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Methoxy and hydroxy derivatives of 3,4-dihydro-3-(di-*n*-propylamino)-2*H*-1-benzopyrans: new synthesis and dopaminergic activity

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Summary — The synthesis of methoxy and hydroxy derivatives of 3,4-dihydro-3-(di-*n*-propylamino)-2*H*-1-benzopyran from readily available or commercial *o*-hydroxybenzaldehydes is described in six steps. The enantiomers of 8-hydroxy-3,4-dihydro-3-(di-*n*-propylamino)-2*H*-1-benzopyran **1b** have been resolved. It is shown that the compound (–)-**1b** is a more selective D-2 agonist, compared to apomorphine.

Résumé — Dérivés méthoxylés et hydroxylés de 3,4-dihydro-3-(di-*n*-propylamino)-2*H*-1-benzopyranes: nouvelle synthèse et activité dopaminergique. *La synthèse de dérivés hydroxylés et méthoxylés du 3,4-dihydro-3-(di-*n*-propylamino)-2H-1-benzopyrane est décrite en six étapes à partir de benzaldéhydes* ortho *hydroxylés aisément préparables ou commerciaux. La résolution des énantiomères du 8-hydroxy-3,4-dihydro-3-(di-*n*-propylamino)-2H-1-benzopyrane* ***1b*** *a été réalisée. Comparativement à l'apomorphine, il est montré que le composé (–)-**1b** est un agoniste plus sélectif des sites D-2.*

3,4-dihydro-3-amino-2*H*-1-benzopyrans / racemic synthesis and resolution / dopaminergic receptors / brain / rat

Introduction

Several reviews outlining the structural requirements for agonist activity at dopamine receptors have been published [1, 2]. Based on the model prepared by McDermed *et al* [3], various teams working on aminotetralins have shown that monophenolic groups at the 5 or 7 position [4, 5] and diphenolic groups at the 5,6 or 5,8 position [4, 6, 7] were associated with high dopaminergic activity. In addition, a *N,N*-dipropyl substituent pattern has also been found to provide maximum potency [5].

Recently, we demonstrated that isosteric replacement of the methylene group at C_4 in the 2-aminotetralins by an oxygen may play an important role in the selective recognition of the serotoninergic or dopaminergic receptors in relation with the positions of the substituent (hydroxyl and methoxyl) on the aromatic ring [8, 9]. In the course of our work on 3-amino-3,4-dihydro-2*H*-1-benzopyrans, we were studying hydroxylated and methoxylated isomers of 5-hydroxy-3-(di-*n*-propylamino)chroman (5-OH-DPAC) **1a** and bisubstituted analogues when Wise *et al* [10] and Horn *et al* [11] described the 6- and 8-hydroxy-3,4-dihydro-3-(di-*n*-propylamino)-2*H*-1-benzopyrans as dopamine agonists (DA). We now report our own results in this area.

The synthetic pathway we reported previously for the preparation of 5-MeO-DPAC and 5-OH-DPAC [8] gives only poor yields when applied to the synthesis of methoxylated, dimethoxylated, hydroxylated and dihydroxylated analogues [9].

We now describe a new and more efficient procedure for the preparation of these compounds. Our method differs significantly from those reported by Wise *et al* [10] and Horn *et al* [11] and its main

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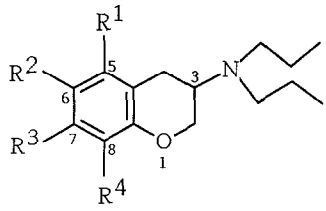
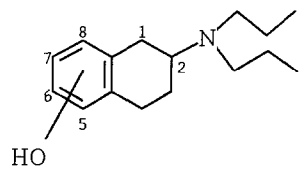
advantage lies in the possibility of preparing both dipropylic or diallylic derivatives. Indeed, the latter products are the best precursors for an easy access to tritiated compounds [12] and their mandatory use in receptor studies.



1 and 2



hydroxy-2-(di-n-propylamino)tetralin

Pharmacological activities were investigated *in vitro* by examining their ability to displace the specific binding of the labeled dopaminergic ligands: [^{3}H] apomorphine and [^{3}H] spiperone for D-2 sites as agonist and antagonist respectively, [^{3}H] SCH 23 390 a selective antagonist for D-1 sites [13–16]. In agreement with a recent report by Horn *et al* [11], we observed that a hydroxyl group on 'the 8 position' was indeed associated with the appearance of affinity for dopaminergic receptors. Moreover, we resolved the 8-hydroxy-3,4-dihydro-3-(di-*n*-propylamino)-2H-1-benzopyran **1b** (8-OH-DPAC). We report here additional information on the selective D-2 activity of the enantiomer (–)-8-OH-DPAC. In the latter case, a comparison was made with unlabeled SCH 23 390 and apomorphine.

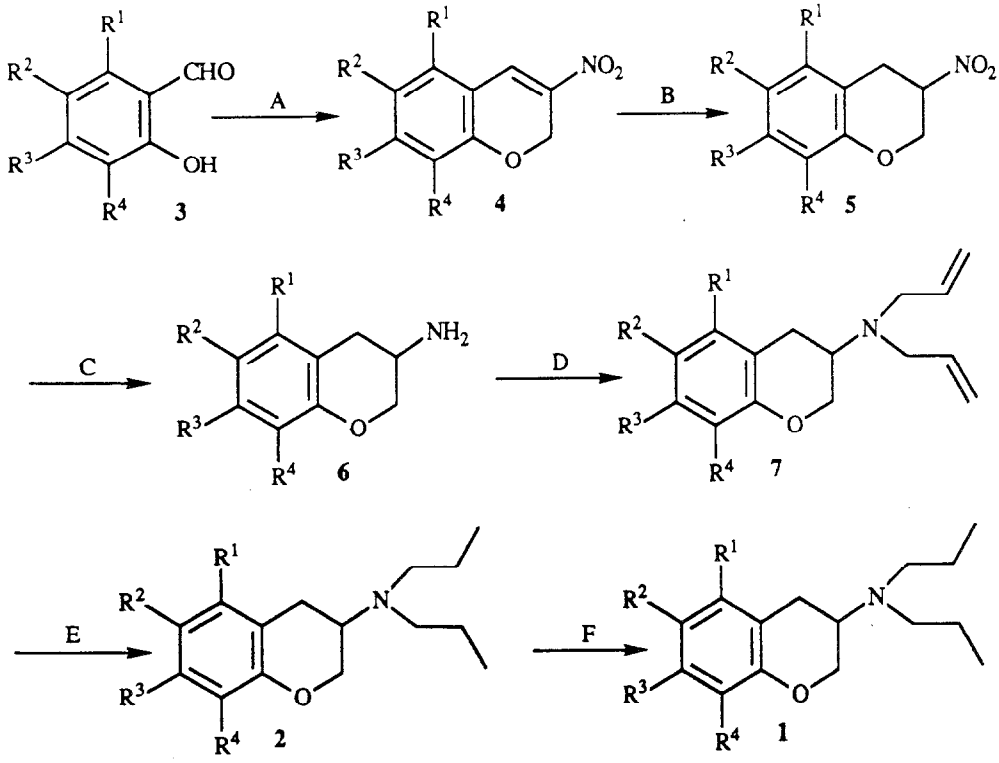
Chemistry

The synthesis of target compounds **1a–d** and **2a–d** is outlined in scheme 1. Readily available or commercial substituted 2-hydroxybenzaldehydes **3** treated by nitroethanol in the presence of di-*n*-butylammonium chloride in isopentyl acetate [17] or by nitroethylene in the presence of di-*n*-butylamine in chloroform [18] afforded the nitroderivatives **4**. The unsaturated compounds reacted with sodium borohydride in the presence of silica gel in a mixture of chloroform and isopropyl alcohol [19] to give the saturated nitrocompounds **5**. The crude products were easily converted into the aminoderivatives **6** by means of a modified procedure using hydrazine in the presence of Raney nickel [20]. The crude amines **6** reacted smoothly with allyl bromide in toluene in the presence of a saturated aqueous potassium carbonate solution to provide exclusively the methoxy or dimethoxy-3,4-dihydro-3-diallylamino-2*H*-1 benzopyrans 7 with an excellent yield from **4**. The catalytic hydrogenation in the presence of palladium on carbon led to partial deallylation of compounds **7** when the reduction was carried out in protic solvents such as methanol or ethanol. Moreover, when ethyl acetate in the presence of triethylamine was used as solvent, the di-*n*-propylamino derivatives **2** were obtained in high yields. The methoxy derivatives were converted to the hydroxy analogues **1** almost quantitatively using 48% hydrobromic acid in acetic acid [21]. The two enantiomers (+)-**1b** and (–)-**1b** were obtained by resolution of (±)-8-methoxy-3,4-dihydro-3-diallylamino-2*H*-1-benzopyran **7b** and conversion of each enantiomer to the corresponding saturated phenolic analogue by the usual process (vide supra). Thus, we obtained the different enantiomers (+)-**7a**, (–)-**7b**, (+)-**2b**, (–)-**2b**, (+)-**1b**, (–)-**1b** using a unique resolution procedure. The separation of the enantiomers of **7b** was achieved by enantioselective crystallisation with optically pure binaphtylphosphoric acid [22] as a chiral resolving agent (scheme). Each of the two enantiomers (+)-**7b** and (–)-**7b** was converted to the di-*n*-propylamino analogs (+)-**2b** and (–)-**2b** by catalytic hydrogenation in the presence of 10% palladium on carbon in ethyl acetate and triethylamine. The 8-hydroxy analogs (+)-**1b** and (–)-**1b** were obtained by demethylation of (+)-**2b** and (–)-**2b** using 48% hydrobromic acid in acetic acid as previously described. The isolated enantiomers of each compound have almost the same specific rotations but with opposite signs.

Pharmacology and discussion

Binding data for 3,4-dihydro-3-(di-*n*-propylamino)-2*H*-1-benzopyrans respectively at [^{3}H] apomorphine and [^{3}H] spiperone-labeled D-2 sites are shown in table I. Data for the apomorphine are also included for comparative purposes. The reason that two different radioligands were used to label the D-2 sites is that the D-2 agonists display a higher affinity for agonist-labeled sites than for antagonist-labeled sites.

As in the case of apomorphine, all compounds tested exhibit a greater affinity for [^{3}H] apomorphine-labeled D-2 sites than for [^{3}H] spiperone labeled D-2



2-7	R^1	R^2	R^3	R^4
a	OCH_3	H	H	H
b	H	H	H	OCH_3
c	H	H	OCH_3	OCH_3
d	H	OCH_3	OCH_3	H

1	R^1	R^2	R^3	R^4
a	OH	H	H	H
b	H	H	H	OH
c	H	H	OH	OH
d	H	OH	OH	H

A) $O_2N\text{-}CH_2\text{-}CH_2OH$, $\underline{n}Bu_2NH_2^+$, Cl^-, $i\text{-}C_5H_{11}OAc$ or $O_2N\text{-}CH{=}CH_2$, $\underline{n}Bu_2NH$, $CHCl_3$ (62-85%);

B) $NaBH_4$, SiO_2, $CHCl_3\text{-}\underline{i}PrOH$;

C) Ni Raney, $H_2N\text{-}NH_2$, EtOH;

D) $Br\text{-}CH_2\text{-}CH{=}CH_2$, K_2CO_3, $PhCH_3\text{-}H_2O$ (79-87% for three steps);

E) H_2, Pd/C, AcOEt, Et_3N (82-86%);

F) HBr, AcOH (90-95%).

Table I. Potency of various substituted 3,4-dihydro-3-(di-*n*-propylamino)-2H-1-benzopyrans to displace *in vitro* the specific binding of [^{3}H] apomorphine and [^{3}H] spiperone to rat striatal membranes. The values (IC_{50}) are expressed in nM ± SEM for 4 separate determinations performed in triplicate. Each displacing compound was used at concentrations ranging from 10^{-11} to 10^{-4} M. In parentheses, apparent Hill coefficient (nH).

Compound		IC_{50}nM (nH)			
		[^{3}H] apomorphine		[^{3}H] spiperone	
Apomorphine		3.3 ± 0.5	(1.01)	86 ± 12	(0.92)
5-MeO-DPAC	**2a**	153 ± 48	(0.98)	16700 ± 1800	(0.96)
8-MeO-DPAC	**2b**	77 ± 4	(1.03)	5860 ± 48	(0.99)
7,8-diMeO-DPAC	**2c**	4130 ± 254	(1.07)	inactive	
6,7-diMeO-DPAC	**2d**	24170 ± 3110	(0.87)	inactive	
5-OH-DPAC	**1a**	29 ± 5	(0.97)	159 ± 20	(0.97)
8-OH-DPAC	**1b**	1.2 ± 0.2	(0.96)	8 ± 62	(1.04)
8-OH-DPAC $[\alpha]_D$ = + 70°	(+)-**1b**	2160 ± 120	(0.94)	9230 ± 240	(0.88)
8-OH-DPAC $[\alpha]_D$ = - 72°	(-)-**1b**	0.88 ± 0.01	(1.03)	42 ± 16	(0.95)
7,8-diOH-DPAC	**1c**	2.2 ± 0.9	(0.99)	106 ± 3	(0.98)
6,7-diOH-DPAC	**1d**	15 ± 3	(0.97)	38 ± 3	(0.97)

Table II. Effect of (–)-8-OH-DPAC (–)-**1b** on *in vitro* [^{3}H] SCH 23390 binding to rat striatal membranes. The values (IC_{50}) are expressed in nM ± Sd of 3 separate determinations performed in triplicate. Each displacing compound was used at concentrations ranging from 10^{-11} to 10^{-7} M.

Compound	IC_{50} nM
8-OH-DPAC (-)-**1b** $[\alpha]_D$ = -72°	101.0 ± 1.5
Apomorphine	12.0 ± 1.5
SCH 23390	1.25 ± 0.12

sites except 6,7 and 7,8-diMeO-DPAC **2c** and **2d**, which were inactive towards the D-2 sites. In every instance, displacement of [^{3}H] apomorphine and [^{3}H] spiperone bound to the D-2 sites with an apparent Hill coefficient close to unity. It is interesting to notice that mono- and dihydroxy derivatives present a greater affinity than the corresponding mono- and dimethoxy compounds. These results differ with those of Cossery *et al* [8] with a series of 5-MeO and OH derivatives in which the relative affinity to the 5 HT_{1A} sites was similar. In this study, it appears also that a hydroxy group, in the 6 position on the benzene ring, reduces the affinity for [^{3}H] spiperone-labeled D-2 sites. Among all tested derivatives, compared to apomorphine, the enantiomer (–)-8-OH-DPAC (–)-**1b** binds to the D-2 sites with high affinity and selectivity. As shown in table II, the IC_{50} value of (–)-**1b** was approximately 10 and 100-fold higher than the IC_{50} values of apomorphine, a mixed D-1 and D-2 agonist, and SCH 23390, a selective D-1 antagonist. These results suggest the highly selective recognition of the D-2 sites by the enantiomer (–)-**1b** compound.

This work supports the conclusions reported by Horn, Wise and coworkers [10, 11, 23, 24] who have shown that substituted mono- and dihydroxy-3,4-dihydro-3-amino-2H-1-benzopyrans, the oxygen isosteres of the corresponding 2-aminotetralins, are potent dopaminergic agonists. However, for the first time, we describe the synthesis of the 8-OH-DPAC enantiomers and our results strongly support the assumption that the (–)-8-OH derivative (–)-**1b** is a selective D-2 agonist. From additional extensive pharmacological studies, *in vivo*, it is apparent that this new derivative might be a promising compound for clinical experiments (unpublished data). Furthermore, when compared to apomorphine, the relative high dopaminergic affinity of 7,8-diOH-DPAC **1c**, a derivative which did not cross the blood-brain barrier like 6,7-diOH-DPAC, could be a very useful starting point in the current search for drugs acting on peripheral D-2 receptors.

Experimental protocols

Chemistry

Melting points were determined on a Kofler hot-stage apparatus and were not corrected. Infrared spectra were determined with a Perkin-Elmer 297 spectrometer. The proton NMR spectra were obtained on a Hitachi-Perkin-Elmer R 24 spectrometer (60 MHz) or a Bruker AM 300 spectrometer (300 MHz). Chemical shifts are denoted in ppm relative to tetramethylsilane (Me_4Si) as an internal signal. Mass spectra were recorded on a R10-10C Nermag mass spectrometer. Optical rotations were obtained on a Jobin Yvon type 71 polarimeter. Wherever analyses are indicated by the symbols of the elements, analytical results were within ± 0.4% of the theoretical values. TLC was carried out with 0.25 mm silica gel 60 F_{254} (E Merck) aluminium plates. Starting materials for all compounds were obtained from Aldrich-Chimie and were used without further purification. (Except for (+) and (–) 2,2'-1,1'-binaphtylphosphoric acid which were purchased from Sigma.)

*5-Methoxy and 8-methoxy-3-nitro-2H-1-benzopyrans **4a** and **4b***
The preparation of the compounds **4a** and **4b** was carried out from nitroethanol [17] and nitroethylene [18] respectively as previously described.

7,8-Dimethoxy-3-nitro-2H-1-benzopyran ***4c***
A mixture of 2-hydroxy-3,4-dimethoxybenzaldehyde [25] (3.64 g, 20 mmol) 2-nitroethanol (3.64 g, 40 mmol) and di-*n*-butylammonium chloride (1.64 g, 10 mmol) in 40 ml of *i*-pentylacetate was placed in a one-necked 100 ml conical flask fitted with a Dean-Stark apparatus. The mixture was vigorously refluxed with stirring for 8 h and then allowed to cool to room temperature. A dark solid was filtered by suction and washed with ethyl acetate. The solvents were combined and then evaporated under reduced pressure. The crude material obtained was directly chromatographed on a silica gel column eluted with CH_2Cl_2. The fractions containing the desired product were evaporated and the residue recrystallized from cyclohexane to give 1.8 g of **4c**.

Another amount of **4c** (1.20 g) was obtained by extraction of the remaining dark solid with dichloromethane, washing of the combined extracts with 0.5 N NaOH, drying ($MgSO_4$), evaporation of the solvent and recrystallization from cyclohexane. The total yield was 63.2%; mp = 160°C; IR (KBr) 3080, 1630, 1595, 1270, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.88 and 3.92 (two s, 6H, OCH_3), 5.29 (s, 2H, OCH_2), 6.60 and 7.01 (two d, J = 8.3 Hz, 2H, aromatic), 7.79 (s, 1H, ethylenic). Anal $C_{11}H_{11}NO_5$ (C, H, N).

6,7-Dimethoxy-3-nitro-2H-1-benzopyran ***4d***
Following the procedure described for **4c**, 2-hydroxy-4,5-dimethoxybenzaldehyde [26] (2.55 g, 14 mmol) was converted to **4d**. After purification, the total yield (2.05 g) was 62%; mp = 154°C; IR (KBr) 3060, 1605, 1240, 1085 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.87 and 3.95 (two s, 6H, OCH_3), 5.22 (s, 2H, OCH_2), 6.45 and 6.65 (two s, 2H, aromatic), 7.77 (s, 1H, ethylenic). Anal $C_{11}H_{11}NO_5$ (C, H, N).

5-Methoxy-3,4-dihydro-3-nitro-2H-1-benzopyran ***5a***
The 5-methoxy-3-nitro-2*H*-1-benzopyran **4a** (0.53 g, 2.66 mmol) was dissolved in a mixture of chloroform (18 ml) and isopropyl alcohol (6 ml). Maintaining vigorous stirring, silica gel (230-400 mesh ASTM, 1.3 g) was then poured into the flask and powdered sodium borohydride (0.243 g, 6.4 mmol) was added portionwise over a period of 15 min. The slurry was stirred for an additional 15 min, while the reaction course was monitored by TLC (eluent CH_2Cl_2). Then, the reaction was stopped by dropwise addition of acetic acid (0.4 ml) and the reaction mixture was stirred for an additional 15 min. The insoluble material was filtered by suction, thoroughly washed with dichloromethane and the solvent evaporated under vacuum. A quantitative yield of crude product was obtained which was used without purification in the subsequent step. For analytical purposes, a sample was purified by column chromatography on silica gel (eluent diethyl ether-petroleum ether 1:4); mp = 101°C; IR (KBr) 1587, 1537, 1237, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.17 (dd, J_1 = 17 Hz, J_2 = 6 Hz, 1H, benzylic CH_2), 3.42 (dd, J_1 = 17 Hz, J_2 = 5.55 Hz, 1H, benzylic CH_2), 3.85 (s, 3H, OCH_3), 4.37 (dd, J_1 = 11 Hz, J_2 = 3.5 Hz, 1H, OCH_2), 4.59 (dd, J_1 = 11 Hz, J_2 = 5.55 Hz, 1H, OCH_2), 4.93 (m, 1H, CH-N), 6.51 (two d, J = 7.9 Hz, 2H, aromatic), 7.11 (t, J = 7.9 Hz, 1H, aromatic). Anal $C_{10}H_{11}NO_4$ (C, H, N).

8-Methoxy-3,4-dihydro-3-nitro-2H-1-benzopyran ***5b***
Using the procedure described for **5a**, **4b** (6.60 g, 32 mmol) was converted to 6.44 g (97%) of crude **5b**. For analytical purposes, a sample was purified by column chromatography on silica gel (eluent CH_2Cl_2); mp = 103°C; IR (KBr), 1580, 1540, 1263, 1113 cm^{-1}, ^1H NMR ($CDCl_3$) δ 3.33 (dd, J_1 = 17 Hz, J_2 = 5.1 Hz, 1H, benzylic CH_2), 3.54 (dd, J_1 = 17 Hz, J_2 = 5.8 Hz, 1H, benzylic CH_2), 3.85 (s, 3H, OCH_3), 4.50 (dd, J_1 = 11.6 Hz, J_2 = 2.6 Hz, 1H, OCH_2), 4.70 (dd, J_1 = 11.6 Hz, J_2 = 6 Hz, 1H, OCH_2), 4.95 (m, 1H, CH-N), 6.73 and 6.76 (two d, J = 8 Hz, 1H aromatic), 6.90 (t, J = 8 Hz, 1H, aromatic). Anal $C_{10}H_{11}NO_4$ (C, H, N).

7,8-Dimethoxy-3,4-dihydro-3-nitro-2H-1-benzopyran ***5c***
Using the procedure described for **5a**, **4c** (1.42 g, 6 mmol) was converted quantitatively to crude **5c**. An analytical sample was obtained by column chromatography on silica gel (eluent CH_2Cl_2); mp = 124°C; IR (KBr), 1540, 1280, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.31 (dd, J_1 = 16.7 Hz, J_2 = 6 Hz, 1H, benzylic CH_2), 3.51 (dd, J_1 = 16.7 Hz, J_2 = 5.7 Hz, 1H benzylic CH_2), 3.83 and 3.85 (two s, 6H, OCH_3), 4.48 (dd, J_1 = 11.6 Hz, J_2 = 2.8 Hz, 1H, OCH_2), 4.68 (dd, J_1 = 11.6 Hz, J_2 = 6 Hz, 1H, OCH_2), 4.94 (m, 1H, CH), 6.57 and 6.82 (two d, J = 8.3 Hz, 2H, aromatic). Anal $C_{11}H_{13}NO_5$ (C, H, N).

6,7-Dimethoxy-3,4-dihydro-3-nitro-2H-1-benzopyran ***5d***
Using the procedure described for **5a**, **4d** (1.78 g, 7.5 mmol) was converted quantitatively to crude **5d**. An analytical sample was obtained by column chromatography on silica gel (eluent CH_2Cl_2); mp = 147°C; IR (KBr), 1600, 1545, 1265, 1135 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.26 (dd, J_1 = 16.4 Hz, J_2 = 6.4 Hz, 1H, benzylic CH_2), 3.49 (dd, J_1 = 16.4 Hz, J_2 = 5.8 Hz, 1H benzylic CH_2), 3.83 and 3.85 (two s, 6H, OCH_3), 4.37 (dd, J_1 = 11.7 Hz, J_2 = 3 Hz, 1H, OCH_3), 4.60 (m, 1H, OCH_2), 4.91 (m, 1H, CH), 6.42 and 6.57 (two s, 2H, aromatic). Anal $C_{11}H_{13}NO_5$ (C, H, N).

5-Methoxy-3,4-dihydro-3-amino-2H-1-benzopyran ***6a***
The crude compound **5a** (0.43 g, 2.05 mmol) was dissolved in ethanol (18 ml) by heating to 80°C and then the solution was cooled to 45°C. Wet Raney nickel (0.4 g) was introduced and 1 ml of 40% hydrazine hydrate solution was added portionwise for 1 h with vigorous stirring. The slurry was stirred at 45°C for an additional 30 min, at which time the reaction was complete, as indicated by TLC (eluent CH_2Cl_2/MeOH 9:1). After cooling, the reaction mixture was filtered on celite and the remaining catalyst washed with ethanol. The evaporation of the filtrate under vacuum to dryness afforded quantitatively the crude amine **6a**, which was of sufficient purity for further use. An analytical sample was obtained by column chromatography on silica gel (eluent diethyl ether/petroleum ether 3:7 then CH_2Cl_2/MeOH 9:1). Data from ^1H NMR and IR spectra and other physical data were identical with those of the same compound prepared previously by another method [9].

8-Methoxy-3,4-dihydro-3-amino-2H-1-benzopyran ***6b***
Following the procedure described for **6a**, **5b** (6.12 g, 29 mmol) afforded quantitatively the crude amine **6b**, which was sufficiently pure for subsequent use. A sample was purified by column chromatography on silica gel. The material was eluted with MeOH/CH_2Cl_2, by gradient elution starting with pure CH_2Cl_2 with the MeOH concentration gradually increasing to 10%. The product was identical in ^1H NMR, IR and TLC data with the amine previously prepared by direct reduction of the unsaturated nitro compound **5** [9].

7,8-Dimethoxy-3,4-dihydro-3-amino-2H-1-benzopyran ***6c***
Using the procedure described for **6a**, **5c** (1.07 g, 4.5 mmol) afforded quantitatively the crude amine **6c**, which was sufficiently pure for further use. The purification by column chromatography (eluent CH_2Cl_2 then CH_2Cl_2/MeOH 95:5) gave an analytical sample; oil; IR (neat) 3350, 3290, 1590, 1275,

1105 cm^{-1}, ^1H NMR ($CDCl_3$) δ 1.78 (broad s, 2H, NH_2), 2.51 (dd, J_1 = 15.6 Hz, J_2 = 7 Hz, 1H benzylic CH_2), 2.97 (dd, J_1 = 15.6 Hz, J_2 = 5.3 Hz, 1H, benzylic CH_2), 3.32 (m, 1H, CH), 3.80 and 3.83 (two s, 6H, OCH_3), 3.82 and 4.18 (two m, 2H, OCH_2), 6.46 and 6.70 (two d, J = 7.7 Hz, 2H, aromatic).

6,7-Dimethoxy-3,4-dihydro-3-amino-2H-1-benzopyran ***6d***
Using the procedure described for **6a**, **5d** (1.43 g, 6 mmol) afforded quantitatively the crude amine **6d**, which was sufficiently pure for further use. The purification by column chromatography (eluent AcOEt) gave an analytical sample; oil; IR (neat) 3300, 1190, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.58 (broad s, 2H, NH_2), 2.50 (dd, J_1 = 16.3 Hz, J_2 = 6.6 Hz, 1H, benzylic CH_2), 2.99 (dd, J_1 = 16.3 Hz, J_2 = 5.4 Hz, 1H, benzylic CH_2), 3.35 (m, 1H, CH), 3.83 (s, 6H, OCH_3), 3.80 and 4.09 (two m, 2H, OCH_2), 6.40 and 6.51 (two s, 2H, aromatic).

5-Methoxy-3,4-dihydro-3-diallylamino-2H-1-benzopyran ***7a***
A solution of crude **6a** (0.322 g, 1.54 mmol) and allyl bromide (1.25 ml, 7.2 mmol) in toluene (9 ml) was warmed at 80–90°C with 4.5 ml of a saturated aqueous K_2CO_3 solution for 48 h. The reaction course was monitored by TLC (eluent AcOEt/petroleum-ether 4:6). When the reaction was achieved, the organic layer was removed, dried over magnesium sulfate and evaporated to give an oily mixture. Chromatography on silica gel of this material (eluent AcOEt/petroleum-ether 1:9) gave 391 mg of pure **7a** [9] (84% from **4a**).

8-Methoxy-3,4-dihydro-3-diallylamino-2H-1-benzopyran ***7b***
Using the procedure described for **7a**, crude **6b** (4.48 g, 25 mmol) was converted to **7b**. Chromatography on silica gel (eluent AcOEt/petroleum-ether 1:9) gave 5.19 g of pure **7b** [9] (80% from **4b**).

7,8-Dimethoxy-3,4-dihydro-3-diallylamino-2H-1-benzopyran ***7c***
Following the procedure reported for **7a**, crude **6c** (0.84 g, 4 mmol) was converted to **7c**. The material was purified by column chromatography using a gradient elution system ranging 10% to 30% AcOEt/petroleum-ether to give 0.914 g of pure **7c** (79% from **4c**); oil; IR (neat) 3072, 1600, 1580, 1280, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.84 (d, J = 8.5 Hz, 2H, benzylic CH_2), 3.24 (m, 1H, CH), 3.25 (d, J = 5 Hz, 4H, NCH_2), 3.83 and 3.84 (two s, 6H, OCH_3), 3.86 (dd, J_1 = 17 Hz, J_2 = 10 Hz, 1H, OCH_2), 4.40 (dd, J_1 = 10 Hz, J_2 = 3.4 Hz, 1H, OCH_2), 5.12 (dd, J_1 = 10 Hz, J_2 = 0.5 Hz, 1H, = CH_2), 5.20 (dd, J = 17 Hz, J_2 = 0.5 Hz, 1H, = CH_2), 5.83 (m, 2H, = CH), 6.48 and 6.74 (two d, J = 8.5 Hz, 2H, aromatic). Anal $C_{17}H_{23}NO_3$ (C, H, N).

6,7-Dimethoxy-3,4-dihydro-3-diallylamino-2H-1-benzopyran ***7d***
Following the procedure reported for **7a**, crude **6d** (1.05 g, 5 mmol) was converted to **7d**. The material was purified by column chromatography eluent AcOEt/petroleum ether 1:9 then 4:6 to give 1.20 g of pure **7d** (83% from **1d**); mp = 42°C; IR (neat) 3075, 1500, 1220, 1125 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.79 (d, J = 8.6 Hz, 2H, benzylic CH_2), 3.25 (m, 1H, CH), 3.27 (d, J = 6 Hz, 4H, $NHCH_2$), 3.80 (s, 6H, OCH_3), 3.82 (t, J = 10 Hz, 1H, OCH_2), 4.26 (dd, J_1 = 10 Hz, J_2 = 3.4 Hz, 1H, OCH_2), 5.12 (dd, J_1 = 10 Hz, J_2 = 0.5 Hz, 2H, = CH_2), 5.19 (dd, J_1 = 15 Hz, J_2 = 0.5 Hz, 2H, = CH_2), 5.82 (m, 2H, = CH), 6.37 and 6.51 (two s, 2H, aromatic). Anal $C_{17}H_{23}NO_3$ (C, H, N).

5-Methoxy-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran ***2a***
A vigorously stirred mixture of **7a** (0.389 g, 1.5 mmol) and 0.039 g of 10% Pd/C in 40 ml of freshly purified [27] ethyl acetate and 2 ml of pure triethylamine was treated by H_2 under atmospheric pressure at room temperature for 45 min. The catalyst was removed by filtration through a celite pad and the solvents evaporated under reduced pressure to give the crude **1a**, which was purified by column chromatography using AcOEt/petroleum-ether (1:9) to AcOEt/petroleum-ether (1:1) gradient to give pure **2a** [8, 9] (0.334 g, 85%).

8-Methoxy-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran ***2b***
This product was prepared by the method described above. Thus 1.5 g of **7b** (5.79 mmol) was converted to 1.31 g of pure **2b** [9] (86%).

7,8-Dimethoxy-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran ***2c***
Following to the procedure for the preparation of **2a**, **7c** (0.97 g, 3.35 mmol) was hydrogenated to give 0.81 g of **2c** (82%); oil; IR (neat) 1582, 1212, 1100, 1085 cm^{-1}; ^1H RMN ($CDCl_3$) δ 0.90 (t, J = 7.5 Hz, 6H, CH_3), 1.47 (m, 4H, CH_2), 2.53 (m, 4H, NCH_2), 2.82 (d, J = 8 Hz, 2H, benzylic CH_2), 3.16 (m, 1H, CH), 3.84 (t, J = 10 Hz, 1H, OCH_2), 3.86 and 3.87 (two s, 6H, OCH_3), 4.40 (dd, J_1 = 10 Hz, J_2 = 3.5 Hz, 1H, OCH_2), 6.49 and 6.76 (two d, J = 8.5 Hz, 2H, aromatic). Anal $C_{17}H_{27}NO_3$ (C, H, N).

6,7-Dimethoxy-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran ***2d***
This product was prepared by the method described for **2a**. Thus **7d** (0.72 g, 2.5 mmol) was converted to 0.60 g of pure **1d** (82%); oil; IR (neat) 1500, 1220, 1130 cm^{-1}; ^1H RMN ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 3H, CH_3); 1.45 (m, 4H, CH_2); 2.48 (m, 4H, NCH_2), 2.76 (m, 2H, CH_2 benzylic), 3.13 (m, 1H, CH), 3.75 (t, J = 10 Hz, 1H, OCH_2), 3.79 (s, 6H, OCH_3), 4.22 (dd, J_1 = 10 Hz, J_2= 3 Hz, 1H, OCH_2), 6.37 and 6.52 (two s, 2H, aromatic). Anal $C_{17}H_{27}NO_3$ (C, H, N).

5-Hydroxy-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran ***1a***
To a solution of **2a** was added 1 ml of hydrobromic acid (0.1 g, 0.38 mmol) in 2 ml of acetic acid. The mixture was refluxed at 130–140°C for 4 h, cooled and then poured with agitation into a mixture of 50 ml saturated sodium bicarbonate, 50 ml dichloromethane and 50 g ice. After decantation, the aqueous phase was extracted several times with dichloromethane. The unified organic layers were dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The crude **1a** was purified by short silica gel column with dichloromethane to obtain 0.09 g of pure **1a** (95%); oil, IR (neat) 3365, 3050, 1580, 1230, 1095; ^1H NMR ($CDCl_3$) δ 0.89 (t, J = 7.9 Hz, 6H, CH_3), 1.48 (m, 4H, CH_2), 2.55 (m, 4H, NCH_2), 2.61 and 2.86 (two dd, J_1 = 6 Hz, J_2 = 17 Hz, 2H, benzylic CH_2), 3.17 (m, 1H, CH), 3.78 (t, J = 10 Hz, 1H, OCH_2), 4.28 (m, 1H, OCH_2), 6.37 and 6.44 (two d, J = 7.9 Hz, 2H, aromatic), 6.93 (t, J = 7.9 Hz, 1H, aromatic) [8, 9]. The hydrochloride derivative of **2a** was prepared using saturated HCl in dry diethyl ether; mp = 210–211°C [28].

8-Hydroxy-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran ***1b***
This compound was prepared by the procedure described above. Thus, **2b** (0.1 g, 0.38 mmol) was converted to 0.09 g of pure **1b** (95%); oil, IR (neat) 3440, 3040, 2955, 2865, 1590, 1200, 1045; ^1H NMR ($CDCl_3$) δ 0.89 (t, J = 7.9 Hz, 6H, CH_3), 1.46 (m, 4H, CH_2), 2.51 (m, 4H, NCH_2), 2.83 (d, J = 7.8 Hz, 2H, benzylic CH_2), 3.19 (m, 1H, CH), 3.83. (t, J = 11.1 Hz, 1H, OCH_2), 4.38 (dd, J_1 = 11.1 Hz, J_2 = 3.3 Hz, 1H, OCH_2), 6.60 (m, 1H, aromatic), 6.74 (m, 2H, aromatic). Anal $C_{15}H_{23}NO_2$ (C, H, N).

7,8-Dihydroxy-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran ***1c***
Following to the procedure for the preparation of **1a**, **2c** (0.12 g, 0.41 mmol) was demethylated and repeatedly extracted

to give crude **1c**, which was purified by column chromatography on silica gel (eluent ethyl acetate/petroleum-ether 4:6). Thus, 0.105 g of pure **1c** (95%) was obtained; oil; IR (neat) 3370, 1595, 1185, 1060; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 7.5 Hz, 6H, CH_3), 1.47 (m, 4H, CH_2), 2.53 (m, 4H, NCH_2), 2.79 (d, J = 8 Hz, 2H, benzylic CH_2), 3.18 (m, 1H, CH), 3.85 (t, J = 10 Hz, 1H, OCH_2), 4.36 (dd, J_1 = 10 Hz, J_2 = 3 Hz, 1H, OCH_2), 5.69 (broad s, 2H, OH), 6.50 (s, 2H, aromatic). Anal $C_{15}H_{23}NO_3$ (C, H, N).

6,7-Dihydroxy-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran ***1d***

This product was prepared by the procedure reported for **1a**. Thus, **2d** (0.142 g, 0.48 mmol) was demethylated by 2.5 ml of acetic acid and 1.25 ml of hydrobromic acid 48% under argon. The extraction, drying on $MgSO_4$ and purification by column chromatography were carefully performed to give 0.115 g (90%) of pure **1d**; oil; IR (neat) 3330, 3040, 1255, 1010; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 7.5 Hz, 6H, CH_3), 1.56 (m, 4H, CH_2), 2.69 (m, 4H, NCH_2), 2.79 (m, 2H, benzylic CH_2), 3.31 (m, 1H, CH), 3.90 (t, J = 10 Hz, 1H, OCH_2), 4.23 (dd, J_1 = 10 Hz, J_2 = 3 Hz, 1H, OCH_2), 5.19 (broad s, 2H, OH), 6.36 and 6.49 (two s, 2H, aromatic). Anal $C_{15}H_{23}NO_3$ (C, H, N).

*(+)-8-Methoxy-3,4-dihydro-3-diallylamino-2H-1-benzopyran (+)-***7b**

A solution of 1.47 g of racemic **7b** (5.67 mmol) in 6 ml methanol was treated with 1.38 g (3.97 mM, 0.7 equivalent) of *S*-(+)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate [(+)-BNPPA] [22] in 40 ml methanol/dichloromethane 9:1. The solvent was then evaporated until precipitation of the salt began. After standing overnight at 4°C, the salt was filtered and washed with cold methanol/ethyl acetate 1:1. The collected crystals were recrystallized from hot methanol (15 ml), and after standing overnight at 4°C filtered and washed as above to give 1.07 g, mp = 156–159°C.

From this salt, the dextrorotatory enantiomer (+)-**7b** was extracted into the organic phase on partitioning between ethyl acetate and ammonium hydroxyde. The ethyl acetate extract, after drying ($MgSO_4$) and evaporating, was filtered over a short column of silica gel (eluent: ethyl acetate) to give 0.455 g of (+)-**7b** (62% from **7b**) as a light yellow oil having the same characteristics of racemic **7b** in TLC, IR and NMR $[\alpha]_D^{20}$ = + 79.1° (c = 1.2, $CHCl_3$).

*(−)-8-Methoxy-3,4-dihydro-3-diallylamino-2H-1-benzopyran (−)-***7b**

The mother liquor from the above described separation of (+)-**7b** was partitioned between ethyl acetate and aqueous ammonia and the organic phase filtered over a short column of silica gel and evaporated. The residue was treated with (−)-BNPPA (3.97 mmol, 0.7 equivalent) in 40 ml methanol/dichloromethane 9:1 to yield, after recrystallization (F = 158–159°C), recovery of the base and filtration on silica gel 0.453 g (61%) of (−)-**7b**, having the same characteristics as (+)-**7b** and the racemic **7b** in TLC, IR an NMR; $[\alpha]_D^{20}$ = − 79.8° (c = 0.21, $CHCl_3$).

*(+)- and (−)-8-methoxy-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (+)-***2b** *and (−)-***2b**

Following the procedure described for the preparation of racemic **2b** using hydrogen in the presence of 10% Pd/C and triethylamine in ethyl acetate, each of the two enantiomers of **7b** was converted to the corresponding enantiomer of **2b**. Thus, (+)-**7b** gave (+)-**2b** (87%), $[\alpha]_D^{20}$ = + 102° (c = 0.4, $CHCl_3$), and (−)-**7b** gave (−)-**2b** (89%), $[\alpha]_D^{20}$ = − 104° (c = 0.6, $CHCl_3$). The two enantiomers showed the same characteristics in TLC, IR and NMR that the racemic **2b**.

*(+)- and (−)-8-Hydroxy-3,4-dihydro-3-(di-n-propylamino)-2H-1-benzopyran (+)-***1b** *and (−)-***1b**

These enantiomers were obtained from (+)-**2b** and (−)-**2b**, respectively by demethylation using HBr 48% in acetic acid, according to the procedure described above for the preparation of the racemic **2b**. Thus, (+)-**2b** gave (+)-**1b** (93%), $[\alpha]_D^{20}$ = + 70° (c = 0.18, $CHCl_3$), and (−)-**2b** gave (−)-**1b** (91%), $[\alpha]_D^{20}$ = − 72° (c = 0,6, $CHCl_3$).

Pharmacology

All experiments were performed with male rats OFA (IFFA CREDO) weighing 200–250 g. After decapitation, the striata were immediately removed and pooled.

Displacement of [^{3}H] apomorphine binding

The [^{3}H]-apomorphine binding assays were performed as previously described [29]. Striatal membranes were prepared in 15 mM Tris-HCl buffer (pH 7.5) containing 1 mM of ethylenediaminetetraacetic acid (EDTA) and 0.01% of ascorbic acid. After two centrifugations at 35 000 *g* for 10 min at 4°C, the suspension was incubated at 37°C for 10 min and centrifuged at 35 000 *g* for 10 min. Membranes were washed twice with Tris-HCl buffer without EDTA and resuspended in Tris-HCl buffer as described below. The incubation mixture consisted of 100 µl membrane (0.1 mg of protein) in 900 µl of 50 mM Tris-HCl buffer, pH 7.5 containing NaCl 120 mM, KCl 5 mM, $CaCl_2$ 2 mM, $MgCl_2$ 1 mM, and 0.1% ascorbic acid and 1 µM pargyline. The final concentration of [^{3}H]-apomorphine (specific activity 29.5 Ci/mmol, NEN) was 0.5 nM in a final volume of 1 ml. Incubations were carried out at 30°C for 30 min. Non-specific binding was determined in the presence of 1 µM cold (−)apomorphine.

Displacement of [^{3}H]spiperone or [^{3}H] SCH 23390 binding

The binding assays were performed as previously described [14]. Striatal membranes were prepared in 50 mM Tris-HCl buffer, pH 7.7 containing 0.1% ascorbic acid and 10 µM pargyline. After two centrifugations at 35 000 *g* for 20 min at 4°C, the suspension was incubated at 37°C for 10 min to block monoamine oxidase activity. The incubation mixture consisted of 400 µl membrane at a protein concentration 0.15–0.20 mg, in 50 mM Tris-HCl buffer, pH 7.7, containing 0.1% ascorbic acid. Binding assays were initiated, by adding 2 nM of [^{3}H] spiperone (specific activity 17 Ci/mmol, Amersham) or 0.5 nM of [^{3}H] SCH 23390 (specific activity 71.3 Ci/mmol, New England Nuclear). The final volume (1 ml) was incubated 15 min or at 37°C 20 min for [^{3}H] spiperone and [^{3}H] SCH 23390 binding respectively. Non specific binding of [^{3}H] spiperone was defined by adding 8 µM of *d*-butaclamol or with 1 mM unlabeled SCH 23390 for [^{3}H] SCH 23390 binding.

Binding was terminated by filtration under vacuum through Whatman GF/C glass fiber filters.

For all experiments, filters were washed twice with ice cold buffer, dried and radioactivity was quantified by scintillation spectroscopy. Displacement studies were analysed by LIGAND computer curve fitting program [30]. Proteins were measured according to Bradford's method [31].

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