Synthesis and Pharmacological Characterization of 2-(4-Chloro-3-hydroxyphenyl)ethylamine and *N*,*N*-Dialkyl Derivatives as Dopamine Receptor Ligands

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2-(4-Chloro-3-hydroxyphenyl)ethylamine (**4**) and some derivatives were synthesized as dopamine (DA) receptor ligands. Amine **4** retains the dopaminergic pharmacophore 2-(3-hydroxyphenyl)ethylamine, and the chlorine atom replaces the "para" hydroxyl group of DA. The derivatives **18a–e** were obtained by introducing on the nitrogen of amine **4** the *n*-propyl and 2-phenylethyl or 3-phenylpropyl groups which can be accommodated by the D-2 receptor lipophilic sites 3C and π_3, respectively. The affinity and selectivity of these compounds for D-1 and D-2 subtypes was determined in radioligand competition assays for the DA receptors of rat striatum membranes using [^{3}H]SCH 23390 (D-1 selective) and [^{3}H]spiperone (D-2 selective) as radioligands. The amine **4** shows about 7-fold lower affinity than DA for both sites and is not able to discriminate between the two subtypes of DA receptors. The introduction of two *n*-propyl groups (**18a**) on the nitrogen atom reduces by one-half and doubles the affinity for D-1 and D-2 binding sites, respectively. The substitution of an *n*-propyl group with different alkylphenyl groups, to give compounds **18b–e**, increases the affinity for the D-2 subtype from 19-fold to 36-fold. These compounds have the same affinity at the D-2 site as the DA agonist *N*-*n*-propyl-*N*-(2-phenylethyl)-2-(3-hydroxyphenyl)ethylamine (**2a**) and are about 20 times more selective than DA for this binding site. In the assay for D-2 receptor mediated inhibition of adenylate cyclase activity, all the tested compounds behaved as D-2 agonists; *N*-*n*-propyl-*N*-[2(4-hydroxyphenyl)ethyl]- (**18d**) and *N*-*n*-propyl-*N*-(2-phenylethyl)-2-(4-chloro-3-hydroxyphenyl)ethylamine (**18b**) were more effective than DA or **2a**. On the other hand, all compounds were less effective than DA in stimulation of adenylate cyclase activity in rat striatal homogenates, a kind of effect which is mediated by the D-1 subtype of DA receptors. These results suggest that the nitrogen substitution enhances the affinity and selectivity for the D-2 receptor. In the adenylate cyclase assay, the compounds behave as potent D-2 agonists.

The neurotransmitter dopamine (DA) (**1**) (Figure 1) plays an important role both in the central nervous system and in the periphery, and disorders associated with dopaminergic pathways have been implicated in several neurological, psychiatric, endocrinological, and cardiovascular diseases.[1] Therefore, compounds which can interact with DA receptors may represent potential therapeutic agents and basic research tools.

The receptors mediating the DA actions are divided in two subpopulations, D-1 and D-2, on the basis of the hypothesis first proposed by Kebabian and Calne.[2] Until now several classes of DA receptor agonists have been discovered such as ergolines, phenethylamines, aporphines, aminotetralins, aminoindans, benzazepines, and benzoquinolines.[3,4] The structure–activity relationships of dopaminergic agonists suggest that the pharmacophore may be the 2-(3-hydroxyphenyl)ethylamine (**2**) moiety.[5] This hypothesis is also supported by dopamine-like actions of *N*-*n*-propyl-*N*-(2-phenylethyl)-2-(3-hydroxyphenyl)ethylamine (**2a**, RU 24213) and *N*-*n*-propyl-*N*-[2-(3-hydroxyphenyl)ethyl]-2-(3-hydroxyphenyl)ethylamine (**2b**, RU 24926).[6]

In order to obtain new dopaminergic agonists, the DA molecule has been modified mainly on the amino group and on the ethylamine chain, but only seldom on the catechol moiety.[7-14] In an earlier work we described the synthesis and binding affinity for D-1 and D-2 subtypes

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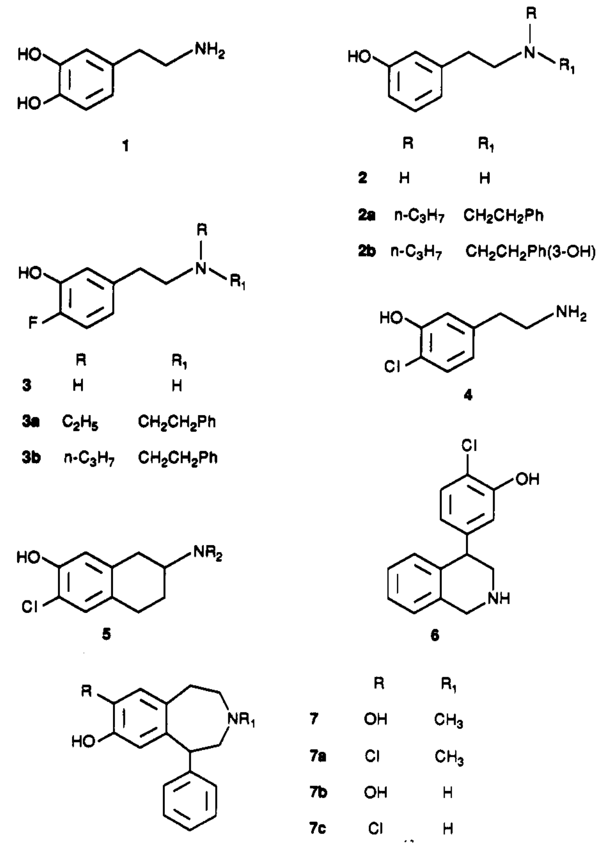

Figure 1

of DA receptors of 2-(4-fluoro-3-hydroxyphenyl)ethylamine (**3**) and some *N,N*-dialkyl derivatives.[14] Amine **3** showed about 2-fold lower affinity than DA for both binding sites, whereas the *N*-ethyl-*N*-(2-phenylethyl) (**3a**) and *N*-*n*-propyl-N-(2-phenylethyl) (**3b**) derivatives had high affinity and selectivity for D-2 binding sites. The behavioral tests on rats indicated that **3b** crosses the blood–brain barrier and exerts an agonistic effect on the central D-2 receptor.[15] The results suggested that the replacement of *p*-OH of DA with a fluorine slightly decreases the affinity for both D-1 and D-2 binding sites, while the introduction on the nitrogen of amine **3** of a 2-phenylethyl group increases the binding affinity and selectivity toward D-2 receptor. The 2-phenylethyl moiety can increase the lipophilicity[16] and, moreover, can interact by π–π stacking with a complementary binding site π_3, selective for the D-2 receptor. This site can accommodate the benzo-fused ring A of apomorphine,[17] or the second aromatic ring of **2a** or **2b**, as illustrated in a conceptual model of DA receptor, and as postulated by Olson.[18,19]

This report describes the synthesis of 2-(4-chloro-3-hydroxyphenyl)ethylamine (**4**) and some N,N-disubstituted derivatives (**18a–e**) (Table I). The chlorine at the 4-position replaces the *p*-OH of DA, which does not seem to be essential for high-affinity binding to D-2 receptors.[16] The inductive effect of chlorine could influence the acidity of the phenolic group and, therefore, could alter the affinity for D-1 and D-2 binding sites. Few examples can be found in the literature on the replacement of catechol hydroxyl groups by a chlorine. Studies on aminotetralins showed that some 2-amino-6-chloro-7-hydroxytetralins (**5**) are weakly effective in the binding assays.[20] Furthermore, Nichols et al. showed that 4-(4-chloro-3-hydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline (**6**) had a weak D-1 antagonistic activity.[21] In the series of benzazepines the 2,3,4,5-tetrahydro-7,8-dihydroxy-3-methyl-1-phenyl-1*H*-3-benzazepine (**7**, SK&F 75670) had only micromolar affinity at D-1 and D-2 receptors and was a weak D-1 agonist.[22] On the other hand, 2,3,4,5-tetrahydro-7-chloro-8-hydroxy-3-methyl-1-phenyl-1*H*-3-benzazepine (**7a**, SCH 23390), obtained by replacing the 7-OH of **7** with a chlorine, has nanomolar affinity for D-1 receptor and is the most selective D-1 antagonist. The 2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepine (**7b**, SK&F 38393) has agonist properties at D-1 receptor while the 7-Cl analog (**7c**, SK&F 83509) is a selective D-1 antagonist, even if less potent than **7a**.[23] It may be concluded that, among the tetrahydrobenzazepines, the 7-chloro substituent enhances the D-1 affinity and contributes to the D-1 antagonistic activity. These considerations prompted us to investigate the variation of D-1 and D-2 binding site affinity induced by substituting the DA-*p*-OH with a chlorine atom.

The N,N-dialkyl derivatives (**18a–e**) were obtained by introducing on the nitrogen of amine **4** the *n*-propyl and 2-phenylethyl groups which may bind respectively to lipophilic sites 3C and π_3 on the D-2 receptor.[18] The 2-phenylethyl moiety was also substituted with a hydroxyl group at the 3 or 4 position of the phenyl ring. In addition, the 3-(4-hydroxyphenyl)propyl moiety was introduced on the nitrogen. These substitutions could explain the structural requirements of the π_3 site located on the D-2 receptor.

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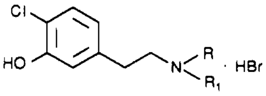
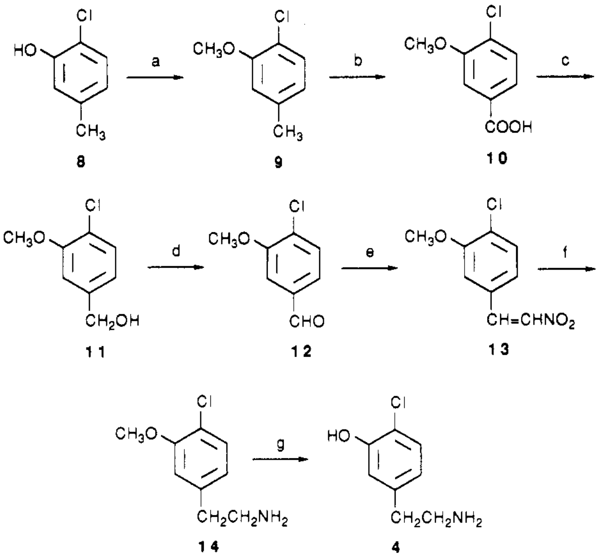
Table I. Inhibition of [^{3}H]SCH 23390 and [^{3}H]Spiperone Binding to Rat Striatal Membranes



drug	R	R_1	IC$_{50}$ (µM)^a [^{3}H]SCH 23390	IC$_{50}$ (µM)^a [^{3}H]spiperone	D-2/D-1 selectivity index^b
4	H	H	25.3 ± 2.4	26.3 ± 1.3	0.96
18a	n-C_3H_7	n-C_3H_7	50.7 ± 1.4	12.9 ± 2.2	3.93
18b	n-C_3H_7	$(CH_2)_2Ph$	24.4 ± 4.02	1.39 ± 0.11	17.55
18c	n-C_3H_7	$(CH_2)_2C_6H_4$(3-OH)	11.2 ± 1.3	0.73 ± 0.06	15.3
18d	n-C_3H_7	$(CH_2)_2C_6H_4$(4-OH)	18.09 ± 3.2	0.9 ± 0.07	20.1
18e	n-C_3H_7	$(CH_2)_3C_6H_4$(4-OH)	16.9 ± 2.7	0.85 ± 0.14	19.88
1, dopamine			3.7 ± 1.02	3.5 ± 0.41	1.06
2a			92.8 ± 1.17	0.75 ± 0.13	123.7

^{a} All values expressed as a mean IC$_{50}$ (concentration of drug producing half-maximal inhibition of the binding) values ± SEM. ^{b} The index was obtained by division of the IC$_{50}$ for the D-1 receptor ([^{3}H]SCH 23390) by that for the D-2 receptor ([^{3}H]spiperone).

Scheme I



^{a} (a) $(CH_3O)_2SO_2$, K_2CO_3, acetone; (b) $KMnO_4$, Pyridine, H_2O; (c) $LiAlH_4$; (d) pyrHCrO$_3$Cl; (e) CH_3NO_2; (f) $LiAlH_4$; (g) HBr 48%, CH_3COOH.

Chemistry

The synthesis of 2-(4-chloro-3-hydroxyphenyl)ethylamine (**4**) was achieved starting from commercially available 4-chloro-3-hydroxytoluene (**8**), which was methylated with dimethyl sulfate and K_2CO_3 to give 4-chloro-3-methoxytoluene (**9**) (Scheme I). Oxidation of the methyl group with $KMnO_4$ in pyridine–water afforded 4-chloro-3-methoxybenzoic acid (**10**) in 92% yield. A previous oxidation method with $KMnO_4$ in water had a yield of 58%.[21] Acid **9** was reduced with $LiAlH_4$ to 4-chloro-3-methoxybenzyl alcohol (**11**). This compound was oxidized to 4-chloro-3-methoxybenzaldehyde (**12**) with pyridinium chlorochromate. Treatment of **12** with nitromethane and reduction of resulting nitrostyrene **13** with $LiAlH_4$ gave 2-(4-chloro-3-methoxyphenyl)ethylamine (**14**). Acylation of **14** with acyl chlorides gave the amides **15a–e** (Figure 2), which were then reduced by $NaBH_4$ and acetic acid in dioxane.[24] The resulting amines **16a–e** were purified as hydrochlorides or hydrobromides and alkylated with iodopropane to afford the alkyl derivatives **17a–e**. The ether cleavage of the methoxy group was carried out with a mixture of HBr 48% and acetic acid. The hydrobromides **18b–e** (Table I) containing the phenylalkyl moiety are uncrystallizable and, after drying, gave an amorphous vitreous solid.

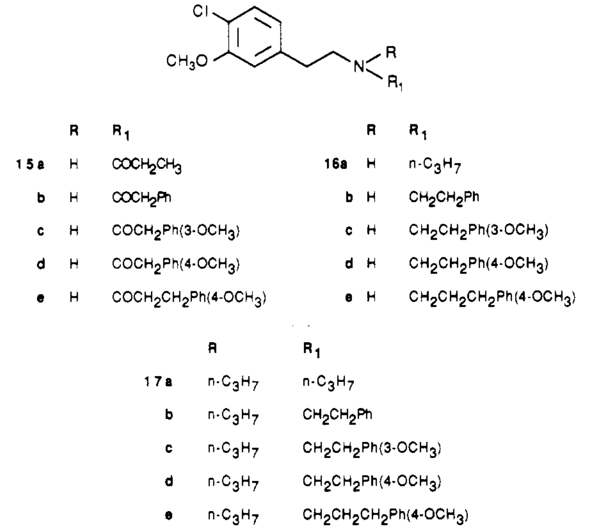


Figure 2. Derivatives of 2-(4-chloro-3-methoxyphenyl)ethylamine.

Results and Discussion

2-(4-Chloro-3-hydroxyphenyl)ethylamine (**4**) and derivatives **18a–e** were tested for their affinity at D-1 and D-2 subtypes of DA receptors using [^{3}H]SCH 23390 (D-1 selective) and [^{3}H]spiperone (D-2 selective) as radioligands.[14]

The results of binding studies (Table I) indicated that the unsubstituted amine **4**, like DA, is not able to discriminate between the two subtypes of DA receptors, and has about 7-fold lower affinity than DA for both sites. We have previously shown[14] that the replacement of the hydroxyl group at the para position of DA with a fluorine atom induces a 2-fold decrease in the affinity for both D-1 and D-2 subtypes; likewise, the same substitution with a chlorine further decreases the affinity for both sites (about 7-fold). Therefore the size of halogen atom influences the affinity for DA receptors. A similar trend was observed with 7-fluoro and 7-chloro derivatives of ADTN (**5**);[20] these decreases might be ascribed to an unfavorale steric effect of the larger chloro substituent or to the higher acidity of

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Table II. Dopaminergic D-2 Receptor Inhibited and D-1 Receptor Stimulated Adenylate Cyclase Activity in Rat Striatum[a]

	inhibition[b]				stimulation			
drug	0.01 μM	0.1 μM	1 μM	10 μM	0.01 μM	0.1 μM	1 μM	10 μM
4	101 ± 2	90 ± 3	87 ± 4	84 ± 2	nd	98 ± 4	95 ± 5	105 ± 6
18a	96 ± 4	88 ± 4	90 ± 3	86 ± 5	nd	101 ± 7	105 ± 4	115 ± 6
18b	93 ± 2	86 ± 4	78 ± 3	76 ± 5	104 ± 3	113 ± 6	118 ± 5	128 ± 7
18c	94 ± 3	91 ± 3	83 ± 5	81 ± 4	103 ± 4	116 ± 4	125 ± 5	128 ± 6
18d	92 ± 3	81 ± 3	74 ± 4	74 ± 3	126 ± 2	130 ± 3	136 ± 3	136 ± 2
18e	96 ± 4	86 ± 4	82 ± 3	82 ± 2	nd	101 ± 4	100 ± 3	110 ± 5
dopamine	95 ± 2	92 ± 3	87 ± 4	83 ± 2	104 ± 2	113 ± 3	110 ± 5	151 ± 4
2a	nd	95 ± 5	86 ± 3	84 ± 2	nd	nd	nd	nd

[a] Results are expressed as percent of adenylate cyclase activity at the listed drug concentration (μM) with respect to basal enzyme activity set at 100%. Each value represents the mean of quadruplicate determinations. Comparable results were obtained in three independent experiments. [b] All compounds were tested in the presence of 0.1 μM SCH 23390; n.d.: not determined.

m-OH.[25] However, in the tetrahydro-3-benzazepine series the replacement of the 7-hydroxy group with a chlorine atom increases the affinity for D-1 receptor. This difference may result from a different interaction of the tetrahydro-3-benzazepines with the DA receptor, as suggested by Weinstock et al.[20]

Transformation of the primary amine **4** into the *N,N*-di-*n*-propyl derivative **18a** reduced by one-half the D-1 affinity and doubled the D-2 affinity. The replacement of a *n*-propyl by a 2-phenylethyl group to give **18b** produced an increase of about 9 times in the affinity for the D-2 receptor. The derivative **18b** differs from **2a** by having the chlorine at the 4-position. The binding data show that, compared to **2a**, **18b** is 2-fold less effective at the D-2 site and 4 times more effective at the D-1 site.

A further increase of D-2 affinity was obtained by introducing a hydroxyl group on the aromatic nucleus of the 2-phenylethyl moiety: the compounds **18c** and **18d** are respectively 36- and 30-fold more effective than amine **4** at the D-2 sites. Also the replacement on **18a** of a *n*-propyl by the 3-(4-hydroxyphenyl)propyl group (**18e**) increases the affinity for D-2 sites. This compound differs from **18d** by having a methylene and shows the same affinity as **18d**. Moreover, it should be noted that derivatives **18c–e** have the same affinity as **2a** at the D-2 binding site.

The determination that **18b–e** are 15–20 times more selective than DA or amine **4** indicates that the nitrogen substitution enhances the affinity and selectivity for the D-2 receptor.

In order to verify whether the tested compounds behave as agonists or antagonists on the two dopaminergic receptors, we have performed functional adenylate cyclase studies in rat striatum. This brain region contains both D-1 receptors associated to stimulation of membrane adenylate cyclase and cAMP formation, and D-2 receptors linked to inhibition of enzyme activity and therefore mediating reduction of intracellular cAMP levels.[26,27]

The assay for D-2 receptor mediated inhibition of adenylate cyclase activity was performed in rat striatum synaptic membranes in the presence of the D-1 receptor antagonist **7a** to block possible effects on D-1 receptors. Both DA and **2a** inhibited basal adenylate cyclase activity in a concentration-dependent manner, with a maximal 17% inhibition at 10^{-5} M. In the same assay, the D-2 selective agonist bromocriptine displayed a similar inhibitory profile (data not shown), in agreement with previous data.[27] All the tested compounds behaved as D-2 agonists in this assay, i.e., inhibited in a concentration-dependent manner the basal adenylate cyclase activity (Table II). The rank order of potency was **18d** ≥ **18b** ≥ **18e** ≥ **18c** > **4** = **18a**. These results are consistent with the lower IC_{50} values shown by **18b**, **18c**, **18e**, and **18d** in the D-2 receptor binding assay, with respect to DA, **4**, and **18a**.

Table III. Effect of Compounds **4**, **18a**, and **18e** on DA-Stimulated Adenylate Cyclase Activity in Rat Striatum[d]

condition	cyclase stimulation (% of basal activity)
10^{-5} M DA	151 ± 5
10^{-5} M DA + **4**	140 ± 6[a]
10^{-5} M DA + **18a**	139 ± 4[b]
10^{-5} M DA + **18e**	132 ± 4[c]

[a] Not statistically different from DA alone. [b] $p < 0.05$. [c] $p < 0.001$. [d] Data represent the mean ± SE of triplicate determinations. Similar results were obtained in three independent experiments.

In the assay for D-1 receptor mediated stimulation of adenylate cyclase activity in rat striatal homogenates, compounds **18b–d** stimulated adenylate cyclase activity and cAMP formation (**18d** > **18c** > **18b**), although to a lesser extent than DA. Compounds **4**, **18a**, and **18e** did not show any stimulatory activity and were also tested as possible antagonists of DA-induced adenylate cyclase stimulation. Results (Table III) show that **18a** and **18e**, when tested at concentration of 10^{-5} M in the presence of 10^{-5} M DA, could indeed partially counteract DA stimulation of cAMP formation, suggesting that they could behave as partial D-1 receptor agonists. Antagonism of DA stimulatory activity was statistically significant for **18a** and **18e**.

In summary, these results demonstrate that compounds **18c–e** behave as potent D-2 agonists. The compounds have weaker activity on dopaminergic D-1 receptors and are less effective than DA.

Experimental Section

Melting points were determined on a Büchi 510 apparatus and are uncorrected. Microanalyses were performed on a 1106 Carlo Erba CHN analyzer, and the results were within ±0.4% of the calculated values. Proton magnetic resonance (NMR) spectra were recorded on a Varian VXR 300-MHz spectrometer with $CDCl_3$ as solvent and are reported in parts per million (δ) downfield from the internal standard tetramethylsilane (Me_4-

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Si). All NMR spectra were consistent with the structures assigned. The IR spectra were run on a Perkin-Elmer Model 297 spectrometer as Nujol mulls or liquid films. The identity of all new compounds was confirmed by both elemental analysis and NMR data; homogeneity was confirmed by TLC on silica gel Merck 60 F_{254}. Solutions were routinely dried over anhydrous sodium sulfate prior to evaporation. Chromatographic purifications were accomplished on Merck-60 silica gel columns, 70–230 mesh ASTM, from Merck (or 230–400 mesh for flash chromatography) with the reported solvent.

4-Chloro-3-methoxytoluene (9). This compound was prepared from 4-chloro-3-hydroxytoluene (8) (20.3 g, 143 mmol), anhydrous K_2CO_3 (30 g, 217 mmol), and $(CH_3O)_2SO_2$ (14.3 mL, 150 mmol) in acetone (250 mL), as previously described:[14] bp 120 °C (36 mmHg) (lit.[28] bp 111 °C, 15 mmHg); yield 80%; NMR δ 7.22 (d, J = 7.9 Hz, 1 H, H-5), 6.72 (m, 2 H, H-2,6), 3.90 (s, 3 H, OCH_3), 2.34 (s, 3 H, CH_3). Anal. (C_8H_9ClO) C, H, N.

4-Chloro-3-methoxybenzoic Acid (10). This compound was prepared from 9 (11.17 g, 71 mmol), potassium permanganate (35 g, 221 mmol), pyridine (36 mL), and water (107 mL) at 50 °C as previously described.[14] The suspension was stirred for 24 h at the same temperature, and 13 h at room temperature. The precipitate was recrystallized from EtOH: mp 217–219 °C; yield 92% (lit.[21] mp 217–220 °C; yield 58%); IR 1685 (C=O) cm^{-1}; NMR δ 7.59 (m, 2 H, H-2,6), 7.48 (d, J = 8 Hz, 1 H, 5-H), 4.68 (s, 1 H, OH), 4.0 (s, 3 H, OCH_3). Anal. ($C_8H_7ClO_3$) C, H, N.

4-Chloro-3-methoxybenzyl Alcohol (11). This compound was prepared from 10 (8.77 g, 47 mmol), anhydrous Et_2O (100 mL), anhydrous dioxane (90 mL), and $LiAlH_4$ (2 g, 53 mmol) as previously described.[14] The residue was purified by silica gel chromatography with ethyl acetate/cyclohexane 1:1 as eluent. The resulting oil was recrystallized from petroleum ether: mp 37–38 °C; bp 158 °C (17 mmHg); yield 82%; NMR δ 7.24 (d, J = 8 Hz, 1 H, H-5), 6.86 (d, J = 1.8 Hz, 1 H, H-2), 6.76 (dd, J = 8 and 1.8 Hz, 1 H, H-6), 4.52 (s, 2 H, OCH_2), 3.81 (s, 3 H, OCH_3), 3.04 (s, 1 H, OH). Anal. ($C_8H_9ClO_2$) C, H, N.

4-Chloro-3-methoxybenzaldehyde (12). This compound was prepared from 11 (8.45 g, 49 mmol) in anhydrous CH_2Cl_2 (50 mL) and pyridinium chlorochromate (16.2 g, 751 mmol) in anhydrous CH_2Cl_2 (60 mL) as previously described.[14] The oily residue was recrystallized from EtOH/H_2O 7:3: mp 52–53 °C [lit[29] (from 95% acetic acid) mp 52–53.5 °C], yield 93%; IR 1715 (C=O) cm^{-1}; NMR δ 9.94 (s, 1 H, CHO), 7.55 (d, J = 7.9 Hz, 1 H, H-5), 7.40 (m, 2 H, H-2,6), 3.98 (s, 3 H, OCH_3). Anal. ($C_8H_7ClO_2$) C, H, N.

2-(4-Chloro-3-methoxyphenyl)nitroethylene (13). A mixture of Na_2CO_3 (2 g, 19 mmol) and methylamine hydrochloride (2 g, 30 mmol) in EtOH (20 mL) was stirred at room temperature for 15 min and then filtered into a solution of 12 (10.9 g, 60 mmol) in EtOH (25 mL). Nitromethane (5.6 mL, 103 mmol) was added and the reaction mixture left in the dark at room temperature for 3 days. The yellow crystalline product was filtered and washed with EtOH: mp 167–168 °C; yield 89%; NMR (acetone-d_6) δ 8.08 (s, 2 H, CH=CH), 7.63 (d, J = 1.9 Hz, 1 H, H-2), 7.54 (d, J = 8.1 Hz, 1 H, H-5), 7.42 (dd, J = 8.1 and 1.9 Hz, 1 H, H-6), 4.0 (s, 3 H, OCH_3). Anal. ($C_9H_8ClNO_3$) C, H, N.

2-(4-Chloro-3-methoxyphenyl)ethylamine Hydrochloride (14). A suspension of 13 (5.34 g, 25 mmol) in anhydrous THF (50 mL) was added to a stirred mixture of $LiAlH_4$ (3.36 g, 80 mmol) in anhydrous THF (40 mL). The mixture was stirred at room temperature for 12 h. The excess $LiAlH_4$ was quenched by successive dropwise additions of H_2O (3.4 mL), 15% NaOH (3.4 mL), and H_2O (10 mL). After filtration, the solution was dried and the residue was distilled, bp 95 °C (0.4 mmHg), yield 55%. The oil was dissolved in absolute EtOH and treated with a solution of HCl in absolute EtOH. After evaporation of the solvent, the residue was recrystallized from i-PrOH: mp 179–180 °C; NMR (DMSO-d_6) δ 7.98 (bs, 3 H, NH_3^+), 7.38 (d, J = 8 Hz, 1 H, H-5), 7.09 (d, J = 2 Hz, 1 H, H-2), 6.87 (dd, J = 8 and 2 Hz, 1 H, H-6), 3.86 (s, 3 H, OCH_3), 3.05 (m, 2 H, NCH_2), 2.88 (t, J = 8.4 Hz, 2 H, $ArCH_2$). Anal. ($C_9H_{13}Cl_2NO$) C, H, N.

General Procedure for Acylation. To a stirred solution of the amine 14 (20 mmol) and triethylamine (20 mmol) in anhydrous Et_2O (25 mL) in an ice bath was added dropwise a solution of the appropriate acyl chloride (20 mmol) in anhydrous Et_2O (10 mL). After ice bath removal, the mixture was stirred at room temperature for 24 h. The suspension was washed with H_2O (5 mL), 2 N HCl (5 mL), 2 N NaOH (5 mL), and brine. The organic layer was dried. Concentration in vacuo gave an oil.

***N*-Propionyl-2-(4-chloro-3-methoxyphenyl)ethylamine (15a).** This compound was prepared from 14 and propionyl chloride. The oil was purified by flash chromatography with ethyl acetate as eluent and recrystallized from ethyl acetate/petroleum ether 1:9: yield 83%; mp 71–72 °C; IR 3325 (NH), 1640 (C=O) cm^{-1}; NMR δ 7.25 (d, J = 7.6 Hz, 1 H, H-5), 6.74 (d, J = 1.7 Hz, 1 H, H-2), 6.70 (dd, J = 7.6 and 1.7 Hz, 1 H, H-6), 5.55 (bs, 1 H, NH), 3.88 (s, 3 H, OCH_3), 3.48 (dt, J = 6.4 Hz, 2 H, NCH_2), 2.80 (t, J = 7.8 Hz, 2 H, $ArCH_2$), 2.15 (q, J = 7.6 Hz, 2 H, $COCH_2$), 1.12 (t, J = 7.6 Hz, 3 H, CH_3). Anal. ($C_{12}H_{16}ClNO_2$) C, H, N.

***N*-(Phenylacetyl)-2-(4-chloro-3-methoxyphenyl)ethylamine (15b).** This compound was prepared from 14 and phenylacetyl chloride. The suspension obtained after stirring was treated with H_2O (10 mL) and the precipitate of 15b was filtered. The organic layer was washed with 2 N HCl, 2 N NaOH, and brine and dried. The solvent was evaporated. The oily residue and the precipitate were recrystallized from EtOH/H_2O 7:3: mp 95–96 °C; yield 62%; IR 3350 (NH), 1635 (C=O) cm^{-1}; NMR δ 7.30 (m, 3 H, ArH), 7.18 (m, 3 H, ArH), 6.64 (d, J = 1.9 Hz, 1 H, H-2), 6.52 (dd, J = 8 and 1.9 Hz, 1 H, H-6), 5.35 (bs, 1 H, NH), 3.84 (s, 3 H, OCH_3), 3.52 (s, 2 H, $COCH_2$) 3.45 (dt, J = 6 Hz, 2 H, NCH_2), 2.70 (t, J = 6.9 Hz, 2 H, $ArCH_2$). Anal. ($C_{17}H_{18}ClNO_2$) C, H, N.

***N*-[(3-Methoxyphenyl)acetyl]-2-(4-chloro-3-methoxyphenyl)ethylamine (15c).** This compound was prepared from 14 and 3-methoxyphenyl)acetyl chloride. The oily residue was purified by column chromatography on silica gel with cyclohexane/ethyl acetate 1:1 as eluent. The combined fractions of pure product were evaporated and the residue was recrystallized from ethyl acetate–petroleum ether 5:5: mp 77–79 °C; yield 48%; IR 3300 (NH), 1640 (C=O) cm^{-1}; NMR δ 7.20 (m, 2 H, ArH), 6.81 (dd, J = 8 and 1.9 Hz, 1 H, ArH), 6.68 (m, 2 H, ArH), 6.64 (d, J = 1.9 Hz, 1 H, ArH), 6.53 (dd, J = 8 and 2 Hz, 1 H, ArH), 5.38 (bs, 1 H, NH), 3.85 and 3.80 (2 s, 6 H, 2 OCH_3), 3.50 (s, 2 H, CH_2CO), 3.45 (m, 2 H, NCH_2), 2.70 (t, J = 7.3 Hz, 2 H, $ArCH_2$). Anal. ($C_{18}H_{20}ClNO_3$) C, H, N.

***N*-[(4-Methoxyphenyl)acetyl]-2-(4-chloro-3-methoxyphenyl)ethylamine (15d).** This compound was prepared from 14 and (4-methoxyphenyl)acetyl chloride. The suspension obtained after stirring was treated with H_2O (10 mL) and the precipitate of 15d was isolated by filtration. The organic layer was washed with 2 N HCl, 2 N NaOH, and brine and dried. The solvent was evaporated. The oily residue and the precipitate were recrystallized from ethyl acetate: mp 94–95 °C; yield 73%; IR 3295 (NH), 1638 (C=O) cm^{-1}; NMR δ 7.18 (d, J = 8 Hz, 1 H, H-5), 7.05 (m, 2 H, ArH), 6.84 (m, 2 H, ArH), 6.62 (d, J = 2 Hz, 1 H, H-2), 6.53 (dd, J = 2 and 8 Hz, 1 H, H-6), 5.35 (bs, 1 H, NH), 3.84 and 3.80 (2 s, 6 H, 2 OCH_3), 3.48 (s, 2 H, CH_2CO), 3.45 (m, 2 H, NCH_2), 2.70 (t, J = 7.2 Hz, 2 H, $ArCH_2$). Anal. ($C_{18}H_{20}ClNO_3$) C, H, N.

N-[3-(4-Methoxyphenyl)propionyl]-2-(4-chloro-3-methoxyphenyl)ethylamine (15e). This compound was prepared from 14 and 3-(4-methoxyphenyl)propionyl chloride. The suspension obtained after stirring was treated with H_2O (10 mL) and the precipitate of 15e was isolated by filtration. The organic layer was washed with 2 N HCl, 2 N NaOH, and brine and dried. The solvent was evaporated. The oily residue and the precipitate were recrystallized from ethyl acetate/petroleum ether 6:4: mp 128–130 °C; yield 62%; IR 3290 (NH), 1632 (C=O) cm^{-1}. NMR δ 7.25 (d, J = 8 Hz, 1 H, H-5), 7.08 (m, 2 H, ArH), 6.82 (m, 2 H, ArH), 6.70 (d, J = 1.9 Hz, 1 H, H-2), 6.58 (dd, J = 8 and 1.9 Hz, 1 H, H-6), 5.35 (bs, 1 H, NH), 3.88 and 3.78 (2 s, 6 H, 2 OCH_3), 3.44 (dt, J = 6 Hz, 2 H, NCH_2), 2.88 (t, J = 7.5 Hz, 2 H, CH_2CO),

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2.72 (t, *J* = 7.5 Hz, 2 H, $ArCH_2CCO$), 2.40 (t, *J* = 7.6 Hz, 2 H, $ArCH_2CN$). Anal. ($C_{19}H_{22}ClNO_3$) C, H, N.

General Procedure for the Preparation of Amines 16a–e. A solution of acetic acid (30 mmol) in anhydrous dioxane (15 mL) was added dropwise to a stirred suspension of $NaBH_4$ (30 mmol) and amides **15a–e** (6 mmol) in anhydrous dioxane (30 mL) in a water bath. After water bath removal, the mixture was refluxed for 3 h. The reaction mixture was concentrated to dryness in vacuo; the excess of reagent was decomposed with water. The suspension was extracted with $CHCl_3$. The extracts were washed with 5% $NaHCO_3$ and brine, dried, and concentrated in vacuo. The oily residue was dissolved in EtOH, and 37% HCl or 48% HBr was added (2 mol of acid/mol of amine); the solution was evaporated to dryness under reduced pressure and the residue was recrystallized.

***N*-*n*-Propyl-2-(4-chloro-3-methoxyphenyl)ethylamine Hydrochloride (16a).** This compound was prepared from **15a**: yield 85%; mp 162–163 °C (from *i*-PrOH); NMR (DMSO-d_6) δ 8.96 (bs, 2 H, NH_2), 7.37 (d, *J* = 8 Hz, 1 H, H-5), 7.09 (d, *J* = 1.9 Hz, 1 H, H-2), 6.84 (dd, *J* = 8 and 1.9 Hz, 1 H, H-6), 3.88 (s, 3 H, OCH_3), 3.14, 2.97, and 2.83 (3 m, 6 H, 3 CH_2), 1.62 (m, 2 H, CCH_2C), 0.92 (t, *J* = 7.4 Hz, 3 H, CH_3). Anal. ($C_{12}H_{19}Cl_2NO$) C, H, N.

***N*-(2-Phenylethyl)-2-(4-chloro-3-methoxyphenyl)ethylamine Hydrochloride (16b).** This compound was prepared from **15b**: yield 87%; mp 199–200 °C (from absolute EtOH/MeOH); NMR (DMSO-d_6) δ 9.30 (bs, 2 H, NH_2), 7.36 (m, 3 H, ArH), 7.27 (m, 3 H, ArH), 7.10 (d, *J* = 1.9 Hz, 1 H, H-2), 6.86 (dd, *J* = 8 and 1.9 Hz, 1 H, H-6), 3.88 (s, 3 H, OCH_3), 3.18 (m, 4 H, 2 NCH_2), 2.98 (m, 4 H, 2 $ArCH_2$). Anal. ($C_{17}H_{21}Cl_2NO$) C, H, N.

***N*-[2-(3-Methoxyphenyl)ethyl]-2-(4-chloro-3-methoxyphenyl)ethylamine Hydrochloride (16c).** This compound was prepared from **15c**: yield 89%; mp 181–182 °C (from absolute EtOH); NMR (DMSO-d_6) δ 9.13 (bs, 2 H, NH_2), 7.38 (d, *J* = 8 Hz, 1 H, H-5), 7.25 (m, 1 H, ArH), 7.10 (d, *J* = 1.9 Hz, 1 H, H-2), 6.86 (m, 4 H, ArH), 3.88 and 3.76 (2 s, 6 H, 2 OCH_3), 3.18 (m, 4 H, 2 NCH_2), 2.95 (m, 4 H, 2 $ArCH_2$). Anal. ($C_{18}H_{23}Cl_2NO_2$) C, H, N.

***N*-[2-(4-Methoxyphenyl)ethyl]-2-(4-chloro-3-methoxyphenyl)ethylamine Hydrobromide (16d).** This compound was prepared from **15d**: yield 75%; mp 228–229 °C (from absolute EtOH); NMR (DMSO-d_6) δ 7.98 (bs, 2 H, NH_2), 7.38 (d, *J* = 8 Hz, 1 H, H-5), 7.27 (m, 2 H, ArH), 7.08 (d, *J* = 1.9 Hz, 1 H, H-2), 6.86 (m, 3 H, ArH), 3.88 and 3.72 (2 s, 6 H, 2 OCH_3), 3.20 and 3.12 (2 m, 4 H, 2 NCH_2), 2.92 and 2.84 (2 m, 4 H, 2 $ArCH_2$). Anal. ($C_{18}H_{23}BrClNO_2$) C, H, N.

***N*-[3-(4-Methoxyphenyl)propyl]-2-(4-chloro-3-methoxyphenyl)ethylamine Hydrochloride (16e).** This compound was prepared from **15e**: yield 81%; mp 209–211 °C (from absolute EtOH); NMR (DMSO-d_6) δ 9.16 (bs, 2 H, NH_2), 7.26 (d, *J* = 8 Hz, 1 H, H-5), 7.14 (m, 2 H, ArH), 7.08 (d, *J* = 2 Hz, 1 H, H-2), 6.88 (m, 3 H, ArH), 3.88 and 3.72 (2 s, 6 H, 2 OCH_3), 3.15 and 2.98 (2 m, 4 H, 2 NCH_2), 2.87 and 2.60 (2 m, 4 H, 2 $ArCH_2$), 1.92 (m, 2 H, CCH_2C). Anal. ($C_{19}H_{25}Cl_2NO_2$) C, H, N.

General Procedure for the Preparation of Amines 17a–e. A suspension of amine hydrochloride or hydrobromide **16a–e** (4 mmol), anhydrous K_2CO_3 (12 mmol), and iodopropane (12 mmol) in acetone (50 mL) was heated to reflux for 5 h. An additional portion of iodopropane (4 mmol) was added and the suspension was refluxed for 3 h. The solvent was evaporated, the residue was treated with H_2O (14 mL), and the suspension was extracted with Et_2O. The extracts were dried, and the solvent was removed in vacuo. The oily residue was pure on TLC and was used without further purification.

***N*,*N*-Di-*n*-propyl-2-(4-chloro-3-methoxyphenyl)ethylamine (17a).** This compound was prepared from **16a**: oil; yield 88%; TLC ($CHCl_3$/MeOH 9:1) R_f = 0.47. Hydrochloride: mp 140–141 °C (from isopropyl acetate); NMR (DMSO-d_6) δ 10.45 (bs, 1 H, NH), 7.28 (d, *J* = 8 Hz, 1 H, H-5), 7.12 (d, *J* = 1.7 Hz, 1 H, H-2), 6.90 (dd, *J* = 8 and 1.7 Hz, 1 H, H-6), 3.88 (s, 3 H, OCH_3), 3.26 (m, 2 H, $ArCH_2$), 3.05 (m, 6 H, 3 NCH_2), 1.70 (m, 4 H, 2 CCH_2C), 0.92 (t, *J* = 7.3 Hz, 6 H, 2 CH_3). Anal. ($C_{15}H_{25}Cl_2NO$) C, H, N.

***N*-*n*-Propyl-*N*-(2-phenylethyl)-2-(4-chloro-3-methoxyphenyl)ethylamine (17b).** This compound was prepared from **16b**: oil; yield 87%; TLC ($CHCl_3$/MeOH 9:1) R_f = 0.63; NMR δ 7.12 (m, 6 H, ArH), 6.72 (m, 2 H, ArH), 3.90 (s, 3 H, OCH_3), 2.78 (m, 8 H, 4 CH_2), 2.54 (m, 2 H, NCH_2CC), 1.50 (m, 2 H, CCH_2C), 0.90 (t, *J* = 7.2 Hz, 3 H, CH_3). Anal. ($C_{20}H_{26}ClNO$) C, H, N.

***N*-*n*-Propyl-*N*-[2-(3-methoxyphenyl)ethyl]-2-(4-chloro-3-methoxyphenyl)ethylamine (17c).** This compound was prepared from **16c**: oil; yield 90%; TLC ($CHCl_3$/MeOH 9:1) R_f = 0.66; NMR δ 7.20 (m, 2 H, ArH), 6.72 (m, 5 H, ArH), 3.88 and 3.70 (2 s, 6 H, 2 OCH_3), 2.75 (m, 8 H, 4 CH_2), 2.52 (m, 2 H, NCH_2CC), 1.50 (m, 2 H, CCH_2C), 0.90 (t, *J* = 7.2 Hz, 3 H, CH_3). Anal. ($C_{21}H_{28}ClNO_2$) C, H, N.

***N*-*n*-Propyl-*N*-[2-(4-methoxyphenyl)ethyl]-2-(4-chloro-3-methoxyphenyl)ethylamine (17d).** This compound was prepared from **16d**: oil; yield 83%; TLC ($CHCl_3$/MeOH 9:1) R_f = 0.68; NMR δ 7.26 (d, *J* = 8 Hz, 1 H, H-5), 7.18 (d, *J* = 8 Hz, 2 H, ArH), 6.88 (d, *J* = 8 Hz, 2 H, ArH), 6.80 (d, *J* = 1.9 Hz, 1 H, H-2), 6.72 (dd, *J* = 8 and 1.9 Hz, 1 H, H-6), 3.88 and 3.80 (2 s, 6 H, 2 OCH_3), 2.75 (m, 8 H, 4 CH_2), 2.52 (m, 2 H, NCH_2CC), 1.52 (m, 2 H, CCH_2C), 0.90 (t, *J* = 7.3 Hz, 3 H, CH_3). Anal. ($C_{21}H_{28}ClNO_2$) C, H, N.

***N*-*n*-Propyl-*N*-[3-(4-methoxyphenyl)propyl]-2-(4-chloro-3-methoxyphenyl)ethylamine (17e).** This compound was prepared from **16e**: oil; yield 88%; TLC ($CHCl_3$/MeOH 9:1) R_f = 0.63; NMR δ 7.25 (d, *J* = 8 Hz, 1 H, H-5), 7.08 (m, 2 H, ArH), 6.83 (m, 2 H, ArH), 6.75 (d, *J* = 2.1 Hz, 1 H, ArH), 6.72 (dd, *J* = 8 and 1.9 Hz, 1 H, H-6), 3.88 and 3.80 (2 s, 6 H, OCH_3), 2.68 (m, 4 H, 2 CH_2), 2.50 (m, 6 H, 3 CH_2), 1.75 (m, 2 H, $ArCCH_2CN$), 1.43 (m, 2 H, $NCCH_2C$), 0.90 (t, *J* = 7.2 Hz, 3 H, CH_3). Anal. ($C_{22}H_{30}ClNO_2$) C, H, N.

General Procedure for Demethylation. A stirred solution of the appropriate methoxylated amine (5 mmol), acetic acid (10 mL), and freshly distilled 48% HBr (10 mL) was refluxed for 4 h. The solution was evaporated in vacuo; the residue was dissolved in absolute ethanol and evaporated in vacuo. This procedure was repeated three times. The residue was dried in vacuo over P_2O_5. Compounds **18b–e** were obtained as vitreous, uncrystallizable solids.

2-(4-Chloro-3-hydroxyphenyl)ethylamine Hydrobromide (4). This compound was prepared from **14**: yield 72%; mp 183–185 °C (from absolute EtOH/EtOAc); NMR (DMSO-d_6) δ 10.1 (bs, 1 H, OH), 7.75 (bs, 3 H, NH_3^+), 7.28 (d, *J* = 8.1 Hz, 1 H, H-5), 6.83 (d, *J* = 2 Hz, 1 H, H-2), 6.67 (dd, *J* = 8.1 and 2 Hz, 1 H, H-6), 3.0 (m, 2 H, NCH_2), 2.78 (t, *J* = 8.6 Hz, 2 H, $ArCH_2$). Anal. ($C_8H_{11}BrClNO$) C, H, N.

***N*,*N*-Di-*n*-propyl-2-(4-chloro-3-hydroxyphenyl)ethylamine Hydrobromide (18a).** This compound was prepared from **17a**: yield 82%; mp 121–123 °C (from EtOH absolute); NMR (DMSO-d_6) δ 10.18 (s, 1 H, OH), 9.30 (bs, 1 H, NH^+), 7.30 (d, *J* = 8.2 Hz, 1 H, H-5), 6.88 (d, *J* = 2.1 Hz, 1 H, H-2), 6.75 (dd, *J* = 8.2 and 2.1 Hz, 1 H, H-6), 3.25, 3.08, and 2.92 (3 m, 8 H, 4 CH_2), 1.68 (m, 4 H, 2 CCH_2C), 0.90 (t, *J* = 7.3 Hz, 6 H, 2 CH_3). Anal. ($C_{14}H_{23}BrClNO$) C, H, N.

***N*-*n*-Propyl-*N*-(2-phenylethyl)-2-(4-chloro-3-hydroxyphenyl)ethylamine Hydrobromide (18b).** This compound was prepared from **17b**. The solution was evaporated in vacuo. The residue was dissolved in 2 N Na_2CO_3 and the solution was extracted with ether. The ether solution was dried and evaporated. The resulting white solid was dissolved in EtOH (15 mL) and treated with 48% HBr (2 mL). The solution was treated following the conditions indicated in the general procedure: yield 94%; TLC ($CHCl_3$/MeOH 9:1) R_f = 0.48; NMR (DMSO-d_6) δ 10.08 (s, 1 H, OH), 9.65 (bs, 1 H, NH^+), 7.27 (m, 6 H, ArH), 6.92 (d, *J* = 2 Hz, 1 H, H-2), 6.80 (dd, *J* = 8.2 and 2 Hz, 1 H, H-6), 3.28, 3.20, and 3.04 (3 m, 10 H, 5 CH_2), 1.75 (m, 2 H, CCH_2C), 0.95 (t, *J* = 7.2 Hz, 3 H, CH_3). Anal. ($C_{19}H_{25}BrClNO$) C, H, N.

***N*-*n*-Propyl-*N*-[2-(3-hydroxyphenyl)ethyl]-2-(4-chloro-3-hydroxyphenyl)ethylamine Hydrobromide (18c).** This compound was prepared from **17c**: yield 93%; TLC ($CHCl_3$/MeOH, 9:1) R_f = 0.33; NMR (DMSO-d_6) δ 10.15 and 9.18 (2 s, 2 H, OH), 9.50 (bs, 1 H, NH^+), 7.30 (d, *J* = 8.2 Hz, 1 H, 5-H), 7.15 (t, *J* = 8.2 Hz, 1 H, ArH), 6.90 (d, *J* = 2 Hz, 1 H, H-2), 6.75 (m, 4 H, ArH), 3.18, 3.07, and 2.95 (3 m, 10 H, 5 CH_2), 1.70 (m, 2 H, CCH_2C), 0.95 (t, *J* = 7.3 Hz, 3 H, CH_3). Anal. ($C_{19}H_{25}BrClNO_2$) C, H, N.

***N*-*n*-Propyl-*N*-[2-(4-hydroxyphenyl)ethyl]-2-(4-chloro-3-hydroxyphenyl)ethylamine Hydrobromide (18d).** This compound was prepared from **17d**: the solution was evaporated in vacuo. The residue was dissolved in 2 N Na_2CO_3 and the solution was extracted with ether. The ether solution was dried and evaporated. The residue was purified by column chromatography with $CHCl_3$/MeOH 9:1 as eluent. The combined fractions of pure product were evaporated and the residue was dissolved in EtOH (15 mL) and treated with 48% HBr (2 mL). The solution was treated following the conditions indicated in the general procedure: yield 68%; TLC ($CHCl_3$/MeOH 9:1) R_f = 0.31; NMR (DMSO-d_6) δ 10.18 and 9.16 (2 s, 2 H, OH), 9.42 (bs, 1 H, NH^+), 7.25 (d, *J* = 8.1 Hz, 1 H, 5-H), 7.10 (m, 2 H, ArH), 6.95 (d, *J* = 2.1 Hz, 1 H, H-2), 6.78 (m, 3 H, ArH), 3.17, 3.08, and 2.90 (3 m, 10 H, 5 CH_2), 1.70 (m, 2 H, CCH_2C), 0.95 (t, *J* = 7.2 Hz, 3 H, CH_3). Anal. ($C_{19}H_{25}BrClNO_2$) C, H, N.

***N*-*n*-Propyl-*N*-[3-(4-hydroxyphenyl)propyl]-2-(4-chloro-3-hydroxyphenyl)ethylamine Hydrobromide (18e).** This compound was prepared from **17e**: yield 94%; TLC ($CHCl_3$/MeOH 9:1) R_f = 0.27; NMR (DMSO-d_6) δ 10.14 and 9.20 (2 s, 2 H, OH), 9.32 (bs, 1 H, NH^+), 7.28 (d, *J* = 8.1 Hz, 1 H, 5-H), 7.02 (m, 2 H, ArH), 6.86 (d, *J* = 2 Hz, 1 H, H-2), 6.70 (m, 3 H, ArH), 3.22, 3.10, 2.96, and 2.54 (4 m, 10 H, 5 CH_2), 1.90 (m, 2 H, $NCCH_2$-CAr), 1.62 (m, 2 H, CCH_2C), 0.90 (t, *J* = 7.3 Hz, 3 H, CH_3). Anal. ($C_{20}H_{27}BrClNO_2$) C, H, N.

Pharmacology. Adult Sprague–Dawley rats were obtained from Charles River (Calco, Italy). [^{3}H]SCH 23390 (specific activity 77.7 Ci/mmol), [^{3}H]spiperone (specific activity 24 Ci/mmol) and [α-^{32}P]ATP (20–30 Ci/mmol) were purchased from New England Nuclear, Boston, MA. Unlabeled SCH 23390 was a generous gift of Dr. Ongini (Essex, Italy). [^{3}H]cAMP (32 Ci/mmol) was purchased from Amersham Int. Ltd., Buckinghamshire, U.K. The following substances were obtained commercially: dopamine hydrochloride (Sigma Chemical Co., St. Louis MO). The *N*-*n*-propyl-*N*-(2-phenylethyl)-2-(3-hydroxyphenyl)ethylamine hydrobromide (RU24213) was synthesized in our laboratory.

Binding Studies. Radioreceptor binding studies were performed using rat striatal membrane preparations as previously described.[14]

Adenylate Cyclase Studies. D-1 receptor-mediated stimulation of membrane adenylate cyclase was measured in striatal homogenates as previously described.[27] Briefly, tissues were homogenized (10 strokes with a Teflon–glass tissue grinder) in cold 80 mM Tris-maleate buffer (pH 7.4). The incubation medium contained 80 mM Tris-maleate, pH 7.4, 500 μM ATP, 2 mM $MgCl_2$, 1 mM cAMP, 0.2 mM EGTA, 0.5 mM IBMX, 10 μM GTP, an ATP-regenerating system consisting of 5 mM phosphocreatine and 60 μg/sample of creatine phosphokinase, approximately 1 μCi of [α-^{32}P]-ATP (20–30 Ci/mmol), and 5000–7000 dpm of [^{3}H]cAMP (32 Ci/mmol) in a final volume of 100 μL, in the absence (basal activity) or presence of DA (10^{-7}–10^{-5} M). The putative dopaminergic compounds were dissolved in methanol at a concentration of 10^{-2} M and tested in vitro at concentrations between 10^{-7} and 10^{-5} M. After a 10-min incubation at 32 °C with 20 μL of homogenate (20–40 μg protein/sample), reactions were terminated by adding 100 μL of a stop solution containing 2% sodium dodecylsulfate, 40 mM ATP, and 1.3 mM cAMP. Cyclic [^{32}P]AMP was then isolated on Dowex and alumina columns according to the method of Salomon et al.[30]

Inhibition of basal adenylate cyclase by dopaminergic D-2 agonists was measured in synaptic plasma membranes as described by Onali et al.[26] Briefly, synaptic membranes prepared from corpus striatum (approximately 20–30 μg protein/sample) were incubated with 80 mM Tris-HCl, pH 7.4, 2 mM $MgCl_2$, 1 mM cAMP, 0.5 mM IBMX, 100 mM NaCl, 1.3 mM DTT, 0.5 mM ATP, 50 μM GTP, 0.33 mM EGTA, an ATP-regenerating system identical to that utilized for the stimulatory condition, [α-^{32}P]ATP, and [^{3}H]cAMP as above. Inhibition dose–response curves with either the selective D-2 agonist bromocriptine or DA were performed in parallel. In the case of DA and of the putative dopaminergic compounds, assays were performed in the presence of the D-1 selective antagonist SCH 23390 at the final concentration of 0.1 μM, to completely eliminate any possible activity on dopaminergic D-1 stimulatory receptors. After a 20-min incubation at 25 °C, samples were terminated with the addition of 100 μL of stop solution and cAMP isolated by double-column chromatography as described above. Columns recovery varied between 60 and 70%.

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