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Original paper

Synthesis and dopaminergic activity of a new oxygen isostere of the 2-aminotetralins: *N,N*-dipropyl-8-hydroxy-3-chromanamine

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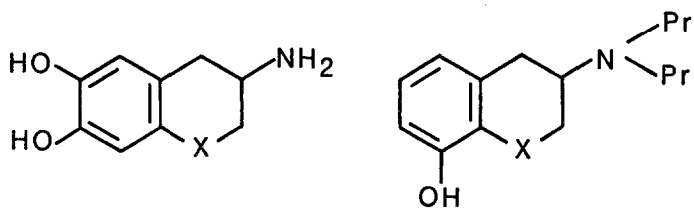
Summary — The synthesis of *N,N*-dipropyl-8-hydroxy-3-chromanamine from 8-methoxy-4-chromanone oxime in seven steps is described. This compound is an oxygen isostere of the dopamine (DA) receptor agonist *N,N*-dipropyl-5-hydroxy-2-aminotetralin. In *in vitro* and *in vivo* tests of dopaminergic activity *N,N*-dipropyl-8-hydroxy-3-chromanamine was found to be a more potent DA agonist than apomorphine.

Résumé — **Synthèse et activité dopaminergique d'un nouvel isostère oxygéné d'amino-2 tétralines: la *N,N*-dipropyl hydroxy-8 chromanamine-3.** *La synthèse de la* N,N-*dipropyl hydroxy-8-chromanamine-3 à partir de la méthoxy-8-chromanone-4 est décrite en 7 étapes. Ce composé est un isostère oxygéné d'un agoniste du récepteur de la dopamine (DA), la* N,N-*dipropyl hydroxy-5 amino-2 tétraline. L'étude de l'activité dopaminergique* in vitro *et* in vivo *indique qu'il s'agit d'un agoniste de la dopamine plus intense que l'apomorphine.*

2-aminotetralin / 3-chromanamines / dopamine / isostere

Introduction

As a part of our program aimed at the development of new dopamine (DA) agonists, we have shown [1] that replacement of a carbon atom (C_4) in 6,7-dihydroxy-2-aminotetralin (Fig. **1a**) by oxygen yields a chromanamine (Fig. **1b**) which displays significant dopaminergic activity. However, the main problem with 6,7-dihydroxy-3-chromanamine is that, like its carbon isostere, it does not pass through the blood—brain barrier to any significant extent. In the case of **1a**, it is known that its polarity [1] and ease of metabolism by COMT (catechol-*o*-methyltransferase) [2, 3] are important factors in this respect. These considerations almost certainly also apply to 6,7-dihydroxy-3-chromanamine.



1a x=CH_2 1c x=O
1b x=O 1d x=CH_2

Fig. 1.

Therefore, in an attempt to obviate these problems, we decided to investigate a more lipophilic analogue that was not a substrate for COMT and, bearing in mind the structure—activity relationships (SAR) of the 2-aminotetralins [4, 5], we chose to synthesize *N,N*-dipropyl-8-hydroxy-3-chromanamine (Fig. **1c**).

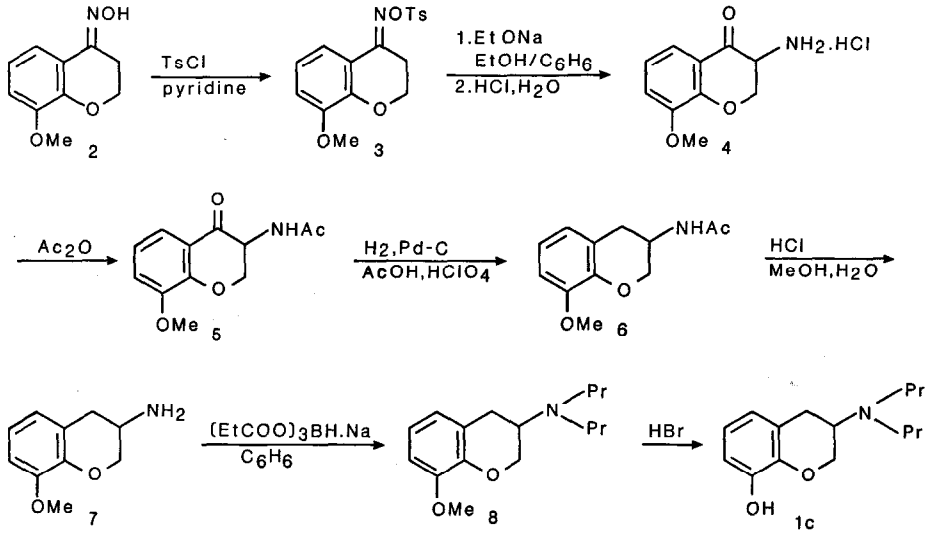
The pharmacological activity of this compound was investigated *in vitro* by studying its ability to displace the specific binding of [^{3}H]*N,N*-dipropyl-5,6-dihydroxy-2-aminotetralin ([^{3}H]DP-5,6-ATN) to homogenates of rat brain corpus striatum [6]. The *in vivo* activity was determined by investigating its ability to decrease striatal levels of one of the main DA metabolites, homovanillic acid (HVA), following i.p. administration. It is known that this is a sensitive test of DA activity *in vivo* [7]. In both cases a comparison was made with the carbon atom analogue (Fig. **1d**) and apomorphine.

Chemistry

Our synthetic route was similar in many respects to the one used previously for the synthesis of 6,7-dihydroxy-3-chromanamine. Conversion of the known 8-methoxy-4-chromanone oxime **2** [8] into the *p*-tolylsulfonyl oxime **3** and subsequent Neber rearrangement gave 3-amino-8-methoxy-4-chromanone **4** in a yield of 73%. Removal of the keto group was achieved in a two-step reaction consisting

of an *N*-acetylation of **4** followed by a catalytic reduction over Pd-C in a mixture of acetic and perchloric acids to yield **6**.

Hydrolysis of **6** with 14% HCl in methanol/water gave the primary amine **7**. The latter was reductively alkylated with propionic acid and sodium borohydride [9] to produce *N,N*-dipropyl-8-methoxy-3-chromanamine **8** in a yield of 83%. Demethylation with 47% HBr led to the end product in high yield, *i.e.*, 93% (Scheme 1).



Scheme 1.

Pharmacology and Discussion

8-Hydroxy-3-chromanamine was found to be a very potent displacer of the specific *in vitro* binding of [^{3}H]DP-5,6-ATN to homogenates of rat brain corpus striatum (Table I)

Table 1. Inhibition of the *in vitro* binding of [^{3}H]DP-5,6-ATN to homogenates of rat corpus striatum.

Compound	K_i (nM)
1c	1.8
1d	2.1
(—)apomorphine	2.6

Binding assays were carried out as described under Pharmacology. K_i values were calculated from IC_{50} values using the Cheng—Prusoff equation and a K_d value of 0.6 nM. The values are the means of 2—4 experiments in which each point was analyzed in triplicate.

having a K_i = 1.8 nM. Its activity was almost the same as that of its carbon atom analogue. A dose—response curve on the striatal levels of HVA *in vivo* also showed that it penetrated readily into the brain and that it is also a potent DA agonist having an ED_{70}% of 0.60 μmol/kg. We have previously shown [7] that **1d** has an ED_{70}% of 0.14 μmol/kg. In additional extensive *in vivo* pharmacological studies on the pre- and post-synaptic dopaminergic activity of **1c**, we have concluded that, although this compound is weaker than **1d** as a post-synaptic DA agonist, it is apparently slightly more selective for DA autoreceptors than its carbon (0.05—5 μmol/kg, i.p.) for the effects of the above compound analogue (Vermuë *et al.*, submitted for publication). In the same study, we also showed that **1c** has only a moderate affinity for serotonin (5-HT) and noradrenaline (NA) receptors.

It is therefore apparent that this new analogue of the 3-chromanamine series readily penetrates the blood—brain barrier and, in addition, that it has a high affinity for the DA receptors. In these respects, it therefore represents a very significant improvement upon 6,7-dihydroxy-3-chromanamine **1b**, which did not penetrate the blood—brain barrier and was more than 10 times weaker than apomorphine in radioligand binding experiments [3].

After this work was completed, a report appeared [10] in which a similar approach to that described here was used to obtain enhanced selectivity for 5-HT_{1A} receptors. The authors suggest that the sp^2 electrons of the oxygen atom are probably conjugated with the π electrons of the aromatic ring and that the resulting structure bears some electronic resemblance to the indole ring.

In conclusion, it is clear from our results and those of others that the substitution of an oxygen for a carbon atom at the 4 position of the 2-aminotetralin ring can lead to potent and selective analogues with interesting pharmacological profiles.

Experimental protocols

Melting points (uncorrected) were determined on a Mettler FP-2 apparatus. Infrared spectra were recorded on a Unicam SP-200 infrared spectrophotometer, and only the important absorptions are given in reciprocal centimeters. The 60 MHz ^1H NMR spectra were recorded on a Hitachi Perkin—Elmer R-24B spectrometer. Chemical shifts are denoted in ppm relative to tetramethylsilane (Mc_4Si) as an internal standard. A Nicolet NT-200 or a Varian XL 100 spectrometer was used for ^{13}C NMR spectra with chloroform-d ($CDCl_3$) as an internal standard. Splitting patterns are designated as follows: a: singlet; d: doublet; t: triplet; q: quartet; m: multiplet. Mass spectra were obtained on an AEI MS-902 instrument (voltage 70 eV, accelerating voltage 8 kV, DI (direct inlet) temperature 100—120°C). Elemental analyses were performed in the microanalytical section of the Chemistry Department, Groningen, and are within ±0.3% of the theoretical values.

8-Methoxy-4-chromanone-O-(p-toluenesulfonyl)oxime **3**
11.6 g (60 mmol) of 8-methoxy-4-chromanone oxime [8] was dissolved in 60 ml of dry pyridine. After cooling the mixture in ice, 12.4 g (65 mmol) of *p*-toluenesulfonyl chloride were added in small portions over a period of 40 min to the stirred solution. It was stirred for an additional 1.5 h at 0°C and then left overnight in the refrigerator. The mixture was then poured into 500 ml of ice—water and the solid product was filtered off and washed with water and cold EtOH. The yield after drying was 19.24 g (92%) of yellow crystals; mp: 133—135°C. IR (nujol): 1620 (C=N), 1590 (Ar), 1360 (—SO_2—), 1280 (C—O), 1185 (—SO_2), 830 (Ar). ^1H NMR ($CDCl_3$): δ 2.40 (s, 3H); 2.95 (t, 2H); 3.80 (s, 3H); 4.25 (t, 2H); 6.80 (m, 2H); 7.25 (d+m, 3H); 7.85 (d, 2H).

3-Amino-8-methoxy-4-chromanone HCl **4**
To a stirred solution of 1.30 g (56 mmol) of sodium in 75 ml of dry EtOH at 0°C under nitrogen, 19.0 g (55 mmol) of **3** dissolved in 100 ml of dry benzene were added dropwise over 1 h. The reaction mixture was left at 0°C for 24 h and for a further 2 h at room temperature. The solid which precipitated (sodium *p*-toluenesulfonate) was filtered off and washed with Et_2O. The organic layer was poured into 200 ml of 2 N HCl solution and stirred for 2 h. The extraction of the organic layer was repeated (2×20 ml of 2 N HCl). The combined red aqueous fractions were washed with Et_2O (3×50 ml) and treated with charcoal. The resulting yellow aqueous solution was reduced in volume under vacuum to about 50 ml. On cooling, a crystalline product was obtained, which was filtered off and washed with ethanol to yield 9.2 g (73%) of **4** as light yellow needles. mp: 212—215°C (dec) (lit. [11] mp: 220°C, dec). IR (nujol): 2900 (NH_3^+), 1680 (C=O), 1600 (Ar), 1580 (C—N), 1275 (C—O). ^1H NMR (Me_2SO-d_6): δ 3.90 (s, 3H); 4.5—5.1 (m, 3H); 7.3 (m, 3H); 9.1 (br, 3H). MS, *m/e* (rel. int.) M^+-HCl 193 (51%), 151 (100%), 150 (49%), 122 (57%). Anal. ($C_{10}H_{12}NO_3Cl$) C, H, Cl.

3-Acetamido-8-methoxy-4-chromanone **5**
To a stirred solution of 6.3 g (27.5 mmol) of **4** and 12 g of NaOAc in 100 ml of EtOAc and 30 ml of water, 11 ml of Ac_2O were added. This mixture was stirred for 4 h at room temperature. Extra EtOAc and water were added and the organic layer was separated off. This layer was then washed with solutions of 0.5 N HCl, dilute $NaHCO_3$ and saturated NaCl. The organic layer was dried over $MgSO_4$ and then reduced in volume under vacuum to about 30 ml. On cooling, a crystalline product was obtained which was filtered off and washed with hexane to yield 5.3 g (82%) of **5** as white needles. mp: 172—177°C. IR (KBr): 3260 (NH), 1680 (C=O), 1635 (C=O), 1540 (NH), 1255 (C—O). ^1H NMR ($CDCl_3$): δ 2.06 (s, 3H); 3.88 (s) and 4.0—4.2 (m, together 4H); 5.0 (m, 2H); 6.5 (br, 1H); 7.2 (m, 3H). MS: *m/e* (rel. int.) 235 (27%), 151 (100%). Anal. ($C_{12}H_{13}NO_4$) C, H, N.

3-Acetamido-8-methoxychroman **6**
5.0 g (21.3 mmol) of **5** and 1.1 g Pd-C (5%) in 50 ml of AcOH and 2 ml of $HClO_4$ (60%) were hydrogenated at 3 atm and 30°C for 24 h. The Pd-C was filtered off and washed with EtOH, the filtrate was reduced in volume to about 10 ml and extracted with CH_2Cl_2/satd. $NaHCO_3$ solution. The aqueous layer was then washed 4 times with CH_2Cl_2. The organic layers were washed with water, dried over $MgSO_4$ and evaporated under vacuum to yield an oil which slowly crystallized. Recrystallization from benzene gave 4.1 g (87%) of **6** as pale yellow crystals. mp: 138—142°C; IR (KBr): 3320 (NH), 1645 (C=O). ^1H NMR ($CDCl_3$): δ 1.95 (s, 3H); 2.70 (d+d, ^2J = 16 Hz and ^3J = 5 Hz, 1H); 3.15 (d+d, ^2J = 16 Hz and ^3J = 3 Hz, 1H); 3.75 (s, 3H); 4.0—4.5 (m, 3H); 6.7 (m, 4H). MS: *m/e* (rel. int.) M^+ 221 (15%), 162 (100%). Anal. ($C_{12}H_{15}NO_3$) C, H, N.

8-Methoxy-3-chromanamine **7**
A solution of 2.95 g (13.3 mmol) of **6** in 70 ml of MeOH and 80 ml of 25% HCl was kept at 90°C under 1 atm of nitrogen for 6 h. After evaporation of the MeOH, the reaction mixture was left at room temperature for 17 h. It was then extracted with CH_2Cl_2 (4×30 ml). The acidic layer was neutralized with $NaHCO_3$, made basic with a solution of 4 N NaOH and then washed with CH_2Cl_2 (4×50 ml). After drying over $MgSO_4$ and removal of the solvent, an oil was obtained which slowly crystallized to yield 1.60 g (67%) of **7**. mp: 37—40°C. IR (film): 3400 (NH), 1600 (Ar), 1500 (C—N), 1270 and 1220 (C—O). ^1H NMR ($CDCl_3$): δ 1.4 (br, 2H); 2.3—3.5 (m, 3H); 3.78 (s, 3H); 4.0 (m, 2H); 6.60 (m, 3H). The free amine was converted into a salt by treatment with a solution of Et_2O/HCl. The salt was very hygroscopic. mp: 110—115°C. MS: *m/e* (rel. int.) M^+-HCl 179 (92%), 162 (100%). Anal. ($C_{10}H_{14}NO_2Cl$·0.5 H_2O) C, H, N.

N,N-*Di*-n-*propyl-8-methoxy-3-chromanamine* **8**
15.0 g (203 mmol) of propionic acid were dissolved in 250 ml of dry benzene under 1 atm of nitrogen. 2.4 g (63 mmol) of $NaBH_4$ was then added and the mixture stirred until the evolution of hydrogen had ceased. The temperature was kept below 17°C. 1.12 g (6.25 mmol) of **7** in 50 ml of benzene were added dropwise to the mixture and then refluxed for 3.5 h. After cooling, the reaction mixture was washed with solutions of 2 N NaOH (2×150 ml) and saturated NaCl. After drying over $MgSO_4$ and removal of the solvent, the resulting oil was subjected to column chromatography, using 120 g of silica gel and EtOAc/benzene, 3:1, as the eluent. This yielded 1.35 g (82%) of **8** as a colorless oil. IR (film): 3050 (C—H), 1600 (Ar), 1500 (C—N), 1270 and 1220 (C—O). ^1H NMR ($CDCl_3$): δ 0.85 (t, 6H); 1.40 (sextet, 4H); 2.45 (t, 4H); 2.5—3.3 (m, 3H); 3.70 (s, 3H); 3.5—4.5 (m, 2H); 6.55 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 11.43 (q); 21.55 (t); 28.12 (t); 52.37 (t); 52.86 (d); 55.45 (q); 68.10 (t); 108.71 (d); 119.78 (d); 121.72 (d); 122.42 (s); 143.54 (s); 148.06 (s). Preparation of an HCl salt gave a white solid. mp: 140—143°C. MS: *m/e* (rel. int.) M^+-HCl 263 (27%), 234 (100%). Anal. ($C_{16}H_{26}NO_2Cl$) C, H, N, Cl.

N,N-*Di*-n-*propyl-8-hydroxy-3-chromanamine* **1c**
Under an atmosphere of nitrogen, 500 mg (1.90 mmol) of **8** (HCl salt) dissolved in 20 ml of 47% HBr solution were kept at 125—130°C for 65 min. After cooling, the reaction mixture was reduced in volume to about 5 ml and then brought to pH 8 by the addition of solutions of $NaHCO_3$ and 4 N NaOH. The solutions was then extracted with CH_2Cl_2 (4×40 ml). After drying over $MgSO_4$ and removal of the solvent, the resulting brown oil was chromatographed on 45 g of silica gel, using EtOAc as the eluent. This yielded 440 mg (93%) of **1c** as a colorless oil. IR (film): 3500 (OH), 3020 (CH), 1610 (Ar), 1500 (C—N). ^1H NMR ($CDCl_3$): δ 0.87 (t, 6H); 1.45 (sextet, 4H); 2.50 (t) and 2.6—3.4 (m, together 7H); 3.78 (d+d, 1H); 4.30 (d+d, 1H); 5.4 (br, 1H); 6.55 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 11.58 (q); 21.67 (t); 27.48 (t); 52.57 (t); 53.32 (d); 68.28 (t); 112.24 (d); 120.54 (d); 120.77 (d); 122.03 (s); 141.43 (s); 144.64 (s). MS: *m/e* (rel. int.) M^+ 249 (24%), 220 (75%), 114 (100%). Preparation of an HCl salt with 1 N HCl in ether yielded a white solid. mp: 170—173°C. Anal. ($C_{15}H_{24}NO_2Cl$) C, H, N, Cl.

Pharmacology

Displacement of [^3H]N,N-*dipropyl-5,6-dihydroxy-2-aminotetralin* ([^3H]*DP-5,6-ATN) binding to rat brain corpus striatum homogenates*
The [^{3}H]DP-5,6-ATN binding assay was performed as previously described [6]. Striatal tissue was obtained from male rats (200—225 g). The incubation mixture consisted of 50 mM Tris-HCl buffer, pH 7.5, containing 1 mM ethylenediaminetetraacetic acid (EDTA) and 0.01% ascorbic acid and the final volume was 1 ml. The concentration of the striatal tissue was 1.7 mg/ml (wet weight) and the final concentration of [^{3}H]DP-5,6-ATN (specific activity 100 Ci/mmol, Amersham, U.K.) was 0.53 nM. Incubations were carried out at 25°C for 30 min. Non-specific binding was determined in the presence of 1 μM d-butaclamol.

Determination of the influence of DA agonists on striatal DA metabolism Male Wistar rats (180—230 g) were injected (i.p.) with solutions of various DA agonists (Table II) dissolved in saline. After 30 min, the animals were sacrificed by cervical dislocation, the brains were removed, placed on dry ice and the corpus striatum was dissected and then stored at −80°C. After weighing the samples, homogenization in $HClO_4$ (0.1 M, 1 ml) and centrifugation (3000 × *g*, 5°C, 15 min), homovanillic acid (HVA) was assayed, using HPLC combined with electrochemical detection following separation on Sephadex G—10 columns, according to the method of Westerink and Mulder [12]. Cerebellar tissue was used as a blank and no corrections were made for the recoveries which were between 80 and 95%.

Table II. Influence of DA agonists on striatal *in vivo* DA metabolism.

Compound	HVA $ED_{70\%}$ (μmol/kg)
1c	0.60
1d	0.14
(−)apomorphine	1.35

The HVA $ED_{70\%}$ is defined as the dose of drug in μmol/kg (i.p.) giving rise to a 30% fall in the *in vivo* levels of rat striatal homovanillic acid (HVA) 30 min after drug administration. The dose range tested was 0.05—5 μmol/kg. The results are the means of 5 determinations. The control levels of HVA were 0.60±0.10 μg/g wet weight.

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