Structure−Activity Relationship Studies on the 5-HT_{1A} Receptor Affinity of 1-Phenyl-4-[ω-(α- or β-tetralinyl)alkyl]piperazines. 4[1]

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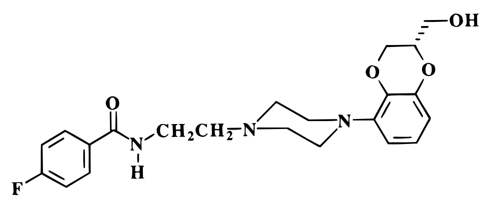
The synthesis of 1-phenylpiperazines, linked in the α or β position of the tetralin moiety on the terminal part of the N-4 alkyl chain, and their radioligand binding affinities for 5-HT_{1A}, 5-HT_{2A}, D-1, D-2, α_1, and α_2 receptors along with SAR studies on the 5-HT_{1A} receptor are reported. Several changes have been carried out on previous structures of type **2**, by inserting the alkyl chain with variable length in the α or β position of the tetralin moiety and by changing the position of the methoxy group on the aromatic ring of the tetralin nucleus. The highest affinity (IC_{50} = 0.50 nM) and selectivity for the 5-HT_{1A} receptor were showed by 1-phenylpiperazine **2a** with a three-membered alkyl chain bearing a 5-methoxytetralin-1-yl ring in the ω position.

The existence of multiple serotonin (5-HT) receptor subsites in mammalian brain tissue has stimulated research to identify selective agents as pharmacological tools in order to evaluate the role of these receptors in various pathological conditions.[2,3] The 5-HT_{1A} serotonin receptor has been the object of several studies since the discovery of its involvement in various physiological functions, such as sleep, appetite, and sexual behavior or pathological states such as anxiety[4,5] and depression.[6,7] The 1-arylpiperazine derivatives constitute one of the most important classes of the 5-HT_{1A} receptor ligands. Structure−activity relationship (SAR) studies focus on the highly active 4-(ω-substitutedalkyl)-1-arylpiperazine (K_i ranging from 10^{-8} to 10^{-10} M) where an amide or imide function is present in the ω position of the alkyl chain. Examples include buspirone, NAN-190, flesinoxan, BMY7378, and ipsapirone.[8] The large number of SAR studies on amide derivatives is justified by the hypothesis that the terminal amide fragment in these compounds stabilizes the 5-HT_{1A} receptor−ligand complex by either π-electron or local dipole−dipole interactions in a region of bulk tolerance adjoining the protonation site.[9] However, desamido-1-arylpiperazine derivatives may also show the same 5-HT_{1A} affinity as corresponding amidic derivatives. This has been reported by some authors.[10] On the other hand, the hypothesis that the amido function does not stabilize the 5-HT_{1A} receptor−ligand complex has been confirmed by us in a recent work[1] on alkylamido derivatives of 1-aryl-4-[(1-tetralinyl)alkyl]piperazines, **1**, where the corresponding desamido compounds **2a**−**c** showed the highest affinity for the 5-HT_{1A} receptor.[11,12] So it can be stated that the amide function is not required for binding with the 5-HT_{1A} receptor.

In keeping with this finding, we have carried out additional work in order to have a better understanding of this class as part of our continuing research program



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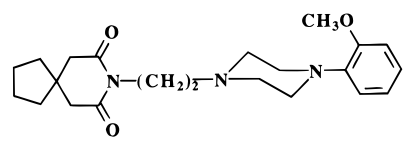
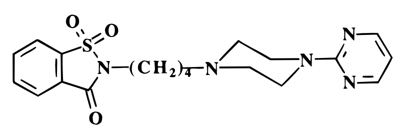


BMY7378



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for developing compounds with high affinity and selectivity for the 5-HT_{1A} receptor. Among the 1-arylpiperazines previously studied with highest affinity for the 5-HT_{1A} receptor, we chose to consider compound **2a** as the reference structure for the present SAR study. This compound shows the best affinity and selectivity values in comparison with compounds **2b**,**c** and their isomers **4**−**6** (Table 1).[1] We now report on the effects of the following structural variations for 5-HT_{1A} receptor affinity and selectivity of compound **2**: (a) the insertion of the alkyl chain in the α or β position of the tetralin moiety, (b) the changing of the position of the methoxy group on the aromatic ring of the tetralin moiety, and (c) the variation of the length of the methylene spacer between the basic nitrogen atom and the tetralin nucleus. The synthesis and radioligand binding affinities for 5-HT_{1A}, 5-HT_{2A}, D-1, D-2, α_1, and α_2 receptors of compounds with general structure **3** are described.

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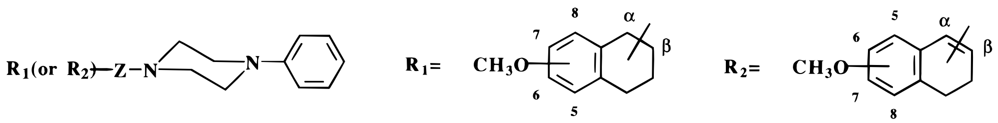
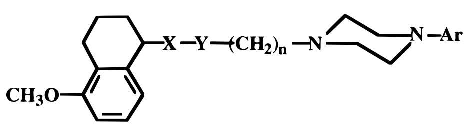
Table 1. Physical Properties



compd	R_1 or R_2	CH_3O	Z α	Z β	formula[a]	mp, °C	recryst solv
2a[b]	R_1	5	$(CH_2)_3$				
4[b]	R_2	8	$(CH_2)_3$				
5[b]	R_1	7	$(CH_2)_3$				
6[b]	R_2	6	$(CH_2)_3$				
17	R_1	5	$(CH_2)_2$		$C_{23}H_{30}N_2O\cdot 2HCl\cdot {}^1/_3H_2O$	238 dec	$MeOH/Et_2O$
18	R_1	6	$(CH_2)_3$		$C_{24}H_{32}N_2O\cdot 2HCl$	212−214	$MeOH/Et_2O$
19	R_1	8	$(CH_2)_3$		$C_{24}H_{32}N_2O\cdot 2HCl$	209	$MeOH/Et_2O$
20	R_1	5	$=CH(CH_2)_2$		$C_{24}H_{30}N_2O\cdot 2HCl$	194−196	$MeOH/Et_2O$
21	R_1	5	$(CH_2)_4$		$C_{25}H_{34}N_2O\cdot 2HCl\cdot H_2O$	204−206	$CHCl_3$/petroleum ether
22	R_2	8		$(CH_2)_2$	$C_{23}H_{28}N_2O\cdot 2HCl$	235	$MeOH/Et_2O$
23	R_2	7		$(CH_2)_2$	$C_{23}H_{28}N_2O\cdot 2HCl$	237	MeOH
24	R_2	6		$(CH_2)_2$	$C_{23}H_{28}N_2O\cdot 2HCl$	217	$MeOH/Et_2O$
25	R_1	5		$(CH_2)_2$	$C_{23}H_{30}N_2O\cdot 2HCl$	240	$MeOH/Et_2O$
26	R_1	6		$(CH_2)_2$	$C_{23}H_{30}N_2O\cdot 2HCl$	218	MeOH
27	R_1	7		$(CH_2)_2$	$C_{23}H_{30}N_2O\cdot 2HCl$	215	$MeOH/Et_2O$

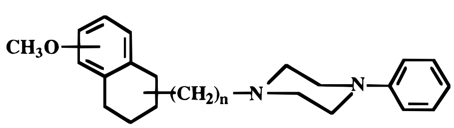
[a] Analyses for C,H,N; results were within ±0.4% of the theoretical values for the formulas given. [b] Formerly published compounds.[11,12]



Ar= a: phenyl
b: 2-CH_3O-phenyl
c: 2-pyridyl

1: X-Y= CONH, NHCO; n= 2, 3

2: X-Y= $(CH_2)_2$; n= 1



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Chemistry

The three pathways described in Scheme 1 were followed to synthesize compounds **17**−**27**. Condensation of triethyl phosphonoacetate with 5-methoxy-1-tetralone (**7a**) according to the Wittig−Horner reaction[13] yielded a mixture of the unsaturated isomeric esters **8**. The subsequent steps to obtain the bromo derivative **11** were carried out as described in the literature[14] for 7-methoxy isomers. The catalytic hydrogenation of **8** afforded the saturated ester **9** which was reduced with $LiAlH_4$ to the alcohol **10**; the latter was treated with PBr_3 to give the alkyl bromide **11**. The target compound **17** was obtained by reaction of **11** with 1-phenylpiperazine. The homologues **18** and **19** were prepared as reported for some of their isomers.[11,12] Reaction of methoxy-1-tetralones **7b,d** with magnesium cyclopropyl bromide gave the intermediate cyclopropylcarbinol derivatives. Following treatment with HBr in acetic acid, the endocyclic unsaturated bromo derivatives **12b,d** were obtained. These were hydrogenated in the presence of 5% Pd−C to compounds **13b,d**. Subsequent reaction with 1-phenylpiperazine led to the final compounds **18** and **19**.

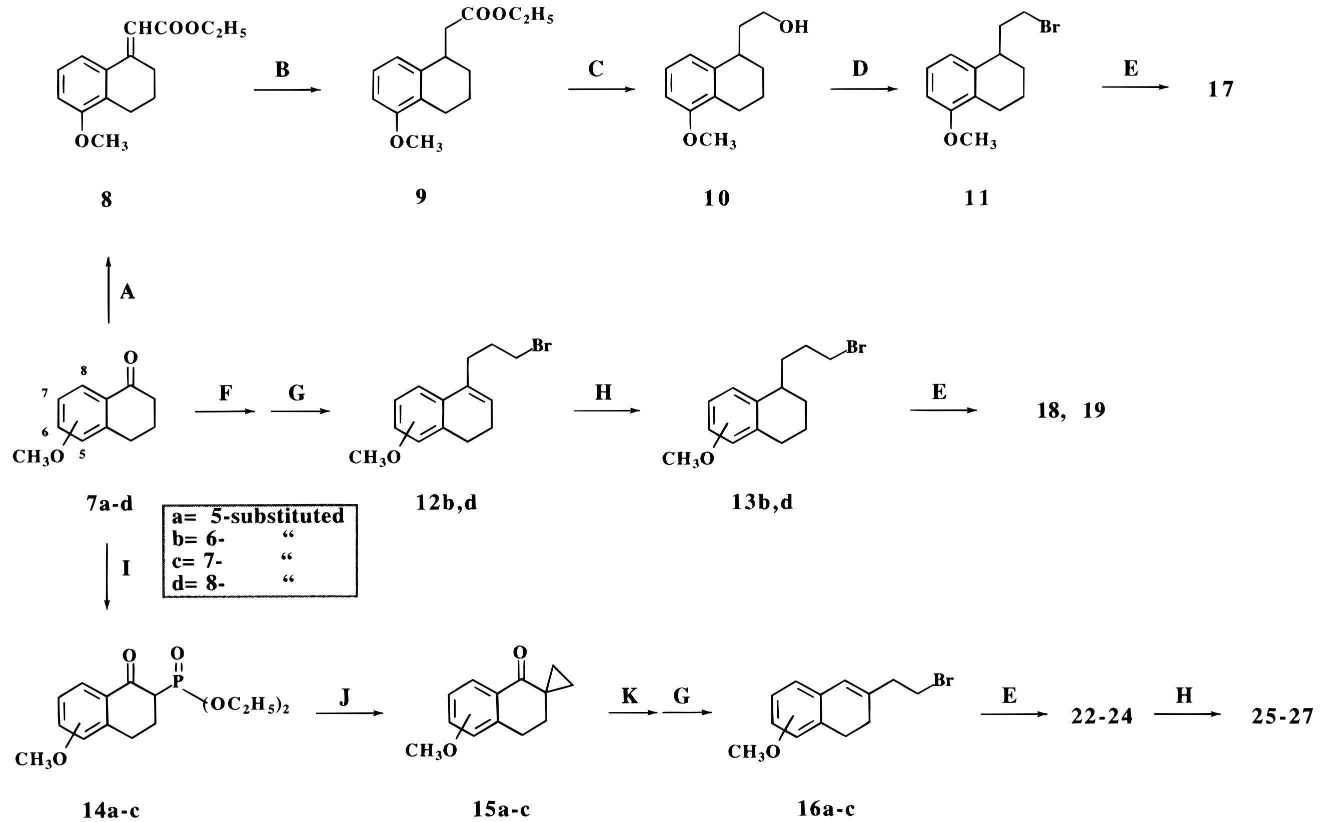
The *β*-keto phosphonate derivatives **14a,c** required for the synthesis of the dihydronaphthalene derivatives having a two-methylene alkyl chain in the *β* position, **22**−**24**, were prepared from the respective methoxy-1-tetralones **7a**−**c** and diethyl chlorophosphate in the presence of lithium diisopropylamide (LDA).[15] Compounds **14a**−**c** underwent condensation with ethylene oxide in the presence of a base[16] to afford the spirocyclic cyclopropyl ketones **15a**−**c**. The reduction of these compounds with $NaBH_4$ and the treatment of the crude intermediates with HBr and glacial acetic acid caused the dehydration and the opening of the spirocyclopropane ring to furnish the key intermediates **16a**−**c**. Reaction of these bromo derivatives with 1-phenylpiperazine afforded the unsaturated target compounds **22**−**24**. The corresponding saturated compounds **25**−**27** were obtained by catalytical hydrogenation.

Pharmacology

Final compounds (Table 2) were evaluated for *in vitro* affinity for dopamine D-1 and D-2, serotonin 5-HT_{1A} and 5-HT_{2A}, 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_{2A} receptors—[^{3}H]ketanserin, rat brain prefrontal cortex membranes; (e) α_1 adrenergic receptors—[^{3}H]prazosin, rat brain cortex membranes; and (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 using eight to nine different concentrations of the drug studied. The specific binding was defined as previously described.[1] In all binding assays, it represents more than 80% of the total binding, except for α_2 (>60%). The results were analyzed by using the program LIGAND to determine IC_{50} values.

Scheme 1[a]



[a] Reagents: (A) NaH (60% mineral oil dispersion), triethyl phosphonoacetate; (B) H_2, Pd−C (10%); (C) $LiAlH_4$; (D) PBr_3; (E) 1-phenylpiperazine; (F) cyclopropyl MgBr; (G) HBr; (H) H_2, Pd−C (5%); (I) LDA, diethyl chlorophosphate; (J) NaH, ethylene oxide; (K) $NaBH_4$.

Table 2. Binding Affinities and Selectivities[a,b]

compd	IC50, nM: 5-HT1A [3H]-8-OH-DPAT	IC50, nM: 5-HT2A [3H]ketanserin	IC50, nM: D-2 [3H]spiroperidol	IC50, nM: α1 [3H]prazosin	IC50, nM: α2 [3H]yohimbine	selectivity vs 5-HT1A receptor, IC50 ratio: 5-HT2	D-2	α1	α2
2a	0.50 ± 0.05[c]	230 ± 25[c]	110 ± 18[c]	43 ± 5[c]	260 ± 35[c]	460	220	86	520
2b	0.77 ± 0.09[c]	330 ± 29[c]	18 ± 2[c]	6.5 ± 0.6[c]	17 ± 2[c]	428	23	8	22
2c	0.54 ± 0.06[c]	250 ± 22[c]	140 ± 12[c]	66 ± 7[c]	48 ± 5[c]	462	259	122	89
4	18.3 ± 5.3[d]	204 ± 8[d]	303 ± 39[d]	49.0 ± 3.7[e]	NT	11	17	3	
5	9.24 ± 0.59[e]	NT[e]	28 ± 2[e]	184 ± 15[e]	NT		3	20	
6	147 ± 14[d]	119 ± 5[d]	157 ± 13[e]	173 ± 10[e]	NT	0.8	1	1	
17	140 ± 15	12 ± 1	210 ± 19	84 ± 8	22 ± 2	0.1	2	0.6	0.2
18	5.4 ± 0.6	160 ± 17	91 ± 9	45 ± 5	170 ± 19	30	17	8	31
19	56 ± 6	610 ± 57	62 ± 7	130 ± 16	140 ± 20	11	1	2	3
20	19 ± 2	580 ± 63	100 ± 10	120 ± 13	290 ± 35	31	5	6	15
21	15 ± 2	420 ± 38	110 ± 9	130 ± 12	770 ± 65	28	7	9	51
22	191 ± 21	241 ± 25	276 ± 30	194 ± 16	357 ± 38	1	1	1	2
23	8.2 ± 0.9	56 ± 6	170 ± 16	88 ± 9	130 ± 14	7	24	11	16
24	7.3 ± 0.8	106 ± 11	136 ± 14	58 ± 6	122 ± 13	15	22	8	18
25	54 ± 6	160 ± 15	130 ± 10	100 ± 9	600 ± 75	3	2	2	11
26	3.7 ± 0.3	86 ± 9	120 ± 13	79 ± 8	160 ± 18	23	32	21	43
27	3.6 ± 0.4	230 ± 19	100 ± 12	80 ± 9	260 ± 31	64	28	22	72
buspirone	30 ± 3	>10 000	280 ± 31	>10 000	>10 000				
8-OH-DPAT	2.1 ± 0.2	>10 000	5.2 ± 0.6	>10 000	810 ± 75				
ketanserin		3.4 ± 0.3							
haloperidol			4.8 ± 0.5						
prazosin				1.4 ± 0.6					
yohimbine					30 ± 3				

[a] NA = not active; NT = not tested. [b] Compounds **17**−**27** showed very high affinity binding values on the D-1 receptor (IC_{50} > 1000 nM). [c] See ref 1. [d] See ref 11. [e] See ref 12.

Results and Discussion

The results of the binding assays are illustrated in Table 2, and the structure−5-HT_{1A} affinity relationships are graphically summarized in Figure 1.

Position of the Methoxy Group on the Aromatic Ring of the Tetralin Nucleus. In previous studies,[11,12] we found that the 5-HT_{1A} receptor affinity and selectivity were very high for 1-phenylpiperazine derivatives having the methoxy group on the tetralin in the 5 position. In fact, compound **2a** exhibited higher affinity (IC_{50} = 0.5 nM) and selectivity than the corresponding 7-methoxy derivative **5**. For the other posi-

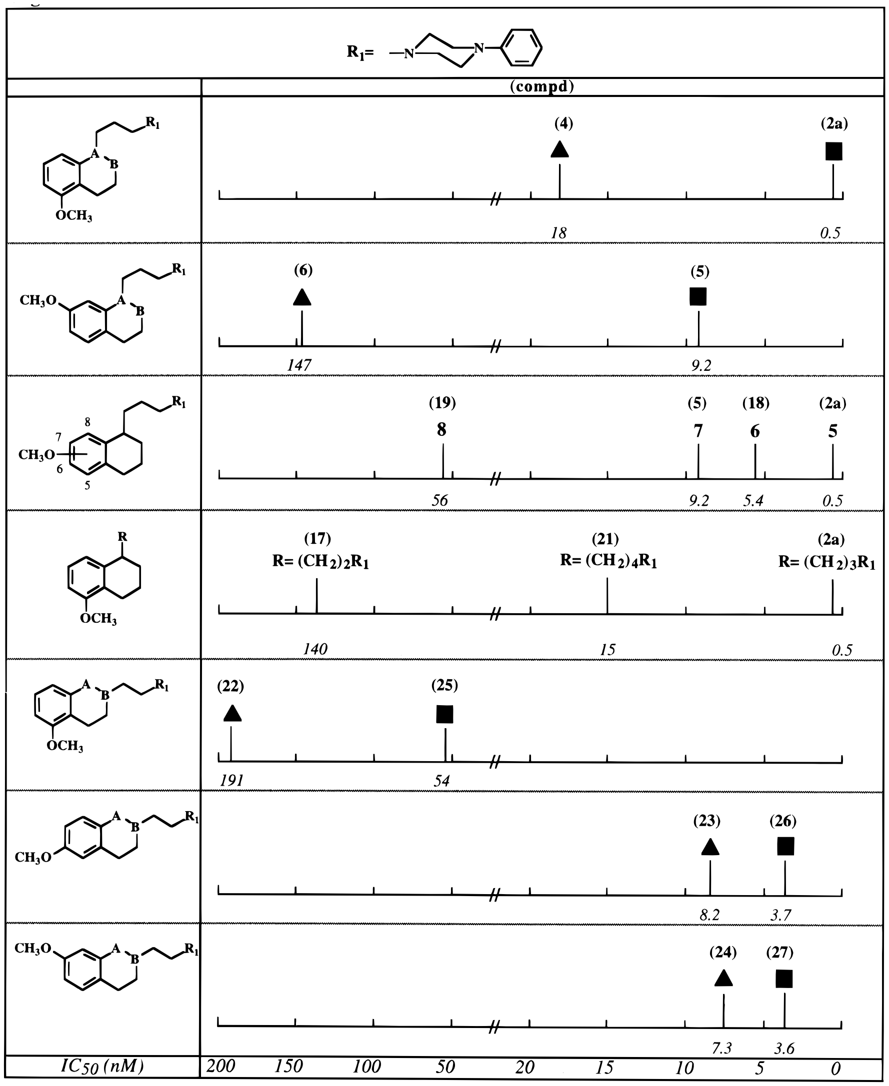


Figure 1. A–B, C=C (▲); A–B, CH–CH (■).

tions on the tetralin ring, the corresponding 6-methoxy derivative **18** showed a slight decrease in 5-HT$_{1A}$ affinity (IC$_{50}$ = 5.4 nM), whereas the 8-methoxy derivative **19** showed a remarkable lowering (IC$_{50}$ = 56 nM) of affinity. In both cases the selectivity values with respect to the other receptors were very low. This points out the importance of the distance between the methoxy group and the alkyl chain. Indeed, when the alkyl chain is in the α position of the tetralin nucleus, the ideal position of the methoxy group is in the 5 position, whereas, when the alkyl chain is in the *β* position, the trend changes. For the latter compounds, the highest values of affinity for the 5-HT$_{1A}$ receptor were observed when the methoxy group was in the 6 or 7 position (**23**, **24**, **26**, and **27**). Instead, when the methoxy group is in the 5 position (**22**) or 8 position (**25**), the affinity values decreased. In this way the spatial relationships between the position of the methoxy group and the alkyl chain on the tetralin nucleus are very evident.

Length of the Chain. The alkyl chain functions as a spacer between the protonation site and the terminal group in arylpiperazine derivatives. We observed that a three-methylene-membered chain is required for a compound to have the highest affinity for the 5-HT$_{1A}$ receptor (**2a**, IC$_{50}$ = 0.5 nM). This value decreases for compounds **21** (n = 4, IC$_{50}$ = 15 nM) and **17** (n = 2, IC$_{50}$ = 140 nM). Thus, when the alkyl chain is in the α position of the tetralin nucleus, its length has to be three methylene units. For this reason we inserted a two-methylene alkyl chain in the *β* derivatives **22**–**27** to obtain a quite similar distance as shown above.

Presence of an Unsaturated Bond on the Tetralin Nucleus. The saturated compounds **2a**, **5**, and **25**–**27** showed higher affinities for the 5-HT$_{1A}$ receptor as compared to the corresponding unsaturated compounds **4**, **6**, and **22**–**24**, respectively. A slight difference in affinity was observed between the exo-unsaturated derivative **20** and the corresponding endo-unsaturated compound **4**.

α or *β* Alkyl Substitution of the Tetralin Ring. The α or *β* position influences the length of the alkyl chain which has to be three- or two-methylene-membered, respectively. Moreover, this also influences the position of the methoxy group on the tetralin ring. Therefore the α derivative **2a**, with three methylene units and the methoxy group on the 5 position, showed a similar affinity value with the *β* derivatives **26** and **27**. These bear two methylene units and the methoxy group on the 6 and 7 positions, respectively. Concerning the selectivity for the other receptors tested, α derivatives such as **2a** are different from the *β* derivatives as the former is more selective.

Conclusion

The SAR of the 1-phenyl-4-[ω-(α- or β-tetralinyl)alkyl]-piperazines, described above, indicates the importance of the distance of the methoxy group on the tetralin ring from the protonation center of the piperazine ring for affinity and selectivity toward the 5-HT_{1A} receptor. In other words, the region of the 5-HT_{1A} sites involved with N-4 substituents must be capable of actively accommodating a chain of three carbon atoms linked to a position of a 5-methoxy-substituted tetralin.

Experimental Section

Chemistry. Column chromatography was performed with 1:30 ICN silica gel 60A (63−200 μm) as the stationary phase. 8-Methoxy-1-tetralone (**7d**) was prepared according to the literature.[17] A 1.5 M solution of LDA in *n*-hexane was purchased from Aldrich Chemical Co. Melting points were determined in open capillaries using 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 either on a Varian EM-390 (TMS as internal standard) or on a Bruker AM 300 WB instrument (where indicated 300 MHz), 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 a HP59970A workstation; only significant *m/z* peaks, with their percent relative intensity indicated in parentheses, are reported herein. All compounds had NMR and mass spectra that were consistent with their structures.

5-Methoxy-1,2,3,4-tetrahydro-1-naphthaleneacetic Acid, Ethyl Ester (9). Triethyl phosphonoacetate (6.2 mL, 31.3 mmol) was added dropwise to a cooled suspension of NaH (60% dispersion in mineral oil, 1.25 g, 31.3 mmol) in anhydrous toluene (20 mL). The mixture was then stirred for 1 h at 50 °C to ensure the reaction was complete. The formed solution was cooled, and 5-methoxy-1-tetralone (**7a**) (3.86 g, 21.9 mmol) in anhydrous toluene (20 mL) was added dropwise. The mixture was refluxed for 4 h, cooled, and then washed with cold water. The separated organic layer was dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude residue was chromatographed (petroleum ether/ethyl acetate, 9:1, as eluent) to yield a mixture of the (*E/Z*)-naphthylidene isomers **8**: GC/MS *m/z* 247 (M^+ + 1, 5), 246 (M^+, 29), 201 (36), 200 (100), 172 (21), 158 (21).

A methanolic solution of the above intermediates was hydrogenated in the presence of 10% palladium on charcoal (100 mg) at 30 kg/cm^2 pressure of H_2 for 18 h at room temperature. The reaction mixture was filtered over Celite and the filtrate evaporated to dryness *in vacuo* to give compound **9** as a pale yellow oil (4.70 g, 86% overall yield): ^{1}H-NMR 1.25 (t, 3H, *J* = 7 Hz, CH_3CH$_2$), 1.77 (br s, 4H, 2 *endo* CH_2), 2.37−2.93 (m, 4H, CH_2CO, benzyl CH_2), 3.13−3.53 (m, 1H, CH), 3.77 (s, 3H, OCH_3), 4.15 (q, 2H, *J* = 7 Hz, CH_3CH_2), 6.57−7.36 (m, 3H, aromatic); GC/MS *m/z* 249 (M^+ + 1, 7), 248 (M^+, 43), 174 (100), 161 (86), 160 (94), 159 (77), 158 (47).

5-Methoxy-1,2,3,4-tetrahydro-1-naphthaleneethanol (10). A solution of compound **9** (4.40 g, 17.7 mmol) in anhydrous THF (20 mL) was added dropwise to a cooled suspension of $LiAlH_4$ (0.68 g, 17.9 mmol) in the same solvent (40 mL). After the mixture stirred overnight at room temperature, the excess of the hydride was destroyed with some drops of water. The mixture was filtered and the filtrate concentrated to dryness. The residue was taken up with CH_2Cl_2. The solution was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was eluted with CH_2Cl_2 to give the alcohol **10** as a colorless oil (3.28 g, 90% yield): ^{1}H-NMR 1.53−2.17 (m, 7H, 2 *endo* CH_2, CH_2CH$_2$O*H*, 1H D_2O exchanged), 2.53−3.10 (m, 3H, benzyl CH_2, CH), 3.57−3.98 (s + m, 5H, CH_3, CH_2O), 6.60−7.33 (m, 3H, aromatic); GC/MS *m/z* 207 (M^+ + 1, 5), 206 (M^+, 32), 162 (100), 161 (56), 131 (23).

1-(2-Bromoethyl)-5-methoxy-1,2,3,4-tetrahydronaphthalene (11). Phosphorus tribromide (4 mL) was added dropwise to a stirred mixture of the alcohol **10** (3.10 g, 15.0 mmol) and pyridine (0.2 mL) in anhydrous toluene at 0 °C. The resulting mixture was warmed and stirred at 70 °C for 6 h. The reaction mixture was then poured into ice−water, the organic layer was separated, and the aqueous layer was extracted twice with diethyl ether. The combined organic layers were washed with a $NaHCO_3$-saturated solution followed by water and then dried over Na_2SO_4 and filtered. The solvent was evaporated *in vacuo*, and the crude residue was passed through a short silica gel column (petroleum ether/ethyl acetate, 4:1, as eluent) to give compound **11** as a colorless oil (2.02 g, 50% yield): ^{1}H-NMR 1.53−2.36 (m, 6H, 2 *endo* CH_2, CH_2CH$_2$Br), 2.48−3.20 (m, 3H, benzyl CH_2, CH), 3.44 (t, 2H, *J* = 7 Hz, CH_2Br), 3.78 (s, 3H, CH_3), 6.56−7.33 (m, 3H, aromatic); GC/MS *m/z* 271 (M^+ + 3, 2), 270 (M^+ + 2, 12), 269 (M^+ + 1, 2), 268 (M^+, 12), 162 (24), 161 (100), 115 (21).

The following compounds **12b,d** and **13b,d** were prepared and purified according to the procedure already reported.[11,12]

4-(3-Bromo-*n*-propyl)-1,2-dihydro-7-methoxynaphthalene (12b): ^{1}H-NMR 1.80−2.45 (m, 4H, CH_2CH_2CH$_2$Br), 2.45−3.00 (m, 4H, 2 *endo* CH_2), 3.40 (t, 2H, *J* = 7 Hz, CH_2Br), 3.80 (s, 3H, CH_3), 5.82 (br t, 1H, vinyl CH), 6.57−7.47 (m, 3H, aromatic); GC/MS *m/z* 283 (M^+ + 3, 3), 282 (M^+ + 2, 21), 281 (M^+ + 1, 4), 280 (M^+, 22), 174 (100), 159 (83), 144 (30), 115 (37).

4-(3-Bromo-*n*-propyl)-1,2-dihydro-5-methoxynaphthalene (12d): ^{1}H-NMR 1.80−2.36 (m, 4H, CH_2CH_2CH$_2$Br), 2.55−3.00 (m, 4H, 2 *endo* CH_2), 3.40 (t, 2H, *J* = 7 Hz, CH_2Br), 3.85 (s, 3H, CH_3), 6.02 (br t, 1H, vinyl CH), 6.70−7.37 (m, 3H, aromatic); GC/MS *m/z* 283 (M^+ + 3, 4), 282 (M^+ + 2, 22), 281 (M^+ + 1, 4), 280 (M^+, 21), 174 (43), 159 (100), 144 (21), 115 (30).

1-(3-Bromo-*n*-propyl)-6-methoxy-1,2,3,4-tetrahydronaphthalene (13b): ^{1}H-NMR (300 MHz) 1.56−2.03 (m, 8H, CH_2CH_2CHCH_2CH_2), 2.66−2.79 (m, 3H, benzyl CH_2, CH), 3.36−3.48 (m, 2H, CH_2Br), 3.76 (s, 3H, CH_3), 6.59−7.09 (m, 3H, aromatic); GC/MS *m/z* 285 (M^+ + 3, 1), 284 (M^+ + 2, 4), 283 (M^+ + 1, 1), 282 (M^+, 4), 162 (13), 161 (100), 115 (11).

1-(3-Bromo-*n*-propyl)-8-methoxy-1,2,3,4-tetrahydronaphthalene (13d): ^{1}H-NMR (300 MHz) 1.44−2.06 (m, 8H, CH_2CH_2CHCH_2CH_2), 2.70−2.80 (m, 2H, benzyl CH_2), 2.95−3.02 (m, 1H, CH), 3.37−3.56 (m, 2H, CH_2Br), 3.80 (s, 3H, CH_3), 6.62−7.09 (m, 3H, aromatic); GC/MS *m/z* 285 (M^+ + 3, 1), 284 (M^+ + 2, 8), 283 (M^+ + 1, 1), 282 (M^+, 8), 161 (100), 115 (9).

Preparation of Diethyl β-Keto Phosphonates 14a−c. General Procedure. A solution of a methoxy-1-tetralone, **7a−c** (4.93 g, 28.0 mmol), in anhydrous THF (20 mL) was added dropwise to a stirred mixture of LDA (1.5 M in *n*-hexane, 20.8 mL, 31.2 mmol) and anhydrous THF (5 mL) at −60 °C. After 45 min, the resulting mixture was treated with diethyl chlorophosphate (5.4 mL, 37.4 mmol) and then allowed to warm to 0 °C over the course of 50 min. After the mixture was cooled to −60 °C, LDA (1.5 M in *n*-hexane, 41.6 mL, 62.4 mmol) was added. The resulting solution was allowed to warm to room temperature and stirred at room temperature for 6 h. A solution of acetic acid in diethyl ether (1 M, 100 mL) was added slowly to the cooled reaction mixture; the resulting suspension was filtered through Celite, and the filtrate was concentrated under reduced pressure. The crude residue was chromatographed ($CHCl_3$/ethyl acetate, 3:2, as eluent) to give compounds **14a−c** as brown oils in 60−65% yield.

2-(Diethoxyphosphinyl)-5-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalene (14a): ^{1}H-NMR 1.10−1.47 (m, 6H, 2 CH$_2$CH_3), 2.13−3.50 (m, 5H, *endo*), 3.86 (s, 3H, OCH_3), 3.95−4.40 (m, 4H, 2 CH_2CH$_3$), 6.93−7.86 (m, 3H, aromatic); GC/MS *m/z* 313 (M^+ + 1, 6), 312 (M^+, 33), 175 (32), 174 (100), 115 (12).

2-(Diethoxyphosphinyl)-6-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalene (14b): ^{1}H-NMR 1.10−1.46 (m, 6H, 2 CH$_2$CH_3), 2.13−3.50 (m, 5H, *endo*), 3.83 (s, 3H, OCH_3), 3.95−4.40 (m, 4H, 2 CH_2CH$_3$), 6.60−8.15 (m, 3H, aromatic); GC/MS *m/z* 313 (M^+ + 1, 7), 312 (M^+, 43), 175 (42), 174 (100).

2-(Diethoxyphosphinyl)-7-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalene (14c): ^{1}H-NMR 1.10−1.50 (m, 6H, 2 CH_2CH_3), 2.16−3.50 (m, 5H, *endo*), 3.85 (s, 3H, OCH_3), 3.96−4.43 (m, 4H, 2 CH_2CH_3), 6.98−7.70 (m, 3H, aromatic); GC/MS *m/z* 313 ($M^+ + 1$, 6), 312 (M^+, 32), 175 (35), 174 (100).

Preparation of Spirocyclic Cyclopropyl Ketones 15a−c. General Procedure. A 100 mL screw-top Pyrex vial was charged with oil free NaH (0.40 g, 16.7 mmol) and anhydrous toluene (20 mL). A phosphonate, **14a**−**c** (4.40 g, 14.1 mmol), in anhydrous toluene (20 mL) was added dropwise under cooling. The reaction mixture was stirred at room temperature for 1 h and then cooled to −10 °C. Ethylene oxide (4.5 mL, 90 mmol) was then added. The vial was fitted with a Teflon screw cap, and the mixture was heated at 130 °C for 6 h. The reaction mixture was cooled, the reaction quenched with water, and the mixture extracted with diethyl ether (three times). The collected organic layers were dried over Na_2SO_4, and the solvent was removed *in vacuo*. The crude residue was eluted with $CHCl_3$ to furnish derivatives **15a**−**c** as colorless oils in 50−59% yield.

3,4-Dihydro-5-methoxy-1-oxonaphthalene-2(1*H*)-spirocyclopropane (15a): ^{1}H-NMR 0.73−0.94 (m, 2H) and 1.25−1.50 (m, 2H) (spirocyclic), 1.95 (br t, 2H, $ArCH_2CH_2$), 2.96 (br t, 2H, $ArCH_2CH_2$), 3.86 (s, 3H, CH_3), 6.94−7.83 (m, 3H, aromatic); GC/MS *m/z* 203 ($M^+ + 1$, 13), 202 (M^+, 100), 201 (60), 174 (23), 159 (25), 115 (35).

3,4-Dihydro-6-methoxy-1-oxonaphthalene-2(1*H*)-spirocyclopropane (15b): ^{1}H-NMR 0.65−0.96 (m, 2H) and 1.30−1.52 (m, 2H) (spirocyclic), 1.98 (br t, 2H, $ArCH_2CH_2$), 2.98 (br t, 2H, $ArCH_2CH_2$), 3.87 (s, 3H, CH_3), 6.70−8.17 (m, 3H, aromatic); GC/MS *m/z* 203 ($M^+ + 1$, 14), 202 (M^+, 100), 201 (85), 174 (23), 148 (34).

3,4-Dihydro-7-methoxy-1-oxonaphthalene-2(1*H*)-spirocyclopropane (15c): ^{1}H-NMR 0.65−0.96 (m, 2H) and 1.30−1.53 (m, 2H) (spirocyclic), 1.97 (br t, 2H, $ArCH_2CH_2$), 2.95 (br t, 2H, $ArCH_2CH_2$), 3.85 (s, 3H, CH_3), 6.95−7.83 (m, 3H, aromatic); GC/MS *m/z* 203 ($M^+ + 1$, 14), 202 (M^+, 100), 201 (57), 174 (26), 159 (25), 120 (37).

3-(2-Bromoethyl)-1,2-dihydromethoxynaphthalenes 16a−c. General Procedure. To a solution of **15a**−**c** (2.62 g, 13.0 mmol) in methanol (40 mL) at 0 °C was added $NaBH_4$ (1.17 g, 30.9 mmol) in several portions. After being stirred at room temperature overnight, the mixture was cooled to 0 °C, and water (25 mL) was carefully added. This was followed by HCl (1 M, 5 mL). The solution was concentrated *in vacuo*, and CH_2Cl_2 (30 mL) was added. After the resulting layers were separated, the aqueous phase was extracted twice with CH_2Cl_2, and the combined organic extracts were dried over Na_2SO_4. Concentration *in vacuo* afforded the crude intermediate which was used directly in the following step.

The crude residue was solubilized in acetic acid (9 mL) and stirred with 20% aqueous HBr (14 mL) for 22 h at room temperature. The mixture was cooled, diluted with water, and alkalized with K_2CO_3. The aqueous layer was extracted three times with CH_2Cl_2. The collected organic layers were dried over Na_2SO_4. Evaporation of the solvent *in vacuo* afforded a residual oil that was chromatographed (petroleum ether/CH_2Cl_2, 1:1, as eluent) to obtain the pure products **16a**−**c** as colorless oils (92−95% overall yield).

3-(2-Bromoethyl)-1,2-dihydro-8-methoxynaphthalene (16a): ^{1}H-NMR 2.20 (br t, 2H, CH_2CH_2Br), 2.56−3.05 (m, 4H, 2 *endo* CH_2), 3.50 (t, 2H, $J = 7$ Hz, CH_2Br), 3.80 (s, 3H, CH_3), 6.25 (br s, 1H, vinyl), 6.77−7.30 (m, 3H, aromatic); GC/MS *m/z* 269 ($M^+ + 3$, 5), 268 ($M^+ + 2$, 36), 267 ($M^+ + 1$, 5), 266 (M^+, 36), 173 (46), 159 (100), 128 (28), 115 (45).

3-(2-Bromoethyl)-1,2-dihydro-7-methoxynaphthalene (16b): ^{1}H-NMR 2.23 (br t, 2H, CH_2CH_2Br), 2.65−2.97 (m, 4H, 2 *endo* CH_2), 3.50 (t, 2H, $J = 7$ Hz, CH_2Br), 3.80 (s, 3H, CH_3), 6.25 (br s, 1H, vinyl), 6.57−7.20 (m, 3H, aromatic); GC/MS *m/z* 269 ($M^+ + 3$, 4), 268 ($M^+ + 2$, 30), 267 ($M^+ + 1$, 4), 266 (M^+, 30), 173 (100), 159 (21), 115 (29).

3-(2-Bromoethyl)-1,2-dihydro-6-methoxynaphthalene (16c): ^{1}H-NMR 2.22 (br t, 2H, CH_2CH_2Br), 2.70 (br t, 4H, 2 *endo* CH_2), 3.50 (t, 2H, $J = 7$ Hz, CH_2Br), 3.75 (s, 3H, CH_3), 6.25 (br s, 1H, vinyl), 6.50−7.17 (m, 3H, aromatic); GC/MS *m/z* 269 ($M^+ + 3$, 10), 268 ($M^+ + 2$, 71), 267 ($M^+ + 1$, 13), 266 (M^+, 75), 173 (67), 159 (100), 144 (30), 128 (34), 115 (46).

4-Substituted 1-Phenylpiperazine Derivatives 17−24. General Procedure. A stirred suspension of the appropriate alkyl halide (2.0 mmol), 1-phenylpiperazine (4.0 mmol), and potassium carbonate (2.0 mmol) in DMF (compounds **20**, **22**−**24**) or acetonitrile (compounds **17**−**19**, **21**) was refluxed overnight. After cooling, the mixture was evaporated to dryness, and water was added to the residue. The aqueous phase was extracted twice with CH_2Cl_2. The collected organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The crude residue was chromatographed, as indicated below, to yield pure compounds **17**−**24** as pale yellow oils.

4-[2-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-ethyl]-1-phenylpiperazine (17): eluted with CH_2Cl_2/ethyl acetate, 3:1, 52% yield; ^{1}H-NMR (300 MHz) 1.64−1.98 (m, 6H, $CH_2CH_2CHCH_2$), 2.47−2.80 [m, 8H, $CH_2N(CH_2)_2$, benzyl CH_2], 2.81−2.87 (m, 1H, CH), 3.21 [br t, 4H, $(CH_2)_2NAr$], 3.80 (s, 3H, CH_3), 6.63−7.28 (m, 8H, aromatic); GC/MS *m/z* 351 ($M^+ + 1$, 10), 350 (M^+, 40), 189 (19), 175 (100), 162 (29).

4-[3-(6-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl]-1-phenylpiperazine (18): eluted with CH_2Cl_2/ethyl acetate, 7:3, 75% yield; ^{1}H-NMR (300 MHz) 1.50−1.88 (m, 8H, $CH_2CH_2CHCH_2CH_2$), 2.38−2.42 [m, 2H, $CH_2N(CH_2)_2$], 2.52−2.72 [m, 7H, benzyl CH_2, CH, $CH_2N(CH_2)_2$], 3.20 [br t, 4H, $(CH_2)_2NAr$], 3.75 (s, 3H, CH_3), 6.57−7.28 (m, 8H, aromatic); GC/MS *m/z* 365 ($M^+ + 1$, 26), 364 (M^+, 94), 175 (100), 162 (46), 120 (25).

4-[3-(8-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl]-1-phenylpiperazine (19): eluted with CH_2Cl_2/ethyl acetate, 7:3, 91% yield; ^{1}H-NMR (300 MHz) 1.35−1.92 (m, 8H, $CH_2CH_2CHCH_2CH_2$), 2.32−2.81 [m, 8H, $CH_2N(CH_2)_2$, benzyl CH_2], 2.96−3.01 (m, 1H, CH), 3.21 [br t, 4H, $(CH_2)_2NAr$], 3.79 (s, 3H, CH_3), 6.63−7.29 (m, 8H, aromatic); GC/MS *m/z* 365 ($M^+ + 1$, 12), 364 (M^+, 44), 175 (100), 162 (17), 132 (16).

4-[1-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-1(*E*)-3-propylidene]-1-phenylpiperazine (20). The title compound was prepared starting from (*E*)-1-(3-chloro-*n*-propylidene)-5-methoxy-1,2,3,4-tetrahydronaphthalene[12] following the procedure described above. Column chromatography was performed with $CHCl_3$ as eluent (49% yield): ^{1}H-NMR (300 MHz) 1.18−1.87 (m, 2H, *endo* CH_2), 2.41−2.60 (m, 6H, $CH_2C{=}CHCH_2CH_2N$), 2.62−2.74 [m, 6H, benzyl CH_2, $CH_2N(CH_2)_2$], 3.23 [br s, 4H, $(CH_2)_2NAr$], 3.81 (s, 3H, CH_3), 6.00 (br t, 1H, vinyl CH), 6.68−7.29 (m, 8H, aromatic); GC/MS *m/z* 363 ($M^+ + 1$, 2), 362 (M^+, 8), 176 (13), 175 (100), 173 (14), 132 (18).

4-[4-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-butyl]-1-phenylpiperazine (21). The title compound was prepared and purified as for compound **20**, starting from 1-(4-chloro-*n*-butyl)-5-methoxy-1,2,3,4-tetrahydronaphthalene,[18] in 73% yield: ^{1}H-NMR (300 MHz) 1.35−1.83 [m, 10H, $CH_2CH_2CH(CH_2)_3$], 2.41 [t, 2H, $J = 7.6$ Hz, $CH_2N(CH_2)_2$], 2.50−2.79 [m, 7H, benzyl CH_2, CH, $CH_2N(CH_2)_2$], 3.21 [br t, 4H, $(CH_2)_2NAr$], 3.79 (s, 3H, CH_3), 6.62−7.28 (m, 8H, aromatic); GC/MS *m/z* 379 ($M^+ + 1$, 17), 378 (M^+, 63), 376 (13), 217 (15), 176 (13), 175 (100).

4-[2-(1,2-Dihydro-8-methoxy-3-naphthalenyl)ethyl]-1-phenylpiperazine (22): eluted with CH_2Cl_2/ethyl acetate, 1:1, 89% yield; ^{1}H-NMR (300 MHz) 2.25 [t, 2H, $J = 8.3$ Hz, $CH_2CH_2N(CH_2)_2$], 2.42−2.54 (m, 2H, *endo* CH_2), 2.60−2.69 [m, 6H, benzyl CH_2, $CH_2N(CH_2)_2$], 2.80 [t, 2H, $J = 8.3$ Hz, $CH_2N(CH_2)_2$], 3.23 [br t, 4H, $(CH_2)_2NAr$], 3.81 (s, 3H, CH_3), 6.22 (s, 1H, vinyl CH), 6.62−7.28 (m, 8H, aromatic); GC/MS *m/z* 349 ($M^+ + 1$, 2), 348 (M^+, 7), 175 (100), 173 (14), 132 (18).

4-[2-(1,2-Dihydro-7-methoxy-3-naphthalenyl)ethyl]-1-phenylpiperazine (23): eluted with CH_2Cl_2/ethyl acetate, 1:1, 80% yield; ^{1}H-NMR (300 MHz) 2.24 [t, 2H, $J = 8.0$ Hz, $CH_2CH_2N(CH_2)_2$], 2.42−2.48 (m, 2H, *endo* CH_2), 2.61−2.80 [m, 8H, benzyl CH_2, $CH_2N(CH_2)_2$], 3.26 [br t, 4H, $(CH_2)_2NAr$], 3.77 (s, 3H, CH_3), 6.20 (s, 1H, vinyl CH), 6.34−7.29 (m, 8H, aromatic); GC/MS *m/z* 349 ($M^+ + 1$, 2), 348 (M^+, 8), 175 (100), 173 (19), 132 (18).

4-[2-(1,2-Dihydro-6-methoxy-3-naphthalenyl)ethyl]-1-phenylpiperazine (24): eluted with CH_2Cl_2/ethyl acetate, 1:1, 87% yield; ^{1}H-NMR (300 MHz) 2.26 [t, 2H, J = 8.1 Hz, $CH_2CH_2N(CH_2)_2$], 2.51−2.60 (m, 2H, *endo* CH_2), 2.70−2.90 [m, 8H, benzyl CH_2, $CH_2N(CH_2)_2$], 3.37 [br t, 4H, $(CH_2)_2NAr$], 3.76 (s, 3H, CH_3), 6.23 (s, 1H, vinyl CH), 6.54−7.32 (m, 8H, aromatic); GC/MS m/z 349 (M^+ + 1, 1), 348 (M^+, 5), 176 (13), 175 (100), 132 (19).

4-[2-(Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)ethyl]-1-phenylpiperazines 25−27. General Procedure. A methanolic solution of compounds **22**−**26** (0.70 g, 2.0 mmol) was hydrogenated at normal pressure and room temperature in the presence of 5% palladium on charcoal (0.1 g), until the uptake ceased. The catalyst was removed by filtration through Celite and the solvent evaporated *in vacuo*. Compounds **25**−**27** were obtained as pale yellow semisolids (quantitative yield).

4-[2-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-ethyl]-1-phenylpiperazine (25): ^{1}H-NMR (300 MHz) 1.35−2.00 (m, 5H, CH_2CHCH_2), 2.40−2.89 [m, 10H, $CH_2N(CH_2)_2$, 2 benzyl CH_2], 3.22 [br t, 4H, $(CH_2)_2NAr$], 3.79 (s, 3H, CH_3), 6.62−7.28 (m, 8H, aromatic); GC/MS m/z 351 (M^+ + 1, 18), 350 (M^+, 72), 176 (13), 175 (100), 162 (15).

4-[2-(6-Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-ethyl]-1-phenylpiperazine (26): ^{1}H-NMR (300 MHz) 1.35−1.95 (m, 5H, CH_2CHCH_2), 2.31−2.84 [m, 10H, $CH_2N(CH_2)_2$, 2 benzyl CH_2], 3.21 [br t, 4H, $(CH_2)_2NAr$], 3.76 (s, 3H, CH_3), 6.60−7.29 (m, 8H, aromatic); GC/MS m/z 351 (M^+ + 1, 19), 350 (M^+, 75), 175 (100), 162 (21), 120 (16).

4-[2-(7-Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-ethyl]-1-phenylpiperazine (27): ^{1}H-NMR (300 MHz) 1.34−1.97 (m, 5H, CH_2CHCH_2), 2.43−2.87 [m, 10H, $CH_2N(CH_2)_2$, 2 benzyl CH_2], 3.21 [br t, 4H, $(CH_2)_2NAr$], 3.75 (s, 3H, CH_3), 6.59−7.29 (m, 8H, aromatic); GC/MS m/z 351 (M^+ + 1, 18), 350 (M^+, 78), 175 (100), 162 (15), 132 (13).

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 sand yellow crystals or crystalline powders.

Pharmacological Methods. All the procedures used to perform the binding assays have been recently reported.[1]

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