1-Aryl-4-[(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)alkyl]piperazines and Their Analogues: Influence of the Stereochemistry of the Tetrahydronaphthalen-1-yl Nucleus on 5-HT_{1A} Receptor Affinity and Selectivity versus α_1 and D_2 Receptors. 5[1]

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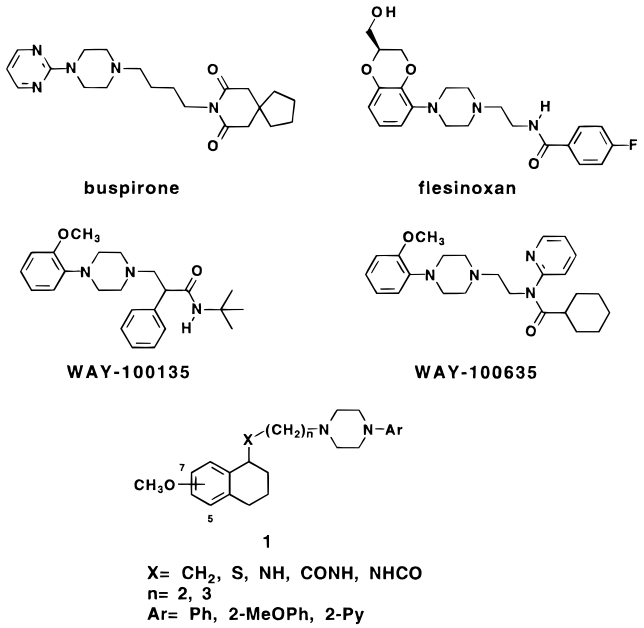
Some 1-aryl-4-[(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl]piperazines and their alkylamino and alkylamido analogues, previously studied as 5-HT_{1A} ligands, were prepared in enantiomerically pure form, and their absolute configuration was determined by chemical correlation or by chiroptical properties. They were evaluated for in vitro 5-HT_{1A}, D_2, and α_1 receptor affinity by radioligand binding assays, to study the influence of the chiral carbon atom of the tetrahydronaphthalene nucleus on the 5-HT_{1A} affinity and selectivity. Results indicated that, as regarding the 5-HT_{1A} receptor affinity, there was no difference in affinity between (−)- and (+)-enantiomers as well as the racemate of each compound. The stereochemistry, instead, influenced the selectivity: all (−)-enantiomers displayed affinity values higher than those of (+)-isomers at D_2 receptors, and conversely, all (+)-enantiomers displayed affinity values higher than those of (−)-isomers at α_1 receptors. As a result of this trend, it is not possible to predict the isomer with a better selectivity profile. However, compounds **(*S*)-(+)-2**, **(*S*)-(+)-4**, and **(*R*)-(+)-6** displayed high affinity for the 5-HT_{1A} receptor (IC_{50} values ranging between 7.0 and 2.3 nM) and good selectivity (≥250-fold) versus both D_2 and α_1 receptors. Furthermore, compounds **(*S*)-(+)-4** and **(*R*)-(−)-4** were submitted to the [^{35}S]GTPγS binding assay for a preliminary evaluation of their intrinsic activity on the 5-HT_{1A} receptor.

Serotonin (5-hydroxytryptamine, 5-HT) is an important neurotransmitter in the peripheral and central nervous system that mediates a wide variety of physiological responses by different receptors.[2−4] Among these receptors, the 5-HT_{1A} receptor subtype is the most studied, and its involvement in psychiatric disorders such as depression[5,6] and anxiety[7] is generally accepted. Long-chain arylpiperazines represent one of the most important classes of 5-HT_{1A} receptor ligands: buspirone, flesinoxan, WAY-100135, and WAY-100635 are the most relevant members of this class. These compounds bind at the 5-HT_{1A} receptor with good or high affinity, but their selectivity versus dopaminergic D_2 and α_1 adrenergic receptors is not always remarkable. Indeed, it is well-known that these three receptors are members of the superfamily of G-protein-coupled receptors, and despite their completely distinct pharmacology, they show common features on their binding site.

We recently reported structure−affinity relationship studies on a class of long-chain arylpiperazines of structure type **1**[8−10] with regards to the 5-HT_{1A} receptor affinity and selectivity versus D_2 and α_1 receptors. In particular we investigated the influence of the following features: (a) the nature of the aryl group on N-1 of the piperazine ring; (b) the presence or the absence of a heteroatom, an amide function, or a double bond in the intermediate alkyl chain and the length of the chain; (c) the position of the methoxy group on the tetralinyl nucleus. The obtained results indicated that only a few of the studied arylpiperazines (compounds **2**−**4**) displayed high 5-HT_{1A} binding affinity (IC_{50} < 1 nM) and also a good selectivity versus D_2 and α_1 receptors (≥100-fold). Before performing further structural modifications on this class of compounds to improve the 5-HT_{1A} affinity and particularly the selectivity, we thought it would be interesting to investigate the role of the asymmetric carbon atom of the tetralinyl moiety on the affinity and selectivity for 5-HT_{1A} receptors. We were encouraged to carry out this program by the interesting results reported for other 1-arylpiperazine compounds,



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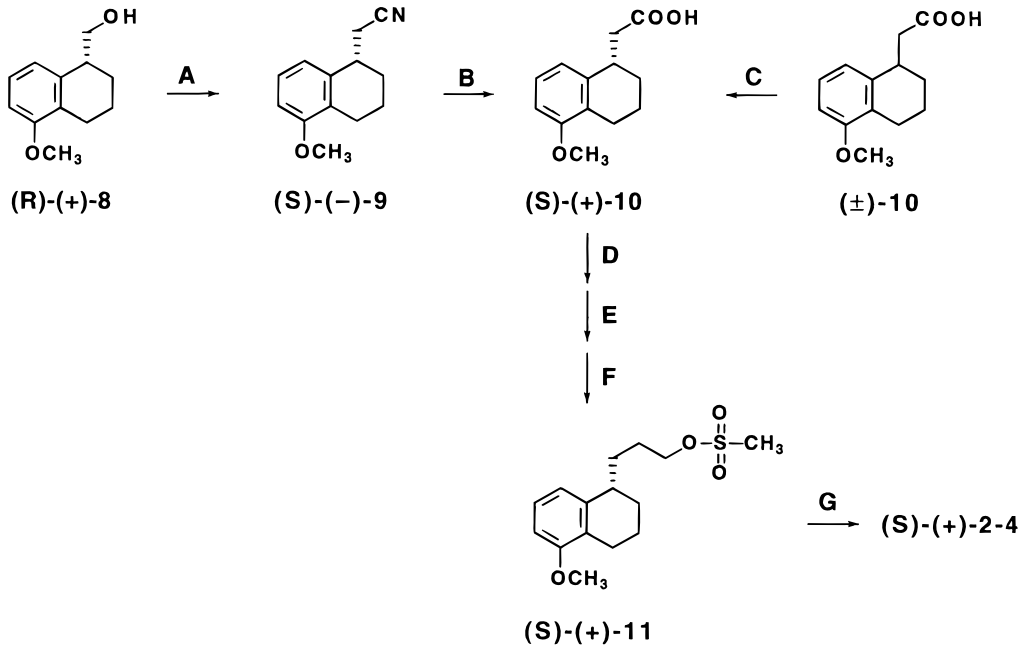
Scheme 1[a]



[a] Reagents: (A) (i) methanesulfonyl chloride, triethylamine, (ii) NaCN; (B) 50% H_2SO_4; (C) (i) (*S*)-(−)-1-phenylethylamine, (ii) 3 N HCl; (D) (i) $SOCl_2$, triethylamine, (ii) CH_2N_2, (iii) Ag^+, MeOH; (E) $LiAlH_4$; (F) methanesulfonyl chloride, triethylamine; (G) 1-arylpiperazines.

acting at the 5-HT_{1A} receptor, which present an asymmetric center in their structure (i.e., flesinoxan and WAY-100135). In particular, (*S*)-(+)-WAY-100135 displayed high stereoselectivity for the 5-HT_{1A} receptor, being markedly more active than the (*R*)-isomer in binding, functional, and behavioral assays.[11]

In the present study we report the synthesis, the assignment of the absolute configuration, and the binding assay on 5-HT_{1A}, D_2, and α_1 receptors of optically active form of compounds **2**−**7**, which were the most representative derivatives for each of the previously reported chemical classes.[8−10] Our aim is to find the structural features, stereochemistry included, that account for affinity and selectivity on the 5-HT_{1A} receptor in order to design highly selective 5-HT_{1A} receptor ligands.

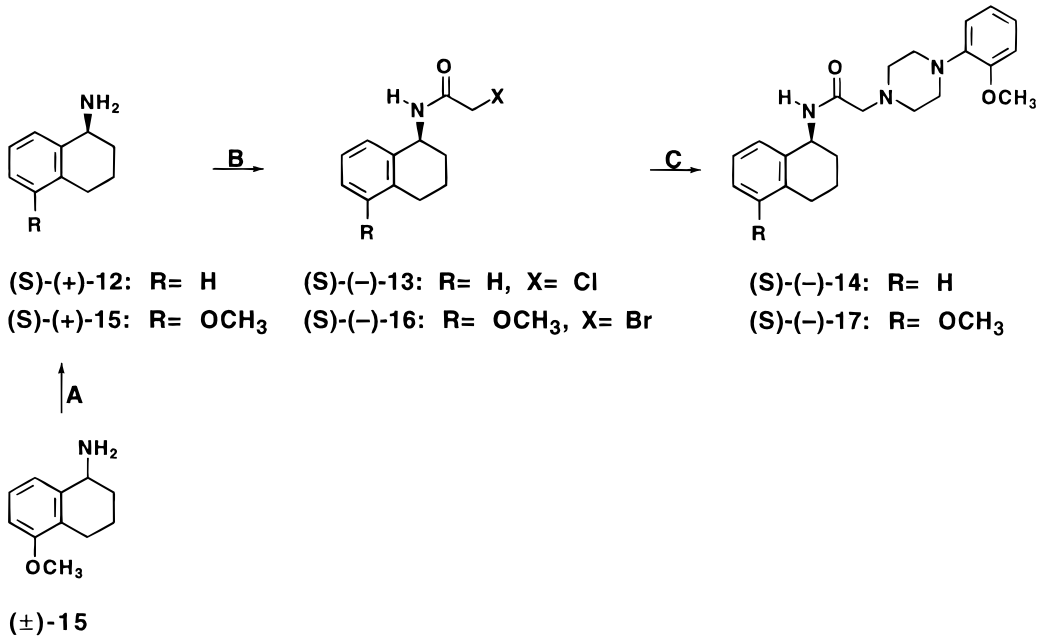
Chemistry

Several attempts to separate enantiomers of compounds **2**−**7** via fractional crystallization of their diastereomeric salts with optically active acids failed. Therefore, the synthesis of the target compounds was achieved starting from an easily accessible optically active intermediate. The synthesis of compounds **(*S*)-(+)-2**−**4** is depicted in Scheme 1. The absolute configuration of the key intermediate **(*S*)-(+)-10** was established by chemical correlation as follows: the optically active alcohol **(*R*)-(+)-8**[12] was activated for displacement as its mesylate ester and then displaced with NaCN to yield nitrile **(*S*)-(−)-9**; this compound was hydrolyzed to give (*S*)-(+)-5-methoxy-1,2,3,4-tetrahydro-1-naphthaleneacetic acid [**(*S*)-(+)-10**]. Because of the low yield and the moderate enantiomeric excess encountered, this synthetic pathway was not useful for preparative purposes, so acid **(*S*)-(+)-10** was obtained in good yield by fractional crystallization of its diastereomeric salt with (*S*)-(−)-1-phenylethylamine. The multistep sequence previously reported[13] afforded the mesylate derivative **(*S*)-(+)-11** which was reacted with the appropriate 1-arylpiperazine to give final compounds **(*S*)-(+)-2**−**4**. Starting from (*R*)-(−)-5-methoxy-1,2,3,4-tetrahydro-1-naphthaleneacetic acid [**(*R*)-(−)-10**], the same synthetic procedure gave compounds **(*R*)-(−)-2**−**4**.

The absolute configuration of the key intermediate **(+)-15** for the synthesis of tetrahydronaphthalenamine derivatives was unknown. We used the circular dichroism (CD) characteristics for its configurational assignment because the absolute configuration of (*S*)-(+)-1,2,3,4-tetrahydro-1-naphthalenamine [**(*S*)-(+)-12**] had been already established.[14] Unfortunately, amine **(*S*)-(+)-12** did not display the Cotton effect, so its derivatization was necessary (Scheme 2). Thus, amine **(*S*)-(+)-12** was transformed with chloroacetyl chloride into the derivative **(*S*)-(−)-13** which was reacted with 1-(2-methoxyphenyl)piperazine to give the derivative **(*S*)-(−)-14**. Similarly (*R*)-(−)-1,2,3,4-tetrahydro-1-naphthalenamine [**(*R*)-(−)-12**] gave derivative **(*R*)-(+)-14**. Racemic 5-methoxy-1,2,3,4-tetrahydro-1-naphthalenamine [**(±)-15**][15] was resolved by fractional crystallization of the diastereomeric salt with (*S*)-(+)-mandelic acid. Optically active amine **(+)-15** was transformed with bromoacetyl chloride into derivative **(−)-16**, and the latter compound was aminated with 1-(2-methoxyphenyl)piperazine to give compound **(−)-17**. Similarly the amine **(−)-15** furnished the amide **(+)-17**. Since both compounds **(*S*)-(−)-14** and **(−)-17** displayed a negative Cotton effect, it was stated that the absolute configuration of amine **(+)-15** was *S*.

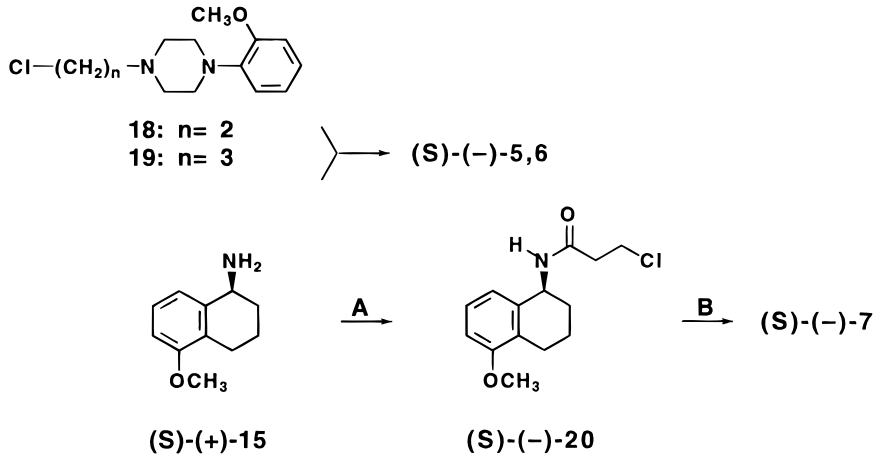
The synthesis of tetrahydronaphthalenamine derivatives **(*S*)-(−)-5**−**7** is reported in Scheme 3. The amine **(*S*)-(+)-15** was treated with chloro derivatives **18** and **19** to give the final amines **(*S*)-(−)-5** and **(*S*)-(−)-6**, respectively. To prepare the amide **(*S*)-(−)-7**, amine **(*S*)-(+)-15** was acylated with 3-chloropropionyl chloride to give chloro derivative **(*S*)-(−)-20**; the amination of the latter with 1-(2-methoxyphenyl)piperazine provided

Scheme 2[a]



[a] Reagents: (A) (i) (*S*)-(+)-mandelic acid, (ii) 5% NaOH; (B) haloacetyl chloride, $NaHCO_3$; (C) 1-(2-methoxyphenyl)piperazine.

Scheme 3[a]



[a] Reagents: (A) 3-chloropropionyl chloride, $NaHCO_3$; (B) 1-(2-methoxyphenyl)piperazine.

the target compound. Compounds **(*R*)-(+)-5**−**7** were prepared in the same way starting from amine **(*R*)-(−)-15**.

Pharmacology

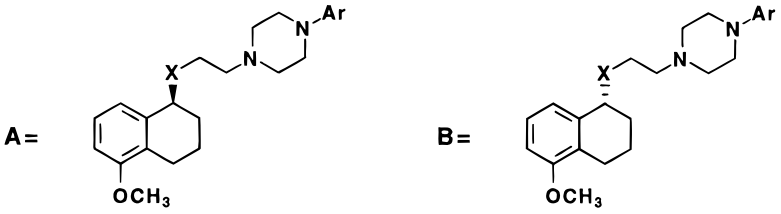
Target compounds in the form of hydrochloride salts (Table 1) were evaluated for in vitro affinity on serotonin 5-HT_{1A}, dopamine D_2, and adrenergic α_1 receptors by radioligand binding assays. The following specific radioligands and tissue sources were used: (a) serotonin 5-HT_{1A} receptors—[^{3}H]-8-OH-DPAT, rat hippocampal membranes; (b) dopamine D_2 receptors—[^{3}H]spiroperidol, rat striatal membranes; (c) α_1 adrenergic receptors-[^{3}H]-prazosin, rat brain cortex membranes. Concentrations required to inhibit 50% of radioligand specific binding (IC_{50}) were determined by using eight to nine different concentrations of the drug studied. Specific binding represents more than 80% of the total in all binding assays. The results were analyzed using the LIGAND program to determine IC_{50} values. A preliminary and qualitative evaluation of the intrinsic activity at human cloned 5-HT_{1A} receptors of compounds **(+)-4** and **(−)-4** was carried out using the [^{35}S]GTPγS binding method.[16]

Results and Discussion

Influence of the Stereochemistry in the Tetralin Moiety. First of all it should be noted that all (−)-isomers present the same relative position in the space of the four groups on the chiral center, but compounds **(−)-2**−**4** are designated as *R*, whereas compounds **(−)-5**−**7** are designated as *S*, according to the Cahn−Ingold−Prelog rule. Analogously, compounds **(+)-2**−**4** are designated as *S*, and compounds **(+)-5**−**7** are designated as *R*.

The results of an extended binding screening (Table 1) indicated that the chirality of the tetralin ring influenced the selectivity more than the affinity for 5-HT_{1A} receptors. In fact, the 5-HT_{1A} receptor affinity values presented no remarkable differences for racemates and (+)- and (−)-enantiomers. All the (−)-enantiomers, except compound **(−)-5**, showed lower affinity versus D_2 receptors than their (+)-isomers and

Table 1. Physical Properties and Binding Affinities



						IC_{50}, nM[a]			selectivity (IC_{50} ratio)	
compd	type	X	Ar	formula[b]	mp, °C	5-HT_{1A}	D_2	α_1	D_2/5-HT_{1A}	α_1/5-HT_{1A}
2[c]	racemic	CH_2	Ph			0.50	110	43	220	86
(*R*)-(−)-2	A	CH_2	Ph	$C_{24}H_{32}N_2O{\cdot}2HCl$	205−206	4.3	880	61	205	14
(*S*)-(+)-2	B	CH_2	Ph	$C_{24}H_{32}N_2O{\cdot}2HCl$	210−213	2.4	610	950	254	396
3[c]	racemic	CH_2	2-MeOPh			0.77	18	6.5	23	8
(*R*)-(−)-3	A	CH_2	2-MeOPh	$C_{25}H_{34}N_2O_2{\cdot}2HCl$	240−242	1.6	150	0.8	94	0.5
(*S*)-(+)-3	B	CH_2	2-MeOPh	$C_{25}H_{34}N_2O_2{\cdot}2HCl{\cdot}{}^1/_2H_2O$	240−246	1.3	38	33	29	25
4[c]	racemic	CH_2	2-Py			0.54	140	66	259	122
(*R*)-(−)-4	A	CH_2	2-Py	$C_{23}H_{31}N_3O{\cdot}2HCl{\cdot}H_2O$	157−163	4.5	880	85	196	19
(*S*)-(+)-4	B	CH_2	2-Py	$C_{23}H_{31}N_3O{\cdot}2HCl$	166−173	2.3	600	580	261	252
5[c]	racemic	NH	2-MeOPh			7.7	380	220	49	29
(*R*)-(+)-5	B	NH	2-MeOPh	$C_{24}H_{33}N_3O_2{\cdot}3HCl{\cdot}{}^1/_3H_2O$	178−179	10	3200	1000	320	100
(*S*)-(−)-5	A	NH	2-MeOPh	$C_{24}H_{33}N_3O_2{\cdot}3HCl{\cdot}H_2O$	205−207	7	650	228	93	33
6[c]	racemic	$NHCH_2$	2-MeOPh			10	1060	881	106	88
(*R*)-(+)-6	B	$NHCH_2$	2-MeOPh	$C_{25}H_{35}N_3O_2{\cdot}3HCl{\cdot}{}^1/_3H_2O$	164−165	7	1900	1700	271	243
(*S*)-(−)-6	A	$NHCH_2$	2-MeOPh	$C_{25}H_{35}N_3O_2{\cdot}3HCl{\cdot}H_2O$	155−157	34	2300	649	68	19
7[c]	racemic	NHCO	2-MeOPh			38	761	153	20	4
(*R*)-(+)-7	B	NHCO	2-MeOPh	$C_{25}H_{33}N_3O_3{\cdot}2HCl{\cdot}H_2O$	192−193	320	870	770	3	2
(*S*)-(−)-7	A	NHCO	2-MeOPh	$C_{25}H_{33}N_3O_3{\cdot}2HCl{\cdot}{}^1/_3H_2O$	187−189	89	2600	240	29	3
8-OH-DPAT						2.5				
buspirone						50				
spiroperidol							0.06			
phentolamine								12		

[a] Data are the mean of three independent determinations (samples in triplicate) each with SEM < 10%. [b] Analyses for C,H,N; results were within ±0.4% of the theoretical values for the formulas given. [c] Formerly published data.[10]

racemates. Conversely, considering α_1 receptors the trend was opposite since all the (+)-enantiomers presented lower affinity than their (−)-isomers and racemates. Consequently, because of the opposite trend of the two enantiomers regarding D_2 and α_1 receptor affinity, it is impossible to predict the isomer with better selectivity, although (+)-enantiomers **(+)-2**, **(+)-4**, and **(+)-6** displayed selectivity greater than 250-fold versus both α_1 and D_2. Among these compounds, **(+)-4** distinguished itself for its 5-HT_{1A} receptor affinity and selectivity, and for this reason it was submitted to a preliminary and qualitative evaluation of its intrinsic activity using the [^{35}S]GTPγS binding assay method. In this assay the agonist 8-OH-DPAT (10 nM) produced about 100% increment of [^{35}S]GTPγS basal level, whereas compound **(+)-4** did not increase the basal level of [^{35}S]-GTPγS, displaying the same behavior as WAY-100635[17] in this experimental condition. Compound **(−)-4** underwent the same biochemical evaluation showing the same behavior as the (+)-isomer. These results indicated that the two enantiomers of compound **4** did not display 5-HT_{1A} agonistic property in this preliminary binding assay in the range of 10^{-4}−10^{-10} M.

Experimental Section

Chemistry. Column chromatography was performed with 1:30 ICN silica gel 60 Å (63−200 μm) as the stationary phase. Melting points were determined in open capillaries on a Gallenkamp electrothermal apparatus. Elemental analyses (C,H,N) were performed on a Carlo Erba model 1106 analyzer; the analytical results were within ±0.4% of the theoretical values for the formula given. Optical rotation was measured with Perkin-Elmer 241 MC polarimeter. CD curves were measured in MeOH with a Cary 61 dichrograph using a 10-mm cell. High-performance liquid chromatography (HPLC) was performed on a Waters Associates liquid chromatograph model 600 equipped with a U6K model injector and a 481 model variable wavelength detector (λ = 254 nm). ^{1}H NMR spectra were recorded, using $CDCl_3$ as solvent, on a Varian EM-390 (TMS as internal standard) or a Bruker AM 300 WB instrument (where indicated 300 MHz); 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 in parentheses, are herein reported. All spectra were in accordance with the assigned structures. Spectral properties of compounds **(*S*)-** and **(*R*)-2**−**7**, **(*S*)-** and **(*R*)-10**, **(*S*)-** and **(*R*)-16**, and **(*S*)-** and **(*R*)-20** were fully consistent with those already reported for their racemic mixture.[9,10,13]

(*S*)-(−)-5-Methoxy-1,2,3,4-tetrahydro-1-naphthaleneacetonitrile [(*S*)-(−)-9]. Methanesulfonyl chloride (1.3 mL, 16.8 mmol) was added to a cooled solution of (*R*)-(+)-5-methoxy-1,2,3,4-tetrahydro-1-naphthalenemethanol [**(*R*)-(+)-8**] (1.52 g, 7.9 mmol) and triethylamine (4.2 mL, 30.1 mmol) in CH_2Cl_2. The resulting mixture was stirred for 1 h at room temperature; then it was washed with ice-cold H_2O, with 3 N HCl, and finally with saturated aqueous $NaHCO_3$. The separated organic layer was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The crude residue was chromatographed (CH_2Cl_2 as eluent) to give 1.84 g (86% yield) of mesylate derivative: $[\alpha]^{20}_D = +11.9°$ (*c* = 3.4, $CHCl_3$). The mesylate (1.82 g, 6.7 mmol) was added to a mixture of NaCN (0.96 g, 19.6 mmol) and 20 mL of 90% ethanol. The mixture was refluxed for 7 h and then concentrated under reduced pressure. The residue was partioned between 10% aqueous Na_2CO_3 and CH_2Cl_2. The separated organic layer was dried over Na_2SO_4 and concentrated in vacuo. The desired compound was chromatographed with petroleum ether/CH_2Cl_2, 1:1, as eluent (0.81 g, 60% yield): $[\alpha]^{20}_D = -21.0°$ (*c* = 1.95, $CHCl_3$);

^{1}H NMR 1.65−2.05 (m, 4H, *endo* CH_2), 2.50−2.80 (m, 4H, CH_2-CN, benzyl CH_2), 3.05−3.30 (m, 1H, CH), 3.80 (s, 3H, CH_3), 6.65−7.30 (m, 3H, aromatic); GC/MS *m/z* 202 ($M^+ + 1$, 4), 201 (M^+, 30), 161 (100), 160 (21), 115 (22).

(*S*)-(+)-5-Methoxy-1,2,3,4-tetrahydro-1-naphthaleneacetic Acid [(*S*)-(+)-10]. A mixture of nitrile **(*S*)-(−)-9** (0.80 g. 4.0 mmol) and 40 mL of 50% H_2SO_4 was refluxed for 4 h. Then the cooled mixture was extracted with $CHCl_3$ (2 × 40 mL). The collected organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was chromatographed ($CHCl_3$ as eluent) to give 0.18 g of the expected acid (20% yield). HPLC analyses on a Daicel Chiralcel OD column using *n*-hexane/2-propanol/trifluoroacetic acid (98:2:0.1), flow rate 1.0 mL/min, indicated that the sample was 70% ee of the acid **(*S*)-10**. This acid displayed the same retention time of a pure sample of **(−)-10** obtained by fractional crystallization of its diastereomeric salt with (*S*)-(−)-1-phenylethylamine.

(*R*)- and (*S*)-4-[3-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl]-1-arylpiperazine Derivatives 2−4. General Procedure. A stirred suspension of the appropriate mesylate (2.0 mmol), 1-arylpiperazine (4.0 mmol), and K_2CO_3 (2.0 mmol) in acetonitrile was refluxed overnight. After cooling, the mixture was evaporated to dryness and H_2O 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 (CH_2Cl_2/MeOH, 19:1, as eluent) to yield target compounds as pale-yellow oils. All compounds displayed ee ≥ 98% (HPLC analysis on a Daicel Chiralcel OD using *n*-hexane/ethanol/diethylamine, 9:1:0.1, as the mobile phase, flow rate 0.8 mL/min).

(*S*)-(+)-4-[3-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl]-1-phenylpiperazine [(*S*)-(+)-2]. Starting from (*S*)-(+)-3-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl methanesulfonate [**(*S*)-(+)-11**] and 1-phenylpiperazine, the title compound was obtained in 92% yield: $[\alpha]^{20}_D$ = +8.3° (*c* = 1.3, $CHCl_3$).

(*S*)-(+)-1-(2-Methoxyphenyl)-4-[3-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl]piperazine [(*S*)-(+)-3]. Starting from mesylate **(*S*)-(+)-11** and 1-(2-methoxyphenyl)piperazine, the title compound was obtained in 85% yield: $[\alpha]^{20}_D$ = +5.8° (*c* = 1.6, $CHCl_3$).

(*S*)-(+)-4-[3-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl]-1-(2-pyridyl)piperazine [(*S*)-(+)-4]. Starting from mesylate **(*S*)-(+)-11** and 1-(2-pyridyl)piperazine, the title compound was obtained in 80% yield: $[\alpha]^{20}_D$ = +9.6° (*c* = 1.5, $CHCl_3$).

(*R*)-(−)-4-[3-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl]-1-phenylpiperazine [(*R*)-(−)-2]. Starting from (*R*)-(−)-3-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl methanesulfonate [**(*R*)-(−)-11**] and 1-phenylpiperazine, the title compound was obtained in 82% yield: $[\alpha]^{20}_D$ = −8.6° (*c* = 1.2, $CHCl_3$).

(*R*)-(−)-1-(2-Methoxyphenyl)-4-[3-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl]piperazine [(*R*)-(−)-3]. Starting from mesylate **(*R*)-(−)-11** and 1-(2-methoxyphenyl)piperazine, the title compound was obtained in 91% yield: $[\alpha]^{20}_D$ = −5.5° (*c* = 1.85, $CHCl_3$).

(*R*)-(−)-4-[3-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl]-1-(2-pyridyl)piperazine [(*R*)-(−)-4]. Starting from mesylate **(*R*)-(−)-11** and 1-(2-pyridyl)piperazine, the title compound was obtained in 79% yield: $[\alpha]^{20}_D$ = −9.7° (*c* = 1.5, $CHCl_3$).

(*S*)-(−)-*N*-(1,2,3,4-Tetrahydronaphthalen-1-yl)chloroacetamide [(*S*)-(−)-13]. Chloroacetyl chloride (0.23 mL, 2.9 mmol) in CH_2Cl_2 was added dropwise to a stirred mixture of the amine **(*S*)-(+)-12** (0.33 g, 2.2 mmol) and $NaHCO_3$ (0.25 g, 3.0 mmol) in CH_2Cl_2, under cooling. The reaction mixture was stirred for 1 h, and then it was washed with brine. The separated organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. The crude residue was chromatographed with CH_2Cl_2/ethyl acetate, 4:1, to give compound **(*S*)-(−)-13** as a white semisolid in nearly quantitative yield: $[\alpha]^{20}_D$ = −77.2° (*c* = 1.0, CH_3OH); ^{1}H NMR 1.75−2.15 (m, 4H, *endo* CH_2CH_2), 2.65−3.00 (m, 2H, benzyl CH_2), 4.05 (s, 2H, CH_2Cl), 5.00−5.30 (m, 1H, CH), 7.00−7.30 (m, 4H, aromatic), 6.80 (br s, 1H, NH); GC/MS *m/z* 225 ($M^+ + 2$, 1), 224 ($M^+ + 1$, 1), 223 (M^+, 4), 188 (23), 146 (37), 131 (21), 130 (100), 129 (43).

(*R*)-(+)-*N*-(1,2,3,4-Tetrahydronaphthalen-1-yl)chloroacetamide [(*R*)-(+)-13]. As above, starting from (*R*)-(−)-1,2,3,4-tetrahydronaphthalenamine **[(*R*)-(−)-12]** (0.34 g, 2.3 mmol) and chloroacetyl chloride (0.19 mL, 2.4 mmol), compound **(*R*)-(+)-13** was obtained as a white semisolid in 93% yield: $[\alpha]^{20}_D$ = +71.4° (*c* = 3.0, CH_3OH). ^{1}H NMR and GC/MS spectra of this compound were identical to those of its enantiomer.

(*S*)-(−)-4-(2-Methoxyphenyl)-*N*-(1,2,3,4-tetrahydronaphthalen-1-yl)-1-piperazinoacetamide [(*S*)-(−)-14]. The derivative **(*S*)-(−)-13** (0.43 g, 1.9 mmol) was refluxed overnight with 1-(2-methoxyphenyl)piperazine (0.73 g, 3.8 mmol) and a slight excess of $NaHCO_3$ in acetonitrile. After cooling, the mixture was concentrated under reduced pressure, and the residue was taken up with water and extracted with $CHCl_3$. The chloroform phase was dried over Na_2SO_4, the solvent was evaporated, and the crude residue was chromatographed (CH_2Cl_2/MeOH, 19:1, as eluent) to give **(*S*)-(−)-14** as a white semisolid (0.60 g, 84% yield): $[\alpha]^{20}_D$ = −13.8° (*c* = 2.35, $CHCl_3$). HPLC analysis on a Daicel Chiralcel OD using *n*-hexane/ethanol/diethylamine (9:1:0.1) as the mobile phase (flow rate 0.8 mL/min) indicated that the material was >98% ee: ^{1}H NMR (300 MHz) 1.68−1.88 and 2.04−2.11 (m, 4H, *endo* CH_2-CH_2), 2.70−2.88 [m, 6H, benzyl CH_2, $CH_2N(CH_2)_2$], 3.02 [br s, 4H, $(CH_2)_2NAr$], 3.13 [d, 2H, *J* = 3.0 Hz, $CH_2N(CH_2)_2$], 3.84 (s, 3H, CH_3), 5.17−5.24 (m, 1H, CH), 6.82−7.25 (m, 8H, aromatic), 7.42 (br d, 1H, NH, D_2O exchanged); GC/MS *m/z* 381 ($M^+ + 2$, 1), 380 ($M^+ + 1$, 7), 379 (M^+, 26), 205 (100), 190 (26).

(*R*)-(+)-4-(2-Methoxyphenyl)-*N*-(1,2,3,4-tetrahydronaphthalen-1-yl)piperazinoacetamide [(*R*)-(+)-14]. Title compound was prepared as above starting from derivative **(*R*)-(+)-13** (0.41 g, 1.8 mmol) and 1-(2-methoxyphenyl)piperazine (0.77 g, 4.0 mmol) in 84% yield: $[\alpha]^{20}_D$ = +13.3° (*c* = 2.2, $CHCl_3$). HPLC analysis on a Daicel Chiralcel OD using *n*-hexane/ethanol/diethylamine (9:1:0.1) as the mobile phase (flow rate 0.8 mL/min) indicated the material was >98% ee. ^{1}H NMR and GC/MS spectra of this compound were identical to those of its enantiomer.

Resolution of 5-Methoxy-1,2,3,4-tetrahydro-1-naphthalenamine [(±)-15]. To a solution of racemic amine **(±)-15** (7.62 g, 43.0 mmol) and (*S*)-(+)-mandelic acid (3.27 g, 21.5 mmol) in MeOH (60 mL) was added diethyl ether (30 mL). The solution was allowed to cool in the refrigerator until crystallization occurred. The crystals were filtered and recrystallized from MeOH/diethyl ether three times to afford 2.80 g of (+)-mandelate salt. The salt was dissolved in water, the ice-cooled solution made basic with 2 N NaOH, and the resulting mixture extracted with CH_2Cl_2 (40 mL). The organic phase was dried over Na_2SO_4, and the solvent was evaporated to dryness to give 1.48 g of pure **(+)-15**: $[\alpha]^{20}_D$ = +15.7° (*c* = 12.8, MeOH). HPLC analyses on a Daicel Chiralcel OD-R column using MeOH/H_2O (9:1) as the mobile phase (flow rate 0.4 mL/min) indicated the material was >98% ee. The collected mother liquors containing the (−)-isomer of **15** were evaporated, dissolved in 40 mL of MeOH, and treated with (*R*)-(−)-mandelic acid (3.27 g, 21.5 mmol). The solution was treated with 30 mL of diethyl ether and kept in the refrigerator overnight. The crystals were filtered off and recrystallized from MeOH/diethyl ether three times to afford 2.50 g of (−)-mandelate salt which was treated as described above for its (+)-isomer to give 1.25 g of amine **(−)-15**: $[\alpha]^{20}_D$ = −11.0° (*c* = 10.6, MeOH). HPLC analyses in the above condition indicated that the material was >98% ee.

(*S*)-(−)-*N*-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)bromoacetamide [S−(−)-16]. This compound was obtained as a semisolid in nearly quantitative yield from the amine **(*S*)-(+)-15** (0.18 g, 1.1 mmol) and bromoacetyl chloride

(0.12 mL, 1.4 mmol) using the same reported procedure for the synthesis of compound **(*S*)-(−)-13**: $[\alpha]^{20}_D = -27.3°$ (c = 1.0, $CHCl_3$).

(*R*)-(+)-*N*-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)bromoacetamide [(*R*)-(+)-16]. As above, starting from amine **(*R*)-(−)-15**, compound **(*R*)-(+)-16** was obtained in the same yield as a white semisolid: $[\alpha]^{20}_D = +31.2°$ (c = 1.0, $CHCl_3$).

(*S*)-(−)-4-(2-Methoxyphenyl)-*N*-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-1-piperazinoacetamide [(*S*)-(−)-17]. Using the procedure reported for the synthesis of compound **(*S*)-(−)-14**, title compound was obtained from **(*S*)-(−)-16** and 1-(2-methoxyphenyl)piperazine in 84% yield as a white semisolid: $[\alpha]^{20}_D = -24.8°$ (c = 1.0, $CHCl_3$). HPLC analysis on a Daicel Chiralcel OD using *n*-hexane/ethanol/diethylamine (9:1:0.1) as the mobile phase (flow rate 0.8 mL/min) indicated the material was >98% ee.

(*R*)-(+)-4-(2-Methoxyphenyl)-*N*-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-1-piperazinoacetamide [(*R*)-(+)-17]. As above, title compound was prepared from **(*R*)-(+)-16** and 1-(2-methoxyphenyl)piperazine in 85% yield as a white semisolid: $[\alpha]^{20}_D = +24.1°$ (c = 1.0, $CHCl_3$). HPLC analysis on a Daicel Chiralcel OD using *n*-hexane/ethanol/diethylamine (9:1:0.1) as the mobile phase (flow rate 0.8 mL/min) indicated the material was >98% ee.

(*R*)- and (*S*)-1-(2-Methoxyphenyl)-4-[*N*-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)aminoalkyl]piperazine Derivatives. General Procedure. A stirred suspension of the appropriate chloroalkyl derivative (4.4 mmol), the appropriate amine (4.0 mmol), and a slight excess of K_2CO_3 in acetonitrile was refluxed overnight. After cooling, the mixture was evaporated to dryness and H_2O 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 (CH_2Cl_2/MeOH, 19:1, as eluent) to yield pure target compound as pale-yellow oil. All compounds displayed ee ≥ 98% (HPLC analysis on a Daicel Chiralcel OD using *n*-hexane/2-propanol/diethylamine, 8:2:0.1, as the mobile phase, flow rate 0.8 mL/min).

(*S*)-(−)-1-(2-Methoxyphenyl)-4-[*N*-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-2-aminoethyl]piperazine [(*S*)-(−)-5]. Starting from the amine **S−(+)-15** and 4-(2-chloroethyl)-1-(2-methoxyphenyl)piperazine (**18**),[18] title compound was obtained in 34% yield: $[\alpha]^{20}_D = -10.6°$ (c = 1.0, $CHCl_3$).

(*R*)-(+)-1-(2-Methoxyphenyl)-4-[*N*-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-2-aminoethyl]piperazine [(*R*)-(+)-5]. Starting from the amine **(*R*)-(−)-15** and derivative **18**, title compound was obtained in 34% yield: $[\alpha]^{20}_D = +14.1°$ (c = 38.0, $CHCl_3$).

(*S*)-(−)-1-(2-Methoxyphenyl)-4-[*N*-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3-amino-*n*-propyl]piperazine [(*S*)-(−)-6]. Starting from the amine **(*S*)-(+)-15** and 4-(3-chloropropyl)-1-(2-methoxyphenyl)piperazine (**19**),[19] title compound was obtained in 41% yield: $[\alpha]^{20}_D = -12.0$ (c = 1.1, $CHCl_3$).

(*R*)-(+)-1-(2-Methoxyphenyl)-4-[*N*-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3-amino-*n*-propyl]piperazine [(*R*)-(+)-6]. Starting from the amine **(*R*)-(−)-15** and compound **19**, title compound was obtained in 35% yield: $[\alpha]^{20}_D = +6.8°$ (c = 1.0, $CHCl_3$).

(*S*)-(−)-*N*-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3-chloropropanamide [(*S*)-(−)-20]. As for compound **(*S*)-(−)-13**, title compound was prepared from the amine **(*S*)-(+)-15** (2.50 g, 14.1 mmol) and 3-chloropropionyl chloride (1.7 mL, 18.3 mmol) in nearly quantitative yield: $[\alpha]^{20}_D = -77.9°$ (c = 1.0, $CHCl_3$).

(*R*)-(+)-*N*-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3-chloropropanamide [(*R*)-(+)-20]. As above, starting from amine **(*R*)-(−)-15**, title compound was obtained in 81% yield: $[\alpha]^{20}_D = +77.7°$(c = 1.0, $CHCl_3$).

(*S*)-(−)-*N*-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-4-(2-methoxyphenyl)-1-piperazinopropanamide [(*S*)-(−)-7]. This compound was obtained from **(*S*)-(−)-20** (0.74 g, 2.8 mmol) and 1-(2-methoxyphenyl)piperazine (1.08 g, 5.6 mmol) as a white semisolid (1.00 g, 86% yield), as for compound **(*S*)-(−)-14**: $[\alpha]^{20}_D = -60.0°$ (c = 1.0, $CHCl_3$). HPLC analysis on a Daicel Chiralcel OD using *n*-hexane/ethanol/diethylamine (8:2:0.1) as the mobile phase (flow rate 0.8 mL/min) indicated the material was >98% ee.

(*R*)-(+)-*N*-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-4-(2-methoxyphenyl)-1-piperazinopropanamide [(*R*)-(+)-7]. As above, starting from the amide **(*R*)-(+)-20**, compound **(*R*)-(+)-7** was obtained in 81% yield: $[\alpha]^{20}_D = +58.5°$ (c = 1.0, $CHCl_3$). HPLC analysis on a Daicel Chiralcel OD using *n*-hexane/ethanol/diethylamine (8:2:0.1) as the mobile phase (flow rate 0.8 mL/min) indicated the material was >98% ee.

Hydrochloride Salts. General Procedure. The hydrochloride salts were prepared by adding an HCl ethereal solution to a methanolic solution of amine. All salts were recrystallized from MeOH/Et_2O except for compounds **(*R*)-(+)-6** and **(*S*)-(−)-6** which were recrystallized from CH_2Cl_2/Et_2O. They were obtained as white to sand-yellow crystals or crystalline powders. Crystallization formulas and melting points are listed in Table 1.

Pharmacological Methods. 1. 5-HT_{1A} Serotonergic Binding Assay. Standard receptor binding methods were used to label 5-HT_{1A} receptors using [^{3}H]-8-OH-DPAT as previously described.[20]

2. D_2 Dopaminergic Binding Assay. Standard receptor binding methods were used to label D_2 receptors using [^{3}H]-spiroperidol as previously described.[20]

3. α_1 Adrenergic Binding Assay. Standard receptor binding methods were used to label α_1 receptors using [^{3}H]-prazosin as previously described.[20]

4. [^{35}S]GTPγS Binding Assay. This assay was performed according to Lazareno et al.[21] with minor modifications. Each assay tube contained in a total volume of 1 mL: incubation buffer (50 mM Tris·HCl, 5 mM $MgCl_2$, 100 mM NaCl, GDP 2 mM, pH 7.4), 8-OH-DPAT or compounds **(+)-4** and **(−)-4** or WAY-100635 with different concentrations (10^{-4}-10^{-10} M), 0.1 nM [^{35}S]GTPγS, and 1 unit of G-protein-coupled serotonergic 5-HT_{1A} receptor (human clone expressed in CHO cells; manufactured for NEN Life Science Products by BioSignal Inc., Montreal, Canada). The reaction was carried out for 30 min at 27 °C. The solution was filtered on Whatman glass fiber GF/A filters and washed two times with 2 mL of 50 mM Tris·HCl, pH 7.4. The nonspecific binding was determined with 10 mM GTPγS. The stimulation by agonist was calculated as the percentage increase above basal level (dpm agonist − dpm no agonist/dpm no agonist × 100).

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