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Synthesis and characterization of selective dopamine D_2 receptor ligands using aripiprazole as the lead compound

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Abstract

A series of compounds structurally related to aripiprazole (**1**), an atypical antipsychotic and antidepressant used clinically for the treatment of schizophrenia, bipolar disorder, and depression, have been prepared and evaluated for affinity at $D_{2\text{-like}}$ dopamine receptors. These compounds also share structural elements with the classical $D_{2\text{-like}}$ dopamine receptor antagonists, haloperidol, *N*-methylspiperone, domperidone and benperidol. Two new compounds, 7-(4-(4-(2-methoxyphenyl)piperazin-1-yl)butoxy)-3,4-dihydroquinolin-2(1*H*)-one oxalate (**6**) and 7-(4-(4-(2-(2-fluoroethoxy)phenyl)piperazin-1-yl)butoxy)-3,4-dihydroquinolin-2(1*H*)-one oxalate (**7**) were found to (a) bind to the D_2 receptor subtype with high affinity (K_i values <0.3 nM), (b) exhibit >50-fold D_2 versus D_3 receptor binding selectivity and (c) be partial agonists at both the D_2 and D_3 receptor subtype.

Keywords

Dopamine D_2 receptor; Aripiprazole; Dopamine partial agonist

1. Introduction

Dopamine receptors belong to a large superfamily of neurotransmitter and hormone receptors which are coupled to their specific effectors function via guanine nucleotide regulatory (G) proteins. Based upon genomic and cDNA cloning studies, it is currently thought that there are five functionally active dopamine receptor subtypes expressed in mammals. These five receptor subtypes have been classified into two major types ($D_{1\text{-like}}$ and $D_{2\text{-like}}$) based on their amino acid sequence and pharmacological properties. The $D_{1\text{-like}}$ receptor subtypes consist of the D_1 (D_{1a}) and the D_5 (D_{1b}) dopamine receptors. The $D_{2\text{-like}}$ receptor subtypes include the D_{2short} (D_{2S}), D_{2long} (D_{2L}), D_3, and D_4 receptors.[1] Stimulation of $D_{1\text{-like}}$ receptors results in an activation of adenylyl cyclase.[2] Stimulation of $D_{2\text{-like}}$ receptors results in an inhibition of adenylyl cyclase activity, mitogenesis, an increase in the release of arachidonic acid and an increase in phosphatidylinositol hydrolysis.[3]

The D_2 and D_3 dopamine receptor subtypes are structurally and pharmacologically similar.[4] Despite these similarities, the D_2 and D_3 receptors differ in the neuroanatomical localization,

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the levels of receptor expression, efficacy in response to agonist stimulation, regulation, desensitization and the intracellular trafficking properties.[5–8] Because of the high degree of homology between D_2 and D_3 receptor binding sites, it has been difficult to develop compounds that can selectively stimulate or block D_2 or D_3 receptors.[3,6,7,9–11] This has also been true for the development of radiotracers for imaging dopamine D_2 and D_3 receptors with the functional imaging technique positron emission tomography or PET. That is, all radiotracers used in PET imaging studies bind with similar affinity to D_2 and D_3 receptors, and receptor density measurements using radiotracers such as the antagonists [^{11}C]raclopride and [^{18}F]fally-pride, and the radiolabeled full agonist, [^{11}C](+)_PHNO, are typically reported as $D_{2/3}$ receptor binding potentials.[12–14] There has been a need to develop highly selective dopamine receptor ligands capable of labeling D_2 versus D_3 and D_3 versus D_2 in order to gain a better insight into the behavioral pharmacology and in vivo regulation of these structurally-similar dopamine receptors in disorders of the central nervous system.

Previously, our group synthesized a series of ((1*H*-indol-3-yl)methyl)piperidin-4-ol analogs and evaluated their affinities and intrinsic activities for dopamine D_2 and D_3 receptors. These compounds share structural elements with the classical $D_{2\text{-like}}$ dopamine receptor antagonists, haloperidol, *N*-methylspiperone and benperidol. Several of the compounds structurally similar to haloperidol were found to have moderate to high affinity and selectivity at D_2 versus D_3 receptors.[15,16] Functional assays revealed that these compounds were antagonists at D_2 receptors.[15,16]

Aripiprazole, 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydro-2(1*H*)-quinolinone (**1**, Fig. 1) has been used for the treatment of schizophrenia and various forms of depression. Aripiprazole has been reported to be an antagonist of postsynaptic dopamine receptor while acting as an agonist of dopamine autoreceptors.[17] Using aripiprazole as a lead compound, we synthesized a series of new compounds and evaluated their binding affinities and intrinsic activities at $D_{2\text{-like}}$ receptors. These modifications include: (a) replacing the *N*-2,3-dichlorophenyl piperazine ring of aripiprazole with amine groups present in typical antipsychotics (haloperidol, benperidol, domperidone and *N*-methylspiperone), (b) replacing the *N*-2,3-dichlorophenyl group of aripiprazole with *N*-methoxyphenyl, or *N*-2-fluoroethoxy groups, (c) changing the length of the carbon atom spacer between the oxygen and nitrogen atoms, and, (d) introduction of a double bond into the 3,4-dihydro-2(1*H*)-quinolinone ring. The goal of this study is to modify the structure of aripiprazole in order to determine if it is possible to identify ligands having a higher affinity and selectivity for D_2 versus D_3 receptors for behavioral pharmacology and PET imaging studies.

2. Chemistry

The syntheses of all target compounds (Fig. 2) are outlined in Schemes 1–4. Compounds **2–10** were prepared as outlined in Scheme 1. Starting from the commercially available 7-(4-bromobutoxy)-3,4-dihydroquinolin-2(1*H*)-one (**20**) and the corresponding piperidines or piperazines, the desired compounds **2–6**, **8–10** and the intermediate **17**[18] were obtained in 67–96% yields. Subsequently, fluoroethylation of the aromatic hydroxyl group of **17** with 1-bromo-2-fluoroethane gave **7** in 59% yield. The piperazine **19** was prepared from 2-methoxy-4-methylaniline (**18**) and bis-(2-chloroethyl)amine hydrochloride in the presence of potassium carbonate in butanol.[19]

Compound **11** was synthesized from 7-(4-bromobutoxy)quinolin-2(1*H*)-one (**21**)[17] and 1-(2-methoxyphenyl)piperazine, whereas **12** was synthesized from **21** and 1-(2-(2-fluoroethoxy)phenyl) piperazine[20] (Scheme 2). Compounds **13**[21] and **14**[21] were prepared from O-alkylation of commercially available 7-hydroxy-3,4-dihydroquinolin-2(1*H*)-one

(**22a**) or 7-hydroxyquinolin-2(1*H*)-one (**22b**) with 1-(3-chloropropyl)-4-(2-methoxyphenyl)piperazine[22] (Scheme 3).

Reaction of 7-(5-bromopentoxy)-3,4-dihydroquinolin-2(1*H*)-one (**23**)[21] and 1-(2-methoxyphenyl)piperazine gave **15**. Dehydrogenation of **15** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gave **16** (Scheme 4).

3. Radioligand binding studies at dopamine receptors

Competitive radioligand binding studies were performed to determine the equilibrium dissociation constants of each compound at human D_2, D_3, and D_4 dopamine receptors (Table 1). For these studies tissue homogenates from stably transfected HEK 293 cells were used in conjunction with the radioligand ^{125}I-IABN. We have previously reported that the benzamide ^{125}I-IABN binds with high affinity and selectively to $D_{2\text{-like}}$ dopamine receptors, but it binds non-selectively to the D_2 and D_3 dopamine receptor subtypes.[23]

First, a comparison was made of the affinity at D_2 and D_3 dopamine receptors of the compounds which have structural elements similar to haloperidol, benperidol, domperidone, and *N*-methylspiperone. Surprisingly, these structural elements did not appear to have an effect on $D_{2\text{-like}}$ receptor affinity or selectivity, with compounds **2**–**5** displaying weak affinity for D_2, D_3, and D_4 receptors. Next, a comparison of substituents at the piperazine moiety of aripiprazole was made in which the 2,3-dichloro substitution pattern of aripiprazole was replaced with either a 2-OCH_3 (compound **6**) or a 2-OCH_2CH_2F (compound **7**) group. We found that both methoxy and 2-fluoroethoxy groups resulted in a 2-fold decrease in affinity at D_3 receptors with a concomitant 14- and 12-fold increase in affinity at D_2 receptors, with compounds **6** and **7** having a 60- and 52-fold selectivity at D_2 receptors, respectively. This level of binding selectivity is 25 to 30 times greater than the lead compound aripiprazole (Table 1). Compounds **6**, **7**, **11**, and **12**, which contain a piperazine moiety and a saturated four carbon chain, exhibited the greatest affinity (K_i values 0.07–0.26 nM, Table 1) and selectivity (39- to 60-fold) at D_2 receptors compared to the D_3 receptor subtype. The positions of the substituents at the piperazine moiety were also compared. Changing the methoxy group from the 2-position on the benzene ring (compound **6**) to the 4-position (compound **8**) decreased both D_2 and D_3 receptors affinity. Substitution on both 2- and 4-positions (compounds **9** and **10**) decreased D_3 receptor affinity but had little effect on D_2 receptor affinity. Decreasing (compounds **13** and **14**) or increasing (compounds **15** and **16**) the length of the four carbon spacer by one carbon atom decreased D_2 receptor affinity, while having little to no effect on D_3 receptor affinity, thereby reducing the receptor subtype binding selectivity (Table 1, Fig. 2). Introduction of a double bond into the 3,4-dihydro-2(1*H*)-quinolinone ring had little effect on both D_2 and D_3 receptors affinity (compounds **11**, **12**, **14** and **16**).

4. Adenylyl cyclase studies with $D_{2\text{-like}}$ receptors

The pharmacological properties of the two compounds with the highest binding selectivity forD_2 dopamine receptors (**6** and **7**) were further evaluated using a whole cell forskolin-dependent adenylyl cyclase inhibition assay. The intrinsic efficacy of these compounds were compared to the full agonist quinpirole, as previously described.[15] Compounds **6** and **7** were found to be partial agonists at both D_2 and D_3 dopamine receptors. The intrinsic efficacy was found to be slightly greater (16–75%) at D_2 receptors compared to D_3 receptors. The intrinsic efficacy of these two compounds at human D_2 receptors is similar to that found for the lead compound aripiprazole, while the efficacy at D_3 receptors was somewhat lower (Fig. 3).

5. Radioligand binding studies at sigma receptors

In vitro binding studies were conducted to determine the affinity of the target compounds at sigma-1 (σ_1) and sigma-2 (σ_2) receptors. Since many structurally-diverse ligands are capable of binding to sigma receptors, we routinely screen our potential CNS PET radiotracers for binding affinity to σ_1 and σ_2 receptors. Any compound which binds with high affinity to σ_1 and/or σ_2 receptors would not be an appropriate candidate for the development of a dopaminergic PET imaging agent since sigma receptors are expressed ubiquitously in the CNS.

The σ_1 binding studies were conducted using the σ_1-selective radioligand, [^{3}H](+)-pentazocine in guinea pig brain membranes; σ_2 sites were assayed in rat liver membranes with [^{3}H]DTG in the presence of 100 nM unlabeled (+)-pentazocine to mask σ_1 sites, or with the σ_2 selective ligand [^{3}H]RHM-1, alone.[24,25] The affinity at σ_1 receptors varied from 150 to >20,000 nM. All of the compounds in this study bound with low affinity (>200 nM) at σ_2 receptors. The affinity of the two compounds with the greatest D_2 receptor selectivity (**6** and **7**) bound to sigma receptors with low affinity (K_i values >500 nM).

6. Discussion

The dopaminergic system has been the most thoroughly studies CNS receptor system using the functional imaging technique, PET. By-and-large, most imaging studies have been conducted using the radiotracer [^{11}C]raclopride, which binds with similar affinity to dopamine D_2 and D_3 receptors. Therefore, PET imaging studies with this radiotracer are typically reported as dopamine $D_{2/3}$ receptor binding potential, which is a measure of the density of D_2 and D_3 receptors in regions of interest such as the caudate and putamen. High affinity, low nonspecific binding radioligands such as [^{18}F]fallypride and [^{11}C]FLB 457[26,27] D_2 and D_3 antagonists have been developed for measuring the density of extrastriatal dopamine $D_{2/3}$ receptors in the CNS.

A number of studies have suggested that there is a differential regulation of dopamine D_2 and D_3 receptors in a variety of CNS disorders. For example, using in vitro quantitative autoradiography, Ryoo et al. reported a 45% *reduction* in D_3 receptors in the ventral striatum, and a 15% *increase* in D_2 receptors in the caudate/putamen of parkinsonian brain.[28] These data were consistent with 6-OHDA and MPTP lesioning studies in animal models of PD.[29,30] Therefore, D_2 and D_3 receptors appear to be regulated in an opposing manner in response to the loss of dopaminergic input in PD. In addition, PET studies of human subjects with a chronic history of cocaine abuse have revealed a reduction in $D_{2/3}$ receptors relative to age-matched controls.[31,32] Similar results have shown that $D_{2/3}$ receptors are reduced in autoradiography[33] and PET[34] imaging studies of rhesus monkeys that have self-administered cocaine. However, autoradiography studies conducted by Staley and Mash reported an upregulation of D_3 receptors in human cocaine overdose victims when compared with age-matched controls.[35] More recently, Volkow et al. reported a difference in [^{11}C]raclopride binding in the striatum versus thalamus in cocaine abusers versus normal controls.[36] Their data demonstrated an increased binding of raclopride in the thalamus, a region of brain having a high density of D_3 receptors, whereas a decrease in raclopride uptake was observed in the striatum, a brain region rich in both D_2 and D_3 receptors. These data suggest that chronic exposure to cocaine may result in a differential regulation of D_2 and D_3 receptors. That is, chronic cocaine abuse leads to an increase in D_3 receptors and a decrease in density of D_2 receptors. The above studies highlight the need to develop PET radiotracers which are capable of imaging D_3 versus D_2 receptors and vice versa.

Over the past decade, our group has focused on the development of ligands having a high affinity and selectivity for D_3 versus D_2 and D_2 versus D_3 receptors as useful probes for studying the behavioral pharmacology of these receptors, and for studying the differential expression of D_2 and D_3 receptors in the CNS with PET. We have recently reported the development of a series of conformationally-flexible benzamide analogs which have the potential for imaging D_3 versus D_2 receptors in the CNS.[37,38] The current study is a continuation of our effort to develop ligands having a high affinity and selectivity for D_2 versus D_3 receptors which could serves a useful D_2-selective behavioral probes and lead compounds for developing D_2-selective PET radiotracers. In these earlier studies, we prepared a number of structural analogs of the classical $D_{2\text{-like}}$ dopamine receptor antagonists, haloperidol, having a high affinity for D_2 versus D_3 receptors.[15,16]

In the current study, we focused on the atypical antipsychotic aripiprazole because this compound was reported to have a modest selectivity for D_2 versus D_3.[39] We explored the possibility of preparing aripiprazole analogs that might have higher affinity and selectivity for D_2 versus D_3 receptors than that of aripiprazole itself. First, the *N*-2,3-dichlorophenyl piperazine ring of aripiprazole was replaced with amine groups present in typical antipsychotics such as haloperidol, benperidol, domperidone, and *N*-methylspiperone. The results of this study revealed that replacing the *N*-2,3-dichlorophenyl piperazine ring of aripiprazole with these amine groups did not result in useful ligands since compounds **2**–**5** had low binding affinity at D_2, D_3, and D_4 receptors. Second, we replaced the *N*-2,3-dichlorophenyl group of aripiprazole with *N*-2-methoxyphenyl group (compound **6**) or *N*-2-(2-fluoroethoxy)phenyl group (compound **7**). Compounds **6** and **7** bind at D_2 receptors with nanomolar affinity and have >50-fold selectivity for human D_2 receptors compared to human D_3 dopamine receptor subtype. These two analogs also bind with low affinity at the D_4 dopamine receptor subtype, as well as σ_1 and σ_2 receptors. These two analogs were evaluated for intrinsic efficacy and found to be partial agonists at both D_2 and D_3 receptors. Third, we changed the position of the methoxy group from the 2-position to the 4-position of the piperazine moiety. Compound **8** (with *N*-4-methoxyphenyl group) lost the binding affinity to both D_2 and D_3 receptors. Substitution on both 2-and 4-positions (compounds **9** and **10**) decrease D_3 receptor affinity but had little effect on D_2 receptor affinity. Fourth, we also introduced a double bond into the tetrahydroisoquinoline ring of **6** and **7**. Compounds **11** and **12** maintain a similar affinity for D_2 receptors with a slight increase in affinity for D_3 receptors. Finally, we changed the length of the carbon spacer in the chain between two ring systems of **6** and **11** from 4-carbon atoms to 3-carbon atoms (compounds **13** and **14**) or 5-carbon chain (compounds **15** and **16**). This change resulted in compounds with nanomolar affinity at both D_2 and D_3 receptors, resulting in a low selectivity for the two receptor subtypes.

The high affinity and good selectivity of compounds **6** and **7** for D_2 versus D_3 receptors indicate that they should be useful probes for studying the behavioral pharmacology of the D_2 receptor. Furthermore, these compounds can be easily radiolabeled with either carbon-11 ($t_{1/2}$ = 20.4 min) and fluorine-18 ($t_{1/2}$ = 109.7 min) and serve as useful PET radiotracers for measuring the density of D_2 receptors in the CNS without interference from labeling dopamine D_3 receptors. The lipophilicities (log *P*) of **6** and **7** (Table 1) also suggest that they will readily cross the blood brain barrier and are good candidates for the development of D_2 receptor selective imaging agents for the functional imaging technique, PET. PET imaging studies with [^{11}C]**6** and [^{18}F]**7** are currently ongoing in our group and will be published separately.

In summary, a series of structural congeners of aripiprazole were synthesized and evaluated for their affinities and efficacies atD_2 and D_3 receptors. The results of the in vitro binding

studies have identified two compounds, **6** and **7**, which will be useful probes for studying the function of the dopamine D_2 versus D_3 receptor in the CNS.

7. Experimental

7.1. Chemical analysis

^{1}H NMR spectra were recorded on a Varian 300 MHz NMR spectrometer. Chemical shifts are reported in δ values (parts per million, ppm) relative to an internal standard of tetramethylsilane (TMS). The following abbreviations are used for multiplicity of NMR signals: br s = broad singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet, s = singlet, t = triplets. Melting points were determined on an electrothermal melting point apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA and were within ±0.4% of the calculated values. Mass spectrometry was provided by the Washington University Mass Spectrometry Resource, an NIH Research Resource (Grant No. P41RR0954). All reactions were carried out under an inert atmosphere of nitrogen. Lipophilicity measurements of the compounds were estimated using the computational program, *C* log *P* (Advanced Chemistry Development, Inc., Toronto, Canada).

7.2. 7-(4-(4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl)butoxy)-3,4-dihydroquinolin-2(1*H*)-one oxalate (2)

A mixture of 7-(4-bromobutoxy)-3,4-dihydroquinolin-2(1*H*)-one (**20**, 1.7 mmol), 4-(chlorophenyl)-4-hydroxypiperidine (1.7 m mol), potassium carbonate (5 equiv) and potassium iodide (1 equiv) in acetonitrile (20 mL) was stirred at reflux overnight. The reaction mixture was evaporated. The resulting residue was suspended in water (25 mL) and filtered. The solid was washed with water and air dried to give the product as white powder (96% yield). The oxalate salt was prepared using 1 equiv of oxalic acid in ethanol and recrystallized from ethanol to give **2** as an off-white powder, mp 178–179 °C; ^{1}H NMR (free base, $CDCl_3$ + DMSO-d_6) δ 9.08 (br s, 1H), 7.47 (d, *J* = 8.7 Hz, 2H), 7.29 (d, *J* = 8.7 Hz, 2H), 7.02 (d, *J* = 8.2 Hz, 1H), 6.49 (dd, *J* = 8.7 and 2.5 Hz, 1H), 6.42 (d, *J* = 2.5 Hz, 1H), 3.95 (t, *J* = 6.0 Hz, 2H), 3.50–3.60 (m, 1H), 2.78–2.89 (m, 4H), 2.43–2.62 (m, 6H), 2.02–2.10 (m, 2H), 1.70–1.80 (m, 6H). Anal. ($C_{24}H_{29}ClN_2$-O_3·$C_2H_2O_4$·0.5H_2O) C, H, N.

7.3. 7-(4-(4-(2-Oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-1-yl)-piperidin-1-yl)butoxy)-3,4-dihydroquinolin-2(1*H*)-one oxalate (3)

Compound **3** was synthesized as described for **2**, from 4-(2-keto-1-benzimidazolinyl)piperidine in 67% yield. Conversion to the oxalate salt gave **3** as an off-white powder, mp 187–188 °C; ^{1}H NMR (free base, $CDCl_3$) δ 9.88 (br s, 1H), 9.37 (s, 1H), 7.21–7.25 (m, 1H), 7.02–7.10 (m, 4H), 6.52–6.55 (m, 2H), 4.24–4.33 (m, 1H), 4.06 (t, *J* = 6.6 Hz, 2H), 3.11–3.15 (m, 2H), 2.87–2.92 (m, 2H), 2.50–2.64 (m, 6H), 2.17–2.24 (m, 2H), 1.71–1.89 (m, 6H). Anal. ($C_{25}H_{30}N_4O_3$·$C_2H_2O_4$·1.25H_2O) C, H, N.

7.4. 7-(4-(4-(5-Chloro-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-1-yl)piperidin-1-yl)butoxy)-3,4-dihydroquinolin-2(1*H*)-one oxalate (4)

Compound **4** was synthesized as described for **2**, from 5-chloro-1-(4-piperidyl)-2-benzimidazolinone in 70% yield. Conversion to the oxalate salt gave **4** as an off-white powder, mp 184–185 °C; ^{1}H NMR (free base, $CDCl_3$) δ 10.10 (br s, 1H), 9.26 (s, 1H), 6.99–7.10 (m, 4H), 6.53–6.77 (m, 2H), 4.15–4.23 (m, 1H), 4.07 (t, *J* = 6.6 Hz, 2H), 3.07–3.11 (m, 2H), 2.87–2.92 (m, 2H), 2.45–2.64 (m, 6H), 2.10–2.17 (m, 2H), 1.68–1.92 (m, 6H). Anal. ($C_{25}H_{29}ClN_4O_3$·$C_2H_2O_4$) C, H, N.

7.5. 7-(4-(3Methyl-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decan-8-yl)butoxy)-3,4-dihydroquinolin-2(1*H*)-one oxalate (5)

Compound **5** was synthesized as described for **2**, from 3-methyl-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one in 72% yield. Conversion to the oxalate salt gave **5** as an off-white powder, mp 241–242 °C; ^{1}H NMR (free base, $CDCl_3$) δ 7.96 (br s, 1H), 7.25–7.30 (m, 2H), 7.04 (d, *J* = 8.2 Hz, 1H), 6.83–6.92 (m, 3H), 6.52 (dd, *J* = 8.2 and 2.2 Hz, 1H), 6.33 (d, *J* = 2.2 Hz, 1H), 4.67 (s, 2H), 3.97 (t, *J* = 6.2 Hz, 2H), 3.00 (s, 3H), 2.86–2.91 (m, 6H), 2.54–2.78 (m, 6H), 1.65–1.85 (m, 6H). Anal. ($C_{27}H_{34}N_4O_3 \cdot C_2H_2O_4$) C, H,N.

7.6. 7-(4-(4-(2-Methoxyphenyl)piperazin-1-yl)butoxy)-3,4-dihydroquinolin-2(1*H*)-one oxalate (6)

Compound **6** was synthesized as described for **2**, from 1-(2-methoxyphenyl)piperazine hydrochloride in 96% yield. Conversion to the oxalate salt gave **6** as an off-white powder, mp 116–117 °C; ^{1}H NMR (free base, $CDCl_3$) δ 7.96 (br s, 1H), 7.04 (d, *J* = 8.2 Hz, 1H), 6.85–7.01 (m, 4H), 6.53 (dd, *J* = 8.2 and 2.4 Hz, 1H), 6.32 (d, *J* = 2.4 Hz, 1H), 3.96 (t, *J* = 6.2 Hz, 2H), 3.86 (s, 3H), 3.10 (br s, 4H), 2.87–2.92 (m, 2H), 2.59–2.67 (m, 4H), 2.45–2.50 (m, 2H), 1.70–1.84 (m, 6H). Anal. ($C_{24}H_{31}N_3O_3 \cdot C_2H_2O_4 \cdot 0.5H_2O$) C, H, N.

7.7. 7-(4-(4-(2-Hydroxyphenyl)piperazin-1-yl)butoxy)-3,4-dihydroquinolin-2(1*H*)-one (17)

Compound **17** was synthesized as described for **2**, from 1-(2-hydroxyphenyl)piperazine in 84% yield as an off-white powder; mp 107–108 °C; ^{1}H NMR (free base, $CDCl_3$) δ 8.15 (br s, 1H), 7.15–7.18 (m, 1H), 7.05–7.10 (m, 1H), 7.04 (d, *J* = 8.2 Hz, 1H), 6.83–6.96 (m, 2H), 6.53 (dd, *J* = 8.2 and 2.3 Hz, 1H), 6.33 (d, *J* = 2.3 Hz, 1H), 3.97 (t, *J* = 6.0 Hz, 2H), 2.87–2.93 (m, 6H), 2.59–2.64 (m, 6H), 2.48 (t, *J* = 7.4 Hz, 2H), 1.66–1.87 (m, 5H). Anal. ($C_{23}H_{29}N_3O_3$) C, H, N.

7.8. 7-(4-(4-(2-(2-Fluoroethoxy)phenyl)piperazin-1-yl)butoxy)-3,4-dihydroquinolin-2(1*H*)-one oxalate (7)

1-Bromo-2-fluoroethane (5.0 mmol) and potassium carbonate (4 equiv) were added into the solution of **17** (1.5 mmol) in acetone (15 mL). The reaction mixture was heated at 65–70 °C for 48 h. The solid was filtered off and washed with acetone. The filtrate was evaporated. The resulting residue was purified by silica gel column chromatography (5% methanol in dichloromethane) to give the product (59% yield). Conversion to the oxalate salt gave **7** as an off-white powder, mp 147–148 °C; ^{1}H NMR (free base, $CDCl_3$) δ 8.07 (br s, 1H), 7.04 (d, *J* = 8.2 Hz, 1H), 6.95–6.99 (m, 3H), 6.85–6.88 (m, 1H), 6.53 (dd, *J* = 8.2 and 2.4 Hz, 1H), 6.32 (d, *J* = 2.4 Hz, 1H), 4.85–4.88 (m, 1H), 4.69–4.72 (m, 1H), 4.29–4.32 (m, 1H), 4.20–4.23 (m, 1H), 3.96 (t, *J* = 6.2 Hz, 2H), 3.14 (br s, 4H), 2.87–2.92 (m, 2H), 2.59–2.64 (m, 6H), 2.45–2.50 (m, 2H), 1.68–1.84 (m, 4H). Anal. ($C_{25}H_{32}FN_3O_3 \cdot C_2H_2O_4 \cdot 0.5H_2O$) C, H, N.

7.9. 7-(4-(4-(4-Methoxyphenyl)piperazin-1-yl)butoxy)-3,4-dihydroquinolin-2(1*H*)-one oxalate (8)

Compound **8** was synthesized as described for **2**, from 1-(4-methoxyphenyl)piperazine hydrochloride in 93% yield. Conversion to the oxalate salt gave **8** as an off-white powder, mp 152–153 °C; ^{1}H NMR (free base, $CDCl_3$) δ 7.61 (br s, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.91 (d, *J* = 7.5 Hz, 2H), 6.84 (d, *J* = 7.5 Hz, 2H), 6.53 (d, *J* = 8.4 Hz, 1H), 6.29 (m, 1H), 3.93–3.98 (m, 2H), 3.77 (s, 3H), 3.10 (br s, 4H), 2.88–2.90 (m, 2H), 2.60–2.64 (m, 6H), 2.45–2.49 (m, 2H), 1.62–1.82 (m, 4H). Anal. ($C_{24}H_{31}N_3O_3 \cdot C_2H_2O_4 \cdot 0.5H_2O$) C, H, N.

7.10. 7-(4-(4-(2,4-Dimethoxyphenyl)piperazin-1-yl)butoxy)-3,4-dihydroquinolin-2(1*H*)-one oxalate (9)

Compound **9** was synthesized as described for **2**, from 1-(2,4-dimethoxyphenyl)piperazine hydrochloride in 71% yield. Conversion to the oxalate salt gave **9** as an off-white powder, mp 167–168 °C; ^{1}H NMR (free base, $CDCl_3$) δ 7.80 (br s, 1H), 7.05 (d, *J* = 8.5 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 1H), 6.41–6.54 (m, 3H), 6.30 (s, 1H), 3.96 (t, *J* = 6.1 Hz, 2H), 3.84 (s, 3H), 3.78 (s, 3H), 3.03 (br s, 4H), 2.87–2.92 (m, 2H), 2.60–2.66 (m, 6H), 2.45–2.50 (m, 2H), 1.68–1.84 (m, 4H). Anal. ($C_{25}H_{33}N_3O_4 \cdot C_2H_2O_4 \cdot 0.5H_2O$) C, H, N.

7.11. 7-(4-(4-(2-Methoxy-4-methylphenyl)piperazin-1-yl)butoxy)-3,4-dihydroquinolin-2(1*H*)-one oxalate (10)

Compound **10** was synthesized as described for **2**, from 1-(2-methoxy-4-methylphenyl)piperazine hydrochloride (**19**) in 95% yield. Conversion to the oxalate salt gave **10** as an off-white powder, mp 146–147 °C; ^{1}H NMR (free base, $CDCl_3$) δ 7.83 (br s, 1H), 6.97 (d, *J* = 8.1 Hz, 1H), 6.77 (d, *J* = 7.8 Hz, 1H), 6.64 (d, *J* = 8.1 Hz, 1H), 6.61 (s, 1H), 6.45 (d, *J* = 8.4 Hz, 1H), 6.24 (s, 1H), 3.88 (t, *J* = 6.1 Hz, 2H), 3.77 (s, 3H), 2.99 (br s, 4H), 2.80–2.85 (m, 2H), 2.50–2.61 (m, 6H), 2.37–2.42 (m, 2H), 2.23 (s, 3H), 1.60–1.74 (m, 4H). Anal. ($C_{25}H_{33}N_3O_3 \cdot C_2H_2O_4 \cdot 1.5H_2O$) C, H, N.

7.12. 1-(2-Methoxy-4-methylphenyl)piperazine hydrochloride (19)[19]

A solution of 2-methoxy-4-methylaniline (**18**, 10.9 mmol), bis-(2-chloroethyl)amine hydrochloride (12.0 mmol), potassium carbonate (15.2 mmol) in 1-butanol (5 mL) was refluxed under nitrogen overnight. The hot reaction mixture was filtered and the filtrate was concentrated under vacuum. The resulting residue was triturated with acetone and filtered to give **19** as an off-white powder (14% yield), mp 212–213 °C (dec); ^{1}H NMR (free base, $CDCl_3$) δ 9.14 (s, 1H), 6.68–6.82 (m, 3H), 3.77 (s, 3H), 3.11–3.19 (m, 8H), 2.25 (s, 3H).

7.13. 7-(4-(4-(2-Methoxyphenyl)piperazin-1-yl)butoxy)quinolin-2(1*H*)-one oxalate (11)

A mixture of 7-(4-bromobutoxy)quinolin-2(1*H*)-one[17] (**21**, 0.78 mmol), 1-(2-methoxyphenyl)piperazine hydrochloride (1.00 mmol), and triethylamine (0.5 mL) in acetonitrile (15 mL) was refluxed overnight. The solvent was evaporated under reduced pressure. The residue was dissolved in dichloromethane, washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4, concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (5% methanol in dichloromethane) to give the product as an oil (62% yield). Conversion to the oxalate salt gave **11** as an off-white powder, mp 180–182 °C; ^{1}H NMR (free base, $CDCl_3$) δ 12.30 (s, 1H), 7.71–7.74 (m, 1H), 7.42–7.45 (m, 1H), 6.78–7.02 (m, 6H), 6.53–6.56 (m, 1H), 4.07–4.10 (m, 2H), 3.86 (s, 3H), 3.11 (br s, 4H), 2.68 (br s, 4H), 2.47–2.52 (m, 2H), 1.72–1.90 (m, 4H). HRMS calcd for $C_{24}H_{30}N_3O_3$ $[M+H]^+$ 408.2287, found: 408.2290.

7.14. 7-(4-(4-(2-(2-Fluoroethoxy)phenyl)piperazin-1-yl)butoxy)quinolin-2(1*H*)-one oxalate (12)

Compound **12** was synthesized as described for **11** from **21** and 1-(2-(2-fluoroethoxy)phenyl)piperazine[20] in 65% yield. Conversion to oxalate salt gave **12** as a white powder, mp 152–154 °C; ^{1}H NMR (free base, $CDCl_3$) δ 12.02 (s, 1H), 7.72 (d, *J* = 9.4 Hz, 1H), 7.44 (d, *J* = 9.4 Hz, 1H), 6.79–6.96 (m, 6H), 6.53 (d, *J* = 9.4 Hz, 1H), 4.78 (dt, *J* = 47.7 and 3.9 Hz, 2H), 4.25 (dt, *J* = 27.6 and 3.9 Hz, 2H), 4.08–4.13 (m, 2H), 3.14 (br s, 4H), 2.67 (br s, 4H), 2.49 (t, *J* = 7.5 Hz, 2H), 1.72–1.90 (m, 4H). HRMS calcd for $C_{25}H_{31}FN_3O_3$ $[M+H]^+$ 440.2349, found: 440.2345.

7.15. 7-(3-(4-(2-Methoxyphenyl)piperazin-1-yl)propoxy)-3,4-dihydroquinolin-2(1*H*)-one oxalate (13)

1-(3-Chloropropyl)-4-(2-methoxyphenyl)piperazine[22] (2.0 mmol) was added to a solution of 7-hydroxy-3,4-dihydroquinolin-2(1*H*)-one (**22a**, 2.0 mmol), sodium methoxide (25% in methanol, 2.0 mmol) in ethanol (10 mL). The mixture was refluxed for 5 h. The solvent was removed in vacuo. The residue was diluted with dichloromethane and washed with water. The organic phase was dried and concentrated. The residue was purified by column chromatography (5% methanol in dichloromethane) to give product as a free base in 67% yield. Conversion to oxalate salt gave **13** as a white powder, mp 115–116 °C; ^{1}H NMR (free base, $CDCl_3$) δ 8.07 (br s, 1H), 6.85–7.05 (m, 5H), 6.53 (dd, *J* = 8.1, and 2.4 Hz, 1H), 6.33 (d, *J* = 2.4 Hz, 1H), 4.00 (t, *J* = 6.3 Hz, 2H), 3.86 (s, 3H), 3.11 (br s, 4H), 2.89 (t, *J* = 7.2 Hz, 2H), 2.57–2.69 (m, 8H), 1.97–2.02 (m, 2H). HRMS calcd for $C_{23}H_{30}N_3O_3$ $[M+H]^+$ 396.2287, found: 396.2284.

7.16. 7-(3-(4-(2-Methoxyphenyl)piperazin-1-yl)propoxy)quinolin-2(1*H*)-one oxalate (14)

Compound **14** was synthesized as described for **13** from 7-hydroxyquinolin-2(1*H*)-one (**22b**) and 1-(3-chloropropyl)-4-(2-methoxyphenyl)piperazine[22] in 52% yield. Conversion to oxalate salt gave **14** as a white powder, mp 143–145 °C; ^{1}H NMR (free base, $CDCl_3$) δ 12.13 (s, 1H), 7.72 (d, *J* = 9.3 Hz, 1H), 7.45 (d, *J* = 9.3 Hz, 1H), 6.81–7.02 (m, 6H), 6.55 (d, *J* = 9.6 Hz, 1H), 4.15 (t, *J* = 6.2 Hz, 2H), 3.87 (s, 3H), 3.13 (br s, 4H), 2.71 (br s, 4H), 2.63 (t, *J* = 7.4 Hz, 2H), 2.03–2.08 (m, 2H). Anal. ($C_{23}H_{27}N_3O_3 \cdot H_2C_2O_4 \cdot H_2O$) C, H, N.

7.17. 7-(5-(4-(2-Methoxyphenyl)piperazin-1-yl)pentyloxy)-3,4-dihydroquinolin-2(1*H*)-one oxalate (15)

Compound **15** was synthesized as described for **2** from 7-(5-bromopentyloxy)-3,4-dihydroquinolin-2(1*H*)-one (**23**)[21] and 1-(2-methoxyphenyl)piperazine hydrochloride in 47% yield. Conversion to oxalate salt gave **15** as a white powder, mp 198–200 °C; ^{1}H NMR (free base, $CDCl_3$) δ 7.90 (br s, 1H), 6.85–7.06 (m, 5H), 6.52 (dd, *J* = 8.4 and 2.4 Hz, 1H), 6.31 (d, *J* = 2.4 Hz, 1H), 3.93 (t, *J* = 6.5 Hz, 2H), 3.87 (s, 3H), 3.11 (br s, 4H), 2.90 (t, *J* = 7.5 Hz, 2H), 2.59–2.66 (m, 6H), 2.44 (t, *J* = 7.5 Hz, 2H), 1.50–1.83 (m, 6H). Anal. ($C_{25}H_{33}N_3O_3 \cdot H_2C_2O_4$) C, H, N.

7.18. 7-(5-(4-(2-Methoxyphenyl)piperazin-1-yl)pentyloxy)quinolin-2(1*H*)-one oxalate (16)

A mixture of **15** (0.28 mmol), and DDQ (0.34 mmol) in dichloromethane (5 mL) was stirred at room temperature overnight. The mixture was washed with saturated $NaHCO_3$ solution, dried, and concentrated in vacuo. The residue was purified by column chromatography (5% methanol in dichloromethane) to give the product as a free base in 75% yield. Conversion to oxalate salt gave **16** as a white powder; mp 229–230 °C. ^{1}H NMR (free base, $CDCl_3$) δ 12.05 (s, 1H), 7.72 (d, *J* = 9.3 Hz, 1H), 7.44 (d, *J* = 9.3 Hz, 1H), 6.79–7.10 (m, 6H), 6.53 (d, *J* = 9.3 Hz, 1H), 4.07 (t, *J* = 6.3 Hz, 2H), 3.86 (s, 3H), 3.11 (br s, 4H), 2.68 (br s, 4H), 2.46 (t, *J* = 6.6 Hz, 2H), 1.82–1.90 (m, 2H), 1.53–1.70 (m, 4H). Anal. ($C_{25}H_{31}N_3O_3 \cdot H_2C_2O_4$) C, H, N.

8. Radiological binding and functional assays

8.1. Dopamine receptor binding assay

The method for the iodination of ^{125}I-IABN using peracetic acid has been previously described.[23] For radioligand binding studies, membrane homogenates from stably transfected HEK 293 cells expressing either the human D_2, D_3, or D_4 receptors were prepared using a polytron tissue homogenizer (Brinkman Instruments, Westbury, NY). The tissue was suspended in 50 mM Tris–HCl, 150 mM NaCl and 1 mM EDTA at pH 7.5 to

approximately 5–20 μg of protein per 50 μL prior to the assay. Assays were performed in a total volume of 150 μL. Binding reactions were carried out for 60 min at 37 °C and the reaction was terminated by rapid filtration over Schleicher and Schuell No. 32 glass fiber filters (Whatman plc, Maidstone, England). After washing filters with buffer, the radioactivity of the ^{125}I-labeled ligand was quantitated using a Packard Cobra gamma counter with an efficiency of 75%. Protein concentrations were determined using a BCA reagent (Pierce, Rockford, Illinois) with bovine serum albumin as the protein standard.

For competition curves using a transfected cell line expressing D_2, D_3, or D_4 dopamine receptors, experiments were performed in triplicate with two concentrations of inhibitor per decade over at least five orders of magnitude. The concentration of the radioligand was approximately equal to the K_d values. Controls containing either no inhibitor or 2 μM(+)-butaclamol were used to define total binding and nonspecific binding, respectively. Competition data for $D_{2\text{-like}}$ dopamine receptors were modeled for a single-site fit using the TABLECURVE program (Jandel Scientific Software, San Rafael, California); the IC_{50} values for the competitive inhibitors were converted to K_i values using the Cheng and Prusoff corrections.[40]

8.2. Sigma receptor binding assays

Test compounds were dissolved in *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO) or ethanol and then diluted in 50 mM Tris–HCl buffer, pH 7.4, containing 150 mM NaCl and 100 mM EDTA. Membrane homogenates were made from guinea pig brain for σ_1 binding assay and rat liver for σ_2 binding assay. Membrane homogenates were diluted with 50 mMTris–HCl buffer, pH 8.0, and incubated at 25 °C in a total volume of 150 μL in 96-well plates with the radioligand and test compounds with concentrations ranging from 0.1 nM to 10 μM. After incubation was completed, the reactions were terminated by the addition of 150 μL of ice-cold wash buffer (10 mM Tris–HCl, 150 mM NaCl, pH 7.4) using a 96-channel transfer pipette (Fisher Scientific, Pittsburgh, PA), and the samples harvested and filtered rapidly through 96-well fiber glass filter plate (Millipore, Billerica, MA) that had been presoaked with 100 μL of 50 mMTris–HCl buffer, pH 8.0, for 1 h. Each filter was washed three times with 200 μL of ice-cold wash buffer. AWallac 1450 MicroBeta liquid scintillation counter (Perkin–Elmer, Boston, MA) was used to quantitate the bound radioactivity.

The σ_1 receptor binding assay was conducted using guinea pig brain membrane homogenates (~300 μg protein) and ~5 nM [^{3}H](+)-pentazocine (34.9 Ci/mmol, Perkin–Elmer, Boston, MA). The incubation time was 90 min. Nonspecific binding was determined from samples that contained 10 μM of cold haloperidol.

The σ_2 receptor binding assays were conducted using rat liver membrane homogenates (~300 μg protein) and ~1 nM [^{3}H]RHM-1 (80 Ci/mmol, American Radiolabeled Chemicals Inc., St. Louis, MO) alone or ~5 nM [^{3}H]DTG (58.1 Ci/mmol, Perkin–Elmer, Boston, MA) in the presence of 1 μM (+)-pentazocine to block σ_1 sites. The incubation time was 60 min for [^{3}H]RHM-1 and 120 min for [^{3}H]DTG. Nonspecific binding was determined from samples that contained 10 μM of cold haloperidol.

Data from the competitive inhibition experiments were modeled using nonlinear regression analysis to determine the concentration of inhibitor that inhibits 50% of the specific binding of the radioligand (IC_{50} value). Competitive curves were best fit to a one-site fit and gave pseudo-Hill coefficients of 0.6–1.0. K_i values were calculated using the method of Cheng and Prusoff[23] and represent mean values ± SEM. The K_d value used for [^{3}H](+)-pentazocine with guinea pig brain homogenates was 7.89 nM; a K_d value of 30.73 nM was used for [^{3}H]DTG with rat liver, while 0.66 nM was used for [^{3}H]RHM-1 with rat liver.[25]

8.3. Whole cell adenylyl cyclase assay

The accumulation of ^{3}H-cyclic AMP in HEK cells was measured by a modification of the method of Shimizu et al.[41] as previously described.[23] Transfected HEK cells were treated with serum-free medium containing 2,8-^{3}H-adenine (ICN) and cells were incubated at 37 °C for 75 min. Cells and drugs diluted in serum-free media containing 0.1 mM 3-isobutyl-1-methylxanthine (Sigma) were mixed to give a final volume of 500 μL and cells were incubated for 20 min at 37 °C. The reaction was stopped by addition of 500 μL of 10% trichloroacetic acid and 1 mM cyclic AMP. After centrifugation, the supernatants were fractionated using Dowex AG1-X8 and neutral alumina to separate the ^{3}H-ATP and the ^{3}H-cyclic AMP. Individual samples were corrected for column recovery by monitoring the recovery of the cyclic AMP using spectrophotometric analysis at OD 259 nm.[23,41]

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Appendix

Elemental analyses

Compound	%C		%H		%N	
	Calcd	Found	Calcd	Found	Calcd	Found
2	59.15	58.79	6.11	5.85	5.31	5.22
3	59.28	59.28	6.36	6.45	10.24	9.85
4	58.01	58.07	5.59	5.86	10.02	10.00
5	63.03	62.95	6.57	6.60	10.14	10.13
6	61.40	61.40	6.74	6.54	8.26	8.20
7	59.99	60.03	6.53	6.55	7.77	7.54
8	61.40	61.62	6.74	6.62	8.26	8.33
9	60.21	60.47	6.74	6.72	7.80	7.70
10	59.99	59.60	7.08	6.79	7.77	7.41
14	59.87	60.09	6.23	6.21	8.38	8.28
15	63.14	62.91	6.87	6.79	8.18	8.00
16	63.39	63.27	6.50	6.48	8.21	8.07
17	69.85	69.72	7.39	7.25	10.62	10.64

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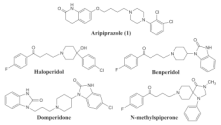


Figure 1.
Structures of the lead compounds.

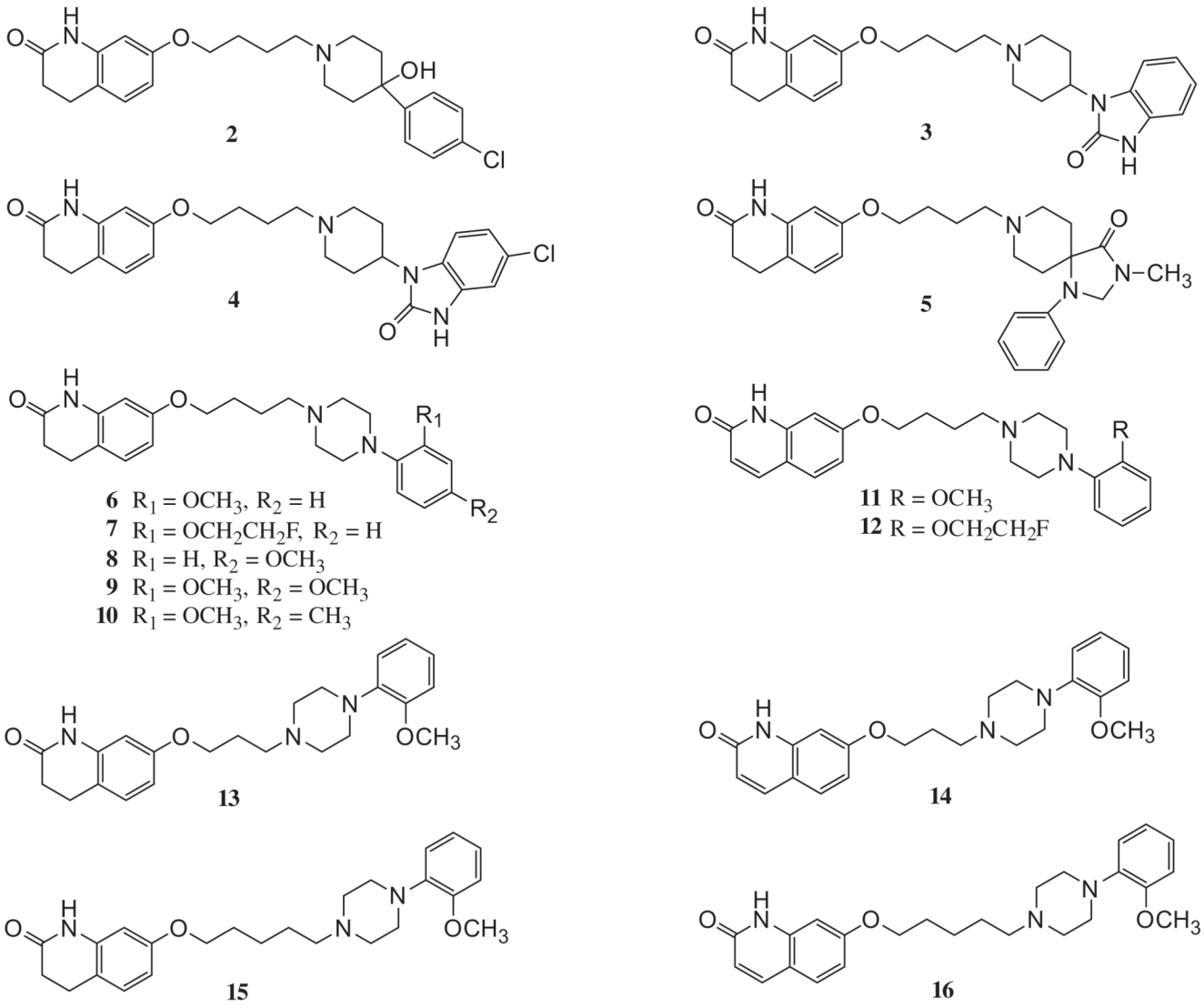


Figure 2.
Structures of the target compounds.

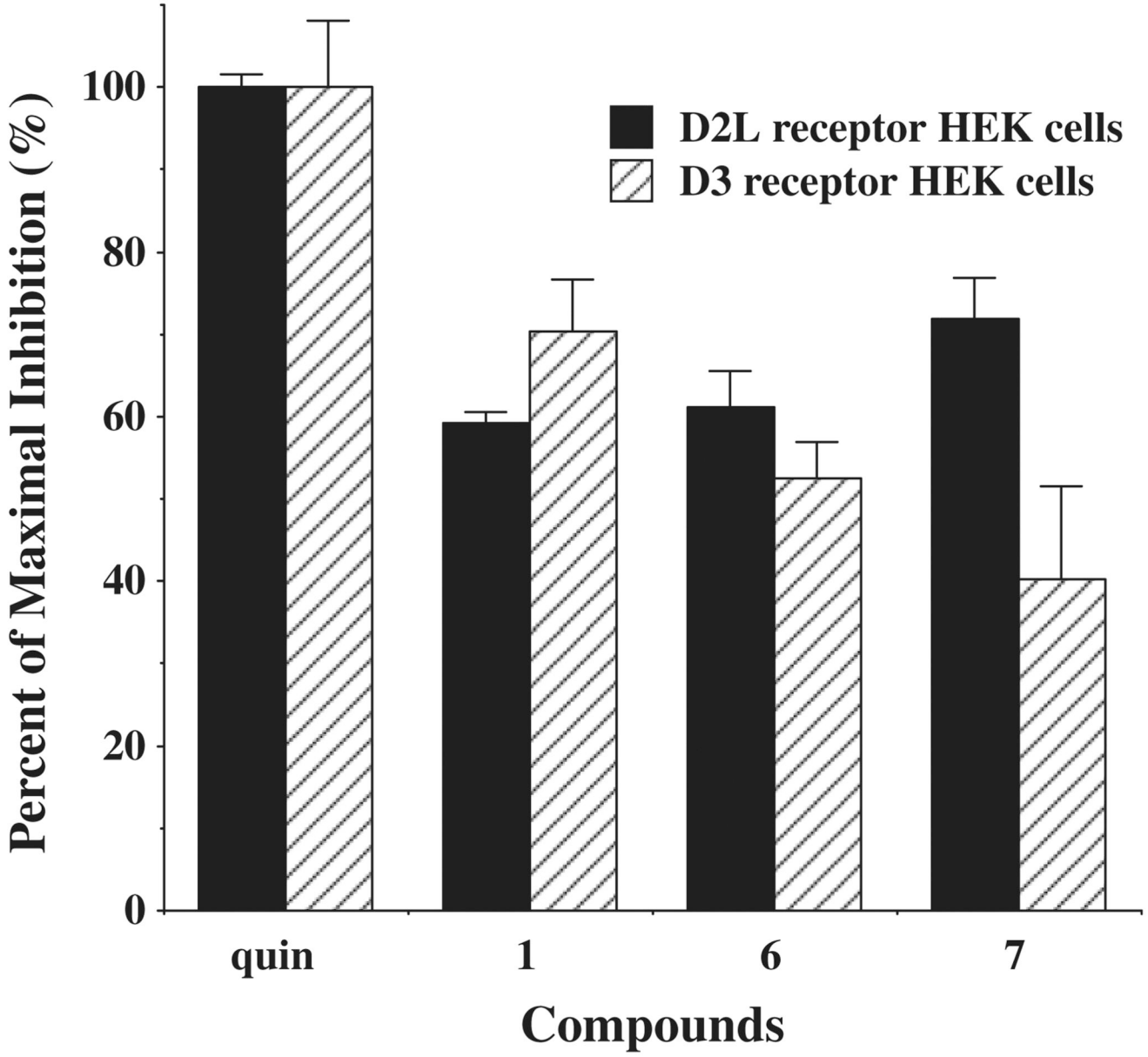
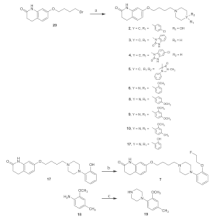


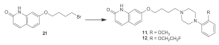
Figure 3.

Intrinsic efficacy at D_2 and D_3 dopamine receptor subtypes for adenylyl cyclase inhibition. Maximal inhibition for forskolin-dependent adenylyl cyclase inhibition was evaluated using the test ligands aripiprazole (**1**), compounds **6** and **7** at concentrations approximately equal to 10× the K_i values. The mean maximal percent inhibition ± SEM. ($n \geq 3$) was obtained by normalizing the data to the mean inhibition achieved using the full agonist quinpirole (quin) at a final concentration of 1 μM for D_{2L} HEK cells (solid bars) and 100 nM for D_3-HEK cells (hatched bars).[42]



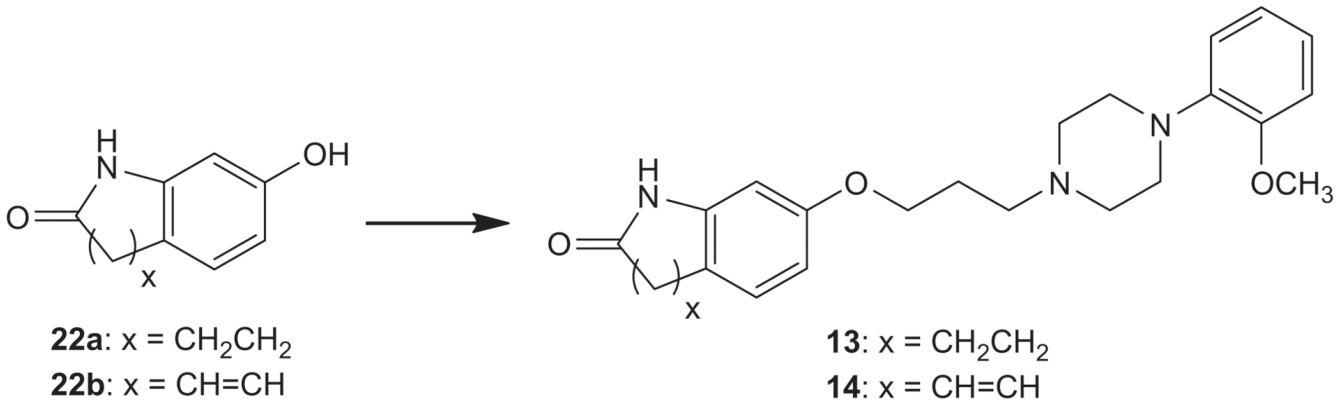
Scheme 1.

Reagents: (a) substituted piperidines or piperazines, K_2CO_3, KI, acetonitrile, heat; (b) 1-bromo-2-fluoroethane, K_2CO_3, acetone, heat; (c) bis-(2-chloroethyl)amine hydrochloride, K_2CO_3, butanol, heat.

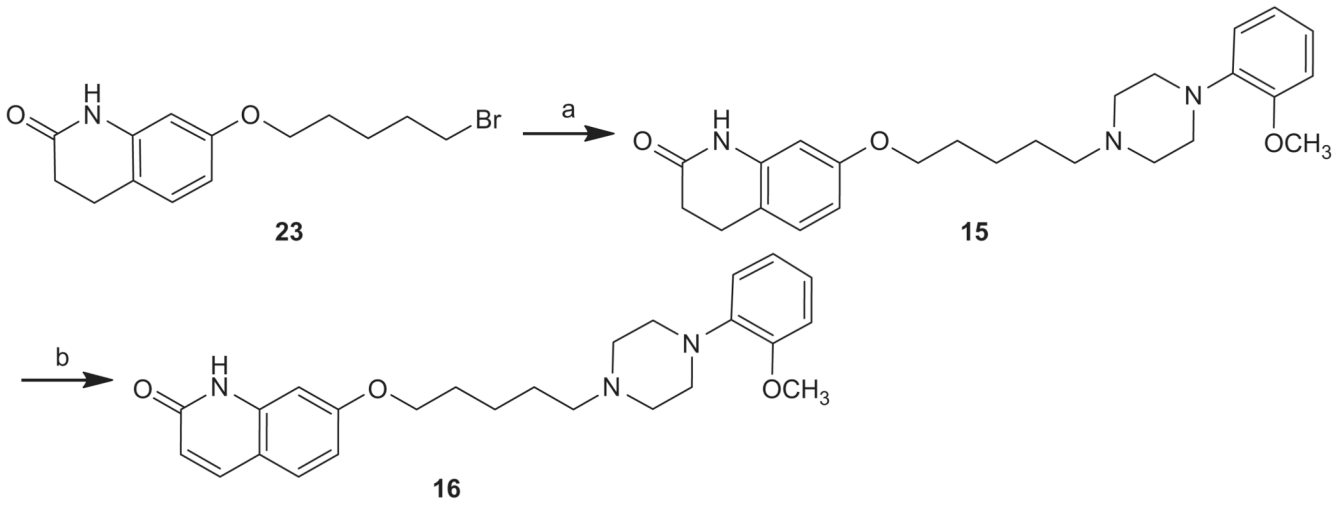


Scheme 2.

Reagents: 1-(2-methoxyphenyl)piperazine hydrochloride or 1-(2-(2-fluoroethoxy)phenyl)piperazine, $N(C_2H_5)_3$, acetonitrile.



Scheme 3.
Reagents: 1-(3-chloropropyl)-4-(2-methoxyphenyl)piperazine, $NaOCH_3$, ethanol.



Scheme 4.

Reagents: (a) 1-(2-methoxyphenyl)piperazine hydrochloride, $N(C_2H_5)_3$, acetonitrile; (b) DDQ, CH_2Cl_2.

Table 1

Binding affinities for dopamine D_2/D_3 and sigma σ_1/σ_2 receptors

Compound	K_i (nM)[a]							
	D_2[b]	D_3[c]	D_4[d]	D_3:D_2[e]	D_4:D_2[f]	σ_1[g]	σ_2[h]	log *P*[i]
2	2604 ± 748	1536 ± 156	1311 ± 100	0.6	0.5	417 ± 105	8269 ± 1771	2.25
3	145 ± 20	879 ± 289	1029 ± 263	6.1	7.1	433 ± 33	36364 ± 5623	2.54
4	309 ± 97	574 ± 80	1352 ± 307	1.9	4.4	158 ± 55	16907 ± 403	3.58
5	611 ± 62	427 ± 36	865 ± 116	0.7	1.4	3087 ± 281	19930 ± 3524	1.17
6	0.22 ± 0.01	13.1 ± 2.3	212 ± 45	60	964	1176 ± 108	598 ± 160	3.63
7	0.26 ± 0.05	13.5 ± 3.5	185 ± 27	52	712	13574 ± 2463	4988 ± 837	3.89
8	102 ± 25	930 ± 239	359 ± 22	9.1	3.5	170 ± 49	665 ± 36	3.43
9	25.3 ± 5.9	785 ± 258	286 ± 27	31	11	620 ± 64	3340 ± 194	3.12
10	4.6 ± 1.0	251 ± 33	27.2 ± 1.7	54	5.9	377 ± 56	6393 ± 276	3.97
11	0.14 ± 0.03	5.4 ± 1.1	30.1 ± 7.3	39	215	2631 ± 235	1309 ± 133	3.67
12	0.07 ± 0.01	2.7 ± 0.5	31.9 ± 9.1	39	456	20904 ± 1594	4952 ± 412	3.93
13	4.8 ± 0.9	7.4 ± 0.7	38.5 ± 6.4	1.5	8.0	759 ± 43	1907 ± 213	3.29
14	2.6 ± 0.5	5.7 ± 1.2	52.7 ± 16.9	2.2	20	2600 ± 464	2838 ± 86	3.34
15	7.3 ± 1.3	7.0 ± 1.6	234 ± 15.4	1.0	32	1349 ± 213	231 ± 5.85	3.94
16	7.4 ± 0.5	3.8 ± 0.1	201 ± 7.6	0.5	27	1614 ± 426	608 ± 17	3.98
Aripiprazole	3.1 ± 0.5	6.8 ± 0.2	168 ± 16.6	2.2	54	ND[j]	ND[j]	4.50

[a] Mean ± SEM, K_i values were determined by at least three experiments.

[b] K_i values for D_2 receptors were measured on human $D_{2(long)}$ expressed in HEK cells using [^{125}I]ABN as the radioligand.

[c] K_i values for D_3 receptors were measured on human D_3 expressed in HEK cells using [^{125}I]ABN as the radioligand.

[d] K_i values for D_4 receptors were measured on human D_4 expressed in HEK cells using [^{125}I]ABN as the radioligand.

[e] K_i for D_3 receptors/K_i for D_2 receptors.

[f] K_i for D_4 receptors/K_i for D_2 receptors.

[g] K_i for inhibiting the binding of [^{3}H](+)-pentazocine to guinea pig brain homogenates.

[h] K_i for inhibiting the binding of [^{3}H]DTG to rat liver homogenates.

[i] Calculated value using the program *C* log *P*.

[j] Not determined.