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Synthesis of 2-(2,3-dimethoxyphenyl)-4-(aminomethyl)imidazole Analogues and their Binding Affinities for Dopamine D_2 and D_3 Receptors

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Abstract—A series of 2-(2,3-dimethoxyphenyl)-4-(aminomethyl)imidazole derivatives was prepared and their affinity for dopamine D_2 and D_3 receptors was measured using in vitro binding assays. Several oxadiazole analogues were also prepared and tested for their affinity for dopamine D_2 and D_3 receptors. The results of receptor binding studies indicated that the incorporation of an imidazole moiety between the phenyl ring and the basic nitrogen did not significantly increase the selectivity for dopamine D_3 receptors, whereas the incorporation of an oxadiazole at the same region resulted in a total loss of affinity for both dopamine receptor subtype binding sites. The most selective compound in this series is 2-(5-bromo-2,3-dimethoxyphenyl)-4-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolinomethyl)imidazole (**5i**), which has a D_3 receptor affinity of 21 nM and a 7-fold selectivity for D_3 versus D_2 receptors. The binding affinity for σ_1 and σ_2 receptors was also measured, and the results showed that several analogues were selective σ_1 receptor ligands.

Introduction

Molecular biology studies have classified dopamine receptors into two major groups, D_1-like (D_1, D_5) and D_2-like (D_2, D_3, and D_4), based on amino acid homology and G-protein coupled second messenger pathways.[1–3] The genomic structures of D_2, D_3 and D_4 receptors contain 6, 5, and 3 introns, respectively, whereas the D_1 and D_5 receptor genes contain no introns within their coding region.[2,4] Amino acid sequence analysis revealed that the dopamine receptors have seven transmembrane spanning regions, which is characteristic of other members of the G-protein coupled receptor superfamily.[5] The D_1 and D_5 receptors share an 80% amino acid sequence identity in their transmembrane domains. The D_2 and D_3 receptors share a 75% amino acid sequence identity in their transmembrane domains, and the D_2 and D_4 receptors share a 53% identity in their transmembrane regions. In situ hybridization studies of dopamine receptor mRNAs in the brain have revealed a distinct difference between D_2 and D_3 receptor expression. D_2 receptor mRNA has been localized mainly in the striatum, the olfactory tubercle, and the nucleus accumbens,[1,6] whereas the D_3 receptor mRNA has been found specifically in limbic regions.[6]

The antipsychotic effects of neuroleptics are thought to be due to their action on the dopaminergic receptors in the mesolimbic system, whereas the extrapyramidal side effects are thought to result from the blockade of D_2 receptors in the striatum.[2,7] The localization of D_3 receptors in the limbic regions of brain suggests that this receptor may be a target for the development of antipsychotics with reduced risk of causing extrapyramidal side effects.[8] This hypothesis is supported by the observation that most conventional neuroleptics display a higher affinity for D_2 versus D_3 receptors and have a tendency to produce extrapyramidal symptoms.[9] In contrast, atypical antipsychotics have a high affinity for both D_2 and D_3 receptors.[10–12] More recent studies have also indicated that D_3 receptor stimulation may

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mediate the reinforcing effects of cocaine. Therefore, D_3 receptor antagonists are potentially useful for the treatment of cocaine abuse.[13–16]

Recently, we reported a number of benzamide analogues that bind with high affinity at both dopamine D_2 and D_3 receptors.[17–19] The common structural feature of those compounds included a substituted benzamide moiety and an *N*-benzyl group. Replacement of the *N*-benzyl group with different *N*-alkyl groups resulted in compounds with a higher affinity for D_2 versus D_3 receptors.[17] However, an increase in steric bulkiness of the N-benzyl region enhanced the affinity and selectivity of structurally-related analogues for D_3 receptors.[20]

The goal of the present study was to determine the effect of modification of the amide region of the benzamide analogues on binding to D_2 and D_3 receptors. A series of 2-phenyl-4-(aminomethyl)imidazoles was found to bind to dopamine D_2 receptors with a wide range of affinity (0.7–3750 nM), but their binding affinity for D_3 receptors was not reported.[21] As part of our research effort to identify compounds with high affinity and selectivity for dopamine D_3 receptors, we investigated a series of 2-(2,3-dimethoxyphenyl)-4-(aminomethyl)imidazoles and related oxadiazole analogues for their binding affinity for D_2 and D_3 receptors. In addition, since many dopamine antagonists bind to sigma receptors, the binding affinity of the synthesized compounds for σ_1 and σ_2 receptors was also measured. The results of our study revealed that replacement of the benzamide moiety with an imidazole ring leads to compounds that are moderately selective for either D_2 or D_3 receptors, with the selectivity being primarily dependent upon the structure of the tertiary amino moiety.

Results

Chemistry

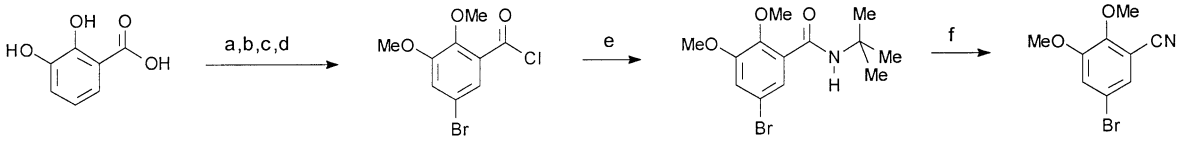
The synthesis of 5-bromo-2,3-dimethoxybenzonitrile was accomplished via the treatment of *N-tert*-butyl-5-bromo-2,3-dimethoxybenzamide with the phosphorus oxychloride.[22] The *N-tert*-butyl-5-bromo-2,3-dimethoxybenzamide was obtained from 2,3-dihydroxybenzoic acid in 5 steps as shown in Scheme 1. The synthesis of aminomethylimidazoles is outlined in Scheme 2. The benzamidine **2a** or **2b** was prepared according to the methods described by Boere et al.[23] The corresponding benzamidine was then condensed with dihydroxyacetone dimer to give **3a** or **3b**.[21] The 2-phenyl-4-(hydroxymethyl)imidazole **3a** or **3b** was then treated with thionyl chloride to form the corresponding 2-phenyl-4-(chloromethyl)imidazole that was subsequently alkylated with an appropriate secondary amine to give the final products. Alternatively, 2-phenyl-4-(hydroxymethyl)imidazole **3a** or **3b** was treated with PCC in dichloromethane to afford the corresponding aldehyde intermediate which then underwent reductive alkylation with an appropriate primary amine using sodium cyanoborohydride in methanol.

The 3-(2,3-dimethoxyphenyl)-5-aminoalkyl-1,2,4-oxadiazole analogues were synthesized according to procedures outlined in Scheme 3.[24,25] The 2,3-dimethoxybenzonitrile was treated with hydroxylamine to give the 2,3-dimethoxybenzamide oxime, **6**, which was then condensed with an appropriate methyl carboxylate to afford compounds **7a**–**d**.

Receptor binding

The in vitro receptor binding results are shown in Table 1. Compound **5a** was reported previously to have a K_i value of 5.1 nM for dopamine D_2 receptors (cloned from African Green Monkey) but binding data for dopamine D_3 receptors was not reported.[21] Therefore, compound **5a** was included for comparison in the current study. The binding affinity of compound **5a** was 9.2 nM for D_2 receptors (Sf9 cells) and 10.1 nM for D_3 receptors. Compound **5b**, which contains a bromo substitution on the phenyl aromatic ring and a diethylamino moiety, displayed a 10-fold decrease in affinity for both D_2 and D_3 receptors in comparison with the binding data of compound **5a**. These results are consistent with the presence of a conserved secondary aromatic binding region in both the D_2 and D_3 dopamine receptor binding sites. While this secondary aromatic binding site is not important for conferring D_2 versus D_3 selectivity, it does play a role in determining binding affinity.

Compound **5c** contains a *N*-(1-benzyl)piperidin-4-yl moiety and thus has two basic nitrogen atoms (not including the basic N within the imidazole ring). The binding affinity of **5c** for both D_2 and D_3 receptors was significantly decreased compared to **5a** and **5b**. When substituted at the 5′-position on the 2-phenyl aromatic ring with a bromo substituent, the subsequent compound, **5d**, had a 6-fold increase in affinity for D_2 receptors and a 15-fold increase in affinity for D_3 receptors. Compounds **5e** and **5f** both contain an *N*-(9-benzyl)-9-azabicyclo[3.3.1]nonan-3-yl moiety, and thus also have two basic nitrogen atoms (not including the basic N within the imidazole ring). Both compounds showed a significantly lower affinity for D_2 and D_3



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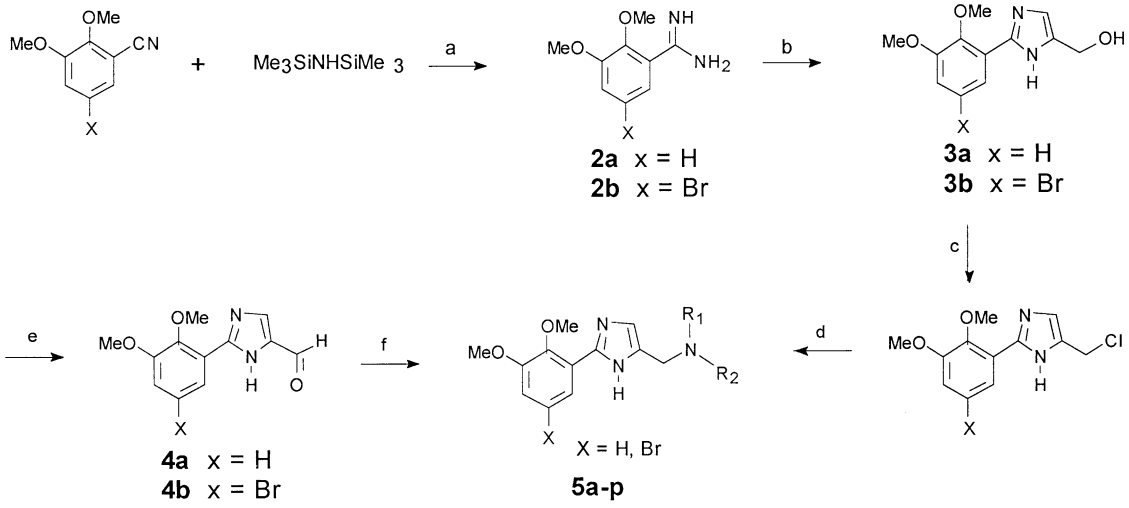
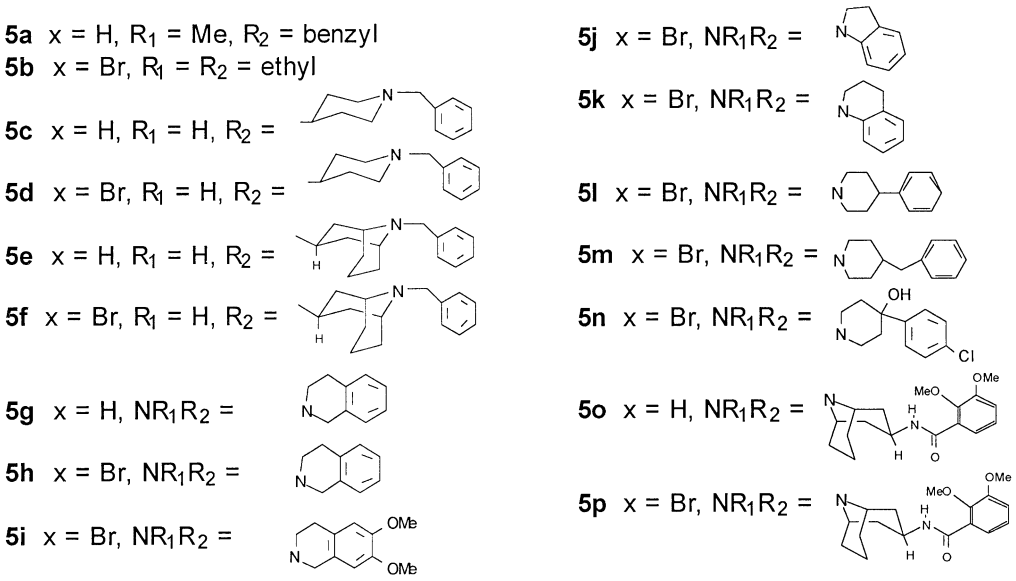
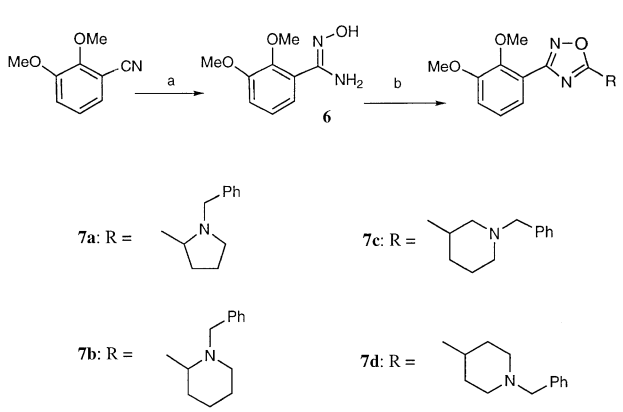
Scheme 1. Reagents: (a) Br_2, acetic acid, rt; (b) Me_2SO_4, acetone, Δ; (c) NaOH, MeOH, Δ; (d) $SOCl_2$, benzene, Δ; (e) *t*-$BuNH_2$, CH_2Cl_2, rt; (f) $POCl_3$, benzene, Δ.





Scheme 2. Reagents: (a) BuLi, ether, 0 °C; (b) 1,3-dihydroxyacetone dimer, NH_4Cl, NH_4OH, 80 °C; (c) $SoCl_2$, benzene, Δ; (d) NHR_1R_2, rt; (e) PCC,CH_2Cl_2; (f) NH_2R, MeOH, $NaBH_3CN$.



Scheme 3. Reagents: (a) NH_2OH HCl, K_2CO_3, ethanol, Δ; (b) RCOOMe, molecular sieve, Δ.

receptors when compared to compound **5a**. A bromo substitution at the 5′-position of the 2-phenyl aromatic moiety to afford compound **5f** resulted in a 3-fold increase in affinity for D_2 receptors and a 9-fold increase in affinity for D_3 receptors when compared to the binding data of **5e**. The increase in affinity and selectivity for D_2 and D_3 receptors by a bromo-substitution at the 5′-position of the 2-phenyl moiety was further demonstrated by the binding data of compounds **5g** and **5h**, both of which contain a 1,2,3,4-tetrahydroisoquinolino moiety. Compound **5h** had a 4-fold higher affinity for D_2 receptors and a 28-fold higher affinity for D_3 receptors than compound **5g**. As a result, compound **5h** is 3-fold selective for D_3 receptors (23.8 nM) versus D_2 receptors (78.2 nM), whereas compound **5g** was a 2-fold selective for D_2 receptors (315.5 nM) versus D_3 receptors (664 nM). When substituted with a 6,7-dimethoxy

Table 1. Binding affinities for dopamine D_2/D_3 and sigma σ_1/σ_2 receptors

Compd	K_i (nM)[a]			
	D_2[b]	D_3[c]	σ_1[d]	σ_2[e]
5a	9.2±2.1	10.1±1.5	16.7±0.7	>1000
5b	97.0±8.4	90.8±31.9	>1000	>1000
5c	1767±568	1707±562	33.6±0.4	140.0±14.6
5d	283.5±132	113.7±53.7	84.7±0.5	>1000
5e	799±353	1310±917	586.2±35.6	>1000
5f	243.1±88	145.9±41.5	>1000	>1000
5g	315.5±140	664±148	>1000	>1000
5h	78.2±29	23.8±11	>1000	>1000
5i	143.0±48.7	21.2±4.7	>1000	>1000
5j	>1000	>1000	>1000	>1000
5k	781.0±72.5	>1000	>1000	>1000
5l	11.9±7.4	10.8±7.6	542.1±19.1	412.0±37.3
5m	15.7±10.8	40.5±23.6	>1000	112.9 ±7.0
5n	13.8±3.2	36.6±15.9	236.3±4.6	>1000
5o	40.9±10.8	57.5±19.4	>1000	>1000
5p	75.9±21.7	146.2±52.7	>1000	>1000
7a	>1000	>1000	>1000	>1000
7b	>1000	>1000	>1000	>1000
7c	>10000	>10000	277.6±6.4	280.3±0.7
7d	594.9±61.0	1472±762	6.6±0.2	250.9±6.8
IABN	0.05±0.006[j]	0.04±0.004[f]	>1000	419.3±31.5
MABN	0.2±0.05	0.4±0.2	>1000	>1000

[a]Mean±SEM, K_i values were determined by at least three experiments.
[b]K_i values for D_2 receptors were measured on rat $D_{2(long)}$ expressed in Sf9 cells using [^{125}I]IABN as the radioligand.
[c]K_i values for D_3 receptors were measured on rat D_3 expressed in Sf9 cells using [^{125}I]IABN as the radioligand.
[d]K_i values for σ_1 receptors were measured on quinea pig brain membranes using [^{3}H](±)-pentazocine as the radioligand.
[e]K_i values for σ_2 receptors were measured on rat liver membranes using [^{3}H]-DTG as the radioligand in the presence of (±)-pentazocine.
[f]K_d values from Scatchard studies.

moiety at the 1,2,3,4-tetrahydroisoquinolino aromatic ring of compound **5h**, the resulting compound, **5i**, had a 2-fold decrease in affinity for D_2 receptors and no change in affinity for D_3 receptors. As a result, compound **5i** was 7-fold more selective for D_3 receptors (21.2 nM) than for D_2 receptors (143.3 nM).

Replacement of the 1,2,3,4-tetrahydroisoquinolino moiety of **5h** with an indolino moiety to afford compound **5j** resulted in a total loss of binding affinity for both D_2 and D_3 receptors. Similar results were observed for compound **5k**, which had a 1,2,3,4-tetrahydroquinolino moiety. The low binding affinity of compounds **5j** and **5k** for D_2 and D_3 receptors is likely due to the weaker basic properties of the anilino nitrogen of the indoline or 1,2,3,4-tetrahydroquinoline.

Compounds with the piperidino substitution (**5l**, **5m**, and **5n**) showed high affinity (10–40 nM) for both D_2 and D_3 receptors. Compound **5l**, which has a (4-phenyl)-piperidino moiety, displayed similar dopamine D_2/D_3 receptor binding affinities to those of compound **5a**. Extension of the distance between the primary aromatic ring (the 2-phenylimidazole) and the secondary aromatic ring resulted in a greater reduction in the binding affinity for D_3 versus D_2 receptors (**5m** versus **5l**). Compound **5n**, which has the (4-hydroxy-4-parachlorophenyl)piperidino moiety present in haloperidol, maintained affinity for D_2 receptors, but had a reduced affinity for D_2 receptors relative to **5l**. The results of the sigma binding assays revealed that, with the exception of **5a**, **5c**, and **7d**, all compounds shown in Table 1 have a low affinity for sigma receptors. Surprisingly, the oxadiazole analogues **7a**–**7d** had no measurable affinity for dopamine D_2 and D_3 receptors.

Discussion

In a previous study, we reported a series of benzamide analogues possessing a high affinity and marginal selectivity for dopamine D_3 versus D_2 receptors.[19] Molecular modeling studies revealed differences in the stereoelectronic properties of the benzamide-binding region of the D_2 and D_3 receptors. These subtle differences in the electrostatic properties of this class of compounds suggests that replacement of the amide group with a heterocyclic ring with similar steric properties may result in a shift in affinity of these compounds for D_2 and D_3 receptors. The goal of the current study was to determine if substituting an imidazole ring for the amide moiety results in D_3-selective compounds. A previous study demonstrated that imidazole derivatives structurally-similar to the analogues reported here bind with moderate affinity to dopamine D_2 receptors, but the affinity of these compounds for D_3 receptors was not determined.[21] The results of the current study revealed that it is possible to prepare compounds having a moderate affinity and modest selectivity for D_3 versus D_2 receptors. The affinity and selectivity of this class of compounds for both D_2 and D_3 receptors was largely dependent on substitution pattern in the 2-phenyl group and the nature of the amine moiety. The most interesting compound resulting from this study was **5i**, which

had a D_3 affinity of ~20 nM and a 7-fold selectivity for D_3 versus D_2 receptors.

Previous studies have proposed that the dopamine D_2-like receptors have three aromatic binding pockets, termed AR1, AR2, and AR3, as well as a site that recognizes a basic nitrogen atom.[28] The benzamide aromatic rings of compounds such as sulpiride and clebopride are thought to bind to the AR1 aromatic binding pocket (primary aromatic binding site), while the benzylic aromatic groups of MABN, IABN, and related analogues (e.g., clebopride) bind to either the AR2 or the AR3 region (Fig. 1).[17] In this study, two compounds, **5o** and **5p**, were made to test the AR1 binding preference of dopamine D_2/D_3 receptors for the benzamide aromatic ring and the (2-phenyl)imidazole aromatic moiety. Compound **5o** showed 50- to 100-fold higher affinity for both D_2 and D_3 receptors than did the corresponding compound **5e**, and compound **5p** showed significantly higher affinity for D_2 receptors than did the corresponding compound **5f**. Therefore, the results suggest that the benzamide aromatic rings of compounds **5o** and **5p** bind to the AR1 region, while the (2-phenyl)imidazole aromatic moiety bind to either the AR2 or AR3 region. The lower preference of the AR1 region of the D_2/D_3 receptors for the (2-phenyl)imidazole aromatic moiety may also account for the decreased affinity of the imidazole analogues (**5e**, **5f**) for D_2/D_3 receptors when compared to the corresponding benzamide analogues (**5o**, **5p**, MABN, IABN). It is of interest to note that compounds **5h** and **5i**, which have the secondary phenyl ring constrained in a 1,2,3,4-tetrahydro-isoquinoline ring system, have a higher affinity for D_3 versus D_2 receptors, whereas **5m** and **5n** have a higher affinity for D_2 versus D_3 receptors. Molecular modeling studies are currently being conducted as a means of determining if **5h** and **5i** interact with different aromatic binding pockets than **5m** and **5n**.

Several 1,2,4-oxadiazole analogues (**7a**–**d**) were also prepared and their affinity for D_2 and D_3 receptors measured. The binding results showed that these compounds had very low affinity for both D_2 or D_3 receptors. The low binding affinity of the oxadiazole analogues for dopamine D_2/D_3 receptors is likely due to the inability to form an intra-molecular hydrogen bound between the ortho methoxy oxygen and a proton donor. Both the NH proton of the amine in benzamides and the 1-NH proton of the imidazole in (2-phenyl)imidazole analogues can be the proton donor capable of forming an intra-molecular hydrogen bond with the ortho methoxy oxygen atom on the phenyl ring in physiological conditions.[19] The formation of an intra-molecular hydrogen bound forces a coplanar conformation of both the (a) amide and the phenyl ring in benzamides and (b) the imidazole ring and the 2-phenyl aromatic ring of the (2-phenyl)imidazole analogues. Thus, the 1,2,4-oxadiazole analogues would likely adapt a non-coplanar conformation between the imidazole moiety and the phenyl ring in binding conditions.

Results from the sigma receptor binding studies indicated that compounds **5a** and **5d** have a relatively high affinity (17–85 nM) for σ_1 receptors. The bromo substitution at the 5′-position of the phenyl aromatic ring decreased the binding affinity of these analogues for both σ_1 and σ_2 receptors (**5a** versus **5b**, **5c** versus **5d**, and **5e** versus **5f**). The high affinity of **7d** for σ_1 receptors and low affinity for σ_2, D_2, and D_3 receptors suggests that this compound may be a useful lead compound for the development of a σ_1-selective ligand.

In conclusion, a number of imidazole and 1,2,4-oxadiazole analogues were prepared and their affinities for dopamine D_2 and D_3 receptors and sigma receptors were measured using in vitro binding assays. The imidazole analogues had a lower affinity for D_2 and D_3 receptors than the benzamide analogues IABN and MABN. However, imidazole analogues **5h** and **5i** possessed a modest affinity and selectivity for D_3 versus D_2 receptors, whereas **5m** and **5n** had a modest affinity and selectivity for D_2 versus D_3 receptors. These data demonstrate the importance of the amine moiety in binding to D_2 and D_3 receptors. The 1,2,4-oxadiazole analogues were devoid of significant binding affinity for both D_2 and D_3 receptors, which is likely attributed to the inability of the 1,2,4-oxadiazole analogues to form an intra-molecular hydrogen bound. The in vitro binding data of the imidazole analogues was consistent with our previous studies with the benzamides[17–19] that: (a) bromo substitution of the 4-position aromatic ring binding in the AR1 site increases affinity for both D_2 and D_3 receptors, (b) a basic nitrogen atom linked at an appropriate position to the primary phenyl aromatic moiety is required for optimal binding to D_2/D_3 receptors, and (c) a secondary aromatic moiety is beneficial for obtaining high affinity dopamine D_2/D_3 receptor binding. The in vitro binding data for compounds **5a**, **5h**, **5i**, **5m**, and **5n** suggest that it is possible to replace the benzamide moiety with a π-deficient heterocyclic ring and maintain a high affinity for D_2 and D_3 receptors. The observation that **5h** and **5i** have a 3- to 7-fold higher affinity for D_3 versus D_2 receptors suggest that this approach may lead to D_3-selective ligands.

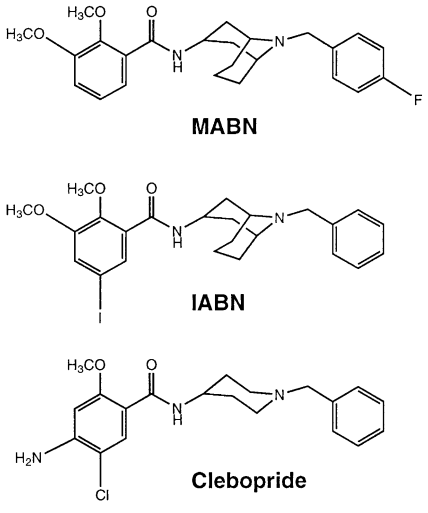


Fig 1. Structures of MABN, IABN, and Clebopride.

Experimental

Chemistry

Melting points were measured on a Fisher–Johns melting point apparatus and are uncorrected. Elemental analyses were performed at Atlantic Microlab, Inc., Norcross, GA, USA. Where molecular formulae were indicated, analyses were found to be within 0.4% of the theoretical values, unless otherwise noted. ^{1}H NMR spectra were recorded at 300 MHz on a Bruker ADVANCE300 spectrometer. All ^{1}H NMR spectra were obtained in either $CDCl_3$ or DMSO-d_6 and results are recorded as parts per million (ppm) downfield to tetramethylsilane (TMS). The following abbreviations are used for multiplicity of NMR signals: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = double doublet, dt = double triplet, dq = double quartet, br = broad. Mass spectrometry studies (high resolution FAB) were conducted by the Washington University Resource for Biomedical and Bio-organic Mass Spectrometry, St. Louis, MO, USA. All starting materials and solvents were purchased from Aldrich, Fisher, or Lancaster, and were used without further purification.

Preparation of 2,3-dimethoxy-5-bromobenzonitrile (1). To a solution of 2,3-dihydroxybenzoic acid (25.0 g, 0.16 mol) in acetic acid (200 mL) was added bromine (25.9 g, 0.16 mol) dropwise. The mixture was stirred at room temperature overnight. The solvent was removed in vacuo to give a solid which was recrystallized from ethyl acetate/hexane to give 2,3-dihydroxy-5-bromobenzoic acid (33.2 g, 88%). Mp 203–204 °C; anal. ($C_7H_5O_4Br$) C, H.

A mixture of 2,3-dihydroxy-5-bromobenzoic acid (25.0 g, 0.11 mol), dimethyl sulfate (48.71 g, 0.38 mol), potassium carbonate (53.4 g, 0.38 mol) in acetone (200 mL) was refluxed overnight. The solid was filtered and the solution was condensed to give a liquid which was than dissolved in methanol (200 mL) and added with NaOH (40%, 12 mL), and refluxed for 2 h. The solvent was removed and the residue was dissolved in water (200 mL) and extracted with ethyl acetate (2×60 mL), the aqueous phase was adjusted to pH ≤ 2 and extracted with ethyl acetate (3×60 mL) and dried over Na_2SO_4. The solvent was removed and the residue was recrystallized from ethyl acetate/hexane to give 2,3-dimethoxy-5-bromobenzoic acid (24.2 g, 86%), mp 199–200 °C. ^{1}H NMR ($CDCl_3$) δ 7.84–7.85 (d, J = 3 Hz, 1H), 7.25–7.26 (d, J = 3 Hz, 1H), 4.07 (s, 3H), 3.93 (s, 3H); analysis ($C_9H_9O_4Br$) C, H.

A solution of 2,3-dimethoxy-5-bromobenzoic acid (20.0 g, 0.08 mol) and thionyl chloride (18.2 g, 0.15 mol) in benzene (200 mL) was stirred at reflux overnight. The solvent was removed and the residue was recrystallized from ethyl acetate/hexane to give 2,3-dimethoxy-5-bromobenzoyl chloride (20.3 g, 95%), mp 65–66 °C. ^{1}H NMR ($CDCl_3$) δ 7.61–7.62 (d, J = 3 Hz, 1H), 7.23–7.24 (d, J = 3 Hz, 1H), 3.90 (s, 6H).

To a solution of 2,3-dimethoxy-5-bromobenzoyl chloride (20.0 g, 0.07 mol) in dry dichloromethane (200 mL) was added *tert*-butylamine (7.3 g, 0.1 mol) and triethylamine (5 mL) dropwise. After stirring overnight at room temperature, the mixture was condensed in vacuo. The residue was dissolved in dichloromethane (100 mL), washed with 0.5 N NaOH, water, and dried over Na_2SO_4. The solvent was removed to afford *N*-*tert*-butyl-2,3-dimethoxy-5-bromobenzamide (22.60 g, 100%). ^{1}H NMR ($CDCl_3$) δ 7.78–7.79 (d, J = 2.4 Hz, 1H), 7.10–7.11 (d, J = 2.5 Hz, 1H), 3.86 (s, 3H), 3.88 (s, 3H), 1.45 (s, 9H).

To a solution of *N*-*tert*-butyl-2,3-dimethoxy-5-bromobenzamide (22.6 g, 0.07 mol) in benzene (100 mL) was added phosphorus oxychloride (109.5 g, 0.7 mol) portion-wise. The mixture was refluxed for 10 h, then the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 (200 mL) and washed with water and dried over Na_2SO_4. The solvent was removed and the residue was recrystallized from ethyl acetate/pentane to give 2,3-dimethoxy-5-bromobenzonitrile (15.3 g, 88%), mp 82–83 °C. ^{1}H NMR ($CDCl_3$) δ 7.25–7.26 (d, J = 3 Hz, 1H), 7.19–7.20 (d, J = 3 Hz, 1H), 4.01 (s, 3H), 3.89 (s, 3H); analysis ($C_9H_8NO_2Br$) C, H, N.

Preparation of 2-(2,3-dimethoxyphenyl)-4-(hydroxymethyl)imidazole (3a). A 2.5 M solution of butyllithium in anhydrous ether (50 mL, 0.125 mol) was added dropwise to a solution of 1,1,1,3,3,3-hexamethyldisilazane (19.37 g, 0.12 mol) in dry ether (200 mL) at 0 °C, and the solution was stirred at 0 °C for 30 min. 2,3-Dimethoxybenzonitrile (8.15 g, 0.05 mol) was then added and the reaction mixture was stirred at room temperature for 4 h. The mixture was poured into ice-cold 2 N HCl (200 mL) and extracted with ether twice. The aqueous phase was adjusted to pH > 10 with 6 N NaOH and extracted with CH_2Cl_2 (3×50 mL) and dried over Na_2SO_4. The solvent was removed and the residue was recrystallized from ethyl acetate/ethanol to give 2,3-dimethoxybenzamidine (5.6 g, 62%), mp 83–85 °C. ^{1}H NMR ($CDCl_3$) δ 7.15–7.18 (dd, J = 1.8, 8 Hz, 1H), 7.07–7.13 (t, J = 4 Hz, 1H), 6.96–6.99 (dd, J = 1.5, 8 Hz, 1H), 5.01 (br s, 3H), 3.89 (s, 3H), 3.87 (s, 3H).

A mixture of 2,3-dimethoxybenzamidine (2.5 g, 0.014 mol), 1,3-dihydroxyacetone dimer (2.5 g, 0.014 mol), and NH_4Cl (3 g, 0.056 mol) in NH_4OH (20 mL) was heated to reflux for 30 min. The mixture was poured into ice-cold water, extracted with CH_2Cl_2, and dried over Na_2SO_4. The solvent was removed and the product was recrystallized from ethyl acetate to give 2-(2,3-dimethoxyphenyl)-4-(hydroxymethyl)imidazole (1.98 g, 61%), mp 154–155 °C. ^{1}H NMR ($CDCl_3$) δ 7.81–7.84 (dd, J = 1.2, 6.7 Hz, 1H), 7.12–7.17 (dt, J = 1, 8 Hz, 1H), 7.06 (s, 1H), 6.89–6.92 (d, J = 8 Hz, 1H), 4.72 (s, 2H), 3.91 (s, 6H); analysis ($C_{12}H_{14}N_2O_3$) C, H, N.

2-(2,3-Dimethoxy-5-bromophenyl)-4-(hydroxymethyl)imidazole (3b). Compound **3b** was obtained by the same method as described in **3a** in 34% yield, mp 162–163 °C. ^{1}H NMR ($CDCl_3$) δ 7.99–8.00 (d, J = 3 Hz, 1H), 7.07 (s, 1H), 7.00–7.01 (d, J = 2.1 Hz, 1H), 4.71 (s, 2H), 3.91 (s, 3H), 3.90 (s, 3H); analysis ($C_{12}H_{13}N_2O_3Br$) C, H, N.

Preparation of 2-(2,3-dimethoxyphenyl)imidazole-4-carboxaldehyde (4a). To a solution of 2-(2,3-dimethoxy-

phenyl)-4-(hydroxymethyl)imidazole (0.23 g, 1.0 mmol) in CH_2Cl_2 (20 mL) was added pyridinium chlorochromate (0.54 g, 2.5 mmol). After stirring at room temperature for 30 min, the solid was filtered off, the solution was washed with 1 N NaOH, water, and dried over Na_2SO_4. The solvent was removed and the product was purified by silica gel column to give 2-(2,3-dimethoxyphenyl)imidazole-4-carboxaldehyde (0.12 g, 52%), mp 129–130 °C. ^{1}H NMR ($CDCl_3$) δ 9.74 (s, 1H), 7.83–7.93 (m, 2H), 7.16–7.22 (t, J = 9 Hz, 1H), 7.00–7.03 (d, J = 9 Hz, 1H), 4.00 (s, 3H), 3.93 (s, 3H); anal. ($C_{12}H_{12}N_2O_3$) C, H, N.

2-(2,3-Dimethoxy-5-bromophenyl)imidazole-4-carboxaldehyde (4b). Compound **4b** was obtained by the same method as described in **4a** in 60% yield, mp 142–143 °C. ^{1}H NMR ($CDCl_3$) δ 9.74 (s, 1H), 8.07–8.08 (dd, J = 2, 10.6 Hz, 1H), 7.88 (s, 1H), 7.10–7.11 (dd, J = 2.3, 8.6 Hz, 1H), 3.99 (s, 3H), 3.92 (s, 3H); anal. ($C_{12}H_{11}N_2O_3Br$) C, H, N.

Preparation of 2-(2,3-dimethoxy-5-bromophenyl)-4-(*N*,*N*-diethylaminomethyl)imidazole (5b). A solution of 2-(2,3-dimethoxy-5-bromophenyl)-4-(hydroxymethyl)-imidazole (0.16 g, 0.5 mmol) thionyl chloride (0.6 g, 5.0 mmol) in CH_2Cl_2 (20 mL) was heated at reflux for 30 min. The solvent was removed in vacuo to afford a brown solid that was dissolved in CH_2Cl_2 (20 mL). Diethylamine (0.06 g, 0.8 mmol) and triethylamine (0.5 mL), was added and the mixture was stirred at room temperature overnight. Solvent was removed in vacuo and the residue was dissolved in CH_2Cl_2 (30 mL) and washed with 0.5 N NaOH, water and dried over Na_2SO_4. The solvent was removed and the residue was purified by silica gel column chromatography and eluted with $CHCl_3$/ethanol (9:1) to give an oil that was then converted into the oxalate salt (0.23 g, 83%), mp 162–164 °C. ^{1}H NMR (free amine in $CDCl_3$) δ 8.00–8.10 (br s, 1H), 6.97–7.10 (m, 2H), 3.90 (s, 3H), 3.89 (s, 3H), 3.62 (s, 2H), 2.50–2.60 (m, 4H), 1.00–1.08 (t, J = 4 Hz, 6H); anal. ($C_{20}H_{26}N_3O_{10}Br \cdot 1/2\ H_2O$) C, H, N.

Preparation of 2-(2,3-dimethoxyphenyl)-4-(1-benzylpiperidin-4-ylaminomethyl)imidazole (5c). A solution of 2 - (2,3 - dimethoxyphenyl)imidazole - 4 - carboxaldehyde (0.23 g, 1.0 mmol) and 4-amino-1-benzylpiperidine (0.19 g, 1.0 mmol) in methanol (20 mL) was stirred at room temperature for 2 h, then $NaBH_3CN$ (0.06 g, 1.0 mmol) was added and the reaction mixture stirred at room temperature overnight. The solvent was removed and the residue was dissolved in CH_2Cl_2 (30 mL), washed with 0.5 N NaOH, water, and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography ($CHCl_3$/ethanol = 8:2) to give an oil that was then converted into the corresponding hydrochloride salt (0.35 g, 67%), mp 173–176 °C. ^{1}H NMR (DMSO-d_6) δ 8.00 (br s, 1H), 7.83–7.85 (m, 1H), 7.71–7.74 (br s, 1H), 7.63 (b, 1H), 7.36–7.43 (m, 5H), 4.58 (s, 2H), 4.27 (s, 2H), 4.05 (s, 3H), 3.93 (s, 3H), 3.70 (m, 1H), 3.45–3.49 (d, J = 12 Hz, 2H), 2.50-2.60 (m, 6H); ms ($C_{24}H_{30}N_4O_2$, M_r = 406.2369) 407.2454 (m + 1).

2-(2,3-Dimethoxy-5-bromophenyl)-4-(1-benzylpiperidin-4-yl-aminomethyl)-imidazole (5d). Twenty-seven percent yield from 2-(2,3-dimethoxy-5-bromophenyl)imidazole-4-carboxaldehyde (**4b**), mp 159–161 °C. ^{1}H NMR (free amine in $CDCl_3$) δ 7.99 (d, J = 3 Hz, 1H), 7.22–7.31 (m, 5H), 7.04 (d, J = 3 Hz, 1H), 6.96 (s, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.81 (br s, 2H), 3.78 (m, 1H), 3.48 (s, 2H), 2.91–2.95 (d, J = 12 Hz, 2H), 1.87–2.00 (m, 4H), 1.67–1.73 (m, 2H); analysis ($C_{24}H_{29}N_4O_2Br \cdot 2H_2O$) C, H, N.

2-(2,3-Dimethoxyphenyl)-4-(9-benzylazabicyclo[3.3.1]nonan-3β-ylaminomethyl)imidazole (5e). Thirty percent yield from 2-(2,3-dimethoxyphenyl)imidazole-4-carboxaldehyde (**4a**), mp 178–180 °C (HCl salt). ^{1}H NMR (DMSO-d_6) δ 7.74–7.78 (dd, J = 1.4, 8 Hz, 1H), 7.40–7.50 (br s, 1H), 7.22–7.32 (m, 5H), 4.18 (s, 2H), 3.90–4.05 (d, J = 12 Hz, 9H), 3.11–3.16 (br s, 2H), 2.30–2.45 (br s, 2H), 1.95–2.10 (m, 4H), 1.45–1.55 (m, 4H); ms ($C_{27}H_{34}N_4O_2$, M_r = 446.2682) 447.2765 (m + 1). Anal. ($C_{27}H_{37}N_4O_2Cl$) C, H, N.

2-(2,3-Dimethoxy-5-bromophenyl)-4-(9-benzylazabicyclo[3.3.1]nonan-3β-ylaminomethyl)imidazole (5f). Forty-six percent yield from 2-(2,3-dimethoxy-5-bromophenyl)imidazole-4-carboxaldehyde (**4b**), mp 193–195 °C. ^{1}H NMR ($CDCl_3$) δ 7.91–7.92 (d, J = 1.9 Hz, 1H), 7.47 (br s, 1H), 7.22–7.30 (m, 5H), 6.99–7.00 (d, J = 1.9 Hz, 1H), 4.15–4.22 (b, 2H), 3.98 (br s, 2H), 3.89 (s, 6H) 3.05–3.15 (br s, 2H), 2.35–2.45 (br s, 2H), 1.90–2.10 (m, 4H), 1.45–1.60 (m, 4H); ms ($C_{27}H_{33}N_4O_2Br$, M_r = 524.1787) 525.1879 (m + 1).

2-(2,3-Dimethoxyphenyl)-4-(1,2,3,4-tetrahydroisoquinolino-aminomethyl)imidazole (5g). Fifty-six percent yield from 2-(2,3-dimethoxyphenyl)-4-(hydroxymethyl)-imidazole (**3a**), mp 163–165 °C (HCl salt). ^{1}H NMR ($CDCl_3$) δ 7.85–7.90 (b, 1H), 7.05–7.20 (m, 5H), 6.95–7.03 (m, 1H), 6.88–6.91 (d, J = 8 Hz, 1H), 3.90 (s, 6H), 3.85 (br s, 2H), 3.78 (s, 2H), 2.81–2.95 (br s, 4H); ms ($C_{21}H_{23}N_3O_2$, M_r = 349.1790) 350.1875 (m + 1).

2-(2,3-Dimethoxy-5-bromophenyl)-4-(1,2,3,4-tetrahydroisoquinolino-aminomethyl)imidazole (5h). Sixty-two percent yield 2-(2,3-dimethoxy-5-bromophenyl)-4-(hydroxy-methyl)imidazole (**3b**), mp 150–152 °C. ^{1}H NMR ($CDCl_3$) δ 8.00–8.10 (br s, 1H), 6.95–7.15 (m, 6H), 3.89 (s, 6H), 3.82 (br s, 2H), 3.77 (s, 2H), 2.80–2.94 (br s, 4H); ms ($C_{21}H_{22}N_3O_2Br$, M_r = 427.0895) 428.0966 (m + 1).

2-(2,3-Dimethoxy-5-bromophenyl)-4-(6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinolinoaminomethyl)imidazole (5i). Seventy-five percent yield from 2-(2,3-dimethoxy-5-bromophenyl)-4-(hydroxymethyl)imidazole (**3b**), mp 103–105 °C. ^{1}H NMR ($CDCl_3$) δ 8.00–8.08 (dd, J = 2, 21 Hz, 1H), 7.06–7.09 (dd, J = 2, 8 Hz, 1H), 6.97–7.05 (m, 1H), 6.59–6.60 (d, J = 3 Hz, 1H), 6.48–6.52 (d, J = 11 Hz, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 3.85 (s, 3H), 3.83 (s, 3H), 3.82 (s, 2H), 3.81 (s, 2H), 2.76–2.85 (m, 4H); anal. ($C_{23}H_{26}N_3O_4Br \cdot H_2O$) C, H, N.

2-(2,3-Dimethoxy-5-bromophenyl)-4-(indolinoaminomethyl)imidazole (5j). Eighty-four percent yield from 2-(2,3-dimethoxy-5-bromophenyl)-4-(hydroxymethyl)imi-

dazole (**3b**), mp 131–132 °C. ^{1}H NMR ($CDCl_3$) δ 7.95–8.05 (br s, 1H), 6.95–7.15 (m, 5H), 6.60–6.75 (br s, 2H), 4.35 (s, 2H), 3.90 (s, 6H), 3.43–3.50 (t, J = 5 Hz, 2H), 2.93–3.00 (t, J = 5 Hz, 2H); anal. ($C_{20}H_{20}N_3O_2Br$) C, H, N.

2-(2,3-Dimethoxy-5-bromophenyl)-4-(1,2,3,4-tetrahydroquinolinoamino-methyl)imidazole (5k). Ninety-five percent yield from 2-(2,3-dimethoxy-5-bromophenyl)-4-(hydroxy-methyl)imidazole (**3b**), mp 120–121 °C. ^{1}H NMR ($CDCl_3$) δ 7.95–8.02 (br s, 1H), 6.93–7.02 (m, 4H), 6.82–6.86 (br s, 1H), 6.65–6.68 (br s, 1H), 4.53 (s, 2H), 3.88–3.90 (d, J = 5.5 Hz, 6H), 3.42–3.52 (m, 2H), 2.73–2.83 (m, 2H), 1.95–2.05 (m, 2H); anal. ($C_{20}H_{22}N_3O_2Br$) C, H, N.

2-(2,3-Dimethoxy-5-bromophenyl)-4-(4-phenylpiperidinoamino-methyl)imidazole (5l). Eighty percent yield from 2-(2,3-dimethoxy-5-bromophenyl)-4-(hydroxymethyl)imidazole (**3b**), mp 130–131 °C. ^{1}H NMR ($CDCl_3$) δ 7.18–7.34 (m, 6H), 6.96–7.05 (m, 2H), 3.88–3.92 (d, J = 1.3 Hz, 9H), 3.60–3.65 (d, J = 8 Hz, 4H), 3.16–3.24 (d, J = 8 Hz, 2H), 2.98–3.06 (d, J = 8 Hz, 2H); anal. ($C_{23}H_{26}N_3O_2Br$) C, H, N.

2-(2,3-Dimethoxy-5-bromophenyl)-4-(4-benzylpiperidinoamino-methyl)imidazole (5m). Seventy percent yield from 2-(2,3-dimethoxy-5-bromophenyl)-4-(hydroxymethyl)imidazole (**3b**), mp 156–158 °C (HCl salt). ^{1}H NMR ($CDCl_3$) δ 8.22–8.25 (d, J = 3 Hz, 1H), 6.97–7.33 (m, 7H), 4.82–4.88 (s, 2H), 4.22 (s, 3H), 3.90 (s, 3H), 3.20–3.45 (m, 4H), 2.56–2.63 (d, J = 8 Hz, 2H), 1.70–1.90 (m, 5H); anal. ($C_{24}H_{30}N_3O_2BrCl_2 \cdot 0.25H_2O$) C, H, N.

2-(2,3-Dimethoxy-5-bromophenyl)-4-(4-hydroxy-4-(4-chlorophenyl)-piperidinoaminomethyl)imidazole (5n). Sixty-seven percent yield from 2-(2,3-dimethoxy-5-bromophenyl)-4-(hydroxymethyl)imidazole (**3b**), mp 90–92 °C. ^{1}H NMR ($CDCl_3$) δ 7.97–8.07 (d, J = 21 Hz, 1H), 7.42–7.46 (d, J = 8 Hz, 2H), 7.29–7.33 (d, J = 8 Hz, 2H), 6.97–7.10 (m, 2H), 3.87–3.94 (d, J = 2 Hz, 8H), 3.63–3.72 (d, J = 9 Hz, 2H), 2.52–2.60 (m, 2H), 1.70–1.85 (m, 4H); anal. ($C_{23}H_{25}N_3O_3BrCl$) C, H, N.

2-(2,3-Dimethoxyphenyl)-4-(3β-(2,3-dimethoxybenzamido)-bicyclo[3.3.1]nonan-9-azamethyl)imidazole (5o). Twenty-nine percent yield from 2-(2,3-dimethoxyphenyl)-4-(hydroxymet hyl)imidazole (**3a**), mp 65–66 °C. ^{1}H NMR ($CDCl_3$) δ 7.79–7.83 (dd, J = 1.5, 8 Hz, 1H), 7.64–7.68 (dd, J = 1.6, 8 Hz, 1H), 7.26 (s, 1H), 7.10–7.16 (m, 2H), 7.02–7.06 (dd, J = 1.5, 8 Hz, 1H), 6.88–6.92 (dd, J = 1.4, 8 Hz, 1H), 4.90–5.00 (m, 1H), 3.88–3.95 (m, 14H), 2.88–2.95 (br s, 2H), 1.60–2.10 (m, 10H); ms ($C_{29}H_{36}N_4O_5$, M_r = 520.2686) 521.2787 (m + 1).

2-(2,3-Dimethoxy-5-bromophenyl)-4-(3β-(2,3-dimethoxybenzamido)-bicyclo[3.3.1]nonan-9-azamethyl)imidazole (5p). Eighteen percent yield from 2-(2,3-dimethoxy-5-bromophenyl)-4-(hydroxymethyl)imidazole (**3b**), mp 83–84 °C. ^{1}H NMR ($CDCl_3$) δ 7.95–8.05 (br s, 1H), 7.64–7.67 (d, J = 8 Hz, 1H), 7.10–7.20 (m, 1H), 6.95–7.05 (m, 3H), 4.90–5.00 (m, 1H), 3.85–3.95 (m, 14H), 2.90–3.05 (br s, 2H), 1.60–2.10 (m, 10H); ms ($C_{29}H_{35}N_4O_5Br$, M_r = 598.1791) 599.1864 (m + 1).

Preparation of 2,3-dimethoxybenzamide oxime (6). A mixture of 2,3-dimethoxybenzonitrile (6.53 g, 0.04 mol), hydroxylamine hydrochloride (8.34 g, 0.12 mol), potassium carbonate (11.06 g, 0.08 mol) and ethanol (100 mL) was refluxed for 16 h. The mixture was poured into ice-cold water and 2 N NaOH was added to adjust the pH ≥ 12. The product was extracted with CH_2Cl_2, washed with water and dried over Na_2SO_4. The solvent was removed and the residue was recrystallized from ethyl acetate/hexane to give 2,3-dimethoxybenzamide oxime (5.38 g, 68%), mp 149–151 °C. ^{1}H NMR ($CDCl_3$) δ 7.24–7.27 (dd, J = 1.6, 8 Hz, 1H), 7.04–7.10 (t, J = 8 Hz, 1H), 6.95–6.98 (dd, J = 1.6, 8 Hz, 1H), 5.50 (br s, 2H), 3.89 (s, 3H), 3.85 (s, 3H); anal. ($C_9H_{12}N_2O_3$) C, H, N.

Preparation of 3-(2,3-dimethoxyphenyl)-5-(1-benzylpyrrolidin-2-yl)-1,2,4-oxadiazole (7a). A solution of 2,3-dimethoxybenzamide oxime (0.4 g, 2.0 mmol) and NaH (0.05 g, 2.0 mmol) in THF (25 mL) was stirred under refluxing for 1 h. After cooling, the mixture was added with *N*-benzyl-DL-Proline methyl ester (0.44 g, 2.0 mmol) and 4 Å molecular sieves (2.0 g) and continued to stir under refluxing overnight. The mixture was poured into ice-cold water and extracted with CH_2Cl_2, washed with water and dried over Na_2SO_4. The solvent was removed and the residue was purified by silica gel column to afford an oil which was converted into the corresponding oxalic salt and recrystallized from ethyl acetate/ethanol to give 3-(2,3-dimethoxyphenyl)-5-(1-benzylpyrrolidin-2-yl)-1,2,4-oxadiazole oxalate (0.45 g, 49%), mp 62–65 °C. ^{1}H NMR (free amine in $CDCl_3$) δ 7.52–7.56 (dd, J = 1.6, 8 Hz, 1H), 7.20–7.34 (m, 5H), 7.13–7.19 (t, J = 8 Hz, 1H), 7.04–7.08 (dd, J = 1.6, 8 Hz, 1H), 4.07–4.12 (dd, J = 2.5, 6 Hz, 1H), 3.94 (s, 3H), 3.92 (s, 5H), 3.07–3.14 (m, 1H), 2.51–2.60 (m, 1H), 2.30–2.36 (m, 1H), 2.20–2.27 (m, 1H), 2.02–2.12 (m, 1H), 1.88–1.94 (m, 1H); anal. ($C_{23}H_{25}N_3O_7 \cdot H_2O$) C, H, N.

3-(2,3-Dimethoxyphenyl)-5-(1-benzylpiperidin-2-yl)-1,2,4-oxadiazole (7b). Fifty-seven percent yield (an oil) from 2,3-dimethoxybenzamide oxime (**6**). ^{1}H NMR (free amine in $CDCl_3$) δ 7.58–7.62 (dd, J = 1.5, 8 Hz, 1H), 7.23–7.35 (m, 5H), 7.15–7.21 (t, J = 8 Hz, 1H), 7.05–7.09 (dd, J = 1.5, 8 Hz, 1H), 4.05–4.09 (t, J = 6 Hz, 1H), 3.96 (s, 3H), 3.93 (s, 3H), 3.50 (d, J = 13 Hz, 1H), 3.25 (d, J = 13 Hz, 1H), 2.95–3.02 (m, 1H), 2.32–2.40 (m, 1H), 1.99–2.05 (m, 2H), 1.76–1.84 (m, 1H), 1.62–1.68 (m, 2H), 1.45–1.56 (m, 1H); anal. ($C_{22}H_{25}N_3O_3$) C, H, N.

3-(2,3-Dimethoxyphenyl)-5-(1-benzylpiperidin-3-yl)-1,2,4-oxadiazole (7c). Sixty-six percent yield from 2,3-dimethoxybenzamide oxime (**6**), mp 139–140 °C (oxalate). ^{1}H NMR (free amine in $CDCl_3$) δ 7.48–7.51 (dd, J = 1.5, 8 Hz, 1H), 7.20–7.32 (m, 5H), 7.13–7.18 (t, J = 8 Hz, 1H), 7.03–7.06 (dd, J = 1.5, 8 Hz, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 3.58 (s, 2H), 3.24–3.33 (m, 1H), 3.13–3.21 (m, 1H), 2.82–2.62 (m, 1H), 2.38–2.45 (m, 1H), 2.09–2.20 (m, 2H), 1.78–1.86 (m, 2H); anal. ($C_{24}H_{27}N_3O_7$) C, H, N.

3-(2,3-Dimethoxyphenyl)-5-(1-benzylpiperidin-4-yl)-1,2,4-oxadiazole (7d). 53% yield from 2,3-dimethoxybenzamide oxime (**6**), mp 69–70 °C, ^{1}H NMR (free

amine in $CDCl_3$) δ 7.49–7.53 (dd, $J = 1.5$, 8 Hz, 1H), 7.25–7.34 (m, 5H), 7.13–7.18 (t, J = 8 Hz, 1H), 7.03–7.07 (dd, $J = 1.5$, 8 Hz, 1H), 3.93 (s, 3H), 3.91 (s, 3H), 3.54 (s, 2H), 2.93–3.06 (m, 3H), 1.96–2.21 (m, 6H); analysis ($C_{22}H_{25}N_3O_3$) C, H, N.

In vitro binding assays

In vitro dopamine receptor binding studies were conducted using membranes prepared from *Spodoptera frugiperda* (Sf9) cells that express a high density of either rat $D_{2(long)}$ or rat D_3 receptors. The radioligand used was [^{125}I]IABN and the assay conditions were as previously described.[17] The K_i values were calculated from the corresponding IC_{50} values using the method of Cheng and Prusoff.[26]

In vitro σ_1 receptor binding affinity was measured in guinea pig brain membranes (Rockland Biological, Gilbertsville, PA, USA) using the σ_1-selective radioligand, [^{3}H](+)-pentazocine (DuPont-NEN, Bilerica, MA, USA) according to the methods as described previously.[27] In vitro σ_2 receptor binding affinity was measured in rat liver membranes using [^{3}H]DTG (DuPont-NEN, Bilerica, MA) as the radioligand in the presence of (+)-pentazocine (100 nM) as previously described.[27]

Elemental analyses

Compd	Form	Element	Calcd	Found
5b	HCl·0.5H_2O	C	43.10	43.16
		H	4.88	4.84
		N	7.54	7.19
5d	Free base·2H_2O	C	55.28	55.27
		H	5.60	5.81
		N	10.74	10.70
5e	HCl	C	61.54	61.50
		H	5.87	5.91
		N	6.53	6.53
5i	Free base·H_2O	C	55.44	54.51
		H	5.57	5.58
		N	8.30	8.19
5j	Free base	C	57.98	58.09
		H	4.87	4.92
		N	10.14	10.07
5k	Free base	C	58.88	58.96
		H	5.18	5.16
		N	9.81	9.72
5l	Free base	C	60.53	60.63
		H	5.74	5.83
		N	9.21	9.13
5m	HCl·1/4H_2O	C	52.62	52.63
		H	5.61	5.68
		N	7.67	7.62
5n	Free base	C	54.40	54.29
		H	4.97	4.98
		N	8.29	8.23
6	—	C	55.09	55.20
		H	6.16	6.17
		N	14.28	14.26
7a	Oxalate salt·H_2O	C	58.34	58.01
		H	5.75	5.42
		N	8.87	8.44
7b	Free base	C	69.64	69.79
		H	6.64	6.77
		N	11.07	10.82
7c	Oxalate salt	C	61.40	61.36
		H	5.80	5.83
		N	8.95	8.90
7d	Free base	C	69.64	69.73
		H	6.64	6.58
		N	11.07	10.97

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