Notes

N-[2-[4-(4-Chlorophenyl)piperazin-1-yl]ethyl]-3-methoxybenzamide: A Potent and Selective Dopamine D_4 Ligand

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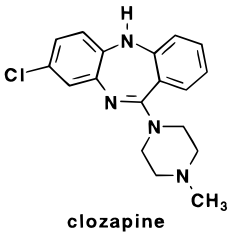
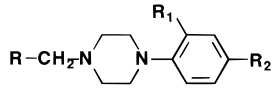
A series of new 1-aryl-4-alkylpiperazines containing a terminal benzamide fragment or a tetralin-1-yl nucleus on the alkyl chain were synthesized and tested for binding at cloned human dopamine D_4 and D_2 receptor subtypes. A SAFIR (structure−affinity relationship) study on this series is herein discussed. The most relevant D_4 receptor affinities were displayed by *N*-[*ω*-[4-arylpiperazin-1-yl]alkyl]-methoxybenzamides (compounds **5**, **16**−**20**), their IC_{50} values ranging between 0.057 and 7.8 nM. Among these, *N*-[2-[4-(4-chlorophenyl)piperazin-1-yl]ethyl]-3-methoxybenzamide (**17**) emerged since it exhibited very high affinity for dopamine D_4 receptor (IC_{50} = 0.057 nM) with selectivity of >10 000 for the D_4 versus the D_2 receptor; compound **17** was also selective versus serotonin 5-HT_{1A} and adrenergic α_1 receptors.

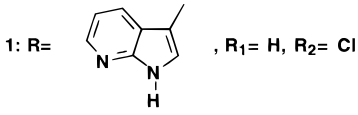
From a survey of the recent literature, it is clear that the discovery of ligands for dopamine D_4 receptor is a priority for many research laboratories.[1] Interest in this area is due to the speculation about the possible involvement in schizophrenia of D_4 receptors.[2−5] In the early 1990s molecular biology techniques showed that the D_2-like receptors are subdivided into D_2, D_3, and D_4 subtypes.[6−8] This latter receptor subtype is located in cortical and other areas of the brain believed to control emotional and cognitive functions.[9,10] Most clinically effective classical antipsychotic drugs bind at dopamine D_2-like receptors, including the D_4 subtype, at therapeutically relevant concentration.[11] It is known that the unwanted extrapyramidal motor side effects (EPS) and hormonal side effects such as hyperprolactinemia, induced during the classical antipsychotic drugs therapy, are due to the block of D_2 receptors concentrated primarily in the nigrostriatal and tubero-infundibular systems of the central nervous system. On the other hand, unlike classical neuroleptics, the atypical antipsychotic clozapine not only causes fewer EPS but also

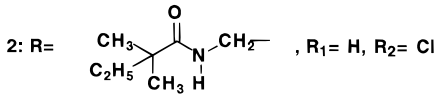


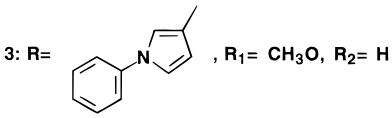
clozapine

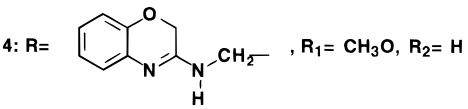
appears to be effective in many schizophrenic patients who are refractory to treatment with traditional neuroleptics. These beneficial effects of clozapine have been assigned to its approximately 10-fold higher affinity for D_4 receptor than D_2 receptor. Unfortunately, clozapine displays high affinity for a variety of other receptors and produces fatal agranulocytosis which occurs in approximately 2% of patients.[12] Therefore, at the moment, new and selective D_4 ligands are needed to evaluate them as potential antipsychotic agents devoid of unwanted EPS and hormonal side effects. Recent reports of D_4 selective ligands highlight that several chemical classes of compounds bind at D_4 receptor and among these several arylpiperazine derivatives (compounds **1**−**4**) can be found (Table 1).[13−16] In a preliminary











letter[17] we reported the high affinity at D_4 receptor of some *N*-1-(2-methoxyphenyl)piperazine derivatives bearing different substituents in the *ω*-position of the *N*-4 alkyl chain (compounds **5** and **6**). In the present study we report a development of the compounds previously

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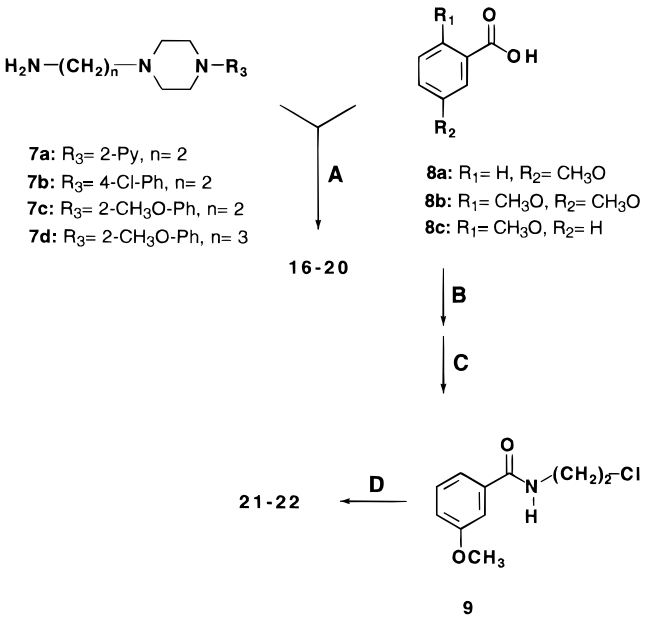
Table 1. Affinities of 1-Arylpiperazine Derivatives **1**−**4** at Cloned Human Dopamine Receptors

compd	K_i, nM		selectivity
	D_4	D_2	
1 (L-745870)[a]	0.43	920	2140
2[b]	8	2519	315
3[c]	0.7	1.3	2
4[d]	3	280	93

[a] See ref 13. [b] See ref 14. [c] See ref 15. [d] See ref 16.

Scheme 1[a]



[a] Reagents: (A) methyl chloroformate, triethylamine; (B) $SOCl_2$; (C) 2-chloroethylamine; (D) 1-(2-methoxybenzyl)piperazine or 1-(4-chlorobenzyl)piperazine.

studied in order to establish the structure−affinity relationship (SAFIR) of this type of compounds toward D_4 receptor and D_4/D_2 selectivity. In particular, considering derivative **5**, the *ω*-position substituted with a benzamide moiety on the *N*-4 alkyl chain, the following modifications were effected: (a) substitution of the 2-methoxyphenyl group on the piperazine ring with other groups (compounds **16**, **21**, and **22**) and also with the 4-chlorophenyl group (compound **17**) which is present in compounds **1** and **2**, two of the most potent D_4 ligands reported in the literature;[13,14] (b) elongation of the alkyl chain (compound **18**); (c) suitable substitution of the benzamide moiety to favor the formation of an intramolecular hydrogen bond between the amidic hydrogen atom and the oxygen atom of the methoxy group (compounds **19** and **20**); (d) isosteric replacement of the amide group with a thiazole ring (compounds **23** and **24**). Furthermore, considering derivative **5**, the *ω*-position substituted with a 1-tetralinyl group on the *N*-4 alkyl chain, the effect on D_4 affinity of the substitution pattern of the tetralin nucleus and of the intermediate alkyl chain length (compounds **25**−**30**) was studied.

Chemistry

Several synthetic routes were followed to obtain the final compounds. The synthesis of final benzamides is reported in Scheme 1. Compounds **16**−**20** were obtained by condensing the amines **7a**−**d** with the appropriate benzoic acids **8a**−**c** in the presence of methyl chloroformate.[18] The other benzamides **21** and **22** were prepared as follows: 3-methoxybenzoic acid (**8a**) was transformed in its acyl chloride by means of $SOCl_2$ and then was reacted with 2-chloroethylamine to give benzamide **9**.[19] This compound was derivatized with 1-(2-methoxybenzyl)piperazine[20] and 1-(4-chlorobenzyl)-piperazine[21] to give final compounds **21** and **22**, respectively. The synthesis of the remaining compounds is reported in Scheme 2. The synthesis of thiazole derivatives **23** and **24** required the key amides **12a,b** which were obtained by alkylating 1-(2-methoxyphenyl)piperazine (**10**) with 2-chloroacetamide and by hydrolyzing nitrile derivative **11**, respectively. Amides **12a,b** were thionated with Lawesson's reagent to give the corresponding thioamides **13a,b** which were condensed with 2-bromo-3′-methoxyacetophenone to give thiazoles **23** and **24**.[22] Tetrahydronaphthalenamine derivatives were prepared starting from the appropriate amines **14a,b** which were acylated with bromoacetyl chloride or 3-chloropropionyl chloride to give the intermediates **15a**−**c**. The reaction of these haloderivatives with 1-(2-methoxyphenyl)piperazine (**10**) provided the target amides **28**−**30**.[23]

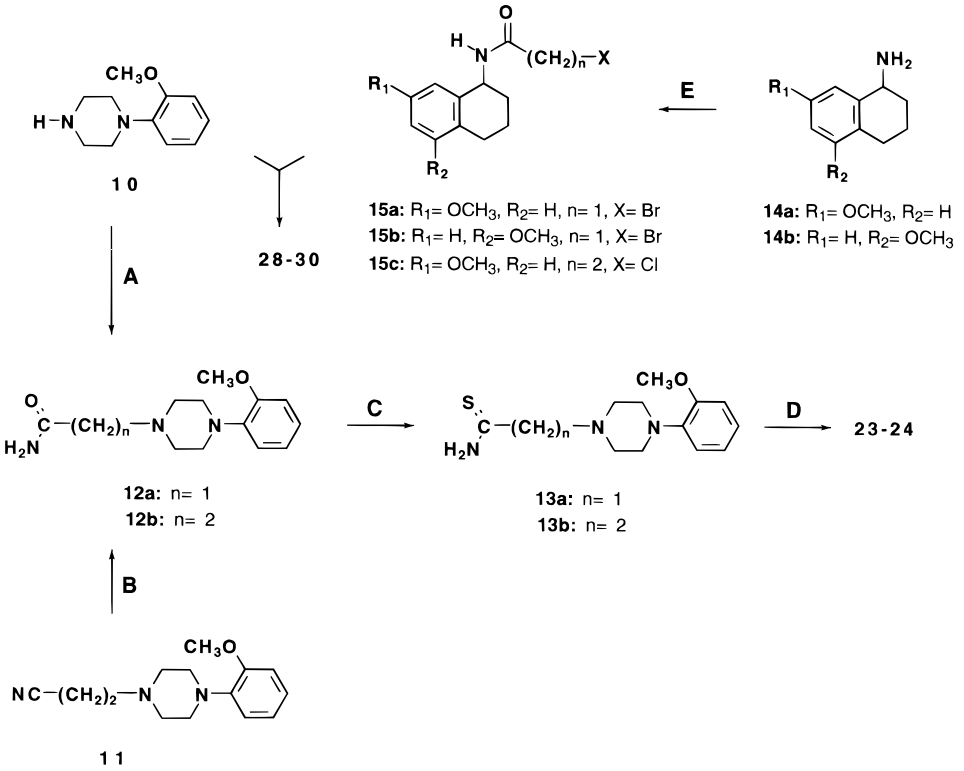
Pharmacology

All final compounds (Table 2 and Table 3) were tested for their in vitro binding affinities for human cloned dopamine $D_{4.2}$ and D_{2S} receptors both in Sf9 cells baculovirus expression. The following specific radioligands were used: (a) dopamine $D_{4.2}$ receptors−[^{3}H]YM 09151−2; (b) dopamine D_{2S} receptors−[^{3}H]spiroperidol. Compounds **5**, **16**, and **17** were also evaluated for in vitro affinity on serotonin 5-HT_{1A} and adrenergic α_1 receptor binding. The following specific radioligands and tissue sources were used: (a) serotonin 5-HT_{1A} receptors−[^{3}H]-8-OH-DPAT, rat hippocampal membranes; (b) α_1 adrenergic receptors−[^{3}H]prazosin, rat brain cortex membranes. Concentrations required to inhibit 50% of radioligand specific binding (IC_{50}) were determined by using eight to nine different concentrations of the drug studied. Specific binding was defined as described in the Experimental Section under Pharmacological Methods; in all binding assays, it represents more than 80% of total binding. The results were analyzed by using the LIGAND program to determine IC_{50} values.

Results and Discussion

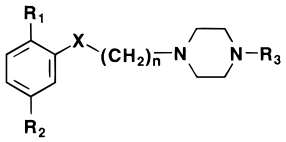
Considering the binding affinity values for D_4 receptor (Table 2), it can be noted that benzamides **5**, **16**, and **17** display the highest IC_{50} values, ranging between 0.057 and 1.0 nM. Elongation of the alkyl chain of derivative **5** yielded benzamide **18** with no significant changes in affinity. The same trend was shown by changing the position of the methoxy group on the benzamide moiety: compounds **19** and **20** displayed binding affinities comparable to that of the reference compound **5**. Among these derivatives it can be noted that a marked increase in affinity and selectivity was shown by compound **17**; it bound at D_4 receptor with an affinity superior by 10000-fold to that for the dopamine D_2 receptor. Compounds **5**, **16**, and **17**, which displayed D_4 affinity values of $\leq$1 nM and a D_4/D_2 IC_{50} ratio of >500-fold, were also evaluated for their affinities

Scheme 2[a]

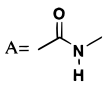


[a] Reagents: (A) 2-chloroacetamide; (B) conc H_2SO_4; (C) Lawesson's reagent; (D) 2-bromo-3′-methoxyacetophenone; (E) bromoacetyl chloride or 3-chloropropionyl chloride, 1.2% NaOH.

Table 2. Physical Properties and Binding Affinities of Derivatives **5**, **6**, **16**−**24**



									IC$_{50}$, nM[a]			
cpd	R_1	R_2	X[b]	*n*	R_3	formula[c]	mp, °C	recryst solv	D_4	D_2	5-HT$_{1A}$	α_1
5[d]	H	OCH_3	A	2	2-CH_3O-Ph				1.0	700	0.09	360
6[d]	H	OCH_3	B	2	2-CH_3O-Ph				3.1[e]	13[e]		
16	H	OCH_3	A	2	2-Py	$C_{19}H_{24}N_4O_2$	111	$CHCl_3$/*n*-hexane	1.0	>1000 (18%)[f]	30	340
17	H	OCH_3	A	2	4-Cl-Ph	$C_{20}H_{24}ClN_3O_2$	152	$CHCl_3$/*n*-hexane	0.057	>1000 (42%)	220	270
18	H	OCH_3	A	3	2-CH_3O-Ph	$C_{22}H_{29}N_3O_3$	102−104	Et_2O/*n*-hexane	2.8	>1000 (33%)		
19	OCH_3	OCH_3	A	2	2-CH_3O-Ph	$C_{22}H_{29}N_3O_4\cdot(COOH)_2$	150−151	MeOH/Et_2O	7.8	250		
20	OCH_3	H	A	2	2-CH_3O-Ph	$C_{21}H_{27}N_3O_3\cdot(COOH)_2$	152−153	MeOH/Et_2O	4.0	810		
21	H	OCH_3	A	2	2-CH_3O-Bz	$C_{22}H_{29}N_3O_3\cdot 2HCl\cdot H_2O$	230−233	MeOH/Et_2O	30	>1000 (13%)		
22	H	OCH_3	A	2	4-Cl-Bz	$C_{21}H_{26}ClN_3O_2\cdot 2HCl\cdot {}^3/_2H_2O$	223−225	MeOH/Et_2O	70	>1000 (12%)		
23	H	OCH_3	C	1	2-CH_3O-Ph	$C_{22}H_{25}N_3O_2S\cdot 3HCl\cdot {}^1/_3H_2O$	181−183	CH_2Cl_2/Et_2O	740	>1000 (22%)		
24	H	OCH_3	C	2	2-CH_3O-Ph	$C_{23}H_{27}N_3O_2S\cdot HCl$	177−178	$CHCl_3$/Et_2O	110	870		
clozapine									23	230		
haloperidol									1.3	4.1		

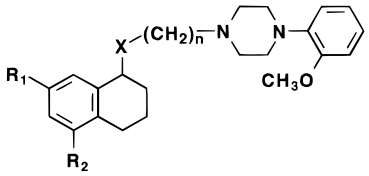
[a] Data are the mean of three independent determinations (samples in triplicate) each with SEM < 10%. [b] Structures for X: A=  ; B=  ; C= 

[c] Analyses for C, H, N; results were within ±0.4% of the theoretical values for the formulas given. [d] Formerly published compounds.[17] [e] Formerly published data.[17] [f] Full IC$_{50}$ not obtained, percentage inhibition at the concentration shown given in parentheses. Values taken from only one experiment.

to both 5-HT$_{1A}$ and α_1 receptors because it is well known that 1-arylpiperazines represent a class of serotonin 5-HT$_{1A}$ ligands and bind with somewhat affinity at adrenergic α_1 receptor. It can be noted that compound **17** was also highly selective versus 5-HT$_{1A}$ receptors (IC$_{50}$ ratio 5-HT$_{1A}$/D_4 = 3860) and α_1 receptor (IC$_{50}$ ratio α_1/D_4 = 4700). Variation of the *N*-1-substituent of piperazine ring from an aryl to a benzyl group (compounds **21** and **22**) resulted in decreasing the D_4 affinity. A drop in D_4 affinity was observed when the amide group was replaced by a thiazole ring (compounds **23** and **24**).

Considering 1-tetralinyl derivatives **25**−**30** (Table 3), the modification effected (variation of the substitution

Table 3. Physical Properties and Binding Affinities of 1-Tetralinyl Derivatives **25**−**30**



								IC$_{50}$, nM[a]	
cpd	R_1	R_2	X	n	formula[b]	mp, °C	recryst solv	D_4	D_2
25[c]	H	OCH_3	CH_2	2				60[d]	20[d]
26[c]	OCH_3	H	CH_2	2				280	150
27[e]	H	OCH_3	NHCO	2				120[d]	761[d]
28	OCH_3	H	NHCO	2	$C_{25}H_{33}N_3O_3$·2HCl	186−187	MeOH/Et_2O	30	650
29	H	OCH_3	NHCO	1	$C_{24}H_{31}N_3O_3$·2HCl	197−203	EtOH/Et_2O	850	>1000 (21%)[f]
30	OCH_3	H	NHCO	1	$C_{24}H_{31}N_3O_3$·2HCl	208−214	EtOH/Et_2O	470	>1000 (13%)

[a] Data are the mean of three independent determinations (samples in triplicate) each with SEM < 10%. [b] Analyses for C, H, N; results were within ±0.4% of the theoretical values for the formulas given. [c] Formerly published compound.[24] [d] Formerly published data.[17] [e] Formerly published compound.[23] [f] Full IC$_{50}$ not obtained, percentage inhibition at the concentration shown given in parentheses. Values taken from only one experiment.

pattern of the tetralin nucleus and of the intermediate alkyl chain length) did not lead to any remarkable D_4 receptor affinity value, IC$_{50}$ ranging between 30 and 850 nM, and for derivatives **25**−**27**, the affinity at 5-HT$_{1A}$ receptor was predominant (see references cited in Table 3). Any SAFIR can be drawn for these derivatives, as regards D_4 affinity.

In conclusion, the main information obtained from this study was that, considering the *N*-[2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]methoxybenzamides, the substitution pattern on the benzamide moiety does not have great relevance for binding affinity at D_4 receptor and the replacement of the 2-methoxyphenyl group in compound **5** with a 4-chlorophenyl group (compound **17**) greatly increased the affinity and selectivity for dopamine D_4 vs D_2. It can be noted that a similar trend was shown by the analogues of compound **2**.[14] Studies are in progress to better define the structural requirements for an optimal affinity at the dopamine D_4 receptor of this class of compounds.

Experimental Section

Chemistry. Column chromatography was performed with 1:30 ICN silica gel 60 Å (63−200 μm) as the stationary phase. Melting points were determined in open capillaries on a Gallenkamp electrothermal apparatus. Elemental analyses (C, H, N) were performed on a Carlo Erba model 1106 analyzer; the analytical results were within ±0.4% of the theoretical values for the formula given. ^{1}H NMR spectra were recorded either on a Varian EM-390 where indicated 90 MHz (TMS as internal standard) or on a Bruker AM 300 WB instrument, with $CDCl_3$ as solvent; all values are reported in ppm (δ). Recording of mass spectra was done on a HP 5995C gas chromatograph/mass spectrometer, electron impact 70 eV, equipped with HP59970A workstation; only significant *m*/*z* peaks, with their % relative intensity in parentheses, are herein reported. All spectra were in accordance with the assigned structures. When necessary, final compounds were transformed into their hydrochloride or hydrogen oxalate salts in the usual manner. Preparation and spectral properties of compound **26** have been already reported.[24]

General Procedure for Preparation of the Benzamides 16−**20.** A mixture of substituted benzoic acid **8a**−**c** (3.5 mmol) in $CHCl_3$ (20 mL) and triethylamine (4.0 mmol) was stirred at room temperature for 15 min. After the mixture cooled at −10 °C, methyl chloroformate (4.0 mmol) was added and the mixture reacted at the same temperature for 1 h. Then a solution of appropriate amine **7a**−**d** (3.8 mmol) in $CHCl_3$ was dropped into the mixture, and the resulting mixture was kept at −10 to − 5 °C for 1 h. After being stirred overnight at room temperature, the reaction mixture was washed with 5% aqueous NaOH and with water and dried over Na_2SO_4. Evaporation of the solvent in vacuo afforded a crude product. Final compounds were purified by column chromatography (eluent CH_2Cl_2/MeOH, 19:1, unless otherwise indicated) to give benzamides **16**−**20**.

***N*-[2-[4-(2-Pyridyl)piperazin-1-yl]ethyl]-3-methoxybenzamide (16).** Starting from 3-methoxybenzoic acid (**8a**) and 4-(2-pyridyl)-1-piperazineethanamine (**7a**),[23] the title compound was obtained in 48% yield: ^{1}H NMR 2.68−2.74 (m, 6H, $CH_2N(CH_2)_2$), 3.59−3.64 (m, 6H, $(CH_2)_2NAr$, $NHCH_2$), 3.83 (s, 3H, CH_3), 6.61−7.50 (m, 8H, aromatic, NH, 1H D_2O exchanged), 8.16−8.18 (m, 1H, aromatic N=CH); GC/MS *m*/*z* 341 (M^+ + 1, 2), 340 (M^+, 8), 246 (73), 221 (34), 176 (100), 147 (60), 121 (92), 107 (86).

***N*-[2-[4-(4-Chlorophenyl)piperazin-1-yl]ethyl]-3-methoxybenzamide (17).** Starting from acid **8a** and 4-(4-chlorophenyl)-1-piperazineethanamine (**7b**),[25] the title compound was obtained in 76% yield: ^{1}H NMR 2.71−2.73 (m, 6H, $CH_2N(CH_2)_2$), 3.21 (br t, 4H, $(CH_2)_2NAr$), 3.60 (q, 2H, J = 5.5 Hz, $NHCH_2$), 3.83 (s, 3H, CH_3), 6.80−7.38 (m, 9H, aromatic, NH, 1H D_2O exchanged); GC/MS *m*/*z* 376 (M^+ + 3, 1), 375 (M^+ + 2, 6), 374 (M^+ + 1, 4), 373 (M^+, 16), 211 (33), 209 (100), 166 (26).

***N*-[3-[4-(2-Methoxyphenyl)piperazin-1-yl]-*n*-propyl]-3-methoxybenzamide (18).** This compound was prepared in 51% yield starting from acid **8a** and 4-(2-methoxyphenyl)-1-piperazinepropanamine (**7d**):[26] ^{1}H NMR 1.79−1.87 (m, 2H, $CH_2CH_2CH_2$), 2.64 (br t, 2H, $CH_2N(CH_2)_2$), 2.68 (br s, 4H, $CH_2N(CH_2)_2$), 3.10 (br s, 4H, $(CH_2)_2NAr$), 3.58 (q, 2H, J = 5.5 Hz, $NHCH_2$), 3.77 and 3.84 (2 s, 6H, 2 CH_3), 6.83−7.44 (m, 8H, aromatic), 8.39 (br s, 1H, NH, D_2O exchanged); GC/MS *m*/*z* 385 (M^+ + 2, 3), 384 (M^+ + 1, 22), 383 (M^+, 89), 368 (100), 221 (57), 205 (85), 192 (56), 135 (99).

***N*-[2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl]-2,5-dimethoxybenzamide (19).** Starting from 2,5-dimethoxybenzoic acid (**8b**) and 4-(2-methoxyphenyl)-1-piperazineethanamine (**7c**),[26] the title compound was obtained in 72% yield: ^{1}H NMR 2.66−2.75 (m, 6H, $CH_2N(CH_2)_2$), 3.13 (br s, 4H, $(CH_2)_2NAr$), 3.62 (q, 2H, J = 5.7 Hz, $NHCH_2$), 3.80, 3.85, and 3.91 (3 s, 9H, 3 CH_3), 6.84−7.02 and 7.76−7.77 (m, 7H, aromatic), 8.54 (br s, 1H, NH, D_2O exchanged); GC/MS *m*/*z* 400 (M^+ + 1, 3), 399 (M^+, 11), 218 (22), 205 (100), 190 (27).

***N*-[2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl]-2-methoxybenzamide (20).** Starting from 2-methoxybenzoic acid (**8c**) and amine **7c**, the title compound was obtained in 56% yield after purification by column chromatography with CH_2Cl_2/ethyl acetate, 1:1, as eluent: ^{1}H NMR 2.64−2.73 (m, 6H, $CH_2N(CH_2)_2$), 3.12 (br s, 4H, $(CH_2)_2NAr$), 3.61 (q, 2H, J = 5.9

Hz, NHCH_2), 3.85 and 3.96 (2 s, 6H, 2 CH_3), 6.84−8.22 (m, 8H, aromatic), 8.42 (br s, 1H, NH); GC/MS *m/z* 368 ($M^+ + 1$, 1), 367 (M^+, 2), 218 (21), 205 (100), 190 (31), 135 (30).

***N*-(2-Chloroethyl)-3-methoxybenzamide (9).** To a cooled mixture containing 2-chloroethylamine hydrochloride (2.04 g, 17.6 mmol) in 1.2% aqueous NaOH (120 mL) was added dropwise under vigorous stirring a CH_2Cl_2 solution (50 mL) of 3-methoxybenzoyl chloride, prepared from the acid **8a** (2.43 g, 16.0 mmol) and $SOCl_2$ (5 mL). Then, the aqueous layer was separated and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and evaporated to dryness under reduced pressure to give nearly pure benzamide **9** as a colorless oil (3.27 g, 96% yield): ^{1}H NMR (90 MHz) 3.55−3.85 (m + s, 7H, CH_2CH_2, CH_3), 6.65−7.45 (m, 5H, aromatic, NH, 1H D_2O exchanged); GC/MS *m/z* 215 ($M^+ + 2$, 1), 213 (M^+, 5), 177 (81), 176 (36), 147 (100).

***N*-[2-[4-(2-Methoxybenzyl)piperazin-1-yl]ethyl]-3-methoxybenzamide (21).** A stirred solution of 1-(2-methoxybenzyl)piperazine (1.73 g, 8.4 mmol), benzamide **9** (1.50 g, 7.0 mmol), and triethylamine (4 mL) in toluene (50 mL) was refluxed for 20 h. Then the solvent was evaporated under reduced pressure and the residue taken up with a 20% aqueous Na_2CO_3 and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and evaporated to dryness. The crude residue was eluted with $CHCl_3$/MeOH, 19:1, to give 0.45 g of benzamide **21** (17% yield) as a pale yellow oil: ^{1}H NMR 2.59−2.64 (m, 10H, $NHCH_2CH_2$, piperazine), 3.53 (q, 2H, J = 5.5 Hz, $NHCH_2CH_2$), 3.60 (s, 2H, benzyl CH_2), 3.80 and 3.83 (2 s, 6H, 2 CH_3), 6.84−7.38 (m, 9H, aromatic, NH); GC/MS *m/z* 384 ($M^+ + 1$, 2), 383 (M^+, 8), 219 (100), 121 (53).

***N*-[2-[4-(4-Chlorobenzyl)piperazin-1-yl]ethyl]-3-methoxybenzamide (22).** As above, starting from 1-(4-chlorobenzyl)piperazine (1.77 g, 9.0 mmol) and the benzamide **9** (1.60 g, 7.5 mmol), the title compound was obtained in 36% yield: ^{1}H NMR 2.51−2.66 (m, 10H, $NHCH_2CH_2$, piperazine), 3.47 (s, 2H, benzyl CH_2), 3.51−3.70 (m, 2H, $NHCH_2CH_2$), 3.84 (s, 3H, CH_3), 6.97−7.38 (m, 9H, aromatic, NH); GC/MS *m/z* 389 ($M^+ + 2$, 1), 388 ($M^+ + 1$, 1), 387 (M^+, 4), 225 (33), 223 (100), 125 (44).

4-(2-Methoxyphenyl)-1-piperazineacetamide (12a). A mixture of the piperazine **10** (3.25 g, 17.0 mmol) and 2-chloroacetamide (3.18 g, 34.0 mmol) in toluene (30 mL) was refluxed overnight in the presence of a slight excess of K_2CO_3. After the mixture cooled, the solvent was removed under reduced pressure. The residue was taken up in H_2O and extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4) and the solvent removed, affording the amide **12a** as a white solid (3.19 g, 75% yield): mp 154−156 °C (from CH_2Cl_2/petroleum ether); ^{1}H NMR (90 MHz) 2.65−2.85 (m, 4H, $CH_2N(CH_2)_2$), 3.00−3.25 (m, 6H, $(CH_2)_2NAr$, $CH_2N(CH_2)_2$), 3.85 (s, 3H, CH_3), 6.30 (br s, 2H, NH_2), 6.80−7.10 (m, 4H, aromatic); GC/MS *m/z* 251 ($M^+ + 2$, 1), 250 ($M^+ + 1$, 9), 249 (M^+, 62), 205 (100), 190 (60), 162 (26), 134 (23), 120 (36).

4-(2-Methoxyphenyl)-1-piperazinepropanamide (12b). 4-(2-Methoxyphenyl)-1-piperazinepropanenitrile[26] (**11**) (3.20 g, 13.0 mmol) was slowly added under vigorous stirring to concentrated H_2SO_4 (10 mL), at room temperature. The mixture was heated for 1 h at 70−80 °C, then poured on ice and subsequently alkalinized with Na_2CO_3 and extracted with CH_2Cl_2; the separated organic layer was dried (Na_2SO_4) and evaporated under reduced pressure to give amide **12b** (2.74 g, 80% yield) as a white powder: mp 147−148 °C (from CH_2Cl_2/petroleum ether); ^{1}H NMR (90 MHz) 2.35−2.95 (m, 8H, $CH_2CH_2N(CH_2)_2$), 3.05−3.30 (m, 4H, $(CH_2)_2NAr$), 3.90 (s, 3H, CH_3), 5.83 and 8.15 (2 br s, 2H, NH_2, D_2O exchanged), 6.90−7.05 (m, 4H, aromatic); GC/MS *m/z* 265 ($M^+ + 2$, 2), 264 ($M^+ + 1$, 17), 263 (M^+, 100), 205 (52), 190 (36), 162 (28), 150 (25), 136 (71), 135 (38), 134 (38), 121 (25), 120 (67).

4-(2-Methoxyphenyl)-1-piperazinethioacetamide (13a). Lawesson's reagent (5.66 g, 14.0 mmol) was added portionwise to a stirred solution of the amide **12a** (3.49 g, 14.0 mmol) in anhydrous THF (30 mL). The suspension was refluxed for 1 h under nitrogen, until it became a yellow solution. After the solution was cooled at room temperature, the formed precipitate was filtered and the filtrate was evaporated to dryness. The residual oil was taken up with 3 N HCl and the aqueous phase was washed with CH_2Cl_2, alkalinized with Na_2CO_3, and extracted with $CHCl_3$. The organic phase was dried (Na_2SO_4) and the solvent removed to give an oil which was chromatographed with $CHCl_3$/MeOH, 9:1, as eluent. The thioamide **13a** was obtained as a yellow solid (3.19 g, 86% yield): mp 130−132 °C (from CH_2Cl_2/petroleum ether); ^{1}H NMR (90 MHz) 2.75−3.00 (m, 4H, $CH_2N(CH_2)_2$), 3.10−3.30 (m, 4H, $(CH_2)_2NAr$), 3.60 (s, 2H, $CH_2N(CH_2)_2$), 3.85 (s, 3H, CH_3), 7.00−7.05 (m, 4H, aromatic), 8.25 and 8.95 (2 br s, 2H, NH_2, D_2O exchanged); GC/MS *m/z* 267 ($M^+ + 2$, 3), 266 ($M^+ + 1$, 7), 265 (M^+, 43), 205 (100), 191 (28), 190 (90), 162 (25), 135 (39), 134 (29), 120 (40).

4-(2-Methoxyphenyl)-1-piperazinepropanethioamide (13b). Lawesson's reagent (4.61 g, 11.4 mmol) was added portionwise to a stirred solution of the amide **12b** (3.00 g, 11.4 mmol) in anhydrous toluene (30 mL). The suspension was refluxed for 1 h under nitrogen, until it became a yellow solution. The reaction mixture was worked up as for derivative **13a**. Thioamide **13b** was obtained as a yellow solid (0.90 g, 28% yield): mp 139−141 °C (from CH_2Cl_2/petroleum ether); ^{1}H NMR (90 MHz) 2.60−3.20 (m, 12H, $3CH_2CH_2$), 3.85 (s, 3H, CH_3), 6.95−7.00 (m, 4H, aromatic), 7.90 and 10.30 (2 br s, 2H, NH_2, D_2O exchanged); GC-MS *m/z* 245 (100), 205 (65), 190 (41), 177 (42), 136 (47), 135 (42), 134 (29), 120 (62).

2-[[4-(2-Methoxyphenyl)piperazin-1-yl]methyl]-4-(3-methoxyphenyl)thiazole (23). A solution of the thioamide **13a** (1.20 g, 4.5 mmol) and 2-bromo-3′-methoxyacetophenone (2.06 g, 9.0 mmol) in anhydrous EtOH was refluxed for 6 h under nitrogen. Evaporation of the solvent afforded an oil which was chromatographed (CH_2Cl_2/MeOH, 49:1, as eluent) to give 1.30 g (73% yield) of pure **23** as a pale yellow oil: ^{1}H NMR 2.95 (br s, 4H, $CH_2N(CH_2)_2$), 3.20 (br s, 4H, $(CH_2)_2NAr$), 3.84 and 3.86 (2 s, 6H, CH_3), 4.08 (br s, 2H, $CH_2N(CH_2)_2$), 6.84−7.46 (m, 9H, aromatic); GC/MS *m/z* 397 ($M^+ + 2$, 4), 396 ($M^+ + 1$, 12), 395 (M^+, 46), 326 (29), 246 (32), 205 (100), 204 (55), 191 (64), 176 (50), 175 (55), 162 (55).

2-[2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl]-4-(3-methoxyphenyl)thiazole (24). As above, starting from the thioamide **13b** (0.90 g, 3.2 mmol) and 2-bromo-3′-methoxyacetophenone (1.47 g, 6.4 mmol), the title compound was obtained as a pale yellow oil (0.72 g, 56% yield): ^{1}H NMR 2.85 and 2.98 (2 br s, 6H, $CH_2CH_2N(CH_2)_2$), 3.18 (br s, 4H, $(CH_2)_2NAr$), 3.34 (br s, 2H, $CH_2CH_2N(CH_2)_2$), 3.85 and 3.86 (2 s, 6H, CH_3), 6.84−7.45 (m, 9H, aromatic); GC/MS 410 ($M^+ + 1$, 1), 409 (M^+, 5), 260 (25), 247 (57), 205 (100), 204 (60), 203 (22), 191 (28), 190 (37).

***N*-(7-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)bromoacetamide (15a).** Following the procedure reported for the synthesis of the amide **9**, the title compound was obtained from 7-methoxy-1,2,3,4-tetrahydro-1-naphthalenamine (**14a**)[27] (1.35 g, 9.9 mmol) and bromoacetyl chloride (0.7 mL, 9.5 mmol) in nearly quantitative yield, as a white solid: mp 101−103 °C (from $CHCl_3$/*n*-hexane); ^{1}H NMR (90 MHz) 1.65−2.15 (m, 4H, *endo* CH_2CH_2), 2.75 (br t, 2H, benzyl CH_2), 3.75 (s, 3H, CH_3), 3.85 (s, 2H, CH_2Br), 4.95−5.25 (m, 1H, C*H*NH), 6.60−7.10 (m, 4H, aromatic, NH); GC/MS *m/z* 299 ($M^+ + 2$, 2), 297 (M^+, 2), 160 (100), 159 (26).

***N*-(7-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3-chloropropanamide (15c).** In the same manner as above, this compound was obtained from the amine **14a** (1.24 g, 7.0 mmol) and 3-chloropropionyl chloride (0.6 mL, 9.1 mmol) in nearly quantitative yield as a white solid: mp 126−127 °C (from CH_2Cl_2/*n*-hexane); ^{1}H NMR (90 MHz) 1.66−2.10 (m, 4H, *endo* CH_2CH_2), 2.45−2.80 (m, 4H, benzyl CH_2, $COCH_2$), 3.70−3.90 (m + s, 5H, CH_3, CH_2Cl), 5.00−5.30 (m, 1H, C*H*NH), 6.20 (br d, 1H, NH), 6.65−7.00 (m, 3H, aromatic); GC/MS *m/z* 269 ($M^+ + 2$, 1), 268 ($M^+ + 1$, 1), 267 (M^+, 4), 160 (100), 159 (25).

***N*-(7-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-4-(2-methoxyphenyl)-1-piperazinepropanamide (28).** The amide **15c** (1.05 g, 3.9 mmol) was refluxed overnight with the piperazine **10** (1.39 g, 7.8 mmol) and a slight excess of $NaHCO_3$ in acetonitrile. After cooling, the mixture was concentrated

under reduced pressure, and the residue was taken up with water and extracted with $CHCl_3$. The chloroform phase was dried over Na_2SO_4, the solvent was evaporated, and the crude residue was chromatographed ($CHCl_3$/MeOH, 19:1 as eluent) to give **28** as a pale yellow semisolid (1.23 g, 78% yield): ^{1}H NMR 1.74−2.01 (m, 4H, *endo* CH_2CH_2), 2.45−3.03 (m, 14H), 3.71 and 3.82 (2 s, 6H, 2 CH_3), 5.05−5.09 (m, 1H, C*H*NH), 6.69−7.02 (m, 7H, aromatic), 8.66 (br s, 1H, NH); GC/MS *m*/*z* 425 ($M^+ + 2$, 2), 424 ($M^+ + 1$, 13), 423 (M^+, 50), 409 (27), 408 (100), 205 (26), 161 (60), 160 (32).

***N*-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-4-(2-methoxyphenyl)-1-piperazineacetamide (29).** Starting from *N*-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)bromoacetamide[23] (**15b**) and 1-(2-methoxyphenyl)piperazine (**10**), the title compound was prepared as above in the same yield: ^{1}H NMR 1.72−1.84 and 1.97−2.04 (mm, 4H, *endo* CH_2CH_2), 2.57−2.73 (m, 6H, benzyl CH_2, $CH_2N(CH_2)_2$), 3.03 (br s, 4H, $(CH_2)_2NAr$), 3.13 (br s, 2H, $CH_2N(CH_2)_2$), 3.80 and 3.83 (2 s, 6H, 2 CH_3), 5.13−5.22 (m, 1H, C*H*NH), 6.71−7.16 (m, 7H, aromatic), 7.42 (br s, 1H, NH, D_2O exchanged); GC/MS *m*/*z* 411 ($M^+ + 2$, 1), 410 ($M^+ + 1$, 5), 409 (M^+, 29), 205 (100), 190 (27).

***N*-(7-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-4-(2-methoxyphenyl)-1-piperazineacetamide (30).** As above and in the same yield, the title compound was prepared starting from compound **15a** and 1-(2-methoxyphenyl)piperazine (**10**): ^{1}H NMR 1.67−1.85 and 2.00−2.10 (mm, 4H, *endo* CH_2CH_2), 2.63−2.80 (mm, 6H, benzyl CH_2, $CH_2N(CH_2)_2$), 3.02 (br s, 4H, $(CH_2)_2NAr$), 3.12 (d, 2H, J = 5.4 Hz, $CH_2N(CH_2)_2$), 3.73 and 3.83 (2 s, 6H, 2 CH_3), 5.14−5.20 (m, 1H, C*H*NH), 6.73−7.02 (m, 7H, aromatic), 7.43 (br d, 1H, NH); GC/MS *m*/*z* 411 ($M^+ + 2$, 1), 410 ($M^+ + 1$, 9), 409 (M^+, 38), 205 (100), 190 (27).

Pharmacological Methods. $D_{4.2}$ Dopaminergic Binding Assay. Binding of [^{3}H]YM-09151-2 for human cloned $D_{4.2}$ dopamine receptor produced in Sf9 cells baculovirus expression (NEN Life Science) was performed according to Hadley et al.[28] with minor modifications. The reaction buffer consisted of 50 mM Tris·HCl, 5 mM $MgCl_2$, 5 mM EDTA, 5 mM KCl, 1.5 mM $CaCl_2$ (pH 7.4), including 500 μL of dopamine $D_{4.2}$ diluted membranes, 0.06 nM of [^{3}H]YM-09151-2 (K_d= 0.06 nM), and 100 μL of various concentrations (10^{-6}−10^{-11} M) of drugs to reach a total volume of 1 mL. After a 60 min incubation at 25 °C, the incubations were terminated by rapid filtration through Whatman GF/C glass fiber filters (presoaked in 0.3% polyethylenimine) with two washes of 1 mL of ice cold buffer (50 mM Tris·HCl, pH 7.4). Nonspecific binding was defined in the presence of haloperidol (1 μM).

D_{2S} Dopaminergic Binding Assay. Binding of [^{3}H]-spiperone for human cloned D_{2S} dopamine receptor produced in Sf9 cells baculovirus expression (NEN Life Science) was performed according to Hadley et al.[28] with minor modifications. The reaction buffer consisted of 50 mM Tris·HCl, 10 mM $MgCl_2$, 1 mM EDTA (pH 7.4), including 500 μL of dopamine D_{2S} diluted membranes, 0.2 nM of [^{3}H]spiperone (K_d = 0.17 nM), and 100 μL of various concentration (10^{-6}−10^{-11} M) of drugs to reach a total volume of 1 mL. After a 60 min incubation at 27 °C, the incubations were terminated by rapid filtration through Whatman GF/C glass fiber filters (presoaked in 0.3% polyethylenimine) with two washes of 1 mL of ice cold buffer (50 mM Tris·HCl, pH 7.4). Nonspecific binding was defined in the presence of haloperidol (1 μM).

5-HT_{1A} Serotonergic Binding Assay. Standard receptor binding methods were used to label 5-HT_{1A} receptors using [^{3}H]-8-OH-DPAT as previously decribed.[29]

α_1 Adrenergic Binding Assay. Standard receptor binding methods were used to label α_1 receptors using [^{3}H]prazosin as previously decribed.[29]

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