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Syntheses and Molecular Structures of 3-*N*,*N*-di-*n*-Propylamino-2-chromanones as New Analogues of Dopamine

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Abstract—A series of 3-*N*,*N*-di-*n*-propylamino-2-chromanones were synthesized as dopamine analogues. The lactone ring was introduced as a means to reduce their propensity to cross the blood–brain barrier and to avoid central side effects, rendering these compounds potentially useful for the treatment of glaucoma. Pharmacological activities were determined *in vitro* on rat striatum, by examining their capacity to displace the specific binding of the labeled dopaminergic ligand ^{3}H sulpiride or ^{3}H spiperone and ^{3}H SCH 23390 for D_2 and D_1 sites, respectively. Compound **6a** showed a weak dopaminergic activity on D_2-receptors and no affinity for D_1-receptors, which can be explained, at least in part, by a weak p*K*a and the presence of an internal hydrogen bonding. Furthermore, computer molecular modelling studies showed that the aromatic ring of **6a** was negatively charged in contrast to the classical D_2-agonists aminotetralin derivatives, hampering a possible interaction with a negatively charged area of the D_2-receptor. These results, taken together, can account for the moderate dopaminergic activities exhibited by these lactone derivatives.

Introduction

Several pharmacological classes of drugs have been used in the treatment of glaucoma. Currently, there are no clinically used dopaminergic drugs, although it was known that both D_2-agonists and antagonists could lower intraocular pressure (IOP) in man and animal.[1,2] The mechanism of this action remains unclear, but it may involve the prejunctional D_2-receptor stimulation in the ciliary body.

D_1- and D_2-receptors have been found at the ocular level. Several dopaminergic antagonists, such as haloperidol or trifluoroperidol, are more active than timolol, a β-adrenergic blocker, used for the conventional treatment of glaucoma. Otherwise, dopamine **I** (Fig. 1) itself induced a drop of IOP which is inhibited by haloperidol.[3] The hydroxydipropylaminotetralin (OH-DPAT, **II**) and the 11-hydroxy *N*-propylnoraporphine containing the hydroxyaminotetralin structure are potent D_2-agonists.[4,5] The D_2-agonist bromocriptine and 6,7-dihydroxyaminotetralin decreased IOP.[6,7] Besides aminochromane derivatives, the oxygen isosteres of aminotetralins exhibited marked activity, particularly 8-hydroxydipropylaminochromane (8-OH-DPAC, **III**) which was remarkably more active on the D_2-receptor than apomorphine.[8,9]

Our research prepared new dopaminergic substances of the D_2-type derived from the aminotetralin skeleton. In the hope of avoiding their well-known central side effects, and to reduce their ability to cross the blood–brain barrier, we replaced the C_3–C_4 linkage of **II** by –O–CO– to obtain a chromanone **IV**.

This paper describes here the synthesis of seven 3-amino-2-chromanone derivatives in order to investigate *in vitro* the D_1/D_2 selectivity, by examining the derivatives ability to displace the specific binding of the labelled dopaminergic ligands: ^{3}H sulpiride and ^{3}H spiperone for D_2 sites and ^{3}H SCH 23390 for D_1 sites.

Results

The synthesis of target compounds **6a–d** and **7a–c** (Scheme 1) began by the preparation of amino acids **3a-d** according to Finkbeiner:[10] condensation of hydantoin with an appropriate 2-methoxybenzaldehyde derivative afforded the corresponding alkylidene compounds **1a–d** with good yields. The catalytic hydrogenation using palladium produced the saturated analogues, except for 5-(2,4,6-trimethoxybenzylidene)-hydantoin (**1e**), which failed to be reduced. Compounds **2a–d** were immediately hydrolyzed by refluxing with barium hydroxide for three days. With the goal of cyclization, the corresponding esters **4a–d** were obtained via the intermediate acyl chloride.

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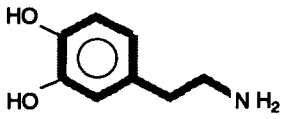
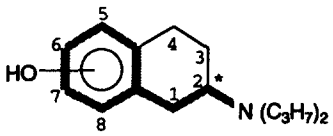
Key words: dopaminergic agents, dopamine rigid analogues, 3-amino-2-chromanone, glaucoma, molecular modelling.

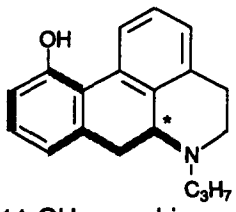


I dopamine

aminotetraline structure:

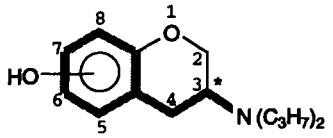


II OH-DPAT



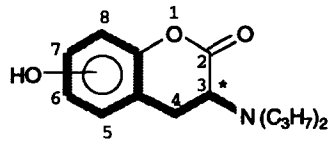
11-OH aporphine

aminochromane derivatives:



III OH-DPAC

aminochromanone derivatives:



IV

Figure 1. Dopamine and structural analogues.

Among direct reductive alkylation of the primary amines **4a–d**, without reduction of ester group, sodium cyanoborohydride[11] and tripropanoyl borohydride[12] can be used. As for us, we used the latter method which gave good yield for **5a–d** (Scheme 1).

The primary amino group was also acylated with propionic anhydride (Scheme 2) to lead to an amide which was reduced, acylated again and again reduced to the final *N*-dipropyl compounds **5a–d**. Reduction of the intermediate amide **8** with $NaBH_4$/AcOH or $NaBH_4$/TFA (trifluoroacetic acid) in THF or dioxan[13] led to reduction of the amide and ester functions into amide alcohol **9** and amino alcohol **10**, respectively.

Treatment of **5a–d** by 47% HBr under reflux led to the corresponding phenols, which subsequently cyclized into the target dipropylaminochromanones **6a–c**, with excellent yield.

On the other hand, cyclization of the unsubstituted compound **5d** failed to give the chromanone ring **6d** with sulfuric acid, polyphosphoric acid, trifluoroacetic anhydride and dicyclohexylcarbodiimide. Finally, **6d** was obtained by the elimination of phenolic hydroxyl from **6c**.[14] The hydrogenolysis of the mesylate of **6c** gave 15% yield of **6d**. Due to the expected instability of compounds **6a–c**, pivaloyl esters **7a–c** were prepared. Compounds **1a**,[15] **2a**,[14] **3a**,[15] **1c**,[16] **2c**,[17] **3c**,[18] **1d**,[19] **2d**,[19] **3d**,[19] as well as **1e**,[20] have been previously mentioned in the literature.

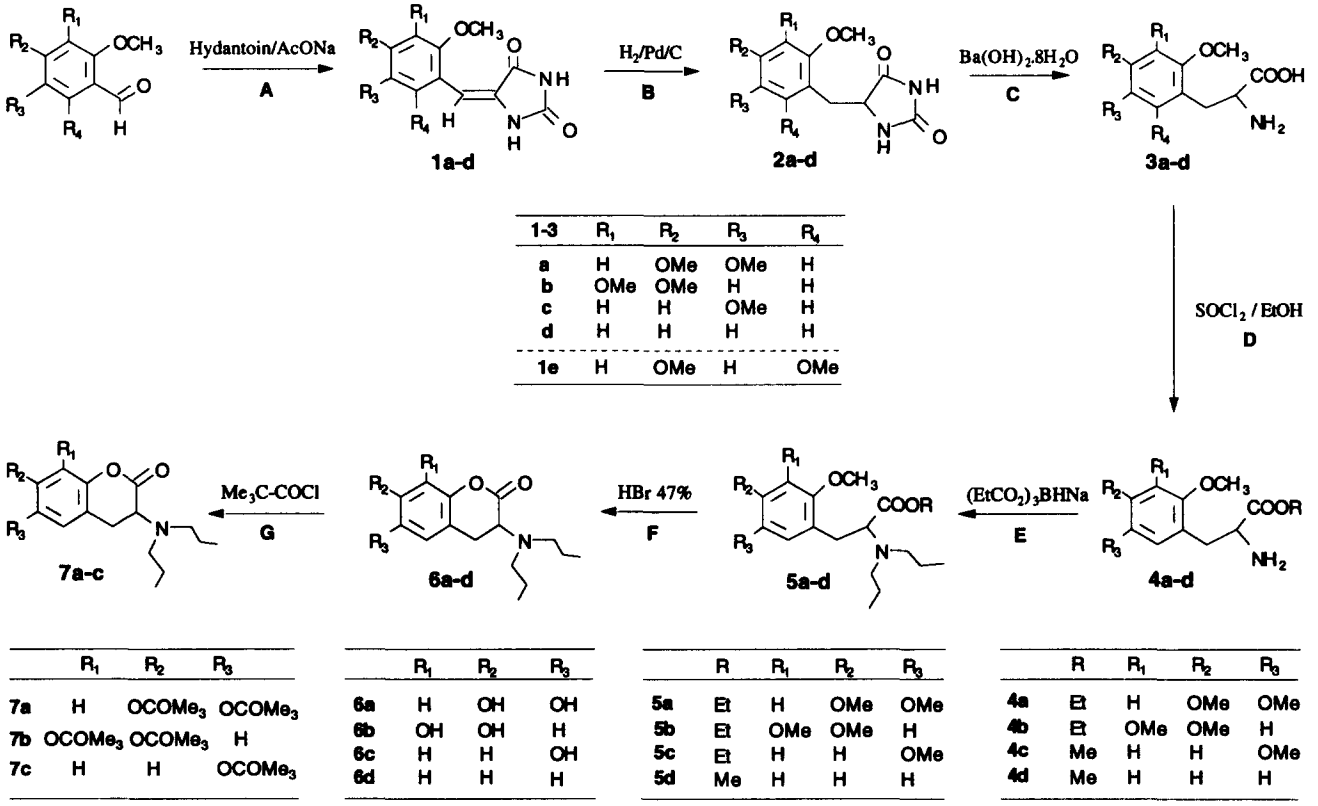
Compound **6a** was evaluated on rat synaptosomes for its activities in binding assays on various receptors: adrenergics, amino acids, biogenic amines, calcium channels, cholinergics, opioids, prostanoids receptors, etc. Only activity on the dopaminergic receptors was detected, with butaclamol and spiperone used as D_1 and D_2 references, respectively. At 0.01 mM, compound **6a** displaced *ca* 40% of the D_2 selective ligand ^3H sulpiride (IC_{50} > 0.5 mM), but only 2.5% of the D_1 selective ligand ^3H SCH 23390. In the same manner, compounds **6b** and **c** showed almost no activity for D_2-receptors (IC_{50} > 0.1 mM and > 1 mM, respectively, to displace ^3H spiperone), as compared with structurally related D_2-agonists 6,7-diOH-DPAC[9] and 5-OH-DPAT.[21]

Discussion

According to Hibert *et al.* in the H_5-helix of the D_2-receptor, serine residues (Ser_{505} and Ser_{508}) play a role in the binding with the catechol moiety.[22,23] The charged Asp_{311} in H_3 is likely to be involved in the cationic neurotransmitter binding. For aromatic neurotransmitters, stabilizing interactions are provided by Phe_{509} and Phe_{617}. Chromanone derivatives could show similar interactions in place of dopamine with the D_2-receptor.

Previous work suggested that a charged form of the nitrogen atom is a prerequisite for binding with Asp_{311} of the D_2-receptor.[24,25] Besides, Harrold *et al.* underlined the importance of the hydrogen bond between the nitrogen proton and the aspartate carbonyl to stabilize the ionic bond between N^+ and the carboxylate anion.[26] The chromanone derivatives were thought to be active as protonated form A (Fig. 2). However, we showed that the intramolecular hydrogen bond form B was prevalent at pH 7.5. This latter form would be inactive because the intramolecular-bonded proton would be unable to establish hydrogen bond with the receptor. Moreover this intramolecular bond can also account in part for the pK_a value 7.31 observed for **6a** which was lower than expected by calculations using Hansch data. This could explain the poor activity observed.

In order to ascertain the existence of the C=O---H–N hydrogen bond in the chromanone series, we chose, as a spectral model, the non-hydroxylated compound **7c** and discarded the bis-hydroxylated compound **6a** [Fig. 2(B)]. In KBr, the absorption at 3400 cm^{-1} remained



1-3	R_1	R_2	R_3	R_4
a	H	OMe	OMe	H
b	OMe	OMe	H	H
c	H	H	OMe	H
d	H	H	H	H
1e	H	OMe	H	OMe

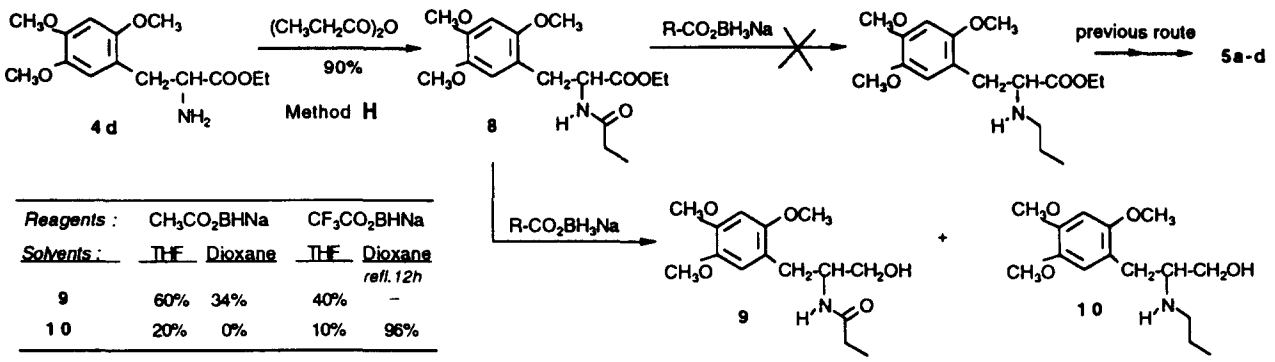
	R_1	R_2	R_3
7a	H	$OCOMe_3$	$OCOMe_3$
7b	$OCOMe_3$	$OCOMe_3$	H
7c	H	H	$OCOMe_3$

	R_1	R_2	R_3
6a	H	OH	OH
6b	OH	OH	H
6c	H	H	OH
6d	H	H	H

	R	R_1	R_2	R_3
5a	Et	H	OMe	OMe
5b	Et	OMe	OMe	H
5c	Et	H	H	OMe
5d	Me	H	H	H

	R	R_1	R_2	R_3
4a	Et	H	OMe	OMe
4b	Et	OMe	OMe	H
4c	Me	H	H	OMe
4d	Me	H	H	H

Scheme 1. General reaction scheme for compounds **1a–d** to chromanones **6a–d** and **7a–c**.



Reagents :	CH_3CO_2BHNa		CF_3CO_2BHNa	
Solvents :	THF	Dioxane	THF	Dioxane *refl. 12h*
9	60%	34%	40%	–
10	20%	0%	10%	96%

Scheme 2. Reaction scheme for compounds **8–10**.

constant, whatever the concentration, and thus was assigned to the intramolecular hydrogen bonding; whereas the band at 3200 cm^{-1}, which varied with the concentration, was assigned to the intermolecular hydrogen bond. The FT–IR spectra of **7c** were in agreement with this hypothesis, i.e. the weak band at 3400 cm^{-1} was consistent with an intramolecular bond. The shoulder in the carbonyl absorbance at 1715 cm^{-1} was compatible with the geometry of the molecule e.g. between 1670 cm^{-1} for a linear alignment and 1760 cm^{-1} for a normal CO absorption.

Further support to explain the poor affinity of such chromanones can be given by the fact that upon removal of the carbonyl function in the chromanone **IV** to yield the chromane **III**, precluding the hydrogen bonding, a more active DA agonist was obtained.

In conclusion, as in **7c**, an intramolecular hydrogen bond between the nitrogen proton and the carbonyl oxygen could be expected in **6a–d** and **7a** and **b**. These predictions were confirmed by conformational study of protonated **6a**. Results of the molecular modelling studies could also explain the poor biological activity of the studied dipropylaminochromanone derivatives.

Molecular Modelling

Attempts to analyze the differences in pharmacological responses of molecule **6a** with the analogous D_2-agonists 5-OH-DPAT, 6,7-diOH-DPAT and 6,7-diOH-

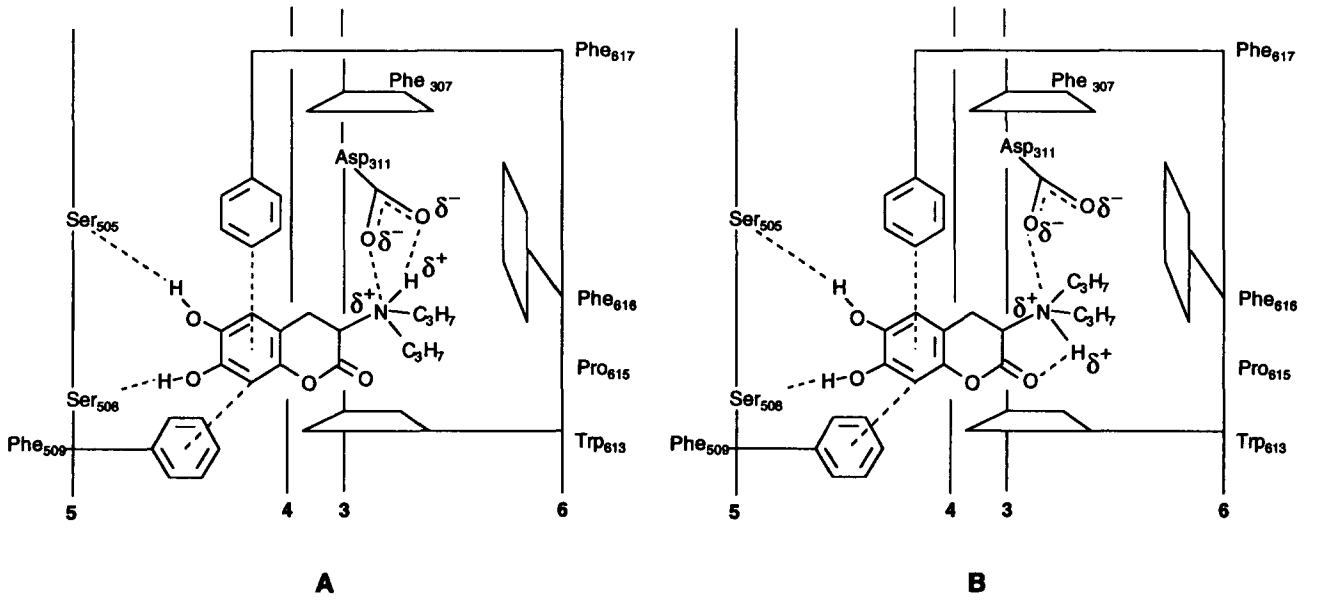


Figure 2. Representation of the interaction between protonated **6a** and D_2-receptor. Comparison of the binding with a reinforced ionic bond (active form A) and with an intramolecular hydrogen bond (inactive form B; recognition sites according to Hibert [23] with author permission).

DPAC (Fig. 1) were made using computer-aided molecular modelling techniques. These techniques show topological, structural and energetic similarities, or differences, between several molecules.[27]

The computer used was an IBM RS6000-540 with a graphics screen. Each molecule was built with a QUANTA program using standard parameters and minimized with a CHARMM force field, using first the steepest-descent algorithm and then the Adapted-Basis-Newton–Raphson algorithm, until convergence.[28] Although, *ca* 50% of **6a** compound will be ionized at pH 7.5, we have studied this form, expected to be the active one. Among the selected references, (2*S*)-5-OH-DPAT was reported to be 120-fold more potent on the D_2-receptor than the (2*R*)-enantiomer,[21] therefore, we performed our molecular modelling studies on each molecule in the analogous configuration.

In order to establish a structural comparison, **6a** was superimposed (not shown) successively with 6,7-diOH-DPAC and with 6,7-diOH-DPAT (5-OH-DPAT is strictly superimposable to 6,7-diOH-DPAT) by a fitting of the aromatic rings (Fig. 3).

To compare more quantitative geometric parameters, several calculations were made. The H–N^+ proton in 6,7-diOH-DPAT is staggered with the axial hydrogen atom (Ha), whereas the dihedral Ha–C^*–N^+–H in **6a** and in 6,7-diOH-DPAC is close to 90 °. In 5 ° steps the grid scan on **6a** showed a possible intramolecular hydrogen bond (d = 1.884 Å) between the H–N^+ proton and the carbonyl oxygen. The existence of the intramolecular hydrogen bond was observed in the protonated analogue **7c** (Scheme 1) by IR spectroscopy.[29] The calculations of the solvent-accessible surfaces were made with a 1.4 Å probe which is approximately the radius of the water molecule. The total solvent-accessible surface areas are almost equal, but the hydrophilic surface area of **6a** is 3.7 times larger than that of 5-OH-DPAT, which has the lowest area. In order to correlate activities and aqueous solubilities, solvation energies were calculated using the total energy method of the DELPHI program.[30] As expected from hydrophilic surfaces values, **6a** has the lowest solvation energy, –61.9 kcal mol^{-1} and 5-OH-DPAT the largest, –54.5 kcal mol^{-1}. The molecular volume of each molecule shows few differences, the values of intersection volumes and union volumes of **6a** with other molecules indicate that their geometries are different. The differences are increasing from 6,7-diOH-DPAC to 6,7-diOH-DPAT and 5-OH-DPAT. The dipole moments have values and directions very dependent on hydroxyl groups and lactone function presences (Fig. 3). The electrostatic potentials for each molecule interacting with a proton probe show that only 5-OH-DPAT bears negative areas on its aromatic carbons (Fig. 3). These negative areas might facilitate interactions with electrophilic areas of D_2-receptors, constituted by Phe_{509} and Phe_{617}.

This study points out some geometric and electrostatic parameters that affect the dopaminergic activity of such D_2-agonists and that can be used for the design of active D_2 ligands. The amino group has to be protonated, and the H–N^+ proton has to be able to form an intermolecular hydrogen bond with Asp_{311} of the D_2-receptor. The direction of this proton depends on the orientation of the dipropylamino chain. This direction 'above' or 'below' the aromatic ring plane plays an important role in the agonist or antagonist activity[31] and the presence of an electron-withdrawing group on the phenolic ring, decreasing electronic density on the catechol moiety, as indicated in our molecular modelling study, could introduce a subtle D_1/D_2 modulation and induce affinity and selectivity changes.[32]

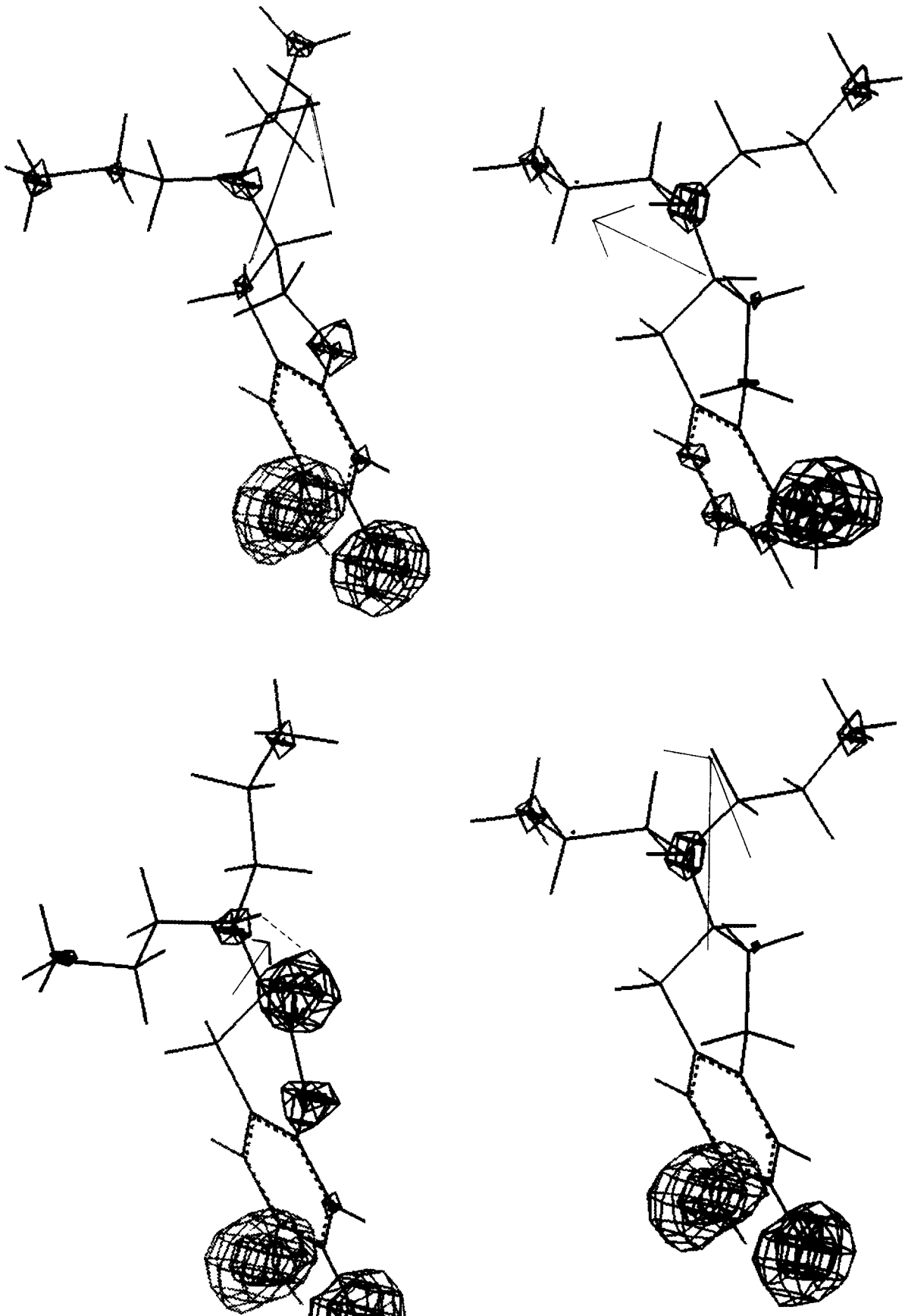


Figure 3. Only negative electrostatic potentials of **6a** and di-OH-DPAC (above), di-OH-DPAT and 5-OH-DPAT (below) in their lowest energy conformations are represented (between −5 and −70 kcal mol^{-1}). Molecules are represented in the same spatial orientation. Note the presence of the intramolecular hydrogen bond in (3*R*)-**6a** and the direction of the N^+–H bond which is more different between **6a** and di-OH-DPAT than between **6a** and di-OH-DPAC. The arrows show the values and the directions of the dipole moments: 1.706 D (**6a**), 6.244 D (di-OH-DPAC), 6.086 D (di-OH-DPAT), 2.640 D (5-OH-DPAT).

In conclusion, 3-*N*,*N*-di-*n*-propylamino-2-chromanone derivatives displayed moderate dopaminergic activity, probably because of weak pK_a, electronic and steric factors and because of intramolecular hydrogen bonds. Among these compounds, **6a** exhibited selective activity for the D_2 subtype.

Experimental

All solvents and reagents were purchased from Merck or Aldrich Chemical. TLC was performed on Merck silica gel (60 F 254) precoated plates. CC was carried out on Merck silica gel 60 (0.063–0.200 nm). Melting points were taken on a Kofler bench and were uncorrected. UV spectra were obtained on a Pye–Unicam SP7-100 (Philips) instrument and are reported in nm. IR spectra were obtained on a Pye–Unicam SP3-100 (Philips) instrument and are reported in wave number (cm^{-1}). Samples were analyzed as potassium bromide (KBr) disks or as film. ^1H NMR spectra were obtained on a Bruker AC200 Fourier transform spectrometer, operating at 200 MHz, on a Bruker AM300FT, operating at 300 MHz, and on a Bruker WP80, operating at 80 MHz. Samples (10–20 mg) were dissolved in DMSO-d_6 or D_2O, or DMSO-d_6 + D_2O, $CDCl_3$ or MeOD-d_4 as solvents. Chemical shift (*d*) data are reported in ppm downfield from internal hexamethyldisiloxane. ^1H NMR data are reported in the following order: chemical shift, multiplicity (*s*, singlet; *d*, doublet; *t*, triplet; *q*, quadruplet; *sext*, sextuplet; *m*, multiplet) and number of protons. ^1H coupling constant (*J* values) are given in Hertz (Hz). ^{13}C NMR data were obtained at 200 MHz and Distortionless Enhancement by the Polarization Transfer (DEPT) program. Mass spectra were obtained on a Nermag quadrupole R-10-10C in electron impact (EI) and FAB.

General procedure for the preparation of alcoxybenzylidene-hydantoin (1a–e)

5-(2,4,5-Trimethoxybenzylidene)-hydantoin (1a) (Method A). Hydantoin (19 g, 0.19 mol), anhydrous sodium acetate (22 g, 0.27 mol) and 2,4,5-trimethoxybenzaldehyde (25 g, 0.13 mol) were successively poured in a solution of glacial acetic acid (36 mL) and acetic anhydride (1 mL). The mixture was mechanically stirred at 170 °C (oil bath) under nitrogen for 3 h. When the temperature reached *ca* 120 °C, 170 mL of water were added dropwise and the mixture stirred at room temperature overnight. The orange precipitate of **1a** was filtered off, washed with water and crystallized from DMF:CH_3CO_2H (50:50), yield 93%, mp 275–278 °C (mp 274–275 °C.[15]). IR (KBr): 3325, 1750, 1705, 1640, 1600, 1500, 1380, 1280, 1200, 1120, 1020, 990, 970, 860, 820 cm^{-1}. NMR (200 MHz; DMSO-d_6): δ 3.78 (3H, *s*, C<u>H</u>$_3$O); 3.82 (6H, *s*, 2C<u>H</u>$_3$O); 6.61 (1H, *s*, Ar-<u>H</u>); 6.70 (1H, *s*, Ar-<u>H</u>); 7.02 (1H, *s*, C<u>H</u>=C). MS (EI): M_r = 278; m/z 278 (M, 100). $C_{13}H_{14}N_2O_5$ M_r = 278.27.

Using a similar experimental procedure to that described above, but replacing 2,4,5-trimethoxybenzaldehyde with the appropriate benzaldehyde, compounds **1b–e** were prepared.

5-(2,3,4-Trimethoxybenzylidene)-hydantoin (1b). Yellow crystals (yield 90%), mp 194–196 °C. IR (KBr): 3200, 2950, 1750, 1720, 1640, 1600, 1510, 1380, 1300, 1220, 1100, 800 cm^{-1}. NMR (200 MHz ; DMSO-d_6): δ 3.73; 3.77; 3.81 (9H, 3*s*, 3C<u>H</u>$_3$O); 6.49 (1H, *s*, C<u>H</u>=C); 6.80; 7.40 (2H, 2*d*, Ar-<u>H</u>); 9.2; 10.86 (2H, 2*s*, N-<u>H</u>). $C_{13}H_{14}N_2O_5$.

5-(2,5-Dimethoxybenzylidene)-hydantoin (1c). Yellow crystals (yield 93%), mp 253–255 °C (mp 249–251 °C.[16]). IR (KBr): 3400, 3200, 2950, 1780, 1720, 1660, 1500, 1390, 1220, 1050 cm^{-1}. NMR (200 MHz; DMSO-d_6): δ 3.73; 3.76 (6H, 2*s*, C<u>H</u>$_3$0); 6.57 (1H, *s*, C<u>H</u>=C); 6.84–7.07 (3H, *m*, Ar-<u>H</u>); 10.86 (2H, *s*, N<u>H</u>). $C_{12}H_{12}N_2O_4$.

5-(2-Methoxybenzylidene)-hydantoin (1d). Yellow crystals (yield 90%), mp 175–180 °C (mp 178 °C[19]). IR (KBr): 3400, 3220, 1750, 1720, 1640, 1600, 1500, 1400, 1300, 1240, 1100, 1020, 700 cm^{-1}. NMR (200 MHz; DMSO-d_6): δ 3.6 (3H, *s*, C<u>H</u>$_3$O); 6.85–7.21 (5H, *m*, Ar-<u>H</u>; C=C<u>H</u>); 9.24; 10.81 (2H, 2*s*, N-<u>H</u>). $C_{11}H_{10}N_2O_5$.

5-(2,4,6-Trimethoxybenzylidene)-hydantoin (1e). Yellow crystals (yield 92%), mp 265–270 °C (mp 258–260 °C[20] for hydrate $0.15H_2O$ without other data). IR (KBr): 3400, 3200, 300, 1760, 1720, 1660, 1600, 1400, 1340, 1200, 1160, 1120, 1040, 800, 650 cm^{-1}. NMR (80 MHz; DMSO-d_6): δ 3.76 (9H, *s*, $3CH_3$); 6.23 (2H, *s*, Ar-<u>H</u>); 6.36 (1H, *s*, C<u>H</u>=C); 9.23; 10.90 (2H, 2*s*, 2N<u>H</u>). Anal. $C_{13}H_{14}N_2O_5$, M_r = 278.27 (C, H, N).

General procedure for the preparation of alcoxybenzylhydantoins (2a–d)

5-(2,4,5-Trimethoxybenzyl)-hydantoin (2a) (Method B). Benzylidene hydantoin (**1a**) (20 g, 73 mmol), obtained as above, was solubilized in 1 N aqueous NaOH solution and 10% Pd/C (2 g). The mixture was treated by molecular H_2 at room temperature and normal pressure. When the reaction was complete (as indicated by TLC), catalyst was filtered on Celite, the hot filtrate was acidified by concentrated HCl until pH 5 and left aside overnight at 0–4 °C to crystallize. White solid, yield 96%, mp 230–235 °C (mp 234 °C[14]). IR (KBr): 3200, 1760, 1710, 1600, 1500, 1460, 1430, 1400, 1380, 1200, 1120, 1035, 820 cm^{-1}. NMR (200 MHz; DMSO-d_6): δ 2.50–3.00 (2H, 2*dd*, C<u>H</u>$_2$); 3.60 (3H, *s*, C<u>H</u>$_3$O); 3.78 (3H, *s*, C<u>H</u>$_3$O); 3.80 (3H, *s*, C<u>H</u>$_3$O); 4.11 (1H, *dd*, C<u>H</u>-CO); 6.64 (1H, *s*, Ar-<u>H</u>); 6.75 (1H, *s*, Ar-<u>H</u>); 7.76 (1H, *s*, N<u>H</u>); 10.56 (1H, *s*, N<u>H</u>). MS (EI): M_r = 280 m/z 281 (M + 1, 10); 181 (M–hydantoin, 100). $C_{13}H_{16}N_2O_5$, M_r = 280.28.

Using a similar experimental procedure to that described above, but replacing **1a** with the appropriate benzylidene hydantoin, compounds **2b–d** were prepared.

5-(2,3,4-Trimethoxybenzyl)-hydantoin (2b). White crystals (yield 98%), mp 170–172 °C. IR (KBr): 3380, 3100, 2900, 2800, 1750, 1710, 1580, 1450, 1400, 1080, 790, 740, 610 cm^{-1}. NMR (200 Mhz; DMSO-d_6): δ 2.70–2.93 (2H, 2*dd*, C$\underline{H}_2$); 3.66; 3.75; 3.82 (9H, 3*s*, 3C$\underline{H}_3$O); 4.91 (1H, *dd*, C$\underline{H}$); 6.69; 6.86 (2H, 2*d*, Ar-$\underline{H}$); 7.67; 10.55 (2H, 2*s*, N-$\underline{H}$). $C_{13}H_{16}N_2O_5$.

5-(2,5-Dimethoxybenzyl)-hydantoin (2c). White solid (yield 96%), mp 165–170 °C (mp 171–173 °C[17]). IR (KBr): 3220, 2950, 1780, 1720, 1600, 1500, 1400, 1300, 1220, 1040, 800, 740, 700 cm^{-1}. NMR (200 MHz; DMSO-d_6): δ 2.70–2.92 (2H, 2*dd*, C$\underline{H}_2$); 3.73; 3.76 (6H, 2*s*, C$\underline{H}_3$O); 4.01 (1H, *dd*, C$\underline{H}$); 6.84–7.07 (3H, *m*, Ar-$\underline{H}$). $C_{12}H_{14}N_2O_4$.

5-(2-Methoxybenzyl)-hydantoin (2d). White solid (yield 96%), mp 189–191 °C (mp 186 °C[19]). IR (KBr): 3200, 2950, 1780, 1720, 1600, 1495, 1400, 1240, 1200, 1120, 1020, 760 cm^{-1}. NMR (200 MHz; DMSO-d_6): δ 2.64–3.10 (2H, *m*, Ar-C$\underline{H}_2$); 3.75 (3H, *s*, C$\underline{H}_3$O); 4.23 (1H, *t*, C$\underline{H}$); 6.85–7.21 (4H, *m*, Ar-$\underline{H}$); 7.75 (1H, *s*, N$\underline{H}$). $C_{11}H_{12}N_2O_3$.

General procedure for the preparation of alcoxyphenylalanine derivatives (3a–d)

3-(2,4,5-Trimethoxyphenyl)-alanine (3a) (Method C). A mixture of compound **2a** (56 g, 0.22 mol), $Ba(OH)_2 \cdot 8H_2O$ (125.8 g, 0.40 mol) and 840 mL water was refluxed for 90 h. The hot crude product was filtered off and washed with hot water. The hot filtrate (80–90 °C) was acidified with 50% H_2SO_4 until pH 6.5. The solid was filtered off and the two precipitates were suspended in boiling water, collected by filtration and recrystallized from 95% ethanol. Compound **3a** was obtained with 72% yield, as a white solid, mp (HCl) 225–230 °C (mp 226 °C[15]). IR (KBr): 3210, 2950, 2450, 1600, 1520, 1400, 1310, 1200, 1040, 840 cm^{-1}. ^1H NMR (200 MHz; D_2O): δ 2.77–3.02 (2H, 2*dd*, C$\underline{H}_2$, J_2 = 14.44 Hz, J_3 = 7.86 Hz, J_3 = 4.67 Hz); 3.71; 3.73; 3.74 (9H, 3*s*, C$\underline{H}_3$O); 3.77 (1H, *dd*, C$\underline{H}$); 6.52; 6.60 (2H, 2*s*, Ar-$\underline{H}$). ^{13}C NMR (200 MHz; D_2O): δ 37.50 (Ar-$\underline{C}H_2$); 55.22; 55.52; 55.74 (3$\underline{C}H_3$O); 55.99 ($\underline{C}$H); 97.78 ($\underline{C}$3); 141.72; 148.10; 151.65 (C-2, C-4, C-5); 115.02 (C-6). $C_{12}H_{17}NO_5$.

Using a similar experimental procedure to that described above, but replacing **2a** with the appropriate benzaldehyde, compounds **3b–d** were prepared.

3-(2,3,4-Trimethoxyphenyl)-alanine (3b). White crystals (yield 74%), mp (HCl) 258–262 °C. IR (KBr): 3250, 2950, 1600, 1480, 1410, 1100, 820, 850, 700 cm^{-1}. NMR (200 MHz; D_2O): δ 2.73–3.25 (2H, 2*dd*, C$\underline{H}_2$, J_2 = 14.52 Hz, J_3 = 8.08 Hz, J_3 = 5.00 Hz); 3.68 (1H, *dd*, CH, J_3 = 8.08 Hz, J_3 = 5.00 Hz); 3.55; 3.61; 3.63 (9H, 3*s*, 3C$\underline{H}_3$O); 6.59; 6.75 (2H, 2*s*, Ar-$\underline{H}$). $C_{12}H_{17}NO_5$.

5-(2,5-Dimethoxyphenyl)-alanine (3c). White solid (yield 68%), mp (HCl) 225–228 °C (mp 225 °C[18]). IR (KBr): 3400, 3050, 2950, 1590, 1600, 1400, 1220, 1040, 860, 810, 700 cm^{-1}. NMR (200 MHz; D_2O): δ 2.76–3.25 (2H, 2*dd*, C$\underline{H}_2$); 3.54; 3.58 (6H, 2*s*, 2C$\underline{H}_3$O); 3.76 (1H, *dd*, C$\underline{H}$); 6.60; 6.79 (3H, 2*d*, 1*s*, Ar-$\underline{H}$). $C_{11}H_{15}NO_4$.

3-(2-Methoxyphenyl)-alanine (3d). White crystals (yield 70%), mp (HCl) 210–212 °C (mp 205–208 °C[19]). IR (KBr): 3400, 3020, 2950, 1600, 1400, 1240, 1020, 750 cm^{-1}. NMR (200 MHz; DMSO + D_2O): δ 2.71 (2H, 2*dd*, Ar-C$\underline{H}_2$); 3.71 (3H, *s*, OC$\underline{H}_3$); 4.09 (1H, *dd*, C$\underline{H}$); 6.73–7.23 (4H, *m*, Ar-$\underline{H}$). $C_{10}H_{13}NO_3$.

General procedure for the preparation of 2-amino-3-(alcoxyphenyl)alkylpropanoates (4a–e)

2-Amino 3-(2,4,5-trimethoxyphenyl) ethyl propanoate (4a) (Method D). $SOCl_2$ (3.6 mL, 0.05 mol) was added dropwise to 200 mL (0.5 mol) cold methanol (–5–0 °C) under nitrogen atmosphere, without rising above 10 °C. The amino acid **3a** (0.025 mol) was added and the yellow solution was refluxed for 4 h. The $SOCl_2$ in excess was evaporated under reduced pressure giving a solid which was recrystallized from 95% EtOH. Compound **4a** was obtained in 80% yield as white crystals, mp (HCl) 210–215 °C. IR (KBr): 3200, 2960, 2820, 2600, 1740, 1600, 1510, 1400, 1300, 1210, 1015, 900, 840, 800 cm^{-1}. NMR (200 MHz; D_2O): δ 1.00 (3H, *t*, C$\underline{H}_3$-CH$_2$); 3.01 (2H, 2*dd*, Ar-C$\underline{H}_2$); 3.57; 3.78; 3.85 (9H, 3*s*, C$\underline{H}_3$O); 4.00 (2H, *q*, C$\underline{H}_2$O); 4.10 (1H, *dd*, C$\underline{H}$); 6.51; 6.60 (2H, 2*s*, Ar-$\underline{H}$). MS (FAB+, glycerol): M_r = 283; m/z 284 ([M + 1]$^+$, 25). Anal. $C_{14}H_{21}NO_5$ M_r = 283.32 (C, H, N, O).

Using a similar experimental procedure to that described above, but replacing **3a** by the appropriate amino acid, compounds **4b–d** were prepared.

2-Amino 3-(2,3,4-trimethoxyphenyl) ethyl propanoate (4b). White crystals (yield 72%), mp (HCl) 155–160 °C. IR (KBr): 3350, 2950, 2840, 1720, 1600, 1480, 1460, 1200, 1140, 800, 760 cm^{-1}. NMR (200 MHz; D_2O): δ 0.98 (3H, *t*, C$\underline{H}_3$-CH$_2$); 3.00 (2H, 2*dd*, Ar-C$\underline{H}_2$); 3.59; 3.78; 3.80 (9H, 3*s*, 3C$\underline{H}_3$O); 4.15 (2H, *q*, C$\underline{H}_2$O); 4.25 (1H, *dd*, C$\underline{H}$); 6.51; 6.60 (2H, 2*s*, Ar-$\underline{H}$). MS (FAB+, glycerol): M_r = 283; m/z 284 ([M + 1]$^+$, 60). Anal. $C_{14}H_{21}NO_5 \cdot 0.25H_2O$, M_r = 287,82 (C, H, N).

2-Amino-3-(2,5-dimethoxyphenyl) methyl propanoate (4c). Compound **4c** was obtained with MeOH in place of EtOH (yield 78%) as white crystals, mp (HCl) 156–159 °C. IR (KBr): 2950, 1740, 1580, 1500, 1400, 1280, 1220, 1080, 1040, 820, 700 cm^{-1}. NMR (200 MHz; DMSO-d_6): δ 3.05 (2H, *d*, Ar-C$\underline{H}_2$); 3.57 (3H, *s*, C$\underline{H}_3$OCO); 3.67; 3.69 (6H, 3*s*, 2C$\underline{H}_3$O); 4.06 (1H, *t*, C$\underline{H}$); 8.69 (2H, *s*, N$\underline{H}_2$). MS (FAB+, glycerol), M_r = 239, m/z 240 (M + 1, 80); 180 (M–CO_2CH_3), 100). Anal. $C_{12}H_{18}NO_4Cl$, M_r = 275.73 (C, H, N, O, Cl).

2-Amino-3-(2-methoxyphenyl) ethyl propanoate (4d). White crystals (yield 78%), mp (HCl) 158–160 °C. IR

(KBr): 3380, 2950, 2840, 1720, 1600, 1490, 1460, 1380, 1240, 1200, 760 cm^{-1}. NMR (200 MHz; D_2O): δ 1.10 (3H, *t*, $C\underline{H}_3$-CH_2); 3.01 (2H, 2*dd*, Ar-$C\underline{H}_2$); 3.57 (3H, 3*s*, $C\underline{H}_3O$); 4.10 (2H, *q*, $C\underline{H}_2O$); 4.25 (1H, *dd*, C<u>H</u>); 6.51–6.60 (2H, 2*s*, Ar-<u>H</u>). Anal. $C_{11}H_{16}NO_3Cl$, M_r = 245.60 (C, H, N).

General procedure for the preparation of 2-N,N-dipropylamino-3-(alcoxyphenyl) alkyl propanoate (5a-d)

2-(N,N-Di-n-propylamino-3-(2,4,5-trimethoxyphenyl) ethyl propanoate (5a) (Method E). Sodium borohydride (2.4 g, 63 mmol) was slowly added to a solution of propionic acid (15 g, 203 mmol) in anhydrous toluene and the mixture was stirred at 0 °C until no hydrogen was evolved. A solution of compounds **4a** (6.25 mmol) in 50 mL anhydrous toluene was added dropwise and the mixture was refluxed for 3 h. After cooling, the solution was washed twice with 2 N NaOH and the aqueous layer was saturated with NaCl. The organic layer was dried ($MgSO_4$) and evaporated to dryness to give an oil (yield 84%) which was converted to the hydrochloride salt, mp (HCl) 131–133 °C. IR (film): 2950, 1720, 1600, 1500, 1460, 1400, 1300, 1220, 1200, 1120, 1100, 1040, 980, 860 cm^{-1}. NMR (200 MHz; $CDCl_3$): δ 0.83 (6H, *m*, $2C\underline{H}_3$-CH_2-CH_2); 1.16 (3H, *t*, $C\underline{H}_3$-CH_2-O); 1.42 (4H, *m*, CH_3-$C\underline{H}_2$-CH_2); 2.60 (4H, *m*, $C\underline{H}_2$-N); 2.90 (2H, *d*, Ar-$C\underline{H}_2$); 3.71 (1H, *t*, C<u>H</u>); 3.78; 3.80; 3.86 (9H, 3*s*, $3C\underline{H}_3O$); 4.15 (2H, *q*, $C\underline{H}_2$-O); 6.47; 6.73 (1H, *s*, Ar-<u>H</u>). Anal. $C_{15}H_{33}NO_5$, M_r = 367.48 (C, H, N, O).

Using a similar experimental procedure to that described above, but replacing **4a** with the appropriate 2-amino-3-arylethyl propanoate, compounds **5b–d** were prepared.

2-(N,N-Di-n-propylamino-3-(2,3,4-trimethoxyphenyl) ethyl propanoate (5b). Compound **5b** was obtained as an oil (yield 86%), which was converted to the hydrochloride salt, mp (HCl) 138–140 °C. IR (film): 2950, 2840, 1720, 1600, 1460, 1280, 1260, 1160, 1100, 1020 cm^{-1}. NMR (200 MHz; $CDCl_3$): δ 0.83 (6H, *m*, $2C\underline{H}_3$-CH_2-CH_2); 1.16 (3H, *t*, $C\underline{H}_3$-CH_2-O); 1.42 (4H, *m*, CH_3-$C\underline{H}_2$-CH_2); 2.56 (4H, *m*, $C\underline{H}_2$-N); 2.90 (2H, *d*, Ar-$C\underline{H}_2$); 3.71 (1H, *t*, C<u>H</u>); 3.76; 3.79; 3.84 (9H, 3*s*, $3C\underline{H}_3O$); 4.20 (2H, *q*, $C\underline{H}_2$-O); 6.47–6.70 (1H, *s*, Ar-<u>H</u>). Anal. $C_{15}H_{33}NO_5$, M_r = 367.48 (C, H, N, O).

2-(N,N-Di-n-propylamino-3-(2,5-dimethoxyphenyl) ethyl propanoate (5c). Compound **5c** was obtained as an oil (yield 81%) which was converted to the hydrochloride salt, mp (HCl) 124–126 °C. IR (film): 2950, 2840, 1720, 1600, 1460, 1280, 1260, 1160, 1100, 1020 cm^{-1}. NMR (200 MHz; $CDCl_3$): δ 0.81 (6H, *t*, $C\underline{H}_3$-CH_2-CH_2); 1.17 (3H, *t*, $C\underline{H}_3$-CH_2O); 1.41 (4H, *sext*, CH_3-$C\underline{H}_2$-CH_2); 2.51 (4H, *m*, $C\underline{H}_2$-N); 2.91 (2H, *dd*, Ar-$C\underline{H}_2$); 3.69 (1H, *dd*, C<u>H</u>); 4.07 (2H, 2*dq*, CH_3-$C\underline{H}_2O$); 6.69–6.75 (3H, *m*, Ar-<u>H</u>). MS (FAB+, glycerol): M_r = 337; m/z 338 (M + 1)$^+$, 10. Anal. $C_{19}H_{31}NO_4$, M_r = 337.46 (C, H, N, O).

2-(N,N-Di-n-propylamino)-3-(2-methoxyphenyl) ethyl propanoate (5d). Starting from **4d** gave **5d** as an oil (yield 82%) which was converted to the hydrochloride salt, mp (HCl) 119–121 °C. IR (film): 2950, 2840, 1720, 1600, 1480, 1460, 1260, 1160, 1180, 1020, 750 cm^{-1}. NMR (200 MHz; $CDCl_3$): δ 0.89 (6H, *t*, $C\underline{H}_3$-CH_2-CH_2); 1.19 (3H, *t*, $C\underline{H}_3$-CH_2O); 1.41 (4H, *sext*, CH_3-$C\underline{H}_2$-CH_2); 2.51 (4H, *m*, $C\underline{H}_2$-N); 2.91 (2H, *dd*, Ar-$C\underline{H}_2$); 3.69 (1H, *dd*, C<u>H</u>); 4.07 (2H, 2*dq*, CH_3-$C\underline{H}_2O$); 6.69–6.75 (3H, *m*, Ar-<u>H</u>). MS (FAB+, glycerol): M_r = 337; m/z 338 (M + 1)$^+$, 10. Anal. $C_{17}H_{27}NO_3$, M_r = 293.40 (C, H, N, O).

General procedure for the preparation of 3-(N,N-dipropylamino)-2-chromanone derivatives (6a–d)

3-(N,N-Di-n-propylamino)-6,7-dihydroxy-2-chromanone (6a) (Method F). Compound **5a** (2.72 mmol) was dissolved in 47% hydrogen bromide (3.5 mL) and refluxed for 3 h. After cooling the solution, it was evaporated to dryness under reduced pressure to give a slightly coloured product, which was crystallized from isopropanol:methanol (9:1) to give **6a** as a solid (yield 90%) which was converted to the hydrobromide salt, pale green crystals, mp (HBr) > 275–277 °C. IR (KBr): 3400, 3200, 2980, 2650, 1750, 1660, 1520, 1450, 1380, 1200, 1150, 880, 900 cm^{-1}. NMR (300 MHz; DMSO-d_6 + D_2O): δ 0.87 (6H, *t*, $2C\underline{H}_3$); 1.69 (4H, *sext*, CH_3-$C\underline{H}_2$); 3.13 (2H, *d*, Ar-$C\underline{H}_2$); 3.23 (4H, *m*, $2C\underline{H}_2$-N); 4.81 (1H, *dd*, C<u>H</u>); 6.53; 6.68 (2H, 2*s*, Ar-<u>H</u>). Anal. $C_{15}H_{21}NO_4 \cdot HBr$, M_r 360.25 (C, H, N, O, Br).

Using a similar experimental procedure to that described above, but replacing **5a** with the appropriate ester derivative, compounds **6b–c** were prepared.

2-(N,N-Di-n-propylamino-3-(2,3,4-trimethoxyphenyl) ethyl propanoate (5b). Compound **5b** was obtained as an oil (yield 86%), which was converted to the hydrochloride salt, mp (HCl) 138–140 °C. IR (film): 2950, 2840, 1720, 1600, 1460, 1280, 1260, 1160, 1100, 1020 cm^{-1}. NMR (200 MHz; $CDCl_3$): δ 0.83 (6H, *m*, $2C\underline{H}_3$-CH_2-CH_2); 1.16 (3H, *t*, $C\underline{H}_3$-CH_2-O); 1.42 (4H, *m*, CH_3-$C\underline{H}_2$-CH_2); 2.56 (4H, *m*, $C\underline{H}_2$-N); 2.90 (2H, *d*, Ar-$C\underline{H}_2$); 3.71 (1H, *t*, C<u>H</u>); 3.76; 3.79; 3.84 (9H, 3*s*, $3C\underline{H}_3O$); 4.20 (2H, *q*, $C\underline{H}_2$-O); 6.47–6.70 (1H, *s*, Ar-<u>H</u>). Anal. $C_{15}H_{33}NO_5$, M_r = 367.48 (C, H, N, O).

2-(N,N-Di-n-propylamino-3-(2,5-dimethoxyphenyl) ethyl propanoate (5c). Compound **5c** was obtained as an oil (yield 81%) which was converted to the hydrochloride salt, mp (HCl) 124–126 °C. IR (film): 2950, 2840, 1720, 1600, 1460, 1280, 1260, 1160, 1100, 1020 cm^{-1}. NMR (200 MHz; $CDCl_3$): δ 0.81 (6H, *t*, $C\underline{H}_3$-CH_2-CH_2); 1.17 (3H, *t*, $C\underline{H}_3$-CH_2O); 1.41 (4H, *sext*, CH_3-$C\underline{H}_2$-CH_2); 2.51 (4H, *m*, $C\underline{H}_2$-N); 2.91 (2H, *dd*, Ar-$C\underline{H}_2$); 3.69 (1H, *dd*, C<u>H</u>); 4.07 (2H, 2*dq*, CH_3-$C\underline{H}_2O$); 6.69–6.75 (3H, *m*, Ar-<u>H</u>). MS (FAB+, glycerol): M_r = 337; m/z 338 (M + 1)$^+$, 10. Anal. $C_{19}H_{31}NO_4$, M_r = 337.46 (C, H, N, O).

2-(N,N-Di-n-propylamino)-3-(2-methoxyphenyl) ethyl propanoate (5d). Starting from **4d** gave **5d** as an oil (yield

82%) which was converted to the hydrochloride salt, mp (HCl) 119–121 °C. IR (film): 2950, 2840, 1720, 1600, 1480, 1460, 1260, 1160, 1180, 1020, 750 cm^{-1}. NMR (200 MHz; $CDCl_3$): δ 0.89 (6H, *t*, CH_3-CH_2-CH_2); 1.19 (3H, *t*, CH_3-CH_2O); 1.41 (4H, *sext*, CH_3-CH_2-CH_2); 2.51 (4H, *m*, CH_2-N); 2.91 (2H, *dd*, Ar-CH_2); 3.69 (1H, *dd*, CH); 4.07 (2H, 2*dq*, CH_3-CH_2O); 6.69–6.75 (3H, *m*, Ar-H). MS (FAB+, glycerol): M_r = 337; m/z 338 $(M + 1)^+$, 10. Anal. $C_{17}H_{27}NO_3$, M_r = 293.40 (C, H, N, O).

*General procedure for preparing 3-(*N,N*-dipropylamino)-2-chromanone derivatives (7a-c)*

*3-(*N,N*-Di-*n*-propylamino)-6,7-dipivaloyl-2-chromanone (7a) (Method G).* The free base of **6a** (1 g, 3.58 mmol) and triethylamine (0.72 g, 7.16 mmol) were solubilized in anhydrous chloroform (40 mL). Pivaloyl chloride (8.59 g, 7.16 mmol) was added dropwise to the solution. After stirring at room temperature for 4 h, the organic layer was washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified on a silica gel column with ethyl acetate: hexane (8:2) as eluent, to afford an oil (yield 77%), mp (HCl) 144–146 °C. IR (KBr): 2950, 2600, 1775, 1750, 1500, 1480, 1420, 1400, 1280, 1140, 1120 cm^{-1}. ^1H NMR (200 MHz; CD_3OD): δ 1.04 (6H, *t*, CH_3-CH_2); 1.32 (18H, *s*, $(CH_3)_3C$); 1.85 (4H, *sext*, CH_3-CH_2); 3.30–3.50 (6H, *m*, CH_2-N, Ar-CH_2); 4.88 (1H, *dd*, CH); 7.04; 7.25 (2H, 2*s*, Ar-H). ^{13}C NMR (200 MHz; $CDCl_3$): δ 11.26 (2CH_3-CH_2); 19.00 (CH_3-CH_2); 26.14 (Ar-CH_2); 27.08 (2$(CH_3)_3C$); 39.08; 39.16 (2$(CH_3)_3C$); 45.89 (2CH_2-N); 58.19 (CH); 112.18 (C-8); 117.40 (C-10); 123.46 (C-5); 139.88; 143.14; 146.91 (C-6, C-7, C-9); 162.71 (CO, lactone); 175.64; 175.65 (CO ester). MS (FAB+, glycerol), M_r = 447: m/z 448 ($[M + H]^+$, 100); 470 $[M + Na]^+$, 5. Anal. $C_{25}H_{37}NO_6 \cdot HCl \cdot 0.25H_2O$, M_r = 488.53 (C, H, N).

Using a similar experimental procedure to that described above, but replacing **6a** with the appropriate dipropylaminochromanone, compounds **7b–c** were prepared.

*3-(*N, N*-Di-*n*-propylamino)-7,8-dipivaloyl-2-chromanone (7b).* As described above in method H, **6b** was converted to **7b** (yield 72%), mp (HCl) 160–162 °C. IR (KBr): 3410, 2980, 2300, 1780, 1760, 1620, 1420, 1120, 1160, 1040 cm^{-1}. NMR (200 MHz; CD_3OD): δ 1.03 (6H, *t*, CH_3-CH_2); 1.34 (18H, *s*, $(CH_3)_3C$), 1.85 (4H, *sext*, CH_3-CH_2); 3.30–3.50 (6H, *m*, CH_2-N, Ar-CH_2); 4.88 (1H, *dd*, CH); 7.09; 7.19 (2H, 2*d*, Ar-H). Anal. $C_{25}H_{38}NO_6 \cdot HCl \cdot 0.5H_2O$, M_r = 493.04 (C, H, N, O, Cl).

*3-(*N,N*-Di-*n*-propylamino) 6-pivaloyl-2-chromanone (7c).* As described above in method G, **6c** was converted to **7c** (yield 80%), mp (HCl) 200–202 °C. IR (KBr): 3400, 3200, 2950, 2940, 1775, 1750, 1500, 1480, 1160, 1110, 900 cm^{-1}. NMR (200 MHz; $CDCl_3$): δ 1.00 (6H, *t*, CH_3-CH_2); 1.31 (9H, *s*, $(CH_3)_3C$); 1.69 (4H, *sext*, CH_3-CH_2); 3.29–3.49 (4H, *m*, CH_2-N, Ar-CH_2); 3.37 (2H, *d*, Ar-CH_2); 4.03 (1H, *t*, CH); 6.89; 7.10 (2H, 2*s*, Ar-H). Anal. $C_{20}H_{29}NO_4 \cdot HCl$, M_r = 383.919 (C, H, N).

*2-(*N*-Propylamide)-3-(2,4,5-trimethoxyphenyl) ethyl propanoate (8).* A solution of **4a** (10 g, 35.33 mmol) in 100 mL water was stirred until complete dissolution and cooled (ice bath). Propionic anhydride (3.96 g, 38.86 mmol) was added dropwise and vigorously stirred for 30 min. Amide precipitate was filtered off, washed with cold water and dried to give a white solid (yield 97%), mp 170–171 °C. IR (KBr): 3300, 3150, 1725, 1640, 1540, 1440, 1400, 1300, 1140, 980, 780 cm^{-1}. ^1H NMR (200 MHz; $CDCl_3$): δ 1.03 (3H, *t*, CH_3-CH_2-CO); 1.28 (3H, *t*, CH_3-CH_2-O); 2.20 (2H, *m*, Ar-CH_2); 3.89; 3.90; 3.91 (9H, 3*s*, CH_3O); 4.15 (2H, *q*, CH_3-CH_2-O); 4.66 (1H, *t*, CH); 6.28 (1H, *d*, NH); 6.48; 6.61 (2H, 2*s*, Ar-H). ^{13}C NMR (200 MHz, $CDCl_3$): δ 9.48 (CH_3-CH_2-CO); 14.07 (CH_3-CH_2-O); 29.40 (CH_2CO); 31.89 (Ar-CH_2); 53.28 (CH); 56.18; 56.28; 56.60 (3CH_3O); 61.09 (CH_2-O); 97.71 (C-3); 115.13 (C-6); 116.09 (C-1); 143.16; 148.85; 151.78 (C-5, C-4, C-2); 172.02 (O-CO); 173.27 (CON). MS (FAB+, glycerol), M_r = 339; m/z 340 $(M + 1)^+$, 20. Anal. $C_{17}H_{25}NO_6$, M_r = 339.39.

*2-(*N*-Propylamide)-3-(2,4,5-trimethoxyphenyl)-propanol (9).* A suspension of $NaBH_4$ (1.89 g, 50 mmol) in 20 mL THF was added to the amide **4e** (3.11 g, 10 mmol) solubilized in 20 mL anhydrous THF. Acetic acid (3 g, 50 mmol) was added dropwise, the solution refluxed under stirring overnight and evaporated under reduced pressure. The chloroformic solution was washed with water and then with 1 N HCl. The organic layer was dried ($MgSO_4$) and evaporated to give an oil which was purified on silica gel column, with EtOAc as the eluent to yield 60% of **4f**, as white crystals, mp 153–155 °C. IR (KBr): 3300, 2950, 1640, 1520, 1400, 1220, 1040 cm^{-1}. NMR (200 MHz; DMSO-d_6): δ 0.89 (3H, *t*, CH_3, J = 8 Hz); 1.97 (2H, *q*, CH_3-CH_2, J = 8 Hz); 240–2.90 (2H, 2*dd*, Ar-CH_2, J_2 = 13.86 Hz, J_3 = 6 Hz, J_3 = 4.8 Hz); 3.10 (2H, *dd*, CH_2OH); 3.74; 3.85 (9H, 2*s*, 3CH_3O); 3.87 (1H, *dd*, CH, J_3 = 6 Hz, J_3 = 4.8 Hz); 4.68 (1H, *t*, CH_2OH, J_3 = 6 Hz); 6.68; 6.90 (2H, 2*s*, Ar-H); 8.76 (1H, *s*, NH). $C_{15}H_{23}NO_5$.

*2-(*N*-Propylamino)-3-(2,4,5-trimethoxyphenyl)-propanol (10).* In the same conditions as above, trifluoroacetic acid in dioxan was used instead of acetic acid and gave a white solid (yield 96%), mp 142–144 °C. IR (KBr): 3300, 2950, 1520, 1460, 1400, 1215, 1205, 1040, 800 cm^{-1}. NMR (200 MHz; DMSO-d_6): δ 0.89 (3H, *t*, CH_3); 1.69 (2H, *sext*, CH_3-CH_2); 2.71–2.94 (2H, *dd*, Ar-CH_2); 3.65; 3.77; 3.80 (9H, 3*s*, 3CH_3); 5.42 (1H, *t*, OH); 6.67; 6.90 (2H, 2*s*, Ar-H); 8.76 (1H, *s*, NH). $C_{15}H_{25}NO_4$.

Dopamine binding assay

D_2 dopamine receptor bindings were measured by using ^3H spiperone (sp. act. 90 Ci $mmol^{-1}$, Amersham) labelled D_2 site in homogenates of rat striata prepared with a Kontes–Duall homogenizer and diluted 1:50.[33] Samples were incubated for 30 min at 37 °C and then filtered over GF/B Whatman filters (pretreated with cold 50 mM Tris pH 7.7 buffer) and rinsed three times with 5

mL of 50 mM Tris pH 7.7 buffer. Filters were counted using standard liquid scintillation techniques. Specific D_2 binding was determined using ^3H spiperone (0.6 nM) with ketanserine for serotoninergic receptors inhibition (1 mM). IC_{50} values were calculated by log-probit analysis, using at least seven concentrations of the drug in triplicate.

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