High Affinity and Selectivity on 5-HT$_{1A}$ Receptor of 1-Aryl-4-[(1-tetralin)alkyl]piperazines. 2

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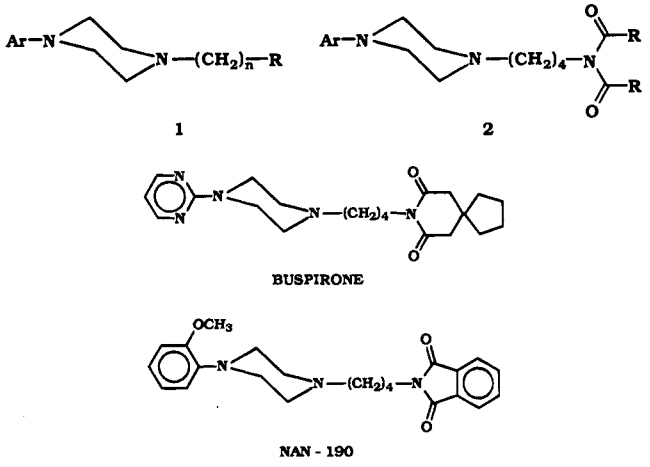
Several 4-alkyl-1-arylpiperazines that present a tetralin moiety on the terminal part of the side chain were synthesized in order to increase the selectivity on the 5-HT$_{1A}$ versus D-2, α_1, σ, and other 5-HT receptors. Many changes have been effected on previous structures of type **3** (1-aryl-4-[3-(1,2-dihydronaphthalen-4-yl)-*n*-propyl]piperazines). Several synthetic procedures were followed to obtain the final products, depending on the presence or absence of a double bond, as well as of a heteroatom on the side chain. In the first case versatile use of Grignard reaction was made, whereas in the second one usual synthetic ways were applied. Final compounds were evaluated for in vitro activity on dopamine D-1 and D-2, serotonin 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1C}$, and 5-HT$_2$, α_1 adrenergic, and σ receptors by radioreceptor binding assay. For the 2-MeO-Ph, 2-pyridyl, and unsubstituted phenyl *N*-piperazine derivatives, low IC$_{50}$ values (0.3 nM) on 5-HT$_{1A}$ receptors and high selectivity values were observed.

Among the classes of compounds that exhibit high affinity for the 5-HT$_{1A}$ subclass of serotonergic receptors, one of the most thoroughly studied is that of the arylpiperazines,[1-3] with structure **1**, including the azapirones **2**, where Ar is usually a pyrimidyl (Buspirone) or 2-methoxyphenyl (NAN-190) group. Investigations



in this field are aimed at finding new antianxiety and antidepressant agents[4,5] in which the serotonergic mechanism predominates. Several structural changes were made on the arylpiperazine compounds **1** because it was observed that, according to Hibert's model,[6,7] the inclusion of appropriate side chains on the basic nitrogen offered an additional site of interaction with the 5-HT$_{1A}$ receptor, resulting in greatly enhanced affinity for this site.

In a recent paper,[8] we described a new model of arylpiperazines, **3**, that presents a dihydronaphthalene nucleus on the terminal part of the side chain and exhibits high values of mixed 5-HT$_{1A}$/D-2 affinity. The lower IC$_{50}$ values toward 5-HT$_{1A}$ of some of the reported compounds[8] led us to explore their selectivity by examining their activity toward other receptors such as 5-HT$_{1B}$, 5-HT$_{1C}$, 5-HT$_2$, D-1, and D-2 receptors. We also investigated binding to α_1 adrenoreceptors because some level of undesired α_1 affinity is often present in arylpiperazine structures, due to the fact that α_1 adrenoreceptors and 5-HT$_{1A}$ receptors are representative members of the same G protein superfamily.[9,10]

In this way we attempted to systematically identify and eliminate those structural features that account for α_1 adrenergic binding. In fact, by modifying NAN-190, a compound with a high affinity for 5-HT$_{1A}$ receptors (K_i = 0.6 nM) that also, unfortunately, has a high affinity for α_1 adrenoreceptors (K_i = 0.8 nM), several other structures with less affinity for α_1 adrenoreceptors were derived; among these, the 1-noradamantane carboxamide derivative[11] **5** has a very high affinity for 5-HT$_{1A}$ sites (K_i = 0.1 nM) and a 460-fold selectivity over α_1 adrenergic receptors. Selectivity toward σ receptors was also investigated because 1-phenylpiperazines can structurally mimic the 2-(phenylamino)ethane moiety which is present in several σ receptor agents.[12]

In order to increase the selectivity for the 5-HT$_{1A}$ receptor, some variations on structures of type **3** were effected, thereby achieving structure **4**: (i) displacement of the double bond from the inside to the outside of the dihydronaphthalene group (**18, 19, 34**) (Table 1), (ii) reduction of the double bond (**22-24, 35, 36, 39, 40, 43, 44**), (iii) insertion of a heteroatom on the chain (**28-31**), (iv) lengthening of the intermediate chain (**20, 21, 26, 27**), and (v) replacement of the benzene ring of the dihydronaphthalene group with one of its cycloisosters (**25**).

Chemistry

Several synthetic procedures were followed to obtain the final products (Table 1), depending on the presence or absence of a double bond (Scheme 1), as well as of a heteroatom on the side chain (Scheme 2).

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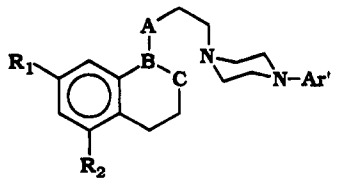
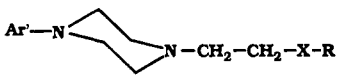
Table 1. Physical Properties



compd	R_1	R_2	A–B–C	Ar'	formula[a]	mp,°C	recryst solv
16[b]	OCH_3	H	CH_2–C=CH	2-OCH_3Ph			
17[b]	H	OCH_3	CH_2–C=CH	2-OCH_3Ph			
18	H	H	(*E*) CH=C–CH_2	2-OCH_3Ph	$C_{24}H_{30}N_2O\cdot 2HCl\cdot {}^2/_3H_2O$	198–199	MeOH/Et_2O
19	H	OCH_3	(*E*) CH=C–CH_2	2-OCH_3Ph	$C_{25}H_{32}N_2O_2\cdot 2HCl\cdot H_2O$	203–204	MeOH/Et_2O
20	OCH_3	H	$(CH_2)_2$–C=CH	2-OCH_3Ph	$C_{26}H_{34}N_2O_2\cdot 2HCl$	205	MeOH/Et_2O
21	H	OCH_3	$(CH_2)_2$–C=CH	2-OCH_3Ph	$C_{26}H_{34}N_2O_2\cdot 2HCl$	204–206	MeOH/Et_2O
22	H	H	CH_2–CH–CH_2	2-OCH_3Ph	$C_{24}H_{32}N_2O\cdot 2HCl$	223–224	$CHCl_3$/petroleum ether
23	OCH_3	H	CH_2–CH–CH_2	2-OCH_3Ph	$C_{25}H_{34}N_2O_2\cdot 2HCl$	208–210	$CHCl_3$/petroleum ether
24	H	OCH_3	CH_2–CH–CH_2	2-OCH_3Ph	$C_{25}H_{34}N_2O_2\cdot 2HCl$	206–207	MeOH/Et_2O
25[c]			CH_2–CH–CH_2	2-OCH_3Ph	$C_{22}H_{30}N_2OS\cdot 2HCl\cdot {}^1/_3H_2O$	224–225	MeOH/Et_2O
26	OCH_3	H	$(CH_2)_2$–CH–CH_2	2-OCH_3Ph	$C_{26}H_{36}N_2O_2\cdot 2HCl$	192–193	MeOH/Et_2O
27	H	OCH_3	$(CH_2)_2$–CH–CH_2	2-OCH_3Ph	$C_{26}H_{36}N_2O_2\cdot 2HCl$	194–196	MeOH/Et_2O
28	OCH_3	H	NH–CH–CH_2	2-OCH_3Ph	$C_{24}H_{33}N_3O_2\cdot 3HCl\cdot H_2O$	149–151	MeOH/Et_2O
29	H	OCH_3	NH–CH–CH_2	2-OCH_3Ph	$C_{24}H_{33}N_3O_2\cdot 3HCl\cdot H_2O$	223–224	MeOH/Et_2O
30	OCH_3	H	S–CH–CH_2	2-OCH_3Ph	$C_{24}H_{32}N_2O_2S\cdot 2HCl$	205–206	$CHCl_3$/petroleum ether
31	H	OCH_3	S–CH–CH_2	2-OCH_3Ph	$C_{24}H_{32}N_2O_2S\cdot 2HCl$	208–210	absolute EtOH
32[b]	OCH_3	H	CH_2–C=CH	2-Py			
33[b]	H	OCH_3	CH_2–C=CH	2-Py			
34	H	OCH_3	(*E*) CH=C–CH_2	2-Py	$C_{23}H_{29}N_3O\cdot 2HCl$	221–222	MeOH/Et_2O
35	OCH_3	H	CH_2–CH–CH_2	2-Py	$C_{23}H_{31}N_3O\cdot 3HCl$	143–145	$CHCl_3$/Et_2O
36	H	OCH_3	CH_2–CH–CH_2	2-Py	$C_{23}H_{31}N_3O\cdot 2HCl\cdot H_2O$	170–171	$CHCl_3$/Et_2O
37[b]	OCH_3	H	CH_2–C=CH	Ph			
38[b]	H	OCH_3	CH_2–C=CH	Ph			
39	OCH_3	H	CH_2–CH–CH_2	Ph	$C_{24}H_{32}N_2O\cdot 2HCl$	198–199	MeOH/Et_2O
40	H	OCH_3	CH_2–CH–CH_2	Ph	$C_{24}H_{32}N_2O\cdot 2HCl$	205–206	MeOH/Et_2O
41[b]	OCH_3	H	CH_2–C=CH	3-CF_3Ph			
42[b]	H	OCH_3	CH_2–C=CH	3-CF_3Ph			
43	OCH_3	H	CH_2–CH–CH_2	3-CF_3Ph	$C_{25}H_{31}F_3N_2O\cdot HCl$	192–193	MeOH/Et_2O
44	H	OCH_3	CH_2–CH–CH_2	3-CF_3Ph	$C_{25}H_{31}F_3N_2O\cdot {}^3/_2HCl$	185–186	MeOH/Et_2O

[a] Analyses for C,H,N. [b] Formerly published compounds.[8] [c] In this compound an unsubstituted [*b*]-fused thiophene ring replaces the benzene ring.



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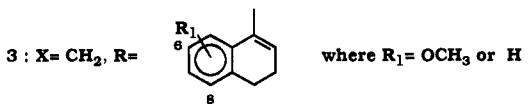

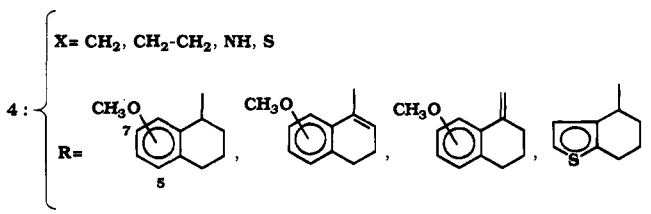

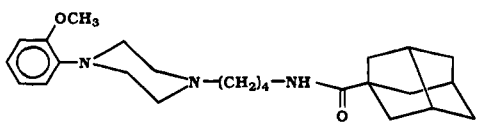

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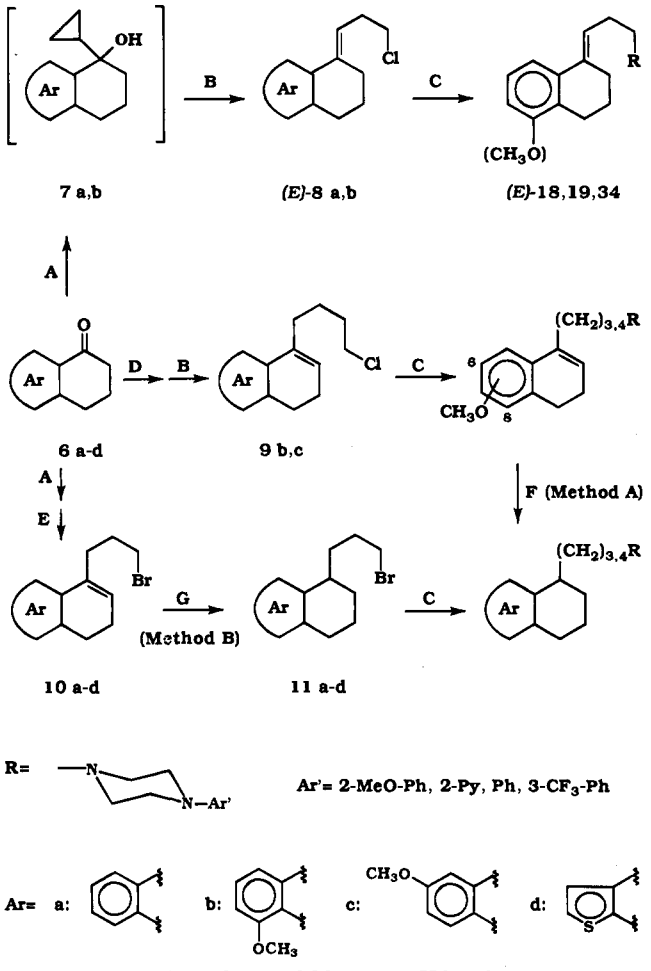
The exocyclically unsaturated compounds *E*-**18**, *E*-**19**, and *E*-**34** were prepared (Scheme 1) starting from the respective 1-tetralones **6a,b**, which were reacted with magnesium cyclopropyl bromide to give alcohols **7a,b**. These intermediates were quickly treated with HCl in acetic acid for a shorter time than previously reported[13] in order to obtain the kinetically favored 3-chloro-*n*-propylidene intermediates *E*-**8a,b** rather than the thermodynamically favored[14] isomers having an endocyclic double bond.[8] Although small amounts of other isomeric compounds were formed, only the *E*-exocyclic unsaturated product was isolated in good yield by column chromatography. However, treatment of **7a,b** with HBr gave mainly 4-(3-bromo-*n*-propyl)-1,2-dihydronaphthalenes.

On the other hand, products *E*-**8a,b** and related derivatives *E*-**18**, *E*-**19** and *E*-**34** can be converted into the corresponding endo unsaturated compounds by stirring in cold acetic acid overnight. Indeed, some differences in GC/MS and ^{1}H NMR spectra between *E*-**8a,b** and their endocyclically unsaturated isomers provided the evidence, confirmed by 300 MHz NMR decoupling experiments, that compounds *E*-**8a,b** and their *N*-arylpiperazine derivatives had the reported structures. Moreover COSY and NOESY experiments were carried out, in order to define the geometry of the double bond.[15]

Finally, neither geometrical isomerism nor the location of the double bond were affected by subsequent reaction[8] with the appropriate *N*-arylpiperazines in DMF to give final products *E*-**18**, *E*-**19**, and *E*-**34**.

Scheme 1[a]



[a] Reagents: (A) cyclopropyl-MgBr; (B) HCl; (C) *N*-arylpiperazines; (D) 4-chloro-*n*-butyl-MgBr; (E) HBr; (F) H_2, Pd/C (10%); (G) H_2, Pd/C (5%).

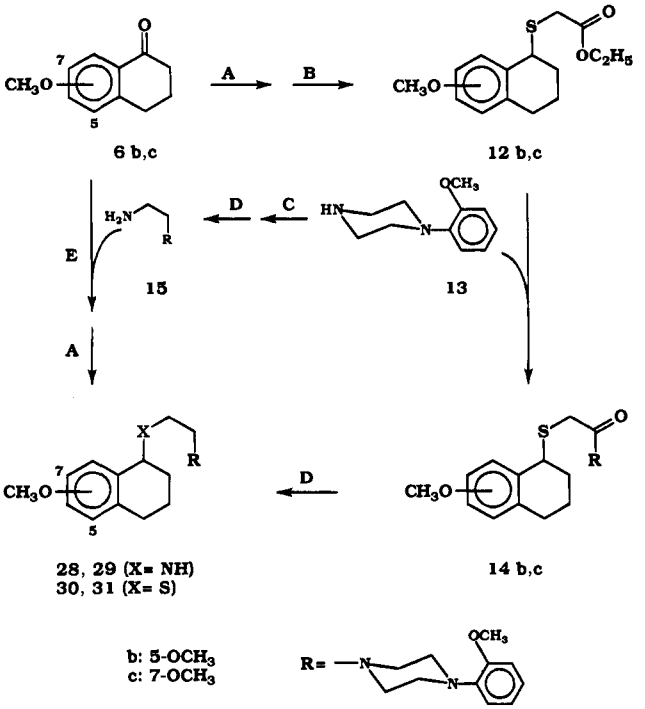
Indeed, additional NOESY experiments on the compound *E*-**34** gave the same results as did *E*-**8b**.

A Grignard reaction was also employed to prepare intermediates **9b,c** from **6b,c** with 1-bromo-4-chloro-*n*-butane and subsequent dehydration. *N*-Arylpiperazines were then reacted as above with chloroderivatives **9b,c** to give products **20** and **21**.

The latter were then reduced to tetralin derivatives **26** and **27**, respectively, by catalytic hydrogenation (method A). Compounds **23, 24, 40,** and **43** were also prepared by method A, starting from formerly reported[8] unsaturated products **16, 17, 38,** and **41,** respectively. An alternative route (method B) originates from the ketones **6a–d**, which were alkylated in the usual manner[8] to yield endocyclically unsaturated bromo derivatives **10a–d**, which were hydrogenated on 5% Pd/C to the compounds **11a–d** in the same way reported under method A. Subsequent derivatization with the appropriate *N*-arylpiperazines led to the final compounds **22, 25, 35, 36, 39,** and **44**. Method B was preferable for preparing those compounds with an arylpiperazine moiety in which the aromatic ring might undergo unwanted hydrogenation; however this method also proved useful in those cases where the requisite intermediates for the method A pathway were not readily available.

Compounds **28** and **29** (Scheme 2) were prepared starting from 1-tetralones **6b,c**. As previously reported,[16] 1-(2-methoxyphenyl)piperazine (**13**) was alkylated with bromoacetonitrile and subsequently reduced with $LiAlH_4$ to amine **15**. The latter was then condensed with the appropriate methoxy-1-tetralone **6b,c** to give intermediate imines, which were reduced[13] to amines **28** and **29** by $NaBH_4$. Compounds **12b,c** were also prepared from **6b,c** as previously described[17] and converted by reaction with 1-(2-methoxyphenyl)piperazine to yield amides **14b,c**. An alternative preparation of **14b,c**, which afforded lower yields, involved hydrolysis of the esters to the corresponding carboxylic acids, conversion of the latter to the acid chlorides by treatment with thionyl chloride, and reaction of the crude acyl chlorides with 1-(2-methoxyphenyl)piperazine. Finally amides **14b,c** were reduced by $LiAlH_4$ to amines **30** and **31**.

Scheme 2[a]



[a] Reagents: (A) $NaBH_4$; (B) ethyl 2-mercaptoacetate, ZnI_2; (C) bromoacetonitrile; (D) $LiAlH_4$; (E) *p*-toluenesulfonic acid.

Pharmacology

Final compounds (Table 2) were evaluated for in vitro activity on dopamine D-1 and D-2, serotonin 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, and 5-HT_2, α_1 adrenergic, and σ receptors by radioreceptor binding assay. All the compounds were used in the form of hydrochloride salts and were water-soluble. The following specific ligands and tissue sources were used (a) dopamine D-1 receptors—[^{3}H]-SCH-23390, rat corpora striata synaptic membranes; (b) dopamine D-2 receptors—[^{3}H]spiroperidol, in the presence of ketanserin as 5-HT_2 blocker, rat corpora striata synaptic membranes; (c) serotonin 5-HT_{1A} receptors—[^{3}H]-8-OH-DPAT, rat brain cortex membranes; (d) serotonin 5-HT_{1B} receptors—[^{3}H]-5-HT, in the presence of 8-OH-DPAT as 5-HT_{1A} blocker, rat corpora striata synaptic membranes; (e) serotonin 5-HT_{1C} receptors—[^{3}H]-5-HT, in the presence of 8-OH-DPAT and RU-24960 as 5-HT_{1A} and 5-HT_{1B} blockers, respectively, rat cerebral cortex membranes; (f) serotonin 5-HT_2 receptors—[^{3}H]-ketanserin, rat brain cortex membranes; (g) α_1 adren-

Table 2. Binding Affinities and Selectivities

	IC_{50}, nM					selectivity, 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	σ [^{3}H]DTG	D-2/5-HT_{1A}	α_1/5-HT_{1A}	σ/5-HT_{1A}
16	2.0 ± 0.67[a]	391 ± 7[a]	90.6 ± 18.1[a]	24.5 ± 2.0	228 ± 16	45	12	114
17	8.8 ± 0.84[a]	770 ± 18[a]	17.4 ± 1.0[a]	32.3 ± 2.9	33.0 ± 3.7	2.0	3.7	3.8
18	1.84 ± 0.18	147 ± 10	12.7 ± 0.8	3.6 ± 0.2	55 ± 8	6.9	2.0	30
19	0.52 ± 0.07	667 ± 13	11.3 ± 0.8	6.0 ± 0.4	52.2 ± 4.8	22	12	100
20	1.53 ± 0.12	209 ± 28	10.6 ± 2.1	15.3 ± 1.0	53.5 ± 5.2	6.9	10	35
21	13.0 ± 1.7	NT[b]	5920 ± 140	96.2 ± 5.9	NT	455	7.4	
22	0.39 ± 0.11	155 ± 13	24.7 ± 1.3	0.14 ± 0.01	NT	63	0.36	
23	1.50 ± 0.21	220 ± 15	51.5 ± 6.5	43.2 ± 3.2	64.1 ± 3.4	34	29	43
24	0.32 ± 0.22	358 ± 21	20.0 ± 1.9	1.94 ± 0.05	59.9 ± 1.7	63	6.1	187
25	1.13 ± 0.08	147 ± 12	24.1 ± 1.8	1.26 ± 0.78	9.7 ± 0.8	21	1.1	8.6
26	8.83 ± 0.97	329 ± 18	50.9 ± 7.2	78.5 ± 8.5	92.8 ± 8.7	5.8	8.9	11
27	1.73 ± 0.22	NT	15.4 ± 0.8	78.3 ± 5.5	NT	8.9	45	
28	40.3 ± 3.3	NT	1200 ± 50	1960 ± 90	NT	30	49	
29	7.01 ± 0.42	3340 ± 40	618 ± 26	149 ± 7	151 ± 12	88	21	22
30	5.94 ± 0.47	111 ± 8	50.2 ± 3.6	116 ± 9	138 ± 12	8.5	20	20
31	1.08 ± 0.08	NT	7.83 ± 0.34	120 ± 7	NT	7.3	111	
32	63.6 ± 0.9[a]	146 ± 28[a]	778 ± 33[a]	152 ± 8	246 ± 15	12	2.4	3.9
33	1.4 ± 0.21[a]	205 ± 10[a]	119 ± 9[a]	123 ± 11	52.0 ± 3.9	85	88	37
34	0.35 ± 0.09	417 ± 22	150 ± 9	72.2 ± 5.3	99.1 ± 8.2	429	206	283
35	3.38 ± 0.12	288 ± 15	328 ± 23	261 ± 20	125 ± 17	97	77	37
36	0.58 ± 0.09	331 ± 15	177 ± 11	31.4 ± 2.8	67.5 ± 5.3	305	54	116
37	147 ± 14[a]	119 ± 5[a]	777 ± 25[a]	157 ± 13	173 ± 10	5.3	1.1	1.2
38	18.3 ± 5.3[a]	204 ± 8[a]	303 ± 39[a]	49.0 ± 3.7	54.4 ± 5.0	17	2.7	3.0
39	9.24 ± 0.59	NT	28 ± 2	184 ± 15	NT	3.0	20	
40	0.36 ± 0.15	170 ± 11	96.7 ± 8.4	78.8 ± 6.3	198 ± 12	269	219	600
41	138 ± 8[a]	1170 ± 43[a]	1290 ± 350[a]	3070 ± 150	NT	9.4	22	
42	55.9 ± 6.1[a]	2370 ± 150[a]	644 ± 56[a]	278 ± 29	NT	12	5.0	
43	88.4 ± 6.3	391 ± 10	1330 ± 70	2930 ± 80	87.5 ± 6.3	15	33	0.99
44	146 ± 12	NT	472 ± 28	7170 ± 220	NT	3.2	49	
buspirone	12.8 ± 1.7	$>10^4$	226 ± 6	4160 ± 320	263 ± 22			
8-OH-DPAT	1.10 ± 0.10							
ketanserin		1.20 ± 0.15						
butaclamol			0.50 ± 0.05					
prazosin				0.44 ± 0.06				
haloperidol					5.64 ± 0.56			

[a] Formerly published data;[8] here reported for comparison. [b] Not tested.

ergic receptors—[^{3}H]prazosin, rat cerebral cortex; and (h) σ receptors—[^{3}H]DTG, guinea pig whole brain without cerebellum. SCH-23390, butaclamol, 8-OH-DPAT, 5-HT, ketanserin, prazosin, and haloperidol were used as reference compounds.

Concentrations required to inhibit 50% of radioligand specific binding (IC_{50}) were determined through two to four independent experiments with samples in triplicate using seven to nine different concentrations of the drug studied. The specific binding was defined as described in the Experimental Section under Pharmacological Methods; in all binding assays, it represented more than 75% of total binding, except for 5-HT_{1B} and 5-HT_{1C} receptors (>60%). The results were analyzed by using the program EBDA to determine IC_{50} values.

Results and Discussion

As regards affinity for 5-HT_{1A} receptors, if we consider all compounds to belong to four groups, divided according to the nature of Ar in structures **3** and **4** (2-MeO-Ph, 2-pyridyl, unsubstituted phenyl, and 3-CF_3-Ph derivatives), the results indicate (Table 2) that in all these groups except the last the reduction of the double bond in positions 3 and 4 of dihydronaphthalene led to an increase in affinity (**22**–**24**), reaching rather low IC_{50} values (0.3 nM), such as in **24**. Apart from the 3-CF_3-phenyl derivatives, the data for the remaining compounds demonstrated that 5-HT_{1A} receptor affinity is optimized in those compounds with the methoxy group in position 5 of the tetralin ring (R_1 = H, R_2 = OCH_3), the highest affinity compounds (IC_{50}s < 1 nM) being **24**, **36**, and **40**.

The position of the double bond also led to remarkable changes in affinity values: the two exo unsaturated derivatives **19** and **34**, again having the methoxy group on the tetralin on the opposite side of the chain, had IC_{50} values of 0.52 and 0.35 nM, respectively, remarkably lower than the corresponding endo unsaturated compounds **17** and **33**, respectively. Other changes were accomplished only in the 2-MeO-Ph derivatives.

The lengthening of the intermediate chain from three to four carbon atoms in unsaturated derivatives **20** and **21**, as well as in saturated derivatives **26** and **27**, led to no significant changes compared to compounds **16**, **17**, **23**, and **24**, respectively, nor did the insertion into the side chain of heteroatoms such as N (**28**, **29**) and S (**30**, **31**). A further variation was the replacement of the benzene ring of the dihydronaphthalene group with one of its cycloisosters, thiophene, and compound **25** also showed good affinity for 5-HT_{1A}.

As regards the affinity for other serotonergic receptors assayed, all the compounds exhibited low affinity, with IC_{50} values in the range of 10^{-6}–10^{-5} nM for 5-HT_{1B} and 5-HT_{1C} receptors and above 10^{-7} nM for the 5-HT_2 receptor (Table 2). For these receptors there was no relationship between the values of IC_{50} and the various changes effected. Selectivity toward the 5-HT_{1A} receptor among serotonin receptor subtypes was, therefore, evident.

As far as the dopaminergic system was concerned, the affinity toward D-1 receptors consistently showed IC_{50} values of above 10^{-6} nM, whereas the affinity toward D-2 receptors was, in some cases, quite considerable (Table 2). Thus, compounds with mixed 5-HT_{1A}/D-2 binding, such as the 2-MeO-Ph derivatives **17–20, 22–27, 30, 31,** and **39**, showed affinity for the D-2 receptor that was near to only 1 order of magnitude lower than the affinity toward the 5-HT_{1A} receptor. However, compounds **34, 36,** and **40,** which were among the most potent 5-HT_{1A} ligands, had D-2/5-HT_{1A} selectivity ratios of 300–400. Thus, the highest D-2/5-HT_{1A} selectivity values occurred with pyridyl or phenyl derivatives bearing the tetralin residue either on the saturated or on the ω-unsaturated alkyl chain.

Compounds **34** and **40** also proved to be the most selective members of the series with regard to their binding to 5-HT_{1A} vs α_1 adrenergic and σ receptors. The α_1/5-HT_{1A} selectivity ratio for both compounds was about 200, and the σ/5-HT_{1A} ratios were about 300 and 600 for **34** and **40,** respectively.

We can, therefore, conclude that certain changes to previously studied structures[8] have led to enormous advantages, especially in the phenyl and pyridyl series; in particular the shifting of the double bond out of the tetralin moiety or its reduction in derivatives where the methoxy group is on the opposite side of the alkyl chain provided compounds **34** and **40**, with high affinity to 5-HT_{1A} as well as with high values of selectivity toward D-2, α_1, and σ receptors.

Experimental Section

Chemistry. Column chromatographies were performed with 1:30 Merck silica gel 40 (0.063–0.200 mm) as the stationary phase. Melting points were determined in open capillaries on a Gallenkamp electrothermal apparatus and are uncorrected. 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 XL-200 (when indicated) or on a Bruker AM 300 WB instrument. The latter was also used for decoupling spectra and carrying out COSY and NOESY experiments. Chemical shifts are reported in parts per million (ppm, δ). Recording of mass spectra was done on an HP 5995C gas chromatograph/mass spectrometer, electron impact 70 eV, equipped with an HP 59970A workstation. All compounds had NMR and mass spectra that were fully consistent with their structure.

1-(3-Chloro-*n*-propylidene)-1,2,3,4-tetrahydronaphthalene (*E*-8a). Title compound was prepared from α-tetralone (**6a**) (0.73 g, 5 mmol) and cyclopropyl bromide (1.21 g, 10 mmol) by a Grignard reaction as we reported.[13] The crude intermediate 1-cyclopropyl-1-tetralol (**7a**) was immediately stirred with 15% HCl in acetic acid (15 mL) for 1 h at room temperature. Then the mixture was weakly alkalized with NaOH and extracted with $CHCl_3$. The dried organic layer was evaporated to dryness, affording a residue which was purified by column chromatography (petroleum ether/THF, 9:1, as eluent). Pure **8a** (0.44 g, 43% overall yield) was a colorless oil: ^{1}H NMR ($CDCl_3$) 1.82 (m, 2H, endo CH_2), 2.50 (br t, 2H, endo allyl CH_2), 2.67 (q, 2H, J = 7.1 Hz, exo allyl CH_2), 2.76 (t, 2H, J = 6.2 Hz, benzyl CH_2), 3.59 (t, 2H, J = 7.1 Hz, CH_2Cl), 5.98 (tt, 1H, J = 7.2 and 1.8 Hz, vinyl CH), 7.04–7.16 (mm, 3H, aromatic), 7.51–7.59 (m, 1H, aromatic C_8H); GC/MS *m/z* 209 (M^+ + 3, 1), 208 (M^+ + 2, 9), 207 (M^+ + 1, 4), 206 (M^+, 28), 157 (100), 141 (22), 129 (78), 128 (36), 115 (43).

1-(3-Chloro-*n*-propylidene)-5-methoxy-1,2,3,4-tetrahydronaphthalene (*E*-8b). From **6b** (1.06 g, 6 mmol) and cyclopropyl bromide (1.45 g, 12 mmol) was prepared **8b** via **7b**, and **8b** was purified as above (petroleum ether/THF, 4:1, as eluent): colorless oil, 48% overall yield; ^{1}H NMR ($CDCl_3$) 1.82 (m, 2H), 2.44 (br t, 2H, endo allyl CH_2), 2.63–2.74 (mm, 4H, exo allyl CH_2, benzyl CH_2), 3.58 (t, 2H, J = 7.1 Hz), 3.80 (s, 3H, CH_3), 5.97 (tt, 1H, J = 7.2 and 1.4 Hz), 6.68–7.21 (mm, 3H, aromatic); GC/MS *m/z* 239 (M^+ + 3, 2), 238 (M^+ + 2, 13), 237 (M^+ + 1, 6), 236 (M^+, 41), 201 (36), 187 (100), 159 (37), 128 (23), 115 (32).

4-(4-Chloro-*n*-butyl)-8-methoxy-1,2-dihydronaphthalene (9b). To a solution of (4-chloro-*n*-butyl)magnesium bromide, prepared from 1-bromo-4-chlorobutane (3.00 g, 18 mmol) and Mg turnings (0.43 g, 18 mmol) in anhydrous THF (20 mL), was added dropwise 5-methoxy-1-tetralone (**6b**) (2.1 g, 12 mmol) in the same solvent (20 mL). After being refluxed for 3 h, the mixture was cooled, treated with a few milliliters of aqueous NH_4Cl saturated solution, and extracted with Et_2O. The organic layer was washed with water, dried (Na_2SO_4), and evaporated to dryness. The residue containing the crude intermediates was solubilized in acetic acid (20 mL) and stirred with 15% aqueous HCl (15 mL) for 4 h at room temperature. Then the mixture was neutralized (Na_2CO_3) and extracted with $CHCl_3$. The separated organic layer was dried (Na_2SO_4), and concentrated under reduced pressure to give a brown-reddish oil, which was chromatographed on a silica gel column (petroleum ether/CH_2Cl_2, 9:1, as eluent); **9b** was obtained as a colorless oil in 75% overall yield: ^{1}H NMR (200 MHz, $CDCl_3$) 1.46–2.02 (mm, 4H, $CH_2CH_2CH_2Cl$), 2.04–2.60 (mm, 4H, 2 allyl CH_2), 2.74 (br t, 2H, benzyl CH_2), 3.53 (t, 2H, J = 7 Hz, CH_2Cl), 4.84 (s, 3H, CH_3), 5.87 (br t, 1H, vinyl CH), 6.72–7.32 (mm, 3H, aromatic); GC/MS *m/z* 253 (M^+ + 3, 2), 252 (M^+ + 2, 10), 251 (M^+ + 1, 5), 250 (M^+, 32), 174 (50), 173 (25), 159 (100), 144 (27), 115 (24).

4-(4-Chloro-*n*-butyl)-6-methoxy-1,2-dihydronaphthalene (9c). As above reported, **9c** was prepared from Grignard reagent and 7-methoxy-1-tetralone (**6c**) in the same amounts: eluted with $CHCl_3$, colorless oil, 68% overall yield; ^{1}H NMR (200 MHz, $CDCl_3$) 1.50–2.04 (mm, 4H, $CH_2CH_2CH_2Cl$), 2.06–2.85 (mm, 6H, allyl and benzyl CH_2), 3.54 (t, 2H, J = 7 Hz, CH_2Cl), 4.83 (s, 3H, CH_3), 5.90 (br t, 1H, vinyl CH), 6.62–7.20 (mm, 3H, aromatic); GC/MS *m/z* 253 (M^+ + 3, 2), 252 (M^+ + 2, 13), 251 (M^+ + 1, 7), 250 (M^+, 41), 174 (65), 173 (34), 159 (100), 144 (32), 128 (25), 115 (31).

1-(3-Bromo-*n*-propyl)-1,2,3,4-tetrahydronaphthalenes 11a–c. 4-(3-Bromo-*n*-propyl)-1,2-dihydronaphthalenes **10a–c** (10 mmol) were solubilized in EtOH (100 mL) and hydrogenated in the presence of 5% palladium on activated carbon (200 mg), at normal pressure and room temperature until theoretical uptake was accomplished. The reaction mixture was filtered through Celite and evaporate to dryness to obtain **11a–c** as a nearly colorless oil (yields > 90%). For analytical purposes samples were purified on a silica gel column (petroleum ether as eluent for **11a** and petroleum ether/CH_2Cl_2, 9:1, for **11b,c**).

1-(3-Bromo-*n*-propyl)-1,2,3,4-tetrahydronaphthalene (11a): ^{1}H NMR ($CDCl_3$) 1.60–2.02 (mm, 8H, $CH_2CH_2CHCH_2CH_2$), 2.70–2.85 (mm, 3H, benzyl CH_2 and CH), 3.35–3.49 (mm, 2H, CH_2Br), 7.01–7.21 (mm, 4H, aromatic); GC/MS *m/z* 255 (M^+ + 3, 0.7), 254 (M^+ + 2, 5), 253 (M^+ + 1, 1), 252 (M^+, 5), 131 (100).

1-(3-Bromo-*n*-propyl)-5-methoxy-1,2,3,4-tetrahydronaphthalene (11b): ^{1}H NMR ($CDCl_3$) 1.60–2.06 (mm, 8H), 2.51–2.85 (mm, 3H), 3.36–3.50 (mm, 2H), 3.80 (s, 3H, CH_3), 6.66 and 6.79 (2d, 2H), 7.10 (t, 1H, J = 8 Hz); GC/MS *m/z* 285 (M^+ + 3, 0.8), 284 (M^+ + 2, 6), 283 (M^+ + 1, 1), 282 (M^+, 6), 161 (100).

1-(3-Bromo-*n*-propyl)-7-methoxy-1,2,3,4-tetrahydronaphthalene (11c): ^{1}H NMR ($CDCl_3$) 1.57–2.01 (mm, 8H), 2.68 (br t, 2H), 2.77 (m, 1H), 3.33–3.54 (mm, 2H), 3.77 (s, 3H, CH_3), 6.64–7.00 (mm, 3H); GC/MS *m/z* 285 (M^+ + 3, 1), 284 (M^+ + 2, 8), 283 (M^+ + 1, 2), 282 (M^+, 9), 161 (100).

4-(3-Bromo-*n*-propyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene (11d). From usual alkylation of 4-keto-4,5,6,7-tetrahydrothianaphthene (**6d**) (2.0 g, 13.1 mmol) with cyclopropyl bromide (1.26 mL, 15.8 mmol) and subsequent column chromatography on silica gel (petroleum ether/$CHCl_3$, 9:1, as eluent, 61% yield) was yielded a mixture of **10d** [GC/MS *m/z* 258 (M^+ + 2, 25), 256 (M^+, 24), 135 (100)] and its exocyclically unsaturated isomers [GC/MS *m/z* 258 (M^+ + 2, 38), 256 (M^+,

38), 163 (100); GC/MS *m/z* 258 ($M^+ + 2$, 27), 256 (M^+, 26), 163 (100)]. The mixture (2.05 g, total 8.0 mmol) was hydrogenated as reported for preparing **11a–c**. An analytical sample of **11d** was obtained eluting from a silica gel column with *n*-hexane: ^{1}H NMR ($CDCl_3$) 1.43–2.02 (mm, 8H), 2.50–2.80 (br t, 3H), 3.36–3.49 (mm, 2H), 6.85 and 7.04 (2d, 2H, J = 5.3 Hz, aromatic); GC/MS *m/z* 260 ($M^+ + 2$, 6), 259 ($M^+ + 1$, 1), 258 (M^+, 6), 137 (100).

2-[(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)thio]-*N*-[*N'*-(2-methoxyphenyl)piperazinyl]acetamide (14b). A mixture of ethyl 2-[(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)thio]acetate (**12b**) (0.84 g, 3.0 mmol) and 1-(2-methoxyphenyl)piperazine (**13**) (1 mL, d = 1.095) was heated in a closed glass tube at 150 °C for 6 h. After cooling it was diluted with CH_2Cl_2 and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (CH_2Cl_2/ethyl acetate, 4:1, as eluent) to give **14b** (0.72 g, 56% yield) as a brown-yellow oil: ^{1}H NMR ($CDCl_3$) 1.77–2.19 (mm, 4H, endo CH_2CH_2), 2.40–2.84 (mm, 2H, benzyl CH_2), 2.98–3.18 (mm, 4H, $(CH_2)_2NAr$), 3.41 (dd, 2H, ν_A = 3.39, ν_B = 3.43, J_{A-B} = 13.5 Hz, SCH_2CO), 3.59–3.96 (mm + 2s, 10H, $CON(CH_2)_2$, 2 CH_3), 4.29 (t, 1H, J = 3.4 Hz, CHS), 6.64–7.12 (mm, 7H, aromatic); GC/MS *m/z* 428 ($M^+ + 2$, 4), 427 ($M^+ + 1$, 13), 426 (M^+, 43), 234 (100), 190 (26), 162 (32), 161 (37), 160 (26), 150 (22), 149 (96), 136 (50).

2-[(7-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)thio]-*N*-[*N'*-(2-methoxyphenyl)piperazinyl]acetamide (14c). Similarly as above, title compound was prepared from **12c** (0.70 g, 2.5 mmol) and **13** (1 mL). The crude product was chromatographed with $CHCl_3$/MeOH, 95:5, as eluent; pure **14c** (0.62 g, 58% yield) was a brown-yellow oil: ^{1}H NMR ($CDCl_3$) 1.71–2.19 (mm, 4H, endo CH_2CH_2), 2.58–2.80 (mm, 2H, benzyl CH_2), 2.96–3.17 (mm, 4H, $(CH_2)_2NAr$), 3.41 (dd, 2H, ν_A = 3.39, ν_B = 3.42, J_{A-B} = 13.7 Hz, SCH_2CO), 3.59–3.96 (mm + 2s, 10H, $CON(CH_2)_2$, 2 CH_3), 4.26 (t, 1H, J = 3.7 Hz, CHS), 6.67–7.08 (mm, 7H, aromatic); GC/MS *m/z* 428 ($M^+ + 2$, 3), 427 ($M^+ + 1$, 9), 426 (M^+, 33), 234 (87), 190 (26), 162 (31), 161 (38), 160 (41), 150 (23), 149 (100), 136 (41).

The following compounds **18–21** and **34** were prepared and purified according to the reaction below reported as method B, where instead of bromo derivatives **11a–d**, chloroderivatives *E*-**8a,b** and **9b,c** were reacted.

1-(2-Methoxyphenyl)-4-[1-(1,2,3,4-tetrahydronaphthalen-1-yl)-(1*E*)-propyliden-3-yl]piperazine (*E*-18): eluted with $CHCl_3$, 71% yield; ^{1}H NMR ($CDCl_3$) 1.82 (m, 2H, endo CH_2), 2.39–2.60 (mm, 6H, $CH_2C{=}CHCH_2CH_2N$), 2.65–2.80 (mm, 6H, benzyl CH_2, $CH_2N(CH_2)_2$), 3.12 (br s, 4H, $(CH_2)_2NAr$), 3.85 (s, 3H, CH_3), 6.00 (tt, 1H, J = 6.9 and 1.7 Hz, vinyl CH), 6.83–7.17 (mm, 7H, aromatic), 7.53–7.60 (m, 1H, aromatic C_8H); GC/MS *m/z* 363 ($M^+ + 1$, 1), 362 (M^+, 6), 205 (100), 190 (22).

1-(2-Methoxyphenyl)-4-[1-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-(1*E*)-propyliden-3-yl]piperazine (*E*-19): eluted with $CHCl_3$/MeOH, 95:5, 60% yield; ^{1}H NMR ($CDCl_3$) 1.80 (m, 2H, endo CH_2), 2.38–2.59 (mm, 6H, $CH_2C{=}CHCH_2CH_2N$), 2.63–2.80 (mm, 6H, benzyl CH_2, $CH_2N(CH_2)_2$), 3.11 (br s, 4H, $(CH_2)_2NAr$), 3.80 and 3.85 (2s, 6H, 2 CH_3), 5.99 (br t, 1H, vinyl CH), 6.65–7.22 (mm, 7H, aromatic); GC/MS *m/z* 393 ($M^+ + 1$, 2), 392 (M^+, 7), 205 (100).

1-(2-Methoxyphenyl)-4-[4-(6-methoxy-1,2-dihydronaphthalen-4-yl)-*n*-butyl]piperazine (20): eluted with $CHCl_3$/Et_2O/MeOH, 5:4:1, 56% yield; ^{1}H NMR (200 MHz, $CDCl_3$) 1.50–1.73 (mm, 4H, $CH_2CH_2CH_2CH_2N$), 2.14–2.19 (mm, 2H, endo CH_2), 2.38–2.54 (mm, 4H, $CH_2CH_2CH_2CH_2N$), 2.61–2.80 (mm, 6H, benzyl CH_2, $CH_2N(CH_2)_2$), 3.12 (br t, 4H, $(CH_2)_2NAr$), 3.79 and 3.86 (2s, 6H, 2 CH_3), 5.87 (t, 1H, J = 4.5 Hz, vinyl CH), 6.64–7.09 (mm, 7H, aromatic); GC/MS *m/z* 408 ($M^+ + 2$, 5), 407 ($M^+ + 1$, 29), 406 (M^+, 100), 205 (23).

1-(2-Methoxyphenyl)-4-[4-(8-methoxy-1,2-dihydronaphthalen-4-yl)-*n*-butyl]piperazine (21): eluted with CH_2Cl_2/MeOH, 95:5, 73% yield; ^{1}H NMR ($CDCl_3$) 1.47–1.65 (mm, 4H), 2.14–2.24 (mm, 2H), 2.38–2.49 (mm, 4H), 2.59–2.77 (mm, 6H), 3.09 (br s, 4H), 3.81 (s, 3H), 3.84 (s, 3H), 5.85 (t, 1H, J = 4.5 Hz), 6.74–7.18 (mm, 7H); GC/MS *m/z* 408 ($M^+ + 2$, 5), 407 ($M^+ + 1$, 31), 406 (M^+, 100).

4-[1-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-(*E*)-propyliden-3-yl]-1-(2-pyridyl)piperazine (*E*-34): eluted with $CHCl_3$/ethyl acetate, 3:2, 61% yield; ^{1}H NMR ($CDCl_3$) 1.83 (m, 2H, endo CH_2), 2.39–2.57 (mm, 6H, $CH_2C{=}CHCH_2CH_2N$), 2.60 (br t, 4H, $CH_2N(CH_2)_2$), 2.70 (t, 2H, J = 6.4 Hz, benzyl CH_2), 3.55 (t, 4H, J = 5.1 Hz, $(CH_2)_2NAr$), 3.80 (s, 3H, CH_3), 5.99 (br t, 1H, vinyl CH), 6.57–7.51 (mm, 6H, aromatic), 8.15–8.22 (m, 1H, aromatic N=CH); GC/MS *m/z* 363 (M^+, 4), 176 (100), 147 (24), 121 (36).

1-Aryl-4-[(1,2,3,4-tetrahydronaphthalen-1-yl)alkyl]piperazines 23, 24, 26, 27, 40, and 43. Method A. General Procedure. 1-Aryl-4-[(1,2-dihydronaphthalen-4-yl)alkyl]piperazines (2 mmol) as hydrochloride salts were solubilized in MeOH (30 mL) and hydrogenated at room temperature and normal pressure in the presence of a catalytic amount of 10% palladium on activated carbon. After 2 h the uptake ceased and the mixture was filtered on Celite. Evaporation of the solvent afforded almost quantitatively a solid, which was recrystallized from solvents reported in Table 1. Spectral data of title compounds refer to the free bases.

1-(2-Methoxyphenyl)-4-[3-(7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl]piperazine (23): ^{1}H NMR (200 MHz, $CDCl_3$) 1.56–1.90 (mm, 8H, $CH_2CH_2CHCH_2CH_2$), 2.46 (br t, 2H, $CH_2N(CH_2)_2$), 2.62–2.84 (mm, 7H, benzyl CH_2 and CH, $CH_2N(CH_2)_2$), 3.12 (br s, 4H, $(CH_2)_2NAr$), 3.78 and 3.86 (2s, 6H, 2 CH_3), 6.63–7.07 (mm, 7H, aromatic); GC/MS *m/z* 396 ($M^+ + 2$, 3), 395 ($M^+ + 1$, 23), 394 (M^+, 84), 205 (100), 192 (33), 150 (23).

1-(2-Methoxyphenyl)-4-[3-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl]piperazine (24): ^{1}H NMR (200 MHz, $CDCl_3$) 1.53–1.89 (mm, 8H), 2.38–2.87 (mm, 9H), 3.13 (br s, 4H), 3.81 and 3.86 (2s, 6H), 6.62–7.17 (mm, 7H); GC/MS *m/z* 396 ($M^+ + 2$, 3), 395 ($M^+ + 1$, 23), 394 (M^+, 83), 205 (100), 192 (34), 150 (22).

1-(2-Methoxyphenyl)-4-[4-(7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-butyl]piperazine (26): ^{1}H NMR (200 MHz, $CDCl_3$) 1.30–1.92 (mm, 10H), 2.44 (t, 2H, J = 7.6 Hz), 2.62–2.83 (mm, 7H), 3.12 (br s, 4H), 3.78 and 3.86 (2s, 6H), 6.63–7.02 (mm, 7H); GC/MS *m/z* 410 ($M^+ + 2$, 3), 409 ($M^+ + 1$, 21), 408 (M^+, 76), 205 (100).

1-(2-Methoxyphenyl)-4-[4-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-butyl]piperazine (27): ^{1}H NMR ($CDCl_3$) 1.30–1.83 (mm, 10H), 2.42 (br t, 2H), 2.51–2.79 (mm, 7H), 3.10 (br s, 4H), 3.79 and 3.85 (2s, 6H), 6.63–7.14 (mm, 7H); GC/MS *m/z* 410 ($M^+ + 2$, 3), 409 ($M^+ + 1$, 24), 408 (M^+, 84), 205 (100).

4-[3-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl]-1-phenylpiperazine (40): ^{1}H NMR ($CDCl_3$) 1.51–1.85 (mm, 8H), 2.41 (br t, 2H), 2.51–2.82 (mm, 7H), 3.20 (t, 4H, J = 5 Hz), 3.79 (s, 3H), 6.62–7.29 (mm, 8H); GC/MS *m/z* 366 ($M^+ + 2$, 4), 365 ($M^+ + 1$, 26), 364 (M^+, 88), 175 (100), 162 (35).

4-[3-(7-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl]-1-[3-(trifluoromethyl)phenyl]piperazine (43): ^{1}H NMR ($CDCl_3$) 1.54–1.88 (mm, 8H), 2.43 (br t, 2H), 2.58–2.82 (mm, 7H), 3.25 (br t, 4H), 3.77 (s, 3H), 6.63–7.38 (mm, 7H); GC/MS *m/z* 434 ($M^+ + 2$, 2), 433 ($M^+ + 1$, 18), 432 (M^+, 62), 243 (100), 230 (35), 188 (20).

1-Aryl-4-[(1,2,3,4-tetrahydronaphthalen-1-yl)alkyl]piperazines 22, 25, 35, 36, 39, and 44. Method B. The procedure was the same as that recently described.[8] Purification on a silica gel column was carried out using an eluent and obtaining a yield reported for each following compound.

1-(2-Methoxyphenyl)-4-[3-(1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl]piperazine (22): eluted with $CHCl_3$, 63% yield; ^{1}H NMR (200 MHz, $CDCl_3$) 1.54–1.92 (mm, 8H, $CH_2CH_2CHCH_2CH_2$), 2.45 (br t, 2H, $CH_2N(CH_2)_2$), 2.62–2.88 (mm, 7H, benzyl CH_2 and CH, $CH_2N(CH_2)_2$), 3.12 (br s, 4H, $(CH_2)_2NAr$), 3.86 (s, 3H, CH_3), 6.82–7.21 (mm, 8H, aromatic); GC/MS *m/z* 366 ($M^+ + 2$, 3), 365 ($M^+ + 1$, 21), 364 (M^+, 78), 205 (100), 192 (31), 150 (25), 91 (21).

1-(2-Methoxyphenyl)-4-[3-(4,5,6,7-tetrahydrobenzo[*b*]thien-4-yl)-*n*-propyl]piperazine (25): eluted with CH_2Cl_2/ethyl acetate, 3:2, 57% yield; ^{1}H NMR (200 MHz, $CDCl_3$) 1.42–2.01 (mm, 8H), 2.45 (t, 2H, J = 7.3 Hz), 2.61–2.81 (mm, 7H), 3.12 (br s, 4H), 3.86 (s, 3H), 6.82–7.05 (mm, 6H); GC/MS *m/z*

372 ($M^+ + 2$, 8), 371 ($M^+ + 1$, 25), 370 (M^+, 100), 205 (59), 192 (25), 150 (25).

4-[3-(7-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl]-1-(2-pyridyl)piperazine (35): eluted with $CHCl_3$/Et_2O, 1:1, 65% yield; ^1H NMR (200 MHz, $CDCl_3$) 1.53–1.89 (mm, 8H), 2.50 (br t, 2H, $CH_2N(CH_2)_2$), 2.61–2.82 (mm, 7H), 3.63 (br t, 4H), 3.76 (s, 3H), 6.58–7.52 (mm, 6H), 8.15–8.21 (m, 1H, aromatic N=CH); GC/MS *m/z* 367 ($M^+ + 2$, 1), 366 ($M^+ + 1$, 10), 365 (M^+, 40), 271 (22), 258 (60), 121 (32), 107 (100), 86 (25), 79 (21), 72 (48).

4-[3-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl]-1-(2-pyridyl)piperazine (36): eluted with $CHCl_3$/ethyl acetate, 1:1, 78% yield; ^1H NMR (200 MHz, $CDCl_3$) 1.52–1.88 (mm, 8H), 2.38–2.85 (mm, 9H), 3.59 (br t, 4H), 3.80 (s, 3H), 6.58–7.52 (mm, 6H), 8.14–8.23 (m, 1H, aromatic N=CH); GC/MS *m/z* 367 ($M^+ + 2$, 2), 366 ($M^+ + 1$, 14), 365 (M^+, 51), 271 (30), 258 (87), 121 (33), 107 (100), 86 (22), 79 (26), 78 (22), 72 (38).

4-[3-(7-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl]-1-phenylpiperazine (39): eluted with $CHCl_3$/MeOH, 95:5, 82% yield; ^1H NMR ($CDCl_3$) 1.53–1.89 (mm, 8H), 2.42 (br t, 2H), 2.54–2.82 (mm, 7H), 3.21 (br t, 4H), 3.74 (s, 3H), 6.63–7.29 (mm, 8H); GC/MS *m/z* 366 ($M^+ + 2$, 3), 365 ($M^+ + 1$, 24), 364 (M^+, 86), 175 (100), 162 (33).

4-[3-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl]-1-[3-(trifluoromethyl)phenyl]piperazine (44): eluted with CH_2Cl_2/MeOH, 95:5, 55% yield; ^1H NMR ($CDCl_3$) 1.52–1.88 (mm, 8H), 2.41 (br t, 2H), 2.56–2.84 (mm, 7H), 3.24 (br t, 4H), 3.79 (s, 3H), 6.60–7.36 (mm, 7H); GC/MS *m/z* 434 ($M^+ + 2$, 3), 433 ($M^+ + 1$, 18), 432 (M^+, 63), 243 (100), 230 (36).

1-(2-Methoxyphenyl)-4-[*N*-(7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-2-aminoethyl]piperazine (28). From a mixture of 7-methoxy-1-tetralone (**6c**) (1.40 g, 8 mmol) and 4-(2-aminoethyl)-1-(2-methoxyphenyl)piperazine (**15**) (1.40 g, 6 mmol) in anhydrous toluene (100 mL), in the presence of a catalytic amount of *p*-toluenesulfonic acid, a water formed which was azeotropically distilled and collected for 1 h. After cooling, the solvent was evaporated; the crude intermediate Schiff's base was solubilized in absolute ethanol (50 mL) and stirred with $NaBH_4$ (0.40 g, 10.6 mmol) for 2 h at room temperature, under nitrogen. After the solvent was removed, the residue was chromatographed on a silica gel column (CH_2Cl_2/MeOH, 95:5, as eluent) to give pure **28** (1.39 g, 59% yield) as an oil: ^1H NMR ($CDCl_3$) 1.64–2.01 (mm, 4H, endo CH_2-CH_2), 2.08 (br s, 1H, D_2O exchanged, NH), 2.52–2.91 (mm, 10H, benzyl CH_2, $NCH_2CH_2N(CH_2)_2$), 3.08 (br s, 4H, $(CH_2)_2$-NAr), 3.73–3.80 (t + s, 4H, CHN, CH_3), 3.84 (s, 3H, CH_3), 6.68–7.01 (mm, 7H, aromatic); GC/MS *m/z* 396 ($M^+ + 1$, 1), 395 (M^+, 3), 206 (37), 205 (100), 190 (28), 162 (22), 161 (40).

1-(2-Methoxyphenyl)-4-[*N*-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-2-aminoethyl]piperazine (29). Title compound was prepared from 5-methoxy-1-tetralone (**6b**) (1.06 g, 6 mmol) and arylpiperazine **15** (1.17 g, 5 mmol) as for compound **28**. The final reaction mixture was diluted in water and extracted three times with diethyl ether. The organic layer was washed with 2 N HCl, and the acidic aqueous phase was alkalized and extracted with diethyl ether. Finally the dried (Na_2SO_4) solution was concentrated in vacuo to give compound **29** (1.28 g, 65% yield) as a colorless oil: ^1H NMR (200 MHz, $CDCl_3$) 1.66–2.07 (mm, 4H), 2.17 (br s, 1H, D_2O exchanged), 2.46–2.93 (mm, 10H), 3.08 (br s, 4H), 3.75–3.83 (t + s, 4), 3.85 (s, 3H), 6.65–7.18 (mm, 7H); GC/MS *m/z* 395 (M^+, 2), 206 (46), 205 (100), 190 (38), 177 (21), 175 (23), 162 (26), 161 (48).

1-(2-Methoxyphenyl)-4-[2-[(7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)thio]ethyl]piperazine (30). To a suspension of $LiAlH_4$ (0.10 g) in dry THF (20 mL) was added, under stirring, the amide **14c** (0.55 g, 1.3 mmol) in the same solvent (15 mL). After the mixture boiled for 5 h, a few drops of water was added to the cooled mixture, which was extracted three times with Et_2O. The evaporation of the solvent and the chromatography of the residue on a silica gel column ($CHCl_3$/Et_2O, 1:1, as eluent) afforded compound **30** as a colorless oil (0.44 g, 83% yield): ^1H NMR (200 MHz, $CDCl_3$) 1.67–2.21 (mm, 4H, endo CH_2CH_2), 2.56–2.85 (mm, 10H, benzyl CH_2, $SCH_2CH_2N(CH_2)_2$), 3.10 (br t, 4H, $(CH)_2NAr$), 3.78 and 3.86 (2s, 6H, 2 CH_3), 4.12 (t, 1H, J = 4 Hz, CHS), 6.67–7.04 (mm, 7H, aromatic); GC/MS *m/z* 414 ($M^+ + 2$, 1), 413 ($M^+ + 1$, 5), 412 (M^+, 17), 219 (24), 205 (100), 190 (30).

1-(2-Methoxyphenyl)-4-[2-[(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)thio]ethyl]piperazine (31). From the same amount of **14b**, compound **31** was prepared (78% yield) and purified ($CHCl_3$/ethyl acetate, 9:1, as eluent) as above: ^1H NMR ($CDCl_3$) 1.73–2.20 (mm, 4H), 2.43–2.83 (mm, 10H), 3.09 (br s, 4H), 3.79 (s, 3H), 3.84 (s, 3H), 4.14 (t, 1H, J = 4 Hz), 6.64–7.14 (mm, 7H); GC/MS *m/z* 414 ($M^+ + 2$, 1), 413 ($M^+ + 1$, 2), 412 (M^+, 7), 205 (100), 190 (27).

Pharmacological Methods. 5-HT_{1A}, 5-HT_2, and D-2 binding assays were performed as previously described.[8]

D-1 Dopaminergic Binding Assay. The binding assay for D-1 dopaminergic receptors was essentially that described by Billard et al.[18] Corpora striata of male Sprague–Dawley rats were homogenized in 100 volumes of Tris-HCl buffer (50 mM, pH 7.4) with a Brinkmann polytron homogenizer (setting 5 for 15 s); the homogenate was then centrifuged at 50000*g* for 10 min. The supernatant was discarded and the pellet washed once. The final pellet was resuspended in 100 volumes of the Tris·HCl buffer described above, which contained 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, and 1 mM $MgCl_2$. Each assay tube contained 0.1 mL of drug dilution, 0.1 mL of [^{3}H]-SCH-23390 to achieve a final concentration of 0.30 nM, and 0.8 mL of resuspended membranes. The tubes were incubated for 15 min at 37 °C, and then incubation was terminated by vacuum filtration through Whatman GF/B filters. The filters were washed four times with 4 mL of ice-cold Tris-HCl buffer, and the radioactivity bound to the filters was measured by liquid scintillation spectrometry. Specific [^{3}H]SCH-23390 binding was defined as the difference between binding in the absence or presence of cold SCH-23390 (1 μM).

5-HT_{1B} Binding Assay. The procedure used in radioligand binding assay has been published in detail elsewhere.[19] Corpora striata from male Sprague–Dawley rats (180–220 g) were homogenized in 50 volumes of ice-cold Tris·HCl buffer (50 mM, pH 7.4, at 22 °C) with a Brinkmann polytron homogenizer (setting 5 for 15 s), and the homogenate was centrifuged at 50000*g* for 10 min. The resultant pellet was then resuspended in the same buffer, incubated for 10 min at 37 °C, and centrifuged twice at 50000*g* for 10 min. The final pellet was resuspended in 200 volumes of the Tris·HCl buffer, pH 7.7, which contained 10 μM pargyline, 4 mM $CaCl_2$, and 0.1% ascorbate. The following were added to each assay tube: 0.1 mL of drug dilution (0.1 mL of distilled water if no competing drug was added), 0.1 mL of [^{3}H]-5-HT in buffer (containing Tris, $CaCl_2$, pargyline, and ascorbate) to achieve a final assay concentration of 2 nM, 0.1 mL of 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) (1 μM), and 0.7 mL of resuspended membranes. The tubes were incubated for 30 min at 37 °C, and incubation was terminated by vacuum filtration through Whatman GF/B filters. The filters were washed three times with 5 mL of ice-cold Tris·HCl buffer, and the radioactivity bound to the filters was measured by liquid scintillation spectrometry. Specific [^{3}H]-5-HT binding was defined as the difference between binding in the absence or presence of 5-HT (10 μM).

5-HT_{1C} Binding Assay. The procedure used in the radioligand binding assay has been published in detail elsewhere.[19] Cerebral cortex from male Sprague–Dawley rats (180–220 g) was homogenized in 50 volumes of ice-cold Tris·HCl buffer (50 mM, pH 7.4, at 22 °C) with a Brinkmann polytron homogenizer (setting 5 for 15 s), and the homogenate was centrifuged at 50000*g* for 10 min. The resultant pellet was then resuspended in the same buffer, incubated for 10 min at 37 °C, and centrifuged twice at 50000*g* for 10 min. The final pellet was resuspended in 60 volumes of the Tris·HCl buffer, pH 7.7, which contained 10 μM pargyline, 4 mM $CaCl_2$, and 0.1% ascorbate. The following were added to each assay tube: 0.1 mL of drug dilution (0.1 mL of distilled water if no competing drug was added), 0.1 mL of [^{3}H]-5-HT in buffer (containing Tris, $CaCl_2$, pargyline, and ascorbate) to achieve a final assay concentration of 2 nM, 0.1 mL of RU-24960 (100 μM), 0.1 mL of 8-OH-DPAT (1 μM), and 0.6 mL of resuspended membranes. The tubes were incubated for 30 min at 37 °C, and incubation

was termined by vacuum filtration through Whatman GF/B filters. The filters were washed twice with 5 mL of ice-cold Tris·HCl buffer, and the radioactivity bound to the filters was measured by liquid scintillation spectrometry. Specific [^{3}H]-5-HT binding was defined as the difference between binding in the absence or presence of 5-HT (10 μM).

α_1 Adrenergic Binding Assay. The binding assay for α_1 adrenergic receptor was essentially as described elsewhere.[20] Cerebral cortex from male Sprague–Dawley rats (180–220 g) was homogenized in 50 volumes of Tris·HCl buffer (50 mM, pH 7.4) with a Brinkmann polytron homogenizer (setting 5 for 15 s); the homogenate was then centrifuged at 50000*g* for 10 min. The supernatant was discarded and the pellet resuspended in the same volume of buffer, incubated at 37 °C for 10 min, and centrifuged twice at 50000*g* for 10 min. The pellet was resuspended in 100 volumes of the Tris·HCl buffer, pH 7.7, which contained 10 μM pargyline and 0.1% ascorbate. Each assay tube contained 0.1 mL of drug dilution, 0.1 mL of [^{3}H]prazosin to achieve a final concentration of 0.20 nM, and 0.8 mL of resuspended membranes and was incubated for 15 min at 37 °C. Incubation was terminated by vacuum filtration through Whatman GF/B filters. The filters were washed twice with 5 mL of ice-cold Tris·HCl buffer, and the radioactivity bound to the filters was measured by liquid scintillation spectrometry. Specific [^{3}H]prazosin binding was defined as the difference between binding in the absence or presence of cold prazosin (3 μM).

σ Binding Assay. The binding assay for σ receptors was essentially as described by Weber et al.[21] Whole male guinea pig brain, without cerebellum, was homogenized in 10 volumes of sucrose (0.32 M) with a Brinkmann polytron homogenizer (setting 5 for 15 s). The homogenate was then centrifuged at 500*g* for 10 min, the pellet was discarded, and the supernatant was centrifuged at 28000*g* for 20 min. The pellet was then resuspended in 10 volumes of the Tris·HCl buffer (50 mM, pH 7.4), incubated at 37 °C for 30 min, and then centrifuged at 22000*g* for 20 min. The final pellet was resuspended in 20 mL of Tris·HCl (50 mM, pH 7.4). Each assay tube contained 0.1 mL of drug dilution, 0.1 mL of [^{3}H]DTG to achieve a final concentration of 0.90 nM, and 0.8 mL of resuspended membranes. The tubes were incubated for 90 min at 25 °C, and incubation was terminated by vacuum filtration through Whatman GF/B filters. The filters were washed three times with 5 mL of ice-cold Tris·HCl buffer, and the radioactivity bound to the filters was measured by liquid scintillation spectrometry. Specific [^{3}H]DTG binding was defined as the difference between binding in the absence or presence of cold haloperidol (1 μM).

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(15) The GC/MS spectra of both bromo- and chloropropyl derivatives of methoxy-1,2-dihydronaphthalene show a base peak value of $M^+ - 77$, corresponding to a methoxy–dihydronaphthalene positive fragment, whereas chloropropylidene derivatives such as *E*-**8a,b** give a base fragment with a mass of $M^+ - 49$ due to the loss of a chloromethylene radical from the side chain. In addition, the triplet of the vinylic proton at δ 6.0 in ^{1}H NMR spectra of all the exocyclically unsaturated compounds prepared was shifted downfield by about 0.1 ppm compared with the corresponding signal in the spectra of the endocyclic isomers. In particular, decoupling and COSY studies on chloropropylidene derivative *E*-**8b** showed the triplet at δ 2.6–2.7 to be coupled with the vinyl signal as well as with the CH_2Cl triplet at δ 3.58, evidence that the double bond was placed on the side chain, whereas a multiplet at δ 1.82 was coupled with benzylic CH_2, as well as with the other allylic CH_2, demonstrating that these signals belong to a tetralin ring. As a result, the typical signal at δ 2.2, due to the allylic endo CH_2 in 1,2-dihydronaphthalene derivatives,[8] is absent in the NMR spectra of compounds *E*-**8a,b** and in those of their derivatives *E*-**18**, *E*-**19**, and *E*-**34**. Also the dd (J_{ortho} = 7.2 Hz, J_{meta} = 0.8 Hz) due to the aromatic H (C_8H) in the α position of the side chain is shifted down from δ 6.9 in the Δ_{endo} to δ 7.2 in the Δ_{exo} compounds; in particular in desmethoxynaphthalene derivatives where the electronic shielding effects of the methoxy group are absent, the aromatic protons appear as a single signal at δ 7.20 in Δ_{endo} compounds, whereas in Δ_{exo} compounds several multiplets appear in the range of δ 7.0–7.2. It would, therefore, appear that the most shifted multiplet at δ 7.5–7.6 likely belongs to the above-mentioned C_8H, which lies in the deshielding field of the exocyclic double bond conjugated with the aromatic ring. In addition, the NOESY spectra of *E*-**8b** and *E*-**34** show a cross-peak between the vinyl tt and the dd at δ 7.2 (J_{ortho} = 7.2 Hz, J_{meta} = 0.8 Hz) of the aromatic C_8H, indicative of the close proximity of these protons, a condition possible only in the *E*-isomer, in which the side chain is trans relative to the tetralin aromatic ring.

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