A Structure−Affinity Relationship Study on Derivatives of *N*-[2-[4-(4-Chlorophenyl)piperazin-1-yl]ethyl]-3-methoxybenzamide, a High-Affinity and Selective D_4 Receptor Ligand

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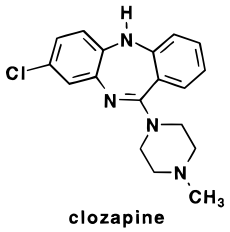
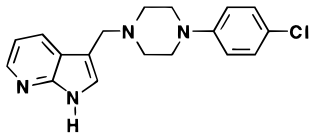
N-[2-[4-(4-Chlorophenyl)piperazin-1-yl]ethyl]-3-methoxybenzamide (**1**), a high-affinity and selective dopamine D_4 receptor ligand, was chosen as a lead, and structural modifications were done on its amide bond and on its alkyl chain linking the benzamide moiety to the piperazine ring and by preparing some semirigid analogues. The binding profile at dopamine D_4 and dopamine D_2, serotonin 5-HT_{1A}, and adrenergic α_1 receptors of 16 new compounds was determined. From the results emerged that the modification of the amide bond and the elongation of the intermediate alkyl chain caused a decrease in dopamine D_4 receptor affinity. All prepared semirigid analogues displayed D_4 receptor affinity values in the same range of the opened counterparts.

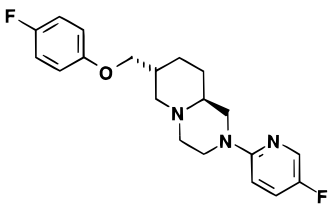
Currently, much research effort is being focused on the discovery of highly selective dopamine D_4 receptor ligands.[1] The reason for the interest in this area derives from the possible involvement of D_4 receptor in schizophrenia.[2−5] Recent advances in molecular biology have identified five cloned human subtypes of dopamine receptor, divided pharmacologically into two classes: D_1-like (D_1 and D_5)[6,7] and D_2-like (D_2, D_3, and D_4).[8−10] Classical antipsychotic drugs are presumed to act by an unselective blockade of D_2-like dopamine receptors.[11] These drugs are useful for the treatment of positive symptoms of schizophrenia, and their use is limited by disabling side effects such as the unwanted extrapyramidal syndrome (EPS), tardive dyskinesia, and hormonal side effects such as hyperprolactinemia.[12] On the other hand, unlike classical neuroleptics, the atypical antipsychotic clozapine can be used to treat both positive and negative symptoms of schizophrenia and it causes fewer cases of EPS.[13] 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 in approximately 2% of patients.[14] In the last five years, several research groups have communicated on a number of series of D_4 receptor ligands. Some of them underwent clinical trials giving somewhat different results. For example, L-745,870 was found to be ineffective as an antipsychotic in humans;[15] on the contrary, CP-293,019 was claimed to display an excellent activity in an in vivo model responsive to antipsychotic drugs, yet lacked the property to produce APO-induced stereotypy and to induce catalepsy.[16] Therefore, to date, new potent and selective D_4 receptor ligands are needed to clarify the role of the D_4 receptors in the etiology of schizophrenia and related disorders. Our research group initiated a research program aimed to discover new D_4 receptor ligands with 1-arylpiperazine structure[17] which led to *N*-[2-[4-(4-chlorophenyl)piperazin-1-yl]ethyl]-3-methoxybenzamide (**1**).[18] This derivative exhibited very high affinity toward dopamine D_4 receptor (K_i = 0.04 nM) with a >10000-fold selectivity versus the D_2 receptor. In the present paper we studied some structural modifications with the aim to put in evidence the fundamental structural requirement for the high affinity and selectivity of compound **1** at D_4 receptor. We first studied the importance of the amide function in compound **1** through the substitution of the amido group with a keto group (compound **28**), the replacing of the amide function with two methylene groups (compound **29**), and the reduction of the amide function (compound **30**). Furthermore, we provided for the synthesis of the corresponding *retro* amide **31** and the methylation of the nitrogen of the amide function (compound **32**). Subsequently, we studied the effect on D_4 receptor binding affinity of the alkyl chain length for the most high affinity compounds (derivatives **1** and **28**) by preparing compounds **33**−**37**. Finally, as we noted that the optimal chain length was of two methylene groups



clozapine



L-745,870



CP-293,019

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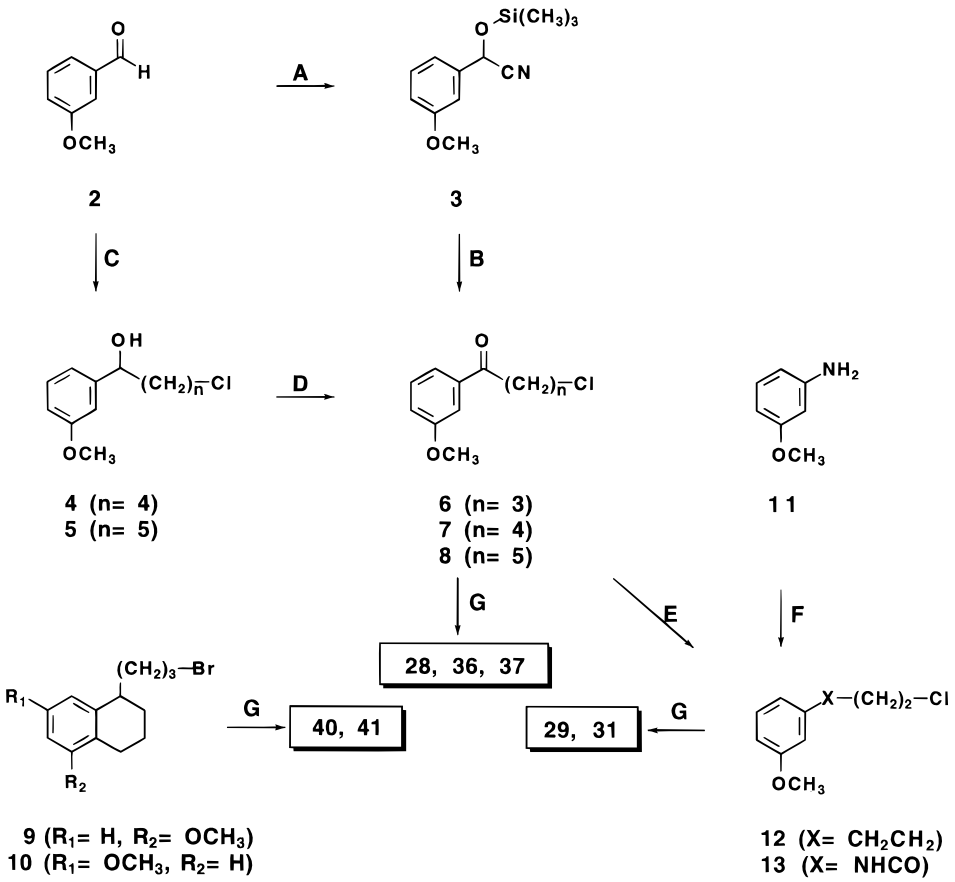
Scheme 1[a]



[a] Reagents: (A) $(CH_3)_3SiCN$, ZnI_2; (B) (i) LDA, $Br(CH_2)_3Cl$, (ii) 2 N HCl; (C) $BrMg(CH_2)_4Cl$ or $BrMg(CH_2)_5Cl$; (D) Jones' reagent; (E) $(CH_3)_3CNH_2{\cdot}BH_3$, $AlCl_3$; (F) $Cl(CH_2)_2COCl$; (G) 1-(4-chlorophenyl)piperazine (**14**).

($n = 2$), some semirigid congeners of compounds **1**, **29**, and **30** were prepared and tested. In particular, compounds **38** and **39**, **40** and **41**, **42** and **43** can be considered structurally related with compounds **1**, **29**, and **30**, respectively.

Chemistry

The final step for the preparation of compounds **28**, **29**, **31**, **36**, **37**, **40**, and **41** was the alkylation of 1-(4-chlorophenyl)piperazine (**14**) with the appropriate alkyl halides (Scheme 1). Among the latter compounds, derivatives **9** and **10** were prepared according to the reported procedure,[19] and the remaining were obtained as described below.

Ketone **6** was prepared as follows: 3-methoxybenzaldehyde (**2**) was reacted with trimethylsilyl cyanide to give the trimethylsilyl cyanohydrin derivative **3**;[20] the latter was transformed into its anion with lithium diisopropylamide (LDA) and then it was alkylated with 1-bromo-3-chloropropane.[21] The protected cyanohydrin so obtained gave the intermediate ketone **6** by subsequent treatment with dilute hydrochloric acid.

The ketones **7** and **8** were obtained from 3-methoxybenzaldehyde (**2**) which was reacted with the appropriate Grignard reagent to give the secondary alcohols **4** and **5**; oxidation of the latter compounds with Jones' reagent gave the key intermediates **7** and **8**.

Chlorobutyl derivative **12** was obtained from ketone **6** by reduction of the carbonyl function with *tert*-butylamino borane complex in the presence of $AlCl_3$.[22]

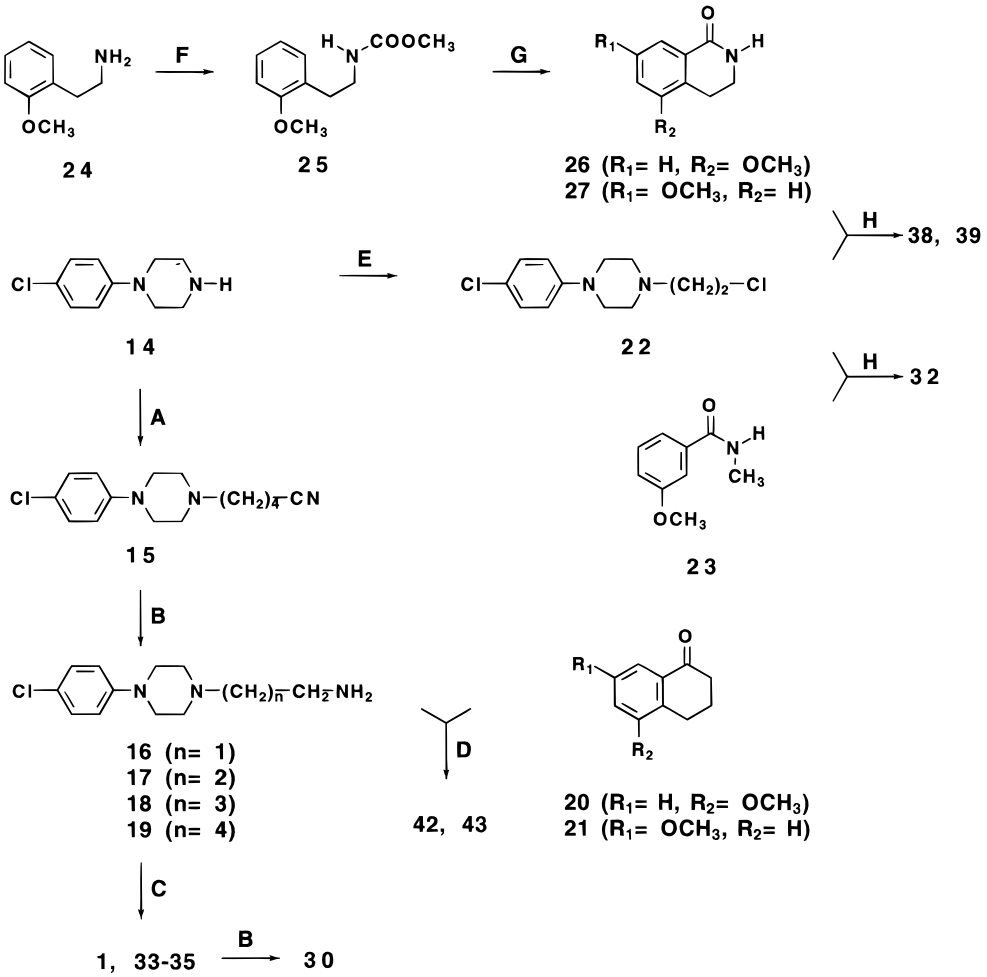
The intermediate anilide **13** was prepared by acylation of 3-methoxyaniline (**11**) with 3-chloropropionyl chloride.

The synthesis of compounds **33**−**35** (Scheme 2) required amines **17**−**19** as the key intermediates. The amines **17** and **18** were prepared as described in the literature.[23] The amine **19** was prepared by alkylating 1-(4-chlorophenyl)piperazine (**14**) with 4-chloropentanenitrile to give compound **15**; reduction of the latter with borane methyl sulfide complex[24] yielded amine **19**. Finally, benzamides **33**−**35** were obtained by condensing 3-methoxybenzoyl chloride with the amines **17**−**19**. Tetrahydronaphthalenamine derivatives **42** and **43** were prepared by condensing methoxy-1-tetralones **20** and **21** with the amine **16**[23] and then reducing the intermediate imines with $NaBH_4$.

The amine **30** was prepared by reducing benzamide **1** with borane methyl sulfide complex.[24]

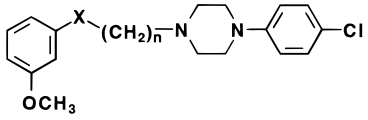
N-Methylated benzamide **32** and cyclic amides **38** and **39** were prepared (Scheme 2) by reacting, under phase-transfer catalysis,[25] 4-(2-chloroethyl)-1-(4-chlorophenyl)-piperazine[26] (**22**) with the *N*-methyl-3-methoxybenzamide[27] (**23**) or intermediate amides **26** and **27**, respectively. Isoquinolinone **26** was prepared, following the same synthetic procedure reported for its isomer **27**,[28] starting from 2-methoxyphenethylamine (**24**) which was reacted with methyl chloroformate to give the carbamate **25**; cyclization of the latter with polyphosphoric acid afforded isoquinolinone **26**.

Scheme 2[a]



[a] Reagents: (A) $Cl(CH_2)_4CN$; (B) $(CH_3)_2S{\cdot}BH_3$; (C) 3-methoxybenzoyl chloride; (D) (i) *p*-toluenesulfonic acid, (ii) $NaBH_4$; (E) $Br(CH_2)_2Cl$; (F) $ClCOOCH_3$, triethylamine; (G) polyphosphoric acid; (H) tetrabutylammonium bromide, KOH.

Table 1. Physical Properties and Binding Affinities of Derivatives **28**−**37**



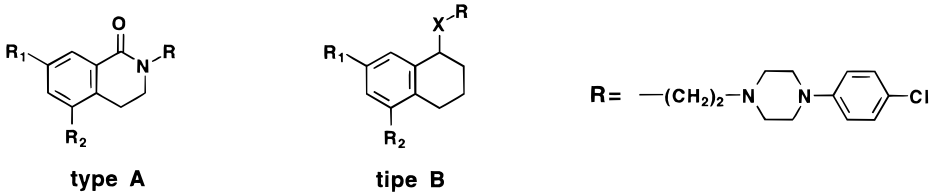
						$K_i \pm$ SEM, nM[a]			
cpd	X	*n*	formula[b]	mp, °C	recryst solv	$D_{4.4}$	D_{2L}	5-HT_{1A}	α_1
1[c]	CONH	2				0.040 ± 0.002	1900 ± 250	147 ± 14	245 ± 30
28	$COCH_2$	2	$C_{21}H_{25}ClN_2O_2$	96−97	$CHCl_3$/*n*-hexane	4.0 ± 0.8	2550 ± 140	183 ± 11	908 ± 37
29	CH_2CH_2	2	$C_{21}H_{27}ClN_2O{\cdot}2HCl{\cdot}^1/_2H_2O$	161	MeOH/Et_2O	204 ± 19	2740 ± 200	514 ± 29	>850 (25%)[d]
30	CH_2NH	2	$C_{20}H_{26}ClN_3O{\cdot}2HCl$	235	MeOH/Et_2O	23 ± 9	5000 ± 210	>850 (16%)	>850 (12%)
31	NHCO	2	$C_{20}H_{24}ClN_3O_2{\cdot}2HCl$	254 dec	MeOH/Et_2O	42 ± 8	282 ± 21	859 ± 93	303 ± 28
32	$CON(CH_3)$	2	$C_{21}H_{26}ClN_3O_2{\cdot}HCl$	237−239	MeOH	180 ± 12	>850 (10%)	>850 (18%)	>850 (22%)
33	CONH	3	$C_{21}H_{26}ClN_3O_2$	121−123	$CHCl_3$/*n*-hexane	5.4 ± 0.7	3950 ± 150	>850 (41%)	437 ± 31
34	CONH	4	$C_{22}H_{28}ClN_3O_2{\cdot}HCl{\cdot}^5/_4H_2O$	191−193	MeOH/Et_2O	25 ± 2	2350 ± 270	397 ± 32	406 ± 40
35	CONH	5	$C_{23}H_{30}ClN_3O_2{\cdot}HCl$	189−190	MeOH/Et_2O	241 ± 35	>850 (22%)	>850 (44%)	470 ± 25
36	$COCH_2$	3	$C_{22}H_{27}ClN_2O_2{\cdot}HCl{\cdot}^3/_2H_2O$	179−180	MeOH/Et_2O	21 ± 8	>850 (20%)	37 ± 6	146 ± 12
37	$COCH_2$	4	$C_{23}H_{29}ClN_2O_2$	75−77	$CHCl_3$/*n*-hexane	280 ± 21	>850 (15%)	45 ± 8	678 ± 35
clozapine						30.0 ± 0.3	876 ± 72	443 ± 13	56 ± 8
haloperidol						1.0 ± 0.1	5.6 ± 0.3	2390 ± 320	146 ± 18

[a] Data are the mean of three independent determinations (samples in triplicate). [b] Analyses for C, H, N; results were within ±0.4% of the theoretical values for the formulas given. [c] See ref 18. [d] Full K_i not obtained, percentage inhibition at the concentration shown given in parentheses. Values taken from only one experiment.

Pharmacology

All final compounds (Tables 1 and 2) were tested for their in vitro binding affinities toward dopamine $D_{4.4}$ and D_{2L}, serotonin 5-HT_{1A}, and α_1 adrenergic receptors. The following specific radioligands and tissue sources were used: (a) dopamine $D_{4.4}$ receptors—[^{3}H]YM 09151-2, human cloned in *Sf*9 baculovirus expression; (b) dopamine D_{2L} receptors—[^{3}H]spiroperidol, human cloned in *Sf*9 baculovirus expression; (c) serotonin 5-HT_{1A} receptors—[^{3}H]-8-OH-DPAT, rat hippocampal

Table 2. Physical Properties and Binding Affinities of Derivatives **38**−**43**



								$K_i \pm$ SEM, nM[a]			
cpd	type	R_1	R_2	X	formula[b]	mp, °C	recryst solv	D_4	D_2	5-HT_{1A}	α_1
38	A	H	OCH_3		$C_{22}H_{26}ClN_3O_2 \cdot 2HCl \cdot {}^3/_2H_2O$	234	MeOH/Et_2O	42 ± 8	3170 ± 120	451 ± 78	631 ± 27
39	A	OCH_3	H		$C_{22}H_{26}ClN_3O_2$	120−122	$CHCl_3$/*n*-hexane	141 ± 15	3960 ± 210	11 ± 1	>850 (33%)[c]
40	B	H	OCH_3	CH_2	$C_{24}H_{31}ClN_2O \cdot 2HCl$	230−231	MeOH/Et_2O	416 ± 24	3400 ± 140	105 ± 15	>850 (34%)
41	B	OCH_3	H	CH_2	$C_{24}H_{31}ClN_2O \cdot 2HCl$	196−198	MeOH	391 ± 25	980 ± 62	708 ± 19	>850 (19%)
42	B	H	OCH_3	NH	$C_{23}H_{30}ClN_3O \cdot 2HCl$	256−258	MeOH	32 ± 6	3180 ± 170	821 ± 29	>850 (27%)
43	B	OCH_3	H	NH	$C_{23}H_{30}ClN_3O \cdot 2HCl \cdot {}^1/_2H_2O$	235 dec	MeOH/Et_2O	46 ± 9	262 ± 12	>850 (37%)	>850 (37%)

[a] Data are the mean of three independent determinations (samples in triplicate). [b] Analyses for C, H, N; results were within ±0.4% of the theoretical values for the formulas given. [c] Full K_i not obtained, percentage inhibition at the concentration shown given in parentheses. Values taken from only one experiment.

membranes; (d) 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 which were used to calculate the inhibition constants (K_i) using the Cheng−Prusoff equation.[29]

Results and Discussion

The results of the in vitro binding experiments on the target compounds **28**−**43** are summarized in Tables 1 and 2. Considering the first group of compounds (derivatives **28**−**32**), where the amide function of compound **1** has been changed, it can be noted that none of these compounds displayed better D_4 receptor affinity than the reference compound **1**. Only compound **28**, where the benzamide moiety was replaced by a benzophenone one, retained a D_4 receptor affinity in the nanomolar range (K_i = 4 nM). The reduced analogue **30** of the lead benzamide **1** and the *retro* amide **31** still retained D_4 receptor affinity (K_i = 23 and 42 nM, respectively). A dramatic loss in D_4 receptor affinity was observed when the amide function was replaced by two methylene groups (compound **29**) or in the case that the amide group was N-methylated (compound **32**), being K_i = 204 and 180 nM, respectively. These data indicated the importance of the secondary benzamide moiety for binding with a possible H-bond at D_4 receptor in this series of compounds. Considering the D_2 receptor it can be noted that compounds **28**−**32** displayed poor receptor affinities. As far as 5-HT_{1A} and α_1 receptor affinities were considered, compounds **28**−**32** displayed K_i values lower than those displayed by the reference compound **1**.

Starting from these results, we prepared the compounds **33**−**37** in order to investigate the effect of the elongation of the alkyl chain on D_4 receptor binding affinity; such a study was limited only to compounds showing the highest D_4 receptor affinity (derivative **1** and **28**). As additional methylene groups were added to extend the length of the spacer, both the benzamide and benzophenone derivatives exhibited similar trends: receptor binding affinities for dopamine D_4 declined with the increasing of the number of atoms in the chain. With regard to D_2 receptor affinity, it can be noted that compounds **33**−**37** displayed poor affinity values, having K_i values always over 850 nM. On the other hand, considering 5-HT_{1A} and α_1 receptor affinities, they were low with the exception of benzophenones **36** and **37** which displayed moderate 5-HT_{1A} receptor affinity (K_i = 37 and 45 nM, respectively). These results indicated that in both class of compounds a four-atom linker (derivative **1** and **28**) provided optimal D_4 receptor affinity. Furthermore, in benzophenone derivatives the elongation of the linker shifted the affinity from D_4 to 5-HT_{1A} receptor. Finally, regarding the semirigid congeners, compounds **38** and **39** can be considered as derived from two possible rotamers of compound **1**. Comparing their D_4 receptor affinity with that of the reference compound **1**, a dramatic loss in D_4 receptor affinity was observed. More correctly, one should compare isoquinolinones **38** and **39** with derivative **32** which is devoid of the hydrogen atom on the amide function. In this way, a great difference in D_4 receptor affinity can not be found. The same behavior was observed when comparing compound **29** (K_i = 204 nM) with tetralin derivatives **40** and **41** (K_i = 416 and 391 nM, respectively) and compound **30** (K_i = 23 nM) with compounds **42** and **43** (K_i = 32 and 46 nM, respectively). The only interesting data from these semirigid congeners derived from compounds **38** and **39**: the 5-HT_{1A} receptor affinity of the latter compound is higher than that of its isomer **38**. Consequently, the compound **38** showed higher D_4 receptor affinity and selectivity than compound **39**. In the other cases of semirigid congeners, both the pair **40**, **41** and **42**, **43**, corresponding to the possible rotamers of **29** and **30**, respectively, displayed D_4 receptor affinity and selectivity values in the same range.

In conclusion, it can be affirmed that the optimal structural conditions for D_4 receptor affinity in this series of compounds are achieved for opened derivatives with a secondary 3-OCH_3-benzamide moiety (compounds **1** and **33**) or a 3-OCH_3-benzophenone group (compounds **28** and **36**) joined to the piperazine ring by two or three methylene groups.

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 (unless otherwise indicated); all chemical shift values are reported in ppm (δ). Recording of mass spectra was done on a HP6890-5973 MSD gas chromatograph/mass spectrometer; only significant *m*/*z* peaks, with their percent 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 salt by adding an HCl ethereal solution to a methanolic solution of the amine; the salts were recrystallized as detailed in Tables 1 and 2.

The following compounds were synthesized by published procedures: 1-(3-bromopropyl)-5-methoxy-1,2,3,4-tetrahydronaphthalene (**9**),[19] 1-(3-bromopropyl)-7-methoxy-1,2,3,4-tetrahydronaphthalene (**10**),[19] 4-(4-chlorophenyl)-1-piperazineethanamine (**16**),[23] 4-(4-chlorophenyl)piperazinepropanamine (**17**),[23] 4-(4-chlorophenyl)-1-piperazinebutanamine (**18**),[23] 4-(2-chloroethyl)-1-(4-chlorophenyl)piperazine (**22**),[26] *N*-methyl-3-methoxybenzamide (**23**),[27] and 7-methoxy-3,4-dihydroisoquinolin-1-one (**27**).[28]

3-Methoxy-α-[(trimethylsilyl)oxy]benzeneacetonitrile (3). 3-Methoxybenzaldehyde (**2**) (2.7 mL, 22.2 mmol) was added to a cooled mixture of trimethylsilyl cyanide (3.2 mL, 24.2 mmol) and a catalytic amount of ZnI_2, under stirring. The mixture was heated at 80 °C for 8 h, then cooled and diluted with CH_2Cl_2. The organic phase was washed with 20% aqueous Na_2CO_3 and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave the crude trimethylsilyl cyanohydrin that was chromatographed (petroleum ether/AcOEt, 4:1 as eluent) to give compound **3** as a pale yellow oil (3.60 g, 69% yield). ^{1}H NMR (90 MHz, TMS was not used): 0.10 [s, 9H, $Si(CH_3)_3$], 3.75 (s, 3H, OCH_3), 5.33 (s, 1H, CH), 6.65−7.30 (m, 4H, aromatic). GC/MS: *m*/*z* 237 ($M^+ + 2$, 2), 236 ($M^+ + 1$, 8), 235 (M^+, 39), 221 (28), 220 (100), 146 (28).

4-Chloro-1-(3-methoxyphenyl)-1-butanone (6). Freshly distilled diisopropylamine (5 mL) was mixed with anhydrous THF (10 mL) under N_2. The solution was cooled at 0 °C and *n*-butyllithium (2.336 M solution in *n*-hexane, 7.7 mL, 18.0 mmol) was added. After 15 min the mixture was cooled at −70 °C, and the trimethysilyl cyanohydrin **3** (3.86 g, 16.4 mmol) in anhydrous THF was added dropwise. The mixture was kept at −70 °C for 30 min, and then 1-bromo-3-chloropropane (1.8 mL, 18.0 mmol) in THF was added. The stirred reaction mixture was allowed to warm at room temperature and so was kept for 2 h; then it was treated with 2 N HCl (20 mL) and MeOH (10 mL) and was stirred overnight at room temperature. Finally, the reaction mixture was diluted with H_2O and extracted with Et_2O. The separated organic layer was washed with 1 N NaOH, then with H_2O, and dried (Na_2SO_4). The solvent was evaporated under reduced pressure, and the crude residue was chromatographed (petroleum ether/AcOEt, 2:1 as eluent) to give ketone **6** as a colorless oil (2.13 g, 61% yield). ^{1}H NMR (90 MHz): 2.03−2.40 [m, 2H, $COCH_2CH_2$], 3.16 (t, 2H, J = 6.0 Hz, $COCH_2$), 3.67 (t, 2H, J = 6.0 Hz, CH_2Cl), 3.85 (s, 3H, CH_3), 7.05−7.70 (m, 4H, aromatic). GC/MS: *m*/*z* 214 ($M^+ + 2$, 9), 213 ($M^+ + 1$, 3), 212 (M^+, 25), 150 (30), 135 (100), 107 (33).

5-Chloro-1-(3-methoxyphenyl)-1-pentanol (4). To a stirred solution of Grignard reagent, prepared from Mg turnings (0.75 g, 30.7 mmol) and 1-bromo-4-chlorobutane (3.0 mL, 26.4 mmol) in anhydrous THF (20 mL), was added dropwise 3-methoxybenzaldehyde (**2**) (3.00 g, 22.0 mmol) in the same solvent (20 mL). After the mixture was refluxed for 3 h and cooled at room temperature, a cooled saturated solution of NH_4Cl (40 mL) was added to the cooled reaction mixture. Extraction with Et_2O and evaporation of the dried (Na_2SO_4) organic layer gave a crude residue which was chromatographed (CH_2Cl_2/AcOEt, 7:3 as eluent) to give alcohol **4** as a colorless liquid (3.20 g, 64% yield). ^{1}H NMR (90 MHz): 1.15−2.13 [m, 7H, $(CH_2)_3CH_2Cl$, OH, 1H D_2O exchanged], 3.50 (br t, 2H, CH_2Cl), 3.80 (s, 3H, CH_3), 4.53−4.75 (m, 1H, C*H*OH), 6.73−7.30 (m, 4H, aromatic). GC/MS: *m*/*z* 230 ($M^+ + 2$, 4), 229 ($M^+ + 1$, 2), 228 (M^+, 12), 137 (99), 109 (100).

6-Chloro-1-(3-methoxyphenyl)-1-hexanol (5). The title compound was prepared from bromo(5-chloropentyl)magnesium and aldehyde **2** in the same manner as above. ^{1}H NMR (90 MHz): 1.05−1.95 [m, 8H, $(CH_2)_4CH_2Cl$], 2.13 (s, 1H, OH, D_2O exchanged), 3.45 (t, 2H, J = 6.0 Hz, CH_2Cl), 3.78 (s, 3H, CH_3), 4.50−4.73 (m, 1H, C*H*OH), 6.73−7.40 (m, 4H, aromatic). GC/MS: *m*/*z* 244 ($M^+ + 2$, 11), 243 ($M^+ + 1$, 5), 242 (M^+, 30), 138 (21), 137 (100), 109 (80).

5-Chloro-1-(3-methoxyphenyl)-1-pentanone (7). Jones' reagent (2.5 mL, prepared by dissolving 40 g of CrO_3 in 80 mL of H_2O and 20 mL of concentrated H_2SO_4) was added dropwise to a cooled solution of the compound **4** (1.01 g, 4.4 mmol) in acetone (50 mL, distilled over $KMnO_4$) and kept at 0 °C. When the addition was over, the reaction mixture was stirred for 6 h at room temperature and then diluted with H_2O. The aqueous phase was extracted with AcOEt (3 × 50 mL), and the collected organic layers were washed with 5% aqueous $NaHCO_3$ and dried (Na_2SO_4). Evaporation of the solvent gave a crude residue which was chromatographed (petroleum ether/CH_2Cl_2, 4:1 as eluent) to give ketone **7** as a colorless oil (0.89 g, 89% yield). ^{1}H NMR (90 MHz): 1.75−1.97 [m, 4H, $(CH_2)_2CH_2Cl$], 2.95 (br t, 2H, $COCH_2$), 3.55 (br t, 2H, CH_2Cl), 3.80 (s, 3H, CH_3), 6.98−7.60 (m, 4H, aromatic). GC/MS: *m*/*z* 228 ($M^+ + 2$, 4), 227 ($M^+ + 1$, 2), 226 (M^+, 13), 135 (100), 107 (30).

6-Chloro-1-(3-methoxyphenyl)-1-hexanone (8). As above, the title compound was obtained from alcohol **5**. ^{1}H NMR (90 MHz): 1.33−2.03 [m, 6H, $(CH_2)_3CH_2Cl$], 2.98 (t, 2H, J = 6.0 Hz, $COCH_2$), 3.55 (t, 2H, J = 6.0 Hz, CH_2Cl), 3.85 (s, 3H, CH_3), 7.03−7.66 (m, 4H, aromatic). GC/MS: *m*/*z* 242 ($M^+ + 2$, 6), 241 ($M^+ + 1$, 3), 240 (M^+, 18), 150 (78), 135 (100), 107 (39).

3-(4-Chlorobutyl)methoxybenzene (12). To a cooled (0 °C), stirred suspension of $AlCl_3$ (1.56 g, 11.7 mmol) in CH_2Cl_2 (30 mL) was added *tert*-butylamine-borane (2.04 g, 23.4 mmol). The mixture was stirred at 0 °C for 10 min. A clear solution resulted. A solution of ketone **6** (0.83 g, 3.9 mmol) in CH_2Cl_2 (30 mL) was added. The resulting mixture was stirred at 0 °C for 2 h. Then cold 1 N HCl (30 mL) was added dropwise to the reaction mixture. The separated organic phase was dried (Na_2SO_4), and the solvent evaporated under reduced pressure. The crude residue was chromatographed (petroleum ether/CH_2Cl_2, 4:1 as eluent) to give chloro derivative **12** as a colorless oil (0.41 g, 53% yield). ^{1}H NMR (90 MHz): 1.66−1.95 [m, 4H, $(CH_2)_2CH_2Cl$], 2.60 (br t, 2H, $ArCH_2$), 3.53 (br t, 2H, CH_2Cl), 3.80 (s, 3H, CH_3), 6.70−7.36 (m, 4H, aromatic). GC/MS: *m*/*z* 200 ($M^+ + 2$, 18), 199 ($M^+ + 1$, 7), 198 (M^+, 50), 163 (33), 122 (66), 121 (100), 91(29).

3-Chloro-*N*-(3-methoxyphenyl)propanamide (13). 3-Chloropropionyl chloride (1.4 mL, 14.8 mmol) in CH_2Cl_2 was added dropwise to a cooled suspension of 3-methoxyaniline (**11**) (1.82 g, 14.8 mmol) and a slight excess of K_2CO_3 in CH_2Cl_2. The resulting mixture was stirred at room temperature for 30 min, and then H_2O was added. The separated organic layer was washed with dilute HCl, dried over Na_2SO_4, and evaporated under reduced pressure. The crude residue was chromatographed (CH_2Cl_2/AcOEt, 1:1 as eluent) to obtain anilide **13** (2.31 g, 73% yield) as a white solid, mp 90−92 °C (from Et_2O/petroleum ether) [lit.[30] 95 °C (from aqueous ethanol)]. ^{1}H NMR (90 MHz): 2.75 (t, 2H, J = 7.0 Hz, $COCH_2$), 3.70 (s, 3H, CH_3), 3.80 (t, 2H, J = 7.0 Hz, CH_2Cl), 6.53−7.30 (m, 4H, aromatic), 8.15 (br s, 1H, NH, D_2O exchanged). GC/MS: *m*/*z* 215 (M^++ 2, 8), 214 ($M^+ + 1$, 3), 213 (M^+, 23), 123 (100), 94 (30).

General Procedure for the Synthesis of Compounds 28, 29, 31, 36, 37, 40, and 41. A stirred suspension of the appropriate alkyl halide (2.0 mmol), piperazine **14** (4.0 mmol), and a slight excess of K_2CO_3 (this reagent was omitted in the case of compounds **28**, **36**, and **37**) in acetonitrile was refluxed

overnight. After cooling, the mixture was evaporated to dryness, and 20% aqueous Na_2CO_3 was added to the residue. The aqueous phase was extracted two times with CH_2Cl_2, and the collected organic layers were dried over Na_2SO_4 and were evaporated under reduced pressure. The crude residue was chromatographed as indicated below to give title compounds.

4-[4-(4-Chlorophenyl)-piperazin-1-yl]-1-(3-methoxyphenyl)-1-butanone (28). Eluted with $CHCl_3$/AcOEt, 7:3; 40% yield. ^{1}H NMR: 1.92−2.02 (m, 2H, $CH_2CH_2CH_2$), 2.46 [t, 2H, J = 7.1, $CH_2N(CH_2)_2$], 2.58 [br t, 4H, $CH_2N(CH_2)_2$], 3.00 (t, 2H, J = 7.0 Hz, $COCH_2$), 3.10 [br t, 4H, $(CH_2)_2NAr$], 3.82 (s, 3H, CH_3), 6.77−7.55 (m, 8H, aromatic). GC/MS: *m*/*z* 374 (M^+ + 2, 14), 373 (M^+ + 1, 10), 372 (M^+, 39), 224 (36), 222 (100), 211 (30), 209 (91), 177 (31), 166 (56), 135 (32).

1-(4-Chlorophenyl)-4-[4-(3-methoxyphenyl)butyl]piperazine (29). Eluted with $CHCl_3$/AcOEt, 7:3; 36% yield. ^{1}H NMR: 1.50−1.70 [m, 4H, $CH_2(CH_2)_2CH_2$], 2.40 [t, 2H, J = 7.4 Hz, $CH_2N(CH_2)_2$], 2.55−2.63 [m, 6H, $ArCH_2$, $CH_2N(CH_2)_2$], 3.15 [br s, 4H, $(CH_2)_2NAr$], 3.78 (s, 3H, CH_3), 6.69−7.24 (m, 8H, aromatic). GC/MS: *m*/*z* 360 (M^+ + 2, 17), 359 (M^+ + 1, 12), 358 (M^+, 47), 211 (35), 209 (100).

3-(4-Chlorophenyl)-*N*-(3-methoxyphenyl)-1-piperazinopropanamide (31). Eluted with $CHCl_3$/AcOEt, 1:1; 75% yield. ^{1}H NMR: 2.53−2.57 [m, 2H, $CH_2N(CH_2)_2$], 2.73−2.79 [m, 6H, $CH_2CH_2N(CH_2)_2$], 3.25 [br t, 4H, $(CH_2)_2NAr$], 3.76 (s, 3H, CH_3), 6.58−7.35 (m, 8H, aromatic), 10.72 (br s, 1H, NH, D_2O exchanged). GC/MS: *m*/*z* 196 (31), 177 (38), 156 (28), 154 (100), 123 (41).

5-[4-(4-Chlorophenyl)-piperazin-1-yl]-1-(3-methoxyphenyl)-1-pentanone (36). Eluted with $CHCl_3$/AcOEt, 7:3; 56% yield. ^{1}H NMR: 1.56−1.66 (m, 2H, CH_2CH_2N), 1.72−1.82 (m, 2H, $COCH_2CH_2$), 2.43 [br t, 2H, $CH_2N(CH_2)_2$], 2.59 [br t, 4H, $CH_2N(CH_2)_2$], 2.98 (t, 2H, J = 7.2 Hz, $COCH_2$), 3.15 [br t, 4H, $(CH_2)_2NAr$], 3.83 (s, 3H, CH_3), 6.79−7.54 (m, 8H, aromatic). GC/MS: *m*/*z* 388 (M^+ + 2, 13), 387 (M^+ + 1, 10), 386 (M^+, 38), 211 (34), 209 (100).

6-[4-(4-Chlorophenyl)-piperazin-1-yl]-1-(3-methoxyphenyl)-1-hexanone (37). Eluted with CH_2Cl_2/AcOEt, 7:3; 23% yield. ^{1}H NMR: 1.37−1.45 [m, 2H, $CH_2(CH_2)_2$], 1.53−1.63 (m, 2H, CH_2CH_2N), 1.70−1.80 (m, 2H, $COCH_2CH_2$), 2.40 [br t, 2H, $CH_2N(CH_2)_2$], 2.59 [br t, 4H, $CH_2N(CH_2)_2$], 2.95 (t, 2H, J = 7.3 Hz, $COCH_2$), 3.16 [br t, 4H, $(CH_2)_2NAr$], 3.83 (s, 3H, CH_3), 6.79−7.53 (m, 8H, aromatic). GC/MS: *m*/*z* 402 (M^+ + 2, 12), 401 (M^+ + 1, 10), 400 (M^+, 35), 211 (35), 209 (100), 177 (31), 166 (56), 135 (32).

1-(4-Chlorophenyl)-4-[3-(1,2,3,4-tetrahydro-5-methoxy-1-naphthalenyl)propyl]piperazine (40). Eluted with $CHCl_3$/AcOEt, 1:1; 81% yield. ^{1}H NMR: 1.54−1.84 [m, 8H, $CH(CH_2CH_2)_2$], 2.40 [br t, 2H, $CH_2N(CH_2)_2$], 2.52−2.77 [m, 7H, benzylic CH_2 and CH, $CH_2N(CH_2)_2$], 3.16 (br t, 4H, $(CH_2)_2NAr$], 3.79 (s, 3H, CH_3), 6.63−7.24 (m, 7H, aromatic). GC/MS: *m*/*z* 400 (M^+ + 2, 27), 399 (M^+ + 1, 22), 398 (M^+, 77), 210 (36), 209 (100), 196 (40).

1-(4-Chlorophenyl)-4-[3-(1,2,3,4-tetrahydro-7-methoxy-1-naphthalenyl)propyl]piperazine (41). Eluted with CH_2Cl_2/AcOEt, 4:1; 95% yield. ^{1}H NMR: 1.57−1.88 [m, 8H, $CH(CH_2CH_2)_2$], 2.41 [br t, 2H, $CH_2N(CH_2)_2$], 2.59−2.74 [m, 7H, benzylic CH_2 and CH, $CH_2N(CH_2)_2$], 3.16 (br t, 4H, $(CH_2)_2NAr$], 3.76 (s, 3H, CH_3), 6.63−7.24 (m, 7H, aromatic). GC/MS: *m*/*z* 400 (M^+ + 2, 11), 399 (M^+ + 1, 9), 398 (M^+, 33), 211 (33), 209 (100), 196 (37).

4-(4-Chlorophenyl)-1-piperazinopentanenitrile (15). The title compounds was prepared in 83% yield from the piperazine **14** and 4-chloropentanenitrile following the procedure described for the synthesis of the above compounds. ^{1}H NMR (90 MHz): 1.50−1.85 [m, 4H, $(CH_2)_2CH_2CN$], 2.20−2.70 [m, 8H, $(CH_2)_2NCH_2$, CH_2CN], 3.00−3.30 [m, 4H, $ArN(CH_2)_2$], 6.75−7.35 (m, 4H, aromatic). GC/MS: *m*/*z* 279 (M^+ + 2, 24), 278 (M^+ + 1, 14), 277 (M^+, 68), 211 (37), 209 (100), 166 (22), 139 (30), 138 (25).

4-(4-Chlorophenyl)-1-piperazinepentanamine (19). Borane-methyl sulfide complex, as 10.0 M BH_3 in excess methyl sulfide (2.0 mL, 20.0 mmol), was dropped into an ice-cooled solution of nitrile **15** (1.16 g, 4.2 mmol) in anhydrous THF (10 mL), under stirring. After being refluxed for 1 h, the reaction mixture was cooled at −10 °C and MeOH was added very carefully dropwise until gas evolution ceased. The mixture was treated with 3 N HCl (5 mL) and was refluxed for 1 h. After cooling, the mixture was alkalized with 3 N NaOH and extracted with CH_2Cl_2 (2 × 50 mL). The collected organic layers were dried over Na_2SO_4, and the solvent was evaporated under reduced pressure to give the amine **19** as a white semisolid in nearly quantitative yield. ^{1}H NMR (90 MHz): 1.25−1.75 [m, 6H, $(CH_2)_3CH_2NH_2$], 2.00 (br s, 2H, NH_2, D_2O exchanged), 2.25−2.90 [m, 8H, $CH_2N(CH_2)_2$, CH_2NH_2], 3.05−3.33 [m, 4H, $ArN(CH_2)_2$], 6.75−7.35 (m, 4H, aromatic). GC/MS: *m*/*z* 283 (M^+ + 2, 2), 282 (M^+ + 1, 3), 281 (M^+, 6), 268 (20), 266 (58), 211 (34), 209 (100), 195 (28), 166 (45), 141 (71), 98 (71).

General Procedure for Preparation of the Benzamides 33−35. To a cooled mixture containing amines **17**−**19** (5.0 mmol) and a slight excess of $NaHCO_3$ was added dropwise a solution of 3-methoxybenzoyl chloride, prepared from 3-methoxybenzoic acid (2.00 g, 11 mmol) in $SOCl_2$ (5 mL), in CH_2Cl_2 (50 mL) under vigorous stirring. Then the aqueous layer was separated and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and evaporated to dryness under reduced pressure. Final compounds were purified by column chromatography ($CHCl_3$/MeOH, 19:1 as eluent) to give benzamides **33**−**35** in 90−95% yield.

***N*-[3-[4-(4-Chlorophenyl)piperazin-1-yl]propyl]-3-methoxybenzamide (33).** ^{1}H NMR: 1.75−1.85 (m, 2H, $CH_2CH_2CH_2$), 2.59−2.66 [m, 6H, $CH_2N(CH_2)_2$], 3.14 [br t, 4H, $(CH_2)_2NAr$], 3.56 (q, 2H, J = 5.5 Hz, $NHCH_2$), 3.72 (s, 3H, CH_3), 6.77−7.44 (m, 8H, aromatic), 8.11 (br s, 1H, NH, D_2O exchanged). GC/MS: *m*/*z* 389 (M^+ + 2, 7), 388 (M^+ + 1, 5), 387 (M^+, 20), 372 (34), 221 (100), 209 (54), 192 (56), 135 (56).

***N*-[4-[4-(4-Chlorophenyl)piperazin-1-yl]butyl]-3-methoxybenzamide (34).** ^{1}H NMR: 1.70−1.75 [m, 4H, $CH_2(CH_2)_2CH_2$], 2.57 [br s, 2H, $CH_2N(CH_2)_2$], 2.72 [br t, 4H, $CH_2N(CH_2)_2$], 3.21 [br t, 4H, $(CH_2)_2NAr$], 3.44−3.49 (m, 2H, $NHCH_2$), 3.81 (s, 3H, CH_3), 6.77−7.34 (m, 9H, aromatic, NH). GC/MS: *m*/*z* 403 (M^+ + 2, 4), 402 (M^+ + 1, 4), 401 (M^+, 11), 386 (20), 235 (100), 209 (57), 135 (51).

***N*-[5-[4-(4-Chlorophenyl)piperazin-1-yl]pentyl]-3-methoxybenzamide (35).** ^{1}H NMR: 1.38−1.46 [m, 2H, $(CH_2)_2CH_2(CH_2)_2$] 1.54−1.68 (m, 4H, $CH_2CH_2CH_2CH_2CH_2$), 2.43 [br t, 2H, $CH_2N(CH_2)_2$], 2.61 [br t, 4H, $CH_2N(CH_2)_2$], 3.16 [br t, 4H, $(CH_2)_2NAr$], 3.43 (q, 2H, J = 5.0, $NHCH_2$), 3.81 (s, 3H, CH_3), 6.21 (br s, 1H, NH, D_2O exchanged), 6.78−7.34 (m, 8H, aromatic). GC/MS: *m*/*z* 417 (M^+ + 2, 5), 416 (M^+ + 1, 4), 415 (M^+, 14), 400 (20), 249 (100), 211 (26), 209 (77), 135 (44).

4-(4-Chlorophenyl)-*N*-[(3-methoxyphenyl)methyl]-1-piperazineethanamine (30). This compound was obtained in nearly quantitative yield from the reduction of benzamide **1** with borane methyl sulfide complex, following the procedure reported for the compound **19**. ^{1}H NMR: 2.06 (br s, 1H, NH, D_2O exchanged), 2.52−2.56 (m, 6H, $CH_2CH_2N(CH_2)_2$], 2.72 [t, 2H, J = 6.0, $CH_2N(CH_2)_2$], 3.11 [br t, 4H, $(CH_2)_2NAr$], 3.79 (s, 5H, $ArCH_2$, CH_3), 6.76−7.25 (m, 8H, aromatic). GC/MS: *m*/*z* 361 (M^+ + 2, 1), 360 (M^+ + 1, 1), 359 (M^+, 3), 211 (24), 210 (21), 209 (77), 179 (21), 166 (30), 138 (23), 121 (70), 70 (100).

***N*-(Methoxycarbonyl)-2-(2-methoxyphenyl)ethylamine (25).** To a solution of 2-methoxyphenetylamine (**24**) (5.00 g, 33.1 mmol) and triethylamine (5.5 mL, 39.5 mmol) in anhydrous THF (50 mL) at 0 °C was carefully added methyl chloroformate (13.1 mL, 169 mmol). The reaction mixture was stirred at room temperature for 24 h. H_2O was added, the aqueous and organic layers were separated, and the former was extracted with Et_2O (3 × 20 mL). The combined organic fractions were washed with 1 N HCl (2 × 50 mL), H_2O (50 mL), and brine (50 mL) and dried over Na_2SO_4. Evaporation of the solvent in vacuo gave compound **25** in nearly quantitative yield. ^{1}H NMR (90 MHz): 2.80 (t, 2H, J = 6.0 Hz, CH_2NH), 3.25−3.55 (m, 2H, $ArCH_2$), 3.73 and 3.83 (2 s, 6H, 2 CH_3), 4.87 (br s, 1H, NH), 6.75−7.35 (m, 4H, aromatic). GC/MS: *m*/*z* 211 (M^+ + 2, 1), 210 (M^+ + 1, 6), 209 (M^+, 40), 134 (100), 122 (26), 121 (52), 119 (37), 91 (80).

5-Methoxy-3,4-dihydroisoquinolin-1-one (26). Carbamate **25** (6.85 g, 32.7 mmol) was added to polyphosphoric acid (40 g) heated at 145 °C, and the mixture was stirred for 10 min. Then the cooled reaction mixture was poured onto ice, and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to give a crude residue which was chromatographed ($CHCl_3$/AcOEt, 1:1 as eluent) to afford compound **26** as a pale yellow semisolid (1.29 g, 22% yield). Spectral properties of the obtained compound were fully consistent with those reported.[31]

***N*-[2-[4-(4-Chlorophenyl)piperazin-1-yl]ethyl]-*N*-methyl-3-methoxybenzamide (32).** A mixture of benzamide **23** (0.88 g, 5.3 mmol), KOH (1.20 g, 21.4 mmol), tetrabutylammonium bromide (0.051 g, 0.16 mmol), and compound **22** (0.70 g, 2.7 mmol) in DMF was heated at 80 °C for 4 h. After cooling, the solvent was removed under reduced pressure and the crude residue was taken up with H_2O. The aqueous phase was extracted with CH_2Cl_2, and the separated organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was chromatographed ($CHCl_3$/AcOEt, 1:1 as eluent) to give compound **32** as a semisolid (0.51 g, 48% yield). ^{1}H NMR (DMSO-d_6):[32] 2.32 and 2.58 [2 br s, 6H, $CH_2N(CH_2)_2$], 2.89, 2.96, 3.02, 3.10 [4 br s, 7H, NCH_3, $(CH_2)_2NAr$], 3.31, 3.57 (2 br s, 2H, CH_3NCH_2), 3.75 (s, 3H, OCH_3), 6.89−7.34 (m, 8H, aromatic). GC/MS: *m*/*z* 389 ($M^+ + 2$, 2), 388 ($M^+ + 1$, 1), 387 (M^+, 5), 222 (23), 211 (34), 209 (100), 166 (21).

***N*-[2-[4-(4-Chlorophenyl)piperazin-1-yl]ethyl]-5-methoxy-3,4-dihydroisoquinolin-1-one (38).** Title compound was obtained from the amide **26** and the compound **22**, following the above-reported procedure. ^{1}H NMR: 2.70 [br s, 6H, $CH_2N(CH_2)_2$], 2.93 (t, 2H, J = 6.7 Hz, $ArCH_2$), 3.14 [br t, 4H, $(CH_2)_2NAr$], 3.58 (t, 2H, J = 6.7 Hz, *endo* $CONCH_2$), 3.72 (t, 2H, J = 6.7 Hz, *exo* $CONCH_2$), 3.83 (s, 3H, CH_3), 6.79−7.68 (m, 7H, aromatic). GC/MS: *m*/*z* 401 ($M^+ + 2$, 1), 400 ($M^+ + 1$, 1), 399 (M^+, 4), 233 (24), 222 (35), 211 (33), 209 (100), 166 (31).

***N*-[2-[4-(4-Chlorophenyl)piperazin-1-yl]ethyl]-7-methoxy-3,4-dihydroisoquinolin-1-one (39).** As for compound **38**, the title compound was obtained from the amide **27** and the derivative **22**. ^{1}H NMR: 2.66−2.71 [m, 6H, $CH_2N(CH_2)_2$], 2.91 (t, 2H, J = 6.7 Hz, $ArCH_2$), 3.14 [br t, 4H, $(CH_2)_2NAr$], 3.59 (t, 2H, J = 6.7 Hz, *endo* $CONCH_2$), 3.73 (t, 2H, J = 6.7 Hz, *exo* $CONCH_2$), 3.82 (s, 3H, CH_3), 6.79−7.58 (m, 7H, aromatic). GC/MS: *m*/*z* 401 ($M^+ + 2$, 2), 400 ($M^+ + 1$, 1), 399 (M^+, 4), 233 (21), 211 (33), 222 (29), 209 (100), 166 (28).

4-(4-Chlorophenyl)-*N*-[3-(1,2,3,4-tetrahydro-5-methoxy-1-naphthalenyl)propyl]-1-piperazineethanamine (42). A mixture of 5-methoxy-1-tetralone (**20**) (1.38 g, 7.8 mmol) and 4-(4-chlorophenyl)-1-piperazinoethanamine (**16**) (1.01 g, 4.2 mmol) in anhydrous toluene (100 mL) was refluxed in the presence of a catalytic amount of *p*-toluenesulfonic acid, and the formed H_2O was azeotropically distilled off and collected with a Dean−Stark trap for 1 h. After cooling, the solvent was evaporated, and the crude intermediate Schiff's base was solubilized in absolute ethanol (50 mL) and treated with $NaBH_4$ (0.38 g, 8.7 mmol) for 2 h at room temperature, under N_2. Then the solvent was removed under reduced pressure, and the residue was partitioned between H_2O and CH_2Cl_2. The separated organic layer was dried (Na_2SO_4) and concentrated in vacuo to give a crude residue which was chromatographed (CH_2Cl_2/MeOH, 95:5 as eluent) to afford amine **42** (1.28 g, 76% yield). ^{1}H NMR: 1.66−2.00 (m, 5H, *endo* CH_2CH_2, NH, 1H D_2O exchanged), 2.48−2.88 [m, 10H, benzylic CH_2, $CH_2CH_2N(CH_2)_2$], 3.13 [br t, 4H, $(CH_2)_2NAr$], 3.75−3.79 (t+s, 4H, CHN, CH_3), 6.68−7.24 (m, 7H, aromatic). GC/MS: *m*/*z* 210 (32), 209 (33), 161 (100).

4-(4-Chlorophenyl)-*N*-[3-(1,2,3,4-tetrahydro-7-methoxy-1-naphthalenyl)propyl]-1-piperazineethanamine (43). As above, the title compound was obtained from amine **16** and 7-methoxy-1-tetralone (**21**). ^{1}H NMR: 1.67−1.99 (m, 4H, *endo* CH_2CH_2), 2.09 (br s, 1H, NH, D_2O exchanged), 2.52−2.87 [m, 10H, benzylic CH_2, $CH_2CH_2N(CH_2)_2$], 3.13 [br t, 4H, $(CH_2)_2NAr$], 3.74−3.81 (t+s, 4H, CHN, CH_3), 6.69−7.24 (m, 7H, aromatic). GC/MS: *m*/*z* 401 ($M^+ + 2$, 1), 400 ($M^+ + 1$, 1), 399 (M^+, 2), 210 (26), 209 (35), 161 (100).

Pharmacological Methods. $D_{4.4}$ Dopaminergic Binding Assay. Binding of [^{3}H]YM-09151-2 for human cloned $D_{4.4}$ dopamine receptor produced in S*f*9 cells baculovirus expression (NEN Life Science) was performed according to Hadley et al.[33] 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 $D_{4.4}$ diluted membranes, 0.15 nM of [^{3}H]YM-09151-2 (K_d = 0.17 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/A 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 10 μM clozapine.

D_{2L} Dopaminergic Binding Assay. Binding of [^{3}H]spiroperidol for human cloned D_{2L} dopamine receptor produced in S*f*9 cells baculovirus expression (NEN Life Science) was performed according to Hadley et al.[33] 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_{2L} diluted membranes, 0.2 nM [^{3}H]spiperone (K_d = 0.20 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 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 10 μM haloperidol.

5-HT_{1A} Serotonergic Binding Assay. Binding experiments were performed according to Borsini et al.[34] with minor modifications. Each tube received 50 mM Tris·HCl (pH 7.6) hippocampus membranes suspension and 1 nM [^{3}H]-8-OH-DPAT in a final volume of 1 mL. For competitive inhibition experiments, various concentrations (10^{-5}−10^{-11} M) of drugs studied were incubated. Nonspecific binding was defined using 1 μM 8-OH-DPAT. Samples were incubated at 37 °C for 20 min and then filtered on Whatman GF/B glass microfiber filters. The K_d value determined for 8-OH-DPAT was 8.8 nM.

α_1 Adrenergic Binding Assay. Binding experiments were performed according to Glossman and Hornung[35] with minor modifications. Each tube received 50 mM Tris·HCl (pH 7.4) rat cerebral cortical membranes suspension and 1 nM [^{3}H]-prazosin in a final volume of 1 mL. For competitive inhibition experiments, various concentrations (10^{-5}−10^{-11} M) of drugs studied were incubated. Nonspecific binding was defined using 1 μM prazosin. Samples were incubated at 25 °C for 50 min and then filtered on Whatman GF/B glass microfiber filters. The filters were presoaked for 50 min in Tris·HCl−polyethylenimine 0.5%. The K_d value determined for prazosin was 0.5 nM.

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Supporting Information Available: Elemental analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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