1-Aryl-4-[(1-tetralinyl)alkyl]piperazines: Alkylamido and Alkylamino Derivatives. Synthesis, 5-HT_{1A} Receptor Affinity, and Selectivity. 3[1]

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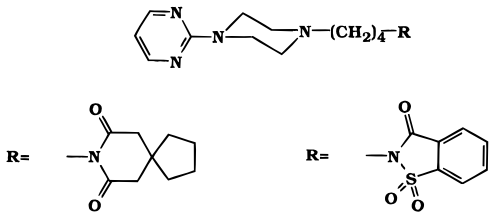
The synthesis and binding profile on 5-HT_{1A}, 5-HT_2, D-1, D-2, α_1, and α_2 receptors of the N-4 long-chain arylpiperazines **22**−**40** are reported, where an amino or amido function is inserted into the intermediate chain linked to the α position of the tetralin nucleus. Unlike the buspirone analogues, for the amido derivatives studied in this paper, the terminal amide function of long-chain piperazines is not important for 5-HT_{1A} receptor affinity binding, and its removal yields high-affinity 5-HT_{1A} receptor agents.

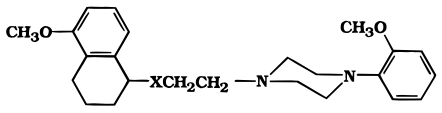
Serotonin (5-hydroxytryptamine, 5-HT) is involved in many physiological and pathophysiological processes in the brain which are mediated by the specific interaction of 5-HT with several different receptors. The classification of these receptor subtypes, their role, and their respective ligands are reported in several recent reviews.[2−8] The 5-HT_{1A} receptors are to date the best-characterized subtypes, and it is generally accepted that they are involved in psychiatric disorders such as depression and anxiety.

Several compounds from different chemical classes possess high affinity for 5-HT_{1A} receptors.[8] Among these, some long-chain arylpiperazine compounds with a terminal amide fragment, such as buspirone (**1**) and ipsapirone (**2**) are effective antianxiety and antidepressant drugs.



1 **2**

However, even if the long-chain arylpiperazines represent the class most throughly studied to date, their selectivity versus dopaminergic D-2 and adrenergic α receptors is not yet clear, with the result that several papers have been published by different researchers.[9−12] In order to contribute toward solving this problem, in two recent papers[1,13] we have described a new model of long-chain arylpiperazines, with a dihydronaphthalene or tetralin nucleus on the terminal part of the side chain. Since for these compounds the affinity and selectivity values on the 5-HT_{1A} receptor were very encouraging, and since we noted that the incorporation of an amine function into the spacer, in place of a methylene group, as in compound **3**, causes an increase in selectivity versus D-2, α_1, and α_2 receptors compared to the corresponding compounds **4**, we decided to insert an amine or amide function into the methylene spacer between the basic nitrogen atom and the tetralin nucleus.



3: X= NH

4: X= CH_2

On the other hand, Misztal et al.[14] assumed that the terminal amide fragment in buspirone-like ligands stabilized the 5-HT_{1A} receptor−ligand complex by either π-electron or local dipole−dipole interaction. However, although a hydrocarbon chain with a terminal amide fragment significantly influences the ability to bind to other receptors, its role is not yet clear.

In the present paper, we therefore report the synthesis and the binding profile on 5-HT_{1A}, 5-HT_2, D-1, D-2, α_1, and α_2 receptors of the N-4 long-chain arylpiperazines **22**−**40** (Table 1) where the −CONHR or −CH_2-NR or −$NRCH_2$ or −NHCO function is linked to the α position of the tetralin nucleus, in place of two methylene groups which were present in the previously reported arylpiperazines.[1] The arylpiperazine and tetralin moieties used for the compounds in the present work are those present in agents with the highest affinity for the 5-HT_{1A} receptor;[13] they are 1-(2-methoxyphenyl)-, 1-phenyl-, and 1-(2-pyridyl)piperazine and 5-methoxy-1,2,3,4-tetrahydronaphthalene. Some compounds present a methyl group on the nitrogen atom of the amide function (**28**−**30**), or of the amine function (**36**), to prevent a possible intramolecular hydrogen bond.

Chemistry

Synthesis of the final compounds is illustrated in Scheme 1. Compounds derived from 5-methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid (**9**) were prepared by reacting 5-methoxy-1-tetralone (**8**) with trimethylsilyl cyanide, giving the trimethylsilyl cyanohydrin derivative, according to the literature.[15] This was hydrolyzed, dehydrated, and then reduced in a single

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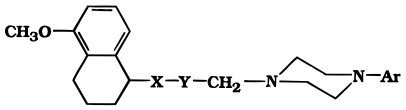
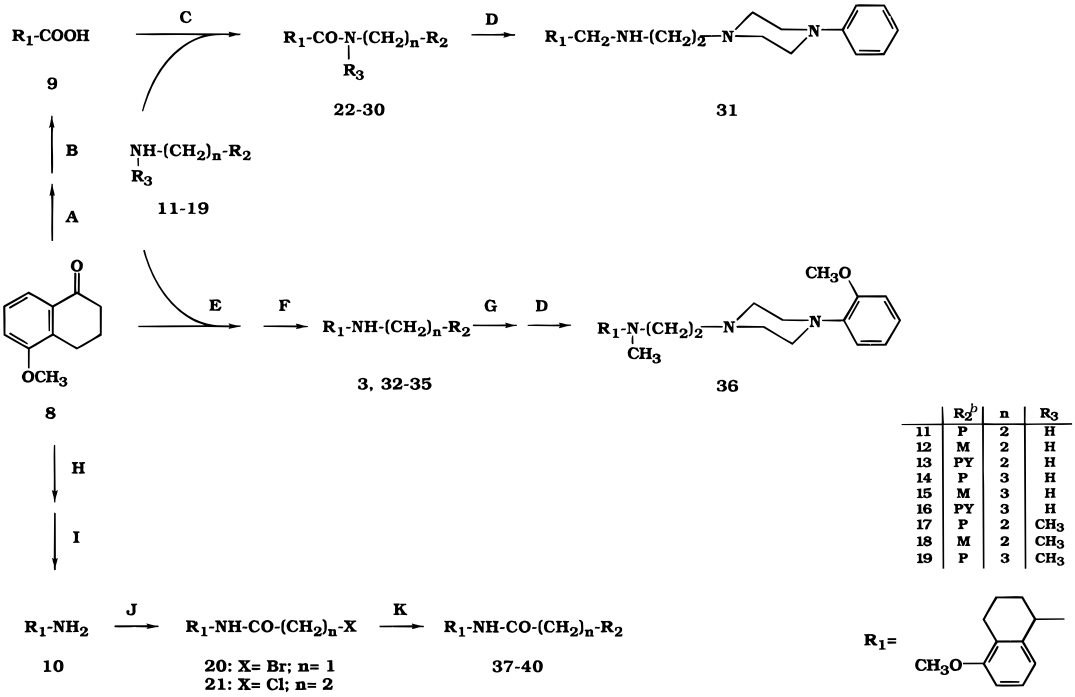
Table 1. Physical Properties



compd	X	Y	Ar	formula[a]	mp, °C	recryst solv
3[b]	NH	CH_2	2-CH_3O-Ph			
4[b]	CH_2	CH_2	2-CH_3O-Ph			
5[b]	CH_2	CH_2	Ph			
6[b]	CH_2	CH_2	2-Py			
7[b]	CH_2	CH_2CH_2	2-CH_3O-Ph			
22	CO	$NHCH_2$	Ph	$C_{24}H_{31}N_3O_2 \cdot HCl$	235−239 dec	MeOH
23	CO	$NHCH_2$	2-CH_3O-Ph	$C_{25}H_{33}N_3O_3 \cdot 2HCl$	150 dec	CH_2Cl_2/Et_2O
24	CO	$NHCH_2$	2-Py	$C_{23}H_{30}N_4O_2 \cdot 3HCl$	210 dec	MeOH/Et_2O
25	CO	$NHCH_2CH_2$	Ph	$C_{25}H_{33}N_3O_2 \cdot 2HCl$	180−185 dec	MeOH/Et_2O
26	CO	$NHCH_2CH_2$	2-CH_3O-Ph	$C_{26}H_{35}N_3O_3 \cdot 2HCl$	194−196	CH_2Cl_2/Et_2O
27	CO	$NHCH_2CH_2$	2-Py	$C_{24}H_{32}N_4O_2 \cdot 2HCl \cdot {}^3/_2H_2O$	213 dec	MeOH/Et_2O
28	CO	$N(CH_3)CH_2$	Ph	$C_{25}H_{33}N_3O_2 \cdot HCl \cdot H_2O$	257−259	MeOH/Et_2O
29	CO	$N(CH_3)CH_2$	2-CH_3O-Ph	$C_{26}H_{35}N_3O_3 \cdot 2HCl$	175−178 dec	CH_2Cl_2/petroleum ether
30	CO	$N(CH_3)CH_2CH_2$	Ph	$C_{26}H_{35}N_3O_2 \cdot 2HCl$	199 dec	MeOH/Et_2O
31	CH_2	$NHCH_2$	Ph	$C_{24}H_{33}N_3O \cdot 3HCl$	242 dec	MeOH/Et_2O
32	NH	CH_2	Ph	$C_{23}H_{31}N_3O \cdot 2HCl \cdot {}^2/_3H_2O$	247 dec	CH_2Cl_2/Et_2O
33	NH	CH_2	2-Py	$C_{22}H_{30}N_4O \cdot 3HCl \cdot {}^1/_2H_2O$	156−159 dec	CH_2Cl_2/Et_2O
34	NH	CH_2CH_2	Ph	$C_{24}H_{33}N_3O \cdot 2HCl$	261−263 dec	MeOH/Et_2O
35	NH	CH_2CH_2	2-CH_3O-Ph	$C_{25}H_{35}N_3O_2 \cdot 2HCl \cdot {}^2/_3H_2O$	144−147 dec	CH_2Cl_2/Et_2O
36	$N(CH_3)$	CH_2	2-CH_3O-Ph	$C_{25}H_{35}N_3O_2 \cdot 2HCl \cdot {}^5/_3H_2O$	141−144 dec	MeOH/Et_2O
37	NH	CO	Ph	$C_{23}H_{29}N_3O_2 \cdot HCl$	244 dec	MeOH/Et_2O
38	NH	$COCH_2$	Ph	$C_{24}H_{31}N_3O_2 \cdot 2HCl$	200−203 dec	MeOH/Et_2O
39	NH	$COCH_2$	2-CH_3O-Ph	$C_{25}H_{33}N_3O_3 \cdot 2HCl$	211−213	MeOH/Et_2O
40	NH	$COCH_2$	2-Py	$C_{23}H_{30}N_4O_2 \cdot 2HCl \cdot {}^1/_2H_2O$	251−253 dec	MeOH/Et_2O

[a] Analyses for C,H,N; results were within ±0.4% of the theoretical values for the formulas given. [b] Formerly published compounds.[1,13]

Scheme 1[a]



	R_2[b]	n	R_3
11	P	2	H
12	M	2	H
13	PY	2	H
14	P	3	H
15	M	3	H
16	PY	3	H
17	P	2	CH_3
18	M	2	CH_3
19	P	3	CH_3

[a] Reagents: (A) $(CH_3)_3SiCN$, ZnI_2; (B) concentrated HCl, CH_3COOH, $SnCl_2 \cdot H_2O$; (C) DCC; (D) $LiAlH_4$; (E) *p*-toluenesulfonic acid; (F) $NaBH_4$; (G) CH_3OCOCl; (H) $NH_2OH \cdot HCl$, CH_3COONa; (I) H_2, Pd/C (10%); (J) $BrCH_2COCl$ or $ClCH_2CH_2COCl$; (K) *N*-arylpiperazines. [b] P, 4-phenylpiperazin-1-yl; M, 4-(2-methoxyphenyl)piperazin-1-yl; PY, 4-(2-pyridyl)piperazin-1-yl.

step to obtain compound **9**. Then amides **22**−**30** were obtained by reacting compound **9** with the corresponding amines **11**−**19**, synthesized as already described,[16,17] in the presence of 1,3-dicyclohexylcarbodiimide (DCC). Amine **31** was prepared from amide **22** by reduction with $LiAlH_4$. Amines **11**−**19** were also used to obtain amines **3** and **32**−**35** according to a recently reported synthetic pathway.[1] The *N*-methylated derivative **36** was obtained by treating **3** with methyl chloroformate[18] to yield its carbamate, which was then reduced with $LiAlH_4$. In order to prepare the naphthalenamine amidic derivatives, 5-methoxy-1,2,3,4-tetrahydro-1-naphthalenamine (**10**) was synthesized by catalytic hydrogenation of the oxime of 5-methoxy-1-tetralone (**8**), as reported.[19] Then amine **10** was acylated with bromoacetyl chloride or 3-chloropropionyl chloride to give

Table 2. Binding Affinities[a] and Selectivities

	IC_{50}, nM					selectivity vs 5-HT_{1A} receptor, IC_{50} ratio			
compd	5-HT_{1A} [^{3}H]-8-OH-DPAT	5-HT_2 [^{3}H]ketanserin	D-2 [^{3}H]spiroperidol	α_1 [^{3}H]prazosin	α_2 [^{3}H]yohimbine	5-HT_2	D-2	α_1	α_2
3	7.7 ± 0.8	2580 ± 150	380 ± 40	220 ± 20	280 ± 40	335	49	29	36
4	0.77 ± 0.09	330 ± 30	18 ± 2	6.5 ± 0.6	17 ± 2	429	23	8	22
5	0.50 ± 0.05	230 ± 30	110 ± 20	43 ± 5	260 ± 30	460	220	86	520
6	0.54 ± 0.06	250 ± 20	140 ± 10	66 ± 7	48 ± 5	463	259	122	89
7	1.73 ± 0.22[b]	NT[c]	15.4 ± 0.8[b]	78.3 ± 5.5[b]	NT[c]		9[b]	45[b]	
22	416 ± 37	1560 ± 160	4040 ± 440	427 ± 46	1850 ± 290	4	10	1	4
23	35 ± 3	1710 ± 160	448 ± 51	166 ± 16	1380 ± 140	49	13	5	40
24	173 ± 20	1270 ± 130	2440 ± 230	838 ± 61	7220 ± 70	7	14	5	42
25	63 ± 7	349 ± 40	783 ± 82	19 ± 2	186 ± 20	6	12	0.3	3
26	16 ± 2	2040 ± 160	116 ± 13	84 ± 9	564 ± 48	128	7	5	35
27	95 ± 9	428 ± 31	819 ± 26	327 ± 48	746 ± 80	5	9	3	8
28	271 ± 20	848 ± 75	882 ± 71	510 ± 22	250 ± 37	3	3	5	1
29	307 ± 30	1070 ± 100	332 ± 45	297 ± 29	183 ± 21	4	1	1	1
30	134 ± 13	134 ± 12	594 ± 55	159 ± 10	144 ± 16	1	4	1	1
31	116 ± 13	1900 ± 130	1100 ± 170	1150 ± 120	1420 ± 180	16	10	10	12
32	92 ± 6	2720 ± 350	1200 ± 150	790 ± 76	310 ± 47	30	13	8	3
33	49 ± 5	9140 ± 820	1850 ± 200	725 ± 55	95 ± 11	187	38	15	2
34	53 ± 5	2690 ± 80	2160 ± 190	626 ± 65	788 ± 98	51	41	12	15
35	10 ± 2	3300 ± 300	1060 ± 90	881 ± 103	458 ± 57	330	106	88	46
36	8.7 ± 1.9	1740 ± 250	73 ± 8	887 ± 62	112 ± 10	200	8	102	13
37	5310 ± 580	>10 000	>10 000	5980 ± 390	>10 000			1	
38	311 ± 32	1200 ± 70	2970 ± 390	313 ± 8	2680 ± 450	4	10	1	9
39	38 ± 6	841 ± 83	761 ± 62	153 ± 7	1250 ± 140	22	20	4	33
40	135 ± 19	726 ± 83	1900 ± 200	534 ± 57	1330 ± 270	5	14	4	10
buspirone	30 ± 3	>10 000	280 ± 30	>10 000	>10 000				
8-OH-DPAT	2.1 ± 0.2	>10 000	5.2 ± 0.6	>10 000	810 ± 80				
ketanserin		3.4 ± 0.3							
haloperidol			4.8 ± 0.5						
prazosin				1.4 ± 0.6					
yohimbine					30 ± 3				

[a] Compounds **22**−**40** showed very high affinity binding values on D-1 receptor (IC_{50} > 1000 nM). [b] Previously published data,[1] here reported for comparison. [c]Not tested.

the intermediates **20** and **21**, respectively. The amination of these halo derivatives with the appropriate *N*-arylpiperazine provided the final amides **37**−**40**.

Pharmacology

Final compounds (Table 2) were evaluated for *in vitro* affinity on dopamine D-1 and D-2, serotonin 5-HT_{1A} and 5-HT_2, and adrenergic α_1 and α_2 receptors by radioligand binding assays. All the compounds were used in the form of hydrochloride salts and were water-soluble. The following specific radioligands and tissue sources were used (a) dopamine D-1 receptors—[^{3}H]SCH-23390, rat striatal membranes; (b) dopamine D-2 receptors—[^{3}H]spiroperidol, rat striatal membranes; (c) serotonin 5-HT_{1A} receptors—[^{3}H]-8-OH-DPAT, rat hippocampus membranes; (d) serotonin 5-HT_2 receptors—[^{3}H]-ketanserin, rat brain prefrontal cortex membranes; (e) α_1-adrenergic receptors—[^{3}H]prazosin, rat brain cortex membranes; (e) α_2-adrenergic receptors—[^{3}H]yohimbine, 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, except for α_2 (>60%). The results were analyzed by using the LIGAND program to determine IC_{50} values.

Results and Discussion

The results of the binding assays are illustrated in Table 2. Considering as a term of comparison the three methylene-spaced arylpiperazine derivatives **4**−**6** (see Table 1), which had been previously studied[1] and were reinvestigated in the Pharmacia laboratories (IC_{50} = 0.77, 0.50, and 0.54 nM, respectively, for the 5-HT_{1A} receptor), it should be noted (see Figure 1) that replacing the α-methylene group in the spacer with a secondary amine group, as for the corresponding compounds **3**, **32**, and **33**, respectively, led to a decrease in affinity for the 5-HT_{1A} receptor, less so for the first compound (IC_{50} = 7.7 nM) than for the other two (IC_{50} = 92 and 49 nM, respectively). Compound **36**, an *N*-methyl derivative of **3**, showed a similar affinity value to **3** (IC_{50} = 8.7 nM). On the other hand, it should be noted that the insertion of an amine function into the 1-(2-methoxyphenyl)-piperazine derivative **3** led to an increase in selectivity versus D-2 and α receptors, compared to the corresponding reference compound **4**, whereas for the phenyl and 2-pyridyl derivatives **32** and **33** we observed a decrease in selectivity compared to **5** and **6**, respectively. Finally, the three-membered amidic derivative **37** proved to have negligible affinity for 5-HT_{1A} receptor (IC_{50} = 5310 nM) compared to the corresponding amino derivative **32** and the reference compound **5**.

We can therefore deduce that, for those derivatives with three atoms in the spacer, a basic moiety at the end of the alkyl chain is required for better affinity than an amide function. Among the amino derivatives, the 1-(2-methoxyphenyl)piperazine derivative **3** proved to have the highest affinity and selectivity for 5-HT_{1A} receptor.

The values of affinity and selectivity for the arylpiperazine derivatives with four atoms in the spacer showed the same behavior. In this case the previously

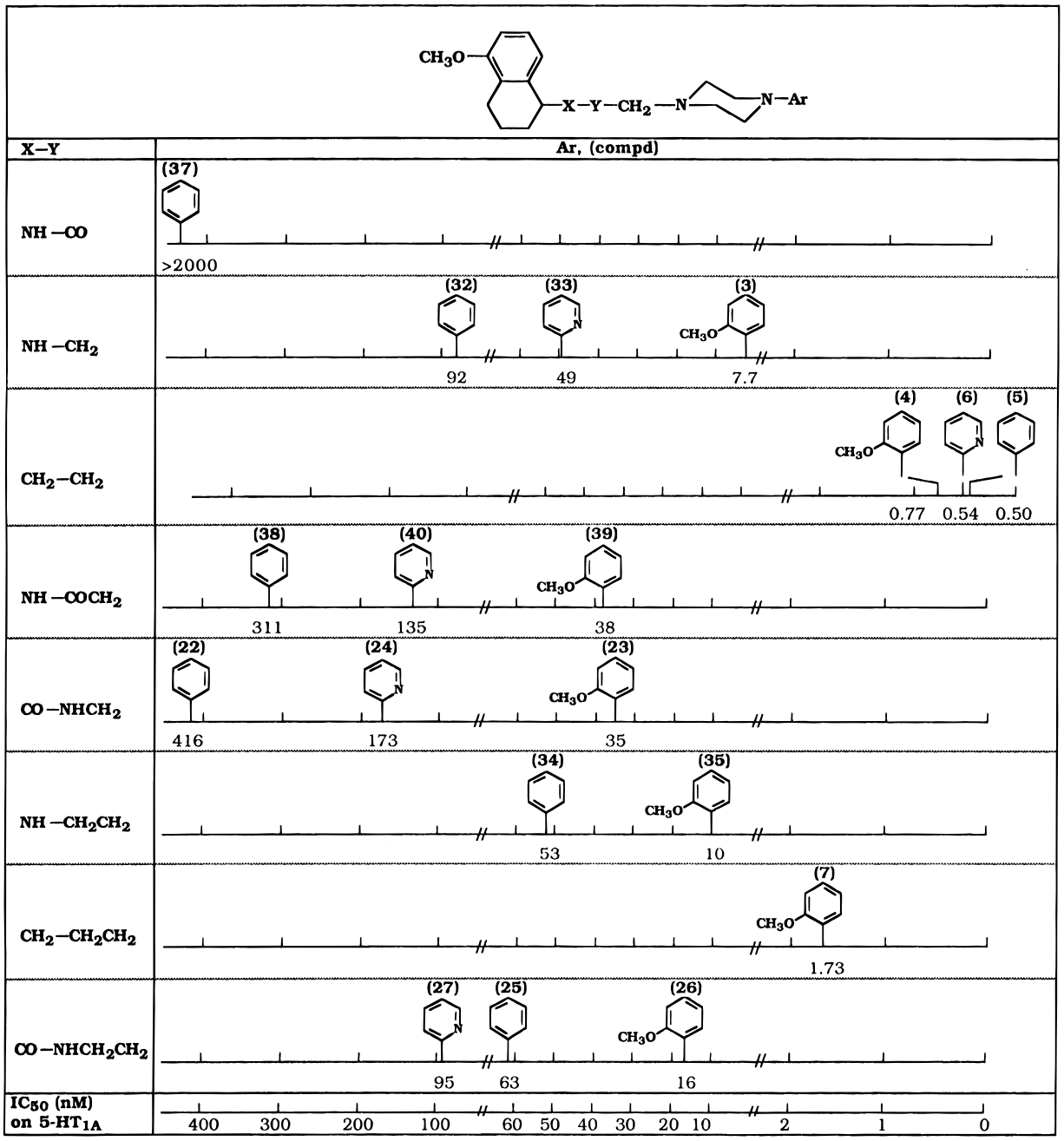


Figure 1.

studied[1] arylpiperazine derivative **7** (see Table 1), with an alkyl spacer of four methylene units (IC_{50} = 1.73 nM), was used as a term of comparison. It should be noted that the corresponding amino compound 1-(2-methoxyphenyl)piperazine derivative **35** showed a slight decrease in affinity (IC_{50} = 10 nM) whereas the amino compound of the 1-phenylpiperazine derivative **34** showed a more remarkable decrease (IC_{50} = 53 nM). Regarding the selectivity versus D-2 and α_1 receptors, we observed the same behavior as above; in fact, the amino derivative of 1-(2-methoxyphenyl)piperazine showed a higher selectivity than the corresponding reference compound **7**, whereas for derivative **34** the selectivity was lower.

For the amido derivatives with four atoms in the spacer, both those derived from 1-aminotetralin, **38**–**40**, and those derived from 1-tetrahydronaphthoic acid, **22**–**24**, showed lower affinity for 5-HT_{1A} receptor than the corresponding amino compounds **34** and **35**. However, among these amido compounds, the 1-(2-methoxyphenyl)piperazine derivatives showed moderate affinities (IC_{50} = 35–38 nM), whereas the others proved to have low affinity, and the relative selectivity values were very poor. The insertion of the methyl group on the amide function, as in **28** and **29**, led to no advantage for affinity. The displacement of the amino group in the intermediate chain from the α position, as in **34**, to the β position, as in **31**, led to a decrease in affinity. The lengthening of the intermediate chain from four to five atoms in amido derivatives **25**–**27** and **30** led to a significant improvement in the affinity for 5-HT_{1A} receptor, and in this group also, the 1-(2-methoxyphenyl)piperazine derivative **26** showed the highest affinity (IC_{50} = 16 nM). As for the affinity for D-1 and 5-HT_2 receptors, the IC_{50} values were very high, making it impossible to carry out a structure–activity relationship (SAR).

In conclusion, in comparison with the arylpiperazine derivatives **4**–**7**,[1] bearing a methylene spacer, of which

the 1-(2-methoxyphenyl)piperazine compound **4** was the least selective, the insertion of an amine function into the corresponding compound led to a slight decrease in affinity and an increase in selectivity only in the 2-methoxyphenyl derivatives **3** and **35**. By contrast, a worsening of affinity and selectivity derives from the insertion of an amide function, even though the lengthening of the intermediate chain led to a lesser decrease in affinity, as in the case of derivatives with five atoms in the spacer, **25**−**27**, and in particular for the 1-(2-methoxyphenyl)piperazine compound **26**. It can therefore be stated that, unlike the buspirone analogues and in agreement with Al-Bermawy,[10] for the amido derivatives in this paper, the terminal amide function of long-chain piperazines is not important for binding, and its removal yields high-affinity 5-HT_{1A} receptor agents.

Experimental Section

Chemistry. Column chromatographies were performed with 1:30 ICN silica gel 60A (63−200 μm) as the stationary phase. Melting points were determined in open capillaries on a Gallenkamp electrothermal apparatus. Elemental analyses were performed by the Microanalytical Section of our department on solid samples only; the analytical results (C,H,N) were within ±0.4% of the theoretical values. ^{1}H NMR spectra were recorded on a Bruker AM 300 WB instrument. Chemical shifts are reported in parts per million (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 percent relative intensity in parentheses, are herein reported. All compounds had NMR and mass spectra that were fully consistent with their structure.

5-Methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxylic Acid (9). A mixture of 5-methoxy-1-tetralone (**8**) (12.5 g, 71 mmol), zinc iodide (0.50 g), and trimethylsilyl cyanide (25.0 g, 252 mmol) was stirred for 48 h at room temperature under nitrogen. The reaction mixture was diluted with $CHCl_3$ and washed with an aqueous $NaHCO_3$ saturated solution. The separated organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give the crude trimethylsilyl cyanohydrin that was chromatographed (petroleum ether/ethyl acetate, 9:1, as eluent). The trimethylsilyl cyanohydrin of **8** (18.4 g, 66.8 mmol) was heated at 140 °C for 65 h in the presence of tin(II) chloride dihydrate (65.0 g, 288 mmol), glacial acetic acid (60 mL), and concentrated hydrochloric acid (60 mL). The reaction mixture was cooled and diluted with 250 mL of $CHCl_3$; then the layers were separated, and the aqueous layer was back-extracted with ether. The basic aqueous layer was cooled, acidified, and extracted three times with $CHCl_3$. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to give a crude product that was chromatographed (CH_2Cl_2/MeOH, 19:1, as eluent) to afford pure **9** as a pale yellow solid (6.06 g, 44% yield): mp 105−106 °C (from petroleum ether); ^{1}H NMR ($CDCl_3$) 1.72−2.51 (mm, 4H, *endo* CH_2CH_2), 2.53−2.79 (mm, 2H, benzyl CH_2), 3.76−3.87 (s + m, 4H, CHCO, CH_3), 6.71−7.15 (mm, 3H, aromatic), 10.80 (br s, 1H, OH, D_2O exchanged); GC/MS *m*/*z* 207 (M^+ + 1, 6), 206 (M^+, 50), 161 (100), 160 (30), 115 (23), 91 (27).

General Procedure for the Preparation of Amides 22−**30.** To a stirred solution of 5-methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid (**9**) (0.52 g, 2.5 mmol) and DCC (0.68 g, 3.3 mmol) in CH_2Cl_2 was added dropwise a solution of the appropriate amine **11**−**19** (3.0 mmol), in the same solvent. The reaction mixture was stirred overnight at room temperature; then a few milliliters of glacial acetic acid was added to decompose the excess reagent. The insoluble urea was removed by filtration, the filtrate was washed with 2 N NaOH, and the organic layer was separated and dried over Na_2SO_4. Evaporation of the solvent in vacuo provided the crude amide which was chromatographed (CH_2Cl_2/MeOH, 19:1, as eluent) to give the expected pure amides **22**−**30** as almost white to pale yellow semisolids.

***N*-[2-(4-Phenylpiperazin-1-yl)ethyl]-5-methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxamide (22).** This compound was prepared in a 73% yield from 4-(2-aminoethyl)-1-phenylpiperazine (**11**) (0.68 g, 3.3 mmol) according to the general procedure: ^{1}H NMR ($CDCl_3$) 1.57−1.87 and 2.28−2.37 (mm, 4H, *endo* CH_2CH_2), 2.41−2.58 and 2.65−2.81 [mm, 8H, benzyl CH_2, $CH_2N(CH_2)_2$], 2.98 [br t, 4H, $(CH_2)_2NAr$], 3.24−3.37 (m, 2H, $NHCH_2$), 3.62−3.66 (s + t, 4H, CHCO, CH_3), 6.10 (br s, 1H, NH), 6.62−7.32 (mm, 8H, aromatic); GC/MS *m*/*z* 394 (M^+ + 1, 1), 393 (M^+, 5), 188 (13), 175 (100), 132 (27).

***N*-[2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl]-5-methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxamide (23).** This compound was prepared according to the general procedure (59% yield) by starting from 4-(2-aminoethyl)-1-(2-methoxyphenyl)piperazine (**12**) (0.75 g, 3.2 mmol): ^{1}H NMR ($CDCl_3$) 1.63−1.89 and 2.29−2.36 (mm, 4H, *endo* CH_2CH_2), 2.41−2.58 and 2.73−2.80 [mm, 8H, benzyl CH_2, $CH_2N(CH_2)_2$], 2.86 [br s, 4H, $(CH_2)_2NAr$], 3.26−3.32 (m, 2H, $NHCH_2$), 3.65 (br t, 1H, CHCO), 3.73 and 3.83 (2 s, 6H, 2 CH_3), 6.09 (br s, 1H, NH), 6.68−7.14 (mm, 7H, aromatic); GC/MS *m*/*z* 424 (M^+ + 1, 5), 423 (M^+, 19), 206 (13), 205 (100), 190 (17).

***N*-[2-[4-(2-Pyridyl)piperazin-1-yl]ethyl]-5-methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxamide (24).** This compound was synthesized from 4-(2-aminoethyl)-1-(2-pyridyl)piperazine (**13**) (0.62 g, 3.0 mmol) according to the general procedure (73% yield): ^{1}H NMR ($CDCl_3$) 1.58−1.93 and 2.28−2.36 (mm, 4H, *endo* CH_2CH_2), 2.38−2.82 [mm, 8H, benzyl CH_2, $CH_2N(CH_2)_2$], 3.24−3.44 [mm, 6H, $(CH_2)_2NAr$, $NHCH_2$], 3.63−3.68 (s + t, 4H, CHCO, CH_3), 6.04 (br s, 1H, NH), 6.58−7.48 (mm, 6H, aromatic), 8.16−8.18 (m, 1H, aromatic N=CH); GC/MS *m*/*z* 395 (M^+ + 1, 9), 394 (M^+, 32), 232 (22), 176 (100), 147 (38), 127 (29), 121 (60).

***N*-[3-(4-Phenylpiperazin-1-yl)-*n*-propyl]-5-methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxamide (25).** Using the general procedure described above, from 4-(3-amino-*n*-propyl)-1-phenylpiperazine (**14**) (1.05 g, 4.8 mmol), this compound was obtained in a 68% yield: ^{1}H NMR ($CDCl_3$) 1.63−1.95 and 2.12−2.22 (mm, 6H, *endo* CH_2CH_2, $CH_2CH_2CH_2$), 2.50−2.75 [mm, 8H, benzyl CH_2, $CH_2N(CH_2)_2$], 3.16 [br t, 4H, $(CH_2)_2NAr$], 3.22−3.40 (m, 2H, $NHCH_2$), 3.64 (t, 1H, J = 5.5 Hz, CHCO), 3.68 (s, 3H, CH_3), 6.34 (br t, 1H, NH), 6.63−7.30 (mm, 8H, aromatic); GC/MS *m*/*z* 408 (M^+ + 1, 10), 407 (M^+, 37), 392 (67), 289 (21), 275 (100), 246 (45), 175 (41), 161 (39).

***N*-[3-[4-(2-Methoxyphenyl)piperazin-1-yl]-*n*-propyl]-5-methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxamide (26).** This compound was prepared from 4-(3-amino-*n*-propyl)-1-(2-methoxyphenyl)piperazine (**15**) (0.90 g, 3.6 mmol) according to the general procedure (72% yield): ^{1}H NMR ($CDCl_3$) 1.69−1.96 and 2.13−2.22 (mm, 6H, *endo* CH_2CH_2, $CH_2CH_2CH_2$), 2.45−2.77 [mm, 8H, benzyl CH_2, $CH_2N(CH_2)_2$], 2.96 [br s, 4H, $(CH_2)_2NAr$], 3.28−3.35 (m, 2H, $NHCH_2$), 3.65 (t, 1H, J = 5.4 Hz, CHCO), 3.72 and 3.83 (2 s, 6H, 2 CH_3), 6.26 (br t, 1H, NH), 6.66−7.14 (mm, 7H, aromatic); GC/MS *m*/*z* 438 (M^+ + 1, 15), 437 (M^+, 53), 423 (27), 422 (100), 288 (32), 276 (26), 275 (87), 246 (44), 205 (73), 190 (32), 161 (35).

***N*-[3-[4-(2-Pyridyl)piperazin-1-yl]-*n*-propyl]-5-methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxamide (27).** This compound was synthesized as above from 4-(3-amino-*n*-propyl)-1-(2-pyridyl)piperazine (**16**) (1.06 g, 4.8 mmol) (64% yield): ^{1}H NMR ($CDCl_3$) 1.57−1.94 and 2.15−2.27 (mm, 6H, *endo* CH_2CH_2, $CH_2CH_2CH_2$), 2.30−2.74 [mm, 8H, benzyl CH_2, $CH_2N(CH_2)_2$], 3.21−3.48 [mm, 6H, $(CH_2)_2NAr$, $NHCH_2$], 3.57−3.77 (s + t, 4H, CHCO, CH_3), 6.23 (br s, 1H, NH), 6.56−7.48 (mm, 6H, aromatic), 8.14−8.17 (m, 1H, aromatic N=CH); GC/MS *m*/*z* 409 (M^+ + 1, 14), 408 (M^+, 51), 406 (40), 314 (43), 289 (39), 246 (68), 161 (51), 107 (100).

***N*-Methyl-*N*-[2-(4-phenylpiperazin-1-yl)ethyl]-5-methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxamide (28).** This compound was obtained in a 68% yield according to the general procedure starting from 4-[2-(methylamino)ethyl]-1-phenylpiperazine (**17**) (1.45 g, 6.6 mmol): ^{1}H NMR (DMSO-d_6)[20] 1.56−1.91 (mm, 4H, *endo* CH_2CH_2), 2.53−2.67 [mm, 8H, benzyl CH_2, $CH_2N(CH_2)_2$], 2.90 and 3.13 (2 s, 3H, NCH_3), 3.11 [br t, 4H, $(CH_2)_2NAr$], 3.32−3.41 and 3.56−3.69 [2 m, 2H, $N(CH_3)CH_2$], 3.74 (s, 3H, OCH_3), 4.11 (br s, 1H, CHCO), 6.50−

7.22 (mm, 8H, aromatic); GC/MS *m/z* 408 ($M^+ + 1$, 3), 407 (M^+, 13), 188 (31), 175 (100), 132 (21).

***N*-[2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl]-*N*-methyl-5-methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxamide (29).** This compound was prepared from 1-(2-methoxyphenyl)-4-[2-(methylamino)ethyl]piperazine (**18**) (0.72 g, 3.3 mmol) as above (78% yield): ^{1}H NMR (DMSO-d_6)[20] 1.59−1.92 (mm, 4H, *endo* CH_2CH_2), 2.52−2.64 [mm, 8H, benzyl CH_2, $CH_2N(CH_2)_2$], 2.90 and 3.14 (2 s, 3H, NCH_3), 2.94 [br s, 4H, $(CH_2)_2NAr$], 3.34−3.39 and 3.55−3.68 [2 m, 2H, $N(CH_3)CH_2$], 3.74 and 3.76 (2 s, 6H, 2 OCH_3), 4.11 (br t, 1H, CHCO), 6.51−7.06 (mm, 7H, aromatic); GC/MS *m/z* 438 ($M^+ + 1$, 2), 437 (M^+, 6), 218 (20), 205 (100), 190 (20).

***N*-Methyl-*N*-[3-(4-phenylpiperazin-1-yl)-*n*-propyl]-5-methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxamide (30).** This compound was prepared according to the general procedure (60% yield) from 4-[3-(methylamino)-*n*-propyl]-1-phenylpiperazine (**19**) (1.35 g, 5.8 mmol): ^{1}H NMR (DMSO-d_6)[20] 1.57−1.89 (mm, 6H, *endo* CH_2CH_2, $CH_2CH_2CH_2$), 2.27−2.64 [mm, 8H, benzyl CH_2, $CH_2N(CH_2)_2$], 2.87 and 3.12 (2 s, 3H, NCH_3), 3.04−3.11 [mm, 4H, $(CH_2)_2NAr$], 3.35 and 3.49 [2 br t, 2H, $N(CH_3)CH_2$], 3.74 and 3.75 (2 s, 3H, OCH_3), 4.11 and 4.18 (2 br t, 1H, CHCO), 6.43−7.21 (mm, 8H, aromatic); GC/MS *m/z* 422 ($M^+ + 1$, 7), 421 (M^+, 25), 419 (30), 406 (47), 303 (29), 289 (100), 260 (73), 258 (27), 175 (38), 161 (61).

4-[*N*-[(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-methyl]-2-aminoethyl]-1-phenylpiperazine (31). To a stirred suspension of $LiAlH_4$ (0.10 g, 2.6 mmol) in anhydrous THF (20 mL) was added amide **22** (1.02 g, 2.6 mmol), in the same solvent. The reaction mixture was refluxed for 2 h. After cooling, a few drops of water was added, the suspension was filtered, and the filtrate was concentrated under reduced pressure. The residue was diluted with water and extracted twice with CH_2Cl_2. The separated organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give a crude residue which was chromatographed (CH_2Cl_2/MeOH, 19:1, as eluent). Pure **31** was a pale yellow oil (0.45 g, 46% yield): ^{1}H NMR ($CDCl_3$) 1.74−1.87 (mm, 4H, *endo* CH_2CH_2), 2.49−2.75 [mm, 9H, benzyl CH_2, $CH_2N(CH_2)_2$, NH, 1H, D_2O exchanged], 2.87 (br t, 2H, $NHCH_2CH_2$), 2.93 (d, 2H, J = 3.4 Hz, $CHCH_2NH$), 3.08−3.10 (mm, 5H, $(CH_2)_2NAr$, $CHCH_2NH$), 3.75 (s, 3H, CH_3), 6.62−7.31 (mm, 8H, aromatic); GC/MS *m/z* 380 ($M^+ + 1$, 1), 379 (M^+, 3), 261 (22), 247 (21), 218 (60), 176 (37), 175 (100).

General Procedure for the Preparation of Amines 32−35. The following compounds were prepared and purified according to the method described for compound **3**,[1] starting from 5-methoxy-1-tetralone (**8**) and 4-(2-aminoethyl)-1-phenylpiperazine (**11**), 4-(2-aminoethyl)-1-(2-pyridyl)piperazine (**13**), 4-(3-amino-*n*-propyl)-1-phenylpiperazine (**14**), and 4-(3-amino-*n*-propyl)-1-(2-methoxyphenyl)piperazine (**15**), respectively.

4-[*N*-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-2-aminoethyl]-1-phenylpiperazine (32): ^{1}H NMR ($CDCl_3$) 1.68−1.98 (mm, 5H, *endo* CH_2CH_2, NH, 1H, D_2O exchanged), 2.48−2.88 [mm, 10H, $CH_2CH_2N(CH_2)_2$, benzyl CH_2], 3.18 [br t, 4H, $(CH_2)_2NAr$], 3.75−3.79 (s + t, 4H, CH_3, $CHNH$), 6.68−7.29 (mm, 8H, aromatic); GC/MS *m/z* 366 ($M^+ + 1$, 1), 365 (M^+, 3), 176 (56), 175 (78), 162 (20), 161 (100), 132 (37).

4-[*N*-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-2-aminoethyl]-1-(2-pyridyl)piperazine (33): ^{1}H NMR ($CDCl_3$) 1.68−2.01 (mm, 5H, *endo* CH_2CH_2, NH, 1H, D_2O exchanged), 2.48−2.88 [mm, 10H, $CH_2CH_2N(CH_2)_2$, benzyl CH_2], 3.51 [br t, 4H, $(CH_2)_2NAr$], 3.55−3.79 (s + t, 4H, CH_3, $CHNH$), 6.58−7.48 (mm, 6H, aromatic), 8.16−8.18 (m, 1H, aromatic N=CH); GC/MS *m/z* 367 ($M^+ + 1$, 2), 366 (M^+, 9), 177 (23), 176 (100), 161 (72), 147 (44), 121 (76).

4-[*N*-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3-amino-*n*-propyl]-1-phenylpiperazine (34): ^{1}H NMR ($CDCl_3$) 1.69−1.98 (mm, 7H, *endo* CH_2CH_2, $CH_2CH_2CH_2$, NH, 1H, D_2O exchanged), 2.41−2.85 [mm, 10H, $NHCH_2$, $CH_2N(CH_2)_2$, benzyl CH_2], 3.16 [br t, 4H, $(CH_2)_2NAr$], 3.70−3.81 (s + t, 4H, CH_3, $CHNH$), 6.66−7.28 (mm, 8H, aromatic); GC/MS *m/z* 380 ($M^+ + 1$, 1), 379 (M^+, 6), 247 (72), 245 (33), 189 (33), 176 (47), 175 (92), 161 (100), 160 (30).

1-(2-Methoxyphenyl)-4-[*N*-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3-amino-*n*-propyl]piperazine (35): ^{1}H NMR ($CDCl_3$) 1.68−1.97 (mm, 7H, *endo* CH_2CH_2, $CH_2CH_2CH_2$, NH, 1H, D_2O exchanged), 2.44−2.84 [mm, 10H, $NHCH_2$, $CH_2N(CH_2)_2$, benzyl CH_2], 3.06 [br s, 4H, $(CH_2)_2NAr$], 3.73 (br t, 1H, $CHNH$), 3.78 and 3.84 (2 s, 6H, 2 CH_3), 6.67−7.14 (mm, 7H, aromatic); GC/MS *m/z* 410 ($M^+ + 1$, 1), 409 (M^+, 3), 261 (29), 247 (59), 245 (31), 219 (35), 205 (100), 190 (46), 161 (87).

1-(2-Methoxyphenyl)-4-[2-[*N*-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methylamino]ethyl]piperazine (36). To a solution of 1-(2-methoxyphenyl)-4-[*N*-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-2-aminoethyl]piperazine (**3**) (2.01 g, 5.1 mmol) in 50 mL of $CHCl_3$ was added 50 mL of 2.4% aqueous NaOH. Then methyl chloroformate (0.79 mL, 10.2 mmol) in $CHCl_3$ was added dropwise to the ice-cooled mixture, under vigorous stirring. The cold mixture was stirred for 1 h and then acidified with 6 N HCl and stirred at 25 °C for 0.5 h. The layers were separated, and the aqueous portion was extracted with $CHCl_3$. The organic portions were combined, washed first with aqueous $NaHCO_3$ and then with water, dried over Na_2SO_4, and concentrated under reduced pressure to yield the oily carbamate derivative. To a stirred suspension of $LiAlH_4$ (0.39 g, 10.3 mmol) in anhydrous THF was added a solution of the carbamate derivative in the same solvent. The mixture was refluxed for 24 h and then cooled, and the excess reagent was decomposed with a few drops of water. The mixture was filtered and the filtrate concentrated under reduced pressure. The residue was diluted with $CHCl_3$ and washed with water. The separated organic layer was dried over Na_2SO_4 and evaporated in vacuo to afford the *N*-methylated derivative **36** (1.76 g, 84% yield): ^{1}H NMR ($CDCl_3$) 1.53−1.62 and 1.93−2.05 (mm, 4H, *endo* CH_2CH_2), 2.27 (s, 3H, NCH_3), 2.38−2.81 [mm, 10H, $NHCH_2$, $CH_2N(CH_2)_2$, benzyl CH_2], 3.08 [br s, 4H, $(CH_2)_2NAr$], 3.79 and 3.90 (m + 2 s, 7H, 2 CH_3, $CHNH$), 6.65−7.35 (mm, 7H, aromatic); GC/MS *m/z* 410 ($M^+ + 1$, 1), 409 (M^+, 4), 205 (31), 204 (25), 161 (100).

***N*-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)bromoacetamide (20).** A cooled solution of 5-methoxy-1,2,3,4-tetrahydro-1-naphthalenamine (**10**) (2.50 g, 14.1 mmol) in CH_2Cl_2, was stirred vigorously with 2% aqueous NaOH (18.3 mmol) while bromoacetyl chloride (1.59 mL, 18.3 mmol) in CH_2Cl_2 was added dropwise. The same NaOH solution was then used in drops to maintain pH at 9, and at costant pH the layers were separated. The organic phase was washed with 3 N HCl and water and then dried over Na_2SO_4 and evaporated under reduced pressure. The crude residue was eluted with $CHCl_3$ to give compound **20** as a white solid (3.23 g, 77% yield): mp 166−167 °C (from $CHCl_3$/*n*-hexane); ^{1}H NMR ($CDCl_3$) 1.73−1.93 and 1.95−2.05 (mm, 4H, *endo* CH_2CH_2), 2.55−2.75 (m, 2H, benzyl CH_2), 3.81 (s, 3H, CH_3), 3.88 (s, 2H, CH_2Br), 5.08−5.14 (m, 1H, $CHNH$), 6.67−7.18 (mm, 4H, aromatic, NH); GC/MS *m/z* 299 ($M^+ + 2$, 3), 297 (M^+, 3), 176 (14), 160 (100), 159 (26).

***N*-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3-chloropropanamide (21).** This compound was prepared from compound **10** (5.12 g, 28.9 mmol), 2% aqueous NaOH (37.7 mmol), and 3-chloropropionyl chloride (3.60 mL, 37.7 mmol) as for compound **20**. The crude residue was chromatographed ($CHCl_3$/ethyl acetate, 9:1, as eluent) to give compound **21** as a white solid (5.52 g, 71% yield): mp 167−168 °C (from Et_2O); ^{1}H NMR ($CDCl_3$) 1.73−2.01 (mm, 4H, *endo* CH_2CH_2), 2.52−2.73 (m + t, 4H, benzyl CH_2, $COCH_2$), 3.73−3.86 (m + s, 5H, CH_3, CH_2Cl), 5.12−5.18 (m, 1H, $CHNH$), 5.95 (br d, 1H, NH), 6.69−7.15 (mm, 3H, aromatic); GC/MS *m/z* 269 ($M^+ + 2$, 2), 268 ($M^+ + 1$, 1), 267 (M^+, 5), 160 (100), 159 (25).

***N*-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-4-phenylpiperazinoacetamide (37).** The derivative **20** (2.03 g, 6.8 mmol) was refluxed overnight with 1-phenylpiperazine (2.21 g, 13.6 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 (CH_2Cl_2/MeOH, 19:1, as eluent) to give **37** as a pale yellow semisolid (2.47 g, 96% yield): ^{1}H NMR ($CDCl_3$) 1.72−1.86 and 1.97−2.04 (mm, 4H, *endo* CH_2-

CH_2), 2.56−2.73 [mm, 6H, benzyl CH_2, $CH_2N(CH_2)_2$], 3.11 [br s, 6H, $(CH_2)_2NAr$, $CH_2N(CH_2)_2$], 3.80 (s, 3H, CH_3), 5.15−5.28 (m, 1H, CHNH), 6.70−7.26 (mm, 8H, aromatic), 7.37 (br d, 1H, NH); GC/MS *m/z* 380 ($M^+ + 1$, 6), 379 (M^+, 25), 175 (100), 161 (26), 132 (26).

***N*-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-4-phenylpiperazinopropanamide (38).** This compound was obtained as described for compound **37** (0.92 g, 59% yield) starting from derivative **21** (1.44 g, 3.9 mmol) and 1-phenylpiperazine (1.27 g, 7.8 mmol): ^{1}H NMR ($CDCl_3$) 1.72−1.96 (mm, 4H, *endo* CH_2CH_2), 2.42 [t, 2H, J = 6.0 Hz, $CH_2N(CH_2)_2$], 2.46−2.60 [mm, 6H, benzyl CH_2, $CH_2N(CH_2)_2$], 2.66 (t, 2H, J = 5.9, $COCH_2$), 2.80−2.95 [mm, 4H, $(CH_2)_2NAr$], 3.69 (s, 3H, CH_3), 5.05−5.11 (m, 1H, CHNH), 6.61−7.26 (mm, 8H, aromatic), 8.70 (br d, 1H, NH); GC/MS *m/z* 394 ($M^+ + 1$, 8), 393 (M^+, 29), 378 (60), 275 (24), 161 (100), 160 (27).

***N*-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-4-(2-methoxyphenyl)piperazinopropanamide (39).** This compound was prepared according to the method described for compound **38** (1.40 g, 52% yield) starting from **21** (1.67 g, 6.2 mmol) and 1-(2-methoxyphenyl)piperazine (2.38 g, 12.4 mmol): ^{1}H NMR ($CDCl_3$) 1.72−1.94 (mm, 4H, *endo* CH_2CH_2), 2.41 [t, 2H, J = 6.0 Hz, $CH_2N(CH_2)_2$], 2.47−2.80 [mm, 12H, benzyl CH_2, $CH_2N(CH_2)_2$, $(CH_2)_2NAr$, $COCH_2$], 3.74 and 3.81 (2 s, 6H, 2 CH_3), 5.05−5.11 (m, 1H, CHNH), 6.65−7.12 (mm, 7H, aromatic), 8.96 (br d, 1H, NH); GC/MS *m/z* 424 ($M^+ + 1$, 11), 423 (M^+, 41), 409 (27), 408 (100), 205 (27), 191 (21), 161 (66), 160 (31).

***N*-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-4-(2-pyridyl)piperazinopropanamide (40).** Compound **40** was synthesized (1.34 g, 61% yield) starting from **21** (1.50 g, 5.6 mmol) and 1-(2-pyridyl)piperazine (1.83 g, 11.2 mmol): ^{1}H NMR ($CDCl_3$) 1.73−2.01 (mm, 4H, *endo* CH_2CH_2), 2.44 [t, 2H, J = 6.0 Hz, $CH_2N(CH_2)_2$], 2.48−2.58 [mm, 6H, benzyl CH_2, $CH_2N(CH_2)_2$], 2.66 (t, 2H, J = 5.8 Hz, $COCH_2$), 3.22−3.32 [mm, 4H, $(CH_2)_2NAr$], 3.71 (s, 3H, CH_3), 5.07−5.28 (m, 1H, CHNH), 6.53−7.48 (mm, 6H, aromatic), 8.13−8.17 (m, 1H, aromatic N=CH), 8.56 (br s, 1H, NH); GC/MS *m/z* 395 ($M^+ + 1$, 8), 394 (M^+, 31), 392 (22), 300 (61), 275 (55), 176 (29), 161 (97), 160 (87), 127 (46), 121 (31), 119 (22), 107 (100).

Hydrochloride Salts: General Procedure. The hydrochloride salts were prepared by adding an HCl ethereal solution to a methanolic solution of amine. Recrystallization solvents, crystallization formulas, and melting points are listed in Table 1. They were obtained as white to sandy yellow crystals or crystalline powders.

Pharmacological Methods. All binding studies were performed in rat brain areas. Male Wistar rats, weighing 175−200 g, were killed by decapitation under light anesthesia and the various brain regions dissected out very quickly on an ice-cold plate. Depending on the receptor to be studied, the different areas were used following the methods described in the next paragraphs.

D-1 Dopaminergic Binding Assay. The binding assay for D-1 dopaminergic receptors was essentially that described by Billard et al.[21] Corpora striata were homogenized in 30 vol (w/v) of ice-cold 50 mM Tris·HCl buffer (pH 7.7 at 25 °C) using a Polytron PT10 homogenizer (setting 5 for 20 s). Homogenates were centrifuged twice for 10 min at 50000*g* with resuspension of the pellet in fresh buffer. The final pellet was resuspended in ice-cold Tris·HCl (50 mM) containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 0.1% ascorbic acid, and 10 μM pargyline (pH 7.1 at 37 °C). Each assay tube contained 50 μL of drug solution, 50 μL of [^{3}H]SCH-23390 to achieve a final concentration of 0.4 nM, and 900 μL of resuspended membranes (3 mg of fresh tissue). The tubes were incubated for 15 min at 37 °C, and the incubation was terminated by rapid filtration under vacuum through Whatman GF/B glass fiber filters. The filters were washed three times with 5 mL of ice-cold 50 mM Tris·HCl buffer (pH 7.7 at 25 °C). The radioactivity bound to the filters was measured by a liquid scintillation counter. Specific [^{3}H]SCH-23390 binding was defined as the difference between binding in the absence or presence of 0.1 μM piflutixol.

D-2 Dopaminergic Binding Assay. The procedure used in radioligand binding assay has been published in detail by Creese et al.[22] Corpora striata were homogenized in 30 vol (w/v) of ice-cold 50 mM Tris·HCl buffer (pH 7.7 at 25 °C) using a Polytron PT10 homogenizer (setting 5 for 20 s). Homogenates were centrifuged twice for 10 min at 50000*g* with resuspension of the pellet in fresh buffer. The final pellet was resuspended in ice-cold Tris·HCl (50 mM) containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 0.1% ascorbic acid, and 10 μM pargyline (pH 7.1 at 37 °C). Each assay tube contained 50 μL of drug solution, 50 μL of [^{3}H]spiroperidol to achieve a final concentration of 0.4 nM, and 900 μL of resuspended membranes (3 mg of fresh tissue). The tubes were incubated for 15 min at 37 °C, and the incubation was terminated by rapid filtration under vacuum through Whatman GF/B glass fiber filters. The filters were washed three times with 5 mL of ice-cold 50 mM Tris·HCl buffer (pH 7.7 at 25 °C). The radioactivity bound to the filters was measured by a liquid scintillation counter. Specific [^{3}H]spiroperidol binding was defined as the difference between binding in the absence or presence of 1 μM (+)-butaclamol.

5-HT$_{1A}$ Serotonergic Binding Assay. The procedure used in radioligand binding assay has been published in detail by Hall et al.[23] Hippocampus was homogenized in 30 vol (w/v) of ice-cold 50 mM Tris·HCl buffer (pH 7.2 at 25 °C) using a Polytron PT10 homogenizer (setting 5 for 20 s). Homogenates were centrifuged twice for 10 min at 50000*g* with resuspension of the pellet in fresh buffer. After the second centrifugation, the pellet was resuspended in homogenization buffer and the suspension incubated 10 min at 37 °C. After it had been centrifuged and washed twice more, the final pellet was resuspended in ice-cold Tris·HCl (50 mM) containing 4 mM $CaCl_2$, 0.1% ascorbic acid, and 10 μM pargyline (pH 7.4 at 25 °C). Each assay tube contained 50 μL of drug solution, 50 μL of [^{3}H]-8-OH-DPAT to achieve a final concentration of 0.8 nM, and 900 μL of resuspended membranes (10 mg of fresh tissue). The tubes were incubated for 30 min at 25 °C, and the incubation was terminated by rapid filtration under vacuum through Whatman GF/B glass fiber filters. The filters were washed three times with 5 mL of ice-cold 50 mM Tris·HCl buffer (pH 7.2 at 25 °C). The radioactivity bound to the filters was measured by a liquid scintillation counter. Specific [^{3}H]-8-OH-DPAT binding was defined as the difference between binding in the absence or presence of 10 μM 5-HT.

5-HT$_2$ Serotonergic Binding Assay. The procedure used in radioligand binding assay has been published in detail by Leysen et al.[24] Prefrontal cortex was homogenized in 30 vol (w/v) of ice-cold 50 mM Tris·HCl buffer (pH 7.2 at 25 °C) using a Polytron PT10 homogenizer (setting 5 for 20 s). Homogenates were centrifuged three times for 10 min at 50000*g* with resuspension of the pellet in fresh buffer. The final pellet was resuspended in ice-cold 50 mM Tris·HCl (pH 7.4 at 37 °C). Each assay tube contained 50 μL of drug solution, 50 μL of [^{3}H]ketanserin to achieve a final concentration of 0.8 nM, and 900 μL of resuspended membranes (5 mg of fresh tissue). The tubes were incubated for 15 min at 37 °C, and the incubation was terminated by rapid filtration under vacuum through Whatman GF/B glass fiber filters. The filters were washed three times with 5 mL of ice-cold 50 mM Tris·HCl buffer (pH 7.2 at 25 °C). The radioactivity bound to the filters was measured by a liquid scintillation counter. Specific [^{3}H]-ketanserin binding was defined as the difference between binding in the absence or presence of 1 μM methysergide.

α_1-Adrenergic Binding Assay. The procedure used in radioligand binding assay has been published in detail by Greengrass and Bremner.[25] Brain cortex was homogenized in 30 vol (w/v) of ice-cold 50 mM Tris·HCl buffer (pH 7.2 at 25 °C) using a Polytron PT10 homogenizer (setting 5 for 20 s). Homogenates were centrifuged twice for 10 min at 50000*g* with resuspension of the pellet in fresh buffer. The final pellet was resuspended in ice-cold 50 mM Tris·HCl (pH 7.4 at 25 C°). Each assay tube contained 50 μL of drug solution, 50 μL of [^{3}H]prazosin to achieve a final concentration of 0.4 nM, and 900 μL of resuspended membranes (10 mg of fresh tissue). The tubes were incubated for 30 min at 25 °C, and the incubation was terminated by rapid filtration under vacuum through Whatman GF/B glass fiber filters. The filters were washed

three times with 5 mL of ice-cold 50 mM Tris·HCl buffer (pH 7.2 at 25 °C). The radioactivity bound to the filters was measured by a liquid scintillation counter. Specific [^{3}H]-prazosin binding was defined as the difference between binding in the absence or presence of 1 μM phentolamine.

α_2-Adrenergic Binding Assay. The procedure used in radioligand binding assay has been published in detail by Perry and U'Prichard.[26] Brain cortex was homogenized in 30 vol (w/v) of ice-cold 5 mM Tris·HCl, 5 mM EDTA buffer (pH 7.3 at 25 °C) using a Polytron PT10 homogenizer (setting 5 for 20 s). Homogenates were centrifuged three times for 10 min at 50000*g* with resuspension of the pellet in fresh buffer. The final pellet was resuspended in ice-cold 50 mM Tris·HCl, 0.5 mM EDTA (pH 7.5 at 25 °C). Each assay tube contained 50 μL of drug solution, 50 μL of [^{3}H]yohimbine to achieve a final concentration of 1 nM, and 900 μL of resuspended membranes (10 mg of fresh tissue). The tubes were incubated for 30 min at 25 °C, and the incubation was terminated by rapid filtration under vacuum through Whatman GF/B glass fiber filters. The filters were washed three times with 5 mL of ice-cold 50 mM Tris·HCl, 0.5 mM EDTA buffer (pH 7.5 at 25 °C). The radioactivity bound to the filters was measured by a liquid scintillation counter. Specific [^{3}H]yohimbine binding was defined as the difference between binding in the absence or presence of 10 μM phentolamine.

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