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Synthesis and dopamine receptor affinities of 1-aminoethylhetero-tetralines

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Summary — A series of 1-aminoethylhetero-tetralines **3–6**, which can be considered as opened-structure analogues of previously studied dopaminergic compounds **2**, were synthesized. In the binding studies, to evaluate D-1 and D-2 activity, no significant affinity was observed towards both dopaminergic receptors.

Résumé — Synthèse et affinité des 1-aminoéthylhétérotétralines pour les récepteurs de la dopamine. *On a synthétisé une série de 1-aminoéthylhétérotétralines **3–6**, qui peuvent être considérées comme des analogues à structure ouverte des composés **2** précédemment étudiés. Dans les études de liaison pour évaluer leurs activités D-1 et D-2, aucune affinité significative n'a été observée vis-à-vis des récepteurs dopaminergiques.*

D-1 receptors / D-2 receptors / dopamine / binding / tetralines

Introduction

In the past decade, considerable effort has been directed towards elucidation of the conformation of the active fragment in dopaminergic agents on different dopamine (DA) receptors: D-1, D-2, pre- and postsynaptic [1–4].

For this purpose, the use of rigid congeners of DA, in which the active fragment is blocked in a fixed conformation is very useful; important information can be obtained by changing the conformational characteristics and by different distances between the nitrogen atom and the aromatic ring.

Therefore several bicyclic and tricyclic compounds such as 2-aminotetralines (ADTN) **1**, *trans*-octahydrobenzo[f]quinolines **2a**, *trans*-hexahydronaphthoxazines (PHNO) **2b** [3–4] and, recently, *trans*-hexahydronaphthothiazines (PHNT) **2c** [5–7] and *trans*-tetrahydrobenzopyranoxazines (PBPO) **2d** [8] have been synthesized (fig 1).

For the tricyclic compounds **2** it was noted that DA agonist activity is present in the *trans* isomers where the DA fragment is contained in an antiperiplanar conformation, namely the phenyl ring is coplanar with the plane of the ethylamine side-chain and the distance between the hydroxyl group at the *meta*-position and the nitrogen atom is a critical structural requirement, as reported by McDermed [9] and Tedesco [10].

Furthermore, the chirality of the carbon atom bearing the amino group depends on the position of the hydroxyl group at the *meta*-position; in fact, for most of DA rigid congeners the activity has been demonstrated to reside in only 1 of the 2 enantiomers.

The observance of all these structural requirements in the above-cited tricyclic compounds involves considerable synthetic difficulties.

Therefore we thought that we would simplify the synthetic procedure by planning bicyclic structures of type **3–6** (fig 2) derived from the corresponding tricyclic ones **2**, which had previously been studied [5, 11, 12].

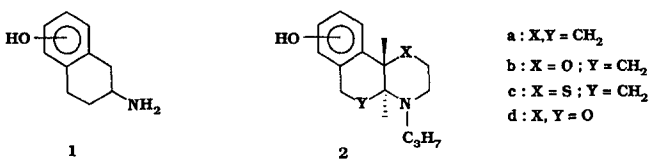


Fig 1.

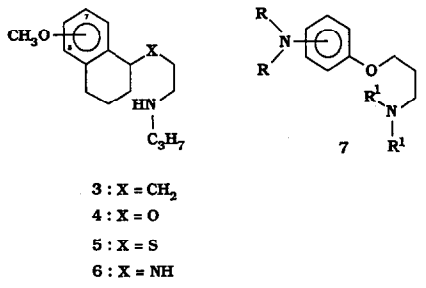


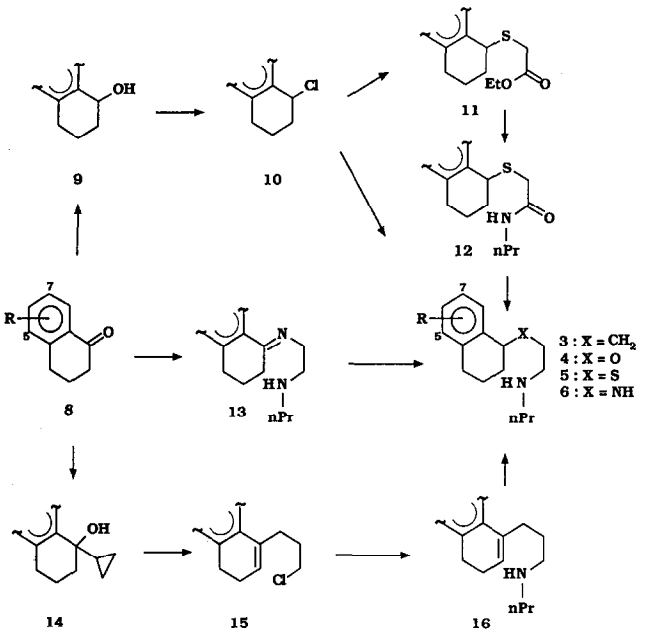
Fig 2. a: 5-OCH_3; b: 7-OCH_3.

We were encouraged in this by the dopaminergic activity shown in some aminoalkoxyanilines **7** recently reported [13], which can be considered to be derived from the opening of 3-(1-propyl-3-piperidinyl)phenol (3-PPP), a well known autoreceptor agonist [14] (fig 2).

In this paper we report the synthesis of 1-aminoethylhetero-tetralines **3–6**, bicyclic compounds which can be considered derived from structures **2**, by cleavage of the C-N bond, with the difference that they have the advantage of being more easily synthesized because neither is the *trans* fusion required nor is a certain chirality imposed.

There are 2 series of compounds: the **3a–6a** may be visualized as incorporating the α-conformer of DA pharmacophore and the **3b–6b** derivatives which embody the β-conformer.

All final synthesized compounds were evaluated for D-1 and D-2 dopaminergic affinity by binding assays.



Scheme 1. a: R = 5-OCH_3; b: R = 7-OCH_3.

Chemistry

The final products **3–6** were synthesized starting from the corresponding methoxytetralones **8a–b**. To prepare compounds **3a–b**, they were reacted with cyclopropylmagnesium bromide; the obtained alcohols **14a, b** were converted to the corresponding chloroderivatives **15a, b**, which by reaction with *n*-propylamine afforded compounds **16a, b**; the latter gave the final products **3a, b** by catalytic hydrogenation.

To synthesize the compounds **4a, b** and **5a, b** the 1-chlorotetraline derivatives **10a, b** obtained from 1-tetralols **9a, b** by reaction with $SOCl_2$ were used as starting material. For the ethers **4a, b**, they were reacted with *N*-*n*-propylethanolamine in the presence of NaH, whereas for the thioethers **5a, b**, they were first reacted with ethyl 2-mercaptoacetate and then with *n*-propylamine; the obtained amides (**12a, b**) by reduction with $LiAlH_4$ afforded the compounds **5a, b.**

The compounds **6a, b** were obtained by addition of *N*-*n*-propylethylenediamine to tetralones **8a, b** and successive reduction of **13a, b** by $NaBH_4$.

All the *O*-methyl derivatives **3–6a, b** were submitted to a demethylation reaction by HBr 48% or by BBr_3, but the compounds **4–5a, b** gave a mixture of products deriving from dealkylation of the side-chain linked to the heteroatoms O, S.

Pharmacology

The final compounds **3–6** as hydrochlorides were evaluated for D-1 and D-2 dopaminergic activity *in vitro* by determining for each compound the ability to displace [^{3}H]SCH23390 and [^{3}H]spiroperidol respectively from specific binding sites on rat striatal membranes [15].

Results and discussion

Seeing that it was difficult to obtain the *O*-demethyl derivatives, all the compounds were tested as methoxy-derivatives; moreover, in recent studies on naphthothiazine derivatives [6–7], it was noted that the affinity of the corresponding methoxy compounds towards DA-receptors is only one order of magnitude less than the hydroxy compounds. Furthermore, the same behaviour was noted for naphthoxazines [16] where the methoxy-derivatives corresponding to the hydroxy compounds are not completely inactive on DA-receptors.

For all compounds **3–6** no significant affinity was observed towards D-1 and D-2 receptors (IC_{50} > 10^{-4} M), as evidenced by their inability to inhibit the binding of the [^{3}H]SCH 23390 and [^{3}H]spiroperidol, selective D-1 and D-2 ligands respectively.

The reason would be that the closed conformation reported in figure 2 for compounds **3–6** should be the very energetically non-preferred and therefore the distance between the methoxy group in the *meta*-position and the nitrogen atom is different from that required by DA-receptors.

Experimental protocols

Chemical synthesis

Melting points were determined in open capillaries using a Büchi–Tottoli apparatus and are uncorrected.

Microanalyses were performed by the microanalytical section of our department: the analytical results (C, H, N) for pure compounds were within ± 0.4% of the theoretical values and are not reported in the present paper.

IR spectra were measured on liquid film with a Perkin–Elmer 1600 FT-IR spectrometer. ^{1}H-NMR spectra were recorded on a Varian EM-390 instrument, using $CDCl_3$ as solvent and TMS as internal standard; 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 HP 59970A work-station; only significant *m/z* peaks, with their bracketed relative intensity, are reported here. All compounds had IR, NMR and mass spectra that were fully consistent with their structure. Column chromatography was performed using 1:40 Carlo Erba RS analytical silica gel (∅ 0.05–0.20 mm) as stationary phase.

*1-Chloro-5-methoxy-1,2,3,4-tetrahydronaphthalene **10a***
Under a nitrogen atmosphere, distilling thionyl chloride (4–5 ml) was allowed to drop upon cooled (ice-water bath) 5-methoxy-1-tetralol **9a** (5.34 g, 30 mmol). Concentration of the reaction mixture to dryness *in vacuo* gave **10a**, as a solid material (5.85 g), which contained a very small amount of 8-methoxy-1,2-dihydronaphthalene. Because of a difficult purification, the crude mixture was used for next reactions. ^{1}H-NMR: 5.27 (t, 1H, CHCl). MS: 198.05 (M^+ + 2, 5); 196.15 (M^+, 17); 161.15 (100); 115.05 (37); 91.15 (21).

*1-Chloro-7-methoxy-1,2,3,4-tetrahydronaphthalene **10b***
As described above, **10b** was prepared from **9b**; it was a dark yellow oil containing corresponding elimination product as impurity. ^{1}H-NMR: 5.24 (t, 1H, CHCl). MS: 198.05 (M^+ + 2, 6); 196.05 (M^+, 20); 161.10 (100); 115.00 (26).

*Ethyl 2-[(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-thio]-acetate **11a***
Crude 1-chloro-5-methoxy-tetraline **10a** (2.77 g) was heated in a closed glass tube at 120°C for 3 h with ethyl 2-mercapto-acetate (≈ 10 ml) and triethylamine (2 ml). After cooling, the reaction mixture was diluted ($CHCl_3$), washed (H_2O), dried (Na_2SO_4) and evaporated *in vacuo* to give an oily residue, which was chromatographed on silica gel column, eluting with CH_2Cl_2/petroleum ether 95:5; pure **11a** (1.69 g, 43% of virtually pure starting product) was obtained as a pale yellow oil. IR: 1732 cm^{-1} (C=O). ^{1}H-NMR: 1.27 (t, 3H, CH_2CH_3); 1.66–2.41 (mm, 4H, *endo* CH_2CH_2); 2.43–3.00 (mm, 2H, benzylic CH_2); 3.24 (dd, 2H, SCH_2 CO, ν_A = 3.19, ν_B = 3.29, J_{A-B} = 14.6 Hz); 3.78 (s, 3H, OCH_3); 4.05–4.40 (mm, 3H, SCH and CH_2CH_3); 6.59–7.20 (mm, 3H, arom). MS: 280.15 (M^+, 2); 161.10 (100); 160.10 (62).

*Ethyl 2-[(7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-thio]-acetate **11b***
In the same way, from crude **10b** was obtained a mixture, which was chromatographed (CH_2Cl_2/petroleum ether 1:1 as eluent). Pure product **11b** (44%, referred to pure **10b**) was a pale yellow oil. IR: 1740 cm^{-1} (C = O). ^{1}H-NMR: 1.30 (t, 3H, CH_2CH_3); 1.63–2.38 (mm, 4H, *endo* CH_2CH_2); 2.47–2.94 (mm, 2H, benzylic CH_2); 3.26 (dd, 2H, SCH_2 CO, ν_A = 3.22, ν_B = 3.30, J_{A-B} = 14.9 Hz); 3.78 (s, 3H, OCH_3); 4.05–4.40 (mm, 3H, SCH and CH_2CH_3); 6.64–7.13 (mm, 3H, arom). MS: 280.10 (M^+, 2); 161.10 (100); 160.10 (68).

*2-[(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-thio]-N-n-propylacetamide **12a***
In a closed glass tube compound **11a** (1.63 g, 5.8 mmol) was heated at 100°C with *n*-propylamine (5 ml) for 4 h. After cooling, the mixture was evaporated to dryness and the residue solubilized in CH_2Cl_2. Purification was carried out by addition of petroleum ether, cooling and filtration of the formed precipitate. The filtrate was evaporated *in vacuo* to give amide **12a** (1.52 g, 89%) as a yellow oil, which became a cream-coloured waxy solid, by standing. IR: 1646 cm^{-1} (C=O). ^{1}H-NMR: 0.94 (t, 3H, CH_2CH_3); 1.55 (m, 2H, CH_2CH_3); 1.70–2.15 (mm, 4H, *endo* CH_2CH_2); 2.43–3.03 (mm, 2H, benzylic CH_2); 3.03–3.49 (mm, 4H, NCH_2 and SCH_2CO); 3.80 (s, 3H, OCH_3); 4.10 (broad, 2H, SCH and NH, D_2O exchanged); 6.60–7.30 (mm, 3H, arom). MS: 293.20 (M^+, < 1); 193.10 (61); 161.10 (100); 160.10 (94); 159.10 (28); 115.05 (26); 101.05 (34); 91.05 (26).

*2-[(7-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-thio]-N-n-propylacetamide **12b***
From ester **11b** in the same way as above was prepared **12b** (waxy needles, 84%). IR: 1648 cm^{-1} (C=O). ^{1}H-NMR: 0.95 (t, 3H, CH_2CH_3); 1.33–2.30 (mm, 7H, CH_2CH_3, *endo* CH_2CH_2 and NH); 2.60–2.92 (mm, 2H, benzylic CH_2); 3.05–3.50 (mm, 4H, NCH_2 and SCH_2CO); 3.80 (s, 3H, OCH_3); 4.09 (broad, 1H, SCH); 6.65–7.12 (mm, 3H, arom). MS: 293.10 (M^+, < 1); 193.10 (46); 161.10 (83); 160.10 (100); 159.10 (25); 115.00 (24); 101.05 (33); 91.05 (23).

*2-[(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-thio]-N-n-propyl-ethylamine **5a***
To a suspension of $LiAlH_4$ (0.30 g) in anhydrous THF (3 ml) was added dropwise a solution of the amide **12a** (1.47 g, 5 mmol) in the same solvent (20 ml). The mixture was first refluxed for 3 h and then stirred overnight at room temperature; finally a few drops of water were added. After extraction (CH_2Cl_2), the organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. The residual brown oil was chromatographed on silica gel eluting with $CHCl_3$/MeOH 95:5 to obtain product **5a** (0.17 g, 12%) as a dark yellow oil. ^{1}H-NMR: 0.92 (t, 3H, CH_2CH_3); 1.35–2.18 (mm, 6H, *endo* CH_2CH_2 and CH_2CH_3); 2.44–3.00 (mm, 9H, benzylic CH_2, $SCH_2CH_2NCH_2$ and NH, D_2O exchanged); 3.80 (s, 3H, OCH_3); 4.10 (broad, 1H, SCH); 6.56–7.30 (mm, 3H, arom). MS: 279.10 (M^+, 11); 161.10 (26); 160.10 (23); 72.05 (100).

Corresponding hydrochloride (**5a**•HCl) was prepared by addition of petroleum ether saturated with $HCl_{(g)}$ to a cooled solution of **5a** in CH_2Cl_2; mp = 151–152°C (from CH_2Cl_2/petroleum ether).

*2-[(7-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-thio]-N-n-propyl-ethylamine **5b***
In the same way, from **12b** was obtained crude **5b** as a brown oil, but an additional amount of $LiAlH_4$ (200 mg) and a longer

reaction time was required (10 h). Column chromatography on silica gel was carried out eluting with $CHCl_3$/MeOH 95:5. Pure **5b** (10%) was a yellow oil. ^{1}H-NMR: 0.92 (t, 3H, CH_2CH_3); 1.35–2.18 (mm, 6H, *endo* CH_2CH_2 and CH_2CH_3); 2.45–3.00 (mm, 9H, benzylic CH_2 and $SCH_2CH_2NHCH_2$); 3.76 (s, 3H, OCH_3); 4.07 (broad, 1H, SCH); 6.64–7.10 (mm, 3H, arom). MS: 279.10 (M^+, 10); 161.15 (25); 160.05 (24); 72.10 (100).

5b hydrochloride was prepared as described above: a waxy solid.

2-[(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-oxy]-N-n-propyl-ethylamine ***4a***

Under a nitrogen atmosphere, to a solution of 2-(propylamino)-ethanol (1.03 g, 10 mmol) in anhydrous toluene (50 ml) were added first NaH (0.24 g, 10 mmol) and then, dropwise, crude **10a** (1.97 g) in the same solvent (50 ml). The mixture was refluxed overnight under stirring, then was treated with a few drops of methanol and diluted with water. Extractions with benzene, drying (Na_2SO_4) and evaporation of the solvent gave an oil, which was chromatographed on silica gel column (CH_2Cl_2/MeOH 9:1 as eluent) to obtain pure **4a** (0.46 g, 17% referred to virtually pure starting product), as a dark yellow semi-solid material. ^{1}H-NMR: 0.92 (t, 3H, CH_2CH_3), 1.47–2.20 (mm, 6H, *endo* CH_2CH_2 and CH_2CH_3); 2.48–3.18 (mm, 6H, CH_2NCH_2 and benzylic CH_2); 3.70–4.06 (s, 3H, OCH_3 and m, 2H, OCH_2); 4.46 (broad, 1H, OCH); 6.12 (s, 1H, NH, D_2O exchanged); 6.68–7.32 (mm, 3H, arom). MS: 263.20 (M^+, < 1); 161.10 (21); 72.10 (100).

Corresponding hydrochloride (**4a**•HCl) was prepared as for **5a**; mp = 144–145°C (from CH_2Cl_2/petroleum ether).

2-[(7-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-oxy]-N-n-propyl-ethylamine ***4b***

Title compound was prepared as **4a**, starting from **10b**. Pure **4b** (yellow oil, 12% if **10b** is supposed pure) was obtained by column chromatography (CH_2Cl_2/MeOH 9:1). ^{1}H-NMR: 0.90 (t, 3H, CH_2CH_3); 1.34–2.21 (mm, 6H, *endo* CH_2CH_2 and CH_2CH_3); 2.41–2.84 (mm, 6H, CH_2NCH_2 and benzylic CH_2); 3.30 (broad, 1H, NH, D_2O exchanged); 3.40–3.70 (mm, 2H, OCH_2); 3.78 (s, 3H, OCH_3); 3.87–4.13 (broad, 1H, OCH); 6.62–7.22 (mm, 3H, arom). MS: 263.20 (M^+, < 1); 161.10 (100); 72.05 (22).

4b hydrochloride was prepared as **5a**•HCl: mp = 147–148°C (from CH_2Cl_2/Et_2O).

N-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-N'-n-propyl-ethylenediamine ***6a***

To a solution of **8a** (1.00 g, 5.7 mmol) in dry toluene (50 ml) were added *N-n*-propylethylenediamine (1.2 g, 11.7 mmol) and *p*-toluenesulfonic acid (catalytic amount). The mixture was stirred, under nitrogen atmosphere, and the water distilled azeotropically during 2 h. Then evaporation of the solvent *in vacuo* afforded a yellow oil, which changes colour (reddish), by standing. The crude product **13a** (GC/MS: M^+ = 260.10) was directly reduced with $NaBH_4$ (1.00 g) in absolute EtOH (40 ml), under nitrogen. After stirring for about 1 h at room temperature, water was added (20 ml) to the mixture; then it was concentrated and extracted ($CHCl_3$). Extracts were dried (Na_2SO_4) and evaporated to give **6a**, as a yellow oil (1.40 g, 94%). ^{1}H-NMR: 0.90 (t, 3H, CH_2CH_3); 1.42 (broad s, 2H, 2NH, D_2O exchanged); 1.49 (m, 2H, CH_2CH_3); 1.65–2.15 (mm, 4H, *endo* CH_2CH_2); 2.27–3.00 (mm, 8H, $NCH_2CH_2NCH_2$ and benzylic CH_2); 3.62–3.88 (m, 1H, CHN); 3.78 (s, 3H, OCH_3); 6.58–7.20 (mm, 3H, arom). MS: 262.20 (M^+, 2); 161.00 (100); 72.10 (21).

6a dihydrochloride: white needles, mp = 173–174°C (from abs EtOH/Et_2O).

N-(7-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-N'-n-propyl-ethylenediamine ***6b***

Starting from **8b** was obtained crude **13b** (GC/MS: M^+ = 260.20), and then **6b** (97%), by similar procedures. ^{1}H-NMR: 0.92 (t, 3H, CH_2CH_3); 1.51 (m, 2H, CH_2CH_3); 1.69–2.02 (mm, 4H, *endo* CH_2CH_2); 1.76 (broad s, 2H, 2NH, D_2O exchanged); 2.47–2.98 (mm, 8H, $NCH_2CH_2NCH_2$ and benzylic CH_2); 3.64–3.85 (m, 1H, CHN); 3.78 (s, 3H, OCH_3); 6.63–7.08 (m, 3H, arom). MS: 262.20 (M^+, 4); 161.10 (100); 160.10 (26).

6b dihydrochloride: white crystals, mp = 204–206°C (from EtOH/Et_2O).

1-Cyclopropyl-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ol ***14a***

To a stirred solution of Grignard's reagent, prepared from Mg turnings (0.340 g, 14 mmol) and bromocyclopropane (1.12 ml, 14 mmol) in anhydrous THF (15 ml) in the presence of catalytic amount of I_2, was added dropwise 5-methoxy-1-tetralone (1.23 g, 7 mmol) in the same solvent (10 ml). After refluxing for 5 h and stirring overnight at room temperature, a saturated solution of NH_4Cl (30 ml) was added to the ice-cooled reaction mixture. Following extraction with Et_2O and evaporation of the dried (Na_2SO_4) organic layer gave an oil, which was chromatographed on silica gel column; eluting with CH_2Cl_2/petroleum ether 1:1, pure **14a** (0.630 g, 41% was obtained as a very viscous oil. ^{1}H-NMR: 0.26–0.75 (mm, 4H, cycloprop CH_2CH_2); 0.93–1.30 (mm, 1H, CH); 1.47 (broad s, 1H, OH, D_2O exchanged); 1.77–2.04 (t, 4H, *endo* CH_2CH_2); 2.53–2.85 (mm, 2H, benzylic CH_2); 3.82 (s, 3H, OCH_3); 6.67–7.42 (mm, 3H, arom). MS: 218.05 (M^+, 35); 200.10 (33); 190.10 (97); 177.00 (100); 172.00 (31); 162.00 (27); 161.10 (24); 159.00 (29); 121.00 (47); 115.00 (34); 91.10 (37).

1-Cyclopropyl-7-methoxy-1,2,3,4-tetrahydronaphthalen-1-ol ***14b***

Similarly as above, 7-methoxy-1-tetralone was reacted to yield **14b** (54%) as a yellow oil eluted with CH_2Cl_2/petroleum ether 1:1 from silica gel column. ^{1}H-NMR: 0.20–0.83 (mm, 4H, cycloprop CH_2CH_2); 0.93–1.30 (mm, 1H, CH); 1.65 (broad, 1H, OH, D_2O exchanged); 1.84–2.10 (t, 4H, *endo* CH_2CH_2); 2.50–2.85 (mm, 2H, benzylic CH_2); 3.78 (s, 3H, OCH_3); 6.66–7.20 (mm, 3H, arom). MS: 218.15 (M^+, 36); 200.15 (34); 190.15 (88); 177.15 (100); 172.15 (28); 162.15 (31); 161.15 (21); 159.15 (32); 147,15 (24); 144.05 (25); 128.05 (25); 121.15 (48); 115.15 (43); 91.15 (36).

4-(3-Chloropropyl)-1,2-dihydro-8-methoxy-naphthalene ***15a***

To a cooled solution of **14a** (0.570 g, 2.6 mmol) in glacial acetic acid (5 ml) was added, under stirring, the same solvent (5 ml), containing 15% of HCl. Stirring was continued overnight, then the solvent was removed *in vacuo* at room temperature. The residue was taken up with H_2O, extracted (CH_2Cl_2), dried (Na_2SO_4) and finally concentrated to afford crude **15a** (0.561 g, 91%) as a brown oil, having satisfactory purity. For analytical purposes a sample was distilled (bp: 78–80°C/0.3 mbar). ^{1}H-NMR: 1.53–2.37 (mm, 4H, CH_2CH_2Cl and *endo* CH_2); 2.46–2.91 (mm, 4H, benzylic CH_2 and CCH_2); 3.55 (t, 2H, CH_2Cl); 3.83 (s, 3H, OCH_3); 5.92 (t, 1H, CCH); 6.71–7.34 (mm, 3H, arom). MS: 238.05 (M^+ + 2, 11); 236.15 (M^+, 32); 174.15 (35); 173.15 (23), 159.05 (100); 144.05 (26); 115.05 (21).

4-(3-Chloropropyl)-1,2-dihydro-6-methoxy-naphthalene ***15b***
Following the above procedure was obtained **15b** (97%) as gold-yellow oil. Analyses on distilled sample (bp = 69–71°C/0.3 mbar). ^{1}H-NMR: 1.78–2.35 (mm, 4H, CH_2CH_2Cl and *endo* CH_2); 2.45–2.80 (mm, 4H, benzylic CH_2 and CCH_2); 3.53 (t, 2H, CH_2Cl); 3.77 (s, 3H, OCH_3); 5.90 (t, 1H, CCH); 6.58–7.12 (mm, 3H, arom). MS: 238.05 (M^+ + 2, 11); 236.05 (M^+, 33); 174.15 (47); 173.15 (33); 159.05 (99); 158.05 (22); 144.05 (36); 128.05 (30); 115.05 (37).

3-(8-Methoxy-1,2-dihydronaphthalen-4-yl)-N-n-propyl-n-propylamine hydrochloride ***16a***
Chloroderivative **15a** (0.500 g, 2.1 mmol) was reacted with *n*-propylamine (5 ml) in a closed glass tube for 4 h at 80°C. The cooled mixture was concentrated *in vacuo* and the residual oil solubilized in CH_2Cl_2. Organic phase was washed with N HCl, dried (Na_2SO_4) and evaporated to dryness. Recrystallization of the residue from CH_2Cl_2/petroleum ether gave **16a** hydrochloride (0.375 g, 60%) as golden yellow plates, mp = 161–163°C. For analytical purposes a sample of free base was prepared. ^{1}H-NMR: 0.90 (t, 3H, CH_2CH_3); 1.35–1.95 (mm, 5H, $CCH_2CH_2CH_2N$, CH_2CH_3 and NH, D_2O exchanged); 1.97–2.33 (mm, 2H, *endo* CH_2); 2.34–2.87 (mm, 8H, $CCH_2CH_2CH_2NCH_2$ and benzylic CH_2); 3.82 (s, 3H, OCH_3); 5.86 (t, 1H, CCH); 6.70–7.20 (mm, 3H, arom). MS: 259.20 (M^+, 11); 128.05 (21); 115.05 (32); 86.05 (24); 85.05 (92); 72.05 (100).

3-(6-Methoxy-1,2-dihydronaphthalen-4-yl)-N-n-propyl-n-propylamine hydrochloride ***16b***
As for **16a**, from **15a** was obtained **16b** hydrochloride (52%), as sand-coloured needles; mp = 110–112°C (from CH_2Cl_2/petroleum ether). Analyses on free base. ^{1}H-NMR: 0.90 (t, 3H, CH_2CH_3); 1.40–1.80 (mm, 4H, $CCH_2CH_2CH_2N$ and CH_2CH_3); 2.13–2.30 (mm, 2H, *endo* CH_2); 2.37–2.72 (mm, 9H, $CCH_2CH_2CH_2NCH_2$, benzylic CH_2 and NH, D_2O exchanged); 3.79 (s, 3H, OCH_3); 5.87 (t, 1H, CCH); 6.63–7.08 (mm, 3H, arom). MS: 259.20 (M^+, 20); 174.10 (50); 128.00 (26); 115.00 (38); 85.05 (80); 72.05 (100).

3-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-N-n-propyl-n-propylamine hydrochloride ***3a***
Compound **16a** hydrochloride (0.325 g, 1.1 mmol) was solubilized in abs EtOH (20 ml) and hydrogenated at normal pressure and room temperature in the presence of 5% palladium on charcoal (0.30 g). After 4 h, the reaction mixture was filtered and the filtrate concentrated *in vacuo*. The residue was recrystallized from MeOH/Et_2O to yield white powder of crystalline **3a** hydrochloride (0.230 g, 70%), mp = 181–182°C (from MeOH/Et_2O). Analytical sample of free base was prepared. ^{1}H-NMR: 0.91 (t, 3H, CH_2CH_3); 1.19–1.98 (mm, 11H, *endo* CH_2CH_2, $CHCH_2CH_2CH_2N$, CH_2CH_3 and NH, D_2O exchanged); 2.40–2.94 (mm, 7H, benzylic CH_2 and CH, CH_2NCH_2); 3.82 (s, 3H, OCH_3); 6.58–7.30 (mm, 3H, arom). MS: 261.20 (M^+, 19); 72.05 (100).

3-(7-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-N-n-propyl-n-propylamine hydrochloride ***3b***
As above, by reduction of **16b** was prepared the compound **3b** hydrochloride (68%); pale yellow crystals, mp = 123–125°C (from CH_2Cl_2/petroleum ether). Analyses on free base. ^{1}H-NMR: 0.94 (t, 3H, CH_2CH_3); 1.32–2.07 (mm, 10H, CH_2CH_3, $CHCH_2CH_2CH_2N$ and *endo* CH_2CH_2); 2.22–2.97 (mm, 7H, CH_2NCH_2, benzylic CH_2 and CH); 3.76 (s, 3H, OCH_3); 6.27 (broad, 1H, NH, D_2O exchanged); 6.58–7.08 (mm, 3H, arom). MS: 261.10 (M^+, 35); 72.05 (100).

Binding experiments

Male Wistar rats from Charles River (Calco, Italy) weighing 200–250 g were used. Animals were killed by decapitation and brains quickly removed; striatal tissues were dissected and homogenized with a Polytron homogenizer for 30 s (setting 5) in 50 vol (based on the wet weight) of ice-cold Tris HCl buffer (50 mM, pH 7.4).

The homogenate was centrifuged at 30 000 *g* for 10 min at 0°C and then washed twice with the same buffer. The final pellet was frozen and stored at –80°C until assayed. At the time of incubation the pellet was resuspended in 90 vol of the respective incubation buffer.

[^{3}H]SCH 23390 binding. Each tube received in a final vol of 1 ml of 50 mM Tris–HCl containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$ and 1 mM $MgCl_2$ (pH 7.4), 4–5 mg of tissue suspension (calculated on the basis of the original wet weight), 1 nM labelled SCH 23390 (New England Nuclear, 74.8 Ci/mmol) and various concentrations (10^{-10}–10^{-4} M) of each tested compound. Specific binding was defined using 10^{-7} M cold SCH 23390. Samples were incubated at 37°C for 15 min and then filtered under vacuum on Whatman GF/C glass microfibre filters. Filters were washed twice with 3 ml of 50 mM ice-cold Tris–HCl buffer (pH 7.4). TE radioactivity retained was determined by liquid scintillation counting using Ready Protein (Beckman).

[^{3}H]Spiroperidol binding. Each tube received in a final vol of 3 ml of 50 mM Tris HCl containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$ and 5.7 mM ascorbic acid (pH 7.4), 4–5 mg of tissue suspension (calculated on the basis of the original weight), 0.3 nM of labelled spiroperidol (New England Nuclear, 21.8 Ci/mmol) and various concentrations (10^{-10} to 10^{-4} M) of each tested compound. Specific binding was defined using 10^{-6} M sulpiride. Samples were incubated at 37°C for 20 min and then filtered *in vacuo* on Whatman GF/C glass microfibre filters. Filters were washed twice with 4 ml of 50 mM ice-cold Tris–HCl buffer (pH 7.4). Radioactivity retained was determined as described above.

Protein determination. Protein measurement was carried out by the method of Lowry *et al* [17] using bovine serum albumin as protein standard.

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