Mixed 5-HT$_{1A}$/D-2 Activity of a New Model of Arylpiperazines: 1-Aryl-4-[3-(1,2-dihydronaphthalen-4-yl)-*n*-propyl]piperazines. 1. Synthesis and Structure–Activity Relationships

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Received April 15, 1993•

A new model of 4-alkyl-1-arylpiperazines containing a terminal dihydronaphthalene fragment on the alkyl chain was synthesized in order to have mixed serotonergic and dopaminergic activity and to pursue the recent alternative approaches to the discovery of novel antipsychotic and anxiolytic agents. Title compounds were evaluated for in vitro activity on dopamine D-2 and serotonin 5-HT$_{1A}$ and 5-HT$_2$ receptors by radioreceptor binding assays. They show high nanomolar affinity for 5-HT$_{1A}$, moderate affinity for D-2, and low affinity for 5-HT$_2$ receptors, and in particular, two compounds, 4-[3-(1,2-dihydro-6-methoxynaphthalen-4-yl)-*n*-propyl]-1-(2-methoxyphenyl)piperazine (8) and 4-[3-(1,2-dihydro-8-methoxynaphthalen-4-yl)-*n*-propyl]-1-(2-pyridyl)piperazine (15), show values (nM) of IC$_{50}$ = 2.0 and 1.4 for 5-HT$_{1A}$ and IC$_{50}$ = 90.6 and 119.3 for D-2, respectively. Some in vivo behavioral studies show compound 8 to be an antagonist on 5-HT$_{1A}$ receptors. These first findings place the new arylpiperazines on the same level as that of the azaspirone class, e.g., 1-(2-methoxyphenyl)-4-[4-(2-phthalimido)-*n*-butyl]piperazine (NAN-190) and buspirone.

Common chlorpromazine-like antipsychotic drugs produce extrapyramidal symptoms (EPS), while antianxiety agents, such as benzodiazepines, present ataxia, sedative phenomena, and signs of drug dependence as side effects.

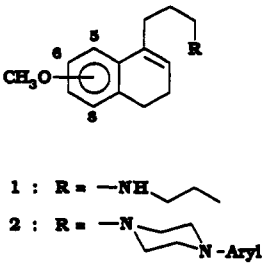
Recent observations[1,2] indicate that improvement of these agents may be attained by combining dopaminergic and serotonergic activities in a single structure. Indeed, at the moment, there is considerable interest in molecules with multireceptorial activity[3] as novel antipsychotic agents of potential clinical significance.

Within this context, examples of compounds having both D-2 and 5-HT$_2$ receptor antagonist properties are setoperone[4] and risperidone,[5,6] which have been evaluated in clinical trials, as well as new molecules which are predicted to be efficacious against negative symptoms of schizophrenia and to have fewer EPS.[7]

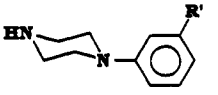
Another example of an atypical neuroleptic drug with reduced side effects is clozapine which, in addition to acting on a specific subclass of dopamine receptors,[8] interacts with significant affinity on a broad range of receptor types (serotonergic, adrenergic, muscarinic, and histaminergic).[9-12]

Formerly, in our laboratories, we have synthesized compounds such as the 1-aminoethylheterotetralin[13,14] derivatives 1, which show no affinity for dopaminergic and serotonergic receptors, although they are open derivatives of active cyclic structures on DA and 5-HT receptors.

In order to achieve this dual affinity for these receptors, we inserted the terminal nitrogen of the side chain of compounds 1 in an arylpiperazine structure. During the last decade, the arylpiperazine moiety has shown to be one of the templates for 5-HT activity,[15] but minor



modifications involve significant changes in affinity and selectivity, since it can also display moderate to high affinity for DA receptors. Actually, the simple arylpiperazines such as TFMPP and mCPP are active on 5-HT$_1$receptors only,[16] whereas the long-chain ones, such



mCPP : R' = Cl

TFMPP : R' = CF$_3$

as 1-(2-methoxyphenyl)-4-[4-(2-phthalimido)-*n*-butyl]-piperazine (NAN-190), buspirone,[17] and others,[18,19] although they can be active on D-2 receptors also, are selective agents on 5-HT$_{1A}$ versus other 5-HT receptors. This latter selectivity depends on the nature of the substituent on N-4 of the piperazine, which binds itself to a receptor accessory site;[20] thus, a multireceptorial approach is essential in preliminary binding studies on these novel compounds.

The *N*-(dihydronaphthalen-4-yl)alkyl-substituted arylpiperazine derivatives presented in this paper have the general structure 2, and they may be considered long-chain arylpiperazines, where the tetralinalkyl moiety on N-4 is the same as that present in our previous compounds[13]

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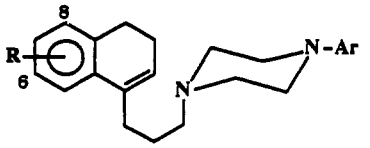
• Abstract published in *Advance ACS Abstracts*, December 15, 1993.

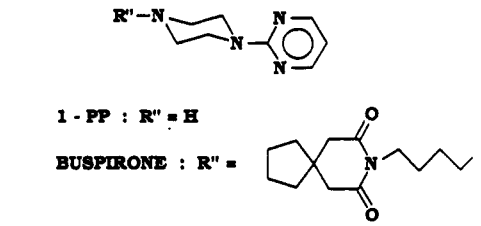
0022-2623/94/1837-0099$04.50/0

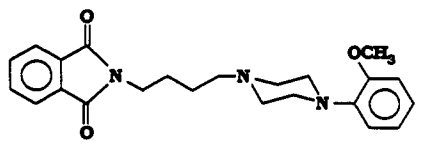
Table 1. Physical Properties and Binding Affinities



compd	R	Ar	mp, °C	formula[b]	IC_{50}, nM (pK_i)[c] 5-HT_{1A}, [^{3}H]-8-OH-DPAT	5-HT_2, [^{3}H]ketanserin	D-2, [^{3}H]spiroperidol
6	6-OCH_3	H	120	$C_{18}H_{26}N_2O\cdot2HCl$	>10^4	>10^4	>10^4
7	H	2-OCH_3-Ph	185–187	$C_{24}H_{30}N_2O\cdot2HCl$	15.7 ± 1.7	104 ● 26	14.7 ± 0.6
8	6-OCH_3	2-OCH_3-Ph	180–182	$C_{25}H_{32}N_2O_2\cdot2HCl$	2.0 ± 0.67 (8.75)	391 ± 7	90.6 ● 18.1 (7.65)
9	6-OCH_3	2-Py	225–226	$C_{23}H_{29}N_3O\cdot2HCl$	63.6 ± 0.9	146 ± 28[d]	778 ● 33
10	6-OCH_3	Ph	186–187	$C_{24}H_{30}N_2O\cdot{}^5/_4HCl$	147 ± 14	119 ± 5[d]	777 ± 25
11	6-OCH_3	3-Cl-Ph	184–185	$C_{24}H_{29}ClN_2O\cdot2HCl$	131 ● 8	133 ± 7[d]	768 ± 17
12	6-OCH_3	3-CF_3-Ph	189–190	$C_{25}H_{29}F_3N_2O\cdot HCl$	138 ± 8	1170 ± 43[d]	1290 ± 350
13	6-OCH_3	2,5-$(OCH_3)_2$-Ph	192–193	$C_{26}H_{34}N_2O_3\cdot2HCl$	161 ± 9	932 ± 22[d]	201 ● 34
14	8-OCH_3	2-OCH_3-Ph	209–210	$C_{25}H_{32}N_2O_2\cdot2HCl$	8.8 ± 0.84	770 ± 18	17.4 ● 1.0
15	8-OCH_3	2-Py	220–222	$C_{23}H_{29}N_3O\cdot{}^5/_2HCl$	1.4 ● 0.21 (8.90)	205 ± 10	119 ± 9 (7.53)
16	8-OCH_3	Ph	185–187[a]	$C_{24}H_{30}N_2O\cdot{}^5/_4HCl$	18.3 ± 5.3	204 ± 8	303 ± 39
17	8-OCH_3	3-Cl-Ph	190–192	$C_{24}H_{29}ClN_2O\cdot HCl$	31.4 ± 9.0	1340 ± 250	484 ± 45
18	8-OCH_3	3-CF_3-Ph	201–202	$C_{25}H_{29}F_3N_2O\cdot HCl$	55.9 ± 6.1	2370 ± 150	644 ± 56
buspirone					12.8 ± 1.7 (7.83)[15]	>10^4	222 ± 6 (7.38)[15]
NAN-190[15]					(8.88)		(8.02)
8-OH-DPAT					1.10 ± 0.10		
ketanserin						1.20 ± 0.15	
butaclamol							0.50 ● 0.05

[a] From methylene chloride/petroleum ether. [b] Analyses for C, H, N. [c] In selected experiments, the K_i was calculated according to the Cheng–Prusoff equation and the pK_i reported. K_d values for the ligands (0.12 nM for spiroperidol, 1.03 nM for 8-OH-DPAT, and 0.5 nM for ketanserin) to be used in the equation were derived from *ad hoc* saturation experiments and the data analyzed by EBDA computerized program. [d] Affinity at [^{3}H]spiroperidol-labeled 5-HT_2 sites, in the presence of sulpiride as a D-2 blocker.





NAN-190

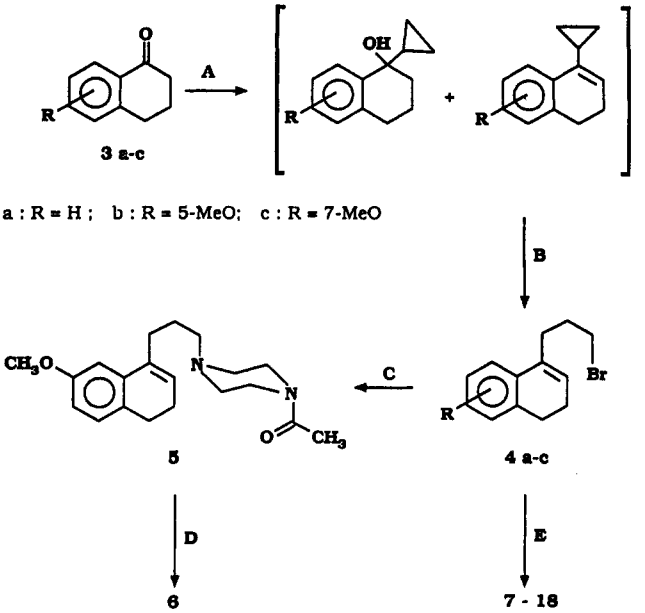
and where the arylpiperazine moiety is the same structural element found in the most active reference compounds.

Six kinds of 1-arylpiperazines were chosen for this work: phenyl, 2-methoxy- and 2,5-dimethoxyphenyl, 2-pyridyl, 3-chlorophenyl, and 3-(trifluoromethyl)phenyl. The 1-(2-pyrimidyl)piperazine (1-PP) was deliberately not employed, since it has been recognized as the main metabolite of buspirone and its congeners, responsible for the α_2 antagonist activity shown by buspirone-like derivatives,[21] and it has even been suggested that 1-PP possesses anxiogenic properties in panic disorder patients.[22]

Chemistry

All compounds 6-18 (Table 1) were synthesized starting from the respective 1-tetralones **3a-c** (Scheme 1), which were alkylated by magnesium cyclopropyl bromide. The intermediates were not isolated; simultaneous cyclopropyl ring cleavage and complete dehydration were achieved by aqueous HBr in acetic acid, and the bromo derivatives **4a-c** were purified by column chromatography.

Scheme 1[a]



[a] Reagents: (A) cyclopropyl–MgBr; (B) HBr; (C) 1-acetylpiperazine; (D) 3 N HCl; (E) *N*-arylpiperazines.

Although in principle this reaction can also produce compounds with an exocyclic double bond, under the conditions described an exclusively endocyclic unsaturated compound was formed. The structure **4** was confirmed by comparing[23] the UV spectrum of **4a** (λ = 266 nm, ϵ = 4170) with that of 1,2-dihydronaphthalene (λ = 264 nm, ϵ = 1790) in $CHCl_3$. Moreover, NMR decoupling experiments were carried out on **4a–c** to elucidate the above structure. In particular, the chemical shift and the shape of the multiplets at about δ 2.2 are characteristic of the allylic *endo* CH_2, also present in the 1,2-dihydronaphthalene and its 4-alkyl derivatives. When these signals

are irradiated, the vinyl and benzyl signals are simplified, neither the CH_2Br triplet at δ 3.4 nor the aliphatic multiplet at δ 2.0 being affected.

1-Acetylpiperazine was then reacted with the bromo derivative **4c** to give the *N*-acetyl derivative **5**, from which the product **6** was obtained by acidic hydrolysis. Similarly, (bromopropyl)naphthalenes **4a–c**, reacted with the appropriate commercially available *N*-arylpiperazines, led to the final compounds **7–18**. Only 1-(2,5-dimethoxyphenyl)piperazine was previously prepared by refluxing 2,5-dimethoxyaniline with bis(2-chloroethyl)amine in toluene. Respective hydrochloride salts were then prepared as samples for pharmacological assays.

Pharmacology

The compounds **7–18** were evaluated for in vitro activity on dopamine D-2 and serotonin 5-HT$_{1A}$ and 5-HT$_2$ receptors by radioreceptor binding assays. 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-2 receptors, [^{3}H]-spiroperidol, rat striatal membranes; (b) serotonin 5-HT$_{1A}$ receptors, [^{3}H]-8-OH-DPAT, rat brain cortex membranes; and (c) serotonin 5-HT$_2$ receptors, [^{3}H]ketanserin, rat brain cortex membranes. 8-OH-DPAT, ketanserin, butaclamol, and buspirone 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 and in Pharmacological Methods; in all three binding assays, it represented more than 75% of total binding. In addition, compounds **8** and **18** were studied in vivo for their ability to antagonize the 8-OH-DPAT-induced syndrome, a test assessing the in vivo antagonist activity of a test compound on 5-HT$_{1A}$ receptors. The choice was based on the fact that compound **8** displayed the highest relative selectivity for 5-HT$_2$/5-HT$_{1A}$ (calculated as the ratio between the two IC_{50} values in the respective binding assays) and the second highest potency on 5-HT$_{1A}$ receptors. Compound **18**, although exhibiting a lower relative selectivity, was the least potent on 5-HT$_2$ receptors and was 7 times less potent than compound **8** on D-2 receptors.

Results and Discussion

As already pointed out, the affinity of compounds **7–18** toward 5-HT$_{1A}$, 5-HT$_2$, and D-2 receptors is essentially due to the presence of the aromatic ring linked to the piperazine. In fact, compound **6** proved to have no affinity at all to the above mentioned receptors (Table 1).

As regards the affinity for 5-HT$_{1A}$ receptors, the pIC_{50} values (Table 2) of compounds **7–18** were all in the range between 8.86 and 6.80; values higher than 8 were found for the 1-(2-methoxyphenyl)piperazine derivatives **8** and **14** (pIC_{50} = 8.70 and 8.06, respectively) and for the 1-(2-pyridyl)piperazine derivative **15** (pIC_{50} = 8.85).

The position of the methoxy group on the tetralin moiety appeared to have a certain influence on affinity. In fact, except for the 2-methoxyphenyl derivatives, compounds **15–18** bearing a methoxy group in the 8-position exhibited a higher affinity in comparison with the corresponding 6-methoxy derivatives **9–12**.

Table 2. Comparison of in Vitro 5-HT$_{1A}$ and D-2 Affinities for 6-Methoxytetralin Derivatives **8–12** (△) and 8-Methoxytetralin Derivatives **14–18** (□)

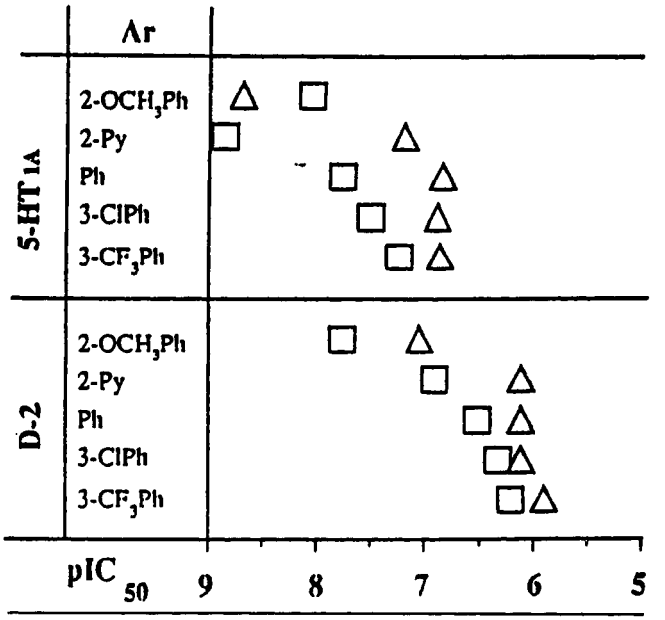


Table 3. Inhibition Effect on Behaviors (forepaw treading and flat body posture) Induced by 8-OH-DPAT in Reserpinized Rats

compd	ED_{50} (mg/kg) after sc administration	IC_{50} (nM) [^{3}H]-8-OH-DPAT
8	0.76[a]	2.0 ● 0.67
18	24.2[a]	55.9 ● 6.1
ratio 18/8	31.7	27.9

[a] The compounds tested are dose-dependent antagonists of the effects produced by 8-OH-DPAT. Neither **8** nor **18** induce forepaw treading or flat body posture when given sc into rats pretreated with reserpine.

As for the affinity for 5-HT$_2$ receptors, the pIC_{50} values were low, between 6.98 and 5.63, and it was impossible to carry out an SAR.

As regards the affinity for D-2 receptors, the pIC_{50} values were low, between 7.83 and 5.89, in a range lower than that for 5-HT$_{1A}$ receptors. We found that the dopaminergic affinity was higher for compounds **7**, **8**, and **14**, all derivatives of 1-(2-methoxyphenyl)piperazine. On D-2 receptors, the position of the methoxy group on the tetralin moiety had the same influence as for 5-HT$_{1A}$ receptors: namely, compounds **14–18** displayed a higher affinity than compounds **9–12**.

The testing of compounds **8** and **18** in the 8-OH-DPAT-induced behavioral syndrome (Table 3) indicated that the two compounds were also able to exert their pharmacological activity when administered subcutaneously in vivo, suggesting that they are able to cross the blood brain barrier.

Compounds **8** and **18** inhibited the 8-OH-DPAT-induced behavior in reserpinized rats dose-dependently, indicating that they may act as antagonists of 8-OH-DPAT. In particular, compound **8** had an ED_{50} value of less than 1 mg/kg. The ratio between the in vivo ED_{50} values of the two compounds matched that between the in vitro IC_{50} values (31.7 and 27.9, respectively).

In addition, neither compound **8** nor **18** when administered alone in reserpinized rats induced treading or flat body posture, indicating that they are devoid of agonist activity.

In similar experimental conditions, pretreatment with buspirone (2 mg/kg, subcutaneously) 30 min before 8-OH-DPAT reduces the forepaw treating (−45%) but not the flat body posture induced by tetralin. However, buspirone (2 mg/kg, subcutaneously), when administered alone in reserpinized rats, is able itself to induce a clear 5-HT_{1A} behavioral syndrome similar in quality to that induced by 8-OH-DPAT. Besides, the flat body posture elicited by buspirone is long-lasting, while its forepaw treating is rapidly induced but lasts under 15 min after treatment.

Hence, in our experimental conditions, buspirone, according to the literature data,[24,25] elicits a partial agonist activity not present in compounds 8 and 18 which appear therefore to be 5-HT_{1A} antagonists, based on behavioral criteria.

On the other hand, further testing is needed to fully prove the antagonist activity of the studied compounds, since it has been shown that the type of response measured (e.g., behavioral and neurochemical, etc.) may give origin to different conclusions.[26] As an example, while 1-(2-methoxyphenyl)-4-[4-(2-phthalimido)-*n*-butyl]piperazine appears to be a full antagonist in certain in vivo tests,[27] it has partial agonist-like properties in others[28] as well as in vitro radioligand experiments studying the sensitivity of the binding to G protein activation.[29]

We can say, therefore, that the arylpiperazines reported in the present paper, and in particular the 2-methoxyphenyl and 2-pyridyl derivatives 8 and 15, respectively, present a very high affinity toward 5-HT_{1A} receptors, comparable to the most active compound having the same Ar group reported in the literature,[17] such as 1-(2-methoxyphenyl)-4-[4-(2-phthalimido)-*n*-butyl]piperazine, thus opening a new avenue for research for new anxiolytics having potent 5-HT_{1A} antagonist activity, based on behavioral criteria. In addition, some of the compounds tested such as 7, 8, 13, and 15 have an affinity for dopamine D-2 receptors in the nanomolar range, which may confer antipsychotic activity.

Experimental Section

Chemistry. Column chromatographies were performed with 1:30 Carlo Erba RS Analytical silica gel (0.05–0.20 mm) as the stationary phase. Melting points were determined in open capillaries on a Büchi-Tottoli apparatus and are uncorrected. Microanalyses 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. UV spectra were obtained by an HP 8452A diode array spectrophotometer. ^{1}H NMR spectra and COSY experiments were recorded on a Varian XL-200 instrument (200 MHz); a Bruker AM 300 WB instrument was used when indicated (300 MHz) and for decoupling spectra. 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 an HP 59970A workstation. All compounds had NMR and mass spectra that were fully consistent with their structure.

4-(3-Bromo-*n*-propyl)-1,2-dihydronaphthalene (4a). To a stirred solution of Grignard's reagent, prepared from Mg turnings (0.29 g, 12 mmol) and bromocyclopropane (0.96 mL, 12 mmol) in anhydrous THF (10 mL), was added dropwise 1-tetralone (**3a**) (1.25 g, 8.5 mmol) in the same solvent (10 mL). After the mixture was refluxed for 2 h and cooled at room temperature, a cool saturated solution of NH_4Cl (30 mL) was added to the ice-cooled reaction mixture. Extraction with Et_2O and evaporation of the dried (Na_2SO_4) organic layer gave the mixture of crude intermediates as an oil, which was solubilized in acetic acid (20 mL) and stirred with 20% aqueous HBr (15 mL) for a day at room temperature. Then, $CHCl_3$ was added, and the separated organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residual oil was chromatographed on a silica gel column (petroleum ether/CH_2Cl_2, 9:1 as eluent) to obtain pure **4a** as a colorless oil (60% overall yield); bp 88 °C (4 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) 2.02–2.12 (mm, 2H, CH_2-CH_2Br), 2.21–2.30 (mm, 2H, *endo* CH_2), 2.57–2.64 mm, 2H, CCH_2), 2.73 (t, 2H, J = 8 Hz, benzyl CH_2), 3.44 (t, 2H, J = 6.6 Hz, CH_2-Br), 5.91 (tt, 1H, J = 1.1, 4.5 Hz, vinyl CH), 7.12–7.25 (mm, 4 H, arom); GC/MS m/z 253 (M^+ + 3, 1), 252 (M^+ + 2, 11), 251 (M^+ + 1, 2) 250 (M^+, 11), 144 (29), 141 (20), 129 (100), 128 (45), 115 (23).

4-(3-Bromo-*n*-propyl)-1,2-dihyro-8-methoxynaphthalene (4b). The above procedure was also followed for 5-methoxy-1-tetralone (**3b**) (9.5 g, 54 mmol); **4b** was obtained as a colorless oil (57% overall yield); bp 108 °C (4 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) 2.05 (m, 2H, CH_2CH_2Br), 2.12–2.25 (mm, 2H, *endo* CH_2), 2.59 (dt, 2H, CCH_2), 2.73 (t, 2H, J = 8.2 Hz, benzyl CH_2), 3.43 (t, 2H, J = 6.6 Hz, CH_2Br), 3.82 (s, 3H, CH_3), 5.91 (t, 1H, J = 4.6 Hz, vinyl CH), 6.76–7.20 (mm, 3H, arom); GC/MS m/z 283 (M^+ + 3, 2), 282 (M^+ + 2, 16), 281 (M^+ + 1, 3), 280 (M^+, 16), 201 (21), 174 (21), 173 (23), 159 (100), 144 (28), 128 (27), 115 (35).

4-(3-Bromo-*n*-propyl)-1,2-dihydro-6-methoxynaphthalene (4c). **4c** was prepared from **3c** (7.5 g, 43 mmol) as described for **4a**; pale yellow oil (66% overall yield), bp 106 °C (4 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) 2.06 (m, 2H, CH_2CH_2Br), 2.18–2.27 (mm, 2H, *endo* CH_2), 2.58 (dt, 2H, CCH_2), 2.65 (t, 2H, J = 8.0 Hz, benzyl CH_2), 3.43 (t, 2H, J = 6.5 Hz, CH_2Br), 3.79 (s, 3 H, CH_3), 5.92 (t, 1H, J = 4.5 Hz, vinyl CH), 6.65–7.07 (mm, 3H, arom); GC/MS m/z 283 (M^+ + 3, 4), 282 (M^+ + 2, 29) , 281 (M^+ + 1, 5), 280 (M^+, 29), 174 (36), 173 (37), 159 (100), 158 (27), 144 (32), 128 (33), 115 (39).

1-Acetyl-4-[3-(1,2-dihydro-6-methoxynaphthalen-4-yl)-*n*-propyl]piperazine (5). The title compound was prepared from the bromo derivative **4c** (2.50 g, 10 mmol) and 1-acetylpiperazine (2.00 g, 15.6 mmol) in DMF (20 mL), as described below in the general procedure for obtaining arylpiperazines 7–18. **5** was eluted from a silica gel column by $CHCl_3$/MeOH, 95:5; colorless oil, bp 156 °C (4 mmHg): ^{1}H NMR ($CDCl_3$), 1.50–1.98 (mm, 2H, $CH_2CH_2CH_2N$), 2.10 (s, 3H, $COCH_3$), 2.12–2.81 (mm, 12H), 3.35–3.75 (mm, 4H, $(CH_2)_2NCO$), 3.84 (s, 3H, OCH_3), 5.92 (br t, 1H, vinyl CH), 6.64–7.19 (mm, 3H, arom); GC/MS m/z 329 (M^+ + 1, 5), 328 (M^+, 26), 154 (38), 141 (100), 99 (25).

1-[3-(1,2-Dihydro-6-methoxynaphthalen-4-yl)-*n*-propyl]-piperazine (6). The *N*-acetyl derivative **5** (1.5 g, 4.5 mmol) was refluxed in 3 N HCl (25 mL) for 2 h. After cooling, the mixture was made alkaline and extracted thrice with $CHCl_3$. The organic layers were dried (Na_2SO_4) and the solvent evaporated to produce compound **6** as a light yellow oil in quantitative yield. Hydrochloride salt was prepared as described in the general procedure for compounds 7–18. Spectra of free base: ^{1}H NMR ($CDCl_3$) 1.62–1.80 (mm, 2H, $CH_2CH_2CH_2N$), 2.00 (br s, 1H, D_2O exchanged, NH), 2.13–2.27 (mm, 2H, *endo* CH_2), 2.31–2.51 (mm, 8H, $CH_2CH_2CH_2N(CH_2)_2$), 2.64 (t, 2H, J = 8 Hz, benzyl CH_2), 2.88 (t, 4H, J = 4.9 Hz, $(CH_2)_2NH$), 3.78 (s, 3H, CH_3), 5.86 (t, 1H, J = 4.5 Hz, vinyl CH), 6.63–7.08 (mm, 3H, arom); GC/MS m/z 288 (M^+ + 2, 2), 287 (M^+ + 1, 10), 286 (M^+, 49), 112 (36), 99 (100), 97 (38).

1-Aryl-4-[3-(1,2-dihydronaphthalen-4-yl)-*n*-propyl]piperazines 7–18. General Procedure. The 4-(3-bromopropyl)-1,2-dihydronaphthalene derivative **4** (3.5 mmol) was refluxed in DMF (10 mL) with an equimolar amount of the appropriate arylpiperazine and sodium carbonate. 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 (Na_2SO_4), the solvent was evaporated, and the crude residue was chromatographed on a silica gel column ($CHCl_3$/ethyl acetate, 1:1, as eluent, unless otherwise indicated). Arylpiperazines 7–18 were obtained as almost colorless to pale yellow oils with a 70–80% yield. Their spectral data refer to the free bases.

7-18·HCl. The respective hydrochloride salts were prepared by adding a HCl ethereal solution to a CH_2Cl_2 solution of **7–18** followed by recrystallization from MeOH/Et_2O, unless otherwise reported in Table 1. **7–18 hydrochlorides** were obtained as white to sand yellow crystals or crystalline powders.

4-[3-(1,2-Dihydro-6-methoxynaphthalen-4-yl)-*n*-propyl]-1-phenylpiperazine (10): ^{1}H NMR (300 MHz, $CDCl_3$) 1.69–1.87 (mm, 2H, $CH_2CH_2CH_2N$), 2.16–2.30 (mm, 2H, *endo* CH_2), 2.41–2.53 (mm, 4H, $CH_2CH_2CH_2N$), 2.57–2.74 (mm, 6 H, benzyl CH_2 and $CH_2N(CH_2)_2$), 3.18–3.27 (br t, 4H, $(CH_2)_2NAr$), 3.81 (s, 3H, CH_3), 5.90 (t, 1H, J = 4.5 Hz, vinyl CH), 6.65–7.33 (mm, 8 H, arom); GC/MS m/z 364 (M^+ + 2, 3), 363 (M^+ + 1, 26), 362 (M^+, 100), 175 (34), 173 (32), 132 (26).

4-[3-(1,2-Dihydronaphthalen-4-yl)-*n*-propyl]-1-(2-methoxyphenyl)piperazine (7): eluted with $CHCl_3/Et_2O$, 1:1, ^{1}H NMR ($CDCl_3$) 1.72–1.83 (mm, 2H), 2.19–2.28 (mm, 2H), 2.43–2.55 (mm, 4H), 2.62–2.78 (mm, 6H), 3.10 (br s, 4H), 3.84 (s, 3H), 5.87 (t, 1H, J = 4.5 Hz), 6.82–7.27 (mm, 8H); GC/MS m/z 364 (M^+ + 2, 3), 363 (M^+ + 1, 27), 362 (M^+, 100), 205 (31), 203 (30), 162 (23).

4-[3-(1,2-Dihydro-6-methoxynaphthalen-4-yl)-*n*-propyl]-1-(2-methoxyphenyl)piperazine (8): ^{1}H NMR ($CDCl_3$) 1.70–1.88 (mm, 2H), 2.15–2.29 (mm, 2H), 2.40–2.55 (mm, 4H), 2.66 (br t, 6H), 3.11 (br s, 4H, $(CH_2)_2NAr$), 3.80 and 3.85 (2s, 6H, 2 CH_3), 5.90 (t, 1 H, J = 4.5 Hz), 6.63–7.10 (mm, 7H); GC/MS m/z 349 (M^+ + 2, 4), 393 (M^+ + 1, 27), 392 (M^+, 100), 205 (21), 203 (25).

4-[3-(1,2-Dihydro-6-methoxynaphthalen-4-yl)-*n*-propyl]-1-(2-pyridyl)piperazine (9): ^{1}H NMR ($CDCl_3$) 1.70–1.90 (mm, 2H), 2.13–2.28 (mm, 2H), 2.38–2.54 (mm, 4H), 2.54–2.74 (mm, 6H), 3.52–3.62 (br t, 4H), 3.78 (s, 3H), 5.88 (t, 1H, J = 4.5 Hz), 6.55–7.52 (mm, 6H), 8.12–8.21 (m, 1H, arom N=CH); GC/MS m/z 365 (M^+ + 2, 2), 364 (M^+ + 1, 16), 363 (M^+, 63), 256 (39), 244 (47), 121 (36), 107 (100), 72 (40).

1-(3-Chlorophenyl)-4-[3-(1,2-dihydro-6-methoxynaphthalen-4-yl)-*n*-propyl]piperazine (11): ^{1}H NMR ($CDCl_3$) 1.67–1.86 (mm, 2H), 2.16–2.30 (mm, 2H), 2.38–2.53 (mm, 4H), 2.54–2.74 (mm, 6H), 3.14–3.26 (br t, 4H), 3.80 (s, 3H), 5.90 (t, 1H, J = 4.5 Hz), 6.65–7.20 (mm, 7H); GC/MS m/z 400 (M^+ + 4, 1), 399 (M^+ + 3, 8), 398 (M^+ + 2, 35), 397 (M^+ + 1, 31), 396 (M^+, 100), 209 (59), 207 (32), 166 (27).

4-[3-(1,2-Dihydro-6-methoxynaphthalen-4-yl)-*n*-propyl]-1-[3-(trifluoromethyl)phenyl]piperazine (12): ^{1}H NMR ($CDCl_3$) 1.69–1.87 (mm, 2H), 2.16–2.30 (mm, 2H), 2.41–2.54 (mm, 4H), 2.57–2.73 (mm, 6H), 3.21–3.31 (br t, 4H), 3.80 (s, 3H), 5.90 (t, 1H, J = 4.5 Hz), 6.64–7.40 (mm, 7H); GC/MS m/z 432 (M^+ + 2, 4), 431 (M^+ + 1, 26), 430 (M^+, 100), 256 (20), 243 (69), 241 (34), 200 (45), 172 (24).

4-[3-(1,2-Dihydro-6-methoxynaphthalen-4-yl)-*n*-propyl]-1-(2,5-dimethoxyphenyl)piperazine (13): ^{1}H NMR ($CDCl_3$) 1.72–1.91 (mm, 2 H), 2.14–2.28 (mm, 2H), 2.39–2.83 (mm, 10H), 3.12 (br s, 4H), 3.75, 3.79, and 3.80 (3s, 9H, 3 CH_3), 5.89 (t, 1H, J = 4.6 Hz), 6.43–7.12 (mm, 6H); GC/MS m/z 424 (M^+ + 2, 4), 423 (M^+ + 1, 27), 422 (M^+, 100).

4-[3-(1,2-Dihydro-8-methoxynaphthalen-4-yl)-*n*-propyl]-1-(2-methoxyphenyl)piperazine (14): eluted with $CHCl_3$/MeOH, 95:5; ^{1}H NMR ($CDCl_3$) 1.71–1.88 (mm, 2H), 2.13–2.27 (mm, 2H), 2.42–2.84 (mm, 10H), 3.12 (br t, 4H), 3.82 and 3.85 (2s, 6H, 2 CH_3), 5.88 (t, 1H, J = 4.5 Hz), 6.75–7.20 (mm, 7H); GC/MS m/z 394 (M^+ + 2, 4), 393 (M^+ + 1, 21), 392 (M^+, 100), 205 (25), 203 (22).

4-[3-(1,2-Dihydro-8-methoxynaphthalen-4-yl)-*n*-propyl]-1-(2-pyridyl)piperazine (15): ^{1}H NMR ($CDCl_3$) 1.67–1.86 (mm, 2H), 2.13–2.28 (mm, 2H), 2.40–2.63 (mm, 8H), 2.73 (t, 2H, J = 8 Hz, benzyl CH_2), 3.50–3.62 (mm, 4H), 3.82 (s, 3H), 5.87 (t, 1H, J = 4.5 Hz), 6.58–7.52 (mm, 6H), 8.16–8.23 (m, 1H, arom N=CH); GC/MS m/z 365 (M^+ + 2, 2), 364 (M^+ + 1, 14), 363 (M^+, 53), 256 (39), 244 (46), 121 (34), 107 (100), 79 (23), 78 (21), 72 (36).

4-[3-(1,2-Dihydro-8-methoxynaphthalen-4-yl)-*n*-propyl]-1-phenylpiperazine (16): ^{1}H NMR ($CDCl_3$) 1.68–1.87 (mm, 2H), 2.15–2.29 (mm, 2H), 2.42–2.55 (br t, 4H), 2.58–2.81 (mm, 6H), 3.15–3.29 (mm, 4H), 3.83 (s, 3H), 5.89 (t, 1H, J = 4.5 Hz), 6.75–7.35 (mm, 8H); GC/MS m/z 364 (M^+ + 2, 3), 363 (M^+ + 1, 25), 362 (M^+, 100), 175 (37), 173 (30), 132 (27).

1-(3-Chlorophenyl)-4-[3-(1,2-dihydro-8-methoxynaphthalen-4-yl)-*n*-propyl]piperazine (17): ^{1}H NMR ($CDCl_3$) 1.66–1.85 (mm, 2H), 2.13–2.28 (mm, 2H), 2.42–2.54 (mm, 4H, $CH_2CH_2CH_2N$), 2.54–2.65 (br t, 4H, $CH_2N(CH_2)_2$), 2.74 (t, 2H, J = 8 Hz, benzyl CH_2), 3.21 (br t, 4H), 3.83 (s, 3H), 5.88 (t, 1H, J = 4.6 Hz), 6.71–7.20 (mm, 7H); GC/MS m/z 400 (M^+ + 4, 1), 399 (M^+ + 3, 8), 398 (M^+ + 2, 34), 397 (M^+ + 1, 30), 396 (M^+, 100), 222 (24), 211 (21), 209 (78), 207 (32), 166 (35).

4-[3-(1,2-Dihydro-8-methoxynaphthalen-4-yl)-*n*-propyl]-1-[3-(trifluoromethyl)phenyl]piperazine (18): ^{1}H NMR ($CDCl_3$) 1.71–1.88 (mm, 2H), 2.14–2.28 (mm, 2H), 2.42–2.80 (mm, 10H), 3.21–3.33 (mm, 4H), 3.83 (s, 3H), 5.88 (t, 1H, J = 4.5 Hz), 6.75–7.38 (mm, 7H); GC/MS m/z 432 (M^+ + 2, 3), 431 (M^+ + 1, 19), 430 (M^+, 69), 256 (31), 243 (100), 241 (34), 200 (57), 172 (20).

Pharmacological Methods. 5-HT$_{1A}$ Binding Assay. The procedure used in the radioligand binding assay has been published in detail elsewhere.[30] Cerebral cortex from male Sprague–Dawley rats (180–220 g) was homogenized in 20 volumes of ice-cold Tris·HCl buffer (50 mM, pH 7.7 at 22 °C) with a Brinkmann Polytron (setting 5 for 15 s), and the homogenate was centrifuged at 50 000g for 10 min. The resulting pellet was then resuspended in the same buffer, incubated for 10 min at 37 °C, and centrifuged at 50 000g for 10 min. The final pellet was resuspended in 80 volumes of the Tris·HCl buffer containing 10 μM pargyline, 4 mM $CaCl_2$, and 0.1% ascorbate. To each assay tube were added the following: 0.1 mL of the drug dilution (0.1 mL of distilled water if no competing drug was added), 0.1 mL of [^{3}H]-8-hydroxy-2-(di-*n*-propylamino)tetralin ([^{3}H]-8-OH-DPAT) in buffer (containing Tris, $CaCl_2$, pargyline, and ascorbate) to achieve a final assay concentration of 0.1 nM, and 0.8 mL of resuspended membranes. The tubes were incubated for 30 min at 37 °C, and the incubations were 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]-8-OH-DPAT binding was defined as the difference between binding in the absence and presence of 5-HT (10 μM).

5-HT$_2$ Binding Assay. The radioligand assay was conducted essentially as reported elsewhere.[31] Frontal 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 (setting 5 for 15 s), and the homogenate was centrifuged at 50 000g for 10 min. The supernatant was discarded, and the pellet was resuspended and preincubated for 10 min at 37 °C. The pellet was washed twice and resuspended in 100 volumes of Tris·HCl buffer as described above. To each tube were added the following: 0.1 mL of the drug dilution (0.1 mL of water if no competing drug was added), 0.1 mL of [^{3}H]ketanserin in Tris·HCl buffer to achieve a final assay concentration of 0.35 nM, and 0.8 mL of resuspended membranes. The tubes were incubated for 15 min at 37 °C, and the incubations were 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]ketanserin binding was defined as the difference between binding in the absence or presence of methysergide (1 μM).

D-2 Dopaminergic Binding Assay. The binding assay for D-2 dopaminergic receptors was essentially as described by Creese et al.[32] 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 (setting 5 for 15 s); the homogenate was then centrifuged at 50 000g for 10 min. The supernatant was discarded and the pellet washed once. The final pellet was resuspended in 250 volumes of the Tris·HCl buffer descibed above containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, and 0.1% pargyline. Each assay tube contained 0.1 mL of the drug dilution, 0.1 mL of [^{3}H]spiroperidol to achieve a final concentration of 0.25 nM, 0.1 mL of ketaserin (400 nM) to saturate the 5-HT$_2$ receptors eventually labeled by the ligand, and 0.7 mL of resuspended membranes. The tubes were incubated for 15 min at 37 °C, and the incubations were terminated by vacuum filtration through Whatman GF/B filters. The filters were washed three 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]spiroperidol binding was defined as the difference between binding in the absence or presence of butaclamol (1 μM).

Behavioral Studies. The procedure used in the behavioral study is described in detail elsewhere.[33] Male Sprague–Dawley rats (200–250 g) were treated intraperitoneally with reserpine (1 mg/kg) 18 h before the test. For observation of behavior, the

animals were placed singly in clear plastic boxes (430- × 90- × 160-mm high) 30 min before administration of the compound under test. Observation sessions began 5 min after administration and were repeated every 5 min over a 30-min period. Flat body posture and forepaw treating were scored by a ranked intensity scale where: 0 = absent, 1 = equivocal, 2 = present, and 3 = intense behavior. The antagonist effects of the test compounds against the behaviors induced by a submaximal dose of 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT, 0.125 mg/kg sc) were evaluated by pretreating the animals with the compounds 30 min before administration of 8-OH-DPAT. The observer was unaware of the pretreatment received by each rat. Each score was summed over the six observation periods, and the ED_{50} was calculated by the Probit method.

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