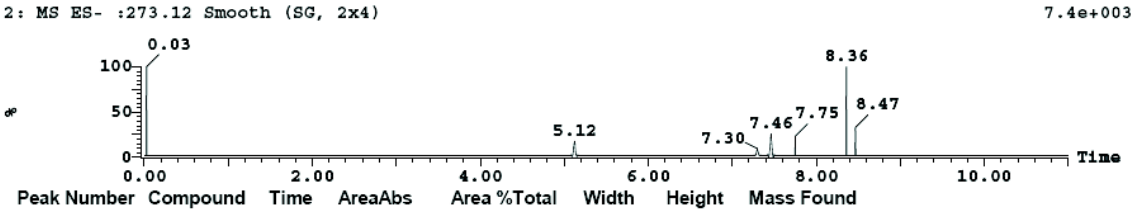
^{13}C DEPT 135-NMR of **11** (15 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).

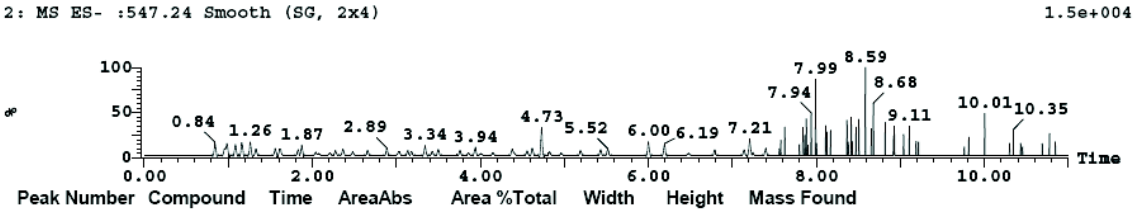
8. Appendix

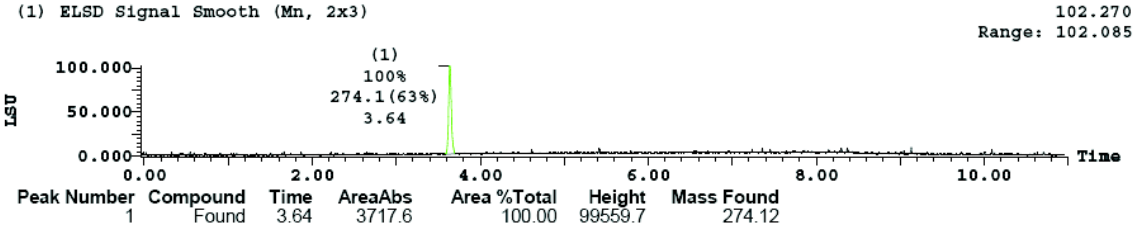
8.1. HT-LC-MS Spectra and UV purity of the obtained compounds 8a-s, 9a-b, 10, and 11

HT-LC-MS Spectrum (SOP 2200) of **8a**. UV purity: 100 %

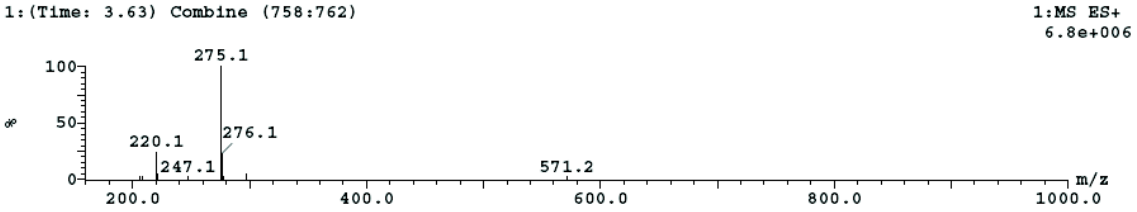




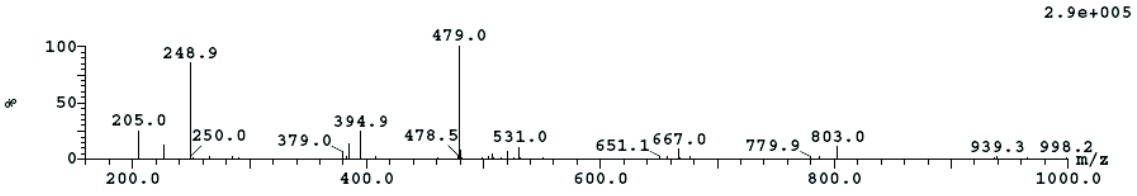




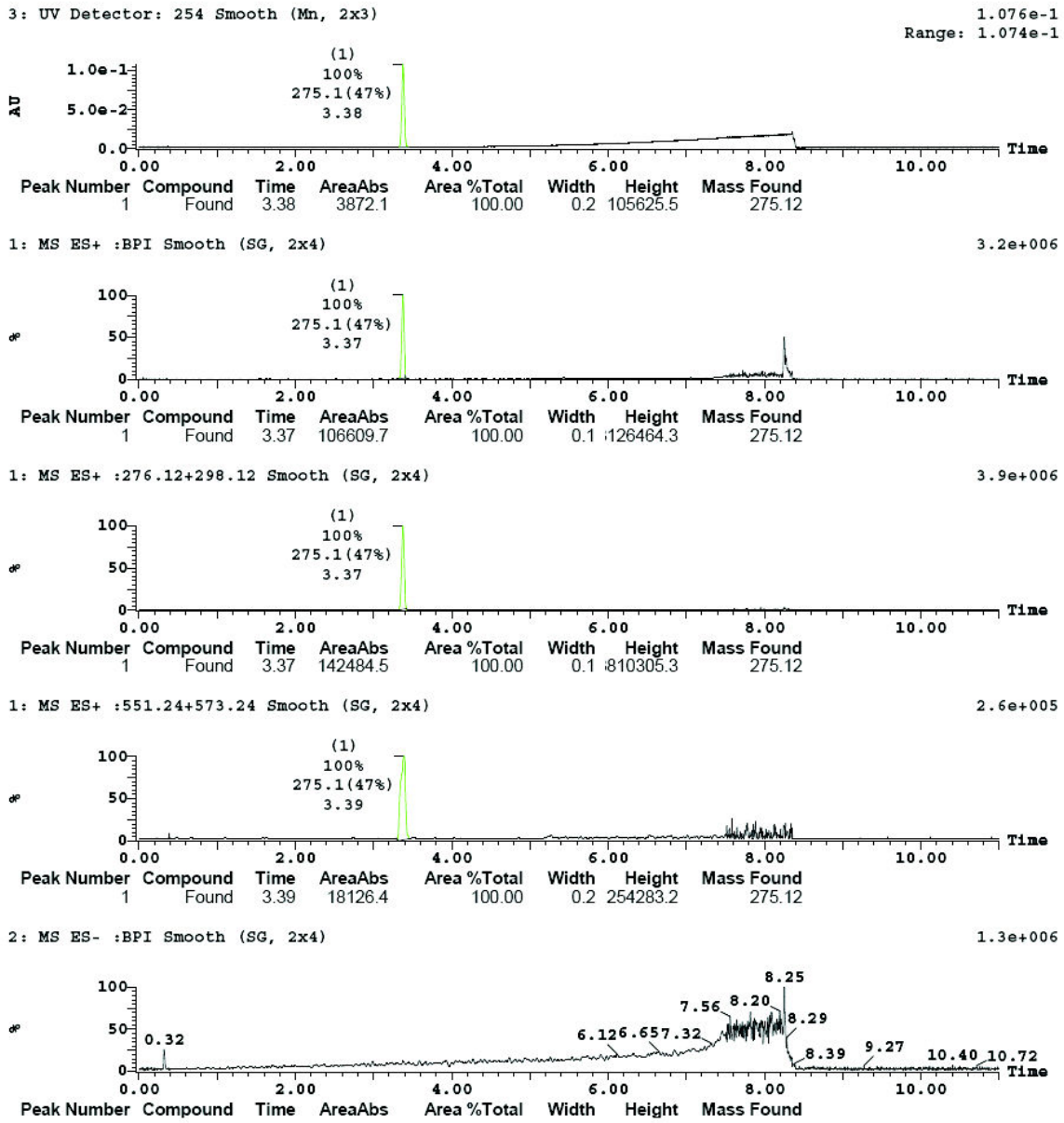
Peak ID Compound Time Mass Found
1 Found 3.63 274.12

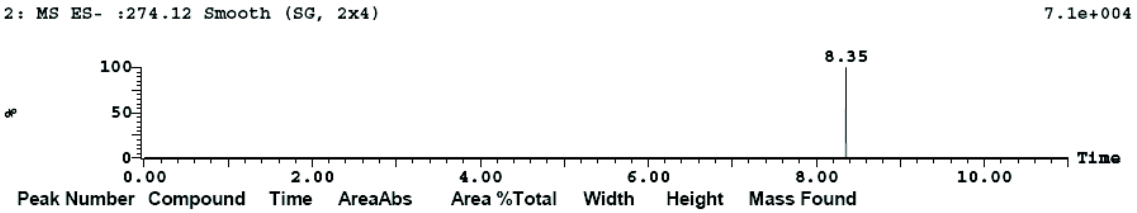


Peak ID Compound Time Mass Found
1 3.63

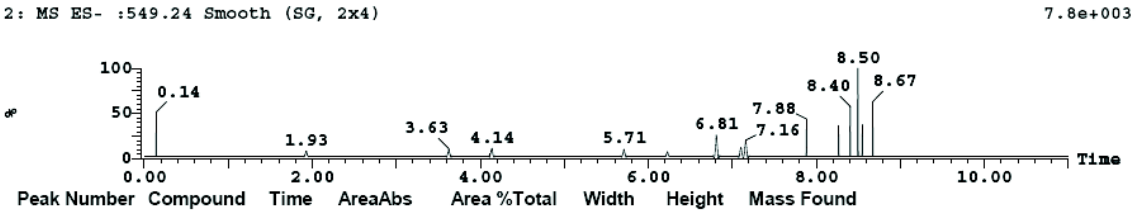


HT-LC-MS Spectrum (SOP 2200) of **8b**. UV purity: 100 %

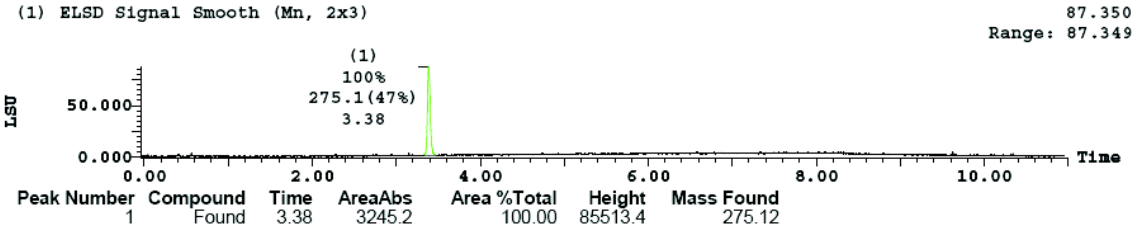




Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found



Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found



Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
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Peak ID	Compound	Time	Mass Found
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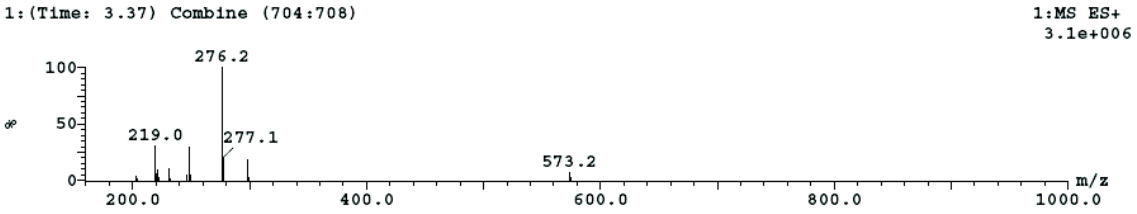

Peak ID	Compound	Time	Mass Found
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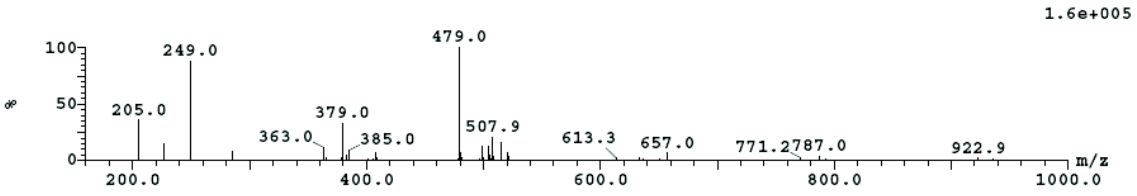
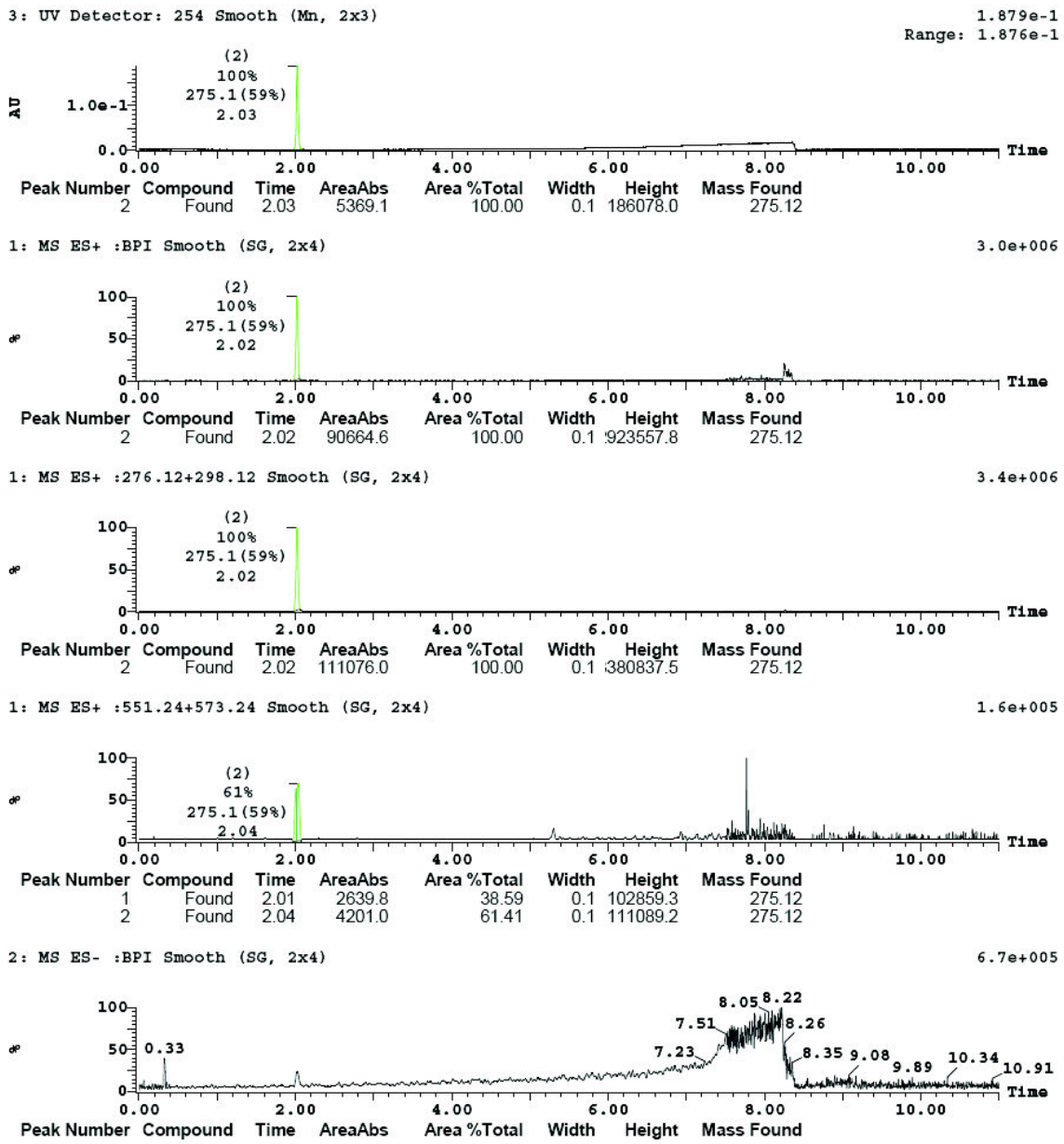
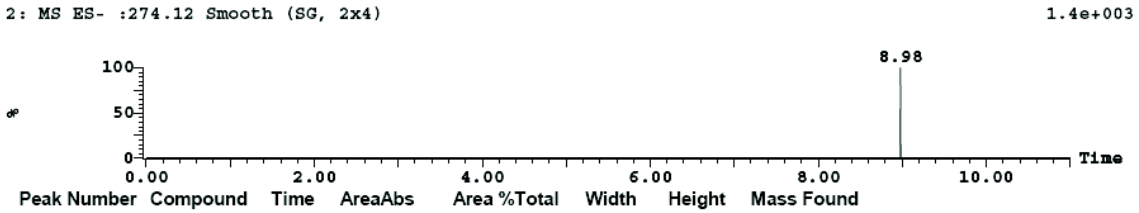
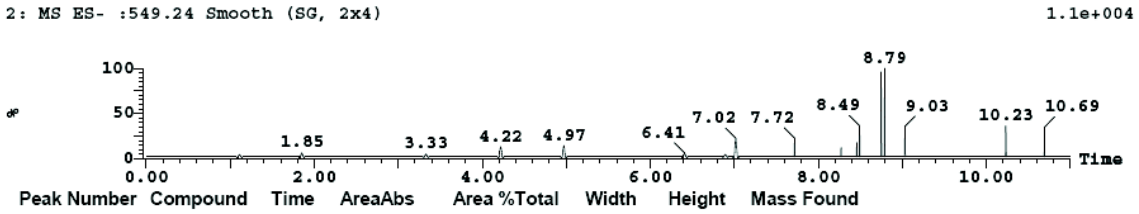
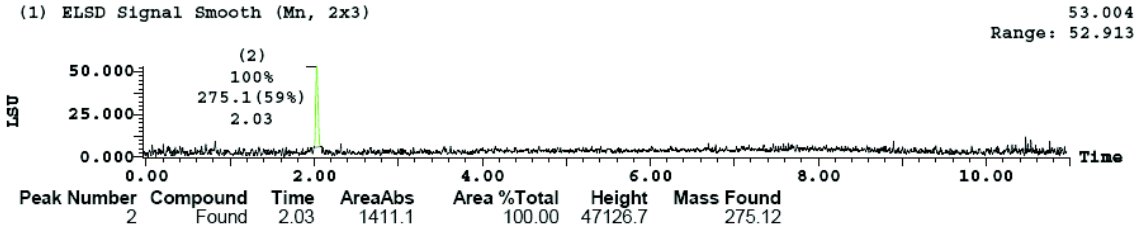


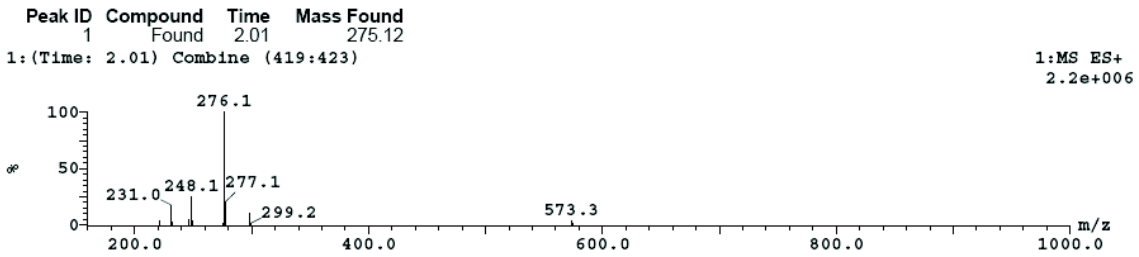
HT-LC-MS Spectrum (SOP 2200) of **8c**. UV purity: 100 %

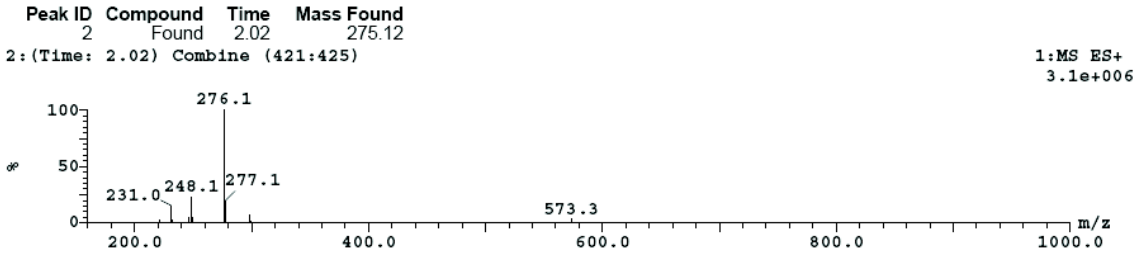


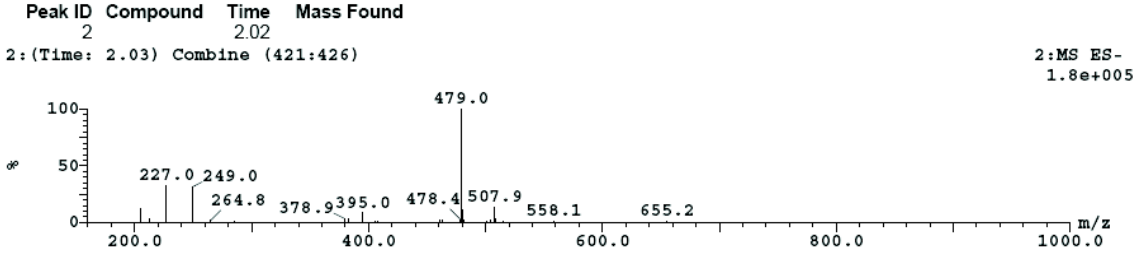




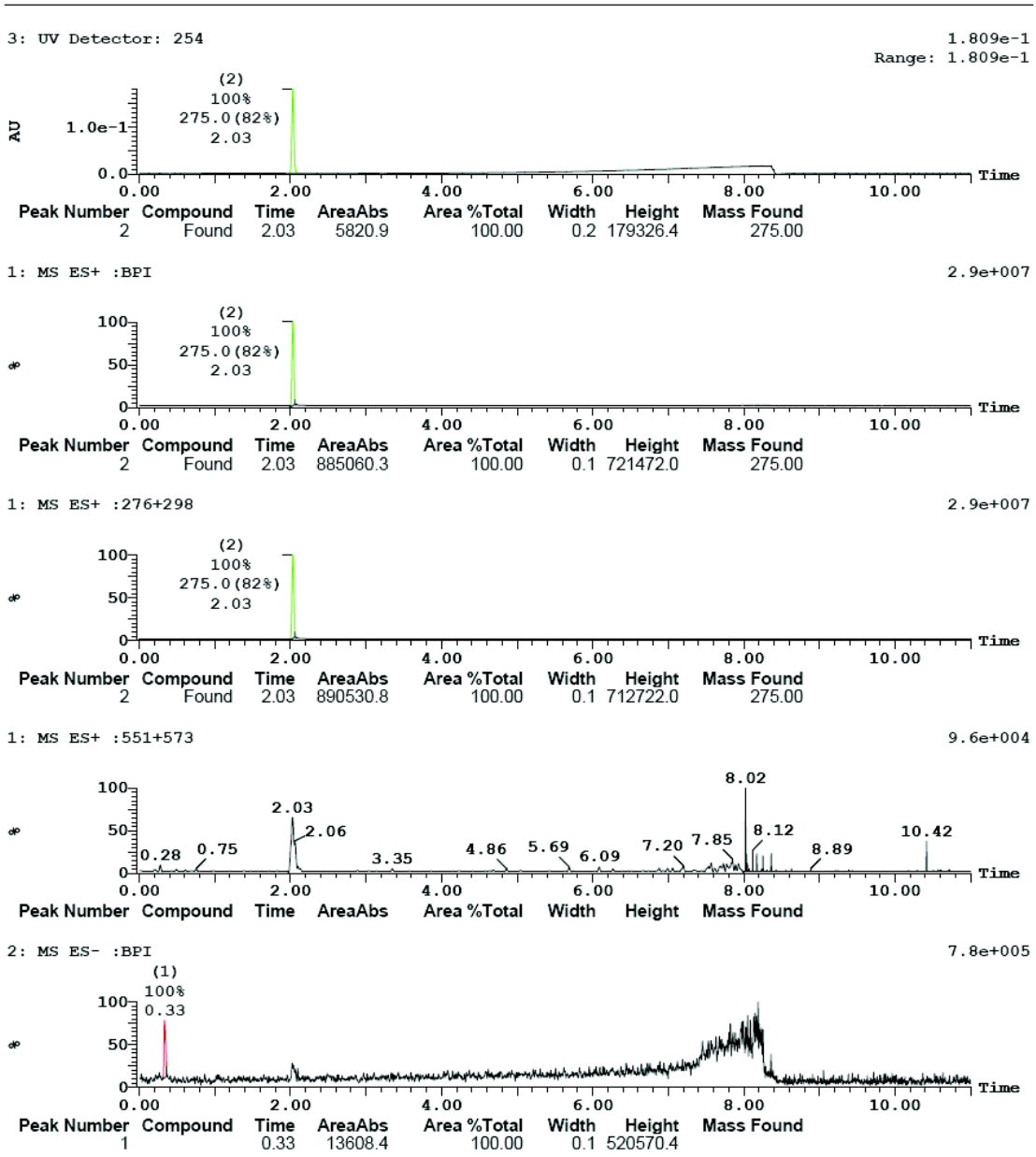


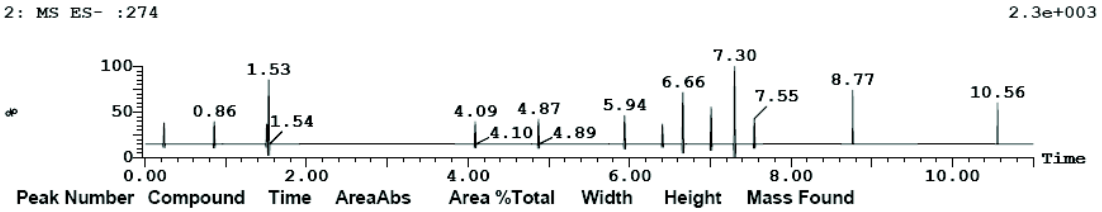




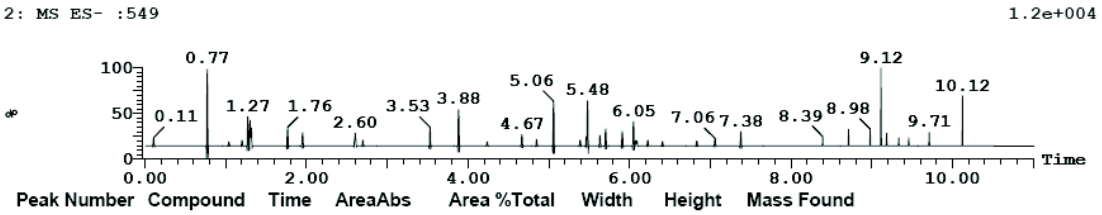


HT-LC-MS Spectrum (SOP 2200) of **8d**. UV purity: 100 %

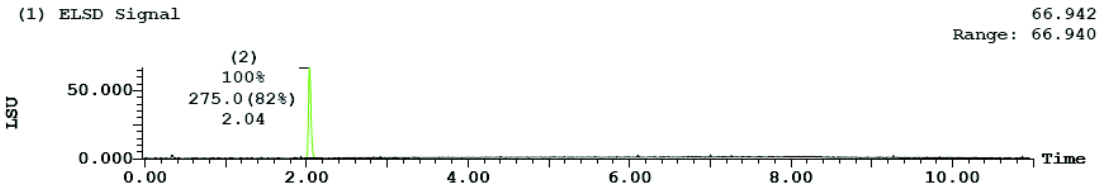




Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

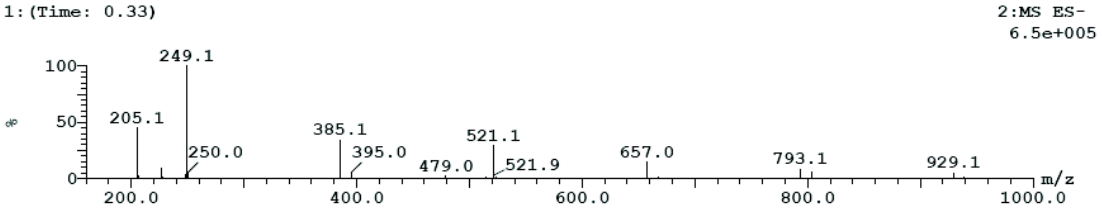


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

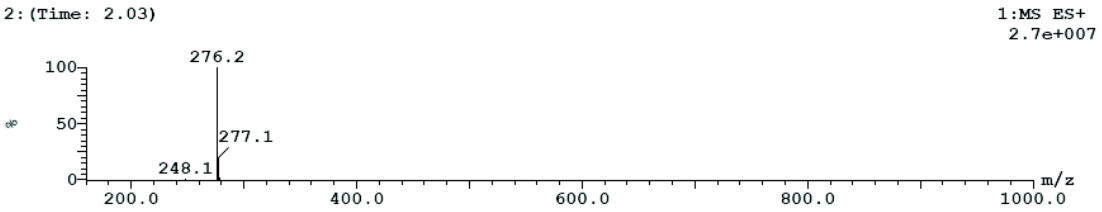


Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
2	Found	2.04	2367.7	100.00	66394.2	275.00

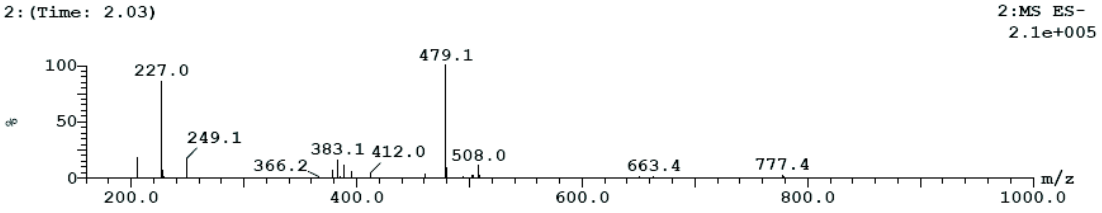
Peak ID	Compound	Time	Mass Found
1		0.33	



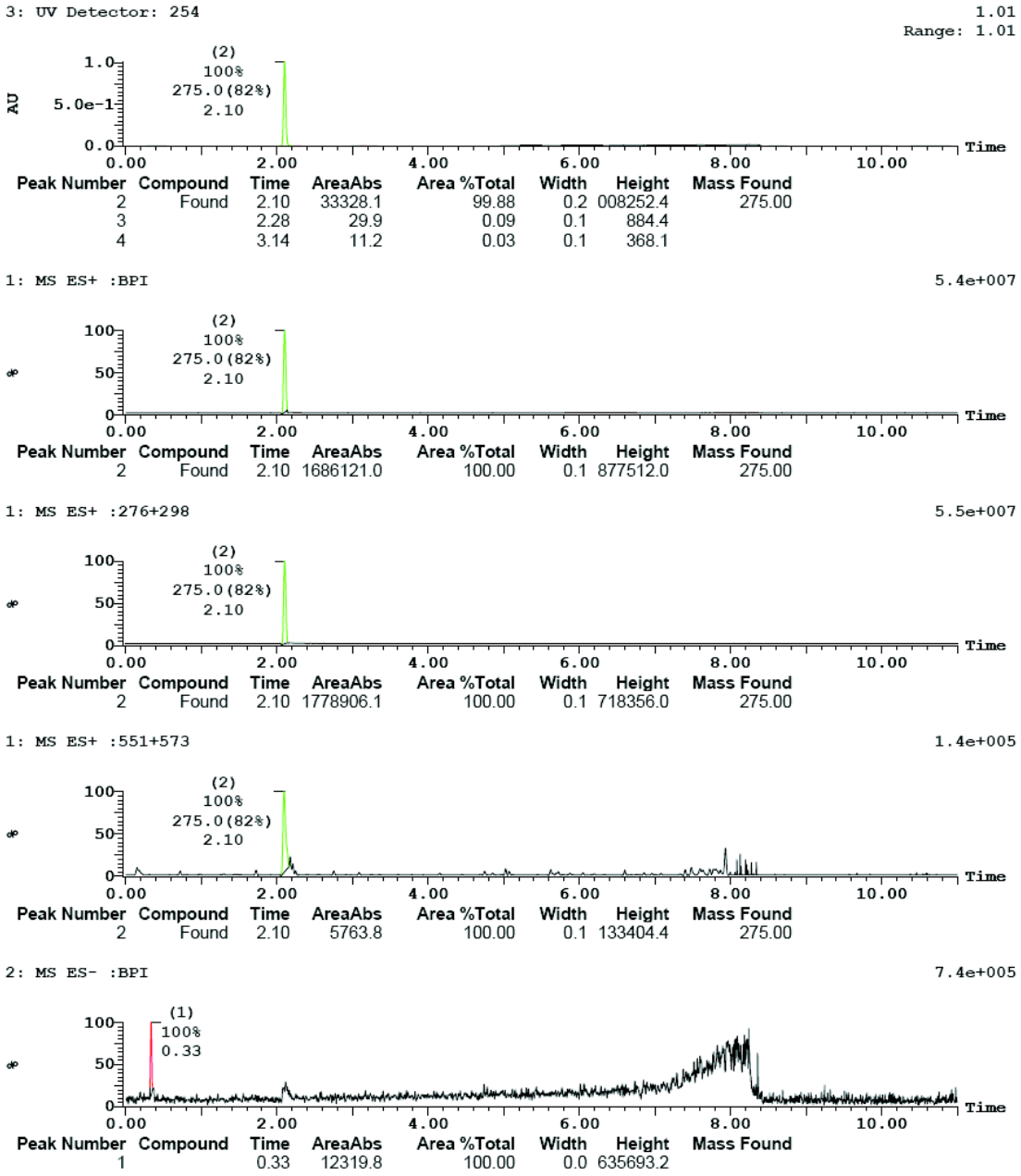
Peak ID	Compound	Time	Mass Found
2	Found	2.03	275.00

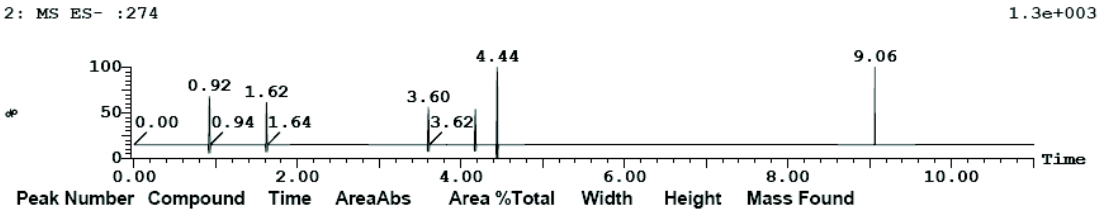


Peak ID	Compound	Time	Mass Found
2		2.03	

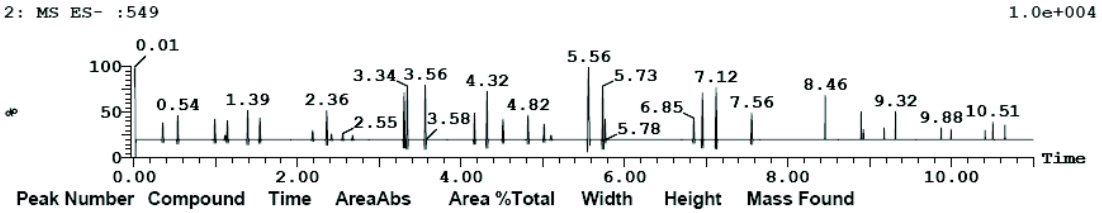


HT-LC-MS Spectrum (SOP 2200) of **8e**. UV purity: 99.9 %

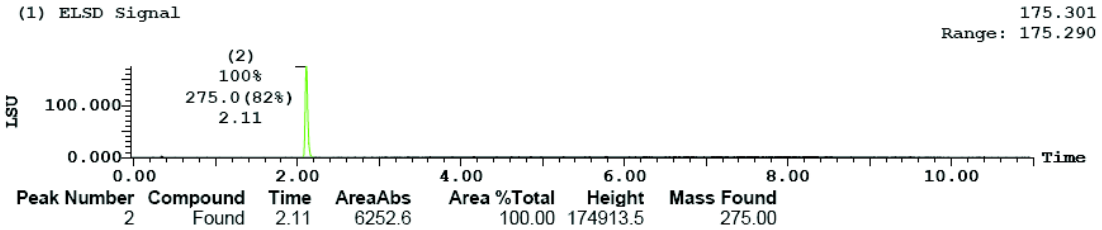




Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

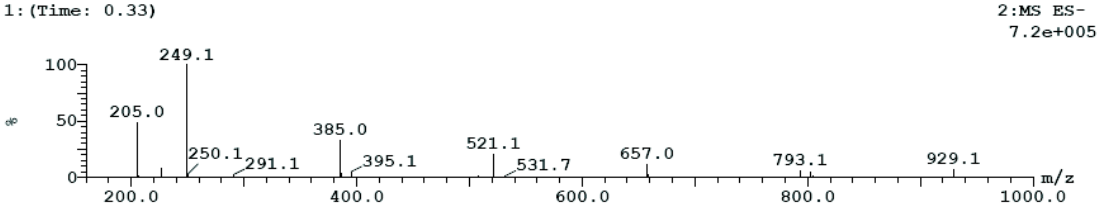


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

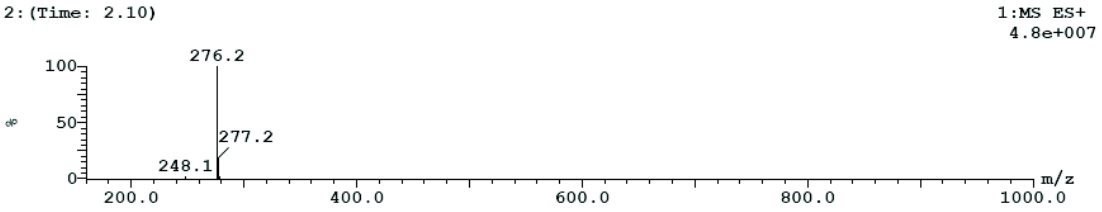


Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
2	Found	2.11	6252.6	100.00	174913.5	275.00

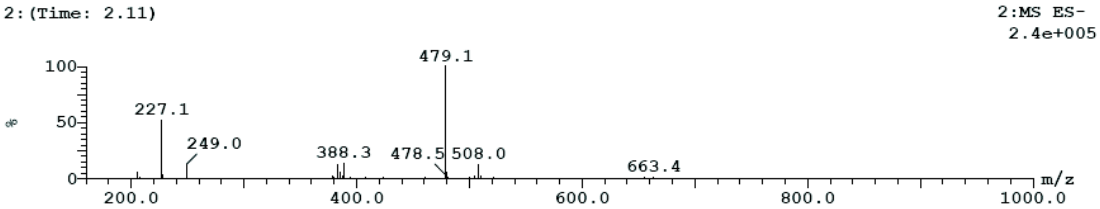
Peak ID	Compound	Time	Mass Found
1		0.33	



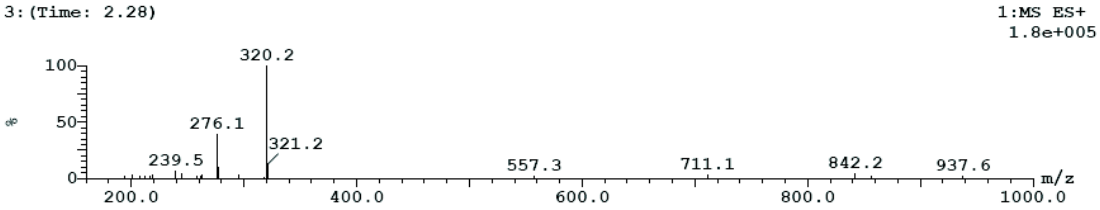
Peak ID	Compound	Time	Mass Found
2	Found	2.10	275.00



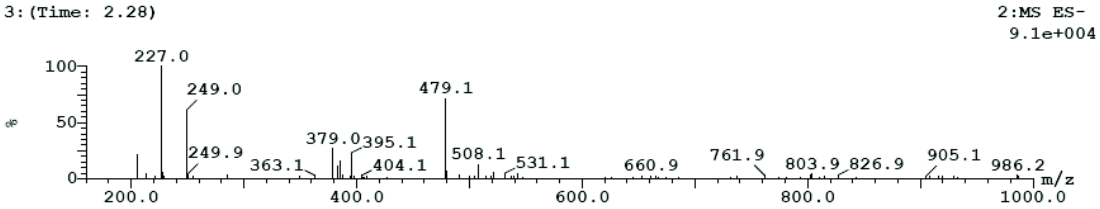
Peak ID	Compound	Time	Mass Found
2		2.10	



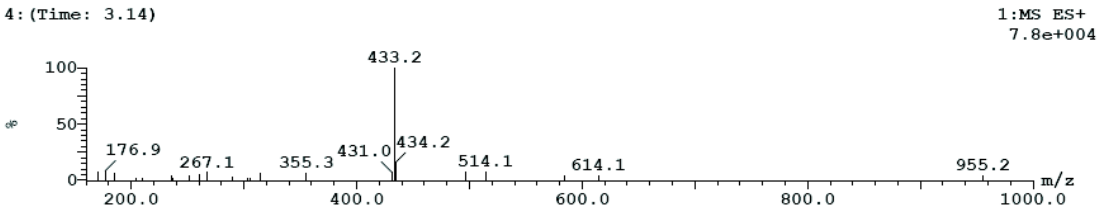
Peak ID	Compound	Time	Mass Found
3		2.28	



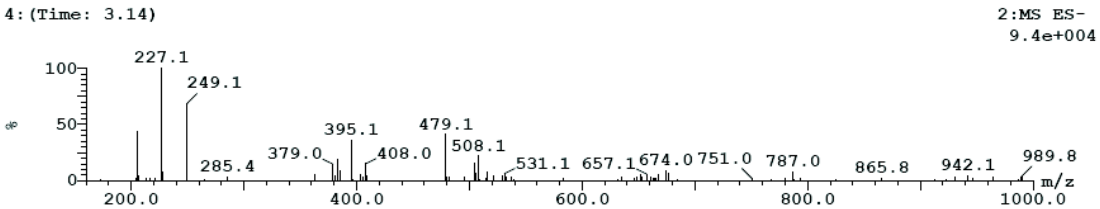
Peak ID	Compound	Time	Mass Found
3		2.28	



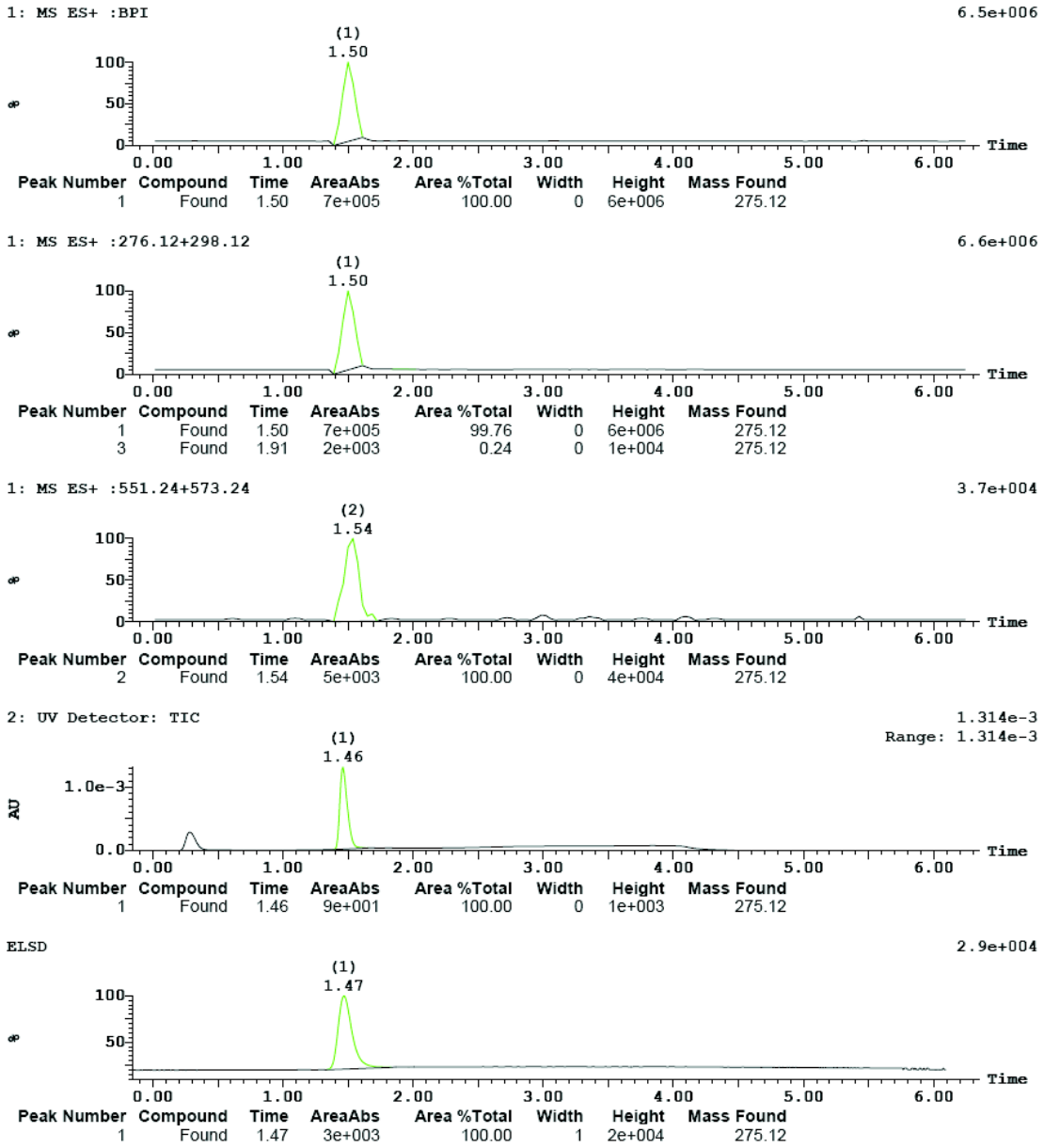
Peak ID	Compound	Time	Mass Found
4		3.14	



Peak ID	Compound	Time	Mass Found
4		3.14	



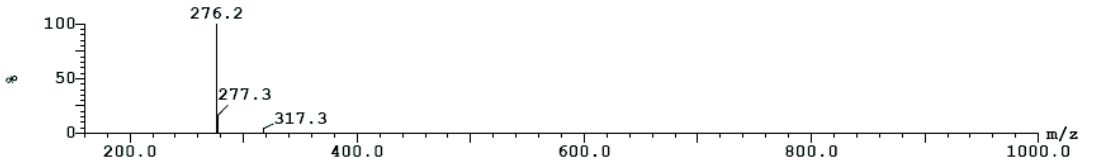
HT-LC-MS Spectrum (SOP 2222) of **8f**. UV purity: 100 %



Peak ID	Compound	Time	Mass Found
1	Found	1.50	275.12

1:(Time: 1.46)

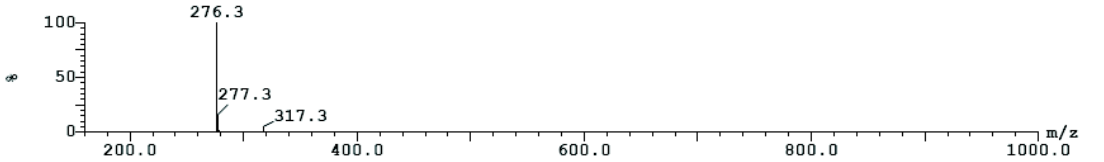
1:MS ES+
5.0e+006



Peak ID	Compound	Time	Mass Found
2	Found	1.54	275.12

2:(Time: 1.54)

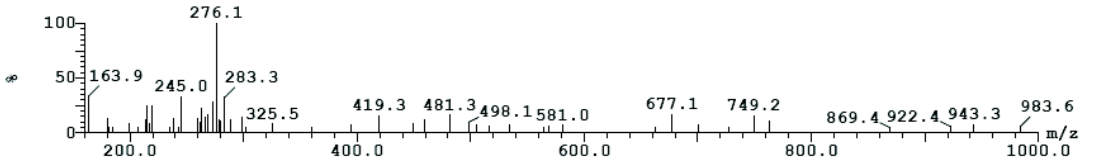
1:MS ES+
5.4e+006



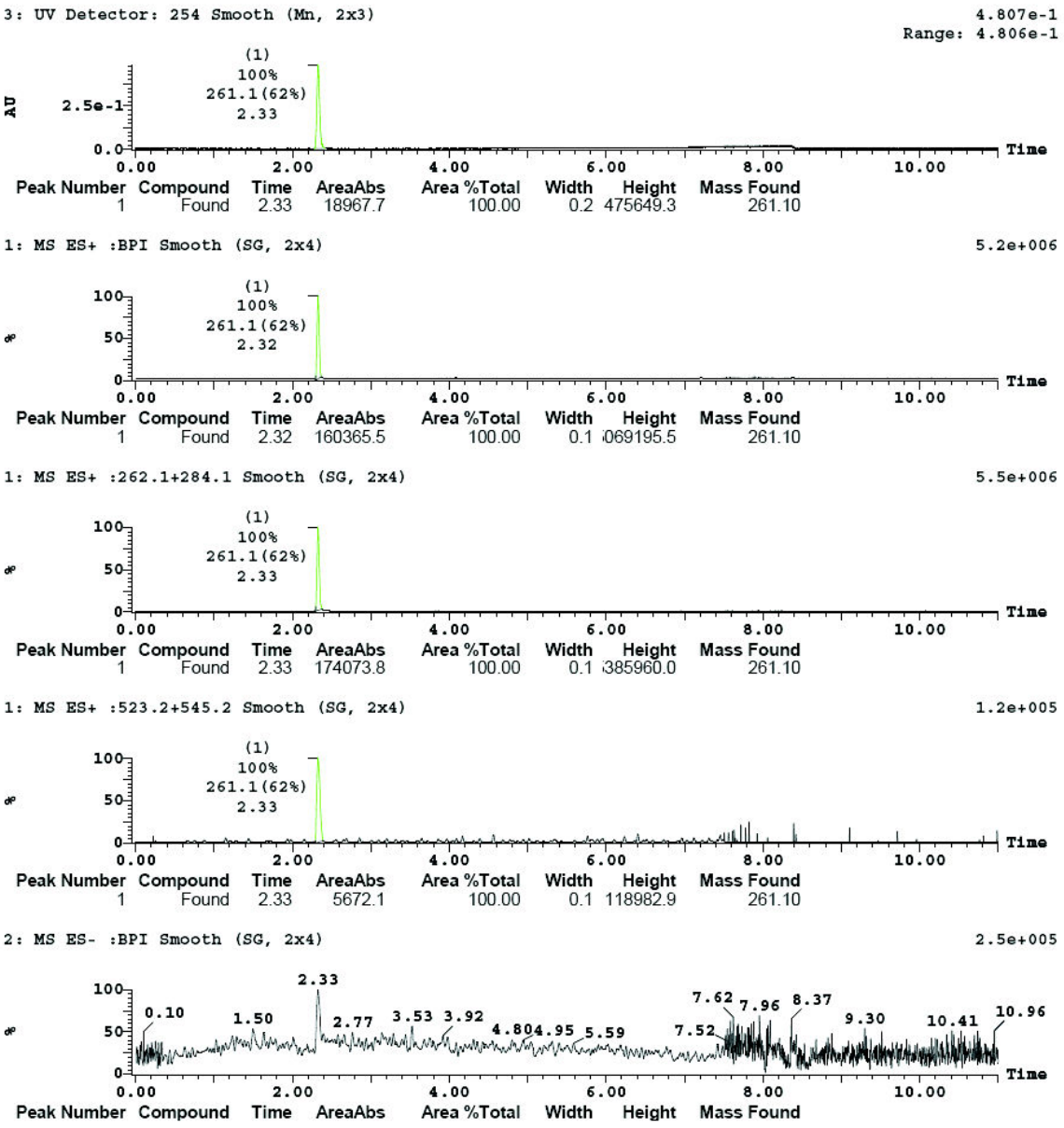
Peak ID	Compound	Time	Mass Found
3	Found	1.91	275.12

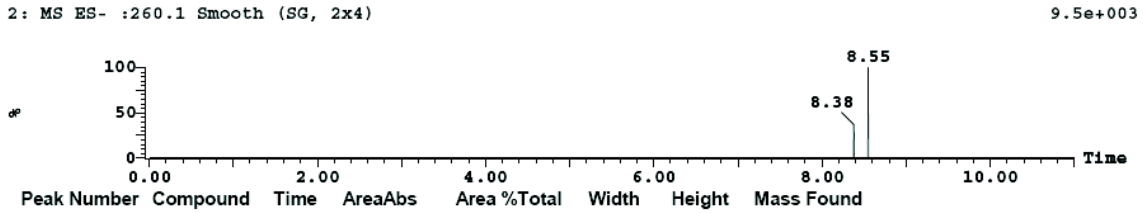
3:(Time: 1.91)

1:MS ES+
2.3e+004

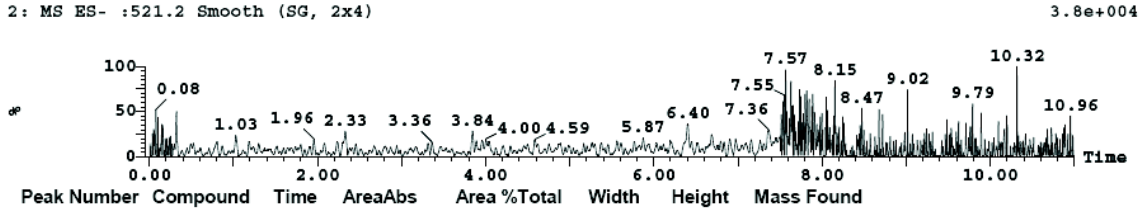


HT-LC-MS Spectrum (SOP 2200) of **8g**. UV purity: 100 %

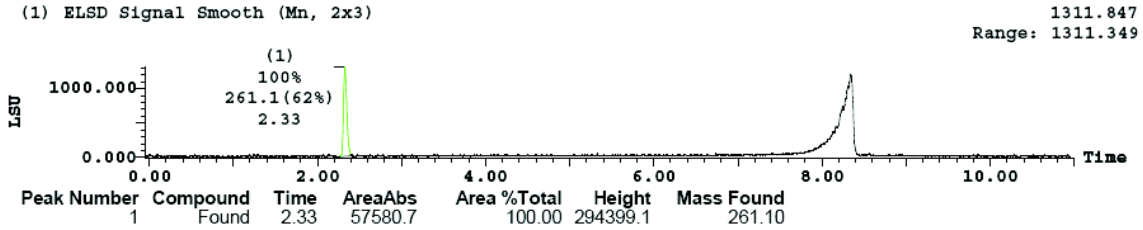




Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

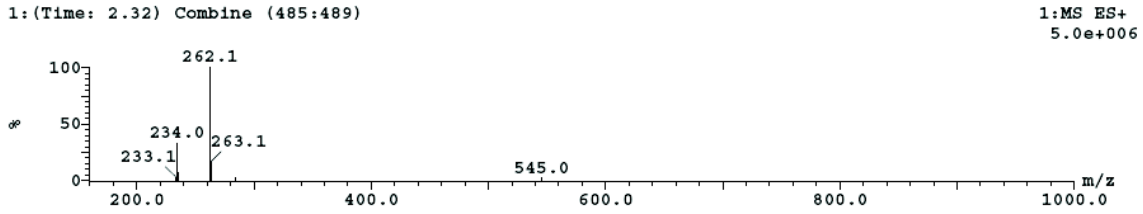


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

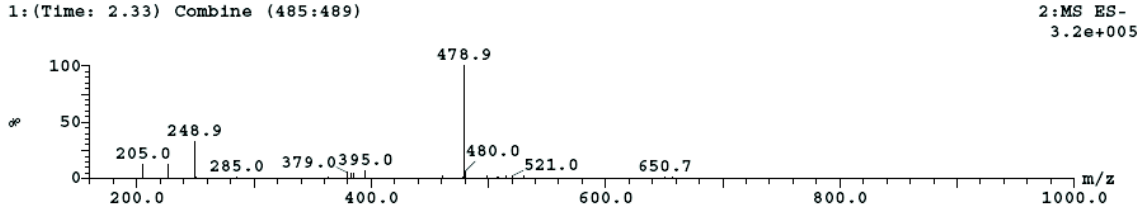


Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1	Found	2.33	57580.7	100.00	294399.1	261.10

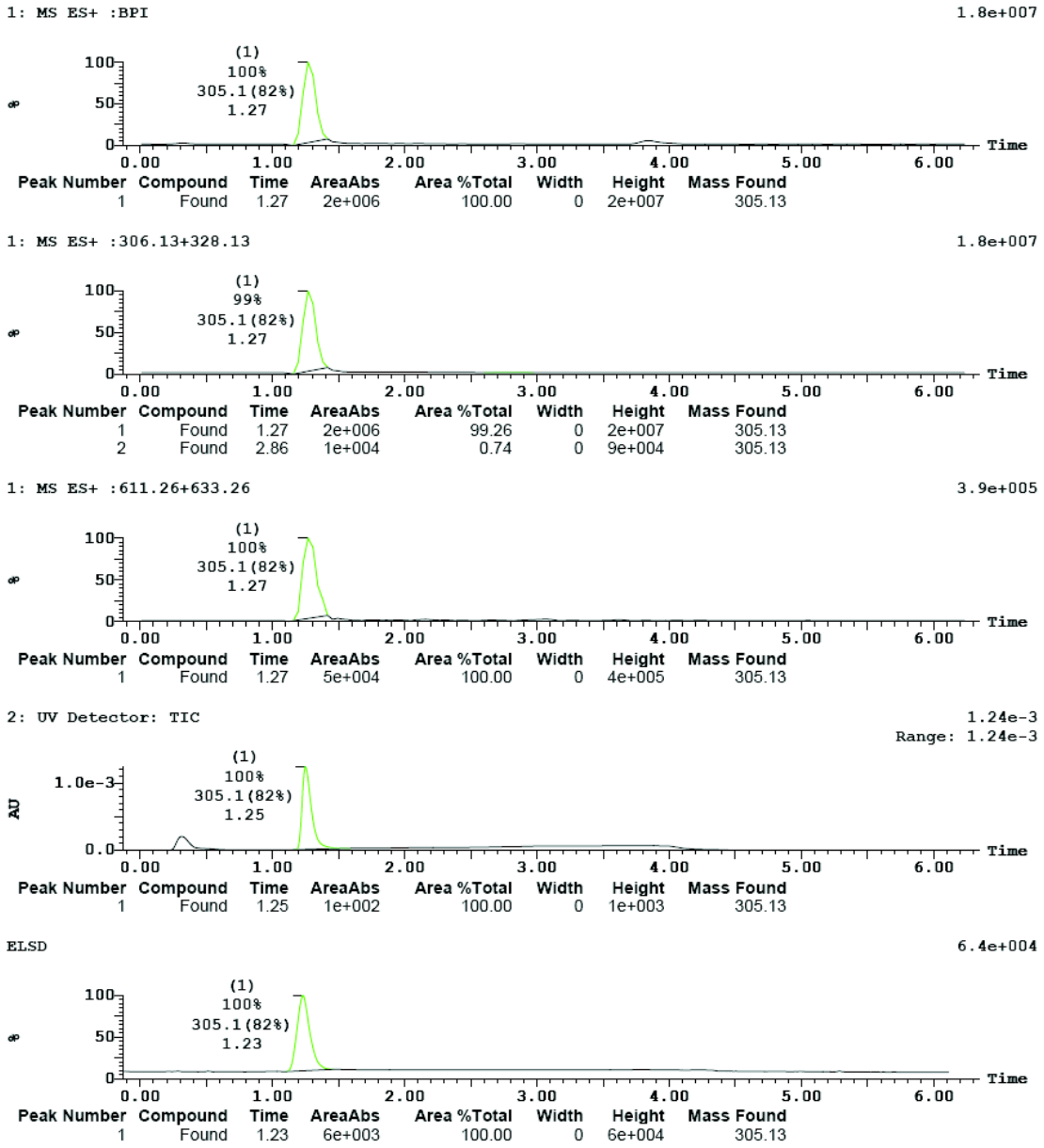
Peak ID	Compound	Time	Mass Found
1	Found	2.32	261.10



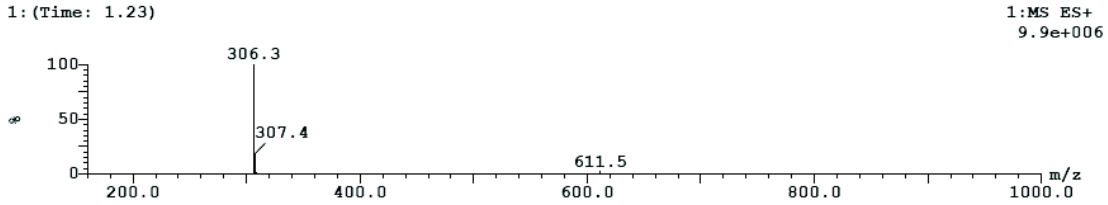
Peak ID	Compound	Time	Mass Found
1		2.32	



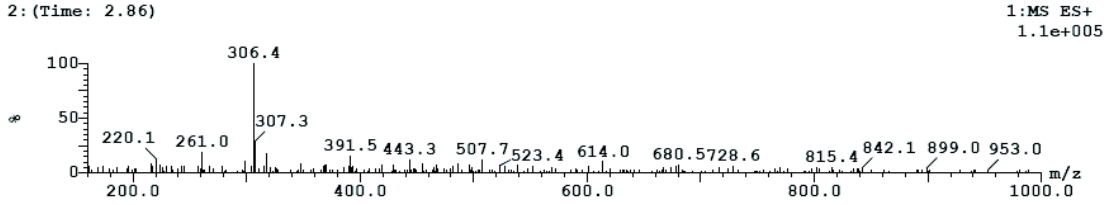
HT-LC-MS Spectrum (SOP 2222) of **8h**. UV purity: 100 %



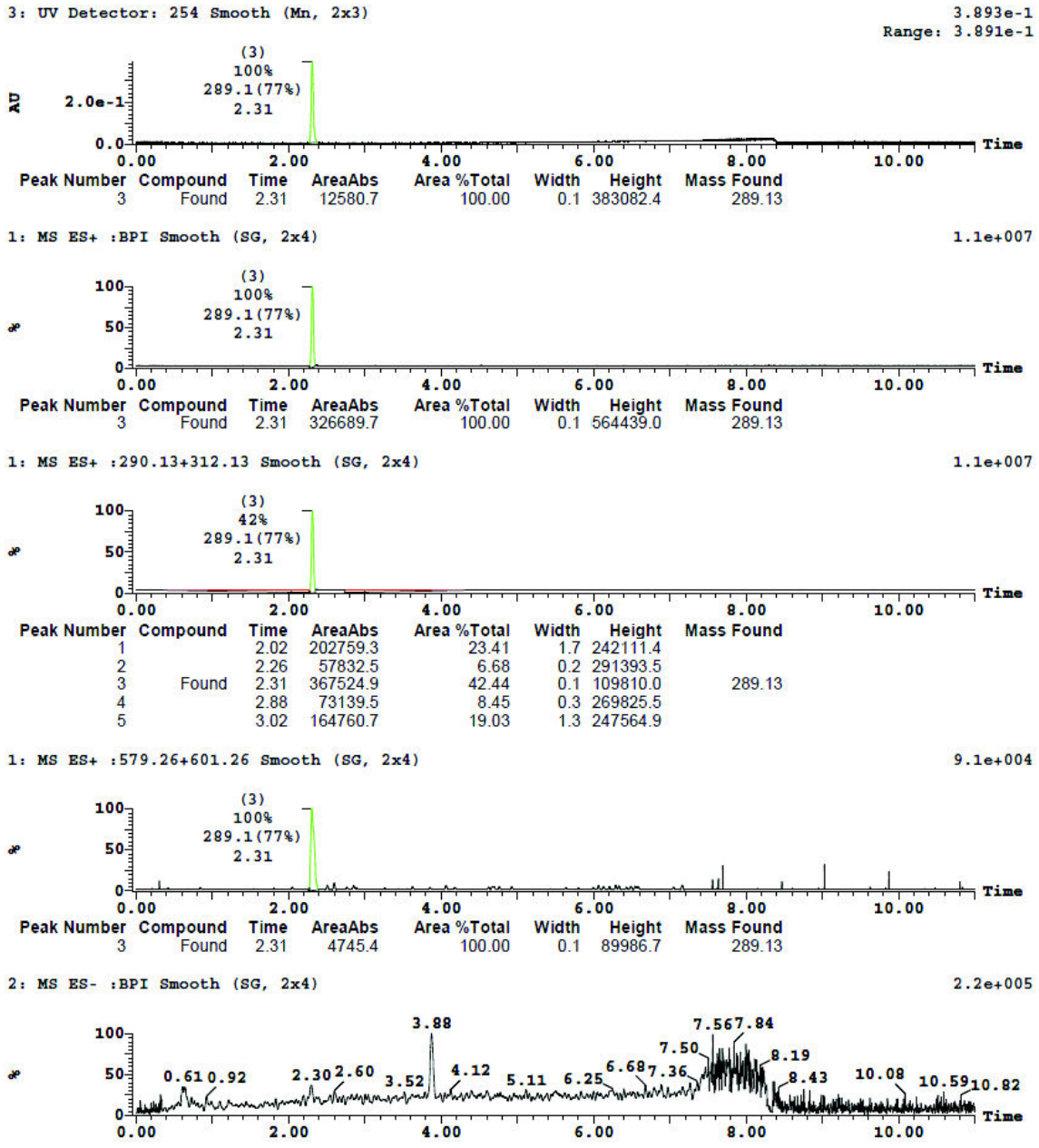
Peak ID	Compound	Time	Mass Found
1	Found	1.27	305.13

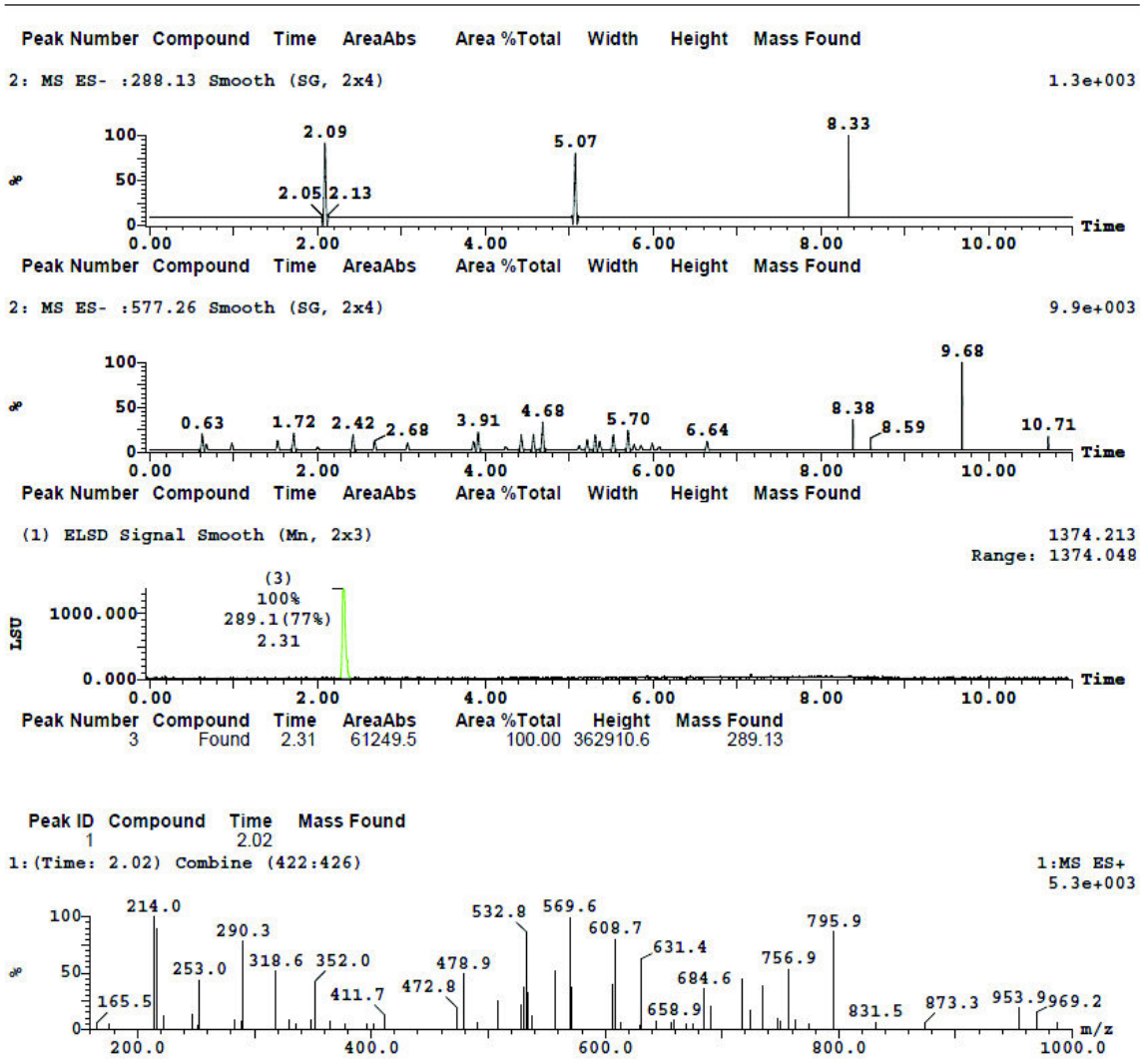


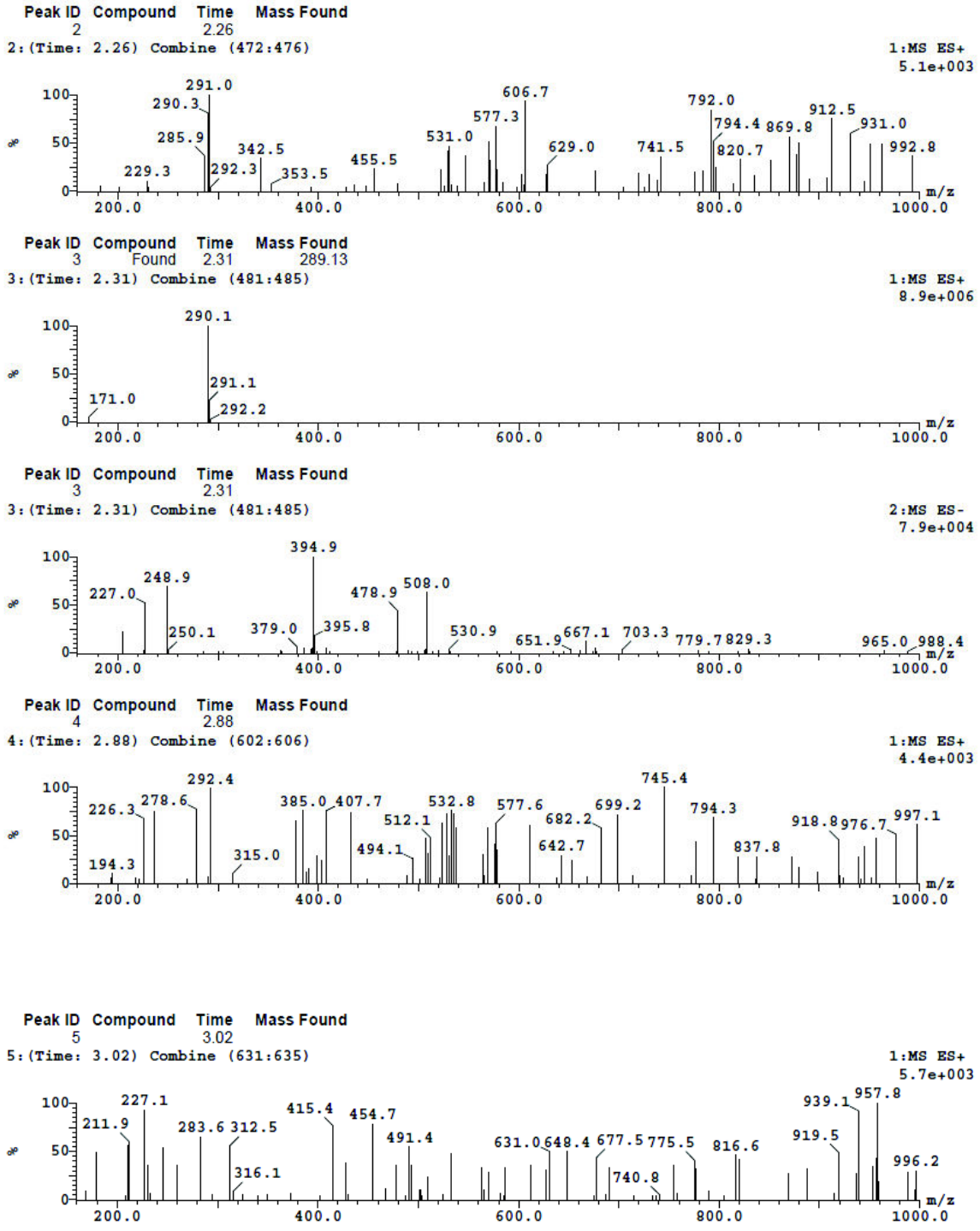
Peak ID	Compound	Time	Mass Found
2	Found	2.86	305.13



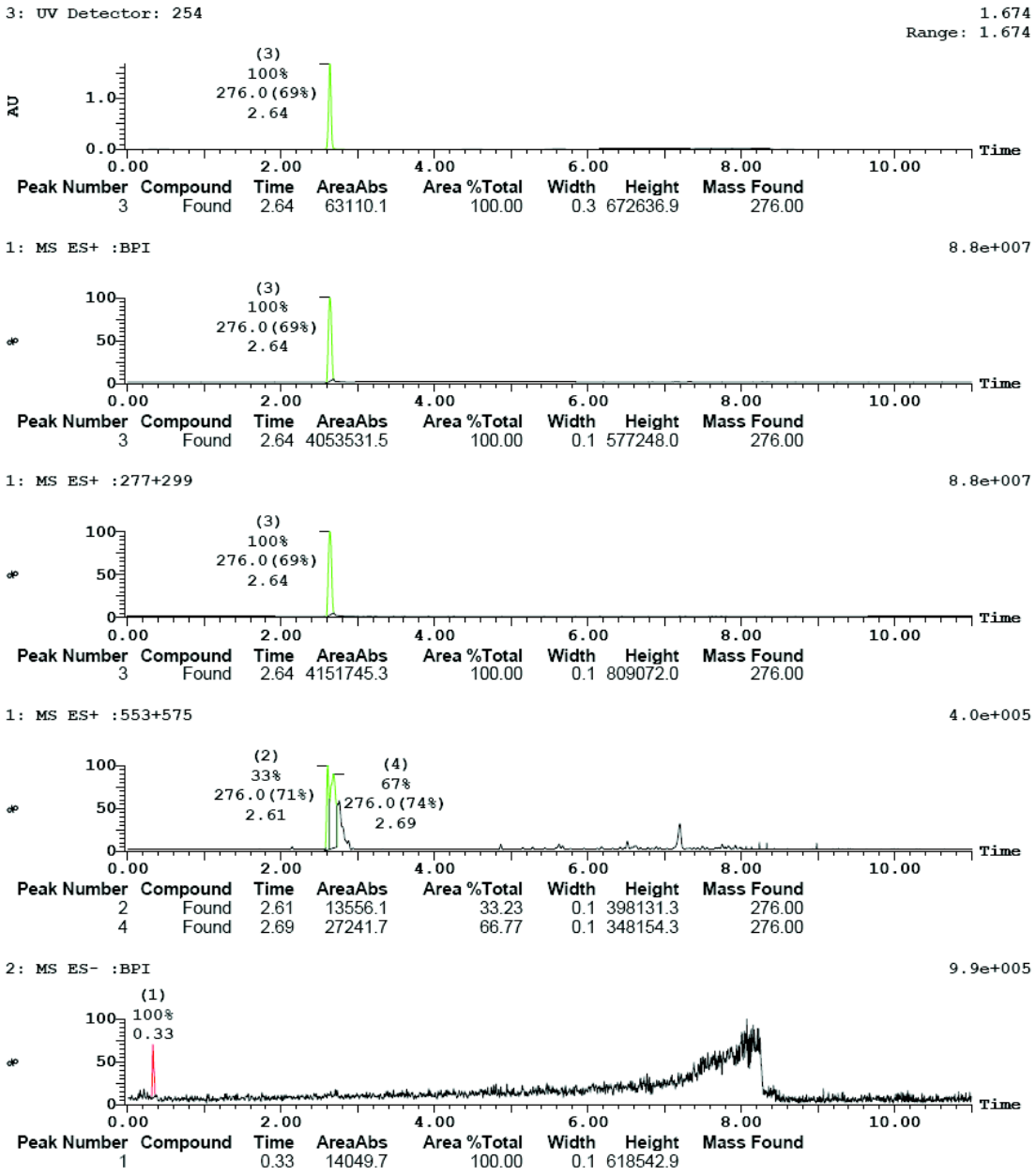
HT-LC-MS Spectrum (SOP 2200) of **8i**. UV purity: 100 %

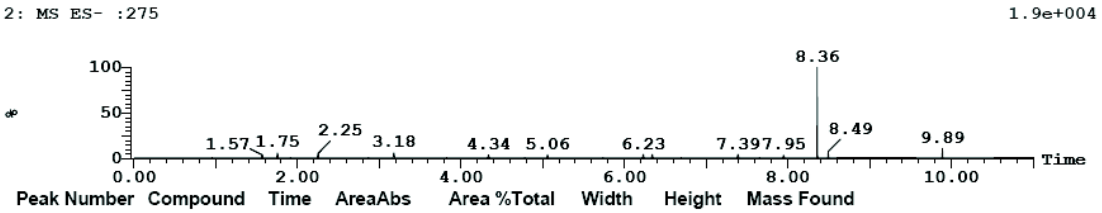




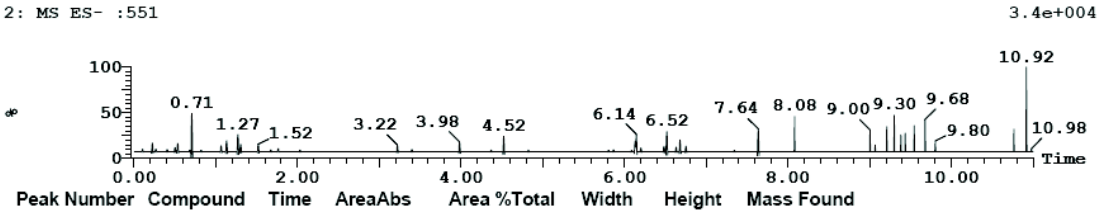


HT-LC-MS Spectrum (SOP 2200) of **8j**. UV purity: 100 %

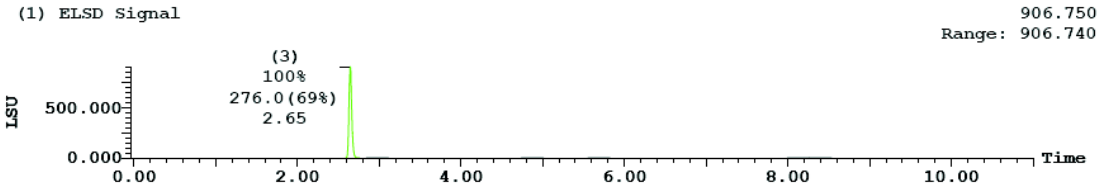




Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

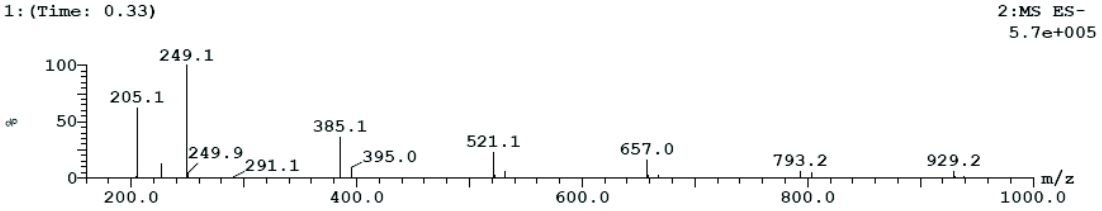


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

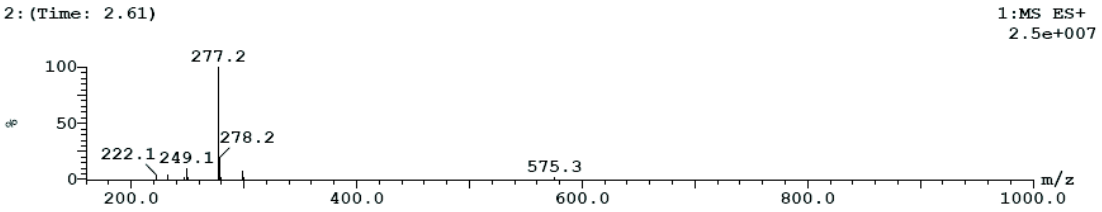


Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
3	Found	2.65	36380.7	100.00	906201.4	276.00

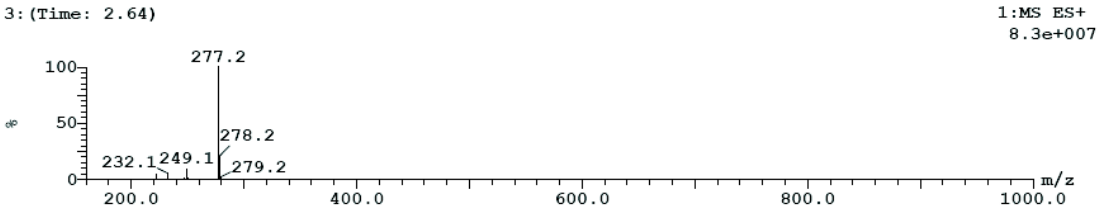
Peak ID	Compound	Time	Mass Found
1		0.33	



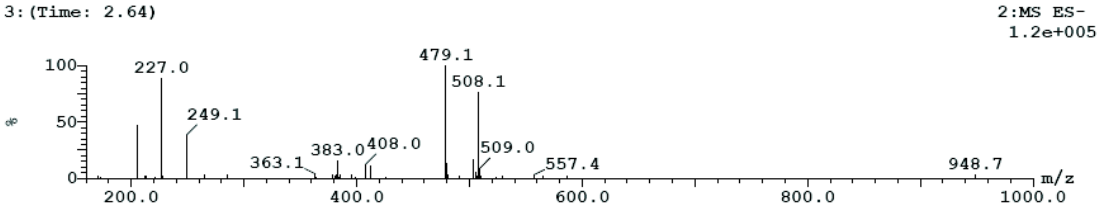
Peak ID	Compound	Time	Mass Found
2	Found	2.61	276.00



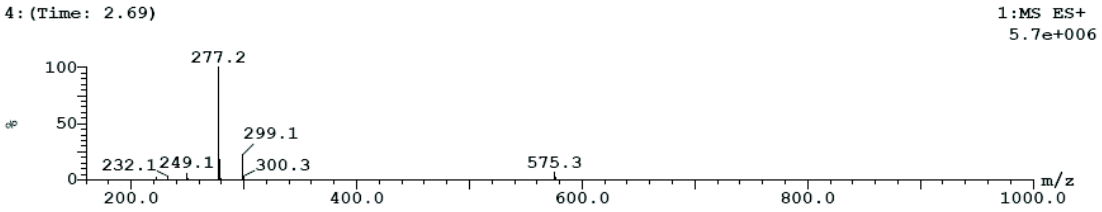
Peak ID	Compound	Time	Mass Found
3	Found	2.64	276.00



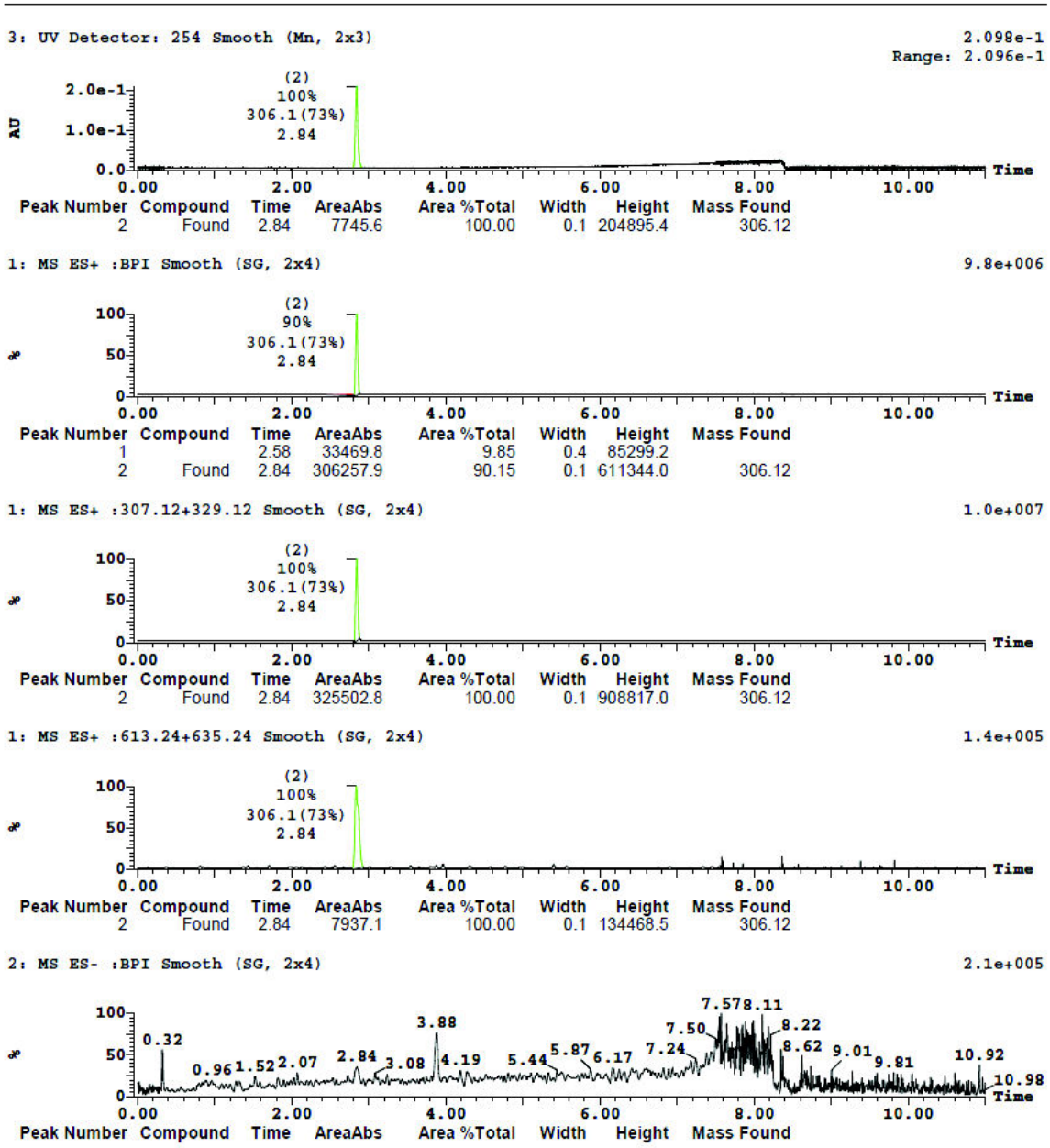
Peak ID	Compound	Time	Mass Found
3		2.64	

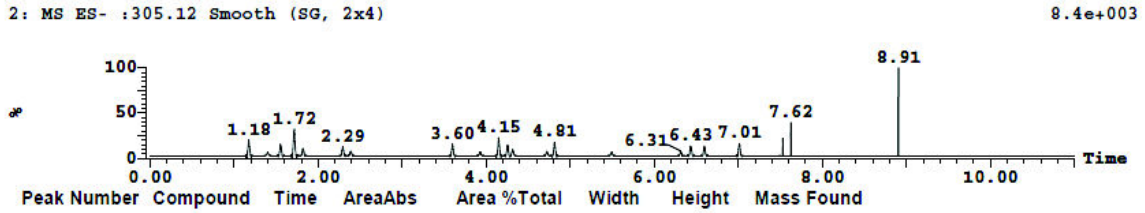


Peak ID	Compound	Time	Mass Found
4	Found	2.69	276.00

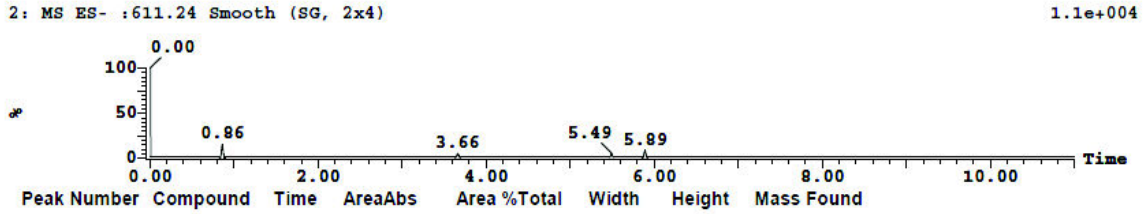


HT-LC-MS Spectrum (SOP 2200) of **8k**. UV purity: 100 %

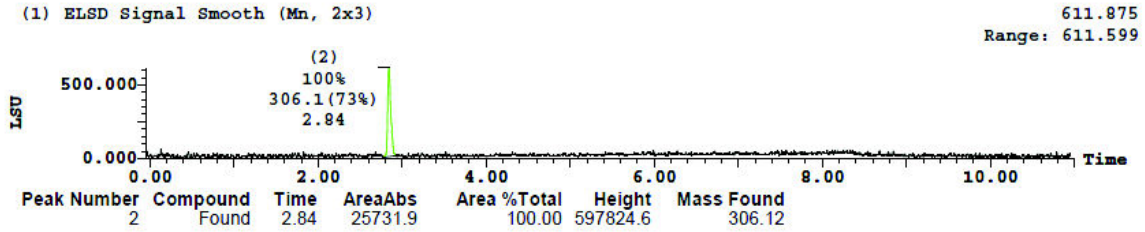




Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

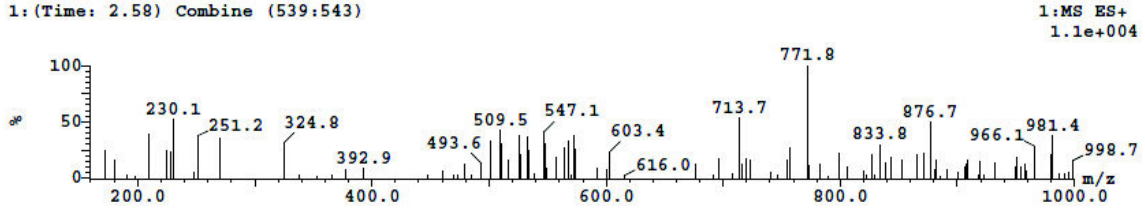


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

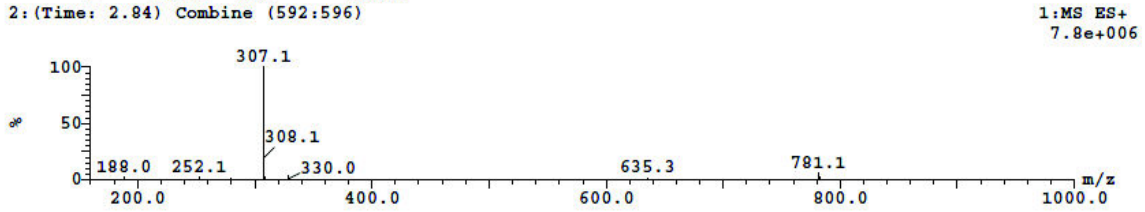


Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
2	Found	2.84	25731.9	100.00	597824.6	306.12

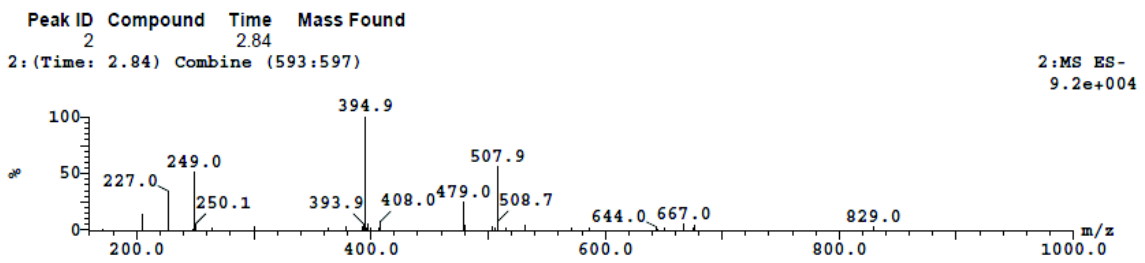
Peak ID	Compound	Time	Mass Found
1		2.58	



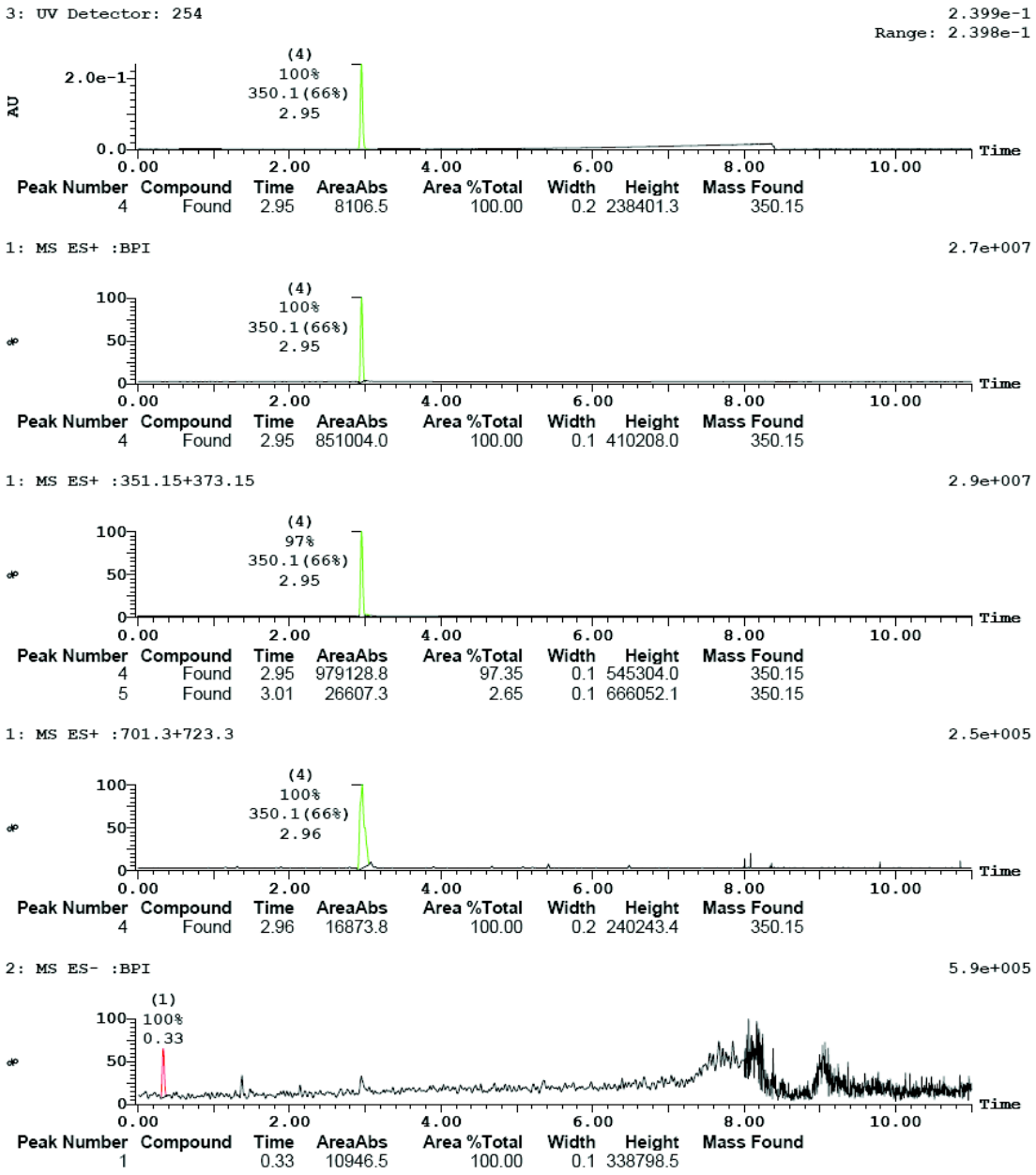
Peak ID	Compound	Time	Mass Found
2	Found	2.84	306.12

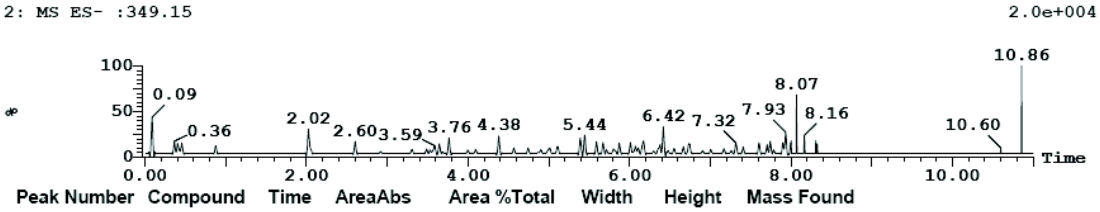


Peak ID	Compound	Time	Mass Found
2		2.84	

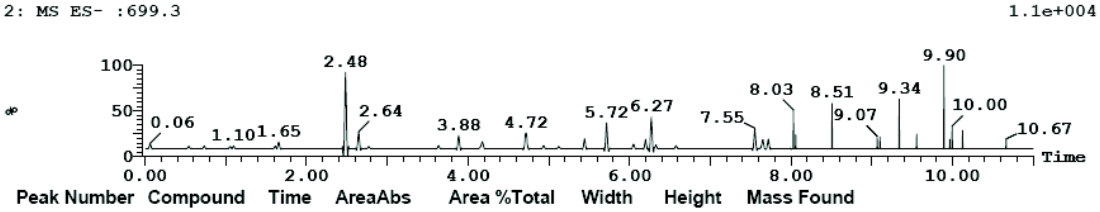


HT-LC-MS Spectrum (SOP 2200) of **8l**. UV purity: 100 %

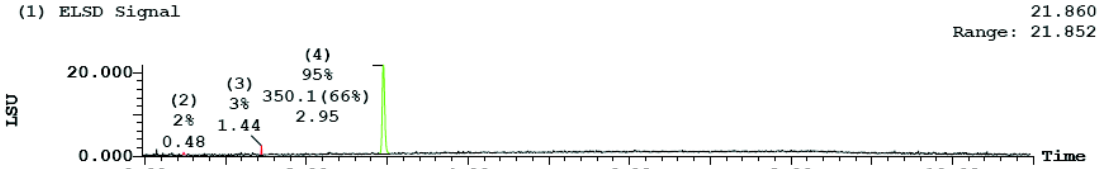




Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

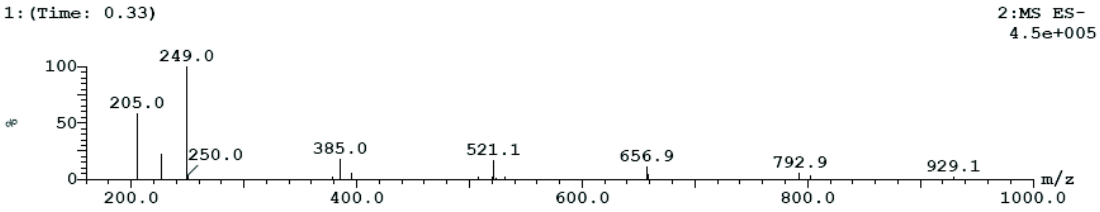


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

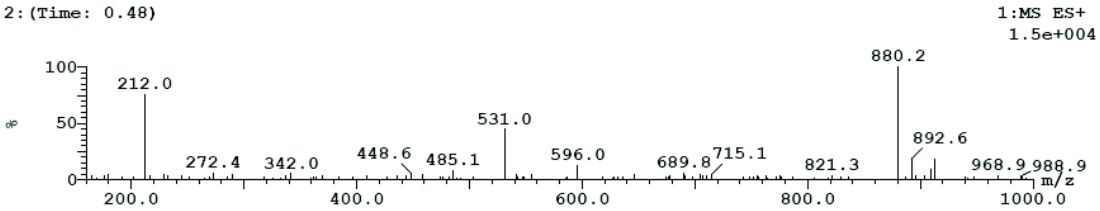


Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
2		0.48	18.3	2.24	862.8	
3		1.44	22.9	2.79	2265.4	
4	Found	2.95	778.2	94.97	21338.2	350.15

Peak ID	Compound	Time	Mass Found
1		0.33	

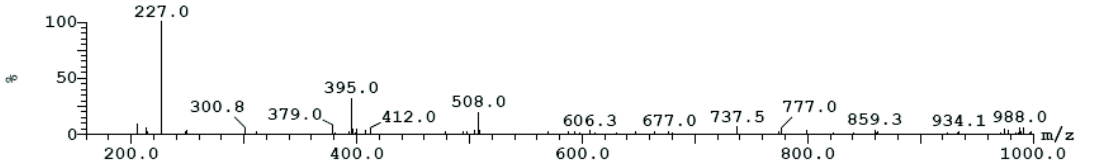


Peak ID	Compound	Time	Mass Found
2		0.48	



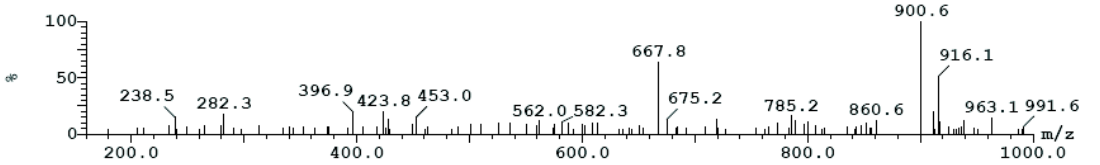
Peak ID	Compound	Time	Mass Found
2		0.48	

2:(Time: 0.48) 2:MS ES- 9.0e+004



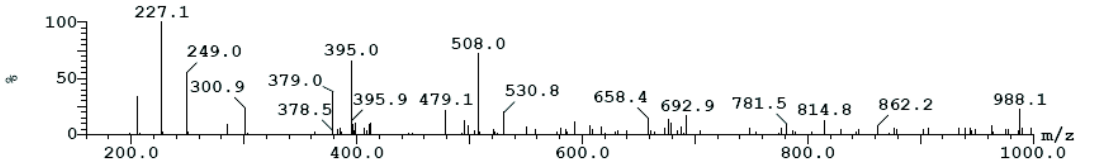
Peak ID	Compound	Time	Mass Found
3		1.44	

3:(Time: 1.44) 1:MS ES+ 5.1e+003



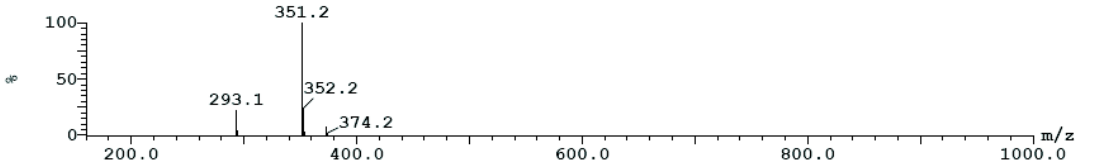
Peak ID	Compound	Time	Mass Found
3		1.44	

3:(Time: 1.44) 2:MS ES- 3.7e+004



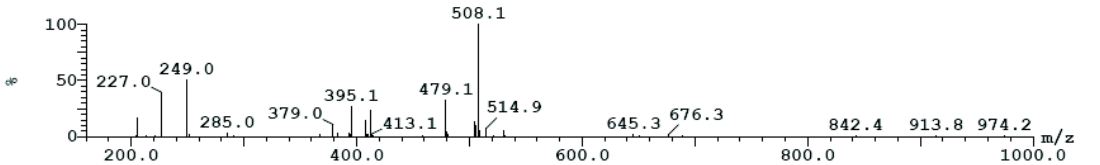
Peak ID	Compound	Time	Mass Found
4	Found	2.95	350.15

4:(Time: 2.95) 1:MS ES+ 2.5e+007



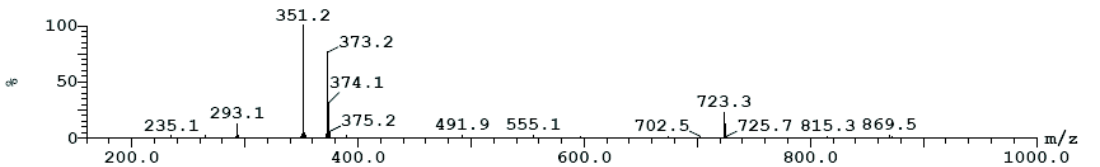
Peak ID	Compound	Time	Mass Found
4		2.95	

4:(Time: 2.95) 2:MS ES- 1.9e+005

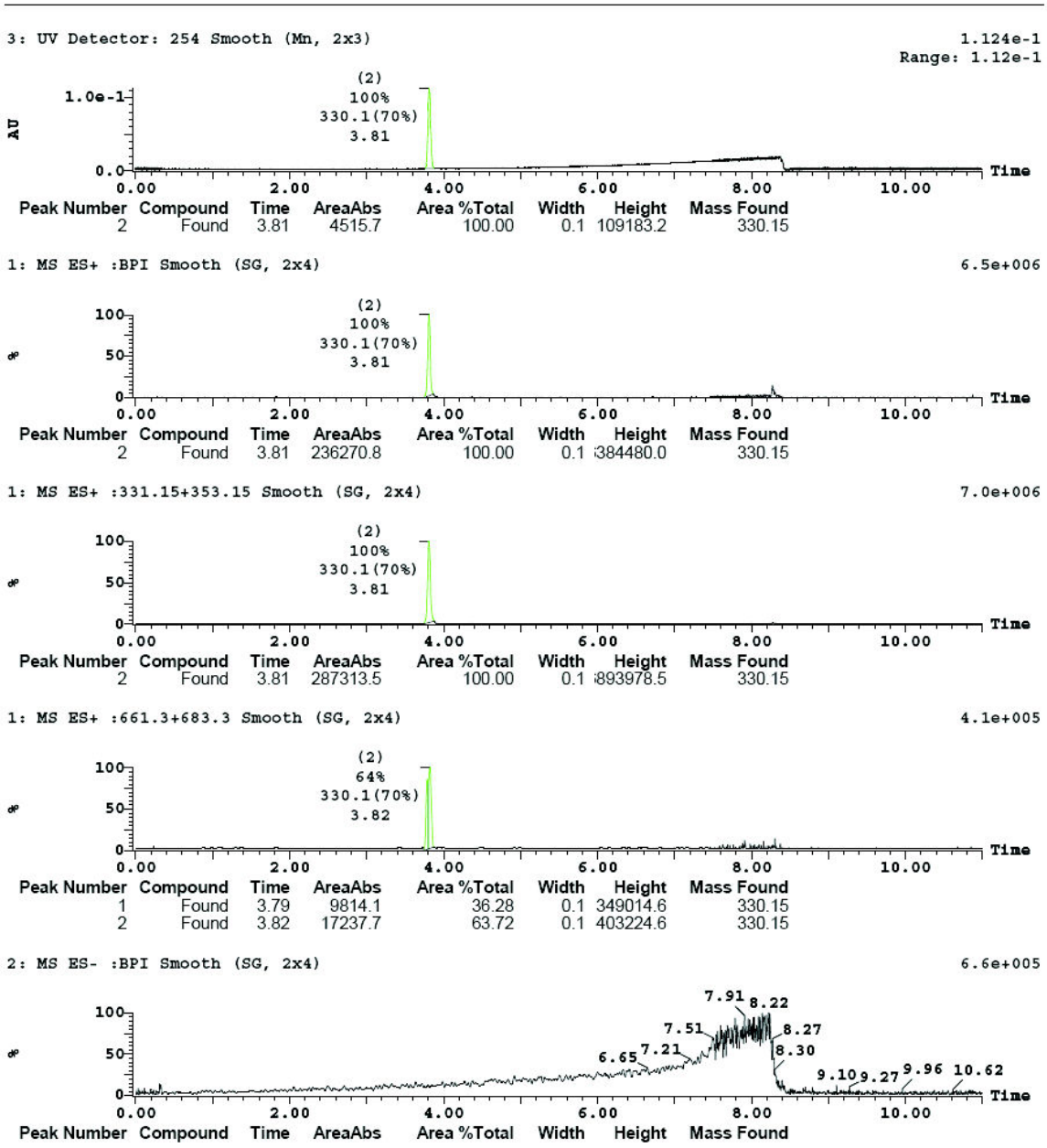


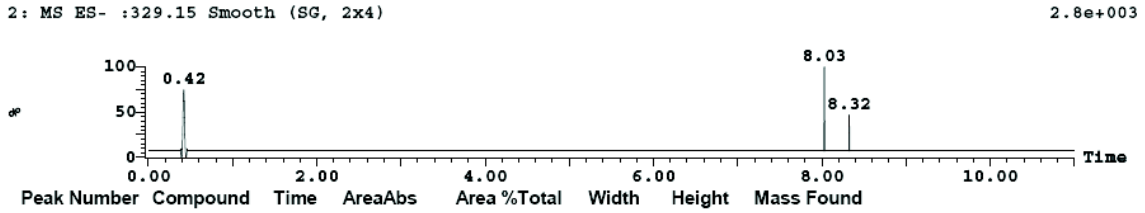
Peak ID	Compound	Time	Mass Found
5	Found	3.01	350.15

5:(Time: 3.01) 1:MS ES+ 3.9e+005

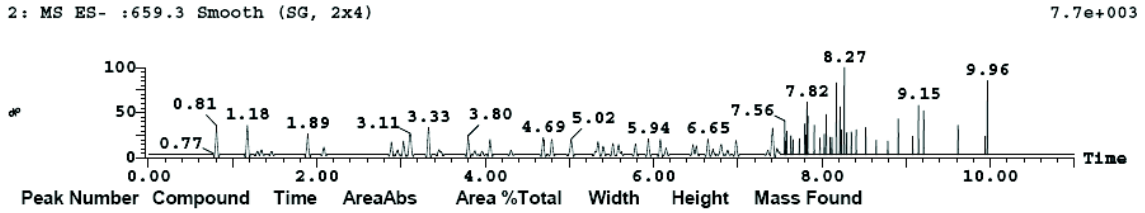


HT-LC-MS Spectrum (SOP 2200) of **8m**. UV purity: 100 %

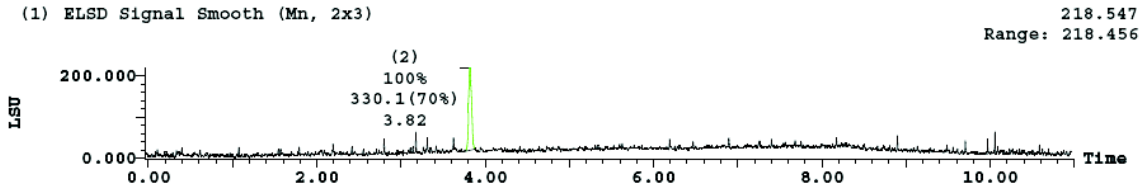




Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

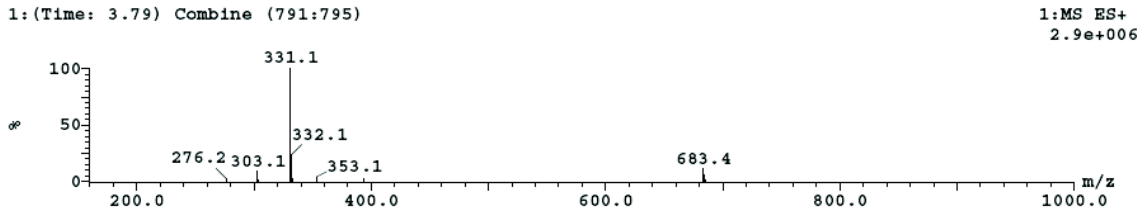


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

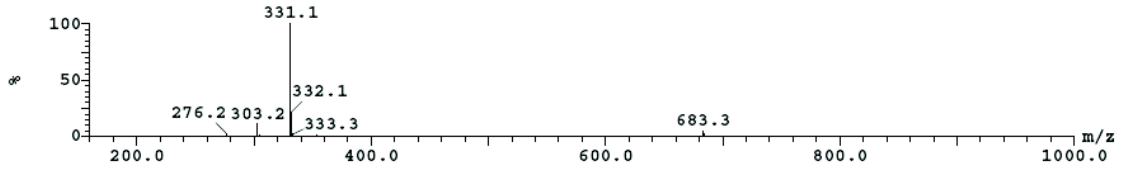


Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
2	Found	3.82	8181.3	100.00	198104.1	330.15

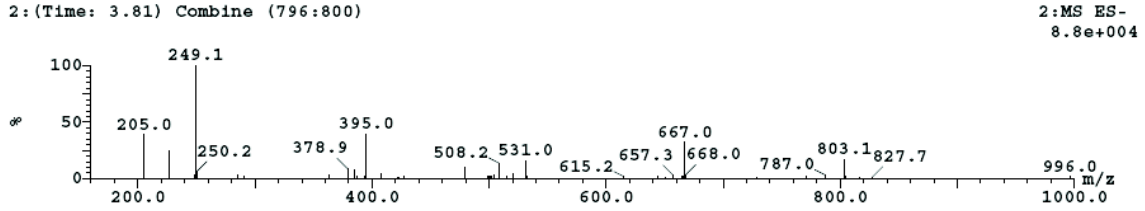
Peak ID	Compound	Time	Mass Found
1	Found	3.79	330.15



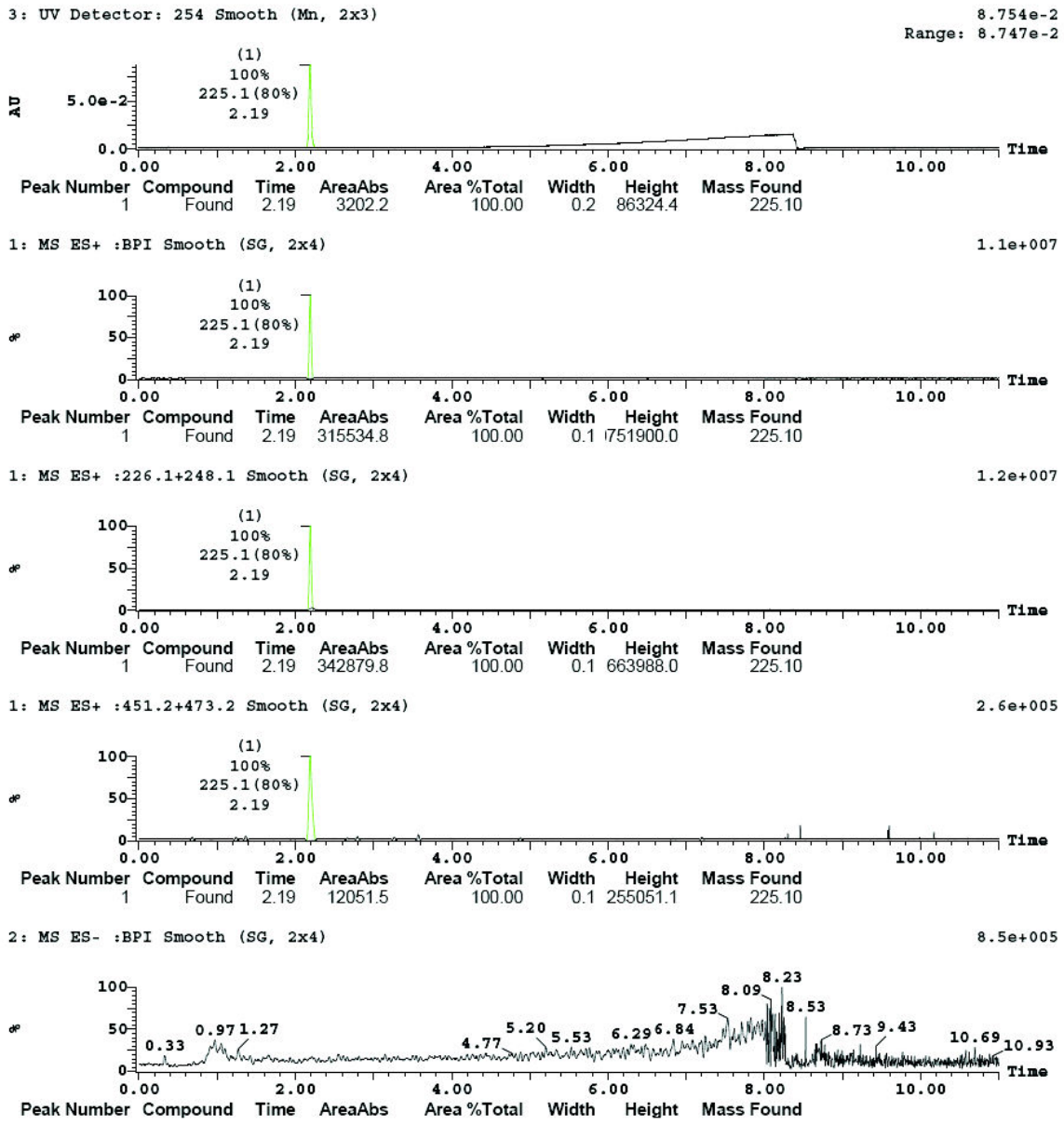
Peak ID	Compound	Time	Mass Found
2	Found	3.81	330.15

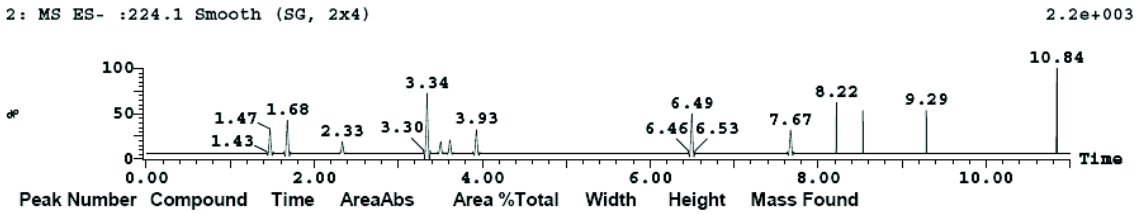


Peak ID	Compound	Time	Mass Found
2		3.81	

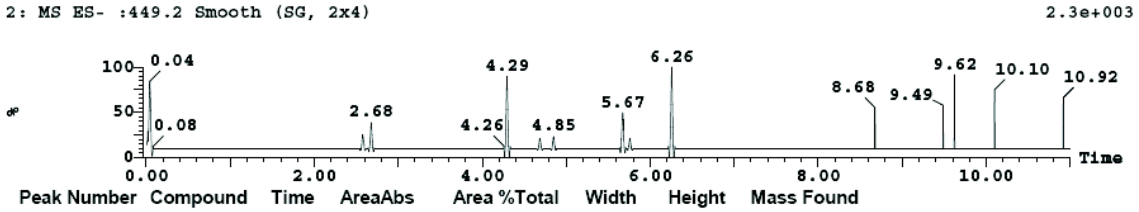


HT-LC-MS Spectrum (SOP 2200) of **8n**. UV purity: 100 %

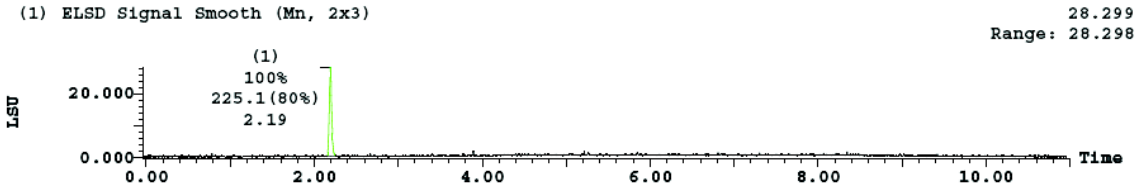




Peak Number | Compound | Time | AreaAbs | Area %Total | Width | Height | Mass Found

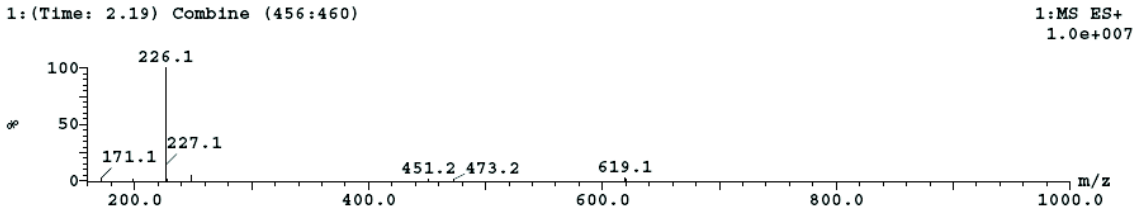


Peak Number | Compound | Time | AreaAbs | Area %Total | Width | Height | Mass Found

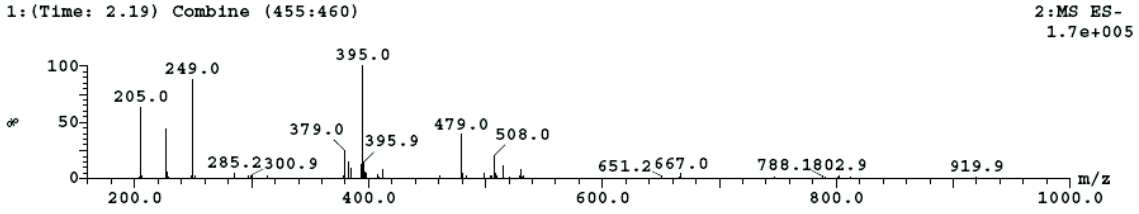


Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1	Found	2.19	933.0	100.00	27739.5	225.10

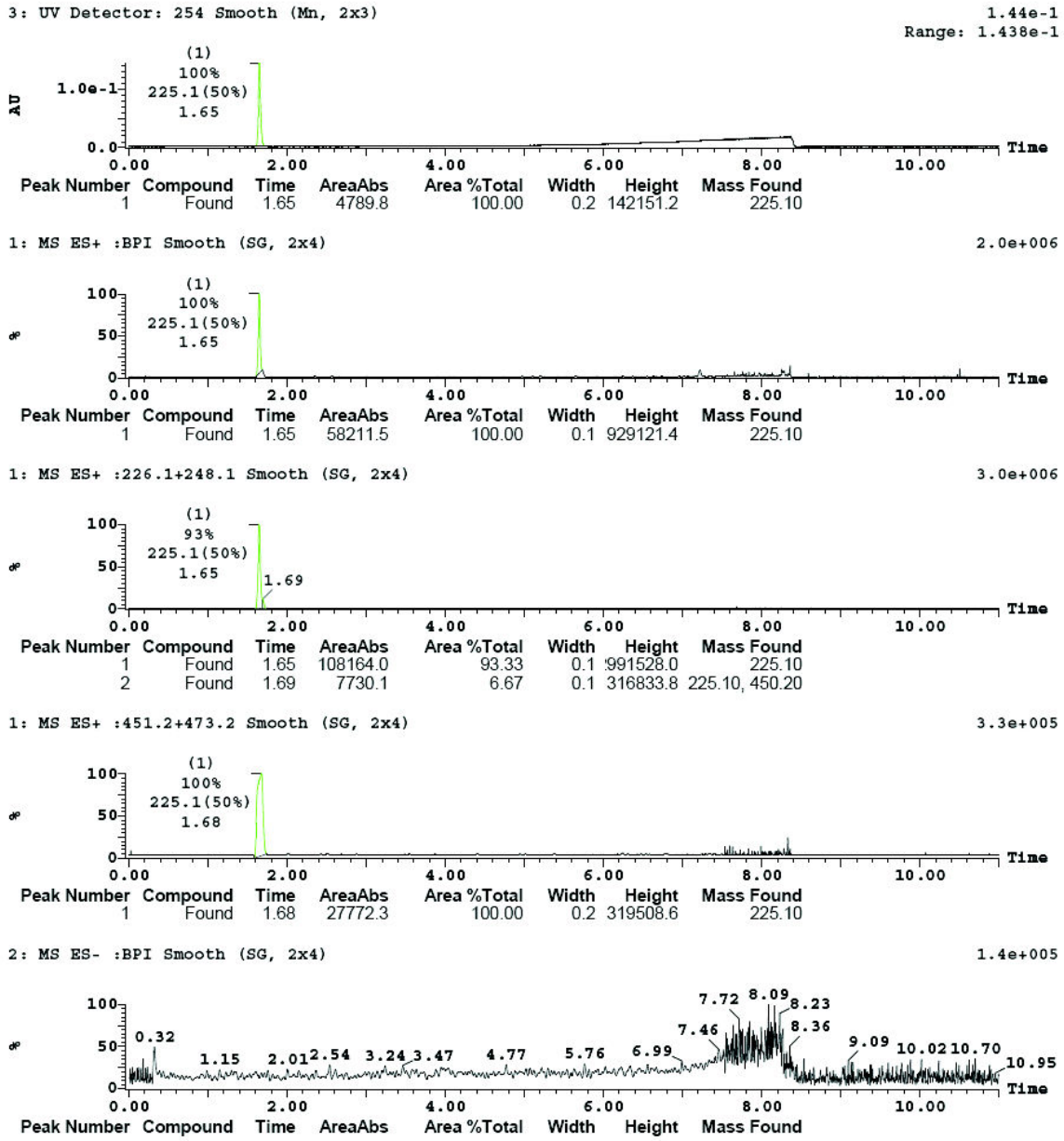
Peak ID	Compound	Time	Mass Found
1	Found	2.19	225.10

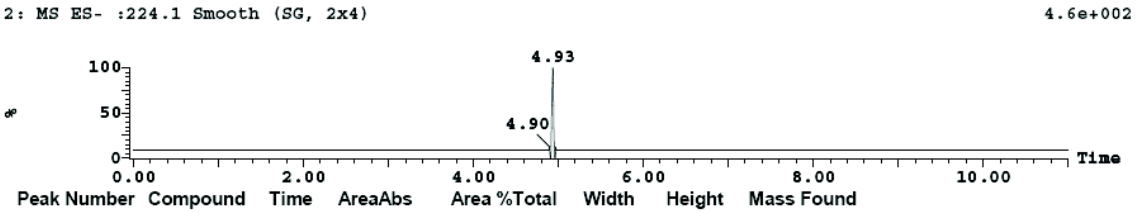


Peak ID	Compound	Time	Mass Found
1		2.19	

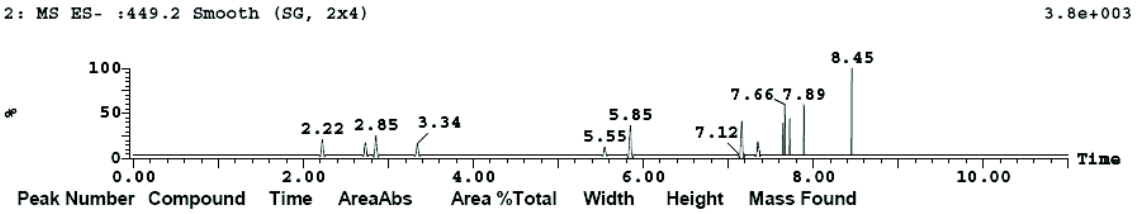


HT-LC-MS Spectrum (SOP 2200) of **8o**. UV purity: 100 %

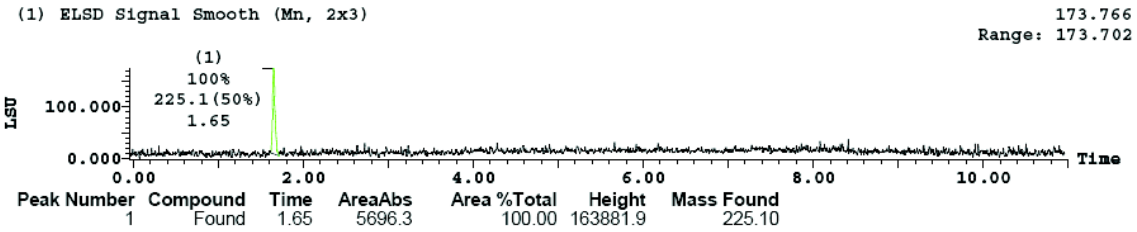




Peak Number | Compound | Time | AreaAbs | Area %Total | Width | Height | Mass Found

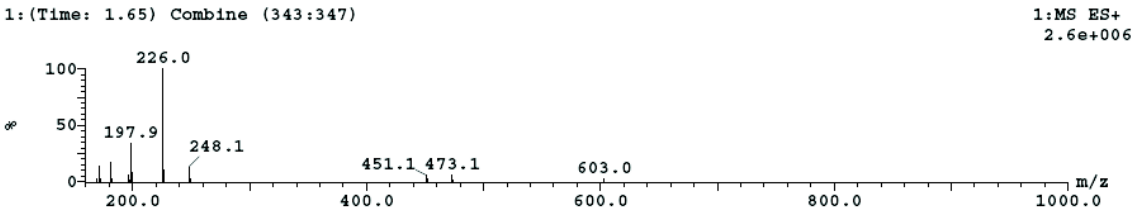


Peak Number | Compound | Time | AreaAbs | Area %Total | Width | Height | Mass Found

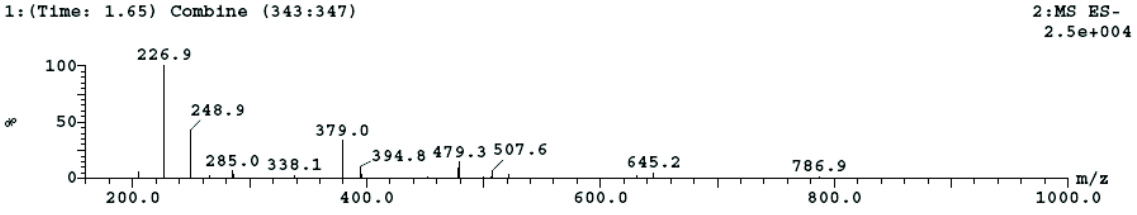


Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1	Found	1.65	5696.3	100.00	163881.9	225.10

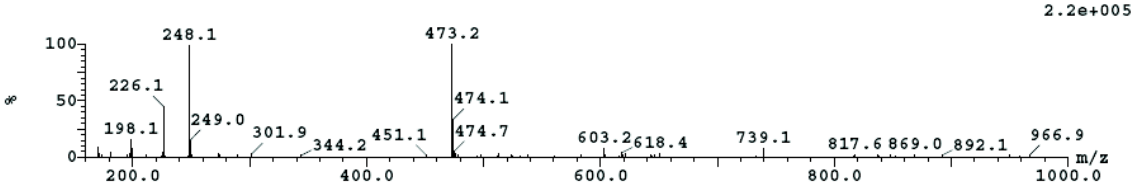
Peak ID	Compound	Time	Mass Found
1	Found	1.65	225.10



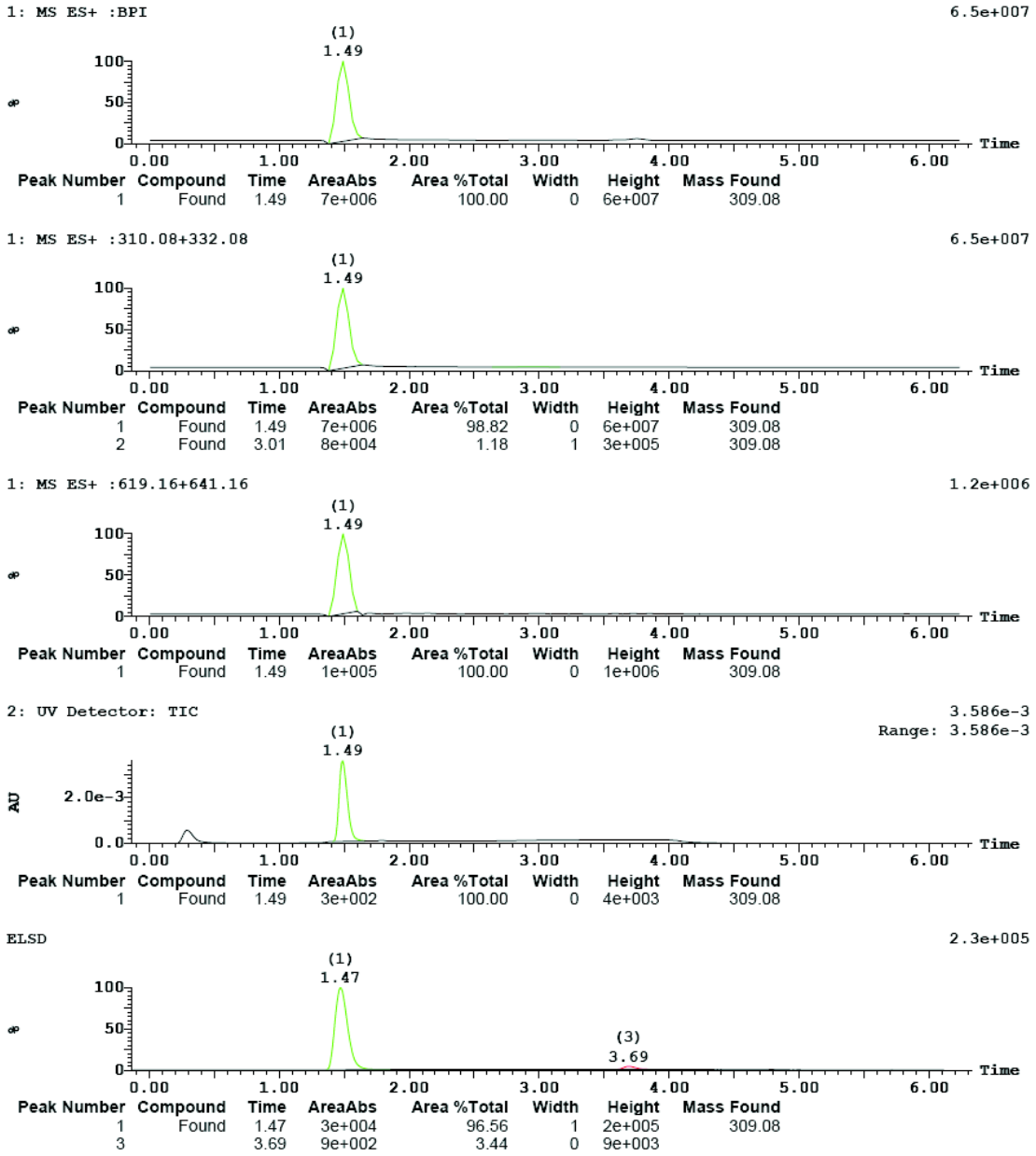
Peak ID	Compound	Time	Mass Found
1		1.65	



Peak ID	Compound	Time	Mass Found
2	Found	1.69	225.10, 450.20

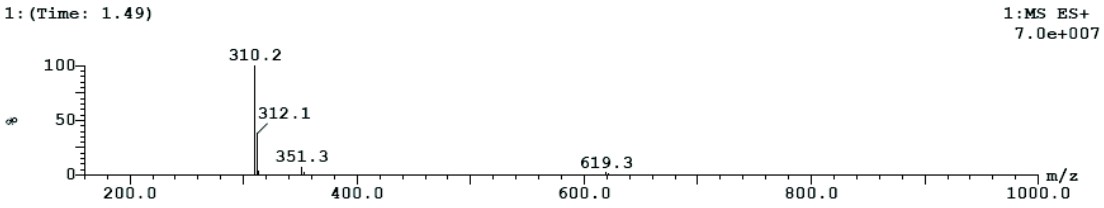


HT-LC-MS Spectrum (SOP 2222) of **8p**. UV purity: 100 %



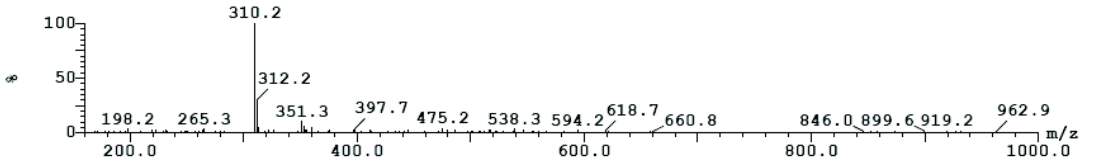
Peak ID	Compound	Time	Mass Found
1	Found	1.49	309.08

1:(Time: 1.49)



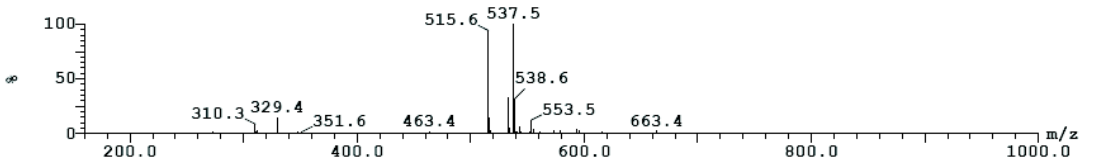
Peak ID	Compound	Time	Mass Found
2	Found	3.01	309.08

2:(Time: 3.01)

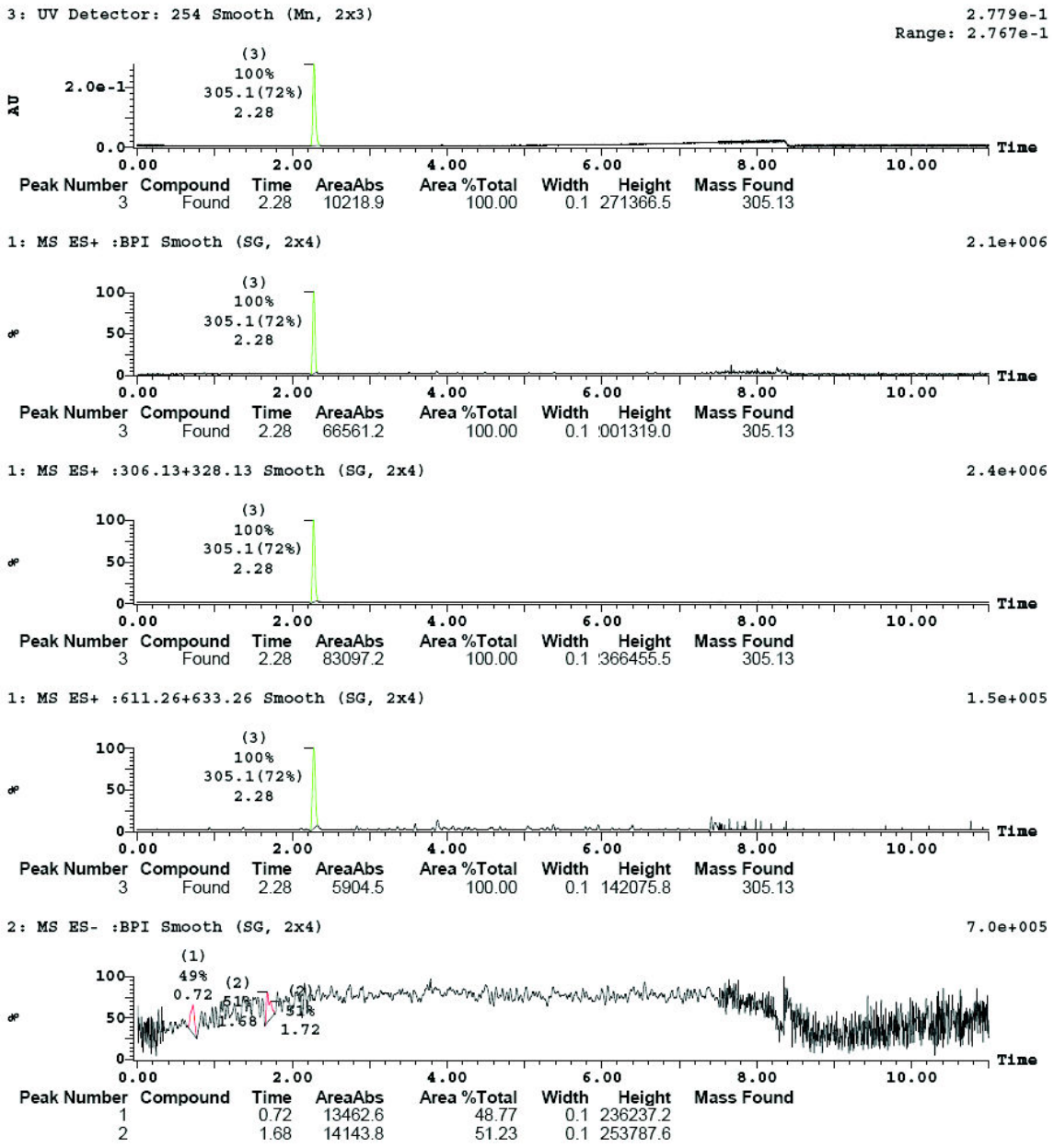


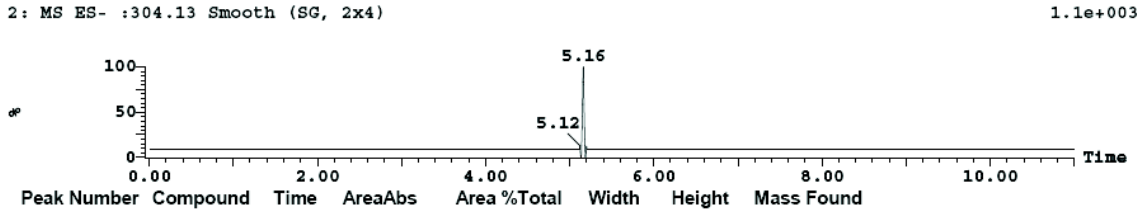
Peak ID	Compound	Time	Mass Found
3		3.69	

3:(Time: 3.69)

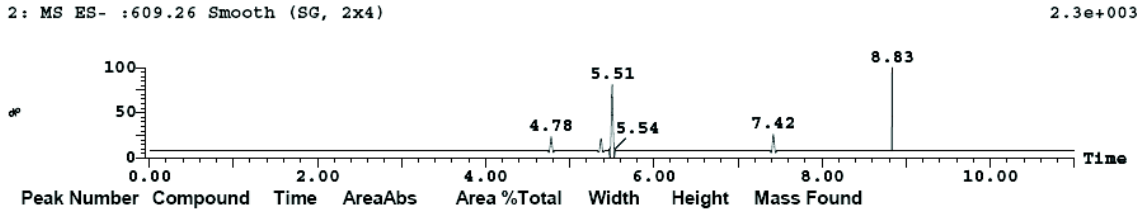


HT-LC-MS Spectrum (SOP 2200) of **8q**. UV purity: 100 %

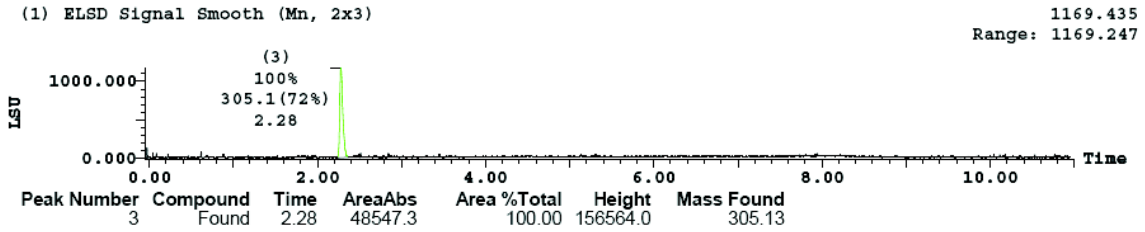




Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

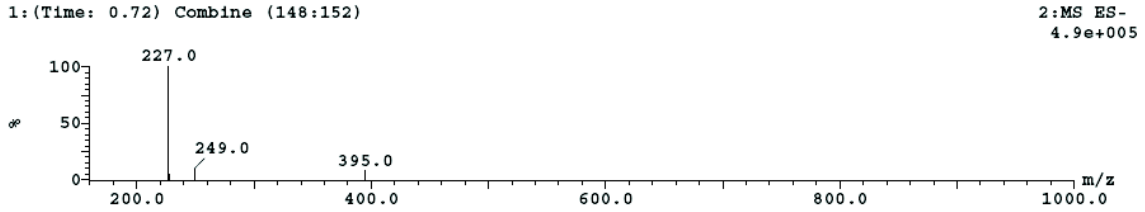


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

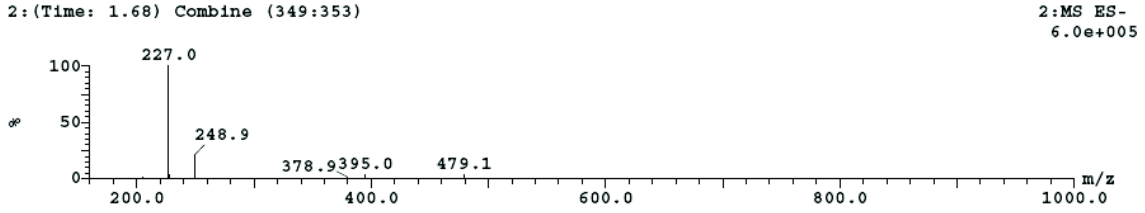


Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
3	Found	2.28	48547.3	100.00	156564.0	305.13

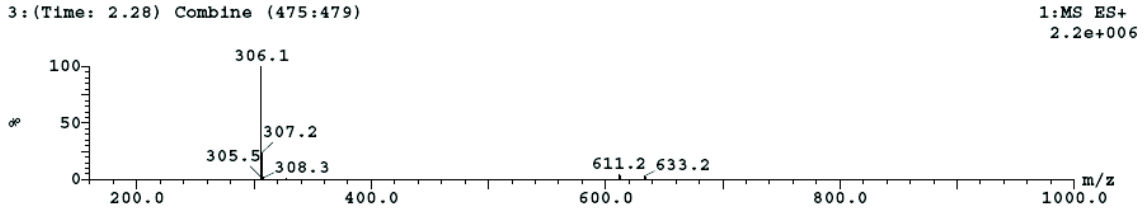
Peak ID	Compound	Time	Mass Found
1		0.72	



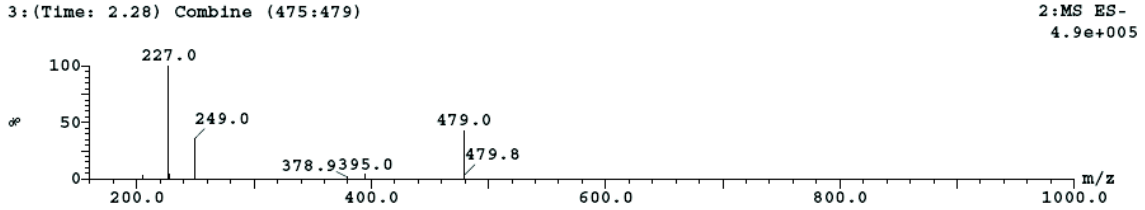
Peak ID	Compound	Time	Mass Found
2		1.68	



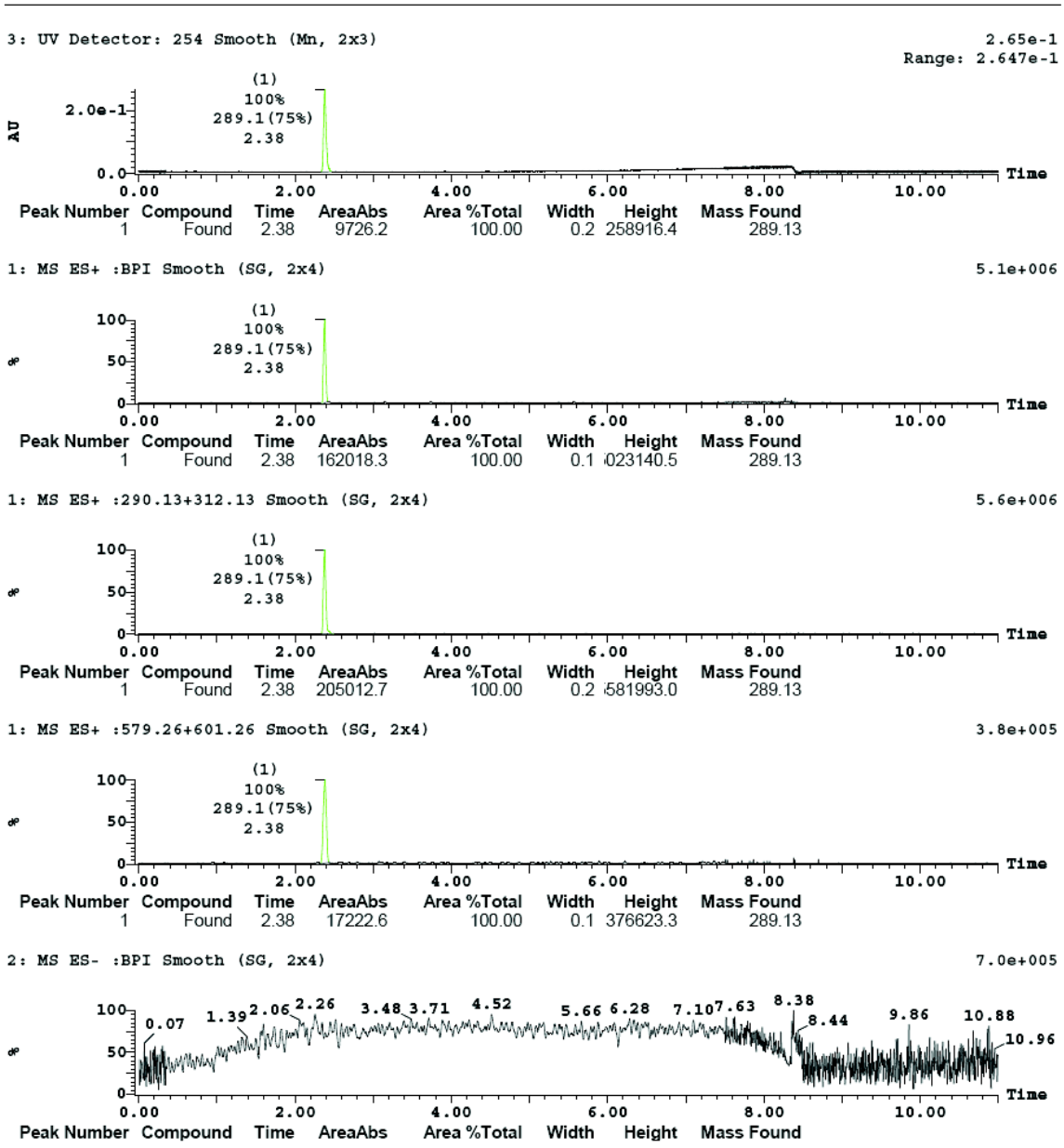
Peak ID	Compound	Time	Mass Found
3	Found	2.28	305.13

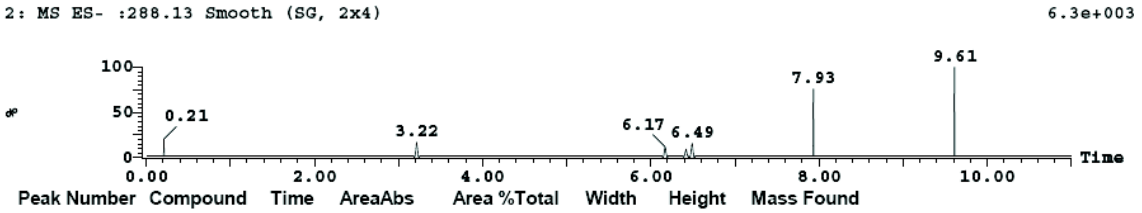


Peak ID	Compound	Time	Mass Found
3		2.28	

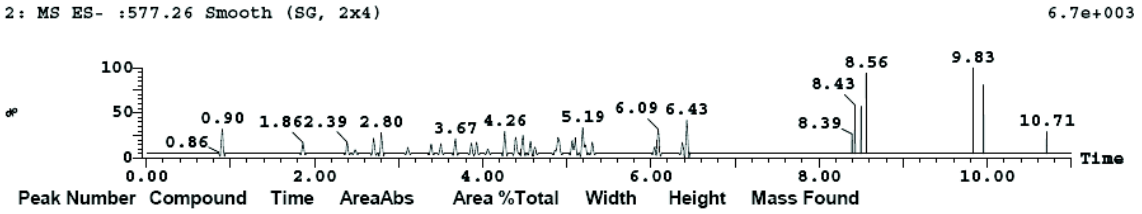


HT-LC-MS Spectrum (SOP 2200) of **8r**. UV purity: 100 %

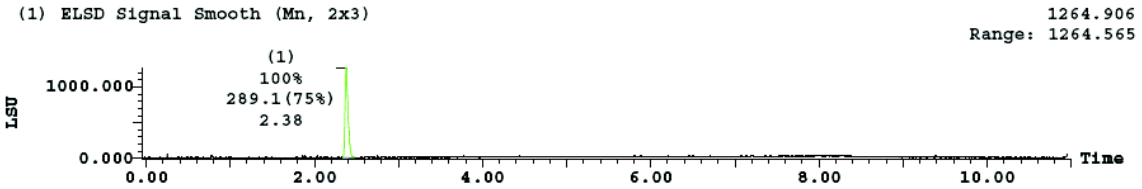




Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

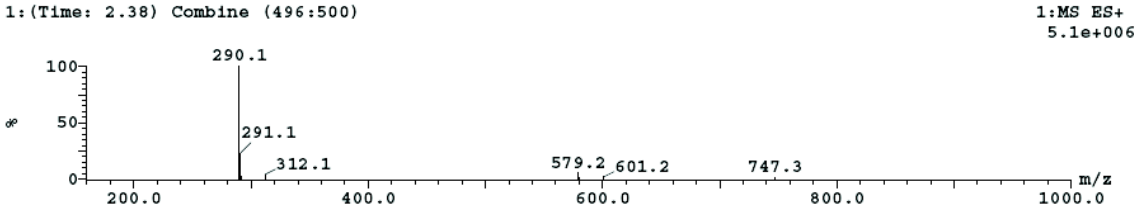


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

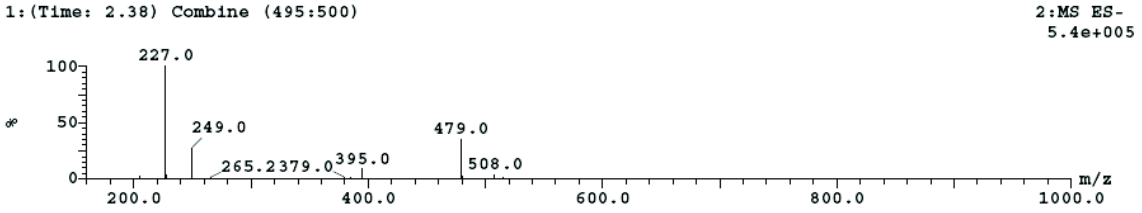


Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1	Found	2.38	51915.8	100.00	252771.4	289.13

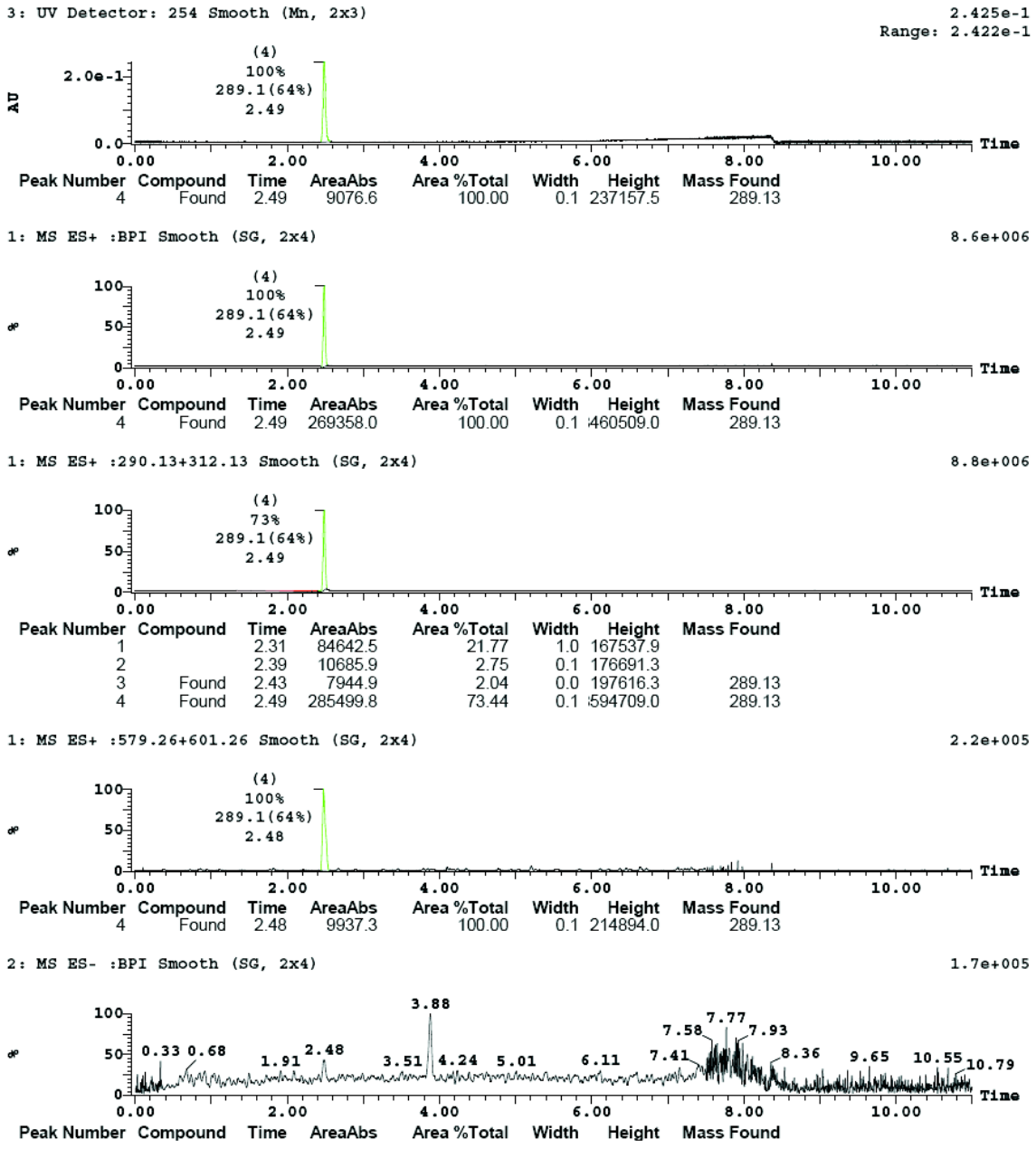
Peak ID	Compound	Time	Mass Found
1	Found	2.38	289.13

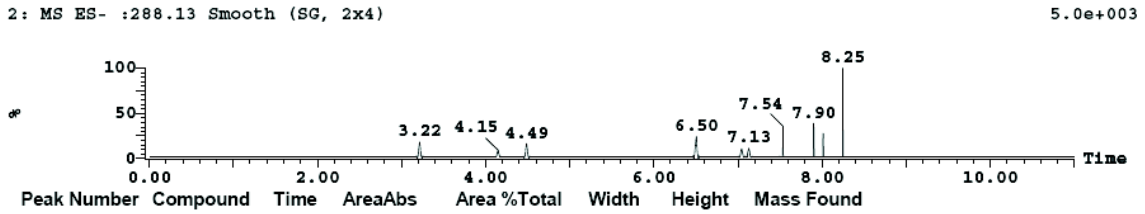


Peak ID	Compound	Time	Mass Found
1		2.38	

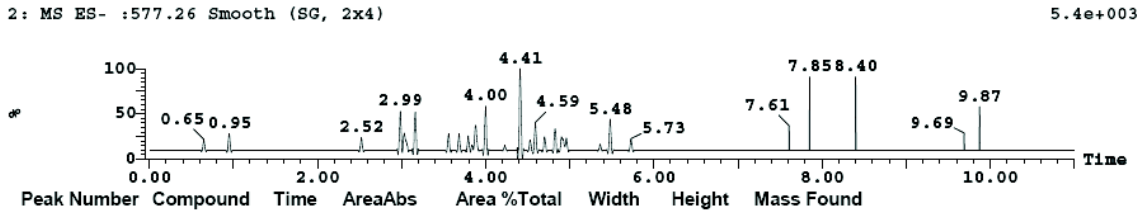


HT-LC-MS Spectrum (SOP 2200) of **8s**. UV purity: 100 %

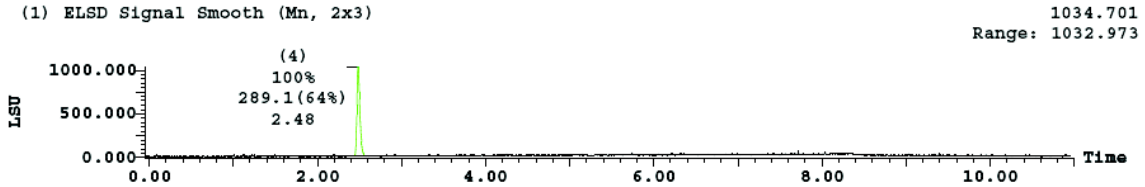




Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

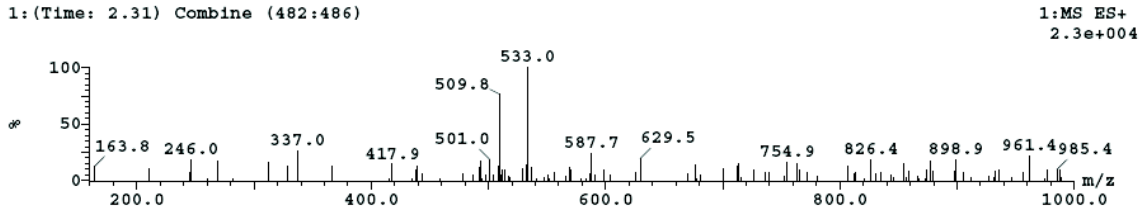


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

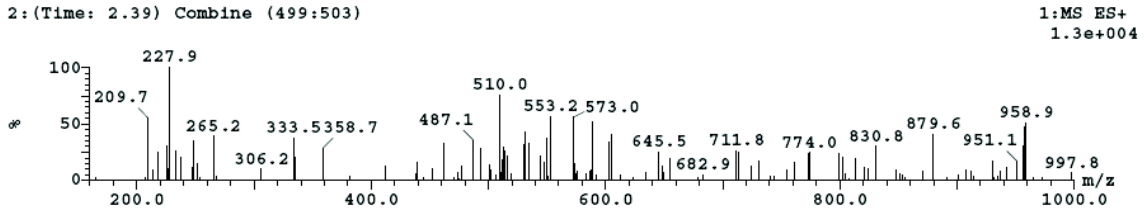


Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
4	Found	2.48	41695.9	100.00	019412.8	289.13

Peak ID	Compound	Time	Mass Found
1		2.31	



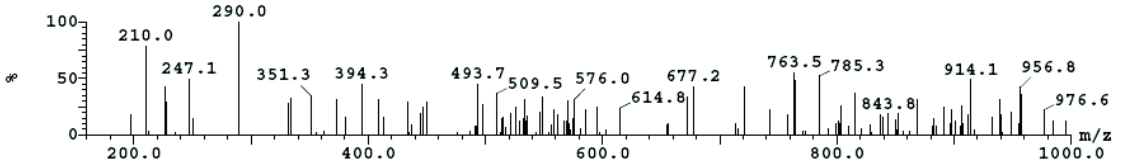
Peak ID	Compound	Time	Mass Found
2		2.39	



Peak ID	Compound	Time	Mass Found
3	Found	2.43	289.13

3:(Time: 2.43) Combine (507:511)

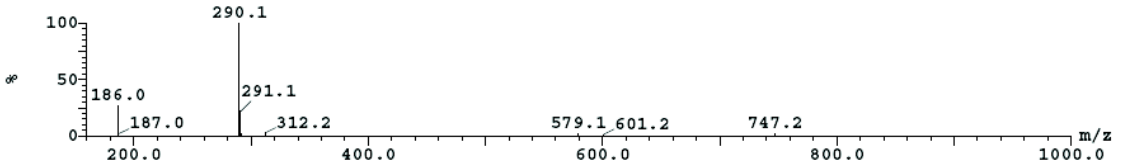
1:MS ES+
1.0e+004



Peak ID	Compound	Time	Mass Found
4	Found	2.49	289.13

4:(Time: 2.48) Combine (517:521)

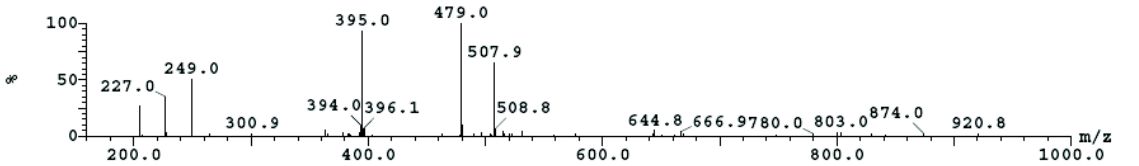
1:MS ES+
6.9e+006



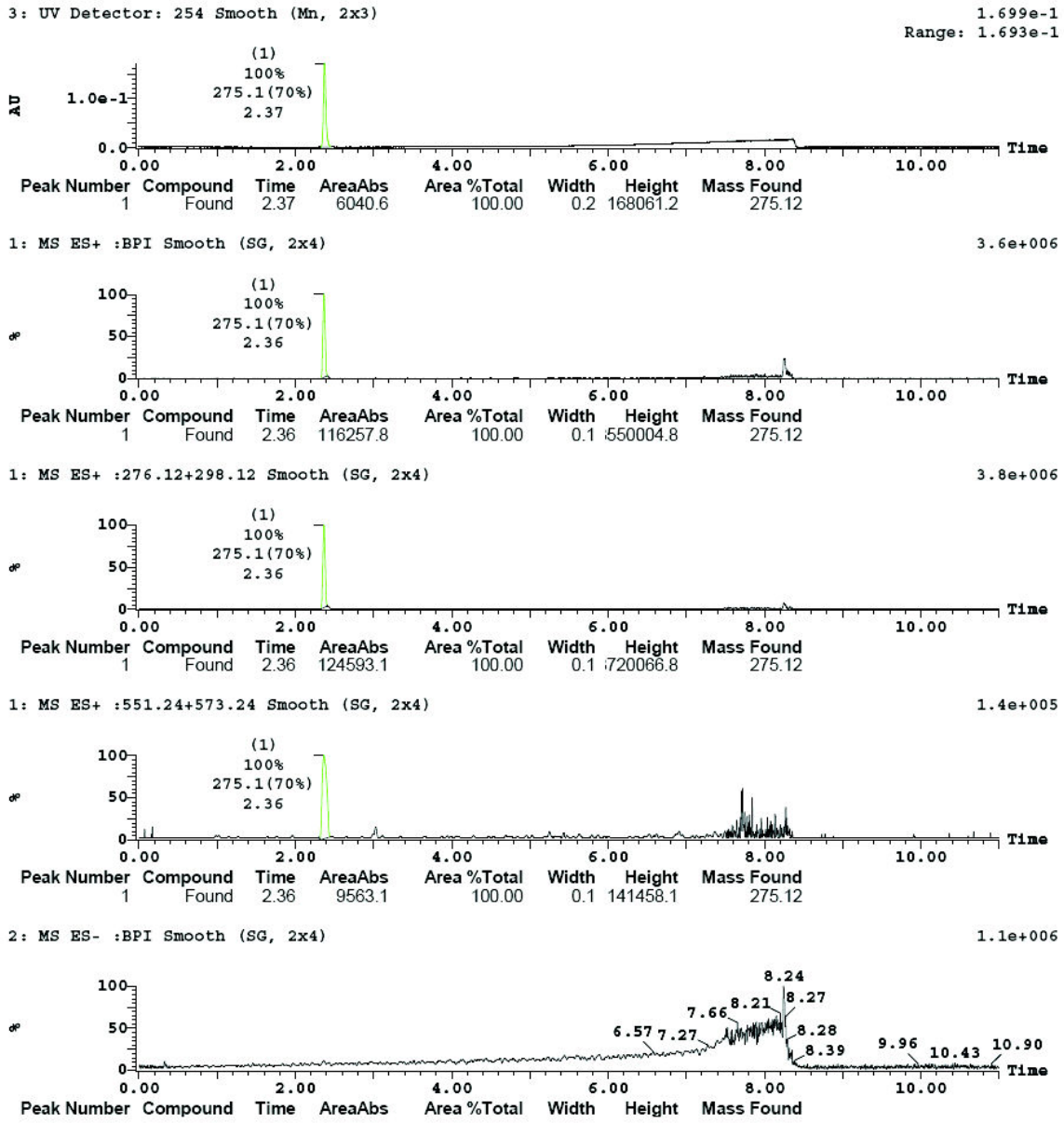
Peak ID	Compound	Time	Mass Found
4		2.49	

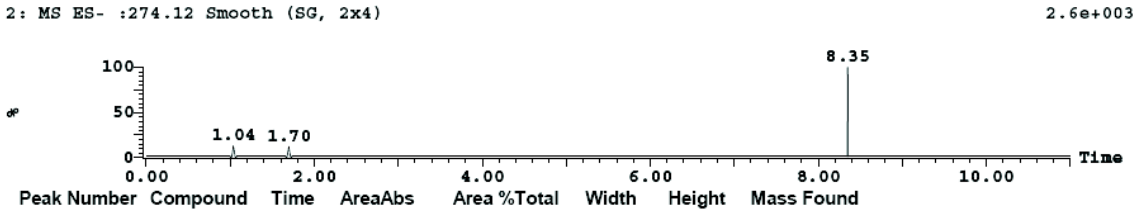
4:(Time: 2.48) Combine (518:522)

2:MS ES-
7.6e+004

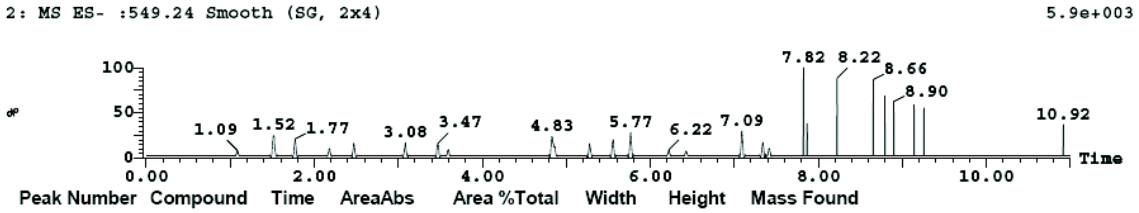


HT-LC-MS Spectrum (SOP 2200) of **9a**. UV purity: 100 %

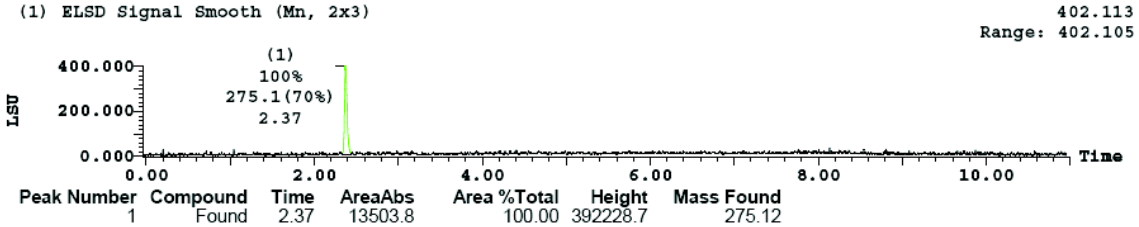




Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

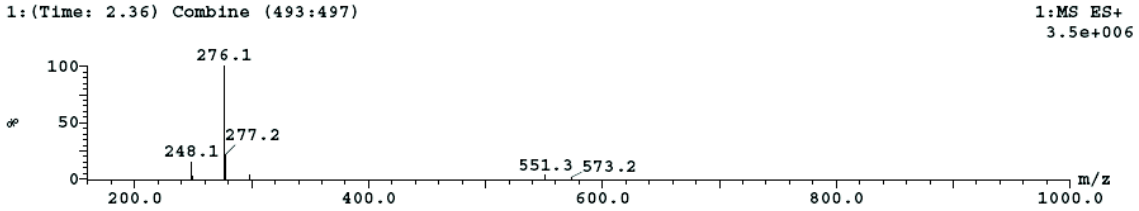


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

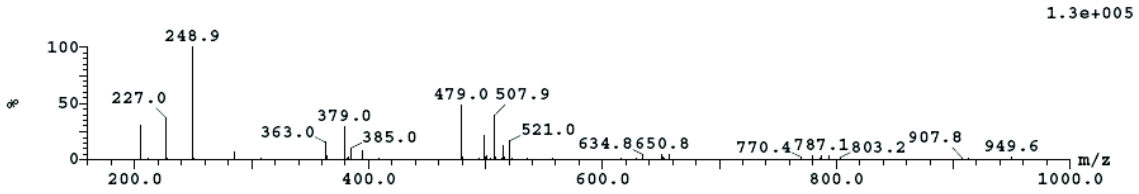


Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1	Found	2.37	13503.8	100.00	392228.7	275.12

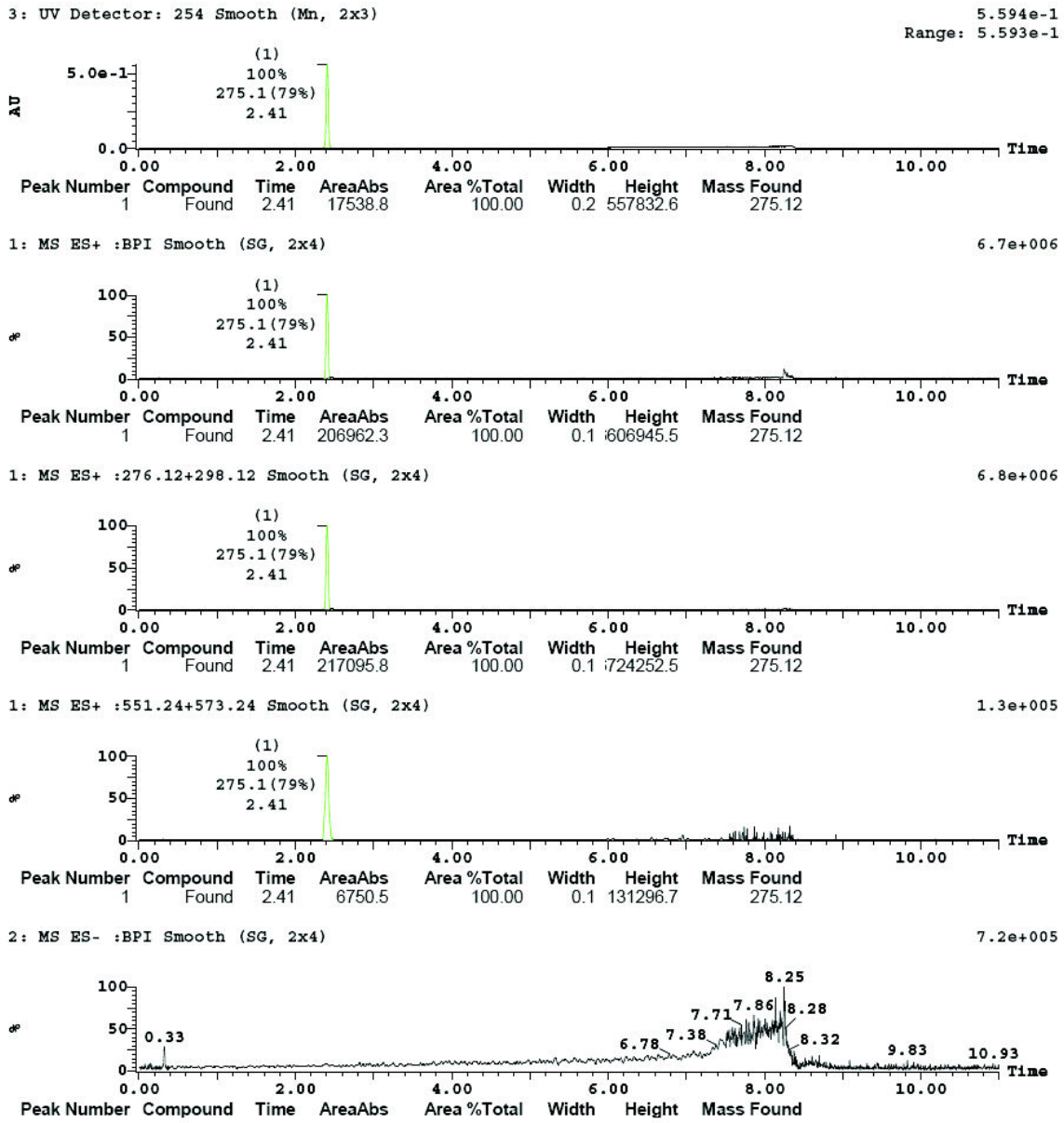
Peak ID	Compound	Time	Mass Found
1	Found	2.36	275.12

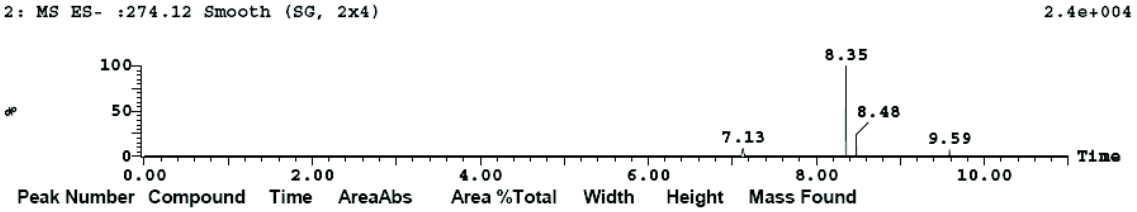


Peak ID	Compound	Time	Mass Found
1		2.36	

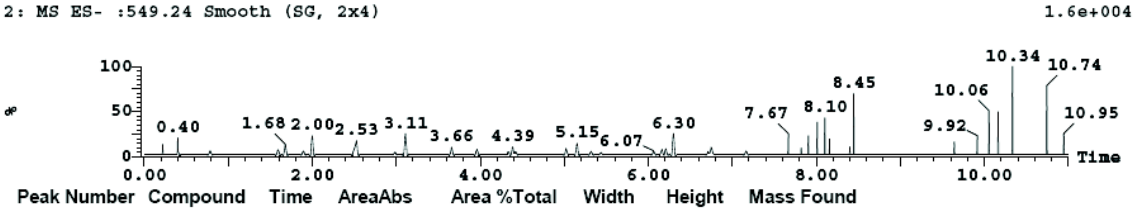


HT-LC-MS Spectrum (SOP 2222) of **9b**. UV purity: 100 %

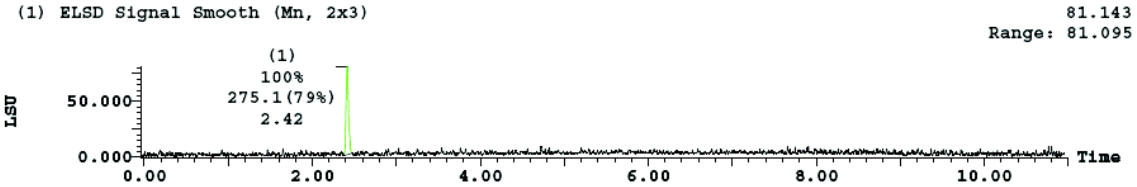




Peak Number | Compound | Time | AreaAbs | Area %Total | Width | Height | Mass Found

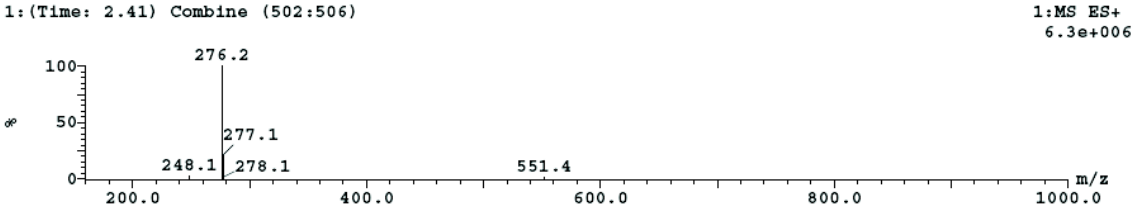


Peak Number | Compound | Time | AreaAbs | Area %Total | Width | Height | Mass Found

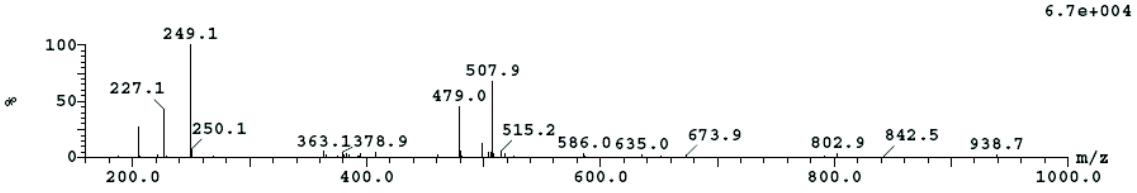


Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1	Found	2.42	2689.6	100.00	78671.3	275.12

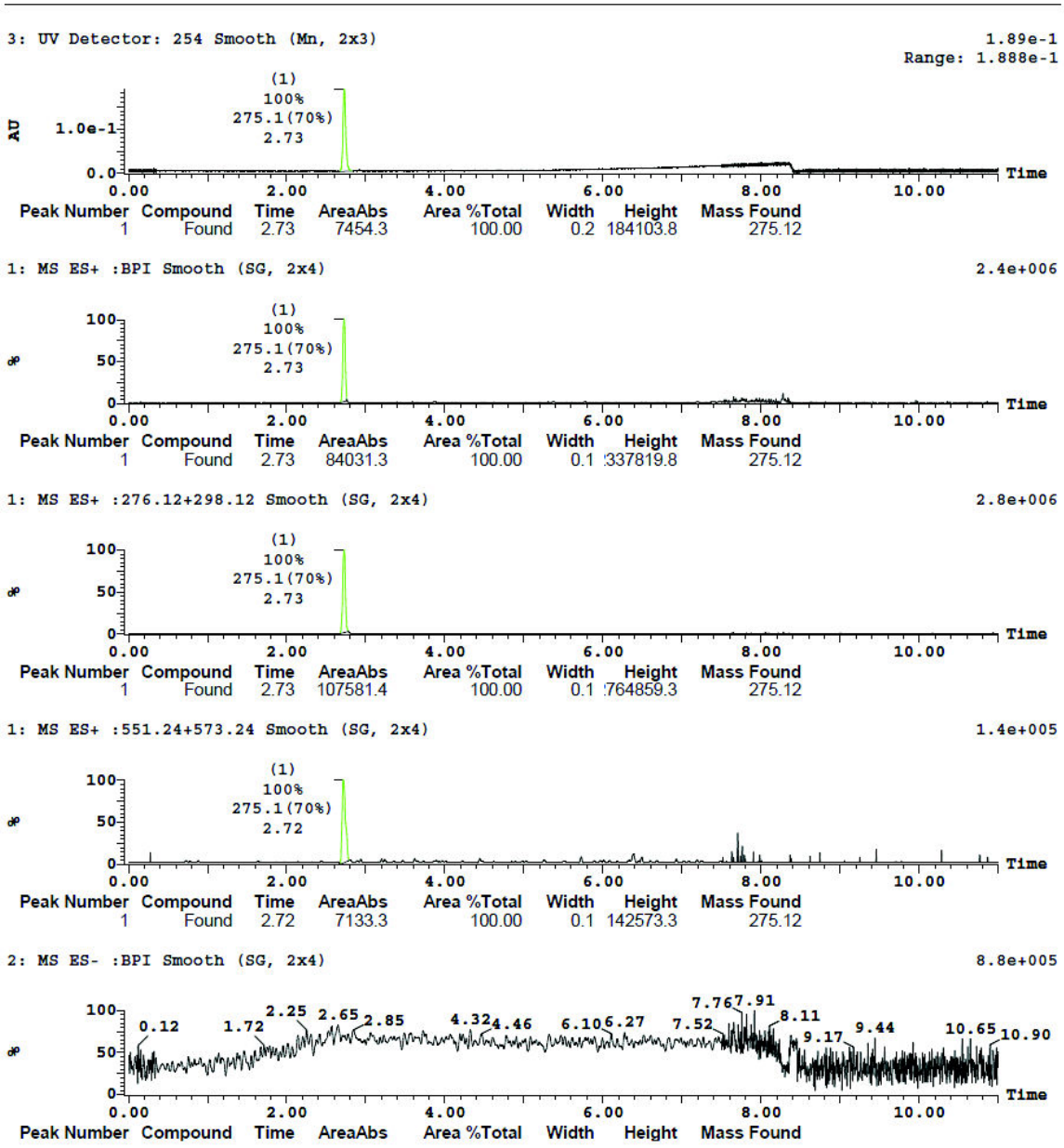
Peak ID	Compound	Time	Mass Found
1	Found	2.41	275.12

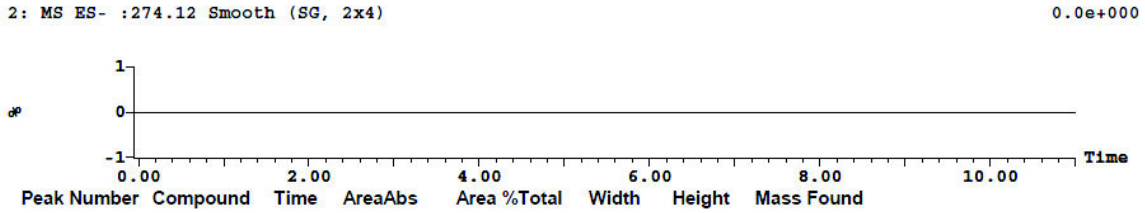


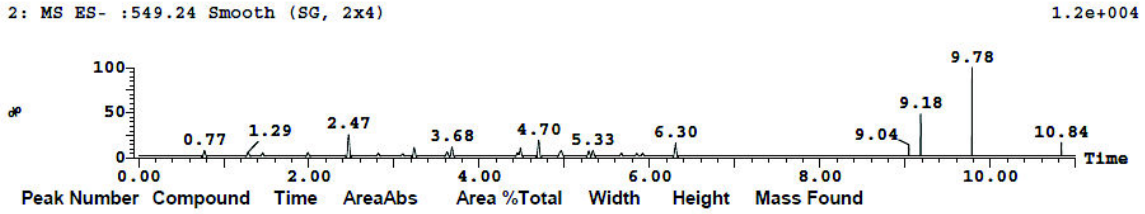
Peak ID	Compound	Time	Mass Found
1		2.41	

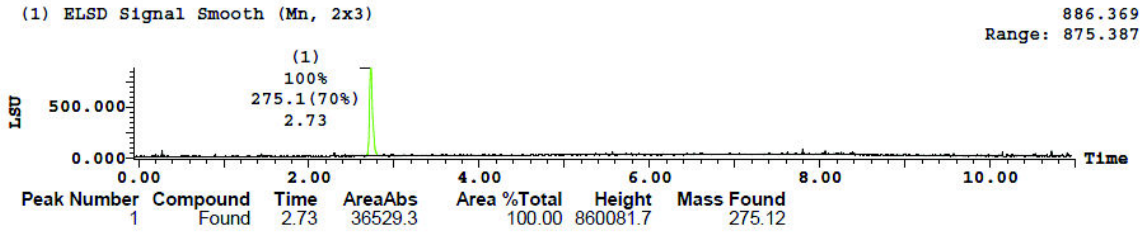


HT-LC-MS Spectrum (SOP 2200) of **10**. UV purity: 100 %

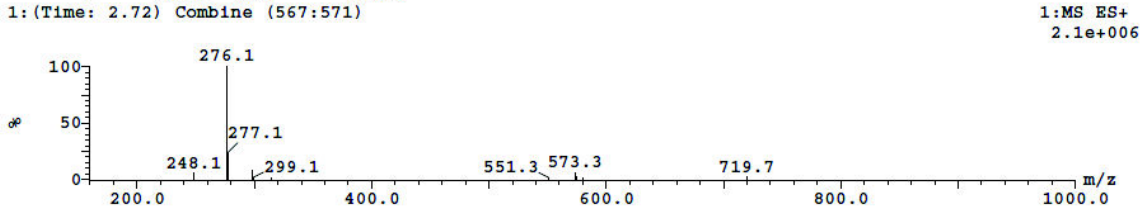




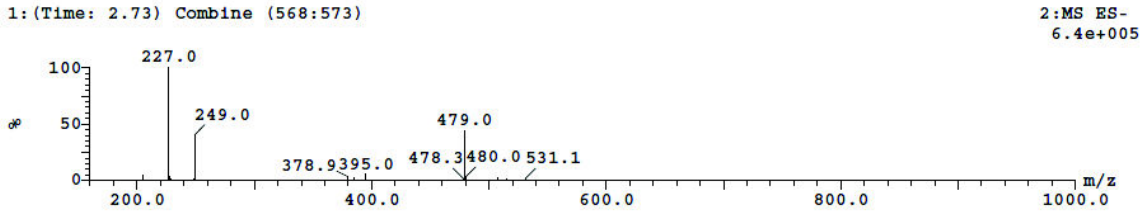




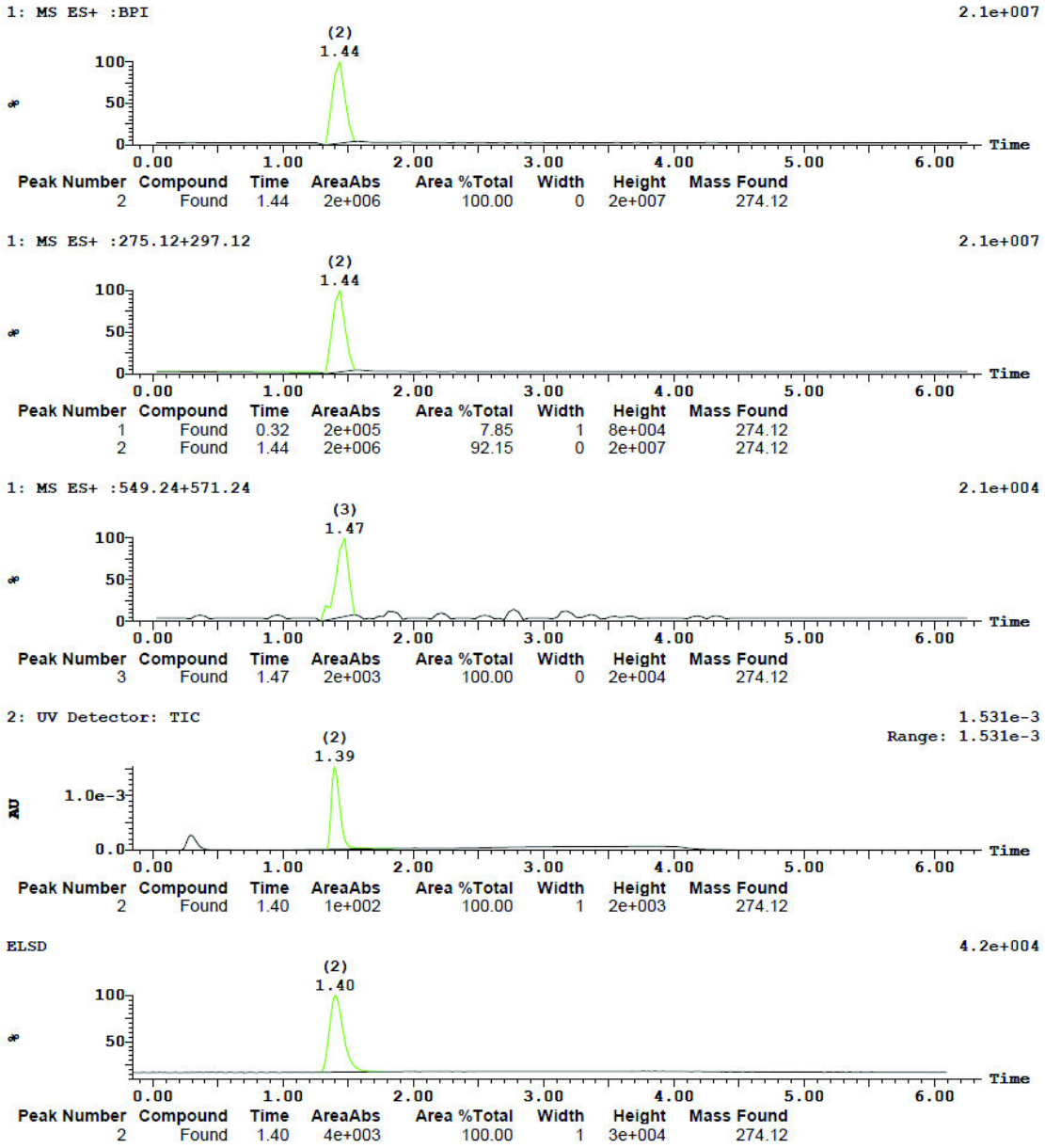
Peak ID	Compound	Time	Mass Found
1	Found	2.73	275.12



Peak ID	Compound	Time	Mass Found
1		2.73	

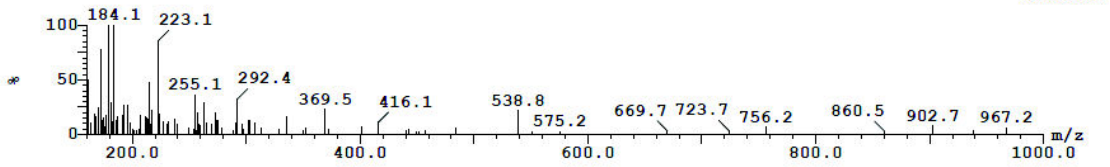


HT-LC-MS Spectrum (SOP 2222) of **11**. UV purity: 100 %



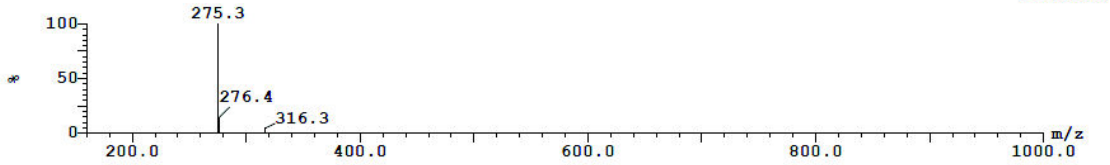
Peak ID	Compound	Time	Mass Found
1	Found	0.32	274.12

1:(Time: 0.32)



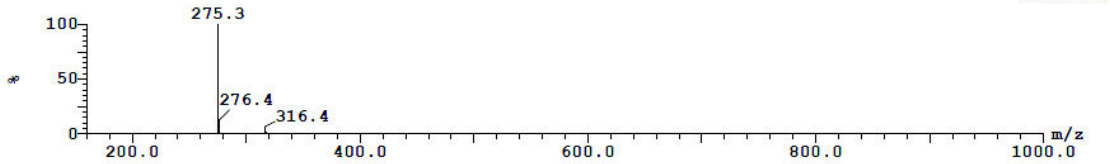
Peak ID	Compound	Time	Mass Found
2	Found	1.44	274.12

2:(Time: 1.40)



Peak ID	Compound	Time	Mass Found
3	Found	1.47	274.12

3:(Time: 1.47)



8.2. HT-LC-MS Methods for the control of identity and purity of compounds 8a-s, 9a-b, 10, and 11

Problem definition	Identity and Purity			
SOP (Standard Operating Procedure)	2200			
Methods	HT-LC-MS			
System	Waters Acquity UPLC® with PDA and ELSD Waters SQD (ESI+/- and APCI+/-)			
Software	MassLynx with OpenLynx			
Column	Waters XBridge™ C8 3.5 µm 4.6 x 50 mm Column Part No. 186003053			
Eluent	A: 99.9 % acetonitrile + 0.1 % TFA B: 99.9 % water + 0.1 % TFA			
Gradient	time (min)	A %	B %	flow (mL/min)
	0	5	95	2.0
	8.00	100	0	2.0
	8.10	10	90	2.0
	8.50	5	95	2.0
	11.00	5	95	2.0
Column temperature	Room temperature			
Injection volume	3 µL			
Sample preparation	Approx. 0.1 mg were dissolved in acetonitrile + water 50/50 in an ultrasonic bath, so that the concentration was 0.5 mM. If necessary, the sample was additionally diluted: 100 µL in 500 µL acetonitrile + water 5/95.			

Problem definition	Identity and Purity			
SOP	2222			
Methods	HT-LC-MS			
System	4 x Waters 1525 Binary HPLC Pump			
	2 x Waters In-Line Degasser AF			
	1 x Waters 2777 Sample Manager			
	1 x Waters 2488 Mux-UV Detector			
	4 x Waters 2420 ELS Detector			
	1 x Waters ZQ-MUX			
Software	MassLynx with OpenLynx			
Column	Chromolith® Flash RP-18e (25-2mm)			
Eluent	A: 99.9 % acetonitrile + 0.1 % formic acid			
	B: 99.9 % water + 0.1 % formic acid			
Gradient	time (min)	A %	B %	flow (mL/min)
	0	5	95	0.8
	1.7	100	0	0.8
	3.0	100	0	0.8
	3.01	0	100	0.8
	6.25	5	95	0.8
Column temperature	Room temperature			
Throughput	416 samples: approx. 11 h			

8.3. Determination of Cu and Pd contents in compound 8f

Sample preparation:	4.8 mg of compound **8f** dissolved in 4.8 mL of DMSO
Measurement:	ICP-MS
Sample introduction:	50 μL/min Meinhard sprayer, quartz cyclone spray chamber, syringe pump
Internal standard:	Rhodium
Calibration:	Addition of standard or additions calibration

Additions [μg/g]:	Cu	Pd
	5	5
	10	10
	15	15
Analytical results:	Cu	Pd
	< 2 μg/g	< 1 μg/g

9. References

[1] B. Witulski, N. Buschmann, U. Bergsträßer, *Tetrahedron* **2000**, *56*, 8473-8480.

[2] T. A. Kelly, D. W. McNeil, J. M. Rose, E. David, C.-K. Shih, P. M. Grob, *J. Med. Chem.* **1997**, *40*, 2430-2433.

[3] "Three-component synthesis of *N*-Boc-4-iodopyrroles and sequential one-pot alkynylation" E. Merkul, C. Boersch, W. Frank, T. J. J. Müller, *Org. Lett.* **2009**, *11*, 2269-2272.

[4] "Efficient one-pot synthesis of 1-aryl 1,2,3-triazoles from aryl halides and terminal alkynes in the presence of sodium azide" J. Andersen, S. Bolvig, X. Liang, *Synlett* **2005**, 2941-2947.

[5] "Rapid synthesis of bis(hetero)aryls by one-pot Masuda borylation – Suzuki coupling sequence and its application to concise total syntheses of meridianins A and G" E. Merkul, E. Schäfer, T. J. J. Müller, *Org. Biomol. Chem.* **2011**, DOI: 10.1039/C1OB05310H.

“Three-component synthesis of ynediones by a glyoxylation/Stephens–Castro coupling sequence”, *Angew. Chem. Int. Ed.* **2011**, *50*, 2966-2969. DOI: 10.1002/anie.201007194.

Heterocycle Synthesis

DOI: 10.1002/anie.201007194

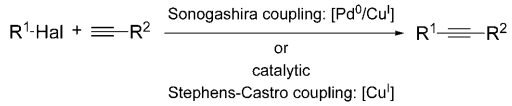
Three-Component Synthesis of Ynediones by a Glyoxylation/Stephens–Castro Coupling Sequence**

*Eugen Merkul, Janis Dohe, Charlotte Gers, Frank Rominger, and Thomas J. J. Müller**

Dedicated to Professor Akira Suzuki on the occasion of his 80th birthday

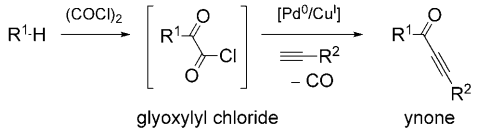
Copper-mediated reactions have been playing an outstanding role in organic chemistry for over a century as manifested in many important transformations and name reactions. Indeed, Ullmann-type reactions can be considered as predecessors of modern cross-couplings. However, copper-mediated transformations have been completely overshadowed by the very dramatic developments in palladium chemistry. Nevertheless, many new remarkable copper-catalyzed processes have appeared in the last decade, thus heralding a renaissance in copper catalysis.[1–5]

In 1963, Stephens and Castro reported a synthesis of diarylacetylenes by a stoichiometric coupling reaction of copper acetylides with aryl iodides, which proceeded in refluxing pyridine under a nitrogen atmosphere.[6] Later, catalytic variants were also developed, some of which allowed milder conditions more tolerant to functional groups.[7] With the advent of the usually more efficient palladium-catalyzed alkynylations[8] and finally the Pd/Cu-catalyzed Sonogashira–Hagihara coupling,[9,10] the Stephens–Castro reaction became far less significant (Scheme 1).



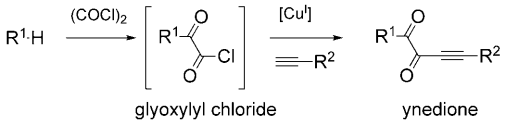
Scheme 1. Sonogashira and catalytic Stephens–Castro alkynylations.

Recently, we reported a new multicomponent approach to alkynones by glyoxylation of electron-rich heterocycles such as indoles and pyrroles with oxalyl chloride under Lewis acid free conditions followed by a novel decarbonylative Sonogashira coupling procedure (Scheme 2).[11]



Scheme 2. Glyoxylation/decarbonylative Sonogashira coupling sequence.

Obviously, if the decarbonylative elimination could be suppressed or excluded, the reaction sequence would lead to the formation of ynediones, highly electrophilic, yet scarcely explored building blocks.[12] The synthesis of 2-oxo-3-butynoates and 2-oxo-3-butynoamides by the Cu-catalyzed coupling of monooxalyl chlorides, described in 2003,[13] was the sole implementation of this intriguing concept. However, prior to our studies, this direct approach was neither extended into a one-pot protocol nor applied to the functionalization of heterocycles. We reasoned that ynediones could be obtained by modifying the glyoxylation/decarbonylative Sonogashira coupling sequence. Possibly, the decarbonylation could be avoided by omitting the Pd precatalyst responsible for the decarbonylative outcome in the coupling step, thus stepping back to the Cu-catalyzed Stephens–Castro reaction (Scheme 3).



Scheme 3. Glyoxylation/Stephens–Castro coupling sequence.

In optimization studies[14] we found that the best results were obtained with 1.0 equivalent of oxalyl chloride, 5 mol% of CuI, 1.0 equivalent of a terminal alkyne, and 3.0 equivalents of triethylamine. In comparison to the corresponding decarbonylative Sonogashira reaction, the coupling step is slower, but essentially complete within 24 h at room temperature. Increasing the reaction temperature diminishes the yield, and prolonged reaction time (48 h) does not increase the yield. The sequence can be performed conveniently on a 5 mmol scale and is preparatively very straightforward (Table 1). The CuI catalyst was obtained from Aldrich (98%) and used as supplied. An ultrapure batch (Alfa Aesar Puratronic, 99.999% (metals basis)) gave the same yield, thus proving that copper is indeed the catalytically

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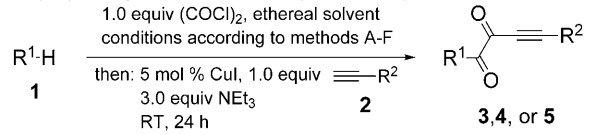
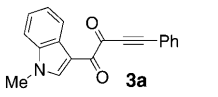
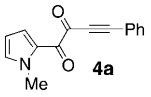
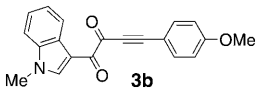
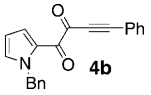
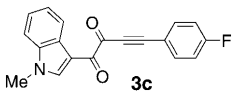
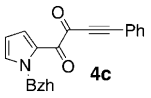
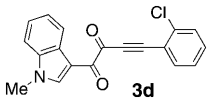
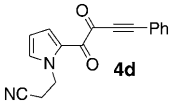
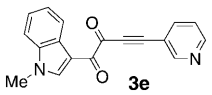
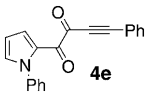
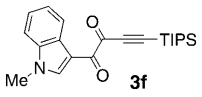
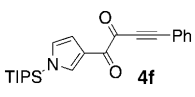
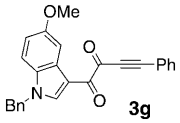
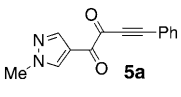
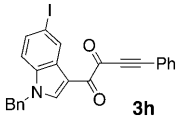
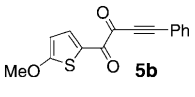
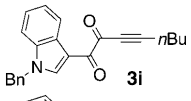
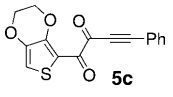
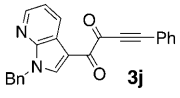
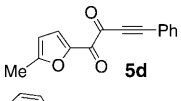
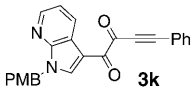
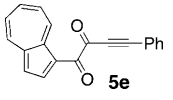
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201007194.

Table 1: Glyoxylation/Stephens–Castro synthesis of ynediones **3**, **4**, and **5**.[a]



Product	Yield [%][b] (method[c])	Product	Yield [%][b] (method[c])
 **3a**	66 (A)	 **4a**	64 (A)
 **3b**	68 (A)	 **4b**	74 (A)
 **3c**	73 (A)	 **4c**	67 (A)
 **3d**	60 (A)	 **4d**	60 (A)
 **3e**	43 (A)	 **4e**	77[d] (C)
 **3f**	74 (A)	 **4f**	44 (C)
 **3g**	57 (A)	 **5a**	47 (D)
 **3h**	35 (A)	 **5b**	53 (E)
 **3i**	2 (A)	 **5c**	66 (E)
 **3j**	62 (B)	 **5d**	38 (F)
 **3k**	59 (B)	 **5e**	33 (A)

[a] Reactions were performed in ethereal solvents [c(**1**) = 0.2 M] using 5.00 mmol of substrate **1**. Abbreviations: Ph = phenyl, Me = methyl, TIPS = triisopropylsilyl, Bu = butyl, Bn = benzyl, PMB = *p*-methoxybenzyl, Bzh = benzhydryl. [b] All yields refer to isolated and purified compounds. [c] Method A: THF, 0 °C to RT, 4 h; method B: DME, 0 °C to 100 °C, 2 h; method C: THF, 0 °C to 50 °C, 4 h; method D: DME, 0 °C to 100 °C, 24 h; method E: 1,4-dioxane, RT to 100 °C, 4 h; method F: 1,4-dioxane, RT to 100 °C, 24 h. [d] According to method A, 33 % of **4e** could be obtained.

active metal. Neither chelating ligands nor phosphanes are required.

The structures of the obtained ynediones **3**, **4**, and **5** were unambiguously supported by NMR spectroscopy, mass spectrometry, and combustion analysis, and later by an X-ray structure analysis of compound **3a** (Figure 1).

The sequence proceeds smoothly in ethereal solvents (THF, DME, or 1,4-dioxane), thus making it possible to perform the glyoxylation step in a wide temperature range. The reaction with electron-rich indoles and 7-azaindoles gives derivatives functionalized in the 3-position exclusively (compounds **3a**–**k**). Generally, pyrroles give 2-substituted regioisomers without noticeable amounts of the 3-substituted isomers (compounds **4a**–**e**). Expectedly, when the substrate has a bulky substituent on the nitrogen atom of the pyrrole ring, the 3-position is functionalized (compound **4f**). To our great delight, other important heterocycles like pyrazole (compound **5a**), thiophene (compounds **5b** and **5c**), and furan (compound **5d**) could be converted to ynediones, although the glyoxylation of these heterocycles to glyoxylyl chlorides has never been described. Interestingly, there is a method describing a direct carboxylation of 1,3,5-trisubstituted pyrazoles with oxalyl chloride.[15] However, with 1-methyl-1*H*-pyrazole we observed no decarbonylation but instead formation of compound **5a**. A further advantage of the described Lewis acid free method is the possibility of reacting substrates that are not compatible with Lewis-acid-mediated Friedel–Crafts conditions and (compound **5d**). Surprising, however, was the observation that thiophenes turned out to be excellent substrates for the described sequence. The more electron-rich 2-methylfuran gave a lower yield of ynedione **5d** along with a by-product resulting from the condensation of two furan molecules with one molecule of oxalyl chloride in 14 % yield.

Furthermore, the electron-rich hydrocarbon azulene could be functionalized as well (compound **5e**).[16] Aryl acetylenes bearing electron-neutral (compounds **3a**, **3g**,**h**, **3j**,**k**, **4a**–**f**, and **5a**–**e**), electron-donating (compound **3b**), or electron-withdrawing (compounds **3c**,**d**) substituents can be carried through the sequence without difficulties. Also heteroaryl (compound **3e**) as well as TIPS-substituted acetylenes (compound **3f**) can be coupled efficiently. However, an alkyl acetylene gave a very poor yield (compound **3i**). In all cases, no decarbonylative products were observed. The products were easily isolated by flash chromatography and were usually obtained in analytically pure form as stable compounds.

The reactivity of the glyoxylation of π nucleophiles can be estimated by considering the nucleophilicity parameters N of the (hetero)aryl substrate as determined by Mayr et al. for some reference nucleophiles.[17] The nucleophilicity parameters of the employed (hetero)arenes range from approximately 1.26 to 6.66, spanning five orders of magnitude (see Table S8 in the Supporting Information).

Azoles, furans, and thiophenes are of paramount importance in the synthesis of products relevant for medicinal chemistry and material science as well as in the synthesis of natural products. Therefore, the described mild and easy-to-perform one-pot functionalization of these prevalent classes of heterocycles opens up remarkable possibilities for their

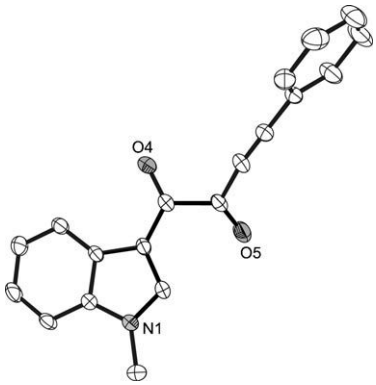
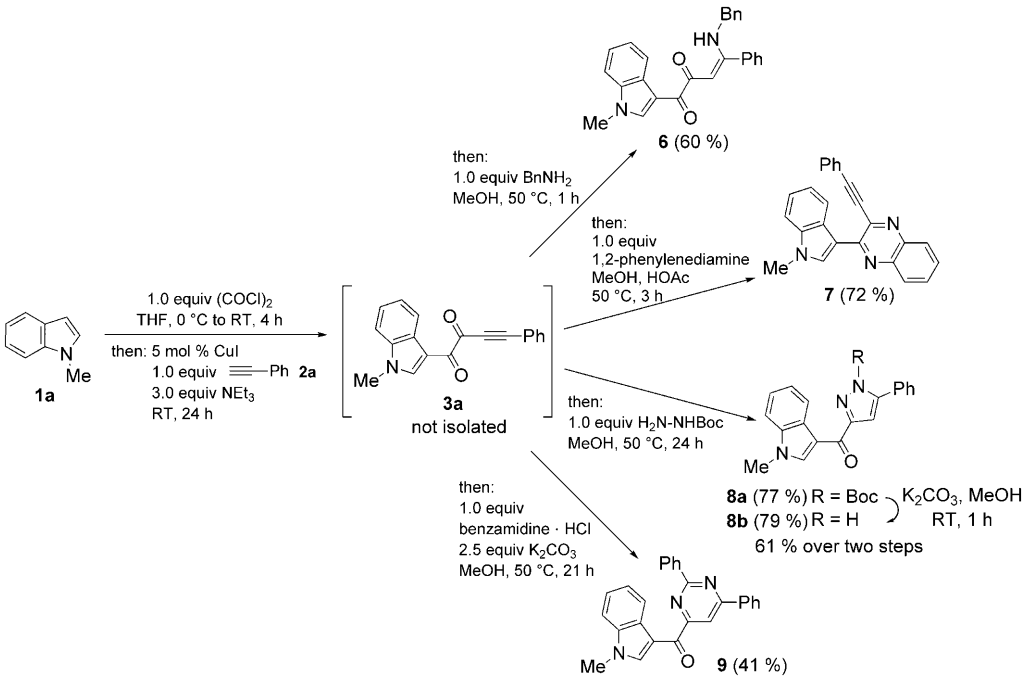


Figure 1. Molecular structure of **3a** (ellipsoids at the 50% probability level; hydrogen atoms were omitted for clarity).[18]

derivatization. Moreover, the obtained ynediones are densely functionalized, possessing a strongly activated Michael system as well as a dione motif, both important structural units in heterocycle synthesis.

As an illustration of the versatility of alkynediones as building blocks, we extended the sequence to the four-component syntheses of various products (Scheme 4). Simply by adding 1.0 equiv of different mono- and dinucleophiles after the glyoxylation/Stephens–Castro coupling sequence furnishing ynedione **3a**, we could achieve the one-pot syntheses of enaminedione **6**, quinoxaline **7**, indoloyl pyrazole **8a**, and indoloyl pyrimidine **9**; the final step of this sequence consists of Michael addition, double carbonyl condensation, and Michael addition/cyclocondensation reactions, respectively.



Scheme 4. Four-component syntheses of enaminedione **6**, quinoxaline **7**, indoloyl pyrazole **8a**, and indoloyl pyrimidine **9**.

It is worth mentioning that *tert*-butoxycarbonyl(Boc)-protected hydrazine can be used for the selective synthesis of the 2-acyl pyrazole **8a** without formation of the corresponding pyridazinone, thus giving direct and very efficient access to 2-acyl pyrazoles. So far, there has been no preparatively useful approach to this class of compounds. This unprecedented strategy is currently under investigation.

In conclusion, we have developed a new three-component approach to heterocyclic ynediones, which are very likely to become important intermediates in the synthesis of diverse, pharmaceutically interesting heterocycles. The use of catalytic Stephens–Castro conditions is crucial for the success of the reaction. The design of new diverse four-component syntheses of heterocycles with the intermediacy of ynediones has been highlighted successfully. It should be emphasized that all reagents in these three- and four-component reactions are required in equimolar ratios, rendering these sequences highly atom economical. Further generalizations of this strategy as well as diverse synthetic applications of ynediones are currently under investigation and will be reported in due course.

Experimental Section

3f: In an oven-dried screw-cap Schlenk flask with a septum a solution of 1-methyl indole (**1a**; 669 mg, 5.00 mmol) in 25 mL of anhydrous THF was placed under argon atmosphere. Argon was bubbled through the solution for 5 min which was cooled to 0 °C. Then, oxalyl chloride (0.44 mL, 5.00 mmol) was added dropwise to the reaction mixture at 0 °C. The mixture was allowed to come to room temperature and was stirred for 4 h. Then, CuI (49 mg, 0.25 mmol), tris(isopropyl)silyl (**2f**; 1.13 mL, 5.00 mmol), and anhydrous triethylamine (2.08 mL, 15.0 mmol) were successively added to the mixture, and the reaction mixture was stirred at room temperature for 24 h. After complete conversion, distilled water (25 mL) was added, the phases were separated, and the aqueous phase was extracted with dichloromethane (3 × 25 mL). The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuo, the residue was adsorbed onto Celite and purified by chromatography on silica gel (petroleum ether/ethyl acetate 7:1) to give the analytically pure **3f** (1.35 g; 74%) as a yellow solid, R_f = 0.25. M.p. 127 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.13–1.17 (m, 21H), 3.86 (s, 3H), 7.33–7.38 (m, 3H), 8.25 (s, 1H), 8.42–8.46 ppm (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.1 (CH), 18.5 (CH_3), 33.8 (CH_3), 103.4 ($C_{quat.}$), 103.9 ($C_{quat.}$), 109.9 (CH), 110.9 ($C_{quat.}$), 122.8 (CH), 123.5

(CH), 124.2 (CH), 127.2 ($C_{quat.}$), 137.3 ($C_{quat.}$), 140.0 (CH), 178.2 ($C_{quat.}$), 180.1 ppm ($C_{quat.}$). EIMS (70 eV) *m*/*z* (%): 367 $[M]^+$ (3), 158 $[M-C_{12}H_{21}OSi]^+$ (100), 130 $[C_9H_8N]^+$ (2). C,H,N analysis calcd (%) for $C_{22}H_{29}NO_2Si$ (367.6): C 71.89, H 7.95, N 3.81; found: C 72.06, H 7.94, N 3.70.

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[1] For recent reviews, see: a) F. Monnier, M. Taillefer, *Angew. Chem.* **2009**, *121*, 7088 – 7105; *Angew. Chem. Int. Ed.* **2009**, *48*, 6954 – 6971; b) G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, *108*, 3054 – 3131; c) I. P. Beletskaya, A. V. Cheprakov, *Coord. Chem. Rev.* **2004**, *248*, 2337 – 2364; d) S. V. Ley, A. W. Thomas, *Angew. Chem.* **2003**, *115*, 5558 – 5607; *Angew. Chem. Int. Ed.* **2003**, *42*, 5400 – 5449; e) K. Kunz, U. Scholz, D. Ganzer, *Synlett* **2003**, 2428 – 2439.

[2] For recent developments in Ullmann-type coupling reactions, see: a) D. Maiti, S. L. Buchwald, *J. Org. Chem.* **2010**, *75*, 1791 – 1794; b) D. Maiti, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 17423 – 17429; c) F. Monnier, M. Taillefer, *Angew. Chem.* **2008**, *120*, 3140 – 3143; *Angew. Chem. Int. Ed.* **2008**, *47*, 3096 – 3099, and references therein.

[3] Recent review on CuAAC ("click") reaction: M. Meldal, C. W. Tornóe, *Chem. Rev.* **2008**, *108*, 2952 – 3015.

[4] For cyanations, see: a) T. Schareina, A. Zapf, W. Mägerlein, N. Müller, M. Beller, *Chem. Eur. J.* **2007**, *13*, 6249 – 6254; b) T. Schareina, A. Zapf, M. Beller, *Tetrahedron Lett.* **2005**, *46*, 2585 – 2588; c) J. Zanon, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 2890 – 2891.

[5] Aromatic Finkelstein reaction: A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 14844 – 14845.

[6] a) C. E. Castro, R. D. Stephens, *J. Org. Chem.* **1963**, *28*, 2163 – 2163; b) R. D. Stephens, C. E. Castro, *J. Org. Chem.* **1963**, *28*, 3313 – 3315; c) C. E. Castro, E. J. Gaughan, D. C. Owsley, *J. Org. Chem.* **1966**, *31*, 4071 – 4078.

[7] a) Mild coupling of acid chlorides: C. Chowdhury, N. G. Kundu, *Tetrahedron* **1999**, *55*, 7011 – 7016; b) Microwave-assisted Cu-catalyzed coupling of acid chlorides: J.-X. Wang, B. Wei, Y. Hu, Z. Liu, Y. Fu, *Synth. Commun.* **2001**, *31*, 3527 – 3532; c) Cu/PPh_3-catalyzed coupling of aryl and vinyl halides: K. Okuro, M. Furuune, M. Enna, M. Miura, M. Nomura, *J. Org. Chem.* **1993**, *58*, 4716 – 4721.

[8] Cassar coupling: a) L. Cassar, *J. Organomet. Chem.* **1975**, *93*, 253 – 257; Dieck–Heck coupling: b) H. A. Dieck, F. R. Heck, *J. Organomet. Chem.* **1975**, *93*, 259 – 263.

[9] a) K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, *16*, 4467 – 4470; b) Y. Tohda, K. Sonogashira, N. Hagihara, *Synthesis* **1977**, 777 – 778; c) K. Sonogashira, *J. Organomet. Chem.* **2002**, *653*, 46 – 49; d) R. Rossi, A. Carpita, F. Bellina, *Org. Prep. Proced. Int.* **1995**, *27*, 127 – 160.

[10] Recent reviews: a) R. Chinchilla, C. Nájera, *Chem. Rev.* **2007**, *107*, 874 – 922; b) H. Doucet, J.-C. Hierso, *Angew. Chem.* **2007**, *119*, 850 – 888; *Angew. Chem. Int. Ed.* **2007**, *46*, 834 – 871.

[11] E. Merkul, T. Oeser, T. J. J. Müller, *Chem. Eur. J.* **2009**, *15*, 5006 – 5011.

[12] For a Au^{III}-catalyzed synthesis of furanones, see: Y. Liu, M. Liu, S. Guo, H. Tu, Y. Zhou, H. Gao, *Org. Lett.* **2006**, *8*, 3445 – 3448.

[13] M. Guo, D. Li, Z. Zhang, *J. Org. Chem.* **2003**, *68*, 10172 – 10174.

[14] For the optimization of the reaction for **3a**, see the Supporting Information.

[15] Direct carboxylation of pyrazoles: C. I. Chiriac, *Synthesis* **1986**, 753 – 755.

[16] For the azulen-1-yl-dicarbonyl (Az) protecting group, see: M. S. M. Timmer, B. L. Stocker, P. T. Northcote, B. A. Burkett, *Tetrahedron Lett.* **2009**, *50*, 7199 – 7204.

[17] H. Mayr, B. Kempf, A. R. Ofial, *Acc. Chem. Res.* **2003**, *36*, 66 – 77.

[18] CCDC 796698 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Supporting Information

69451 Weinheim, Germany

Three-Component Synthesis of Ynediones by a Glyoxylation/ Stephens–Castro Coupling Sequence**

*Eugen Merkul, Janis Dohe, Charlotte Gers, Frank Rominger, and Thomas J. J. Müller**

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Supporting Information

Table of Contents

1. General Considerations

All cross coupling reactions were carried out in oven-dried Schlenk glassware using septa and syringes under nitrogen or argon atmosphere. Tetrahydrofuran was dried using *MBraun* system MB-SPS-800, and triethylamine was refluxed under argon over ketyl sodium, distilled and stored in a Schlenk flask over potassium hydroxide pellets under argon atmosphere. Dry methanol was purchased by *Sigma-Aldrich Chemie GmbH*.

Compounds **1b**-**f** were prepared according to the literature procedure.[1] Compound **1i** was prepared according to the literature procedure.[2] Commercial grade reagents were used as supplied without further purification and were purchased from *Acros Organics*, *Sigma-Aldrich Chemie GmbH*, *Fluka AG*, *ABCR GmBH & Co. KG, Alfa Aesar GmbH & Co. KG*, *Riedel-de Haën, Maybridge,* and *Merck Serono KGaA*. Oxalyl chloride was obtained from *Merck Serono KGaA* and used neat without further purification.

The content of Pd (4 μg/g) in copper(I) iodide was determined in the laboratory Elementaranalytik of *Merck Serono KGaA*.

The purification of products was performed on silica gel 60 (0.015-0.040 mm) from *Merck Serono KGaA* Darmstadt using flash technique and under pressure of 2 bar. The purification of alkynediones was performed on Biotage SP-1 system using cartridges filled with ca. 340 g silica gel. The crude mixtures were adsorbed on Celite 545 (0.02-0.10 mm) from *Merck Serono KGaA* Darmstadt before chromatographic purification.

The reaction progress was monitored qualitatively using TLC Silica gel 60 F_{254} 5 x 7.5 cm aluminium sheets obtained by *Merck Serono KGaA* Darmstadt. The spots were detected with UV light at 254 nm and using aqueous potassium permanganate solution.

^{1}H, ^{13}C, and 135-DEPT NMR spectra were recorded on Bruker Advanced DRX 500 spectrometer. $CDCl_3$ and DMSO-d_6 were used as deuterated solvents. TMS was used as reference (δ = 0.0) or the resonances of the solvents were locked as internal standards ($CDCl_3$: ^{1}H δ 7.26, ^{13}C δ 77.0; DMSO-d_6: ^{1}H δ 2.50, ^{13}C δ 39.4). The multiplicities of signals were abbreviated as follows: s: singlet; d: doublet; t: triplet; dd: doublet of doublets; ddd: doublet of doublets of doublets; dt: doublet of triplets; td: triplet of doublets; tt: triplet of triplets; m: multiplet and br: broad signal. The type of carbon atoms was determined on the basis of 135-DEPT NMR spectra.

EI mass spectra were measured on Finnigan MAT 8200 spectrometer.

IR spectra were obtained on Bruker Vector 22 FT-IR. The solids were measured as KBr pellets and oils as films on KBr plates. The intensity of signals is abbreviated as follows: s (strong), m (medium) and w (weak).

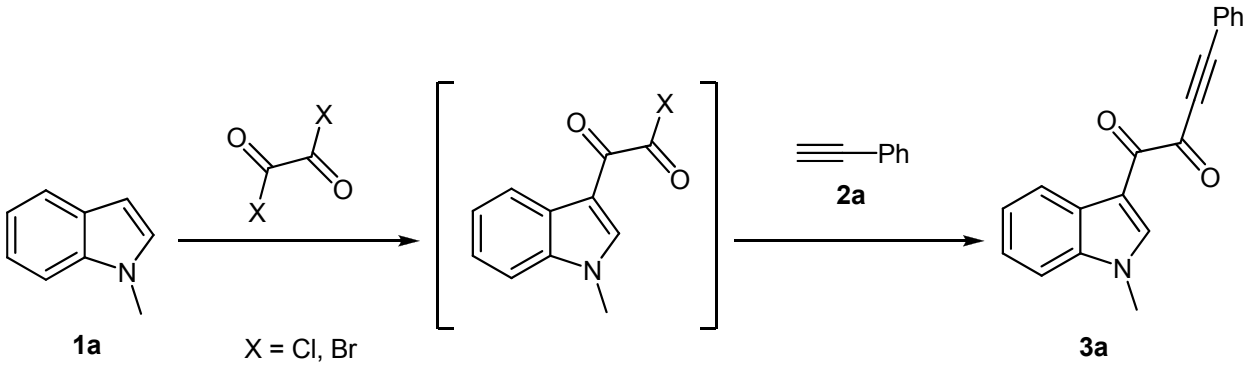
The melting points (uncorrected) were measured on Büchi Melting Point B-540.

Combustion analyses were carried out on Perkin Elmer Series II Analyser 2400 in the microanalytical laboratory of Institut für Pharmazeutische und Medizinische Chemie der Heinrich-Heine-Universität Düsseldorf.

The X-ray structure analysis was performed on Bruker APEX at Ruprecht-Karls-Universität Heidelberg.

2. Preparation of Ynediones 3a-k, 4a-f and 5a-e via Glyoxylation □ *Stephens-Castro* Coupling Sequence

2.1. Optimization of the Synthetic Procedure with 1-Methyl-1H-indole (1a)



The optimization of the procedure is depicted in ***Table 1***.

Table 1. Optimization of the synthesis of indolyl alkynedione **3a**.

Entry	Glyoxylation step[a]		*Stephens-Castro* coupling step[b]		Isolated yield of **3a** (%)
	$(COX)_2$ (1.00 equiv) Solvent	Reaction temperature and time	Catalyst Phenylacetylene **2a** Base	Reaction temperature and time	
1	$(COCl)_2$ THF	0 °C[c] → RT[d] 4 h	5 mol % CuI 1.00 equiv (**2a**) <u>5 mL NEt_3</u>[e]	RT 24 h	63 %
2	$(COCl)_2$ THF	0 °C → RT 4 h	<u>1 mol % CuI</u> 1.00 equiv (**2a**) 3.00 equiv NEt_3	RT 24 h	16 %
3	**$(COCl)_2$ THF**	**0 °C → RT 4 h**	**5 mol % CuI 1.00 equiv (2a) 3.00 equiv NEt_3**	**RT 24 h**	**66 %**

[a] The optimization reactions were performed on a 5.00 mmol scale (*c* (**1a**) = 0.2 *M*).

[b] The order in which the reagents appear in the table corresponds to the order in which they were added to the reaction mixture.

[c] The reaction vessel was cooled for 15 min in a water/ice bath.

[d] The reaction vessel was placed in a water bath.

[e] Reaction parameters or reagents different from the optimal conditions (entry 3, in bold) are underlined.

Table 1 (continuation). Optimization of the synthesis of indolyl alkynedione **3a**.

Entry	Glyoxylation step		*Stephens-Castro* coupling step		Isolated yield of **3a** (%)
	$(COX)_2$ (1.00 equiv) Solvent	Reaction temperature and time	Catalyst Phenylacetylene **2a** Base	Reaction temperature and time	
4	$(COCl)_2$ THF	0 °C → RT 4 h	5 mol % CuI 1.10 equiv (**2a**) 3.00 equiv NEt_3	RT 24 h	66 %
5	$(COCl)_2$ THF 5 mol % CuI	0 °C → RT 4 h	-[f] 1.00 equiv (**2a**) 3.00 equiv NEt_3	RT 24 h	58 %
6	$(COCl)_2$ THF	0 °C → RT 4 h	5 mol % CuI 1.00 equiv (**2a**) 3.00 eq. NEt_3	60 °C 2 h	34 %
7	$(COCl)_2$ (1.5 equiv) THF	0 °C → RT 4 h	5 mol % CuI 2.00 equiv (**2a**) 4.00 equiv NEt_3	RT 24 h	41 %
8	$(COCl)_2$ THF	0 °C → 60 °C 1 h	5 mol % CuI 1.00 equiv (**2a**) 3.00 equiv NEt_3	RT 24 h	67 %
9	$(COCl)_2$ THF	0 °C → RT 4 h	5 mol % CuI 1.00 equiv (**2a**) 3.00 equiv NEt_3	60 °C 24 h	16 %
10	$(COCl)_2$ THF	0 °C → 60 °C 1 h	5 mol % CuI 1.00 equiv (**2a**) 3.00 equiv NEt_3	60 °C 4 h	10 %
11	$(COCl)_2$ THF	0 °C → 60 °C 1 h	5 mol % CuI 1.00 equiv (**2a**) 3.00 equiv NEt_3	RT 21 h	59 %
12	$(COCl)_2$ THF	0 °C → 60 °C 1 h	5 mol % CuI 1.00 equiv (**2a**) 3.00 equiv NEt_3	RT 48 h	48 %
13	$(COCl)_2$ THF	0 °C → RT 4 h	5 mol % CuI 1.00 equiv (**2a**) 2.00 equiv NEt_3	RT 24 h	51 %

[f] 5 mol % CuI were already added in the glyoxylation step.

Table 1 (continuation). Optimization of the synthesis of indolyl alkynedione **3a**.

Entry	Glyoxylation step		*Stephens-Castro* coupling step		Isolated yield of **3a** (%)
	$(COX)_2$ (1.00 equiv) Solvent	Reaction temperature and time	Catalyst Phenylacetylene **2a** Base	Reaction temperature and time	
14	$(COCl)_2$ THF	0 °C → RT 4 h	5 mol % CuI 1.00 equiv (**2a**) 3.00 equiv NEt_3	RT 48 h	65 %
15	$(COCl)_2$ THF	0 °C → RT 4 h	5 mol % AuI 1.00 equiv (**2a**) 3.00 equiv NEt_3	RT 24 h	no reaction
16	$(COBr)_2$ THF	0 °C → RT 4 h	5 mol % CuI 1.00 equiv (**2a**) 3.00 equiv NEt_3	RT 24 h	no reaction
17	$(COCl)_2$ THF	0 °C → RT 4 h	5 mol % CuI 1.00 equiv (**2a**) 3.00 equiv NEt_3	40 °C 24 h	64 %
18	$(COCl)_2$ THF	0 °C → RT 4 h	5 mol % CuI 5 mol % 1,10-phenanthroline 1.00 equiv (**2a**) 3.00 equiv NEt_3	RT 24 h	42 %
19	$(COCl)_2$ THF	0 °C → RT 4 h	5 mol % CuI 1.00 equiv (**2a**) 3.00 equiv NEt^iPr_2[g]	RT 24 h	no reaction
20	$(COCl)_2$ THF	0 °C → RT 4 h	5 mol % CuI 1.00 equiv (**2a**) 3.00 equiv TMEDA[h]	RT 24 h	no reaction
21	$(COCl)_2$ THF	0 °C → RT 4 h	5 mol % CuI 1.00 equiv (**2a**) 3.00 equiv DMAP[i]	RT 24 h	no reaction

[g] DIPEA, Hünig´s base.

[h] *N*,*N*,*N´*,*N´*-Tetramethylethylenediamine.

[i] 4-Dimethylaminopyridine.

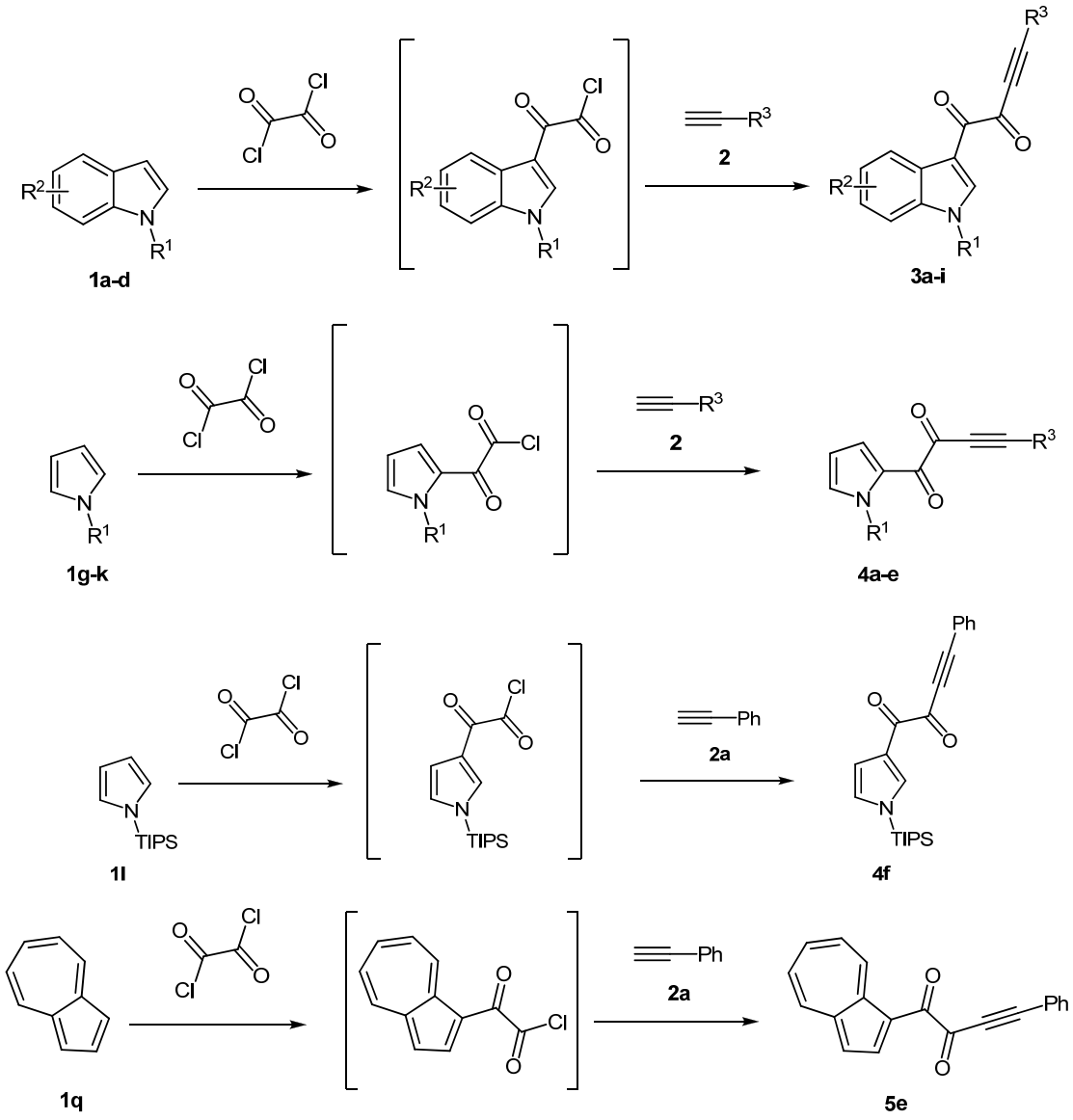
Table 1 (continuation). Optimization of the synthesis of indolyl alkynedione **3a**.

Entry	Glyoxylation step		*Stephens-Castro* coupling step		Isolated yield of **3a** (%)
	$(COX)_2$ (1.00 equiv) Solvent	Reaction temperature and time	Catalyst Phenylacetylene **2a** Base	Reaction temperature and time	
22	$(COCl)_2$ 1,4-dioxane	RT → 100 °C[j] 4 h	5 mol % CuI 1.00 equiv (**2a**) 3.00 equiv NEt_3	RT 24 h	10 %
23	$(COCl)_2$ 1,4-dioxane	RT → 100 °C 1 h	5 mol % CuI 1.00 equiv (**2a**) 3.00 equiv NEt_3	RT 24 h	48 %
24	$(COCl)_2$ 1,4-dioxane	RT 4 h	5 mol % CuI 1.00 equiv (**2a**) 3.00 equiv NEt_3	RT 24 h	62 %
25	$(COCl)_2$ 1,4-dioxane	RT 1 h	5 mol % CuI 1.00 equiv (**2a**) 3.00 equiv NEt_3	RT 24 h	61 %

[j] The reaction vessel was placed in a preheated oil bath.

The conditions shown in *entry 3* were considered as optimized and were used in the general procedure for the preparation of compounds **3a-i**, **4a-d** and **5e** (procedure A).

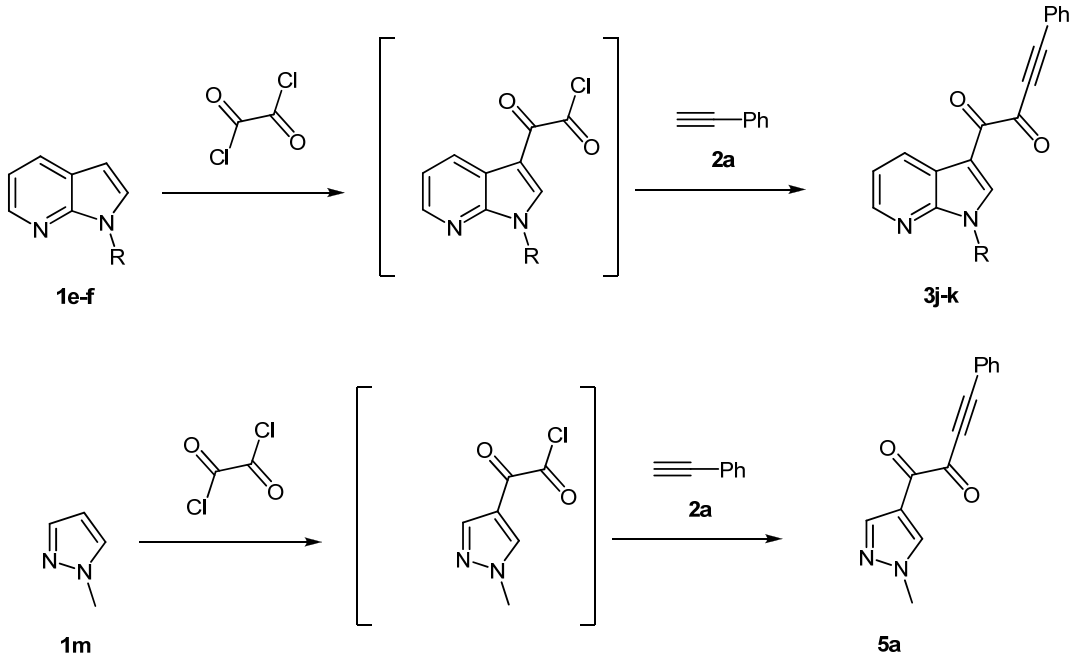
2.2. General Procedure for the Preparation of Compounds 3a-i, 4a-d, 5e and 4e-f (Procedures A and C)



5.00 mmol of *N*-substituted indole **1a-d** or pyrrole **1g-l** (or azulene **1q**) in dry THF (25 mL) were placed under argon atmosphere in a screw-cap Schlenk vessel with septum, degassed with argon and cooled to 0 °C (water/ice, for 15 min). Then, oxalyl chloride (0.44 mL, 5.00 mmol) was added dropwise to the reaction mixture at 0 °C. The mixture was allowed to come to room temperature (water bath) or 50 °C (for **1k-l**, preheated oil bath) and was stirred for 4 h. Then, CuI (49 mg, 0.25 mmol), 5.00 mmol of terminal alkyne **2** and dry triethylamine (2.08 mL, 15.0 mmol) were successively added to the mixture and stirring at room temperature was continued for 24 h. After complete conversion (product monitored by TLC) water (25 mL) was added, the phases were separated and the aqueous phase was extracted with dichloromethane (3-5 x 25 mL, monitored by TLC). The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuo the residue was absorbed onto Celite® and purified chromatographically on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl acetate to give the alkynediones **3a-i**, **4a-d** and **5e**.

The experimental details are given in ***Table 2.***

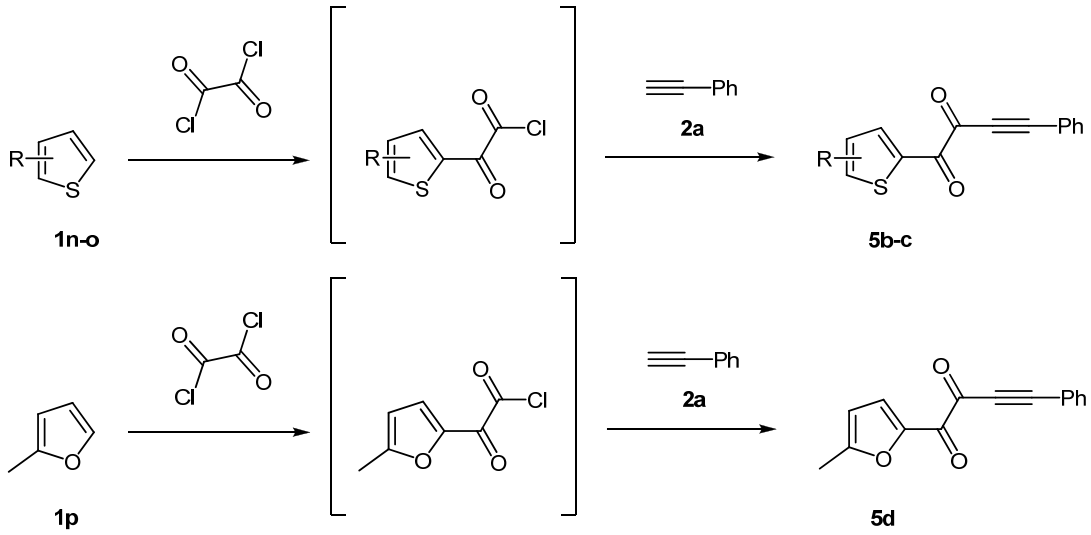
2.3. General Procedure for the Preparation of Compounds 3j-k and 5a (Procedures B and D)



5.00 mmol of *N*-substituted 7-azaindole **1e-f** or pyrazole **1m** in dry DME (25 mL) were placed under argon atmosphere in a screw-cap Schlenk vessel with septum, degassed with argon and cooled to 0 °C (water/ice, for 15 min). Then, oxalyl chloride (0.44 mL, 5.00 mmol) was added dropwise to the reaction mixture at 0 °C. The mixture was allowed to come to room temperature (water bath), stirred for 15 min. and then stirred at 100 °C (preheated oil bath) for 2 h in case of 7-azaindoles **1e-f** and for 24 h in case of pyrazole **1m**. Then, after cooling to room temperature (water bath, for 15 min), CuI (49 mg, 0.25 mmol), phenylacetylene **2a** (0.57 mL, 5.00 mmol) and dry triethylamine (2.08 mL, 15.0 mmol) were successively added to the mixture and stirring at room temperature was continued for 24 h. After complete conversion (product monitored by TLC) water (25 mL) was added, the phases were separated and the aqueous phase was extracted with dichloromethane (3-5 x 25 mL, monitored by TLC). The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuo the residue was absorbed onto Celite® and purified chromatographically on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl acetate to give the analytically pure alkynediones **3j-k** or **5a**.

The experimental details are given in ***Table 2.***

2.4. General Procedure for the Preparation of Compounds 5b-c and 5d (Procedures E and F)



5.00 mmol of thiophene **1n-o** or furan **1p** in dry 1,4-dioxane (25 mL) were placed under argon atmosphere in a screw-cap Schlenk vessel with septum and degassed with argon. Then, oxalyl chloride (0.44 mL, 5.00 mmol) was added dropwise to the reaction mixture at room temperature. The mixture was then stirred at 100 °C (preheated oil bath) for 4 h (for 24 h in case of furan **1p**). Then, after cooling to room temperature (water bath, for 15 min), CuI (49 mg, 0.25 mmol), phenylacetylene **2a** (0.57 mL, 5.00 mmol) and dry triethylamine (2.08 mL, 15.0 mmol) were successively added to the mixture and stirring at room temperature was continued for 24 h. After complete conversion (product monitored by TLC) water (25 mL) was added, the phases were separated and the aqueous phase was extracted with dichloromethane (3-5 x 25 mL, monitored by TLC). The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuo the residue was absorbed onto Celite® and purified chromatographically on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl acetate to give the analytically pure alkynediones **5b-e**.

The experimental details are given in ***Table 2.***

Table 2. Experimental details of the three-component glyoxylation-*Stephens-Castro* coupling sequence for the synthesis of indolyl ynediones **3a-e**.

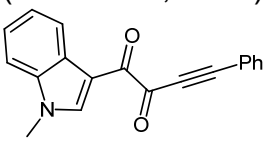
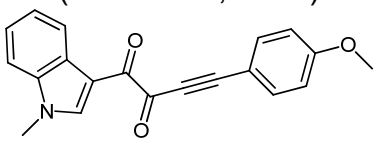
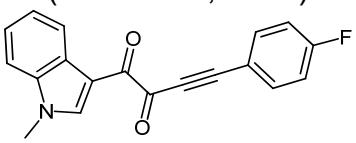
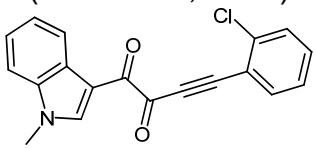
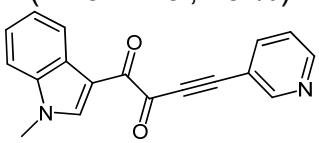
Entry	*N*-Substituted indole **1** (5.00 mmol)	Alkyne **2** (5.00 mmol)	Ynedione **3** (isolated yield %)	Chromatographic purification (eluent) R_f (eluent)
1	1-Methyl-1*H*-indole (*Merck*) 669 mg **1a**	Phenylacetylene (*Merck*) 0.57 mL **2a**	948 mg (3.30 mmol, 66 %)  **3a**	PE-EA = 3:1 R_f (PE-EA = 3:1): 0.39
2	669 mg **1a**	4-Ethynylanisole (*Maybridge*) 661 mg **2b**	1.08 g (3.40 mmol, 68 %)  **3b**	PE-EA = 4:1 R_f (PE-EA = 4:1): 0.10
3	669 mg **1a**	4-Fluoro-phenylacetylene (*Alfa Aesar*) 0.58 mL **2c**	1.12 g (3.66 mmol, 73 %)  **3c**	PE-EA = 3:1 R_f (PE-EA = 3:1): 0.20
4	669 mg **1a**	2-Chloro-phenylacetylene (*ABCR*) 697 mg **2d**	970 mg (3.01 mmol, 60 %)  **3d**	PE-EA = 4:1 R_f (PE-EA = 4:1): 0.20
5	669 mg **1a**	3-Ethynylpyridine (*Aldrich*) 526 mg **2e**	613 mg (2.13 mmol, 43 %)  **3e**	PE-EA = 1:1 R_f (PE-EA = 1:1): 0.22

Table 2 (continuation). Experimental details of the three-component glyoxylation-*Stephens-Castro* coupling sequence for the synthesis of indolyl alkynediones **3f-i**.

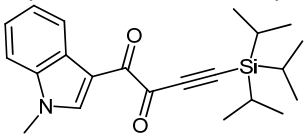
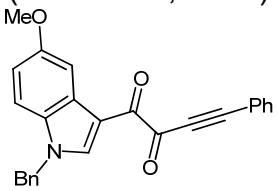
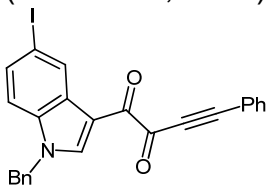
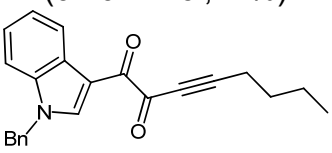
Entry	*N*-Substituted indole **1** (5.00 mmol)	Alkyne **2** (5.00 mmol)	Ynedione **3** (isolated yield %)	Chromatographic purification (eluent) R_f (eluent)
6	669 mg **1a**	Triisopropylsilyl-acetylene (*Fluka*) 1.13 mL **2f**	1.35 g (3.68 mmol, 74 %)  **3f**	PE-EA = 7:1 R_f (PE-EA = 7:1): 0.25
7	1-Benzyl-5-methoxy-1*H*-indole[1] 1.19 g **1b**	0.57 mL **2a**	1.13 g (2.87 mmol, 57 %)  **3g**	PE-EA = 5:1 R_f (PE-EA = 5:1): 0.38
8	1-Benzyl-5-iodo-1*H*-indole[1] 1.67 g **1c**	0.57 mL **2a**	864 mg (1.77 mmol, 35 %)  **3h**	PE-EA = 7:1 R_f (PE-EA = 7:1): 0.23
9	1-Benzyl-1*H*-indole[1] 1.04 g **1d**	1-Hexyne (*Acros*) 0.59 mL **2h**	36 mg (0.10 mmol, 2 %)  **3i**	PE-EA = 10:1 R_f (PE-EA = 10:1): 0.25

Table 2 (continuation). Experimental details of the three-component glyoxylation-*Stephens-Castro* coupling sequence for the synthesis of 7-azaindolyl alkynediones **3j-k**.

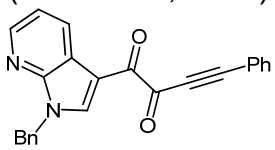
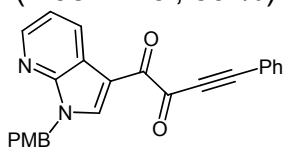
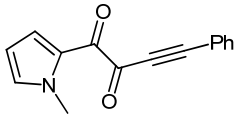
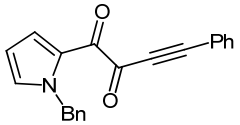
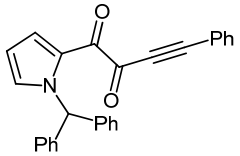
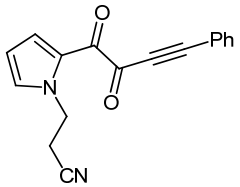
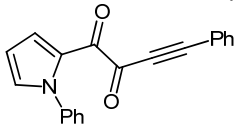
Entry	*N*-Substituted 7-azaindole **1** (5.00 mmol)	Alkyne **2** (5.00 mmol)	Ynedione **3** (isolated yield %)	Chromatographic purification (eluent) R_f (eluent)
10	1-Benzyl-1*H*-pyrrolo[2,3-*b*]-pyridine[1] 1.04 g **1e**	0.57 mL **2a**	1.13 g (3.10 mmol, 62 %)  **3j**	PE-EA = 4:1 R_f (PE-EA = 4:1): 0.29
11	1-(4-Methoxy-benzyl)-1*H*-pyrrolo[2,3-*b*]-pyridine[1] 1.19 g **1f**	0.57 mL **2a**	1.16 g (2.95 mmol, 59 %)  **3k**	PE-EA = 3:1 R_f (PE-EA = 3:1): 0.30

Table 2 (continuation). Experimental details of the three-component glyoxylation-*Stephens-Castro* coupling sequence for the synthesis of pyrrolyl alkynediones **4a-e**.

Entry	*N*-Substituted pyrrole **1** (5.00 mmol)	Alkyne **2** (5.00 mmol)	Ynedione **4** (isolated yield %)	Chromatographic purification (eluent) R_f (eluent)
12	1-Methyl-1*H*-pyrrole (*Merck*) 420 mg **1g**	Phenylacetylene (*Merck*) 0.57 mL **2a**	754 mg (3.18 mmol, 64 %)  **4a**	PE-EA = 7:1 R_f (PE-EA = 7:1): 0.34
13	1-Benzyl-1*H*-pyrrole (*Aldrich*) 810 mg **1h**	0.57 mL **2a**	1.16 g (3.70 mmol, 74 %)  **4b**	PE-EA = 9:1 R_f (PE-EA = 9:1): 0.13
14	1-Benzhydryl-1*H*-pyrrole[2] 1.17 g **1i**	0.57 mL **2a**	1.31 g (3.36 mmol, 67 %)  **4c**	PE-EA = 9:1 R_f (PE-EA = 9:1): 0.20
15	1-(2-Cyanoethyl)-1*H*-pyrrole (*Aldrich*) 607 mg **1j**	0.57 mL **2a**	830 mg (3.00 mmol, 60 %)  **4d**	PE-EA = 2:1 R_f (PE-EA = 2:1): 0.36
16	1-Phenyl-1*H*-pyrrole (*ABCR*) 723 mg **1k**	0.57 mL **2a**	1.15 g (3.84 mmol, 77 %)[a]  **4e**	PE-EA = 9:1 R_f (PE-EA = 9:1): 0.24

[a] According to procedure A, 491 mg (1.64 mmol, 33 %) of **4e** were obtained.

Table 2 (continuation). Experimental details of the three-component glyoxylation-*Stephens-Castro* coupling sequence for the synthesis of pyrrolyl alkynedione **4f-e** and pyrazolyl alkynedione **5a**.

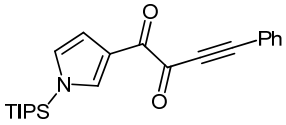
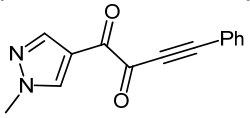
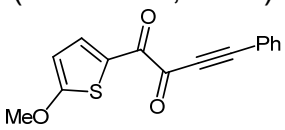
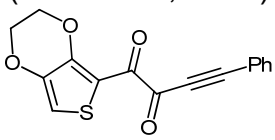
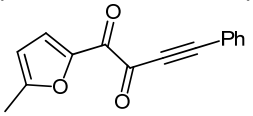
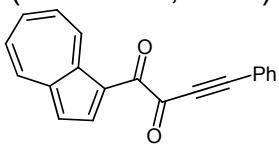
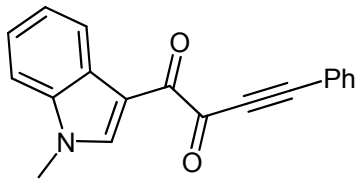
Entry	*N*-Substituted pyrrole or pyrazole **1** (5.00 mmol)	Alkyne **2** (5.00 mmol)	Ynedione **4** or **5** (isolated yield %)	Chromatographic purification (eluent) R_f (eluent)
17	1-(Triisopropyl-silyl)-1*H*-pyrrole (*Alfa Aesar*) 1.18 g **1l**	0.57 mL **2a**	836 mg (2.20 mmol, 44 %)  **4f**	PE-EA = 20:1 R_f (PE-EA = 20:1): 0.24
18	1-Methyl-1*H*-pyrazole (*Aldrich*) 415 mg **1m**	0.57 mL **2a**	564 mg (2.37 mmol, 47 %)  **5a**	PE-EA = 3:1 Rf (PE-EA = 3:1): 0.13

Table 2 (continuation). Experimental details of the three-component glyoxylation-*Stephens-Castro* coupling sequence for the synthesis of thienyl, furyl and azulenyl alkynediones **5b-c**, **5d** and **5e**, respectively.

Entry	Furan, thiophene or azulene **1** (5.00 mmol)	Alkyne **2** (5.00 mmol)	Ynedione **5** (isolated yield %)	Chromatographic purification (eluent) R_f (eluent)
19	2-Methoxythiophene (*Alfa Aesar*) 577 mg **1n**	Phenylacetylene (*Merck*) 0.57 mL **2a**	712 mg (2.63 mmol, 53 %)  **5b**	PE-EA = 10:1 R_f (PE-EA = 10:1): 0.20
20	2,3-Dihydrothieno-[3,4-*b*][1,4]dioxine (*Aldrich*) 711 mg **1o**	0.57 mL **2a**	978 mg (3.28 mmol, 66 %)  **5c**	PE-EA = 20:1 R_f (PE-EA = 20:1): 0.30
21	2-Methylfuran (*Merck*) 415 mg **1p**	0.57 mL **2a**	457 mg (1.92 mmol, 38 %)  **5d**	PE-EA = 10:1 R_f (PE-EA = 10:1): 0.15
22	(4*Z*,6*Z*,8*Z*)-Azulene (Azulene) (*Alfa Aesar*) 647 mg **1q**	0.57 mL **2a**	462 mg (1.63 mmol, 33 %)  **5e**	PE-EA = 8:1 R_f (PE-EA = 8:1): 0.29

2.5. Spectroscopic Data of Compounds 3a-k

2.5.1. 1-(1-Methyl-1*H*-indol-3-yl)-4-phenylbut-3-yne-1,2-dione (3a)

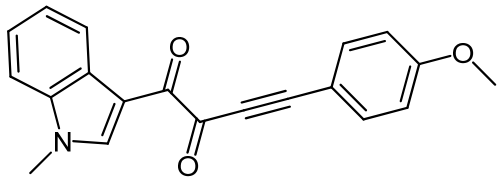


$C_{19}H_{13}NO_2$

287.31

948 mg (3.30 mmol, 66 % yield) as a yellow solid. Mp 129-130 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.87 (s, 3 H), 7.35-7.43 (m, 5 H), 7.46-7.51 (m, 1 H), 7.69-7.72 (m, 2 H), 8.33 (s, 1 H), 8.45-8.49 (m, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 33.8 (CH_3), 87.7 (C_{quat}), 97.6 (C_{quat}), 110.0 (CH), 110.9 (C_{quat}), 119.8 (C_{quat}), 122.8 (CH), 123.6 (CH), 124.2 (CH), 127.2 (C_{quat}), 128.6 (CH), 131.3 (CH), 133.7 (CH), 137.3 (C_{quat}), 140.3 (CH), 178.7 (C_{quat}), 180.2 (C_{quat}). EI + MS (*m/z* (%)): 287 (M^+, 11), 158 ($(M-C_9H_5O)^+$, 100), 130 ($C_9H_8N^+$, 6), 103 (7), 77 ($C_6H_5^+$, 6). IR (KBr): $\tilde{\nu}$ 2203 (m) cm^{-1}, 1646 (s), 1627 (s), 1528 (m), 1466 (m), 1379 (w), 1283 (w), 1131 (w), 1075 (m), 1033 (m), 881 (w), 772 (w), 758 (w), 741 (m), 689 (w). Anal. calcd for $C_{19}H_{13}NO_2$ (287.3): C 79.43, H 4.56, N 4.88. Found: C 79.25, H 4.46, N 4.86.

2.5.2. 4-(4-Methoxyphenyl)-1-(1-methyl-1*H*-indol-3-yl)but-3-yne-1,2-dione (3b)

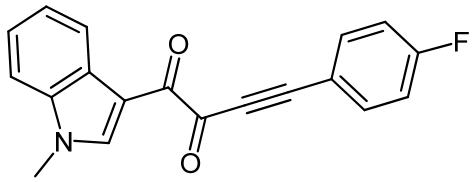


$C_{20}H_{15}NO_3$

317.34

1.08 g (3.40 mmol, 68 % yield) as a yellow solid. Mp 141-142 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.85 (s, 3 H), 3.88 (s, 3 H), 6.92 (d, *J* = 8.8 Hz, 2 H), 7.34-7.40 (m, 3 H), 7.67 (d, *J* = 8.8 Hz, 2 H), 8.34 (s, 1 H), 8.45-8.50 (m, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 34.0 (CH_3), 55.7 (CH_3), 88.3 (C_{quat}), 99.4 (C_{quat}), 110.2 (CH), 111.2 (C_{quat}), 111.8 (C_{quat}), 114.6 (CH), 123.0 (CH), 123.8 (CH), 124.4 (CH), 127.5 (C_{quat}), 136.2 (CH), 137.5 (C_{quat}), 140.5 (CH), 162.4 (C_{quat}), 178.8 (C_{quat}), 180.8 (C_{quat}). EI + MS (*m/z* (%)): 317 (M^+, 8), 158 ($(M-C_{10}H_7O_2)^+$, 100), 130 ($C_9H_8N^+$, 5), 103 (4), 77 ($C_6H_5^+$, 3). IR (KBr): $\tilde{\nu}$ 2162 (m) cm^{-1}, 1625 (s), 1597 (s), 1524 (m), 1508 (s), 1466 (m), 1442 (w), 1377 (m), 1289 (w), 1256 (s), 1168 (w), 1112 (w), 1073 (m), 1032 (s), 883 (w), 836 (w), 808 (w), 790 (w), 715 (m), 575 (w), 542 (w). Anal. calcd for $C_{20}H_{15}NO_3$ (317.3): C 75.70, H 4.76, N 4.41. Found: C 75.42, H 4.78, N 4.48.

2.5.3. 4-(4-Fluorophenyl)-1-(1-methyl-1*H*-indol-3-yl)but-3-yne-1,2-dione (3c)

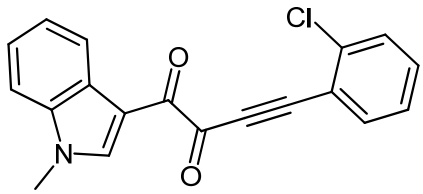


$C_{19}H_{12}FNO_2$

305.30

1.12 g (3.66 mmol, 73 % yield) as a yellow solid. Mp 156 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.87 (s, 3 H), 7.08-7.13 (m, 2 H), 7.35-7.40 (m, 3 H), 7.68-7.73 (m, 2 H), 8.33 (s, 1 H), 8.44-8.48 (m, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 33.9 (CH_3), 87.7 (d, *J* = 1.8 Hz, C_{quat}), 96.5 (C_{quat}), 110.0 (CH), 110.9 (C_{quat}), 115.9 (d, *J* = 3.7 Hz, C_{quat}), 116.3 (d, *J* = 22.9 Hz, CH), 122.8 (CH), 123.7 (CH), 124.3 (CH), 127.3 (C_{quat}), 136.1 (d, *J* = 9.2 Hz, CH), 137.3 (C_{quat}), 140.3 (CH), 164.3 (d, *J* = 254.8 Hz, C_{quat}), 178.5 (C_{quat}), 180.0 (C_{quat}). EI + MS (*m/z* (%)): 305 (M^+, 6), 158 ($(M-C_9H_4FO)^+$, 100), 130 ($C_9H_8N^+$, 6), 103 (7), 77 ($C_6H_5^+$, 5). IR (KBr): $\tilde{\nu}$ 2204 (m) cm^{-1}, 1655 (s), 1619 (s), 1544 (w), 1509 (m), 1459 (m), 1366 (m), 1216 (m), 1126 (m), 1070 (m), 1028 (m), 881 (w), 842 (m), 811 (m), 743 (m), 719 (m), 575 (w), 537 (m). Anal. calcd for $C_{19}H_{12}FNO_2$ (305.3): C 74.75, H 3.96, N 4.59. Found: C 74.79, H 3.95, N 4.47.

2.5.4. 4-(2-Chlorophenyl)-1-(1-methyl-1*H*-indol-3-yl)but-3-yne-1,2-dione (3d)

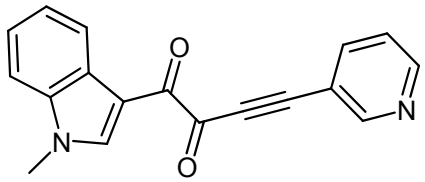


$C_{19}H_{12}ClNO_2$

321.76

970 mg (3.01 mmol, 60 % yield) as a yellow solid. Mp 148-150 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.87 (s, 3 H), 7.30 (td, *J* = 7.6 Hz, *J* = 0.9 Hz, 1 H), 7.35-7.38 (m, 3 H), 7.41 (td, *J* = 7.6 Hz, *J* = 1.6 Hz, 1 H), 7.47 (dd, *J* = 8.2 Hz, *J* = 0.9 Hz, 1 H), 7.71 (dd, *J* = 7.9 Hz, *J* = 1.6 Hz , 1 H), 8.33 (s, 1 H), 8.45-8.49 (m, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 33.9 (CH_3), 91.6 (C_{quat}), 93.2 (C_{quat}), 110.0 (CH), 110.9 (C_{quat}), 120.1 (C_{quat}), 122.8 (CH), 123.6 (CH), 124.3 (CH), 126.8 (CH), 127.2 (C_{quat}), 129.7 (CH), 132.1 (CH), 135.3 (CH), 137.3 (C_{quat}), 137.9 (C_{quat}), 140.3 (CH), 178.4 (C_{quat}), 179.8 (C_{quat}). EI + MS (*m/z* (%)): 323 ($M(^{37}Cl)^+$, 2), 321 ($M(^{35}Cl)^+$, 5), 158 ($(M-C_9H_4ClO)^+$, 100), 130 ($C_9H_8N^+$, 6), 103 (5), 77 ($C_6H_5^+$, 5). IR (KBr): $\tilde{\nu}$ 3115 (w) cm^{-1}, 2207 (m), 1667 (m), 1626 (s), 1524 (m), 1460 (m), 1375 (m), 1290 (m), 1226 (m), 1128 (m), 1073 (m), 1028 (m), 879 (m), 774 (m), 750 (s), 693 (w), 622 (w), 527 (w). Anal. calcd for $C_{19}H_{12}ClNO_2$ (321.8): C 70.92, H 3.76, N 4.35. Found: C 70.87, H 3.85, N 4.13.

2.5.5. 1-(1-Methyl-1*H*-indol-3-yl)-4-(pyridin-3-yl)but-3-yne-1,2-dione (3e)

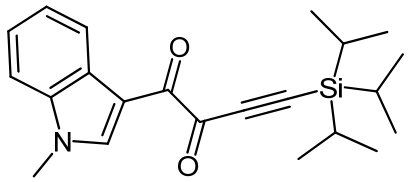


$C_{18}H_{12}N_2O_2$

288.30

613 mg (2.13 mmol, 43 % yield) as a yellow-orange solid. Mp 144-146 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.88 (s, 3 H), 7.33-7.40 (m, 4 H), 7.98 (dt, *J* = 7.9 Hz, *J* = 1.9 Hz, 1 H), 8.34 (s, 1 H), 8.43-8.47 (m, 1 H), 8.69 (dd, *J* = 5.0 Hz, *J* = 1.6 Hz, 1 H), 8.91 (d, *J* = 1.6 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 33.9 (CH_3), 90.1 (C_{quat}), 93.2 (C_{quat}), 110.1 (CH), 110.8 (C_{quat}), 117.2 (C_{quat}), 122.7 (CH), 123.3 (CH), 123.8 (CH), 124.4 (CH), 127.2 (C_{quat}), 137.3 (C_{quat}), 140.3 (CH), 140.4 (CH), 151.1 (CH), 153.8 (CH), 178.1 (C_{quat}), 179.5 (C_{quat}). EI + MS (*m/z* (%)): 288 (M^+, 7), 158 ((M-$C_8H_4NO)^+$, 100), 130 ($C_9H_8N^+$, 6), 103 (6), 77 ($C_6H_5^+$, 6). IR (KBr): $\tilde{\nu}$ 2207 (m) cm^{-1}, 1661 (m), 1620 (s), 1578 (w), 1525 (m), 1466 (m), 1412 (m), 1377 (m), 1336 (w), 1279 (m), 1225 (w), 1191 (w), 1125 (w), 1075 (m), 1024 (m), 880 (m), 811 (w), 773 (m), 744 (m), 705 (m), 638 (m), 573 (w), 519 (w). Anal. calcd for $C_{18}H_{12}N_2O_2$ (288.3): C 74.99, H 4.20, N 9.12. Found: C 74.99, H 4.14, N 9.40.

2.5.6. 4-(Triisopropylsilyl)-1-(1-methyl-1*H*-indol-3-yl)but-3-yne-1,2-dione (3f)

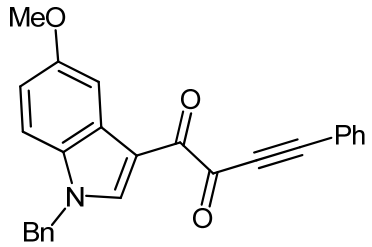


$C_{22}H_{29}NO_2Si$

367.56

1.35 g (3.68 mmol, 74 % yield) as a yellow solid. Mp 127 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.13-1.17 (m, 21 H), 3.86 (s, 3 H), 7.33-7.38 (m, 3 H), 8.25 (s, 1 H), 8.42-8.46 (m, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 11.1 (CH), 18.5 (CH_3), 33.8 (CH_3), 103.4 (C_{quat}), 103.9 (C_{quat}), 109.9 (CH), 110.9 (C_{quat}), 122.8 (CH), 123.5 (CH), 124.2 (CH), 127.2 (C_{quat}), 137.3 (C_{quat}), 140.0 (CH), 178.2 (C_{quat}), 180.1 (C_{quat}). EI + MS (*m/z* (%)): 367 (M^+, 3), 158 ((M-$C_{12}H_{21}OSi)^+$, 100), 130 ($C_9H_8N^+$, 2). IR (KBr): $\tilde{\nu}$ 2941 (m) cm^{-1}, 2864 (m), 2146 (w), 1664 (s), 1633 (s), 1522 (m), 1466 (m), 1374 (m), 1258 (m), 1176 (m), 1124 (m), 1073 (s), 1033 (m), 994 (m), 868 (s), 801 (w), 748 (s), 718 (w), 681 (m), 583 (w). Anal. calcd for $C_{22}H_{29}NO_2Si$ (367.6): C 71.89, H 7.95, N 3.81. Found: C 72.06, H 7.94, N 3.70.

2.5.7. 1-(1-Benzyl-5-methoxy-1*H*-indol-3-yl)-4-phenylbut-3-yne-1,2-dione (3g)

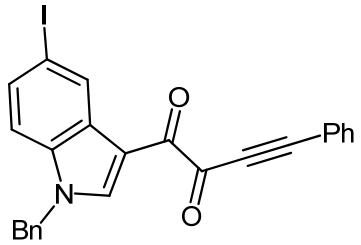


$C_{26}H_{19}NO_3$

393.43

1.13 g (2.87 mmol, 57 % yield) as an orange solid. Mp 112 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.90 (s, 3 H), 5.33 (s, 2 H), 6.91 (dd, *J* = 8.8 Hz, *J* = 2.5 Hz, 1 H), 7.15-7.19 (m, 3 H), 7.29-7.35 (m, 3 H), 7.38-7.42 (m, 2 H), 7.46-7.51 (m, 1 H), 7.68-7.72 (m, 2 H), 8.00 (d, *J* = 2.5 Hz, 1 H), 8.38 (s, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 51.4 (CH_2), 55.7 (CH_3), 87.7 (C_{quat}), 97.5 (C_{quat}), 104.1 (CH), 111.0 (C_{quat}), 111.5 (CH), 114.6 (CH), 119.7 (C_{quat}), 126.9 (CH), 128.3 (CH), 128.5 (C_{quat}), 128.6 (CH), 129.1 (CH), 131.2 (CH), 131.5 (C_{quat}), 133.6 (CH), 135.1 (C_{quat}), 139.5 (CH), 157.2 (C_{quat}), 178.5 (C_{quat}), 180.2 (C_{quat}). EI + MS (*m/z* (%)): 393 (M^+, 1), 265 ($C_{17}H_{15}NO_2^+$, 15), 264 ($C_{17}H_{14}NO_2^+$, 86), 129 ($C_9H_5O^+$, 5), 91 ($C_7H_7^+$, 100), 65 ($C_5H_5^+$, 4). IR (KBr): $\tilde{\nu}$ 2194 (m) cm^{-1}, 1655 (s), 1624 (s), 1510 (m), 1479 (m), 1453 (m), 1398 (m), 1262 (m), 1208 (m), 1178 (m), 1142 (m), 1121 (m), 1102 (w), 1040 (m), 1013 (m), 907 (w), 854 (m), 781 (w), 758 (m), 740 (m), 702 (m), 644 (w), 538 (w). Anal. calcd for $C_{26}H_{19}NO_3$ (393.4): C 79.37, H 4.87, N 3.56. Found: C 79.21, H 5.03, N 3.51.

2.5.8. 1-(1-Benzyl-5-iodo-1*H*-indol-3-yl)-4-phenylbut-3-yne-1,2-dione (3h)

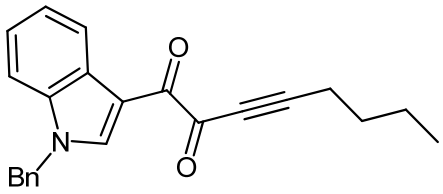


$C_{25}H_{16}INO_2$

489.30

864 mg (1.77 mmol, 35 % yield) as a yellow solid. Mp 153-163 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.35 (s, 2 H), 7.06 (d, *J* = 8.5 Hz, 1 H), 7.13-7.17 (m, 2 H), 7.28-7.36 (m, 3 H), 7.39-7.44 (m, 2 H), 7.47-7.53 (m, 1 H), 7.54 (dd, *J* = 8.5 Hz, *J* = 1.6 Hz, 1 H), 7.68-7.72 (m, 2 H), 8.38 (s, 1 H), 8.87 (d, *J* = 1.6 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 51.4 (CH_2), 87.5 (C_{quat}), 88.1 (C_{quat}), 98.1 (C_{quat}), 110.5 (C_{quat}), 112.5 (CH), 119.6 (C_{quat}), 126.9 (CH), 128.5 (CH), 128.7 (CH), 129.2 (CH), 129.6 (C_{quat}), 131.4 (CH), 131.6 (CH), 132.8 (CH), 133.7 (CH), 134.7 (C_{quat}), 135.9 (C_{quat}), 139.8 (CH), 178.0 (C_{quat}), 180.0 (C_{quat}). EI + MS (*m/z* (%)): 489 (M^+, 0.6), 433 ($(M-C_2O_2)^+$, 1), 360 ($C_{16}H_{11}INO^+$, 39), 129 ($C_9H_5O^+$, 6), 91 ($C_7H_7^+$, 100), 65 ($C_5H_5^+$, 5). IR (KBr): $\tilde{\nu}$ 2205 (m) cm^{-1}, 1655 (s), 1629 (s), 1560 (w), 1510 (m), 1459 (m), 1389 (m), 1305 (w), 1162 (m), 1104 (m), 1079 (w), 1022 (m), 882 (m), 808 (w), 787 (w), 775 (w), 759 (m), 731 (m), 700 (m), 686 (w), 648 (w), 579 (w), 538 (w). Anal. calcd for $C_{25}H_{16}INO_2$ (489.3): C 61.37, H 3.30, N 2.86. Found: C 61.21, H 3.52, N 2.92.

2.5.9. 1-(1-Benzyl-1*H*-indol-3-yl)oct-3-yne-1,2-dione (3i)

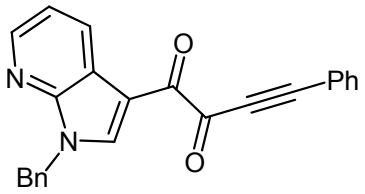


$C_{23}H_{21}NO_2$

343.42

36 mg (0.10 mmol, 2 % yield) as a brown solid. Mp 84-86 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.94 (t, *J* = 7.6 Hz, 3 H), 1.48 (sext, *J* = 7.6 Hz, 2 H), 1.64 (quint, *J* = 7.3 Hz, 2 H), 2.50 (t, *J* = 7.3 Hz, 2 H), 5.36 (s, 2 H), 7.15-7.19 (m, 2 H), 7.26-7.36 (m, 6 H), 8.37 (s, 1 H), 8.46 (d, *J* = 7.9 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.5 (CH_3), 19.3 (CH_2), 22.0 (CH_2), 29.6 (CH_2), 51.2 (CH_2), 80.2 (C_{quat}), 102.1 (C_{quat}), 110.6 (CH), 111.3 (C_{quat}), 122.9 (CH), 123.6 (CH), 124.3 (CH), 127.0 (CH), 127.5 (C_{quat}), 128.4 (CH), 129.1 (CH), 135.2 (C_{quat}), 136.8 (C_{quat}), 139.6 (CH), 178.6 (C_{quat}), 180.6 (C_{quat}). EI + MS (*m/z* (%)): 343 (M^+, 5), 234 ($(M-C_7H_9O)^+$, 100), 91 ($C_7H_7^+$, 92), 65 ($C_5H_5^+$, 7), 43 ($C_3H_7^+$, 5). IR (KBr): $\tilde{\nu}$ 3108 (w) cm^{-1}, 3031 (w), 2959 (w), 2931 (w), 2870 (w), 2211 (m), 1653 (s), 1633 (s), 1527 (m), 1493 (w), 1467 (w), 1449 (w), 1391 (m), 1198 (m), 1159 (m), 1140 (w), 1055 (w), 979 (w), 816 (w), 780 (m), 748 (m), 732 (m). Anal. calcd for $C_{23}H_{21}NO_2$ (343.4): C 80.44, H 6.16, N 4.08. Found: C 80.22, H 6.16, N 4.03.

2.5.10. 1-(1-Benzyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-4-phenylbut-3-yne-1,2-dione (3j)

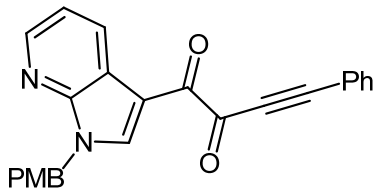


$C_{24}H_{16}N_2O_2$

364.40

1.13 g (3.10 mmol, 62 % yield) as a yellow solid. Mp 121 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.55 (s, 2 H), 7.27-7.37 (m, 6 H), 7.38-7.43 (m, 2 H), 7.47-7.51 (m, 1 H), 7.67-7.71 (m, 2 H), 8.46 (dd, *J* = 4.7 Hz, *J* = 1.6 Hz, 1 H), 8.49 (s, 1 H), 8.71 (ddd, *J* = 7.9 Hz, *J* = 1.6 Hz, *J* = 0.6 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 48.8 (CH_2), 87.4 (C_{quat}), 98.1 (C_{quat}), 109.9 (C_{quat}), 119.5 (CH), 119.5 (C_{quat}), 119.6 (C_{quat}), 127.8 (CH), 128.3 (CH), 128.6 (CH), 129.0 (CH), 131.1 (CH), 131.4 (CH), 133.7 (CH), 135.8 (C_{quat}), 139.0 (CH), 145.3 (CH), 148.2 (C_{quat}), 177.8 (C_{quat}), 180.2 (C_{quat}). EI + MS (*m/z* (%)): 364 (M^+, 1), 308 ($(M-C_2O_2)^+$, 3), 235 ($C_{15}H_{11}N_2O^+$, 99), 129 (8), 91 ($C_7H_7^+$, 100). IR (KBr): $\tilde{\nu}$ 3142 (w) cm^{-1}, 2202 (s), 1644 (s), 1597 (w), 1575 (w), 1519 (m), 1445 (m), 1425 (w), 1391 (m), 1356 (w), 1297 (w), 1236 (w), 1171 (m), 1123 (w), 1076 (w), 1029 (m), 881 (m), 793 (w), 774 (w), 759 (m), 730 (w), 699 (w), 681 (w), 642 (w), 622 (w), 555 (w), 536 (w), 505 (w). Anal. calcd for $C_{24}H_{16}N_2O_2$ (364.4): C 79.11, H 4.43, N 7.69. Found: C 79.20, H 4.14, N 7.43.

2.5.11. 1-(1-(4-Methoxybenzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-4-phenylbut-3-yne-1,2-dione (3k)



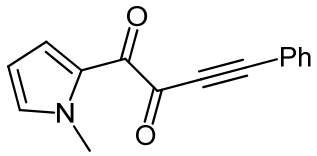
$C_{25}H_{18}N_2O_3$

394.42

1.16 g (2.95 mmol, 59 % yield) as a yellow solid. Mp 117 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.78 (s, 3 H), 5.47 (s, 2 H), 6.85-6.89 (m, 2 H), 7.27-7.30 (m, 2 H), 7.32 (dd, *J* = 7.9 Hz, *J* = 4.7 Hz, 1 H), 7.38-7.43 (m, 2 H), 7.49 (tt, *J* = 7.6 Hz, *J* = 1.3 Hz, 1 H), 7.67-7.70 (m, 2 H), 8.45 (s, 1 H), 8.47 (dd, *J* = 4.7 Hz, *J* = 1.6 Hz, 1 H), 8.70 (dd, *J* = 7.9 Hz, *J* = 1.6 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 48.3 (CH_2), 55.3 (CH_3), 87.5 (C_{quat}), 98.0 (C_{quat}), 109.8 (C_{quat}), 114.4 (CH), 119.5 (CH), 119.6 (C_{quat}), 119.7 (C_{quat}), 127.8 (C_{quat}), 128.7 (CH), 129.5 (CH), 131.1 (CH), 131.4 (CH), 133.7 (CH), 138.9 (CH), 145.3 (CH), 148.2 (C_{quat}), 159.6 (C_{quat}), 177.9 (C_{quat}), 180.2 (C_{quat}). EI + MS (*m/z* (%)): 394 (M^+, 1), 265 ((M-C_9H_5O)$^+$, 24), 121 ($C_8H_9O^+$, 100), 71 (11), 57 (11). IR (KBr): $\tilde{\nu}$ 3132 (w) cm^{-1}, 2958 (w), 2929 (w), 2834 (w), 2203 (s), 1661 (s), 1648 (s), 1614 (w), 1576 (w), 1521 (s), 1510 (s), 1490 (w), 1445 (m), 1422 (m), 1393 (s), 1296 (w), 1242 (s), 1189 (w), 1177 (s), 1166 (m), 1121 (m), 1073 (w), 1030 (s), 924 (w), 881 (s), 814 (m), 793 (w), 776 (w), 762 (m), 750 (s), 690 (m), 648 (w), 619 (w), 584 (w), 533 (w), 510 (w). Anal. calcd for $C_{25}H_{18}N_2O_3$ (394.4): C 76.13, H 4.60, N 7.10. Found: C 75.94, H 4.89, N 6.89.

2.6. Spectroscopic Data of Compounds 4a-f

2.6.1. 1-(1-Methyl-1*H*-pyrrol-2-yl)-4-phenylbut-3-yne-1,2-dione (4a)

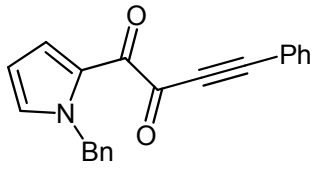


$C_{15}H_{11}NO_2$

237.25

754 mg (3.18 mmol, 64 % yield) as a yellow-brown oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.02 (s, 3 H), 6.23 (dd, *J* = 4.1 Hz, *J* = 2.2 Hz, 1 H), 7.01-7.04 (m, 1 H), 7.33 (dd, *J* = 4.1 Hz, *J* = 1.6 Hz, 1 H), 7.37-7.42 (m, 2 H), 7.48 (tt, *J* = 7.6 Hz, *J* = 1.3 Hz, 1 H), 7.63-7.67 (m, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 37.8 (CH_3), 87.6 (C_{quat}), 97.5 (C_{quat}), 110.2 (CH), 119.7 (C_{quat}), 125.4 (CH), 126.5 (C_{quat}), 128.8 (CH), 131.5 (CH), 133.7 (CH), 134.7 (CH), 177.1 (C_{quat}), 178.2 (C_{quat}). EI + MS (*m/z* (%)): 237 (M^+, 4), 209 (6), 181 (11), 129 ((M-$C_6H_6NO)^+$, 10), 108 ((M-$C_9H_5O)^+$, 100), 80 ($C_5H_6N^+$, 5), 53 ((C_3O+H)$^+$, 8). IR (film): $\tilde{\nu}$ 3112 (w) cm^{-1}, 3059 (w), 2953 (w), 2182 (s), 1634 (s), 1525 (m), 1489 (m), 1463 (m), 1444 (m), 1404 (s), 1335 (m), 1281 (m), 1239 (w), 1125 (m), 1092 (m), 1061 (m), 1027 (m), 913 (m), 877 (m), 799 (w), 754 (s), 689 (m), 635 (w), 602 (w), 538 (m), 515 (w). Anal. calcd for $C_{15}H_{11}NO_2$ (237.3): C 75.94, H 4.67, N 5.90. Found: C: 75.90, H 4.87, N 5.74.

2.6.2. 1-(1-Benzyl-1*H*-pyrrol-2-yl)-4-phenylbut-3-yne-1,2-dione (4b)

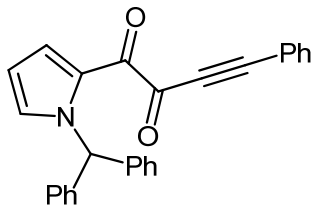


$C_{21}H_{15}NO_2$

313.35

1.16 g (3.70 mmol, 74 % yield) as a yellow-red oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.63 (s, 2 H), 6.30 (dd, *J* = 4.4 Hz, *J* = 2.5 Hz, 1 H), 7.11 (dd, *J* = 2.5 Hz, *J* = 1.6 Hz, 1 H), 7.15-7.18 (m, 2 H), 7.25-7.30 (m, 1 H), 7.30-7.35 (m, 2 H), 7.36-7.41 (m, 3 H), 7.47 (tt, *J* = 7.6 Hz, *J* = 1.3 Hz, 1 H), 7.61-7.65 (m, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 52.8 (CH_2), 87.4 (C_{quat}), 97.4 (C_{quat}), 110.6 (CH), 119.6 (C_{quat}), 125.9 (CH), 127.3 (CH), 127.8 (CH), 128.6 (CH), 128.8 (CH), 131.3 (CH), 133.5 (CH), 133.9 (CH), 137.2 (C_{quat}), 176.8 (C_{quat}), 177.9 (C_{quat}). EI + MS (*m/z* (%)): 313 (M^+, 4), 184 ((M-$C_9H_5O)^+$, 100), 149 (9), 129 ($C_9H_5O^+$, 6), 91 ($C_7H_7^+$, 32). IR (film): $\tilde{\nu}$ 3110 (w) cm^{-1}, 3064 (w), 3033 (w), 2931 (w), 2205 (s), 1634 (s), 1523 (w), 1490 (w), 1488 (w), 1455 (w), 1444 (w), 1411 (s), 1341 (w), 1279 (m), 1234 (w), 1174 (w), 1121 (m), 1086 (s), 1033 (s), 999 (w), 914 (m), 876 (m), 799 (w), 751 (s), 689 (s), 609 (m), 538 (w). Anal. calcd for $C_{21}H_{15}NO_2$ (313.4): C 80.49, H 4.82, N 4.47. Found: C 80.34, H 5.04, N 4.48.

2.6.3. 1-(1-Benzhydryl-1*H*-pyrrol-2-yl)-4-phenylbut-3-yne-1,2-dione (4c)

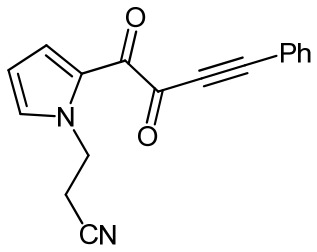


$C_{27}H_{19}NO_2$

389.45

1.31 g (3.36 mmol, 67 % yield) as an orange oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.27 (dd, *J* = 4.1 Hz, *J* = 2.5 Hz, 1 H), 6.90-6.93 (m, 1 H), 7.05-7.10 (m, 4 H), 7.28-7.40 (m, 8 H), 7.44-7.50 (m, 2 H), 7.59-7.62 (m, 2 H), 7.84 (s, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 65.2 (CH), 87.4 (C_{quat}), 97.3 (C_{quat}), 110.3 (CH), 119.6 (C_{quat}), 126.4 (C_{quat}), 126.5 (CH), 128.0 (CH), 128.5 (CH), 128.6 (CH), 128.7 (CH), 131.3 (CH), 133.0 (CH), 133.6 (CH), 139.7 (C_{quat}), 176.8 (C_{quat}), 177.8 (C_{quat}). EI + MS (*m/z* (%)): 389 (M^+, 3), 260 ((M-$C_9H_5O)^+$, 28), 167 ($C_{13}H_{11}^+$, 100), 165 (($C_{13}H_{11}$-2H)$^+$, 54), 152 (26), 129 ($C_9H_5O^+$, 23), 115 (6), 75 (7). IR (film): $\tilde{\nu}$ 3063 (w) cm^{-1}, 3031 (w), 2926 (w), 2186 (s), 1714 (w), 1634 (s), 1519 (w), 1495 (m), 1454 (m), 1412 (s), 1359 (w), 1276 (m), 1224 (m), 1185 (w), 1118 (w), 1083 (m), 1031 (s), 1000 (w), 932 (m), 914 (m), 877 (m), 796 (w), 750 (s), 698 (s), 643 (m), 613 (m), 538 (w), 518 (w). Anal. calcd for $C_{27}H_{19}NO_2$ (389.5): C 83.27, H 4.92, N 3.60. Found: C 83.16, H 4.75, N 3.50.

2.6.4. 3-(2-(2-Oxo-4-phenylbut-3-ynoyl)-1*H*-pyrrol-1-yl)propanenitrile (4d)

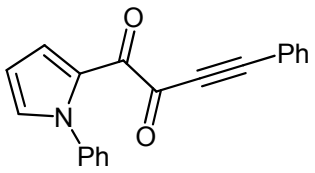


$C_{17}H_{12}N_2O_2$

276.29

830 mg (3.00 mmol, 60 % yield) as yellow-brown oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.95 (t, *J* = 6.3 Hz, 2 H), 4.61 (t, *J* = 6.3 Hz, 2 H), 6.34 (dd, *J* = 4.1 Hz, *J* = 2.5 Hz, 1 H), 7.22 (dd, *J* = 2.2 Hz, *J* = 1.6 Hz, 1 H), 7.39-7.43 (m, 2 H), 7.47-7.52 (m, 2 H), 7.65-7.68 (m, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 20.0 (CH_2), 45.8 (CH_2), 87.2 (C_{quat}), 97.9 (C_{quat}), 111.2 (CH), 117.1 (C_{quat}), 119.3 (C_{quat}), 125.5 (C_{quat}), 126.9 (CH), 128.7 (CH), 131.5 (CH), 133.6 (CH), 134.6 (CH), 176.7 (C_{quat}), 177.2 (C_{quat}). EI + MS (*m/z* (%)): 276 (M^+, 6), 248 (7), 220 (14), 147 ($(M-C_9H_5O)^+$, 100), 129 ($C_9H_5O^+$, 31), 107 (5), 79 ($C_5H_5N^+$, 6). IR (film): $\tilde{\nu}$ 3114 (w) cm^{-1}, 2967 (w), 2195 (s), 1633 (s), 1525 (w), 1489 (w), 1469 (w), 1444 (w), 1412 (m), 1347 (w), 1281 (m), 1239 (w), 1169 (w), 1123 (m), 1088 (m), 1041 (m), 898 (m), 876 (w), 754 (s), 689 (m), 606 (w), 538 (w). Anal. calcd for $C_{17}H_{12}N_2O_2$ (276.3): C 73.90, H 4.38, N 10.14. Found: C 73.64, H 4.16, N 9.94.

2.6.5. 4-Phenyl-1-(1-phenyl-1*H*-pyrrol-2-yl)but-3-yne-1,2-dione (4e)

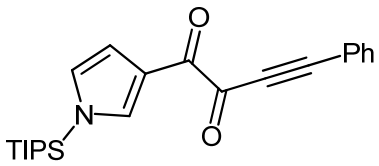


$C_{20}H_{13}NO_2$

299.32

1.15 g (3.84 mmol, 77 % yield) as a yellow solid. Mp 74-75 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.42 (dd, *J* = 4.1 Hz, *J* = 2.5 Hz, 1 H), 7.17 (dd, *J* = 2.5 Hz, *J* = 1.6 Hz, 1 H), 7.30-7.39 (m, 4 H), 7.40-7.48 (m, 4 H), 7.49 (dd, *J* = 4.1 Hz, *J* = 1.6 Hz, 1 H), 7.59-7.62 (m, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 87.3 (C_{quat}), 97.5 (C_{quat}), 111.2 (CH), 119.5 (C_{quat}), 126.0 (CH), 126.1 (CH), 126.8 (C_{quat}), 128.2 (CH), 128.6 (CH), 128.9 (CH), 131.3 (CH), 133.6 (CH), 134.4 (CH), 139.9 (C_{quat}), 175.7 (C_{quat}), 177.7 (C_{quat}). EI + MS (*m/z* (%)): 299 (M^+, 3), 271 (5), 243 (3), 170 (($M-C_9H_5O)^+$, 100), 115 (19). IR (KBr): $\tilde{\nu}$ 2201 (m) cm^{-1}, 1671 (m), 1638 (s), 1560 (w), 1543 (w), 1509 (w), 1491 (m), 1442 (w), 1412 (m), 1363 (w), 1281 (m), 1203 (w), 1130 (w), 1090 (m), 1043 (m), 985 (m), 895 (m), 872 (w), 769 (s), 748 (s), 690 (m), 595 (w), 536 (w). Anal. calcd for $C_{20}H_{13}NO_2$ (299.3): C 80.25, H 4.38, N 4.68. Found: C 80.11, H 4.51, N 4.63.

2.6.6. 1-(1-(Triisopropylsilyl)-1*H*-pyrrol-3-yl)-4-phenylbut-3-yne-1,2-dione (4f)



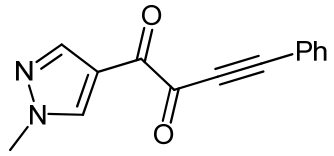
$C_{23}H_{29}NO_2Si$

379.57

836 mg (2.20 mmol, 44 % yield) as an orange oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.12 (d, *J* = 7.6 Hz, 18 H), 1.49 (sept, *J* = 7.6 Hz, 3 H), 6.79 (dd, *J* = 2.8 Hz, *J* = 2.2 Hz, 1 H), 6.93 (dd, *J* = 2.8 Hz, *J* = 1.3 Hz, 1 H), 7.38-7.42 (m, 2 H), 7.46-7.50 (m, 1 H), 7.66-7.69 (m, 2 H), 7.81-7.83 (m, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 11.4 (CH_3), 17.6 (CH), 87.5 (C_{quat}), 97.2 (C_{quat}), 111.9 (CH), 119.7 (C_{quat}), 122.1 (C_{quat}), 126.2 (CH), 128.6 (CH), 131.2 (CH), 133.6 (CH), 134.7 (CH), 178.6 (C_{quat}), 181.5 (C_{quat}). EI + MS (*m/z* (%)): 380 (M^+, 1), 156 (12), 155 ($C_{11}H_7O^+$, 100), 149 (21), 127 ($C_{10}H_7^+$, 27), 101 ($C_8H_5^+$, 4), 94 (24), 77 ($C_6H_5^+$, 6). IR (film): $\tilde{\nu}$ 2949 (m) cm^{-1}, 2869 (m), 2200 (s), 1651 (s), 1520 (s), 1489 (m), 1464 (m), 1392 (w), 1261 (m), 1223 (m), 1150 (w), 1093 (s), 1067 (s), 1018 (w), 993 (w), 956 (w), 923 (w), 883 (m), 836 (w), 796 (w), 755 (s), 690 (m), 660 (m), 634 (w), 577 (w), 527 (w). Anal. calcd for $C_{23}H_{29}NO_2Si$ (379.6): C 72.78, H 7.70, N 3.69. Found: C 72.58, H 7.91, N 3.50.

2.7. Spectroscopic Data of Compounds 5a-e

2.7.1. 1-(1-Methyl-1*H*-pyrazol-4-yl)-4-phenylbut-3-yne-1,2-dione (5a)

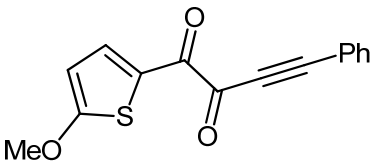


$C_{14}H_{10}N_2O_2$

238.24

564 mg (2.37 mmol, 47 % yield) as a yellow solid. Mp 112 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.98 (s, 3 H), 7.40-7.44 (m, 2 H), 7.49-7.53 (m, 1 H), 7.68-7.71 (m, 2 H), 8.20 (s, 1 H), 8.32 (s, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 39.4 (CH_3), 86.9 (C_{quat}), 98.9 (C_{quat}), 117.9 (C_{quat}), 119.4 (C_{quat}), 128.7 (CH), 131.6 (CH), 133.8 (CH), 135.7 (CH), 142.7 (CH), 177.0 (C_{quat}), 179.3 (C_{quat}). EI + MS (*m/z* (%)): 238 (M^+, 0.4), 237 ($(M-H)^+$, 0.8), 210 ($(M-CO)^+$, 4), 182 ($(M-C_2O_2)^+$, 10), 129 ($C_9H_5O^+$, 17), 110 (7), 109 ($C_5H_5N_2O^+$, 100). IR (KBr): $\tilde{\nu}$ 3129 (w) cm^{-1}, 2203 (m), 1657 (s), 1536 (m), 1489 (w), 1444 (w), 1276 (w), 1214 (w), 1115 (m), 968 (w), 895 (m), 769 (m), 754 (m), 680 (w), 655 (w), 621 (w), 592 (w), 539 (w). Anal. calcd for $C_{14}H_{10}N_2O_2$ (238.2): C 70.58, H 4.23, N 11.76. Found: C 70.73, H 4.45, N 11.80.

2.7.2. 1-(5-Methoxythiophen-2-yl)-4-phenylbut-3-yne-1,2-dione (5b)

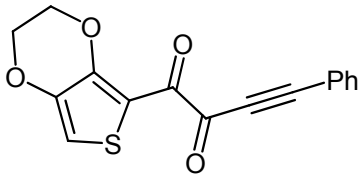


$C_{15}H_{10}O_3S$

270.30

712 mg (2.63 mmol, 53 % yield) as a yellow solid. Mp 83 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.03 (s, 3 H), 6.37 (d, *J* = 4.4 Hz, 1 H), 7.39-7.43 (m, 2 H), 7.48-7.52 (m, 1 H), 7.66-7.70 (m, 2 H), 7.99 (d, *J* = 4.4 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 60.9 (CH_3), 87.2 (C_{quat}), 98.4 (C_{quat}), 108.0 (CH), 119.5 (C_{quat}), 128.7 (CH), 131.5 (CH), 133.7 (CH), 139.3 (CH), 176.7 (C_{quat}), 177.2 (C_{quat}), 177.2 (C_{quat}), 178.5 (C_{quat}). EI + MS (*m/z* (%)): 270 (M^+, 1), 242 ($(M\text{-}CO)^+$, 1), 214 ($(M\text{-}C_2O_2)^+$, 7), 141 ($C_6H_5O_2S^+$, 100), 129 ($C_9H_5O^+$, 13), 98 (14), 85 (12), 71 (13), 57 (11). IR (KBr): $\tilde{\nu}$ 3106 (w) cm^{-1}, 3092 (w), 2208 (s), 2187 (s), 1637 (s), 1595 (m), 1535 (m), 1471 (s), 1421 (s), 1354 (m), 1325 (m), 1269 (w), 1233 (m), 1221 (m), 1113 (m), 1056 (s), 999 (w), 981 (m), 925 (w), 876 (m), 799 (w), 782 (w), 754 (s), 733 (w), 683 (m), 618 (m), 583 (w), 536 (w), 514 (w). Anal. calcd for $C_{15}H_{10}O_3S$ (270.3): C 66.65, H 3.73. Found: C 66.42, H 4.02.

2.7.3. 1-(2,3-Dihydrothieno[3,4-*b*][1,4]dioxin-7-yl)-4-phenylbut-3-yne-1,2-dione (5c)

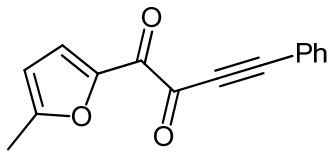


$C_{16}H_{10}O_4S$

298.31

978 mg (3.28 mmol, 66 % yield) as an orange solid. Mp 117 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.25-4.28 (m, 2 H), 4.40-4.43 (m, 2 H), 6.89 (s, 1 H), 7.39-7.43 (m, 2 H), 7.50 (tt, *J* = 7.6 Hz, *J* = 1.3 Hz, 1 H), 7.65-7.69 (m, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 63.9 (CH_2), 65.5 (CH_2), 86.5 (C_{quat}), 99.1 (C_{quat}), 111.3 (C_{quat}), 113.9 (CH), 119.4 (C_{quat}), 128.7 (CH), 131.5 (CH), 133.7 (CH), 141.8 (C_{quat}), 149.5 (C_{quat}), 177.4 (C_{quat}), 177.5 (C_{quat}). EI + MS (*m/z* (%)): 298 (M^+, 0.5), 270 ($(M\text{-}CO)^+$, 3), 242 ($(M\text{-}C_2O_2)^+$, 12), 169 ($C_7H_5O_3S^+$, 100), 143 (9), 141 ($C_6H_5O_2S^+$, 3), 129 ($C_9H_5O^+$, 17), 113 ($C_4HO_2S^+$, 7), 97 (C_4HOS^+, 3). IR (KBr): $\tilde{\nu}$ 3095 (w) cm^{-1}, 2944 (w), 2189 (s), 1651 (s), 1637 (s), 1595 (w), 1479 (s), 1432 (s), 1365 (s), 1318 (w), 1265 (m), 1184 (w), 1161 (m), 1086 (s), 1009 (m), 995 (w), 918 (m), 885 (s), 851 (w), 760 (m), 735 (s), 688 (m), 560 (w), 542 (w), 510 (w). Anal. calcd for $C_{16}H_{10}O_4S$ (298.3): C 64.42, H 3.38. Found: C 64.59, H 3.55.

2.7.4. 1-(5-Methylfuran-2-yl)-4-phenylbut-3-yne-1,2-dione (5d)

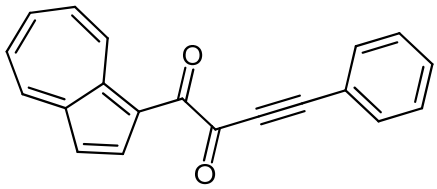


$C_{15}H_{10}O_3$

238.24

457 mg (1.92 mmol, 38 % yield) as an orange solid. Mp 81 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.47 (s, 3 H), 6.29 (d, *J* = 3.8 Hz, 1 H), 7.39-7.44 (m, 2 H), 7.49-7.53 (m, 1 H), 7.66-7.70 (m, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 14.3 (CH_3), 87.0 (C_{quat}), 98.7 (C_{quat}), 110.4 (CH), 119.4 (C_{quat}), 127.5 (CH), 128.7 (CH), 131.6 (CH), 133.8 (CH), 147.6 (C_{quat}), 161.9 (C_{quat}), 172.8 (C_{quat}), 176.2 (C_{quat}). EI + MS (*m/z* (%)): 238 (M^+, 0.7), 210 ($(M-CO)^+$, 21), 182 ($(M-C_2O_2)^+$, 35), 130 (10), 129 ($C_9H_5O^+$, 100), 109 ($(M-C_9H_5O)^+$, 99), 75 (11). IR (KBr): $\tilde{\nu}$ 2925 (w) cm^{-1}, 2198 (s), 1653 (s), 1573 (w), 1504 (s), 1444 (m), 1370 (w), 1329 (w), 1274 (m), 1210 (w), 1142 (m), 1032 (m), 1011 (m), 999 (m), 873 (w), 953 (m), 883 (m), 812 (w), 759 (s), 689 (m), 659 (w), 592 (w), 541 (w), 514 (w). Anal. calcd for $C_{15}H_{10}O_3$ (238.2): C 75.62, H 4.23. Found: C 75.87, H 4.44.

2.7.5. 1-((4*Z*,6*Z*,8*Z*)-Azulen-1-yl)-4-phenylbut-3-yne-1,2-dione (5e)



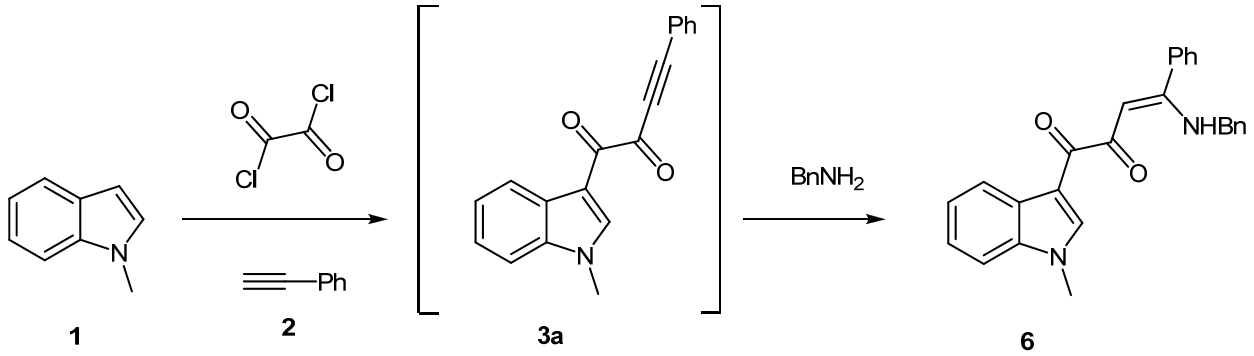
$C_{20}H_{12}O_2$

284.31

462 mg (1.63 mmol, 33 % yield) as a brown solid. Mp 103 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.32 (d, *J* = 4.4 Hz, 1 H), 7.37-7.42 (m, 2 H), 7.45-7.50 (m, 1 H), 7.63 (t, *J* = 9.8 Hz, 1 H), 7.66-7.69 (m, 2 H), 7.75 (t, *J* = 9.8 Hz, 1 H), 7.89-7.95 (m, 1 H), 8.51-8.54 (m, 2 H), 9.92 (d, *J* = 9.8 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 87.8 (C_{quat}), 97.2 (C_{quat}), 119.2 (C_{quat}), 119.7 (CH), 119.7 (C_{quat}), 128.6 (CH), 129.6 (CH), 131.1 (CH), 131.2 (CH), 133.5 (CH), 138.8 (CH), 139.7 (CH), 140.2 (CH), 142.9 (CH), 143.5 (C_{quat}), 147.3 (C_{quat}), 179.7 (C_{quat}), 183.6 (C_{quat}). EI + MS (*m/z* (%)): 284 (M^+, 1), 256 ($(M-CO)^+$, 0.3), 228 ($(M-C_2O_2)^+$, 1), 156 (12), 155 ($C_{11}H_7O^+$,100), 149 (21), 129 ($C_9H_5O^+$, 4) 127 ($C_{10}H_7^+$, 27), 101 ($C_8H_5^+$, 4), 94 (24), 77 ($C_6H_5^+$, 6). IR (KBr): $\tilde{\nu}$ 2203 (m) cm^{-1}, 1641 (s), 1625 (s), 1599 (w), 1589 (w), 1576 (w), 1539 (w), 1491 (m), 1458 (w), 1447 (w), 1414 (m), 1394 (s), 1323 (w), 1275 (m), 1227 (w), 1182 (w), 1147 (m), 1053 (m), 1032 (m), 1020 (s), 997 (w), 966 (w), 922 (w), 893 (m), 856 (m), 802 (w), 773 (s), 745 (s), 712 (s), 677 (m), 610 (m). Anal. calcd for $C_{20}H_{12}O_2$ (284.3): C 84.49, H 4.25. Found: C 84.27, H 4.36.

3. One-Pot Reactions with Ynediones as Intermediates

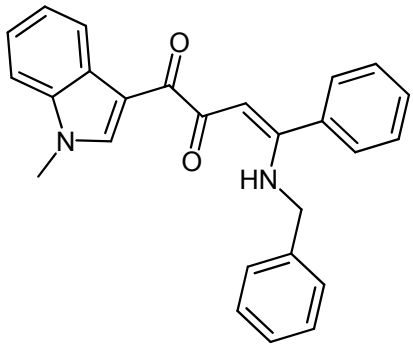
3.1. One-Pot Four Component Glyoxylation □ *Stephens-Castro* □ *Michael*-Addition Sequence



1 **2** **3a** **6**

N-Methyl-1*H*-indole **1a** (669 mg, 5.00 mmol) in dry THF (25 mL) was placed under argon atmosphere in a screw-cap Schlenk vessel with septum, degassed with argon and cooled to 0 °C (water/ice, for 15 min). Then, oxalyl chloride (0.44 mL, 5.00 mmol) was added dropwise to the reaction mixture at 0 °C. The mixture was allowed to come to room temperature (water bath) and was stirred for 4 h. Then, CuI (49 mg, 0.25 mmol), phenylacetylene **2a** (0.57 mL, 5.00 mmol) and dry triethylamine (2.08 mL, 15.0 mmol) were successively added to the mixture and stirring at room temperature was continued for 24 h. After complete conversion (product monitored by TLC) methanol (5 mL) and benzylamine (0.55 mL, 5.00 mmol) were added, and the mixture was stirred for 1 h at 50 °C (preheated oil bath). After removal of the solvents in vacuo the residue was absorbed onto Celite® and purified chromatographically on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl acetate PE-EA = 3:1, 1 Vol % triethylamine.

(*Z*)-4-(Benzylamino)-1-(1-methyl-1*H*-indol-3-yl)-4-phenylbut-3-ene-1,2-dione (6)

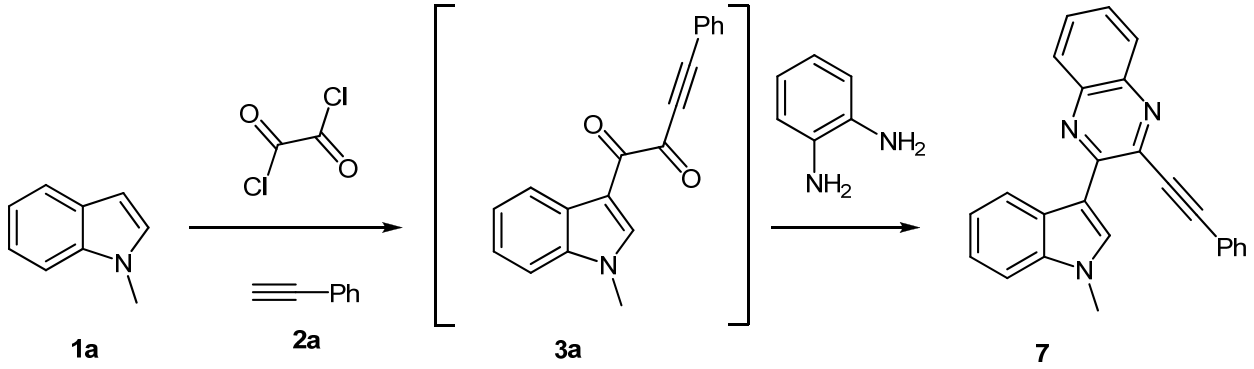


$C_{26}H_{22}N_2O_2$

394.47

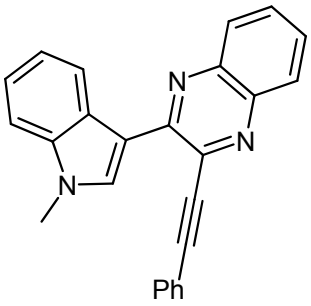
1.18 g (2.99 mmol, 60 % yield) as a yellow solid. Mp 143-146 °C. R_f (PE-EA = 3:1, 1 Vol % NEt_3) = 0.37. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.83 (s, 3 H), 4.50 (d, *J* = 6.3 Hz, 2 H), 6.06 (s, 1 H), 7.23-7.38 (m, 8 H), 7.40-7.47 (m, 6 H), 8.46-8.51 (m, 1 H), 8.56 (s, 1 H), 11.64 (t, *J* = 5.4 Hz, 1 H, NH). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 33.5 (CH_3), 48.8 (CH_2), 93.8 (CH), 109.6 (CH), 112.5 (C_{quat}), 122.8 (CH), 122.8 (CH), 123.4 (CH), 127.0 (CH), 127.6 (CH), 127.7 (CH), 127.7 (C_{quat}), 128.6 (CH), 128.9 (CH), 130.0 (CH), 134.6 (C_{quat}), 137.0 (C_{quat}), 137.9 (C_{quat}), 140.1 (CH), 168.9 (C_{quat}), 186.9 (C_{quat}), 187.0 (C_{quat}). EI + MS (*m/z* (%)): 394 (M^+, 7), 236 ($C_{16}H_{14}NO^+$, 100), 158 ($C_{10}H_8NO^+$, 11), 130 ($C_9H_8N^+$, 3), 91 ($C_7H_7^+$, 50), 65 ($C_5H_5^+$, 2). IR (KBr): $\tilde{\nu}$ 3126 (w) cm^{-1}, 3054 (w), 1626 (m), 1561 (s), 1511 (m), 1482 (m), 1465 (m), 1420 (w), 1368 (m), 1329 (s), 1267 (m), 1213 (m), 1152 (w), 1124 (w), 1070 (m), 1038 (w), 907 (w), 847 (w), 820 (w), 750 (s), 722 (m), 697 (m), 618 (w), 598 (w), 570 (w), 541 (w). Anal. calcd for $C_{26}H_{22}N_2O_2$ (394.5): C 79.16, H 5.62, N 7.10. Found: C 79.07, H 5.83, N 6.84.

3.2. One-Pot Four-Component Synthesis of 2-(1-Methyl-1*H*-indol-3-yl)-3-(phenylethynyl)quinoxaline (7)



N-Methyl-1*H*-indole **1a** (669 mg, 5.00 mmol) in dry THF (25 mL) was placed under argon atmosphere in a screw-cap Schlenk vessel with septum, degassed with argon and cooled to 0 °C (water/ice bath, for 15 min). Then, oxalyl chloride (0.44 mL, 5.00 mmol) was added to the reaction mixture at 0 °C. The mixture was allowed to come to room temperature (water bath) and was stirred for 4 h. Then, CuI (49 mg, 0.25 mmol), phenylacetylene **2a** (0.57 mL, 5.00 mmol) and dry triethylamine (2.08 mL, 15.0 mmol) were successively added to the mixture and stirring at room temperature was continued for 24 h. After complete conversion (product monitored by TLC) methanol (5 mL), glacial acetic acid (5 mL) and 1,2-phenylenediamine (541 mg, 5.00 mmol) were added, and the mixture was stirred for 3 h at 50 °C (preheated oil bath). After removal of the solvents in vacuo the residue was absorbed onto Celite® and purified chromatographically on silica gel with dichloromethane.

2-(1-Methyl-1*H*-indol-3-yl)-3-(phenylethynyl)quinoxaline (7)

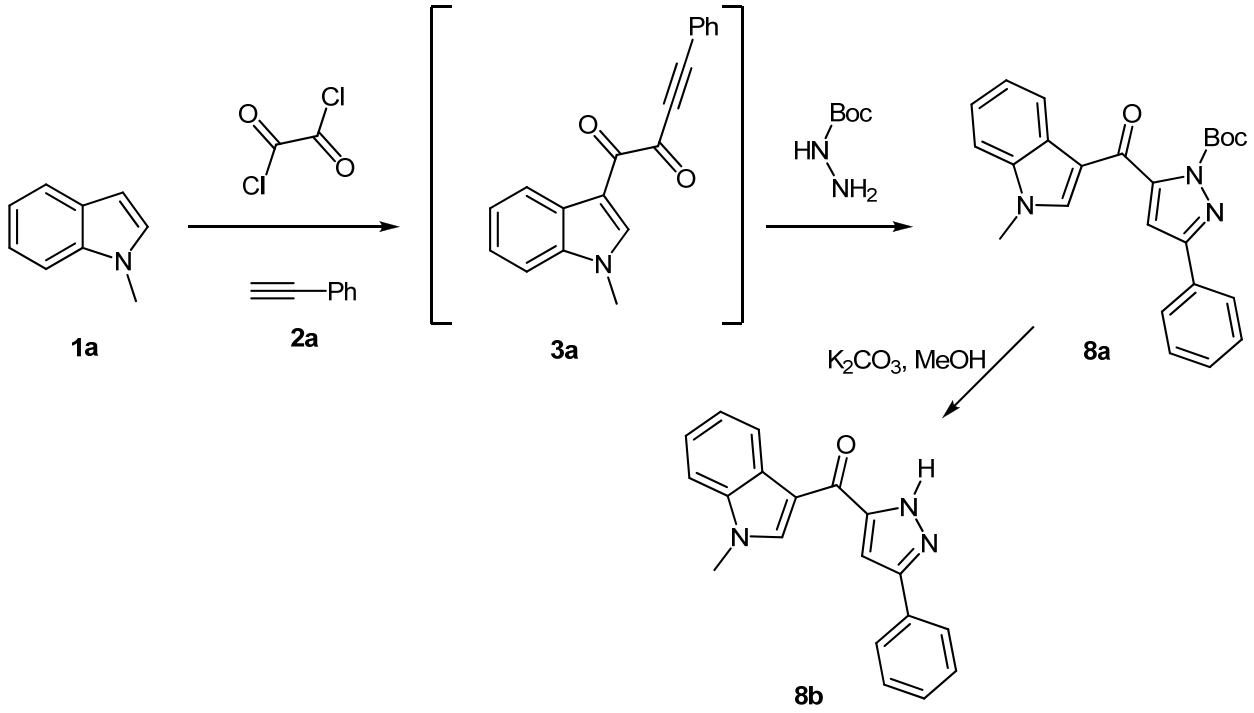


$C_{25}H_{17}N_3$

359.42

1.29 g (3.59 mmol, 72 % yield) as a yellow solid. Mp 157-158 °C. R_f (dichloromethane) = 0.67. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.89 (s, 3 H), 7.30-7.43 (m, 6 H), 7.59-7.62 (m, 2 H), 7.64-7.68 (m, 1 H), 7.70-7.75 (m, 1 H), 8.06 (dd, *J* = 8.5 Hz, *J* = 1.6 Hz, 1 H), 8.13 (dd, *J* = 8.2 Hz, *J* = 1.3 Hz, 1 H), 8.44 (s, 1 H), 8.74-8.77 (m, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 33.4 (CH_3), 89.7 (C_{quat}), 94.0 (C_{quat}), 109.5 (CH), 112.4 (C_{quat}), 121.4 (CH), 122.0 (C_{quat}), 122.9 (CH), 122.9 (CH), 127.5 (C_{quat}), 128.6 (CH), 128.6 (CH), 128.7 (CH), 128.8 (CH), 129.6 (CH), 130.4 (CH), 132.0 (CH), 132.6 (CH), 137.0 (C_{quat}), 137.3 (C_{quat}), 139.4 (C_{quat}), 141.1 (C_{quat}), 150.6 (C_{quat}). EI + MS (*m/z* (%)): 359 (M^+, 97), 358 ($(M-H)^+$, 100), 344 ($(M-CH_3)^+$, 10), 282 ($(M-C_6H_5)^+$, 3), 231 (11), 203 ($C_{15}H_9N^+$, 3), 180 (12), 156 ($C_{10}H_8N_2^+$, 10). IR (KBr): $\tilde{\nu}$ 2211 (m) cm^{-1}, 1655 (w), 1638 (w), 1536 (s), 1491 (m), 1477 (m), 1456 (m), 1425 (w), 1406 (w), 1373 (m), 1339 (w), 1237 (w), 1215 (m), 1129 (m), 1113 (m), 1084 (m), 1012 (w), 938 (w), 748 (s), 683 (w), 613 (w), 528 (w). Anal. calcd for $C_{25}H_{17}N_3$ (359.4): C 83.54, H 4.77, N 11.69. Found: C 83.40, H 4.62, N 11.62.

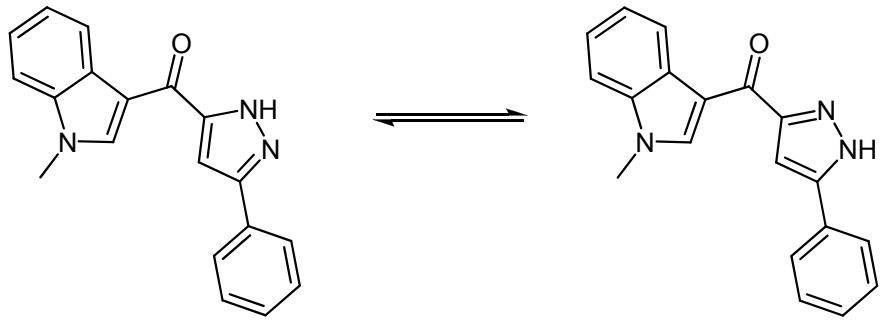
3.3. Selective One-Pot Four-Component Synthesis of 2-Acylpyrazoles by Glyoxylation □ *Stephens-Castro* □ *Michael*-Addition □ Cyclocondensation Sequence



N-Methyl-1*H*-indole **1a** (669 mg, 5.00 mmol) in dry THF (25 mL) was placed under argon atmosphere in a screw-cap Schlenk vessel with septum, degassed with argon and cooled to 0 °C (water/ice, for 15 min). Then, oxalyl chloride (0.44 mL, 5.00 mmol) was added dropwise to the reaction mixture at 0 °C. The mixture was allowed to come to room temperature (water bath) and was stirred for 4 h. Then, CuI (49 mg, 0.25 mmol), phenylacetylene **2a** (0.57 mL, 5.00 mmol), and dry triethylamine (2.08 mL, 15.0 mmol) were successively added to the mixture and stirring at room temperature was continued for 24 h. After complete conversion (product monitored by TLC) methanol (5 mL) and *tert*-butyl carbazate (667 mg, 5.00 mmol) were added, and the mixture was stirred for 24 h at 50 °C (preheated oil bath, product monitored by TLC). After removal of the solvents in vacuo the residue was absorbed onto Celite® and purified chromatographically on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl acetate PE-EA = 3:1 → 2:1, 1 Vol % triethylamine. After drying in vacuo, compound **8a** (1.55 g, 3.86 mmol, 77 % yield) was obtained as a pale brown solid. R_f (PE-EA = 3:1) = 0.15. Mp 179-184 °C. It was used without further purification.

The obtained compound was suspended in methanol (19 mL) and treated with potassium carbonate (1.35 g, 9.64 mmol). After stirring for 1 h at room temperature (water bath), the mixture was adsorbed on Celite® and purified chromatographically on silica gel with dichloromethane-methanol-aqueous ammonia as eluent (DCM-NH_3 = 100:1 → DCM-MeOH-NH_3 = 100:1:1 → DCM-MeOH-NH_3 = 100:2:1, stepwise gradient). After drying in vacuo, compound **8b** (923 mg, 3.06 mmol, 79 % yield) was obtained as a pale yellow solid.

(1-Methyl-1*H*-indol-3-yl)(3-phenyl-1*H*-pyrazol-5-yl)methanone (8b)

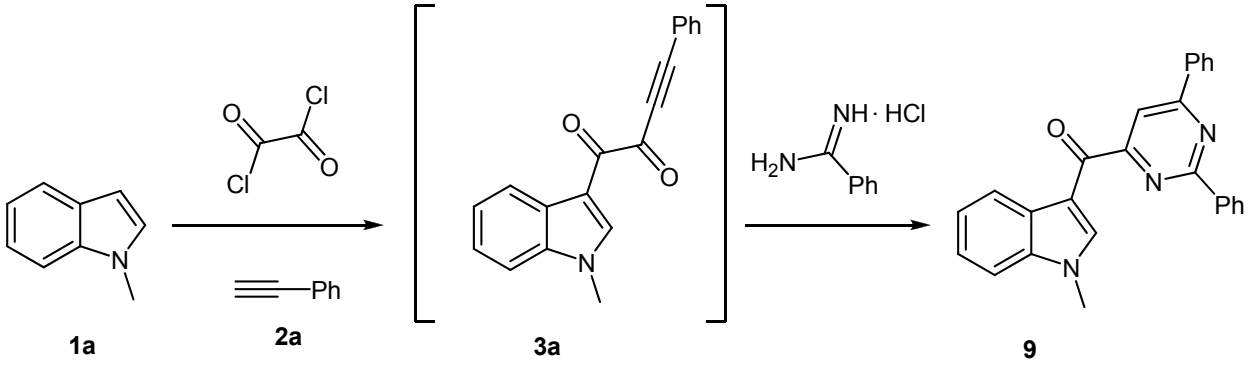


$C_{19}H_{15}N_3O$

301.34

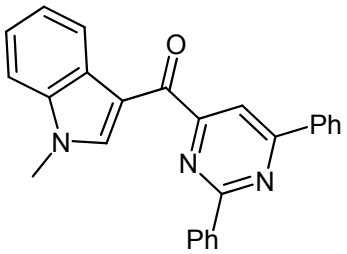
923 mg (3.06 mmol, 61 % total yield over two steps) as a pale yellow solid. Colorless solid was obtained after further purification by suspending in dichloromethane, sonication in ultrasound bath, filtration and drying in vacuo overnight. Mp 224-225 °C. ^{1}H NMR (DMSO-d_6, 500 MHz, 100 °C): δ 3.94 (s, 3 H), 7.25-7.41 (m, 4 H), 7.45-7.51 (m, 2 H), 7.56 (d, *J* = 7.9 Hz, 1 H), 7.9 (br, 2 H), 8.4 (br, 1 H), 8.7 (br, 1 H), 13.5 (br, 1 H, N<u>H</u>). EI + MS (*m/z* (%)): 301 (M^+, 9), 158 ((M-$C_9H_7N_2$)$^+$, 71), 131 ((C_9H_8N+H)$^+$, 100), 130 ($C_9H_8N^+$, 41), 114 (13), 103 ($C_7H_5N^+$, 24), 89 (17), 77 ($C_6H_5^+$, 90), 63 (11), 51 ($C_4H_3^+$, 18). IR (KBr): $\tilde{\nu}$ 3240 (w) cm^{-1}, 3136 (w), 2923 (w), 1593 (s), 1574 (m), 1516 (s), 1491 (w), 1472 (m), 1461 (m), 1418 (w), 1399 (w), 1380 (w), 1364 (m), 1259 (w), 1222 (m), 1178 (w), 1128 (w), 1081 (m), 1013 (w), 990 (w), 960 (w), 913 (w), 823 (w), 784 (w), 772 (m), 754 (m), 692 (w), 672 (w), 613 (w), 578 (w), 507 (w). Anal. calcd for $C_{19}H_{15}N_3O$ (301.3): C 75.73, H 5.02, N 13.94. Found: C 75.66, H 5.07, N 13.92.

3.4. One-Pot Four-Component Synthesis of (1-Methyl-1*H*-indol-3-yl)(2,6-diphenylpyrimidin-4-yl)methanone (9)



N-Methyl-1*H*-indole **1a** (669 mg, 5.00 mmol) in dry THF (25 mL) was placed under argon atmosphere in a screw-cap Schlenk vessel with septum, degassed with argon and cooled to 0 °C (water/ice bath, for 15 min). Then, oxalyl chloride (0.44 mL, 5.00 mmol) was added to the reaction mixture at 0 °C. The mixture was allowed to come to room temperature (water bath) and was stirred for 4 h. Then, CuI (49 mg, 0.25 mmol), phenylacetylene **2a** (0.57 mL, 5.00 mmol) and dry triethylamine (2.08 mL, 15.0 mmol) were successively added to the mixture and stirring at room temperature was continued for 24 h. After complete conversion (product monitored by TLC) methanol (5 mL), benzamidine hydrochloride (791 mg, 5.00 mmol) and potassium carbonate (1.75 g, 12.5 mmol) were added, and the mixture was stirred for 21 h at 50 °C (preheated oil bath, product monitored by TLC). After removal of the solvents in vacuo the residue was absorbed onto Celite® and purified chromatographically on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl acetate PE-EA = 10:1, 1 Vol % triethylamine. After drying in vacuo, compound **9** (800 mg, 2.05 mmol, 41 % yield) was obtained as a yellow solid. Further purification was performed by recrystallization from dichloromethane/*n*-pentane to give the analytically pure **9** as yellow crystals.

(1-Methyl-1*H*-indol-3-yl)(2,6-diphenylpyrimidin-4-yl)methanone (9)

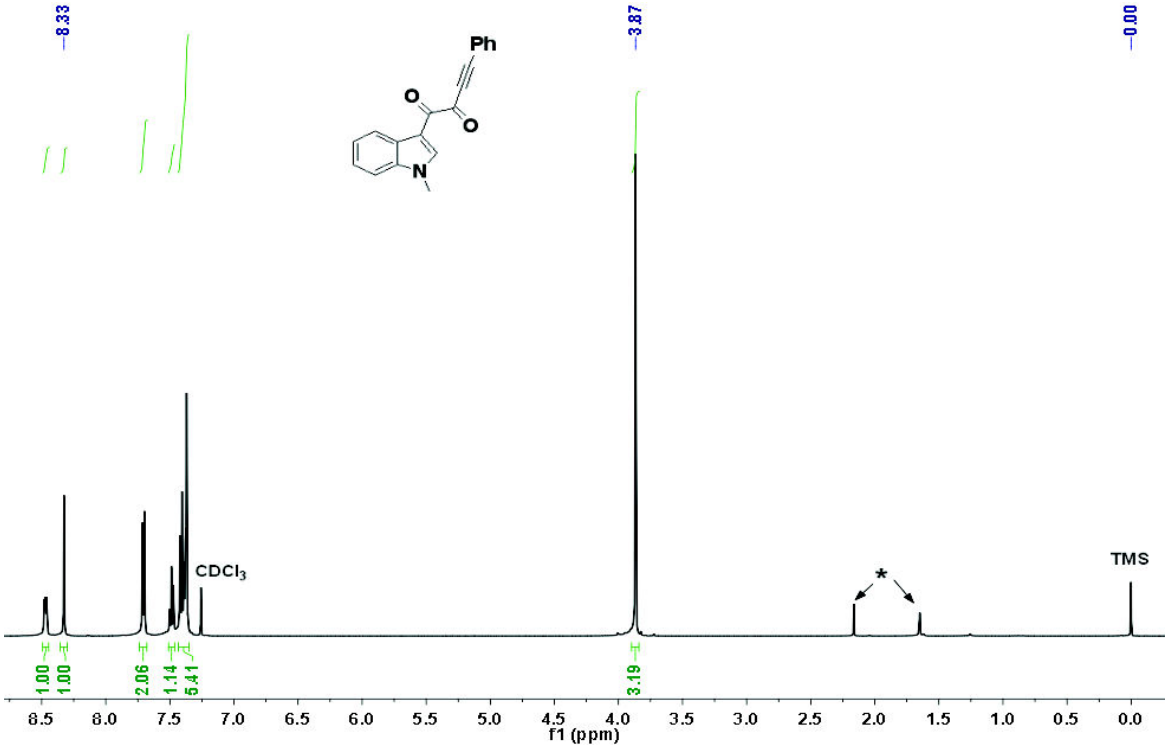


$C_{26}H_{19}N_3O$

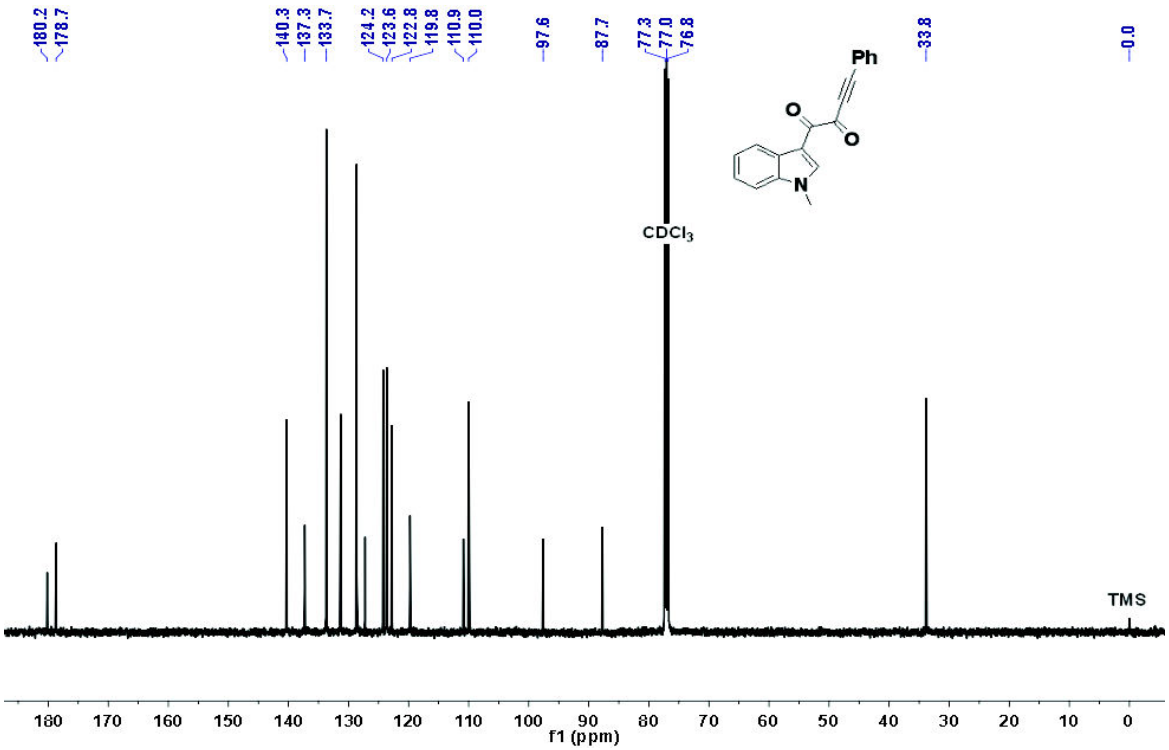
389.45

800 mg (2.05 mmol, 41 % yield) as a yellow solid. R_f (PE-EA = 10:1): 0.31. Mp 196 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.88 (s, 3 H), 7.34-7.41 (m, 3 H), 7.52-7.59 (m, 6 H), 8.30-8.34 (m, 2 H), 8.35 (s, 1 H), 8.60-8.65 (m, 3 H), 8.85 (s, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 33.8 (CH_3), 109.7 (CH), 112.7 (CH), 113.7 (C_{quat}), 123.0 (CH), 123.3 (CH), 123.8 (CH), 127.4 (CH), 128.0 (C_{quat}), 128.4 (CH), 128.7 (CH), 129.0 (CH), 130.9 (CH), 131.2 (CH), 136.8 (C_{quat}), 137.1 (C_{quat}), 137.9 (C_{quat}), 140.8 (CH), 163.8 (C_{quat}), 163.9 (C_{quat}), 165.7 (C_{quat}), 185.2 (C_{quat}). EI + MS (*m/z* (%)): 389 (M^+, 11), 191 (10), 189 (15), 159 (12), 158 ($C_{10}H_8NO^+$, 100), 130 ($C_9H_8N^+$, 9), 77 ($C_6H_5^+$, 10), 57 (19), 43 (56), 42 (23), 41 (18). IR (KBr): $\tilde{\nu}$ 3132 (w) cm^{-1}, 1620 (s), 1566 (m), 1522 (s), 1460 (m), 1420 (w), 1403 (w), 1373 (s), 1232 (w), 1197 (w), 1125 (w), 1086 (w), 932 (w), 916 (w), 893 (w), 779 (w), 718 (s), 736 (s), 691 (m), 657 (w), 644 (w), 632 (w), 579 (w), 544 (w). Anal. calcd for $C_{26}H_{19}N_3O$ (389.5): C 80.18, H 4.92, N 10.79. Found: C 79.97, H 5.07, N 10.82.

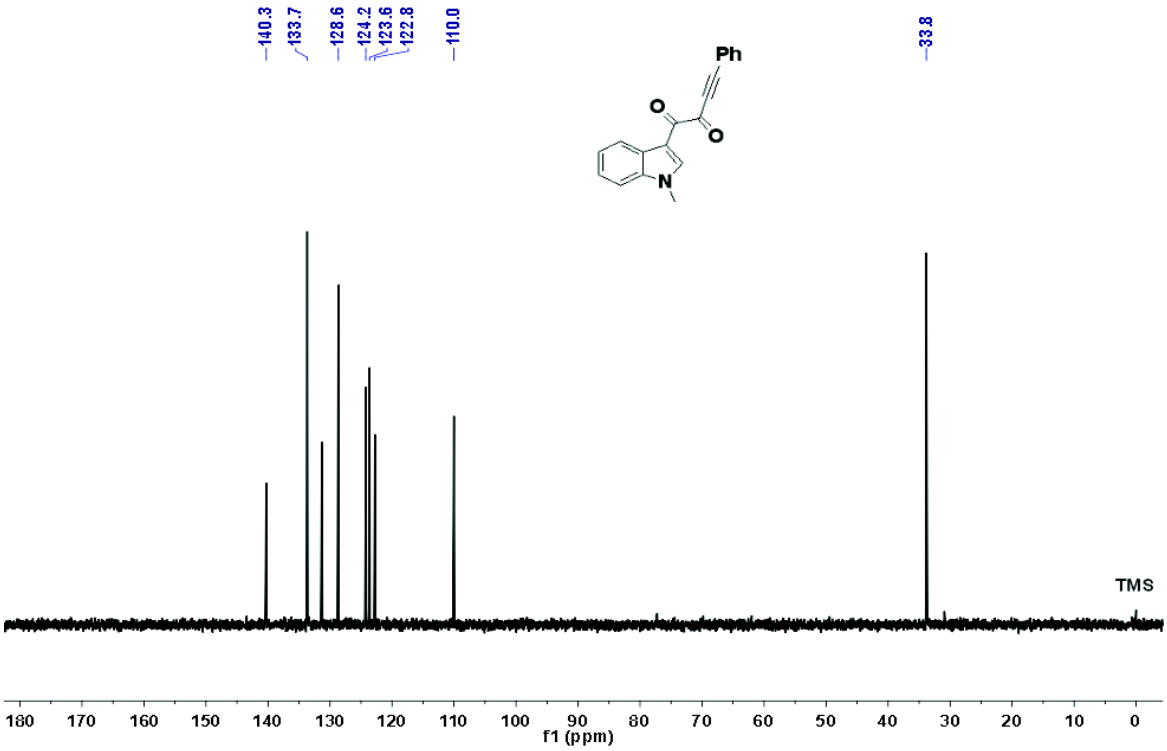
4. ^{1}H and ^{13}C NMR Spectra of Compounds 3a-k



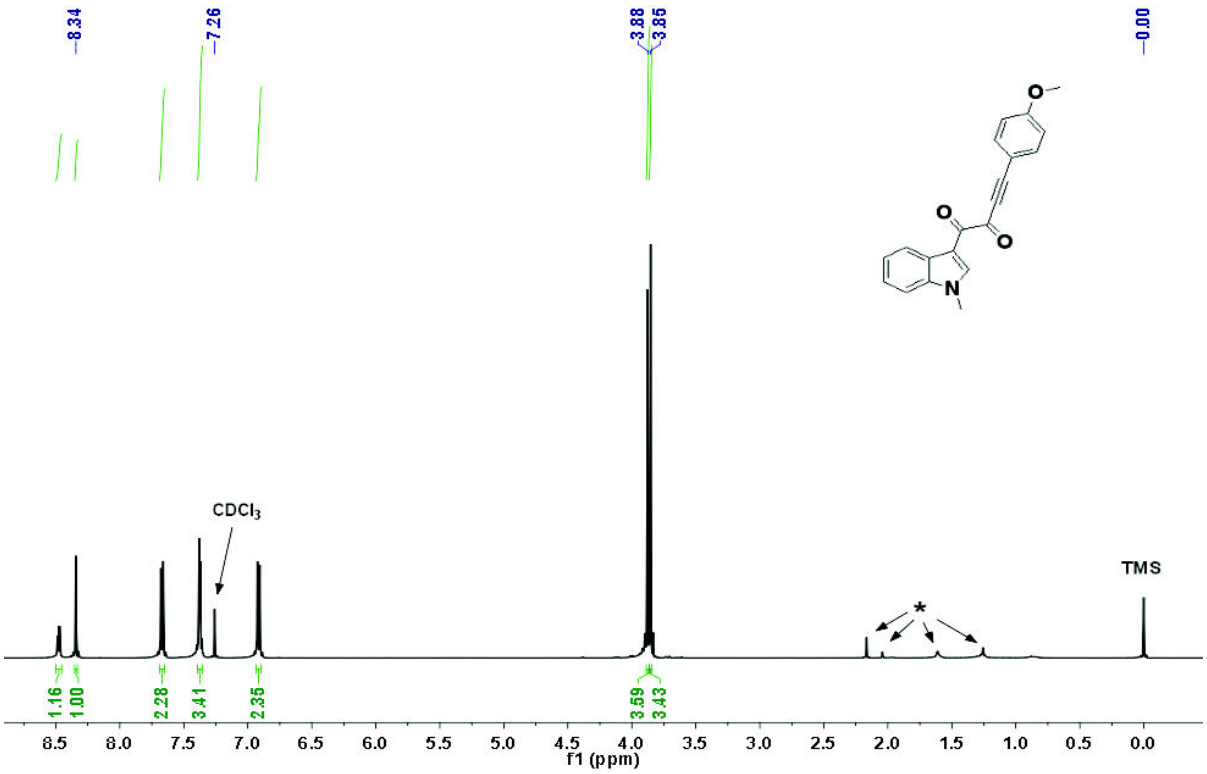
^{1}H NMR of **3a** in $CDCl_3$ at 296 K (δ in ppm). *Impurities from residual solvents.



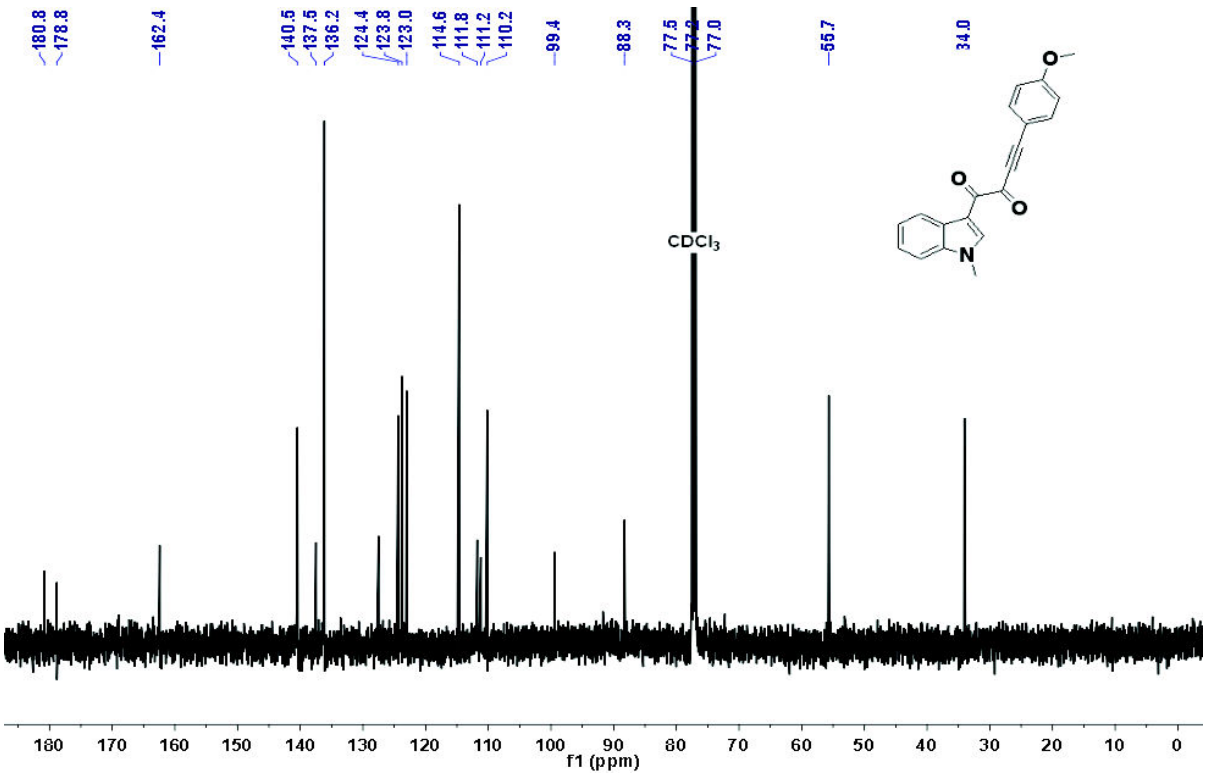
^{13}C NMR of **3a** in $CDCl_3$ at 297 K (δ in ppm).



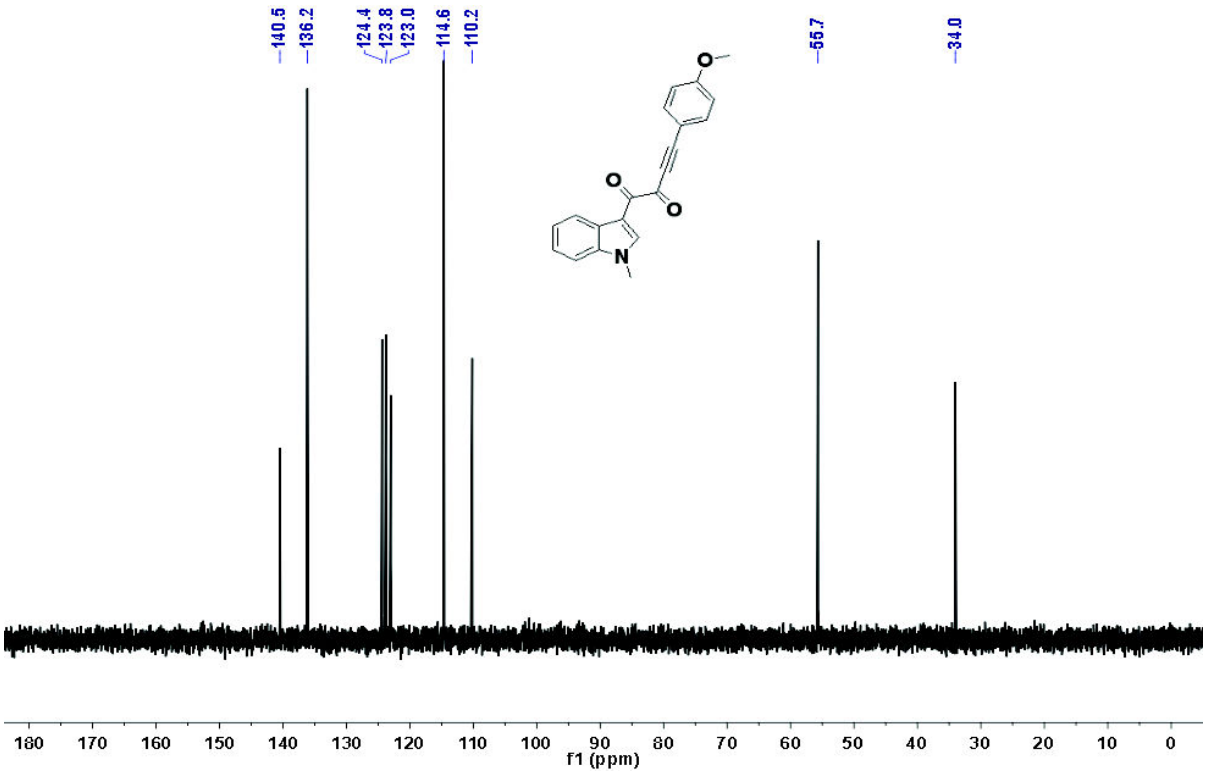
^{13}C DEPT 135-NMR of **3a** in $CDCl_3$ at 297 K (δ in ppm).



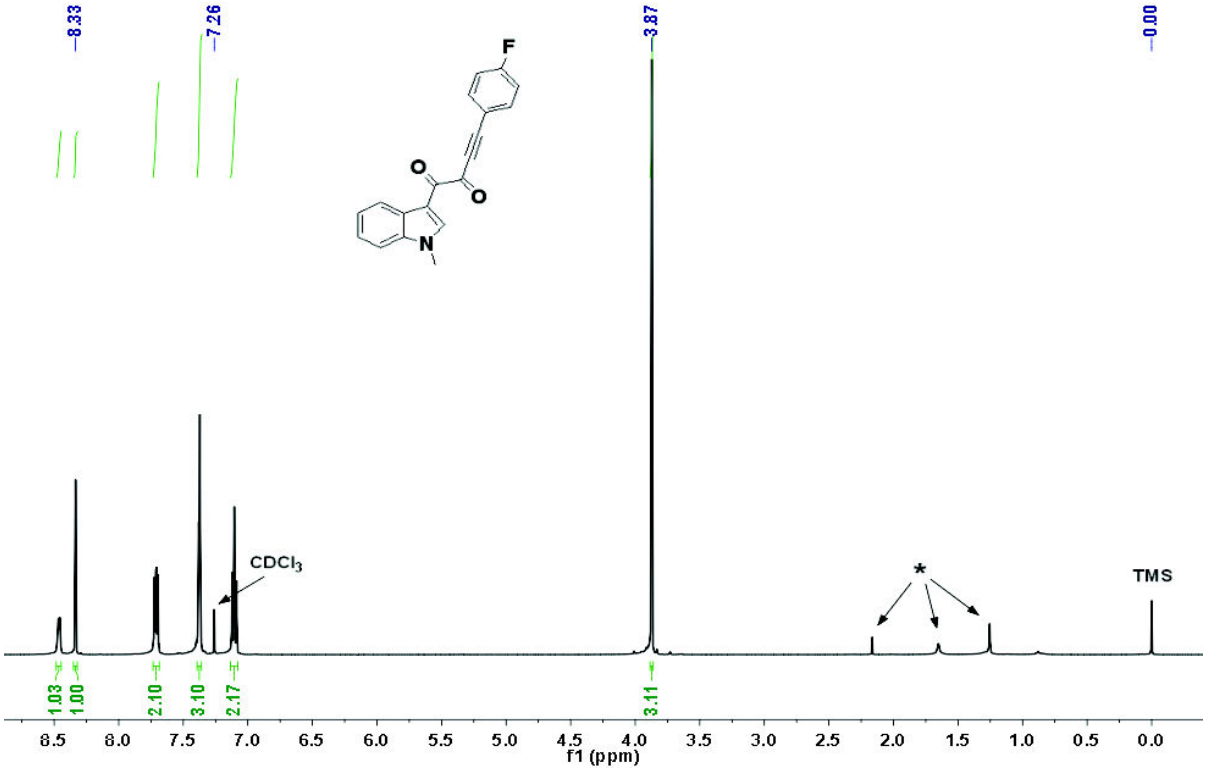
^{1}H NMR of **3b** in $CDCl_3$ at 299 K (δ in ppm). *Impurities from residual solvents.



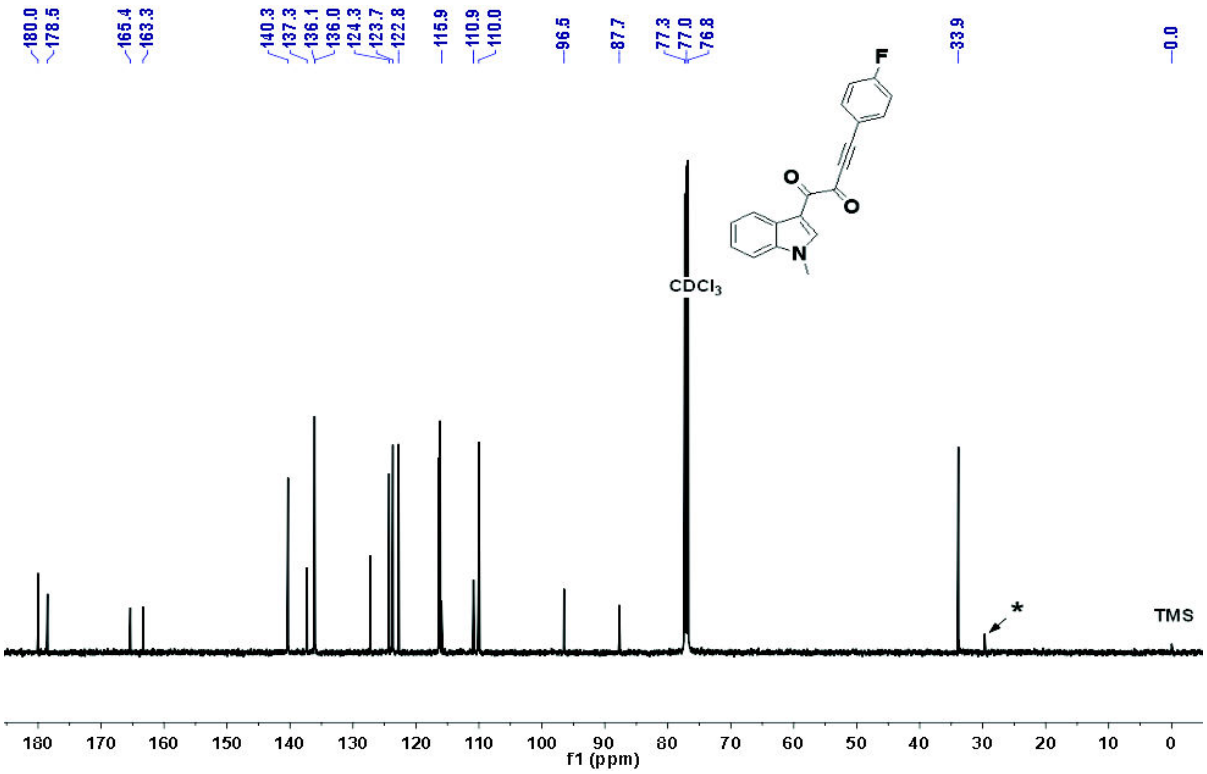
^{13}C NMR of **3b** in $CDCl_3$ at 299 K (δ in ppm).



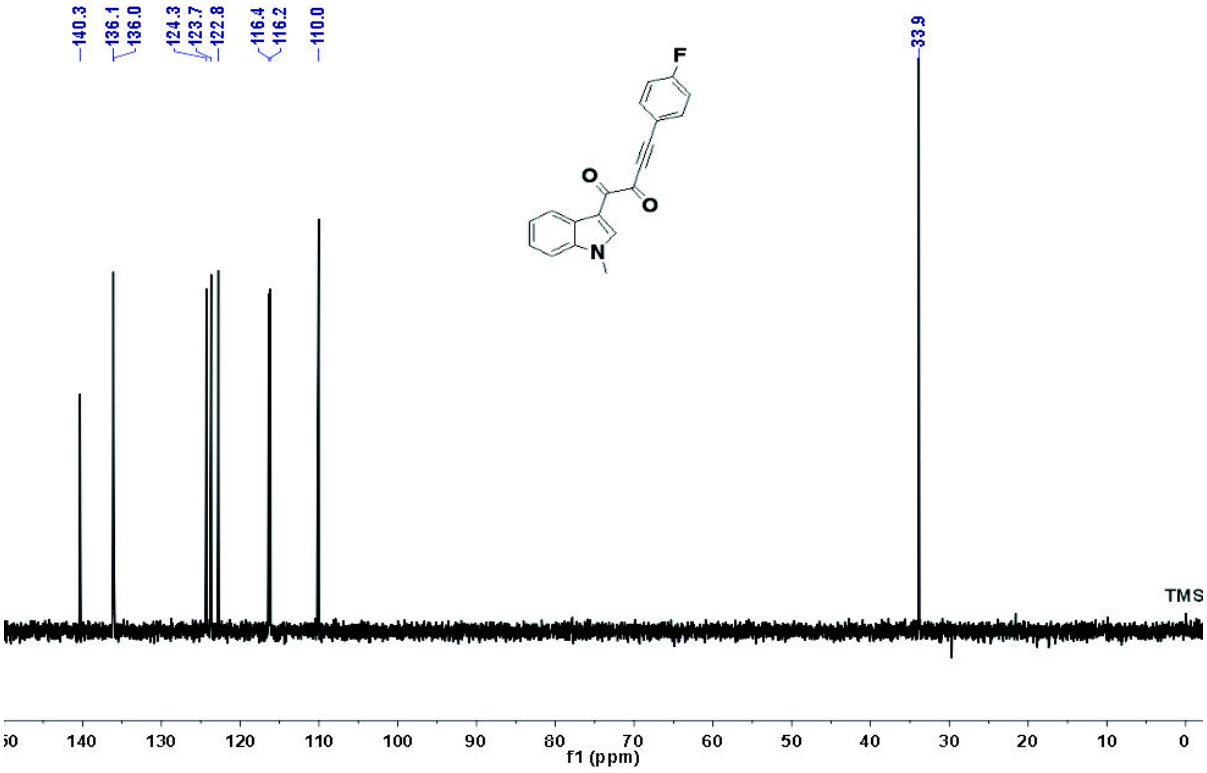
^{13}C DEPT 135-NMR of **3b** in $CDCl_3$ at 299 K (δ in ppm).



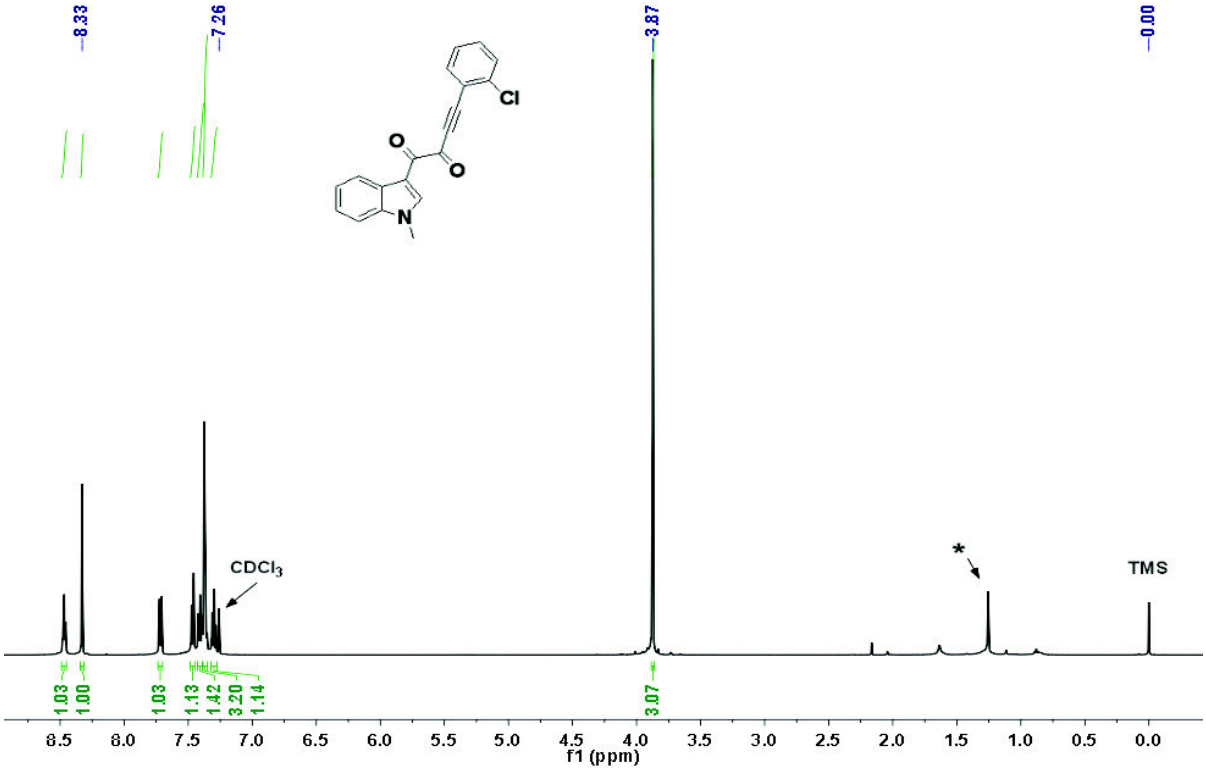
^{1}H NMR of **3c** in $CDCl_3$ at 298 K (δ in ppm). *Impurities from residual solvents.



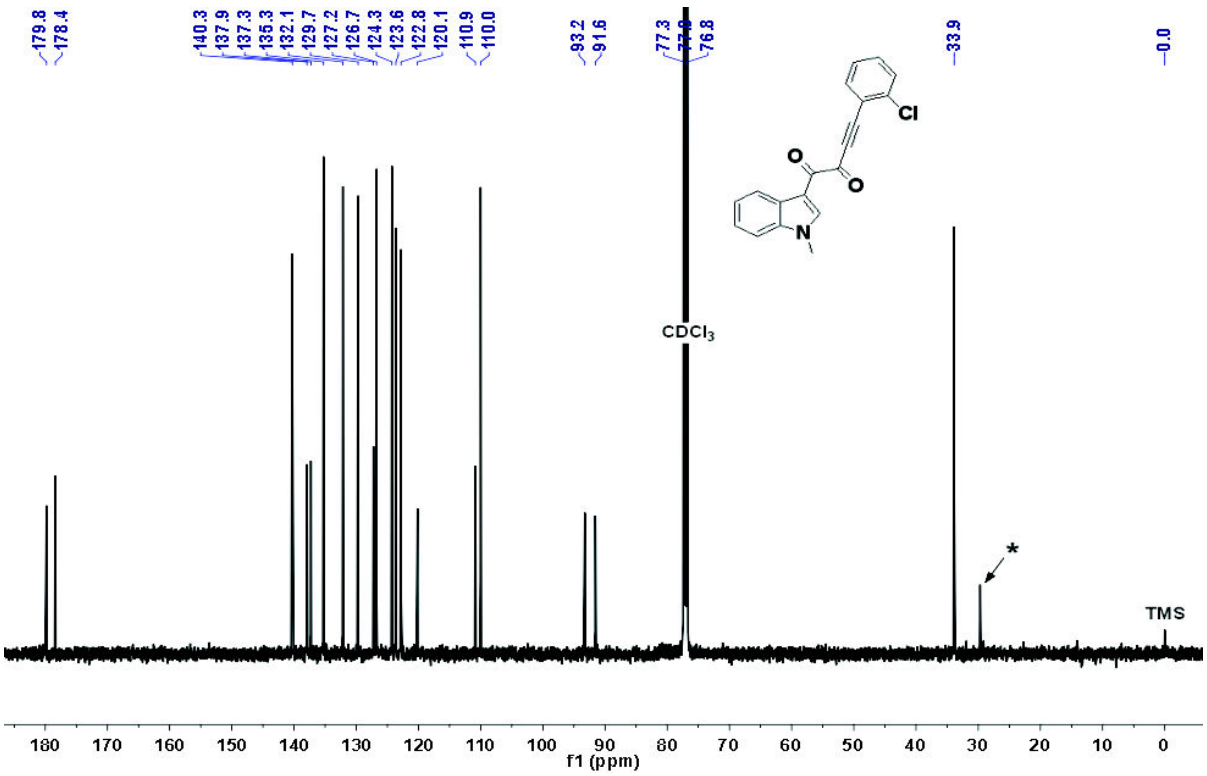
^{13}C NMR of **3c** in $CDCl_3$ at 298 K (δ in ppm).



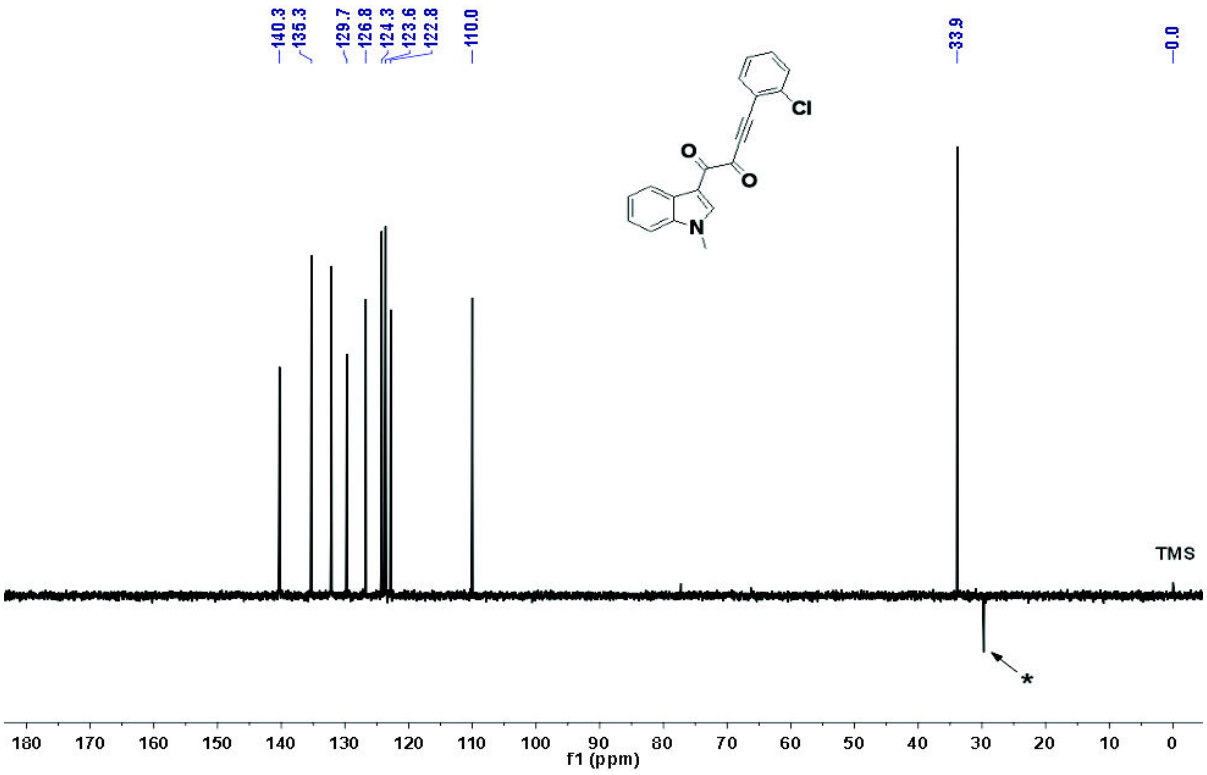
^{13}C DEPT 135-NMR of **3c** in $CDCl_3$ at 298 K (δ in ppm).



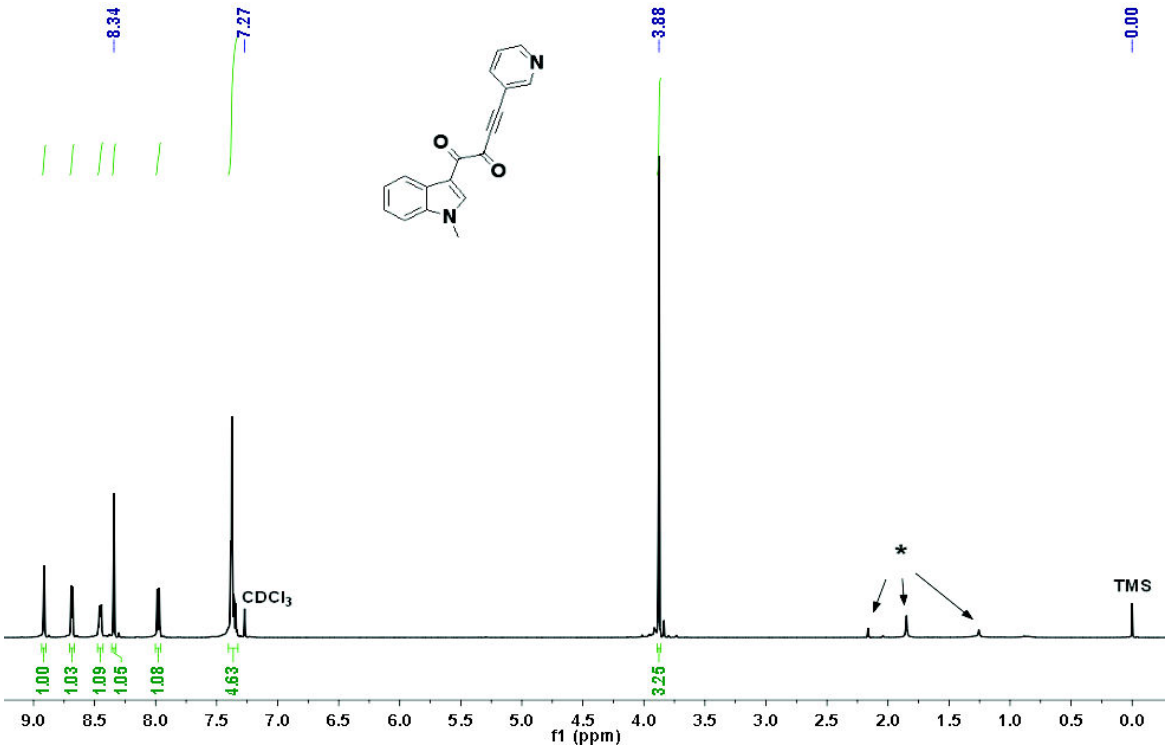
^{1}H NMR of **3d** in $CDCl_3$ at 297 K (δ in ppm). *Impurities from residual solvents.



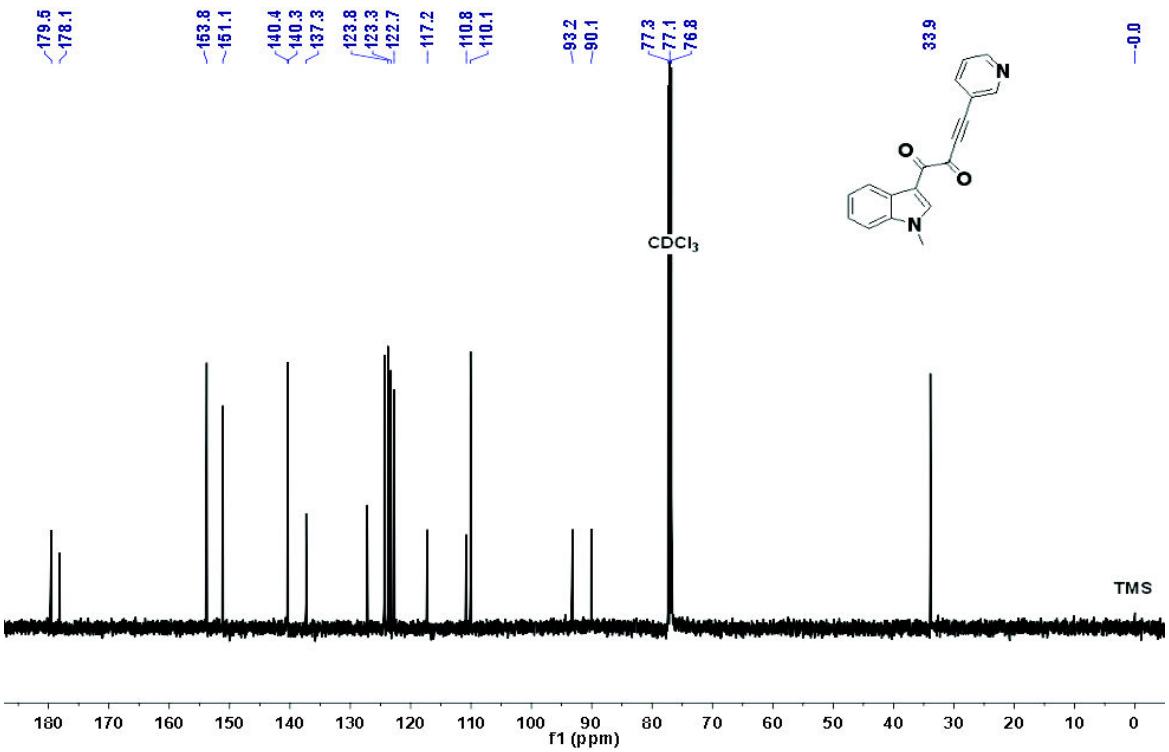
^{13}C NMR of **3d** in $CDCl_3$ at 298 K (δ in ppm). *Impurities from residual solvents.



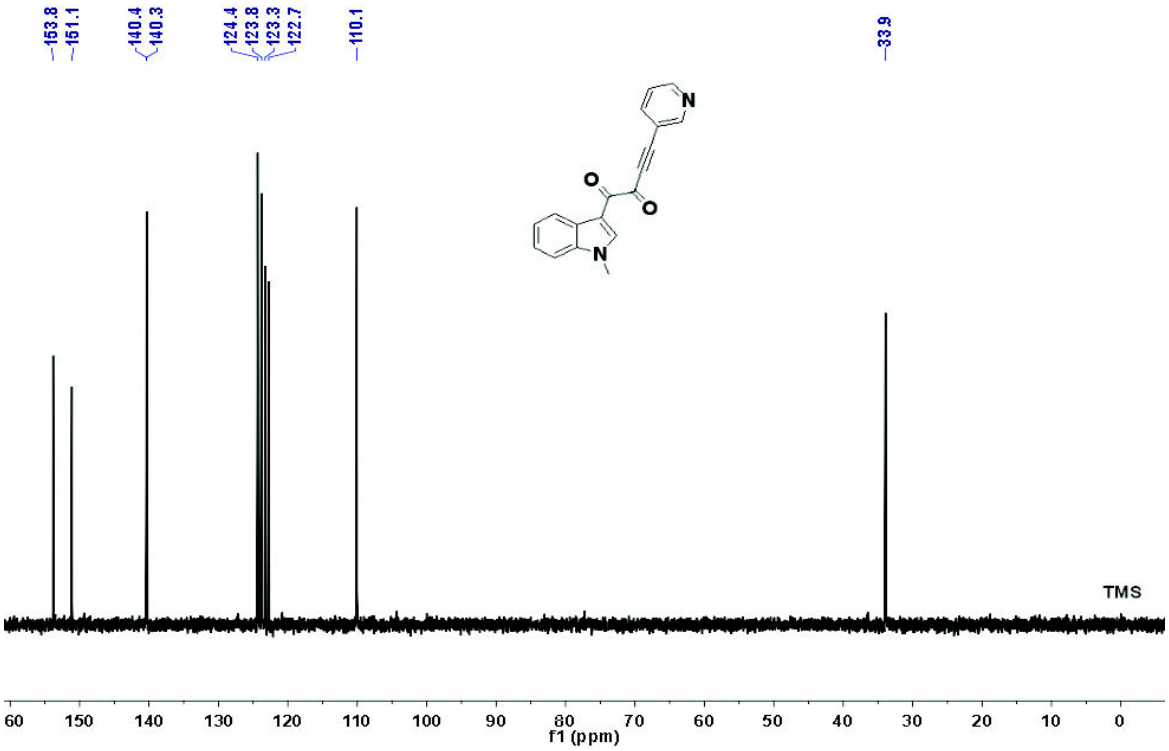
^{13}C DEPT 135-NMR of **3d** in $CDCl_3$ at 298 K (δ in ppm). *Impurities from residual solvents.



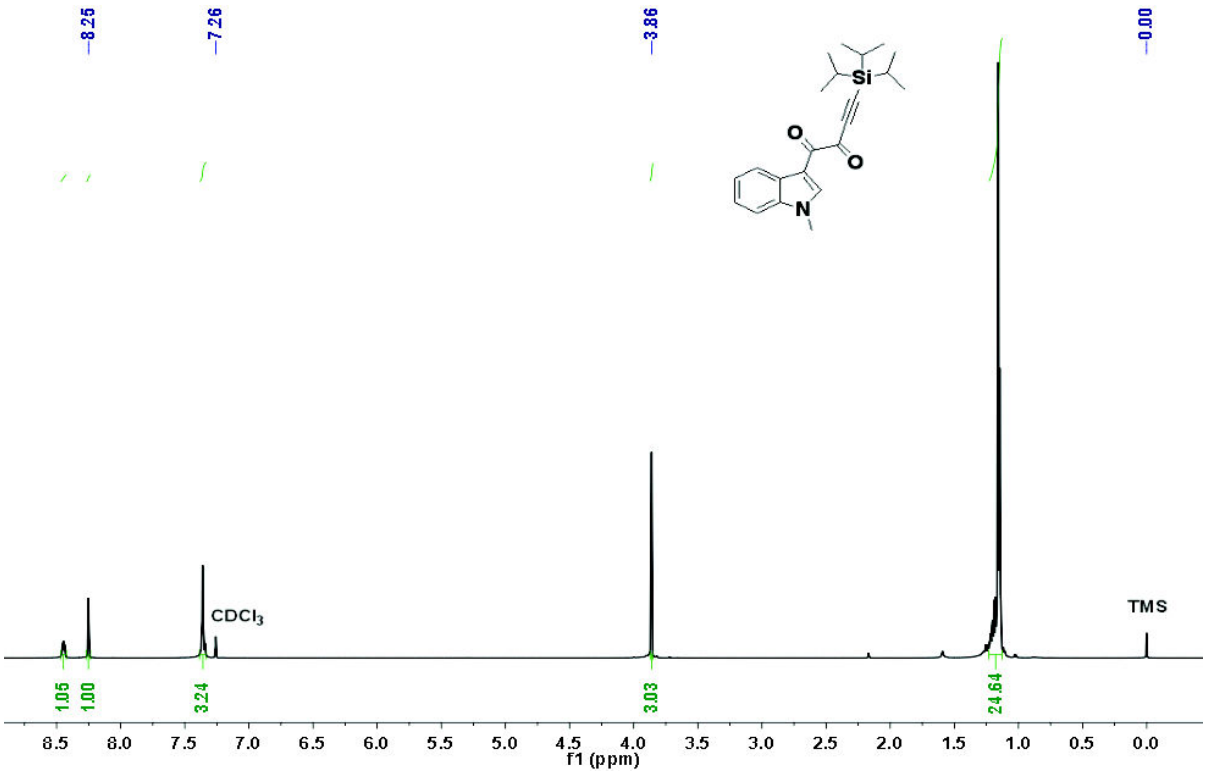
^{1}H NMR of **3e** in $CDCl_3$ at 299 K (δ in ppm). *Impurities from residual solvents.



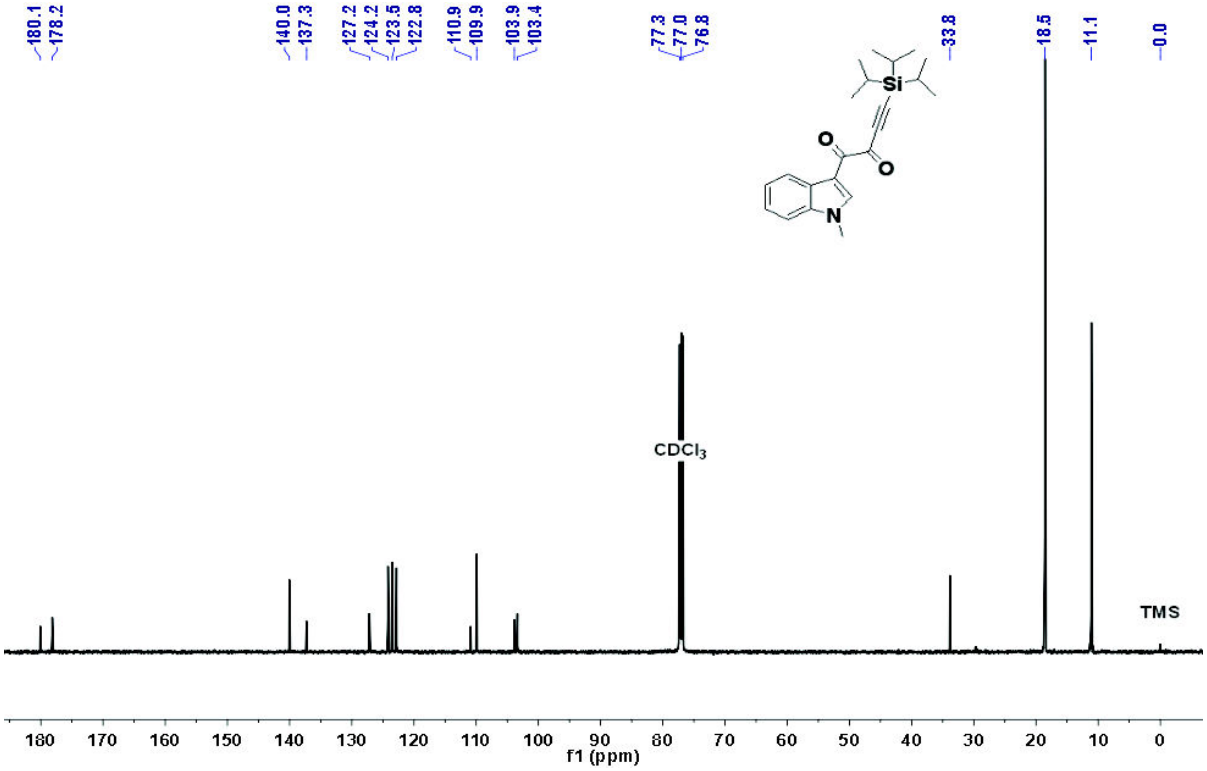
^{13}C NMR of **3e** in $CDCl_3$ at 299 K (δ in ppm).



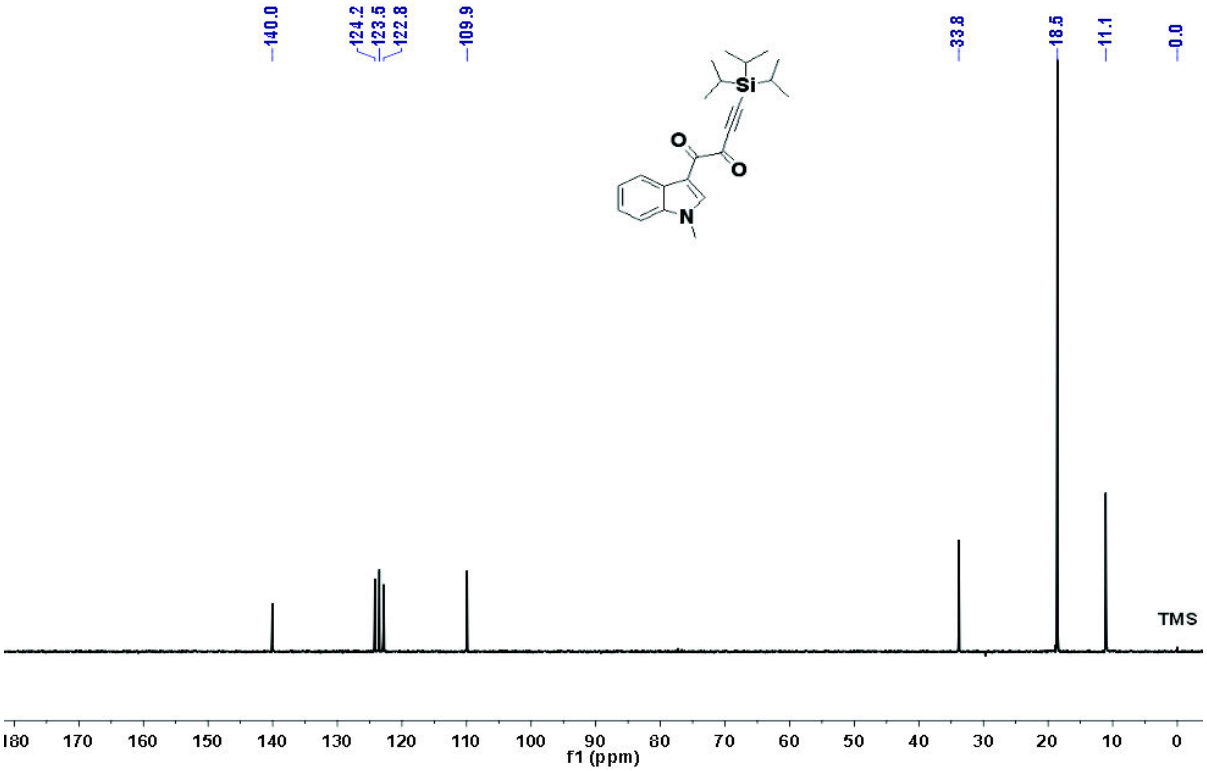
^{13}C DEPT 135-NMR of **3e** in $CDCl_3$ at 299 K (δ in ppm).



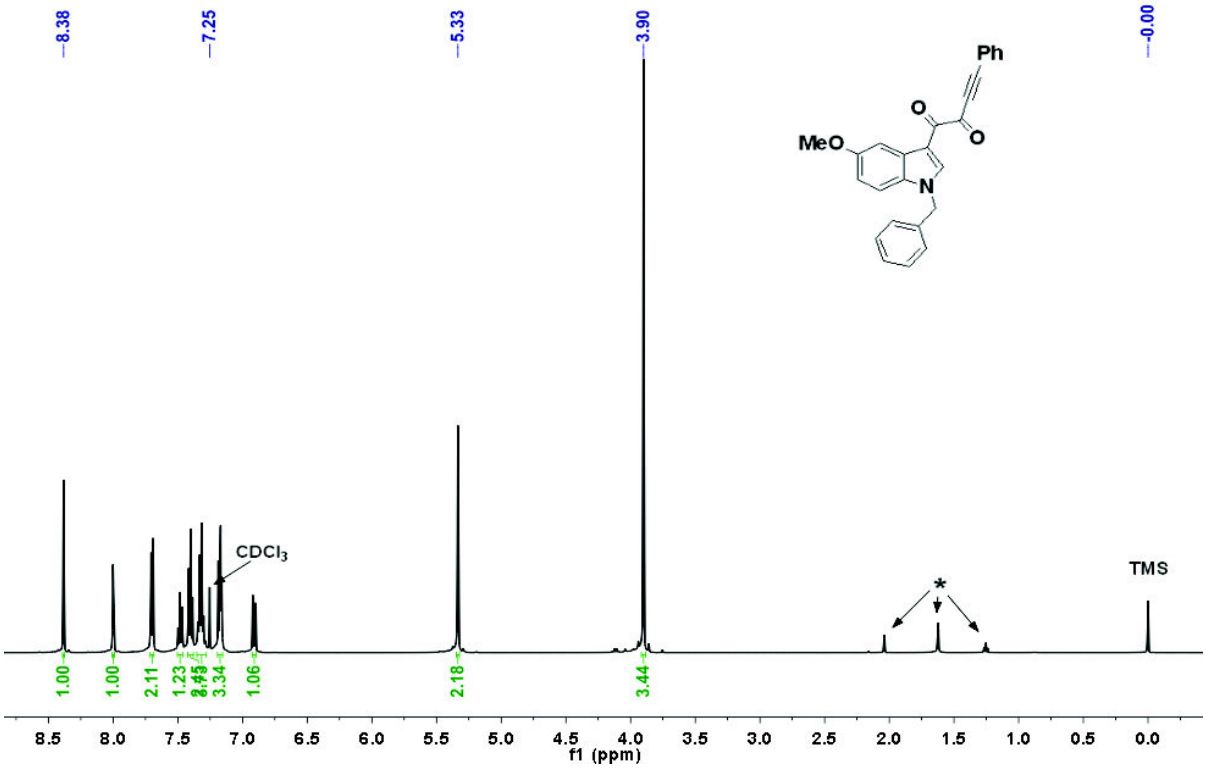
^{1}H NMR of **3f** in $CDCl_3$ at 298 K (δ in ppm).



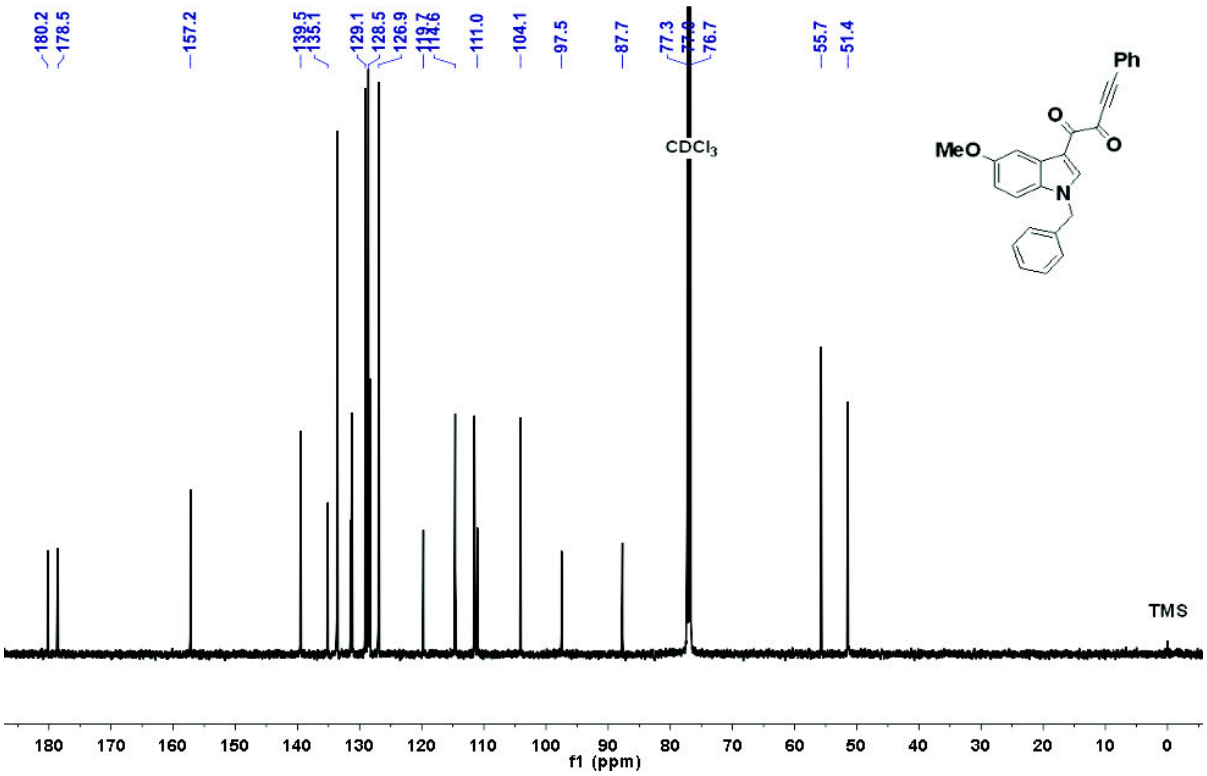
^{13}C NMR of **3f** in $CDCl_3$ at 298 K (δ in ppm).



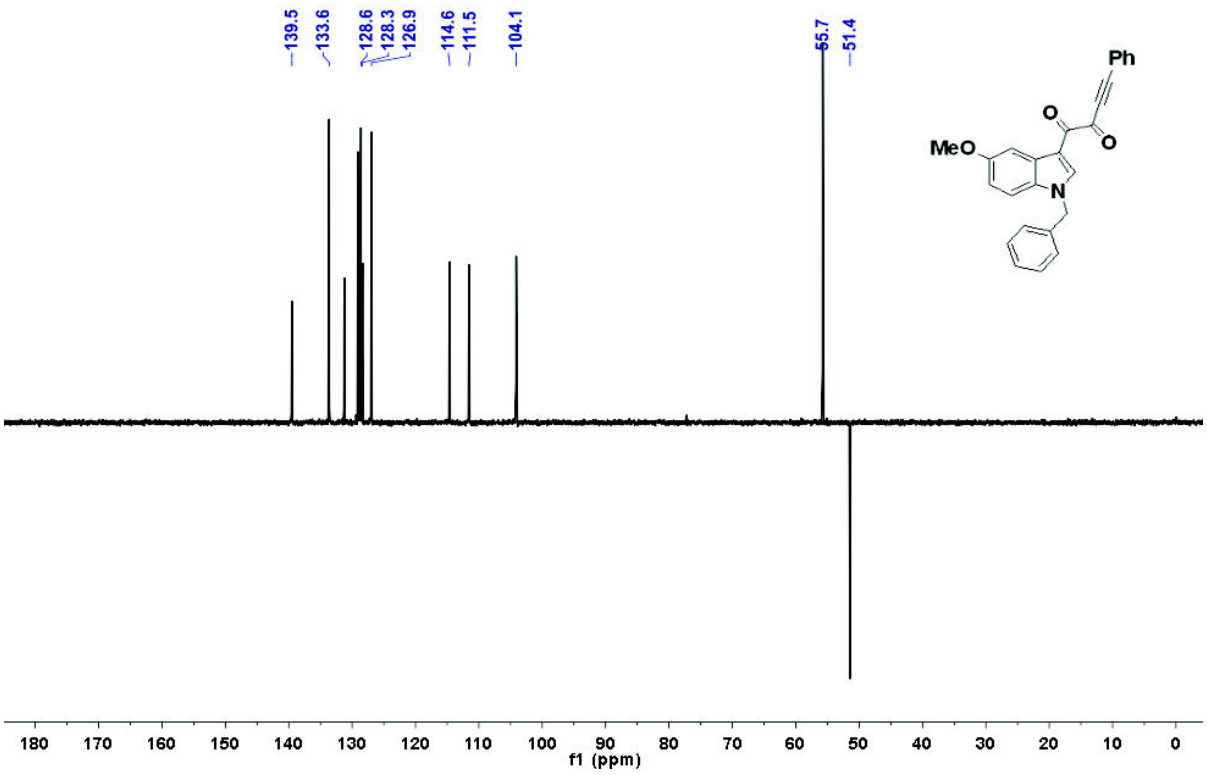
^{13}C DEPT 135-NMR of **3f** in $CDCl_3$ at 298 K (δ in ppm).



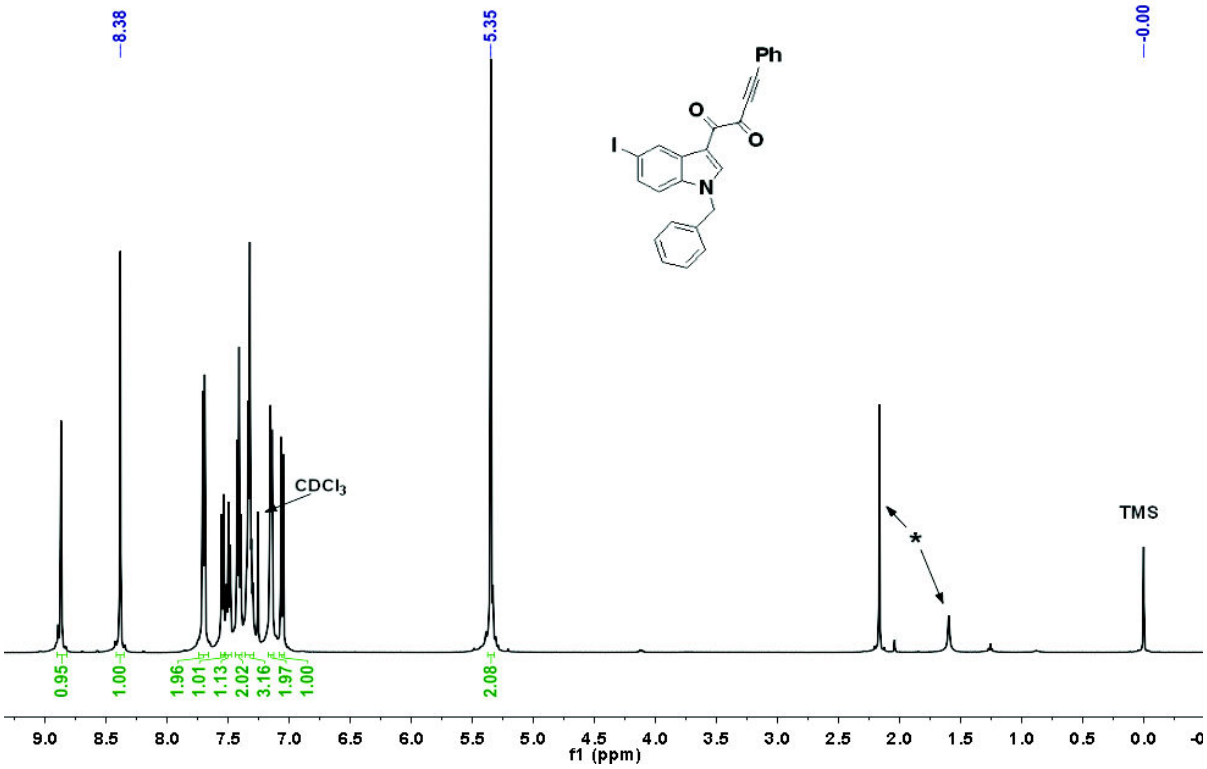
^{1}H NMR of **3g** in $CDCl_3$ at 298 K (δ in ppm). *Impurities from residual solvents.



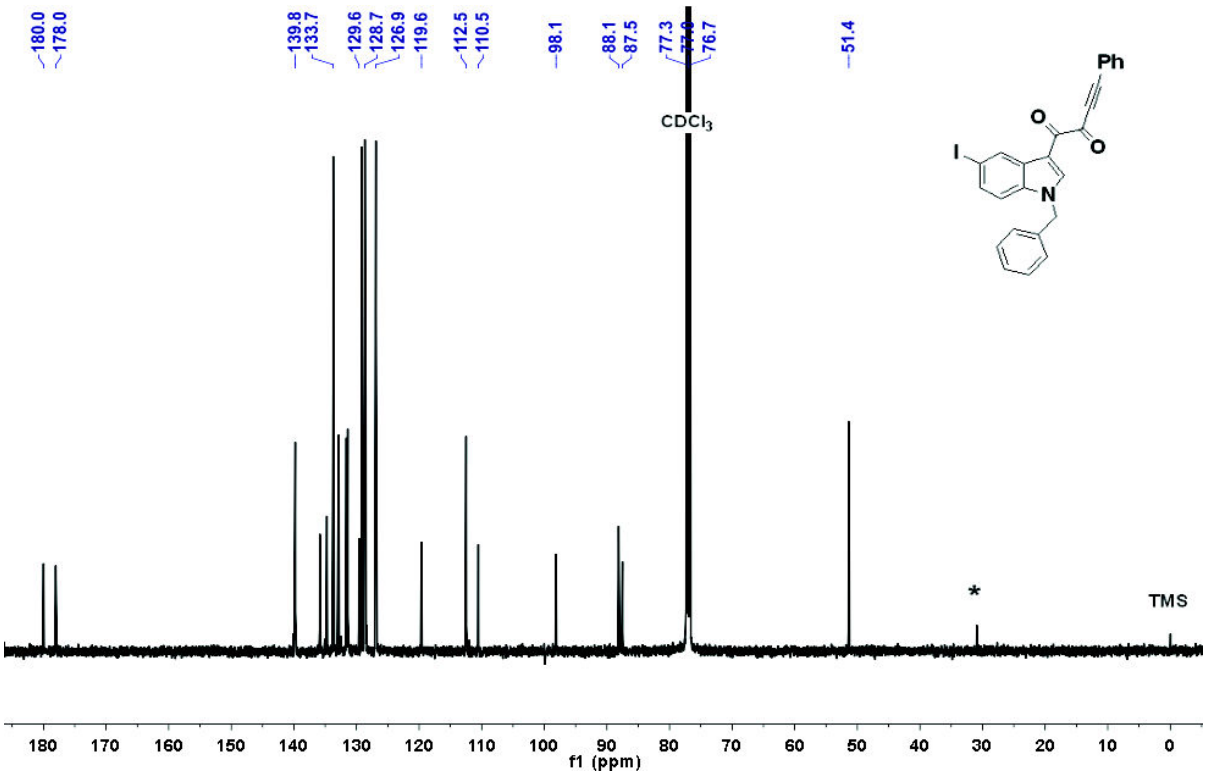
^{13}C NMR of **3g** in $CDCl_3$ at 299 K (δ in ppm).



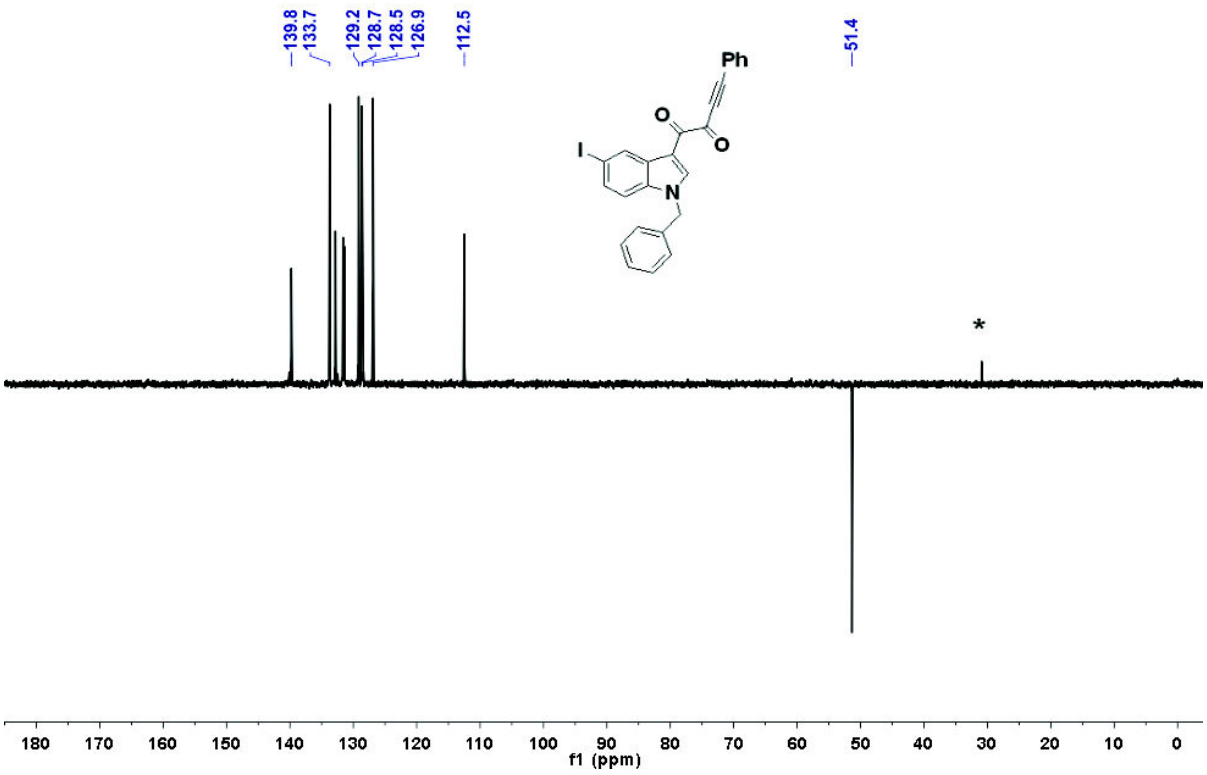
^{13}C DEPT 135-NMR of **3g** in $CDCl_3$ at 299 K (δ in ppm).



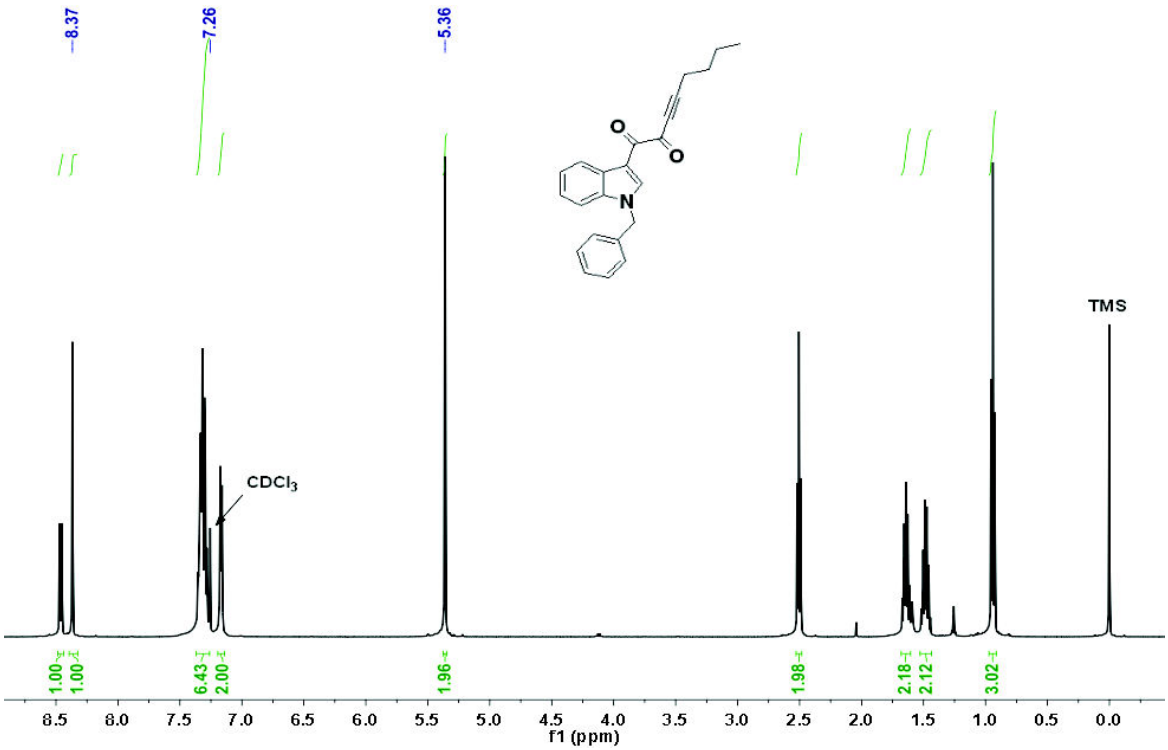
^{1}H NMR of **3h** in $CDCl_3$ at 298 K (δ in ppm). *Impurities from residual solvents.



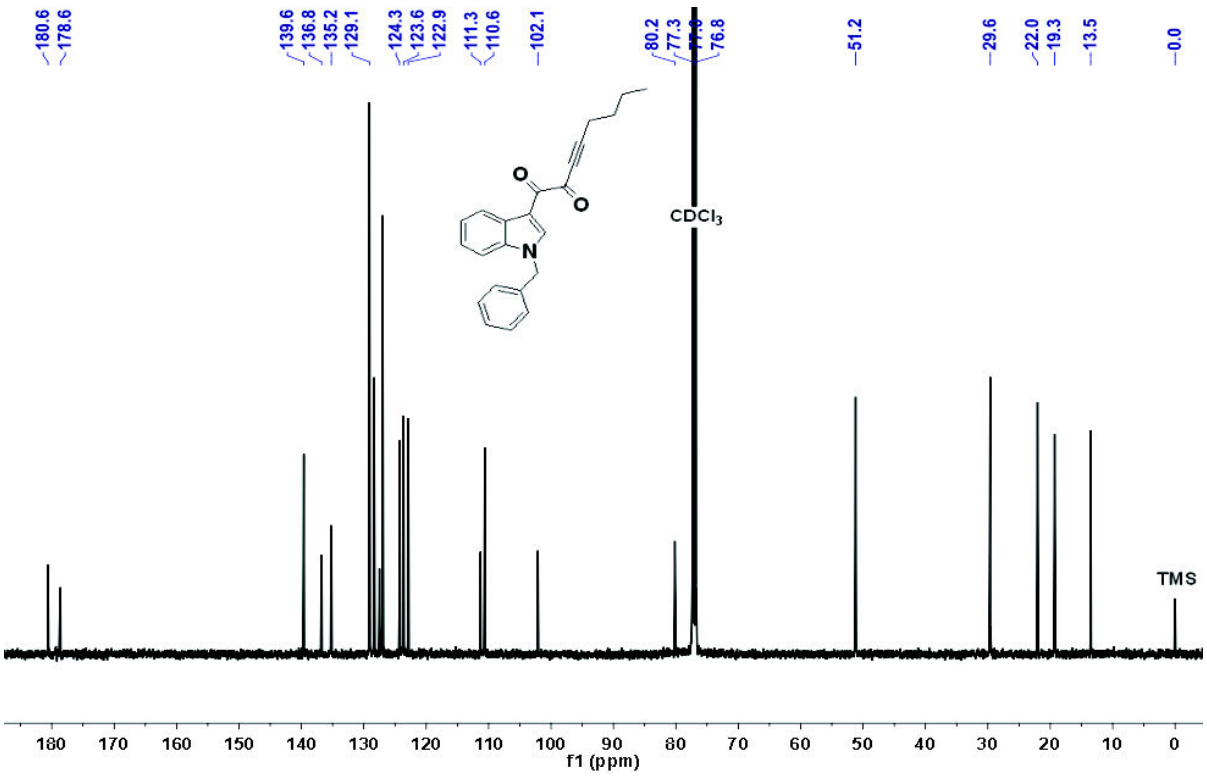
^{13}C NMR of **3h** in $CDCl_3$ at 298 K (δ in ppm). *Impurities from residual solvents.



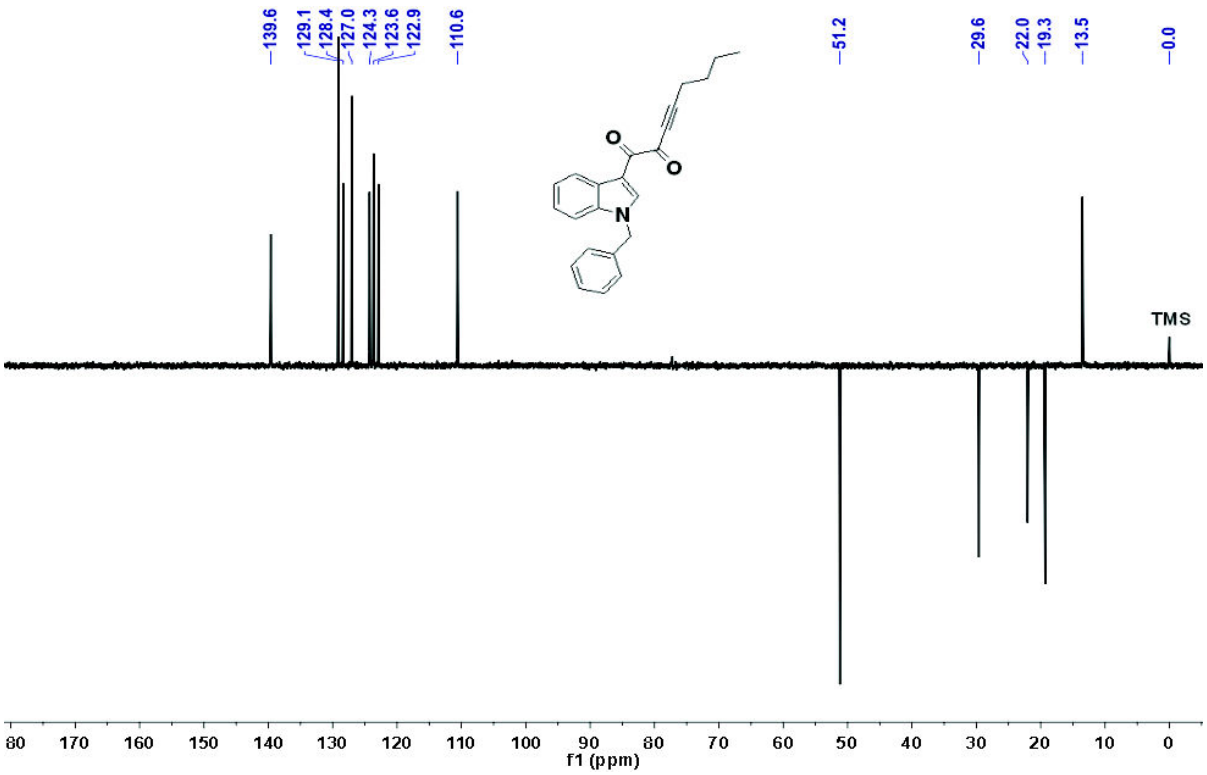
^{13}C DEPT 135-NMR of **3h** in $CDCl_3$ at 298 K (δ in ppm). *Impurities from residual solvents.



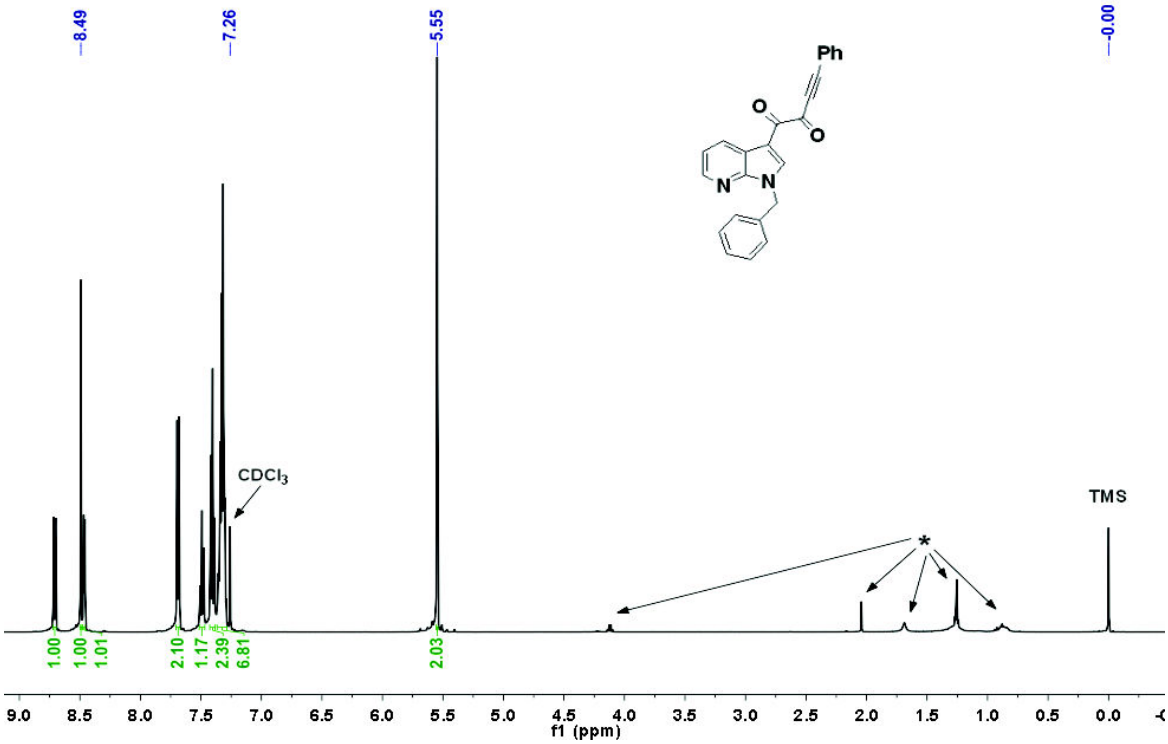
^{1}H NMR of **3i** in $CDCl_3$ at 297 K (δ in ppm).



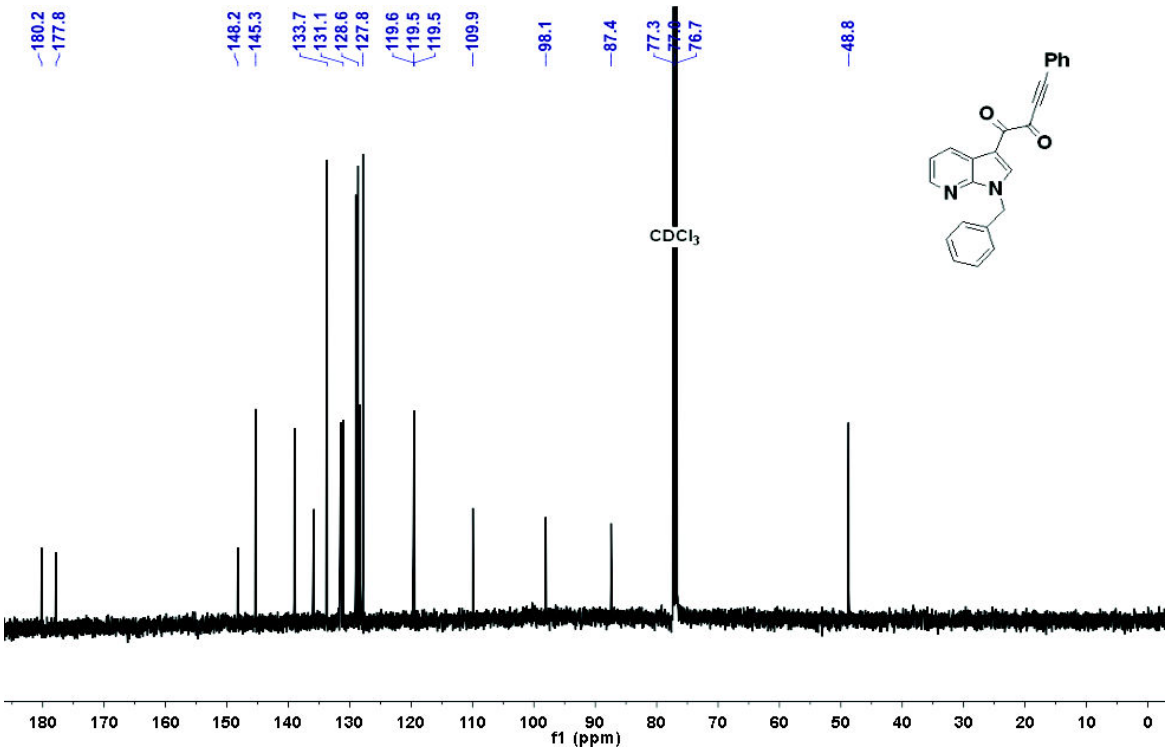
^{13}C NMR of **3i** in $CDCl_3$ at 297 K (δ in ppm).



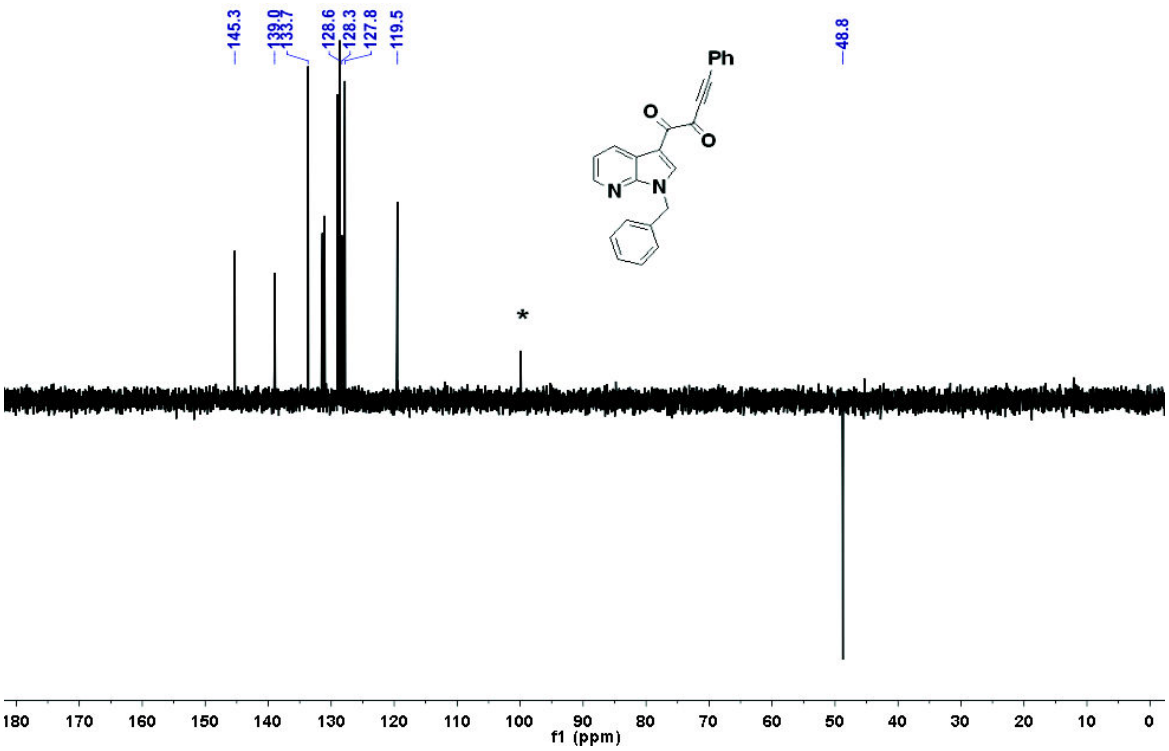
^{13}C DEPT 135-NMR of **3i** in $CDCl_3$ at 297 K (δ in ppm).



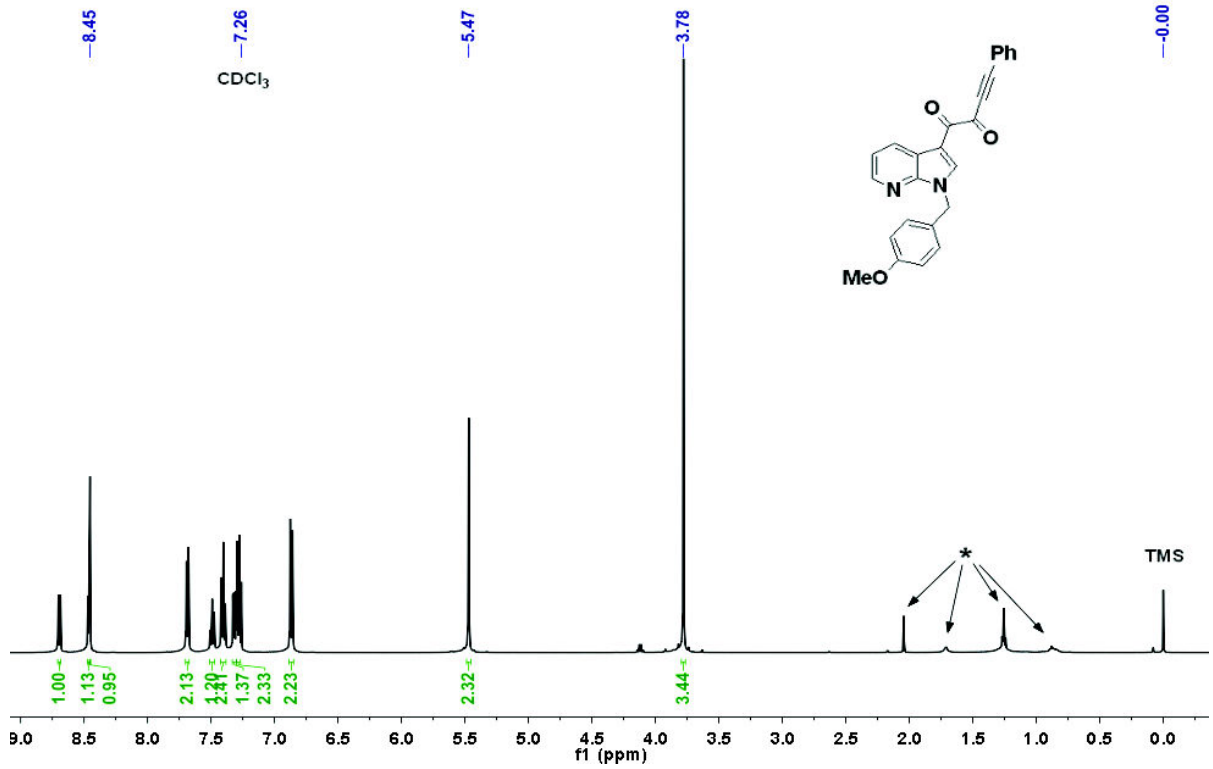
^{1}H NMR of **3j** in $CDCl_3$ at 297 K (δ in ppm). *Impurities from residual solvents.



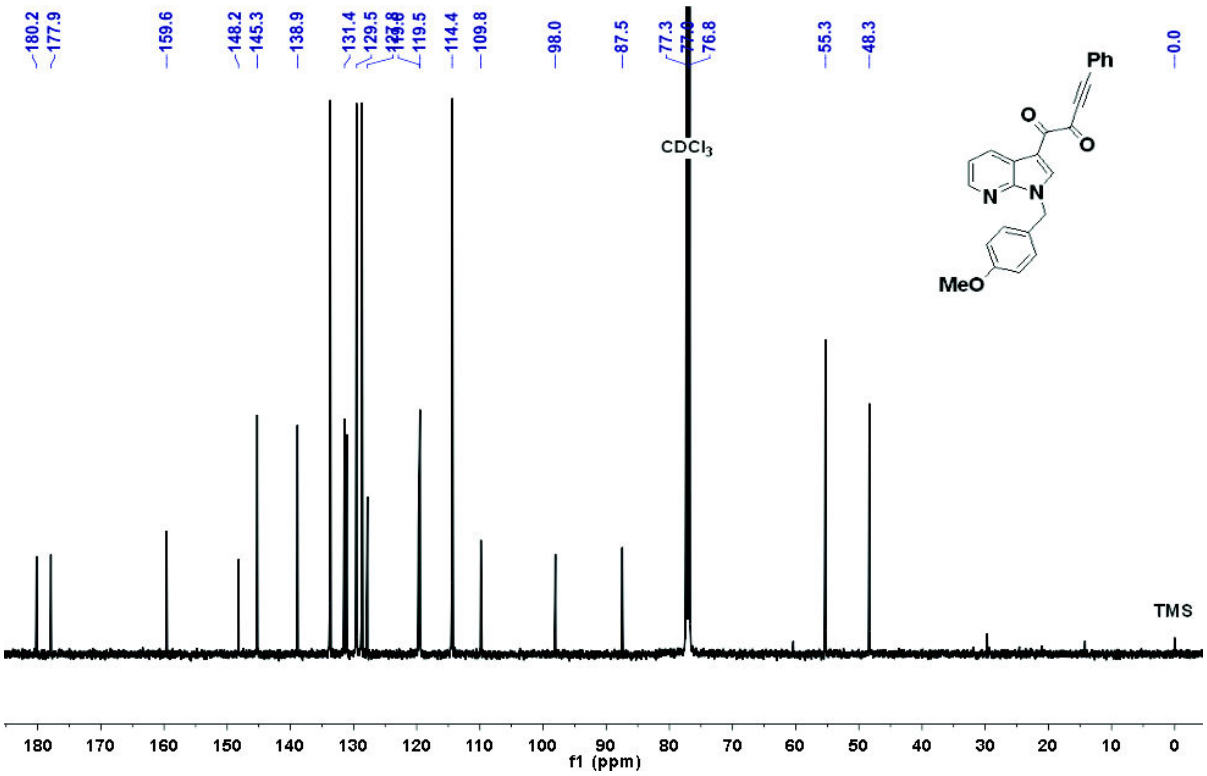
^{13}C NMR of **3j** in $CDCl_3$ at 297 K (δ in ppm).



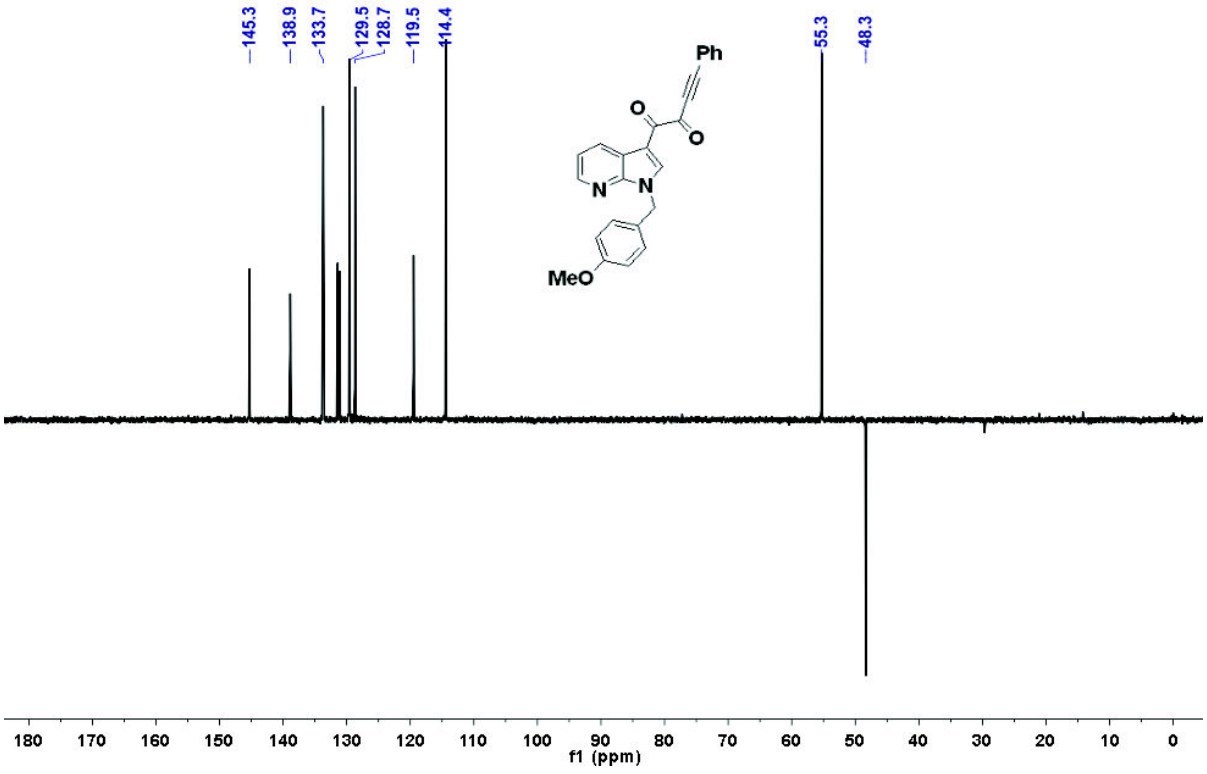
^{13}C DEPT 135-NMR of **3j** in $CDCl_3$ at 297 K (δ in ppm). *Impurities from residual solvents.



^{1}H NMR of **3k** in $CDCl_3$ at 295 K (δ in ppm). *Impurities from residual solvents.

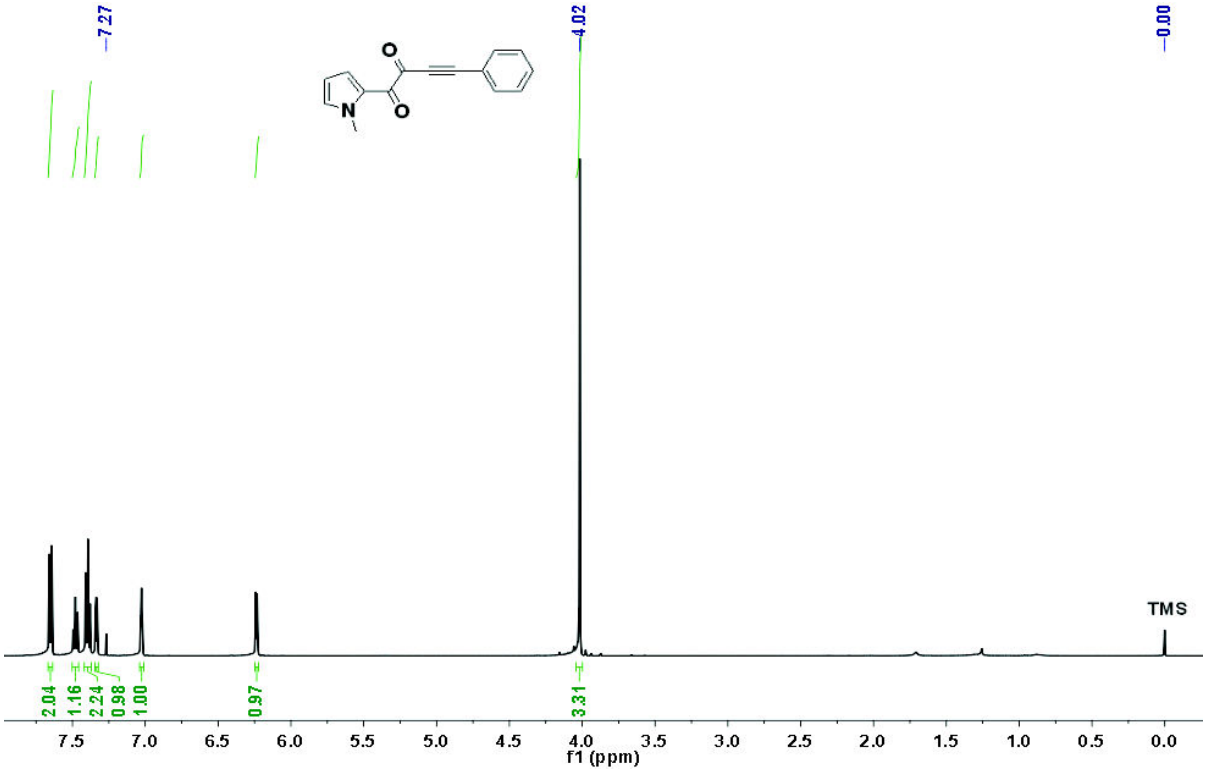


^{13}C NMR of **3k** in $CDCl_3$ at 295 K (δ in ppm).

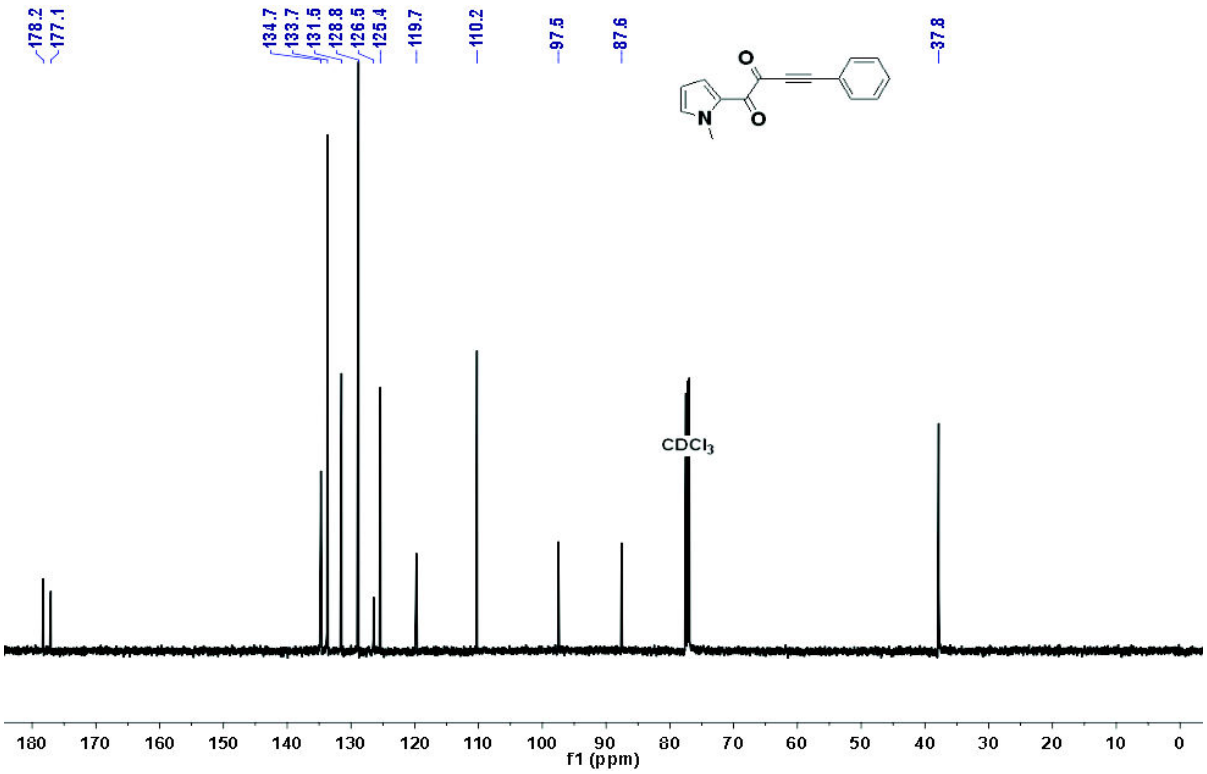


^{13}C DEPT 135-NMR of **3k** in $CDCl_3$ at 295 K (δ in ppm).

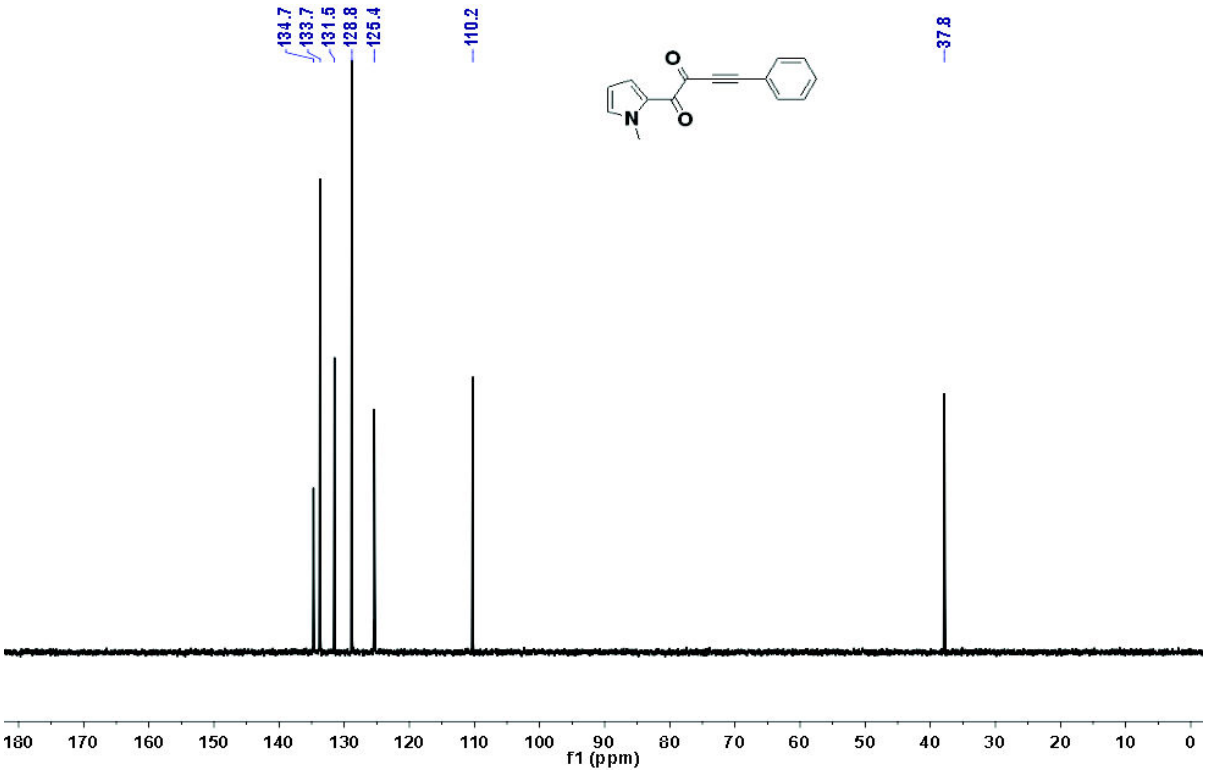
5. ^{1}H and ^{13}C NMR Spectra of Compounds 4a-f



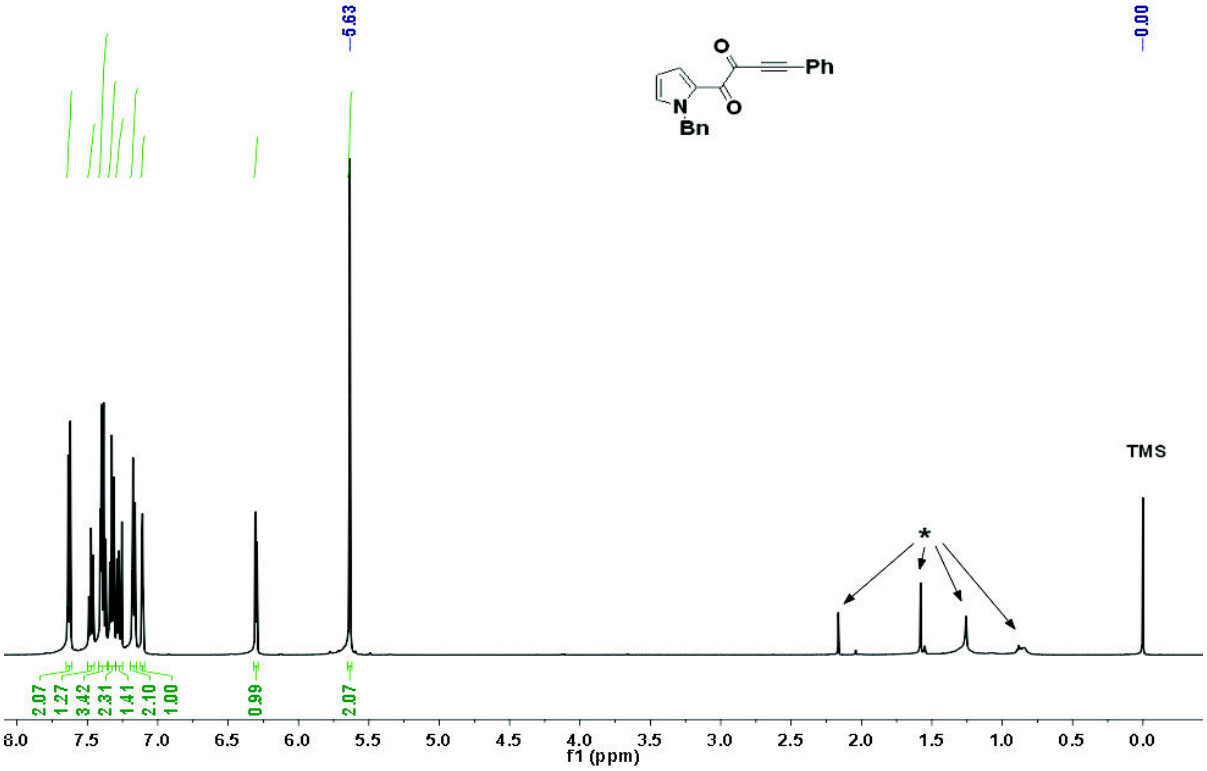
^{1}H NMR of **4a** in $CDCl_3$ at 299 K (δ in ppm).



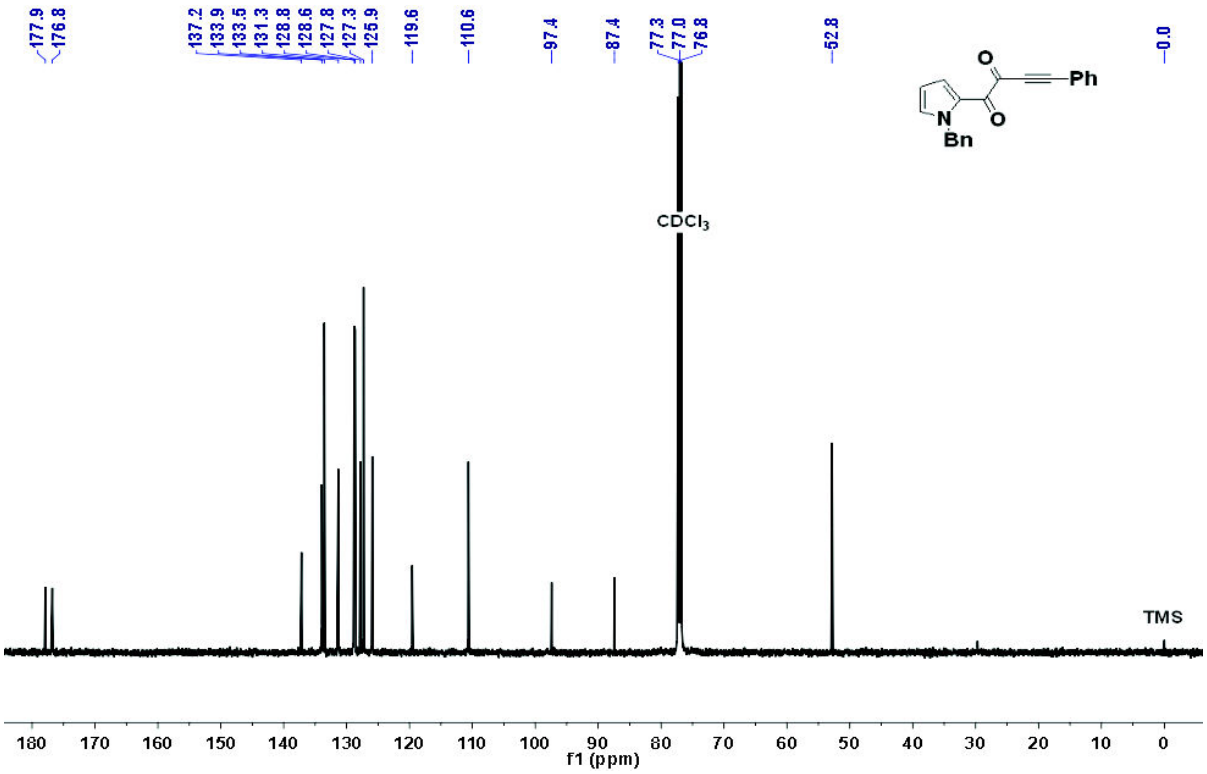
^{13}C NMR of **4a** in $CDCl_3$ at 299 K (δ in ppm).



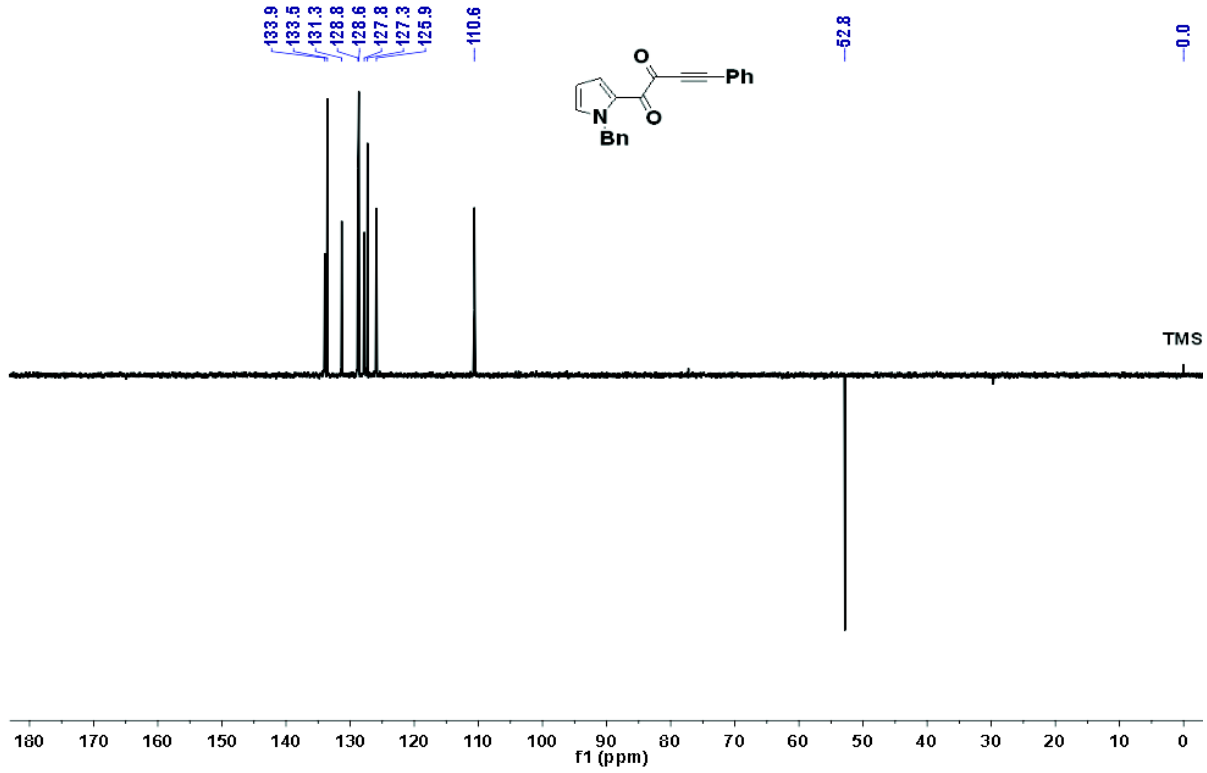
^{13}C DEPT 135-NMR of **4a** in $CDCl_3$ at 299 K (δ in ppm).



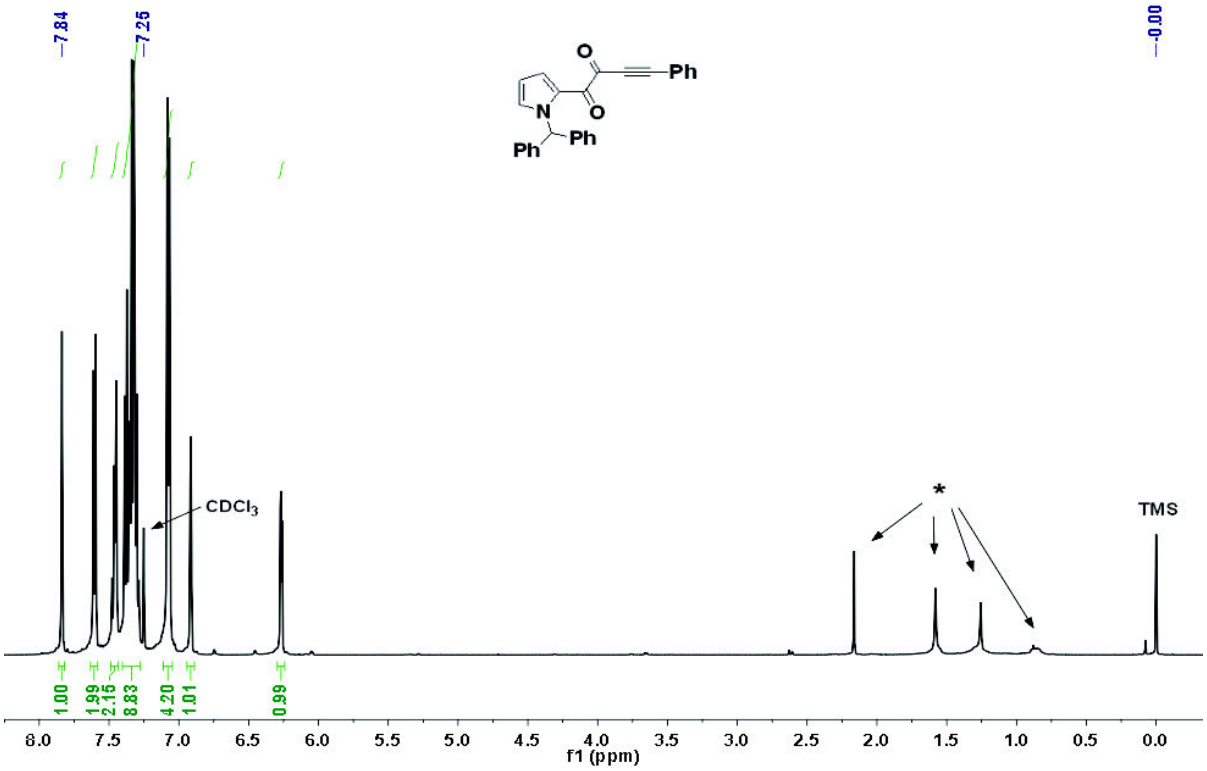
^{1}H NMR of **4b** in $CDCl_3$ at 298 K (δ in ppm). *Impurities from residual solvents.



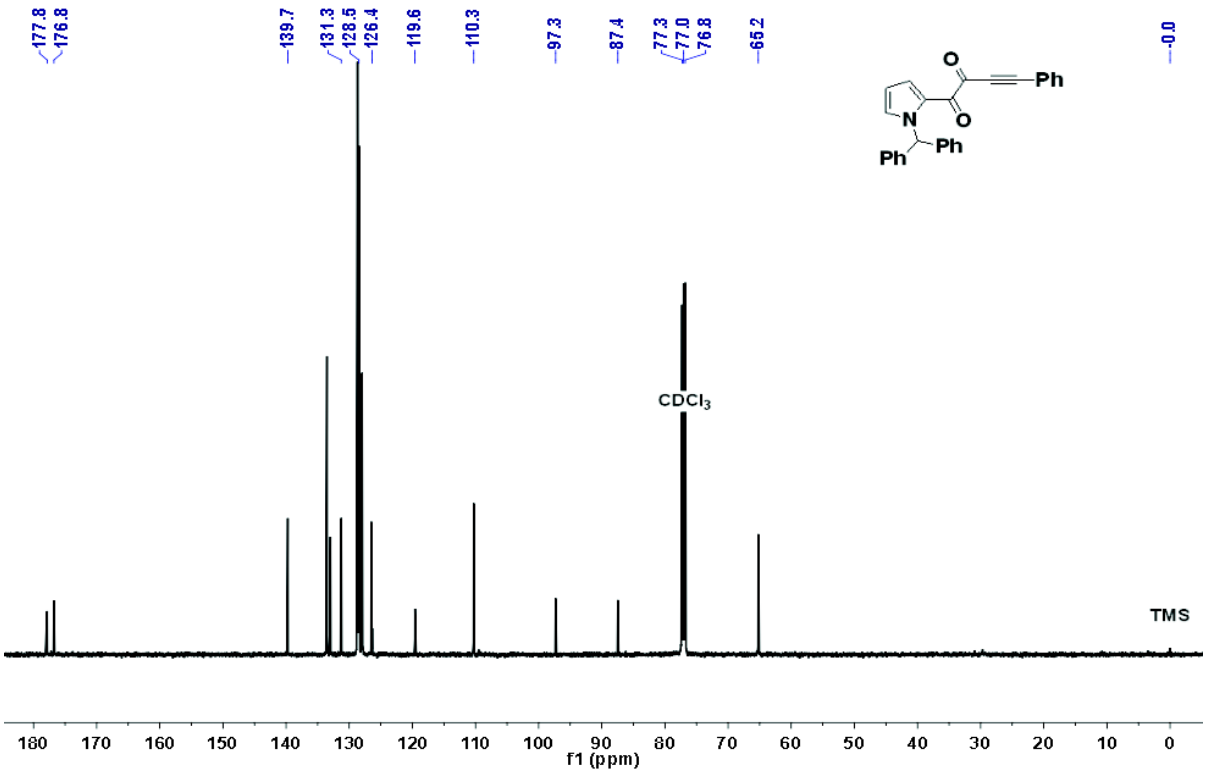
^{13}C NMR of **4b** in $CDCl_3$ at 298 K (δ in ppm).



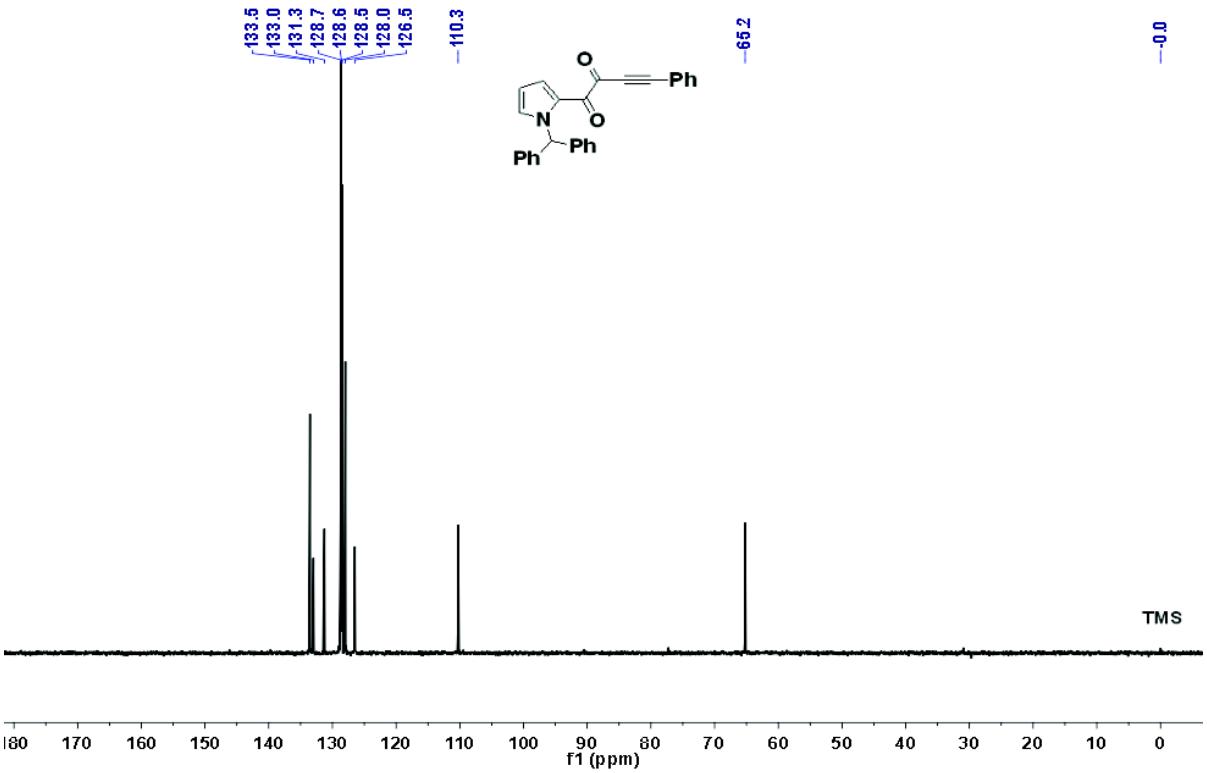
^{13}C DEPT 135-NMR of **4b** in $CDCl_3$ at 298 K (δ in ppm).



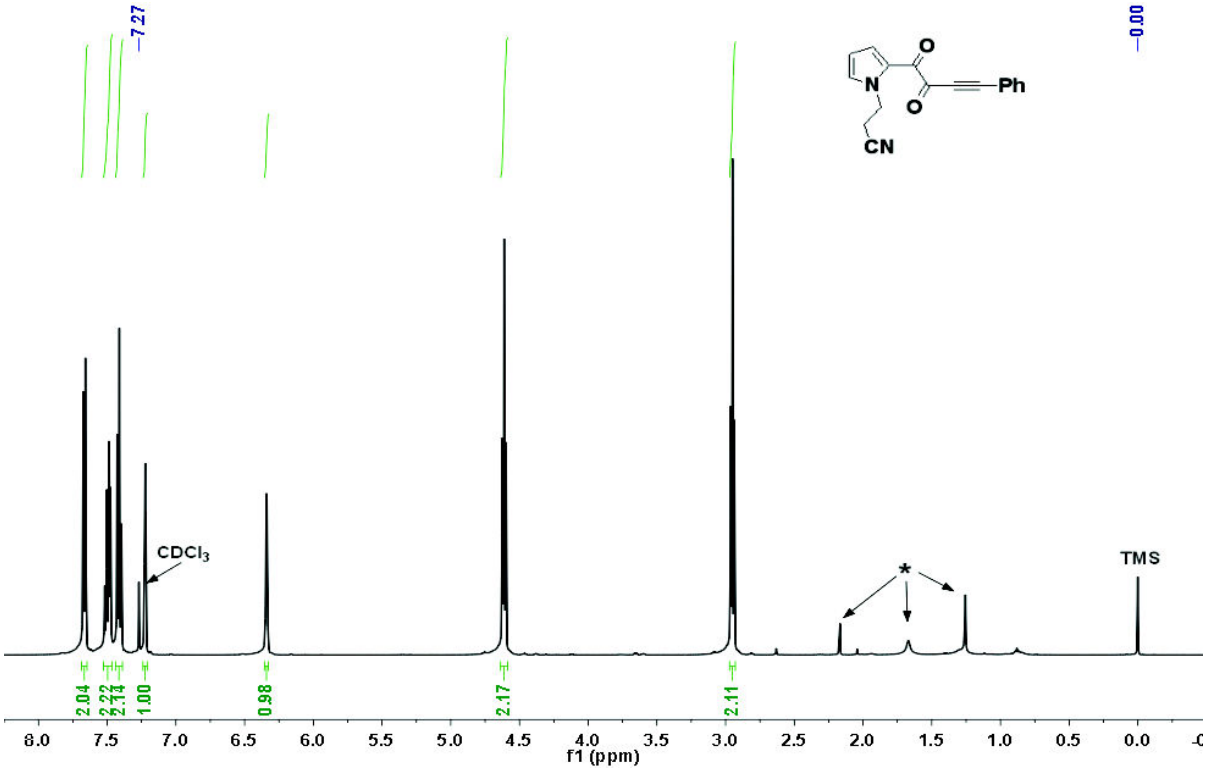
^{1}H NMR of **4c** in $CDCl_3$ at 298 K (δ in ppm). *Impurities from residual solvents.



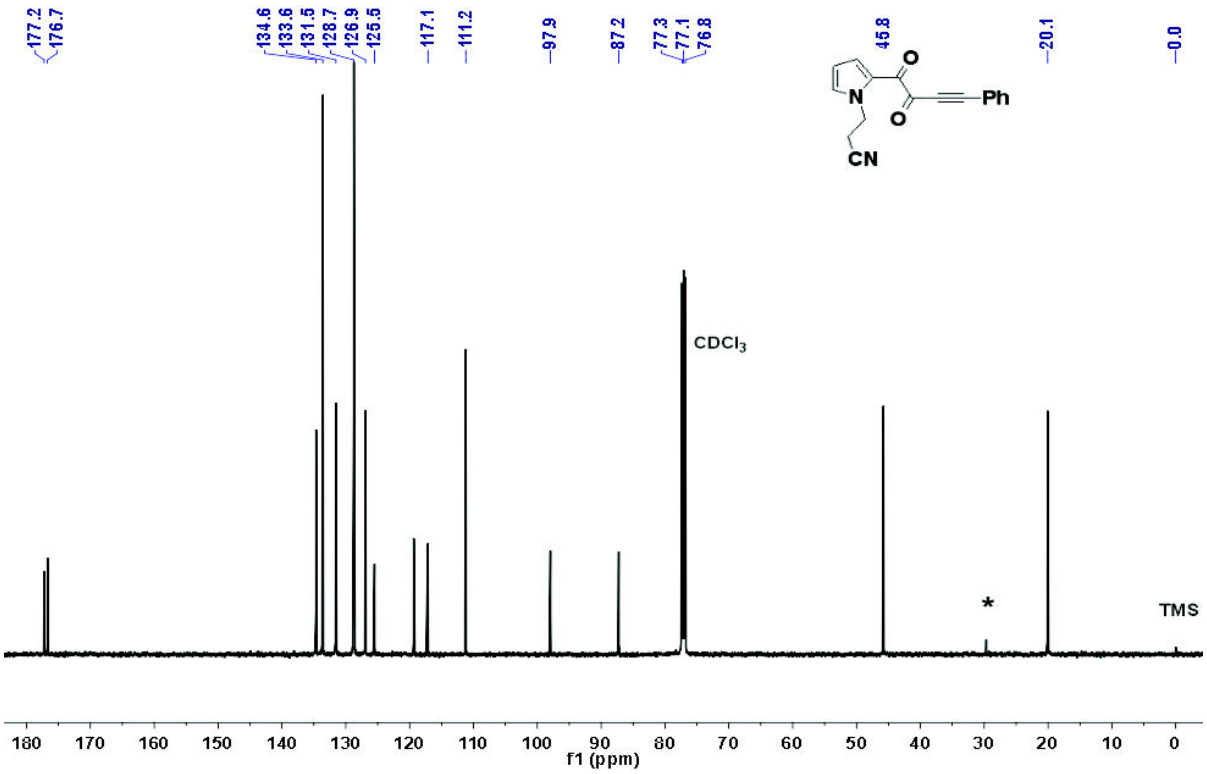
^{13}C NMR of **4c** in $CDCl_3$ at 298 K (δ in ppm). *Impurities from residual solvents.



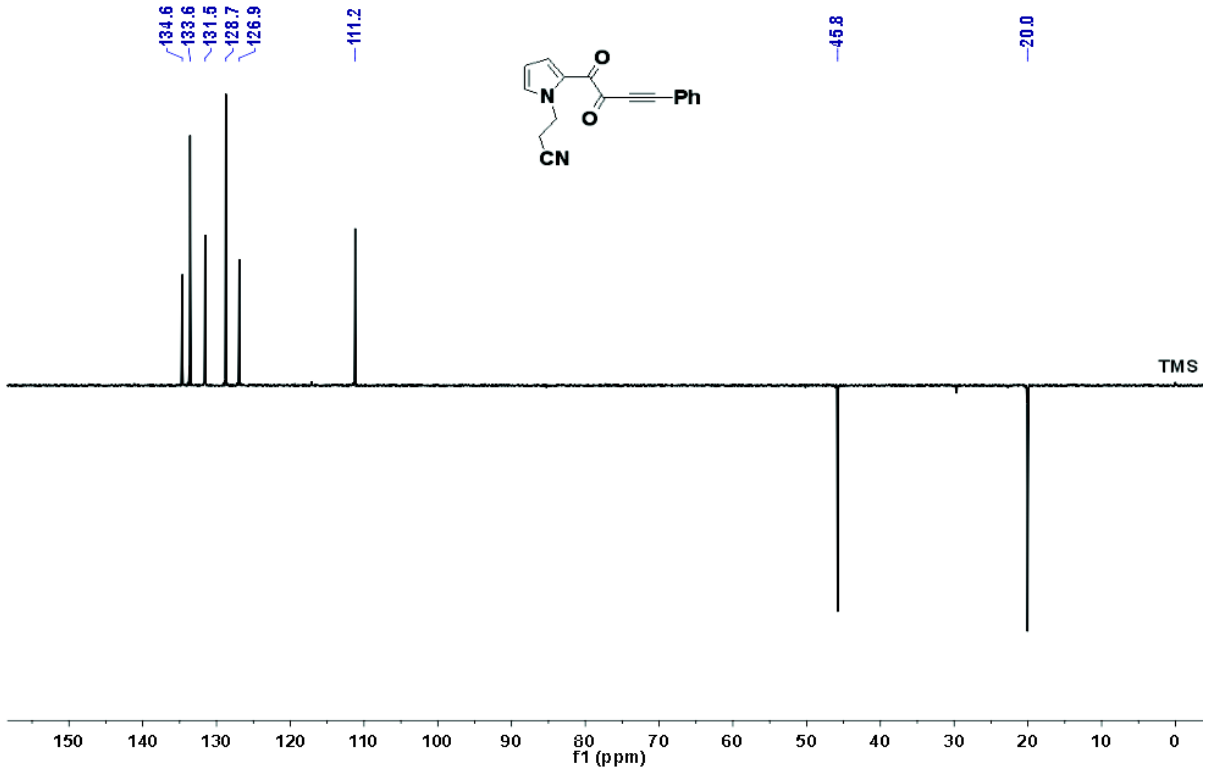
^{13}C DEPT 135-NMR of **4c** in $CDCl_3$ at 298 K (δ in ppm).



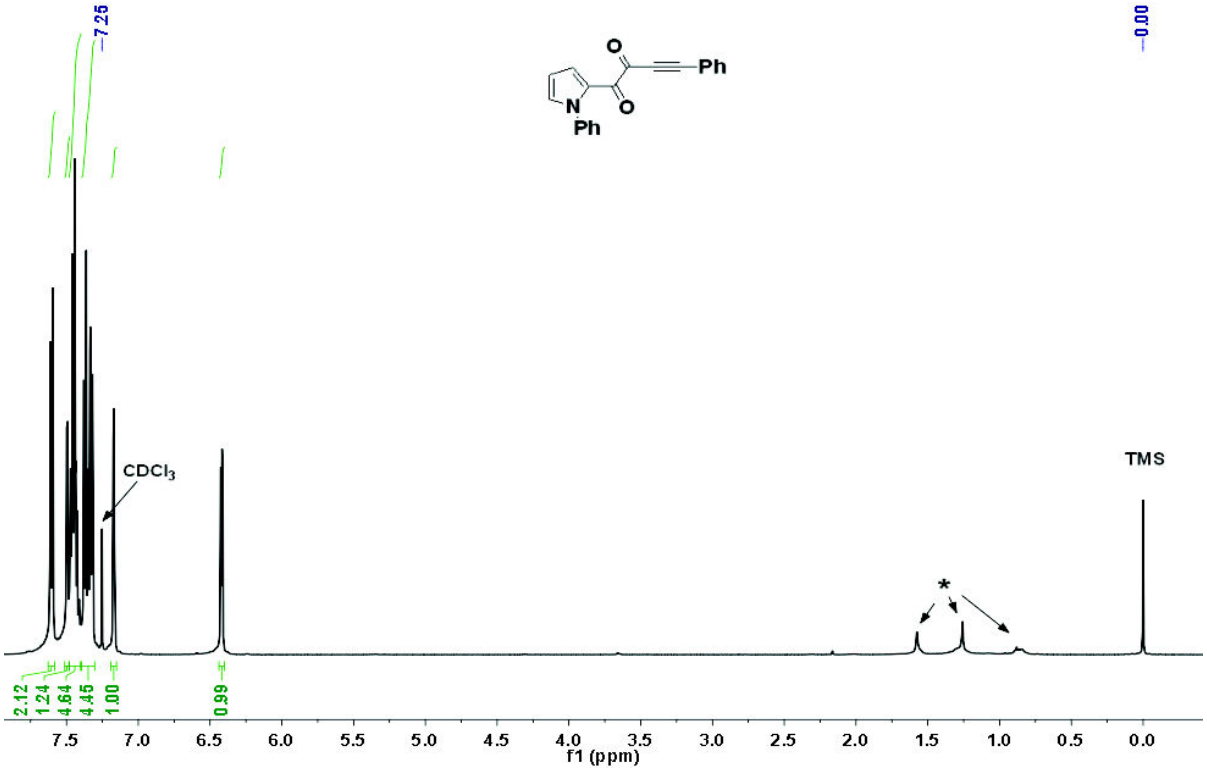
^{1}H NMR of **4d** in $CDCl_3$ at 297 K (δ in ppm). *Impurities from residual solvents.



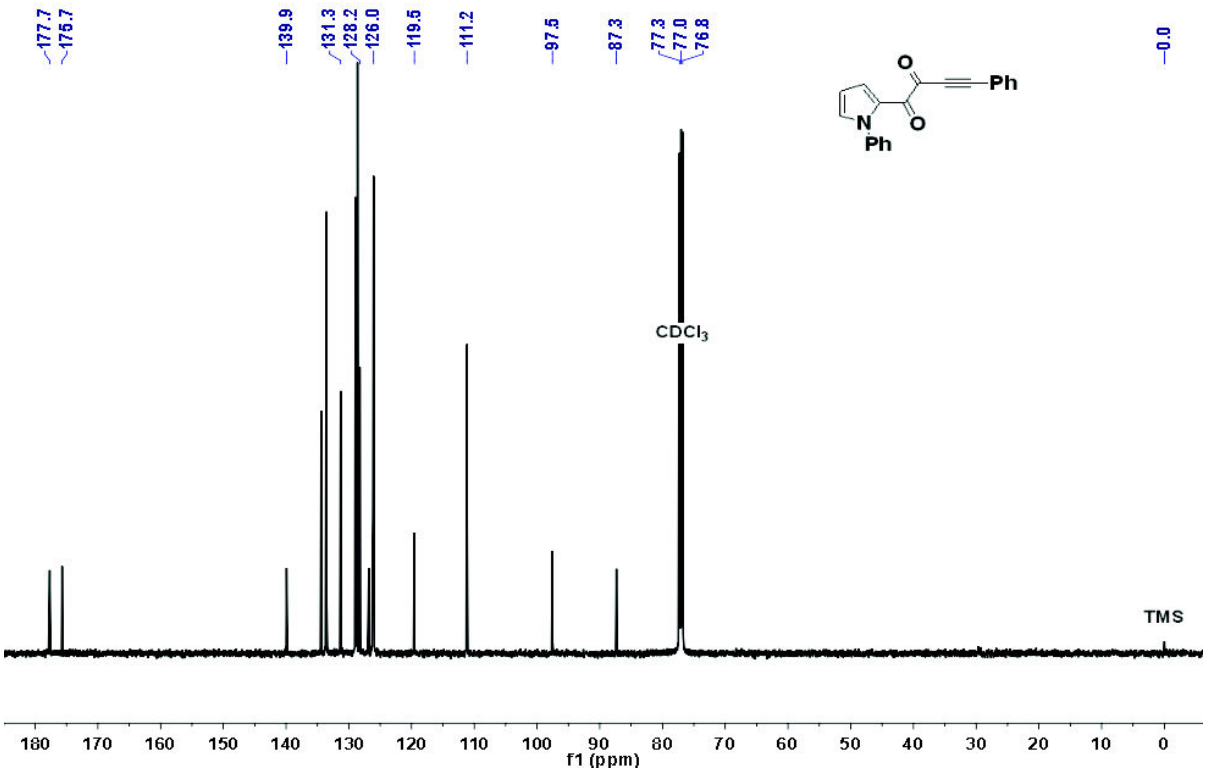
^{13}C NMR of **4d** in $CDCl_3$ at 298 K (δ in ppm). *Impurities from residual solvents.



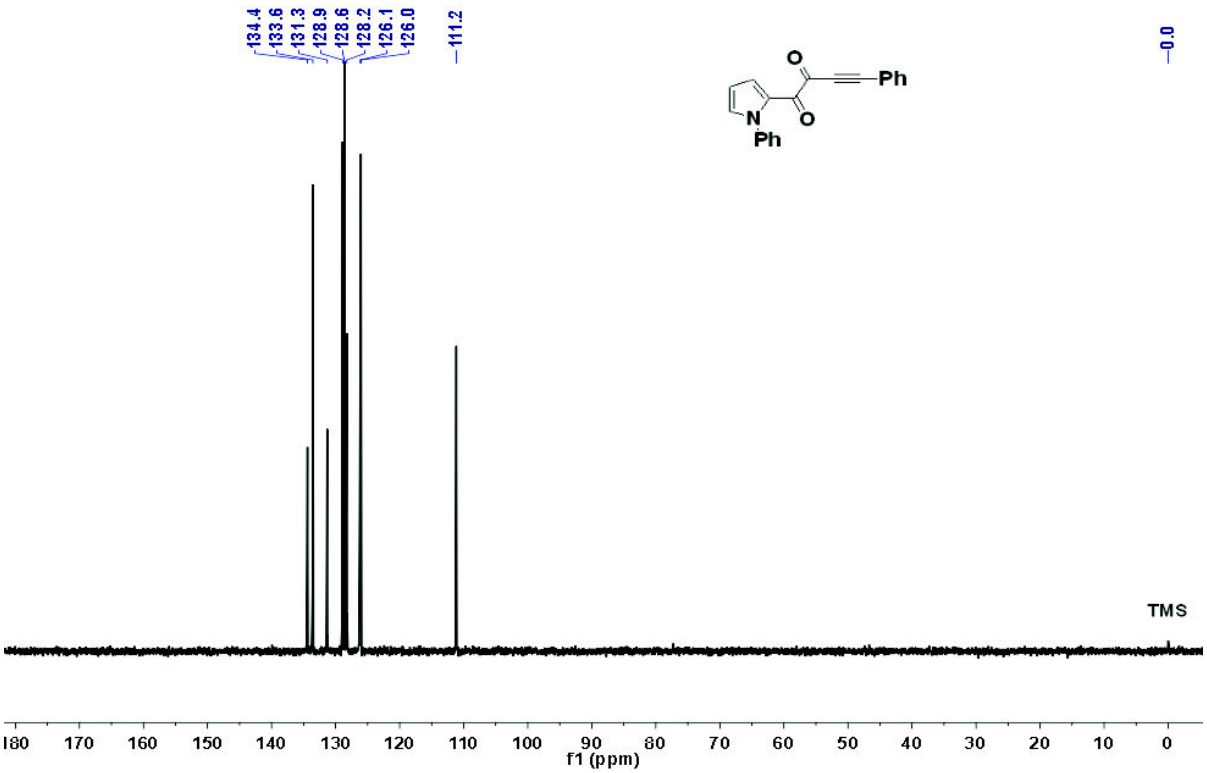
^{13}C DEPT 135-NMR of **4d** in $CDCl_3$ at 298 K (δ in ppm).



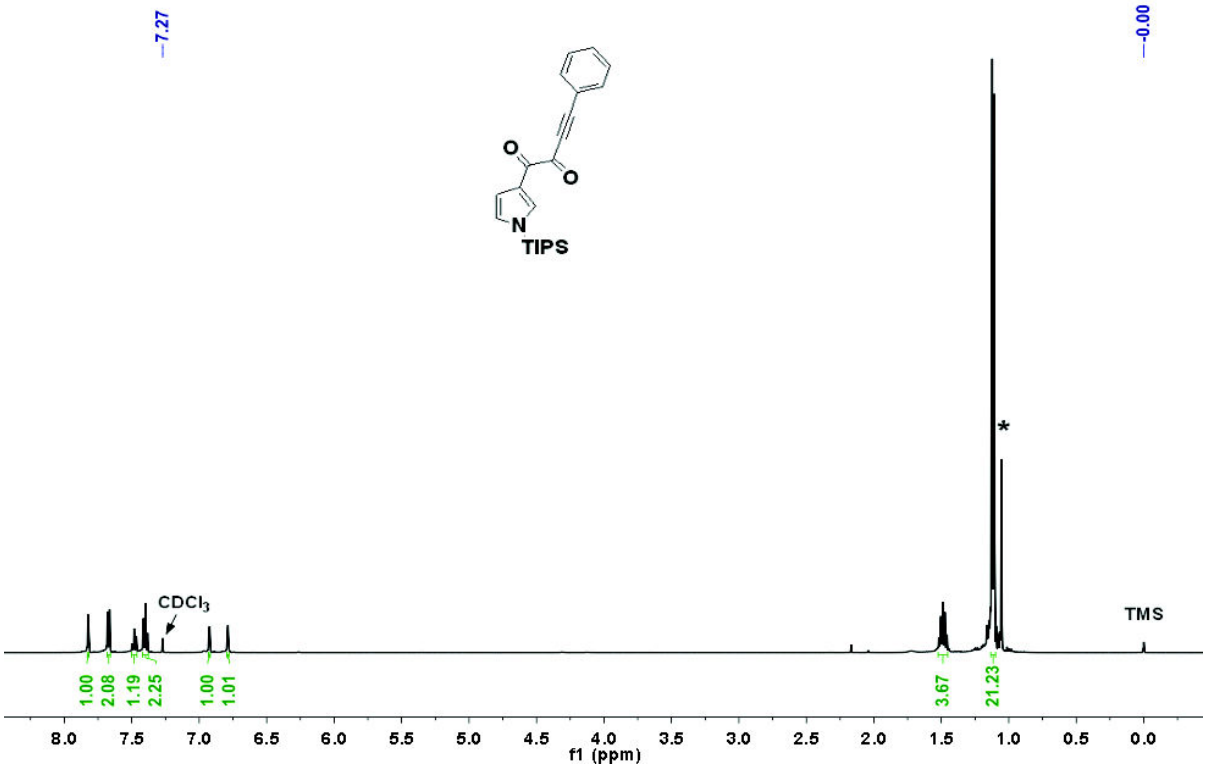
^{1}H NMR of **4e** in $CDCl_3$ at 298 K (δ in ppm). *Impurities from residual solvents.



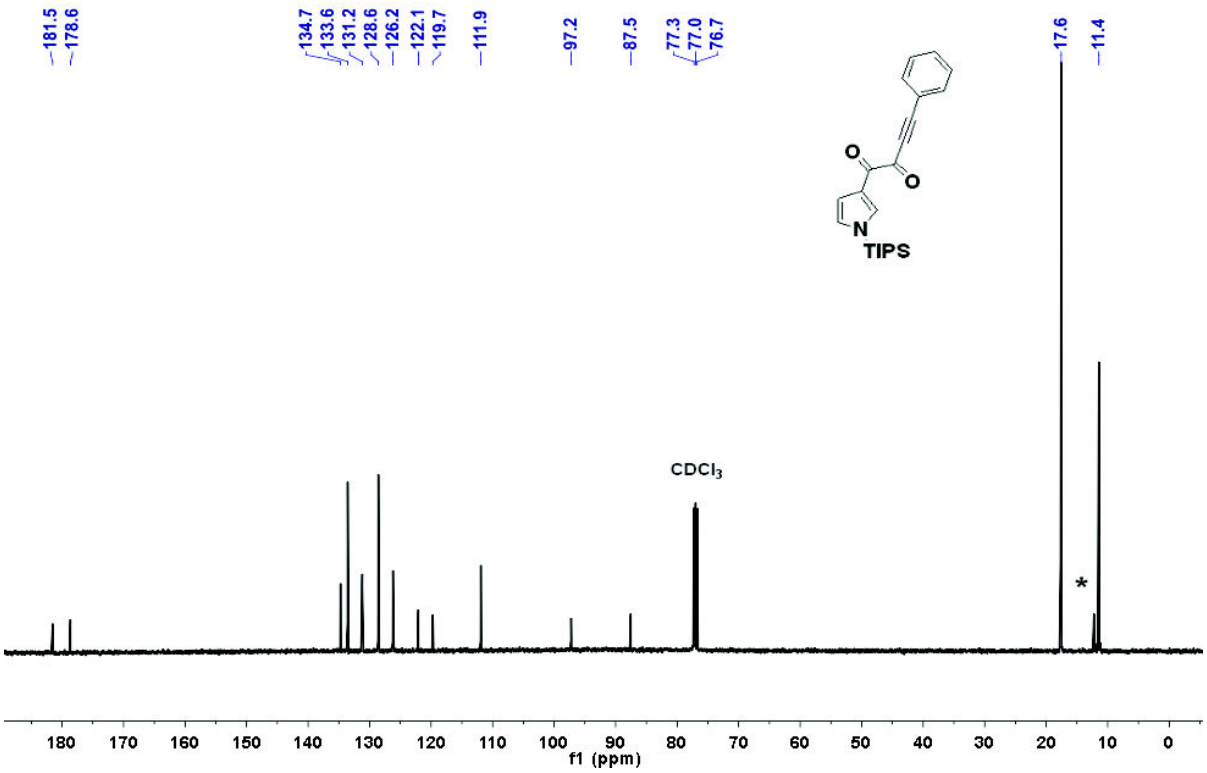
^{13}C NMR of **4e** in $CDCl_3$ at 298 K (δ in ppm).



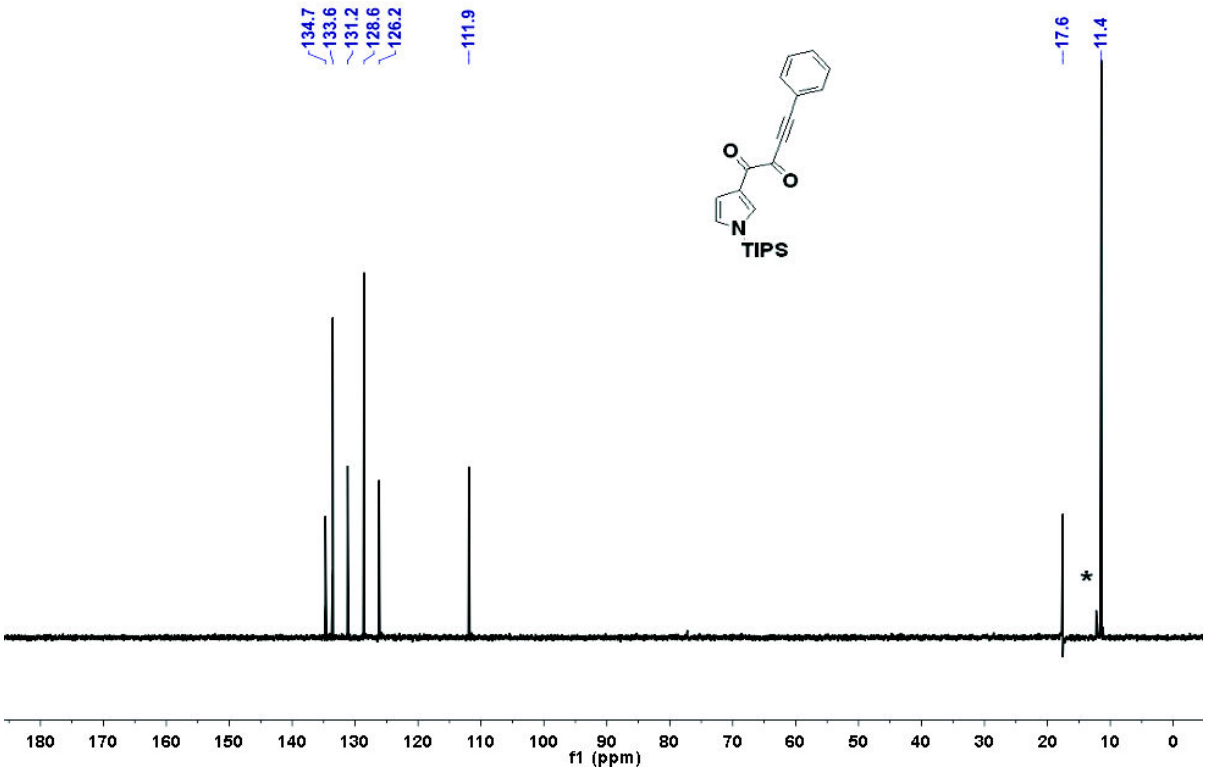
^{13}C DEPT 135-NMR of **4e** in $CDCl_3$ at 298 K (δ in ppm).



^{1}H NMR of **4f** in $CDCl_3$ at 298 K (δ in ppm). *Impurities from residual solvents.

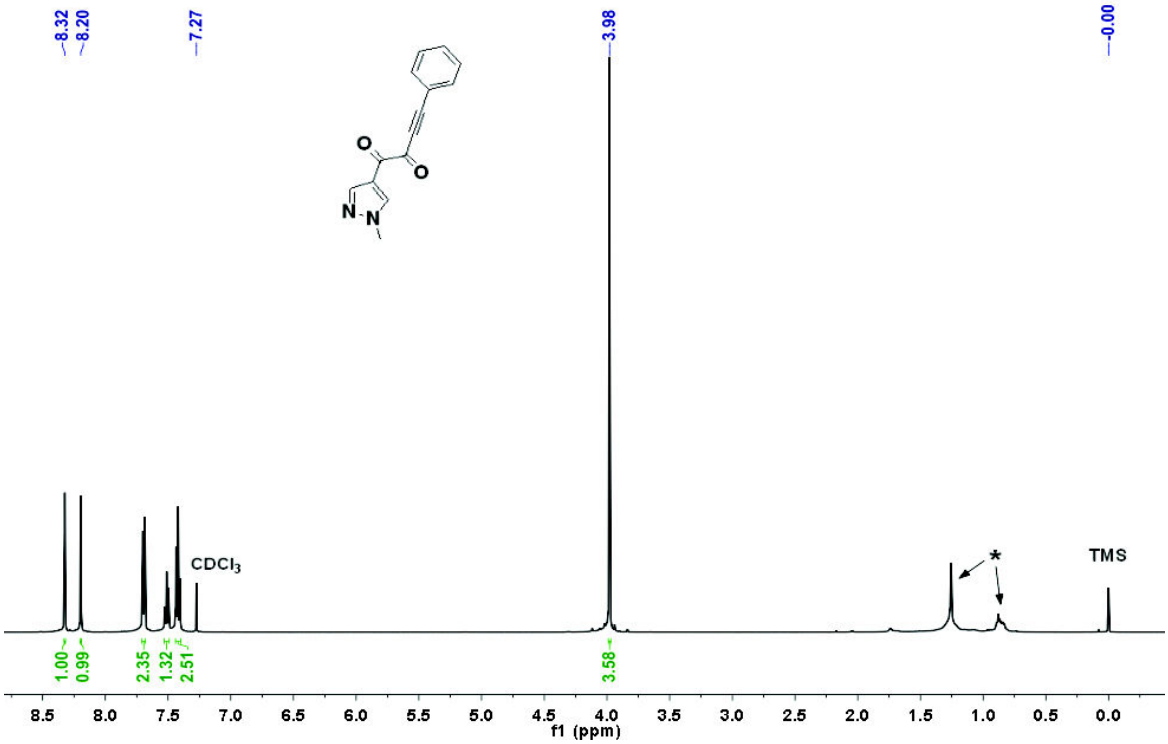


^{13}C NMR of **4f** in $CDCl_3$ at 298 K (δ in ppm). *Impurities from residual solvents.

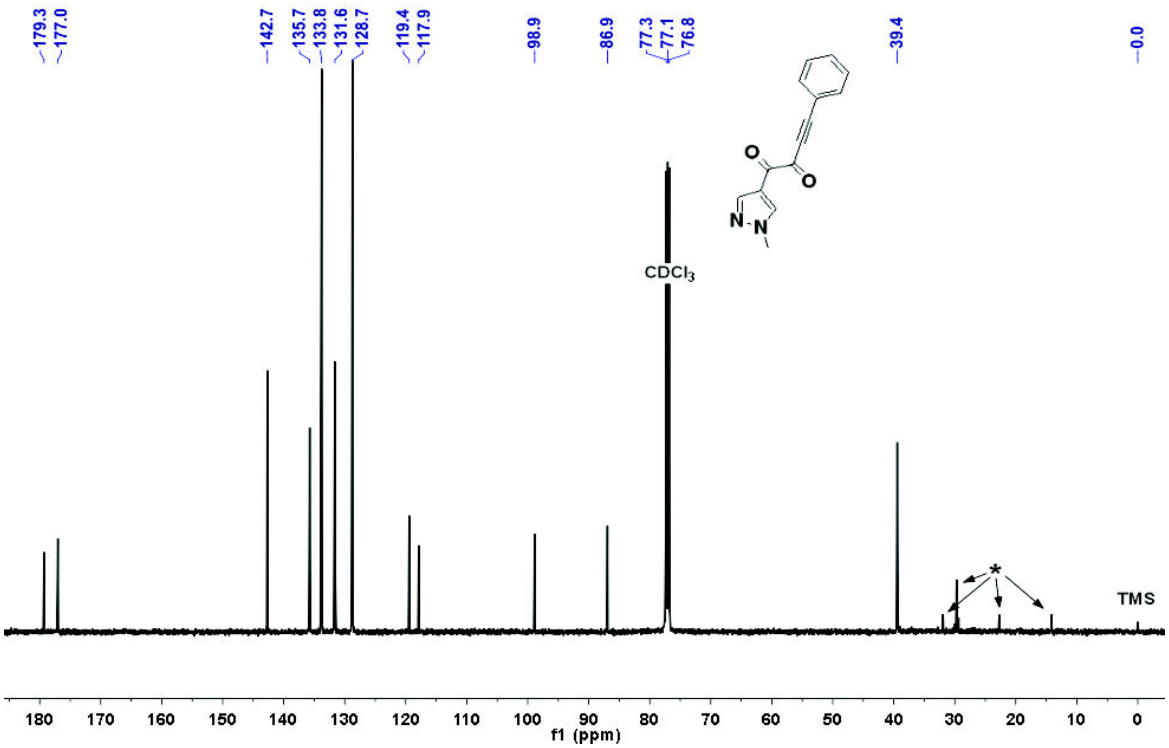


^{13}C DEPT 135-NMR of **4f** in $CDCl_3$ at 297 K (δ in ppm). *Impurities from residual solvents.

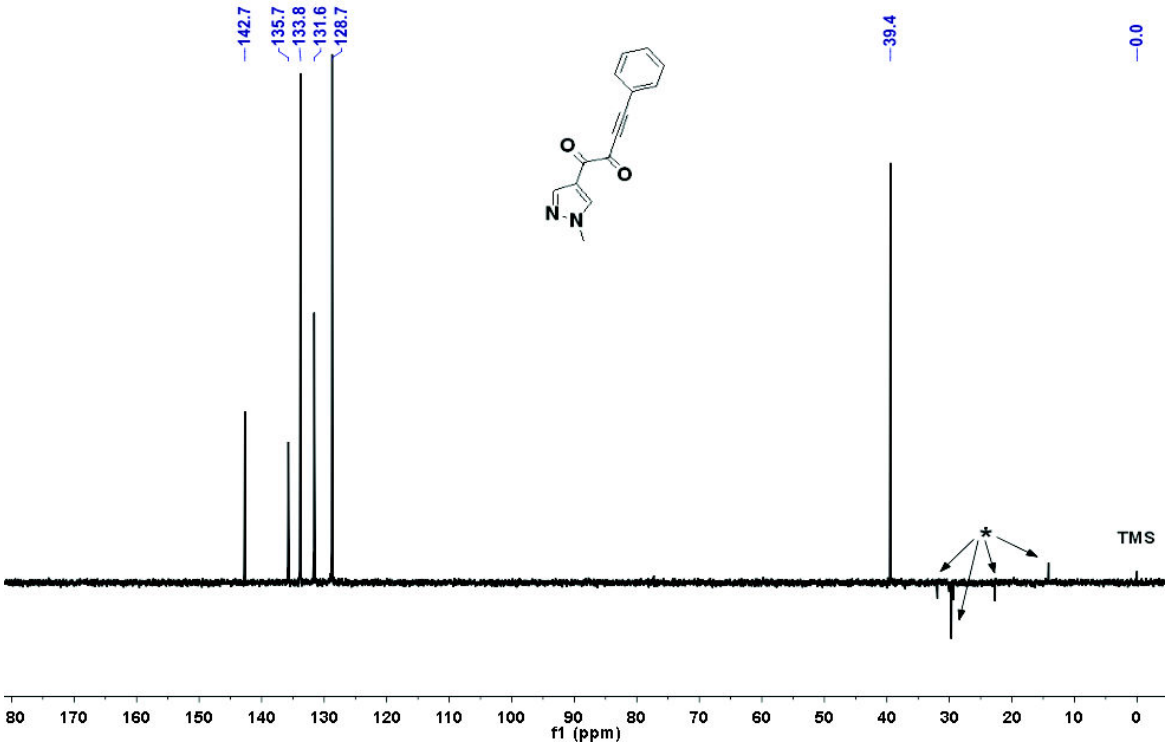
6. ^{1}H and ^{13}C NMR Spectra of Compounds 5a-e



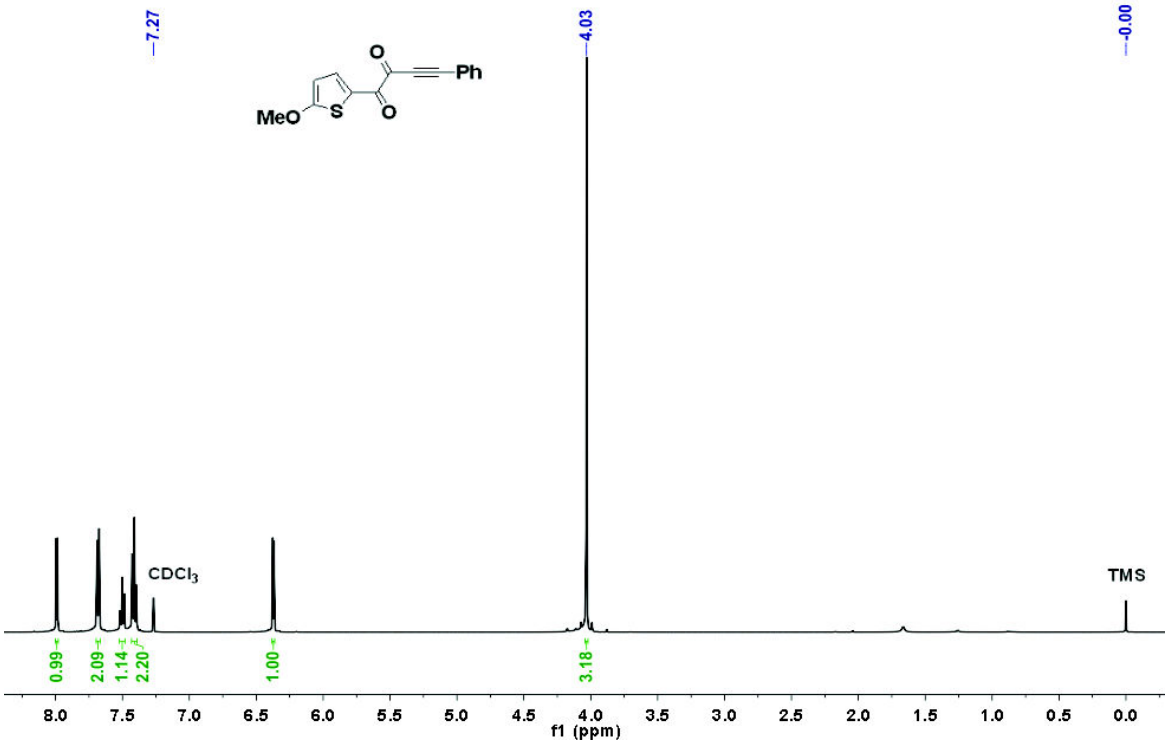
^{1}H NMR of **5a** in $CDCl_3$ at 295 K (δ in ppm). *Impurities from residual solvents.



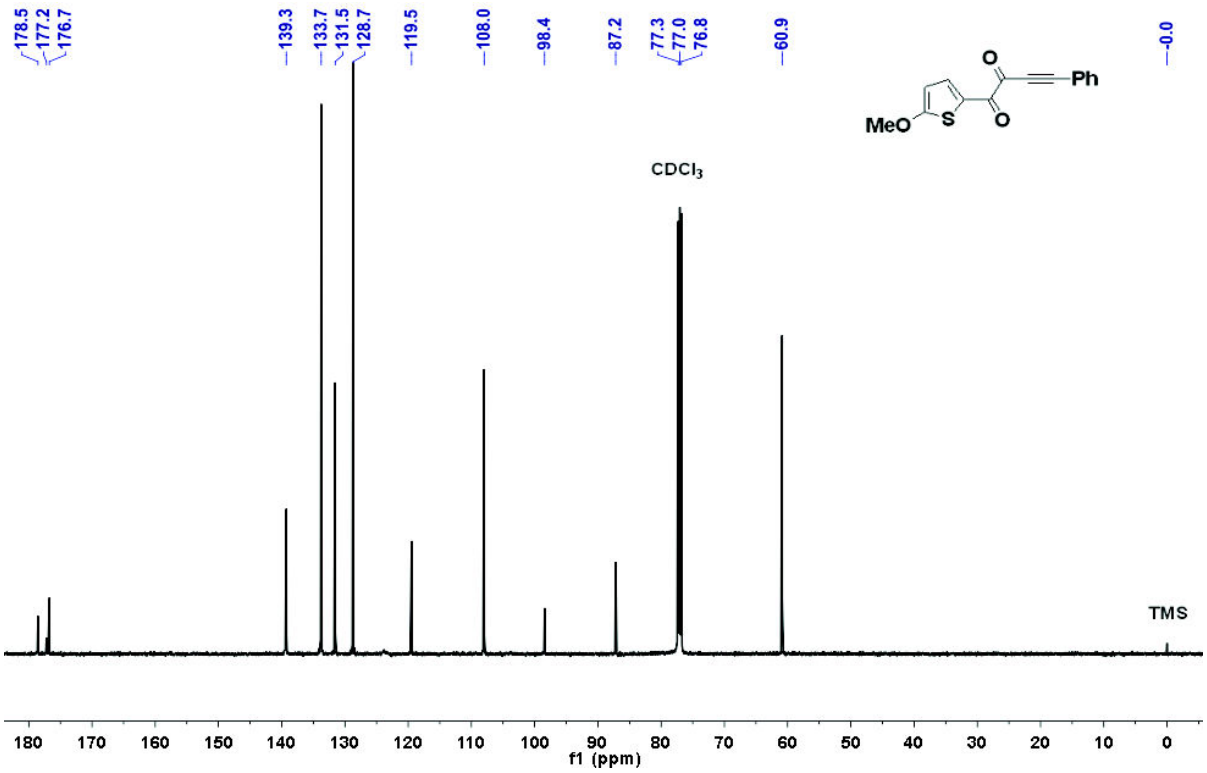
^{13}C NMR of **5a** in $CDCl_3$ at 296 K (δ in ppm). *Impurities from residual solvents.



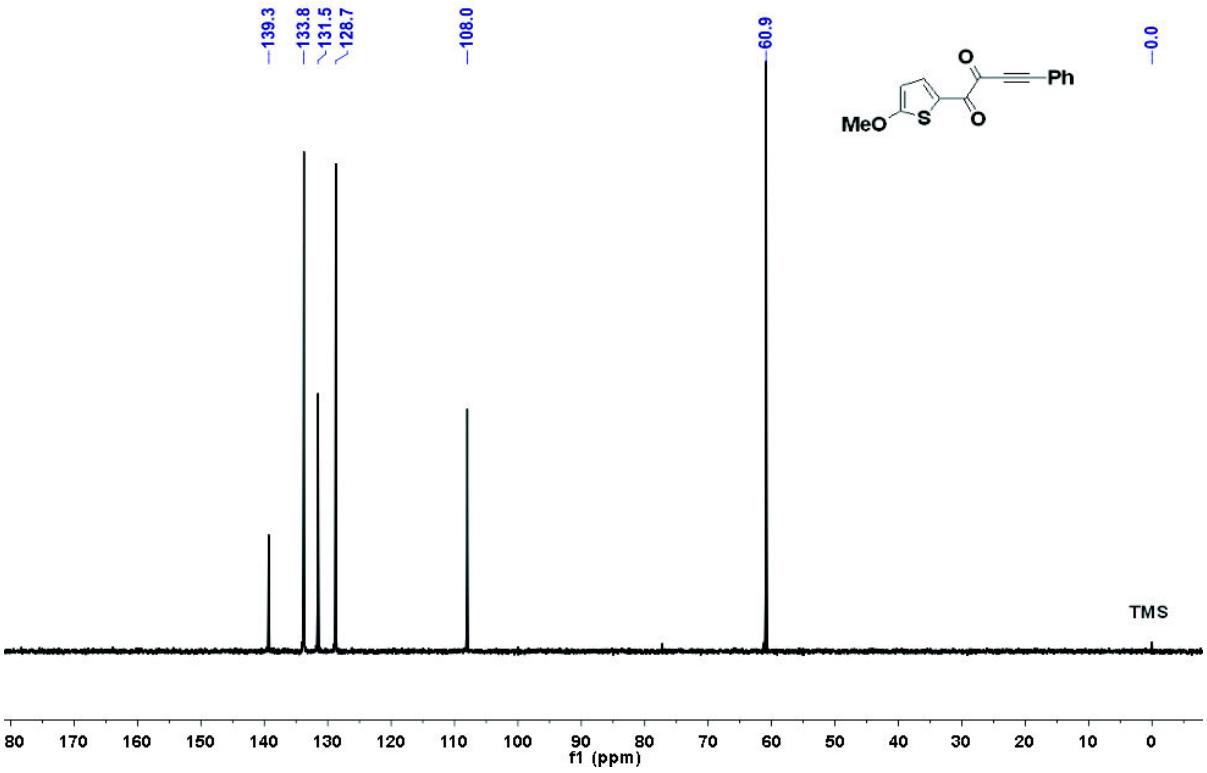
^{13}C DEPT 135-NMR of **5a** in $CDCl_3$ at 295 K (δ in ppm). *Impurities from residual solvents.



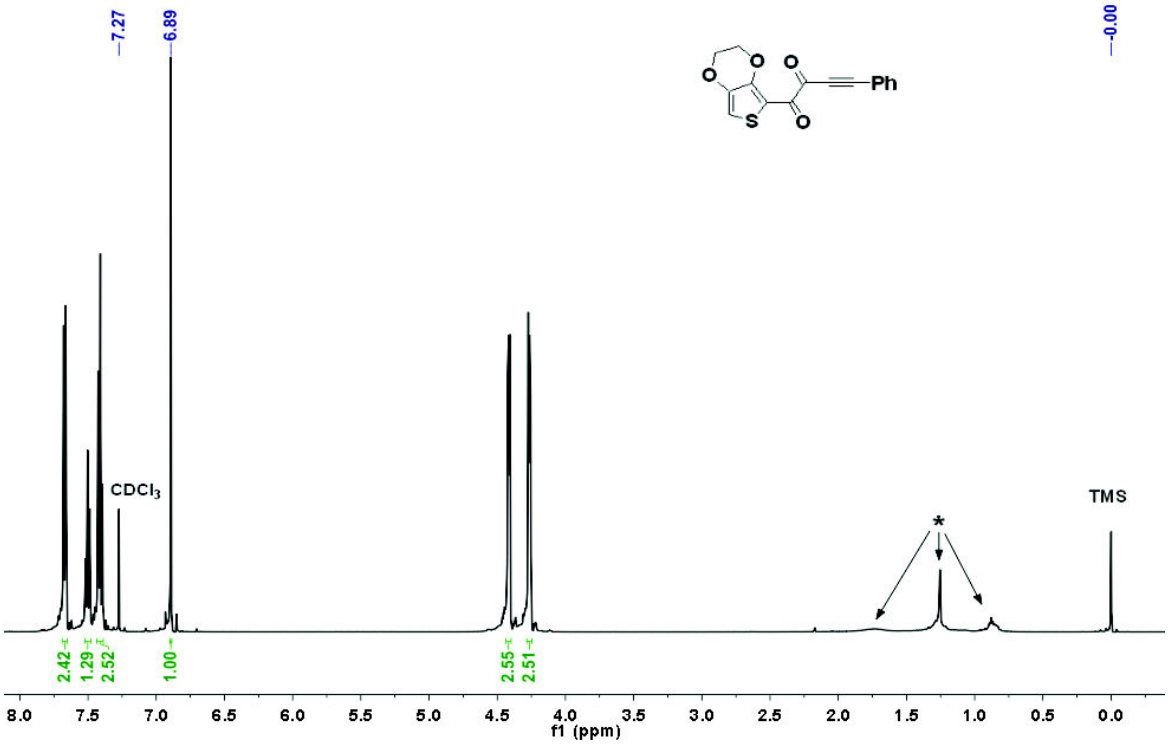
^{1}H NMR of **5b** in $CDCl_3$ at 296 K (δ in ppm).



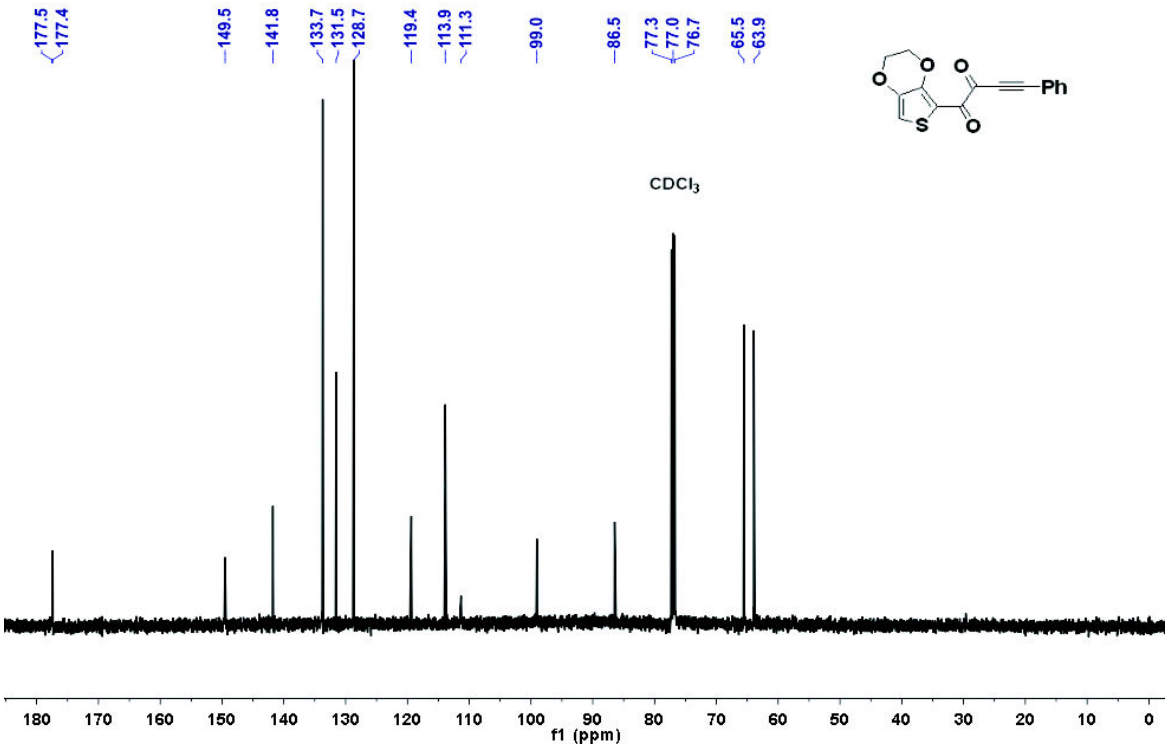
^{13}C NMR of **5b** in $CDCl_3$ at 296 K (δ in ppm).



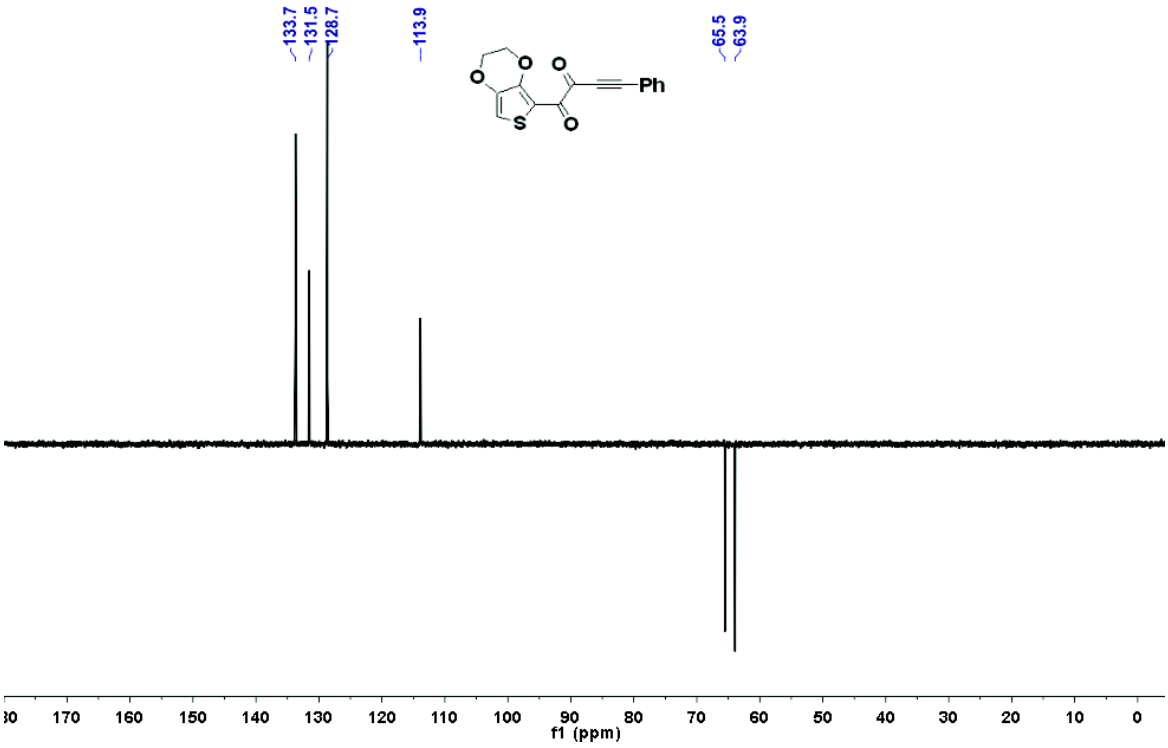
^{13}C DEPT 135-NMR of **5b** in $CDCl_3$ at 296 K (δ in ppm).



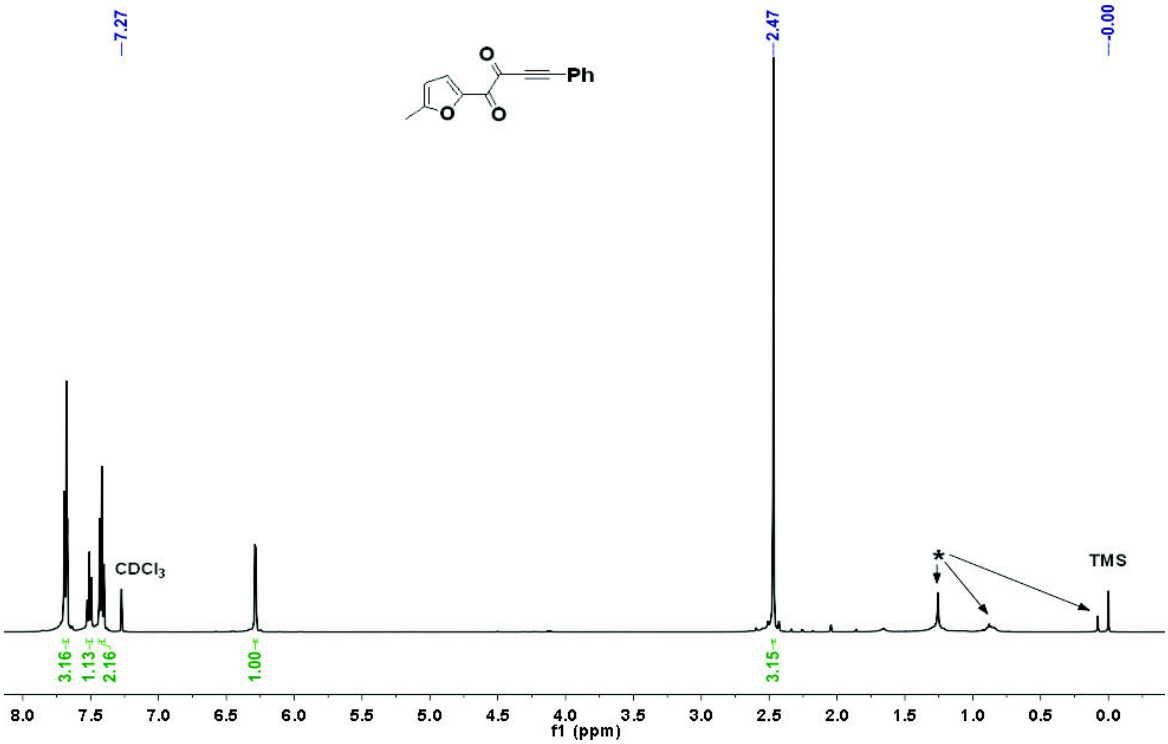
^{1}H NMR of **5c** in $CDCl_3$ at 296 K (δ in ppm). *Impurities from residual solvents.



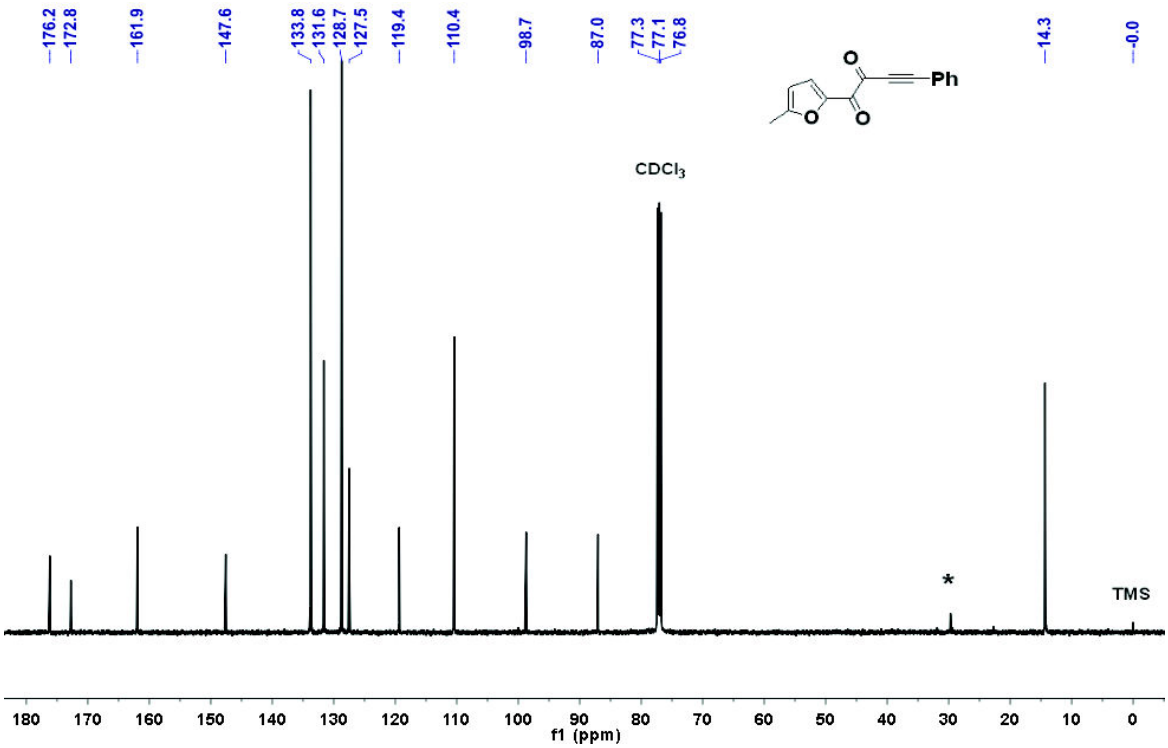
^{13}C NMR of **5c** in $CDCl_3$ at 296 K (δ in ppm).



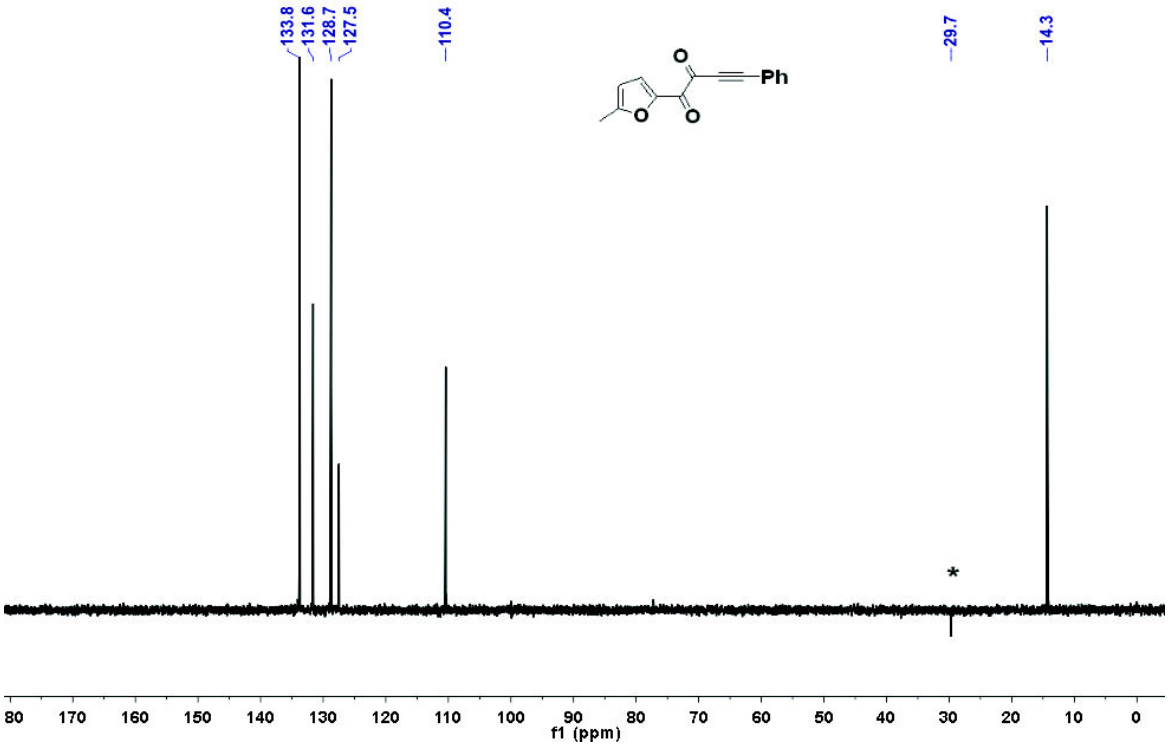
^{13}C DEPT 135-NMR of **5c** in $CDCl_3$ at 296 K (δ in ppm).



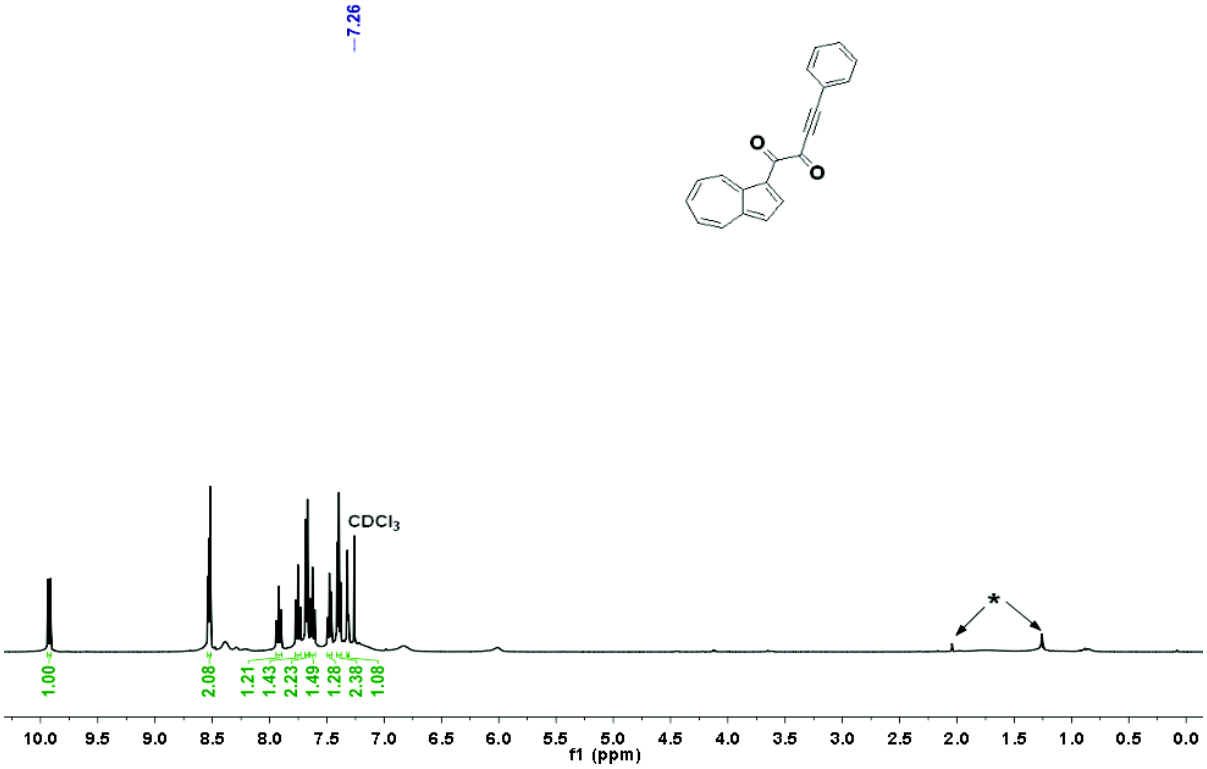
^{1}H NMR of **5d** in $CDCl_3$ at 295 K (δ in ppm). *Impurities from residual solvents.



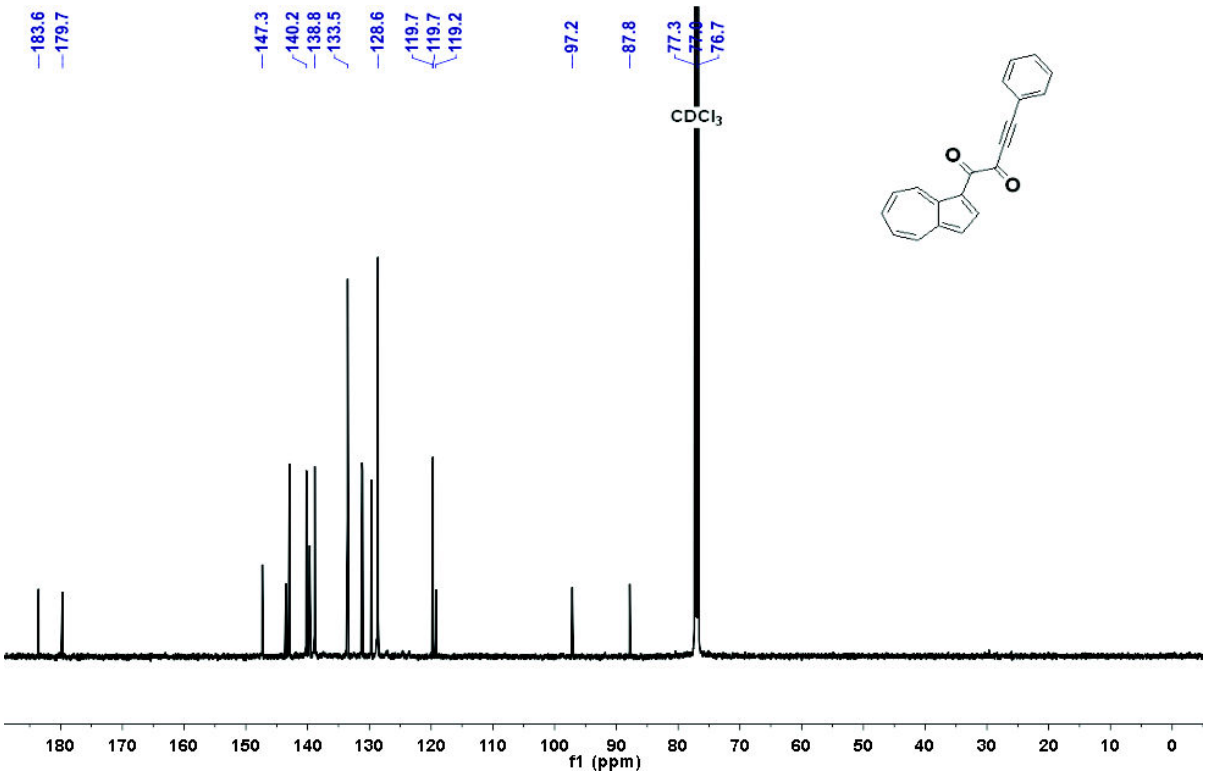
^{13}C NMR of **5d** in $CDCl_3$ at 296 K (δ in ppm). *Impurities from residual solvents.



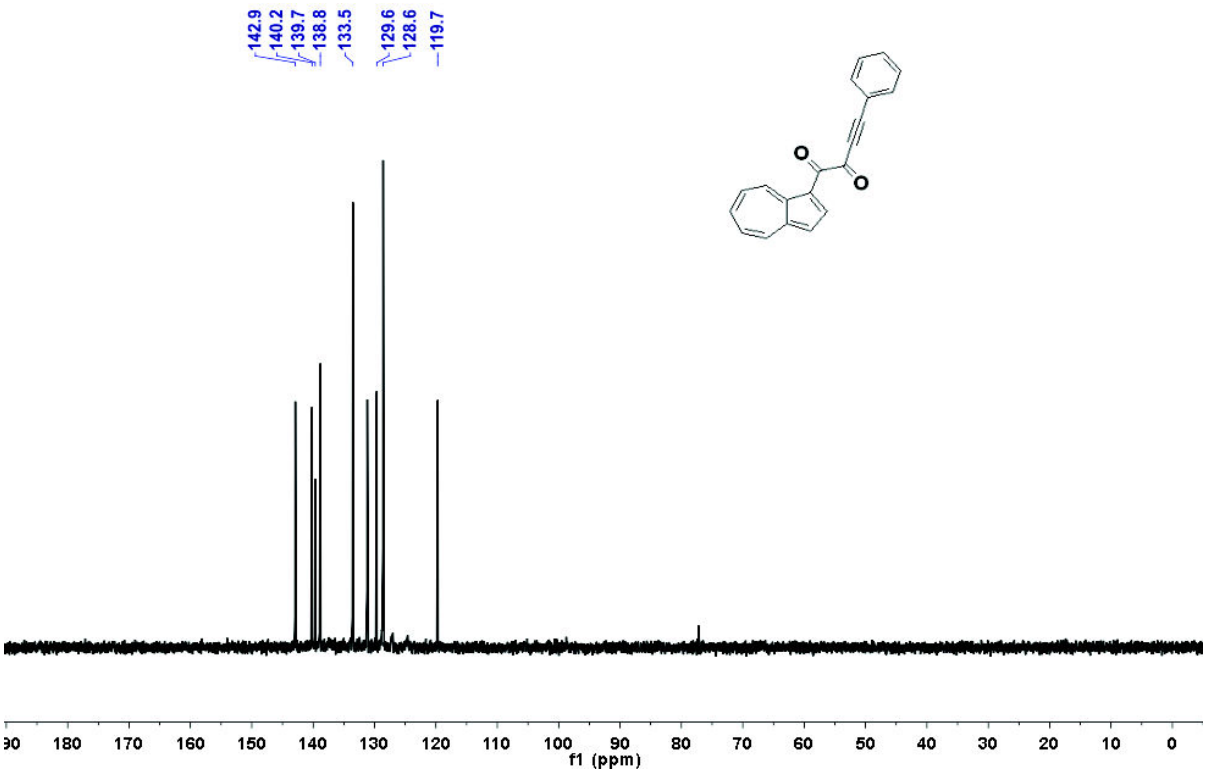
^{13}C DEPT 135-NMR of **5d** in $CDCl_3$ at 295 K (δ in ppm). *Impurities from residual solvents.



^{1}H NMR of **5e** in $CDCl_3$ at 298 K (δ in ppm). *Impurities from residual solvents.

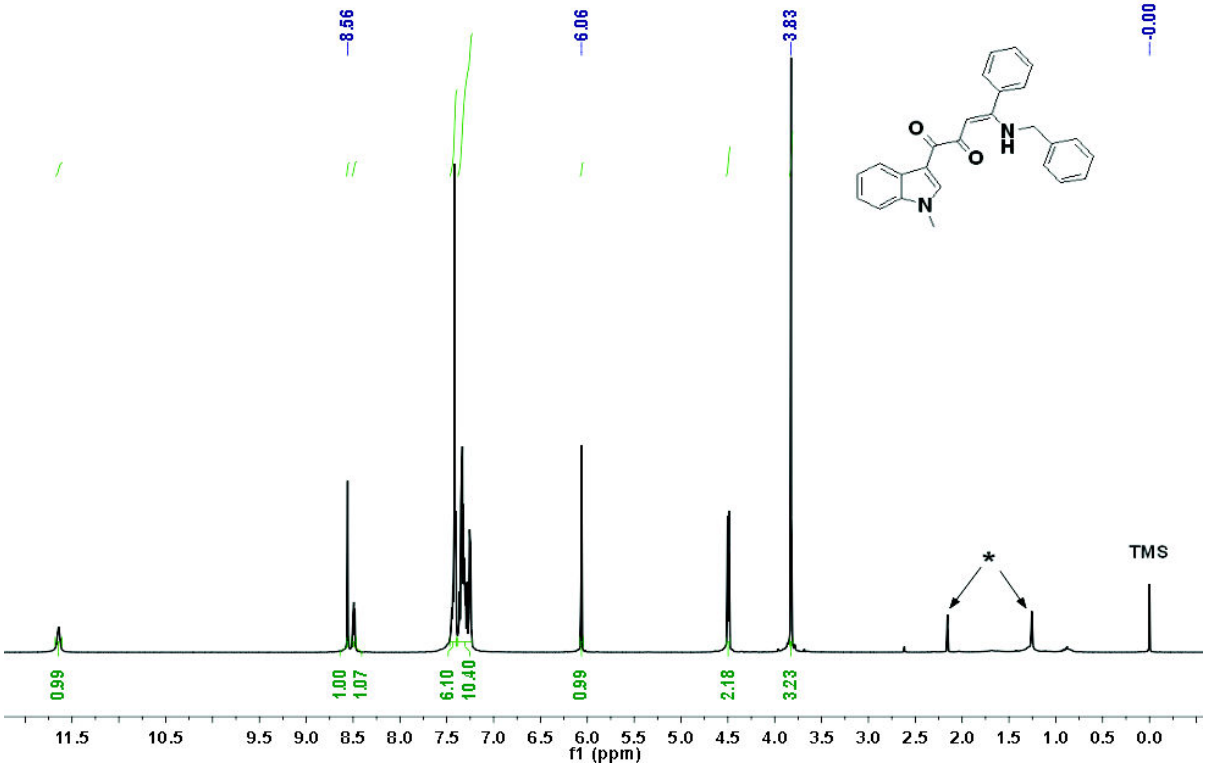


^{13}C NMR of **5e** in $CDCl_3$ at 298 K (δ in ppm).

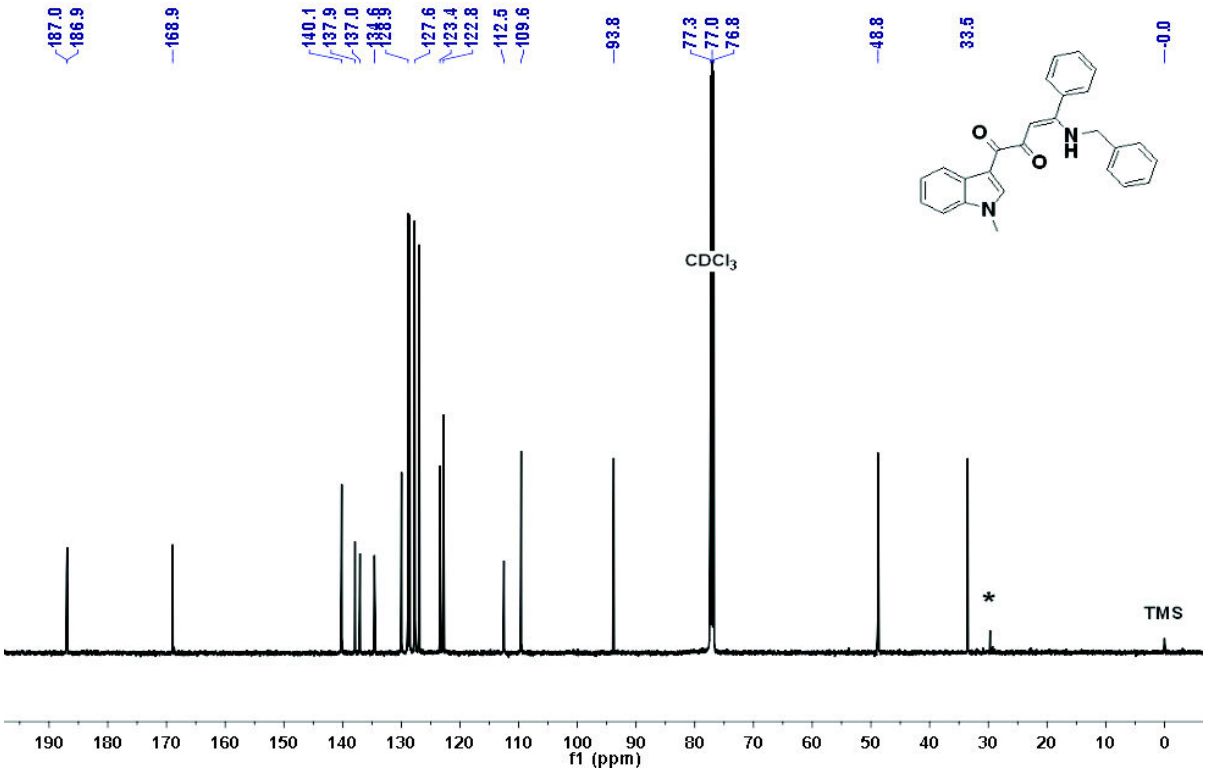


^{13}C DEPT 135-NMR of **5e** in $CDCl_3$ at 298 K (δ in ppm).

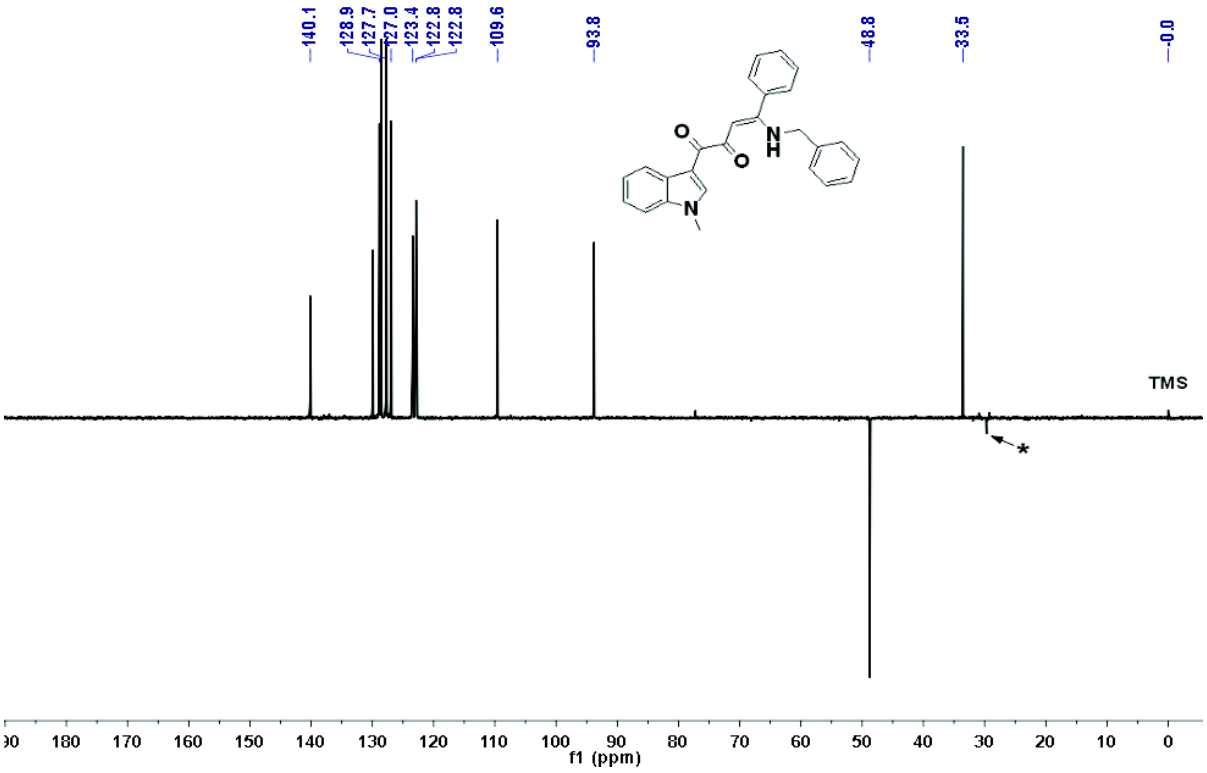
7. ^{1}H and ^{13}C NMR Spectra of Compounds 6, 7 and 9



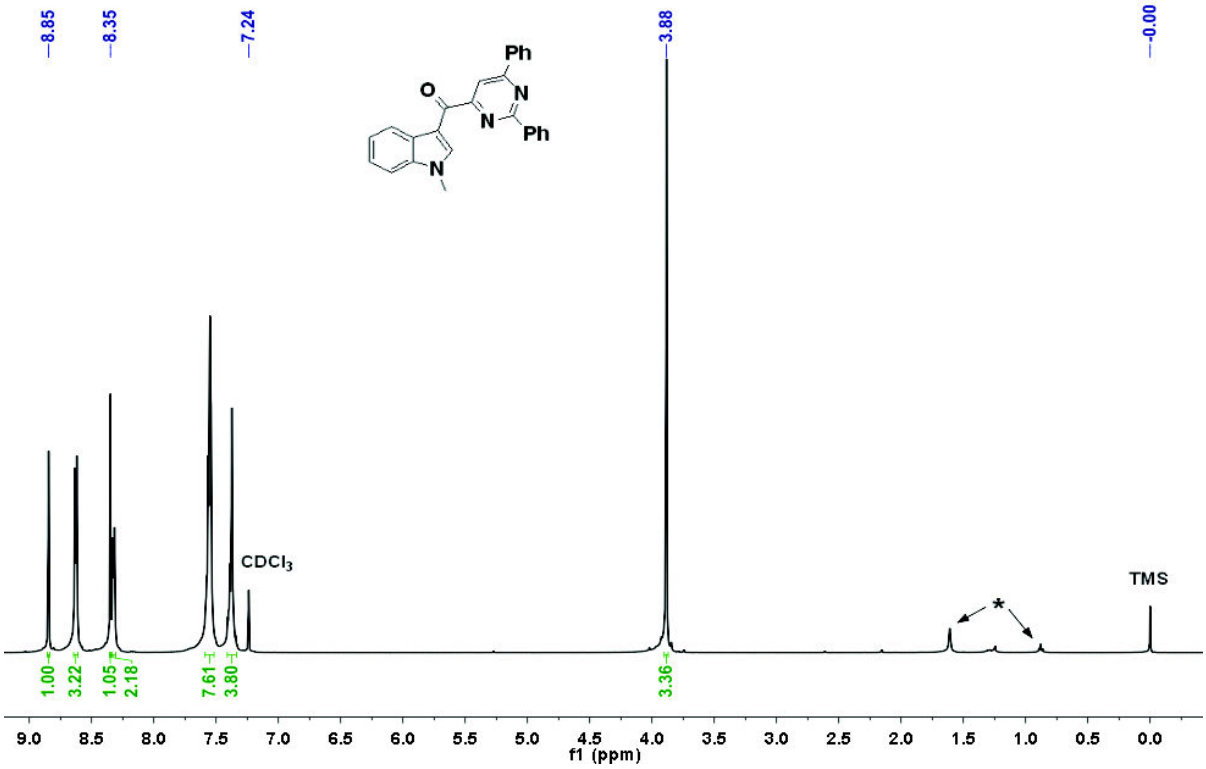
^{1}H NMR of **6** in $CDCl_3$ at 298 K (δ in ppm). *Impurities from residual solvents.



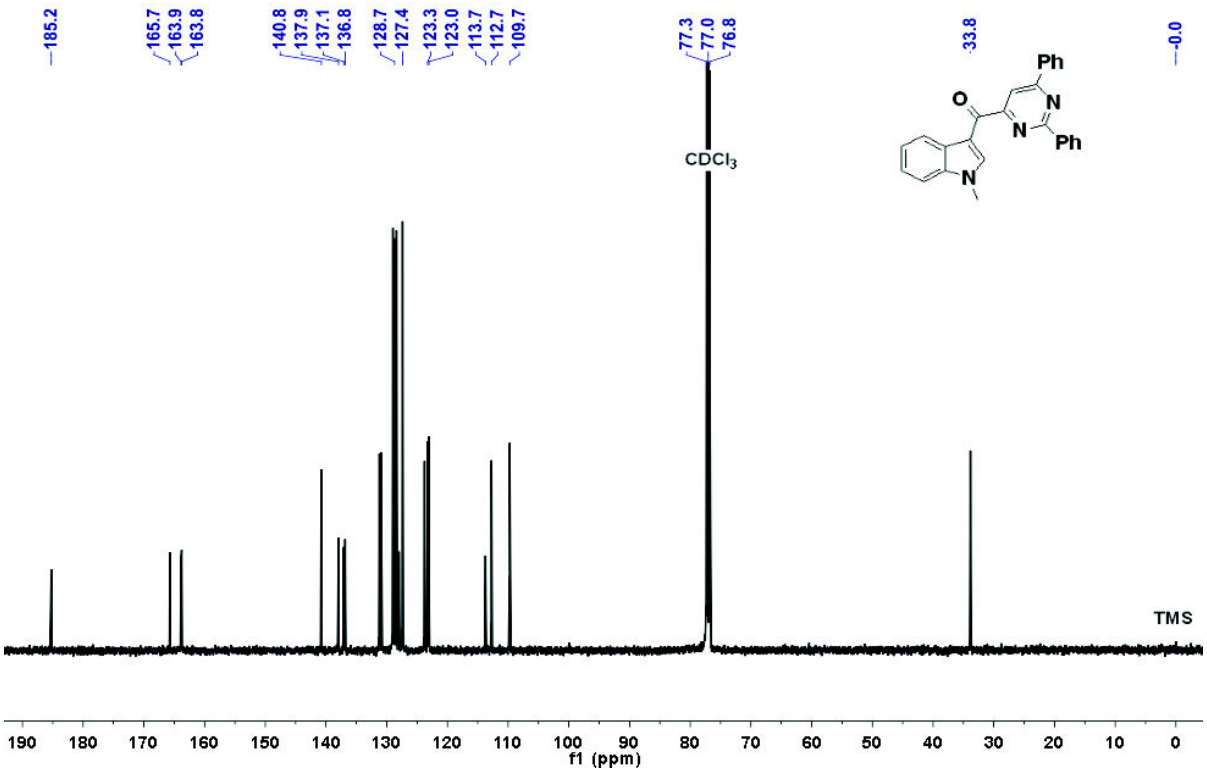
^{13}C NMR of **6** in $CDCl_3$ at 299 K (δ in ppm). *Impurities from residual solvents.



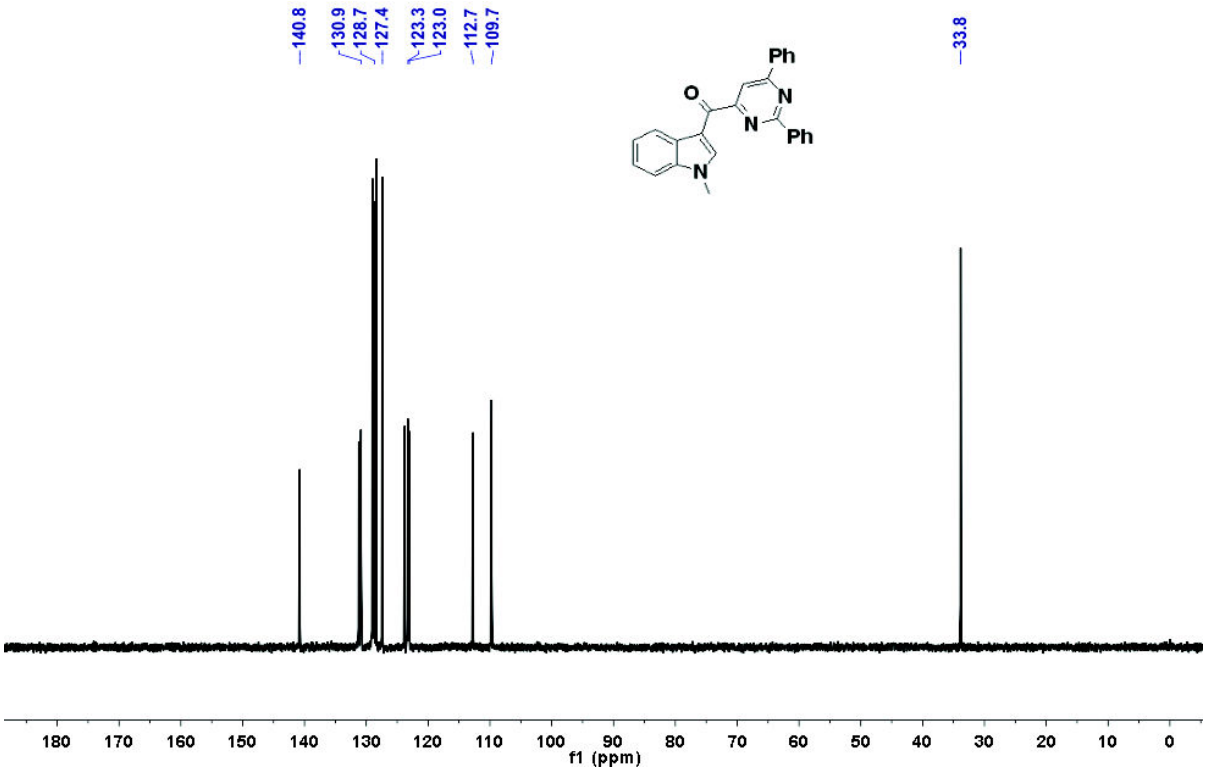
^{13}C DEPT 135-NMR of **6** in $CDCl_3$ at 298 K (δ in ppm). *Impurities from residual solvents.



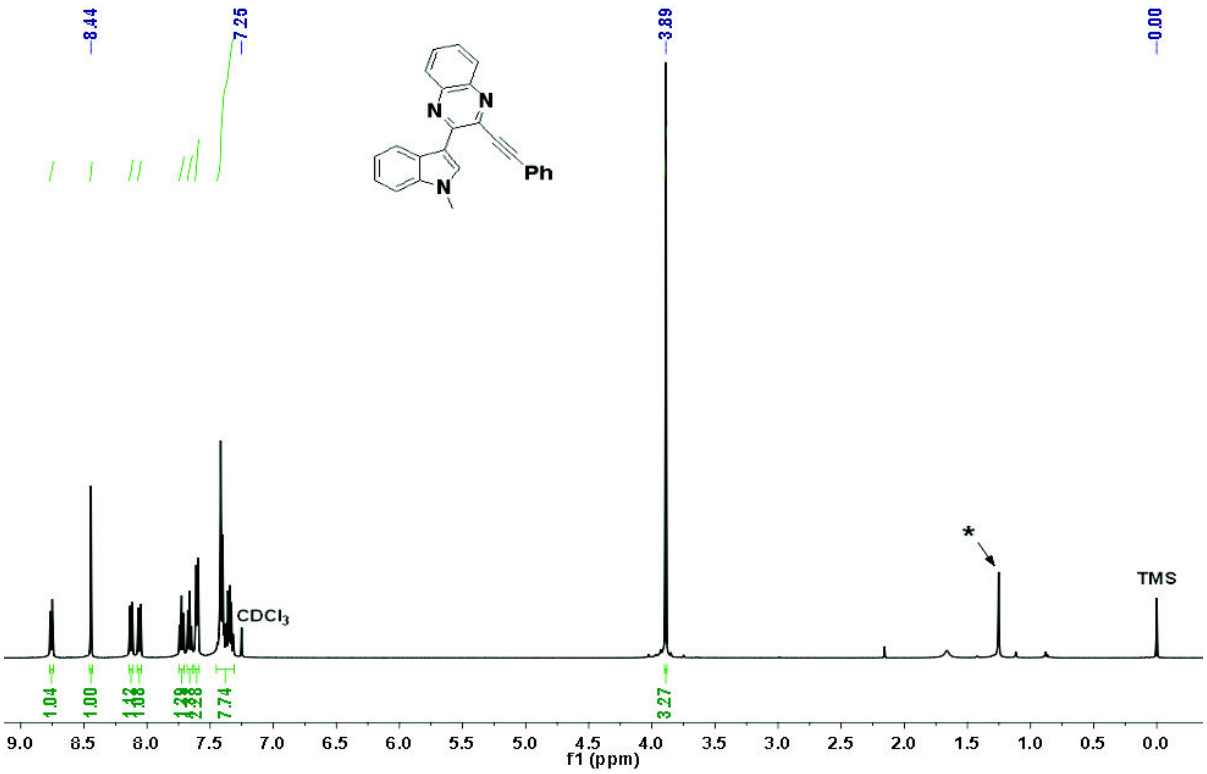
^{1}H NMR of **7** in $CDCl_3$ at 298 K (δ in ppm). *Impurities from residual solvents.



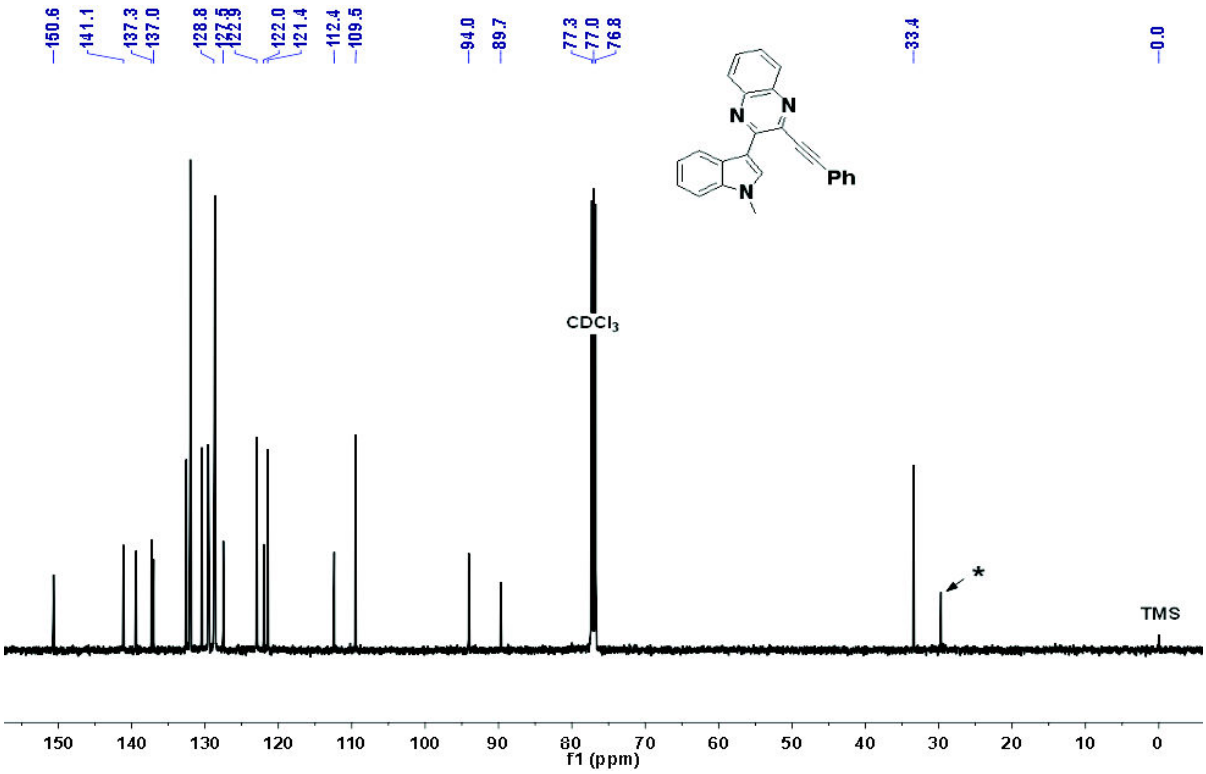
^{13}C NMR of **7** in $CDCl_3$ at 298 K (δ in ppm).



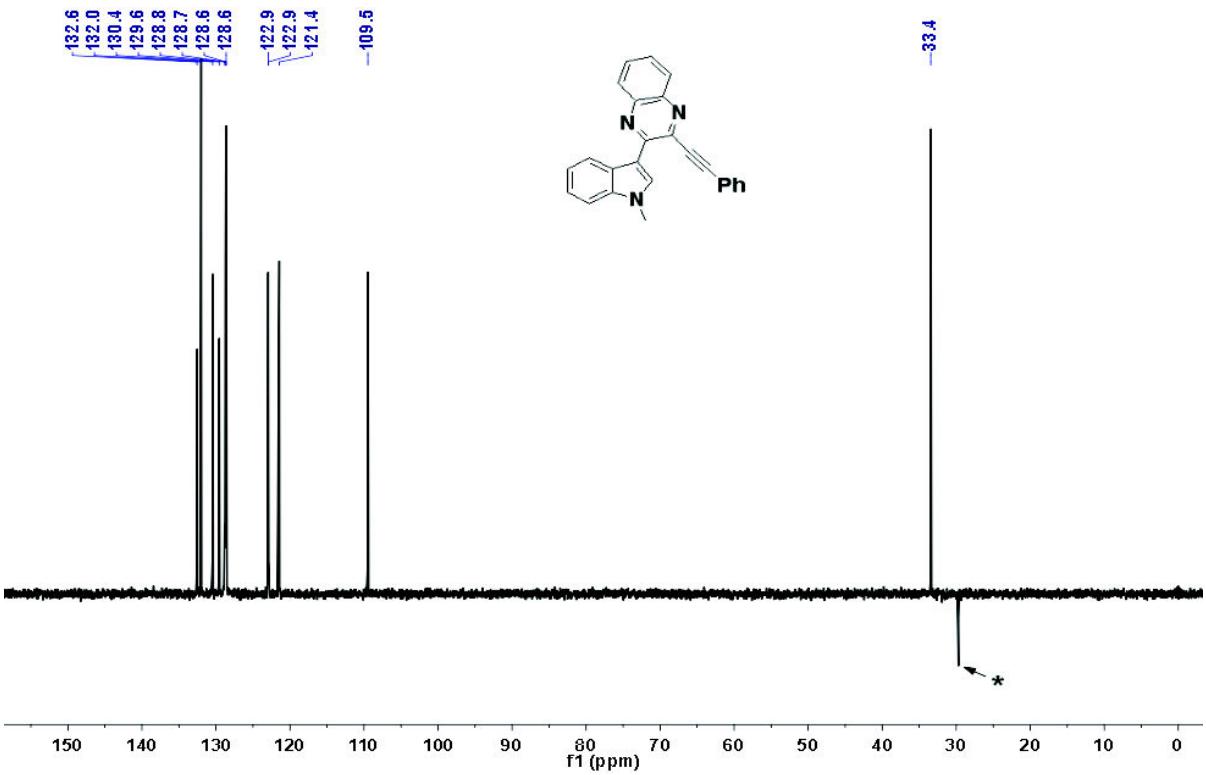
^{13}C DEPT 135-NMR of **7** in $CDCl_3$ at 298 K (δ in ppm).



^{1}H NMR of **9** in $CDCl_3$ at 297 K (δ in ppm). *Impurities from residual solvents.



^{13}C NMR of **9** in $CDCl_3$ at 298 K (δ in ppm). *Impurities from residual solvents.



^{13}C DEPT 135-NMR of **9** in $CDCl_3$ at 298 K (δ in ppm). *Impurities from residual solvents.

8. Crystallographic Data of Compound 3a

Table 3. Crystal data and structure refinement for 1-(1-methyl-1*H*-indol-3-yl)-4-phenylbut-3-yne-1,2-dione (**3a**).

Empirical formula	$C_{19}H_{13}NO_2$
Formula weight	287.31
Temperature	200(2) K
Wavelength	0.71073 Å
Crystal system	triclinic
Space group	$P\bar{1}$
Z	2
Unit cell dimensions	a = 7.1512(15) Å α = 82.834(4) deg. b = 9.500(2) Å β = 78.622(4) deg. c = 11.479(3) Å γ = 71.956(4) deg.
Volume	725.3(3) $Å^3$
Density (calculated)	1.32 g/cm^3
Absorption coefficient	0.09 mm^{-1}
Crystal shape	polyhedron
Crystal size	0.31 x 0.20 x 0.11 mm^3
Crystal color	orange
Theta range for data collection	2.8 to 28.4 deg.
Index ranges	$-9 \le h \le 9$, $-12 \le k \le 12$, $-15 \le l \le 14$
Reflections collected	7335
Independent reflections	3564 (R(int) = 0.1129)
Observed reflections	2655 ($I > 2\sigma(I)$)
Absorption correction	None
Max. and min. transmission	0.99 and 0.97
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3564 / 0 / 200
Goodness-of-fit on F^2	1.11
Final R indices ($I > 2\sigma(I)$)	R1 = 0.075, wR2 = 0.159
Largest diff. peak and hole	0.29 and -0.32 $eÅ^{-3}$

Table 4. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for **3a**. U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

Atom	x	y	z	U_{eq}
C1	0.1907(4)	0.1256(3)	1.2186(2)	0.0354(5)
N1	0.2007(3)	0.1024(2)	1.0941(1)	0.0257(4)
C2	0.1302(3)	0.2081(2)	1.0104(2)	0.0265(5)
C3	0.1508(3)	0.1450(2)	0.9042(2)	0.0242(4)
C4	0.0828(3)	0.2198(2)	0.7969(2)	0.0242(4)
O4	0.0775(2)	0.1593(2)	0.7100(1)	0.0349(4)
C5	0.0182(3)	0.3906(2)	0.7885(2)	0.0295(5)
O5	0.0936(3)	0.4614(2)	0.8359(2)	0.0463(5)
C6	-0.1318(4)	0.4645(2)	0.7139(2)	0.0332(5)
C7	-0.2597(3)	0.5392(2)	0.6600(2)	0.0300(5)
C11	-0.4164(3)	0.6285(2)	0.5976(2)	0.0287(5)
C12	-0.3840(4)	0.7435(3)	0.5150(2)	0.0410(6)
C13	-0.5369(5)	0.8278(3)	0.4553(3)	0.0530(8)
C14	-0.7185(4)	0.7993(3)	0.4763(3)	0.0506(7)
C15	-0.7511(4)	0.6864(3)	0.5583(2)	0.0427(6)
C16	-0.5999(4)	0.6006(3)	0.6188(2)	0.0347(5)
C21	0.2726(3)	-0.0348(2)	1.0451(2)	0.0234(4)
C22	0.3613(3)	-0.1742(2)	1.0974(2)	0.0292(5)
C23	0.4170(4)	-0.2922(2)	1.0273(2)	0.0359(6)
C24	0.3851(4)	-0.2743(2)	0.9092(2)	0.0364(6)
C25	0.2980(3)	-0.1349(2)	0.8569(2)	0.0283(5)
C26	0.2418(3)	-0.0134(2)	0.9251(2)	0.0232(4)

Table 5. Hydrogen coordinates and isotropic displacement parameters ($Å^2$) for **3a**.

Atom	x	y	z	U_{eq}
H1A	0.1334	0.2315	1.2313	0.053
H1B	0.3253	0.0906	1.2387	0.053
H1C	0.1067	0.0701	1.2694	0.053
H2	0.0745	0.3109	1.0224	0.032
H12	-0.2589	0.7636	0.5000	0.049
H13	-0.5161	0.9061	0.3992	0.064
H14	-0.8216	0.8574	0.4343	0.061
H15	-0.8769	0.6674	0.5732	0.051
H16	-0.6221	0.5227	0.6749	0.042
H22	0.3821	-0.1868	1.1777	0.035
H23	0.4790	-0.3886	1.0598	0.043
H24	0.4236	-0.3588	0.8639	0.044
H25	0.2775	-0.1235	0.7766	0.034

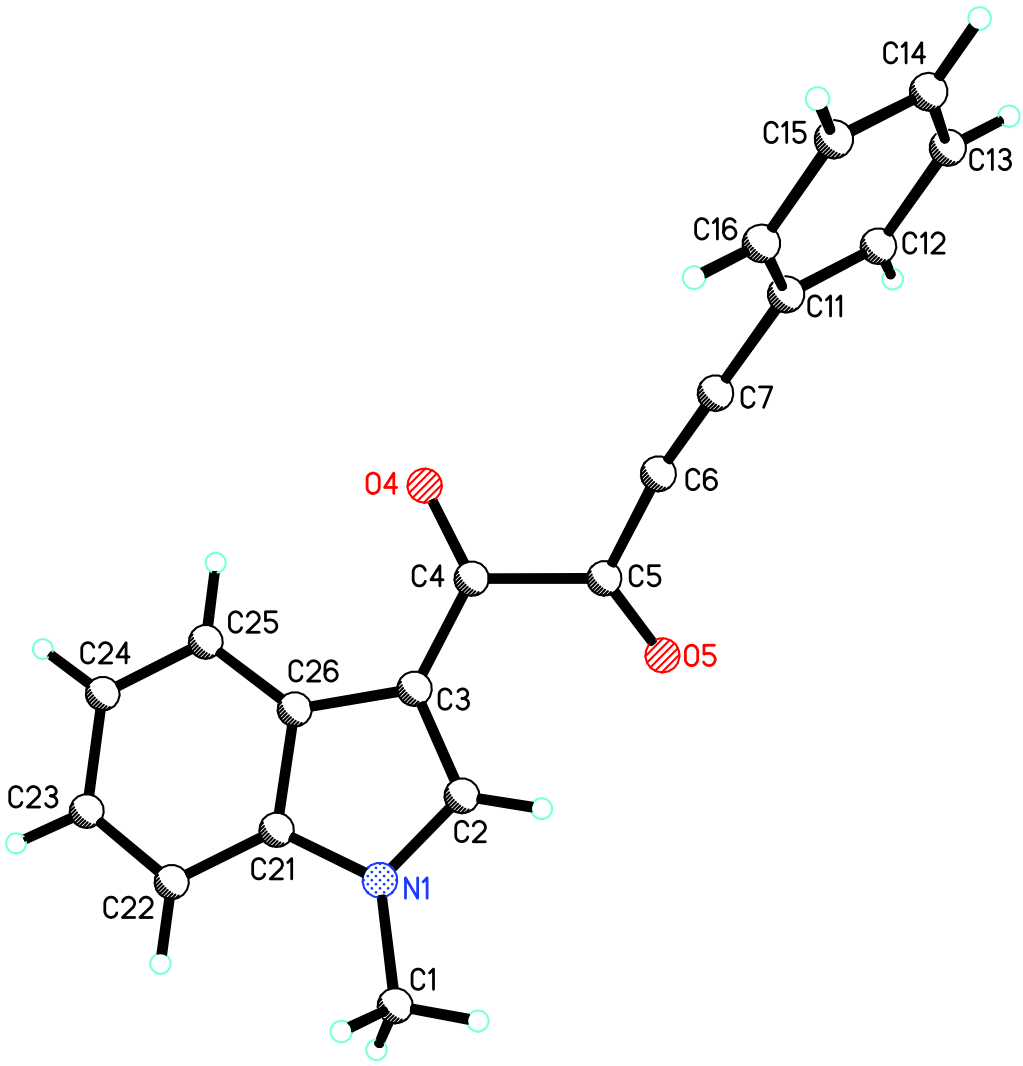
Table 6. Anisotropic displacement parameters ($Å^2$) for **3a**. The anisotropic displacement factor exponent takes the form: $-2\ pi^2\ (h^2\ a^{*2}\ U_{11} + ... + 2\ h\ k\ a^*\ b^*\ U_{12})$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C1	0.0497(14)	0.0323(12)	0.0234(11)	-0.0032(9)	-0.0093(10)	-0.0083(10)
N1	0.0310(9)	0.0231(8)	0.0220(9)	0.0020(7)	-0.0067(7)	-0.0065(7)
C2	0.0317(11)	0.0200(9)	0.0268(11)	0.0032(8)	-0.0073(9)	-0.0067(8)
C3	0.0263(10)	0.0196(9)	0.0258(10)	0.0027(8)	-0.0065(8)	-0.0058(8)
C4	0.0247(10)	0.0229(9)	0.0236(10)	0.0034(8)	-0.0057(8)	-0.0060(8)
O4	0.0467(10)	0.0301(8)	0.0260(8)	0.0033(6)	-0.0123(7)	-0.0068(7)
C5	0.0396(12)	0.0246(10)	0.0252(11)	0.0075(8)	-0.0113(9)	-0.0106(9)
O5	0.0693(13)	0.0294(8)	0.0496(11)	0.0121(8)	-0.0308(10)	-0.0209(8)
C6	0.0442(13)	0.0241(10)	0.0291(11)	0.0070(9)	-0.0111(10)	-0.0076(10)
C7	0.0407(13)	0.0254(10)	0.0226(10)	0.0017(8)	-0.0071(9)	-0.0082(9)
C11	0.0378(12)	0.0238(10)	0.0212(10)	0.0004(8)	-0.0085(9)	-0.0029(9)
C12	0.0456(14)	0.0406(13)	0.0375(13)	0.0126(11)	-0.0171(11)	-0.0132(11)
C13	0.0676(19)	0.0456(15)	0.0454(15)	0.0220(12)	-0.0290(14)	-0.0137(14)
C14	0.0500(16)	0.0486(15)	0.0471(15)	0.0028(12)	-0.0260(13)	0.0027(13)
C15	0.0344(13)	0.0532(15)	0.0384(14)	-0.0117(12)	-0.0086(11)	-0.0049(11)
C16	0.0432(14)	0.0323(12)	0.0269(11)	-0.0021(9)	-0.0048(10)	-0.0093(10)
C21	0.0235(10)	0.0234(10)	0.0226(10)	0.0012(8)	-0.0043(8)	-0.0068(8)
C22	0.0326(11)	0.0274(11)	0.0243(10)	0.0064(8)	-0.0107(9)	-0.0036(9)
C23	0.0415(13)	0.0232(11)	0.0348(12)	0.0069(9)	-0.0111(10)	0.0014(10)
C24	0.0459(14)	0.0221(10)	0.0340(12)	-0.0040(9)	-0.0059(11)	0.0006(10)
C25	0.0337(12)	0.0256(10)	0.0217(10)	0.0015(8)	-0.0042(9)	-0.0046(9)
C26	0.0244(10)	0.0212(9)	0.0236(10)	0.0048(8)	-0.0076(8)	-0.0065(8)

Table 7. Bond lengths (Å) and angles (deg) for **3a**.

C1-N1	1.457(3)
C1-H1A	0.9800
C1-H1B	0.9800
C1-H1C	0.9800
N1-C2	1.350(2)
N1-C21	1.391(3)
C2-C3	1.386(3)
C2-H2	0.9500
C3-C4	1.436(3)
C3-C26	1.452(3)
C4-O4	1.225(3)
C4-C5	1.539(3)
C5-O5	1.213(3)
C5-C6	1.456(3)
C6-C7	1.198(3)
C7-C11	1.437(3)
C11-C16	1.387(3)
C11-C12	1.399(3)
C12-C13	1.387(3)
C12-H12	0.9500
C13-C14	1.377(4)
C13-H13	0.9500
C14-C15	1.381(4)
C14-H14	0.9500
C15-C16	1.388(3)
C15-H15	0.9500
C16-H16	0.9500
C21-C22	1.396(3)
C21-C26	1.417(3)
C22-C23	1.373(3)
C22-H22	0.9500
C23-C24	1.399(3)
C23-H23	0.9500
C24-C25	1.393(3)
C24-H24	0.9500
C25-C26	1.386(3)
C25-H25	0.9500
N1-C1-H1A	109.5
N1-C1-H1B	109.5
H1A-C1-H1B	109.5
N1-C1-H1C	109.5
H1A-C1-H1C	109.5
H1B-C1-H1C	109.5
C2-N1-C21	109.22(16)
C2-N1-C1	125.76(18)
C21-N1-C1	124.88(16)
N1-C2-C3	110.25(18)
N1-C2-H2	124.9
C3-C2-H2	124.9
C2-C3-C4	126.74(18)
C2-C3-C26	106.68(16)
C4-C3-C26	126.45(19)
O4-C4-C3	125.52(19)
O4-C4-C5	117.10(17)
C3-C4-C5	117.34(18)
O5-C5-C6	120.96(19)
O5-C5-C4	122.60(18)
C6-C5-C4	116.35(19)
C7-C6-C5	172.5(2)
C6-C7-C11	178.7(2)
C16-C11-C12	119.8(2)

C16-C11-C7	120.12(19)
C12-C11-C7	120.1(2)
C13-C12-C11	119.1(3)
C13-C12-H12	120.4
C11-C12-H12	120.4
C14-C13-C12	120.8(2)
C14-C13-H13	119.6
C12-C13-H13	119.6
C13-C14-C15	120.2(2)
C13-C14-H14	119.9
C15-C14-H14	119.9
C14-C15-C16	119.9(3)
C14-C15-H15	120.1
C16-C15-H15	120.1
C11-C16-C15	120.2(2)
C11-C16-H16	119.9
C15-C16-H16	119.9
N1-C21-C22	129.43(19)
N1-C21-C26	108.10(16)
C22-C21-C26	122.5(2)
C23-C22-C21	116.87(19)
C23-C22-H22	121.6
C21-C22-H22	121.6
C22-C23-C24	121.77(19)
C22-C23-H23	119.1
C24-C23-H23	119.1
C25-C24-C23	121.3(2)
C25-C24-H24	119.4
C23-C24-H24	119.4
C26-C25-C24	118.33(19)
C26-C25-H25	120.8
C24-C25-H25	120.8
C25-C26-C21	119.29(17)
C25-C26-C3	134.97(18)
C21-C26-C3	105.74(18)


C14
C15
C13
C16
C12
C11
C7
C6
O4
C4
C5
O5
C25
C24
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C3
C23
C2
C21
N1
C22
C1

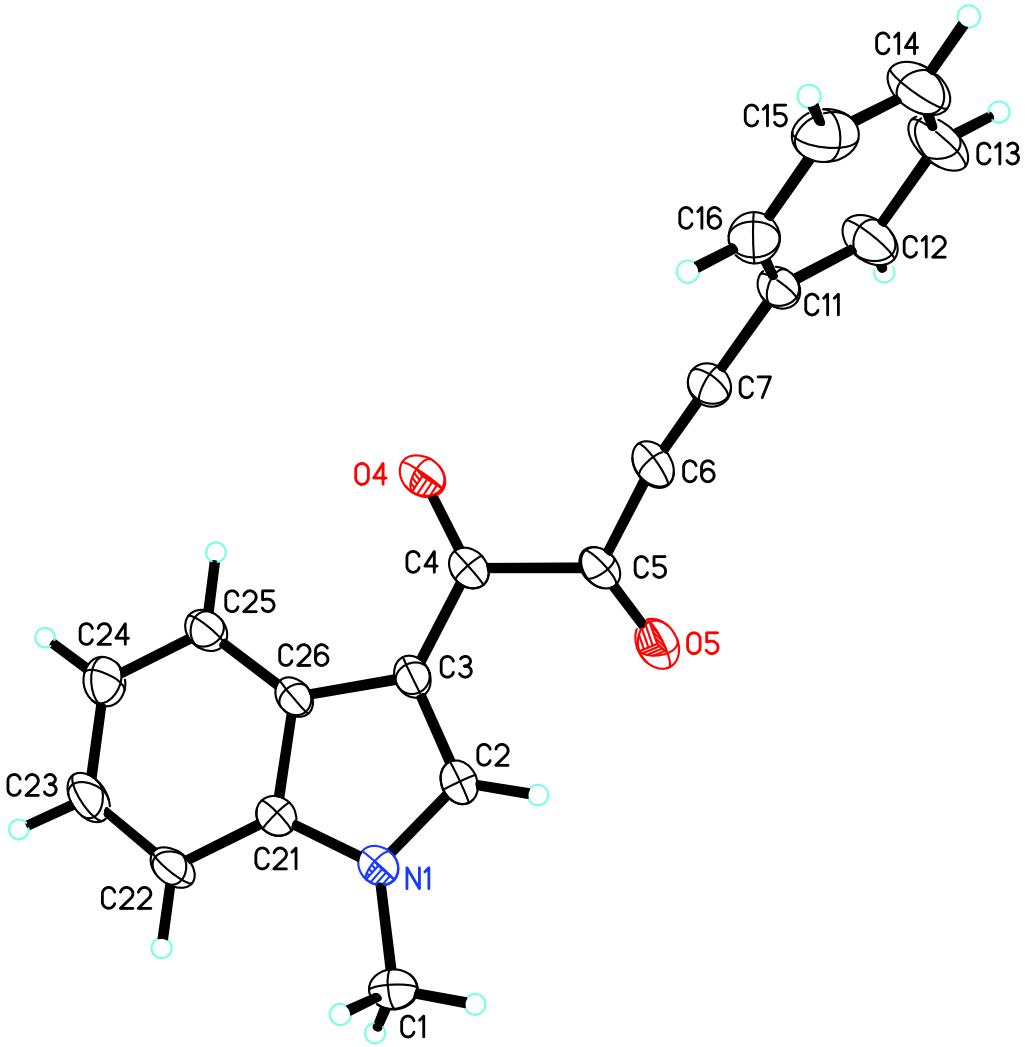


Figure 1. X-ray analysis of compound **3a**.

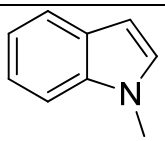
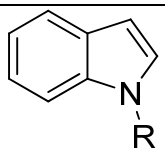
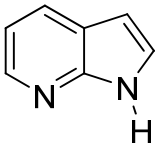
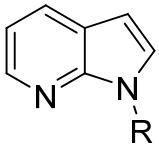
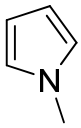
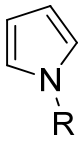
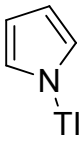
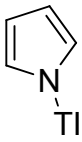
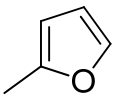
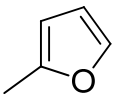
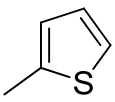
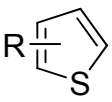
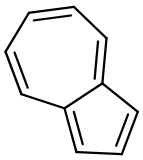
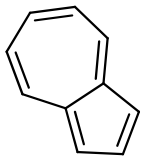
Short experimental part: orange crystal (polyhedron), dimensions 0.31 x 0.20 x 0.11 mm^3, crystal system triclinic, space group $P\bar{1}$, Z = 2, a = 7.1512(15) Å, b = 9.500(2) Å, c = 11.479(3) Å, alpha = 82.834(4) deg, beta = 78.622(4) deg, gamma = 71.956(4) deg, V = 725.3(3) $Å^3$, rho = 1.316 g/cm^3, T = 200(2) K, $Theta_{max}$ = 28.38 deg, radiation Mo Kalpha, lambda = 0.71073 Å, 0.3 deg omega-scans with CCD area detector, covering a whole sphere in reciprocal space, 7335 reflections measured, 3564 unique (R(int) = 0.1129), 2655 observed ($I > 2\sigma(I)$), intensities were corrected for Lorentz and polarization effects, no empirical absorption correction was applied, due to the low absorption of the crystal and the low redundancy of the data, mu = 0.09 mm^{-1}, T_{min} = 0.97, T_{max} = 0.99, structure solved by direct methods and refined against F^2 with a Full-matrix least-squares algorithm using the SHELXTL-PLUS (6.10) software package[2], 200 parameters refined, hydrogen atoms were treated using appropriate riding models, goodness of fit 1.11 for observed reflections, final residual values R1(F) = 0.075, $wR(F^2)$ = 0.159 for observed reflections, residual electron density -0.32 to 0.29 $eÅ^{-3}$. CCDC 796698 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Lit. 1: (program SADABS 2008/1 for absorption correction)
G. M. Sheldrick, Bruker Analytical X-ray-Division, Madison, Wisconsin 2008

Lit. 2: (software package SHELXTL 2008/1 for structure solution and refinement)
Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122.

9. Nucleophilicity Parameters of Substrates

Table 8. Estimation of nucleophilicity parameters *N* of substrates successfully converted to ynediones.

Reference nucleophile with known parameter *N*	Parameter *N*[a]	Substrates similar to or identical with the reference nucleophiles
	5.75	 R = Me, Bn
	3.87	 R = Bn, PMB
	5.85	 R = Me, Bn, Ph, Bzh, Cyanoethyl
	3.12	
	3.61	
	1.26	 R = OMe, $O(CH_2)_2O$
	6.66	

[a] The parameters refer to reactions in CH_2Cl_2 at 20 °C.

10. References

[1] C. A. Merlic, Y. You, D. M. McInnes, A. L. Zechmann, M. M. Miller, Q. Deng, *Tetrahedron* **2001**, *57*, 5199-5212.

[2] L. Mandell, J. U. Piper, C. E. Pesterfield, *J. Org. Chem*. **1963**, *28*, 574-575.

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Consecutive Three-Component Synthesis of Ynones by Decarbonylative Sonogashira Coupling

Eugen Merkul,[a] Thomas Oeser,[b] and Thomas J. J. Müller*[a]

Dedicated to Armin de Meijere on the occasion of his 70th birthday

Alkynones are important intermediates in organic syntheses,[1] and due to their bifunctional electrophilicity they have found broad application as three-carbon building blocks in heterocyclic synthesis. Therefore, efficient, mild, and catalytic methodologies for their preparation are highly desirable. Besides catalytic acylations of terminal[2] and silylated[3] alkynes the carbonylative alkynylation of aryl iodides following the Sonogashira protocol represents an elegant three-component synthesis of alkynones, which were as well elaborated into one-pot syntheses of pharmaceutically relevant heterocycles such as pyrazoles[4] and pyrimidines.[5]

Carbonylations of aryl halides usually require carbon monoxide or molybdenum hexacarbonyl as suitable CO sources. However, the effective concentration of CO in the reaction medium plays a crucial role for the outcome of carbonylative alkynylation. An alternative mode, which also dispenses the use of aryl halides, could be a decarbonylation of an α-dicarbonyl compound. Rhodium-mediated decarbonylations of aldehydes (Tsuji–Wilkinson reaction) are well precedented,[6] however, the process becomes catalytic only at temperatures over 200 °C and most applications in total syntheses have remained stoichiometric.[7] Decarbonylations of acid chlorides are less common.[8] In 2002, iridium-catalyzed decarbonylative homologizations of aroyl chlorides in boiling xylene were reported.[9] Palladium complexes are not commonly used for decarbonylations. Besides decarbonylative carbostannylations,[10] Gooßen has reported decarbonylative Heck reactions with reaction times of 16 h at 160 °C in NMP as a solvent.[11] Just recently, the same group has introduced Pd/Cu-catalyzed decarboxylative cross-couplings of α-oxocarboxylates with aromatic bromides[12] and chlorides[13] at high temperatures and long reaction times. Interestingly, although oxalyl chloride has been applied in the presence of aluminium chloride as a phosgene surrogate for Friedel–Crafts acylations[14] or as a source of carbon monoxide in stoichiometric copper-mediated synthesis of cyclopentadienones from organolithium and organozirconium compounds[15] there is no report of its use in any catalytic application. In continuation of our program to develop transition metal catalyzed multicomponent syntheses of heterocycles[16] and functional organic materials,[17] we report our first findings on consecutive three-component synthesis of alkynones by decarbonylative Sonogashira coupling starting from electron-rich heterocycles and oxalyl chloride as a source of the CO building block via intermediary glyoxylyl chlorides. Conceptually, this methodology complements the carbonylative alkynylation of halides of heterocycles with diminished electron density.[5]

It has been known for quite some time that many indole derivatives directly and without Lewis acid activation react with oxalyl chloride in a Friedel–Crafts acylation to furnish indole-3-glyoxylyl chlorides **1** in high yields.[18] Due to the generality and smoothness of this glyoxylation the idea was now to use the notoriously unstable and reactive indole-3-glyoxylyl chlorides **1** as synthetic equivalents of acid chlorides in transition metal catalyzed cross-coupling reactions. Therefore, for establishing a decarbonylative alkynylation we first tested indole-3-glyoxylyl chlorides **1** without substitution (**1a**) and with a benzyl substituent (**1b**) on the indole nitrogen atom in a model reaction with 1-hexyne (**2a**) under modified Sonogashira conditions[19] (Scheme 1, Table 1). Immediately, it was apparent that only the benzyl derivative **1b** can be transformed into the corresponding alkynone **3b** (entries 3–9).

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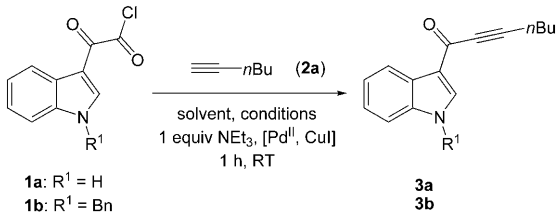


Scheme 1. Optimization of the decarbonylative Sonogashira coupling of indole-3-glyoxylyl chlorides **1** and 1-hexyne (**2a**).

Table 1. Optimization of the decarbonylative Sonogashira coupling of indole-3-glyoxylyl chlorides **1** and 1-hexyne (**2a**).[a]

Entry	Compound **1**	Solvent	Catalyst system	Ynone **3** (isolated yield/%)
1	**1a**: R^1 = H	THF	2 mol% $[PdCl_2(PPh_3)_2]$ 4 mol% CuI	**3a** (–, no reaction)
2[b]	**1b**: R^1 = Bn	THF	2 mol% $[PdCl_2(PPh_3)_2]$ 4 mol% CuI	**3b** (–, no reaction)
3	**1b**	THF	1 mol% $[PdCl_2(PPh_3)_2]$ 2 mol% CuI	**3b** (n.i.)[c]
4	**1b**	THF	2 mol% $[PdCl_2(PPh_3)_2]$ 4 mol% CuI	**3b** (n.i.)[c]
5	**1b**	DME	2 mol% $[PdCl_2(PPh_3)_2]$ 2 mol% CuI	**3b** (61)
6[d,e]	**1b**	DME	5 mol% $[PdCl_2(PPh_3)_2]$ 2 mol% CuI	**3b** (n.i.)[c]
7	**1b**	CH_2Cl_2	2 mol% $[PdCl_2(PPh_3)_2]$ 4 mol% CuI	**3b** (n.i.)[c]
8	**1b**	THF	1 mol% $[PdCl_2(PPh_3)_2$ 1 mol% CuI	**3b** (80)
9[f]	**1b**	THF	1 mol% $[PdCl_2(PPh_3)_2]$ 1 mol% CuI	**3b** (70)
10[f,g]	**1b**	THF	1 mol% $[PdCl_2(PPh_3)_2]$ 1 mol% CuI	**3b** (–, no reaction)
11	**1b**	THF	0.1 mol% $[PdCl_2(PPh_3)_2]$ 1 mol% CuI	**3b** (–, no reaction)
12	**1b**	THF	1 mol% $[PdCl_2(dppf)]$ 1 mol% CuI	**3b** (–, no reaction)

[a] The reactions were performed in 5 mL of solvent (c(**1**) = 0.2 M) using 1.5 equiv of **2a** for 1 h and at room temperature unless otherwise stated. [b] Reaction performed at 0 °C. [c] TLC indicates coupling without decarbonylation and the formation of compound **3b** which was not isolated. [d] The reaction time was 48 h. [e] The reaction was performed under 1 atm of CO. [f] 1.0 equiv of **2a** was applied. [g] 2 mol% of PPh_3 were added to the reaction mixture.

Although the desired alkynone **3b** could be immediately detected by TLC monitoring of the reaction it was only isolable if the formation of the non-decarbonylated byproduct could be suppressed. Therefore, the influence of the ratios of the substrates, the catalysts and the solvent were studied qualitatively. Besides spectroscopic and combustion analytical characterization the structure of compound **3b** was unambiguously corroborated by an X-ray structure analysis (Figure 1).[20]

The most crucial point for the successful transformation and high conversion is the well-balanced equimolar ratio of $[PdCl_2(PPh_3)_2]$ and CuI (entries 5, 8, and 9). Dimethoxyethane (DME) and THF are both good solvents. Performing the reaction under a CO atmosphere to block the decarbonylation resulted in the formation of the ynone (entry 6), whereas the addition of 2 mol% of PPh_3 completely stopped the conversion (entry 10). Switching the palladium catalyst precursor to $[PdCl_2(dppf)]$ did not result in ynone formation (entry 12). Therefore, the most favorable conditions for the development of a sequence with the decarbonylative Sonogashira coupling suggest the use of an equimolar ratio of glyoxylyl chloride **1b** and alkyne **2a** giving a clean reaction and 70% isolated yield of alkynone **3b** (entry 9). Hence, the mechanistic rationale of this new decarbonylative Sonogashira coupling can be rationalized as follows (Scheme 2).

After the oxidative addition of indole-3-glyoxylyl chloride (**1**), adduct **4** undergoes a migratory de-insertion and elimination of carbon monoxide furnishing the acyl–Pd species **5**. The driving force of this reaction is the apparent relative instability of the dicarbonyl species **4** compared with the acyl species **5**. Then, transmetalation of the in situ generated copper acetylide to **5** gives rise to the formation of the acyl-alkynyl-Pd complex **6**, which undergoes reductive elimination to give the alkynone **3** and the catalytically active Pd^0 species to start a new catalytic cycle.

Encouraged by these initial successful experiments we decided to combine the formation of relatively labile glyoxylyl chloride **1** and the subsequent decarbonylative alkynylation to a consecutive three-component reaction in a one-pot transformation. Indeed, *N*-substituted indoles (X = CH) and 7-aza-indoles (X = N) **7** or pyrroles **8** were glyoxylated with oxalyl chloride in THF or DME on a 5 mmol scale and the transient glyoxylyl chlorides **1** were reacted with equimolar amounts of the alkynes **2** for 1 h at room temperature

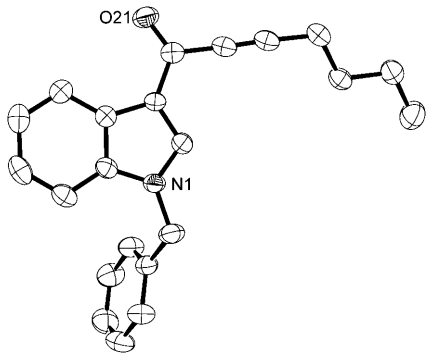
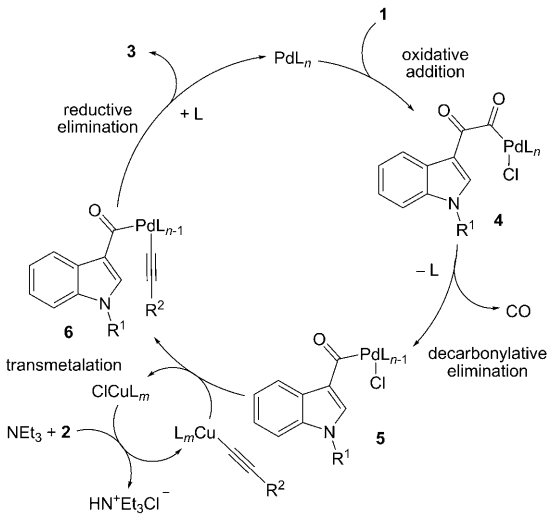
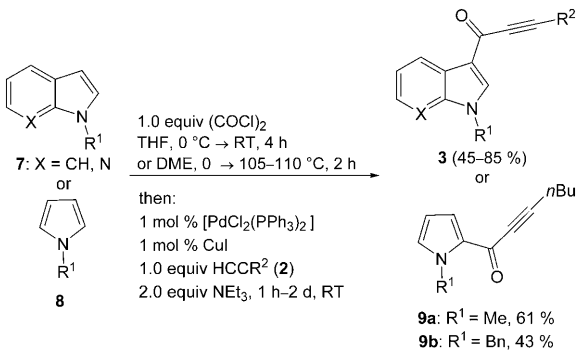


Figure 1. Molecular structure of alkynone **3b** (hydrogen atoms were omitted for clarity).



Scheme 2. Mechanistic rationale of the decarbonylative Sonogashira coupling of indole-3-glyoxylyl chlorides **1** and terminal alkynes **2**.

for 1–48 h in the presence of two equivalents of triethylamine and catalytic amounts of $[PdCl_2(PPh_3)_2]$ and CuI to give the corresponding alkynones **3** and **9** in moderate to good yields (Scheme 3, Table 2). The presence of two stoichiometrically necessary equivalents of triethylamine assures that the hydrogen chloride formed upon glyoxylation is bound and that the decarbonylative Sonogashira coupling occurs by scavenging the hydrochloric acid from the catalytic cycles. Expectedly, as a consequence of the regioselective glyoxylation of pyrroles in the 2-position the ynones **9** were obtained by the same protocol, simultaneously illustrating the methodological potential for the application to electron-rich π systems.



Scheme 3. Three-component glyoxylation-decarbonylative alkynylation synthesis of alkynones **3** and **9**.

With this versatile alkynone synthesis in hand, we tested the application of the products in pyrimidine synthesis. As previously shown, 4-(indol-3-yl)- and 4-(7-aza-indol-3-yl)-2-amino pyrimidines, which are structurally related to the marine natural products class of meridianins, have displayed a considerable potential as kinase inhibitors.[5] Therefore,

Table 2. Three-component glyoxylation-decarbonylative alkynylation synthesis of alkynones **3** and **9**.[a]

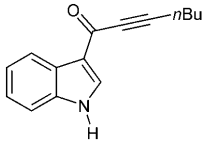
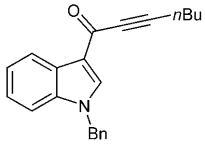
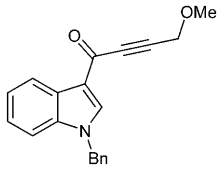
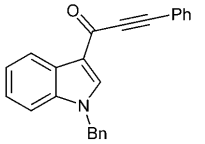
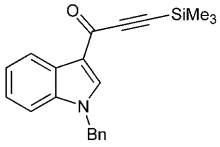
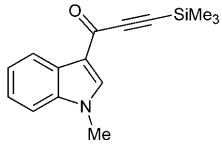
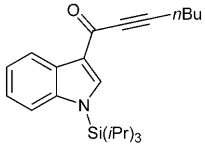
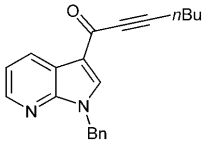
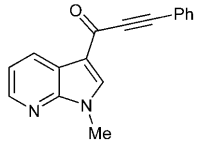
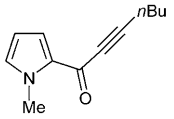
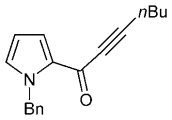
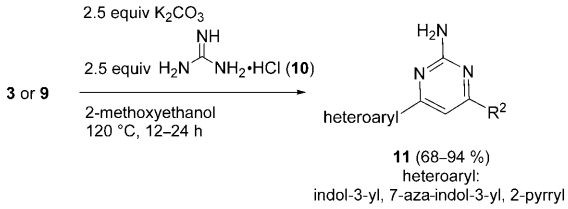
Entry	*N*-Substituted indole or 7-aza-indole **7**	Alkyne **2**	Ynone **3** (isolated yield/%)
1	**7a**: X = CH, R^1 = Si(*i*Pr)$_3$	**2a**: R^2 = *n*Bu	 **3a** (43)[b]
2	**7b**: X = CH, R^1 = Bn	**2a**	 **3b** (74)
3	**7b**	**2b**: R^2 = CH$_2$OMe	 **3c** (66)
4	**7b**	**2c**: R^2 = Ph	 **3d** (85)
5	**7b**	**2d**: R^2 = SiMe$_3$	 **3e** (76)
6	**7c**: X = CH, R^1 = Me	**2d**	 **3f** (64)
7	**7a**	**2a**	 **3g** (45)
8[c]	**7d**: X = N, R^1 = Bn	**2a**	 **3h** (63)
9[c]	**7e**: X = N, R^1 = Me	**2c**	 **3i** (61)
10[d]	**8a**: R^1 = Me	**2a**	 **9a** (61)

Table 2. (Continued)

Entry	*N*-Substituted indole or 7-aza-indole **7**	Alkyne **2**	Ynone **3** (isolated yield/%)
11[e]	**8b**: R^1 = Bn	**2a**	 **9b** (43)

[a] The sequences were performed in 25 mL of solvent (c(**7**) = 0.2 M) and in the acylation step the reaction vessel was allowed to come from 0 °C (external water/ice cooling) to room temperature for 4 h unless otherwise stated. For the subsequent decarbonylative alkynylation step, 1 mol % of $[PdCl_2(PPh_3)_2]$, 1 mol % of CuI, 1.0 equiv of alkyne **2** and 2.0 equiv of triethylamine were added. [b] After addition of 1.1 equiv of TBAF (1 M in THF) to the reaction mixture and stirring at room temperature the product **3a** was obtained. [c] The reaction was performed in DME as a solvent and the acylation step was carried out at 105-110 °C for 2 h. [d] The decarbonylative alkynylation step was carried out for 2 d. [e] The decarbonylative alkynylation step was carried out overnight.

upon reacting indolyl (X = CH) and 7-aza-indolyl (X = N) substituted alkynones **3** or the pyrrolyl ynones **9** with an excess of guanidinium hydrochloride (**10**) and potassium carbonate in 2-methoxyethanol at 120 °C for 12–24 h the 2-amino pyrimidines **11** were obtained in good to excellent yields (Scheme 4, Table 3).



Scheme 4. Cyclocondensation of alkynones **3** and **9** to 4-(indol-3-yl)-, 4-(7-aza-indol-3-yl)-, and 4-(pyrrol-2-yl)-2-amino pyrimidines **11**.

Compounds **11e** and **11f** can be considered as *N*-alkyl derivatives of the naturally occurring meridianin G.[21] The structures of the 2-amino pyriminidines **11** were unambiguously supported by NMR spectroscopy and mass spectrometry, and later by an X-ray structure analysis of compound **11b** (Figure 2).[20]

In conclusion, we have disclosed a new consecutive three-component synthesis of alkynones by glyoxylation of very easily accessible indole, 7-aza-indole, and pyrrole derivatives with oxalyl chloride and subsequent Pd/Cu-catalyzed decarbonylative alkynylation of the heteroaryl glyoxylyl chlorides with terminal alkynes. This new Sonogashira protocol proceeds considerably faster than carbonylative alkynylations of (hetero)aryl iodides with carbon monoxide[5] and a lower catalyst loading is needed. The mild conditions for decarbonylations are unprecedented, and the reagents are only applied in equimolar quantities with a high tolerance for various substituents. The application of the alkynones in a subsequent transformation to pyrimidines also illustrates the

Table 3. Synthesis of 4-(indol-3-yl)-, 4-(7-aza-indol-3-yl)-, and 4-(pyrrol-2-yl)-2-amino pyrimidines **11**.[a]

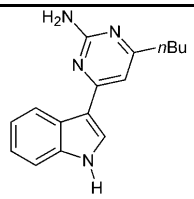
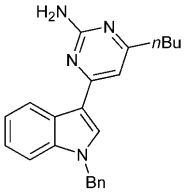
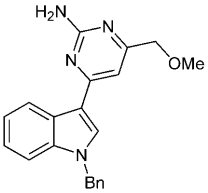
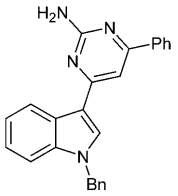
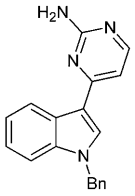
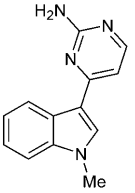
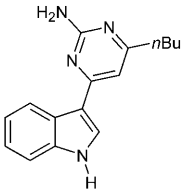
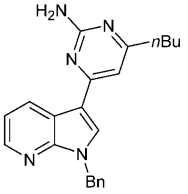
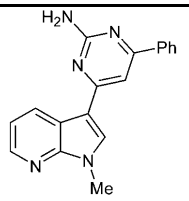
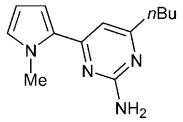
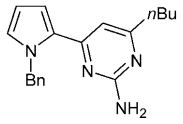
Entry	Ynone **3** or **9**	2-Amino pyimindine **11** (isolated yield/%)
1	**3a**	 **11a** (81)
2	**3b**	 **11b** (86)
3	**3c**	 **11c** (88)
4	**3d**	 **11d** (82)
5	**3e**	 **11e** (88)[b]
6	**3f**	 **11f** (68)[b]
7	**3g**	 **11a** (68)[b]
8	**3h**	 **11g** (81)

Table 3. (Continued)

Entry	Ynone **3** or **9**	2-Amino pyimindine **11** (isolated yield/%)
9	**3i**	 **11h** (86)
10	**9a**	 **11i** (92)
11	**9b**	 **11j** (94)

[a] The reactions were performed at c(**3** or **9**) = 0.2 M in 2-methoxyethanol. [b] TMS and TIPS were deprotected in the course of the reaction.

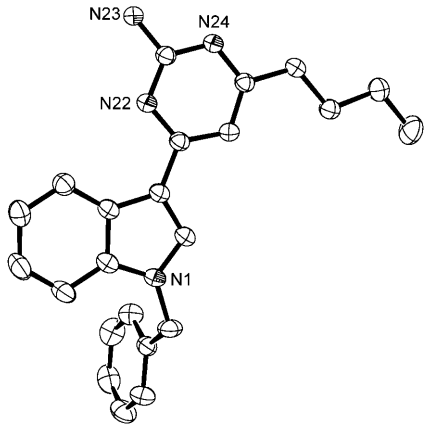


Figure 2. Molecular structure of 2-amino pyrimidine **11b** (hydrogen atoms were omitted for clarity).

vast potential to diversity-oriented syntheses of heterocycles. Studies expanding the scope of this novel access to alkynones and their elaboration towards multi-component syntheses of heterocycles are currently underway. In addition, the stage has been set for the methodological expansion to further decarbonylative cross-couplings that are currently under investigation.

Experimental Section

General methods and further reactions are given in the Supporting Information.

Three-component synthesis of alkynone 3b: *N*-Benzyl-1*H*-indole (**7a**) (1.04 g, 5.00 mmol) in dry THF (25 mL) was placed under argon in a screw-cap vessel with septum, degassed with argon and cooled to 0 °C (water/ice). Then, oxalyl chloride (0.44 mL, 5.00 mmol) was added to the reaction mixture at 0 °C. The mixture was allowed to come to room temperature and was stirred for 4 h. Then, $[PdCl_2(PPh_3)_2]$ (35 mg, 0.05 mmol), CuI (10 mg, 0.05 mmol), 1-hexyne (**2a**) (0.59 mL, 5.00 mmol), and dry triethylamine (1.39 mL, 10.0 mmol) were successively added to the mixture and stirring at room temperature was continued for 1 h. The evolution of CO can be observed. After complete conversion (monitored by TLC) saturated brine (25 mL) was added, and the mixture was extracted with dichloromethane (3 × 25 mL). The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuo the residue was absorbed onto Celite and chromatographed on silica gel with hexanes/ethyl acetate to give the alkynone **3b** (1.17 g, 74%) as a yellow solid. M.p. 84–85 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.44–8.38 (m, 1H), 7.90 (s, 1H), 7.39–7.13 (m, 8H), 5.35 (s, 2H), 2.44 (t, J = 7.5 Hz, 2H), 1.62 (quint, J = 8.3 Hz, 2H), 1.47 (sext, J = 8.3 Hz, 2H), 0.94 ppm (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 171.8 (C_{quat}), 138.1 (CH), 137.3 (C_{quat}), 135.5 (C_{quat}), 129.1 (CH), 128.3 (CH), 127.1 (CH), 126.1 (C_{quat}), 123.8 (CH), 123.0 (CH), 122.6 (CH), 118.9 (C_{quat}), 110.3 (CH), 91.0 (C_{quat}), 80.6 (C_{quat}), 50.9 (CH_2), 30.0 (CH_2), 22.1 (CH_2), 18.7 (CH_2), 13.6 ppm (CH_3); EI+MS: m/z (%): 315 (100) [M^+], 91 (40) [$C_7H_7^+$]; IR (KBr): $\tilde{\nu}$ = 730, 752, 771, 827, 1027, 1184, 1237, 1360, 1386, 1440, 1453, 1465, 1486, 1495, 1522, 1576, 1607, 2226, 2870, 2932, 2955 3119 cm^{-1}; elemental analysis calcd (%) for $C_{22}H_{21}NO$: C 83.78, H 6.71, N 4.44; found: C 83.64, H 6.71, N 4.43.

2-Aminopyrimidine 11b: In a screw-cap vessel under argon the alkynone **3b** (315 mg, 1.00 mmol) was dissolved in 2-methoxyethanol (5 mL). Then, potassium carbonate (346 mg, 2.50 mmol), and guanidinium hydrochloride (**10**) (239 mg, 2.50 mmol) were added and the mixture was stirred at 120 °C over night. Then, after cooling to room temperature saturated brine (20 mL) was added, and the mixture was extracted with dichloromethane (5 × 20 mL). The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuo the residue was absorbed onto Celite and chromatographed on silica gel with dichloromethane and dichloromethane/methanol/aqueous ammonia (100:1:1) to give the 2-amino pyrimidine **11b** (305 mg, 86%) as a pale yellow solid. M.p. 174–175 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 27 °C, TMS): δ = 8.40–8.33 (m, 1H), 7.84 (s, 1H), 7.35–7.18 (m, 6H), 7.18–7.11 (m, 2H), 6.89 (s, 1H), 5.35 (s, 2H), 5.05 (s, 2H, NH_2), 2.60 (t, J = 7.5 Hz, 2H), 1.72 (quint, J = 7.5 Hz, 2H), 1.42 (sext, J = 7.5 Hz, 2H), 0.95 ppm (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 27 °C, TMS): δ = 171.4 (C_{quat}), 163.1 (C_{quat}), 162.5 (C_{quat}), 137.4 (C_{quat}), 136.5 (C_{quat}), 130.3 (CH), 128.9 (CH), 127.9 (CH), 126.9 (CH), 126.3 (C_{quat}), 122.6 (CH), 121.7 (CH), 121.2 (CH), 114.8 (C_{quat}), 110.3 (CH), 106.4 (CH), 50.5 (CH_2), 37.8 (CH_2), 31.2 (CH_2), 22.6 (CH_2), 14.0 ppm (CH_3); EI+MS: m/z (%): 356 (27) [M^+], 341 (3) [M^+-CH_3], 268 (7) [$M^+-C_2H_5$], 314 (100) [$M^+-C_3H_6$], 223 (5) [$M^+-C_{10}H_{13}$], 91 (14) [$C_7H_7^+$]; IR (KBr): $\tilde{\nu}$ = 743, 1175, 1385, 1456, 1469, 1521, 1577, 1628, 1645, 2860, 2927, 2956, 3442, 3463 cm^{-1}; elemental analysis calcd (%) for $C_{23}H_{24}N_4$: C 77.50, H 6.79, N 15.72; found: C 77.45, H 6.75, N 15.77.

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Keywords: acylation · alkynones · C–C coupling · multicomponent reactions · pyrimidines

[1] For a review, see e.g. R. A. Bol′shedvorskaya, L. I. Vereshchagin, *Russ. Chem. Rev.* **1973**, *42*, 225–240.
[2] Y. Tohda, K. Sonogashira, N. Hagihara, *Synthesis* **1977**, 777–778.
[3] See e.g. a) L. Birkofer, A. Ritter, H. Uhlenbrauck, *Chem. Ber.* **1963**, *96*, 3280–3288; b) D. R. M. Walton, F. Waugh, *J. Organomet. Chem.* **1972**, *37*, 45–56; c) H. Newman, *J. Org. Chem.* **1973**, *38*, 2254–2255; d) J. S. Yadav, B. V. S. Reddy, M. S. Reddy, *Synlett* **2003**, 1722–1724.
[4] M. S. Mohamed Ahmed, A. Mori, *Org. Lett.* **2003**, *5*, 3057–3060.

[5] A. S. Karpov, E. Merkul, F. Rominger, T. J. J. Müller, *Angew. Chem.* **2005**, *117*, 7112–7117; *Angew. Chem. Int. Ed.* **2005**, *44*, 6951–6956.
[6] a) J. Tsuji, K. Ohno, *Tetrahedron Lett.* **1965**, *6*, 3969–3971; b) J. Tsuji, K. Ohno, *Tetrahedron Lett.* **1967**, *8*, 2173–2176; c) P. Fristrup, M. Kreis, A. Palmelund, P.-O. Norrby, R. Madsen, *J. Am. Chem. Soc.* **2008**, *130*, 5206–5215.
[7] a) M. Tanaka, T. Ohshima, H. Mitsuhashi, M. Maruno, T. Wakamatsu, *Tetrahedron* **1995**, *51*, 11693–11702; b) F. E. Ziegler, M. Belema, *J. Org. Chem.* **1997**, *62*, 1083–1094; c) C.-M. Zeng, M. Han, D. F. Corey, *J. Org. Chem.* **2000**, *65*, 2264–2266; d) J. P. Malerich, T. J. Maimone, G. I. Elliott, D. Trauner, *J. Am. Chem. Soc.* **2005**, *127*, 6276–6283; e) A. Padwa, H. Zhang, *J. Org. Chem.* **2007**, *72*, 2570–2582.
[8] J. Tsuji, K. Ohno, *J. Am. Chem. Soc.* **1968**, *90*, 94–98.
[9] T. Yasukawa, T. Satoh, M. Miura, M. Nomura, *J. Am. Chem. Soc.* **2002**, *124*, 12680–12681.
[10] Y. Nakao, J. Satoh, E. Shirakawa, T. Hiyama, *Angew. Chem.* **2006**, *118*, 2329–2332; *Angew. Chem. Int. Ed.* **2006**, *45*, 2271–2274.
[11] a) L. J. Gooßen, J. Paetzold, *Angew. Chem.* **2002**, *114*, 1285–1289; *Angew. Chem. Int. Ed.* **2002**, *41*, 1237–1241; b) L. J. Gooßen, J. Paetzold, *Angew. Chem.* **2004**, *116*, 1115–1118; *Angew. Chem. Int. Ed.* **2004**, *43*, 1095–1098.
[12] L. J. Gooßen, F. Rudolphi, C. Oppel, N. Rodríguez, *Angew. Chem.* **2008**, *120*, 3085–3088; *Angew. Chem. Int. Ed.* **2008**, *47*, 3043–3045.
[13] L. J. Gooßen, B. Zimmermann, T. Knauber, *Angew. Chem.* **2008**, *120*, 7211–7214; *Angew. Chem. Int. Ed.* **2008**, *47*, 7103–7106.
[14] D. M. Ketcha, G. W. Gribble, *J. Org. Chem.* **1985**, *50*, 5451–5457.
[15] C. Chen, C. Xi, Y. Jiang, X. Hong, *J. Am. Chem. Soc.* **2005**, *127*, 8024–8025.
[16] For reviews, see a) B. Willy, T. J. J. Müller, *ARKIVOC* **2008**, 195–208; b) D. M. D′Souza, T. J. J. Müller, *Chem. Soc. Rev.* **2007**, *36*, 1095–1108; c) T. J. J. Müller, *Chim. Oggi* **2007**, *25*, 70–78; d) T. J. J. Müller, *Targets Heterocycl. Syst.* **2006**, *10*, 54–65.
[17] a) T. J. J. Müller, D. M. D′Souza, *Pure Appl. Chem.* **2008**, *80*, 609–620; b) T. J. J. Müller in *Functional Organic Materials—Synthesis Strategies, and Applications* (Eds.: T. J. J. Müller, U. H. F. Bunz), Wiley-VCH, Weinheim, **2007**, 179–223.
[18] M. E. Speeter, W. C. Anthony, *J. Am. Chem. Soc.* **1954**, *76*, 6208–6210.
[19] a) A. S. Karpov, T. J. J. Müller, *Org. Lett.* **2003**, *5*, 3451–3454; b) D. M. D′Souza, T. J. J. Müller, *Nat. Protoc.* **2008**, *3*, 1660–1665.
[20] CCDC 710258 (**3b**) and CCDC 710259 (**11b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[21] The NMR-spectroscopic data of compound **11e** are identical with *N*-benzyl meridianin G, see G. Simon, H. Couthon-Gourves, J.-P. Haelters, B. Corbel, N. Kervarec, F. Michaud, L. Meijer, *J. Heterocycl. Chem.* **2007**, *44*, 793–801.

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Supporting Information

Consecutive Three-Component Synthesis of Ynones by Decarbonylative Sonogashira Coupling

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Supporting Information

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1. General Considerations

All cross coupling reactions were carried out in oven-dried Schlenk glassware using septa and syringes under nitrogen or argon atmosphere. THF was dried using *MBraun* system MB-SPS-800, dry DME was purchased from *Aldrich* and triethylamine was refluxed under argon over ketyl sodium, distilled and stored in a Schlenk flask over potassium hydroxide pellets under argon atmosphere.

The starting materials were prepared according to literature procedures: 1-Benzyl-1*H*-indole (**7b**),[1] 1-Benzyl-1*H*-pyrrolo[2,3-*b*]pyridine (**7d**),[1] 1-Methyl-1*H*-pyrrolo[2,3-*b*]pyridine (**7e**),[1] 1-(Triisopropylsilyl)-1*H*-indole (**7a**),[2],[3] (1-Benzyl-1*H*-indol-3-yl)-oxoacetylchloride (**1b**).[4] 1-Methyl-1*H*-indole (**7c**) is commercially available by *Merck Serono KGaA*. Commercial grade reagents were used as supplied without further purification and were purchased from *Acros Organics N. V.*, *Aldrich Chemie GmbH*, *Fluka AG*, *ABCR GmBH & Co. KG, Riedel-de Haën, BRL* and *Merck Serono KGaA*.

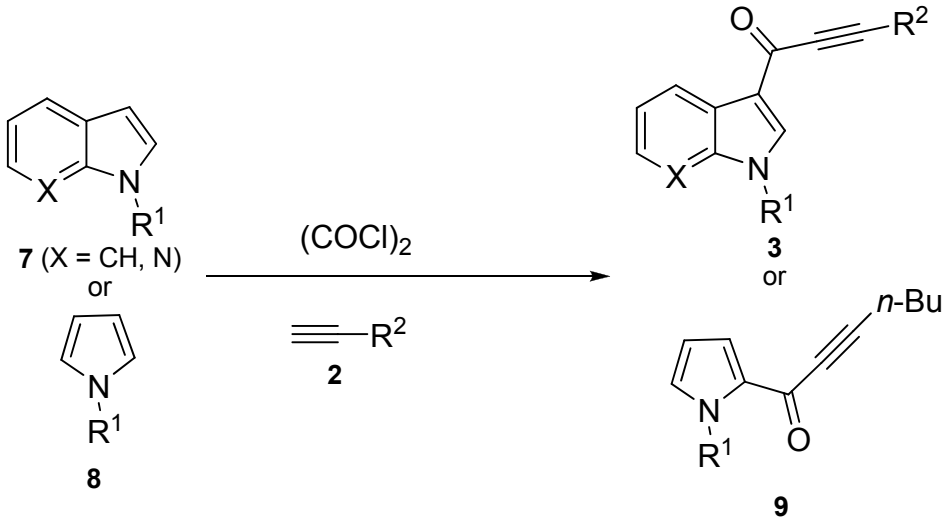
The purification of products was performed on silica gel 60 (0.015-0.040 mm) from *Merck Serono KGaA* Darmstadt using flash technique and under pressure of 2 bar. The crude mixtures were adsorbed on Celite 545 (0.02-0.10 mm) from *Merck Serono KGaA* Darmstadt before chromatographic purification.

The reaction progress was monitored qualitatively using TLC Silica gel 60 F_{254} 5 x 7.5 cm aluminium sheets obtained by *Merck Serono KGaA* Darmstadt. The spots were detected with UV light at 254 nm and using aqueous potassium permanganate solution.

^{1}H, ^{13}C, and 135-DEPT NMR spectra were recorded on Bruker DRX 300 and DRX 500 spectrometers. $CDCl_3$, acetone-d_6 and DMSO-d_6 were used as deutereted solvents. TMS was used as reference (δ = 0.0) or the resonances of the solvents were locked as internal standard ($CDCl_3$: ^{1}H δ 7.24, ^{13}C δ 77.2; acetone-d_6: ^{1}H δ 2.05, ^{13}C δ 29.9/206.7; DMSO-d_6: ^{1}H δ 2.50, ^{13}C δ 39.5). The multiplicities of signals were abbreviated as follows: s: singulett; d: dublett; t: triplett; q: quartett; quint: quintett; sext: sextett, dd: dublett of dubletts, dt: dublett of tripletts, td: triplett of dubletts, m: multiplett and br: broad signal. The type of carbon atoms was determined on the basis of 135-DEPT NMR spectra. EI mass spectra were measured on Varian MAT 311 A and Finnigan MAT 8200. IR spectra were obtained on Bruker Vector 22 FT-IR. The solids were measured as KBr pellets and oils as films on KBr plates. The intensity of signals is abbreviated as follows: s (strong), m (medium) and w (weak). The melting points (uncorrected) were measured on Reichert-Jung Thermovar. Combustion analyses were carried out in the

microanalytical laboratory of the Organisch-Chemisches Institut der Universität Heidelberg and in the microanalytical laboratory of Institut für Pharmazeutische Chemie in Düsseldorf.
X-ray structures were measured on Bruker Smart APEX and Brucker Smart CCD.
Crystal data: Compound **3b**: Colorless crystal (irregular), dimensions 0.27 x 0.07 x 0.05 mm^3, crystal system monoclinic, space group $P2_1/n$, Z = 4, a = 12.616(1) Å, b = 7.4046(9) Å, c = 19.386(2) Å, □ = 90.0 deg, □ = 104.449(3) deg, □ = 90.0 deg, V=1753.8(4) $Å^3$, □ = 1.195 g/cm^3, T = 200(2) K, $□_{max}$= 22.46 deg, radiation Mo K□, □ = 0.71073 Å, 0.3 deg omega-scans with CCD area detector, covering a whole sphere in reciprocal space, 10845 reflections measured, 2278 unique (R(int) = 0.046), 1771 observed (I >2□(I)), intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied using SADABS (program SADABS V2.03 for absorption correction, G. M. Sheldrick, Bruker Analytical X-ray-Division, Madison, Wisconsin 2001) based on the Laue symmetry of the reciprocal space, □ = $0.07mm^{-1}$, T_{min} = 0.98, T_{max} = 1.00, structure solved by direct methods and refined against F^2 with a Full-matrix least-squares algorithm using the SHELXTL (6.12) software package (software package SHELXTL V6.12 for structure solution and refinement, G. M. Sheldrick, Bruker Analytical X-ray-Division, Madison, Wisconsin 2001), 301 parameters refined, hydrogen atoms were refined isotropically, goodness of fit 1.06 for observed reflections, final residual values R1(F) = 0.039, wR(F^2) = 0.083 for observed reflections, residual electron density -0.14 to 0.12 $eÅ^{-3}$. Compound **11b**: colorless crystal (polyhedron), dimensions 0.50 x 0.14 x 0.10 mm^3, crystal system triclinic, space group $P\bar{1}$, Z = 2, a = 6.4203(3) Å, b = 10.0329(4) Å, c = 15.2326(7) Å, □ = 98.2440(10) deg, □ = 91.0590(10) deg, □ = 90.5330(10) deg, V = 970.82(7) $Å^3$, □ = 1.219 g/cm^3, T = 200(2) K, $□_{max}$ = 27.48 deg, radiation Mo K□, □ = 0.71073 Å, 0.3 deg omega-scans with CCD area detector, covering a whole sphere in reciprocal space, 9852 reflections measured, 4397 unique (R(int)=0.034), 2913 observed (I >2□(I)), intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied using SADABS (program SADABS V2.03 for absorption correction, G. M. Sheldrick, Bruker Analytical X-ray-Division, Madison, Wisconsin 2001) based on the Laue symmetry of the reciprocal space, □ = $0.07mm^{-1}$, T_{min}=0.96, T_{max}=0.99, structure solved by direct methods and refined against F^2 with a Full-matrix least-squares algorithm using the SHELXTL-PLUS (5.10) software package (software package SHELXTL V5.10 for structure solution and refinement, G. M. Sheldrick, Bruker Analytical X-ray-Division, Madison, Wisconsin 1997), 254 parameters refined, hydrogen atoms were treated using appropriate riding models, except of the hydrogen atoms of N23, which were refined isotropically, goodness of fit 1.02 for observed reflections, final residual values R1(F)=0.048, wR(F^2)=0.101 for observed reflections, residual electron density -0.17 to 0.24 $eÅ^{-3}$.

2. Three-Component Glyoxylation-Decarbonylative Alkynylation Synthesis of Alkynones 3 and 9



5.00 mmol of *N*-substituted 1*H*-(7-aza)indole **7** or pyrrole **8** in dry THF (25 mL) were placed under argon in a screw-cap vessel with septum, degassed with argon and cooled to 0 °C (water/ice). Then, oxalyl chloride (0.44 mL, 5.00 mmol) was added to the reaction mixture at 0 °C. The mixture was allowed to come to room temperature and was stirred for 4 h. Then, $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol), CuI (10 mg, 0.05 mmol), 5.00 mmol of terminal alkyne **2** and dry triethylamine (1.39 mL, 10.0 mmol) were successively added to the mixture and stirring at room temperature was continued for 1 h. The evolution of CO can be observed. After complete conversion (the evolution of CO ceased, the product formation was monitored by TLC) saturated brine (25 mL) was added, and the mixture was extracted with dichloromethane (3 x 25 mL). The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuo the residue was absorbed onto celite and chromatographed on silica gel with hexanes/ethylacetate or petrolether (boiling range 40-60 °C)/ethyl acetate to give the alkynones **3** or **9** (For experimental details see Table 1).

Table 1. Experimental details of the three-component glyoxylation-decarbonylative alkynylation synthesis of ynones **3** and **9**.

Entry	*N*-substituted (7-aza)indole **7** or pyrrole **8**	Alkyne **2**	Ynone **3** or **9** (isolated yield %)	Chromatographic purification R_f (eluent)
1	1.37 g (5.00 mmol) of **7a**	0.59 mL (5.00 mmol) of **2a**	479 mg (43 %)[a] of **3a**	DCM R_f (DCM) : 0.26
2	1.04 g (5.00 mmol) of **7b**	0.59 mL (5.00 mmol) of **2a**	1.17 g (74 %) of **3b**	HE-EE = 10:1 → 6:1 R_f (PE-EE = 7:1) : 0.27
3	1.04 g (5.00 mmol) of **7b**	0.44 mL (5.00 mmol) of **2b**	1.00 g (66 %) of **3c**	PE-EE = 7:1 → 5:1 → 3:1 R_f (PE-EE = 3:1) : 0.19
4	1.04 g (5.00 mmol) of **7b**	0.56 mL (5.00 mmol) of **2c**	1.42 g (85 %) of **3d**	PE-EE = 10:1 → 7:1 → 5:1 R_f (PE-EE = 5:1) : 0.27
5	1.04 g (5.00 mmol) of **7b**	0.73 mL (5.00 mmol) of **2d**	1.27 g (76 %) of **3e**	PE-EE[b] R_f (PE-EE = 8:1) : 0.31
6	676 mg (5.00 mmol) of **7c**	0.73 mL (5.00 mmol) of **2d**	819 mg (64 %) of **3f**	PE-EE[b] R_f (PE-EE = 6:1) : 0.23
7	1.37 g (5.00 mmol) of **7a**	0.59 mL (5.00 mmol) of **2a**	855 mg (45 %) of **3g**	PE-EE = 100:1 → 50:1 → 20:1 R_f (PE-EE = 20:1) : 0.33
8	1.04 g (5.00 mmol) of **7d**	0.59 mL (5.00 mmol) of **2a**	990 mg (63 %) of **3h**	PE-EE = 7:1 → 5:1 R_f (PE-EE = 5:1) : 0.27
9	661 mg (5.00 mmol) of **7e**	0.56 mL (5.00 mmol) of **2c**	793 mg (61 %) of **3i**	PE-EE[c] R_f (PE-EE = 2:1) : 0.23
10	410 mg (5.00 mmol) of **8a**	0.59 mL (5.00 mmol) of **2a**	577 mg (61 %)[d] of **9a**	PE-EE = 20:1 R_f (PE-EE = 20:1) : 0.26
11	0.79 mL (5.00 mmol) of **8b**	0.59 mL (5.00 mmol) of **2a**	574 mg (43 %)[e] of **9b**	PE-EE = 20:1 R_f (PE-EE = 20:1) : 0.32

[a] After addition of 1.1 equiv of TBAF (1 *M* in THF) to the reaction mixture and stirring at room temperature for 5 min. the product **3a** was obtained.

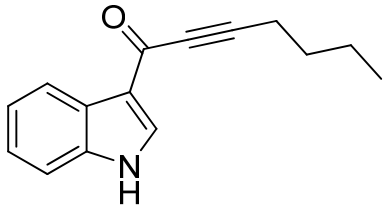
[b] The chromatographic purification was performed on the SP1 purification system of Biotage using a SNAP-cartridge (silica gel, 50 g). The TLC-method was applied using PE-EE gradient.

[c] The chromatographic purification was performed on the SP1 purification system of Biotage using a SNAP-cartridge (silica gel, 100 g). The TLC-method was applied using PE-EE gradient.

[d] The decarbonylative alkynylation step was carried out for 2 d.

[e] The decarbonylative alkynylation step was carried out overnight.

2.1. 1-(1*H*-Indol-3-yl)hept-2-yn-1-one (3a)

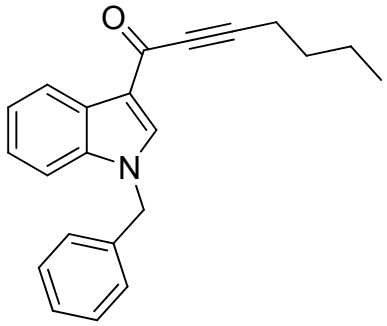


$C_{15}H_{15}NO$

225.29

479 m (43 % yield) as a yellow solid. Mp. 108-109 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 0.93 (t, *J* = 7.3 Hz, 3 H), 1.45 (sext, *J* = 7.3 Hz, 2 H), 1.59 (quint, *J* = 7.3 Hz, 2 H), 2.50 (t, *J* = 7.3 Hz, 2 H), 7.19-7.27 (m, 2 H), 7.51 (d, *J* = 8.2 Hz, 1 H), 8.13 (dd, *J* = 7.6 Hz, *J* = 0.6 Hz, 1 H), 8.22 (d, *J* = 3.2 Hz, 1 H), 12.2 (br, 1 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 13.4 (CH_3), 17.8 (CH_2), 21.5 (CH_2), 29.5 (CH_2), 80.3 (C_{quat}), 90.6 (C_{quat}), 112.5 (CH), 118.2 (C_{quat}), 121.0 (CH), 122.2 (CH), 123.3 (CH), 124.7 (C_{quat}), 136.9 (CH), 136.9 (C_{quat}), 171.0 (C_{quat}). EI + MS (*m/z* (%)): 225 (M^+, 100), 196 ((M-C_2H_5)$^+$, 29), 183 ((M-C_3H_7+H)$^+$, 48), 168 ((M-C_4H_9)$^+$, 20), 154 (57), 144 ($C_9H_6NO^+$, 32), 127 (14), 117 ($C_8H_7N^+$, 20), 89 (10). IR (KBr): $\tilde{\nu}$ 3214 (s) cm^{-1}, 2953 (m), 2215 (m), 1592 (m), 1568 (s), 1519 (m), 1491 (w), 1456 (m), 1422 (s), 1382 (m), 1315 (m), 1229 (m), 1188 (w), 1123 (w), 1090 (w), 1050 (w), 1011 (w), 992 (w), 902 (w), 886 (w), 861 (w), 768 (w), 756 (m), 732 (w), 675 (w), 623 (w), 577 (w), 517 (w). Anal. calcd. for $C_{15}H_{15}NO$ (225.3) : C 79.97, H 6.71, N 6.22. Found: C 79.82, H 6.79, N 6.19.

2.2. 1-(1-Benzyl-1*H*-indol-3-yl)hept-2-yn-1-one (3b)

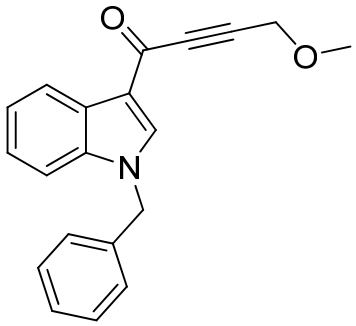


$C_{22}H_{21}NO$

315.41

1.17 g (74 % yield) as a yellow solid. Mp. 84-85 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.94 (t, J = 7.5 Hz, 3 H), 1.47 (sext, J = 8.3 Hz, 2 H), 1.62 (quint, J = 8.3 Hz, 2 H), 2.44 (t, J = 7.5 Hz, 2 H), 5.35 (s, 2 H), 7.13-7.39 (m, 8 H), 7.90 (s, 1 H), 8.38-8.44 (m, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.6 (CH_3), 18.7 (CH_2), 22.1 (CH_2), 30.0 (CH_2), 50.9 (CH_2), 80.6 (C_{quat}), 91.0 (C_{quat}), 110.3 (CH), 118.9 (C_{quat}), 122.6 (CH), 123.0 (CH), 123.8 (CH), 126.1 (C_{quat}), 127.1 (CH), 128.3 (CH), 129.1 (CH), 135.5 (C_{quat}), 137.3 (C_{quat}), 138.1 (CH), 171.8 (C_{quat}). EI + MS (*m/z* (%)): 315 (M^+, 100), 91 ($C_7H_7^+$, 40). IR (KBr): $\tilde{\nu}$ 3119 (w) cm^{-1}, 2955 (w), 2932 (w), 2870 (w), 2226 (w), 1607 (s), 1576 (w), 1522 (s), 1495 (s), 1486 (s), 1465 (w), 1453 (m), 1440 (w), 1386 (s), 1360 (w), 1237 (w), 1184 (s), 1027 (w), 827 (w), 771 (w), 752 (m), 730 (w). UV/Vis (CH_2Cl_2) λ_{max} (ε): 258 nm (12900), 272 (8700), 326 (16900). Anal. calcd. for $C_{22}H_{21}NO$ (315.4) : C 83.78, H 6.71, N 4.44. Found: C 83.64, H 6.71, N 4.43.

2.3. 1-(1-Benzyl-1*H*-indol-3-yl)-4-methoxybut-2-yn-1-one (3c)

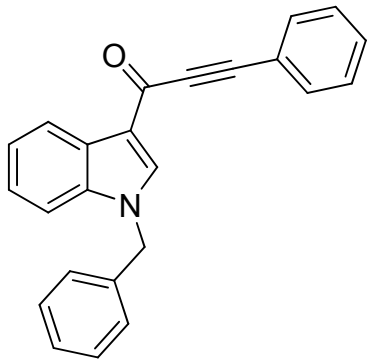


$C_{20}H_{17}NO_2$

303.35

1.00 g (66 % yield) as a brown solid (crystallization from dichloromethane/pentane gave upon cooling brown crystals). Mp. 109-111 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.43 (s, 3 H), 4.33 (s, 2 H), 5.35 (s, 2 H), 7.17 (d, *J* = 7.3 Hz, 2 H), 7.25-7.37 (m, 6 H), 7.94 (s, 1 H), 8.40 (d, *J* = 7.6 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 51.0 (CH_2), 58.1 (CH_3), 59.9 (CH_2), 84.3 (C_{quat}), 85.1 (C_{quat}), 110.5 (CH), 118.5 (C_{quat}), 122.6 (CH), 123.3 (CH), 124.1 (CH), 125.9 (C_{quat}), 127.0 (CH), 128.3 (CH), 129.1 (CH), 135.3 (C_{quat}), 137.3 (C_{quat}), 138.6 (CH), 170.6 (C_{quat}). EI + MS (*m/z* (%)): 303 (M^+, 32), 91 ($C_7H_7^+$, 100), 65 ($C_5H_5^+$, 12). IR (KBr): $\tilde{\nu}$ 3450 (m) cm^{-1}, 3119 (m), 3057 (m), 2989 (m), 2938 (m), 2822 (m), 2234 (m), 1609 (s), 1528 (s), 1487 (m), 1467 (m), 1453 (m), 1443 (m), 1392 (s), 1374 (m), 1241 (w), 1190 (s), 1166 (m), 1109 (m), 1029 (w), 952 (w), 871 (m), 750 (m), 740 (m). UV/Vis (CH_2Cl_2) λ_{max} (ε): 268 nm (20800), 282 (17900), 338 (19100). Anal. calcd. for $C_{20}H_{17}NO_2$ (303.4) : C 79.19, H 5.65, N 4.62. Found: C 78.90, H 5.48, N 4.72.

2.4. 1-(1-Benzyl-1*H*-indol-3-yl)-3-phenylprop-2-yn-1-one (3d)

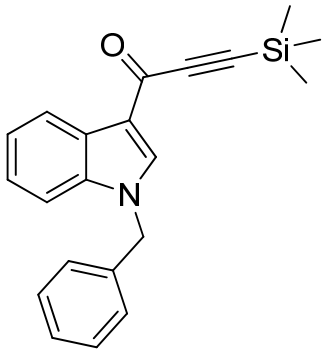


$C_{24}H_{17}NO$

335.40

1.42 g (85 % yield) as a brown solid (recrystallization from hot ethylacetate gave upon cooling red crystals). Mp. 160-162 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.38 (s, 2 H), 7.16-7.20 (m, 2 H), 7.25-7.46 (m, 9 H), 7.59-7.63 (m, 2 H), 8.02 (s, 1 H), 8.46 (dt, *J* = 7.6 Hz, *J* = 0.9 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 51.0 (CH_2), 87.9 (C_{quat}), 87.9 (C_{quat}), 110.5 (CH), 118.9 (C_{quat}), 120.7 (C_{quat}), 122.6 (CH), 123.2 (CH), 124.0 (CH), 126.1 (C_{quat}), 127.1 (CH), 128.3 (CH), 128.6 (CH), 129.1 (CH), 130.1 (CH), 132.7 (CH), 135.4 (C_{quat}), 137.3 (C_{quat}), 138.2 (CH), 171.3 (C_{quat}). EI + MS (*m/z* (%)): 335 (M^+, 6), 307 ($(M\text{-}CO)^+$, 1), 216 ($(M\text{-}CO\text{-}C_7H_7)^+$, 3), 129 ($C_9H_5O^+$, 6), 91 ($C_7H_7^+$, 100), 65 ($C_5H_5^+$, 100). IR (KBr): $\tilde{\nu}$ 3431 (m) cm^{-1}, 3109 (w), 3060 (w), 3032 (w), 2226 (m), 2195 (m), 1600 (s), 1521 (s), 1490 (m), 1461 (m), 1446 (m), 1389 (s), 1338 (w), 1275 (w), 1254 (w), 1174 (s), 1064 (m), 949 (m), 795 (w), 752 (s), 732 (m), 693 (m). UV/Vis (CH_2Cl_2) λ_{max} (ε): 268 nm (20800), 282 (17900), 338 (19100). Anal. calcd. for $C_{24}H_{17}NO$ (335.4) : C 85.95, H 5.11, N 4.18. Found: C 85.78, H 5.11, N 4.04.

2.5. 1-(1-Benzyl-1*H*-indol-3-yl)-3-(trimethylsilyl)prop-2-yn-1-one (3e)

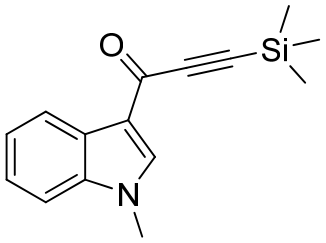


$C_{21}H_{21}NOSi$

331.48

1.27 g (76 % yield) as a brown oil (crystallization from dichloromethane/pentane gave upon cooling pale yellow crystals). Mp. 128-129 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.27 (s, 9 H), 5.36 (s, 2 H), 7.15-7.40 (m, 8 H), 7.89 (s, 1 H), 8.37-8.43 (m, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ -0.6 (CH_3), 51.0 (CH_2), 94.4 (C_{quat}), 102.4 (C_{quat}), 110.4 (CH), 118.6 (C_{quat}), 122.6 (CH), 123.1 (CH), 124.0 (CH), 126.0 (C_{quat}), 127.2 (CH), 128.4 (CH), 129.1 (CH), 135.2 (C_{quat}), 137.4 (C_{quat}), 138.4 (CH), 170.9 (C_{quat}). EI + MS (*m/z* (%)): 331 (M^+, 100), 316 ($(M-CH_3)^+$, 6), 288 ($(M-CH_3-CO)^+$, 9), 91 ($C_7H_7^+$, 40). IR (KBr): $\tilde{\nu}$ 3109 (w) cm^{-1}, 3032 (w), 2961 (w), 2903 (w), 2161 (w), 1606 (s), 1576 (m), 1522 (s), 1485 (m), 1464 (m), 1455 (m), 1441 (m), 1385 (s), 1358 (m), 1252 (m), 1177 (s), 1150 (m), 1068 (m), 956 (s), 856 (s), 848 (s), 771 (m), 762 (s), 753 (s), 740 (m). UV/Vis (CH_2Cl_2) λ_{max} (ε): 260 nm (13500), 274 (9500), 334 (17800), 340 (16000). Anal. calcd. for $C_{21}H_{21}NOSi$ (331.5) : C 76.09, H 6.39, N 4.23. Found: C 76.15, H 6.46, N 4.24.

2.6. 1-(1-Methyl-1*H*-indol-3-yl)-3-(trimethylsilyl)prop-2-yn-1-one (3f)

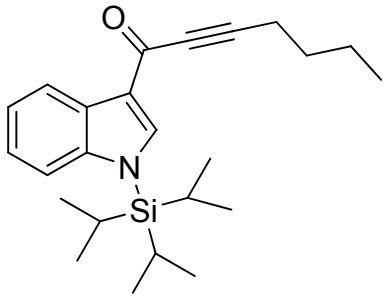


$C_{15}H_{17}NOSi$

255.39

819 mg (64 % yield) as a pale yellow solid (crystallization from dichloromethane/pentane gave upon cooling pale yellow needles). Mp. 103-104 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.31 (s, 9 H), 3.86 (s, 3 H), 7.28-7.35 (m, 3 H), 7.85 (s, 1 H), 8.35-8.40 (m, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ -0.5 (CH_3), 33.7 (CH_3), 94.1 (C_{quat}), 102.4 (C_{quat}), 109.8 (CH), 118.1 (C_{quat}), 122.5 (CH), 123.0 (CH), 123.9 (CH), 125.7 (C_{quat}), 137.8 (C_{quat}), 139.1 (CH), 170.8 (C_{quat}). EI + MS (*m/z* (%)): 255 (M^+, 100), 240 ($(M\text{-}CH_3)^+$, 26), 212 ($(M\text{-}CH_3\text{-}CO)^+$, 71), 158 ($(M\text{-}C_5H_9Si)^+$, 60), 139 (12), 130 ($C_9H_8N^+$, 14), 120 (17), 103 (20), 77 (16). IR (KBr): $\tilde{\nu}$ 3443 (m) cm^{-1}, 3115 (m), 3055 (m), 2963 (m), 2900 (m), 2151 (w), 1678 (w), 1606 (s), 1576 (m), 1527 (s), 1485 (m), 1465 (s), 1423 (w), 1392 (m), 1375 (s), 1336 (m), 1252 (s), 1212 (s), 1167 (w), 1149 (m), 1127 (m), 1089 (s), 1050 (m), 1011 (w), 952 (s), 859 (s), 768 (s), 741 (s), 709 (w), 633 (w), 617 (w), 571 (w). Anal. calcd. for $C_{15}H_{17}NOSi$ (255.4) : C 70.54, H 6.71, N 5.48. Found: C 70.38, H 6.73, N 5.25.

2.7. 1-(1-(Triisopropylsilyl)-1*H*-indol-3-yl)hept-2-yn-1-one (3g)

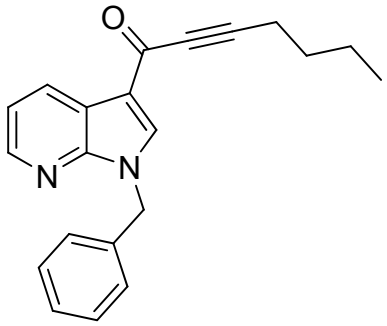


$C_{24}H_{35}NOSi$

381.63

855 mg (45 % yield) as an orange oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.98 (t, *J* = 7.6 Hz, 3 H), 1.18 (d, *J* = 7.6 Hz, 18 H), 1.54 (sext, *J* = 7.6 Hz, 2 H), 1.66 (quint, *J* = 7.6 Hz, 2 H), 1.73 (sept, *J* = 7.6 Hz, 3 H), 2.49 (t, *J* = 6.9 Hz, 2 H), 7.23-7.26 (m, 1 H), 7.28 (td, *J* = 7.3 Hz, *J* = 1.3 Hz, 1 H), 7.50 (d, *J* = 8.2 Hz, 1 H), 8.08 (s, 1 H), 8.38-8.42 (m, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 12.7 (CH_3), 17.7 (CH), 18.0 (CH_3), 18.7 (CH_2), 22.1 (CH_2), 30.1 (CH_2), 80.8 (C_{quat}), 90.8 (C_{quat}), 114.1 (CH), 121.8 (C_{quat}), 122.3 (CH), 122.7 (CH), 123.4 (CH), 128.0 (C_{quat}), 141.7 (C_{quat}), 142.7 (CH), 172.2 (C_{quat}). EI + MS (*m/z* (%)): 382 (M^+, 1), 225 ($(M-C_9H_{21}Si+H)^+$, 38), 196 (16), 183 (31), 167 (24), 154 (100), 139 (12), 131 (22), 127 (39), 116 (36), 103 (21), 89 (52), 75 (59), 61 (30), 41 (69). IR (KBr): $\tilde{\nu}$ 3160 (m) cm^{-1}, 2953 (m), 2931 (m), 2869 (m), 2215 (m), 1592 (s), 1569 (s), 1519 (s), 1492 (m), 1456 (m), 1422 (s), 1382 (m), 1314 (m), 1229 (s), 1189 (m), 1123 (m), 1011 (w), 992 (w), 902 (w), 889 (w), 861 (m), 769 (m), 755 (s), 732 (m), 675 (w), 623 (w), 577 (w), 516 (w). Anal. calcd. for $C_{24}H_{35}NOSi$ (381.6) : C 75.53, H 9.24, N 3.67. Found: C 75.41, H 9.46, N 3.44.

2.8. 1-(1-Benzyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)hept-2-yn-1-one (3h)

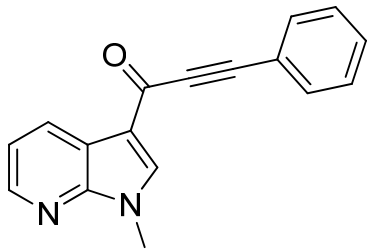


$C_{21}H_{20}N_2O$

316.40

990 mg (63 % yield) as an orange oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.93 (t, J = 7.3 Hz, 3 H), 1.45 (sext, J = 7.6 Hz, 2 H), 1.60 (quint, J = 7.3 Hz, 2 H), 2.43 (t, J = 7.3 Hz, 2 H), 5.53 (s, 2 H), 7.25-7.38 (m, 6 H), 7.96 (s, 1 H), 8.42 (d, J = 4.7 Hz, 1 H), 8.63 (d, J = 7.9 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.5 (CH_3), 18.7 (CH_2), 22.0 (CH_2), 29.9 (CH_2), 48.5 (CH_2), 80.1 (C_{quat}), 92.0 (C_{quat}), 117.1 (C_{quat}), 118.3 (C_{quat}), 119.0 (CH), 127.8 (CH), 128.2 (CH), 129.0 (CH), 130.8 (CH), 136.1 (C_{quat}), 137.0 (CH), 144.9 (CH), 148.4 (C_{quat}), 171.7 (C_{quat}). EI + MS (*m/z* (%)): 317 ($(M+H)^+$, 28), 288 ($(M-CO)^+$, 3), 207 ($C_{14}H_{11}N_2^+$, 20), 91 ($C_7H_7^+$, 100), 65 ($C_5H_5^+$, 17). IR (KBr): $\tilde{\nu}$ 3103 (w) cm^{-1}, 3057 (w), 3032 (w), 2959 (m), 2933 (m), 2872 (m), 2213 (m), 1614 (s), 1574 (m), 1523 (s), 1445 (m), 1425 (m), 1395 (m), 1359 (w), 1305 (m), 1255 (m), 1237 (m), 1179 (s), 1117 (m), 1028 (w), 890 (s), 867 (s), 835 (m), 801 (m), 779 (m), 737 (m), 699 (m), 634 (m), 576 (s). Anal. calcd. for $C_{21}H_{20}N_2O$ (316.4) : C 79.72, H 6.37, N 8.85. Found: C 79.54, H 6.38, N 8.80.

2.9. 1-(1-Methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-3-phenylprop-2-yn-1-one (3i)

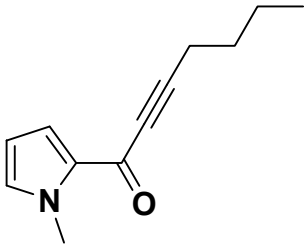


$C_{17}H_{12}N_2O$

260.29

793 mg (61 % yield) as an orange solid. Mp. 107-108 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.98 (s, 3 H), 7.25-7.29 (m, 1 H), 7.38-7.43 (m, 2 H), 7.43-7.49 (m, 1 H), 7.64-7.68 (m, 2 H), 8.12 (s, 1 H), 8.42 (dd, *J* = 4.7 Hz, *J* = 1.6 Hz, 1 H), 8.64 (dd, *J* = 7.9 Hz, *J* = 1.6 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 32.3 (CH_3), 87.5 (C_{quat}), 88.7 (C_{quat}), 116.8 (C_{quat}), 118.5 (C_{quat}), 119.1 (CH), 120.7 (C_{quat}), 128.8 (CH), 130.5 (CH), 130.9 (CH), 132.9 (CH), 138.6 (CH), 145.1 (CH), 148.7 (C_{quat}), 171.3 (C_{quat}). EI + MS (*m/z* (%)): 260 (M^+, 72), 232 ($(M-CO)^+$, 100), 231 ($(M-CO-H)^+$, 91), 159 ($C_9H_7N_2O^+$, 21), 131 (15), 129 (23), 116 (14). IR (KBr): $\tilde{\nu}$ 3449 (m) cm^{-1}, 2198 (m), 1609 (s), 1572 (w), 1524 (m), 1491 (w), 1446 (s), 1406 (w), 1380 (w), 1304 (w), 1274 (w), 1120 (w), 1086 (m), 948 (m), 801 (w), 772 (w), 729 (w), 693 (w). Anal. calcd. for $C_{17}H_{12}N_2O$ (260.3) : C 78.44, H 4.65, N 10.76. Found: C 78.21, H 4.44, N 10.87.

2.10. 1-(1-Methyl-1*H*-pyrrol-2-yl)hept-2-yn-1-one (9a)

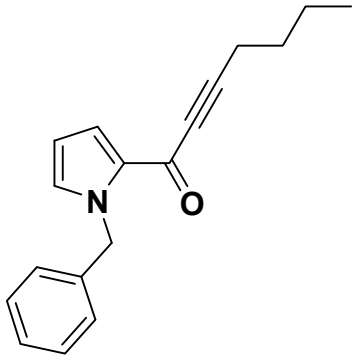


$C_{12}H_{15}NO$

189.25

577 mg (61 % yield) as an orange oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.95 (t, *J* = 7.3 Hz, 3 H), 1.44-1.53 (m, 2 H), 1.58-1.65 (m, 2 H), 2.43 (t, *J* = 7.3 Hz, 2 H), 3.93 (s, 3 H), 6.15 (dd, *J* = 4.1 Hz, *J* = 2.5 Hz, 1 H), 6.83 (t, *J* = 2.2 Hz, 1 H), 7.15 (dd, *J* = 4.1 Hz, *J* = 1.9 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.5 (CH_3), 18.7 (CH_2), 22.0 (CH_2), 29.9 (CH_2), 37.3 (CH_3), 80.2 (C_{quat}), 91.8 (C_{quat}), 108.8 (CH), 123.5 (CH), 132.1 (CH), 132.3 (C_{quat}), 167.4 (C_{quat}). EI + MS (*m/z* (%)): 189 (M^+, 22), 160 ($(M-C_2H_5)^+$, 28), 147 ($(M-C_3H_7+H)^+$, 53), 146 ($(M-C_3H_7)^+$, 52), 132 ($(M-C_4H_9)^+$, 17), 121 (15), 120 (58), 119 ($C_7H_5NO^+$, 19), 118 ($(M-C_4H_9-CH_3)^+$, 87), 117 (33), 108 ($C_6H_6NO^+$, 31), 104 (17), 94 (41), 91 (24), 81 (50), 80 (34), 79 (34), 78 (27), 77 (24), 67 (17), 66 (16), 65 ($C_4H_3N^+$, 29), 55 (13), 54 (11), 53 (C_3HO^+, 88), 52 (21), 51 (27), 43 (24), 42 (38), 41 ($C_2H_3N^+$, 47), 39 ($C_3H_3^+$, 100). IR (Film): $\tilde{\nu}$ 3109 (w) cm^{-1}, 2959 (s), 2873 (m), 2251 (m), 2207 (s), 1614 (s), 1525 (m), 1464 (m), 1403 (s), 1328 (m), 1243 (s), 1122 (m), 1090 (w), 1056 (m), 1021 (w), 982 (w), 960 (w), 906 (m), 868 (m), 832 (m), 737 (s), 706 (w), 605 (w). Anal. calcd. for $C_{12}H_{15}NO$ (189.3) : C 76.16, H 7.99, N 7.40. Found: C 75.97, H 7.95, N 7.35.

2.11. 1-(1-Benzyl-1*H*-pyrrol-2-yl)hept-2-yn-1-one (9b)

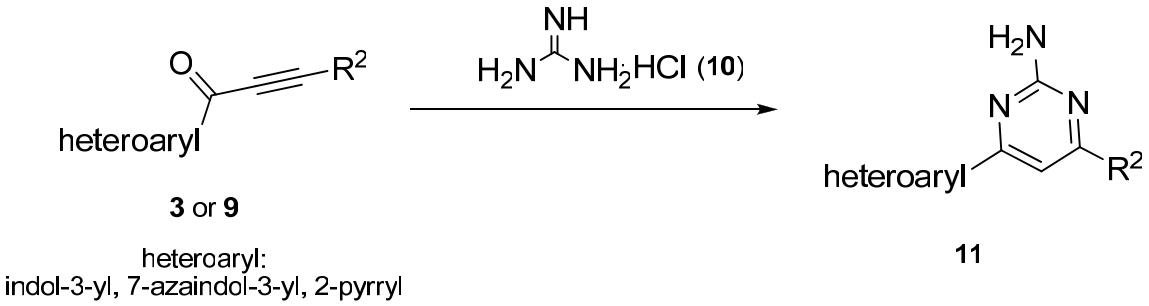


$C_{18}H_{19}NO$

265.35

574 mg (43 % yield) as an orange oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.94 (t, *J* = 7.6 Hz, 3 H), 1.47 (sext, *J* = 7.6 Hz, 2 H), 1.60 (quint, *J* = 7.3 Hz, 2 H), 2.41 (t, *J* = 7.3 Hz, 2 H), 5.57 (s, 2 H), 6.19-6.22 (m, 1 H), 6.91-6.94 (m, 1 H), 7.13 (d, *J* = 7.6 Hz, 2 H), 7.21-7.23 (m, 1 H), 7.23-7.31 (m, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.5 (CH_3), 18.7 (CH_2), 22.0 (CH_2), 29.9 (CH_2), 52.4 (CH_2), 80.3 (C_{quat}), 91.9 (C_{quat}), 109.4 (CH), 124.2 (CH), 127.3 (CH), 127.6 (CH), 128.6 (CH), 131.5 (CH), 131.7 (C_{quat}), 137.7 (C_{quat}), 167.2 (C_{quat}). EI + MS (*m/z* (%)): 265 (M^+, 3), 236 ((M-C_2H_5)$^+$, 2), 223 ((M-C_3H_7+H)$^+$, 11), 222 ((M-C_3H_7)$^+$, 9), 196 (43), 129 (14), 94 ($C_5H_4NO^+$, 25), 91 ($C_7H_7^+$, 100), 65 ($C_4H_3N^+$, 21), 53 (C_3HO^+, 3), 41 (6). IR (Film): $\tilde{\nu}$ 3108 (w) cm^{-1}, 3065 (w), 3032 (w), 2958 (m), 2932 (m), 2872 (m), 2240 (m), 2206 (m), 1614 (s), 1524 (m), 1496 (w), 1466 (m), 1455 (m), 1402 (s), 1358 (m), 1335 (s), 1252 (m), 1237 (s), 1199 (w), 1117 (s), 1080 (m), 1027 (w), 982 (w), 959 (w), 906 (m), 867 (m), 832 (m), 737 (s), 694 (m), 645 (w), 607 (w), 570 (w). Anal. calcd. for $C_{18}H_{19}NO$ (265.4): C 81.47, H 7.22, N 5.28. Found: C 81.43, H 7.11, N 5.02.

3. Synthesis of 2-Amino Pyrimidines 11



3 or **9**

heteroaryl:
indol-3-yl, 7-azaindol-3-yl, 2-pyrryl

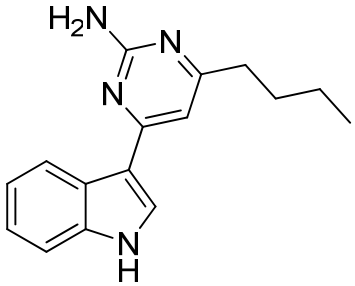
11

In a screw-cap vessel 1.00 mmol of the alkynone **3** or **9** was dissolved under nitrogen in 2-methoxyethanol (5 mL). Then, potassium carbonate (346 mg, 2.50 mmol) and guanidinium hydrochloride (**10**) (239 mg, 2.50 mmol) were added and the mixture was stirred at 120°C over night. Then, saturated brine (20 mL) was added and the mixture was extracted with dichloromethane (5 x 20 mL, monitored by TLC). The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuo the residue was absorbed onto celite and chromatographed on silica gel with dichloromethane/methanol/aqueous ammonia (For experimental details see Table 2).

Table 2. Experimental details of the synthesis of 2-amino pyrimidines **11**.

Entry	Ynone **3** or **9**	Guanidinium hydrochloride (**10**)	2-Amino pyrimidine **11** (isolated yield %)	Chromatographic purification (eluent)
1	290 mg (1.29 mmol) of **3a**	308 mg (3.23 mmol)	277 mg (81 %) of **11a**	DCM-MeOH-NH_3 = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1
2	315 mg (1.00 mmol) of **3b**	239 mg (2.50 mmol)	305 mg (86 %) of **11b**	DCM → DCM-MeOH-NH_3 = 100:1:1
3	303 mg (1.00 mmol) of **3c**	239 mg (2.50 mmol)	304 mg (88 %) of **11c**	DCM-MeOH-NH_3 = 100:1:1
4	335 mg (1.00 mmol) of **3d**	239 mg (2.50 mmol)	310 mg (82 %) of **11d**	DCM-MeOH-NH_3 = 200:1:1 → 100:1:1
5	658 mg (1.99 mmol) of **3e**	473 mg (4.95 mmol)	527 mg (88 %) of **11e**	DCM → DCM-MeOH-NH_3 = 200:1:1 → 100:1:1
6	255 mg (1.00 mmol) of **3f**	239 mg (2.50 mmol)	153 mg (68 %) of **11f**	DCM-MeOH-NH_3 = 100:1:1
7	672 mg (1.76 mmol) of **3g**	420 mg (4.40 mmol)	321 mg (68 %) of **11a**	DCM-MeOH-NH_3 = 100:1:1 → 100:3:1
8	907 mg (2.87 mmol) of **3h**	685 mg (7.17 mmol)	826 mg (81 %) of **11g**	DCM → DCM-MeOH-NH_3 = 200:1:1 → 100:1:1
9	260 mg (1.00 mmol) of **3i**	239 mg (2.50 mmol)	258 mg (86 %) of **11h**	DCM-MeOH-NH_3 = 100:1:1
10	503 mg (2.66 mmol) of **9a**	635 mg (6.64 mmol)	566 mg (92 %) of **11i**	DCM → DCM-MeOH-NH_3 = 100:1:1
11	356 mg (1.34 mmol) of **3k**	320 mg (3.35 mmol)	384 mg (94 %) of **9j**	DCM → DCM-MeOH-NH_3 = 100:1:1

3.1. 4-Butyl-6-(1*H*-indol-3-yl)pyrimid-2-yl-amine (11a)

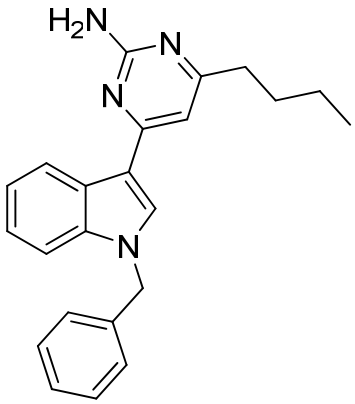


$C_{16}H_{18}N_4$

266.34

277 mg (81 % yield from **3a**) as a yellow solid. From **3g** the same procedure gave 321 mg (68 % yield) as a yellow solid. Mp. 153-158 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 0.91 (t, *J* = 7.3 Hz, 3 H), 1.35 (sext, *J* = 7.3 Hz, 2 H), 1.66 (quint, *J* = 7.6 Hz, 2 H), 2.50 (t, *J* = 7.6 Hz, 2 H), 6.37 (s, 2 H, N$\underline{H}_2$), 6.94 (s, 1 H), 7.10-7.15 (m, 1 H), 7.15-7.20 (m, 1 H), 7.45 (d, *J* = 7.9 Hz, 1 H), 8.19 (d, *J* = 2.8 Hz, 1 H), 8.60 (d, *J* = 7.9 Hz, 1 H), 11.6 (br, 1H, N$\underline{H}$). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 13.9 (CH_3), 22.0 (CH_2), 30.6 (CH_2), 36.9 (CH_2), 103.9 (CH), 111.8 (CH), 114.0 (C_{quat}), 120.2 (CH), 121.9 (CH), 122.4 (CH), 125.5 (C_{quat}), 127.9 (CH), 137.0 (C_{quat}), 162.7 (C_{quat}), 163.6 (C_{quat}), 169.8 (C_{quat}). EI + MS (*m/z* (%)): 266 (M^+, 9), 224 ((M-C_3H_7+H)$^+$, 100). IR (KBr): $\tilde{\nu}$ 3486 (m) cm^{-1}, 3296 (m), 3127 (m), 2950 (m), 2928 (m), 2861 (m), 1754 (w), 1636 (m), 1575 (s), 1535 (s), 1493 (m), 1456 (m), 1430 (m), 1340 (w), 1319 (w), 1279 (w), 1246 (w), 1215 (m), 1175 (w), 1133 (m), 1110 (w), 1011 (w), 967 (w), 934 (w), 829 (w), 797 (w), 743 (m), 616 (w), 537 (w). Anal. calcd. for $C_{16}H_{18}N_4$ (266.3) : C 72.15, H 6.81, N 21.04. Found: C 71.99, H 6.79, N 21.08.

3.2. 4-(1-Benzyl-1*H*-indol-3-yl)-6-butylpyrimid-2-yl-amine (11b)

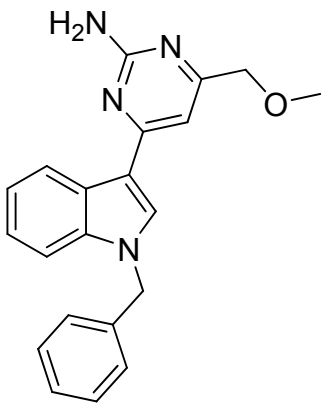


$C_{23}H_{24}N_4$

356.46

305 mg (86 % yield) as a pale yellow solid. Mp. 174-175 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.95 (t, J = 7.5 Hz, 3 H), 1.42 (sext, J = 7.5 Hz, 2 H), 1.72 (quint, J = 7.5 Hz, 2 H), 2.60 (t, J = 7.5 Hz, 2 H), 5.05 (s, 2 H, N$\underline{H}_2$), 5.35 (s, 2 H), 6.89 (s, 1 H), 7.11-7.18 (m, 2 H), 7.18-7.35 (m, 6 H), 7.84 (s, 1 H), 8.33-8.40 (m, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.0 (CH_3), 22.6 (CH_2), 31.2 (CH_2), 37.8 (CH_2), 50.5 (CH_2), 106.4 (CH), 110.3 (CH), 114.8 (C_{quat}), 121.2 (CH), 121.7 (CH), 122.6 (CH), 126.3 (C_{quat}), 126.9 (CH), 127.9 (CH), 128.9 (CH), 130.3 (CH), 136.5 (C_{quat}), 137.4 (C_{quat}), 162.5 (C_{quat}), 163.1 (C_{quat}), 171.4 (C_{quat}). EI + MS (*m/z* (%)): 356 (M^+, 27), 341 ($(M-CH_3)^+$, 3), 268 ($(M-C_2H_5)^+$, 7), 314 ($(M-C_3H_7+H)^+$, 100), 223 ($(M-C_3H_7+H-C_7H_7)^+$, 5), 91 ($C_7H_7^+$, 14). IR (KBr): $\tilde{\nu}$ 3463 (s) cm^{-1}, 3442 (s), 2956 (w), 2927 (w), 2860 (w), 1645 (m), 1628 (m), 1577 (s), 1521 (m), 1469 (m), 1456 (w), 1385 (m), 1175 (w), 743 (m). UV/Vis (CH_2Cl_2) λ_{max} (ε): 246 nm (14200), 264 (10100), 290 (9100), 328 (23500), 340 (18300). Anal. calcd. for $C_{23}H_{24}N_4$ (356.5) : C 77.50, H 6.79, N 15.72. Found: C 77.45, H 6.75, N 15.77.

3.3. 4-(1-Benzyl-1*H*-indol-3-yl)-6-(methoxymethyl)pyrimid-2-yl-amine (11c)

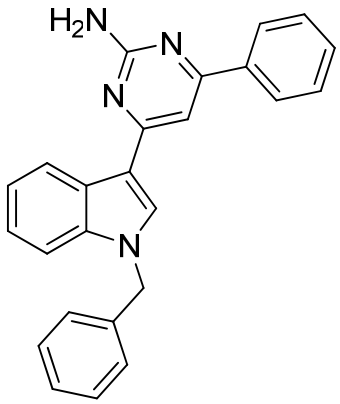


$C_{21}H_{20}N_4O$

344.41

304 mg (88 % yield) as a pale yellow solid. Mp. 183-188 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.51 (s, 3 H), 4.40 (s, 2 H), 5.1 (br, 2 H, N$\underline{H}_2$), 5.35 (s, 2 H), 7.11 (s, 1 H), 7.13-7.17 (m, 2 H), 7.22-7.33 (m, 6 H), 7.87 (s, 1 H), 8.43-8.46 (m, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 50.5 (CH_2), 59.0 (CH_3), 74.6 (CH_2), 104.0 (CH), 110.2 (CH), 114.6 (C_{quat}), 121.4 (CH), 122.1 (CH), 122.7 (CH), 126.3 (C_{quat}), 126.9 (CH), 128.0 (CH), 128.9 (CH), 130.6 (CH), 136.4 (C_{quat}), 137.5 (C_{quat}), 162.9 (C_{quat}), 163.4 (C_{quat}), 167.3 (C_{quat}). EI + MS (*m/z* (%)): 344 (M^+, 43), 314 ($M\text{-}OCH_3+H)^+$, 85), 223 ($(M\text{-}OCH_3\text{-}C_7H_7)^+$, 15), 91 ($C_7H_7^+$, 100), 65 ($C_5H_5^+$, 14), 58 (22), 43 (68). IR (KBr): $\tilde{\nu}$ 3460 (m) cm^{-1}, 3299 (m), 3170 (m), 2925 (w), 2819 (w), 1591 (s), 1546 (s), 1496 (w), 1473 (m), 1454 (m), 1429 (m), 1410 (m), 1389 (m), 1359 (w), 1304 (w), 1231 (w), 1199 (m), 1187 (m), 1130 (m), 1040 (w), 959 (w), 846 (w), 826 (w), 790 (w), 752 (m), 738 (m), 697 (w), 633 (w), 573 (w). Anal. calcd. for $C_{21}H_{20}N_4O$ (344.4) : C 73.23, H 5.85, N 16.27. Found: C 72.99, H 5.87, N 16.42.

3.4. 4-(1-Benzyl-1*H*-indol-3-yl)-6-phenylpyrimid-2-yl-amine (11d)

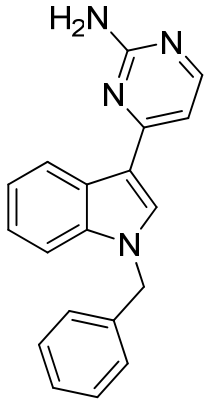


$C_{25}H_{20}N_4$

376.45

310 mg (82 % yield) as a yellow solid (crystallization from dichloromethane/pentane gave citric yellow crystals). Mp. 171-173 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.16 (s, 2 H, N$\underline{H}_2$), 5.37 (s, 2 H), 7.16 (d, *J* = 7.3 Hz, 2 H), 7.23-7.35 (m, 6 H), 7.43 (s, 1 H), 7.44-7.52 (m, 3 H), 7.92 (s, 1 H), 8.03-8.07 (m, 2 H), 8.43 (d, *J* = 7.3 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 50.5 (CH_2), 104.0 (CH), 110.4 (CH), 114.9 (C_{quat}), 121.4 (CH), 121.8 (CH), 122.7 (CH), 126.3 (C_{quat}), 126.9 (CH), 127.0 (CH), 127.9 (CH), 128.7 (CH), 128.9 (CH), 130.1 (CH), 130.4 (CH), 136.5 (C_{quat}), 137.5 (C_{quat}), 138.1 (C_{quat}), 163.2 (C_{quat}), 163.4 (C_{quat}), 165.2 (C_{quat}). EI + MS (*m/z* (%)): 376 (M^+, 100), 285 ((M-C_7H_7)$^+$, 8), 91 ($C_7H_7^+$, 87). IR (KBr): $\tilde{\nu}$ 3482 (w) cm^{-1}, 3324 (m), 3184 (m), 3055 (w), 1653 (m), 1566 (s), 1510 (s), 1468 (m), 1439 (m), 1403 (m), 1379 (m), 1357 (w), 1316 (m), 1233 (m), 1180 (m), 1068 (w), 1029 (w), 917 (w), 824 (w), 772 (m), 736 (m), 697 (m), 630 (m). Anal. calcd. for $C_{25}H_{20}N_4$ (376.5) : C 79.76, H 5.35, N 14.88. Found: C 79.71, H 5.18, N 14.86.

3.5. 4-(1-Benzyl-1*H*-indol-3-yl)pyrimid-2-yl-amine (11e)



$C_{19}H_{16}N_4$

300.36

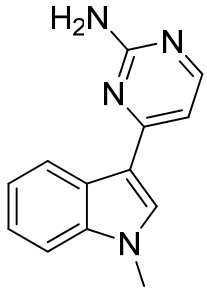
527 mg (88 % yield) as a pale yellow solid (recrystallization from hot ethylacetate gave upon cooling a colorless solid). Mp. 174-175 °C (Lit.[5]: 162-164 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.08 (s, 2 H, N<u>H</u>$_2$), 5.34 (s, 2 H), 6.97 (dd, *J* = 5.4 Hz, *J* = 0.6 Hz, 1 H), 7.14 (d, *J* = 7.3 Hz, 2 H), 7.22-7.31 (m, 6 H), 7.83 (s, 1 H), 8.22 (dd, *J* = 5.4 Hz, *J* = 0.6 Hz, 1 H), 8.39 (d, *J* = 7.6 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 50.5 (CH_2), 107.5 (CH), 110.3 (CH), 114.5 (C_{quat}), 121.4 (CH), 121.8 (CH), 122.8 (CH), 126.2 (C_{quat}), 126.9 (CH), 128.0 (CH), 128.9 (CH), 130.5 (CH), 136.4 (C_{quat}), 137.5 (C_{quat}), 157.6 (CH), 162.7 (C_{quat}), 163.1 (C_{quat}). EI + MS (*m/z* (%)): 300 (M^+, 100), 91 ($C_7H_7^+$, 89), 65 ($C_5H_5^+$, 9). IR (KBr): $\tilde{\nu}$ 3457 (w) cm^{-1}, 3299 (w), 3154 (w), 1624 (m), 1574 (s), 1534 (m), 1455 (s), 1331 (w), 1244 (w), 1221 (w), 1184 (m), 1097 (w), 885 (w), 812 (w), 743 (m), 698 (w), 631 (w), 572 (w). Anal. calcd. for $C_{19}H_{16}N_4$ (300.3) : C 75.98, H 5.37, N 18.65. Found: C 75.97, H 5.37, N 18.44.

NMR spectra of **11e** in acetone-d_6 and DMSO-d_6 are in agreement with *N*-benzyl meridianin G[5]:

^{1}H NMR (acetone-d_6, 500 MHz): δ 5.52 (s, 2 H), 5.9 (brs, 2 H, N<u>H</u>$_2$), 7.03 (d, *J* = 5.4 Hz, 1 H), 7.14-7.21 (m, 2 H), 7.25-7.30 (m, 3 H), 7.30-7.35 (m, 2 H), 7.44-7.47 (m, 1 H), 8.15 (d, *J* = 5.4 Hz, 1 H), 8.22 (s, 1 H), 8.60-8.63 (m, 1 H). ^{13}C NMR (acetone-d_6, 125 MHz): δ 50.9 (CH_2), 106.9 (CH), 111.4 (CH), 115.2 (C_{quat}), 121.7 (CH), 123.3 (CH), 123.7 (CH), 127.6 (C_{quat}), 128.0 (CH), 128.6 (CH), 129.6 (CH), 132.0 (CH), 138.4 (C_{quat}), 138.6 (C_{quat}), 158.3 (CH), 163.7 (C_{quat}), 165.0 (C_{quat}).

^{1}H NMR (DMSO-d_6, 500 MHz): δ 5.49 (s, 2 H), 6.45 (s, 2 H, N<u>H</u>$_2$), 6.98 (d, *J* = 5.4 Hz, 1 H), 7.13-7.21 (m, 2 H), 7.24-7.30 (m, 3 H), 7.30-7.35 (m, 2 H), 7.52 (d, *J* = 7.6 Hz, 1 H), 8.13 (d, *J* = 5.4 Hz, 1 H), 8.37 (s, 1 H), 8.57-8.61 (m, 1 H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 49.5 (CH_2), 105.3 (CH), 110.7 (CH), 113.4 (C_{quat}), 120.7 (CH), 122.2 (CH), 122.6 (CH), 126.0 (C_{quat}), 127.2 (CH), 127.6 (CH), 128.6 (CH), 131.6 (CH), 136.9 (C_{quat}), 137.5 (C_{quat}), 157.2 (CH), 162.1 (C_{quat}), 163.5 (C_{quat}).

3.6. 4-(1-Methyl-1*H*-indol-3-yl)pyrimid-2-yl-amine (11f)

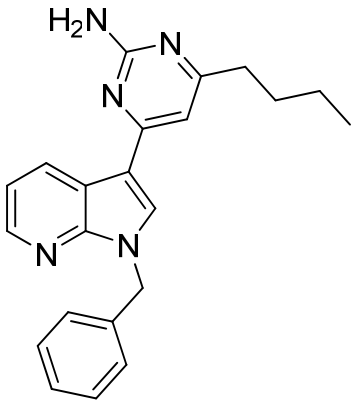


$C_{13}H_{12}N_4$

224.26

153 mg (68 % yield) as a colorless solid. Mp. 216-219 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 3.85 (s, 3 H), 6.42 (s, 2 H, N$\underline{H}_2$), 6.94 (d, *J* = 5.4 Hz, 1 H), 7.15-7.19 (m, 1 H), 7.22-7.26 (m, 1 H), 7.50 (d, *J* = 8.2 Hz, 1 H), 8.11 (d, *J* = 5.4 Hz, 1 H), 8.18 (s, 1 H), 8.59 (d, *J* = 7.9 Hz, 1 H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 32.8 (CH_3), 105.0 (CH), 110.1 (CH), 112.5 (C_{quat}), 120.4 (CH), 121.9 (CH), 122.4 (CH), 125.6 (C_{quat}), 132.0 (CH), 137.4 (C_{quat}), 157.0 (CH), 162.1 (C_{quat}), 163.4 (C_{quat}). EI + MS (*m/z* (%)): 224 (M^+, 100), 183 (86), 172 (14), 168 (16), 155 (34), 139 (35), 127 (16), 118 (15), 113 (20), 101 (15), 91 (12), 77 (31), 63 (20), 51 (13), 42 (40). IR (KBr): $\tilde{\nu}$ 3455 (m) cm^{-1}, 3292 (w), 3158 (w), 1625 (m), 1575 (s), 1536 (s), 1480 (m), 1458 (s), 1419 (w), 1372 (m), 1327 (w), 1235 (w), 1219 (m), 1155 (w), 1129 (w), 1106 (w), 1017 (w), 886 (w), 816 (w), 743 (m), 677 (w), 567 (w). Anal. calcd. for $C_{13}H_{12}N_4$ (224.3) : C 69.62, H 5.39, N 24.98. Found: C 69.53, H 5.56, N 25.11.

3.7. 4-(1-Benzyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-6-butylpyrimid-2-yl-amine (11g)

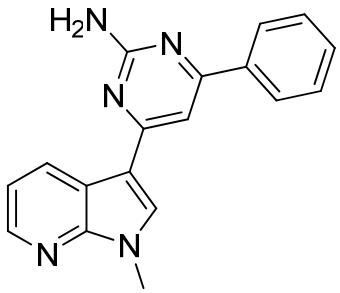


$C_{22}H_{23}N_5$

357.45

826 mg (81 % yield) as a yellow solid (crystallization from dichloromethane/pentane gave upon cooling citric yellow crystals). Mp. 133-135 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.95 (t, J = 7.3 Hz, 3 H), 1.41 (sext, J = 7.6 Hz, 2 H), 1.70 (quint, J = 7.6 Hz, 2 H), 2.58 (t, J = 7.9 Hz, 2 H), 5.05 (s, 2 H, N$\underline{H}_2$), 5.54 (s, 2 H), 6.79 (s, 1 H), 7.22 (dd, J = 7.9 Hz, J = 4.7 Hz, 1 H), 7.24-7.35 (m, 5 H), 7.87 (s, 1 H), 8.41 (d, J = 4.4 Hz, 1 H), 8.68 (d, J = 7.9 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.9 (CH_3), 22.6 (CH_2), 31.1 (CH_2), 37.8 (CH_2), 48.1 (CH_2), 105.9 (CH), 113.2 (C_{quat}), 117.4 (CH), 118.5 (C_{quat}), 127.6 (CH), 127.9 (CH), 128.8 (CH), 129.2 (CH), 130.4 (CH), 137.0 (C_{quat}), 143.9 (CH), 148.5 (C_{quat}), 162.0 (C_{quat}), 163.1 (C_{quat}), 171.6 (C_{quat}). EI + MS (*m/z* (%)): 357 (M^+, 17), 315 ((M-C_3H_7+H)$^+$, 100), 91 ($C_7H_7^+$, 40), 56 ($C_5H_5^+$, 5). IR (KBr): $\tilde{\nu}$ 3484 (m) cm^{-1}, 3296 (m), 3154 (m), 2955 (m), 2926 (m), 2858 (w), 1632 (m), 1579 (s), 1540 (s), 1468 (m), 1455 (m), 1422 (m), 1392 (m), 1358 (w), 1296 (w), 1227 (w), 1186 (w), 1131 (w), 812 (w), 777 (w), 728 (w), 697 (w), 620 (w). Anal. calcd. for $C_{22}H_{23}N_5$ (357.5) : C 73.92, H 6.49, N 19.59. Found: C 73.95, H 6.65, N 19.51.

3.8. 4-(1-Methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-6-phenylpyrimid-2-yl-amine (11h)

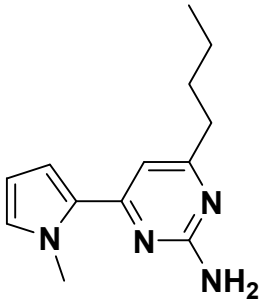


$C_{18}H_{15}N_5$

301.35

258 mg (86 % yield) as a yellow solid (crystallization from dichloromethane/methanol gave yellow crystals). Mp. 186 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 3.93 (s, 3 H), 6.63 (s, 2 H, N$\underline{H_2}$), 7.26 (dd, *J* = 7.9 Hz, *J* = 4.7 Hz, 1 H), 7.49-7.56 (m, 3 H), 7.63 (s, 1 H), 8.17-8.21 (m, 2 H), 8.37 (dd, *J* = 4.7 Hz, *J* = 1.6 Hz, 1 H), 8.63 (s, 1 H), 9.01 (dd, *J* = 7.9 Hz, *J* = 1.6 Hz, 1 H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 31.3 (CH_3), 100.6 (CH), 111.6 (C_{quat}), 116.9 (CH), 118.3 (C_{quat}), 126.7 (CH), 128.5 (CH), 130.1 (CH), 131.1 (CH), 132.3 (CH), 137.7 (C_{quat}), 143.3 (CH), 148.2 (C_{quat}), 162.9 (C_{quat}), 163.2 (C_{quat}), 163.9 (C_{quat}). EI + MS (*m/z* (%)): 301 (M^+, 100), 224 ((M-C_6H_5)$^+$, 1), 155 (($C_{10}H_7N_2$)$^+$, 12), 131 (($C_8H_7N_2$)$^+$, 19). IR (KBr): $\tilde{\nu}$ 3488 (w) cm^{-1}, 3296 (w), 3180 (w), 1624 (m), 1573 (s), 1534 (s), 1478 (m), 1453 (w), 1419 (w), 1391 (m), 1304 (w), 1222 (w), 1130 (w), 923 (w), 820 (w), 768 (m), 733 (w), 700 (w), 646 (w), 590 (w), 548 (w). Anal. calcd. for $C_{18}H_{15}N_5$ (301.4) : C 71.74, H 5.02, N 23.24. Found: C 71.73, H 5.20, N 22.95.

3.9. 4-Butyl-6-(1-methyl-1*H*-pyrrol-2-yl)pyrimid-2-yl-amine (11i)

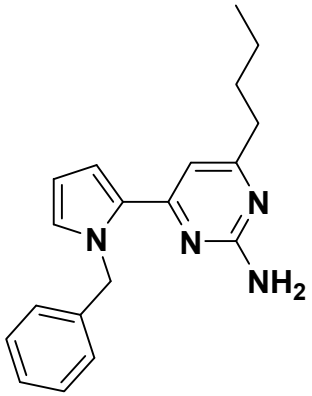


$C_{13}H_{18}N_4$

230.31

566 mg (92 % yield) as a yellow solid. Mp. 78-79 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.94 (t, *J* = 7.6 Hz, 3 H), 1.39 (sext, *J* = 7.6 Hz, 2 H), 1.67 (sept, *J* = 7.6 Hz, 2 H), 2.55 (t, *J* = 7.9 Hz, 2 H), 4.00 (s, 3 H), 5.07 (s, 2 H, N$\underline{H_2}$), 6.16 (dd, *J* = 3.8 Hz, *J* = 2.8 Hz, 1 H), 6.70-6.74 (m, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.9 (CH_3), 22.5 (CH_2), 31.1 (CH_2), 37.5 (CH_3), 37.7 (CH_2), 106.7 (CH), 108.0 (CH), 113.1 (CH), 128.1 (CH), 130.2 (C_{quat}), 159.8 (C_{quat}), 162.6 (C_{quat}), 171.3 (C_{quat}). EI + MS (*m/z* (%)): 230 (M^+, 5), 201 ($(M-C_2H_5)^+$, 8), 188 ($(M-C_3H_7+H)^+$, 100), 145 ($C_8H_7N_3^+$, 6), 106 (11), 105 (17), 104 (11), 80 ($C_4H_4N_2^+$, 12), 78 ($C_4H_2N_2^+$, 10), 43 ($C_3H_7^+$, 32), 42 (14), 41 ($C_2H_3N^+$, 13). IR (KBr): $\tilde{\nu}$ 3482 (m) cm^{-1}, 3292 (w), 3151 (w), 2952 (w), 2859 (w), 1627 (m), 1584 (s), 1560 (w), 1544 (m), 1490 (w), 1450 (w), 1418 (w), 1383 (w), 1323 (w), 1235 (w), 1145 (w), 1093 (w), 1070 (w), 832 (w), 791 (w), 723 (m), 683 (w), 607 (w), 548 (w). Anal. calcd. for $C_{13}H_{18}N_4$ (230.3) : C 67.80, H 7.88, N 24.33. Found: C 67.66, H 8.00, N 24.07.

3.10. 4-(1-Benzyl-1*H*-pyrrol-2-yl)-6-butylpyrimid-2-yl-amine (11j)

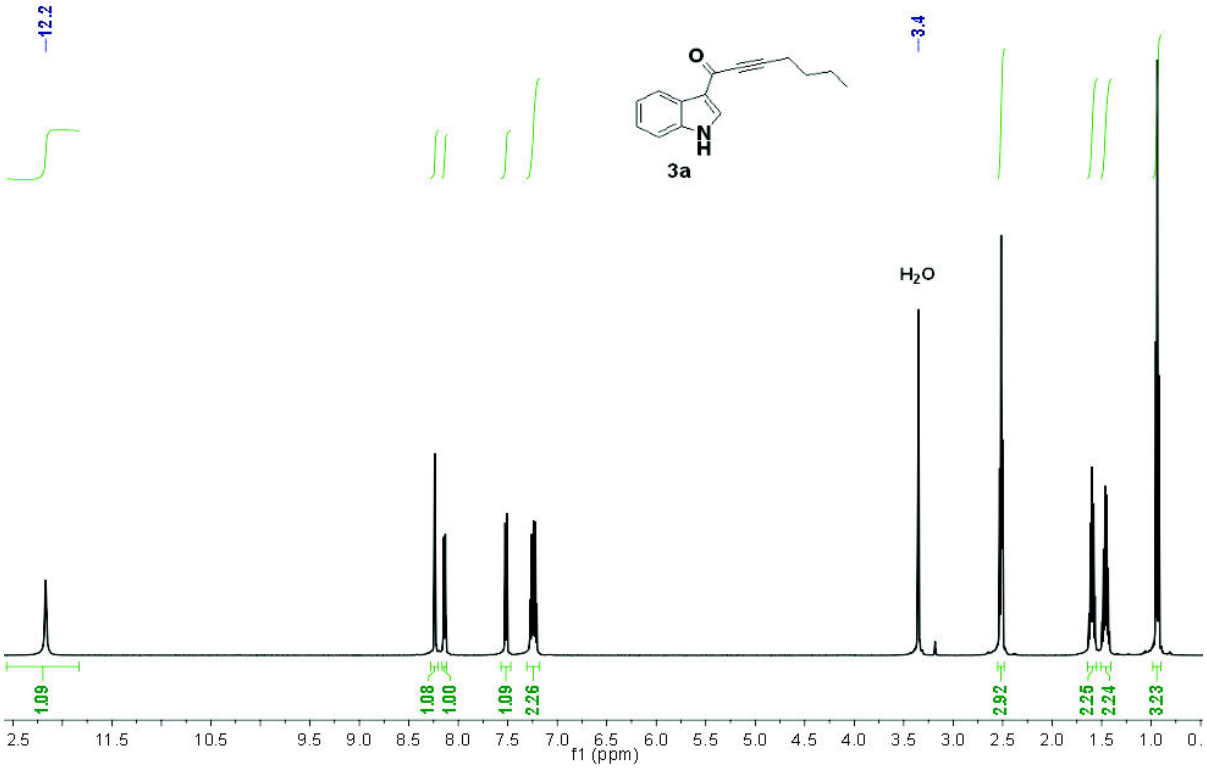


$C_{19}H_{22}N_4$

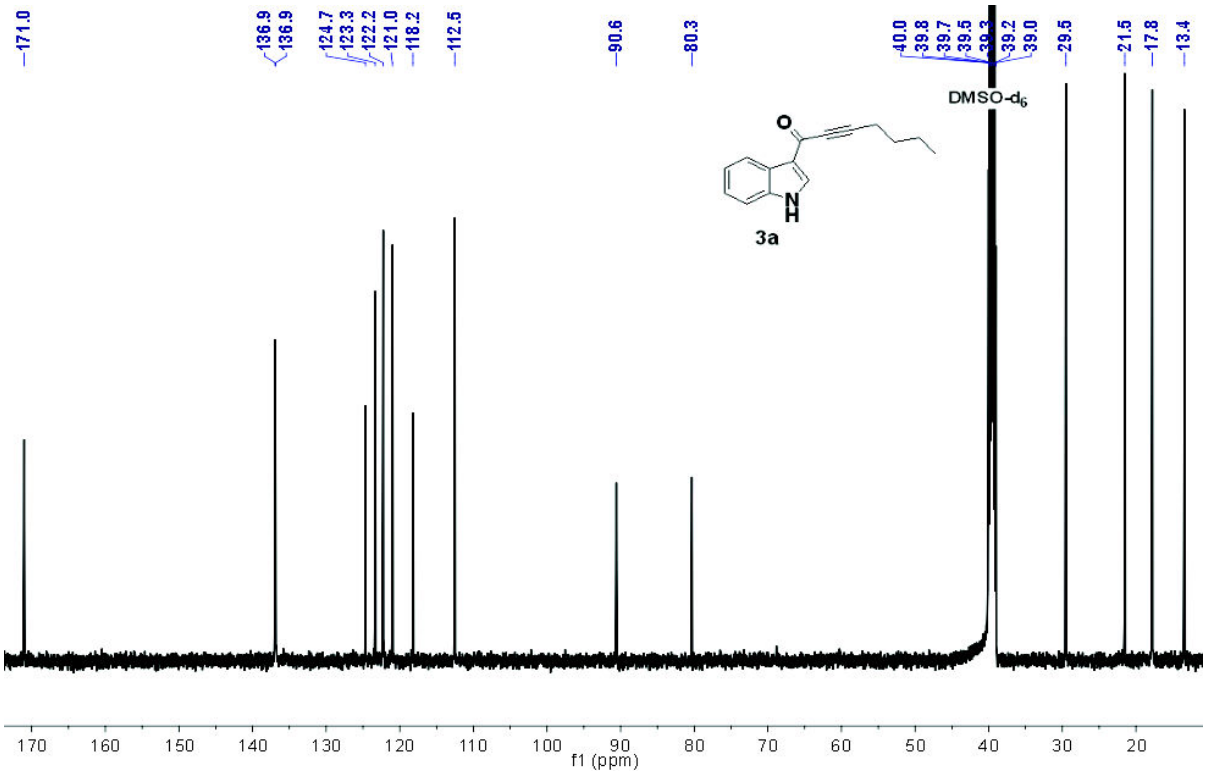
306.40

384 mg (94 % yield) as a yellow solid. Mp. 90 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.92 (t, *J* = 7.3 Hz, 3 H), 1.37 (sext, *J* = 7.6 Hz, 2 H), 1.60-1.67 (m, 2 H), 2.49-2.54 (m, 2 H), 4.88 (s, 2 H, N$\underline{H}_2$), 5.76 (s, 2 H), 6.23 (dd, *J* = 3.8 Hz, *J* = 2.5 Hz, 1 H), 6.70 (s, 1 H), 6.79 (dd, *J* = 3.8 Hz, *J* = 1.9 Hz, 1 H), 6.82 (dd, *J* = 2.5 Hz, *J* = 1.9 Hz, 1 H), 7.03-7.07 (m, 2 H), 7.17-7.22 (m, 1 H), 7.23-7.28 (m, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.9 (CH_3), 22.5 (CH_2), 31.0 (CH_2), 37.7 (CH_2), 52.4 (CH_2), 106.7 (CH), 108.7 (CH), 113.5 (CH), 126.6 (CH), 127.1 (CH), 127.7 (CH), 128.5 (CH), 129.8 (C_{quat}), 139.4 (C_{quat}), 159.6 (C_{quat}), 162.4 (C_{quat}), 171.3 (C_{quat}). EI + MS (*m/z* (%)): 306 (M^+, 8), 264 ((M-C_3H_7+H)$^+$, 17), 229 (18), 187 (9), 156 ($C_3H_{10}N^+$, 12), 91 ($C_7H_7^+$, 100), 86 (12), 84 (22), 51 (13), 49 (50), 47 (10). IR (KBr): $\tilde{\nu}$ 3481 (m) cm^{-1}, 3290 (w), 3143 (m), 2957 (w), 2930 (w), 2870 (w), 1629 (m), 1578 (s), 1543 (s), 1482 (m), 1453 (m), 1437 (m), 1422 (m), 1414 (m), 1389 (w), 1359 (m), 1283 (w), 1230 (w), 1139 (w), 1088 (m), 1033 (w), 970 (w), 907 (w), 847 (w), 827 (w), 782 (w), 726 (s), 692 (w), 642 (w), 618 (w), 564 (w). Anal. calcd. for $C_{19}H_{22}N_4$ (306.4) : C 74.48, H 7.24, N 18.29. Found: C 74.29, H 7.18, N 18.45.

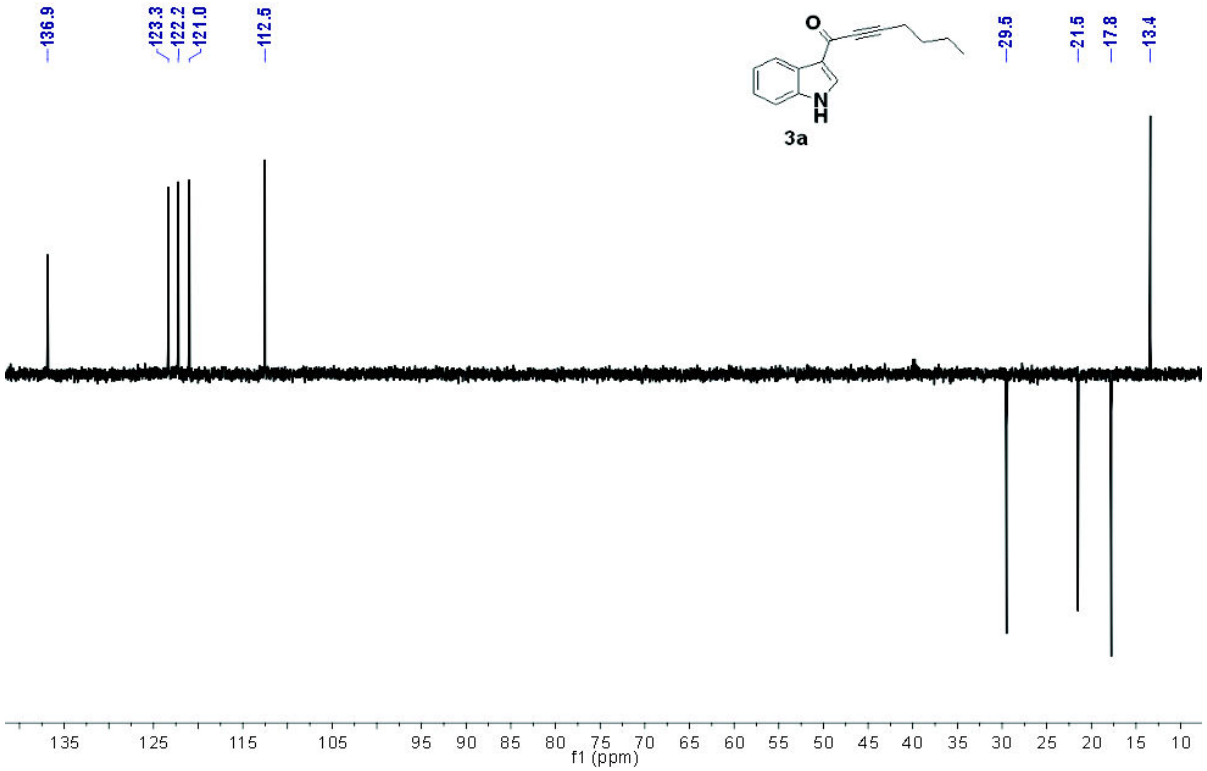
4. ^{1}H and ^{13}C MNR Spectra of Compounds 3a-i, 9a-b, and 11a-j



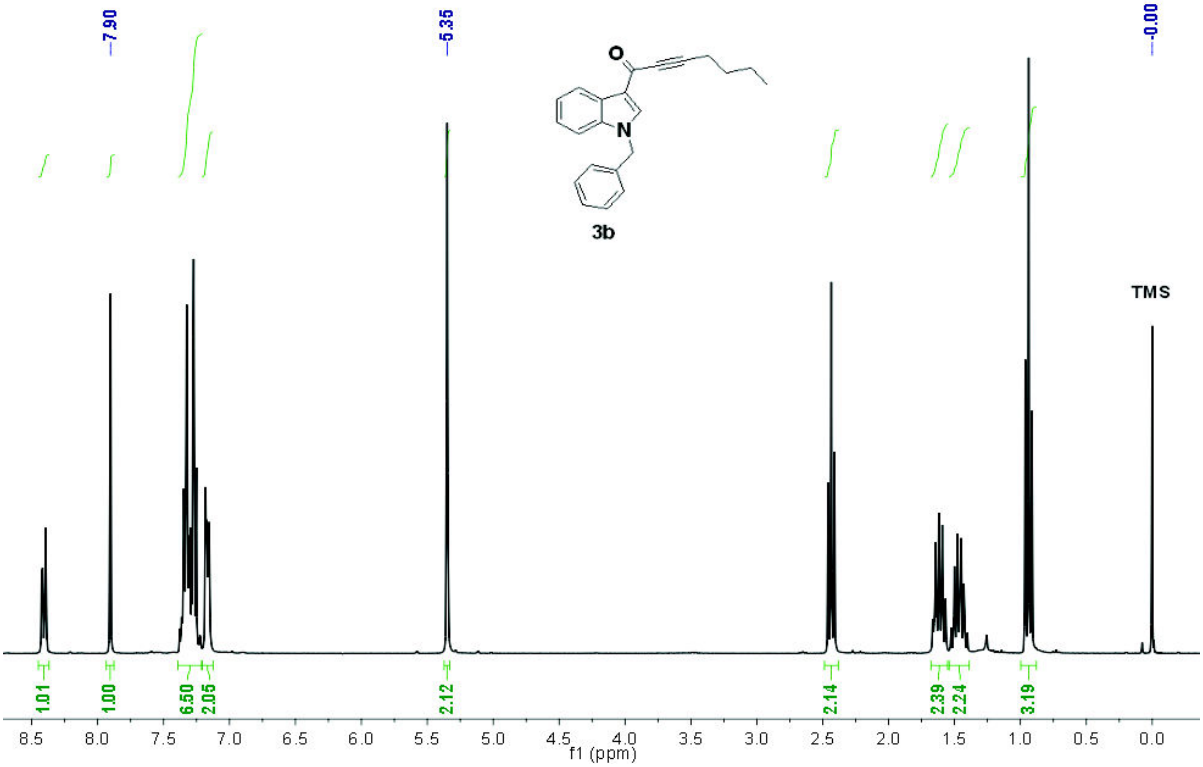
^{1}H NMR of **3a** in DMSO-d_6 at 298 K (δ in ppm).



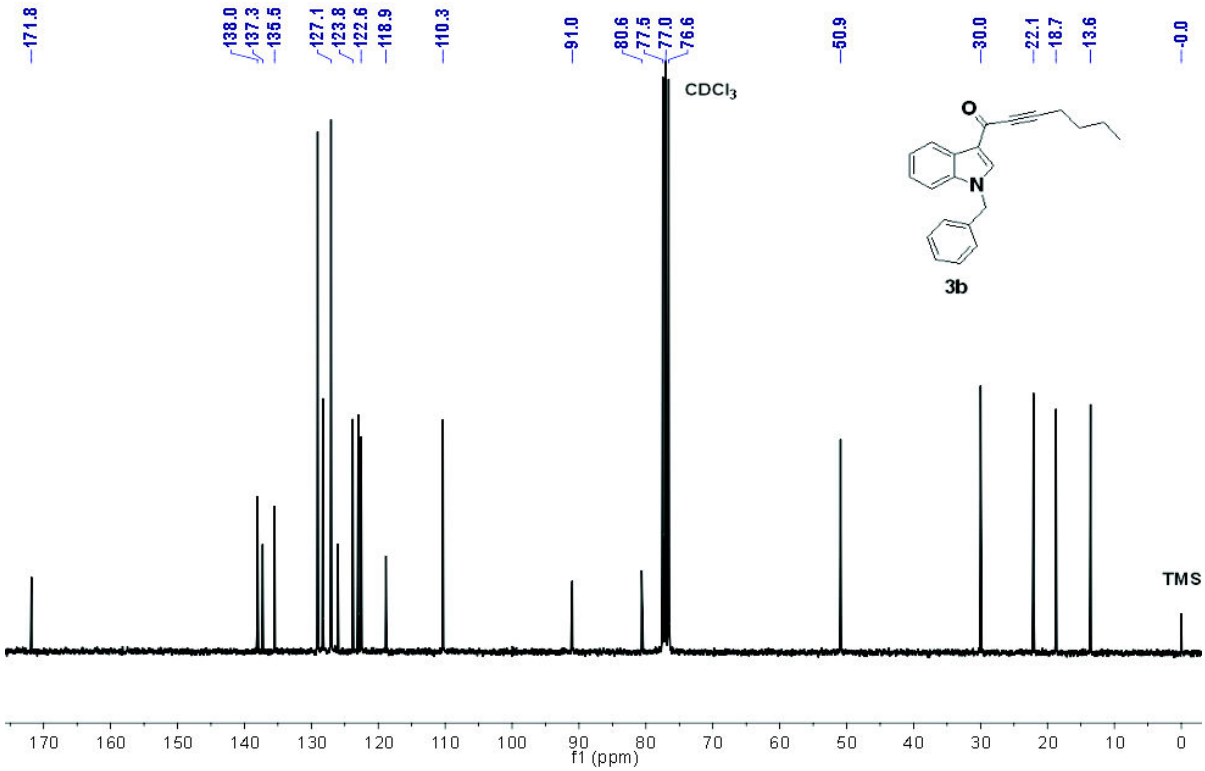
^{13}C NMR of **3a** in DMSO-d_6 at 298 K (δ in ppm).



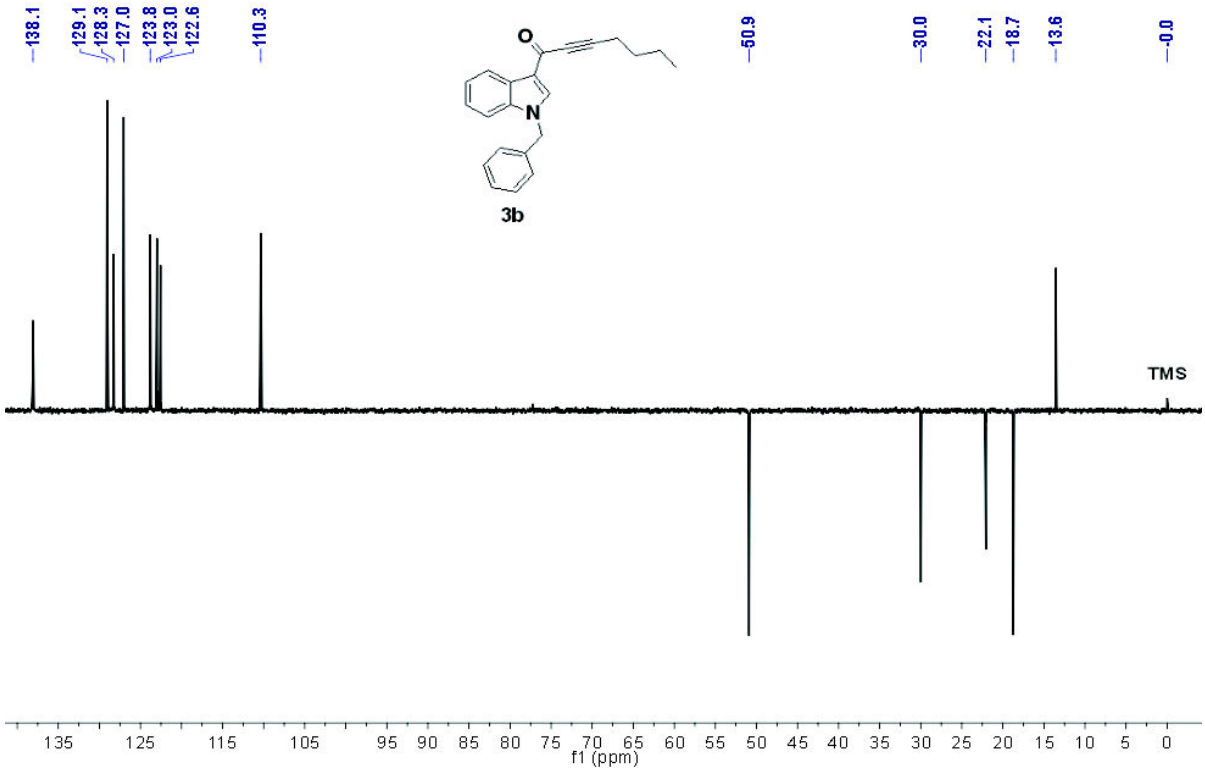
^{13}C DEPT 135-NMR of **3a** in DMSO-d_6 at 298 K (δ in ppm).



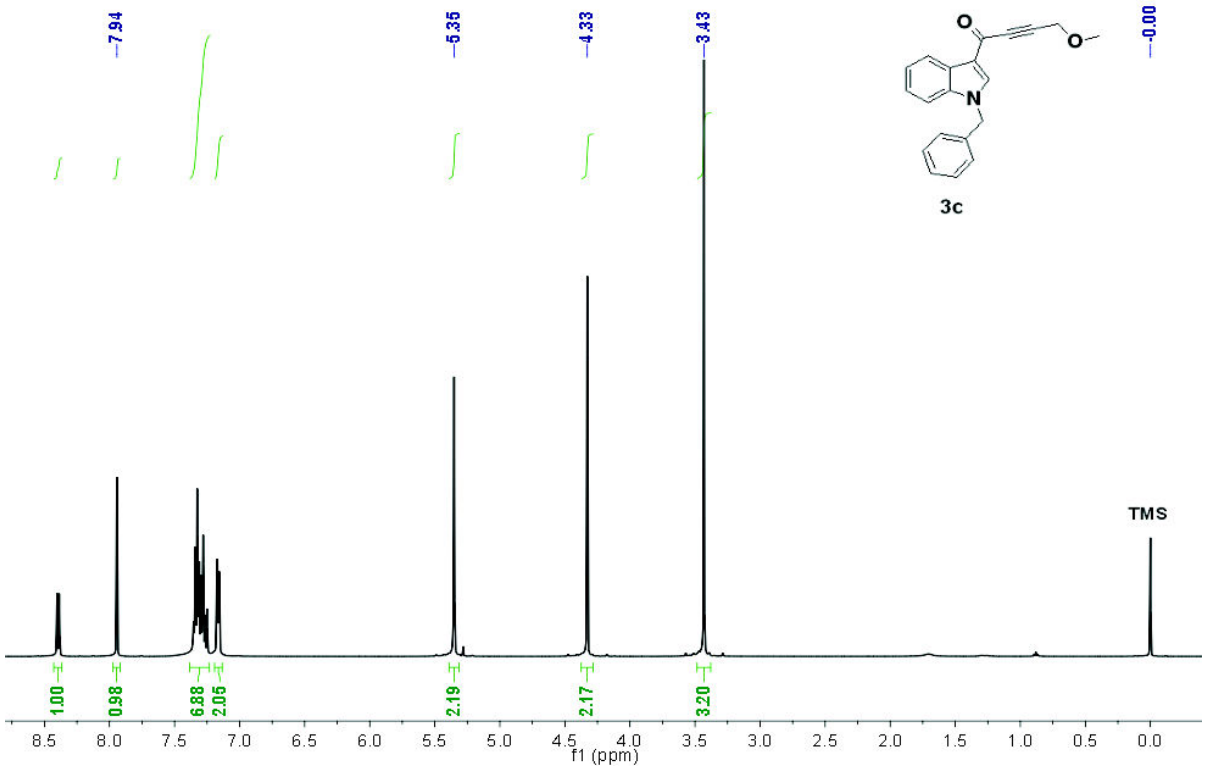
^{1}H NMR of **3b** in $CDCl_3$ at 298 K (δ in ppm).



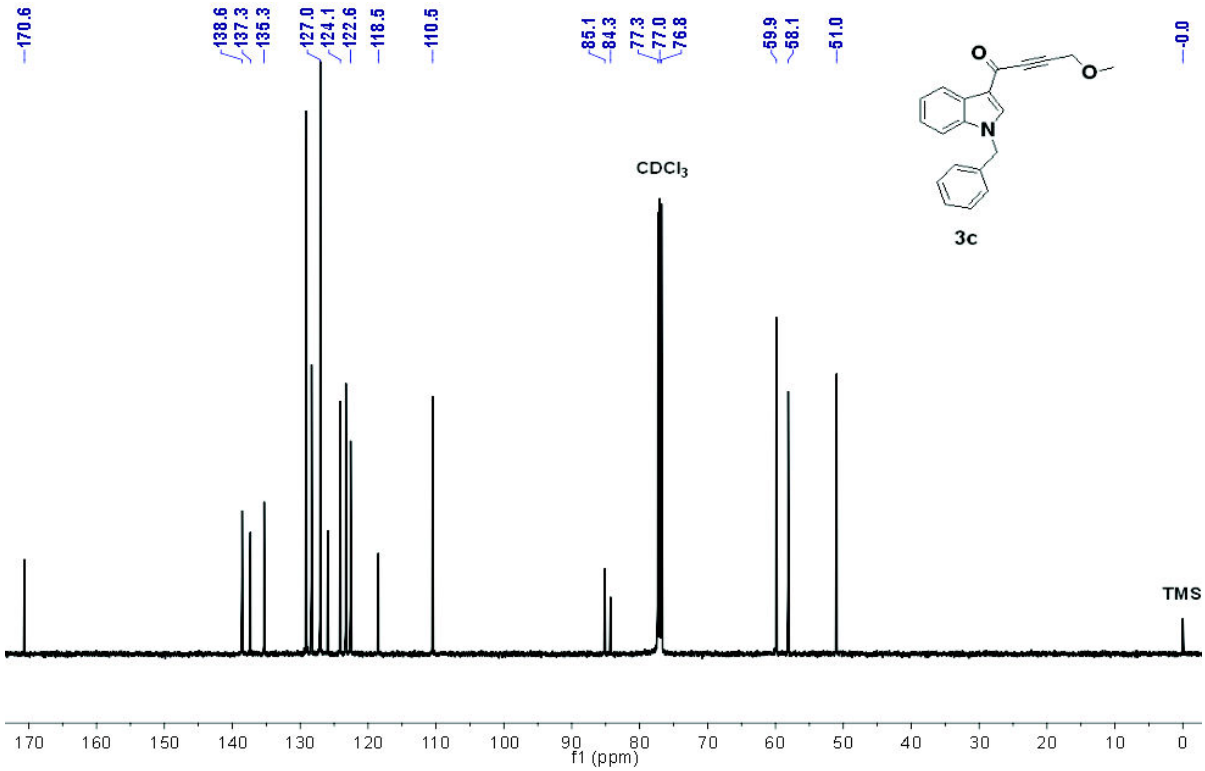
^{13}C NMR of **3b** in $CDCl_3$ at 298 K (δ in ppm).



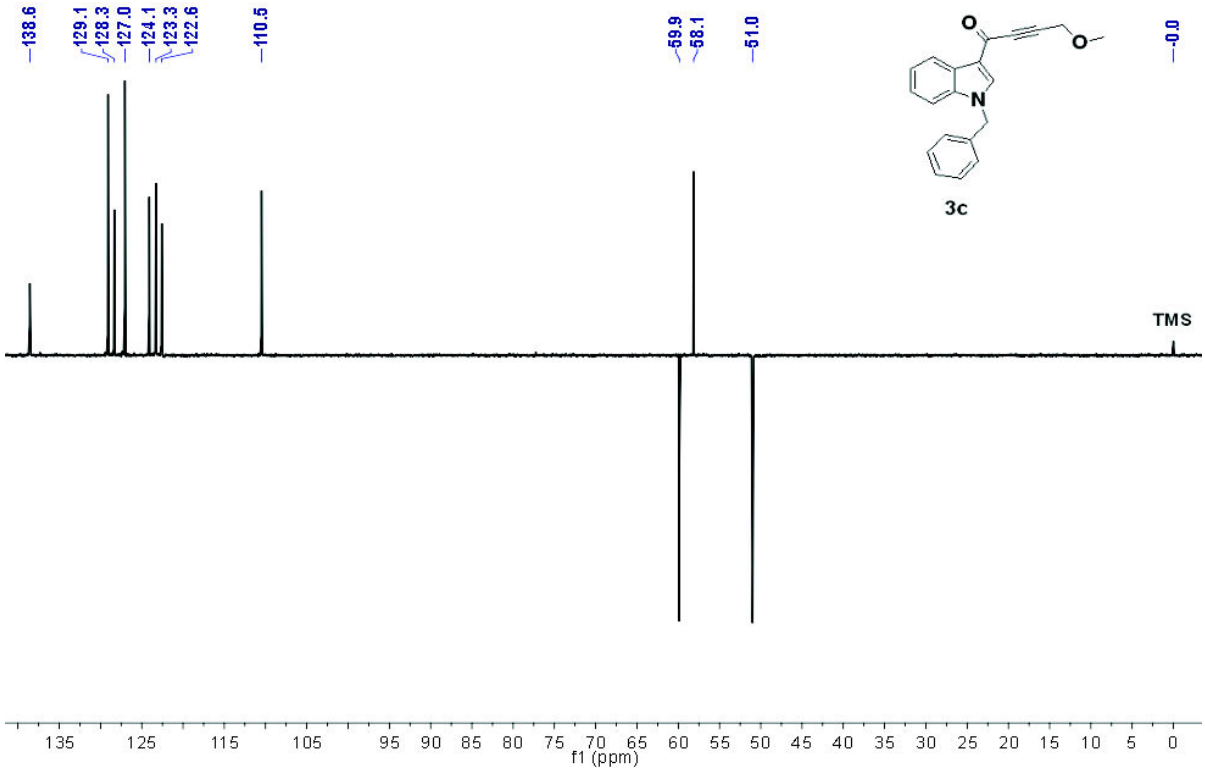
^{13}C DEPT 135-NMR of **3b** in $CDCl_3$ at 297 K (δ in ppm).



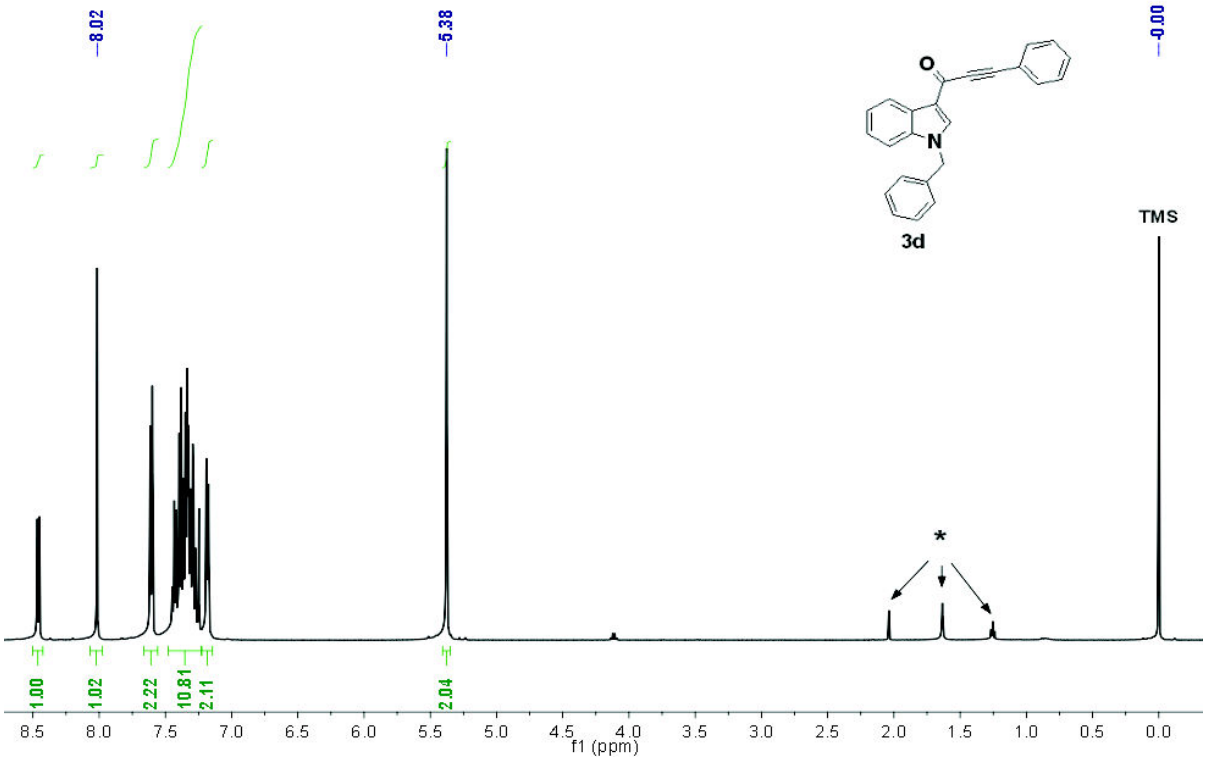
^{1}H NMR of **3c** in $CDCl_3$ at 297 K (δ in ppm).



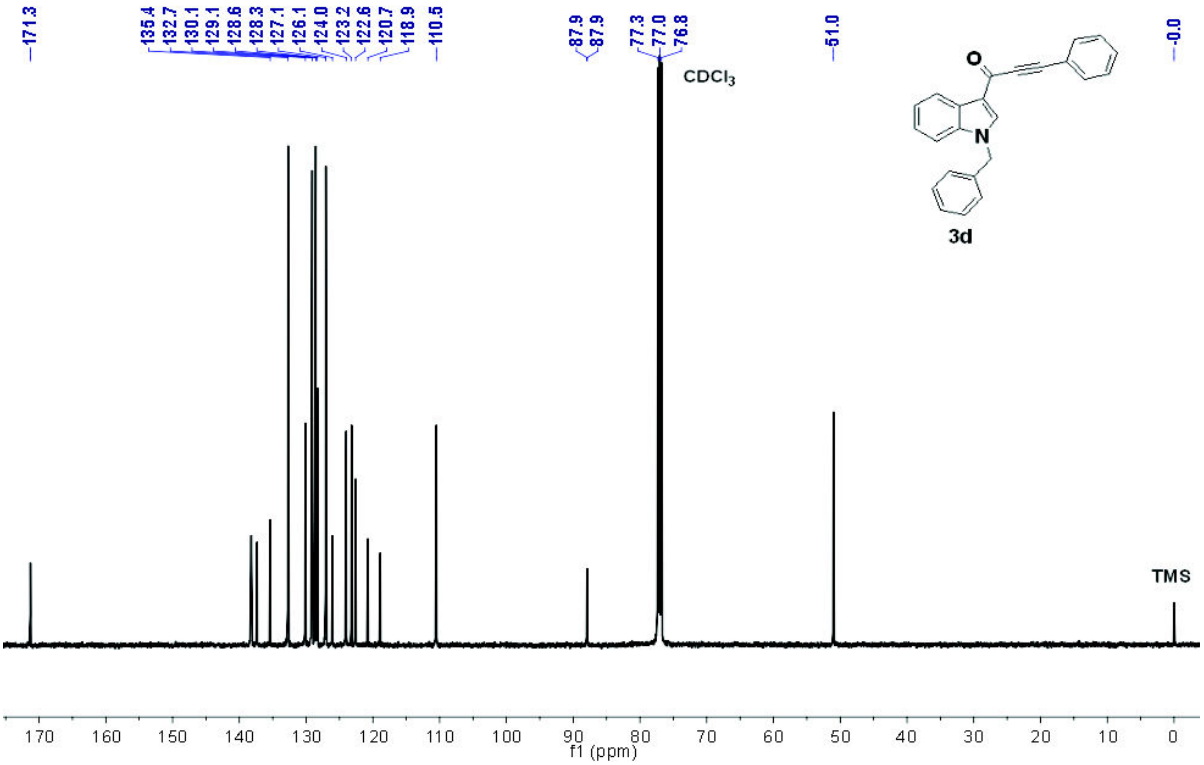
^{13}C NMR of **3c** in $CDCl_3$ at 297 K (δ in ppm).



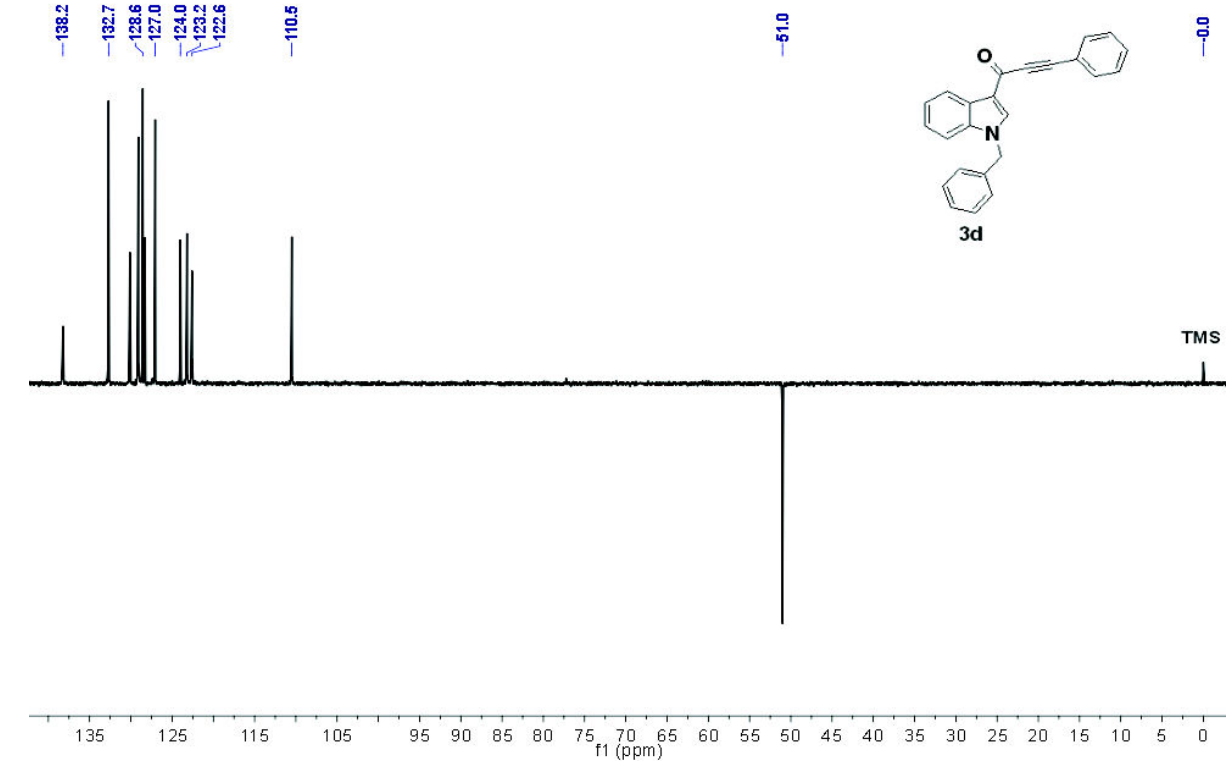
^{13}C DEPT 135-NMR of **3c** in $CDCl_3$ at 297 K (δ in ppm).



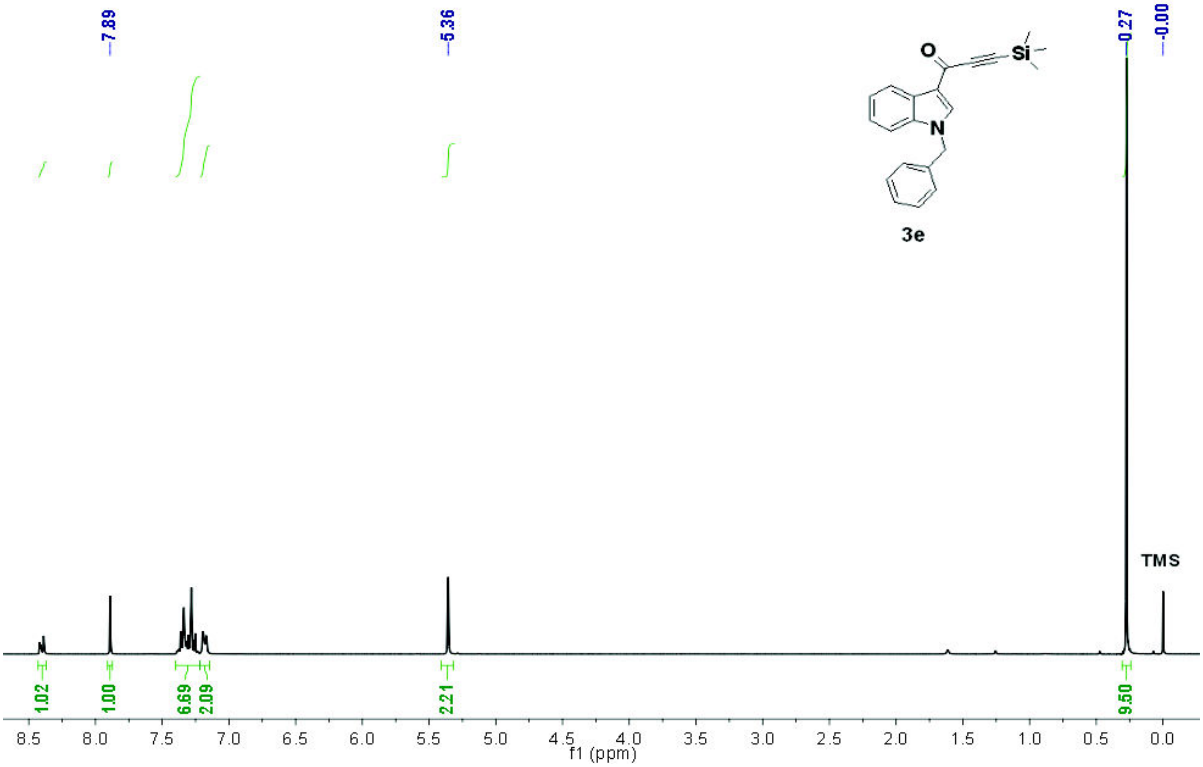
^{1}H NMR of **3d** in $CDCl_3$ at 297 K (δ in ppm). *Impurities from residual solvents.



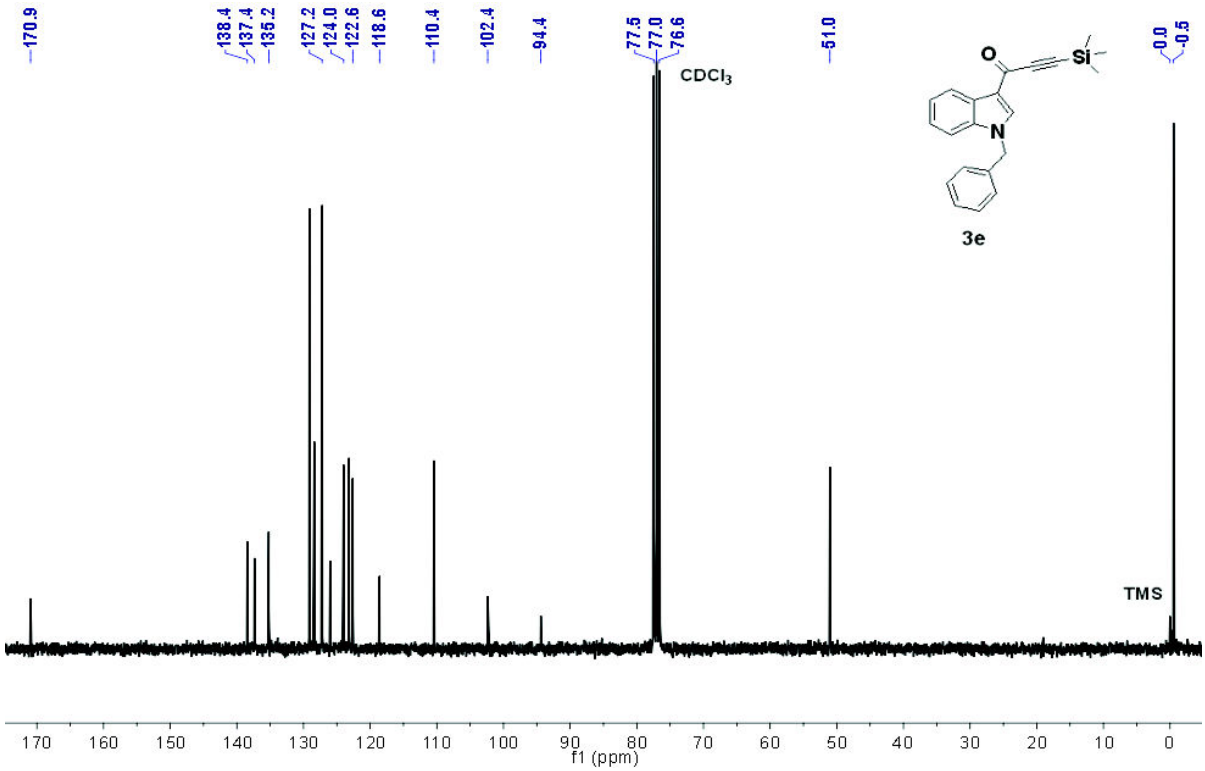
^{13}C NMR of **3d** in $CDCl_3$ at 297 K (δ in ppm).



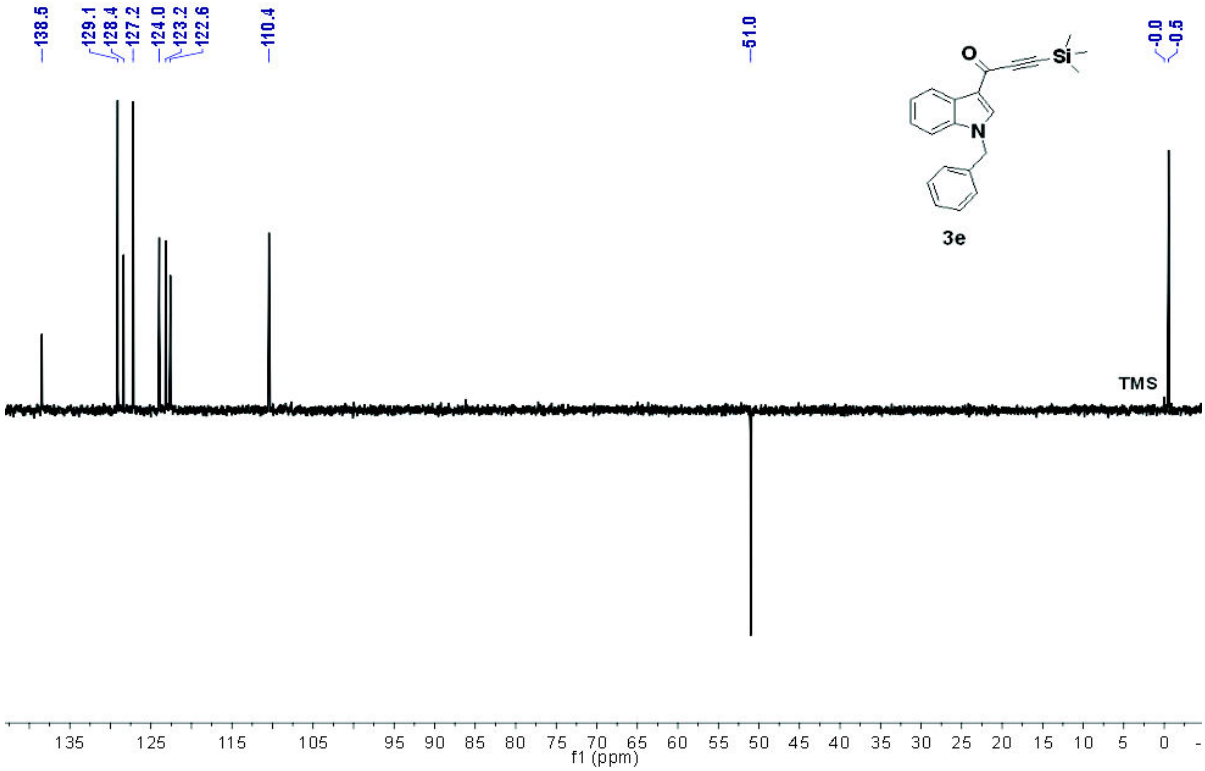
^{13}C DEPT 135-NMR of **3d** in $CDCl_3$ at 297 K (δ in ppm).



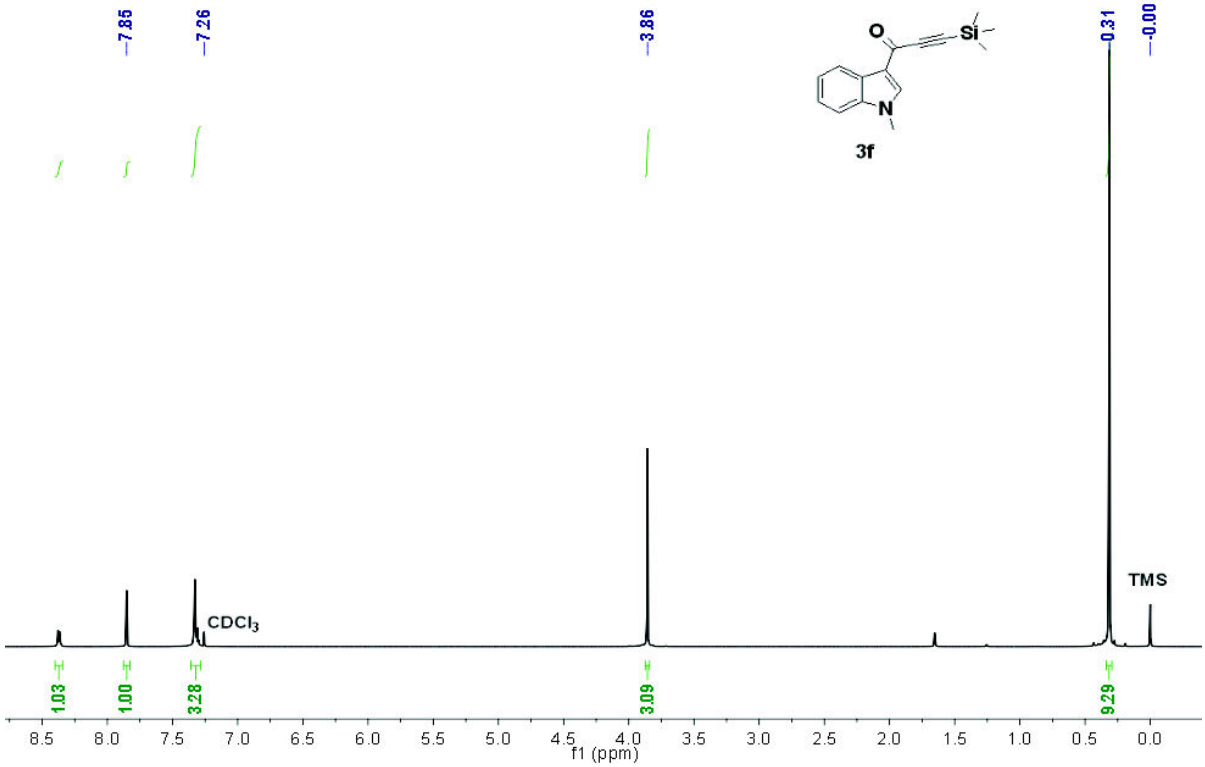
^{1}H NMR of **3e** in $CDCl_3$ at 297 K (δ in ppm).



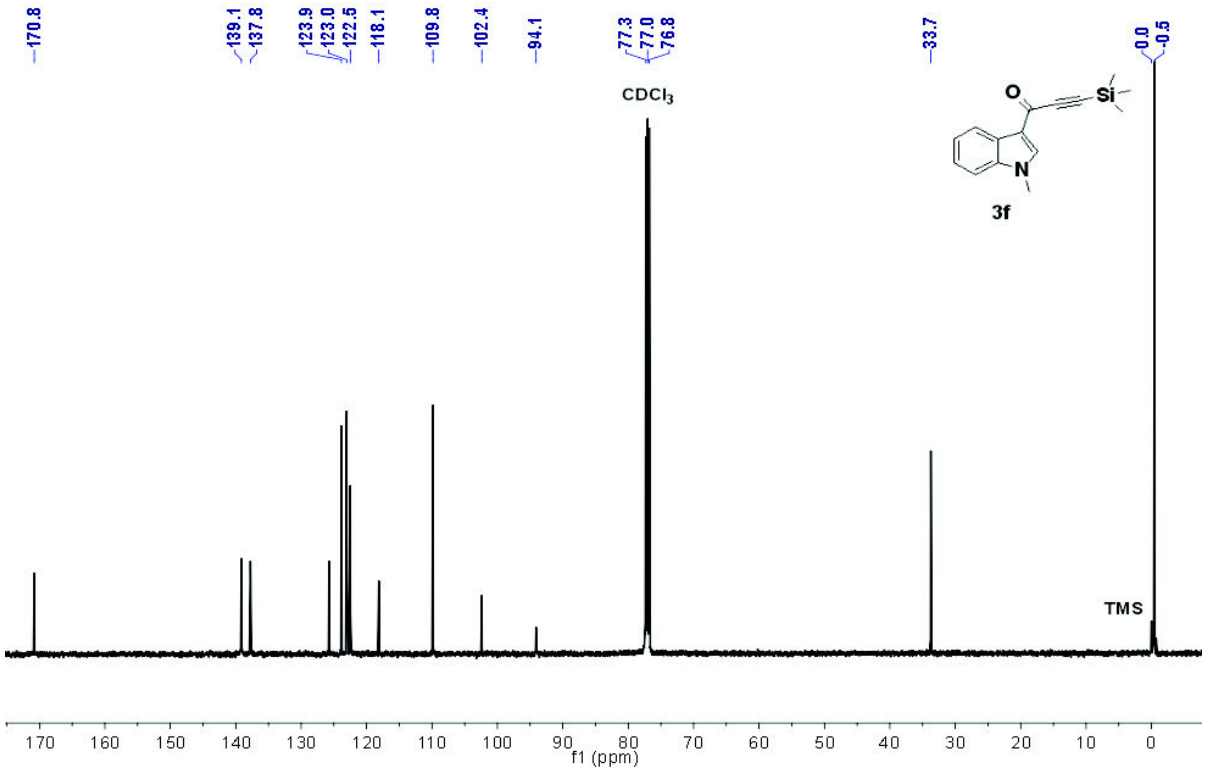
^{13}C NMR of **3e** in $CDCl_3$ at 297 K (δ in ppm).



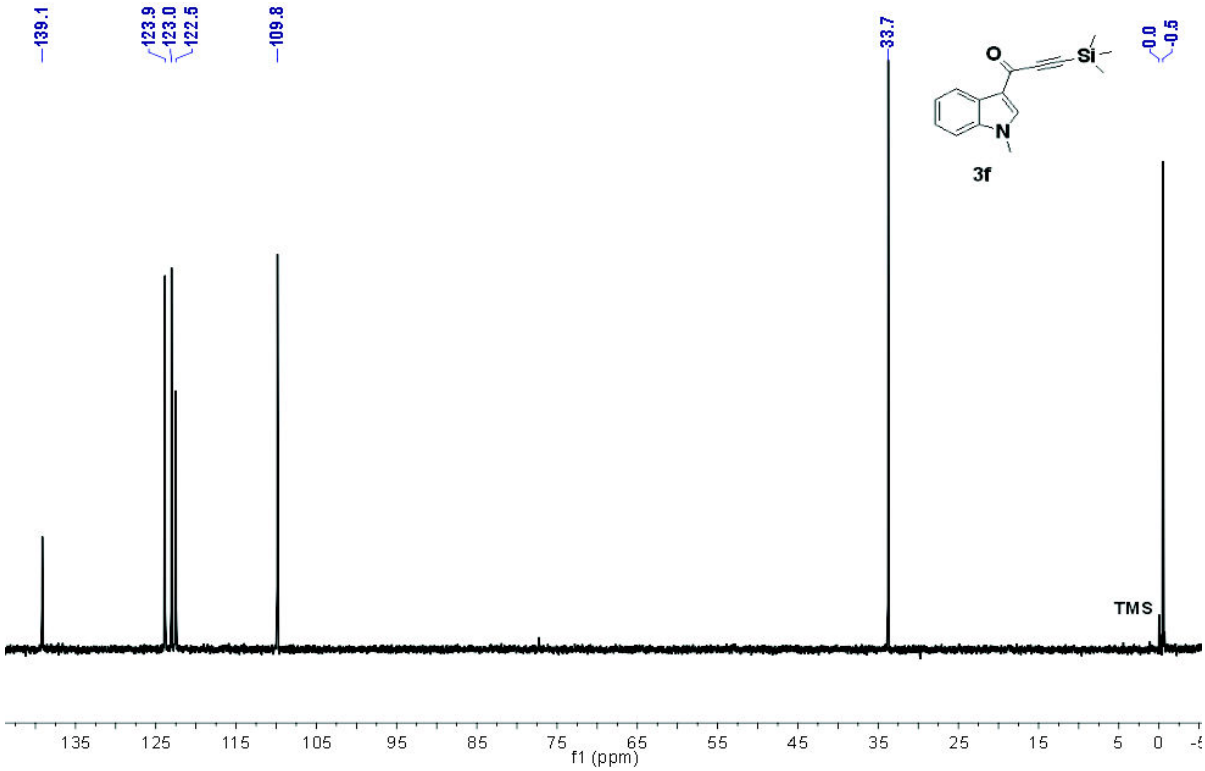
^{13}C DEPT 135-NMR of **3e** in $CDCl_3$ at 297 K (δ in ppm).



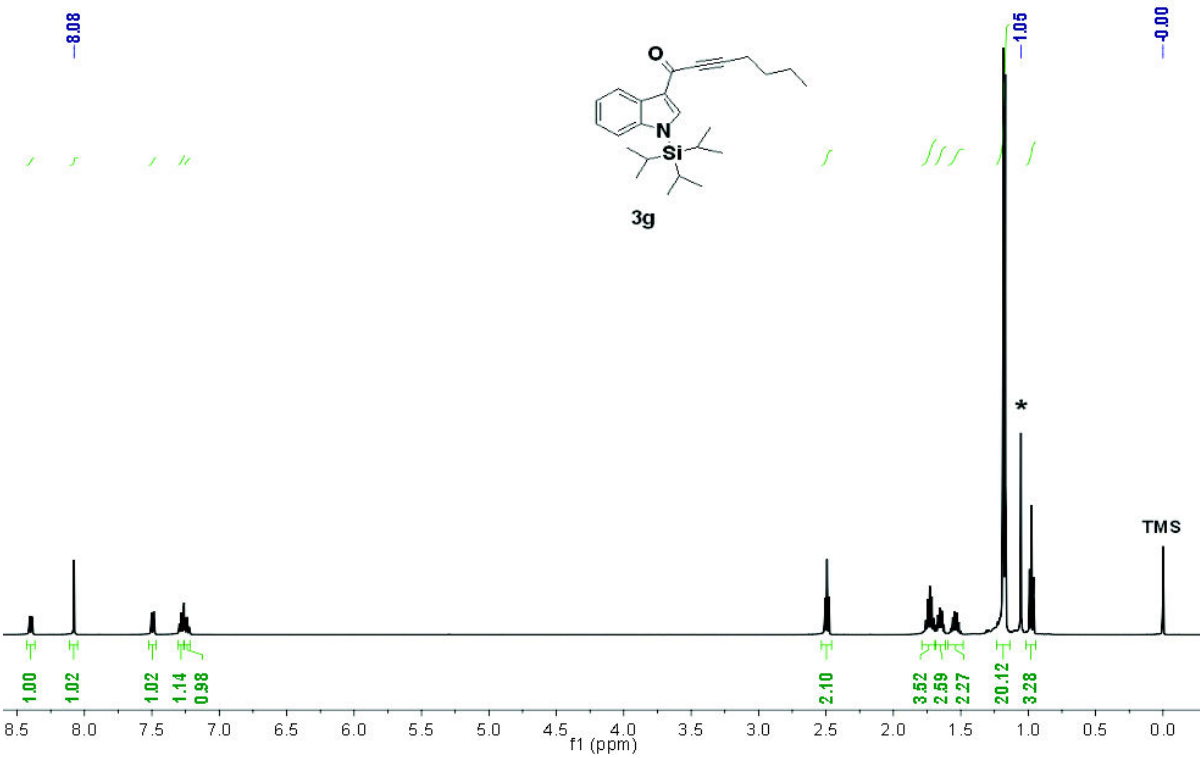
^{1}H NMR of **3f** in $CDCl_3$ at 297 K (δ in ppm).



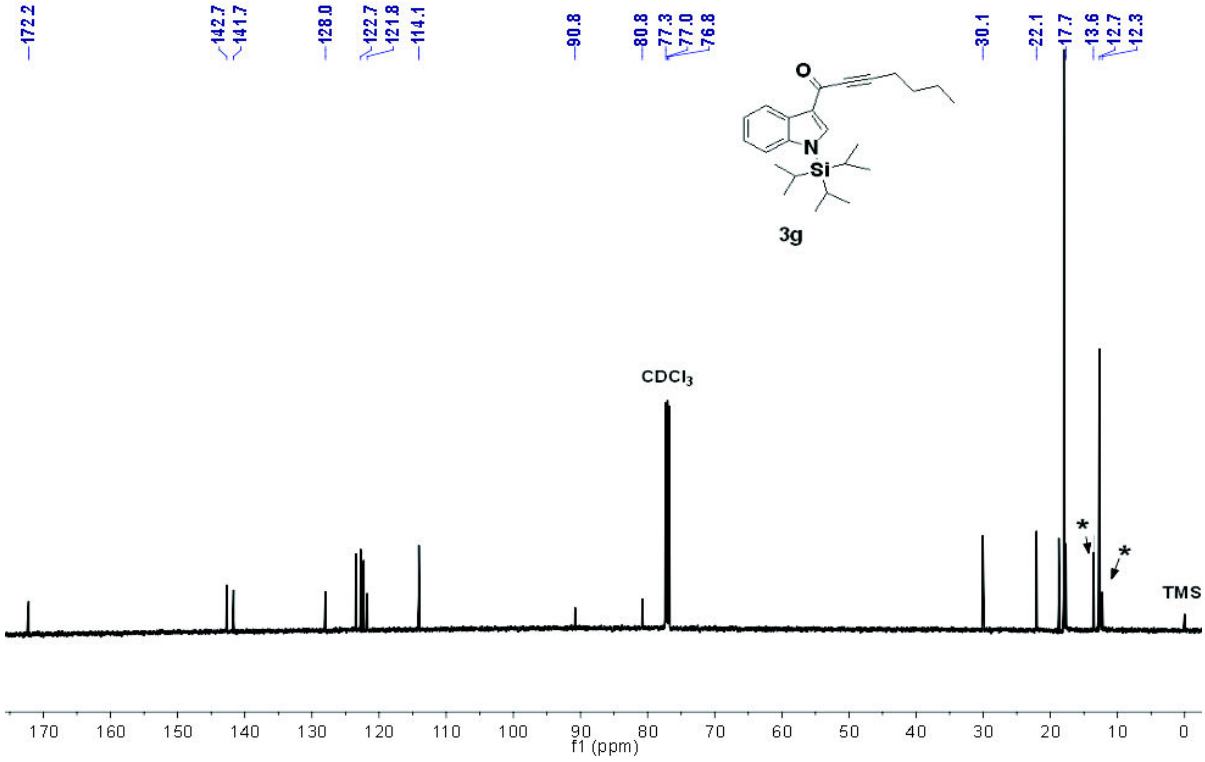
^{13}C NMR of **3f** in $CDCl_3$ at 297 K (δ in ppm).



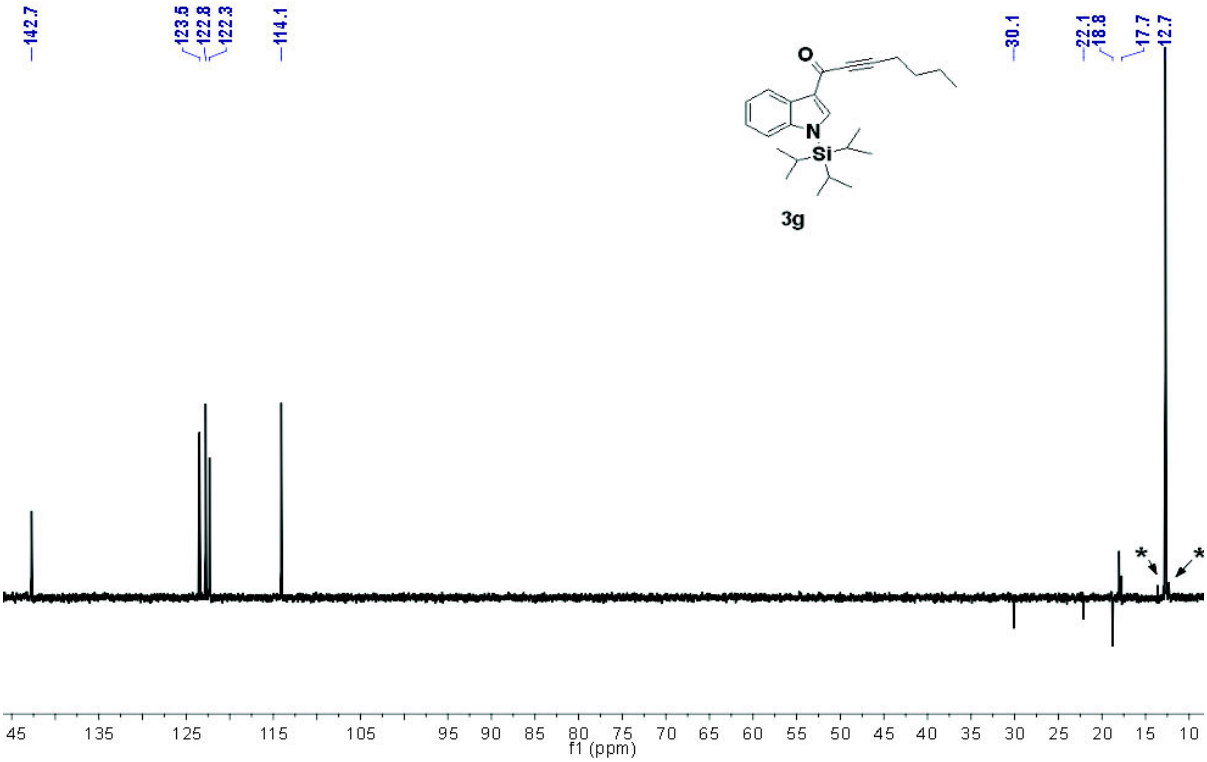
^{13}C DEPT 135-NMR of **3f** in $CDCl_3$ at 297 K (δ in ppm).



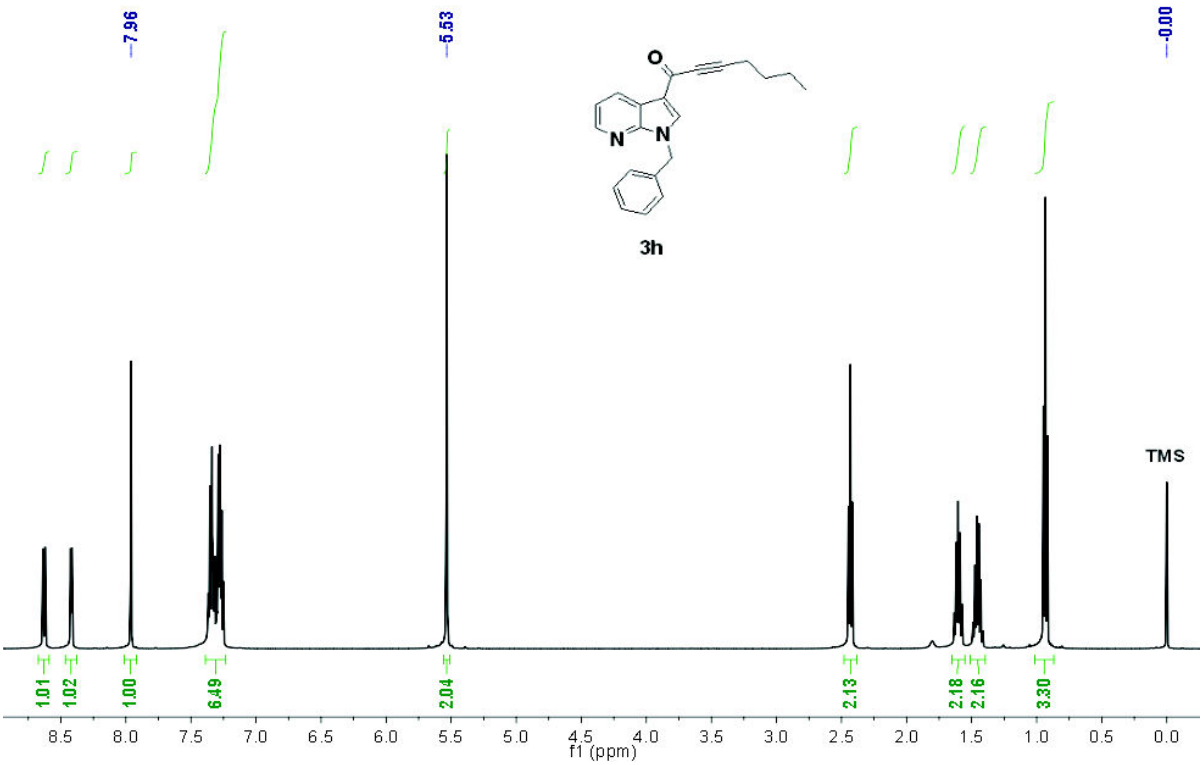
^{1}H NMR of **3g** in $CDCl_3$ at 297 K (δ in ppm). *Residual Water in $CDCl_3$.



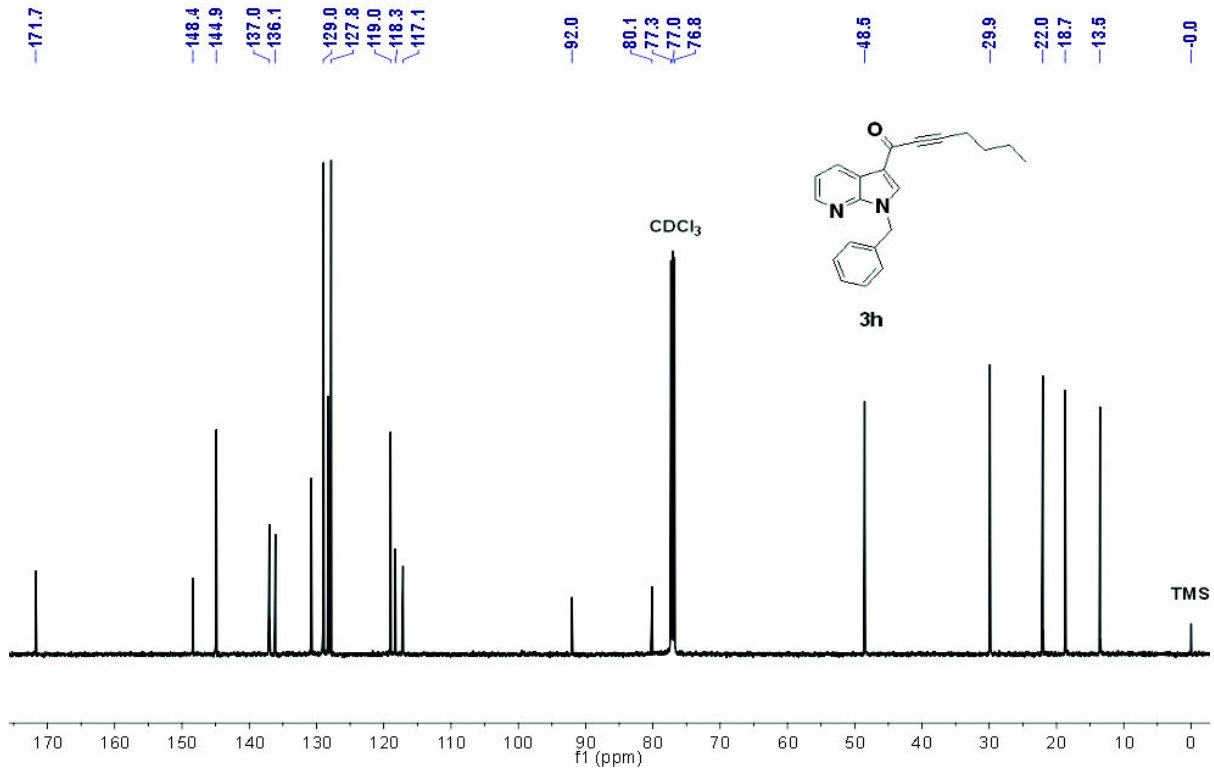
^{13}C NMR of **3g** in $CDCl_3$ at 297 K (δ in ppm). *Impurities from residual solvents.



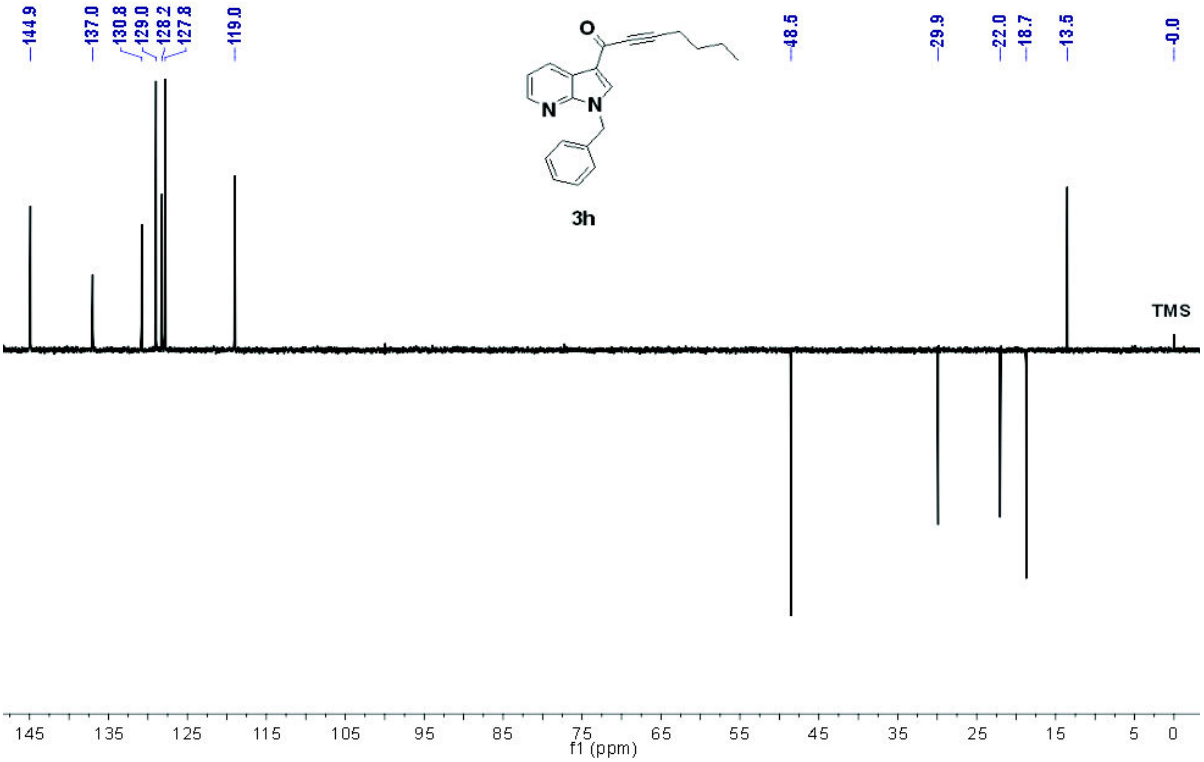
^{13}C DEPT 135-NMR of **3g** in $CDCl_3$ at 297 K (δ in ppm). *Impurities from residual solvents.



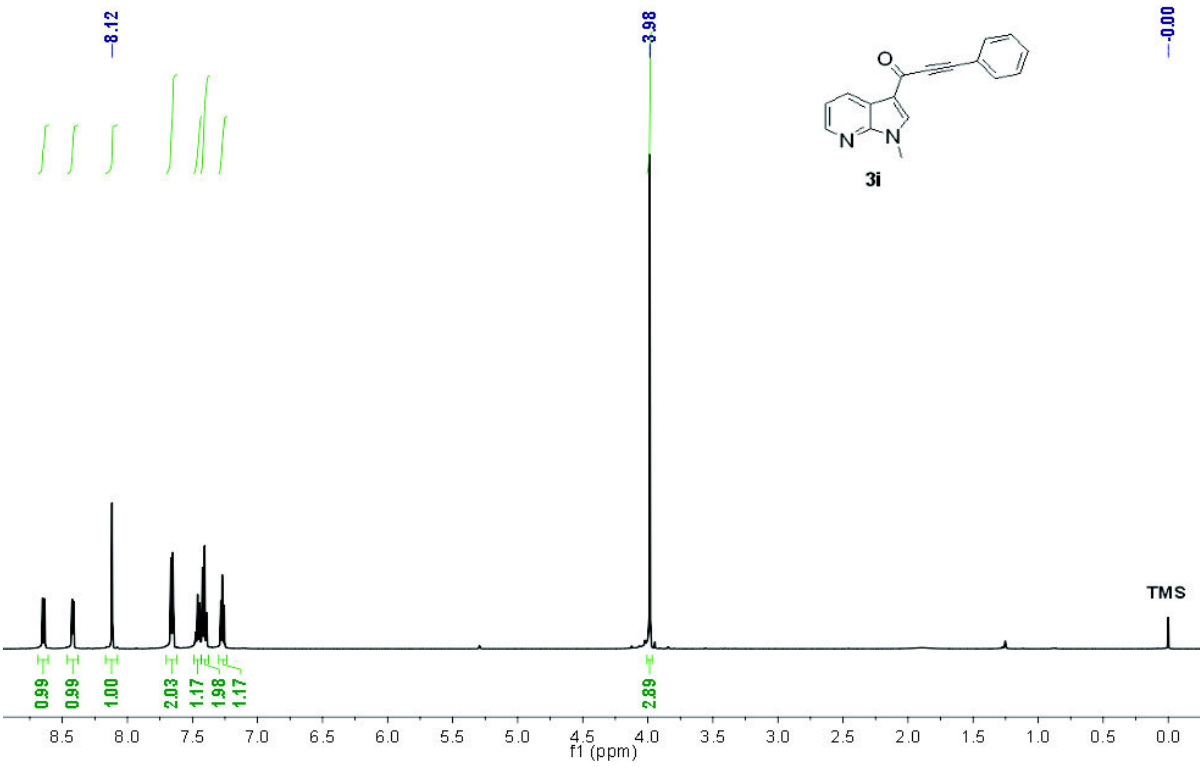
^{1}H NMR of **3h** in $CDCl_3$ at 297 K (δ in ppm).



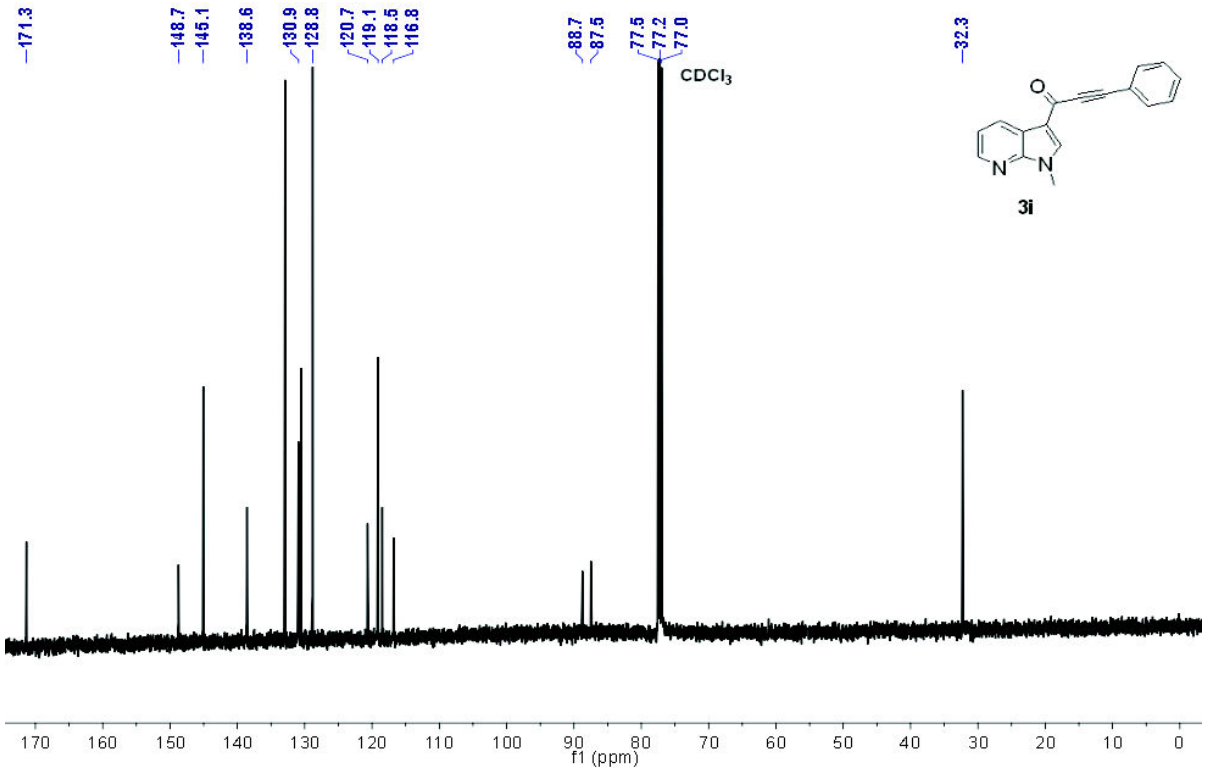
^{13}C NMR of **3h** in $CDCl_3$ at 297 K (δ in ppm).



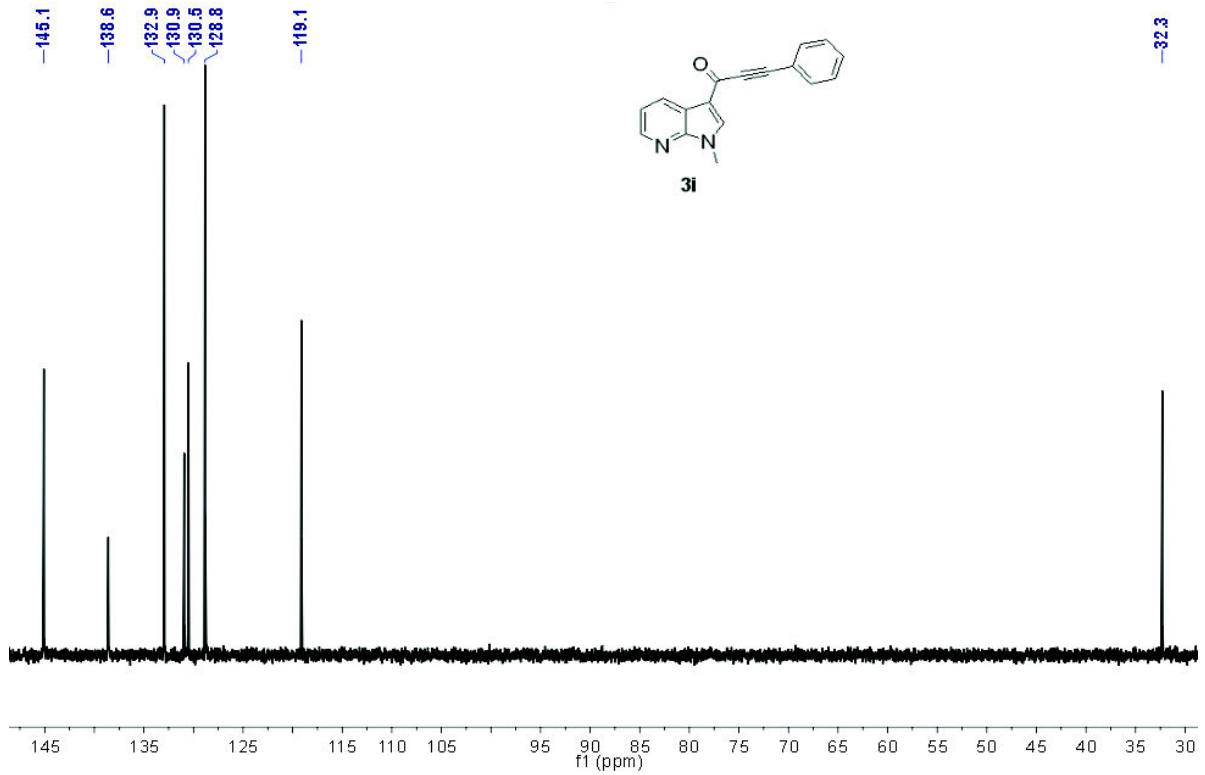
^{13}C DEPT 135-NMR of **3h** in $CDCl_3$ at 297 K (δ in ppm).



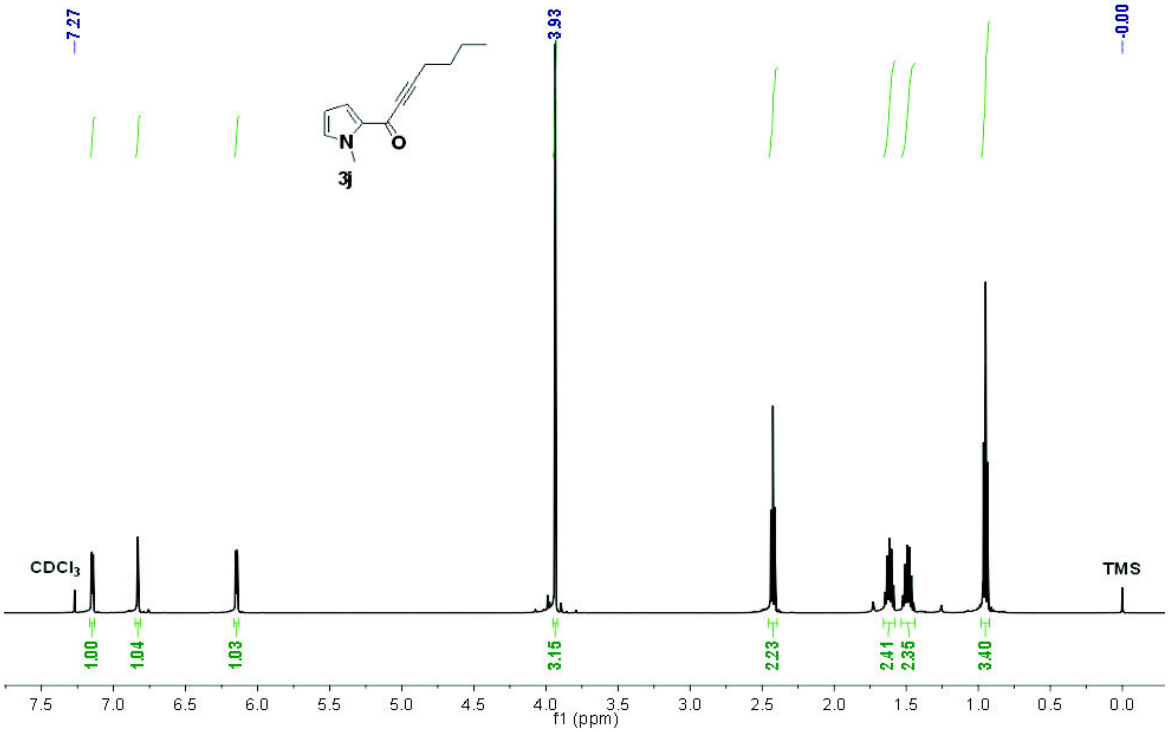
^{1}H NMR of **3i** in $CDCl_3$ at 297 K (δ in ppm).



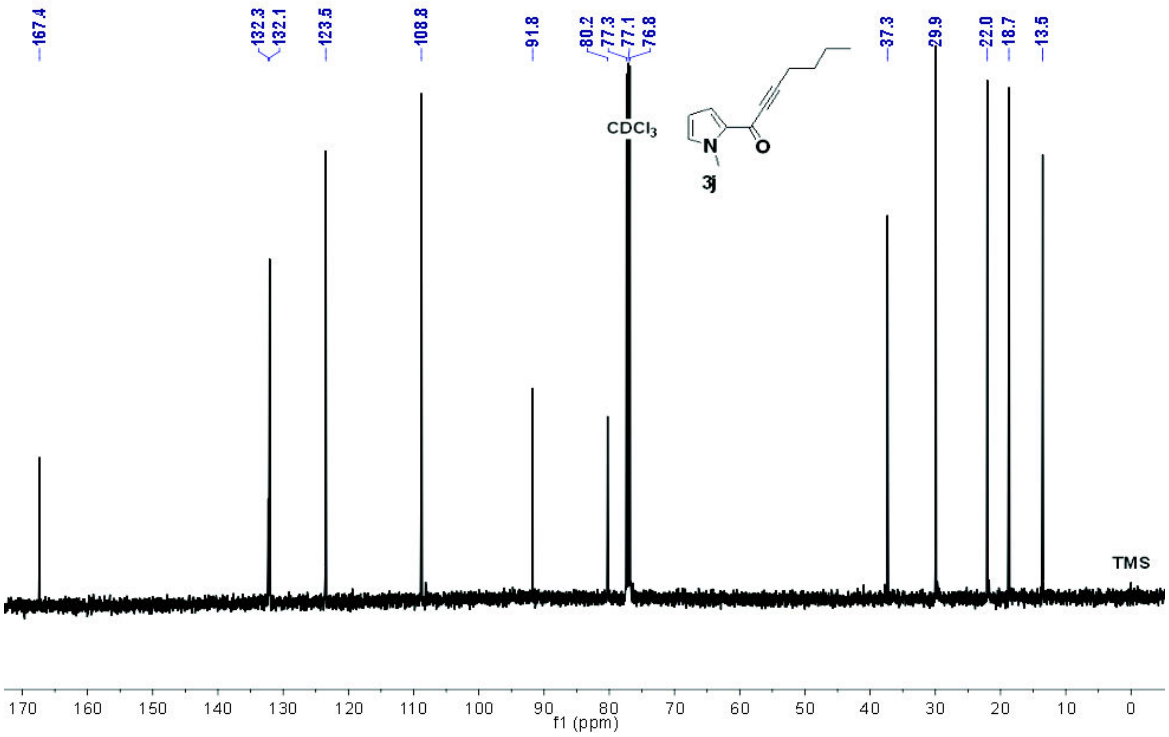
^{13}C NMR of **3i** in $CDCl_3$ at 297 K (δ in ppm).



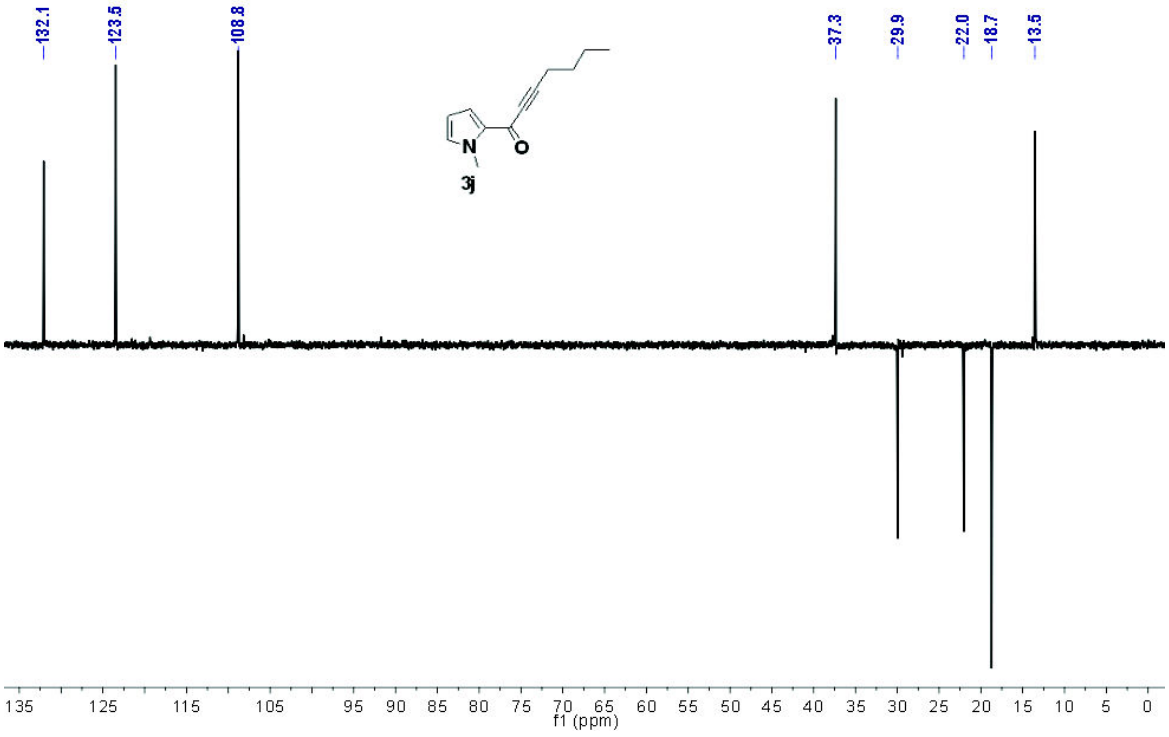
^{13}C DEPT 135-NMR of **3i** in $CDCl_3$ at 297 K (δ in ppm).



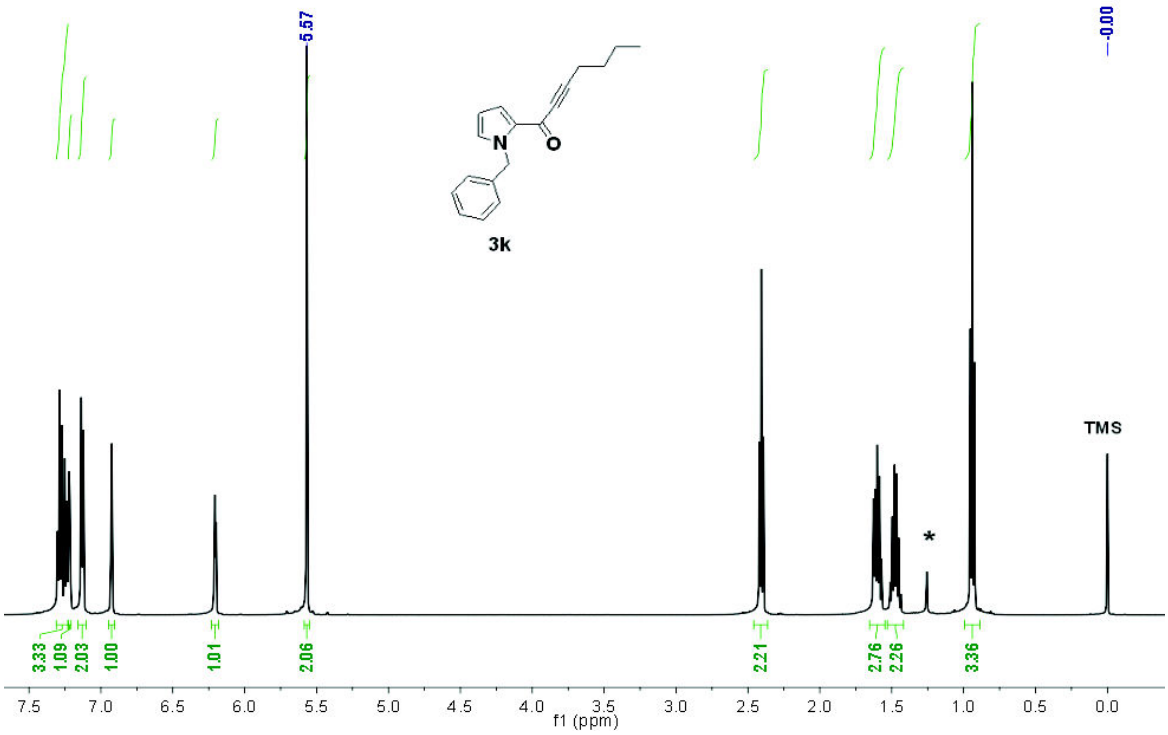
^{1}H NMR of **9a** in $CDCl_3$ at 299 K (δ in ppm).



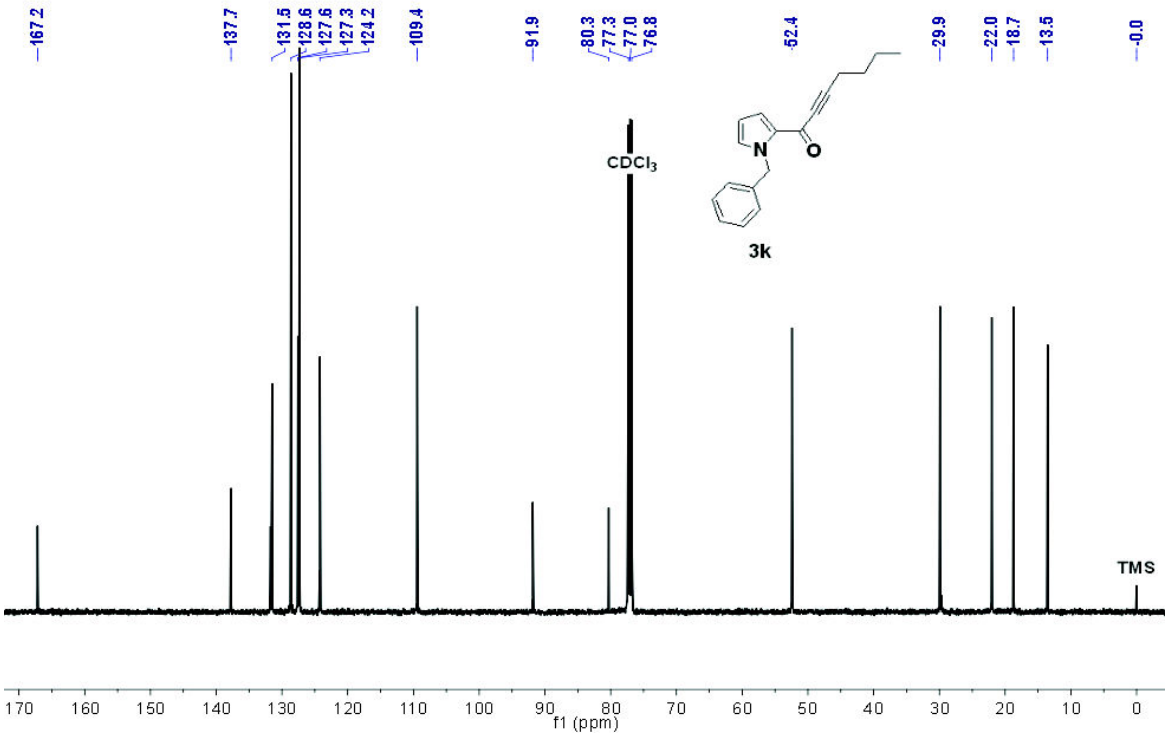
^{13}C NMR of **9a** in $CDCl_3$ at 300 K (δ in ppm).



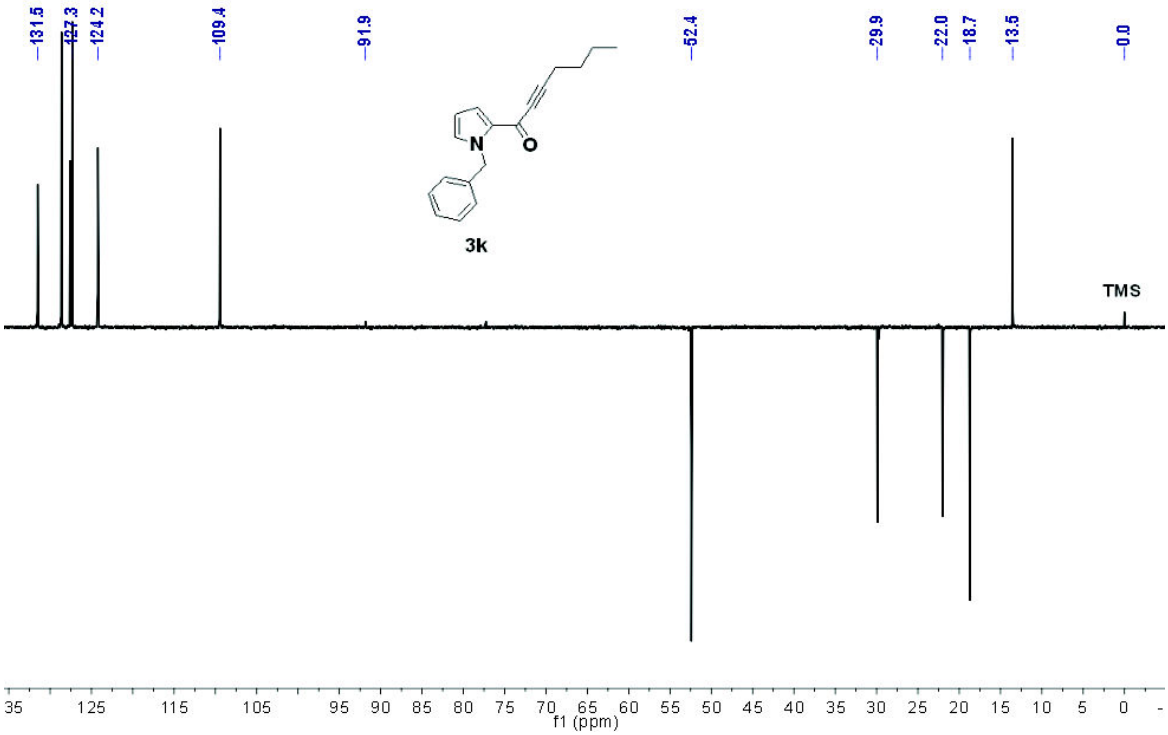
^{13}C DEPT 135-NMR of **9a** in $CDCl_3$ at 299 K (δ in ppm).



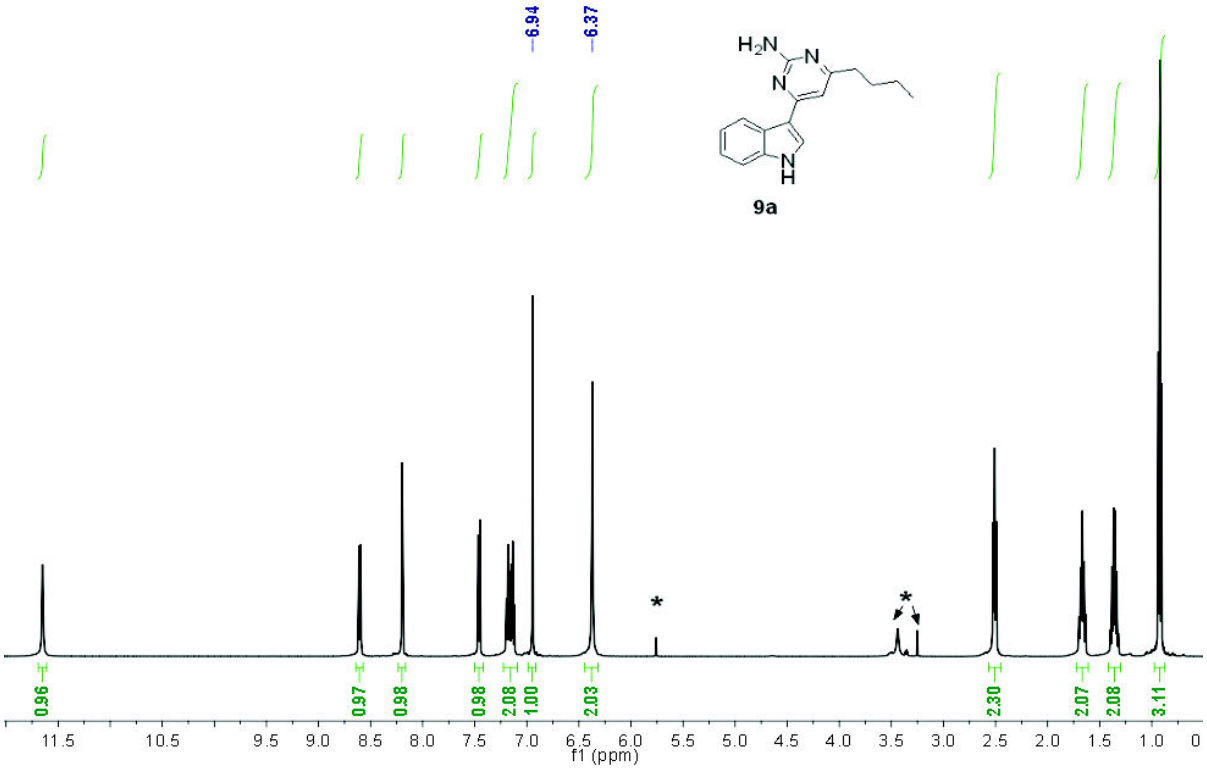
^{1}H NMR of **9b** in $CDCl_3$ at 297 K (δ in ppm). *Residual Water in $CDCl_3$.



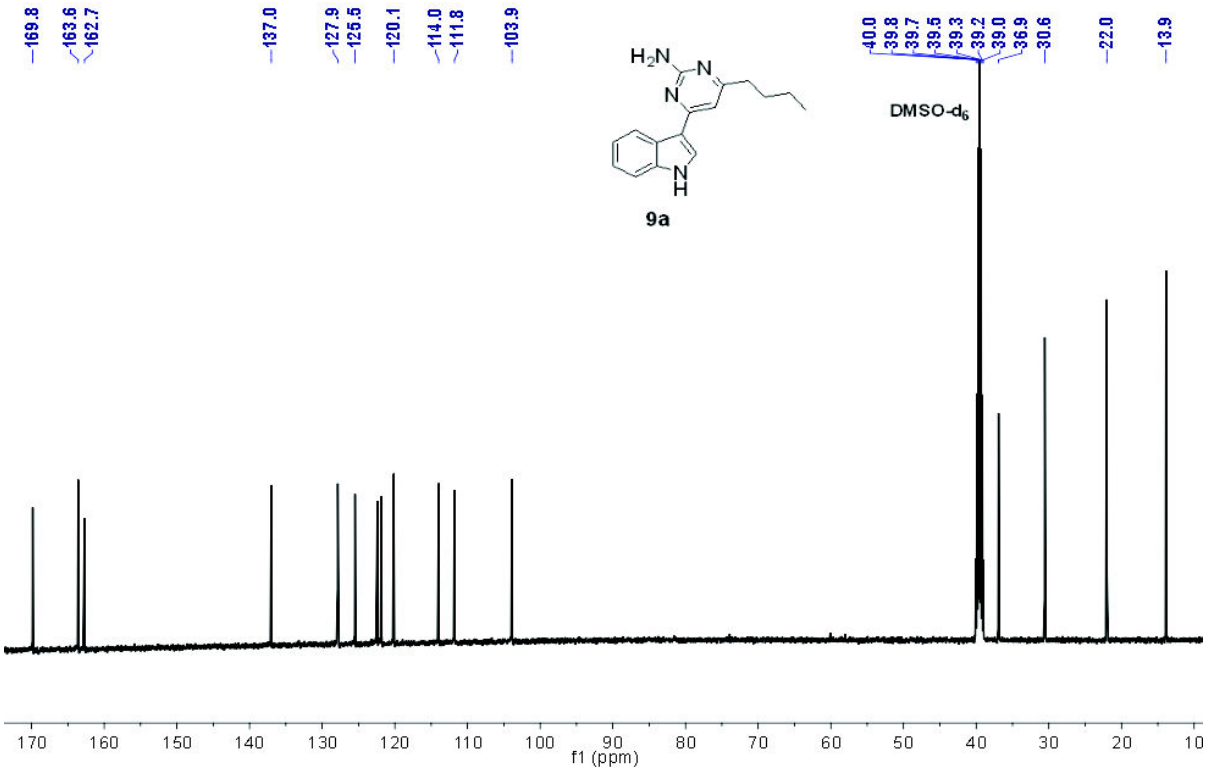
^{13}C NMR of **9b** in $CDCl_3$ at 297 K (δ in ppm).



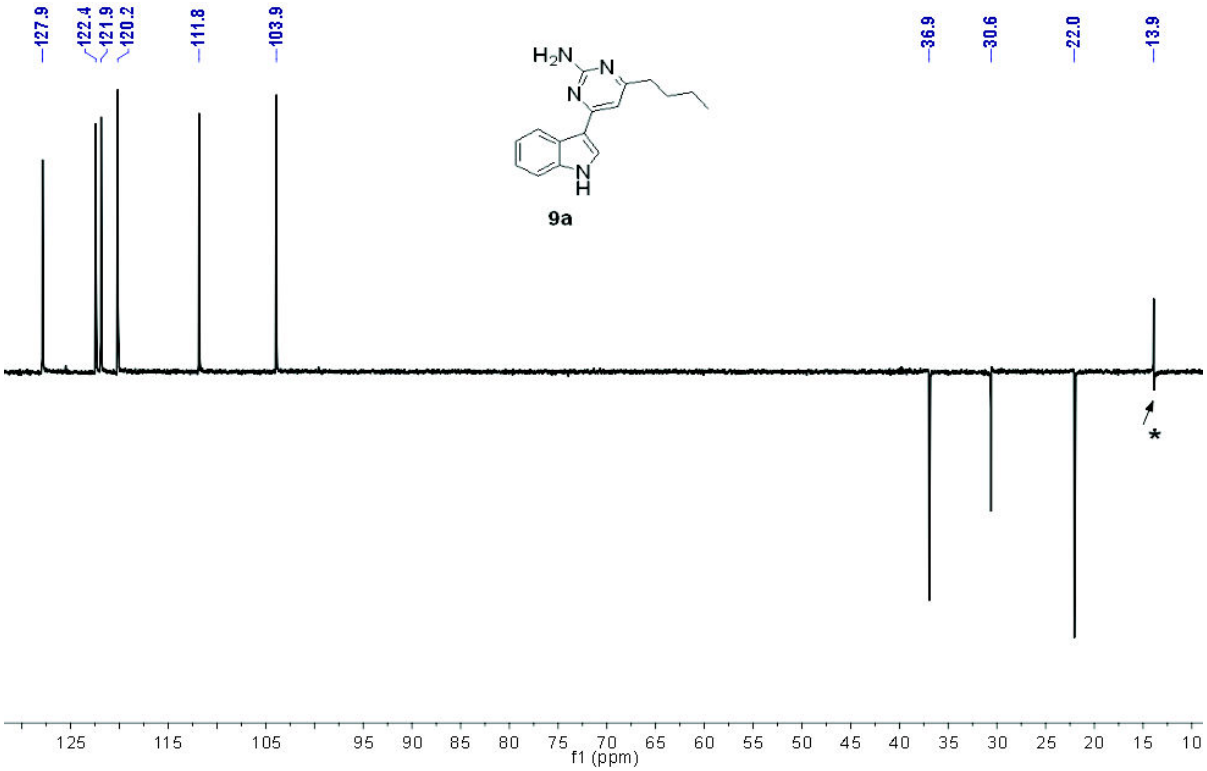
^{13}C DEPT 135-NMR of **9b** in $CDCl_3$ at 297 K (δ in ppm).



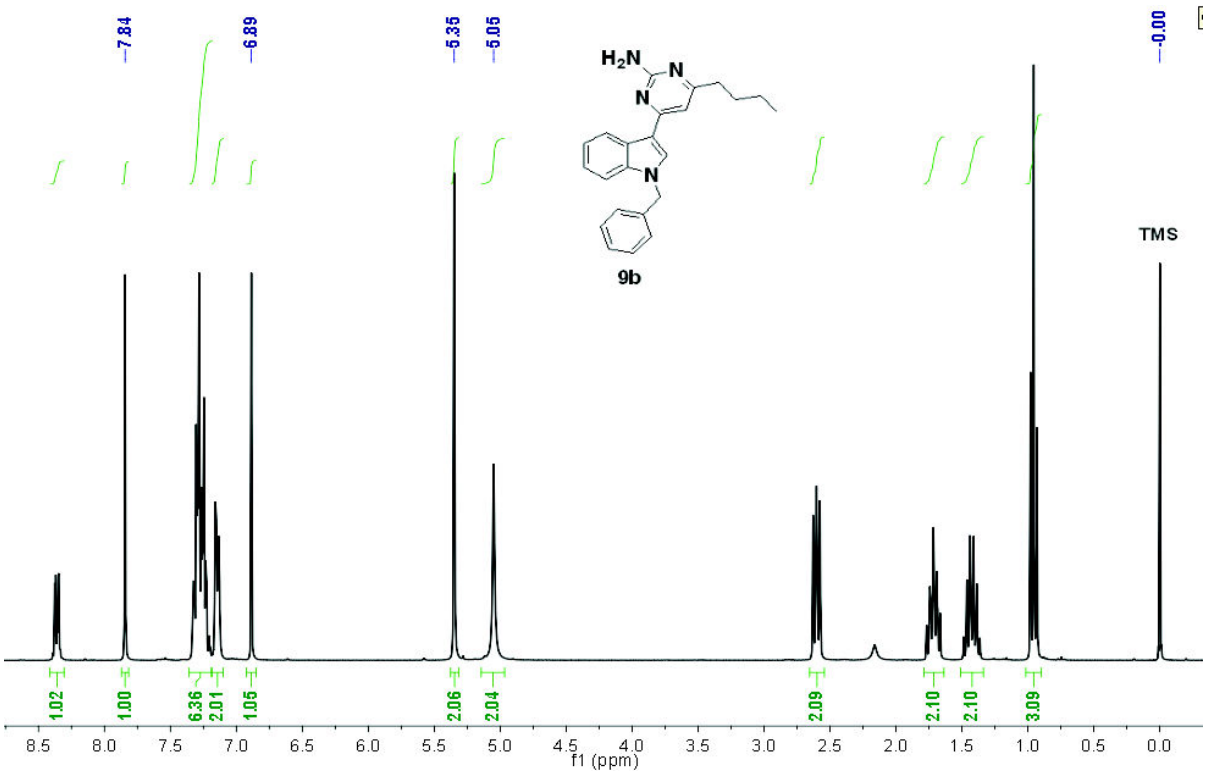
^{1}H NMR of **11a** in DMSO-d_6 at 297 K (δ in ppm). *Impurities from residual solvents.



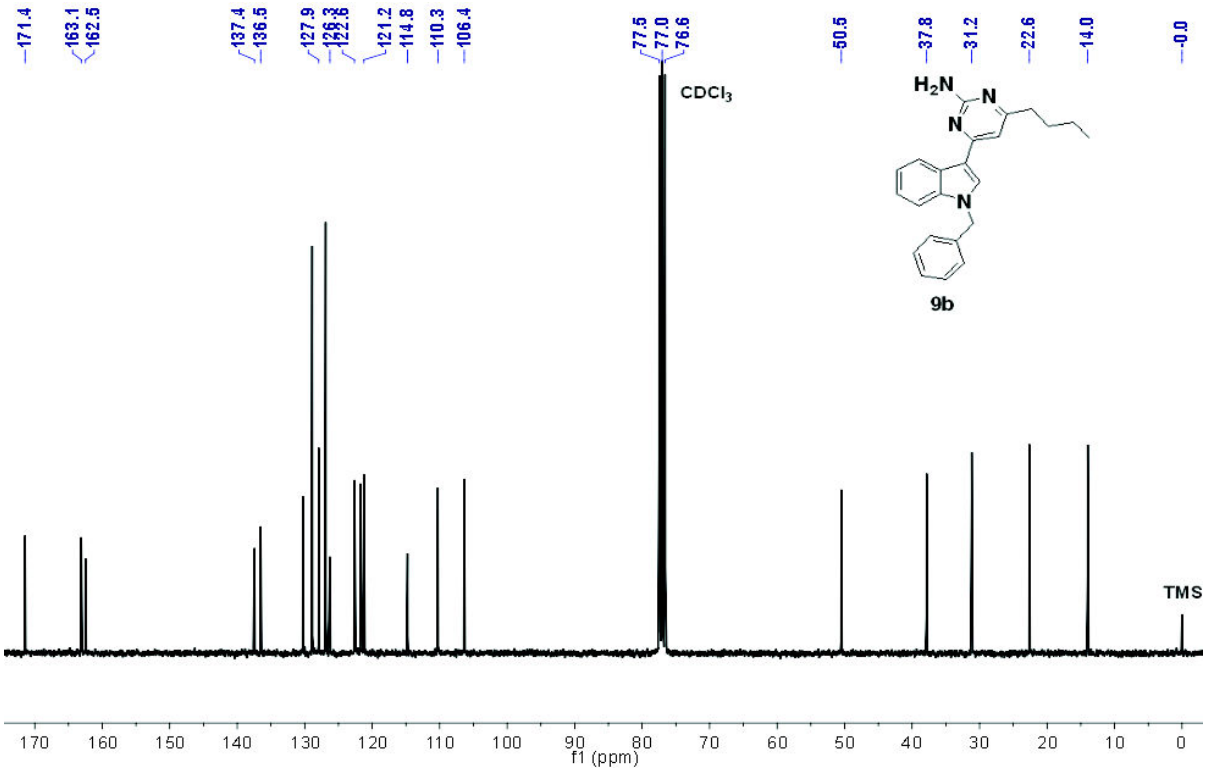
^{13}C NMR of **11a** in DMSO-d_6 at 298 K (δ in ppm).



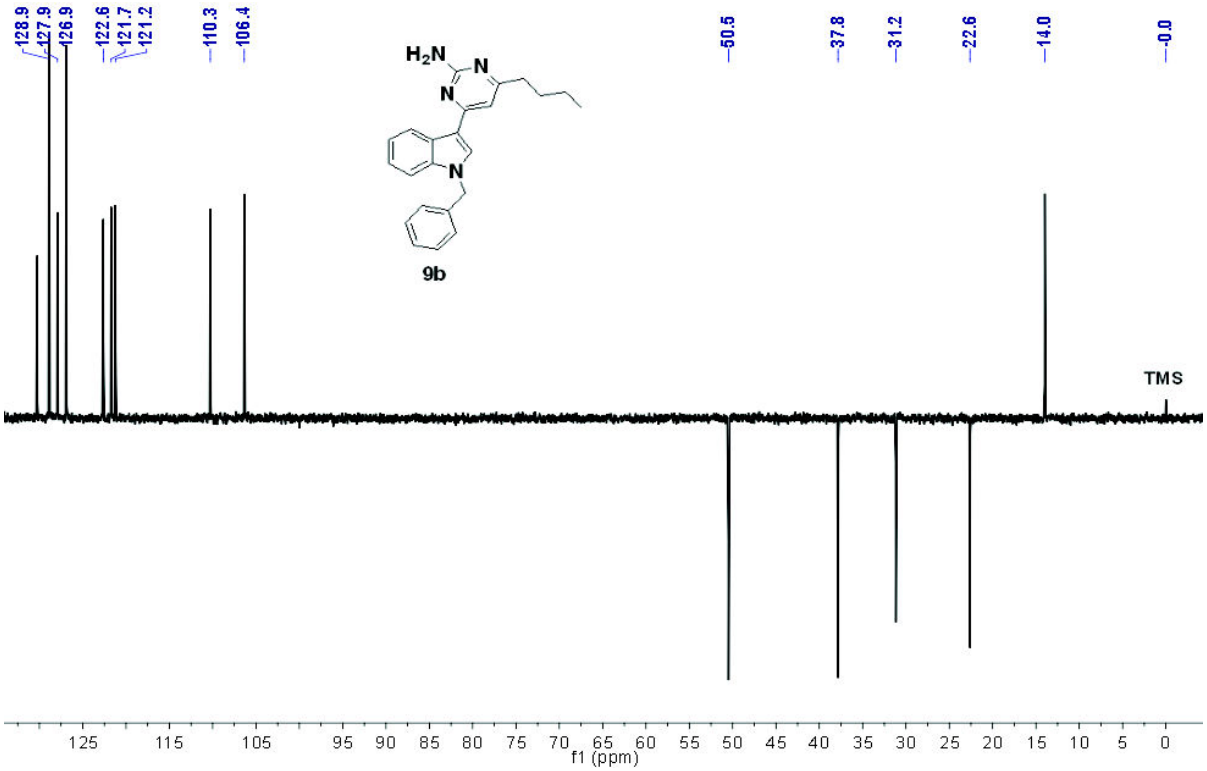
^{13}C DEPT 135-NMR of **11a** in DMSO-d_6 at 298 K (δ in ppm). *Impurities from residual solvents.



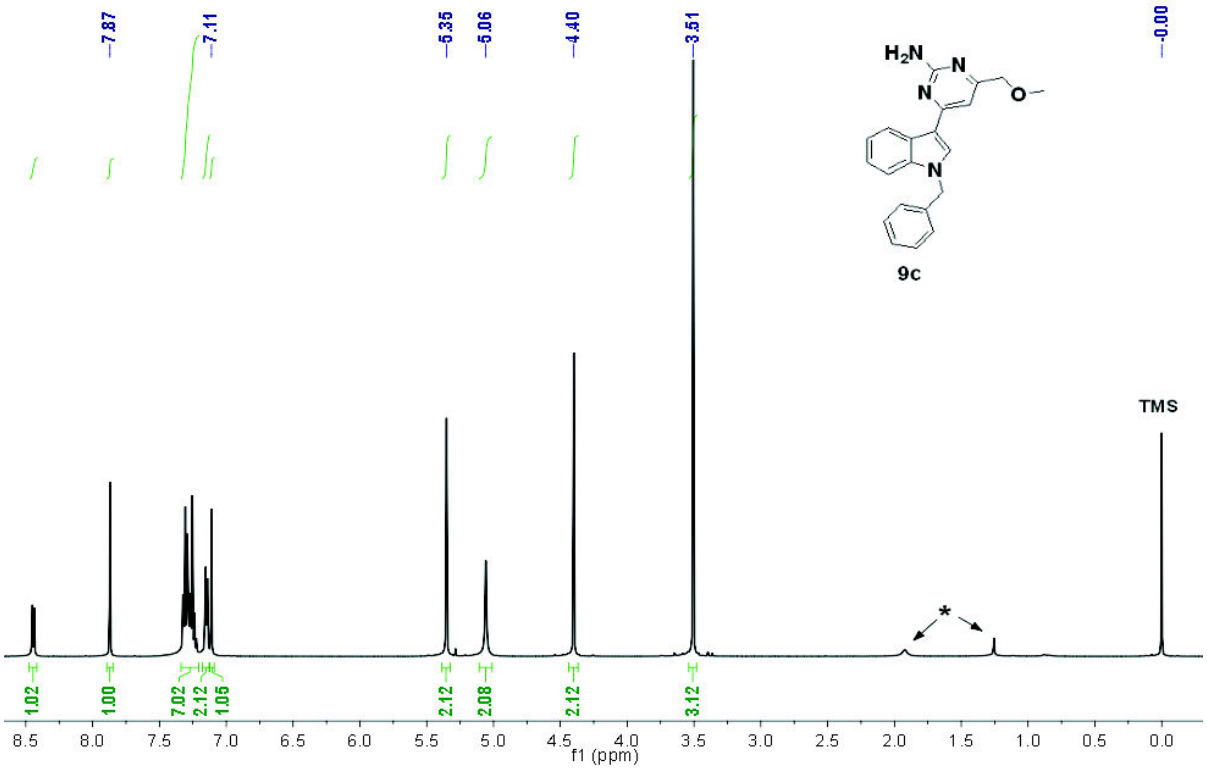
^{1}H NMR of **11b** in $CDCl_3$ at 300 K (δ in ppm).



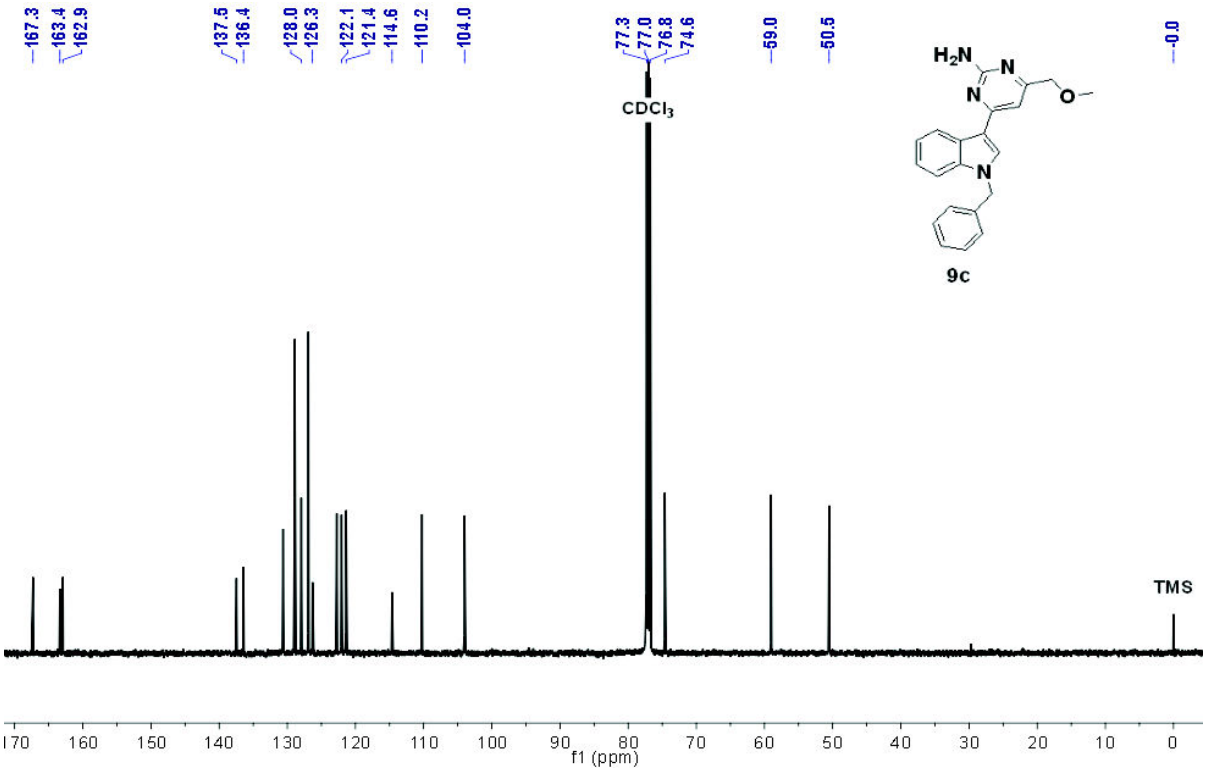
^{13}C NMR of **11b** in $CDCl_3$ at 300 K (δ in ppm).



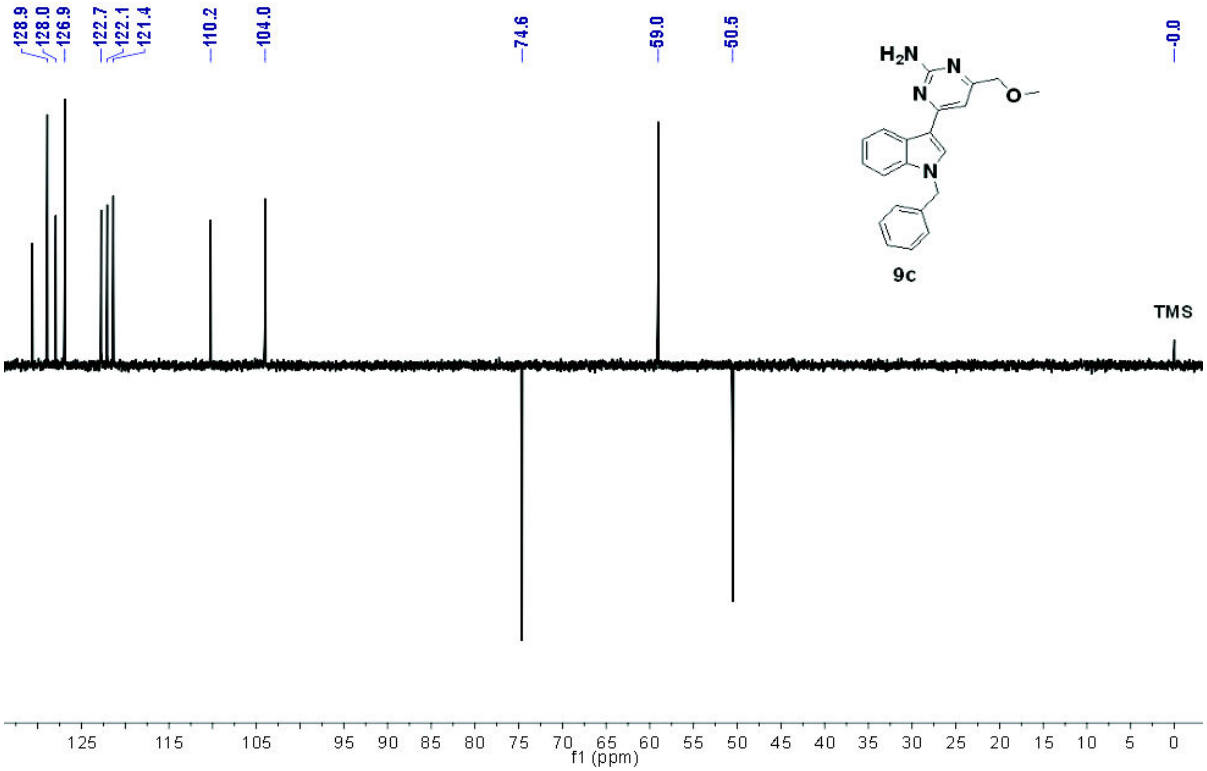
^{13}C DEPT 135-NMR of **11b** in $CDCl_3$ at 300 K (δ in ppm).



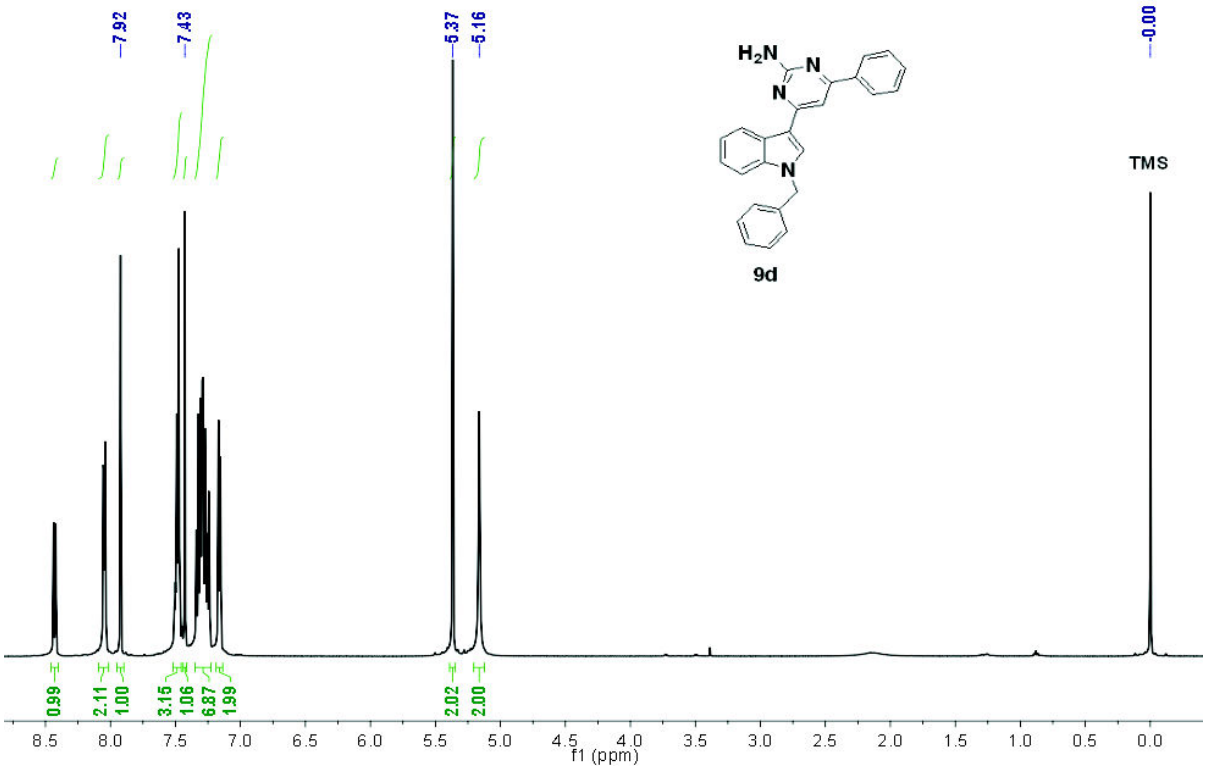
^{1}H NMR of **11c** in $CDCl_3$ at 297 K (δ in ppm). *Impurities from residual solvents.



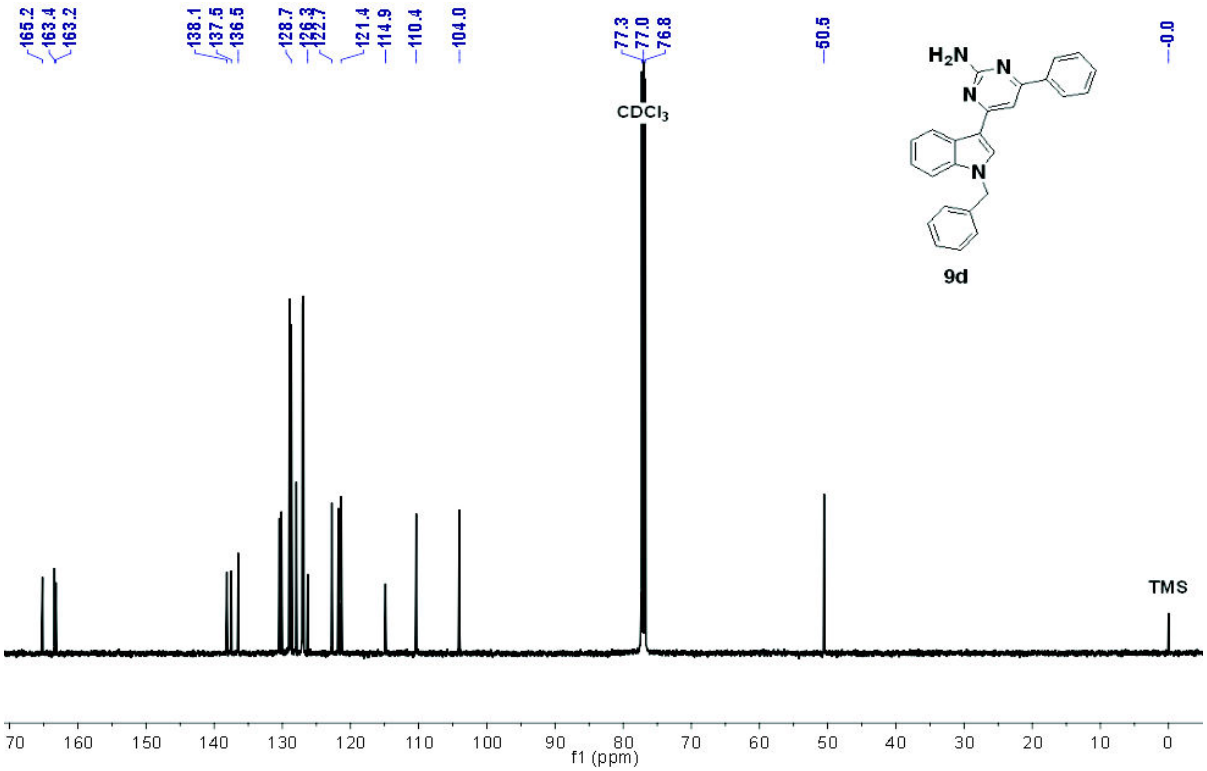
^{13}C NMR of **11c** in $CDCl_3$ at 298 K (δ in ppm).



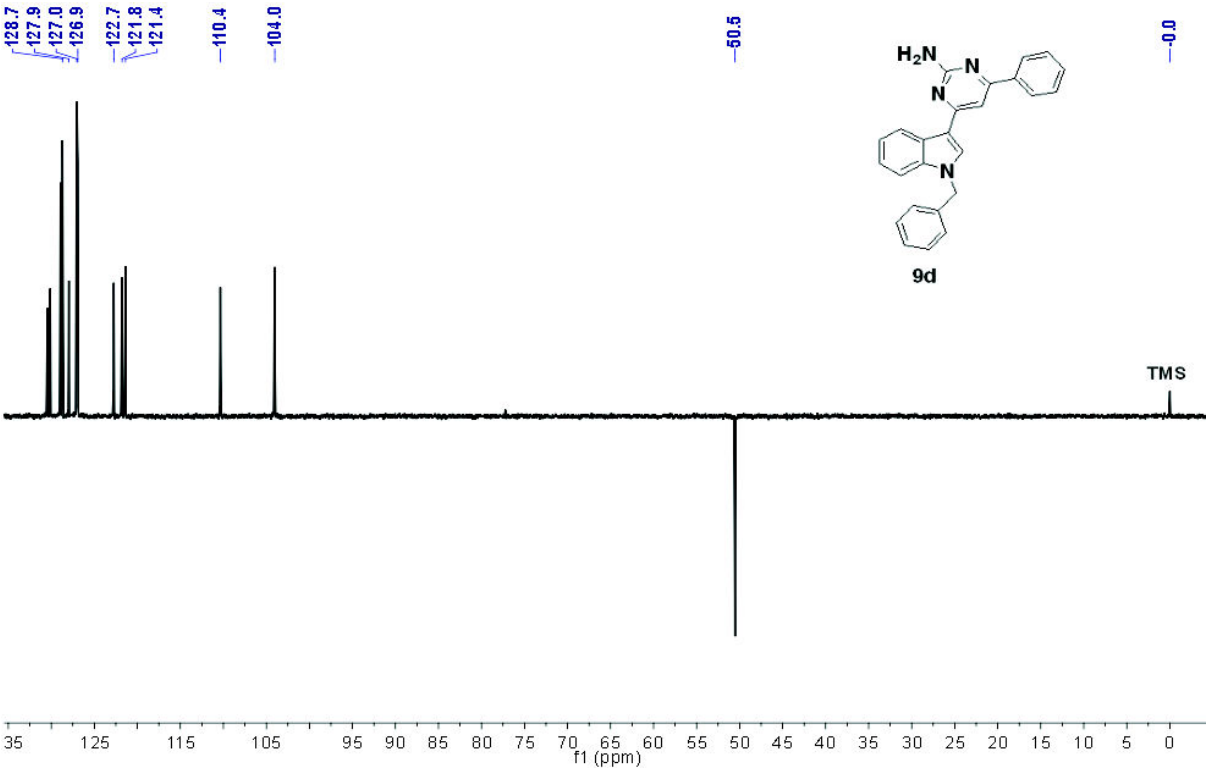
^{13}C DEPT 135-NMR of **11c** in $CDCl_3$ at 298 K (δ in ppm).



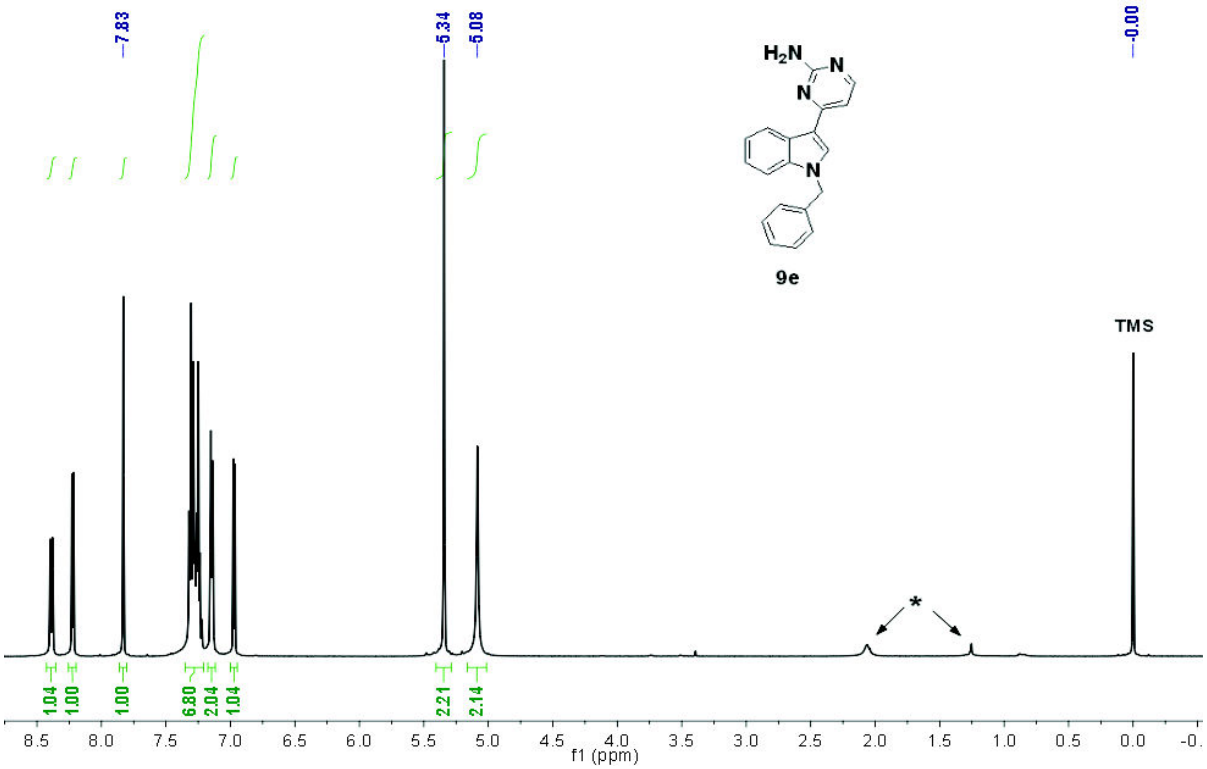
^{1}H NMR of **11d** in $CDCl_3$ at 296 K (δ in ppm).



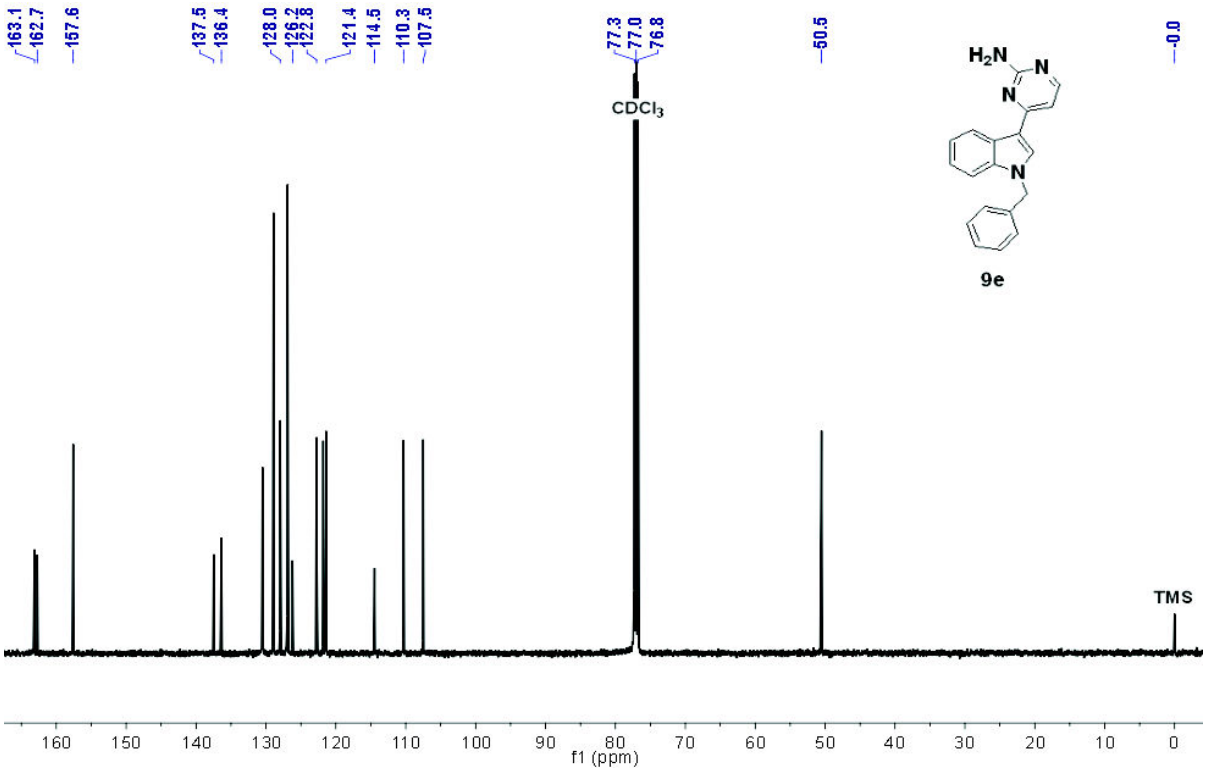
^{13}C NMR of **11d** in $CDCl_3$ at 297 K (δ in ppm).



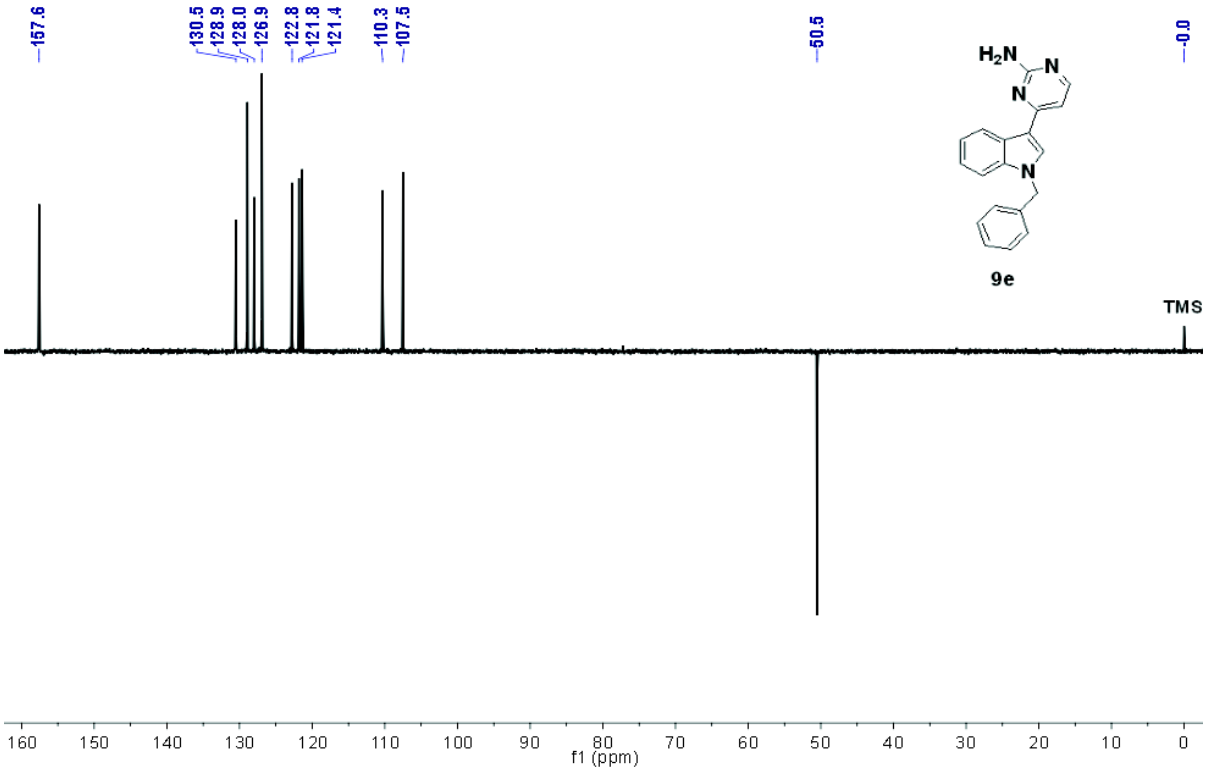
^{13}C DEPT 135-NMR of **11d** in $CDCl_3$ at 297 K (δ in ppm).



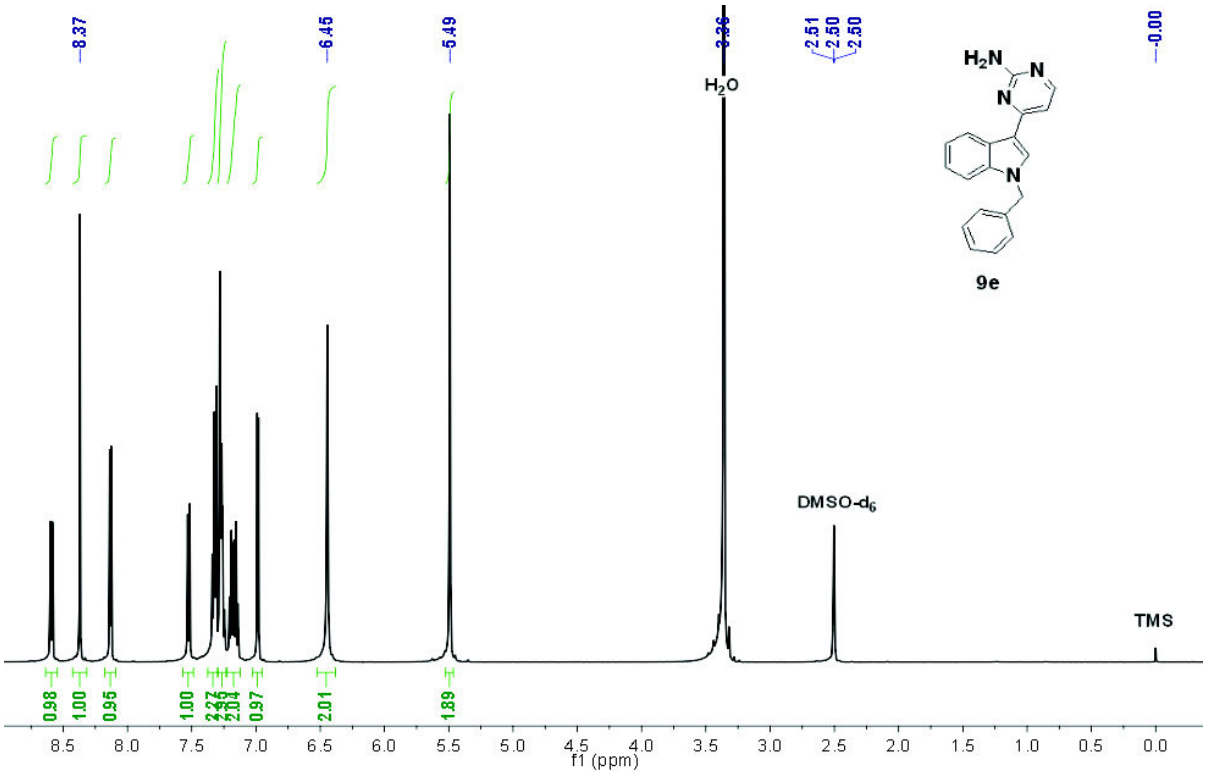
^{1}H NMR of **11e** in $CDCl_3$ at 297 K (δ in ppm). *Impurities from residual solvents.



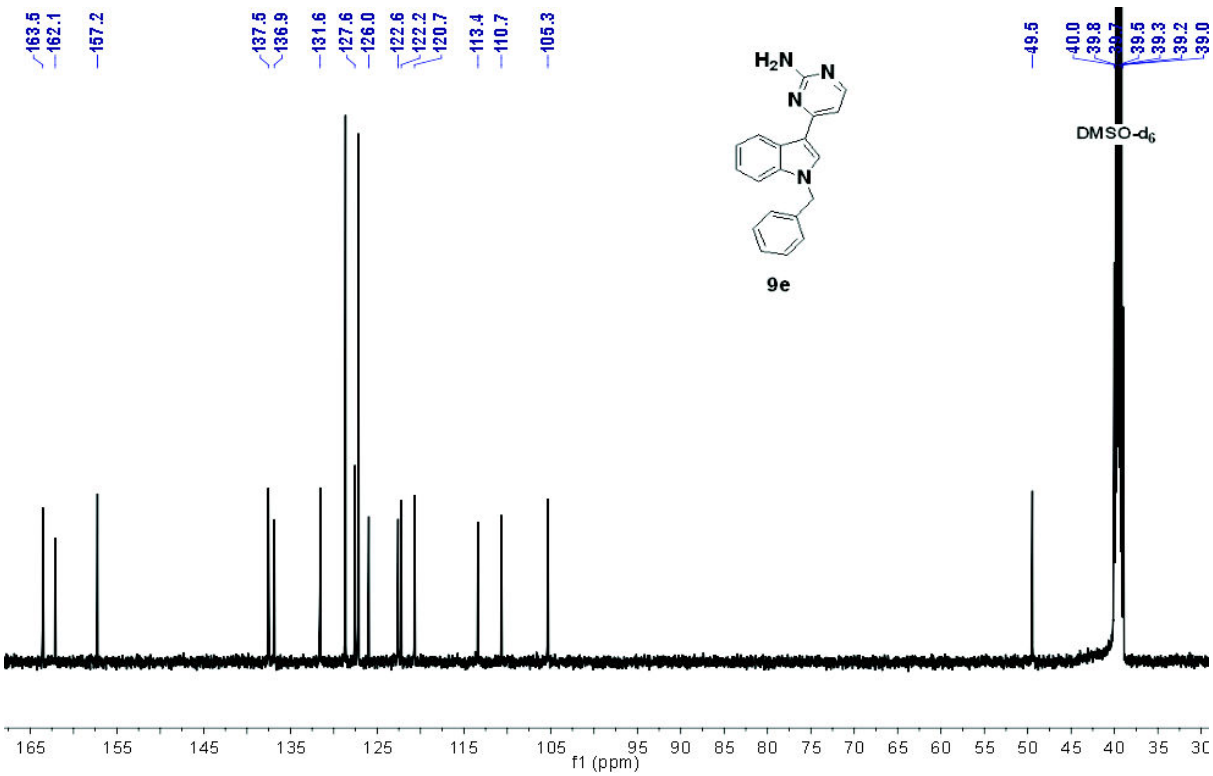
^{13}C NMR of **11e** in $CDCl_3$ at 297 K (δ in ppm).



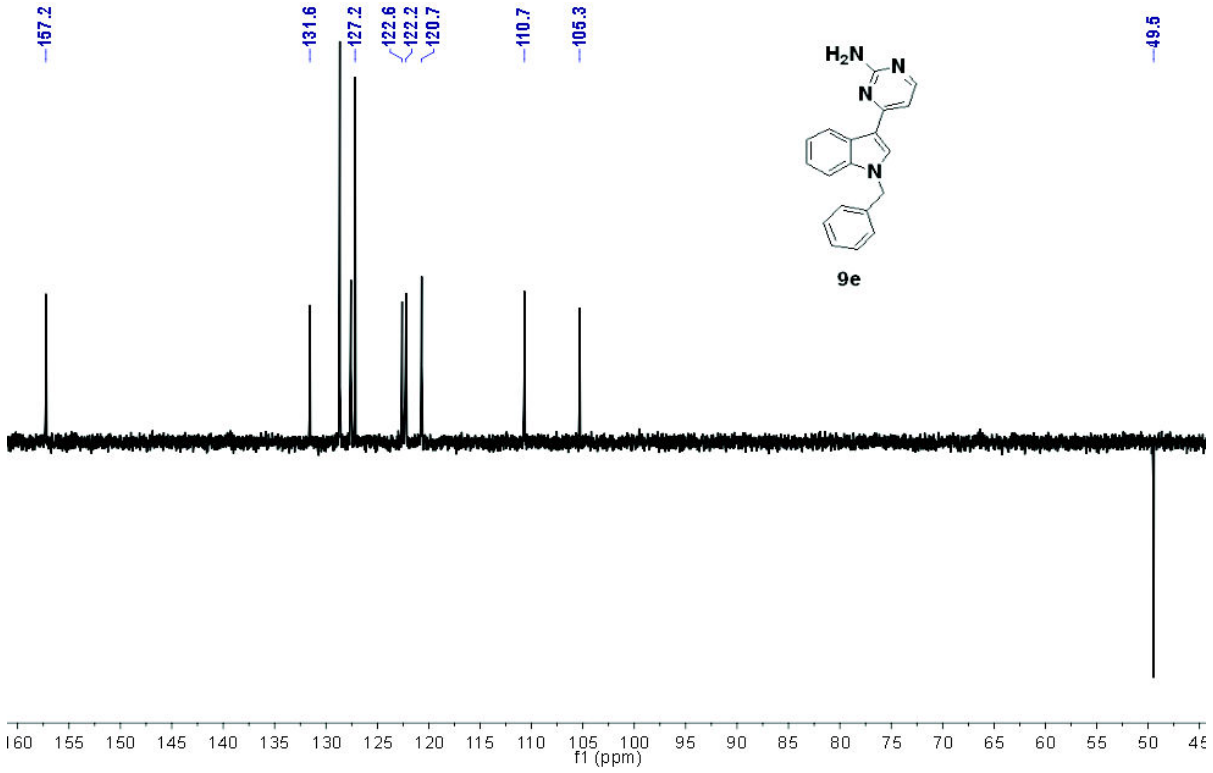
^{13}C DEPT-135 NMR of **11e** in $CDCl_3$ at 297 K (δ in ppm).



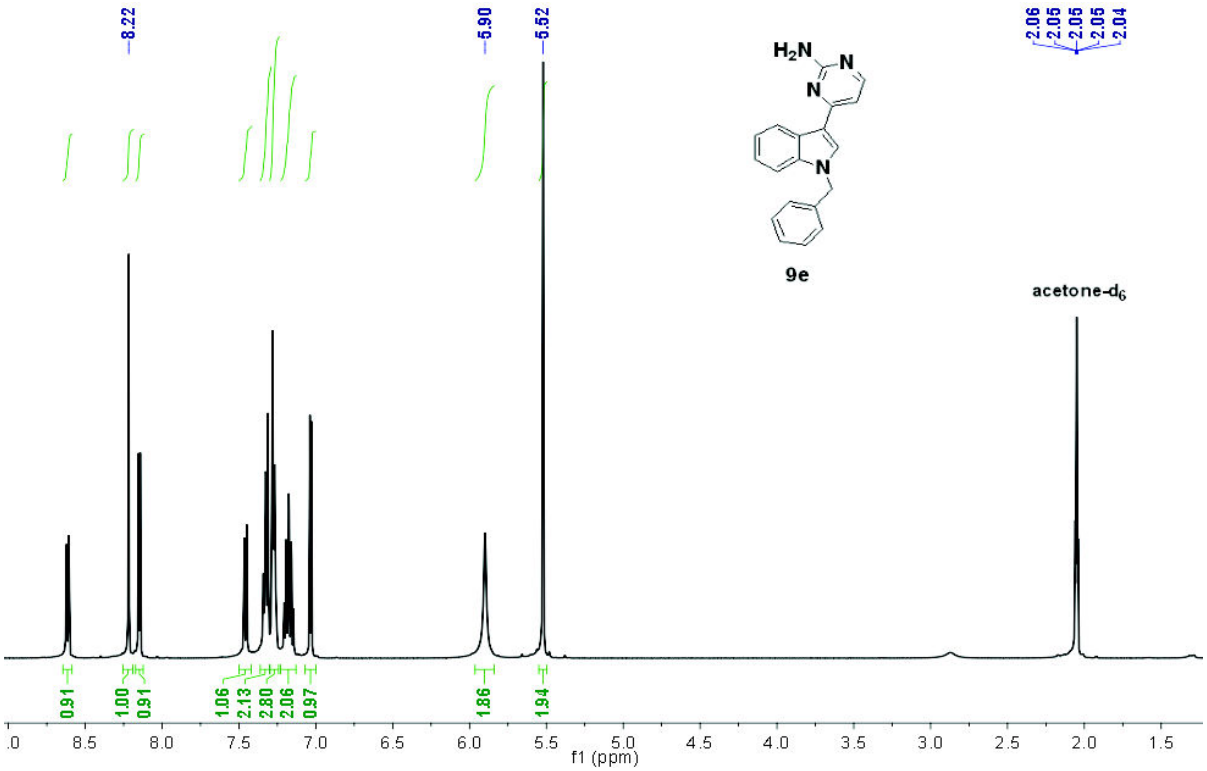
^{1}H NMR of **11e** in DMSO-d_6 at 298 K (δ in ppm).



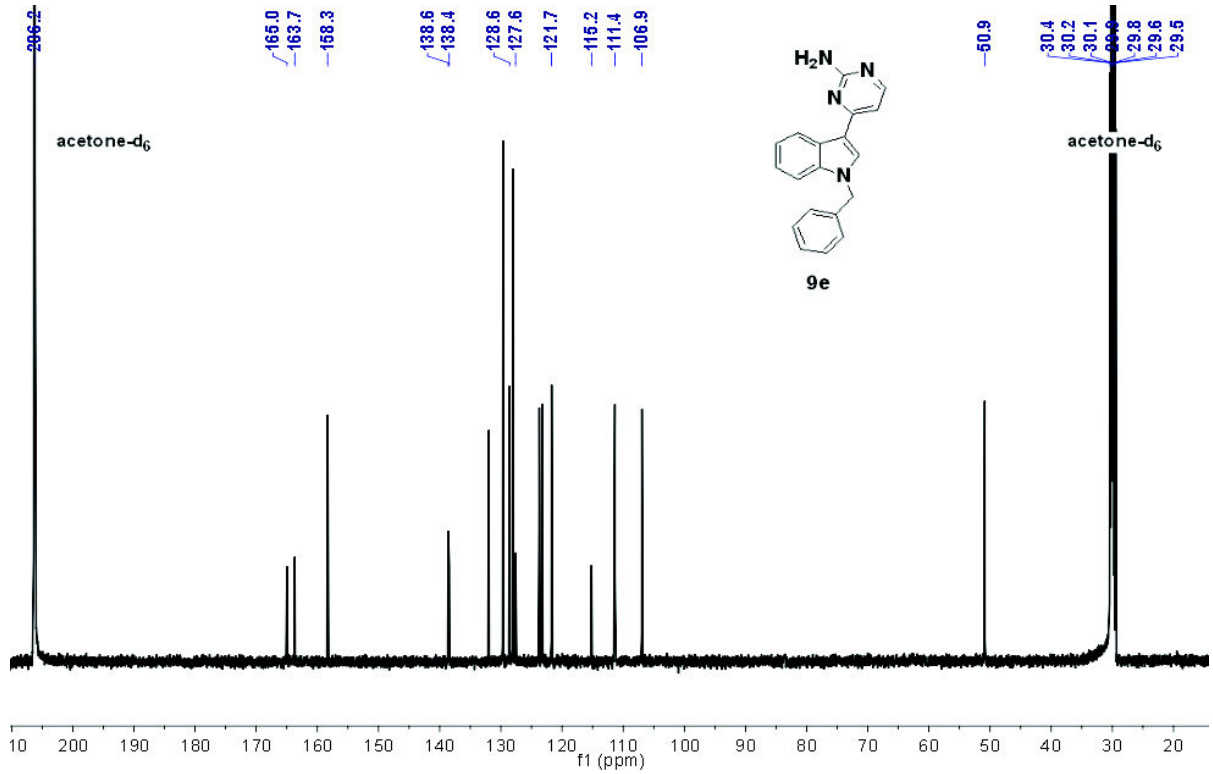
^{13}C NMR of **11e** in DMSO-d_6 at 298 K (δ in ppm).



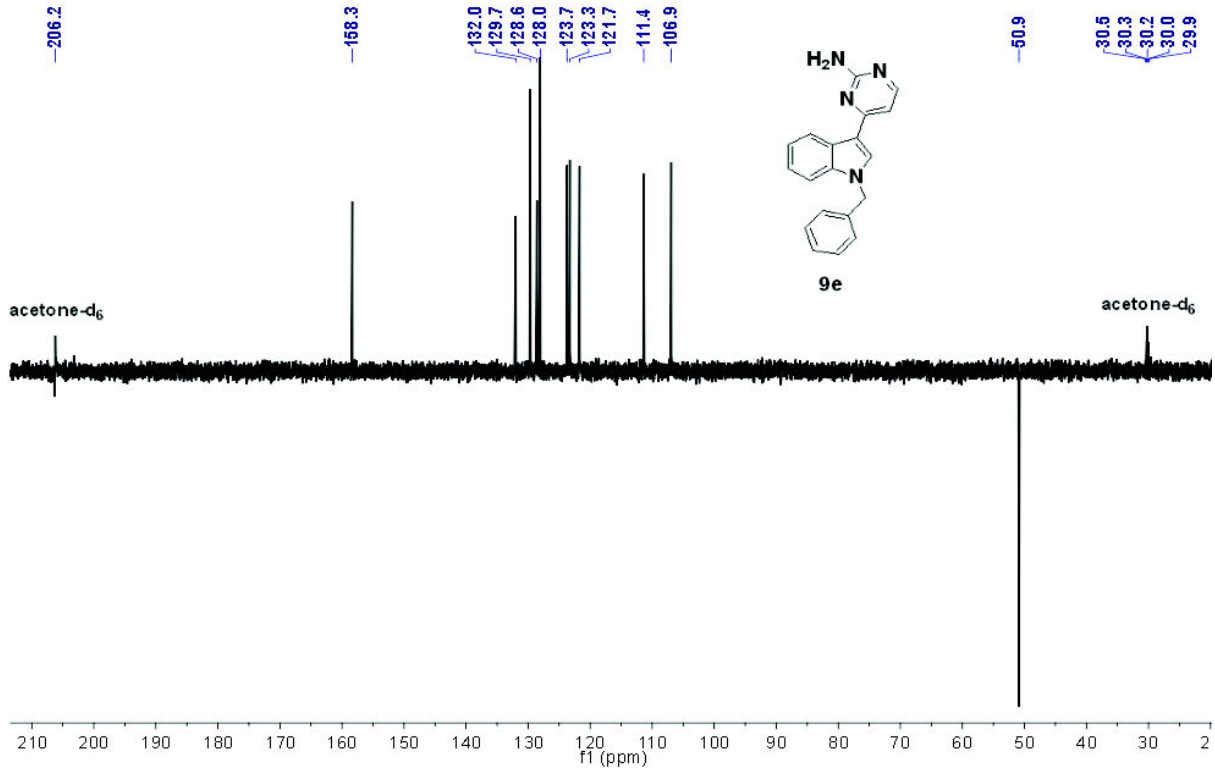
^{13}C DEPT 135-NMR of **11e** in DMSO-d_6 at 298 K (δ in ppm).



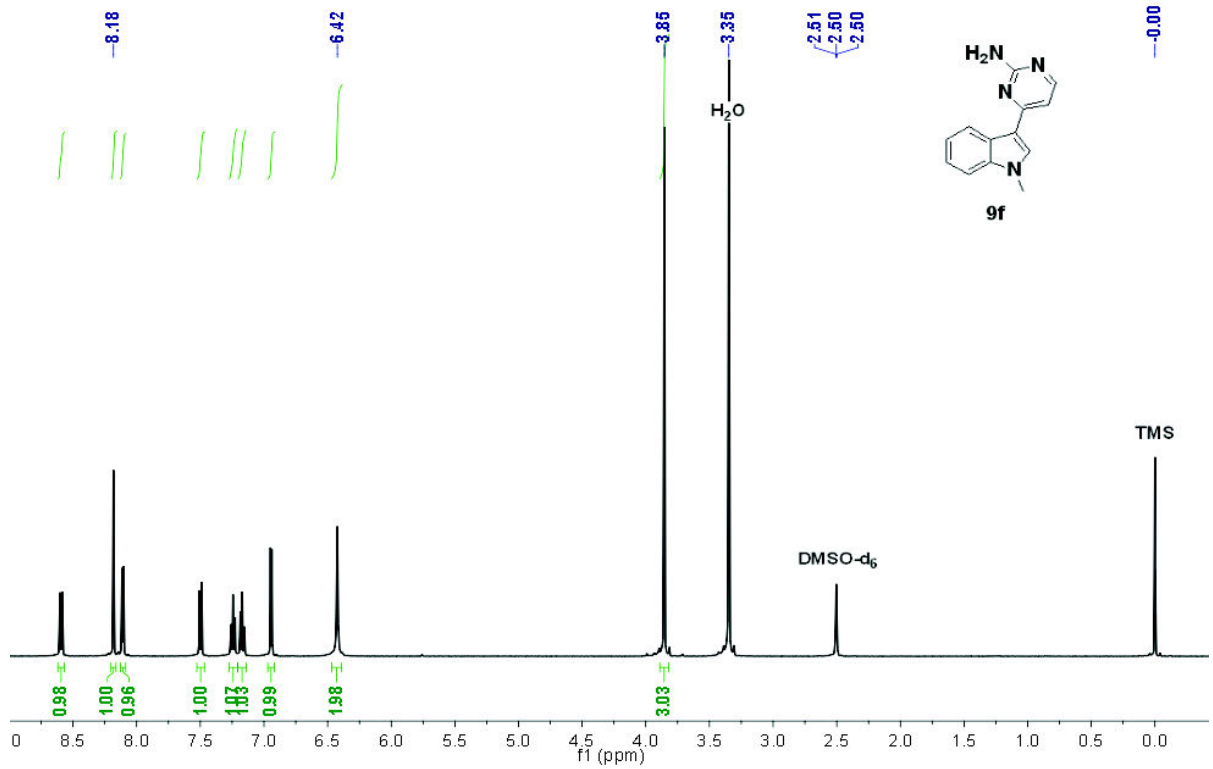
^{1}H NMR of **11e** in acetone-d_6 at 298 K (δ in ppm).



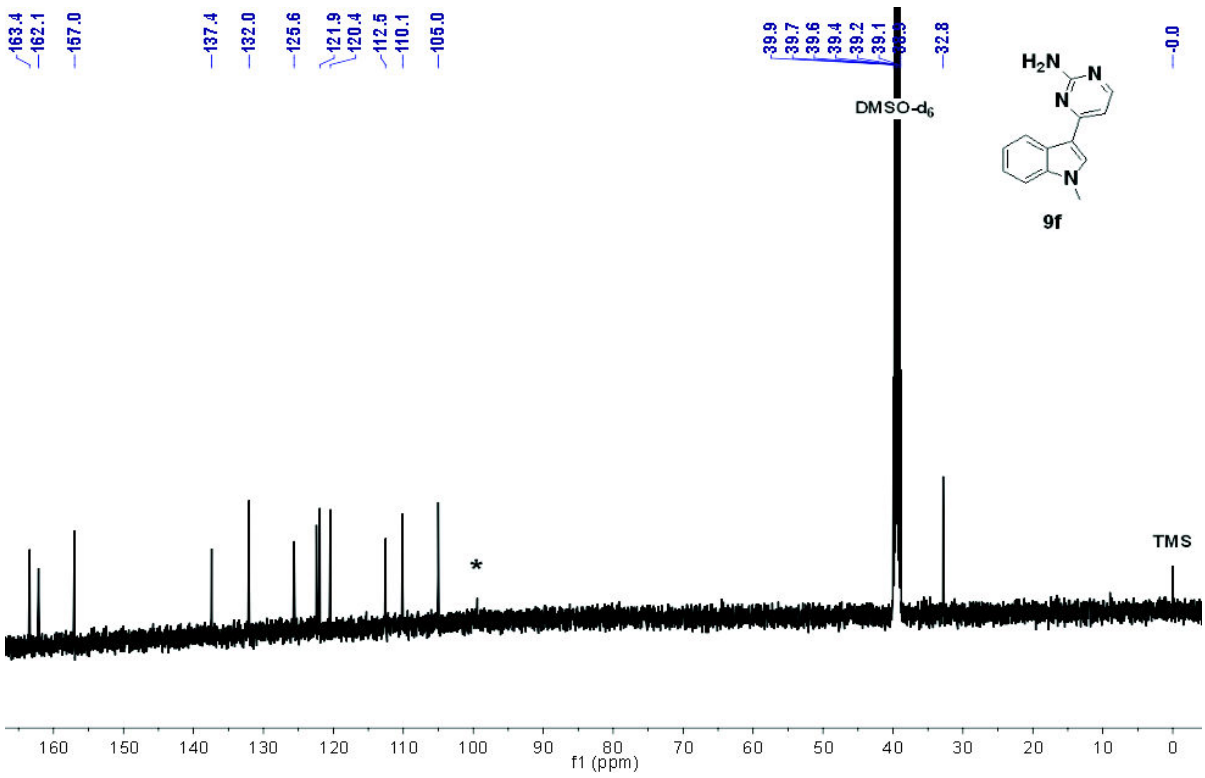
^{13}C NMR of **11e** in acetone-d_6 at 298 K (δ in ppm).



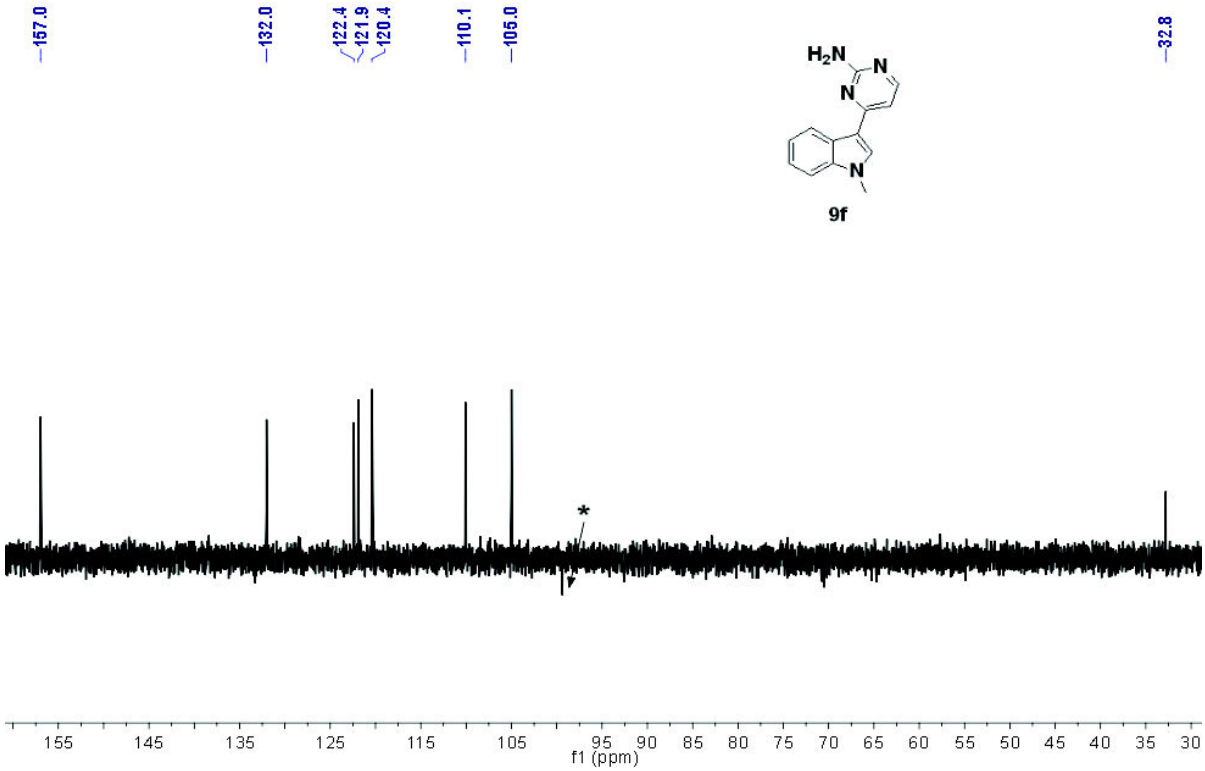
^{13}C DEPT 135-NMR of **11e** in acetone-d_6 at 298 K (δ in ppm).



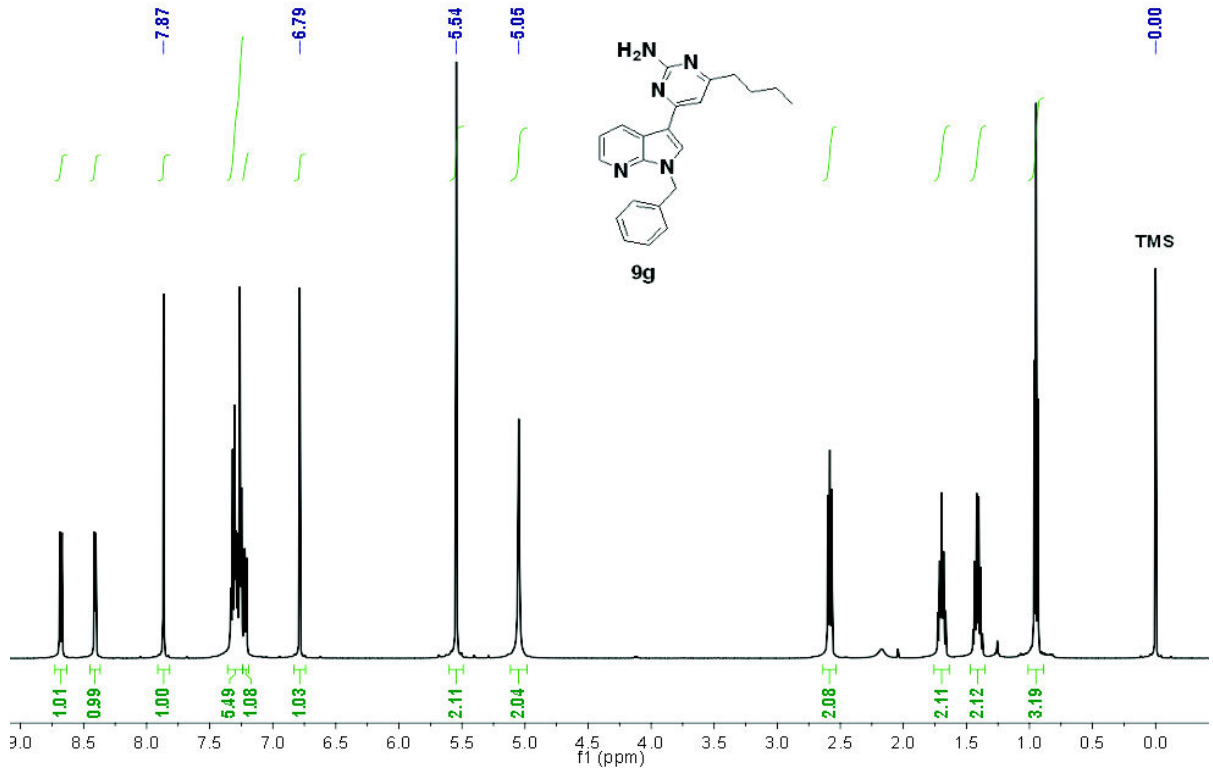
^{1}H NMR of **11f** in DMSO-d_6 at 298 K (δ in ppm).



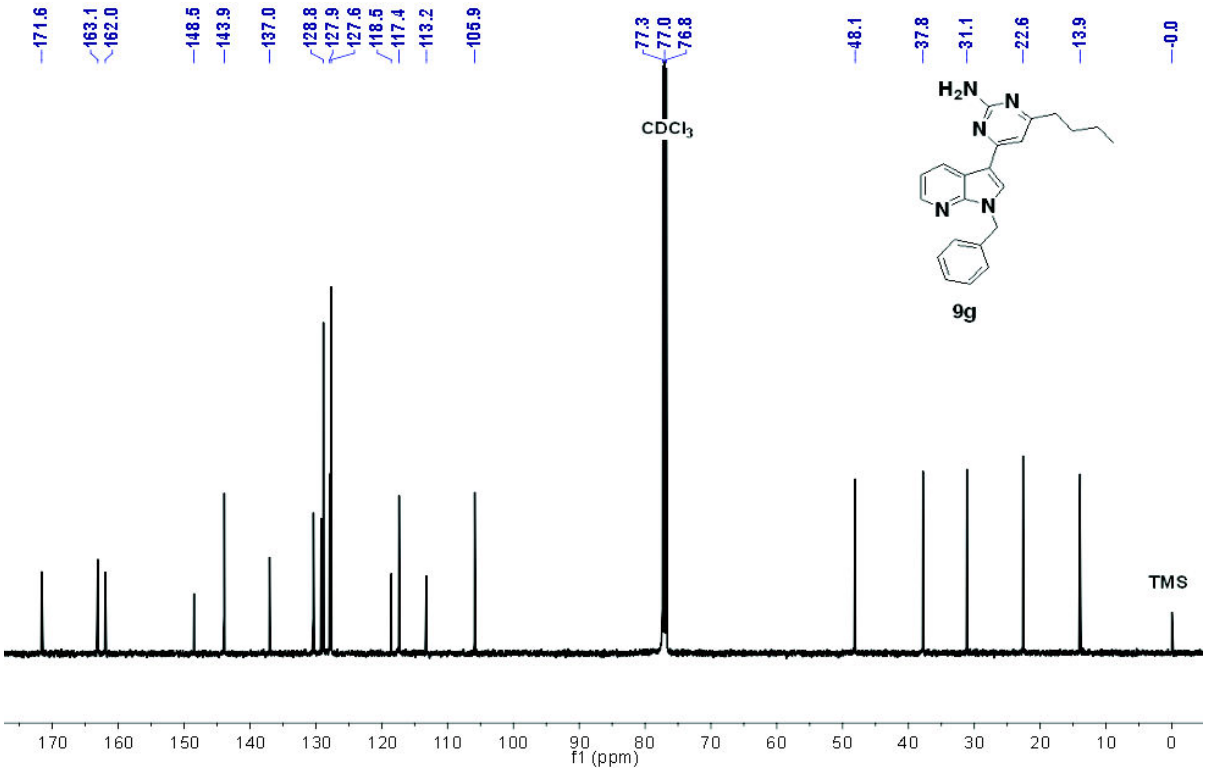
^{13}C NMR of **11f** in DMSO-d_6 at 298 K (δ in ppm).



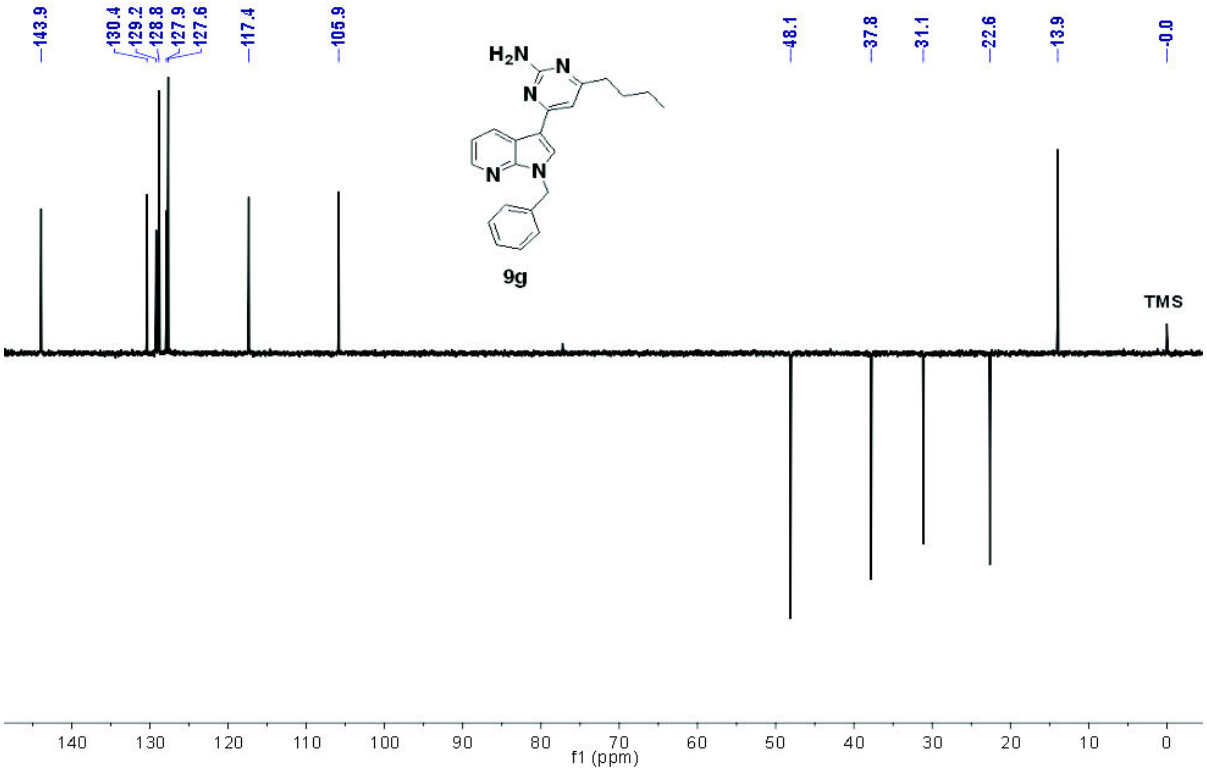
^{13}C DEPT 135-NMR of **11f** in DMSO-d_6 at 298 K (δ in ppm).



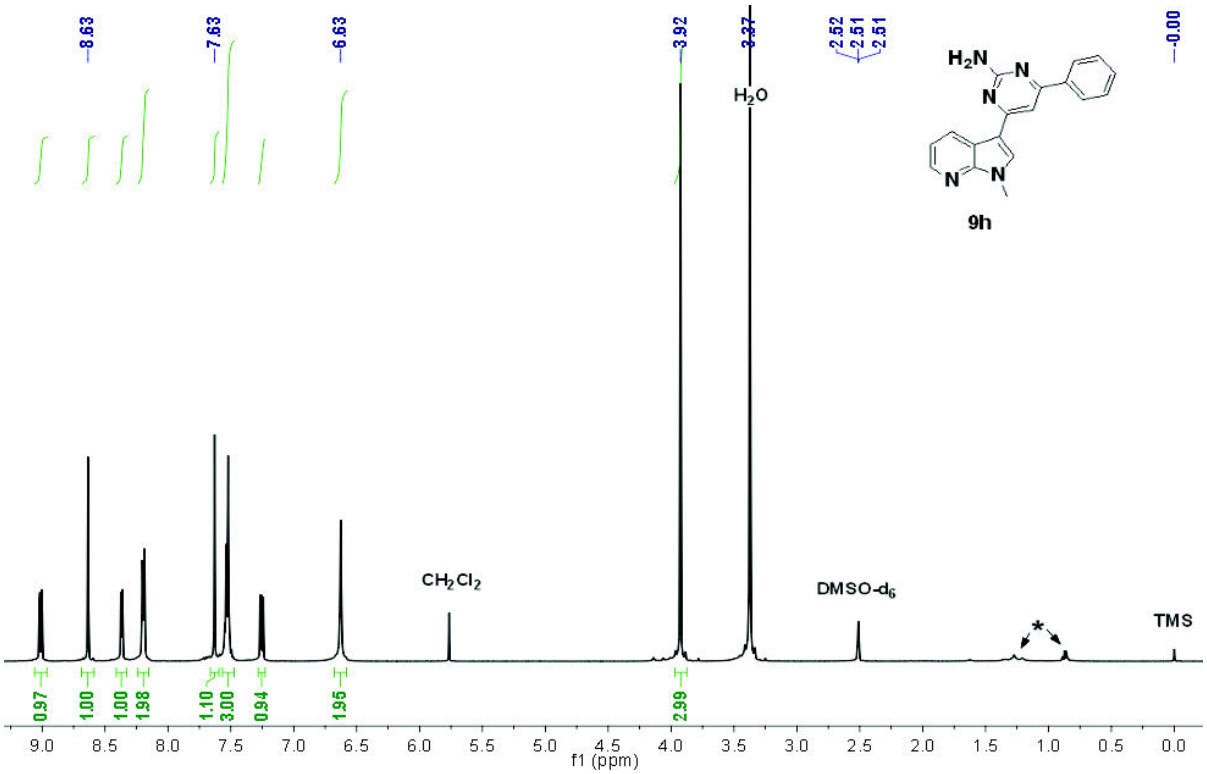
^{1}H NMR of **11g** in $CDCl_3$ at 296 K (δ in ppm).



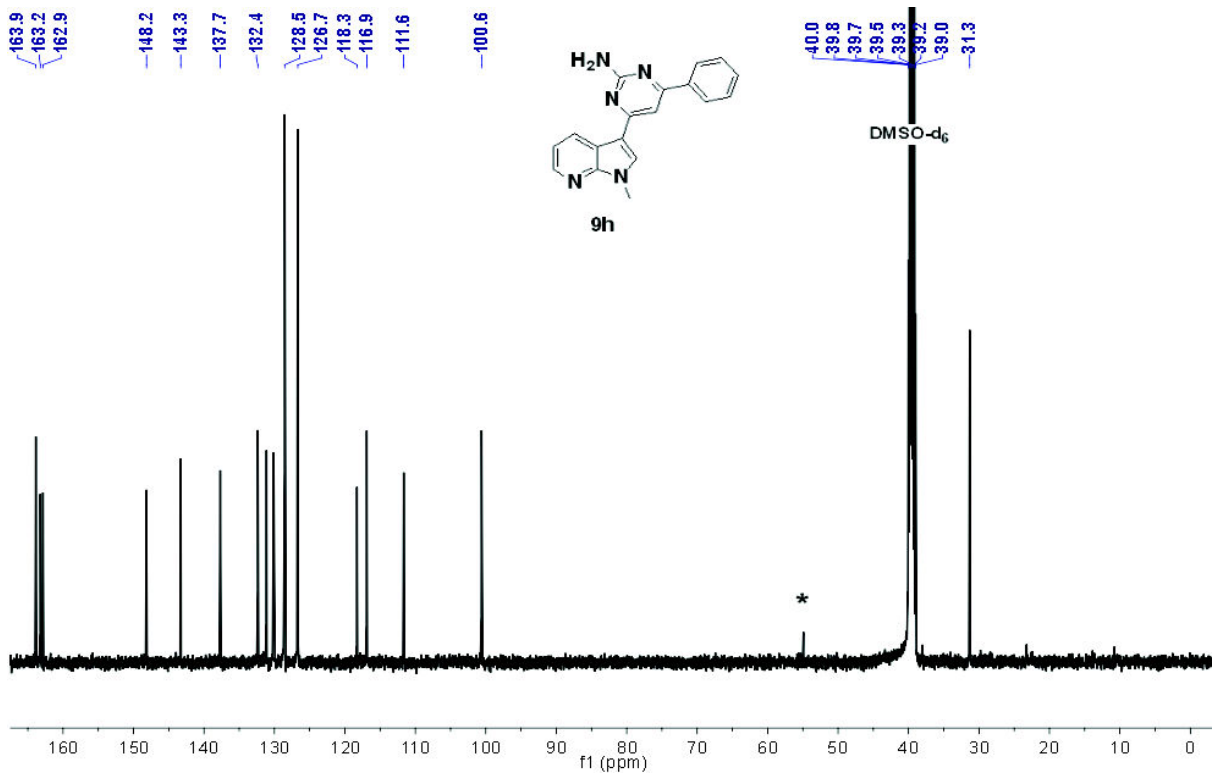
^{13}C NMR of **11g** in $CDCl_3$ at 297 K (δ in ppm).



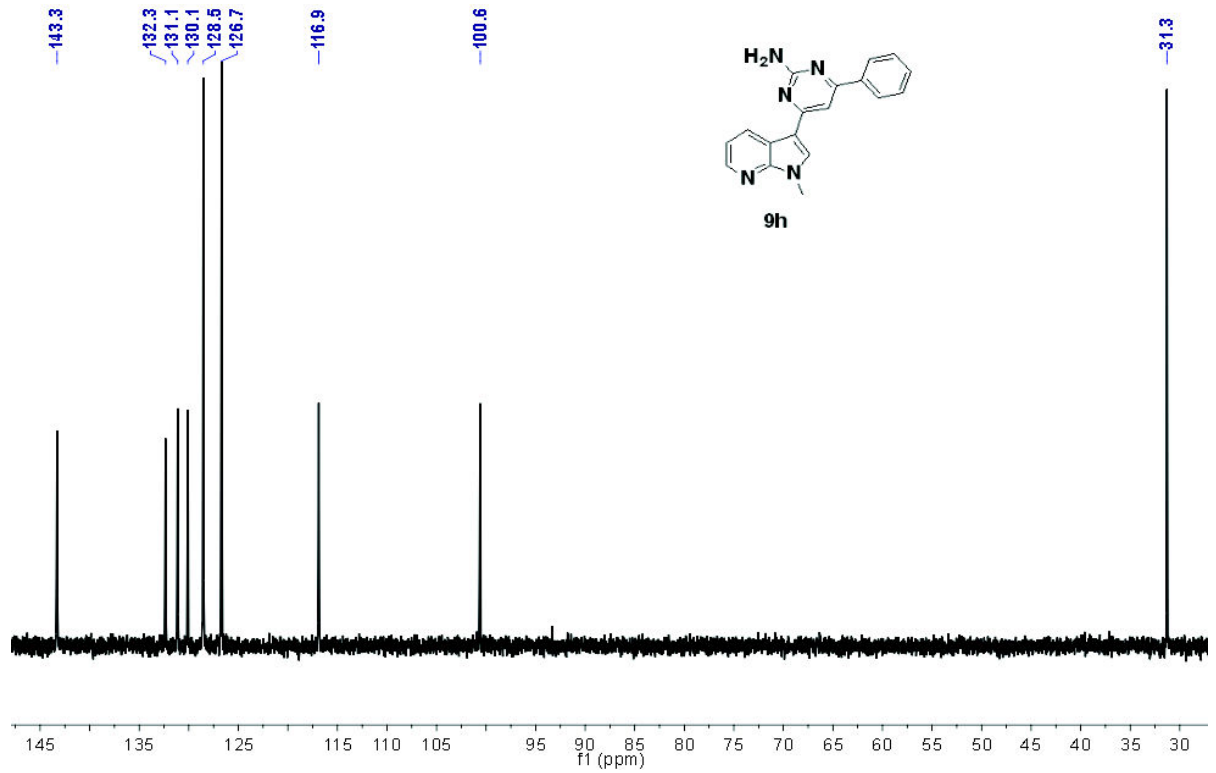
^{13}C DEPT 135-NMR of **11g** in $CDCl_3$ at 297 K (δ in ppm).



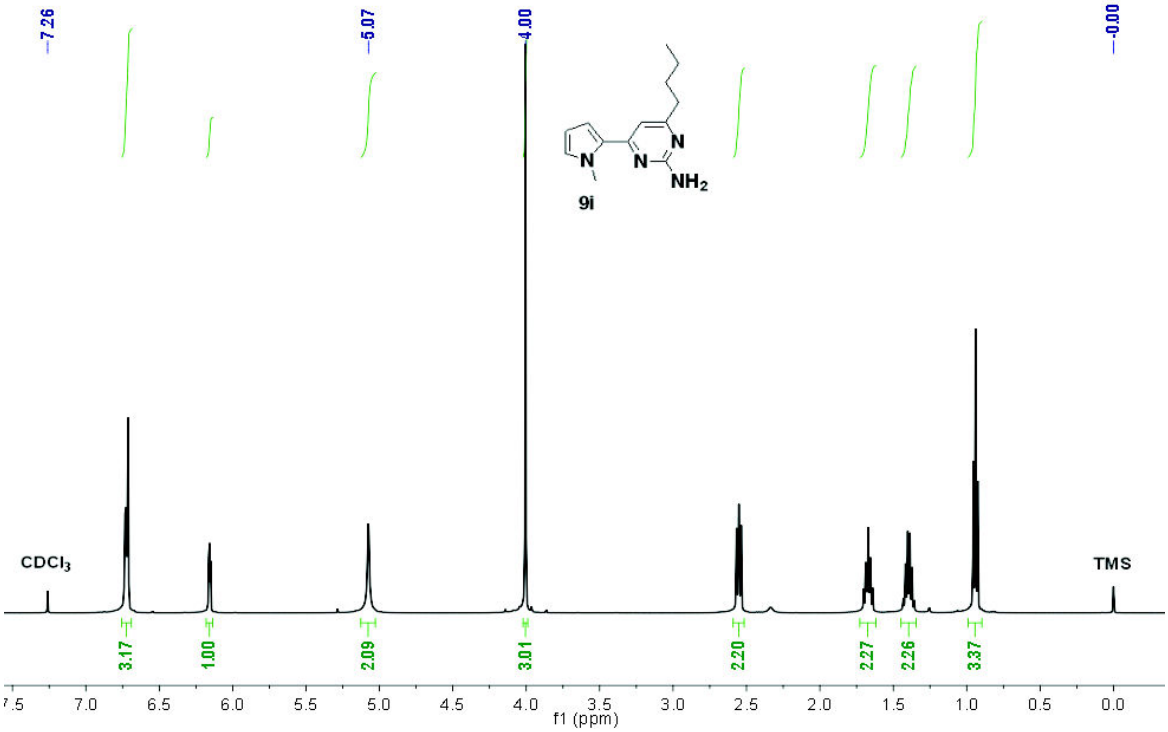
^{1}H NMR of **11h** in DMSO-d_6 at 297 K (δ in ppm). *Impurities from residual solvents.



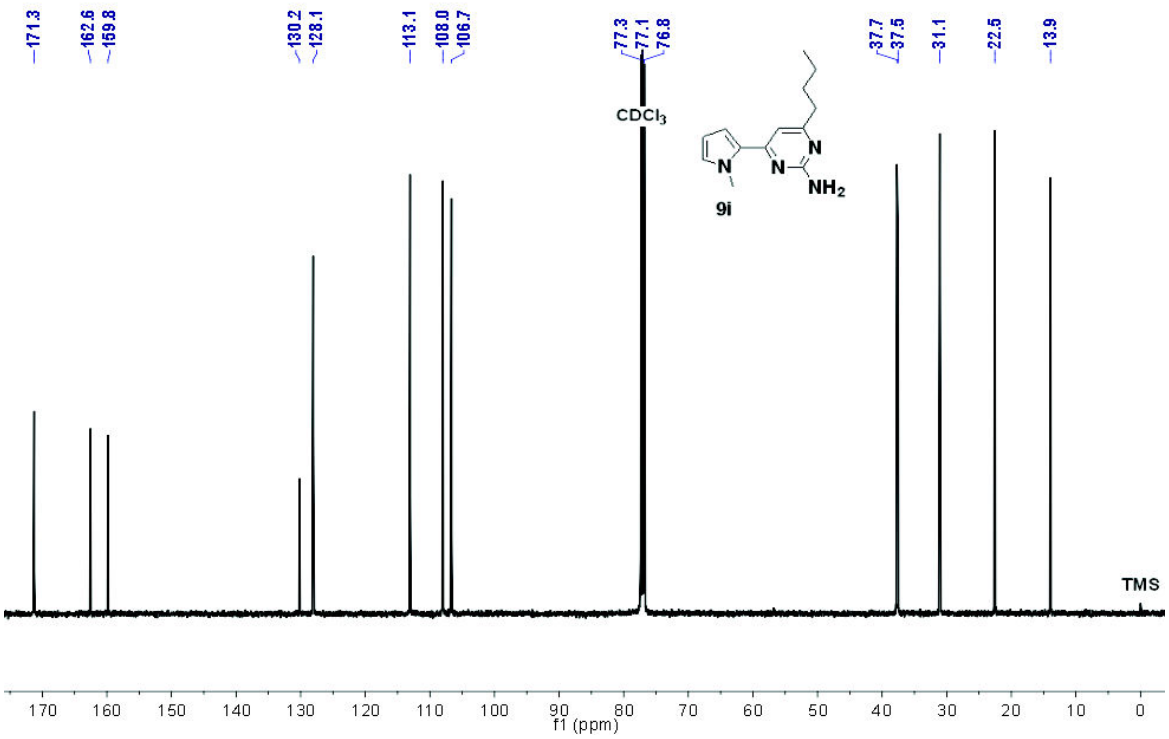
^{13}C NMR of **11h** in DMSO-d_6 at 298 K (δ in ppm). *Impurities from residual solvents.



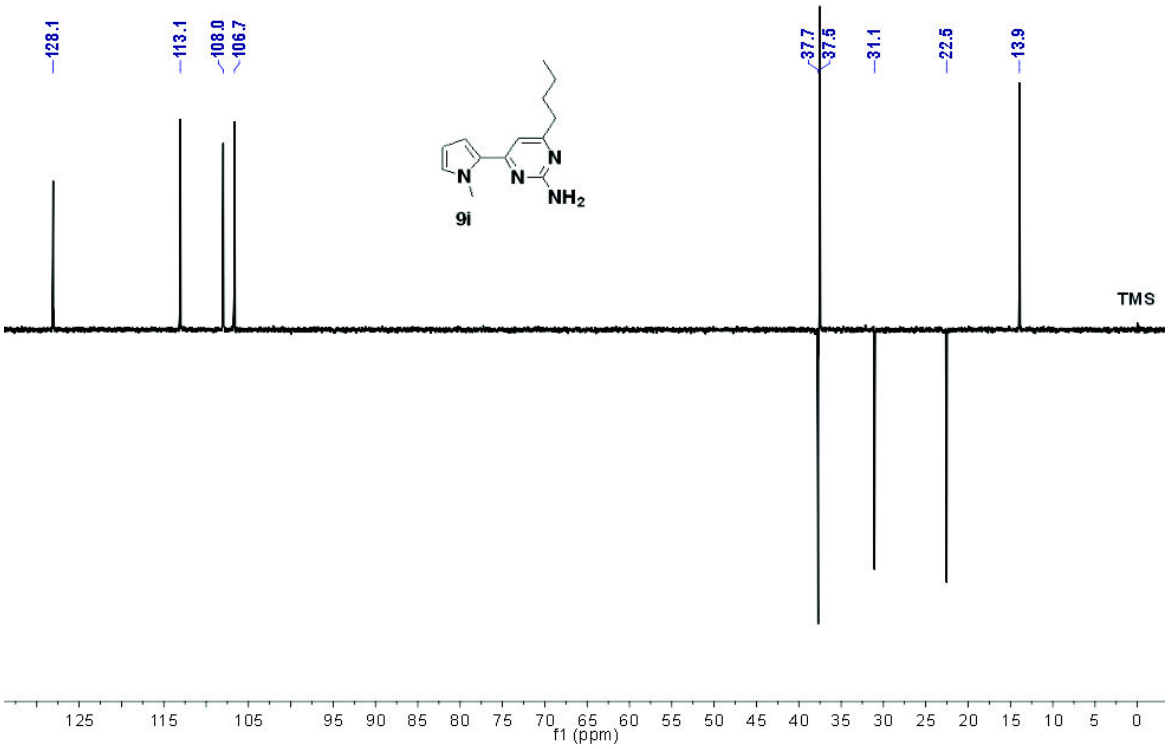
^{13}C DEPT 135-NMR of **11h** in $CDCl_3$ at 297 K (δ in ppm).



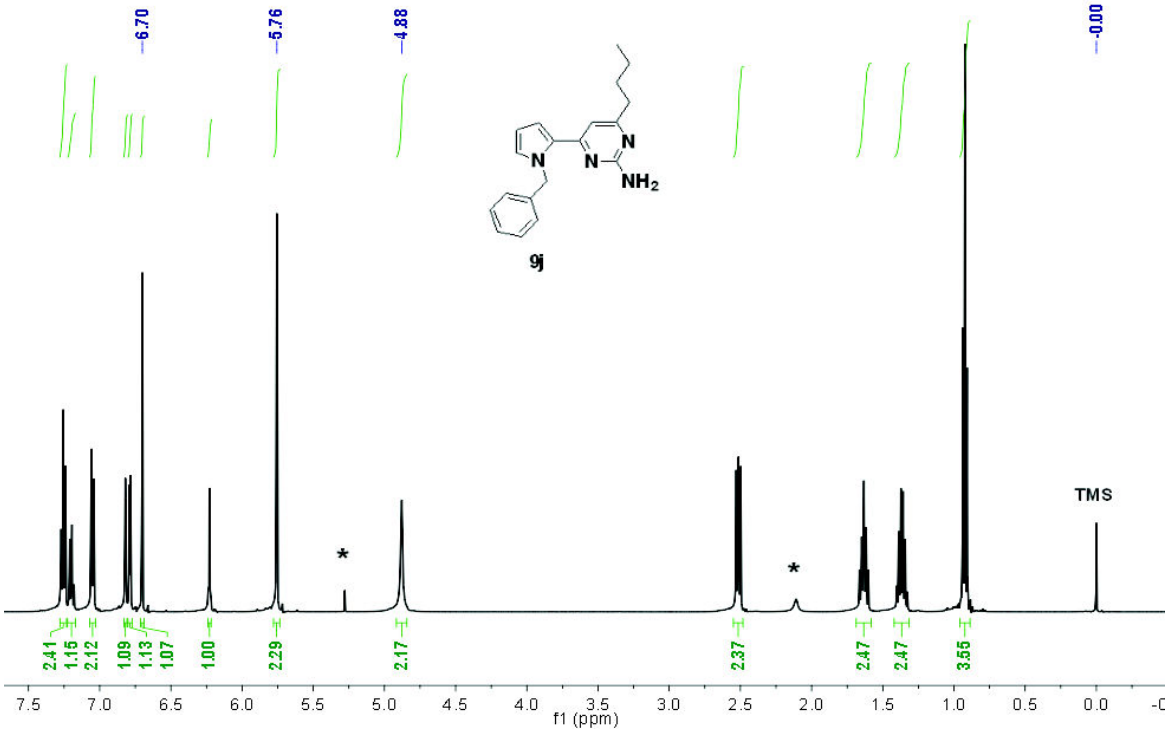
^{1}H NMR of **11i** in $CDCl_3$ at 298 K (δ in ppm).



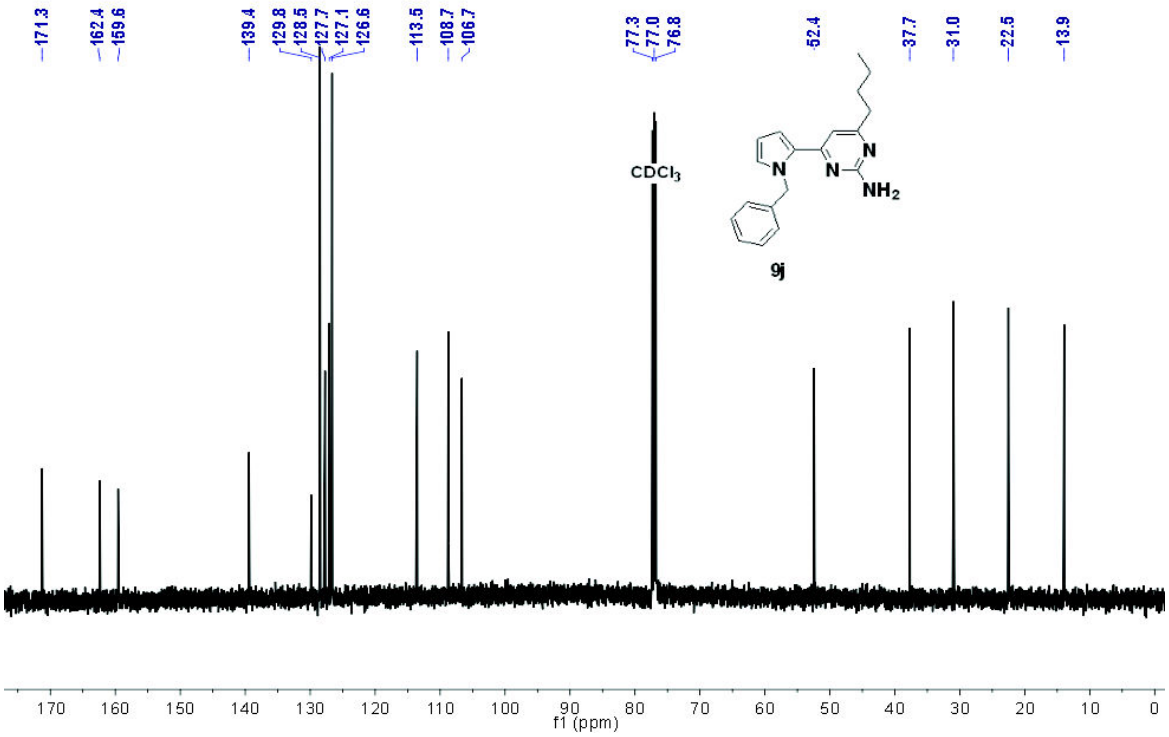
^{13}C NMR of **11i** in $CDCl_3$ at 298 K (δ in ppm).



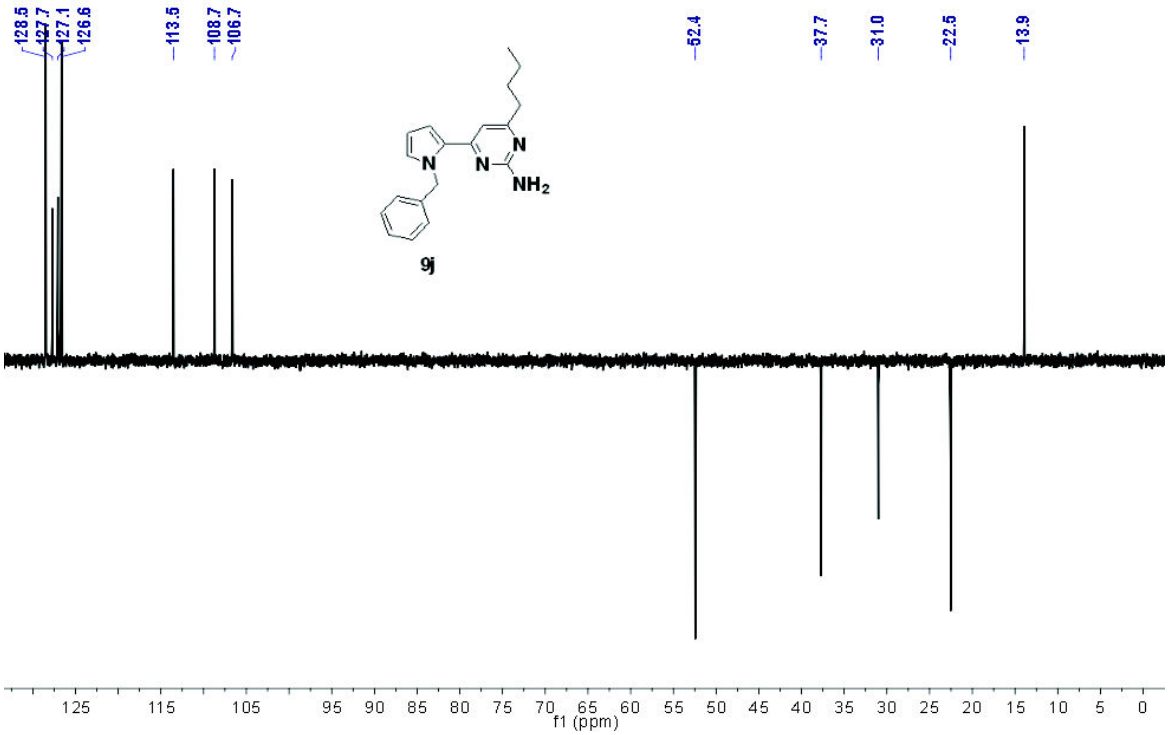
^{13}C DEPT 135-NMR of **11i** in $CDCl_3$ at 298 K (δ in ppm).



^{1}H NMR of **11j** in $CDCl_3$ at 297 K (δ in ppm). *Impurities from residual solvents.



^{13}C NMR of **11j** in $CDCl_3$ at 297 K (δ in ppm).



^{13}C DEPT 135-NMR of **11j** in $CDCl_3$ at 297 K (δ in ppm).

5. Crystallographic Data of Compounds 3b and 11b

Table 3. Crystal data and structure refinement for 1-(1-Benzyl-1*H*-indol-3-yl)hept-2-yn-1-one (**3b**).

Empirical formula	$C_{22}H_{21}NO$	
Formula weight	315.40	
Temperature	200(2) K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group	$P2_1/n$	
Z	4	
Unit cell dimensions	a = 12.616(1) Å	α = 90.0 deg.
	b = 7.4046(9) Å	β =104.449(3) deg.
	c = 19.386(2) Å	γ = 90.0 deg.
Volume	1753.8(4) $Å^3$	
Density (calculated)	1.20 g/cm^3	
Absorption coefficient	0.07 mm^{-1}	
Crystal shape	irregular	
Crystal size	0.27 x 0.07 x 0.05 mm^3	
Crystal color	colorless	
Theta range for data collection	1.8 to 22.5 deg.	
Index ranges	$-13\leq h\leq 13$, $-7\leq k\leq 7$, $-20\leq l\leq 20$	
Reflections collected	10845	
Independent reflections	2278 (R(int) = 0.0456)	
Observed reflections	1771 ($I > 2\sigma(I)$)	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00 and 0.98	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	2278 / 0 / 301	
Goodness-of-fit on F^2	1.06	
Final R indices ($I>2\sigma(I)$)	R1 = 0.039, wR2 = 0.083	
Largest diff. peak and hole	0.12 and -0.14 $eÅ^{-3}$	

Table 4. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for **3b**. U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

Atom	x	y	z	U_{eq}
O21	0.0616(1)	0.0165(2)	0.6613(1)	0.0493(4)
N1	0.2650(1)	0.1526(2)	0.8863(1)	0.0375(4)
C2	0.2745(2)	0.1268(2)	0.8191(1)	0.0362(5)
C3	0.1741(2)	0.0931(2)	0.7736(1)	0.0317(5)
C4	0.0959(2)	0.0996(2)	0.8163(1)	0.0324(5)
C5	-0.0176(2)	0.0781(3)	0.8021(1)	0.0389(5)
C6	-0.0675(2)	0.1002(3)	0.8571(1)	0.0460(6)
C7	-0.0069(2)	0.1418(3)	0.9256(1)	0.0483(6)
C8	0.1047(2)	0.1617(3)	0.9414(1)	0.0435(6)
C9	0.1550(2)	0.1401(2)	0.8860(1)	0.0343(5)
C10	0.3539(2)	0.2034(3)	0.9475(1)	0.0473(6)
C11	0.3659(2)	0.0773(3)	1.0102(1)	0.0391(5)
C12	0.3411(2)	-0.1046(3)	1.0018(1)	0.0490(6)
C13	0.3539(2)	-0.2160(4)	1.0604(1)	0.0571(7)
C14	0.3924(2)	-0.1475(4)	1.1277(1)	0.0593(7)
C15	0.4189(2)	0.0317(4)	1.1367(1)	0.0570(7)
C16	0.4054(2)	0.1443(3)	1.0783(1)	0.0473(6)
C21	0.1524(2)	0.0607(2)	0.6981(1)	0.0358(5)
C22	0.2431(2)	0.0850(3)	0.6654(1)	0.0397(5)
C23	0.3160(2)	0.1095(3)	0.6368(1)	0.0397(5)
C24	0.4078(2)	0.1378(3)	0.6046(1)	0.0421(5)
C25	0.5175(2)	0.0923(3)	0.6553(1)	0.0404(5)
C26	0.6123(2)	0.1108(3)	0.6209(1)	0.0478(6)
C27	0.7214(2)	0.0733(4)	0.6724(2)	0.0660(7)
H2	0.3439(16)	0.130(2)	0.8091(9)	0.037(5)
H5	-0.0597(15)	0.047(2)	0.7551(10)	0.036(5)
H6	-0.1462(18)	0.086(2)	0.8480(10)	0.051(6)
H7	-0.0425(16)	0.159(3)	0.9629(11)	0.050(6)
H8	0.1470(14)	0.188(2)	0.9882(10)	0.039(5)
H10A	0.3378(16)	0.329(3)	0.9628(10)	0.056(6)
H10B	0.4208(17)	0.206(3)	0.9305(10)	0.054(6)
H12	0.3165(16)	-0.151(3)	0.9555(12)	0.054(6)
H13	0.3339(17)	-0.342(3)	1.0522(11)	0.064(7)
H14	0.4005(17)	-0.228(3)	1.1669(12)	0.067(7)
H15	0.4447(17)	0.083(3)	1.1835(12)	0.062(7)
H16	0.4260(15)	0.271(3)	1.0844(10)	0.050(6)
H24A	0.3950(15)	0.060(3)	0.5595(11)	0.056(6)
H24B	0.4088(15)	0.266(3)	0.5877(10)	0.053(6)
H25A	0.5159(14)	-0.033(3)	0.6731(9)	0.042(5)
H25B	0.5274(14)	0.173(2)	0.6990(10)	0.041(5)
H26A	0.6024(16)	0.026(3)	0.5795(11)	0.052(6)
H26B	0.6116(14)	0.239(3)	0.6003(9)	0.047(6)
H27A	0.718(2)	-0.053(4)	0.6904(14)	0.090(9)
H27B	0.734(2)	0.166(4)	0.7118(15)	0.100(10)
H27C	0.785(2)	0.080(3)	0.6476(13)	0.082(8)

Table 5. Hydrogen coordinates and isotropic displacement parameters ($Å^2$) for **3b.**

Atom	x	y	z	U_{eq}
H2	0.3439(16)	0.130(2)	0.8091(9)	0.037(5)
H5	-0.0597(15)	0.047(2)	0.7551(10)	0.036(5)
H6	-0.1462(18)	0.086(2)	0.8480(10)	0.051(6)
H7	-0.0425(16)	0.159(3)	0.9629(11)	0.050(6)
H8	0.1470(14)	0.188(2)	0.9882(10)	0.039(5)
H10A	0.3378(16)	0.329(3)	0.9628(10)	0.056(6)
H10B	0.4208(17)	0.206(3)	0.9305(10)	0.054(6)
H12	0.3165(16)	-0.151(3)	0.9555(12)	0.054(6)
H13	0.3339(17)	-0.342(3)	1.0522(11)	0.064(7)
H14	0.4005(17)	-0.228(3)	1.1669(12)	0.067(7)
H15	0.4447(17)	0.083(3)	1.1835(12)	0.062(7)
H16	0.4260(15)	0.271(3)	1.0844(10)	0.050(6)
H24A	0.3950(15)	0.060(3)	0.5595(11)	0.056(6)
H24B	0.4088(15)	0.266(3)	0.5877(10)	0.053(6)
H25A	0.5159(14)	-0.033(3)	0.6731(9)	0.042(5)
H25B	0.5274(14)	0.173(2)	0.6990(10)	0.041(5)
H26A	0.6024(16)	0.026(3)	0.5795(11)	0.052(6)
H26B	0.6116(14)	0.239(3)	0.6003(9)	0.047(6)
H27A	0.718(2)	-0.053(4)	0.6904(14)	0.090(9)
H27B	0.734(2)	0.166(4)	0.7118(15)	0.100(10)
H27C	0.785(2)	0.080(3)	0.6476(13)	0.082(8)

Table 6. Anisotropic displacement parameters ($Å^2$) for **3b**. The anisotropic displacement factor exponent takes the form: $-2\ pi^2\ (h^2\ a^{*2}\ U_{11} + ... + 2\ h\ k\ a^*\ b^*\ U_{12})$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O21	0.0430(10)	0.0589(10)	0.0406(9)	-0.0080(7)	0.0002(7)	0.0000(7)
N1	0.0402(11)	0.0426(10)	0.0272(10)	0.0017(7)	0.0038(8)	-0.0076(8)
C2	0.0378(14)	0.0375(12)	0.0335(13)	0.0033(9)	0.0092(11)	-0.0003(9)
C3	0.0346(12)	0.0311(11)	0.0274(11)	0.0009(8)	0.0039(9)	0.0019(8)
C4	0.0366(13)	0.0260(11)	0.0348(12)	0.0026(8)	0.0092(10)	0.0020(9)
C5	0.0381(14)	0.0327(12)	0.0443(14)	0.0022(9)	0.0074(12)	0.0017(9)
C6	0.0426(15)	0.0391(13)	0.0608(17)	0.0090(10)	0.0211(13)	0.0045(10)
C7	0.0649(18)	0.0395(14)	0.0494(15)	0.0085(10)	0.0311(14)	0.0078(11)
C8	0.0577(16)	0.0395(13)	0.0346(13)	0.0027(10)	0.0141(12)	-0.0008(10)
C9	0.0427(13)	0.0295(11)	0.0313(12)	0.0031(8)	0.0103(10)	-0.0014(9)
C10	0.0508(16)	0.0506(16)	0.0346(13)	-0.0002(11)	-0.0004(11)	-0.0156(12)
C11	0.0377(13)	0.0445(14)	0.0321(12)	0.0003(9)	0.0033(9)	-0.0029(9)
C12	0.0543(15)	0.0501(15)	0.0374(14)	-0.0009(11)	0.0017(11)	-0.0037(11)
C13	0.0644(17)	0.0474(16)	0.0532(17)	0.0069(13)	0.0029(12)	-0.0040(12)
C14	0.0635(17)	0.0672(19)	0.0451(16)	0.0176(14)	0.0094(12)	0.0071(13)
C15	0.0673(17)	0.0672(18)	0.0320(15)	-0.0019(12)	0.0039(12)	0.0080(13)
C16	0.0549(15)	0.0464(15)	0.0355(13)	-0.0045(11)	0.0013(10)	0.0003(11)
C21	0.0402(14)	0.0287(12)	0.0363(12)	-0.0004(9)	0.0053(11)	0.0050(9)
C22	0.0472(14)	0.0401(13)	0.0299(12)	-0.0001(9)	0.0059(11)	0.0061(10)
C23	0.0502(14)	0.0361(12)	0.0309(12)	0.0011(9)	0.0067(11)	0.0068(10)
C24	0.0529(15)	0.0406(14)	0.0350(13)	0.0029(10)	0.0152(11)	0.0034(10)
C25	0.0526(15)	0.0344(14)	0.0357(13)	0.0022(10)	0.0137(11)	0.0017(10)
C26	0.0544(16)	0.0453(15)	0.0465(14)	-0.0005(12)	0.0181(12)	-0.0031(11)
C27	0.0494(17)	0.075(2)	0.074(2)	0.0022(16)	0.0156(15)	-0.0014(14)

Table 7. Bond lengths (Å) and angles (deg) for **3b**.

O21-C21	1.233(2)	C6-C5-H5	120.8(11)
N1-C2	1.350(2)	C4-C5-H5	120.6(11)
N1-C9	1.390(2)	C5-C6-C7	121.1(2)
N1-C10	1.464(2)	C5-C6-H6	119.5(12)
C2-C3	1.373(3)	C7-C6-H6	119.3(12)
C2-H2	0.943(19)	C8-C7-C6	121.7(2)
C3-C4	1.437(3)	C8-C7-H7	118.0(12)
C3-C21	1.442(3)	C6-C7-H7	120.3(12)
C4-C5	1.399(3)	C7-C8-C9	117.3(2)
C4-C9	1.405(3)	C7-C8-H8	122.3(11)
C5-C6	1.376(3)	C9-C8-H8	120.4(11)
C5-H5	0.961(18)	C8-C9-N1	129.78(18)
C6-C7	1.392(3)	C8-C9-C4	122.33(19)
C6-H6	0.97(2)	N1-C9-C4	107.89(16)
C7-C8	1.372(3)	N1-C10-C11	113.36(17)
C7-H7	0.95(2)	N1-C10-H10A	107.8(11)
C8-C9	1.385(3)	C11-C10-H10A	108.4(11)
C8-H8	0.951(18)	N1-C10-H10B	106.4(12)
C10-C11	1.511(3)	C11-C10-H10B	111.1(12)
C10-H10A	1.01(2)	H10A-C10-H10B	109.7(17)
C10-H10B	0.98(2)	C16-C11-C12	118.65(19)
C11-C16	1.381(3)	C16-C11-C10	119.15(19)
C11-C12	1.383(3)	C12-C11-C10	122.17(18)
C12-C13	1.380(3)	C13-C12-C11	120.6(2)
C12-H12	0.94(2)	C13-C12-H12	120.9(13)
C13-C14	1.372(3)	C11-C12-H12	118.5(13)
C13-H13	0.97(2)	C14-C13-C12	120.2(3)
C14-C15	1.370(3)	C14-C13-H13	121.8(13)
C14-H14	0.95(2)	C12-C13-H13	118.0(13)
C15-C16	1.382(3)	C15-C14-C13	119.8(2)
C15-H15	0.96(2)	C15-C14-H14	122.2(13)
C16-H16	0.97(2)	C13-C14-H14	118.0(13)
C21-C22	1.451(3)	C14-C15-C16	120.2(2)
C22-C23	1.199(3)	C14-C15-H15	121.3(13)
C23-C24	1.462(3)	C16-C15-H15	118.4(13)
C24-C25	1.521(3)	C11-C16-C15	120.5(2)
C24-H24A	1.03(2)	C11-C16-H16	119.0(11)
C24-H24B	1.00(2)	C15-C16-H16	120.5(11)
C25-C26	1.513(3)	O21-C21-C3	123.00(18)
C25-H25A	0.99(2)	O21-C21-C22	120.09(17)
C25-H25B	1.019(19)	C3-C21-C22	116.91(18)
C26-C27	1.511(3)	C23-C22-C21	177.7(2)
C26-H26A	1.00(2)	C22-C23-C24	177.8(2)
C26-H26B	1.03(2)	C23-C24-C25	112.53(17)
C27-H27A	1.00(3)	C23-C24-H24A	108.1(11)
C27-H27B	1.01(3)	C25-C24-H24A	110.6(11)
C27-H27C	1.03(3)	C23-C24-H24B	110.5(11)
C2-N1-C9	108.40(16)	C25-C24-H24B	109.6(11)
C2-N1-C10	125.72(18)	H24A-C24-H24B	105.3(15)
C9-N1-C10	125.61(17)	C26-C25-C24	112.80(17)
N1-C2-C3	110.84(18)	C26-C25-H25A	109.0(11)
N1-C2-H2	120.3(11)	C24-C25-H25A	109.7(11)
C3-C2-H2	128.8(11)	C26-C25-H25B	111.5(10)
C2-C3-C4	106.27(17)	C24-C25-H25B	108.0(10)
C2-C3-C21	126.41(18)	H25A-C25-H25B	105.5(15)
C4-C3-C21	127.32(18)	C27-C26-C25	112.5(2)
C5-C4-C9	119.00(18)	C27-C26-H26A	109.0(11)
C5-C4-C3	134.41(18)	C25-C26-H26A	110.0(12)
C9-C4-C3	106.57(17)	C27-C26-H26B	110.2(10)
C6-C5-C4	118.6(2)	C25-C26-H26B	108.9(10)

H26A-C26-H26B	106.1(15)
C26-C27-H27A	107.1(15)
C26-C27-H27B	108.6(15)
H27A-C27-H27B	112(2)
C26-C27-H27C	111.5(14)
H27A-C27-H27C	108(2)
H27B-C27-H27C	109(2)

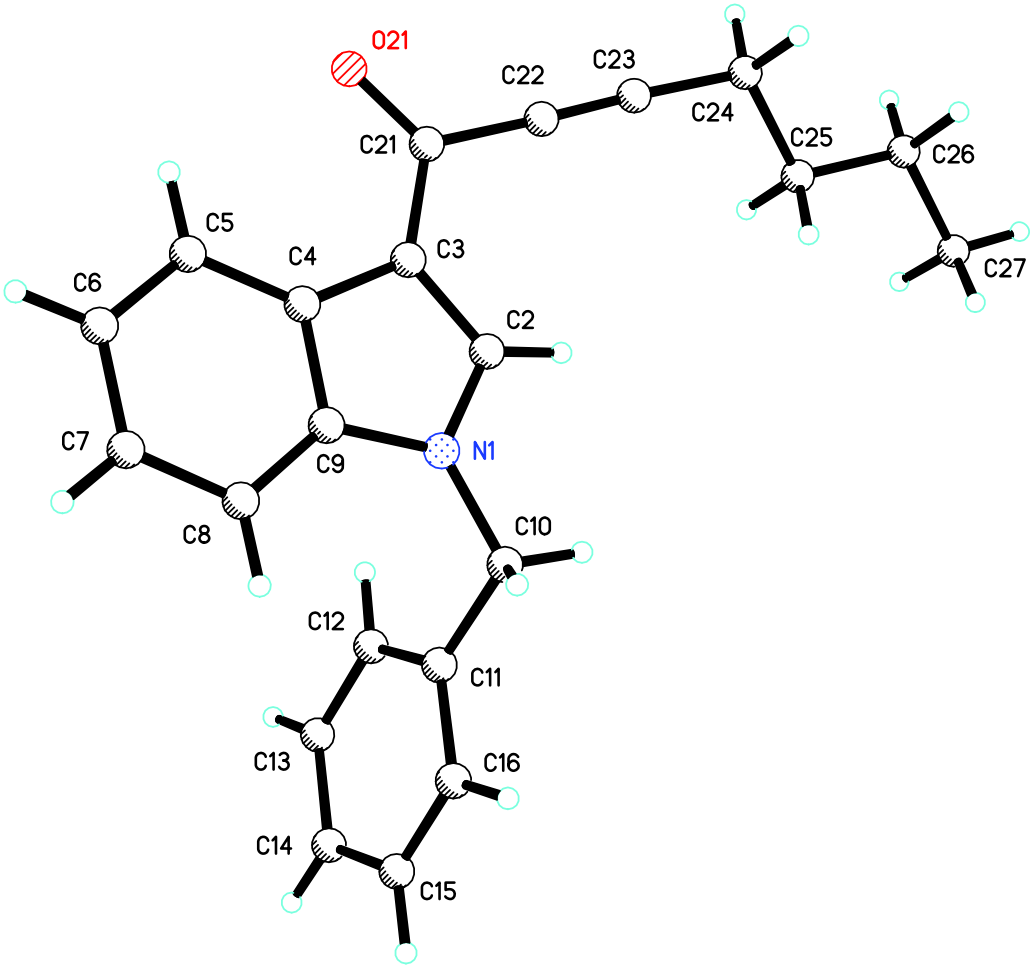


Figure 1. X-ray analysis of compound **3b**.

Table 8. Crystal data and structure refinement for 4-(1-Benzyl-1*H*-indol-3-yl)-6-butylpyrimid-2-yl-amine (**11b**).

Empirical formula	$C_{23}H_{24}N_4$
Formula weight	356.46
Temperature	200(2) K
Wavelength	0.71073 Å
Crystal system	triclinic
Space group	$P\bar{1}$
Z	2
Unit cell dimensions	a = 6.4203(3) Å α = 98.244(1) deg.
	b = 10.0329(4) Å β = 91.059(1) deg.
	c = 15.2326(7) Å γ = 90.533(1) deg.
Volume	970.82(7) $Å^3$
Density (calculated)	1.22 g/cm^3
Absorption coefficient	0.07 mm^{-1}
Crystal shape	polyhedron
Crystal size	0.50 x 0.14 x 0.10 mm^3
Crystal color	colorless
Theta range for data collection	2.0 to 27.5 deg.
Index ranges	$-8 \le h \le 8$, $-13 \le k \le 12$, $-19 \le l \le 19$
Reflections collected	9852
Independent reflections	4397 (R(int) = 0.0336)
Observed reflections	2913 ($I > 2\sigma(I)$)
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.99 and 0.96
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	4397 / 0 / 254
Goodness-of-fit on F^2	1.02
Final R indices ($I > 2\sigma(I)$)	R1 = 0.048, wR2 = 0.101
Largest diff. peak and hole	0.24 and -0.17 $eÅ^{-3}$

Table 9. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for **11b**. U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

Atom	x	y	z	U_{eq}
N1	-0.3081(2)	-0.2350(1)	0.8412(1)	0.0341(3)
C2	-0.2486(2)	-0.1462(2)	0.7865(1)	0.0329(4)
C3	-0.0675(2)	-0.1864(1)	0.7445(1)	0.0295(3)
C4	-0.0112(2)	-0.3119(1)	0.7751(1)	0.0296(3)
C5	-0.1645(2)	-0.3374(2)	0.8362(1)	0.0328(4)
C6	-0.1578(3)	-0.4490(2)	0.8811(1)	0.0424(4)
C7	0.0040(3)	-0.5373(2)	0.8620(1)	0.0490(5)
C8	0.1538(3)	-0.5163(2)	0.8000(1)	0.0449(4)
C9	0.1484(2)	-0.4050(2)	0.7561(1)	0.0356(4)
C10	-0.4924(2)	-0.2228(2)	0.8961(1)	0.0392(4)
C11	-0.4447(2)	-0.1956(1)	0.9946(1)	0.0326(4)
C12	-0.2609(3)	-0.1347(2)	1.0292(1)	0.0440(4)
C13	-0.2256(3)	-0.1109(2)	1.1202(1)	0.0525(5)
C14	-0.3728(3)	-0.1473(2)	1.1769(1)	0.0518(5)
C15	-0.5560(3)	-0.2079(2)	1.1433(1)	0.0508(5)
C16	-0.5917(3)	-0.2323(2)	1.0523(1)	0.0419(4)
C21	0.0471(2)	-0.1116(1)	0.6849(1)	0.0282(3)
N22	0.2312(2)	-0.1620(1)	0.6567(1)	0.0310(3)
C23	0.3358(2)	-0.0919(2)	0.6020(1)	0.0295(3)
N23	0.5194(2)	-0.1421(2)	0.5723(1)	0.0392(3)
H23A	0.562(3)	-0.2164(17)	0.5909(11)	0.046(5)
H23B	0.588(2)	-0.1084(17)	0.5289(11)	0.047(5)
N24	0.2754(2)	0.0241(1)	0.5748(1)	0.0301(3)
C25	0.0915(2)	0.0741(1)	0.6050(1)	0.0282(3)
C26	-0.0288(2)	0.0077(1)	0.6595(1)	0.0305(3)
C27	0.0324(2)	0.2057(1)	0.5752(1)	0.0324(3)
C28	-0.1637(2)	0.2725(2)	0.6128(1)	0.0345(4)
C29	-0.2092(3)	0.4028(2)	0.5766(1)	0.0410(4)
C30	-0.4012(3)	0.4728(2)	0.6171(1)	0.0571(5)

Table 10. Hydrogen coordinates and isotropic displacement parameters ($Å^2$) for **11b**.

Atom	x	y	z	U_{eq}
H2	-0.3224	-0.0671	0.7784	0.039
H6	-0.2603	-0.4636	0.9230	0.051
H7	0.0137	-0.6141	0.8917	0.059
H8	0.2618	-0.5800	0.7877	0.054
H9	0.2509	-0.3919	0.7139	0.043
H10A	-0.5756	-0.3071	0.8831	0.047
H10B	-0.5788	-0.1487	0.8795	0.047
H12	-0.1585	-0.1091	0.9904	0.053
H13	-0.0989	-0.0692	1.1434	0.063
H14	-0.3480	-0.1306	1.2392	0.062
H15	-0.6581	-0.2331	1.1824	0.061
H16	-0.7182	-0.2745	1.0293	0.050
H23A	0.562(3)	-0.2164(17)	0.5909(11)	0.046(5)
H23B	0.588(2)	-0.1084(17)	0.5289(11)	0.047(5)
H26	-0.1599	0.0421	0.6792	0.037
H27A	0.0168	0.1905	0.5098	0.039
H27B	0.1501	0.2699	0.5903	0.039
H28A	-0.1486	0.2918	0.6782	0.041
H28B	-0.2831	0.2095	0.5985	0.041
H29A	-0.2301	0.3830	0.5114	0.049
H29B	-0.0874	0.4643	0.5887	0.049
H30A	-0.5219	0.4117	0.6063	0.086
H30B	-0.4274	0.5541	0.5900	0.086
H30C	-0.3780	0.4977	0.6812	0.086

Table 11. Anisotropic displacement parameters ($Å^2$) for **11b**. The anisotropic displacement factor exponent takes the form: $-2\ pi^2\ (h^2\ a^{*2}\ U_{11} + ... + 2\ h\ k\ a^*\ b^*\ U_{12})$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
N1	0.0344(7)	0.0402(7)	0.0299(7)	0.0120(6)	0.0077(6)	0.0000(6)
C2	0.0361(8)	0.0352(8)	0.0294(8)	0.0115(7)	0.0046(7)	0.0009(7)
C3	0.0320(8)	0.0319(8)	0.0257(7)	0.0070(6)	0.0025(6)	-0.0012(6)
C4	0.0334(8)	0.0302(8)	0.0253(7)	0.0052(6)	-0.0001(6)	-0.0045(6)
C5	0.0385(9)	0.0334(8)	0.0275(8)	0.0074(6)	0.0016(7)	-0.0042(7)
C6	0.0522(10)	0.0394(9)	0.0386(9)	0.0154(7)	0.0081(8)	-0.0042(8)
C7	0.0637(12)	0.0364(9)	0.0509(11)	0.0195(8)	0.0031(9)	0.0009(9)
C8	0.0513(10)	0.0341(9)	0.0512(10)	0.0124(8)	0.0031(8)	0.0051(8)
C9	0.0385(9)	0.0334(8)	0.0352(8)	0.0053(7)	0.0031(7)	0.0006(7)
C10	0.0324(8)	0.0541(10)	0.0329(8)	0.0116(7)	0.0082(7)	-0.0041(7)
C11	0.0367(8)	0.0301(8)	0.0319(8)	0.0070(6)	0.0056(7)	0.0014(7)
C12	0.0431(10)	0.0446(10)	0.0441(10)	0.0049(8)	0.0054(8)	-0.0050(8)
C13	0.0549(11)	0.0501(11)	0.0481(11)	-0.0062(9)	-0.0073(9)	0.0005(9)
C14	0.0744(14)	0.0468(11)	0.0330(9)	0.0009(8)	-0.0004(9)	0.0122(10)
C15	0.0690(13)	0.0492(11)	0.0360(9)	0.0102(8)	0.0182(9)	0.0035(9)
C16	0.0442(10)	0.0464(10)	0.0364(9)	0.0091(7)	0.0106(8)	-0.0053(8)
C21	0.0287(8)	0.0326(8)	0.0240(7)	0.0062(6)	0.0002(6)	-0.0023(6)
N22	0.0299(7)	0.0352(7)	0.0299(6)	0.0106(5)	0.0043(5)	0.0010(5)
C23	0.0280(8)	0.0349(8)	0.0267(7)	0.0077(6)	0.0014(6)	-0.0006(6)
N23	0.0311(7)	0.0463(9)	0.0455(8)	0.0224(7)	0.0121(6)	0.0090(6)
N24	0.0292(7)	0.0342(7)	0.0285(6)	0.0097(5)	0.0043(5)	0.0003(5)
C25	0.0291(8)	0.0324(8)	0.0233(7)	0.0049(6)	-0.0001(6)	-0.0011(6)
C26	0.0291(8)	0.0347(8)	0.0288(8)	0.0074(6)	0.0056(6)	0.0023(6)
C27	0.0344(8)	0.0328(8)	0.0319(8)	0.0105(6)	0.0042(7)	-0.0009(7)
C28	0.0365(9)	0.0353(8)	0.0328(8)	0.0075(7)	0.0053(7)	0.0020(7)
C29	0.0435(9)	0.0352(9)	0.0456(10)	0.0100(7)	0.0022(8)	0.0043(7)
C30	0.0552(11)	0.0447(11)	0.0711(13)	0.0059(9)	0.0037(10)	0.0152(9)

Table 12. Bond lengths (Å) and angles (deg) for **11b**.

N1-C2	1.3613(17)	N23-C23-N22	116.78(13)
N1-C5	1.3818(19)	N24-C23-N22	126.36(13)
N1-C10	1.4572(18)	C23-N24-C25	116.55(11)
C2-C3	1.3735(19)	N24-C25-C26	121.20(13)
C3-C4	1.4499(19)	N24-C25-C27	114.94(12)
C3-C21	1.4621(19)	C26-C25-C27	123.86(13)
C4-C9	1.399(2)	C25-C26-C21	118.30(13)
C4-C5	1.4136(19)	C25-C27-C28	117.38(12)
C5-C6	1.393(2)	C27-C28-C29	112.51(12)
C6-C7	1.380(2)	C28-C29-C30	112.52(14)
C7-C8	1.396(2)		
C8-C9	1.382(2)		
C10-C11	1.512(2)		
C11-C16	1.383(2)		
C11-C12	1.384(2)		
C12-C13	1.386(2)		
C13-C14	1.374(2)		
C14-C15	1.375(3)		
C15-C16	1.388(2)		
C21-N22	1.3435(18)		
C21-C26	1.399(2)		
N22-C23	1.3487(17)		
C23-N23	1.3465(18)		
C23-N24	1.3480(18)		
N24-C25	1.3497(17)		
C25-C26	1.3796(18)		
C25-C27	1.5059(19)		
C27-C28	1.515(2)		
C28-C29	1.519(2)		
C29-C30	1.521(2)		
C2-N1-C5	108.69(12)		
C2-N1-C10	125.30(13)		
C5-N1-C10	126.01(12)		
N1-C2-C3	110.84(13)		
C2-C3-C4	106.06(12)		
C2-C3-C21	125.69(13)		
C4-C3-C21	128.18(13)		
C9-C4-C5	118.82(13)		
C9-C4-C3	134.78(13)		
C5-C4-C3	106.38(13)		
N1-C5-C6	129.51(14)		
N1-C5-C4	108.03(12)		
C6-C5-C4	122.46(15)		
C7-C6-C5	117.09(15)		
C6-C7-C8	121.50(15)		
C9-C8-C7	121.42(16)		
C8-C9-C4	118.66(14)		
N1-C10-C11	114.07(12)		
C16-C11-C12	118.90(14)		
C16-C11-C10	118.54(14)		
C12-C11-C10	122.56(13)		
C11-C12-C13	120.31(16)		
C14-C13-C12	120.37(17)		
C13-C14-C15	119.86(16)		
C14-C15-C16	119.93(16)		
C11-C16-C15	120.63(16)		
N22-C21-C26	121.40(12)		
N22-C21-C3	116.68(13)		
C26-C21-C3	121.91(13)		
C21-N22-C23	116.16(12)		
N23-C23-N24	116.86(13)		

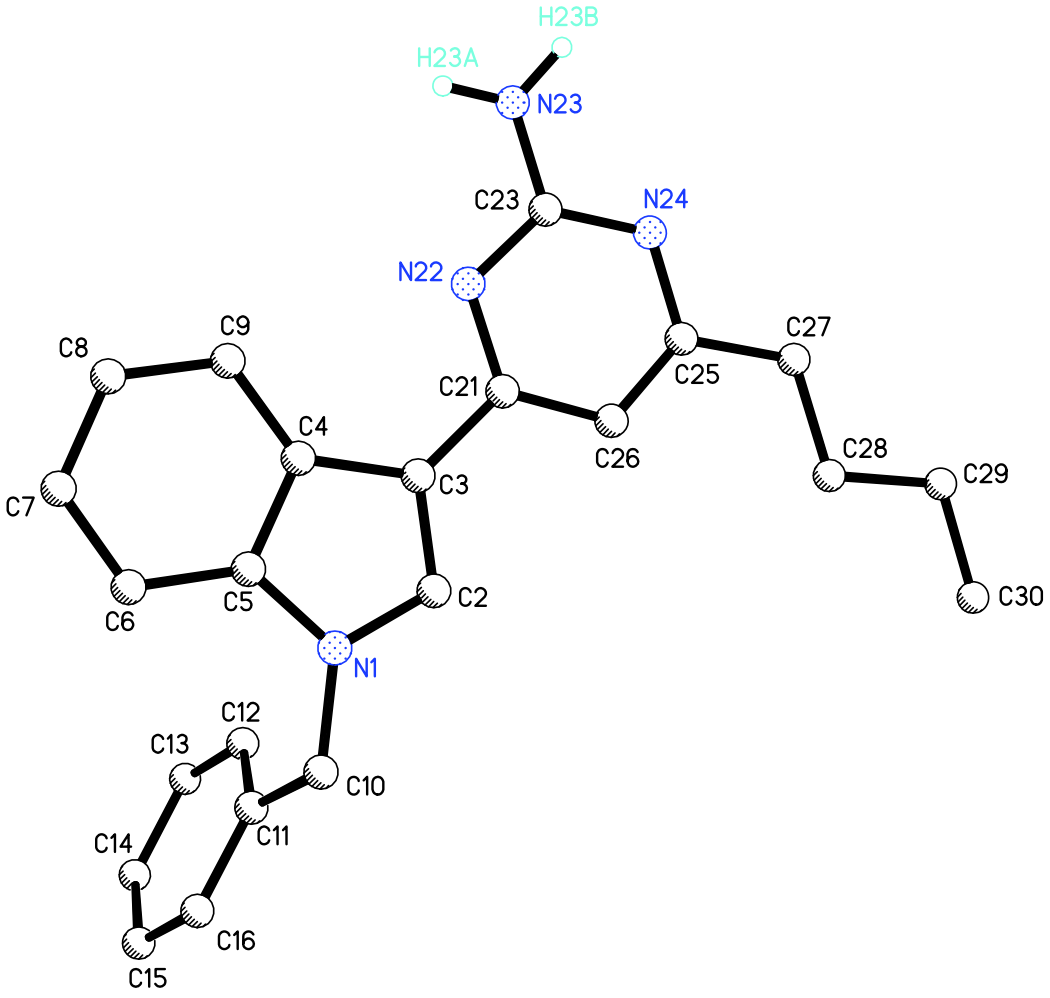


Figure 2. X-ray analysis of compound **11b**.

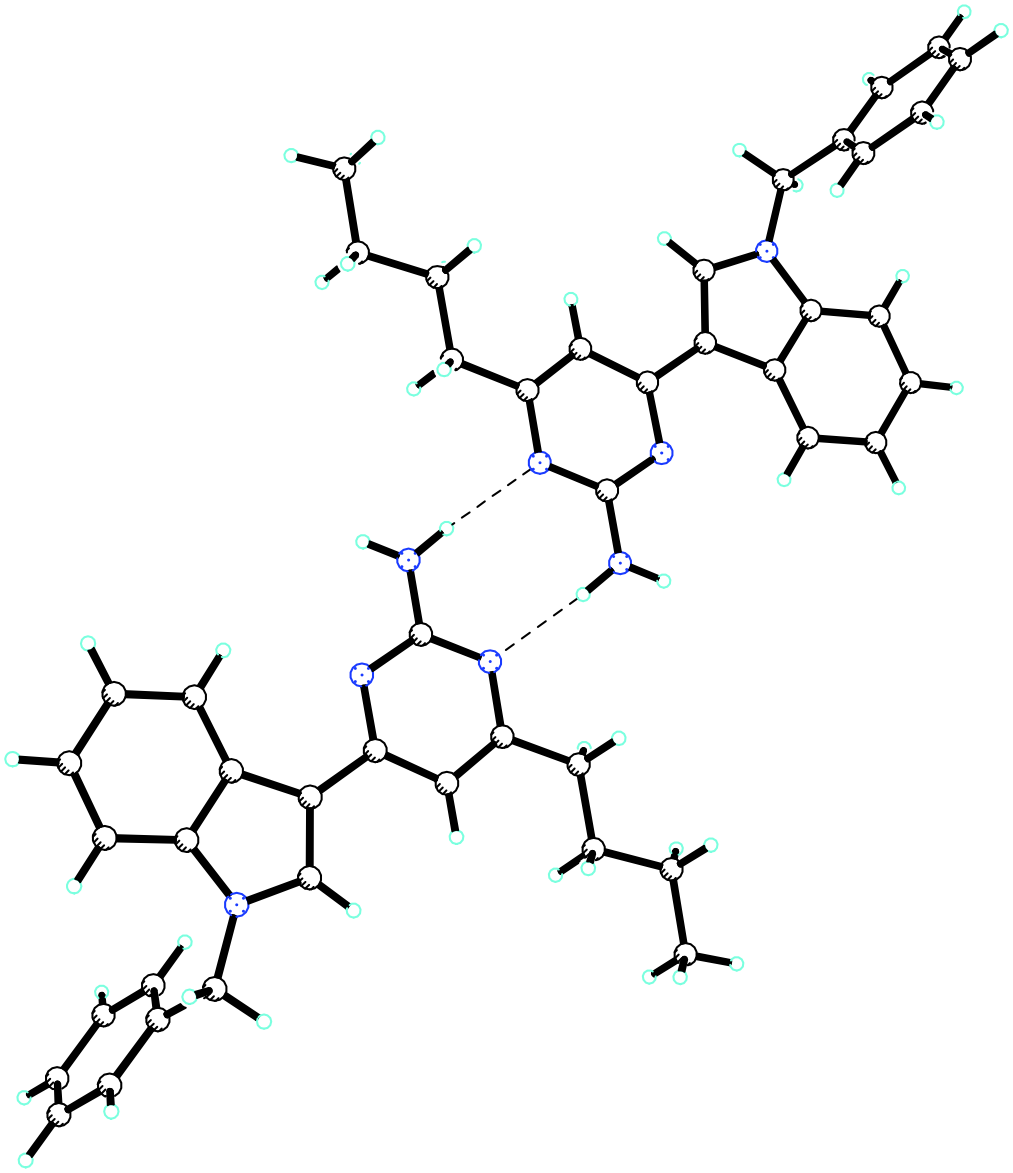


Figure 3. Intermolecular hydrogen bond formation in the crystal of **11b**.

References:

[1] C. A. Merlic, Y. You, D. M. McInnes, A. L. Zechmann, M. M. Miller, Q. Deng, *Tetrahedron* **2001**, *57*, 5199-5212.

[2] using *n*-BuLi: M. Amat, F. Seffar, N. Llor, J. Bosch, *Synthesis* **2001**, *2*, 267-275.

[3] using NaH: V. Vaillancourt, K. F. Albizati, *J. Am. Chem. Soc*. **1993**, *115*, 3499-3502.

[4] S. Battaglia, E. Boldrini, F. Da Settimo, G. Dondio, C. La Motta, A. M. Marini, G. Primofiore, *Eur. J. Med. Chem*. **1999**, *34*, 93-105.

[5] G. Simon, H. Couthon-Gourves, J.-P. Haelters, B. Corbel, N. Kervarec, F. Michaud, L. Meijer, *J. Heterocycl. Chem*. **2007**, *44*, 793-801.

“Three-component synthesis of *N*-Boc-4-iodopyrroles and sequential one-pot alkynylation”, Eugen Merkul, Christina Boersch, Walter Frank, Thomas J. J. Müller, *Org. Lett*. **2009**, *11*, 2269-2272. DOI: 10.1021/ol900581a.

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Three-Component Synthesis of *N*-Boc-4-iodopyrroles and Sequential One-Pot Alkynylation[||]

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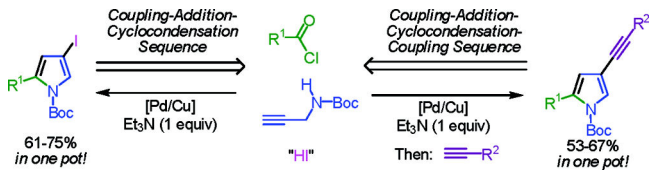
ABSTRACT



(Hetero)aryl-, alkenyl-, and selected alkyl-substituted acid chlorides can be efficiently coupled with *N*-Boc-protected propargylamine to produce ynones which are converted in a one-pot fashion to 2-substituted *N*-Boc-4-iodopyrroles. Upon addition of a further alkyne, another Sonogashira coupling can be carried out in a one-pot fashion. This sequentially Pd/Cu-catalyzed process represents a very mild and efficient entry to 2,4-disubstituted *N*-Boc-pyrroles.

Among five-membered heterocycles, pyrroles are the most prominent ones[1] since they constitute important classes of natural products,[2] synthetic pharmaceuticals,[3] and electrically conducting materials such as polypyrroles.[4] Therefore, the development of new pyrrole syntheses and synthetic strategies has remained an ongoing challenge.[5] In particular, multicomponent approaches have inevitably become increasingly important due to their elegance and practicability.[6] Furthermore, the quest for mild synthetic methods for compounds with unusual substitution patterns such as 2,4-disubstituted pyrroles has turned out to be nontrivial.[7] As part of our program to develop multicomponent syntheses of heterocycles initiated by transition-metal catalysis,[8] a strategy based upon alkynones via Sonogashira coupling[9] becomes apparent. Here, we communicate a concise, one-pot synthesis of Boc-protected 2-substituted 4-iodopyrroles and first examples of sequentially Pd/Cu-catalyzed subsequent alkynylations, also in a one-pot fashion.

In the past years, the Sonogashira coupling of acid chlorides with terminal alkynes using only 1 equiv of triethylamine has proven to be a very effective tool for the formation of ynones,[10] which can be further reacted with various nucleophiles in a one-pot fashion,[11] opening an entry to many consecutive multicomponent syntheses of hetero-

[||] Dedicated to Prof. Dr. Matthias W. Haenel on the occasion of his 65th birthday.

[†] Institut für Organische Chemie and Makromolekulare Chemie.

[‡] Institut für Anorganische Chemie and Strukturchemie.

[§] X-ray structure analysis.

(1) For some recent reviews, see: (a) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.-F. *Chem. Rev.* **2008**, *108*, 264. (b) Schmuck, C.; Rupprecht, D. *Synthesis* **2007**, 3095. (c) Walsh, C. T.; Garneau-Tsodikova, S.; Howard-Jones, A. R. *Nat. Prod. Rep.* **2006**, *23*, 517. (d) Banwell, M. G.; Goodwin, T. E.; Ng, S.; Smith, J. A.; Wong, D. J. *Eur. J. Org. Chem.* **2006**, 3043. (e) Fürstner, A. *Angew. Chem. Int. Ed.* **2003**, *42*, 3582. (f) Hoffmann, H.; Lindel, T. *Synthesis* **2003**, 1753.

(2) For excellent reviews, see, e.g.: (a) Gossauer, A. *Die Chemie der Pyrrole*; Springer Verlag: Berlin, 1974. (b) Gossauer, A. In *Houben-Weyl, Methoden der Organischen Chemie*; Kreher, R., Ed.; G. Thieme Verlag: Stuttgart, 1994; Bd. E6a, p 556. (c) Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1996; Vol. 2, p 119. (d) Fürstner, A. *Synlett* **1999**, 1523.

(3) Gribble, G. W. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1996; Vol. 2, p 207.

(4) For an interesting review, see, e.g.: MacDiarmid, A. G. *Synth. Met.* **1997**, *84*, 27.

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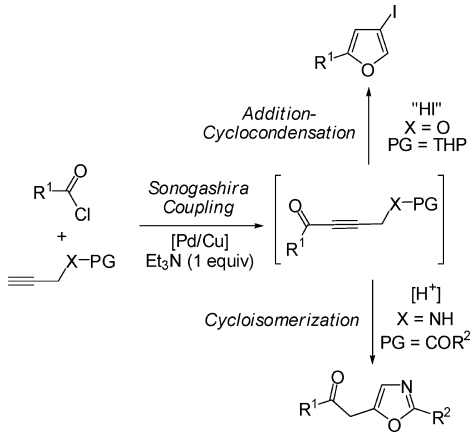
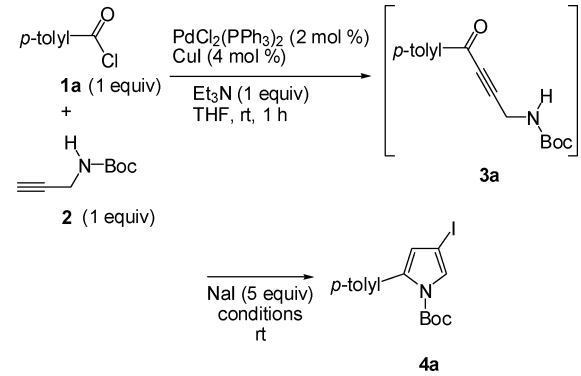
cycles.[8,9] Most interestingly, the subsequent additions to alkynones are restricted to not only Brønsted basic conditions but also Brønsted acid mediated transformations for the one-pot synthesis of halofurans,[12] and oxazoles[13] via the intermediacy of propargyl ketone derivatives can be easily realized as a consequence of the mild reaction conditions of the Sonogashira coupling (Scheme 1).

Scheme 1. Switching Conditions from Brønsted Basic to Brønsted Acidic Conditions Leading to Coupling−Addition−Cyclocondensation and Coupling−Cycloisomerization Sequences via Propargyl Ketone Derivatives



Halopyrroles[14,15] are valuable synthetic building blocks for synthetic transformations, and therefore, a multicomponent access would be highly desirable. For the three-component synthesis of the 4-iodopyrroles with a nitrogen protecting group, propargyl amides appear to be the most suitable starting materials. Since the cycloisomerization to an oxazole under acidic conditions could jeopardize this endeavor, the choice of the right nitrogen protecting group plays a key role. The Boc group is a versatile carbamate protecting group for the pyrrole nitrogen atom, useful for many transformations on the pyrrole core and easily removable. Therefore, upon reacting toluoyl chloride (**1a**) and *N*-Boc-protected propargylamine (**2**) under modified Sonogashira conditions, the intermediate alkynone **3a**[16] was obtained. Without isolation, the concluding addition−cyclocondensation furnishes the *N*-Boc-4-iodo-2-*p*-tolylpyrrole (**4a**) (Scheme 2). The final addition−cyclocondensation step

Scheme 2. Optimization of the One-Pot Coupling−Addition−Cyclocondensation Synthesis of 4-Iodopyrrole **4a**



was optimized for the sequence by variation of the amount of PTSA · H_2O, the added cosolvent, and the reaction time

(5) For some recent syntheses, see: (a) Kim, Y.; Kim, J.; Park, S. B. *Org. Lett.* **2009**, *11*, 17. (b) Lygin, A. V.; Larionov, O. V.; Korotkov, V. S.; de Meijere, A. *Chem.—Eur. J.* **2009**, *15*, 227. (c) Wang, Y.-F.; Toh, K. K.; Chiba, S.; Narasaka, K. *Org. Lett.* **2008**, *10*, 5019. (d) Cacchi, S.; Fabrizi, G.; Filisti, E. *Org. Lett.* **2008**, *10*, 2629. (e) Attanasi, O. A.; Favi, G.; Filippone, P.; Giorgi, G.; Mantellini, F.; Moscatelli, G.; Spinelli, D. *Org. Lett.* **2008**, *10*, 1983. (f) Chiba, S.; Wang, Y.-F.; Lapointe, G.; Narasaka, K. *Org. Lett.* **2008**, *10*, 313. (g) Zhang, Z.; Zhang, J.; Tan, J.; Wang, Z. *J. Org. Chem.* **2008**, *73*, 5180. (h) Yin, G.; Wang, Z.; Chen, A.; Gao, M.; Wu, A.; Pan, Y. *J. Org. Chem.* **2008**, *73*, 3377. (i) Bremner, W. S.; Organ, M. G. *J. Comb. Chem.* **2008**, *10*, 142. (j) Dong, H.; Shen, M.; Redford, J. E.; Stokes, B. J.; Pumphrey, A. L.; Driver, T. G. *Org. Lett.* **2007**, *9*, 5191. (k) Martín, R.; Larsen, C. H.; Cuenca, A.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 3379. (l) Istrate, F. M.; Gagosz, F. *Org. Lett.* **2007**, *9*, 3181. (m) Shindo, M.; Yoshimura, Y.; Hayashi, M.; Soejima, H.; Yoshikawa, T.; Matsumoto, K.; Shishido, K. *Org. Lett.* **2007**, *9*, 1963. (n) Reeves, J. T.; Song, J. J.; Tan, Z.; Lee, H.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2007**, *9*, 1875. (o) Peng, L.; Zhang, X.; Ma, J.; Zhong, Z.; Wang, J. *Org. Lett.* **2007**, *9*, 1445. (p) Rivero, M. R.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 973. (q) Su, S.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 7744. (r) Milgram, B. C.; Eskildsen, K.; Richter, S. M.; Scheidt, W. R.; Scheidt, K. A. *J. Org. Chem.* **2007**, *72*, 3941. (s) Misra, N. C.; Panda, K.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2007**, *72*, 1246. (t) Shi, D.; Dou, G.; Shi, C.; Li, Z.; Ji, S.-J. *Synthesis* **2007**, 3117. (u) Crawley, M. L.; Goljer, I.; Jenkins, D. J.; Mehlmann, J. F.; Nogle, L.; Dooley, R.; Mahaney, P. E. *Org. Lett.* **2006**, *8*, 5837. (v) Winkler, J. D.; Ragains, J. R. *Org. Lett.* **2006**, *8*, 4031. (w) Binder, J. T.; Kirsch, S. F. *Org. Lett.* **2006**, *8*, 2151. (x) Lu, L.; Chen, G.; Ma, S. *Org. Lett.* **2006**, *8*, 835. (y) Nad, S.; Roller, S.; Haag, R.; Breinbauer, R. *Org. Lett.* **2006**, *8*, 403. (z) Martín, R.; Rodríguez Rivero, M.; Buchwald, S. L. *Angew. Chem. Int. Ed* **2006**, *45*, 7079. (aa) Freifeld, I.; Shojaei, H.; Langer, P. *J. Org. Chem.* **2006**, *71*, 4965. (bb) Fuchibe, K.; Ono, D.; Akiyama, T. *Chem. Commun.* **2006**, 2271. (cc) Peschko, C.; Winklhofer, C.; Terpin, A.; Steglich, W. *Synthesis* **2006**, 3048. (dd) Spaggiari, A.; Vaccari, D.; Davoli, P.; Prati, F. *Synthesis* **2006**, 995. (ee) Magnus, N. A.; Staszak, M. A.; Udodong, U. E.; Wepsiec, J. P. *Org. Process Res. Dev.* **2006**, *10*, 899. (ff) Wurz, R. P.; Charette, A. B. *Org. Lett.* **2005**, *7*, 2313. (gg) Larionov, O. V.; de Meijere, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 5664. (hh) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260. (ii) Kamijo, S.; Kanazawa, C.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 9260. (jj) Bharadwaj, A. R.; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 2465. (kk) Minetto, G.; Raveglia, L. F.; Taddei, M. *Org. Lett.* **2004**, *6*, 389. (ll) Siriwardana, A. I.; Kathriarachchi, K. K. A. D. S.; Nakamura, I.; Gridnev, I. D.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 13898. (mm) Yu, M.; Pagenkopf, B. L. *Org. Lett.* **2003**, *5*, 5099. (nn) Gabriele, B.; Salerno, G.; Fazio, A. *J. Org. Chem.* **2003**, *68*, 7853. (oo) Bullington, J. L.; Wolff, R. R.; Jackson, P. F. *J. Org. Chem.* **2002**, *67*, 9439. (pp) Smith, N. D.; Huang, D.; Cosford, N. D. P. *Org. Lett.* **2002**, *4*, 3537. (qq) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074. (rr) Grigg, R.; Savic, V. *Chem. Commun.* **2000**, 873.

(6) For a recent highlight describing multicomponent strategies, see: Balme, G. *Angew. Chem. Int. Ed.* **2004**, *43*, 6238. For some recent multicomponent pyrrole syntheses, see: (a) Lu, Y.; Arndtsen, B. A. *Org. Lett.* **2009**, *11*, 1369. (b) Tejedor, D.; López-Tosco, S.; González-Platas, J.; García-Tellado, F. *Chem.—Eur. J.* **2009**, *15*, 838. (c) Yadav, J. S.; Reddy, B. V. S.; Srinivas, M.; Divyavani, C.; Basha, J.; Sarma, A. V. S. *J. Org. Chem.* **2008**, *73*, 3252. (d) Lu, Y.; Arndtsen, B. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 5430. (e) Khalili, B.; Jajarmi, P.; Eftekhari-Sis, B.; Hashemi, M. M. *J. Org. Chem.* **2008**, *73*, 2090. (f) Liu, X.-t.; Huang, L.; Zheng, F.-j.; Zhan, Z.-p. *Adv. Synth. Catal.* **2008**, *350*, 2778. (g) Galliford, C. V.; Scheidt, K. A. *J. Org. Chem.* **2007**, *72*, 1811. (h) Cyr, D. J. S.; Martin, N.; Arndtsen, B. A. *Org. Lett.* **2007**, *9*, 449. (i) Cyr, D. J. S.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2007**, *129*, 12366. (j) Cadierno, V.; Gimeno, J.; Nebra, N. *Chem.—Eur. J.* **2007**, *13*, 9973. (k) Tejedor, D.; González-Cruz, D.; García-Tellado, F.; Marrero-Tellado, J. J.; Rodríguez, M. L. *J. Am. Chem. Soc.* **2004**, *126*, 8390. (l) Dhawan, R.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2004**, *126*, 468. (m) Braun, R. U.; Müller, T. J. J. *Synthesis* **2004**, 2391. (n) Nishibayashi, Y.; Yoshikawa, M.; Inada, Y.; Milton, M. D.; Hidai, M.; Uemura, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 2681. (o) Braun, R. U.; Zeitler, K.; Müller, T. J. J. *Org. Lett.* **2001**, *3*, 3297.

Table 1. Optimization of the Final Addition−Cyclocondensation Step within the One-Pot Three-Component Synthesis of 4-Iodopyrrole **4a**

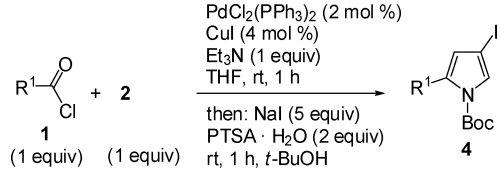
entry	PTSA · H_2O (equiv)	added cosolvent	reaction time (h)	4-iodopyrrole **4a** (isolated yield, %)
1	1.0	MeOH	22[a]	60
2	1.0	*t*-BuOH	19[a]	65
3	2.0	*t*-BuOH	19	70
4	2.0	*t*-BuOH	1	69

[a] After 1 h the reaction was not complete according to TLC monitoring.

(Table 1). The best conditions smoothly provided the desired product **4a** in 69% isolated yield within 1 h upon applying 2 equiv of PTSA·H_2O and *t*-BuOH as the alcoholic additive (entry 4). Interestingly, the yields of **4a** were higher than that of the isolated intermediate ynone **3a**.[16]

With this mild, quick and practical protocol in hand we set out to screen the scope of this reaction (Scheme 3, Table

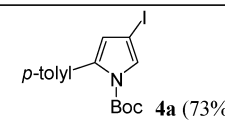
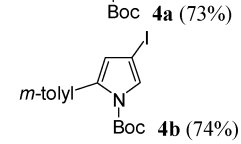
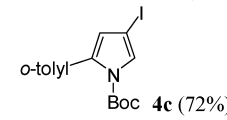
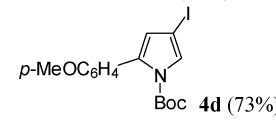
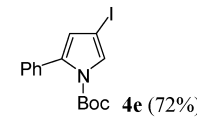
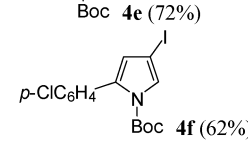
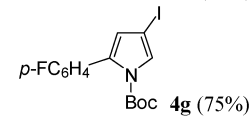
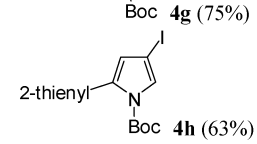
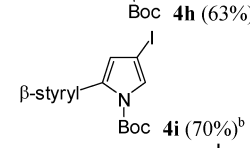
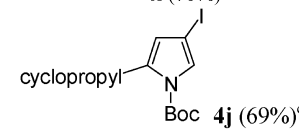
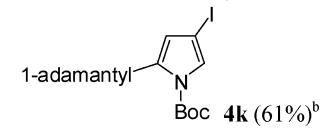
Scheme 3. One-Pot Three-Component Synthesis of 4-Iodopyrroles **4**



2). Upon upscaling to a 5 mmol level, an even higher yield of the 4-iodopyrrole **4a** can be obtained (Table 2, entry 1 vs Table 1, entry 4). Further upscaling to 30 mmol furnished compound **4d** in 77% isolated yield (73% yield on the 5 mmol scale, Table 2, entry 4). The structures of the 4-iodopyrroles **4** were unambiguously assigned by spectroscopic characterization and combustion analysis and later corroborated by an X-ray crystal structure analysis for compound **4d** (Figure 1).[17]

The sequence starts with easily accessible starting materials and gives good yields of 4-iodopyrroles **4**, and it is easy to perform with a simple catalyst system and under mild conditions.[18] It was found to be quite general with respect to the underlying acid chlorides **1**. Aromatic substituents bearing electroneutral (entry 5), electron-withdrawing (entries 6 and 7), and electron-donating (entries 1−4) substituents even in the *ortho*-position (entry 3) are tolerated. Furthermore, heteroaryl (entry 8), alkenyl (entry 9), cyclopropyl (entry 10), and sterically demanding adamantyl (entry 11) substituents can be effectively carried through the sequence.

Table 2. One-Pot Three-Component Synthesis of 4-Iodopyrroles **4**

entry	acid chloride **1**	4-iodo pyrrole **4** (isolated yield %)[a]
1	R^1 = *p*-MeC_6H_4 (**1a**)	 **4a** (73%)
2	R^1 = *m*-MeC_6H_4 (**1b**)	 **4b** (74%)
3	R^1 = *o*-MeC_6H_4 (**1c**)	 **4c** (72%)
4	R^1 = *p*-$MeOC_6H_4$ (**1d**)	 **4d** (73%)
5	R^1 = Ph (**1e**)	 **4e** (72%)
6	R^1 = *p*-ClC_6H_4 (**1f**)	 **4f** (62%)
7	R^1 = *p*-FC_6H_4 (**1g**)	 **4g** (75%)
8	R^1 = 2-thienyl (**1h**)	 **4h** (63%)
9	R^1 = β-styryl (**1i**)	 **4i** (70%)[b]
10	R^1 = cyclopropyl (**1j**)	 **4j** (69%)[c]
11	R^1 = 1-adamantyl (**1k**)	 **4k** (61%)[b]

[a] All reactions were performed on 5 mmol scale. [b] The reaction time for the coupling step was 21 h. [c] The reaction time for the coupling step was 3 h.

However, for nonaromatic acid chlorides, the reaction times of coupling were slightly longer than 1 h.

(7) (a) Kiren, S.; Hong, X.; Leverett, C. A.; Padwa, A. *Org. Lett.* **2009**, *11*, 1233. (b) Zanatta, N.; Schneider, J. M. F. M.; Schneider, P. H.; Wouters, A. D.; Bonacorso, H. G.; Martins, M. A. P.; Wessjohann, L. A. *J. Org. Chem.* **2006**, *71*, 6996. (c) Rosenmund, P.; Grübel, K. *Angew. Chem.* **1968**, *80*, 702.

(8) D'Souza, D. M.; Müller, T. J. J. *Chem. Soc. Rev.* **2007**, *36*, 1095.

(9) (a) Willy, B.; Müller, T. J. J. *ARKIVOC* **2008**, *1*, 195. (b) Müller, T. J. J. *Chim. Oggi/Chem. Today* **2007**, *25*, 70. (c) Müller, T. J. J. *Targets Heterocycl. Systems* **2006**, *10*, 54.

(10) (a) Karpov, A. S.; Müller, T. J. J. *Org. Lett.* **2003**, *5*, 3451. (b) D'Souza, D. M.; Müller, T. J. J. *Nat. Protoc.* **2008**, *3*, 1660.

(11) (a) Karpov, A. S.; Oeser, T.; Müller, T. J. J. *Chem. Commun.* **2004**, 1502. (b) Karpov, A. S.; Müller, T. J. J. *Synthesis* **2003**, 2815.

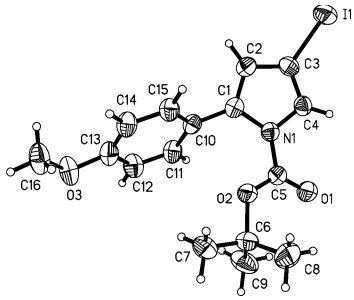
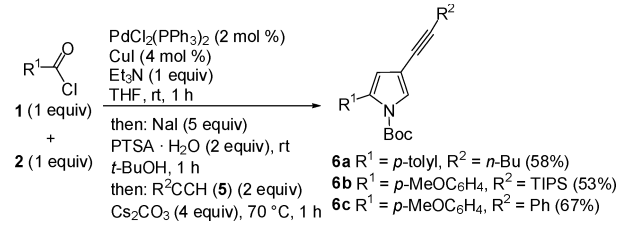


Figure 1. ORTEP plot of compound **4d**.

The obtained 4-iodopyrroles **4** are highly useful synthetic building blocks,[19] and the first scouting experiments were performed in the sense of a sequentially Pd/Cu-catalyzed reaction[20] since the catalyst system should be still operative after the coupling−addition−cyclocondensation sequence. Therefore, just upon addition of another terminal alkyne **5** to the reaction mixture, *N*-Boc-2-aryl-4-alkynylpyrroles **6** were obtained in good yields (Scheme 4). The conditions are sufficiently mild to leave the Boc group uncleaved. In comparison to the coupling−addition−cyclocondensation−coupling one-pot synthesis (58% yield), the two-step synthesis of the alkynyl pyrrole **6a** furnishes a comparable overall yield (61%).

Scheme 4. Coupling−Addition−Cyclocondensation−Coupling Sequence to 4-Alkynyl-*N*-Boc-pyrroles **6**



In conclusion, we disclose an efficient one-pot three-component synthesis of 2-substituted *N*-Boc-4-iodopyrroles that can easily be upscaled to multigrams, and we also show preliminary examples of a coupling−addition−cyclocondensation−coupling sequence to 4-alkynyl-*N*-Boc-pyrroles in good yields. This latter principle appears to be quite general and further terminating cross-coupling reactions can be easily envisioned. Studies taking advantage of this versatile one-pot multicomponent strategy to iodopyrroles as valuable building blocks for the synthesis of 2,4-disubstituted pyrrole derivatives are currently underway.

Acknowledgment. The financial support of this work by Merck Serono, Darmstadt, and the Fonds der Chemischen Industrie is gratefully acknowledged.

Supporting Information Available: Experimental procedures and characterization of compounds **3a**, **3b**, **4**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL900581A

(12) (a) Karpov, A. S.; Merkul, E.; Oeser, T.; Müller, T. J. J. *Eur. J. Org. Chem.* **2006**, 2991. (b) Karpov, A. S.; Merkul, E.; Oeser, T.; Müller, T. J. J. *Chem. Commun.* **2005**, 2581.

(13) (a) Merkul, E.; Grotkopp, O.; Müller, T. J. J. *Synthesis* **2009**, 502. (b) Merkul, E.; Müller, T. J. J. *Chem. Commun.* **2006**, 4817.

(14) For noncatalytic accesses to halopyrroles from ynones, see: (a) Ghosez, L.; Franc, C.; Denonne, F.; Cuisinier, C.; Touillaux, R. *Can. J. Chem.* **2001**, *79*, 1827. (b) Franc, C.; Denonne, F.; Cuisinier, C.; Ghosez, L. *Tetrahedron Lett.* **1999**, *40*, 4555. (c) Masquelin, T.; Obrecht, D. *Synthesis* **1995**, 276.

(15) For coupling reactions with iodopyrroles, see: Liu, J.-H.; Chan, H.-W.; Wong, H. N. C. *J. Org. Chem.* **2000**, *65*, 3274.

(16) The alkynone **3a** can be isolated and was obtained in 59% yield.

(17) Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 723307 (**4d**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk).

(18) **Typical procedure (4d).** $PdCl_2(PPh_3)_2$ (70 mg, 0.10 mmol) and CuI (39 mg, 0.20 mmol) were placed under argon in a flame-dried screw-cap vessel. Then 25 mL of dry THF was added, and the mixture was degassed with argon. Dry triethylamine (0.69 mL, 5.00 mmol), 4-methoxybenzoyl chloride (**1d**) (879 mg, 5.00 mmol), and *tert*-butyl prop-2-ynylcarbamate (**2**) (776 mg, 5.00 mmol) were successively added to the mixture which was then stirred at room temperature for 1 h. Then, sodium iodide (3.79 g, 25.0 mmol), toluene-4-sulfonic acid monohydrate (1.94 g, 10.0 mmol), and 5 mL of *tert*-butyl alcohol were successively added to the mixture, which was stirred at room temperature for 1 h. The reaction mixture was diluted with 50 mL of brine, the phases were separated, and the aqueous phase was extracted with dichloromethane (3 × 25 mL). The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuo, the residue was absorbed onto Celite and chromatographed on silica gel with petroleum ether (boiling range 40−60 °C)/ethyl acetate (PE−EE = 100:1) to give 1.46 g (73%) of analytically pure *tert*-butyl 4-iodo-2-(4-methoxyphenyl)-1*H*-pyrrole-1-carboxylate (**4d**) as a colorless solid: mp 71−72 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.39 (s, 9 H), 3.82 (s, 3 H), 6.20 (d, J = 1.9 Hz, 1 H), 6.88 (d, J = 8.8 Hz, 2 H), 7.24 (d, J = 8.8 Hz, 2 H), 7.39 (d, J = 1.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.6 (CH_3), 55.3 (CH_3), 64.4 (C_{quat}), 84.2 (C_{quat}), 113.1 (CH), 120.3 (CH), 125.3 (C_{quat}), 126.7 (CH), 130.4 (CH), 136.5 (C_{quat}), 147.9 (C_{quat}), 159.3 (C_{quat}); EI + MS (/z) 399 (M^+, 3), 343 ($(M - C_4H_8)^+$, 11), 299 ($(M - C_5H_8O_2)^+$, 16), 298 ($(M - C_5H_9O_2)^+$, 13), 171 ($(M - C_5H_9O_2I)^+$, 6), 156 (12), 128 (11), 57 ($C_4H_9^+$, 100), 41 (34); IR (KBr) $\tilde{\nu}$ 1734 cm^{-1}, 1511, 1370, 1337, 1293, 1251, 1180, 1151, 1032, 847, 808. Anal. Calcd for $C_{16}H_{18}INO_3$ (399.2): C, 48.14; H, 4.54; N, 3.51. Found: C, 48.36; H, 4.37; N, 3.34.

(19) Boc as an electron-withdrawing group allows the 4-iodopyrroles **4**, which are notoriously unstable with electron-donating groups at the pyrrole nitrogen, to be handled. They are storable for months in refrigerator under argon without decomposition.

(20) (a) For a review, see e.g.: Müller, T. J. J. *Top. Organomet. Chem.* **2006**, *19*, 149. (b) For recent examples, see e.g.: Liao, W.-W.; Müller, T. J. J. *Synlett* **2006**, 3469. (c) See also ref 12b.

Three-Component Synthesis of *N*-Boc 4-Iodo Pyrroles and Sequential One-Pot Alkynylation

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Supporting Information

1. General Considerations

All cross coupling reactions were carried out in oven-dried Schlenk glassware using septa and syringes under nitrogen or argon atmosphere. THF was dried using *MBraun* system MB-SPS-800, and triethylamine was refluxed under argon over ketyl sodium, distilled and stored in a Schlenk flask over potassium hydroxide pellets under argon atmosphere. Dry methanol was purchased by *Sigma-Aldrich Chemie GmbH*.

tert-Butyl prop-2-ynylcarbamate (**2**) was prepared according to literature procedure[1] but is also commercially available by *Synthonix*. Commercial grade reagents were used as supplied without further purification and were purchased from *Acros Organics*, *Sigma-Aldrich Chemie GmbH*, *Fluka AG*, *ABCR GmBH & Co. KG, Alfa Aesar GmbH & Co. KG*, *Riedel-de Haën,* and *Merck Serono KGaA*.

The purification of products was performed on silica gel 60 (0.015-0.040 mm) from *Merck Serono KGaA* Darmstadt using flash technique and under pressure of 2 bar. The crude mixtures were adsorbed on Celite 545 (0.02-0.10 mm) from *Merck Serono KGaA* Darmstadt before chromatographic purification.

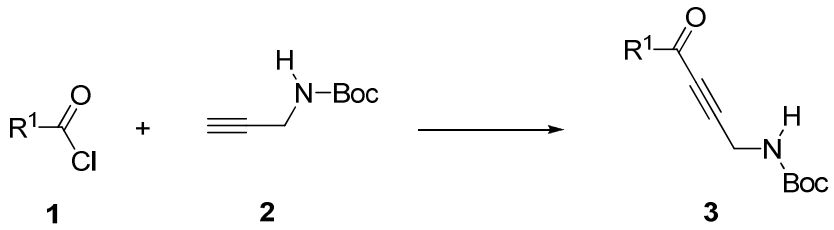
The reaction progress was monitored qualitatively using TLC Silica gel 60 F_{254} 5 x 7.5 cm aluminium sheets obtained by *Merck Serono KGaA* Darmstadt. The spots were detected with UV light at 254 nm and using aqueous potassium permanganate solution.

^{1}H, ^{13}C, and 135-DEPT NMR spectra were recorded on Bruker DRX 500 spectrometer. TMS was used as reference ($\delta = 0.0$) or the resonance of the solvent was locked as internal standard ($CDCl_3$: ^{1}H δ 7.24, ^{13}C δ 77.2). The multiplicities of signals were abbreviated as follows: s: singulett; d: dublett; t: triplett; dd: dublett of dubletts, m: multiplett and br: broad signal. The type of carbon atoms was determined on the basis of 135-DEPT NMR spectra. EI mass spectra were measured on Finnigan MAT 8200 spectrometer. IR spectra were obtained on Bruker Vector 22 FT-IR. The solids were measured as KBr pellets and oils as films on KBr plates. The intensity of signals is abbreviated as follows: s (strong), m (medium) and w (weak). The melting points (uncorrected) were measured on Reichert-Jung Thermovar. Combustion analyses were carried out on Perkin Elmer Series II Analyser 2400 in the microanalytical laboratory of Institut für Pharmazeutische und Medizinische Chemie der Heinrich-Heine-Universität Düsseldorf.

X-ray structure was measured on Stoe IPDS.

2. Synthesis of Ynones 3 by Modified *Sonogashira* Coupling

2.1. General Procedure



1 **2** **3**

$PdCl_2(PPh_3)_2$ (28 mg, 0.04 mmol) and CuI (16 mg, 0.08 mmol) were placed under argon in a screw-cap vessel, which was then dried with a heat gun and cooled to the room temperature. Then, 10 mL of dry THF were added and the mixture was degassed with argon. Dry triethylamine (0.28 mL, 2.00 mmol), 2.00 mmol of the acid chloride **1** and *tert*-butyl prop-2-ynylcarbamate (**2**) (310 mg, 2.00 mmol) were successively added to the mixture which was stirred at room temperature for 1 h (monitored by TLC). The reaction mixture was diluted with 50 mL brine, the phases were separated and the aqueous phase was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuo the residue was absorbed onto celite and chromatographed on silica gel with petrolether (boiling range 40-60 °C)/ethyl acetate (PE-EE) to give the ynones **3**.

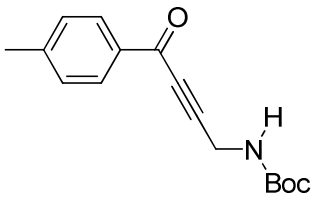
The experimental details are depicted in Table 1.

Table 1. Experimental details of the synthesis of ynones **3** by modified *Sonogashira* coupling.

Entry	Acid chloride **1**	Ynone **3** (isolated yield %)	Chromatographic purification R_f (eluent)
1	316 mg (2.00 mmol) **1a**	295 mg (1.08 mmol, 54 %) **3a**	PE-EE = 7:1 R_f (PE-EE = 7:1) : 0.16
2	352 mg (2.00 mmol) **1d**	343 mg (1.19 mmol, 59 %) **3b**	PE-EE = 5:1 → 4:1 → 3:1 R_f (PE-EE = 3:1) : 0.41

2.2. Spectroscopic and Analytical Data of Compounds 3a and 3b

2.2.1. tert-Butyl 4-oxo-4-*p*-tolylbut-2-ynylcarbamate (3a)

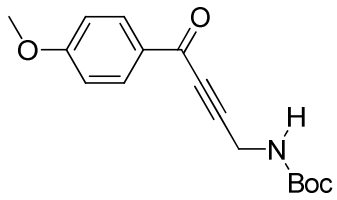


$C_{16}H_{19}NO_3$

273.33

According to the general procedure 295 mg (54 % yield) were obtained as a beige solid. Mp 70-71 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.48 (s, 9 H), 2.43 (s, 3 H), 4.22 (d, J = 4.1 Hz, 2 H), 5.0 (br, 1 H), 7.27 (d, J = 7.9 Hz, 2 H), 8.01 (d, J = 8.2 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.8 (CH_3), 28.3 (CH_3), 30.8 (CH_2), 80.5 (C_{quat}), 81.0 (C_{quat}), 90.1 (C_{quat}), 129.3 (CH), 129.8 (CH), 134.1 (C_{quat}), 145.5 (C_{quat}), 155.2 (C_{quat}), 177.4 (C_{quat}). EI + MS (*m/z* (%)): 273 (M^+, 0.2), 258 ($(M-CH_3)^+$, 0.7), 217 ($(M-C_4H_9+H)^+$, 13), 200 ($(M-C_4H_9O)^+$, 7), 173 ($(M-C_5H_9O_2+H)^+$, 4), 161 (9), 144 (15), 129 (17), 119 ($C_8H_7O^+$, 28), 115 (11), 91 ($C_7H_7^+$, 27), 65 ($C_5H_5^+$, 12), 59 (19), 57 ($C_4H_9^+$, 100), 41 (38), 39 ($C_3H_3^+$, 13). IR (KBr): $\tilde{\nu}$ 3377 (s) cm^{-1}, 2986 (w), 2968 (m), 2934 (w), 2227 (m), 2187 (w), 1689 (s), 1647 (s), 1607 (s), 1574 (m), 1519 (s), 1461 (w), 1449 (w), 1425 (w), 1394 (w), 1365 (m), 1293 (s), 1266 (s), 1213 (w), 1179 (s), 1115 (w), 1099 (m), 1047 (w), 1020 (w), 926 (m), 896 (m), 866 (m), 837 (m), 790 (w), 768 (w), 740 (m), 680 (m), 594 (m), 505 (w). Anal. calcd for $C_{16}H_{19}NO_3$ (273.3): C 70.31, H 7.01, N 5.12. Found: C 70.10, H 7.21, N 5.13.

2.2.2. tert-Butyl 4-(4-methoxyphenyl)-4-oxobut-2-ynylcarbamate (3b)



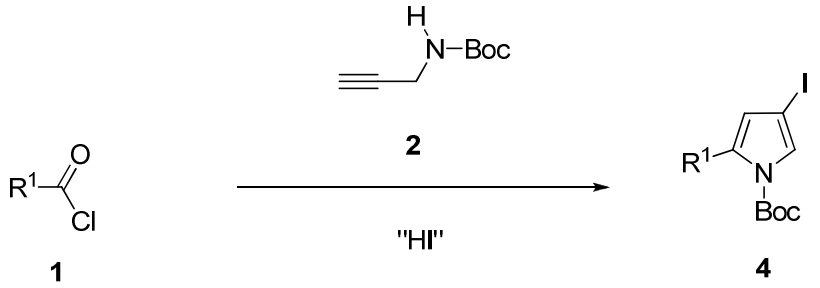
$C_{16}H_{19}NO_4$

289.33

According to the general procedure 343 mg (59 % yield) were obtained as a beige solid. Mp 106-107 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.48 (s, 9 H), 3.89 (s, 3 H), 4.21 (d, J = 4.1 Hz, 2 H), 4.9 (br, 1 H), 6.94 (d, J = 8.8 Hz, 2 H), 8.09 (d, J = 8.8 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.3 (CH_3), 30.8 (CH_2), 55.6 (CH_3), 80.5 (C_{quat}), 81.0 (C_{quat}), 89.8 (C_{quat}), 113.9 (CH), 129.8 (C_{quat}), 132.1 (CH), 155.3 (C_{quat}), 164.6 (C_{quat}), 176.3 (C_{quat}). EI + MS (*m/z* (%)): 289 (M^+, 0.7), 233 ($(M-C_4H_9+H)^+$, 32), 216 ($(M-C_4H_9O)^+$, 9), 189 ($(M-C_5H_9O_2+H)^+$, 5), 177 (10), 160 ($C_{10}H_8O_2^+$, 23), 145 (20), 135 ($C_8H_7O_2^+$, 38), 107 ($C_7H_7O^+$, 5), 92 ($C_7H_8^+$, 13), 77 ($C_6H_5^+$, 14), 59 (15), 57 ($C_4H_9^+$, 100), 41 (42), 39 ($C_3H_3^+$, 10). IR (KBr): $\tilde{\nu}$ 3330 (s) cm^{-1}, 3020 (w), 2978 (m), 2935 (w), 2843 (w), 2232 (m), 2183 (w), 1687 (s), 1631 (s), 1598 (s), 1572 (s), 1528 (s), 1456 (w), 1428 (m), 1392 (w), 1368 (w), 1355 (w), 1257 (s), 1169 (s), 1120 (w), 1098 (m), 1053 (w), 1023 (m), 938 (w), 905 (w), 853 (m), 786 (w), 762 (w), 737 (w), 689 (w), 653 (w), 653 (w), 627 (w), 599 (w), 517 (w). Anal. calcd for $C_{16}H_{19}NO_4$ (289.3): C 66.42, H 6.62, N 4.84. Found: C 66.33, H 6.68, N 4.80.

3. Three-Component Synthesis of Pyrroles 4 by Coupling-Addition-Cyclocondensation Sequence

3.1. General Procedure



$PdCl_2(PPh_3)_2$ (70 mg, 0.10 mmol) and CuI (39 mg, 0.20 mmol) were placed under argon in a screw-cap vessel, which was then dried with a heat gun and cooled to the room temperature. Then, 25 mL of dry THF were added and the mixture was degassed with argon. Dry triethylamine (0.69 mL, 5.00 mmol), 5.00 mmol of the acid chloride **1** and *tert*-butyl prop-2-ynylcarbamate (**2**) (776 mg, 5.00 mmol) were successively added to the mixture which was stirred at room temperature until the conversion was complete (monitored by TLC). Then, sodium iodide (3.79 g, 25.0 mmol), toluene-4-sulfonic acid monohydrate (1.94 g, 10.0 mmol) and 5 ml of *tert*-butanol were successively added to the mixture which was stirred at room temperature for 1 h (monitored by TLC). The reaction mixture was diluted with 50 mL brine, the phases were separated and the aqueous phase was extracted with dichloromethane (3 x 25 mL). The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuo the residue was absorbed onto celite and chromatographed on silica gel with petrolether (boiling range 40-60 °C)/ethyl acetate (PE-EE) to give the pyrroles **4**.

The experimental details are depicted in Table 2.

Table 2. Experimental details of the synthesis of pyrroles **4** by coupling-addition-cyclocondensation sequence.

Entry	Acid chloride **1**	Reaction time (1st step)	Pyrrole **4** (isolated yield)	Chromatographic purification R_f (eluent)
1	789 mg (5.00 mmol) **1a**	1 h	1.40 g (3.65 mmol, 73 %) **4a**	PE/EE = 100:1 R_f (PE/EE = 100:1) = 0.34
2	789 mg (5.00 mmol) **1b**	1 h	1.42 g (3.70 mmol, 74 %) **4b**	PE/EE = 100:1 R_f (PE/EE = 100:1) = 0.27
3	773 mg (5.00 mmol) **1c**	1 h	1.38 g (3.60 mmol, 72 %) **4c**	PE/EE = 100:1 R_f (PE/EE = 100:1) = 0.22
4	879 mg (5.00 mmol) **1d**	1 h	1.46 g (3.66 mmol, 73 %)[1] **4d**	PE/EE = 100:1 R_f (PE/EE = 100:1) = 0.31
5	710 mg (5.00 mmol) **1e**	1 h	1.32 g (3.58 mmol, 72 %) **4e**	PE/EE = 100:1 R_f (PE/EE = 100:1) = 0.23
6	875 mg (5.00 mmol) **1f**	1 h	1.24 g (3.08 mmol, 62 %) **4f**	PE/EE = 100:1 R_f (PE/EE = 100:1) = 0.32
7	793 mg (5.00 mmol) **1g**	1 h	1.49 g (3.84 mmol, 75 %) **4g**	PE/EE = 100:1 R_f (PE/EE = 100:1) = 0.22

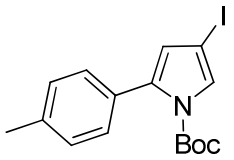
1. When the reaction was performed on 30 mmol scale, 9.23 g (23.1 mmol, 77 % yield) of the pyrrole **4e** could be isolated.

Continuation of Table 2.

Entry	Acid chloride **1**	Reaction time (1st step)	Pyrrole **4** (isolated yield)	Chromatographic purification R_f (eluent)
8	733 mg (5.00 mmol) **1h**	1 h	1.19 g (3.17 mmol, 63 %) **4h**	PE/EE = 100:1 R_f (PE/EE = 100:1) = 0.31
9	859 mg (5.00 mmol) **1i**	21 h	1.38 g (3.48 mmol, 70 %) **4i**	PE/EE = 100:1 R_f (PE/EE = 100:1) = 0.21
10	533 mg (5.00 mmol) **1j**	3 h	1.15 g (3.46 mmol, 69 %) **4j**	PE/EE = 100:1 R_f (PE/EE = 100:1) = 0.35
11	1.02 g (5.00 mmol) **1k**	21 h	1.31 g (3.07 mmol, 61 %) **4k**	PE R_f (PE) = 0.27

3.2. Spectroscopic and Analytical Data of Compounds 4a-k

3.2.1. tert-Butyl 4-iodo-2-*p*-tolyl-1*H*-pyrrole-1-carboxylate (4a)

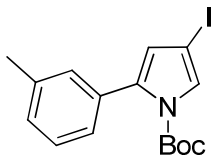


$C_{16}H_{18}INO_2$

383.22

According to the general procedure 1.40 g (73 % yield) were obtained as a colorless solid. Mp 57 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.38 (s, 9 H), 2.37 (s, 3 H), 6.21 (d, J = 1.9 Hz, 1 H), 7.15 (d, J = 7.9 Hz, 2 H), 7.20 (d, J = 8.2 Hz, 2 H), 7.40 (d, J = 1.9 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.3 (CH_3), 27.6 (CH_3), 64.4 (C_{quat}), 84.2 (C_{quat}), 120.4 (CH), 126.8 (CH), 128.4 (CH), 129.0 (CH), 129.9 (C_{quat}), 136.8 (C_{quat}), 137.5 (C_{quat}), 147.9 (C_{quat}). EI + MS (*m/z* (%)): 383 (M^+, 16), 327 ((M-C_4H_9+H)$^+$, 30), 283 ((M-$C_5H_9O_2$+H)$^+$, 77), 191 (12), 155 ((M-$C_5H_9O_2$-I)$^+$, 11), 154 (17), 57 ($C_4H_9^+$, 100), 41 (43), 39 (12). IR (KBr): $\tilde{\nu}$ 3144 (w) cm^{-1}, 2988 (w), 1734 (s), 1686 (m), 1655 (m), 1638 (w), 1561 (w), 1544 (w), 1510 (m), 1475 (m), 1370 (s), 1335 (s), 1297 (s), 1250 (m), 1152 (s), 987 (m), 901 (w), 848 (m), 829 (w), 807 (m), 766 (m), 583 (w). Anal. calcd for $C_{16}H_{18}INO_2$ (383.2): C 50.15, H 4.73, N 3.65. Found: C 50.36, H 4.85, N 3.59.

3.2.2. tert-Butyl 4-iodo-2-*m*-tolyl-1*H*-pyrrole-1-carboxylate (4b)

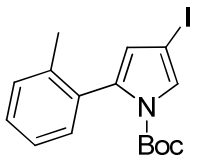


$C_{16}H_{18}INO_2$

383.22

According to the general procedure 1.42 g (74 % yield) were obtained as a colorless solid. Mp 52 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.35 (s, 9 H), 2.36 (s, 3 H), 6.22-6.24 (m, 1 H), 7.08-7.15 (m, 3 H), 7.21-7.25 (m, 1 H), 7.40-7.42 (m, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.3 (CH_3), 27.5 (CH_3), 64.3 (C_{quat}), 84.2 (C_{quat}), 120.5 (CH), 126.2 (CH), 126.9 (CH), 127.6 (CH), 128.4 (CH), 129.8 (CH), 132.8 (C_{quat}), 136.7 (C_{quat}), 137.1 (C_{quat}), 147.9 (C_{quat}). EI + MS (*m/z* (%)): 383 (M^+, 0.2), 327 ((M-C_4H_9+H)$^+$, 1), 283 ((M-$C_5H_9O_2$+H)$^+$, 5), 156 ((M-$C_5H_9O_2$-I+H)$^+$, 1), 155 ((M-$C_5H_9O_2$-I)$^+$, 3), 57 ($C_4H_9^+$, 100), 41 (22). IR (KBr): $\tilde{\nu}$ 3134 (w) cm^{-1}, 2981 (m), 1728 (s), 1612 (w), 1587 (w), 1554 (w), 1494 (w), 1467 (m), 1363 (s), 1335 (s), 1295 (s), 1248 (s), 1147 (s), 1094 (m), 1047 (m), 1025 (m), 983 (w), 903 (m), 886 (m), 844 (s), 820 (m), 789 (s), 766 (s), 704 (s), 659 (w), 616 (w), 590 (m), 535 (m). Anal. calcd for $C_{16}H_{18}INO_2$ (383.2): C 50.15, H 4.73, N 3.65. Found: C 50.18, H 4.63, N 3.72.

3.2.3. tert-Butyl 4-iodo-2-*o*-tolyl-1*H*-pyrrole-1-carboxylate (4c)

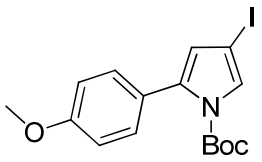


$C_{16}H_{18}INO_2$

383.22

According to the general procedure 1.38 g (72 % yield) were obtained as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.25 (s, 9 H), 2.12 (s, 3 H), 6.14-6.15 (m, 1 H), 7.14-7.20 (m, 3 H), 7.23-7.28 (m, 1 H), 7.46 (d, J = 1.3 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.9 (CH_3), 27.4 (CH_3), 64.3 (C_{quat}), 83.9 (C_{quat}), 120.0 (CH), 125.2 (CH), 126.0 (CH), 128.3 (CH), 129.3 (CH), 130.0 (CH), 133.3 (C_{quat}), 135.2 (C_{quat}), 137.7 (C_{quat}), 147.8 (C_{quat}). EI + MS (*m/z* (%)): 383 (M^+, 2), 327 ((M-C_4H_9+H)$^+$, 4), 283 ((M-$C_5H_9O_2$+H)$^+$, 9), 156 ((M-$C_5H_9O_2$-I+H)$^+$, 15), 155 ((M-$C_5H_9O_2$-I)$^+$, 20), 154 (34), 127 (19), 89 (18), 78 (16), 57 ($C_4H_9^+$, 100), 41 (30). IR (Film): $\tilde{\nu}$ 3148 (m) cm^{-1}, 3062 (m), 2980 (s), 2932 (m), 1744 (s), 1605 (w), 1556 (m), 1501 (m), 1474 (s), 1395 (m), 1367 (s), 1334 (s), 1293 (s), 1246 (s), 1151 (s), 1113 (s), 1077 (m), 1047 (w), 986 (s), 942 (w), 905 (s), 846 (s), 814 (m), 798 (m), 764 (s), 725 (m), 667 (w), 604 (w), 589 (m), 520 (w). Anal. calcd for $C_{16}H_{18}INO_2$ (383.2): C 50.15, H 4.73, N 3.65. Found: C 50.10, H 4.73, N 3.55.

3.2.4. tert-Butyl 4-iodo-2-(4-methoxyphenyl)-1*H*-pyrrole-1-carboxylate (4d)

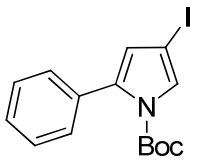


$C_{16}H_{18}INO_3$

399.22

According to the general procedure 1.46 g (73 % yield) were obtained as a colorless solid. Mp 71-72 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.39 (s, 9 H), 3.82 (s, 3 H), 6.20 (d, J = 1.9 Hz, 1 H), 6.88 (d, J = 8.8 Hz, 2 H), 7.24 (d, J = 8.8 Hz, 2 H), 7.39 (d, J = 1.9 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.6 (CH_3), 55.3 (CH_3), 64.4 (C_{quat}), 84.2 (C_{quat}), 113.1 (CH), 120.3 (CH), 125.3 (C_{quat}), 126.7 (CH), 130.4 (CH), 136.5 (C_{quat}), 147.9 (C_{quat}), 159.3 (C_{quat}). EI + MS (*m/z* (%)): 399 (M^+, 3), 343 ((M-C_4H_9+H)$^+$, 11), 299 ((M-$C_5H_9O_2$+H)$^+$, 16), 298 ((M-$C_5H_9O_2$)$^+$, 13), 171 ((M-$C_5H_9O_2$-I)$^+$, 6), 156 (12), 128 (11), 57 ($C_4H_9^+$, 100), 41 (34). IR (KBr): $\tilde{\nu}$ 3145 (m) cm^{-1}, 2986 (m), 2934 (w), 2832 (w), 1734 (s), 1609 (m), 1576 (w), 1557 (w), 1511 (s), 1476 (m), 1460 (m), 1435 (w), 1370 (s), 1337 (s), 1293 (s), 1251 (s), 1180 (s), 1151 (s), 1108 (m), 1032 (s), 985 (m), 904 (m), 847 (s), 833 (m), 808 (s), 771 (m), 675 (w), 629 (w), 615 (w), 594 (m), 528 (w), 511 (w). Anal. calcd for $C_{16}H_{18}INO_3$ (399.2): C 48.14, H 4.54, N 3.51. Found: C 48.36, H 4.37, N 3.34.

3.2.5. tert-Butyl 4-iodo-2-phenyl-1*H*-pyrrole-1-carboxylate (4e)

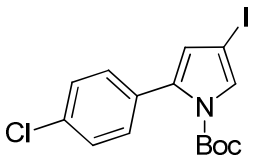


$C_{15}H_{16}INO_2$

369.20

According to the general procedure 1.32 g (72 % yield) were obtained as a colorless solid. Mp 65-66 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.34 (s, 9 H), 6.24 (d, J = 1.9 Hz, 1 H), 7.29-7.37 (m, 5 H), 7.42 (d, J = 1.9 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.5 (CH_3), 64.4 (C_{quat}), 84.3 (C_{quat}), 120.7 (CH), 127.0 (CH), 127.7 (CH), 127.7 (CH), 129.2 (CH), 132.9 (C_{quat}), 136.6 (C_{quat}), 147.9 (C_{quat}). EI + MS (*m/z* (%)): 369 (M^+, 2), 313 ($(M-C_4H_9+H)^+$, 3), 269 ($(M-C_5H_9O_2)^+$, 8), 141 ($(M-C_5H_9O_2-I)^+$, 12), 114 (11), 57 ($C_4H_9^+$, 100), 41 (32). IR (KBr): $\tilde{\nu}$ 3150 (w) cm^{-1}, 2969 (w), 1749 (s), 1474 (w), 1445 (w), 1370 (m), 1296 (s), 1261 (m), 1148 (s), 1081 (w), 1032 (w), 986 (w), 903 (w), 849 (w), 820 (w), 771 (w), 745 (w), 693 (w), 664 (w), 593 (w). Anal. calcd for $C_{15}H_{16}INO_2$ (369.2): C 48.80, H 4.37, N 3.79. Found: C 48.68, H 4.57, N 3.62.

3.2.6. tert-Butyl 4-iodo-2-(*p*-chlorophenyl)-1*H*-pyrrole-1-carboxylate (4f)

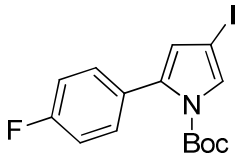


$C_{15}H_{15}ClINO_2$

403.64

According to the general procedure 1.24 g (62 % yield) were obtained as a colorless solid. Mp 64 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.39 (s, 9 H), 6.24 (d, J = 1.9 Hz, 1 H), 7.23-7.26 (m, 2 H), 7.31-7.34 (m, 2 H), 7.42 (d, J = 1.9 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.6 (CH_3), 64.4 (C_{quat}), 84.7 (C_{quat}), 121.0 (CH), 127.3 (CH), 127.9 (CH), 130.5 (CH), 131.3 (C_{quat}), 133.8 (C_{quat}), 135.3 (C_{quat}), 147.7 (C_{quat}). EI + MS (*m/z* (%)): 405 ($M(^{37}Cl)^+$, 0.2), 403 ($M(^{35}Cl)^+$, 1.0), 349 ($(M(^{37}Cl)-C_4H_9+H)^+$, 0.4), 347 ($(M(^{35}Cl)-C_4H_9+H)^+$, 1.7), 305 ($(M(^{37}Cl)-C_5H_9O_2+H)^+$, 2.0), 303 ($(M(^{35}Cl)-C_5H_9O_2+H)^+$, 6.3), 177 ($(M(^{37}Cl)-C_5H_9O_2-I)^+$, 0.5), 175 ($(M(^{35}Cl)-C_5H_9O_2-I)^+$, 1.4), 57 ($C_4H_9^+$, 100), 41 (16). IR (KBr): $\tilde{\nu}$ 3145 (m) cm^{-1}, 2988 (w), 1735 (s), 1638 (w), 1498 (w), 1467 (w), 1398 (w), 1369 (s), 1339 (m), 1297 (s), 1252 (w), 1153 (s), 1090 (w), 1016 (w), 987 (w), 904 (w), 847 (m), 808 (m), 768 (m), 596 (w). Anal. calcd for $C_{15}H_{15}ClINO_2$ (403.6): C 44.63, H 3.75, N 3.47. Found: C 44.74, H 3.84, N 3.41.

3.2.7. tert-Butyl 4-iodo-2-(*p*-fluorophenyl)-1*H*-pyrrole-1-carboxylate (4g)

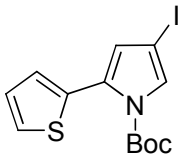


$C_{15}H_{15}FINO_2$

387.19

According to the general procedure 1.49 g (75 % yield) were obtained as a colorless solid. Mp 74 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.38 (s, 9 H), 6.23 (d, J = 1.9 Hz, 1 H), 7.01-7.07 (m, 2 H), 7.26-7.30 (m, 2 H), 7.42 (d, J = 1.9 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.6 (CH_3), 64.3 (C_{quat}), 84.5 (C_{quat}), 114.7 (d, J = 21.1 Hz, CH), 120.9 (CH), 127.0 (CH), 128.9 (C_{quat}), 130.9 (d, J = 8.2 Hz, CH), 135.5 (C_{quat}), 147.8 (C_{quat}), 162.5 (d, J = 247.4 Hz, C_{quat}). EI + MS (*m/z* (%)): 387 (M^+, 2), 331 ($(M-C_4H_9+H)^+$, 3), 287 ($(M-C_5H_9O_2+H)^+$, 9), 159 ($(M-C_5H_9O_2-I)^+$, 9), 57 ($C_4H_9^+$, 100), 41 (28). IR (KBr): $\tilde{\nu}$ 3147 (w) cm^{-1}, 3135 (w), 2984 (w), 1733 (s), 1593 (w), 1552 (w), 1508 (m), 1474 (w), 1370 (s), 1337 (s), 1297 (s), 1250 (m), 1224 (m), 1160 (s), 1096 (w), 1017 (w), 990 (w), 904 (w), 849 (m), 812 (m), 766 (m), 720 (w), 611 (w), 585 (w), 524 (w). Anal. calcd for $C_{15}H_{15}FINO_2$ (387.2): C 46.53, H 3.90, N 3.62. Found: C 46.52, H 3.96, N 3.44.

3.2.8. tert-Butyl 2-(2-thienyl)-4-iodo-1*H*-pyrrole-1-carboxylate (4h)

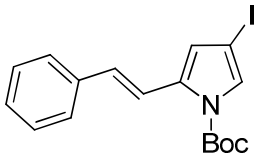


$C_{13}H_{14}INO_2S$

375.23

According to the general procedure 1.19 g (63 % yield) were obtained as a colorless solid. Mp 55 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.41 (s, 9 H), 6.37 (d, J = 1.9 Hz, 1 H), 7.01 (dd, J = 5.0 Hz, J = 3.5 Hz, 1 H), 7.05 (dd, J = 3.5 Hz, J = 1.3 Hz, 1 H), 7.32 (dd, J = 5.0 Hz, J = 1.3 Hz, 1 H), 7.44 (d, J = 1.9 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.6 (CH_3), 64.1 (C_{quat}), 84.5 (C_{quat}), 122.6 (CH), 126.2 (CH), 126.5 (CH), 127.7 (CH), 128.3 (CH), 128.5 (C_{quat}), 133.0 (C_{quat}), 147.6 (C_{quat}). EI + MS (*m/z* (%)): 375 (M^+, 2), 319 ($(M-C_4H_9+H)^+$, 5), 275 ($(M-C_5H_9O_2+H)^+$, 9), 147 ($(M-C_5H_9O_2-I)^+$, 2), 57 ($C_4H_9^+$, 100), 41 (20). IR (KBr): $\tilde{\nu}$ 3152 (w) cm^{-1}, 2979 (w), 1750 (s), 1655 (w), 1638 (w), 1560 (w), 1543 (w), 1509 (w), 1475 (w), 1420 (w), 1371 (m), 1345 (w), 1305 (s), 1295 (s), 1255 (w), 1219 (w), 1158 (m), 1141 (m), 1081 (w), 932 (w), 903 (w), 850 (w), 818 (w), 768 (w), 699 (w), 592 (w). Anal. calcd for $C_{13}H_{14}INO_2S$ (375.2): C 41.61, H 3.76, N 3.73. Found: C 41.75, H 3.82, N 3.48.

3.2.9. tert-Butyl 2-(phenylethenyl)-4-iodo-1*H*-pyrrole-1-carboxylate (4i)

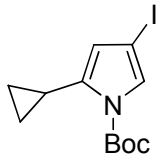


$C_{17}H_{18}INO_2$

395.23

According to the general procedure 1.38 g (70 % yield) were obtained as a colorless solid. Mp 84 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.61 (s, 9 H), 6.60 (s, 1 H), 6.87 (d, J = 16.4 Hz, 1 H), 7.21-7.26 (m, 1 H), 7.30-7.36 (m, 3 H), 7.46 (d, J = 7.3 Hz, 2 H), 7.67 (d, J = 16.4 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.0 (CH_3), 65.3 (C_{quat}), 84.7 (C_{quat}), 117.2 (CH), 118.3 (CH), 126.5 (CH), 126.7 (CH), 127.7 (CH), 128.6 (CH), 129.6 (CH), 136.0 (C_{quat}), 137.1 (C_{quat}), 148.1 (C_{quat}). EI + MS (*m/z* (%)): 395 (M^+, 2), 339 ($(M-C_4H_9+H)^+$, 15), 295 ($(M-C_5H_9O_2+H)^+$, 11), 167 ($(M-C_5H_9O_2-I)^+$, 13), 57 ($C_4H_9^+$, 100), 41 (18). IR (KBr): $\tilde{\nu}$ 3160 (m) cm^{-1}, 3123 (w), 3078 (w), 3056 (w), 3024 (w), 2978 (m), 2929 (w), 1813 (w), 1752 (s), 1624 (w), 1596 (w), 1575 (w), 1493 (m), 1471 (m), 1454 (m), 1384 (s), 1370 (s), 1301 (s), 1259 (s), 1237 (s), 1155 (s), 1109 (s), 1077 (s), 1029 (s), 984 (w), 962 (s), 906 (s), 848 (s), 804 (s), 770 (s), 747 (s), 694 (s), 645 (w), 610 (m), 586 (m), 546 (w), 514 (w). Anal. calcd for $C_{17}H_{18}INO_2$ (395.2): C 51.66, H 4.59, N 3.54. Found: C 51.60, H 4.75, N 3.51.

3.2.10. tert-Butyl 2-(cyclopropyl)-4-iodo-1*H*-pyrrole-1-carboxylate (4j)

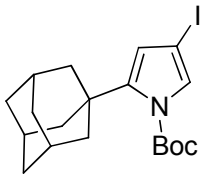


$C_{12}H_{16}INO_2$

333.17

According to the general procedure 1.15 g (69 % yield) were obtained as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.56-0.60 (m, 2 H), 0.83-0.88 (m, 2 H), 1.59 (s, 9 H), 2.14-2.21 (m, 1 H), 5.89 (dd, J = 1.9 Hz, J = 1.3 Hz, 1 H), 7.25 (d, J = 1.9 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 7.1 (CH_2), 9.4 (CH), 28.0 (CH_3), 63.7 (C_{quat}), 84.0 (C_{quat}), 116.2 (CH), 125.7 (CH), 139.7 (C_{quat}), 148.1 (C_{quat}). EI + MS (*m/z* (%)): 333 (M^+, 4), 277 ((M-C_4H_9+H)$^+$, 15), 233 ((M-$C_5H_9O_2$+H)$^+$, 8), 106 ((M-$C_5H_9O_2$-I+H)$^+$, 13), 105 ((M-$C_5H_9O_2$-I)$^+$, 5), 57 ($C_4H_9^+$, 100), 41 (19). IR (Film): $\tilde{\nu}$ 3157 (m) cm^{-1}, 3087 (m), 3007 (s), 2980 (s), 2933 (s), 1744 (s), 1560 (s), 1478 (s), 1458 (s), 1352 (s), 1303 (s), 1238 (s), 1159 (s), 1118 (s), 1080 (s), 1048 (s), 908 (s), 885 (s), 849 (s), 802 (s), 757 (s), 667 (w), 647 (w), 590 (s). Anal. calcd for $C_{12}H_{16}INO_2$ (333.2): C 43.26, H 4.84, N 4.20. Found: C 43.49, H 5.03, N 3.91.

3.2.11. tert-Butyl 2-(1-adamantyl)-4-iodo-1*H*-pyrrole-1-carboxylate (4k)



$C_{19}H_{26}INO_2$

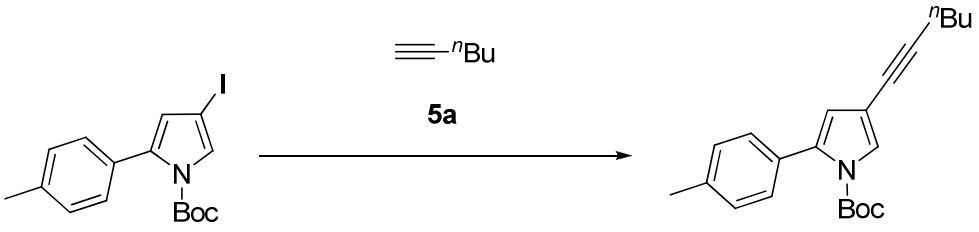
427.32

According to the general procedure 1.31 g (61 % yield) were obtained as a colorless solid. Mp 151 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.58 (s, 9 H), 1.68-1.78 (m, 6 H), 2.0 (br, 3 H), 2.05-2.08 (m, 6 H), 6.07-6.09 (m, 1 H), 7.24-7.27 (m, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.2 (CH_3), 28.9 (CH), 35.7 (C_{quat}), 36.9 (CH_2), 40.7 (CH_2), 63.6 (C_{quat}), 83.9 (C_{quat}), 117.6 (CH), 128.0 (CH), 147.7 (C_{quat}), 148.3 (C_{quat}). EI + MS (*m/z* (%)): 427 (M^+, 2), 371 ((M-C_4H_9+H)$^+$, 6), 327 ((M-$C_5H_9O_2$+H)$^+$, 18), 270 (4), 57 ($C_4H_9^+$, 100), 41 (7). IR (KBr): $\tilde{\nu}$ 3166 (w) cm^{-1}, 2980 (m), 2908 (s), 2849 (s), 2677 (w), 1748 (s), 1543 (w), 1489 (m), 1452 (m), 1395 (w), 1368 (s), 1316 (s), 1297 (s), 1255 (s), 1234 (s), 1163 (s), 1137 (s), 1105 (m), 1089 (s), 1011 (s), 976 (w), 937 (w), 899 (m), 849 (m), 819 (w), 804 (s), 764 (m), 679 (w), 644 (w), 590 (w), 533 (w). Anal. calcd for $C_{19}H_{26}INO_2$ (427.3): C 53.40, H 6.13, N 3.28. Found: C 53.46, H 6.22, N 3.11.

4. Synthesis of Pyrroles 6

4. 1. Synthesis of Pyrrole 6a by *Sonogashira* Coupling of Pyrrole 4a

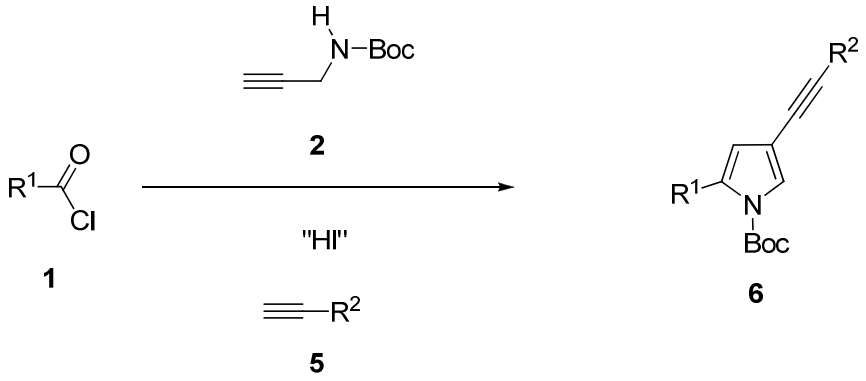
4.1.1. Procedure



$PdCl_2(PPh_3)_2$ (28 mg, 0.04 mmol) and CuI (16 mg, 0.08 mmol) were placed under argon in a screw-cap vessel, which was then dried with a heat gun and cooled to the room temperature. Then, 10 mL of dry THF were added and the mixture was degassed with argon. Cesium carbonate (2.63 g, 8.00 mmol), *tert*-Butyl 4-iodo-2-*p*-tolyl-1*H*-pyrrole-1-carboxylate (**4a**) (766 mg, 2.00 mmol) and 1-hexyne (**5a**) (0.47 ml, 4.00 mmol) were successively added to the mixture which was stirred at 70 °C for 1 h until the conversion was complete (monitored by TLC). The reaction mixture was diluted with 20 mL brine, the phases were separated and the aqueous phase was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuo the residue was absorbed onto celite and chromatographed on silica gel with petrolether (boiling range 40-60 °C)/ethyl acetate = 200:1 to give 598 mg (89 % yield) of **6a** as a brown oil. R_f (PE-EE = 150:1) : 0.23.

4.2. Three-Component Synthesis of Pyrroles 6 by Coupling-Addition-Cyclocondensation-Coupling Sequence

4.2.1. Procedure



$PdCl_2(PPh_3)_2$ (28 mg, 0.04 mmol) and CuI (16 mg, 0.08 mmol) were placed under argon in a screw-cap vessel, which was then dried with a heat gun and cooled to the room temperature. Then, 10 mL of dry THF were added and the mixture was degassed with argon. Dry triethylamine (0.28 mL, 2.00 mmol), acid chloride **1** (2.00 mmol) and *tert*-butyl prop-2-ynylcarbamate (**2**) (310 mg, 2.00 mmol) were successively added to the mixture which was stirred at room temperature until the conversion was complete (monitored by TLC). Then, sodium iodide (1.51 g, 10.0 mmol), toluene-4-sulfonic acid monohydrate (776 mg, 4.00 mmol) and 2 ml of *tert*-butanol were successively added to the mixture which was stirred at room temperature for 1 h (monitored by TLC). After that, cesium carbonate (2.63 g, 8.00 mmol) and terminal alkyne **5** (4.00 mmol) were successively added to the mixture which was stirred at 70 °C for 1 h until the conversion was complete (monitored by TLC). The reaction mixture was diluted with 20 mL brine, the phases were separated and the aqueous phase was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuo the residue was absorbed onto celite and chromatographed on silica gel.

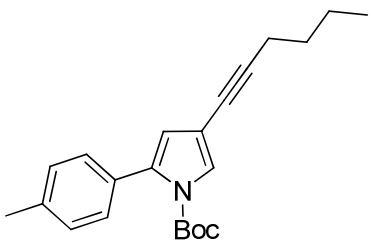
The experimental details are depicted in Table 3.

Table 3. Experimental details of the synthesis of pyrroles **6** by Coupling-Addition-Cyclocondensation-Coupling Sequence.

Entry	Acid chloride **1**	Terminal alkyne **5**	Pyrrole **6** (isolated yield %)	Chromatographic purification R_f (eluent)
1	316 mg (2.00 mmol) **1a**	0.47 mL (4.00 mmol) **5a**	391 mg (1.16 mmol, 58 %) **6a**	PE R_f (PE) : 0.13
2	352 mg (2.00 mmol) **1d**	0.89 mL (4.00 mmol) **5b**	481 mg (1.06 mmol, 53 %) **6b**	PE → PE-EE = 100:1 R_f (PE-EE = 100:1) : 0.10
3	352 mg (2.00 mmol) **1d**	0.45 mL (4.00 mmol) **5c**	502 mg (1.34 mmol, 67 %) **6c**	PE-EE = 100:1 → 90:1 → 80:1 → 70:1 → 60:1 R_f (PE-EE = 20:1) : 0.20

4.3. Spectroscopic and Analytical Data of Compounds 6

4.3.1. tert-Butyl 4-(hex-1-ynyl)-2-*p*-tolyl-1*H*-pyrrole-1-carboxylate (6a)

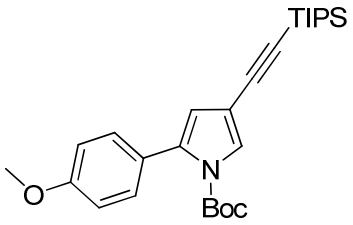


$C_{22}H_{27}NO_2$

337.46

According to the general procedure 391 mg (58 % yield) were obtained as an orange oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.94 (t, J = 7.3 Hz, 3 H), 1.38 (s, 9 H), 1.41-1.50 (m, 2 H), 1.53-1.60 (m, 2 H), 2.36-2.40 (m, 5 H), 6.16 (d, J = 1.9 Hz, 1 H), 7.13-7.16 (m, 2 H), 7.19-7.22 (m, 2 H), 7.40 (d, J = 1.9 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.7 (CH_3), 19.2 (CH_2), 21.3 (CH_3), 22.0 (CH_2), 27.6 (CH_3), 30.9 (CH_2), 73.9 (C_{quat}), 83.9 (C_{quat}), 90.3 (C_{quat}), 107.4 (C_{quat}), 116.6 (CH), 124.9 (CH), 128.3 (CH), 129.1 (CH), 130.6 (C_{quat}), 135.0 (C_{quat}), 137.3 (C_{quat}), 148.6 (C_{quat}). EI + MS (*m/z* (%)): 337 (M^+, 0.5), 281 ($(M-C_4H_9+H)^+$, 2), 237 ($(M-C_5H_9O_2+H)^+$, 2), 57 ($C_4H_9^+$, 100), 41 (20). IR (Film): $\tilde{\nu}$ 3149 (w) cm^{-1}, 2959 (s), 2933 (s), 2872 (s), 1739 (s), 1532 (m), 1488 (m), 1456 (m), 1394 (m), 1368 (s), 1337 (s), 1256 (s), 1219 (m), 1156 (s), 1121 (s), 1025 (m), 989 (m), 847 (m), 813 (s), 765 (m), 718 (w), 635 (w), 610 (m). Anal. calcd for $C_{22}H_{27}NO_2$ (337.5): C 78.30, H 8.06, N 4.15. Found: C 78.12, H 8.19, N 4.34.

4.3.2. ***tert*-Butyl 4-(2-(triisopropylsilyl)ethynyl)-2-(4-methoxyphenyl)-1*H*-pyrrole-1-carboxylate (6b)**

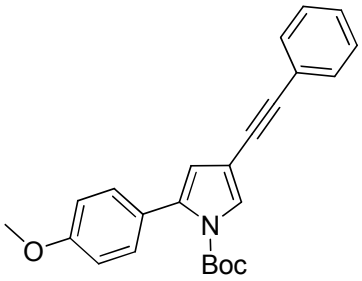


$C_{27}H_{39}NO_3Si$

453.69

According to the general procedure 481 mg (53 % yield) were obtained as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.11 (s, 21 H), 1.39 (s, 9 H), 3.82 (s, 3 H), 6.20 (d, J = 1.9 Hz, 1 H), 6.86-6.90 (m, 2 H), 7.22-7.26 (m, 2 H), 7.48 (d, J = 1.9 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.6 (CH), 18.9 (CH_3), 27.9 (CH_3), 55.5 (CH_3), 84.3 (C_{quat}), 90.8 (C_{quat}), 100.9 (C_{quat}), 107.3 (C_{quat}), 113.3 (CH), 116.8 (CH), 126.1 (C_{quat}), 126.3 (CH), 130.6 (CH), 135.0 (C_{quat}), 148.7 (C_{quat}), 159.4 (C_{quat}). EI + MS (*m/z* (%)): 453 (M^+, 2), 397 ((M-C_4H_9+H)$^+$, 2), 354 ((M-$C_5H_9O_2$+H)$^+$, 2), 285 ((M-CH_3-TIPS+4H)$^+$, 95), 241 ((M-C_4H_9-TIPS+2H)$^+$, 13), 191 (10), 185 (12), 135 (18), 131 (19), 129 (27), 125 (12), 113 (11), 112 (10), 111 (20), 105 (26), 103 (16), 99 (15), 98 (15), 97 (34), 96 (13), 95 (13), 87 (11), 85 (36), 84 (15), 83 (35), 82 (12), 81 (11), 77 (38), 75 (16), 73 (47), 71 (57), 70 (19), 69 (42), 67 (11), 61 (22), 60 (37), 59 (12), 57 ($C_4H_9^+$, 100). IR (Film): $\tilde{\nu}$ 2943 (s) cm^{-1}, 2866 (s), 2156 (m), 1744 (s), 1614 (w), 1578 (w), 1529 (w), 1489 (m), 1464 (m), 1367 (s), 1330 (s), 1249 (s), 1154 (s), 1109 (m), 1039 (m), 1016 (w), 995 (m), 981 (w), 920 (w), 883 (m), 848 (m), 819 (m), 798 (w), 765 (m), 742 (w), 677 (m), 607 (w), 517 (w). Anal. calcd for $C_{27}H_{39}NO_3Si$ (453.7): C 71.48, H 8.66, N 3.09. Found: C 71.25, H 8.55, N 3.02.

4.3.3. tert-Butyl 2-(4-methoxyphenyl)-4-(2-phenylethynyl)-1*H*-pyrrole-1-carboxylate (6c)



$C_{24}H_{23}NO_3$

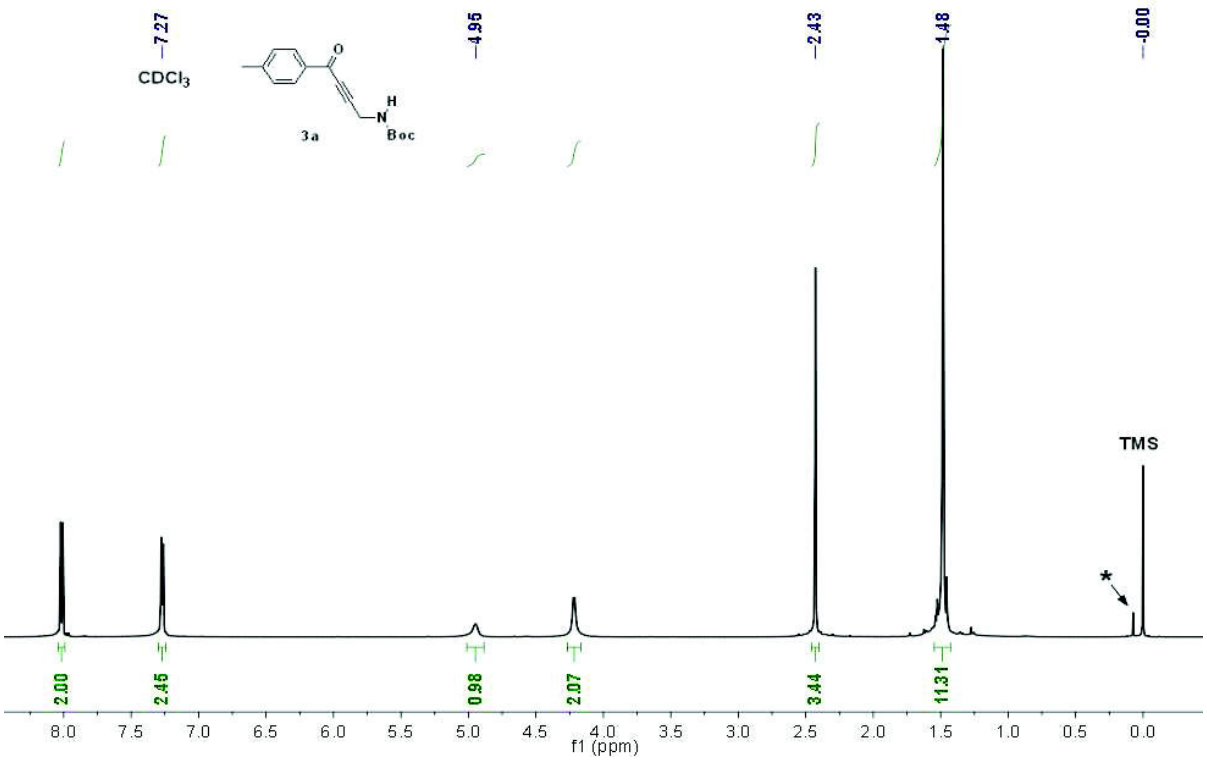
373.44

According to the general procedure 502 mg (67 % yield) were obtained as an orange oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.40 (s, 9 H), 3.82 (s, 3 H), 6.26 (d, J = 1.9 Hz, 1 H), 6.87-6.91 (m, 2 H), 7.25-7.34 (m, 5 H), 7.47-7.51 (m, 2 H), 7.55 (d, J = 1.9 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.8 (CH_3), 55.4 (CH_3), 83.6 (C_{quat}), 84.3 (C_{quat}), 89.6 (C_{quat}), 106.9 (C_{quat}), 113.3 (CH), 116.4 (CH), 123.8 (C_{quat}), 125.7 (CH), 126.0 (C_{quat}), 128.1 (CH), 128.5 (CH), 130.7 (CH), 131.6 (CH), 135.3 (C_{quat}), 148.7 (C_{quat}), 159.4 (C_{quat}). EI + MS (*m/z* (%)): 373 (M^+, 0.5), 317 ((M-C_4H_9+H)$^+$, 0.7), 284 ((M-CH_3-Ph+3H)$^+$, 27), 241 ((M-C_4H_9-Ph+2H)$^+$, 4), 191 (10), 135 (6), 97 (10), 88 (13), 85 (15), 73 (16), 71 (18), 70 (18), 61 (20), 57 ($C_4H_9^+$, 30), 55 (11), 45 ($C_2H_5O^+$, 17), 43 ($C_2H_3O^+$, 100). IR (KBr): $\tilde{\nu}$ 3146 (w) cm^{-1}, 2979 (w), 2836 (w), 2217 (w), 1741 (s), 1616 (m), 1578 (w), 1533 (m), 1483 (s), 1459 (w), 1442 (m), 1366 (s), 1346 (s), 1280 (s), 1248 (s), 1177 (m), 1148 (s), 1098 (m), 1035 (m), 991 (m), 975 (m), 847 (m), 819 (m), 755 (m), 690 (m), 632 (w), 610 (w), 583 (w), 525 (w). Anal. calcd for $C_{24}H_{23}NO_3$ (373.4): C 77.19, H 6.21, N 3.75. Found: C 77.18, H 6.38, N 3.53.

5. ^{1}H and ^{13}C NMR Spectra

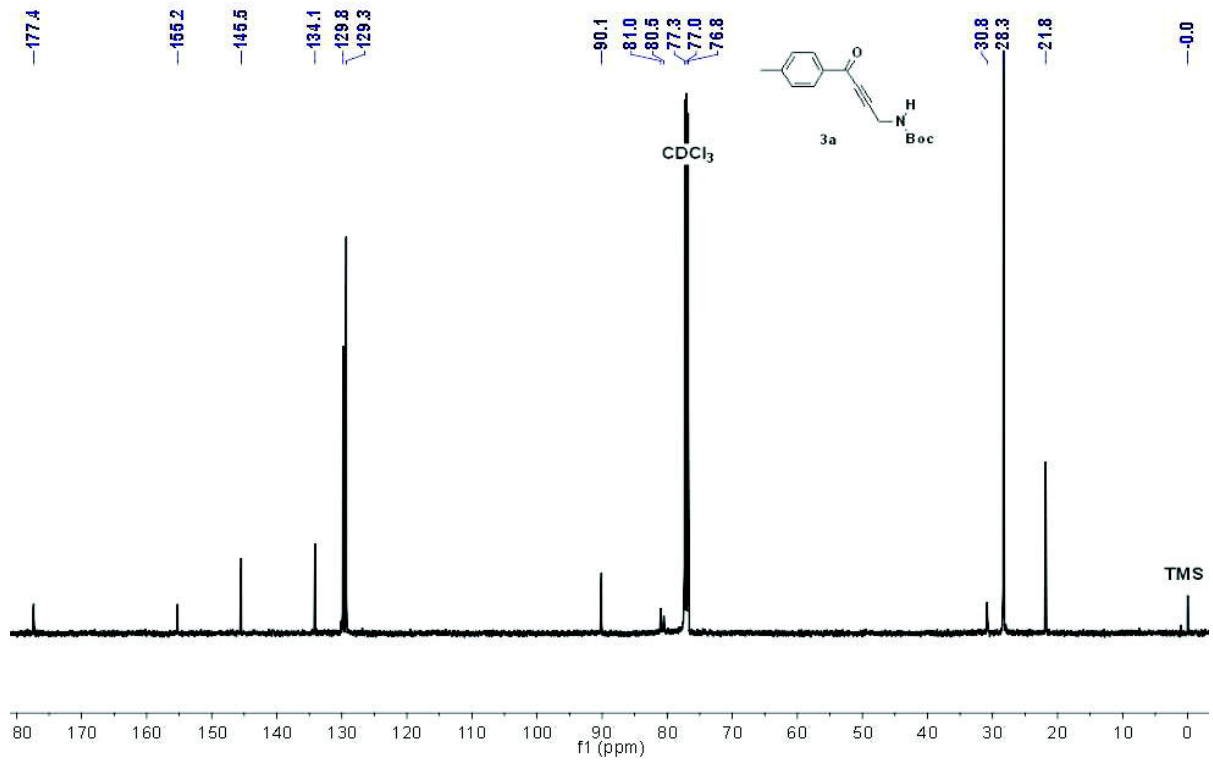
5.1. ^{1}H and ^{13}C NMR Spectra of Compounds 3a and 3b

^{1}H NMR of **3a** in $CDCl_3$ at 297 K

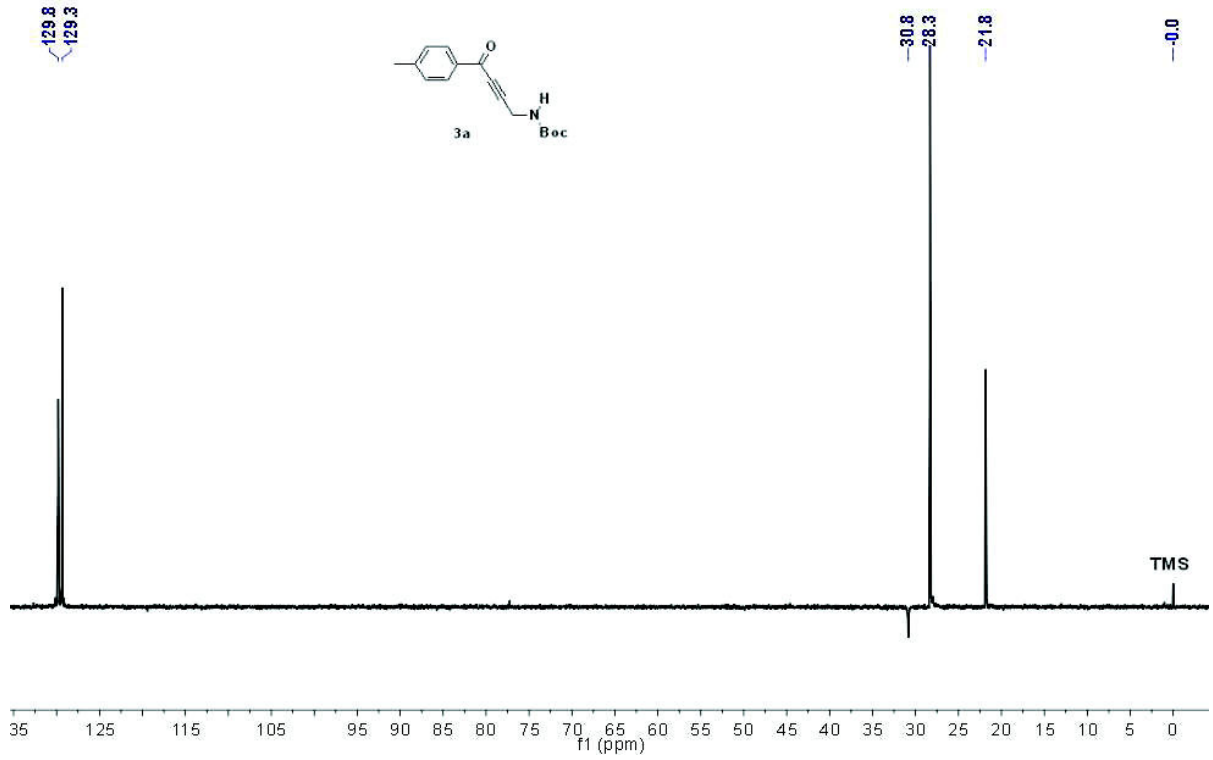


*Impurities from residual solvents.

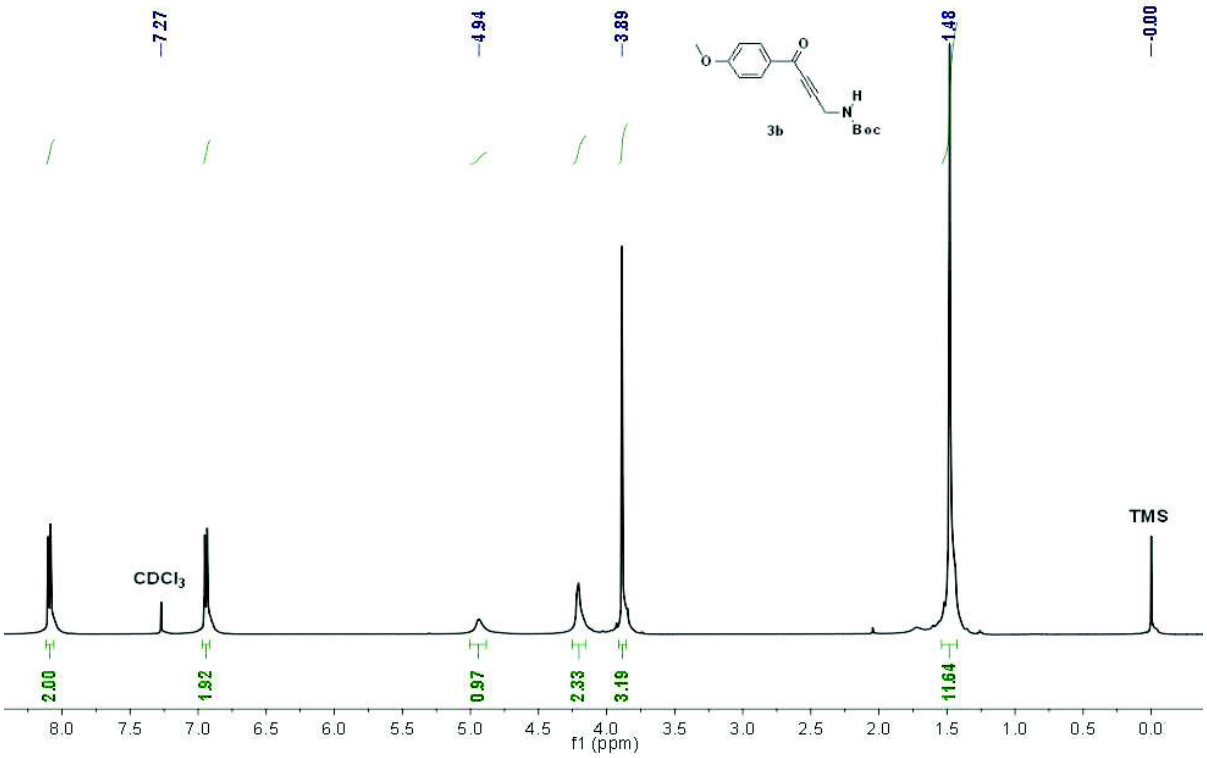
^{13}C NMR of **3a** in $CDCl_3$ at 297 K



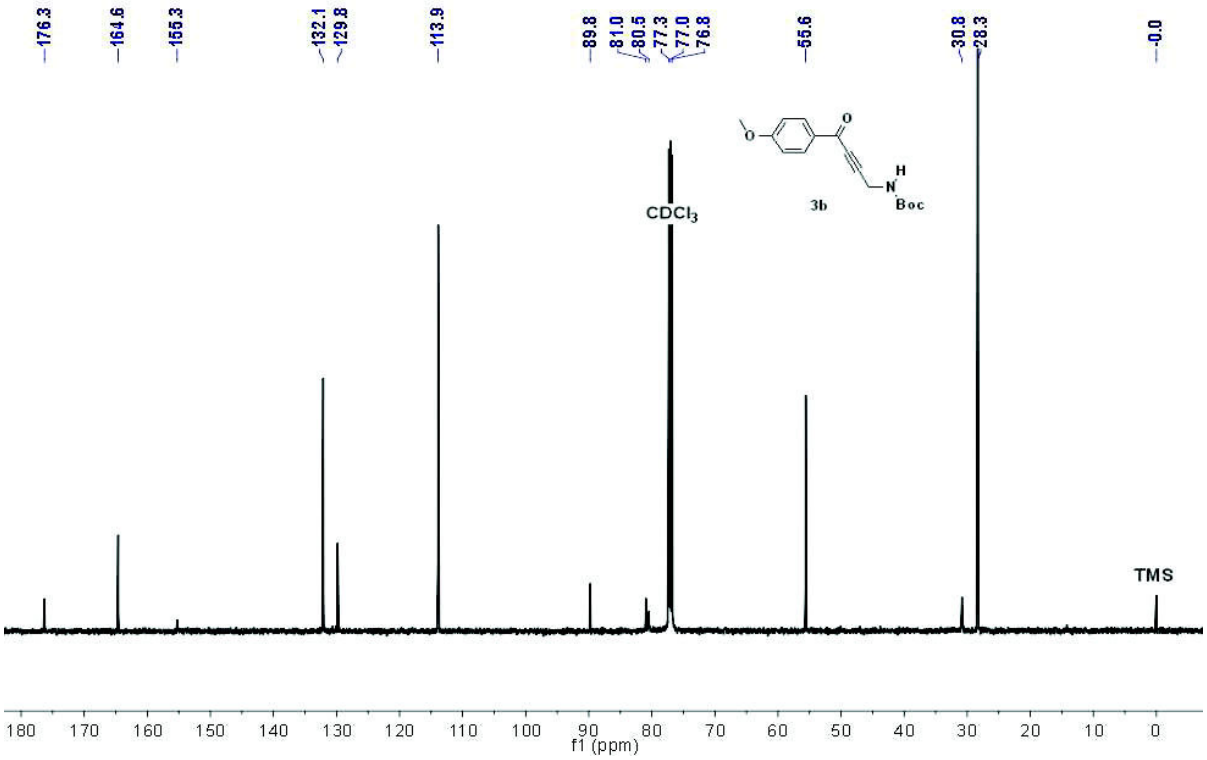
^{13}C DEPT 135 of **3a** in $CDCl_3$ at 297 K



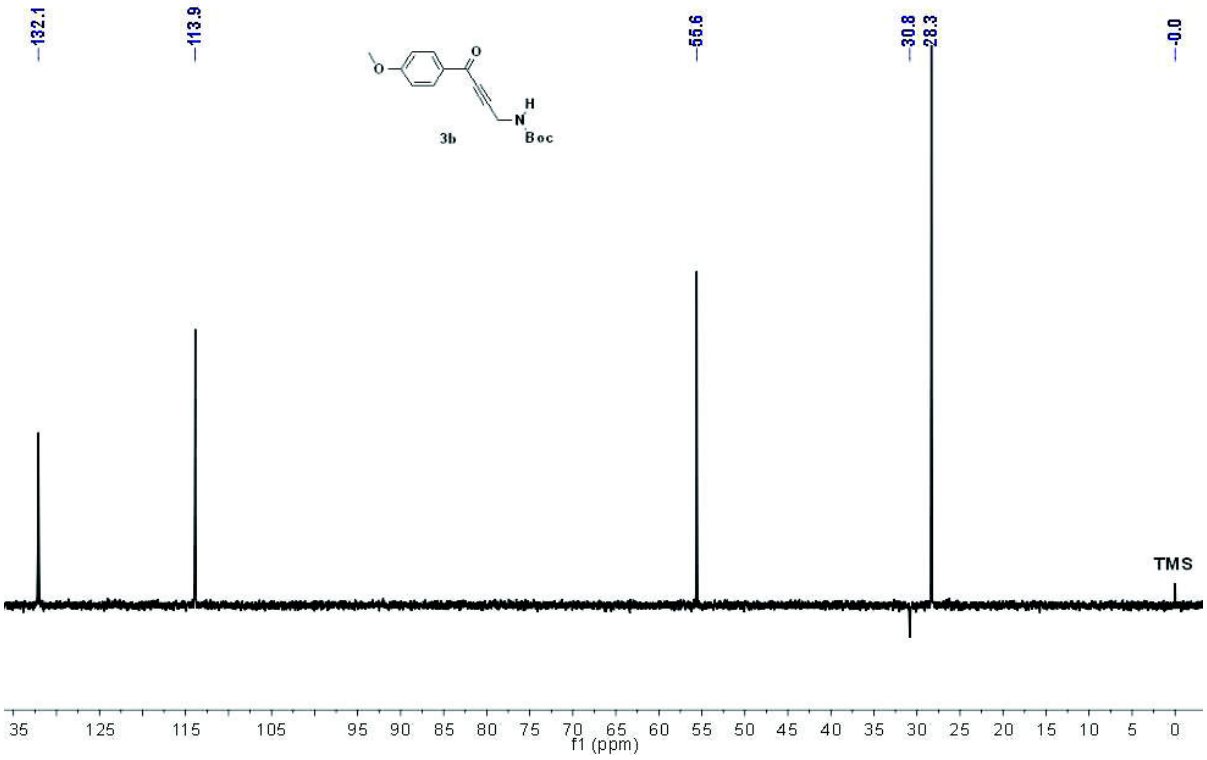
^{1}H NMR of **3b** in $CDCl_3$ at 297 K



^{13}C NMR of **3b** in $CDCl_3$ at 297 K

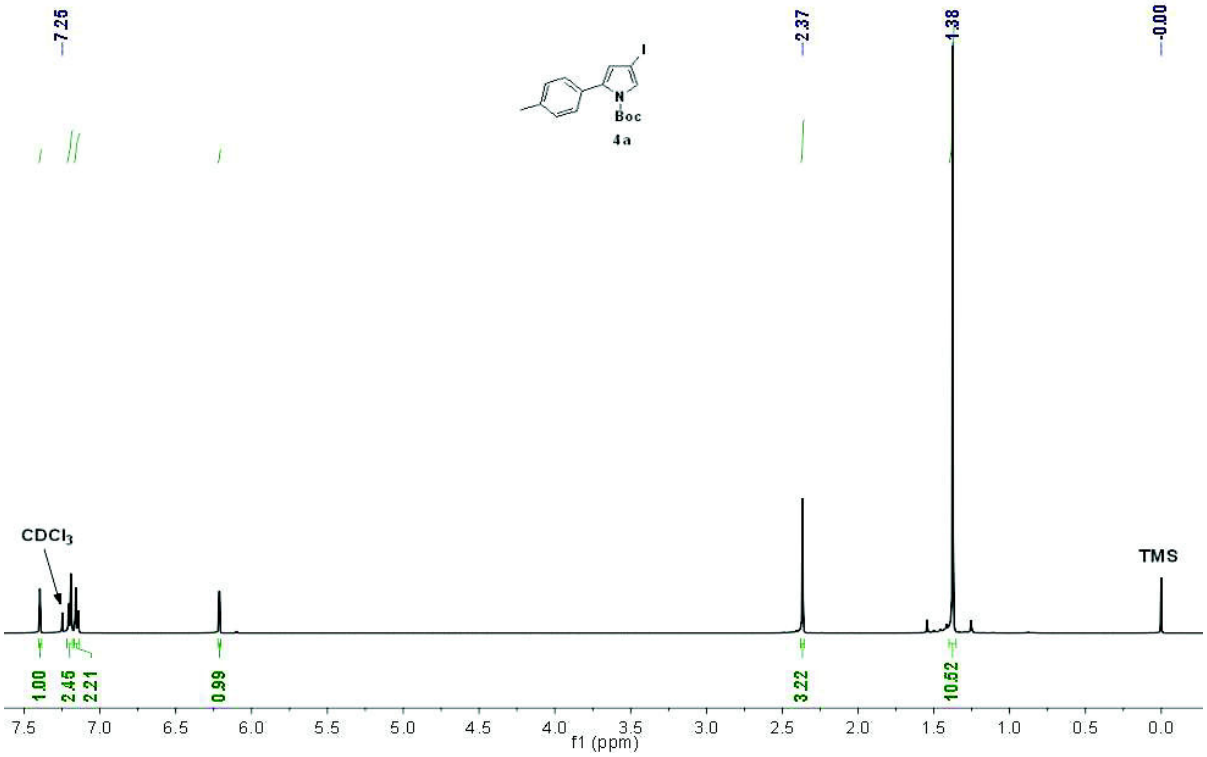


^{13}C DEPT 135 of **3b** in $CDCl_3$ at 297 K

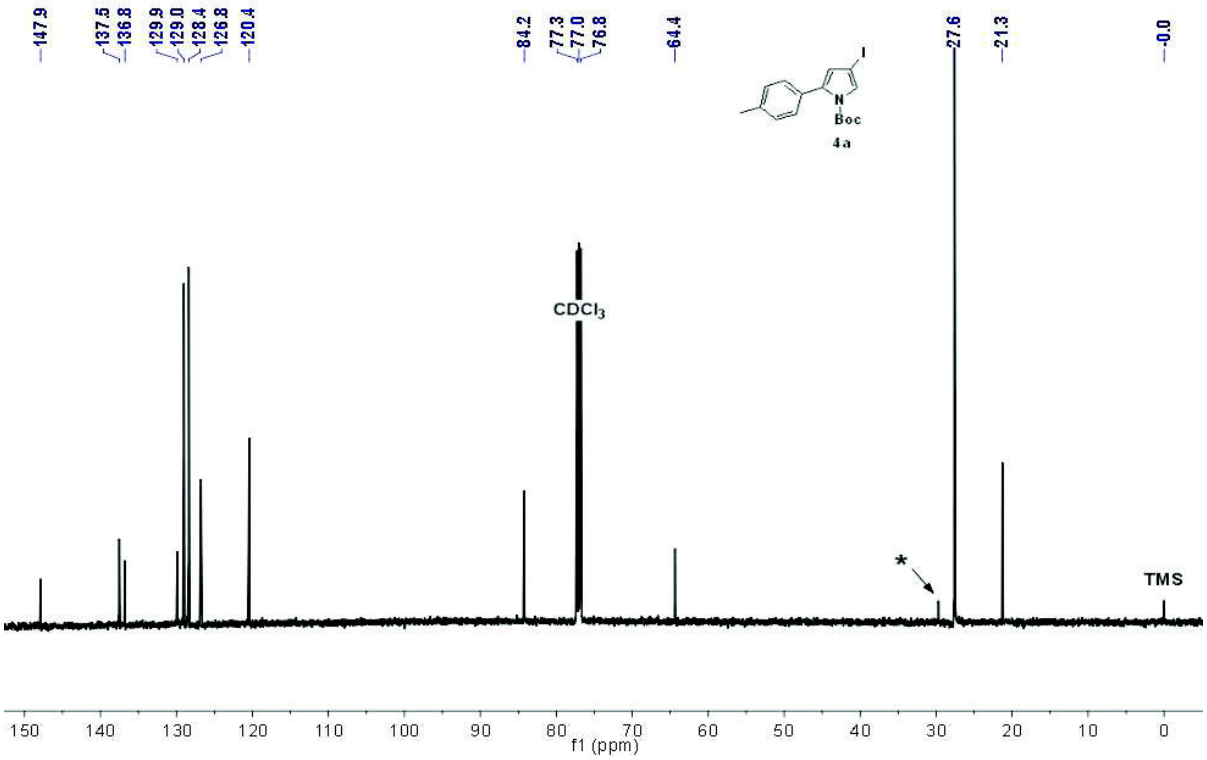


5.2. ^{1}H and ^{13}C NMR Spectra of Compounds 4a-k

^{1}H NMR of **4a** in $CDCl_3$ at 297 K

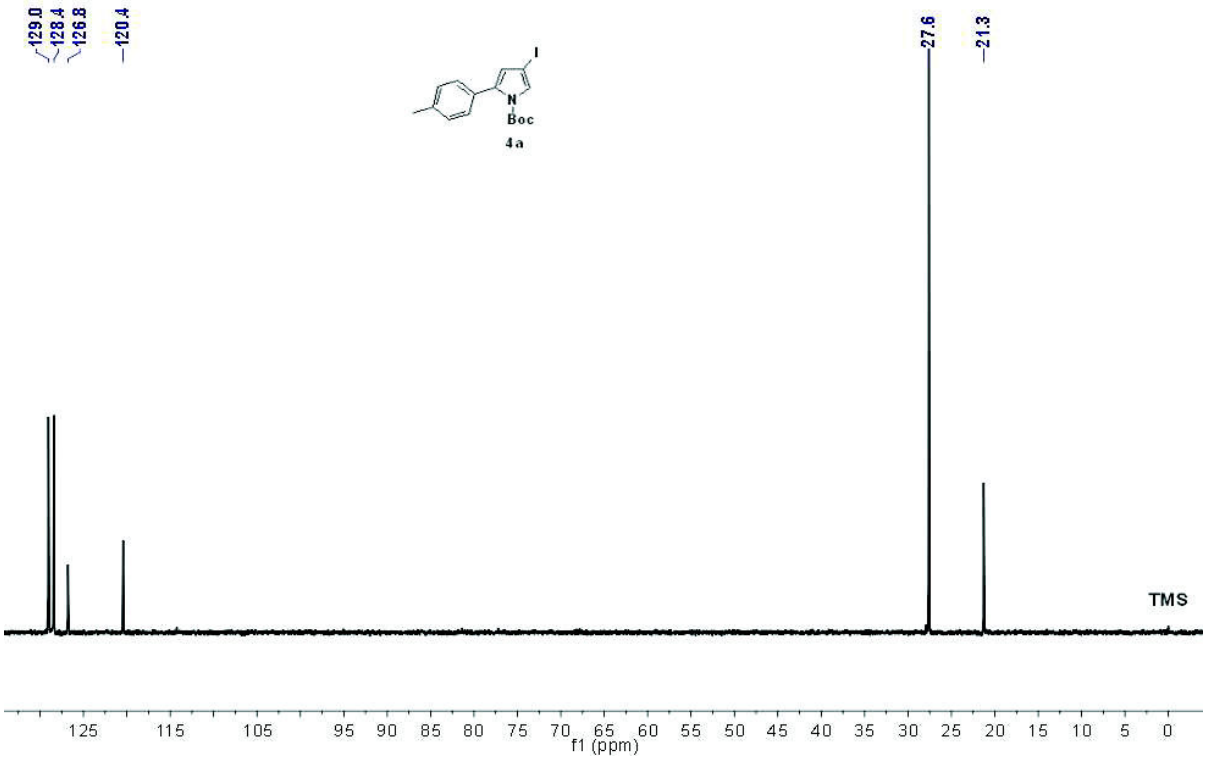


^{13}C NMR of **4a** in $CDCl_3$ at 297 K

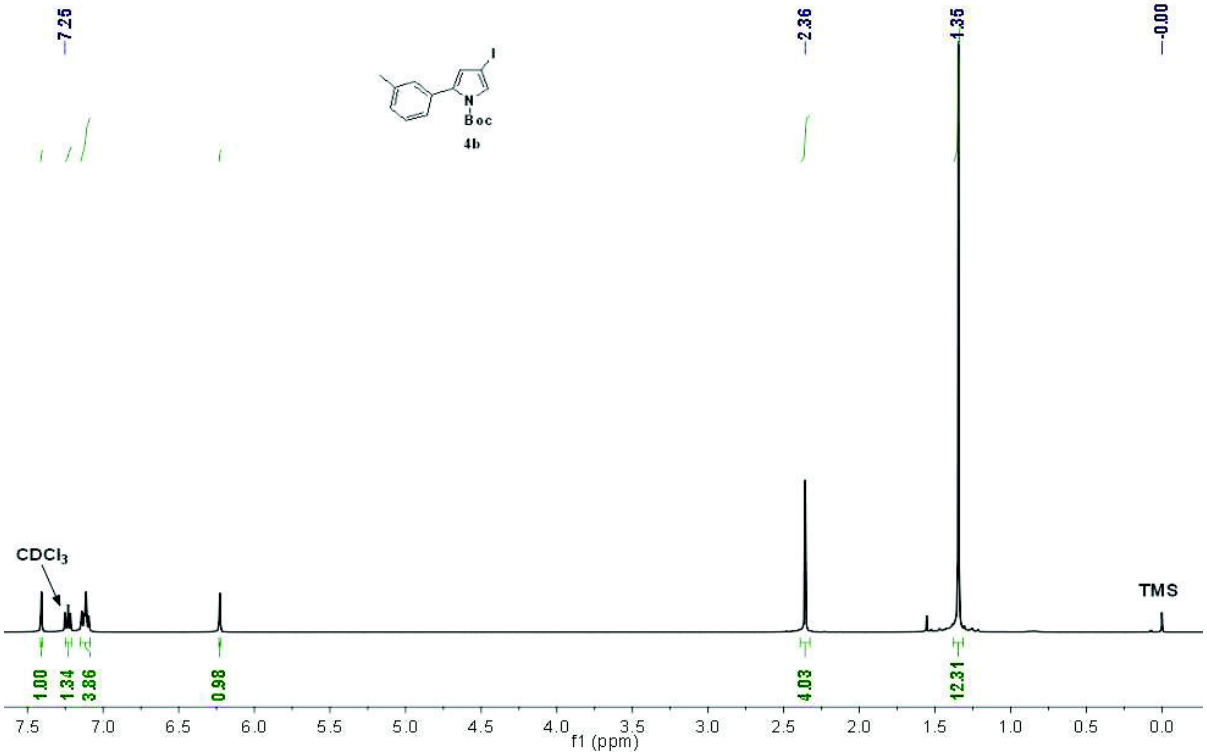


*Impurities from residual solvents.

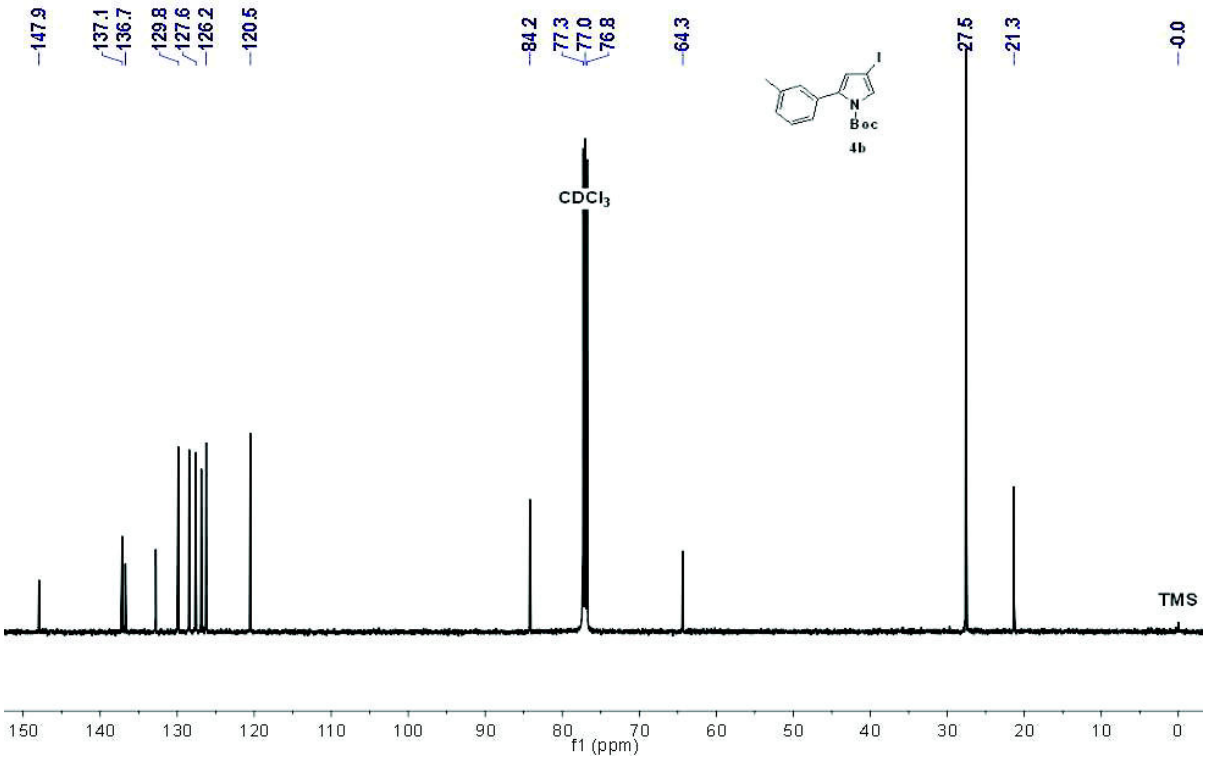
^{13}C DEPT 135 of **4a** in $CDCl_3$ at 296 K



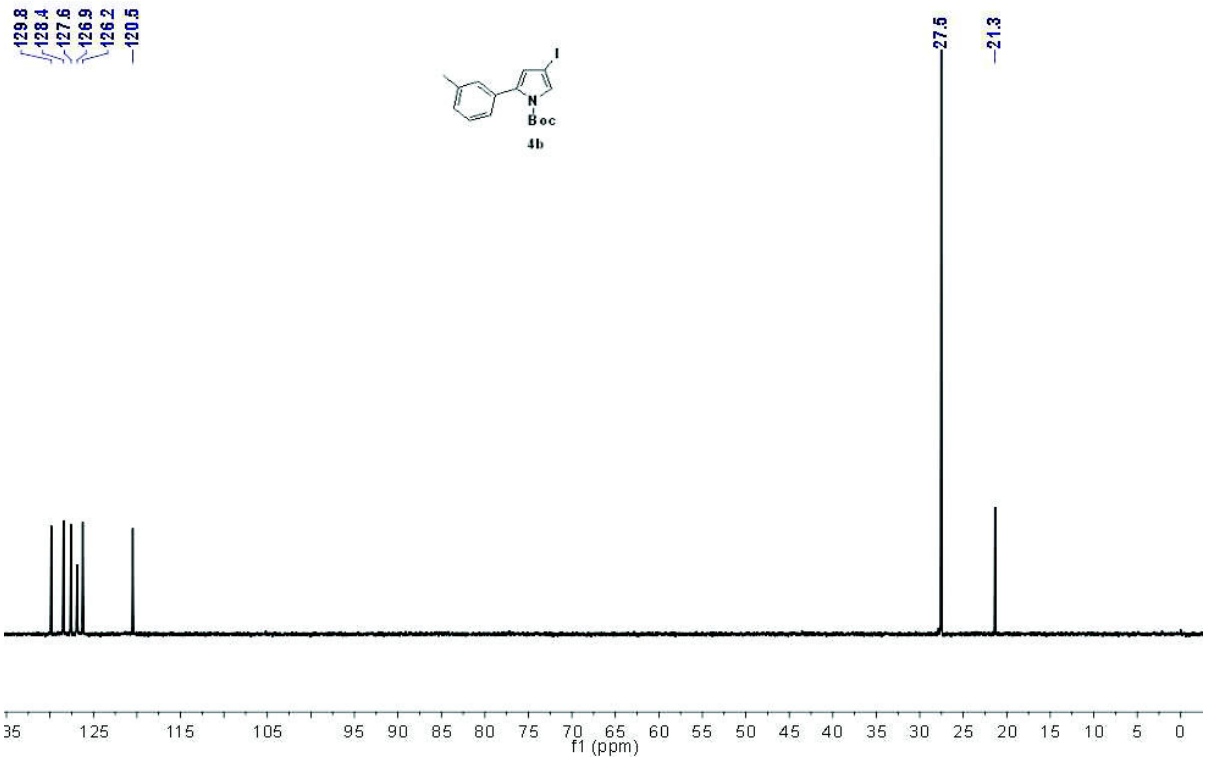
^{1}H NMR of **4b** in $CDCl_3$ at 296 K



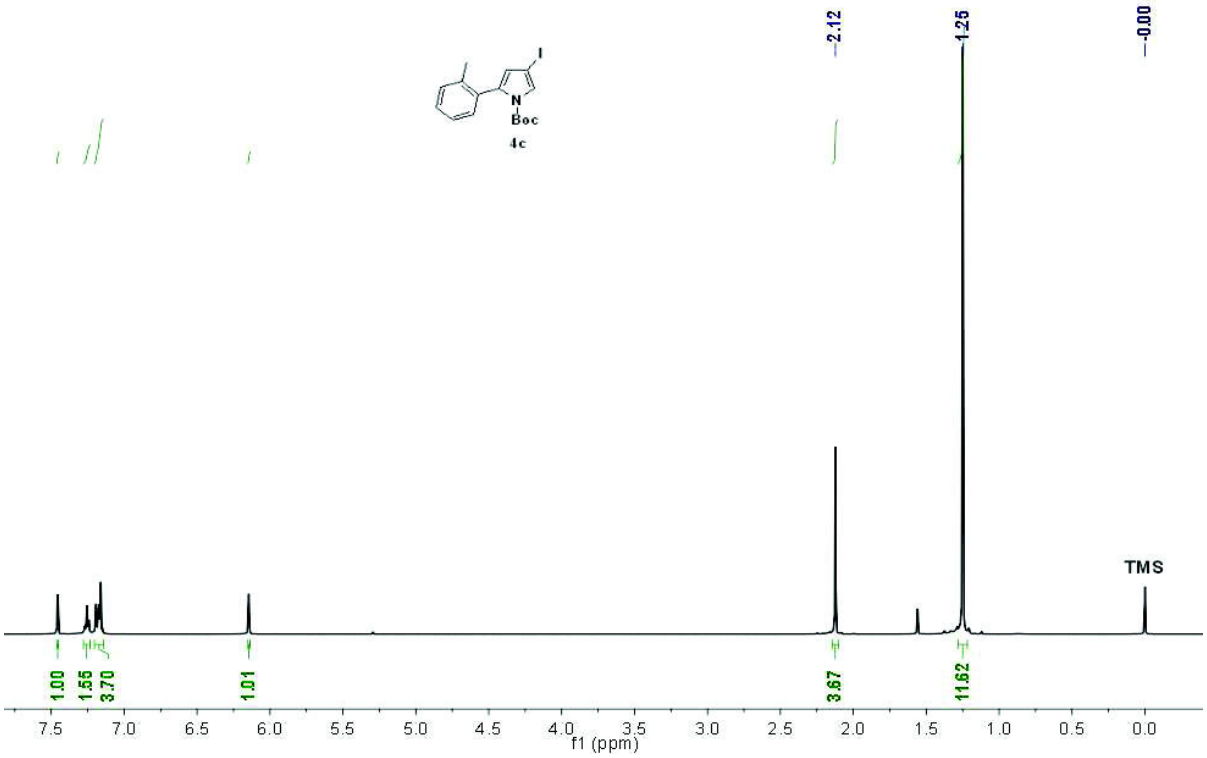
^{13}C NMR of **4b** in $CDCl_3$ at 296 K



^{13}C DEPT 135 of **4b** in $CDCl_3$ at 296 K

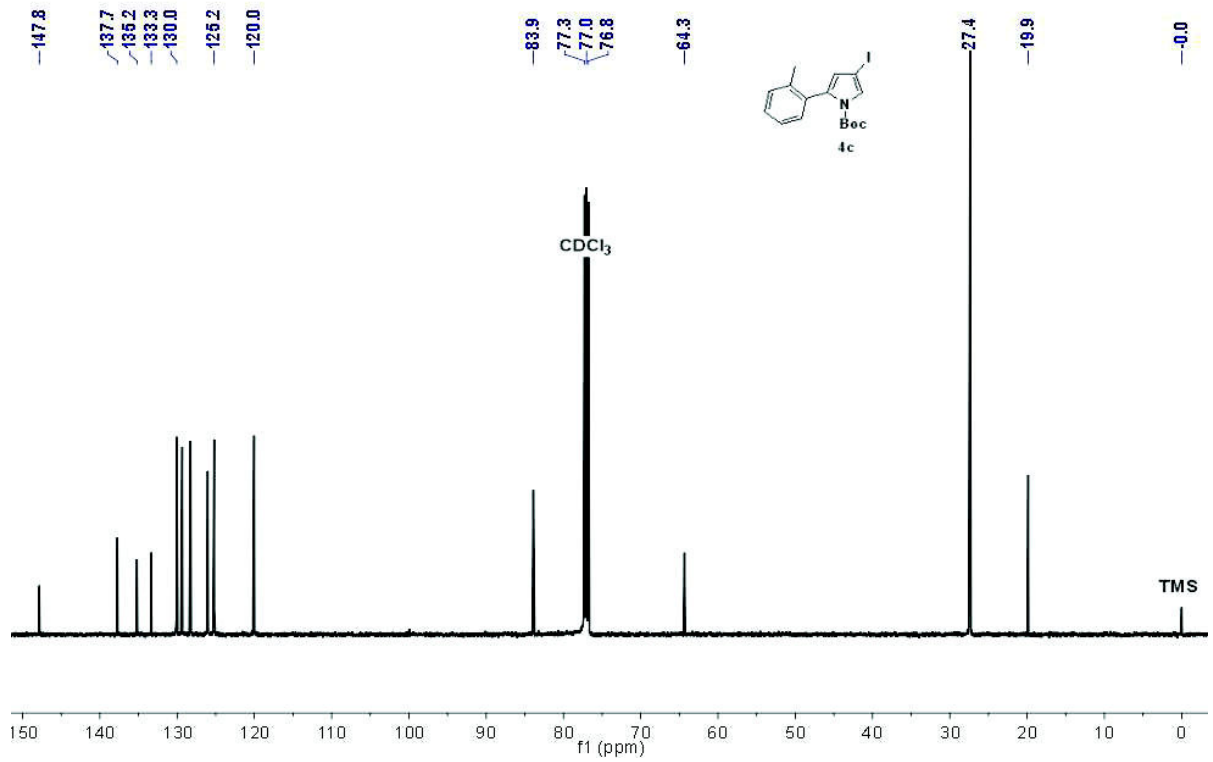


^{1}H NMR of **4c** in $CDCl_3$ at 297 K

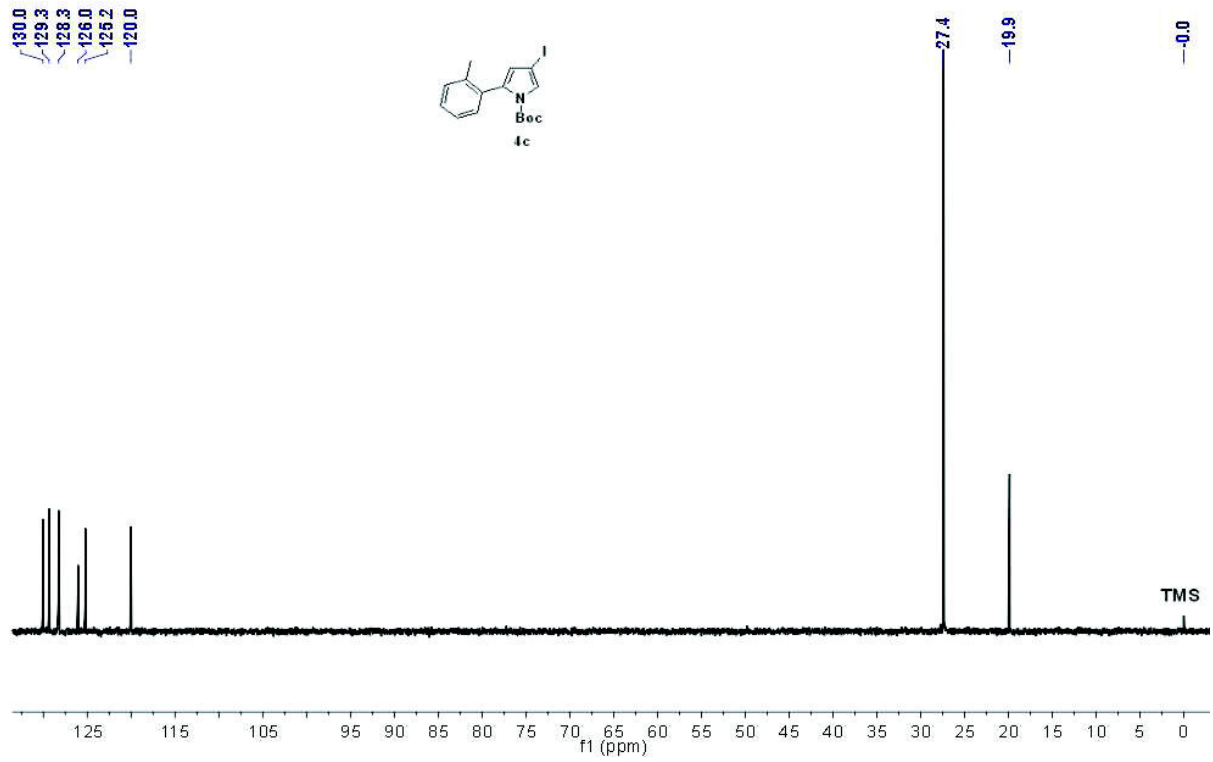


*Impurities from residual solvents.

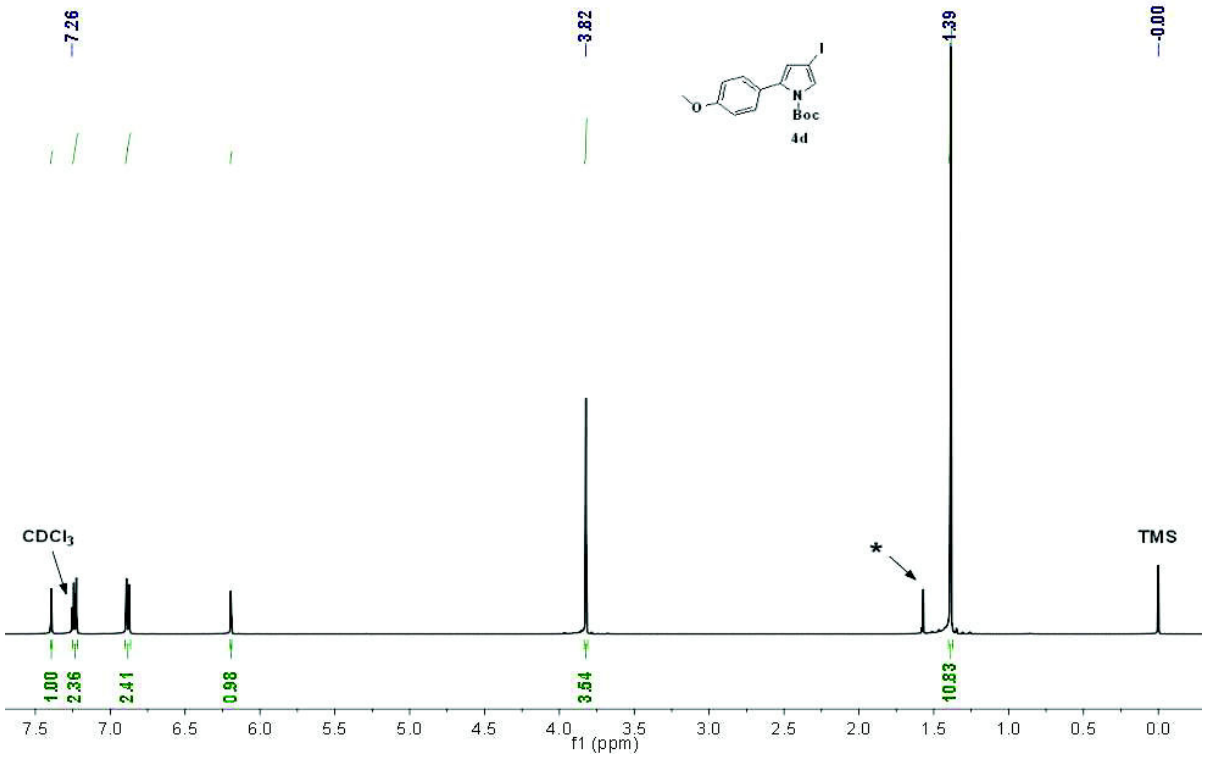
^{13}C NMR of **4c** in $CDCl_3$ at 297 K



^{13}C DEPT 135 of **4c** in $CDCl_3$ at 297 K

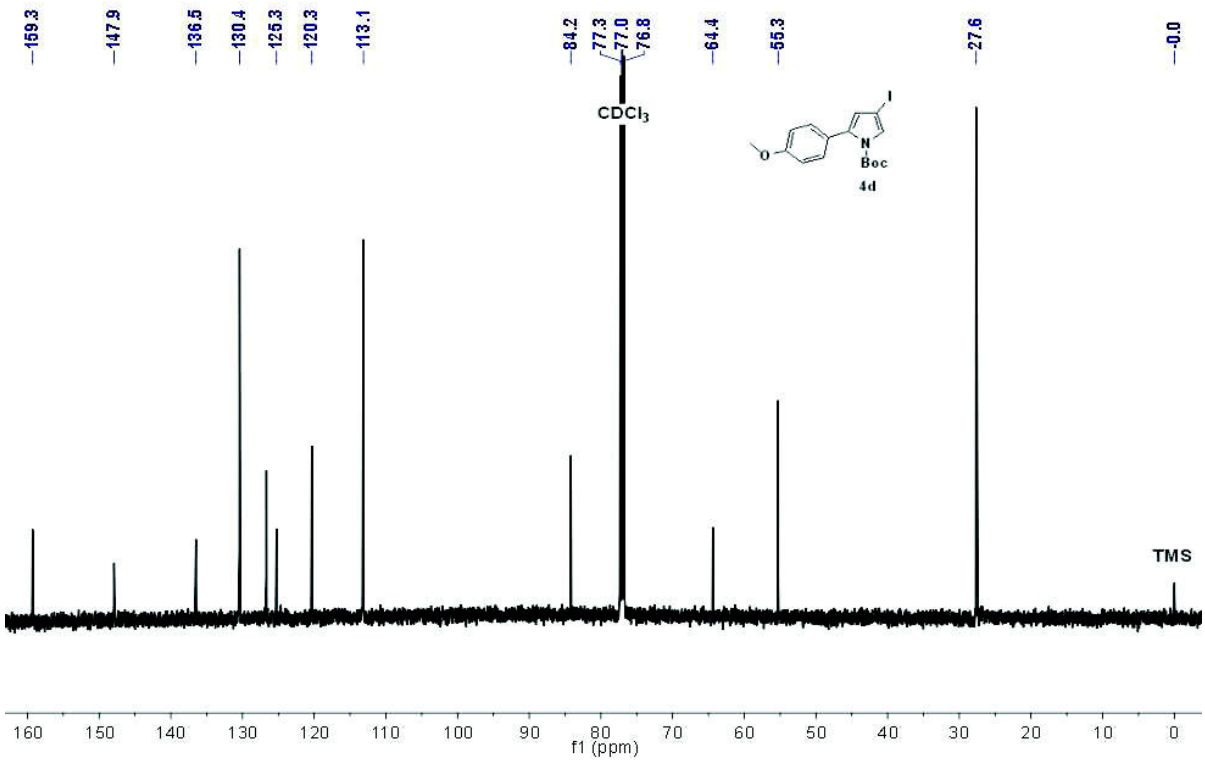


^{1}H NMR of **4d** in $CDCl_3$ at 297 K

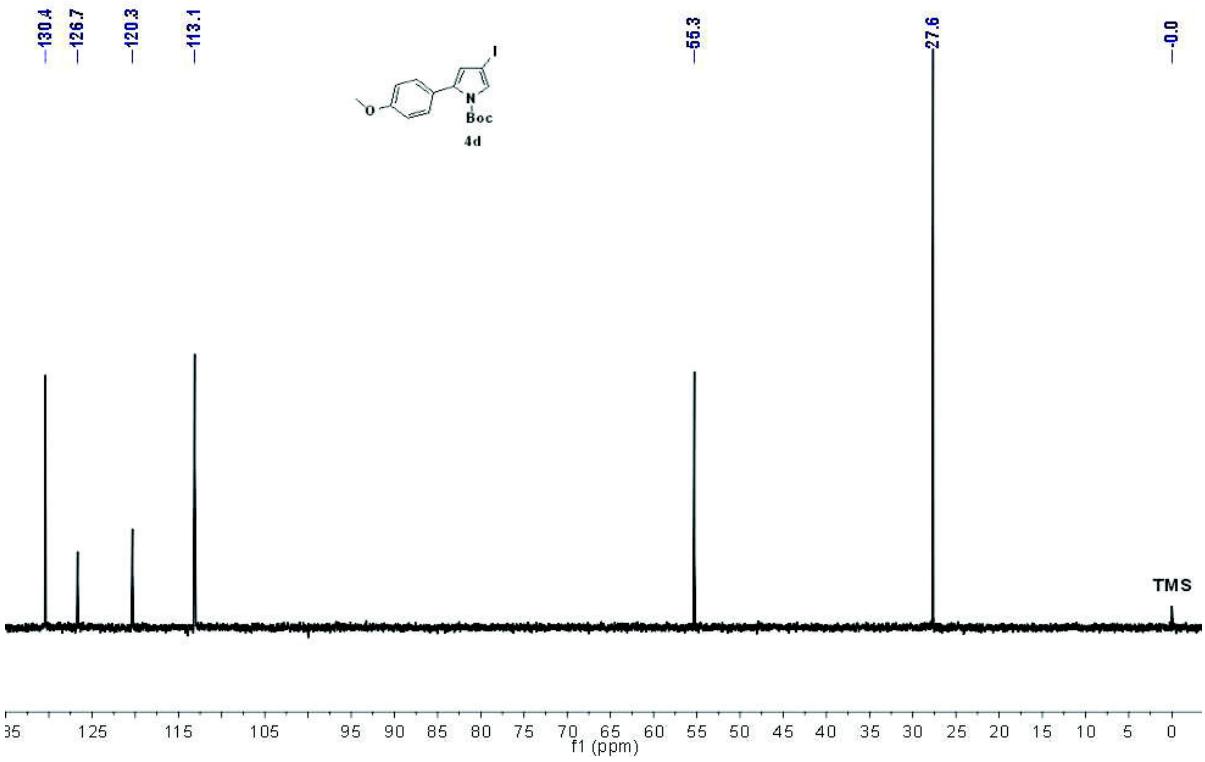


*Impurities from residual solvents.

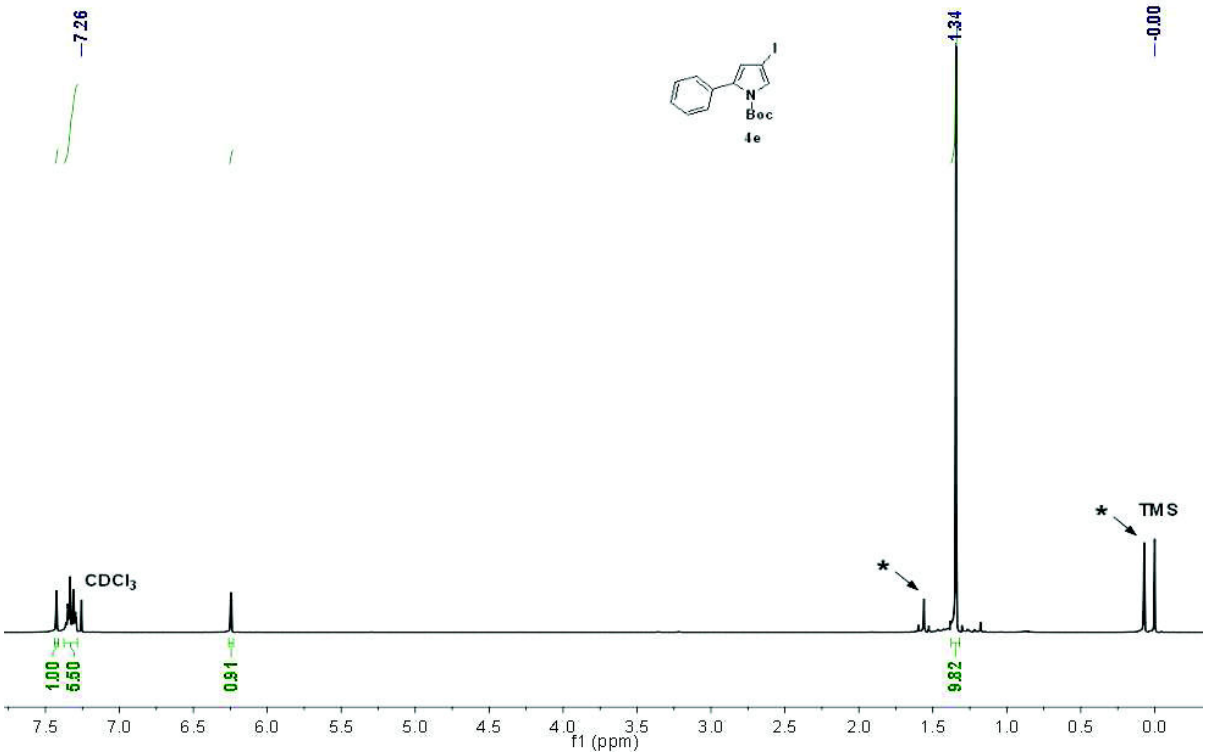
^{13}C NMR of **4d** in $CDCl_3$ at 297 K



^{13}C DEPT 135 of **4d** in $CDCl_3$ at 297 K

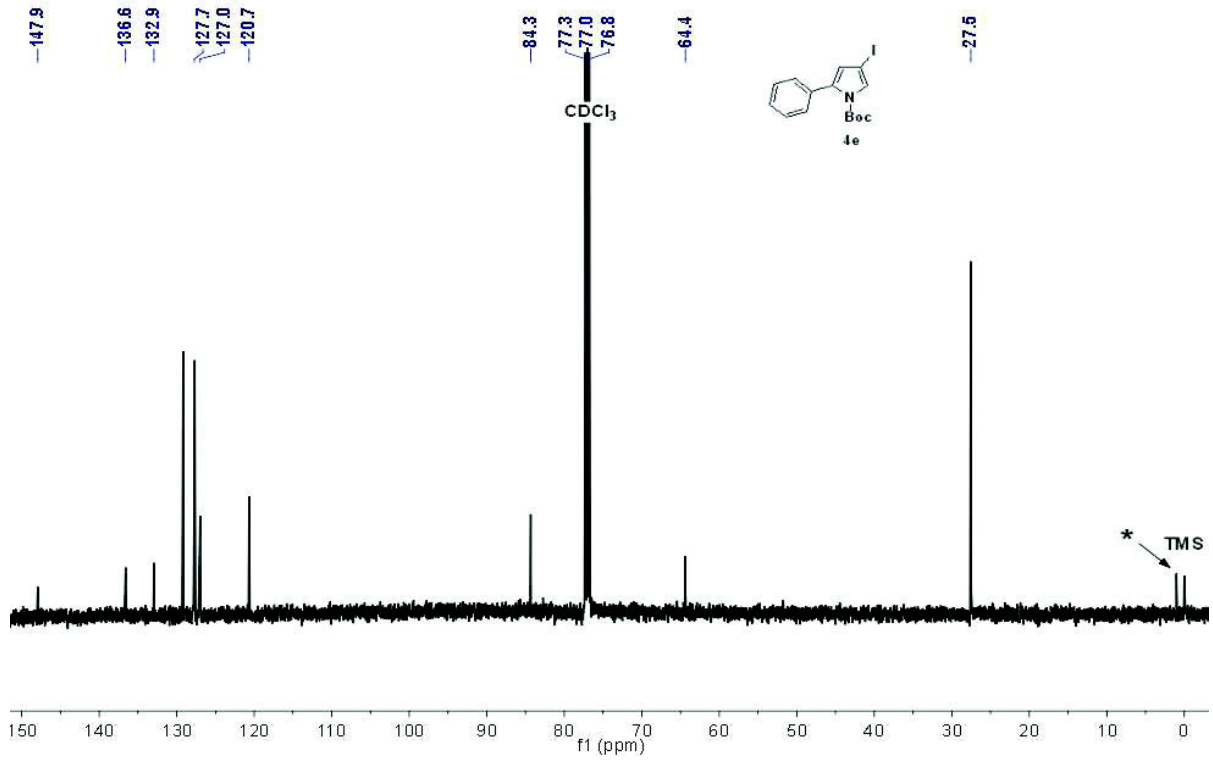


^{1}H NMR of **4e** in $CDCl_3$ at 297 K



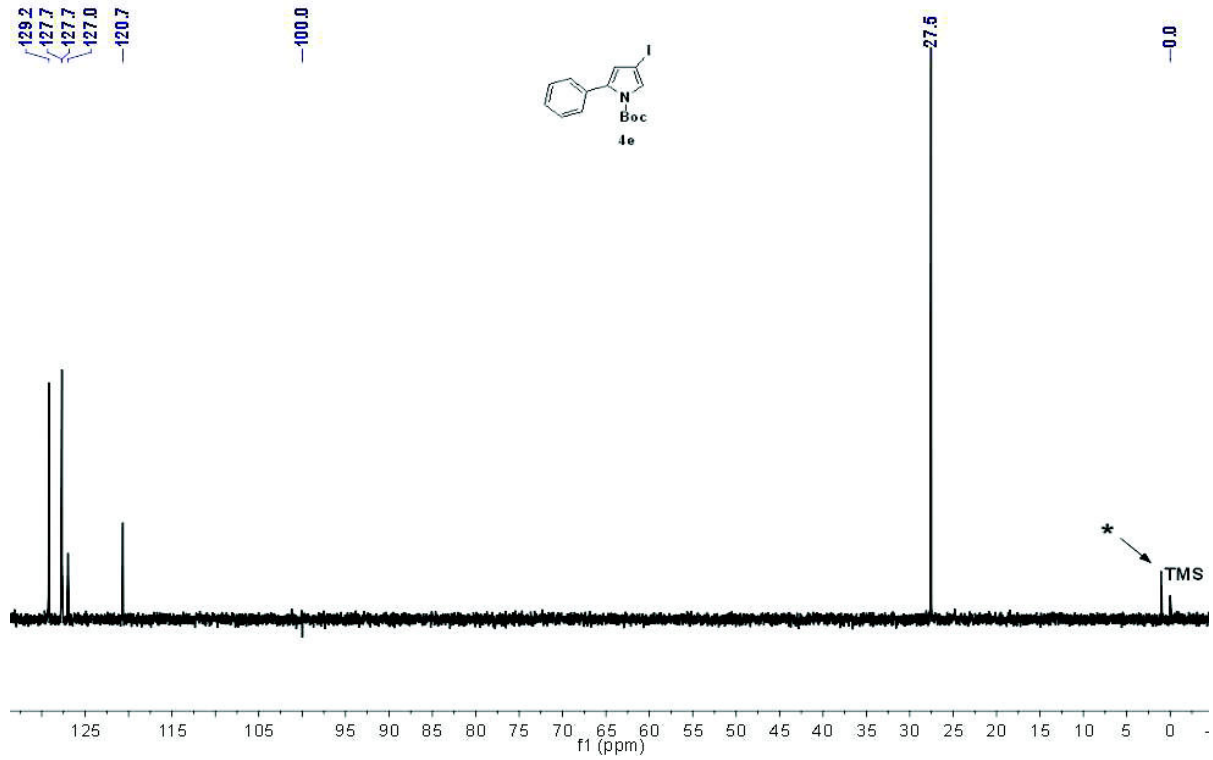
*Impurities from residual solvents.

^{13}C NMR of **4e** in $CDCl_3$ at 297 K



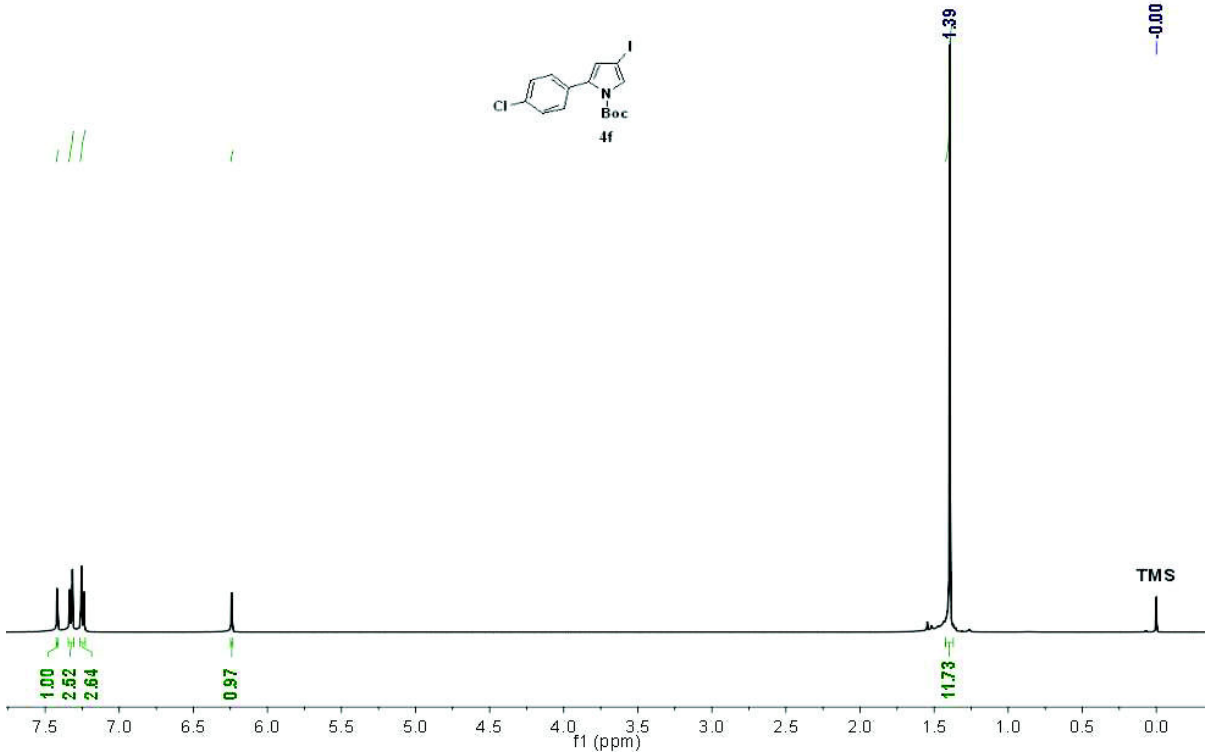
*Impurities from residual solvents.

^{13}C DEPT 135 of **4e** in $CDCl_3$ at 298 K

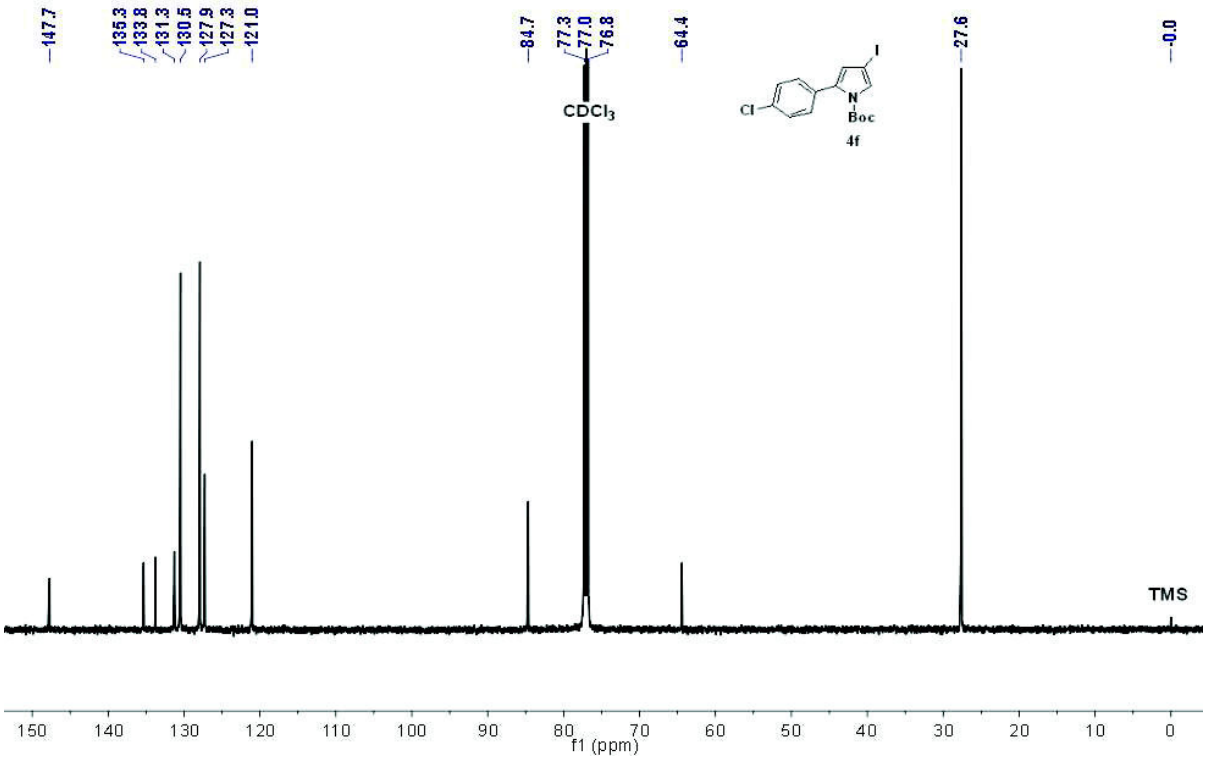


*Impurities from residual solvents.

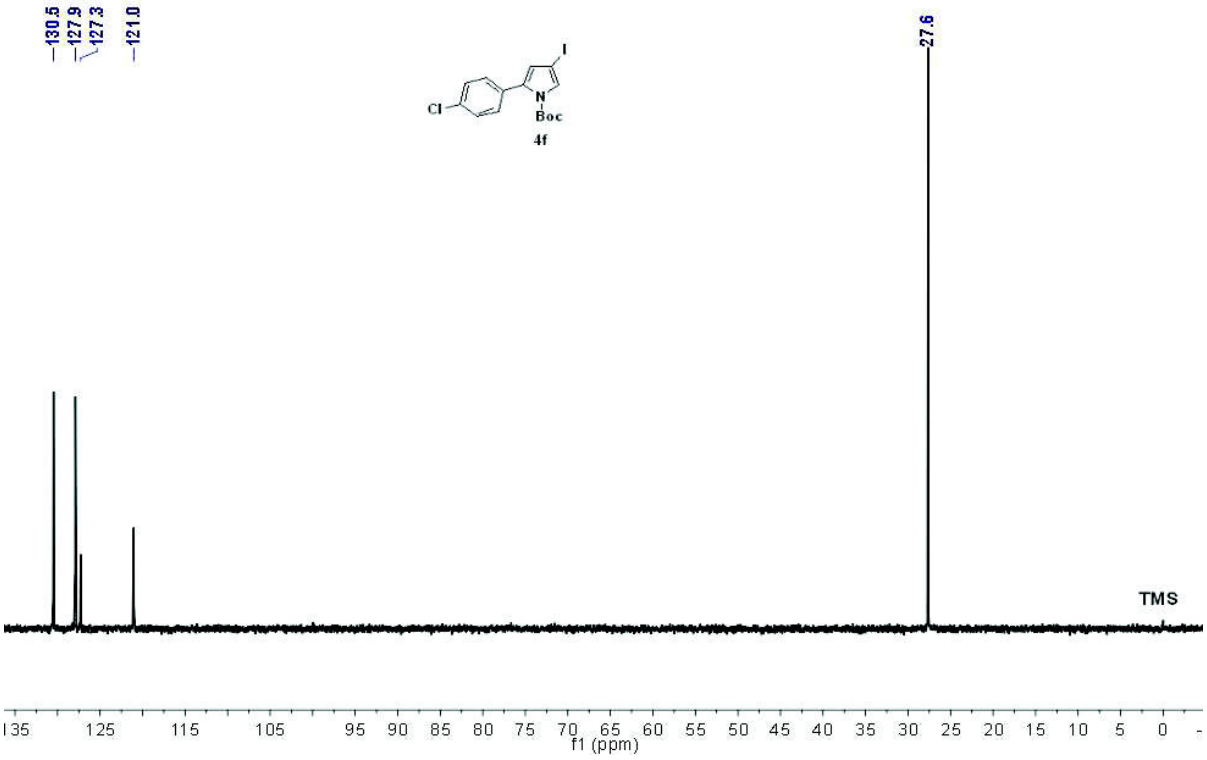
^{1}H NMR of **4f** in $CDCl_3$ at 297 K



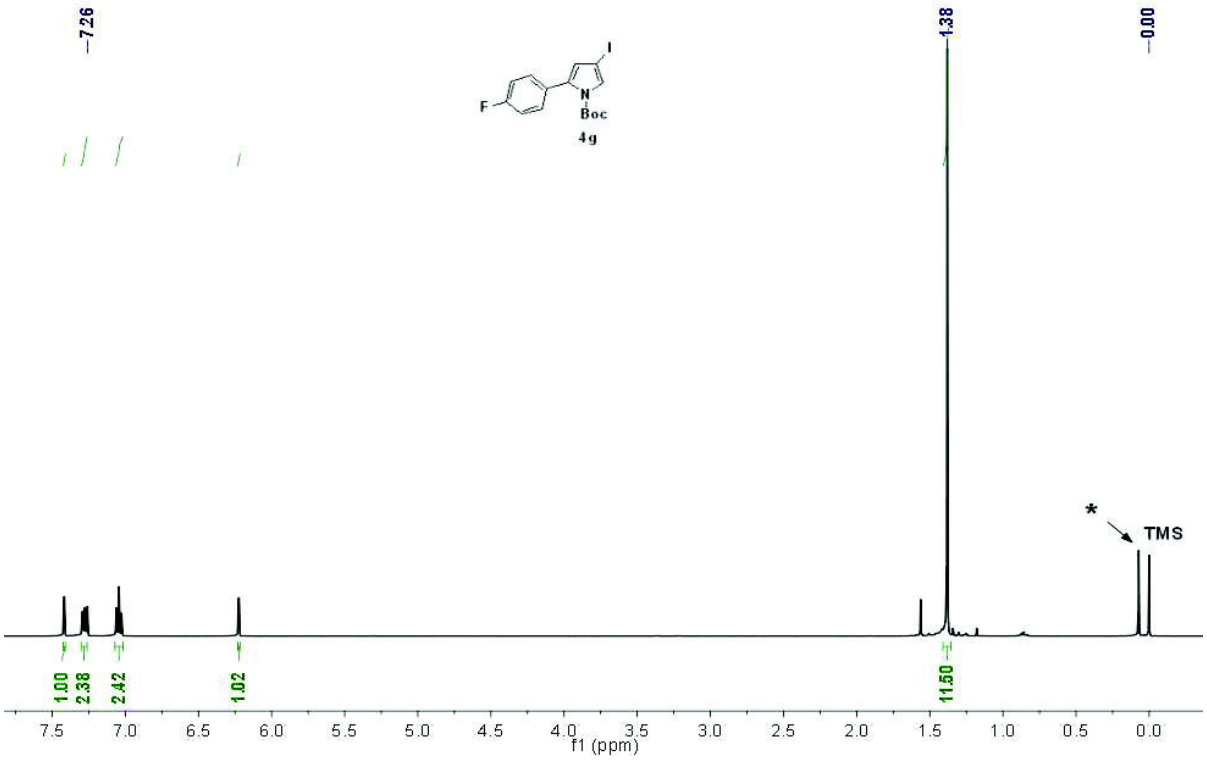
^{13}C NMR of **4f** in $CDCl_3$ at 297 K



^{13}C DEPT 135 of **4f** in $CDCl_3$ at 297 K

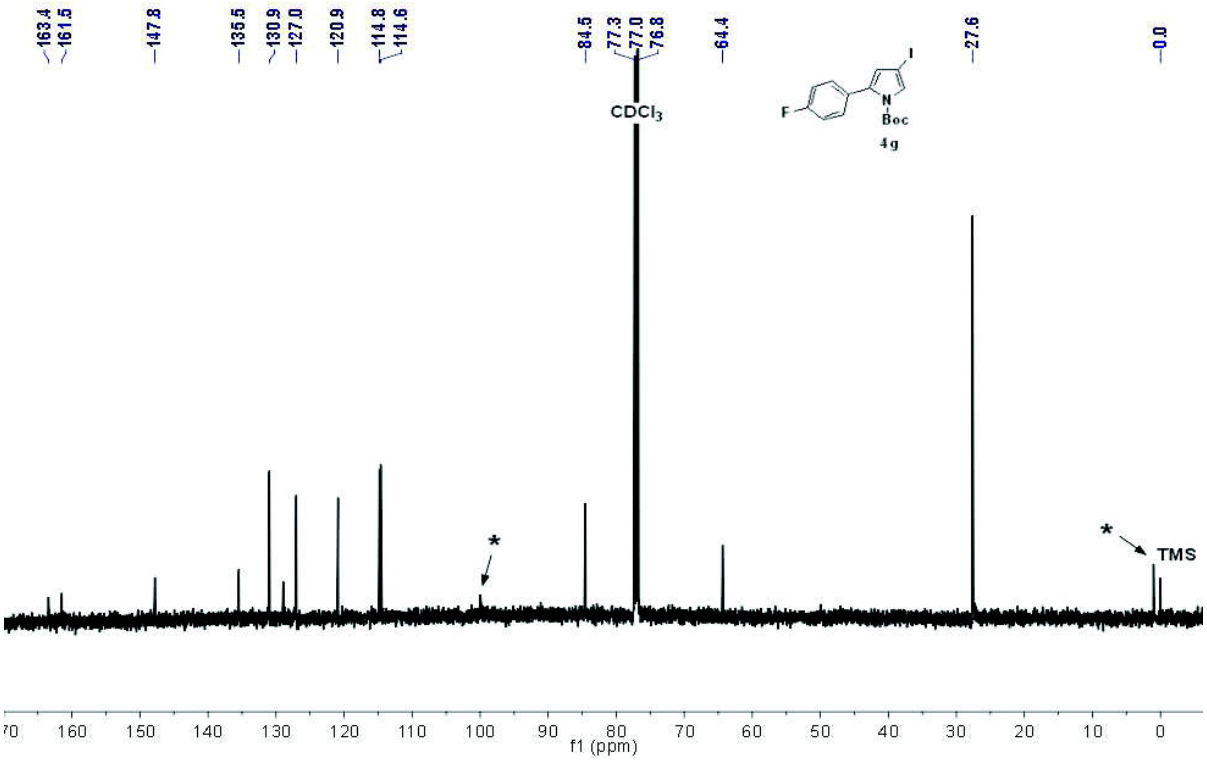


^{1}H NMR of **4g** in $CDCl_3$ at 297 K



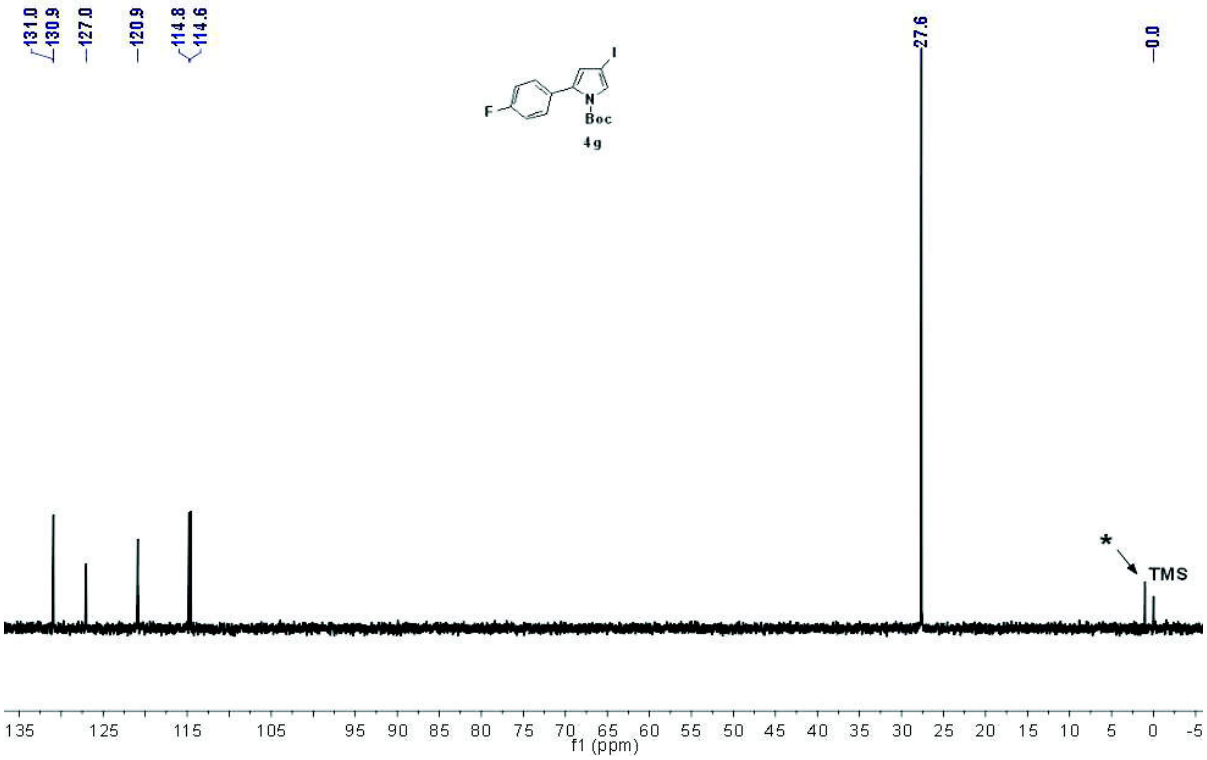
*Impurities from residual solvents.

^{13}C NMR of **4g** in $CDCl_3$ at 298 K



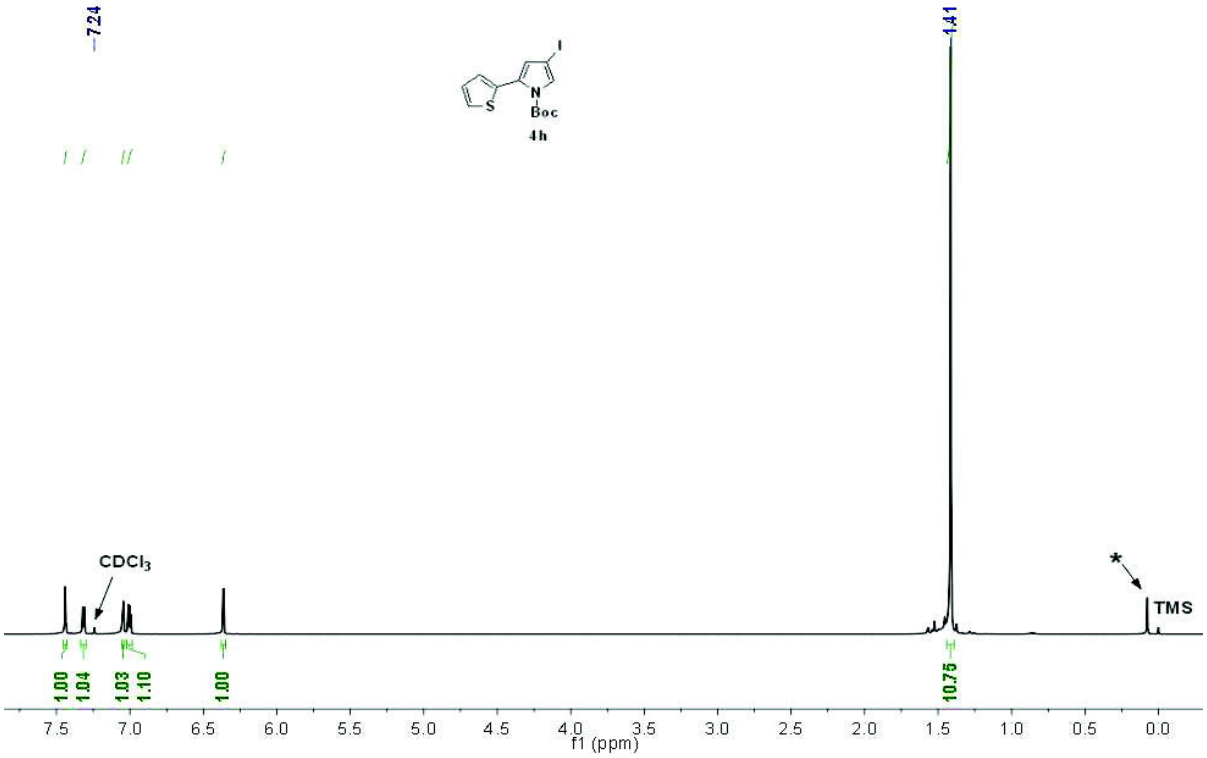
*Impurities from residual solvents.

^{13}C DEPT 135 of **4g** in $CDCl_3$ at 298 K



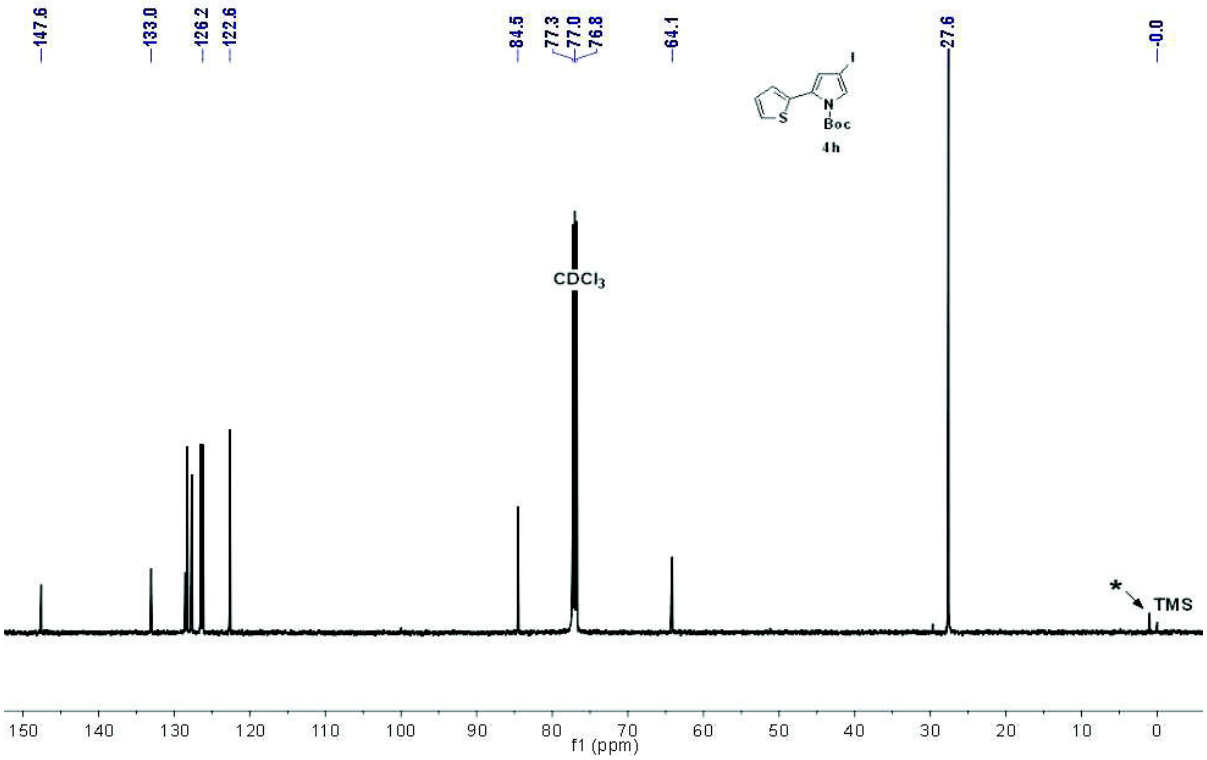
*Impurities from residual solvents.

^{1}H NMR of **4h** in $CDCl_3$ at 298 K



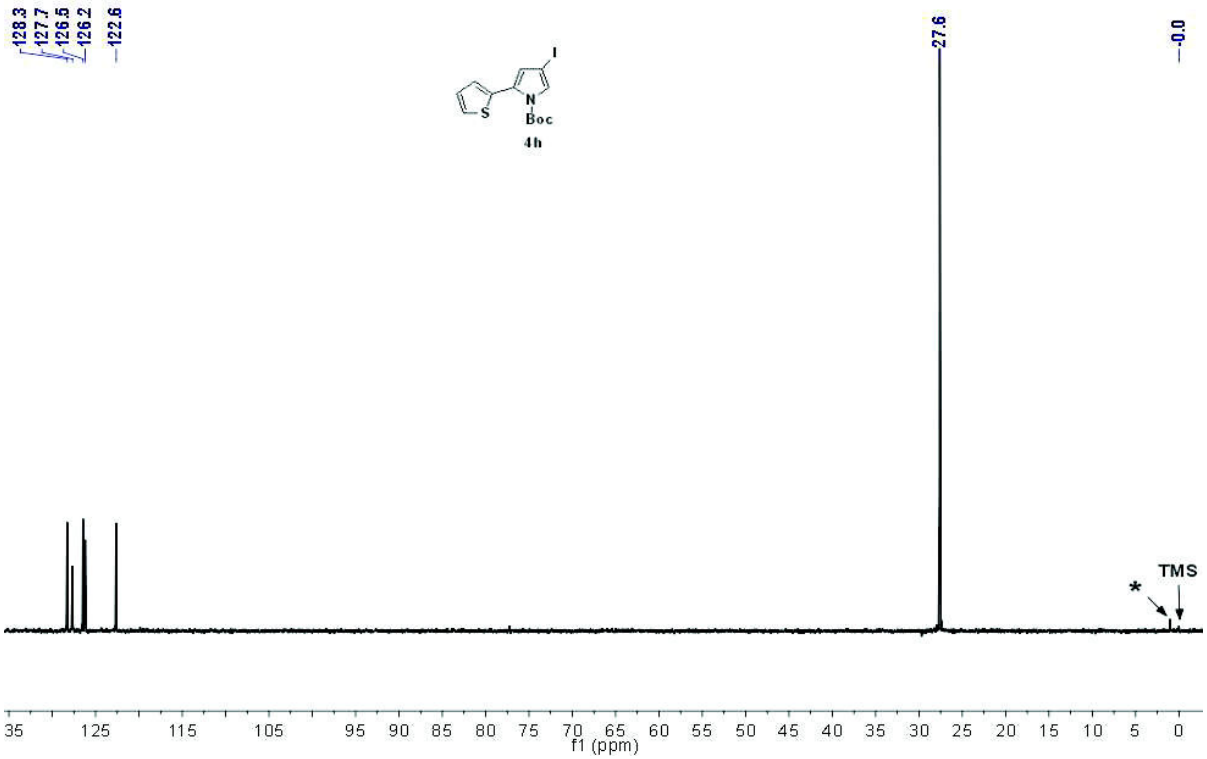
*Impurities from residual solvents.

^{13}C NMR of **4h** in $CDCl_3$ at 297 K



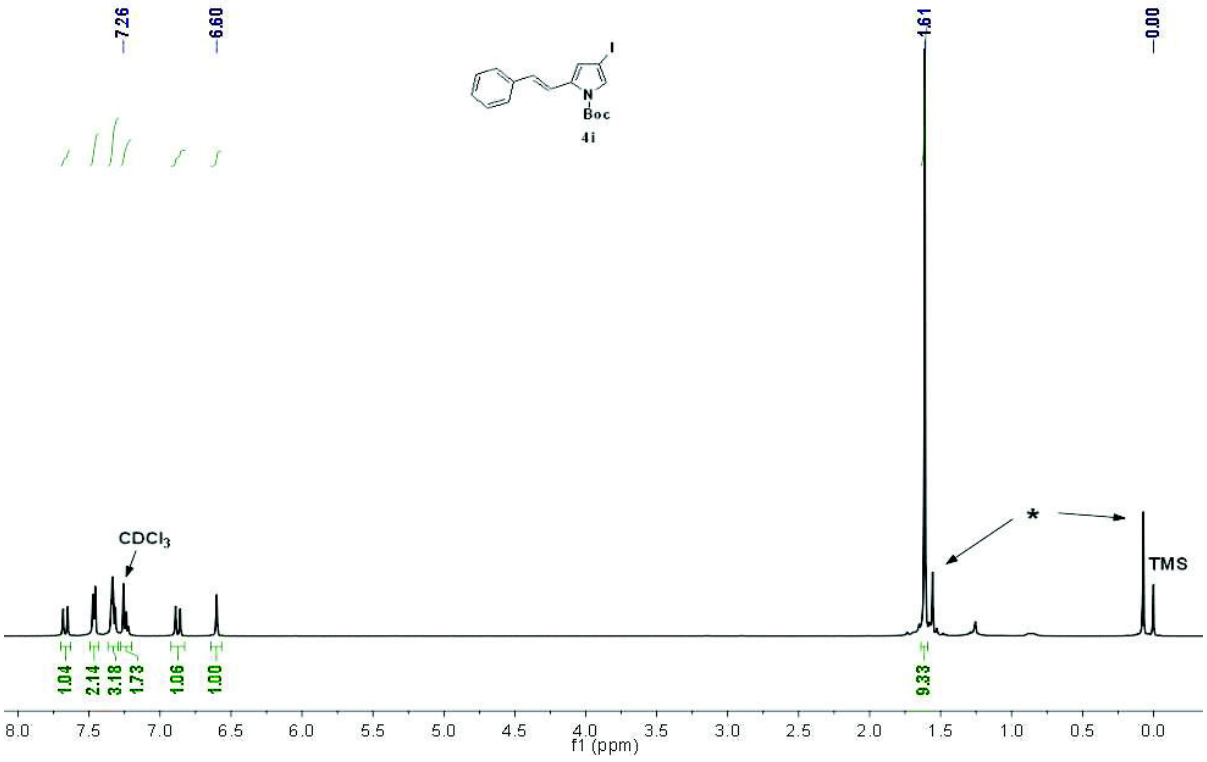
*Impurities from residual solvents.

^{13}C DEPT 135 of **4h** in $CDCl_3$ at 297 K



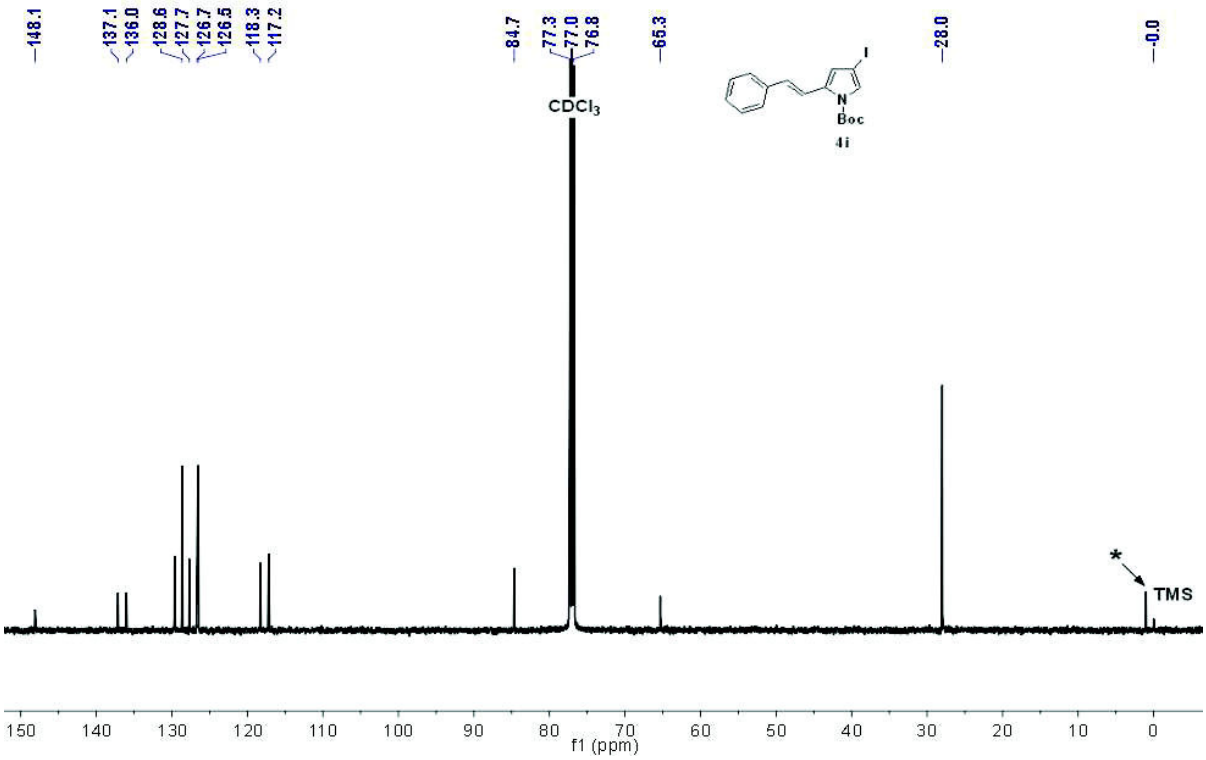
*Impurities from residual solvents.

^{1}H NMR of **4i** in $CDCl_3$ at 297 K



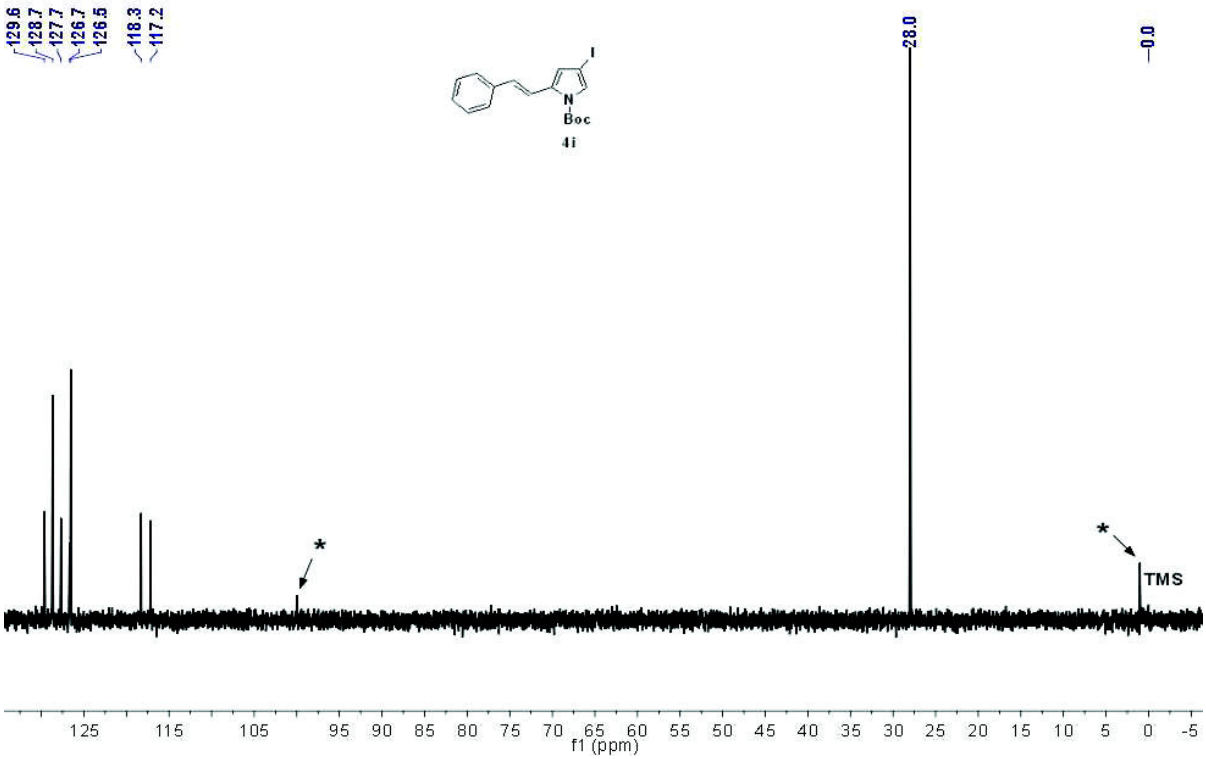
*Impurities from residual solvents.

^{13}C NMR of **4i** in $CDCl_3$ at 297 K



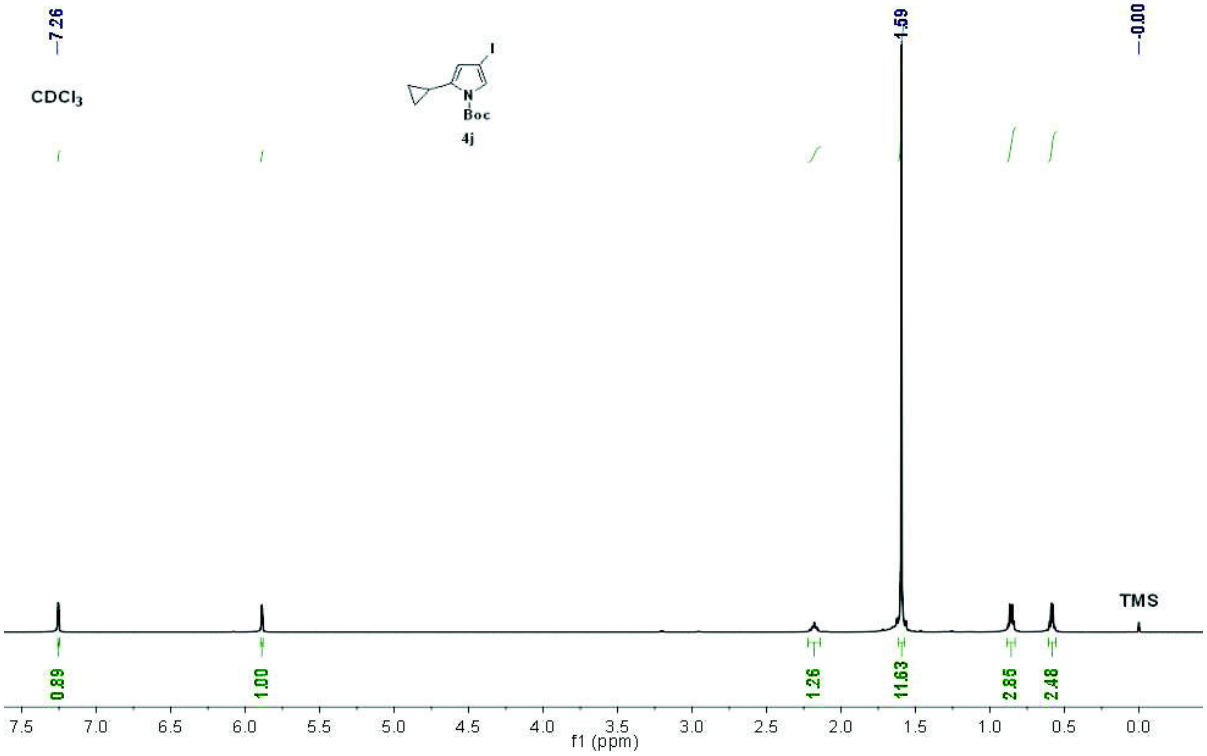
*Impurities from residual solvents.

^{13}C DEPT 135 of **4i** in $CDCl_3$ at 297 K

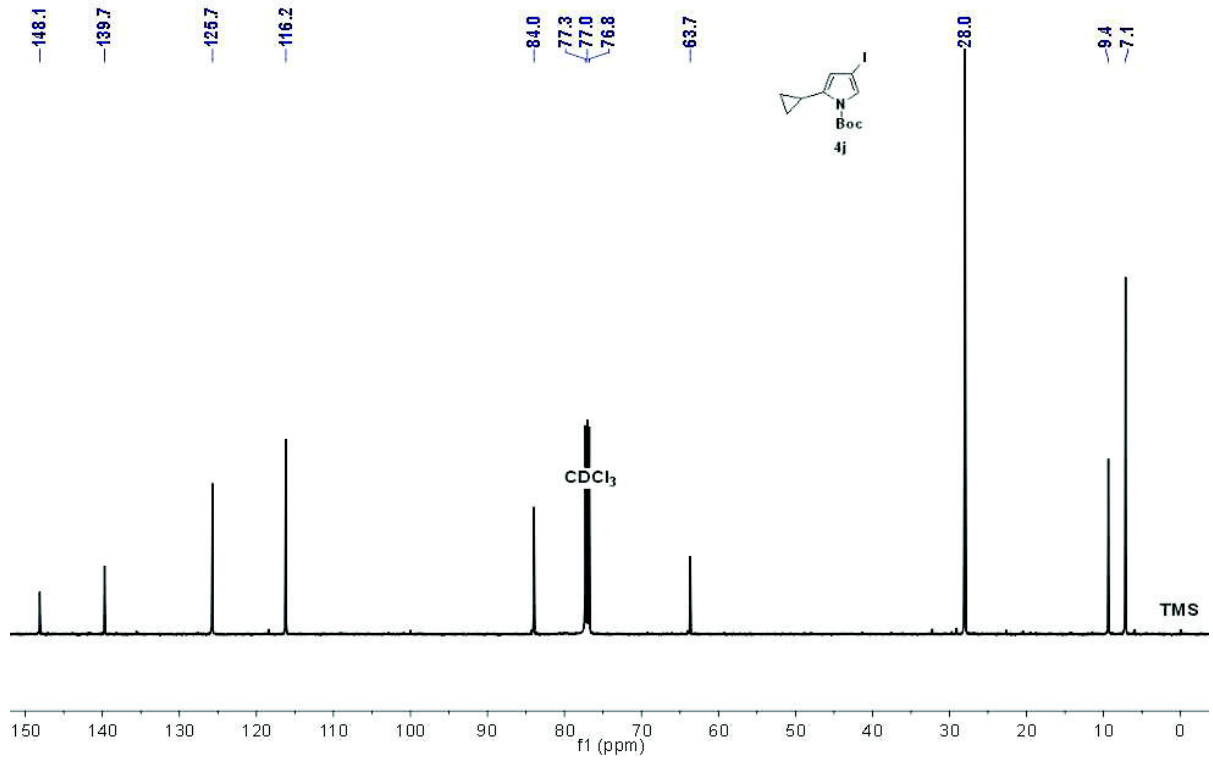


*Impurities from residual solvents.

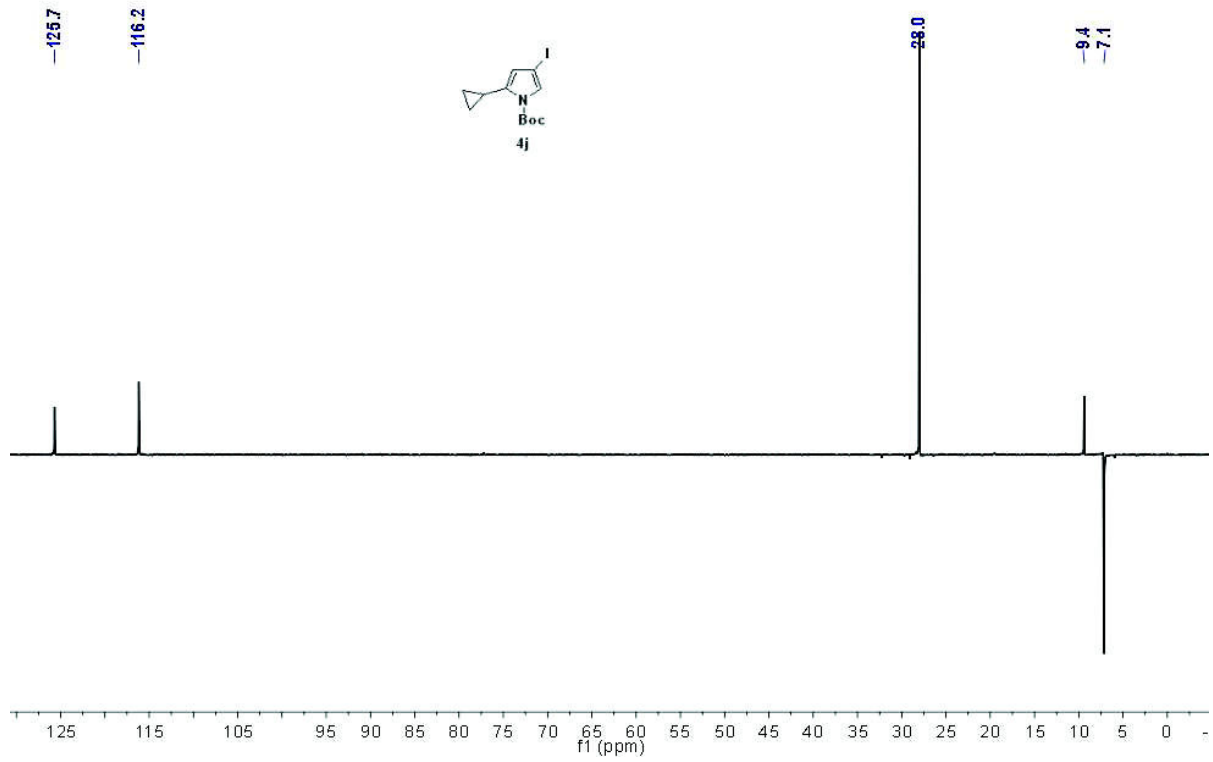
^{1}H NMR of **4j** in $CDCl_3$ at 297 K



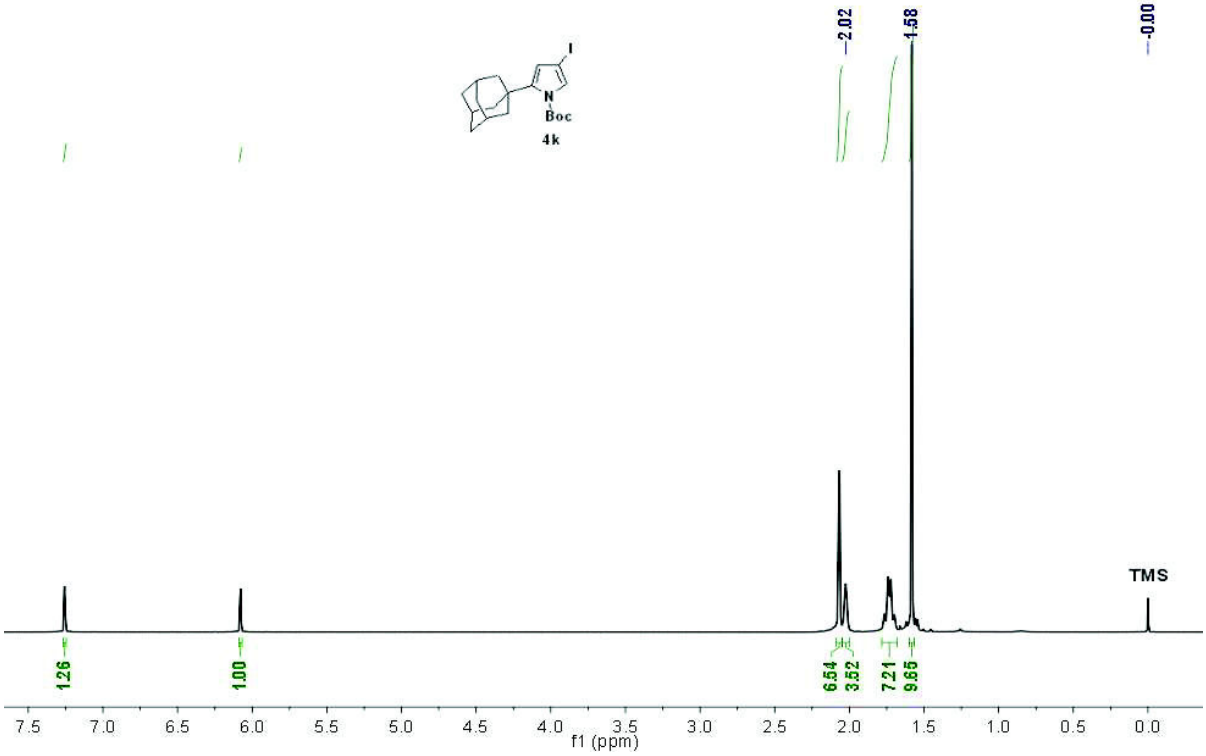
^{13}C NMR of **4j** in $CDCl_3$ at 297 K



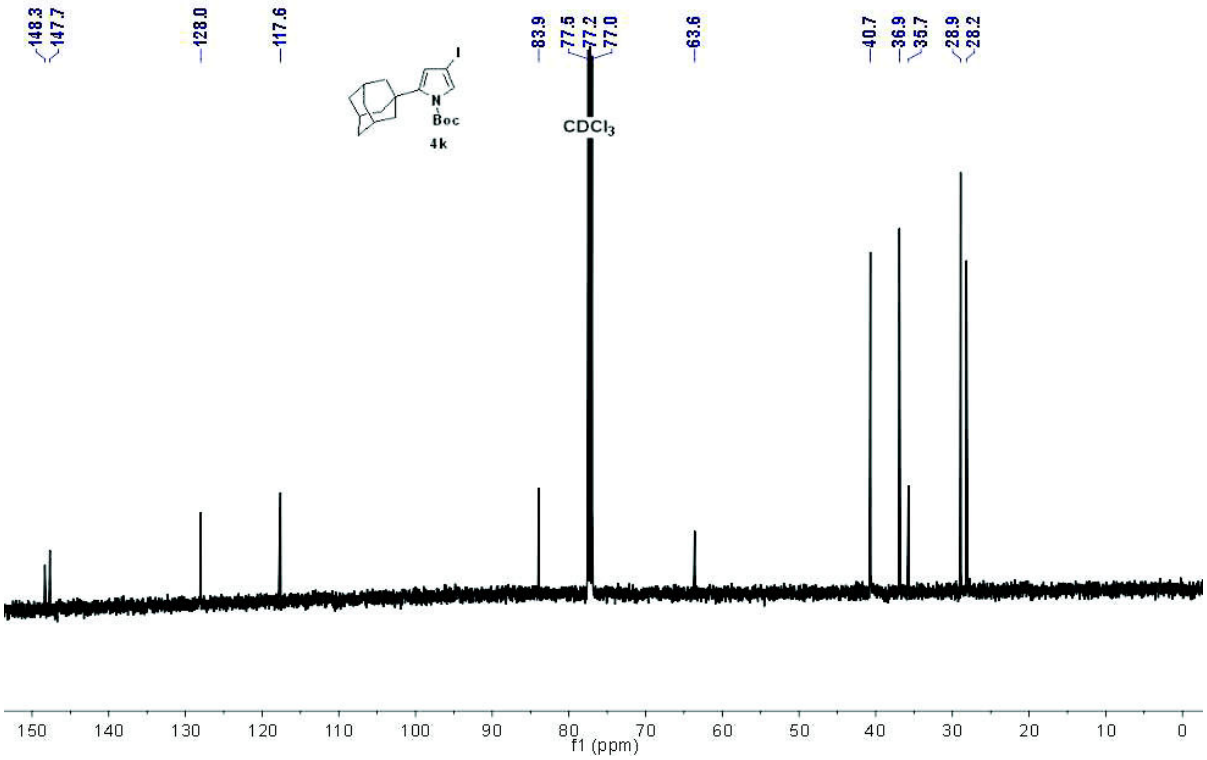
^{13}C DEPT 135 of **4j** in $CDCl_3$ at 297 K



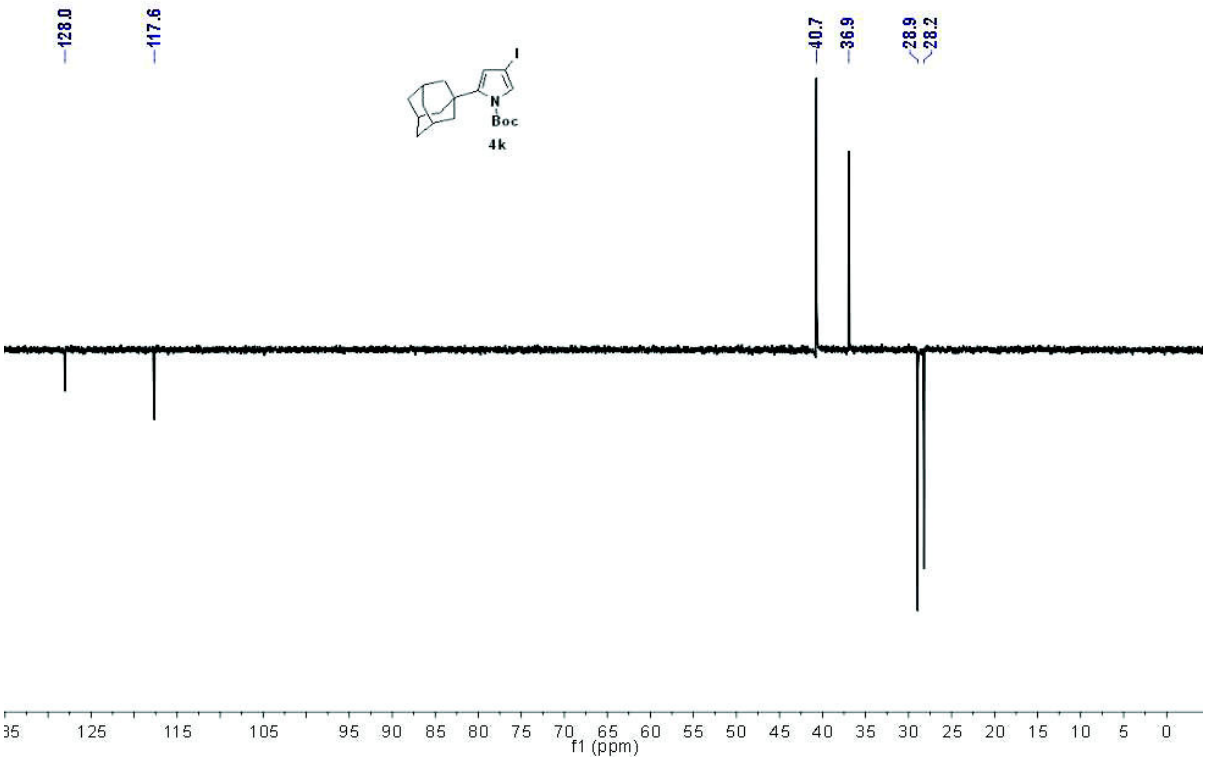
^{1}H NMR of **4k** in $CDCl_3$ at 298 K



^{13}C NMR of **4k** in $CDCl_3$ at 298 K

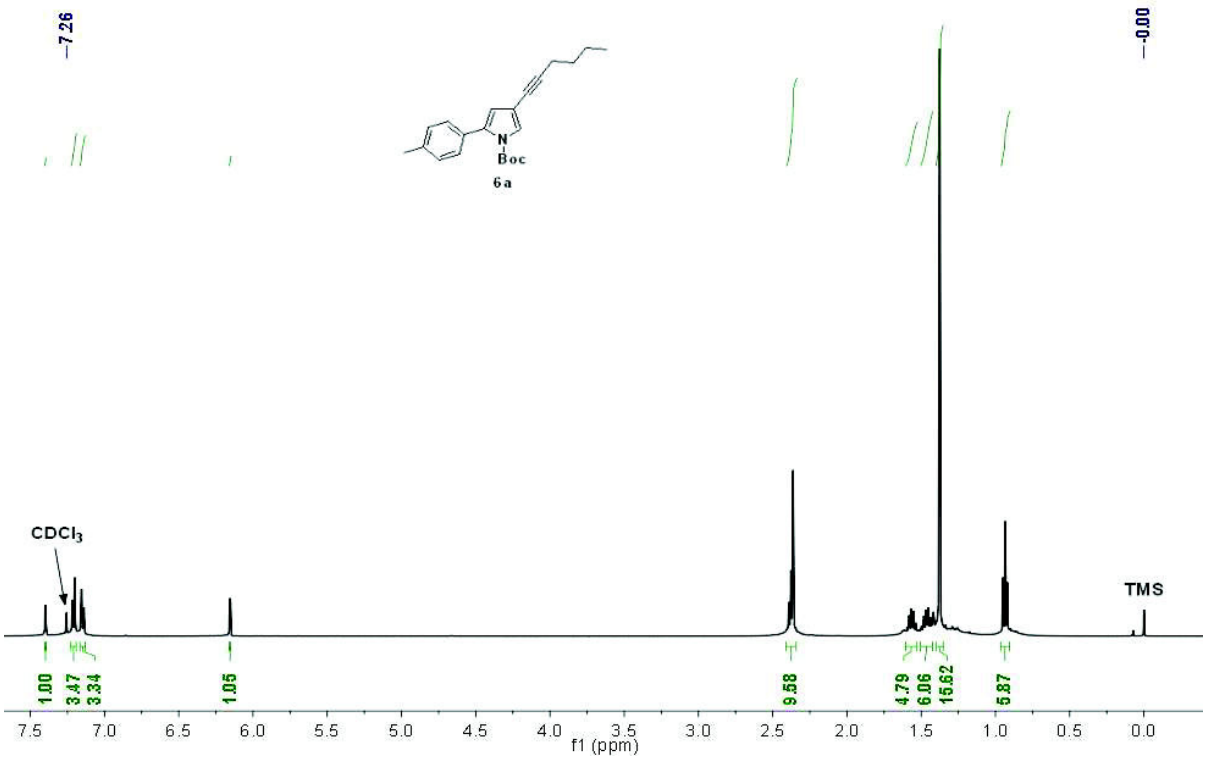


^{13}C DEPT 135 of **4k** in $CDCl_3$ at 298 K

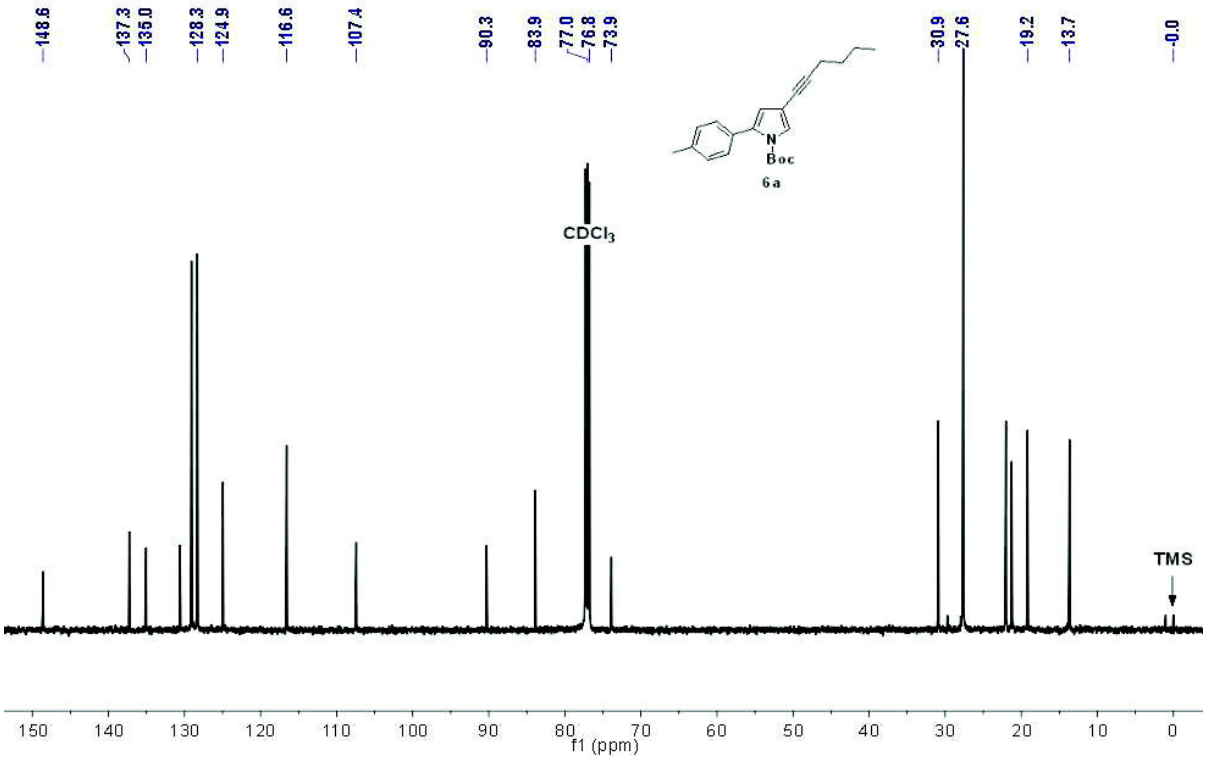


5.3. ^{1}H and ^{13}C NMR Spectra of Compounds 6

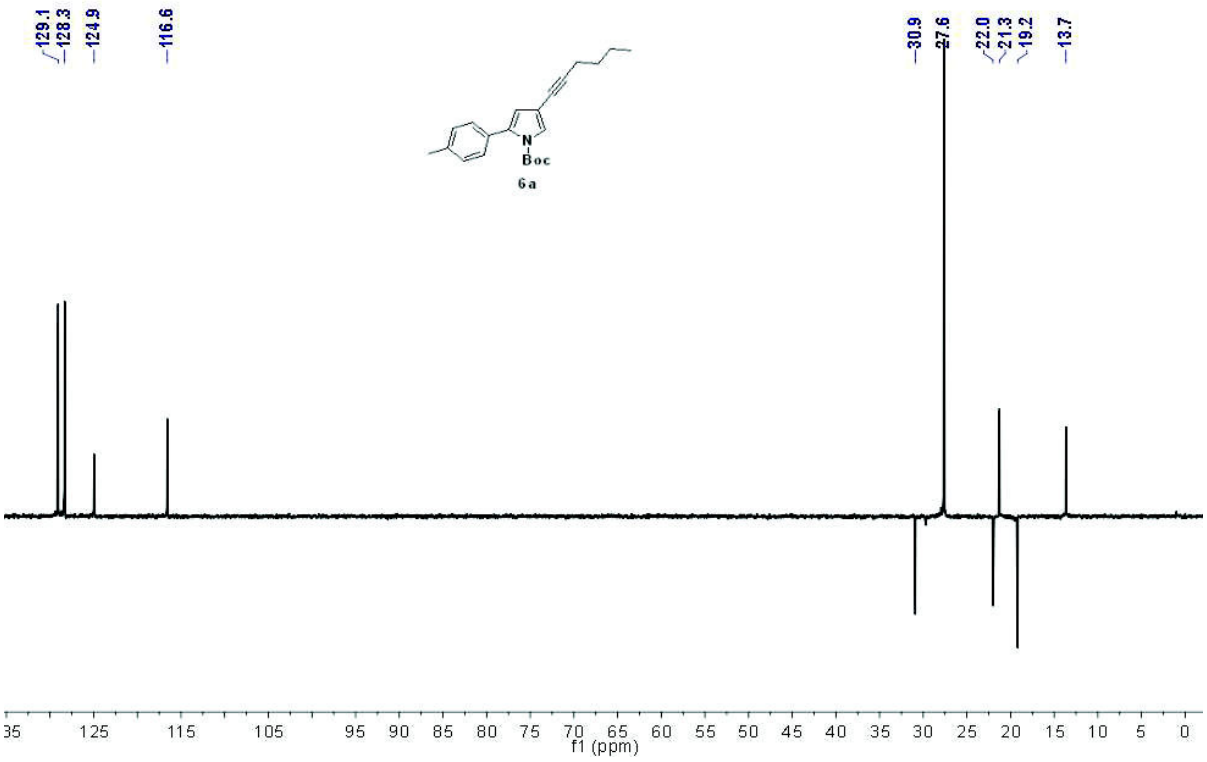
^{1}H NMR of **6a** in $CDCl_3$ at 297 K



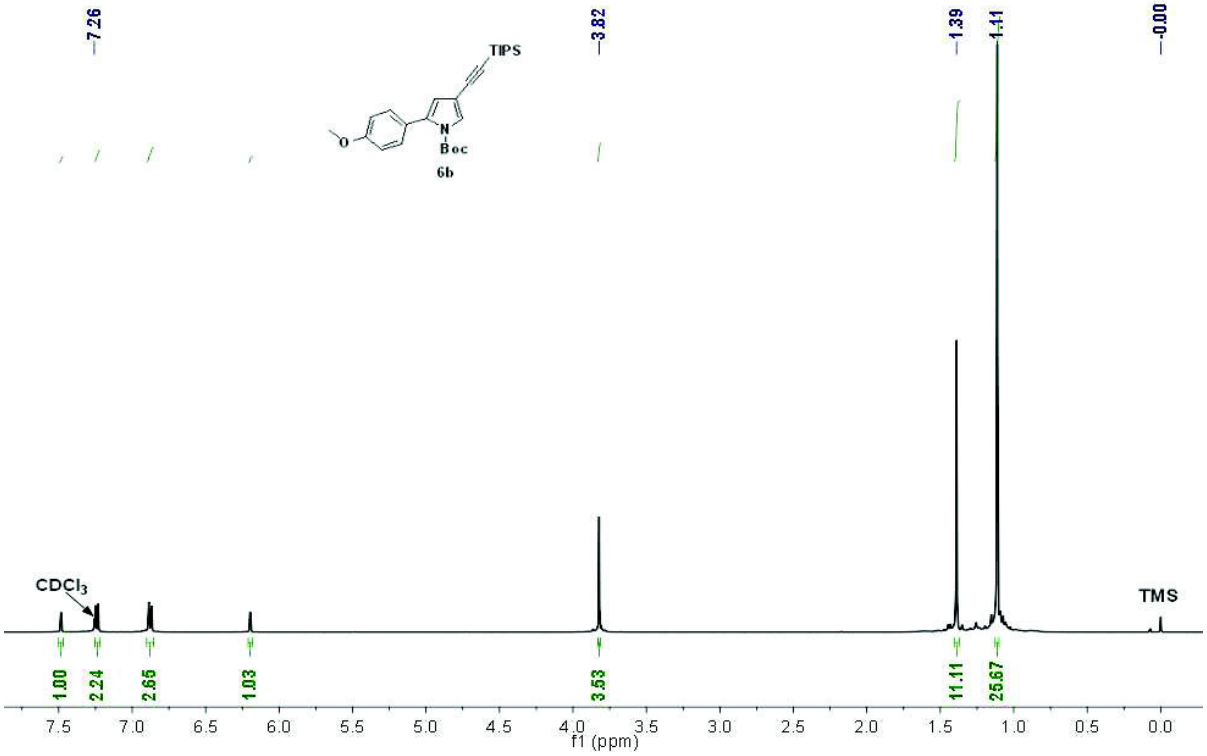
^{13}C NMR of **6a** in $CDCl_3$ at 296 K



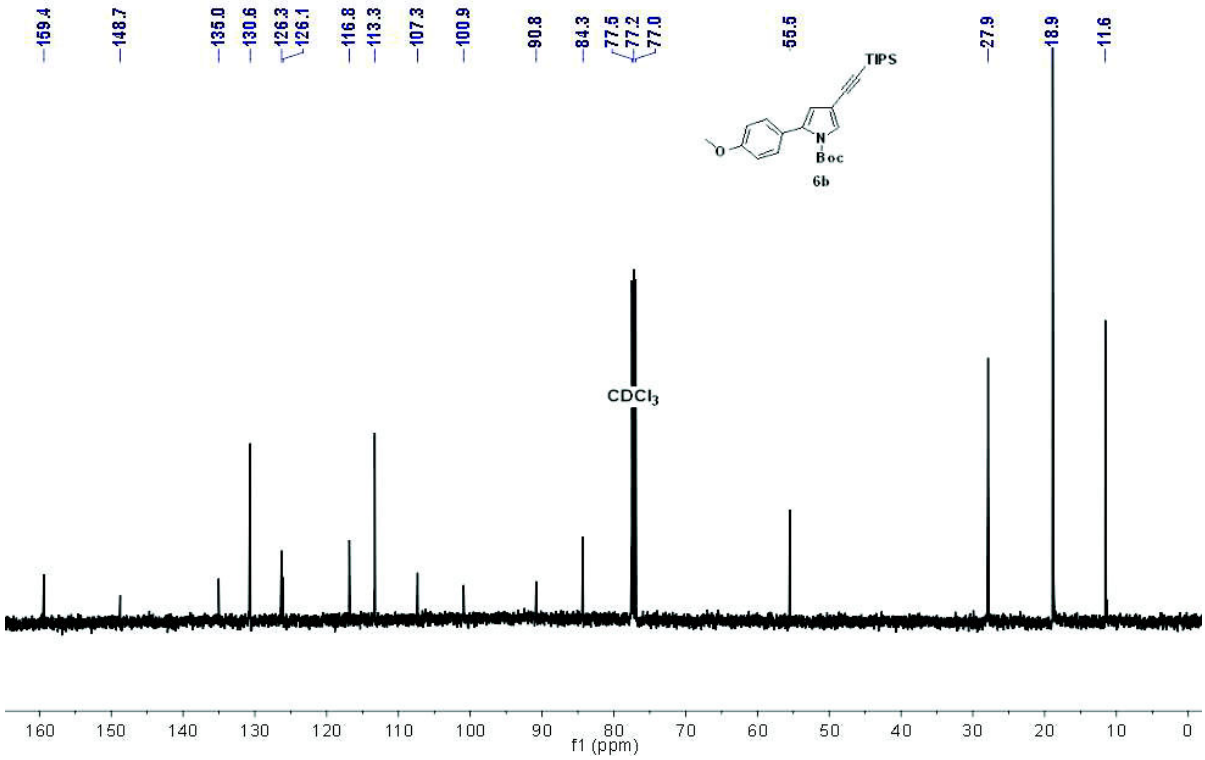
^{13}C DEPT 135 of **6a** in $CDCl_3$ at 296 K



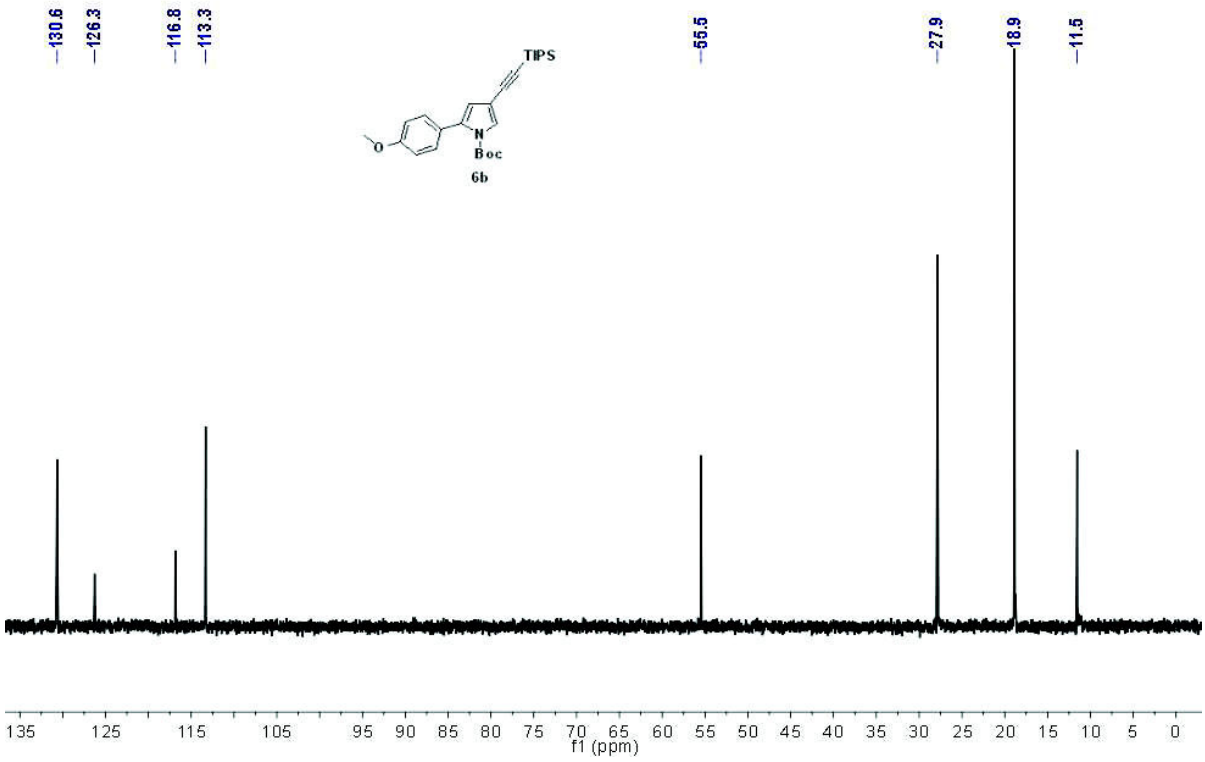
^{1}H NMR of **6b** in $CDCl_3$ at 298 K



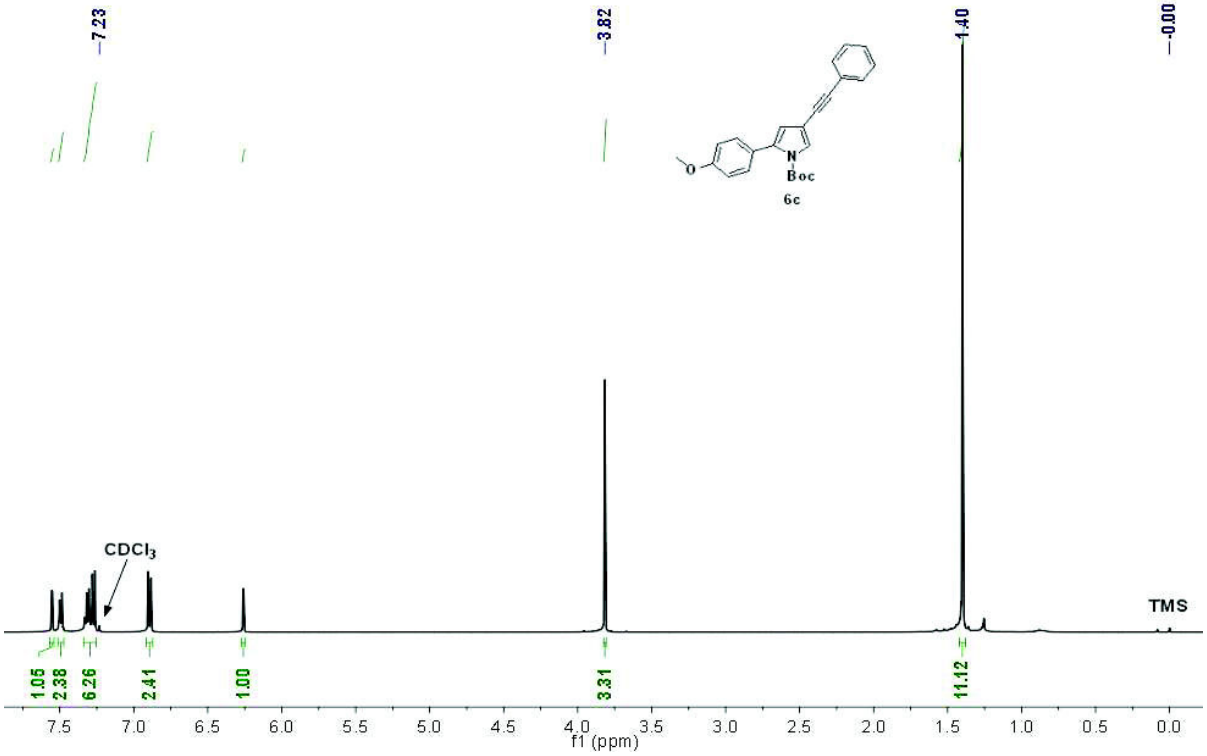
^{13}C NMR of **6b** in $CDCl_3$ at 298 K



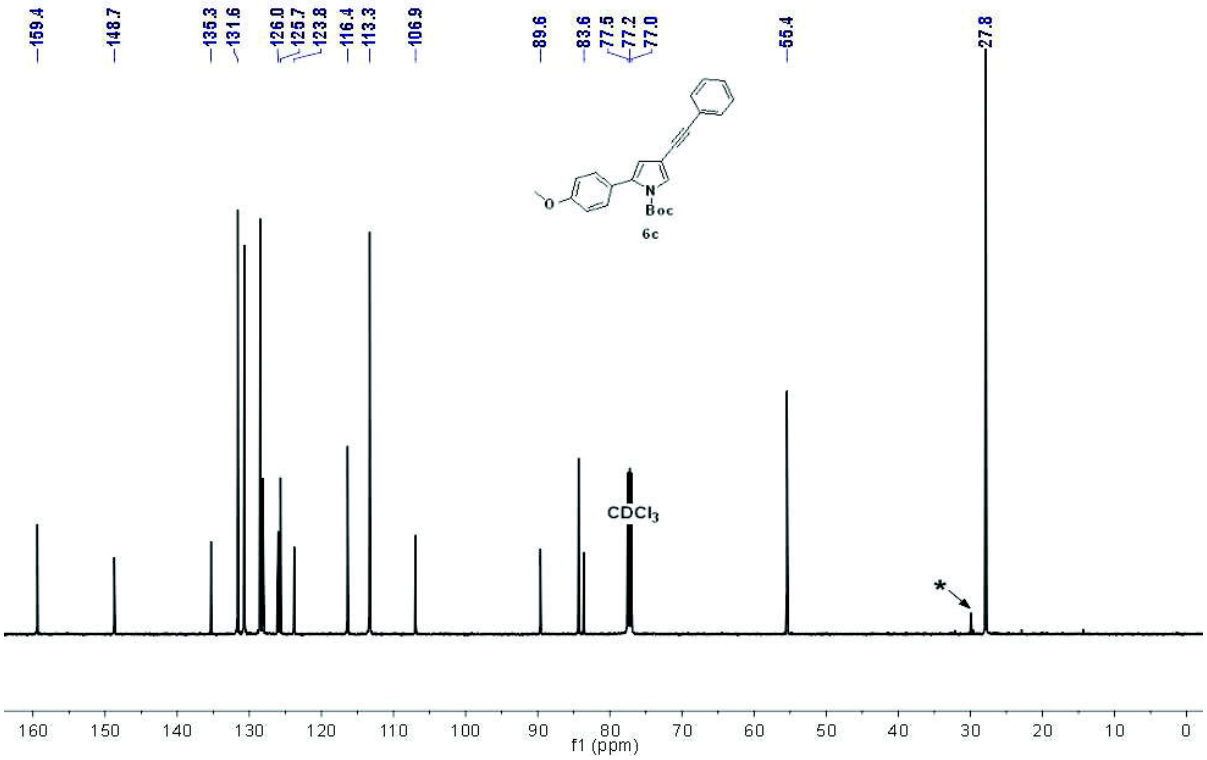
^{13}C DEPT 135 of **6b** in $CDCl_3$ at 298 K



^{1}H NMR of **6c** in $CDCl_3$ at 296 K

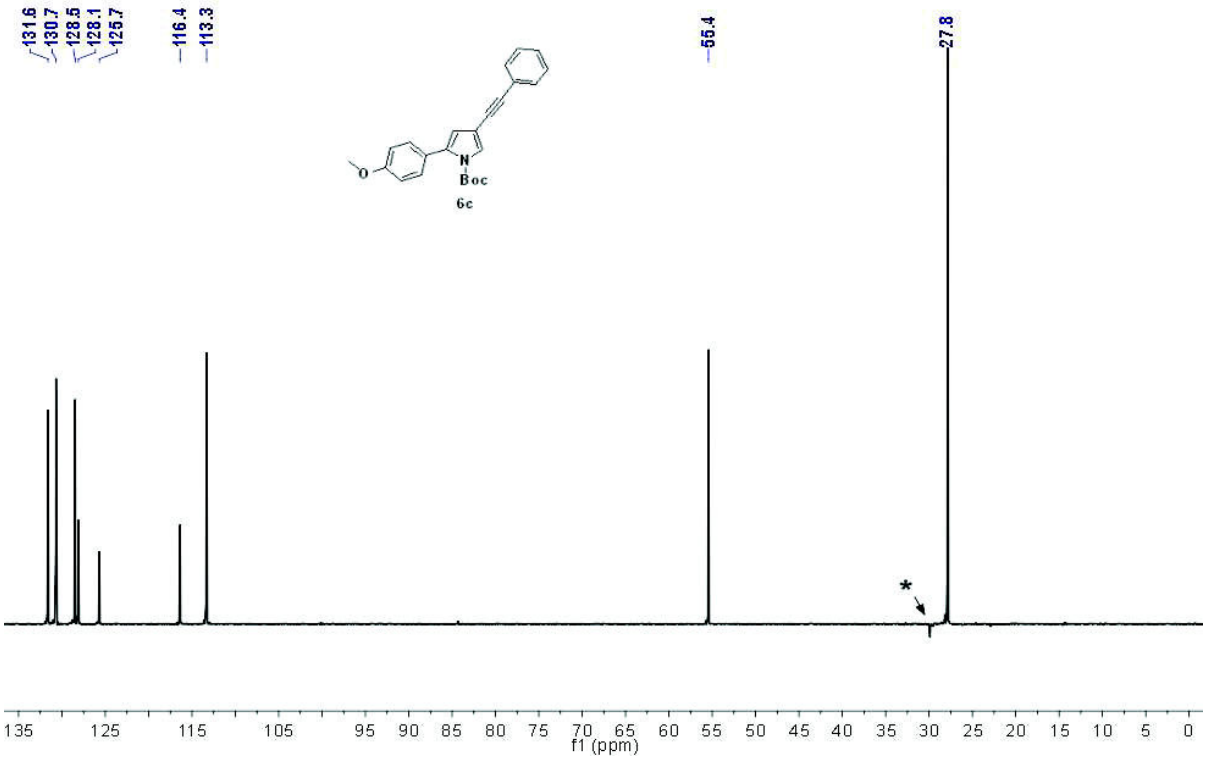


^{13}C NMR of **6c** in $CDCl_3$ at 296 K



*Impurities from residual solvents.

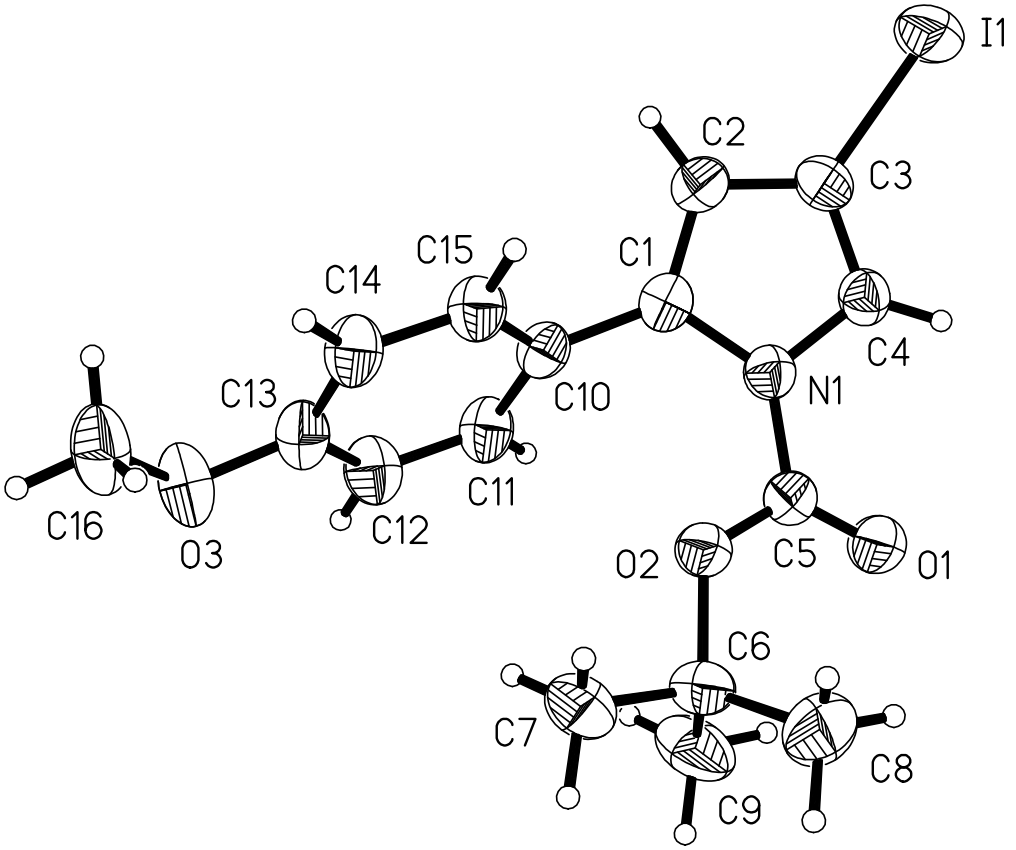
^{13}C DEPT 135 of **6c** in $CDCl_3$ at 296 K



*Impurities from residual solvents.

6. Crystallographic Data of Compound 4d

Figure 1. Molecular structure of tert-Butyl 4-iodo-2-(4-methoxyphenyl)-1*H*-pyrrole-1-carboxylate (**4d**) in the crystal (50% probability ellipsoids).



(**4d**): yellow crystal (cube), dimensions 0.15 x 0.15 x 0.15 mm^3, crystal system triclinic, space group P-1, Z=2, a= 9.3344(8) Å, b= 9.5233(8) Å, c= 10.9791(9) Å, alpha= 77.329(9) deg, beta= 68.367(9) deg, gamma= 69.877(10) deg, V= 847.06(14) $Å^3$, rho= 1.565 g/cm^3, T=223(2) K, $2Theta_{max}$= 25.00 deg, radiation Mo Kalpha, lambda=0.71073 Å, mu=1.899 mm^{-1} STOE IPDS, 12191 reflections measured, 2864 unique (R(int)=0.040), 2570 observed (I >2□(I)), intensities were corrected for Lorentz and polarization effects., mu=0.18mm^{-1}, structure solved by direct methods and refined against F^2 with a full-matrix least-squares algorithm using SHELXS-97 and SHELXL-97, respectively, 194 parameters refined, hydrogen atoms were treated using appropriate riding models, goodness of fit 1.147, final residual values R1(F)=0.030, w$R(F^2)$=0.081 for observed reflections, residual electron density -0.32 to 0.80 e$Å^{-3}$. CCDC 723307 contains the supplementary crystallographic data for this structure. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

Table 1: Crystal data and structure refinement for **4d**.

Empirical formula	$C_{16}H_{18}INO_3$
Formula weight	399.22
Temperature	223(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Z	2
Unit cell dimensions	a = 9.3344(8) Å α = 77.329(9)°. b = 9.5233(8) Å β = 68.367(9)°. c = 10.9791(9) Å γ = 69.877(10)°.
Volume	847.06(14) $Å^3$
Density (calculated)	1.565 mg/m^3
Absorption coefficient	1.899 mm^{-1}
F(000)	396
Crystal size	0.15 x 0.15 x 0.15 mm^3
Theta range for data collection	2.01 to 25.00°.
Index ranges	$-11 \le h \le 11$, $-11 \le k \le 11$, $-13 \le l \le 13$
Reflections collected	12191
Independent reflections	2864 (R(int) = 0.0403)
Completeness to theta = 25.00°	96.2 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2864 / 0 / 194
Goodness-of-fit on F^2	1.147
Final R indices ($I>2\sigma(I)$)	R1 = 0.0301, wR2 = 0.0807
R indices (all data)	R1 = 0.0331, wR2 = 0.0817
Largest diff. peak and hole	0.796 and -0.317 $eÅ^{-3}$

Table 2: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **4d**. U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

Atom	x	y	z	U_{eq}
I(1)	4283(1)	7397(1)	4241(1)	62(1)
O(1)	5918(3)	8737(2)	-1396(2)	59(1)
O(2)	8066(2)	6669(2)	-1887(2)	42(1)
O(3)	11005(3)	484(3)	-2357(3)	60(1)
N(1)	6368(2)	6787(2)	189(2)	38(1)
C(1)	6997(3)	5294(3)	681(3)	38(1)
C(2)	6406(3)	5248(3)	2028(3)	42(1)
C(3)	5446(3)	6713(3)	2359(3)	41(1)
C(4)	5419(3)	7633(3)	1235(3)	39(1)
C(5)	6741(3)	7506(3)	-1118(3)	40(1)
C(6)	8731(4)	7162(3)	-3322(3)	48(1)
C(7)	10219(4)	5844(4)	-3756(3)	56(1)
C(8)	9211(5)	8574(4)	-3472(4)	74(1)
C(9)	7518(5)	7346(5)	-4004(3)	71(1)

C(11)	7597(3)	3602(3)	-1037(3)	45(1)
C(12)	8591(4)	2417(3)	-1749(3)	49(1)
C(13)	10095(3)	1617(3)	-1579(3)	46(1)
C(14)	10542(3)	2025(3)	-664(3)	47(1)
C(10)	8044(3)	4047(3)	-123(3)	38(1)
C(15)	9532(3)	3227(3)	49(3)	43(1)
C(16)	12551(4)	-353(4)	-2208(4)	67(1)

Table 3: Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for **4d**.

Atom	x	y	z	U_{eq}
H(21)	6605	4391	2627	50
H(41)	4857	8662	1174	47
H(71)	10774	6034	-4688	83
H(72)	9902	4935	-3599	83
H(73)	10931	5722	-3258	83
H(81)	8253	9406	-3185	111
H(82)	9796	8807	-4389	111
H(83)	9893	8414	-2938	111
H(91)	6574	8178	-3683	107
H(92)	7207	6430	-3817	107
H(93)	7998	7549	-4947	107
H(111)	6596	4127	-1161	54
H(121)	8267	2138	-2353	58
H(141)	11532	1484	-527	56
H(151)	9852	3498	660	52
H(161)	13059	-1161	-2771	100
H(162)	12410	-772	-1297	100
H(163)	13225	310	-2455	100

Table 4: Anisotropic displacement parameters ($Å^2$ x 10^3) for **4d**. The anisotropic displacement factor exponent takes the form: $-2\ pi^2\ (h^2\ a^{*2}\ U_{11} + ... + 2\ h\ k\ a^*\ b^*\ U_{12})$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
I(1)	68(1)	66(1)	38(1)	-9(1)	-7(1)	-12(1)
O(1)	70(1)	42(1)	45(1)	-4(1)	-16(1)	4(1)
O(2)	42(1)	40(1)	36(1)	-3(1)	-10(1)	-9(1)

O(3)	49(1)	51(1)	79(2)	-29(1)	-15(1)	-5(1)
N(1)	37(1)	36(1)	39(1)	-5(1)	-12(1)	-9(1)
C(1)	33(1)	36(1)	45(1)	-3(1)	-14(1)	-11(1)
C(2)	39(1)	40(2)	42(1)	1(1)	-13(1)	-10(1)
C(3)	37(1)	48(2)	37(1)	-9(1)	-8(1)	-12(1)
C(4)	37(1)	37(1)	41(1)	-7(1)	-9(1)	-8(1)
C(5)	44(1)	37(1)	38(1)	-4(1)	-15(1)	-10(1)
C(6)	52(2)	53(2)	35(1)	-3(1)	-10(1)	-17(1)
C(7)	48(2)	65(2)	46(2)	-13(1)	-3(1)	-15(2)
C(8)	85(2)	59(2)	67(2)	2(2)	-5(2)	-36(2)
C(9)	70(2)	95(3)	47(2)	-20(2)	-28(2)	-3(2)
C(11)	38(1)	40(2)	60(2)	-8(1)	-21(1)	-8(1)
C(12)	46(2)	48(2)	61(2)	-13(1)	-21(1)	-16(1)
C(13)	40(1)	37(2)	57(2)	-10(1)	-11(1)	-10(1)
C(14)	37(1)	41(2)	62(2)	-9(1)	-18(1)	-6(1)
C(10)	38(1)	34(1)	42(1)	-1(1)	-13(1)	-13(1)
C(15)	39(1)	41(2)	51(2)	-7(1)	-16(1)	-10(1)
C(16)	46(2)	53(2)	88(2)	-25(2)	-9(2)	-2(2)

Table 5: Bond lengths (Å) and angles (deg) for **4d**.

I(1)-C(3)	2.078(3)	C(12)-H(121)	0.9400
O(1)-C(5)	1.206(3)	C(13)-C(14)	1.388(4)
O(2)-C(5)	1.314(3)	C(14)-C(15)	1.385(4)
O(2)-C(6)	1.497(3)	C(14)-H(141)	0.9400
O(3)-C(13)	1.361(4)	C(10)-C(15)	1.399(4)
O(3)-C(16)	1.438(4)	C(15)-H(151)	0.9400
N(1)-C(4)	1.385(4)	C(16)-H(161)	0.9700
N(1)-C(1)	1.407(3)	C(16)-H(162)	0.9700
N(1)-C(5)	1.419(3)	C(16)-H(163)	0.9700
C(1)-C(2)	1.370(4)	C(5)-O(2)-C(6)	121.6(2)
C(1)-C(10)	1.473(4)	C(13)-O(3)-C(16)	116.9(3)
C(2)-C(3)	1.416(4)	C(4)-N(1)-C(1)	109.2(2)
C(2)-H(21)	0.9400	C(4)-N(1)-C(5)	120.0(2)
C(3)-C(4)	1.351(4)	C(1)-N(1)-C(5)	130.2(2)
C(4)-H(41)	0.9400	C(2)-C(1)-N(1)	106.3(2)
C(6)-C(8)	1.517(4)	C(2)-C(1)-C(10)	128.1(2)
C(6)-C(9)	1.518(4)	N(1)-C(1)-C(10)	125.6(2)
C(6)-C(7)	1.518(5)	C(1)-C(2)-C(3)	108.2(2)
C(7)-H(71)	0.9700	C(1)-C(2)-H(21)	125.9
C(7)-H(72)	0.9700	C(3)-C(2)-H(21)	125.9
C(7)-H(73)	0.9700	C(4)-C(3)-C(2)	108.6(2)
C(8)-H(81)	0.9700	C(4)-C(3)-I(1)	124.5(2)
C(8)-H(82)	0.9700	C(2)-C(3)-I(1)	126.9(2)
C(8)-H(83)	0.9700	C(3)-C(4)-N(1)	107.7(2)
C(9)-H(91)	0.9700	C(3)-C(4)-H(41)	126.2
C(9)-H(92)	0.9700	N(1)-C(4)-H(41)	126.2
C(9)-H(93)	0.9700	O(1)-C(5)-O(2)	128.2(2)
C(11)-C(12)	1.370(5)	O(1)-C(5)-N(1)	121.2(3)
C(11)-C(10)	1.406(4)	O(2)-C(5)-N(1)	110.5(2)
C(11)-H(111)	0.9400	O(2)-C(6)-C(8)	109.3(2)
C(12)-C(13)	1.407(4)	O(2)-C(6)-C(9)	109.6(2)

C(8)-C(6)-C(9)	113.7(3)
O(2)-C(6)-C(7)	101.4(2)
C(8)-C(6)-C(7)	110.2(3)
C(9)-C(6)-C(7)	111.9(3)
C(6)-C(7)-H(71)	109.5
C(6)-C(7)-H(72)	109.5
H(71)-C(7)-H(72)	109.5
C(6)-C(7)-H(73)	109.5
H(71)-C(7)-H(73)	109.5
H(72)-C(7)-H(73)	109.5
C(6)-C(8)-H(81)	109.5
C(6)-C(8)-H(82)	109.5
H(81)-C(8)-H(82)	109.5
C(6)-C(8)-H(83)	109.5
H(81)-C(8)-H(83)	109.5
H(82)-C(8)-H(83)	109.5
C(6)-C(9)-H(91)	109.5
C(6)-C(9)-H(92)	109.5
H(91)-C(9)-H(92)	109.5
C(6)-C(9)-H(93)	109.5
H(91)-C(9)-H(93)	109.5
H(92)-C(9)-H(93)	109.5
C(12)-C(11)-C(10)	121.3(2)
C(12)-C(11)-H(111)	119.4
C(10)-C(11)-H(111)	119.4
C(11)-C(12)-C(13)	120.3(3)
C(11)-C(12)-H(121)	119.9
C(13)-C(12)-H(121)	119.9
O(3)-C(13)-C(14)	125.3(3)
O(3)-C(13)-C(12)	115.6(3)
C(14)-C(13)-C(12)	119.2(3)
C(15)-C(14)-C(13)	120.2(3)
C(15)-C(14)-H(141)	119.9
C(13)-C(14)-H(141)	119.9
C(15)-C(10)-C(11)	117.8(3)
C(15)-C(10)-C(1)	119.2(2)
C(11)-C(10)-C(1)	123.0(2)
C(14)-C(15)-C(10)	121.3(3)
C(14)-C(15)-H(151)	119.3
C(10)-C(15)-H(151)	119.3
O(3)-C(16)-H(161)	109.5
O(3)-C(16)-H(162)	109.5
H(161)-C(16)-H(162)	109.5
O(3)-C(16)-H(163)	109.5
H(161)-C(16)-H(163)	109.5
H(162)-C(16)-H(163)	109.5

Table 6: Torsion angles (deg) for **4d**.

C(4)-N(1)-C(1)-C(2)	0.6(3)
C(5)-N(1)-C(1)-C(2)	171.1(2)
C(4)-N(1)-C(1)-C(10)	179.0(2)
C(5)-N(1)-C(1)-C(10)	-10.6(4)
N(1)-C(1)-C(2)-C(3)	-1.2(3)
C(10)-C(1)-C(2)-C(3)	-179.5(2)
C(1)-C(2)-C(3)-C(4)	1.4(3)
C(1)-C(2)-C(3)-I(1)	-177.57(17)
C(2)-C(3)-C(4)-N(1)	-1.0(3)
I(1)-C(3)-C(4)-N(1)	178.00(16)
C(1)-N(1)-C(4)-C(3)	0.2(3)
C(5)-N(1)-C(4)-C(3)	-171.4(2)
C(6)-O(2)-C(5)-O(1)	-2.2(4)
C(6)-O(2)-C(5)-N(1)	179.8(2)
C(4)-N(1)-C(5)-O(1)	-21.5(4)
C(1)-N(1)-C(5)-O(1)	168.9(3)
C(4)-N(1)-C(5)-O(2)	156.6(2)
C(1)-N(1)-C(5)-O(2)	-13.0(3)
C(5)-O(2)-C(6)-C(8)	63.7(3)
C(5)-O(2)-C(6)-C(9)	-61.5(3)
C(5)-O(2)-C(6)-C(7)	-179.9(2)
C(10)-C(11)-C(12)-C(13)	-0.1(4)
C(16)-O(3)-C(13)-C(14)	0.2(4)
C(16)-O(3)-C(13)-C(12)	179.9(3)
C(11)-C(12)-C(13)-O(3)	-178.5(3)
C(11)-C(12)-C(13)-C(14)	1.2(4)
O(3)-C(13)-C(14)-C(15)	178.2(3)
C(12)-C(13)-C(14)-C(15)	-1.4(4)
C(12)-C(11)-C(10)-C(15)	-0.8(4)
C(12)-C(11)-C(10)-C(1)	-178.7(3)
C(2)-C(1)-C(10)-C(15)	-57.1(4)
N(1)-C(1)-C(10)-C(15)	124.8(3)
C(2)-C(1)-C(10)-C(11)	120.8(3)
N(1)-C(1)-C(10)-C(11)	-57.3(3)
C(13)-C(14)-C(15)-C(10)	0.5(4)
C(11)-C(10)-C(15)-C(14)	0.6(4)
C(1)-C(10)-C(15)-C(14)	178.6(2)

7. References

1. G. P. Moloney, G. R. Martin, N. Mathews, H. Hobbs, S. Dodsworth, P. Y. Sang, C. Knight, M. Maxwell, R. C. Glen, *J. Chem. Soc., Perkin. Trans. 1* **1999**, 2713.

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COMMUNICATION

Rapid synthesis of bis(hetero)aryls by one-pot Masuda borylation–Suzuki coupling sequence and its application to concise total syntheses of meridianins A and G†‡ §

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3-(Hetero)aryl substituted indoles, 7-azaindoles, and pyrroles can be obtained in a very concise fashion *via* a one-pot Masuda borylation–Suzuki coupling sequence. The concise total syntheses of the marine natural products meridianins A (5) and G (4i) nicely illustrate the utility of this methodology.

Indoles and pyrroles belong to the most important heterocycles. They are widespread in nature[1] and represent privileged structures found in a plethora of biologically and pharmacologically active compounds.[2] In particular, indoles with 5- or 6-membered heterocyclic substituents in the 3-position have aroused considerable attention due to a remarkable spectrum of biological activity. For example, meridianins[3] and variolins[4] (Fig. 1) are small marine alkaloids consisting of indole and 7-azaindole frameworks connected to a 2-aminopyrimidine ring, the essential structural element for the kinase inhibitory activity of these natural products.

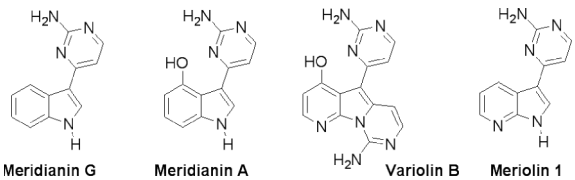

Fig. 1 3-Substituted indoles as natural products and bioactive compounds.

Recently, we synthesized some members of the meridianin family using the carbonylative Sonogashira coupling reaction as a key step.[5] The simplified 7-azaindole analogue of variolin B (later called meriolin 1)[6] has attracted our attention because it is very active on kinases and human cancer cell lines with IC_{50} values (*i.e.* concentration reducing cell proliferation by 50%) of 0.18 and 0.14 μM against HCT116 (colon carcinoma) and A2780 (ovarian carcinoma), respectively. 7-Azaindole is an increasingly important structural motif due to its strong ability to bind to the hinge region of kinases and act as a kinase inhibitor. We are particularly interested in investigating the structure–activity relationship of 3-heteroaryl substituted 7-azaindoles. Therefore, a robust and general synthetic methodology to decorate (aza)indoles with diverse heterocyclic residues is highly desirable.

The Suzuki–Miyaura cross-coupling reaction[7] is an extremely important tool for the construction of biaryls, as emphasized by awarding the Nobel Prize 2010 to Akira Suzuki in recognition of the enormous utility of this Pd-catalyzed transformation. As the nucleophilic component of this coupling, pinacol boronic esters[8] are stable reagents and can be also accessed *via* Pd-catalyzed approaches such as Miyaura (B_2pin_2/$PdCl_2$dppf/KOAc)[9] and Masuda (HBpin/$PdCl_2$dppf/NEt_3)[10] borylations. The Masuda protocol utilizes pinacolborane,[11] thus being a more elegant and atom economical approach. The catenation of Masuda and Suzuki reactions into a one-pot fashion has been described by several groups pioneered by the work of Baudoin in 2000.[12] However, the strategy has never been generalized and no simple catalytic system has been disclosed for the flexible introduction of various heterocycles on pharmaceutically relevant heterocyclic scaffolds such as indoles or related systems.[13] Herein, we report a strikingly simple one-pot procedure which was established to efficiently synthesize a variety of 3-(hetero)aryl substituted (7-aza)indoles, pyrroles, and other electron-rich (hetero)aryls.

N-Boc protected (aza)indolyl[14] iodides **1** are easily accessible, stable to storage and can be successfully used as valuable building blocks in cross-coupling reactions. The direct Suzuki coupling of **1** with heteroaryl boronic acids or esters is strongly limited by the accessibility of the latter. We reasoned that iodides **1** could be converted to the corresponding pinacol esters[15] **2** and then reacted en route with heterocyclic halides **3**, which are readily available (Scheme 1).

According to this strategy, the iodides **1** are reacted with pinacolborane and triethylamine as a base in 1,4-dioxane. After completed transformation (as monitiored by TLC), methanol is added which scavenges excess of pinacolborane. One equivalent of mostly commercially available halide **3** is added followed by caesium carbonate to promote the Suzuki coupling. Concurrently,

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† Electronic supplementary information (ESI) available: Experimental procedures and characterization of compounds **1a**, **1c**, **1f**, **1j**, **2a**, **4a–4u** and **5**. See DOI: 10.1039/c1ob05310h

‡ Dedicated to Anna Merkul, née Seifert, on the occasion of her 60th birthday.

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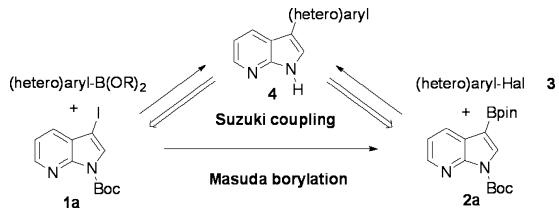
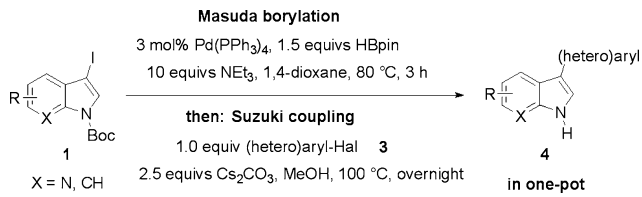


Scheme 1 Synthetic concept for 3-(hetero)aryl substituted 7-azaindoles **4**.

the alcoholic carbonate solution cleaves the Boc protective group, thus directly furnishing the desired products **4** without the need for an additional deprotection step (Scheme 2).



Scheme 2 Masuda borylation–Suzuki coupling sequence.

This methodology exemplifies sequential catalysis, since a single Pd-precatalyst promotes both transformations.[16] No exotic ligands are required and no additional catalyst portion has to be added in the second reaction step. The yield did not increase upon addition of further 3 mol% $Pd(PPh_3)_4$, which performed best for the described substrates. $PdCl_2(PPh_3)_2$ was only slightly less efficient (64% *vs.* 61% for **4f**), but the typical precatalyst for Masuda borylations, $PdCl_2$dppf, failed to give the desired product in a good yield (39% for **4f**). K_2CO_3 can be used instead of Cs_2CO_3 with slightly decreased efficiency.

Interestingly, in a related approach to substituted 7-azaindolyl pyrimidines, a stepwise protocol consisting of Miyaura borylation and Suzuki coupling with two different (!) Pd-precatalysts was utilized, and the protective phenylsulfonyl group remained uncleaved.[17]

The scope of the presented sequence is remarkable since it allows the introduction of a great variety of different 6-membered aryl substituents or nitrogen heterocycles (Fig. 2). Functional groups including cyano, free hydroxy and amino groups on (hetero)aryl halides are tolerated and give good yields. (Hetero)aromatic iodides, bromides and chlorides (see the color code of Fig. 2) can be reacted according to the expected oxidative addition tendency of the halide and its position in the (hetero)cycle. Pharmacophore motifs such as 2-aminopyrimidine, 2-aminopyridine, and even 2,6-diaminopyridine can be introduced without difficulties. It should be emphasized that upon using the reverse approach, *i.e.* the direct coupling with heteroaryl boronic acids or pinacol esters, the observed functional and structural diversity can hardly be realized: especially *ortho*-nitrogen atom containing boronic reagents are particularly challenging coupling partners.[18] Not only indoles and 7-azaindoles but also iodo pyrroles[19] can be reacted and give 2,4-disubstituted pyrroles (**4k–4n**), which represent an interesting and rare substitution pattern. Furthermore, *N*-Bn 4-iodo pyrazole, 3-iodo thiophene, 2,5-disubstituted 4-iodo furan[20] as well as 2-amino 5-iodo pyridine, 2-amino 5-iodo pyrimidine and electron-rich iodo arenes can be functionalized with (hetero)aryl substituents with

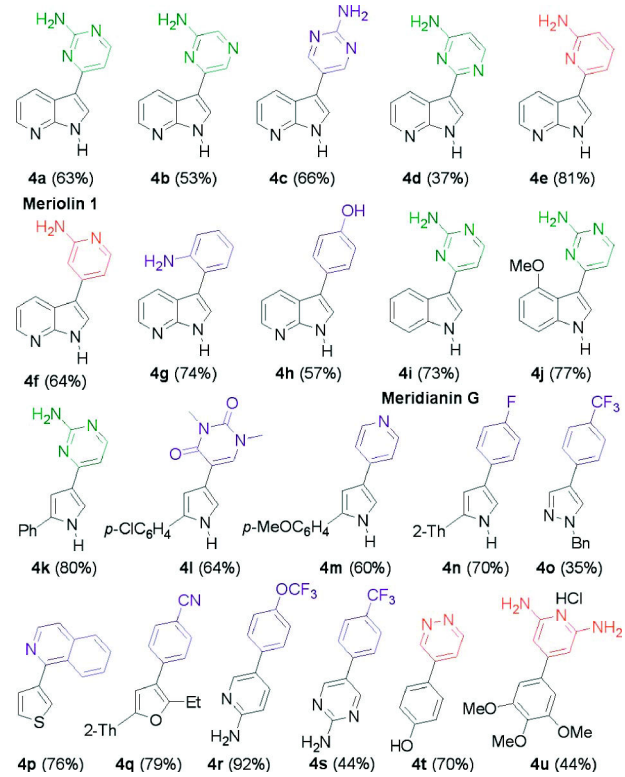
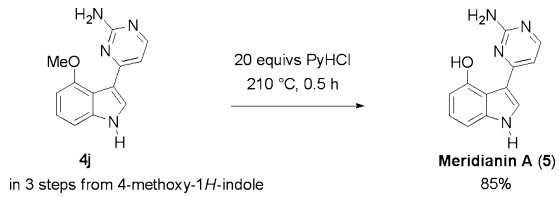


Fig. 2 Scope of the Masuda borylation–Suzuki coupling sequence (isolated yields). Color code for the applied heterocyclic halides **3**: violet = iodide, brown = bromide, green = chloride. Th = thienyl.

comparable efficiency (**4o–4u**). Free hydroxy and amino groups on the substrates are well tolerated (**4r–4t**). The yields of the isolated products are fair to very good and the compounds can be obtained analytically pure by simple flash chromatography.

With this practical and versatile methodology in hand, we set out to perform very concise total syntheses of meridianins A (**5**)[23] and G (**4i**) in order to illustrate the utility in alkaloid synthesis. Starting from commercially available 4-methoxy-1*H*-indole, the former natural product was obtained in four steps and 54% total yield. The one-pot Masuda borylation–Suzuki coupling sequence was used as a key step to prepare *O*-Me-meridianin A (**4j**), which was then demethylated by PyHCl[21] in the final step (Scheme 3). It is worth mentioning that this strategy represents the first targeted synthesis of this natural product since the sole approach by Fresneda and Molina delivered 15% (19 mg) of meridianin A in 5 steps from 4-benzyloxy-7-bromo-1*H*-indole, which is not commercially available.[22] The presented procedure[23] gives also access to other interesting hydroxylated 3-aryl and 3-heteroaryl substituted indoles. Syntheses of further natural products can be easily envisioned and are currently underway.

The presented sequence consisting of Masuda borylation and Suzuki coupling is tailored to efficiently synthesize 3-(hetero)aryl substituted (aza)indoles, many of them are biologically active compounds. Moreover, the obtained 2,4-di(hetero)aryl substituted pyrroles represent a new promising scaffold. The most exciting feature of this preparatively extremely simple transformation is the possibility to directly connect readily available heterocyclic halides in a one-pot fashion without the need for sophisticated catalysts, ligands or additives. Considering the huge pool of



Scheme 3 Final step of the total synthesis of meridianin A.

commercially available or easily accessible heteroaromatic halides, this methodology is a quite general concept.

The full scope of the sequence as well as structure–activity studies and the biological data of analogues based on 7-azaindole will be reported in near future.

Notes and references

1 For recent reviews, see: A. J. Kochanowska-Karamyan and M. T. Hamann, *Chem. Rev.*, 2010, **110**, 4489; H. Fan, J. Peng, M. T. Hamann and J.-F. Hu, *Chem. Rev.*, 2008, **108**, 264.

2 For a recent minireview on indole alkaloid marine natural products as a source of drug leads, see: W. Gul and M. T. Hamann, *Life Sci.*, 2005, **78**, 442.

3 M. D. Lebar and B. J. Baker, *Aust. J. Chem.*, 2010, **63**, 862; A. M. Seldes, M. F. R. Brasco, L. H. Franco and J. A. Palermo, *Nat. Prod. Res.*, 2007, **21**, 555; L. H. Franco, E. Bal de Kier Joffé, L. Puricelli, M. Tatian, A. M. Seldes and J. A. Palermo, *J. Nat. Prod.*, 1998, **61**, 1130.

4 N. B. Perry, L. Ettouati, M. Litaudon, J. W. Blunt, M. H. G. Munro, S. Parkin and H. Hope, *Tetrahedron*, 1994, **50**, 3987; G. Trimurtulu, D. J. Faulkner, N. B. Perry, L. Ettouati, M. Litaudon, J. W. Blunt, M. H. G. Munro and G. B. Jameson, *Tetrahedron*, 1994, **50**, 3993; Recent review on variolins and related alkaloids: S. R. Walker, E. J. Carter, B. C. Huff and J. C. Morris, *Chem. Rev.*, 2009, **109**, 3080.

5 A. S. Karpov, E. Merkul, F. Rominger and T. J. J. Müller, *Angew. Chem., Int. Ed.*, 2005, **44**, 6951.

6 A. Echalier, K. Bettayeb, Y. Ferandin, O. Lozach, M. Clément, A. Valette, F. Liger, B. Marquet, J. C. Morris, J. A. Endicott, B. Joseph and L. Meijer, *J. Med. Chem.*, 2008, **51**, 737.

7 M. Prieto, E. Zurita, E. Rosa, L. Muoz, P. Lloyd-Williams and E. Giralt, *J. Org. Chem.*, 2004, **69**, 6812; N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457; N. Miyaura, T. Yanagi and A. Suzuki, *Synth. Commun.*, 1981, **11**, 513.

8 C. E. Tucker, J. Davidson and P. Knochel, *J. Org. Chem.*, 1992, **57**, 3482.

9 T. Ishiyama, M. Murata and N. Miyaura, *J. Org. Chem.*, 1995, **60**, 7508.

10 M. Murata, T. Oyama, S. Watanabe and Y. Masuda, *J. Org. Chem.*, 2000, **65**, 164; M. Murata, S. Watanabe and Y. Masuda, *J. Org. Chem.*, 1997, **62**, 6458.

11 For a method for practical large-scale preparation of pinacolborane, see: T. Kikuchi, Y. Nobuta, J. Umeda, Y. Yamamoto, T. Ishiyama and N. Miyaura, *Tetrahedron*, 2008, **64**, 4967.

12 For reported one-pot Masuda borylation–Suzuki coupling sequences, see: P.-E. Broutin, I. Čerňa, M. Campaniello, F. Leroux and F. Colobert, *Org. Lett.*, 2004, **6**, 4419; M. Penhoat, V. Levacher and G. Dupas, *J. Org. Chem.*, 2003, **68**, 9517; O. Baudoin, D. Guénard and F. Guéritte, *J. Org. Chem.*, 2000, **65**, 9268.

13 For a sequence applied in a bisindole synthesis using XPhos, see: H. A. Duong, S. Chua, P. B. Huleatt and C. L. L. Chai, *J. Org. Chem.*, 2008, **73**, 9177.

14 B. Witulski, N. Buschmann and U. Bergsträßer, *Tetrahedron*, 2000, **56**, 8473.

15 For a direct Ir-catalyzed borylation of *N*-Boc protected heterocycles, see: V. A. Kallepalli, F. Shi, S. Paul, E. N. Onyeozili, R. E. Maleczka Jr. and M. R. Smith III, *J. Org. Chem.*, 2009, **74**, 9199.

16 T. J. J. Müller, *Top. Organomet. Chem.*, 2006, **19**, 149.

17 S. Huang, R. Li, P. J. Connolly, S. Emanuel and S. A. Middleton, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 4818.

18 For strategies developed for the Suzuki coupling of 2-pyridyl pinacolboronates, see: D. X. Yang, S. L. Colletti, K. Wu, M. Song, G. Y. Li and H. C. Shen, *Org. Lett.*, 2009, **11**, 381; J. Z. Deng, D. V. Paone, A. T. Ginnetti, H. Kurihara, S. D. Dreher, S. A. Weissman, S. R. Stauffer and C. S. Burgey, *Org. Lett.*, 2009, **11**, 345.

19 For a one-pot preparation of 2-substituted *N*-Boc 4-iodo pyrroles, see: E. Merkul, C. Boersch, W. Frank and T. J. J. Müller, *Org. Lett.*, 2009, **11**, 2269.

20 For a one-pot preparation of (di)substituted (3)4-iodo furans, see: A. S. Karpov, E. Merkul, T. Oeser and T. J. J. Müller, *Chem. Commun.*, 2005, 2581; A. S. Karpov, E. Merkul, T. Oeser and T. J. J. Müller, *Eur. J. Org. Chem.*, 2006, 2991.

21 C. R. Schmid, C. A. Beck, J. S. Cronin and M. A. Staszak, *Org. Process Res. Dev.*, 2004, **8**, 670.

22 P. M. Fresneda, P. Molina and J. A. Bleda, *Tetrahedron*, 2001, **57**, 2355.

23 Typical procedure (Compound **4j**): tetrakis(triphenylphosphane)-palladium(0) (35 mg, 0.03 mmol, 3 mol%) and *tert*-butyl 3-iodo-4-methoxy-1*H*-indole-1-carboxylate (**1c**) (373 mg, 1.00 mmol) were placed under argon atmosphere in a dry screw-cap vessel with septum. Then, 5 mL of dry 1,4-dioxane were added and the mixture was degassed with argon. Dry triethylamine (1.39 mL, 10.0 mmol) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.22 mL, 1.50 mmol) were successively added to the mixture which was stirred at 80 °C (preheated oil bath) for 3 h (monitored by TLC). Then, after cooling to room temperature (water bath), 5 mL of dry methanol, 2-amino-4-chloropyrimidine **3a** (134 mg, 1.00 mmol) and caesium carbonate (823 mg, 2.50 mmol) were successively added and the mixture was stirred at 100 °C (preheated oil bath) overnight for 15 h. Then, after cooling to room temperature (water bath) the solvents were removed *in vacuo* and the residue was adsorbed onto Celite® and purified chromatographically on silica gel with dichloromethane–methanol-aqueous ammonia to give after drying *in vacuo* at 70 °C overnight 185 mg (77%) of the analytically pure compound **4j** as a colorless solid, mp 221–222 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 3.87 (s, 3 H), 6.27 (s, 2 H, N*H*$_2$), 6.63 (d, J = 6.9 Hz, 1 H), 7.06–7.12 (m, 2 H), 7.26 (dd, J = 5.4 Hz, J = 0.9 Hz, 1 H), 7.85 (d, J = 2.5 Hz, 1 H), 8.15 (d, J = 5.4 Hz, 1 H), 11.6 (br, 1 H, N*H*). ^{13}C NMR (DMSO-d_6, 125 MHz): δ (ppm) 55.0 (CH$_3$), 101.2 (CH), 105.5 (CH), 109.7 (CH), 114.4 (C$_{quat}$), 115.4 (C$_{quat}$), 122.7 (CH), 127.5 (CH), 138.8 (C$_{quat}$), 153.2 (C$_{quat}$), 157.0 (CH), 161.8 (C$_{quat}$), 163.2 (C$_{quat}$). EI MS (*m*/*z* (%)): 240 (M$^+$, 50), 239 (M$^+$ – H, 21), 211 (M$^+$ – CH$_3$O + H, 20), 202 (M$^+$ – C$_2$H$_2$N + 2 H, 11), 58 (CH$_4$N$_3^+$, 41), 43 (C$_2$H$_3$O$^+$, 100). IR (KBr): $\tilde{\nu}$ 3465 (m) cm^{-1}, 3313 (m), 3165 (m), 1644 (m), 1624 (m), 1575 (s), 1555 (s), 1506 (s), 1459 (s), 1414 (m), 1320 (m), 1245 (m), 1088 (m), 733 (m). Anal. calcd for C$_{13}$H$_{12}$N$_4$O (240.3): C 64.99, H 5.03, N 23.32. Found: C 64.86, H 4.85, N 23.25. Synthesis of meridianin A (**5**): pyridinium hydrochloride (1.18 g, 10.0 mmol) was placed in a dry screw-cap vessel under argon atmosphere. Then, **4j** (120 mg, 0.50 mmol) was added and the mixture was heated to 210 °C (preheated oil bath). After 0.5 h the mixture was cooled to 50 °C (preheated oil bath) and methanol was added to dissolve the residue. The solvents were removed *in vacuo* and the residue was adsorbed onto Celite® and purified chromatographically on silica gel with dichloromethane–methanol–aqueous ammonia to give after drying *in vacuo* at 70 °C overnight 96 mg (85%) of the analytically pure meridianin A (**5**) as a bright yellow fine crystalline solid, mp 264–276 °C. (Lit.:[3,22] 164–168 °C). ^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 6.39 (dd, J = 7.9 Hz, J = 0.9 Hz, 1 H), 6.76 (s, 2 H, N*H*$_2$), 6.82 (dd, J = 8.2 Hz, J = 0.9 Hz, 1 H), 7.00 (t, J = 7.9 Hz, 1 H), 7.14 (d, J = 5.4 Hz, 1 H), 8.14 (d, J = 5.4 Hz, 1 H), 8.25 (d, J = 3.2 Hz, 1 H), 11.8 (br, 1 H, N*H*), 13.62 (s, 1 H, O*H*). ^{13}C NMR (DMSO-d_6, 125 MHz): δ (ppm) 102.3 (CH), 104.3 (CH), 105.5 (CH), 113.7 (C$_{quat}$), 114.3 (C$_{quat}$), 124.4 (CH), 128.4 (CH), 139.2 (C$_{quat}$), 152.0 (C$_{quat}$), 158.4 (CH), 160.4 (C$_{quat}$), 161.7 (C$_{quat}$). EI MS (*m*/*z* (%)): 226 (M$^+$, 100), 225 (M$^+$ – H, 13), 209 (M$^+$ – OH, 2), 197 (M$^+$ – COH, 6), 185 (M$^+$ – CH$_2$N$_2$ + H, 18), 158 (M$^+$ – C$_3$H$_4$N$_2$, 6). IR (KBr): $\tilde{\nu}$ 3429 (m) cm^{-1}, 3342 (m), 1638 (m), 1593 (s), 1562 (m), 1532 (m), 1469 (m), 1444 (m), 1401 (m), 1321 (m), 1227 (m), 719 (m). Anal. calcd for C$_{12}$H$_{10}$N$_4$O (226.2): C 63.71, H 4.46, N 24.76. Found: C 63.48, H 4.61, N 24.72.

Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Rapid synthesis of bis(hetero)aryls by one-pot Masuda borylation □ Suzuki coupling sequence and its application to concise total syntheses of meridianins A and G **

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[**] This work was supported by Merck Serono, Darmstadt

Supporting Information

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1. General Considerations

All cross coupling reactions were carried out in oven-dried Schlenk glassware using septa and syringes under nitrogen or argon atmosphere. THF and 1,4-dioxane were dried using *MBraun* system MB-SPS-800, and triethylamine was refluxed under argon atmosphere over ketyl sodium, distilled and stored in a Schlenk flask over potassium hydroxide pellets under argon atmosphere. Dry methanol was purchased from *Sigma-Aldrich Chemie GmbH*.

4,4,5,5-Tetramethyl-1,3,2-dioxaborolane (pinacolborane) was purchased from *Sigma-Aldrich Chemie GmbH* and used as supplied. Tetrakis(triphenylphosphane)-palladium(0) and cesium carbonate were purchased from *Merck Serono KGaA*.

Commercial grade reagents were used as supplied without further purification and were purchased from *Acros Organics*, *Sigma-Aldrich Chemie GmbH*, *Fluka AG*, *ABCR GmBH & Co. KG, Alfa Aesar GmbH & Co. KG*, *Aces Pharma Inc., Interchim Inc., Synthonix Inc., Synchem OHG* and *Merck Serono KGaA*.

Compounds **1h**-**1i**, **1k**-**1n** and **3a**-**3q** are commercially available (see ***Table 1***). Compounds **1a**-**1c**,[1] **1d**-**1g**[2] and **1j**[3] were prepared according to the literature procedures.

The purification of products was performed on silica gel 60 (0.015-0.040 mm) from *Merck Serono KGaA* Darmstadt using flash technique and under pressure of 2 bar. The crude mixtures were adsorbed on Celite® 545 (0.02-0.10 mm) from *Merck Serono KGaA* Darmstadt before chromatographic purification.

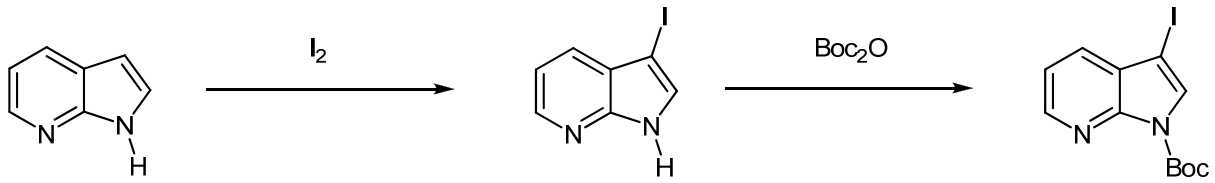
The reaction progress was monitored qualitatively using TLC Silica gel 60 F_{254} 5 x 7.5 cm aluminium sheets obtained by *Merck Serono KGaA* Darmstadt. The spots were detected with UV light at 254 nm and using aqueous potassium permanganate solution.

^{1}H, ^{13}C, and 135-DEPT NMR spectra were recorded on Bruker DRX 500 spectrometer. Acetone-d_6, $CDCl_3$ and DMSO-d_6 were used as deuterated solvents. TMS was used as reference (δ = 0.0) or the resonances of the solvents were locked as internal standards (acetone-d_6: ^{1}H δ 2.05, ^{13}C δ 30.8; $CDCl_3$: ^{1}H δ 7.26, ^{13}C δ 77.0; DMSO-d_6: ^{1}H δ 2.50, ^{13}C δ 39.4). The multiplicities of signals were abbreviated as follows: s: singlet; d: doublet; t: triplet; dd: doublet of doublets, ddd: doublet of doublets of doublets, dt: doublet of triplets, td: triplet of doublets, tt: triplet of triplets, q: quartet, quint: quintet, sext: sextet, m: multiplet and br: broad signal. The type of carbon atoms was determined on the basis of 135-DEPT NMR spectra.

EI mass spectra were measured on Finnigan MAT 8200 spectrometer. IR spectra were obtained on Bruker Vector 22 FT-IR. The solids were measured as KBr pellets and oils as films on KBr plates. The intensity of signals is abbreviated as follows: s (strong), m (medium) and w (weak). The melting points (uncorrected) were measured on Reichert-Jung Thermovar. Combustion analyses were carried out on Perkin Elmer Series II Analyser 2400 in the microanalytical laboratory of Institut für Pharmazeutische und Medizinische Chemie der Heinrich-Heine-Universität Düsseldorf.

2. Preparation of Starting Materials 1a, 1c, 1f and 1j

2.1. Preparation of tert-butyl 3-iodo-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (1a)[1]



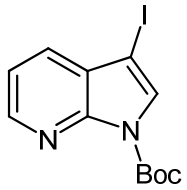
1a

A solution of iodine (25.7 g, 101 mmol) in 180 mL DMF was dropped to the solution of 7-azaindole (12.1 g, 100 mmol) and potassium hydroxide (16.5 g, 250 mmol) in 180 mL DMF at room temperature and the mixture was stirred for 45 min. The reaction mixture was then poored on 1 L ice water containing 1 % ammonia and 0.2 % sodium disulfite. The precipitate was filtered, washed with ice water and dried in vacuo to obtain 23.7 g (97.2 mmol, 97 % yield) of a yellow solid.

The obtained solid was used without further purification for the next step. It was suspended in 180 mL dichloromethane, 4-dimethylaminopyridine (1.21 g, 9.72 mmol) was added and di-*tert*-butyl dicarbonate (32.8 g, 146 mmol), dissolved in 180 mL dichloromethane, was added dropwise for 30 min. The mixture was stirred for 30 min. at room temperature, washed with 200 mL 0.1 *N* HCl, and the aqueous phase was extracted with dichloromethane (2 x 100 mL). The combined organic layers were dried with sodium sulphate, the solvents were removed under reduced pressure and the residue was adsorbed onto Celite® and purified chromatographically on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl acetate (PE-EtOAc = 5:1, R_f (PE-EtOAc = 20:1): 0.14) to give 31.6 g (91.8 mmol, 94 % yield; 92 % total yield over two steps) of **1a** as an orange oil, which solidifies upon storage in refrigerator.

[1] B. Witulski, N. Buschmann, U. Bergsträßer, *Tetrahedron* **2000**, *56*, 8473-8480.

tert-Butyl 3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (1a)



$C_{12}H_{13}IN_2O_2$

344.15

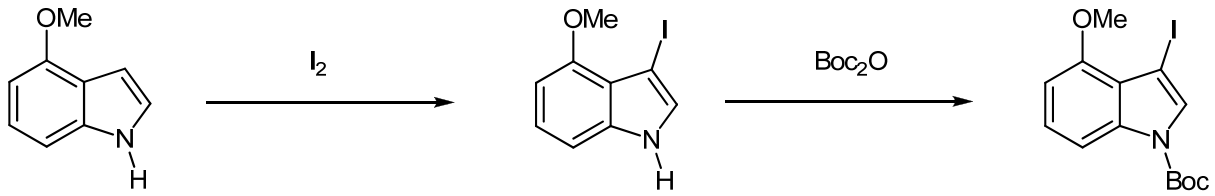
31.6 g (91.8 mmol, 92 % yield over two steps) as a yellow oil (solidified upon storage in refrigerator). Mp 79 °C. ^{1}H NMR (acetone-d_6, 300 MHz): δ 1.67 (s, 9 H), 7.36 (dd, *J* = 8.1 Hz, *J* = 4.8 Hz, 1 H), 7.75 (dd, *J* = 8.1 Hz, *J* = 1.5 Hz, 1 H), 7.99 (s, 1 H), 8.44 (dd, *J* = 4.8 Hz, *J* = 1.5 Hz, 1 H). ^{13}C NMR (acetone-d_6, 75 MHz): δ 28.1 (CH_3), 61.9 (C_{quat}), 84.8 (C_{quat}), 120.1 (CH), 125.8 (C_{quat}), 130.1 (CH), 132.1 (CH), 146.6 (CH), 147.8 (C_{quat}), 147.9 (C_{quat}). EI + MS (*m/z* (%)): 344 (M^+, 7), 271 ($(M-C_4H_9O)^+$, 3), 245 (10), 244 ($(M-C_5H_9O_2+H)^+$, 100), 217 ($(M-I)^+$, 5), 162 ($C_8H_6N_2O_2^+$, 13), 144 ($C_8H_4N_2O^+$, 1), 127 (I^+, 2), 117 ($C_7H_5N_2^+$, 14), 116 ($C_7H_4N_2^+$, 8), 57 ($C_4H_9^+$, 22).

Data reported in the literature:

T. A. Kelly, D. W. McNeil, J. M. Rose, E. David, C.-K. Shih, P. M. Grob, *J. Med. Chem*. **1997**, *40*, 2430-2433.

^{1}H NMR ($CDCl_3$): δ 1.70 (s, 9 H), 7.28 (dd, *J* = 8.5 Hz, 1 H), 7.72 (dd, *J* = 8.1 Hz, 1 H), 7.80 (s, 1 H), 8.49 (dd, *J* = 5.1 Hz, 1 H).

2.2. Preparation of tert-butyl 3-iodo-4-methoxy-1H-indole-1-carboxylate (1c)[1]



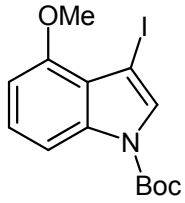
1c

A solution of iodine (2.57 g, 10.1 mmol) in 15 mL DMF was dropped to the solution of 4-methoxy-1*H*-indole (1.50 g, 10.0 mmol) and potassium hydroxide (1.65 g, 25.0 mmol) in 15 mL DMF at room temperature and the mixture was stirred for 45 min. The reaction mixture was then poored on 200 mL ice water containing 1 % ammonia and 0.2 % sodium disulfite. The precipitate was filtered, washed with ice water and dried in vacuo to obtain 3.34 g (8.58 mmol, 86 % yield) of a gray solid.

The obtained solid was used without further purification for the next step. It was suspended in 15 mL dichloromethane, 4-dimethylaminopyridine (106 mg, 0.86 mmol) was added and di-*tert*-butyl dicarbonate (2.90 g, 12.9 mmol), dissolved in 15 mL dichloromethane, was added dropwise for 25 min. The mixture was stirred for 30 min at room temperature, washed with 15 mL 0.1 *N* HCl, and the aqueous phase was extracted with dichloromethane (4 x 15 mL, monitored by TLC). The combined organic layers were dried with sodium sulphate, the solvents were removed under reduced pressure and the residue was adsorbed onto Celite® and purified chromatographically on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl acetate (PE-EtOAc = 100:1 → 50:1 (stepwise gradient), R_f (PE-EtOAc = 50:1): 0.21) to give 3.08 g (8.24 mmol, 96 % yield; 82 % total yield over two steps) of **1c** as a pale yellow oil, which solidifies upon storage in refrigerator to a pale yellow amorphous solid.

[1] B. Witulski, N. Buschmann, U. Bergsträßer, *Tetrahedron* **2000**, *56*, 8473-8480.

tert-Butyl 3-iodo-4-methoxy-1_H_-indole-1-carboxylate (1c)

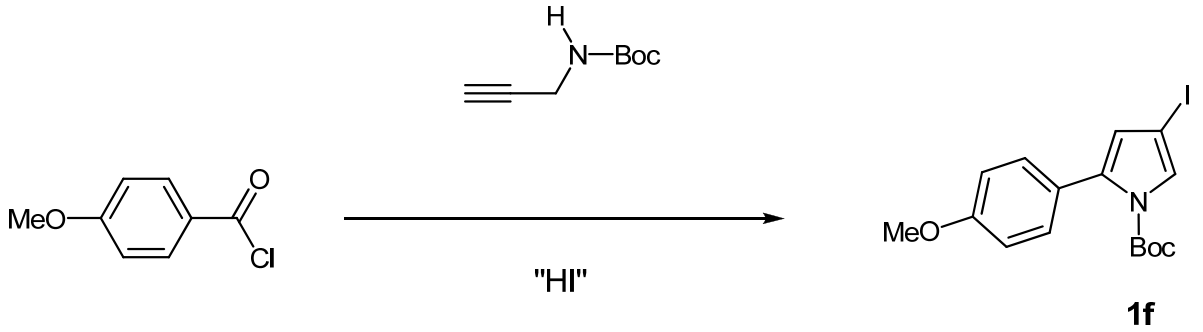


$C_{14}H_{16}INO_3$

373.19

3.08 g (8.24 mmol, 82 % yield over two steps) as a pale yellow oil (solidified upon storage in refrigerator). Mp 68 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.64 (s, 9 H), 3.92 (s, 3 H), 6.67 (d, *J* = 8.2 Hz, 1 H), 7.24 (t, *J* = 8.2 Hz, 1 H), 7.61 (s, 1 H), 7.80 (d, *J* = 8.2 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 28.1 (CH_3), 55.4 (CH_3), 57.6 (C_{quat}), 84.2 (C_{quat}), 104.0 (CH), 108.0 (CH), 119.6 (C_{quat}), 125.9 (CH), 130.0 (CH), 136.5 (C_{quat}), 148.5 (C_{quat}), 153.2 (C_{quat}). EI + MS (*m/z* (%)): 373 (M^+, 33), 317 ($(M-C_4H_9+H)^+$, 100), 273 ($(M-C_4H_9+H-CO_2)^+$, 56), 258 ($(M-C_4H_9+H-CO_2-CH_3)^+$, 23), 57 ($C_4H_9^+$, 83). IR (film): $\tilde{\nu}$ 3151 (w) cm^{-1}, 2979 (s), 2937 (m), 2837 (w), 1732 (s), 1606 (m), 1586 (s), 1494 (s), 1427 (s), 1394 (m), 1370 (s), 1339 (s), 1286 (s), 1153 (s), 1124 (s), 1046 (s), 955 (w), 903 (w), 852 (m), 819 (w), 775 (m), 735 (m), 696 (w), 668 (w), 597 (w). Anal. calcd for $C_{14}H_{16}INO_3$ (373.2): C 45.06, H 4.32, N 3.75. Found: C 45.07, H 4.11, N 3.56.

2.3. Preparation of tert-butyl 4-iodo-2-(4-methoxyphenyl)-1H-pyrrole-1-carboxylate (1f)[2]

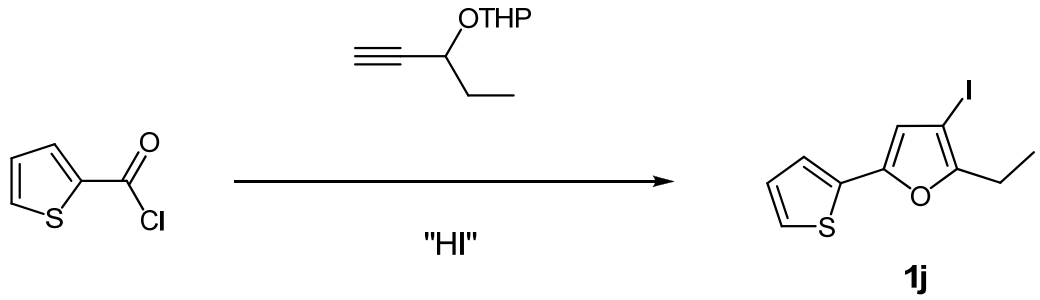


1f

$PdCl_2(PPh_3)_2$ (425 mg, 0.60 mmol, 2 mol %) and CuI (233 mg, 1.20 mmol, 4 mol %) were placed under argon atmosphere in a screw-cap vessel, which was then dried with a heat gun and cooled to room temperature (water bath). Then, 150 mL of dry THF were added and the mixture was degassed with argon. Dry triethylamine (4.16 mL, 30.0 mmol), 4-methoxybenzoyl chloride (5.28 g, 30.0 mmol), and *tert*-butyl prop-2-ynylcarbamate (4.66 g, 30.0 mmol) were successively added to the mixture which was stirred at room temperature for 1 h (monitored by TLC). Then, sodium iodide (22.7 g, 150 mmol), toluene-4-sulfonic acid monohydrate (11.6 g, 60.0 mmol) and 30 ml of *tert*-butanol were successively added to the mixture which was stirred at room temperature for 1 h (monitored by TLC). The reaction mixture was diluted with 300 mL brine, the phases were separated and the aqueous phase was extracted with dichloromethane (3 x 150 mL). The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuo the residue was absorbed onto Celite® and purified chromatographically on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl acetate (PE-EtOAc = 100:1) to give 9.23 g (23.1 mmol, 77 % yield) of the desired product (**1f**) as a colorless solid.

[2] Three-component synthesis of *N*-Boc-4-iodopyrroles and sequential one-pot alkynylation E. Merkul, C. Boersch, W. Frank, T. J. J. Müller, *Org. Lett.* **2009**, *11*, 2269-2272.

2.4. Preparation of 2-ethyl-3-iodo-5-(thiophen-2-yl)furan (1j)[3]



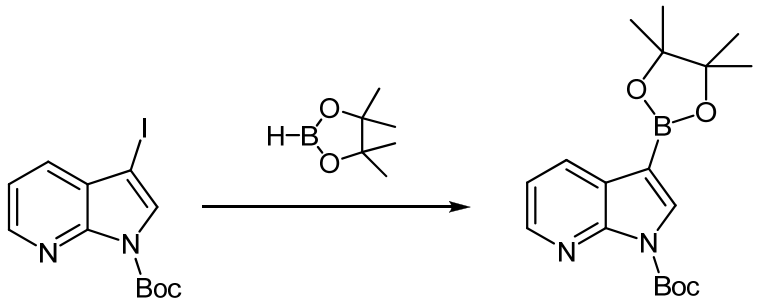
1j

$PdCl_2(PPh_3)_2$ (142 mg, 0.20 mmol, 2 mol %) and CuI (78 mg, 0.40 mmol, 4 mol %) were placed under argon atmosphere in a screw-cap vessel, which was then dried with a heat gun and cooled to room temperature (water bath). Then, 50 mL of dry THF were added and the mixture was degassed with argon. Dry triethylamine (1.39 mL, 10.0 mmol), thiophene-2-carbonyl chloride (1.50 g, 10.0 mmol), and tetrahydro-2-(pent-1-yn-3-yloxy)-2*H*-pyran (4.66 g, 10.0 mmol) were successively added to the mixture which was stirred at room temperature for 2 h (monitored by TLC). Then, sodium iodide (7.57 g, 50.0 mmol), toluene-4-sulfonic acid monohydrate (2.14 g, 11.0 mmol) and 30 ml of methanol were successively added to the mixture which was stirred at room temperature for 2 h (monitored by TLC). After removal of the solvents in vacuo the residue was absorbed onto Celite® and purified chromatographically on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl acetate (PE-EtOAc = 10:1) to give 2.72 g (8.93 mmol, 89 % yield) of **1j** as an orange oil.

A novel one-pot three-component synthesis of 3-halofurans and sequential Suzuki coupling A. S. Karpov, E. Merkul, T. Oeser, T. J. J. Müller, *Chem. Commun.* **2005**, 2581-2583.

[3] One-pot three-component synthesis of 3-halofurans and 3-chloro-4-iodofurans A. S. Karpov, E. Merkul, T. Oeser, T. J. J. Müller, *Eur. J. Org. Chem.* **2006**, 2991-3000.

3. Preparation of *tert*-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (2a)

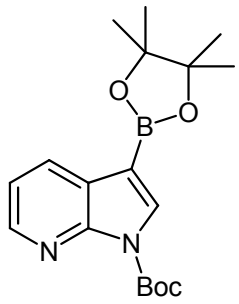


1a **2a**

Tetrakis(triphenylphosphane)-palladium(0) (35 mg, 0.03 mmol, 3 mol %) and *tert*-butyl 3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (**1a**) (344 mg, 1.00 mmol) were placed under argon atmosphere in a dry screw-cap vessel with septum. Then, 5 mL of dry dioxane were added and the mixture was degassed with argon. Dry triethylamine (1.39 mL, 10.0 mmol, 10.0 equiv), and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.22 mL, 1.50 mmol, 1.50 equiv) were successively added to the mixture which was stirred at 80 °C (preheated oil bath) for 3 h (monitored by TLC). Then, after cooling to room temperature (water bath), the solvent was removed in vacuo and the residue was absorbed onto Celite® and purified chromatographically* on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl acetate (PE-EtOAc = 5:1) to give 291 mg (0.85 mmol, 85 % yield) of **2a** as a yellow solid. Recrystallization from *n*-pentane gave colorless crystals.

*The purification was performed on Biotage SP-1 system using a 50 g silica gel SNAP cartridge.

tert-Butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1_H_-pyrrolo[2,3-_b_]pyridine-1-carboxylate (2a)



$C_{18}H_{25}BN_2O_4$

344.21

291 mg (0.85 mmol, 85 % yield) as a yellow solid. R_f (PE-EtOAc = 5:1): 0.30. Mp 97-98 °C. ^{1}H NMR (acetone-d_6, 500 MHz): δ 1.37 (s, 12 H), 1.68 (s, 9 H), 7.28 (dd, *J* = 7.6 Hz, *J* = 4.7 Hz, 1 H), 8.05 (s, 1 H), 8.21 (dd, *J* = 7.9 Hz, *J* = 1.9 Hz, 1 H), 8.40 (dd, *J* = 4.7 Hz, *J* = 1.6 Hz, 1 H). ^{13}C NMR (acetone-d_6, 125 MHz): δ 26.2 (CH_3), 29.2 (CH_3), 85.3 (C_{quat}), 85.6 (C_{quat}), 120.7 (CH), 127.7 (C_{quat}), 132.2 (CH), 137.6 (CH), 146.5 (CH), 149.5 (C_{quat}), 150.8 (C_{quat}), 207.1 (C_{quat}). EI + MS (*m/z* (%)): 344 (M^+, 10), 244 (100), 229 (28), 185 (10), 171 (9), 158 (37), 144 (62), 118 (12), 57 (13). Anal. calcd for $C_{18}H_{25}BN_2O_4$ (344.2): C 62.81, H 7.32, N 8.14. Found: C 62.75, H 7.39, N 8.10.

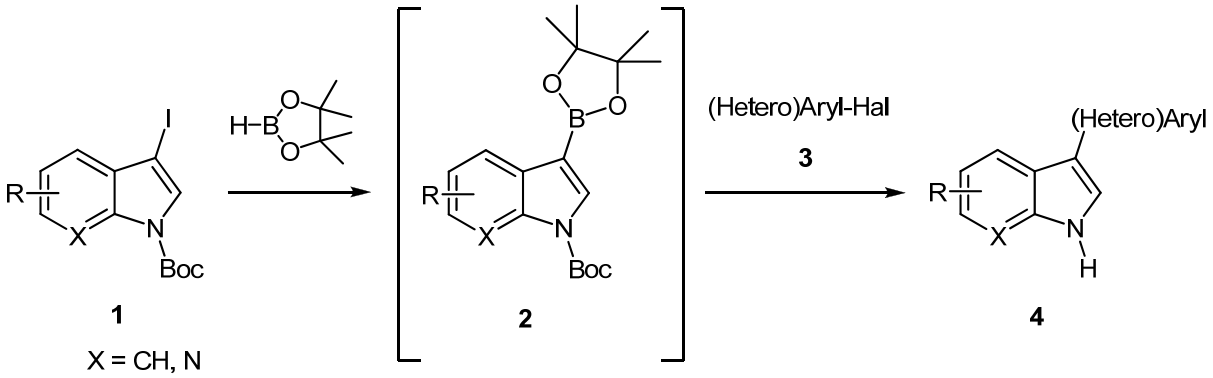
Data reported in the literature:

V. A. Kallepalli, F. Shi, S. Paul, E. N. Onyeozili, R. E. Maleczka Jr., M. R. Smith III, *J. Org. Chem.* **2009**, *74*, 9199-9201.

White solid. Mp 115-117 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.33 (br s, 12 H), 1.62 (br s, 9 H), 7.16-7.18 (dd, *J* = 7.8 Hz, *J* = 4.6 Hz, 1 H), 8.01 (br s, 1 H), 8.20-8.22 (dd, *J* = 7.8 Hz, *J* = 1.7 Hz, 1 H), 8.45-8.46 (dd, *J* = 4.9 Hz, *J* = 1.7 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 24.8 (CH_3), 28.1 (CH_3), 83.5 (C_{quat}), 84.3 (C_{quat}), 118.8 (CH), 126.1 (C_{quat}), 130.9 (CH), 135.4 (CH), 145.1 (CH), 147.6 (C_{quat}), 149.3 (C_{quat}), 207.1 (C_{quat}). GCMS (EI) (*m/z* (%)): 244 (100), 229 (38), 187 (35), 158 (37), 144 (46), 117 (11). ^{11}B NMR ($CDCl_3$, 96 MHz): δ 30.2. Anal. calcd for $C_{18}H_{25}BN_2O_4$ (344.2): C 62.81, H 7.32, N 8.14. Found: C 63.18, H 7.59, N 8.09.

4. Preparation of Compounds 4a-u by the *Masuda* Borylation – *Suzuki* Coupling Sequence

4.1. General Procedure



Tetrakis(triphenylphosphane)-palladium(0) (35 mg, 0.03 mmol, 3 mol %) and *tert*-butyl 3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (**1a**) (344 mg, 1.00 mmol) were placed under argon atmosphere in a dry screw-cap vessel with septum. Then, 5 mL of dry dioxane were added and the mixture was degassed with argon. Dry triethylamine (1.39 mL, 10.0 mmol, 10.0 equiv), and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.22 mL, 1.50 mmol, 1.50 equiv)* were successively added to the mixture which was stirred at 80 °C (preheated oil bath) for 3 h (monitored by TLC). Then, after cooling to room temperature (water bath), 5 mL of dry methanol, 1.00 mmol of (hetero)aryl halide **3** and cesium carbonate (823 mg, 2.50 mmol, 2.50 equiv) were successively added and the mixture was stirred at 100 °C overnight (preheated oil bath; for exact reaction times, see ***Table 2***). Then, after cooling to room temperature (water bath) the solvents were removed in vacuo and the residue was absorbed onto Celite® and purified chromatographically on silica gel with dichloromethane-methanol-aqueous ammonia (isocratic or stepwise gradient). The obtained bis(hetero)aryls **4** can be further purified by suspending in dichloromethane, sonication in ultrasound bath for 0.5-1.0 h, filtration and drying in vacuo overnight.

*For the preparation of compounds **4r**-**4t**, 3.00 equiv (0.44 mL, 3.00 mmol) of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (pinacolborane) were used.

The experimental details are given in ***Table 1***.

Table 1. Experimental details for the synthesis of bis(hetero)aryls **4**.

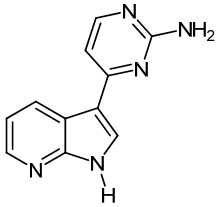
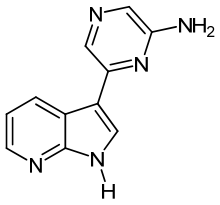
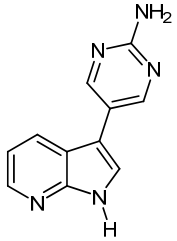
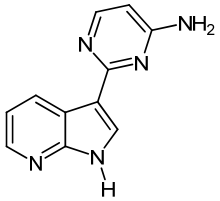
Entry	Substrate **1**	(Hetero)aryl halide **3**	Bis(hetero)aryl **4** (isolated yield %)	Chromatographic purification (eluent) UV purity
1	*tert*-Butyl 3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate 344 mg (1.00 mmol) **1a**	4-Chloro-pyrimidin-2-amine (*Synchem*) 134 mg (1.00 mmol) **3a**	Pale yellow solid 134 mg (0.63 mmol, 63 %)  **4a**	DCM-MeOH-NH_3 = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 → 100:6:1 HT-LC-MS: 100 %
2	344 mg (1.00 mmol) **1a**	6-Chloro-pyrazin-2-amine *(Synthonix)* 132 mg (1.00 mmol) **3b**	Green-brown solid 112 mg (0.53 mmol, 53 %)  **4b**	DCM-MeOH-NH_3 = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 → 100:6:1 → 100:7:1 HT-LC-MS: 100 %
3	344 mg (1.00 mmol) **1a**	5-Iodo-pyrimidin-2-amine (*Alfa Aesar*) 228 mg (1.00 mmol) **3c**	Pale yellow solid 139 mg (0.66 mmol, 66 %)  **4c**	DCM-MeOH-NH_3 = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 HT-LC-MS: 100 %
4	344 mg (1.00 mmol) **1a**	2-Chloro-pyrimidin-4-amine (*Aldrich*) 134 mg (1.00 mmol) **3d**	Beige solid 79 mg (0.37 mmol, 37 %)  **4d**	DCM-MeOH-NH_3 = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 → 100:6:1 HT-LC-MS: 98.1 %

Table 1 (continuation). Experimental details for the synthesis of bis(hetero)aryls **4**.

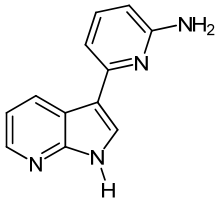
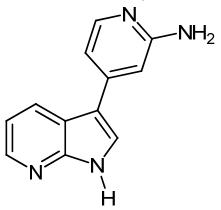
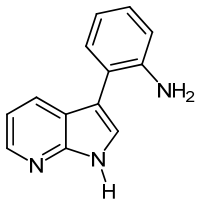
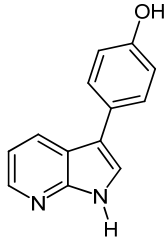
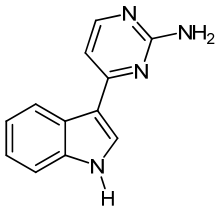
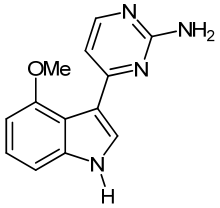
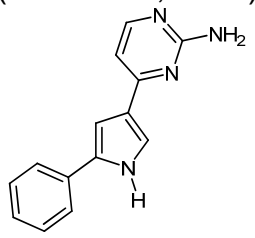
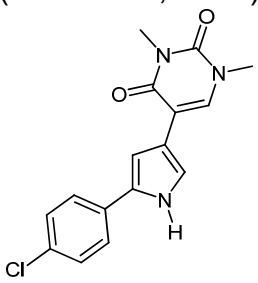
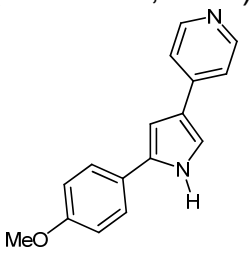
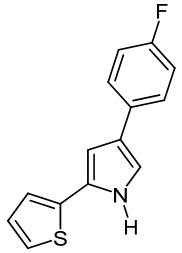
Entry	Substrate **1**	(Hetero)aryl halide **3**	Bis(hetero)aryl **4** (isolated yield %)	Chromatographic purification (eluent) UV purity
5	*tert*-Butyl 3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate 344 mg (1.00 mmol) **1a**	6-Bromo-pyridin-2-amine (*ABCR*) 177 mg (1.00 mmol) **3e**	Pale yellow solid 170 mg (0.81 mmol, 81 %)  **4e**	DCM-MeOH-NH_3 = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 → 100:6:1 HT-LC-MS: 100 %
6	344 mg (1.00 mmol) **1a**	4-Bromo-pyridin-2-amine (*Interchim*) 173 mg (1.00 mmol) **3f**	Yellow solid 135 mg (0.64 mmol, 64 %)  **4f**	DCM-MeOH-NH_3 = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 → 100:6:1 → 100:7:1 HT-LC-MS: 100 %
7	344 mg (1.00 mmol) **1a**	2-Iodo-benzen-amine (*Merck*) 221 mg (1.00 mmol) **3g**	Pale yellow solid 154 mg (0.74 mmol, 74 %)  **4g**	DCM-MeOH-NH_3 = 100:1:1 HT-LC-MS: 100 %
8	344 mg (1.00 mmol) **1a**	4-Iodo-phenol (*Alfa Aesar*) 222 mg (1.00 mmol) **3h**	Beige solid 120 mg (0.57 mmol, 57 %)  **4h**	DCM-MeOH-NH_3 = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 → 100:6:1 HT-LC-MS: 97.5 %

Table 1 (continuation). Experimental details for the synthesis of bis(hetero)aryls **4**.

Entry	Substrate **1**	(Hetero)aryl halide **3**	Bis(hetero)aryl **4** (isolated yield %)	Chromatographic purification (eluent) UV purity
9	*tert*-Butyl 3-iodo-1*H*-indole-1-carboxylate 343 mg (1.00 mmol) **1b**	4-Chloro-pyrimidin-2-amine (*Synchem*) 134 mg (1.00 mmol) **3a**	Pale yellow solid 154 mg (0.73 mmol, 73 %)  **4i**	DCM-MeOH-NH_3 = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 HT-LC-MS: 99.6 %
10	*tert*-Butyl 3-iodo-4-methoxy-1*H*-indole-1-carboxylate 373 mg (1.00 mmol) **1c**	134 mg (1.00 mmol) **3a**	Colorless solid 185 mg (0.77 mmol, 77 %)  **4j**	DCM-MeOH-NH_3 = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 → 100:6:1 HT-LC-MS: 100 %
11	*tert*-Butyl 4-iodo-2-phenyl-1*H*-pyrrole-1-carboxylate 369 mg (1.00 mmol) **1d**[a]	134 mg (1.00 mmol) **3a**	Rosa solid 190 mg (0.80 mmol, 80 %)  **4k**	DCM-MeOH-NH_3 = 100:1:1 → 100:2:1 HT-LC-MS: 98.2 %

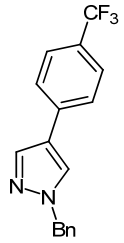
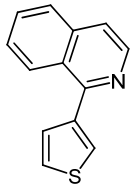
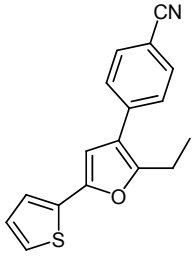
[a] Three-component synthesis of *N*-Boc-4-iodopyrroles and sequential one-pot alkynylation E. Merkul, C. Boersch, W. Frank, T. J. J. Müller, *Org. Lett.* **2009**, *11*, 2269-2272.

Table 1 (continuation). Experimental details for the synthesis of bis(hetero)aryls **4**.

Entry	Substrate **1**	(Hetero)aryl halide **3**	Bis(hetero)aryl **4** (isolated yield %)	Chromatographic purification (eluent) R_f (eluent) UV purity
12	*tert*-Butyl 2-(4-chloro-phenyl)-4-iodo-1*H*-pyrrole-1-carboxylate 404 mg (1.00 mmol) **1e**[a]	5-Iodo-1,3-dimethyl-pyrimidine-2,4(1*H*,3*H*)-dione (5-Iodo-1,3-dimethyl-uracil) (*Aldrich*) 269 mg (1.00 mmol) **3i**	Rosa solid 202 mg (0.64 mmol, 64 %)  **4l**	PE-EtOAc = 2:1 → 1:1 R_f (PE-EtOAc = 1:1): 0.32 HT-LC-MS: 100 %
13	*tert*-Butyl 4-iodo-2-(4-methoxy-phenyl)-1*H*-pyrrole-1-carboxylate 399 mg (1.00 mmol) **1f**[a]	4-Iodo-pyridine (*ABCR*) 214 mg (1.00 mmol) **3j**	Beige solid 151 mg (0.60 mmol, 60 %)  **4m**	DCM-MeOH-NH_3 = 100:1:1 → 100:2:1 → 100:3:1 HT-LC-MS: 100 %
14	*tert*-Butyl 4-iodo-2-(thiophen-2-yl)-1*H*-pyrrole-1-carboxylate 375 mg (1.00 mmol) **1g**[a]	1-Fluoro-4-iodobenzene (*ABCR*) 224 mg (1.00 mmol) **3k**	Pale gray solid 170 mg (0.70 mmol, 70 %)  **4n**	PE-EtOAc = 10:1 R_f (PE-EtOAc = 10:1): 0.21 HT-LC-MS: 100 %

[a] Three-component synthesis of *N*-Boc-4-iodopyrroles and sequential one-pot alkynylation E. Merkul, C. Boersch, W. Frank, T. J. J. Müller, *Org. Lett.* **2009**, *11*, 2269-2272.

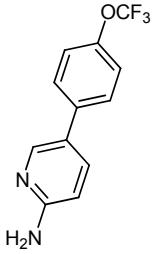
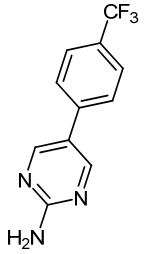
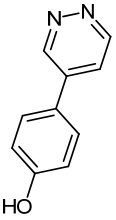
Table 1 (continuation). Experimental details for the synthesis of bis(hetero)aryls **4**.

Entry	Substrate **1**	(Hetero)aryl halide **3**	Bis(hetero)aryl **4** (isolated yield %)	Chromatographic purification (eluent) R_f (eluent) UV purity
15	1-Benzyl-4-iodo-1*H*-pyrazole (*ABCR*) 284 mg (1.00 mmol) **1h**	1-(Trifluoromethyl)-4-iodobenzene (*Alfa Aesar*) 278 mg (1.00 mmol) **3l**	Colorless solid 106 mg (0.35 mmol, 35 %)  **4o**	PE-EtOAc = 7:1 R_f (PE-EtOAc = 7:1): 0.17 HT-LC-MS: 100 %
16	3-Iodothiophene (*Alfa Aesar*) 219 mg (1.00 mmol) **1i**	1-Iodoisoquinoline (*Aldrich*) 263 mg (1.00 mmol) **3m**	Colorless solid 161 mg (0.76 mmol, 76 %)  **4p**	PE-EtOAc = 5:1 R_f (PE-EtOAc = 5:1): 0.35 HT-LC-MS: 100 %
17	2-Ethyl-3-iodo-5-(thiophen-2-yl)furan[b] 304 mg (1.00 mmol) **1j**	4-Iodobenzonitrile (*ABCR*) 234 mg (1.00 mmol) **3n**	Pale yellow solid 221 mg (0.79 mmol, 79 %)  **4q**	PE-EtOAc = 20:1 R_f (PE-EtOAc = 20:1): 0.36 Crystallization by suspension in *n*-pentane, sonication in ultrasound bath, filtration and drying in vacuo overnight HT-LC-MS: 100 %

[b] A novel one-pot three-component synthesis of 3-halofurans and sequential Suzuki coupling A. S. Karpov, E. Merkul, T. Oeser, T. J. J. Müller, *Chem. Commun.* **2005**, 2581-2583.

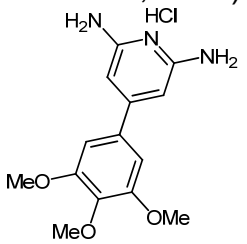
One-pot three-component synthesis of 3-halofurans and 3-chloro-4-iodofurans A. S. Karpov, E. Merkul, T. Oeser, T. J. J. Müller, *Eur. J. Org. Chem.* **2006**, 2991-3000.

Table 1 (continuation). Experimental details for the synthesis of bis(hetero)aryls **4**.

Entry	Substrate **1**	(Hetero)aryl halide **3**	Bis(hetero)aryl **4** (isolated yield %)	Chromatographic purification (eluent) UV purity
18	5-Iodo-pyridin-2-amine (*Alfa Aesar*) 227 mg (1.00 mmol) **1k**	1-Iodo-4-(trifluoro-methoxy)-benzene (*Alfa Aesar*) 294 mg (1.00 mmol) **3o**	Colorless solid 233 mg (0.92 mmol, 92 %)[c]  **4r**	DCM-MeOH-NH_3 = 100:1:1 HT-LC-MS: 100 %
19	5-Iodo-pyrimidin-2-amine (*Alfa Aesar*) 228 mg (1.00 mmol) **1l**	1-(Trifluoro-methyl)-4-iodobenzene (*Alfa Aesar*) 278 mg (1.00 mmol) **3l**	Colorless solid 105 mg (0.44 mmol, 44 %)[c]  **4s**	DCM-MeOH-NH_3 = 100:1:1 HT-LC-MS: 100 %
20	4-Iodophenol (*Alfa Aesar*) 225 mg (1.00 mmol) **1m**	4-Bromopyridazine hydrochloride[d] (*Aces Pharma*) 212 mg (1.00 mmol) **3p**	Rosa solid 121 mg (0.70 mmol, 70 %)[c]  **4t**	DCM-MeOH-NH_3 = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 → 100:6:1 → 100:7:1 HT-LC-MS: 100 %

[c] 3.00 equiv of HBpin have been used in the *Masuda* borylation step.
[d] Since the bromide **3p** was used as a hydrochloride, 3.0 equiv of Cs_2CO_3 were applied in the *Suzuki* coupling step.

Table 1 (continuation). Experimental details for the synthesis of bis(hetero)aryls **4**.

Entry	Substrate **1**	(Hetero)aryl halide **3**	Bis(hetero)aryl **4** (isolated yield %)	Chromatographic purification (eluent) UV purity
21	5-Iodo-1,2,3-trimethoxy-benzene (*Alfa Aesar*) 300 mg (1.00 mmol) **1n**	4-Bromopyridine-2,6-diamine (*ABCR*) 192 mg (1.00 mmol) **3q**	Orange solid 136 mg (0.44 mmol, 44 %)[e]  **4u**	DCM-MeOH-NH_3 = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 Purified by dissolving in 1.25 *M* HCl in EtOH (*Fluka*), precipitation with *n*-pentane, filtration and drying in vacuo overnight at 70 °C HT-LC-MS: 98.5 %

[e] The yield was determined after formation of the hydrochloride with solution of HCl in EtOH.

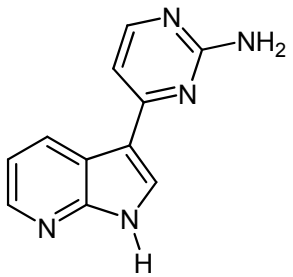
Table 2. Reaction times[a] in the synthesis of bis(hetero)aryls **4**.

Bis(hetero)aryl **4**	*Masuda* borylation step	*Suzuki* coupling step	Bis(hetero)aryl **4**	*Masuda* borylation step	*Suzuki* coupling step
4a	3 h	49 h	**4l**	4 h	23 h
4b	3 h	24 h	**4m**	4 h	19 h
4c	3 h	24 h	**4n**	4 h	19 h
4d	3 h	67 h	**4o**	4 h	18 h
4e	3 h	20 h	**4p**	4 h	17 h
4f	3 h	24 h	**4q**	4 h	23 h
4g	3 h	24 h	**4r**	4 h	17 h
4h	3 h	24 h	**4s**	4 h	18 h
4i	3 h	24 h	**4t**	3 h	19 h
4j	3 h	15 h	**4u**	4 h	18 h
4k	4 h	17 h			

[a] The reaction times for the *Suzuki* coupling step are not optimized. The actual reaction times might be much shorter than indicated. The actual reaction times of the *Masuda* borylation step may also be shorter in some cases.

4.2. Spectroscopic Data of the Compounds 4a-u

4.2.1. 4-(1*H*-Pyrrolo[2,3-*b*]pyridin-3-yl)pyrimidin-2-amine (*Meriolin 1*, 4a)



$C_{11}H_9N_5$

211.22

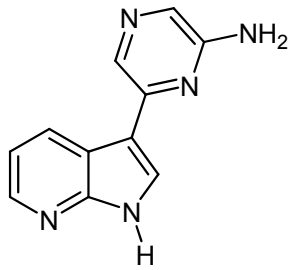
134 mg (0.63 mmol, 63 % yield) as a pale yellow solid. Mp 258-271 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 6.50 (s, 2 H, N$\underline{H}_2$), 7.06 (d, *J* = 5.4 Hz, 1 H), 7.19 (dd, *J* = 7.9 Hz, *J* = 4.7 Hz, 1 H), 8.14 (d, *J* = 5.4 Hz, 1 H), 8.29 (dd, *J* = 4.7 Hz, *J* = 1.6 Hz, 1 H), 8.35 (d, *J* = 2.8 Hz, 1 H), 8.93 (dd, *J* = 7.9 Hz, *J* = 1.6 Hz, 1 H), 12.2 (br, 1 H, N$\underline{H}$). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 104.9 (CH), 112.4 (C_{quat}), 116.6 (CH), 117.7 (C_{quat}), 128.3 (CH), 130.7 (CH), 143.3 (CH), 149.1 (C_{quat}), 157.2 (CH), 162.0 (C_{quat}), 163.5 (C_{quat}). EI + MS (*m/z* (%)): 212 (16), 211 (M^+, 100), 210 ($(M-H)^+$, 38), 195 ($(M-NH_2)^+$, 2), 170 (14).

Data reported in the literature:

P. M. Fresneda, P. Molina, J. A. Bleda, *Tetrahedron* **2001**, *57*, 2355-2363.

Yellow prisms. Mp 286-289 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.47 (s, 2 H, N$\underline{H}_2$), 7.05 (d, *J* = 5.13 Hz, 1 H, H-5´), 7.13 (dd, *J* = 8.12 Hz, *J* = 4.7 Hz, 1 H, H-5), 8.14 (d, *J* = 5.13 Hz, 1 H, H-6´), 8.28 (dd, *J* = 8.12 Hz, *J* = 1.28 Hz, 1 H, H-6), 8.33 (s, 1 H, H-2), 8.92 (dd, *J* = 4.7 Hz, *J* = 1.28 Hz, 1 H, H-4), 12.17 (s, 1 H, N$\underline{H}$). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 105.0 (C-5´), 112.5 (C-3), 116.6 (C-5), 117.8 (C-3a), 128.3 (C-2), 130.6 (C-6), 143.4 (C-4), 143.4 (C-7a), 157.2 (C-6´), 162.0 (C-4´), 163.5 (C-2´). EI + MS (*m/z* (%)): 212 (M^++1, 35), 211 (M^+, 100), 210 (68), 195 (11), 170 (48), 142 (31). IR (nujol): $\tilde{\nu}$ 3473 (m) cm^{-1}, 3294 (m), 3133 (m), 1670 (s), 1565 (s), 1223 (m). Anal. calcd for $C_{11}H_9N_5$ (211.2): C 62.55, H 4.29, N 33.16. Found: C 62.73, H 4.45, N 33.22.

4.2.2. 6-(1*H*-Pyrrolo[2,3-*b*]pyridin-3-yl)pyrazin-2-amine (4b)

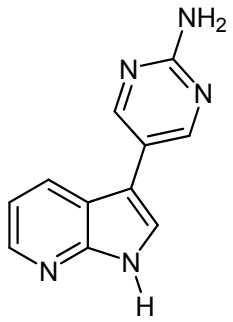


$C_{11}H_9N_5$

211.22

112 mg (0.53 mmol, 53 % yield) as a green-brown solid. Mp 241-243 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 6.36 (s, 2 H, N<u>H</u>$_2$), 7.17 (dd, *J* = 7.9 Hz, *J* = 4.7 Hz, 1 H), 7.67 (s, 1 H), 8.22 (d, *J* = 2.5 Hz, 1 H), 8.27-8.30 (m, 2 H), 8.82 (dd, *J* = 7.9 Hz, *J* = 1.6 Hz, 1 H), 12.1 (br, 1 H, N<u>H</u>). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 111.6 (C_{quat}), 116.3 (CH), 117.8 (C_{quat}), 125.8 (CH), 127.6 (CH), 127.9 (CH), 130.1 (CH), 143.2 (CH), 147.7 (C_{quat}), 149.0 (C_{quat}), 155.0 (C_{quat}). EI + MS (*m/z* (%)): 211 (M^+, 100), 184 ($C_{10}H_8N_4^+$, 23), 58 (13), 43 (32), 41 (10). IR (KBr): $\tilde{\nu}$ 3317 (s) cm^{-1}, 3146 (s), 1645 (m), 1575 (w), 1541 (s), 1522 (m), 1495 (m), 1470 (m), 1434 (s), 1366 (w), 1323 (w), 1295 (m), 1280 (w), 1245 (w), 1218 (w), 1139 (w), 1121 (w), 1030 (w), 1001 (w), 886 (w), 825 (w), 796 (w), 772 (w), 697 (w), 633 (w), 586 (w), 528 (w). Anal. calcd for $C_{11}H_9N_5$ (211.2): C 62.55, H 4.29, N 33.16. Found: C 62.47, H 4.38, N 32.92.

4.2.3. 5-(1*H*-Pyrrolo[2,3-*b*]pyridin-3-yl)pyrimidin-2-amine (4c)

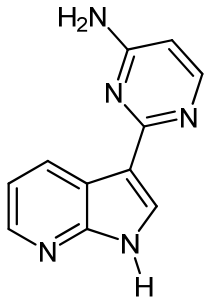


$C_{11}H_9N_5$

211.22

139 mg (0.66 mmol, 66 % yield) as a pale yellow solid. Mp 272 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 6.61 (s, 2 H, N<u>H</u>$_2$), 7.13 (dd, *J* = 7.9 Hz, *J* = 4.7 Hz, 1 H), 7.80 (d, *J* = 2.5 Hz, 1 H), 8.20 (dd, *J* = 7.9 Hz, *J* = 1.3 Hz, 1 H), 8.27 (dd, *J* = 4.7 Hz, *J* = 1.6 Hz, 1 H), 8.60 (s, 2 H), 11.9 (br, 1 H, N<u>H</u>). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 108.9 (C_{quat}), 115.7 (CH), 117.0 (C_{quat}), 117.6 (C_{quat}), 122.3 (CH), 127.3 (CH), 142.8 (CH), 148.7 (C_{quat}), 155.4 (CH), 161.9 (C_{quat}). EI + MS (*m/z* (%)): 211 (M^+, 100), 184 (10), 170 (12), 156 (13), 142 (22). IR (KBr): $\tilde{\nu}$ 3136 (s) cm^{-1}, 1670 (m), 1618 (m), 1534 (s), 1492 (s), 1423 (w), 1335 (w), 1293 (w), 1272 (w), 1219 (w), 1132 (w), 961 (w), 895 (w), 797 (w), 770 (m), 609 (w). Anal. calcd for $C_{11}H_9N_5$ (211.2): C 62.55, H 4.29, N 33.16. Found: C 62.73, H 4.13, N 32.99.

4.2.4. 2-(1*H*-Pyrrolo[2,3-*b*]pyridin-3-yl)pyrimidin-4-amine (4d)

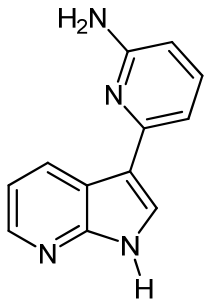


$C_{11}H_9N_5$

211.22

79 mg (0.37 mmol, 37 % yield) as a beige solid. Mp 239 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 6.23 (d, *J* = 6.0 Hz, 1 H), 6.7 (br, 2 H, N<u>H</u>$_2$), 7.16 (dd, *J* = 7.9 Hz, *J* = 4.4 Hz, 1 H), 8.08-8.11 (m, 2 H), 8.25 (dd, *J* = 4.4 Hz, *J* = 1.6 Hz, 1 H), 8.87 (dd, *J* = 7.9 Hz, *J* = 1.6 Hz, 1 H), 12.0 (br, 1 H, N<u>H</u>). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 101.4 (CH), 114.2 (C_{quat}), 116.3 (CH), 118.2 (C_{quat}), 128.0 (CH), 130.4 (CH), 142.9 (CH), 149.0 (C_{quat}), 155.0 (CH), 162.4 (C_{quat}), 163.1 (C_{quat}). EI + MS (*m/z* (%)): 211 (M^+, 100), 210 ($(M-H)^+$, 11), 195 ($(M-NH_2)^+$, 4), 144 (19), 58 (25), 43 (49). IR (KBr): $\tilde{\nu}$ 3418 (m) cm^{-1}, 3316 (m), 3210 (m), 1632 (m), 1579 (s), 1557 (m), 1533 (s), 1467 (s), 1435 (m), 1398 (w), 1369 (m), 1340 (w), 1297 (w), 1238 (w), 1124 (w), 1050 (w), 1019 (w), 984 (w), 901 (w), 828 (m), 803 (w), 777 (w), 671 (w), 599 (w), 530 (w). Anal. calcd for $C_{11}H_9N_5$ (211.2): C 62.55, H 4.29, N 33.16. Found: C 62.48, H 4.37, N 32.99.

4.2.5. 6-(1*H*-Pyrrolo[2,3-*b*]pyridin-3-yl)-pyridin-2-amine (4e)

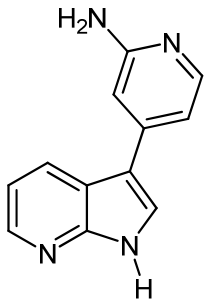


$C_{12}H_{10}N_4$

210.24

170 mg (0.81 mmol, 81 % yield) as a pale yellow solid. Mp 157-158 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 5.87 (s, 2 H, N<u>H</u>$_2$), 6.26 (dd, *J* = 8.2 Hz, *J* = 0.6 Hz, 1 H), 7.00 (dd, *J* = 7.6 Hz, *J* = 0.6 Hz, 1 H), 7.12 (dd, *J* = 7.9 Hz, *J* = 4.7 Hz, 1 H), 7.36 (t, *J* = 7.9 Hz, 1 H), 8.04 (d, *J* = 2.5 Hz, 1 H), 8.24 (dd, *J* = 4.4 Hz, *J* = 1.6 Hz, 1 H), 8.86 (dd, *J* = 7.9 Hz, *J* = 1.6 Hz, 1 H), 11.9 (br, 1 H, N<u>H</u>). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 104.2 (CH), 107.3 (CH), 114.6 (C_{quat}), 115.9 (CH), 117.8 (C_{quat}), 125.0 (CH), 130.3 (CH), 137.3 (CH), 142.7 (CH), 149.0 (C_{quat}), 152.8 (C_{quat}), 159.1 (C_{quat}). EI + MS (*m/z* (%)): 210 (M^+, 100), 209 ($(M-H)^+$, 15), 194 ($(M-NH_2)^+$, 5), 183 (26), 182 (15), 155 (16), 39 (11). IR (KBr): $\tilde{\nu}$ 3139 (m) cm^{-1}, 2892 (m), 1633 (m), 1595 (m), 1578 (s), 1528 (s), 1493 (w), 1469 (s), 1454 (s), 1412 (w), 1369 (w), 1339 (w), 1311 (w), 1295 (m), 1273 (w), 1186 (w), 1157 (w), 1129 (w), 895 (w), 819 (w), 800 (s), 771 (m), 733 (w), 675 (w), 630 (w), 582 (w), 525 (w). Anal. calcd for $C_{12}H_{10}N_4$ (210.2): C 68.56, H 4.79, N 26.65. Found: C 68.32, H 4.87, N 26.86.

4.2.6. 4-(1*H*-Pyrrolo[2,3-*b*]pyridin-3-yl)-pyridin-2-amine (4f)

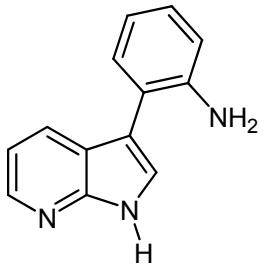


$C_{12}H_{10}N_4$

210.24

135 mg (0.64 mmol, 64 % yield) as a yellow solid. Mp 263-270 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 5.85 (s, 2 H, N$\underline{H}_2$), 6.87 (dd, *J* = 5.4 Hz, *J* = 1.6 Hz, 1 H), 6.89 (s, 1 H), 7.20 (dd, *J* = 7.9 Hz, *J* = 4.7 Hz, 1 H), 7.90 (d, *J* = 5.4 Hz, 1 H), 8.00 (d, *J* = 2.5 Hz, 1 H), 8.30 (dd, *J* = 4.7 Hz, *J* = 1.6 Hz, 1 H), 8.33 (dd, *J* = 8.2 Hz, *J* = 1.6 Hz, 1 H), 12.1 (br, 1 H, N$\underline{H}$). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 104.0 (CH), 109.6 (CH), 112.3 (C_{quat}), 116.2 (CH), 117.0 (C_{quat}), 125.2 (CH), 127.6 (CH), 143.0 (C_{quat}), 143.0 (CH), 147.9 (CH), 149.1 (C_{quat}), 160.3 (C_{quat}). EI + MS (*m/z* (%)): 210 (M^+, 100), 210 ((M-H)$^+$, 25), 183 (33), 182 (20), 170 (32), 155 (25), 142 (10), 63 (11), 41 (10), 39 (10). IR (KBr): $\tilde{\nu}$ 3314 (m) cm^{-1}, 3191 (m), 1639 (m), 1607 (s), 1538 (m), 1525 (m), 1507 (w), 1421 (s), 1365 (w), 1323 (w), 1289 (s), 1243 (w), 1174 (w), 1146 (w), 1071 (w), 992 (w), 881 (w), 835 (w), 802 (m), 778 (m), 627 (w), 579 (w). Anal. calcd for $C_{12}H_{10}N_4$ (210.2): C 68.56, H 4.79, N 26.65. Found: C 68.36, H 4.82, N 26.89.

4.2.7. 2-(1*H*-Pyrrolo[2,3-*b*]pyridin-3-yl)-benzenamine (4g)

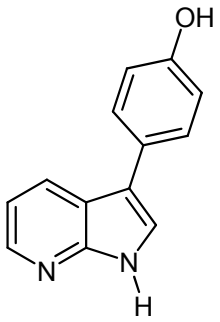


$C_{13}H_{11}N_3$

209.25

154 mg (0.74 mmol, 74 % yield) as a pale yellow solid. Mp 147 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 4.77 (s, 2 H, N<u>H</u>$_2$), 6.64 (td, *J* = 7.6 Hz, *J* = 1.3 Hz, 1 H), 6.80 (dd, *J* = 8.2 Hz, *J* = 1.3 Hz, 1 H), 7.01-7.05 (m, 1 H), 7.08 (dd, *J* = 7.9 Hz, *J* = 4.7 Hz, 1 H), 7.16 (dd, *J* = 7.6 Hz, *J* = 1.6 Hz, 1 H), 7.58 (d, *J* = 2.5 Hz, 1 H), 7.87 (dd, *J* = 7.9 Hz, *J* = 1.6 Hz, 1 H), 8.26 (dd, *J* = 4.7 Hz, *J* = 1.6 Hz, 1 H), 11.8 (br, 1 H, N<u>H</u>). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 111.9 (C_{quat}), 115.0 (CH), 115.4 (CH), 116.4 (CH), 118.3 (C_{quat}), 118.8 (C_{quat}), 124.1 (CH), 127.3 (CH), 127.7 (CH), 130.2 (CH), 142.7 (CH), 145.7 (C_{quat}), 148.6 (C_{quat}). EI + MS (*m/z* (%)): 209 (M^+, 100), 208 ($(M-H)^+$, 93), 193 ($C_{13}H_9N_2^+$, 12), 181 (39), 154 (33), 128 (22), 127 (35), 117 ($C_7H_5N_2^+$, 11), 77 (20). IR (KBr): $\tilde{\nu}$ 3364 (m) cm^{-1}, 3142 (s), 3029 (m), 2913 (m), 1614 (s), 1581 (m), 1536 (m), 1490 (m), 1448 (m), 1418 (m), 1339 (w), 1290 (m), 1265 (m), 1152 (w), 1107 (w), 963 (m), 937 (w), 896 (w), 797 (m), 774 (s), 750 (s), 645 (w), 621 (m), 590 (w), 514 (w). Anal. calcd for $C_{13}H_{11}N_3$ (209.3): C 74.62, H 5.30, N 20.08. Found: C 74.43, H 5.14, N 19.95.

4.2.8. 4-(1*H*-Pyrrolo[2,3-*b*]pyridin-3-yl)phenol (4h)

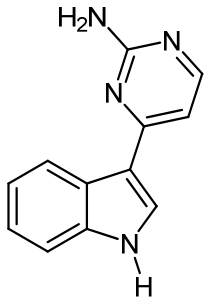


$C_{13}H_{10}N_2O$

210.23

120 mg (0.57 mmol, 57 % yield) as a beige solid. Mp 244 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 6.85-6.89 (m, 2 H), 7.12 (dd, *J* = 7.9 Hz, *J* = 4.7 Hz, 1 H), 7.50-7.54 (m, 2 H), 7.69 (d, *J* = 2.2 Hz, 1 H), 8.21 (dd, *J* = 8.2 Hz, *J* = 1.3 Hz, 1 H), 8.26 (dd, *J* = 4.7 Hz, *J* = 1.6 Hz, 1 H), 9.39 (s, 1 H, O<u>H</u>), 11.76 (s, 1 H, N<u>H</u>). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 114.5 (C_{quat}), 115.6 (CH), 115.6 (CH), 117.3 (C_{quat}), 122.2 (CH), 125.8 (C_{quat}), 127.3 (CH), 127.4 (CH), 142.6 (CH), 148.9 (C_{quat}), 155.5 (C_{quat}). EI + MS (*m/z* (%)): 210 (M^+, 100), 209 ($(M-H)^+$, 10), 182 (14), 181 (12), 154 (13), 127 (10), 105 (14), 97 (10), 71 (11), 57 (11). IR (KBr): $\tilde{\nu}$ 3387 (m) cm^{-1}, 3000 (m), 2673 (m), 1604 (m), 1583 (m), 1548 (s), 1504 (m), 1488 (m), 1461 (s), 1438 (s), 1386 (w), 1340 (w), 1324 (m), 1299 (w), 1256 (s), 1169 (m), 1142 (m), 1097 (s), 1043 (w), 964 (m), 836 (s), 817 (m), 797 (m), 774 (m), 578 (m), 540 (m), 503 (w). Anal. calcd for $C_{13}H_{10}N_2O$ (210.2): C 74.27, H 4.79, N 13.33. Found: C 74.04, H 4.86, N 13.62.

4.2.9. 4-(1*H*-Indol-3-yl)-pyrimidin-2-amine (*Meridianin G*, 4i)



$C_{12}H_{10}N_4$

210.23

154 mg (0.73 mmol, 73 % yield) as a pale yellow solid. Mp 195-197 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 6.42 (s, 2 H, N$\underline{H}_2$), 7.02 (dd, *J* = 5.4 Hz, *J* = 0.6 Hz, 1 H), 7.10-7.15 (m, 1 H), 7.15-7.20 (m, 1 H), 7.43-7.46 (m, 1 H), 8.10 (d, *J* = 5.4 Hz, 1 H), 8.20 (d, *J* = 2.5 Hz, 1 H), 8.59 (d, *J* = 7.9 Hz, 1 H), 11.7 (br, 1 H, N$\underline{H}$). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 105.2 (CH), 111.7 (CH), 113.6 (C_{quat}), 120.1 (CH), 121.8 (CH), 122.3 (CH), 125.2 (C_{quat}), 128.1 (CH), 136.9 (C_{quat}), 156.9 (CH), 162.6 (C_{quat}), 163.4 (C_{quat}). EI + MS (*m/z* (%)): 211 (15), 210 (M^+, 100), 209 ($(M-H)^+$, 34), 169 (60), 141 (10), 140 (14), 105 (12), 97 (12), 85 (10), 83 (10), 71 (12), 57 (14).

Data reported in the literature:

B. Jiang, C.-g. Yang, *Heterocycles* **2000**, *53*, 1489-1498.

Mp 262.2-264.3 °C (EtOAc/MeOH). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.39 (br s, 2 H), 7.02 (d, *J* = 5.3 Hz, 1 H), 7.15 (m, 2 H), 7.45 (d, *J* = 7.9 Hz, 1 H), 8.11 (d, *J* = 5.3 Hz, 1 H), 8.19 (s, 1 H), 8.59 (d, *J* = 7.4 Hz, 1 H), 11.65 (br s, 1 H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 105.2, 111.7, 113.6, 120.2, 121.9, 122.3, 125.3, 128.1, 136.9, 156.9, 162.6, 163.4. EI + MS (*m/z* (%)): 210 (M^+, 100), 209 (35), 169 (48), 155 (4), 140 (9), 114 (8), 89 (4). IR (KBr): $\tilde{\nu}$ 3408 cm^{-1}, 3329 , 3174, 1661, 1568, 1453, 1414, 1246, 1119. HRMS calcd for $C_{12}H_{10}N_4$: 210.0923. Found: 210.0914.

M. A. A. Radwan, M. El-Sherbiny, *Bioorg. Med. Chem.* **2007**, *15*, 1206-1211.

Mp 263-265 °C. ^{1}H NMR (DMSO-d_6, 270 MHz): δ 6.4 (br s, 2 H, N<u>H</u>$_2$), 7.03 (d, 1 H, H-5´), 7.15 (m, 2 H, H-5, H-6), 7.44-7.46 (d, 1 H, H-7), 8.11 (d, 1 H, H-6´), 8.19 (s, 1 H, H-2), 8.58-8.61 (d, 1 H, H-4), 11.65 (br s, 1 H, N<u>H</u>). ^{13}C NMR (DMSO-d_6, 300 MHz): δ 105.2 (C-5´), 111.71 (C-7), 113.70 (C-3), 120.21 (C-3a), 121.85 (C-6), 122.32 (C-5), 125.30 (C-4), 128.10 (C-2), 136.90 (C-7a), 156.91 (C-6´), 162.62 (C-4´), 163.40 (C-2´). EI + MS (*m/z* (%)): 210 (M^+, 100), 209 (36), 169 (49), 155 (4), 140 (10), 114 (8). IR (KBr): $\tilde{\nu}$ 3409 (NH_2) cm^{-1}, 3329 (NH_2), 3172 (NH), 1659, 1569, 1454, 1416, 1241, 1129, 808, 741, 684. Anal. calcd for $C_{12}H_{10}N_4$ (210.2): C 68.56, H 4.79, N 26.65. Found: C 68.72, H 4.76, N 26.47.

G. Simon, H. Couthon-Gourves, J.-P. Haelters, B. Corbel, N. Kervarec, F. Michaud, L. Meijer, *J. Het. Chem.* **2007**, *44*, 793-801.

Yellow powder. Mp 183-185 °C. ^{1}H NMR (acetone-d_6): δ 5.91 (br s, N<u>H</u>$_2$), 7.04 (d, *J* = 5.3 Hz, 1 H, H-5´), 7.10-7.22 (m, 2 H, H-5, H-6), 7.46 (d, *J* = 7.3 Hz, 1 H, H-7), 8.12 (m, 2 H, H-6´, H-2), 8.58 (d, *J* = 7.7 Hz, 1 H, H-4), 10.86 (br s, N<u>H</u>). ^{13}C NMR (acetone-d_6): δ 111.5 (C-5´), 117.2 (C-7), 120.2 (C-3), 126.0/127.7/128.0 (C-4/C-5/C-6), 131.4 (C-3a), 133.0 (C-2), 143.0 (C-7a), 162.7 (C-6´), 168.7/169.5 (C-2´/C-4´). IR (KBr): $\tilde{\nu}$ 3408 cm^{-1}, 3329, 3173, 1660, 1568, 1520, 1452, 1413, 1246, 751, 735. Anal. calcd for $C_{12}H_{10}N_4$ (210.2): C 68.56, H 4.79. Found: C 68.45, H 4.78.

E. Rossignol, A. Youssef, P. Moreau, M. Prudhomme, F. Anizon, *Tetrahedron* **2007**, *63*, 10169-10176.

Beige powder.

F. Tibiletti, M. Simonetti, K. M. Nicholas, G. Palmisano, M. Parravicini, F. Imbesi, S. Tollari, A. Penoni, *Tetrahedron* **2010**, *66*, 1280-1288.

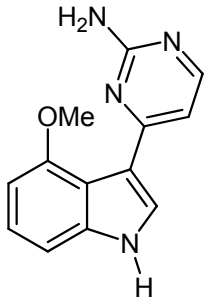
Dark-brown solid. Mp 183 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.40 (br, 2H), 7.01 (d, *J* = 5.3 Hz, 1 H), 7.18-7.19 (m, 2 H), 7.42 (d, *J* = 7.9 Hz, 1 H), 8.08 (d, *J* = 5.3 Hz, 1 H), 8.18 (d, *J* = 2.9 Hz, 1 H), 8.56 (d, *J* = 7.9 Hz, 1 H), 11.64 (br, 1H). MS (CI): *m/z* 211 (M+1). Anal. calcd for $C_{12}H_{10}N_4$: C 68.56, H 4.79, N 26.65. Found: C 68.47, H 4.81, N 26.72.

L. Núñez-Pons, R. Forestieri, R. M. Nieto, M. Varela, M. Nappo, J. Rodríguez, C. Jiménez, F. Castelluccio, M. Carbone, A. Ramos-Espla, M. Gavagnin, C. Avila, *Polar Biol.* **2010**, *33*, 1319-1329.

^{1}H NMR (DMSO-d_6, 600 MHz): δ 6.38 (s, N$\underline{H}_2$), 7.00 (d, *J* = 5.3 Hz, 1 H, H-5´), 7.10 (t, *J* = 6.8 Hz, 1 H, H-6), 7.16 (t, *J* = 6.8 Hz, 1 H, H-5), 7.42 (d, *J* = 7.9 Hz, 1 H, H-7), 8.08 (d, *J* = 5.3 Hz, 1 H, H-6´), 8.17 (d, *J* = 2.4 Hz, 1 H, H-2), 8.56 (d, *J* = 7.8 Hz, 1 H, H-4), 11.93 (br s, 1 H, N$\underline{H}$). ^{13}C NMR (DMSO-d_6, 300 MHz): δ 105.3 (d, C-5´), 111.8 (d, C-7), 113.2 (s, C-3), 120.2 (d, C-6), 121.9 (d, C-4), 122.4 (d, C-5), 125.2 (s, C-7a), 128.2 (d, C-2), 137.0 (s, C-3a), 157.0 (d, C-6´).

The NMR spectra are in good agreement with those reported in the literature. However, the melting point deviates immensely from the melting point reported by *Jiang* and *Radwan*.

4.2.10. 4-(4-Methoxy-1*H*-indol-3-yl)pyrimidin-2-amine (4j)

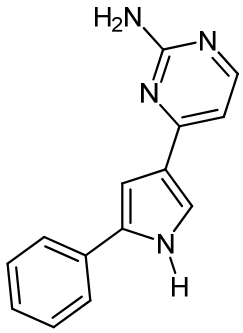


$C_{13}H_{12}N_4O$

240.26

185 mg (0.77 mmol, 77 % yield) as a colorless solid. Mp 221-222 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 3.87 (s, 3 H), 6.27 (s, 2 H, N$\underline{H}_2$), 6.63 (d, *J* = 6.9 Hz, 1 H), 7.06-7.12 (m, 2 H), 7.26 (dd, *J* = 5.4 Hz, *J* = 0.9 Hz, 1 H), 7.85 (d, *J* = 2.5 Hz, 1 H), 8.15 (d, *J* = 5.4 Hz, 1 H), 11.6 (br, 1 H, N$\underline{H}$). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 55.0 (CH_3), 101.2 (CH), 105.5 (CH), 109.7 (CH), 114.4 (C_{quat}), 115.4 (C_{quat}), 122.7 (CH), 127.5 (CH), 138.8 (C_{quat}), 153.2 (C_{quat}), 157.0 (CH), 161.8 (C_{quat}), 163.2 (C_{quat}). EI + MS (*m/z* (%)): 240 (M^+, 50), 239 ($(M-H)^+$, 21), 211 ($(M-CH_3O+H)^+$, 20), 202 ($(M-C_2H_2N+2H)^+$, 11), 58 ($CH_4N_3^+$, 41), 43 ($C_2H_3O^+$, 100). IR (KBr): $\tilde{\nu}$ 3465 (m) cm^{-1}, 3313 (m), 3165 (m), 1644 (m), 1624 (m), 1575 (s), 1555 (s), 1506 (s), 1459 (s), 1414 (m), 1359 (w), 1320 (m), 1275 (w), 1245 (m), 1212 (w), 1168 (w), 1130 (w), 1088 (m), 970 (w), 884 (w), 815 (w), 778 (w), 733 (m), 706 (w), 630 (w). Anal. calcd for $C_{13}H_{12}N_4O$ (240.3): C 64.99, H 5.03, N 23.32. Found: C 64.86, H 4.85, N 23.25.

4.2.11. 4-(5-Phenyl-1*H*-pyrrol-3-yl)pyrimidin-2-amine (4k)

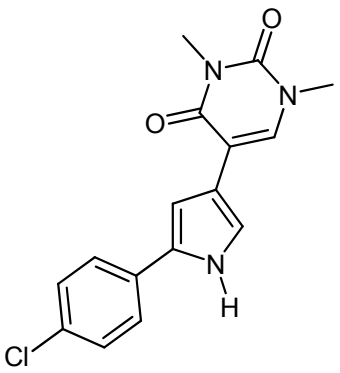


$C_{14}H_{12}N_4$

236.27

190 mg (0.80 mmol, 80 % yield) as a rosa solid. Mp 257 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 6.35 (s, 2 H, N$\underline{H}_2$), 6.87 (d, *J* = 5.0 Hz, 1 H), 7.06-7.08 (m, 1 H), 7.18-7.23 (m, 1 H), 7.37-7.41 (m, 2 H), 7.58-7.60 (m, 1 H), 7.66-7.70 (m, 2 H), 8.12 (d, *J* = 5.0 Hz, 1 H), 11.7 (br, 1 H, N$\underline{H}$). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 104.0 (CH), 104.9 (CH), 120.7 (CH), 123.5 (CH), 123.9 (C_{quat}), 126.0 (CH), 128.7 (CH), 132.1 (C_{quat}), 132.4 (C_{quat}), 157.5 (CH), 161.2 (C_{quat}), 163.5 (C_{quat}). EI + MS (*m/z* (%)): 237 (16), 236 (M^+, 100), 235 ($(M-H)^+$, 22), 195 (35), 133 (13). IR (KBr): $\tilde{\nu}$ 3408 (m) cm^{-1}, 3141 (w), 1631 (m), 1567 (s), 1543 (s), 1509 (w), 1455 (s), 1416 (m), 1369 (w), 1281 (w), 1203 (m), 1156 (w), 1110 (w), 1071 (w), 1031 (w), 990 (w), 926 (w), 900 (w), 874 (w), 815 (m), 793 (w), 751 (s), 694 (m), 593 (w), 528 (w). Anal. calcd for $C_{14}H_{12}N_4$ (236.3): C 71.17, H 5.12, N 23.71. Found: C 71.30, H 5.30, N 23.98.

4.2.12. 5-(5-(4-Chlorophenyl)-1*H*-pyrrol-3-yl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (4l)

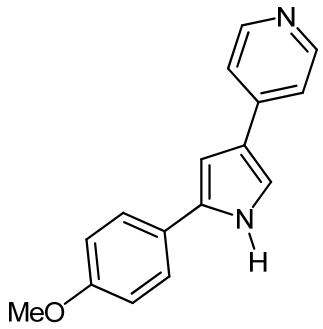


$C_{16}H_{14}ClN_3O_2$

315.75

202 mg (0.64 mmol, 64 % yield) as a rosa solid. Mp 256 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 3.25 (s, 3 H), 3.38 (s, 3 H), 6.93 (dd, *J* = 2.5 Hz, *J* = 1.6 Hz, 1 H), 7.41-7.45 (m, 2 H), 7.49 (dd, *J* = 2.5 Hz, *J* = 1.6 Hz, 1 H), 7.61-7.64 (m, 2 H), 8.04 (s, 1 H), 11.4 (br, 1 H, N<u>H</u>). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 27.6 (CH_3), 36.3 (CH_3), 103.3 (CH), 107.3 (C_{quat}), 116.7 (C_{quat}), 118.7 (CH), 124.8 (CH), 128.7 (CH), 129.8 (C_{quat}), 131.4 (C_{quat}), 137.8 (CH), 150.5 (C_{quat}), 161.5 (C_{quat}). EI + MS (*m/z* (%)): 317 ((M(^{37}Cl)$^+$, 36), 316 (20), 315 (M(^{35}Cl)$^+$, 100), 258 (22), 229 (11), 217 (27), 203 (13), 201 (28), 189 (18), 154 (13), 140 (14), 116 (10). IR (KBr): $\tilde{\nu}$ 3378 (m) cm^{-1}, 1694 (s), 1653 (s), 1627 (s), 1565 (w), 1515 (w), 1443 (m), 1404 (w), 1357 (w), 1231 (w), 1130 (m), 1048 (w), 928 (w), 828 (w), 800 (w), 754 (w), 726 (w), 608 (w), 540 (w). Anal. calcd for $C_{16}H_{14}ClN_3O_2$ (315.8): C 60.86, H 4.47, N 13.31. Found: C 60.93, H 4.71, N 13.11.

4.2.13. 4-(5-(4-Methoxyphenyl)-1*H*-pyrrol-3-yl)pyridine (4m)

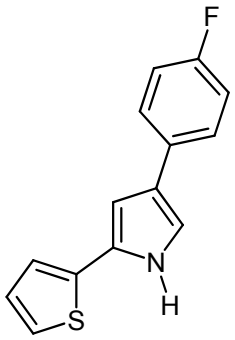


$C_{16}H_{14}N_2O$

250.30

151 mg (0.60 mmol, 60 % yield) as a beige solid. Mp 181-183 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 3.77 (s, 3 H), 6.93-7.00 (m, 3 H), 7.53-7.59 (m, 3 H), 7.60-7.65 (m, 2 H), 8.40-8.45 (m, 2 H), 11.6 (br, 1 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 55.0 (CH_3), 102.0 (CH), 114.1 (CH), 118.2 (CH), 118.8 (CH), 121.8 (C_{quat}), 124.9 (CH), 125.1 (C_{quat}), 133.0 (C_{quat}), 142.9 (C_{quat}), 149.6 (CH), 157.7 (C_{quat}). EI + MS (*m/z* (%)): 251 (21), 250 (M^+, 100), 236 (13), 235 ($(M-CH_3)^+$, 89), 207 (39), 206 (20), 205 (15), 180 (11), 179 (11), 178 (13), 153 (11), 152 (35), 151 (18), 128 (11), 127 (15), 126 (12), 125 (11), 102 (10), 89 (13), 77 (19), 76 (12), 63 (15), 51 (15). IR (KBr): $\tilde{\nu}$ 3114 (m) cm^{-1}, 3065 (m), 2991 (m), 2893 (m), 2834 (m), 1602 (s), 1543 (m), 1533 (w), 1505 (s), 1464 (m), 1440 (w), 1429 (m), 1376 (w), 1306 (w), 1287 (m), 1251 (s), 1216 (m), 1180 (m), 1165 (w), 1111 (w), 1094 (w), 1066 (w), 1038 (m), 1001 (m), 935 (w), 834 (m), 795 (s), 750 (w), 738 (w), 691 (m), 667 (w), 638 (w), 610 (w), 525 (m). Anal. calcd for $C_{16}H_{14}N_2O$ (250.3): C 76.78, H 5.64, N 11.19. Found: C 76.51, H 5.80, N 11.20.

4.2.14. 4-(4-Fluorophenyl)-2-(thiophen-2-yl)-1*H*-pyrrole (4n)

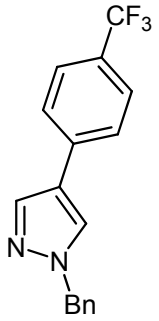


$C_{14}H_{10}FNS$

243.30

170 mg (0.70 mmol, 70 % yield) as a pale gray solid. Mp 163 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 6.67-6.69 (m, 1 H), 7.05 (dd, *J* = 5.0 Hz, *J* = 3.8 Hz, 1 H), 7.11-7.16 (m, 2 H), 7.26 (dd, *J* = 3.5 Hz, *J* = 0.9 Hz, 1 H), 7.29 (dd, *J* = 2.5 Hz, *J* = 1.9 Hz, 1 H), 7.35 (dd, *J* = 5.0 Hz, *J* = 0.9 Hz, 1 H), 7.58-7.64 (m, 2 H), 11.48 (s, 1 H, N<u>H</u>). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 103.3 (CH), 115.2 (d, *J* = 21.1 Hz, CH), 116.1 (CH), 120.9 (CH), 122.7 (CH), 123.5 (C_{quat}), 126.0 (d, *J* = 8.2 Hz, CH), 127.1 (C_{quat}), 127.7 (CH), 131.9 (d, *J* = 2.7 Hz, C_{quat}), 135.9 (C_{quat}), 160.2 (d, *J* = 241.9 Hz, C_{quat}). EI + MS (*m/z* (%)): 244 (18), 243 (M^+, 100), 242 ($(M-H)^+$, 14), 215 (14), 183 (11), 133 (18), 122 (19). IR (KBr): $\tilde{\nu}$ 3412 (s) cm^{-1}, 3123 (w), 1655 (w), 1578 (w), 1535 (w), 1501 (m), 1420 (w), 1300 (w), 1224 (m), 1161 (w), 1130 (m), 1098 (w), 1047 (w), 1010 (w), 924 (w), 840 (s), 811 (w), 793 (s), 770 (m), 685 (s), 662 (m), 597 (w), 577 (w), 538 (m), 515 (s). Anal. calcd for $C_{14}H_{10}FNS$ (243.3): C 69.11, H 4.14, N 5.76. Found: C 69.29, H 4.35, N 5.68.

4.2.15. 1-Benzyl-4-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole (4o)

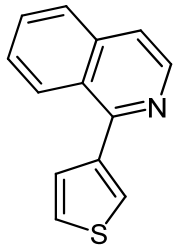


$C_{17}H_{13}F_3N_2$

302.29

106 mg (0.35 mmol, 35 % yield) as a colorless solid. Mp 106 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.35 (s, 2 H), 7.26-7.30 (m, 2 H), 7.31-7.40 (m, 3 H), 7.52-7.56 (m, 2 H), 7.56-7.60 (m, 2 H), 7.67 (s, 1 H), 7.86 (s, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 56.3 (CH_2), 122.2, 124.2 (q, *J* = 272.2 Hz, C_{quat}), 125.4, 125.8 (q, *J* = 3.7 Hz, CH), 126.6, 127.8, 128.2 (q, *J* = 33.0 Hz, C_{quat}), 128.3, 128.9, 136.0, 136.1 (q, *J* = 1.8 Hz, CH), 137.1. EI + MS (*m/z* (%)): 303 (10), 302 (M^+, 49), 301 ($(M-H)^+$, 51), 91 ($C_7H_7^+$, 100), 65 ($C_5H_5^+$, 11). IR (KBr): $\tilde{\nu}$ 3106 (w) cm^{-1}, 2925 (w), 2852 (w), 1620 (m), 1456 (w), 1432 (w), 1337 (s), 1229 (w), 1158 (s), 1113 (s), 1080 (m), 1062 (m), 1000 (w), 953 (w), 842 (m), 729 (m), 693 (w), 597 (w), 510 (w), 453 (w). Anal. calcd for $C_{17}H_{13}F_3N_2$ (302.3): C 67.54, H 4.33, N 9.27. Found: C 67.70, H 4.31, N 9.02.

4.2.16. 1-(Thiophen-3-yl)isoquinoline (4p)



$C_{13}H_9NS$

211.28

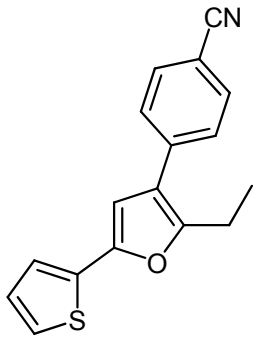
161 mg (0.76 mmol, 76 % yield) as a colorless solid. Mp 91-92 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.49 (dd, *J* = 5.0 Hz, *J* = 2.8 Hz, 1 H), 7.54 (dd, *J* = 5.0 Hz, *J* = 1.3 Hz, 1 H), 7.55-7.59 (m, 1 H), 7.61 (d, *J* = 5.7 Hz, 1 H), 7.67-7.71 (m, 1 H), 7.72 (dd, *J* = 2.8 Hz, *J* = 1.3 Hz, 1 H), 7.87 (d, *J* = 8.2 Hz, 1 H), 8.28 (d, *J* = 8.5 Hz, 1 H), 8.57 (d, *J* = 5.7 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 119.9 (CH), 125.7 (CH), 126.1 (CH), 126.9 (C_{quat}), 127.0 (CH), 127.2 (CH), 127.3 (CH), 129.2 (CH), 130.0 (CH), 136.8 (C_{quat}), 140.7 (C_{quat}), 142.2 (CH), 155.9 (C_{quat}). EI + MS (*m/z* (%)): 212 (12), 211 (M^+, 57), 210 ($(M-H)^+$, 100), 166 ($C_{12}H_8N^+$, 13), 139 (9), 128 ($C_9H_6N^+$, 3), 84 ($C_4H_4S^+$, 10), 83 ($C_4H_3S^+$, 4). IR (KBr): $\tilde{\nu}$ 3047 (w) cm^{-1}, 1614 (w), 1579 (w), 1552 (m), 1524 (w), 1494 (w), 1452 (w), 1415 (m), 1333 (m), 1306 (m), 1215 (w), 1192 (w), 1138 (w), 1061 (w), 1018 (w), 988 (w), 963 (w), 901 (m), 867 (m), 833 (m), 810 (s), 792 (m), 774 (m), 753 (s), 708 (w), 683 (s), 661 (w), 639 (w), 612 (w), 567 (w), 514 (w). Anal. calcd for $C_{13}H_9NS$ (211.3): C 73.90, H 4.29, N 6.63. Found: C 73.72, H 4.22, N 6.62.

Data reported in the literature:

K. L. Billingsley, T. E. Barder, S. L. Buchwald, *Angew. Chem.* **2007**, *119*, 5455-5459; *Angew. Chem. Int. Ed.* **2007**, *46*, 5359-5363.

Yellow solid. Mp 74-75 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.49 (ddd, *J* = 6 Hz, *J* = 3 Hz, *J* = 1 Hz, 1 H), 7.55 (dt, *J* = 1.6 Hz, 1 H), 7.57 (dt, *J* = 1.8 Hz, 1 H), 7.62 (d, *J* = 6 Hz, 1 H), 7.69 (dt, *J* = 1.8 Hz, 1 H), 7.72 (dt, *J* = 1.3 Hz, 1 H), 7.87 (d, *J* = 8 Hz, 1 H), 8.29 (d, *J* = 8 Hz, 1 H), 8.58 (d, *J* = 6 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 119.8, 125.6, 126.0, 126.9, 127.1, 127.3, 129.1, 130.0, 130.5, 136.7, 140.6, 142.1, 155.8. IR (neat): $\tilde{\nu}$ 3105 cm^{-1}, 3049, 1620, 1582, 1555, 1498, 1418, 1337, 1309. Anal. calcd for $C_{13}H_9NS$ (211.3): C 73.90, H 4.29. Found: C 73.79, H 4.25.

4.2.17. 4-(2-Ethyl-5-(thiophen-2-yl)furan-3-yl)benzonitrile (4q)

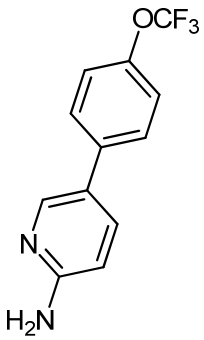


$C_{17}H_{13}NOS$

279.36

221 mg (0.79 mmol, 79 % yield) as a pale yellow solid (after crystallization by suspension in *n*-pentane, sonication in ultrasound bath, filtration and drying in vacuo overnight). Mp 108 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.34 (t, *J* = 7.6 Hz, 3 H), 2.85 (q, *J* = 7.6 Hz, 2 H), 6.60 (s, 1 H), 7.05 (dd, *J* = 5.0 Hz, *J* = 3.8 Hz, 1 H), 7.24 (dd, *J* = 5.0 Hz, *J* = 0.9 Hz, 1 H), 7.27 (dd, *J* = 3.5 Hz, *J* = 0.9 Hz, 1 H), 7.47-7.51 (m, 2 H), 7.66-7.70 (m, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 12.8 (CH_3), 20.6 (CH_2), 105.6 (CH), 110.0 (C_{quat}), 119.0 (C_{quat}), 121.0 (C_{quat}), 122.6 (CH), 124.2 (CH), 127.7 (CH), 128.0 (CH), 132.4 (CH), 133.2 (C_{quat}), 138.7 (C_{quat}), 147.9 (C_{quat}), 153.5 (C_{quat}). EI + MS (*m/z* (%)): 280 (12), 279 (M^+, 59), 265 (18), 264 ($(M\text{-}CH_3)^+$, 100), 166 (22), 164 (17), 131 (13), 129 (13), 111 (23). IR (KBr): $\tilde{\nu}$ 2975 (w) cm^{-1}, 2222 (s), 1606 (s), 1503 (w), 1203 (w), 1177 (w), 1133 (w), 1060 (m), 983 (m), 947 (w), 840 (m), 799 (m), 707 (s), 567 (m), 549 (m). Anal. calcd for $C_{17}H_{13}NOS$ (279.4): C 73.09, H 4.69, N 5.01. Found: C 72.99, H 4.43, N 4.91.

4.2.18. 5-(4-(Trifluoromethoxy)phenyl)pyridin-2-amine (4r)

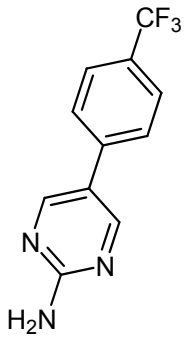


$C_{12}H_9F_3N_2O$

254.21

233 mg (0.92 mmol, 92 % yield) as a colorless solid. Mp 98-101 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 6.12 (s, 2 H, N$\underline{H}_2$), 6.54 (d, *J* = 8.5 Hz, 1 H), 7.34-7.38 (m, 2 H), 7.65-7.68 (m, 2 H), 7.70 (dd, *J* = 8.5 Hz, *J* = 2.5 Hz, 1 H), 8.24 (d, *J* = 2.5 Hz, 1 H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 108.1 (CH), 120.2 (q, *J* = 255.7 Hz, C_{quat}), 121.6 (CH), 122.6 (C_{quat}), 127.1 (CH), 135.6 (CH), 137.6 (C_{quat}), 146.0 (CH), 147.0 (q, *J* = 1.8 Hz, C_{quat}), 159.5 (C_{quat}). EI + MS (*m/z* (%)): 255 (13), 254 (M^+, 100), 185 ($(M\text{-}CF_3)^+$, 30), 158 (12). IR (KBr): $\tilde{\nu}$ 3490 (w) cm^{-1}, 3466 (w), 3298 (w), 3150 (w), 1638 (s), 1634 (s), 1603 (m), 1562 (w), 1494 (s), 1423 (w), 1389 (m), 1249 (s), 1147 (s), 1017 (w), 997 (w), 857 (w), 827 (w), 806 (w), 671 (w), 537 (w), 509 (w). Anal. calcd for $C_{12}H_9F_3N_2O$ (254.2): C 56.70, H 3.57, N 11.02. Found: C 56.64, H 3.57, N 10.75.

4.2.19. 5-(4-(Trifluoromethyl)phenyl)pyrimidin-2-amine (4s)



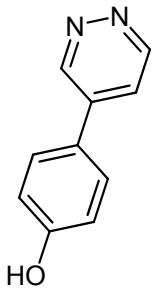
$C_{11}H_8F_3N_3$

239.20

105 mg (0.44 mmol, 44 % yield) as a colorless solid. Mp < 176 °C (subl.)*. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 6.93 (s, 2 H, N<u>H</u>$_2$), 7.73-7.76 (m, 2 H), 7.82-7.86 (m, 2 H), 8.65 (s, 2 H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 120.6 (C_{quat}), 124.5 (q, *J* = 272.2 Hz, C_{quat}), 125.8 (CH), 125.9 (q, *J* = 3.7 Hz, CH), 127.3 (q, *J* = 32.1 Hz, C_{quat}), 139.5 (C_{quat}), 156.5 (CH), 163.3 (C_{quat}). EI + MS (*m/z* (%)): 240 (13), 239 (M^+, 100), 238 ($(M-H)^+$, 26), 211 (10), 198 (13), 170 (28), 169 (12), 151 (12), 120 (17). IR (KBr): $\tilde{\nu}$ 3478 (w) cm^{-1}, 3321 (w), 3165 (w), 1661 (m), 1638 (m), 1599 (m), 1550 (w), 1528 (w), 1482 (m), 1424 (w), 1382 (w), 1324 (s), 1300 (m), 1224 (w), 1174 (m), 1133 (m), 1112 (m), 1071 (m), 1013 (w), 838 (m), 799 (w), 721 (w), 664 (w), 639 (w), 599 (w), 517 (w). Anal. calcd for $C_{11}H_8F_3N_3$ (239.2): C 55.23, H 3.37, N 17.57. Found: C 55.23, H 3.44, N 17.46.

*Slow sublimation with not clearly detectable sublimation point.

4.2.20. 4-(Pyridazin-4-yl)phenol (4t)



$C_{10}H_8N_2O$

172.18

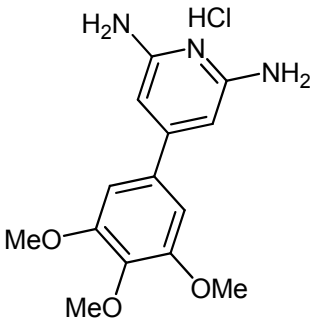
121 mg (0.70 mmol, 70 % yield) as a rosa solid. Mp 242 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 6.91-6.95 (m, 2 H), 7.76-7.80 (m, 2 H), 7.88 (dd, *J* = 5.4 Hz, *J* = 2.5 Hz, 1 H), 9.14 (dd, *J* = 5.4 Hz, *J* = 1.3 Hz, 1 H), 9.55 (dd, *J* = 2.5 Hz, *J* = 1.3 Hz, 1 H), 10.2 (br, 1 H, O<u>H</u>). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 116.4 (CH), 122.0 (CH), 124.2 (C_{quat}), 128.7 (CH), 137.2 (C_{quat}), 149.0 (CH), 151.5 (CH), 159.6 (C_{quat}). EI + MS (*m/z* (%)): 173 (13), 172 (M^+, 100), 118 (41), 115 (30), 91 (10), 89 (16). IR (KBr): $\tilde{\nu}$ 3448 (w) cm^{-1}, 3073 (w), 1615 (w), 1574 (s), 1515 (m), 1444 (w), 1390 (w), 1360 (w), 1285 (s), 1242 (w), 1177 (m), 1111 (w), 1046 (w), 979 (w), 839 (w), 812 (m), 789 (w), 745 (w), 665 (w), 571 (w). Anal. calcd for $C_{10}H_8N_2O$ (172.2): C 69.76, H 4.68, N 16.27. Found: C 69.49, H 4.91, N 16.10.

Data reported in the literature:

R. Stoermer, O. Gaus, *Ber. dtsch. Chem. Ges.* **1912**, *45*, 3104-3113.

Long colorless needles (EtOH). Mp 242 °C. Anal. calcd for $C_{10}H_8N_2O$ (172.2): N 15.92. Found: N 16.23.

4.2.21. 4-(3,4,5-Trimethoxyphenyl)pyridine-2,6-diamine hydrochloride (4u)



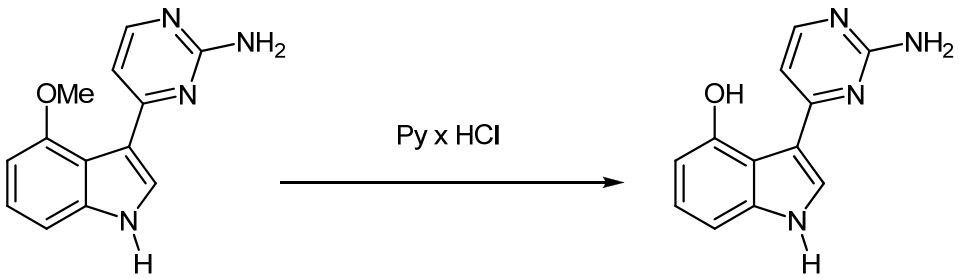
$C_{14}H_{18}ClN_3O_3$

311.76

136 mg (0.44 mmol, 44 % yield) as an orange solid (after crystallization with *n*-pentane from 1.25 *M* HCl in EtOH, filtration, washing with *n*-pentane, and drying in vacuo overnight at 70 °C). Mp 128-135 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.34 (t, *J* = 7.6 Hz, 3 H), 2.85 (q, *J* = 7.6 Hz, 2 H), 6.60 (s, 1 H), 7.05 (dd, *J* = 5.0 Hz, *J* = 3.8 Hz, 1 H), 7.24 (dd, *J* = 5.0 Hz, *J* = 0.9 Hz, 1 H), 7.27 (dd, *J* = 3.5 Hz, *J* = 0.9 Hz, 1 H), 7.47-7.51 (m, 2 H), 7.66-7.70 (m, 2 H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 12.8 (CH_3), 20.6 (CH_2), 105.6 (CH), 110.0 (C_{quat}), 119.0 (C_{quat}), 121.0 (C_{quat}), 122.6 (CH), 124.2 (CH), 127.7 (CH), 128.0 (CH), 132.4 (CH), 133.2 (C_{quat}), 138.7 (C_{quat}), 147.9 (C_{quat}), 153.5 (C_{quat}). EI + MS (*m/z* (%)): 276 (17), 275 ((M-HCl)$^+$, 100), 260 ((M-HCl-CH_3)$^+$, 17), 217 ($C_{11}H_{11}N_3O_2^+$, 20), 108 ($C_5H_6N_3^+$, 5). IR (KBr): $\tilde{\nu}$ 3410 (m) cm^{-1}, 3334 (m), 3207 (m), 2941 (w), 2837 (w), 2741 (w), 1645 (s), 1588 (m), 1518 (w), 1492 (w), 1463 (w), 1413 (w), 1378 (m), 1325 (m), 1267 (w), 1245 (w), 1169 (w), 1127 (s), 999 (m), 965 (w), 831 (w), 807 (w), 757 (w), 720 (w), 562 (w), 524 (w). Anal. calcd for $C_{14}H_{18}ClN_3O_3$ (311.8): C 53.93, H 5.82, N 13.48. Found: C 53.73, H 6.03, N 13.35.

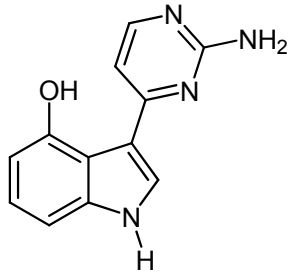
4.3. Synthesis of Meridianin A (5)

Synthesis of 3-(2-aminopyrimidin-4-yl)-1*H*-indol-4-ol (*Meridianin A*, 5*)*



Pyridinium hydrochloride (1.18 g, 10.0 mmol) was placed in a dry screw-cap vessel under argon atmosphere. Then, 4-(4-methoxy-1*H*-indol-3-yl)pyrimidin-2-amine (**4j**) (120 mg, 0.50 mmol) was added and the mixture was heated to 210 °C (preheated oil bath). After 30 min, the mixture was cooled to 50 °C (preheated oil bath) and methanol was added to dissolve the residue. The reaction mixture was monitored by TLC. The mixture was adsorbed on Celite® and the solvents were removed under reduced pressure. The residue was purified chromatographically on silica gel with dichloromethane-methanol-aqueous ammonia DCM-MeOH-NH_3 = 100:1:1 → 100:2:1 → 100:3:1→ 100:4:1 (stepwise gradient). After drying in vacuo, *meridianin A* (**5**) was obtained as a bright yellow fine crystalline solid.

Spectroscopic data of 3-(2-aminopyrimidin-4-yl)-1*H*-indol-4-ol (*Meridianin A*, 5)



$C_{12}H_{10}N_4O$

226.23

96 mg (0.43 mmol, 85 % yield) as a bright yellow fine crystalline solid. Mp 264-276 °C. (Lit.: 164-168 °C). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 6.39 (dd, *J* = 7.9 Hz, *J* = 0.9 Hz, 1 H), 6.76 (s, 2 H, N$\underline{H}_2$), 6.82 (dd, *J* = 8.2 Hz, *J* = 0.9 Hz, 1 H), 7.00 (t, *J* = 7.9 Hz, 1 H), 7.14 (d, *J* = 5.4 Hz, 1 H), 8.14 (d, *J* = 5.4 Hz, 1 H), 8.25 (d, *J* = 3.2 Hz, 1 H), 11.8 (br, 1 H, N$\underline{H}$), 13.62 (s, 1 H, O$\underline{H}$). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 102.3 (CH), 104.3 (CH), 105.5 (CH), 113.7 (C_{quat}), 114.3 (C_{quat}), 124.4 (CH), 128.4 (CH), 139.2 (C_{quat}), 152.0 (C_{quat}), 158.4 (CH), 160.4 (C_{quat}), 161.7 (C_{quat}). EI + MS (*m/z* (%)): 226 (M^+, 100), 225 ($(M-H)^+$, 13), 209 ($(M-OH)^+$, 2), 197 ($(M-COH)^+$, 6), 185 ($(M-CH_2N_2+H)^+$, 18), 158 ($(M-C_3H_4N_2)^+$, 6). IR (KBr): $\tilde{\nu}$ 3429 (m) cm^{-1}, 3342 (m), 1638 (m), 1593 (s), 1562 (m), 1532 (m), 1469 (m), 1444 (m), 1401 (m), 1321 (m), 1272 (w), 1227 (m), 1194 (w), 1167 (w), 820 (w), 802 (w), 775 (w), 719 (m), 617 (w). Anal. calcd for $C_{12}H_{10}N_4O$ (226.2): C 63.71, H 4.46, N 24.76. Found: C 63.48, H 4.61, N 24.72.

The NMR spectra are in good agreement with reported spectra of *psammopemmin A* (M. S. Butler, R. J. Capon, C. C. Lu, *Austr. J. Chem.* **1992**, *45*, 1871-1877), which might confer the structure reassignment of *psammopemmin A* by *Baker* (M. D. Lebar, B. J. Baker, *Austr. J. Chem.* **2010**, *63*, 862-866).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.38 (dd, *J* = 0.7 Hz, *J* = 0.7 Hz, 1 H), 6.68 (br s, 2 H, N$\underline{H}_2$), 6.81 (dd, *J* = 7.7 Hz, *J* = 0.7 Hz, 1 H), 6.98 (dd, *J* = 7.7 Hz, *J* = 7.7 Hz, 1 H), 7.12 (d, *J* = 5.4 Hz, 1 H), 8.12 (br d, *J* = 5.4 Hz, 1 H), 8.22 (d, *J* = 2.5 Hz, 1 H), 11.75 (br s, 1 H, N$\underline{H}$), 13.55 (s, 1 H, O$\underline{H}$). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 102.3, 104.3, 105.4, 113.7, 114.3, 124.3, 128.3, 139.2, 152.0, 158.3, 160.7, 161.7.

Data reported in the literature:

L. H. Franco, E. Bal de Kier Joffé, L. Puricelli, M. Tatian, A. M. Seldes, J. A. Palermo, *J. Nat. Prod.* **1998**, *61*, 1130-1132.

Yellow needles (MeOH-H_2O). Mp 164-168 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 6.36 (dd, *J* = 7.1 Hz, *J* = 0.7 Hz, H-5), 6.69 (s, N$\underline{H}_2$), 6.78 (dd, *J* = 7.5 Hz, *J* = 0.7 Hz, H-7), 6.96 (dd, *J* = 7.5 Hz, *J* = 7.1 Hz, H-6), 7.09 (d, *J* = 5.4 Hz, H-5´), 8.10 (d, *J* = 5.4 Hz, H-6´), 8.20 (d, *J* = 1.2 Hz, H-2), 11.71 (brs, N$\underline{H}$), 13.55 (s, O$\underline{H}$). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 102.4 (C-7), 104.5 (C-5´), 105.6 (C-5), 113.8 (C-3), 114.5 (C-3a), 124.4 (C-6), 128.5 (C-2), 139.4 (C-7a), 152.1 (C-4), 158.5 (C-6´), 160.6 (C-4´), 161.9 (C-2´). HREIMS calcd for $C_{12}H_{10}N_4O$: 226.0855. Found: 226.0857. IR (KBr): $\tilde{\nu}$ 3437 cm^{-1}, 3351, 3200, 2924, 1647, 1605, 1533, 1469, 1326, 820, 721. UV (CH_3Cl) γ_{max} (logε) 248 (3.68), 356 (3.58) nm.

NMR spectra of *meridianin A* are in good agreement with those given by *Palermo*.

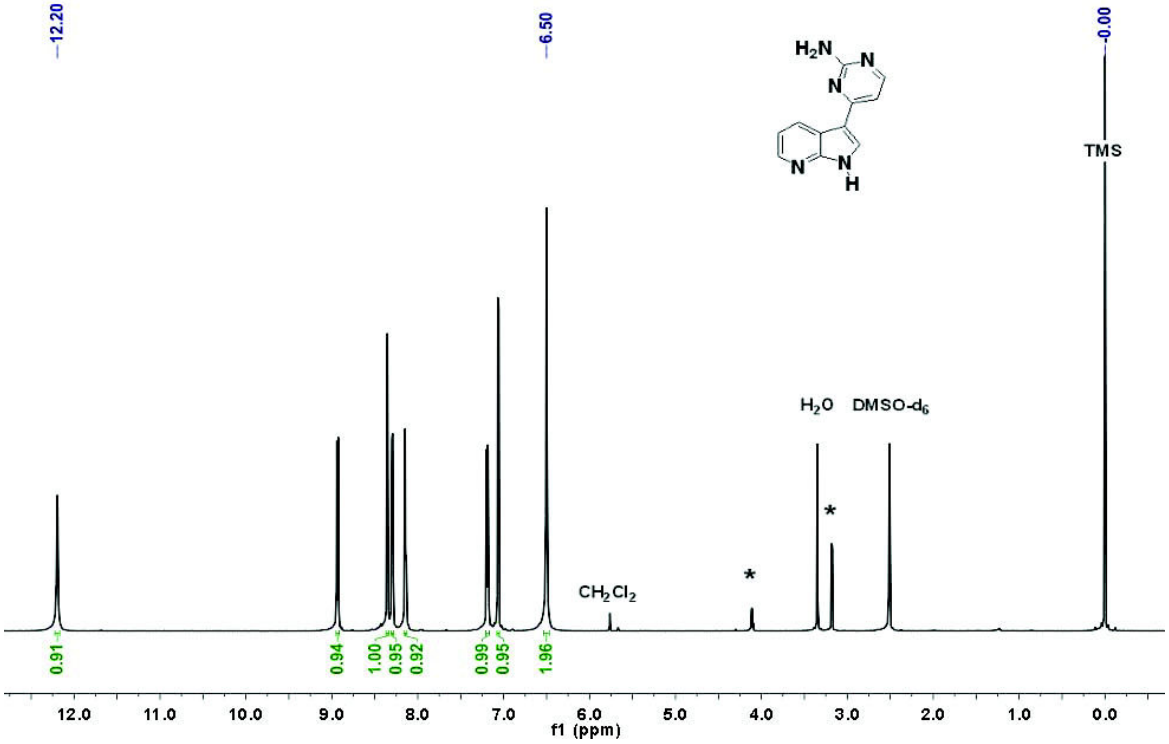
P. M. Fresneda, P. Molina, J. A. Bleda, *Tetrahedron* **2001**, *57*, 2355-2363.

Yellow prisms (EtOH-hexane). Mp 164-168 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.13 (dd, *J* = 7.8 Hz, *J* = 0.9 Hz, 1 H, H-5), 7.48 (brs, 2 H, N$\underline{H}_2$), 7.57 (dd, *J* = 8.1 Hz, *J* = 0.9 Hz, 1 H), 7.74 (dd, *J* = 7.8 Hz, 1 H, H-6), 7.88 (d, *J* = 5.7 Hz, 1 H, H-5´), 8.88 (d, *J* = 5.7 Hz, 1 H, H-6´), 9.0 (s, 1 H, H-2), 11.8 (s, 1 H, N$\underline{H}$), 13.9 (s, 1 H, O$\underline{H}$). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 102.3 (C-7), 104.4 (C-5´), 105.4 (C-5), 113.7 (C-3), 114.4 (C-3a), 124.4 (C-6), 128.4 (C-2), 139.2 (C-7a), 152.0 (C-4), 158.4 (C-6´), 160.5 (C-4´), 161.7 (C-2´). IR (nujol): $\tilde{\nu}$ 3456 (m) cm^{-1}, 3416 (m), 3340 (m), 3181 (m), 1627 (m), 1586 (s), 1532 (s), 1270 (s), 1124 (s), 1072 (s). EI + MS (*m/z* (%)): 226 (M^+, 100), 185 (26), 167 (16), 149 (59). Anal. calcd for $C_{12}H_{10}N_4O$ (226.2): C 63.71, H 4.46, N 24.76. Found: C 63.57, H 4.31, N 24.93.

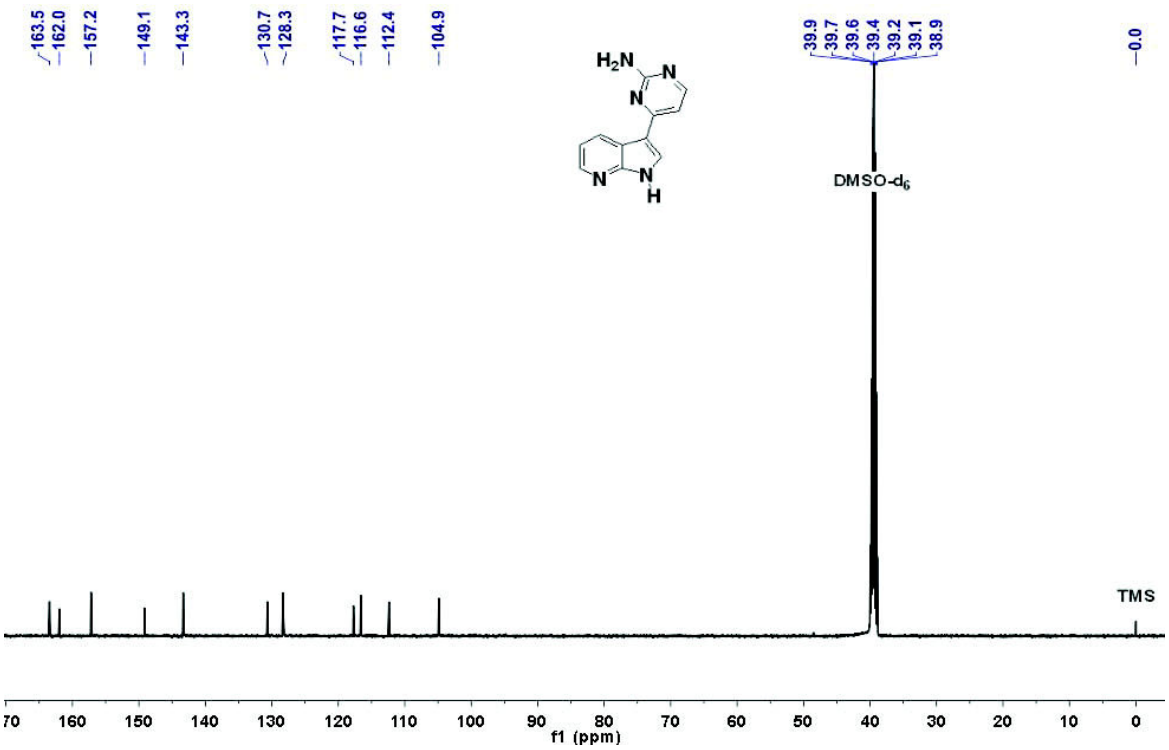
The ^{13}C NMR values are in good agreement with those given by *Fresneda* and *Molina*, but the ^{1}H NMR values deviate considerably.

However, the melting point deviates immensely from the melting point reported both by *Palermo* as well as *Fresneda* and *Molina*.

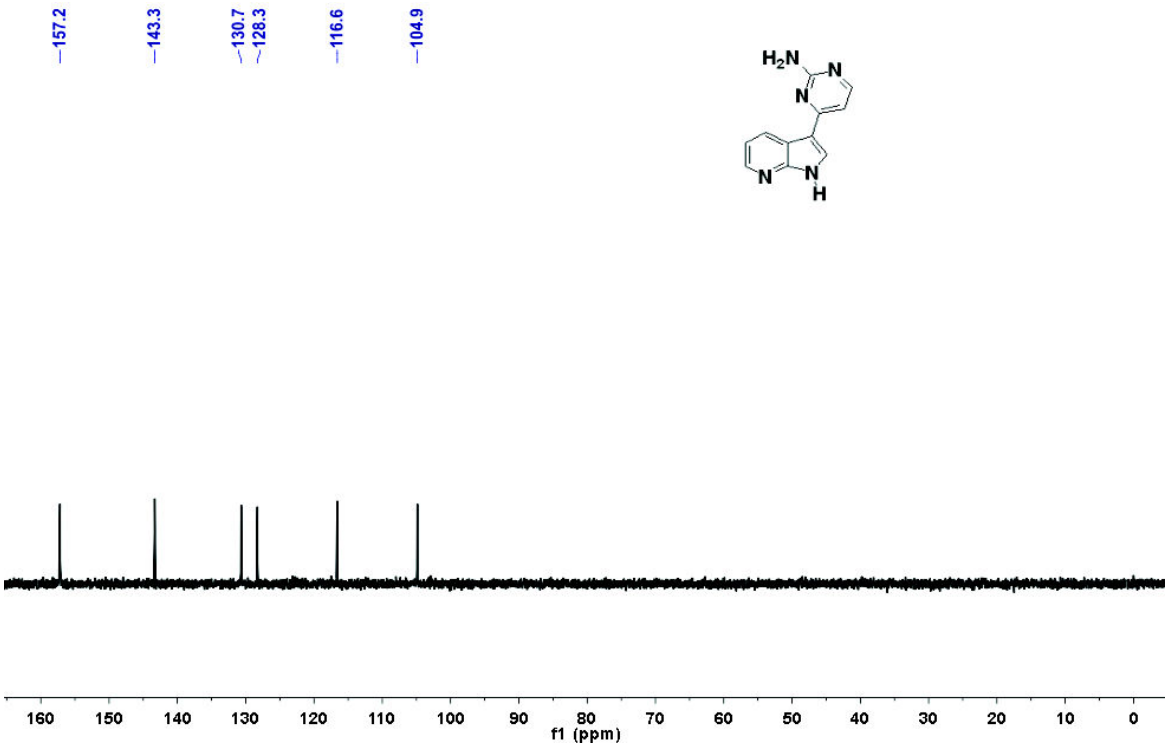
5. ^{1}H and ^{13}C NMR Spectra of Compounds 4a-u and 5



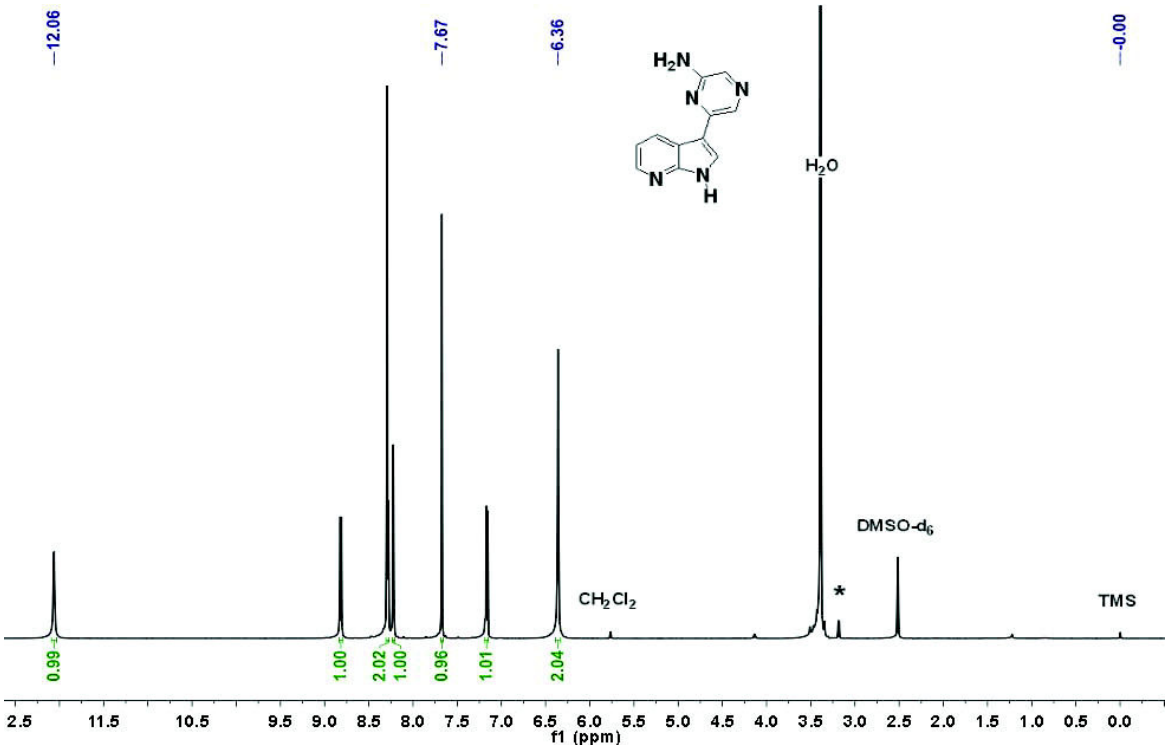
^{1}H NMR of **4a** (15 mg) in 0.7 mL DMSO-d_6 at 297 K (δ in ppm). *Impurities from residual solvents.



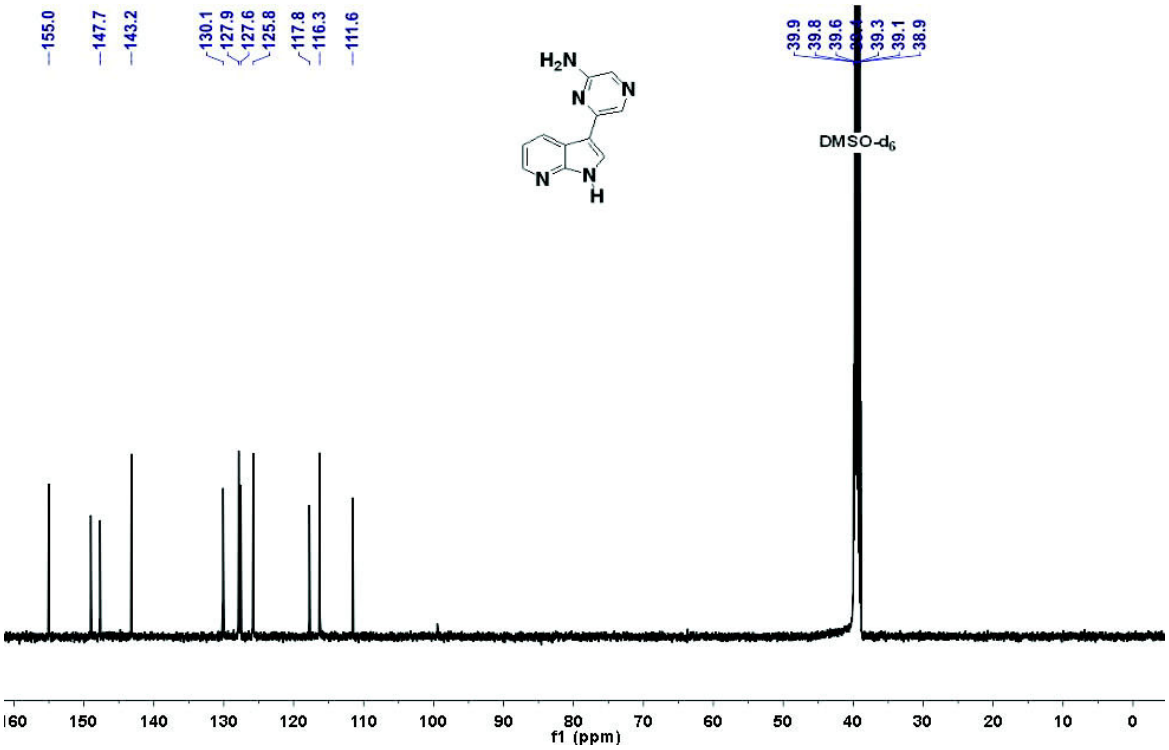
^{13}C NMR of **4a** (15 mg) in 0.7 mL DMSO-d_6 at 297 K (δ in ppm).



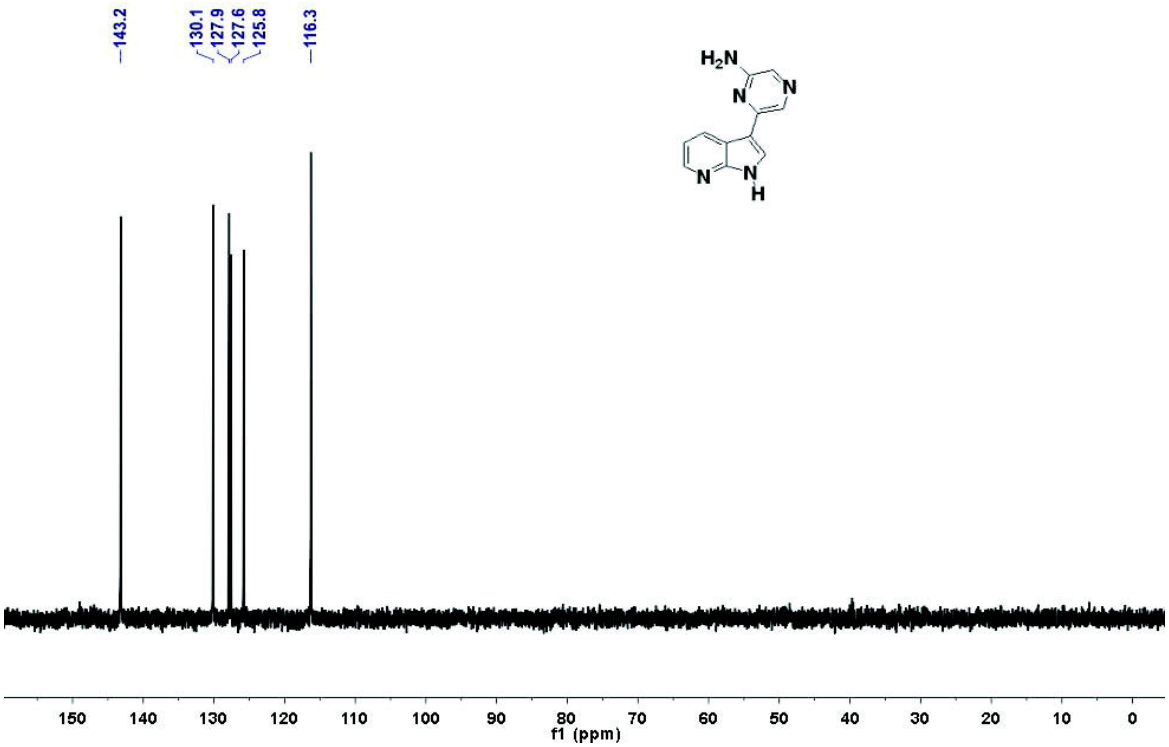
^{13}C DEPT 135-NMR of **4a** (15 mg) in 0.7 mL DMSO-d_6 at 297 K (δ in ppm).



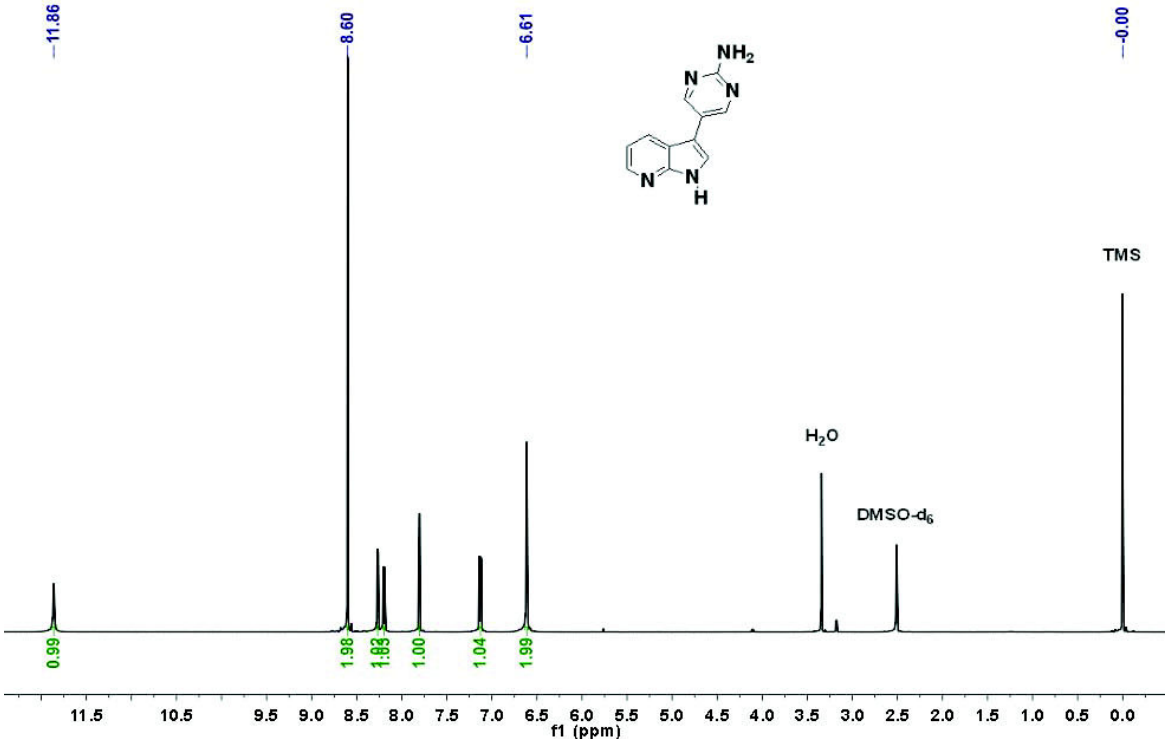
^{1}H NMR of **4b** (15 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm). *Impurities from residual solvents.



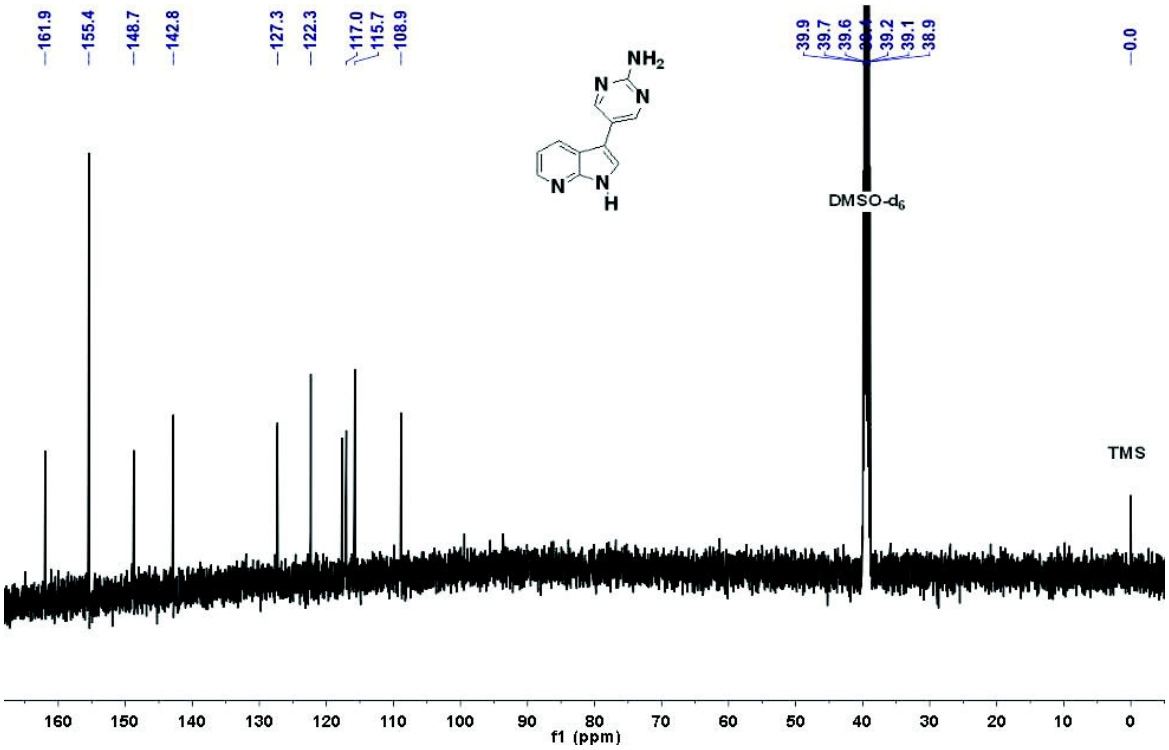
^{13}C NMR of **4b** (15 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).



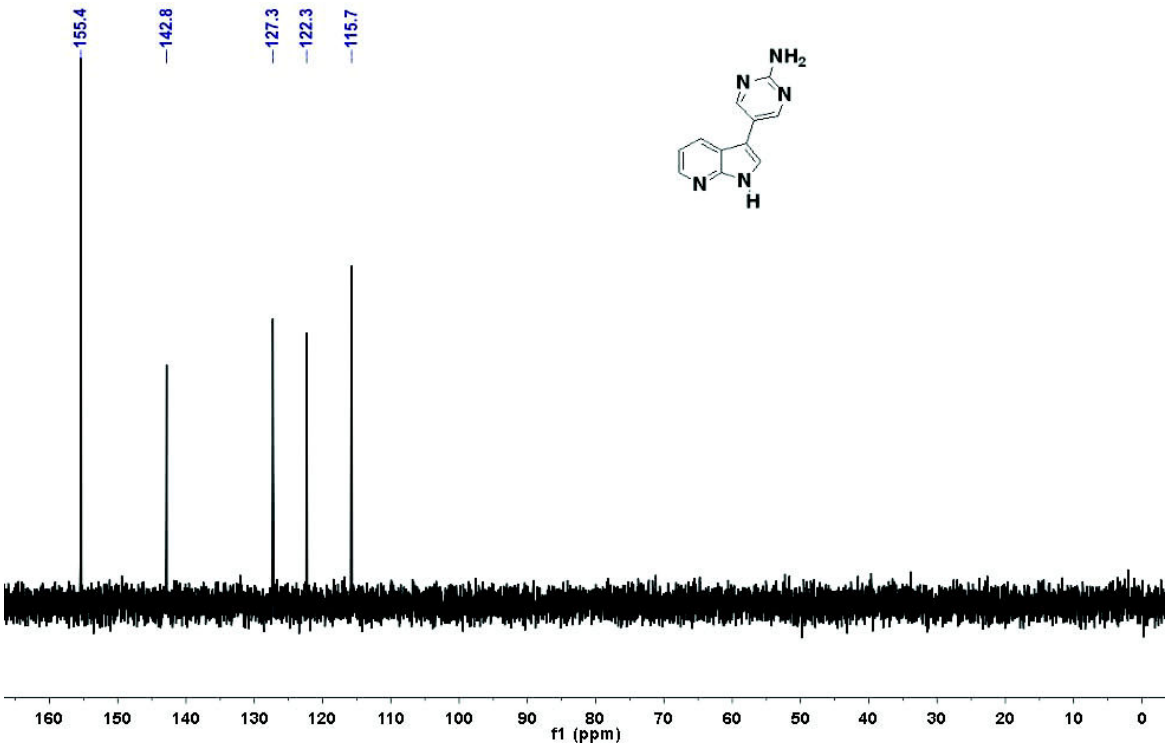
^{13}C DEPT 135-NMR of **4b** (15 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).



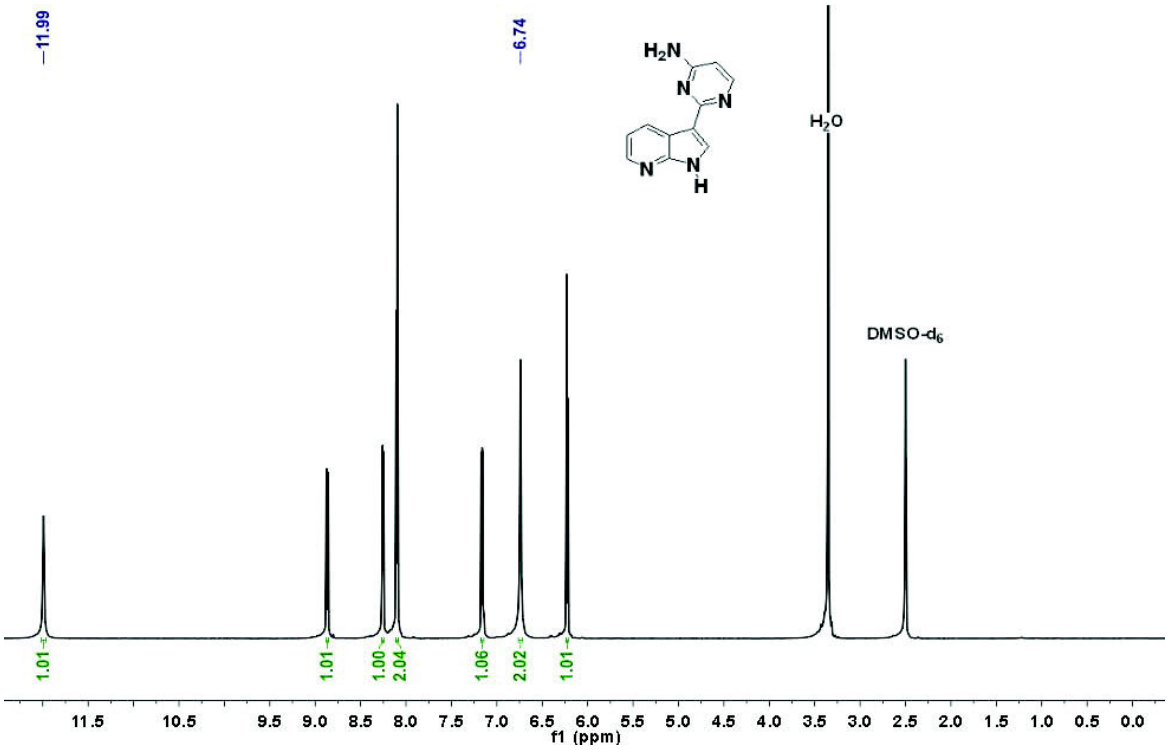
^{1}H NMR of **4c** (15 mg) in 0.7 mL DMSO-d_6 at 299 K (δ in ppm).



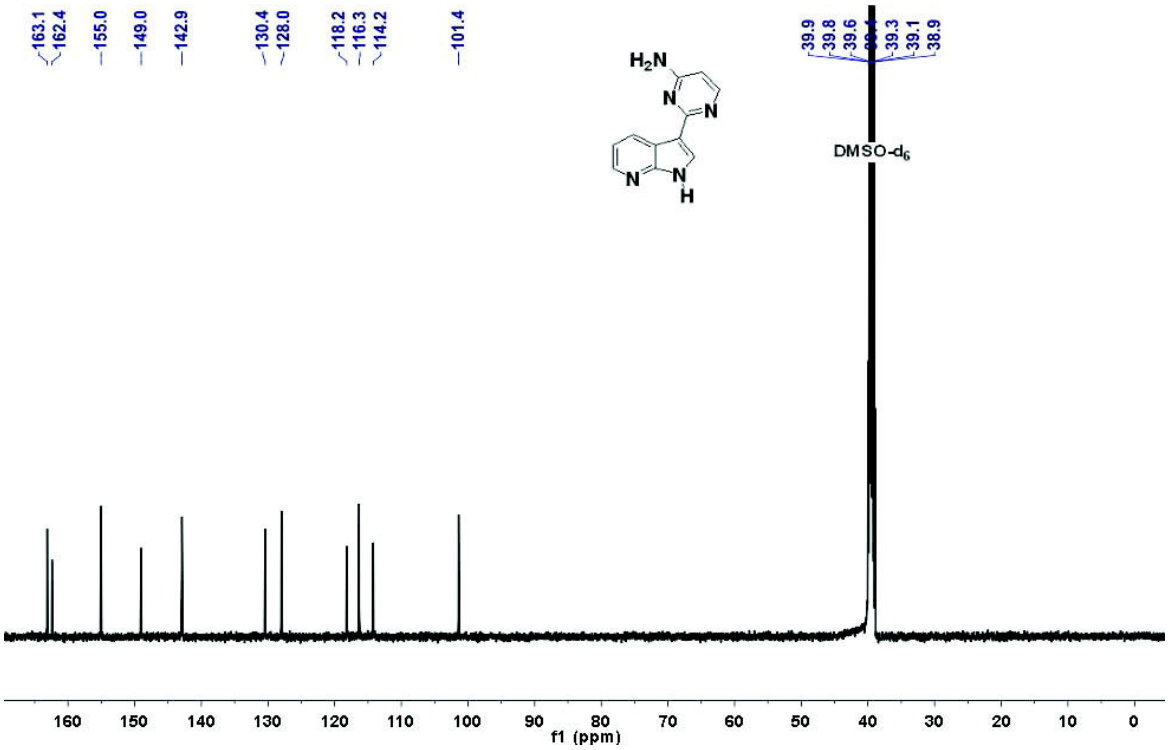
^{13}C NMR of **4c** (15 mg) in 0.7 mL DMSO-d_6 at 299 K (δ in ppm).



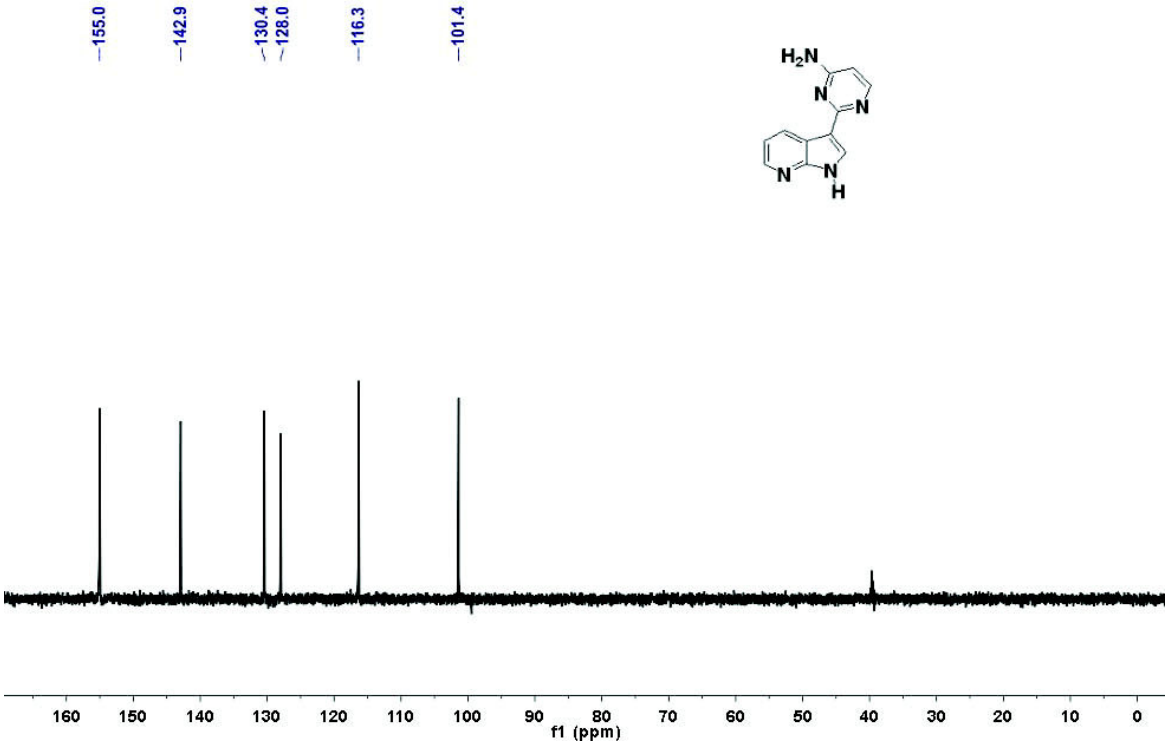
^{13}C DEPT 135-NMR of **4c** (15 mg) in 0.7 mL DMSO-d_6 at 299 K (δ in ppm).



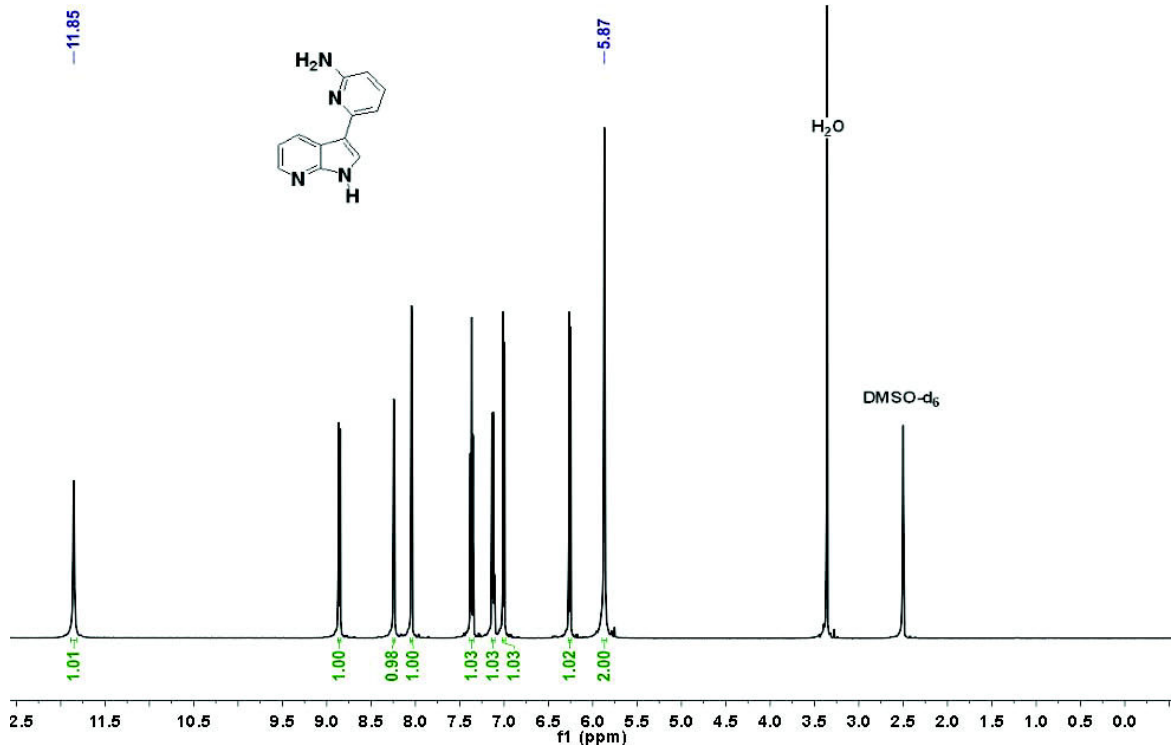
^{1}H NMR of **4d** (15 mg) in 0.7 mL DMSO-d_6 at 297 K (δ in ppm).



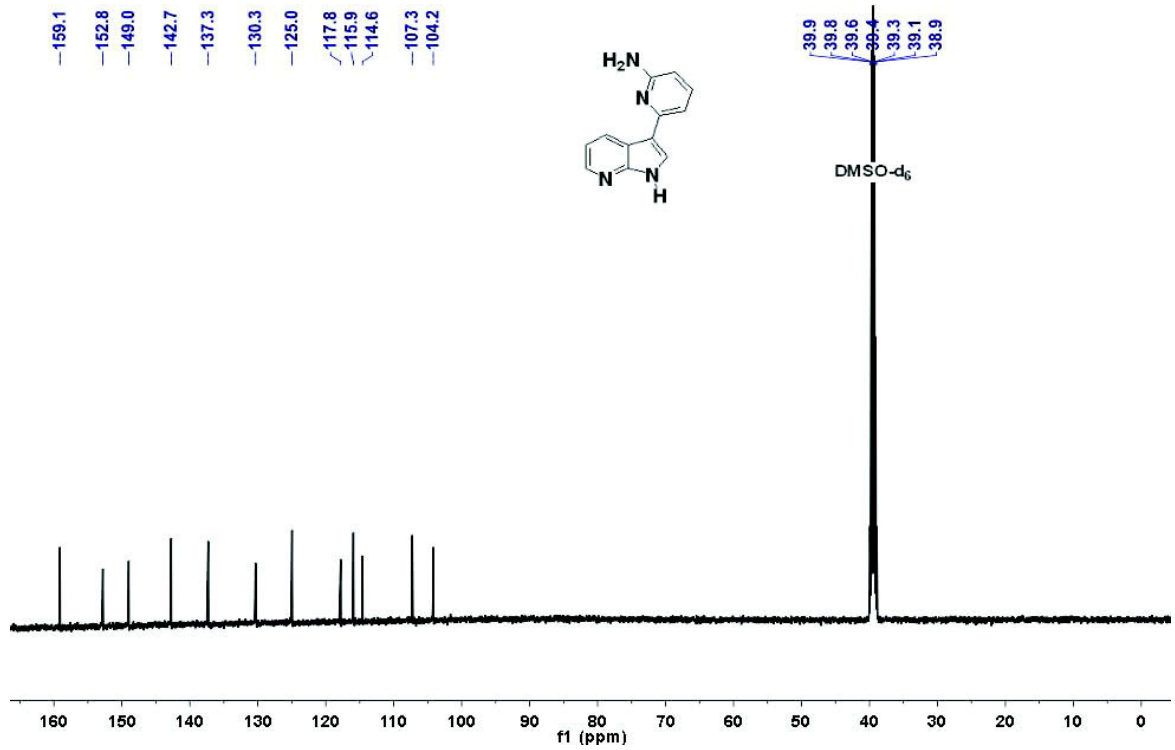
^{13}C NMR of **4d** (15 mg) in 0.7 mL DMSO-d_6 at 297 K (δ in ppm).



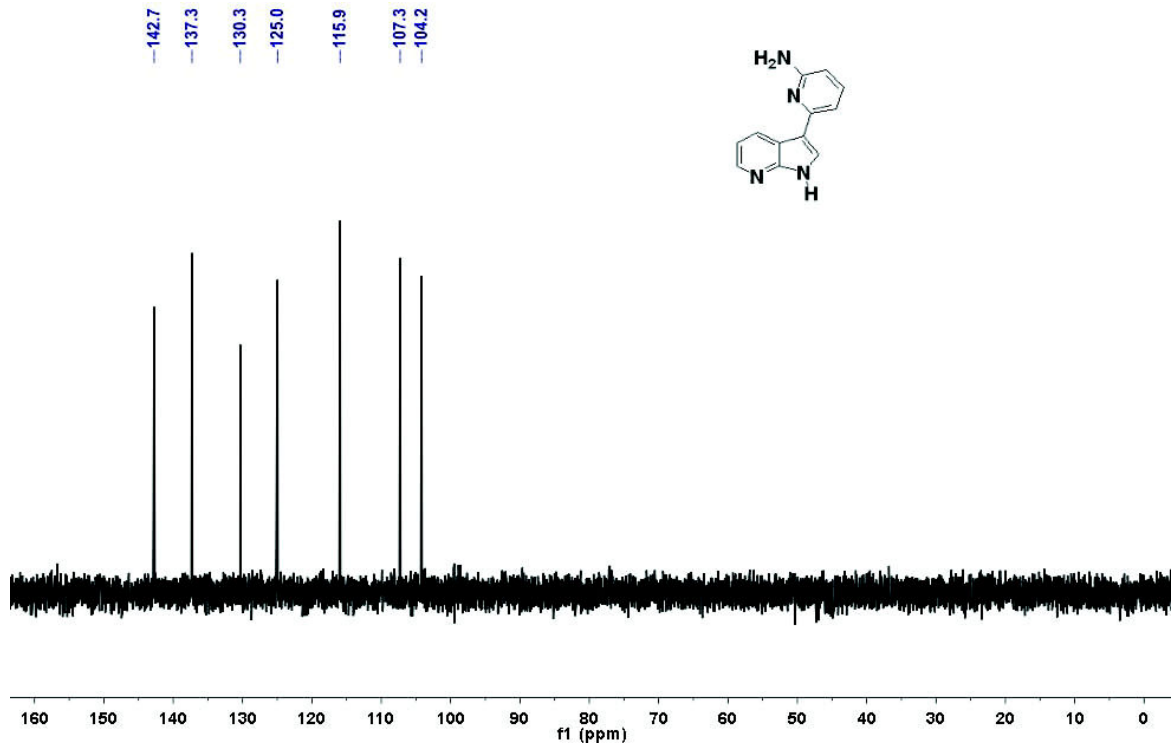
^{13}C DEPT 135-NMR of **4d** (15 mg) in 0.7 mL DMSO-d_6 at 297 K (δ in ppm).



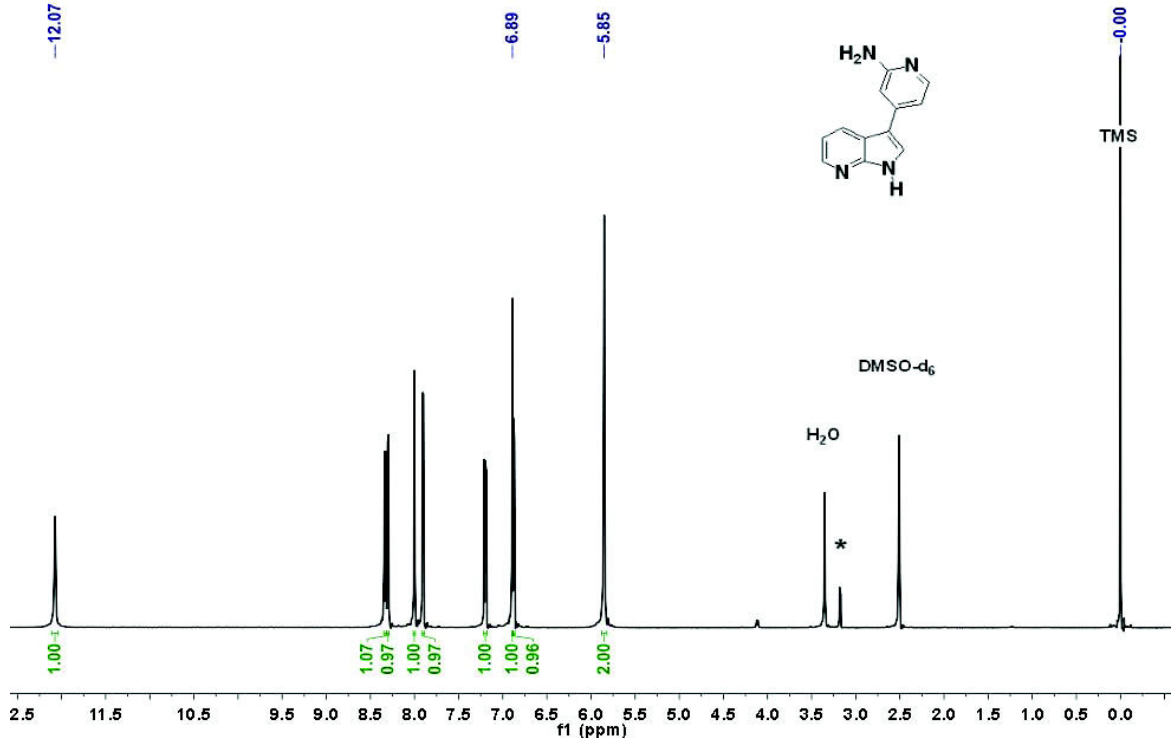
^{1}H NMR of **4e** (15 mg) in 0.7 mL DMSO-d_6 at 299 K (δ in ppm).



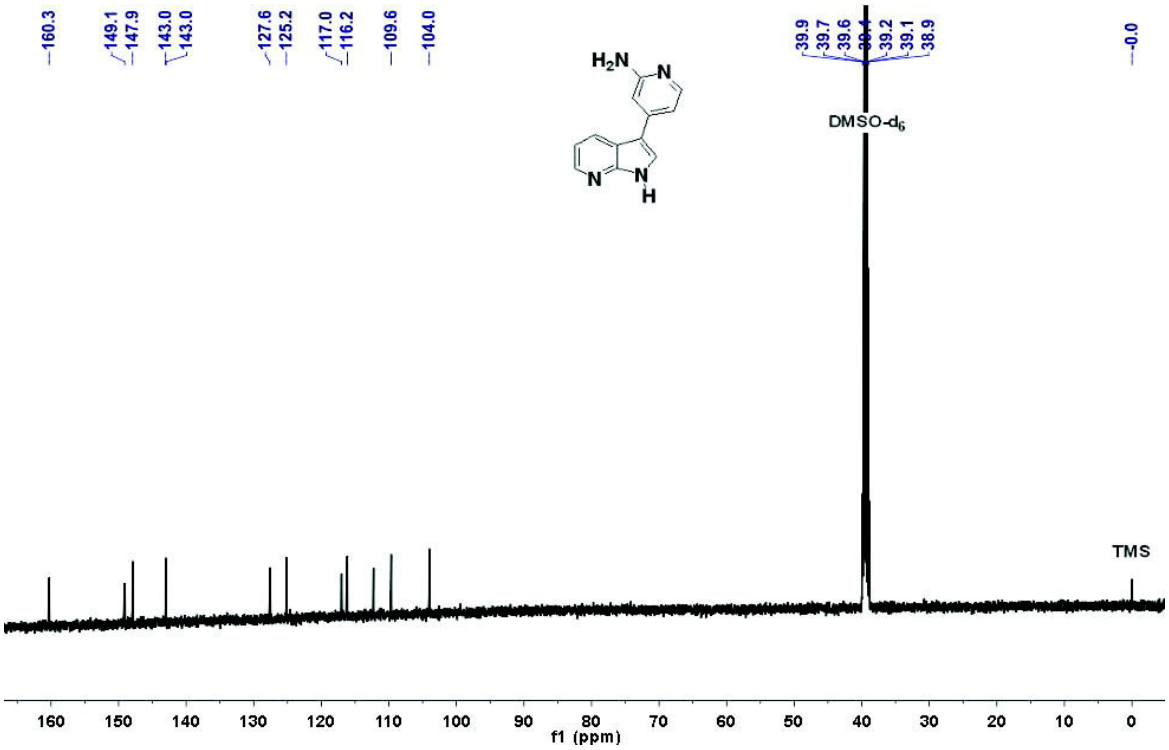
^{13}C NMR of **4e** (15 mg) in 0.7 mL DMSO-d_6 at 299 K (δ in ppm).



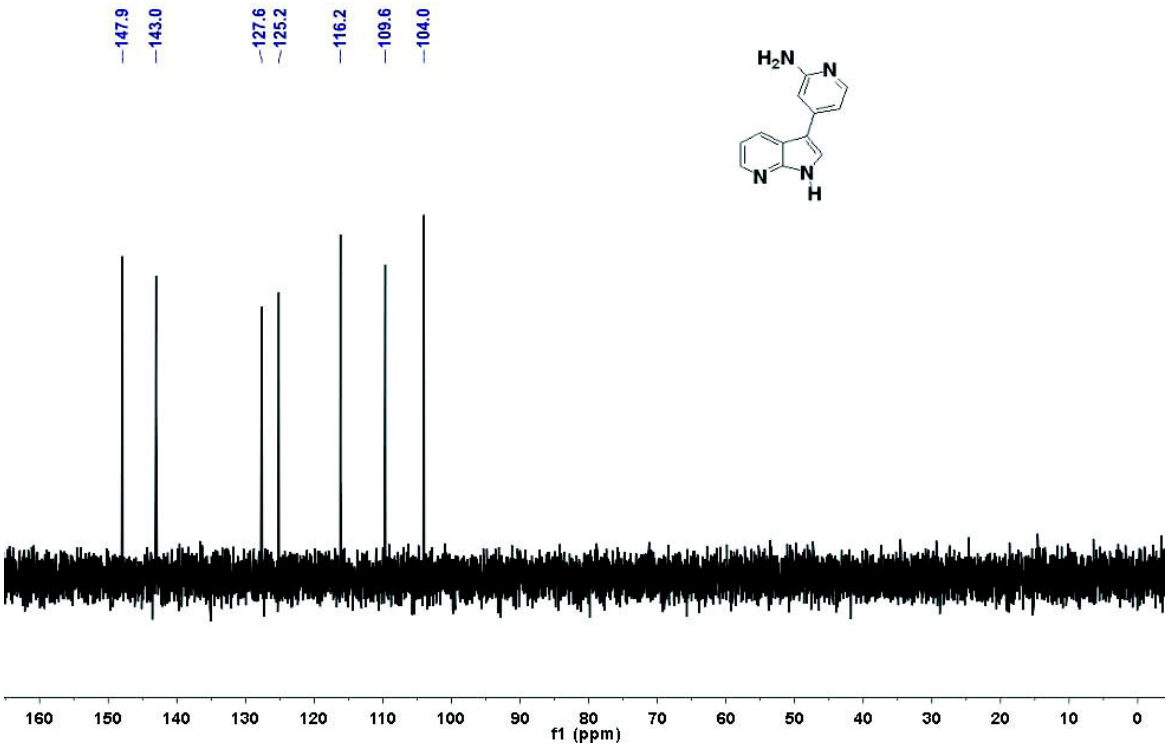
^{13}C DEPT 135-NMR of **4e** (15 mg) in 0.7 mL DMSO-d_6 at 299 K (δ in ppm).



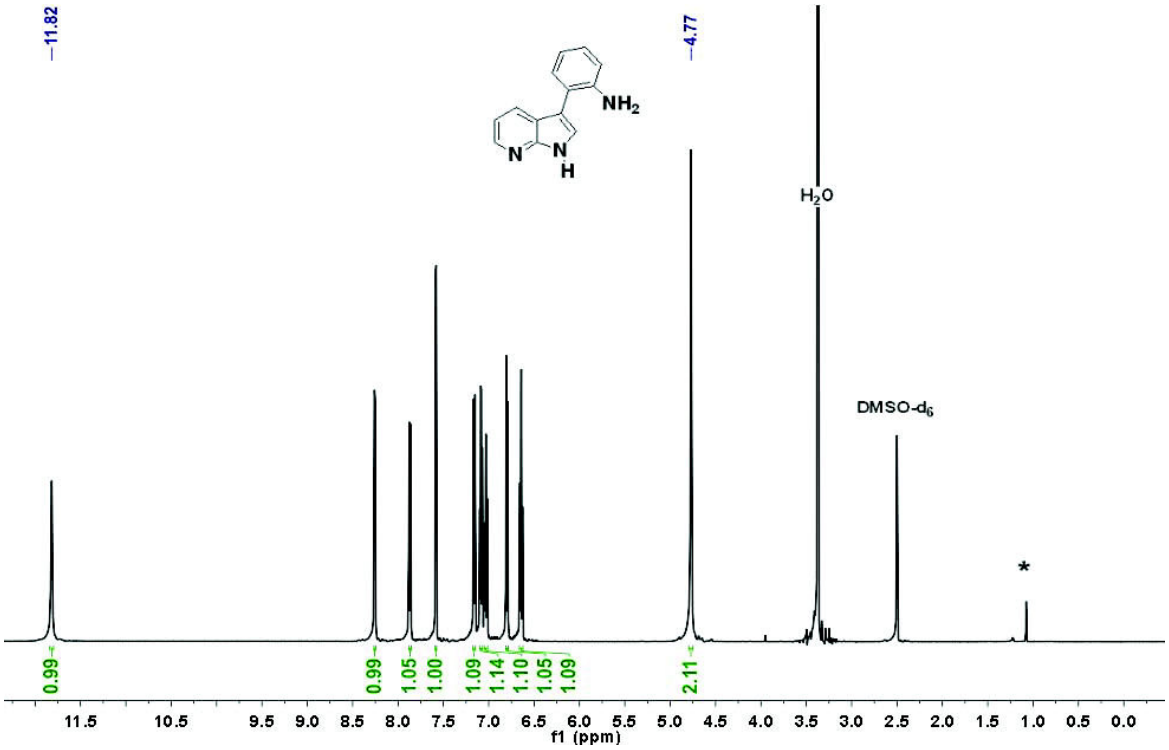
^{1}H NMR of **4f** (15 mg) in 0.7 mL DMSO-d_6 at 298 K (δ in ppm). *Impurities from residual solvents.



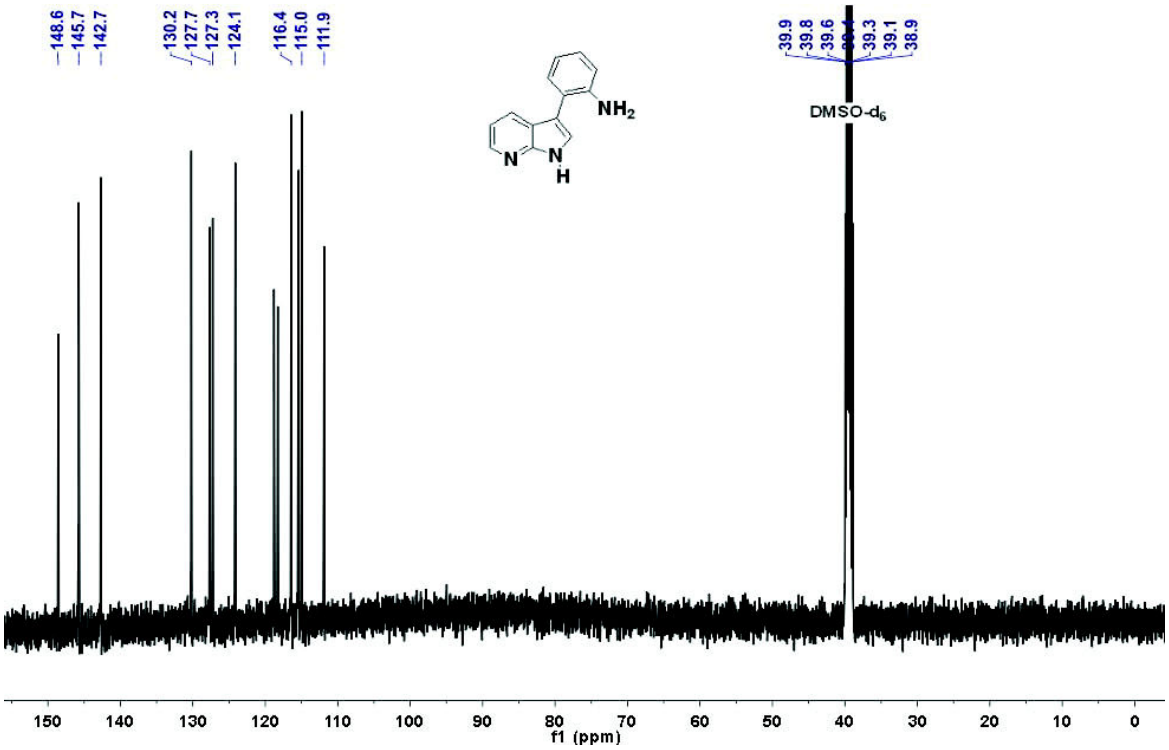
^{13}C NMR of **4f** (15 mg) in 0.7 mL DMSO-d_6 at 298 K (δ in ppm).



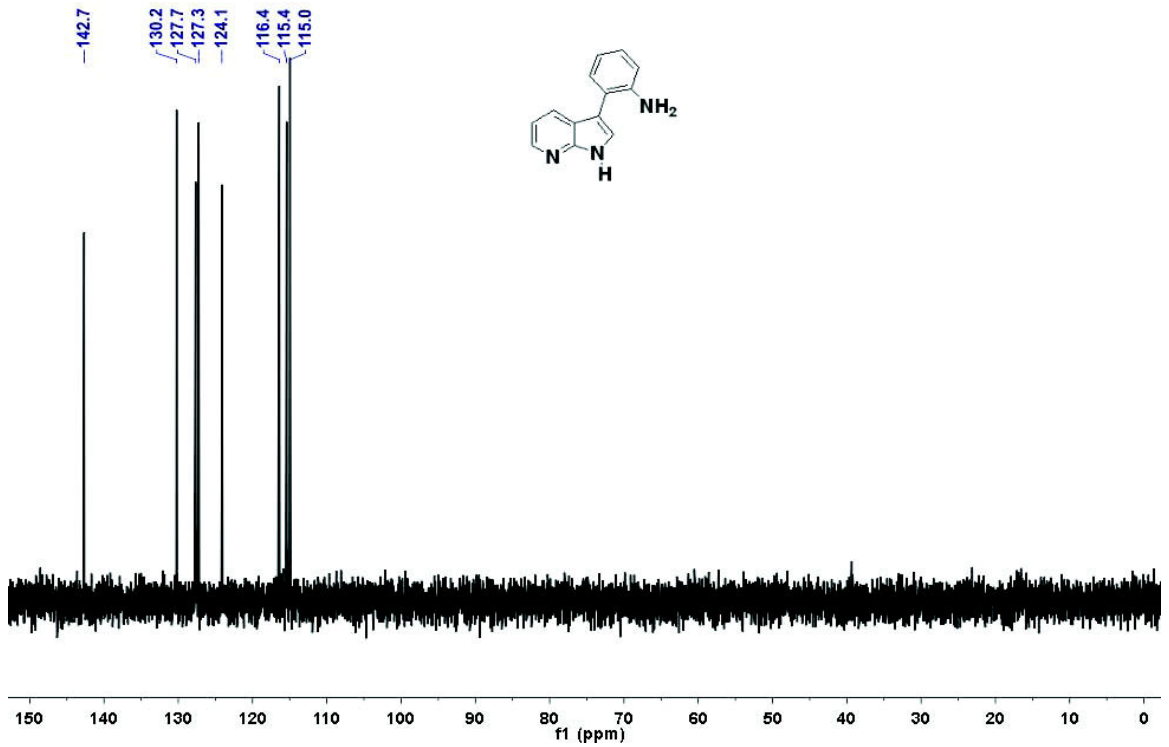
^{13}C DEPT 135-NMR of **4f** (15 mg) in 0.7 mL DMSO-d_6 at 298 K (δ in ppm).



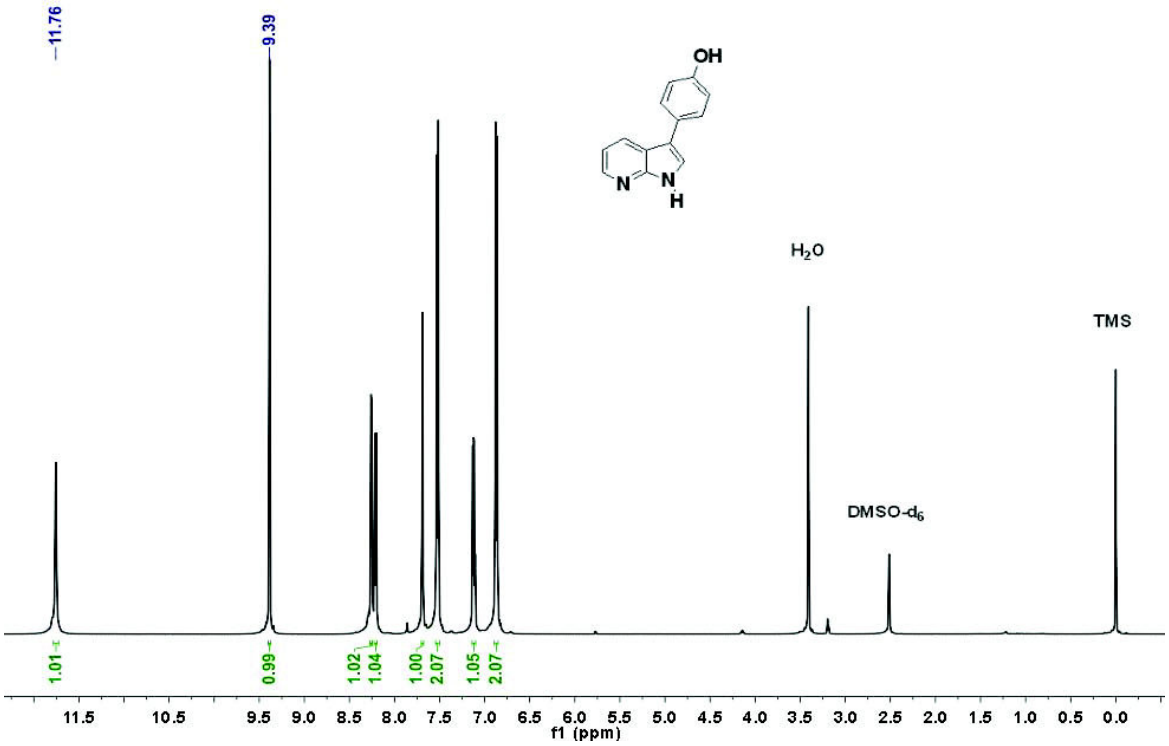
^{1}H NMR of **4g** (15 mg) in 0.7 mL DMSO-d_6 at 298 K (δ in ppm). *Impuruties from residual solvents.



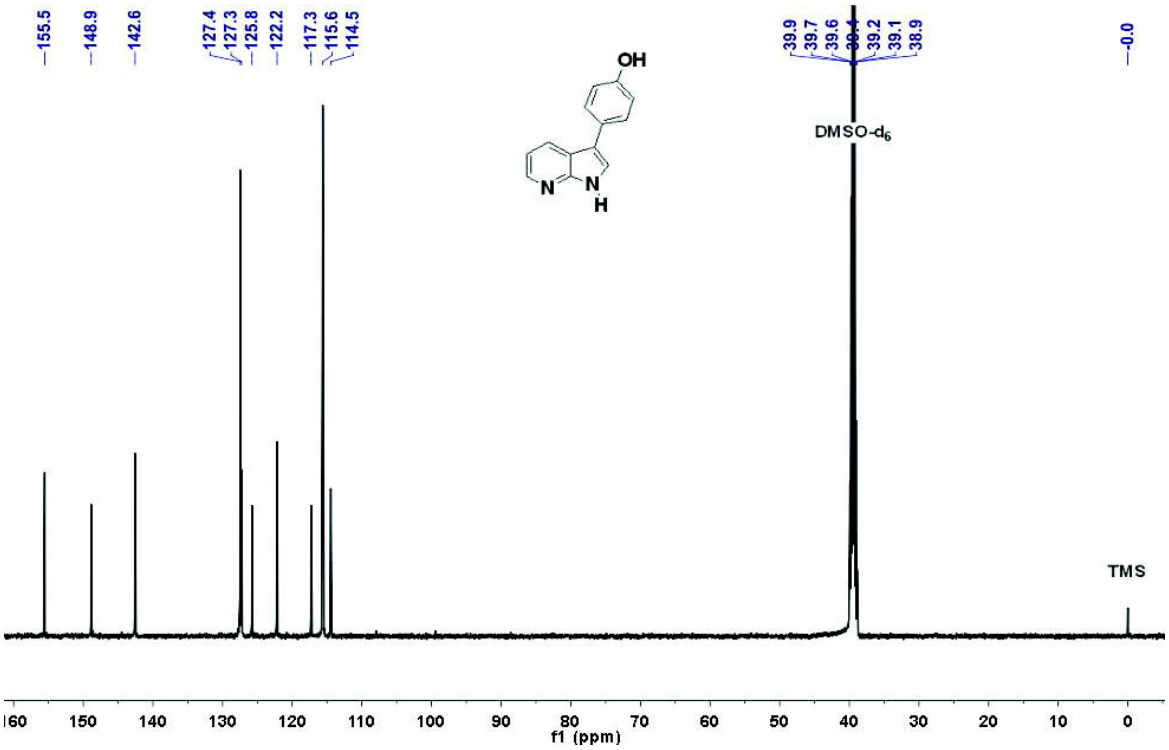
^{13}C NMR of **4g** (15 mg) in 0.7 mL DMSO-d_6 at 297 K (δ in ppm).



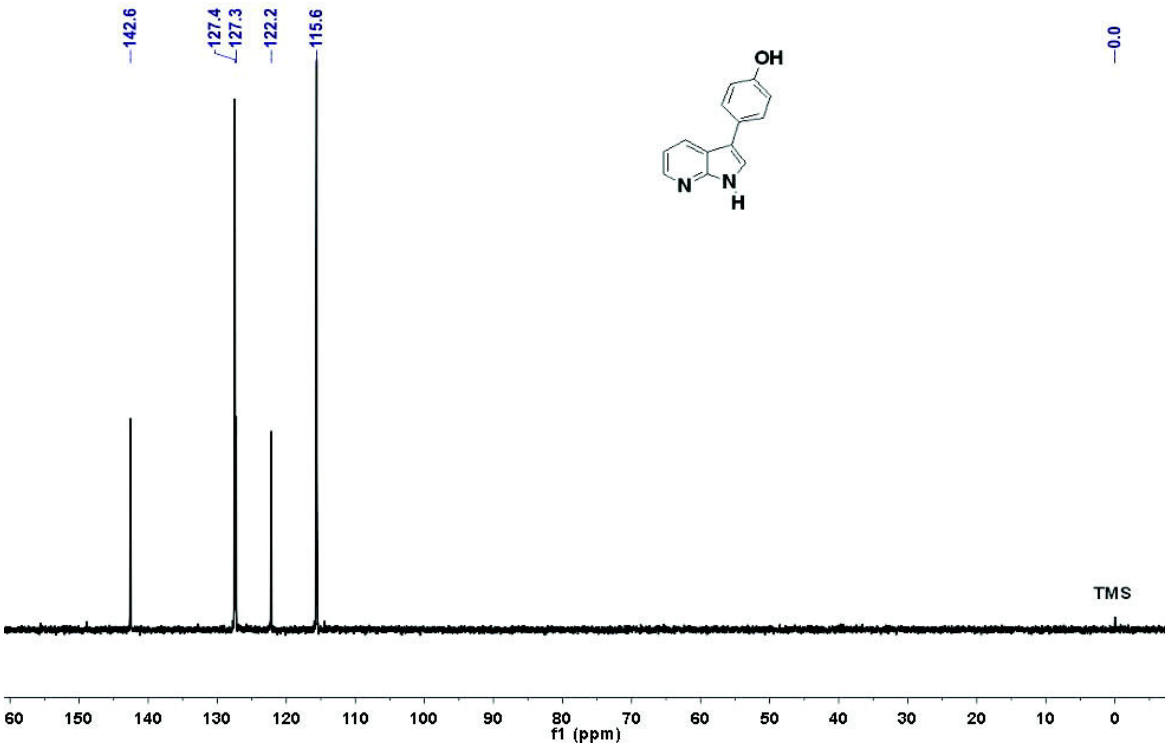
^{13}C DEPT 135-NMR of **4g** (15 mg) in 0.7 mL DMSO-d_6 at 298 K (δ in ppm).



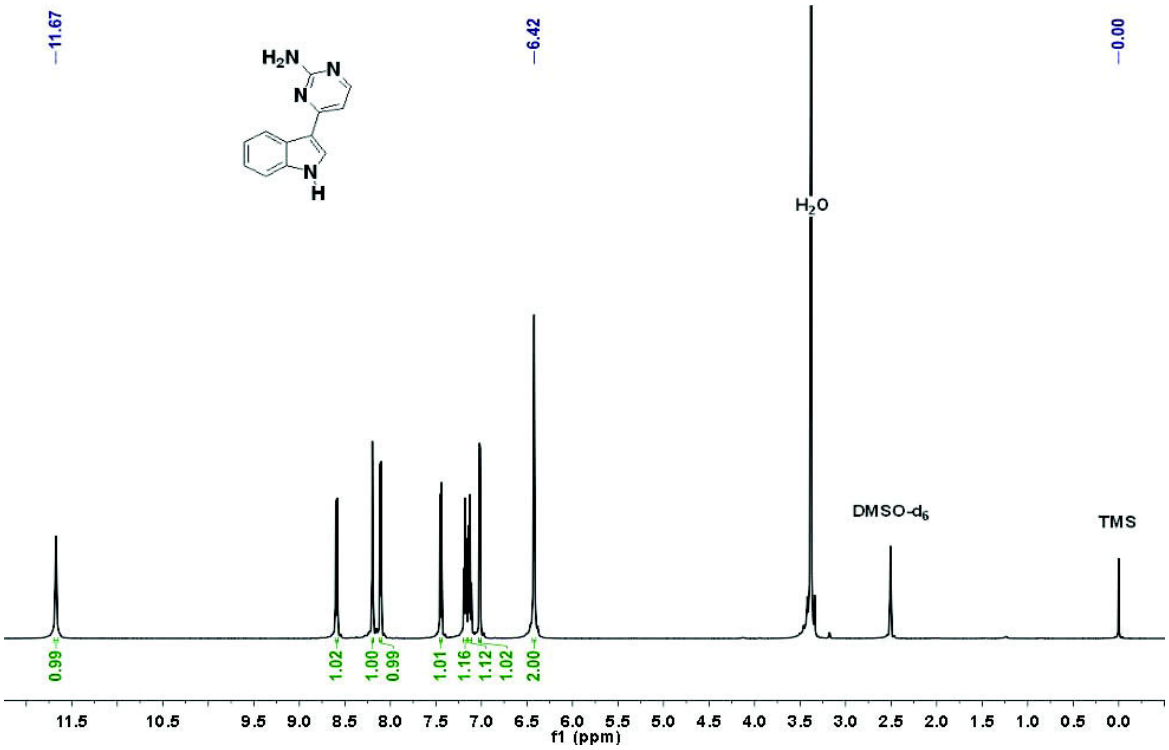
^{1}H NMR of **4h** (30 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).



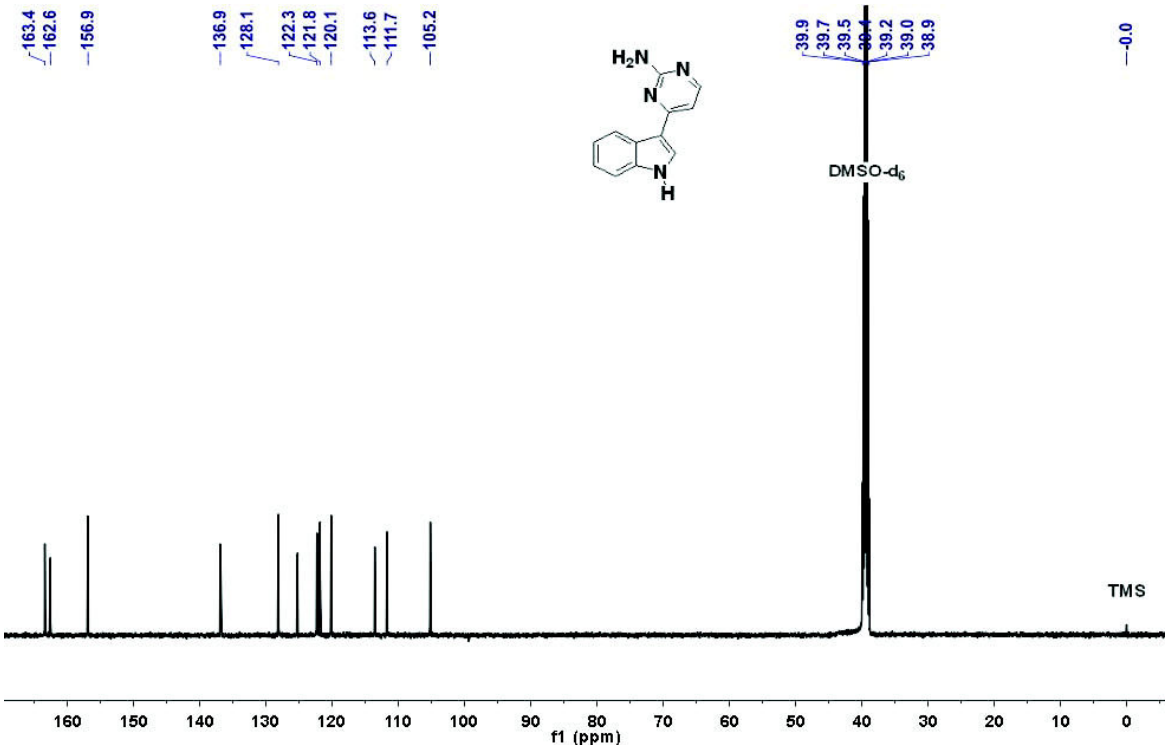
^{13}C NMR of **4h** (30 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).



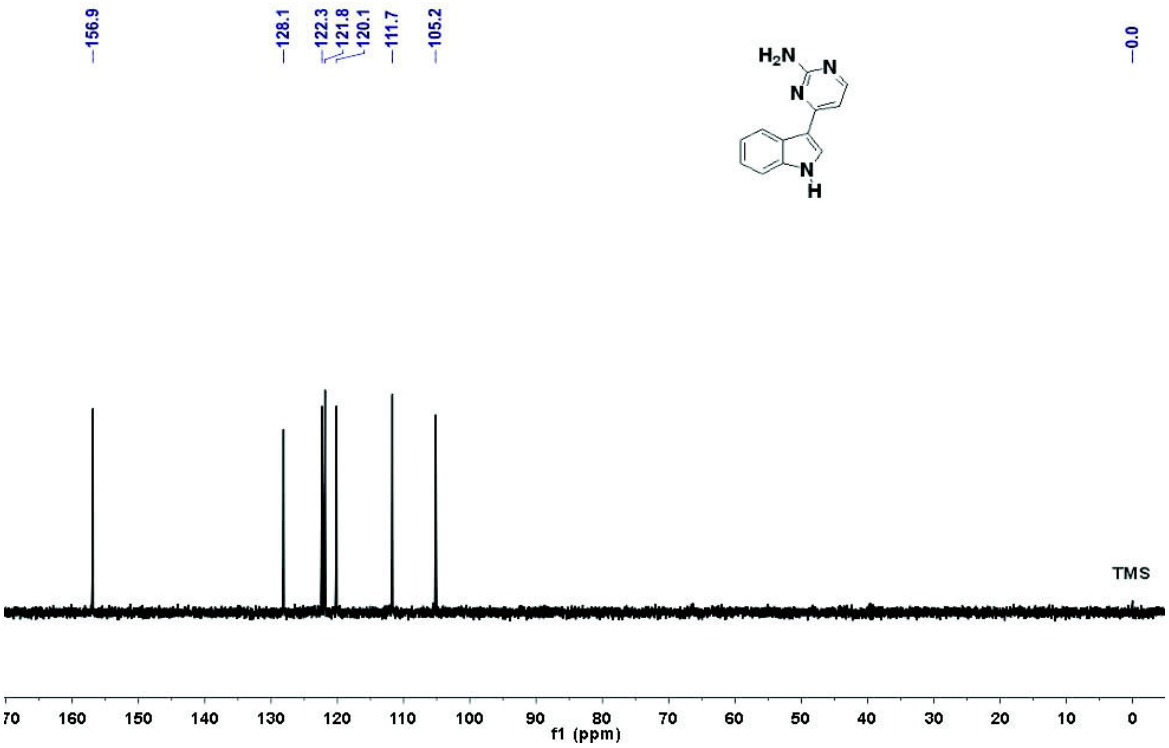
^{13}C DEPT 135-NMR of **4h** (30 mg) in 0.7 mL DMSO-d_6 at 295 K (δ in ppm).



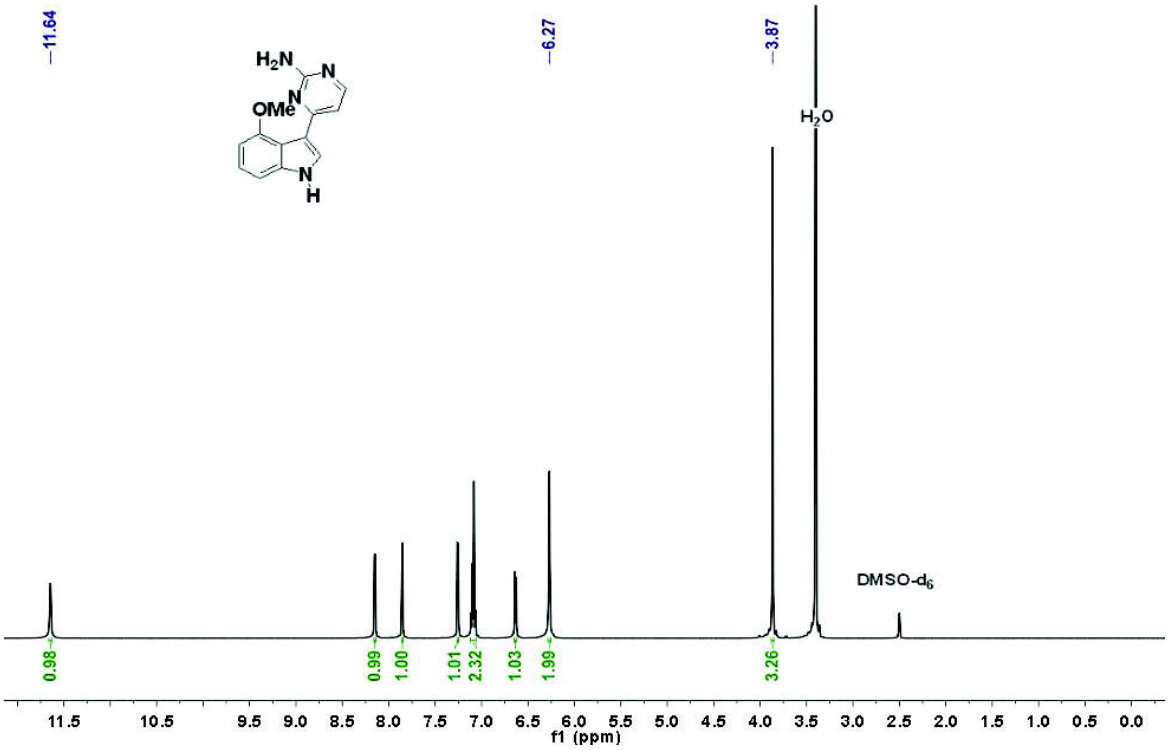
^{1}H NMR of **4i** (15 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).



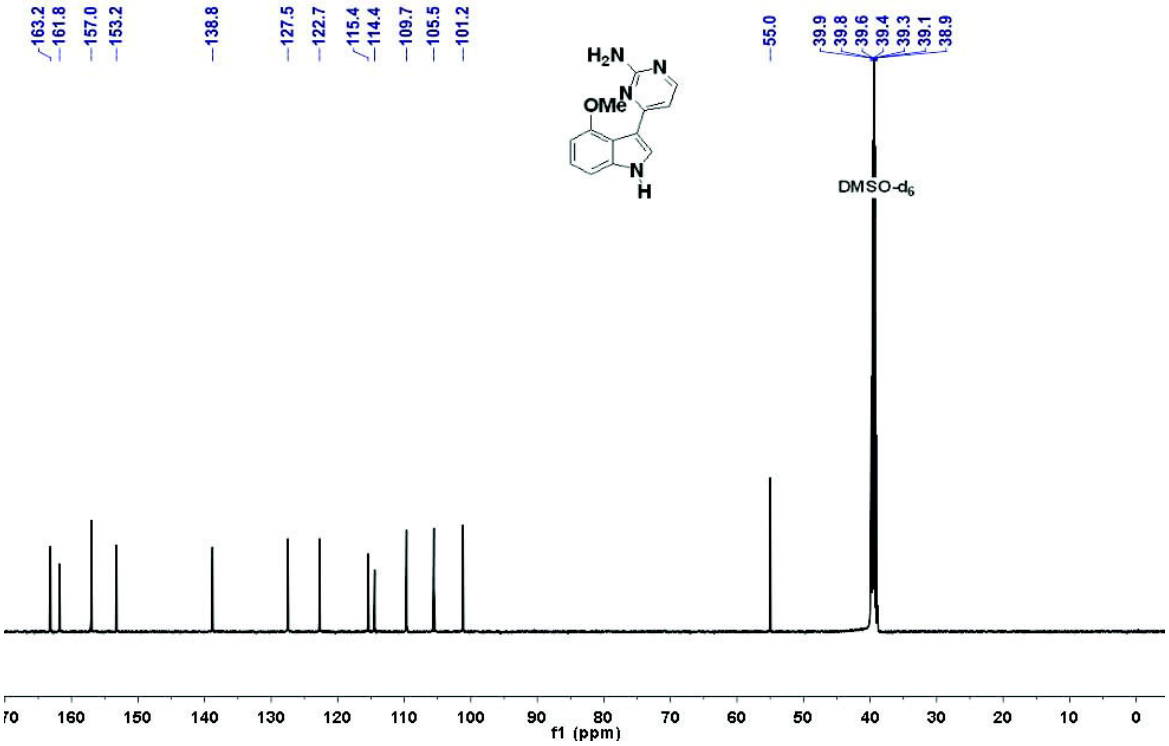
^{13}C NMR of **4i** (15 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).



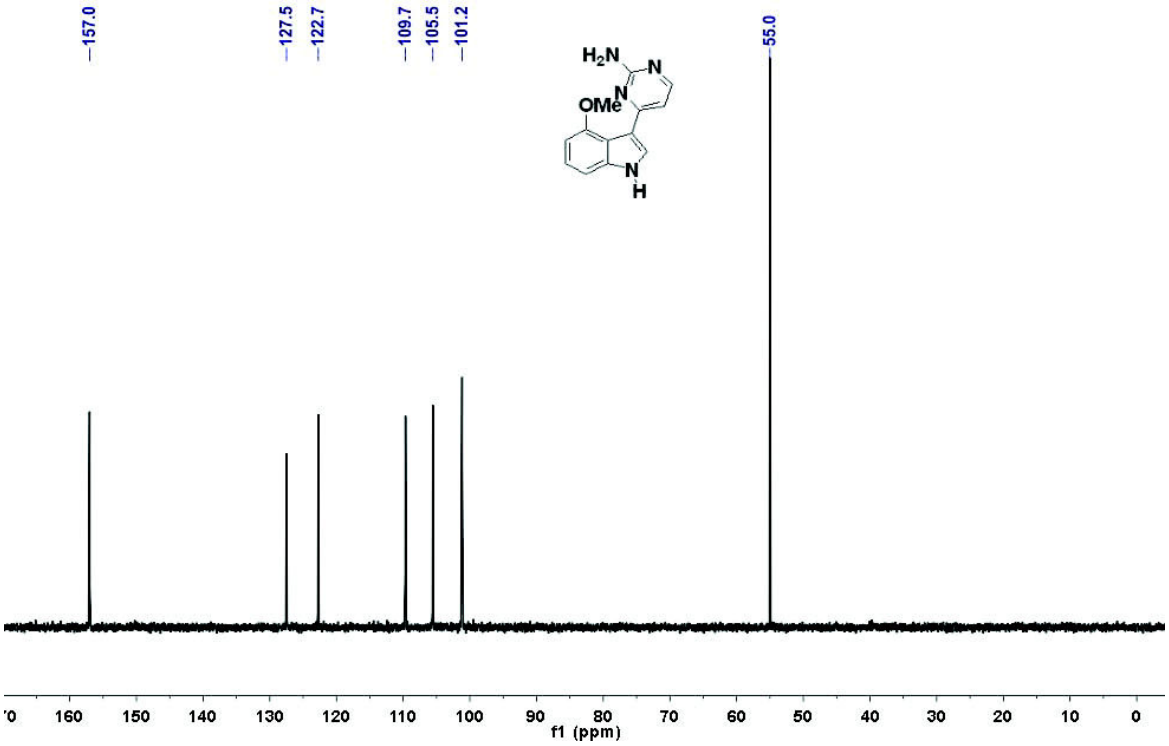
^{13}C DEPT 135-NMR of **4i** (15 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).



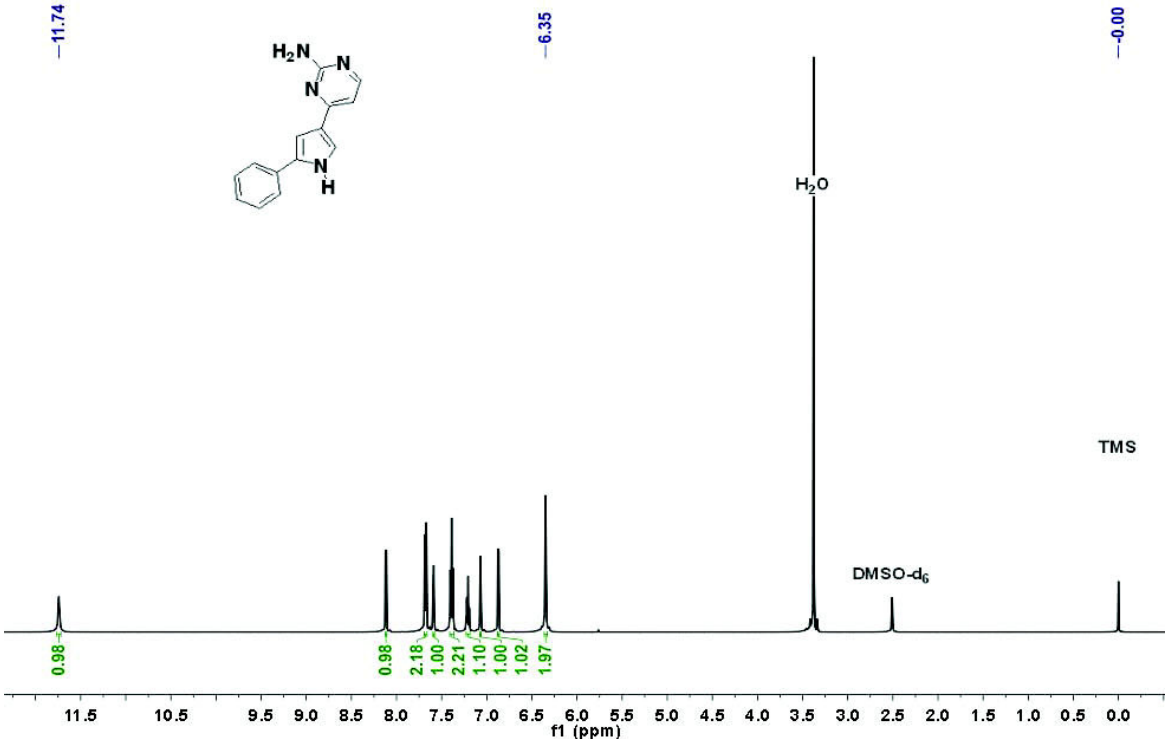
^{1}H NMR of **4j** (30 mg) in 0.7 mL DMSO-d_6 at 297 K (δ in ppm).



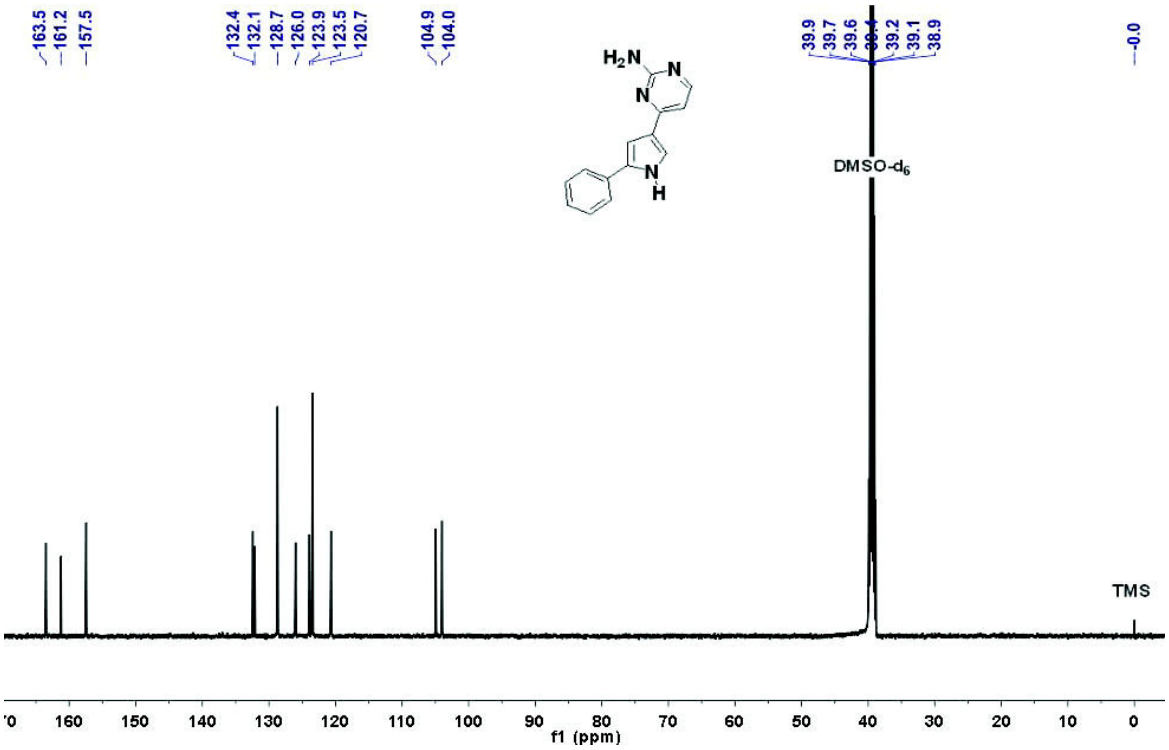
^{13}C NMR of **4j** (30 mg) in 0.7 mL DMSO-d_6 at 298 K (δ in ppm).



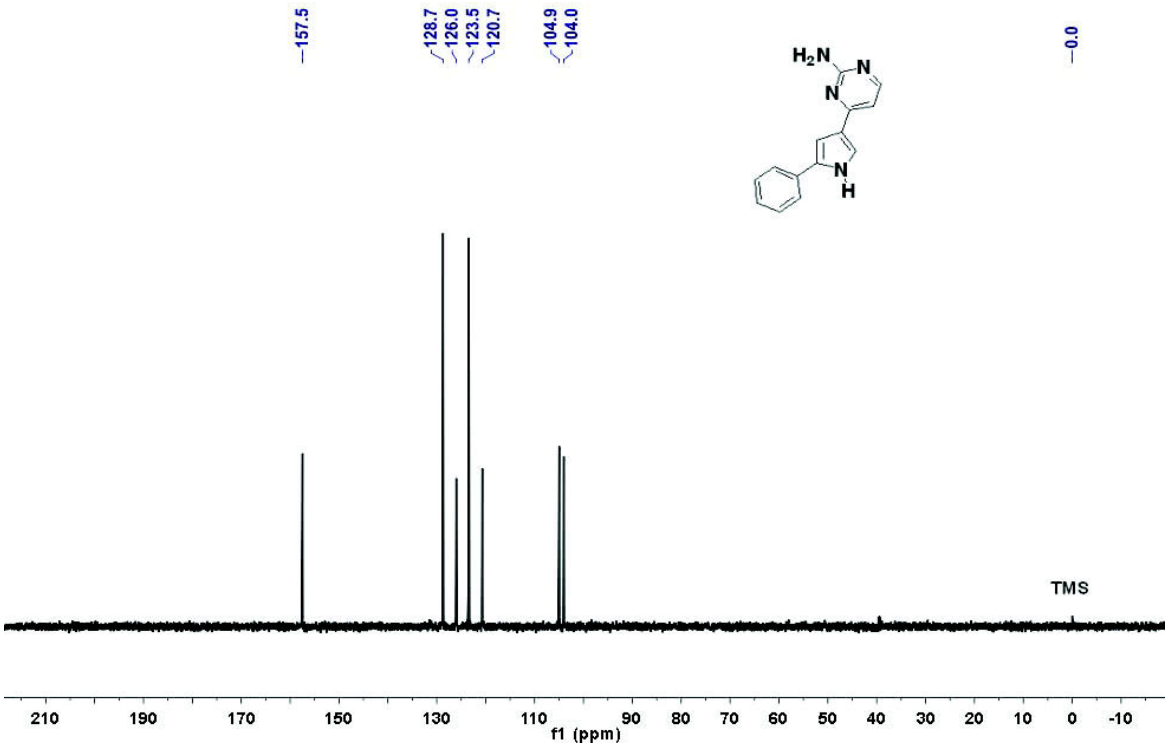
^{13}C DEPT 135-NMR of **4j** (30 mg) in 0.7 mL DMSO-d_6 at 297 K (δ in ppm).



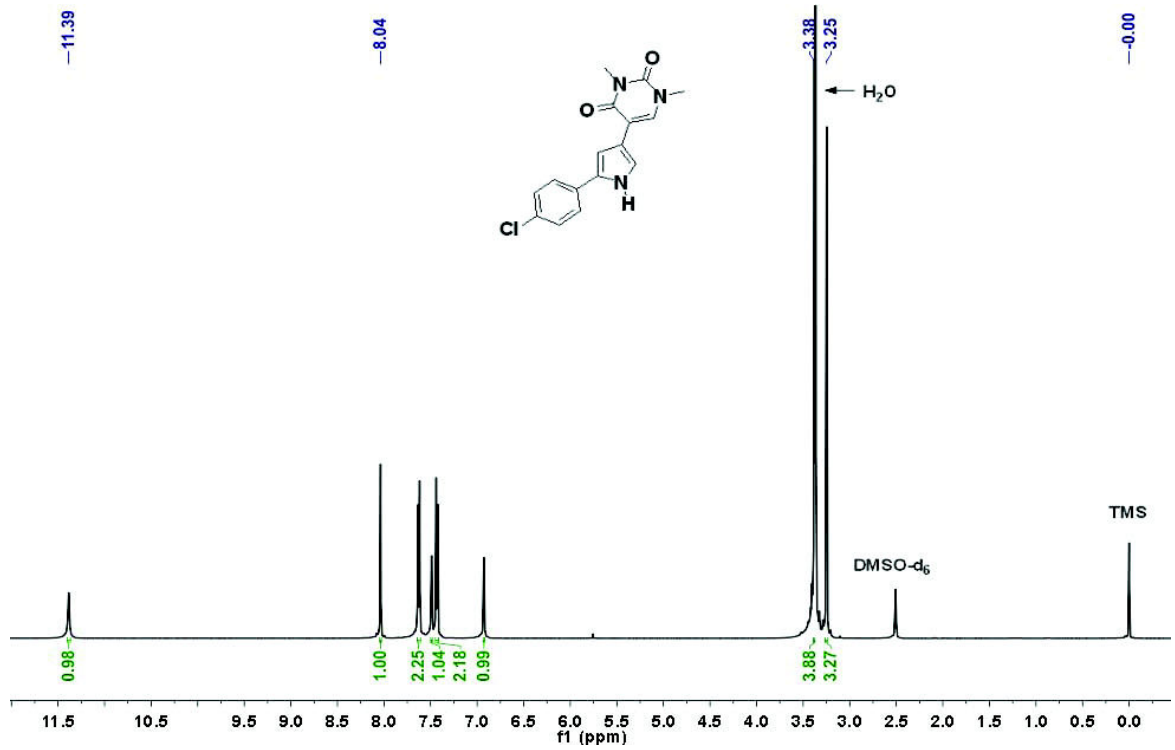
^{1}H NMR of **4k** (20 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).



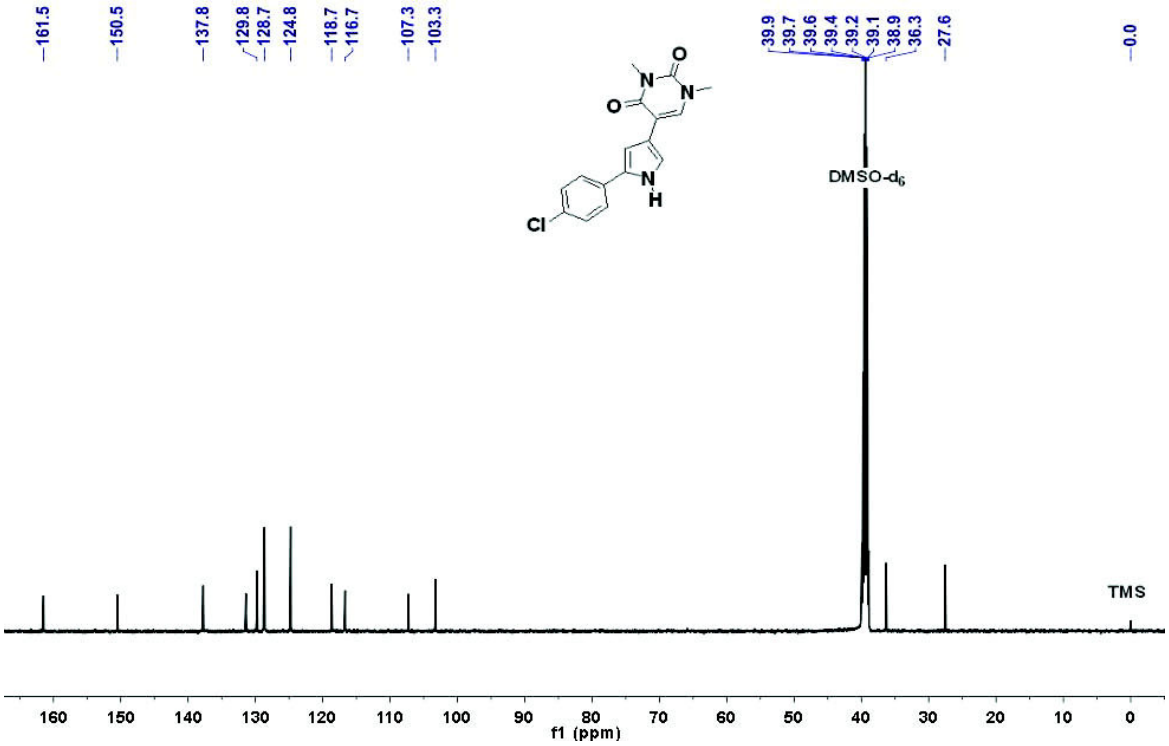
^{13}C NMR of **4k** (20 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).



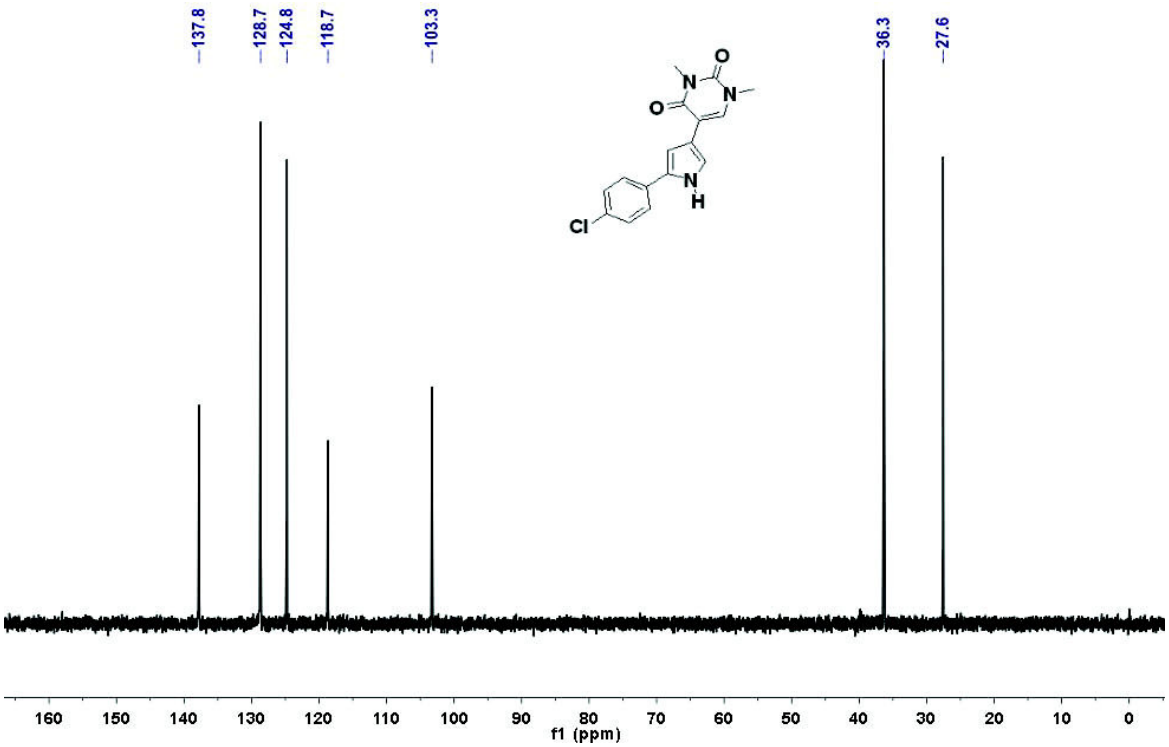
^{13}C DEPT 135-NMR of **4k** (20 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).



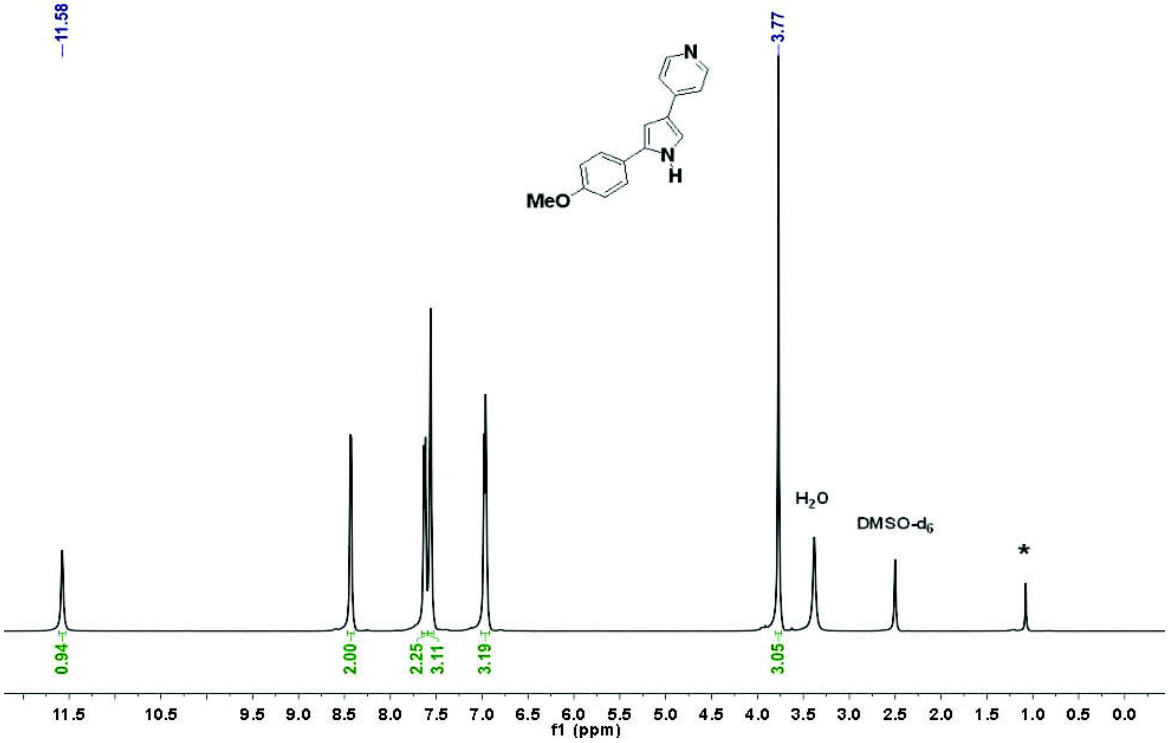
^{1}H NMR of **4l** (20 mg) in 0.7 mL DMSO-d_6 at 298 K (δ in ppm).



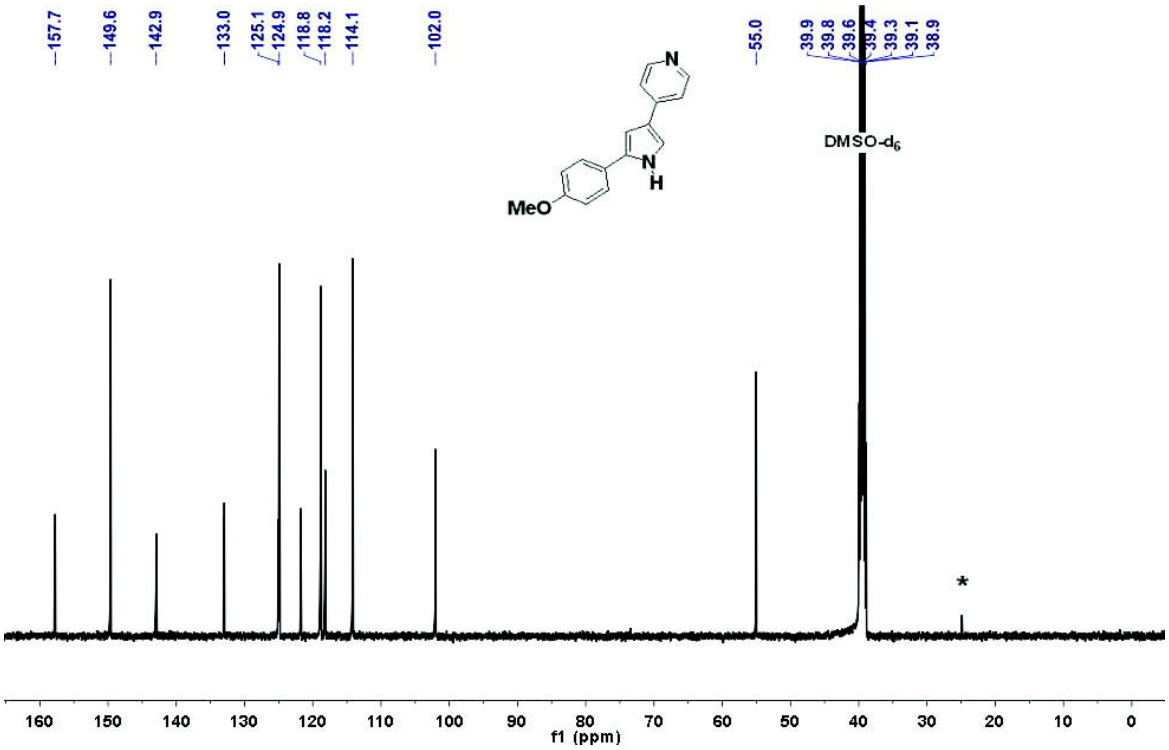
^{13}C NMR of **4l** (20 mg) in 0.7 mL DMSO-d_6 at 298 K (δ in ppm).



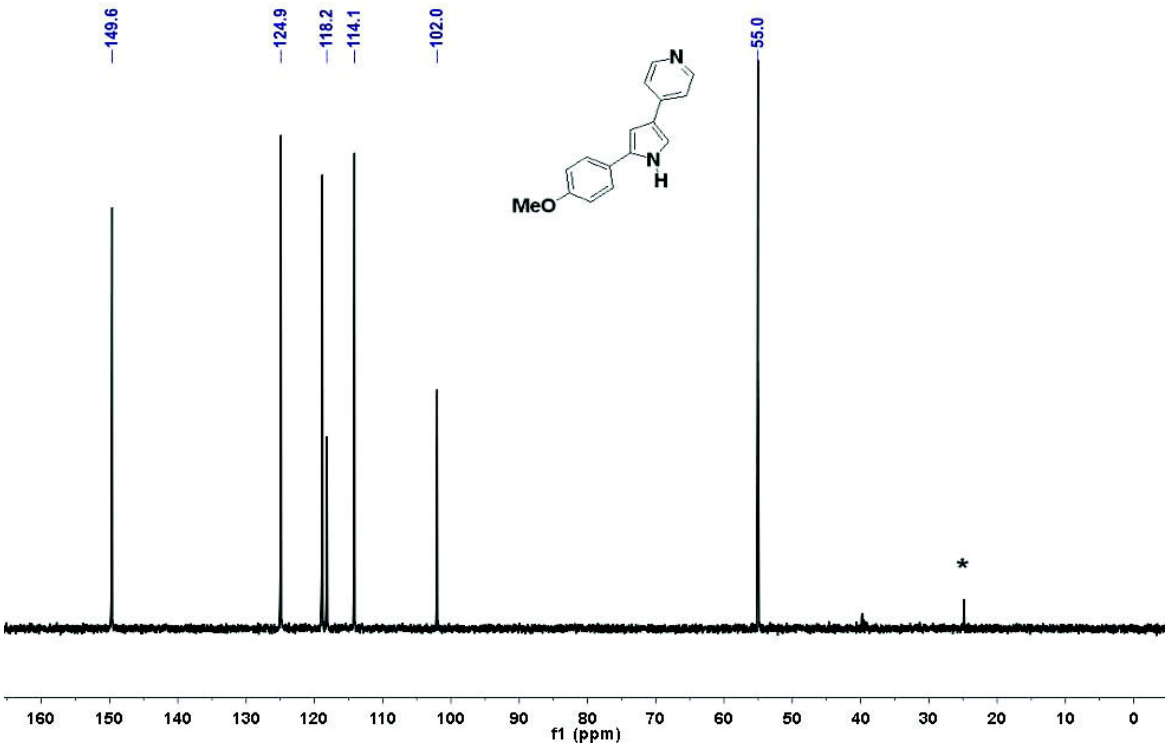
^{13}C DEPT 135-NMR of **4l** (20 mg) in 0.7 mL DMSO-d_6 at 298 K (δ in ppm).



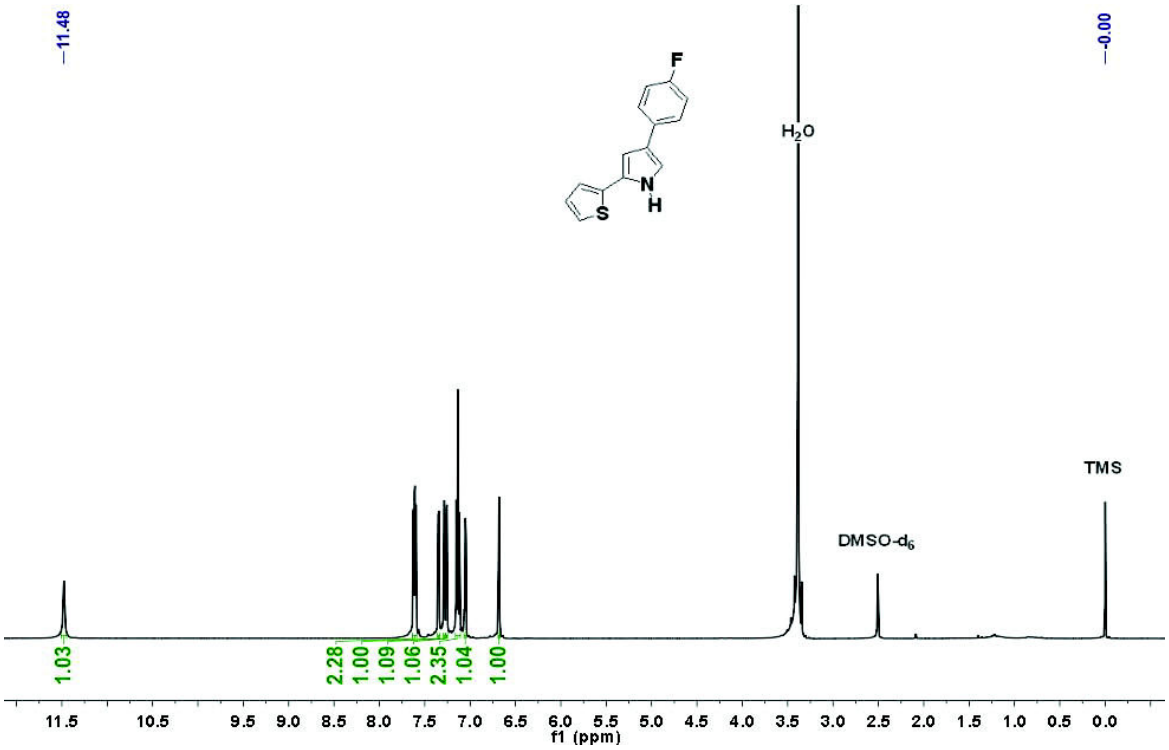
^{1}H NMR of **4m** (15 mg) in 0.7 mL DMSO-d_6 at 297 K (δ in ppm). *Impurities from residual solvents.



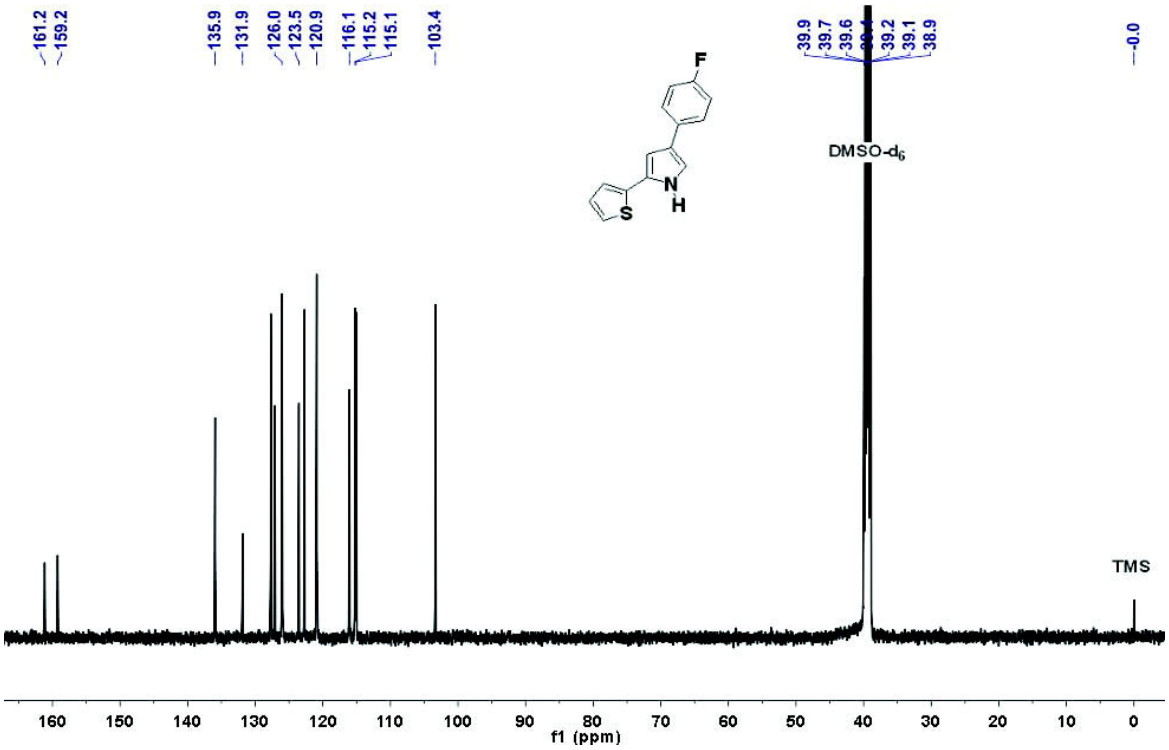
^{13}C NMR of **4m** (15 mg) in 0.7 mL DMSO-d_6 at 297 K (δ in ppm). *Impurities from residual solvents.



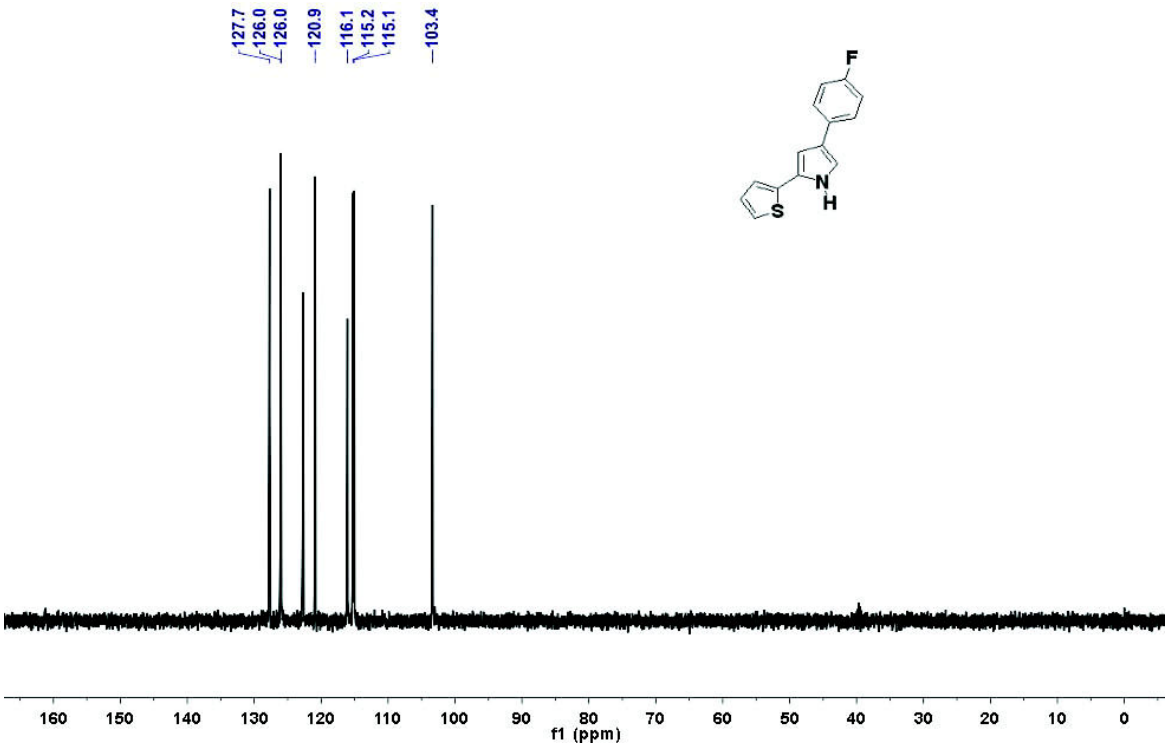
^{13}C DEPT 135-NMR of **4m** (15 mg) in 0.7 mL DMSO-d_6 at 297 K (δ in ppm). *Impurities from residual solvents.



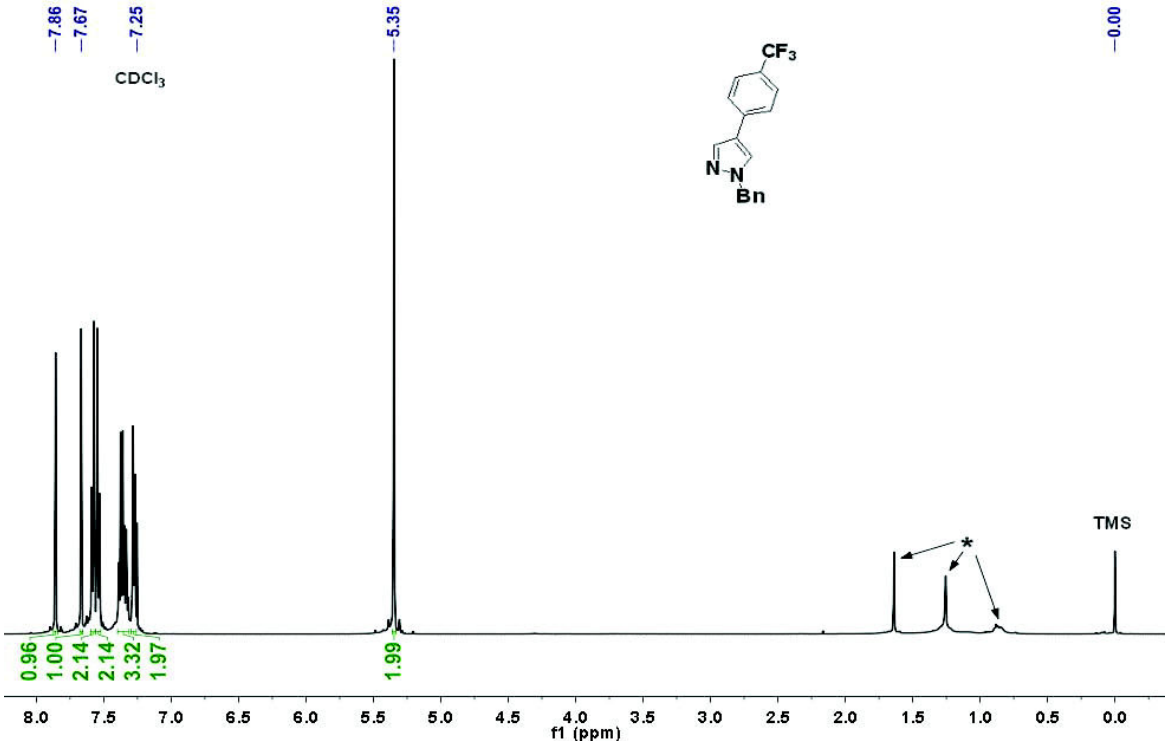
^{1}H NMR of **4n** (20 mg) in 0.7 mL DMSO-d_6 at 298 K (δ in ppm).



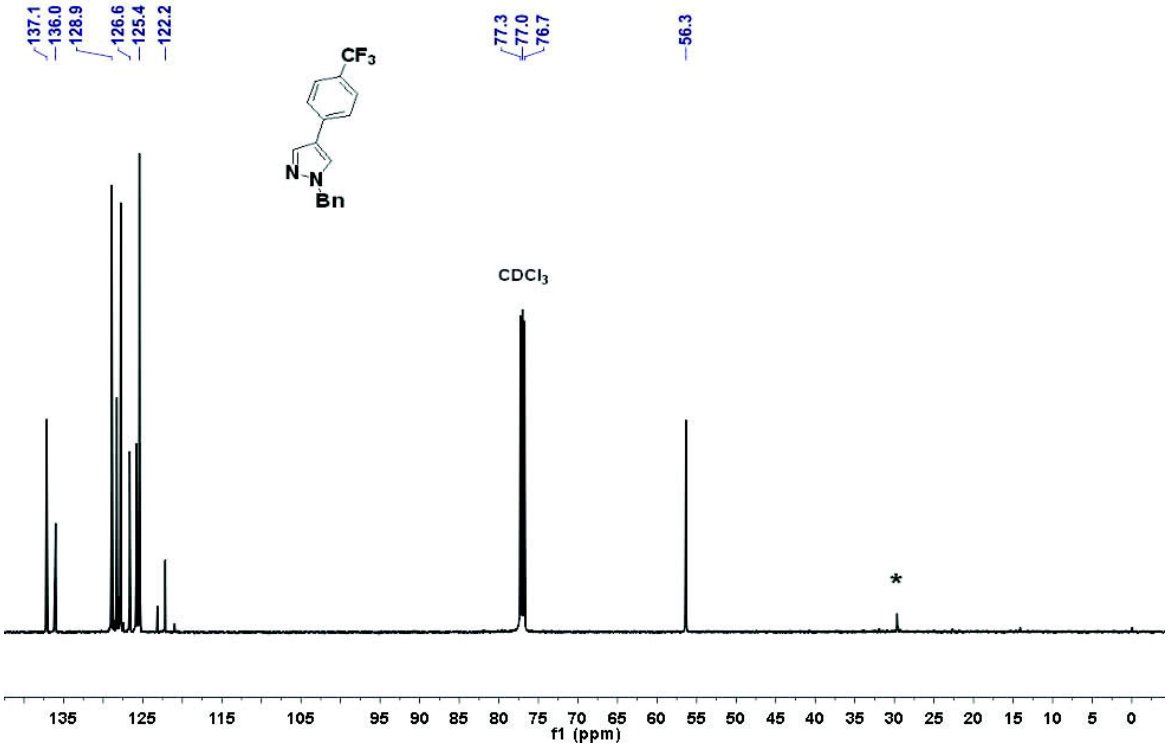
^{13}C NMR of **4n** (20 mg) in 0.7 mL DMSO-d_6 at 299 K (δ in ppm).



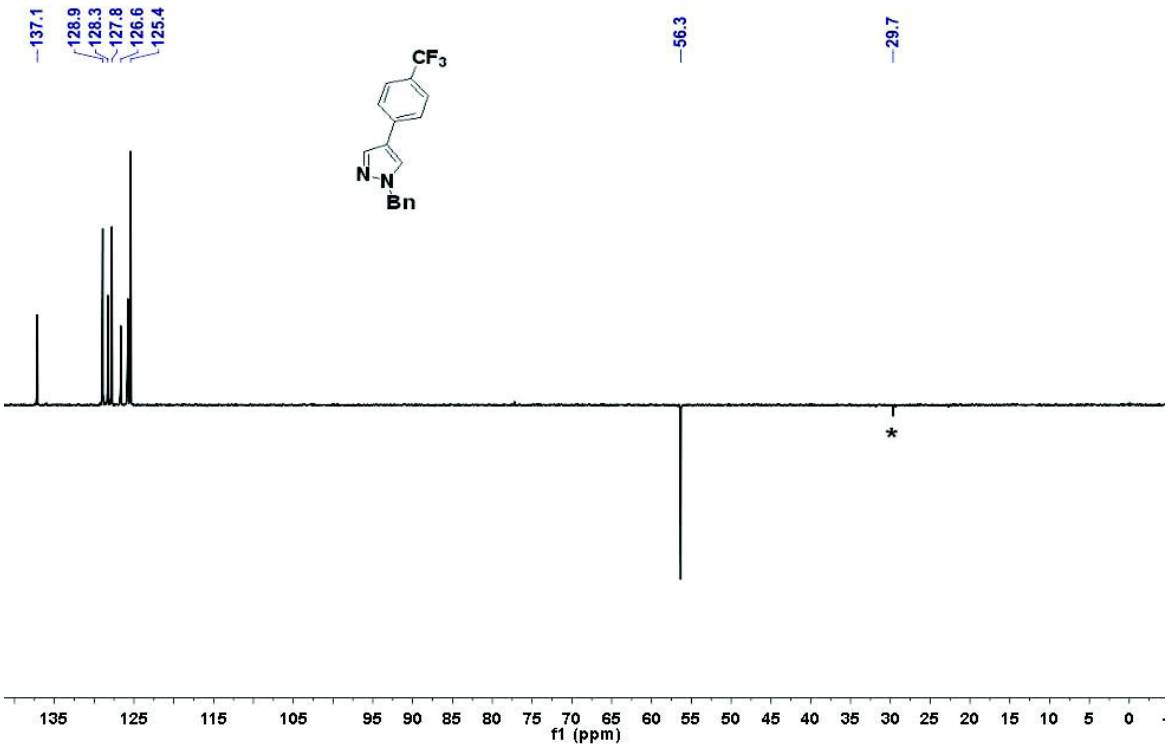
^{13}C DEPT 135-NMR of **4n** (20 mg) in 0.7 mL DMSO-d_6 at 298 K (δ in ppm).



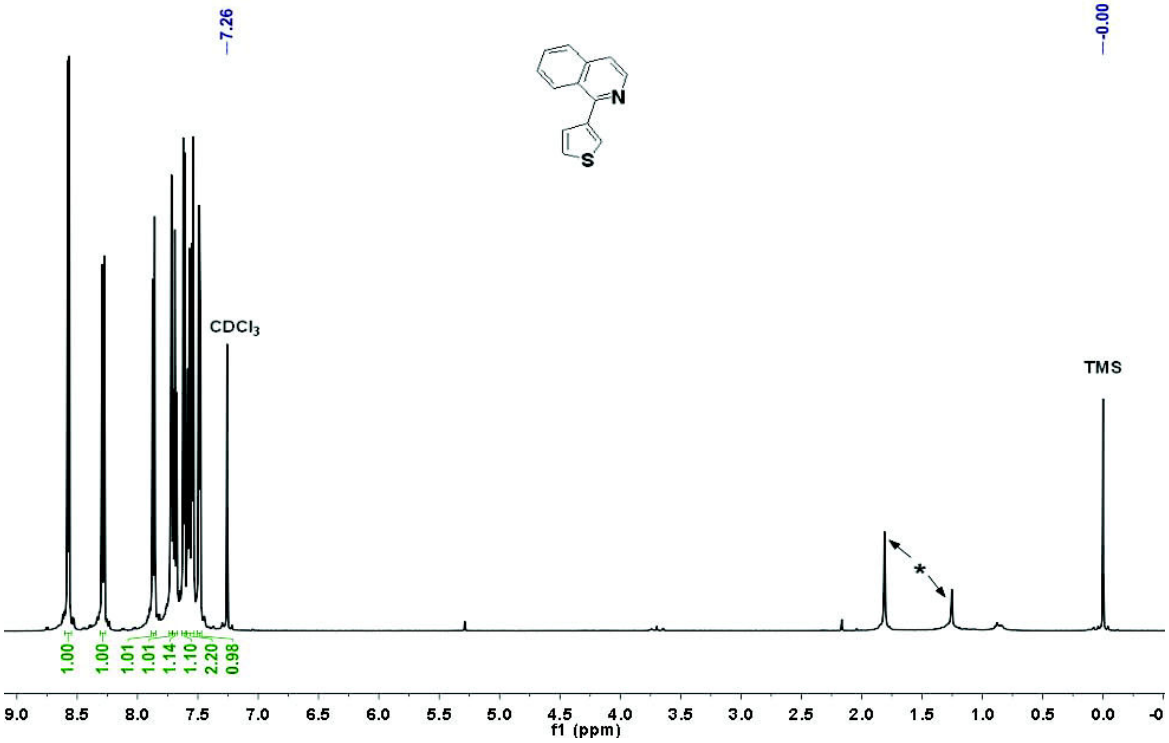
^{1}H NMR of **4o** (50 mg) in 0.7 mL $CDCl_3$ at 297 K (δ in ppm). *Impurities from residual solvents.



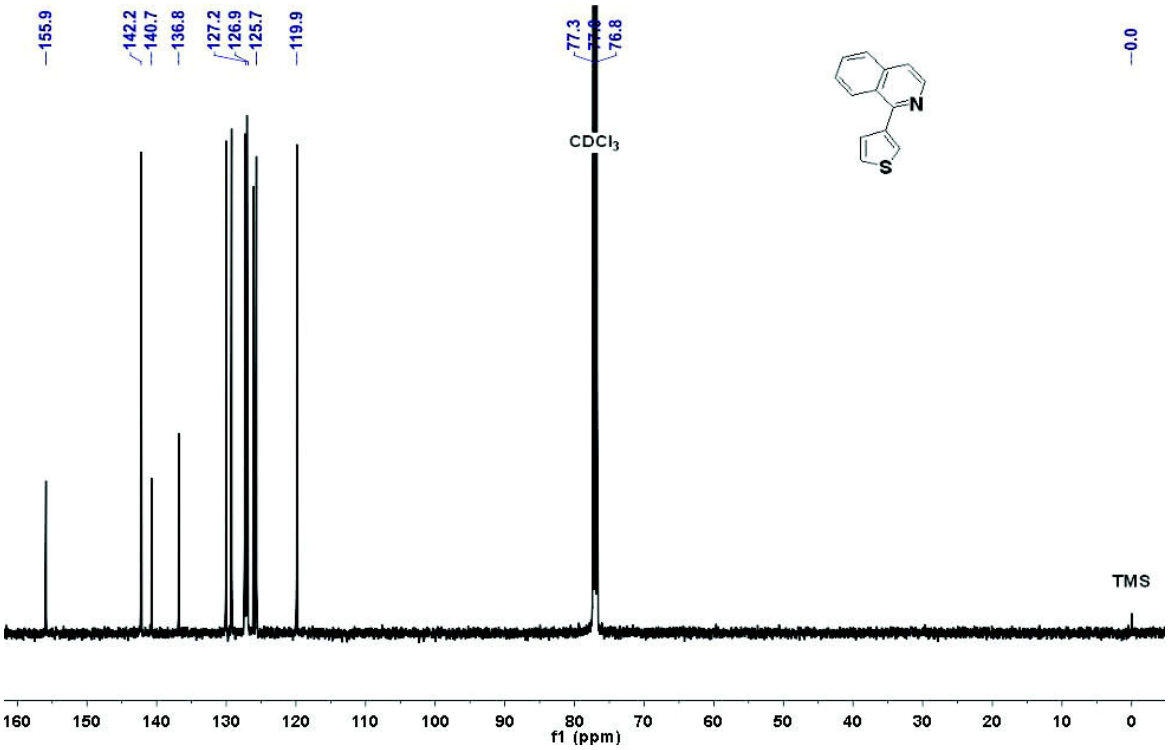
^{13}C NMR of **4o** (50 mg) in 0.7 mL $CDCl_3$ at 298 K (δ in ppm). *Impurities from residual solvents.



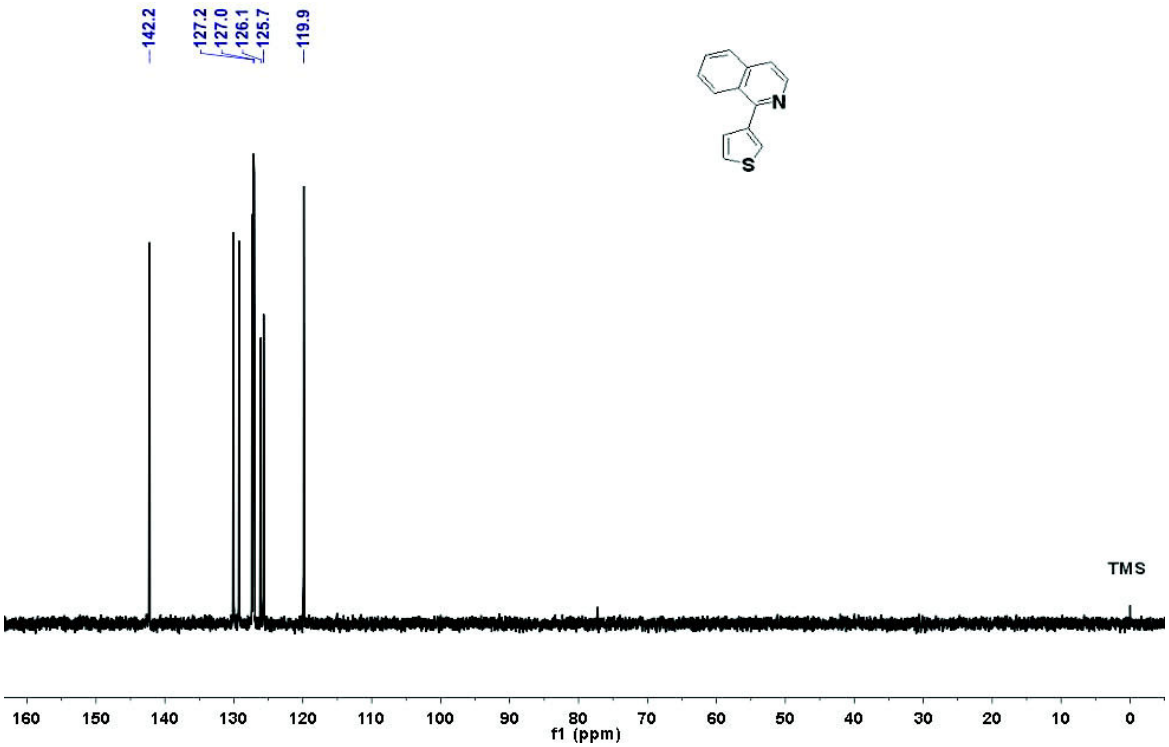
^{13}C DEPT 135-NMR of **4o** (50 mg) in 0.7 mL $CDCl_3$ at 297K (δ in ppm). *Impurities from residual solvents.



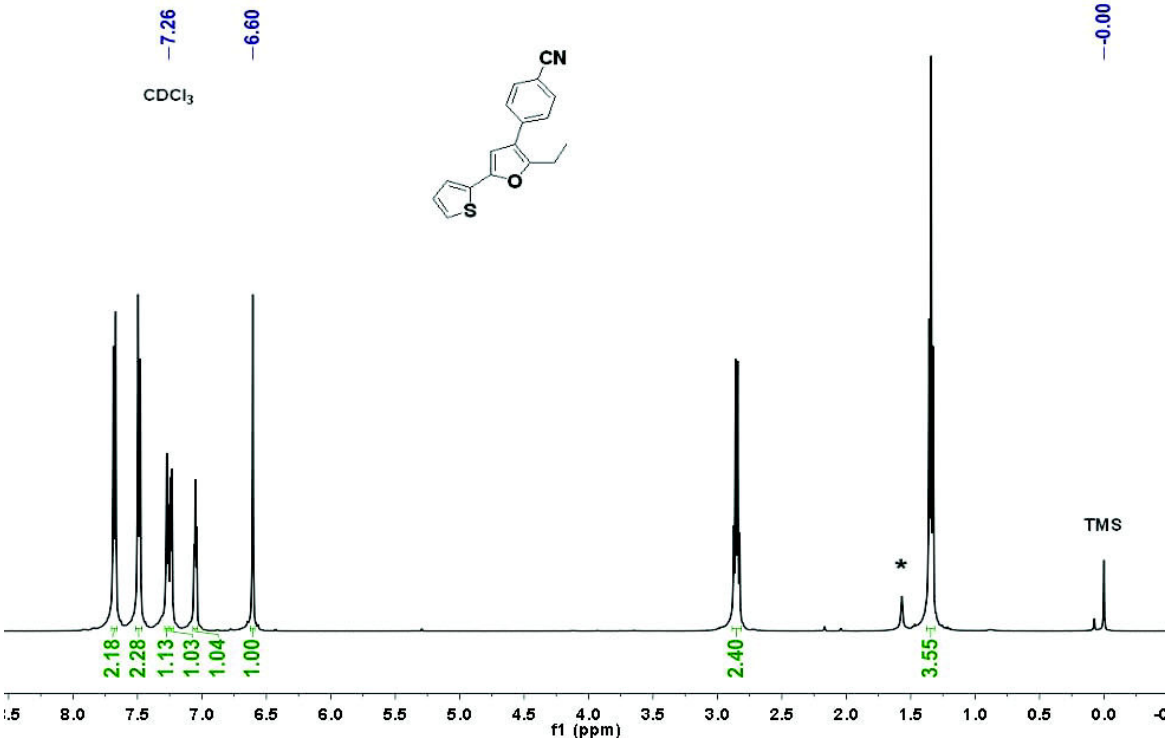
^{1}H NMR of **4p** (20 mg) in 0.7 mL $CDCl_3$ at 296 K (δ in ppm). *Impurities from residual solvents.



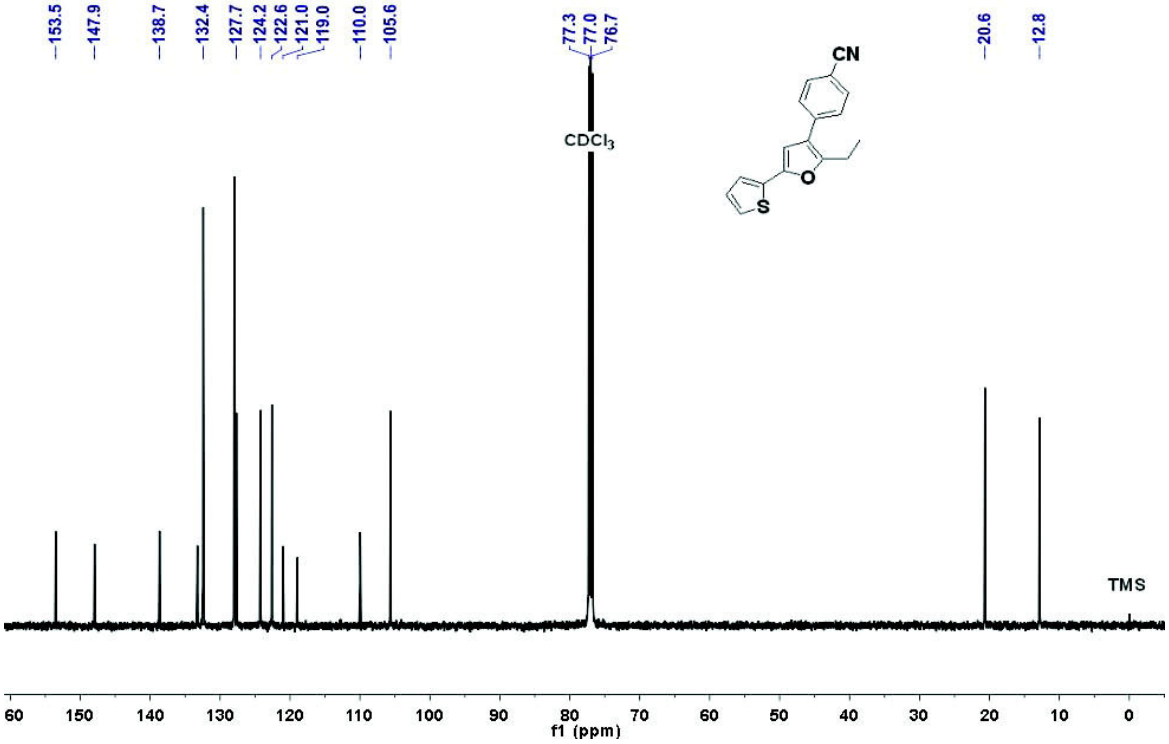
^{13}C NMR of **4p** (20 mg) in 0.7 mL $CDCl_3$ at 296 K (δ in ppm).



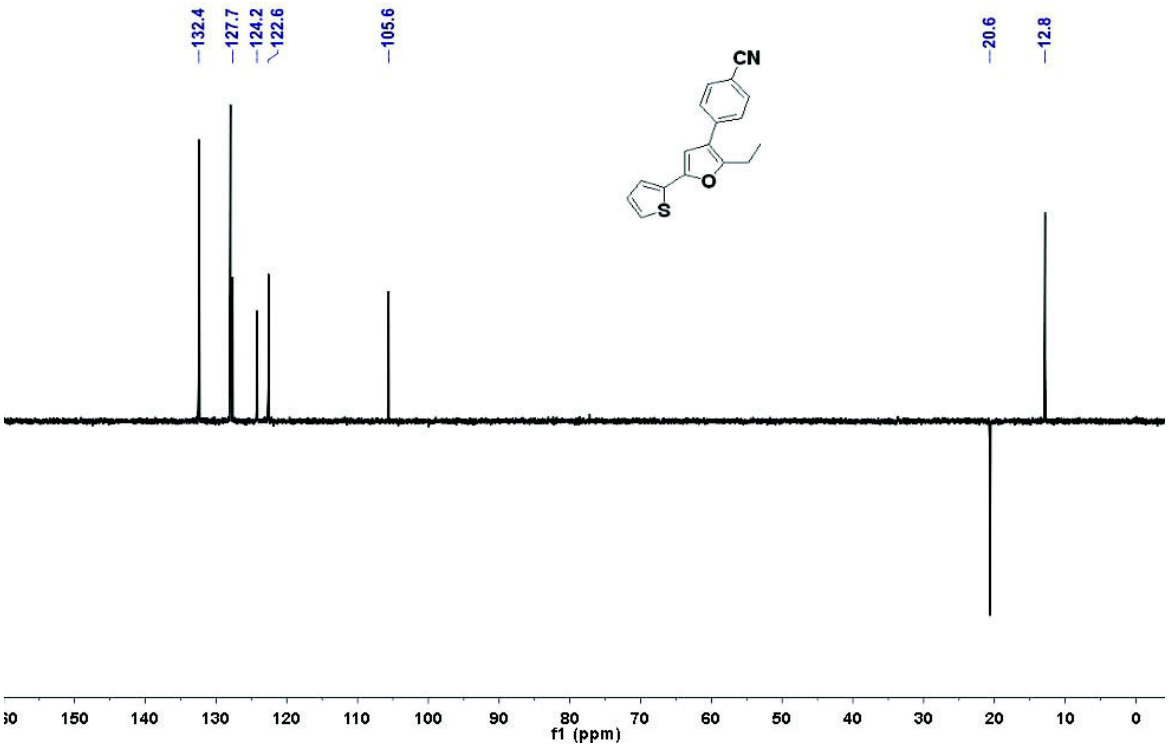
^{13}C DEPT 135-NMR of **4p** (20 mg) in 0.7 mL $CDCl_3$ at 296 K (δ in ppm).



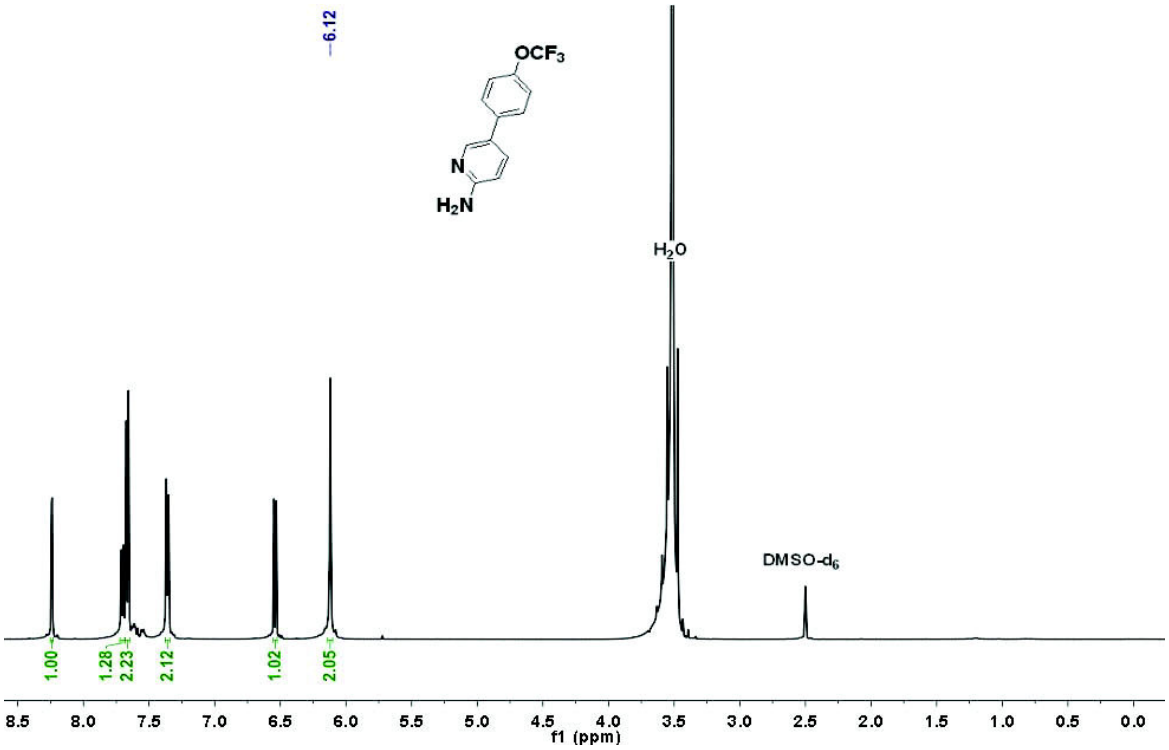
^{1}H NMR of **4q** (20 mg) in 0.7 mL $CDCl_3$ at 298 K (δ in ppm). *Impurities from residual solvents.



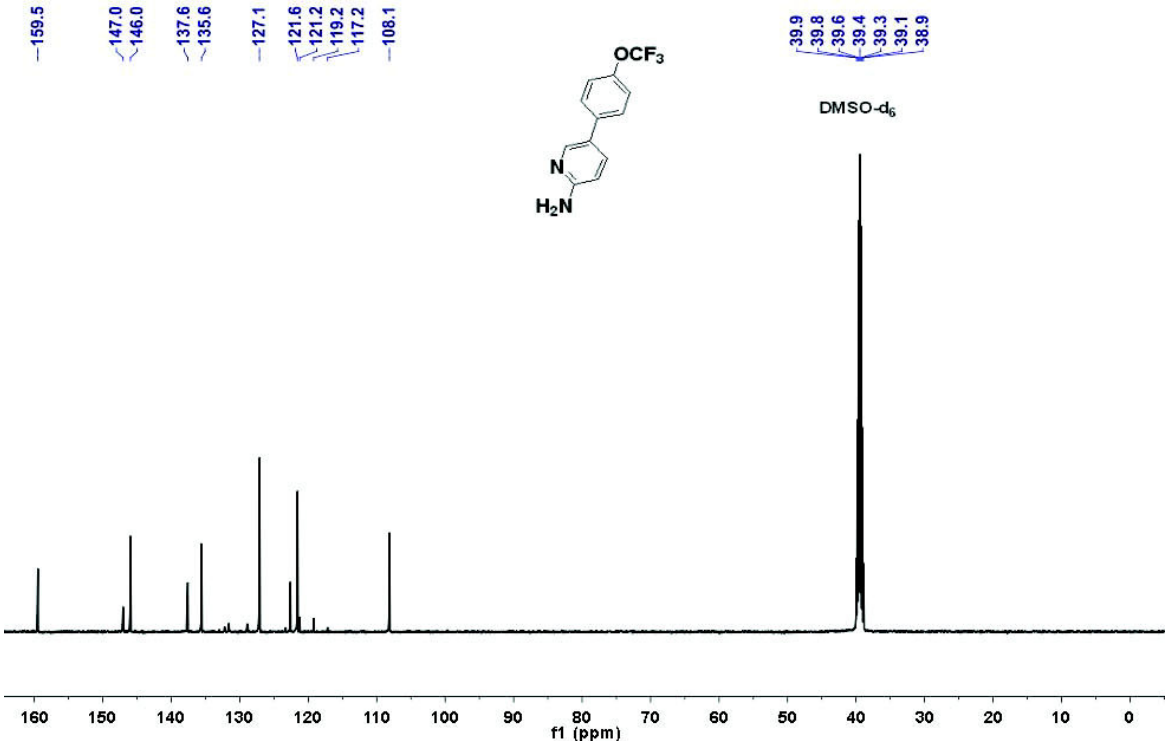
^{13}C NMR of **4q** (20 mg) in 0.7 mL $CDCl_3$ at 298 K (δ in ppm).



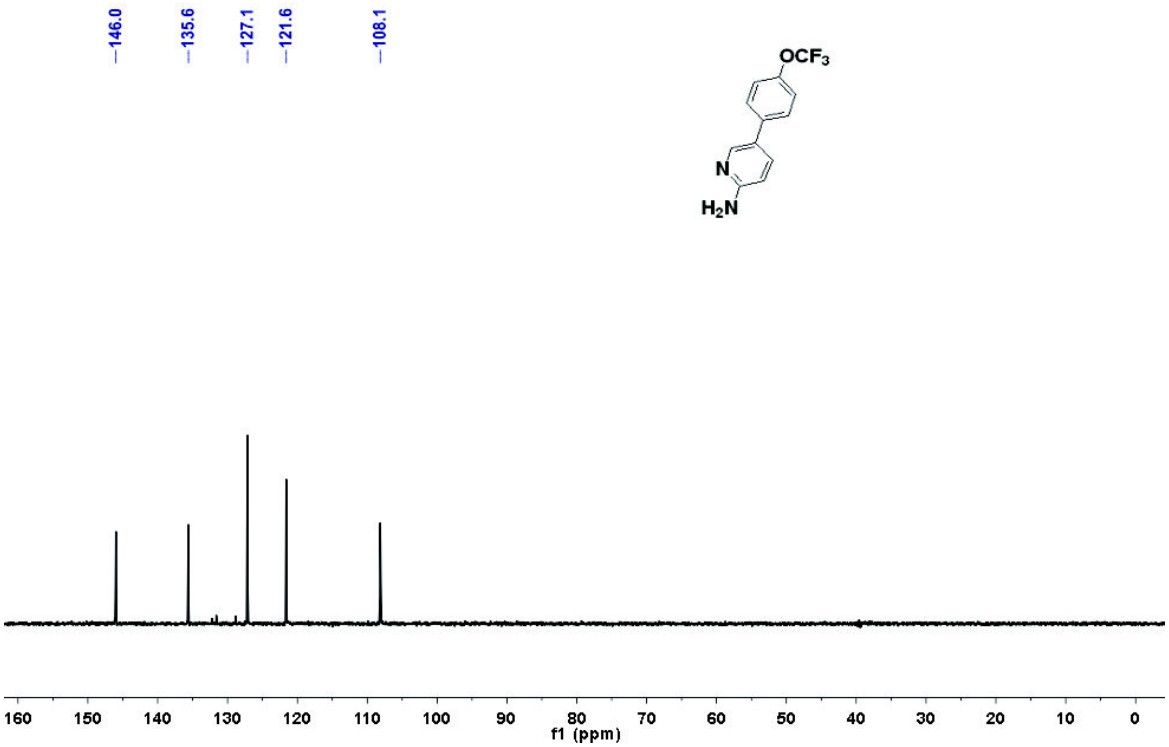
^{13}C DEPT 135-NMR of **4q** (20 mg) in 0.7 mL $CDCl_3$ at 298 K (δ in ppm).



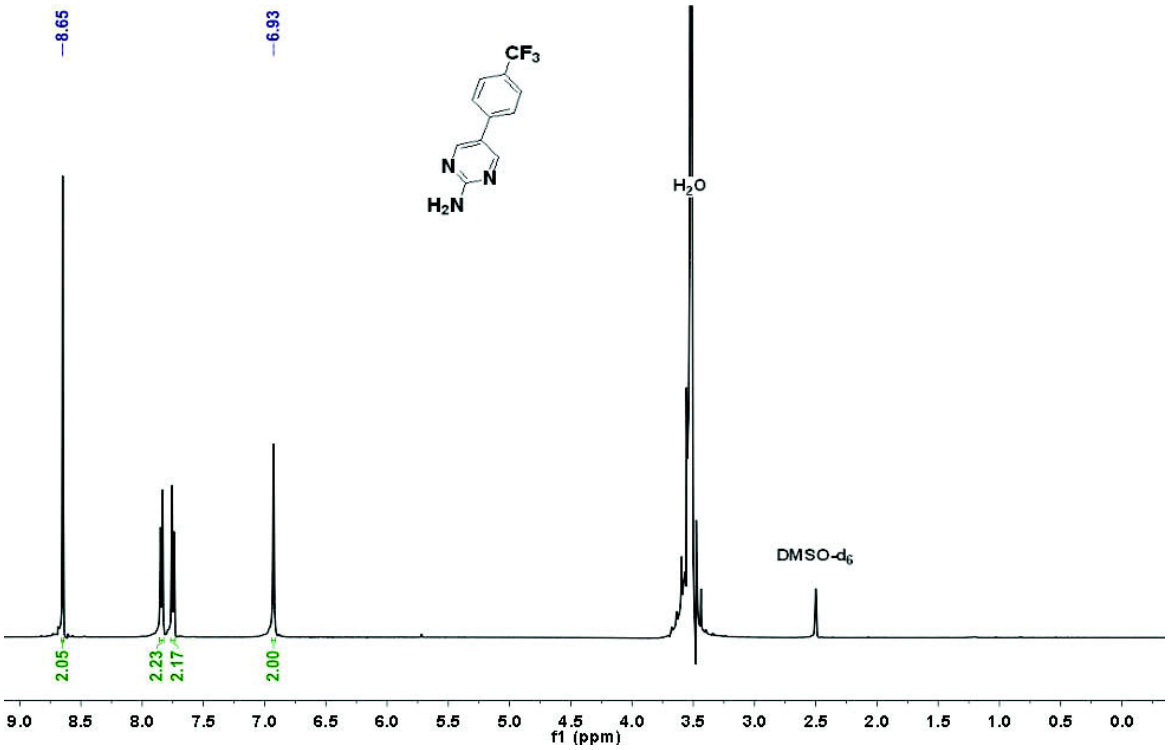
^{1}H NMR of **4r** (30 mg) in 0.7 mL $CDCl_3$ at 296 K (δ in ppm).



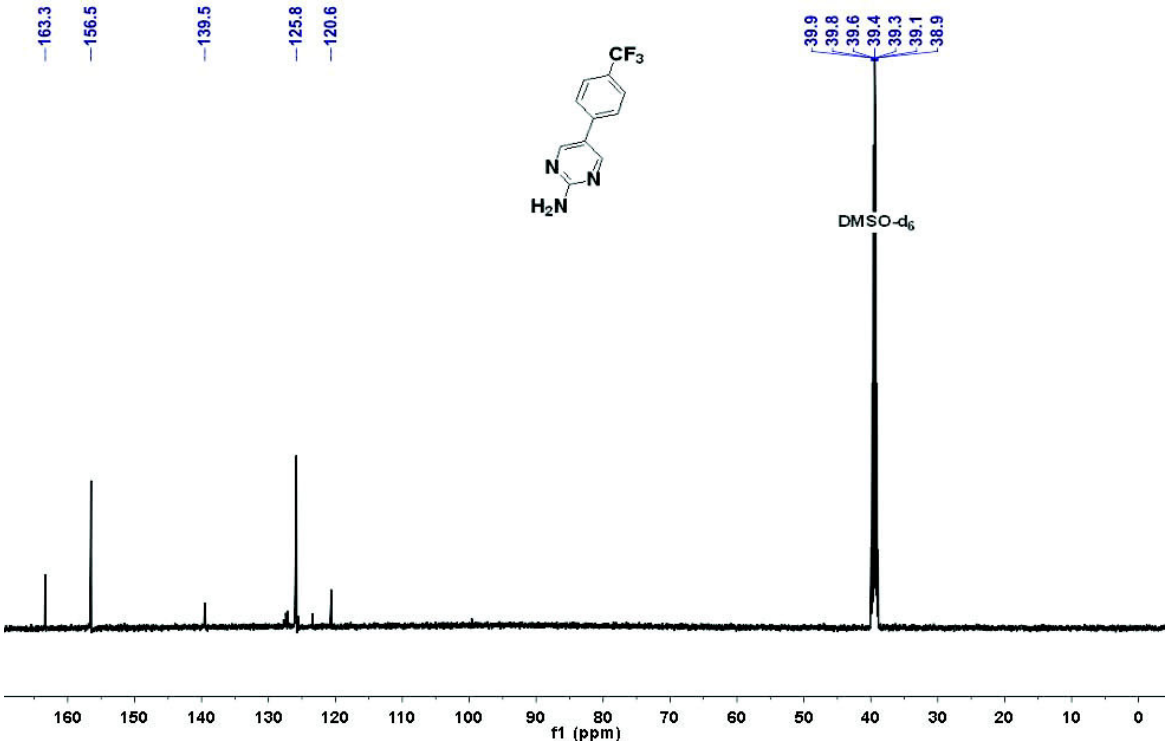
^{13}C NMR of **4r** (30 mg) in 0.7 mL $CDCl_3$ at 296 K (δ in ppm).



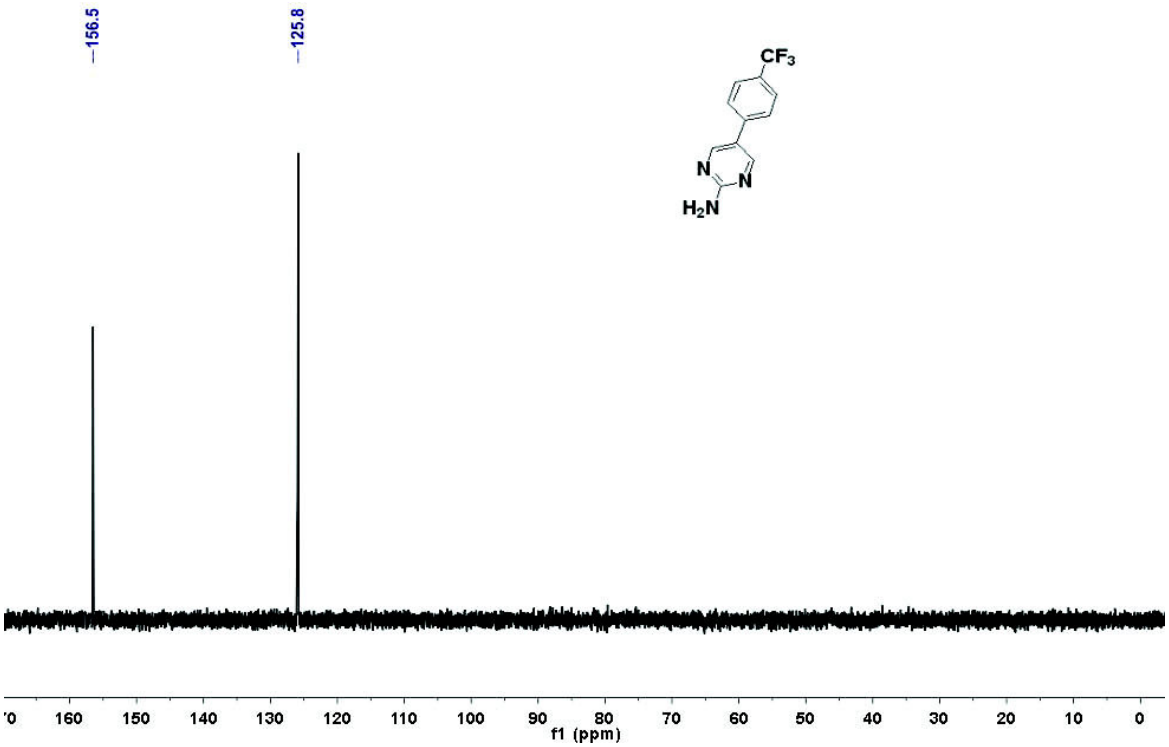
^{13}C DEPT 135-NMR of **4r** (30 mg) in 0.7 mL $CDCl_3$ at 296 K (δ in ppm).



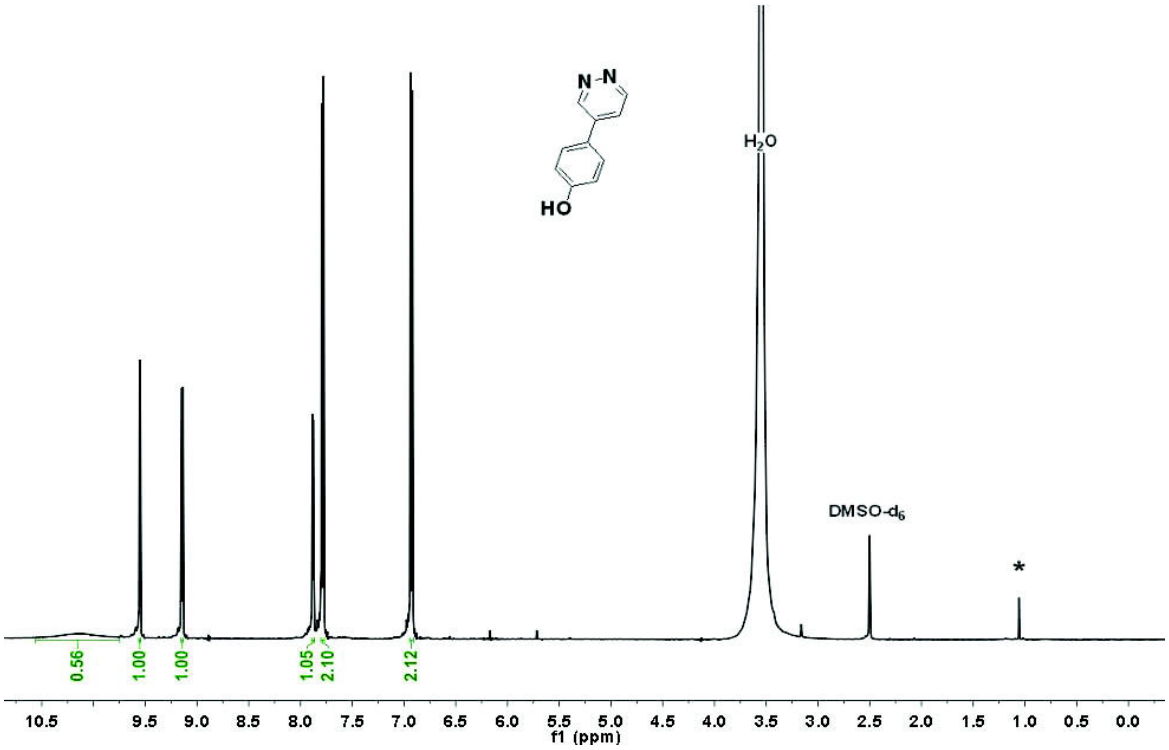
^{1}H NMR of **4s** (15 mg) in 0.7 mL $CDCl_3$ at 297 K (δ in ppm).



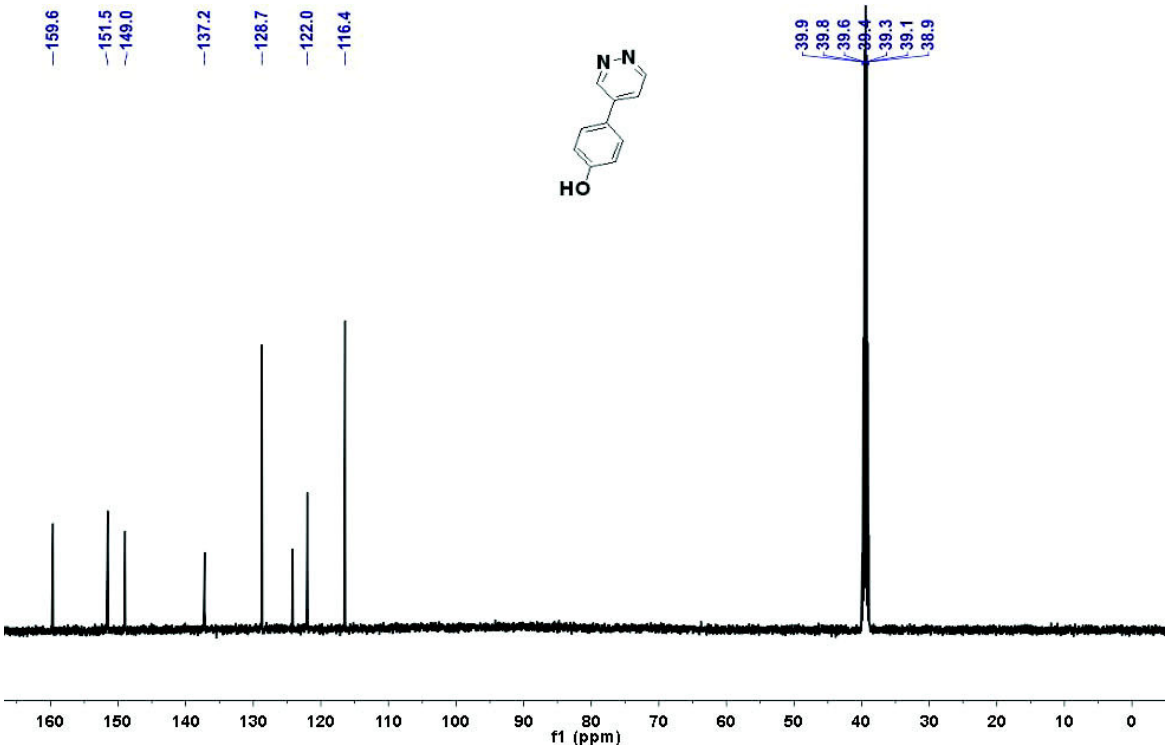
^{13}C NMR of **4s** (15 mg) in 0.7 mL $CDCl_3$ at 297 K (δ in ppm).



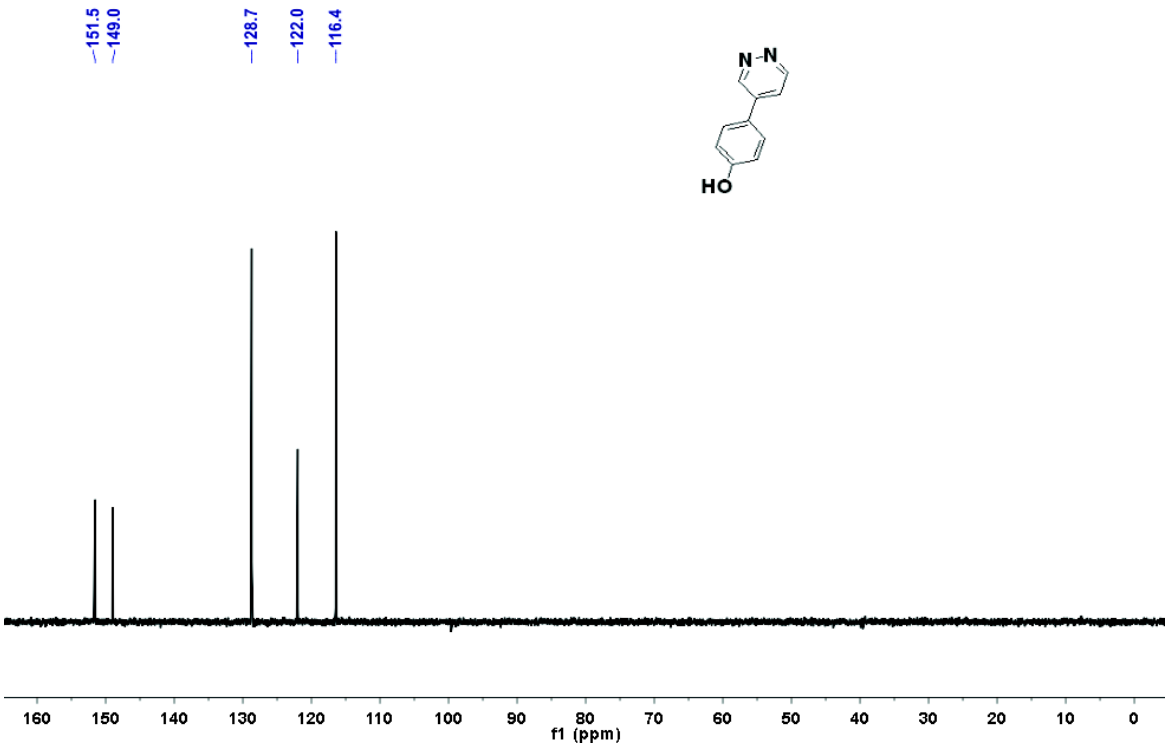
^{13}C DEPT 135-NMR of **4s** (15 mg) in 0.7 mL $CDCl_3$ at 297 K (δ in ppm).



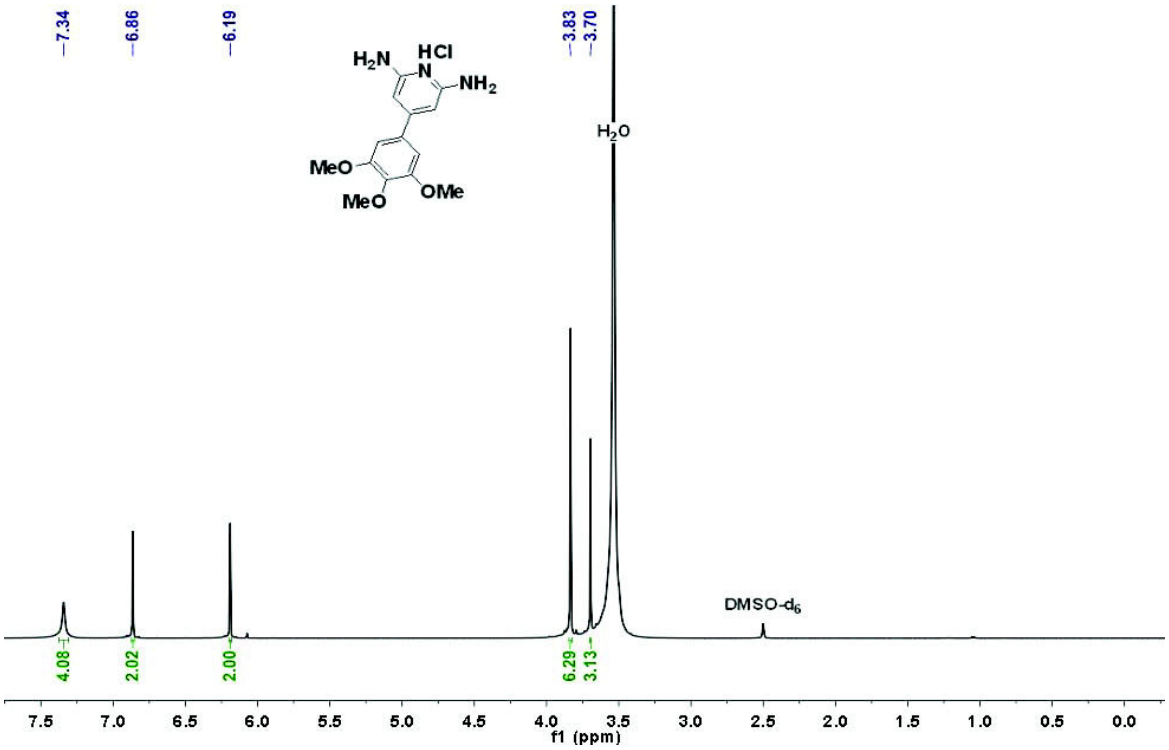
^{1}H NMR of **4t** (20 mg) in 0.7 mL DMSO-d_6 at 297 K (δ in ppm). *Impurities from residual solvents.



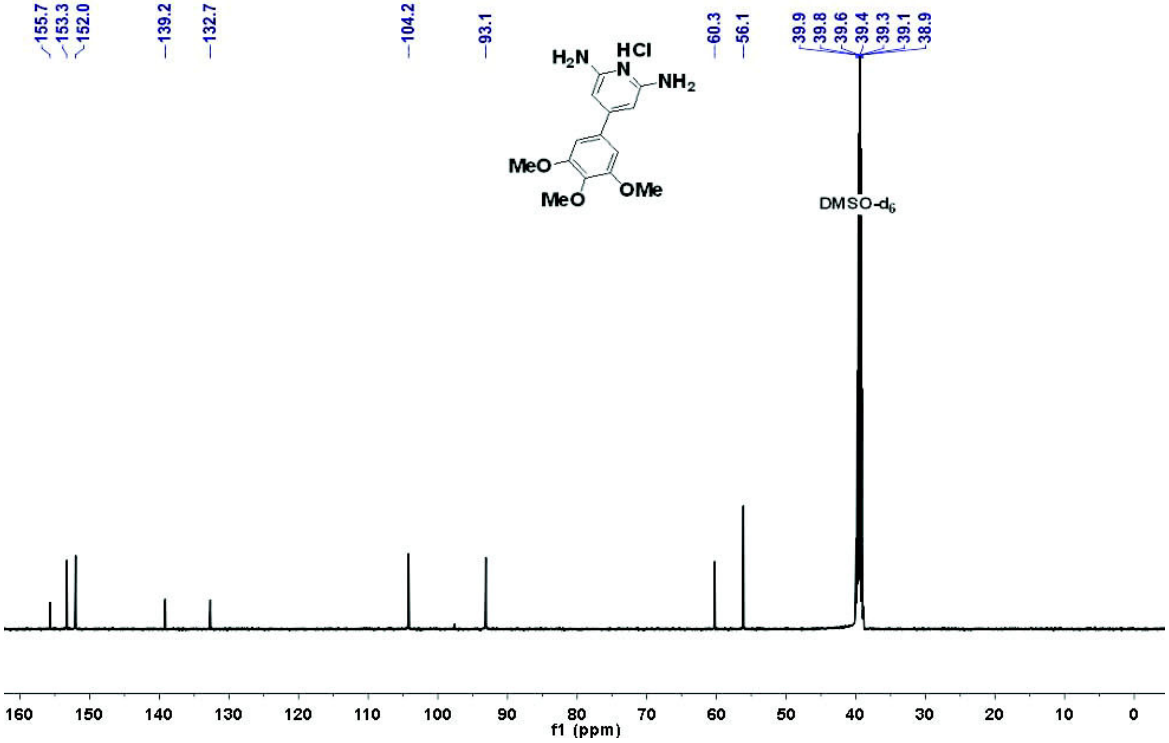
^{13}C NMR of **4t** (20 mg) in 0.7 mL DMSO-d_6 at 297 K (δ in ppm).



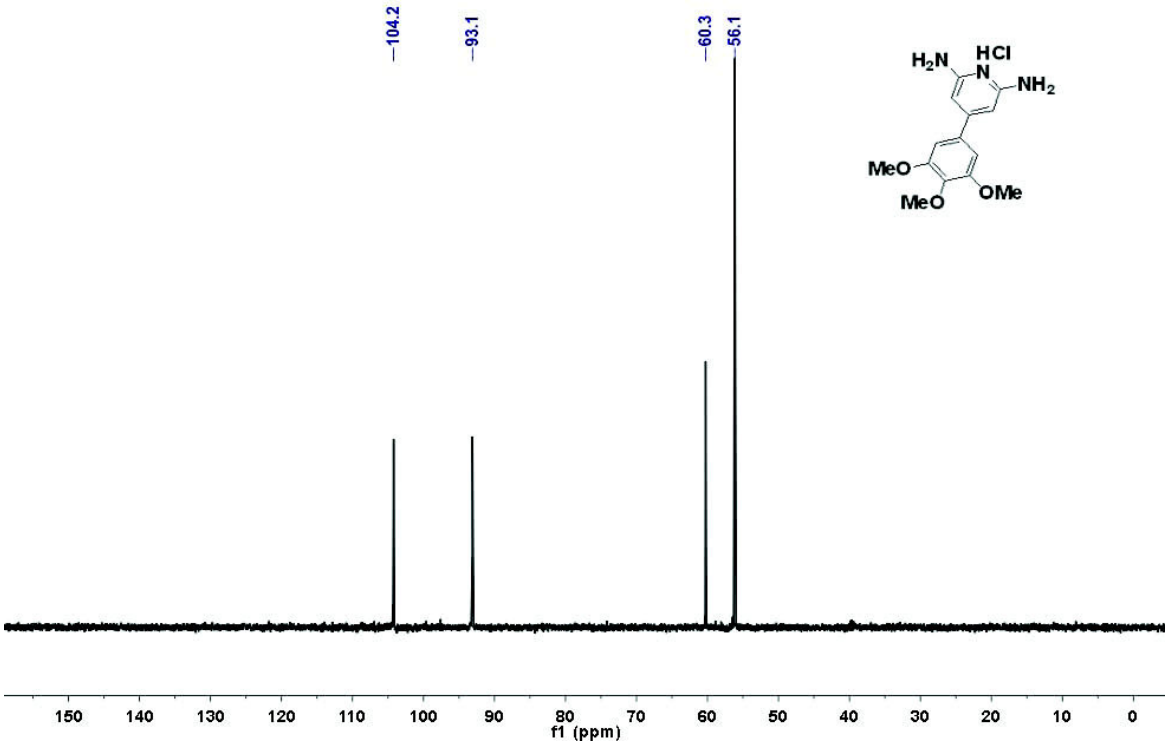
^{13}C DEPT 135-NMR of **4t** (20 mg) in 0.7 mL DMSO-d_6 at 297 K (δ in ppm).



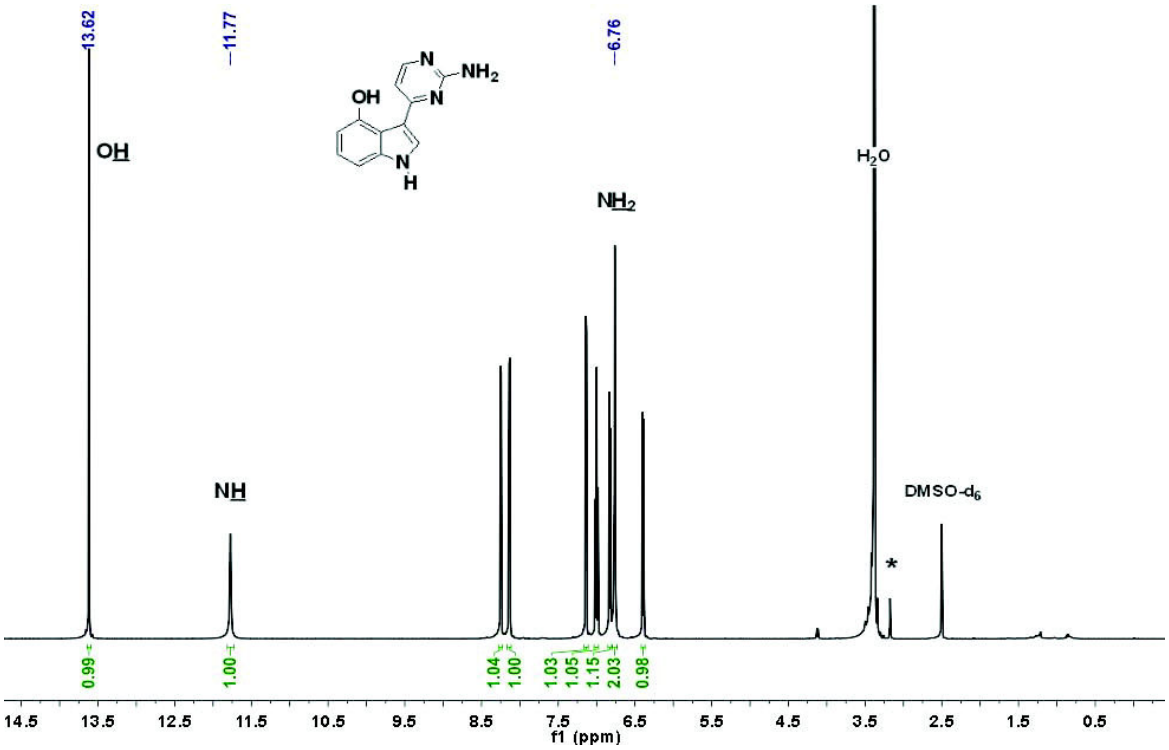
^{1}H NMR of **4u** (20 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).



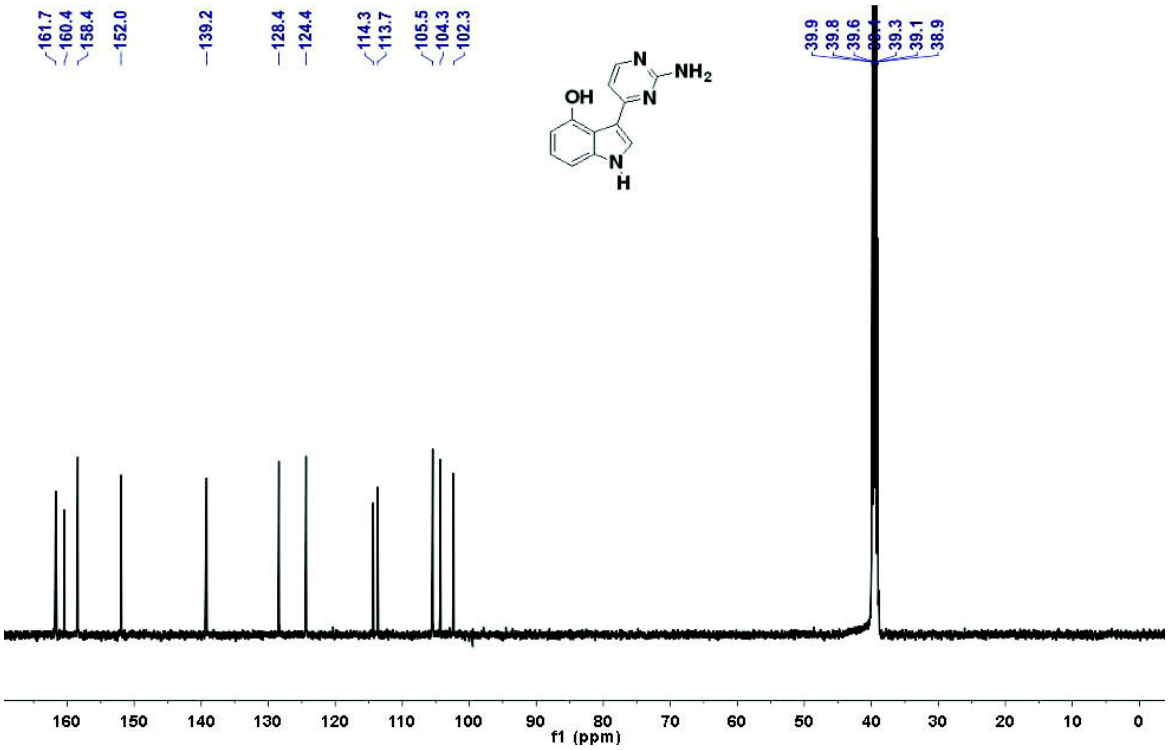
^{13}C NMR of **4u** (20 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).



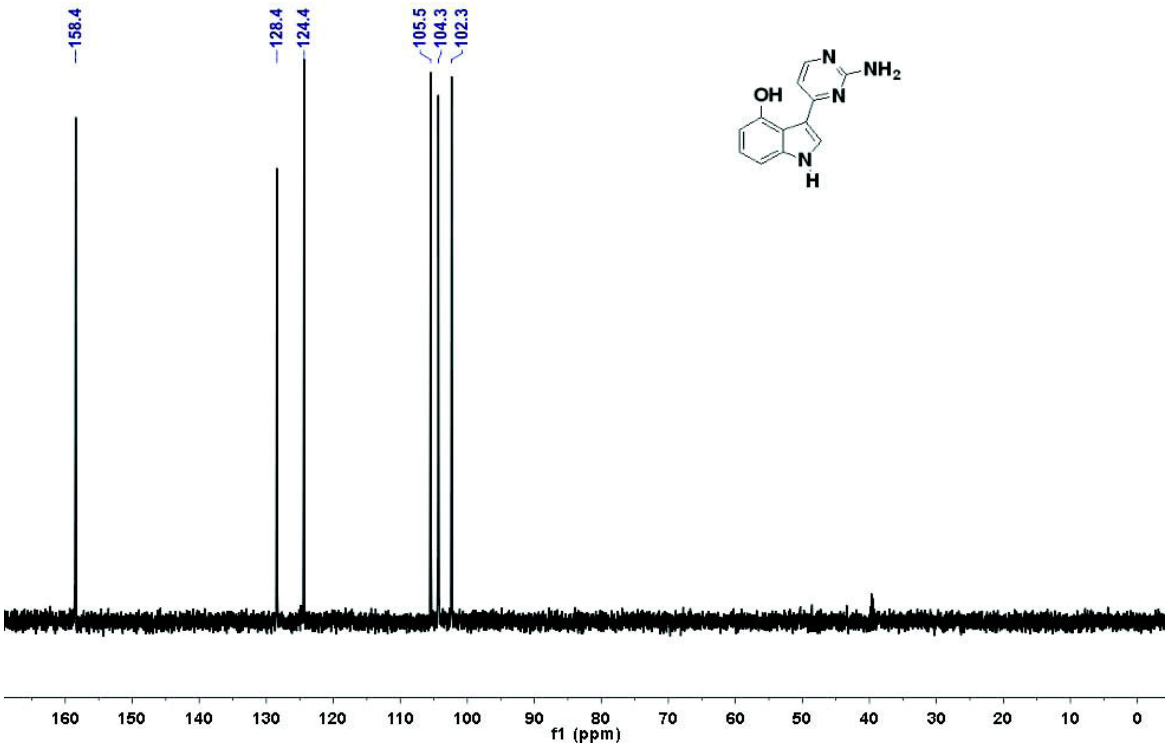
^{13}C DEPT 135-NMR of **4u** (20 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).



^{1}H NMR of **5** (30 mg) in 0.7 mL DMSO-d_6 at 298 K (δ in ppm). *Impurities from residual solvents.



^{13}C NMR of **5** (30 mg) in 0.7 mL DMSO-d_6 at 298 K (δ in ppm).

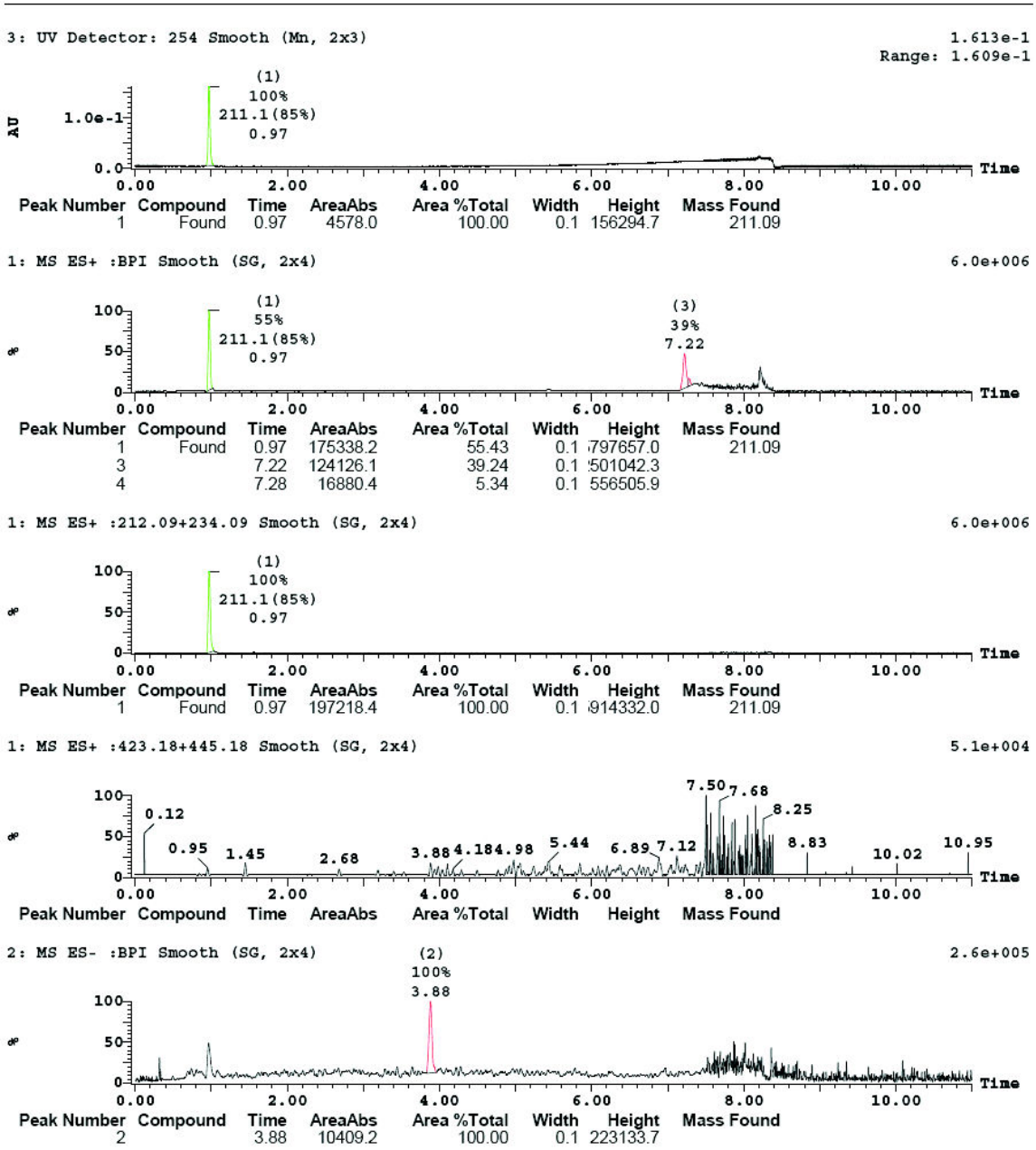


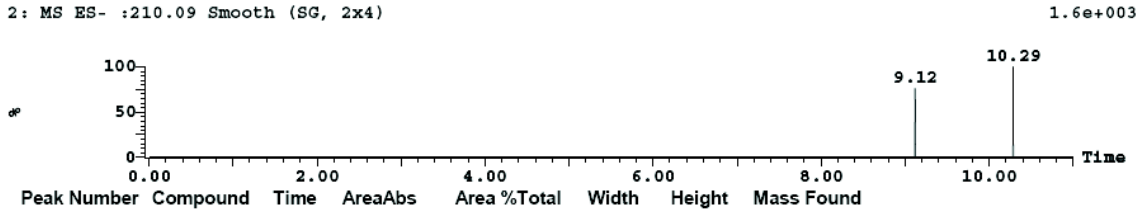
^{13}C DEPT 135-NMR of **5** (30 mg) in 0.7 mL DMSO-d_6 at 297 K (δ in ppm).

6. Appendix

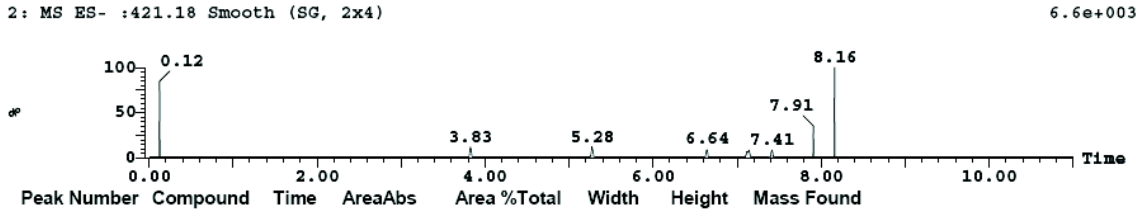
6.1. UV Purity of Compounds 4a-u and 5

HT-LC-MS Spectrum (SOP 2200) of **4a**. UV purity: 100 %

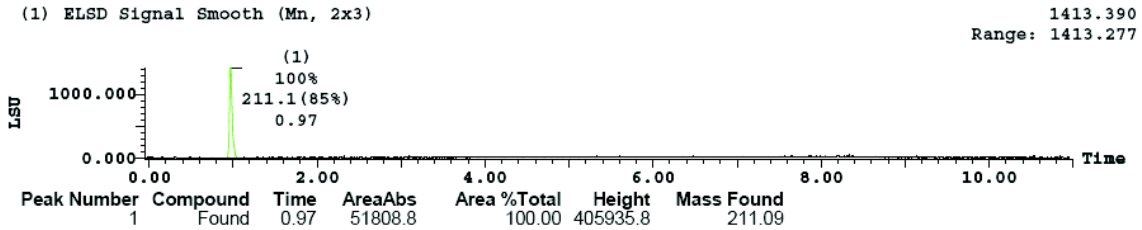




Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found



Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found



Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
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Peak ID	Compound	Time	Mass Found
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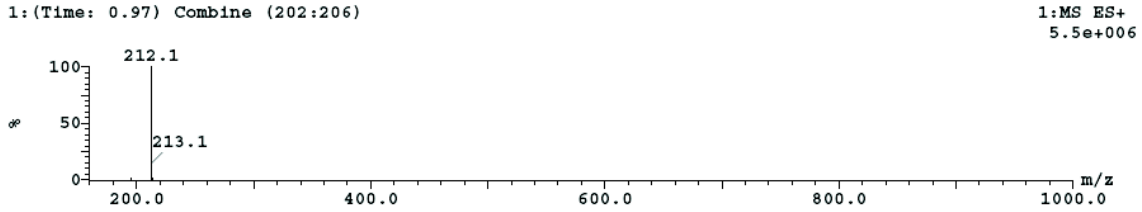

Peak ID	Compound	Time	Mass Found
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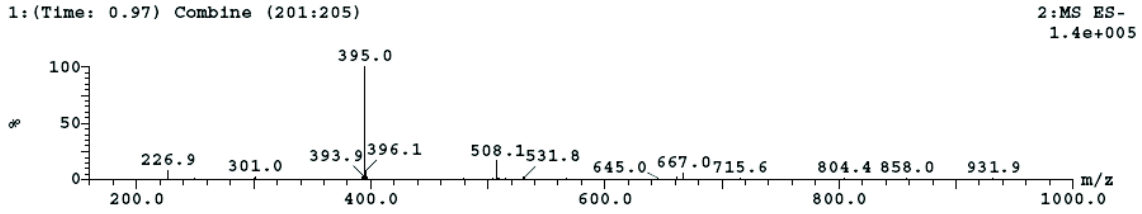

Peak ID	Compound	Time	Mass Found
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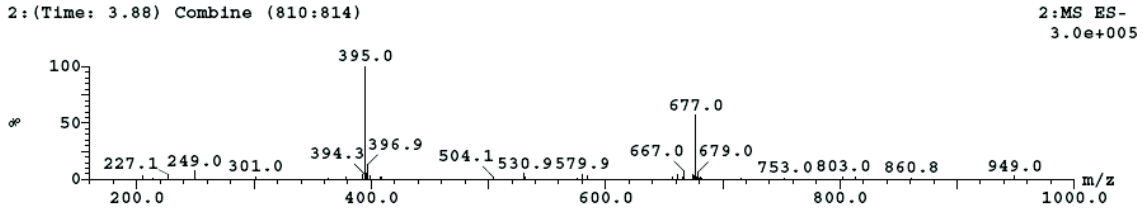

Peak ID	Compound	Time	Mass Found
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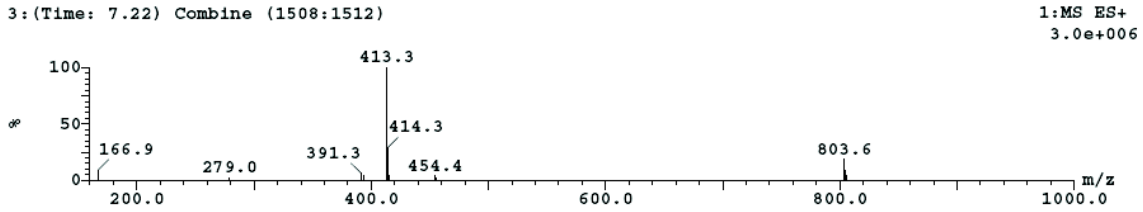

Peak ID	Compound	Time	Mass Found
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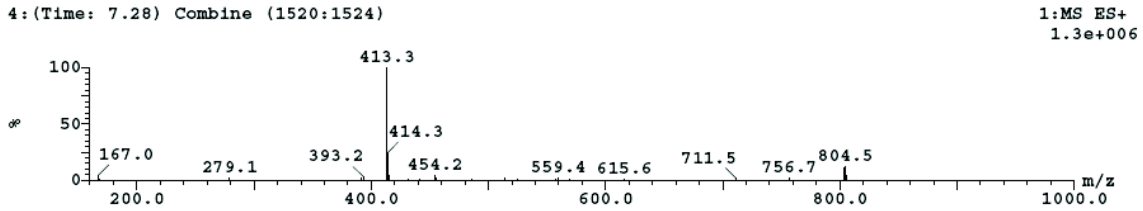
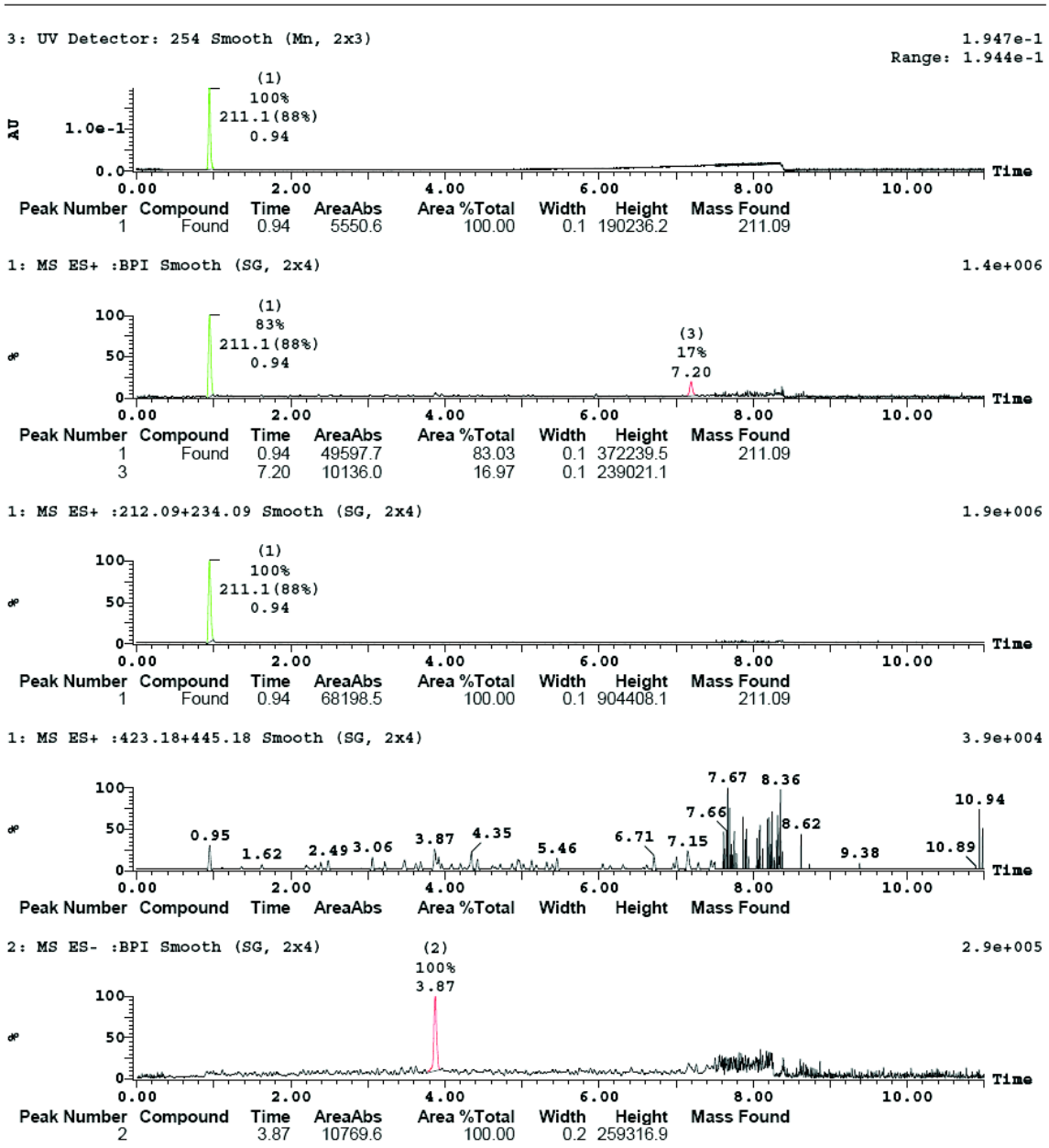
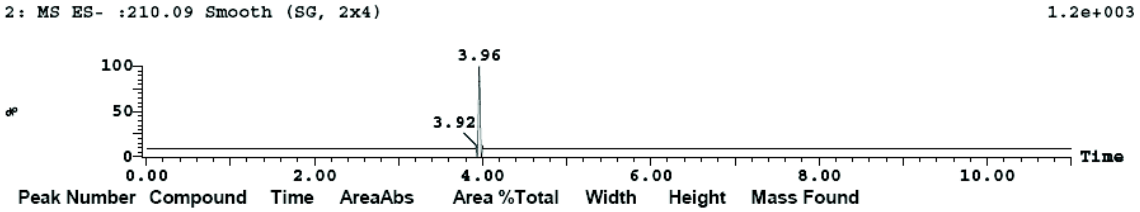
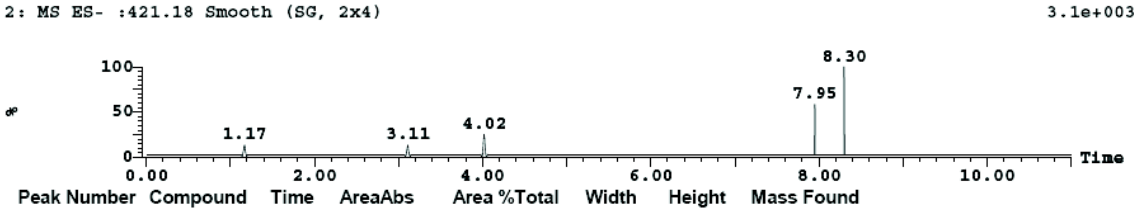


HT-LC-MS Spectrum (SOP 2200) of **4b**. UV purity: 100%

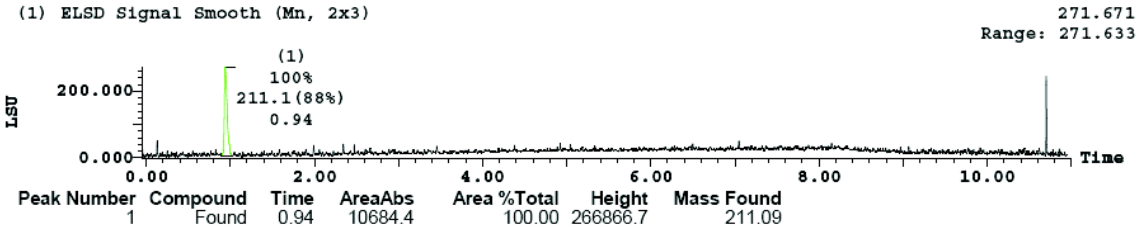




Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found



Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found



Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
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Peak ID	Compound	Time	Mass Found
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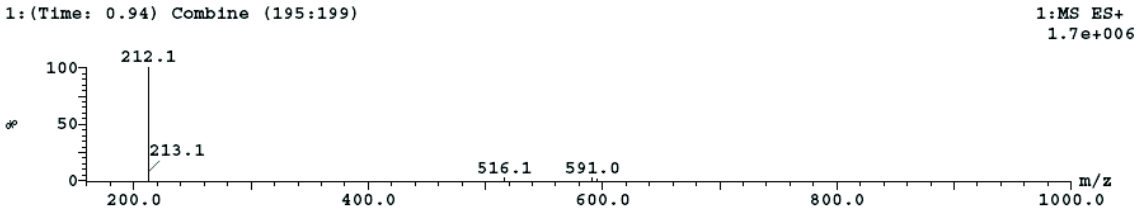
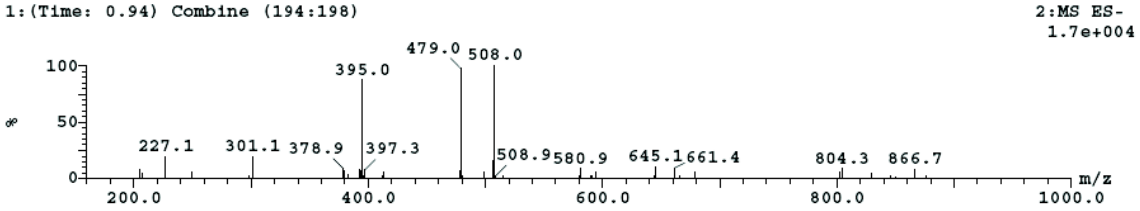


Peak ID	Compound	Time	Mass Found
1		0.94	



Peak ID	Compound	Time	Mass Found
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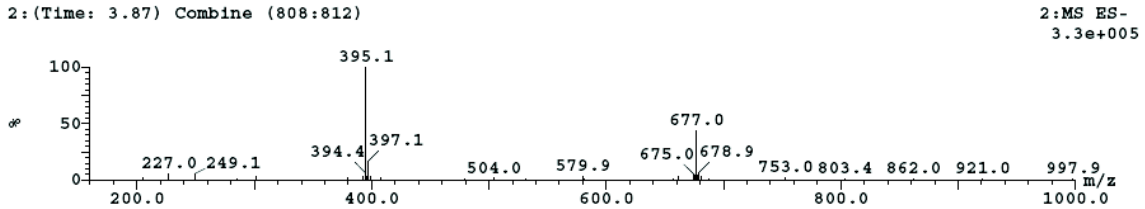

Peak ID	Compound	Time	Mass Found
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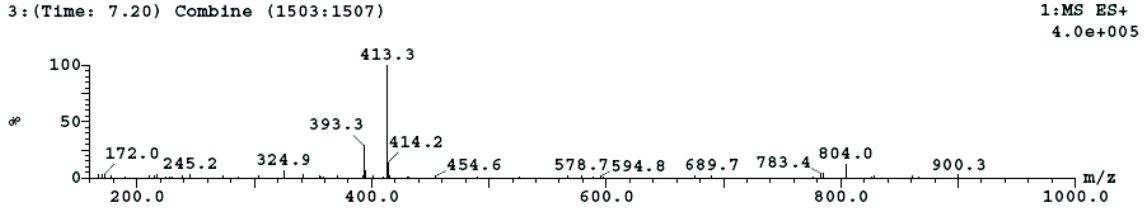
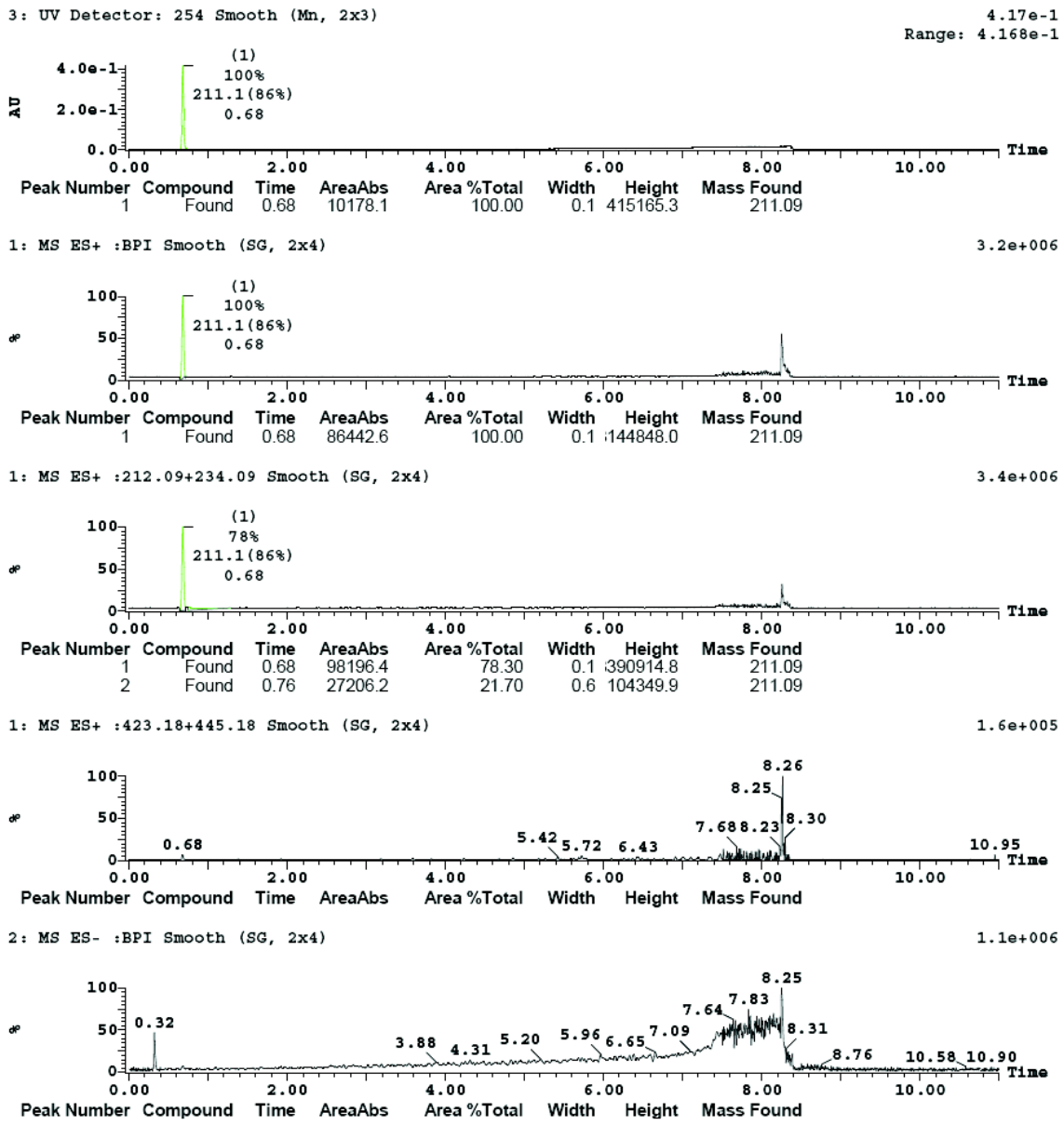
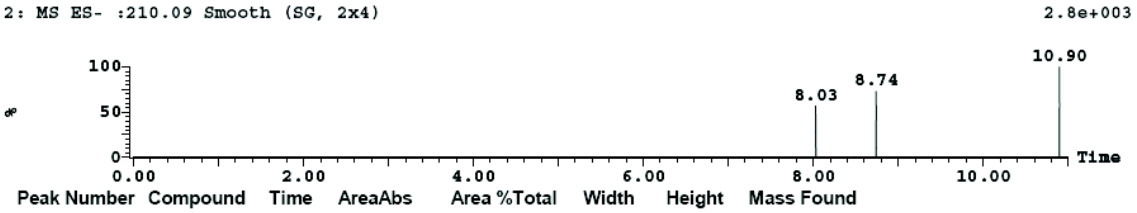
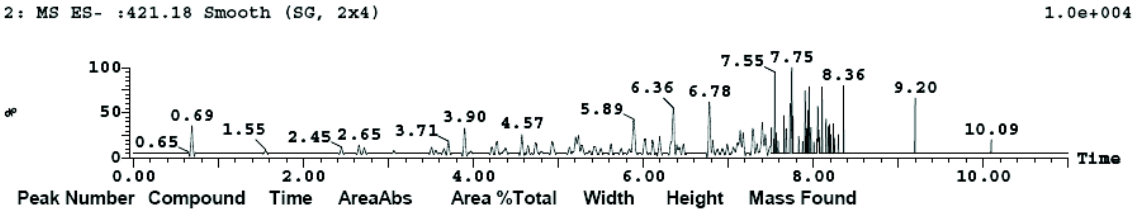


HT-LC-MS Spectrum (SOP 2200) of **4c**. UV purity: 100 %




2: MS ES- :210.09 Smooth (SG, 2x4)
2.8e+003
10.90
8.74
8.03
Time
Peak Number Compound Time AreaAbs Area %Total Width Height Mass Found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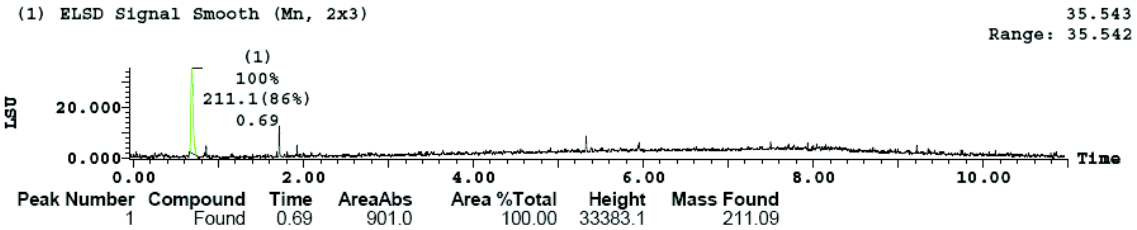
8.36
6.36 6.78
9.20
0.69
1.55
2.45 2.65
3.71
3.90
4.57
5.89
0.65
10.09
Time
Peak Number Compound Time AreaAbs Area %Total Width Height Mass Found


(1) ELSD Signal Smooth (Mn, 2x3)
35.543
Range: 35.542
(1)
100%
211.1(86%)
0.69
LSU
Time
Peak Number Compound Time AreaAbs Area %Total Height Mass Found
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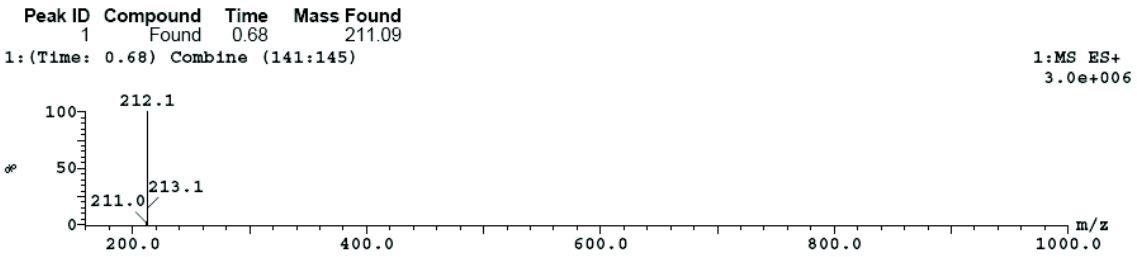
Peak ID Compound Time Mass Found
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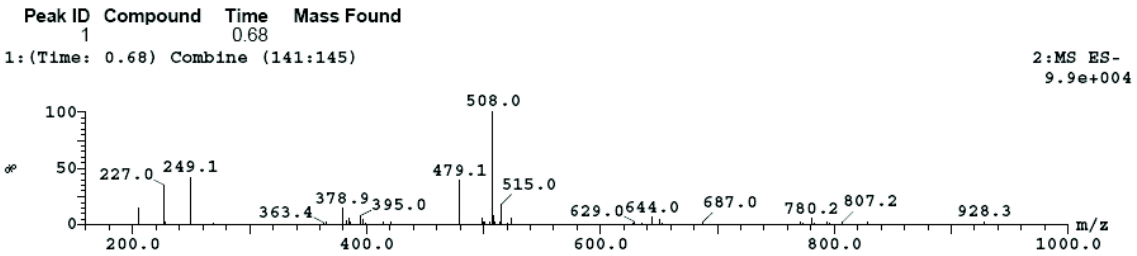
1:MS ES+
3.0e+006
212.1
213.1
211.0
m/z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227.0
249.1
479.1
515.0
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378.9
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644.0
687.0
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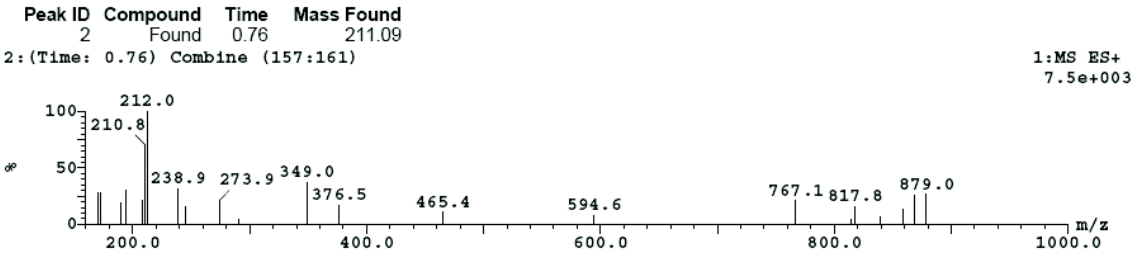
928.3
m/z


Peak ID Compound Time Mass Found
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273.9
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376.5
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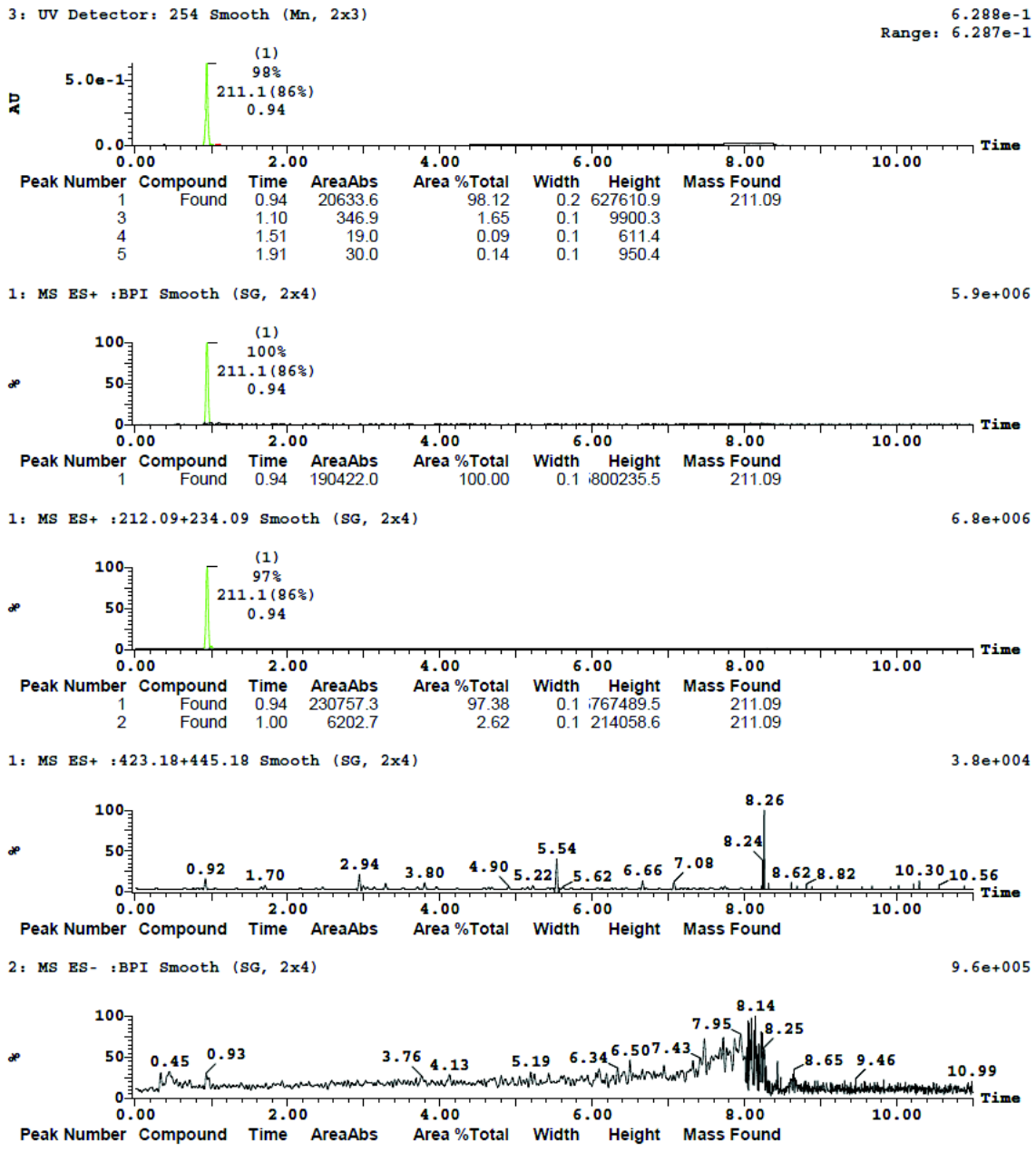
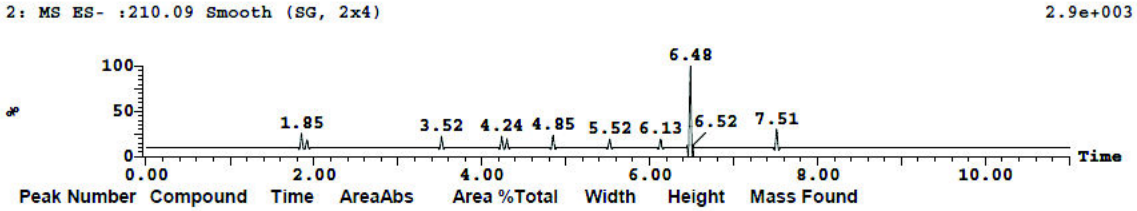
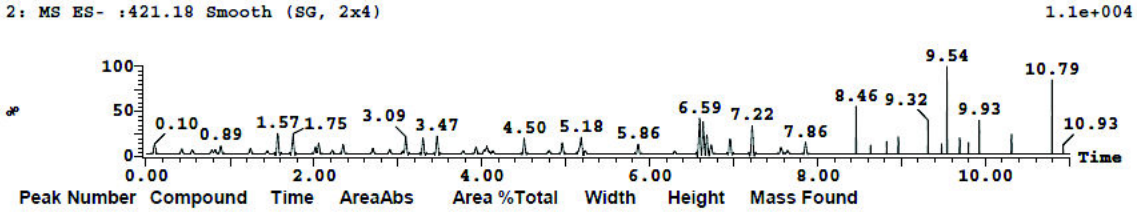
594.6
767.1
817.8
879.0
m/z

HT-LC-MS Spectrum (SOP 2200) of **4d**. UV purity: 98.1 %

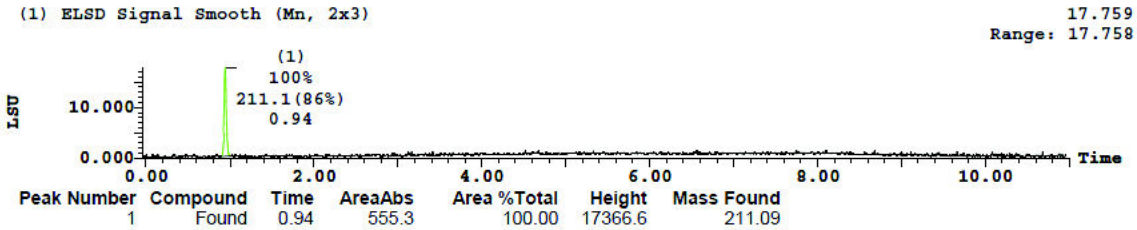




Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found



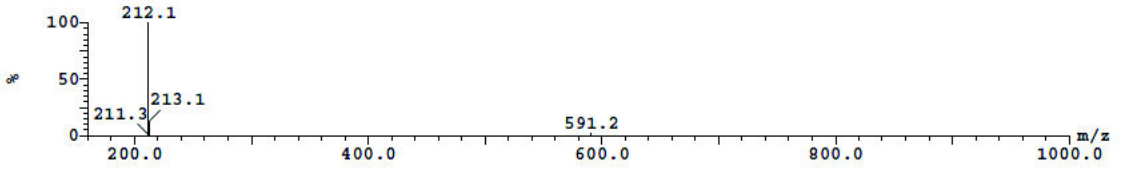
Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found



Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1	Found	0.94	555.3	100.00	17366.6	211.09

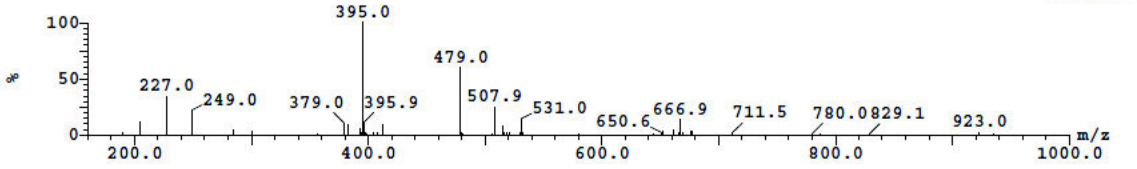
Peak ID	Compound	Time	Mass Found
1	Found	0.94	211.09

1:(Time: 0.94) Combine (195:200)



Peak ID	Compound	Time	Mass Found
1		0.94	

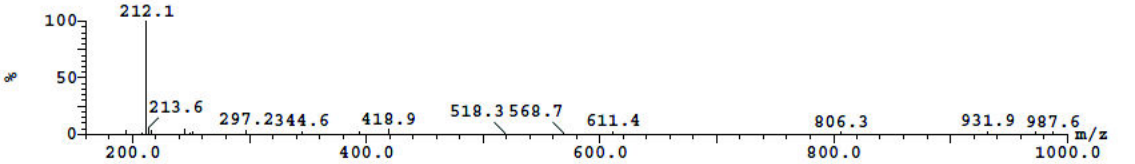
1:(Time: 0.94) Combine (195:199)



Peak ID	Compound	Time	Mass Found
2	Found	1.00	211.09

2:(Time: 1.00) Combine (207:211)

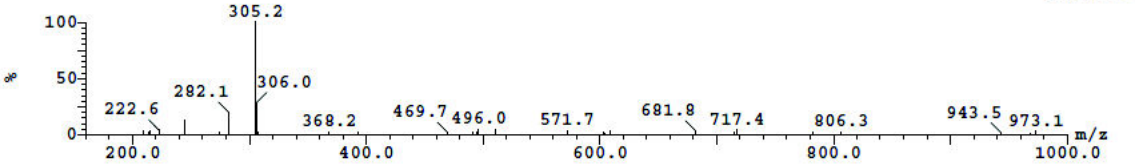
1:MS ES+
2.4e+005



Peak ID	Compound	Time	Mass Found
3		1.10	

3:(Time: 1.10) Combine (228:232)

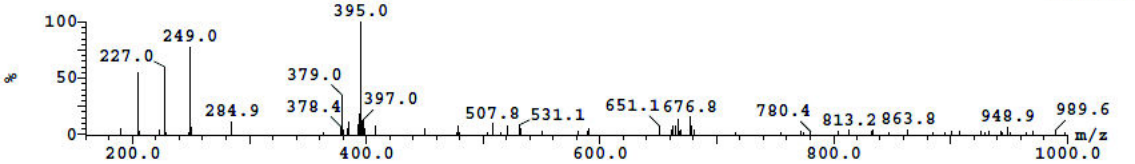
1:MS ES+
1.7e+005



Peak ID	Compound	Time	Mass Found
3		1.10	

3:(Time: 1.10) Combine (228:232)

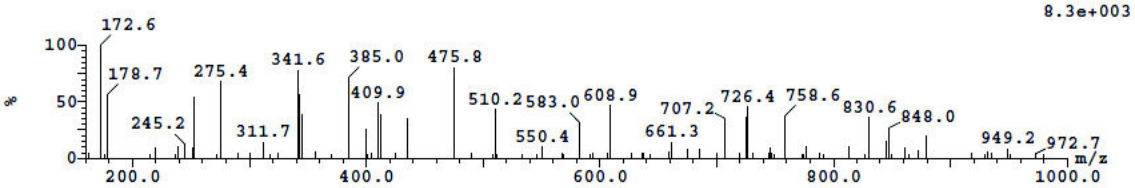
2:MS ES-
1.2e+005

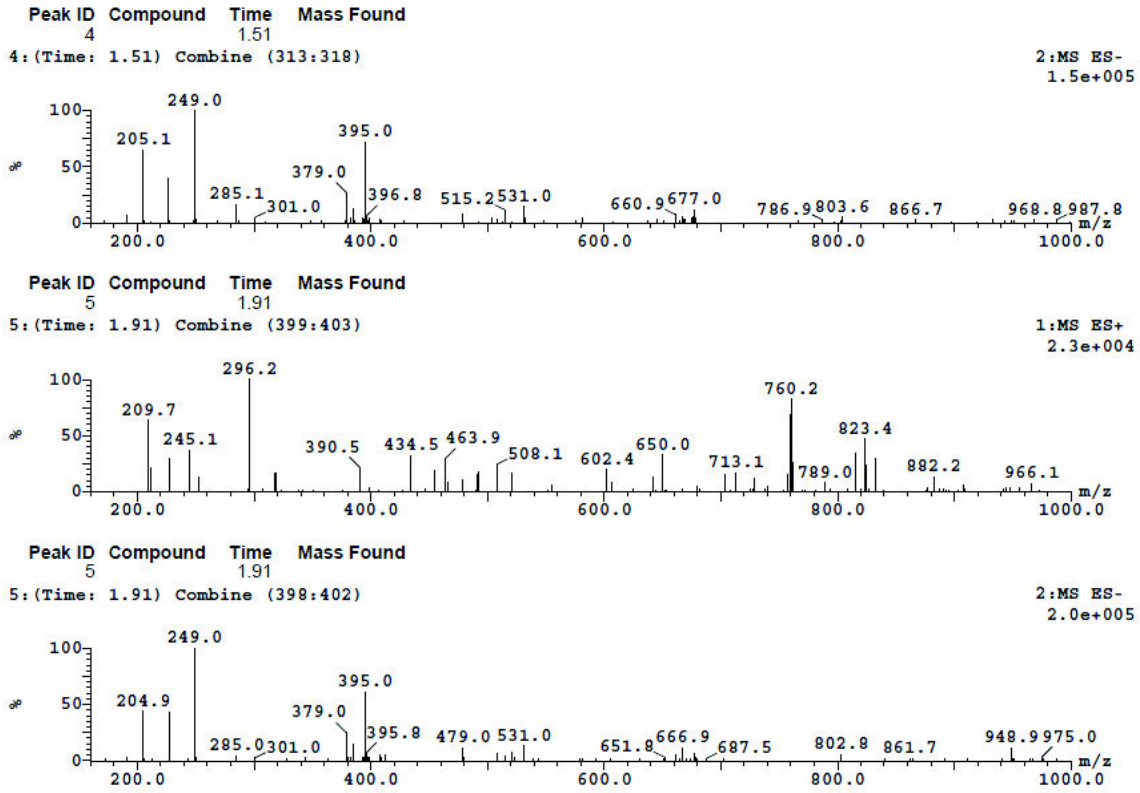


Peak ID	Compound	Time	Mass Found
4		1.51	

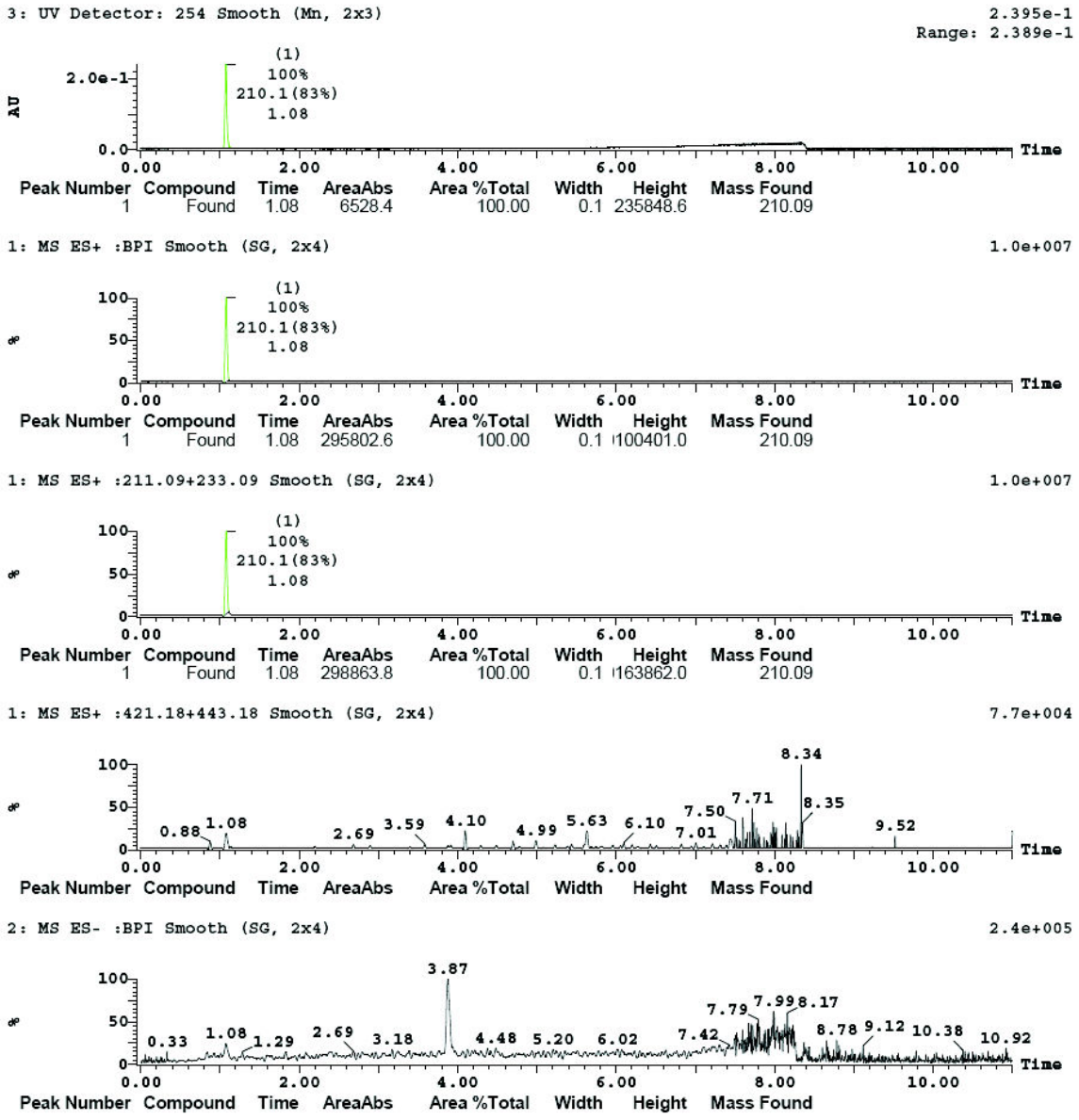
4:(Time: 1.51) Combine (314:318)

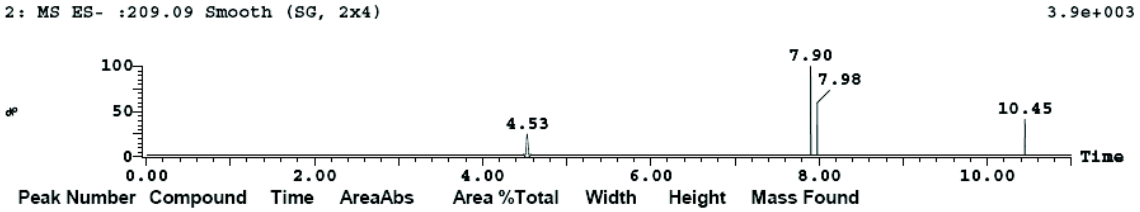
1:MS ES+
8.3e+003



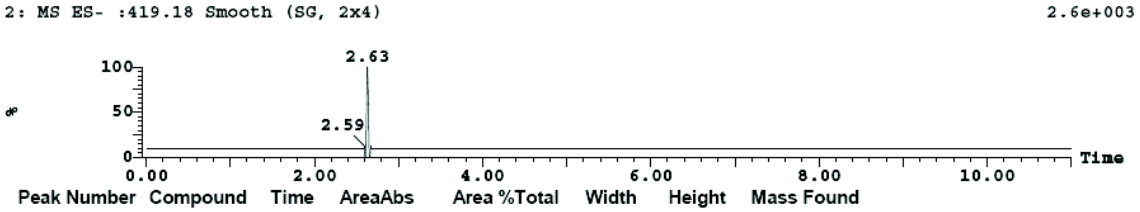

Peak ID Compound Time Mass Found
4 1.51
4:(Time: 1.51) Combine (313:318)
2:MS ES-
1.5e+005
249.0
205.1
395.0
379.0
285.1
301.0
396.8
515.2
531.0
660.9
677.0
786.9
803.6
866.7
968.8
987.8
m/z
Peak ID Compound Time Mass Found
5 1.91
5:(Time: 1.91) Combine (399:403)
1:MS ES+
2.3e+004
296.2
209.7
245.1
390.5
434.5
463.9
508.1
602.4
650.0
713.1
760.2
789.0
823.4
882.2
966.1
m/z
Peak ID Compound Time Mass Found
5 1.91
5:(Time: 1.91) Combine (398:402)
2:MS ES-
2.0e+005
249.0
204.9
395.0
379.0
285.0
301.0
395.8
479.0
531.0
651.8
666.9
687.5
802.8
861.7
948.9
975.0
m/z

HT-LC-MS Spectrum (SOP 2200) of **4e**. UV purity: 100 %

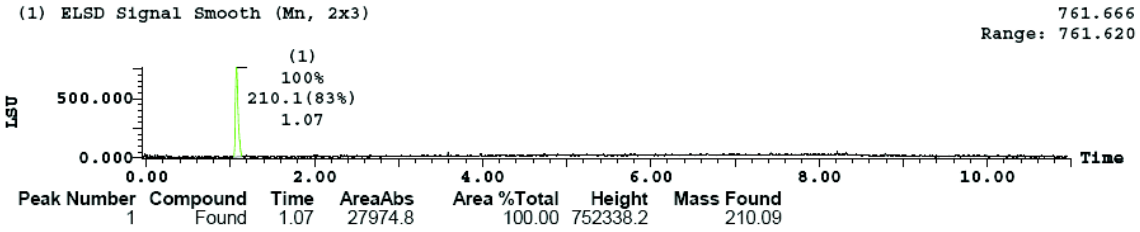




Peak Number Compound Time AreaAbs Area %Total Width Height Mass Found

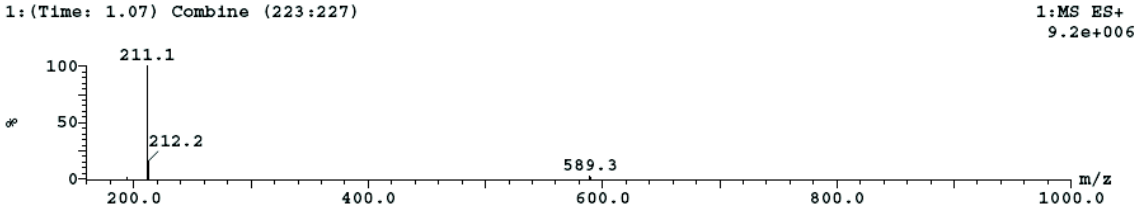


Peak Number Compound Time AreaAbs Area %Total Width Height Mass Found

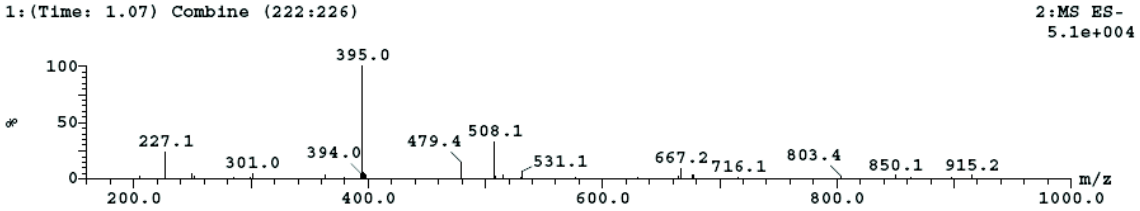


Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1	Found	1.07	27974.8	100.00	752338.2	210.09

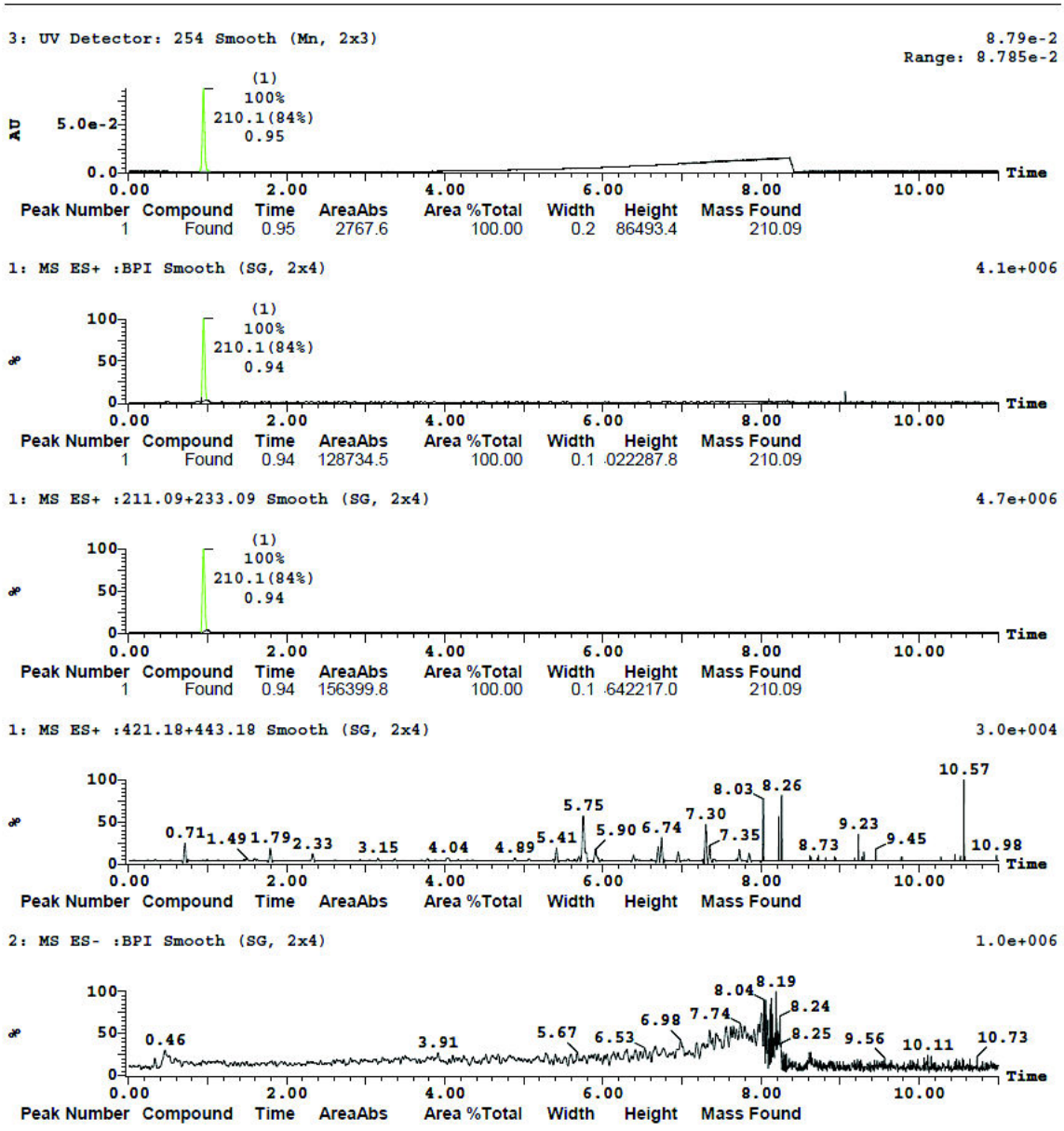
Peak ID	Compound	Time	Mass Found
1	Found	1.08	210.09

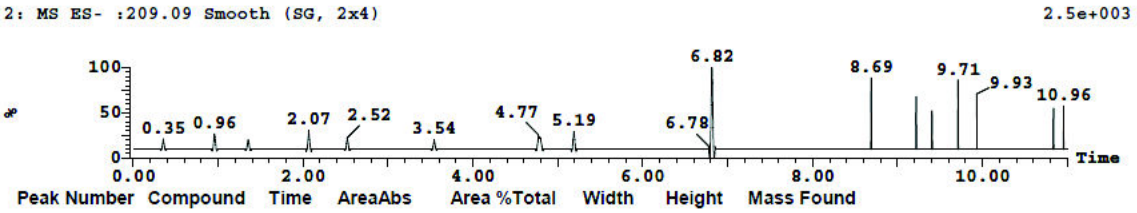


Peak ID	Compound	Time	Mass Found
1		1.08	

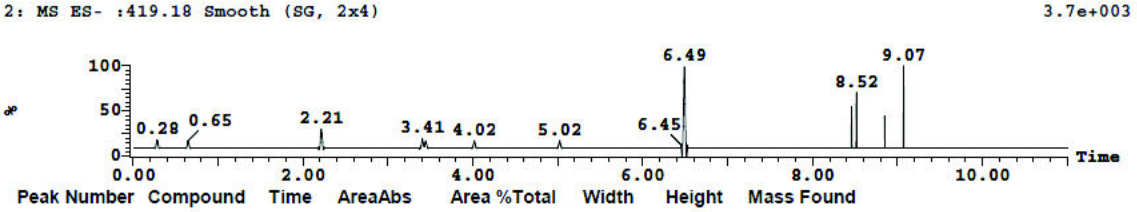


HT-LC-MS Spectrum (SOP 2200) of **4f**. UV purity: 100 %

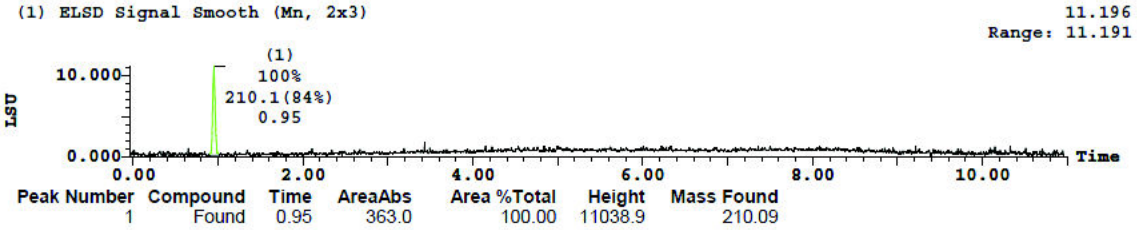




Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

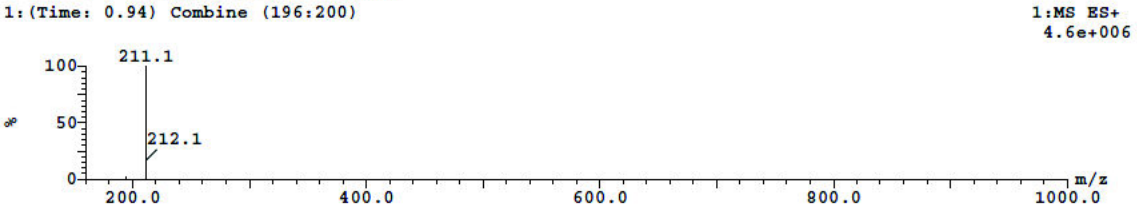


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

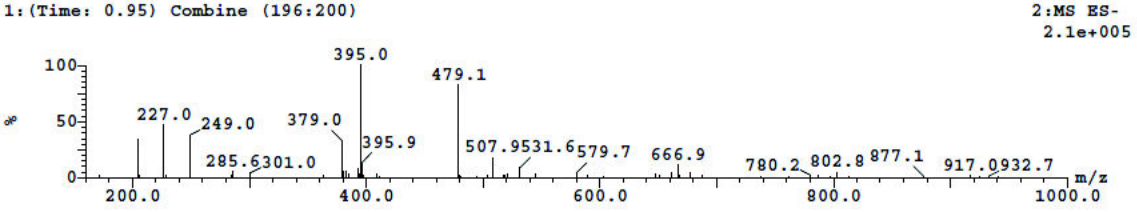


Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1	Found	0.95	363.0	100.00	11038.9	210.09

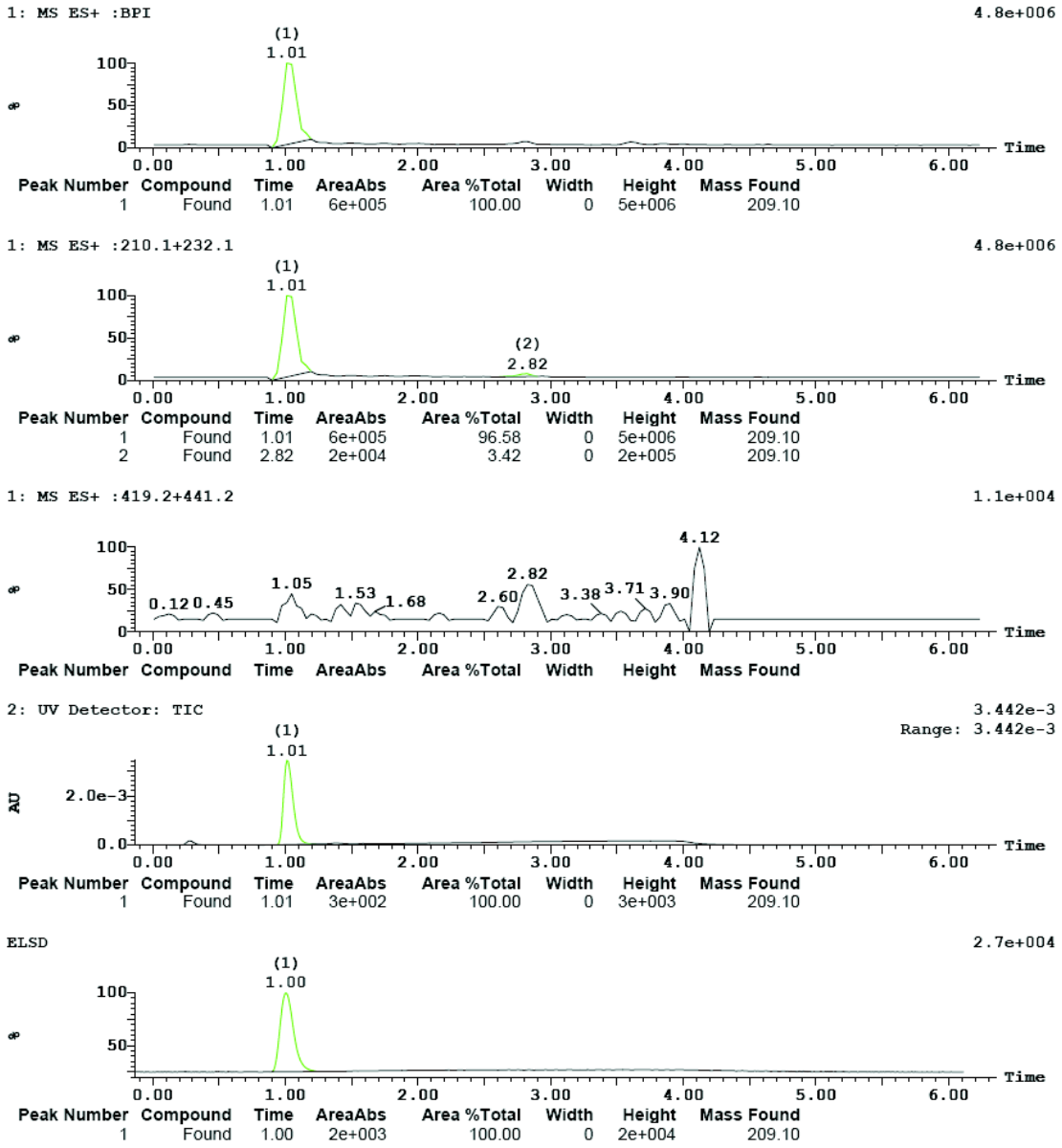
Peak ID	Compound	Time	Mass Found
1	Found	0.94	210.09



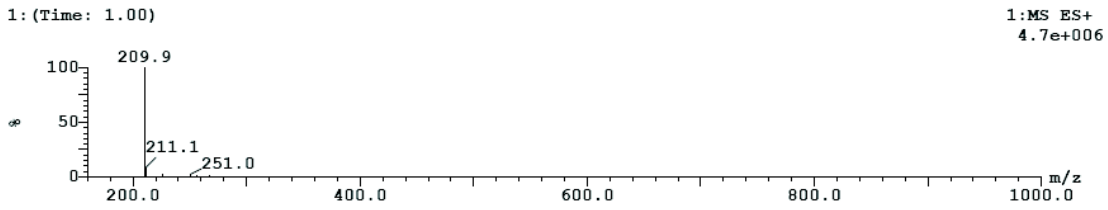
Peak ID	Compound	Time	Mass Found
1		0.94	



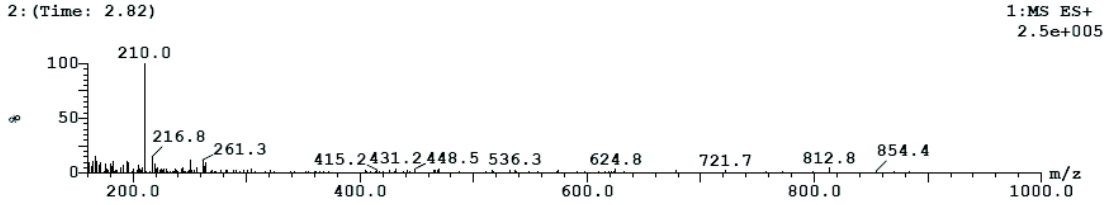
HT-LC-MS Spectrum (SOP 2222) of **4g**. UV purity: 100 %



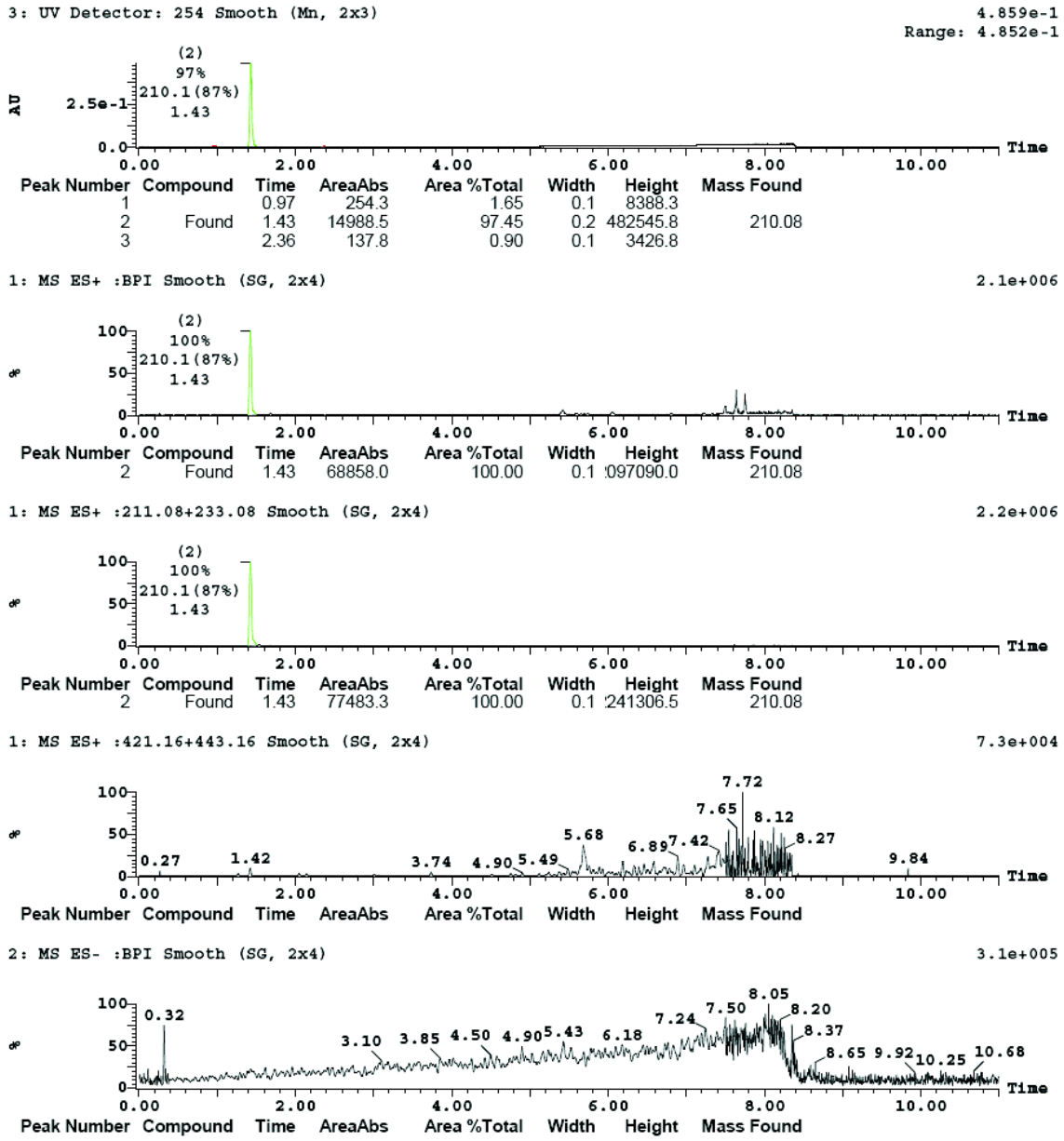
Peak ID	Compound	Time	Mass Found
1	Found	1.01	209.10

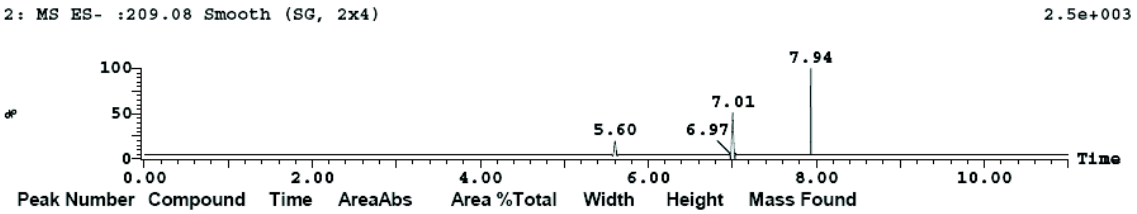


Peak ID	Compound	Time	Mass Found
2	Found	2.82	209.10

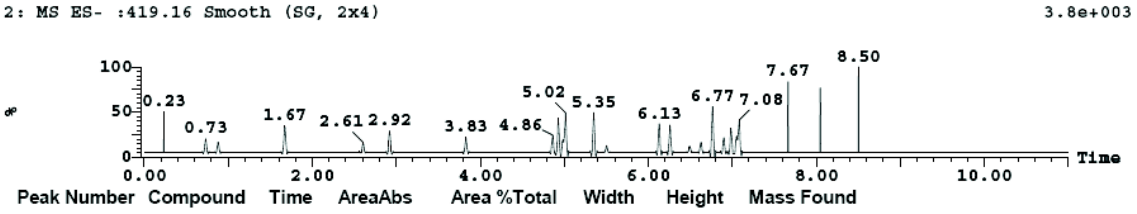


HT-LC-MS Spectrum (SOP 2200) of **4h**. UV purity: 97.5 %

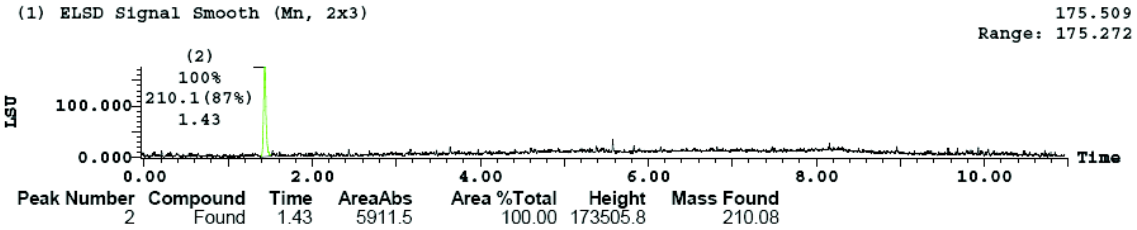




Peak Number Compound Time AreaAbs Area %Total Width Height Mass Found

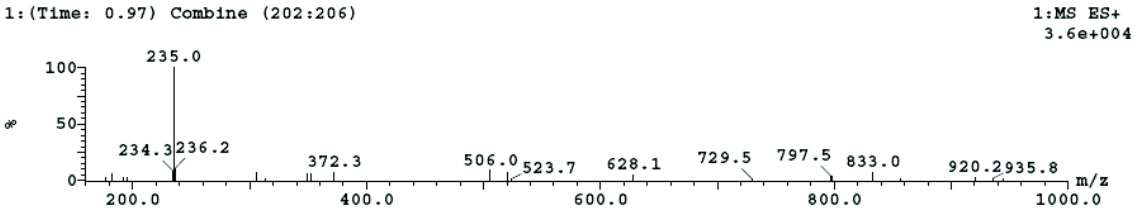


Peak Number Compound Time AreaAbs Area %Total Width Height Mass Found

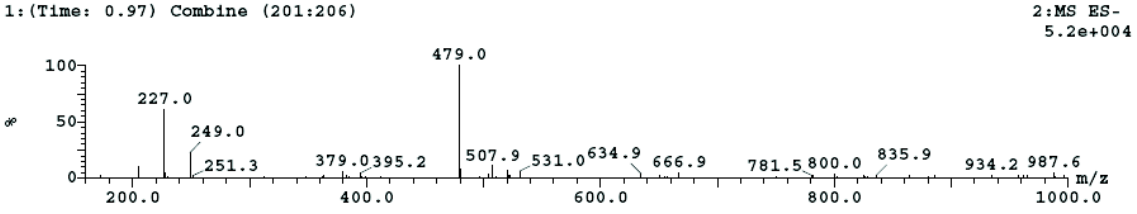


Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
2	Found	1.43	5911.5	100.00	173505.8	210.08

Peak ID	Compound	Time	Mass Found
1		0.97	



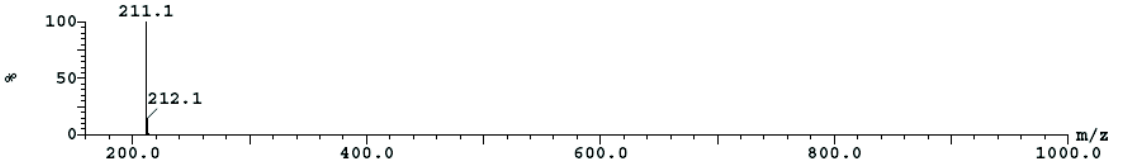
Peak ID	Compound	Time	Mass Found
1		0.97	



Peak ID	Compound	Time	Mass Found
2	Found	1.43	210.08

2:(Time: 1.43) Combine (297:301)

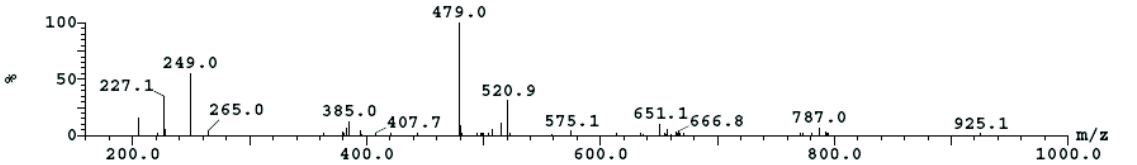
1:MS ES+
2.1e+006



Peak ID	Compound	Time	Mass Found
2		1.43	

2:(Time: 1.43) Combine (298:302)

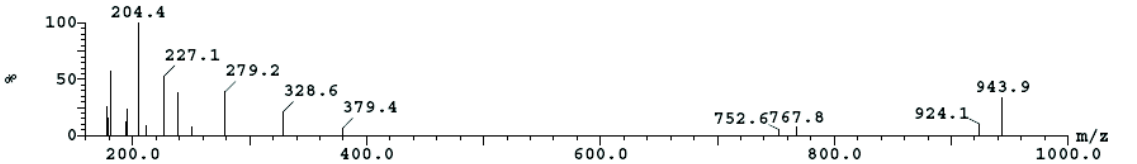
2:MS ES-
8.7e+004



Peak ID	Compound	Time	Mass Found
3		2.36	

3:(Time: 2.36) Combine (493:497)

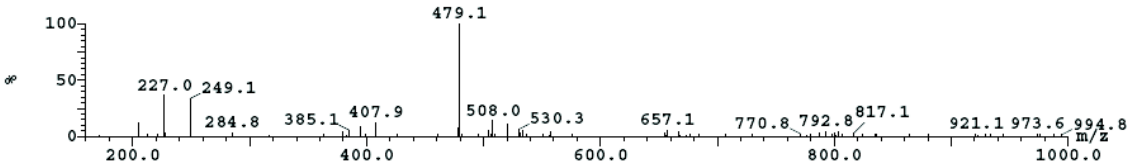
1:MS ES+
4.1e+003



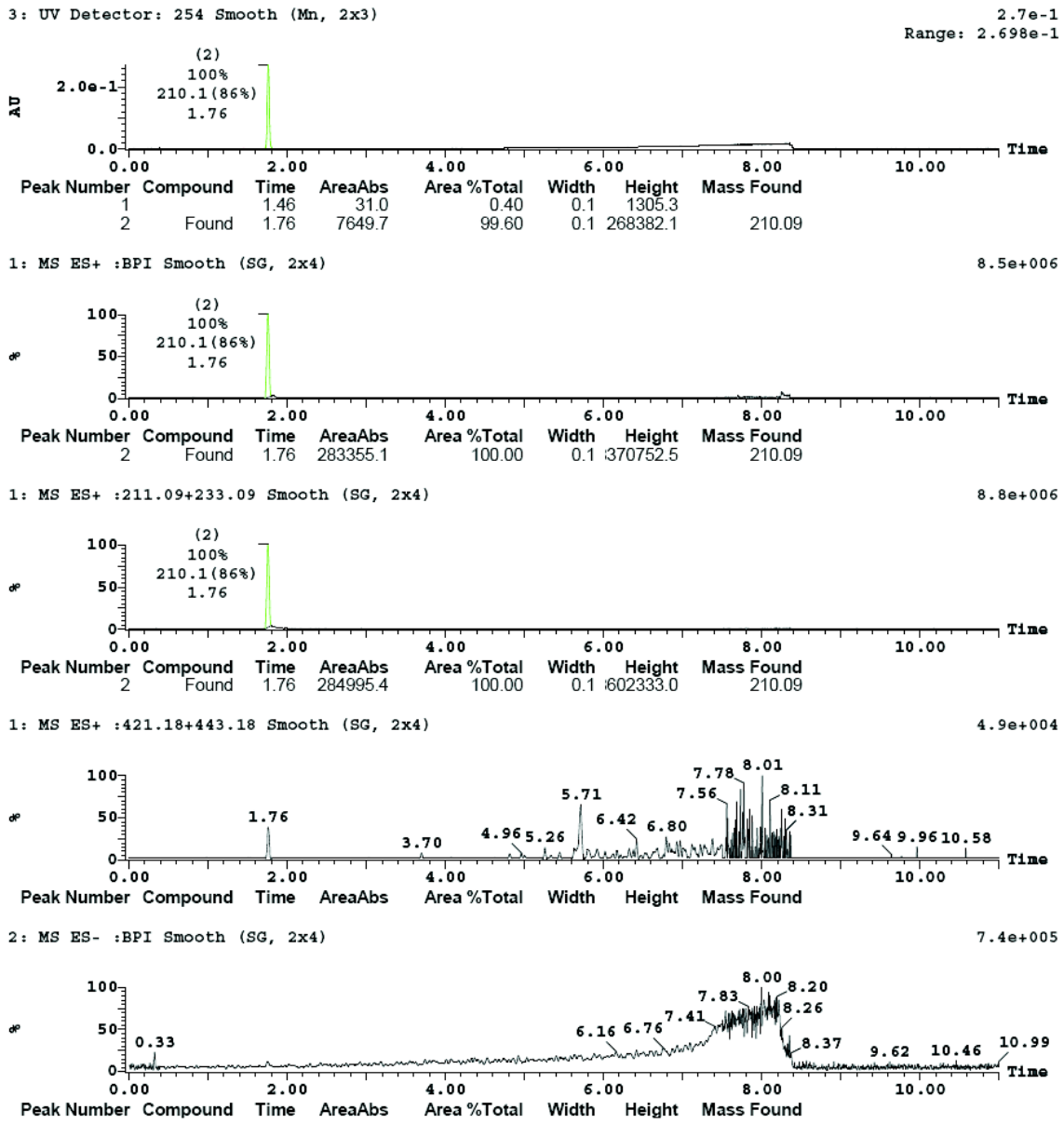
Peak ID	Compound	Time	Mass Found
3		2.36	

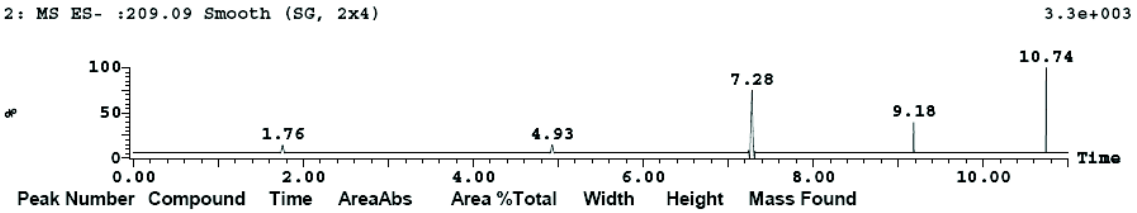
3:(Time: 2.36) Combine (492:497)

2:MS ES-
6.8e+004

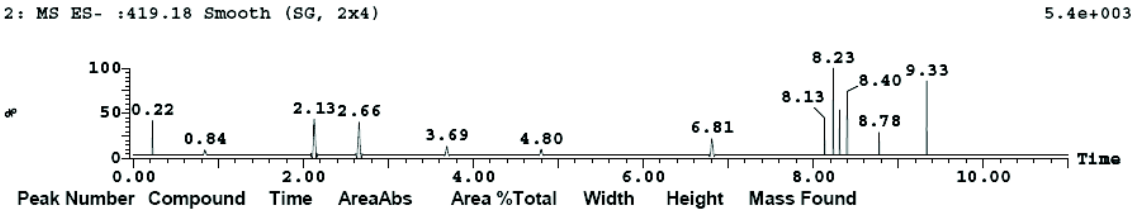


HT-LC-MS Spectrum (SOP 2200) of **4i**. UV purity: 99.6 %

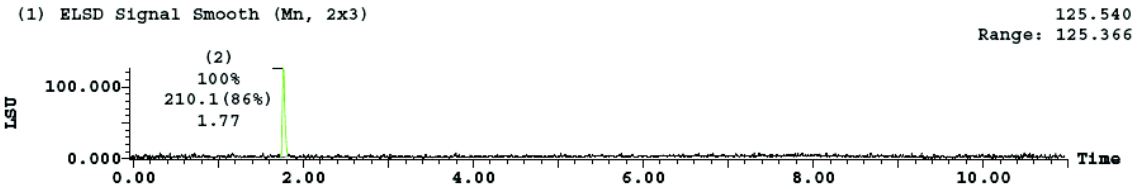




Peak Number Compound Time AreaAbs Area %Total Width Height Mass Found

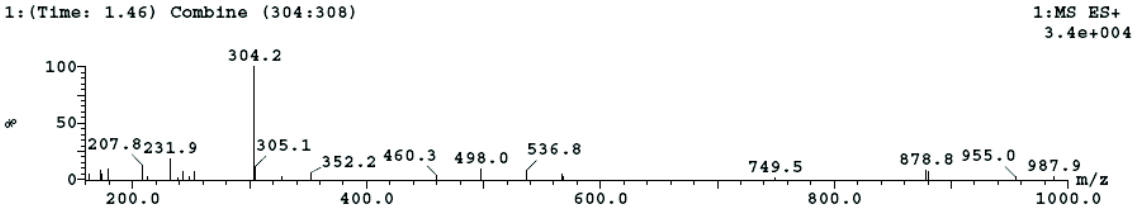


Peak Number Compound Time AreaAbs Area %Total Width Height Mass Found

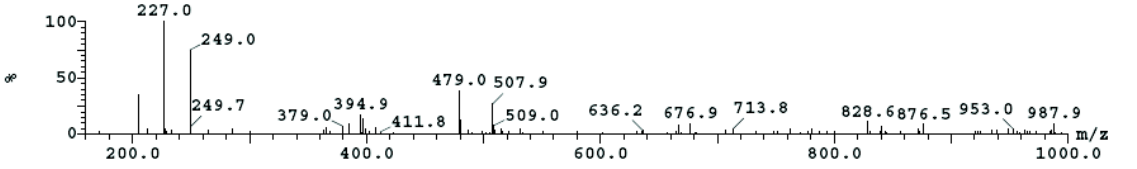


Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
2	Found	1.77	4075.8	100.00	123023.5	210.09

Peak ID	Compound	Time	Mass Found
1		1.46	



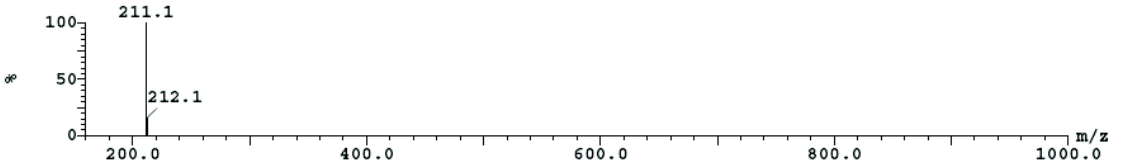
Peak ID	Compound	Time	Mass Found
1		1.46	



Peak ID	Compound	Time	Mass Found
2	Found	1.76	210.09

2:(Time: 1.76) Combine (366:370)

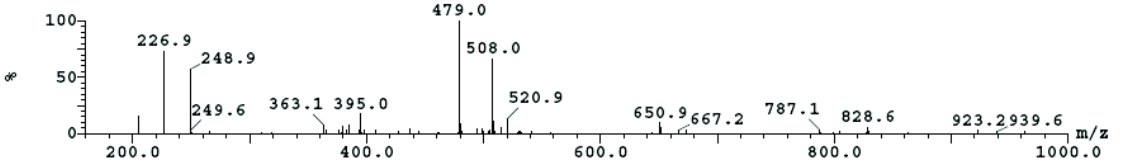
1:MS ES+
8.3e+006



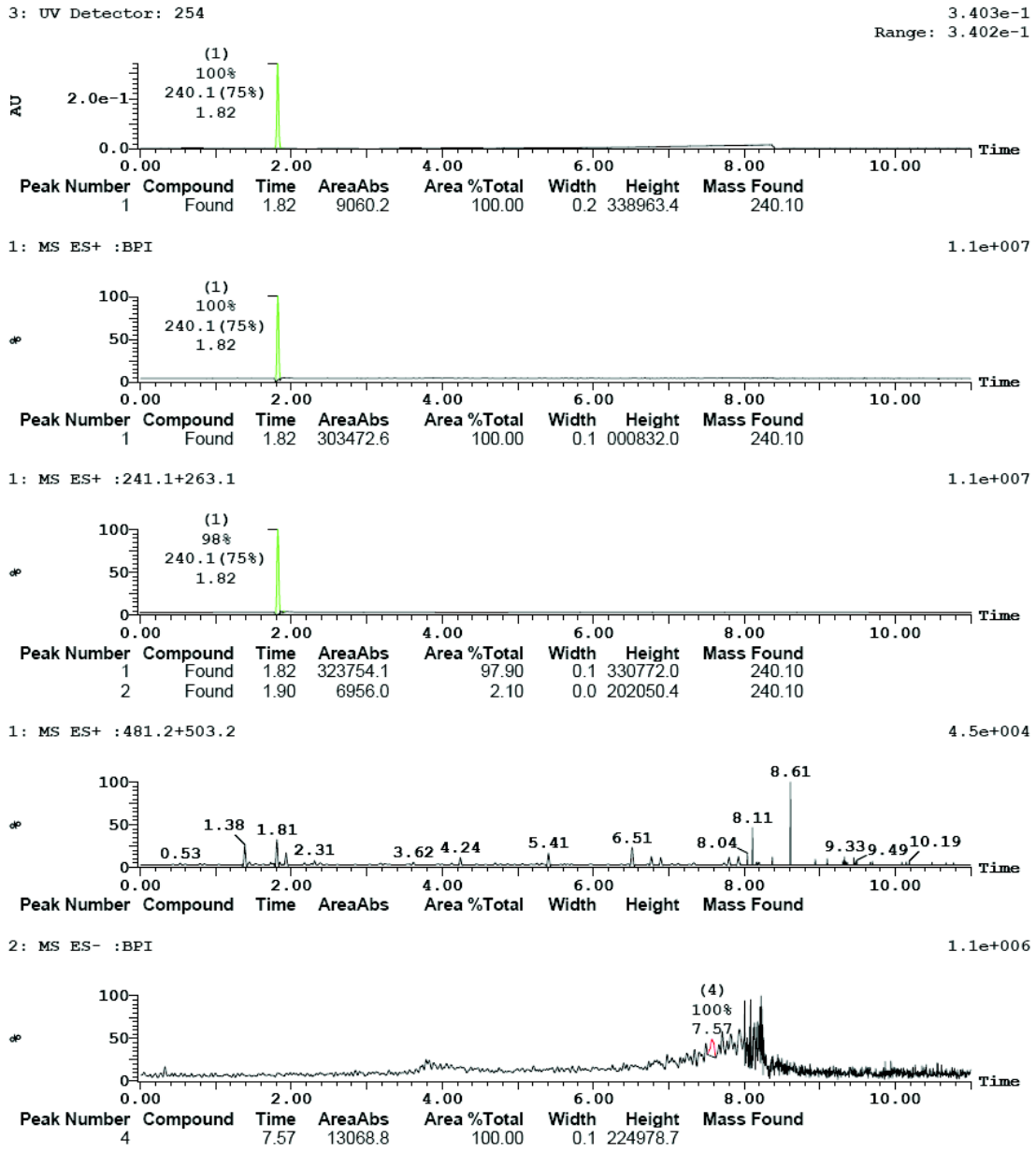
Peak ID	Compound	Time	Mass Found
2		1.76	

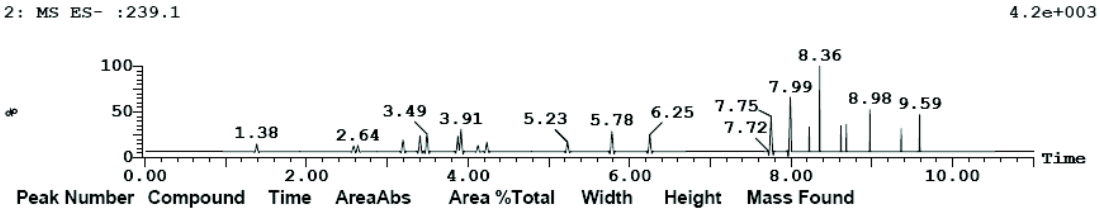
2:(Time: 1.77) Combine (367:371)

2:MS ES-
1.0e+005

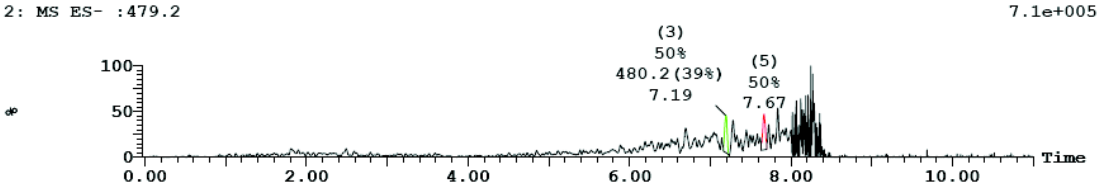


HT-LC-MS Spectrum (SOP 2200) of **4j**. UV purity: 100 %

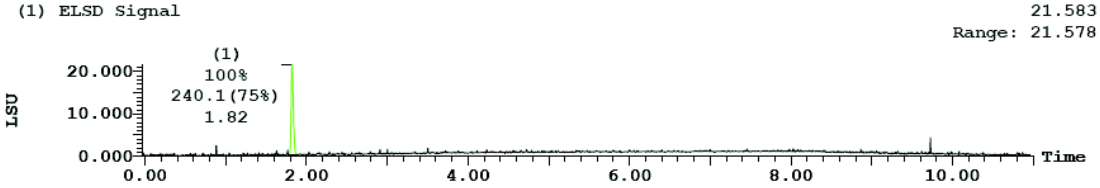




Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

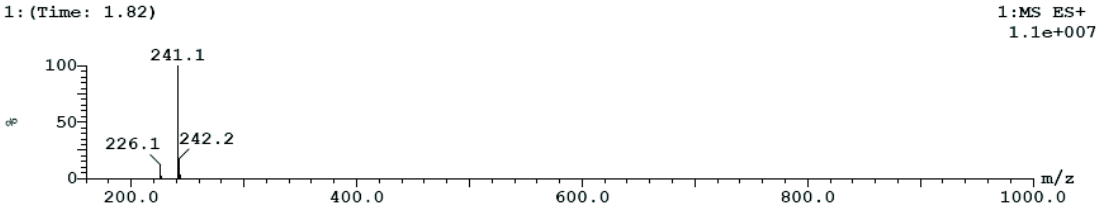


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
3	Found	7.19	10652.8	49.77	0.1	287871.5	480.20
5		7.67	10751.6	50.23	0.1	280238.9	

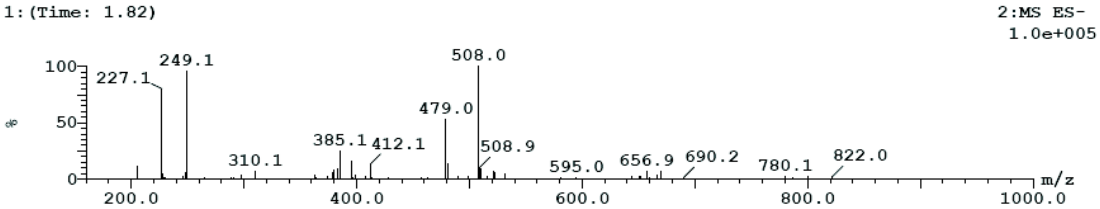


Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1	Found	1.82	671.5	100.00	21220.9	240.10

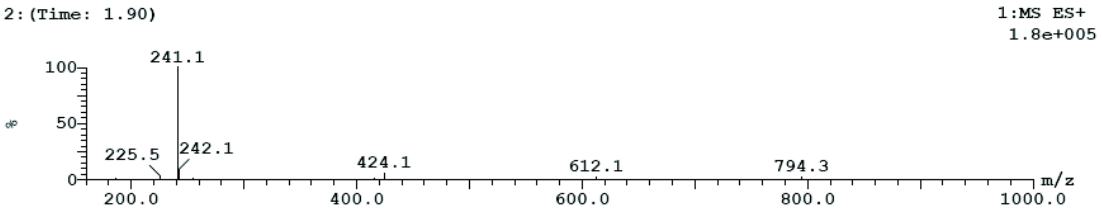
Peak ID	Compound	Time	Mass Found
1	Found	1.82	240.10



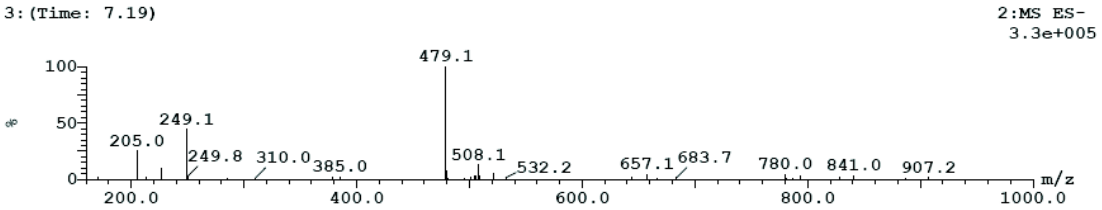
Peak ID	Compound	Time	Mass Found
1		1.82	



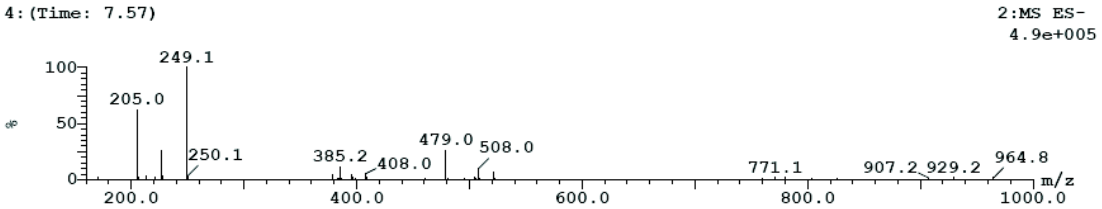
Peak ID	Compound	Time	Mass Found
2	Found	1.90	240.10



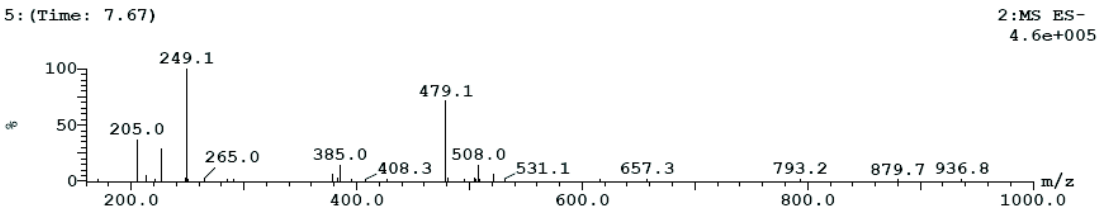
Peak ID	Compound	Time	Mass Found
3	Found	7.19	480.20



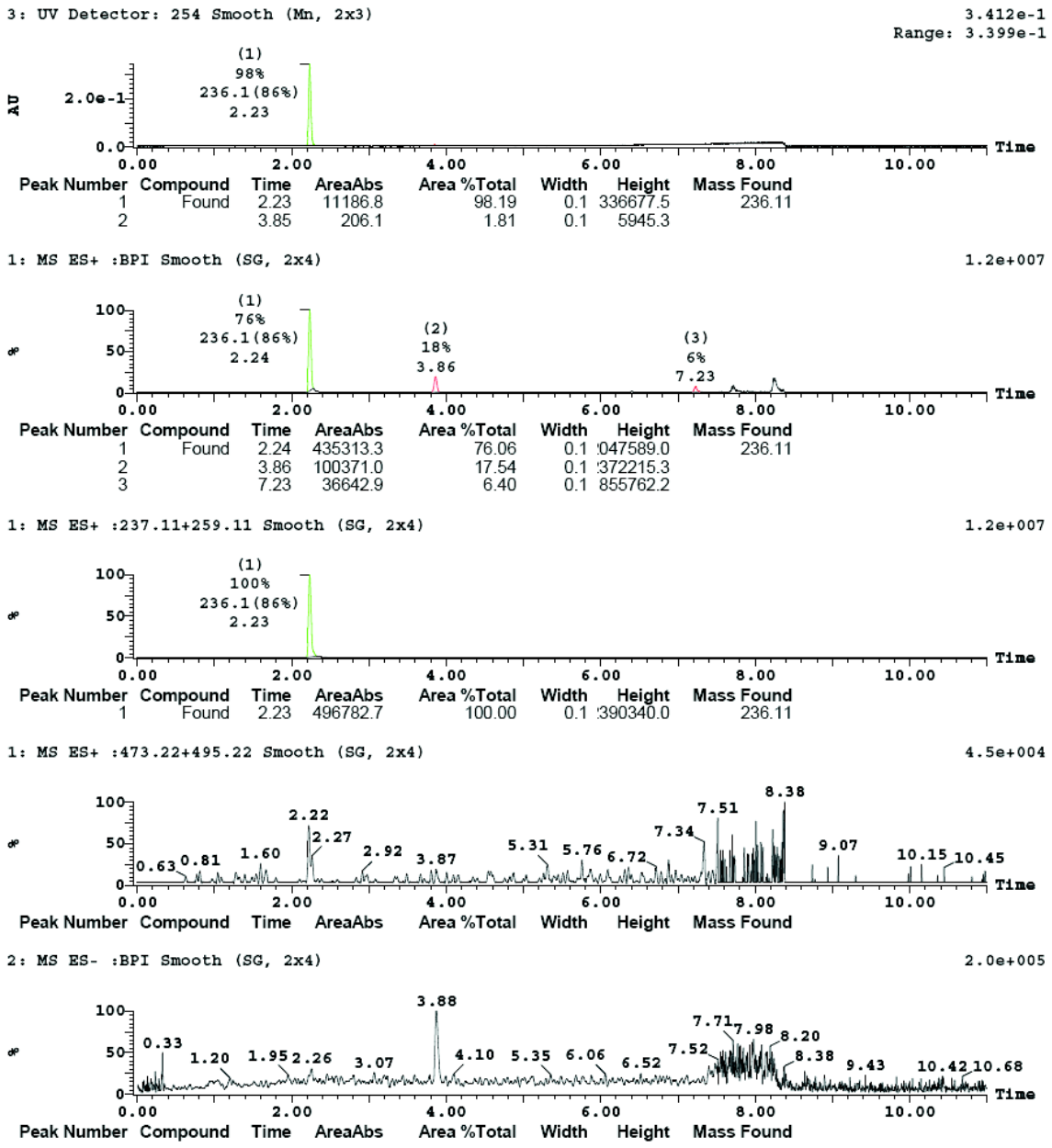
Peak ID	Compound	Time	Mass Found
4		7.57	

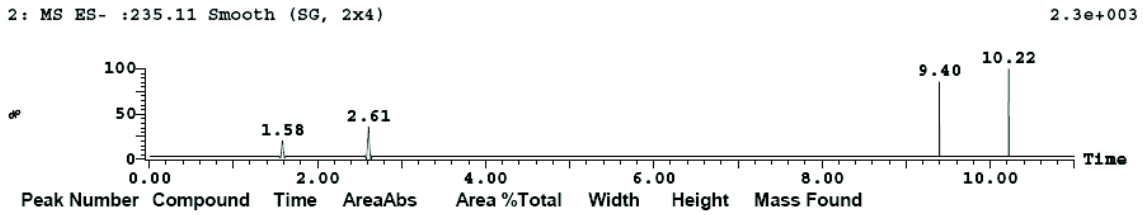


Peak ID	Compound	Time	Mass Found
5		7.67	

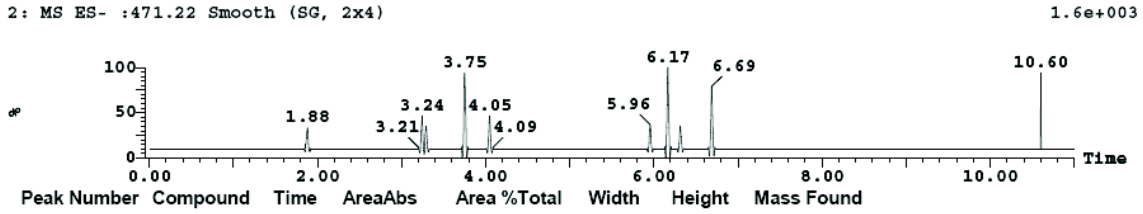


HT-LC-MS Spectrum (SOP 2200) of **4k**. UV purity: 98.2 %

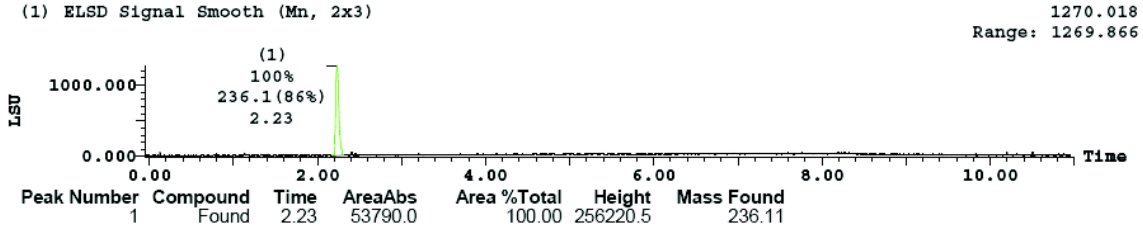




Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

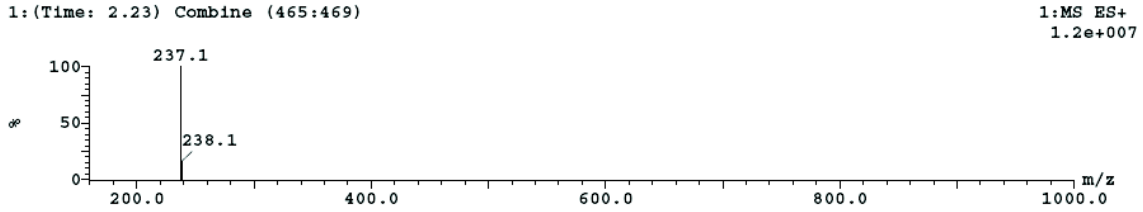


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

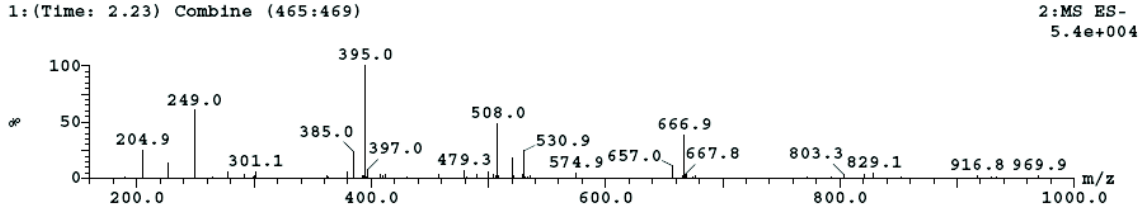


Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1	Found	2.23	53790.0	100.00	256220.5	236.11

Peak ID	Compound	Time	Mass Found
1	Found	2.24	236.11



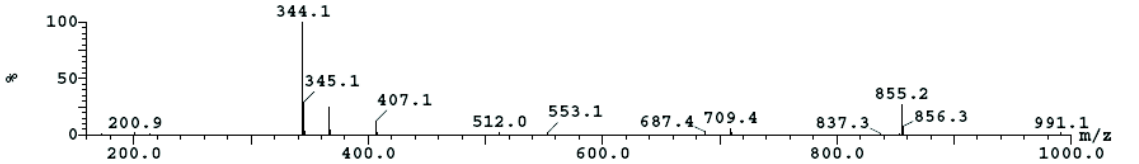
Peak ID	Compound	Time	Mass Found
1		2.24	



Peak ID	Compound	Time	Mass Found
2		3.86	

2:(Time: 3.86) Combine (806:810)

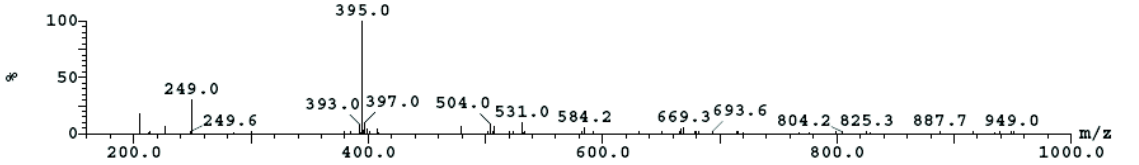
1:MS ES+
2.5e+006



Peak ID	Compound	Time	Mass Found
2		3.86	

2:(Time: 3.85) Combine (803:807)

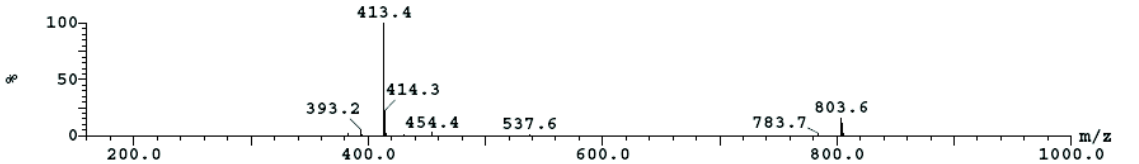
2:MS ES-
1.1e+005



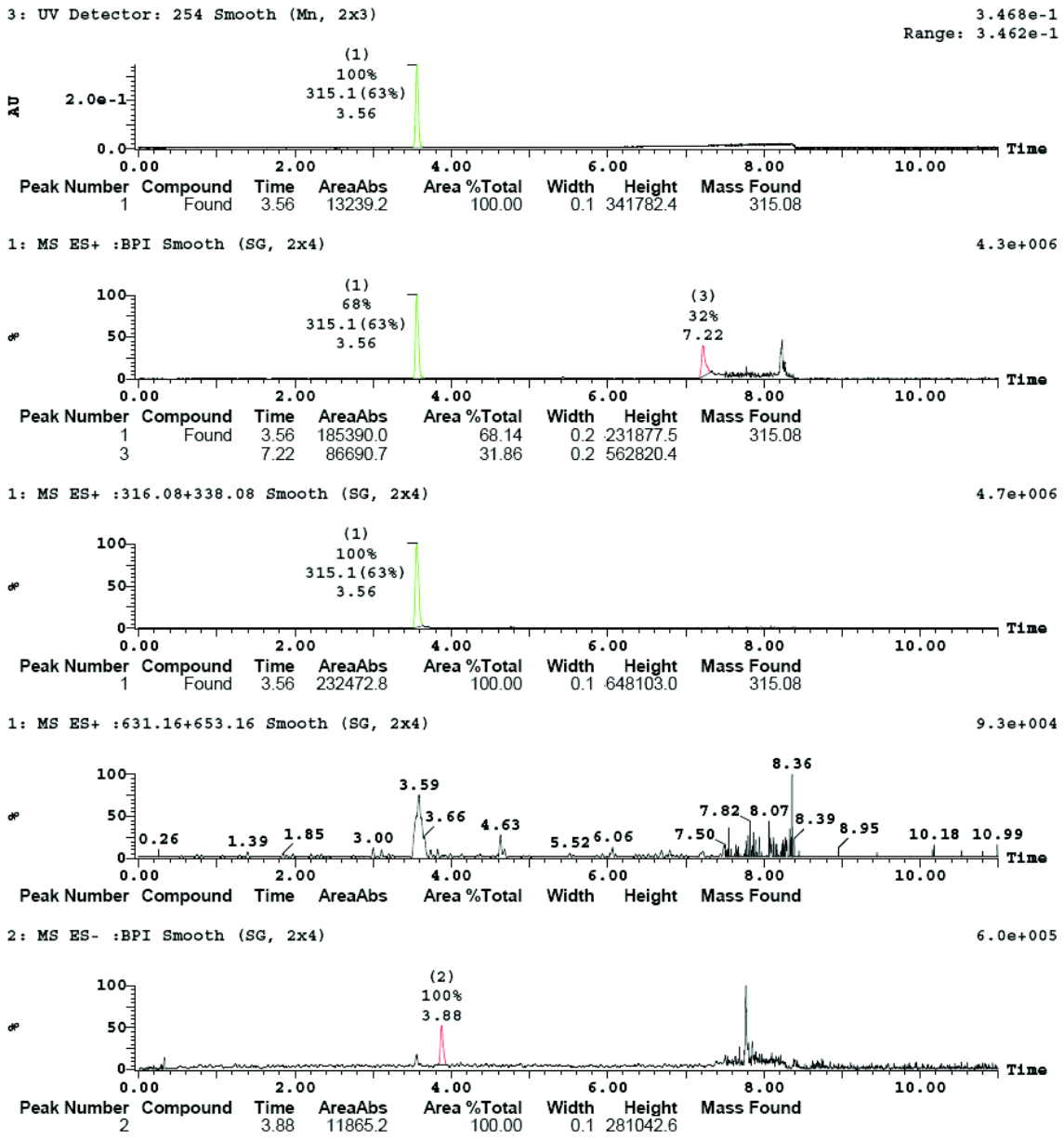
Peak ID	Compound	Time	Mass Found
3		7.23	

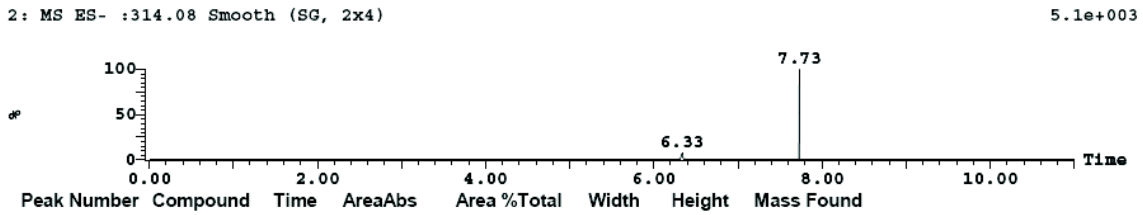
3:(Time: 7.23) Combine (1509:1513)

1:MS ES+
1.3e+006

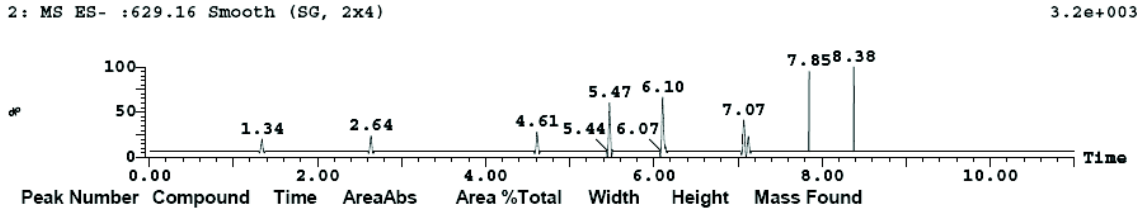


HT-LC-MS Spectrum (SOP 2200) of **4l**. UV purity: 100 %

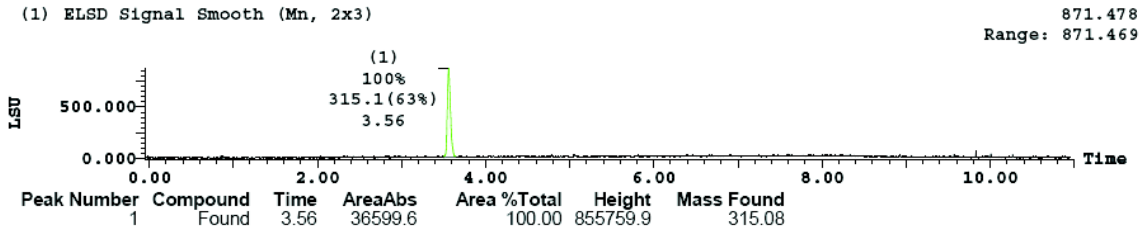




Peak Number | Compound | Time | AreaAbs | Area %Total | Width | Height | Mass Found

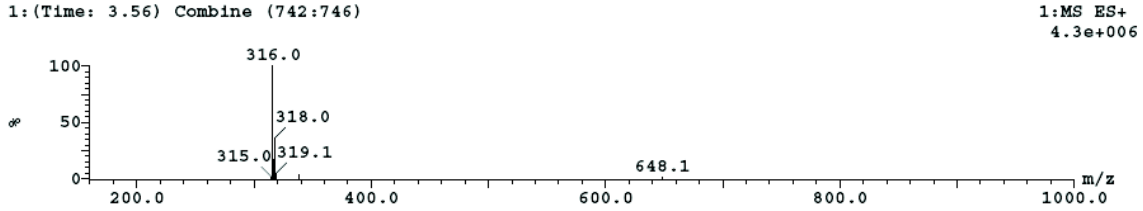


Peak Number | Compound | Time | AreaAbs | Area %Total | Width | Height | Mass Found

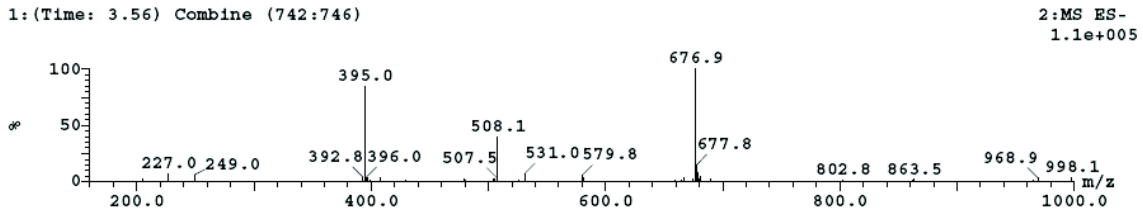


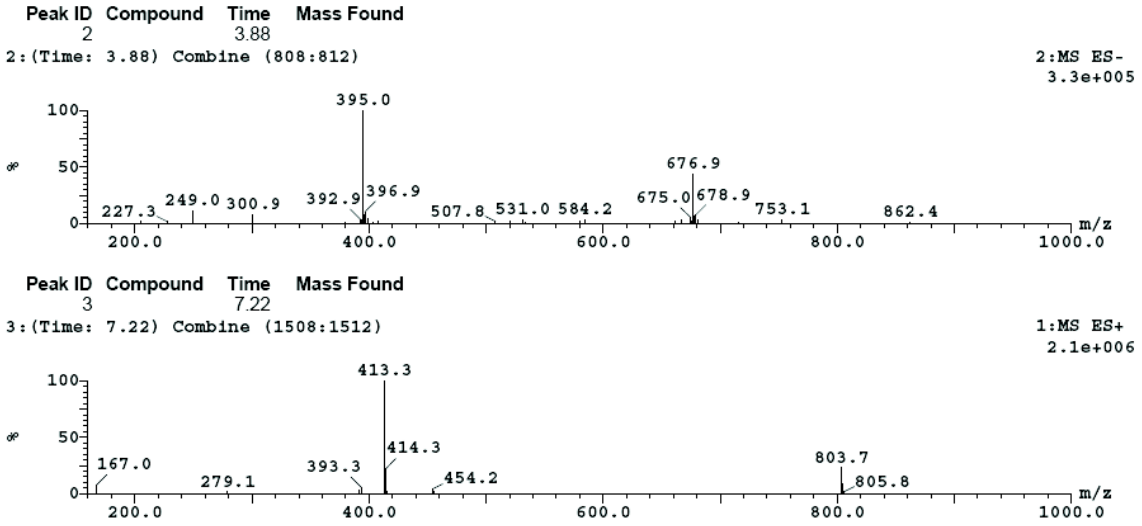
Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1	Found	3.56	36599.6	100.00	855759.9	315.08

Peak ID	Compound	Time	Mass Found
1	Found	3.56	315.08

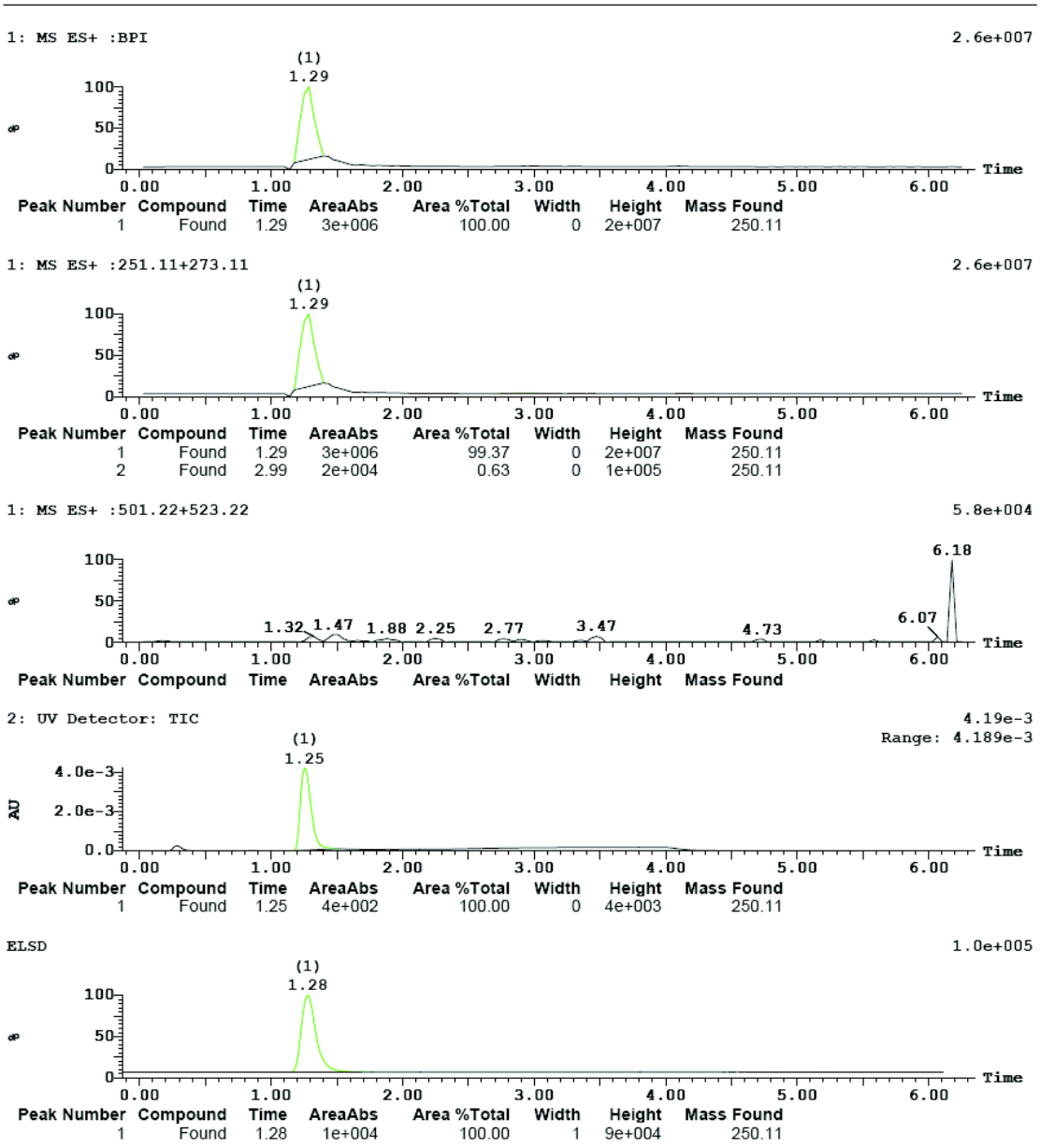


Peak ID	Compound	Time	Mass Found
1		3.56	

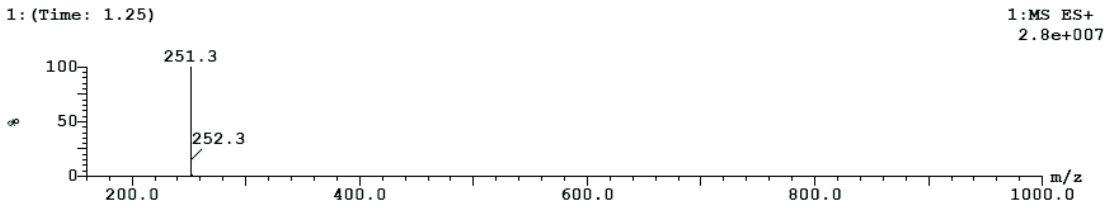




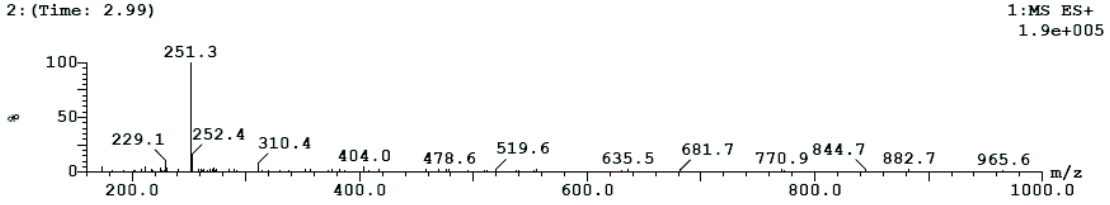
HT-LC-MS Spectrum (SOP 2222) of **4m**. UV purity: 100 %



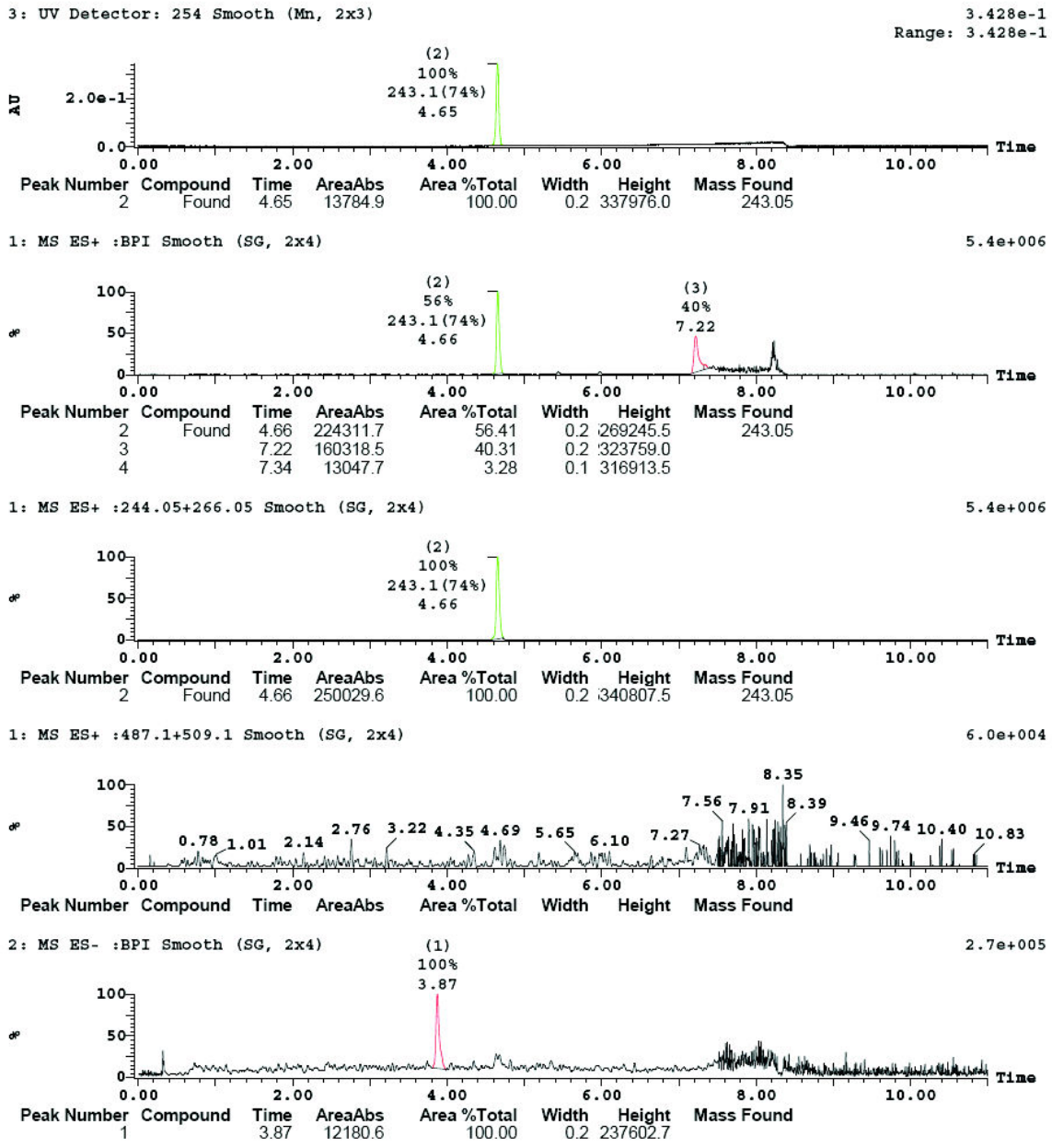
Peak ID	Compound	Time	Mass Found
1	Found	1.29	250.11

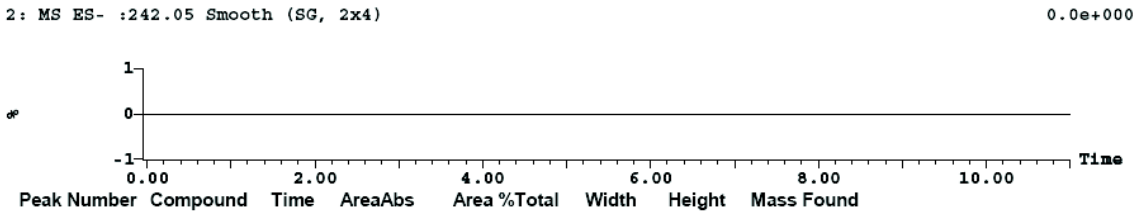


Peak ID	Compound	Time	Mass Found
2	Found	2.99	250.11

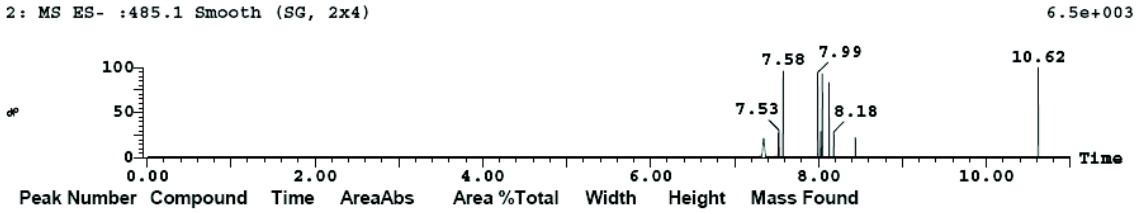


HT-LC-MS Spectrum (SOP 2200) of **4n**. UV purity: 100 %

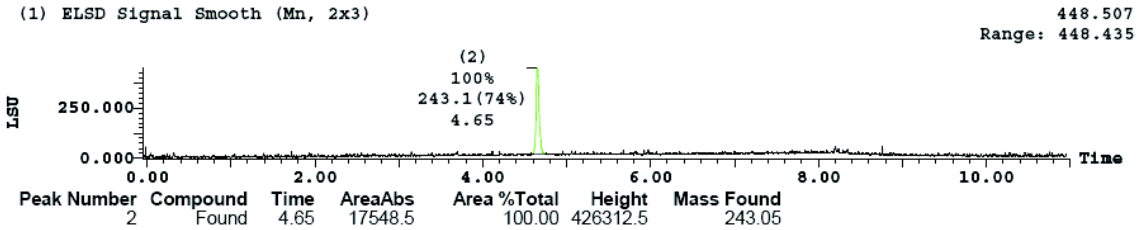




Peak Number Compound Time AreaAbs Area %Total Width Height Mass Found

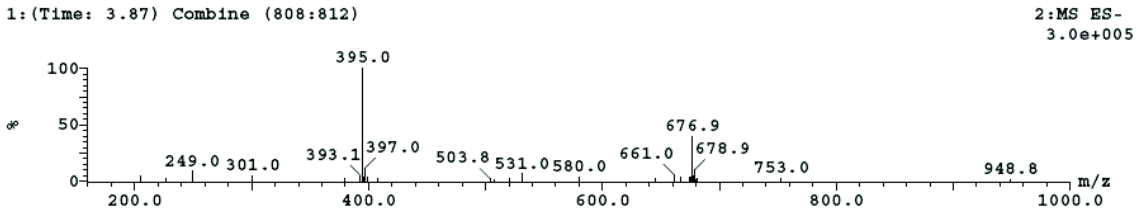


Peak Number Compound Time AreaAbs Area %Total Width Height Mass Found

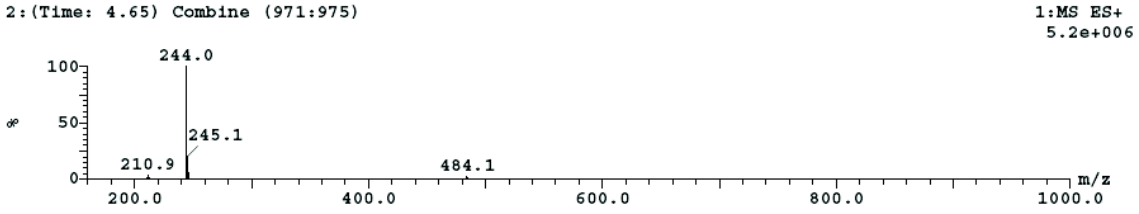


Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
2	Found	4.65	17548.5	100.00	426312.5	243.05

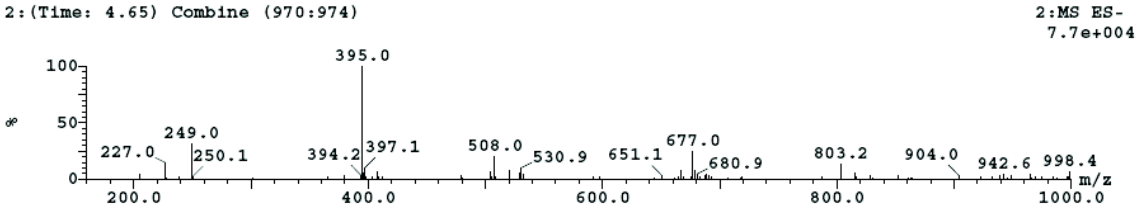
Peak ID	Compound	Time	Mass Found
1		3.87	



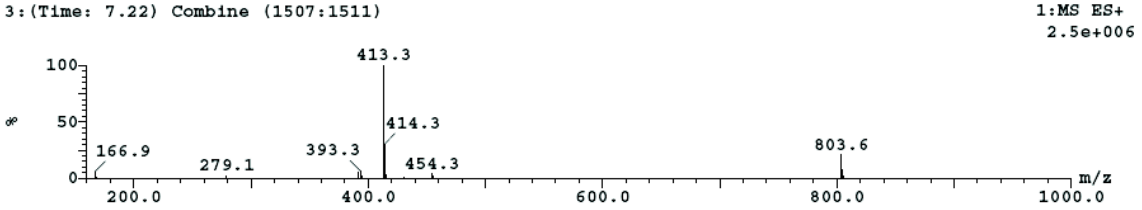
Peak ID	Compound	Time	Mass Found
2	Found	4.66	243.05



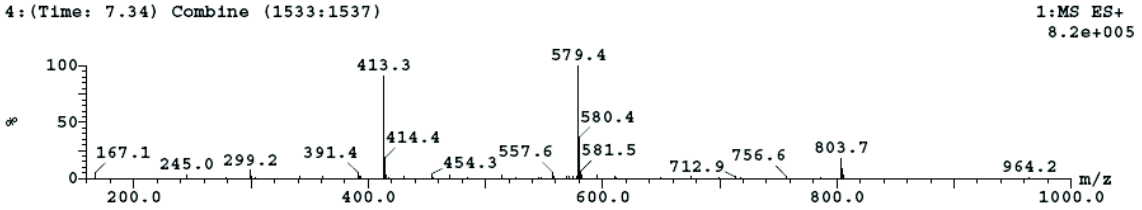
Peak ID	Compound	Time	Mass Found
2		4.66	



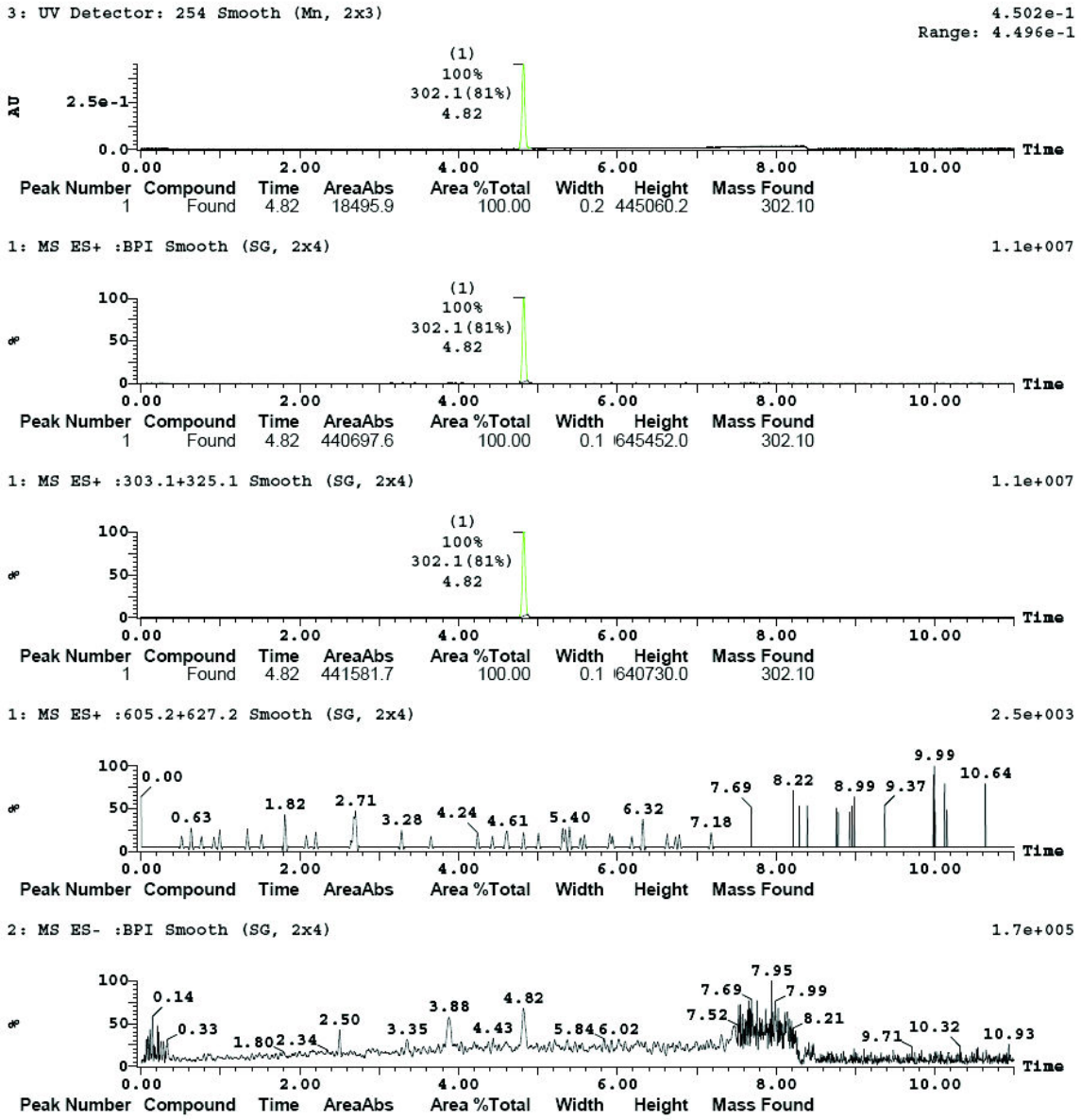
Peak ID	Compound	Time	Mass Found
3		7.22	

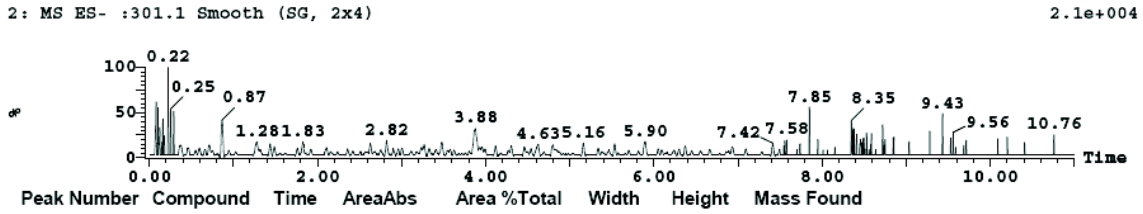


Peak ID	Compound	Time	Mass Found
4		7.34	

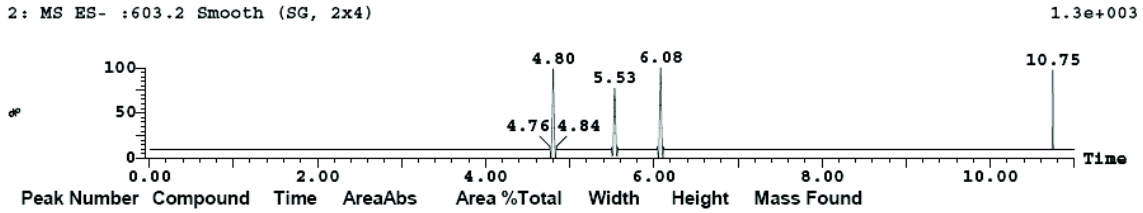


HT-LC-MS Spectrum (SOP 2200) of **4o**. UV purity: 100 %

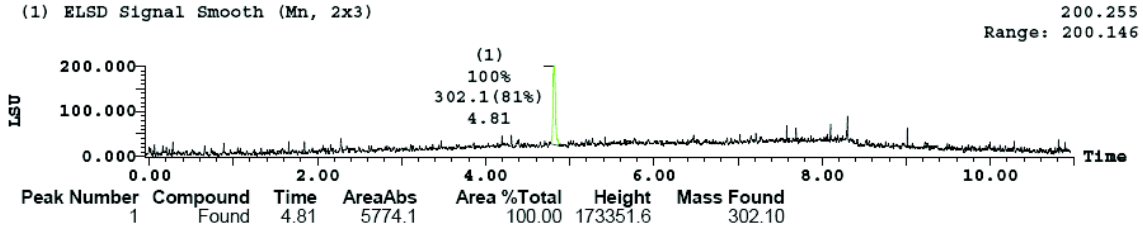




Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

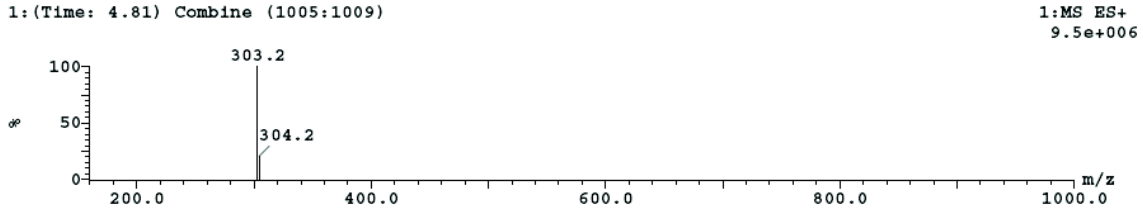


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

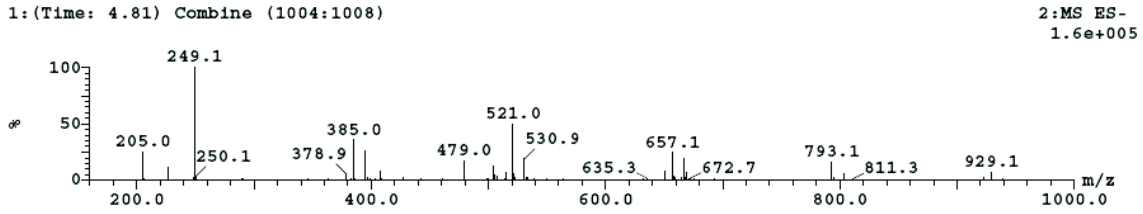


Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1	Found	4.81	5774.1	100.00	173351.6	302.10

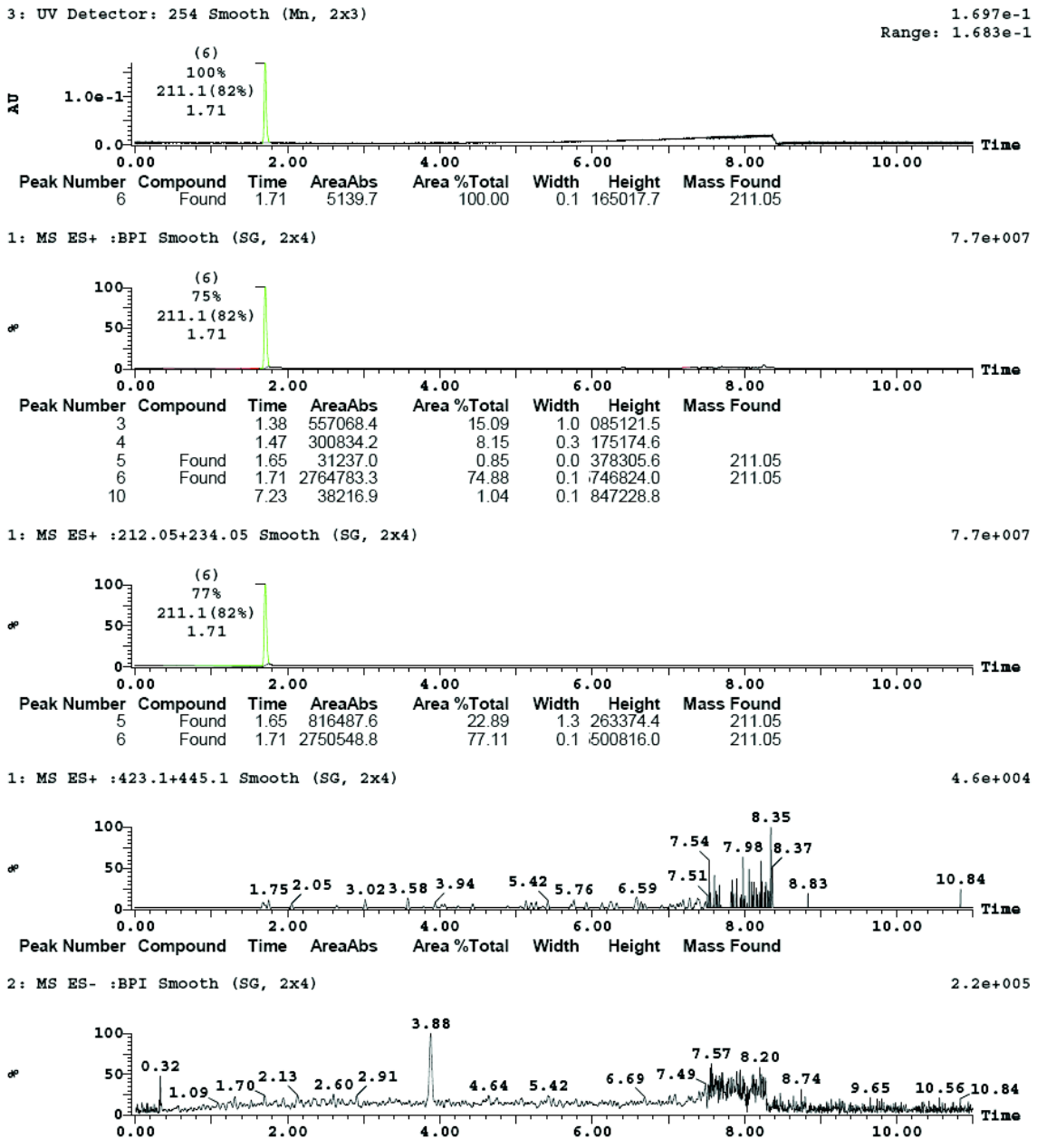
Peak ID	Compound	Time	Mass Found
1	Found	4.82	302.10



Peak ID	Compound	Time	Mass Found
1		4.82	

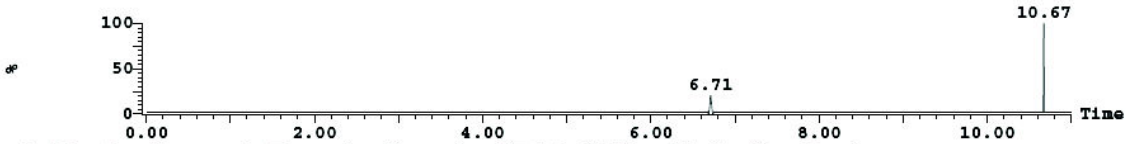


HT-LC-MS Spectrum (SOP 2200) of **4p**. UV purity: 100 %



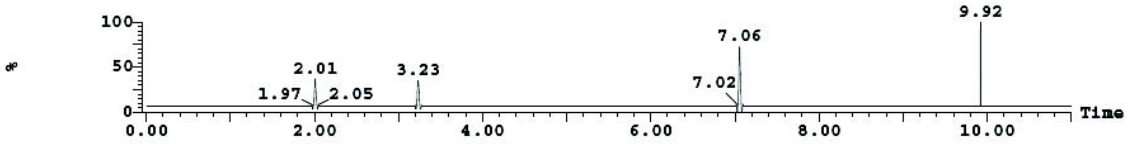
Peak Number Compound Time AreaAbs Area %Total Width Height Mass Found

2: MS ES- :210.05 Smooth (SG, 2x4) 2.0e+003



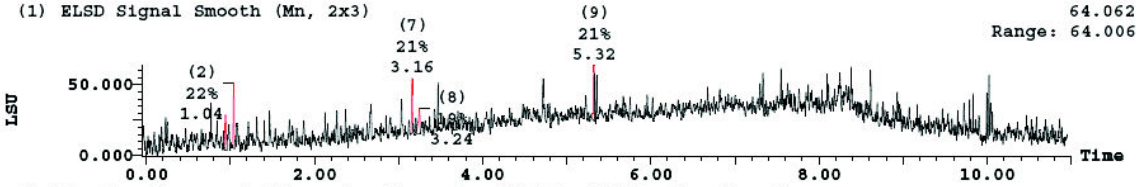
Peak Number Compound Time AreaAbs Area %Total Width Height Mass Found

2: MS ES- :421.1 Smooth (SG, 2x4) 1.6e+003



Peak Number Compound Time AreaAbs Area %Total Width Height Mass Found

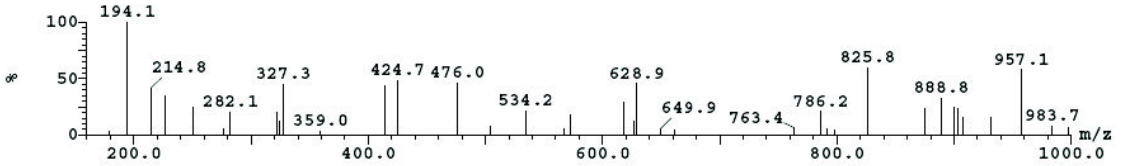
(1) ELSD Signal Smooth (Mn, 2x3) 64.062
Range: 64.006



Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1		0.94	371.8	16.90	25138.2	
2		1.04	487.7	22.17	46176.1	
7		3.16	466.2	21.19	39158.9	
8		3.25	417.1	18.96	17590.3	
9		5.32	457.5	20.79	39418.6	

Peak ID	Compound	Time	Mass Found
1		0.94	

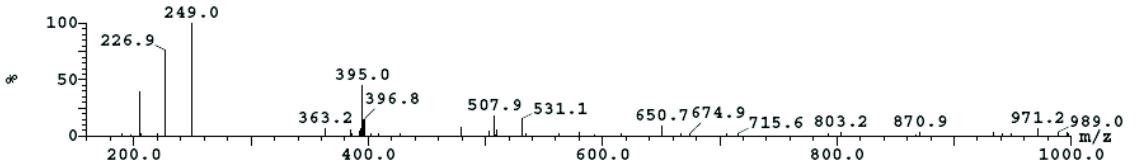
1:(Time: 0.94) Combine (196:200) 1:MS ES+
7.8e+003



Peak ID	Compound	Time	Mass Found
1		0.94	

1:(Time: 0.94) Combine (195:199)

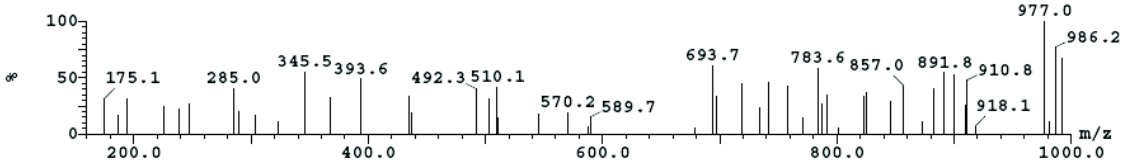
2:MS ES-
2.0e+004



Peak ID	Compound	Time	Mass Found
2		1.04	

2:(Time: 1.04) Combine (216:220)

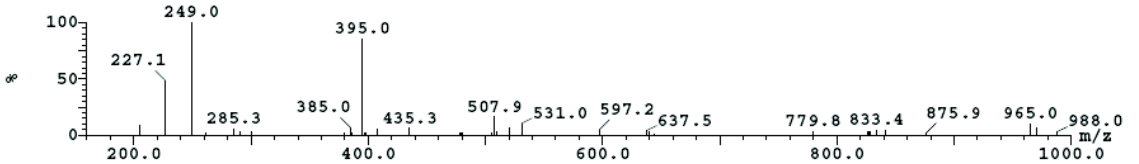
1:MS ES+
5.5e+003



Peak ID	Compound	Time	Mass Found
2		1.04	

2:(Time: 1.04) Combine (215:220)

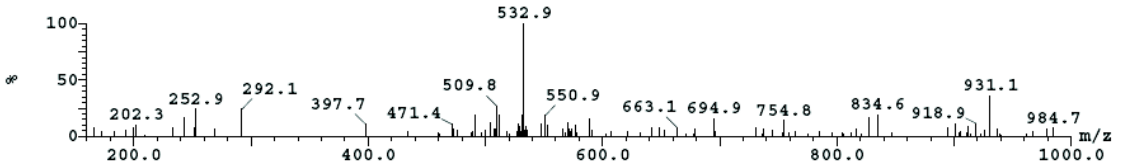
2:MS ES-
2.3e+004



Peak ID	Compound	Time	Mass Found
3		1.38	

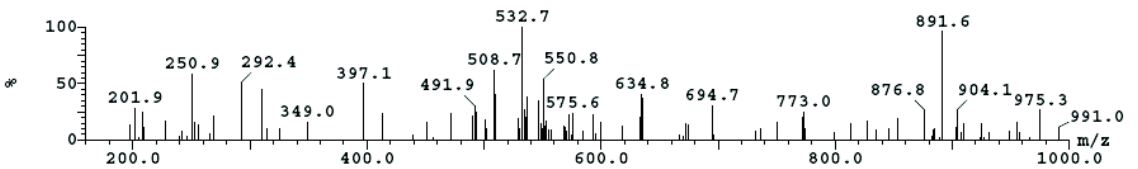
3:(Time: 1.38) Combine (286:290)

1:MS ES+
3.5e+004



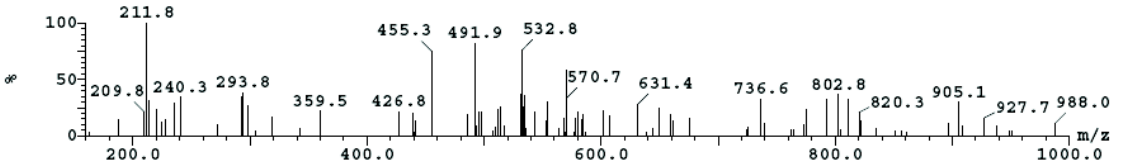
Peak ID	Compound	Time	Mass Found
4		1.47	

4:(Time: 1.47) Combine (306:310)



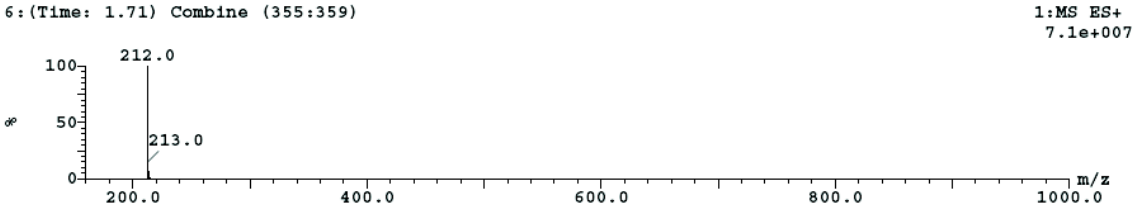
Peak ID	Compound	Time	Mass Found
5	Found	1.65	211.05

5:(Time: 1.65) Combine (343:347)



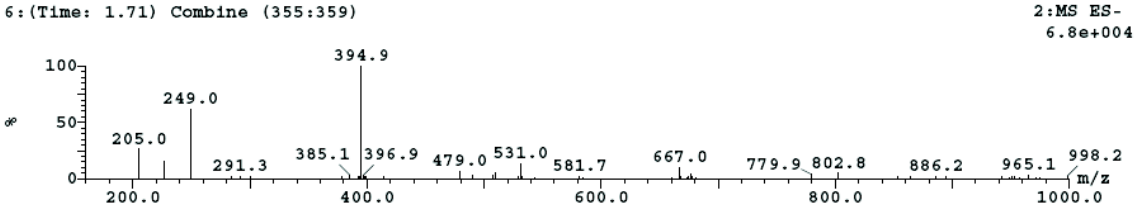
Peak ID	Compound	Time	Mass Found
6	Found	1.71	211.05

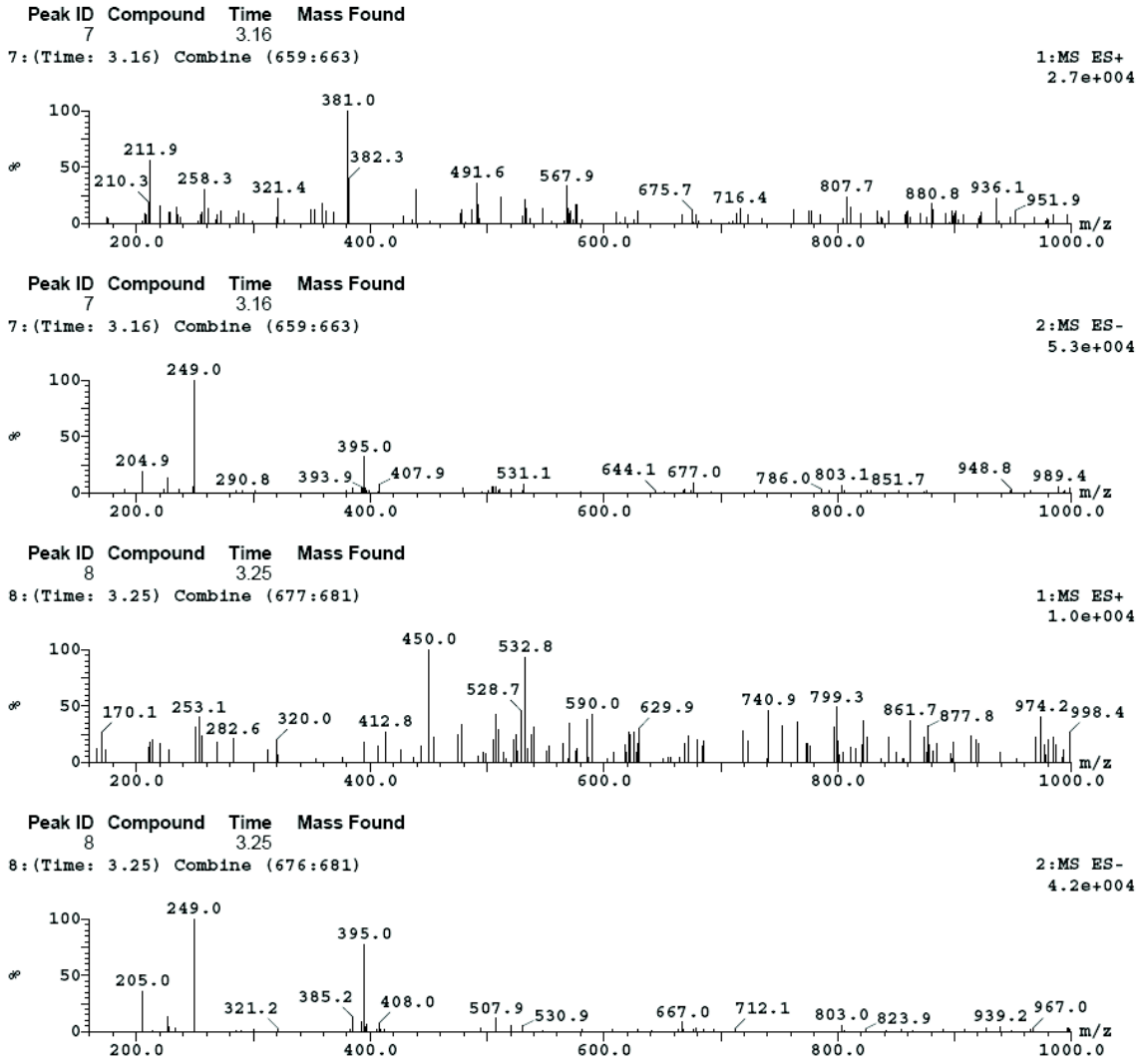
6:(Time: 1.71) Combine (355:359)

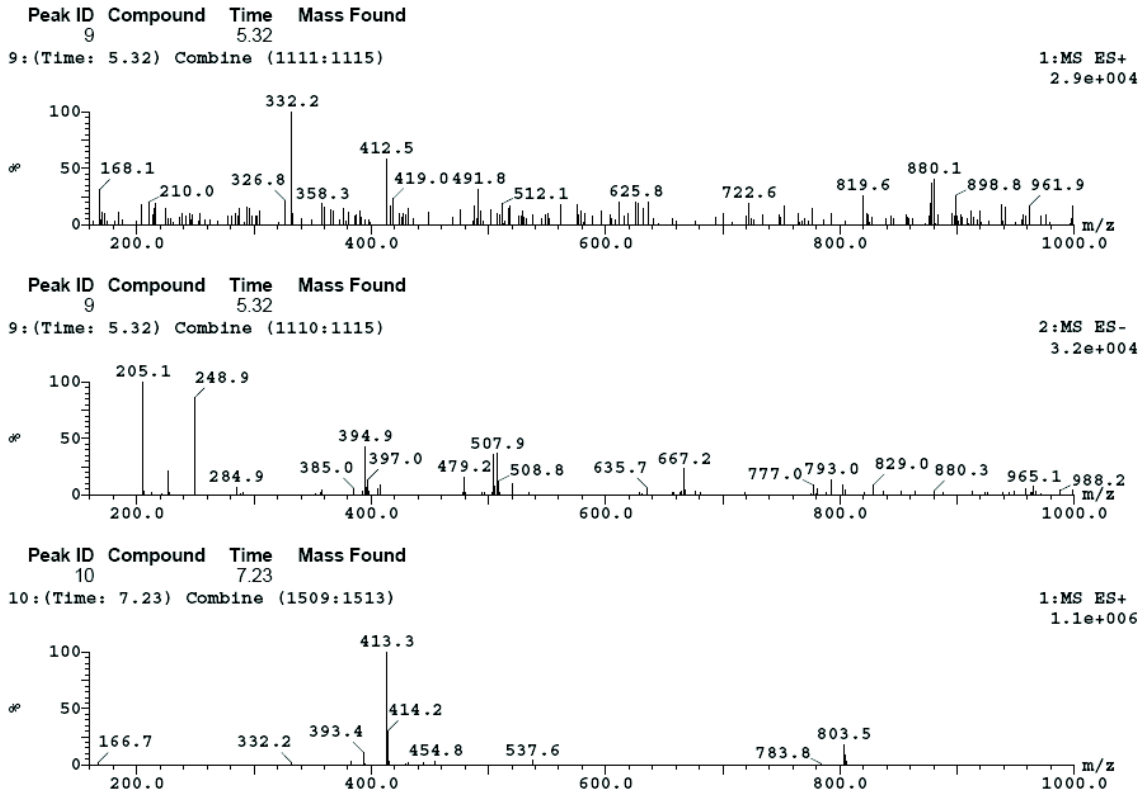


Peak ID	Compound	Time	Mass Found
6		1.71	

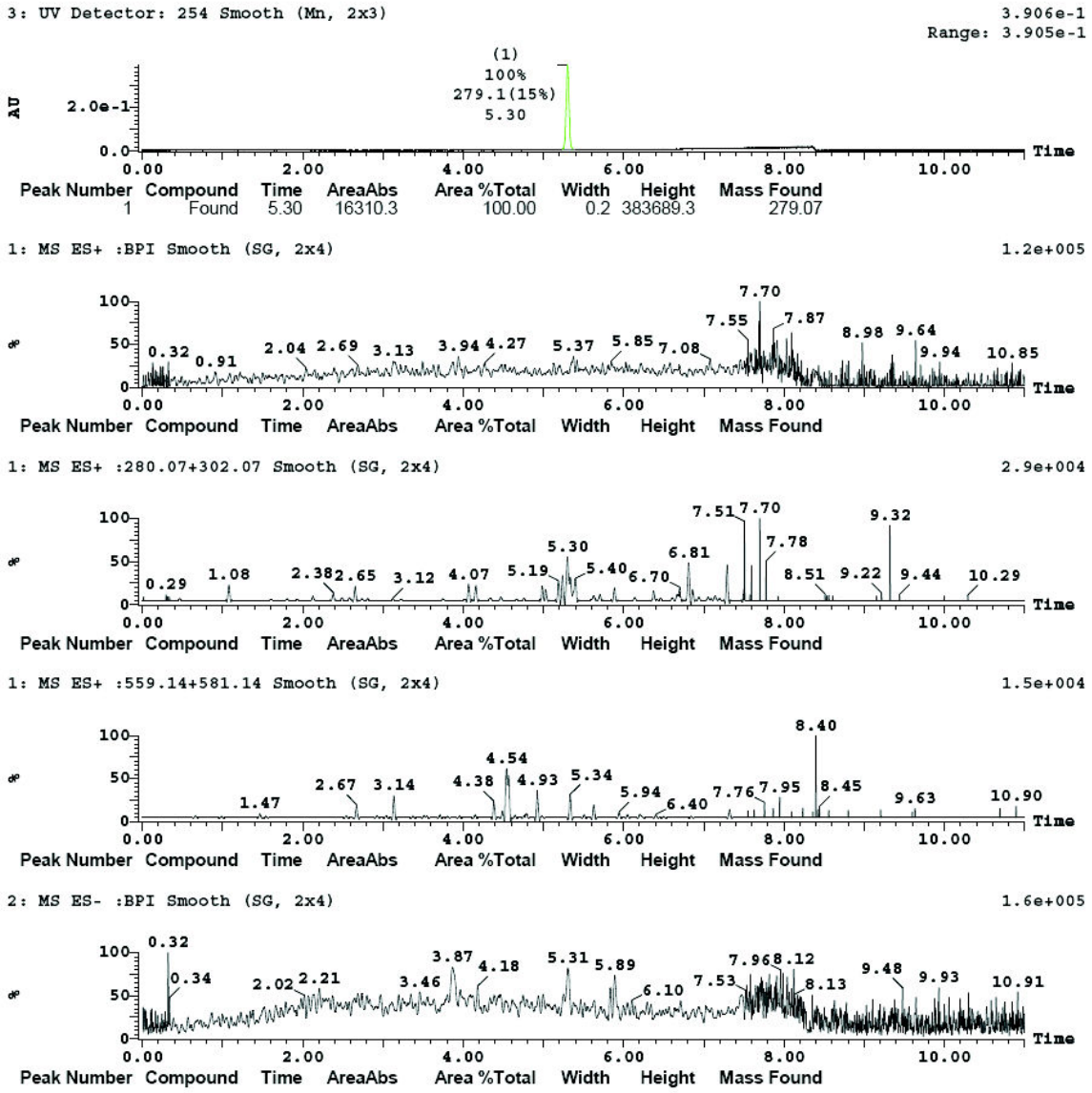
6:(Time: 1.71) Combine (355:359)

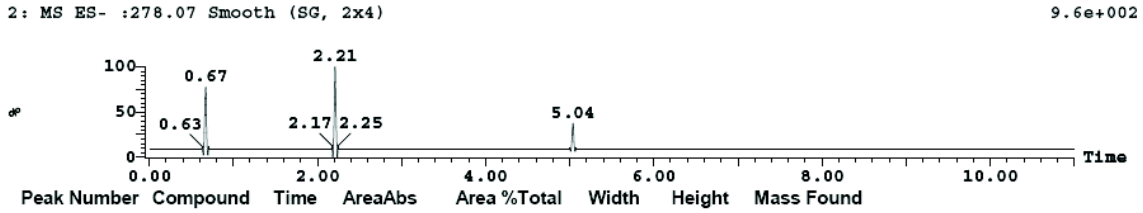



Peak ID Compound Time Mass Found
7 3.16
7:(Time: 3.16) Combine (659:663)
1:MS ES+
2.7e+004
381.0
382.3
211.9
210.3
258.3
321.4
491.6
567.9
675.7
716.4
807.7
880.8
936.1
951.9
m/z
Peak ID Compound Time Mass Found
7 3.16
7:(Time: 3.16) Combine (659:663)
2:MS ES-
5.3e+004
249.0
395.0
204.9
290.8
393.9
407.9
531.1
644.1
677.0
786.0
803.1
851.7
948.8
989.4
m/z
Peak ID Compound Time Mass Found
8 3.25
8:(Time: 3.25) Combine (677:681)
1:MS ES+
1.0e+004
450.0
532.8
528.7
170.1
253.1
282.6
320.0
412.8
590.0
629.9
740.9
799.3
861.7
877.8
974.2
998.4
m/z
Peak ID Compound Time Mass Found
8 3.25
8:(Time: 3.25) Combine (676:681)
2:MS ES-
4.2e+004
249.0
395.0
205.0
321.2
385.2
408.0
507.9
530.9
667.0
712.1
803.0
823.9
939.2
967.0
m/z

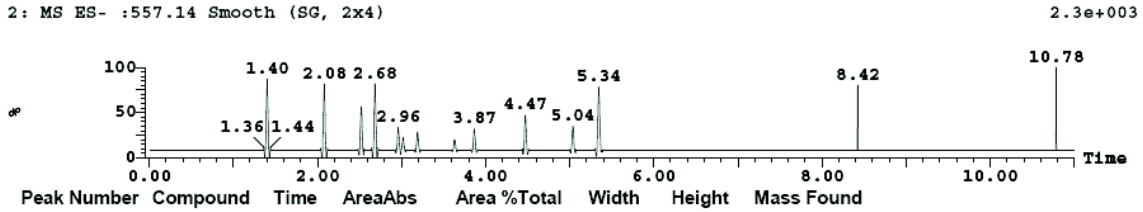

Peak ID Compound Time Mass Found
9 5.32
9:(Time: 5.32) Combine (1111:1115)
1:MS ES+
2.9e+004
100
50
0
%
332.2
412.5
168.1
210.0
326.8
358.3
419.0491.8
512.1
625.8
722.6
819.6
880.1
898.8
961.9
m/z
200.0
400.0
600.0
800.0
1000.0
Peak ID Compound Time Mass Found
9 5.32
9:(Time: 5.32) Combine (1110:1115)
2:MS ES-
3.2e+004
205.1
248.9
394.9
507.9
284.9
385.0
397.0
479.2
508.8
635.7
667.2
777.0
793.0
829.0
880.3
965.1
988.2
Peak ID Compound Time Mass Found
10 7.23
10:(Time: 7.23) Combine (1509:1513)
1:MS ES+
1.1e+006
413.3
414.2
393.4
166.7
332.2
454.8
537.6
783.8
803.5

HT-LC-MS Spectrum (SOP 2200) of **4q**. UV purity: 100 %

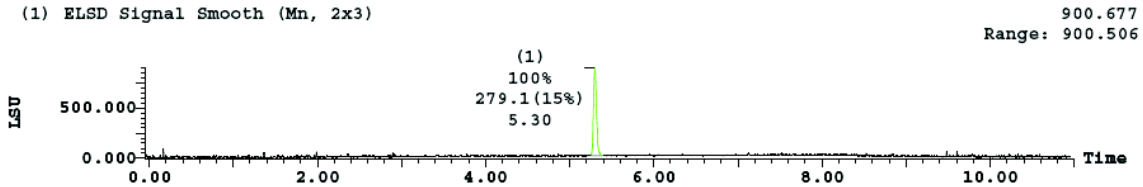




Peak Number Compound Time AreaAbs Area %Total Width Height Mass Found

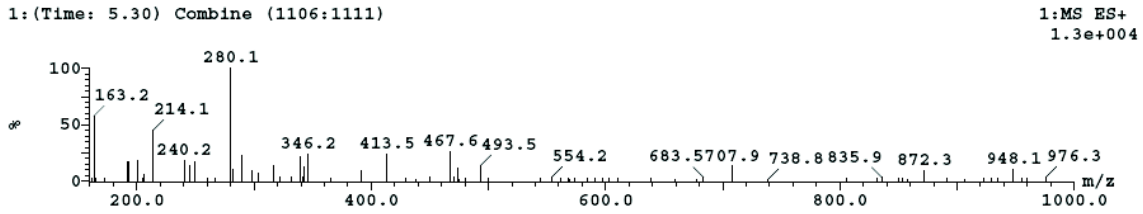


Peak Number Compound Time AreaAbs Area %Total Width Height Mass Found

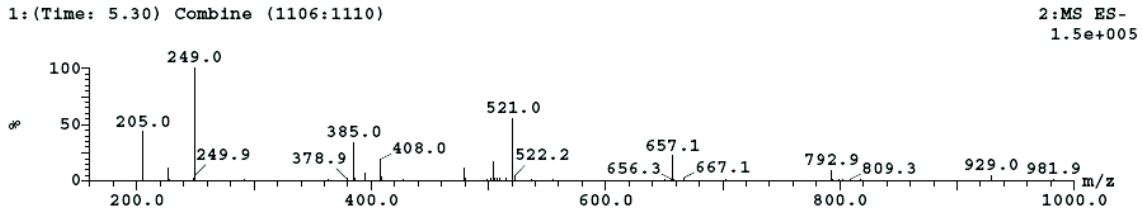


Peak Number Compound Time AreaAbs Area %Total Height Mass Found
1 Found 5.30 35801.8 100.00 875425.1 279.07

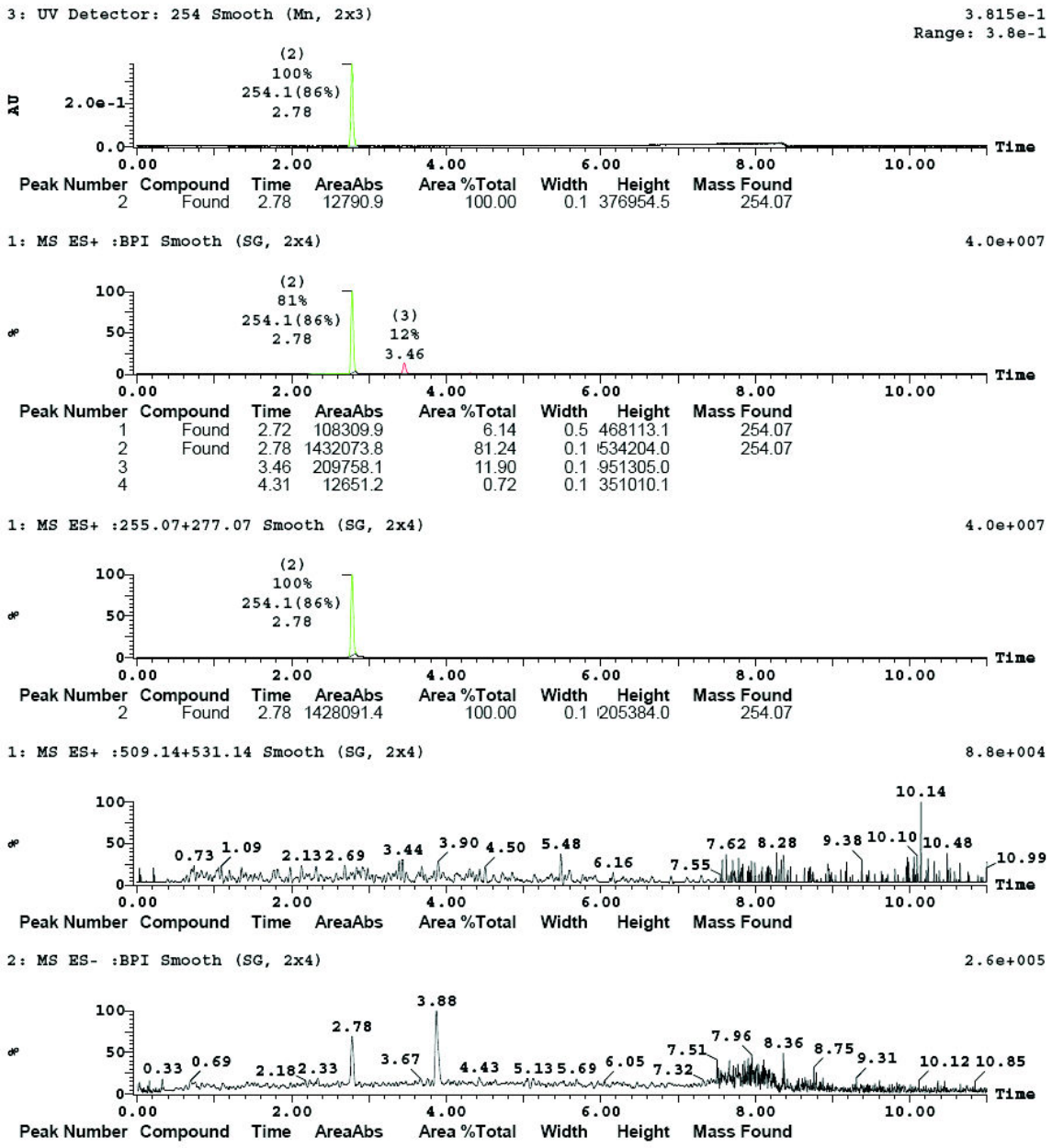
Peak ID Compound Time Mass Found
1 Found 5.30 279.07

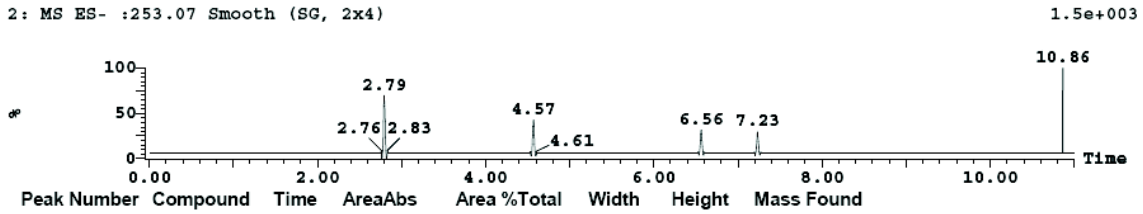


Peak ID Compound Time Mass Found
1 5.30

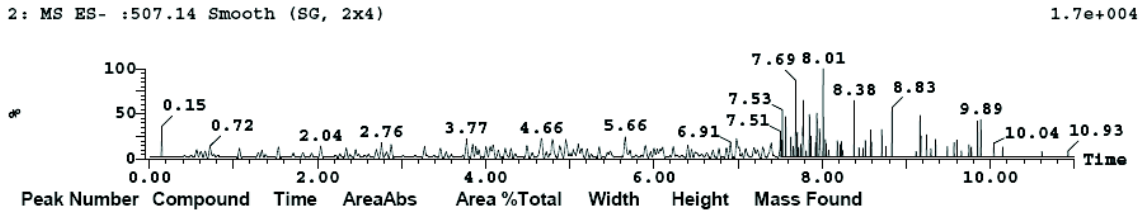


HT-LC-MS Spectrum (SOP 2200) of **4r**. UV purity: 100 %

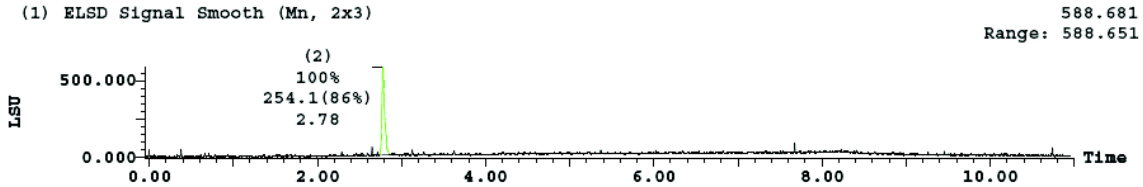




Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

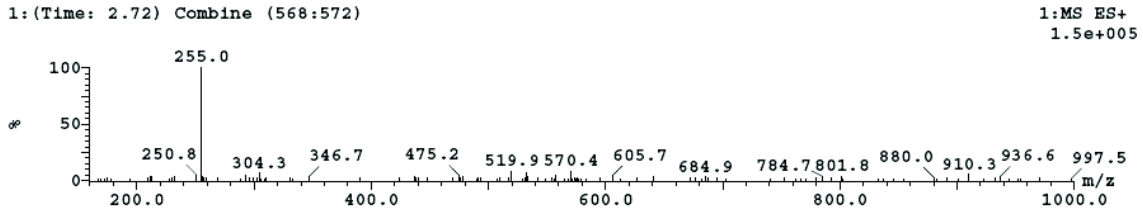


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

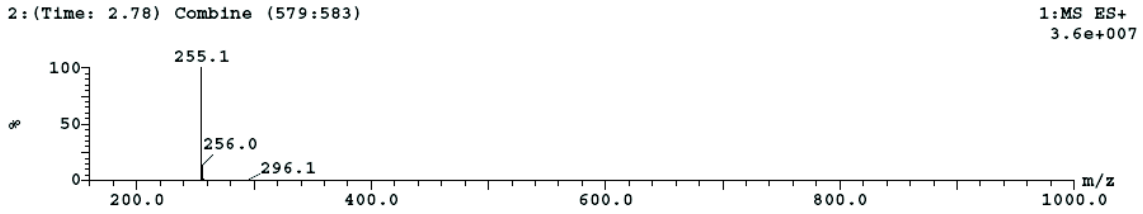


Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
2	Found	2.78	21465.3	100.00	570638.0	254.07

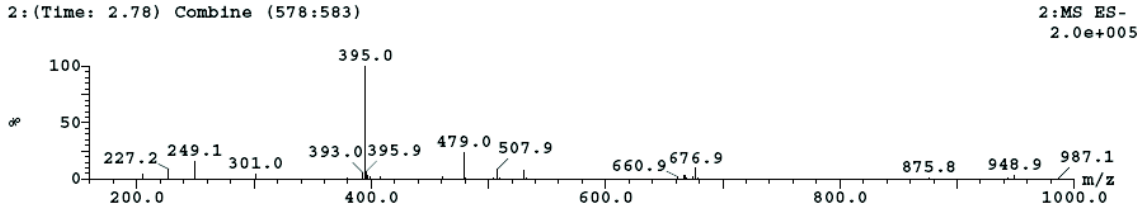
Peak ID	Compound	Time	Mass Found
1	Found	2.72	254.07



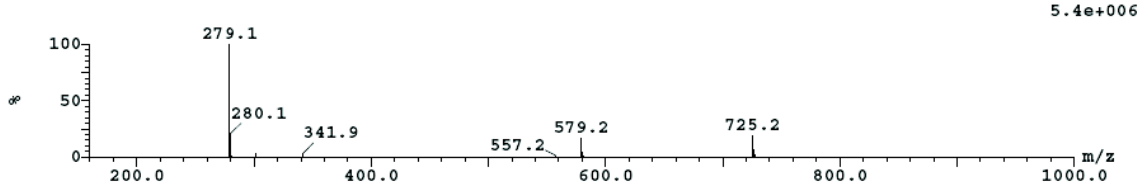
Peak ID	Compound	Time	Mass Found
2	Found	2.78	254.07



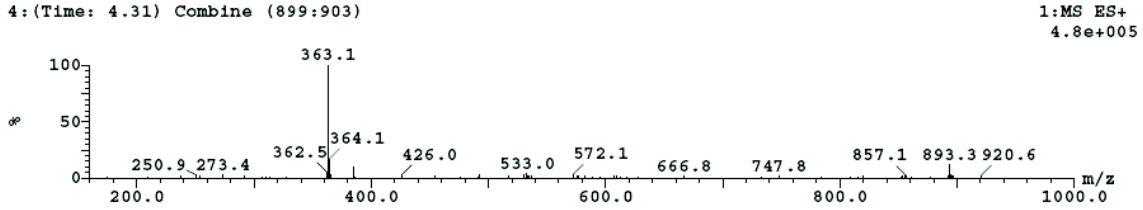
Peak ID	Compound	Time	Mass Found
2		2.78	



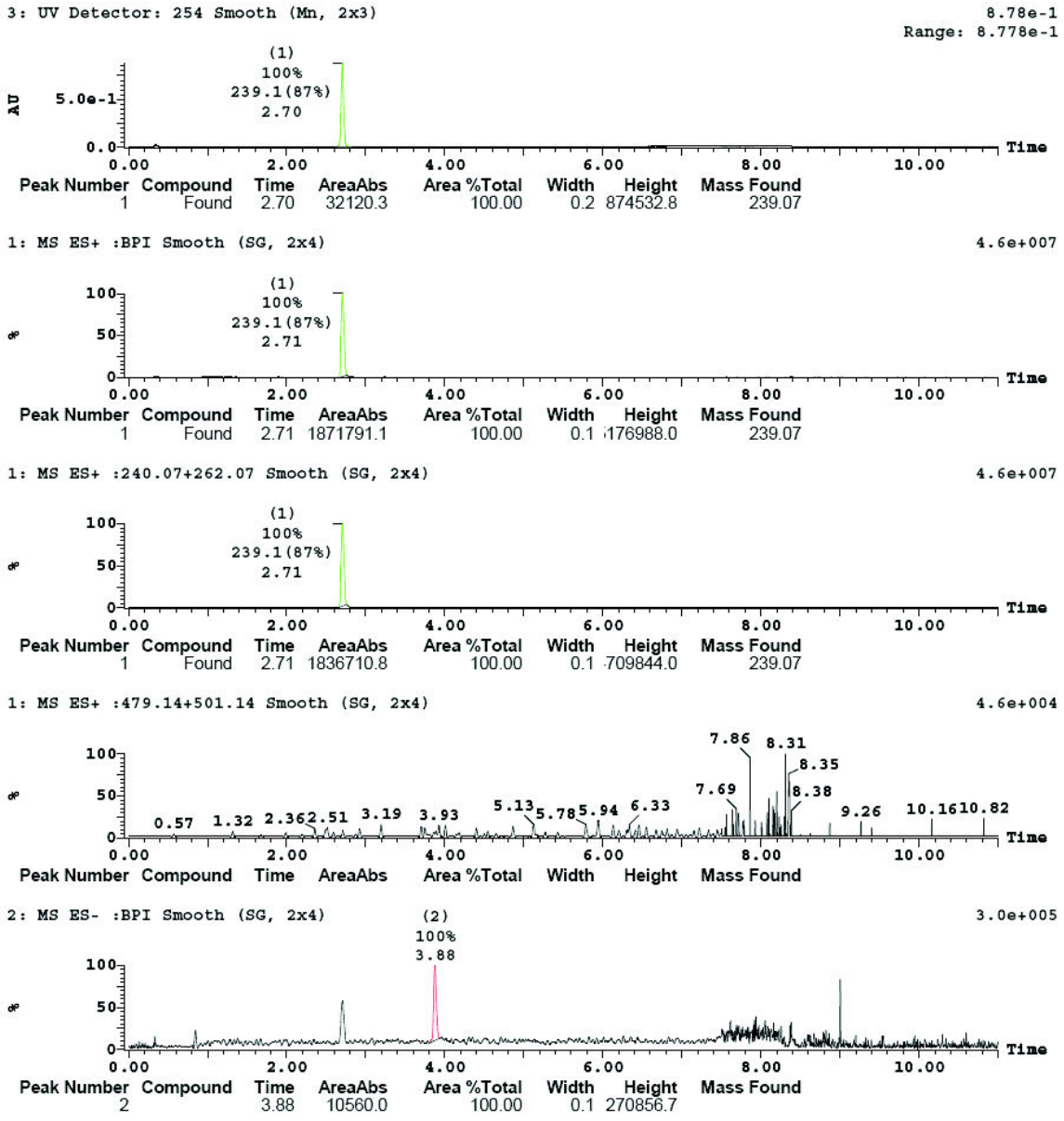
Peak ID	Compound	Time	Mass Found
3		3.46	

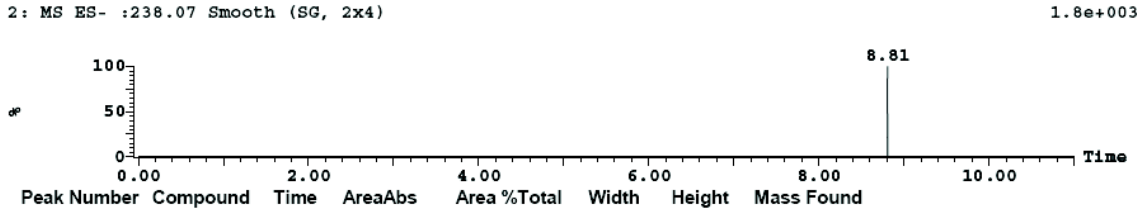


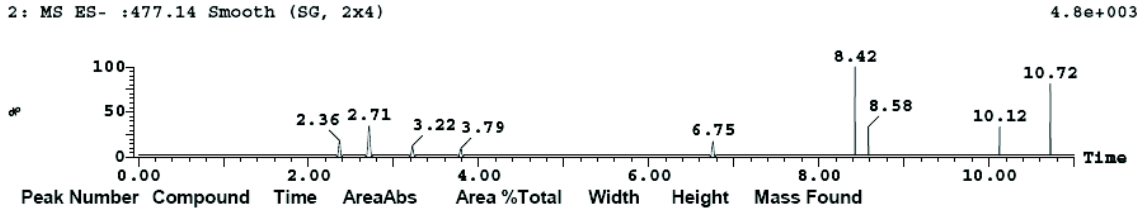
Peak ID	Compound	Time	Mass Found
4		4.31	

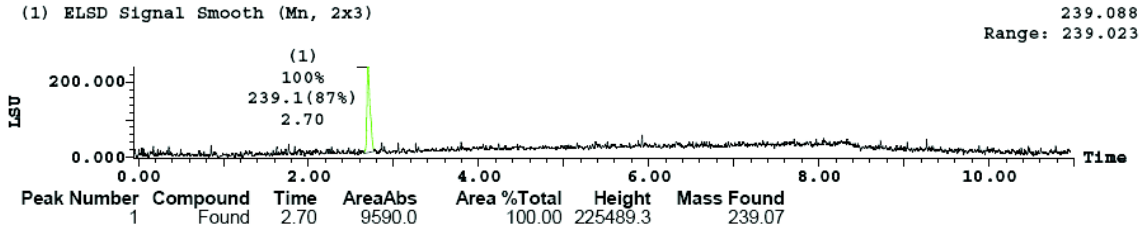


HP-LC-MS Spectrum (SOP 2200) of **4s**. UV purity: 100 %

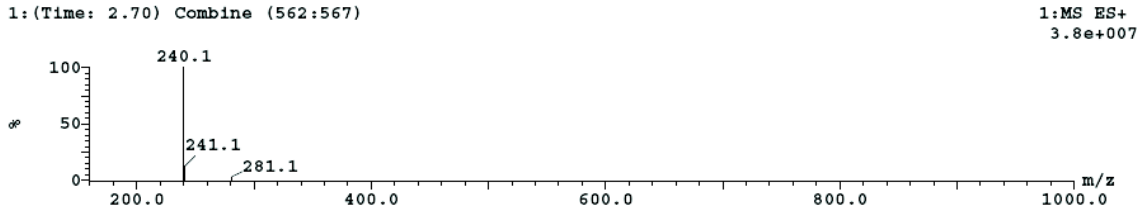




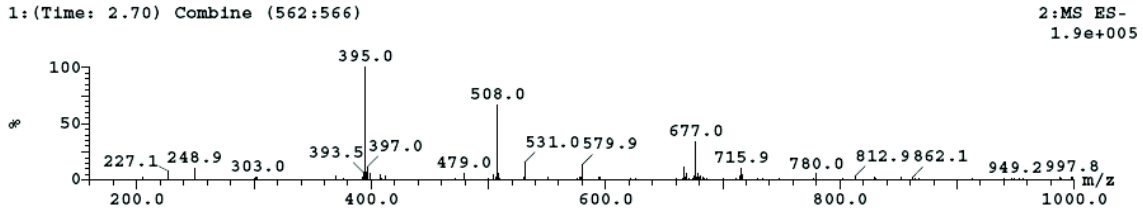




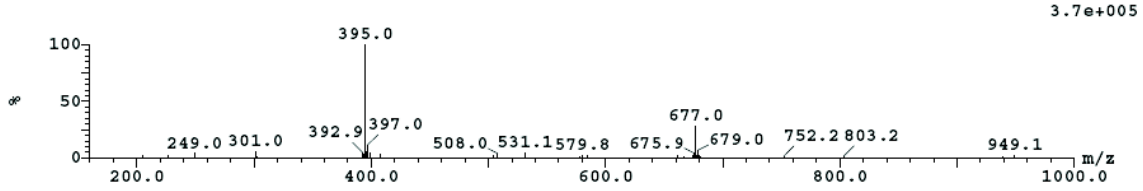
Peak ID Compound Time Mass Found
1 Found 2.71 239.07



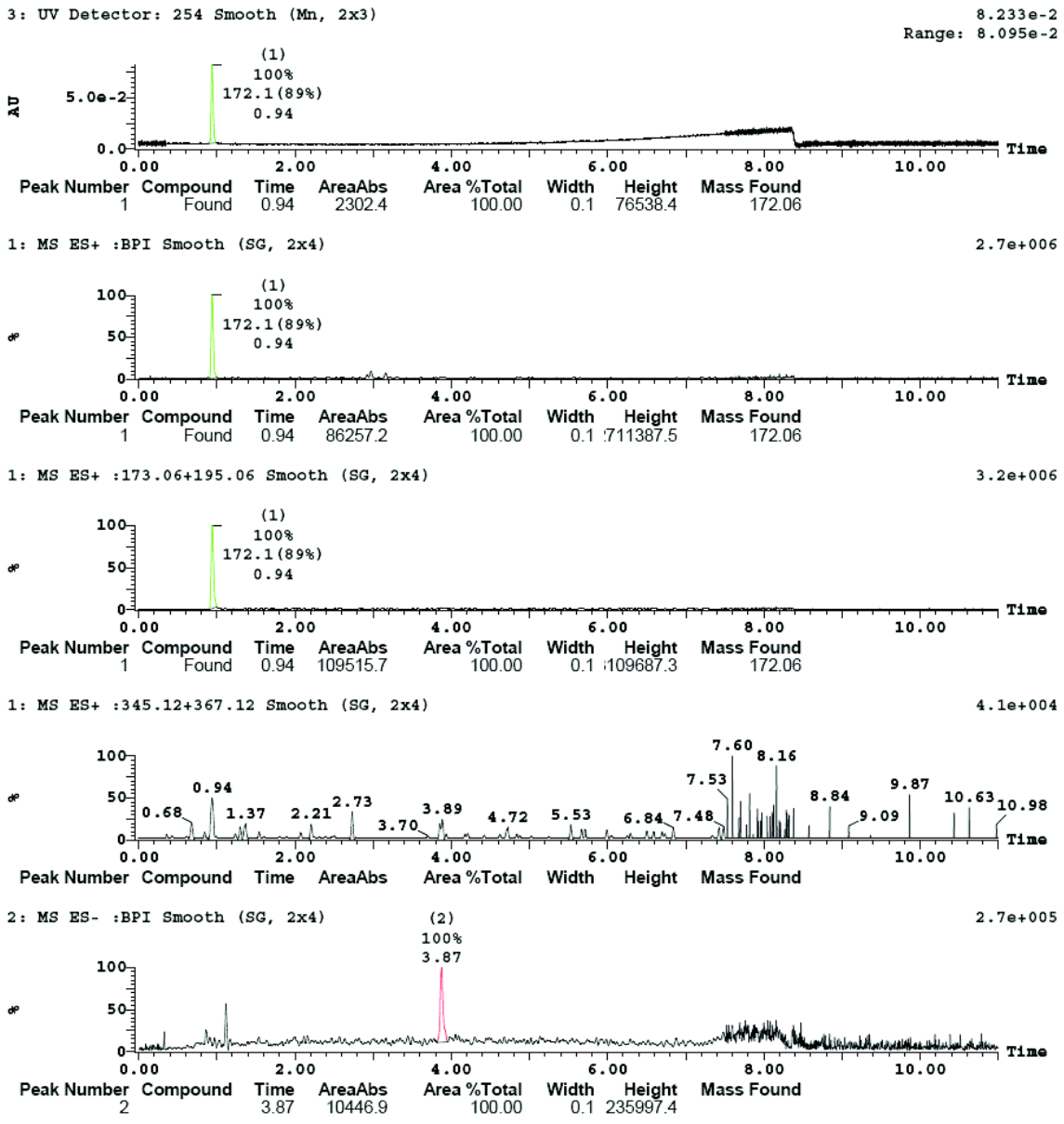
Peak ID Compound Time Mass Found
1 2.71

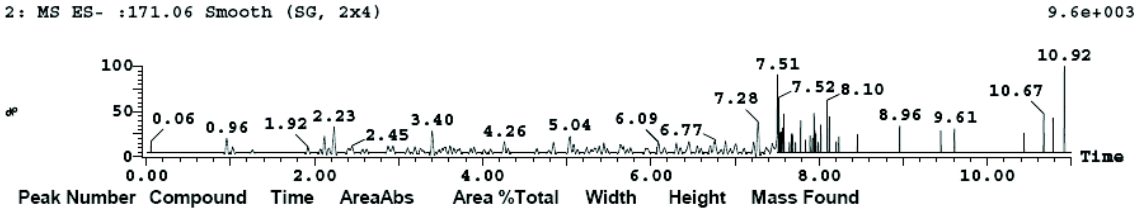


Peak ID Compound Time Mass Found
2 3.88



HP-LC-MS Spectrum (SOP 2200) of **4t**. UV purity: 100 %





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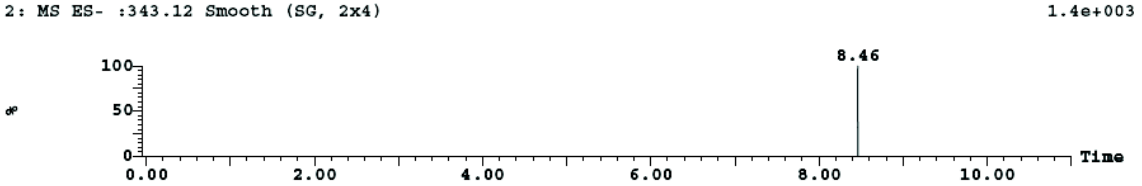
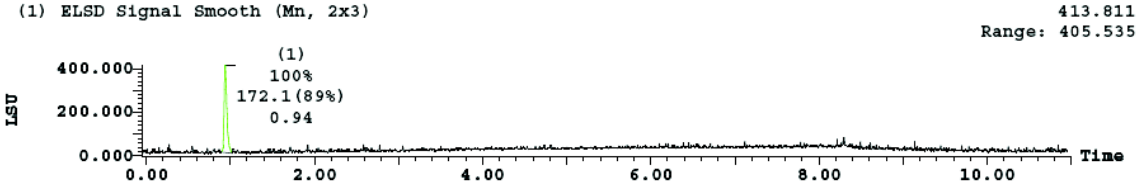
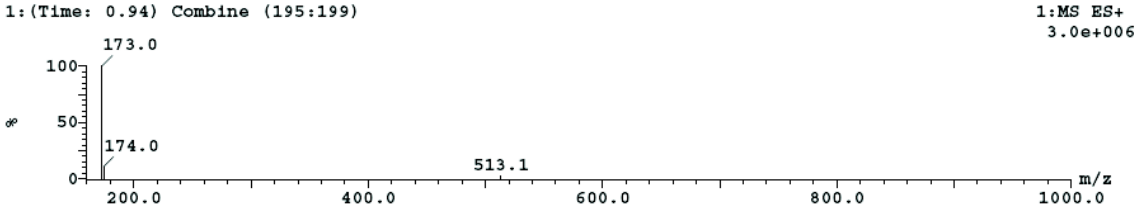


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

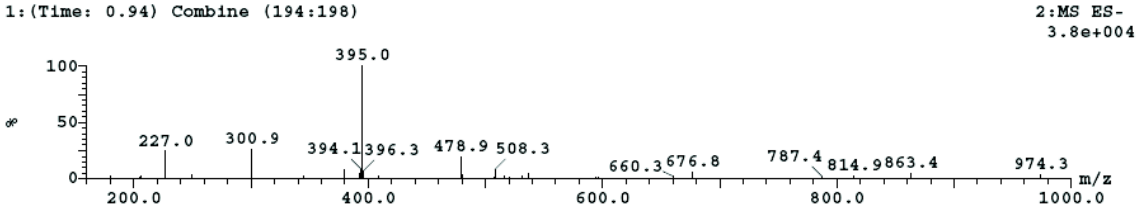


Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1	Found	0.94	15239.2	100.00	398287.6	172.06

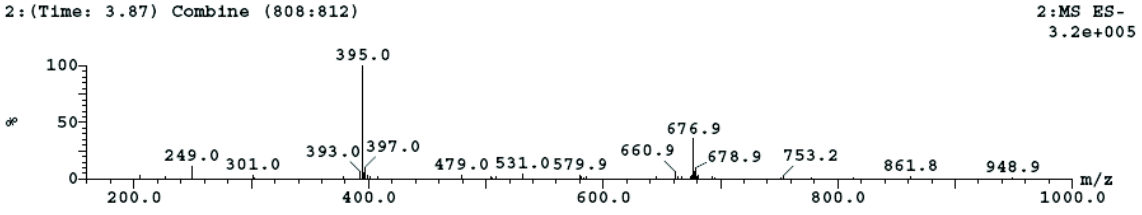
Peak ID	Compound	Time	Mass Found
1	Found	0.94	172.06



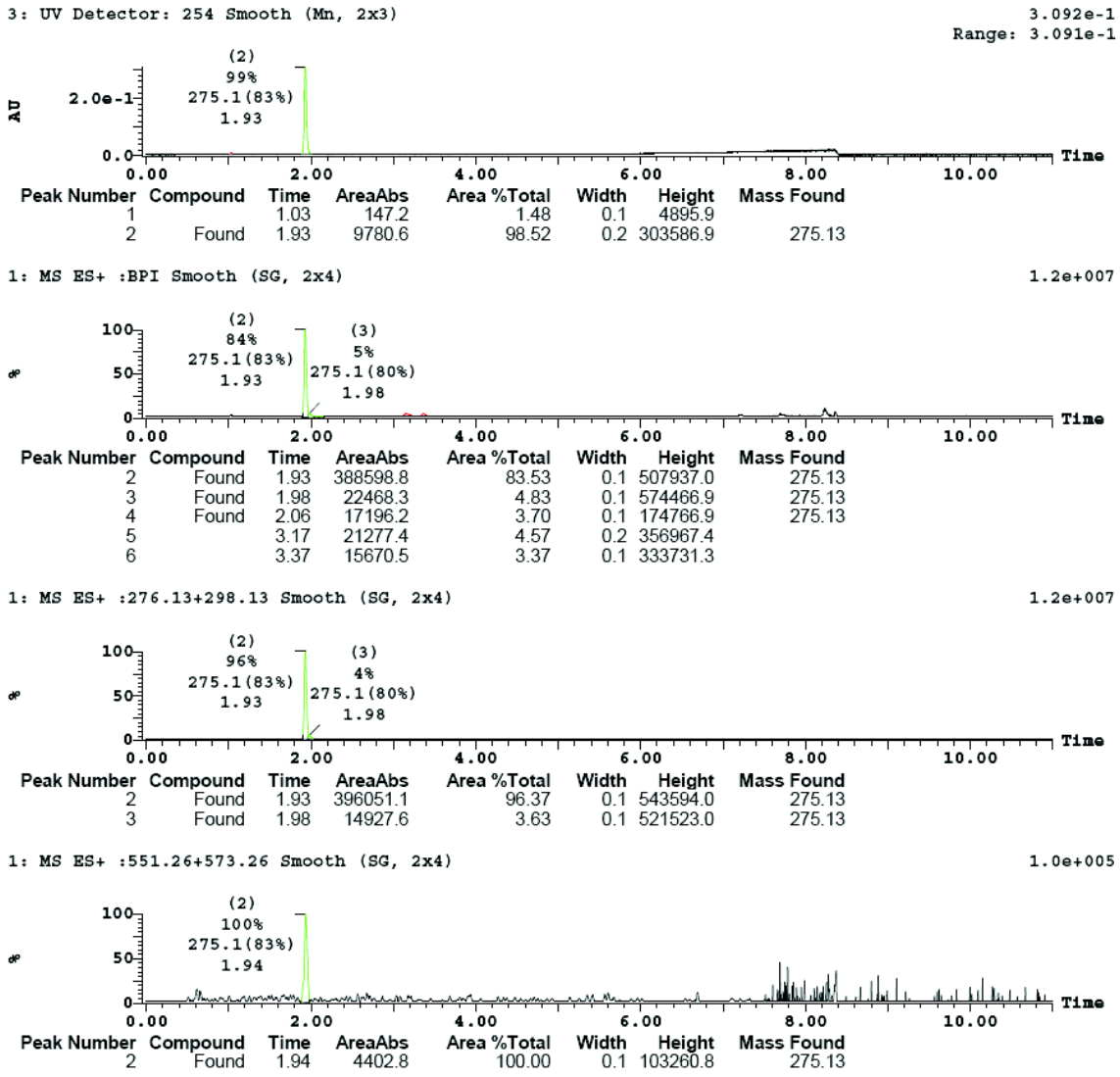
Peak ID	Compound	Time	Mass Found
1		0.94	

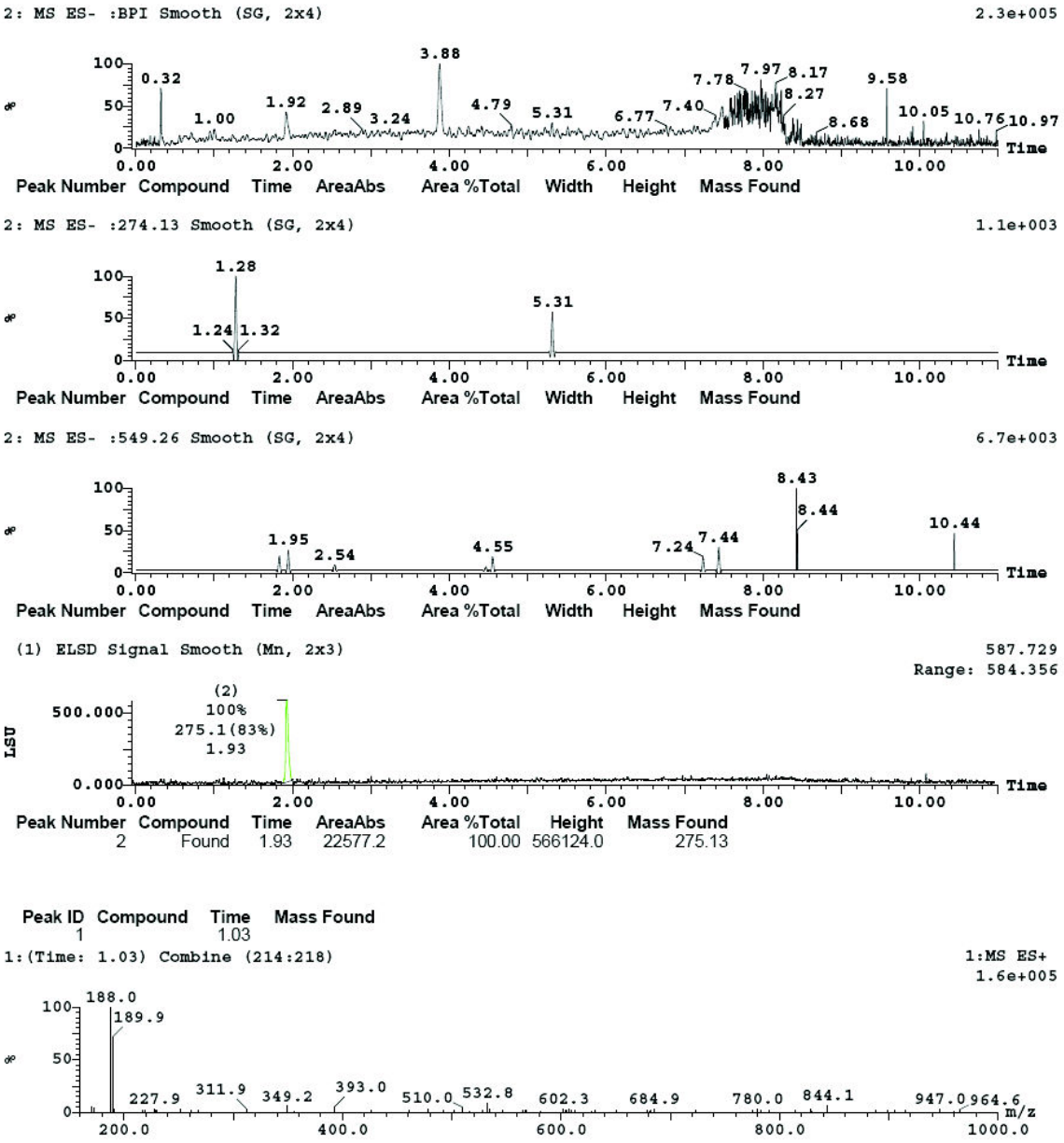


Peak ID	Compound	Time	Mass Found
2		3.87	



HT-LC-MS Spectrum (SOP 2200) of **4u**. UV purity: 98.5 %

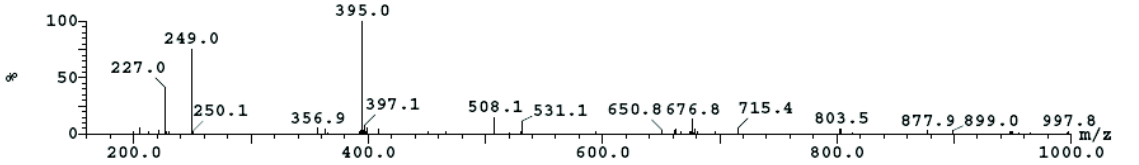



2: MS ES- :BPI Smooth (SG, 2x4)
2.3e+005
0.32
1.00
1.92
2.89
3.24
3.88
4.79
5.31
6.77
7.40
7.78
7.97
8.17
8.27
8.68
9.58
10.05
10.76
10.97
Time
Peak Number Compound Time AreaAbs Area %Total Width Height Mass Found
2: MS ES- :274.13 Smooth (SG, 2x4)
1.1e+003
1.24
1.28
1.32
5.31
Time
Peak Number Compound Time AreaAbs Area %Total Width Height Mass Found
2: MS ES- :549.26 Smooth (SG, 2x4)
6.7e+003
1.95
2.54
4.55
7.24
7.44
8.43
8.44
10.44
Time
Peak Number Compound Time AreaAbs Area %Total Width Height Mass Found
(1) ELSD Signal Smooth (Mn, 2x3)
587.729
Range: 584.356
(2)
100%
275.1(83%)
1.93
500.000
0.000
LSU
Time
Peak Number Compound Time AreaAbs Area %Total Height Mass Found
2 Found 1.93 22577.2 100.00 566124.0 275.13
Peak ID Compound Time Mass Found
1 1.03
1:(Time: 1.03) Combine (214:218)
1:MS ES+
1.6e+005
188.0
189.9
227.9
311.9
349.2
393.0
510.0
532.8
602.3
684.9
780.0
844.1
947.0
964.6
m/z

Peak ID	Compound	Time	Mass Found
1		1.03	

1:(Time: 1.03) Combine (213:218)

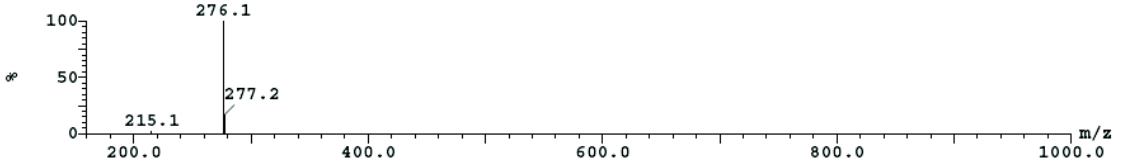
2:MS ES-
2.8e+004



Peak ID	Compound	Time	Mass Found
2	Found	1.93	275.13

2:(Time: 1.93) Combine (401:405)

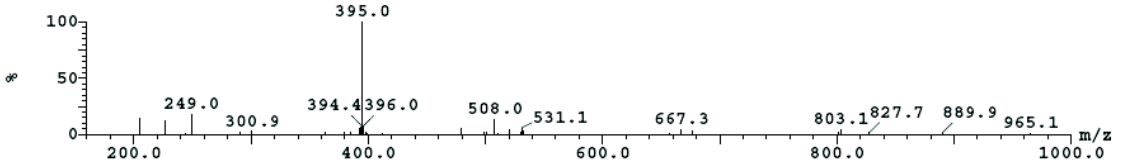
1:MS ES+
1.0e+007



Peak ID	Compound	Time	Mass Found
2		1.93	

2:(Time: 1.93) Combine (401:405)

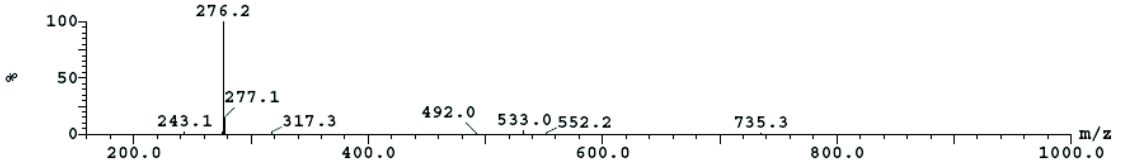
2:MS ES-
1.1e+005



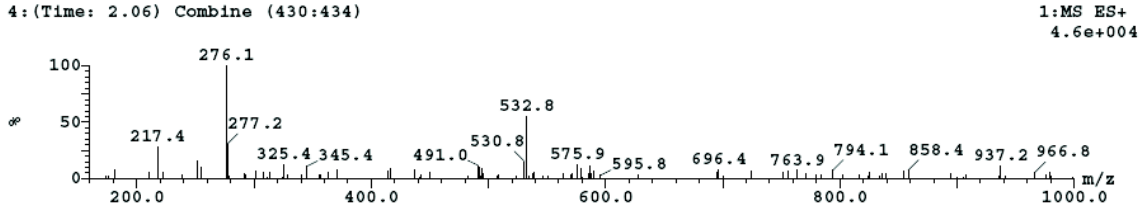
Peak ID	Compound	Time	Mass Found
3	Found	1.98	275.13

3:(Time: 1.98) Combine (412:416)

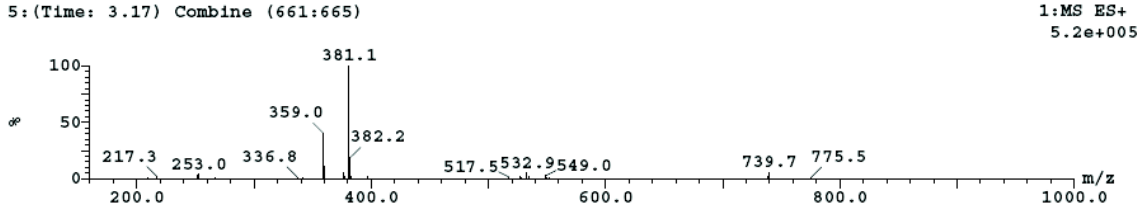
1:MS ES+
5.4e+005



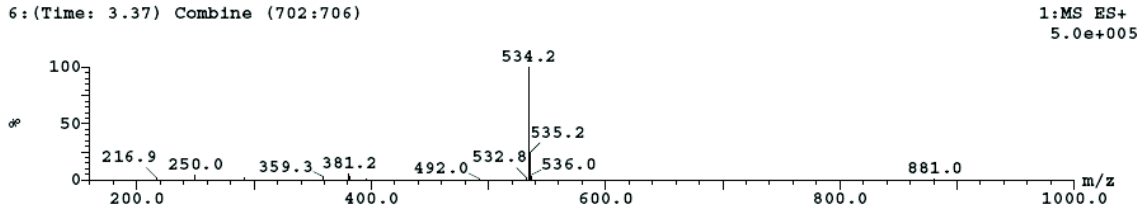
Peak ID	Compound	Time	Mass Found
4	Found	2.06	275.13



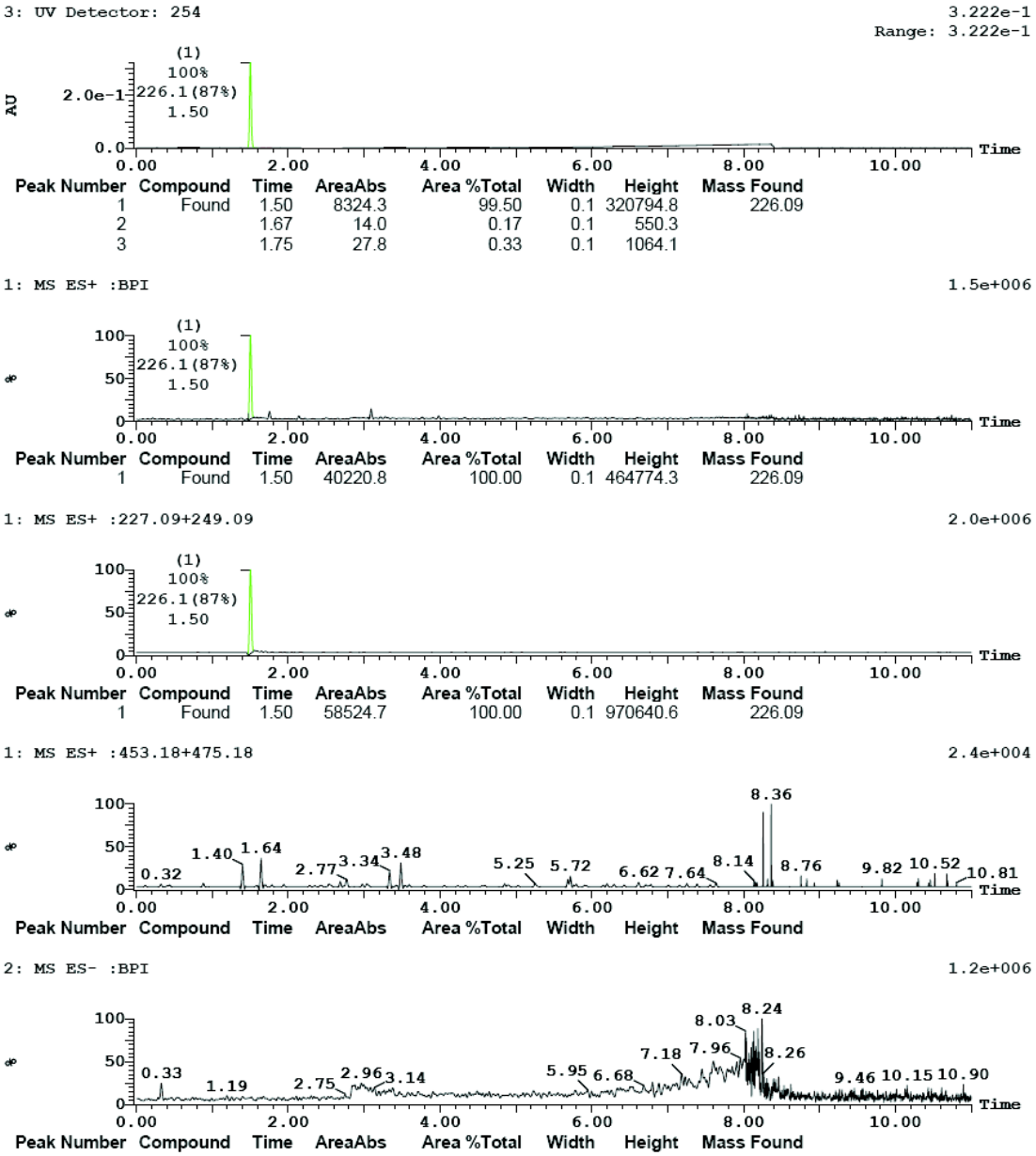
Peak ID	Compound	Time	Mass Found
5		3.17	

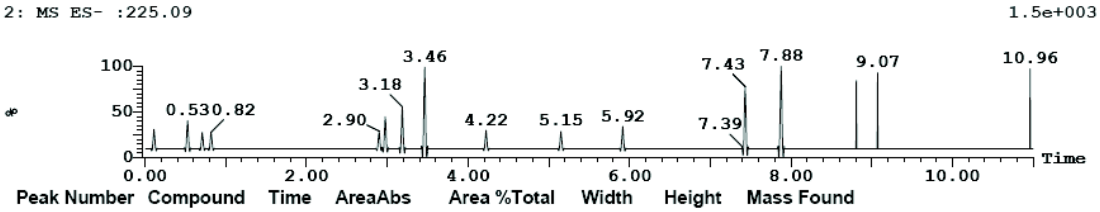


Peak ID	Compound	Time	Mass Found
6		3.37	

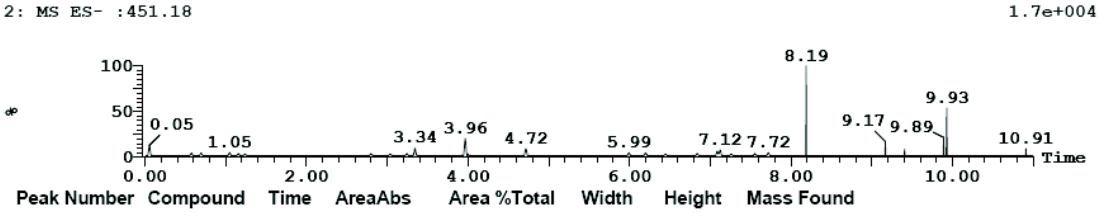


HT-LC-MS Spectrum (SOP 2200) of **5** (*meridianin A*). UV purity: 99.5 %

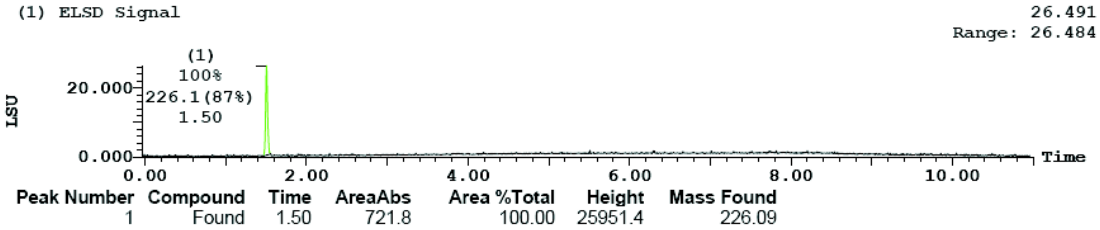




Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

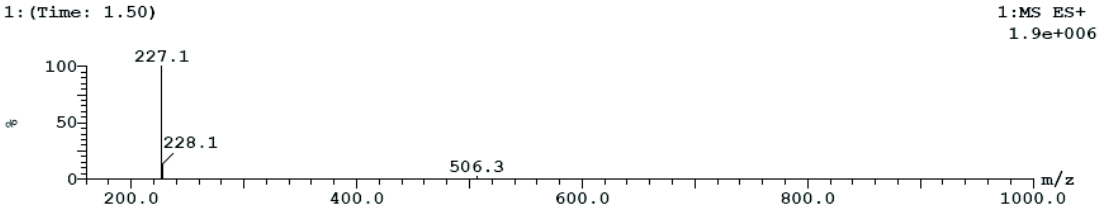


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

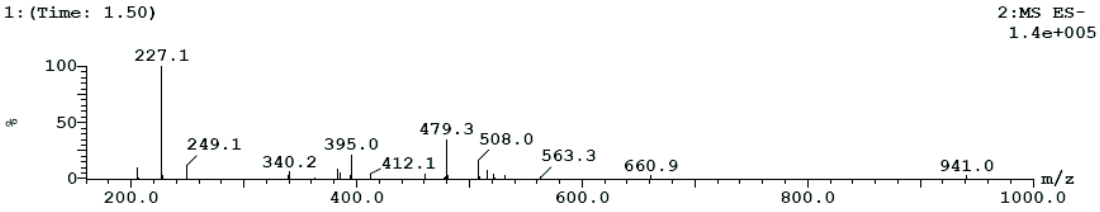


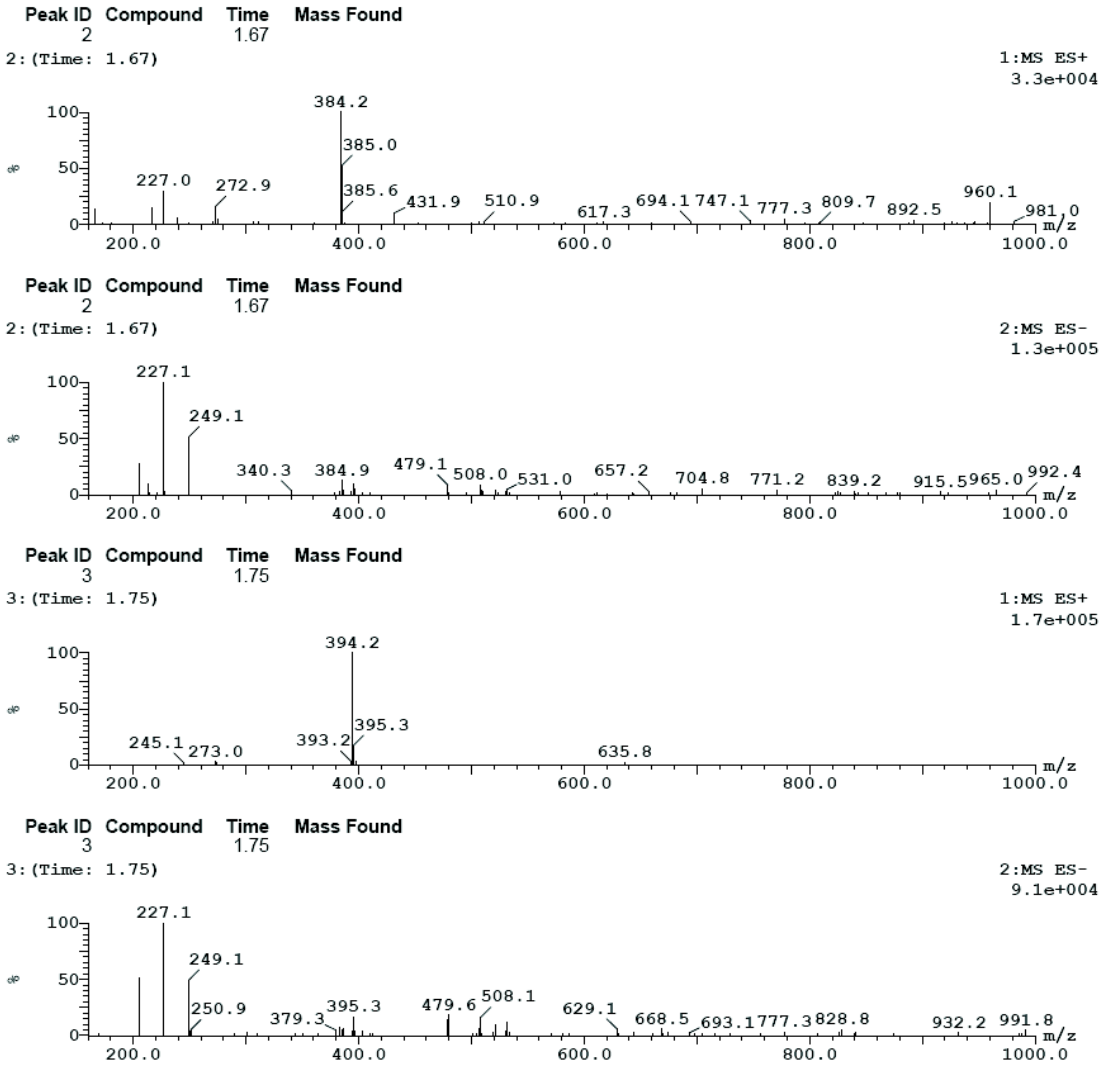
Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1	Found	1.50	721.8	100.00	25951.4	226.09

Peak ID	Compound	Time	Mass Found
1	Found	1.50	226.09



Peak ID	Compound	Time	Mass Found
1		1.50	




Peak ID Compound Time Mass Found
2 1.67
2:(Time: 1.67)
1:MS ES+
3.3e+004
384.2
385.0
227.0
272.9
385.6
431.9
510.9
617.3
694.1
747.1
777.3
809.7
892.5
960.1
981.0
m/z
Peak ID Compound Time Mass Found
2 1.67
2:(Time: 1.67)
2:MS ES-
1.3e+005
227.1
249.1
340.3
384.9
479.1
508.0
531.0
657.2
704.8
771.2
839.2
915.5
965.0
992.4
m/z
Peak ID Compound Time Mass Found
3 1.75
3:(Time: 1.75)
1:MS ES+
1.7e+005
394.2
395.3
245.1
273.0
393.2
635.8
m/z
Peak ID Compound Time Mass Found
3 1.75
3:(Time: 1.75)
2:MS ES-
9.1e+004
227.1
249.1
250.9
379.3
395.3
479.6
508.1
629.1
668.5
693.1
777.3
828.8
932.2
991.8
m/z

6.2. HT-LC-MS Methods for the Control of Identity and Purity of Compounds 4a-u and 5

Problem Definition	Identity and Purity			
SOP	2200			
Methods	HT-LC-MS			
System	Waters Acquity UPLC® with PDA and ELSD			
	Waters SQD (ESI+/- and APCI+/-)			
Software	MassLynx with OpenLynx			
Column	Waters XBridge C8 3.5 µm			
	4.6 x 50 mm Column			
	Part No. 186003053			
Eluent	A: 99.9 % acetonitrile + 0.1 % TFA			
	B: 99.9 % water + 0.1 % TFA			
Gradient	time (min)	A %	B %	flow (mL/min)
	0	5	95	2.0
	8.00	100	0	2.0
	8.10	10	90	2.0
	8.50	5	95	2.0
	11.00	5	95	2.0
Column temperature	Room temperature			
Injection volume	3 µl			
Sample Preparation	Approx. 0.1 mg were dissolved in acetonitrile + water 50/50 in an ultrasonic bath, so that the concentration was 0.5 mM.			
	If necessary, the sample was additionally diluted: 100 µl in 500 µl acetonitrile + water 5/95.			

Problem Definition	Identity and Purity			
SOP	2222			
Methods	HT-LC-MS			
System	4 x Waters 1525 Binary HPLC Pump			
	2 x Waters In-Line Degasser AF			
	1 x Waters 2777 Sample Manager			
	1 x Waters 2488 Mux-UV Detector			
	4 x Waters 2420 ELS Detector			
	1 x Waters ZQ-MUX			
Software	MassLynx with OpenLynx			
Column	Chromolith® Flash RP-18e (25-2mm)			
Eluent	A: 99.9 % acetonitrile + 0.1 % formic acid			
	B: 99.9 % water + 0.1 % formic acid			
Gradient	time (min)	A %	B %	flow (mL/min)
	0	5	95	0.8
	1.7	100	0	0.8
	3.0	100	0	0.8
	3.01	0	100	0.8
	6.25	5	95	0.8
Column temperature	Room temperature			
Throughput	416 samples: approx. 11 hours			

7. References

[1] B. Witulski, N. Buschmann, U. Bergsträßer, *Tetrahedron* **2000**, *56*, 8473-8480.

[2] E. Merkul, C. Boersch, W. Frank, T. J. J. Müller, *Org. Lett.* **2009**, *11*, 2269-2272.

[3] A. S. Karpov, E. Merkul, T. Oeser, T. J. J. Müller, *Chem. Commun.* **2005**, 2581-2583; A. S. Karpov, E. Merkul, T. Oeser, T. J. J. Müller, *Eur. J. Org. Chem.* **2006**, 2991-3000.

“One-pot synthesis of diazine-bridged bisindoles and concise synthesis of marine alkaloid hyrtinadine A”, Boris O. A. Tasch, Eugen Merkul, Thomas J. J. Müller, *Eur. J. Org. Chem*. **2011**, 4532-4535. DOI: 10.1002/ejoc.201100680.

DOI: 10.1002/ejoc.201100680

One-Pot Synthesis of Diazine-Bridged Bisindoles and Concise Synthesis of the Marine Alkaloid Hyrtinadine A

Boris O. A. Tasch,[a] Eugen Merkul,[a] and Thomas J. J. Müller*[a]

Dedicated to Prof. em. Dr. Leonhard Birkofer on the occasion of his 100th birthday

Keywords: Alkaloids / Arylation / Boron / C–C coupling / Multicomponent reactions / Palladium

Diazine-bridged bisindoles are readily obtained from *N*-Boc-protected 3-iodoindoles and 3-iodo-7-azaindole in a pseudo three-component reaction involving a one-pot Masuda borylation–Suzuki arylation sequence. Some of the title compounds display promising cytotoxic properties. The versatility of this methodology is illustrated by a very concise total synthesis of the marine alkaloid hyrtinadine A.

Introduction

Heterocycles bridging two identical indole substituents are common scaffolds in many pharmaceutically interesting natural products,[1] such as hamacanthins,[2] nortopsentins,[3] and lynamicins.[4] Inspired by marine alkaloids of the meridianin and variolin family,[5,6] we identified the structurally related, novel bisindole alkaloid hyrtinadine A (Scheme 1)[7] as a suitable target to scrutinize the scope of the Masuda borylation–Suzuki coupling sequence[8] of nitrogen heterocycles, which we applied recently in a concise synthesis of meridianin A and 7-azaindole analogues. Hyrtinadine A, isolated from an Okinawan marine sponge of the *Hyrtios* genus, was found to be highly cytotoxic against murine leukemia L1210 and human epidermoid carcinoma KB cell lines. The sole total synthesis of hyrtinadine A was realized by a Pd-catalyzed coupling of indiumorganyls as a key step.[9] Although a twofold cross-coupling with heterocyclic substrates and an unsymmetrical substitution of the pyrimidyl core were achieved, this methodology appears to be very limited. A major drawback is the overstoichiometrical use of the precious indolyl organoindium reagent, which is also associated with the need for organolithium or organomagnesium precursors not tolerant towards functional groups. Herein we report the adaptation of the Masuda borylation–Suzuki coupling sequence to diheteroaryl-substituted diazines and its application to a concise total synthesis of hyrtinadine A.

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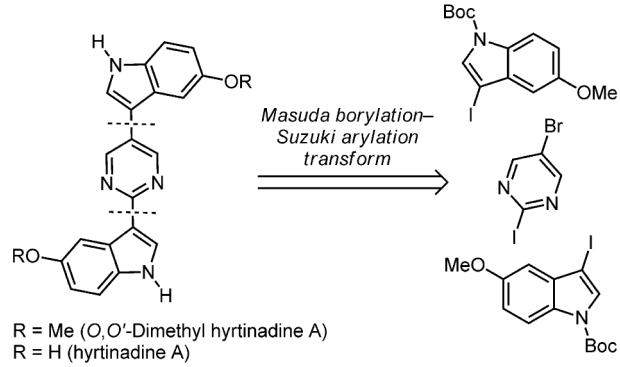
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201100680.

Results and Discussion

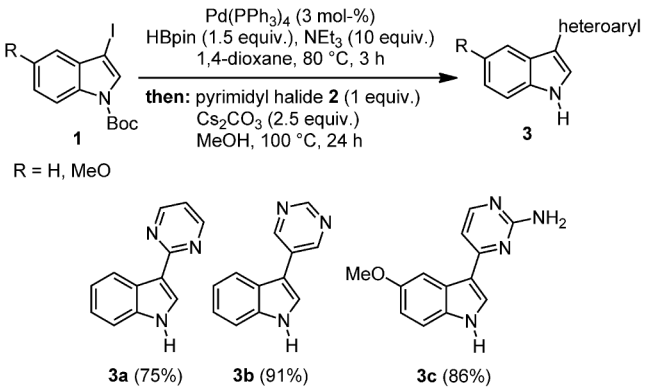
The Suzuki–Miyaura cross-coupling reaction is one of the most versatile tools for the preparation of biaryls in a short and efficient manner.[10] Pinacolboronates[11] are stable esters and can be readily applied as coupling partners in Suzuki coupling reactions. Most advantageously, their preparation proceeds by palladium-catalyzed Miyaura[12] or Masuda[13] borylation under mild conditions and tolerates a lot of polar functionality. The Masuda borylation has the advantage of using pinacolborane as a borylating agent, which is definitely more atom economical and elegant than applying bispinacolato diboron. Therefore, the advantages of performing a Masuda borylation and a subsequent Suzuki coupling in a one-pot sequence lie at hand. Prior to our studies, this sequence has not generally been used for the preparation of heteroaromatic biaryls.[14] Just recently, we established this conceptually elegant sequence for N-heterocycles, such as indoles and pyrroles,[8] which are both ubiquitous in nature and constitute important building



Scheme 1. Retrosynthetic analysis of hyrtinadine A.

blocks of many biologically active compounds with significant relevance in medicinal chemistry.[15]

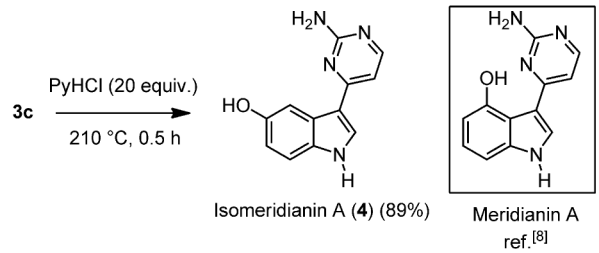
Our retrosynthetic analysis of hyrtinadine A suggests the Masuda borylation–Suzuki coupling as a key transform (Scheme 1), which is projected as a one-pot reaction in the sense of a sequentially palladium-catalyzed process.[16]



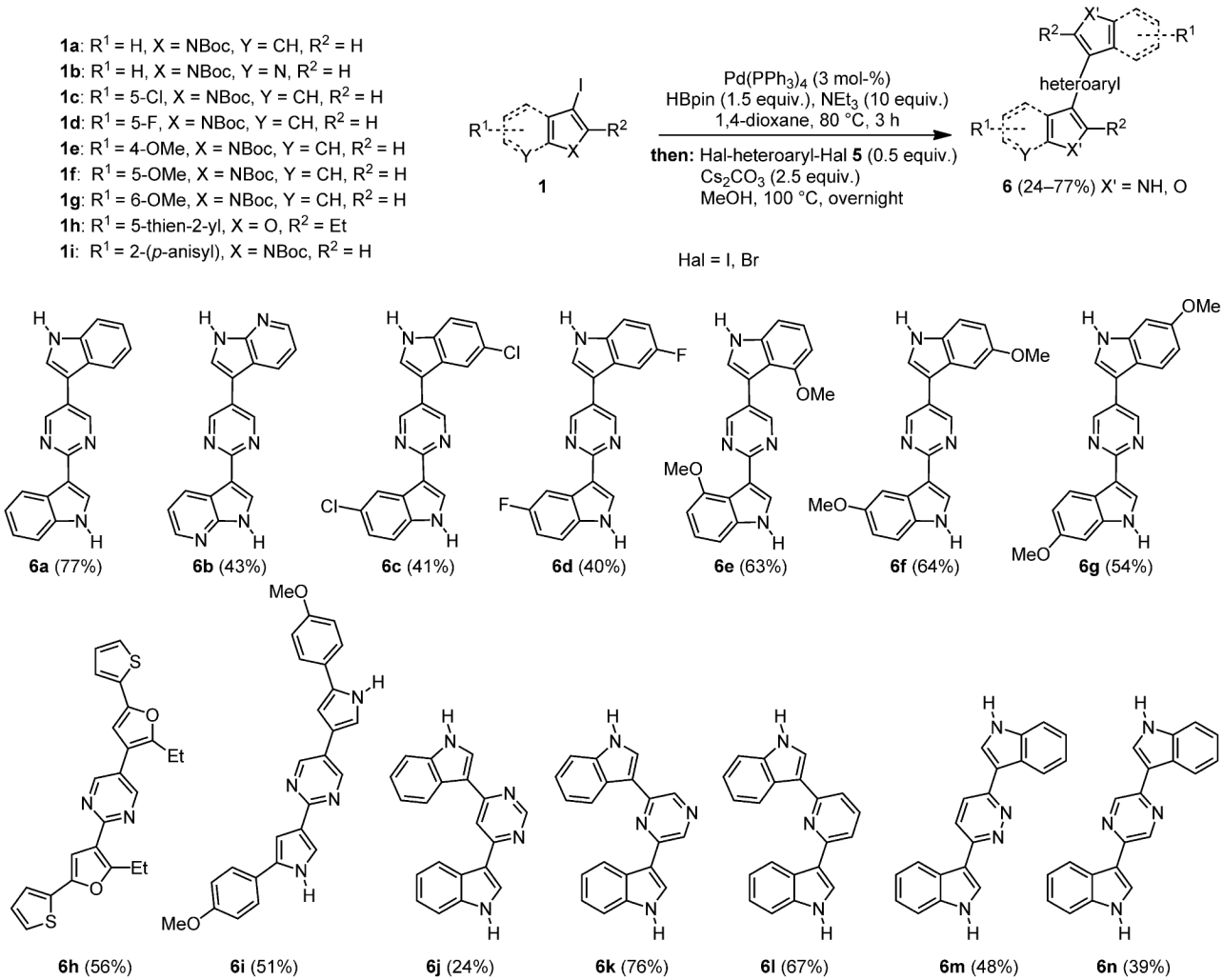
Scheme 2. One-pot Masuda borylation–Suzuki arylation synthesis of heteroaryl-substituted indoles **3**.

Moreover, the Boc protecting group is concomitantly cleaved under the terminal Suzuki conditions, accounting for the efficiency of the sequence. As a consequence, *N*-Boc-3-iodo-5-methoxyindole and 5-bromo-2-iodopyrimidine are the electrophilic coupling partners; the former is readily available from commercially available starting materials.[17]

According to this strategy, we first scouted the applicability of the sequence to the synthesis of structural subunits **3a**–**c**, using the standard conditions[8] for the sequence (Scheme 2).



Scheme 3. Synthesis of isomeridianin A (**4**) by demethylation of **3c**.



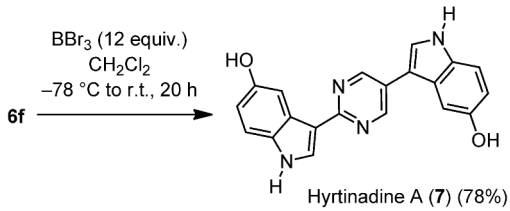
Scheme 4. One-pot Masuda borylation–Suzuki arylation synthesis of diazine-bridged bisheteroaryls **6**.

After generating the boronate intermediate by Masuda borylation of indoles **1** with pinacolborane, methanol, 2-bromopyrimidine (**2a**), 5-bromopyrimidine (**2b**), or 4-chloro-2-aminopyrimidine (**2c**), and cesium carbonate were subsequently added to the reaction mixture to give, after the Suzuki arylation step, 3-pyrimidyl-substituted indoles **3** in good to excellent isolated yields. For quenching the excess amount of pinacolborane, the addition of anhydrous methanol has proven to furnish highest yields in the two-step sequence. For demethylation of **3c**, heating in the melt of pyridinium chloride (PyHCl)[18] was applied to give the literature unknown isomeridianin A (**4**) in a very good yield (Scheme 3).

With this convenient sequential Masuda borylation–Suzuki arylation protocol in hand we set out to perform the sequence as a pseudo-three-component synthesis, that is, the ratio of the in situ generated heterocyclic pinacolester to the dihalodiazine was chosen as 2:1. Starting from 3-iodo-substituted heterocycles such as indoles **1a**, **1c**–**g**, 7-azaindole (**1b**), 2-ethyl-5-thien-2-yl-furane (**1h**),[19] and 5-(*p*-anisyl)pyrrole (**1i**),[20] after Masuda borylation with pinacolborane the Suzuki arylation step with various diiodo-, dibromo-, or bromoiodo-substituted diazines **5** furnishes bis(heteroaryl) substituted diazines **6** in a one-pot fashion in moderate to good yields (Scheme 4).

In particular, 2,5-bis(methoxyindol-3-yl)pyrimidines **6e**–**g** can be readily obtained by this one-pot procedure, with the literature unknown compound **6f** being *O*,*O*′-dimethyl hyrtinadine A, a precursor of the natural product. Thus, by virtue of the one-pot Masuda borylation–Suzuki arylation sequence as a key step, the total synthesis of hyrtinadine A can be conducted in a very concise fashion. Starting from commercially available 5-methoxy-1*H*-indole, after iodination, Boc protection, and Masuda borylation–Suzuki coupling sequence, dimethyl hyrtinadine A (**6f**) is accessible in good yield.

However, unexpectedly the final demethylation with PyHCl furnished hyrtinadine A (**7**) in only 39% yield. Therefore, we sought an alternative deprotection method.[21] Gratifyingly, demethylation of **6f** using BBr_3 gave hyrtinadine A in 78% yield (Scheme 5).



Scheme 5. Synthesis of hyrtinadine A (**7**) by demethylation of *O*,*O*′-dimethyl hyrtinadine A (**6f**).

The biological activities of *O*-methyl isomeridianin A (**3c**), isomeridianin A (**4**), selected diazine-bridged bisheteroaryls **6**, and hyrtinadine A (**7**) were evaluated by screening against a broad panel of 102–121 kinases at the Division of Signal Transduction Therapy (DSTT), University of Dundee, UK, and by determining the IC_{50} values in viability assays with HCT116 (colon carcinoma) and A2780 (ovarian carcinoma) cell lines (Table 1).[22] Interestingly, *O*,*O*′-dimethyl hyrtinadine A (**6f**) as well as the chloro analogue (**6c**) show a low micromolar activity in viability assays, which however seems not to be correlated with kinase inhibitory activity. Fascinatingly, precursor **6f** was more active than the natural product in viability assays.

Table 1. Biological data of selected compounds **3**, **4**, **6**, and **7**.

	Number of kinases with >50% inhibition at 1 μM / Number of kinases tested	IC_{50} (HCT116) [μm][a]	IC_{50} (A2780) [μm][a]
3c	7/110	>10	>10
4	8/110	>10	>10
6a	0/102	>10	>10
6b	7/121	>10	>10
6c	1/121	5.3	0.9
6e	0/121	>10	>10
6f	0/110	3.7	4.5
6m	0/121	>10	3.3
7	3/121	>10	>10

[a] IC_{50}: concentration reducing cell proliferation by 50%.

Conclusions

In summary we have successfully adapted the one-pot Masuda borylation–Suzuki arylation sequence to a general synthesis of diazine-bridged bisheteroaryls in the sense of a one-pot pseudo-three-component reaction. The procedure is another showcase for sequential Pd-catalyzed processes, which can be easily performed without the need for exotic ligands or the excessive use of expensive reagents. Besides the concise total synthesis of the marine alkaloid hyrtinadine A, several bisheteroaryl analogues have been efficiently prepared in a straightforward fashion. Studies directed towards the syntheses of structurally more complex marine alkaloids, kinase inhibitors, and oligomeric heteroarenes using the Masuda borylation–Suzuki arylation are currently underway.

Experimental Section

Synthesis of 6f: Tetrakis(triphenylphosphane)palladium(0) (69 mg, 0.06 mmol, 3 mol-%) and *tert*-butyl 3-iodo-5-methoxy-1*H*-indole-1-carboxylate (**1f**; 746 mg, 2.00 mmol) were placed under an argon atmosphere in a dry screw-cap vessel with a septum. Then, dry 1,4-dioxane (10 mL) was added, and the mixture was degassed with argon (5 min). Dry triethylamine (1.0 mL) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.45 mL, 3.00 mmol) were successively added to the mixture, which was then stirred at 80 °C (preheated oil bath) for 3 h (monitored by TLC). Then, after cooling to room temperature (water bath), dry methanol (10 mL), 5-bromo-2-iodopyrimidine (**5a**; 289 mg, 1.00 mmol), and cesium carbonate (1.63 g, 5.00 mmol) were successively added. The mixture was stirred at 100 °C overnight (preheated oil bath). Then, after cooling to room temperature, the solvents were removed under reduced pressure. The residue was purified by flash chromatography on silica gel (dichloromethane/methanol/aqueous ammonia) to give compound **6f** as a yellow solid (238 mg, 0.64 mmol, 64% yield). For full analytical details, see the Supporting Information.

Synthesis of 7 (Demethylation of Compound 6f; Synthesis of Hyrtinadine A): 3,3′-(Pyrimidine-2,5-diyl)bis(5-methoxy-1*H*-indole) (**6e**; 185 mg, 0.50 mmol) was placed in a dry screw-cap vessel under an argon atmosphere. Then, dry dichloromethane (15 mL) was added. The suspension was cooled to –78 °C (acetone/dry ice bath) and tribromoborane (0.58 mL, 6.00 mmol) was slowly added. The mixture was allowed to reach room temperature and continuously stirred for 20 h. The reaction progress was monitored by TLC. Then the mixture was cooled to 0 °C (water/ice bath), and water (3 mL) followed by saturated potassium carbonate solution (30 mL) were slowly added. The resulting yellow precipitate was filtered and purified by flash chromatography on silica gel (dichloromethane/methanol/aqueous ammonia) to give hyrtinadine A (**7**) as a yellow solid [147 mg, 0.43 mmol, 78% yield (contained one molecule of MeOH)]. For full analytical details, see the Supporting Information.

Supporting Information (see footnote on the first page of this article): Experimental procedures, spectroscopic and analytical data and copies of the NMR spectra of compounds **3**, **4**, **6**, and **7**.

Acknowledgments

The authors cordially thank Merck KGaA, Darmstadt and the Fonds der Chemischen Industrie (scholarship to B. O. A. T.) for financial support and Dr. Dieter Dorsch and Dr. Christian Sirrenberg (Merck Serono R&D, Merck KGaA Darmstadt) for providing biological tests.

[1] a) K. S. Ryan, C. S. Drennan, *Chem. Biol.* **2009**, *16*, 351–364; b) for a review on bis- and trisindols, see: L. Gupta, A. Talwar, P. M. S. Chauhan, *Curr. Med. Chem.* **2007**, *14*, 1789–1803; c) for a review on bisindoles, see: C.-G. Yang, H. Huang, B. Jiang, *Curr. Org. Chem.* **2004**, *8*, 1691–1720.

[2] a) X. Guinchard, Y. Vallée, J.-N. Denis, *Org. Lett.* **2007**, *9*, 3761–3764; b) S. P. Gunasekera, P. J. McCarthy, M. Kelly-Borges, *J. Nat. Prod.* **1994**, *57*, 1437–1441.

[3] a) P. Diana, A. Carbone, P. Barraja, A. Montalbano, A. Martorana, G. Dattolo, O. Gia, J. D. Via, G. Cirricione, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2342–2346; b) F. Y. Miyake, K. Jakushijin, D. A. Horne, *Org. Lett.* **2000**, *2*, 2121–2123.

[4] K. A. McArthur, S. S. Mitchell, G. Tsueng, A. Rheingold, D. J. White, J. Grodberg, K. S. Lam, B. C. M. Potts, *J. Nat. Prod.* **2008**, *71*, 1732–1737.

[5] For a recent review on variolins and related alkaloids, see: S. R. Walker, E. C. Carter, B. C. Huff, J. C. Morris, *Chem. Rev.* **2009**, *109*, 3080–3098.

[6] For a synthesis of meridianins by carbonylative Sonogashira coupling, see: A. S. Karpov, E. Merkul, F. Rominger, T. J. J. Müller, *Angew. Chem.* **2005**, *117*, 7112–7117; *Angew. Chem. Int. Ed.* **2005**, *44*, 6951–6956.

[7] T. Endo, M. Tsuda, J. Fromont, J. Kobayashi, *J. Nat. Prod.* **2007**, *70*, 423–424.

[8] E. Merkul, E. Schäfer, T. J. J. Müller, *Org. Biomol. Chem.* **2011**, *9*, 3139–3141.

[9] Á. Mosquera, R. Riveiros, J. P. Sestelo, L. A. Sarandeses, *Org. Lett.* **2008**, *10*, 3745–3748.

[10] a) M. Prieto, E. Zurita, E. Rosa, L. Muoz, P. Lloyd-Williams, E. Giralt, *J. Org. Chem.* **2004**, *69*, 6812–6820; b) A. Suzuki, *J. Organomet. Chem.* **2002**, *653*, 83–90; c) S. P. Stanforth, *Tetrahedron* **1998**, *54*, 263–303; d) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457–2483; e) N. Miyaura, T. Yanagi, A. Suzuki, *Synth. Commun.* **1981**, *11*, 513–519.

[11] C. E. Tucker, J. Davidson, P. Knochel, *J. Org. Chem.* **1992**, *60*, 3482–3485.

[12] T. Ishiyama, M. Murata, N. Miyaura, *J. Org. Chem.* **1995**, *60*, 7508–7510.

[13] a) K. L. Billingsley, S. L. Buchwald, *J. Org. Chem.* **2008**, *73*, 5589–5591; b) C. S. Krämer, T. J. Zimmermann, M. Sailer, T. J. J. Müller, *Synthesis* **2002**, 1163–1170; c) M. Murata, T. Oyama, S. Watanabe, Y. Masuda, *J. Org. Chem.* **2000**, *65*, 164–168; d) M. Murata, S. Watanabe, Y. Masuda, *J. Org. Chem.* **1997**, *62*, 6458–6459.

[14] a) H. A. Duong, S. Chua, P. B. Huleatt, C. L. L. Chai, *J. Org. Chem.* **2008**, *73*, 9177–9180; b) A. S. Abreu, P. M. T. Ferreira, M.-J. R. P. Queiroz, I. C. F. R. Ferreira, R. C. Calhelha, L. M. Estevinho, *Eur. J. Org. Chem.* **2005**, 2951–2957; c) P.-E. Broutin, I. Čerňa, M. Campaniello, F. Leroux, F. Colobert, *Org. Lett.* **2004**, *6*, 4419–4422; d) M. Penhoat, V. Levacher, G. Dupas, *J. Org. Chem.* **2003**, *68*, 9517–9520; e) O. Baudoin, M. Cesario, D. Guénard, F. Guéritte, *J. Org. Chem.* **2002**, *67*, 1199–1207; f) O. Baudoin, D. Guénard, F. Guéritte, *J. Org. Chem.* **2000**, *65*, 9268–9271.

[15] For recent reviews, see: a) A. J. Kochanowska-Karamyan, M. T. Hamann, *Chem. Rev.* **2010**, *110*, 4489–4497; b) H. Fan, J. Peng, M. T. Hamann, J. F. Hu, *Chem. Rev.* **2008**, *108*, 264–287.

[16] T. J. J. Müller, *Top. Organomet. Chem.* **2006**, *19*, 149–205.

[17] B. Witulski, N. Buschmann, U. Bergsträßer, *Tetrahedron* **2000**, *56*, 8473–8480.

[18] a) C. R. Schmid, C. A. Beck, J. S. Cronin, M. A. Staszak, *Org. Process Res. Dev.* **2004**, *8*, 670–673; b) V. Prey, *Ber. Dtsch. Chem. Ges.* **1941**, *74*, 1219–1225; c) V. Prey, *Ber. Dtsch. Chem. Ges.* **1942**, *75*, 350–356.

[19] For a one-pot preparation of (di)substituted (3)4-iodofurans, see: a) A. S. Karpov, E. Merkul, T. Oeser, T. J. J. Müller, *Chem. Commun.* **2005**, 2581–2583; b) A. S. Karpov, E. Merkul, T. Oeser, T. J. J. Müller, *Eur. J. Org. Chem.* **2006**, 2991–3000.

[20] For a one-pot preparation of 2-substituted *N*-Boc-4-iodopyrroles, see: E. Merkul, C. Boersch, W. Frank, T. J. J. Müller, *Org. Lett.* **2009**, *11*, 2269–2272.

[21] BBr_3 has been used for demethylation in the synthesis of hyrtiosine B: J. Bergman, T. Janosik, A.-L. Johnsson, *Synthesis* **1999**, *4*, 580–582.

[22] G. R. Nakayama, M. C. Caton, M. P. Nova, Z. Parandoosh, *J. Immunol. Methods* **1997**, *204*, 205–208. A2780 [ovarian tumor cell line; European Collection of Cell Culture (ECACC) 93112519] or HCT116 (colon tumor cell line; ATCC CCL-247) (for a description of kinase assays and viability assays, see the Supporting Information). Collaboration with Merck Serono.

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SUPPORTING INFORMATION

DOI: 10.1002/e□oc.201100□80
Title: One□Pot Synthesis o□Dia□ine□Bridged Bisindoles and Concise Synthesis o□the □arine Al□aloid Hyrtinadine A
Author(s): Boris O. A. □asch□□ugen □er□ul□□ho□as □. □. □ □ller□

Table of Contents

1 General Considerations

All cross-coupling reactions were carried out in oven-dried Schlenk glassware using septa and syringes under nitrogen or argon atmosphere. THF and 1,4-dioxane were dried using an *MBraun* system MB-SPS-800. Triethylamine was refluxed under argon over ketyl sodium, distilled and stored in a Schlenk flask over potassium hydroxide pellets under argon atmosphere. Dry methanol was purchased from *Sigma-Aldrich Chemie GmbH*. 4,4,5,5-Tetramethyl-1,3,2-dioxaborolane (pinacolyl borane) was purchased from *Sigma-Aldrich Chemie GmbH*. Tetrakis(triphenylphosphane)palladium(0) and cesium carbonate were purchased from *Merck Serono KGaA*. Commercial grade reagents were used as supplied without further purification and were purchased from *Sigma-Aldrich Chemie GmbH*, *Acros Organics N. V.*, *ABCR GmbH & Co. KG*, *Alfa Aesar GmbH & Co. KG*, *Merck Serono KGaA*, *Jiangsu* and *Synthonix Inc.*.

The purification of products was performed on silica gel 60 (0.015-0.040 mm) from *Merck Serono KGaA* using flash technique and under pressure of 2 bar. The crude mixtures were adsorbed on Celite® 545 (0.02-0.10 mm) from *Merck Serono KGaA* before chromatographic purification. The reaction progress was monitored qualitatively using TLC Silica gel 60 F_{254} 5 x 7.5 cm aluminium sheets obtained by *Merck Serono KGaA*. The spots were detected with UV light at 254 nm and using aqueous potassium permanganate solution.

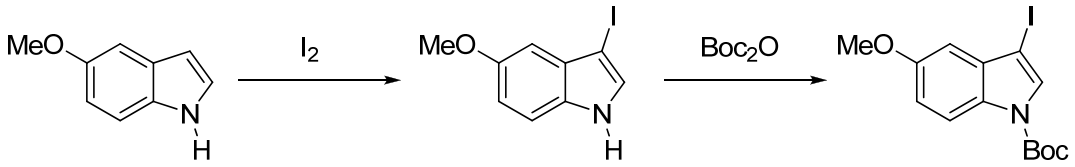
^{1}H, ^{13}C, and 135-DEPT NMR spectra were recorded on *Bruker* DRX 500 spectrometer. $CDCl_3$ and DMSO-d_6 were used as deuterated solvents. TMS was used as reference (δ 0.0) or the resonances of the solvents were locked as internal standards (acetone-d_6: ^{1}H δ 2.05, ^{13}C δ 30.8; $CDCl_3$: ^{1}H δ 7.26, ^{13}C δ 77.0; DMSO-d_6: ^{1}H δ 2.50, ^{13}C δ 39.4). The multiplicities of the signals were abbreviated as follows: s: singlet; d: doublet; t: triplet; dd: doublet of doublets; ddd: doublet of doublets of doublets; dt: doublet of triplets; td: triplet of doublets; tt: triplet of triplets; q: quartet; quint: quintet; sext: sextet; m: multiplet and br: broad signal. The type of carbon atoms was determined on the basis of 135-DEPT NMR spectra. EI mass spectra were measured on *Finnigan* MAT 8200 spectrometer. IR spectra were obtained on *Bruker* Vector 22 FT-IR. The solids were measured as KBr pellets and oils as films on KBr plates. The intensity of signals is abbreviated as follows: s (strong), m (medium) and w (weak). The melting points (uncorrected) were measured on *Reichert-Jung* Thermovar. HT-LC-MS spectra were measured in the Molecule Analytics laboratory of Central Analytical Services, *Merck Serono KGaA* Darmstadt. Combustion analyses were carried out on *Perkin Elmer* Series II Analyser 2400 in the microanalytical laboratory of Institut für Pharmazeutische und Medizinische Chemie der Heinrich-Heine-Universität Düsseldorf. Kinase assays were performed at the Division of Signal Transduction Therapy (DSTT),

University of Dundee, UK. Viability assays were performed at *Merck Serono KGaA*, Darmstadt.

2 Preparation of Starting Materials

2.1 Synthesis of *N*-Boc 3-Iodo-indoles 1[1]

2.1.1 Preparation of *tert*-butyl 3-iodo-5-methoxy-1*H*-indole-1-carboxylate (1f)



1f

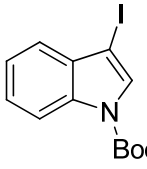
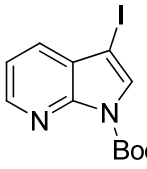
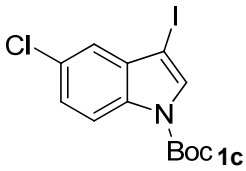
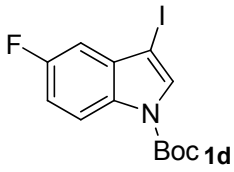
A solution of iodine (5.14 g, 20.2 mmol, 1.01 equiv) in 30 mL DMF was dropped to the solution of 5-methoxy-1*H*-indole (2.97 g, 20.0 mmol) and potassium hydroxide (3.30 g, 50.0 mmol, 2.50 equiv) in 30 mL DMF at room temperature and the mixture was stirred for 45 min. The reaction mixture was then poored on 400 mL of ice water containing 0.5 % ammonia and 0.1 % sodium disulfite. The mixture was placed in a refrigerator to ensure the complete precipitation. The precipitate was filtered, washed with 200 mL ice water and dried in vacuo to obtain 5.12 g (18.8 mmol, 94 % yield) of a beige solid. It was used without further purification for the next step.

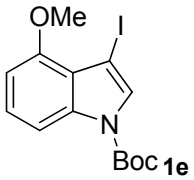
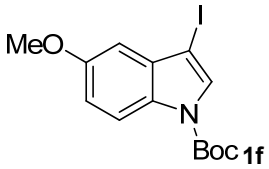
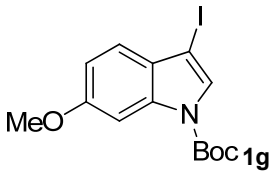
The obtained solid was suspended in 35 mL dichloromethane. 4-Dimethylaminopyridine (231 mg, 188 mmol, 10 mol %) and di-*tert*-butyl dicarbonate (6.33 g, 28.1 mmol, 1.50 equiv), dissolved in 35 mL dichloromethane, were added and the mixture was stirred for 30 min at room temperature, washed with 35 mL 0.1 *N* HCl and the aqueous phase was extracted with dichloromethane (3 x 35 mL, monitored by TLC). The combined organic layers were dried with sodium sulfate, the solvents were removed under reduced pressure, the residue was adsorbed onto Celite® and purified chromatographically on silica gel with n-hexane/ethyl acetate (He/EtOAc = 50:1), (R_f (He/EtOAc = 50:1): 0.27) to give 6.79 g (18.2 mmol, 97 % yield, 91 % total yield over two steps) of **1f** as a colorless solid.

The experimental details are given in **Table 1**.

[1] The procedure is described in B. Witulski, N. Buschmann, U. Bergsträßer, *Tetrahedron* **2000**, *56*, 8473-8480.

Table 1: Experimental details for the synthesis of *N*-Boc 3-iodo indoles **1a-g**.

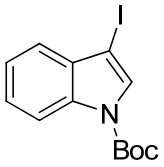
Entry	Indole	3-Iodo indole	*N*-Boc 3-Iodo indole **1** (isolated yield %)	Chromatographic purification (eluent) R_f (eluent)
1	20.0 g (171 mmol) 1*H*-Indole (*Acros*)	Yellow solid 32.8 g (135 mmol, 79 %)	Pale brown oil 11.3 g (32.9 mmol, 80 %) Total yield: 63 %  **1a**	He/EtOAc = 50:1 R_f (He/EtOAc = 50:1): 0.38
2	12.1 g (100 mmol) 1*H*-Pyrrolo[2,3-*b*]pyridine (7-Azaindole) (*ABCR*)	Yellow solid 23.7 g (97.2 mmol, 97 %)	Yellow oil 31.6 g (91.8 mmol, 94 %) Total yield: 92 %  **1b**	He/EtOAc = 20:1 R_f (He/EtOAc = 20:1): 0.14
3	0.93 g (6.00 mmol) 5-Chloro-1*H*-indole (*Aldrich*)	Yellow solid 1.04 g (3.74 mmol, 62 %)	Colorless solid 1.39 g (3.67 mmol, 99 %) Total yield: 61 %  **1c**	He/EtOAc = 50:1 R_f (He/EtOAc = 50:1): 0.41
4	0.82 g (6.00 mmol) 5-Fluoro-1*H*-indole (*Aldrich*)	Yellow solid 0.91 g (3.47 mmol, 58 %)	Colorless solid 1.25 g (3.47 mmol, quant.) Total yield: 58 %  **1d**	He/EtOAc = 50:1 R_f (He/EtOAc = 50:1): 0.41

5	1.50 g (10.0 mmol) 4-Methoxy-1*H*-indole (*ABCR*)	Grey solid 3.34 g (8.58 mmol, 86 %)	Pale yellow oil 3.08 g (8.24 mmol, 96 %) Total yield: 82 %  **1e**	He/EtOAc = 50:1 R_f (He/EtOAc = 50:1): 0.21
6	2.97 g (20.0 mmol) 5-Methoxy-1*H*-indole (*ABCR*)	Beige solid 5.12 g (18.8 mmol, 94 %)	Colorless solid 6.79 g (18.2 mmol, 97 %) Total yield: 91 %  **1f**	He/EtOAc = 50:1 R_f (He/EtOAc = 50:1): 0.27
7	0.80 g (5.40 mmol) 6-Methoxy-1*H*-indole (*Merck*)[1]	Yellow solid 1.27 g (4.67 mmol, 86 %)	Pale yellow solid 1.61 g (4.32 mmol, 94 %) Total yield: 81 %  **1g**	He/EtOAc = 20:1 R_f (He/EtOAc = 20:1): 0.38

[1] 6-Methoxy-1*H*-indole was prepared in the laboratories of *Merck Serono KGaA*, Darmstadt, and chromatographically purified with n-hexane/ethyl acetate (He/EtOAc = 1:1) before use.

2.2 Spectroscopic Data of *N*-Boc 3-Iodo-indoles 1

2.2.1 *tert*-Butyl 3-iodo-1*H*-indole-1-carboxylate (1a)



$C_{13}H_{14}INO_2$

343.16

11.3 g (32.9 mmol, 63 % yield over two steps) as a pale brown oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.66 (s, 9 H), 7.28-7.32 (m, 1 H), 7.33-7.36 (m, 1 H), 7.36-7.40 (m, 1 H), 7.72 (s, 1 H), 8.12 (d, *J* = 7.3 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 28.1 (CH_3), 65.4 (C_{quat}), 84.2 (C_{quat}), 115.0 (CH), 121.4 (CH), 123.3 (CH), 125.3 (CH), 130.0 (CH), 132.0 (C_{quat}), 134.8 (C_{quat}), 148.6 (C_{quat}). EI + MS (*m*/*z* (%)): 343 (M^+, 14), 287 ((M-C_4H_9+H)$^+$, 59), 270 ((M-C_4H_9O+H)$^+$, 6), 243 ((M-$C_5H_9O_2$+H)$^+$, 79), 116 ($C_8H_6N^+$, 30), 115 ($C_8H_5N^+$, 22), 88 (10), 57 ($C_4H_9^+$, 100), 41 (13). IR (film): $\tilde{\nu}$ 3151 (w), 3052 (w), 2979 (m), 2932 (w), 1747 (s), 1731 (s), 1606 (w), 1528 (w), 1476 (m), 1449 (s), 1375 (s), 1358 (s), 1336 (m), 1311 (m), 1249 (m), 1211 (m), 1148 (m), 1112 (m), 1054 (m), 1016 (w), 938 (w), 854 (w), 800 (w), 769 (m), 745 (m), 672 (w), 589 (w) cm^{-1}. Anal. calcd. for $C_{13}H_{14}INO_2$ (343.2): C 45.50, H 4.11, N 4.08. Found: C 45.24, H 4.30, N 3.89.

Data reported in the literature:[1]

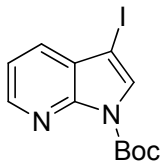
Colorless solid (*n*-pentane), mp: 36-40 °C. ^{1}H NMR (400 MHz): δ 1.68 (s, 9 H), 7.29-7.43 (m, 3 H), 7.73 (s, 1 H), 8.13 (d, *J* = 8.1 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 28.1 (q), 65.4 (s), 115.1 (d), 121.5 (d), 123.3 (d), 125.3 (d), 130.1 (d), 132.0 (s), 134.9 (s), 148.7 (s). EI + MS (*m*/*z* (%)): 343 (M^+, 69), 287 (100), 270 (13), 243 (98), 116 (28), 57 (98). Anal. calcd. for $C_{13}H_{14}INO_2$ (343.16): C 45.50, H 4.11, N 4.08. Found C 45.37, H 3.66, N 3.96.

Data reported in the literature:[2]

^{1}H NMR ($CDCl_3$): δ 1.69 (s, 9 H), 7.20-7.41 (m, 3 H), 7.72 (s, 1 H), 8.15 (d, *J* = 5.0 Hz, 1 H).

[2] T. A. Kelly, D. W. McNeil, J. M. Rose, E. David, C.-K. Shih, P. M. Grob, *J. Med. Chem.* **1997**, *40*, 2430-2433.

2.2.2 *tert*-Butyl 3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (1b)



$C_{12}H_{13}IN_2O_2$

344.15

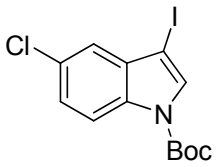
31.6 g (91.8 mmol, 92 % yield over two steps) as a yellow oil (solidified upon storage in refrigerator), mp: 79 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.66 (s, 9 H), 7.22 (dd, *J* = 7.9 Hz, *J* = 4.7 Hz, 1 H), 7.61 (dd, *J* = 7.9 Hz, *J* = 1.6 Hz, 1 H), 7.78 (s, 1 H), 8.50 (dd, *J* = 4.7 Hz, *J* = 1.6 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 27.4 (CH_3), 61.3 (C_{quat}), 83.8 (C_{quat}), 118.5 (CH), 124.3 (C_{quat}), 128.9 (CH), 129.9 (CH), 145.3 (CH), 146.0 (C_{quat}), 146.6 (C_{quat}). EI + MS (*m*/*z* (%)): 344 (M^+, 4), 245 (8), 244 ((M-$C_5H_9O_2$+H)$^+$, 100), 117 ($C_7H_5N_2^+$, 23), 116 ($C_7H_4N_2^+$, 10), 90 (10), 57 ($C_4H_9^+$, 26).

Data reported in the literature:[3]

^{1}H NMR ($CDCl_3$): δ 1.70 (s, 9 H), 7.28 (dd, *J* = 8.5 Hz, 1 H), 7.72 (dd, *J* = 8.1 Hz, 1 H), 7.80 (s, 1 H), 8.49 (dd, *J* = 5.1 Hz, 1 H).

[3] T. A. Kelly, D. W. McNeil, J. M. Rose, E. David, C.-K. Shih, P. M. Grob, *J. Med. Chem.* **1997**, *40*, 2430-2433.

2.2.3 *tert*-Butyl 5-chloro-3-iodo-1*H*-indole-1-carboxylate (1c)

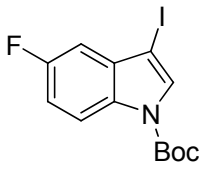


$C_{13}H_{13}ClINO_2$

377.61

1.39 g (3.67 mmol, 61 % yield over two steps) as a colorless solid, mp: 106 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.66 (s, 9 H), 7.31 (dd, *J* = 8.8 Hz, *J* = 2.0 Hz, 1 H), 7.38 (d, *J* = 2.0 Hz, 1 H), 7.73 (s, 1 H), 8.03-8.08 (m, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 28.1 (CH_3), 64.0 (C_{quat}), 84.8 (C_{quat}), 116.2 (CH), 121.2 (CH), 125.6 (CH), 129.2 (C_{quat}), 131.3 (CH), 133.3 (C_{quat}), 133.4 (C_{quat}), 148.3 (C_{quat}). EI + MS (*m*/*z* (%)): 377 (M^+, 8), 320 (29), 279 (14), 278 (6), 277 ((M-$C_5H_9O_2$+H)$^+$, 43), 150 (16), 114 (20), 57 (100), 41 (15). IR (KBr): $\tilde{\nu}$ 3001 (w), 2970 (w), 2932 (w), 2916 (w), 2866 (w), 1749 (w), 1732 (s), 1475 (w), 1460 (w), 1445 (m), 1394 (w), 1358 (s), 1339 (w), 1308 (w), 1267 (m), 1248 (s), 1203 (m), 1151 (s), 1121 (m), 1053 (s), 1038 (m), 953 (m), 937 (w), 856 (m), 839 (w), 810 (w), 793 (s), 760 (m), 721 (m), 633 (m) cm^{-1}. Anal. calcd. for $C_{13}H_{13}ClINO_2$ (377.6): C 41.35, H 3.47, N 3.71. Found: C 41.49, H 3.57, N 3.64.

2.2.4 *tert*-Butyl 5-fluoro-3-iodo-1*H*-indole-1-carboxylate (1d)

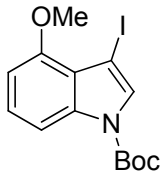


$C_{13}H_{13}FINO_2$

361.15

1.25 g (3.47 mmol, 58 % yield over two steps) as a colorless solid, mp: 76 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.66 (s, 9 H), 7.05-7.10 (m, 2 H), 7.75 (s, 1 H), 8.09 (br, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 28.1 (CH_3), 64.4 (d, *J* = 4.1 Hz, C_{quat}), 84.6 (C_{quat}), 107.2 (d, *J* = 24.9 Hz, CH), 113.3 (d, *J* = 25.1 Hz, CH), 116.3 (d, *J* = 9.0 Hz, CH), 131.2 (C_{quat}), 131.6 (CH), 133.3 (d, *J* = 10.1 Hz, C_{quat}), 148.4 (C_{quat}), 159.9 (d, *J* = 240.6 Hz, C_{quat}). EI + MS (*m*/*z* (%)): 361 (M^+, 10), 305 (32), 261 ((M-$C_5H_9O_2$+H)$^+$, 51), 134 (24), 133 (21), 57 ($C_4H_9^+$, 100). IR (KBr): $\tilde{\nu}$ 2980 (m), 2887 (w), 2357 (w), 2332 (w), 1730 (m), 1603 (w), 1589 (w), 1472 (m), 1456 (w), 1441 (m), 1396 (w), 1366 (s), 1348 (m), 1337 (w), 1308 (w), 1252 (s), 1240 (m), 1202 (m), 1148 (s), 1105 (m), 1072 (w), 1053 (m), 1036 (m), 972 (m), 945 (w), 843 (s), 812 (m), 795 (s), 758 (m), 744 (m), 698 (w), 685 (w), 662 (m), 648 (w), 611 (m) cm^{-1}. Anal. calcd. for $C_{13}H_{13}FINO_2$ (361.2): C 43.23, H 3.63, N 3.88. Found: C 43.15, H 3.82, N 3.78.

2.2.5 *tert*-Butyl 3-iodo-4-methoxy-1*H*-indole-1-carboxylate (1e)

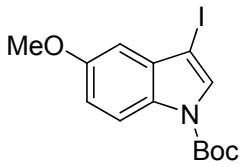


$C_{14}H_{16}INO_3$

373.19

3.08 g (8.24 mmol, 82 % yield over two steps) as a pale yellow oil (solidified upon storage in refrigerator), mp: 68 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.64 (s, 9 H), 3.92 (s, 3 H), 6.67 (d, *J* = 8.2 Hz, 1 H), 7.24 (t, *J* = 8.2 Hz, 1 H), 7.61 (s, 1 H), 7.80 (d, *J* = 8.2 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 28.1 (CH_3), 55.4 (CH_3), 57.6 (C_{quat}), 84.2 (C_{quat}), 104.0 (CH), 108.0 (CH), 119.6 (C_{quat}), 125.9 (CH), 130.0 (CH), 136.5 (C_{quat}), 148.5 (C_{quat}), 153.2 (C_{quat}). EI + MS (*m*/*z* (%)): 373 (M^+, 33), 317 ((M-C_4H_9+H)$^+$, 100), 273 ((M-$C_5H_9O_2$+H)$^+$, 56), 258 ((M-$C_5H_9O_2$-CH_3+H)$^+$, 23), 57 ($C_4H_9^+$, 83). IR (film): $\tilde{\nu}$ 3151 (w), 2979 (s), 2937 (m), 2837 (w), 1732 (s), 1606 (m), 1586 (s), 1494 (s), 1427 (s), 1394 (m), 1370 (s), 1339 (s), 1286 (s), 1153 (s), 1124 (s), 1046 (s), 955 (w), 903 (w), 852 (m), 819 (w), 775 (m), 735 (m), 696 (w), 668 (w), 597 (w) cm^{-1}. Anal. calcd. for $C_{14}H_{16}INO_3$ (373.2): C 45.06, H 4.32, N 3.75. Found: C 45.07, H 4.11, N 3.56.

2.2.6 *tert*-Butyl 3-iodo-5-methoxy-1*H*-indole-1-carboxylate (1f)



$C_{14}H_{16}INO_3$

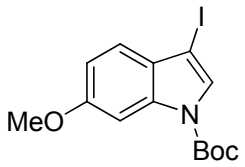
373.19

6.79 g (18.2 mmol, 91 % yield over two steps) as a colorless solid, mp: 114 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.65 (s, 9 H), 3.89 (s, 3 H), 6.83 (d, *J* = 2.5 Hz, 1 H), 6.96 (dd, *J* = 8.8 Hz, *J* = 2.5 Hz, 1 H), 7.70 (s, 1 H), 8.0 (br, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 28.1 (CH_3), 55.7 (CH_3), 65.1 (C_{quat}), 84.1 (C_{quat}), 103.6 (CH), 114.5 (CH), 116.0 (CH), 129.4 (C_{quat}), 130.5 (CH), 132.9 (C_{quat}), 148.6 (C_{quat}), 156.5 (C_{quat}). EI + MS (*m*/*z* (%)): 373 (M^+, 41), 317 ((M-C_4H_9+H)$^+$, 100), 273 ((M-$C_4H_9O_2$+H)$^+$, 65), 258 ((M-$C_5H_9O_2$-CH_3+H)$^+$, 22). IR (KBr): $\tilde{\nu}$ 3158 (w), 3003 (w), 2978 (w), 2934 (w), 2836 (w), 1855 (w), 1729 (w), 1656 (w), 1622 (w), 1579 (w), 1528 (w), 1482 (m), 1439 (m), 1372 (s), 1280 (m), 1250 (s), 1204 (m), 1161 (s), 1120 (m), 1054 (m), 1028 (m), 959 (w), 931 (w), 845 (m), 802 (m), 783 (m), 753 (m), 669 (m), 626 (w), 558 (w) cm^{-1}. Anal. calcd. for $C_{14}H_{16}INO_3$ (373.2): C 45.06, H 4.32, N 3.75. Found: C 45.20, H 4.43, N 4.00.

Data reported in the literature:[3]

^{1}H NMR ($CDCl_3$): δ 1.63 (s, 9 H), 3.89 (s, 3 H), 6.83 (d, *J* = 1.0 Hz, 1 H), 7.00 (dd, *J* = 5.1 Hz, 1 H), 7.69 (s, 1 H), 8.01 (d, *J* = 5.0 Hz, 1 H). MS (CI) (*m*/*z*, (%)) 374 ((M+H)$^+$, 65), 318 (100).

2.2.7 *tert*-Butyl 3-iodo-6-methoxy-1*H*-indole-1-carboxylate (1g)

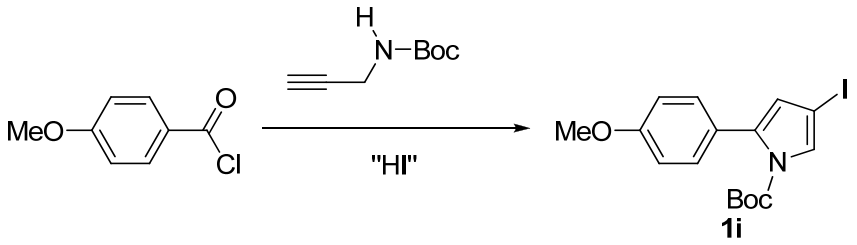


$C_{14}H_{16}INO_3$

373.19

1.61 g (4.32 mmol, 81 % yield over two steps) as a pale yellow solid, mp: 135 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.66 (s, 9 H), 3.88 (s, 3 H), 6.93 (dd, *J* = 8.6 Hz, *J* = 2.3 Hz, 1 H), 7.25-7.26 (m, 1 H), 7.59 (s, 1 H), 7.73 (br, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 28.1 (CH_3), 55.7 (CH_3), 65.2 (C_{quat}), 84.1 (C_{quat}), 98.2 (CH), 112.8 (CH), 122.0 (CH), 125.9 (C_{quat}), 128.7 (CH), 135.7 (C_{quat}), 148.8 (C_{quat}), 158.6 (C_{quat}). EI + MS (*m*/*z* (%)): 373 (M^+, 14), 318 ((M-C_4H_9+2H)$^+$, 10), 317 ((M-C_4H_9+H)$^+$, 100), 273 ((M-$C_4H_9O_2$+H)$^+$, 67), 272 (12), 258 ((M-$C_5H_9O_2$-CH_3+H)$^+$, 51), 57 ($C_4H_9^+$, 72). IR (KBr): $\tilde{\nu}$ 3165 (w), 3009 (w), 2988 (w), 2968 (w), 2930 (w), 2905 (w), 2887 (w), 2831 (w), 1726 (s), 1618 (w), 1541 (w), 1526 (w), 1487 (m), 1456 (w), 1441 (m), 1369 (s), 1327 (s), 1306 (w), 1288 (w), 1259 (m), 1223 (s), 1159 (s), 1148 (s), 1136 (m), 1105 (m), 1049 (m), 1032 (s), 960 (m), 924 (w), 887 (w), 858 (w), 833 (m), 797 (m), 762 (m), 735 (w), 633 (w), 623 (w) cm^{-1}. Anal. calcd. for $C_{14}H_{16}INO_3$ (373.2): C 45.06, H 4.32, N 3.75. Found: C 45.07, H 4.56, N 3.57.

2.3 Preparation of *tert*-butyl 4-iodo-2-(4-methoxyphenyl)-1*H*-pyrrole-1-carboxylate (1i)[4]



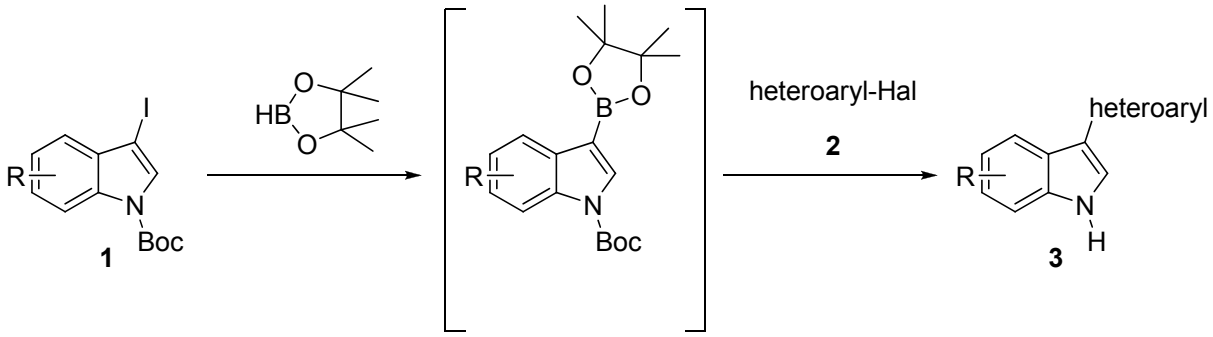
1i

$PdCl_2(PPh_3)_2$ (425 mg, 0.60 mmol, 2 mol %) and CuI (233 mg, 1.20 mmol, 4 mol %) were placed under argon atmosphere in a dry screw-cap vessel. Then, 150 mL of dry THF were added and the mixture was degassed with argon (5 min). Dry triethylamine (4.16 mL, 30.0 mmol), 4-methoxybenzoyl chloride (5.28 g, 30.0 mmol), and *tert*-butyl prop-2-ynylcarbamate (4.66 g, 30.0 mmol) were successively added to the mixture, which was stirred at room temperature for 1 h (monitored by TLC). Then, sodium iodide (22.7 g, 150 mmol), toluene-4-sulfonic acid monohydrate (11.6 g, 60.0 mmol) and 30 mL of *tert*-butanol were successively added to the mixture, which was stirred at room temperature for 1 h (monitored by TLC). The reaction mixture was diluted with 300 mL brine, the phases were separated and the aqueous phase was extracted with dichloromethane (3 x 150 mL). The combined organic layers were dried with anhydrous sodium sulfate. After filtration and removal of the solvents under reduced pressure, the residue was absorbed onto Celite® and purified chromatographically on silica gel with petroleum ether (boiling range 40-60 °C)/ethyl acetate (PE/EtOAc = 100:1) to give 9.23 g (23.1 mmol, 77 % yield) of the desired product (**1i**) as a colorless solid.

[4] The procedure is described in E. Merkul, C. Boersch, W. Frank, T. J. J. Müller, *Org. Lett.* **2009**, *11*, 2269-2272.

3 Preparation of Compounds 3 and 6 by the *Masuda* Borylation–*Suzuki* Coupling Sequence

3.1 Synthesis of Biaryls 3a-c by the *Masuda* Borylation–*Suzuki* Coupling Sequence



Tetrakis(triphenylphosphane)-palladium(0) (35 mg, 0.03 mmol, 3 mol %) and *tert*-butyl 3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (**1a**) (344 mg, 1.00 mmol) were placed under argon atmosphere in a dry screw-cap vessel with septum. Then, 5 mL of dry 1,4-dioxane were added and the mixture was degassed with argon (5 min). Dry triethylamine (1.39 mL, 10.0 mmol) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.22 mL, 1.50 mmol) were successively added to the mixture, which was stirred at 80 °C (preheated oil bath) for 3 h (monitored by TLC). Then, after cooling to room temperature (water bath), 5 mL of dry methanol, 1.00 mmol of heteroaryl halide **2**, and cesium carbonate (823 mg, 2.50 mmol) were successively added. The mixture was stirred at 100 °C overnight (preheated oil bath). Then, after cooling to room temperature, the solvents were removed under reduced pressure, the residue was absorbed onto Celite® and purified chromatographically on silica gel with dichloromethane/methanol/aqueous ammonia. The obtained compounds **3** can be further purified by suspending in dichloromethane, sonication for 0.5-1 h in an ultrasound bath, filtration and drying under reduced pressure overnight.

The experimental details are given in **Table 2** and **Table 3**.

Table 2: Experimental details for the synthesis of biaryls **3a-c**.

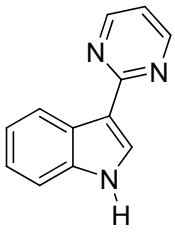
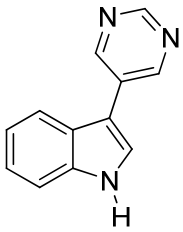
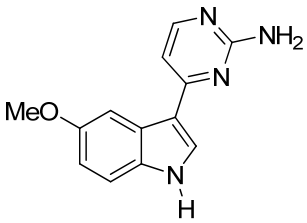
Entry	Substrate **1**	Heteroarylhalide **2**	Biaryl **3** (isolated yield %)	Chromatographic purification (eluent) UV purity
1	343 mg (1.00 mmol) **1a**	162 mg (1.00 mmol) 2-Bromopyrimidine (*ABCR*) **2a**	Pale beige solid 146 mg (0.75 mmol, 75 %)  **3a**	DCM/MeOH/NH_3 = 100:1:1
2	343 mg (1.00 mmol) **1a**	161 mg (1.00 mmol) 5-Bromopyrimidine (*Synthonix*) **2b**	Pale yellow solid 178 mg (0.91 mmol, 91 %)  **3b**	DCM/MeOH/NH_3 = 100:1:1
3	746 mg (2.00 mmol) **1f**	259 mg (2.00 mmol) 4-Chloropyrimidin-2-amine (*Synchem*) **2c**	Yellow solid 413 mg (1.72 mmol, 86 %)  **3c**	DCM/MeOH/NH_3 = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 HT-LC-MS: 100 %

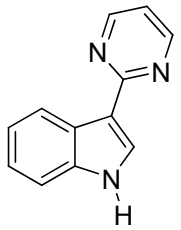
Table 3: Reaction times in the synthesis of biaryls **3a-c**.[1]

Entry	Biaryl **3**	*Masuda* borylation step	*Suzuki* coupling step
1	**3a**	3 h	24 h
2	**3b**	3 h	24 h
3	**3c**	3 h	24 h

[1] The reaction times for the *Suzuki* coupling step are not optimized. The actual reaction times might be much shorter than indicated. The actual reaction times for the *Masuda* borylation step may also be shorter in some cases.

3.2 Spectroscopic Data of Biaryls 3

3.2.1 3-(Pyrimidin-2-yl)-1*H*-indole (3a)

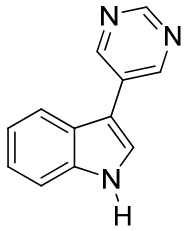


$C_{12}H_9N_3$

195.22

146 mg (0.75 mmol, 75 % yield) as a pale beige solid, mp: 158 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.12-7.13 (m, 3 H), 7.45-7.49 (m, 1 H), 8.22 (d, *J* = 2.5 Hz, 1 H), 8.51-8.54 (m, 1 H), 8.76 (d, *J* = 5.0 Hz, 2 H), 11.7 (br, 1 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 111.9 (CH), 114.7 (C_{quat}), 177.0 (CH), 120.4 (CH), 121.9 (CH), 121.9 (CH), 125.5 (C_{quat}), 129.2 (CH), 137.0 (C_{quat}), 157.0 (CH), 163.7 (C_{quat}). EI + MS (*m*/*z* (%)): 195 (M^+, 100), 168 (5), 167 (6), 142 ((M-$C_3H_3N)^+$, 48), 115 (14), 88 (6), 57 (6). IR (KBr): $\tilde{\nu}$ 3141 (w), 2906 (w), 1618 (w), 1578 (m), 1539 (s), 1453 (m), 1422 (m), 1357 (m), 1271 (w), 1235 (w), 1175 (w), 1130 (w), 1102 (w), 1010 (w), 975 (w), 804 (w), 757 (m), 642 (w), 578 (w) cm^{-1}. Anal. calcd. for $C_{12}H_9N_3$ (195.2): C 73.83, H 4.65, N 21.52. Found: C 73.86, H 4.63, N 21.51.

3.2.2 3-(Pyrimidin-5-yl)-1*H*-indole (3b)

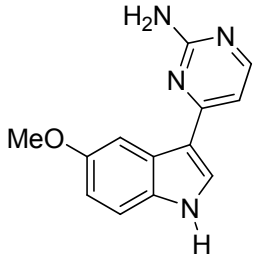


$C_{12}H_9N_3$

195.22

178 mg (0.91 mmol, 91 % yield) as a pale yellow solid, mp: 218 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.12-7.17 (m, 1 H), 7.18-7.23 (m, 1 H), 7.48-7.52 (m, 1 H), 7.92 (d, *J* = 7.9 Hz, 1 H), 7.99 (d, *J* = 2.5 Hz, 1 H), 9.04 (s, 1 H), 9.16 (s, 2 H), 11.7 (br, 1 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 108.5 (C_{quat}), 112.2 (CH), 118.9 (CH), 120.4 (CH), 122.0 (CH), 124.5 (C_{quat}), 125.1 (CH), 130.0 (C_{quat}), 136.9 (C_{quat}), 153.6 (CH), 155.1 (CH). EI + MS (*m*/*z* (%)): 195 (M^+, 100), 194 ($(M-H)^+$, 21), 141 (23), 140 (22), 117 (11), 114 (11), 113 (13), 111 (16), 109 (11), 97 (25), 95 (16), 85 (19), 83 (21), 81 (15), 71 (30), 70 (15), 69 (17), 57 (26), 55 (16), 43 (9). IR (KBr): $\tilde{\nu}$ 3166 (m), 3107 (s), 3064 (m), 2979 (m), 2938 (m), 1620 (w), 1581 (m), 1556 (m), 1536 (s), 1454 (m), 1418 (w), 1312 (w), 1275 (w), 1252 (w), 1168 (s), 1123 (w), 1094 (w), 1016 (w), 959 (w), 879 (w), 766 (w), 732 (s), 717 (w), 641 (w), 622 (w) cm^{-1}. Anal. calcd. for $C_{12}H_9N_3$ (195.2): C 73.83, H 4.65, N 21.52. Found: C 73.57, H 4.94, N 21.23.

3.2.3 4-(5-Methoxy-1*H*-indol-3-yl)pyrimidin-2-amine (3c)



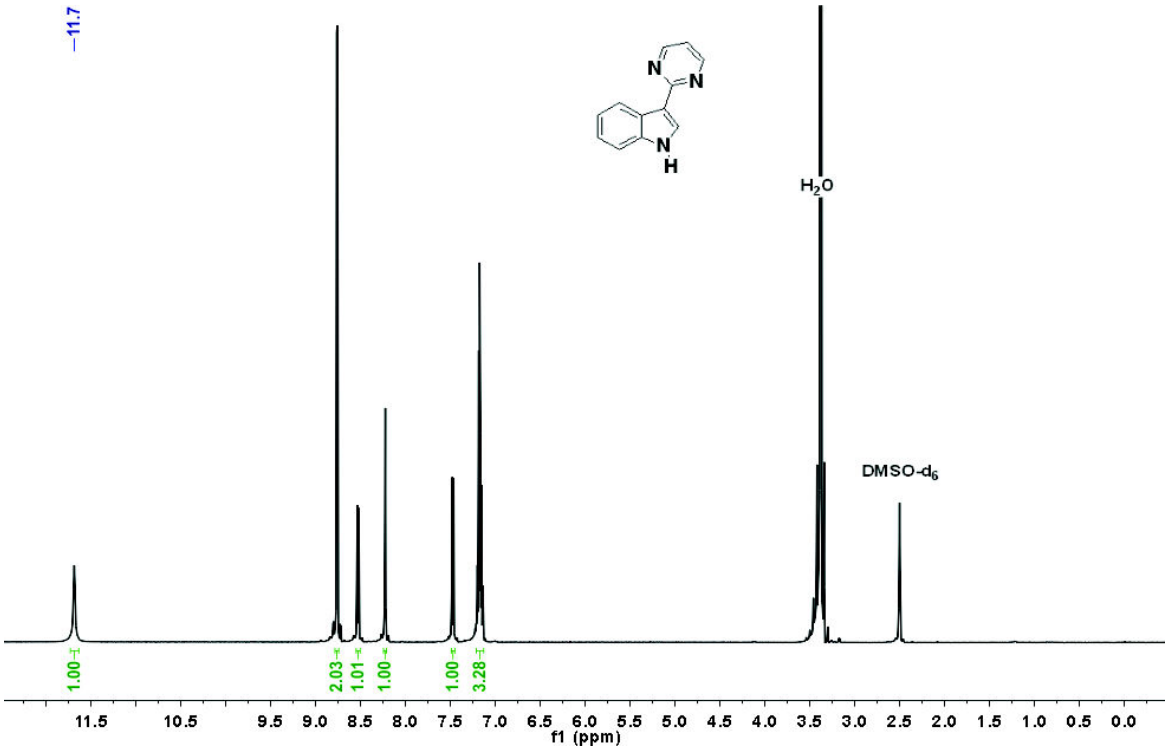
$C_{13}H_{12}N_4O$

240.26

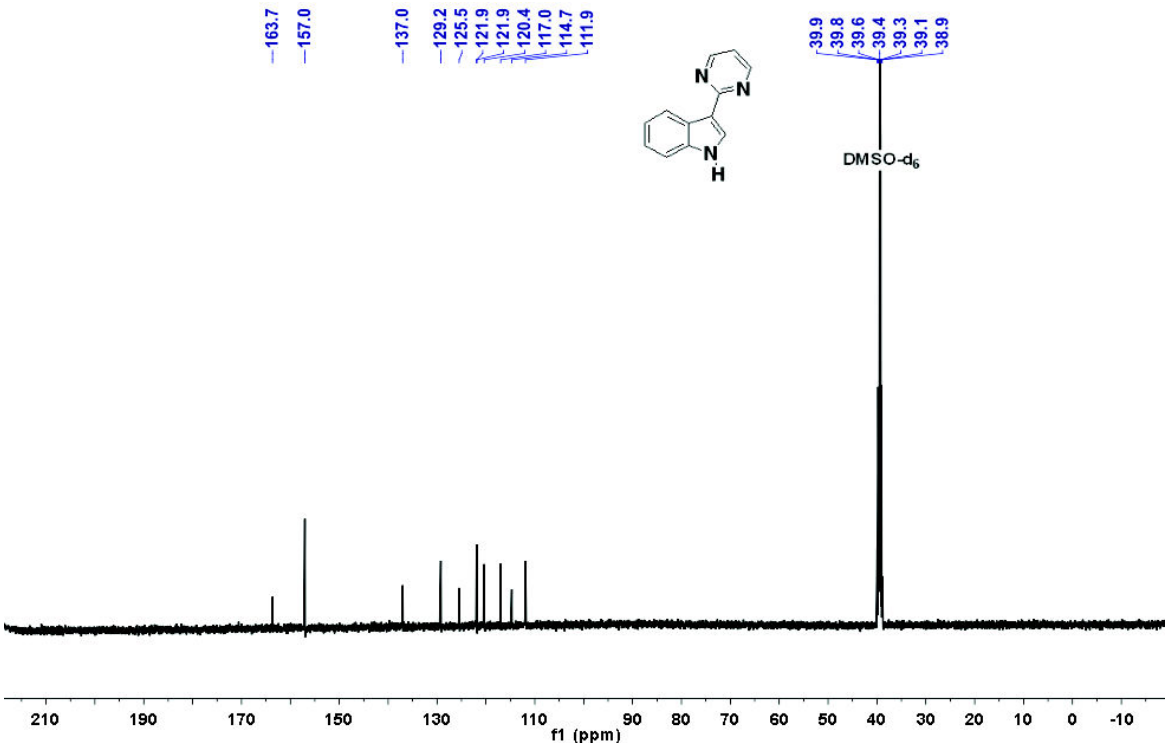
413 mg (1.72 mmol, 86 % yield) as a colorless solid, mp: 204 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 3.84 (s, 3 H), 6.44 (s, 2 H, N$\underline{H}_2$), 6.82 (dd, *J* = 8.5 Hz, *J* = 2.5 Hz, 1 H), 6.99 (d, *J* = 5.4 Hz, 1 H), 7.33 (d, *J* = 8.8 Hz, 1 H), 8.09 (d, *J* = 5.4 Hz, 1 H), 8.12 (d, *J* = 2.5 Hz, 1 H), 8.15 (d, *J* = 2.8 Hz, 1 H), 11.6 (br, 1 H, N$\underline{H}$). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 55.4 (CH_3), 104.4 (CH), 105.0 (CH), 111.8 (CH), 112.2 (CH), 113.2 (C_{quat}), 125.8 (C_{quat}), 128.6 (CH), 131.9 (C_{quat}), 154.3 (C_{quat}), 156.7 (CH), 162.7 (C_{quat}), 163.4 (C_{quat}). EI + MS (*m*/*z* (%)): 240 (M^+, 100), 239 ($(M-H)^+$, 34), 225 ($(M-CH_3)^+$, 13), 211 ($(M-CH_3-NH_2+H)^+$, 11), 210 ($(M-CH_3-NH_2)^+$, 8), 197 (38), 155 (11), 112 (10), 111 (10), 97 (14), 85 (16), 71 (18), 69 (12), 57 (18), 55 (9), 43 ($C_2H_3O^+$, 8). IR (KBr): $\tilde{\nu}$ 3360 (m), 3129 (w), 1626 (m), 1575 (s), 1530 (m), 1482 (m), 1456 (s), 1338 (w), 1293 (w), 1269 (w), 1211 (w), 1163 (w), 1070 (w), 1037 (w), 819 (w), 694 (w), 630 (w) cm^{-1}. Anal. calcd. for $C_{13}H_{12}N_4O$ (240.3): C 64.99, H 5.03, N 23.32. Found: C 64.94, H 4.97, N 23.56.

3.3 ^{1}H NMR and ^{13}C NMR Spectra of Biaryls 3

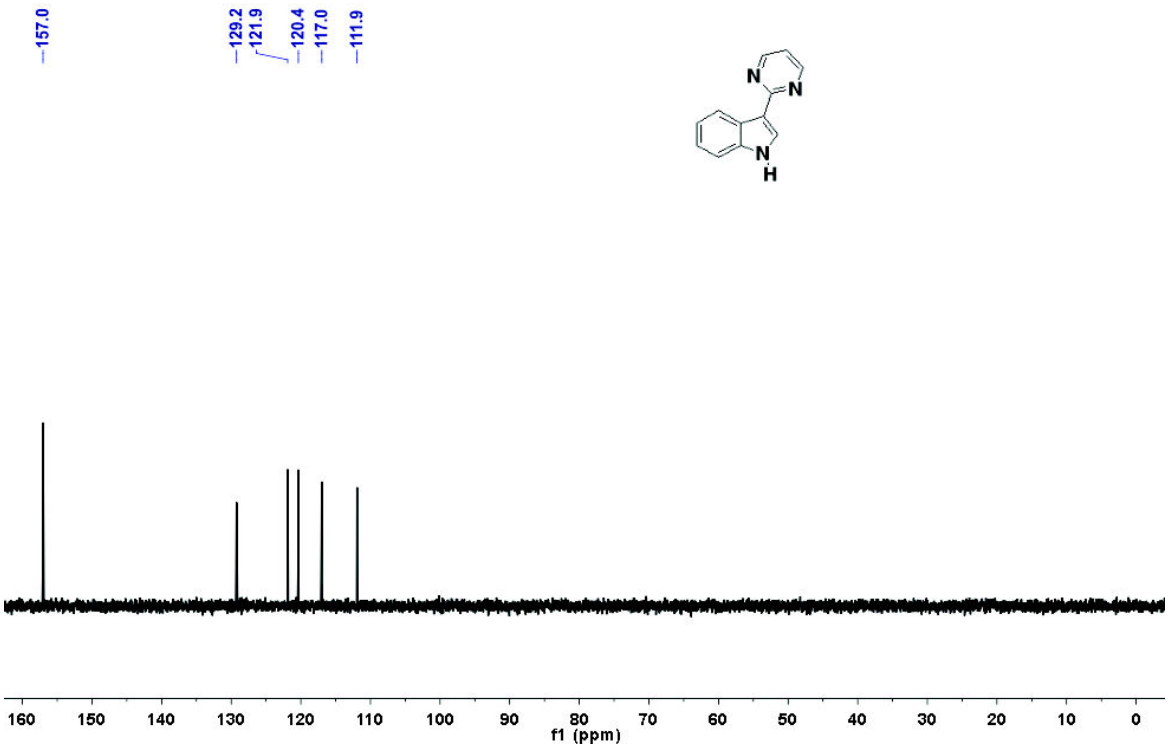
3.3.1 3-(Pyrimidin-2-yl)-1*H*-indole (3a)



^{1}H NMR of **3a** (15 mg) in 0.7 mL DMSO-d_6 at 299 K (δ in ppm).

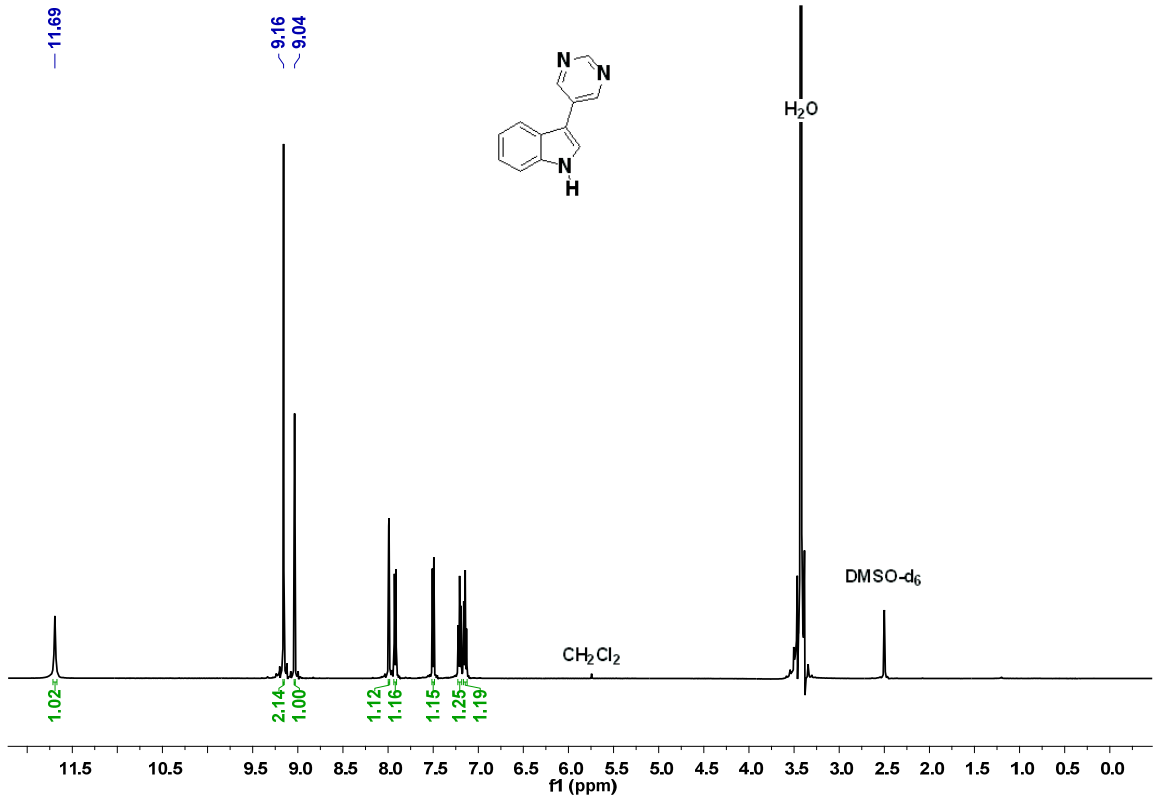


^{13} C NMR of **3a** (15 mg) in 0.7 mL DMSO-d_6 at 299 K (δ in ppm).

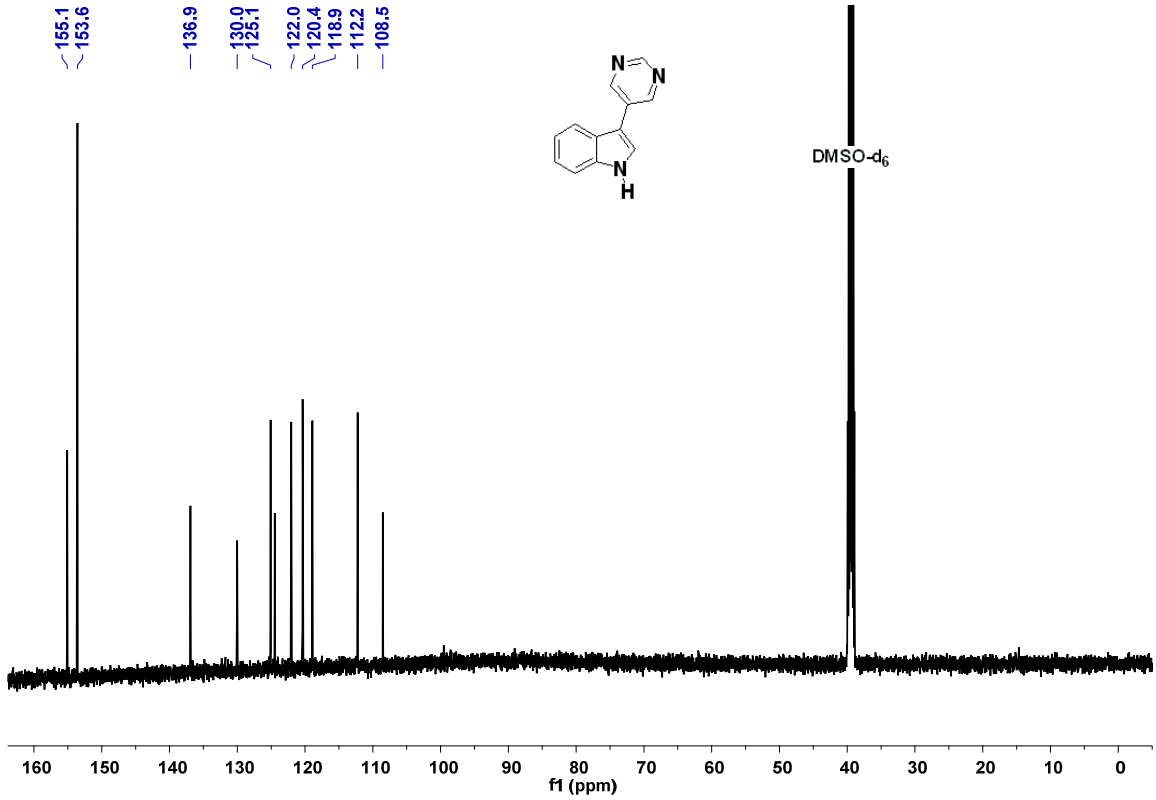


^{13} C 135-DEPT NMR of **3a** (15 mg) in 0.7 mL DMSO-d_6 at 299 K (δ in ppm).

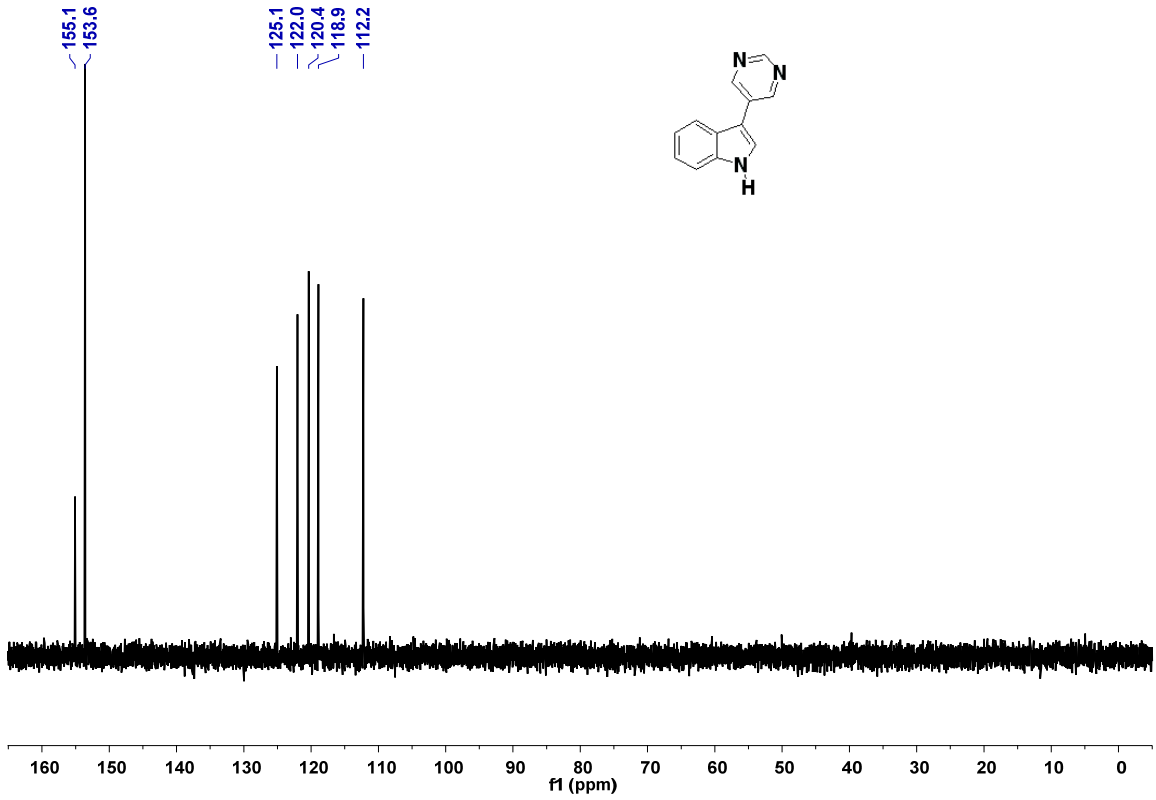
3.3.2 3-(Pyrimidin-5-yl)-1*H*-indole (3b)



^{1}H NMR of **3b** (15 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).

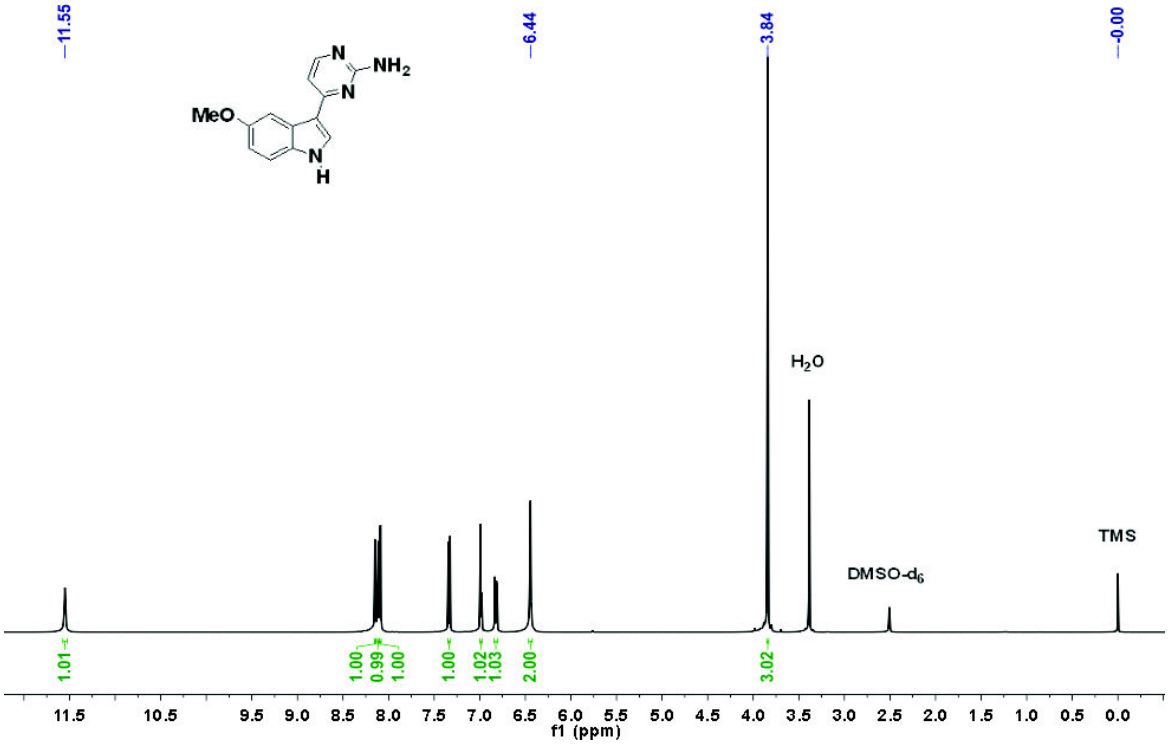


^{13}C NMR of **3b** (15 mg) in 0.7 mL DMSO-d_6 at 297 K (δ in ppm).

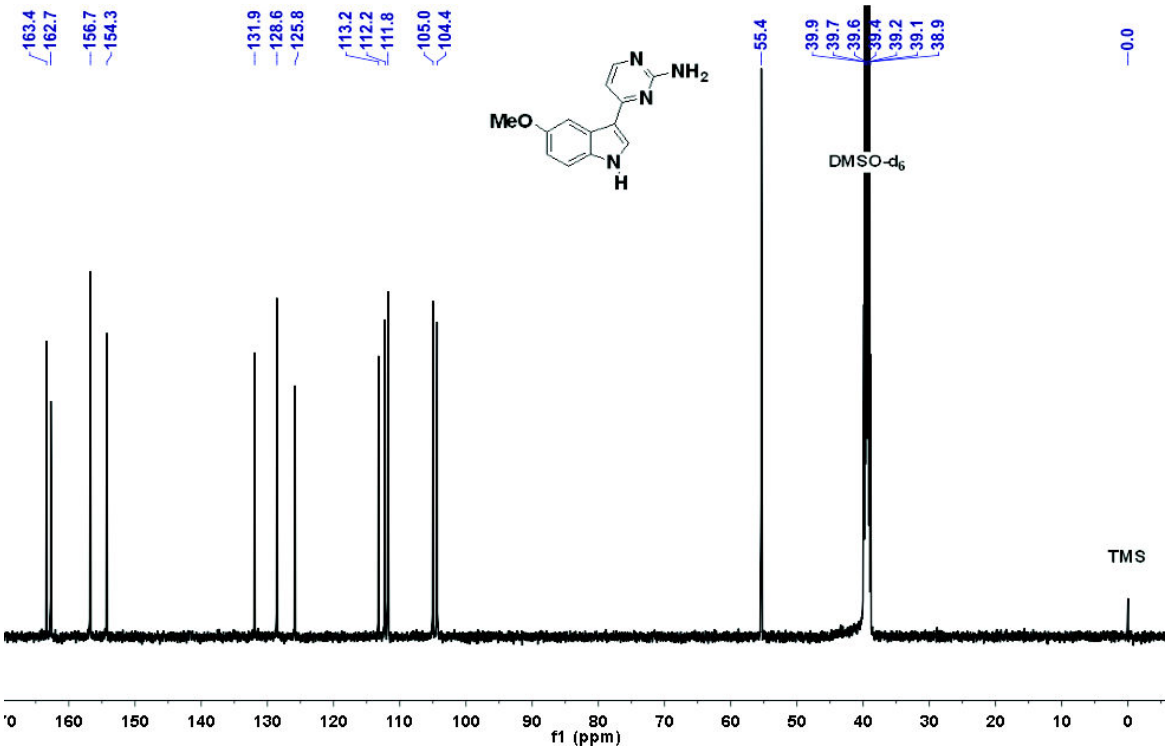


^{13}C 135-DEPT NMR of **3b** (15 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).

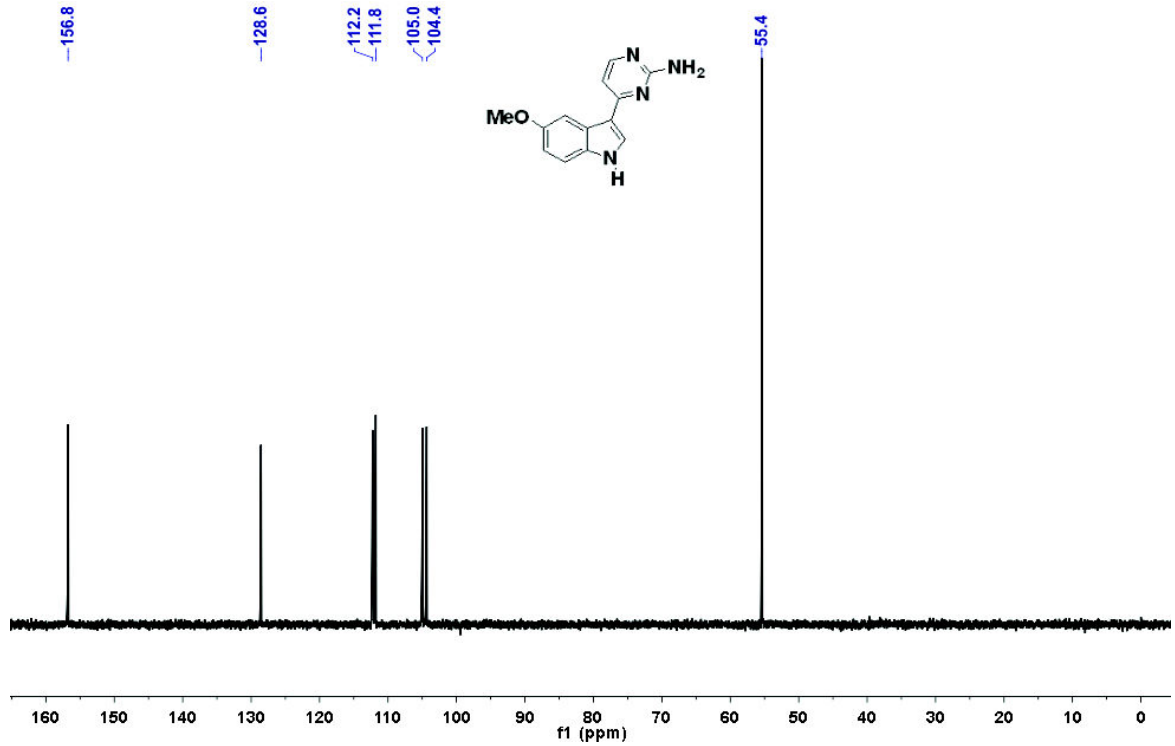
3.3.3 4-(5-Methoxy-1*H*-indol-3-yl)pyrimidin-2-amine (3c)



^{1}H NMR of **3c** (30 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).

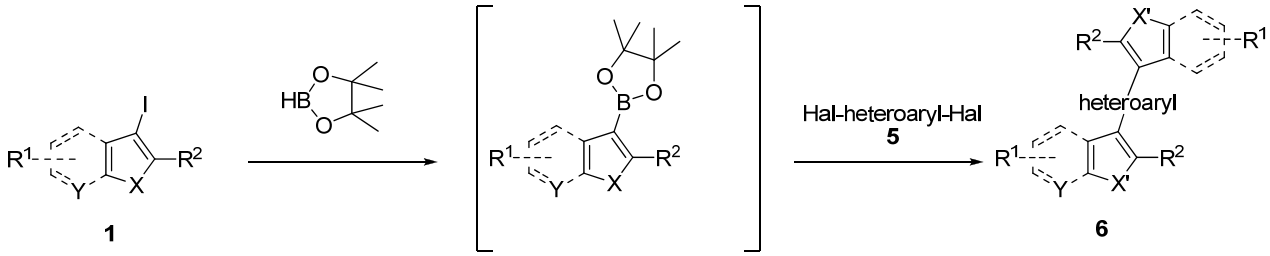


^{13}C NMR of **3c** (30 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).



^{13}C 135-DEPT NMR of **3c** (30 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).

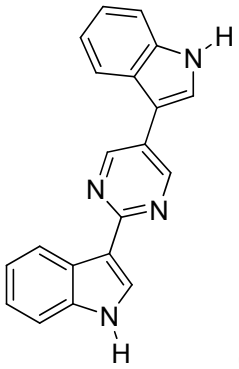
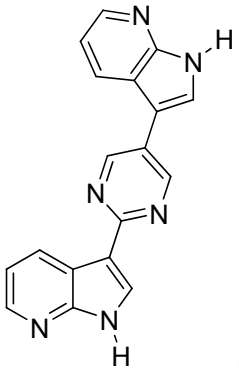
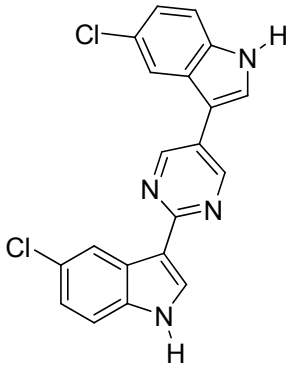
3.4 Synthesis of Bisindoles and Analogues 6 by the *Masuda* Borylation–*Suzuki* Coupling Sequence

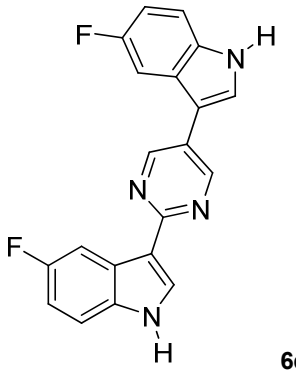
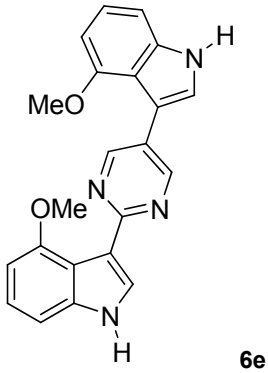
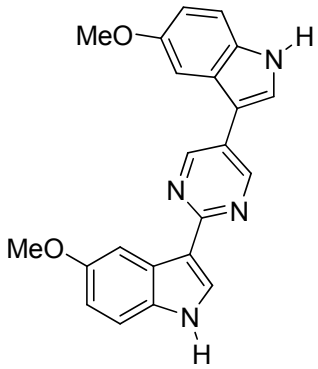


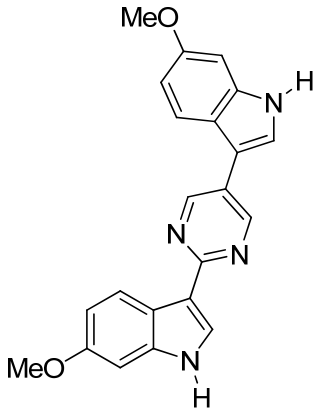
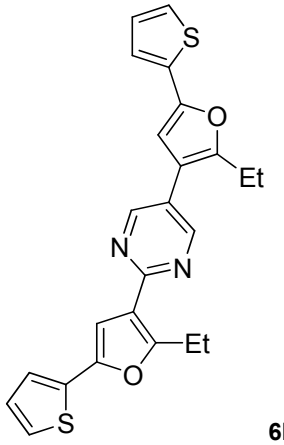
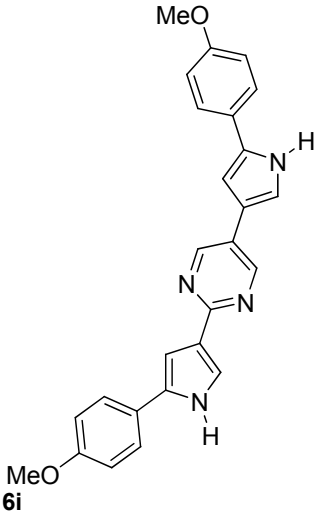
Tetrakis(triphenylphosphane)-palladium(0) (69 mg, 0.06 mmol, 3 mol %) and iodide **1** (2.00 mmol) were placed under argon atmosphere in a dry screw-cap vessel with septum. Then, 10 mL of dry 1,4-dioxane were added and the mixture was degassed with argon (5 min). Dry triethylamine (1.0 mL) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.45 mL, 3.00 mmol) were successively added to the mixture which was stirred at 80 °C (preheated oil bath) for 3 h (monitored by TLC). Then, after cooling to room temperature (water bath), 10 mL of dry methanol, 1.00 mmol of linker **5** and cesium carbonate (1.63 g, 5.00 mmol) were successively added. The mixture was stirred at 100 °C overnight (preheated oil bath). Then, after cooling to room temperature, the solvents were removed under reduced pressure. The residue was absorbed onto Celite® and purified chromatographically on silica gel with dichloromethane/methanol/aqueous ammonia. The product was then dried at 70 °C under reduced pressure overnight, or dried in a drying closet at 100 °C for 24 to 48 h under normal pressure, in order to obtain the correct elemental analyses. The obtained compounds **6** can be further purified by suspending in dichloromethane, sonication for 0.5-1 h in an ultrasound bath, filtration and drying in vacuo overnight.

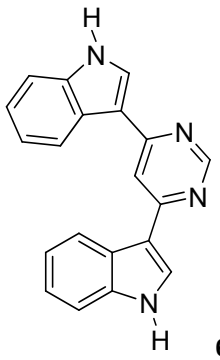
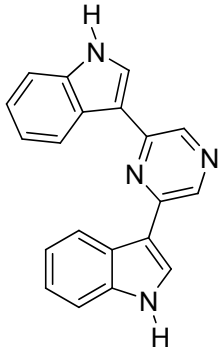
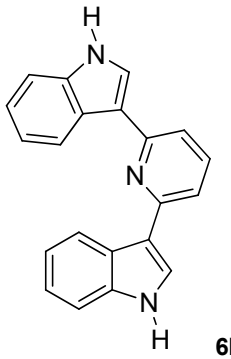
The experimental details are given in **Table 4** and **Table 5**.

Table 4: Experimental details for the synthesis of bisindoles and their analogues **6a-n**.

Entry	Substrate **1**	Linker **5**	Bisindole **6** (isolated yield %)	Chromatographic purification (eluent) UV purity
1	686 mg (2.00 mmol) **1a**	289 mg (1.00 mmol) 5-Bromo-2-iodopyrimidine (*Jiangsu*) **5a**	Pale yellow solid 240 mg (0.77 mmol, 77 %)  **6a**	DCM/MeOH/NH_3 = 100:1:1 → 100:2:1 HT-LC-MS: 100 %
2	688 mg (2.00 mmol) **1b**	289 mg (1.00 mmol) 5-Bromo-2-iodopyrimidine (*Jiangsu*) **5a**	Pale yellow solid 134 mg (0.43 mmol, 43 %)  **6b**	DCM/MeOH/NH_3 = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 → 100:6:1 → 100:7:1 HT-LC-MS: 100 %
3	755 mg (2.00 mmol) **1c**	289 mg (1.00 mmol) 5-Bromo-2-iodopyrimidine (*Jiangsu*) **5a**	Yellow solid 155 mg (0.41 mmol, 41 %)  **6** **c**	DCM/MeOH/NH_3 = 100:1:1 HT-LC-MS: 100 %

4	722 mg (2.00 mmol) **1d**	289 mg (1.00 mmol) 5-Bromo-2-iodopyrimidine (*Jiangsu*) **5a**	Yellow solid 137 mg (0.40 mmol, 40 %)  **6d**	$DCM/MeOH/NH_3$ = 100:1:1
5	1.49 mg (4.00 mmol) **1e**	578 mg (2.00 mmol) 5-Bromo-2-iodopyrimidine (*Jiangsu*) **5a**	Yellow solid 465 mg (1.25 mmol, 63 %)  **6e**	$DCM/MeOH/NH_3$ = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 → 100:6:1 → 100:7:1 HT-LC-MS: 100 %
6	746 mg (2.00 mmol) **1f**	289 mg (1.00 mmol) 5-Bromo-2-iodopyrimidine (*Jiangsu*) **5a**	Yellow solid 238 mg (0.64 mmol, 64 %)  **6f**	$DCM/MeOH/NH_3$ = 100:1:1 HT-LC-MS: 100 %

7	746 mg (2.00 mmol) **1g**	289 mg (1.00 mmol) 5-Bromo-2-iodopyrimidine (*Jiangsu*) **5a**	Pale yellow solid 201 mg (0.54 mmol, 54 %)  **6g**	DCM/MeOH/NH_3 = 100:1:1 HT-LC-MS:100%
8	608 mg (2.00 mmol) **1h**	289 mg (1.00 mmol) 5-Bromo-2-iodopyrimidine (*Jiangsu*) **5a**	Yellow solid 242 mg (0.56 mmol, 56 %)  **6h**	DCM/MeOH/NH_3 = 100:1:1
9	798 mg (2.00 mmol) **1i**	289 mg (1.00 mmol) 5-Bromo-2-iodopyrimidine (*Jiangsu*) **5a**	Pale red solid 215 mg (0.51 mmol, 51 %)  **6i**	DCM/MeOH/NH_3 = 100:1:1

10	686 mg (2.00 mmol) **1a**	339 mg (1.00 mmol) 4,6-Diiodopyrimidine (*Synthonix*) **5b**	Pale yellow solid 75 mg (0.24 mmol, 24 %)  **6j**	DCM/MeOH/NH_3 = 100:1:1
11	686 mg (2.00 mmol) **1a**	342 mg (1.00 mmol) 2,6-Diiodopyrazine (*Synthonix*) **5c**	Yellow solid 237 mg (0.76 mmol, 76 %)  **6k**	DCM/MeOH/NH_3 = 100:1:1
12	686 mg (2.00 mmol) **1a**	242 mg (1.00 mmol) 2,6-Dibromopyridine (*Alfa Aesar*) **5d**	Yellow solid 207 mg (0.67 mmol, 67 %)  **6l**	DCM/MeOH/NH_3 = 100:1:1

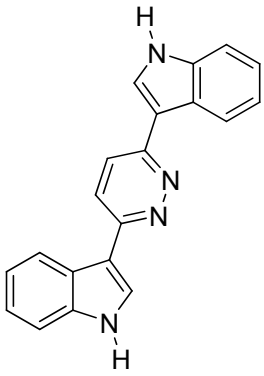
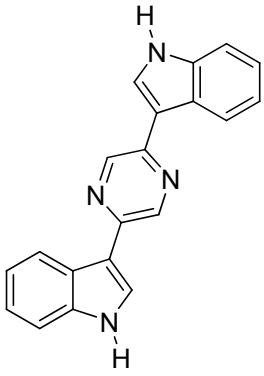
13	686 mg (2.00 mmol) **1a**	342 mg (1.00 mmol) 3,6-Diiodopyridazine (*Aldrich*) **5e**	Yellow solid 150 mg (0.48 mmol, 48 %)  **6m**	$DCM/MeOH/NH_3$ = 100:1:1 HT-LC-MS: 100 %
14	686 mg (2.00 mmol) **1a**	245 mg (1.00 mmol) 2,5-Dibromopyrazine (*Synthonix*) **5f**	Yellow solid 120 mg (0.39 mmol, 39 %)  **6n**	$DCM/MeOH/NH_3$ = 100:1:1

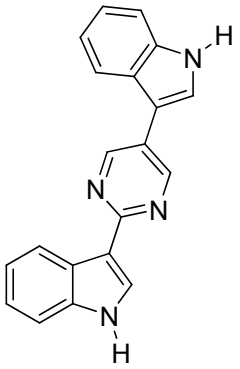
Table 5: Reaction times in the synthesis of bisindoles and their analogues **6a-n**.[a]

Entry	Bisindole **6**	*Masuda* borylation step	*Suzuki* coupling step
1	**6a**	3 h	24 h
2	**6b**	3 h	24 h
3	**6c**	3 h	20 h
4	**6d**	3 h	20 h
5	**6e**	3 h	24 h
6	**6f**	3 h	24 h
7	**6g**	3 h	20 h
8	**6h**	3 h	20 h
9	**6i**	3 h	19 h
10	**6j**	3 h	19 h
11	**6k**	3 h	20 h
12	**6l**	3 h	20 h
13	**6m**	3 h	20 h
14	**6n**	3 h	19 h

[a] The reaction times for the *Suzuki* coupling step are not optimized. The actual reaction times might be much shorter than indicated. The actual reaction times for the *Masuda* borylation step may also be shorter in some cases.

3.5 Spectrological Data of Bisindoles and Analogues 6

3.5.1 3-3-(Pyrimidin-2,5-diyl)bis(1*H*-indole) (6a)

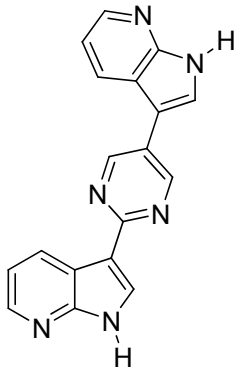


$C_{20}H_{14}N_4$

310.35

240 mg (0.77 mmol, 77 % yield) as a pale yellow, scaly solid, mp: 318 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.13-7.25 (m, 4 H), 7.46-7.55 (m, 2 H), 7.90-8.00 (m, 2 H), 8.25 (s, 1 H), 8.60-8.63 (m, 1 H), 9.14 (s, 2 H), 11.6 (br, 1 H, NH), 11.7 (br, 1 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 109.4 (C_{quat}), 111.9 (CH), 112.1 (CH), 114.9 (C_{quat}), 119.0 (CH), 120.1 (CH), 120.3 (CH), 121.8 (CH), 121.9 (CH), 121.9 (CH), 124.0 (CH), 124.7 (C_{quat}), 125.1 (C_{quat}), 125.5 (C_{quat}), 128.6 (CH), 136.8 (C_{quat}), 137.1 (C_{quat}), 153.9 (CH), 160.6 (C_{quat}). EI + MS (*m*/*z* (%)): 310 (M^+, 80), 204 (8), 155 (15), 141 (23), 97 (10), 85 (10), 71 (14), 57 (24), 55 (11), 44 (100). IR (KBr): $\tilde{\nu}$ 3389 (s), 1614 (w), 1546 (m), 1454 (m), 1326 (w), 1229 (w), 1178 (w), 1118 (w), 1092 (w), 801 (w), 745 (m), 590 (w), 546 (w), 515 (w) cm^{-1}. Anal. calcd. for $C_{20}H_{14}N_4$ (310.4): C 77.40, H 4.55, N 18.05. Found: C 77.22, H 4.47, N 18.02.

3.5.2 3,3□-(Pyrimidine-2,5-diyl)bis(1*H*-pyrrolo[2,3-*b*]pyridine) (6b)

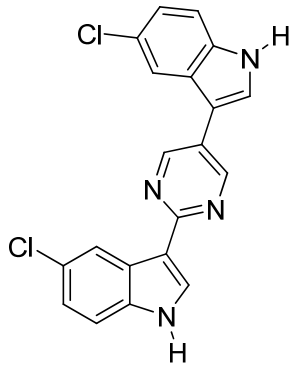


$C_{18}H_{12}N_6$

312.33

134 mg (0.43 mmol, 43 % yield) as a pale yellow solid, mp: > 370 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.22 (dd, *J* = 7.9 Hz, *J* = 4.4 Hz, 1 H), 7.27 (dd, *J* = 7.9 Hz, *J* = 4.7 Hz, 1 H), 8.16 (d, *J* = 2.2 Hz, 1 H), 8.33-8.36 (m, 3 H), 8.44 (d, *J* = 7.9 Hz, 1 H), 8.87 (dd, *J* = 7.9 Hz, *J* = 1.3 Hz, 1 H), 9.21 (s, 2 H), 12.2 (br, 1 H, NH), 12.3 (br, 1 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 108.0 (C_{quat}), 113.5 (C_{quat}), 116.3 (CH), 116.8 (CH), 116.9 (C_{quat}), 117.9 (C_{quat}), 124.5 (CH), 124.9 (C_{quat}), 127.7 (CH), 128.6 (CH), 129.9 (CH), 143.3 (CH), 143.3 (CH), 149.0 (C_{quat}), 149.2 (C_{quat}), 153.8 (CH), 160.1 (C_{quat}). EI + MS (*m*/*z* (%)): 313 (23), 312 (M^+, 100), 156 (14), 143 (18), 142 (79), 115 (14). IR (KBr): $\tilde{\nu}$ 3448 (w), 3141 (m), 3090 (m), 3039 (m), 2883 (m), 2823 (m), 1585 (w), 1537 (s), 1498 (m), 1468 (m), 1436 (w), 1415 (w), 1368 (w), 1335 (w), 1314 (w), 1277 (s), 1188 (w), 1130 (w), 1034 (w), 992 (m), 956 (w), 926 (w), 896 (m), 795 (m), 768 (s), 659 (w), 632 (w), 586 (w), 513 (w) cm^{-1}. Anal. calcd. for $C_{18}H_{12}N_6$ (312.3): C 68.24, H 3.98, N 26.53. Found: C 68.01, H 3.99, N 26.45.

3.5.3 3,3'-(Pyrimidine-2,5-diyl)bis(5-chloro-1*H*-indole) (6c)

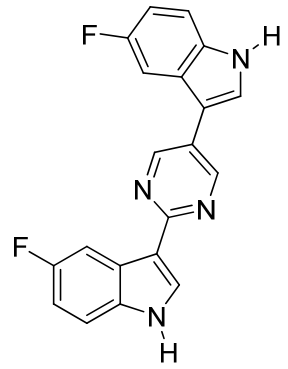


$C_{20}H_{12}Cl_2N_4$

379.24

155 mg (0.41 mmol, 41 % yield) as a yellow solid, mp: 265-268 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.15-7.25 (m, 2 H), 7.50 (d, *J* = 3.0 Hz, 1 H), 7.52 (d, *J* = 3.1 Hz, 1 H), 7.96 (s, 1 H), 8.01 (d, *J* = 1.7 Hz, 1 H), 8.30 (d, *J* = 1.7 Hz, 1 H), 8.61-8.62 (m, 1 H), 9.129 (s, 1 H), 9.131 (s, 1 H), 11.80 (s, 1 H, NH), 11.86 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 109.6 (C_{quat}), 113.8 (CH), 113.9 (CH), 114.7 (C_{quat}), 118.6 (CH), 121.3 (CH), 122.1 (CH), 122.2 (CH), 124.9 (C_{quat}), 125.1 (C_{quat}), 125.3 (C_{quat}), 125.9 (C_{quat}), 126.1 (CH), 126.8 (C_{quat}), 130.3 (CH), 135.5 (C_{quat}), 135.8 (C_{quat}), 154.3 (CH), 160.5 (C_{quat}). EI + MS (*m*/*z* (%)): 382 (M(^{37}C^{37}C)$^+$, 12), 381 (15), 380 (M(^{37}C^{35}C)$^+$, 66), 379 (25), 378 (M(^{35}Cl^{35}Cl)$^+$, 100), 337 (19), 277 (22), 176 (34), 175 (72), 149 (51), 140 (49). IR (KBr): $\tilde{\nu}$ 2361 (w), 2332 (w), 1543 (s), 1520 (m), 1447 (s), 1420 (w), 1379 (w), 1362 (w), 1302 (m), 1223 (w), 1179 (w), 1157 (w), 1132 (m), 1099 (m), 1072 (w), 1036 (w), 995 (w), 930 (w), 889 (m), 879 (m), 845 (m), 787 (s), 748 (w), 714 (w), 619 (m) cm^{-1}. Anal. calcd. for $C_{20}H_{12}Cl_2N_4$ (379.2): C 63.34, H 3.19, N 14.77. Found: C 63.50, H 3.46, N 14.51.

3.5.4 3,3'-(Pyrimidine-2,5-diyl)bis(5-fluoro-1*H*-indole) (6d)

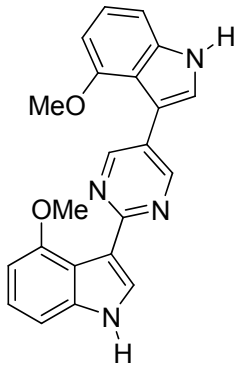


$C_{20}H_{12}F_2N_4$

346.33

137 mg (0.40 mmol, 40 % yield) as a yellow solid, mp: 288-289 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.08-7.16 (m, 2 H), 7.46-7.52 (m, 2 H), 7.72 (dd, *J* = 10.2 Hz, *J* = 2.3 Hz, 1 H), 8.02 (d, *J* = 2.6 Hz, 1 H), 8.26-8.32 (m, 2 H), 9.12 (s, 2 H), 11.70 (s, 1 H, NH), 11.78 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 104.3 (d, *J* = 24.1 Hz, CH), 106.8 (d, *J* = 24.5 Hz, CH), 110.0 (d, *J* = 32.5 Hz, CH), 110.1 (d, *J* = 32.1 Hz, CH), 110.4 (d, *J* = 4.0 Hz, C_{quat}), 113.2-113.4 (m, 2 CH), 115.1 (d, *J* = 4.5 Hz, C_{quat}), 124.9-125.1 (m, 2 C_{quat}), 126.1 (d, *J* = 11.1 Hz, C_{quat}), 126.3 (CH), 130.5 (CH), 133.7 (C_{quat}), 133.9 (C_{quat}), 154.1 (CH), 157.8 (d, *J* = 232.4 Hz, C_{quat}), 158.0 (d, *J* = 232.3 Hz, C_{quat}), 160.6 (C_{quat}). EI + MS (*m*/*z* (%)): 347 (23), 346 (M^+, 100), 173 (24), 160 (20), 159 (76), 158 (32), 133 (10), 132 (19). IR (KBr): $\tilde{\nu}$ 3447 (m), 3288 (w), 3115 (w), 2357 (w), 2336 (w), 1844 (w), 1626 (w), 1582 (w), 1545 (s), 1522 (w), 1487 (m), 1448 (s), 1383 (w), 1331 (w), 1306 (w), 1263 (m), 1221 (w), 1176 (w), 1159 (w), 1144 (s), 1123 (m), 1090 (w), 1036 (w), 995 (w), 974 (w), 930 (s), 920 (s), 878 (m), 835 (s), 789 (s), 746 (s), 669 (w), 636 (s), 621 (m) cm^{-1}. Anal. calcd. for $C_{20}H_{12}F_2N_4$ (346.3): C 69.36, H 3.49, N 16.18. Found: C 69.13, H 3.68, N 16.07.

3.5.5 3,3'-(Pyrimidine-2,5-diyl)bis(4-methoxy-1*H*-indole) (6e)

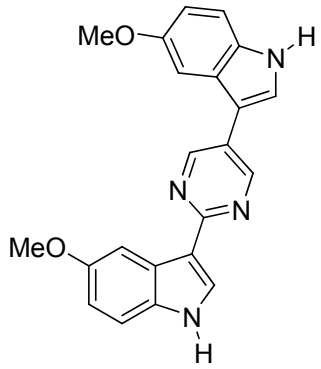


$C_{22}H_{18}N_4O_2$

370.40

465 mg (1.25 mmol, 63 % yield) as a yellow solid, mp: 300 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 3.79 (s, 3 H), 3.86 (s, 3 H), 6.59-6.64 (m, 2 H), 7.06-7.14 (m, 4 H), 7.61 (d, *J* = 2.5 Hz, 1 H), 7.74 (d, *J* = 2.5 Hz, 1 H), 8.93 (s, 2 H), 11.53 (d, *J* = 2.2 Hz, 1 H, NH), 11.58 (d, *J* = 1.9 Hz, 1 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 54.9 (CH_3), 55.2 (CH_3), 100.0 (CH), 101.2 (CH), 105.0 (CH), 105.2 (CH), 109.6 (C_{quat}), 114.7 (C_{quat}), 115.4 (C_{quat}), 116.6 (C_{quat}), 122.5 (CH), 122.6 (CH), 123.6 (CH), 125.5 (C_{quat}), 127.1 (CH), 138.4 (C_{quat}), 138.4 (C_{quat}), 153.5 (C_{quat}), 154.1 (C_{quat}), 155.3 (CH), 160.3 (C_{quat}). EI + MS (*m*/*z* (%)): 371 (25), 370 (M^+, 100), 369 ($(M-H)^+$, 32), 341 (34), 326 (25), 325 (15), 199 (13), 185 (20), 184 (21), 183 (25), 171 (23), 170 (22), 169 (48), 162 (13), 157 (17), 156 (36), 155 (32), 143 (11), 142 (23), 141 (11), 130 (11), 129 (23), 128 (26), 115 (11). IR (KBr): $\tilde{\nu}$ 3422 (w), 3120 (w), 1617 (w), 1584 (w), 1540 (s), 1508 (m), 1461 (s), 1383 (w), 1355 (w), 1319 (m), 1280 (m), 1252 (m), 1235 (m), 1183 (w), 1092 (s), 992 (w), 969 (w), 939 (w), 801 (w), 777 (m), 731 (s), 692 (w), 626 (w) cm^{-1}. Anal. calcd. for $C_{22}H_{18}N_4O_2$ (370.4): C 71.34, H 4.90, N 15.13. Found: C 71.15, H 5.15, N 15.15.

3.5.6 3,3'-(Pyrimidine-2,5-diyl)bis(5-methoxy-1*H*-indole) (6f)

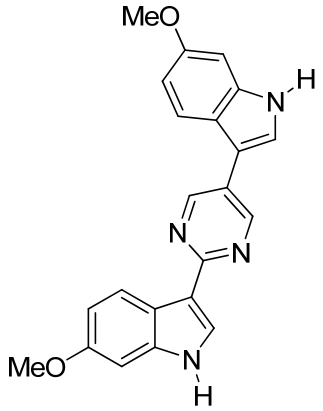


$C_{22}H_{18}N_4O_2$

370.40

238 mg (0.64 mmol, 64 % yield) as a yellow solid, mp: 220 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 3.85 (s, 6 H), 6.85-6.86 (m, 1 H), 6.86-6.88 (m, 1 H), 7.38-7.40 (m, 2 H), 7.41 (d, *J* = 4.4 Hz, 1 H), 7.90 (d, *J* = 2.8 Hz, 1 H), 8.15 (d, *J* = 2.5 Hz, 1 H), 8.21 (d, *J* = 2.8 Hz, 1 H), 9.14 (s, 2 H), 11.46 (d, *J* = 2.2 Hz, 1 H, NH), 11.56 (d, *J* = 2.2 Hz, 1 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 55.3 (CH_3), 55.3 (CH_3), 100.5 (CH), 103.8 (CH), 109.3 (C_{quat}), 111.7 (CH), 112.1 (CH), 112.5 (CH), 112.7 (CH), 114.6 (C_{quat}), 124.5 (CH), 124.9 (C_{quat}), 125.0 (C_{quat}), 126.0 (C_{quat}), 128.9 (CH), 131.8 (C_{quat}), 132.1 (C_{quat}), 153.7 (CH), 154.2 (C_{quat}), 154.3 (C_{quat}), 160.6 (C_{quat}). EI + MS (*m*/*z* (%)): 370 (M^+, 100), 369 ($(M-H)^+$, 12), 355 ($(M-CH_3)^+$, 9), 327 (16), 240 (20), 185 (19), 163 (14), 156 (17), 142 (25), 128 (14). IR (KBr): $\tilde{\nu}$ 3291 (m), 1624 (m), 1585 (m), 1544 (s), 1487 (s), 1447 (s), 1367 (w), 1327 (w), 1306 (w), 1281 (m), 1259 (w), 1212 (m), 1156 (m), 1131 (w), 1031 (m), 993 (w), 919 (m), 861 (w), 798 (m), 735 (w), 641 (w), 526 (w) cm^{-1}. Anal. calcd. for $C_{22}H_{18}N_4O_2$ (370.4): C 71.34, H 4.90, N 15.13. Found: C 71.19, H 5.03, N 15.20.

3.5.7 3,3'-(Pyrimidine-2,5-diyl)bis(6-methoxy-1*H*-indole) (6g)

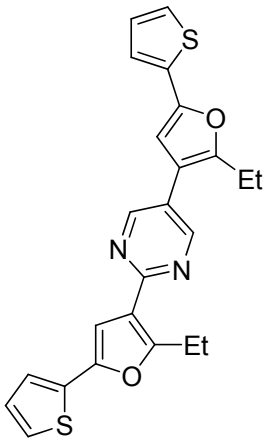


$C_{22}H_{18}N_4O_2$

370.40

201 mg (0.54 mmol, 54 % yield) as a pale yellow solid, mp: 291-293 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 3.80 (s, 6 H), 6.79 (dd, *J* = 8.7 Hz, *J* = 2.3 Hz, 1 H), 6.82 (dd, *J* = 8.7 Hz, *J* = 2.3 Hz, 1 H), 6.96-6.98 (m, 2 H), 7.78 (d, *J* = 2.5 Hz, 1 H), 7.81 (d, *J* = 8.7 Hz, 1 H), 8.08 (d, *J* = 2.7 Hz, 1 H), 8.43 (d, *J* = 8.7 Hz, 1 H), 9.07 (s, 2 H), 11.37 (d, *J* = 1.8 Hz, 1 H, NH), 11.44 (d, *J* = 2.0 Hz, 1 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 55.3 (CH_3), 55.4 (CH_3), 95.0 (CH), 95.2 (CH), 109.6 (C_{quat}), 110.4 (CH), 110.5 (CH), 115.1 (C_{quat}), 119.1 (C_{quat}), 119.9 (C_{quat}), 120.0 (CH), 122.7 (CH), 122.8 (CH), 125.3 (C_{quat}), 127.5 (CH), 138.0 (C_{quat}), 138.04 (C_{quat}), 153.8 (CH), 156.1 (C_{quat}), 160.7 (C_{quat}). EI + MS (*m*/*z* (%)): 371 (25), 370 (M^+, 100), 355 ((M-CH_3)$^+$, 38), 185 (18), 177 (14), 170 (11), 156 (16), 142 (17). IR (KBr): $\tilde{\nu}$ 3530 (w), 3381 (m), 2963 (w), 2885 (w), 2831 (w), 2324 (w), 1622 (m), 1541 (s), 1499 (m), 1450 (m), 1435 (m), 1412 (w), 1352 (m), 1327 (m), 1288 (m), 1263 (m), 1232 (m), 1200 (s), 1165 (m), 1149 (s), 1119 (s), 1090 (m), 1024 (s), 991 (m), 939 (s), 874 (w), 858 (w), 808 (s), 752 (w), 729 (w), 702 (m), 642 (m), 617 (m) cm^{-1}. Anal. calcd. for $C_{22}H_{18}N_4O_2$ (370.4): C 71.34, H 4.90, N 15.13. Found: C 71.43, H 5.15, N 15.37.

3.5.8 2,5-Bis(2-ethyl-5-(thiophen-2-yl)furan-3-yl)pyrimidine (6h)



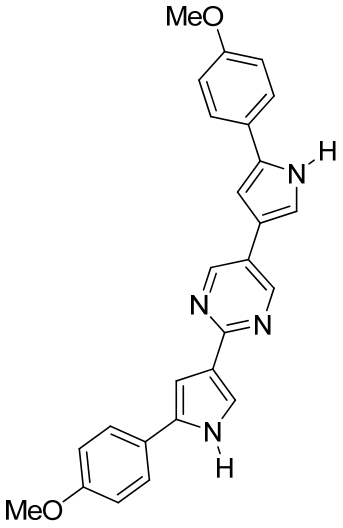
$C_{24}H_{20}N_2O_2S_2$

432.56

242 mg (0.56 mmol, 56 % yield) as a yellow solid, mp: 158-159 °C. EI + MS (*m*/*z* (%)): 432 (M^+, 9), 262 (32), 255 ((M-$C_{10}H_9OS)^+$, 10), 254 (61), 240 (17), 239 (100), 230 (23), 201 (54), 183 (30), 178 (19), 172 (22), 163 (18), 152 (10), 149 (12). IR (KBr): $\tilde{\nu}$ 2972 (w), 2932 (w), 2922 (w), 2855 (w), 2357 (w), 1568 (w), 1468 (m), 1427 (m), 1394 (m), 1362 (w), 1315 (w), 1256 (w), 1198 (m), 1119 (m), 1045 (m), 1016 (m), 989 (m), 928 (w), 847 (m), 800 (s), 685 (s), 646 (m), 633 (m) cm^{-1}. Anal. calcd. for $C_{24}H_{20}N_2O_2S_2$ (432.6): C 66.64, H 4.66, N 6.48. Found: C 66.82, H 4.79, N 6.32.

After drying the compound was found to be insoluble in common deuterated solvents.

3.5.9 2,5-Bis(5-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)pyrimidine (6i)

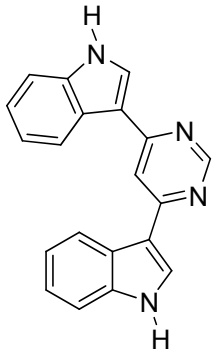


$C_{26}H_{22}N_4O_2$

422.48

215 mg (0.51 mmol, 51 % yield) as a pale red solid, mp: 320-323 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 3.77 (brs, 6 H), 6.90-7.00 (m, 6 H), 7.43-7.54 (m, 2 H), 7.58-7.64 (m, 4 H), 8.92 (s, 2 H), 11.49 (m, 1 H, NH), 11.55 (m, 1 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 55.29 (CH_3), 55.31 (CH_3), 101.7 (CH), 103.8 (CH), 114.41 (CH), 114.42 (CH) 116.5 (CH), 118.5 (C_{quat}), 120.7 (CH), 125.13 (CH), 125.15 (CH), 125.3 (C_{quat}), 125.46 (C_{quat}), 125.47 (C_{quat}), 125.51 (C_{quat}), 132.7 (C_{quat}), 133.1 (C_{quat}), 152.6 (CH), 157.94 (C_{quat}), 157.96 (C_{quat}), 159.7 (C_{quat}). EI + MS (*m*/*z* (%)): 423 (29), 422 (M^+, 100), 407 ($(M\text{-}CH_3)^+$, 27), 211 (17), 203 (13), 182 (13), 168 (12). IR (KBr): $\tilde{\nu}$ 2962 (w), 2838 (w), 1719 (w), 1686 (w), 1655 (w), 1638 (w), 1609 (w), 1570 (m), 1534 (w), 1492 (s), 1459 (w), 1439 (m), 1396 (w), 1280 (m), 1248 (s), 1211 (w), 1181 (m), 1114 (m), 1024 (m), 941 (m), 924 (w), 830 (s), 807 (s), 667 (w), 640 (w), 620 (w), 553 (m), 518 (w) cm^{-1}. Anal. calcd. for $C_{26}H_{22}N_4O_2$ (422.5): C 73.92, H 5.25, N 13.26. Found: C 73.63, H 5.15, N 13.53.

3.5.10 4,6-Di(1*H*-indol-3-yl)pyrimidine (6j)

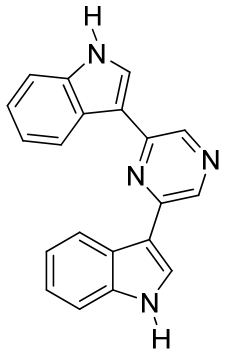


$C_{20}H_{14}N_4$

310.35

75 mg (0.24 mmol, 24 %) as a yellow solid, mp: 275-276 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.13-7.25 (m, 4 H), 7.45-7.52 (m, 2 H), 8.25 (s, 1 H), 8.48 (d, *J* = 7.3 Hz, 2 H), 8.59 (d, *J* = 8.2 Hz, 2 H), 9.07 (s, 1 H), 11.82 (s, 2 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 109.8 (CH), 112.2 (CH), 113.8 (C_{quat}), 120.7 (CH), 122.2 (CH), 122.3 (CH), 125.5 (C_{quat}), 128.8 (CH), 137.3 (C_{quat}), 158.8 (CH), 161.3 (C_{quat}). EI + MS (*m*/*z* (%)): 311 (22), 310 (M^+, 100), 309 (59), 282 (13), 194 ((M-$C_8H_6N)^+$, 11), 155 (23), 141 (23), 140 (19), 128 (13), 114 (18). IR (KBr): $\tilde{\nu}$ 2284 (s), 3144 (w), 1655 (w), 1586 (s), 1541 (m), 1503 (m), 1432 (s), 1334 (w), 1290 (m), 1231 (m), 1209 (w), 1125 (m), 1009 (w), 991 (w), 869 (m), 772 (m), 749 (s), 617 (w), 598 (w), 586 (w), 569 (w), 534 (m) cm^{-1}. Anal. calcd. for $C_{20}H_{14}N_4$ (310.4): C 77.40, H 4.55, N 18.05. Found: C 77.31, H 4.80, N 18.16.

3.5.11 2,6-Di(1*H*-indol-3-yl)pyrazine (6k)

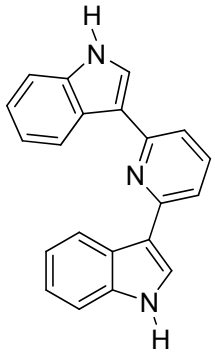


$C_{20}H_{14}N_4$

310.35

237 mg (0.76 mmol, 76 % yield) as a yellow solid, mp: 283-285 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.16-7.25 (m, 4 H), 7.53 (d, *J* = 7.8 Hz, 2 H), 8.31 (d, *J* = 2.7 Hz, 2 H), 8.54 (d, *J* = 7.8 Hz, 2 H), 8.88 (s, 2 H), 11.72 (s, 2 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 112.3 (CH), 113.2 (C_{quat}), 120.5 (CH), 121.4 (CH), 122.2 (CH), 125.5 (C_{quat}), 126.9 (CH), 136.9 (CH), 137.3 (C_{quat}), 150.1 (C_{quat}). EI + MS (*m*/*z* (%)): 311 (25), 310 (M^+, 100), 309 (26), 155 ($C_{10}H_7N_2^+$, 14), 141 ($C_{10}H_7N^+$, 32), 140 (22). IR (KBr): $\tilde{\nu}$ 3089 (w), 1686 (w), 1655 (w), 1587 (w), 1541 (s), 1510 (s), 1491 (m), 1439 (s), 1407 (w), 1323 (w), 1302 (w), 1238 (m), 1141 (m), 1123 (m), 1039 (w), 1006 (w), 961 (w), 822 (w), 789 (w), 750 (m), 735 (m), 623 (w), 581 (m), 524 (m) cm^{-1}. Anal. calcd. for $C_{20}H_{14}N_4$ (310.4): C 77.40, H 4.55, N 18.05. Found: C 77.21, H 4.67, N 18.05.

3.5.12 2,6-Di(1*H*-indol-3-yl)pyridine (6l)

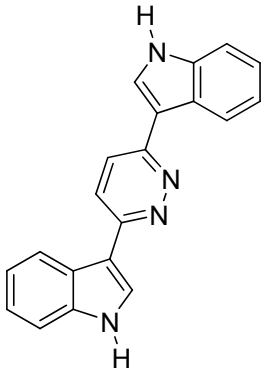


$C_{21}H_{15}N_3$

309.36

207 mg (0.67 mmol, 67 % yield) as a yellow solid, mp: 297-298 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.12-7.24 (m, 4 H), 7.51 (d, *J* = 7.9 Hz, 2 H), 7.62 (d, *J* = 7.8 Hz, 2 H), 7.76 (t, *J* = 7.8 Hz, 1 H), 8.14 (d, *J* = 2.6 Hz, 2 H), 8.54 (d, *J* = 7.9 Hz, 2 H), 11.52 (s, 2 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 111.9 (CH), 115.8 (CH), 116.2 (C_{quat}), 119.8 (CH), 121.4 (CH), 121.6 (CH), 125.3 (C_{quat}), 125.8 (CH), 136.6 (CH), 137.1 (C_{quat}), 154.6 (C_{quat}). EI + MS (*m*/*z* (%)): 310 (24), 309 (M^+, 100), 308 (38), 154 (18), 141 (14), 140 (21), 127 (11), 126 (11). IR (KBr): $\tilde{\nu}$ 3054 (w), 1787 (w), 1685 (w), 1655 (w), 1593 (m), 1563 (m), 1546 (m), 1484 (w), 1456 (m), 1420 (w), 1338 (w), 1333 (w), 1311 (w), 1263 (w), 1239 (m), 1157 (w), 1143 (w), 1118 (w), 1093 (s), 1011 (m), 939 (w), 852 (m), 801 (s), 742 (s), 662 (w), 640 (w), 616 (w), 589 (m), 527 (s) cm^{-1}. Anal. calcd. for $C_{21}H_{15}N_3$ (309.4): C 81.53, H 4.89, N 13.58. Found: C 81.41, H 4.64, N 13.80.

3.5.13 3,6-Di(1*H*-indol-3-yl)pyridazine (6m)

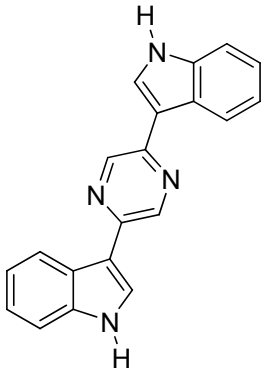


$C_{20}H_{14}N_4$

310.35

150 mg (0.48 mmol, 48 % yield) as a yellow solid, mp: > 300 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.17-7.24 (m, 4 H), 7.47-7.51 (m, 2 H), 8.07 (s, 2 H), 8.25 (d, *J* = 2.8 Hz, 2 H), 8.59-8.63 (m, 2 H), 11.66 (s, 2 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 112.0 (CH), 113.1 (C_{quat}), 120.5 (CH), 122.3 (CH), 122.5 (CH), 123.6 (CH), 125.2 (C_{quat}), 126.8 (CH), 137.4 (C_{quat}), 154.5 (C_{quat}). EI + MS (*m*/*z* (%)): 310 (M^+, 7), 170 (37), 150 (12), 149 (100), 141 (15), 113 (13), 83 (11). IR (KBr): $\tilde{\nu}$ 1614 (w), 1562 (m), 1537 (w), 1512 (w), 1454 (m), 1437 (m), 1366 (w) 1340 (m), 1325 (w), 1263 (m), 1234 (m), 1119 (m), 1084 (m), 1074 (m), 1040 (w), 1005 (m), 976 (m), 932 (w), 866 (m), 824 (m), 741 (s), 640 (m) cm^{-1}. Anal. calcd. for $C_{20}H_{14}N_4$ (310.4): C 77.40, H 4.55, N 18.05. Found: C 77.17, H 4.54, N 17.93.

3.5.14 2,5-Di(1*H*-indol-3-yl)pyrazine (6n)



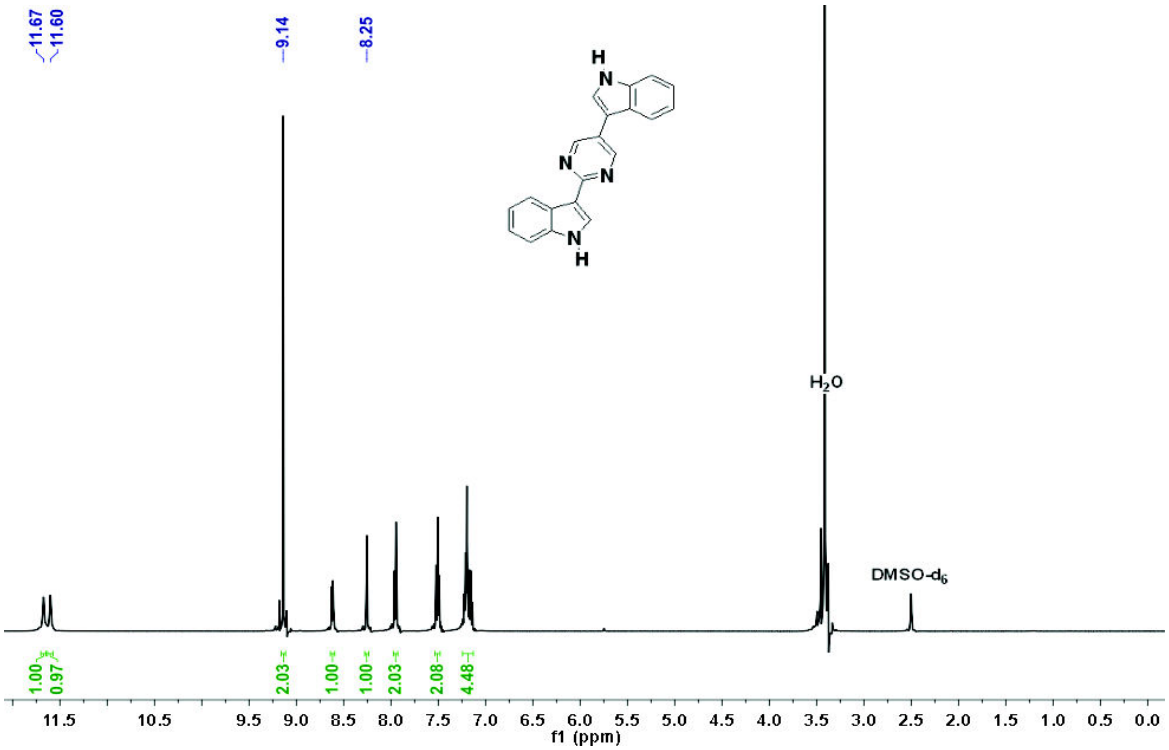
$C_{20}H_{14}N_4$

310.35

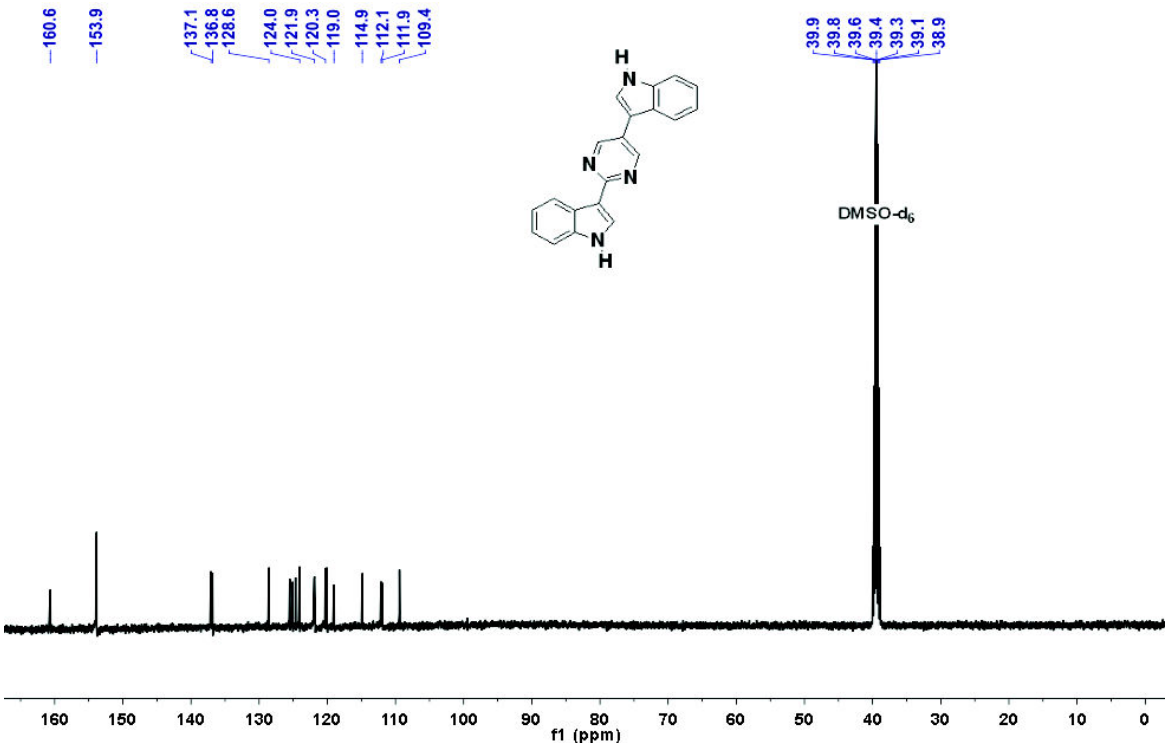
120 mg (0.39 mmol, 39 % yield) as a yellow solid, mp: > 300 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 6.27-6.36 (m, 4 H), 6.62 (d, *J* = 7.8 Hz, 2 H), 7.38 (d, *J* = 2.7 Hz, 2 H), 7.59 (d, *J* = 7.8 Hz, 2 H), 8.28 (s, 2 H), 10.77 (s, 2 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 112.1 (CH), 112.9 (C_{quat}), 120.3 (CH), 121.6 (CH), 122.1 (CH), 125.4 (C_{quat}), 125.8 (CH), 137.1 (C_{quat}), 140.3 (CH), 146.8 (C_{quat}). EI + MS (m/z (%)): 311 (23), 310 (M^+, 100), 309 (13), 155 (21), 141 (42), 140 (13). IR (KBr): $\tilde{\nu}$ 1614 (w), 1545 (m), 1483 (w), 1456 (m), 1421 (m), 1340 (m), 1263 (w), 1232 (m), 1173 (m), 1142 (m), 1117 (m), 1099 (m), 1063 (w), 1028 (m), 1005 (w), 972 (m), 908 (w), 839 (m), 825 (m), 742 (s), 642 (w) cm^{-1}. Anal. calcd. for $C_{20}H_{14}N_4$ (310.4): C 77.40, H 4.55, N 18.05. Found: C 77.25, H 4.55, N 17.80.

3.6 ^{1}H NMR and ^{13}C NMR Spectra of Bisindoles and Analogues 6

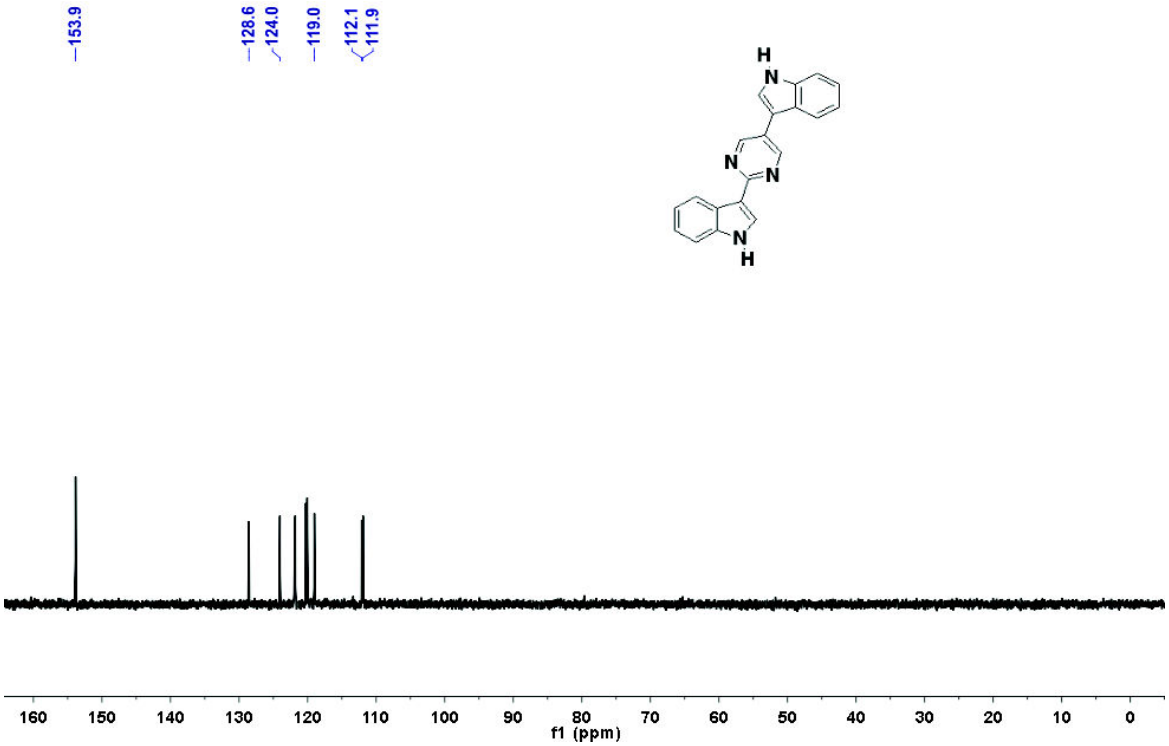
3.6.1 3-3□-(Pyrimidin-2,5-diyl)bis(1*H*-indole) (6a)



^{1}H NMR of **6a** (20 mg) in 0.7 mL DMSO-d_6 at 299 K (δ in ppm).

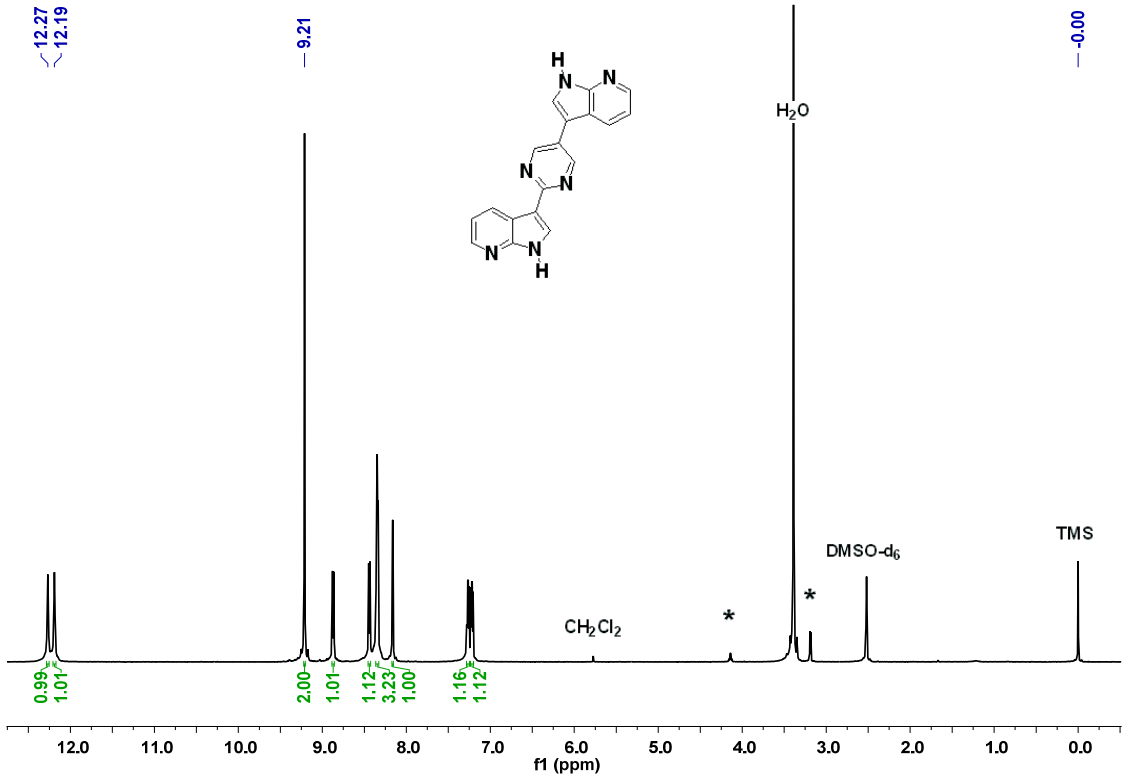


^{13}C NMR of **6a** (20 mg) in 0.7 mL DMSO-d_6 at 299 K (δ in ppm).

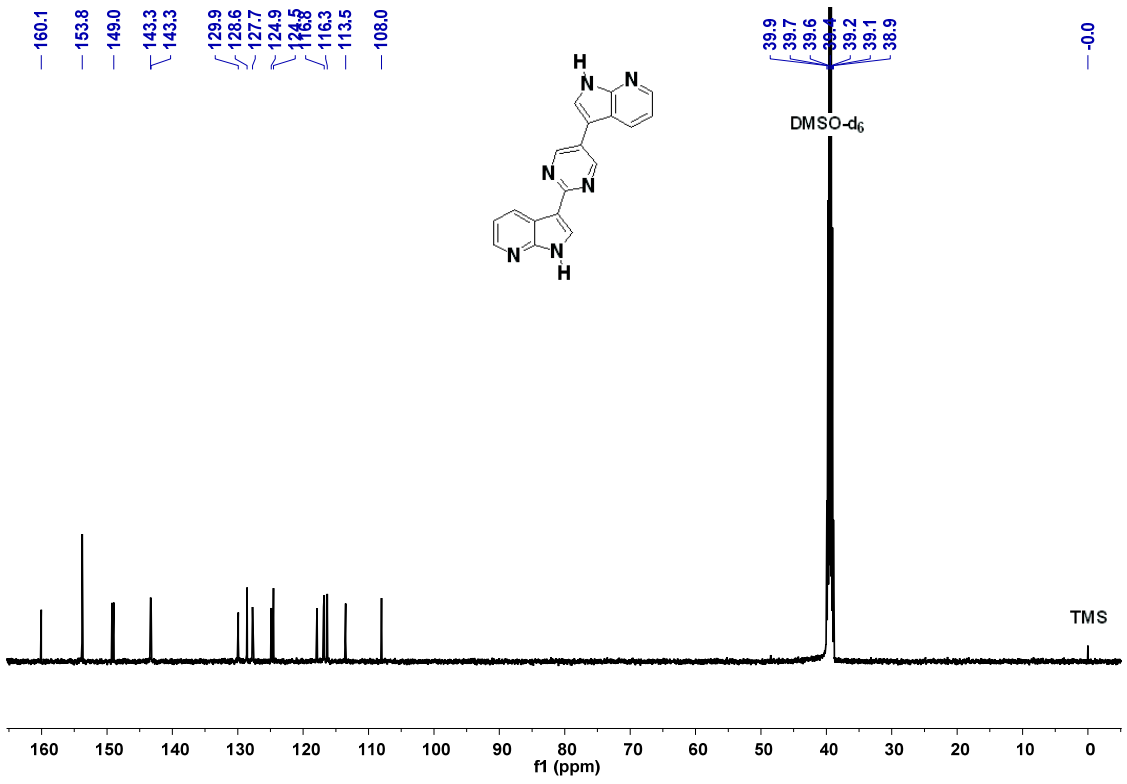


^{13}C 135-DEPT NMR of **6a** (20 mg) in 0.7 mL DMSO-d_6 at 299 K (δ in ppm).

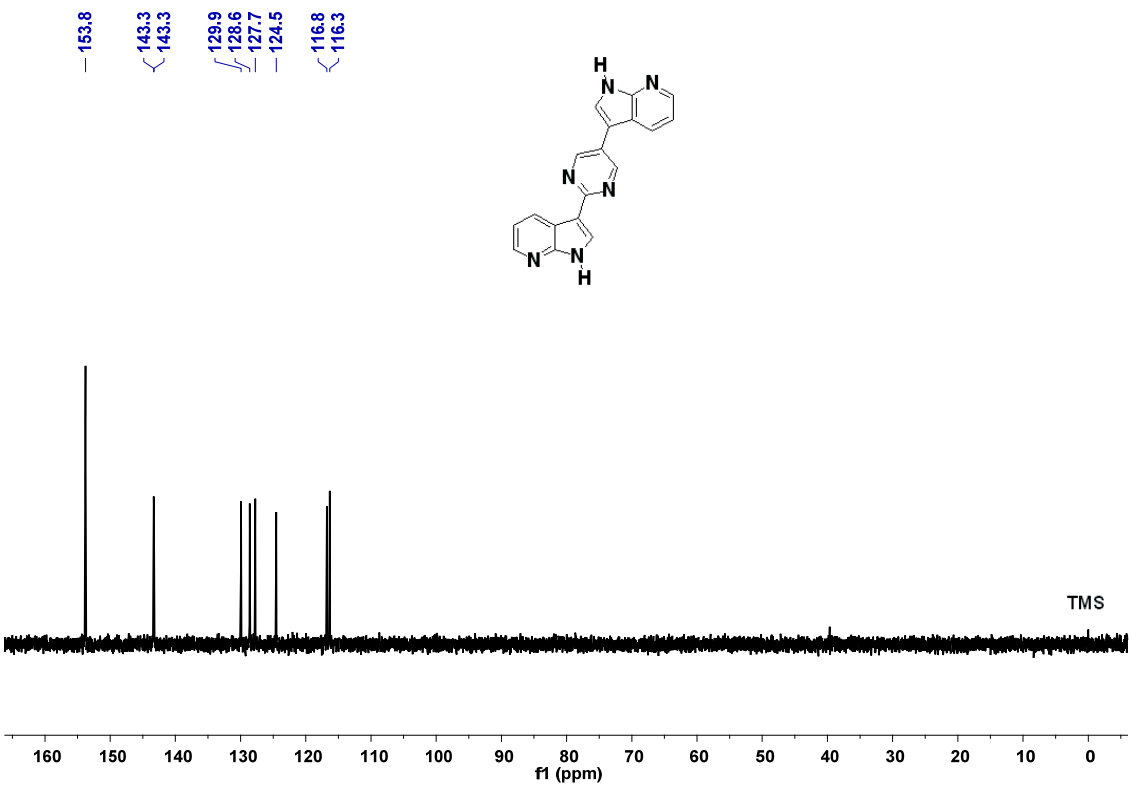
3.6.2 3,3-(Pyrimidine-2,5-diyl)bis(1*H*-pyrrolo[2,3-*b*]pyridine) (6b)



^{1}H NMR of **6b** (20 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm). *Impurities from residual solvents.

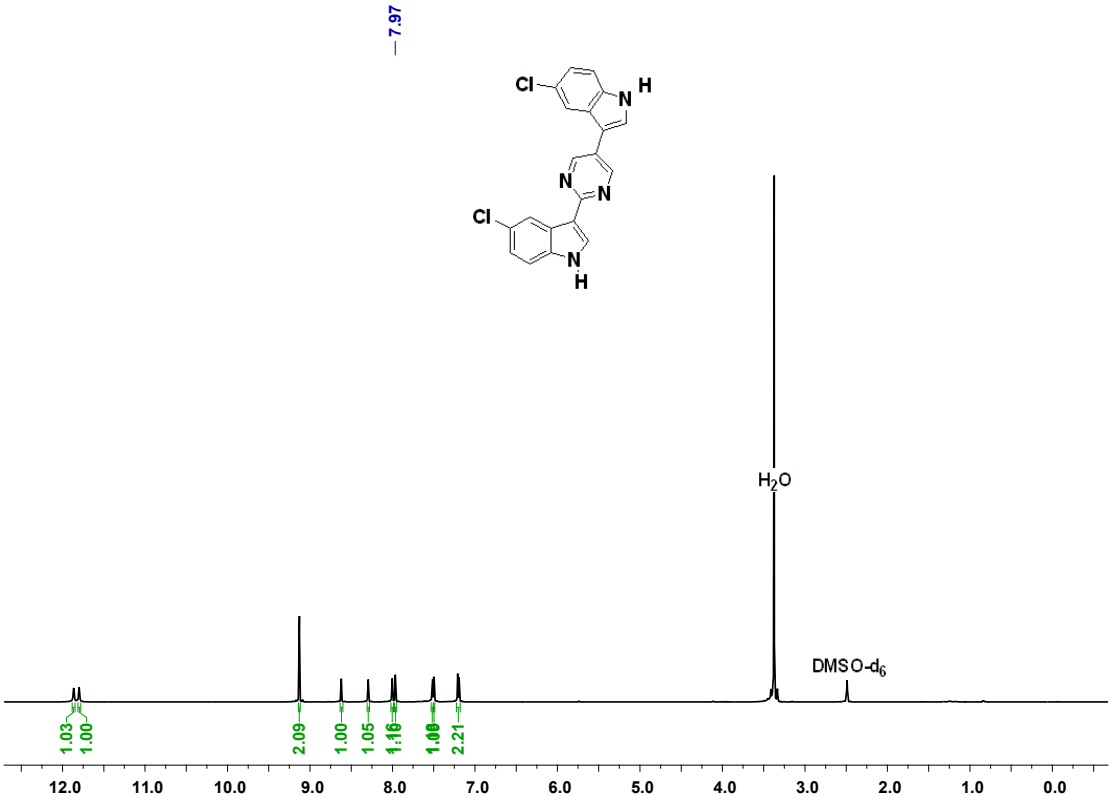


^{13}C NMR of **6b** (20 mg) in 0.7 mL DMSO-d_6 at 297 K (δ in ppm).

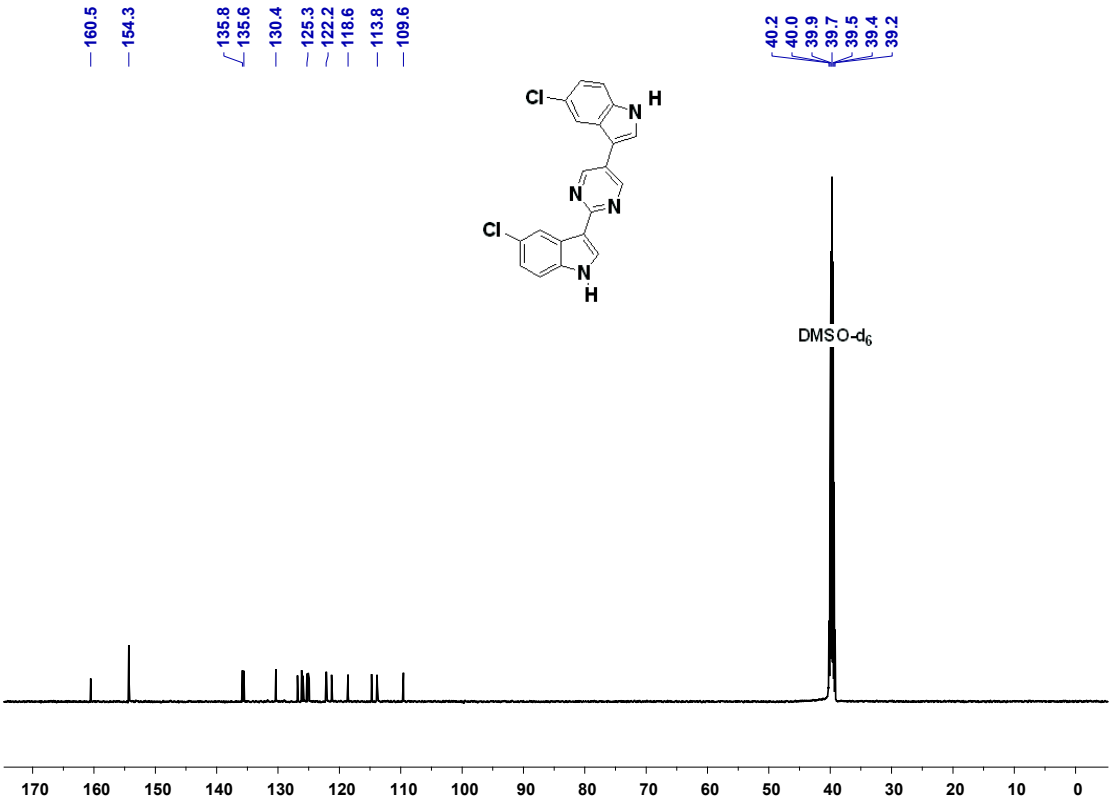


^{13}C 135-DEPT NMR of **6b** (20 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).

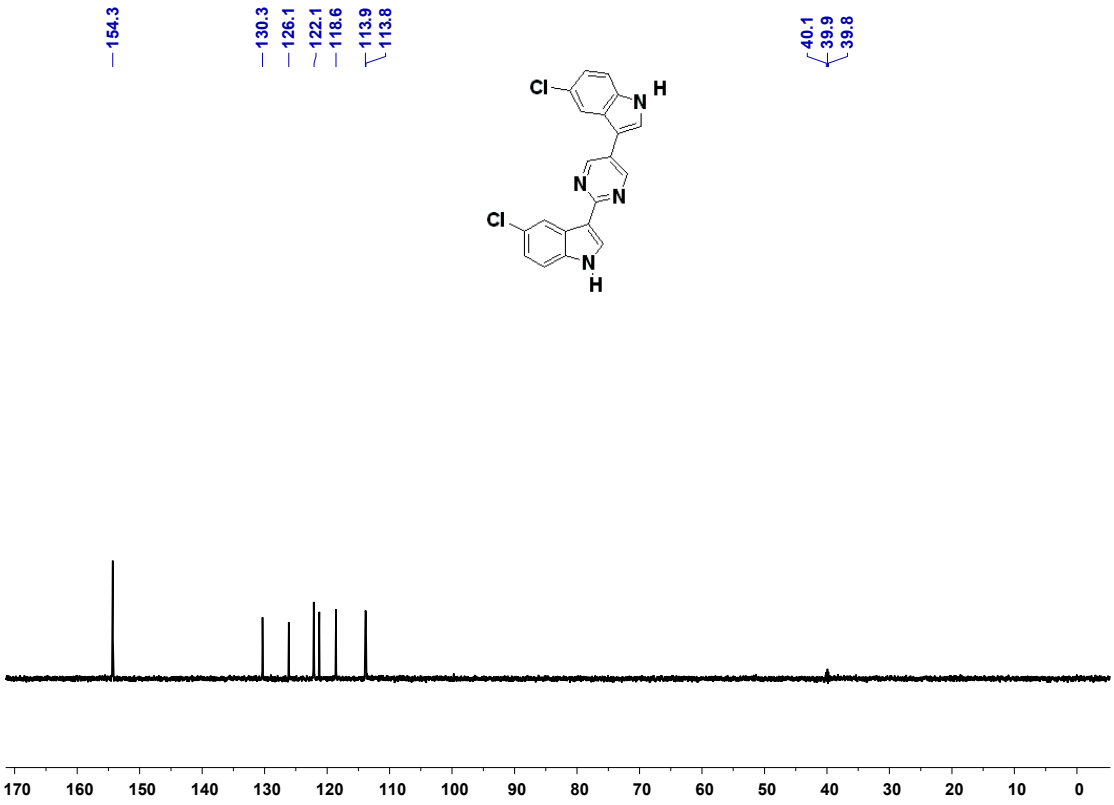
3.6.3 3,3'-(Pyrimidine-2,5-diyl)bis(5-chloro-1*H*-indole) (6c)



^{1}H NMR of **6c** (20 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).

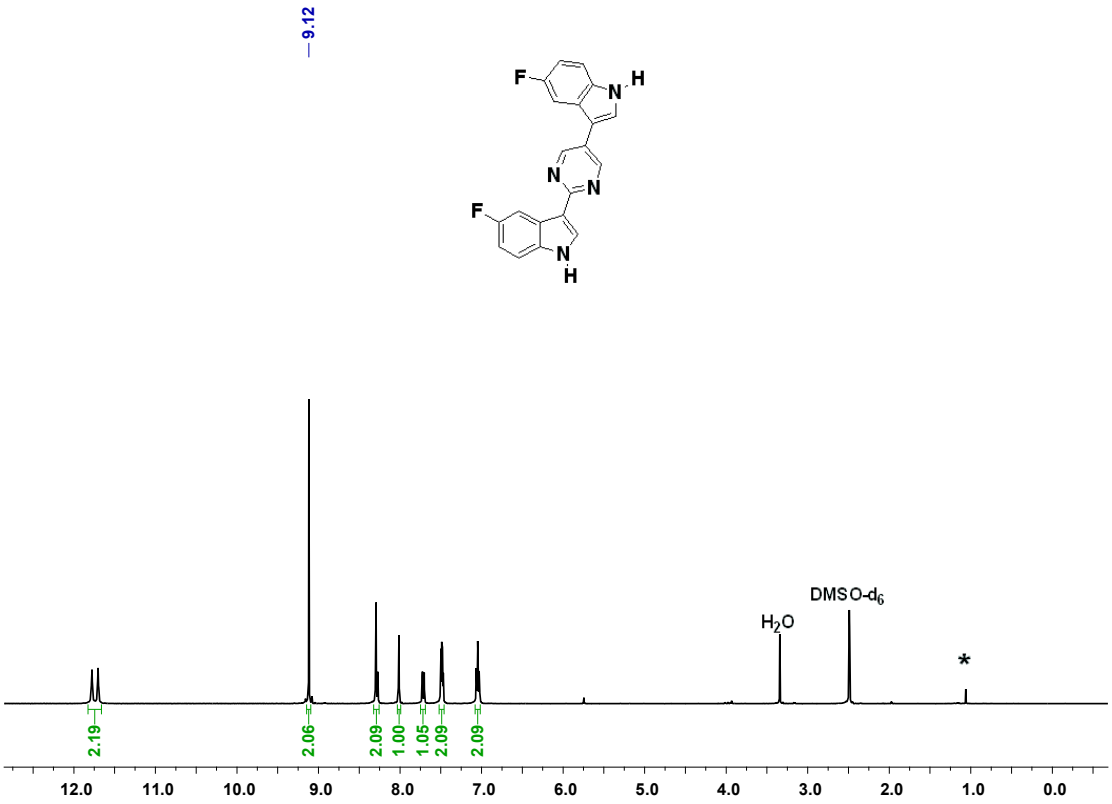


^{13}C NMR of **6c** (20 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).

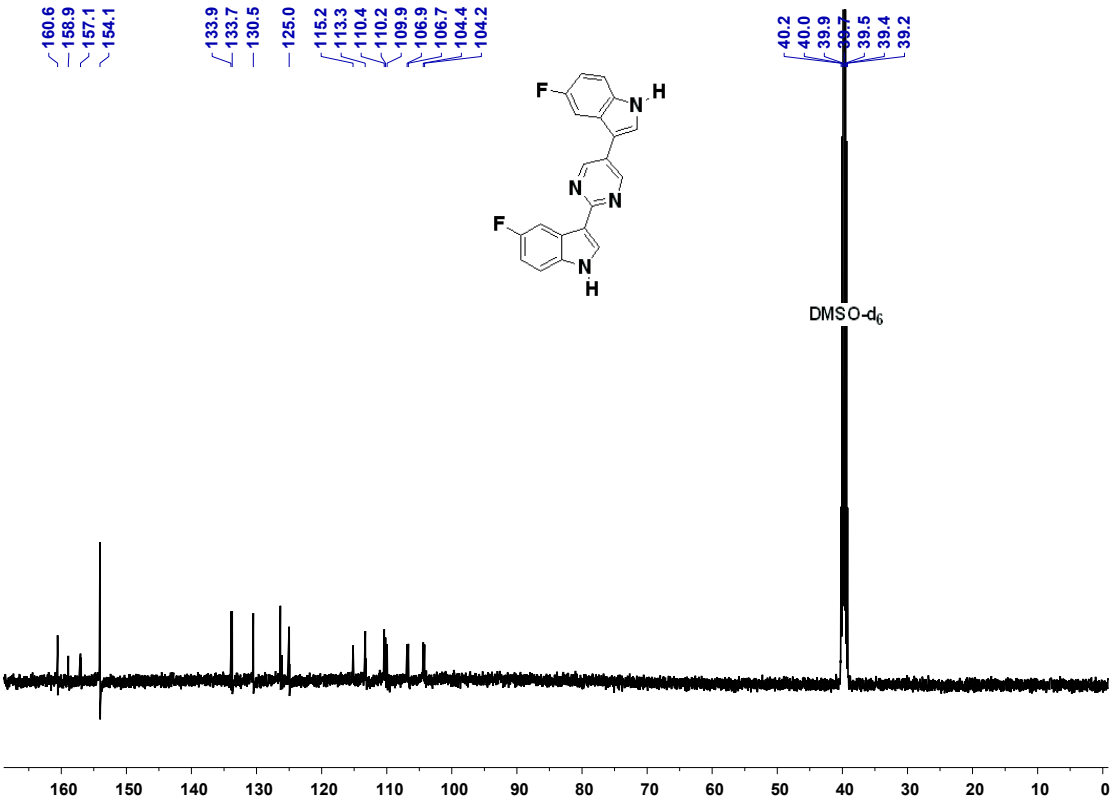


^{13}C 135-DEPT NMR of **6c** (20 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).

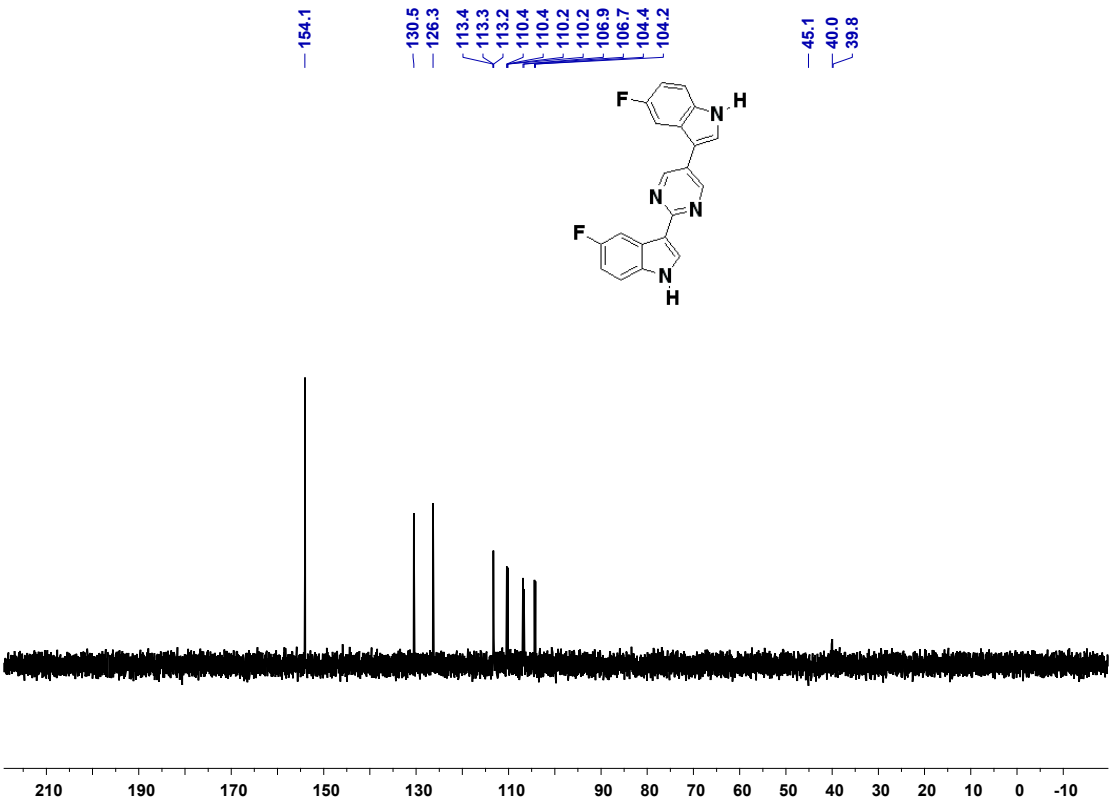
3.6.4 3,3'-(Pyrimidine-2,5-diyl)bis(5-fluoro-1*H*-indole) (6d)



^{1}H NMR of **6d** (15 mg) in 0.7 mL DMSO-d_6 at 298 K (δ in ppm). *Impurities from residual solvents.

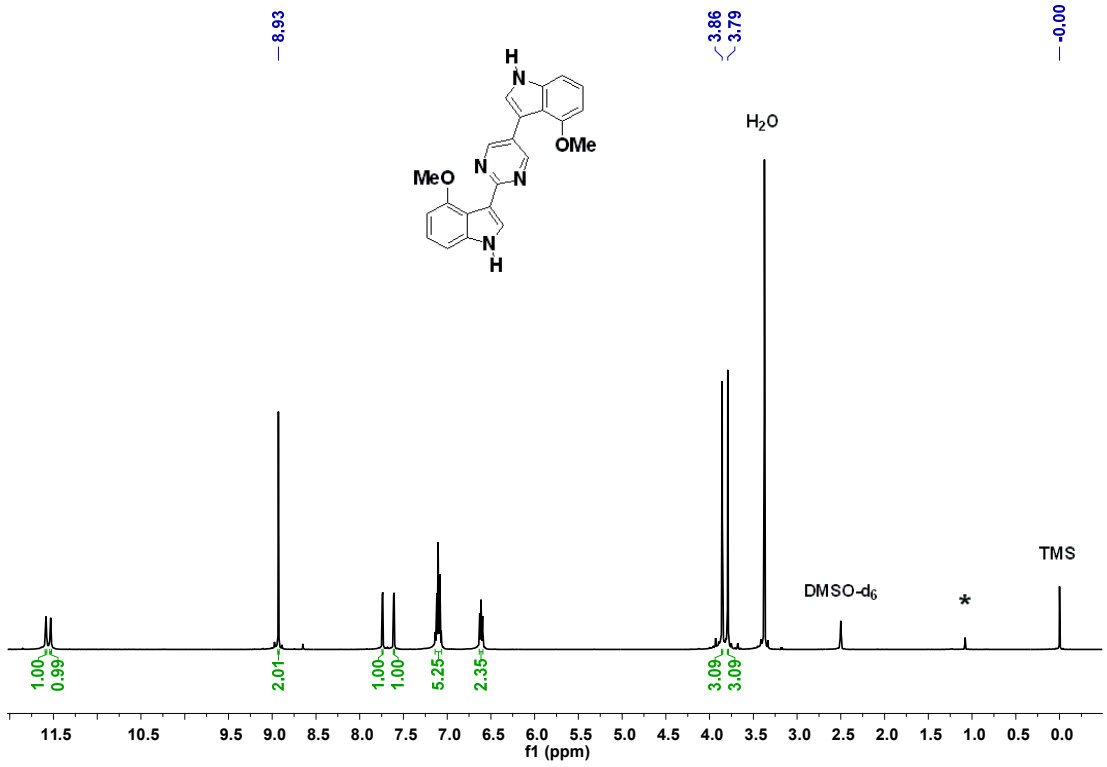


^{13}C NMR of **6d** (15 mg) in 0.7 mL DMSO-d_6 at 298 K (δ in ppm).

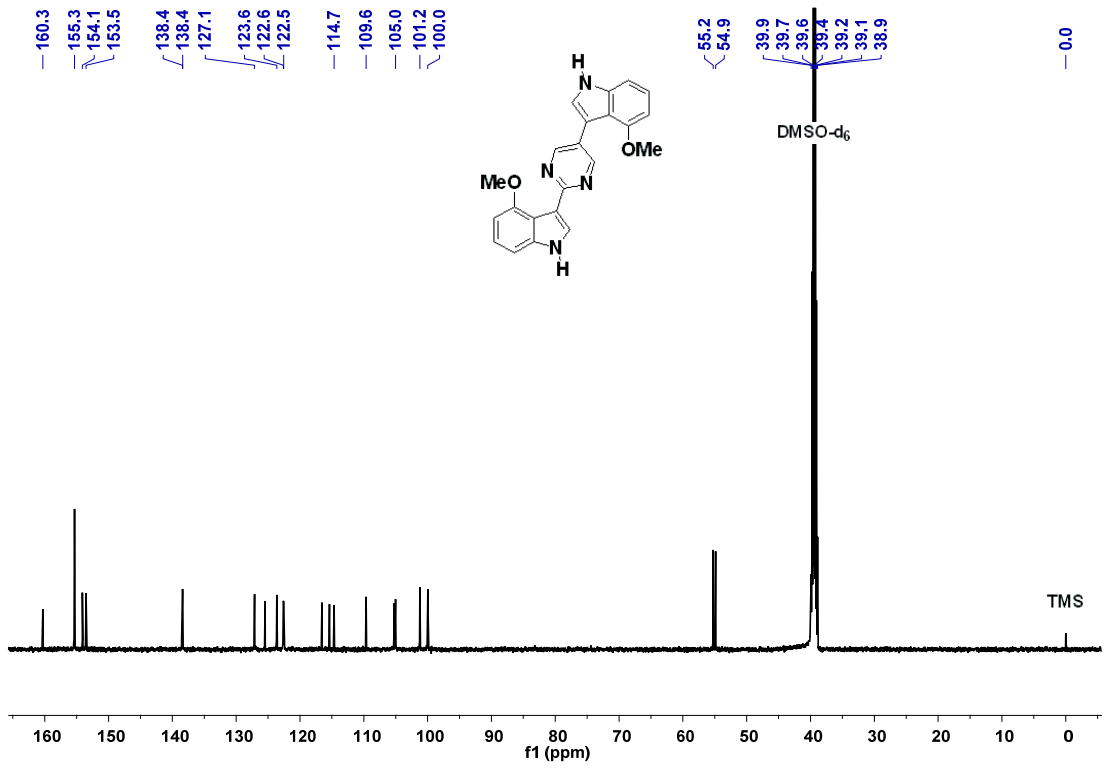


^{13}C 135-DEPT NMR of **6d** (15 mg) in 0.7 mL DMSO-d_6 at 298 K (δ in ppm).

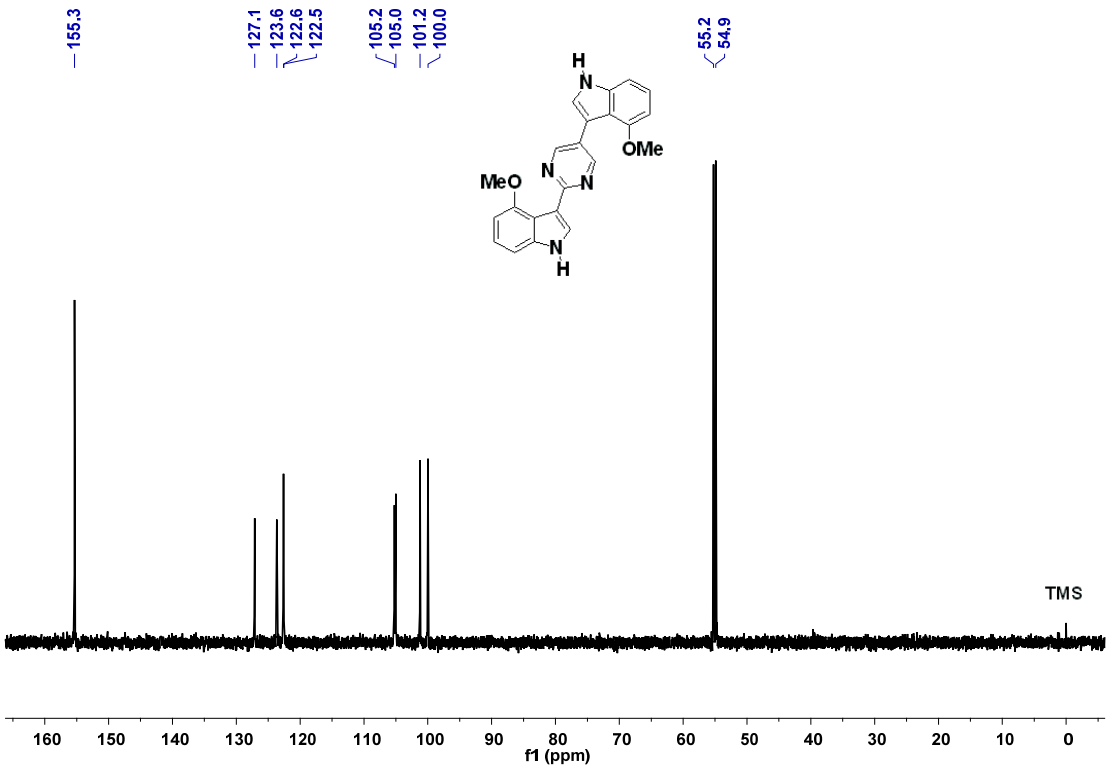
3.6.5 3,3'-(Pyrimidine-2,5-diyl)bis(4-methoxy-1*H*-indole) (6e)



^{1}H NMR of **6e** (20 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm). *Impurities from residual solvents.

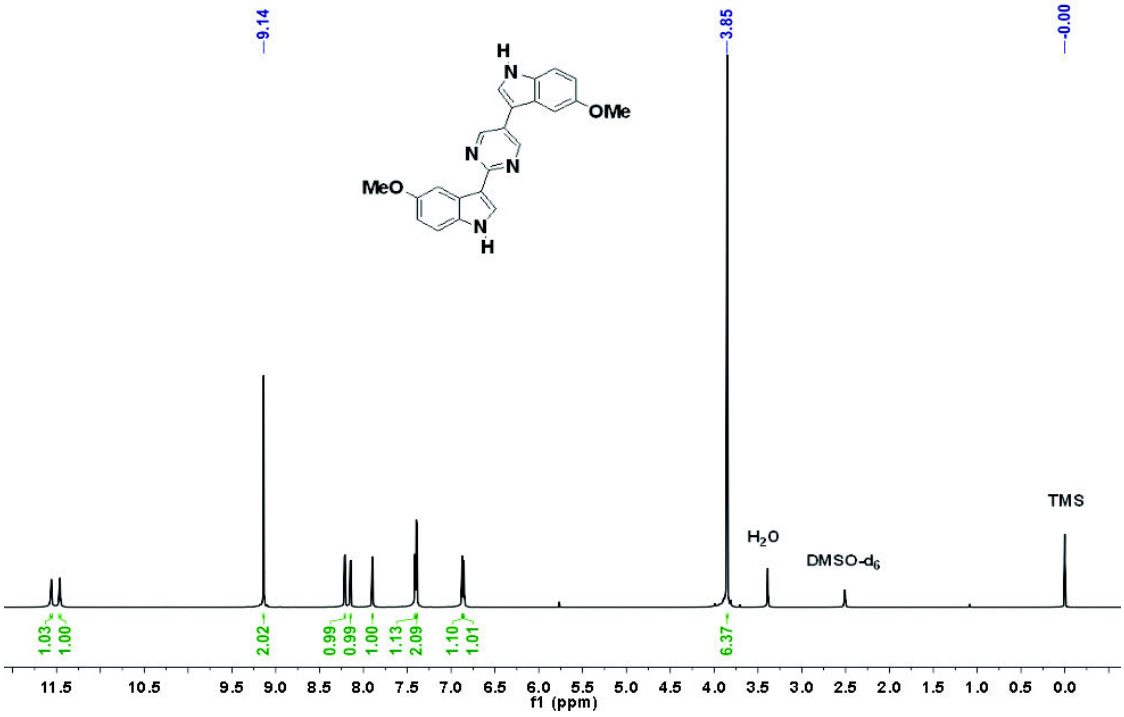


^{13}C NMR of **6e** (20 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).

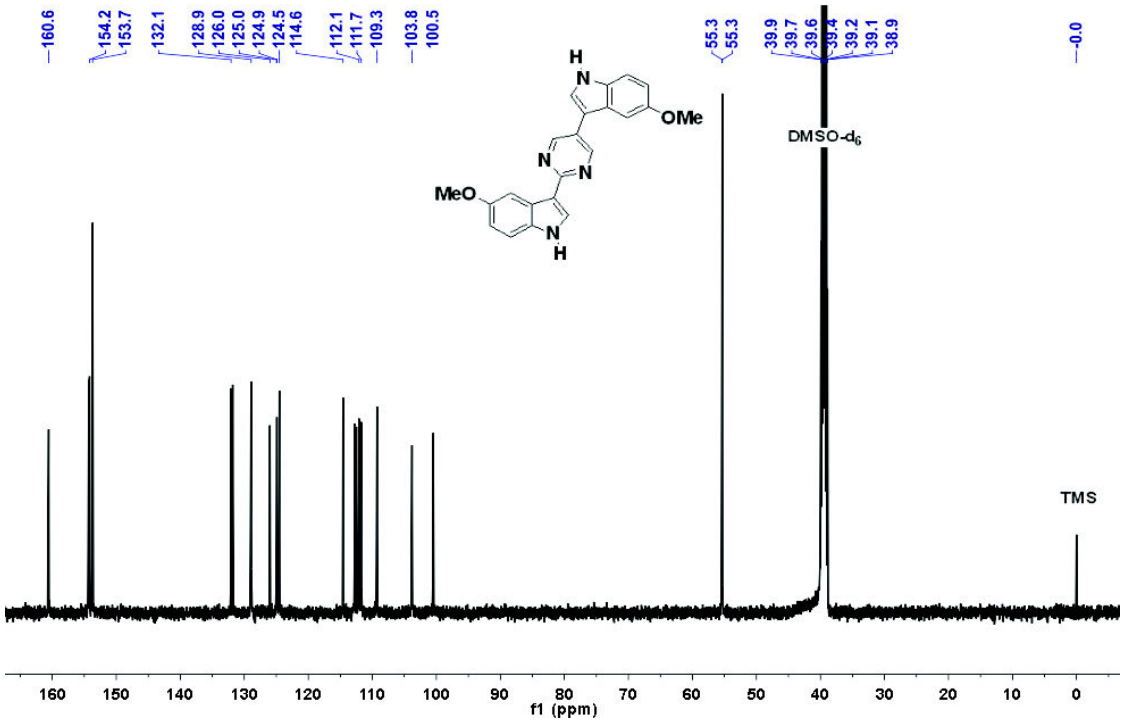


^{13}C 135-DEPT NMR of **6e** (20 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).

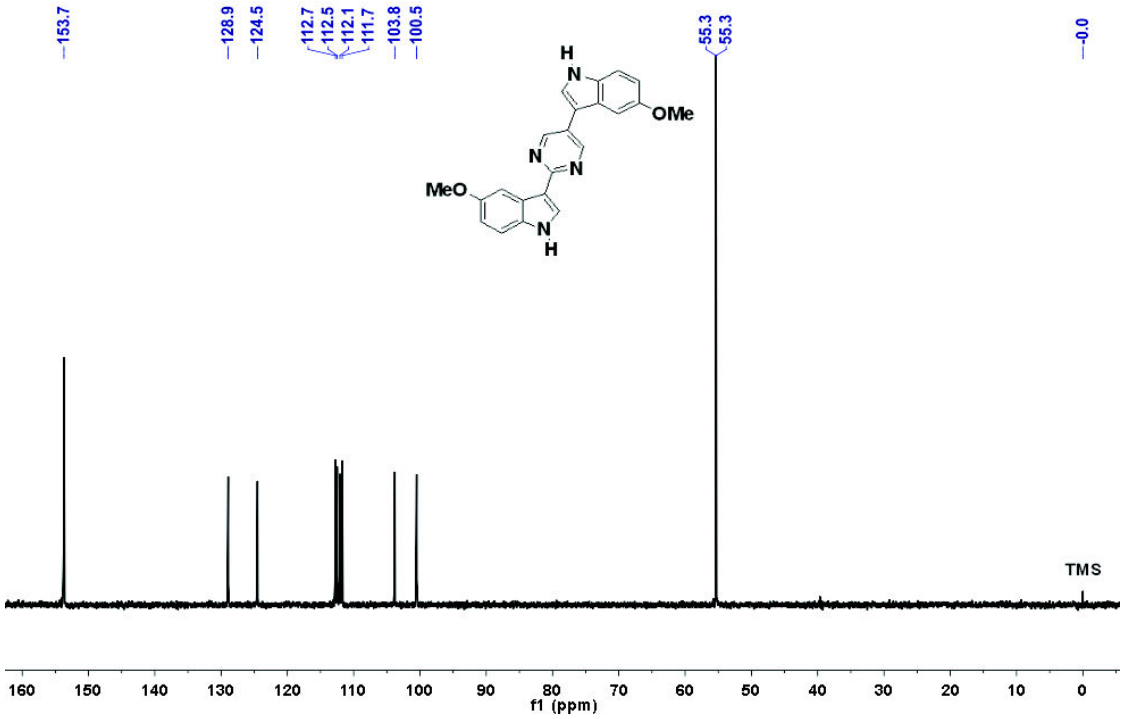
3.6.6 3,3'-(Pyrimidine-2,5-diyl)bis(5-methoxy-1*H*-indole) (6f)



^{1}H NMR of **6f** (30 mg) in 0.7 mL DMSO-d_6 at 295 K (δ in ppm).

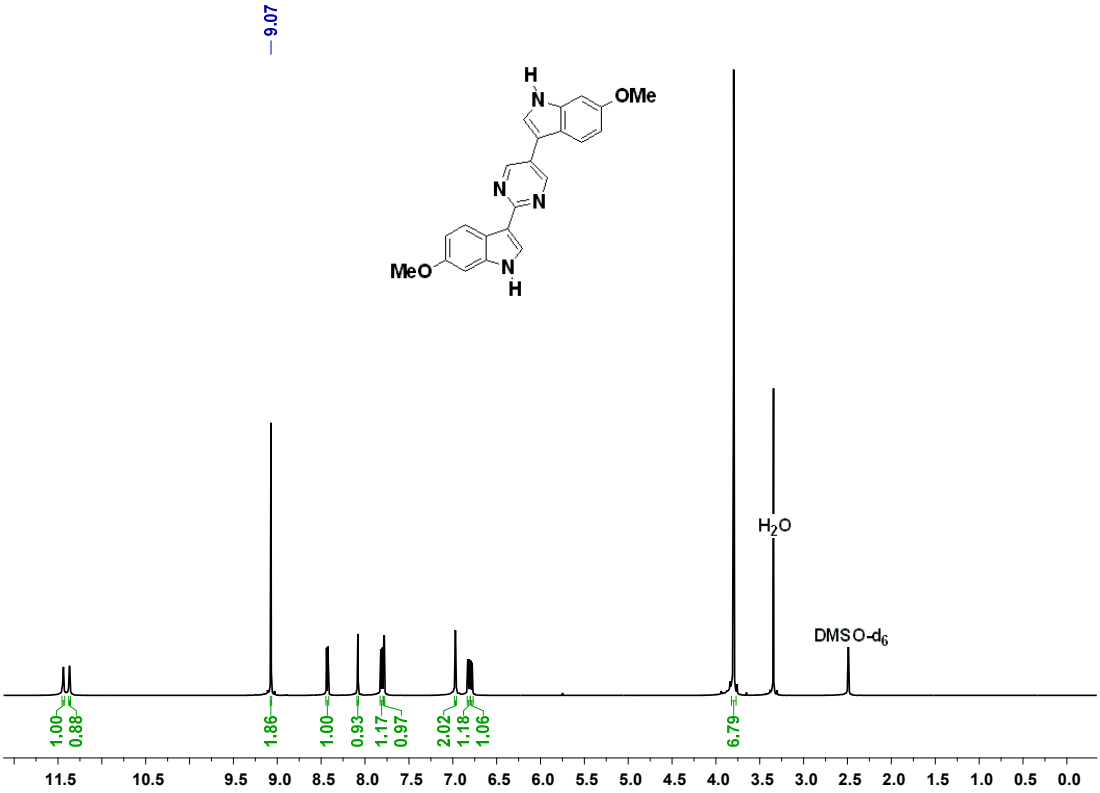


^{13}C NMR of **6f** (30 mg) in 0.7 mL DMSO-d_6 at 295 K (δ in ppm).

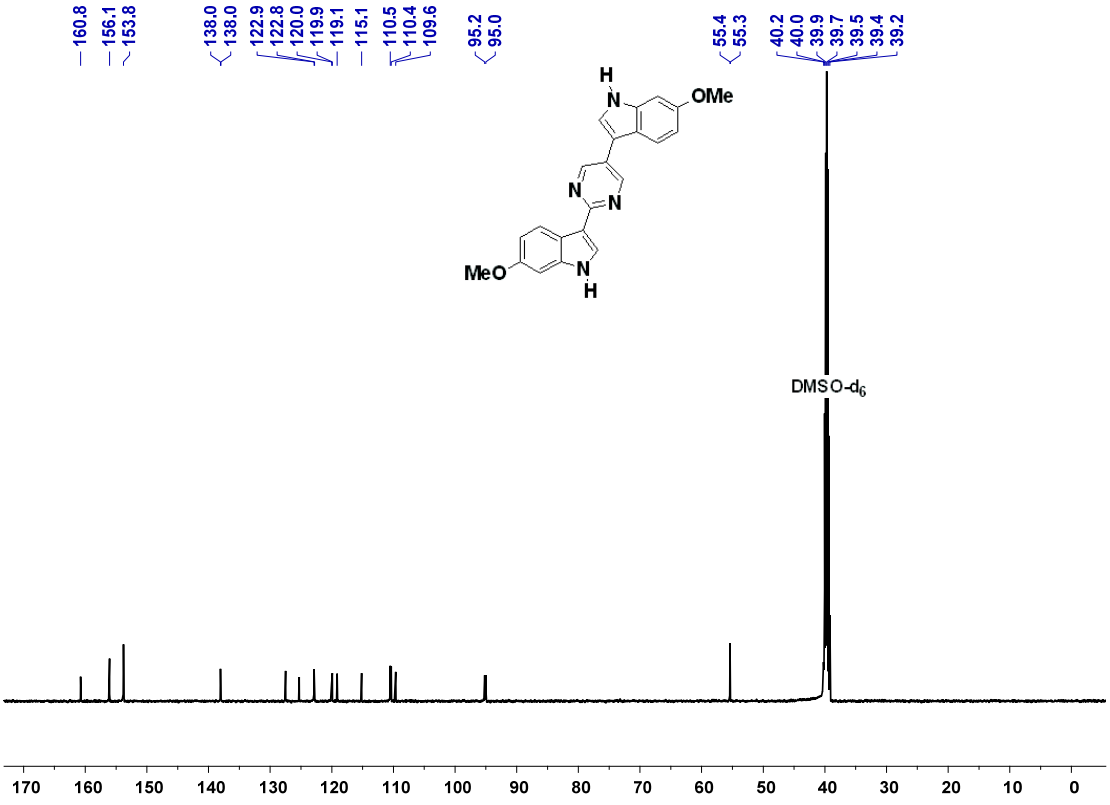


^{13}C 135-DEPT NMR of **6f** (30 mg) in 0.7 mL DMSO-d_6 at 295 K (δ in ppm).

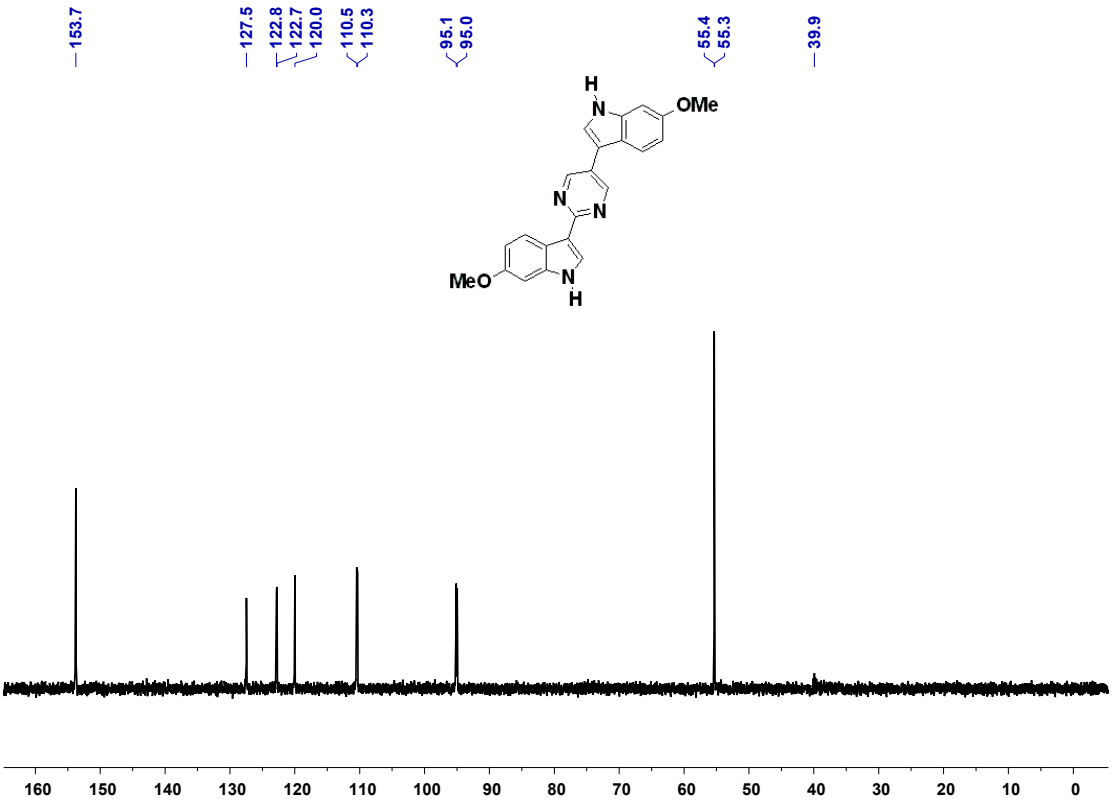
3.6.7 3,3'-(Pyrimidine-2,5-diyl)bis(6-methoxy-1*H*-indole) (6g)



^{1}H NMR of **6g** (16 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).

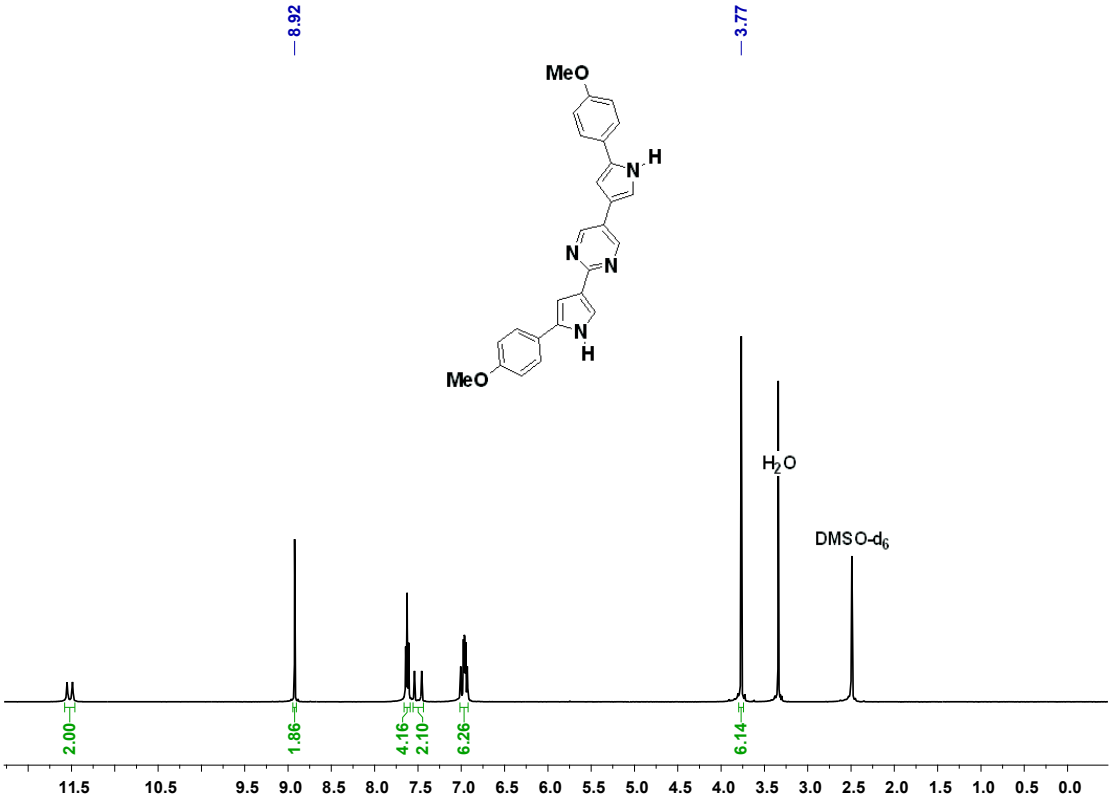


^{13}C NMR of **6g** (16 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).

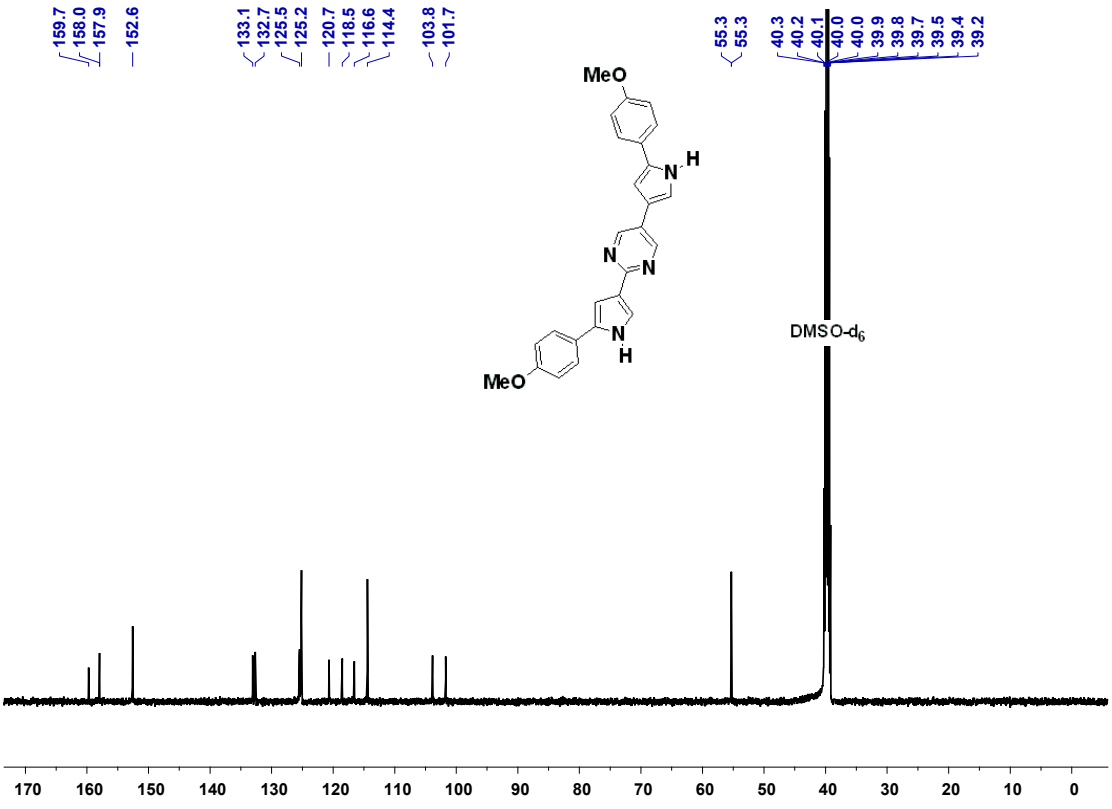


^{13}C 135-DEPT NMR of **6g** (16 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).

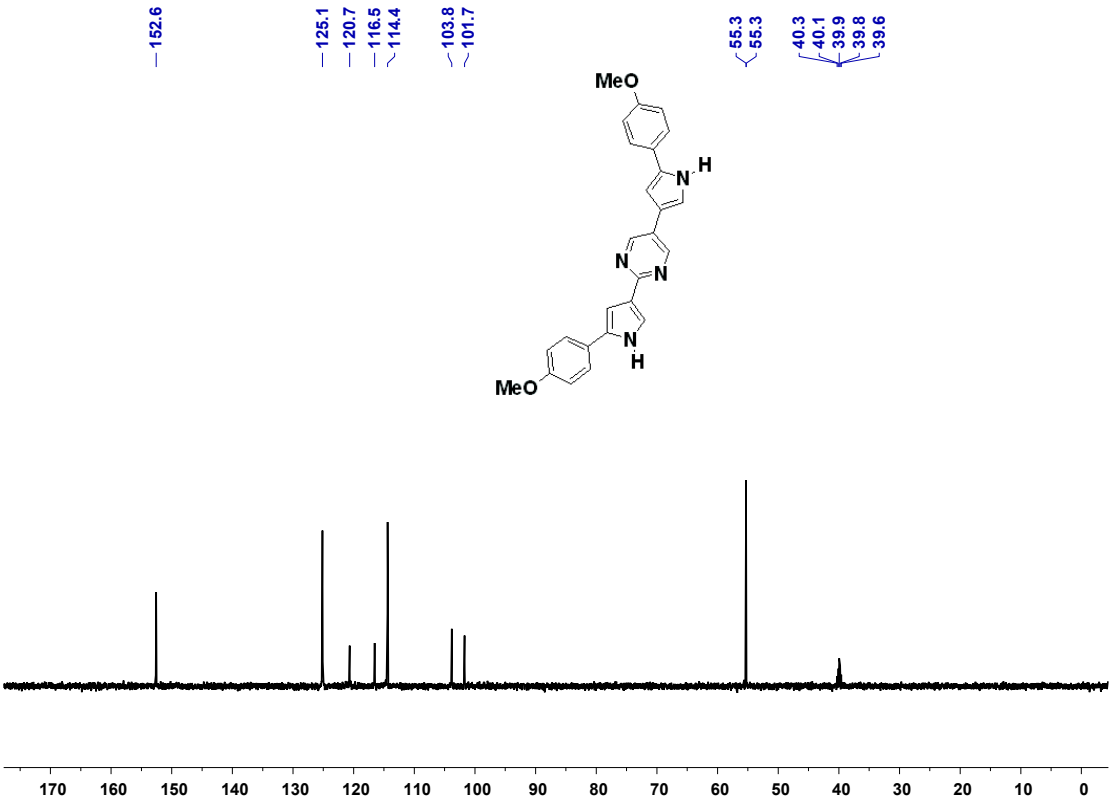
3.6.8 2,5-Bis(5-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)pyrimidine (6i)



^{1}H NMR of **6i** (20 mg) in 0.7 mL DMSO-d_6 at 297 K (δ in ppm).

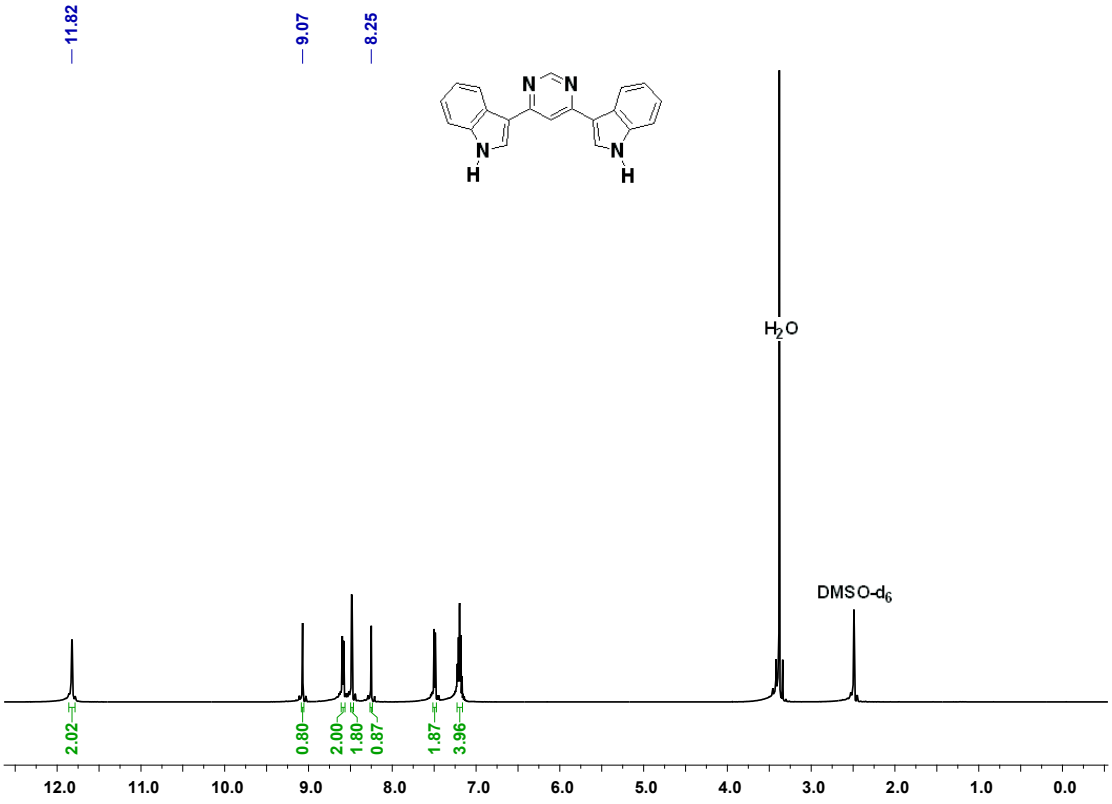


^{13}C NMR of **6i** (20 mg) in 0.7 mL DMSO-d_6 at 297 K (δ in ppm).

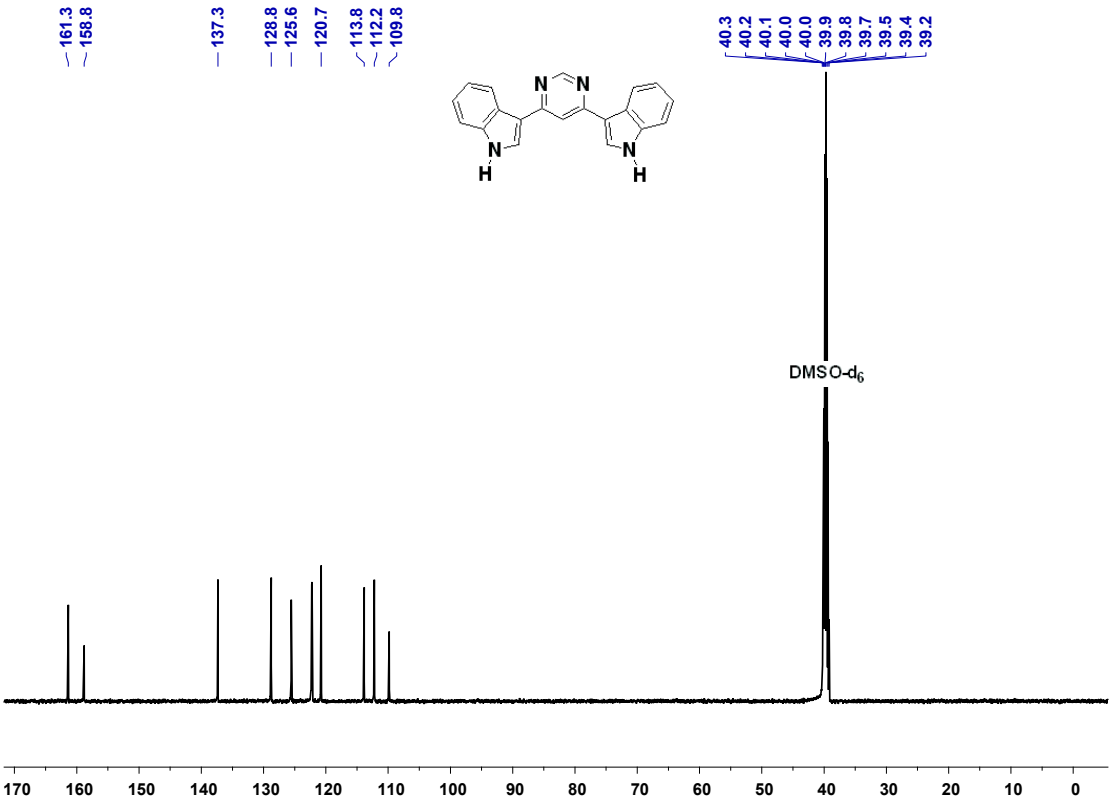


^{13}C 135-DEPT NMR of **6i** (20 mg) in 0.7 mL DMSO-d_6 at 297 K (δ in ppm).

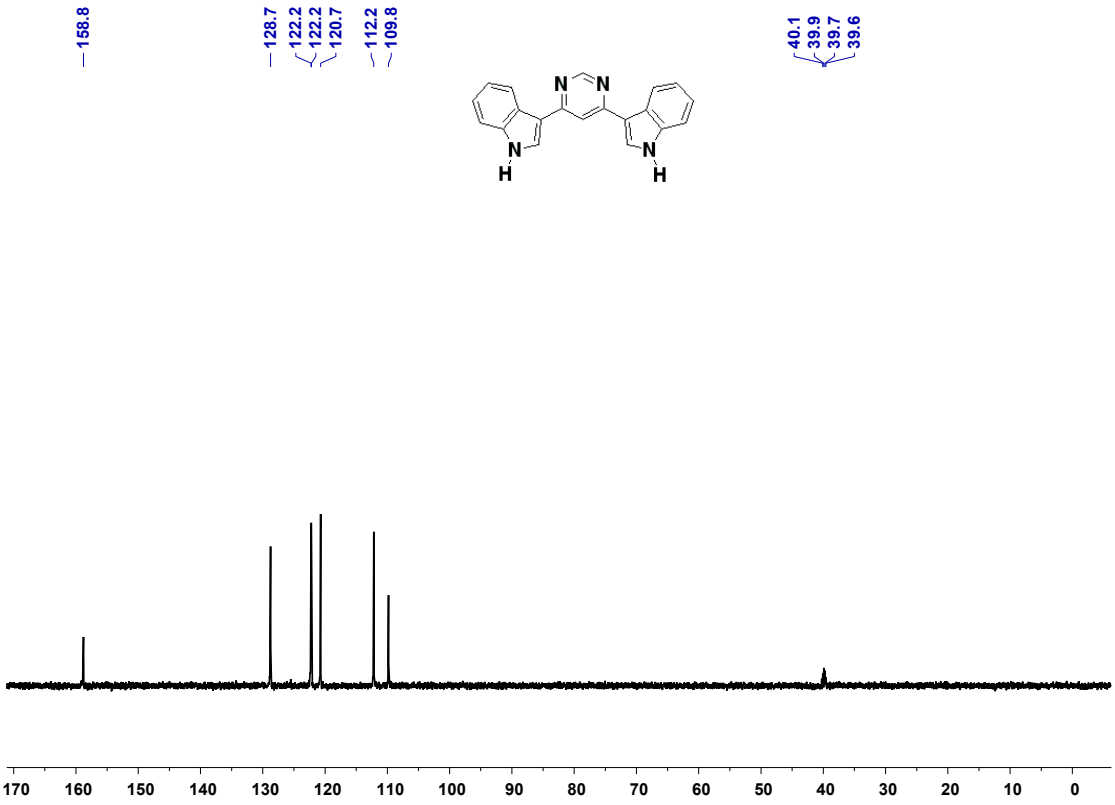
3.6.9 4,6-Di(1*H*-indol-3-yl)pyrimidine (6j)



^{1}H NMR of **6j** (30 mg) in 0.7 mL DMSO-d_6 at 298 K (δ in ppm).

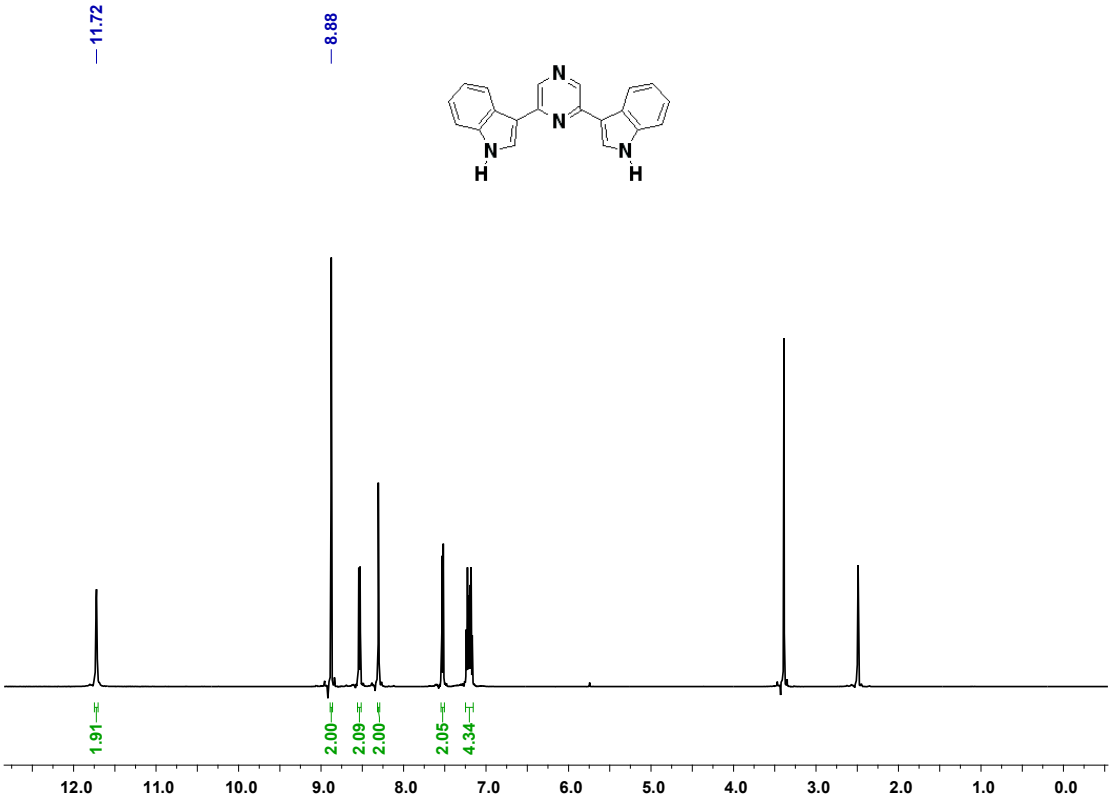


^{13}C NMR of **6j** (30 mg) in 0.7 mL DMSO-d_6 at 298 K (δ in ppm).

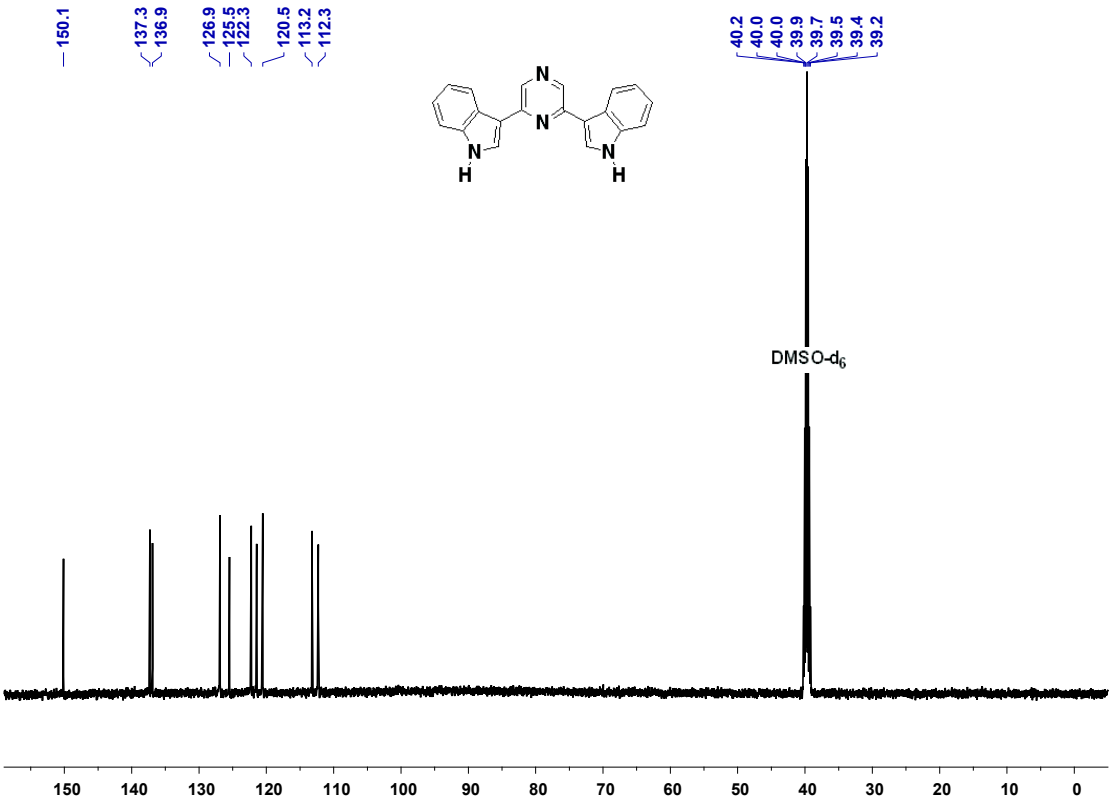


^{13}C 135-DEPT NMR of **6j** (30 mg) in 0.7 mL DMSO-d_6 at 298 K (δ in ppm).

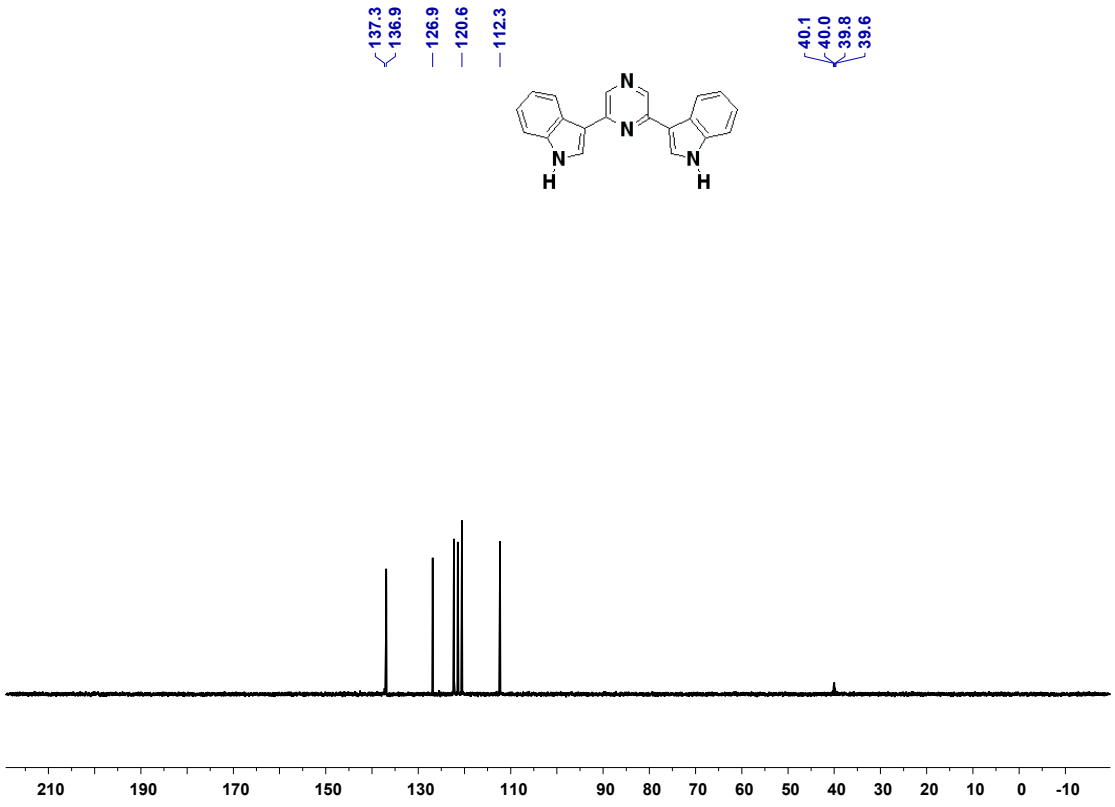
3.6.10 2,6-Di(1*H*-indol-3-yl)pyrazine (6k)



^{1}H NMR of **6k** (30 mg) in 0.7 mL DMSO-d_6 at 298 K (δ in ppm).

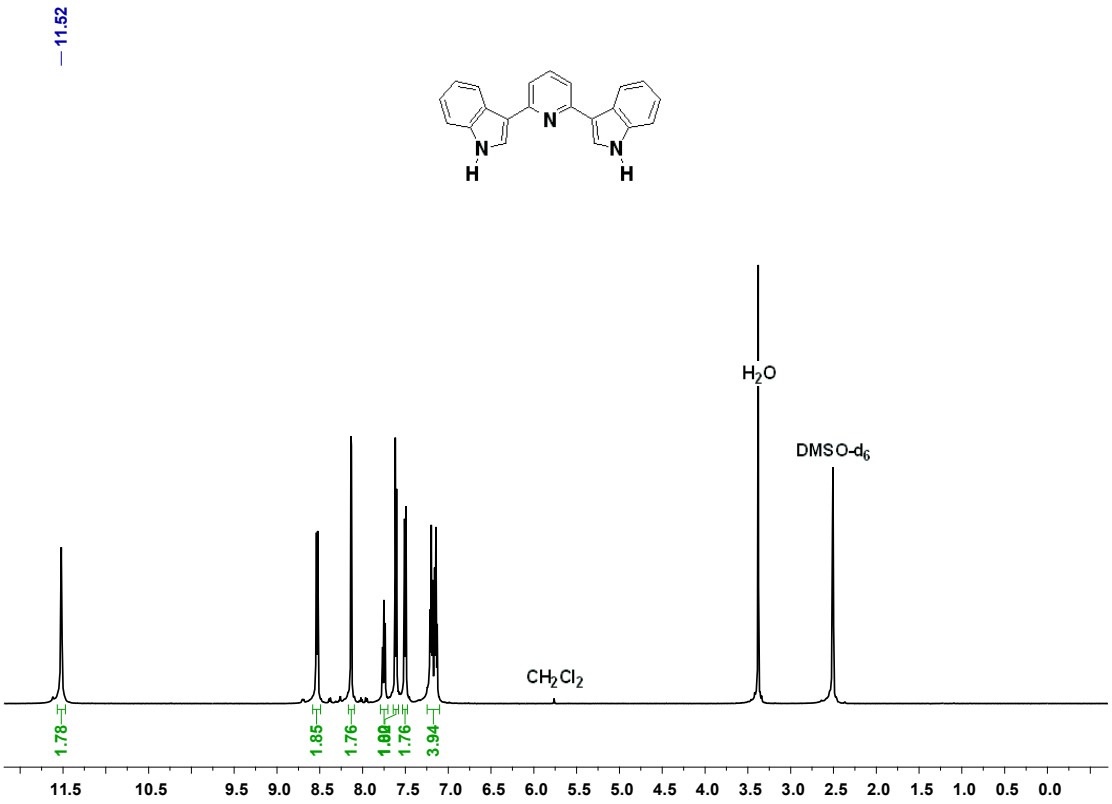


^{13}C NMR of **6k** (30 mg) in 0.7 mL DMSO-d_6 at 298 K (δ in ppm).

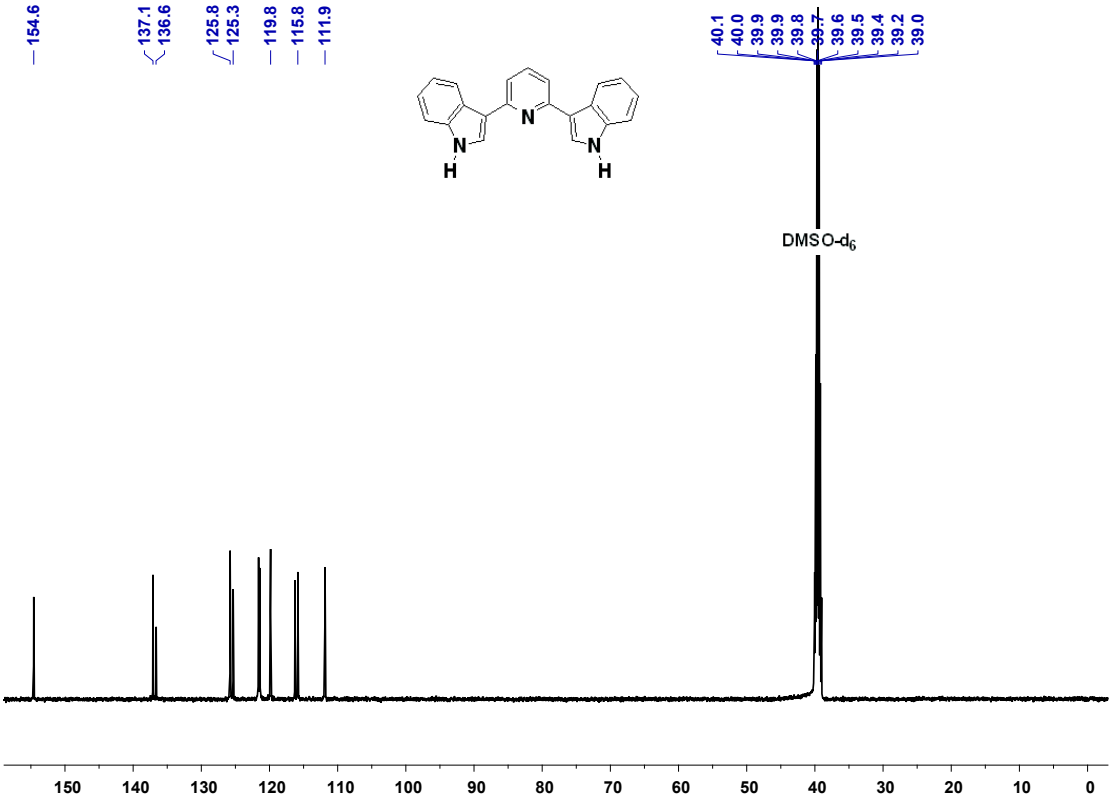


^{13}C 135-DEPT NMR of **6k** (30 mg) in 0.7 mL DMSO-d_6 at 298 K (δ in ppm).

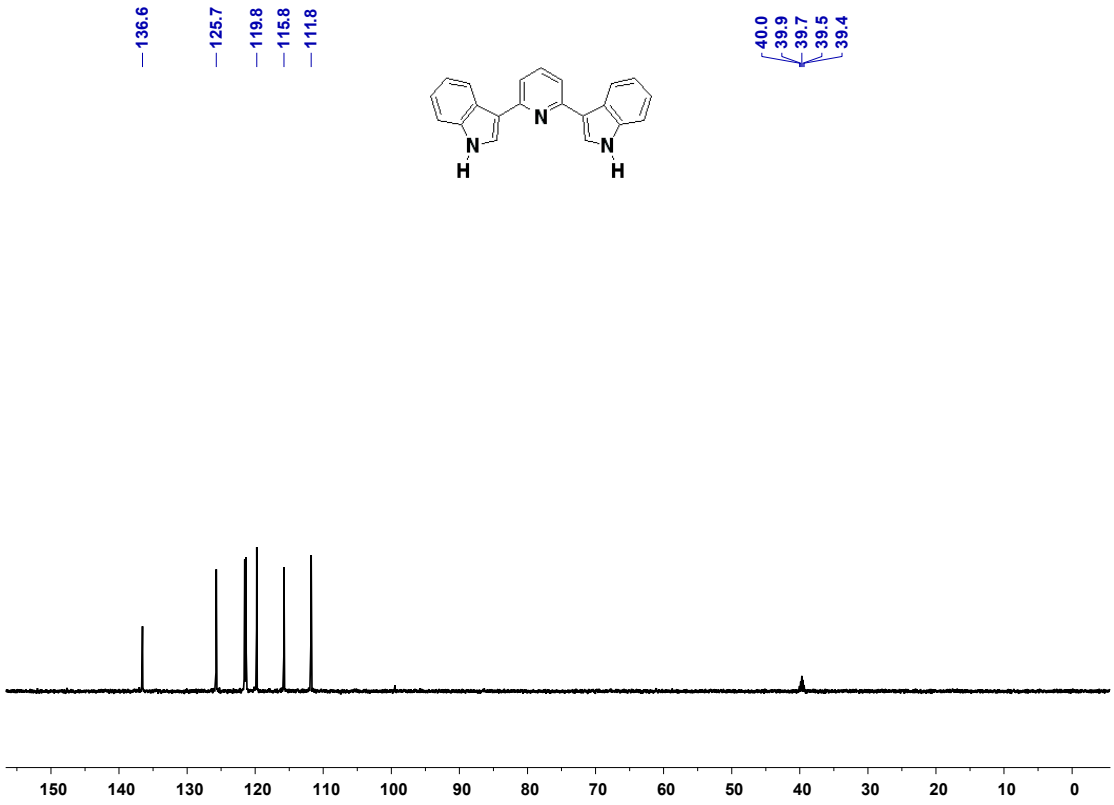
3.6.11 2,6-Di(1*H*-indol-3-yl)pyridine (6l)



^{1}H NMR of **6l** (25 mg) in 0.7 mL DMSO-d_6 at 297 K (δ in ppm).

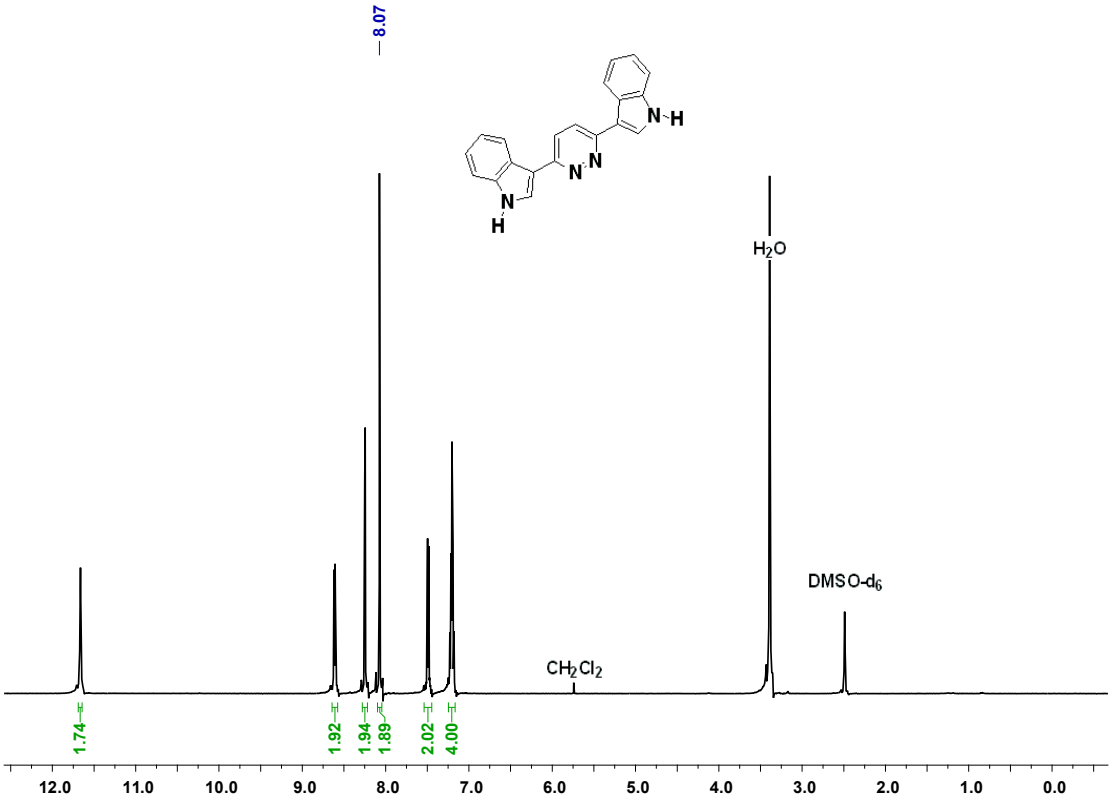


^{13}C NMR of **6l** (25 mg) in 0.7 mL DMSO-d_6 at 297 K (δ in ppm).

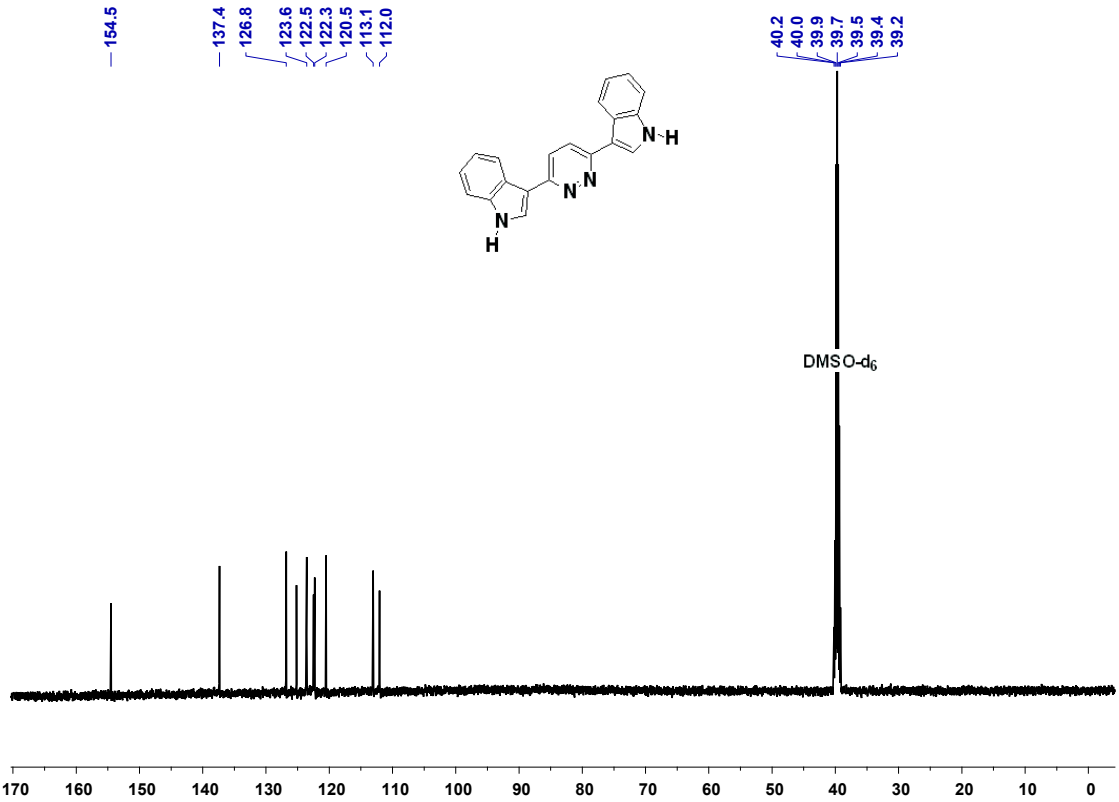


^{13}C 135-DEPT NMR of **6l** (25 mg) in 0.7 mL DMSO-d_6 at 297 K (δ in ppm).

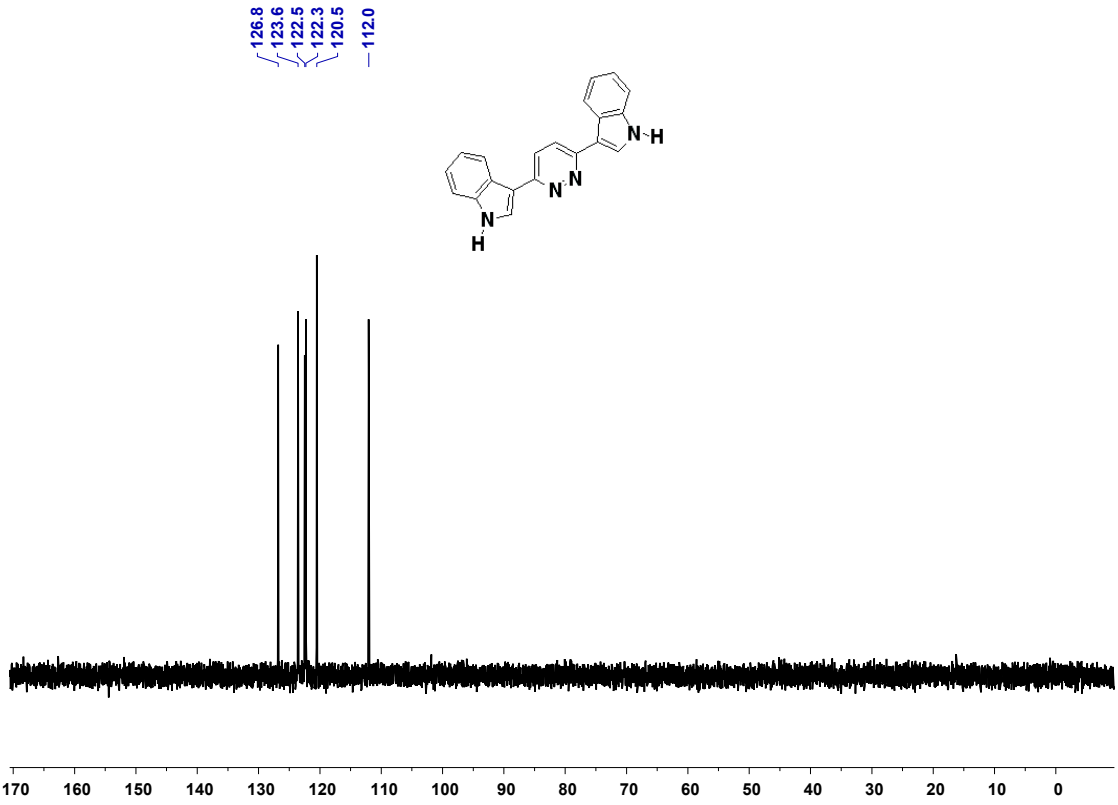
3.6.12 3,6-Di(1*H*-indol-3-yl)pyridazine (6m)



^{1}H NMR of **6m** (20 mg) in 0.7 mL DMSO-d_6 at 299 K (δ in ppm).

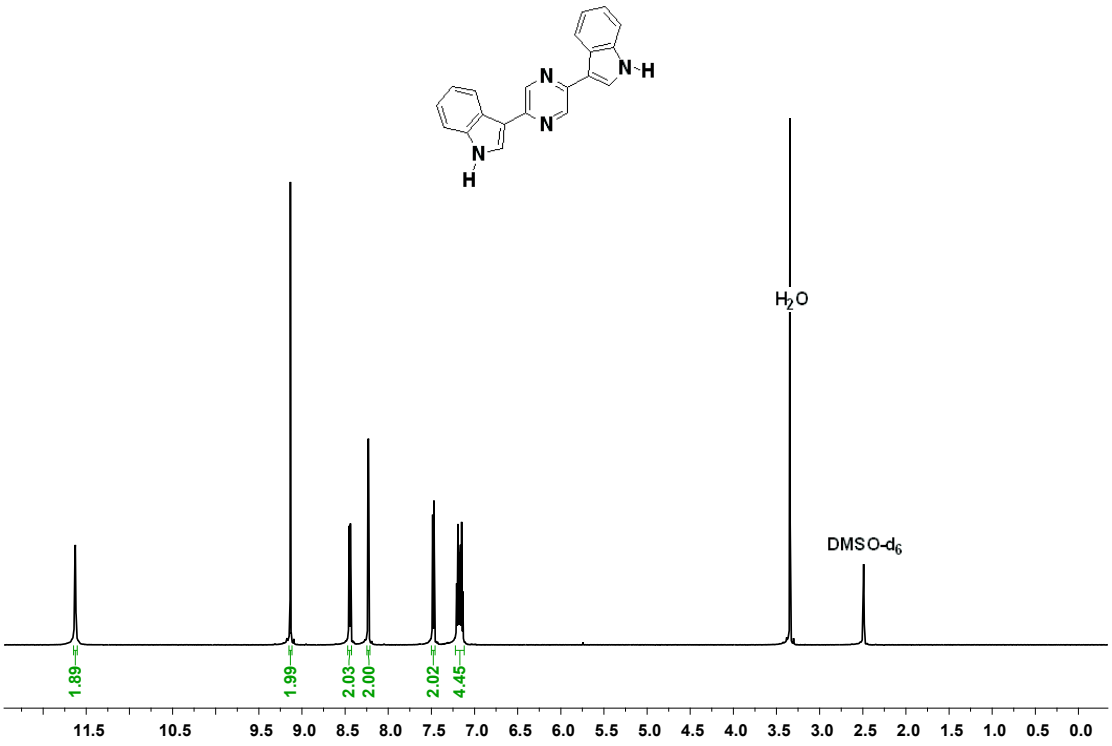


^{13}C NMR of **6m** (20 mg) in 0.7 mL DMSO-d_6 at 299 K (δ in ppm).

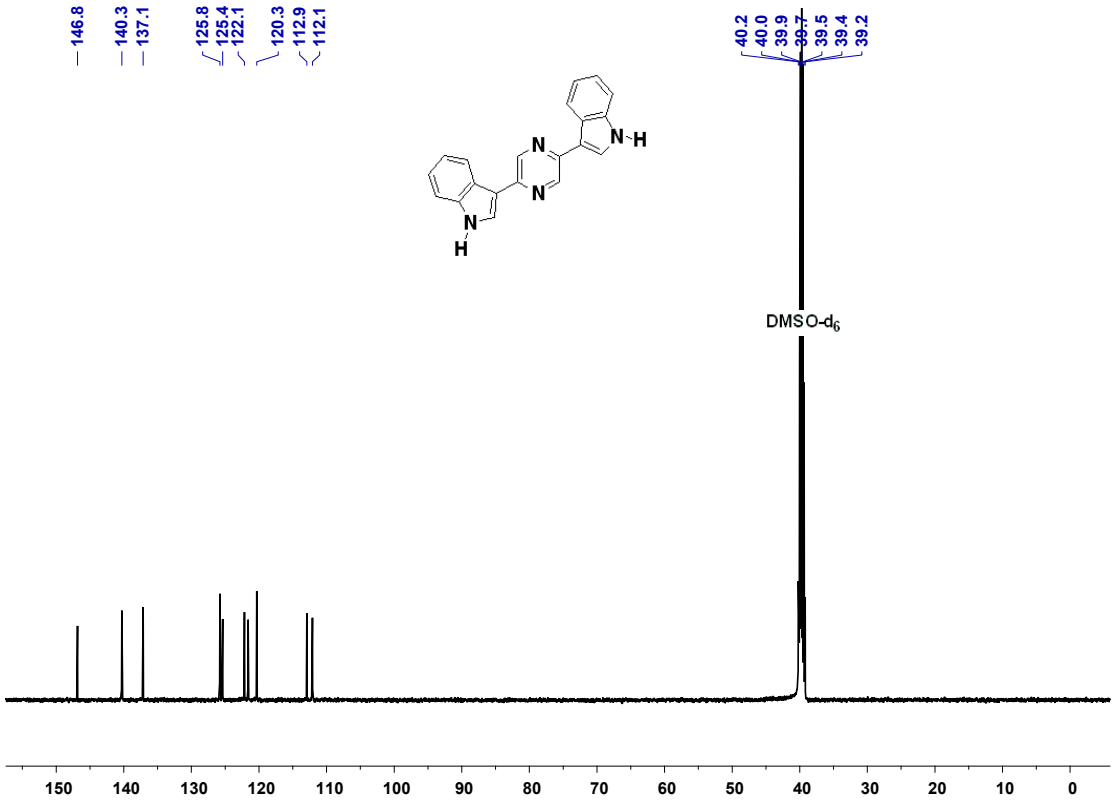


^{13}C 135-DEPT NMR of **6m** (20 mg) in 0.7 mL DMSO-d_6 at 299 K (δ in ppm).

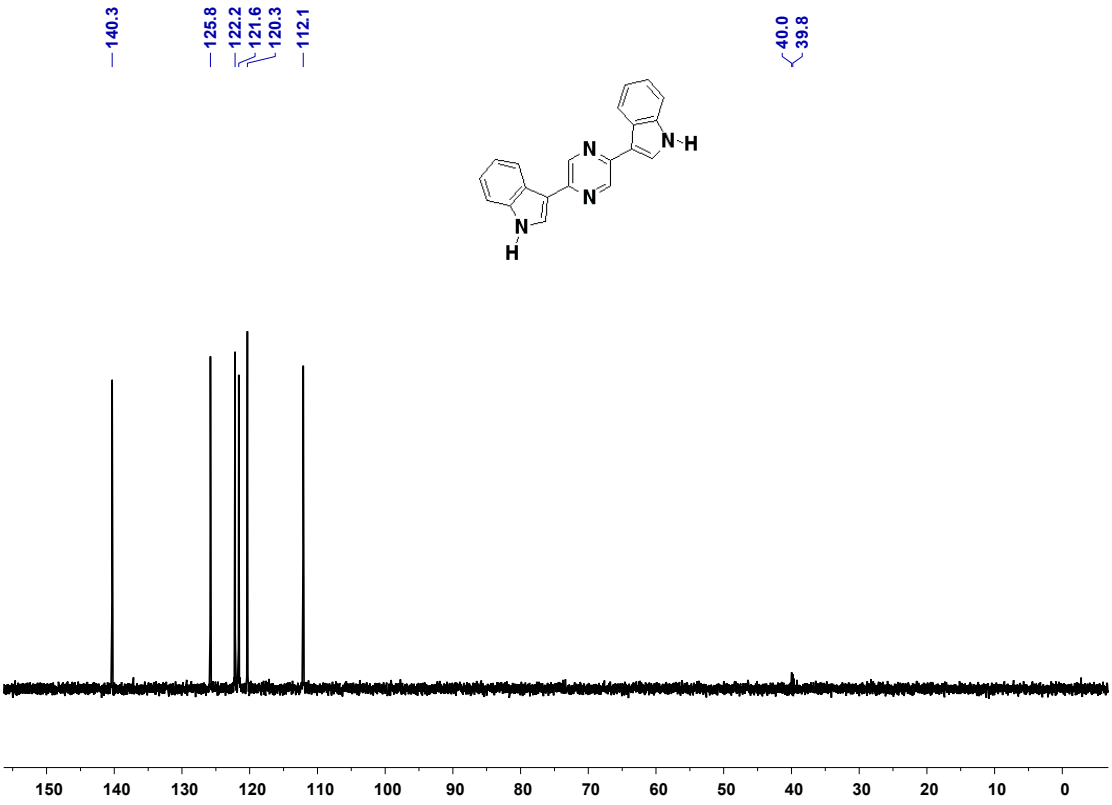
3.6.13 2,5-Di(1*H*-indol-3-yl)pyrazine (6n)



^{1}H NMR of **6n** (15 mg) in 0.7 mL DMSO-d_6 at 297 K (δ in ppm).

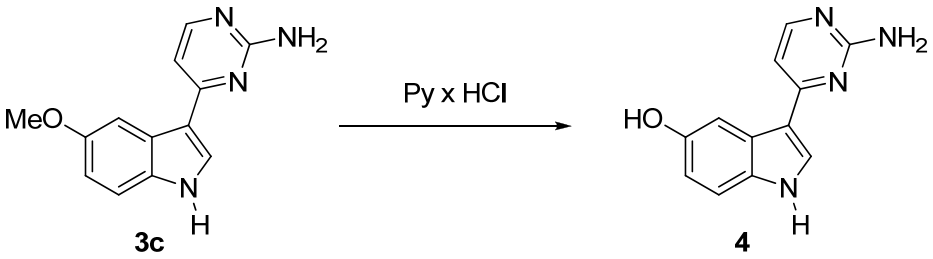


^{13}C NMR of **6n** (15 mg) in 0.7 mL DMSO-d_6 at 297 K (δ in ppm).



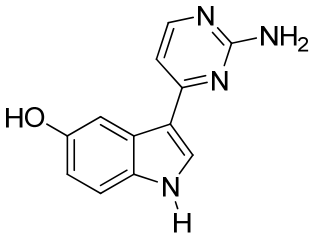
^{13}C 135-DEPT NMR of **6n** (15 mg) in 0.7 mL DMSO-d6 at 297 K (δ in ppm).

4 Synthesis of *Isomeridianin A* (4)



Pyridinium hydrochloride (1.18 g, 10.0 mmol) was placed in a dry screw-cap vessel under argon atmosphere. Then, 4-(5-methoxy-1*H*-indol-3-yl)pyrimidin-2-amine (**3c**) (120 mg, 0.50 mmol) was added and the mixture was heated to 210 °C (preheated oil bath). After 30 min the mixture was cooled to 50 °C (preheated oil bath) and methanol was added to dissolve the residue. The reaction mixture was monitored by TLC. The reaction mixture was adsorbed onto Celite® and the solvents were removed under reduced pressure. The residue was purified chromatographically on silica gel with dichloromethane/methanol/aqueous ammonia ($DCM/MeOH/NH_3$ = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 → 100:6:1 → 100:7:1 (stepwise gradient)). After drying under reduced pressure *isomeridianin A* (**4**) was obtained as a pale rose solid. HT-LC-MS: 100 %.

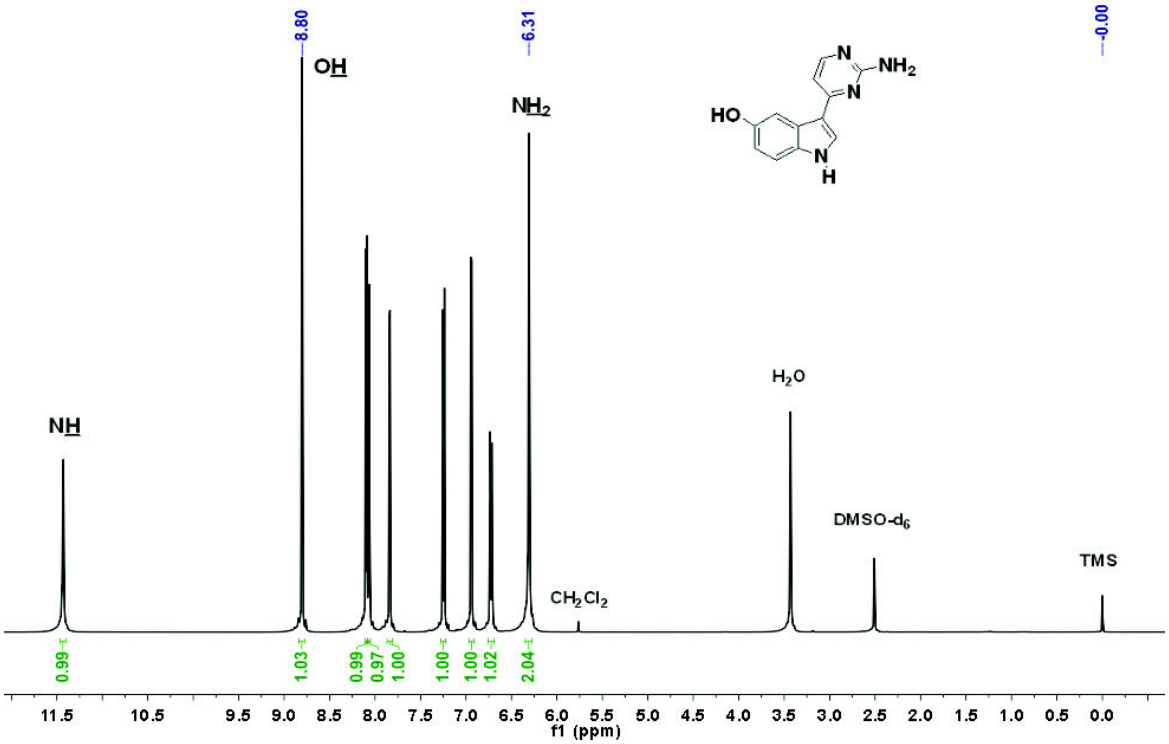
4.1 3-(2-Aminopyrimidin-4-yl)-1*H*-indol-5-ol (*Isomeridianin A*, 4)



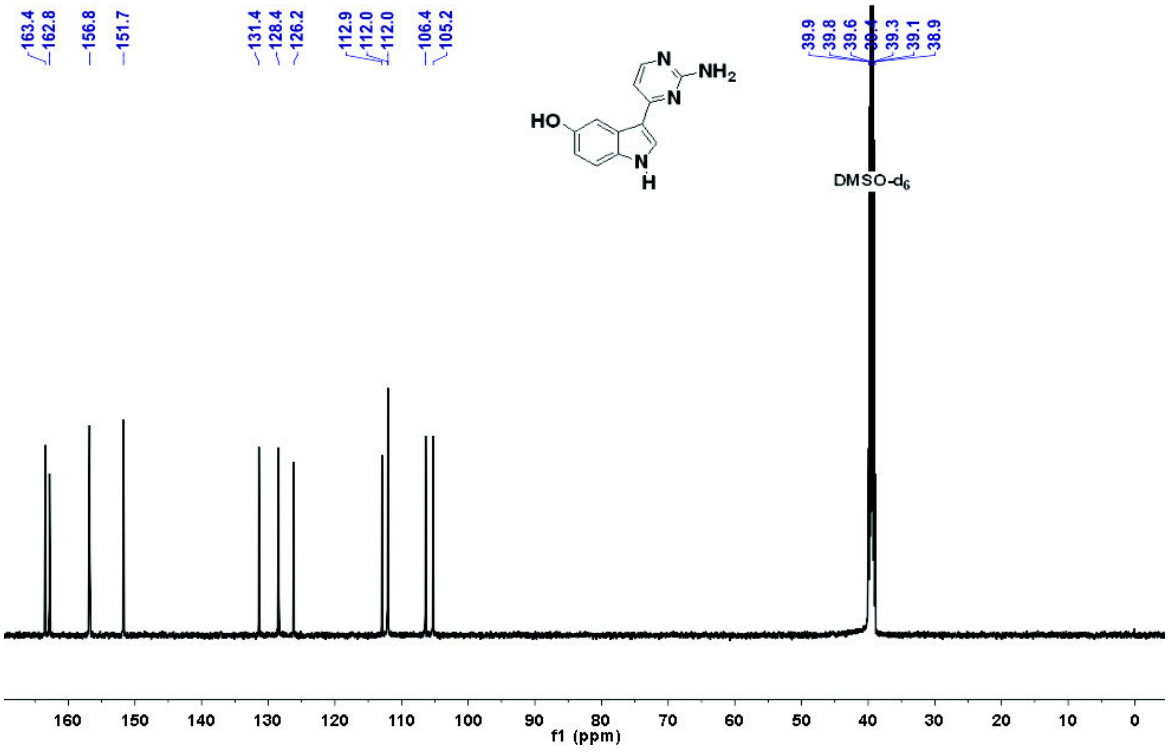
$C_{12}H_{10}N_4O$

226.23

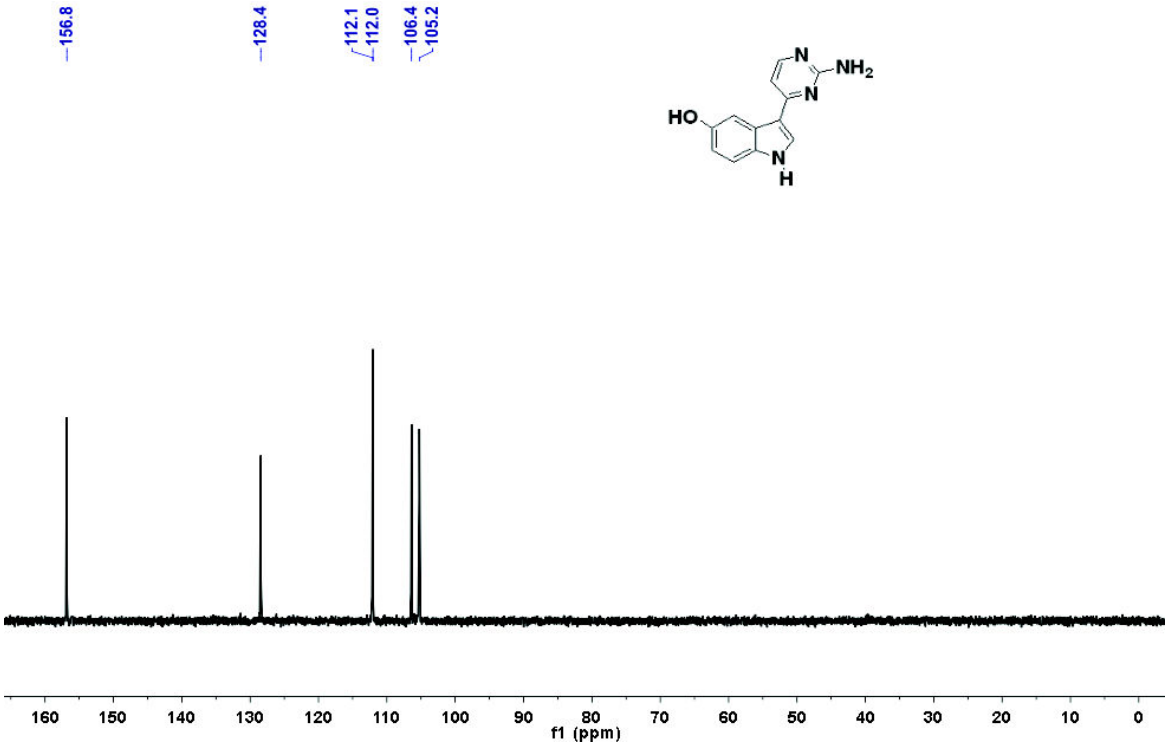
100 mg (0.44 mmol, 89 % yield) as a pale rose scaly solid, mp: 293 °C (dec.). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 6.31 (s, 2 H, N$\underline{H}_2$), 6.72 (dd, *J* = 8.5 Hz, *J* = 2.5 Hz, 1 H), 6.94 (d, *J* = 5.4 Hz, 1 H), 7.24 (d, *J* = 8.8 Hz, 1 H), 7.84 (d, *J* = 2.2 Hz, 1 H), 8.07 (d, *J* = 2.8 Hz, 1 H), 8.10 (d, *J* = 5.4 Hz, 1 H), 8.80 (s, 1 H, O$\underline{H}$), 11.44 (d, *J* = 2.5 Hz, 1 H, N$\underline{H}$). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 105.2 (CH), 106.4 (CH), 112.0 (CH), 112.0 (CH), 112.9 (C_{quat}), 126.2 (C_{quat}), 128.4 (CH), 131.4 (C_{quat}), 151.7 (C_{quat}), 156.8 (CH), 162.8 (C_{quat}), 163.4 (C_{quat}). EI + MS (*m*/*z* (%)): 226 (M^+, 100), 225 ($(M-H)^+$, 18), 197 ($(M-COH)^+$, 7), 185 ($(M-CH_2N_2+H)^+$, 57), 158 ($(M-C_3H_4N_2)^+$, 4). IR (KBr): $\tilde{\nu}$ 3387 (m), 3278 (m), 1591 (s), 1543 (m), 1526 (m), 1497 (w), 1472 (s), 1451 (m), 1429 (m), 1367 (w), 1332 (w), 1285 (w), 1263 (w), 1232 (m), 1211 (m), 1172 (m), 1057 (w), 988 (w), 942 (w), 896 (w), 868 (w), 822 (m), 795 (w), 698 (m), 636 (w), 585 (w), 559 (w) cm^{-1}. Anal. calcd. for $C_{12}H_{10}N_4O$ (226.2): C 63.71, H 4.46, N 24.76. Found: C 63.77, H 4.57, N 24.84.



^{1}H NMR of **4** (30 mg) in 0.7 mL DMSO-d_6 at 295 K (δ in ppm).



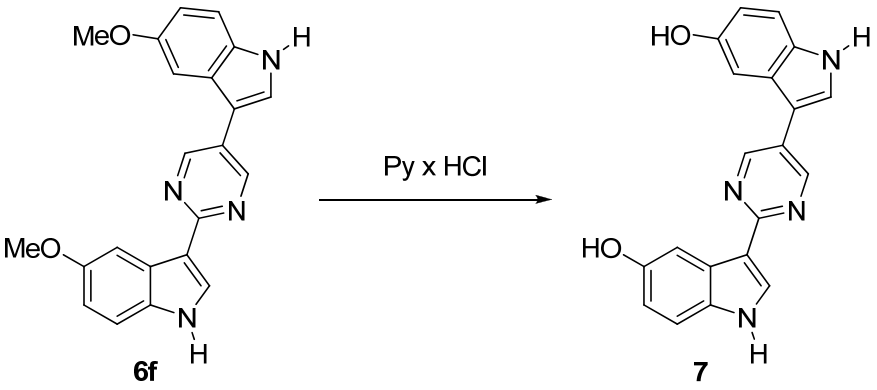
^{13}C NMR of **4** (30 mg) in 0.7 mL DMSO-d_6 at 295 K (δ in ppm).



^{13}C 135-DEPT NMR of **4** (30 mg) in 0.7 mL DMSO-d_6 at 295 K (δ in ppm).

5 Synthesis of *Hyrtinadine A* (7)

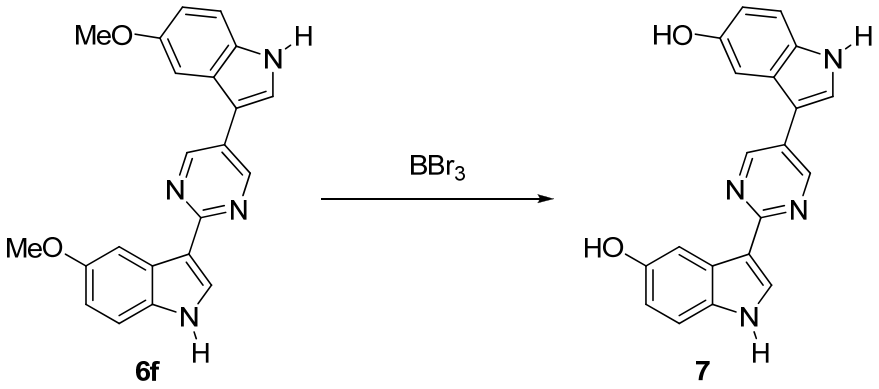
5.1 Synthesis of 3,3'-(Pyrimidine-2,5-diyl)bis(1*H*-indol-5-ol) (*Hyrtinadine A*, 7), Method I



6f **7**

Pyridinium hydrochloride (2.36 g, 20.0 mmol) was placed in a dry screw-cap vessel under argon atmosphere. Then, 3,3'-(pyrimidine-2,5-diyl)bis(5-methoxy-1*H*-indole) (**6f**) (185 mg, 0.50 mmol) was added and the mixture was heated to 210 °C (preheated oil bath). After 30 min the mixture was cooled to 50 °C (preheated oil bath) and methanol was added to dissolve the residue. The reaction mixture was monitored by TLC. The reaction mixture was adsorbed onto Celite® and the solvents were removed under reduced pressure. The residue was purified chromatographically on silica gel with dichloromethane/methanol/aqueous ammonia (DCM/MeOH/NH_3 = 100:1:1 → 100:2:1 → 100:3:1 → 100:4:1 → 100:5:1 → 100:6:1 → 100:7:1 (stepwise gradient)). After drying under reduced pressure *hyrtinadine A* (**7**) was obtained as a yellow solid (65 mg, 0.19 mmol, 38 % yield). HT-LC-MS: 100 %.

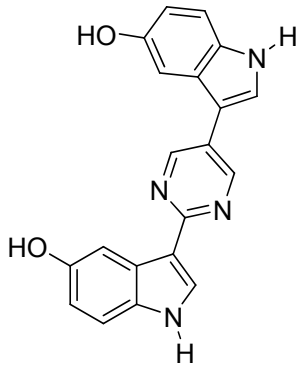
5.2 Synthesis of 3,3'-(Pyrimidine-2,5-diyl)bis(1*H*-indol-5-ol) (*Hyrtinadine A*, 7), Method II



6f **7**

3,3'-(Pyrimidine-2,5-diyl)bis(5-methoxy-1*H*-indole) (**6f**) (185 mg, 0.50 mmol) was placed in a dry screw-cap vessel under nitrogen atmosphere. Then, 15 mL of dry dichloromethane were added. The suspension was cooled to -78 °C (acetone/dry ice bath) and tribromoborane (0.58 mL, 6.00 mmol) was slowly added. The mixture was allowed to reach room temperature and continuously stirred for 20 h. The reaction progress was monitored by TLC. Then the mixture was cooled to 0 °C (water/ice bath) and 3 mL of water followed by 30 mL of saturated potassium carbonate solution were slowly added. The resulting yellow precipitate was filtered, dried under reduced pressure and purified chromatographically on silica with dichloromethane/methanol/ammonia (DCM/MeOH/NH_3 = 100:7:1 → 100:8:1 → 100:9:1 → 100:10:1 (stepwise gradient)). After drying under reduced pressure *hyrtinadine A* (**7**) was obtained as a yellow solid (147 mg, 0.43 mmol, 78 % (contained 1 molecule MeOH)).

5.2.1 3,3′-(Pyrimidine-2,5-diyl)bis(1*H*-indol-5-ol) (*Hyrtinadine A*, 7)



$C_{20}H_{14}N_4O_2$

342.35

147 mg (0.43 mmol, 78 % yield) as a yellow solid, mp: 296 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 6.68 (dd, *J* = 8.6 Hz, *J* = 2.4 Hz, 1 H), 6.71 (dd, *J* = 8.7 Hz, *J* = 2.1 Hz, 1 H), 7.19 (d, *J* = 2.0 Hz, 1 H), 7.25 (d, *J* = 8.6 Hz, 1 H), 7.28 (d, *J* = 8.7 Hz, 1 H), 7.80 (d, *J* = 2.6 Hz, 1 H), 7.96 (d, *J* = 2.3 Hz, 1 H), 8.11 (d, *J* = 2.8 Hz, 1 H), 8.84 (brs, 2 H), 8.98 (s, 2 H), 11.30 (d, *J* = 2.0 Hz, 1 H, NH), 11.39 (d, *J* = 2.2 Hz, 1 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 102.8 (CH), 106.4 (CH), 108.7 (C_{quat}), 112.2 (CH), 112.3 (CH), 112.4 (CH), 112.8 (CH), 114.9 (C_{quat}), 124.5 (CH), 125.2 (C_{quat}), 125.6 (C_{quat}), 126.6 (C_{quat}), 129.0 (CH), 131.5 (C_{quat}), 131.6 (C_{quat}), 151.9 (C_{quat}), 152.0 (C_{quat}), 153.7 (CH), 160.8 (C_{quat}). EI + MS (*m*/*z* (%)): 343 (23), 342 (M^+, 100), 171 (18), 157 (29). IR (KBr): $\tilde{\nu}$ 3387 (m), 3127 (w), 1715 (w), 1624 (m), 1582 (m), 1547 (s), 1535 (s), 1493 (m), 1468 (m), 1448 (s), 1369 (m), 1313 (w), 1283 (m), 1252 (m), 1227 (m), 1203 (m), 1153 (m), 1128 (w), 1099 (w), 1045 (w), 993 (w), 978 (w), 922 (s), 860 (w), 822 (m), 791 (s), 764 (w), 742 (w), 696 (w), 681 (w), 663 (m), 625 (s), 607 (m) cm^{-1}. Anal. calcd. for $C_{20}H_{14}N_4O_2 \cdot$MeOH (342.4 + 32.0): C 67.37, H 4.85, N 14.96. Found: C 67.18, H 4.99, N 15.28.

Data reported in the literature:[5]

Colorless amorphous solid. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 6.69 (br d, *J* = 8.6 Hz, 1 H), 6.71 (br d, *J* = 8.6 Hz, 1 H), 7.20 (br s, 1 H), 7.26 (d, *J* = 8.6 Hz, 1 H), 7.29 (d, *J* = 8.6 Hz, 1 H), 7.79 (s, 1 H), 7.97 (br s, 1 H), 8.11 (s, 1 H), 8.85 (br s, 1 H, OH), 8.87 (br s, 1 H, OH), 9.00 (s, 2 H), 11.3 (br s, 1 H, NH), 11.4 (br s, 1 H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 102.7 (CH), 106.2 (CH), 108.6 (C_{quat}), 112.0 (CH), 112.2 (CH), 112.6 (CH), 112.6 (CH), 114.2 (C_{quat}), 124.2 (CH), 125.0 (C_{quat}), 125.4 (C_{quat}), 126.4 (C_{quat}), 128.7 (CH), 131.3 (C_{quat}), 131.5

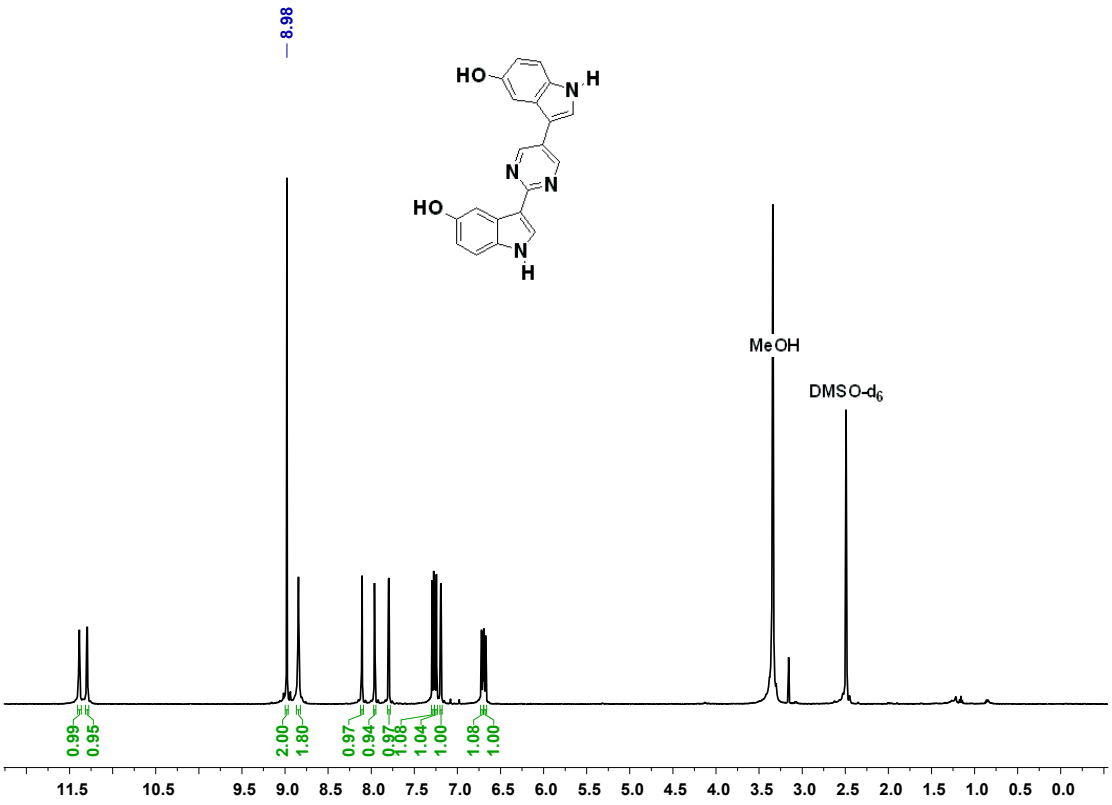
[5] T. Endo, M. Tsuda, J. Fromont, J. Kobayashi, *J. Nat. Prod.* **2007**, *70*, 423-424.

(C_{quat}), 151.7 (C_{quat}), 151.8 (C_{quat}), 153.5 (2 CH), 160.7 (C_{quat}). ESIMS (pos) (*m/z* (%)): 343 $(M+H)^+$. HRESIMS calcd for $C_{20}H_{14}N_4O_2$ 343.1195 $(M+H)^+$, found 343.1191. IR (KBr): $\tilde{\nu}$ 3390 cm^{-1}. UV (MeOH): λ_{max} (ε_{max}) 339 nm (3100), 277 (7600).

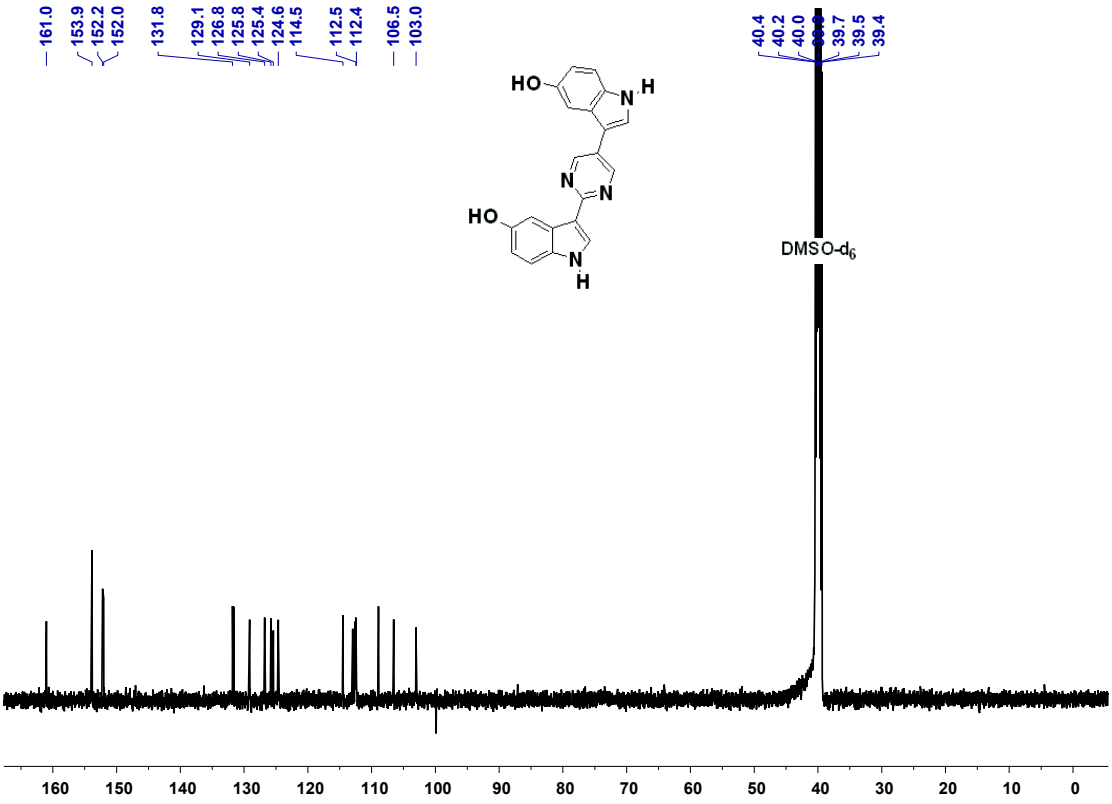
Data reported in the literature:[6]

White solid, mp: > 220 °C (dec.). ^1H NMR (DMSO-d_6, 500 MHz, dual cryoprobe $^1H/^{13}C$): δ 6.69 (dd, *J* = 8.6 Hz, *J* = 2.2 Hz, 1 H), 6.72 (dd, *J* = 8.6 Hz, *J* = 2.2 Hz, 1 H), 7.20 (br s, 1 H), 7.26 (d, *J* = 8.6 Hz, 1 H), 7.29 (d, *J* = 8.6 Hz, 1 H), 7.80 (d, *J* = 2.5 Hz, 1 H), 7.97 (d, *J* = 2.2 Hz, 1 H), 8.11 (d, *J* = 2.5 Hz, 1 H), 8.86 (br s, 2 H), 8.99 (s, 2 H), 11.31 (br s, 1 H), 11.39 (br s, 1 H). ^{13}C NMR (DMSO-d_6, 125 MHz, dual cryoprobe $^1H/^{13}C$): δ 102.7 (CH), 106.2 (CH), 108.5 (C_{quat}), 112.0 (CH), 112.1 (CH), 112.2 (CH), 112.6 (CH), 114.1 (C_{quat}), 124.3 (CH), 125.0 (C_{quat}), 125.4 (C_{quat}), 126.4 (C_{quat}), 128.8 (CH), 131.3 (C_{quat}), 131.4 (C_{quat}), 151.7 (C_{quat}), 151.8 (C_{quat}), 153.5 (2 CH), 160.6 (C_{quat}). EI + MS (*m/z* (%)): 342 (M^+, 100), 317 (7), 171 (11), 157 (16), 84 (10). IR (ATR): $\tilde{\nu}$ 3420 (br), 1659 (br), 1049, 1001 (s), 823, 760 cm^{-1}. HRMS calcd. for $C_{20}H_{14}N_4O_2 \cdot$342.1111 (M^+). Found: 342.1099. UV (MeOH): λ_{max} (ε_{max}) 339 nm (4295), 277 (6644).

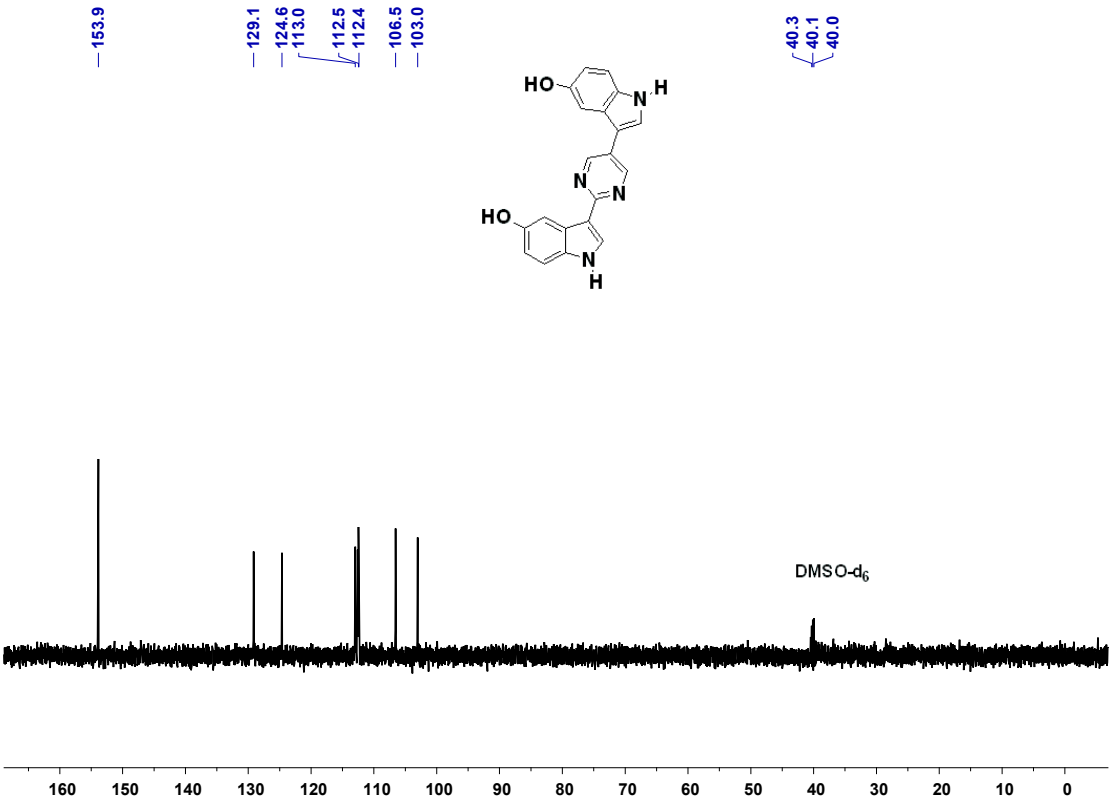
[6] Á. Mosquera, R. Riveiros, J. P. Sestelo, L. A. Sarandeses, *Org. Lett.* **2008**, *10*, 3745-3748.



^{1}H NMR of **7** (16 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).



^{13}C NMR of **7** (16 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).

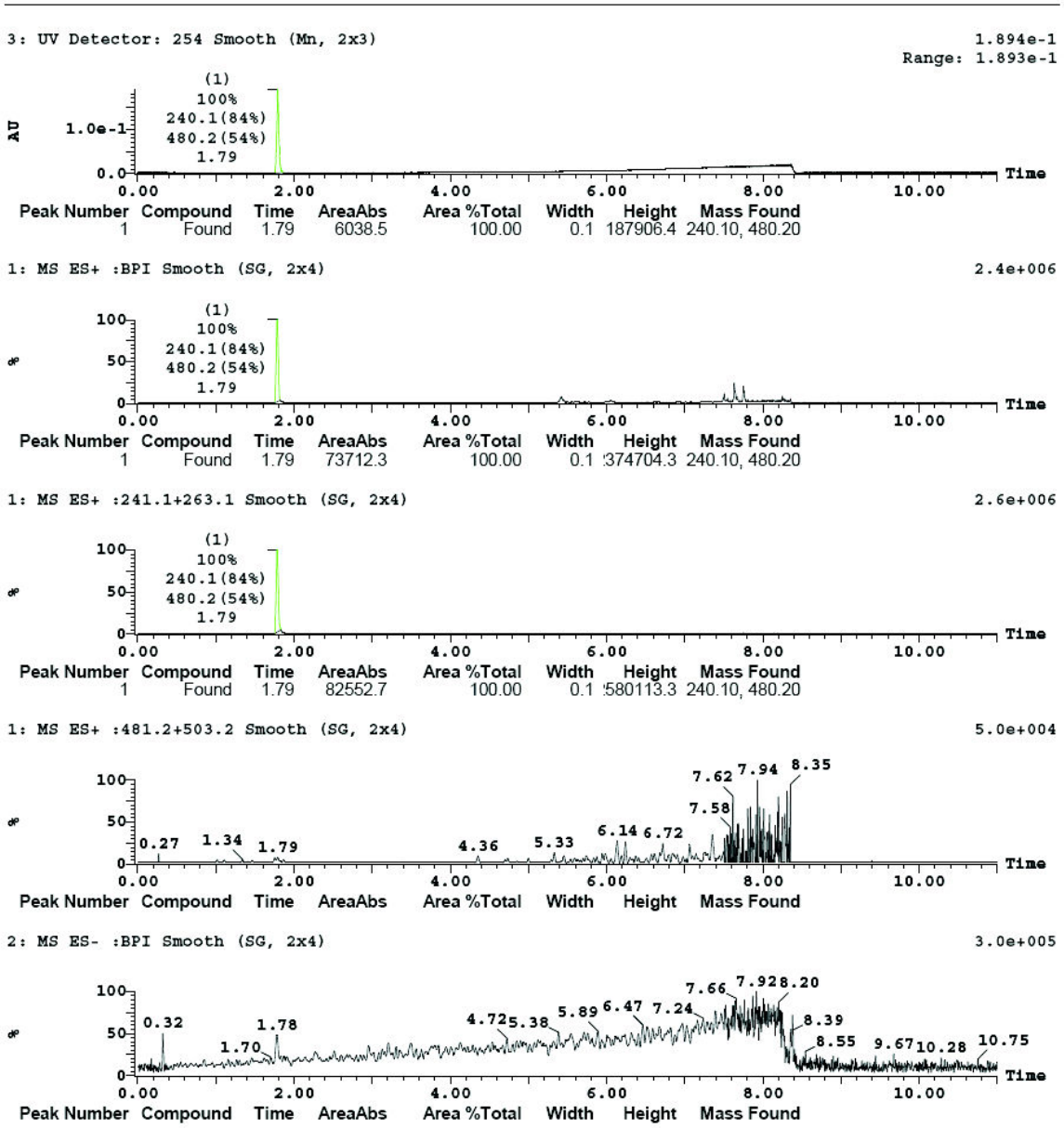


^{13}C 135-DEPT NMR of **7** (16 mg) in 0.7 mL DMSO-d_6 at 296 K (δ in ppm).

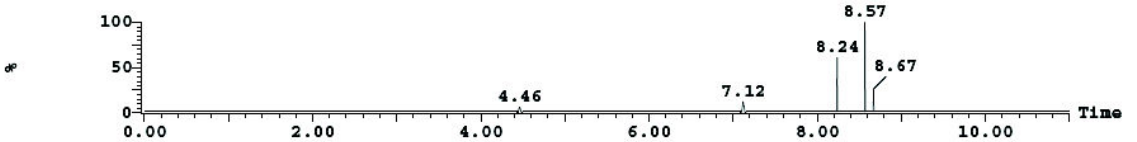
6 Appendix

6.1 UV Purity of Compounds 3, 4, 6, and 7

HT-LC-MS Spectrum (SOP 2200) of **3c** (*O*-Methyl isomeridianin A).UV purity: 100 %

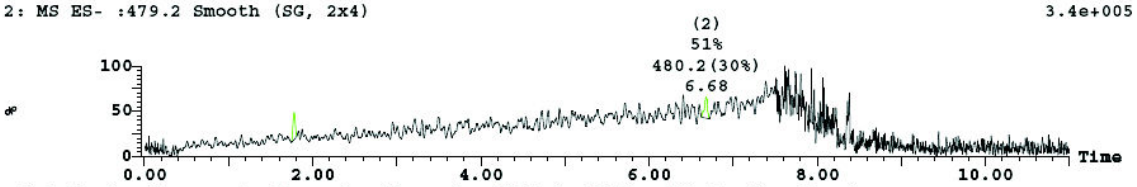


2: MS ES- :239.1 Smooth (SG, 2x4) 7.9e+003



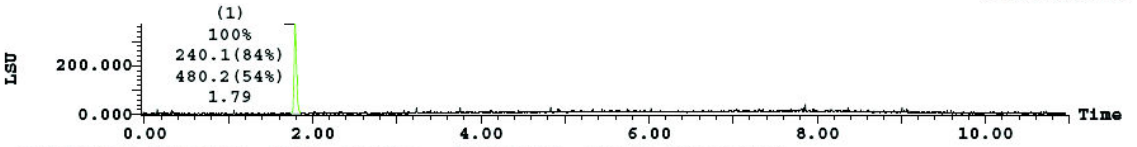
Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

2: MS ES- :479.2 Smooth (SG, 2x4) 3.4e+005



Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1	Found	1.78	3125.3	49.05	0.1	100215.9	240.10, 480.20
2	Found	6.68	3246.3	50.95	0.1	79584.7	480.20

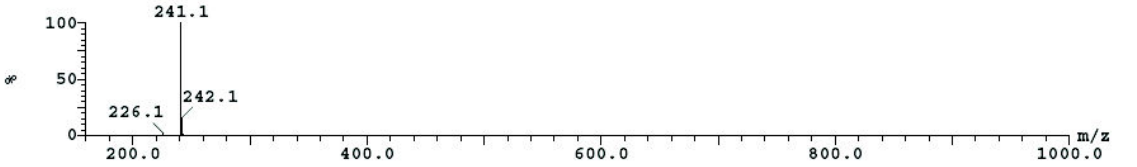
(1) ELSD Signal Smooth (Mn, 2x3) 371.133
Range: 371.047



Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1	Found	1.79	12439.9	100.00	367756.7	240.10, 480.20

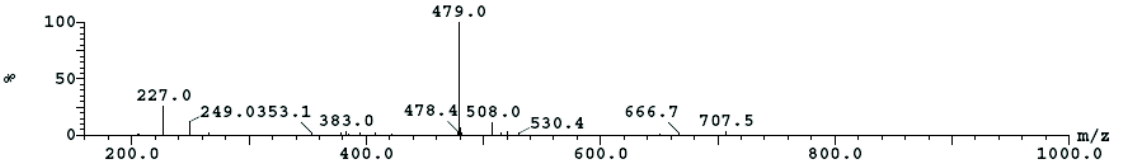
Peak ID	Compound	Time	Mass Found
1	Found	1.79	240.10

1:(Time: 1.79) Combine (372:376) 1:MS ES+
2.5e+006



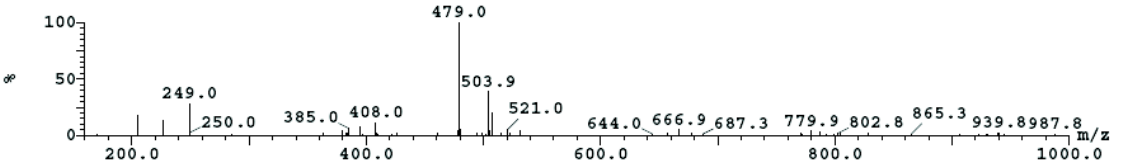
Peak ID	Compound	Time	Mass Found
1	Found	1.79	480.20

1:(Time: 1.79) Combine (372:377) 2:MS ES-
1.6e+005

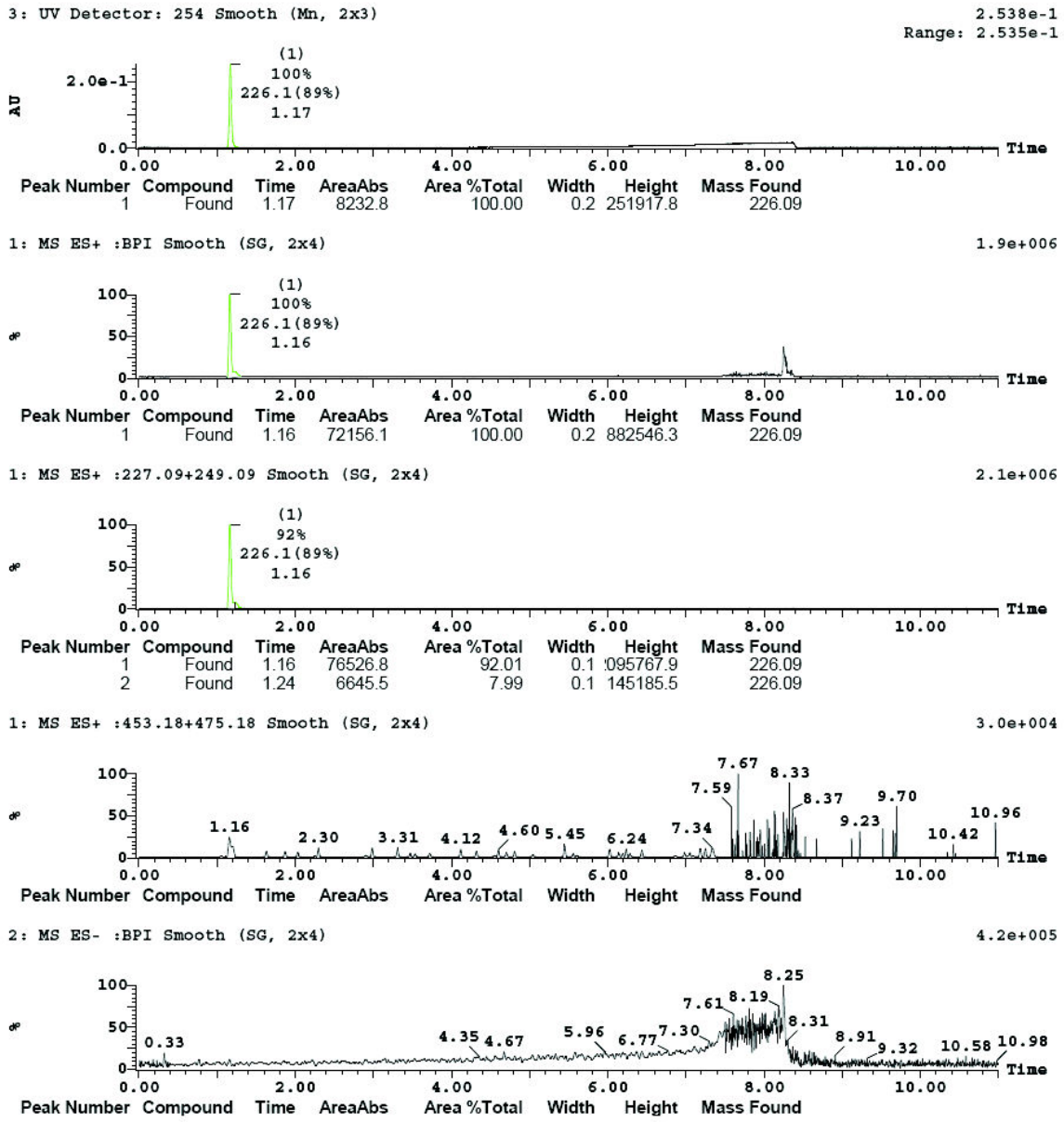


Peak ID	Compound	Time	Mass Found
2	Found	6.68	480.20

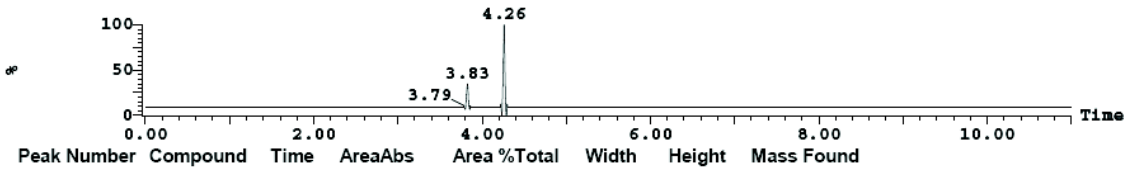
2:(Time: 6.68) Combine (1395:1399) 2:MS ES-
2.1e+005



HT-LC-MS Spectrum (SOP 2200) of **4** (*Isomeridianin A*). UV purity: 100 %

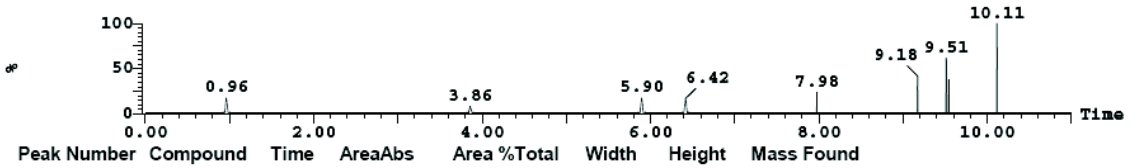


2: MS ES- :225.09 Smooth (SG, 2x4) 2.0e+003



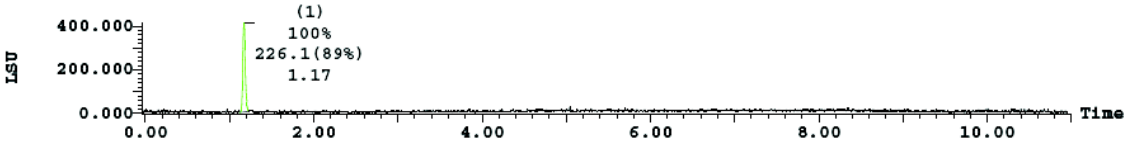
Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

2: MS ES- :451.18 Smooth (SG, 2x4) 5.7e+003



Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

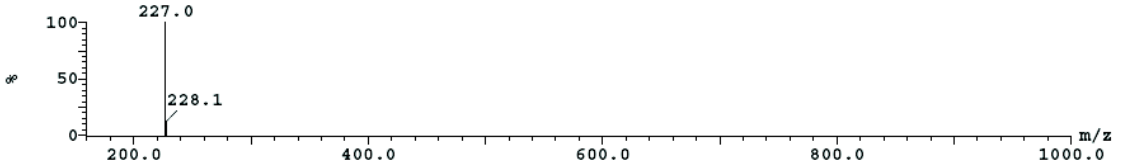
(1) ELSD Signal Smooth (Mn, 2x3) 414.472
Range: 414.364



Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1	Found	1.17	13713.1	100.00	407249.6	226.09

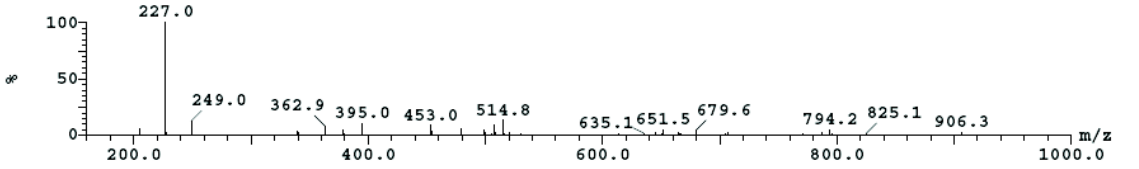
Peak ID	Compound	Time	Mass Found
1	Found	1.16	226.09

1:(Time: 1.16) Combine (242:246) 1:MS ES+ 2.0e+006



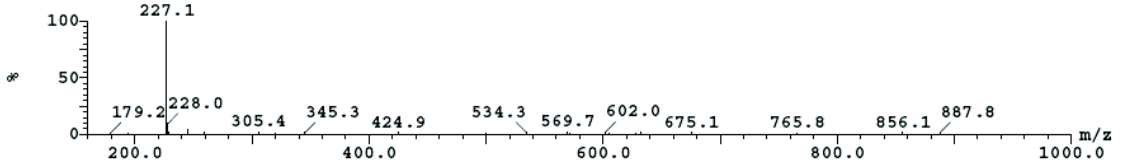
Peak ID	Compound	Time	Mass Found
1		1.16	

1:(Time: 1.17) Combine (242:247) 2:MS ES- 6.1e+004

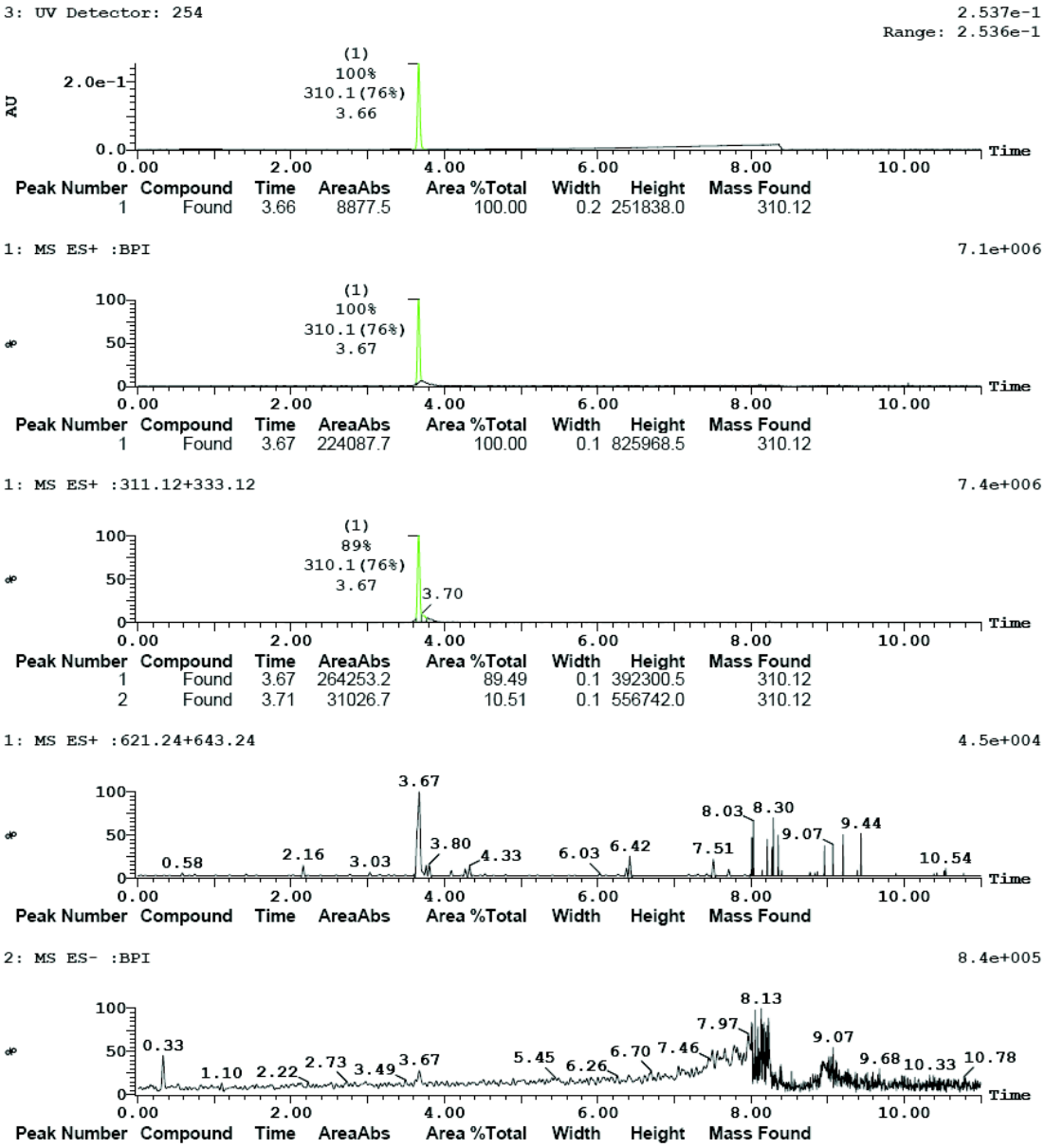


Peak ID	Compound	Time	Mass Found
2	Found	1.24	226.09

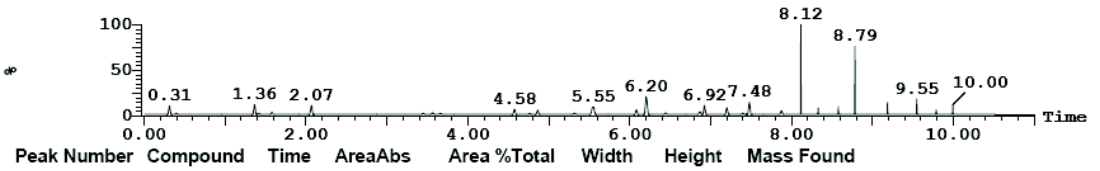
2:(Time: 1.24) Combine (258:262) 1:MS ES+ 1.4e+005



HT-LC-MS Spectrum (SOP 2200) of **6a**. UV purity: 100 %

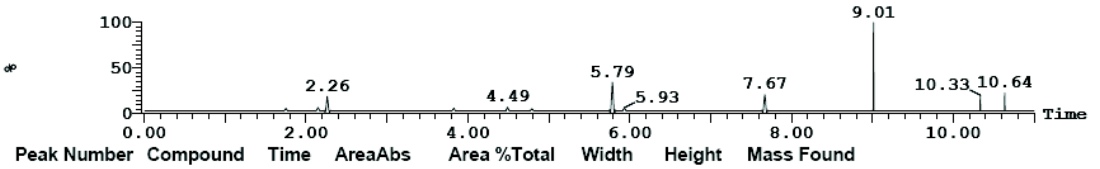


2: MS ES- :309.12 2.2e+004



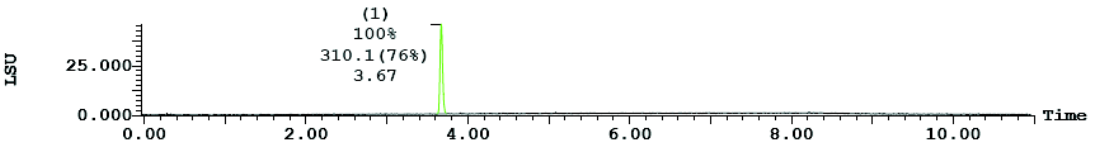
Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

2: MS ES- :619.24 1.3e+004



Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

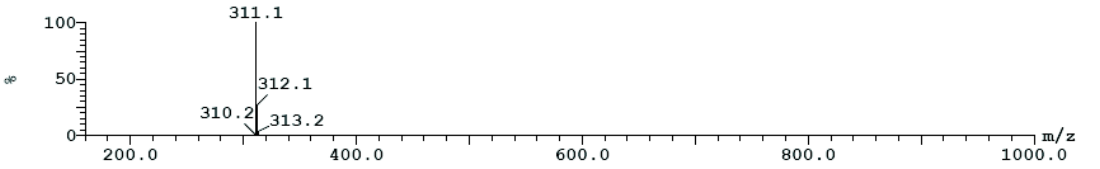
(1) ELSD Signal 46.036
Range: 46.032



Peak ID	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1	Found	3.67	1677.6	100.00	45310.4	310.12

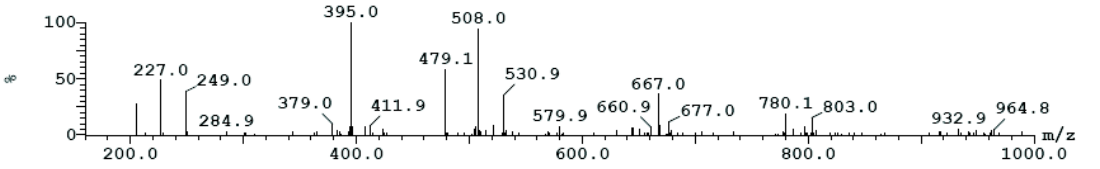
Peak ID	Compound	Time	Mass Found
1	Found	3.67	310.12

1:(Time: 3.66) 1:MS ES+
7.2e+006



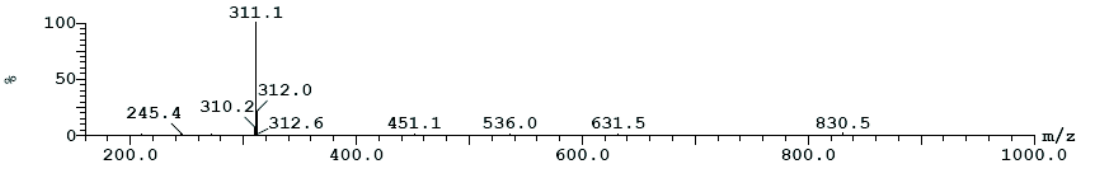
Peak ID	Compound	Time	Mass Found
1		3.67	

1:(Time: 3.66) 2:MS ES-
2.1e+005

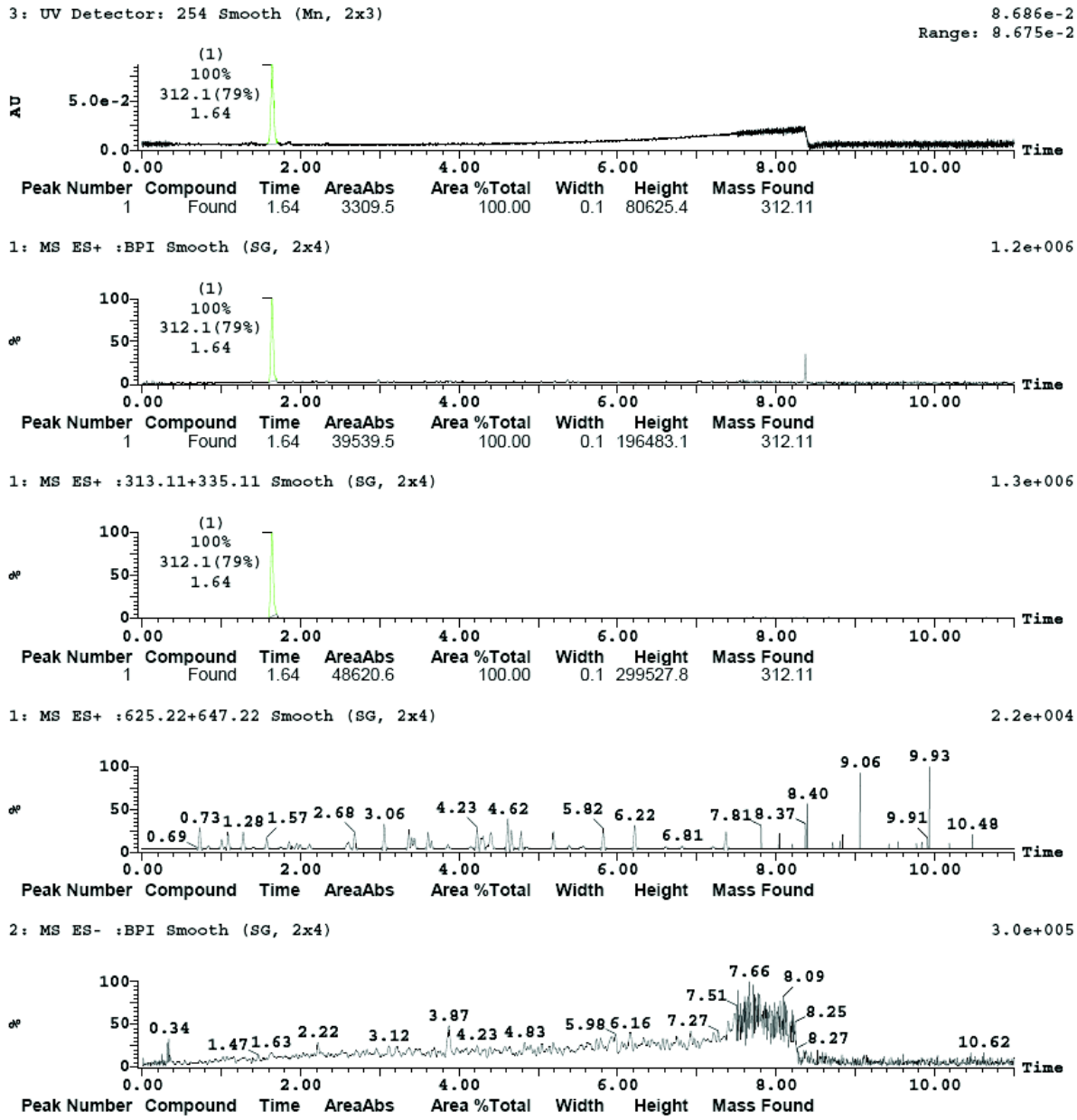


Peak ID	Compound	Time	Mass Found
2	Found	3.71	310.12

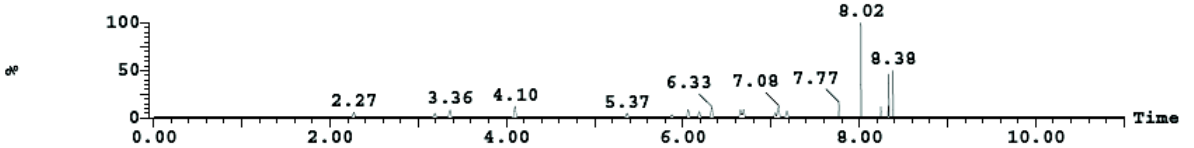
2:(Time: 3.71) 1:MS ES+
6.5e+005



HT-LC-MS Spectrum (SOP 2200) of **6b**. UV purity: 100 %

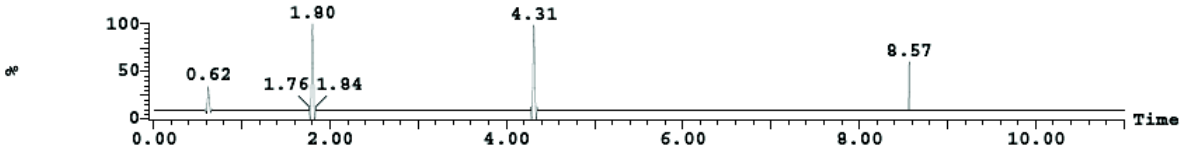


2: MS ES- :311.11 Smooth (SG, 2x4) 1.4e+004



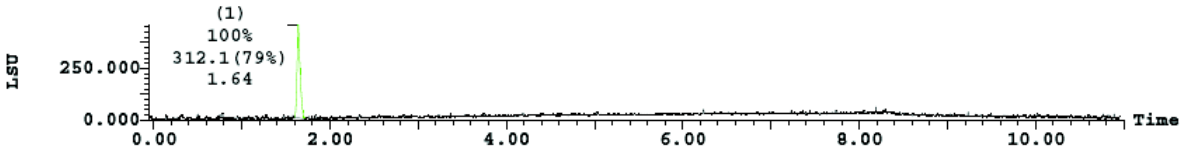
Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

2: MS ES- :623.22 Smooth (SG, 2x4) 2.8e+003



Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

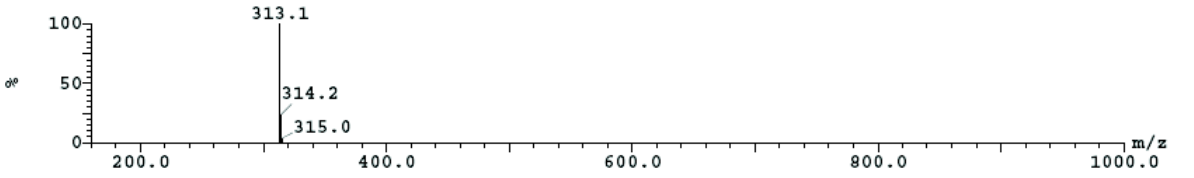
(1) ELSD Signal Smooth (Mn, 2x3) 460.079
Range: 459.688



Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1	Found	1.64	18123.6	100.00	449423.5	312.11

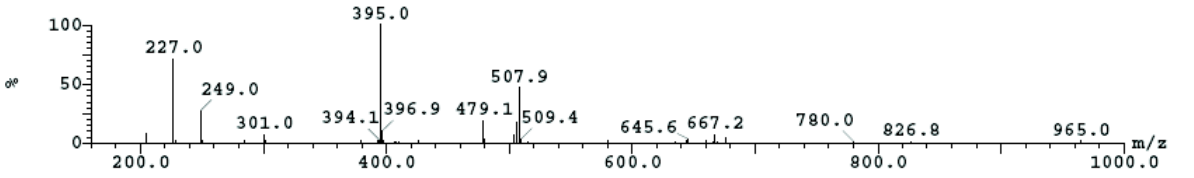
Peak ID	Compound	Time	Mass Found
1	Found	1.64	312.11

1:(Time: 1.64) Combine (342:346) 1:MS ES+
1.3e+006

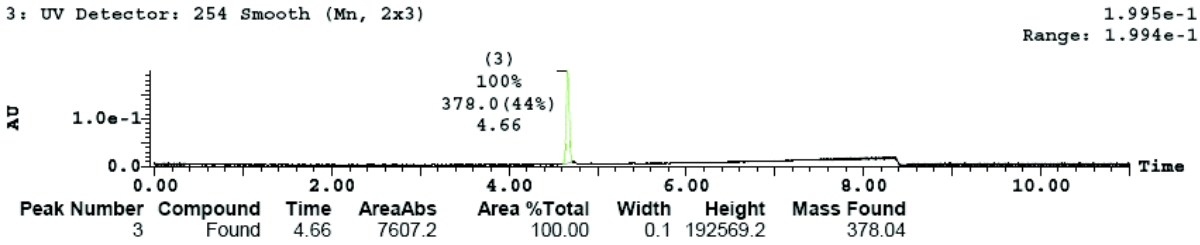


Peak ID	Compound	Time	Mass Found
1		1.64	

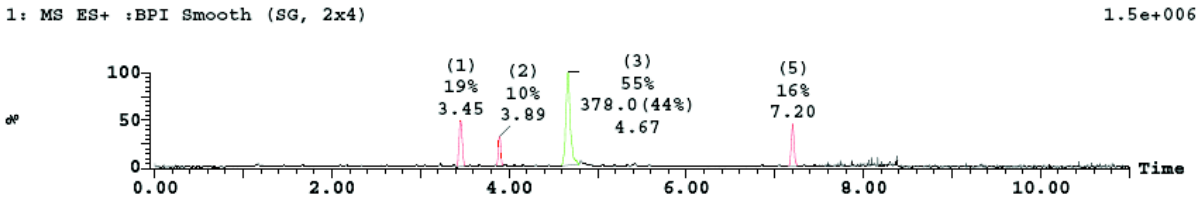
1:(Time: 1.64) Combine (341:345) 2:MS ES-
5.4e+004



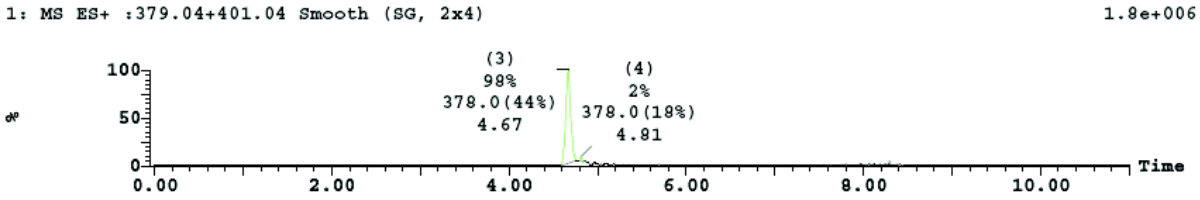
HT-LC-MS Spectrum (SOP 2200) of **6c**. UV purity: 100 %



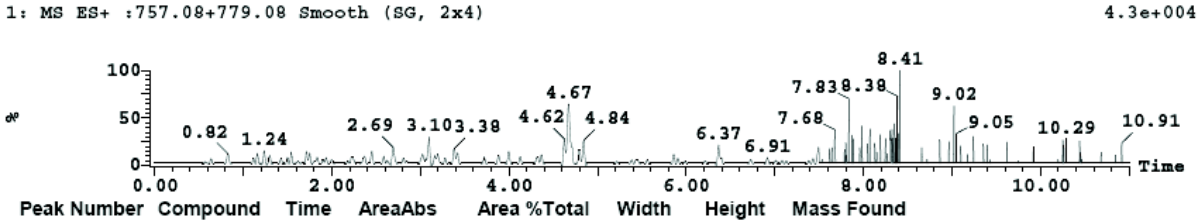
Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
3	Found	4.66	7607.2	100.00	0.1	192569.2	378.04



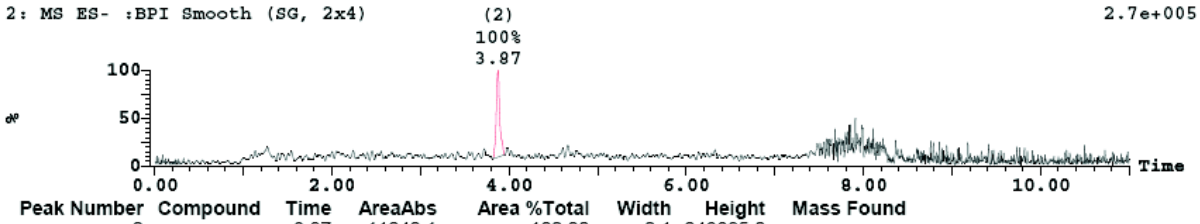
Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		3.45	29878.7	19.29	0.1	724481.6	
2		3.89	14956.1	9.66	0.1	453954.3	
3	Found	4.67	85860.2	55.43	0.2	463304.8	378.04
5		7.20	24197.4	15.62	0.1	672461.3	



Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
3	Found	4.67	112543.2	98.20	0.2	717395.4	378.04
4	Found	4.81	2063.2	1.80	0.1	75015.3	378.04

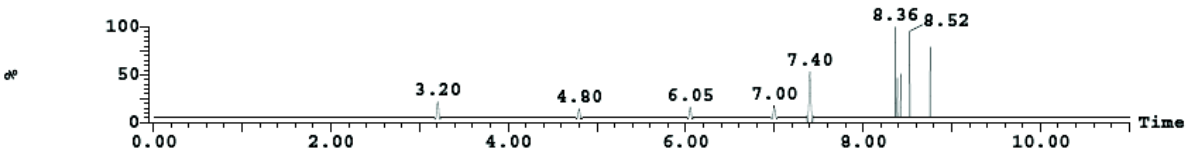


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found



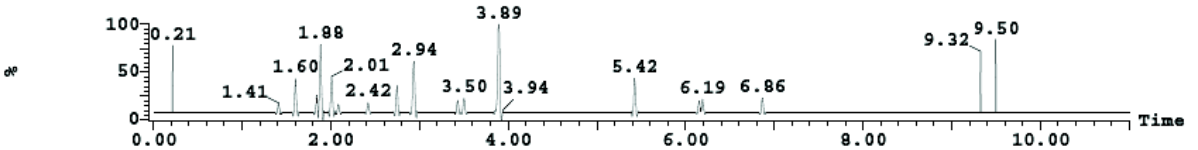
Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
2		3.87	11240.1	100.00	0.1	243385.0	

2: MS ES- :377.04 Smooth (SG, 2x4) 2.8e+003



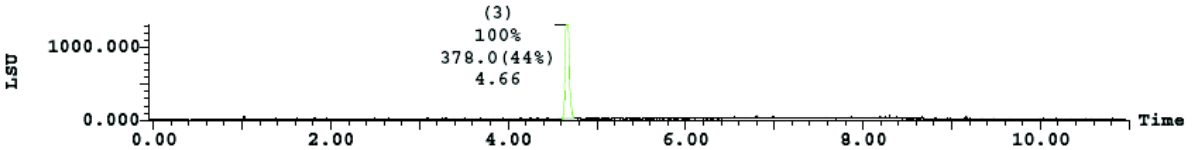
Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

2: MS ES- :755.08 Smooth (SG, 2x4) 3.0e+003



Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

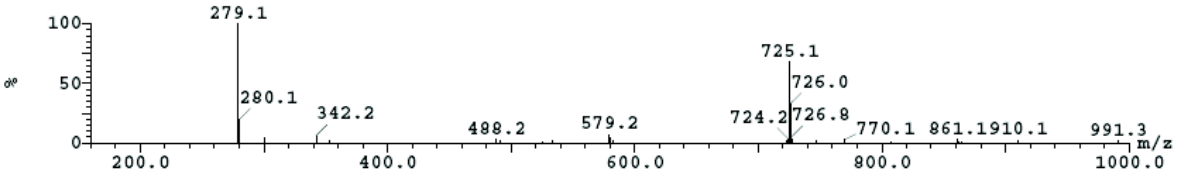
(1) ELSD Signal Smooth (Mn, 2x3) 1315.807
Range: 1315.768



Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
3	Found	4.66	72967.3	100.00	290244.5	378.04

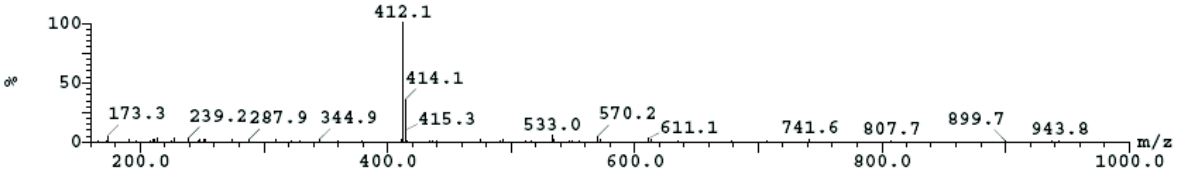
Peak ID	Compound	Time	Mass Found
1		3.45	

1:(Time: 3.45) Combine (720:724) 1:MS ES+ 8.4e+005



Peak ID	Compound	Time	Mass Found
2		3.89	

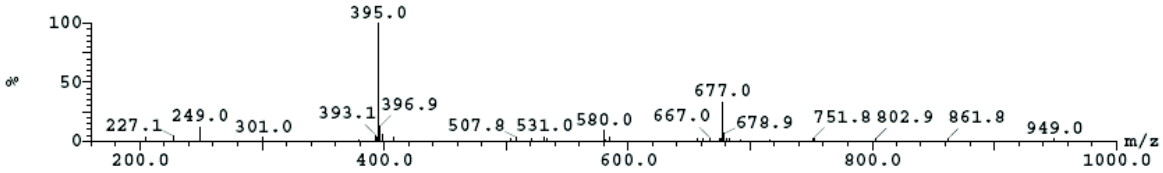
2:(Time: 3.89) Combine (812:816) 1:MS ES+ 5.6e+005



Peak ID	Compound	Time	Mass Found
2		3.89	

2:(Time: 3.87) Combine (808:812)

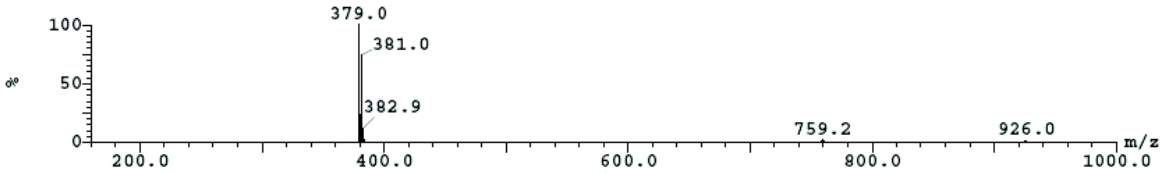
2:MS ES-
3.0e+005



Peak ID	Compound	Time	Mass Found
3	Found	4.67	378.04

3:(Time: 4.66) Combine (972:976)

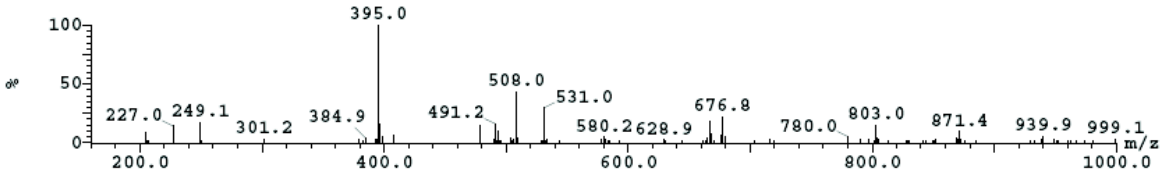
1:MS ES+
1.5e+006



Peak ID	Compound	Time	Mass Found
3		4.67	

3:(Time: 4.66) Combine (971:976)

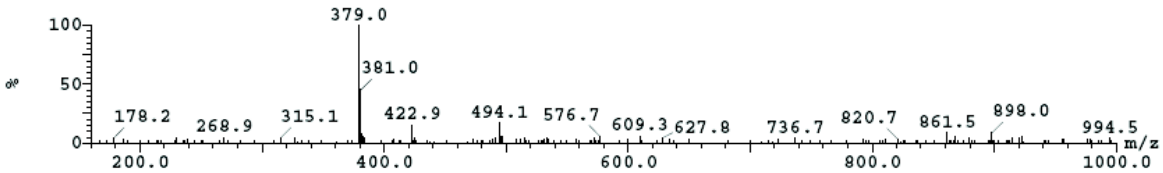
2:MS ES-
6.2e+004



Peak ID	Compound	Time	Mass Found
4	Found	4.81	378.04

4:(Time: 4.81) Combine (1004:1008)

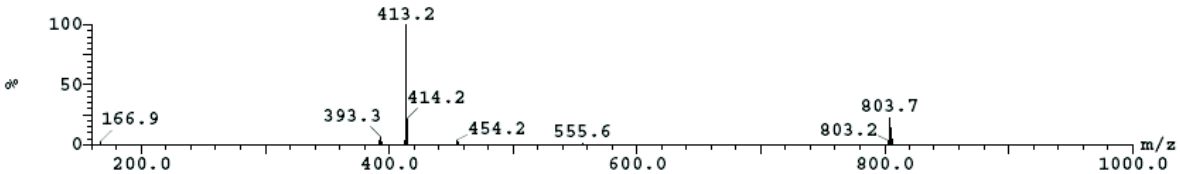
1:MS ES+
1.5e+005



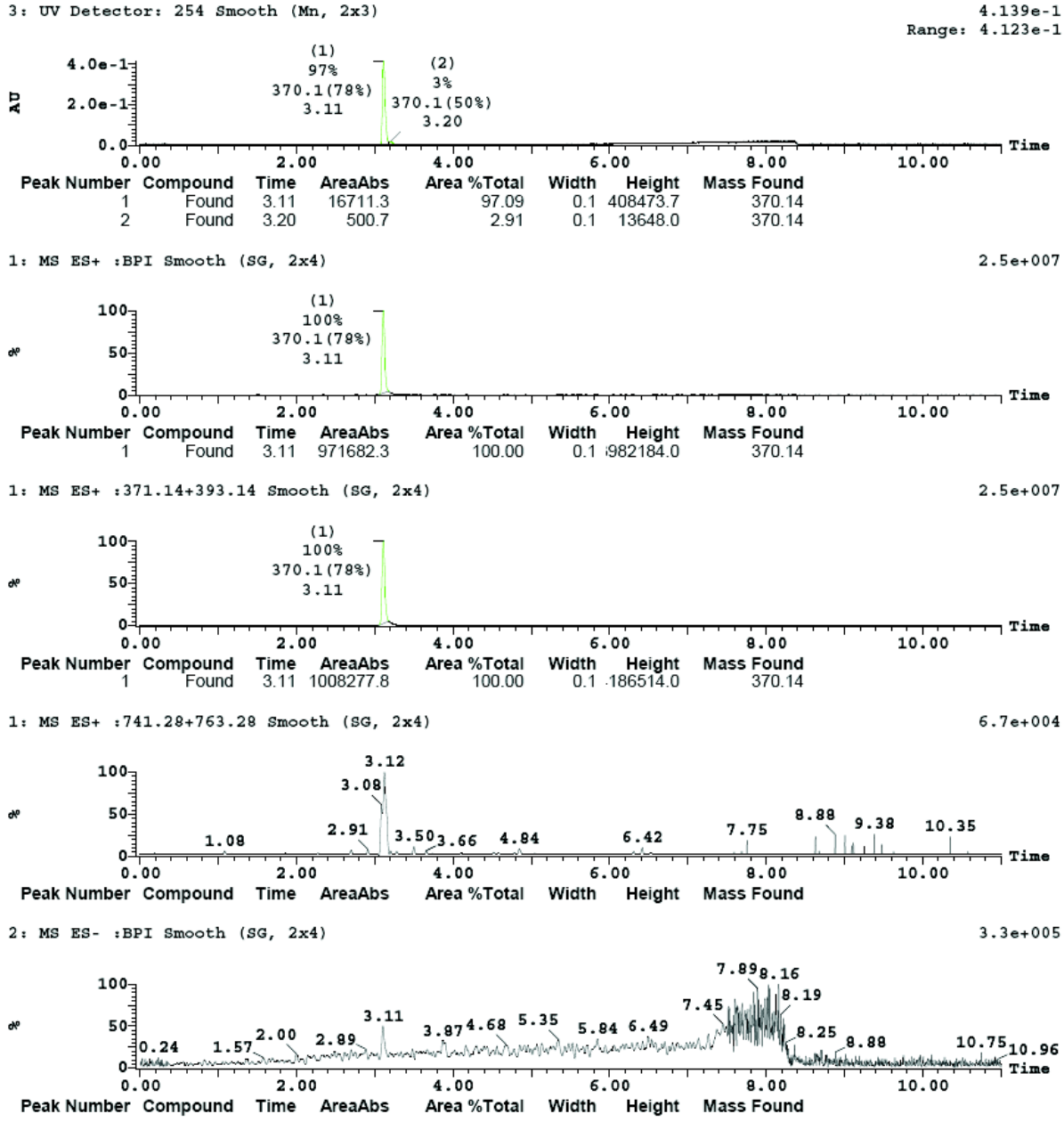
Peak ID	Compound	Time	Mass Found
5		7.20	

5:(Time: 7.20) Combine (1504:1508)

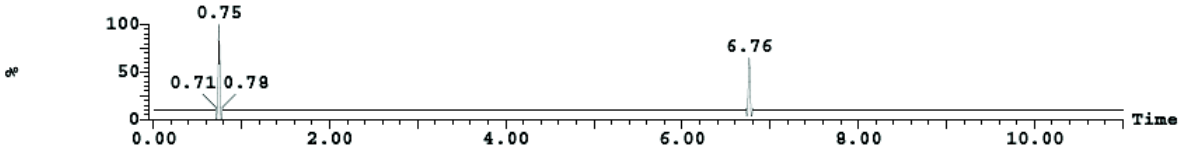
1:MS ES+
7.4e+005



HT-LC-MS Spectrum (SOP 2200) of **6e**. UV purity: 100 %

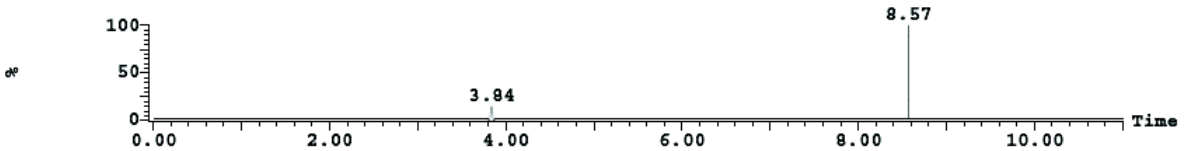


2: MS ES- :369.14 Smooth (SG, 2x4) 6.6e+002



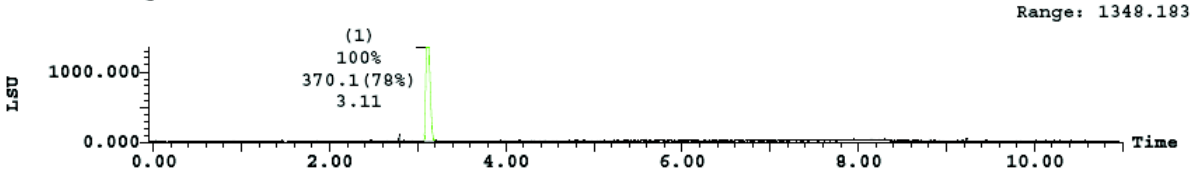
Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

2: MS ES- :739.28 Smooth (SG, 2x4) 3.6e+003



Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

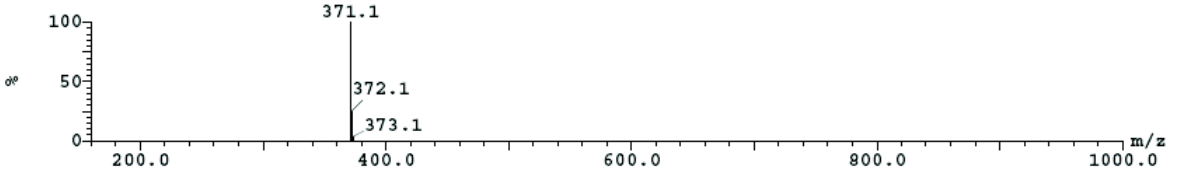
(1) ELSD Signal Smooth (Mn, 2x3) 1348.196
Range: 1348.183



Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1	Found	3.11	79126.6	100.00	332446.5	370.14

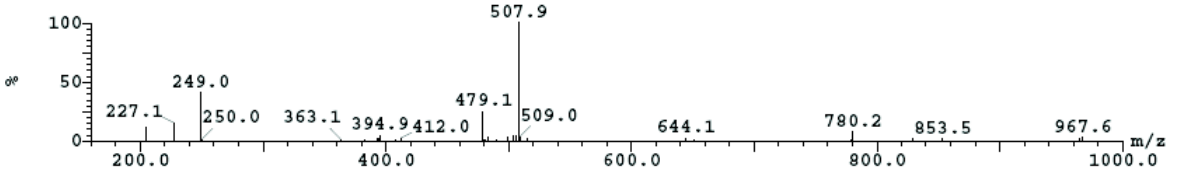
Peak ID	Compound	Time	Mass Found
1	Found	3.11	370.14

1:(Time: 3.11) Combine (648:653) 1:MS ES+
2.2e+007



Peak ID	Compound	Time	Mass Found
1		3.11	

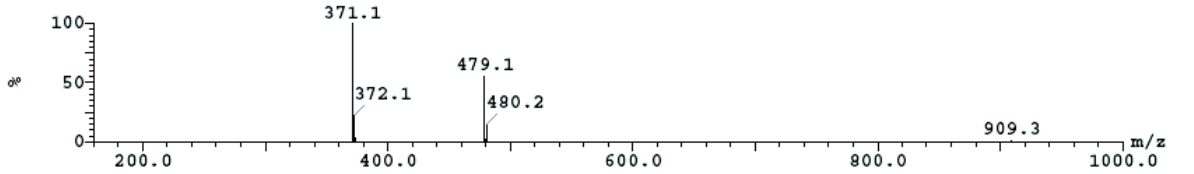
1:(Time: 3.11) Combine (648:652) 2:MS ES-
2.3e+005



Peak ID	Compound	Time	Mass Found
2	Found	3.20	370.14

2:(Time: 3.20) Combine (669:673)

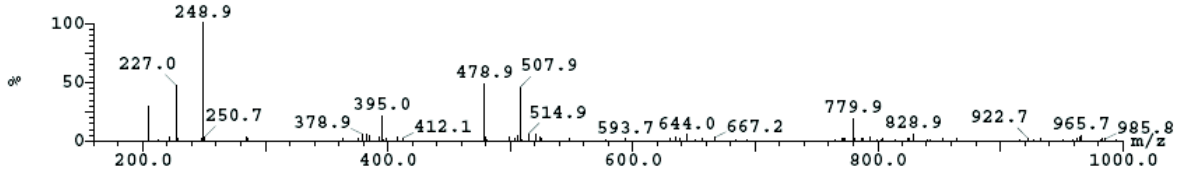
1:MS ES+
7.9e+005



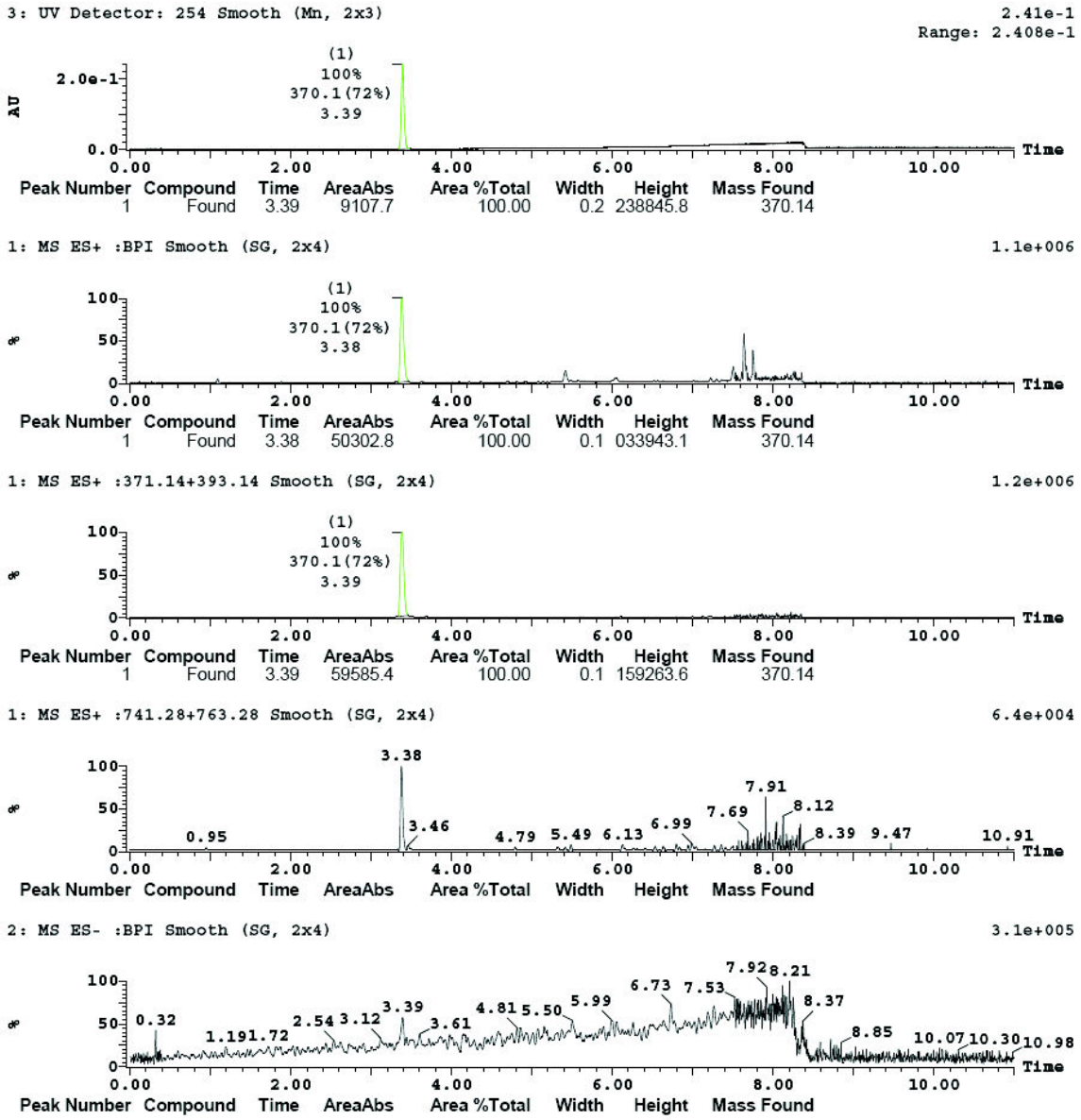
Peak ID	Compound	Time	Mass Found
2		3.20	

2:(Time: 3.20) Combine (668:673)

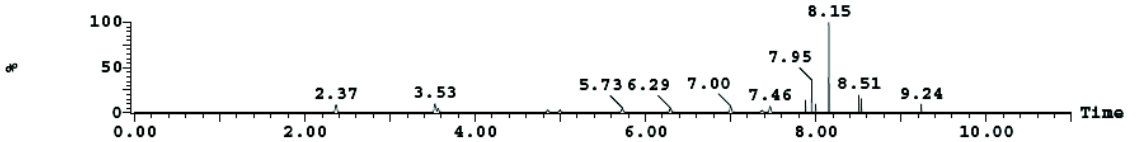
2:MS ES-
6.4e+004



HT-LC-MS Spectrum (SOP 2200) of **6f**. UV purity: 100 %

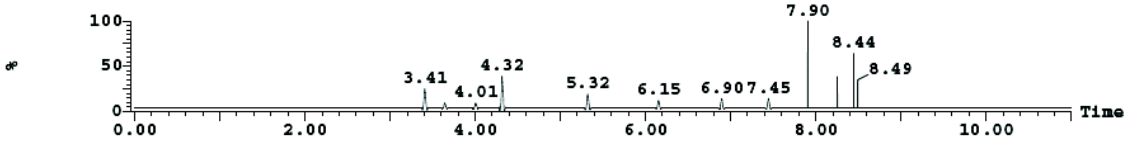


2: MS ES- :369.14 Smooth (SG, 2x4) 1.6e+004



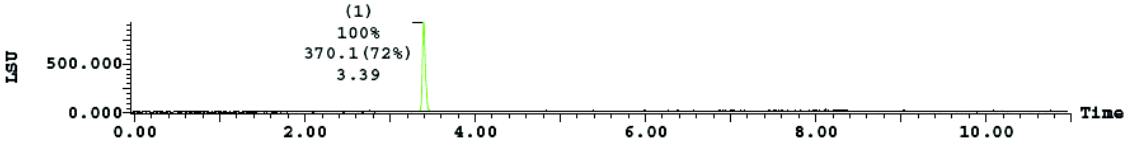
Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

2: MS ES- :739.28 Smooth (SG, 2x4) 5.0e+003



Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

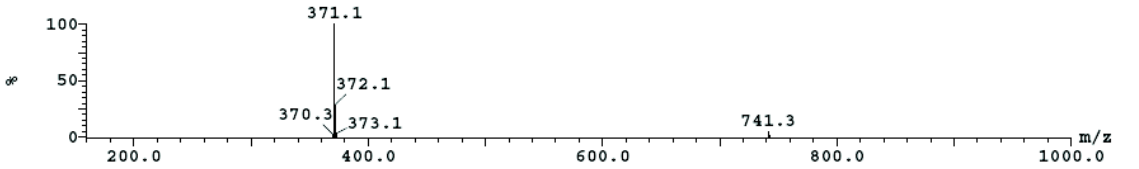
(1) ELSD Signal Smooth (Mn, 2x3) 927.961
Range: 921.215



Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1	Found	3.39	36320.4	100.00	913767.3	370.14

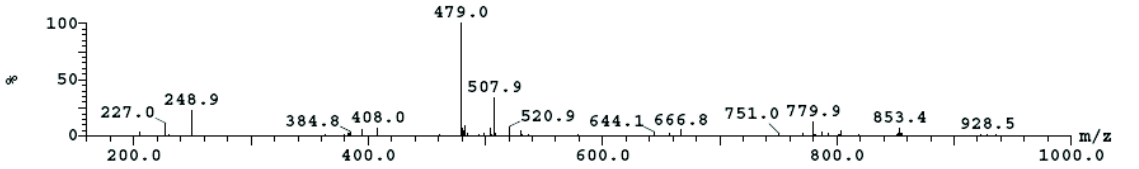
Peak ID	Compound	Time	Mass Found
1	Found	3.38	370.14

1:(Time: 3.38) Combine (706:710) 1:MS ES+ 1.2e+006

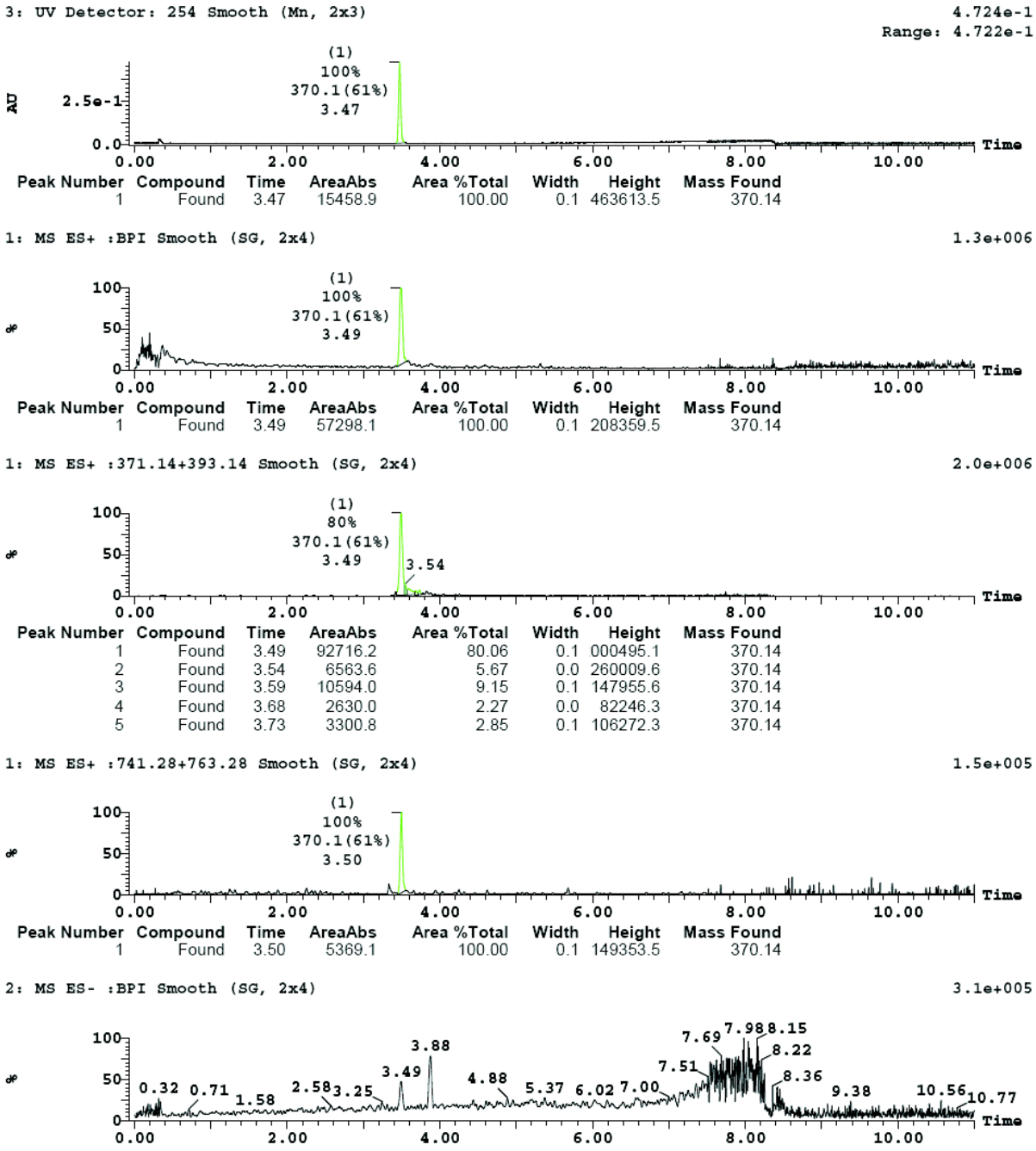


Peak ID	Compound	Time	Mass Found
1		3.38	

1:(Time: 3.39) Combine (708:712) 2:MS ES- 1.8e+005

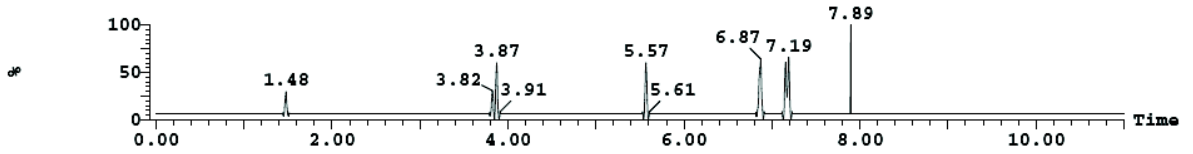


HT-LC-MS Spectrum (SOP 2200) of **6g**. UV purity: 100 %



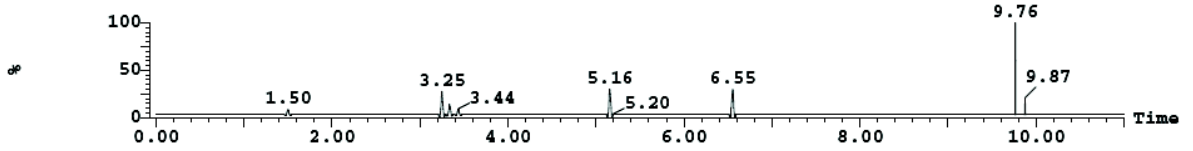
Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

2: MS ES- :369.14 Smooth (SG, 2x4) 1.7e+003



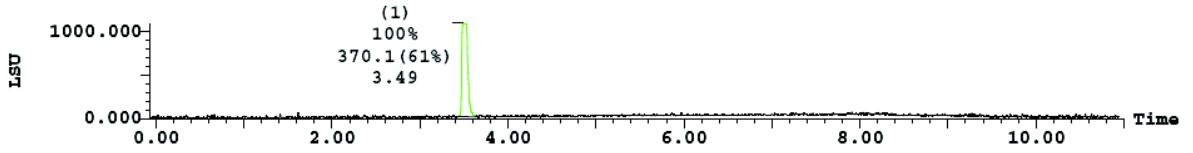
Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

2: MS ES- :739.28 Smooth (SG, 2x4) 6.3e+003



Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

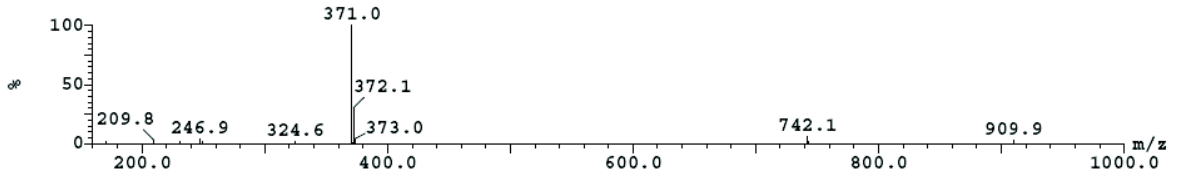
(1) ELSD Signal Smooth (Mn, 2x3) 1097.710
Range: 1097.403



Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1	Found	3.49	83542.4	100.00	075435.6	370.14

Peak ID	Compound	Time	Mass Found
1	Found	3.49	370.14

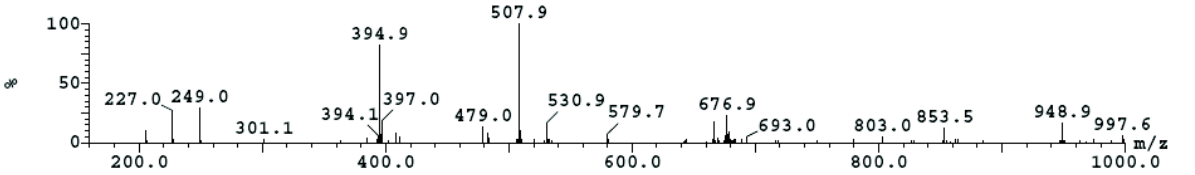
1:(Time: 3.47) Combine (725:729) 1:MS ES+
1.1e+006



Peak ID	Compound	Time	Mass Found
1		3.49	

1:(Time: 3.47) Combine (725:729)

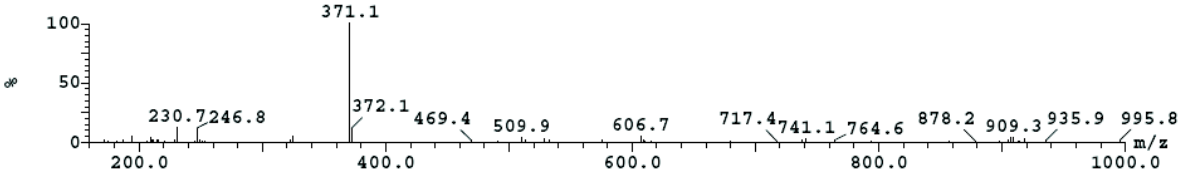
2:MS ES-
1.4e+005



Peak ID	Compound	Time	Mass Found
2	Found	3.54	370.14

2:(Time: 3.54) Combine (740:744)

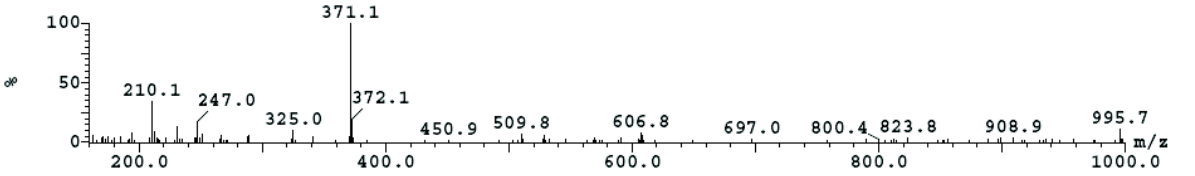
1:MS ES+
3.2e+005



Peak ID	Compound	Time	Mass Found
3	Found	3.59	370.14

3:(Time: 3.59) Combine (749:753)

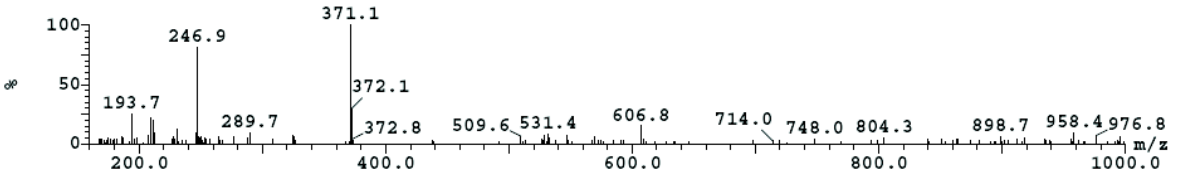
1:MS ES+
1.6e+005



Peak ID	Compound	Time	Mass Found
4	Found	3.68	370.14

4:(Time: 3.68) Combine (769:773)

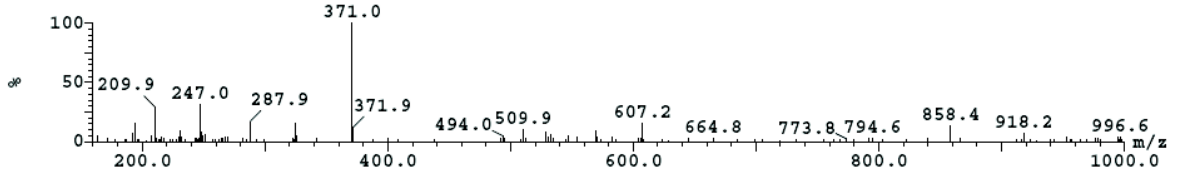
1:MS ES+
1.0e+005



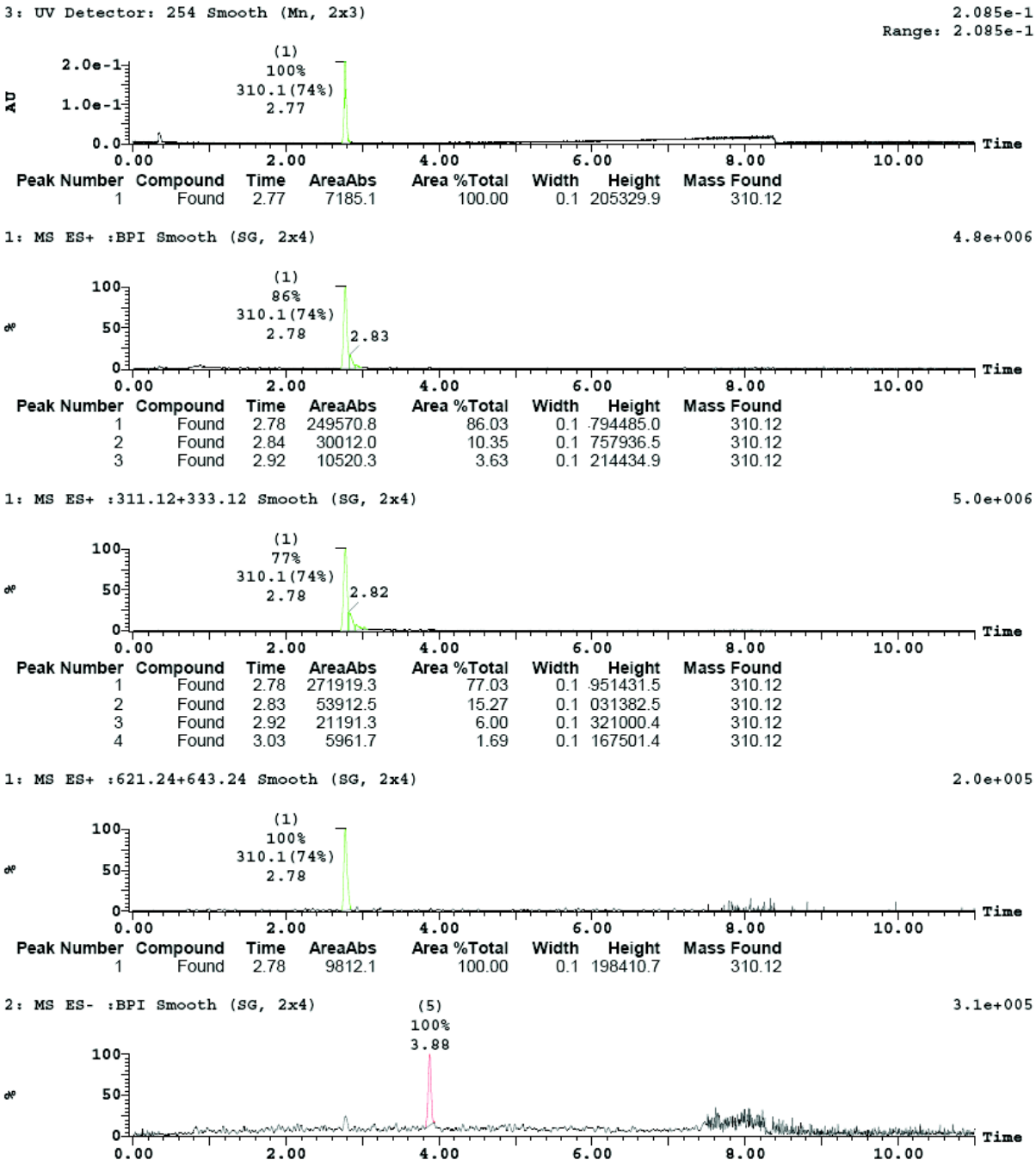
Peak ID	Compound	Time	Mass Found
5	Found	3.73	370.14

5:(Time: 3.73) Combine (780:784)

1:MS ES+
1.4e+005

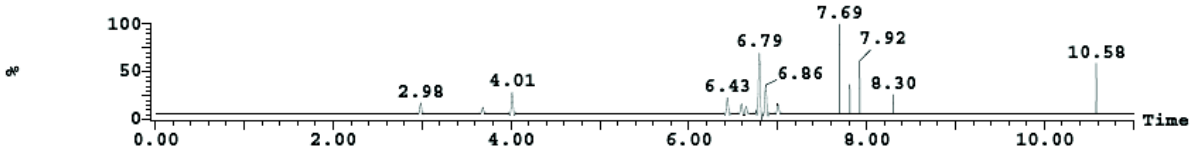


HT-LC-MS Spectrum (SOP 2200) of **6m**. UV purity: 100 %



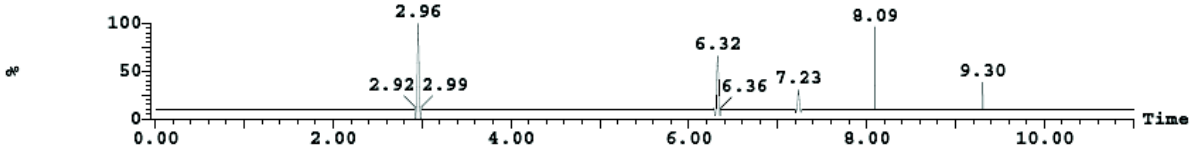
Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
5		3.88	11570.7	100.00	0.1	266584.0	

2: MS ES- :309.12 Smooth (SG, 2x4) 5.5e+003



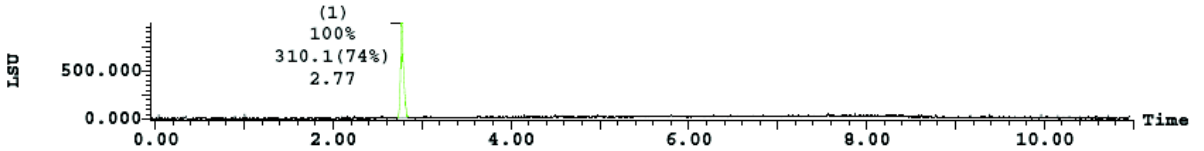
Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

2: MS ES- :619.24 Smooth (SG, 2x4) 3.7e+003



Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

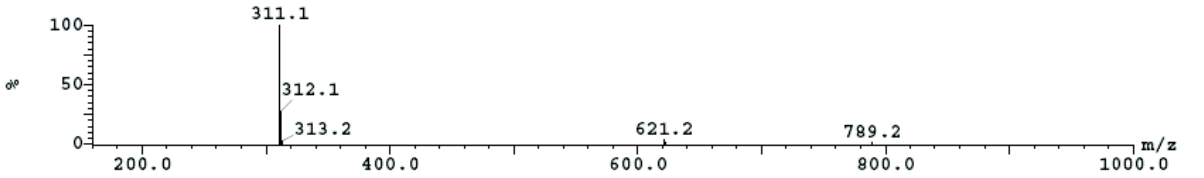
(1) ELSD Signal Smooth (Mn, 2x3) 985.307
Range: 985.160



Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1	Found	2.77	39578.6	100.00	970720.3	310.12

Peak ID	Compound	Time	Mass Found
1	Found	2.78	310.12

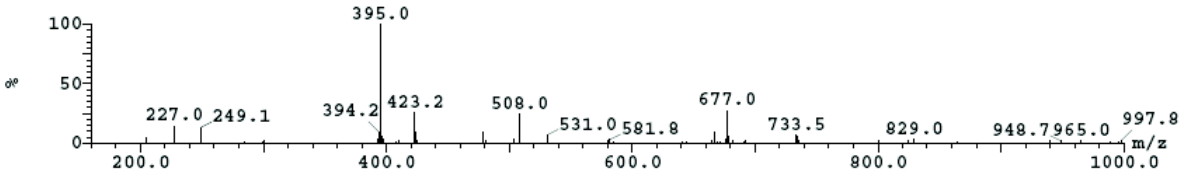
1:(Time: 2.77) Combine (578:582) 1:MS ES+
4.6e+006



Peak ID	Compound	Time	Mass Found
1		2.78	

1:(Time: 2.77) Combine (577:582)

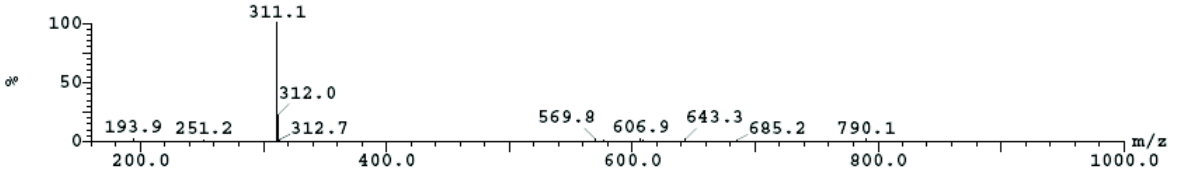
2:MS ES-
8.8e+004



Peak ID	Compound	Time	Mass Found
2	Found	2.84	310.12

2:(Time: 2.83) Combine (591:595)

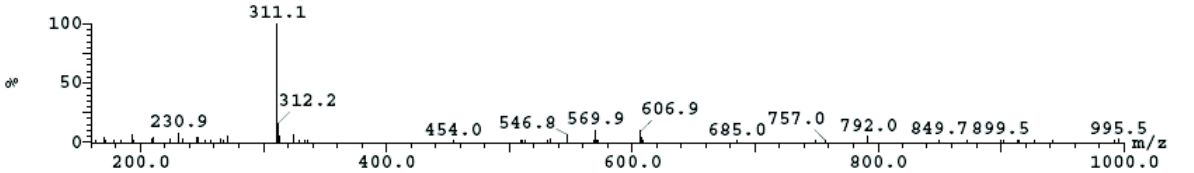
1:MS ES+
9.9e+005



Peak ID	Compound	Time	Mass Found
3	Found	2.92	310.12

3:(Time: 2.92) Combine (608:612)

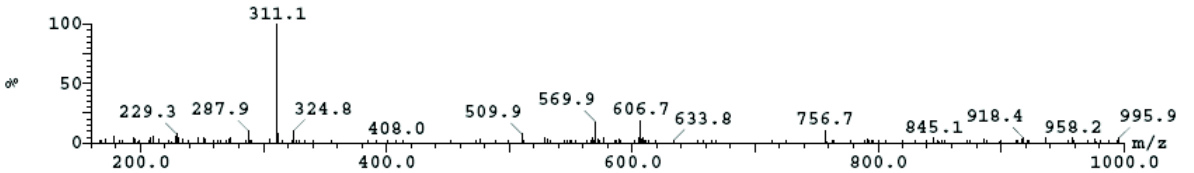
1:MS ES+
3.3e+005



Peak ID	Compound	Time	Mass Found
4	Found	3.03	310.12

4:(Time: 3.03) Combine (631:635)

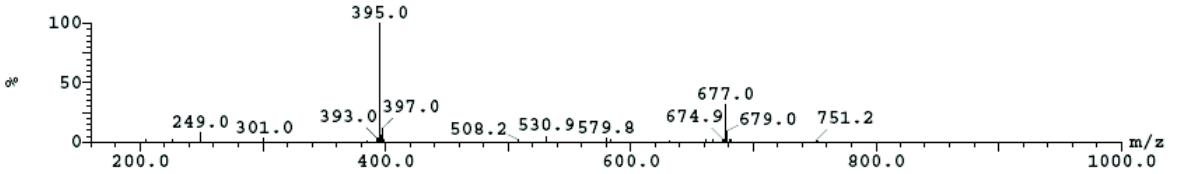
1:MS ES+
1.8e+005



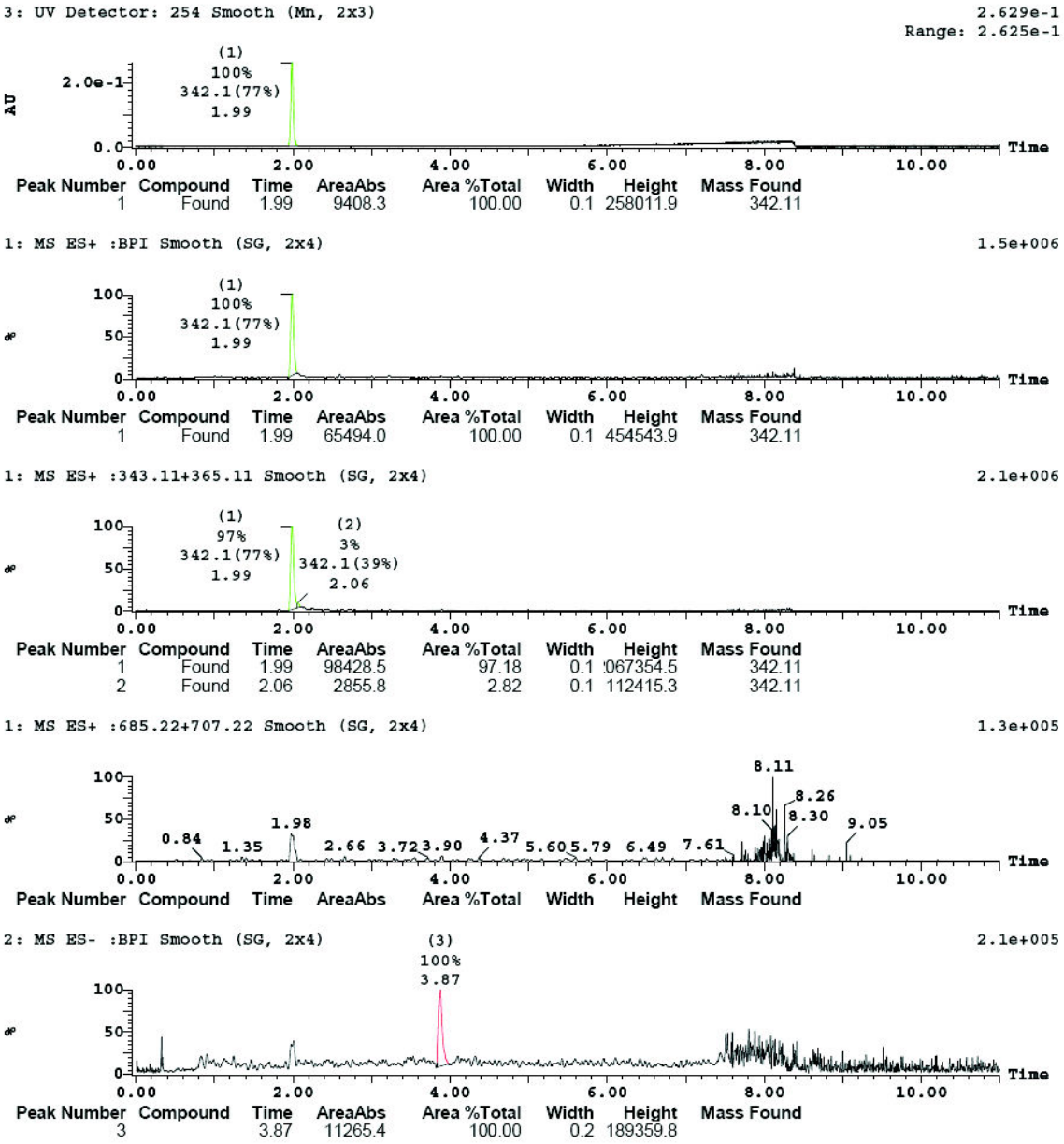
Peak ID	Compound	Time	Mass Found
5		3.88	

5:(Time: 3.88) Combine (809:813)

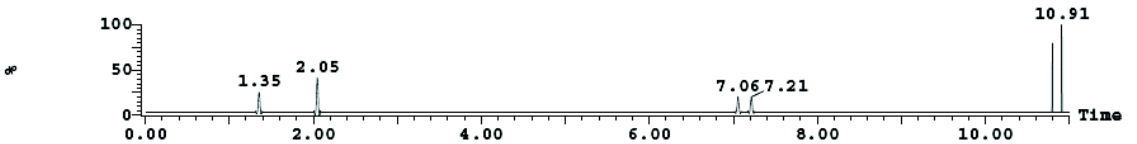
2:MS ES-
3.6e+005



HT-LC-MS Spectrum (SOP 2200) of **7** (*Hyrtinadine A*). UV purity: 100 %

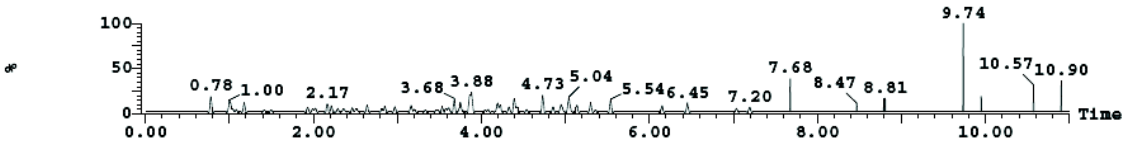


2: MS ES- :341.11 Smooth (SG, 2x4) 2.2e+003



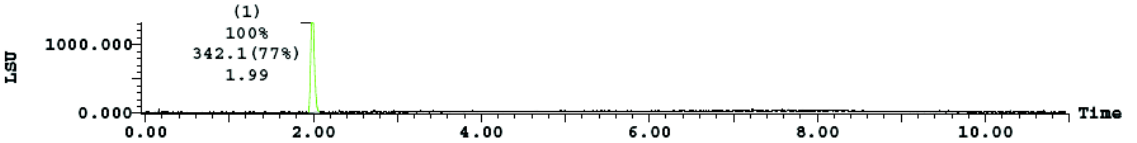
Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

2: MS ES- :683.22 Smooth (SG, 2x4) 1.3e+004



Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found

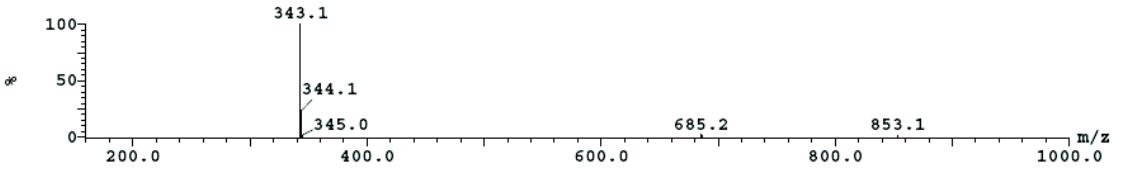
(1) ELSD Signal Smooth (Mn, 2x3) 1315.949
Range: 1315.843



Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1	Found	1.99	71489.5	100.00	305945.6	342.11

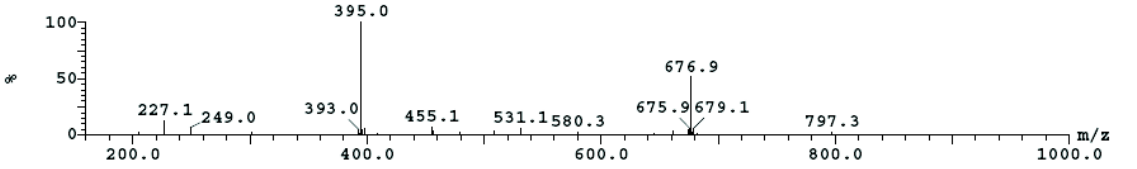
Peak ID	Compound	Time	Mass Found
1	Found	1.99	342.11

1:(Time: 1.99) Combine (414:418) 1:MS ES+
2.1e+006

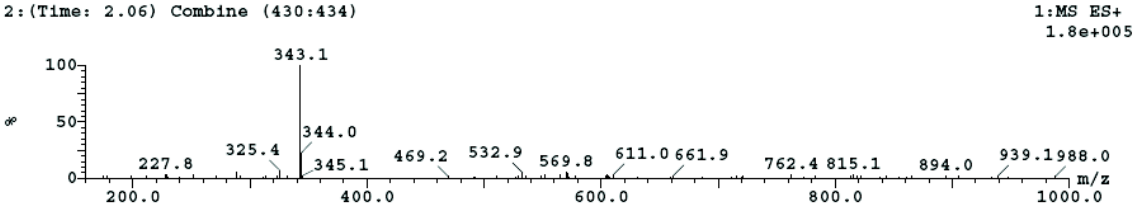


Peak ID	Compound	Time	Mass Found
1		1.99	

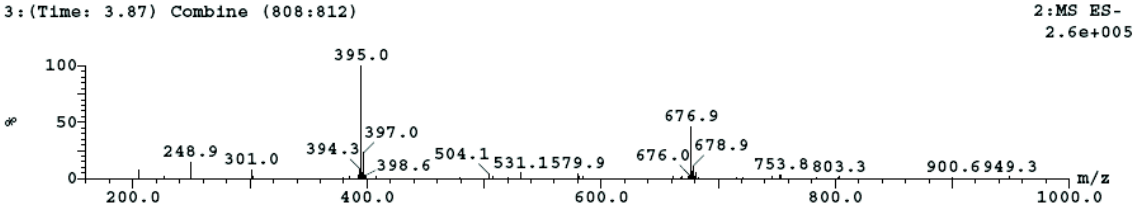
1:(Time: 1.99) Combine (413:417) 2:MS ES-
9.5e+004



Peak ID	Compound	Time	Mass Found
2	Found	2.06	342.11



Peak ID	Compound	Time	Mass Found
3		3.87	



6.2 HT-LC-MS Methods for the Control of Identity and Purity of Compounds 3, 4, 6 and 7

Problem Definition	Identity and Purity			
SOP (Standart Operation Procedure)	2200			
Methods	HT-LC-MS			
System	Waters Acquity UPLC® with PDA and ELSD Waters SQD (ESI+/- and APCI+/-)			
Software	MassLynx with OpenLynx			
Column	Waters XBridge™ C8 3.5 µm 4.6 x 50 mm Column Part No. 186003053			
Eluent	A: 99.9 % acetonitrile + 0.1 % TFA B 99.9 % water + 0.1 % TFA			
Gradient	time (min)	A %	B %	flow (mL/min)
	0	5	95	2.0
	8.00	100	0	2.0
	8.10	10	90	2.0
	8.50	5	95	2.0
	11.00	5	95	2.0
Column temperature	Room temperature			
Injection volume	3 µL			
Sample preparation	Approx. 0.1 mg were dissolved in acetonitrile + water 50/50 in an ultrasound bath, so that the concentration was 0.5 mM. If necessary, the sample was additionally diluted: 100 µL in 500 µL acetonitrile + water 5/95.			

6.3 Biological Data

6.3.1 DSTT Kinase Assays[7]

The kinase assays were carried out at room temperature. Compounds were pre-incubated in the presence of the enzyme and peptide/protein substrate for 5 min before initiation of the reaction by adding ATP. Assays were incubated at room temperature before termination by the addition of 5 µL orthophosphoric acid. The assays were then harvested onto P81 Unifilter Plates (wash buffer was 50 mM orthophosphoric acid) and dried in air. The dry Unifilter plates were then sealed on the addition of MicroScint O and were counted in Packard Topcount NXT scintillation counters.

6.3.2 Viability Assays[8]

A2780 (ovarian tumor cell line; European Collection of Cell Culture (ECACC) 93112519) or HCT116 (colon tumor cell line, ATCC CCL-247) cells were plated in 96-well plates at 2000 cells per well and incubated for 24 h at 37 °C in DMEM (Dulbecco's modified Eagle medium) supplemented with FCS (fetal calf serum or fetal bovine serum). The test compounds were diluted in DMSO, added to the culture plates and incubation was continued for 72 h. At the end of the compound incubation period AlamarBlue reagent (BUF012B, Serotec) was added and the 96-well plates were further incubated. The plates were measured with a fluorescence reader.

[7] J. Bain, L. Plater, M. Elliott, N. Shpiro, C. J. Hastie, H. McLauchlan, I. Klevernic, J. S. C. Arthur, D. R. Alessi, P. Cohen, *Biochem. J.* **2007**, *408*, 297-315.

[8] G. R. Nakayama, M. C. Caton, M. P. Nova, Z. Parandoosh, *J. Immunol. Methods* **1997**, *204*, 205-208.

There is no substitute for hard work.

Thomas Alva Edison