Binding and Preliminary Evaluation of 5-Hydroxy- and 10-Hydroxy-2,3,12,12a-tetrahydro-1*H*-[1]benzoxepino[2,3,4-*ij*]isoquinolines as Dopamine Receptor Ligands

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The *N*-methyl, *N*-ethyl, and *N*-*n*-propyl derivatives of 5-hydoxy- and 10-hydroxy-2,3,12,12a-tetrahydro-1*H*-[1]benzoxepino[2,3,4-*ij*]isoquinolines were prepared as monophenolic ligands for the dopamine receptor and evaluated for their affinity at D_1-like and D_2-like subtypes. All compounds showed very low D_1 affinities. This could be ascribed to the absence of a catechol nucleus or of the β-phenyldopamine pharmacophore. Only the *N*-methyl-5-hydroxy- (**5a**), *N*-methyl-10-hydroxy- (**6a**), and *N*-methyl-4-bromo-10-methoxy-2,3,12,12a-tetrahydro-1*H*-[1]-benzoxepino[2,3,4-*ij*]isoquinolines (**26a**) bound the D_2 receptors with low affinity, in the same range as dopamine. In compounds **5a** and **6a**, the 2-(3-hydroxyphenyl)ethylamine moiety does not meet the requirements of the D_2 agonist pharmacophore: namely, the 2-(3-hydroxyphenyl)-ethylamine does not reach the *trans*, fully extended conformation. The three compounds did not interact with recombinant human D_4 receptors, and only **5a** showed low affinity for rat recombinant D_3 receptors. Analysis of the influence of Na^+ on [^{3}H]spiperone binding showed that **5a** displays a potential dopamine D_2 agonist profile, whereas **6a** probably has a dopamine D_2 antagonist activity. The D_2 agonist activity of **5a** was proved by the effects on prolactin release from primary cultures of rat anterior pituitary cells.

Introduction

The neurotransmitter dopamine (DA) is involved in the regulation of several functions, including locomotor activity, emotion, cognition, and neuroendocrine secretion. Degeneration of DA neurons in the substantia nigra contributes to the pathogenesis of Parkinson's disease, and imbalance in the limbic DA pathways is thought to contribute to psychotic disorders such as schizophrenia.[1] The actions of DA are mediated by five different receptor subtypes classified into two families: D_1-like (D_1 and D_5) and D_2-like (D_2, D_3, and D_4).

Several structurally different compounds are available as potent and selective ligands for D_2 receptors,[2] but far fewer agents have been found to be selective for the D_1 receptor. The 6-chloro-7-hydroxy-1-phenyl-2,3,4,5-tetrahydrobenzazepine (SCH 23390)[3] has been the prototypical D_1 ligand of the benzazepine class which includes both agonists and antagonists. In the past few years, new D_1-selective full agonists have been identified such as 1-aminomethyl-5,6-dihydroxy-3-phenylisochroman[4] and *trans*-10,11-dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine.[5]

The structure−activity relationship studies with various classes of dopaminergic agents have established that the D_1 receptor agonist pharmacophore may be depicted by the DA in the *trans* extended conformation. Moreover, an aromatic ring at the β-position of the ethylamine chain and a catecholic nucleus are essential for D_1 receptor activation.[5] Instead, the requirements for D_2 receptor activation are much less stringent and the D_2 agonist pharmacophore may be described by the 2-(3-hydroxyphenyl)ethylamine in the *trans*, fully extended conformation.[6,7]

Most of the dopaminergic agents contain a catechol group. This imparts high activity but is also responsible for the low oral bioavailability of the compounds, for their sensitivity toward oxidation and methylation.

Site-directed mutagenesis studies indicate that the pharmacophore primary attachment points on the D_2 receptors are an aspartic acid residue in the third transmembrane domain (TM3; electrostatic interaction with the protonated amino group) and a serine residue in TM5 (hydrogen-bonding interaction with the *m*-hydroxyl group).[8,9] Many aporphines possess the ability to activate DA receptors, and several studies have shown that the catechol function of *R*-(−)-apomorphine (**1**) (Chart 1) is not a prerequisite for dopaminergic activity: *R*-(−)-11-hydroxy-*N*-*n*-propylnoraporphine (**2**) is a DA agonist and induces strong stereotyped behaviors in the rat, nearly as potently as *R*-(−)-apomorphine.[10] These findings support the hypothesis that also a single hydroxy group may confer affinity and activity at DA receptors.

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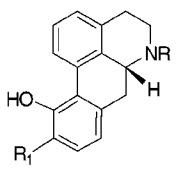
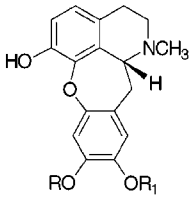
Chart 1



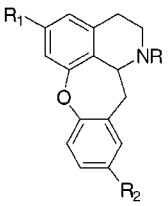
1 R = CH_3 ; R_1 = OH

2 R = n-C_3H_7; R_1 = H



3 R = R_1 = CH_3 : cularidine

4 R =H; R_1 = CH_3 : celtisine



5 R_1 = OH; R_2 = H

6 R_1 = H; R_2 = OH

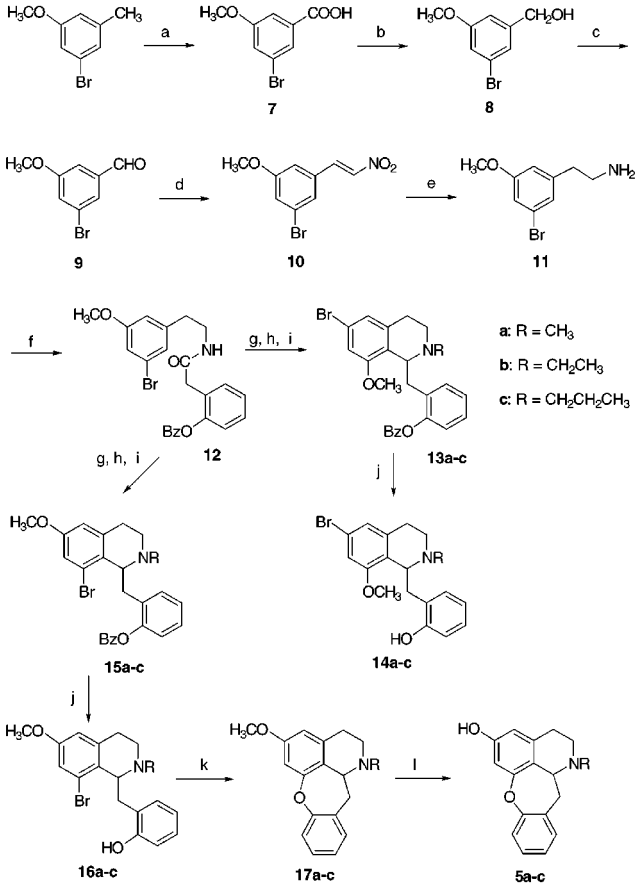
Our previous studies have been directed toward the synthesis and characterization of monohydroxylated DA receptor ligands which do not suffer the drawbacks induced by the catechol nucleus.[11,12] With the aim of extending knowledge on the monophenolic ligands of DA receptors, in the present work we synthesized some *N*-alkyl derivatives of the 5- or 10-hydroxy-2,3,12,12a-tetrahydro-1*H*-[1]benzoxepino[2,3,4-*ij*]isoquinoline. This tetracyclic system was chosen considering that the cularine alkaloids cularidine (**3**) and celtisine (**4**) (Chart 1) showed high affinity for D_1-like and D_2-like receptors labeled with [^{3}H]SCH 23390 and [^{3}H]raclopride, respectively (IC_{50} (nM): **3**, D_1 = 80, D_2 = 320; **4**, D_1 = 60, D_2 = 30).[13]

The benzoxepinoisoquinoline skeleton showed structural similarity to the tetracyclic system of the dopaminergic agonist *R*-(−)-apomorphine (**1**). From an inspection of **3** and **4** (Chart 1) it is evident that the hydroxy group is placed at a position *para* to the ethylamine chain. Considering that a hydroxy group *meta* to the ethylamine chain seems to be more critical for the interaction with the receptors,[5,7] in the new compounds (structures **5** and **6**), the hydroxy group was introduced at position 5 or 10 in order to set the 2-(3-hydroxyphenyl)ethylamine moiety into the tetracyclic system.

Chemistry

The *N*-alkyl derivatives of 5-hydroxy-2,3,12,12a-tetrahydro-1*H*-[1]benzoxepino[2,3,4-*ij*]isoquinolines **5a**−**c** were prepared as outlined in Scheme 1. The key intermediate 2-(3-bromo-5-methoxyphenyl)ethylamine **(11)** was prepared starting from 3-bromo-5-methoxytoluene. This was oxidized with $KMnO_4$ to 3-bromo-5-methoxybenzoic acid **(7)**. Reduction of the acid **7** with lithium aluminum hydride provided the alcohol **8**. Subsequent oxidation with pyridinium chlorochromate gave the aldehyde **9**. Amine **11** was obtained by reaction of **9** with nitromethane and reduction of the resulting nitrostyrene **10** with zinc amalgam and 37% HCl. Condensation of amine **11** with 2-benzyloxyphenylacetic acid gave the amide **12**. The Bischler Napieralski cyclization of amide **12** with phosphoryl chloride gave

Scheme 1[a]

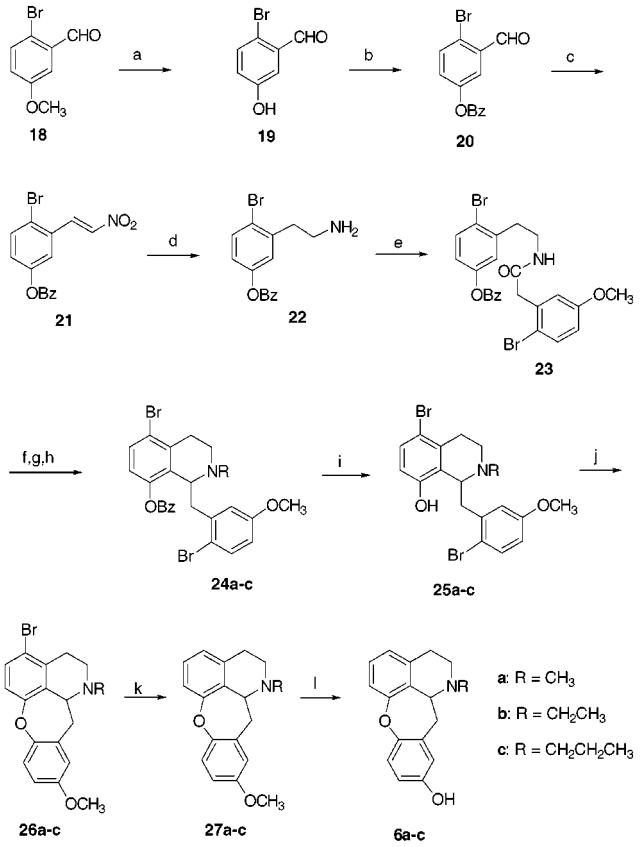


[a] Reagents: (a) $KMnO_4$, pyridine, H_2O; (b) $LiAlH_4$; (c) pyridinium chlorochromate; (d) CH_3NO_2; (e) Zn(Hg), 37% HCl; (f) 2-benzyloxyphenylacetic acid; (g) $POCl_3$, CH_3CN; (h) RI, CH_3CN; (i) $NaBH_4$; (j) EtOH, HCl; (k) K_2CO_3, CuO, pyridine; (l) 48% HBr.

unstable 3,4-dihydroisoquinolines. This drawback was overcome by transformation of crude 3,4-dihydrobenzylisoquinolines into the quaternary alkyl iodides. The nonisolated salts were reduced to tetrahydroisoquinolines **13a**−**c** and **15a**−**c** by sodium borohydride. The cyclization reaction afforded a mixture of isomeric 1-benzyl-6-bromo-8-methoxy- **(13a,b)** and 1-benzyl-8-bromo-6-methoxy-1,2,3,4-tetrahydroisoquinolines **(15a**−**c)** which were separated by column chromatography. This result is in disagreement with previous syntheses which afforded only 6-methoxytetrahydroisoquinolines.[14,15] The *O*-benzyl ethers **13a,b** and **15a**−**c** were cleaved with 37% HCl to afford the phenol derivatives **14a,b** and **16a**−**c**. The intramolecular Ullmann cyclization of compounds **16a**−**c** with potassium carbonate and copper oxide in pyridine gave the oxepines **17a**−**c**. The *N*-*n*-propyl derivatives **13c**, **14c**, and **16c** are highly unstable, and for this reason, **15c** was transformed into **17c** without isolation of the intermediate **16c.** The *O*-methyl ethers **17a**−**c** were cleaved with 48% hydrobromic acid.

The *N*-alkyl derivatives of 10-hydroxy-2,3,12,12a-tetrahydro-1*H*-[1]benzoxepino[2,3,4-*ij*]isoquinolines **6a**−**c** were prepared by similar procedures starting from 2-bromo-5-benzyloxybenzaldehyde through the intermediate 2-(2-bromo-5-benzyloxyphenyl)ethylamine **(22)** as outlined in Scheme 2. The presence of bromine at position 2 prevented the formation of a mixture of isomeric tetrahydroisoquinolines. Debromination of com-

Scheme 2[a]



[a] Reagents: (a) 48% HBr, CH_3COOH; (b) benzyl chloride, K_2CO_3; (c) CH_3NO_2; (d) Zn(Hg), 37% HCl; (e) 2-bromo-5-methoxyphenylacetic acid; (f) $POCl_3$, CH_3CN; (g) RI, CH_3CN; (h) $NaBH_4$; (i) HCl; (j) K_2CO_3, CuO, pyridine; (k) 10% Pd/C, H_2; (l) 48% HBr.

pounds **26a**−**c** was accomplished by reduction with palladium on charcoal.

NMR spectra for the oxalate salts of the compounds **6a**−**c**, **5a**−**c**, and **25a**−**c** showed a very broad signal (basically a deformation of the baseline). These signals disappeared after D_2O addition, and they can be assigned to both phenolic and oxalic acid hydroxy groups.

Pharmacology

The binding affinities (pK_i) were determined in DA D_1 and D_2 receptor assays. It is important to emphasize that the affinities for D_1 and D_2 receptors are referred to D_1-like (D_1 and D_5) and D_2-like (D_2, D_3, and D_4) families of DA receptors. Rat striatal membrane was used as the tissue source; [^{3}H]SCH 23390 and [^{3}H]-spiperone were used as radioligands for the D_1 and D_2 receptors, respectively. Selected compounds were also tested for their ability to compete with [^{3}H]spiperone from recombinant rat D_3 and recombinant human D_4 receptors. All compounds were tested as racemates.

Furthermore, compounds **5a** and **6a**, showing higher D_2 affinity, were pharmacologically studied in vitro by evaluating their effects on prolactin (PRL) release in primary cultures of rat anterior pituitary cells, to assess their agonist activity. Previous studies indicate that D_2 receptors on lactotroph pituitary cells inhibit PRL release via inhibition of adenylate cyclase. On the other hand, there is evidence for a dual role of DA in both stimulating and inhibiting PRL secretion through activation of the same DA receptor.[16,17]

Results and Discussion

Table 1 displays the binding test results for monohydroxybenzoxepinoisoquinolines (**5a**−**c**, **6a**−**c**) and for their methoxylated (**17a**−**c**, **27a**−**c**) and brominated (**26a**−**c**) precursors.

As far as the affinities for D_1 receptors are concerned, all compounds show lower binding affinity than DA or *R*-(−)-apomorphine. Among the compounds substituted at the 5 position, only the *N*-methyl and *N*-ethyl derivatives **5a,b** and **17a** show D_1 affinity. Demethylation of **17a**−**c** increases only the affinity of the *N*-ethyl derivative **17b**. In the series with the hydroxyl group at position 10, the *N*-methyl and *N*-ethyl derivatives **6a**,**b** show D_1 affinity, while the *N*-propyl derivative **6c** is inactive, as observed also for the 5-OH analogue **6c**. Compounds **26a**−**c**, with a bromine at position 4, show D_1 affinity, and debromination decreases the affinity of the *N*-ethyl derivative **26b**. An unexpected result is that the demethylation of the *n*-propyl derivative **27c** decreases the affinity.

Binding data for D_2 receptors indicate that **5a** binds with higher affinity than DA, while compounds **6a** and **26a** are equipotent to DA. In the series having a 5-methoxy group, the *N*-*n*-propyl derivative **17c** is the most active. In the series having a 10-methoxy or 10-hydroxy group, the *N*-methyl derivatives **6a** and **26a** show the highest affinity.

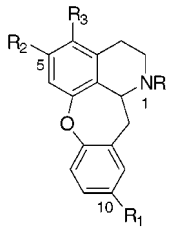
The *N*-methyl derivatives **5a**, **6a**, and **26a** show higher selectivity for D_2 receptors over D_1 than do DA or apomorphine. Previous studies on aporphine showed that *N*-ethyl- and *N*-*n*-propylnorapomorphine show higher affinity at the D_2 receptor than apomorphine, whereas in our compounds the *N*-methyl derivatives bind with higher affinity than the *N*-ethyl and *N*-*n*-propyl analogues.[18]

Binding studies were carried out also on the 1-benzyltetrahydroisoquinoline intermediates. These compounds are synthetic precursors of benzoxepinoisoquinolines and were investigated considering that the 1-(2,5-dimethoxy-4-propylbenzyl)-2-methyl-6-chloro-7-hydroxy-1,2,3,4-tetrahydroisoquinoline shows high affinity for D_1 receptors.[19] Binding data for 1-benzyltetrahydroisoquinolines are shown in Table 2. Compounds **14a,b** and **16a,b** bind with low affinity at both D_1 and D_2 receptors. On the other hand, compounds **25a**−**c** show affinity only for D_1 receptors, the *N*-methyl derivative being equipotent to DA. From the comparison of pK_i values of 1-benzyltetrahydroisoquinoline **25a** with those of benzoxepinoisoquinoline **26a**, it is evident that cyclization decreases D_1 affinity and increases D_2 affinity. Data obtained for the 1-benzyltetrahydroisoquinolines indicate that compounds **14a,b**−**16a,b,** containing the hydroxyl group on the benzyl ring, are nonselective for D_1 and D_2 receptors. On the other hand, introduction of the hydroxyl group at position 8 of the isoquinoline ring increases D_1 selectivity, and the methyl derivative **25a** shows D_1 affinity comparable to that of DA.

The derivatives **5a**, **6a**, and **26a** were also evaluated for their affinity at the cloned rat D_3 receptor and human D_4 receptor. None of the compounds bound the D_4 receptor, and only **5a** showed D_3 affinity ($K_i = 1.48 \times 10^{-6}$, $pK_i = 5.83 \pm 0.09$).

Compounds **5a** and **6a**, displaying the highest D_2 affinities, were selected to evaluate the possible agonist

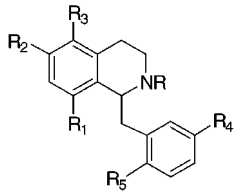
Table 1. pK_i Values for the 2,3,12,12a-Tetrahydro-1*H*-[1]benzoxepino[2,3,4-*ij*]isoquinolines and Reference Compounds at Striatal D_1 and D_2 DA Receptors[a]



compd	R	R_1	R_2	R_3	pK_i D_1	pK_i D_2
5a	Me	H	OH	H	5.54 ± 0.06	6.56 ± 0.11
5b	Et	H	OH	H	5.46 ± 0.06	5.19 ± 0.15
5c	*n*-Pr	H	OH	H	<5	<5
17a	Me	H	OCH_3	H	5.37 ± 0.04	5.03 ± 0.25
17b	Et	H	OCH_3	H	<5	5.07 ± 0.04
17c	*n*-Pr	H	OCH_3	H	<5	5.46 ± 0.15
6a	Me	OH	H	H	5.32 ± 0.016	6.14 ± 0.05
6b	Et	OH	H	H	5.17 ± 0.39	<5
6c	*n*-Pr	OH	H	H	<5	<5
26a	Me	OCH_3	H	Br	5.12 ± 0.06	6.07 ± 0.19
26b	Et	OCH_3	H	Br	5.46 ± 0.23	<5
26c	*n*-Pr	OCH_3	H	Br	5.61 ± 0.32	<5
27a	Me	OCH_3	H	H	5.28 ± 0.07	5.91 ± 0.20
27b	Et	OCH_3	H	H	<5	5.73 ± 0.16
27c	*n*-Pr	OCH_3	H	H	5.41 ± 0.26	<5
dopamine					6.38 ± 0.14	6.14 ± 0.08
R-(−)-apomorphine					6.74 ± 0.05	7.26 ± 0.13
SCH 23390					9.13 ± 0.02	NT[b]
haloperidol					7.15 ± 0.03	8.67 ± 0.11

[a] Values represent the mean ± SEM of at least three independent experiments. The slope of the curve for new compounds does not differ significantly from unity. Binding ligands were: D_1, [^{3}H]SCH 23390; D_2, [^{3}H]spiperone. [b] NT = not tested.

Table 2. pK_i Values for the 1-Benzyl-1,2,3,4-tetrahydroisoquinolines at Striatal D_1 and D_2 DA Receptors[a]



compd	R	R_1	R_2	R_3	R_4	R_5	pK_i D_1	pK_i D_2
14a	Me	OCH_3	Br	H	H	OH	5.77 ± 0.17	5.74 ± 0.27
14b	Et	OCH_3	Br	H	H	OH	5.25 ± 0.06	5.66 ± 0.25
16a	Me	Br	OCH_3	H	H	OH	4.93 ± 0.16	5.15 ± 0.15
16b	Et	Br	OCH_3	H	H	OH	5.52 ± 0.10	5.51 ± 0.20
25a	Me	OH	H	Br	OCH_3	Br	6.41 ± 0.05	<5
25b	Et	OH	H	Br	OCH_3	Br	5.81 ± 0.04	<5
25c	*n*-Pr	OH	H	Br	OCH_3	Br	5.13 ± 0.09	<5

[a] See footnotes for Table 1. For binding affinity of reference compounds, see Table 1.

or antagonist properties. It is known that the presence of Na^+ in the incubation medium converts the D_2 receptor high-affinity state into a low-affinity state and causes a shift of the agonist competition curve to the right.[20] Analysis of the influence of Na^+ on [^{3}H]spiperone binding caused a slight shift, toward the right, of the competition curves of compound **5a** (pK_i values 6.89 ± 0.20 without Na^+ and 6.28 ± 0.12 with Na^+) and of *R*-(−)-apomorphine (pK_i values 7.18 ± 0.10 without Na^+ and 6.97 ± 0.15 with Na^+). The presence of Na^+ in the incubation medium did not change the pK_i values of **6a** (pK_i values 6.06 ± 0.13 without Na^+ and 5.98 ± 0.20 with Na^+) nor those of haloperidol (pK_i values 8.60 ± 0.16 without Na^+ and 8.61 ± 0.28 with Na^+). These results suggest that **5a** displays a potential DA D_2 agonist profile, whereas **6a** probably has a DA D_2 antagonist activity.

DA is generally believed to inhibit PRL pituitary secretion by stimulating D_2 receptors on lactotrophs, an effect which involves inhibition of adenylyl cyclase, yet some studies showed that DA can also stimulate PRL release from lactotrophs, and both stimulatory and inhibitory actions of DA are likely mediated by the same D_2 receptor subtype.[17,21] Compounds **5a** and **6a** were studied in vitro by evaluating their effects on PRL release from primary cultures of rat anterior pituitary cells. Compound **5a** at low concentrations stimulates and at higher concentrations inhibits PRL release (Figure 1). It can be hypothesized that the PRL-stimulating activity demonstrated by **5a** is due to the

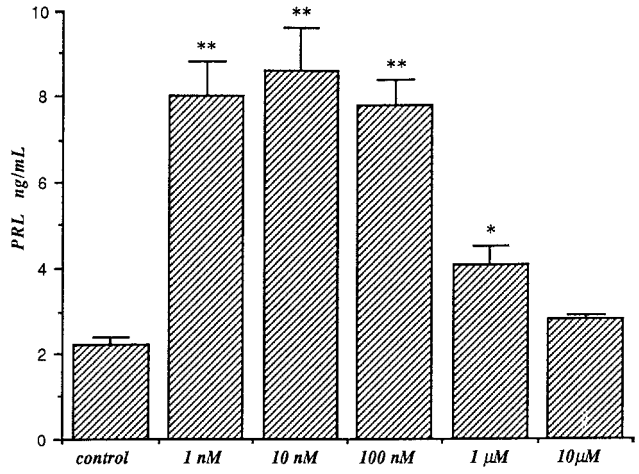


Figure 1. Effect of **5a** on PRL release from anterior pituitary cell cultures in vitro after a 1-h incubation; group means ± SEM, $n = 6-8$, $*p < 0.001$ and $**p < 0.01$ vs control.

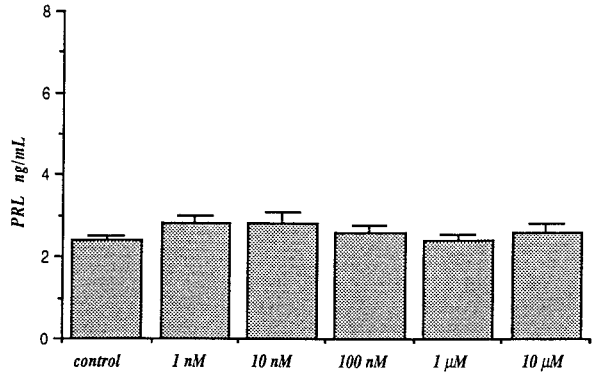


Figure 2. Effect of **6a** on PRL release from anterior pituitary cell cultures in vitro after a 1-h incubation; group means ± SEM, $n = 6-8$.

higher affinity of **5a** with D_2 "stimulatory" receptors, an effect which is overwhelmed at higher concentrations, where D_2 inhibitory effects counteract stimulatory ones. This finding is similar to the effect of quinpirole, a specific D_2 receptor agonist with low selectivity for the D_3 receptor, as is the case with compound **5a**, which has been shown to stimulate PRL release only at low concentrations (1−100 pM).[22] On the contrary, the lack of activity by **6a** on PRL secretion (Figure 2) could be explained by the D_2 antagonist profile seen in the binding test.

The moderate or low affinities for D_1 and D_2 receptors of the compounds screened do not allow us to define extensive structure−activity relationships. However, it is evident that all compounds have weak interactions with the receptors. The very low affinity for the D_1 receptor may be ascribed to the lack of the catechol nucleus or of the "*trans*-β-phenyldopamine" moiety that has been depicted as the D_1 pharmacophore.[5]

Moreover, Dreiding models and Figure 3 show that the ethylamine chain of the 2-(3-hydroxyphenyl)ethylamine moiety in the 5-OH-benzoxepinoisoquinolines is in a folded conformation, whereas in the 10-OH-benzoxepinoisoquinolines it does not reach the *trans*, fully extended, and antiperiplanar conformation required for interaction with D_2 receptors.[7]

In conclusion, the 5- or 10-monohydroxylated tetrahydrobenzoxepinoisoquinolines synthesized show weak affinity for DA receptors. The benzoxepine skeleton does not affect the selectivity, and the higher affinities observed with the natural alkaloids cularidine and celtisine may be ascribed to the different position of the hydroxyl groups or to the presence of the methoxy groups.

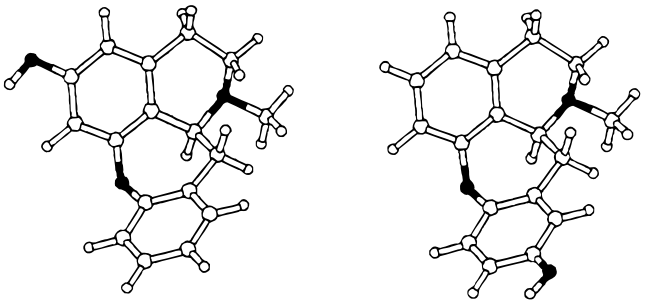


Figure 3. Tridimensional model of the structures of **5** and **6**.

Experimental Section

Melting points were determined on a Buchi 510 apparatus and are uncorrected. Microanalyses were performed on a 1106 Carlo Erba CHN analyzer, and the results were within ±0.4% of the calculated values. ^{1}H NMR spectra were recorded on a Varian VXR 200-MHz spectrometer. Chemical shifts are reported in parts per million (δ) downfield from the internal standard tetramethylsilane (Me_4Si). The IR spectra were run on a Perkin-Elmer model 297 spectrometer as Nujol mulls or liquid films. The identity of all new compounds was confirmed by both elemental analysis and NMR data; homogeneity was confirmed by TLC on silica gel Merck 60 F_{254}. Solutions were routinely dried over anhydrous sodium sulfate prior to evaporation. Chromatographic purifications were performed by Merck 60 70−230 mesh ASTM silica gel columns from Merck with the reported solvent.

3-Bromo-5-methoxybenzoic Acid (7). Potassium permanganate (26.81 g, 170 mmol) was added in small portions to a vigorously stirred mixture of 3-bromo-5-methoxytoluene (10.55 g, 53 mmol), pyridine (27 mL), and H_2O (80 mL) at 75 °C. After stirring for 24 h at the same temperature and 2 h at room temperature, the mixture was filtered. MnO_2 was suspended in hot H_2O and again filtered off. The pyridine was removed from filtrates, as an azeotrope with H_2O, by distillation under reduced pressure. The resulting aqueous solution was extracted with Et_2O and acidified with 2 N H_2SO_4. The precipitate was filtered off and recrystallized from EtOH/H_2O (8/2) to give 19.64 g (50%) of pure **7**: mp 193−195 °C; IR 1670 (ν C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.82 (m, 1H, ArH), 7.56 (m, 1H, ArH), 7.30 (m, 1H, ArH), 3.84 (s, 3H, OCH_3). Anal. ($C_8H_7BrO_3$) C, H.

3-Bromo-5-methoxybenzyl Alcohol (8). To a 0 °C magnetically stirred suspension of **7** (5.20 g, 23 mmol) in anhydrous Et_2O (108 mL) was added portionwise $LiAlH_4$ (950 mg, 25 mmol). The ice bath was removed, the mixture was heated for 5 min and stirred at room temperature for 3 h, and the excess $LiAlH_4$ was quenched by successive dropwise additions of 1 mL of H_2O, 1 mL of 15% NaOH, and 3 mL of H_2O. The solution was filtered, and the filtrate was dried and concentrated under reduced pressure. The residue was recrystallized from Et_2O/petroleum ether to give 4.04 g (81%) of pure **8**: mp 45−46 °C; IR 3300 (ν OH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.09 (s, 1H, ArH), 6.97 (m, 1H, ArH), 6.82 (m, 1H, ArH), 4.63 (d, 2H, CH_2), 3.79 (s, 3H, OCH_3), 1.93 (t, 1H, OH). Anal. ($C_8H_9BrO_2$) C, H.

3-Bromo-5-methoxybenzaldehyde (9). A solution of **8** (5 g, 23 mmol) in anhydrous CH_2Cl_2 (50 mL) was added to the magnetically stirred suspension of pyridinium chlorochromate (7.53 g, 35 mmol) in anhydrous CH_2Cl_2 (37 mL). After 2 h, Et_2O (53 mL) was added, and the reaction mixture was allowed to stand in a refrigerator overnight. The suspension was filtered on silica gel, and the solvent was evaporated under reduced pressure. The oily residue was crystallized from EtOH/

H_2O (7/3) to give 7.13 g (95%) of pure **9:** mp 45−46 °C; IR 1695 (ν C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.90 (s, 1H, CHO), 7.59 (m, 1H, ArH), 7.31 (m, 2H, ArH), 3.87 (s, 3H, OCH_3). Anal. ($C_8H_7BrO_2$) C, H.

2-(3-Bromo-5-methoxyphenyl)nitroethylene (10). A mixture of Na_2CO_3 (0.3 g, 2.8 mmol) and methylamine hydrochloride (0.3 g, 4.3 mmol) in EtOH (3 mL) was stirred at room temperature for 15 min and filtered into a solution of **9** (2 g, 9.3 mmol) in EtOH (3.8 mL). Nitromethane (0.6 mL, 11 mmol) was added, and the mixture was stoppered and left in the dark at room temperature for 1 day. The yellow crystalline product was filtered and washed with EtOH, yielding 800 mg (72%) of **10**: mp 127−129 °C; ^1H NMR ($CDCl_3$) δ 7.89 and 7.53 (d, 4H, $2CH_2$), 7.26 (m, 1H, ArH), 7.18 (m, 1H, ArH), 6.97 (m, 1H, ArH), 3.84 (s, 3H, OCH_3). Anal. ($C_9H_8BrNO_3$) C, H, N.

2-(3-Bromo-5-methoxyphenyl)ethylamine Oxalate (11). To a stirred mixture of **10** (1 g, 3.9 mmol) at 45−50 °C were added 37% HCl (7 mL), CH_3OH (14 mL), and zinc amalgam [from zinc (4 g) and mercury(II) chloride (0.4 g)]. The mixture was stirred at 55 °C for 3 h. After removal of an inorganic substance, the mixture was made basic with 28% NH_4OH. The solvent was evaporated off and the residual solid was extracted with $CHCl_3$ after addition of an excess of 28% NH_4OH. The extract was washed with H_2O, dried, and evaporated to leave the ethylamine derivative as a pale brownish oil. The residue was converted to the oxalate salt and crystallized from *i*-PrOH/Et_2O to give 930 mg (74%) of pure **11**: mp 201−203 °C; ^1H NMR (DMSO-d_6) δ 8.10 (bs, 3H, NH_3^+), 7.06 (m, 2H, ArH), 6.90 (m, 1H, ArH), 3.79 (s, 3H, OCH_3), 3.06 (m, 2H, CH_2N), 2.87 (t, 2H, CH_2C). Anal. ($C_9H_{12}BrNO\cdot H_2C_2O_4$) C, H, N.

***N*-(3-Bromo-5-methoxyphenethyl)-2-benzyloxyphenylacetamide (12).** A slurry of 2-(3-bromo-5-methoxyphenyl)-ethylamine (free base, 740 mg, 3.2 mmol) and 2-benzyloxyphenylacetic acid (780 mg, 3.2 mmol) in xylene (3 mL) was refluxed under N_2 for 8 h with azeotropic removal of H_2O. After cooling, the oily residue was crystallized from cyclohexane to give 930 mg (64%) of pure **12**: mp 48−50 °C; IR 3260 (ν NH), 1580−1615 (ν C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42−7.20 (m, 7H, ArH), 7.00−6.85 (m, 3H, ArH), 6.75 (m, 1H, ArH), 6.48 (m, 1H, ArH), 5.80 (bs, 1H, NH), 5.00 (s, 2H, CH_2O), 3.71 (s, 3H, OCH_3), 3.56 (s, 2H, CH_2O), 3.37 (m, 2H, CH_2N), 2.58 (t, 2H, $ArCH_2$). Anal. ($C_{24}H_{24}BrNO_3$) C, H, N.

General Procedure for the Synthesis of 1,2,3,4-Tetrahydroisoquinolines 13a,b and 15a−c. A solution of **12** (300 mg, 0.66 mmol) in dry acetonitrile (5.5 mL) was treated with phosphoryl chloride (0.6 mL) and refluxed under N_2 for 1 h; the solvent was evaporated off and the excess of reagent was removed in vacuo. A solution of the residue in $CHCl_3$ was rapidly washed (1 N NaOH and H_2O), dried, and evaporated under reduced pressure. The unstable 3,4-dihydrobenzylisoquinoline in acetonitrile (4 mL) and the appropriate alkyl iodide were refluxed under N_2 for 3 h. Evaporation gave the crude alkylammonium iodide which was reduced in $CHCl_3$ (1.1 mL) and CH_3OH (6.6 mL) by adding $NaBH_4$ (200 mg, 5.3 mmol) in portions and then stirring for 30 min at room temperature. The solvent was evaporated off, H_2O was added, and the mixture was extracted with $CHCl_3$; the organic phase was dried and the residue was chromatographed on silica gel eluting with ethyl acetate. The isomers **13a,b** and **15a−c** were obtained.

1-(2-Benzyloxybenzyl)-6-bromo-8-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (13a): obtained from **12** and methyl iodide (1.05 mL, 17 mmol); R_f 0.46 (eluent AcOEt); yield 25% (75 mg); ^1H NMR ($CDCl_3$) δ 7.50−7.30 (m, 5H, ArH), 7.13 (m, 2H, ArH), 6.85 (m, 3H, ArH), 6.65 (m, 1H, ArH), 5.04, (s, 2H, OCH_2), 4.26 (m, 1H, CHN), 3.38 (s, 3H, OCH_3), 3.36−2.40 (m, 6H, CH_2), 2.34 (s, 3H, NCH_3). Anal. ($C_{25}H_{26}BrNO_2$) C, H, N.

1-(2-Benzyloxybenzyl)-8-bromo-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (15a): obtained from **12** and methyl iodide (1.05 mL, 17 mmol); R_f 0.42 (eluent AcOEt); yield 30% (90 mg); ^1H NMR ($CDCl_3$) δ 7.50−7.10 (m, 7H, ArH), 6.91 (m, 3H, ArH), 6.60 (m, 1H, ArH), 5.09, (s, 2H, OCH_2), 4.20 (m, 1H, CHN), 3.74 (s, 3H, OCH_3), 3.09−2.40 (m, 6H, CH_2), 2.28 (s, 3H, NCH_3). Anal. ($C_{25}H_{26}BrNO_2$) C, H, N.

1-(2-Benzyloxybenzyl)-6-bromo-2-ethyl-8-methoxy-1,2,3,4-tetrahydroisoquinoline (13b): obtained from **12** and ethyl iodide (1.4 mL, 17 mmol); R_f 0.55 (eluent AcOEt); yield 30% (93 mg); ^1H NMR (DMSO-d_6) δ 7.53−7.20 (m, 5H, ArH), 7.17−7.10 (m, 1H, ArH), 7.08−6.90 (m, 2H, ArH), 6.88−6.60 (m, 3H, ArH), 5.00 (s, 2H, OCH_2), 4.45 (m, 1H, CHN), 3.65 (s, 3H, OCH_3), 3.60−2.48 (m, 8H, CH_2), 0.98 (t, 3H, N−C−CH_3). Anal. ($C_{26}H_{28}BrNO_2$) C, H, N.

1-(2-Benzyloxybenzyl)-8-bromo-2-ethyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline (15b): obtained from **12** and ethyl iodide (1.4 mL, 17 mmol); R_f 0.48 (eluent AcOEt); yield 40% (123 mg); ^1H NMR (DMSO-d_6) δ 7.56−7.32 (m, 5H, ArH), 7.27−7.16 (m, 1H, ArH), 7.15−7.00 (m, 2H, ArH), 6.98−6.80 (m, 3H, ArH), 5.14 (s, 2H, OCH_2), 4.58 (m, 1H, CHN), 3.75 (s, 3H, OCH_3), 3.67−2.58 (m, 8H, CH_2), 1.00 (t, 3H, N−C−CH_3). Anal. ($C_{26}H_{28}BrNO_2$) C, H, N.

1-(2-Benzyloxybenzyl)-8-bromo-6-methoxy-2-propyl-1,2,3,4-tetrahydroisoquinoline (15c): obtained from **12** and propyl iodide (1.7 mL, 17 mmol); R_f 0.66 (eluent AcOEt); yield 20% (64 mg); ^1H NMR (DMSO-d_6) δ 7.57−7.26 (m, 5H, ArH), 7.23−7.07 (m, 2H, ArH), 7.00−6.81 (m, 3H, ArH), 6.77−6.56 (m, 1H, ArH), 5.15 (s, 2H, OCH_2), 4.48−4.22 (m, 1H, CHN), 3.77 (s, 3H, OCH_3), 3.15−2.27 (m, 8H, CH_2), 1.48−1.17 (m, 2H, N−C−CH_2−C), 0.65 (t, 3H, N−C−C−CH_3). Anal. ($C_{27}H_{30}BrNO_2$) C, H, N.

6-Bromo-1-(2-hydroxybenzyl)-8-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline Oxalate (14a). A solution of **13a** (500 mg, 1.1 mmol) in 37% HCl−ethanol 1:1 (20 mL) was refluxed for 1 h under N_2. After removal of the solvent, water and ethyl ether were added; the aqueous phase was made basic with saturated $NaHCO_3$ solution, extracted with $CHCl_3$, and dried (Na_2SO_4). The residue was converted to the oxalate salt and crystallized from *i*-PrOH/Et_2O to give 381 mg (40%) of pure **14a**: mp 184−186 °C; ^1H NMR (DMSO-d_6) δ 12.5 (s, 1H, OH), 9.0 (bs, 1H, NH), 7.10−6.90 (m, 3H, ArH), 6.82−6.60 (m, 3H, ArH), 4.22 (m, 1H, CH−N), 3.70 (s, 3H, OCH_3), 3.60−2.63 (m, 6H, CH_2), 2.60 (s, 3H, N−CH_3). Anal. ($C_{18}H_{20}BrNO_2\cdot H_2C_2O_4$) C, H, N.

6-Bromo-2-ethyl-1-(2-hydroxybenzyl)-8-methoxy-1,2,3,4-tetrahydroisoquinoline Oxalate (14b). Obtained from **13b** with the same procedure as **14a**. The residue was converted to the oxalate salt and crystallized from *i*-PrOH/Et_2O to give 385 mg (75%) of pure **14b**: mp 106−108 °C; ^1H NMR (DMSO-d_6) δ 12.40 (s, 1H, OH), 7.15−6.88 (m, 3H, ArH), 6.80−6.62 (m, 3H, ArH), 4.00−3.84 (m, 1H, CH−N), 3.75 (s, 3H, OCH_3), 3.58−2.46 (m, 8H, CH_2), 1.00 (t, 3H, N−C−CH_3). Anal. ($C_{19}H_{22}BrNO_2\cdot H_2C_2O_4$) C, H, N.

8-Bromo-1-(2-hydroxybenzyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline Oxalate (16a). Obtained from **15a** with the same procedure as **14a**. The residue was converted to the oxalate salt and crystallized from *i*-PrOH/Et_2O to give 373 mg (52%) of pure **16a**: mp 205−207 °C; ^1H NMR (DMSO-d_6) δ 12.3 (s, 1H, OH), 8.0 (bs, 1H, NH), 7.20−7.00 (m, 3H, ArH), 6.86−6.62 (m, 3H, ArH), 4.25−4.17 (m, 1H, CH−N), 3.80 (s, 3H, OCH_3), 3.72−2.76 (m, 6H, CH_2), 2.58 (s, 3H, N−CH_3). Anal. ($C_{18}H_{20}BrNO_2\cdot H_2C_2O_4$) C, H, N.

8-Bromo-1-(2-hydroxybenzyl)-2-ethyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline Oxalate (16b). Obtained from **15b** with the same procedure as **14a**. The residue was converted to the oxalate salt and crystallized from *i*-PrOH/Et_2O to give 385 mg (75%) of pure **16b**: mp 116−118 °C; ^1H NMR (DMSO-d_6) δ 12.30 (s, 1H, OH), 7.12−6.95 (m, 3H, ArH), 6.90−6.60 (m, 3H, ArH), 4.40 (m, 1H, CH−N), 3.60 (s, 3H, OCH_3), 3.31−2.70 (m, 8H, CH_2), 1.12 (t, 3H, N−C−CH_3). Anal. ($C_{19}H_{22}BrNO_2\cdot H_2C_2O_4$) C, H, N.

8-Bromo-1-(2-hydroxybenzyl)-6-methoxy-2-propyl-1,2,3,4-tetrahydroisoquinoline Oxalate (16c). Obtained from **15c** with the same procedure as **14a**. The residue was converted to the oxalate salt and crystallized from *i*-PrOH/Et_2O to give 317 mg (60%) of pure **16c**: mp 112−114 °C; ^1H NMR (DMSO-d_6) δ 12.15 (s, 1H, OH), 7.18−6.96 (m, 3H, ArH), 6.85−6.64 (m, 3H, ArH), 4.05−3.86 (m, 1H, CH−N), 3.78 (s,

3H, OCH_3), 3.72−2.34 (m, 8H, CH_2), 1.60−1.12 (m, 2H, N−C−CH_2−C), 0.61 (t, 3H, N−C−C−CH_3). Anal. ($C_{20}H_{24}BrNO_2 \cdot H_2C_2O_4$) C, H, N.

5-Methoxy-1-methyl-2,3,12,12a-tetrahydro-1*H*-[1]benzoxepino[2,3,4-*ij*]isoquinoline Oxalate (17a). A mixture of **16a** (400 mg, 1.1 mmol), anhydrous pyridine (15 mL), and anhydrous potassium carbonate (1.2 g, 8.2 mmol) was heated to 135 °C, under N_2, and copper(II) oxide (400 mg, 4 mmol) was added. The resulting mixture was heated at 160 °C, with stirring, for 5 h. After cooling, the solution was filtered through silica gel, which was washed thoroughly with CH_2Cl_2. The solvent was removed under vacuum and the residue was taken into CH_2Cl_2 and washed with H_2O, with 10% cupric sulfate, and another time with H_2O. The dried extracts were purified by silica gel column chromatography (eluent ethyl acetate/cyclohexane 9/1). The base was converted to the oxalate salt and crystallized from *i*-PrOH/Et_2O to give 260 mg (64%) of **17a**: mp 143−144 °C; ^{1}H NMR (DMSO-d_6) δ 7.28−7.20 (m, 3H, ArH), 7.18−7.10 (m, 1H, ArH), 6.82−6.71 (m, 2H, ArH), 4.85 (dd, J = 11.8, 3.6 Hz, 1H, H-12a), 3.77 (s, 3H, OCH_3), 3.55−2.90 (m, 6H, CH_2), 2.84 (s, 3H, NCH_3). Anal. ($C_{18}H_{19}NO_2 \cdot H_2C_2O_4$) C, H, N.

1-Ethyl-5-methoxy-2,3,12,12a-tetrahydro-1*H*-[1]benzoxepino[2,3,4-*ij*]isoquinoline Oxalate (17b). Obtained from **16b** with the same procedure as **17a**. The base was converted to the oxalate salt and crystallized from *i*-PrOH/Et_2O to give 297 mg (70%) of **17b**: mp 191−193 °C; ^{1}H NMR (DMSO-d_6) δ 7.25−7.18 (m, 3H, ArH), 7.16−7,05 (m, 1H, ArH), 6.78−6.69 (m, 2H, ArH), 4.90 (dd, J = 11.9, 3.8 Hz, 1H, H-12a), 3.75 (s, 3H, OCH_3), 3.48−2,84 (m, 8H, CH_2), 1.25 (t, 3H, N−C−CH_3). Anal. ($C_{19}H_{21}NO_2 \cdot H_2C_2O_4$) C, H, N.

5-Methoxy-1-propyl-2,3,12,12a-tetrahydro-1*H*-[1]benzoxepino[2,3,4-*ij*]isoquinoline Oxalate (17c). Obtained from **16c** with the same procedure as **17a**. The base was converted to the oxalate salt and crystallized from *i*-PrOH/Et_2O to give 220 mg (50%) of **17c**: mp 216−218 °C; ^{1}H NMR (DMSO-d_6) δ 7.27−7.20 (m, 3H, ArH), 7.18−7.05 (m, 1H, ArH), 6.78−6.65 (m, 2H, ArH), 4.80 (dd, J = 10.6, 2.9 Hz, 1H, H-12a), 3.75 (s, 3H, OCH_3), 3.50−3.18 (m, 4H, CH_2), 3.12−2.78 (m, 4H, CH_2), 1.80−1.59 (m, 2H, N−C−CH_2−C), 0.96 (t, 3H, N−C−C−CH_3). Anal. ($C_{20}H_{23}NO_2 \cdot H_2C_2O_4$) C, H, N.

5-Hydroxy-1-methyl-2,3,12,12a-tetrahydro-1*H*-[1]benzoxepino[2,3,4-*ij*]isoquinoline Oxalate (5a). Compound **17a** (oxalate salt, 210 mg, 0.57 mmol) was dissolved in 48% hydrobromic acid−acetic acid 1:1 (20 mL) and heated at 130 °C under N_2 for 2 h. The reaction mixture was diluted with H_2O, neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The extracts were dried and evaporated to give a residue which was converted to the oxalate salt and crystallized from *i*-PrOH/Et_2O to give 81 mg (40%) of pure **5a**: mp 168−170 °C; ^{1}H NMR (DMSO-d_6) δ 7.29−7.13 (m, 3H, ArH), 7.15−7.05 (m, 1H, ArH), 6.58−6.47 (m, 2H, ArH), 4.74 (dd, J = 11.7, 3.7 Hz, 1H, H-12a), 3.50−2.84 (m, 6H, CH_2), 2.80 (s, 3H, NCH_3). Anal. ($C_{17}H_{17}NO_2 \cdot H_2C_2O_4$) C, H, N.

1-Ethyl-5-hydroxy-2,3,12,12a-tetrahydro-1*H*-[1]benzoxepino[2,3,4-*ij*]isoquinoline Oxalate (5b). Obtained from **17b** with the same procedure as **5a**. Crystallized from *i*-PrOH/Et_2O to give 144 mg (68%) of pure **5b**: mp 130−132 °C; ^{1}H NMR (DMSO-d_6) δ 7.28−7.16 (m, 3H, ArH), 7.14−7.04 (m, 1H, ArH), 6.55−6.46 (m, 2H, ArH), 4.80 (dd, J = 11.8, 3.9 Hz, 1H, H-12a), 3.45−2.72 (m, 8H, CH_2), 1.22 (t, 3H, N−C−CH_3). Anal. ($C_{18}H_{19}NO_2 \cdot H_2C_2O_4$) C, H, N.

5-Hydroxy-1-propyl-2,3,12,12a-tetrahydro-1*H*-[1]benzoxepino[2,3,4-*ij*]isoquinoline Oxalate (5c). Obtained from **17c** with the same procedure as **5a**. Crystallized from *i*-PrOH/Et_2O to give 130 mg (59%) of pure **5c**: mp 135−137 °C; ^{1}H NMR (DMSO-d_6) δ 7.28−7.20 (m, 3H, ArH), 7.18−7.15 (m, 1H, ArH), 6.58−6.45 (m, 2H, ArH), 4.76 (dd, J = 10.6, 2.9 Hz, 1H, H-12a), 3.48−3.17 (m, 4H, CH_2), 3.08−2.69 (m, 4H, CH_2), 1.80−1.57 (m, 2H, N−C−CH_2−C), 0.92 (t, 3H, N−C−C−CH_3). Anal. ($C_{19}H_{21}NO_2 \cdot H_2C_2O_4$) C, H, N.

2-Bromo-5-hydroxybenzaldehyde (19). A stirred solution of 2-bromo-5-methoxybenzaldehyde[23] (1 g, 4.6 mmol), acetic acid (5 mL), and freshly distilled 48% HBr (5 mL) was heated, under N_2, at 100 °C for 3 h. The solution was diluted with H_2O, made basic with 2 N NaOH, and washed with Et_2O. The aqueous layer was acidified to pH 1 with 2 N HCl and extracted with Et_2O. The organic extracts were dried over Na_2SO_4. The solution was filtered, and the filtrate was dried and concentrated under reduced pressure. The residue was recrystallized from CH_3COOH/H_2O (1/10) to give 407 mg (44%) of pure **19**: mp 135−136 °C (Lit.[24] mp 134 °C). Anal. ($C_7H_5BrO_2$) C, H.

2-(5-Benzyloxy-2-bromophenyl)nitroethylene (21). A mixture of Na_2CO_3 (160 mg, 1.5 mmol) and methylamine hydrochloride (150 mg, 2.2 mmol) in EtOH (3 mL) was stirred at room temperature for 15 min and filtered into a solution of 2-bromo-5-benzyloxybenzaldehyde[25] (1.3 g, 4.5 mmol) in EtOH (8 mL). Nitromethane (0.3 mL, 6.8 mmol) was added, and the mixture was stoppered and left in the dark at room temperature for 6 days. The yellow crystalline product was filtered and washed with EtOH yielding 368 mg (50%) of **21**: mp 116−118 °C; ^{1}H NMR ($CDCl_3$) δ 8.35 (d, 1H, $CHNO_2$, J = 13.59 Hz), 7.54 (m, 1H, ArH), 7.45 (d, 1H, CH=, J = 13.59 Hz), 7,0.40 (m, 5H, ArH), 7.13 (m, 1H, ArH), 6.97 (m, 1H, ArH), 5.05 (s, 2H, OCH_2Ph). Anal. ($C_{15}H_{12}BrNO_3$) C, H, N.

2-(5-Benzyloxy-2-bromophenyl)ethylamine Oxalate (22). Zinc amalgam [from zinc (2 g) and mercury(II) chloride (200 mg)] was added to a stirred mixture of **21** (500 mg, 1.5 mmol), 37% HCl (3.5 mL), and methanol (7 mL), at 45−50 °C. The mixture was stirred at 55 °C for 3 h. After removal of an inorganic substance, the mixture was made basic with 28% NH_4OH. The solvent was evaporated off and the residual solid was extracted with $CHCl_3$ after addition of an excess of 28% NH_4OH. The extract was washed with water, dried, and evaporated to leave compound **22** as a pale brownish oil. The residue was converted to the oxalate salt and crystallized from *i*-PrOH/Et_2O to give 559 mg (94%) of pure **22**: mp 178−180 °C; ^{1}H NMR (DMSO-d_6) δ 8.15 (br s, 3H, NH_3^+), 7.30−7.57 (m, 6H, ArH), 7.08 (m, 1H, ArH), 6.91 (m, 1H, ArH), 5.13 (s, 2H, OCH_2Ph), 3.00 (m, 4H, $2CH_2$). Anal. ($C_{15}H_{16}BrNO \cdot H_2C_2O_4$) C, H, N.

***N*-(5-Benzyloxy-2-bromophenethyl)-2-bromo-5-methoxyphenylacetamide (23).** A slurry of **22** (free base, 1 g, 3.27 mmol) and 2-bromo-5-methoxyphenylacetic acid (780 mg, 3.2 mmol) in xylene (1.5 mL) was refluxed under N_2 for 6.5 h with azeotropic removal of H_2O. After cooling, the oily residue was crystallized from cyclohexane to give 1.43 g (82%) of pure **23**: mp 124−126 °C; IR 3300 (ν NH), 1630 (ν C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.50−7.30 (m, 7H, ArH), 6.85−6.60 (m, 4H, ArH), 5.50 (br s, 1H, NH), 5.00 (s, 2H, OCH_2Ph), 3.75 (s, 3H, OCH_3), 3.63 (s, 2H, CH_2CO), 3.52 (q, 2H, CH_2N), 2.90 (t, 2H, $ArCH_2$). Anal. ($C_{24}H_{23}Br_2NO_3$) C, H, N.

General Procedure for the Synthesis of 1,2,3,4-Tetrahydroisoquinolines 24a−c. Compound **23** (500 mg, 0.94 mmol) in dry acetonitrile (8 mL) was treated with phosphoryl chloride (0.86 mL) and refluxed under N_2 for 1 h. The solvent was evaporated off and the excess of reagent was removed in vacuo. A solution of the residue in $CHCl_3$ was rapidly washed (1 N NaOH and H_2O), dried, and evaporated under reduced pressure. The base in acetonitrile (6 mL) and the appropriate alkyl iodide was refluxed under N_2 for 3 h. Evaporation gave the crude alkylammonium iodide, which was reduced in $CHCl_3$ (1.5 mL) and CH_3OH (9.5 mL) by adding sodium borohydride (300 mg, 7.9 mmol) in portions and then stirring for 30 min at room temperature. The solvent was evaporated off, and H_2O and $CHCl_3$ were added; the organic phase was dried, and the residue was chromatographed on silica gel eluting with ethyl acetate. The residue was converted to the oxalate salt and crystallized from *i*-PrOH/Et_2O.

8-Benzyloxy-5-bromo-1-(2-bromo-5-methoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline oxalate (24a): obtained from **23** and methyl iodide (1.5 mL, 24 mmol); yield 33% (192 mg); mp 179−181 °C; ^{1}H NMR (DMSO-d_6) δ 7.55−7.25 (m, 7H, ArH), 7.12−6.62 (m, 3H, ArH), 5.03 (s, 2H, OCH_2Ph), 4.25 (m, 1H, H-1), 3.76 (s, 3H, OCH_3), 3.30−2.80 (m, 6H, $3CH_2$), 2.25 (s, 3H, NCH_3). Anal. ($C_{25}H_{25}Br_2NO_2 \cdot H_2C_2O_4$) C, H, N.

8-Benzyloxy-5-bromo-1-(2-bromo-5-methoxybenzyl)-2-ethyl-1,2,3,4-tetrahydroisoquinoline oxalate (24b): obtained from **23** and ethyl iodide (1.9 mL, 24 mmol); yield 53% (317 mg); mp 139−141 °C; ^{1}H NMR (DMSO-d_6) δ 7.52−7.22 (m, 7H, ArH), 6.88−6.66 (m, 3H, ArH), 4.90 (s, 2H, OCH_2Ph), 4.55 (m, 1H, H-1), 3.55 (s, 3H, OCH_3), 3.22−2.50 (m, 8H, $4CH_2$), 0.92 (t, 3H, C−CH_3). Anal. ($C_{26}H_{27}Br_2NO_2\cdot H_2C_2O_4$) C, H, N.

8-Benzyloxy-5-bromo-1-(2-bromo-5-methoxybenzyl)-2-propyl-1,2,3,4-tetrahydroisoquinoline oxalate (24c): obtained from **23** and propyl iodide (2.4 mL, 24 mmol); yield 43% (262 mg); mp 138 dec °C; ^{1}H NMR (DMSO-d_6) δ 7.52−7.25 (m, 7H, ArH), 6.90−6.65 (m, 3H, ArH), 5.10 (s, 2H, OCH_2Ph), 4.30 (m, 1H, H-1), 3.62 (s, 3H, OCH_3), 3.25−2.20 (m, 8H, $4CH_2$), 1.20 (m, 2H, C−CH_2−C), 0.58 (t, 3H, CH_3). Anal. ($C_{27}H_{29}Br_2NO_2\cdot H_2C_2O_4$) C, H, N.

5-Bromo-8-hydroxy-1-(2-bromo-5-methoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline Oxalate (25a). A solution of **24a** (220 mg, 0.36 mmol) in 37% HCl−EtOH 1:1 (10 mL) was refluxed for 1 h under N_2. After removal of the solvent, H_2O and Et_2O were added; the aqueous phase was made basic with saturated $NaHCO_3$, extracted with $CHCl_3$, and dried. The residue was converted to the oxalate salt and crystallized from *i*-PrOH/Et_2O to give 122 mg (64%) of pure **25a**: mp 239−241 °C; ^{1}H NMR (DMSO-d_6) δ 7.38 (dd, 2H, ArH), 6.94 (m, 1H, ArH), 6.75 (m, 2H, ArH), 4.35 (m, 1H, H-1), 3.72 (s, 3H, OCH_3), 3.58−2.43 (m, 6H, $3CH_2$), 2.35 (s, 3H, NCH_3). Anal. ($C_{18}H_{19}Br_2NO_2\cdot H_2C_2O_4$) C, H, N.

5-Bromo-2-ethyl-8-hydroxy-1-(2-bromo-5-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline Oxalate (25b). Obtained from **24b** with the same procedure as **25a**. The residue was converted to the oxalate salt and crystallized from *i*-PrOH/Et_2O to give 88 mg (45%) of pure **25b**: mp 188−190 °C; ^{1}H NMR (DMSO-d_6) δ 7.42 (m, 1H, ArH), 7.30 (m, 1H, ArH), 6.90 (m, 1H, ArH), 6.74 (m, 1H, ArH), 6.60 (m, 1H, ArH), 4.52 (m, 1H, H-1), 3.68 (s, 3H, OCH_3), 3.54−2.52 (m, 8H, $4CH_2$), 0.98 (t, 3H, C−CH_3). Anal. ($C_{19}H_{21}Br_2NO_2\cdot H_2C_2O_4$) C, H, N.

5-Bromo-8-hydroxy-1-(2-bromo-5-methoxybenzyl)-2-propyl-1,2,3,4-tetrahydroisoquinoline Oxalate (25c). Obtained from **24c** with the same procedure as **25a**. The residue was converted to the oxalate salt and crystallized from *i*-PrOH/Et_2O to give 90 mg (45%) of pure **25c**: mp 145−147 °C; ^{1}H NMR (DMSO-d_6) δ 7.42−7.30 (m, 2H, ArH), 7.00−6.58 (m, 3H, ArH), 4.28 (m, 1H, H-1), 3.70 (s, 3H, OCH_3), 3.50−2.52 (m, 8H, $4CH_2$), 1.28 (m, 2H, C−CH_2−C), 0.60 (t, 3H, CH_3). Anal. ($C_{20}H_{23}Br_2NO_2\cdot H_2C_2O_4$) C, H, N.

4-Bromo-10-methoxy-1-methyl-2,3,12,12a-tetrahydro-1*H*-[1]benzoxepino[2,3,4-*ij*]isoquinoline Oxalate (26a). A mixture of **25a** (270 mg, 0.61 mmol), anhydrous pyridine (10 mL), and anhydrous potassium carbonate (670 mg, 4.8 mmol) was heated at 135 °C under N_2, and copper(II) oxide (220 mg, 2.2 mmol) was added. The resulting mixture was heated at 160 °C for 5 h. After cooling, the solution was filtered through silica gel, which was washed thoroughly with CH_2Cl_2. The solvent was removed under vacuum and the residue was taken into CH_2Cl_2 and washed with H_2O, with 10% cupric sulfate, and another time with H_2O. The extracts were dried and evaporated. The residue was purified by silica gel column chromatography (ethyl acetate/cyclohexane 9/1). The base was converted to the oxalate salt and crystallized from *i*-PrOH/Et_2O to give 170 mg (62%) of pure **26a**: mp 219−221 °C; ^{1}H NMR (DMSO-d_6) δ 7.58 (d, 1H, ArH), 7.16 (m, 2H, ArH), 6.85−6.70 (m, 2H, ArH), 4.64 (dd, 1H, J = 12.25, 3.70 Hz, H-12a), 3.69 (s, 3H, OCH_3), 3.40−2.82 (m, 6H, $3CH_2$), 2.70 (s, 3H, NCH_3). Anal. ($C_{18}H_{18}BrNO_2\cdot H_2C_2O_4$) C, H, N.

4-Bromo-1-ethyl-10-methoxy-2,3,12,12a-tetrahydro-1*H*-[1]benzoxepino[2,3,4-*ij*]isoquinoline Oxalate (26b). Obtained from **25b** with the same procedure as **26a**. The base was converted to the oxalate salt and crystallized from *i*-PrOH/Et_2O to give 195 mg (69%) of pure **26b**: mp 202−203 °C; ^{1}H NMR (DMSO-d_6) δ 7.50 (m, 1H, ArH), 7.10 (m, 2H, ArH), 6.75 (m, 1H, ArH), 6.70 (m, 1H, ArH), 4.85 (dd, 1H, J = 10.99, 3.05 Hz, H-12a), 3.68 (s, 3H, OCH_3), 3.40−3.16 (m, 4H, $2CH_2$), 3.00−2.62 (m, 2H, CH_2), 2.44 (m, 2H, CH_2), 1.15 (t, 3H, CH_3). Anal. ($C_{19}H_{20}BrNO_2\cdot H_2C_2O_4$) C, H, N.

4-Bromo-1-propyl-10-methoxy-2,3,12,12a-tetrahydro-1*H*-[1]benzoxepino[2,3,4-*ij*]isoquinoline Oxalate (26c). Obtained from **25c** with the same procedure as **26a**. The base was converted to the oxalate salt and crystallized from *i*-PrOH/Et_2O to give 120 mg (41%) of pure **26c**: mp 214−216 °C; ^{1}H NMR (DMSO-d_6) δ 7.50 (m, 1H, ArH), 7.08 (m, 2H, ArH), 6.70 (m, 2H, ArH), 4.76 (dd, 1H, J = 10.80, 2.90 Hz, H-12a), 3.64 (s, 3H, OCH_3), 3.36−3.10 (m, 4H, $2CH_2$), 2.88−2.58 (m, 4H, $2CH_2$), 1.58 (m, 2H, C−CH_2−C), 0.88 (t, 3H, CH_3). Anal. ($C_{20}H_{22}BrNO_2\cdot H_2C_2O_4$) C, H, N.

10-Methoxy-1-methyl-2,3,12,12a-tetrahydro-1*H*-[1]benzoxepino[2,3,4-*ij*]isoquinoline Oxalate (27a). A mixture of **26a** (free base, 170 mg, 0.47 mmol) and EtOH (180 mL) was hydrogenated at room temperature over 10% Pd/C (50 mg) at 1 bar. After absorption of the calculated hydrogen amount, the catalyst was filtered, and the solvent was evaporated. The residue was basified with aqueosus NH_4OH and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and evaporated. The base was converted to the oxalate salt and crystallized from *i*-PrOH/Et_2O to give 160 mg (91%) of pure **27a**: mp 184−187 °C; ^{1}H NMR (DMSO-d_6) δ 7.30−7.05 (m, 4H, ArH), 6.75 (m, 2H, ArH), 4.86 (dd, 1H, J = 12.45, 4.02 Hz, H-12a), 3.71 (s, 3H, OCH_3), 3.55−2.95 (m, 6H, $3CH_2$), 2.77 (s, 3H, NCH_3). Anal. ($C_{18}H_{19}NO_2\cdot H_2C_2O_4$) C, H, N.

1-Ethyl-10-methoxy-2,3,12,12a-tetrahydro-1*H*-[1]benzoxepino[2,3,4-*ij*]isoquinoline Oxalate (27b). Obtained from **26b** with the same procedure as **27a**. The base was converted to the oxalate salt and crystallized from *i*-PrOH/Et_2O to give 110 mg (58%) of pure **27b**: mp 181−183 °C; ^{1}H NMR (DMSO-d_6) δ 7.24 (m, 1H, ArH), 7.10 (m, 3H, ArH), 6.76 (m, 1H, ArH), 6.70 (m, 1H, ArH), 4.98 (dd, 1H, J = 11.02, 3.85 Hz, H-12a), 3.68 (s, 3H, OCH_3), 3.48−2.82 (m, 8H, $4CH_2$), 1.22 (t, 3H, CH_3). Anal. ($C_{19}H_{21}NO_2\cdot H_2C_2O_4$) C, H, N.

10-Methoxy-1-propyl-2,3,12,12a-tetrahydro-1*H*-[1]benzoxepino[2,3,4-*ij*]isoquinoline Oxalate (27c). Obtained from **26c** with the same procedure as **27a**. The base was converted to the oxalate salt and crystallized from *i*-PrOH/Et_2O to give 90 mg (49%) of pure **27a**: mp 146−148 °C; ^{1}H NMR (DMSO-d_6) δ 7.24 (m, 1H, ArH), 7.10 (m, 2H, ArH), 6.76 (m, 2H, ArH), 4.92 (dd, 1H, J = 10.90, 2.98 Hz, H-12a), 3,68 (s, 3H, OCH_3), 3.50−3.20 (m, 4H, $2CH_2$), 3.14−2.80 (m, 4H, $2CH_2$), 1.68 (m, 2H, C−CH_2−C), 0.96 (t, 3H, CH_3). Anal. ($C_{20}H_{23}NO_2\cdot H_2C_2O_4$) C, H, N.

10-Hydroxy-1-methyl-2,3,12,12a-tetrahydro-1*H*-[1]benzoxepino[2,3,4-*ij*]isoquinoline Oxalate (6a). Compound **27a** (600 mg, 1.6 mmol) was dissolved in 48% hydrobromic acid−acetic acid 1:1 (20 mL) and heated at 130 °C under N_2 for 2 h. The reaction mixture was diluted with H_2O, neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The extracts were dried and evaporated to give a residue which was converted to the oxalate salt and crystallized from *i*-PrOH/Et_2O to give 520 mg (90%) of pure **6a**: mp 212−213 °C; ^{1}H NMR (DMSO-d_6) δ 9.18 (s, 1H, OH), 7.13 (m, 1H, ArH), 6.95 (m, 3H, ArH), 6.53 (m, 2H, ArH), 4.25 (dd, 1H, J = 11.72, 3.67 Hz, H-12a), 3.28−2.60 (m, 6H, $3CH_2$), 2.48 (s, 3H, NCH_3). Anal. ($C_{17}H_{17}NO_2\cdot H_2C_2O_4$) C, H, N.

1-Ethyl-10-hydroxy-2,3,12,12a-tetrahydro-1*H*-[1]benzoxepino[2,3,4-*ij*]isoquinoline Oxalate (6b). Obtained from **27b** with the same procedure as **6a**. The base was converted to the oxalate salt and crystallized from *i*-PrOH/Et_2O to give 460 mg (59%) of pure **6b**: mp 202−204 °C; ^{1}H NMR (DMSO-d_6) δ 7.22 (m, 1H, ArH), 7.02 (m, 3H, ArH), 6.52 (m, 2H, ArH), 4.98 (dd, 1H, J = 11.20, 3.20 Hz, H-12a), 3.50−2.80 (m, 8H, $4CH_2$), 1.28 (t, 3H, CH_3). Anal. ($C_{18}H_{19}NO_2\cdot H_2C_2O_4$) C, H, N.

10-Hydroxy-1-propyl-2,3,12,12a-tetrahydro-1*H*-[1]benzoxepino[2,3,4-*ij*]isoquinoline Oxalate (6c). Obtained from **27c** with the same procedure as **6a**. The base was converted to the oxalate salt and crystallized from *i*-PrOH/Et_2O to give 520 mg (64%) of pure **6c**: mp 122−124 °C; ^{1}H NMR (DMSO-d_6) δ 7.20 (m, 1H, ArH), 7.00 (m, 2H, ArH), 6.2 (m, 2H, ArH), 4.88 (dd, 1H, J = 10.80, 2.85 Hz, H-12a), 3.44−2.72 (m, 8H,

$4CH_2$), 1.2 (m, 2H, $C-CH_2-C$), 0.80 (t, 3H, CH_3). Anal. ($C_{19}H_{21}NO_2 \cdot H_2C_2O_4$) C, H, N.

Pharmacology. 1. Radioligand Competition Assays in Rat Striatal Membranes. Male Sprague−Dawley rats (300−350 g body weight) were obtained from the breeding facilities at the University of Santiago. Rats were killed by decapitation, and brains were rapidly removed and dissected on an ice-cold plate. [^{3}H]Spiperone (95 or 104 Ci/mmol) and [^{3}H]SCH 23390 (85 Ci/mmol) were purchased from Amersham International (England), unlabeled *R*-(+)-SCH 23390 HCl and *R*-(−)-apomorphine HCl from Research Biochemicals Inc., dopamine HCl, haloperidol, and sulpiride HCl from Sigma. Reference drugs or new compounds were stored in 1 mM solutions at −20 °C and diluted to the required concentration on ice immediately before binding assays.

Striatal membrane preparations were obtained by homogenization (Polytron homogenizer, setting 6 for 10 s) of tissue in 50 mM Tris-HCl (pH 7.7 at 25 °C, about 100 μL/mg of tissue) containing 5 mM EDTA. Homogenates were centrifuged (49000*g* for 15 min at 4 °C; Sorvall RC-26 plus), then resuspended in 50 mM Tris-HCl buffer (pH 7.4 at 25 °C) and centrifuged again (same conditions). Final pellets were stored at −80 °C until assay.

Just before the binding assay, pellets were resuspended (1.25 mg original wet weight/750 μL for D_2 binding assays, 1.00 mg/750 μL for D_1 binding assays) in 50 mM Tris-HCl buffer (pH 7.4 at 25 °C) containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, and 1 mM $MgCl_2$. For agonist or antagonist properties assays (compounds **5a** and **6a**), pellets were resuspended in 50 mM Tris-HCl buffer (pH 7.4 at 25 °C) (without Na^+) or 120 mM NaCl (presence of Na^+). For D_2 binding assays, aliquots of striatal membrane preparations were added to ice-cold tubes containing (a) 100 μL of [^{3}H]spiperone plus 50 μL of ketanserin (final concentration 50 nM, to block 5-HT_{2A} receptors) and either (b) 100 μL of buffer (total binding) or (c) 100 μL of sulpiride (final concentration 10 μM to allow quantification of specific binding by [^{3}H]spiperone) or (d) 100 μL of new or reference drug. For D_1 binding assays, the same procedure was followed except that (a) was 100 μL of [^{3}H]SCH 23390 plus 50 μL of buffer and (c) was 100 μL of unlabeled SCH 23390 (final concentration 1 μM, to allow quantification of specific binding by [^{3}H]SCH 23390). The final assay volume was, thus, in all cases 1 mL. All assays were performed in duplicate.

Incubations (15 min at 37 °C) were stopped by rapid filtration under vacuum through GF-52 glass-fibers filters (Schleicher and Schuell) in a Brandel (M-30) cell harvester. Filters were rinsed three times with 3 mL of ice-cold 50 mM Tris-HCl buffer (pH 7.4).

2. Binding to Cloned DA D_3 and D_4 Receptors. Rat (Sf9) D_3 receptor: Membranes from *Spodoptera frugiperda* (Sf9) insect cells infected with baculovirus to express the rat recombinant D_3 DA receptor (lot no. OYI-19M, Research Biochemicals International, Natick, MA) were suspended in incubation buffer (0.5 mL of membranes to 24.5 mL of incubation buffer (Tris-HCl 50 mM, pH 7.4, containing 5 mM KCl, 1.5 mM $CaCl_2$, 5 mM EDTA, 120 mM NaCl, and 5.0 mM $MgCl_2$)).

Aliquots (500 μL) of membranes were added to ice-cold tubes containing (a) 20 μL of [^{3}H]spiperone (104 Ci/mmol) and either (b) 20 μL of buffer (total binding) or (c) 20 μL of haloperidol (final concentration 10 μM) to allow quantification of unspecific binding by [^{3}H]spiperone or (d) 20 μL of new drug. The final assay volume was thus in all cases 540 μL.

Incubations (1 h at 27 °C) were stopped by filtration under vacuum, through Whatman GF/C glass-fiber filters presoaked in 0.3% polyethylenimine, in a Brandel (M-30) cell harvester. Filters were rinsed with incubation buffer.

Human (CHO, K1) D_4 receptor: Cells, transfected to express the human recombinant $D_{4,2}$ DA receptor (lot no. YBH-19SA-G, Research Biochemicals International, Natick, MA), were resuspended and homogenized (Polytron homogenizer, setting 6 at 10 s) in 8 mL of incubation buffer followed by centrifugation at 900*g* for 10 min at 4 °C (Sorvall RC-26 plus). The supernatant was removed and saved. Following the addition of 5 mL of incubation buffer, the pellet was rehomogenized and centrifuged again (same conditions). Both supernatants were then pooled and centrifuged at 40000*g* for 30 min, and the resulting pellets were resuspended and homogenized in 5 mL of incubation buffer and centrifuged again (same conditions). The final pellet was resuspended in 7.5 mL of incubation buffer (Tris-HCl 50 mM, pH 7.4, containing 5 mM KCl, 1.5 mM $CaCl_2$, 5 mM EDTA, 120 mM NaCl, 1 mM phenylmethanesulfonyl fluoride, and 1 μg/mL leupeptin).

Aliquots (140 μL) of membrane preparations were added to ice-cold tubes containing (a) 20 μL of [^{3}H]spiperone (104 Ci/mmol), final concentration 0.5 nM, and either (b) 40 μL of buffer (total binding) or (c) 40 μL of haloperidol (final concentration 10 μM) to allow quantification of unspecific binding by [^{3}H]spiperone or (d) 40 μL of new drug. The final assay volume was thus in all cases 200 μL.

Incubation (2 h at 27 °C) was stopped by filtration under vacuum, through Whatman GF/B glass-fiber filters presoaked in 0.1% polyethylenimine, in a Brandel (M-30) cell harvester. Filters were rinsed with incubation buffer and dried.

In all binding experiments radioactivity was determined by liquid scintillation counting in a Beckman LS6000LL apparatus and competition analyses were carried out with the aid of the Prism program (GraphPad); K_i values were calculated as $K_i = IC_{50}/(1 + L/K_d)$, where L is the concentration and K_d is the apparent dissociation constant of the ligand. The dissociation constants (K_d) of [^{3}H]SCH 23390 and [^{3}H]spiperone were 0.5 and 0.25, respectively.

3. PRL Release from Anterior Pituitary Cell Cultures. Anterior pituitary cell cultures were obtained as previously described.[26] Male Wistar rats (200−220 g) were sacrificed by decapitation; the anterior pituitaries were explanted, minced with a blade into small fragments, and sequentially incubated in DMEM at 37 °C in a Dubnoff shaking bath, with 0.5% trypsin (type XII S) for 15 min, 0.02% deoxyribonuclease I for 1 min, 0.1% soybean trypsin inhibitor for 4 min, and 2 and 1 mM EDTA (in Ca^{2+}- and Mg^{2+}-free EBSS) for 4 and 15 min, respectively. The remaining tissue fragments were mechanically dispersed into single cells by gentle suction and extrusion through a narrow tip Pasteur pipet; the cell suspension was then filtered through a 100-μm nylon mesh and centrifuged at 1000*g* for 10 min. Finally, cells were checked for viability by Trypan blue exclusion test, counted by a hemocytometer (approximately 2 million cells/pituitary), plated into 24-well dishes (300 000 cells/dish), and incubated with DMEM supplemented with 10% newborn calf serum, at 37 °C in air/CO_2 95/5%. After 2−3 days in culture, release experiments were performed by 1-h incubations with graded concentrations of testing substances in DMEM (supplemented with 0.1% BSA, 0.006% ascorbic acid, and 40 IU/mL aprotinin); release aliquots were stored at −20 °C until assay. Cell culture reagents were purchased from Sigma, except DMEM and serum from Gibco.

PRL concentrations were measured by radioimmunoassay. Rat PRL standard and antibody (raised in the rabbit) were supplied by the NIDDK Rat Pituitary Hormone Distribution Program. Tracer PRL was iodinated with $Na^{125}I$ by the chloramine T method. Separation of bound from free fraction was performed by anti-rabbit goat serum (1:360) supplemented with 3% poly(ethylene glycol). After centrifuging, radioactivity in the pellets was counted in a γ-counter. Sensitivity of the assay was 50 pg/tube; ED_{50} was 490 pg/tube.

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