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Synthesis of 2-(5-Bromo-2,3-dimethoxyphenyl)-5-(aminomethyl)-1*H*-pyrrole Analogues and Their Binding Affinities for Dopamine D_2, D_3, and D_4 Receptors

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Abstract—A series of 2-(5-bromo-2,3-dimethoxyphenyl)-5-(aminomethyl)-1*H*-pyrrole analogues was prepared and their affinity for dopamine D_2, D_3, and D_4 receptors was measured using in vitro binding assays. The results of receptor binding studies indicated that the incorporation of a pyrrole moiety between the phenyl ring and the basic nitrogen resulted in a significant increase in the selectivity for dopamine D_3 receptors. The most selective compound in this series is 2-(5-bromo-2,3-dimethoxyphenyl)-5-(2-(3-pyridal)piperidinyl)methyl-1*H*-pyrrole (**6p**), which has a D_3 receptor affinity of 4.3 nM, a 20-fold selectivity for D_3 versus D_2 receptors, and a 300-fold selectivity for D_3 versus D_4 receptors. This compound is predicted to be a useful ligand for studying the functional role of dopamine D_3 receptors in vivo.

Introduction

Mulitple neurological and neuropsychiatric disorders, including Parkinson's disease. Tourette's syndrome, tardive dyskinesia, schizophrenia, schizoaffective disorders and addiction to psychostimulants, have been linked to an alteration in the function of the dopaminergic system.[1–3] There are two major pharmacologic classes of receptors that mediate dopaminergic neurotransmission, dopamine D_1-like (D_1, D_5) and D_2-like (D_2, D_3, and D_4) receptors.[1–3] Agonist stimulation of the D_1-like receptors causes an increase in adenylyl cyclase activity and a stimulation of K^+ efflux.[2] Agonist activation of the D_2-like receptors results in an inhibition of adenylyl cyclase activity, an increase in the release of arachadonic acid, and an increase in phosphatidylinositol hydrolysis.[2] A complete understanding of the pharmacological and physiological roles of the different subtypes of the D_1-like and D_2-like receptors has been hindered by a lack of compounds with selectivity for each individual dopamine subtype.

The clinical effects of antipsychotics are thought to be due to their action on the D_2-like receptors in the mesolimbic system, whereas the extrapyramidal side effects are thought to result after chronic blockade of D_2-like receptors in the striatrum.[1,3] The localization of D_3 receptors in the limbic regions of brain suggest that this receptor subtype may be a target for the development of antipsychotics, with a reduced risk of causing extrapyramidal side effects.[1,4–6] This hypothesis is supported by the observation that most typical antipsychotics display a higher affinity for D_2 versus D_3 receptors and have a tendency to produce extrapyramidal symptoms.[1,5] In contrast, atypical antipsychotics have a high affinity for both D_2 and D_3 receptors and a low risk of antipsychotic side effects.[5,6] Therefore, a dopamine antagonist that binds with high affinity at D_3 receptors and a lower affinity at D_2 receptors is predicted to be a useful antipsychotic with a decreased probability of causing extrapyramidal side effects. A number of recent studies have also indicated that D_3 receptor stimulation may mediate the reinforcing effects of cocaine.[7–10] Therefore, D_3 receptor antagonists may be useful for the treatment of cocaine abuse.[8–10]

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Recently, we reported a number of naphthamide analogues that bind with high affinity at dopamine D_3 receptors with a reduced affinity for D_2 receptors.[11] Unfortunately, the majority of these compounds also possessed a high affinity for sigma receptors, limiting their utility as dopamine D_3 receptor probes. In a subsequent study, we reported the synthesis and in vitro binding of a number of imidazole analogues having a modest D_3 receptor affinity and a reduced affinity for dopamine D_2 receptors.[12] These compounds possessed a low affinity for sigma receptors, indicating that they may be useful agents for studying the function of dopamine D_3 receptors in vivo. For example, compound **1c** (Fig. 1) has a 4-fold higher affinity for D_3 versus D_2 receptors and a negligible affinity for σ_1 and σ_2 receptors (Table 1).

Previous studies have shown that replacing the benzamide moiety of sultopride with a pyrrole ring (i.e., DU 122290; Fig. 1) resulted in an improvement in the D_3 selectivity of this class of compounds.[13] This study lead to the identification of a number of pyrrole analogues possessing a modest affinity and selectivity for D_3 versus D_2 receptors.[14,15] The goal of the current study was to replace the imidazole moiety of compounds such as **1** with a pyrrole ring in order to determine the effect of this structural change on D_3, D_2, σ_1, and σ_2 receptor affinity. In addition, in vitro binding assays were conducted on a number of D_3-selective compounds in order to determine their affinity for dopamine D_4 receptors. The results of this study revealed a number of compounds having a high affinity for dopamine D_3 receptors versus D_2 and D_4 receptors. All compounds tested had low affinity for σ_1 and σ_2 receptors. Several of the compounds reported below are expected to be useful probes in studying the functional role of dopamine D_3 receptors in vivo.

Results

Chemistry

The synthesis of 2-(2,3-dimethoxyphenyl)-1*H*-pyrrole and 2-(5-bromo-2,3-dimethoxyphenyl)-1*H*-pyrrole was accomplished via the sequence of reactions outlined in Scheme 1. Mannich reaction with the appropriate secondary amine gave the final product in moderate to high yield. The corresponding 2-(2-(4-bromo-1-methoxynaphthyl)-1*H*-pyrrole analogues were synthesized in a similar manner as outlined in Scheme 2.

Receptor binding

The in vitro receptor binding results are shown in Tables 1 and 2. The binding affinity of compounds **5a** was 44.6 nM for D_2 receptors, and 99.4 nM for D_3 receptors. Compound **6a**, which contains a 5-bromo substitution on the benzamide aromatic ring, displayed a modest in affinity for D_2 receptors and a 26-fold increase in affinity for dopamine D_3 receptors in comparison with the binding data of compound **5a**. These results are consistent with our previous study on structurally-related imidazole analogues.[12] Addition of a 6,7-dimethoxy group in the 1,2,3,4-tetrahydroisoquinoline moiety of **6a** (i.e., **6b**) did not alter the affinity for D_2 and D_3 receptors. However, this substitution resulted in a 2.5-fold reduction in affinity for dopamine D_4 receptors (Table 2). Furthermore, a comparison of the in vitro binding affinity of **6b** versus that of **1b** (Table 2) indicated that substitution of the imidazole ring with a pyrrole results in an improvement in affinity for D_2 and D_3 receptors and an increase in D_3 selectivity. Substitution of the 1-position of the 1,2,3,4-tetrahydroisoquinoline moiety of **6b** with a methyl group had no effect on D_2 receptor affinity but resulted in a 6-fold reduction in D_3 affinity. This is in

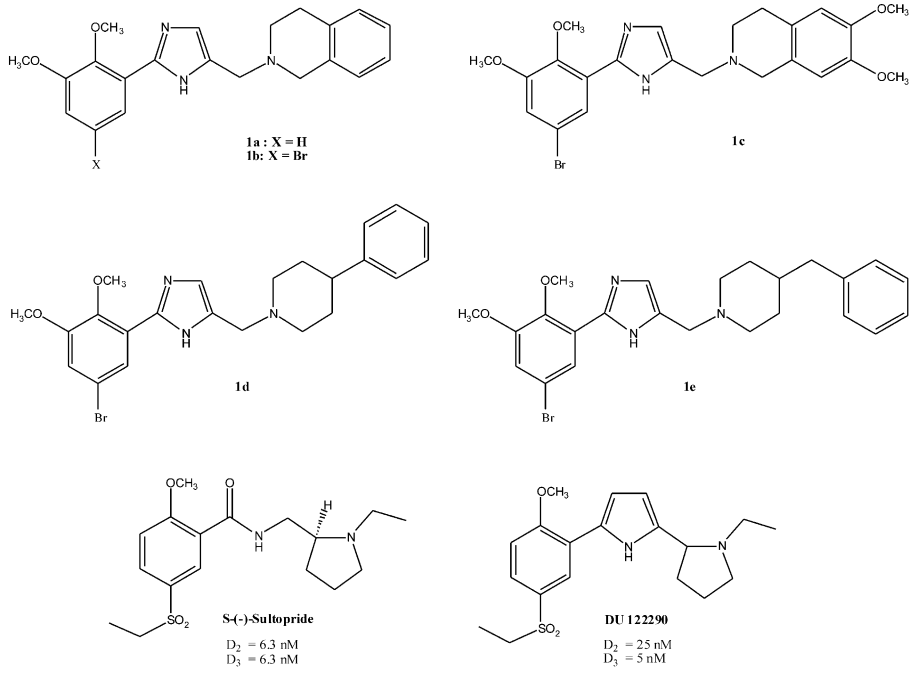


Figure 1.

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	44.6±11.8	99.4±19.8	ND	ND
6a	29.5±1.5	3.8±1.2	>1000	>1000
6b	33.4±6.0	3.9±0.5	>1000	460±27
6c	26.3±4.8	23.8±7.3	>1000	500±11
6d	26.2±12.8	8.6±3.0	>1000	52±5
6e	373.0±40.0	1560±165	>1000	>1000
6f	51.2±12.0	12.0±6.7	>1000	>1000
6g	6.6±0.6	0.6±0.2	275±22	704±21
6h	13,920±3150	5425±1630	136±8	286±11
6i	19.0±2.6	1.9±0.6	166±31	512±10
6j	10.9±4.1	5.4±3.8	167±14	219±36
6k	22.3±3.0	14.1±0.9	112±4	352±7
6l	27.8±11.0	2.6±21.4	>1000	>1000
6m	135.6±1.9	98.4±23.7	>1000	>1000
6n	31.5±6.7	21.0±10.7	>1000	>1000
6o	34.4±5.8	14.5±5.7	>1000	>1000
6p	86.8±7.3	4.3±2.5	>1000	>1000
6q	17.4±1.2	1.7±0.6	390±38	307±12
6r	169.1±15.1	21.9±2.8	>1000	>1000
11a	303.0±52.0	59.5±3.7	>1000	26±2
11b	253.6±54.2	20.1±1.8	>1000	>1000
11c	354.2±41.4	27.5±2.0	>1000	>1000
11d	198.7±137.0	35.2±8.9	309±6	87±6
1a	315.5±140	664±148	>1000	>1000
1b	78.2±29.0	23.8±11.0	>1000	>1000
1c	143.0±48.7	21.2±4.7	>1000	>1000
1d	11.9±7.4	10.8±7.6	542±19	>1000
1e	15.7±10.8	40.5±23.6	>1000	412±37

[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 guinea 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.

contrast to methyl substitution in the 3-position of the 1,2,3,4-tetrahydroisoquinoline moiety (**6d**), which possessed an affinity for D_2 and D_3 receptors similar to **6b**. Surprisingly, addition of a phenyl group in the 1-position of the 1,2,3,4-tetrahydroisoquinoline (**6f**) had a lower effect on D_2 and D_3 receptor affinity than the corresponding methyl substitution (i.e., compare **6b** versus **6f** and **6b** vs **6c**).

Compounds **6m**, **6n**, and **6o** were prepared to explore the effect of replacing the benzene ring of **6a** with aromatic rings of increased steric demand. This substitution generally led to a decreased in affinity for D_3 receptors. For example, the 4,6-benzo-1,2,3,4-tetrahydroisoquinoline analogue (**6m**) had a significantly lower affinity for D_2 and D_3 receptors relative to that of compound **6a**. The two 1,2,3,4-tetrahydro-9*H*-pyrido[3,4-b]bindole analogues, **6n** and **6o**, had a similar D_2 affinity to **6a**. However, both **6n** and **6o** had a lower affinity for D_3 receptors relative to **6a**.

The most potent analogue in this series of compounds was the diethylamino compound, **6g**, which had a subnanomolar affinity for D_3 receptor and a 10-fold selectivity for D_3 versus D_2 receptors and a 20-fold selectivity for D_3 versus D_4 receptors (Table 2). Addition of a phenyl group to give the corresponding dibenzyl analogue, **6h**, resulted in a complete loss in affinity for both D_2 and D_3 receptors.

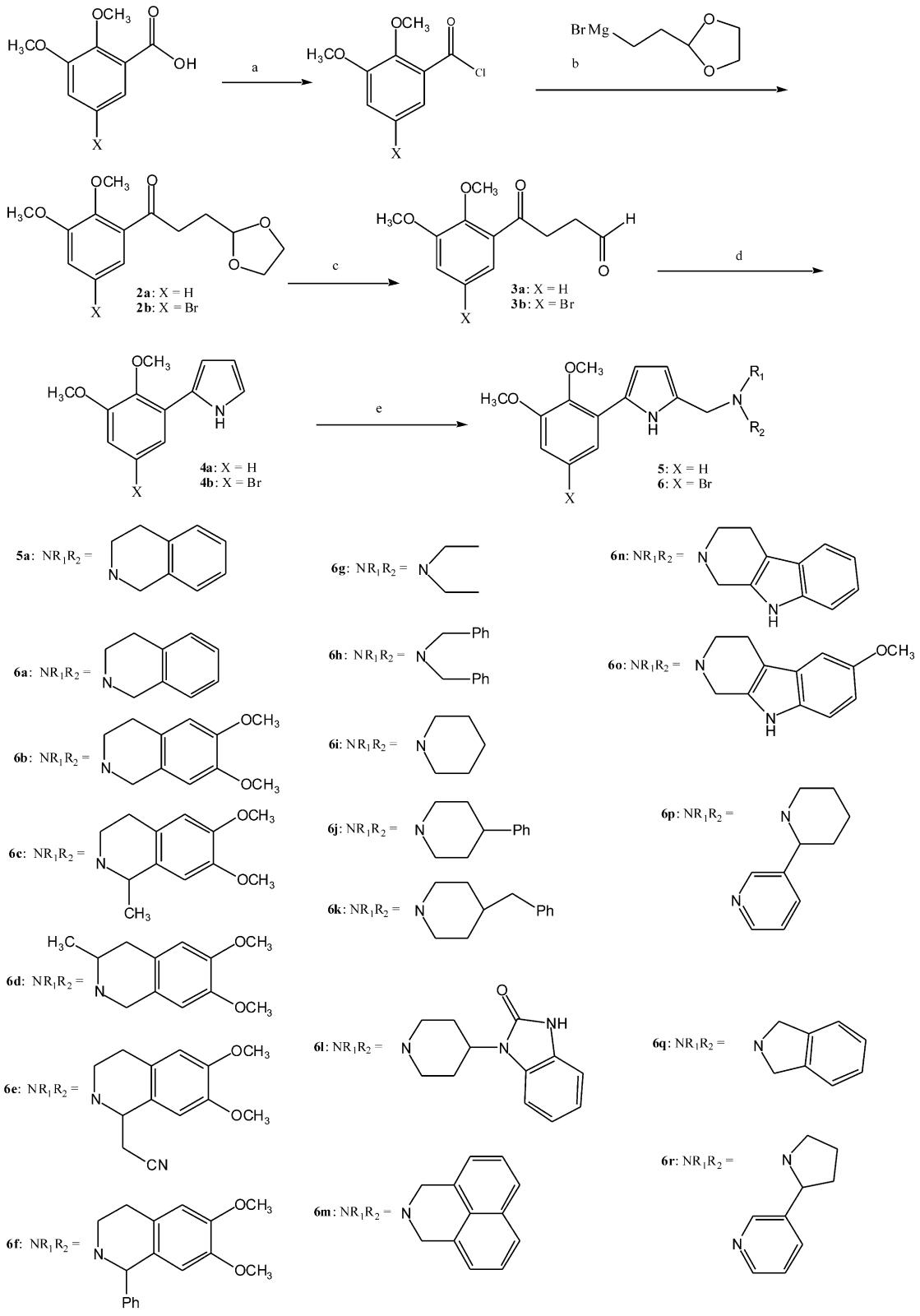
The piperidinylmethyl analogue, **6i**, also had a high affinity for dopamine D_3 receptors and a D_3/D_2 selectivity ratio and a D_3/D_4 selectivity ratio of ~10 (Table 2). Compounds **6j**, **6k**, **6l**, and **6p** demonstrate the effect of an aromatic ring in the piperidine ring of **6i**. Substitution of either the 2- or 4-position of the piperidine ring resulted in either no change or a modest reduction in affinity for dopamine D_2 and D_3 receptors. However, this substitution resulted in a pronounced reduction in affinity for dopamine D_4 receptors. For example, compounds **6l** and **6p** had a low affinity for dopamine D_4 receptors, whereas compound **6i** had a D_4 affinity of 18.4 nM (Table 2).

Compounds **6q** and **6r** were prepared in order to explore the effect of a five-membered amine moiety versus the corresponding six-membered ring. This structural change had no effect on dopamine receptor affinity for the benz-fused system (compare **6a** and **6q**), whereas a dramatic reduction in D_2 and D_3 affinity, and an increase in D_4 affinity, was observed with the corresponding 2-(3-pyridnyl)analogues (i.e., **6p** vs **6r**).

Another interesting observation was the replacement of the 5-bromo-2,3-dimethoxyphenyl group with the corresponding 4-bromo-1-methoxynaphthyl moiety. Our previous studies have shown this substitution to result in an increase in dopamine D_3 receptor affinity and no change in dopamine D_2 receptor affinity for a series of structurally-related benzamide derivatives.[11] Surprisingly, this structural change resulted in an unexpected decrease in the affinity of the pyrrole analogues for both dopamine D_2 and D_3 receptors (Table 1). Finally, the affinity of compound **6a**–**r** and **11a**–**d** for sigma receptors was also measured. With the exception of compound **11a**, all compounds in this series displayed either a low or negligible affinity for σ_1 and σ_2 receptors (Table 1).

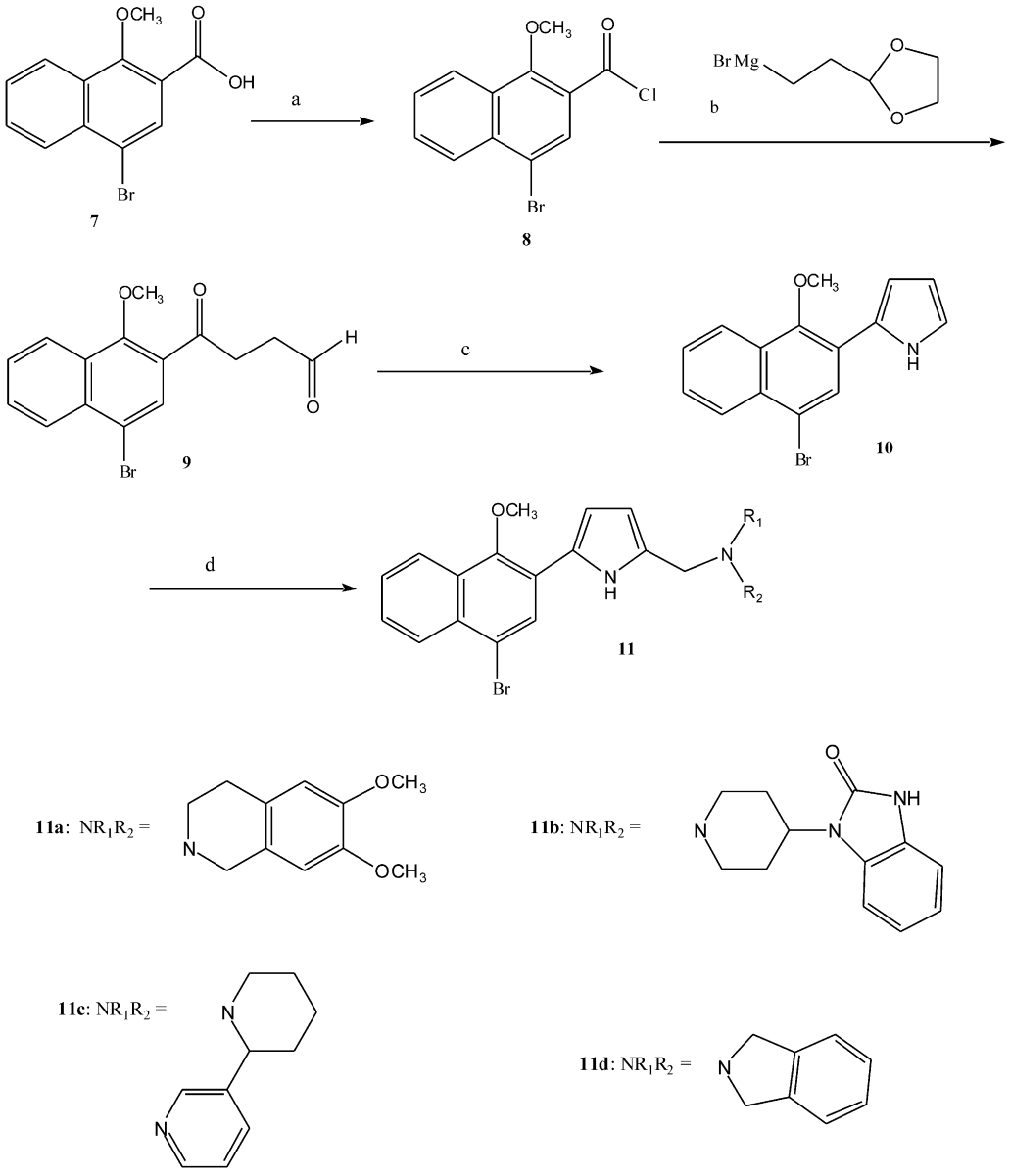
Discussion

In an earlier study, we reported a series of benzamide analogues possessing a high affinity for dopamine D_2 and D_3 receptors.[16] 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 suggested that isoteric replacement of the amide group with a heterocyclic ring could produce in a shift in affinity of these compounds for D_2 and D_2 receptors. These observations led to the synthesis and evaluation of a series of imidazole analogues as potential dopamine D_3-selective ligands.[12] The most noteworthy compound to come from this follow-up study was **1c** (Fig. 1), which had a modest affinity for dopamine D_3 receptors and a D_2/D_3 selectivity ratio of



Scheme 1. Reagents: (a) $SOCl_2$/benzene; (b) Grignard reagent/CuBr/−70 °C/THF, then aqueous acid; (c) 2 N HCl/methanol; (d) ammonium acetate/ethanol; (e) formaldehyde/amine.

~7 (Table 1). While this research was being conducted, it was reported that the isoteric substitution of a pyrrole ring for the benzamide moiety of (*S*)-sultopride resulted in a compound (i.e., DU 122290) with an improved D_2/D_3 selectivity ratio relative to the parent compound (Fig. 1). This study led to the synthesis of a number of pyrrole-based analogues displaying a high affinity and modest selectivity for dopamine D_3 versus D_2 receptors.[14,15]



Scheme 2. Reagents (a) $SOCl_2$/benzene; (b) Grignard reagent/CuBr/−70 °C/THF, then aqueous acid; (c) ammonium acetate/ethanol; (d) formaldehyde/diethylamine.

The goal of the current study was to prepare a number of pyrrole analogues of our imidazole-based compounds. The results of the current study revealed that the pyrrole analogues had a high affinity and greater D_2/D_3 selectivity ratio than the corresponding imidazole analogues. For example, a comparison of **5a** versus **1a**, **6a** versus **1b**, **6d** versus **1c** and **6j** versus **1d** reveals that the corresponding pyrrole analogue has a higher affinity for both D_2 and D_3 receptors and, with the exception of **1a** and **5a**, a higher D_2/D_3 selectivity ratio than the corresponding imidazole analogue. Furthermore, the imidazole analogue **1e** was somewhat selective for D_2 versus D_3 receptors whereas the corresponding pyrrole, **6k**, had a higher affinity for D_3 receptors than D_2 receptors. These data suggest that the pyrrole ring, which is a π-excessive heteroaromatic ring, represents a better isoteric substitution for the benzamide moiety than an imidazole ring, which is a π-deficient heteroaromatic ring. Further studies are needed with other π-deficient and π-excessive heteroaromatic ring systems to test this hypothesis.

A second goal of this study was to determine the effect of the location of the aromatic ring in the tertiary amine moiety on D_2-like dopamine receptor binding. Benz-fused systems such as the 1,2,3,4-tertrahydroisoquinoline analogues, **6a** and **6b**, displayed a high D_3 affinity and modest D_2/D_3 selectivity ratio. Increasing the degree of steric bulk of the benz-fused system, such as in the 4,5-benz-1,2,3,4-tetrahydroisoquinolone analogue, **6m**, and the 1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole analogues, **6n** and **6o**, resulted in a reduction in affinity for dopamine D_2 and D_3 receptors. Both the diethylaminomethyl analogue, **6g**, and the piperidinylmethyl analogue, **6i**, had a high D_3 affinity and a 10-fold selectivity for D_3 versus D_2 receptors. Substitution of the

Table 2. In vitro binding data for dopamine D4 receptors

Compd	K_i (nM)[a]				
	D_2[b]	D_3[c]	D_4[d]	D_2/D_3 ratio[e]	D_4/D_3 ratio[f]
1	143±48.9	21.2±4.7	244±41	6.7	11.5
6a	29.5±1.5	3.8±1.2	40±20	7.8	10.5
6b	33.4±6.0	3.9±0.5	98.5±51.7	8.6	25.3
6g	6.6±0.6	0.64±0.2	12.9±4.5	10.3	20
6i	19.1±2.6	1.9±0.6	18.4±4.1	10	9.7
6l	27.8±11.0	2.6±1.4	3.074±924	10.7	1182
6p	86.8±7.3	4.3±2.5	1.272±598	20.2	296
6q	17.4±1.2	1.7±0.6	47.9±19.0	10.2	28
6r	1.69±15.1	21.9±2.8	491±65	7.7	22.4

[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 for inhibiting the binding of [^{125}I]IABN to human $D_{4,4}$ receptors.
[e]K_i for D_2/Ki for D_3.
[f]K_i for D_4/Ki for D_3.

4-position of the piperidine ring with a phenyl group, **6j**, or a phenylmethyl group, **6k**, resulted in a reduction in D_3 affinity relative to the unsubstituted compound, **6i**. However, substitution of the 4-position of **6i** with a 4–2-keto-1-benzimidazolinyl group, **6l**, or the 2-position with a 3-pyridyl group, **6p**, resulted in compounds with a high D_3 affinity and moderate D_2/D_3 selectivity ratio (Table 2). In addition, this substitution had a large effect on the affinity of these compounds for dopamine D_4 receptors. That is, the affinity of **6i** for D_4 receptors was 18.4 nM, whereas the affinity of **6l** and **6p** for the dopamine D_4 receptor was 3074 and 1272 nM, respectively. The compound displaying the highest affinity and selectivity for D_3 versus D_2 and D_4 receptors is **6p**, which has a D_2/D_3 selectivity ratio of 20.2 and a D_4/D_3 selectivity ratio of 296.

The final goal of this structure–activity relationship study was to replace the 5-bromo-2,3-dimethoxy phenyl group with a 2-(4-bromo-1-methoxynaphthyl) group. Our previous studies with structurally-related benzamide analogues indicated that this substitution resulted in an improvement in the D_3 affinity and D_2/D_3 selectivity ratio of this class of compounds.[11] An unexpected result of this study was that the introduction of a 2-(5-bromo-1-methoxy)naphthyl group into the pyrrole series of compounds resulted in a dramatic reduction in affinity for both D_2 and D_3 receptors. Molecular modeling studies are currently being conducted to determine the orientation of the aromatic rings within dopamine D_2 and D_3 receptor binding sites.

In conclusion, a number of 2-(5-bromo-2,3-dimethoxy)-1*H*-pyrrole analogues were prepared and their affinities for dopamine D_2, D_3 and D_4 receptors and sigma receptors were measured using in vitro binding assays. The pyrrole analogues had a higher affinity for D_2 and D_3 receptors than the imidazole analogues reported in an earlier study. Several of the pyrrole compounds had a high affinity for dopamine D_3 receptors and a D_2/D_3 selectivity ratio ranging from 10 to 20. These compounds also had a relatively low affinity for D_4 receptors when compared to their affinity for dopamine D_3 receptors. With the exception of compound **11a**, all compounds had a low affinity for σ_1 and σ_2 receptors. The most noteworthy compound identified in this study is **6p**, which has a high D_3 affinity with excellent D_2/D_3 and D_4/D_3 selectivity ratios. This compound is predicted to be useful for studying the functional role of D_3 receptors in vivo.

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-(5-bromo-2,3-dimethoxyphenyl)-1*H*-pyrrole (4b). A solution of 2-(2-bromoethyl)-1,3-dioxolane (12.5 g, 69 mmol) in anhydrous tetrahydrofuran (20 mL) was added to a stirred suspension of magnesium (3 g, 123 mmol) in anhydrous tetrahydrofuran (80 mL) and the reaction mixture was stirred at ambient temperature for 30 min. The solution was transferred under a nitrogen atmosphere to a three-necked round bottom flask (500 mL) and cooled to 0 °C. Powder copper bromide (9.3 g, 65 mmol) was slowly added and the reaction mixture was stirred at 5–15 °C for 20 min. The reaction mixture was cooled to −70 °C (dry ice–acetone) and a solution of 5-bromo-2,3-dimethylbenzoyl chloride (15.37 g, 55 mmol) in anhydrous tetrahydrofuran (100 mL) was added slowly over 15 min and the reaction mixture was stirred at that temperature for an additional 60 min. The dry ice–acetone bath was removed and the mixture was stirred at ambient temperature for 18 h. The mixture was poured into an ice cold 2 N solution of aqueous HCl (200 mL) and the mixture was extracted with ether (3×100 mL). The combined organic layers were dried (sodium sulfate) and concentrated in vacuo to give an oil that was purified by silica gel column chromatography (hexane/ethyl acetate, 8:2) to give **2b** (10.89 g, 57%). This material was dissolved in a 1:1 mixture of 2 N HCl in methanol and the mixture was stirred at ambient temperature for 16 h.

Volatile components were removed to give crude **3b** as a yellow oil. Ethanol (100 mL) and ammonium acetate (19 g) were added and the reaction mixture was stirred at reflux for 2 h. The mixture was poured into cold water (250 mL) and washed with ethyl acetate (3×100 mL). Volatile components were removed in vacuo and the residue was purified by silica gel column chromatography (hexane/ethyl acetate, 9:10 to give **4b** as a fluffy white solid (8.95 g; 96%), mp 80–81 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.84 (s, 1H), 7.35 (d, 1H, J = 2.4 Hz), 6.88–6.91 (m, 1H), 6.83 (d, 1H, J = 1.9 Hz), 6.58–6.60 (m, 1H), 6.25–6.30 9m, 1H), 3.88 s, 3H), 3.81 (s, 3H). Analysis ($C_{12}H_{12}NO_2Br$) C, H, N.

2-(2,3-Dimethoxyphenyl)-1*H*-pyrrole (4a). Compound **4a** was obtained by the same method as described for **4b** in an overall yield of 17% from 2,3-dimethoxybenzoyl chloride, mp 58–59 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22–7.26 (m, 1H), 7.02–7.08 (m, 1H), 6.88–6.90 (m, 1H), 6.73–6.77 (m, 1H), 6.59–6.62 (m, 1H), 6.59–6.62 (m, 1H), 6.27–6.30 (m, 1H), 3.90 (s, 3H), 3.84 (s, 3H). Analysis ($C_{12}H_{13}NO_2$) C, H, N.

2-(2-(4-Bromo-1-methoxynaphthyl)-1*H*-pyrrole (11). Compound **11** was obtained by the same method as described for **4b** in an overall yield of 28% from 8, mp 118–120 (dec.). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.90 (s, 1H), 8.07–8.23 (m, 2H), 8.04 (s, 1H), 7.53–7.62 (m, 2H), 6.96–6.97 (m, 1H), 6.68–6.69 (m, 1H), 6.33–6.36 (m, 1H), 3.85 (s, 3H). Analysis ($C_{15}H_{12}NOBr$)C, H, N.

2-(2,3-Dimethoxyphenyl)-5-(1,2,3,4-tetrahydroisoquinolino)methyl-1*H*-pyrrole (5a). A solution of 1,2,3,4-tetrahydroisoquinoline (0.13 g, 1 mmol), 30% aqueous formaldehyde (0.081 g) and acetic acid (0.08 g) in ethanol (25 mL) was stirred at ambient temperature for 30 min. At that time 2-(2,3-dimethoxyohenyl-1*H*-pyrrole (0.2 g, 1.0 mmol) was added and reaction mixture was stirred at ambient temperature for an additional 18 h. The solvent was removed and the product was purified by silica gel column chromatography (dichloromethane/ethanol, 9.75:0.25) to give **5a** as a white solid, which was converted to the corresponding oxalate salt (0.33 g, 75%), mp 172–174 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88–7.21 (m, 7H), 6.70–6.73 (m, 1H), 6.52–6.54 (m, 1H), 6.12–6.14 (m, 1H), 3.86 (s, 3H), 3.74 (s, 2H), 3.73 (s, 3H), 3.67 (s, 2H), 2.89–2.93 (m, 2H), 2.77–2.81 (m, 2H). Analysis ($C_{24}H_{26}N_2O_6$) 1/2 H_2O) C, H, N.

2-(5-Bromo-2,3-dimethoxyphenyl)-5-(1,2,3,4-tetrahydroisoquinolino)methyl-1*H*-pyrrole (6a). Compound **6a** was obtained by the same method as described for **5a** in 69% yield, mp 128–130 °C (HCl salt). ^{1}H NMR ($CDCl_3$) δ (300 MHz, $CDCl_3$) δ 7.32 (d, 1H, J = 2.3 Hz), 7.10–7.15 (m, 4H), 6.99–7.01 (m, 1H), 6.81 (d, 1H, J = 2.3 Hz), 6.51–6.53 (m, 1H), 6.13–6.16 (m, 1H), 3.85 (s, 6H), 3.73 (s, 2H), 3.64 (s, 2H), 2.93–2.95 (m, 2H), 2.83–2.85 (m, 2H); ms ($C_{22}H_{23}N_2O_2Br$, M_r = 426.0943) 427.0996 (M + 1).

2-(5-Bromo-2,3-dimethoxyphenyl)-5-(4,5-dimethoxy-1,2,3,4-tetrahydroisoquinolino)methyl-1*H*-pyrrole (6b). Compound **6b** was obtained by the same method as described for **5a** in 98% yield, mp 84–86 °C (free amine). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.91 (s, 1H), 7.31 (d, 1H, J = 1.9 Hz), 6.81 (d, 1H, J = 2.0 Hz), 6.60 (s, 1H), 6.51 (t, 1H, J = 2.9 Hz), 6.48 (s, 1H), 6.13 (t, 1H, J = 2.9 Hz), 3.85 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 3.73 (s, 2H), 3.72 (s, 3H), 3.57 (s, 2H), 2.82 (d, 2H, J = 4.9 Hz), 2.77 (d, 2H, J = 4.9 Hz). Analysis ($C_{24}H_{27}N_2O_4Br$) C, H, N.

2-(5-Bromo-2,3-dimethoxyphenyl)-5-(4,5-dimethoxy-2-methyl-1,2,3,4-tetrahyroisoquinolino)methyl-1*H*-pyrrole (6c). Compound **6c** was obtained by the same method as described for **5a** in 49% yield, mp 164–166 °C (oxalate salt). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.90 (s, 1H), 7.31–7.32 (m, 1H), 6.81–6.82 (m, 1H), 6.58 (s, 1H), 6.49–6.52 (m, 2H), 6.07–6.09 (m, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.83 (s, 3H), 3.79 (s, 2H), 3.74 (s, 3H), 3.05–3.15 (m, 1H), 2.74–2.92 (m, 4H), 1.40 (s, 3H). Analysis ($C_{27}H_{31}N_2O_8 \cdot H_2O$) C, H, N.

2-(5-Bromo-2,3-dimethoxyphenyl)-5-(4,5-dimethoxy-8-methyl-1,2,3,4-tetrahydroisoquinolino)methyl-1*H*-pyrrole (6d). Compound **6d** was obtained by the same method as described for **5a** in 67% yield, mp 164–166 °C (oxalate salt). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.11 (s, 1H), 7.34 (s, 1H), 6.87 (s, 1H), 6.63–6.69 (m, 1H), 6.54–6.57 (m, 1H), 6.45 (s, 1H), 6.09–6.11 (m, 1H), 3.88 (s, 2H), 3.85 (s, 12H), 3.26 (s, 4H), 2.72–2.77 (m, 1H), 1.45 (s, 3H). Analysis ($C_{27}H_{31}N_2O_8$) C, H, N.

2-(5-Bromo-2,3-dimethoxyphenyl)-5-(2-cyanomethyl-4,5-dimethoxy - 1,2,3,4 - tetrahydroisoquinolino)methyl - 1*H* - pyrrole (6e). Compound **6e** was obtained by the same method as described for **5a** in 88% yield, mp 104–106 °C (free amine). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.93 (s, 1H), 7.34 (d, 1H, J = 2.3 Hz), 6.82 (d, 1H, J = 2.3 Hz), 6.61 (s, 1H), 6.59 (s, 1H), 6.51 (t, 1H, J = 3.0 Hz), 6.10 (t, 1H, J = 3.0 Hz), 3.87 (s, 6H), 3.85 (s, 5H), 3.82 (s, 3H), 3.08–3.17 (m, 1H), 2.82–2.90 (m, 2H), 2.70–2.76 (m, 2H), 2.55–2.67 (m, 2H). Analysis ($C_{26}H_{28}N_3O_4Br$) C, H, N.

2-(5-Bromo-2,3-dimethoxyphenyl)-5-(4,5-dimethoxy-2-phenyl-1,2,3,4-tetrahydroisoquinolino)methyl-1*H*-pyrrole (6f). Compound **6f** was obtained by the same method as described for **5a** in 57% yield, mp 121–123 °C (free amine). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.22–7.38 (m, 6H), 6.80 (d, 1H, J = 2.2 Hz), 6.59 (s, 1H), 6.46 (t, 1H, J = 2.9 Hz), 6.16 (s, 1H), 6.03 (t, 1H, J = 2.9 Hz), 3.88 (s, 3H), 3.85 (s, 3H), 3.77 (s, 5H), 3.59 (s, 3H), 3.40 (s, 1H), 2.96–3.16 (m, 2H), 2.53–2.73 (m, 2H). Analysis ($C_{30}H_{31}N_2O_4Br$) C, H, N.

Preparation of 2-(5-bromo-2,3-dimethoxyphenyl)-5-diethylaminomethyl-1*H*-pyrrole (6g). Compound **6g** was obtained by the same method as described for **5a** in 70% yield, mp 140–141 °C (oxalate salt). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.95 (s, 1H), 7.31–7.32 (m, 1H), 6.80–6.81 (m, 1H), 6.48–6.50 (m, 1H), 6.04–6.05 (m, 1H), 3.88 (s, 3H), 3.80 (s, 3H), 3.64 (s, 2H), 2.55 (q, 4H, J = 7.2 Hz), 1.06 (t, 6H, J = 7.1 Hz). Analysis ($C_{19}H_{25}N_2O_6Br$) C, H, N.

2-(5-Bromo-2,3-dimethoxyphenyl)-5-diphenylmethylaminomethyl-1*H*-pyrrole (6h). Compound **6h** was obtained by the same method as described for **5a** in 50% yield, mp

247 °C (dec., oxalate salt). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.42 (m, 5H), 7.30–7.35 (m, 5H), 7.20–7.25 (m, 2H), 6.81 (d, 1H, J = 6.0 Hz), 6.46 (t, 1H, J = 5.1 Hz), 6.09 (t, 1H, J = 5.1 Hz), 3.91 (s, 3H, 3.77 (s, 3H), 3.60 (s, 4H), 3.57 (s, 2H).

2-(5-Bromo-2,3-dimethoxyphenyl)-5-piperinylmethyl-1*H*-pyrrole (6i). Compound **6i** was obtained by the same method as described for **5a** in 87% yield, mp 182–184 °C (oxalate salt). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.91 (m, 1H), 7.30–7.31 (m, 1H), 6.80–6.82 (m, 1H), 6.46–6.48 (m, 1H), 6.03–6.05 (m, 1H), 3.88 (s, 3H), 3.79 (s, 3H), 3.51 (s, 2H), 2.40 (s, 4H), 1.51–1.61 (m, 4H), 1.43 (s, 2H). Analysis ($C_{20}H_{25}N_2O_6Br$) C, H, N.

2-(5-Bromo-2,3-dimethoxyphenyl)-5-(4-phenylpiperidinyl)-methyl-1*H*-pyrrole (6j). Compound **6j** was obtained by the same method as described for **5a** in 71% yield, mp 158–160 °C (oxalate salt). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.91 (s, 1H), 7.17–7.33 (m, 6H), 6.81–6.82 (m, 1H), 6.48–6.50 (m, 1H) 6.06–6.08 (m, 1H), 3.88 (s, 3H), 3.80 (s, 3H), 3.59 (s, 2H), 3.00–3.05 (m, 2H), 2.47–2.55 (m, 1H), 2.08–2.16 (m, 2H), 1.75–1.82 (m, 4H). Analysis ($C_{26}H_{29}N_2O_6Br$) C, H, N.

2-(5-Bromo-2,3-dimethoxyphenyl)-5-(4-phenylmethylpiperidinyl)methyl-1*H*-pyrrole (6k). Compound **6k** was obtained by the same method as described for **5a** in 55% yield, mp 137–139 °C (oxalate salt). ^{1}H NMR (300 MHz, $CDCl_3$ δ 9.89 (s, 1H), 7.11–7.31 (m, 6H), 6.81–6.82 (m, 1H), 6.46–6.48 (m, 1H), 6.01–6.03 (m, 1H), 3.88 (s, 3H), 3.78 (s, 3H), 3.52 (s, 2H), 2.86–2.89 (m, 2H), 2.52–2.54 (m, 2H), 1.91–1.98 (m, 2H), 1.53–1.61 (m, 3H), 1.22–1.34 (m, 2H). Analysis ($C_{27}H_{31}N_2O_6Br$) C, H, N.

2-(5-Bromo-2,3-dimethoxyphenyl)-5-(4-(2-keto-1-benzimidazolinyl)piperidinyl)methyl-1*H*-pyrrole (6l). Compound **6l** was obtained by the same method as described for **5a** in 46% yield, mp 189–191 °C (free amine). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.90 (s, 1H), 8.80 (s, 1H), 7.33 (d, 1H, J = 2.3 Hz), 7.07–7.09 (m, 3H), 6.83 (d, 1H, J = 2.3 Hz), 6.49 (t, 1H, J = 3.1 Hz), 6.10 (t, 1H, J = 3.1 Hz), 3.90 (s, 3H), 3.84 (s, 3H), 3.61 (s, 2H), 3.05–3.10 (m, 2H), 2.42–2.52 (m, 2H), 2.15–2.25 (m, 2H), 1.80–1.87 (m, 2H). Analysis ($C_{25}H_{27}N_4O_3Br$) C, H, N.

2-(5-Bromo-2,3-dimethoxyphenyl)-5-(4,5-benzo-1,2,3,4-tetrahydroisoquinolino)methyl-1*H*-pyrrole (6m). Compound **6m** was obtained by the same method as described for **5a** in 50% yield, mp 88–89 °C (free amine). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.70 (d, 2H, J = 8.2 Hz), 7.39 (t, 2H, J = 7.6 Hz), 7.31 (d, 1H, J = 2.3 Hz), 7.16 (d, 2H, J = 7.1 Hz), 6.79 (d, 1H, J = 2.3 Hz), 6.53 (t, 1H, J = 3.1 Hz), 6.15 (t, 1H, J = 3.1 Hz), 4.01 (s, 4H), 3.85 (s, 2H), 3.82 (s, 3H), 3.60 (s, 3H). Analysis ($C_{27}H_{25}N_2O_6Br$) C, H, N.

2-(5-Bromo-2,3-dimethoxyphenyl)-5-(1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole)methyl)-1*H*-pyrrole (6n). Compound **6n** was obtained by the same method as described for **5a** in 95% yield, mp 100–101 °C (free amine). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.92 (s, 1H), 7.65 (s, 1H), 7.47 (d, 1H, J = 7.1 Hz), 7.32 (d, 1H, J = 2.2 Hz), 7.26–7.30 (m, 1H), 7.08–7.15 (m, 2H), 6.81 (d, 1H, J = 2.2 Hz), 6.52 (t, 1H, J = 3.0 Hz), 6.13 (t, 1H, J = 3.0 Hz), 3.85 (s, 3H), 3.81 (s, 2H), 3.74 (s, 3H), 3.68 (s, 2H), 2.81–2.95 (m, 4H). Analysis ($C_{24}H_{24}N_3O_2Br$) C, H, N.

2-(5-Bromo-2,3-dimethoxyphenyl)-5-(1-(1,2,3,4-tetrahydro-9H-pyrido[3,4-*b*]indole)methyl)-1*H*-pyrrole (6o). Compound **6o** was obtained by the same method as described for **5a** in 89% yield, mp 82–83 °C (free amine). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.93 (s, 1H), 7.54 (s, 1H), 7.32 (d, 2H, J = 2.3 Hz), 7.18 (d, 1H, J = 8.6 Hz), 6.93 (d, 1H, J = 2.3 Hz), 6.77–6.82 (m, 2H), 6.52 (t, 1H, J = 3.0 Hz), 6.13 (t, 1H, J = 3.0 Hz), 3.86 (s, 6H), 3.81 (s, 2H), 3.74 (s, 3H), 3.68 (s, 2H), 2.93 (t, 2H, J = 5.6 Hz), 2.80 (t, 2H, J = 5.6 Hz). Analysis ($C_{25}H_{26}N_3O_3Br$) C, H, N.

2-(5-Bromo-2,3-dimethoxyphenyl)-5-(2-(3-pyridyl)-piperidinyl)methyl-1*H*-pyrrole (6p). Compound **6p** was obtained by the same method as described for **5a** in 73% yield, mp 139–140 °C (free amine). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.84 (s, 1H), 8.62 (s, 1H), 8.48–8.50 (m, 1H), 7.77–7.80 (m, 1H), 7.24–7.31 (m, 2H), 6.82 (d, 1H, J = 2.2 Hz), 6.43 (t, 1H, J = 3.0 Hz), 5.94 (t, 1H, J = 3.0 Hz), 3.91 (s, 3H), 3.84 (s, 3H), 3.61 (d, 2H, J = 14.2 Hz), 316–3.21 (m, 2H), 3.02–3.10 (m, 3H), 2.03–2.11 (m, 2H), 1.76–1.84 (m, 2H). Analysis ($C_{23}H_{26}N_3O_2Br$) C, H, N.

2-(5-Bromo-2,3-dimethoxyphenyl)-5-(3,4-benzopyrrolidinyl)methyl-1*H*-pyrrole (6q). Compound **6q** was obtained by the same method as described for **5a** in 37% yield, mp 185–187 °C (free amine). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.32 (d, 1H, J = 2.3 Hz), 7.19 (s, 4H), 6.81 (d, 1H, J = 2.3 Hz), 6.52 (t, 1H, J = 3.1 Hz), 6.13 (t, 1H, J = 3.1 Hz), 3.97 (s, 4H), 3.93 (s, 2H), 3.86 (s, 3H), 3.77 (s, 3H). Analysis ($C_{23}H_{23}N_2O_6Br$) C, H, N.

2-(5-Bromo-2,3-dimethoxyphenyl)-5-(2-(3-pyridyl)pyrrolidinyl)methyl-1*H*-pyrrole (6r). Compound **6r** was obtained by the same method as described for **5a** in 73% yield, mp 71–74 °C (dioxalate salt). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.48–8.50 (m, 1H), 7.76–7.83 (m, 1H), 7.29–7.38 (m, 3H), 6.82 (d, 1H, J = 2.2 Hz), 6.44 (t, 1H, J = 3.1 Hz), 6.00 (s, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 3.20–3.50 (m, 5H), 2.25–2.45 (m, 4H). Analysis ($C_{26}H_{28}N_3O_{10}Br{\cdot}2H_2O$) C, H, N.

2-(2-(4-Bromo-1-methoxynapthyl)-5-(4,5-dimethoxy-1,2,3,4-tetrahydroisoquinolino)methyl-1*H*-pyrrole (11a). Compound **11a** was obtained by the same method as described for **5a** in 78% yield from 10, mp 196–198 °C (oxalate salt). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.05 (s, 1H), 8.05–8.18 (m, 2H), 8.04 (s, 1H), 7.50–7.60 (m, 2H), 6.62 (s, 2H), 6.50 (s, 1H), 6.19–6.23 (m, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 3.62 (s, 2H), 2.80–2.90 (m, 6H). Analysis ($C_{29}H_{29}N_2O_7Br$) C, H, N.

2-(2-(4-Bromo-1-methoxynaphthyl)-5-(4-(2-keto-1-benzimidazolin-yl)piperidinyl)methyl-1*H*-pyrrole (11b). Compound **11b** was obtained by the same method as described for **5a** in 75% yield from 10, mp 202 °C (dec., free amine). ^{1}H NMR (300 MHz. $CDCl_3$) δ 8.12–8.18

(m, 2H), 8.03 (s, 1H), 7.52–7.61 (m, 2H), 7.30–7.32 (m, 1H), 7.07 (s, 4H), 6.58–6.60 (m, 1H), 6.17–6.20 (m, 1H), 4.36–4.40 (m, 1H) 3.90 (s, 3H), 3.74 (s, 2H), 3.11–3.22 (m, 2H), 2.48–2.55 (m, 2H), 2.20–2.28 (m, 2H), 1.83–1.87 (m, 2H). Analysis ($C_{28}H_{27}N_4O_2Br$) C, H, N.

2-(2-(4-Bromo-1-methoxynaphthyl)-5-(2-(3-pyridyl)-piperidinyl)methyl-1*H*-pyrrole (11c). Compound **11c** was obtained by the same method as described for **5a** in 91% yield from 10, mp 85–87 °C (oxalate salt). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.90 (s, 1H), 8.70 (s, 1H), 8.50–8.53 (m, 1H), 8.10–8.16 (m, 2H), 8.00 (s, 1H), 7.80–7.83 (m, 1H), 7.50–7.60 (m, 2H), 7.27–7.33 (m, 1H) 6.53–6.57 (m, 1H), 5.98–6.02 (m, 1H), 3.88 (s, 3H), 3.65–3.70 (m, 2H), 3.08–3.25 (m, 4H), 2.05–2.15 (m, 1H), 1.58–1.85 (m, 4H). Analysis ($C_{30}H_{30}N_3O_9Br$) C, H, N.

2-(5-Bromo-2,3-dimethoxyphenyl)-5-(3,4-benzopyrrolidinyl)methyl-1*H*-pyrrole (11d). Compound **11d** was obtained by the same method as described for **5a** in 42% yield from 10, mp 193–194 °C (free amine). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.05 (s, 1H), 8.05–8.15 (m, 2H), 8.03 (s, 1H), 7.50–7.55 (m, 2H), 7.20 (s, 4H), 6.60–6.65 (m, 1H), 6.19–6.22 (m, 1H), 4.01 (s, 4H), 3.99 (s, 2H), 3.83 (s, 3H). Analysis ($C_{26}H_{23}N_2O_5Br$) C, H, N.

In vitro binding assays

In vitro dopamine receptor binding studies were conducted using membranes prepared from (a) *Spodoptera frugiperda* (Sf9) cells that express a high density of either rat $D_{2(long)}$ or rat D_3 or (b) HEK 293 cells expressing human $D_{4.4}$ receptors. The radioligand used was [^{125}I]IABN and the assay conditions have been previously described.[17] The K_i values were calculated from the corresponding IC_{50} values using the method of Cheng and Prusoff.[18]

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.[19] In vitro σ_2 receptor binding affinity was measured in rat liver membranes using [^{3}H]DTG (DuPont-NEN, Bilerica, MA, USA) as the radioligand in the presence of (+)-pentazocine (100 nM) as previously described.[19]

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