Oxygen Isosteric Derivatives of 3-(3-Hydroxyphenyl)-*N*-*n*-propylpiperidine

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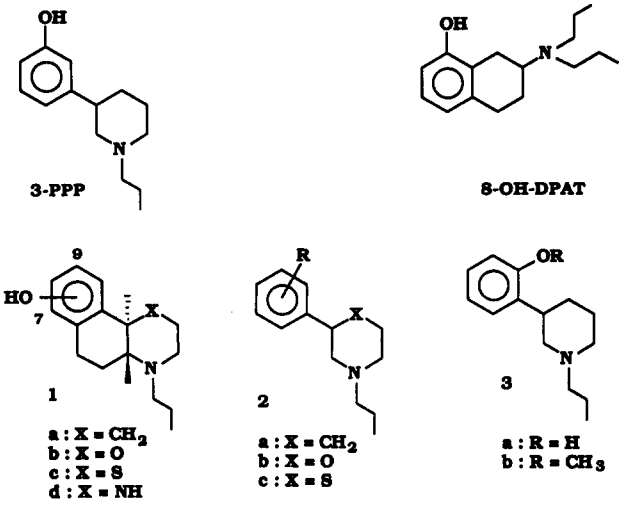
Some substituted 3-phenylmorpholines (**10a–e,j,k**) and 3-thienylmorpholines (**10f,g**), isosteres of 3-(3-hydroxyphenyl)-*N*-*n*-propylpiperidine (3-PPP), were prepared and submitted to binding assays on D-2 dopaminergic and 5-HT_1 and 5-HT_2 serotonergic receptors, in comparison with 3-PPP and its analogue **3a,b**. The results show the loss of D-2 affinity for all morpholines, while a certain activity was still observable for piperidine derivatives. Regarding the serotonergic affinity, only chloro and methoxy derivatives (**10a–d**) were moderately active on the 5-HT_{1A} receptor, either when the substituent was in the C-2 or C-3 position, whereas no tested compounds showed affinity toward the 5-HT_2 receptor.

In the last years we have been interested in the synthesis and pharmacological activity of some tricyclic angular compounds, **1**, which are rigid dopamine (DA) congeners.

In particular we previously prepared benzoquinoxalines **1d** and naphthothiazines **1c**, in which the saturated rings are trans-fused and the hydroxyl group is on the C-7 or on the C-9 position.[1] Binding assays in order to find the more active compound between enantiomeric forms indicated that the 9-OH **1c** derivative, with 4a*R*, 10b*R* chirality, possessed the higher value of affinity on D-2 receptors.[2] This behavior was observed by other authors[3] for the naphthoxazines **1b**, where the most D-2 active compound is the 9-OH derivative which has the same chirality as 9-OH **1c**.

These results indicate that the presence of an oxygen or sulfur atom in compounds **1b,c** does not compromise the D-2 affinity which is present in the corresponding tricyclic benzoquinolines **1a**, other dopaminergic agonists previously studied by Cannon.[4]



Besides these DA tricyclic congeners, **1a–d**, the DA semirigid bicyclic structure of the 3-(3-hydroxyphenyl)-*N*-*n*-propylpiperidine (3-PPP) was found to be highly selective for presynaptic and postsynaptic brain DA receptors.[5]

In this paper we investigated, similarly to the tricyclic series **1a,b**, the influence on D-2 activity in morpholine derivatives **2b**, obtained by replacing the C-4 of 3-PPP piperidine ring with an oxygen atom; the 3-PPP analogs containing sulfur in the same position (**2c**) were found completely inactive on the dopaminergic system by other authors.[6] Our aim was also to study the influence of the position of the OH group on the benzene ring in structures **2b** seeing that in 2-aminotetralins (ADTN) the DA activity disappears simply by changing the position of the hydroxyl group from C-5 or C-7 to C-8 on the benzene ring and that the obtained 8-OH-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) is selectively active on 5-HT_{1A} receptors.[7] Therefore we considered the affinity on the serotonergic system, too.

Furthermore in this work, for the morpholine derivatives **2b**, we studied the pharmacological effects when replacing the OH group with other substituents as well as the effect of the phenol moiety replacement with an heterocyclic bioisostere,[8] since the clinical utility of 3-PPP, e.g. as antischizophrenic agent, is limited by a relatively low oral bioavailability and by a short duration of action,[9] due to

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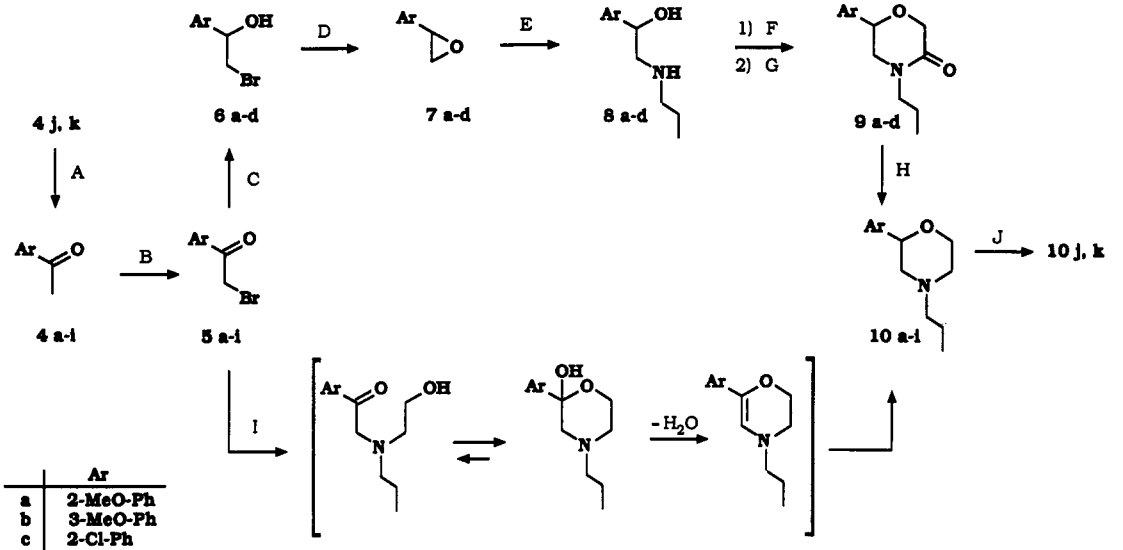
Scheme I



	Ar
a	2-MeO-Ph
b	3-MeO-Ph
c	2-Cl-Ph
d	3-Cl-Ph
e	3-NO_2
f	2-thienyl
g	3-thienyl
h	2-BzO-Ph
i	3-BzO-Ph
j	2-OH-Ph
k	3-OH-Ph

Reagents:

(A) BzCl, KOH, EtOH; (B) Br_2, Et_2O or benzene; (C) $NaBH_4$, dioxane/H_2O; (D) KOH, Et_2O/H_2O; (E) n-$PrNH_2$, neat; (F) $ClCOCH_2Br$, NaOH, CH_2Cl_2/H_2O; (G) KOH, iso-PrOH; (H) $LiAlH_4$, THF; (I) $OH(CH_2)_2NH(CH_2)_2CH_3$, HCOOH; (J) H_2, 10%Pd/C;

the presence of the phenol moiety. The synthesized compounds are listed in Scheme I; moreover, in order to outline a more complete comparison of the pharmacological results, 3-(2-hydroxyphenyl)- (**3a**) and 3-(2-methoxyphenyl)-4-*n*-propylpiperidine (**3b**) were prepared[10] and tested together with (*S*)-(−)-3-PPP.

Chemistry

The compounds **4a–g,j,k** and **5a,b** are commercially available.

Two different methods were used to obtain arylmorpholines **10a–i**, starting from corresponding arylketones **4a–i** and by subsequent α-bromination to compound **5a–i**, as shown in Scheme I.

The first one involved carbonyl reduction by $NaBH_4$ to the bromohydrins **6a–d** and oxirane ring closure in alkaline medium. Epoxides **7a–d** were reacted with *N*-*n*-propylamine to yield amino alcohols **8a–d**, which were cyclized to morpholinones **9a–d**, via *N*-bromoacetyl derivatives. Final compounds **10a–d** were achieved by reduction with $LiAlH_4$.

However by this synthetic route some of the final compounds and intermediates were obtained only in very poor yield.

Alternatively, one-pot reaction[11] on α-bromoketones **5e–i** with 2-(propylamino)ethanol and formic acid, was performed to give mixtures from which products **10e–i** were achieved by flash column chromatography.

Attempts to obtain (hydroxyphenyl)morpholines **10j,k** from methoxy derivatives **10a,b** by cleavage with HBr or BBr_3 failed; therefore corresponding starting products **4j,k** were previously benzylated to compounds **4h,i**.

Compounds **10j,k** were then prepared by hydrogenolysis of the corresponding benzyl derivatives **10h,i**. Both methods gave unsatisfactory results for some heteroaromatic derivatives, such as the 2-pyridyl, 4-(2-amino)-thiazolyl, and for the 2-nitrophenyl derivative.

Pharmacology

The final compounds **10a–g,j,k** together with compound **3a**, its methoxy derivative **3b**, and (*S*)-(−)-3-PPP (Sigma Chemicals), were all evaluated as the hydrochloride for "in vitro" D-2 dopaminergic, and 5-HT_1 and 5-HT_2 serotonergic activities, by radioreceptor binding assays. For each compound, the ability to displace specific ligands was determined as follows: (a) [^{3}H]spiroperidol, from D-2 specific binding sites of rat striatal membranes; (b) [^{3}H]-5-HT (serotonin), from 5-HT_1 sites of rat hippocampus; (c) [^{3}H]ketanserin, from 5-HT_2 sites of rat cortex.

Concentrations required to inhibit 50% of radioligand specific binding (IC_{50}) were determined as mean values ±SD from three separate experiments with samples in triplicate, using at least six different concentrations of the displacer and only for compounds which showed a significant affinity in the explorative assays.

Results and Discussion

All compounds **10a–g,j,k** were completely inactive on D-2 receptor, whereas compounds **3a,b** had IC_{50} values of 7×10^{-6} M and 8×10^{-6} M, respectively. Good agreement with the literature[12] was found for IC_{50} of (S)-(−)-3-PPP: 7×10^{-7} M.

The pharmacological data clearly indicate that the dopaminergic activity: (a) is present in 3-phenylpiperidine derivatives either when OH group is in an ortho (**3a**) or in a meta position (3-PPP), even if the latter favors a higher affinity for the receptor; (b) disappears completely when C-4 of the 3-PPP piperidine ring is replaced by an oxygen atom, so that the oxazine **10k** behaves as the reported[6] corresponding thiazines **2c**.

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Table I. Inhibition of [^{3}H]-5-HT (12 nM) Specific Binding to Rat Hippocampus

compound	IC_{50} (M)[a]
5-HT	$(2 \pm 0.8) \times 10^{-8}$
8-OH-DPAT	$(1 \pm 0.4) \times 10^{-7}$
10a	$(1 \pm 0.3) \times 10^{-6}$
10b	$(1 \pm 0.5) \times 10^{-6}$
10c	$(3 \pm 1.2) \times 10^{-6}$
10d	$(5 \pm 1.1) \times 10^{-6}$

[a] IC_{50} values represent the concentrations required to inhibit 50% of radioligand specific binding.

Therefore, we can suppose that the nature of X atom present at C-4 in the semirigid bicyclic structures **2** is determinant for dopaminergic affinity, since the molecular conformation can change depending on the nature of X, unlike the rigid tricyclic compounds **1**, where the affinity remains for X = CH_2, O, S.

In the binding experiments on the 5-HT_1 receptor, only compounds **10a–d** were found to have a moderate affinity. Their IC_{50} values are listed in Table I. Moreover, when the samples were incubated with 5×10^{-6} M 8-OH-DPAT, which completely displaces the specific binding of [^{3}H]-5-HT on the 5-HT_{1A} receptor, the maximal displacement, in the presence of **10a–d** and 8-OH-DPAT, did not change, indicating that the tested compounds were displacing the labeled serotonin from the 5-HT_{1A} receptors, a view which is confirmed by the fact that none of the compounds was active on 5-HT_2 receptors ($IC_{50} > 10^{-5}$).

These results show that 5-HT_1 serotonergic affinity is appreciably present in 2-phenyloxazine derivatives, when the benzene ring is 2- or 3-chloro as well as 2- or 3-methoxy-substituted (**10a–d**). Therefore we can say that the position of these substituents is not important for the 5-HT_1 activity. The fact that the position of the methoxy group is not important for both D-2 and 5-HT_1 activities seems to agree with the results of Hacksell[13] for the unsubstituted enantiomers of 2-(dipropylamino)tetralin. Besides, 5-HT_1 affinity disappears in all hydroxylated tested compounds (3-PPP, **3a**, **10j,k**).

Moreover it has been recently reported[14] that for 8-OH-DPAT the serotonergic 5-HT_1 activity doesn't disappear when OH or MeO are substituted with other groups in 2-aminotetralin derivatives.

Experimental Section

Chemistry. The term "dried" refers to the drying of an organic solution over anhydrous sodium sulfate. Conventional and flash column chromatography were performed with 1:30 Carlo Erba RS Analytical silica gel (0.05–0.20 mm) and 1:50 Merck silica gel 60 (0.040–0.063 mm, 230–400 mesh ASTM), respectively, as stationary phases. 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: the analytical results (C, H, N) were within ±0.4% of the theoretical values. ^{1}H NMR spectra were recorded either on a Varian EM-390 (90 MHz) or on a Varian XL-200 instrument when indicated (200 MHz), using TMS as internal standard. Chemical shifts are reported in parts per million (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.

2′-(Benzyloxy)acetophenone (4h). A mixture of 13.6 g (0.1 mol) of 2′-hydroxyacetophenone (**4j**), benzyl chloride (0.2 mol), and KOH (0.2 mol) in EtOH (150 mL) was refluxed for 6 h. After cooling, the reaction mixture was filtered and the solvent evaporated under reduced pressure. The residue was taken up with CH_2Cl_2 and washed with 2 N NaOH. Dried organic layer was evaporated to give **4h** (21.2 g, 94% yield), bp 115–118 °C (0.3 mbar) [lit.[15] 182–184 °C (11 mm)].

3′-(Benzyloxy)acetophenone (4i). In the same way, from **4k** (0.1 mol) was prepared **4i** (96% yield), bp 96–98 °C (0.3 mbar) [lit.[16] 167–170 °C (0.5 mm)].

Bromination of Acetophenone Derivatives. General Procedure. An equimolar amount of bromine was slowly dropped into a stirred solution of acetophenone derivative (50 mmol) in the appropriate solvent (100 mL) under nitrogen atmosphere in the darkness at room temperature. Then the reaction mixture was washed with a Na_2CO_3 saturated solution and dried. Evaporation of the solvent under reduced pressure afforded 2-bromoacetophenone derivative, which was stored under vacuum in the dark and cold.

2-Bromo-2′-(benzyloxy)acetophenone (5h): prepared from **4h** in Et_2O: 65% yield; mp 79–81 °C (from CH_2Cl_2/petroleum ether); ^{1}H NMR ($CDCl_3$) 4.51 (s, 2 H, CH_2O), 5.17 (s, 2 H, CH_2Br), 6.84–7.91 (mm, 9 H, Ar); GC/MS m/z 306 ($M^+ + 2$, <1), 304 (M^+, <1), 225 (20), 91 (100). Anal. ($C_{15}H_{13}BrO_2$) C, H.

2-Bromo-3′-(benzyloxy)acetophenone (5i): prepared from **4i** in Et_2O; 70% yield; mp 58–60 °C (from $CHCl_3$/petroleum ether); ^{1}H NMR ($CDCl_3$) 4.40 (s, 2 H, CH_2O), 5.11 (s, 2 H, CH_2Br), 6.92–7.90 (mm, 9 H, Ar); GC/MS m/z 306 ($M^+ + 2$, 2), 304 (M^+, 2), 91 (100). Anal. ($C_{15}H_{13}BrO_2$) C, H.

3-(Bromoacetyl)thiophene (5g). The reaction was carried out in anhydrous diethyl ether (Aldrich Sure/Seal) and in the presence of $AlCl_3$ (catalytic amount), starting from **4g**. The mixture was worked up as reported in the general procedure, but not heating over 30 °C: 82% yield; mp 62–63 °C (from petroleum ether) [lit.[17] 62–63 °C].

2-Bromo-3′-chloroacetophenone (5d). Benzene was used as the solvent for bromination of **4d**: 96% yield; mp 42–44 °C (from petroleum ether) [lit.[18] 39.5–40 °C (from absolute EtOH)].

2-Bromo-3′-nitroacetophenone (5e): from **4e** in benzene in 69% yield, mp 95–98 °C (from $CHCl_3$/hexane) [lit.[19] 96 °C (from Et_2O/ligroin)].

(2-Methoxyphenyl)oxirane (7a). To a solution of bromo ketone **5a** (4.56 g, 20 mmol) in dioxane (20 mL) was added $NaBH_4$ (0.53 g, 14 mmol) in H_2O (6 mL). The mixture was stirred at room temperature for 1 h, then neutralized with 10% H_2SO_4, diluted with H_2O, and extracted with diethyl ether. Obtained compound **6a** was reacted in the same ethereal solution with KOH (1.63 g, 29 mmol) in H_2O (15 mL). Resulting stirred mixture was refluxed for 30 min. After cooling, the organic layer was separated, washed with H_2O, and dried. Evaporation of the solvent under reduced pressure gave compound **7a** (2.52 g, 84%) as an oil: bp 40 °C (0.3 mbar); ^{1}H NMR ($CDCl_3$) 2.54–2.76 (m, 1 H) and 2.97–3.18 (m, 1 H, CH_2O), 3.83 (s, 3 H, OCH_3), 4.17 (m, 1 H, CHO), 6.77–7.36 (mm, 4 H, Ar); GC/MS m/z 150 (M^+, 18), 137 (27), 121 (26), 119 (39), 107 (31), 91 (100), 77 (35). Anal. ($C_9H_{10}O_2$) C, H.

(3-Methoxyphenyl)oxirane (7b): prepared as above from **5b** in 96% yield, bp 47 °C (0.3 mbar) [lit.[20] 77 °C (1 mm)].

(2-Chlorophenyl)oxirane (7c). An amount of 2.47 g (16 mmol) of 2′-chloroacetophenone, **4c**, was solubilized in benzene and brominated as reported above. Obtained crude oil **5c** (3.55

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g) was taken up in dioxane and reacted with 0.41 g of $NaBH_4$ in 10 mL of H_2O for 1 h. Then the mixture was diluted (H_2O, 100 mL), neutralized with 10% H_2SO_4, and extracted with diethyl ether. The ethereal solution of crude product **6c** was refluxed with 1.3 g of KOH in H_2O (10 mL) for 40 min. After cooling, separated organic layer was washed with water and dried, and the solvent was evaporated to yield 2.42 g (47% total yield) of **7c**. Purified by distillation as a pale yellow oil: bp 41 °C (0.3 mbar); ^1H NMR ($CDCl_3$) 2.55–2.73 (m, 1 H) and 3.15 (dd, 1 H, CH_2O), 4.18 (dd, 1 H, CHO), 7.17–7.47 (mm, 4 H, Ar): GC/MS m/z 156 ($M^+ + 2$, 3), 154 (M^+, 13), 119 (45), 91 (30), 89 (100). Anal. (C_8H_7ClO) C, H.

(3-Chlorophenyl)oxirane (7d). From **5d**, via **6d**, was prepared **7d**, as described for **7a**; 100% yield, bp 35 °C (0.3 mbar) [lit.[18] 60 °C (0.1 mm)].

1-(2-Methoxyphenyl)-2-(*n*-propylamino)ethanol (8a). Fifteen millimoles of (2-methoxyphenyl)oxirane (**7a**) was heated in a closed glass tube with *n*-propylamine (3 mL) for 4 h at 100 °C. After cooling, excess of reagent was evaporated under reduced pressure and the residual oil distilled: 98% yield; bp 120 °C (0.3 mbar), it solidifies upon standing; ^1H NMR ($CDCl_3$) 0.90 (t, 3 H, CH_2CH_3), 1.25–1.73 (mm, 3 H, CH_2CH_3 and 1 of $CHCH_2N$), 2.50–3.06 (mm, 5 H, 1 of $CHCH_2N$, $NCH_2CH_2CH_3$, and NH,OH, 2 H exchange with D_2O), 3.80 (s, 3 H, OCH_3), 5.06 (dd, 1 H, J = 5, 9 Hz, CHO), 6.76–7.57 (mm, 4 H, Ar); GC/MS m/z 209 (M^+, <1), 72 (100). Anal. ($C_{12}H_{19}NO_2$) C, H, N.

1-(3-Methoxyphenyl)-2-(*n*-propylamino)ethanol (8b). As above, from **7b** reacted at 150 °C, was obtained **8b** as an oil: 94% yield; bp 106 °C (0.3 mbar); ^1H NMR ($CDCl_3$) 0.90 (t, 3 H, CH_2CH_3), 1.48 (m, 2 H, CH_2CH_3), 2.35–2.85 (mm, 4 H, CH_2NCH_2), 2.94 (s, 2 H, NH and OH, exchange with D_2O), 3.80 (s, 3 H, OCH_3), 4.70 (dd, 1 H, J = 5, 9 Hz, CHO), 6.72–7.38 (mm, 4 H, Ar); GC/MS m/z 209 (M^+, 1), 72 (100). Anal. ($C_{12}H_{19}NO_2$) C, H, N.

1-(2-Chlorophenyl)-2-(*n*-propylamino)ethanol (8c) was obtained from **7c** in the same way as **8a** (98% yield). **8c** was an oil, which solidifies upon standing: bp 100 °C (0.3 mbar); ^1H NMR ($CDCl_3$) 0.88 (t, 3 H, CH_2CH_3), 1.47 (m, 2 H, CH_2CH_3), 2.45–3.11 (mm, 4 H, CH_2NCH_2), 3.33 (s, 2 H, NH and OH exchange with D_2O), 5.15 (dd, 1 H, J = 4, 10 Hz, CHO), 7.12–7.78 (mm, 4 H, Ar); GC/MS m/z 213 (M^+, <1), 72 (100). Anal. ($C_{11}H_{16}ClNO$) C, H, N.

1-(3-Chlorophenyl)-2-(*n*-propylamino)ethanol (8d). Similarly, from **7d** at 140 °C was prepared **8d** (98% yield) as a white waxy powder: mp 129–132 °C (from $CHCl_3$/*n*-hexane); ^1H NMR ($CDCl_3$) 0.89 (t, 3 H, CH_2CH_3), 1.49 (m, 2 H, CH_2CH_3), 2.40–2.95 (mm, 4 H, CH_2NCH_2), 3.13 (s, 2 H, NH and OH, exchange with D_2O), 4.70 (dd, 1 H, J = 5, 10 Hz, CHO), 7.18–7.44 (mm, 4 H, Ar); GC/MS m/z 213 (M^+, <1), 72 (100). Anal. ($C_{11}H_{16}ClNO$) C, H, N.

6-(2-Methoxyphenyl)-4-*n*-propylmorpholin-3-one (9a). General Procedure. A solution of **8a** (12 mmol) in CH_2Cl_2 (25 mL) was stirred vigorously with 1.2% aqueous NaOH (15.6 mmol), and bromoacetyl chloride (15.6 mmol) in CH_2Cl_2 (10 mL) was added dropwise under cooling. The same NaOH solution was then used in drops for maintenance of pH at 9; when this value was not changing, the separated organic layer was washed with 3 N HCl and then with H_2O. Finally it was dried and evaporated to dryness under reduced pressure. The residue (crude intermediate) was solubilized in 2-propanol (20 mL), added to a suspension of KOH (24 mmol) in the same solvent (15 mL), and stirred overnight. The mixture was concentrated under gentle warming, diluted with H_2O, and extracted with CH_2Cl_2. The organic layer was dried and evaporated in vacuo to give crude **9a**, which was purified by column chromatography on silica gel (CH_2Cl_2/ethyl acetate, 4:1 as eluent): pale yellow oil (79% yield); bp 95–97 °C (0.3 mbar); ^1H NMR ($CDCl_3$) 0.93 (t, 3 H, CH_2CH_3), 1.61 (m, 2 H, CH_2CH_3), 3.08–3.70 (mm, 4 H, CH_2NCH_2), 3.84 (s, 3 H, OCH_3), 4.36 (dd, 2 H, ν_A = 4.30, ν_B = 4.42, J = 16 Hz, CH_2CO), 5.12 (dd, 1 H, J = 4, 10 Hz, CHO), 6.80–7.58 (mm, 4 H, Ar); GC/MS m/z 249 (M^+, 34), 113 (82), 91 (51), 85 (44), 84 (100). Anal. ($C_{14}H_{19}NO_3$) C, H, N.

The following compounds **9b–d** were obtained as above:

6-(3-Methoxyphenyl)-4-*n*-propylmorpholin-3-one (9b): purified as above (same eluent): pale yellow oil (45% yield) from **8b**; bp 136–138 °C (0.3 mbar); ^1H NMR ($CDCl_3$) 0.92 (t, 3 H, CH_2CH_3), 1.61 (m, 2 H, CH_2CH_3), 3.10–3.68 (mm, 4 H, CH_2NCH_2), 3.81 (s, 3 H, OCH_3), 4.35 (dd, 2 H, ν_A = 4.29, ν_B = 4.40, J = 16 Hz, CH_2CO), 4.76 (dd, 1 H, J = 4, 10 Hz, CHO), 6.77–7.42 (mm, 4 H, Ar); GC/MS m/z 249 (M^+, 27), 134 (24), 113 (80), 91 (27), 85 (40), 84 (100). Anal. ($C_{14}H_{19}NO_3$) C, H, N.

6-(2-Chlorophenyl)-4-*n*-propylmorpholin-3-one (9c): pale yellow oil (92% yield) from **8c**; bp 102 °C (0.3 mbar); ^1H NMR ($CDCl_3$) 0.93 (t, 3 H, CH_2CH_3), 1.60 (m, 2 H, CH_2CH_3), 3.13–3.65 (mm, 4 H, CH_2NCH_2), 4.37 (dd, 2 H, ν_A = 4.32, ν_B = 4.43, J = 17 Hz, CH_2CO), 5.12 (dd, 1 H, J = 4, 10 Hz, CHO), 7.20–7.70 (mm, 4 H, Ar); GC/MS m/z 255 ($M^+ + 2$, 11), 253 (M^+, 32), 113 (100), 103 (33), 89 (25), 85 (41), 84 (98). Anal. ($C_{13}H_{16}ClNO_2$) C, H, N.

6-(3-Chlorophenyl)-4-*n*-propylmorpholin-3-one (9d): yellow oil (76% yield) from **8d**; bp 123–125 °C (0.3 mbar); ^1H NMR ($CDCl_3$) 0.93 (t, 3 H, CH_2CH_3), 1.60 (m, 2 H, CH_2CH_3), 3.10–3.63 (mm, 4 H, CH_2NCH_2), 4.34 (dd, 2 H, ν_A = 4.29, ν_B = 4.40, J = 17 Hz, CH_2CO), 4.75 (dd, 1 H, J = 4, 10 Hz, CHO), 7.13–7.46 (mm, 4 H, Ar); GC/MS m/z 255 ($M^+ + 2$, 6), 253 (M^+, 15), 113 (100), 103 (29), 85 (39), 84 (90). Anal. ($C_{13}H_{16}ClNO_2$) C, H, N.

2-(2-Methoxyphenyl)-4-*n*-propylmorpholine Hydrochloride (10a·HCl). General Procedure. A solution of **9a** (5 mmol) in dry (Aldrich, Sure/Seal) THF (20 mL) was dropped into a stirred suspension of $LiAlH_4$ (5 mmol) in the same solvent (10 mL), and the mixture was refluxed for 4 h. After cooling, the excess of hydride was destroyed with H_2O and the solid filtered and washed with CH_2Cl_2. After adding a few milliliters of 3 N HCl to the filtrate, it was concentrated. Residual aqueous phase was thrice extracted with CH_2Cl_2 (50 mL), and the organic layer was dried and evaporated to dryness in vacuo. The hygroscopic residue was taken up several times with absolute ethanol and then recrystallized from dichloroethane/*n*-hexane to afford **10a**·HCl as white crystals (90% yield), mp 168–171 °C. Analyses on free base: ^1H NMR ($CDCl_3$) 0.90 (t, 3 H, CH_2CH_3), 1.51 (m, 2 H, CH_2CH_3) 1.73–2.45 (mm, 4 H, $CHCH_2NCH_2CH_2CH_3$), 2.78 (dq, 1 H) and 3.02 (dt, 1 H, J_{gem} = 11 Hz, NCH_2CH_2O), 3.68–4.16 (mm, 2 H, OCH_2), 3.79 (s, 3 H, OCH_3), 4.96 (dd, 1 H, J = 3, 11 Hz, CHO), 6.75–7.57 (mm, 4 H, Ar); GC/MS m/z 235 (M^+, 26), 206 (100), 91 (27), 84 (56), 70 (62), 57 (45), 43 (46), 42 (93). Anal. ($C_{14}H_{22}ClNO_2$) C, H, N.

2-(3-Methoxyphenyl)-4-*n*-propylmorpholine hydrochloride (10b·HCl) was obtained as above, in 84% yield as white crystals, mp 191–192 °C (from CH_2Cl_2/petroleum ether). Spectra of free base: ^1H NMR ($CDCl_3$) 0.90 (t, 3 H, CH_2CH_3), 1.51 (m, 2 H, CH_2CH_3), 1.87–2.45 (mm, 4 H, $CHCH_2NCH_2CH_2CH_3$), 2.65–3.04 (mm, 2 H, NCH_2CH_2O), 3.63–4.19 (mm, 2 H, OCH_2), 4.56 (dd, 1 H, J = 3, 10 Hz, CHO), 6.71–7.27 (mm, 4 H, Ar); GC/MS m/z 235 (M^+, 18), 206 (64), 84 (55), 70 (62), 57 (47), 43 (45), 42 (100). Anal. ($C_{14}H_{22}ClNO_2$) C, H, N.

2-(2-Chlorophenyl)-4-*n*-propylmorpholine Hydrochloride (10c·HCl). According to the general procedure **10c**·HCl was prepared in 93% yield from **9c** as white crystals, mp 214–215 °C (from CH_2Cl_2/petroleum ether). Analyses on free base: ^1H NMR ($CDCl_3$) 0.90 (t, 3 H, CH_3), 1.52 (m, 2 H, CH_2CH_3), 1.63–2.45 (mm, 2 H, $CHCH_2NCH_2CH_2CH_3$), 2.76 (dq, 1 H) and 3.07 (dt, 1 H, J_{gem} = 11 Hz, NCH_2CH_2O), 3.68–4.16 (mm, 2 H, OCH_2), 4.93 (dd, 1 H, J = 3, 10 Hz, CHO), 7.10–7.67 (mm, 4 H, Ar); GC/MS m/z 241 ($M^+ + 2$, 3), 239 (M^+, 7), 210 (59), 84 (53), 70 (61), 57 (45), 43 (47), 42 (100). Anal. ($C_{13}H_{19}Cl_2NO$) C, H, N.

2-(3-Chlorophenyl)-4-*n*-propylmorpholine Hydrochloride (10d·HCl). In the same way, **9d** yielded title compound (90%) as white crystals, mp 217–219 °C (from CH_2Cl_2/petroleum ether). Analyses on free base: ^1H NMR ($CDCl_3$) 0.92 (t, 3 H, CH_3), 1.52 (m, 2 H, CH_2CH_3), 1.84–2.47 (mm, 4 H, $CHCH_2NCH_2CH_2CH_3$), 2.85 (br t, 2 H, J = 13 Hz, NCH_2CH_2O), 3.64–4.16 (mm, 2 H, OCH_2), 4.53 (dd, 1 H, J = 3, 10 Hz, CHO), 7.18–7.45 (mm, 4 H, Ar); GC/MS m/z 241 ($M^+ + 2$, 3), 239 (M^+, 10), 210 (55), 84 (48), 70 (58), 57 (47), 43 (45), 42 (100). Anal. ($C_{13}H_{19}Cl_2NO$) C, H, N.

2-Aryl-4-*n*-propylmorpholines 10e–i. General Procedure. To ice-cooled 98–100% formic acid (0.2 mol) and 2-(propylamino)ethanol (0.2 mol) was added the appropriate bromo derivative **5e–i** (0.1 mol), and the mixture was refluxed for 20 h at 180 °C. After cooling, the residue was taken up (CH_2Cl_2) and the organic layer washed (H_2O) and dried. By evaporation of the solvent under reduced pressure was obtained a products mixture, from which pure compounds **10e–i** were isolated by means of flash

column chromatography. Hydrochloride salt were prepared as described for **10a**·HCl.

The following compounds were prepared according to the above general procedure:

2-(3-Nitrophenyl)-4-*n*-propylmorpholine (10e): eluent $CHCl_3$/ethyl acetate, 9:1; pale yellow oil (10% yield); ^1H NMR ($CDCl_3$) 0.94 (t, 3 H, CH_3), 1.55 (m, 2 H, CH_2CH_3), 1.89–2.63 (mm, 4 H, $CHCH_2NCH_2CH_2CH_3$), 2.90 (br t, 2 H, J = 13 Hz, NCH_2CH_2O), 3.52–4.22 (mm, 2 H, OCH_2), 4.67 (dd, 1 H, J = 3, 11 Hz, CHO), 7.26–8.40 (mm, 4 H, Ar); GC/MS m/z 250 (M^+, 16), 221 (100), 84 (61), 70 (71), 57 (41), 43 (43), 42 (95).

10e·HCl: sand-colored crystals, mp 203–206 °C (from CH_2Cl_2/petroleum ether). Anal. ($C_{13}H_{19}ClN_2O_3$) C, H, N.

2-(2-Thienyl)-4-*n*-propylmorpholine (10f): from crude **5f**; eluent CH_2Cl_2/ethyl acetate, 4:1; oil (8% yield of virtually pure starting product); ^1H NMR ($CDCl_3$) 0.92 (t, 3 H, CH_3), 1.52 (m, 2 H, CH_2CH_3), 2.07–2.46 (mm, 4 H, $CHCH_2NCH_2CH_2CH_3$), 2.72 (dq, 1 H) and 3.00 (dt, 1 H, J_{gem} = 12 Hz, NCH_2CH_2O), 3.77–4.13 (mm, 2 H, OCH_2), 4.83 (dd, 1 H, J = 3, 11 Hz, CHO), 6.88–7.34 (mm, 3 H, Ar); GC/MS m/z 211 (M^+, 27), 182 (36), 111 (29), 110 (26), 84 (62), 70 (72), 57 (45), 42 (100).

10f·HCl: cream-colored crystals, mp 220 °C dec (from CH_2Cl_2/petroleum ether). Anal. ($C_{11}H_{18}ClNOS$) C, H, N.

2-(3-Thienyl)-4-*n*-propylmorpholine (10g): eluent CH_2Cl_2/ethyl acetate, 1:1; oil (9% yield); ^1H NMR ($CDCl_3$) 0.92 (t, 3 H, CH_3), 1.52 (m, 2 H, CH_2CH_3), 1.98–2.48 (mm, 4 H, $CHCH_2NCH_2CH_2CH_3$), 2.74 (dq, 1 H) and 2.96 (dt, 1 H, J_{gem} = 12 Hz, NCH_2CH_2O), 3.64–4.11 (mm, 2 H, OCH_2), 4.65 (dd, 1 H, J = 3, 11 Hz, CHO), 7.00–7.35 (mm, 3 H, Ar); GC/MS m/z 211 (M^+, 21), 182 (73), 111 (28), 110 (29), 84 (52), 70 (66), 57 (41), 42 (100).

10g·HCl: cream colored crystals, mp 212 °C dec (from CH_2Cl_2/petroleum ether). Anal. ($C_{11}H_{18}ClNOS$) C, H, N.

2-[2-(Benzyloxy)phenyl]-4-*n*-propylmorpholine (10h): eluent CH_2Cl_2/ethyl acetate, 1:1; dark yellow oil (19% yield); bp 97 °C (0.4 mbar); ^1H NMR ($CDCl_3$) 0.88 (t, 3 H, CH_3), 1.49 (m, 2 H, CH_2CH_3), 1.88 (t, 1 H, J = 11 Hz, 1 of $NCH_2CH_2CH_3$), 2.06–2.50 (mm, 3 H, $CHCH_2N$ and 1 of $NCH_2CH_2CH_3$), 2.75 (dq, 1 H) and 3.12 (dt, 1 H, J_{gem} = 11 Hz, NCH_2CH_2O), 3.70–4.16 (mm, 2 H, OCH_2), 4.96 (d) and 5.09 (s, 3 H, CHO and CH_2Ar), 6.81–7.62 (mm, 9 H, Ar); GC/MS m/z 311 (M^+, 29), 282 (98), 91 (100), 84 (54), 70 (49), 57 (39), 43 (36), 42 (75). Anal. ($C_{20}H_{25}NO_2$) C, H, N.

2-[3-(Benzyloxy)phenyl]-4-*n*-propylmorpholine (10i): eluent petroleum ether/ethyl acetate, 1:1; light brown oil (12% yield); bp 147 °C (0.5 mbar); ^1H NMR ($CDCl_3$) 0.90 (t, 3 H, CH_3), 1.52 (m, 2 H, CH_2CH_3), 1.88–2.46 (mm, 4 H, $CHCH_2NCH_2CH_2CH_3$), 2.86 (br t, 2 H, J = 13 Hz, NCH_2CH_2O), 3.65–4.15 (mm, 2 H, OCH_2), 4.54 (dd, 1 H, J = 3, 10 Hz, CHO), 5.06 (s, 2 H, CH_2Ar), 6.79–7.55 (mm, 9 H, Ar); GC/MS m/z 311 (M^+, 24), 282 (100), 91 (79), 84 (51), 70 (44), 57 (34), 43 (29), 42 (67). Anal. ($C_{13}H_{19}NO_2$) C, H, N.

2-(2-Hydroxyphenyl)-4-*n*-propylmorpholine (10j). A methanolic solution of **10h** (1.60 g, 5.14 mmol) was hydrogenated at normal pressure and room temperature in the presence of 10% palladium on charcoal (0.2 g), until the uptake ceased. The catalyst was removed by filtration through Celite and the solvent evaporated in vacuo. Compound **10j** was obtained as a yellow oil (quantitative yield), which solidified after distillation: bp 59–61 °C (2 mbar); ^1H NMR (200 MHz, $CDCl_3$) 0.94 (t, 3 H, CH_3), 1.57 (m, 2 H, CH_2CH_3), 2.22–2.88 (mm, 7 H, $CHCH_2NCH_2CH_2CH_3$, NCH_2CH_2O and OH, 1 H exchanges with D_2O), 3.68–3.97 (mm, 2 H, OCH_2), 4.82 (dd, 1 H, J = 3, 4 Hz, CHO), 6.73–7.25 (mm, 4 H, Ar); GC/MS m/z 221 (M^+, 46), 192 (51), 121 (20), 91 (26), 84 (56), 74 (32), 42 (100). Anal. ($C_{13}H_{19}NO_2$) C, H, N.

10j·HCl was a caramel-like solid, which did not crystallize.

2-(3-Hydroxyphenyl)-4-*n*-propylmorpholine (10k). Title compound was prepared in quantitative yield from 0.93 g (3 mmol) of **10i** as described above, using dioxane as solvent: yellow oil, solidified upon standing; bp 124–126 °C (0.5 mbar); ^1H NMR (200 MHz, $CDCl_3$) 0.89 (t, 3 H, CH_3), 1.54 (m, 2 H, CH_2CH_3), 2.04–2.41 (mm, 4 H $CH_2CH_2NCH_2CH_2CH_3$), 2.94 (br dd, 2 H, NCH_2CH_2O), 3.79–4.06 (mm, 2 H, OCH_2), 4.55 (dd, 1 H, J = 2, 10 Hz, CHO), 6.71–7.25 (mm, 5 H, Ar and OH, 1 H exchanges with D_2O); GC/MS m/z 221 (M^+, 25), 192 (94), 121 (21), 84 (52), 70 (66), 42 (100). Anal. ($C_{13}H_{19}NO_2$) C, H, N.

Pharmacological Methods. Adult male Wistar rats from Charles River (Calco, Italy) weighing 200–250 g, were used. Animals were killed by decapitation, and the brain was quickly removed and the various areas dissected and immediately frozen on dry ice.

Membrane Preparation. Striatum, used for the binding of dopamine receptors, was homogenized with a potter homogenizer in 50 volumes (based on the wet weight) of ice-cold Tris-HCl buffer (50 mM, pH 7.4). The homogenate was centrifuged at 30000*g* for 10 min and then washed twice with the same buffer.

Hippocampus, used for the binding of 5-HT_1 receptors, was homogenized with a polytron homogenizer for 30 sec in 25 volumes (based on the wet weight) of ice-cold Tris-HCl buffer (50 mM, pH 7.6). The homogenate was centrifuged at 30000*g* for 15 min and then washed with the same buffer. The pellet was resuspended in 25 volumes of buffer and incubated at 37 °C for 10 min. After the incubation, the homogenate was centrifuged at 30000*g* for 15 min.

Cortex, used for the binding of 5-HT_2 receptors, was homogenized with a polytron homogenizer for 30 sec in 25 volumes (based on the wet weight) of ice-cold Tris-HCl buffer (50 mM, pH 7.4). The homogenate was centrifuged at 37000*g* for 20 min and then washed three times with the same buffer.

For the three membrane preparations described above, the final pellets were frozen and stored at −80 °C until assayed. In these conditions no appreciable loss of binding is observed up to 2 months following membrane preparation.

At the time of incubation the membranes were resuspended in 40 volumes of the respective incubation buffer.

Binding Experiments. [^{3}H]Spiroperidol Binding. Each tube contained a final volume of 3 mL of 50 mM Tris-HCl (pH 7.4) containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 5.7 mM ascorbic acid, 4–5 mg of tissue suspension (based on the original weight), 0.3 nM labeled spiroperidol (Amersham, 116 Ci mmol^{-1}), and various concentrations (10^{-10} to 10^{-4} M) of the test compound. Specific binding was defined using 10^{-6} M *l*-sulpiride. Samples were incubated at 37 °C for 20 min and then filtered on Whatman GF/C glass microfiber filters. Filters were washed twice with 5 mL of cold (4 °C) 50 mM Tris-HCl (pH 7.4). The radioactivity retained was determined as described above. The use of a low nanomolar concentration of tritiated ligand and the definition of the specific binding by *l*-sulpiride allows the specific labeling of dopamine D_2 receptors.

[^{3}H]-5-HT Binding. Each tube contained a final volume of 1 mL of 50 mM Tris-HCl (pH 7.6) containing 4 mM $CaCl_2$, 5.7 mM ascorbic acid, 10 μM pargyline, 10 mg of tissue suspension (based on the original weight), 12 nM labeled 5-HT (New England Nuclear, 25 Ci mmol^{-1}), and various concentrations (10^{-9} to 10^{-4} M) of the test compound. Specific binding was defined using 10^{-5} M cold 5-HT. Samples were incubated at 37 °C for 15 min. Then the reaction was stopped with 4 mL of cold (4 °C) 50 mM Tris-HCl (pH 7.4), and the samples were filtered on Whatman GF/B glass microfiber filters. Filters were washed three times with 4 mL of 50 mM Tris-HCl (pH 7.4). The radioactivity retained was determined as described above. The amount of [^{3}H]-5-HT binding displaceable by 5×10^{-6} M 8-OH-DPAT was defined as that due to the labeling of 5-HT_{1A} receptors and was equivalent to 80% of total binding.

[^{3}H]Ketanserin Binding. Each tube, in a final volume of 1 mL of 50 mM Tris HCl (pH 7.4), contained 8–10 mg of tissue suspension (based on the original weight), 1.2 nM labeled Ketanserin (New England Nuclear, 60 Ci mmol^{-1}), and various concentrations (10^{-9} to 10^{-4} M) of the test compound. Specific binding was defined using 10^{-5} M cold ketanserin. Samples were incubated at 37 °C for 30 min. Then the reaction was stopped and the samples filtered, and the filters were washed as described for the binding of [^{3}H]-5-HT. The radioactivity retained was determinated as described above.