

Structure–affinity relationships of halogenated predicentrine and glaucine derivatives at D₁ and D₂ dopaminergic receptors: halogenation and D₁ receptor selectivity

Marcelo Asencio,^a Claudio Hurtado-Guzmán,^a John J. López,^a Bruce K. Cassels,^{a,b,*} Philippe Protais^{c,✉} and Abdeslam Chagraoui^c

^a*Department of Chemistry and Millennium Institute for Advanced Studies in Cell Biology and Biotechnology (CBB), Faculty of Sciences, University of Chile, Casilla 653, Santiago, Chile*

^b*Programme of Molecular and Clinical Pharmacology, ICBM, Faculty of Medicine, University of Chile, Santiago 7, Casilla 70.000, Chile*

^c*Laboratoire de Physiologie, Faculté de Médecine et de Pharmacie, Université de Rouen, 7600 Rouen-cedex, Rouen, France*

Abstract—Halogenation of the aporphine alkaloid boldine at the 3-position leads to increased affinity for rat brain D₁-like dopaminergic receptors with some selectivity over D₂-like receptors. A series of 3-halogenated and 3,8-dihalogenated (halogen = Cl, Br or I) derivatives of predicentrine (9-*O*-methylboldine) and glaucine (2,9-di-*O*-methylboldine) were prepared and assayed for binding at D₁ and D₂ sites. Halogenation of predicentrine led to strong increases in affinity for D₁-like receptors, while the affinities for D₂-like receptors were either practically unchanged or reduced three- to fourfold. Halogenated glaucine derivatives did not show any clear trend towards enhanced selectivity, and the affinities were poor and similar to or worse than the values previously recorded for glaucine itself. Together with earlier work on boldine derivatives, these results suggest that the 2-hydroxy group on the aporphine skeleton may determine a binding mode favoring D₁-like over D₂-like receptors, with enhanced affinity when the C-3 position is halogenated.

1. Introduction

Early pharmacological studies carried out on dopamine (DA) receptors enabled these to be classified into two major groups: D₁, which activate the enzyme adenylate cyclase (AC), and D₂, which do not activate this enzyme and were later shown to decrease its activity.^{1,2} Until now, however, a total of five different molecular forms of DA receptors have been described, originally based on cloning studies. Cloned DA receptors include the ‘D₁-like’ D₁ and D₅, and the ‘D₂-like’ D₂ (which is expressed in a long and a short form), D₃ and D₄.^{3–8} In spite of this diversity, and of the fact that alternative transduction mechanisms have been demonstrated,⁹

the previous classification into D₁ (or D₁-like) and D₂ (or D₂-like) receptors, positively or negatively coupled to AC, is still widely used in preliminary studies.

Dopaminergic neurotransmission is intimately bound to the physiopathology and treatment of neuropsychiatric disorders, in particular schizophrenia and Parkinson’s disease (PD). For example, the discovery that L-DOPA can alleviate the symptoms of patients with PD has been an incentive for the search for many years of molecules with similar pharmacological properties, that is, which could afford similar benefits to those achieved with L-DOPA. While attention was initially focussed on D₂ receptor agonists, the pharmacology of D₁ receptors had been somewhat neglected, in part due to the lack of specific ligands. This situation has been partly reverted with the discovery of the paradigmatic 1-phenylbenzazepine antagonist SCH-23390 (**1**),^{10,11} and the D₁-selective tetracyclic agonists dihydrexidine (**2**) and (*S*)-dinapsoline (**3**).^{12–14} These compounds have made

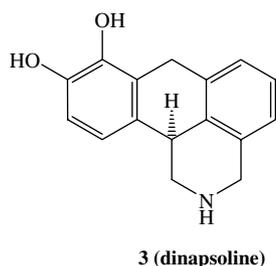
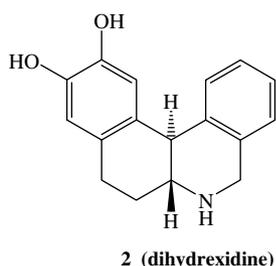
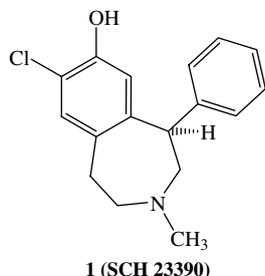
Keywords: Aporphines; Halogenated predicentrines; Halogenated glaucines; Dopamine receptor affinities.

* Corresponding author. Tel.: +56 2 271 3881; fax: +56 2 271 3888;

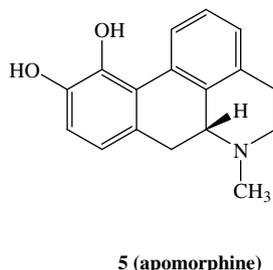
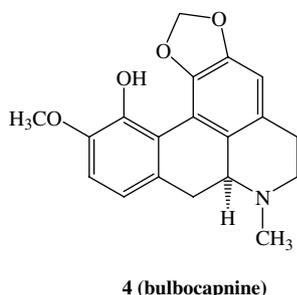
e-mail: bcassels@uchile.cl

✉ Deceased.

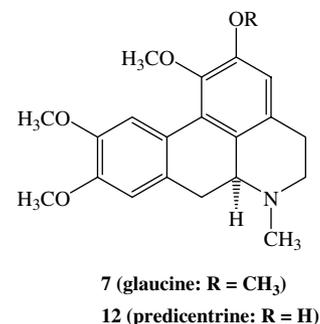
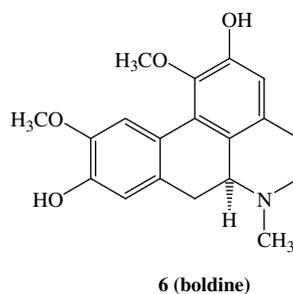
it possible to study the pharmacological effects on these receptors and thus reconsider the potential use of D₁ receptor agonists or antagonists in the treatment of neuropsychiatric illnesses. Of particular current interest is the blockade by such compounds of the reinstatement of drug-seeking behaviour.¹⁵⁻¹⁷



Among the diverse structural classes that have been evaluated for dopaminergic activity, many are synthetic and a few are natural aporphine alkaloids sharing the 5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinoline skeleton.¹⁸ The nonselective D₁/D₂ antagonist (6a*S*)-bulbocapnine (**4**),¹⁹ the nonselective agonist (6a*R*)-apomorphine (APO, **5**)²⁰ and some of its derivatives were among the first pharmacological tools for the study of DA receptors, and their use enabled the identification of a number of structural features, which seem to affect their dopaminergic activities. Clinically, subcutaneous apomorphine is used as an antiparkinsonian drug (Apokinin[®]), and a sublingual preparation has recently been marketed as a treatment for male erectile dysfunction (Uprima[®]).

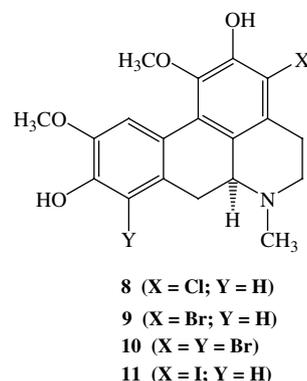


A report on the 'neuroleptic-like' actions of bulbocapnine (**4**), its close (6a*S*) analogues corytuberine, boldine (**6**) and glaucine (**7**),²¹ and the fact that boldine is readily available in relatively large amounts prompted us to study this alkaloid and some of its derivatives as dopaminergic ligands.



Using radioligand displacement techniques (³H]SCH 23390 for D₁-like and [³H]raclopride for D₂-like receptors), the IC₅₀ values of boldine for both major DA receptor types were determined in rat striatal homogenates and proved to be 0.4 μM for D₁-like and 0.5 μM for D₂-like receptors, respectively. In similar experiments, glaucine [(6a*S*)-1,2,9,10-tetramethoxyaporphine (**7**)] showed 10-fold lower affinities for both major receptor types. In vivo, both alkaloids elicited biochemical and behavioural effects suggestive of DA receptor antagonism.²² In spite of the greater in vitro binding affinity of boldine, its in vivo activities were weaker than those of glaucine, which was interpreted as a result of its poor access to the CNS, and can be related to its demonstrably unfavourable pharmacokinetics.^{22,23}

As halogenated boldine derivatives might be expected to be more lipophilic and thus to have better absorption and distribution properties, as well as being more stable metabolically, several of these compounds were examined in the same in vitro binding models. These assays showed that the affinities of 3-chloro- (**8**), 3-bromo- (**9**), 3,8-dibromo- (**10**) and 3-iodoboldine (**11**) for D₁-like receptors are greater than that of boldine and rise with the atomic number of the halogen, leading to significant selectivity, especially for 3-bromo- and 3-iodoboldines. In particular, 3-iodoboldine showed *K*_i values of 2 nM for D₁-like and 68 nM for D₂-like receptors, respectively.²⁴



Since it has been suggested that a dysfunction of the D₁ receptor may be involved in the negative symptoms and cognitive deficits observed in schizophrenia, and the antipsychotic potential of D₁ antagonists remains insufficiently explored,²⁵⁻²⁷ and it has recently been reported

that blockade of this receptor reduces the liability of relapse into drug-seeking behaviour,^{15–17} it seems legitimate to search for new D₁-selective dopaminergic antagonists with possibly novel transduction mechanisms.

Considering the marked trends towards greater affinity and selectivity observed in the halogenated boldine analogues, and assuming that more favourable pharmacokinetics might be achieved by *O*-methylation of one or both of the hydroxyl groups, which can be glucuronidated in vivo, boldine was converted into predi-centrine (**12**, with the usual numbering scheme for aporphines) and glaucine (**7**). A number of halopredicentrine and haloglaucine derivatives were prepared, and their affinities for D₁-like and D₂-like striatal receptors were determined using the same protocols as previously published for the halogenated boldine derivatives.²⁴

2. Results and discussion

Boldine (**6**) was extracted from *Peumus boldus* bark using a previously described method,²⁸ and *O*-methylated with diazomethane to afford glaucine (**7**) and predi-centrine (**12**).²⁹ Predicentrine and glaucine were halogenated by adding *N*-halosuccinimides (NXS, X = Cl, Br or I) to solutions of the alkaloids in trifluoroacetic acid, following a similar procedure to that used earlier for boldine.²⁴ NXS (1 M equiv) led in each instance to the formation of the 3-halo derivative, while the same reagents in excess produced the 3,8-dichloro or dibromo but not the diiodo derivatives. The regioselectivity of the halogenations was confirmed by HMQC/HMBC NMR experiments.

Table 1. Inhibition of [³H]SCH 23390 or [³H]raclopride binding to rat striatal binding sites by halogenated 1,2,9,10-tetraoxygenated aporphine derivatives

Compounds	K _i (nM) on specific binding		D ₂ /D ₁ ratio
	[³ H]SCH 23390	[³ H]raclopride	
6	294 ^a	366 ^a	1.2
7	2868 ^a	2,831 ^a	1.0
8	60 ^b	507 ^b	8.5
9	49 ^b	739 ^b	15
10	152 ^b	1345 ^b	8.8
11	2 ^b	68 ^b	34
12	243	761	3.1
13	15	613	41
14	36	866	24
15	6	831	139
16	8566	7423	0.9
17	27,794	7958	0.3
18	522	2359	4.5
19	35,074	10,405	0.3
20	2110	4514	2.1

IC₅₀ values were obtained from concentration–response curves with *n* = 4 at each concentration using ORIGIN 5.0, and K_i values were calculated using the Cheng and Prusoff equation,³³ with K_D(SCH 23390) = 0.7 nM,³⁴ and K_D(raclopride) = 1.2 nM.³⁵

^a Data from Ref. 22.

^b Data from Ref. 24.

Binding affinities were determined in rat striatal membranes by means of competition binding assays versus [³H]SCH 23390 (D₁-like) or [³H]raclopride (D₂-like), and are summarized in Table 1. Replacement of the C-3 hydrogen atom of predi-centrine by bromine (**13**) raised the affinity of this alkaloid for the [³H]SCH 23390-labelled site 20-fold while iodine (**15**) raised it 50-fold, but the affinity for the [³H]raclopride-labelled site was only doubled at most. Bromination on both C-3 and C-8 (**14**) had a less marked effect, and comparison of the 3-bromoderivatives of either boldine or predi-centrine (**9** and **13**, respectively) with their 3,8-dibromo counterparts (**10** and **14**) revealed two- to threefold decreases in affinity for both major receptor types. Thus, an additional halogen atom at C-8 does not contribute to DA receptor binding and seems to be a hindrance. The similarity of these trends in both boldine and predi-centrine derivatives suggests analogous binding modes. In the case of 3-iodopredicentrine (**15**, K_i = 6 nM), although this compound does not bind D₁-like receptors quite as strongly as 3-iodoboldine (**11**, K_i = 2 nM), it attains much greater selectivity (140-fold) over D₂-like receptors.

Unlike the cases of boldine and predi-centrine derivatives, halogenation of glaucine at C-3 or C-3 and C-8 does not lead consistently to increased affinity for either major receptor type. Although 3-bromo- (**18**) and 3-iodoglaucine (**20**) show a slight trend towards D₁ selectivity without significant loss of affinity, the very weakly binding 3-chloro- (**16**), 3,8-dichloro- (**17**) and 3,8-dibromoglaucine (**19**) exhibit no selectivity or even somewhat lower affinity at [³H]SCH 23390-labelled sites than at those labelled with [³H]raclopride. These observations suggest that in this family of compounds the presence of a hydroxyl group at C-2 favours both affinity and selectivity for D₁-like receptors.

It has been speculated in the case of the boldine derivatives that substitution at C-3 with halogen atoms of increasing size might favour hydrophobic interactions with a complementary region in the D₁-like receptor, particularly in the case of iodine, although enhanced aromatic stacking interactions and some distortion of the tetrahydropyridine ring might also increase receptor binding.²⁴ This now seems to be confirmed by the increase in the D₁ binding affinity for the halogenated predi-centrines. A systematic study of D₁ receptor antagonism by ring D-substituted 11-hydroxyaporphines carried out over a decade ago in the Lilly Research Laboratories did not bring to light any analogues rivaling the affinity of 3-haloboldines or halopredicentines for these sites.³⁰ The suggestion by the Lilly team that a hydroxyl group at C-11 'is critical for imparting affinity for the D-1 receptor' does not hold for our compounds, and may be an indication that 2- and 11-hydroxyaporphines bind to this receptor in different orientations. An additional argument favouring this hypothesis is the suggestion by Neumeyer and co-workers, also based on 11-hydroxy compounds, that a hydroxyl group at C-2 decreases aporphine affinity for dopamine receptors,^{31,32} instead of increasing it as seen when the boldine and predi-centrine derivatives are

compared with the C-2-methoxylated, C-3 or C-3/C-8 halogenated glaucines. Furthermore, our compounds seem to be relatively insensitive to structural modification on the C-11-unsubstituted ring D.

Although additional synthetic work is clearly necessary, together with more detailed studies on their pharmacological actions, we postulate that 2-hydroxyaporphines bearing a hydrophobic substituent at C-3 may represent a template for the development of novel, potent D₁-like dopaminergic ligands showing good selectivity as far as D₂-like receptors are concerned. Future research should determine if such compounds may prove useful for the discovery of novel inhibitors of the reinstatement of drug-seeking behaviour or of a new series of atypical antipsychotics with reduced adverse effects.

3. Conclusions

Our results demonstrate that the aporphine skeleton is a fruitful scaffold for the construction of potent dopamine receptor ligands with selectivity for D₁/D₅ over D₂-like receptors. Specifically, introduction of a halogen atom at C-3 of predicentrine [(6*aS*)-2-hydroxy-1,9,10-trimethoxyaporphine] results in compounds that bind to D₁-like receptors with low nanomolar affinities, and up to 140 times better than their binding affinities for D₂-like receptors. These results are in contrast with earlier work indicating that 2,11-dihydroxyaporphines show weak affinity for dopamine receptors, and suggest that 2-hydroxy- and 11-hydroxyaporphines may interact with them in different orientations. Considering that the parent (6*aS*)-aporphines boldine (**6**) and glaucine (**7**) block dopamine receptors *in vivo*, the close structural congeners described here, particularly **13** and **15**, may be interesting leads for the development of useful drugs acting via dopamine receptor antagonism.

4. Experimental

4.1. Binding assays: materials

[³H]SCH 23390 and [³H]raclopride were purchased from New England Nuclear. Binding experiments were performed on Wistar rat (Charles River, France) striatal membranes. Each striatum was homogenized in 2 mL of ice-cold Tris-HCl buffer (50 mM, pH = 7.4 at 22 °C) with a Polytron (4 s, maximal scale) and immediately diluted with Tris buffer. The homogenate was centrifuged either twice ([³H]SCH 23390 binding experiments) or four times ([³H]raclopride binding experiments) at 20,000g for 10 min at 4 °C with resuspension in the same volume of Tris buffer between centrifugations. For [³H]SCH 23390 binding experiments, the final pellet was resuspended in Tris buffer containing 5 mM MgSO₄, 0.5 mM EDTA, and 0.02% ascorbic acid (Tris-Mg buffer), and the suspension was briefly sonicated and diluted to a protein concentration of 1 mg/mL. For [³H]raclopride binding experiments, the final pellet was resuspended in Tris buffer containing 120 mM NaCl, 5 mM KCl, 1 mM CaCl₂ and 0.1%

ascorbic acid (Tris-ions buffer), and the suspension was treated as described above.

4.2. Radioligand binding assays

For [³H]SCH 23390 binding experiments, a 100 µL aliquot of freshly prepared striatal membrane suspension (100 µg of protein) was incubated for 1 h at 25 °C with 100 µL of Tris buffer containing [³H]SCH 23390 (0.25 nM final concentration) and 800 µL of Tris-Mg buffer containing the required drugs. Nonspecific binding was determined in the presence of 30 µM SK&F 38393 and represented around 2–3% of total binding. For [³H]raclopride binding experiments, a 200 µL aliquot of freshly prepared striatal membrane suspension (200 µg of protein) was incubated for 1 h at 25 °C with 200 µL of Tris-ions buffer containing [³H]raclopride (0.5 nM final concentration) and 400 µL of Tris-ions buffer containing the drug being investigated. Nonspecific binding was determined in the presence of 50 µM apomorphine and represented ~5–7% of total binding. In both cases, incubations were stopped by addition of 3 mL of ice-cold buffer (Tris-Mg buffer or Tris-ions buffer, as appropriate) followed by rapid filtration through Whatman GF/B filters. Tubes were rinsed with 3 mL of ice-cold buffer. After the filters had been dried, radioactivity was counted in 4 mL BCS scintillation liquid at an efficiency of 45%. Filter blanks corresponded to approximately 0.5% of total binding and were not modified by the drugs.

4.3. General chemical procedures

Melting points were determined on a Reichert-Jung Galen III Kofler hot stage. Optical rotations were determined with a Schmidt-Haensch Polartronic electronic polarimeter. NMR spectra were recorded in CDCl₃ using a Bruker AMX 300 instrument, operating at 300.13 MHz (¹H) or 75.48 MHz (¹³C). Assignments were confirmed by HMQC and HMBC NMR experiments carried out using the standard Bruker software, inv4gstp and inv4gslplrnd, respectively. Electron impact mass spectra (70 eV) were recorded with a Hewlett-Packard Mass Spectra Acta 5973 instrument.

4.4. Preparation of predicentrine (**12**) and glaucine (**7**)

Boldine (**6**), isolated from *Peumus boldus* (boldo) bark and crystallized in CHCl₃ as the 1:1 complex with this solvent, was methylated with diazomethane in MeOH-Et₂O and the higher R_f products (**7** and **12**) were separated from unreacted boldine and isolated by column chromatography on silica gel 60 (Merck), eluting with EtOAc-MeOH 9:1.²⁹

4.5. General halogenation procedure

A solution of the appropriate aporphine (**7** or **12**) (1 g) in TFA (20 mL) was treated with *N*-halosuccinimide (1 or 2 M equiv depending upon whether the mono- or dihalogenated product was desired) at room temperature (20 °C). After 2 h stirring, the mixture was poured into cold water (100 mL), the aqueous solution was

adjusted to pH 8–9 with concd NH₃, extracted with CHCl₃ (5 × 50 mL) and subjected to column chromatography on silica gel 60 (Merck), eluting with EtOAc to isolate the halogenated derivatives. The yields, melting points, ¹H NMR, mass spectral data and elemental analyses are presented below.

4.5.1. 3-Bromopredicentrine (13). Obtained in 55% yield; hydrobromide (H₂O) mp 192–193 °C (decomp.); base [α]_D¹⁸ +109 (*c* 0.60, EtOH); ¹H NMR δ 2.54 (3H, s, *N*-CH₃), 3.63 (3H, s, 1-*O*-CH₃), 3.90 (3H, s, 10-*O*-CH₃), 3.93 (3H, s, 9-*O*-CH₃), 6.79 (1H, s, 8-H), 7.89 (1H, s, 11-H); MS *m/z* (rel. abund. %) 421 (79)/419 (81) (M)⁺, 420 (100)/418 (87) (M-H)⁺, 406 (50)/404 (52) (M-CH₃)⁺, 390 (32)/388 (29) (M-OCH₃)⁺, 379 (15)/377 (16) (M-CH₃N=CH₂)⁺, 340 (26) (M-Br)⁺. Anal. Calcd for C₂₀H₂₂BrNO₄·HBr·0.5H₂O: C, 47.08; H, 4.74; N, 2.75. Found: C, 46.85; H, 5.17; N, 2.67.

4.5.2. 3,8-Dibromopredicentrine (14). Obtained in 24% yield; base mp 189–190 °C (EtOH); [α]_D¹⁸ +127 (*c* 0.25, CHCl₃); ¹H NMR δ 2.58 (3H, s, *N*-CH₃), 3.62 (3H, s, 1-*O*-CH₃), 3.90 (3H, s, 9-*O*-CH₃), 3.92 (3H, s, 10-*O*-CH₃), 7.92 (1H, s, 11-H); MS *m/z* (rel. abund. %) 501 (35)/499 (74)/497 (38) (M)⁺, 500 (58)/498 (100)/496 (49) (M-H)⁺, 486 (14)/484 (34)/482 (20) (M-CH₃)⁺, 470 (10)/468 (20)/466 (14) (M-OCH₃)⁺, 458 (6)/456 (13)/454 (11) (M-CH₃N=CH₂)⁺, 420 (26)/418 (27) (M-Br)⁺. Anal. Calcd for C₂₀H₂₁Br₂NO₄·HCl·3H₂O: C, 40.74; H, 4.79; N, 2.38. Found: C, 40.45; H, 4.18; N, 2.42.

4.5.3. 3-Iodopredicentrine (15). Obtained in 49% yield; hydrochloride (H₂O) mp > 225 °C; ¹H NMR δ 2.57 (3H, s, *N*-CH₃), 3.61 (3H, s, 1-*O*-CH₃), 3.91 (3H, s, 9-*O*-CH₃), 3.94 (3H, s, 10-*O*-CH₃), 6.79 (1H, s, 8-H), 7.90 (1H, s, 11-H); MS *m/z* (rel. abund. %) 467 (100) (M)⁺, 466 (90) (M-H)⁺, 452 (41) (M-CH₃)⁺, 436 (27) (M-OCH₃)⁺, 425 (M-H₃N=CH₂)⁺, 340 (22) (M-I)⁺. Anal. Calcd for C₂₀H₂₂INO₄·HCl·1.5H₂O: C, 45.26; H, 4.94; N, 2.64. Found: C, 45.07; H, 5.26; N, 2.65.

4.5.4. 3-Chloroglaucine (16). Obtained in 24% yield; base (*i*-PrOH) mp 121–122 °C; [α]_D¹⁸ +111 (*c* 0.6, CHCl₃); ¹H NMR δ 2.56 (3H, s, *N*-CH₃), 3.73 (3H, s, 1-*O*-CH₃), 3.90 (3H, s, 9-*O*-CH₃), 3.93 (3H, s, 2-*O*-CH₃), 3.95 (3H, s, 10-*O*-CH₃), 6.78 (1H, s, 8-H), 7.97 (1H, s, 11-H); MS *m/z* (rel. abund. %) 391 (32)/389 (98) (M)⁺, 390 (50)/388 (100) (M-H)⁺, 376 (22)/374 (58) (41) (M-CH₃)⁺, 360 (12)/358 (58) (M-OCH₃)⁺, 354 (30) (M-Cl)⁺, 331 (13) (M-CH₃N=CH₂)⁺.

4.5.5. 3,8-Dichloroglaucine (17). Obtained in 27% yield; hydrochloride (Et₂O) mp 205–206 °C; base [α]_D¹⁸ +129 (*c* 0.2, AcOEt); ¹H NMR δ 2.50 (3H, s, *N*-CH₃), 3.65 (3H, s, 1-*O*-CH₃), 3.85 (3H, s, 2-*O*-CH₃), 3.86 (3H, s, 9-*O*-CH₃), 3.88 (3H, s, 10-*O*-CH₃), 7.83 (1H, s, 11-H); MS *m/z* (rel. abund. %) 427 (12)/425 (62)/423 (89) (M)⁺, 426 (25)/424 (84)/422 (100) (M-H)⁺, 412 (7)/410 (38)/408 (59) (M-CH₃)⁺, 396 (4)/394 (21)/392 (31) (M-OCH₃)⁺, 390 (20)/388 (53) (M-Cl)⁺, 384 (28)/382 (17)/380 (28) (M-CH₃N=CH₂)⁺.

4.5.6. 3-Bromoglaucine (18). Obtained in 58% yield; hydrobromide (H₂O) mp > 225 °C (decomp.); base [α]_D¹⁸ +127 (*c* 0.3, EtOH); ¹H NMR δ 2.49 (3H, s, *N*-CH₃), 3.68 (3H, s, 1-*O*-CH₃), 3.87 (3H, s, 2-*O*-CH₃), 3.89 (3H, s, 9-*O*-CH₃), 3.89 (3H, s, 10-*O*-CH₃), 6.74 (1H, s, 8-H), 7.90 (1H, s, 11-H); MS *m/z* (rel. abund. %) 435 (87)/433 (89) (M)⁺, 434 (100)/432 (90) (M-H)⁺, 420 (54)/418 (60) (M-CH₃)⁺, 404 (32)/402 (30) (M-OCH₃)⁺, 392 (1)/390 (16) (M-CH₃N=CH₂)⁺, 354 (45) (M-Br)⁺. Anal. Calcd for C₂₁H₂₄BrNO₄·HBr·H₂O: C, 47.30; H, 5.10; N, 2.63. Found: C, 47.45; H, 5.39; N, 2.57.

4.5.7. 3,8-Dibromoglaucine (19). Obtained in 47% yield; (hydrobromide) mp 203–205 °C (H₂O/*i*-PrOH); base [α]_D¹⁸ +155 (*c* 0.3, EtOH); ¹H NMR δ 2.57 (3H, s, *N*-CH₃), 3.71 (3H, s, 1-*O*-CH₃), 3.91 (3H, s, 2-*O*-CH₃), 3.92 (3H, s, 9-*O*-CH₃), 3.94 (3H, s, 10-*O*-CH₃), 7.93 (1H, s, 11-H); MS *m/z* (rel. abund. %) 515 (44)/513 (79)/511 (44) (M)⁺, 514 (61)/512 (100)/510 (51) (M-H)⁺, 500 (22)/498 (44)/496 (20) (M-CH₃)⁺, 484 (13)/482 (24)/480 (13) (M-OCH₃)⁺, 472 (9)/470 (20)/468 (16) (M-CH₃N=CH₂)⁺, 434 (48)/432 (50) (M-Br)⁺. Anal. Calcd for C₂₁H₂₃Br₂NO₄·HBr·0.5H₂O·0.5C₃H₈O: C, 43.15; H, 4.94; N, 2.29. Found: C, 43.21; H, 4.50; N, 2.42.

4.5.8. 3-Iodoglaucine (20). Obtained in 26% yield; hydrochloride (H₂O) mp 160–162 °C; ¹H NMR δ 2.56 (3H, s, *N*-CH₃), 3.72 (3H, s, 1-*O*-CH₃), 3.92 (3H, s, 2-*O*-CH₃), 3.93 (3H, s, 9-*O*-CH₃), 3.93 (3H, s, 10-*O*-CH₃), 6.78 (1H, s, 8-H), 7.94 (1H, s, 11-H); MS *m/z* (rel. abund. %) 481 (100) (M)⁺, 480 (83) (M-H)⁺, 466 (53) (M-CH₃)⁺, 450 (27) (M-OCH₃)⁺, 438 (10) (M-CH₃N=CH₂)⁺, 354 (24) (M-I)⁺. Anal. Calcd for C₂₁H₂₄INO₄·HCl·5.5H₂O: C, 40.89; H, 5.88; N, 2.27. Found: C, 40.32; H, 5.57; N, 2.27.

Acknowledgements

This research was funded by the Presidential Chair in Science (B.K.C., Chile, 1996), and by ICM grant No. P99-031-F. An exchange program between France and Chile (ECOS/CONICYT) and scholarships to M.A. from CONICYT and the French Embassy made this work possible. The principal author is grateful to the Alexander von Humboldt Foundation (Germany) for a generous donation of equipment.

References and notes

1. Keabian, J. W.; Calne, D. B. *Nature* **1979**, *277*, 93.
2. Stoof, J. C.; Keabian, J. W. *Life Sci.* **1984**, *35*, 2281.
3. Bunzow, J. R.; Van Tol, H. H. M.; Grandy, D. K.; Albert, P.; Salon, J.; Christie, M.; Machida, C. A.; Neve, K. A.; Civelli, O. *Nature* **1988**, *336*, 783.
4. Giros, B.; Sokoloff, P.; Martres, M.-P.; Riou, J.-F.; Emorine, L.-J.; Schwartz, J.-C. *Nature* **1989**, *342*, 923.
5. Dearry, A.; Gingrich, J. A.; Falardeau, P.; Freneau, R. T., Jr.; Bates, M. D.; Caron, M. G. *Nature* **1990**, *347*, 72.
6. Sokoloff, P.; Giros, B.; Martres, M.-P.; Bouthenet, M.-L.; Schwartz, J.-C. *Nature* **1990**, *347*, 146.

7. Van Tol, H. H. M.; Bunzow, R. R.; Guan, H. C.; Sunahara, R. K.; Seeman, P.; Niznik, H. B.; Civelli, O. *Nature* **1991**, *350*, 610.
8. Sunahara, R. K.; Guan, H. C.; O'Dowd, B. F.; Seeman, P.; Laurier, L. G.; Ng, G.; George, S. R.; Torchia, J.; Van Tol, H. H. M.; Niznik, H. B. *Nature* **1991**, *350*, 614.
9. Kilts, J. D.; Connery, H. S.; Arrington, W. G.; Lewis, M. M.; Lawler, C. P.; Oxford, G. S.; O'Malley, K. L.; Todd, R. D.; Blake, B. L.; Nichols, D. E.; Mailman, R. B. *J. Pharmacol. Exp. Ther.* **2002**, *301*, 1179.
10. Billard, W.; Ruperto, V.; Crosby, G.; Iorio, L. C.; Barnett, A. *Life Sci.* **1984**, *35*, 1885.
11. O'Boyle, K. M.; Waddington, J. L. *Eur. J. Pharmacol.* **1984**, *98*, 433.
12. Ghosh, D.; Snyder, S. E.; Watts, V. J.; Mailman, R. B.; Nichols, D. E. *J. Med. Chem.* **1996**, *39*, 549.
13. Doll, M. K.-H.; Nichols, D. E.; Kilts, J. D.; Prioleau, C.; Lawler, C. P.; Lewis, M. M.; Mailman, R. B. *J. Med. Chem.* **1999**, *42*, 935.
14. Sit, S.-Y.; Xie, K.; Jacutin-Porte, S.; Taber, M. T.; Gulwadi, A. G.; Korpinen, C. D.; Burris, K. D.; Molski, T. F.; Ryan, E.; Xu, C.; Wong, H.; Zhu, J.; Krishnananthan, S.; Gao, Q.; Verdoorn, T.; Johnson, G. *J. Med. Chem.* **2002**, *45*, 3660.
15. Eiler, W. J. A., II; Seyoum, R.; Foster, K. L.; Mailey, C.; June, H. L. *Synapse* **2003**, *48*, 45.
16. Khroyan, T. V.; Platt, D. M.; Rowlett, J. K.; Spealman, R. D. *Psychopharmacol* **2003**, *168*, 124.
17. Anderson, S. M.; Bari, A. A.; Pierce, R. C. *Psychopharmacol* **2003**, *168*, 132.
18. Neumeyer, J. L.; Arana, G. W.; Ram, V. J.; Baldessarini, R. J. In *Dopamine Receptor Agonists*; Carlsson, A., Nilsson, J. L. G., Eds.; Swedish Pharmaceutical: Stockholm, 1983; pp 11–24.
19. Miller, R. J.; Kelly, P. H.; Neumeyer, J. L. *Eur. J. Pharmacol.* **1976**, *35*, 77.
20. Goldman, M. E.; Keabian, J. W. *Mol. Pharmacol.* **1984**, *25*, 18.
21. Zetler, G. *Arch. Int. Pharmacodyn. Thér.* **1988**, *296*, 255.
22. Asencio, M.; Delaquerrière, B.; Cassels, B. K.; Speisky, H.; Comoy, E.; Protais, P. *Pharmacol. Biochem. Behav.* **1999**, *62*, 7.
23. Jiménez, I.; Speisky, H. *Phytother. Res.* **2000**, *14*, 254.
24. Sobarzo-Sánchez, E. M.; Arbaoui, J.; Protais, P.; Cassels, B. K. *J. Nat. Prod.* **2000**, *63*, 480.
25. Okubo, Y.; Suhara, T.; Suzuki, K.; Kobayashi, K.; Inoue, O.; Terasaki, O.; Someya, Y.; Sassa, T.; Sudo, Y.; Matsushima, E.; Iyo, M.; Tateno, Y.; Toru, M. *Nature* **1997**, *385*, 634.
26. Peacock, L.; Gerlach, J. *Biol. Psychiat.* **2001**, *50*, 501.
27. Kapur, S.; McClelland, R. A.; VanderSpek, S. C.; Wadenberg, M. L.; Baker, G.; Nobrega, J.; Zipursky, R. B.; Seeman, P. *Neuroreport* **2002**, *13*, 831.
28. Speisky, H.; Cassels, B. K.; Lissi, E. A.; Videla, L. A. *Biochem. Pharmacol.* **1991**, *41*, 1575.
29. (a) Tschesche, R.; Welzel, P.; Legler, G. *Tetrahedron Lett.* **1965**, 445; (b) Asencio, M.; Cassels, B. K.; Speisky, H. *Bol. Soc. Chil. Quím.* **1993**, *38*, 331.
30. Schaus, J. M.; Titus, R. D.; Foreman, M. M.; Mason, N. R.; Truex, L. L. *J. Med. Chem.* **1990**, *33*, 600.
31. Neumeyer, J. L.; Reischig, D.; Arana, G. W.; Campbell, A.; Baldessarini, R. J.; Kula, N. S.; Watling, K. J. *J. Med. Chem.* **1983**, *26*, 516.
32. Cox, R. F.; Neumeyer, J. L.; Waszczak, B. L. *J. Pharmacol. Exp. Ther.* **1988**, *247*, 355.
33. Cheng, Y. C.; Prusoff, W. H. *Biochem. Pharmacol.* **1973**, *22*, 3099–3108.
34. Schulz, D. W.; Stanford, E. J.; Wyrick, S. W.; Mailman, R. B. *J. Neurochem.* **1985**, *45*, 1601–1611.
35. Kohler, C.; Hall, H.; Ögren, S. O.; Gawell, L. *Biochem. Pharmacol.* **1985**, *34*, 2251–2259.