

Recent advances in dopamine D₂ receptor ligands in the treatment of neuropsychiatric disorders

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Abstract

Dopamine is a biologically active amine synthesized in the central and peripheral nervous system. This biogenic mono-amine acts by activating five types of dopamine receptors (D_{1–5}Rs), which belong to the G protein-coupled receptor family. Antagonists and partial agonists of D₂Rs are used to treat schizophrenia, Parkinson's disease, depression, and anxiety. The typical pharmacophore with high D₂R affinity comprises four main areas, namely aromatic moiety, cyclic amine, central linker and aromatic/heteroaromatic lipophilic fragment. From the literature reviewed herein, we can conclude that 4-(2,3-dichlorophenyl), 4-(2-methoxyphenyl)-, 4-(benzo[b]thiophen-4-yl)-1-substituted piperazine, and 4-(6-fluorobenzo[d]isoxazol-3-yl)piperidine moieties are critical for high D₂R affinity. Four to six atoms chains are optimal for D₂R affinity with 4-butoxyl as the most pronounced one. The bicyclic aromatic/heteroaromatic systems are most frequently occurring as lipophilic appendages to retain high D₂R affinity. In this review, we provide a thorough overview of the therapeutic potential of D₂R modulators in the treatment of the aforementioned disorders. In addition, this review summarizes current knowledge about these diseases, with a focus on the dopaminergic pathway underlying these pathologies. Major attention is paid to the structure, function, and pharmacology of novel D₂R ligands, which have been developed in the last decade (2010–2021), and belong to the 1,4-disubstituted aromatic cyclic amine group. Due to the abundance of data,

allosteric D₂R ligands and D₂R modulators from patents are not discussed in this review.

KEY WORDS

anxiety, D₂ receptor agonist, D₂ receptor antagonist, D₂ receptor modulators, D₂ receptor partial agonist, depression, dopamine, dopamine D₂ receptor, Parkinson's disease, schizophrenia

1 | INTRODUCTION

The dopamine D₂ subtype receptor (D₂R) represents an important target in the treatment of classic CNS illnesses such as schizophrenia, depression, Parkinson's disease (PD), and anxiety which affect many people worldwide. Recently, D₂R became an interesting target in the treatment of restless leg syndrome.^{1,2} In general, CNS disorders are among the most expensive medical conditions as the total cost of illnesses of the brain was estimated 798 billion EUR in Europe in 2010).³ However, the management of such disorders are limited. Schizophrenia treatment is efficient for only about half of patients, with a preferable suppression of only positive symptoms.⁴ The treatment of depressive or anxiety disorders with drugs can cause severe side-effects such as weight gain, sexual dysfunction, sedation, confusion, dizziness or blurred vision.^{5,6} Side effects are common also at anti-PD drugs which may lead to motor complications (such as dyskinesia and motor fluctuations), and other adverse effects (psychosis, nausea, and impulse control disorders and related behaviors).⁷

The aim of this review is to discuss new ligands targeting D₂Rs, prepared since 2010, from the perspective of modern medicinal chemistry including the structure–activity relationship (SAR). The analyzed literature of ligands affecting D₂Rs that were included can be divided into five main categories for the potential treatment of schizophrenia, PD, depression, and anxiety according to mechanism of action, namely (i) D₂R agonists mainly useful for the management of PD or depression, (ii) partial D₂R agonists comprising modern and well-tolerated antipsychotic compounds, (iii) selective and nonselective D₂R antagonists, classical antipsychotic compounds useful for the management of anxiety, (iv) so-called biased ligands, and (v) so-called bivalent ligands targeting homo- or heterodimers of DRs. Although former groups (i–iii) are self-explaining, the latter requires detailed explanation. Biased ligands are based on the hypothesis of selective modulation of downstream D₂R signaling pathways (i.e., canonical GPCR dependent and noncanonical β-arrestin 2-dependent), determining the efficacy and side effects of such compounds.^{4,8} Bivalent ligands are compounds bearing two pharmacophores covalently tethered by a spacer, binding simultaneously at adjacent orthosteric sites of dimeric or oligomeric GPCR receptor complex.^{9–11}

Basic information about dopamine and its receptors (especially D₂Rs) will be discussed in this introduction, along with known facts about schizophrenia, PD, depression, and anxiety from the perspective of D₂Rs and their ligands. In the second part of this review, medicinal chemistry is discussed to systematically analyze the function and pharmacology of novel D₂R modulators, which are a part of the 1,4-disubstituted cyclic amine group, according to their structure. We deduce the key information obtained from SAR studies and summarize the most effective compounds for the treatment of anxiety, depression, PD, and schizophrenia. Finally, we highlight compounds with bias behavior for canonical or noncanonical D₂R signaling pathways, or for D₂-selective over other D₂-like receptors and bivalent ligands.

1.1 | Dopamine

Dopamine (DA), or 3,4-dihydroxyphenethylamine, is a biogenic catecholamine and neurotransmitter first discovered in the peripheral tissues and body fluids of mammals

The major biosynthesis pathway of DA begins with the conversion of L-tyrosine into L-DOPA by hydroxylation catalyzed by the enzyme tyrosine hydroxylase.^{12,13} L-DOPA is subsequently decarboxylated by the aromatic amino acid decarboxylase to DA. DA is biosynthesized in neurons, immune system cells,¹⁴ and other peripheral tissue cells.^{15–17} L-tyrosine is produced by the liver and is delivered to dopaminergic neurons via active transport.¹⁸ Once DA is synthesized in neurons, it is either stored in synaptic vesicles at high millimolar concentrations^{19,20} for subsequent release, or it is hydroxylated to norepinephrine.²¹ DA is released into the synaptic cleft, in most cases, by exocytosis induced upon membrane depolarization.^{22–24} Upon release, DA in the synaptic cleft binds to DRs postsynaptically (D₁–D₅) or to presynaptic autoreceptors (D₂Rs and D₃Rs).^{25–27} Biosynthesis, neurotransmission, and degradation of DA and major functions of D₂ autoreceptors are depicted in Figure 1.^{13,28,29} Postsynaptic mechanisms will be discussed later.

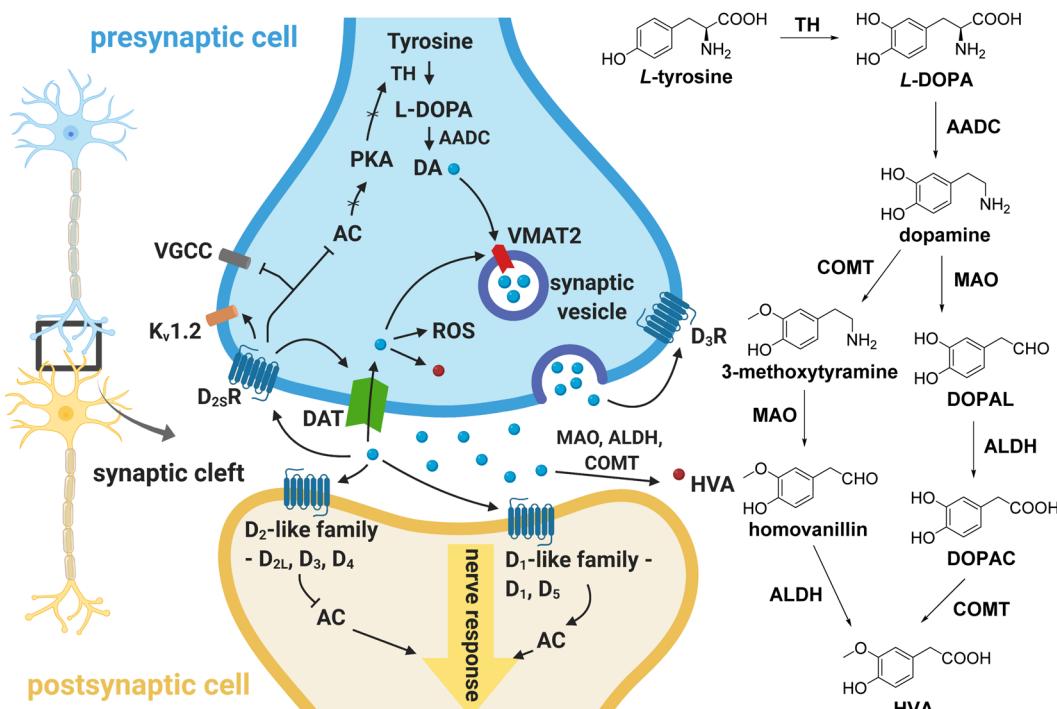


FIGURE 1 Schematic representation of biosynthesis, neurotransmission, and degradation of DA and functions of autoreceptor D₂Rs. Upon release, DA in the synaptic cleft can bind to DRs postsynaptically (D₁–D₅Rs), or to presynaptic autoreceptors (D₂Rs and D₃Rs). After postsynaptic trigger of action potential, DA is released back into the cleft and is subsequently transported back to the presynaptic neuron by a DAT or a norepinephrine transporter. After returning to the presynaptic neuron, DA is transported from the cytoplasm to storage vesicles by VMAT2, located on vesicular membranes. The DA that remains in the cytoplasm is degraded to the final degradation product, homovanillic acid. However, DA is very sensitive to oxidation, yielding reactive quinones and ROS, which can cause oxidative stress, leading to cell damage and neurodegeneration.^{12,13} AADC, aromatic L-amino acid decarboxylase; AC, adenylate cyclase; ALDH, aldehyde dehydrogenase; COMT, catechol-O-methyl transferase; DA, dopamine; DAT, dopamine transporter; DOPAC, 3,4-dihydroxyphenylacetic acid; DOPAL, 3,4-dihydroxyphenylaldehyde; HVA, homovanillic acid; K_v1.2, potassium voltage-gated channel subfamily A member 2; L-DOPA, levodopa, L-3,4-dihydroxyphenylalanine; MAO, monoamine oxidase; PKA, protein kinase A; ROS, reactive oxygen species; TH, tyrosine hydroxylase; VGCC, voltage-gated calcium channel; VMAT2, vesicular monoamine transporter 2. [Color figure can be viewed at wileyonlinelibrary.com]

Functions of DA autoreceptors²⁸ consist mainly of (i) modulation of the exocytic release of DA from axon terminals to the synaptic cleft,^{30–33} (ii) activation of dopamine transporter DAT,^{32,34–41} and (iii) inhibition of DA synthesis via tyrosine hydroxylase inhibition.^{42,43} Tyrosine hydroxylase catalyzes the hydroxylation of tyrosine to L-DOPA,⁴⁴ a rate-limiting step of dopamine synthesis.⁴⁵

There are approximately 400,000 dopaminergic neurons in the human brain,⁴⁶ each occurring in specific regions.⁴⁷ Dopaminergic neurons were first mapped by A. Dahlström and K. Fuxe in 1964.⁴⁸ To-date, four main pathways have been distinguished, characterized in Table 1, for the dopaminergic system in the human brain (Figure 2).^{18,49} DA also has a variety of functions outside the CNS—mainly in the immune,⁵⁰ cardiovascular,^{51,52} renal,⁵³ and gastrointestinal⁵⁴ (GI) systems including pancreas⁵⁵ modulating insulin and glucagon secretion, which also explains the side effects like gaining weight and prediabetes associated with antipsychotic medication.^{56–58}

TABLE 1 Basic information about human dopaminergic pathways in the brain

Pathway	Location	Function
Nigrostriatal	DA neurons project from the substantia nigra (pars compacta) to the striatum	Movement, motor control, and sensory stimuli
Mesolimbic	DA neurons project from the ventral tegmental area to the amygdala, pyriform cortex, lateral septal nuclei, and nucleus accumbens	Pleasure and reward-seeking behaviors, addiction, emotion, and perception
Mesocortical	Dopaminergic fibers originate in the ventral tegmental area and project to frontal cortex and septohippocampal regions	Cognition, memory, attention, emotional behavior, and learning
Tuberoinfundibular	This pathway originates in the hypothalamic nuclei (arcuate nucleus and periventricular nucleus) and projects into the pituitary gland	Control of the hypothalamic pituitary endocrine system, inhibition of prolactin secretions

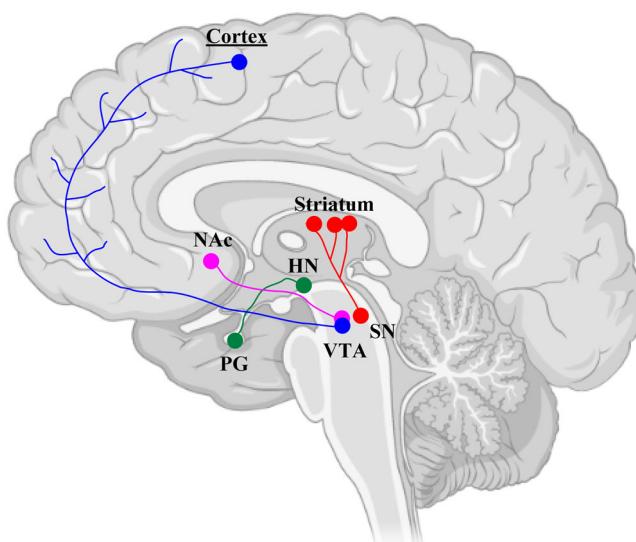


FIGURE 2 Distribution of the four major dopaminergic pathways in the human brain. Blue, mesocortical pathway; Green, tuberoinfundibular pathway; HN, hypothalamic nuclei; NAc, nucleus accumbens; PG, pituitary gland; Purple, mesolimbic pathway; Red, nigrostriatal pathway; SN, substantia nigra; VTA, ventral tegmental area. [Color figure can be viewed at wileyonlinelibrary.com]

DA primarily mediates its effect through the activation of DRs.²¹ There are five DR subtypes that are members of the GPCR group,¹⁸ and are further divided into two classes according to structure. The D₁-like family includes D₁Rs and D₅Rs. On the other hand, D₂₋₄Rs belong to the D₂-like family.^{18,21,49} Their basic characteristics are given in Table 2.^{18,59-62} The main difference between both families is the fact that receptors in the D₁-like family activate adenylate cyclase (AC), which leads to production of cyclic adenosine monophosphate (cAMP), whereas those in the D₂-like family inhibit AC.

1.2 | Dopamine receptor type 2

A crucial question in drug discovery is what structural attributes determine the subtype-selectivity of potential drugs. More importantly, across all dopamine receptor families, residues delineating the binding site display near identity, imposing a challenge for developing selective ligands.⁶³ Bearing in mind such high conservation between subtype species and to achieve desirable receptor selectivity (>100 fold), the ligands must extend towards the extracellular space of the binding pocket.⁶⁴ For instance, the selectivity for D₃R is driven by the second extracellular loop that accommodates aryl amide connected to an amine-containing scaffold by a flexible four-chain linker.^{65,66} Thus, such a subtle difference between D₂R and D₃R backbones can lead to a change in selectivity even though ligands can exert structural resemblances in occupying binding pockets of respective receptors. The structure of D₂R (Figure 3) in the inactivated-state conformation was resolved in January 2018 in a complex with risperidone,⁶⁷ and the D₂R shares a 75% homology with D₃R and a 53% homology with D₄R transmembrane domains.⁶⁸ So far, the structure-based drug discovery has relied on the co-crystal structure of haloperidol, risperidone and spiperone, respectively, within the D₂R.^{67,69,70} However, the current demand to find new and safer antipsychotics also revealed the active form of D₂R in the lipid membrane upon activation by agonist using the cryo-EM approach.⁷¹ Likewise, for D₃R, agonist binding and receptor activation were elucidated for D₃R-selective ligands, namely for PD128907 and pramipexole.⁷² Collectively, with antagonist-bound ligands of D₂R/D₃R, these studies provide the basis for designing the specific D₂R/D₃R molecules targeting multiple human central nervous system disorders.

D₂R is encoded by gene *DRD2*, which contains 6 introns (Table 2).⁶⁰ Alternative splicing of 87 bp exon leads to the generation of two major D₂R variants: D_{2S} (D₂-short) and D_{2L} (D₂-long) receptors.^{73,74} These two D₂R isoforms differ by 29 amino acids (Table 2) in the third intracellular loop, and thus have different properties. The "short" version of D₂Rs is exclusively expressed presynaptically as an autoreceptor, while, the "long" version is mainly found on the postsynaptic cell (Figure 1).^{75,76} Other D₂Rs functions are listed in Table 2.

The highest levels of D₂Rs in the human brain are expressed in the striatum, the olfactory tubercle, and the nucleus accumbens (NAc).⁶⁰ D₂Rs are also found in the ventral tegmental area (VTA), substantia nigra, septum, amygdala, cortical areas, and hippocampus (Table 2).^{68,77-79} Similarly to other GPCRs D₂Rs can be clustered to homo/heterodimers or higher oligomeric assemblies with other GPCRs.⁸⁰ The study by Zawarynski found D₂R dimers in human and rat brain.⁸¹

The main activation pathway is based on the fact that D₂Rs are coupled to G $\alpha_{i/o}$ and inhibit adenylate cyclase (AC).^{68,82-84} In their inactive states, all three subunits (α , β , γ) of G-protein are closely associated. Upon activation, represented by binding of the agonist (e.g., DA), splitting of the complex occurs, and G $\alpha_{i/o}$ -subunit a $\beta\gamma$ -complex can induce proprietary pathways (Figure 4 left).⁸⁶ Apart from this main activation pathway, D₂Rs can also induce the G protein-independent cascade (β -arrestin cascade) (Figure 4 right).^{87,88} This cascade is induced by an agonist, and begins with the creation of a complex of proteins composed of protein kinase B (Akt), β -arrestin 2, and protein phosphatase 2A (PP2A). This protein complex mediates the deactivation of Akt,^{85,89} which then deactivates GSK3 α/β . Once activated, β -arrestin 2 becomes the inhibitor for this G protein-independent signaling pathway induced by DA.^{85,89-91} The recruitment of β -arrestin to the D₂R results in clathrin-mediated receptor internalization (similarly to PKC-mediated internalization in the G protein-dependent cascade),⁶⁰ which is followed either by degradation of D₂R through an endosomal-lysosomal system or by cell surface recycling.⁹²⁻⁹⁶ This G

TABLE 2 Basic characters of five human dopamine receptors

DR subtype	D ₁ -like family		D ₂ -like family		D ₄
	D ₁	D ₅	D ₂	D ₃	
Gene symbol	DRD1	DRD5	DRD2	DRD3	DRD4
Locus (human)	5q35.1	4p16.1	11q23.1	3q13.3	11q15.5
Number of introns in the coding region	-	-	6	5	3
Pseudogenes	-	-	-	-	DRD5P1, DRD5P2
Presence of splice variants	-	-	Yes—D _{2S} , D _{2L} , D _{2Lo}	Yes	Yes
Amino acids	446	477	D _{2S} —414; D _{2L} —443; D _{2Lo} —445	400	387
Molecular weight	49,300	52,951	D _{2S} —47,347; D _{2L} —50,619	44,225	41,487
G-protein coupling	Gαs; Gαolf	Gαs; Gαq	Gαi; Gαo; Gβγ	Gαi; Gαo; Gβγ	Gαi; Gαo; Gβγ
Signalling molecules	AC↑, cAMP, PKA, DARPP-32, ERK	PLC, PKC, IP ₃	AC↓, cAMP, PKA, DARPP-32, L/N-type calcium channel, GIRK, β-arrestin2, Akt, GSK-3 (D ₂ , D ₃)		
Localization	High concentrations in the substantia nigra, olfactory bulb, nucleus accumbens, caudate, putamen, and striatum. Low levels in the cerebellum, hippocampus, thalamus, hypothalamus, and kidneys	The cortex, substantia nigra, hypothalamus, hippocampus, dental gyrus, kidneys, heart, blood vessels, adrenal glands, GI tract, and sympathetic ganglia	High levels in the caudate, putamen, striatum, nucleus accumbens, ventral tegmental area, substantia nigra, olfactory bulb and tubercle; low levels in the hypothalamus, septum, kidneys, cortex, heart, blood vessels, adrenal glands, GI tract, and sympathetic ganglia	Expressed only in the CNS—olfactory bulb, nucleus accumbens, striatum, substantia nigra, hippocampus, and hypothalamus	The substantia nigra, hippocampus, thalamus, frontal cortex, amygdala, hypothalamus, mesencephalon, nucleus accumbens, frontal cortex, kidneys, heart, blood vessels, adrenal glands, GI tract, and sympathetic ganglia. Lowest receptor found in CNS of all DRs

TABLE 2 (Continued)

DR subtype	D ₁ -like family		D ₂ -like family		D ₄
	D ₁	D ₅	D ₂	D ₃	
Function	Voluntary movements, regulation of growth and development, regulation of feeding, attention, reward, sleep, impulse control, reproductive behaviors, working memory, learning, control of rennin in kidney	Pain process, affective functions, endocrine functions of DA	Working memory, reward-motivation functions, regulation of blood pressure, renal functions, GI motility, vasodilatations	Endocrine function, cognitions, emotions, regulation of locomotor functions	Regulation of renal functions, GI motility, vasodilatations, blood pressure, modulations of cognitive functions
Selective agonists	SKF-38393, SKF-81297, fenoldopam	-	Bromocriptine, pergolide, cabergoline, ropinirole.	7OH-DPAT, pramipexole, rotigotine, PD-128907.	A-412997, ABT-670, PD-168077
Selective antagonists	SCH-23390, SCH-39166, SKF-83366	-	Haloperidol, raclopride, sulpiride, spiperone, risperidone	Nafadotride, GR-103691, GR-218231, SB-277011A, NGB-2904, PG-01037, ABT-127	A-381393, FAUC213, L-745870, L-750667

Abbreviations: AC, adenylyl cyclase; cAMP, cyclic adenosine monophosphate; DARPP-32, 32-kDa and cAMP-regulated phosphoprotein; D_{2L}, D₂ long; D_{2Lo}, D₂ longer; D_{2S}, D₂ short; ERK, extracellular signal-regulated kinase; GSK-3, glycogen synthase kinase 3; IP₃, inositol triphosphate; PKC, protein kinase C; PLC, phospholipase C.

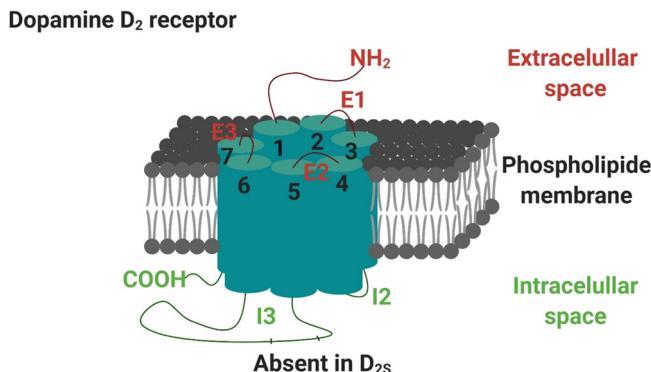


FIGURE 3 Schematic representation of D₂ receptors. COOH, C-terminus; D_{2s}, D₂-short; E1-E3, extracellular loops; I2-I3, intracellular loops; NH₂, N-terminus; 1-7, transmembrane domains. [Color figure can be viewed at wileyonlinelibrary.com]

protein-independent pathway comprises the second, or late, phase of the D₂R response and has a slower onset, longer duration, and no plausible explanation for a desensitization mechanism. On the other hand, the G protein-dependent cascade (Gα_{i/o} and Gβγ pathways) comprises the first, or early, phase and exhibits rapid onset and desensitization.⁶⁰

In the next section, we provide a brief description of the diseases in which D₂Rs play a major role (schizophrenia, depression, PD, and anxiety), with focus on those receptors, as well as others.

1.3 | Schizophrenia

Schizophrenia is a complex disorder with myriad symptoms,⁹⁷ affecting an approximate 1% of adult population.⁹⁸ Symptoms typically appear for the first time at a relatively young age (generally 18–30 years)⁹⁹ and can be divided into three major classes: positive, negative, and cognitive.⁹⁷ Positive ("something extra") symptoms include mainly hallucinations (auditory, visual, gustatory and/or tactile), delusion (fixed, false beliefs), and bizarre and disorganized speech and behaviors. Meanwhile, a lack of normal thoughts, behaviors, and feelings is the core of the negative symptoms ("something is missing"). These symptoms include anhedonia, avolition/passivity, asociality or social withdrawal, and alogia. Cognitive symptoms include difficulties with attention, deficits in memory, abnormalities in executive functions, disorders of verbal fluency, and social cognitive deficits.⁹⁷ Classically, schizophrenia is a disease that manifests in three stages: the prodromal phase, first episode, and chronic phase.¹⁰⁰ For more details, readers are kindly asked to read the review by Wójciak P.¹⁰¹

The etiology of schizophrenia has not yet been clearly elucidated; however, various genes, along with nongenetic factors, such as viral infections, perinatal obstetric problems, hormonal misbalance, early childhood adversity, maternal stress, lack of nutrition or drug abuse have been shown to play a crucial role in the development of the disease.^{102–107} The pathophysiology has been thoroughly studied and is being explained by various hypotheses. The dopamine hypothesis remains the most common explanation for the neurochemical nature of the disease, but has been altered many times since its introduction.^{4,103,108,109} Besides the DA hypothesis, there is number of other hypotheses, which include serotonin (5-HT),^{4,110,111} glutamate,^{4,112,113} GABA,^{4,114,115} or acetylcholine^{4,114,116} systems. But for the purpose of this review, we will consider the modified DA hypothesis only.

It has long been known that dopaminergic drugs (e.g., amphetamine, L-DOPA, cocaine) can cause psychotic symptoms in humans, manifesting similarly to the positive symptoms of schizophrenia.^{117,118} In addition, it has been found that amphetamine-induced psychotic state in humans and animals can be alleviated or abolished by

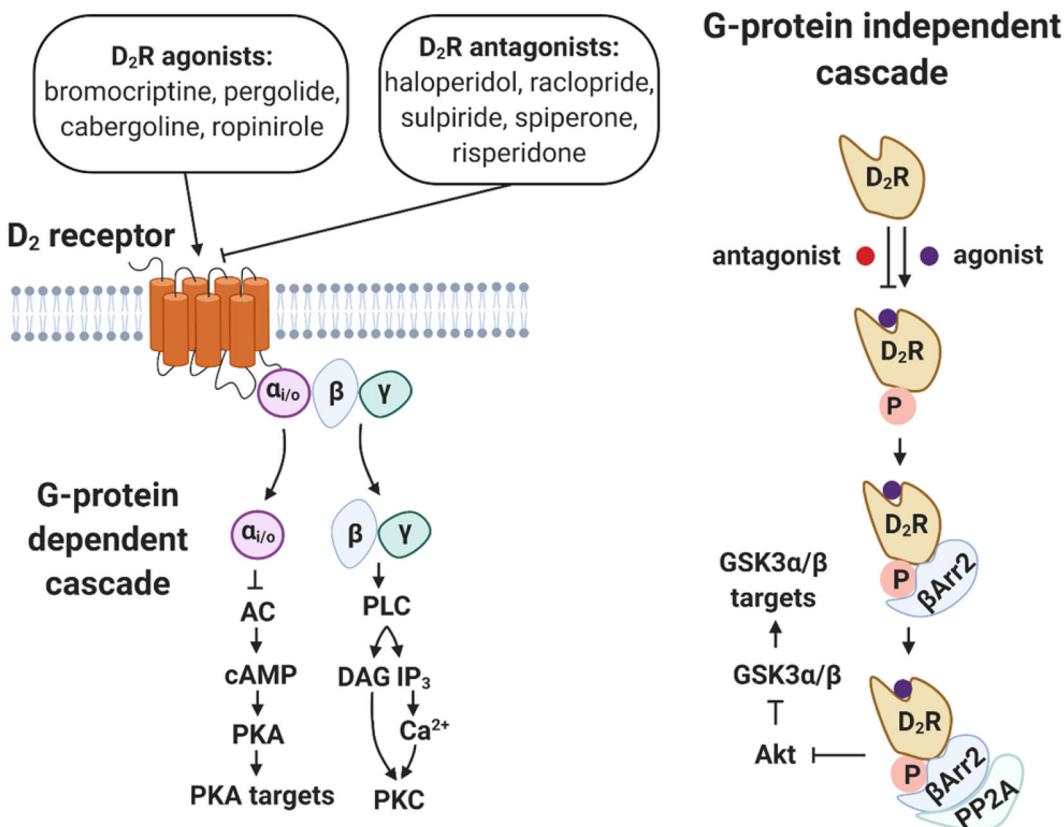


FIGURE 4 Schematic illustration of the G protein-dependent (left) and -independent (right) signaling cascade for D₂Rs.^{48,81,85} The G protein-dependent pathway for D₂Rs is depicted by G_{i/o} subunit-induced AC-cAMP-PKA-DARPP 32 cascade. After binding of the agonist to D₂R, splitting of the complex takes place, where the α_{i/o}-subunit negatively regulates AC, leading to downregulation of PKA. The main targets of PKA include CREB, ionotropic glutamate receptors, certain ion channels, and DARPP-32. Another cascade induced by D₂Rs is Gβγ-mediated activation of PLC, leading to increased cytoplasmic concentration of Ca²⁺. This pathway further modulates L- and N-type calcium channels and GIRKs. Both of these G protein-dependent pathways converge on, among other targets, phosphorylating two ionotropic glutamate receptors (GluA1 and GluN2B). G protein-independent D₂R signaling is represented by the β-arrestin 2-Akt-GSK3 cascade. Upon agonist binding, a complex of proteins composed of Akt, β-arrestin 2, and PP2A is created. This protein complex mediates the dephosphorylation (deactivation) of Akt, which deactivates GSK3α/β once activated. AC, adenylate cyclase; Akt, protein kinase B; cAMP, cyclic adenosine monophosphate; GSK3, glycogen synthase kinase; IP₃, inositol triphosphate; PKA, protein kinase A; PLC, phospholipase C; PP2A, protein phosphatase 2A; βArr2, beta-arrestin 2. [Color figure can be viewed at wileyonlinelibrary.com]

coadministration with DR antagonists.¹¹⁹⁻¹²² These studies support the theory that hyperactivity of DA causes positive symptoms of schizophrenia; however, it does not elucidate the receptor type involved.¹⁰³

Additionally, N-methyl-D-aspartate (NMDA) receptor antagonists (phencyclidine (PCP) and ketamine) have been found to induce both positive and negative symptoms of schizophrenia in nonschizophrenics.¹²³ This finding led to the proposal of the “glutamate hypothesis of schizophrenia.”^{103,112,124} The schematic illustration of negative, cognitive, and positive symptoms in schizophrenic’s brain, with regard to glutamate NMDA receptors, is depicted in Figure 5. Experimental evidence shows hypoactivity of glutamatergic neurotransmission in the prefrontal cortex (PFC) of the brains of schizophrenic patients.¹²⁵⁻¹²⁷ Hypofunctional glutamate NMDA receptors located on GABA

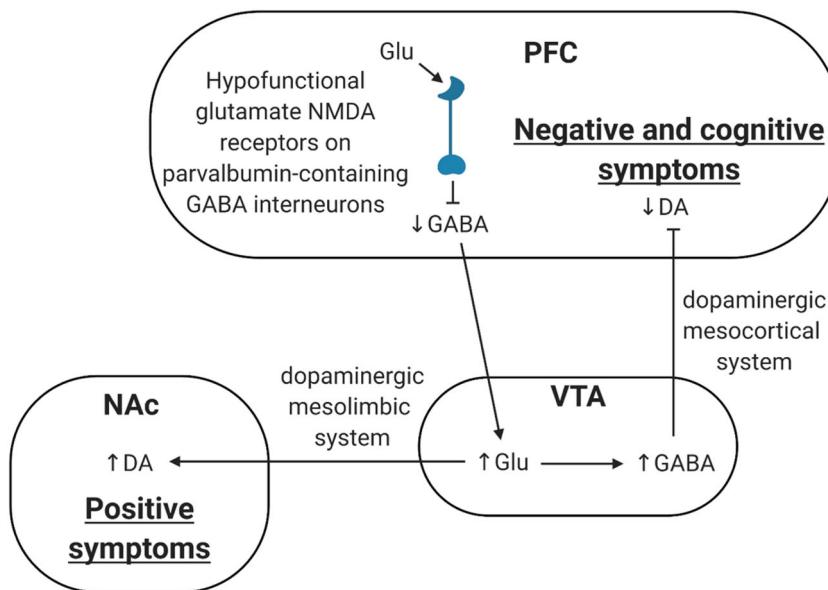


FIGURE 5 Schematic illustration of negative, cognitive, and positive symptoms in the brain of a schizophrenic. Decreased activity of glutamate NMDA receptors localized to GABA interneurons leads to decreased release of GABA in the PFC, resulting in increased glutamate concentration in the VTA. The increased concentration of glutamate in the VTA modulates the DA mesolimbic system, which leads to increased concentration of DA in the NAc, resulting in positive symptoms of schizophrenia. Meanwhile, the enhanced glutamate released in the VTA activates GABAergic interneurons, leading to hyperactivity of GABA in this region, resulting in suppression of the dopaminergic mesocortical pathway, which leads to lower levels of DA in the PFC, presenting as negative and cognitive symptoms. DA, dopamine; GABA, gamma amino butyric acid; Glu, glutamate; NAc, nucleus accumbens; PFC, prefrontal cortex; VTA, ventral tegmental area. [Color figure can be viewed at wileyonlinelibrary.com]

interneurons result in hyperactivity of cortical glutamate projections to the VTA. The increased concentration of glutamate in this region affects DA mesolimbic and mesocortical pathways (Table 2; Figure 2) leading to the outbreak of negative and positive symptoms.^{103,125–127} The increased concentration of glutamate in VTA modulates the DA mesolimbic system, which leads to hyperactivity of DA in the NAc, resulting in positive symptoms of schizophrenia.¹⁰³ Furthermore, the enhanced glutamate released in VTA activates GABAergic interneurons, resulting in hyperactivity of GABA in this region and reduced release of DA in the PFC and leading to negative symptoms.¹⁰³ The reason for hypoactivity of the glutamate NMDA receptors on the GABA interneurons of schizophrenic patients is not understood, but it is believed that it may be due to neurodevelopmental abnormalities and/or dysfunctional genes.¹⁰³

We can assume that positive symptoms are linked with the hyperactivity of striatal presynaptic D₂Rs due of overstimulation of mesolimbic DA pathway. The negative and cognitive symptoms, meanwhile, are associated with hypoactivity of D₁Rs in the prefrontal cortex due to hypostimulation of the mesocortical DA system by hyperactivity of GABAergic interneurons in VTA.^{4,103,128–130}

1.3.1 | Current treatment of schizophrenia and the relevance to D₂R

The drugs for treatment of schizophrenia are termed as “neuroleptics” or “antipsychotics” (structures are shown in Figure 6) and are classified into three groups according to intrinsic activity of ligands toward D₂Rs and other

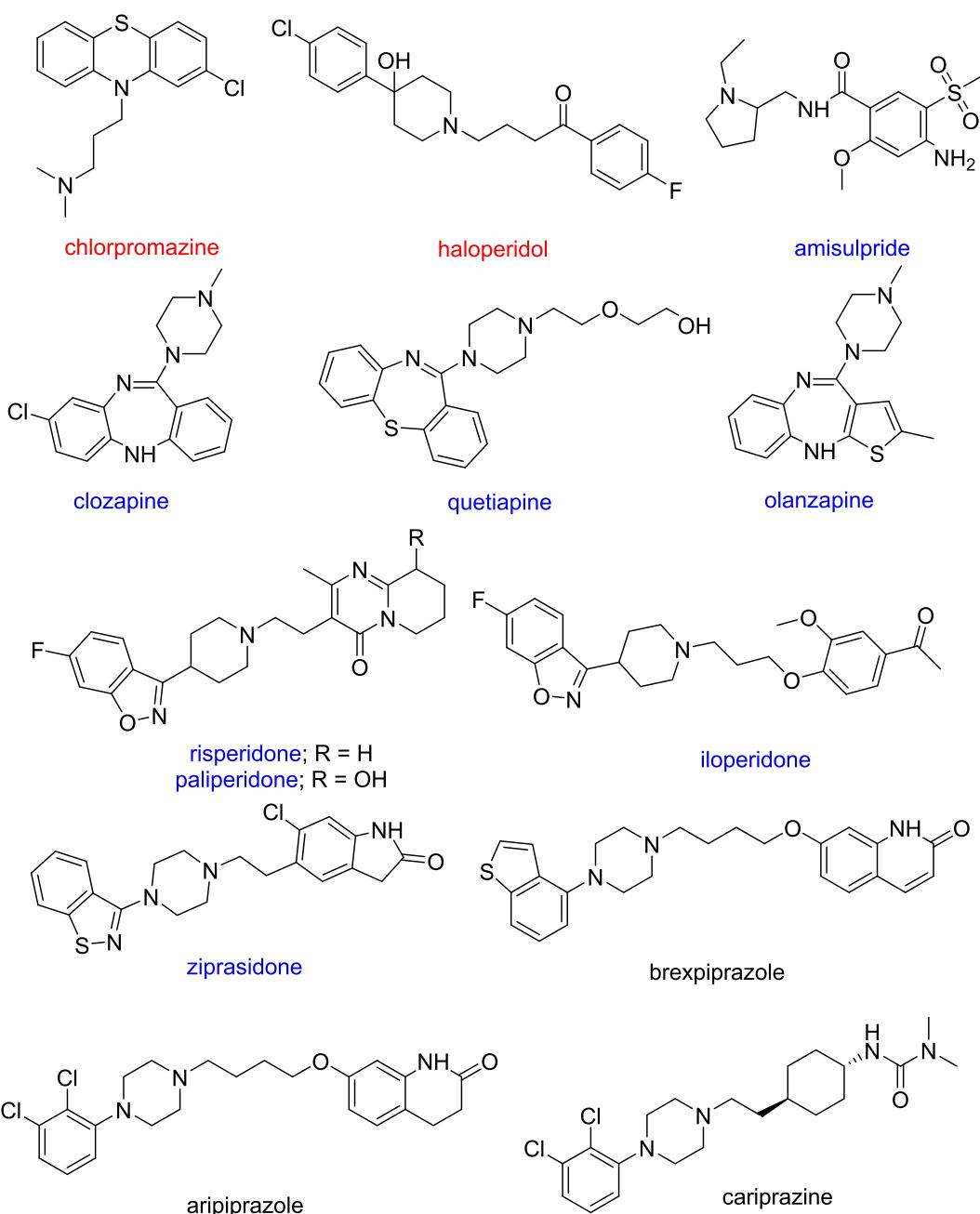


FIGURE 6 Chemical structures of selected neuroleptics. Red color→first generation antipsychotics; blue color→second generation antipsychotics; black color→third generation antipsychotics. [Color figure can be viewed at wileyonlinelibrary.com]

"antipsychotic receptors." First-generation antipsychotics are mainly D₂R antagonists. Neuroleptics belonging to the second group are multitarget antagonists, with higher antagonistic activity for serotonin 2A receptors (5-HT_{2A}Rs) than for D₂Rs. The third class of drugs for treatment of schizophrenia are multitarget ligands with partial agonism towards D₂Rs.⁴ At the beginning of this chapter, we would like to address that currently used

antipsychotics have significant limitations. They are targeted towards reducing mainly the positive symptoms,¹³¹ possess severe metabolic side effects,^{103,132–134} and are only effective in about half the patients.¹³⁵

The first antipsychotic drug, chlorpromazine (Figure 6), was synthesized in 1950 and released in the market in 1953 (trade name Largactil).¹³⁶ Most first-generation drugs belong to four basic chemical subgroups: tricyclic phenothiazines (e.g., chlorpromazine), tricyclic thioxanthenes (e.g., thiothixene), butyrophenones (e.g., haloperidol [Figure 6]), and diphenylbutylamines (e.g., pimozide). According to the mechanism of action described above, a vast number of other compounds can be classified as first-generation antipsychotics. However, they do not fit structurally into these four groups (e.g., molindone).^{4,133} The first generation of neuroleptics exhibits primarily D₂R antagonism in the human brain. However, these drugs do not have a selectivity for DA pathways in the CNS and therefore can lead to a range of side-effects, including extrapyramidal symptoms (blockade D₂Rs in the nigrostriatal pathway), elevated prolactin levels (antagonism towards D₂Rs in the tuberoinfundibular system), or in high doses, negative and cognitive symptoms caused by the blockade of D₂Rs in the mesocortical pathway.⁴

In the 1970s, clozapine (Figure 6) was launched in the market. However, it was soon withdrawn due to serious side effects, including agranulocytosis (white blood cell reduction).¹³⁷ Nevertheless, clozapine was reintroduced in 1989 after studies demonstrated its effectiveness, primarily in patients who had or developed resistance to "safer" antipsychotics.^{133,138} Clozapine reintroduction marked the beginning of the second generation of antipsychotics, also referred to as "atypical" antipsychotics characterized by very low frequency of extrapyramidal side effects that are typical for the first-generation of antipsychotics. The unique properties of clozapine spurred further development, and drugs like olanzapine, quetiapine, risperidone, or ziprasidone (Figure 6) were introduced.

The latest "third-generation" include aripiprazole, cariprazine, and brexpiprazole (Figure 6). This subclass of drugs has been created based on their mechanism of action on DRs. They are D₂R partial agonists, so they are better tolerated at higher D₂R occupancies than D₂R antagonist antipsychotics.⁴ For more details about the pharmacology of antipsychotics, please refer to the review by Stępnicki et al.⁴

All licensed neuroleptics exhibit D₂R affinity at therapeutic doses, and this property plays a key role in their mechanism of action.^{139–142} However, they also bind to some human receptors (Table 3).

It means that currently used antipsychotics are kind of promiscuous drugs, and the implication of other receptors in the schizophrenia treatment should be discussed.¹³³ Indeed, selective D₁, D₃, and D₄ receptor antagonists have not been shown to be as effective as neuroleptics,^{147–149} and D₁ agonists possess limited clinical efficacy.^{150–152} For serotonin receptors, the evidence of 5-HT_{1A}R agonism/partial agonism is inconclusive.^{153,154} The role of the 5-HT_{2A}R antagonism is neither necessary nor a major contributor to

TABLE 3 Binding affinities (K_i in nM) for selected antipsychotics to some human receptors

Drug	D ₁	D ₂	D ₃	D ₄	D ₅	5-HT _{1A}	5-HT _{2A}	5-HT _{2C}	5-HT ₃	5-HT ₆	5-HT ₇	α_1	H ₁	M ₁ ACh	M ₃ ACh
chlorpromazine	112	2.0	3.0	24	133	2,116	3.3	12	977	17	21	2.6*	0.2	47	47
haloperidol	83	2.0	5.8	15	147	1,202	107	6,027	>	5,306	378	17°	3,002	>	>
amisulpride	>	3.0	2.4	2,369	>	>	8,304	>	>	4,154	73	>	>	>	>
clozapine	189	431	283	39	235	373	9.3	13	241	14	18	6.8°	2.0	14	25
iloperidone	43	0.4	11	14	319	21	1.7	9.6	>	63	112	0.3°	12	4,898	>
olanzapine	58	72	37	19	90	2,063	3.0	13	202	6.0	105	44°	4.9	24	51
paliperidone	41	9.4	3.2	54	29	542	1.9	48	>	2,414	2.7	>	5.6	>	>
quetiapine	712	567	404	1,202	1,738	431	471	1,840	>	1,864	308	8.1°	7.5	858	1,943
risperidone	61	4.9	56	19		427	0.9	31	>	2,241	6.6	2.7°	5.2	>	>
ziprasidone	30	4.0	7.4	105	152	76	0.5	4.5	>	61	6.0	2.6°	130	>	>
aripiprazole	3,870	1.0	4.6	514	1,676	5.6	8.7	22	628	642	10	>	29	6,776	4,677
brexpiprazole	160	0.3	1.1	6.3		0.1	0.5	12-34		58	3.7	>	19	67% at 10µM	
cariprazine		0.5	0.08			2.5	20	130	< 1,000	110	25				

Note: Data were obtained from the PDSP database (<https://pdsp.unc.edu/databases/kidb.php>). Values are either PDSP certified data or the average of all data in the database. Red color—first (typical) generation; blue color—second (atypical) generation, black color—third generation, > corresponds to >10,000; *(K_d in nM,¹⁴³ °(K_d in nM,¹⁴⁴); brexpiprazole—ref.¹⁴⁵; cariprazine—ref.¹⁴⁶ Affinity to D₂R is highlighted in bold.

antipsychotic action.¹³⁴ On the other hand, pimavanserin (an inverse agonist at 5-HT_{2AR}) has recently been approved for the treatment of psychosis associated with PD.¹⁵⁵ 5-HT_{2C}R antagonism has been associated mainly with side-effects including weight gain, diabetes and sexual disturbances.^{133,134,144} 5-HT₃Rs antagonists have been beneficial as add-ons to standard antipsychotic treatment to manage negative symptoms,¹⁵⁶ and have shown activity in behavioral models for cognitive symptoms.^{157,158} Preclinical findings suggest that also a blockade of 5-HT₇Rs may also be beneficial against schizophrenia-like cognitive deficits.¹⁵⁹ Histamine H₁Rs are thought to be associated with sedation,^{160,161} but this effect could be beneficial in some cases.¹⁶² It is believed that binding to α₁ receptors is responsible for side effects like orthostatic hypertension, dizziness, and reflex tachycardia.¹³³ Affinity of antipsychotics for muscarinic acetylcholine receptor M₁ (M₁AChRs) has been associated with dry mouth, blurred vision, constipation, and cognitive impairment.¹³³ Pancreatic M₃AChRs are associated to control cholinergic-dependent insulin release, which might lead to hyperglycemia and type II diabetes mellitus.¹⁶³ For instance, clozapine and olanzapine, both potent M₃AChR antagonists (Figure 6, Table 3), displayed the highest clinical incidence of diabetes as a side effect.¹⁶⁴ Moreover, blocking the human ether-à-go-go-related gene (hERG) potassium channel induces QT interval prolongation, which is associated with potentially fatal arrhythmia.¹⁶⁵ For more information about side effects of neuroleptics, please refer to the following references.^{134,144,166–168}

1.4 | Depression

Major depressive disorder (MDD; also known simply as depression) is a heterogeneous mental illness of mood affecting 3% of global population,^{169,170} and is induced by biological, psychological, genetic and social aspects.¹⁷¹ Interestingly, it is not entirely known why women suffer from depression up to twice as often as men.¹⁷² Symptoms of MDD include feelings of sadness or emptiness, anhedonia, pessimistic thoughts, suicidal ideas, sleep disorders like insomnia, difficulty concentrating, forgetfulness, and loss of appetite and libido, and about 50% patients also suffer from anxiety disorders.¹⁰³

Similarly to schizophrenia, MDD is caused by genetic and environmental factors, including stress, emotional, sexual, and physical abuse, parental separation or divorce, and drug abuse in the family.^{173–175} The monoamine hypothesis was postulated more than 50 years ago, but it is still considered as the main hypothesis to explain the pathophysiology of MDD.^{103,171} It was found that reserpine, a hypertension drug introduced in 1953, caused MDD symptoms in nondepressed patients.¹⁷¹ It has been found that reserpine caused depletion of catecholamines (5-HT¹⁷⁶ and noradrenaline¹⁷⁷ [NA]) by inhibiting the vesicular uptake of these biogenic amines.¹⁰³ Conversely, iproniazid, formerly an antituberculosis drug, was found to induce euphoria in patients and was shown to be an inhibitor of the MAO enzyme.¹⁷⁸ Imipramine, a tricyclic drug formerly used for the treatment of schizophrenia, also elevated mood.¹⁷⁹ This drug has been shown to be an SERT and norepinephrine transporter (NET) inhibitor. Because of these findings, it has been suggested that depression is caused by decreased concentrations of NA and 5-HT in the human brain.^{180–182} Later, the original hypothesis was reformulated to monoamine signaling pathways¹⁰³ involving 5-HTRs,¹⁸³ adrenergic receptors,¹⁸⁴ DRs,⁴⁹ protein kinase C (PKC),¹⁸⁵ and protein kinase A (PKA),¹⁸⁶ leading to decreased cAMP, inositol triphosphate (IP₃), and brain-derived neurotropic factor¹⁸⁷ (BDNF) formation.¹⁰³

In general, there is no doubt that DA is involved in depression, despite many contradictory findings. For instance, human *in vivo* neuroimaging studies in depressed patients have shown mixed results for the availability of D₂Rs in the striatum: increased striatal D₂R levels,^{188–190} no differences,^{191–196} and even decreased density of striatal D₂Rs compared to healthy subjects.¹⁹⁷ DA involvement can be demonstrated by the fact that depressive patients suffer from various mood-related symptoms: increased negative affect (depressed mood, guilt) and decreased positive affect (anhedonia, decreased motivation).^{198,199} Namely, anhedonia ("inability to experience pleasure")²⁰⁰ is the major symptom of depression that has been directly linked with dopamine dysregulations,^{201,202}

as feeling pleasure is mediated by well-developed mesocorticolimbic circuitry.²⁰³ In more detail, the origin of this symptom can be explained by a reduction of multifunctional protein p11 (also known as annexin II light chain, S100A10) in cholinergic interneurons of the NAc, which in turn causes a lack of DA response, leading to an outbreak of anhedonia.¹⁹⁸ On the contrary, increased negative effects can be effectively mitigated with antidepressants that upregulate serotonin and/or with noradrenaline neurotransmission; while these drugs are relatively ineffective at improving decreased positive effect like adhedonia.^{198,204,205}

1.4.1 | Current treatment of depression and the relevance to D₂R

Antidepressants are divided into several classes—tricyclic antidepressants (e.g., amitriptyline, imipramine, trimipramine, doxepin), MAO inhibitors (e.g., phenelzine, tranylcypromine, moclobemide), selective serotonin reuptake inhibitors (e.g., fluoxetine, citalopram, paroxetine, and sertraline), serotonin and noradrenaline reuptake inhibitors (e.g., duloxetine, venlafaxine), selective noradrenaline reuptake inhibitors (e.g., reboxetine), noradrenaline and selective serotonin antidepressants (e.g., mirtazapine), serotonin antagonist and reuptake inhibitors (e.g., trazodone), and noradrenergic and dopamine reuptake inhibitors (e.g., bupropion).¹⁰³ In the next section, we will focus mainly on the role of DA and its receptors in treatment of depression.

Interestingly, combination therapy of neuroleptics with antidepressants is often more effective than antidepressant monotherapy.²⁰⁶ Atypical and third-generation antipsychotics are currently used in combination with antidepressants for management of psychotic depression,²⁰⁷ improving the efficacy of antidepressants in treatment of resistant depression^{208–210} and as monotherapy.²⁰⁶ The antidepressant effects of currently-used neuroleptics involve rapid disengagement and reduced activation of DRs.²⁰⁷ Other mechanisms hypothesized to explain the antidepressant activity of antipsychotics include:^{207,211,212}

- (1) Regulation of nondopamine neurotransmitter receptors: 5-HT_{1A} agonism→increased DA levels in the frontal cortex; antagonism 5-HT_{2A}→increased DA levels in the frontal cortex; antagonism 5-HT_{2C}→increased DA and NA in the frontal cortex; 5-HT₆ antagonism→increased DA, NA, and glutamate level in the frontal cortex and hippocampus; 5-HT₇ antagonism→increased 5-HT level in the prefrontal cortex; α_2 antagonism→increased DA, NA, and 5-HT level in the frontal cortex.
- (2) Blockade of 5-HT, NA and DA reuptake
- (3) Effects on sleep mediated by the 5-HT_{2C} antagonism^{213,214}
- (4) Decrease in cortisol levels and increase in BDNF levels

The results of human studies involving various neuroleptics with antidepressant effects are summarized in Table 4.^{212,237–240} The United States Food and Drug Administration (FDA) has approved the use of aripiprazole, brexpiprazole, and slow-release quetiapine as an adjunctive medication in the management of depressive disorders,^{207,212,239} and the combination of olanzapine and fluoxetine has been approved in treatment of resistant depression.²⁴¹

The use of dopamine agonists in the treatment of MDD stems from the fact that DA mesocortical and mesolimbic systems (Table 1) are associated with key symptoms of MDD—anhedonia, decreased energy, and reduced motivation.^{201,242,243} The mechanism of action of DA agonists in the management of MDD have not been elucidated, but some plausible explanations have been suggested: DR activation to modulate motivation, concentration, and pleasure; release of BDNF; and stimulation of the dopaminergic system in the NAc.²⁴⁴ The results of human studies on various DRs agonists with antidepressant effects are summarized in Table 5.^{29,244}

TABLE 4 Positive results of human studies with various neuroleptics with antidepressant effects

Antipsychotic	Antidepressant	Results	References
Olanzapine	Fluoxetine	Combination showed a significantly greater decrease in MADRS score than fluoxetine alone in 1 of 2 trials and the pooled analysis.	[215]
Olanzapine	Fluoxetine	Combination demonstrated superior efficacy compared with either agent alone.	[216]
Olanzapine	Fluoxetine	Combination demonstrated longer time-to-relapse than fluoxetine alone.	[217]
Quetiapine	Paroxetine	A significant decreased through the study period in HAM-D scores.	[218]
Quetiapine	Various	Significant change from baseline in HAM-A and HAM-D scores. Significant increase in response and remission rates with combination versus placebo.	[219]
Quetiapine	Various	Combination showed a significantly greater decrease in MADRS score versus placebo.	[220]
Quetiapine	Various	Significantly greater change in MADRS score compared with placebo.	[221]
Quetiapine	Mono	Significant changes in MADRS scale compared with placebo.	[222]
Quetiapine	Mono	Significant changes in HAM-D scale compared with placebo.	[223]
Risperidone	Citalopram	Trend toward a longer time to relapse in the combination group.	[224]
Risperidone	Various	Significant improvement in rates of remission and response with combination therapy versus placebo.	[225]
Risperidone	Various	Significant improvement in rate of response and remission with combination versus placebo.	[226]
Ziprasidone	Escitalopram	Ziprasidone significantly improved HAM-D scores.	[227]
Aripiprazole	Various	Significant increase in response and remission rates with combination versus placebo.	[228]
Aripiprazole	Various	Significant increase in response and remission rates with combination versus placebo.	[229]
Aripiprazole	Various	Significant increase in response and remission rates with combination versus placebo.	[230]
Aripiprazole	Various	Improvements over baseline noted in CGI-S scores.	[231]
Aripiprazole	Mono	Better response and remission rates in treatment groups compared to placebo.	[232]
Aripiprazole	Mono	Better remission rate in treatment group.	[233]
Brexpiprazole	Mono	Better response rate in treatment group.	[234]
Brexpiprazole	Mono	Better response rate in treatment group.	[235]
Cariprazine	Adjunctive treatment	Better response rate in treatment group.	[236]

Abbreviations: CGI-S, Clinical Global Impression-Severity Scale; HAM-A, Hamilton Rating Scale for Anxiety; HAM-D, Hamilton Rating Scale for Depression; MADRS, Montgomery-Asberg Depression Rating Scale.

TABLE 5 The positive results of studies with various DA agonists with antidepressant effects

DA agonist	Results	References
Bromocriptine	Reduction in the HDRS	[245]
	Improve depressed mood, insomnia, retardation, psychic anxiety, gastrointestinal symptoms, and general somatic symptoms	-
	Effective in treatment of antidepressant-resistant depression	[246]
Cabergoline	Dramatic improvement in energy loss and fatigue	[247]
Pergolide	Improvement/significant improvement in CGI-GIS	[248]
	Improvement in mood, interest, and energy	-
	Pergolide may be useful as an antidepressant adjuvant	[249]
Pramipexole	Significant improvement compared to placebo by measure of HAM-D, MADRS, and CGI-IS	[250]
	Moderate to marked improvement in CGI-IS	[251]
	Effective and safe in the treatment of unipolar depression as an adjunct	-
	Improvement by measure MADRS and CGI-IS	[252]
	Pramipexole adjunction to antidepressant treatment may be effective and well tolerated in patients with resistant major depression	-
	Pramipexole augmentation of antidepressant treatment was relatively safe and presumably effective in the long-term course of treatment resistant depression	[253]
	Significant reduction on the MADRS	[254]
	Addition of pramipexole to antidepressant treatment may be effective and well tolerated in patients with stage 2 treatment-resistant MDD	-
	Reduction in HDRS-21 total score	[255]
Ropinirole	Pramipexole augmentation therapy may be effective and well tolerated in refractory depressed patients	-
	Great reduction in MADRS and CGI-IS	[256]
	Ropinirole augmentation of antidepressants was effective and relatively well tolerated in selected cases of treatment-resistant depression	-

Abbreviations: CGI-GIS, Clinical Global Impressions Global Improvement Scale; CGI-IS, Clinical Global Impression-Improvement Scale; HAM-D, Hamilton Psychiatric Rating Scale for Depression; HDRS, Hamilton Depression Rating Scale; HDRS-21, Hamilton Depression Rating Scale 21-item version; MADRS, Montgomery-Åsber Depression Rating Scale.

1.5 | Anxiety

Anxiety is a normal emotional reaction to an imminent or perceived threat, and is characterized by fear and worries.¹⁰³ Outbreaks of most anxiety illnesses occur in childhood, adolescence, or early adulthood²⁵⁷ and are often accompanied by depression and other illnesses, and thus can be seen as a risk factor for other illnesses.²⁵⁸ Female sex (women are up to twice as vulnerable),^{259,260} MDD, and family history of anxiety are the main risk factors for anxiety disorders.²⁶¹ Similarly to previous diseases, genetic predisposition has been associated with a greater risk for anxiety disorders via increased amygdala reactivity and reduced amygdala connectivity to other brain areas, such as the hippocampus.²⁶¹

Indeed, patients with focal bilateral amygdala lesions,^{262,263} fail to show fear-induced behavior confirming that the amygdala plays a major role in the physiology of fear and thus anxiety.^{103,262,264} Additionally, results of brain

imaging studies have revealed that patients suffering from various anxiety disorders show increased activation in the amygdala region.^{265–272} In addition to increased amygdala activity, decreased activity of the ventromedial prefrontal cortex (VMPFC), the orbitofrontal cortex (OFC), and the anterior cingulate cortex has been shown in anxiety patients.^{266,273–275}

On the other hand, “worry,” a second symptom of anxiety disorder, represents the cognitive aspects of anxiety,²⁷⁶ and has been defined as “a chain of thoughts and pictures.”^{276,277} The “worry circuit” involves the prefrontal cortex (OFC and dorsolateral prefrontal cortex), thalamus, and striatum.¹⁰³ Increased dorsolateral prefrontal cortex activity is associated with a deficit in continuous attention and elevated spontaneous generation of negative thoughts.^{103,277}

It has been suggested that the dopaminergic system plays a critical role in the regulation of anxiety-like behaviors.^{278–285} However, the precise mechanism is still not fully understood. Some studies have revealed that altered dopaminergic projections in the VTA,²⁸⁶ mesolimbic system,²⁸⁷ hippocampus,²⁸⁸ NAc,²⁸⁹ and amygdala^{290–292} explain alteration in anxiety-like responses. Other studies have demonstrated low expression of striatal D₂Rs in patients with generalized social anxiety disorder,^{293,294} however, other reported unchanged expression.²⁹⁵ Interestingly, a negative correlation was observed between a change in prefrontal D₂R availability and a change in self-reported social anxiety symptoms in patients with social anxiety disorder.²⁹⁶ Another study revealed elevated D₂R availability in patients with social anxiety disorder within the orbitofrontal cortex and the right dorsolateral prefrontal cortex.²⁹⁷

1.5.1 | Management of anxiety disorders

Several nonpharmacological and pharmacological approaches are available for the treatment of anxiety disorders. An example of a nonpharmacological approach is cognitive behavior therapy, which was shown to cause a clinical improvement in up to 75% of patients with social anxiety disorder.^{298,299} Meta-analysis suggests a combination of nonpharmacological with pharmacological approaches as the most effective treatment.³⁰⁰

Although the pathophysiology of anxiety disorders is not fully explained, there are several classes of drugs which can be divided according to the systems they effect: serotonin, adrenergic, glutamate, endocannabinoid, and DA drugs or different neuropeptides.^{301,302} They might be also categorized as antidepressant, benzodiazepines, anti-epileptics, and atypical antipsychotics. In the following section, we mainly discuss the effect of antipsychotics (D₂R ligands) in the treatment of anxiety.

As clearly demonstrated by various studies with D₁R antagonist SCH23390 or sulpiride (D₂ and D₃ receptor antagonist)^{303–306} the role of DA in anxiety is rather complex and is probably related to the interaction of DA neurons in VTA and basolateral amygdala^{278,291,307} with cholinergic, glutamatergic, opioidergic, or histaminergic systems in various parts of the brain, which may influence anxiety-like behaviors.²⁷⁸ For more details about DRs in the NAc, hippocampus, and prefrontal cortex, refer to Bast and Feldon.³⁰⁸ For the purposes of this review, the effects of dopamine D₂R ligands in animal models of anxiety are summarized in Table 6.²⁷⁸

The anxiogenic-like effect is linked to an increase in dopaminergic transmission involving both D₁ and D₂Rs;³¹⁴ therefore, we will discuss only DA antagonists in the next section. Due to the complex action of antipsychotics, a plausible mechanism of action of neuroleptics in treatment of anxiety disorders has not been established, but it has been hypothesized that blocking 5-HT_{2A} and partial agonism towards 5-HT_{1A} receptors may explain their action in management of anxiety disorders.^{315–317} However, haloperidol also (strong D₂R antagonist with no affinity for above-mentioned 5-HTRs—Table 3) showed anxiolytic properties,^{318,319} contrasting the above hypothesis. Therefore, more studies are required to reveal and confirm the exact mechanism of action of antipsychotics in the treatment of anxiety disorders. The efficacy on anxiety disorder of second and third generation of antipsychotics as adjunctive therapy and/or monotherapy is summarized in Table 7.^{315,340–342}

TABLE 6 Results of D₂R ligands in animal models of anxiety

D ₂ R ligand	Site of injection	Effect	References
Apomorphine	Amygdala	Anxiolytic	[305]
Apomorphine	Hippocampus	Anxiogenic	[306]
Quinpirole	VTA	Anxiolytic	[309]
Quinpirole	Hippocampus	Anxiogenic	[288]
Quinpirole	Basolateral amygdala	Anxiogenic	[310]
Sulpiride	Basolateral amygdala	Anxiolytic	[309]
Sulpiride	Basolateral amygdala	Anxiolytic	[311]
Sulpiride	Basolateral amygdala	Anxiolytic	[310]
Sulpiride	Amygdala	Anxiogenic	[305]
Raclopride	Basolateral amygdala	Anxiolytic	[291]
Raclopride	Central amygdala	Anxiogenic	[291]
Eticlopride	Central amygdala	Anxiolytic	[291]
Apomorphine + nicotine	Ventral hippocampus + i.p.	Anxiolytic	[306]
Apomorphine + morphine	Central amygdala + i.p.	Anxiolytic	[312]
Quinpirole + nicotine	Dorsal hippocampus + i.p.	Anxiogenic	[288]
Quinpirole + histamine	Coinjection in basolateral amygdala	Anxiolytic	[310]
Sulpiride + nicotine	Dorsal hippocampus + i.p.	Anxiolytic	[288]
Sulpiride + nicotine	Ventral hippocampus + i.p.	Anxiolytic	[306]
Sulpiride + nicotine	VTA + central amygdala	Anxiolytic	[303]
Sulpiride + nicotine	VTA + central amygdala	Anxiolytic	[304]
Sulpiride + morphine	Central amygdala + i.p.	Anxiogenic	[312]
Sulpiride + histamine	Coinjection in basolateral amygdala	Anxiolytic	[310]
Sulpiride + MK801	Coinjection in dorsal hippocampus	Anxiogenic	[313]

Abbreviations: apomorphine, nonselective DA agonist at D₂- and D₁-like receptors; eticlopride, selective D₂Rs antagonist; quinpirole, D₂ and D₃Rs agonist; raclopride, D₂ and D₃Rs antagonist; sulpiride, D₂ and D₃Rs antagonist.

1.6 | PD

PD is a complex progressive neurodegenerative illness, first described by James Parkinson in 1817.^{103,343} PD is primarily a disease of the elderly, occurring in 1% of the population over 60 years of age and 3% over 80 years. Men are approximately twice as prone to PD.^{344,345} The exact mechanism is unknown, but a protective effect of female sex hormones, a sex-associated genetic mechanism, or sex-specific differences in exposure to environmental risk factors may explain this male preponderance.^{103,346} In addition, genetic factors play a significant role,^{103,343} but it is believed that the age is the highest risk factor for PD.³⁴⁷

Characteristic features of PD are neuronal loss in specific brain areas of the substantia nigra³⁴³ and widespread accumulation of α-synuclein, a pathological protein aggregates called Lewy bodies consisting of tau proteins, heat shock proteins, ubiquitin, parkin, oxidized/nitrated proteins, cytoskeletal proteins, and more.^{346,348} The dopaminergic neuronal loss results in the denervation of the DA nigrostriatal pathway (Table 1), leading to

TABLE 7 The positive results of efficacy of second and third generation of antipsychotics in the management of anxiety disorders (generalized anxiety disorder, social anxiety disorder, and panic disorder)

Antipsychotic	Result	References
<i>Generalized anxiety disorder</i>		
Risperidone	Significantly reduction in anxiety symptoms	[320]
Olanzapine	Olanzapine may have a salutary effect on anxiety for some GAD patients	[321]
Ziprasidone	Improvement in anxiety symptoms	[322]
Quetiapine	Significant improvement in symptoms and quality of life	[323–333]
Aripiprazole	Significant improvement in anxiety, overall functioning, and quality of life	[334]
<i>Social anxiety disorder</i>		
Olanzapine	Olanzapine was superior to placebo on the primary outcome measures in the preliminary study of SAD	[335]
Risperidone	Improvement in anxiety symptoms	[320]
Quetiapine	Reduction of anxiety symptoms	[336]
<i>Panic disorder</i>		
Olanzapine	Olanzapine is potentially effective and safe in panic disorders	[337,338]
Risperidone	Significant improvement in anxiety symptoms	[320]
Sulpiride	Sulpiride monotherapy in refractory panic disorders showed significant clinical improvement	[339]

reduced DA levels in the striatum^{103,343} and thus alteration of the motor cortex–basal ganglia–motor thalamus–motor cortex loop. It determines the association with motor symptoms including tremors, hypokinesia or akinesia, muscle rigidity, and postural defects.^{103,343} Apart from DA systems, cholinergic, adenosinergic, glutamatergic, GABAergic, noradrenergic, serotonergic, and histaminergic systems are altered in PD.³⁴⁹ These changes in these neurotransmission systems are suspected to be responsible for the development of nonmotor deficits, which often even precede the motor symptoms by years or even decades. Nonmotor symptoms involve dementia or other forms of cognitive loss, depression, anxiety, psychosis, hallucinations, sleep disorders, constipation, and olfactory dysfunction.^{103,343,350–352}

There are several different mechanisms explaining the PD pathogenesis:

- (1) α-synuclein misfolding and aggregation suggest a prion-like theory of the disease as a single injection of synthetic misfolded α-synuclein into the striatum will spread into the various brain areas and result in the formation of Lewy bodies.^{103,353}
- (2) Mitochondrial dysfunction highlighting reactive oxygen species (ROS; O₂⁻; H₂O₂; OH[•]), a culprit for damage to cellular proteins, altering normal cellular function and resulting in cell death.¹⁰³
- (3) Dysfunctional ubiquitin-proteasome and the autophagy-lysosome systems protein clearance systems, which is responsible for the degradation of α-synuclein.^{354, 355–358}
- (4) Neuroinflammation, as it is believed that α-synuclein can directly modulate microglial activation and induce inflammatory processes.^{359–361} On the contrary, neuroinflammation itself can cause α-synuclein misfolding.³⁶²

The involvement of DA and D₂Rs in the pathophysiology of PD can be demonstrated by the fact that bradykinesia is a clinical core symptom of PD, is very closely associated with DA deficiency,^{363,364} and reacts well to

the dopaminergic treatment.^{365,366} In detail, the neuronal loss of the dark-pigmented DA neuron results in a significant reduction in the level of striatal DA, DA-synthesizing enzymes (i.e., tyrosine hydroxylase and DOPA-decarboxylase), and metabolites of DA (i.e., homovanillic acid, dihydroxy-phenylacetic acid, and 3-methoxytyramine).^{363,367–369} Presynaptically, the DA turnover rate in the striatum of PD patients becomes accelerated, as evidenced by an increase in the ratio of homovanillic acid:DA.^{363,367} Next, there is an upregulation (hypersensitivity) of striatal postsynaptically located DRs.^{370,371} These two mechanisms operate in a synergistic manner to maximize the physiological effectiveness of the remaining DA neurons.³⁶⁷ While PET studies revealed enhancement in the density of D₂Rs in the putamen and caudate in early-stage PD patients, advanced PD patients had normal or even decreased densities.^{371,372} It is not clear whether such changes are caused by chronic dopaminergic therapy or occur as a result of structural adaptation of the postsynaptic DA system to the progressive reduction in DA nigrostriatal neurons.³⁷³

As we know, there is a significant reduction in the density of DA neurons in the substantia nigra pars compacta of PD patients, and dopaminergic enhancement is needed in this region of the brain. However, at the same time, DA substitution leads to “DA overdosing” in the less-affected VTA-striatal circuitry and anterior dorsal nigrostriatal circuitry, causing adverse effects on cognition.^{365,374–378} Notably, there is reduced dopamine transporter (DAT) availability in the ventral striatum of PD patients with impulsive control disorder, suggesting a reduced DA clearance from the synaptic cleft that amplifies the overdosing impact of DA therapy.^{365,379,380}

1.6.1 | Current treatment of PD and the relevance to D₂R

Lack of DA could be primarily handled by DA substitution, however, DA itself does not cross the blood-brain barrier (BBB) in appreciable amounts. On the other hand L-DOPA easily gains access to the human brain.³⁸¹ L-DOPA (a chemical precursor of DA, Figure 1) is still the gold standard for treatment of PD; however, its use is complicated with motor deficits, including motor response oscillations and drug-induced dyskinesia.^{59,346}

To increase the availability of DA, inhibitors of aromatic amino acid decarboxylase (Figure 1; carbidopa, benserazide) and catechol-O-methyltransferase degrading L-DOPA at the periphery (Figure 1; entacapone, opicapone, tolcapone) are used. Furthermore, inhibitors of monoamine oxidase type B (Figure 1; irreversible inhibitors—selegiline, rasagiline; reversible inhibitor—safinamide)³⁸² are also used, as they prolong and increase synaptic DA levels.³⁴⁶

To increase the dopaminergic tone in the brain, DA agonists are now therapeutically considered for management in relatively early-onset PD patients. DA agonists have much longer half-lives ($t_{1/2} = 5\text{--}7\text{ h}$) than L-DOPA ($t_{1/2} = 1\text{ h}$)^{381,383}, resulting in more persistent stimulation of DRs.⁵⁹ Furthermore, metabolites of these agents do not generate toxic free radicals.³⁸⁴ DA agonists have also been associated with neuroprotective features such as free-radical scavenging and decreased release and synthesis of DA via stimulation of presynaptic autoreceptors.^{59,385–388} The first members of this class were ergoline DA agonists (bromocriptine, cabergoline, dihydroergocryptine, lisuride and pergolide), which, however, possess affinity towards 5-HT₂Rs, especially 5-HT_{2B}Rs, resulting in pleuropulmonary and cardiac valvular fibrosis.^{59,346} Thus, currently used agents are all nonergoline DA agonists (pramipexole, ropinirole, piribedil, apomorphine, rotigotine), which lack this side effect. Pharmacological features of currently used nonergoline DA agonists, their mechanism of action, and positive results of their efficacy in the treatment of PD are summarized in Table 8.^{59,424,425}

Parkinson's disease psychosis (PDP) develops in up to 60% of PD.^{352,426–429} PDP is characterized by hallucinations, delusions, illusions, and false senses of presence.^{352,428} The etiology of PDP is thought to be multifactorial,^{352,428} and can be induced by using of dopaminergic drugs. The pathophysiology has been associated with change in cholinergic and serotonergic systems and in brain structure.^{430–432} Management of PDP is very difficult because the antipsychotics used for treatment may worsen motor function by blocking D₂Rs.⁴³³ Antipsychotic drugs such as pimavanserin, clozapine, olanzapine, and quetiapine have been used for the treatment

TABLE 8 Pharmacological features of currently used nonergoline DA agonists, with their chemical structures and positive features on their efficacy in management of PD

Drug	Pharmacological features/efficacy in management of PD
Pramipexole	<p>$K_i D_1R < 10 \mu M$; $K_i D_2R = 1.0 \mu M$ ($1.6 \mu M$); $K_i D_3R = 10 nM$; $K_i D_4R = 0.13 \mu M$; $K_i D_5R < 10 \mu M$</p> <ul style="list-style-type: none"> Safe, effective as monotherapy in early to moderate episode of PD^{389–391} Reduced motor symptoms of PD + reduced anhedonia in PD patients with depression³⁹¹ Possess antioxidant property^{392,393} Monotherapy, starting PD treatment, reduction the incidence of dyskinesia, and motor fluctuations compared to L-DOPA^{394–396} Decrease risk of dyskinesia and of wearing-off phenomena³⁹⁵ In advanced PD, reduced in UPDRS scores³⁹⁷ and a decrease in the L-DOPA dose³⁹⁸ As adjunctive therapy to L-DOPA—improved ADL scores³⁹⁹ De novo PD—compared to placebo—improvement in ADL and UPDRS scores⁴⁰⁰ Early PD—improvement of UPDRS scores⁴⁰¹ Mechanism of action: Binding to D₂, D₃, and D₄Rs, it is thought that it can stimulate dopamine activity on nerves of striatum and substantia nigra⁴⁰²
Ropinirole	<p>$K_i D_1R < 10 \mu M$; $K_i D_2R = 0.63 \mu M$ ($1 \mu M$); $K_i D_3R = 40 \mu M$; $K_i D_4R = 0.79 \mu M$; $K_i D_5 < 10 \mu M$</p> <ul style="list-style-type: none"> Efficacy in early and advanced PD^{403–405} Effective as adjunct therapy⁴⁰⁶ Monotherapy, effective^{407–409} Monotherapy, early PD, lower risk of dyskinesia and “off time”⁴¹⁰ Monotherapy, early PD, lower risk for dyskinesia than L-DOPA⁴⁰⁴ Advanced PD, reduced dose of L-DOPA⁴¹¹ Advanced PD—reduced “off time,” increased “on time” and “on time” without dyskinesia and better scores on depression⁴¹² Reduction in L-DOPA dose and “time off”⁴¹³ Mechanism of action: High relative in vitro specificity and full intrinsic activity at D₂ and D₃Rs, binding with higher affinity to D₃ than to D₂ and D₄ receptors. Although precise mechanism of action is still unknown, it is believed that it stimulates of postsynaptic D₂-type receptors in caudate putamen.⁴⁰²
Rotigotine	<p>$K_i D_1R = 79 nM$; $K_i D_2R = 13 nM$; $K_i D_3R = 0.6 nM$; $K_i D_4R = 4.0 nM$ ($15 nM$, $6.3 nM$); $K_i D_5R = 5.0 nM$</p> <ul style="list-style-type: none"> Safe and effective in early PD⁴¹⁴ Monotherapy, early PD, reduction in UPDRS score^{415,416} Advanced PD, decrease in UPDRS score + “off time”⁴¹⁷ Add-on to L-DOPA, advanced PD, reduction “off time”⁴¹⁸ Significantly improvement of sleep quality⁴¹⁹ Mechanism of action: Specificity for D₃ and D₂ receptors. The precise mechanism of action is still unknown, it is believed that this DA agonist stimulates postsynaptic D₂-type autoreceptors within substantia nigra leading to improved dopaminergic transmission in motor areas in basal ganglia, notably caudate nucleus/putamen regions.⁴⁰²

(Continues)

TABLE 8 (Continued)

Drug	Pharmacological features/efficacy in management of PD
Piribedil	<p>$K_i D_1R < 10 \mu M$; $K_i D_2R = 0.13 \mu M$ ($0.16 \mu M$); $K_i D_3R = 0.25 \mu M$; $K_i D_4R = 0.32 \mu M$; $K_i D_5R < 10 \mu M$</p> <ul style="list-style-type: none"> • Add-on to L-DOPA, improvement in motor symptoms^{420,421} • Monotherapy, early stage PD, effective in motor symptoms⁴²² • <i>Mechanism of action:</i> It selectively and directly stimulates D_1Rs and postsynaptic D_2Rs in the nigrostriatal pathway and D_3Rs receptor in the limbic pathway⁴²¹
Apomorphine	<p>$K_i D_1R = 0.4 \mu M$; $K_i D_2R = 32 nM$ ($79 nM$); $K_i D_3R = 25 nM$;</p> <p>$K_i D_4R = 4.0 nM$; $K_i D_5R = 16 nM$</p> <ul style="list-style-type: none"> • Reduce “off time,” improvement in motor deficits and suppression of dyskinesia⁴²³ • <i>Mechanism of action:</i> It stimulates postsynaptic D_2-type receptors within the caudate putamen⁴⁰²

Note: Values of D_2R refers to D_{2S} and D_{2L} . Data by apomorphine are recorded after subcutaneous administration. The K_i value of rotigotine for D_4R refers to $D_{4.2}$, $D_{4.4}$, and $D_{4.7}$.

Abbreviations: ADL, the activities of daily living; UPDRS, United Parkinson's Disease Rating Scale.

of PDP,⁴²⁹ but pimavanserin is the first and only US FDA-approved medication for the treatment of hallucinations and delusions associated with PDP, which do not exacerbate motor dysfunction.³⁵² It is a 5-HT_{2A}R inverse agonist and antagonist with affinity for 5-HT_{2C}R and no meaningful activity on any other GPCR.^{434,435} Clozapine, in contrast to quetiapine and olanzapine, demonstrated superiority over placebo trials in reducing psychotic symptoms, and did not exacerbate motor function issues.^{429,436}

2 | MEDICINAL CHEMISTRY PART

As discussed in the introduction, the vast majority of articles dealing with D_2Rs and their ligands have addressed the management of (i) PD, (ii) depression, (iii) schizophrenia, (iv) anxiety, or these articles were focused on the development of (v) selective D_2R ligands, (vi) biased ligands, and (vii) bivalent ligands. We also discussed basic information about D_2R and its role in the diseases mentioned above. In the next chapter, we go into more detail about biased agonism, multivalent ligands, selectivity within D_2 -like receptors, and multitarget drugs. In the case of selectivity for D_2Rs and biased agonism, the studies found to identify the structural fragments responsible for the above properties will also be commented.

2.1 | Selectivity for D_2R within D_2 -like family receptors

D_2 -like receptors share a $G_{a_i/o}$ -coupled mechanism but differ substantially in localization within the human brain, and thus they have various functions (see Table 2). However, there is a high degree of amino acid homology within this receptor's family, namely D_3 and D_4 receptors share 75% and 53% homology, respectively, with the D_2 receptors⁴³⁷ and furthermore, the nearly identical orthosteric binding site for D_2 and D_3Rs .^{65,438–440} Hence, the discovery of novel selective compounds in this subgroup of receptors is still a great challenge in the field of

medicinal chemistry. As we discussed above, D₂Rs are associated especially in the pathophysiology of schizophrenia, PD, MDD and anxiety disorders. On the other hand, altered D₃R signaling is linked with PD, substance use disorder, depression, schizophrenia, and restless leg syndrome.^{441–450} Furthermore, activation of D₄Rs may be useful for the management of cognitive deficits in schizophrenia^{451–454} and attention-deficit hyperactivity disorder.^{454,455} On the other hand, D₄R antagonistic properties may be used for the treatment of substance use disorders and L-DOPA-induced dyskinesias.^{59,454,456–462} Given abundant evidence, some scientific groups have sought to create selective D₂R,^{463,464} D₃R,^{465–485} or D₄R^{456,486–488} ligands, which can be useful tools to probe the roles of D₂-like receptor subtypes in vivo and could potentially lead to new pharmacotherapeutics for the management of a variety of disorders. For better traceability of ligand selectivity, we would like to introduce a so-called selectivity factor. Ligand showing selectivity higher than 2–10 to one receptor compared to the other, we will use the designation of preference ligands, selectivity in the range 10–100 will be referred to as a moderate selectivity, and selectivity exceeding a factor of 100 will be assigned for highly selective ligands.

Following part of the review will be concentrated to determination of structural fragments responsible for D₂Rs selectivity.

Novel analogs of (R)-5-(methylamino)-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-2(1H)-one (sumanirole, **1**, Figure 7) provided clue to D₂R agonistic selectivity over D₃Rs.⁴⁸⁹ On the ground of molecular modeling and simulation data, **1** and the derivatives described in this seminal article activated D₂ and D₃ receptors in an akin way. However, amino acid sequence variations between these receptors in two regions, extracellular loop 2 (EL2) and N-terminal segment of transmembrane 5 (TM5), may manage the receptor subtype selectivity of **1** and the analogs prepared in this study.⁴⁸⁹ Compounds **1** exhibited agonistic properties for D₂ and D₃ receptors with preference for D₂Rs.

An extensive chemical/stereochemical SAR study investigated and highlighted the importance of chirality and composition in the linkers for bitopic ligands based on **1** (Figure 7).⁴⁹⁰ It was found that a relative *trans* stereochemistry in the central linker between sumanirole moiety and indole core (representative derivative **2**, moderate selective D₂R agonist, Figure 7) retains high binding mode at D₂R while providing selectivity for D₂R. Furthermore, it was shown for the first time how inversion in the cycloprop-1,2-diyl linker stereochemistry could modulate D₂ (**3a**, moderately selective D₂R agonist, Figure 7) or D₃ (**3b**, preferential D₃R agonist, Figure 7) receptor preferential binding in a diastereospecific way, independently from the lipophilic appendage (Figure 12). In the computational studies, the authors identified an area of nonconservation amino acid sequence in the EL2 region of D₂ and D₃ receptors, which may dictate the subtype selectivity.⁴⁹⁰

1-[2-(2-Fluoroethoxy)phenyl]piperazine derivatives (**4**, **4a–b**, Figure 7) were chosen to understand why adding different moieties like 4-(thiophen-3-yl)benzamide (in **4a**) versus 3,4-dihydro-2(1H)-quinolinone (in **4b**) to the short ligand **4** modulates their selectivity for D₃ or D₂ receptors.⁴⁹¹ In cumulative simulations, there were various hydration patterns in the second binding site in D₂ or D₃ receptors. Furthermore, long-chained derivatives (**4a–b**) interact with amino-acid residues in EL1 and EL2. More specifically, the amino acid residue Trp in EL1 (Trp^{EL1}) was observed to be more flexible in D₂ than in D₃ receptors. On the other hand, EL2 was observed to be more exposed to the binding pocket in D₃ compared to D₂ receptors. Molecular mechanics Poisson–Boltzmann surface area calculations indicated that Trp^{EL1} contributes more to the binding energies of **4a–b** in D₂ compared to D₃ receptors, while Lys^{EL2} in EL2 exhibited an undesirable impact on binding energies in D₂Rs.⁴⁹¹

Between the years 2010–2022, a large number of studies were reported describing the identification of fragments responsible for selectivity for D₃Rs.^{467,492–500} However, these receptors do not represent primary focus of this review and will therefore not be commented.

2.2 | Biased agonism or functional selectivity

Biased agonism and functional selectivity (Figure 8) can be considered synonyms and, therefore can be used interchangeably.^{501–506} These concepts are defined as the ability of a ligand to preferentially activate a specific

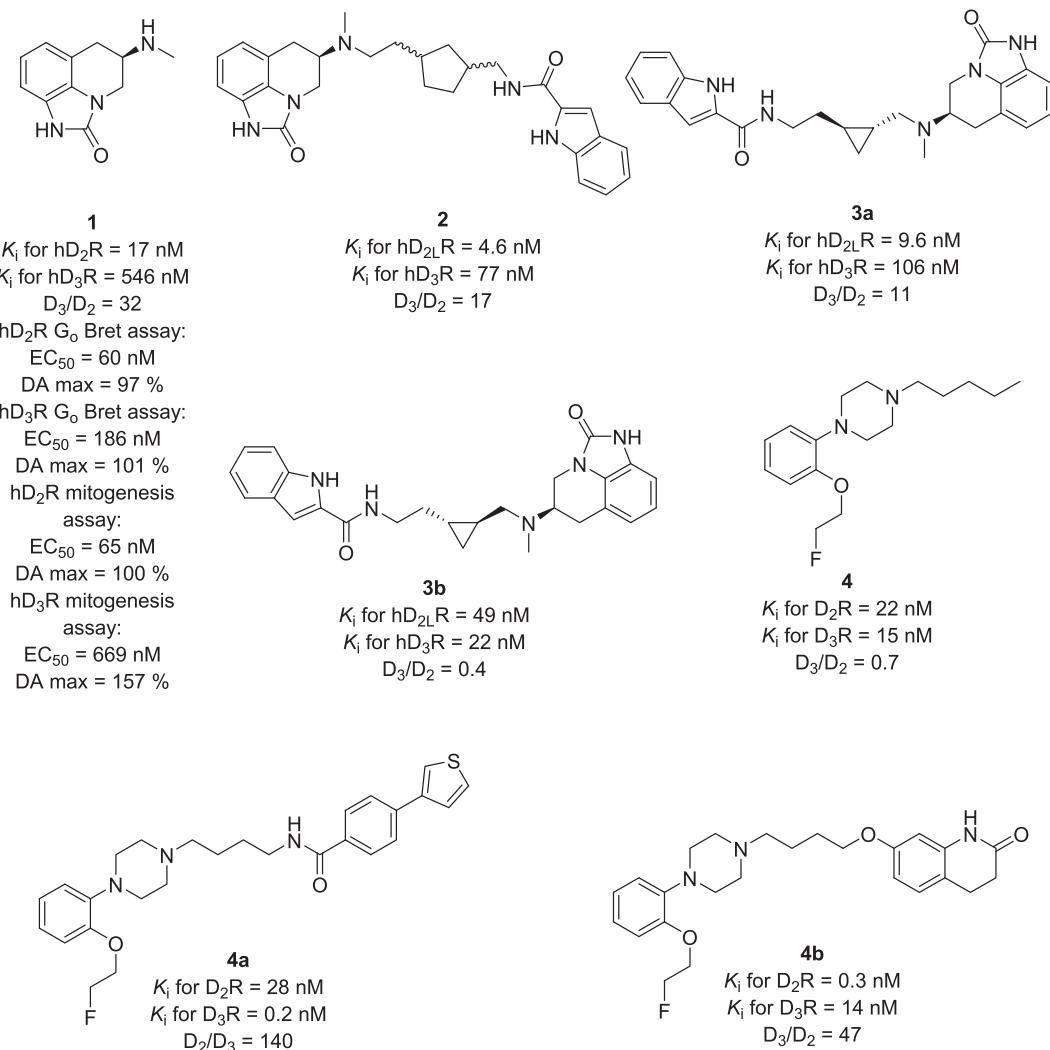


FIGURE 7 Schematic representations of ligands 1, 2, 3a–b, 4, and 4a–b delineating structural fragments responsible for selectivity for D₂Rs. [Color figure can be viewed at wileyonlinelibrary.com]

signaling pathway over another after binding to the receptor, thereby stabilizing the various conformations of the GPCR.^{501,507–511} The advantage of drugs with biased agonism/functional selectivity is the notion that they can selectively activate therapeutically relevant signaling pathways while avoiding those that contribute to unwanted side effects.^{501,507,508}

It was demonstrated that the mutation of His393^{6,55} to Ala led to an increase in affinity of 1,4-disubstituted phenylpiperazines to the dopamine D_{2L}R.⁵¹² This alteration was most likely caused by the reduced steric hindrance in this area of the binding site. In an ongoing study, the role of the steric hindrance imposed by the residue His393^{6,55} was investigated for the receptor activation modulated by 1,4-disubstituted aromatic piperidines or piperazines (1,4-DAPs).⁵¹³ Modifications of derivatives and site-directed mutagenesis of D₂Rs were used to inspect the structural basis of ligand efficacy. The operational model of agonism was used to quantify the functional selectivity of derivatives between its ability to inhibit cAMP accumulation and induce ERK1/2 phosphorylation. Whereas substantial ligand-biased signaling was observed for the D_{2L} wild-type receptor, an overall increase in

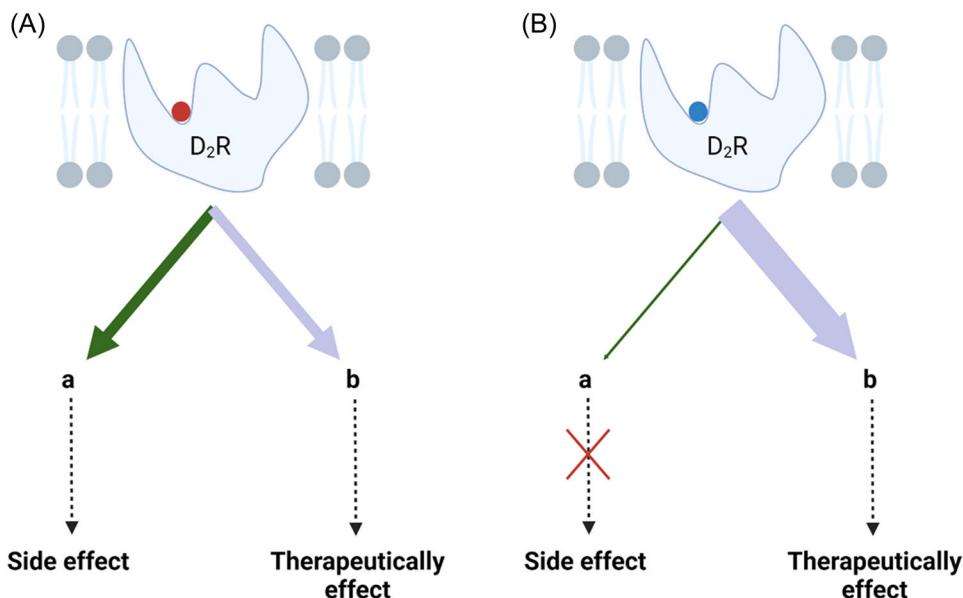


FIGURE 8 Schematic representation of biased agonism: (A) classical no-biased agonist; (B) biased agonist. [Color figure can be viewed at wileyonlinelibrary.com]

agonistic properties was observed for the D_{2L} His393^{6,55}Ala mutant without remarkable functional selectivity.⁵¹³ Chemical substitutions of the phenyl moiety connected with piperazine resulted in the functionally selective ligand FAUC350 (5, Figure 9). Compound 5 showed partial agonistic properties in the stimulation of ERK1/2 phosphorylation (efficacy = 55%) and antagonistic properties in the inhibition of cAMP accumulation. Overall, His393^{6,55} was found a crucial determinant of ligand-biased signaling in D₂Rs.⁵¹³

The small family of triazolylalkoxybenzene compounds designed from previous studies,^{477,514,515} was used to find molecular determinants of biased agonism at the D₂Rs.⁵¹⁶ Heterocyclic dopamine bioisostere 5-hydroxy substituted aminotetraline fragment was used as an aromatic head (Figure 12), resulting in the final compounds (S)-6 and (R)-6 (Figure 9).⁵¹⁷ The strong influence of the stereochemistry of aminotetraline derivatives on functional selectivity at D₂Rs was observed. Whereas (S)-6 behaved as a full agonist with no functional selectivity, the biased agonist (R)-6 induced substantial β-arrestin2 recruitment at D₂Rs. Molecular docking simulations indicated that the nature of the head group (in this case aminotetraline fragment) might allosterically influence the conformation of the lipophilic appendage, thus affecting the overall binding mode of the ligand.⁵¹⁶ The lipophilic core of the D₂R agonist (S)-6 was found to occupy a topologically distinct receptor domain compared to (R)-6 in molecular docking simulations.

2.3 | Multivalent ligands: Bitopic and bivalent ligands

Multivalent ligands are defined as molecules that can occupy more than one binding site simultaneously. There are two basic groups of such ligands (Figure 10)⁵⁰⁸:

- (1) Bitopic ligands
- (2) Bivalent ligands—bind the orthosteric sites of two separate receptors

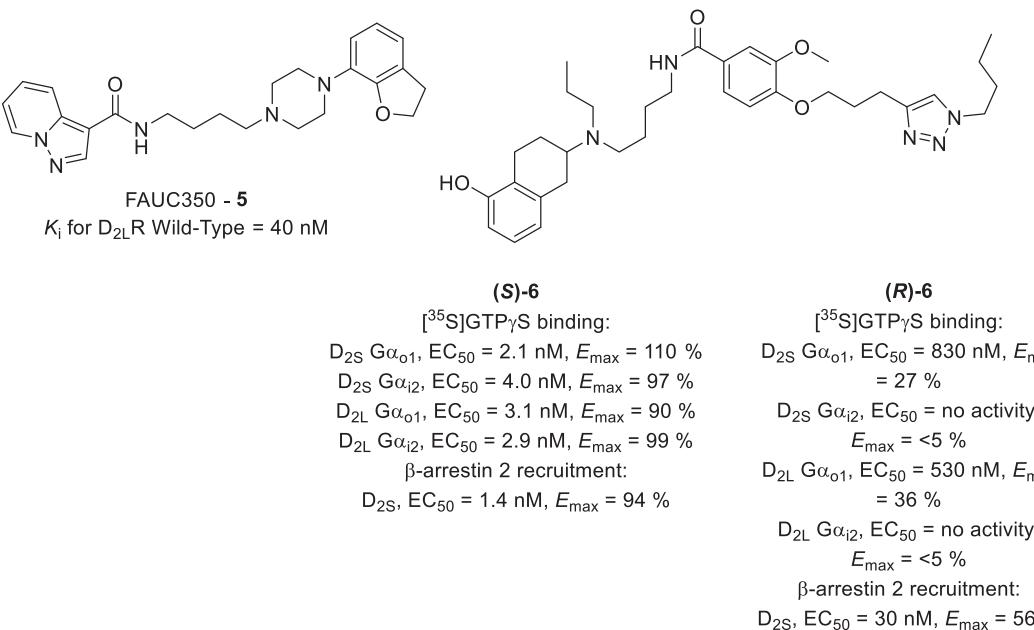


FIGURE 9 Schematic representations of D₂ ligands 5, (S)-6 and (R)-6 with the aim of investigating molecular fragments responsible for biased agonism.

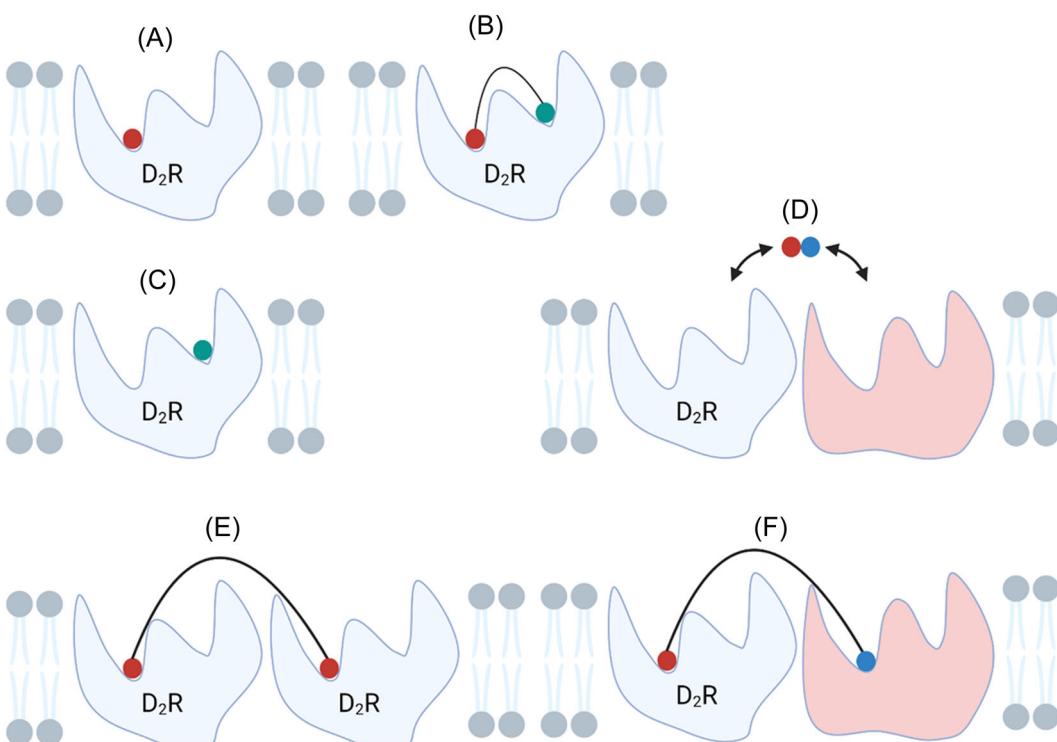


FIGURE 10 Schematic representation of binding mode of D₂R ligands: (A) ligand targets orthosteric binding site; (B) bitopic ligand targets both orthosteric and allosteric binding sites; (C) ligand targets allosteric binding site; (D) dual-target ligand; (E) homobivalent ligand; (F) heterobivalent ligand. [Color figure can be viewed at wileyonlinelibrary.com]

2.3.1 | Bitopic ligands

A bitopic ligand can be classified as a chemical structure possessing both an allosteric and orthosteric pharmacophore connected via an optimal linker, which allows the simultaneous binding of two various binding sites within a single receptor.^{508,518–520} These ligands have some advantages as they may provide improvements in receptor affinity compared to classical orthosteric-targeting molecules; may enhance receptor selectivity; may possess bias agonism, and do not require the endogenous ligand to induce biological effect compared to allosteric-targeting ligands.⁵⁰⁸ The first negative allosteric modulator for dopamine D₂ and D₃ receptors was SB269652 acting as bitopic ligand.^{521–523}

For D₂R, the orthosteric binding site or ligand-binding site was covered by the C-terminal segment of the extracellular loop 2, which is stabilized by a disulfide bond between Cys107^{3,25} on transmembrane helix 3 and Cys182^{42,50} on extracellular loop 2.^{70,524} Endogenous ligand (DA) and phenylpiperazines bind this binding site.^{471,489,491,508,525–527} The binding of these ligands is stabilized by a salt bridge between Asp114^{3,32} in transmembrane helix 3 and the protonated nitrogen on the piperazine ring or aliphatic amine in DA molecule.^{70,471,525,526,528} On the other hand, the allosteric binding site (also referred as a secondary binding site) is the area where moiety (in most cases, aromatic/heteroaromatic lipophilic fragment), connected via the optimal central linker with arylpiperazines, binds.^{491,529,530} However, as discussed above, this review does not address pure allosteric ligands. For more information on allosteric ligands, we refer readers to a review by Fasciani et al.⁵³¹

2.3.2 | Bivalent ligands

Bivalent ligands are modulators bearing two pharmacophores tethered covalently by an appropriate spacer and target the orthosteric sites of two separate receptors.^{9,508,532} These ligands are required to bear the following parts, (i) a pharmacophore that binds the receptor-binding site and has a suitable attachment point for either the spacer or linker, (ii) a linker that does not reduce the ligand's receptor affinity and exhibits a suitable degree of aqueous solubility, and (iii) a spacer that is of suitable length which links the two pharmacophores and can bridge the gap between two receptors.^{508,532} However, achieving all these structural factors typically result in derivatives with poor solubility profile, high molecular weight, and extreme lipophilicity, making them undesirable for use in a clinical setting. Despite this fact, bivalent ligands may be used as probes for determining the presence and function of homo- and hetero-dimers of the D₂R and other receptors in native tissues.^{508,533} There are two main classes of bivalent modulators based on their pharmacophores, namely homobivalent, which contain two identical pharmacophores, and heterobivalent, which contain two different pharmacophores.¹⁰

D₂R can exist in homomeric^{534–537} and heteromeric^{538,539} complexes. In addition, homodimers of D₂Rs might represent an interesting target in the management of schizophrenia.⁵⁴⁰ Therefore, some scientific groups have developed bivalent ligands targeting D₂Rs that are discussed below.

A Hill slope value of less than one is considered to reflect negative cooperativity or the poor ability of a ligand to bind to pre-coupled GPCRs with a higher affinity than uncoupled receptors.⁵⁴¹ Agonists often show Hill slopes between 0.5 and 0.7, and antagonists tend to have Hill slope values close to one.⁵⁴¹ On the other hand, bivalent ligands binding dimerized complex of proteins display Hill slope values higher than 1.5.⁵⁴¹

2.4 | Multitarget drugs

In addition to the above-mentioned multivalent ligands, a large number of so-called multitarget drugs have been developed in the last 12 years. Since the Lock and Key model proposed by E. Fischer in 1894,⁵⁴² drug development

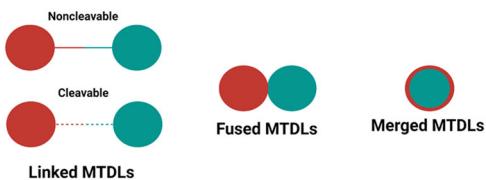


FIGURE 11 Schematic illustration of the degree of integration between two pharmacophores in MTDLs. MTDLs, multitarget-directed ligands. [Color figure can be viewed at wileyonlinelibrary.com]

has focused primarily on the development of selective molecules that acts at only one disease mechanism, the so-called “one drug, one target” approach.⁵⁴³ However, complex diseases such as, for example, schizophrenia involve multiple disrupted signalling pathways and/or target proteins, and action on a single target is therefore not sufficient to achieve satisfactory therapeutic effects.^{4,544,545} Therefore, there is a trend to develop multitarget-directed ligands (MTDLs) that are able to manipulate multiple targets simultaneously to increase efficiency of drugs.⁵⁴⁶

There are three approaches to multitarget drugs utilized in clinical practice^{546–549}: (i) the first is multiple-medication therapy, also referred to as drug cocktails; (ii) the second approach is multicompound medication, also known as single-pill drug combinations; (iii) and the third approach is MTDLs, by which one active drug has multiple biological activities and therefore modulating multiple targets simultaneously. The third approach has many advantages over the first two, for example, administration of a single entity with different mechanisms of action is not endowed with different bioavailability and pharmacokinetics like in the case of combination therapy.⁵⁴⁸ The pharmacophore-based approach is one of the main methods used to generate MTDLs,⁵⁵⁰ and based on the degree of integration between pharmacophores, MTDLs can be categorized as linked, fused or merged (Figure 11).^{546,547,551}

2.5 | 1,4-Disubstituted aromatic/heteroaromatic cyclic amine derivatives targeting dopamine D₂Rs—their structure, function, and pharmacological profiles

Various mathematical algorithms based on the analysis of physicochemical properties of drugs have been proposed to predict their ability to cross the BBB.^{552–564} We will use the algorithm invented by Gupta et al.⁵⁵² to calculate so-called BBB score for selected D₂R modulators to predict whether these derivatives can permeate through the BBB. This algorithm was chosen because it has a high predictive value confirmed in several in vivo studies.^{565,566} According to this algorithm, if the ligand has a BBB score ranging between 4 and 5, it has a 54.5% probability of crossing the BBB. The score between 5 and 6 resulted a 90.3% probability. In this review, we exploited the software MarvinSketch (<http://www.chemaxon.com>; v. 18.24.0) to calculate the required physico-chemical properties.

Many of the most potent and widely used neuroleptics belong to the group of 1,4-DAPs. As listed in Table 3 and shown in Figure 6, this group is well recognized because it binds not only to DRs, but also to other monoamine GPCRs, especially 5-HTRs. The classic template scaffold with D₂R affinity is depicted in Figure 12. The biological activity of 1,4-DAPs is encoded by an aromatic head, which controls intrinsic activity, and an amine moiety, which is responsible for the formation of a hydrogen bond to the crucial residue Asp^{3,32} in the transmembrane helix 3 of D₂R.⁵²⁸ A linker controls subtype selectivity; namely, 4-methylene-, E-olefin- and lactam-containing tethers are mostly associated with D₃R selectivity,^{66,567–572} 3-methylene linker was found suitable for D₂R selectivity,^{512,567} and short chains, like one methylene group, enhance D₄R affinity.^{528,573–578} Lipophilic appendage on the opposite side of the ligand orchestrates receptor affinity. Herewith, we will discuss the structural features of a large family of ligands with D₂R affinity, containing most often piperazine, homopiperazine, piperidine, and tropane moieties. These cyclic amines are generally directly attached to the aromatic head. At the second tail of the specific D₂R

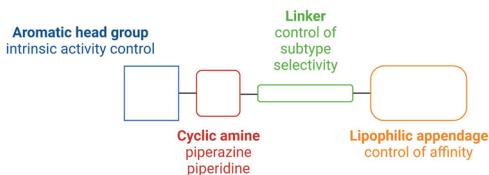


FIGURE 12 Representative structure of D₂Rs ligands belonging to 1,4-DAPs family. [Color figure can be viewed at wileyonlinelibrary.com]

ligands, the lipophilic appendage is usually connected to the central linker via an ether bond. At the forefront of this large chapter, we analyze the structural similarities and differences of the aromatic heads of D₂R modulators. We also focus on the suitability of various lipophilic appendages of D₂R analogs. At the beginning of each subchapter, we provide SAR analysis highlighting some ligand representatives. Subsequently, we discuss the top-ranked compounds selected for in vivo testing for their functional activities on the targeted receptors.

From the structural perspective, the medicinal chemistry part of this review is subdivided according to (i) main structural features of the particular family of compounds, or (ii) the highlighted structural leads that were selected for additional testing, for instance, through in vivo experiments with animal models for the specific disease.

2.5.1 | Various aromatic heads connected to cyclic amines as D₂R modulators

2.5.1.1 | 4-(2,3-Dichlorophenyl)-1-substituted piperazines as D₂R modulators

4-(2,3-Dichlorophenyl)-1-piperazine is a motif that can be found in the structures of FDA-approved drugs, namely aripiprazole (**7**) and cariprazine (**8**) (Table 3; Figure 6). These drugs belong to the third-generation antipsychotics.⁴ Additionally, **8** is indicated for the management of acute manic or mixed episodes associated with bipolar I disorder as monotherapy only.⁵⁷⁹ The FDA has approved the use of **7** as an adjunctive medication in the management of depressive disorders²³⁹ and bipolar I disorder.^{580–582} Thus, the templates of **7** and **8** are extensively pursued in the search of new analogs with D₂R affinity.

It can be deduced the central linker has a moderate impact on affinity at D₂Rs. Examples of compounds that have high D₂R affinity are **9a**⁴⁶⁶ and **10b**⁵⁸³ (Figure 13), which have a total of 6 atoms in the central linker. Shortening or lengthening of the central linker leads to a decrease in D₂R affinity (e.g., **9a** compared to **9b**⁴⁶⁶ or **10b** compared to **10a** and **10c**⁵⁸³) (Figure 13). In addition to the affinity, the modifications within the central linker strongly affect both functional and subtype selectivity. One study showed that the incorporation of a fluorine atom to the central linker led to the preparation of **11** (Figure 13) with high selectivity for D₃Rs over D₂Rs.⁴⁹² Compounds **12a** and **12b** with aromatic ring in the center of the linker (Figure 13) exhibited biased behavior for noncanonical D₂R signaling and were inactive in cAMP signaling.⁵⁸⁴

Besides additions to various substitutions within the central linker, a broad family of 4-(2,3-dichlorophenyl)-1-piperazine ligands with various lipophilic fragments have been developed. It has been shown that lipophilic moieties strongly influence functional and subtype selectivity. D₂R modulation by compounds bearing a lipophilic 3,4-dihydroisoquinolin-1(2H)-one (**13**,⁵⁸⁴ Figure 14) fragment revealed β-arrestin-biased behavior compared to **7**. Another example of lipophilic fragment-containing ligands with D₂R functional activity are derivatives **14a** (2-methylbenzo[d]thiazole moiety) and **14b** (N-methylbenzo[d]thiazol-2-amine, Figure 14).⁵⁸⁵ Compound **14a** exhibited no biased behavior for canonical and noncanonical D₂R signaling, and **14b** was observed as a biased canonical D₂R modulator. 3'-Carbamoyl-[1,1'-biphenyl]-3-yl carbamate (**15a**, Figure 14) exhibited a decrease in D₂R affinity and an increase in selectivity for D₃Rs, compared to its structural isomer **15aa** (4'-carbamoyl-[1,1'-biphenyl]-4-yl carbamate, Figure 14).⁵⁸⁶

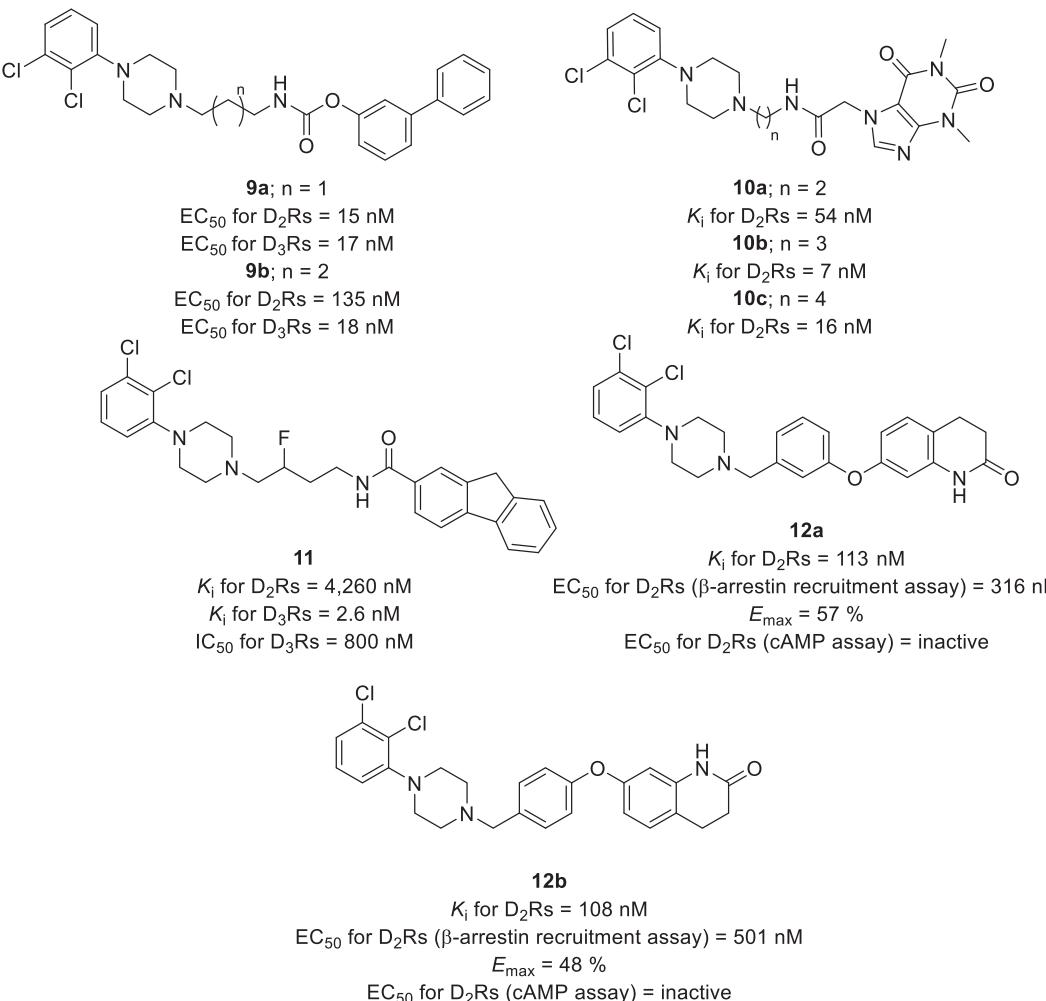


FIGURE 13 Chemical structures of representative endowed with 4-(2,3-dichlorophenyl)-1-piperazine moiety: **9a–b**, **10a–c**, **11**, and **12a–b** with various central linkers.

New selective β -arrestin-biased D₂R agonists **16a–c** (Table 9) based on **7** have been developed.⁵⁸⁴ Benzo[d]thiazole (**16a**), 1H-indazole (**16b**), and 3,4-dihydroisoquinolin-1(2H)-one (**16c**) were used to explain the role of G protein-independent D₂R cascade signaling in neuropsychiatric illnesses like schizophrenia.⁵⁸⁴ As a continuation of previous work, a new selective G protein-biased (Gi/o) D₂R partial agonist, **14b** (Figure 14, Table 9), has been developed.⁵⁸⁵ Compound **14b** exhibited partial agonism for Gi/o signaling towards D₂R, high affinity towards D₃R, 5-HT_{1A}, 5-HT_{2B}, 5-HT_{2C}, and H₁ receptors ($K_i < 100$ nM), and moderate affinity for D₄Rs, 5-HT_{1D}, 5-HT₃, 5-HT₆, 5-HT₇, and H₂ receptors and SERT ($K_i \leq 450$ nM). The unique bias profile of **14b** makes it a potentially useful chemical compound for elucidating the role of G protein-dependent D₂R signaling under both physiological and pathological conditions.⁵⁸⁵ In summary, tiny modifications like variation in the central linker length, heteroatom location in the benzothiazole ring, and incorporation of small electron-donating group (EDG) in lipophilic fragment can be used to develop compounds with completely inverted properties, for example **14b** (biased for canonical D₂R signaling) versus **16a** (biased for noncanonical D₂R; Table 9).

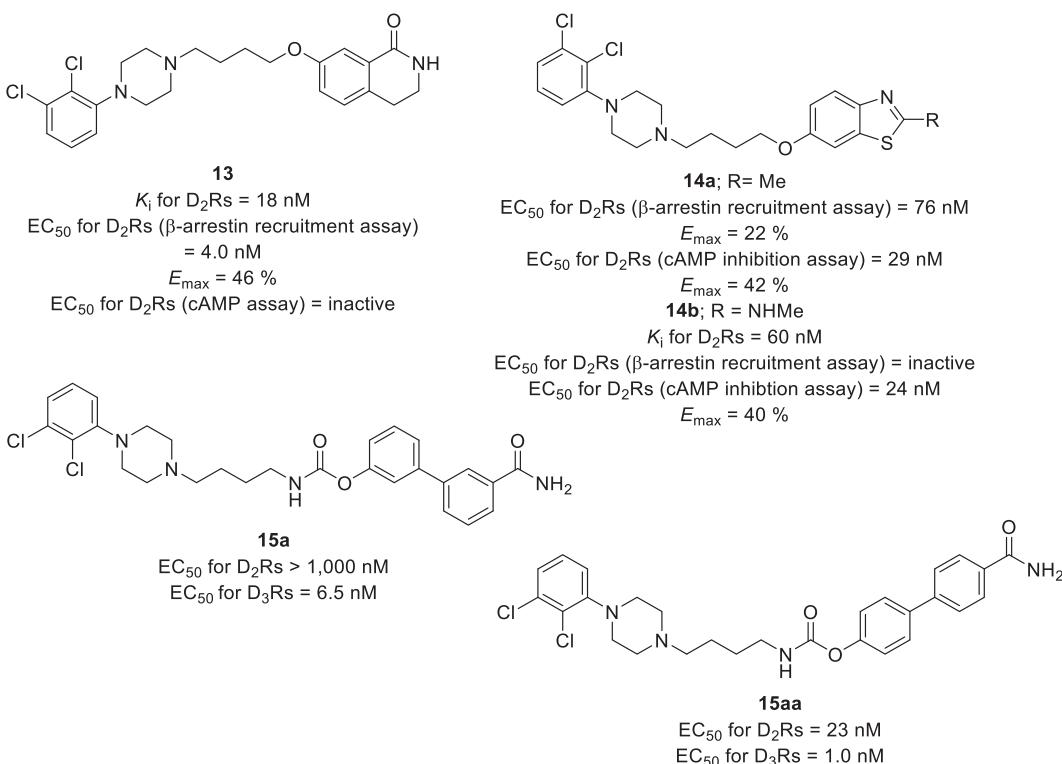


FIGURE 14 Representative chemical structures bearing 4-(2,3-dichlorophenyl)-1-piperazine moiety: **13**, **14a–b**, **15a**, and **15aa**, with different lipophilic appendages.

The pyrazolo[1,5-*a*]pyridine analogs **17a** and **17b** (Figure 15), derived from the template of **7** and compounds from an early patent,⁵⁸⁷ have also been examined.⁵⁸⁸ Compound **17a** exhibited a high affinity for D₂ and D₃Rs and moderate affinity for D₄, 5-HT_{1A} and α₁Rs (Table 9). Meanwhile, **17b** revealed a high affinity for D₂, D₃, D₄, 5-HT_{1A}, 5-HT_{2A}, and pα₁Rs (Table 9). Functional assay with [³⁵S]GTPyS binding and inhibition of β-arrestin-2 recruitment consistently demonstrated that both **17a** and **17b** showed partial agonism for D_{2s}R G-protein activation, and antagonism for the recruitment of β-arrestin-2 at D_{2s}Rs (Table 9). However, **17a** preferentially activated coupling of Gα_{o1} at D₃Rs with a 100-fold selectivity over coupling Gα_{o1} at D_{2s}Rs (Table 9). On the other hand, **17b** promoted Gα_{o1} coupling at D_{2s}Rs with a 30-fold selectivity over Gα_{o1} coupling at the D₃Rs (Table 9). Furthermore, **17a** treatment (3 mg/kg, i.p.) showed a significant influence on auditory startle response in mice, indicating an effect on CNS activity.⁵⁸⁸

A tailored virtual library with almost 13,000 compounds bearing 4-(2,3-dichlorophenyl)-1-piperazine fragments, connected to various chemical fragments via a linker, was docked to the D₂R model.⁵⁸⁹ Eighteen top-ranked ligands were prepared, leading to the discovery of compound **18** (Table 9). Compound **18** activated β-arrestin-2 recruitment but showed no detectable stimulation of G protein signaling (Table 9).⁵⁸⁹

Ágai-Csongor et al.⁵⁹⁰ described a series of compounds bearing a cyclohexyl moiety in the linker attached to 2,3-dichlorophenylpiperazine, leading to the discovery of **8**. These derivatives were based on 3-pyridylsulfonamide analog **19** (Figure 16), which exhibited high affinity for D₂/D₃Rs and significant antipsychotic efficacy, coupled with a beneficial cognitive and extrapyramidal side-effect profile.^{591–593} During the resynthesis of **19**, the persistent impurity **19a** was detected and subsequently isolated and tested. Although **19a** exhibited decreased affinity for D₂/D₃Rs, it was about 10 times more active in vivo than **19** (Figure 16).⁵⁹⁰ Thus, the study predicted that small amide

TABLE 9 Top-ranked compounds with 4-(2,3-dichlorophenyl)-1-piperazine scaffold: **14b**, **16a-c**, **17a-b**, and **18**, with their properties and chemical structures

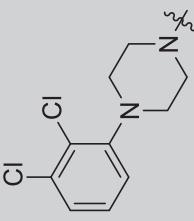
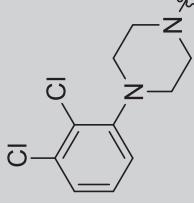
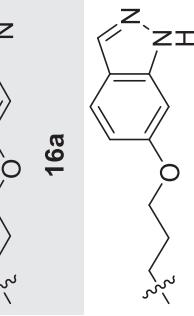
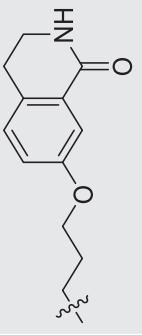
Chemical structures	Binding affinities	Functional activities	BBB score ^a	Behavioral test
	<p>K_i for D₂Rs = 60 nM</p> <p>K_i for D₃Rs = 35 nM</p> <p>K_i for D₄Rs = 280 nM</p> <p>K_i for 5-HT_{1A}Rs = 55 nM</p> <p>K_i for 5-HT_{1D}Rs = 390 nM</p> <p>K_i for 5-HT_{2B}Rs = 12 nM</p> <p>K_i for 5-HT_{2C}Rs = 58 nM</p> <p>K_i for 5-HT₃Rs = 330 nM</p> <p>K_i for 5-HT₆Rs = 350 nM</p> <p>K_i for 5-HT₇Rs = 100 nM</p> <p>K_i for SERT = 450 nM</p> <p>K_i for H₁Rs = 56 nM</p> <p>K_i for H₂Rs = 310 nM</p>	<p>EC₅₀ for D₂Rs (β-arrestin recruitment assay) = inactive</p> <p>EC₅₀ for D₂Rs (cAMP inhibition assay) = 24 nM</p> <p>E_{max} = 40%</p>	4.67	-

TABLE 9 (Continued)

Chemical structures	Binding affinities	Functional activities	BBB score ^a	Behavioral test
	K_i for D ₂ Rs = 30 nM	EC ₅₀ for D ₂ Rs (β -arrestin recruitment assay) = 126 nM E_{max} = 88%	5.06	-
	K_i for D ₂ Rs = 104 nM	EC ₅₀ for D ₂ Rs (β -arrestin recruitment assay) = 200 nM E_{max} = 78%	4.78	-
	K_i for D ₂ Rs = 18 nM	EC ₅₀ for D ₂ Rs (β -arrestin recruitment assay) = 20 nM E_{max} = 84%	4.72	-

(Continues)

TABLE 9 (Continued)

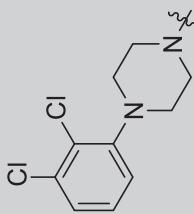
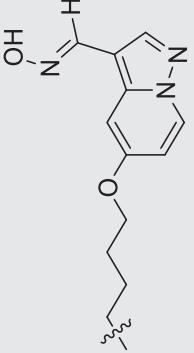
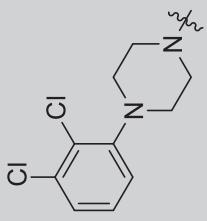
Chemical structures	Binding affinities	Functional activities	BBB score ^a	Behavioral test
	K_i for $D_{2L}Rs = 4.6 \text{ nM}$ K_i for $D_{2S}Rs = 3.2 \text{ nM}$ K_i for $D_3Rs = 6.9 \text{ nM}$ K_i for $D_4Rs = 57 \text{ nM}$ K_i for $5-HT_{1A}Rs = 95 \text{ nM}$ K_i for $5-HT_{2A}Rs = 240 \text{ nM}$ K_i for $\alpha_1Rs = 18 \text{ nM}$	EC_{50} for $D_{2S}RsG\alpha_{o1} = 190 \text{ nM}$ $E_{max} = 64\%$ EC_{50} for $D_{2S}RsG\alpha_{i2} = 650 \text{ nM}$ $E_{max} = 27\%$ EC_{50} for $D_3RsG\alpha_{o1} = 1.9 \text{ nM}$ $E_{max} = 79\%$ IC_{50} for $D_2Rs (\beta\text{-arrestin-2 recruitment assay}) = 360 \text{ nM}$	4.65	17a (3 mg/kg, i.p.) significant influence on auditory startle response
	K_i for $D_{2L}Rs = 0.2 \text{ nM}$ K_i for $D_{2S}Rs = 0.3 \text{ nM}$ K_i for $D_3Rs = 0.7 \text{ nM}$ K_i for $D_4Rs = 6.0 \text{ nM}$ K_i for $5-HT_{1A}Rs = 4.2 \text{ nM}$ K_i for $5-HT_{2A}Rs = 4.0 \text{ nM}$ K_i for $\alpha_1Rs = 6.6 \text{ nM}$	EC_{50} for $D_{2S}RsG\alpha_{o1} = 1.3 \text{ nM}$ $E_{max} = 65\%$ EC_{50} for $D_{2S}RsG\alpha_{i2} = 240 \text{ nM}$ $E_{max} = 27\%$ EC_{50} for $D_3RsG\alpha_{o1} = 39 \text{ nM}$ $E_{max} = 68\%$ IC_{50} for $D_2Rs (\beta\text{-arrestin-2 recruitment assay}) = 3.8 \text{ nM}$	4.06	-

TABLE 9 (Continued)

Chemical structures	Binding affinities	Functional activities	BBB score ^a	Behavioral test
	Et -	D _{2S} [³⁵ S]GTPyS: inactive EC ₅₀ for D _{2S} R _s (β -arrestin-2 recruitment assay) = 320 nM	5.15	-

^aThe calculations were realized according to the reference.⁵²**18** $E_{max} = 16\%$

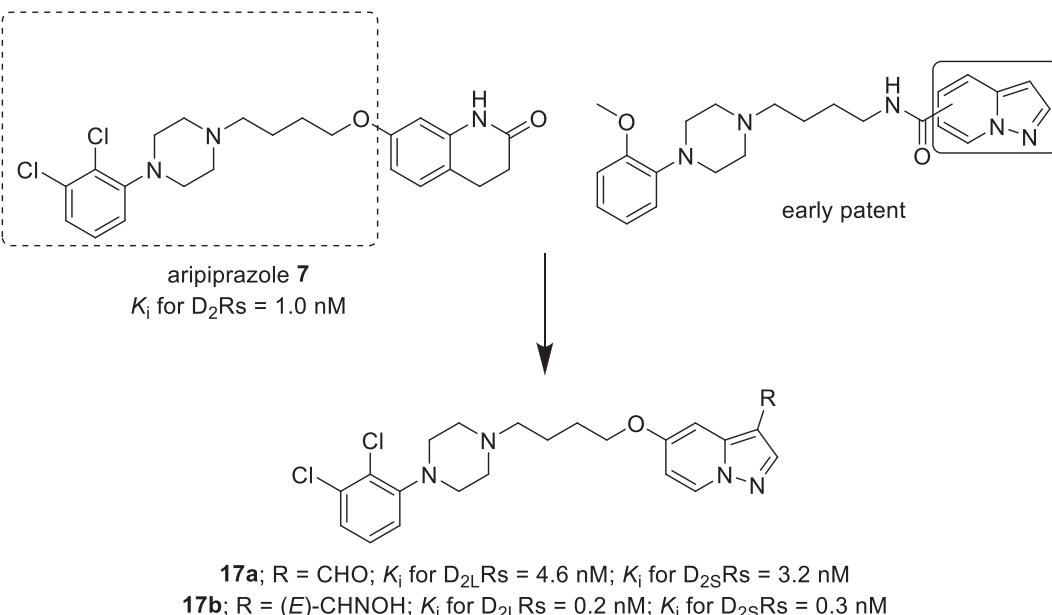


FIGURE 15 Schematic representation of the pyrazolo[1,5-a]pyridine designs of **17a** and **17b**, derivatives from aripiprazole (1), and related molecules from an early patent.

functional groups on the cyclohexyl moiety highly enhance affinity for D_2/D_3Rs . The most promising representative of this group was shown to be **8**, known as cariprazine, a novel third-generation antipsychotic drug.^{4,146,579,590} Furthermore, **8** was found to show bias toward the cAMP pathway over ERK1/2 phosphorylation at $D_{2L}Rs$.⁵⁹⁴ On the other hand, **8** did not possess significant bias for the $G_{i/o}$ cascade over the β -arrestin2 pathway at D_2Rs .⁵⁹⁵

2.5.1.2 | 4-(2-methoxyphenyl)-1-substituted piperazines as D_2Rs modulators

Chemical moiety 4-(2-methoxyphenyl)-1-substituted piperazine can be found in numerous chemical entities, with some unique properties. For instance, Y-QA31 (**20**) exhibited antipsychotic-like properties in preclinical animal models of schizophrenia (Table 10).⁵⁹⁶ Other examples include HBK-14 (**21a**) and HBK-15 (**21b**), showing anxiolytic-like and antidepressant activities in animal models (Table 10).³¹⁷ The chemical structures of the derivatives mentioned above are endowed with 4-(2-methoxyphenyl)-1-piperazine as the central structural motif (Figure 17).

Researchers have sought to develop selective 4-(2-methoxyphenyl)-1-piperazine D_3R ligands from structurally related D_2Rs ligands by applying distinct modifications to the central linkers. Introduction of a hydroxy group (**22a** vs. **22b**; Figure 18) to the central linker connecting to a 4-(2-methoxyphenyl)-1-piperazine fragment with a lipophilic fragment created selective D_3R analogs.⁵⁹⁷ Bioisosteric replacement of amide bonds for triazole heterocycle with optimal length of linker (comparing the affinities **23a**, **23b**, and **23c**; Figure 18) also yielded selective D_3R modulation.⁵⁹⁸ The best aliphatic linker of caffeine D_2R ligands was 1,5-pentane-diyl (**24a-c**; **25a-c** [Figure 18]) or 4-butoxy-yl (**26a-c** [Figure 18]).⁵⁹⁹⁻⁶⁰¹ Besides this, the incorporation of an ether bond was more effective for reaching D_2R affinity than the introduction of an amide bond in the central linker (**27a** related to **27b** [Figure 18]).⁶⁰²

Considering the nature of the lipophilic appendages, the steric clashes of the potentially representative functional group is critical for subtype selectivity. The 6-Phenyl-3,4-dihydroisoquinolin-1(2H)-one congener **28a** (Figure 19) displayed moderate selectivity for D_3Rs ($D_{2S}/D_3 = 50$), whereas the 3,4-dihydroisoquinolin-1(2H)-one analog **28b** (Figure 19) exhibited mild preference for D_3R ($D_{2S}/D_3 = 4$).⁴⁷⁶ Another example is 4-(1*H*-1,2,3-triazol-4-yl)aniline

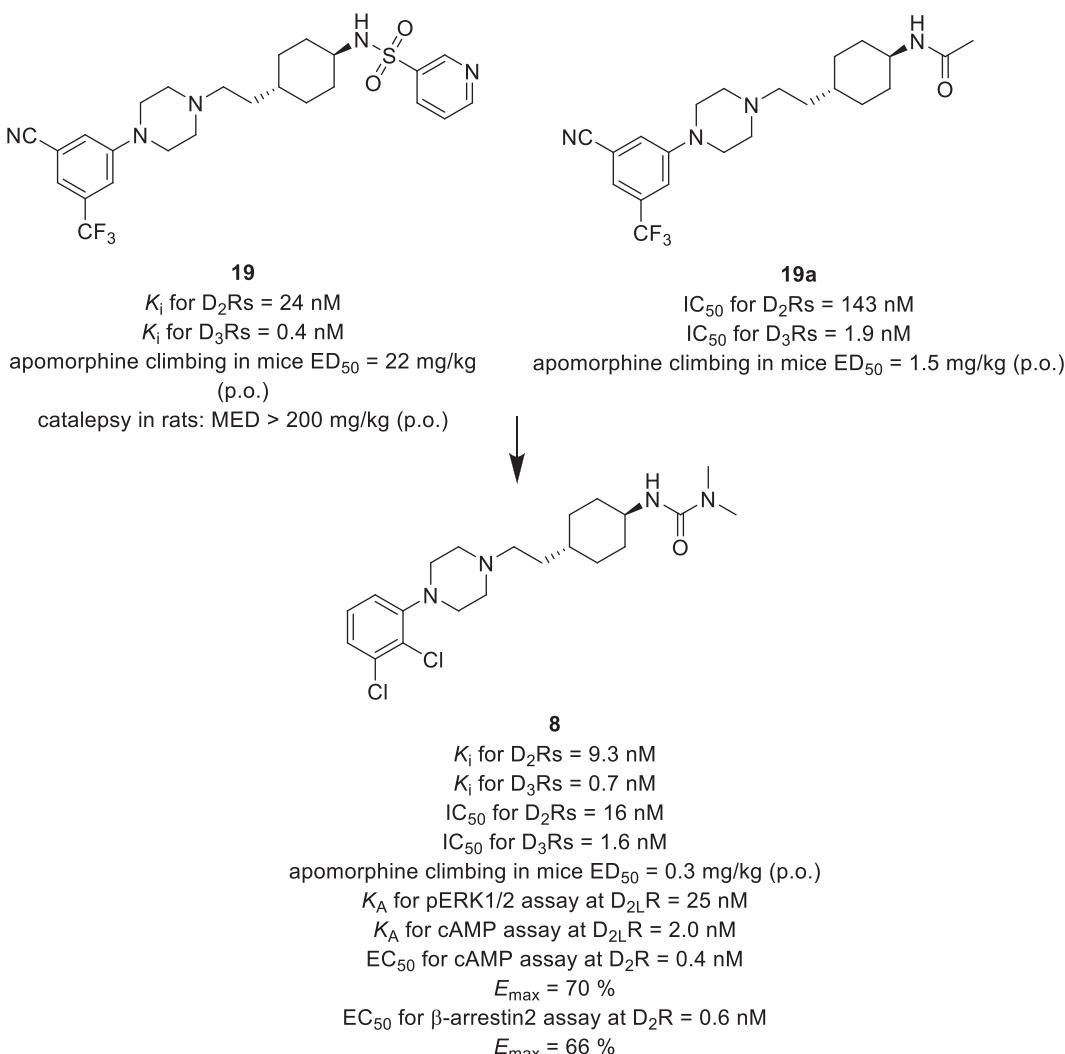


FIGURE 16 Chemical structure of the 3-pyridylsulfonamide analog **19** and acetamide derivative **19a** with their binding affinities and activities in vivo. **19a** was used as a building block for obtaining cariprazine (**8**).

(29c; Figure 19) a pharmacophore that has moderate selectivity for D₃Rs (D_{2S}/D₃ = 74). On the other hand, compounds containing a bromine (29b, Figure 19) or hydrogen (29a; Figure 19) atom at the same position of the phenyl ring attached to 1,2,3-triazole core revealed no selectivity at all.⁶⁰³ In summary, countless ligands bearing various central linkers or lipophilic appendages have been discovered to modulate DRs. For affinity toward D₂Rs, an aliphatic or ether-containing central linker seems crucial to connect the 4-(2-methoxyphenyl)-1-piperazine scaffold with different lipophilic aromatic/heteroaromatic appendages.

An in vivo study investigating **20** (Y-QA31; D₂R antagonist, Figure 17, Table 10) in mouse models of schizophrenia was reported.⁵⁹⁶ Compound **20** treatment (10–40 mg/kg, p.o.) significantly reduced MK-801-induced hyperlocomotion and methamphetamine-induced prepulse inhibition disruption in a dose-dependent manner. Furthermore, treatment with **20** (1.0 mg/kg, p.o.) effectively alleviated the MK-801-induced disruption of novel object recognition. Treatment with **20** did not affect spontaneous locomotion or induce cataleptic response

TABLE 10 Highlighted 4-(2-methoxyphenyl)-1-piperazine derivatives **20**, **21a–b**, **24c**, **25c**, **30a–b**, and **31**, with their properties and chemical structures

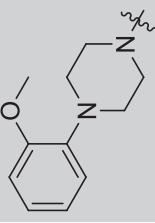
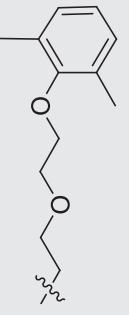
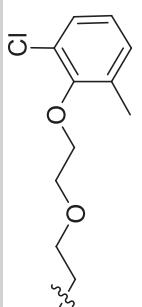
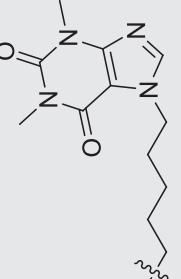
Chemical structures	Binding affinities	Functional activities	BBB score ^a	Behavioral test
	K_i for $D_2Rs = 52 \text{ nM}$ K_i for $D_3Rs = 0.3 \text{ nM}$ K_i for $5-HT_{1A}Rs = 8.4 \text{ nM}$ K_i for $\alpha_{1A}Rs = 15 \text{ nM}$ K_i for $\alpha_{1B}Rs = 57 \text{ nM}$	IC_{50} for $D_2Rs = 220 \text{ nM}$ IC_{50} for $D_3Rs = 1.7 \text{ nM}$ IC_{50} for $5-HT_{1A}Rs = 12 \text{ nM}$ IC_{50} for $5-HT_{1B}Rs = 678 \text{ nM}$ IC_{50} for $5-HT_{2C}Rs = 839 \text{ nM}$ IC_{50} for $\alpha_{1A}Rs = 46 \text{ nM}$ IC_{50} for $\alpha_{1B}Rs = 171 \text{ nM}$ IC_{50} for $H_1Rs = 569 \text{ nM}$	3.66	20 (10–40 mg/kg, p.o., mice)–inhibition of MK-801-induced hyperlocomotion 20 (10–40 mg/kg, p.o., mice)–inhibition of methamphetamine-induced prepulse inhibition disruption 20 (120 mg/kg, mice)–no catalepsy
20				
	K_i for $D_2Rs = 219 \text{ nM}$ K_i for $5-HT_{1A}Rs = 41 \text{ nM}$ K_i for $5-HT_{2A}Rs = 264 \text{ nM}$ K_i for $5-HT_7Rs = 156 \text{ nM}$ K_i for $\alpha_1Rs = 23 \text{ nM}$	IC_{50} for $5-HT_{1A}Rs = 64 \text{ nM}$ IC_{50} for $5-HT_7Rs = 77 \text{ nM}$	5.21	21a (FST mice–2.5 and 5 mg/kg, i.p.; FST rats–5 mg/kg, i.p.)–antidepressant-like activity 21a (four-plate test–2.5 and 5 mg/kg, i.p., mice; EPM–2.5 mg/kg, i.p., rat)–anxiolytic-like properties
21a				

TABLE 10 (Continued)

Chemical structures	Binding affinities	Functional activities	BBB score ^a	Behavioral test
	K_i for D ₂ Rs = 54 nM K_i for 5-HT _{1A} Rs < 1 nM K_i for 5-HT _{2A} Rs = 109 nM K_i for SERT = 529 nM K_i for α ₁ Rs = 34 nM K_i for α ₁ Rs = 13 nM	IC ₅₀ for 5-HT _{1A} Rs = 19 nM IC ₅₀ for 5-HT ₇ Rs = 220 nM	5.23	21b (FST mice—1.3, 2.5, and 5 mg/kg, i.p.; FST rats—1.3 and 2.5 mg/kg, i.p.)—antidepressant-like activity 21b (four-plate test—2.5 and 5 mg/kg, i.p., mice; EPM—5 mg/kg, i.p., rat)—anxiolytic-like properties
			4.12	24c (FST mice—0.6 and 1.3 mg/kg, i.p.)—antidepressant-like effect

(Continues)

TABLE 10 (Continued)

Chemical structures	Binding affinities	Functional activities	BBB score ^a	Behavioral test
	K_i for D ₂ Rs = 30 nM K_i for 5-HT _{1A} Rs = 8.0 nM K_i for 5-HT _{2A} Rs = 47 nM K_i for 5-HT ₇ Rs = 26 nM	Partial agonist at D ₂ Rs— EC ₅₀ = 67 nM; IC ₅₀ = 3.0 nM Partial agonist at 5-HT _{1A} Rs— EC ₅₀ = 16 nM; IC ₅₀ = 38 nM Antagonist at 5-HT ₇ Rs— IC ₅₀ = 0.79 μM	3.72	25c (10 and 20 mg/kg, i.p., mice) decreased D- amphetamine-induced hyperactivity
	K_i for D ₂ Rs = 162 nM K_i for 5-HT _{1A} Rs = 32 nM K_i for 5-HT _{2A} Rs = 159 nM K_i for 5-HT ₇ Rs = 89 nM	-	5.18	30a (four-plate test, mice—2.5 and 5 mg/kg, i.p.)— anxiolytic-like activity
	K_i for D ₂ Rs = 189 nM K_i for 5-HT _{1A} Rs = 5.0 nM K_i for 5-HT _{2A} Rs = 245 nM K_i for 5-HT ₇ Rs = 70 nM	-	5.18	30b (four-plate test, mice—2.5 and 5 mg/kg, i.p.)— anxiolytic-like activity

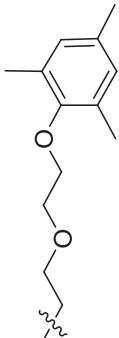
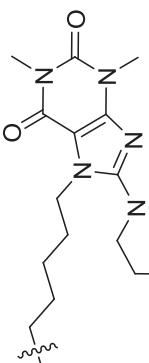
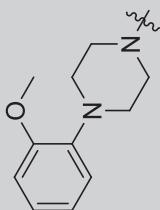
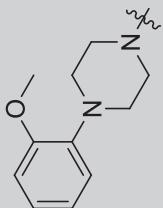


TABLE 10 (Continued)



Chemical structures	Binding affinities	Functional activities	BBB score ^a	Behavioral test
	K_i for $D_{2L}Rs = 0.2\text{ nM}$ K_i for $D_{2s}Rs = 0.1\text{ nM}$ K_i for $D_3Rs = 3.3\text{ nM}$ K_i for $D_4Rs = 0.7\text{ nM}$ K_i for $D_1Rs = 860\text{ nM}$ K_i for $5-HT_{1A}Rs = 6.6\text{ nM}$ K_i for $5-HT_{2ARs} = 100\text{ nM}$ K_i for $\alpha_1Rs = 0.6\text{ nM}$	EC_{50} for $D_{2s}RsGa_{OA} = 0.7\text{ nM}$ $E_{max} = 50\%$ EC_{50} for $D_{2s}RsGd_{i2} = 120\text{ nM}$ $E_{max} = 21\%$ EC_{50} for $D_3RsGa_{OA} = 18\text{ nM}$ $E_{max} = 76\%$	3.61	31 (1.5 mg/kg, via an osmotic Alzet mini pump, rat) – inhibition of amphetamine-induced hyper-locomotor activity

^aThe calculations were realized according to the reference. [552](#)

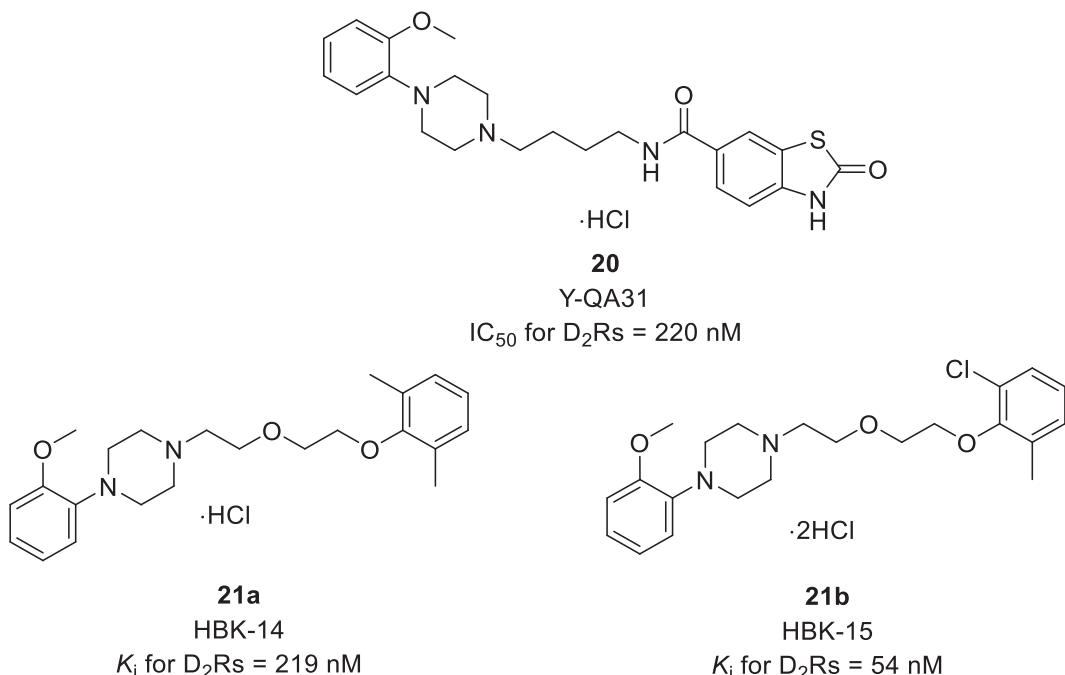


FIGURE 17 Representative ligands bearing 4-(2-methoxyphenyl)-1-piperazine with antipsychotic (**20**) and anxiolytic and antidepressant (**21a–b**) properties.

until its dose reached 120 mg/kg,⁵⁹⁶ and thus represents a potential candidate for further research as an antipsychotic drug.

In another study,³¹⁷ antidepressant- and anxiolytic-like effects of 2-methoxyphenylpiperazine derivatives **21a** (HBK-1; Figure 17, Table 10) and **21b** (HBK-15; Figure 17, Table 10)⁶⁰⁴ were determined. Compound **21a** exhibited antidepressant activity in FSTs (mice—2.5 and 5 mg/kg, i.p.; rats—5 mg/kg, i.p.), and anxiolytic-like properties in four-plate (2.5 and 5 mg/kg, i.p.) and EPM tests (2.5 mg/kg, i.p.) in mice and rats, respectively. Similarly, **21b** also displayed antidepressant activity in FSTs (mice—1.3, 2.5, and 5 mg/kg, i.p.; rats—1.3 and 2.5 mg/kg, i.p.) and anxiolytic-like properties in four-plate (5 mg/kg, i.p.) and EPM tests (2.5 and 5 mg/kg, i.p.) in mice and rats, respectively. Among these two piperazine derivatives, **21b** exhibited stronger antidepressant-like properties, whereas **21a** imparted higher anxiolytic-like activity.³¹⁷

A small family of 4-(2-methoxyphenyl)-1-substituted piperazines derived from **21a** and **21b** (Figure 17, Table 10)^{317,604} has been developed as potential anxiolytics.⁶⁰⁵ Compounds **30a** and **30b** (Table 10) were active in the four-plate test in mice (2.5 and 5.0 mg/kg, i.p.), but displayed no locomotor activity in mice at anxiolytic-like doses.⁶⁰⁵

The study of pyrazolo[1,5-a]pyridine D₂R modulators aimed to identify molecular determinants of functional selectivity for activation of G protein-dependent and independent D₂Rs pathways.⁶⁰² Due to excellent binding properties towards D₂Rs, **31** (Table 10) was selected for further evaluation of functional selectivity. Compound **31** is a biased ligand in the G protein-dependent D_{2S}Rs cascade. **31** (1.5 mg/kg, administered via an Alzet osmotic mini pump) inhibited amphetamine-induced hyper-locomotor activity in rats more significantly than **7**.⁶⁰²

Caffeine derivatives⁶⁰⁰ affecting 5-HT/DA systems were built on **24** (Figure 20), which exhibited an antidepressant-like effect in the FST and anxiolytic activity in the four-plate test in mice.⁶⁰⁶ The aim of the study was to understand the effect of the ethoxy group in position 8 (**24**) of the purine-2,6-dione moiety and the impact of the linker length between the purine-2,6-dione moiety and the piperazine core on binding affinities for 5-HT

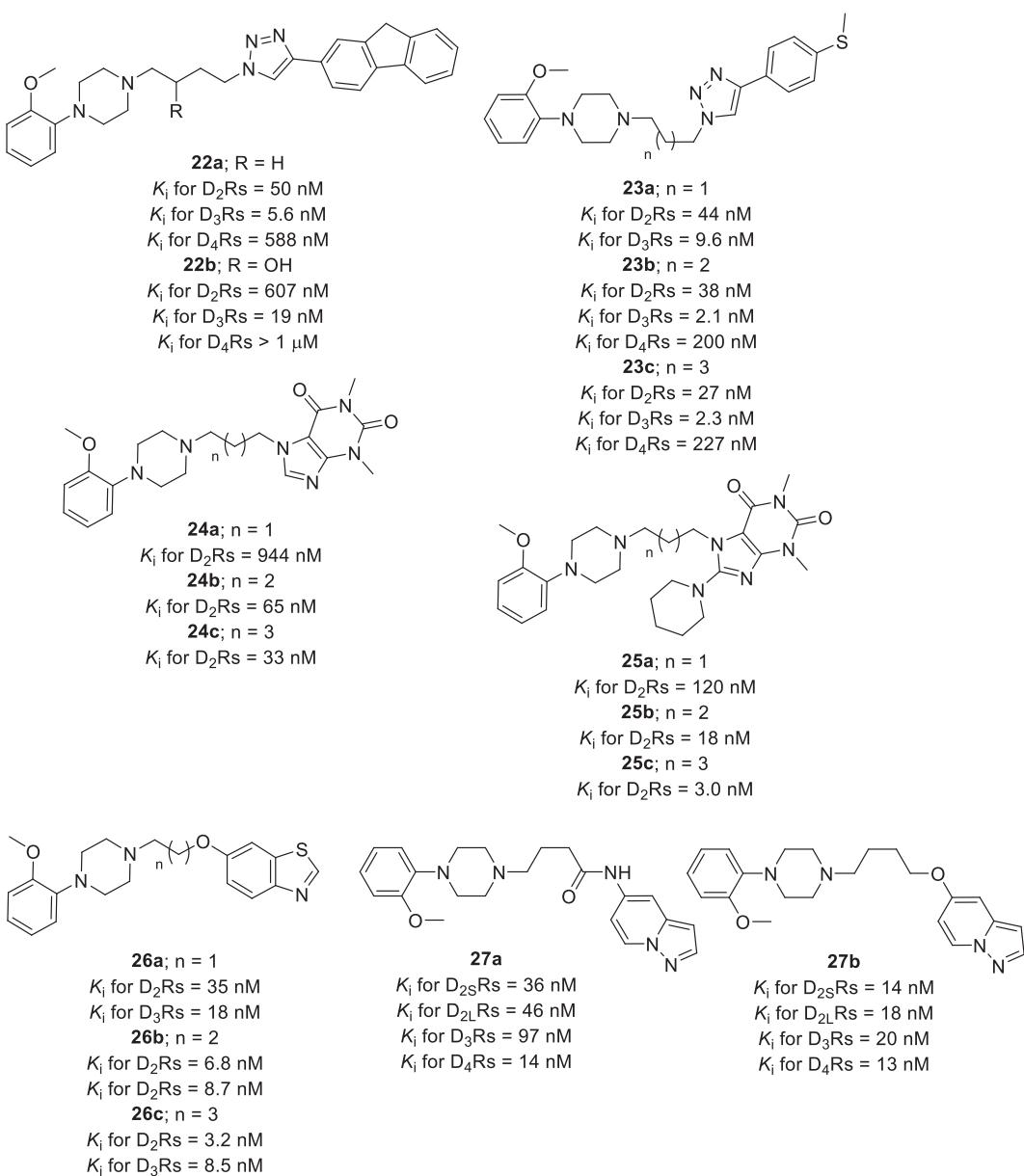


FIGURE 18 Chemical structures of representatives with 4-(2-methoxyphenyl)-1-piperazine moieties **22a-b**, **23a-c**, **24a-c**, **25a-c**, **26a-c**, and **27a-b**.

receptors ($5-\text{HT}_{1A}$, $5-\text{HT}_{2A}$, $5-\text{HT}_6$ and $5-\text{HT}_7$) and D_2Rs . Given the promising binding affinities for $5-\text{HT}_{1A}\text{Rs}$ and selectivity over other 5-HT receptors, **24c** (Figures 18 and 20, Table 10) was selected for a behavioral study.⁶⁰⁰ Treatment with **24c** (0.6 and 1.3 mg/kg, i.p.) produced a significant antidepressant-like effect in mouse FST compared to imipramine (10 and 20 mg/kg, i.p.; tricyclic antidepressant drug). Furthermore, WAY100635 treatment (0.3 mg/kg, s.c.; $5-\text{HT}_{1A}\text{R}$ antagonist) completely canceled out the antidepressant-like activity of **24c** (0.6 mg/kg, i.p.), suggesting that **24c** exhibits its antidepressant-like effect through $5-\text{HT}_{1A}\text{Rs}$.⁶⁰⁰

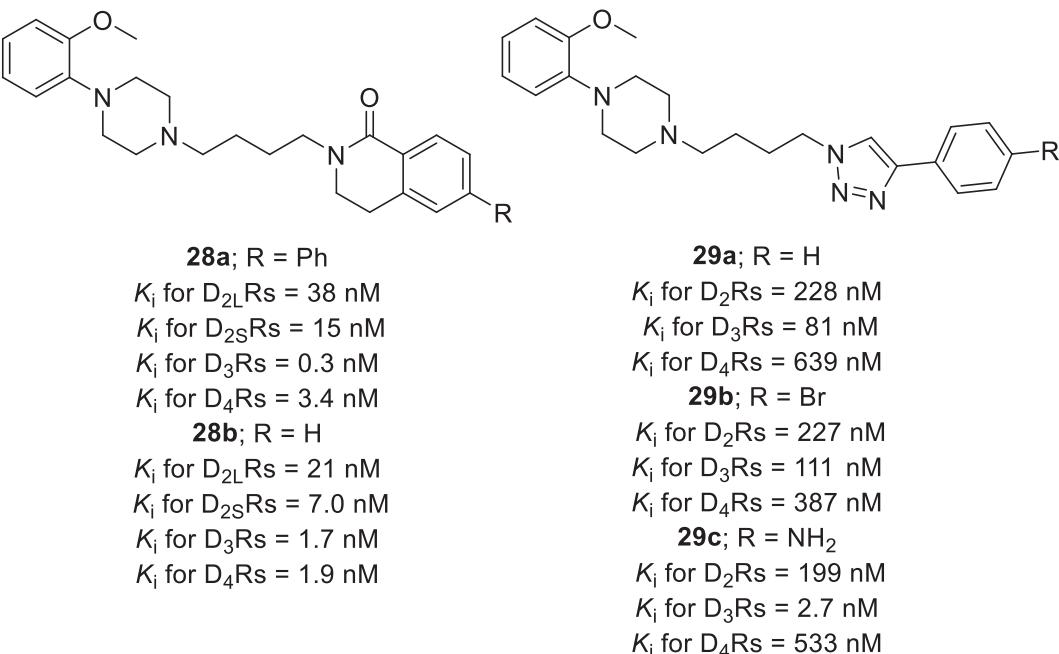


FIGURE 19 Chemical structures of 4-(2-methoxyphenyl)-1-piperazine derivatives **28a–b** and **29a–c** with various lipophilic appendages.

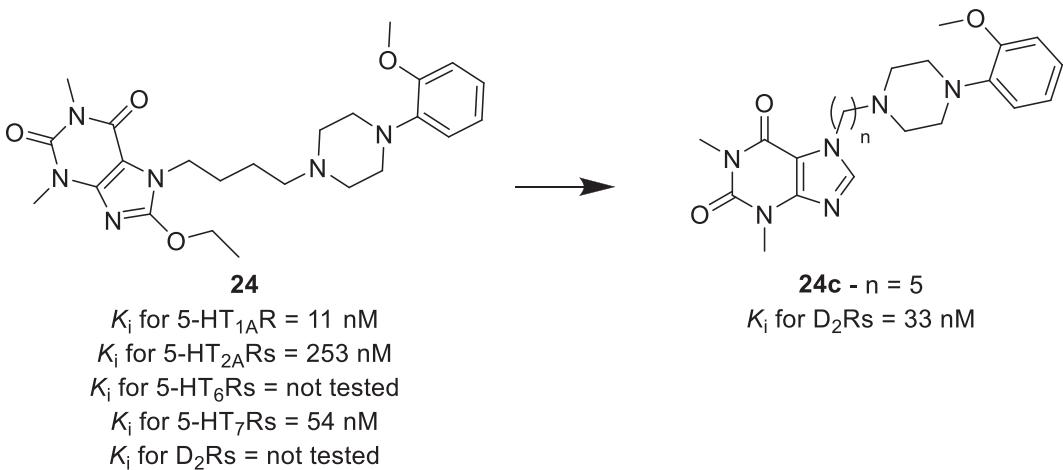


FIGURE 20 Chemical structures of caffeine derivatives **24** and **24c** connected with 4-(2-methoxyphenyl)-1-alkyl substituted piperazine with their binding affinities for 5-HT/DA system.

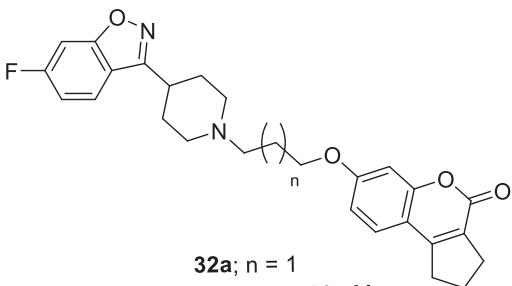
A new series of purine-2,6-diones as novel multitarget 5-HT/DA receptor modulators has been developed with particular focus on two regions: (i) the amino moiety in the 8 position of purine-2,6-dione system, and (ii) the linker length between the purine-2,6-dione and piperazine moieties.⁵⁹⁹ The aim of the study was to determine the affinity for 5-HTRs (5-HT_{1A}, 5-HT_{2A}, 5-HT₆, and 5-HT₇ receptors) and D₂Rs. **25c** (D₂R partial agonist, Figure 18, Table 10) was selected for further in vivo studies (mice, 10 and 20 mg/kg, i.p.) due to a well-balanced affinity for 5-HT/DA receptors, significantly decreasing D-amphetamine-induced hyperactivity, suggesting antipsychotic activity.⁵⁹⁹

2.5.1.3 | Ligands based on brexpiprazole, risperidone, and ziprasidone in modulating D₂Rs

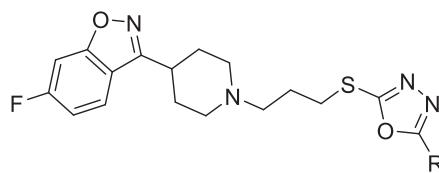
Brexipiprazole (Figure 6, Table 3) belongs to the third generation of antipsychotics.⁴ Structurally, it contains a 4-(benzo[b]thiophen-4-yl)piperazine fragment. Brexpiprazole has been approved for the treatment of schizophrenia as a monotherapy, and for the management of MDD as an adjunctive drug to antidepressants.⁶⁰⁷ Risperidone (Figure 6, Table 3), a molecule with a 4-(6-fluorobenzo[d]isoxazol-3-yl)piperidine moiety in its chemical structure, is a second-generation antipsychotic drug.⁴ Since its initial FDA-approval 25 years ago, risperidone continues to be a fundamental treatment option in schizophrenia, bipolar I disorder, and autism-related irritability.⁶⁰⁸ Ziprasidone (Figure 6, Table 3), a small-molecule drug possessing a 4-(benzo[d]isothiazol-3-yl)piperazine system, is a second generation antipsychotic agent.⁴ Ziprasidone is used to treat schizophrenia, bipolar mania, and acute agitation in schizophrenic patients.⁶⁰⁹⁻⁶¹²

Here, we discuss structural aspects related to the above-mentioned antipsychotics from the perspective of D₂R interactions and binding. The investigators frequently tested their top-ranked candidates of potential antipsychotic effect for affinity toward some off-target receptors (especially H₁, 5-HT_{2C}). These off-target receptors and their relevance in the treatment of schizophrenia were discussed in detail in the section “1.3.1 Current treatment of schizophrenia and the relevance to D₂R.”

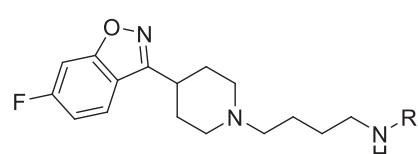
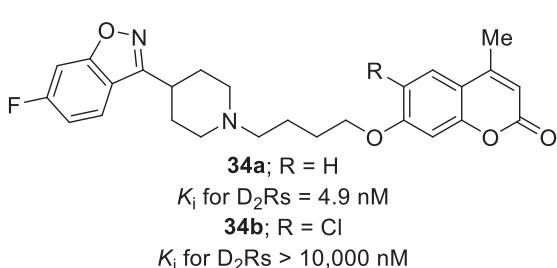
2.5.1.3.1 | Risperidone-based modulators of D₂Rs. The 4-(6-fluorobenzo[d]isoxazol-3-yl)piperidine fragment from risperidone was amalgamated to a family of sulfonamide-^{613,614} or 1,3,4-oxadiazole-containing⁶¹⁵ congeners that are well tolerated for their affinity to D₂Rs. A butoxy chain was the best option to receive D₂R ligands, with excellent affinity toward D₂Rs.^{616,617} For instance, **32b** (4-butoxy-yl; Figure 21) retained D₂R affinity on a low nanomolar scale, **32c** (5-pentoxy-yl; Figure 21) exhibited D₂R affinity within submicromolar range, and **32a**



32b; n = 2
 K_i for D₂Rs = 24 nM
32c; n = 3
 K_i for D₂Rs = 698 nM



33b; R = Ph
 K_i for D₂Rs = 2,969 nM



35b; R = benzo[b]thiophene-2-sulfonamide
 K_i for D₂Rs = 2.0 nM

FIGURE 21 Highlighted risperidone-based D₂R ligands **32a-c**, **33a-b**, **34a-b**, and **35a-b** with alternatives for central linker and/or aromatic region.

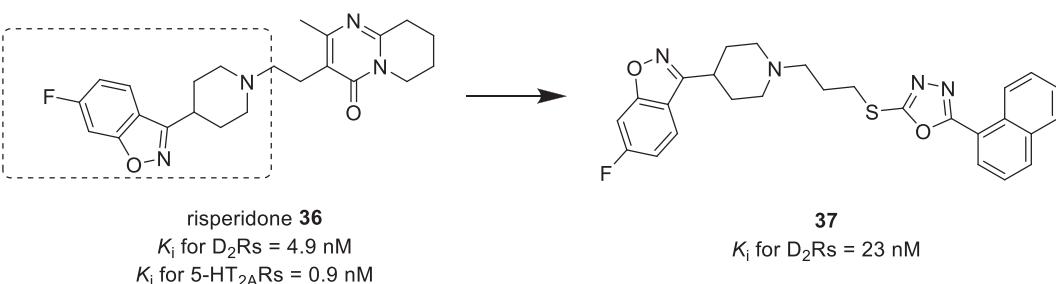


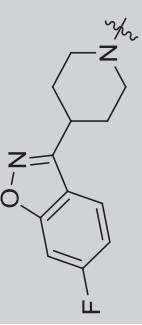
FIGURE 22 Chemical structures and binding affinities of **36** and the risperidone-derived **37**.

(3-propoxy-yl; Figure 21) exhibited no D_2Rs affinity at all.⁶¹⁷ In addition to modifications within the central linker, various substitutions in the lipophilic aromatic fragment have enabled D_2R affinity fluctuations. For example, the 4-methoxy-phenyl derivative **33a** (Figure 21) showed high D_2R affinity, whereas the phenyl-containing compound **33b** (Figure 21) exhibited negligible D_2R affinity.⁶¹⁵ A chlorine addition to position 6 of the coumarin scaffold yielded D_2R affinity drop (**34a** compared to **34b**; Figure 21).⁶¹⁶ Additionally, the size of the aromatic appendage affected D_2R binding. The thiophene derivative **35a** (Figure 21) displayed low D_2R affinity, while bulkier benzo[b] thiophene-containing **35b** (Figure 21) demonstrated much higher D_2R affinity.⁶¹³ The same rules can be applied for D_2R affinity in risperidone derivatives as we can see in 4-(2-methoxyphenyl)-1-substituted piperazine family, for example, the optimal linker length was associated with 4-butoxy-yl, and correctly substituted aromatic lipophilic appendages are essential for high D_2R affinity.

Derivatives of 2-substituted-5-thiopropylpiperidine-1,3,4-oxadiazole were developed as novel antipsychotic drugs that act on D_2 , D_3 , $5-HT_{1A}$, and $5-HT_{2A}$ receptors, with low affinity for the $5-HT_{2C}$ and H_1 receptors. Their design was focused on the ability of these agents to effectively counteract positive and negative symptoms of schizophrenia and improve cognition without the weight gain typically observed as a side-effect.⁶¹⁵ Among the novel derivatives, **37** (Figure 22, Table 11) generated a high affinity to desired receptors and low affinity to off-target (undesired) receptors. Given the preliminary perspective, **37** was subjected to other studies, including a safety profile (the drug was well-tolerated even at the highest dose tested of $LD_{50} > 2000$ mg/kg). Furthermore, **37** significantly inhibited apomorphine-induced climbing behavior ($ED_{50} = 3.7$ mg/kg, p.o.) and MK-801-induced hyperactivity ($ED_{50} = 3.6$ mg/kg, p.o.), without causing catalepsy ($ED_{50} > 300$ mg/kg, p.o.) in mice. These results suggest that **37** offers antipsychotic activity and a low propensity to induce unwanted extrapyramidal motor disturbances at therapeutic doses. In addition, **37** (20 mg/kg, p.o., in rats) showed an acceptable pharmacokinetic profile ($t_{1/2} \approx 8.6$ h; bioavailability $\approx 55\%$).⁶¹⁵

A set of coumarin analogs derived from **38a**, **38b**, and **36** (Figure 23) has been discovered, containing potential multireceptor-targeting neuroleptics.⁶¹⁶ Coumarin derivatives **38a** and **38b** (Figure 23) have been shown to modulate DA/5-HT systems in a study designed to develop novel antipsychotics that modulate DRs (D_2 and D_3Rs) and 5-HT receptors ($5-HT_{1A}$ and $5-HT_{2A}Rs$) concomitantly, with low affinity for H_1 and $5-HT_{2C}$ receptors.^{618,619} These derivatives may effectively treat the positive and negative symptoms and the cognitive impairment associated with schizophrenia, without causing weight gain.⁶¹⁶ The 4-Methyl-8-chloro-2H-chromen-2-one moiety **38** (Figure 23, Table 11) exhibited the best binding profile for the desired receptors, along with low affinity to off-target receptors, and thus was selected for further studies. Compound **38** acted as antagonist towards D_2Rs , D_3Rs , $5-HT_{1A}$, and $5-HT_{2A}$ receptors, and displayed a promising safety profile ($LD_{50} > 2000$ mg/kg). Oral administration of **38** (12 mg/kg; rats) resulted in a $t_{1/2}$ of 6.7 h with 32% bioavailability. Additionally, **38** (0.3, 0.9, and 2.7 mg/kg, p.o.) caused negligible weight gain in mice that experienced chronic dosing (28 days). Furthermore, this compound inhibited apomorphine-induced climbing behavior ($ED_{50} = 0.1$ mg/kg, p.o.) and MK-801-induced hyperactivity ($ED_{50} = 0.3$ mg/kg, p.o.), without causing catalepsy at the highest tested doses ($ED_{50} = 81$ mg/kg, p.o.) in mice.⁶¹⁶

TABLE 11 Highlighted compounds 35b, 37, 38, 39, 40a, 42, and 44 in the risperidone-based group with their chemical structures and properties

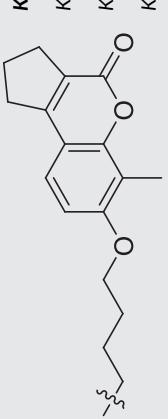
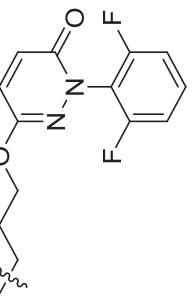
Chemical structures	Binding affinities	Functional activities	BBB score ^a	PD/PK ^b properties	Behavioral test
	K_i for $D_2Rs = 2.0\text{ nM}$ K_i for $D_3Rs = 1.1\text{ nM}$ K_i for $D_4Rs = 14\text{ nM}$ K_i for $D_1Rs = 3.3\text{ nM}$ K_i for $5-HT_{1A}Rs = 110\text{ nM}$ K_i for $5-HT_{2A}Rs = 0.6\text{ nM}$ K_i for $5-HT_6Rs = 6.5\text{ nM}$ K_i for $5-HT_7Rs = 1.6\text{ nM}$ K_i for $H_1Rs = 69\text{ nM}$ K_i for $5-HT_{2C}Rs = 540\text{ nM}$ K_i for $\alpha_1Rs = 0.8\text{ nM}$ K_i for $\alpha_2Rs = 1.9\text{ nM}$	K_b for $D_2Rs = 17\text{ nM}$ K_b for $D_3Rs = 2.3\text{ nM}$ K_b for $D_4Rs = 23\text{ nM}$ K_b for $D_1Rs = 37\text{ nM}$ K_b for $5-HT_{2A}Rs = 8.8\text{ nM}$ K_b for $5-HT_6Rs = 9.9\text{ nM}$ K_b for $5-HT_7Rs = 7.8\text{ nM}$ K_b for $H_1Rs = 140\text{ nM}$ K_b for $\alpha_1Rs = 1.8\text{ nM}$ K_b for $\alpha_2Rs = 25\text{ nM}$	3.74	-	$35b$ (10 mg/kg, p.o., rat)—reversed hyperlocomotion induced by MK-801 $35b$ (FST—0.3–3 mg/kg, p.o., rat)—antidepressant-like properties $35b$ (100 mg/kg, p.o., rat)—no catalepsy

(Continues)

TABLE 11 (Continued)

Chemical structures	Binding affinities	Functional activities	BBB score ^a	PD/PK ^b properties	Behavioral test
	K_i for $D_2Rs = 23\text{ nM}$ K_i for $D_3Rs = 7.7\text{ nM}$ K_i for $5-HT_{1A}Rs = 4.6\text{ nM}$ K_i for $5-HT_{2A}Rs = 1.1\text{ nM}$ K_i for $H_1Rs > 10,000\text{ nM}$ K_i for $5-HT_{2C}Rs = 861\text{ nM}$	-	3.55	$LD_{50} > 2000\text{ mg/kg}$ $t_{1/2}^c \approx 8.6\text{ h};$ bioavailability $\approx 55\%$	$ED_{50} = 3.7\text{ mg/kg, p.o., mice}$ -inhibition of apomorphine-induced climbing behavior $ED_{50} = 3.6\text{ mg/kg, p.o., mice}$ -inhibition of MK-801-induced hyperactivity $ED_{50} > 300\text{ mg/kg, p.o., mice}$ -for catalepsy
	K_i for $D_2Rs = 2.6\text{ nM}$ K_i for $D_3Rs = 4.3\text{ nM}$ K_i for $5-HT_{1A}Rs = 3.3\text{ nM}$ K_i for $5-HT_{2A}Rs = 0.3\text{ nM}$ K_i for $H_1Rs = 1125\text{ nM}$ K_i for $5-HT_{2C}Rs = 1701\text{ nM}$	IC_{50} for $D_2Rs = 26\text{ nM}$ IC_{50} for $D_3Rs = 25\text{ nM}$ IC_{50} for $5-HT_{1A}Rs = 12\text{ nM}$ IC_{50} for $5-HT_{2A}Rs = 39\text{ nM}$	3.84	$LD_{50} > 2000\text{ mg/kg}$ $ED_{50} = 0.1\text{ mg/kg, p.o., mice}$ -inhibition of apomorphine-induced climbing behavior $ED_{50} = 0.3\text{ mg/kg, p.o., mice}$ -inhibition of MK-801-induced hyperactivity $ED_{50} = 81\text{ mg/kg, p.o., mice}$ -for catalepsy	$ED_{50} = 0.3, 0.9,$ and $2.7\text{ mg/kg, p.o., mice}$ -negligible weight gain $ED_{50} = 12\text{ mg/kg, p.o., rat}$ $t_{1/2} = 6.7\text{ h}$ and bioavailability 32%

TABLE 11 (Continued)

Chemical structures	Binding affinities	Functional activities	BBB score ^a	PD/PK ^b properties	Behavioral test
	K_i for $D_2Rs = 13 \text{ nM}$ K_i for $D_3Rs = 14 \text{ nM}$ K_i for $5-HT_{1A}Rs = 7.8 \text{ nM}$ K_i for $5-HT_{2A}Rs = 2.2 \text{ nM}$ K_i for $H_1Rs = 1825 \text{ nM}$	-	3.75	$LD_{50} > 2000 \text{ mg/kg}$	39 ($ED_{50} = 0.6 \text{ mg/kg, p.o., mice}$) -inhibition of apomorphine-induced climbing behavior 39 ($ED_{50} = 0.3 \text{ mg/kg, p.o., mice}$) reduction of MK-801-induced hyperactivity 39 ($ED_{50} = 66 \text{ mg/kg, p.o., mice}$) -for catalepsy
	K_i for $D_2Rs = 0.5 \text{ nM}$ K_i for $5-HT_{1A}Rs = 5.9 \text{ nM}$ K_i for $5-HT_{2A}Rs = 0.3 \text{ nM}$ K_i for $5-HT_6Rs = 0.5 \text{ nM}$ K_i for $H_1Rs = 1998 \text{ nM}$ K_i for $\alpha_1Rs = 1098 \text{ nM}$	-	3.71	-	40a ($ED_{50} = 0.3 \text{ mg/kg, p.o., mice}$) -inhibition of MK-801-induced hyperactivity 40a ($ED_{50} = 0.5 \text{ mg/kg, p.o., mice}$) -inhibition of apomorphine-induced climbing behavior 40a ($ED_{50} = 24 \text{ mg/kg, p.o., mice}$) -for catalepsy

(Continues)

TABLE 11 (Continued)

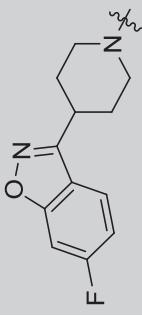
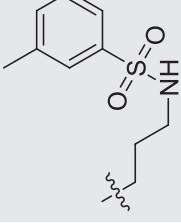
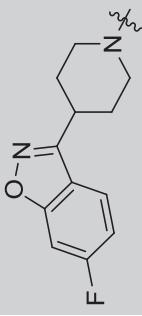
Chemical structures	Binding affinities	Functional activities	BBB score ^a	PD/PK ^b properties	Behavioral test
	K_i for D _{2S} Rs = 18 nM K_i for D ₃ Rs = 20 nM K_i for D ₄ Rs = 17 nM K_i for D ₁ Rs = 30 nM K_i for 5-HT _{1A} Rs = 173 nM K_i for 5-HT _{2A} Rs = 2.0 nM K_i for 5-HT ₆ Rs = 16 nM K_i for 5-HT ₇ Rs = 0.5 nM K_i for H ₁ Rs = 116 nM K_i for 5-HT _{2C} Rs = 630 nM K_i for α _{1A} Rs = 0.8 nM K_i for α _{2C} Rs = 8.5 nM	K_b for D _{2S} Rs = 2.4 nM K_b for D ₃ Rs = 3.9 nM K_b for D ₄ Rs = 22 nM K_b for D ₁ Rs = 140 nM K_b for 5-HT _{2A} Rs = 3.4 nM K_b for 5-HT ₆ Rs = 24 nM K_b for 5-HT ₇ Rs = 0.1 nM K_b for α _{1A} Rs = 0.2 nM K_b for H ₁ Rs = 116 nM	4.33	42 (10 mg/kg, i.p.)— $C_{max}^{d,l}$ = 656 ng/g in brain and 210 ng/ml in plasma	42 (MED ^e = 3 mg/kg, i.p., rat)— reversed MK-801-induced hyperactivity
	K_i for D _{2S} Rs = 2.4 nM K_i for D ₃ Rs = 3.9 nM K_i for D ₄ Rs = 22 nM K_i for D ₁ Rs = 140 nM K_b for 5-HT _{2A} Rs = 3.4 nM K_b for 5-HT ₆ Rs = 24 nM K_b for 5-HT ₇ Rs = 0.1 nM K_b for α _{1A} Rs = 0.2 nM K_b for H ₁ Rs = 116 nM K_i for 5-HT _{2C} Rs = 630 nM K_i for α _{2C} Rs = 8.5 nM	K_b for D _{2S} Rs = 2.4 nM K_b for D ₃ Rs = 3.9 nM K_b for D ₄ Rs = 22 nM K_b for D ₁ Rs = 140 nM K_b for 5-HT _{2A} Rs = 3.4 nM K_b for 5-HT ₆ Rs = 24 nM K_b for 5-HT ₇ Rs = 0.1 nM K_b for α _{1A} Rs = 0.2 nM K_b for H ₁ Rs = 116 nM K_i for 5-HT _{2C} Rs = 630 nM K_i for α _{2C} Rs = 8.5 nM	42 (FST—0.3 and 1.0 mg/kg, i.p., rat)—antidepressant properties	42 (up to 30 mg/kg, i.p., rat)—no catalepsy	42 (MED ^e = 3 mg/kg, i.p., rat)— reversed MK-801-induced hyperactivity

TABLE 11 (Continued)

Chemical structures	Binding affinities	Functional activities	BBB score ^a	PD/PK ^b properties	Behavioral test
	-	IC ₅₀ for D ₂ Rs = 3.0 nM IC ₅₀ for 5-HT _{2A} Rs = 15 nM	4.17	44-t _{1/2} = 0.54 h (5 mg/kg, i.v.) and t _{1/2} = 2.00 h (25 mg/kg, p.o.) in mice 44-K_p value of 1.72 after 1 h and 4.03 after 4 h later	44 (10 mg/kg, i.g., mice) possessed sedative effect in the FST

44^aThe calculations were performed according to reference.⁵⁵²^bPharmacodynamics/pharmacokinetics.^cPharmacokinetic in vivo half-life.^dMaximal serum concentration.^eMinimum effective dose.

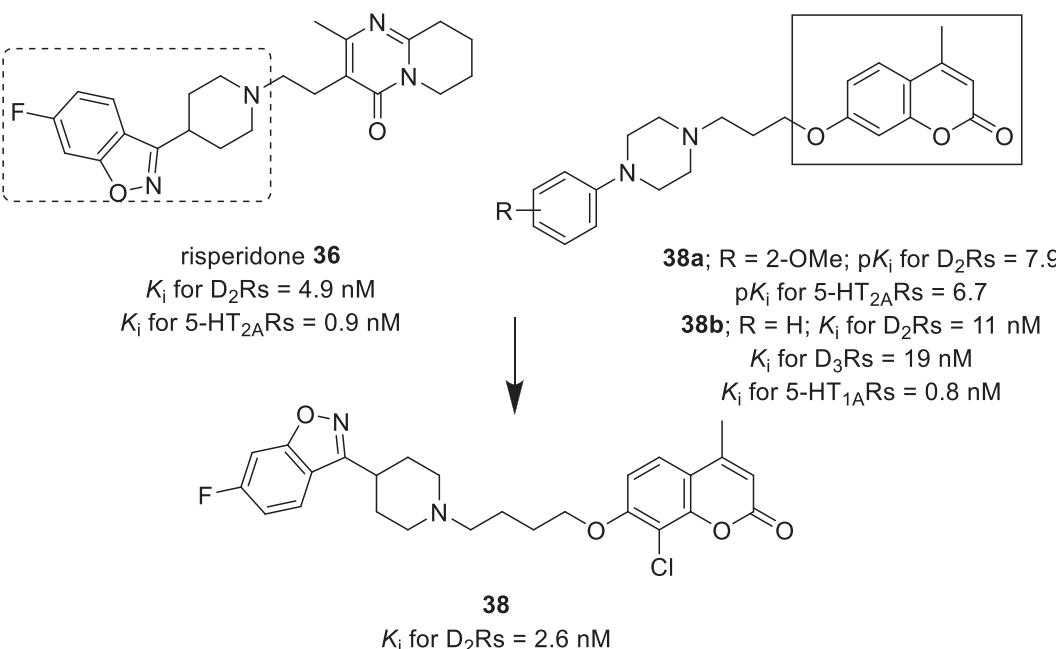


FIGURE 23 Design of coumarin derivative **38**, connected via a 4-butyloxy linker with a 4-(6-fluorobenzo[d]isoxazol-3-yl)piperidine moiety. Parent compounds, specifically **36** and coumarin ligands **38a** and **38b**, are also displayed.

Continuing with the research, the novel coumarin analogs exploited structural features of **38**⁶¹⁶ (Figure 23, Table 11). Indeed, they turned out to be high-affinity binders for D_2 , 5-HT_{1A}, and 5-HT_{2A} receptors, with low affinity for H₁Rs.⁶¹⁷ Compound **39** (Table 11) emerged as the best candidate and was selected for further in vivo evaluation. This compound significantly inhibited apomorphine-induced cage climbing behavior in mice (ED_{50} = 0.6 mg/kg, p.o.) and reduced MK-801-induced hyperactivity (ED_{50} = 0.3 mg/kg, p.o.). In addition, **39** exhibited a promising safety profile ($LD_{50} >$ 2000 mg/kg), with low tendency to induce catalepsy in mice (ED_{50} = 66 mg/kg, p.o.).⁶¹⁷

A series of 3(2H)-pyridazinone analogs built upon **36** and **40** have been developed as potential neuroleptics targeting D_2 , 5-HT_{1A} and 5-HT_{2A} receptors (Figure 24).⁶²⁰ Compound **40** exhibited favorable safety and pharmacokinetic profiles ($LD_{50} >$ 2000 mg/kg), with a positive response in the model for the treatment of neuropathic pain.⁶²¹ Due to excellent binding affinities, **40a** (Figure 24, Table 11) was chosen for further biological evaluations in mice, where it significantly inhibited MK-801-induced hyperactivity (ED_{50} = 0.3 mg/kg, p.o.). Furthermore, **40a** (ED_{50} = 0.5 mg/kg, p.o.) inhibited apomorphine-induced cage climbing behavior in mice pointing out to its antipsychotic-like properties and displayed a high cataleptic threshold (ED_{50} = 24 mg/kg, p.o.).⁶²⁰

Large family of novel arylsulfonamide derivatives with multimodal receptors profile has been evaluated as potential drugs for the treatment of behavioral and psychological symptoms of dementia.⁶¹³ Based on the molecular modeling studies, the authors reported 81 multifunctional molecules with affinity for D_2 Rs and 5-HT (5-HT₆, 5-HT₇, and 5-HT_{2A}) receptors. The family was designed by combining the 5-HT₇ receptor blocking arylsulfonamide fragment (based on SB-258719⁶²²; **41**; Figure 25) connected via 4-N-butylsulfonamide central linker with 4-(6-fluorobenzo[d]isoxazol-3-yl)piperidine moiety (Figure 25). According to the binding profile, **35b** (Figure 25, Table 11) was selected for further studies. Compound **35b** revealed antagonistic properties at all four main targets with K_b < 20 nM. Furthermore, **35b** did not bind to muscarinic receptors and only weakly blocked hERG channels, thus achieving high selectivity for the therapeutic targets of interest.⁶¹³ Thanks to the promising in

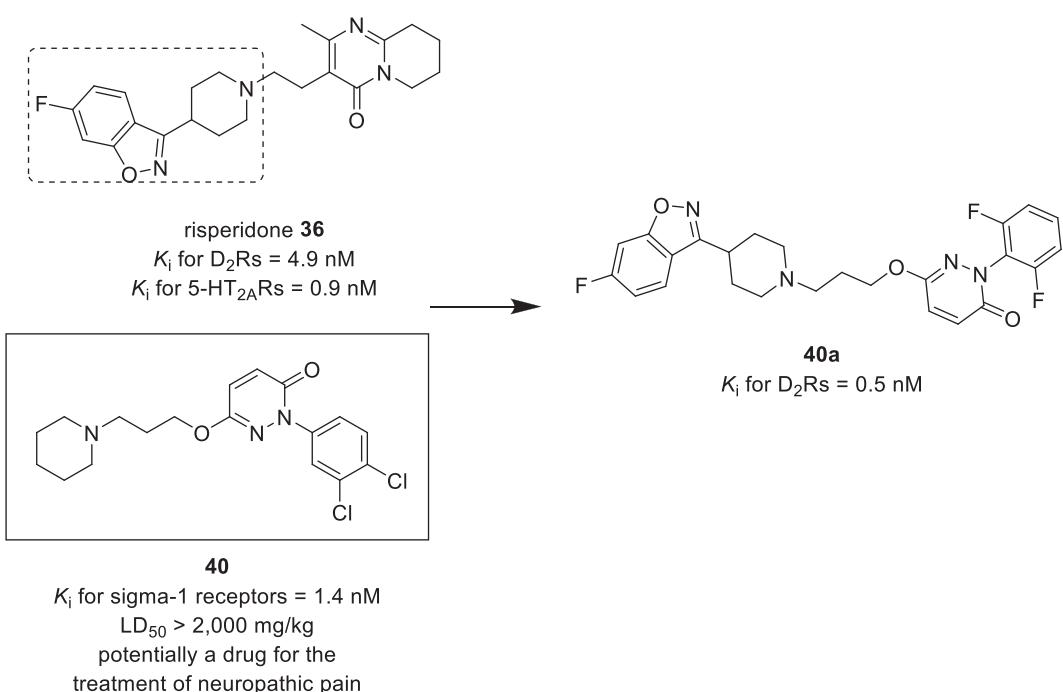


FIGURE 24 Design of novel 3(2H)-pyridazinone analog **40a** from **36** and **40**.

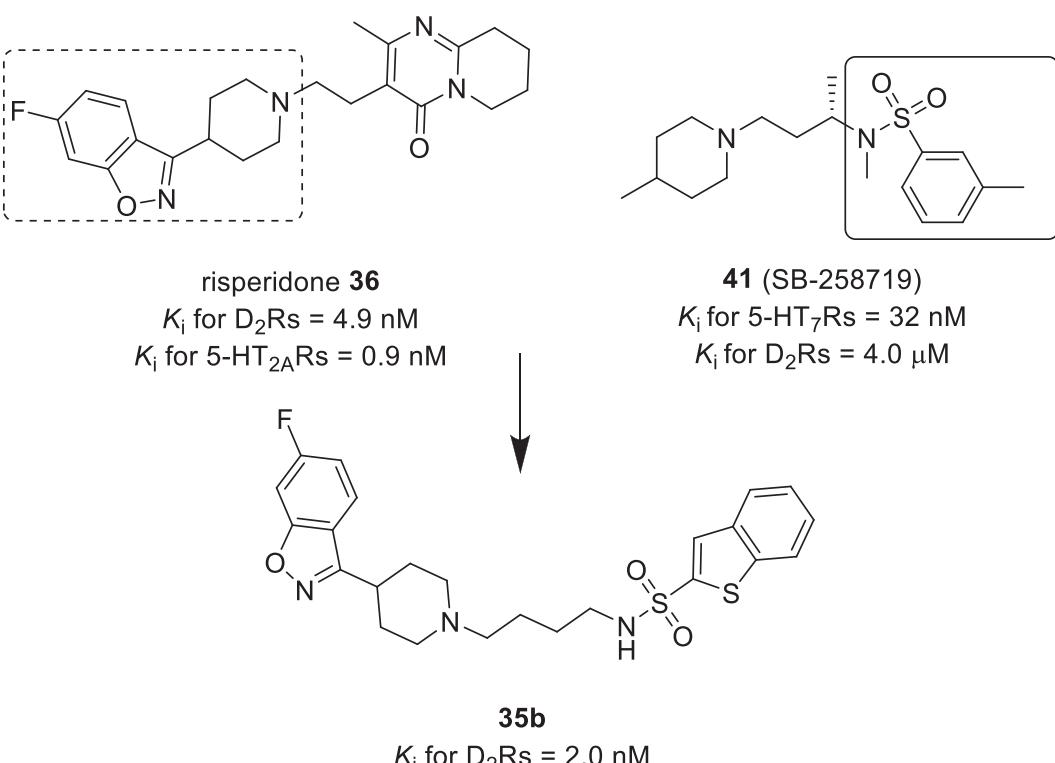


FIGURE 25 Design of benzo[b]thiophene-2-sulfonamide **35b** connected via a 4-N-butylsulfonamide linker with a 4-(6-fluorobenzod[d]isoxazole-3-yl)piperidine core derived from **41** (SB-258719) and **36**.

vitro profile, **35b** was chosen for behavioral experiments in rats. Treatment with **35b** dose-dependently reversed hyperlocomotion and head-twitches induced by MK-801 and 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI), with minimum effective doses of 10 and 3 mg/kg p.o., and thus demonstrating a pronounced antipsychotic-like effect. Furthermore, **35b** (0.3–3 mg/kg, p.o.) showed antidepressant-like properties in FST test. In addition, **35b** (100 mg/kg, p.o.) did not disrupt memory in the passive avoidance test and did not significantly modify spontaneous locomotor activity or induce catalepsy. This compound demonstrated antipsychotic and antidepressant properties in the absence of cognitive or motor impairment and thus represents a promising drug candidate for the treatment of behavioral and psychological symptoms of dementia.⁶¹³

3-Methylbenzenesulfonamide **42**⁶²³ (ADN-1184; Table 11) was generated as potential drug for management of behavioral and psychological symptoms of dementia.⁶²⁴ Compound **42** exhibited antagonist properties for D₂/5-HT_{2A}/5-HT₆ and 5-HT₇ receptors. It reversed MK-801-induced hyperactivity and stereotypies and inhibited conditioned avoidance response (with minimum effective dose 3 mg/kg, i.p.) suggesting that **42** had antipsychotic-like properties. This compound **42** also decreased immobility time in the FTS at administered doses (0.3 and 1 mg/kg, i.p.). Notably, **42** (up to 30 mg/kg, i.p.) did not impair memory performance in the passive avoidance test or elicit significant catalepsy, and only modestly inhibited spontaneous locomotor activity.⁶²⁴

Another arylsulfonamide analogs based on **36** and **43** (FW01, Figure 26) have been identified to act dually against D₂ and 5-HT_{2A} in an antagonistic manner.⁶¹⁴ Compound **43** is known to possess high 5-HT_{1A}, moderate 5-HT_{2A}, and weak D₃ receptor affinities.^{614,625} Among the newly developed derivatives, **44** (D₂R antagonist, Figure 26, Table 11) emerged as the lead candidate. Pharmacokinetic data revealed that **44** possesses a t_{1/2} of 0.54 h (5 mg/kg, i.v.) and t_{1/2} of 2.00 h (25 mg/kg, p.o.) in mice. Additionally, **44** showed K_p values of 1.72 and 4.03

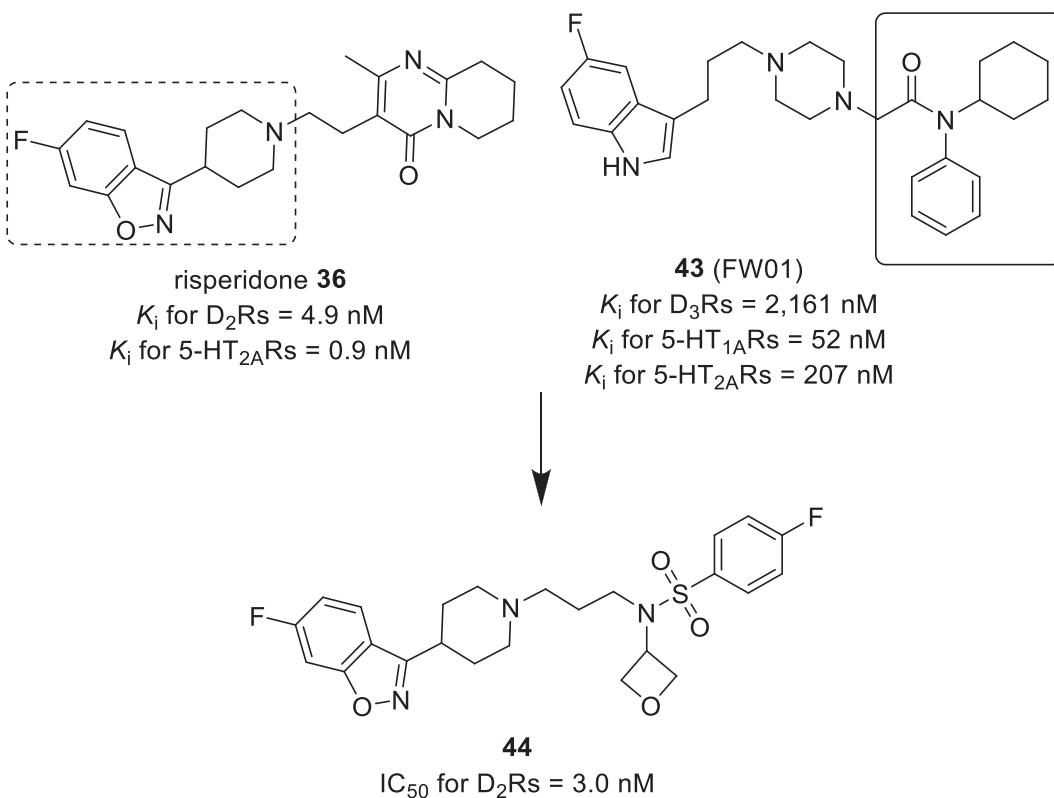


FIGURE 26 Design of the 4-fluorophenylsulfonamide analog **44**, from **36** and **43** (FW01).

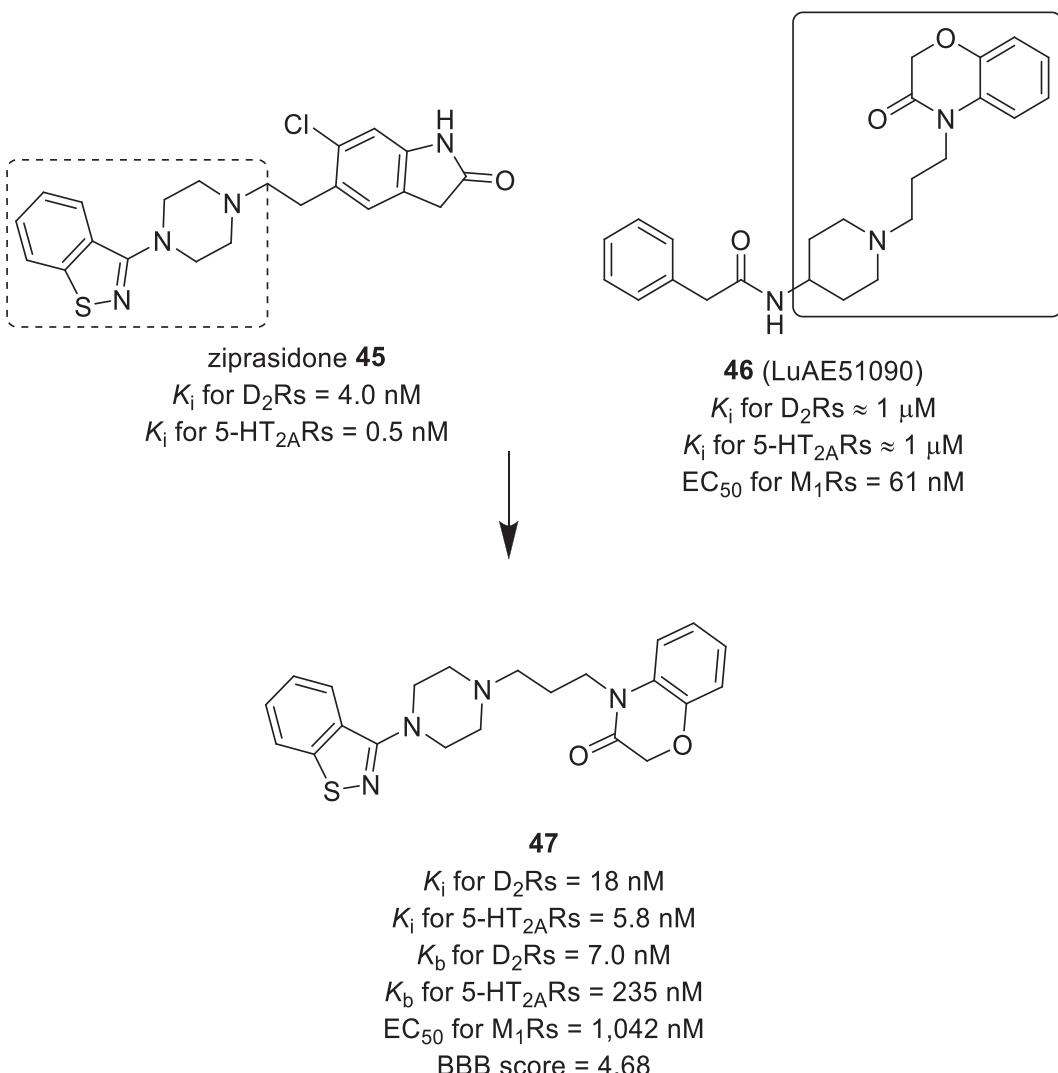


FIGURE 27 Design of a 4-propyl-2H-benzo[b][1,4]oxazin-3(4H)-one analog 47, from 46 (LuAE51090) and ziprasidone (45), and their binding affinities, functional activities, and chemical structures.

after 1 and 4 h, respectively, demonstrating its central availability. It was also found to have a sedative effect on FST performance in mice (10 mg/kg, i.g.).⁶¹⁴

2.5.1.3.2 | Ziprasidone-based D_2R ligands. The following chapter is devoted to multireceptor targeting derivatives bearing 4-propyl-2H-benzo[b][1,4]oxazin-3(4H)-one system.⁶²⁶ The study aimed to combine affinity for D_2 , $5-HT_{2A}$, and M_1ACh receptors. The hypothesis was that targeting M_1AChRs can ameliorate patients' cognitive deficits when suffering from schizophrenia and other CNS disorders.^{627,628} Compound 46 (LuAE51090, Figure 27) served as a structural template with known M_1AChR allosteric agonist properties.⁶²⁹ In the tested subset, 47 (Figure 27) showed functional activity towards the M_1AChRs and antagonist properties towards $5-HT_{2A}$ and D_2Rs .⁶²⁶

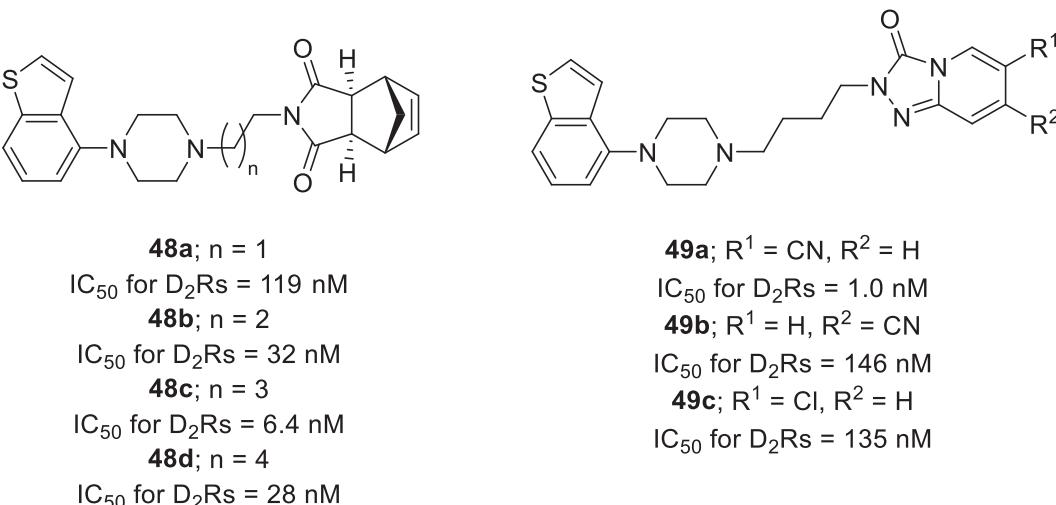


FIGURE 28 Highlighted brexpiprazole-based D_2R modulators **48a-d** and **49a-c** with modifications within central linkers or aromatic lipophilic appendages.

2.5.1.3.3 | Brexpiprazole-based D_2R analogs. Of the brexpiprazole-derived analogs, (3a*R*,4*R*,7*S*,7*aS*)-2-(4-(4-(Benzothiophen-4-yl)piperazin-1-yl)butyl)-3*a*,4,7,7*a*-tetrahydro-1*H*-4,7-methanoisoindole-1,3(2*H*)-dione (**48c**, Figure 28) showed the highest affinity for D_2R compared to ethane-1,2-diyl (**48a**, Figure 28), 1,3-propane-diyl (**48b**, Figure 28), and 1,5-pentane-diyl counterparts (**48d**, Figure 28).¹⁶³ The position of the functional group in the aromatic, lipophilic region was shown to drive D_2R affinity. 3-Oxo-2,3-dihydro-[1,2,4]triazolo[4,3-*a*]pyridine-6-carbonitrile (**49a**, Figure 28) exhibited high D_2R activity, whereas 3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-*a*]pyridine-7-carbonitrile (**49b**, Figure 28) and 6-chloro-[1,2,4]triazolo[4,3-*a*]pyridin-3(2*H*)-one (**49c**, Figure 28) revealed reduction of D_2R activity by the factors 146 and 135, respectively.⁶³⁰

Synthesis and biological evaluation of *N*-substituted cyclic imides connected to 4-(benzothiophen-4-yl)piperazine fragment with potential antipsychotic properties have been reported.¹⁶³ The molecular hybridization method for a multireceptor drug design including 5-HT_{1A}R, 5-HT_{2A}R and D_2R , derived from buspirone **50** (Figure 29), tandospirone **51** (Figure 29), and brexpiprazole **52** (Figure 29), was applied to generate a new series of D_2Rs modulators.¹⁶³ Compound **50** (K_i for D_2Rs = 484 nM⁶³¹) is a well-established drug used for the management of general anxiety.⁶³² Compound **51** (K_i for D_2Rs = 1700 nM⁶³³), an azaspirone derivative, is also used for the management of anxiety disorders.⁶³⁴ In the novel family, **48c** (D_2R antagonist, Figures 28 and 29, Table 12) exhibited high binding affinities for the receptors of interest, and therefore was subjected to behavioral and other studies.¹⁶³ This compound exhibited low affinities for off-target receptors and channels (5-HT_{2C}, H₁, α_{1A}, M₃ACh receptors and hERG channels), and thus low potential to cause serious adverse effects associated with antipsychotic drugs. In addition, **48c** (ED_{50} = 1.8 mg/kg) attenuated PCP-induced hyperlocomotion in mice at the dose of 3 mg/kg (i.g.). This compound also displayed low potential for catalepsy (ED_{50} = 14 mg/kg, p.o.) in mice. In rats, oral bioavailability of **48c** (10 mg/kg, p.o.) was 32% with a half-life ($t_{1/2}$) of 3.3 h.¹⁶³

A series of [1,2,4]triazolo[4,3-*a*]pyridin-3(2*H*)-one derivatives showed the combined antipsychotic actions of **48c**¹⁶³ (Figure 30) and trazodone (**53**, Figure 30) with D_2 , 5-HT_{1A}, and 5-HT_{2A} receptor affinity.⁶³⁰ Compound **53** is mainly used to treat MDD and anxiety disorders.⁶³⁵⁻⁶³⁷ Compound **49d** (D_2R partial agonist, Figure 30, Table 12) displayed significant inhibition of the quipazine-induced head-twitch response (0.3 mg/kg, p.o.), demonstrating 5-HT_{2A}Rs antagonistic efficacy *in vivo*.⁶³⁰ Additionally, **49d** (0.3 and 1 mg/kg, p.o.) reduced PCP-induced hyperactivity in mice.⁶³⁰

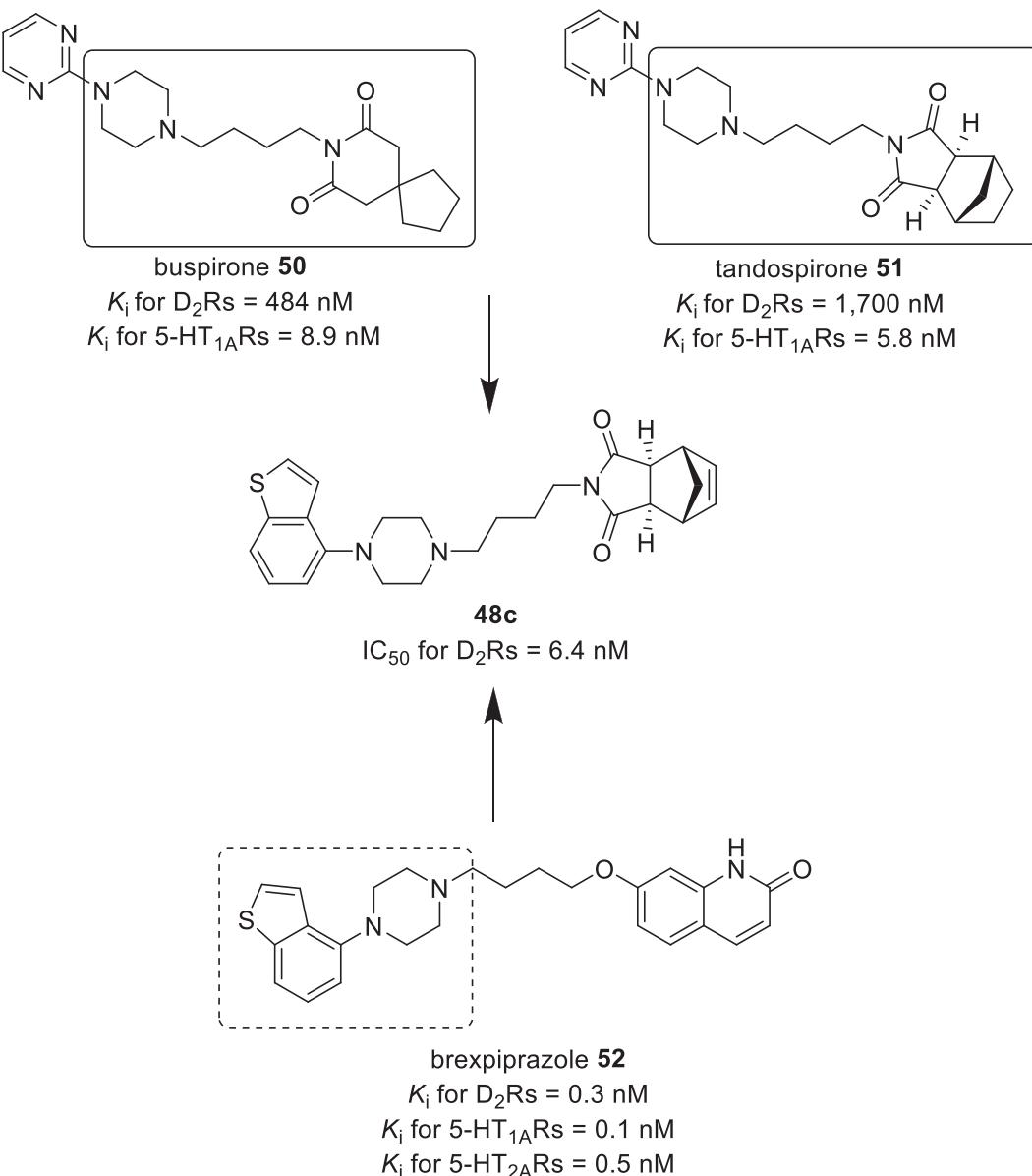


FIGURE 29 Design of the brexpiprazole derivative 48c with a cyclic imide moiety based on buspirone (50), tandospirone (51), and brexpiprazole (52).

4-(Benzo[b]thiophen-4-yl)piperazin-1-yl) derivatives based on 36 (Figure 31) and 52 (Figure 31) were developed as D₂R modulators with potential applicability for schizophrenia therapy.⁶³⁸ SAR study concentrated on D₂Rs and 5-HT receptors (5-HT_{1A} and 5-HT_{2A}), with respect to substitutions in the arylpiperazine/arylpiperidine moieties and substituents attached to the 6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one fragments. Due to perspective results from binding affinities, 54 (D₂R antagonist, Figure 31, Table 12) was selected for further studies. This compound was metabolically stable in human liver microsomes (84% and 70% of unchanged form of 54 after 30 and 60 min, respectively) with a $t_{1/2}$ of 6.14 h. Oral administration of 54 to dogs (1 mg/kg) resulted in 97% bioavailability. Compound 54 also showed a favorable pharmacological profile with low activities for α_1 , 5-HT_{2C},

TABLE 12 Highlighted compounds **48c**, **49d**, and **54** in the brexpiprazole-based group, with their chemical structures and properties

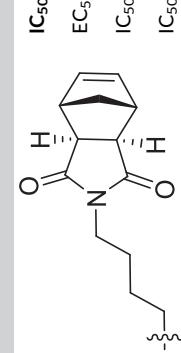
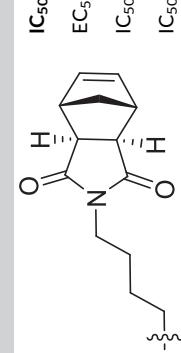
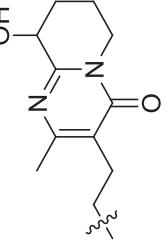
Chemical structures	Functional activities	BBB score ^a	PD/PK ^b properties	Behavioral test
	<p>IC_{50} for $D_2Rs = 6.4\text{ nM}$</p> <p>EC_{50} for $5-HT_{1A}Rs = 3.6\text{ nM}$</p> <p>$IC_{50}$ for $5-HT_{2A}Rs = 25\text{ nM}$</p> <p>$IC_{50}$ for $5-HT_{2C}Rs = 341\text{ nM}$</p> <p>$IC_{50}$ for $H_1Rs = 195\text{ nM}$</p> <p>IC_{50} for $\alpha_{1A}Rs = 178\text{ nM}$</p>	5.07	$48c$ (10 mg/kg, p.o., rat)– $t_{1/2}^c = 3.3\text{ h}$ and bioavailability = 32%	$48c$ ($ED_{50} = 1.8\text{ mg/kg, i.g., mice}$)–attenuated PCP-induced hyperlocomotion $48c$ ($ED_{50} = 14\text{ mg/kg, p.o., mice}$)–catalepsy
	<p>IC_{50} for $D_2Rs = 12\text{ nM}$</p> <p>EC_{50} for $D_2Rs = 14\text{ nM}$</p>	4.39	-	$49d$ (0.3 and 1 mg/kg, p.o., mice)–reduction of PCP-induced hyperactivity

TABLE 12 (Continued)

Chemical structures	Functional activities	BBB score ^a	PD/PK ^b properties	Behavioral test
	<p>IC_{50} for $D_2Rs = 3.3\text{ nM}$</p> <p>EC_{50} for 5-HT_{1ARs} = 9.8 nM</p> <p>IC_{50} for 5-HT_{2ARs} = 2.9 nM</p> <p>IC_{50} for 5-HT_{2CRs} = 32 nM</p> <p>IC_{50} for $H_1Rs = 177\text{ nM}$</p> <p>IC_{50} for $\alpha_1Rs = 151\text{ nM}$</p>	4.39	<p>54—stable in human liver microsomes (84% and 70% of unchanged form of 54 after 30 and 60 min, respectively) with $t_{1/2}^{\text{d}} = 6.14\text{ h}$</p> <p>54 (1 mg/kg, p.o.)—97% bioavailability</p>	<p>54 ($ED_{50} = 0.02\text{ mg/kg}$, i.g., mice)—reduction PCP-induced hyperactivity</p> <p>54 ($ED_{50} = 0.8\text{ mg/kg}$, p.o., mice)—for catalepsy</p>

^aThe calculations were realized according to reference 552.^bPharmacodynamics/pharmacokinetics.^cPharmacokinetic in vivo half-life.^dPharmacokinetic in vitro half-life.

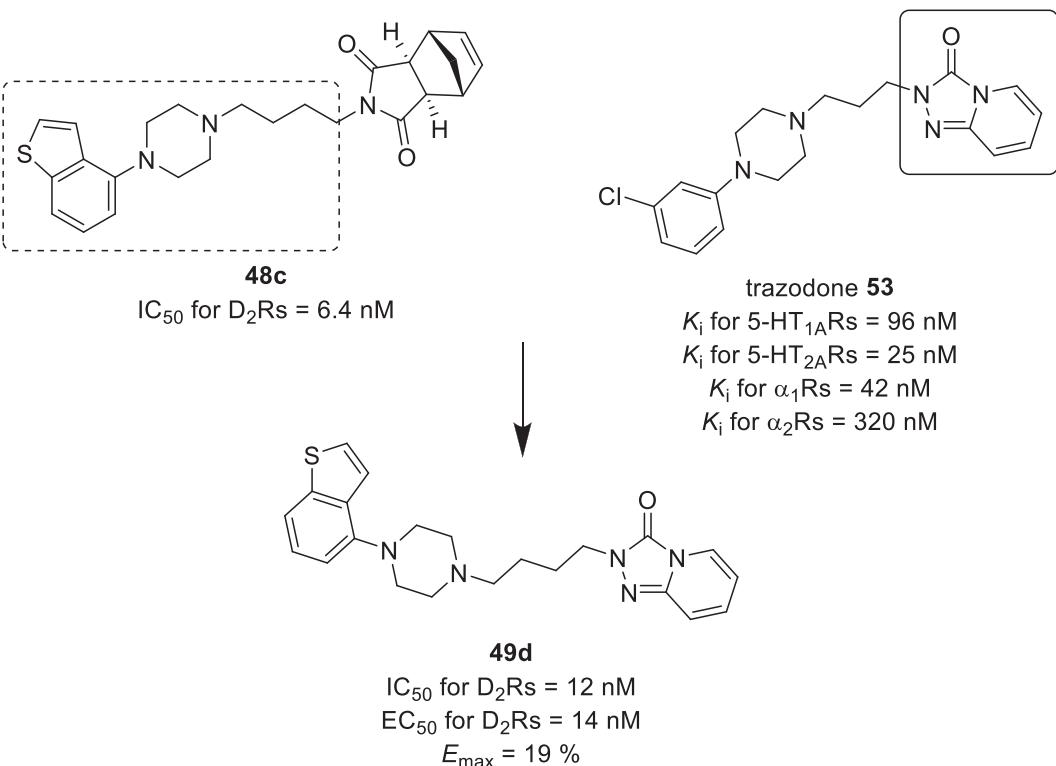


FIGURE 30 Design of the [1,2,4]triazolo[4,3-a]pyridin-3(2H)-one analog **49d** from **48c** and trazodone (**53**).

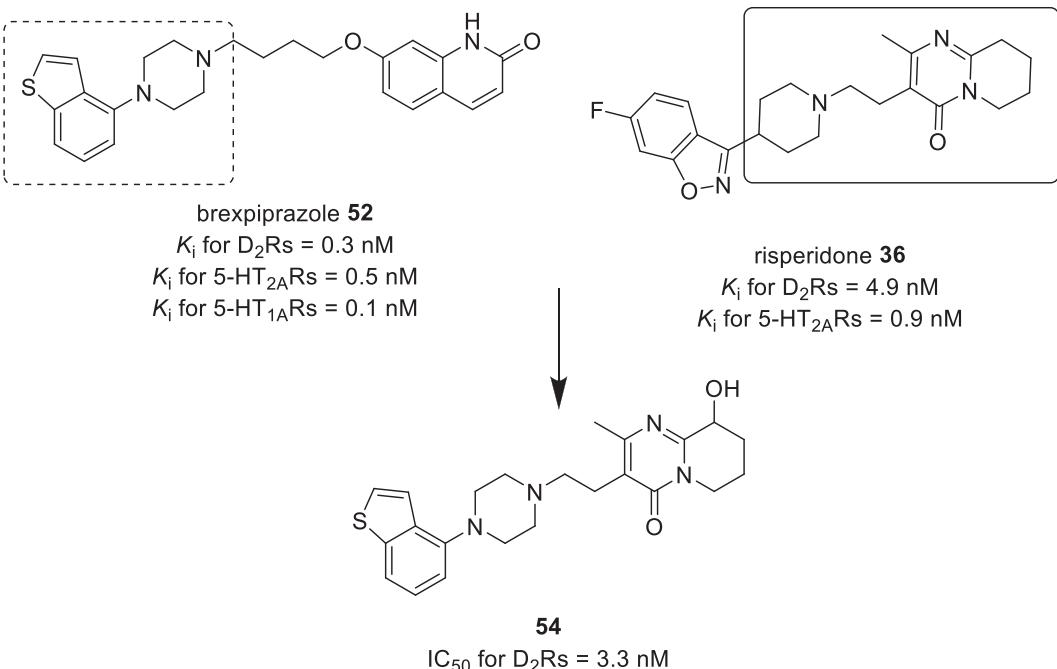


FIGURE 31 Design of the 6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one derivative **54**, from **36** and **52**.

and H₁ receptors and for hERG channels, suggesting potential antipsychotic properties with a low propensity for inducing orthostatic hypotension, weight gain and QT prolongation. In animal models, 54 (ED₅₀ = 0.02 mg/kg, i.g.) reduced PCP-induced hyperactivity, with a high threshold for catalepsy (ED₅₀ = 0.8 mg/kg, p.o.) induction in mice.⁶³⁸

2.5.1.4 | 4-(Pyridin-2-yl)/4-(pyrimidin-2-yl)-1-substituted piperazine analogs in binding to D₂Rs

Pyridine, a six membered heterocycle containing one nitrogen atom in its ring, has been found in biologically occurring compounds such as nicotinic acid, vitamin B₆, and nicotinamide adenine dinucleotide.^{639,640} It is therefore not surprising that medicinal chemists use this fragment for the synthesis of drugs with wide range of therapeutic effects, for example, anticancer, antidiabetic, and antimicrobial agents, or drugs for treatment of neurological diseases.^{639,641–643}

Pyrimidine is a flat, six membered heterocyclic compound bearing two nitrogen atoms in its ring.^{639,644} These two nitrogens are in meta-position with each other.⁶⁴⁴ The pyrimidine scaffold has received great interest since it was discovered to be part of human nucleic acids and some vitamins (e.g., thiamine, riboflavin and folic acid).^{644,645} Thus, it is frequently used as an important pharmacophore for the synthesis of many agents with anticancer and antimicrobial properties, or for management of neurological illnesses.^{639,644} In the following lines, we discuss with compounds that contain pyrimidine or pyridine rings in their structure, and their impact on D₂Rs.

It can be summarized that central linker has a great effect on affinity at D₂Rs. The initial compound 2-(3-(4-(pyrimidin-2-yl)piperazin-1-yl)propyl)-3,4-dihydroisoquinolin-1(2H)-one (55a, Figure 32) exhibited no binding affinity toward D₂Rs, but its butane-1,4-diyI analog (55b, Figure 32) showed 61% displacement at 10 μM.⁶⁴⁶ Another example is 2-((4-(pyridin-2-yl)piperazin-1-yl)methyl)-1H-indole (56a, Figure 32), which activated canonical

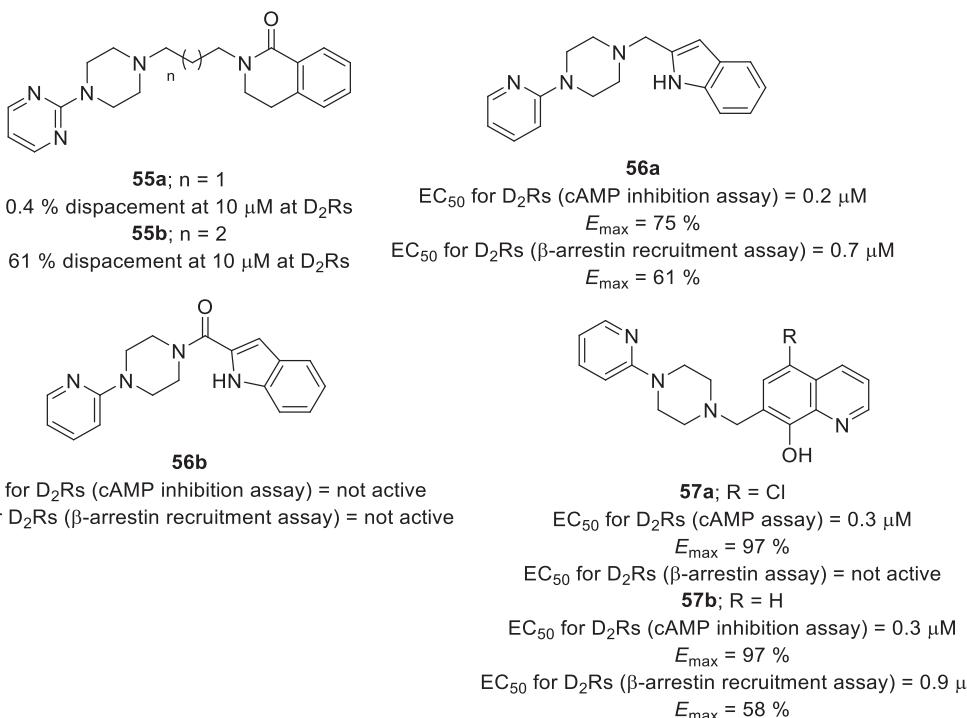


FIGURE 32 Highlighted D₂R modulators 55a–b, 56a–b, and 57a–b bearing 4-(pyridin-2-yl)/4-(pyrimidin-2-yl)-1-substituted piperazine derivatives.

and noncanonical signaling of D₂Rs with submicromolar EC₅₀ values, whereas (1H-indol-2-yl)(4-(pyridin-2-yl)piperazin-1-yl)methanone (**56b**, Figure 32) was inactive.⁶⁴⁷

Different substitutions within the lipophilic aromatic fragment strongly influenced the D₂Rs functional activity. 5-Chloro-7-((4-(pyridin-2-yl)piperazin-1-yl)methyl)quinolin-8-ol (**57a**, Figure 32) exhibited biased agonism for the canonical D₂R signaling cascade, while 7-((4-(pyridin-2-yl)piperazin-1-yl)methyl)quinolin-8-ol (**57b**, Figure 32) was agonistic towards canonical and partially agonistic (according to E_{max} value) toward noncanonical D₂R signaling pathways.⁶⁴⁸

2.5.1.5 | Analogs bearing 4-(piperazin-1-yl)-indole or 4-(1,2,3,6-tetrahydropyridin-4-yl)-indole systems in affinity for D₂Rs

Indole or benzo[b]pyrrole is an organic planar heteroaromatic compound containing a six-membered benzene ring fused to the five-membered nitrogen-bearing pyrrole ring.^{649,650} This structure fragment is a universal constituent of pharmacologically active natural molecules.^{649,651} Tryptophan, an indole/benzo[b]pyrrole containing essential amino acid, is used as a building block in protein biosynthesis. In addition, this compound is found to be a biochemical precursor for different molecules in human body, for example, melanin of 5-HT.^{649,652} Thus, the unique pharmacological profile of natural compounds bearing indole moieties has motivated many medicinal chemists to synthesize new potential drugs with various properties.⁶⁴⁹ In this part of the review, we focus on the compound-bearing indole core and how it influences D₂Rs.

Inspired by **7**, D₂R β-arrestin-biased indole-based modulators have been developed (Figure 33).⁶⁵³ Crystal structure of turkey β₁ adrenergic receptor in complex with an indole-piperazine moiety (**58**, Figure 33) showed that the indole sits in the orthosteric site near transmembrane helix 5 and extracellular loop 2. The indole-NH moiety forms a hydrogen bond with serine 5.42 in transmembrane helix 5.⁶⁵⁴ Like D₂Rs, β₁ adrenergic receptors are members of GPCRs family.^{49,655} Therefore, design strategy has focused on the replacement of the 2,3-dichlorophenyl-piperazine fragment of aripiprazole with an indole-piperazine moiety.⁶⁵³ In functional activities, only **58a** (Figure 33) exerted significant biased features for β-arrestin2 recruitment, and therefore **58a** represents a potential tool to elucidate the noncanonical D₂R signaling pathway in diseases such as schizophrenia.⁶⁵³

Novel 5-HT₆R antagonists and D₂R partial agonists have been prepared as potential drugs for the treatment of behavioral and psychological dementia symptoms.⁶⁵⁶ These novel analogs were based on structures of **7** (Figure 34) and 1-(phenylsulfonyl)-4-(piperazin-1-yl)-1H-0indole (**59**; K_i for 5-HT₆R = 1.0 nM⁶⁵⁷; Figure 34). The concept of this dual receptor-targeting approach (5-HT₆/D₂ receptors) has already been proposed by Kołaczkowski et al.^{613,623,624} Compound **59a** was characterized by strong antagonism towards 5-HT₆Rs and by partial blocking and agonistic activity towards D₂Rs.⁶⁵⁶ Due to high affinity for the main targets (D₂ and 5-HT₆ receptors) and no significant activity towards off-targets (M₁AChRs and hERG channels), **59a** (Figure 34, Table 13) was subjected to further studies. It exhibited potent antidepressant (Porsolt FST in rats, 1 mg/kg, i.p.) and anxiolytic-like properties in the Vogel conflict drinking (rats, 1 mg/kg, i.p.) and open field tests (rats, 3 mg/kg, i.p.). In operant conditioning tests, **59a** (1 mg/kg, i.p., rats) enhanced response for sweet rewards in the saccharin self-administration test, consistent with anti-anhedonic properties. In addition, **59a** (3 mg/kg, i.p.) facilitated extinction of nonreinforced response for sweet rewards, suggesting procognitive activity.⁶⁵⁶

3-(1,2,3,6-Tetrahydropyridin-4-yl)-1H-indole ligands with arylsulfonamide functional groups have been developed to mitigate behavioral and psychological symptoms of dementia.⁶⁵⁸ The study exploited computer-aided drug design constructing a series of multifunctional ligands, combining a 5-HT₇ receptor-blocking arylsulphonamide moiety (SB-258719; **41**; Figure 35) with 3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole (**60**, Figure 35), a fragment displaying SERT inhibition and high affinity for D₂Rs.^{613,622–624,658} Compound **60a** (Figure 35, Table 13) was the top-ranked candidate of this series in vitro. Binding studies revealed that **60a** was a partial agonist of D₂Rs, with antagonistic properties towards 5-HT₆ and SERT. Additionally, **60a** (1.3 mg/kg, i.p.) exhibited antipsychotic-like activity in MK-801-induced hyperlocomotion test in mice. It also displayed antidepressant- (FST) and anxiolytic-like activity (four-plate test) in mice (0.6–1.3 mg/kg, i.p.). Furthermore, **60a**

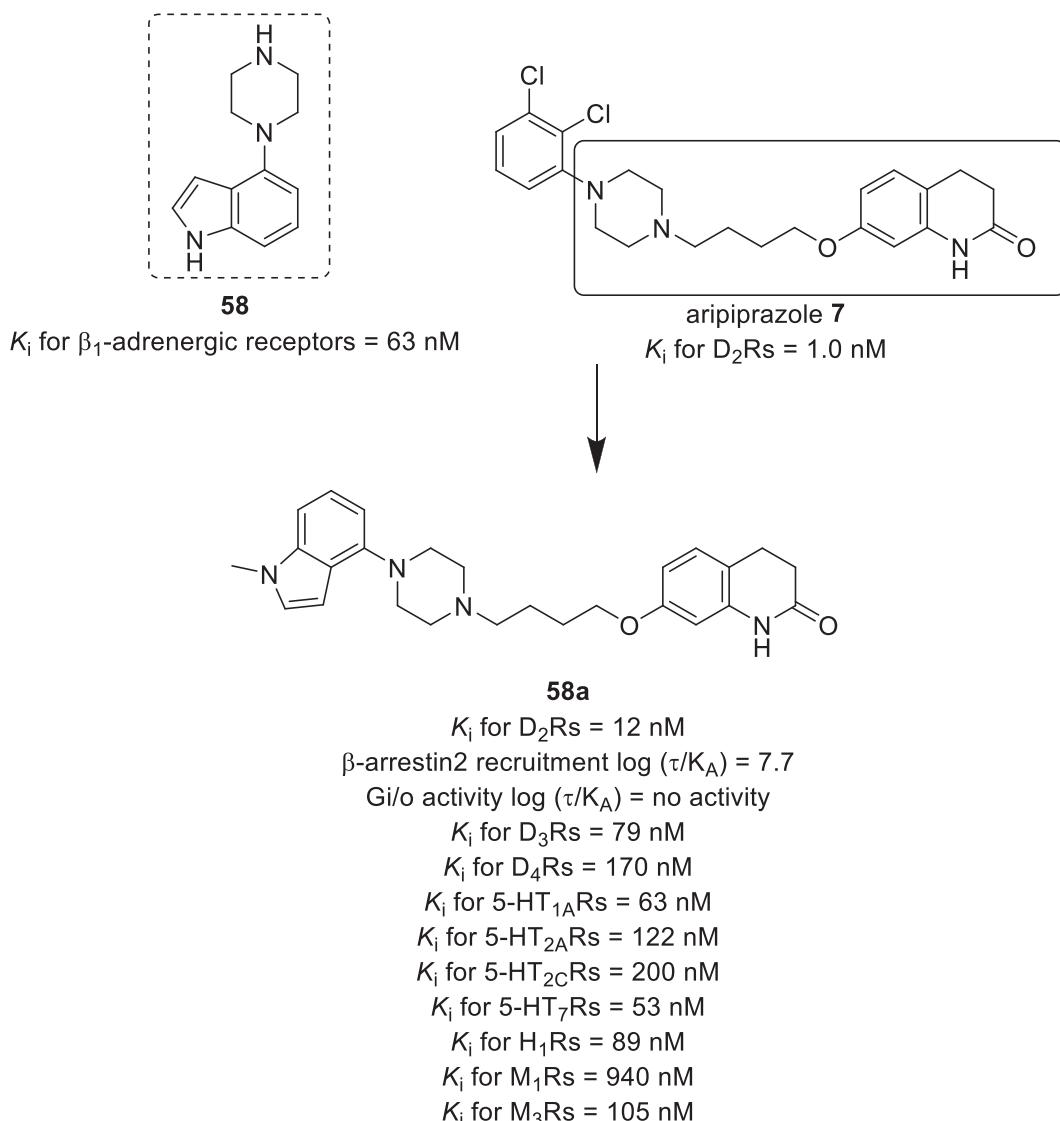


FIGURE 33 Design of the (4-(1-methyl-1H-indol-4-yl)piperazin-1-yl)butoxy derivative **58a**, based on **7** and **58**.

did not cause catalepsy ($ED_{50} > 100$ mg/kg, i.p.) and inhibited spontaneous locomotor activity (up to 10 mg/kg) in mice. It also demonstrated memory-enhancing properties and ameliorated memory deficit induced by the anticholinergic agent scopolamine (0.3 mg/kg, i.p.). In summary, these results suggest that **60a** may be beneficial in managing both cognitive and noncognitive (behavioral and psychological) symptoms of dementia.⁶⁵⁸

Originally, structure-based virtual screening identified a novel class of antagonists to D_2 Rs.⁶⁵⁹ Building on that, a small family of 3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole ligands has emerged as modulators of DA/5-HT systems.⁶⁶⁰ Compound **61** (D2AAK1,⁶⁵⁹ Figure 36) was highlighted as the lead for targeting D_2 , 5- HT_{1A} , and 5- HT_{2A} receptors. Given the promising binding affinities and functional activities for desired aminergic GPCRs, **62** (D_2 R antagonist, Figure 36, Table 13) was selected for behavioral studies.⁶⁶⁰ In mice, **62** (50 mg/kg, i.p.) coadministration with amphetamine (5 mg/kg) decreased amphetamine-induced hyperactivity, highlighting its

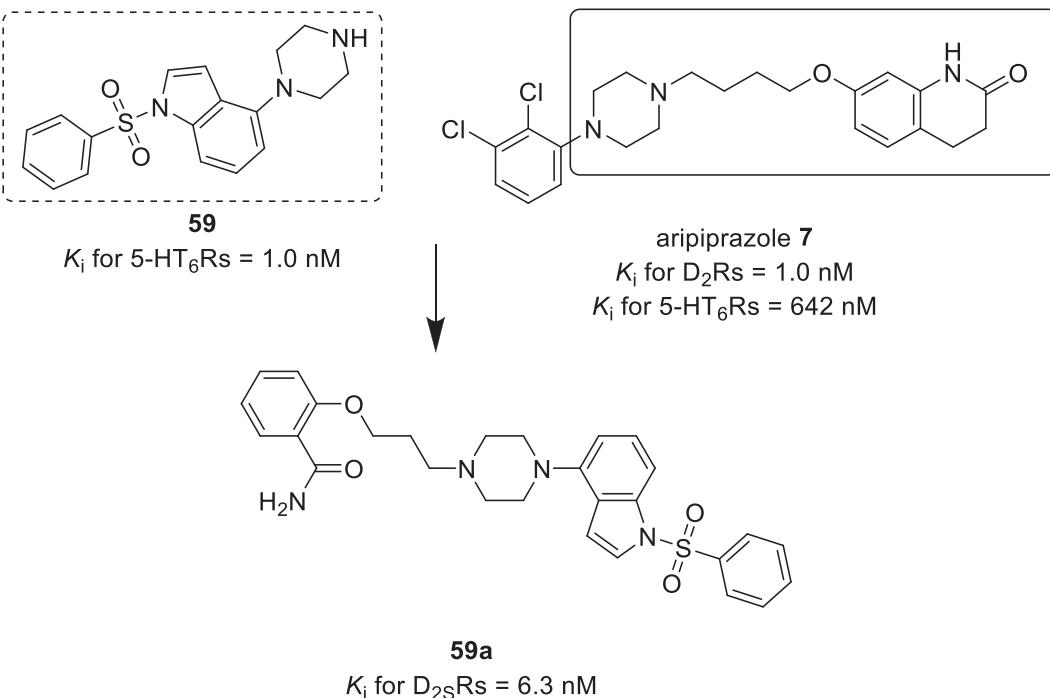


FIGURE 34 Design of the (4-(1-(phenylsulfonyl)-1H-indol-4-yl)piperazin-1-yl)propoxy analog **59a**, from **7** and **59**.

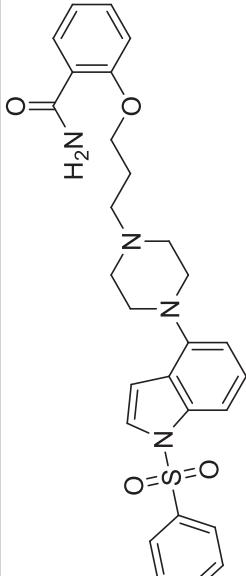
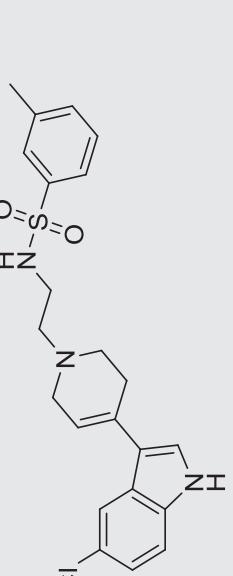
antipsychotic activity. Additionally, **62** (50 mg/kg, i.p., mice) decreased immobility time in the antidepressant FST in mice and displayed a procognitive effect.⁶⁶⁰

Compound **61** (Figure 36, Table 13) was subjected to a biochemical study revealing D₂ and 5-HT_{2A} receptor antagonism and 5-HT_{1A} receptor partial agonism.⁶⁶¹ Its coadministration (100 mg/kg, i.p.) with amphetamine (5 mg/kg, s.c.) decreased amphetamine-induced hyperactivity in mice, suggesting a neuroleptic effect. Treatment with **61** (100 mg/kg, i.p., mice) also showed anxiolytic-like properties in the EPM test, along with pro-cognitive potential.⁶⁶¹

2.5.1.6 | Haloperidol analogs as D₂R modulators

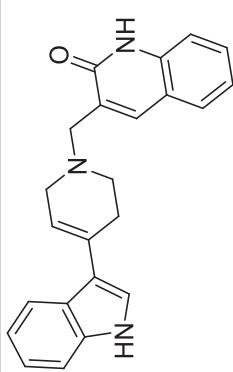
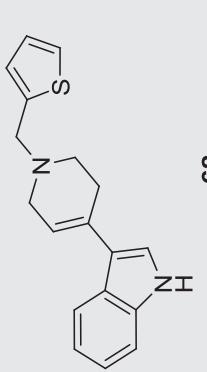
Haloperidol (**63**; Figure 37), a molecule containing a 4-(4-chlorophenyl)piperidin-4-ol moiety, is typical neuroleptic agent with noticeable D₂R antagonism.^{4,62} According to a meta-analysis from 2013, haloperidol was the top-ranked neuroleptic agent with the most profound extrapyramidal side effects of a group of 15 neuroleptics.⁶⁶² It can be concluded that extrapyramidal side effects of neuroleptics are linked to their association kinetics with D₂Rs.⁶⁶³ For example, **63** exhibited an undesirable fast association (k_{on})/slow dissociation (k_{off}) profile ($k_{on} = 1.3 \times 10^9 \text{ M}^{-1} \text{ min}^{-1}$, $k_{off} = 0.6 \text{ min}^{-1}$) with D₂Rs, which might contribute to its on-target side effects (extrapyramidal side effects) and satisfactory off-target profile (see Table 3, no affinity for 5-HT_{2C}, H₁, M₁ACh, and M₃ACh receptors) compared to clozapine (**64**, Figure 37). On the other hand, **64** displayed the desired slow association/rapid dissociation profile ($k_{on} = 8.2 \times 10^7 \text{ M}^{-1} \text{ min}^{-1}$, $k_{off} = 1.7 \text{ min}^{-1}$), which results in practically no on-target (extrapyramidal) side effects, but also displayed an inconvenient pharmacological profile (**64** exhibited affinity for many aminergic GPCRs, contributing to its off-target side effects, see Table 3).^{663,664} Fast dissociation of a D₂R antagonist (e.g., **63**) might allow a fraction of D₂Rs to be occupied by transiently high concentrations of DA released into the synaptic cleft, whereas a D₂R antagonist with a slow dissociation rate (for instance, **63**) would promote insurmountable antagonism and thus could cause extrapyramidal side-effects. Reduced affinity at D₂Rs is generally associated with

TABLE 13 Highlighted compounds **59a**, **60a**, **61**, and **62** bearing 4-(piperazin-1-yl)-indole or 4-(1,2,3,6-tetrahydropyridin-4-yl)-indole fragments, with their chemical structures and properties

Chemical structures	Binding affinities	Functional activities	BBB score ^a	Behavioral test
	K_i for $D_2Rs = 6.3\text{ nM}$ K_i for $D_3Rs = 0.1\text{ nM}$ K_i for $D_4Rs = 7.1\text{ nM}$ K_i for $5-HT_{1AR}s = 6.7\text{ nM}$ K_i for $5-HT_{2AR}s = 29\text{ nM}$ K_i for $5-HT_6Rs = 1.0\text{ nM}$ K_i for $5-HT_7Rs = 180\text{ nM}$ K_i for $\alpha_1Rs = 17\text{ nM}$ K_i for $H_1Rs = 160\text{ nM}$	K_b for $D_{2i}Rs = 3.7\text{ nM}$ EC_{50} for $D_{2i}Rs = 54\text{ nM}$ K_b for $D_3Rs = 91\text{ nM}$ K_b for $5-HT_{1AR}s = 47\text{ nM}$ K_b for $5-HT_6Rs = 1.8\text{ nM}$ K_b for $\alpha_{1A}Rs = 6.7\text{ nM}$	2.97	59a (1 mg/kg, i.p., rat)—antidepressant and anxiolytic-like properties 59a (1 mg/kg, i.p., rat)—active in the saccharin self-administration test
	K_i for $D_2Rs = 33\text{ nM}$ K_i for $5-HT_{1AR}s = 1.8\text{ nM}$ K_i for $5-HT_6Rs = 6.4\text{ nM}$ K_i for $5-HT_7Rs = 0.8\text{ nM}$ K_i for $SERT = 50\text{ nM}$	EC_{50} for $D_{2i}Rs = 56\text{ nM}$ $E_{max} = 56\%$ K_b for $D_{2i}Rs = 2.1\text{ nM}$ K_b for $5-HT_6Rs = 5.6\text{ nM}$ IC_{50} for 5-HT uptake = 17 nM	4.44	60a (1.3 mg/kg, i.p., mice)—antipsychotic-like activity in MK 801-induced hyperlocomotion test 60a (0.6–1.3 mg/kg, i.p., mice)—antidepressant- and anxiolytic-like activity 60a ($ED_{50} > 100$ mg/kg, i.p., mice)—no catalepsy 60a (0.3 mg/kg, i.p., mice)—memory-enhancing properties

(Continues)

TABLE 13 (Continued)

Chemical structures	Binding affinities	Functional activities	BBB score ^a	Behavioral test
	K_i for D ₂ Rs = 58 nM K_i for 5-HT _{1A} Rs = 125 nM K_i for 5-HT _{2A} Rs = 358 nM	K_b for D ₂ Rs = 4.5 nM IC_{50} for 5-HT _{2A} Rs = 931 nM EC_{50} for 5-HT _{1A} Rs = 597 nM E_{max} = 39%	4.38	61 (100 mg/kg, i.p., mice)–decreasing amphetamine-induced hyperactivity 61 (100 mg/kg, i.p., mice)–anxiolytic-like properties 61 (100 mg/kg, i.p., mice)–proognitive impact
	K_i for D ₂ Rs = 72 nM K_i for 5-HT _{1A} Rs = 305 nM K_i for 5-HT _{2A} Rs = 171 nM	K_b for D ₂ Rs = 5.0 nM E_{max} for 5-HT _{1A} Rs = 67% IC_{50} for 5-HT _{2A} Rs = 2415 nM	5.14	62 (50 mg/kg, i.p., mice)–decreasing amphetamine-induced hyperactivity 62 (50 mg/kg, i.p., mice)–antidepressant properties 62 (50 mg/kg, i.p., mice)–proognitive effect

^aThe calculations were realized according to reference.⁵⁵²

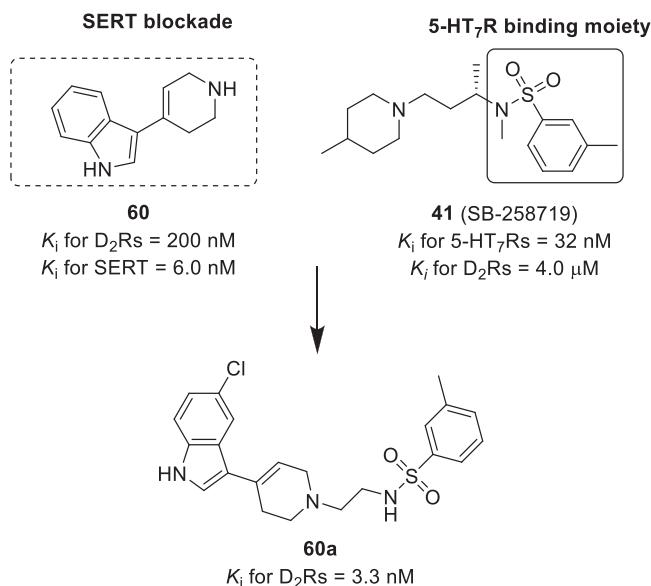


FIGURE 35 The 4-(5-Chloro-1H-indol-3-yl)-3,6-dihydropyridin-1(2H)-yl)ethyl analog **60a**, generated from computer-aided design with structural similarity to **41** and **60**.

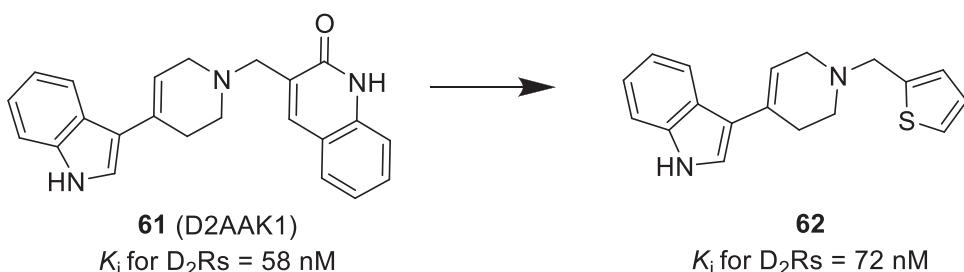


FIGURE 36 The 3-(1-(Thiophen-2-ylmethyl)-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole analog **62** and its pattern molecule, **61**.

decreasing k_{on} , and thus a compound with reduced D₂R affinity compared to **63** would probably not produce extra-pyramidal side effects.⁶⁶⁴

One SAR study aimed to obtain a compound structurally related to **63** with a clozapine-like kinetic profile (slow association/rapid dissociation) and haloperidol-like pharmacological profile.⁶⁶⁴ In total, 50 compounds were synthesized. SAR elucidation concentrated on four different regions: (i) the 4-Cl-phenyl fragment as aromatic head group, (ii) the 4-F-phenyl core as aromatic/heteroaromatic lipophilic fragment, (iii) the keto-alkyl moiety as a central linker, and (iv) the piperidinol element structure as a cyclic amine (Figure 12). All newly developed derivatives retained antagonism toward D₂Ls. Switching the position of fluorine on the 4-F-phenyl core and/or introducing an extra fluorine atom (e.g., **65a** with 2,3-F, Figure 37) from the structure of **63** (4-F) reduced the D₂L response two-fold (pK_a). Modifying ketone-alkyl linker also resulted in decreased D₂R binding affinity when compared to **63**. For instance, converting the ketone (**63**) to a truncated alkyl-chain (**65d**, 1,3-propane-diyl, Figure 37) cyclic moiety (**65b**, cis-1,2-cyclopropane-diyl, Figure 37) or elongation of ketone-alkyl chain (**65c**, pentane-1-one-1,5-diyl, Figure 37) yielded a significant drop in D₂R affinity. In this family, **65a-d** exhibited reduced, but still acceptable, affinities towards D₂Rs compared to **63**, as well as improved kinetic

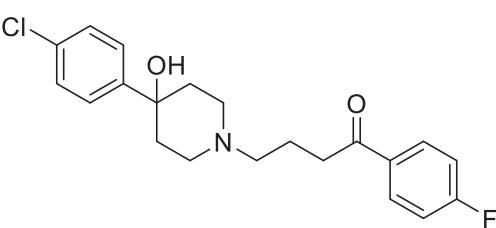
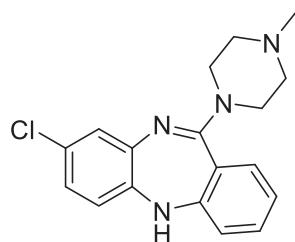
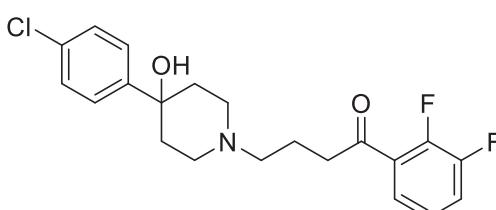
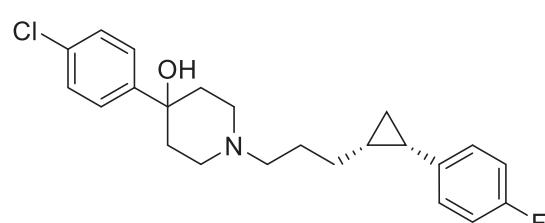
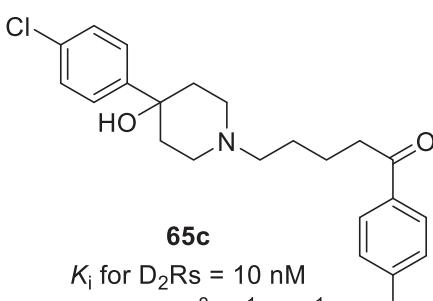
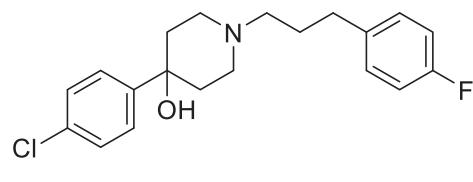
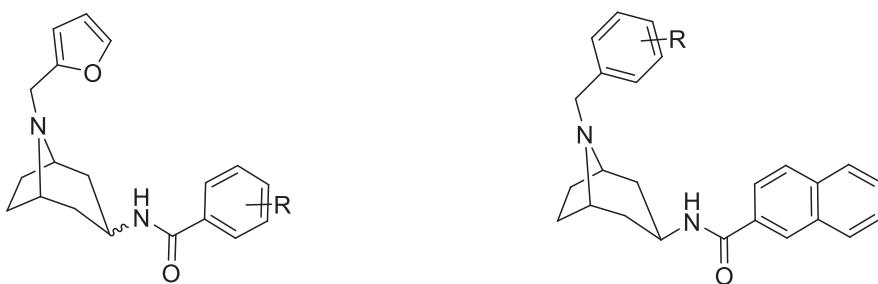
haloperidol **63** K_i for D₂Rs = 0.5 nM K_i for D₂Rs = 2.0 nM $k_{on} = 1.3 \times 10^9 \text{ M}^{-1} \text{ min}^{-1}$ $k_{off} = 0.6 \text{ min}^{-1}$ clozapine **64** K_i for D₂Rs = 431 nM $k_{on} = 8.2 \times 10^7 \text{ M}^{-1} \text{ min}^{-1}$ $k_{off} = 1.7 \text{ min}^{-1}$ **65a** K_i for D₂Rs = 40 nM $k_{on} = 3.0 \times 10^7 \text{ M}^{-1} \text{ min}^{-1}$ $k_{off} = 1.3 \text{ min}^{-1}$ **65b** K_i for D₂Rs = 32 nM $k_{on} = 4.5 \times 10^7 \text{ M}^{-1} \text{ min}^{-1}$ $k_{off} = 1.4 \text{ min}^{-1}$ **65c** K_i for D₂Rs = 10 nM $k_{on} = 1.4 \times 10^8 \text{ M}^{-1} \text{ min}^{-1}$ $k_{off} = 1.7 \text{ min}^{-1}$ **65d** K_i for D₂Rs = 63 nM $k_{on} = 2.3 \times 10^7 \text{ M}^{-1} \text{ min}^{-1}$ $k_{off} = 1.5 \text{ min}^{-1}$

FIGURE 37 Chemical structures of haloperidol (**63**), clozapine (**64**), and haloperidol-like analogs **65a-d** with improved pharmacokinetics compared to **63**.

parameters (similar to **64**), and thus represent a novel class of potential candidates for the treatment of schizophrenia without extrapyramidal side-effects and hyperprolactinemia.⁶⁶⁴

2.5.1.7 | Tropane ring as a cyclic amine in modulating D₂Rs

To-date, approximately 200 various tropane alkaloids have been identified and isolated.⁶⁶⁵ Probably the most famous tropane alkaloid, derived from *Erythroxylum coca*, is cocaine.^{666,666} Cocaine is centrally available and inhibits all three monoamine transporters—DAT, NET, and SERT—with similar potency,⁶⁶⁷ as tropane itself can serve as a replacement for the piperidine or piperazine ring. This section is devoted to tropane ligands and their effect on D₂Rs.



α66a; R = 2,3-OMe; K_i for D₂Rs > 100,000 nM

β66a; R = 2,3-OMe; K_i for D₂Rs = 26 nM

β66b; R = 3,4-OMe; K_i for D₂Rs = 68,800 nM

β66c; R = 2-Me; K_i for D₂Rs = 118 nM

β66d; R = 4-Me; K_i for D₂Rs = 0.4 nM

FIGURE 38 Highlighted D₂R ligands **α66a** and **β66a-d** bearing tropane rings as cyclic amines, with different substitutions for aromatic heads or aromatic lipophilic tails.

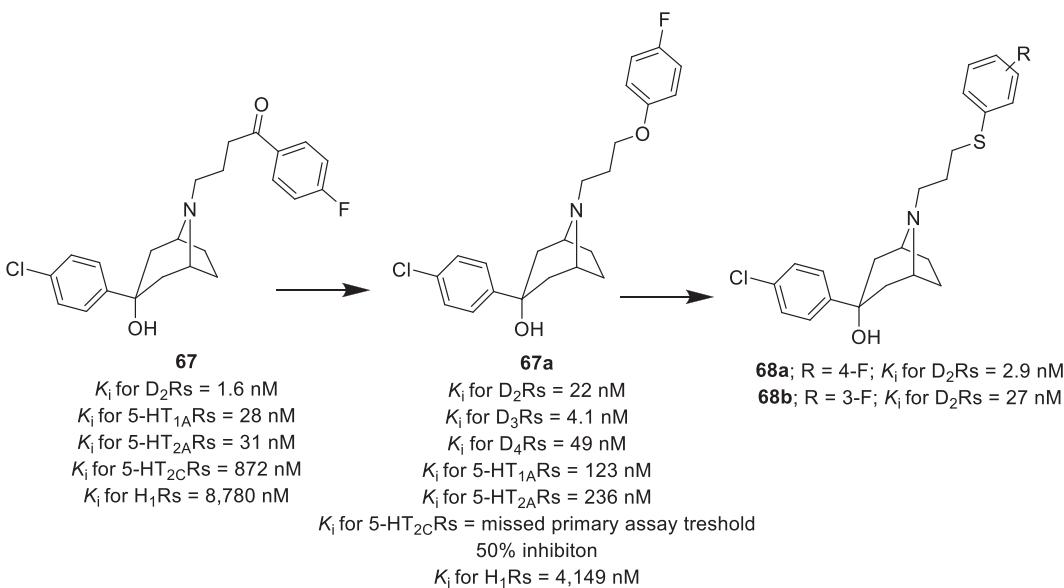


FIGURE 39 Design of 8-substituted-3-(4-chlorophenyl)tropan-3-ol ligands **67a** and **68a-b** from the maternal scaffold of **67**.

Only β-tropane derivatives are endowed with high D₂R affinity (**β66a** in comparison with **α66a** (Figure 38)).⁶⁶⁸ The proper substitution of an aromatic moiety connected with tropane (for instance, (**β66a** compared to **β66b**, Figure 38))⁶⁶⁸ or lipophilic aromatic fragment (e.g., **β66c** correlated to **β66d**, Figure 38)⁶⁶⁹ positively impact D₂R affinity. D₂R affinity is also greatly affected by various substitutions within the aromatic moiety attached to tropane and to the lipophilic aromatic tail (Figure 12).

Derivatives of 8-substituted-3-(4-Cl-phenyl)tropan-3-ol with multimodal affinity have been developed as new antipsychotics, modulating D₂, 5-HT_{1A}, and 5-HT_{2A} receptors and exhibiting no activity at 5-HT_{2C} and H₁ receptors.⁶⁷⁰ Compound **67** (Figure 39) became a valid starting template for the new family.⁶⁷¹ **67a** (Figure 39) exhibited the most promising activities on the receptors of interest, and no significant affinity for 5-HT_{2C} or H₁

receptors.⁶⁷⁰ Compound **68a–b** (Figure 39, Table 14), derived from **67a**, showed potent binding to D₂Rs, although **68b** exhibited an 9-fold lower affinity compared to **68a**.⁶⁷² This D₂R binding affinity turned out to be similar to that of the literature reported value for olanzapine (K_i; 20 nM).⁶⁷³ Spurred on by this observation, the authors selected **68a** and **68b** for comparative evaluation in animal models predictive of antipsychotic efficacy and extra-pyramidal side effects.⁶⁷² Compounds **68a** (ED₅₀ = 0.2 mg/kg, i.p.) and **68b** (ED₅₀ = 3.1 mg/kg, i.p.) inhibited apomorphine-climbing behavior in mice, suggesting antipsychotic properties. These results (values of ED₅₀) are consistent with the fact, that **68a** is more potent than **68b** towards D₂Rs. A catalepsy bar test revealed that the minimum adverse effective dose of **68a** for inducing catalepsy in rats was 0.6 mg/kg (i.p.) (or 3× times higher than its ED₅₀ value for reversal of apomorphine-induced climbing behavior). Meanwhile, **68b** induced catalepsy in rats with the minimum adverse effective dose of 12.7 mg/kg (i.p.), which is 4.1-times higher than the ED₅₀ of its reversal of apomorphine-induced climbing behavior. These results are consistent with the hypothesis that further moderation of the binding affinity for D₂Rs would attenuate catalepsy potential in humans.⁶⁷²

The aim of another study⁶⁶⁸ was the synthesis of acyl derivatives in the chemical group of 3β-aminotropanes as potential modulators of 5-HT_{1A}, 5-HT_{2A}, and D₂Rs. A **β69** (N-benzyltropane, Figure 40) derivative was characterized by the most favorable binding affinities for target receptors, and exhibited strong 5-HT_{2A}Rs antagonism (5, 10, and 20 mg/kg, i.p.) in the head twitch test.⁶⁶⁸

Another series of 3β-aminotropanes based on **β69** (Figure 40) have been synthesized with a purpose to examine if the presence of a 2-, 3-, or 4-substituent (Me, OMe, F, Cl, Br, CF₃) in the benzyl ring would enhance the activity (5-HT_{1A}, 5-HT_{2A}, and D₂Rs) of the investigated analogs of **β69**.⁶⁶⁹ The compound **β70** (Figure 40, Table 14) was subjected to further evaluation due to high affinities for the main targets.⁶⁶⁹ This compound (1.3 mg/kg, i.p.) exhibited antagonistic activity against DOI-induced head twitches in mice, suggesting antagonistic properties on 5-HT_{2A}Rs. Furthermore, **β70** (10 mg/kg, i.p.) reduced apomorphine-induced climbing behavior in mice, suggesting D₂R antagonism. Importantly, **β70** was stable in human liver microsomes (*t*_{1/2} > 45 min).⁶⁶⁹

As a continuation of previous studies,^{668,669} various 3β-aminotropanes were developed with atypical antipsychotic profiles.⁶⁷⁴ These modulators were evaluated for their affinity toward D₂, 5-HT_{1A}, and 5-HT_{2A} receptors. The purpose of this study was to continue searching for new compounds with antipsychotic potential in group of derivatives based on **β66d**⁶⁶⁹ (Figure 38). These new ligands possessed a quinoline or naphthalene ring connected with a tropane core via amide bonds in the equatorial (β) position, as well as variously substituted benzyl moieties connected to the nitrogen atom of tropane in position 8. Among the synthesized analogs, **β71a** (D₂R antagonist, Figure 40, Table 14) and **β71b** (D₂R antagonist, Figure 40, Table 14) had the most promising binding profile for the main targets and thus were selected for further biological studies. Both **β71a** and **β71b** (both compounds at 5 and 10 mg/kg, i.p.) significantly reduced MK-801-induced locomotor hyperactivity in mice. Similarly, **β71a** (5 and 10 mg/kg, i.p.) and **β71b** (only at 10 mg/kg, i.p.) markedly reduced locomotor hyperactivity induced by D-amphetamine in mice. These results suggest that **β71a** and **β71b** possess antipsychotic potential. In addition, **β71b** (5 mg/kg, i.p.) exhibited antidepressant properties during FSTs in mice.⁶⁷⁴

2.5.1.8 | Bivalent ligands in modulating D₂Rs

Homobivalent ligands of the atypical antipsychotic **64** (Figure 41) have been obtained with the aim of producing derivatives with increased affinity, selectivity, efficacy, or activity towards D₂Rs.¹⁰ The design of these analogs is depicted in Figure 41. Ligands based on **64** with attachments on the N_{4'} were synthesized in previous studies,^{675–677} and modification at this position was well tolerated. Therefore, the authors suggested¹⁰ that this position was suitable for introducing a linker to produce homobivalent ligands. The most ideal length of a central linker connected in position N_{4'} of piperazine ring was 16 atoms (72b, Figure 41) for D₂R, compared to trials with 14 atoms (72a, Figure 41) and with 18 atoms (72c, Figure 41). Hill slopes for 72a–c were closed to 1, suggesting that these derivatives did not exhibit positive cooperative binding.¹⁰

The chemical structures and binding affinities for D₂Rs of new homobivalent 2-methoxyphenyl piperazine ligands **73a–g**⁵⁴¹ are summarized in Table 15. The authors used a vanilline-derived carbocyclic moiety, which could

(Continues)

TABLE 14 Highlighted D₂R modulators 68a–b, β70, and β71a–b bearing a tropane ring as a cyclic amine, with their chemical structures and properties

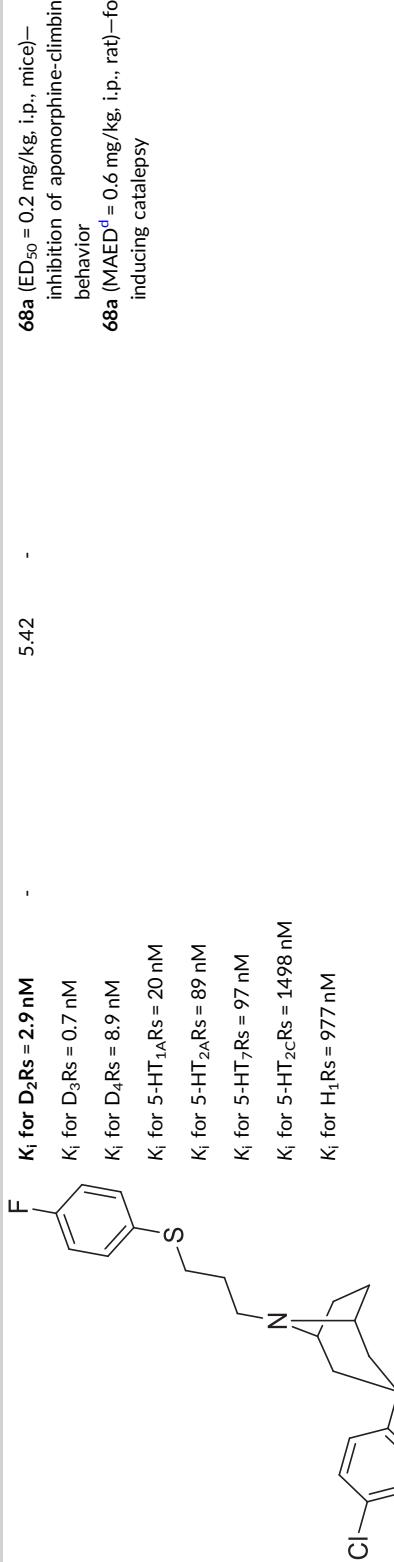
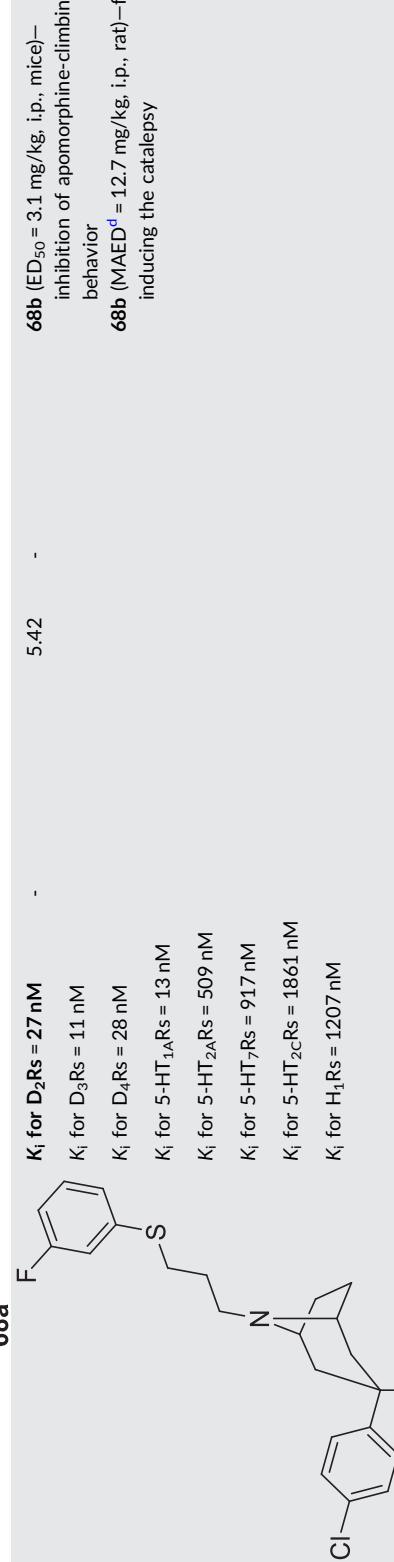
Chemical structures	Binding affinities	Functional activities	BBB score ^a	PD/PK ^b properties	Behavioral test
 <p>F K_i for D₂Rs = 2.9 nM K_i for D₃Rs = 0.7 nM K_i for D₄Rs = 8.9 nM K_i for 5-HT_{1A}Rs = 20 nM K_i for 5-HT_{2A}Rs = 89 nM K_i for 5-HT₇Rs = 97 nM K_i for 5-HT_{2C}Rs = 1498 nM K_i for H₁Rs = 977 nM</p>	K_i for D ₂ Rs = 2.9 nM K_i for D ₃ Rs = 0.7 nM K_i for D ₄ Rs = 8.9 nM K_i for 5-HT _{1A} Rs = 20 nM K_i for 5-HT _{2A} Rs = 89 nM K_i for 5-HT ₇ Rs = 97 nM K_i for 5-HT _{2C} Rs = 1498 nM K_i for H ₁ Rs = 977 nM	5.42	-	68a (ED_{50} = 0.2 mg/kg, i.p., mice)—inhibition of apomorphine-climbing behavior 68a (MAED ^d = 0.6 mg/kg, i.p., rat)—for inducing catalepsy	
 <p>F K_i for D₂Rs = 27 nM K_i for D₃Rs = 11 nM K_i for D₄Rs = 28 nM K_i for 5-HT_{1A}Rs = 13 nM K_i for 5-HT_{2A}Rs = 509 nM K_i for 5-HT₇Rs = 917 nM K_i for 5-HT_{2C}Rs = 1861 nM K_i for H₁Rs = 1207 nM </p>	K_i for D ₂ Rs = 27 nM K_i for D ₃ Rs = 11 nM K_i for D ₄ Rs = 28 nM K_i for 5-HT _{1A} Rs = 13 nM K_i for 5-HT _{2A} Rs = 509 nM K_i for 5-HT ₇ Rs = 917 nM K_i for 5-HT _{2C} Rs = 1861 nM K_i for H ₁ Rs = 1207 nM	5.42	-	68b (ED_{50} = 3.1 mg/kg, i.p., mice)—inhibition of apomorphine-climbing behavior 68b (MAED ^d = 12.7 mg/kg, i.p., rat)—for inducing the catalepsy	

TABLE 14 (Continued)

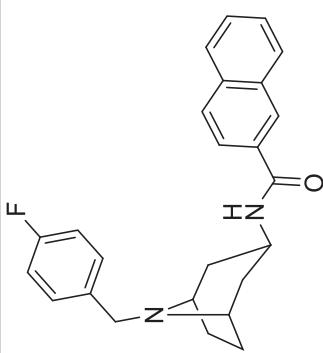
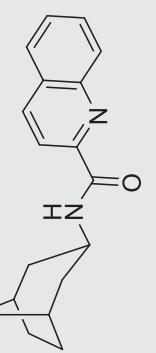
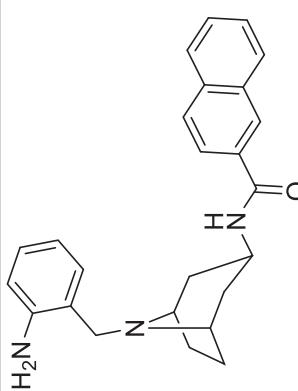
Chemical structures	Binding affinities	Functional activities	BBB score ^a	PD/PK ^b properties	Behavioral test
	K_i for $D_2Rs = 137 \text{ nM}$ K_i for $5-HT_{1A}Rs = 218 \text{ nM}$ K_i for $5-HT_{2A}Rs = 209 \text{ nM}$	-	4.93	$\beta70-t_{1/2}^c > 45 \text{ min}$ human liver microsomes	$\beta70$ (10 mg/kg, i.p., mice)—reduction of apomorphine-induced climbing behavior
	K_i for $D_2Rs = 7.4 \text{ nM}$ K_i for $5-HT_{1A}Rs = 44 \text{ nM}$	IC_{50} for $D_2Rs = 37 \text{ nM}$ IC_{50} for $5-HT_{1A}Rs = 131 \text{ nM}$	4.84	-	$\beta71a$ (5 and 10 mg/kg, i.p., mice)—reduction of MK-801-induced locomotor hyperactivity $\beta71a$ (5 and 10 mg/kg, i.p., mice)—reduction of locomotor hyperactivity induced by D-amphetamine

TABLE 14 (Continued)

Chemical structures	Binding affinities	Functional activities	BBB score ^a	PD/PK ^b properties	Behavioral test
	K_i for $D_2Rs = 42\text{ nM}$ K_i for $5-HT_{1A}Rs = 53\text{ nM}$	IC_{50} for $D_2Rs = 210\text{ nM}$ IC_{50} for $5-HT_{1A}Rs = 160\text{ nM}$	4.59 -		$\beta71b$ (5 and 10 mg/kg, i.p., mice)—reduction of MK-801-induced locomotor hyperactivity $\beta71b$ (10 mg/kg, i.p., mice)—reduction of locomotor hyperactivity induced by D-amphetamine $\beta71b$ (FST—5 mg/kg, i.p., mice)—antidepressant properties

 $\beta71b$

K_i for $5-HT_{2A}Rs = 47\text{ nM}$
 IC_{50} for $5-HT_{2A}Rs = 174\text{ nM}$

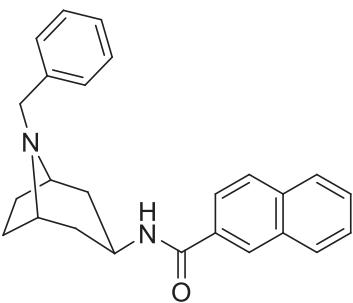
Note: Affinity to D_2R is highlighted in bold.

^aThe calculations were performed according to the reference.⁵⁵²

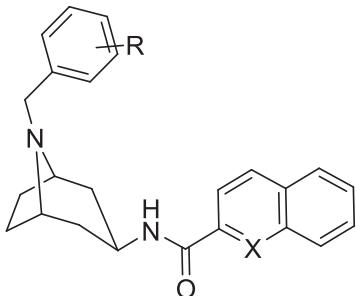
^bPharmacodynamics/pharmacokinetics.

^cPharmacokinetic in vitro half-life.

^dMinimum adverse effective dose.

**β69**

K_i for D_2Rs = 82 nM
 K_i for $5-HT_{1A}Rs$ = 304 nM
 K_i for $5-HT_{2A}Rs$ = 2.5 nM

**β70; R = 4-F; X = CH; K_i for D_2Rs = 137 nM**

β71a; R = 4-Me; X = N; K_i for D_2Rs = 7.4 nM
β71b; R = 2-NH₂; X = CH; K_i for D_2Rs = 42 nM

FIGURE 40 Highlighted 3 β -aminotropane ligands **β69**, **β70**, and **β71a–b**, with their chemical structures and binding affinities.

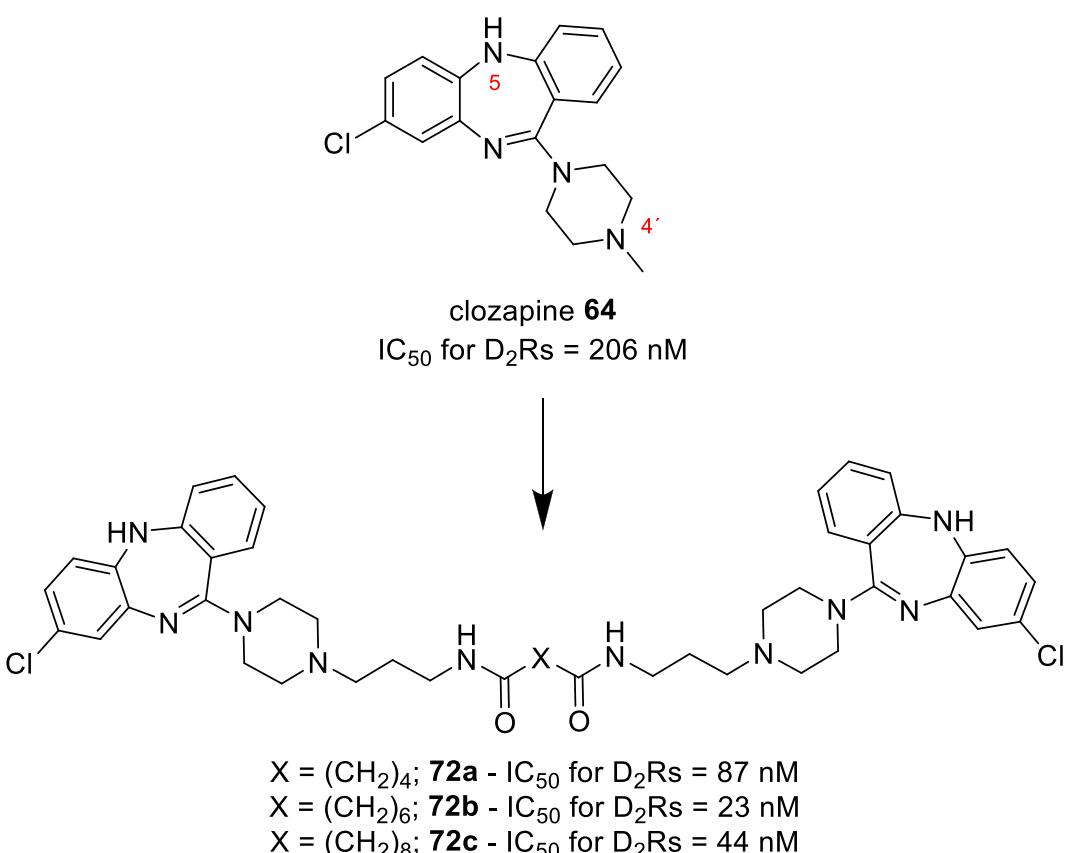


FIGURE 41 Design of homobivalent ligands **72a–c** based on the atypical antipsychotic clozapine (**64**).

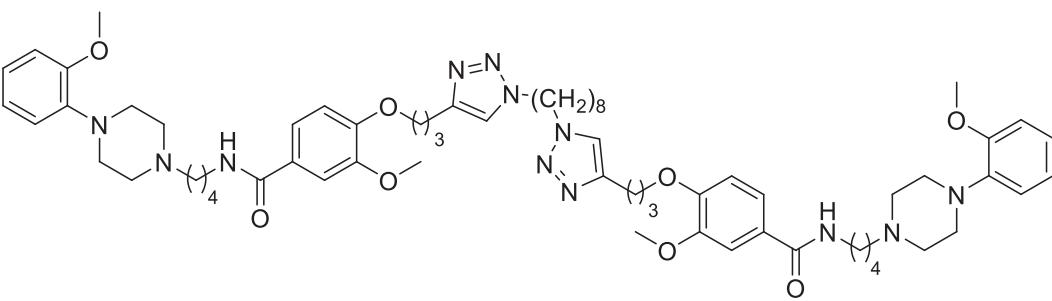
TABLE 15 Chemical structures and binding affinities of 2-methoxyphenyl piperazine homobivalent ligands **73a-g**

73a-g

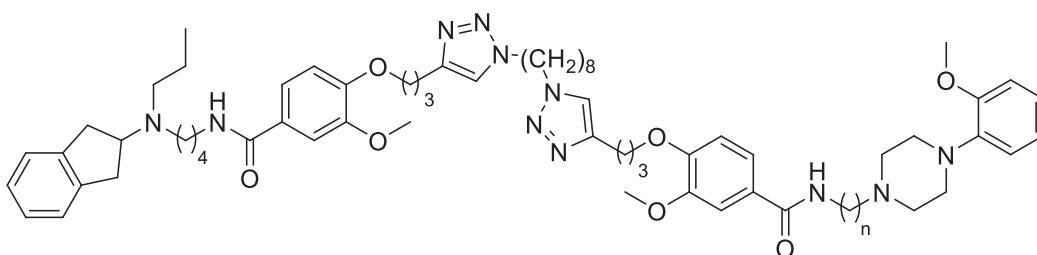
Compound	n	X	K_i for D _{2L} Rs (nM)
73a	1	(CH ₂) ₈	16
73b	3	(CH ₂) ₈	22
73c	3	(CH ₂) ₁₀	23
73d	4	(CH ₂) ₁₀	17
73e	1	CH ₂ (CH ₂ OCH ₃) ₂ CH ₂	3.3
73f	3	CH ₂ (CH ₂ OCH ₃) ₂ CH ₂	2.8
73g	3	CH ₂ (CH ₂ OCH ₃) ₃ CH ₂	4.8

easily react in the *para*-position with part of linker sequence by a Williamson ether synthesis and attach to the 2-methoxyphenyl piperazine scaffold by reductive amination.⁵⁴¹ Dimerization and construction of a linker by click chemistry should result in spacer units of approximately 25 Å, which is in agreement with SAR study of previously described bivalent GPCR ligands.^{541,678,679} All homobivalent 2-methoxyphenyl piperazine ligands showed high affinity for D₂Rs. Introduction of an oxygen atom in spacer linker resulted in high affinities of **73e** (18 spacer atoms) and **73f** (22 spacer atoms) as compared to **73a** (18 spacer atoms) and **67b** (22 spacer atoms), which possessed alkyl spacer linkers. Hill slope values for **73a-c** fell between 1.5 and 2.0, suggesting positive cooperative binding. On the other, the Hill slope value for **73d** (26 spacer atoms) was close to one, indicating that lengthening of the distance beyond 24 atoms (**73c**) leads to a reduction of a bridging binding mode by increasing the confinement volume.⁵⁴¹ Oligo(ethylene glycol) ligands **73e-g** exhibited Hill slopes close to one. Thus, it is clear that the length and physicochemical properties of the spacer have impacts on binding modes, and that a hydrophobic molecular bridge (in **73a-c**) in tandem with a linker length of approximately 25 Å appears best for the bivalent binding of two interacting receptor promoters.⁵⁴¹

In another article, Kühnorn et al. reported a development of bivalent 2-methoxyphenyl piperazine analogs, **74a-c**, derived from **73b** (Table 15) to target D₂Rs.⁶⁸⁰ These ligands possessed in their chemical structure N-(4-arylcarboxamido)butyl moieties connected to 2-methoxyphenyl piperazine scaffolds, which have been described as D₂R partial agonists and antagonists.^{477,513,569,681} In heterobivalent ligands (**74b** and **74c**), the 2-methoxyphenyl piperazine moiety has been replaced with N-propylaminoindane.⁵²⁸ The chemical structures and binding affinities for D₂Rs of these analogs are summarized in Figure 42. Heterobivalent ligands **74b** and **74c** showed higher affinity for D₂Rs compared to the homobivalent 2-methoxyphenyl piperazine analog **74a**. In addition, shortening the linker



K_i for D_{2L}R_s = 110 nM



74c; n = 1; K_i for D_{2L}R_s = 14 nM

FIGURE 42 Chemical structures and binding affinities of bivalent 2-methoxyphenyl piperazine ligands **74a–c** for D₂R_s.

connecting the 2-methoxyphenyl piperazine system and the benzamide core from butylene to methylene in **74c** was well tolerated. Furthermore, **74c** showed mild partial agonistic properties towards D₂R_s (EC_{50} = 380 nM with efficacy 13% compared to the full agonist quinpirole [100%]).⁶⁸⁰

In a continuation of prior studies,^{541,680} 2-methoxyphenyl piperazine homobivalent ligands based on **73e–g** (Table 15) and **74a** (Figure 42) were developed to target D₂R_s.⁶⁸² Oligoethylene glycol moieties (**73e–g**; Table 15) seemed to be associated with high D₂R binding affinity,⁵⁴¹ so the authors decided to use this structural motif as a central linker. The triazole core connected with a vanilline-derived carbocyclic moiety (for instance, **73f**, Table 15) from previous studies^{541,680} was replaced by an arylamide ring. The design of novel homobivalent 2-methoxyphenyl piperazine ligands **75a–g** is depicted in Figure 43. Chemical structures and binding affinities towards D₂R_s of **75a–g** are restated in Table 16. In general, ligands with N-butane-4-ylbenzamide as a linker connecting the piperazine ring with the arylamide scaffold showed higher affinity toward D₂R_s compared to ligands bearing N-propane-3-ylbenzamide as a linker (for instance, **75a** [propylene] in comparison with **75b** [butylene]). Benzamide, **75b**, exhibited almost the same affinity for D₂R_s as pyrazolo[1,5-a]pyridine-3-carboxamide (**75g**). Changing the amount (4, 5, 6, or 8) of ethylene glycol units in the central linker had little impact on affinity of ligands **75c–f** for D₂R_s. In addition, analysis of the binding curves displayed Hill slopes very close to one for all prepared ligands.⁶⁸²

Haloperidol-based bivalent ligands were designed for targeting D₂R.⁶⁸³ These ligands were derived from compound **63**, using polymethylene spacer element bound via ester bond. According to the value of Hill slope close to two, it was found that homobivalent ligand **76** (Figure 44) occupied simultaneously two adjacent binding sites at D₂, D₃ and D₄ receptors.

New series of heterobivalent D₂R/neurotensin receptor subtype 1 (NTS₁R) ligands, comprising neurotensin (8–13) (NT(8–13)), NTS₁R agonist, covalently bound to 2-methoxyphenylpiperazine moiety (D₂R pharmacophore),

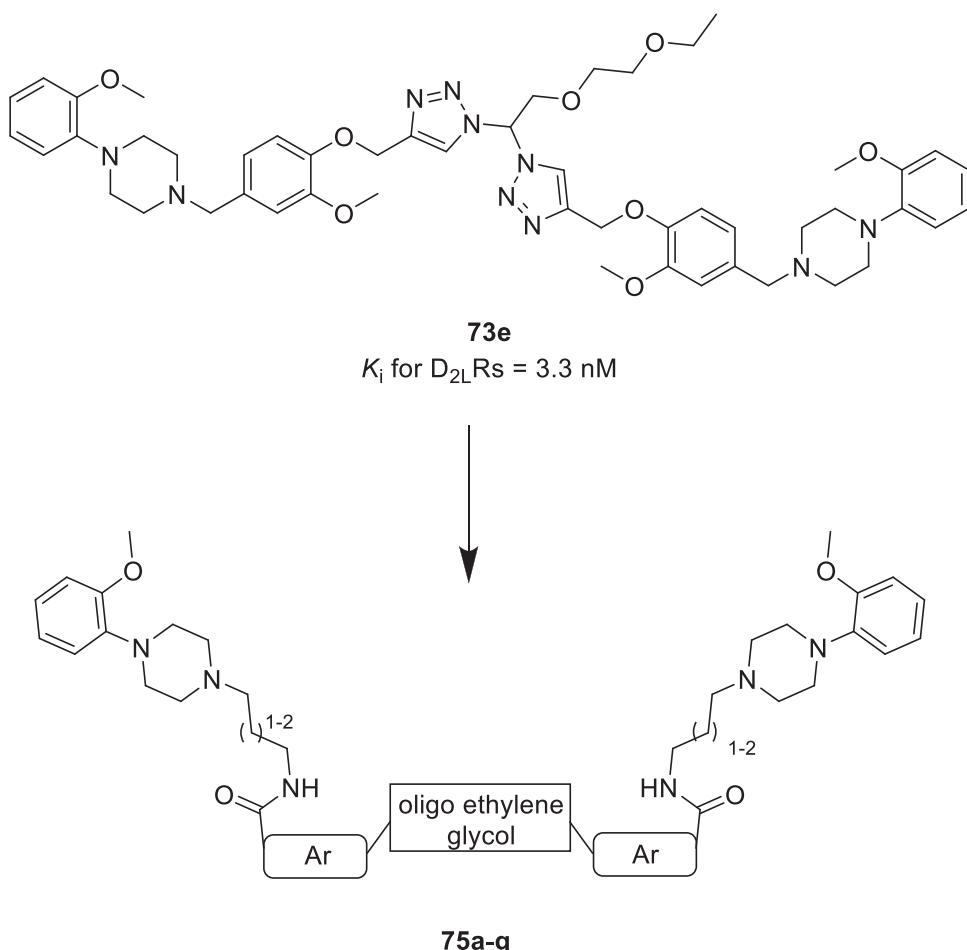
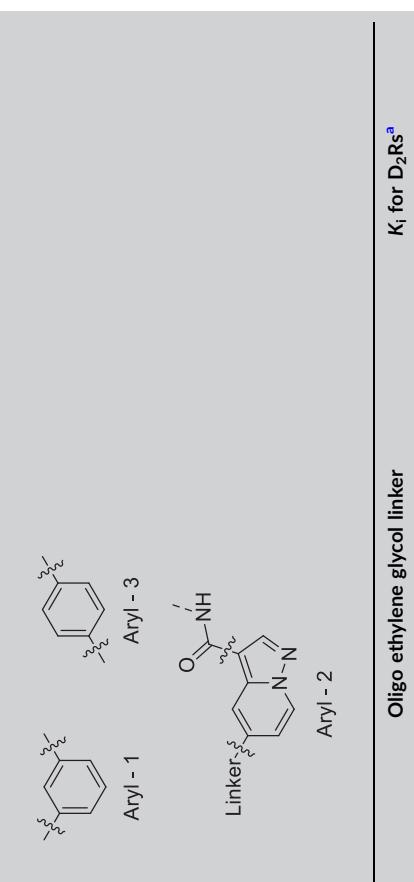
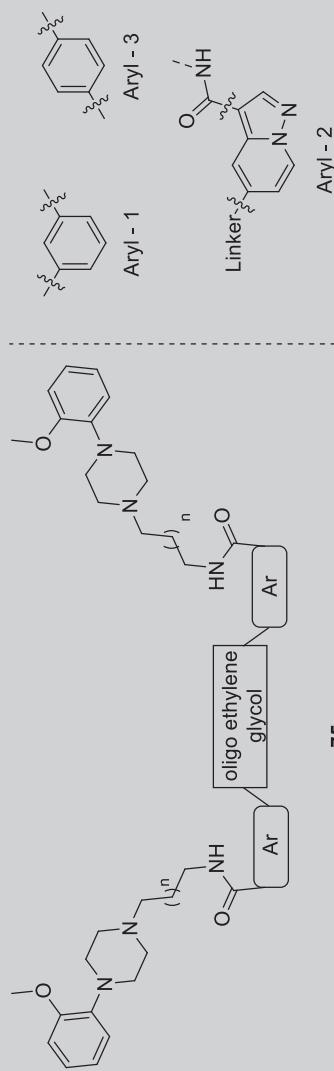


FIGURE 43 Design of homobivalent 2-methoxyphenyl piperazine ligands 75a–g with an oligo ethylene glycol motif as a linker, based on 73e.

has been discovered.⁶⁸⁴ D₂Rs and NTS₁Rs are closely associated and colocalized *in vivo*.^{685,686} Evidence for the interaction of these receptors was found by using bioluminescence resonance energy transfer, coimmunoprecipitation, and attenuation of dopaminergic signaling in cotransfected human cells.^{539,684,687} Furthermore, central administration of the neuropeptide in animals was shown to mimic the effects of antipsychotic action, considering this neuropeptide to have endogenous neuroleptic molecule.⁶⁸⁸ To obtain heterobivalent D₂R/NTS₁R modulators, the authors connected the 2-methoxyphenylpiperazine moiety⁵²⁸ to NT(8–13) via an affinity-generating biphenyltriazole-moiety^{477,514} (lipophilic appendage) and ω -amino acid-functionalized polyethylene glycol spacers.⁶⁸⁴ Optimal connection points for the attachment of the pharmacophores with the linker were identified by using the crystal structures of D₃R⁶⁵ and NTS₁R.^{689,690} The proper length of linker was generated by using a D₂R/NTS₁R heterodimer model consisting of the NTS₁R crystal structure⁶⁹⁰ and the D₂R homology model⁵¹⁵ which was based on the D₃R crystal structure. The authors suggested that the high-affinity K_i values represent a bivalent receptor-bridging binding mode of 77a–c (Figure 45) to D₂R/NTS₁R heterodimers, whereas the low-affinity K_i values reflect a monovalent-binding mode to D₂Rs as a monomer or within a homo-/heterodimer.⁶⁸⁴ Therefore, 77a–c possessed a 200 to 4713-fold preference for the high-affinity bivalent interaction with D₂R/NTS₁R heterodimer over monovalent-binding action to D₂R mono-expressing membranes.⁶⁸⁴

TABLE 16 Chemical structures and binding affinities for D₂Rs of 2-methoxyphenyl piperazine ligands 75a-g with oligo ethylene glycol motifs as linkers

Compound	n	Aryl type	Oligo ethylene glycol linker	K _i for D ₂ Rs ^a
75a	1	1	-O(CH ₂ CH ₂ O) ₄ -	16
75b	2	1	-O(CH ₂ CH ₂ O) ₄ -	6.6
75c	2	3	-CH ₂ O(CH ₂ CH ₂ O) ₄ CH ₂ -	25
75d	2	3	-CH ₂ O(CH ₂ CH ₂ O) ₅ CH ₂ -	20
75e	2	3	-CH ₂ O(CH ₂ CH ₂ O) ₆ CH ₂ -	40
75f	2	3	-CH ₂ O(CH ₂ CH ₂ O) ₈ CH ₂ -	38
75g	2	2	-O(CH ₂ CH ₂ O) ₄ -	1.8

^aK_i in nM.

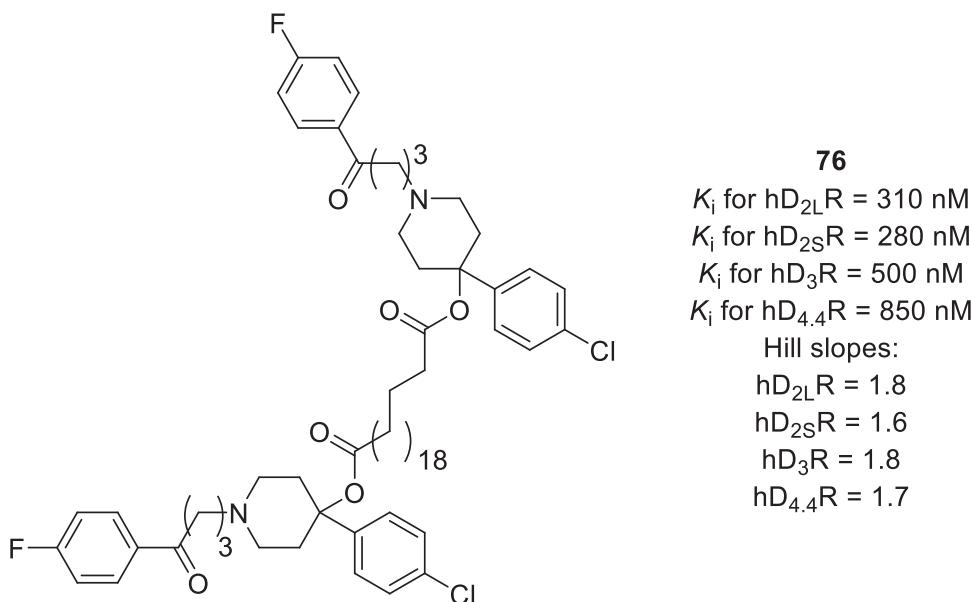


FIGURE 44 Chemical structure of homobivalent ligand 76 based on haloperidol (63).

As a continuation of previous work,⁶⁸⁴ homobivalent D₂R ligand 78 (Figure 46) modulating the dynamic equilibrium of D₂R homo- and heterodimers has been prepared.⁶⁹¹ In this study, 78 was designed by replacing the NT(8–13) fragment with a DR antagonistic moiety (2-methoxyphenylpiperazine). Employing bioluminescence resonance energy transfer,^{692,693} the authors found out that 78 comprising a 92-atom spacer was able to foster D₂R-homodimerization whereas simultaneously decreasing interactions of D₂Rs with NTS₁R.⁶⁹¹

2.5.2 | Various lipophilic appendages as D₂R modulators

The following section analyzes D₂R modulators from the point of structural resemblance in aromatic/heteroaromatic lipophilic region (Figure 12). The most crucial observation is that the amide bond is widely used for linking aromatic heads and lipophilic appendages in D₂R analogs. Therefore, it is crucial to determine essential aspects for D₂R affinity. However, analogs included in this subgroup showed a high preference for D₃Rs over D₂Rs, especially ligands with N-butane-4-yl carboxamide linkers (for more details about D₃Rs, see reviews^{446,694,695}). We would like to emphasize that the focus of this review is on D₂Rs and associated ligands; thus the molecules in this section will be analyzed only from the perspective of these receptors.

2.5.2.9 | Aryl/heteroaryl amides as lipophilic fragments in modulated D₂Rs

Substituted benzamides are known as pharmacophores in the group of antipsychotics. Antipsychotics are best represented by the antiemetic agent metoclopramide, the first-generation antipsychotics sulpiride and clebopride, and the second generation drugs remoxipride, raclopride, and amisulpride.^{133,696} For more information about the group of benzamides and their implication in the therapy of various disorders, readers are kindly directed to the review by M. Asif.⁶⁹⁷

D₂R affinity is immensely affected by substitution within an aromatic or heteroaromatic system in the proximity of cyclic amines (most commonly represented piperazine) at position 4. In general, the substituents of the phenyl ring should be placed in position 2 (compare the affinities for 79a, 79b, and 79c, Figure 47).⁴⁸⁴ Cyclic amine (80a,

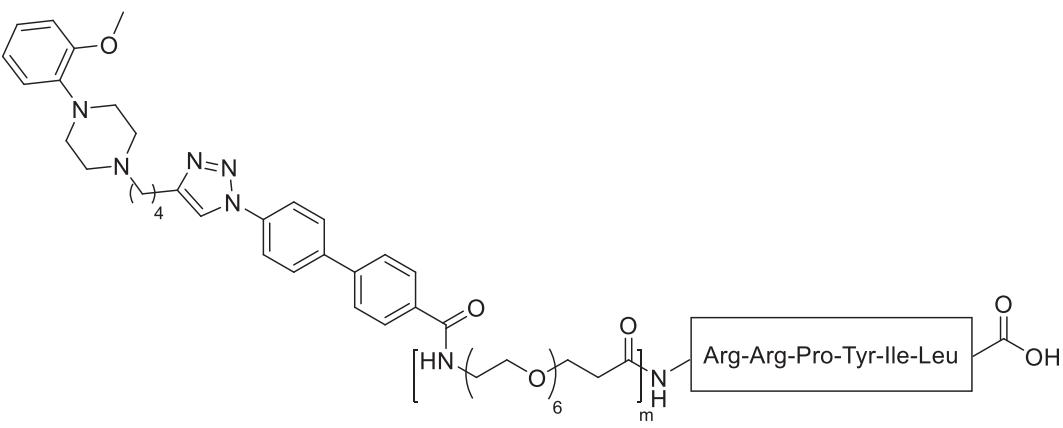


FIGURE 45 Heterobivalent D₂R/NTS₁R ligands 77a–c. K_i high-affinity = K_i values for the high-affinity binding site of biphasic competition curves; K_i low-affinity = K_i values for the low-affinity binding site of biphasic competition curves.⁶⁸⁴

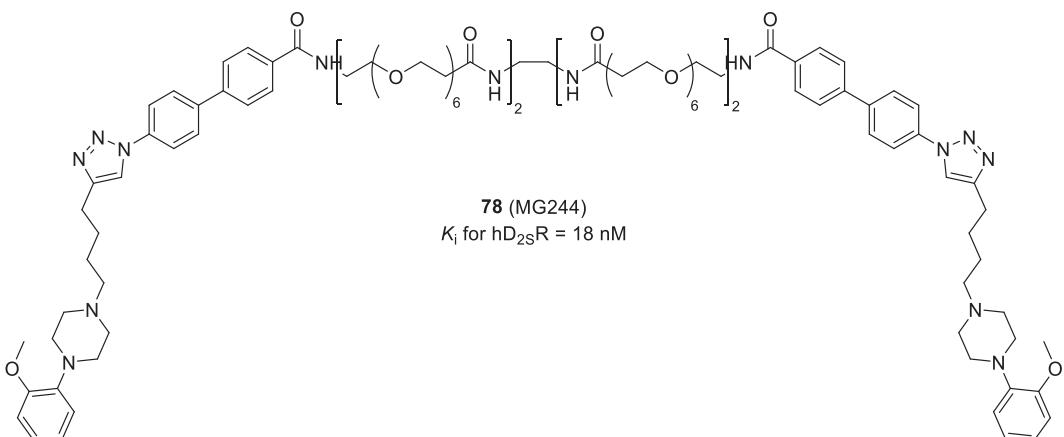


FIGURE 46 Chemical structure of 2-methoxyphenylpiperazine homobivalent ligand 78.

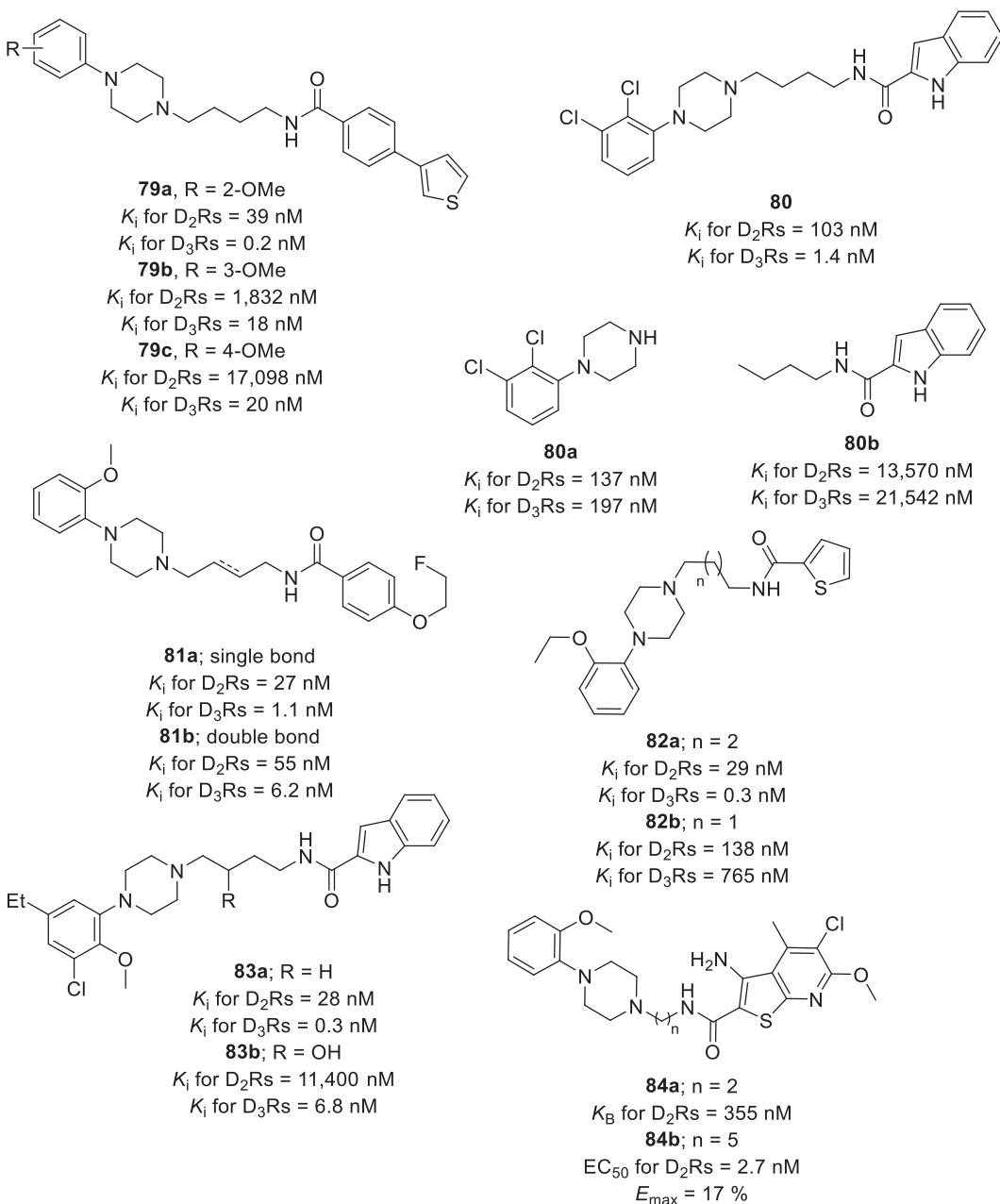
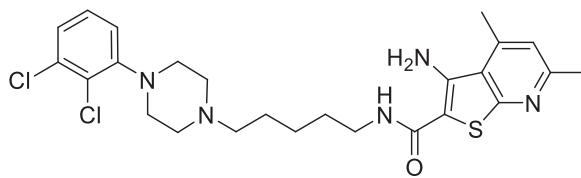


FIGURE 47 Highlighted D₂R ligands 79a–c, 80, 80a–b, 81a–b, 82a–b, 83a–b, and 84a–b, bearing various aryl/heteroaryl benzamides.

Figure 47) is required for interaction with Asp^{3,32} in transmembrane domain 3, and thus 80a possessed high D₂Rs affinity over 80b (Figure 47), which lacks cyclic amine (see also structure of 80, Figure 47).^{467,479,495,499} The growing bulkiness of the diaza-cycloaliphatic system (e.g., piperazine, homopiperazine) decreases the electrostatic interaction between the ligand and Asp^{3,32} D₂R affinity is affected accordingly.⁴⁹⁵ A double bond (81a compared to 81b, Figure 47) in the central linker showed a small impact on D₂R affinity.^{468,698} As discussed above,⁵²⁸ elongation of the chain with an amide bond (N-but-4-ylbenzamide, 82a; related to N-prop-3-ylbenzamide 82b, Figure 47)



85

 K_i for D₂Rs = 355 nM**FIGURE 48** Chemical structure of highlighted heteroaryl benzamide 85.**TABLE 17** Highlighted compound 85 with heteroaryl carboxamide moiety as lipophilic appendage, along with chemical structure and properties

Chemical structures	Binding affinities	Functional activities	BBB score ^a
fx46	K_i for D ₂ Rs = 355 nM	K_A (inhibition of FSK-induced cAMP production) at D ₂ Rs = 1.0 nM K_A (ERK1/2 phosphorylation) at D ₂ Rs = 13 nM	3.91

^aThe calculations were performed according to the reference.⁵⁵²

generated selectivity for D₃Rs over D₂Rs.^{471,484,699} Another observation from the SAR is that the N-butyl-3-hydroxy-4-ylbenzamide derivative (83b, K_i ratio D₂/D₃R = 1676; Figure 47) showed high selectivity for D₃ over D₂ receptors (e.g., 83a; K_i ratio D₂/D₃R = 93) in comparison with 83a (Figure 47).^{473,479} The central linker also highly affected the functional activity of the ligand. N-(4-(2-methoxyphenyl)piperazin-1-yl)ethane-2-ylbenzamide (84a, Figure 47) resulted as antagonist, whereas N-(4-(2-methoxyphenyl)piperazin-1-yl)pentane-5-ylbenzamide (84b, Figure 47) was found to be a partial agonist.⁷⁰⁰

A family of piperazine derivatives bearing 3-amino-thieno[2,3-*b*]pyridine-2-carboxamides was developed to establish a SAR study investigating the affinity and efficacy of distinct privileged scaffolds for biased D₂R signaling.⁷⁰⁰ A huge number of the D₂R modulators incorporated 2-methoxyphenylpiperazine or 2,3-dichlorophenylpiperazine fragments as aromatic head connected to cyclic amine (Figure 12). The use of thiophene as heteroaromatic lipophilic appendage (Figure 12) has previously been linked to increased D₂R affinity due to its electron-rich system and its ability to form hydrophobic interactions within a binding pocket, essentially acting as an isostere of benzene.⁶⁹⁹ Therefore, the authors used these moieties to obtain new derivatives. The most promising compound, 85 (Figure 48, Table 17), exhibited biased agonism towards the cAMP cascade induced by D₂Rs over ERK1/2 phosphorylation.⁷⁰⁰

2.5.2.10 | 3,4-Dihydroquinolin-2(1H)-one ligands for modulating D₂Rs

The third-generation antipsychotic drug 7 (Figure 15) tethers 2,3-dichlorophenyl piperazine (as an aromatic head) with 3,4-dihydroquinolin-2(1H)-one (representing lipophilic heteroaromatic fragment) moieties. The US FDA has approved the use of 7 as an adjunctive medication in the management of depressive disorders²³⁹ and bipolar I disorder.^{580–582} 3,4-Dihydroquinolin-2(1H)-one scaffold-containing ligands have been shown to possess an affinity for D₂Rs; these ligands are discussed and reviewed in this chapter. Indeed, the moiety has been linked via different central linkers to cyclic amine solely or to an aromatic moiety via cyclic amine. The character of the central linker showed a moderate impact on D₂R affinity.⁷⁰¹ Compounds 86a (Figure 49, 3-propoxy-yl) and 86c (Figure 49, 5-pentoxy-yl) linked with 3,4-dihydroquinolin-2(1H)-one moieties exhibited similar D₂R affinity. Notably, 86b (Figure 49, 4-butoxy-yl) exhibited a higher D₂R affinity than its counterparts 86a and 86c.⁷⁰¹ Modifications within

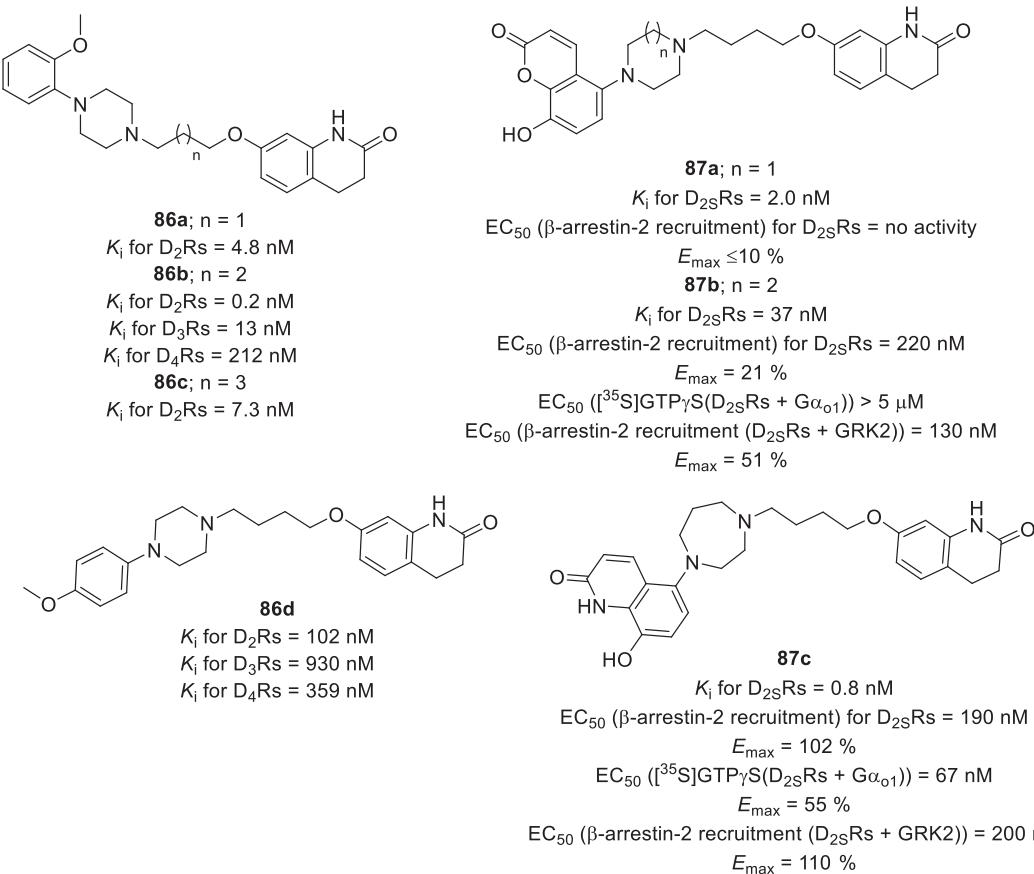


FIGURE 49 Highlighted D₂R ligands 86a–d and 87a–c bearing 3,4-dihydroquinolin-2(1H)-one scaffolds as lipophilic aromatic fragments.

the cyclic amine influenced D₂R affinity and functional selectivity.⁷⁰² Accordingly, (4-(8-hydroxy-2-oxo-2H-chromen-5-yl)piperazin-1-yl)butoxy derivative (87a, Figure 49) showed high D₂R affinity and no activity in recruitment of β -arrestin-2 at D_{2S}Rs. Its homopiperazine counterpart (87b, Figure 49) possessed reduced D₂R affinity and exhibited functional activity in the recruitment of β -arrestin-2 in D_{2S}Rs.⁷⁰² In addition to the modifications within the cyclic amine, substitutions in aromatic moieties also affected D₂R affinity and functional and subtype selectivity. For instance, 86b ((4-(2-methoxyphenyl)piperazin-1-yl)butoxy analog) revealed a highly selective pattern for D₂Rs over D₄Rs and moderate selectivity for D₂Rs over D₃Rs, but (4-(4-methoxyphenyl)piperazin-1-yl)butoxy ligands (86d, Figure 49) showed tendency for D₂Rs.⁷⁰¹ 8-Hydroxy-5-(4-(4-(2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)oxy)butyl)-1,4-diazepan-1-yl)quinolin-2(1H)-one derivative (87c, Figure 49) showed full agonistic properties for the recruitment of β -arrestin2 while this compound was substantially less efficacious for the induction of D_{2S}R-promoted guanine nucleotide exchange as a measure of canonical G α _o protein activation, whereas 7-(4-(4-(8-hydroxy-2-oxo-2H-chromen-5-yl)-1,4-diazepan-1-yl)butoxy)-3,4-dihydroquinolin-2(1H)-one (87b) possessed biased behavior for recruitment of β -arrestin-2.⁷⁰²

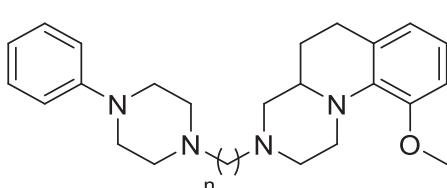
These findings show that small structural modifications within the central linker, cyclic amine, or aromatic moiety within 3,4-dihydroquinolin-2(1H)-one scaffold-containing compounds can tune the properties of the compound.

2.5.2.11 | Tricyclic moiety as a lipophilic fragment for modulating D₂Rs

Tricyclic moieties are classically associated with tricyclic antidepressants. Indeed, one such drug establishing a new class of drugs called tricyclic antidepressants (TCA), imipramine, was approved by the FDA in 1959 for the management of MDD. The classification of TCAs was based on the molecular core, in part because the mechanism of action was unknown at the time of discovery.⁷⁰³ For more information about TCAs, the readers are kindly directed to the following reviews.^{703–706}

Antipsychotics can also contain tricyclic moieties. The introduction of neuroleptic drugs dates back to 1950, when chlorpromazine, the first antipsychotic drug belonging to the family of phenothiazines, was prepared in France by the chemist Paul Charpentier as a result of research on new antihistaminic drugs.⁴ Apart from the family of phenothiazines, thioxanthenes, and dibenzepines are also well-known antipsychotic agents from the first generation of neuroleptics with tricyclic fragment. Clozapine, olanzapine, and quetiapine form the second-generation of antipsychotics with tricyclic fragments.⁴

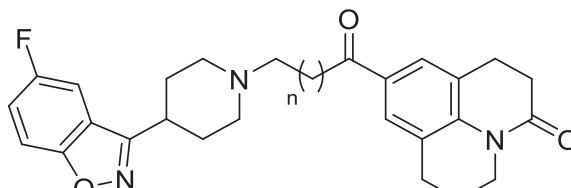
This part of the review discusses D₂R modulators endowed with tricyclic scaffolds in their structure. In general, tricyclic fragments were well tolerated, and substitution had negligible impact on D₂R affinity.^{707–709} Central linkers connecting cyclic amines and tricyclic moieties had subtle to strong effects on D₂R activity. Compounds **88a** (ethane-1,2-diyl analog, Figure 50), **88b** (propane-1,3-diyl analog, Figure 50), and **88c** (butane-1,4-diyl analog, Figure 50) showed almost identical D₂R affinity.⁷¹⁰ On the other hand, in the series **89a–d** (Figure 50), derivative **89a**, with the shortest methylene tether, significantly reduced D₂R affinity compared to other derivatives.⁷⁰⁷ High D₂R affinity can be ensured by proper substitution of aromatic moiety linked to a cyclic amine. The optimal substitution was located at position 2 on the phenyl system connected to the piperazine ring. A 2-OMe-phenyl



88a; n = 2; K_i for D₂Rs = 360 nM

88b; n = 3; K_i for D₂Rs = 373 nM

88c; n = 4; K_i for D₂Rs = 317 nM

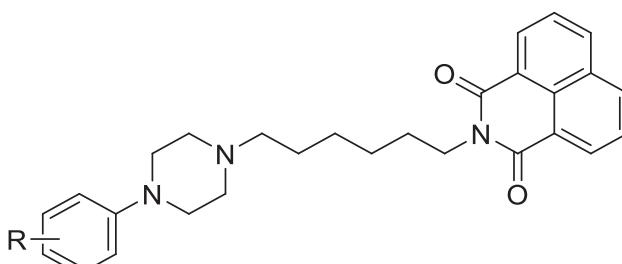


89a; n = 0; K_i for D₂Rs = 900 nM

89b; n = 1; K_i for D₂Rs = 58 nM

89c; n = 2; K_i for D₂Rs = 18 nM

89d; n = 3; K_i for D₂Rs = 32 nM



90a; R = 2-OMe; K_i for D₂Rs = 10 nM

90b; R = 3-OMe; K_i for D₂Rs = 271 nM

90c; R = 4-OMe; K_i for D₂Rs = 40,040 nM

FIGURE 50 Top-ranked D₂R ligands **88a–c**, **89a–d**, and **90a–c** bearing tricyclic moieties and lipophilic aromatic fragments.

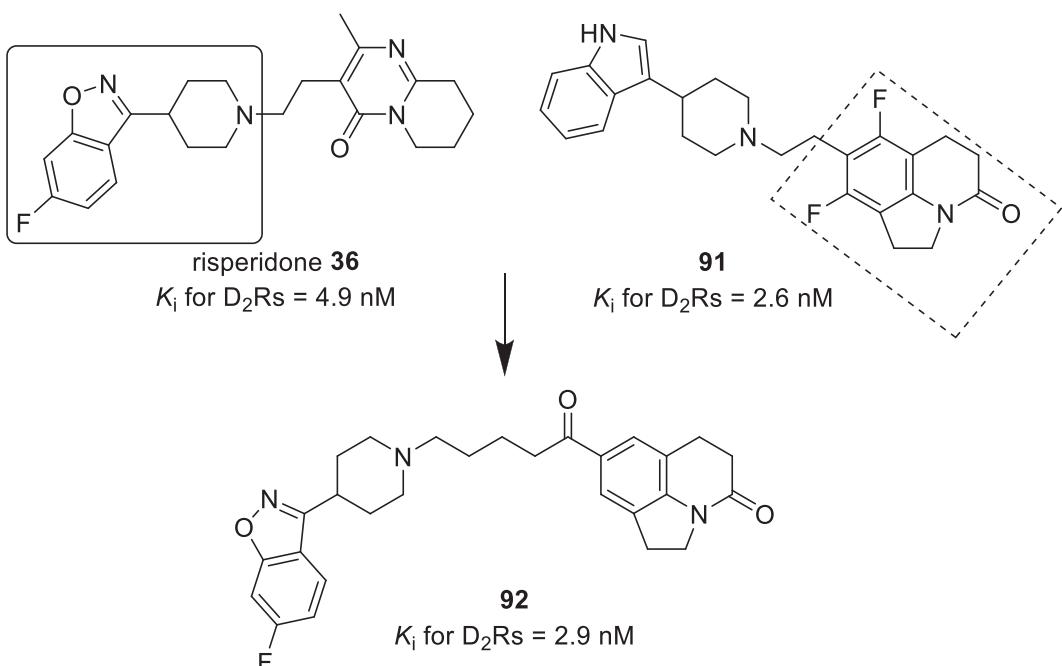


FIGURE 51 Schematic design of the multifunctional ligand 92 with a tricyclic moiety derived from 91 and 36.

piperazine derivative (90a, Figure 50) exhibited a much higher D₂R affinity compared to its counterpart 90b (3-OMe-Ph, Figure 50) and 90c (4-OMe-Ph, Figure 50).⁷⁰⁹

Compounds 91⁷¹¹ (Figure 51) and 36 (Figure 51) were used as building blocks to generate tricyclic derivatives connected to the piperidine ring (Figure 12).⁷⁰⁷ The aim of this study was to develop multireceptor ligands (DA/5-HT) with antipsychotic features. Accordingly, 92 (D₂R antagonist, Figure 51, Table 18) was inspected to bind main targets and off-target. It showed low binding activity to the off-target sites (5-HT_{2C}, H₁ and α₁, hERG channel), but revealed excellent affinities for the on-target receptors (D₂, D₃ and 5-HT_{1A}, 5-HT_{2A}, 5-HT₆ receptors). Compound 92 showed dose-dependent inhibition of apomorphine-induced climbing behavior with an ED₅₀ value of 0.6 mg/kg (p.o.), MK-801-induced motor behavior (ED₅₀ = 0.3 mg/kg, p.o.), and a conditioned avoidance response with little cataleptic effect (ED₅₀ = 79 mg/kg, p.o.) in mice.⁷⁰⁷ Negligible weight gain and serum prolactin level changes were detected during administration of the compound 92 (0.6, 1.8, and 5.4 mg/kg) in mice under chronic dosing conditions (28 days, p.o.), supporting that 92 exhibits low affinity for off-target receptors (especially 5-HT_{2C}). Furthermore, 92 (10 mg/kg, p.o.) had a favorable pharmacokinetic profile with oral bioavailability of 59% and t_{1/2} 2.0 h in rats. It also exhibited procognitive features in a novel object recognition model in rats (0.1 and 0.3 mg/kg, p.o.).⁷⁰⁷

2.5.2.12 | 5- or 7-Hydroxy-2-aminotetralin or 4,5,6,7-tetrahydrobenzo[d]thiazole-2,6-diamine analogs in modulating D₂Rs

7-Hydroxy-N,N-dipropyl-2-aminotetralin (93, 7-OH-DPAT, Figure 52) is a synthetic drug with moderate selectivity for D₃Rs.⁷¹² Its regioisomer, 5-OH-DPAT (94, Figure 52) is a potent D₂/D₃R modulator.⁷¹² However, only (S)-5-OH-DPAT is active as an agonist, whereas (R)-enantiomer showed weak antagonistic properties towards D₂Rs.⁷¹³ The 2-Aminothiazolidium moiety (see in 95, Figure 52) is considered as a bioisosteric replacement of the hydroxyl phenyl moiety (Figure 52).⁷¹⁴ Pramipexole (96, Figure 52), a D₂R binder bearing 4,5,6,7-tetrahydrobenzo[d]thiazole-2,6-diamine, was introduced into the therapy of PD.^{59,715}

TABLE 18 Highlighted compound **92**, bearing a tricyclic appendage as a lipophilic appendage, with chemical structure and properties

Chemical structures	Binding affinities	BBB		PD/PK ^b properties	Behavioral test
		Functional activities	score ^a		
	K_i for $D_2Rs = 2.9\text{ nM}$ K_i for $D_3Rs = 1.7\text{ nM}$ K_i for $5-HT_{1A}Rs = 8.6\text{ nM}$ K_i for $5-HT_{2A}Rs = 0.7\text{ nM}$ K_i for $5-HT_{2C}Rs = 616\text{ nM}$ K_i for $5-HT_6Rs = 5.6\text{ nM}$ K_i for $H_1Rs = 630\text{ nM}$ K_i for $\alpha_1Rs = 431\text{ nM}$	IC_{50} for $D_{2L}Rs = 9.0\text{ nM}$ IC_{50} for $D_3Rs = 26\text{ nM}$ IC_{50} for $5-HT_{1A}Rs = 589\text{ nM}$ IC_{50} for $5-HT_{2A}Rs = 257\text{ nM}$ IC_{50} for $5-HT_6Rs = 178\text{ nM}$ IC_{50} for $hERG = 2905\text{ nM}$	4.27	92 (10 mg/kg, p.o., rat)—bioavailability of 59% and $t_{1/2}^{\text{c}} = 2.0\text{ h}$	92 ($ED_{50} = 0.6\text{ mg/kg, p.o., mice}$)—inhibition of apomorphine-induced climbing behavior
92				92 ($ED_{50} = 0.3\text{ mg/kg, p.o., mice}$)—inhibition of MK-801-induced motor behavior	92 ($ED_{50} = 79\text{ mg/kg, p.o., mice}$)—for catalepsy 92 (0.1 and 0.3 mg/kg, p.o., rat)—procognition features

Note: Affinity to D_2R is highlighted in bold.^aThe calculations were performed according to the reference.⁵⁵²^bPharmacodynamics/pharmacokinetics.^cPharmacokinetic in vivo half-life.

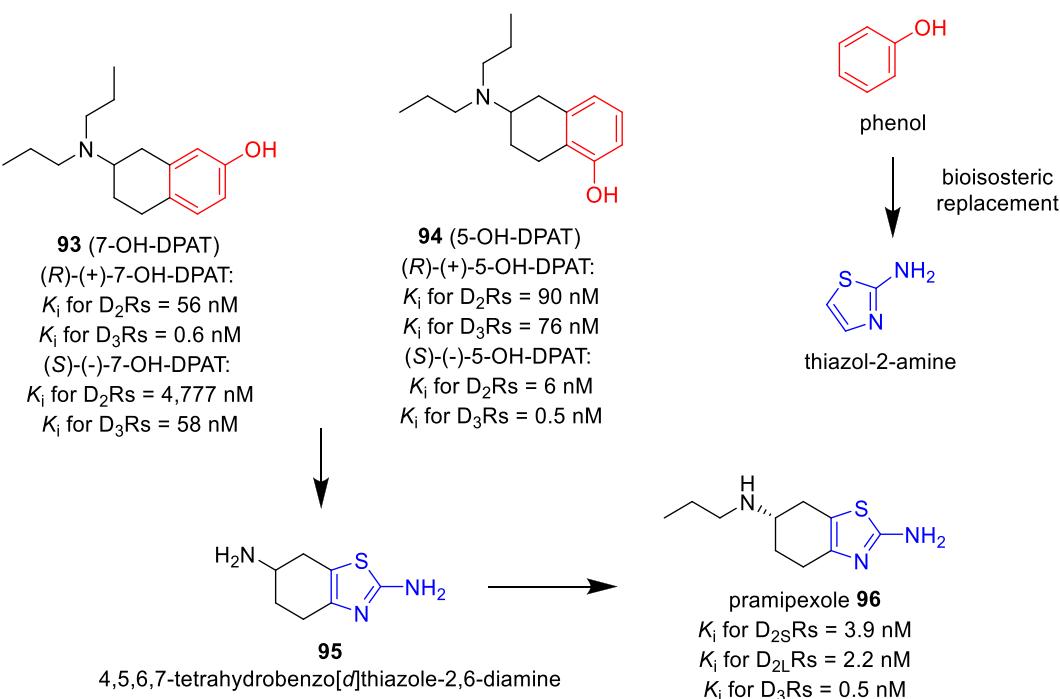


FIGURE 52 Chemical structures of 7- (93) and 5-OH-DPAT (94) and pramipexole (96) with binding affinities for D_2R/D_3R . [Color figure can be viewed at wileyonlinelibrary.com]

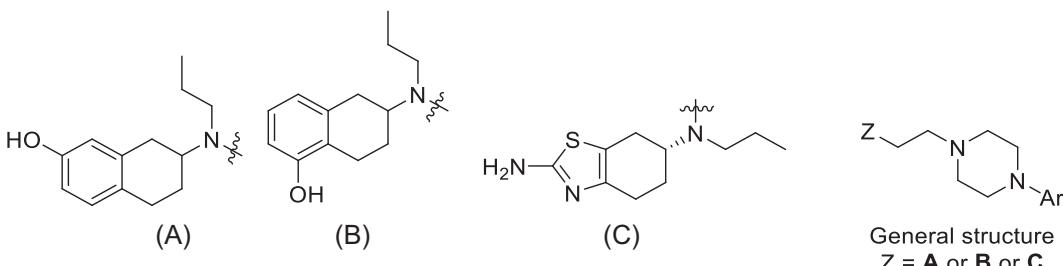


FIGURE 53 General structure of 93-, 94-, or 96-derived $D_{2/3}R$ analogs coupled with arylpiperazine moieties via a 1,2-ethane-diyl central linker.

Herein, only selected ligands bearing 93, 94, or 95 are discussed. To preserve the highest activity, ethane-1,2-diyl between cyclic amine and 93, 94, or 95 fragments are fundamental. It can be postulated that $(-)$ -enantiomer binds better with DRs compared to the $(+)$ -enantiomer if the core scaffold is 2-aminothiazole.^{716–718} The general structure of ligands discussed in this subgroup of D_2R modulators is depicted in Figure 53.

Novel D_2/D_3 receptor full-agonists were reported that possess potent antioxidant properties and implications to treat PD.⁷¹⁴ Novel derivatives were inspired by the structures of 97, 98, and 99 (Figure 54, Table 19) and showed promising anti-PD profiles (agonistic affinity for D_2/D_3Rs).^{719–722} New D_3R -moderately selective (100a, Figure 54, Table 19) and highly selective (100, Figure 54, Table 19) ligands were full agonists for both D_2Rs and D_3Rs . Additionally, 100a and 100b displayed potent radical scavenging activity. At a dose of 10 $\mu\text{mol}/\text{kg}$ (s.c.), 100a reversed a reserpine-induced hypokinetic condition (reserpine; 5 mg/kg, s.c.) to a normal state in rat. At the same dose, 100b completely restored locomotion to its normal state. Both 100a and 100b were selected for evaluation in

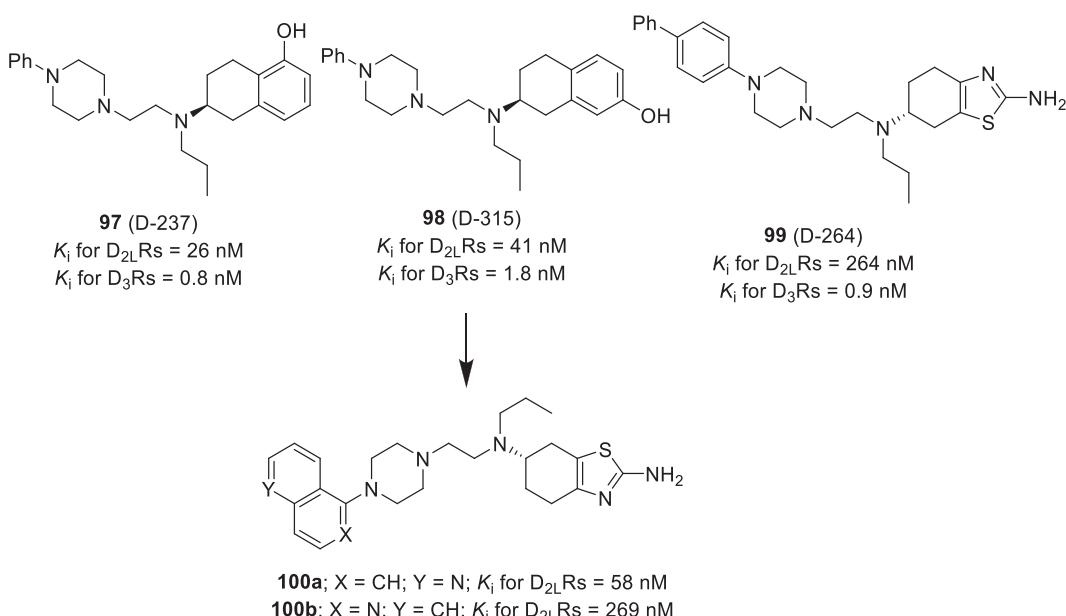


FIGURE 54 Design of the pramipexole-based ligands **100a–b** from **97**, **98**, and **99**.

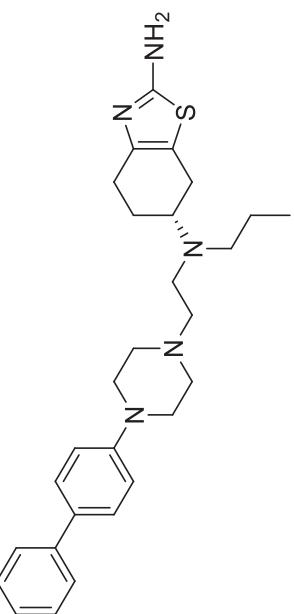
rats carrying a unilateral lesion in the medial forebrain bundle induced by the administration of the 6-OHDA. The peak effects were reached at 7.5 h with 2648 total rotations and at 7 h with 3688 total rotations for **100a** (10 $\mu\text{mol}/\text{kg}$, s.c.) and **100b** (10 $\mu\text{mol}/\text{kg}$ s.c.), respectively.⁷¹⁴

Furthermore, activity of **99** (D-264; Figure 54) and of **100b** (D-301; Figure 54) towards D_2Rs and D_3Rs was reported.⁷²³ The study indicated that **100b** exhibited higher intrinsic ability to activate D_3Rs than did **99**, whereas intrinsic activity on D_2Rs was similar.⁷²³ In addition, **99**^{720,721} (Table 19) was evaluated in a mouse model of PD, was revealed to significantly improve behavioral performance in attenuating both MPTP- and lactacystin-induced DA neuron loss (dose: 1 and 5 mg/kg, i.p.). It also blocked proteasomal inhibition and microglial activation in the substantia nigra.⁷²⁴

It is well-established that the iron level is elevated in PD patients' substantia nigra region.^{725,726} New D_2/D_3Rs ligands⁷²⁷ with both antioxidant effects and chelating capacity for iron were developed from the iron chelators **101** (VK-28, Figure 55) and **102** (M30, Figure 55)^{728,729} using knowledge from an earlier study.⁷¹⁴ The study in question introduced an iron-binding 8-hydroxyquinoline moiety into **100c**⁷¹⁴ (Figure 55). According to the results from functional analysis, (-)-**100d** (D_2R agonist, Figure 55, Table 19) was selected for further evaluation.⁷²⁷ In vitro complexation studies with (-)-**100d** exhibited effective iron chelation. Additionally, (-)-**100d** exhibited antioxidant activity in a deoxyribose antioxidant assay. Treatment with (-)-**100d** (10 $\mu\text{mol}/\text{kg}$, s.c.) reversed reserpine-induced hypokinesia (reserpine; 5 mg/kg, s.c.) to a normal level of locomotion compared to the control animals and even demonstrated significant improvement of locomotion for the study duration. Furthermore, (-)-**100d** (0.5 $\mu\text{mol}/\text{kg}$) produced a high number of rotations in 6-hydroxydopamine (6-OHDA) lesioned rats, and the activity persisted for more than 11 h (number of rotations was 7081).⁷²⁷

(-)-**100e** (D_2R agonist, Figure 56, Table 19) was selected for detailed biological evaluation given its high binding affinities for D_2/D_3Rs .⁷³⁰ In vitro complexation studies with (-)-**100e** demonstrated effective iron chelation. In addition, (-)-**100e** exhibited antioxidant capacity in deoxyribose and in 1,1-diphenyl-2-picryl-hydrazyl (DPPH) antioxidant assays. In vivo, (-)-**100e** (5 $\mu\text{mol}/\text{kg}$, i.p.) produced a high number of rotations in 6-OHDA lesioned rats, and the activity remained for more than 10 h (total number of rotations was 3199). The study showed that

TABLE 19 Highlighted compounds **99**, **100a–b**, and (-)-**100d–o** bearing hydroxy-2-amino-tetralin or 4,5,6,7-tetrahydrobenzo[d]thiazole-2,6-diamine system as lipophilic appendages, with chemical structure and properties

Chemical structures	Binding affinities	Functional activities	BBB score ^a	Behavioral test
	K_i for $D_{2L}Rs = 264\text{ nM}$ $E_{max} = 104\%$	EC_{50} for $D_2Rs = 39\text{ nM}$ $E_{max} = 93\%$	4.42	99 (1 and 5 mg/kg, i.p., mice)—improvement of behavioral performance attenuating MPTP- and lactacystin-induced DA neuron loss
	K_i for $D_{2L}Rs = 58\text{ nM}$ $E_{max} = 104\%$	EC_{50} for $D_2Rs = 14\text{ nM}$ $E_{max} = 101\%$	4.09	100a (10 $\mu\text{mol}/\text{kg}$, s.c., rat)—active in the reserpine-induced hypokinetic condition PD test 100a (10 $\mu\text{mol}/\text{kg}$, s.c., rat)—effective in the 6-OHDA PD test

(Continues)

TABLE 19 (Continued)

Chemical structures	Binding affinities	Functional activities	BBB score ^a	Behavioral test
	K_i for $D_{2L}Rs = 269 \text{ nM}$ K_i for $D_3Rs = 2.2 \text{ nM}$	EC_{50} for $D_2Rs = 116 \text{ nM}$ $E_{max} = 88\%$ EC_{50} for $D_3Rs = 0.5 \text{ nM}$ $E_{max} = 95\%$	4.09	100b (10 $\mu\text{mol}/\text{kg}$, s.c., rat)—active in the reserpine-induced hypokinetic condition PD test 100b (10 $\mu\text{mol}/\text{kg}$, s.c., rat)—effective in the 6-OHDA PD test
	K_i for $D_{2L}Rs = 3.8 \text{ nM}$ K_i for $D_3Rs = 1.3 \text{ nM}$	EC_{50} for $D_2Rs = 4.5 \text{ nM}$ $E_{max} = 106\%$ EC_{50} for $D_3Rs = 1.6 \text{ nM}$ $E_{max} = 93\%$	3.70	(-)100d (10 $\mu\text{mol}/\text{kg}$, s.c., rat)—active in reserpine induced hypokinetic PD test (-)100d (0.5 $\mu\text{mol}/\text{kg}$, i.p., rat)—effective in the 6-OHDA PD test
100b				(-)-100d

TABLE 19 (Continued)

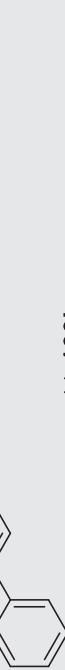
Chemical structures	Binding affinities	Functional activities	BBB score ^a	Behavioral test
	K_i for $D_{2L}Rs = 27 \text{ nM}$ K_i for $D_3Rs = 5.0 \text{ nM}$	EC_{50} for $D_2Rs = 34 \text{ nM}$ $E_{max} = 110\%$ EC_{50} for $D_3Rs = 6.8 \text{ nM}$ $E_{max} = 89\%$	3.22	(-)100e (5 $\mu\text{mol}/\text{kg}$, i.p., rat)—effective in the 6-OHDA PD test
	K_i for $D_{2L}Rs = 39 \text{ nM}$ K_i for $D_3Rs = 2.2 \text{ nM}$	EC_{50} for $D_2Rs = 3.0 \text{ nM}$ $E_{max} = 107\%$ EC_{50} for $D_3Rs = 1.3 \text{ nM}$ $E_{max} = 93\%$	4.07	(-)100f (5 $\mu\text{mol}/\text{kg}$, s.c., rat)—active in reserpine-induced hypolocomotion PD test
(-)100e		(-)100f		

(Continues)

TABLE 19 (Continued)

Chemical structures	Binding affinities	Functional activities	BBB score ^a	Behavioral test
	- K_i for $D_2Rs = 3.0\text{ nM}$ $E_{max} = 107\%$	EC_{50} for $D_2Rs = 3.0\text{ nM}$ $E_{max} = 107\%$	4.09	(-)100g (2.5, 5, and 10 $\mu\text{mol/kg}$, i.p., rat) —effective in the 6-OHDA PD test
	K_i for $D_{2L}Rs = 42\text{ nM}$ K_i for $D_3Rs = 0.4\text{ nM}$ $E_{max} = 81\%$	EC_{50} for $D_2Rs = 4.7\text{ nM}$ $E_{max} = 81\%$	3.32	(-)100h (10 $\mu\text{mol/kg}$, i.p., rat)—active in reserpine-induced hypokinesia PD test
(-)100g (D-512)	K_i for $D_{2L}Rs = 42\text{ nM}$ K_i for $D_3Rs = 0.4\text{ nM}$ $E_{max} = 81\%$	EC_{50} for $D_2Rs = 2.2\text{ nM}$ $E_{max} = 58\%$	(-)100h (5 $\mu\text{mol/kg}$, i.p., rat)—effective in the 6-OHDA PD test	(-)100h (173 μM , fruit fly)—attenuated aggregation of α -synuclein and exhibited neuroprotective properties in synucleinopathy PD model
(-)100h (D-520)				

TABLE 19 (Continued)

Chemical structures	Binding affinities	Functional activities	BBB score ^a	Behavioral test
	K_i for D _{2L} Rs = 233 nM K_i for D ₃ Rs = 1.4 nM	EC ₅₀ for D ₂ Rs = 42 nM E _{max} = 98% EC ₅₀ for D ₃ Rs = 5.9 nM E _{max} = 82%	2.39	(-)100i (173 μM, fruit fly)—attenuated aggregation of α-synuclein and exhibited neuroprotective properties in synucleinopathy PD model
	K_i for D _{2L} Rs = 369 nM K_i for D ₃ Rs = 1.7 nM	EC ₅₀ for D ₂ Rs = 16 nM E _{max} = 116% EC ₅₀ for D ₃ Rs = 0.1 nM E _{max} = 96%	3.69	(-)100j (5 μmol/kg, i.p., rat)—effective in reserpine-induced aknesia PD test (-)100j (10 μmol/kg, i.p., rat)—effective in the 6-OHDA PD test

(Continues)

TABLE 19 (Continued)

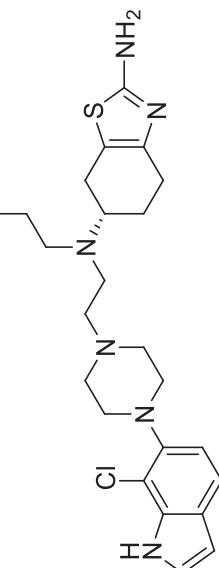
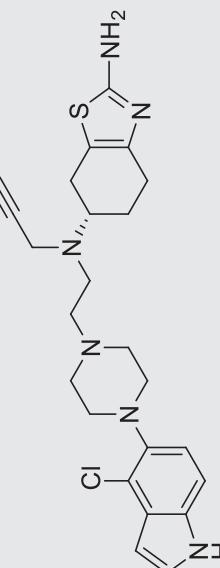
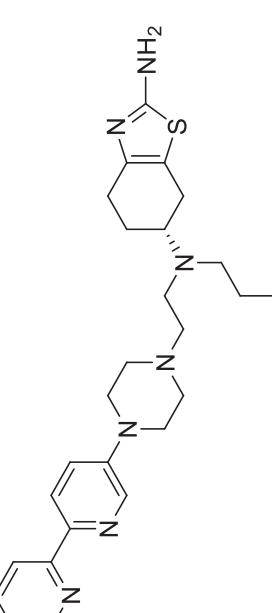
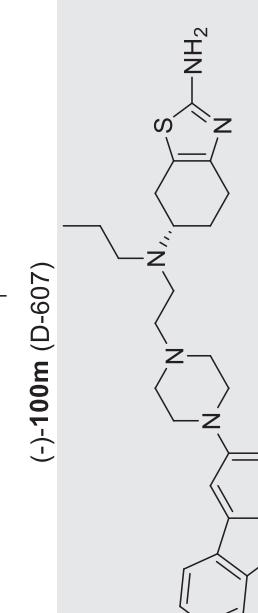
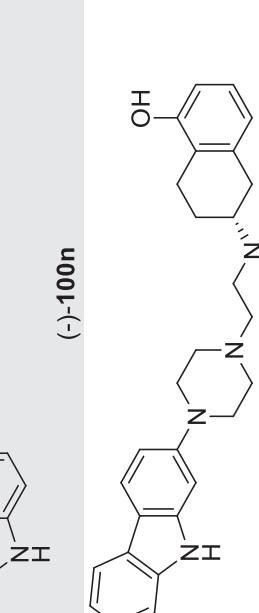
Chemical structures	Binding affinities	Functional activities	BBB score ^a	Behavioral test
	K_i for D _{2L} Rs = 16 nM E_{max} = 101%	EC ₅₀ for D ₂ Rs = 3.2 nM E_{max} = 101%	4.09	(-)100k (10 μmol/kg, i.p., rat)—active in reserpine-induced akinesia PD test
	K_i for D _{2L} Rs = 87 nM E_{max} = 27%	EC ₅₀ for D ₂ Rs = 22 nM E_{max} = 27%	4.09	(-)100l (10 μmol/kg, i.p., rat)—active in reserpine-induced akinesia PD test
(-)-100k		K_i for D ₃ Rs = 14 nM E_{max} = 94%	EC ₅₀ for D ₃ Rs = 11 nM E_{max} = 94%	(-)100l

TABLE 19 (Continued)

Chemical structures	Binding affinities	Functional activities	BBB score ^a	Behavioral test
	K_i for $D_{2L}Rs = 674 \text{ nM}$ $E_{max} = 101\%$	EC_{50} for $D_2Rs = 52 \text{ nM}$ $E_{max} = 100\%$	3.62	(-)100m (10 $\mu\text{mol}/\text{kg}$, s.c., rat)—active in reserpine-induced akinesia PD test (-)100m (0.1 and 0.25 mg/ml, fruit fly)—toxicity reduction in synucleinopathy PD model
	K_i for $D_3Rs = 13 \text{ nM}$ $E_{max} = 83\%$	EC_{50} for $D_3Rs = 14 \text{ nM}$ $E_{max} = 83\%$	3.49	(-)100m (5 mg/kg, i.p., mice)—neuroprotective properties against MPP ⁺ -induced toxicity
(-)100m (D-607)	K_i for $D_{2L}Rs = 135 \text{ nM}$ $E_{max} = 87\%$	EC_{50} for $D_2Rs = 49 \text{ nM}$ $E_{max} = 87\%$	3.49	(-)100m (10 $\mu\text{mol}/\text{kg}$, i.p., rat)—active in reserpine-induced akinesia PD model
	K_i for $D_3Rs = 3.8 \text{ nM}$ $E_{max} = 93\%$	EC_{50} for $D_3Rs = 1.0 \text{ nM}$ $E_{max} = 93\%$	3.89	(-)100n (10 $\mu\text{mol}/\text{kg}$, i.p., rat)—active in reserpine-induced akinesia PD test
	K_i for $D_{2L}Rs = 71 \text{ nM}$ $E_{max} = 85\%$	EC_{50} for $D_2Rs = 0.9 \text{ nM}$ $E_{max} = 85\%$	3.89	(-)100o (10 $\mu\text{mol}/\text{kg}$, i.p., rat)—active in reserpine-induced akinesia PD test

^aThe calculations were performed according to the reference.⁵²

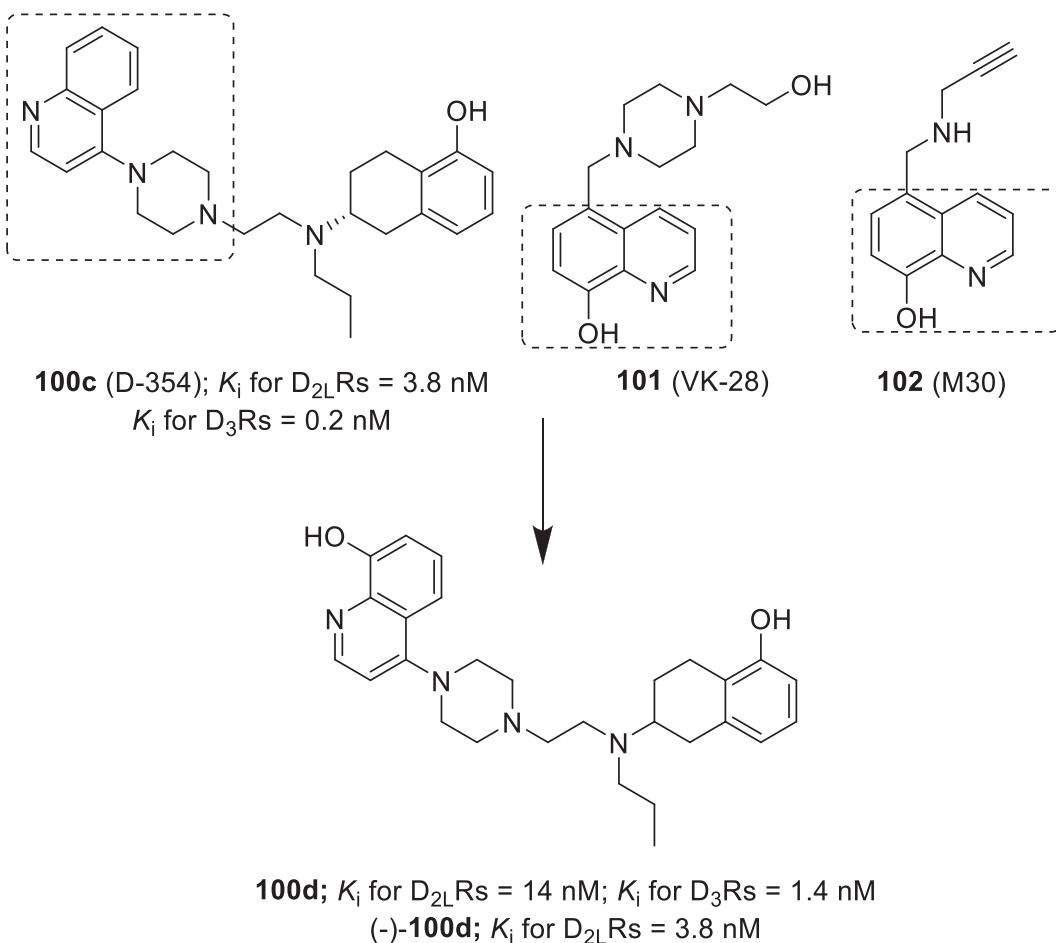


FIGURE 55 Schematic representation of the quinoline-8-ol derivative **100d** design from iron chelators **101** (VK-28) and **102** (M30), and **100c**.

pretreatment with (-)-**100e** (2 mg/kg) significantly protected against MPTP-induced dopaminergic cell loss in substantia nigra.⁷³⁰

Some indole derivatives are well-known for their radical scavenging ability.^{731,732} Thus, multifunctional drugs with implications in PD treatment based on the structure of **100b** (Figure 54), with an indole core directly attached to the piperazine ring, were published.⁷³³ A D₃R ligand with high affinity, (-)-**100f** (D₂R agonist, Figure 56, Table 19), displayed strong antioxidant capacity in the DPPH antioxidant assay. Moreover, (-)-**100f** (5 μmol/kg, s.c.) was effective in treating reserpine-induced hypolocomotion in rat.⁷³³

The compound (-)-**100g** (2.5, 5, and 10 μmol/kg, i.p.) was tested in rats with unilateral lesions induced by 6-OHDA in the medial forebrain bundle.⁷³⁴ The compound (-)-**100g** (D-512, D₂R agonist, Figure 56, Table 19) protected MN9D cells from 6-OHDA and MPTP toxicity in all the concentration ranges of the drug (5, 10, 20, and 30 μmol). It also inhibited sodium nitroprusside-induced lipid peroxidation in MN9D cells in a dose-dependent manner, with the highest dose (20 μmol) producing an almost 100% protection. Treatment with (-)-**100g** (20 μmol) inhibited caspase 3/7 activity in MN9D cells, confirming potential to protect the cells from apoptosis in the presence of 6-OHDA.⁷³⁴ The highest neuroprotective effect of (-)-**100g** against 6-OHDA-induced cytotoxicity in PC12 cells was observed at 10 μM.⁷³⁵ Treatment with (-)-**100g** (0.5 mg/kg) was effective in abrogating striatal DA

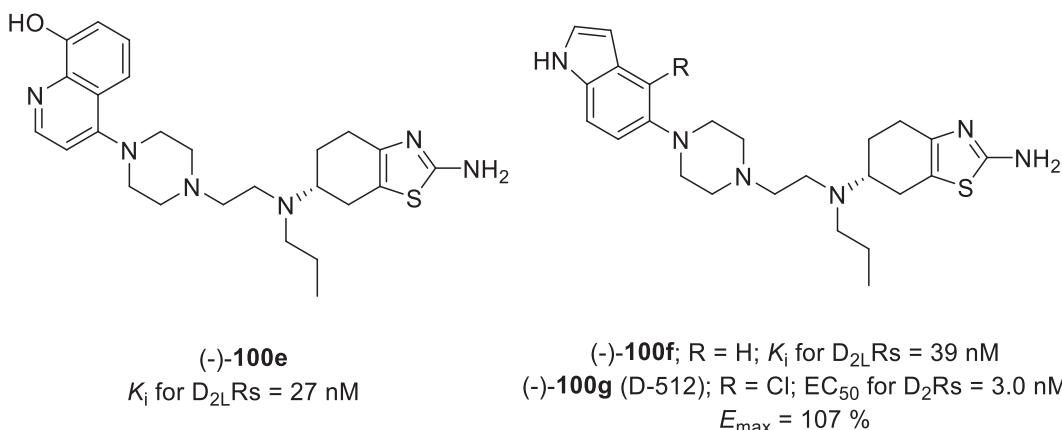


FIGURE 56 Chemical structures of the N6-propyl-4,5,6,7-tetrahydrobenzo[d]thiazole-2,6-diamine analogs (-)-100e-g.

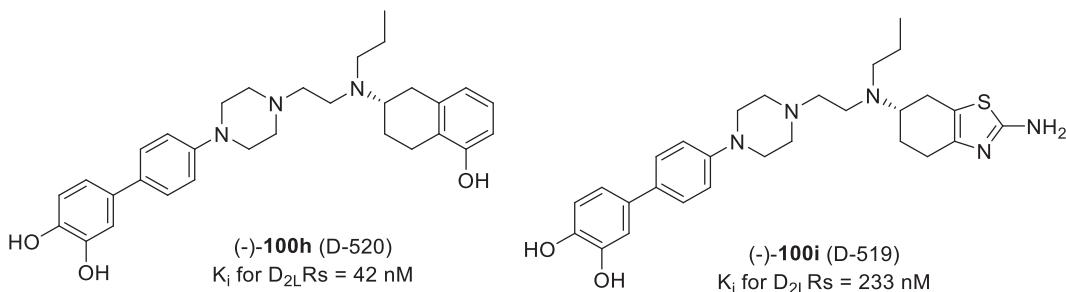


FIGURE 57 Chemical structures of the 4'-(piperazin-1-yl)-[1,1'-biphenyl]-3,4-diol derivatives (-)-100h-i as potential antiparkinsonian drugs.

depletion induced by MPTP and in protecting against MPTP-induced substantia nigra pars compacta dopaminergic cell loss.⁷³⁵

Continuing with (-)-100g as a promising lead candidate, antioxidant ability was investigated in buthionine sulfoximine- and 6-OHDA-induced oxidative stress models in PC12 cells.⁷³⁶ The depletion of cytoplasmatic glutathione levels is one indicator of oxidative stress, which occurs in the substantia nigra of PD brain.^{736,737} Buthionine sulfoximine is an irreversible inhibitor of glutamate-cysteine ligase, a key enzyme in the biosynthesis of glutathione.⁷³⁸ Treatment with (-)-100g was capable to restore the level of glutathione against buthionine sulfoximine- and 6-OHDA-induced glutathione depletion at 20 and 10 μM , respectively.⁷³⁶

In another study, (-)-100g was compared to ropinirole (Table 6) for its ability to stimulate spontaneous motor activity and reverse Parkinsonian akinesia in rats.⁷³⁹ Treatment with (-)-100g was found to be more effective than that with ropinirole. Pharmacokinetic analysis revealed resulting blood plasma levels and brain uptake of (-)-100g was higher than those of ropinirole. Both drugs enhanced spontaneous movement, but (-)-100g showed a longer duration of action. Only (-)-100g was significantly capable of reversing forelimb akinesia.⁷³⁹

A large body of evidence has demonstrated that ligands with dihydroxy groups can effectively modulate the aggregation of α -synuclein.⁷⁴⁰⁻⁷⁵⁰ To pursue this hypothesis, two hydroxyl groups at different positions on the biphenyl ring of 99 (Figure 54) were introduced with the aim of downregulating the aggregation of α -synuclein.⁷¹⁶ The 4'-(Piperazin-1-yl)-[1,1'-biphenyl]-3,4-diol derivatives (-)-100h (D-520, D₂R agonist, Figure 57, Table 19) and (-)-100i (D-519, D₂R agonist, Figure 57, Table 19) were selected for evaluation of anti-PD effects. Treatment with

(*-*)-**100h** (10 µmol/kg, i.p.) reversed reserpine-induced hypokinesia in rats. At a dose of 5 µmol/kg, it also caused large numbers of rotations in rats with unilateral lesions in the medial forebrain bundle induced by 6-OHDA. Additionally, (*-*)-**100h** (5 and 10 µmol) revealed a high protective effect (nearly 25%–30% protection from 6-OHDA-induced toxicity) in MN9D cells. Data from a thioflavin-T assay and from transmission electron microscopy analysis revealed that (*-*)-**100h** inhibited α-synuclein aggregation.⁷¹⁶

In the follow-up study, (*-*)-**100h** and (*-*)-**100i** (Figure 57, Table 19) were evaluated *in vivo* in the synucleinopathy PD model of the fruit fly *Drosophila melanogaster*.⁷⁵¹ At a dose of 173 µM, both compounds significantly attenuated aggregation of α-synuclein and exhibited neuroprotective properties.⁷⁵¹

Apart from α-synuclein, (*-*)-**100h** (Figure 57) also revealed an anti-Aβ profile, which could be of high therapeutic interest in other dementias.⁷⁵² PD mostly turns into typical dementia, which is characterized not only by accumulation of α-synuclein in cortical and limbic areas of the brain, but also by high levels of diffused Aβ plaques in the striatum and neocortical areas.⁷⁵² The effect of (*-*)-**100h** on disassembly of α-synuclein aggregates was monitored for 15 days. *In vitro*, co-incubation of (*-*)-**100h** (86 µM) with α-synuclein (43 µM) resulted in a reduction of protein aggregation by 80% and 85% at Days 10 and 15, respectively.⁷⁵² In the control group, PC12 cells exposed solely to α-synuclein exhibited a 76% decrease in cell viability at Day 15. Thus, the presence of (*-*)-**100h** may disaggregate α-synuclein fibrils and prevent monomers from further aggregation.⁷⁵² Furthermore, (*-*)-**100h** inhibited oligomer formation of Aβ (10 µM) in all tested concentrations (i.e., 1, 10, and 20 µM). Similarly to its effect on α-synuclein, (*-*)-**100h** initiated disaggregation of the formed aggregates of Aβ and also inhibited Aβ formation. Administration of (*-*)-**100h** in water (1 mg/ml) to *Drosophila* flies for 14 days significantly suppressed Aβ-induced toxicity.⁷⁵²

Structural optimization of the neuroprotective anti-PD agent **99** (Figure 54) was examined to improve *in vivo* efficacy, especially enhancing of BBB permeation, without compromising multifunctional agonist profile towards D₂/D₃Rs or neuroprotective properties.⁷¹⁷ Based on binding affinities for D₂/D₃ receptors, (*-*)-**100j** (D₂R agonist, Figure 58, Table 19) was selected as the lead molecule for further testing. This compound showed antioxidant properties in DPPH assays. Furthermore, (*-*)-**100j** (5 µmol/kg, i.p.) was highly effective in reversing akinesia induced by reserpine in rats. At a 10 µmol/kg dose, (*-*)-**100j** was effective in an *in vivo* PD model of 6-OHDA lesioned rats. In

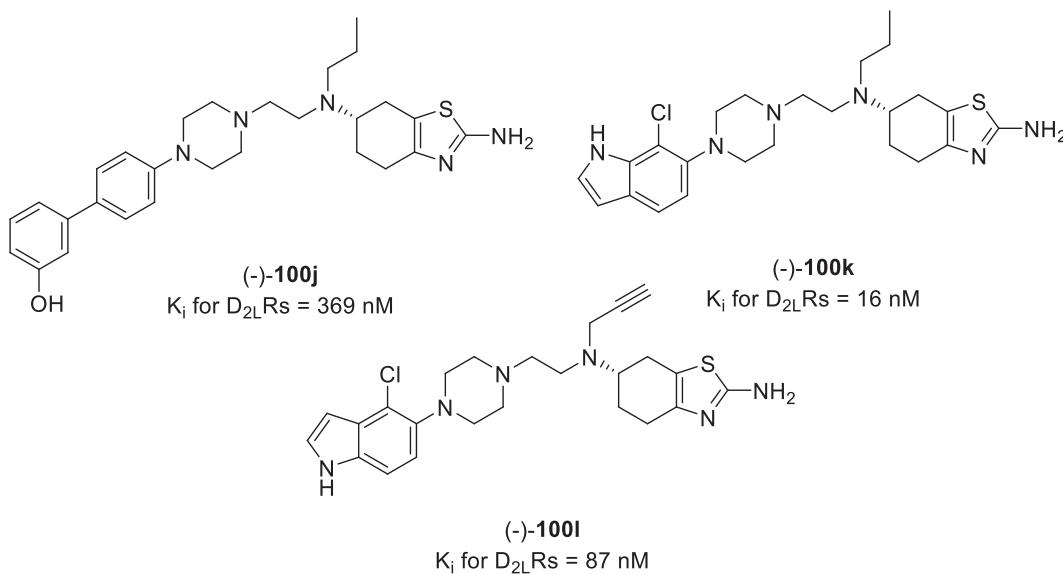


FIGURE 58 Chemical structures of the (*-*)-4,5,6,7-tetrahydrobenzo[d]thiazole-2,6-diamine analogs (*-*)-**100j**–**l**.

addition, (-)-**100j** exhibited significant neuroprotection in MN9D cells against MPTP-induced neurotoxicity at doses of 5 or 10 μ M.⁷¹⁷

Development of highly potent D₂/D₃R agonists based on (-)-**100g** (Figure 56) also took into account a combination of different indole positions on the piperazine ring.⁷¹⁸ In the study, (-)-**100k** (Figure 58, Table 19) was identified as a full agonist of both D₂Rs and D₃Rs, whereas (-)-**100l** (Figure 58, Table 19) exhibited partial agonism at D₂Rs and full agonism at D₃Rs. These two compounds were subjected to reserpine-induced hypolocomotion in rats. Treatment with (-)-**100l** (10 μ mol/kg, i.p.) was less effective than that with (-)-**100k** (10 μ mol/kg, i.p.) in enhancing locomotor activity in this model. Furthermore, (-)-**100k** possessed antioxidant properties in a DPPH assay and was neuroprotective at a dose of 20 μ M in PC12 cells against 6-OHDA-induced toxicity.⁷¹⁸

The iron-chelating D₂/D₃R agonist (-)-**100m** (Figure 59, Table 19), originating from (-)-**100e** (Figure 56), with a bipyridyl moiety connected to its piperazine ring was prepared.⁷⁵³ This compound showed full agonist activity on both D₂/D₃Rs. It was subjected to ongoing studies and displayed preferential iron (II) chelation and ability to reverse akinesia (induced by reserpine) in rat models of PD (10 μ mol/kg, s.c.).⁷⁵³

At a dose of 5 μ M, (-)-**100m** (Figure 59) was subjected to a follow-up study⁷⁵⁴ to identify its neuroprotective effect in PC12 cells against 6-OHDA-induced toxicity. In a *D. melanogaster* model overexpressing α -synuclein protein, (-)-**100m** (0.1 and 0.25 mg/ml) exhibited significant toxicity reduction. It also displayed neuroprotective properties against MPTP-induced toxicity in mice at a dose of 5 mg/kg.⁷⁵⁴

Design, synthesis, and pharmacological characterization of carbazole D₂/D₃Rs agonists derived from (-)-**100g** (Figure 56) was reported to find potential symptomatic and neuroprotective agents for the treatment of PD.⁷⁵⁵ Carbazole can be considered a useful scaffold, well-known for its neuroprotective behavior.^{756–762} Accordingly, a carbazole core attached to a piperazine ring generated multifunctional drugs.⁷⁵⁵ In the resulting subset, (-)-**100n** (Figure 60, Table 19) and (-)-**100o** (Figure 60, Table 19) showed full agonism for both D₂/D₃Rs. Treatment with

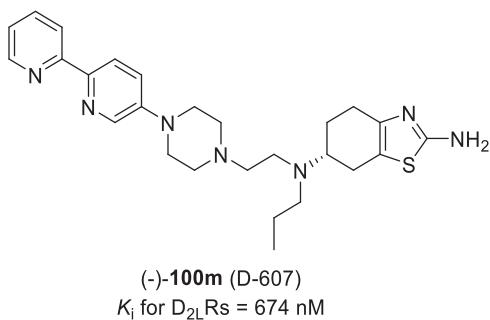


FIGURE 59 Chemical structure of the bipyridyl-piperazine derivative (-)-**100m**.

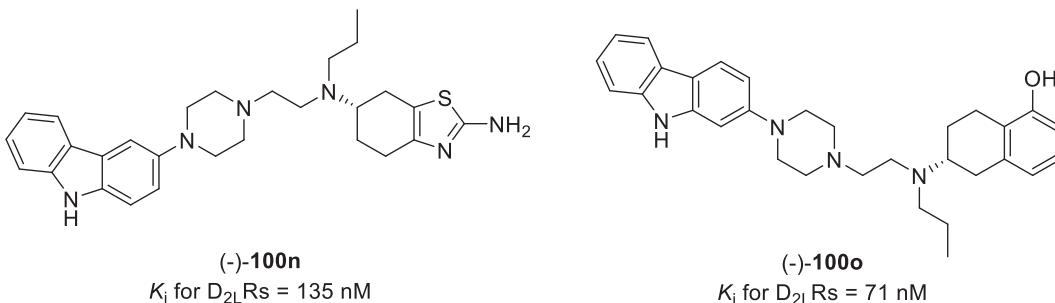


FIGURE 60 Chemical structures of the carbazole derivatives (-)-**100n-o**.

(*-*)-**100n** and with (*-*)-**100o** (both at 10 μ mol/kg, i.p.) significantly reversed reserpine-induced akinesia in rats. At 20 μ M, ROS reduction by 76% and 93% (induced by 6-OHDA in PC12 cells) was observed for (*-*)-**100n** and (*-*)-**100o**, respectively suggesting their antioxidant capacity. Furthermore, (*-*)-**100n** and (*-*)-**100o** possessed neuroprotective features against 6-OHDA-induced toxicity in PC12 cells. At a dose of 173 μ M, (*-*)-**100n** and (*-*)-**100o** mitigated aggregation and reduced toxicity of α -synuclein (1.25 mg/ml) in a cell-based *in vitro* assay.⁷⁵⁵

2.5.3 | Miscellaneous 4-(aryl)-1-substituted cyclic amines as D₂R ligands

The β -Arrestin-biased D₂R modulators UNC9975 (**103**) and UNC9994 (**104**; Figure 61, Table 20) have been discovered pursuing the known “tuned-properties” of **7** (Figure 15). The SAR study concentrated on different functional groups connected to the phenyl ring and attached to piperazine or other cyclic amines, various linkers in the middle region, and a variety of bicyclic aromatic systems as the lipophilic fragment of **7**.⁷⁶³ In functional activities assays, **103** and **104** did not activate G_i-mediated signaling cascades. These compounds were partial agonists for the D₂R-mediated β -arrestin-2 translocation in both Tango and DiscoveRx assays. Compound **103** emerged as a potent partial agonist in a D₂R-mediated BRET-based β -arrestin-2 recruitment assay and a p-ERK reporter assay. The multiple functional activity implied that both **103** and **104** are β -arrestin-biased partial D₂R agonists that selectively activate β -arrestin recruitment and signaling, and are simultaneously inactive at G_i-mediated signal transduction pathways.⁷⁶³ Treatment with **103** ($ED_{50} = 0.4$ mg/kg, i.p.) inhibited d-amphetamine-induced hyperlocomotion in mice. Treatment with **103** ($ED_{50} = 0.3$ mg/kg for wild-type; $ED_{50} = 0.8$ mg/kg for β -arrestin-2 knockout mice) also effectively inhibited PCP-induced hyperlocomotion. At a dose of 2 mg/kg (i.p.), **104** significantly inhibited PCP-induced hyperlocomotion in wild-type mice, but this antipsychotic-like effect was completely absent in β -arrestin-2 knockout mice.⁷⁶³ This finding suggests that the antipsychotic-like activity of **103** and **104** requires β -arrestin. In addition, **103** (5.0 mg/kg, i.p.) failed to induce catalepsy in wild-type mice, whereas **63** (Figure 37, 2 mg/kg), used as positive control, caused catalepsy. On the other hand, **103** (5.0 mg/

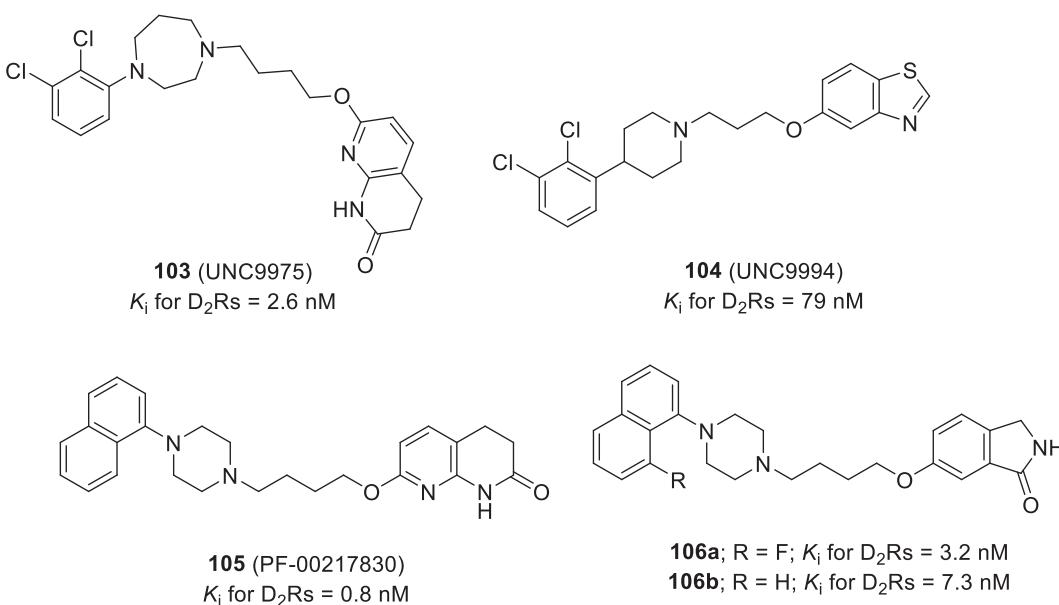


FIGURE 61 Chemical structures of miscellaneous 4-(aryl)-1-substituted cyclic amines **103**, **104**, **105**, and **106a–b**.

TABLE 20 Highlighted compounds 103–105, 106a–b, 107, 110, and 111a–b with chemical structures and properties

Chemical structures	Binding affinities	Functional activities	BBB score ^a	PD/PK ^b properties	Behavioral test
	K_i for D ₂ Rs = 2.6 nM K_i for D ₃ Rs = 11 nM	D ₂ -mediated β-arrestin-2 translocation Tango assay: EC ₅₀ = 1.1 nM, E _{max} = 43%	4.74	-	103 (ED ₅₀ = 0.4 mg/kg, i.p., mice)– inhibition of D ₁ -induced hyperlocomotion
	K_i for D ₄ Rs = 178 nM K_i for D ₅ Rs = 513 nM	D ₂ -mediated β-arrestin-2 translocation DiscoverRx assay: EC ₅₀ = 5.7 nM, E _{max} = 19%			103 (ED ₅₀ = 0.3 mg/kg for wild-type mice; ED ₅₀ = 0.8 mg/kg for β-arrestin-2 knockout mice)– inhibition of PCP-induced hyperlocomotion
	K_i for 5-HT _{1A} Rs = 29 nM K_i for 5-HT _{2A} Rs = 7.4 nM	D ₂ -mediated BRET-based β-arrestin-2 recruitment assay: EC ₅₀ = 6.0 nM, E _{max} = 20%			103 (5.0 mg/kg, i.p., wild-type mice)– no catalepsy
		K_i for 5-HT _{2B} Rs = 1.1 nM K_i for 5-HT _{2C} Rs = 99 nM	ERK phosphorylation reporter assay: EC ₅₀ = 2.2 nM, E _{max} = 32%		103 (5.0 mg/kg, i.p., β-arrestin-2 knockout mice)– induction of catalepsy
103 (UNC9975)	K_i for H ₁ Rs = 6.1 nM	pA ₂ for 5-HT _{2A} Rs = 102 nM IC ₅₀ for 5-HT _{2B} Rs = 76 nM EC ₅₀ for 5-HT _{2C} Rs = 324 nM pA ₂ for H ₁ Rs = 35 nM			

(Continues)

TABLE 20 (Continued)

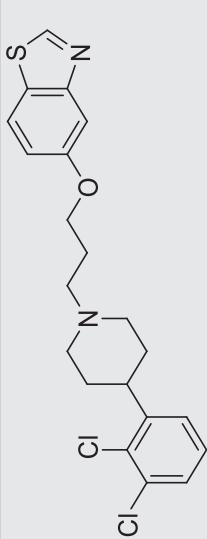
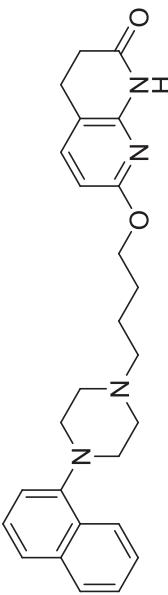
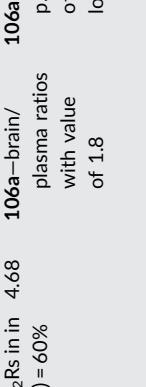
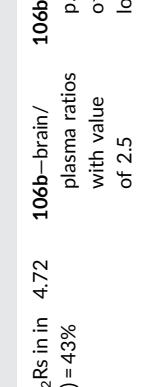
Chemical structures	Binding affinities	Functional activities	BBB score ^a	PD/PK ^b properties	Behavioral test
	K_i for D ₂ Rs = 79 nM K_i for D ₃ Rs = 17 nM K_i for D ₄ Rs = 138 nM K_i for 5-HT _{1A} Rs = 26 nM 104 (UNC9994) K_i for 5-HT _{2A} Rs = 140 nM K_i for 5-HT _{2B} Rs = 25 nM K_i for 5-HT _{2C} Rs = 512 nM K_i for H ₁ Rs = 2.4 nM K_i for D ₂ Rs = 0.8 nM K_i for 5-HT _{1A} Rs = 3.7 nM K_i for 5-HT _{2A} Rs = 0.1 nM	D ₂ -mediated β-arrestin-2 translocation Tango assay: EC ₅₀ = 6.1 nM, E _{max} = 91% D ₂ -mediated β-arrestin-2 translocation DiscoverRx assay: EC ₅₀ = 448 nM, E _{max} = 64% EC ₅₀ for 5-HT _{1A} Rs = 933 nM IC ₅₀ for 5-HT _{2B} Rs = 501 nM pA ₂ for H ₁ Rs = 79 nM Intrinsic activity at D ₂ Rs in vivo (mouse, p.o.) = 46%	5.07	-	104 (2 mg/kg, i.p., mice)–inhibition of PCP-induced hyperlocomotion
			4.35	105 (1 mg/kg, i.v., rat)– $t_{1/2}$ = 14 h $t_{1/2}$ = 6.8 h and bioavailability 19% 105 (3 mg/kg, p.o., monkey) $t_{1/2}$ = 14 h and bioavailability 21%	105 (MED^d = 0.3 mg/kg, p.o., rat) –inhibition of spontaneous locomotor activity 105 (10 mg/kg, p.o., rat) –no catalepsy

TABLE 20 (Continued)

Chemical structures	Binding affinities	Functional activities	BBB score ^a	PD/PK ^b properties	Behavioral test
	K_i for D ₂ Rs = 3.2 nM K_i for 5-HT _{1A} Rs (SPA bead/membrane based assay) = 1.0 nM K_i for 5-HT _{2A} Rs = 1.8 nM	Intrinsic activity at D ₂ Rs in vivo (mouse, p.o.) = 60%	4.68	106a-brain/plasma ratios with value of 1.8	106a (MED = 1 mg/kg, p.o., rat)–inhibition of spontaneous locomotor activity
	K_i for D ₂ Rs = 7.3 nM K_i for 5-HT _{1A} Rs (SPA bead/membrane based assay) = 2.2 nM K_i for 5-HT _{2A} Rs = 5.0 nM	Intrinsic activity at D ₂ Rs in vivo (mouse, p.o.) = 43% Intrinsic activity at 5-HT _{1A} Rs = 67%	4.72	106b-brain/plasma ratios with value of 2.5	106b (MED = 1 mg/kg, p.o., rat)–inhibition of spontaneous locomotor activity
	K_i for D ₂ Rs = 110 nM K_i for 5-HT _{1A} Rs = 90 nM K_i for 5-HT _{2A} Rs = 2320 nM	-	5.12	-	107 (15 mg/kg, p.o., mice)–inhibition of apomorphine-induced climbing behavior 107 (30 mg/kg, mice) no catalepsy

(Continues)

TABLE 20 (Continued)

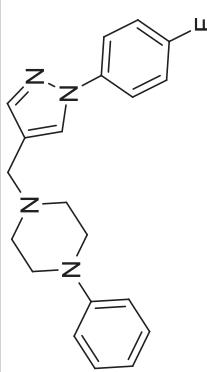
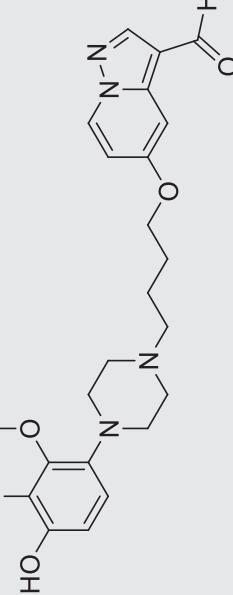
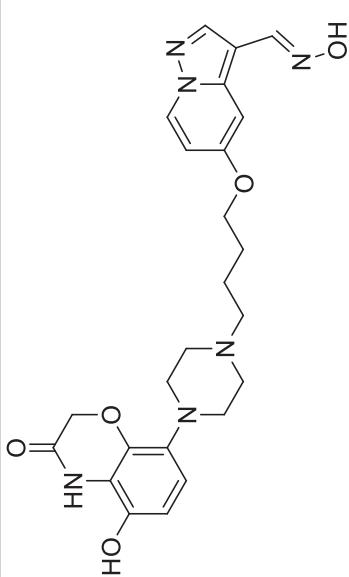
Chemical structures	Binding affinities	Functional activities	BBB score ^a	PD/PK ^b properties	Behavioral test
	K_i for D ₂ Rs = 70 nM K_i for 5-HT _{1A} Rs = 60 nM K_i for 5-HT _{2A} Rs = 920 nM	-	5.13	-	110 (15 mg/kg, p.o., mice) – inhibition of apomorphine-induced climbing behavior 110 (30 mg/kg, mice) – no catalepsy
	K_i for D ₂ Rs = 1.1 nM K_i for D _{2S} Rs = 0.7 nM K_i for D ₃ Rs = 1.2 nM K_i for D ₄ Rs = 10 nM K_i for 5-HT _{1A} Rs = 21 nM K_i for α ₁ Rs = 11 nM	EC_{50} (β-arrestin-2 recruitment [D_{2S} Rs]) = 68 nM EC_{50} (³⁵ S[GTP] γ S [D_{2S} Rs + Gα _o]) > 1 μM	2.22	-	
110 (LASSBio-664)					111a

TABLE 20 (Continued)

Chemical structures	Binding affinities	Functional activities	BBB score ^a	PD/PK ^b properties	Behavioral test
	K_i for $D_{2L}Rs = 1.0 \text{ nM}$ K_i for $D_{2S}Rs = 1.0 \text{ nM}$	EC_{50} (β -arrestin-2 recruitment [$D_{2S}Rs$] = 110 nM)	1.68	-	-
	K_i for $D_3Rs = 0.4 \text{ nM}$	$E_{max} = 44\%$			
	K_i for $D_4Rs = 3.9 \text{ nM}$				
	K_i for $5-HT_{1A}Rs = 19 \text{ nM}$	EC_{50} ([^{35}S]GTPyS [$D_{2S}Rs + G\alpha_{o1}$] > 1 μM)			
	K_i for $5-HT_{2A}Rs = 880 \text{ nM}$				
	K_i for $q_1Rs = 17 \text{ nM}$				

111b

^aThe calculations were performed by the reference.⁵⁵²^bPharmacodynamics/pharmacokinetics.^cPharmacokinetic *in vivo* half-life.^dMinimum effective dose.

kg, i.p.) caused catalepsy in β -arrestin-2 knockout mice. These results collectively show that β -arrestin recruitment and signaling are protective against motoric side effects.⁷⁶³

As a part of ongoing studies, **103** and **104** were evaluated for their antischizophrenic properties in mice.⁷⁶⁴ Treatment with **103** (0.5 mg/kg) and **104** (2 mg/kg) reduced hyperlocomotion in an open field test in NR1 knockdown mice. Treatment with **103** restored phenylcyclidine-induced prepulse inhibition, which is disrupted in schizophrenia,⁷⁶⁵⁻⁷⁶⁷ at a dose of 0.2 and 1 mg/kg in wild-type mice and in β -arrestin-knockdown mice. Treatment with **103** (0.5 mg/kg) also improved novel object recognition memory and partially normalized social behavior. Besides, **103** induced a much lower level of catalepsy than **63** (Figure 37).⁷⁶⁴

Design of compounds incorporating in the 3,4-dihydroquinolin-2(1H)-one moiety was inspired by the chemical structure of **7** (Figure 15).⁷⁶⁸ Initially, the study examined the effect of an extra nitrogen atom in the molecule. Secondly, the impact of replacing the 2,3-dichlorophenyl system with other aromatic/heteroaromatic systems was examined. The effect of fluorine atoms in different positions of the naphthalene ring connected with piperazine was also studied. These analogs exhibited a high affinity for D₂, 5-HT_{1A}, and 5-HT_{2A} receptors.⁷⁶⁸ The resulting **105** (PF-00217830; D₂R partial agonist, Figure 61, Table 20), with high affinities for determined targets, emerged as a partial agonist to D₂Rs (intrinsic activity 38%). This compound inhibited spontaneous locomotor activity in rats in a dose-dependent manner, with a minimum effective dose 0.3 mg/kg (p.o.), suggesting antipsychotic efficacy. It also did not cause a cataleptic response (10 mg/kg, p.o., rats). The pharmacokinetic profile of **105** showed oral bioavailability in rats and monkeys, at 19% and 21% with t_{1/2} values of 6.8 and 14 h, respectively.⁷⁶⁸ Compound **105** also successfully completed a phase 2 clinical trial.⁷⁶⁹

Pharmacological profiles of the molecules derived from **7** revealed D₂R partial agonism with intrinsic activity ranging between 30% and 55%, 5-HT_{1A} partial agonism (60%–90%), and 5-HT_{2A} antagonism.⁷⁷⁰ The scope of the study was to investigate the effect of the replacement of 3,4-dihydro-2(1H)-one scaffolds by variously substituted 6-alkoxyisoindolin-1-one moieties, and 2,3-dichlorophenyl with different aromatic/heteroaromatic systems connected with the piperazine ring on the activity. The best optimally balanced profiles in this group of compounds were those of **106a** (Figure 61, Table 20) and **106b** (Figure 61, Table 20). Both of these compounds inhibited spontaneous locomotor activity in rats in a dose-dependent manner with a minimum effective dose of 1 mg/kg (p.o.). Additionally, both showed promising brain/plasma ratios (1.8 and 2.5).⁷⁷⁰

A new series of arylpiperazine derivatives were studied by Neves et al.⁷⁷¹ to search for a new antipsychotic lead-compound. As a result, **107** (LASSBio-579; Figure 62, Table 20), **108** (LASSBio-580, Figure 62), and **109** (LASSBio-581, Figure 62) were developed by the isosteric replacement between pyrazole and a 1,2,3-triazole heterocyclic ring.^{771,772} Treatment with **107** (30 mg/kg, i.p.) inhibited the stereotyped behavior in rodents induced by amphetamine.⁷⁷³ The molecular scaffolds of ligands **107**–**109** were examined, revealing D₂, 5-HT_{1A}, and 5-HT_{2A} receptor affinities. The molecular diversity was assessed in three different regions of the molecules: (i) isosteric replacement of the heterocyclic ring at the biaryl motif, generating pyrazole and 1,2,3-triazole ligands; (ii) addition of different substitutions at the para-biaryl position; and (iii) various substitutions at the para-position of phenyl connected with piperazine ring.⁷⁷¹ Based on the binding affinities, **110** (Figure 62, Table 20) and **107** were selected for in vivo evaluation. **110** and **107** (15 mg/kg, p.o.) inhibited the apomorphine-induced climbing behavior in mice. They also did not cause catalepsy in mice in the apomorphine-induced climbing test.⁷⁷¹

Hydroxy-substituted heteroarylpirazinines based on **87b**⁷⁰² (Figure 49) have been discovered, targeting β -arrestin D₂R signaling.⁷⁷⁴ In functional activities assays, 5-hydroxy-8-(piperazin-1-yl)-2H-benzo[b][1,4]oxazin-3(4H)-one derivatives **111a** and **111b** (Figure 63, Table 20) yielded substantial β -arrestin-2 recruitment, while being offering nearly zero activation of canonical cascades (in GTPyS binding assay).⁷⁷⁴

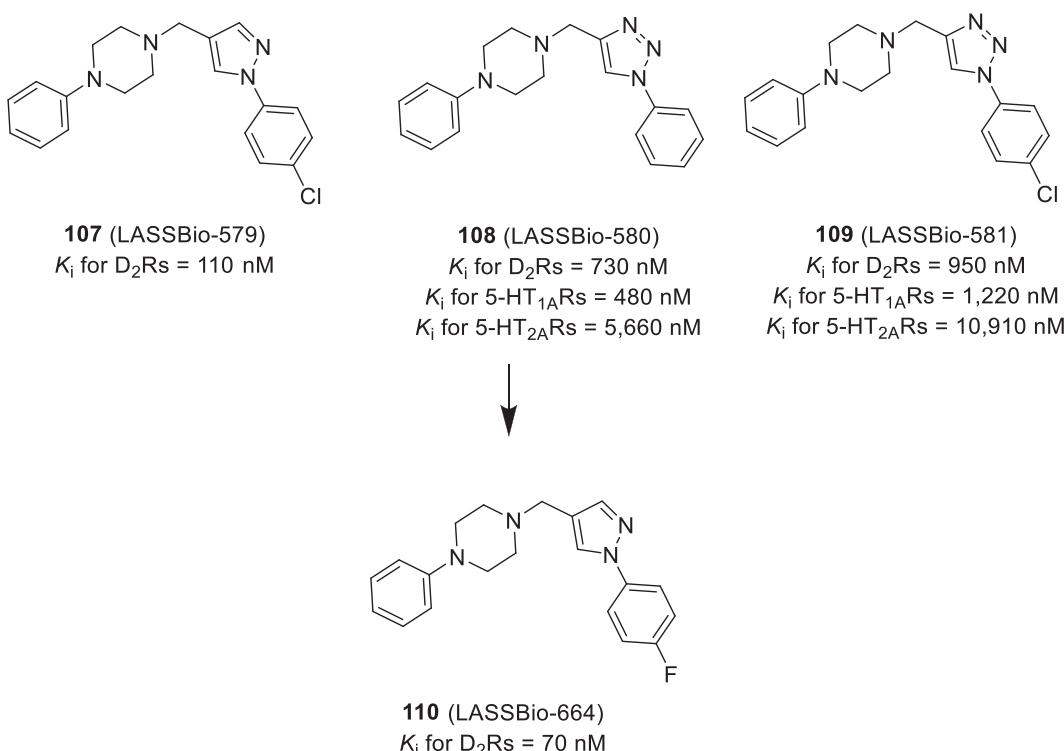
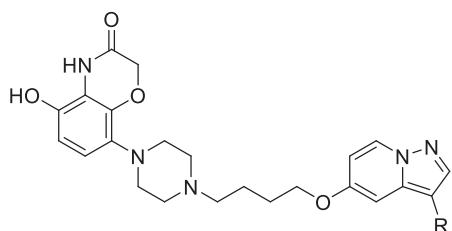


FIGURE 62 Design of 1-((1-(4-fluorophenyl)-1H-pyrazol-4-yl)methyl)-4-phenylpiperazine derivative **110** analogs from parent compounds **107–109**.



111a; $R = \text{CHO}$; K_i for $D_{2L}Rs = 1.1 \text{ nM}$; K_i for $D_{2S}Rs = 0.7 \text{ nM}$
111b; $R = (E)\text{-CHNOH}$; K_i for $D_{2L}Rs = 1.0 \text{ nM}$; K_i for $D_{2S}Rs = 1.0 \text{ nM}$

FIGURE 63 5-Hydroxy-8-(piperazin-1-yl)-2H-benzo[b][1,4]oxazin-3(4H)-one derivative **111a–b** with high activity at β -arrestin-2-recruitment.

3 | DISCUSSION

A large number of ligands affecting D_2Rs have been developed since 2010. In Section 2.5 titled “1,4-Disubstituted aromatic/heteroaromatic cyclic amine derivatives affecting dopamine D_2Rs —their structure, function, and pharmacological profiles,” we discussed mainly representatives with the most common aromatic/heteroaromatic features attached to cyclic amines (piperazine, homopiperazine, piperidine, or tropane). SAR studies dealing with various lipophilic appendages were also described. Initially, we identified the molecules from a structural perspective, specifically emphasizing the 1,4-disubstituted aromatic/heteroaromatic cyclic amine (1,4-DACA) group. However, this classical pharmacophore does

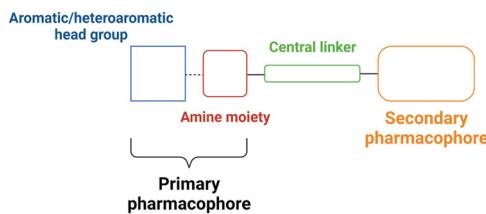


FIGURE 64 Schematic representation of the general pharmacophore for D₂ and D₃ receptors. The pharmacophore consists of a primary pharmacophore that binds to the orthosteric binding site, a central linker, and a secondary pharmacophore that binds to the allosteric (second) binding site. The dashed line between the aromatic/heteroaromatic head group and the amine moiety indicates that these fragments may be represented by a bicyclic system. [Color figure can be viewed at wileyonlinelibrary.com]

not cover the entire literature on D₂R modulators prepared between 2010 and 2022. In the following parts, we designated the D₂R modulators that do not structurally fit into the 1,4-DACA group or did not contain the necessary data (top-ranked candidate evaluated in vivo as a potential drug for management of schizophrenia, PD, depression or anxiety, or proved to be selective D₂R, biased or bivalent ligand) so we discussed them in detail in section "2.5 1,4-Disubstituted aromatic/heteroaromatic cyclic amine derivatives affecting dopamine D₂Rs—their structure, function, and pharmacological profiles." These analogs fall within the more general pharmacophore of D₂R and even D₃R, as shown in Figure 64. This pharmacophore consists of the so-called primary pharmacophore, which is further composed of aromatic/heteroaromatic head and amine moieties, a central linker, and a so-called secondary pharmacophore.^{490,527,775-777} The primary pharmacophore binds to the orthosteric binding site, whereas the secondary pharmacophore binds to the allosteric (secondary) binding site.^{776,777} Over the literature, synonymous designations for aromatic/heteroaromatic heads have been used, for example, A-ring,^{768,770} the left-hand side phenyl ring,^{584,585,595} aryl/heteroaryl head group⁴⁶⁷ or aromatic core structure (π_1).⁶⁰² Other names used for the primary pharmacophore are: fragment I,⁶⁴⁶ head group,⁵⁹⁴ basic residue⁶⁰¹ or base moiety.^{163,630} The central linker was referred to as a linker^{163,467,602,646} or spacer^{589,601,700} and the secondary pharmacophore was referred to as fragment II,⁶⁴⁶ B-ring,⁷⁷⁰ the right-hand side moiety,^{584,585,595} tail group,⁵⁹⁴ heterocyclic unit,⁷⁰⁰ aryl/heteroaryl tail group,⁴⁶⁷ lipophilic system (π_2),⁶⁰² or lipophilic appendage.⁵⁸⁹

3.1 | Primary pharmacophore

In addition to the above-mentioned 1,4-DACA, some specific fragments were used as primary pharmacophores, namely 7-piperazinyl and 7-piperidinyl-3,4-dihydroquinazolin-2(1H)-one,⁷⁷⁸ 5-piperidinyl and 5-piperazinyl-1H-benzo[d]imidazole-2(3H)-one,⁷⁷⁹ 4-(1-benzimidazolinone)piperidine,⁷⁸⁰ sumanirole,^{489,490,776,777} tranylcypromine,⁴⁷² pramipexole,⁴⁶⁹ 2-phenylcyclopropylmethylamine,⁵²⁷ eticlopride,^{479,775} 1,2,3,4-tetrahydro-3-quinolinamine,⁷⁷⁶ tetracyclic,⁷⁸¹ tetrahydroisoquinoline,^{480,498,594,595,600,782-787} or 1,3-disubstituted morpholine.^{438,474,490,493,788} Various aliphatic,^{477,515,516,602,789-793} bicyclic⁷⁹⁴⁻⁷⁹⁷ or spirocyclic⁷⁹⁸ amines have also been used for amine moiety. Generally, ligands with D₂R selectivity were obtained using sumanirole^{489,490,776,777} (1, Figure 7) or 2-phenylcyclopropylmethylamine⁵²⁷ as a primary pharmacophore. On the other hand, eticlopride⁷⁷⁵ or tetrahydroisoquinoline-based^{480,498,782,785} derivatives exhibited D₃R selectivity.

3.2 | Central linker

The most common linkage between the primary and secondary pharmacophores was mediated via an aliphatic linker that is terminated by an ether^{585,588,602,605,616,617,620,656,701,763,768,788} or a secondary amide^{473,479,489,515,516,583,602,700,776,785,788,799} bond. The aliphatic ether was further modified by adding a

double bond,⁷⁸⁸ a triple bond, an aromatic, cyclohexyl ring or a cyclopropyl rings,^{584,800} or switched to a cyclic ether,^{483,793,801} thio-ether,^{488,670,672} an aliphatic linker without any heteroatom^{599,600,670,672,802} or an aromatic amine.⁴⁷⁸ Furthermore, aliphatic secondary amide was modified by adding a double bond,⁶⁹⁸ a hydroxy group,^{473,479,483,490} a fluorine atom,⁴⁸³ a cyclopropyl ring,^{480,490,498,776,788} a cyclobutyl ring,^{469,472} a cyclopentyl ring,⁴⁹⁰ a cyclohexyl ring,^{469,490} a 1,2,3-triazole moiety,⁴⁹⁰ or by conversion to a cyclic amide,^{476,646,709} a tertiary amide,⁶¹⁴ an aliphatic amine,⁴⁹² an aliphatic ketone,^{488,670,672,707,781} a cyclic ketone,⁶⁷⁰ an aliphatic sulfonamide,^{613,658} a cyclic sulfonamide,^{708,709} a cyclic imide,^{163,482,699,708,709} a 1,3,4-oxadiazole ring⁶¹⁵ or a various triazole ring: 1,2,3-triazole^{597,598,603,803} or 1,2,4-triazole.^{474,794–798} In general, the incorporation of a hydroxy group in the central linker region increases the selectivity for D₃R.^{469,473,479,483} It was further observed that bioisosteric replacement of the amide group with various triazoles also provided D₃R selective ligands.^{474,597,598,603,794–798,803}

3.3 | Secondary pharmacophore

For the allosteric binding site, in addition to variously substituted benzamides^{466–469,472,473,477,484,783,799} or 3,4-dihydroquinolin2-(1H)-one moiety,^{800,804} also fragments such as 6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one,⁸⁰⁵ xanthine core,⁸⁰² trazodone,⁸⁰⁶ phthalimide,⁴⁸² imidazolidine-2-one,⁸⁰⁷ talipexole⁸⁰⁸ or 2-aminomethylchromane⁸⁰⁹ were used. Following the discovery of cariprazine containing urea group, various urea-based derivatives such as aliphatic sulfonamides, amides, carbamates^{527,590,594,595,700} or cyclic or aliphatic scaffolds were implicated as secondary pharmacophore.^{163,475,783}

3.4 | Bivalent ligands

In addition to the bivalent ligands discussed above, which structurally fit into the 1,4-DACA group, a number of other bivalent ligands have been prepared based on 5-OH-DPAT,^{810–812} N-(*p*-aminophenethyl)spiperone,⁸¹³ (R)-apomorphine,⁸¹⁴ ropinirole^{815,816} or 2-aminoindane.⁸¹⁷

For more bivalent ligands beyond D₂Rs, please see the reviews.^{508,530}

4 | SUMMARY

Schizophrenia is a complex disorder with myriad symptoms⁹⁷ affecting approximately 1% of the adult population.⁹⁸ The treatment of schizophrenia is efficient for only about half of the patients, with a preferable suppression of only positive symptoms.⁴ MDD is a heterogeneous mental illness of mood affecting 3% of the global population.^{169,170} There is emerging and compelling evidence of substantial prevalence of anxiety disorders coinciding with MDD (4%–25%).⁸¹⁸ The management of MDD or anxiety disorders with drugs can cause severe side-effects such as sexual dysfunction, weight gain, confusion, blurred vision, sedation, or dizziness,^{5,6} which can greatly affect the patient's everyday life. PD is primarily a disease of the elderly, occurring in 1% of the population over 60 years and 3% at 80 years.³⁴³ Common side effects caused by anti-PD drugs include motor complications (such as motor fluctuations and dyskinesia), and other adverse effects (nausea, psychosis, and impulse control disorders and related behaviors).⁷ This high prevalence of CNS disorders and severe side-effects of drugs used for management generates an enormous healthcare cost and many social problems, thus creating the need to develop new effective and safe drugs. CNS illnesses are among the most expensive medical conditions (the total cost of disorders of the brain was estimated 798 billion EUR in Europe in 2010).³

D₂Rs play a key role in the management of CNS disorders such as schizophrenia, PD, MDD, and anxiety. Within the last ten years, immense progress has been made in understanding of the D₂R signaling cascade. D₂R antagonists and partial

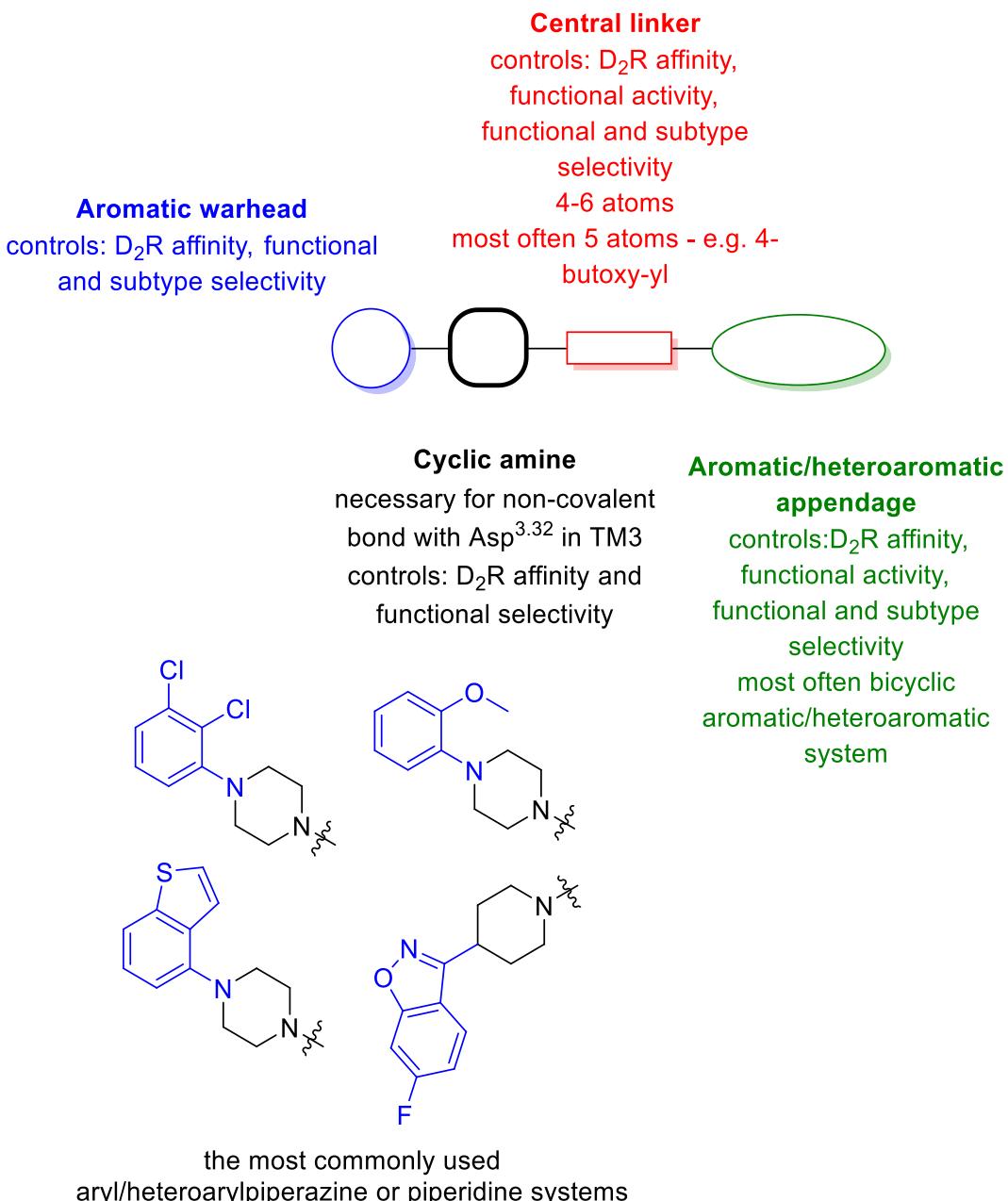


FIGURE 65 General SAR disclosing “universal” pharmacophore for high D₂R antagonism/partial agonism in a group of 1,4-disubstituted aromatic cyclic piperazines or piperidines. [Color figure can be viewed at wileyonlinelibrary.com]

agonists (so-called neuroleptics) are used for the treatment of schizophrenia, MDD, and anxiety. The typical pharmacophore comprises four main parts: aromatic moiety, cyclic amine, central linker and aromatic/heteroaromatic lipophilic fragment. Figure 65 illustrates how the structure and affinity for D₂R correlates. Aromatic moiety influences D₂R affinity and functional and subtype selectivity, and usually is connected directly with a cyclic amine. Cyclic amines affect functional selectivity, and are necessary for high D₂R affinity because they form noncovalent bonds with Asp^{3,32} in transmembrane domain 3 of D₂Rs. In general, to obtain ligands with high D₂R affinity, it has been shown that

TABLE 21 Highlighted compounds with unique properties—D₂R selective modulators, bivalent D₂R ligands, biased behavior for non- or canonical D₂R pathways, potential drugs for treatment of anxiety, MDD, schizophrenia, and PD

D ₂ R selective modulators	Chemical compound	K _i for D ₂ -like receptors (nM)	Functional activity	References
31 (Table 10)	K _i for D _{2s} Rs = 0.1	EC ₅₀ for D _{2s} RsGα _{oA} = 0.7 nM	[602]	
	K _i for D _{2s} Rs = 0.2	E _{max} = 50%		
	K _i for D _{2s} Rs = 3.3	EC ₅₀ for D ₃ RsGα _{oA} = 18 nM		
	K _i for D ₄ Rs = 0.7	E _{max} = 76%		
86b (Figure 49)	K _i for D ₂ Rs = 0.2	-		[701]
	K _i for D ₃ Rs = 13			
	K _i for D ₄ Rs = 212			
Bivalent D ₂ R ligands	Chemical compound	K _i for D ₂ Rs (nM)	Hill slope	References
73a (Table 15)	K _i = 16	1.5–2		[541]
73b (Table 15)	K _i = 22	2		
73c (Table 15)	K _i = 23	1.6–1.7		
76 (Figure 44)	K _i for D _{2s} Rs = 310	D ₂ LRs = 1.8		[683]
	K _i for D _{2s} Rs = 280	D _{2s} Rs = 1.6		
77a (Figure 45)	K _i = 42	-		[684]
77b (Figure 45)	K _i = 140	-		
77c (Figure 45)	K _i = 410	-		
78 (Figure 46)	K _i = 18	-		[691]
D ₂ R ligands with bias behavior for non- or canonical D ₂ R pathways	Chemical compound	K _i for D ₂ Rs (nM)	Functional activity at D ₂ Rs	References
12a (Figure 13)	K _i = 113	EC ₅₀ for β-arrestin = 316 nM		[584]

(Continues)

TABLE 21 (Continued)

Chemical compound	D ₂ R ligands with bias behavior for non- or canonical D ₂ R pathways	K _i for D ₂ Rs (nM)	Functional activity at D ₂ Rs	References
12b (Figure 13)	K _i = 108	E _{max} = 57% cAMP: inactive	EC ₅₀ for β-arrestin = 501 nM E _{max} = 48%	[582]
13 (Figure 14)	K _i = 18	cAMP: inactive	EC ₅₀ for β-arrestin = 4.0 nM E _{max} = 46%	[585]
14b (Figure 14)	K _i = 60	cAMP: inactive	β-arrestin: inactive	[584]
16a (Table 9)	K _i = 30	EC ₅₀ for cAMP = 24 nM E _{max} = 40%	EC ₅₀ for β-arrestin = 126 nM E _{max} = 88%	[586]
16b (Table 9)	K _i = 104	cAMP: inactive	EC ₅₀ for β-arrestin = 200 nM E _{max} = 78%	[587]
16c (Table 9)	K _i = 18	cAMP: inactive	EC ₅₀ for β-arrestin = 20 nM E _{max} = 84%	[588]
31 (Table 10)	K _i for D _{2L} Rs = 0.2	cAMP: inactive	EC ₅₀ for Gα _o A = 0.7 nM	[602]

TABLE 2.1 (Continued)

Chemical compound	D ₂ R ligands with bias behavior for non- or canonical D ₂ R pathways	K _i for D _{2S} Rs (nM)	K _i for D ₂ Rs (nM)	Functional activity at D ₂ Rs	References
57a (Figure 32)	-	K _i = 0.1	E _{max} = 50%	EC ₅₀ for Gα _{i2} = 120 nM E _{max} = 21%	[648]
58a (Figure 33)	K _i = 12	E _{max} = 97%	EC ₅₀ for β-arrestin: inactive β-arrestin recruitment log (τ/K _a) = 7.7	G _{i/o} activity log (τ/K _a) = no activity	[653]
85 (Figure 48; Table 17)	K _i = 355	E _{max} = 97%	K _a (inhibition of FSK-induced cAMP production) = 1.0 nM K _a (ERK1/2 phosphorylation) = 13 nM	EC ₅₀ for β-arrestin = 220 nM E _{max} = 21%	[700]
87b (Figure 49)	K _i = 37	E _{max} = 97%	EC ₅₀ for Gα _{o1} > 5 μM EC ₅₀ for β-arrestin (D _{2S} Rs + GRK2) = 1300 nM E _{max} = 51%	EC ₅₀ for β-arrestin (Tango assay) = 1.1 nM, E _{max} = 43% EC ₅₀ for β-arrestin (DiscoverRx assay) = 5.7 nM, E _{max} = 19% EC ₅₀ for β-arrestin (BRET assay) = 6.0 nM, E _{max} = 20%	[763]
103 (Figure 61; Table 20)	K _i = 2.6	E _{max} = 97%	EC ₅₀ for ERK (Phosphorylation reporter assay) = 2.2 nM, E _{max} = 32% EC ₅₀ for β-arrestin (Tango assay) = 6.1 nM, E _{max} = 91% EC ₅₀ for β-arrestin (DiscoverRx assay) = 448 nM, E _{max} = 64%	K _i = 79	(Continues)

TABLE 21 (Continued)

<u>D₂R ligands with bias behavior for non- or canonical D₂R pathways</u>		Functional activity at D ₂ Rs				References
Chemical compound	K _i for D _{2Rs} (nM)	EC ₅₀ for β-arrestin = 68 nM E _{max} = 38%	EC ₅₀ for Gα _{o1} > 1 μM	EC ₅₀ for Gα _{o1} > 1 μM E _{max} = 44%	EC ₅₀ for Gα _{o1} > 1 μM	[774]
111a (Figure 63; Table 20)	K _i for D _{2L} Rs = 1.1 K _i for D _{2S} Rs = 0.7					
111b (Figure 63; Table 20)	K _i for D _{2L} Rs = 1.0 K _i for D _{2S} Rs = 1.0					
<u>Novel D₂R ligands with anxiolytic properties</u>						
Chemical compound	K _i for D _{2Rs} (nM)	Functional activity at D _{2Rs}	Animal species	Dose	Behavioral test	References
21a (Table 10)	K _i = 219	-	Mice	2.5 and 5 mg/kg; i.p.	FPT	[317]
21b (Table 10)	K _i = 54	-	Rats	2.5 mg/kg; i.p.	EPMT	
30a (Table 10)	K _i = 162	-	Mice	2.5 and 5 mg/kg; i.p.	FPT	[605]
30b (Table 10)	K _i = 189	-	Rats	5 mg/kg; i.p.	EPMT	
59a (Figure 34; Table 13)	K _i = 6.3	K _b = 3.7 nM	Mice	2.5 and 5 mg/kg; i.p.	FPT	[656]
60a (Figure 35; Table 13)	K _i = 3.3		Rats	1 mg/kg; i.p.	Vogel conflict drinking test	
				3 mg/kg; i.p.	OPF	[658]
				K _b = 2.1 nM	0.6–1.3 mg/kg; i.p.	FPT

TABLE 21 (Continued)

Novel D ₂ R ligands with anxiolytic properties				Animal species	Dose	Behavioral test	References
Chemical compound	K _i for D ₂ Rs (nM)	Functional activity at D ₂ Rs	EC ₅₀ = 56 nM				
61 (Figure 36; Table 13)	K _i = 58	K _b = 4.5 nM	E _{max} = 56%	Mice	100 mg/kg; i.p.	EPMT	[659]
21a (Table 10)	K _i = 219	-	-	Mice	2.5 and 5 mg/kg; i.p.	FST	[317]
21b (Table 10)	K _i = 54	-	-	Rats	5 mg/kg; i.p.	FST	
35b (Figure 25; Table 11)	K _i = 2.0	K _b = 17 nM	-	Mice	1.3, 2.5, and 5 mg/kg; i.p.	FST	
42 (Table 11)	K _i = 18	K _b = 2.4 nM	-	Rats	1.3 and 2.5 mg/kg; i.p.	FST	
59a (Figure 34; Table 13)	K _i = 6.3	K _b = 3.7 nM	EC ₅₀ = 54 nM	Rats	0.6 and 1.3 mg/kg; i.p.	FST	[600]
60a (Figure 35; Table 13)	K _i = 3.3	K _b = 2.1 nM	-	Mice	0.6–1.3 mg/kg; i.p.	FST	[658]

(Continues)

TABLE 21 (Continued)

<u>D₂R analogs with antidepressant features</u>						References
Chemical compound	K _i for D ₂ Rs (nM)	Functional activity at D ₂ Rs	Animal species	Dose	Behavioral test	
		EC ₅₀ = 56 nM E _{max} = 56%	Mice	50 mg/kg; i.p.	FST	[660]
62 (Figure 36; Table 13)	K _i = 72	K _b = 5.0 nM	Mice	5 mg/kg; i.p.	FST	[674]
β71b (Figure 40; Table 14)	K _i = 42	IC ₅₀ = 24.0 nM	Mice			
<u>D₂R derivatives with antipsychotic effects</u>						References
Chemical compound	K _i for D ₂ Rs (nM)	Functional activity at D ₂ Rs	Animal species	Dose	Behavioral test	
20 (Figure 17; Table 10)	K _i = 52	IC ₅₀ = 220 nM	Mice	10–40 mg/kg; p.o.	MK-801	[596]
25c (Figure 18; Table 10)	K _i = 3.0	EC ₅₀ = 67 nM IC ₅₀ = 3.0 nM	Mice	10–40 mg/kg; p.o. >120 mg/kg	Methamphetamine Catalepsy	
31 (Table 10)	K _i for D _{2L} Rs = 0.2	EC ₅₀ for Ga _{oA} = 0.7 nM E _{max} = 50%	Rats	10 and 20 mg/kg; i.p. 1.5 mg/kg; via Alzet osmotic mini pump	D-amphetamine Amphetamine	[599]
35b (Figure 25; Table 11)	K _i for D _{2S} Rs = 0.1	EC ₅₀ for Ga _{oA} = 120 nM E _{max} = 21%	Rats	MED = 10 mg/kg; p.o.	MK-801	[613]
37 (Figure 22; Table 11)	K _i = 23	K _b = 17 nM	Rats	100 mg/kg; p.o.	Catalepsy	
			Mice	ED ₅₀ = 3.7 mg/kg; p.o.	Apomorphine	[615]

TABLE 21 (Continued)

Chemical compound	K _i for D ₂ Rs (nM)	Functional activity at D ₂ Rs	Animal species	Dose	Behavioral test	References
38 (Figure 23; Table 11)	K _i = 2.6	C ₅₀ = 26 nM	Mice	ED ₅₀ = 3.6 mg/kg; p.o.	MK-801	[616]
39 (Table 11)	K _i = 13	-	Mice	ED ₅₀ > 300 mg/kg; p.o.	Catalepsy	
40a (Figure 24; Table 11)	K _i = 0.5	-	Mice	ED ₅₀ = 0.1 mg/kg; p.o.	Apomorphine	[617]
42 (Table 11)	K _i = 18	K _b = 2.4 nM	Mice	ED ₅₀ = 0.3 mg/kg; p.o.	Catalepsy	
48c (Figures 28–30; Table 12)	-	C ₅₀ = 6.4 nM	Mice	ED ₅₀ = 81 mg/kg; p.o.	Apomorphine	[620]
49d (Figure 30; Table 12)	-	C ₅₀ = 12 nM	Mice	ED ₅₀ = 0.6 mg/kg; p.o.	Apomorphine	
54 (Figure 31; Table 12)	-	C ₅₀ = 3.3 nM	Rats	ED ₅₀ = 0.3 mg/kg; i.p.	Catalepsy	[624]
60a (Figure 35; Table 13)	K _i = 3.3	K _b = 2.1 nM	Rats	up to 30 mg/kg; i.p.	Catalepsy	
			Mice	3 mg/kg; intragastric	PCP	[163]
			Mice	ED ₅₀ = 14 mg/kg; p.o.	Catalepsy	
			Mice	0.3 and 1 mg/kg; p.o.	PCP	[630]
			Mice	ED ₅₀ = 0.02 mg/kg; intragastric	PCP	
			Mice	ED ₅₀ = 0.8 mg; i.p.	Catalepsy	[638]
			Mice	1.3 mg/kg; i.p.	MK-801	[658]

(Continues)

TABLE 21 (Continued)

D₂R derivatives with antipsychotic effects				Animal species	Dose	Behavioral test	References
Chemical compound	K_i for D₂Rs (nM)	Functional activity at D₂Rs					
		EC ₅₀ = 56 nM		Mice	ED ₅₀ > 100 mg/kg; i.p.	Catalepsy	
		E _{max} = 56%		Mice	100 mg/kg; i.p.	Amphetamine	[659]
61 (Figure 36; Table 13)	K_i = 58	K_b = 4.5 nM					
62 (Figure 36; Table 13)	K_i = 72	K_b = 5.0 nM		Mice	50 mg/kg; i.p.	Amphetamine	[660]
68a (Figure 39; Table 14)	K_i = 2.9	-		Mice	ED ₅₀ = 0.2 mg/kg; i.p.	Apomorphine	[672]
				Rats	MAED = 0.6 mg/kg; i.p.	Catalepsy	
68b (Figure 39; Table 14)	K_i = 27	-		Mice	ED ₅₀ = 3.1 mg/kg; i.p.	Apomorphine	
				Rats	MAED = 12.7 mg/ kg; i.p.	Catalepsy	
					10 mg/kg; i.p.	Apomorphine	[669]
β70 (Figure 40; Table 14)	K_i = 137	-		Mice			
β71a (Figure 40; Table 14)	K_i = 7.4	IC₅₀ = 37 nM		Mice	5 and 10 mg/kg; i.p.	MK-801	[674]
β71b (Figure 40; Table 14)	K_i = 42	IC₅₀ = 210 nM		Mice	5 and 10 mg/kg; i.p.	D-amphetamine	
				Mice	5 and 10 mg/kg; i.p.	MK-801	
92 (Figure 51; Table 18)	K_i = 2.9	IC₅₀ = 9.0 nM		Mice	10 mg/kg; i.p.	D-amphetamine	
				Mice	ED ₅₀ = 0.6 mg/kg; p.o.	Apomorphine	[707]
				Mice	ED ₅₀ = 0.3 mg/kg; p.o.	MK-801	
				Mice	ED ₅₀ = 79 mg/kg; p.o.	Catalepsy	

TABLE 21 (Continued)

D₂R derivatives with antipsychotic effects						
Chemical compound	K _i for D ₂ Rs (nM)	Functional activity at D ₂ Rs	Animal species	Dose	Behavioral test	References
103 (Figure 61; Table 20)	K _i = 2.6	EC ₅₀ for β-arrestin (Tango assay) = 1.1 nM, E _{max} = 43%	Mice	ED ₅₀ = 0.4 mg/kg; i.p.	D-amphetamine	[763,764]
		EC ₅₀ for β-arrestin (DiscoverRx assay) = 5.7 nM, E _{max} = 19%				
		EC ₅₀ for β-arrestin (BRET assay) = 6.0 nM, E _{max} = 20%				
		EC ₅₀ for ERK (Phosphorylation reporter assay) = 2.2 nM, E _{max} = 32%				
104 (Figure 61; Table 20)	K _i = 79	EC ₅₀ for β-arrestin (Tango assay) = 6.1 nM, E _{max} = 91%	Mice	2 mg/kg; i.p.	PCP	
		EC ₅₀ for β-arrestin (DiscoverRx assay) = 448 nM, E _{max} = 64%				
105 (Figure 61; Table 20)	K _i = 0.8	Intrinsic activity in vivo (mouse, p.o.) = 60%	Rats	MED = 0.3 mg/kg; p.o.	Spontaneous locomotor activity	[768]
				>10 mg/kg; p.o.	Catalepsy	

(Continues)

TABLE 21 (Continued)

D₂R derivatives with antipsychotic effects						
Chemical compound	K _i for D ₂ Rs (nM)	Functional activity at D ₂ Rs	Animal species	Dose	Behavioral test	References
107 (Figure 62; Table 20)	K _i = 110	-	Mice	15 mg/kg; p.o.	Apomorphine	[771]
			Mice	>30 mg/kg	Catalepsy	
110 (Figure 62; Table 20)	K _i = 70	-	Mice	15 mg/kg; p.o.	Apomorphine	
			Mice	>30 mg/kg	Catalepsy	
Novel D₂R modulators with clinical potential for treatment of PD						
Chemical compounds	K _i for D ₂ Rs (nM)	Functional activity at D ₂ Rs	Animal species	Dose	Behavioral test	References
99 (Figure 54; Table 19)	K _i = 264	EC ₅₀ = 39 nM <i>E</i> _{max} = 104%	Mice	1 and 5 mg/kg; i.p.	MPTP	[724]
100a (Figure 54; Table 19)	K _i = 58	EC ₅₀ = 14 nM <i>E</i> _{max} = 104%	Rats	10 μmol/kg; s.c.	Lactacystin	
100b (Figure 54; Table 19)	K _i = 269	EC ₅₀ = 116 nM <i>E</i> _{max} = 88%	Rats	10 μmol/kg; s.c.	Reserpine	[714]
(-)100d (Figure 55; Table 19)	K _i = 3.8	EC ₅₀ = 4.5 nM <i>E</i> _{max} = 106%	Rats	10 μmol/kg; s.c.	6-OHDA	
(-)100e (Figure 56; Table 19)	K _i = 27	EC ₅₀ = 34 nM <i>E</i> _{max} = 110%	Rats	0.5 μmol/kg; i.p.	Reserpine	[727]
(-)100f (Figure 56; Table 19)	K _i = 39	EC ₅₀ = 3.0 nM <i>E</i> _{max} = 107%	Mice	5 μmol/kg; i.p.	6-OHDA	[730]
				2 mg/kg	MPTP	
				5 μmol/kg; s.c.	Reserpine	[733]
(-)100g (Figure 56; Table 19)	-	EC ₅₀ = 3.0 nM <i>E</i> _{max} = 107%	Rats	2.5, 5, and 10 μmol/kg; i.p.	6-OHDA	[734,739]

TABLE 21 (Continued)

Chemical compounds	K_i for D ₂ Rs (nM)	Functional activity at D ₂ Rs	Animal species	Dose	Behavioral test	References
(-)-100h (Figure 57; Table 19)	$K_i = 42$	$EC_{50} = 4.7 \text{ nM}$ $E_{\max} = 81\%$	Rats	10 $\mu\text{mol}/\text{kg}$; i.p.	Reserpine	[716]
(-)-100j (Figure 58; Table 19)	$K_i = 233$	$EC_{50} = 42 \text{ nM}$ $E_{\max} = 98\%$	Rats	5 $\mu\text{mol}/\text{kg}$; i.p.	6-OHDA	[751]
(-)-100k (Figure 58; Table 19)	$K_i = 369$	$EC_{50} = 16 \text{ nM}$ $E_{\max} = 116\%$	Rats	173 μM	Synucleinopathy PD model	[717]
(-)-100l (Figure 58; Table 19)	$K_i = 16$	$EC_{50} = 3.2 \text{ nM}$ $E_{\max} = 101\%$	Rats	10 $\mu\text{mol}/\text{kg}$; i.p.	Reserpine	[718]
(-)-100m (Figure 59; Table 19)	$K_i = 87$	$EC_{50} = 22 \text{ nM}$ $E_{\max} = 27\%$	Rats	10 $\mu\text{mol}/\text{kg}$; s.c.	Reserpine	[753,754]
(-)-100o (Figure 60; Table 19)	$K_i = 135$	$EC_{50} = 52 \text{ nM}$ $E_{\max} = 87\%$	Rats	0.1 and 0.25 mg/ml; p.o.	Synucleinopathy PD model	
(-)-100p (Figure 60; Table 19)	$K_i = 71$	$EC_{50} = 0.9 \text{ nM}$ $E_{\max} = 85\%$	Mice	5 mg/kg; i.p.	MPTP	[755]

Abbreviations: D-amphetamine, D-amphetamine-induced hyperactivity; apomorphine, apomorphine-induced climbing behavior; EPM, elevated plus maze test; FST, forced swim test; methamphetamine, methamphetamine-induced prepulse inhibition disruption; MAED, minimum adverse effective dose; MED, minimum effective dose; reserpine, reserpinized PD animal model; MK-801, MK-801-induced hyperlocomotion/hyperactivity; MPTP, MPTP-induced depletion of DA animal model; lactacystin, lactacystin-induced depletion of DA animal model; OPT, open field test; PCP, phencyclidine-induced hyperlocomotion; 6-OHDA, 6-OHDA lesioned PD animal model.

TABLE 22 A potential explanation for the positive benefits in the treatment of schizophrenia, PD, depression, or anxiety of mixed D₂R modulators affecting other DA (D₃Rs) or 5-HT (5-HT_{1A}, 5HT₂, 5-HT₆, and 5-HT₇ receptors) GPCRs

Target	Illness	Mechanism of action
D ₂ Rs	Schizophrenia	60%–80% blockade of striatal D ₂ Rs for treatment of positive symptoms of schizophrenia ¹³⁴ For partial agonists, this “therapeutic window” is higher ¹³⁴
D ₃ Rs	Schizophrenia	D ₃ Rs antagonism modulates DA neuron activity in VTA through regulation of GABA release by striatonigral GABA terminals which express D ₃ Rs, thus normalizing DA release in PFC ⁸¹⁹ —beneficial for management of cognitive and negative symptoms of schizophrenia
	PD	D ₃ Rs activation produce—inhibition of DA reuptake and breakdown in synaptic terminals, reduction in α-synuclein accumulation, enhancement in BDNF secretion, amelioration of neuroinflammation and oxidative stress injury ⁴⁵⁰
5-HT _{1A} Rs	PD	Inhibition of striatal neurons (e.g., medium spiny neurons and cholinergic interneurons) by stimulation of post-synaptic 5-HT _{1A} Rs—management of parkinsonism ⁸²⁰ Post-synaptic 5-HT _{1A} R agonist enhanced striatal DA release by inhibiting striatal GABAergic interneurons—beneficial for parkinsonism ⁸²⁰
		Activation of post-synaptic 5-HT _{1A} Rs produced inhibition of cortico-striatal glutamatergic neurons—treatment of parkinsonism and dyskinesia ⁸²⁰
	Cognitive impairment	Pre-synaptic 5-HT _{1A} R agonist induced inhibition of 5-HT neuron activity via stimulating 5-HT _{1A} autoreceptors in Raphe nuclei—management of dyskinesia ⁸²⁰
	Depression	Post-synaptic 5-HT _{1A} R partial agonist increased of cholinergic and glutamatergic neuron activities in the basal forebrain ⁸²⁰
	Anxiety	Post-synaptic 5-HT _{1A} R antagonist enhanced of hippocampal neurons activity and hippocampal acetylcholine release ⁸²⁰
5-HT ₂ Rs ^a	PD	Post-synaptic 5-HT ₂ R antagonist increased striatal DA release and activity of nigral DA neurons ⁸²⁰
	Cognitive impairment	Post-synaptic 5-HT ₂ R antagonist enhanced NMDA receptor-mediated transmission in the cerebral cortex ⁸²⁰
	Mood disorders (depression and anxiety)	Post-synaptic 5-HT ₂ R antagonist regulated cortical neuron activity and down-modulated of 5-HT ₂ Rs in cerebral cortex ⁸²⁰
	Psychosis	Post-synaptic 5-HT ₂ R inverse agonist (pivamanserin) possibly regulated cortical neuron activity ⁸²⁰

TABLE 22 (Continued)

Target	Illness	Mechanism of action
5-HT ₆ Rs		
PD		5-HT ₆ R antagonist inhibited of striatal cholinergic interneurons ⁸²⁰
Cognitive impairment		5-HT ₆ R antagonist may decrease the release of GABA in the PFC, which subsequently disinhibits glutamate and/or acetylcholine release ¹⁵⁸
		5-HT ₆ R antagonist may reduce GABAergic interneuron excitability, resulting in disinhibition and a subsequent enhancement of synaptic plasticity in synapses and brain areas expressing 5-HT ₆ Rs ⁸²¹
		5-HT ₆ R antagonist may exhibit pro-cognitive impacts through the reduction of mammalian Target of Rapamycin (mTOR) signaling ⁸²²
		5-HT ₆ R antagonist may influence the cognition through interaction with Fyn-tirosine kinase ⁸²³ or DARPP-32 ⁸²⁴
		Chronic administration of 5-HT ₆ R antagonist enhanced the number of neural cell adhesion molecule polysialyllic acid-immunoreactive neurons in the dentate gyrus and in the entorhinal and perirhinal regions of the cortex which effects synaptic plasticity ^{158,825}
Depression		5-HT ₆ R antagonist may increase brain noradrenergic and/or dopaminergic neurotransmission in hippocampus ⁸²⁶
		5-HT ₆ R agonist may enhance extracellular GABA levels and reduce stimulated glutamatergic neurotransmission ⁸²⁶
Anxiety		5-HT ₆ R antagonist may show anxiolytic-like effect through interaction between 5-HT ₆ R and the benzodiazepine system ⁸²⁶
		5-HT ₆ R agonist may enhance extracellular GABA levels and reduce stimulated glutamatergic neurotransmission ⁸²⁶
5-HT ₇ Rs		
Schizophrenia		Blockade of 5-HT ₇ Rs increases DA levels in rat PFC ⁸²⁷ —positively modulation of negative and cognitive symptoms of schizophrenia ⁸²⁸

^aIt is still controversial which 5-HT₂Rs subtype is involved in the action of 5-HT₂Rs antagonists, both 5-HT_{2A} and 5-HT_{2C} receptors are likely to be involved in modulating of summarized effects.⁸²⁰

4-(2,3-dichlorophenyl), 4-(2-methoxyphenyl)-, 4-(benzo[b]thiophen-4-yl)-1-substituted piperazine, or 4-(6-fluorobenzo[d]isoxazol-3-yl)piperidine moieties are crucial. Central linker greatly affects D₂R affinity, functional activity and subtype selectivity. A central linker with four to six atoms of length ensures high D₂R affinity. From there, it seems that the best option for high D₂R affinity is achieved by using 4-butoxy-yl as a central linker. Lipophilic fragments impact D₂R affinity, functional activity, and subtype selectivity. The bicyclic aromatic/heteroaromatic system is most often used as a lipophilic appendage to retain high D₂R affinity.

From a pharmacodynamic perspective, it can be concluded that D₂R agonists are mainly useful for the management of PD. The scientific group of prof. A. Dutta is devoted in the development of aromatic congeners connected to a piperazine ring and linked via an ethane-1,2-diyl central linker to bicyclic heteroaromatic 5- or 7-hydroxy-2-aminotetralin or 4,5,6,7-tetrahydrobenzo[d]thiazole-2,6-diamine systems to obtain D₂R agonists or partial agonists.^{714,716–718,723,724,727,730,733–736,739,751–755} However, these novel D₂R modulators show mild, moderate, or high selectivity for D₃Rs and act as agonists or partial agonists at these receptors.

Immense progress has been recently achieved in medicinal and pharmacological research concerning D₂R modulators. Many potent selective or mixed D₂R ligands have been prepared that differentially affect D₂Rs and other receptors (especially D₃, 5-HT_{1A}, 5-HT_{2A}, 5-HT₆, and 5-HT₇ receptors) and show different therapeutic impacts. These potential clinical uses of newly developed D₂R modulators are summarized in Table 21 and mainly

include the treatment of CNS disorders (schizophrenia, PD, MDD, and anxiety). Table 22 shows how the other above-mentioned receptors (i.e., D₃, 5-HT_{1A}, 5-HT_{2A}, 5-HT₆, and 5-HT₇Rs) may be beneficial in the therapy of the selected CNS disorders. D₃Rs ligands have shown effects on schizophrenia, depression, and PD.^{450,694,819,829} Modulation of 5-HT receptors, especially 5-HT_{1A},^{820,830,831} 5-HT₂,^{820,830,832} 5-HT₆,^{158,820,826,833} and 5-HT₇,^{159,828} receptors, offers potential to control various CNS disorders such as PD, schizophrenia, depression, or anxiety.

Despite extensive research and plentiful novel findings, further efforts should be invested in the active development of new selective or mixed D₂R modulators due to the low effectiveness of current neuroleptics (D₂R partial agonists/antagonists) in treating negative and cognitive symptoms of schizophrenia and reducing or eliminating side effects of antipsychotics and DRs agonists. We believe that this review could serve as the basis for future research and development of novel DR ligands with desired properties.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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