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Suggested Citation:
Lange-Asschenfeldt, C., Brouzou, K. O., & Christl, J. (2025). Comparative receptor pharmacology of antipsychotic drugs based on normalized binding affinity data and breadth of interaction. European Neuropsychopharmacology, 99, 31–40. https://doi.org/10.1016/j.euroneuro.2025.07.011

European Neuropsychopharmacology 99 (2025) 31–40

Contents lists available at ScienceDirect

European Neuropsychopharmacology

journal homepage: www.sciencedirect.com/journal/european-neuropsychopharmacology

Comparative receptor pharmacology of antipsychotic drugs based on normalized binding affinity data and breadth of interaction

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ARTICLE INFO

Keywords:
Antipsychotic drugs
Binding affinity
Breadth
Receptor pharmacology
Atypicality
Neuroscience-based nomenclature

ABSTRACT

The pharmacology of antipsychotic drugs (APDs) is exceedingly complex with many of them showing a broad receptor interaction spectrum. We aimed to provide a reference work on receptor binding affinity, to quantify the breadth of receptor interaction of APDs and to analyze implications on clinical efficacy and classification. Binding affinity data were obtained from an open-source database and normalized to allow for direct comparison of affinity profiles across compounds and quantification of the receptor interaction breadth at the level of (1) individual drugs and (2) defined receptor groups. Breadth data were correlated with clinical efficacy data taken from the literature and analyzed in relation to chemical structure and taxonomy, particularly the Neuroscience-based Nomenclature (NbN). Normalized affinity profiles of 35 worldwide used APDs for 25 receptors and receptor interaction breadth for drugs and defined receptor groups were calculated and presented in graphical and tabular form. High breadth values were associated with tricyclic basic structure but were not associated with clinical efficacy. The NbN classification did not show full correspondence with our in-depth statistical analysis of receptor group-related breadth values. In sum, our study provides a representative multireceptor profiling of the worldwide most frequently used APDs and offers a way to quantify and compare the breadth of receptor interaction at the level of individual compounds as well as receptor groups within compounds.

1. Introduction

Schizophrenia spectrum disorders (SSDs) form a group of chronic, debilitating diseases of complex etiology affecting over 1% of the population worldwide and causing considerable distress to the individual and society. Included are positive (delusions, hallucinations, disorganized speech and thought), negative (affective flattening, avolition, anhedonia, social withdrawal), and dyscognitive symptoms (impairment in attention, learning, and working memory) (Marder and Cannon, 2019).

Antipsychotic drugs (APDs) are the mainstay of treatment and have traditionally been classified based on chemical structure, broad mechanism of action (MoA) and side effect profile (typical vs. atypical) or epoch of introduction: first (FGAs), second (SGAs) and third generation APDs (TGAs) (McCutcheon et al., 2024). More recently, the Neuroscience-based Nomenclature (NbN; currently 2nd revision: NbN2r) has been implemented in the scientific context as a pharmacologically more precise approach (https://nbn2r.com) (Zemach & Zohar, 2025; Zohar et al., 2015). However, while relying basically on expert judgement, at present it lacks validation and is yet to be widely adopted in clinical settings (McCutcheon et al., 2024).

Several receptor systems have been implicated in the MoA of APDs, above all dopamine and serotonin (5-HT) receptors. However, some potent compounds such as the 'gold standard' atypical APD clozapine and, more recently, xanomeline, a muscarinic agent recently approved in the United States (Meyer et al., 2025), lack significant (at least D_2 receptor-specific) dopaminergic binding affinity. Antipsychotic drugs are also heterogeneous regarding the breadth of their receptor interaction spectrum. Some compounds, such as the benzamide amisulpride are fairly selective dopamine D_2 receptor antagonists while others, such as olanzapine, show broad binding profiles. As SSDs appear to be polygenic disorders and many APDs act on a multitude of molecular targets, it has been contended that non-selectivity might be a criterion for higher effectiveness (Roth et al., 2004).

Aim of the present paper is, first, to provide a reference work of receptor binding affinity data ('fingerprints') for a large panel of APDs, using an open-source database of *in vitro* receptor binding studies. Second, we aimed to quantify the breadth of receptor interaction of the

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https://doi.org/10.1016/j.euroneuro.2025.07.011
Received 1 May 2025; Received in revised form 20 July 2025; Accepted 24 July 2025
Available online 23 August 2025

individual APDs by normalizing binding data according to a calculation established by Ray (2010). Third, we investigated whether the calculated receptor breadth was associated with (1) clinical efficacy and (2) basic chemical structure (tricyclicity). Fourth, we were interested if the breadth of interaction of salient receptor groups (i.e., serotonin, dopamine, norepinephrine etc.) were matched by the current NbN classification.

2. Methods

2.1. Receptor affinities

Receptor binding affinity data (K_i values in nM) of APDs listed in the National Institute of Mental Health Psychoactive Drug Screening Program (NIMH-PDSP) K_i database (https://pdsp.unc.edu/ databases/kiDownload/; date of last retrieval: October 15, 2024) (Jensen & Roth, 2008). This comprehensive database provides a large amount of data collected from studies in the literature and is continuously updated. Median K_i values of binding assays with human cloned receptors were considered.

2.2. Data normalization

The method of Ray (2010) was used for data normalization. Our goal was to obtain *relative* binding affinity data for APDs so that multi-receptor affinity profiles of the studied drugs could be directly compared by factoring out absolute potencies. Thus, in the first step, raw K_i values were log-transformed to $pK_i = -\log_{10} K_i$. Raw K_i values spanned 5 orders of magnitude, thus, a normalized pKi value (npK_i) for a given drug at a defined receptor was calculated as

$$npK_i = 5 + pK_i - pK_{imax}$$

with pK_{imax} representing the maximum pK_i value for each drug within the panel of receptors under study. If a binding affinity in an assay is too low to be measured, $K_i > 10{,}000$ nM is reported in the NIMH-PDSP database (at this value, no specific binding takes place any more). As part of the normalization process, npK_i was set to zero in such cases.

Thus, high affinities have high values and for each drug, the highest affinity at any receptor of a given drug will be $npK_i = 5$ (regardless of the absolute affinity). An $npK_i = 4$ at another receptor for this drug would mean ten-fold lower binding affinity and so on, so each unit of npK_i represents one order of magnitude of the K_i value. Table S1 provides two exemplary calculations of npK_i values.

2.3. Breadth statistics

Ray (2010) also introduced an index of breadth (B) as a quantitative parameter to compare the interaction of individual drugs with multiple target structures of psychoactive drugs. For any given drug, this value is obtained by simply summing up the npK_i values of all target structures (receptors):

$$B = \sum npK_i$$

The higher the B value, the more target structures are bound by the drug. Thus, this value may be viewed as a measure of receptor binding diversity (or inverse selectivity). To give greater weight to lower K_i values we used the modified breadth statistics:

$$B_{sq} = \sqrt{\sum (npK_i)^2}$$

The B_{sq} value can also be used to quantify the breadth not only at the whole compound level but also at the level of groups of receptors within a given compound. We term this value the *group related breadth* $B_{sq}G$. For example, $B_{sq}G(D_{1/5})$ for an individual APD is calculated from the summed npK_i values of the D_1 and D_5 receptor (instead of the whole set of 25 receptors) of this compound. This is performed to determine the weight of a group of related receptors (or a single receptor) in an individual compound in comparison with other compounds. For example, a high $B_{sq}G(D_{2/3/4})$ value for a given drug indicates a broad interaction, i. e., a high weight of these dopaminergic receptors in this respective drug. Table S1 shows an example of a $B_{sq}G$ calculation.

2.4. Inferential statistics

Student's *t*-test was used to measure statistically significant differences in B_{sq} between tricyclic and non-tricyclic APDs. To assess possible relationships of B_{sq} and clinical efficacy of APDs, standardized mean difference (SMD) values were taken from the meta-analysis of Huhn et al. (2019) and Spearman's correlation coefficient rho was calculated on a scale of −1 to 1. Possible differences in $B_{sq}G$ of various receptors/receptor groups were analyzed among the four NbN2r classes (1) dopamine D_2 receptor antagonists (D_2-RAnt), (2) dopamine D_2 and serotonin 5-HT_{1A} receptor partial agonists/antagonists (D_2/5-HT_{1A}-RPAnt), (3) dopamine D_2, serotonin 5-HT_2 receptor and α adrenoceptor antagonists (D_2/5-HT_2/α_2-RAnt), and (4) dopamine D_2, serotonin 5-HT_2 receptor antagonists (D_2/5-HT_2-RAnt), using one-way ANOVA followed by Tukey's *post-hoc* test to test for multiple comparisons. We note here that quetiapine, an original dopamine D_2, serotonin 5-HT_2 receptor and α adrenoceptor antagonist and norepinephrine uptake inhibitor (D_2/5-HT_2/α_2-RAnt + NERI), which represents a group of its own in the NbN2r, was assigned to the group of D_2/5-HT_2/α_2-RAnts. The significance of all tests during testing was set at 5 % ($p < 0.05$), representing a confidence level of 95%. GraphPad Prism 10 was used for statistical processing.

3. Results

3.1. Normalized receptor binding affinity

Data were collected for 35 APDs which are listed together with their NbN classification in Table 1. Median raw K_i values of these compounds at 25 receptors are provided in Table S2. After log-transformation, data were normalized to npK_i values (Table S3). Normalized receptor binding profiles of the different APDs are depicted in Figs. 1 to 5. Herein, APDs are organized according to their chemical classes in order to visualize the connection between chemical structure and receptor binding similarities. Compounds were roughly categorized in tricyclic vs. non-tricyclic drugs. In the diagrams, npK_i values for individual drugs are arranged in decreasing order. According to Ray (2010), an approximately more than 100-fold drop in affinity relative to the receptor with the highest affinity for each compound ($npK_i = 3$ in our data set, dashed line in the diagrams) marks the limit of perceptible (i. e., potentially relevant) receptor interaction.

Tricyclic antipsychotic drugs (APDs)

Figs. 1 and 2 demonstrate the receptor interaction profiles of APDs with a tricyclic structure. Particularly the *phenothiazines* with aliphatic and piperidine residues display a broad (diverse) receptor interaction spectrum including considerable adrenergic and muscarinic affinitiy (Fig. 1A). Compounds with a piperazine residue – including the thioxanthine derivatives flupenthixol and thiothixene (Fig. 1B) – show a more pronounced normalized binding affinity for D_2-like dopamine receptors which represent the highest npK_i values ($D_3 > D_2$ in all drugs except chlorprothixene). A distinguished group within the tricyclic APDs is formed by compounds with a seven-membered heterocyclic core structure, the sometimes so called "*epines*", depicted in Fig. 2. As becomes clearly visible, these drugs display higher affinites at serotonin (specifically the 5-HT_{2A} receptor followed by the 5-HT_{2C}, the 5-HT_6, and the 5-HT_7 receptors) than dopamine receptors, exhibiting an 'atypical' profile. In addition, in this latter group, npK_i values are in the functionally relevant range also for the α_{1A} and α_{2C} adrenoceptors. A marked affinity at muscarinic M_1 and M_4 receptors characterize the binding

Table 1
Overview of antipsychotic drugs (APDs) analyzed in this study.

Drug	Neuroscience-based Nomenclature (NbN2r)		Chemical class	typical / atypical
	Pharmacological domain (Receptor)	Mode of action (abbreviation)		
Amisulpride	Dopamine	D_2-RAnt	Benzamide	atypical
Aripiprazole	Dopamine, serotonin	D_2/5-HT_{1A}-RPAnt	Phenylpiperazine	atypical
Asenapine	Dopamine, serotonin, norepiphrenine	D_2/5-HT_2/α_2-RAnt	Dibenzoxepin(o)pyrrol	atypical
Blonanserin	Dopamine, serotonin	D_2/5-HT_2-RAnt	Cyclooctapyridine	atypical
Brexpiprazole	Dopamine, serotonin	D_2/5-HT_{1A}-RPAnt	Phenylpiperazine	atypical
Cariprazine	Dopamine, serotonin	D_2/5-HT_{1A}-RPAnt	Phenylpiperazine	atypical
Chlorpromazine	Dopamine, serotonin	D_2/5-HT_2-RAnt	Phenothiazine (aliphatic)	*typical*
Chlorprothixene	Dopamine, serotonin	D_2/5-HT_2-RAnt	Thioxanthine	*typical*
Clozapine	Dopamine, serotonin, norepiphrenine	D_2/5-HT_2/α_2-RAnt	Dibenzodiazepine	atypical
Flupenthixol	Dopamine, serotonin	D_2/5-HT_2-RAnt	Thioxanthine	*typical*
Fluphenazine	Dopamine	D_2-RAnt	Phenothiazine (piperazine)	*typical*
Fluspirilene	N/C		Diphenylbutylpiperidine	*typical*
Haloperidol	Dopamine	D_2-RAnt	Butyrophenone	*typical*
Iloperidone	Dopamine, serotonin	D_2/5-HT_2-RAnt	Benzisoxazole	atypical
Loxapine	Dopamine, serotonin	D_2/5-HT_2-RAnt	Dibenzoxazepine	*typical*
Lurasidone	Dopamine, serotonin	D_2/5-HT_2-RAnt	Benzisothiazole	atypical
Melperone	N/C		Butyrophenone	*typical*
Mesoridazine	N/C		Phenothiazine (piperidine)	*typical*
Molindone	N/C		Dihydroindolone	*typical*
Olanzapine	Dopamine, serotonin	D_2/5-HT_2-RAnt	Thienobenzodiazepine	atypical
Paliperidone	Dopamine, serotonin, norepiphrenine	D_2/5-HT_2/α_2-RAnt	Benzisoxazole	atypical
Perphenazine	Dopamine	D_2-RAnt	Phenothiazine (piperazine)	*typical*
Pimozide	Dopamine	D_2-RAnt	Diphenylbutylpiperidine	*typical*
Pipamperone	N/C		Butyrophenone	*typical*
Quetiapine	Dopamine, serotonin, norepiphrenine	D_2/5-HT_2/ α_2-RAnt + NERI	Dibenzothiazepine	atypical
Remoxipride	N/C		Benzamide	atypical
Risperidone	Dopamine, serotonin, norepiphrenine	D_2/5-HT_2/α_2-RAnt	Benzisoxazole	atypical
Sertindole	Dopamine, serotonin	D_2/5-HT_2-RAnt	Phenylindole	atypical
Sulpiride	Dopamine	D_2-RAnt	Benzamide	atypical
Thioridazine	Dopamine, serotonin	D_2/5-HT_2-RAnt	Phenothiazine (piperidine)	*typical*
Thiothixene	N/C		Thioxanthine	*typical*
Trifluoperazine	Dopamine, serotonin	D_2/5-HT_2-RAnt	Phenothiazine (piperazine)	*typical*
Xanomeline	N/C		Thiadiazol-tetrahydropyridine	atypical
Ziprasidone	Dopamine, serotonin	D_2/5-HT_2-RAnt	Benzisothiazole	atypical
Zotepine	Dopamine, serotonin	D_2/5-HT_2-RAnt	Dibenzothiepine	atypical

RAnt, receptor antagonist; RPAnt, receptor partial agonist/antagonist; NERI, norepinephrine reuptake inhibitor; N/C, not classified in the NbN2r

profile of phenothiazines with piperidine residues and the "epines" clozapine, olanzapine, and quetiapine.

Non-tricyclic antipsychotic drugs (APDs)

As evidenced by Fig. 3, *butyrophenones, diphenylbutylpiperidines,* and the *phenylpiperazines* share in common a relatively high selectivity for D_2-like dopamine receptor binding. Of note, also 5-HT_{2A} receptor binding is functionally relevant in almost all of these drugs, albeit to a lesser extent. Other serotonin receptors such as the 5-HT_{2C}, the 5-HT_6 and the 5-HT_7 receptor may also contribute to the compounds' MoA.

A relatively high binding affinity to D_2-like dopamine receptors with at least equal to higher affinity to serotonin 5-HT_{2A} receptors characterizes the group of *benzisoxazoles* and *benzisothiazoles* (Fig. 4A and B). In addition, npK_i values are in the functionally relevant range also for the α_{1A} and α_{2C} adrenoceptors here. *Benzamides* show a high selectivity for D_2-like dopamine receptor binding. Besides this circumstance, 5-HT_7 receptor binding is in the functionally relevant range for amisulpride and remoxipride and just so the other serotonin receptor subtypes in remoxipride (Fig. 5). Muscarinic activity is negligible in all of the three last mentioned groups.

Normalized binding affinity profiles of the remaining APDs that do not fall in any of the abovementioned structural groups, are depicted in Fig. 5. It emerges that blonanserin is highly selective for D_2 and D_3 receptor binding and the *phenylindole* sertindole shows a profile similar to the compounds shown in Figs. 2, 4A and B. Xanomeline is a unique substance with a predominant muscarinic receptor profile. However, its affinity profile is not selective as there is considerable binding affinity at all analyzed 5-HT receptors, α_1 adrenoceptors and even D_2-like receptor binding is not negligible.

3.2. Breadth statistics

Compound-related breadth B_{sq}

Based on the work of Ray (2010), the index of breadth B_{sq} was used to quantify receptor (non-)selectivity of APDs. Data are provided in Table S4 and presented graphically in Fig. 6A. As evidenced by Fig. 6B, B_{sq} is significantly higher in tricyclic versus non-tricyclic APDs ($t = 3.74$, $df = 33$, $p = 0.0007$). To determine a possible association between breadth and clinical efficacy in APDs, we correlated B_{sq} with the SMDs of APDs with data taken from the meta-analysis of Huhn et al. (2019). We found no significant correlation for positive (Spearman's rho = -0.083, p = 0.73, n = 19), negative (Spearman's rho = -0.36, p = 0.13, n = 19), or overall (Spearman's rho = -0.30, p = 0.13, n = 27) symptoms (Fig. S1).

Receptor group-related breadth $B_{sq}G$

As described above, the B_{sq} value may also be calculated based on receptor groups for individual drugs ($B_{sq}G$, Table S5). The data demonstrate for example the primary significance of 5-$HT_{2A/C}$ and hardly less 5-HT_6 and 5-HT_7 receptor binding affinity in atypical in contrast to typical APDs (even when classified in the same NbN2r class, e. g., ziprasidone vs. trifluoperazine). Serotonin 5-HT_{1A} receptor binding dominates in aripiprazole, brexpiprazole, and cariprazine (D_2/5-HT_{1A}-RPAnts). It is least pronounced in the NbN2r class of D_2-RAnts which for their part fall into the top half of the $B_{sq}G(D_{2/3/4})$ column. Binding at the $\alpha_{2A/2C}$ receptor is most pronounced in aripiprazole and brexpiprazole and the D_2/5-HT_2/NE-RAnts paliperidone, risperidone and clozapine as well as quetiapine. Antipsychotic drugs with high $B_{sq}G(M_{1/4})$ and $B_{sq}G$ (H) values are almost all tricyclic (with the exception of xanomeline) irrespective of their classification according to NbN2r or typical vs. atypical.

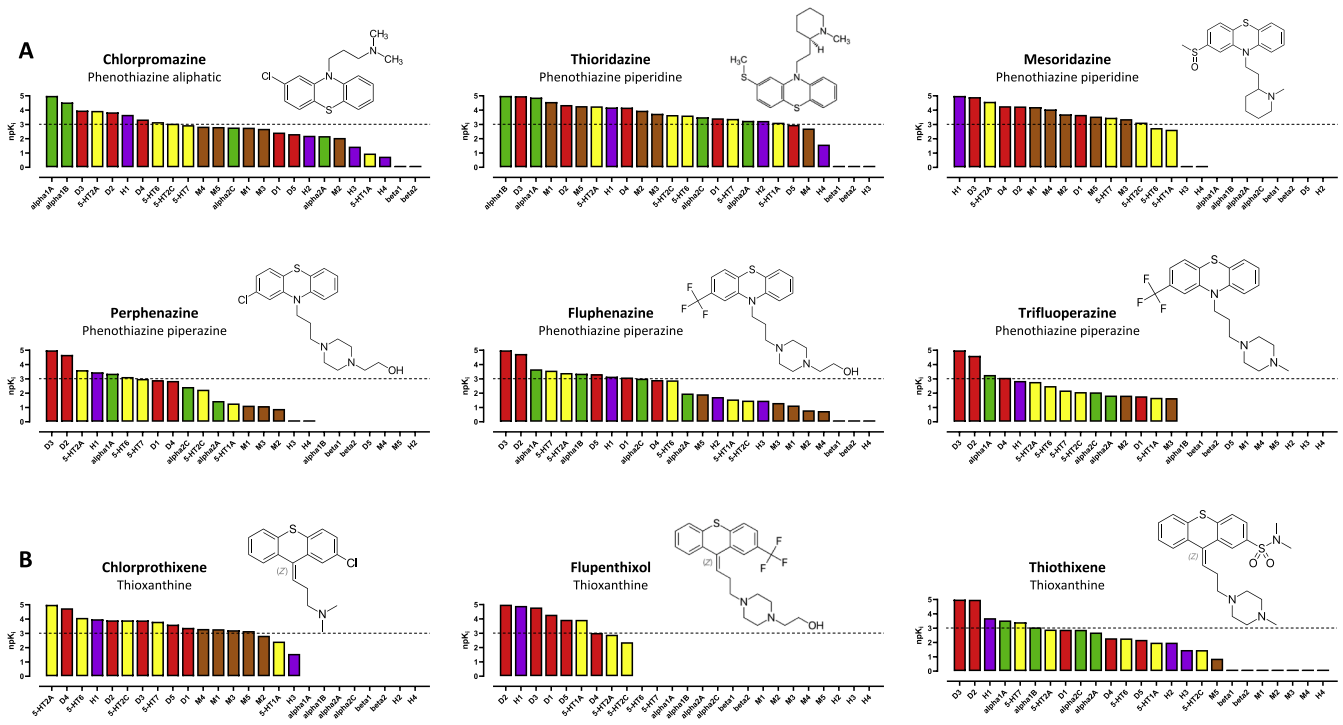

Fig. 1. Normalized receptor affinity profiles: Tricyclic antipsychotic drugs (APDs) I:
(A) Phenothiazine and (B) thioxanthene derivatives. Vertical axes represent normalized pK_i (npK_i), horizontal axes represent target receptors, arranged in the order of decreasing affinity for each individual drug. $npK_i = 5$ is assigned to the receptor with the highest affinity, $npK_i = 0$ means no specific affinity of the drug at the corresponding receptor. Different classes of receptors are labeled with colors: red: dopamine, yellow: serotonin, green: norepinephrine (α), dark blue: norepinephrine (β), brown: muscarine, violet: histamine receptors. Dashed line represents a 100-fold drop in affinity relative to the receptor with maximum affinity.

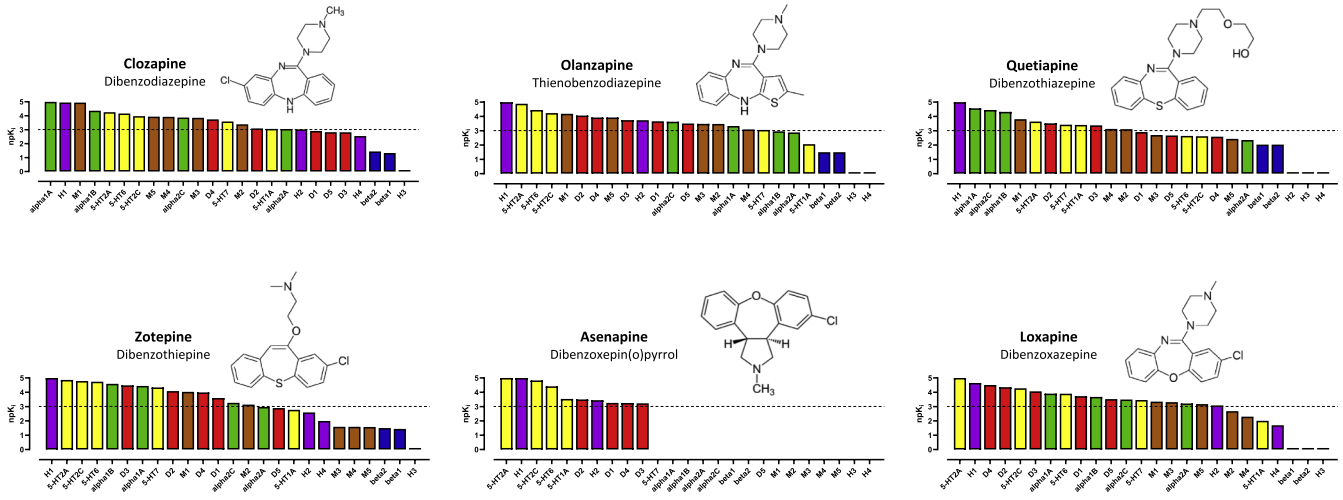

Fig. 2. Normalized receptor affinity profiles: Tricyclic antipsychotic drugs (APDs) II:
Compounds with 7-membered heterocyclic core structure („epines"). Vertical axes represent normalized pK_i (npK_i), horizontal axes represent target receptors, arranged in the order of decreasing affinity for each individual drug. $npK_i = 5$ is assigned to the receptor with the highest affinity, $npK_i = 0$ means no specific affinity of the drug at the corresponding receptor. Different classes of receptors are labeled with colors: red: dopamine, yellow: serotonin, green: norepinephrine (α), dark blue: norepinephrine (β), brown: muscarine, violet: histamine receptors. Dashed line represents a 100-fold drop in affinity relative to the receptor with maximum affinity.

To evaluate the NbN classification of APDs, we aimed to determine statistical differences between breadth values of salient receptors/receptor groups among the four NbN2r classes of APDs. Fig. 7 illustrates the results of the one-way ANOVA tests. A significant difference was found for $B_{sq}G(D_{2/3/4})$ ($F = 5.24$, $p < 0.01$, Fig. 7A). Testing for multiple comparisons with Tukey's test revealed a statistical significance only between the D_2-RAnt and the D_2/5-HT_2-RAnt groups ($p < 0.01$). $B_{sq}G(5\text{-}HT_{2A/C})$ also significantly differed among the groups ($F = 8.88$, $p < 0.001$, Fig. 7B) with group differences between the D_2-RAnt and the D_2/5-HT_2-RAnt ($p < 0.001$) and the D_2-RAnt and D_2/5-HT_2/$α_2$-RAnt ($p < 0.01$) groups. $B_{sq}G(5\text{-}HT_{1A})$ showed a marked overall statistical significance ($F = 12.13$, $p < 0.0001$, Fig. 7C); intergroup differences were obtained for the D_2/5-HT_{1A}-RPAnt vs. D_2-RAnt ($p < 0.0001$), D_2/5-HT_{1A}-RPAnt vs. D_2/5-HT_2/$α_2$-RAnt ($p < 0.01$) and the D_2/5-HT_{1A}-RPAnt vs. D_2/5-HT_2-RAnt ($p < 0.001$) groups. Finally, the analysis revealed a statistical significance for $B_{sq}G(α_{2A/C})$ ($F = 7.35$, $p < 0.01$, Fig. 7E) with

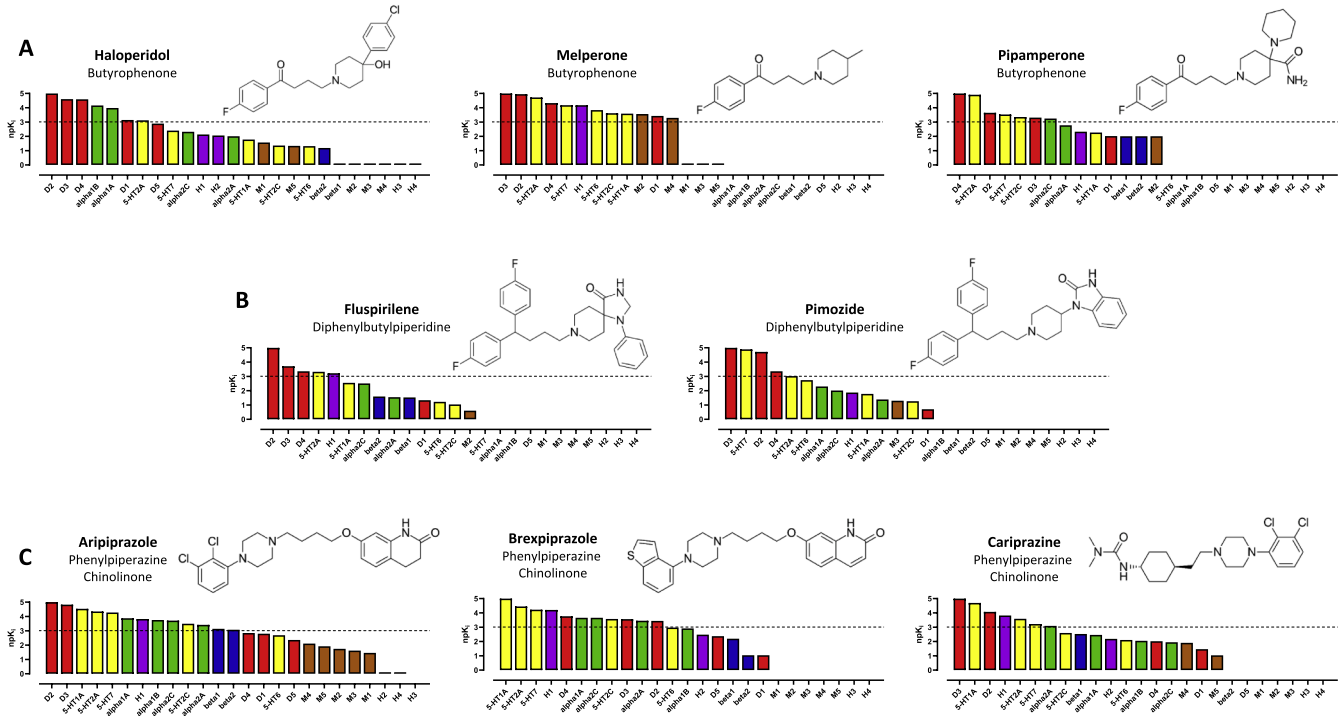

Fig. 3. Normalized receptor affinity profiles: Non-tricyclic antipsychotic drugs (APDs) I:
(A) Butyrophenone, (B) diphenylbutylpiperidine, and (C) phenylpiperazine derivatives. Vertical axes represent normalized pK_i (npK_i), horizontal axes represent target receptors, arranged in the order of decreasing affinity for each individual drug. $npK_i = 5$ is assigned to the receptor with the highest affinity, $npK_i = 0$ means no specific affinity of the drug at the corresponding receptor. Different classes of receptors are labeled with colors: red: dopamine, yellow: serotonin, green: norepinephrine (α), dark blue: norepinephrine (β), brown: muscarine, violet: histamine receptors. Dashed line represents a 100-fold drop in affinity relative to the receptor with maximum affinity.

intergroup differences between the D_2-RAnt vs. D_2/5-HT_{1A}-RPAnt ($p < 0.05$) and the D_2-RAnt vs. D_2/5-HT_2-RAnt ($p < 0.01$) groups. No statistical significance was seen for $B_{sq}G(5\text{-}HT_{6/7})$, and $B_{sq}G(M_{1/4})$ among the four groups, respectively.

4. Discussion

In this article, we present normalized receptor binding affinity profiles of APDs and provide an approach to quantify the breadth of the binding spectrum. We propose it as a reference work on their multi-receptor affinity pharmacology. In the following sections, implications for the importance of individual receptor groups as well as clinical efficacy and, last but not least, the current APD classification will be discussed.

4.1. Dopamine receptors

According to the dopamine hypothesis of schizophrenia, striatal dopamine D_2-like receptor blockade plays an essential role for the MoA of APDs (Grace & Uliana, 2023). This MoA applies to most APDs (Kaar et al., 2020), however, important exceptions are: clozapine (Remington et al., 2016), (more or less) xanomeline (Meyer et al., 2025) and the phenylpiperazine derivatives aripiprazol, brexpiprazol, and cariprazine which act as D_2/5-HT_{1A}-RPAnts (Partial agonism is characterized by only partial efficacy or reduced intrinsic activity inspite of full receptor binding); these partial agonists stabilize against variable activities of the natural ligand by enhancing receptor activity in case of low levels of the endogenous ligand and blocking it at high levels (Meyer, 2024).

In the present study, D_2-like receptor npK_i values were in the significant range for all compounds (including clozapine and xanomeline). Exceptions for the D_4 receptor were: perphenazine, fluphenazine, molindone, quetiapine, and blonanserine. On the contrary, in clozapine, the latter receptor displayed the highest relative binding affinity of all dopamine receptors. This receptor actually has been related to this drug's unique MoA and a research target of novel therapeutic agents (Lindsley and Hopkins, 2017). Not surprisingly, values for $B_{sq}(D_{2/3/4})$ were highest in typical APDs. In contrast, the D_1-like receptors (D_1, D_5) fell outside this range in a clear majority of compounds indicating a subordinate role in antipsychotic MoA.

4.2. Serotonin receptors

A more favorable side effect profile (mainly regarding EPS including tardive dyskinesia) and clinical efficacy against cognitive and negative symptoms of SSDs are defining characteristics of atypical APDs. Most importantly, the higher affinity at the 5-HT_{2A} compared to the D_2 receptor has been considered relevant for 'atypicality' (Meltzer, 2013). Moreover, this receptor appears to be involved in the pathophysiology of SSDs as its blockade leads to decreased dopamine transmission in the mesolimbic system (Aringhieri et al., 2018) and dysregulated 5-HT_{2A} receptor binding was found in *post mortem* frontal cortex of schizophrenia patients (Muguruza et al., 2013). Our presentation of normalized binding affinities facilitates the identification of 'atypical' profiles ($= npK_i$ 5-$HT_{2A} > D_2$) at a glance as follows: asenapine, clozapine, iloperidone, lurasidone, olanzapine, quetiapine, risperidone, xanomeline, ziprasidone, and zotepine. However, the typical APDs chlorprothixene, loxapine, and pipamperone share this profile as well. All of the aforementioned compounds listed so far in the NbN2r system are either classified as dopamine/serotonin or dopamine/serotonin/norepinephrine antagonists.

5-HT_{2C} receptors tonically inhibit prefrontal dopamine (and norepinephrine) release (Millan et al., 1998) and thus, antagonism at this receptor along with 5-HT_{2A} receptor blockade may contribute to improve negative symptoms and cognition in SSDs. Another important

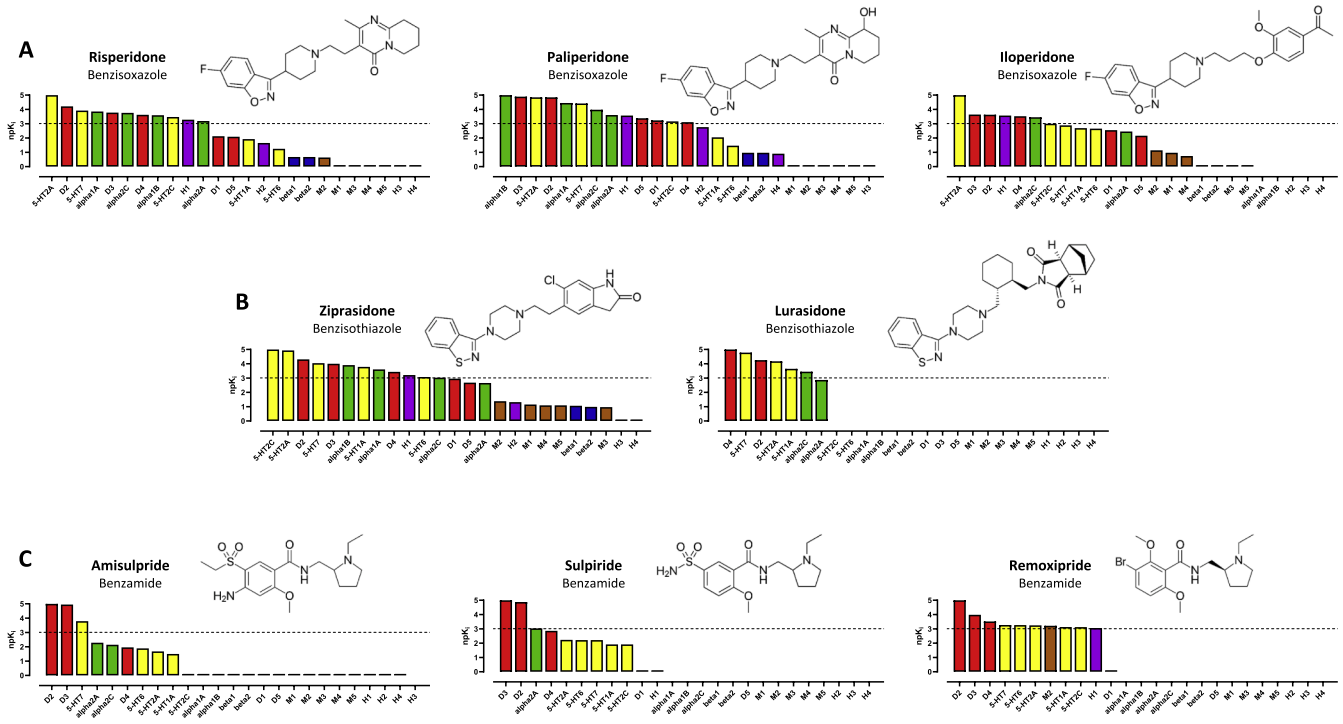

Fig. 4. Normalized receptor affinity profiles: Non-tricyclic antipsychotic drugs (APDs) II:
(A) Benzisoxazole, (B) benzisothiazole, and (C) benzamide derivatives. Vertical axes represent normalized pK_i (npK_i), horizontal axes represent target receptors, arranged in the order of decreasing affinity for each individual drug. $npK_i = 5$ is assigned to the receptor with the highest affinity, $npK_i = 0$ means no specific affinity of the drug at the corresponding receptor. Different classes of receptors are labeled with colors: red: dopamine, yellow: serotonin, green: norepinephrine (α), dark blue: norepinephrine (β), brown: muscarine, violet: histamine receptors. Dashed line represents a 100-fold drop in affinity relative to the receptor with maximum affinity.

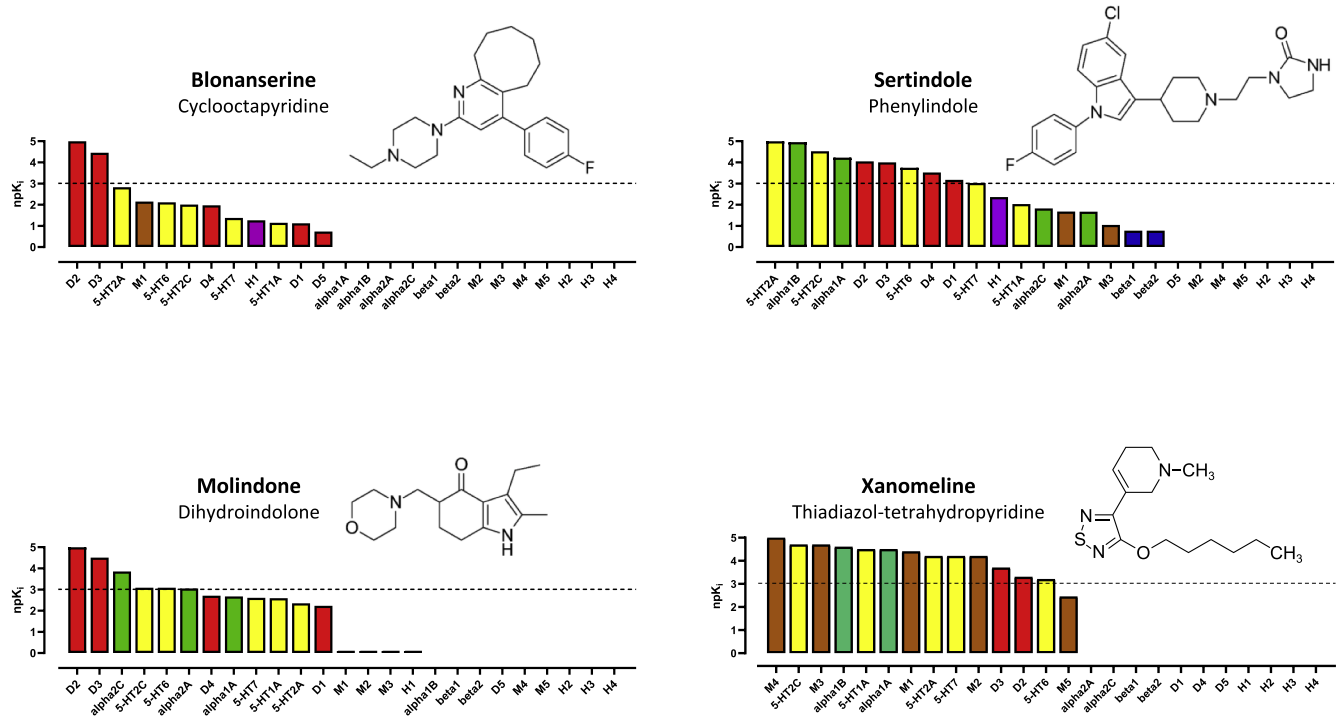

Fig. 5. Normalized receptor affinity profiles: Non-tricyclic antipsychotic drugs (APDs) III:
Other compounds. Vertical axes represent normalized pK_i (npK_i), horizontal axes represent target receptors, arranged in the order of decreasing affinity for each individual drug. $npK_i = 5$ is assigned to the receptor with the highest affinity, $npK_i = 0$ means no specific affinity of the drug at the corresponding receptor. Different classes of receptors are labeled with colors: red: dopamine, yellow: serotonin, green: norepinephrine (α), dark blue: norepinephrine (β), brown: muscarine, violet: histamine receptors. Dashed line represents a 100-fold drop in affinity relative to the receptor with maximum affinity.

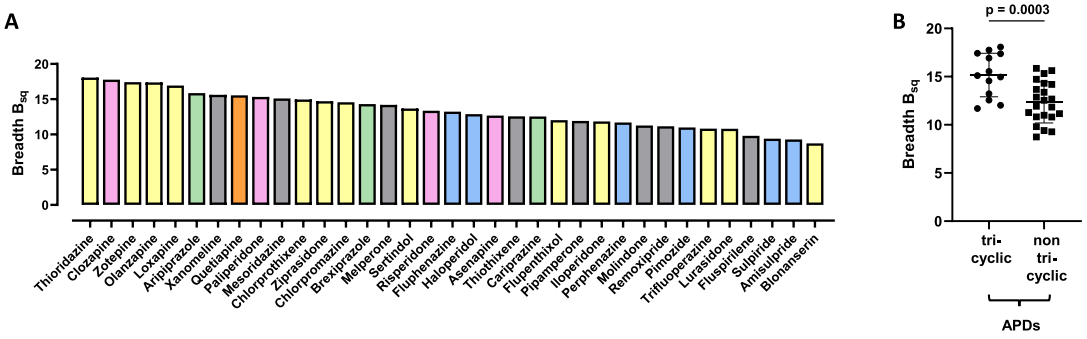

Fig. 6. Breadth (B_{sq}) of receptor interaction and compared clinical efficacy of individual antipsychotic drugs (APDs) and drug classes. (A) Thirty-five APDs arranged in the order of decreasing breadth (increasing selectivity). Colors indicate group assignement according to the Neuroscience-based Nomenclature, 2nd revision (NbN2r), as follows: light blue: dopamine receptor antagonists (D_2-RAnts), yellow: dopamine, serotonin receptor antagonists (D_2/5-HT_2-RAnts), magenta: dopamine, serotonin, norepinephrine receptor antagonists (D2/$_5$-HT_2/α_2-RAnts), orange: dopamine, serotonin, norepinephrine receptor antagonists and norepinephrine reuptake inhibitor (D_2/5-HT_2/α_2-RAnt + NERI), light green: dopamine, serotonin receptor partial agonists (D_2/5-HT_{1A}-RPAnts). (B) Breadth B_{sq} of 35 APDs and basic chemical structure: tricyclic compounds are significantly less selective regarding the set of 25 receptors considered in this study (Student's *t*-test).

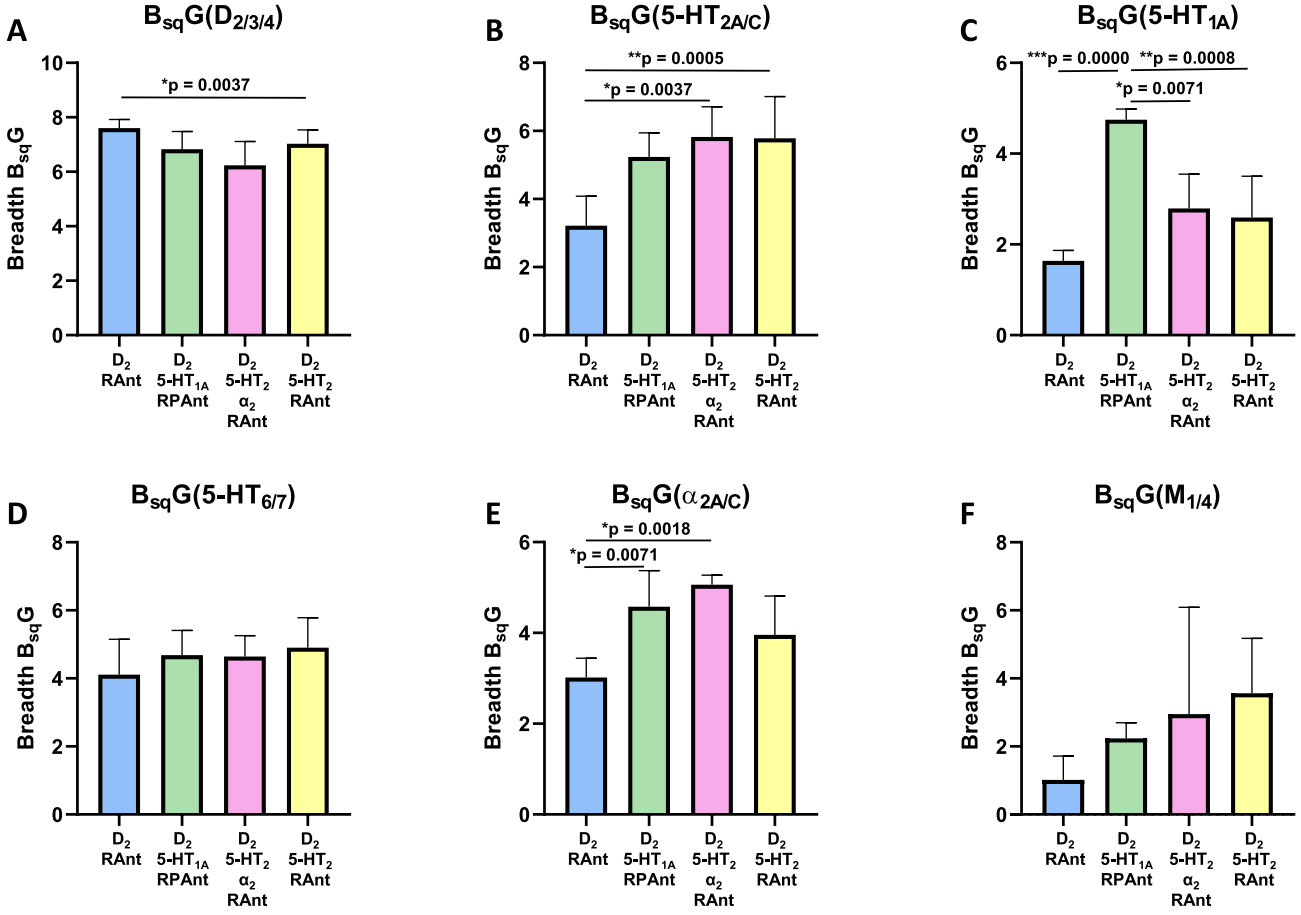

Fig. 7. Comparison of receptor group-related breadth $B_{sq}G$ of salient receptor groups in four APD classes according to the Neuroscience-based Nomenclature, 2nd revision (NbN2r). $B_{sq}G$ is calculated as the root of the sum of squares of npK_i values of the receptors indicated in brackets, as detailed in the Methods section, and is introduced here as a measure of the weight of a receptor group regarding a drug's mechanism of action. (A) D_2-like receptors, (B) 5-HT_2 receptors, (C) 5-HT_{1A} receptor, (D) 5-HT_6 and 5-HT_7 receptors, (E) α_2 adrenoceptors, (F) muscarinic receptors. One-way ANOVA followed by Tukey's *post-hoc* test (*$p < 0.01$, **$p < 0.001$, ***$p < 0.0001$); values are means ± standard deviations. Color coding of APD classes according to NbN2r is the same as in Fig. 6A and Table S5. *Abbreviations*: RAnt, receptor antagonists; RPAnt, receptor partial agonists (antagonists); NERI, norepinephrine reuptake inhibitor. NB: Quetiapine which originally constitutes a group of its own (D_2/5-HT_2-RAnt and NERI) was assigned to the D_2/5-HT_2-RAnts.

aspect is, of course, weight gain as a side effect (Kusumi et al., 2015; Meltzer & Massey, 2011). Our data show high values for B_{sq}(5-$HT_{2A/C}$), particularly for dopamine/serotonin type APDs according to the NbN2r classification. This also included APDs formerly categorized as typical APDs.

Regarding the 5-HT_{1A} receptor, our data illustrate significant binding for a large number of APDs (typical and atypical alike), but all of them falling either into the D_2/5-HT_2-RAnt or D_2/5-HT_2/α_2-RAnt or (most

pronounced) the D_2/5-HT_{1A}-RPAnt categories in the NbN2r. An exception is xanomeline, which has not been classified yet but displays considerable binding affinity at the 5-HT_{1A} receptor. Partial 5-HT_{1A} receptor agonism facilitates prefrontal dopamine release (Bortolozzi et al., 2010) and reduces the activity of γ-aminobutyric acid (GABA) interneurons, leading to disinhibition of glutamatergic neurons (Lladó-Pelfort et al., 2012). Moreover, clinical studies indicate that 5-HT_{1A} receptor agonism mediates procognitive effects in SSD (Kusumi et al., 2015). Thus, partial agonism at this receptor seems to be an important complement to 5-HT_{2A} antagonism. A commonality of several (low potency) FGAs, many SGAs and all TGAs is a functionally relevant 5-HT_6 and 5-HT_7 receptor binding. These receptors, too, play a role in improving cognition in preclinical and clinical studies of SSDs (Meneses, 2014).

4.3. α Adrenoceptors

α Adrenoceptor blockade is thought to contribute to antipsychotic actions of APDs. Specifically, α_1 adrenoceptor antagonism may suppress positive symptoms, while blocking α_2 adrenoceptors relieve negative and cognitive symptoms via actions on prefrontal cortical noradrenaline and dopamine release, dopaminergic mesocorticolimbic circuitry and direct and indirect facilitation of serotonergic neurotransmission (Maletic et al., 2017). Accordingly, functionally relevant npK_i values of $\alpha_{1A/B}$ subtypes were calculated in the majority of all APDs in our study whereas $\alpha_{2A/C}$ subtypes reached relevant orders of magnitude almost exclusively in atypical APDs. These receptors are also determinant for side effects: blockade of α_{2A} adrenoceptors for weight gain and of α_1 subtypes for orthostatic hypotension.

4.4. Muscarinic receptors

Muscarinic cholinergic neurotransmission promotes cognitive processes, including memory, learning and sensory perception. Particularly M_1 and M_4 receptors have received significant attention in psychotropic drug development for their potential benefit in relieving psychosis and enhancing cognition as their (allosteric) activation robustly modulates dopamine signaling in the striatum and the prefrontal cortex in schizophrenia (Foster et al., 2021). Significant npK_i values of both receptors were found for clozapine, olanzapine, and xanomeline (Figs. 3 and 5, Table S3). Xanomeline and clozapine had the highest values for $B_{sq}(M_{1/4})$ of all APDs. Significant muscarinic receptor binding also occurs in other tricyclic compounds such as the phenothiazines. M_1 and M_4 receptor binding has a strong impact on the side effect profile: on the one hand it mediates the typical central and peripheral anticholinergic side effects and on the other helps offset EPS induced by D_2 receptor binding.

4.5. Histamine receptors

The histaminergic system plays a significant role in sleep-wake cycle and appetite regulation, cognition, and arousal and histamine receptors are widely distributed in the CNS. Originating from the tuberomammillary nucleus of the posterior hypothalamus, histaminergic pathways project into almost all of the major regions in the brain. Hypothalamic blockade of the H_1 receptor is responsible for APD-induced sedation and weight gain. The H_3 receptor is involved in cortical arousal regulation and the modulation of learning and memory. It is an auto-receptor regulating histamine synthesis and release and its blockade promotes wakefulness and cognitive functions such as memory consolidation and retrieval (Kaita et al., 2024) and might provide benefit for the treatment of dyscognitive symptoms in SSD (Nishii et al., 2025). Last but not least, histamine receptors have been implicated in SSD pathophysiology. For example, indirect evidence from *post mortem* studies of SSD patients suggests increased histaminergic signaling via these receptors (Cheng et al., 2021). Our data show significant H_1 receptor binding for tricyclic APDs with particularly high npK_i values for the heterocyclic "epines". Relevant H_1 receptor binding also occurs in benzisoxazoles and the benzisothiazole ziprasidone. Binding affinities at other histamine receptor subtypes were of minor significance in this dataset.

4.6. Quantification of binding diversity: breadth B_{sq}, chemical structure, and clinical efficacy

Our data illustrate that APDs licensed around the world possess a spectrum of varying breadth of pharmacological properties. We applied a method introduced by Ray (2010), who studied the binding profiles of psychedelic drugs, to normalize affinity (K_i) data in a way that factors out potency so that the multireceptor affinity of different APDs can be directly compared. This method facilitates to quantify and compare the breadth of receptor interactions of different APDs/APD classes by using the value B_{sq}. As an example, we held the receptor breadth against the chemical structure of the APDs. These data show the significant influence of a tricyclic basic structure on receptor breadth (Fig. 6B), irrespective of their assignment to any class or characteristics such as atypicality or potency.

Based on the broad receptor action of clozapine, a highly potent and in several aspects unique APD, it has been argued that pleiotropic CNS drugs might be more effective than selective ones. Due to their complex pharmacology, the former are sometimes called 'dirty drugs' or 'magic shotguns' as opposed to the latter as 'magic bullets' (Roth et al., 2004). One rationale for this is the putatively polygenic etiology of major psychiatric diseases such as SSDs and a broad array of molecular targets implicated by genetic studies (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Moreover, several rather unsuccessful attempts have been made to develop highly selective APDs such as D_4 receptor selective drugs or compounds with 5-HT_{2A}/D_4 receptor antagonism (Roth et al., 2004). However, we found no statistically significant correlation between receptor breadth B_{sq} and APD clinical efficacy, neither regarding positive nor negative symptoms. Highly potent APDs can be both non-selective (high breadth) agents such as clozapine or olanzapine or selective drugs such as the benzamides.

4.7. Receptor group-specific breadth $B_{sq}(G)$ as an approach to evaluate neuroscience-based nomenclature (NbN) of antipsychotic drugs (APDs)

With the introduction of the NbN 10 years ago, a pharmacologically driven classification system became available for the first time (Zohar et al., 2015). While it has become the standard in the scientific literature, it has not yet become established in clinical practice, where the dichotomy of typical vs. atypical APDs still predominates (the historically oriented FGA/SGA – and sometimes TGA – grouping is practically used synonymously) (McCutcheon et al., 2024). Atypicality was defined as a lower propensity to EPS, including tardive dyskinesia, and hyperprolactinaemia as well as better therapeutic efficacy, particularly regarding negative and cognitive symptoms of schizophrenia (Kinon & Lieberman, 1996). However, the typical/atypical dichotomy has several shortcomings: First, the boundary is not clear-cut: several atypical drugs such as risperidone produce more EPS (and hyperprolactinaemia) than typical drugs such as chlorpromazine. In addition, it is in some way a dosing artefact with many atypical APDs adopting typical features at higher dosages (Leucht et al., 2024). Second, there is no clear distinction in terms of clinical efficacy, even at the level of negative or dyscognitive symptoms (Baldez et al., 2021). Third and most important to the clinician, the atypical group is extremely heterogeneous and MoAs are obscured with this terminology which complicates the development of treatment strategies (i. e., drug switch, combination). In these aspects, the pharmacologically driven NbN offers an improvement to researchers and clinicians alike. Of note, the NbN is rather descriptive and basically relies on expert judgement. However, constructing $B_{sq}G$ values from our normalized binding data enabled us to analyze the weight of selected

receptors/receptor groups within a specific drug's binding spectrum. Our study included a test, whether these weights are reflected by the current NbN classification, with the following conclusions (see Fig. 7):

(1) Consistent with the NbN, *D_2-RAnts* form a separate group since $B_{sq}G(D_{2/3/4})$ differed significantly from the other groups: (I) against D_2/5-HT_2/α-RAnts regarding 5-$HT_{2A/C}$ (Fig. 7B) and $\alpha_{2A/C}$ (Fig. 7E), (II) against and D_2/5-HT_2-RAnts regarding 5-$HT_{2A/C}$ (Fig. 7B), and (III) against D_2/5-HT_{1A}-RPAnts regarding 5-HT_{1A} (Fig. 2C) and $\alpha_{2A/C}$ (Fig. 7E).
(2) The $B_{sq}G$(5-HT_{1A}) of the *D_2/5-HT_{1A}-RPAnts* differed significantly from that of all other NbN groups (Fig. 2C), suggesting a distinct MoA in consistence with the NbN.
(3) $B_{sq}G$ of the *D_2/5-HT_2-RAnts* showed statistical significance (I) against the D_2-RAnts regarding $D_{2/3/4}$ (Fig. 7A) and 5-$HT_{2A/C}$ (Fig. 7B), but not 5-HT_{1A} and $\alpha_{2A/C}$ (Fig. 7C and E), and (II) against the D_2/5-HT_{1A}-RPAnts regarding 5-HT_{1A} (Fig. 7C), but not other receptors.
(4) Also less clear-cut, $B_{sq}G$ of *D_2/5-HT_2/α-RAnts* showed statistical significance (I) against D_2-RAnts regarding 5-$HT_{2A/C}$ (Fig. 7B) and $\alpha_{2A/C}$ (Fig. 7E) and (II) against D_2/5-HT_{1A}-RPAnts regarding 5-HT_{1A} (Fig. 7C), but not other receptors.

Taken together, APDs analyzed in this study display distinctive MoA profiles that only partially align with the NbN systematic. Thus, more research (probably using more complex methods such as tissue-based or *in vivo* models, see below) is needed to validate this current classification system.

4.8. Limitations

This study has several limitations that need to be addressed. First, our analysis is solely based on human cloned receptors. As opposed to native tissue, recombinant receptors do not represent the full spectrum of signaling pathways as one receptor subtype may, for example, activate a range of different G-proteins (Gaitonde et al., 2024). In addition, more complex receptor interactions like receptor oligomerization or cross-talk between second messengers does not occur at this resricted level. Second, we analyzed affinity data without considering intrinsic activity or agonist / partial agonist dynamics, questions of functional selectivity or biased agonism. Third, *in vitro* data as in this and similar studies are of limited value in anticipating (beneficial or adverse) clinical effects since, for example, pharmacokinetic variables were not considered. Fourth, we would like to state the dynamic nature of the PDSP database which is continuously updated and individual receptor K_i values may be subject to change over time as new studies emerge.

5. Conclusion

In this work, we provide a reference work for binding affinity data of 35 APDs licensed worldwide. By normalizing binding affinity data of APDs on the single drug level, it becomes possible to directly compare and visualize the multireceptor affinity profiles of the different compounds. We have shown that summing up normalized binding affinity values on the level of a) the whole set of receptors of an individual drug or b) a receptor group within this drug yields a simple quantitative measure of a) this drug's receptor interaction breadth and b) the weight of a certain receptor group regarding the drug's binding spectrum. We also showed that the breadth of receptor interaction is significantly associated with a tricyclic chemical structure and did not *per se* correlate with clinical efficacy in APDs. Finally, statistical analysis of the group breadth of individual receptor systems revealed only partial correspondence with the NbN classification which has yet to be validated, probably using more complex, e.g., tissue-based or *in vivo* models.

Role of the funding source

No funding.

CRediT authorship contribution statement

Christian Lange-Asschenfeldt: Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing. **Katja Brouzou:** Data curation, Writing – review & editing. **Julia Christl:** Data curation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

No funding.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2025.07.011.

References

Aringhieri, S., Carli, M., Kolachalam, S., Verdesca, V., Cini, E., Rossi, M., McCormick, P. J., Corsini, G.U., Maggio, R., Scarselli, M., 2018. Molecular targets of atypical antipsychotics: from mechanism of action to clinical differences. Pharmacol. Ther. 192, 20–41.

Baldez, D.P., Biazus, T.B., Rabelo-da-Ponte, F.D., Nogaro, G.P., Martins, D.S., Kunz, M., Czepielewski, L.S., 2021. The effect of antipsychotics on the cognitive performance of individuals with psychotic disorders: network meta-analyses of randomized controlled trials. Neurosci. Biobehav. Rev. 126, 265–275.

Bortolozzi, A., Masana, M., Díaz-Mataix, L., Cortés, R., Scorza, M.C., Gingrich, J.A., Toth, M., Artigas, F., 2010. Dopamine release induced by atypical antipsychotics in prefrontal cortex requires 5-HT(1A) receptors but not 5-HT(2A) receptors. Int. J. Neuropsychopharmacol. 13, 1299–1314.

Cheng, L., Liu, J., Chen, Z., 2021. The histaminergic system in neuropsychiatric disorders. Biomolecules. https://doi.org/10.3390/biom11091345.

Foster, D.J., Bryant, Z.K., Conn, P.J., 2021. Targeting muscarinic receptors to treat schizophrenia. Behav. Brain Res. https://doi.org/10.1016/j.bbr.2021.113201.

Gaitonde, S.A., Avet, C., de la Fuente Revenga, M., Blondel-Tepaz, E., Shahraki, A., Pastor, A.M., Talagayev, V., Robledo, P., Kolb, P., Selent, J., González-Maeso, J., Bouvier, M., 2024. Pharmacological fingerprint of antipsychotic drugs at the serotonin 5-HT_{2A}receptor. Mol. Psychiatry 29, 2753–2764.

Grace, A.A., Uliana, D.L., 2023. Insights into the mechanism of action of antipsychotic drugs derived from animal models: standard of care versus novel targets. Int. J. Mol. Sci. https://doi.org/10.3390/ijms241512374.

Huhn, M., Nikolakopoulou, A., Schneider-Thoma, J., Krause, M., Samara, M., Peter, N., Arndt, T., Bäckers, L., Rothe, P., Cipriani, A., Davis, J., Salanti, G., Leucht, S., 2019. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. Lancet 394, 939–951.

Jensen, N.H., Roth, B.L., 2008. Massively parallel screening of the receptorome. Comb. Chem. High Throughput Screen. (11), 420–426.

Kaar, S.J., Natesan, S., McCutcheon, R., Howes, O.D., 2020. Antipsychotics: mechanisms underlying clinical response and side-effects and novel treatment approaches based on pathophysiology. Neuropharmacology. https://doi.org/10.1016/j.neuropharm.2019.107704.

Kaita, S., Morishita, Y., Kobayashi, K., Nomura, H., 2024. Histamine H_3 receptor inverse agonists/antagonists influence intra-regional cortical activity and inter-regional synchronization during resting state: an exploratory cortex-wide imaging study in mice. Mol. Brain. https://doi.org/10.1186/s13041-024-01165-8.

Kinon, B.J., Lieberman, J.A., 1996. Mechanisms of action of atypical antipsychotic drugs: a critical analysis. Psychopharmacology 124, 2–34 (Berl).

Kusumi, I., Boku, S., Takahashi, Y., 2015. Psychopharmacology of atypical antipsychotic drugs: from the receptor binding profile to neuroprotection and neurogenesis. Psychiatry Clin. Neurosci. 69, 243–258.

Leucht, S., Priller, J., Davis, J.M., 2024. Antipsychotic drugs: a concise review of history, classification, indications, mechanism, efficacy, side effects, dosing, and clinical application. Am. J. Psychiatry 181, 865–878.

Lindsley, C.W., Hopkins, C.R., 2017. Return of D4 dopamine receptor antagonists in drug discovery. J. Med. Chem. 60, 7233–7243.

Lladó-Pelfort, L., Santana, N., Ghisi, V., Artigas, F., Celada, P., 2012. 5-HT1A receptor agonists enhance pyramidal cell firing in prefrontal cortex through a preferential action on GABA interneurons. Cereb. Cortex 22, 1487–1497.

Maletic, V., Eramo, A., Gwin, K., Offord, S.J., Duffy, R.A., 2017. The role of norepinephrine and its α-adrenergic receptors in the pathophysiology and treatment of major depressive disorder and schizophrenia: a systematic review. Front. Psychiatry. https://doi.org/10.3389/fpsyt.2017.00042.

McCutcheon, R.A., Cannon, A., Parmer, S., Howes, O.D., 2024. How to classify antipsychotics: time to ditch dichotomies? Br. J. Psychiatry 224, 20–25.

Marder, S.R., Cannon, T.D., 2019. Schizophrenia. N. Engl. J. Med. 381, 1753–1761.

Meltzer, H.Y., 2013. Update on typical and atypical antipsychotic drugs. Annu. Rev. Med. 64, 393–406.

Meneses, A., 2014. Memory formation and memory alterations: 5-HT6 and 5-HT7 receptors, novel alternative. Rev. Neurosci. 25, 325–356.

Meltzer, H.Y., Massey, B.W., 2011. The role of serotonin receptors in the action of atypical antipsychotic drugs. Curr. Opin. Pharmacol. 11, 59–67.

Meyer, J.M., Kramer, K., Vuocolo, S., Kaul, I., Miller, A.C., 2025. From theory to therapy: unlocking the potential of muscarinic receptor activation in schizophrenia with the dual M1/M4 muscarinic receptor agonist xanomeline and trospium chloride and insights from clinical trials. Int. J. Neuropsychopharmacol. https://doi.org/10.1093/ijnp/pyaf015.

Meyer, J.M., 2024. How antipsychotics work in schizophrenia: a primer on mechanisms. CNS Spectr. 30, e6. https://doi.org/10.1017/S1092852924002244.

Millan, M.J., Dekeyne, A., Gobert, A., 1998. Serotonin (5-HT)2C receptors tonically inhibit dopamine (DA) and noradrenaline (NA), but not 5-HT, release in the frontal cortex in vivo. Neuropharmacology 37, 953–955.

Muguruza, C., Moreno, J.L., Umali, A., Callado, L.F., Meana, J.J., González-Maeso, J., 2013. Dysregulated 5-HT(2A) receptor binding in postmortem frontal cortex of schizophrenic subjects. Eur. Neuropsychopharmacol. 23, 852–864.

Nishii, Y., Sakuma, K., Hamanaka, S., Iwata, N., Kishi, T., 2025. Efficacy and safety of histamine H3 receptor antagonist/inverse agonist including betahistine for schizophrenia: a systematic review and meta-analysis. Neuropsychopharmacol. Rep. https://doi.org/10.1002/npr2.70034.

Ray, T.S., 2010. Psychedelics and the human receptorome. PLoS ONE 5 (2), e9019. https://doi.org/10.1371/journal.pone.0009019.

Remington, G., Lee, J., Agid, O., Takeuchi, H., Foussias, G., Hahn, M., Fervaha, G., Burton, L., Powell, V., 2016. Clozapine's critical role in treatment resistant schizophrenia: ensuring both safety and use. Expert Opin. Drug Saf. 15, 1193–1203.

Roth, B.L., Sheffler, D.J., Kroeze, W.K., 2004. Magic shotguns versus magic bullets: selectively non-selective drugs for mood disorders and schizophrenia. Nat. Rev. Drug Discov. 3, 353–359.

Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014. Biological insights from 108 schizophrenia-associated genetic loci. Nature 511, 421–427.

Zemach, S., Zohar, J., 2025. The importance of proper naming - a review of neuroscience-based nomenclature (NbN). Asian J. Psychiatry. https://doi.org/10.1016/j.ajp.2024.104317.

Zohar, J., Stahl, S., Möller, H.J., Blier, P., Kupfer, D., Yamawaki, S., Uchida, H., Spedding, M., Goodwin, G.M., Nutt, D., 2015. A review of the current nomenclature for psychotropic agents and an introduction to the neuroscience-based nomenclature. Eur. Neuropsychopharmacol. 25, 2318–2325.