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Synthesis and Preliminary Pharmacological Evaluation of 5-Hydroxy- and 5,6-Dihydroxy-1,2,3,7,12,12a-hexahydrobenzo [5,6]cyclohepta[1,2,3-*ij*]isoquinoline Derivatives as Dopamine Receptor Ligands

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Abstract—A series of 5-hydroxy- and 5,6-dihydroxy-1,2,3,7,12,12a-hexahydrobenzo[5,6]cyclohepta[1,2,3-*ij*]isoquinoline derivatives (**5a**–**e** and **6a**–**e**) were synthesized as conformationally rigid analogues of 1-benzyltetrahydroisoquinoline and evaluated for their affinity at D_1 and D_2 dopamine receptors. All compounds showed lower D_1 and D_2 affinities than dopamine. The 5-hydroxy-1-methyl-2,3,12,12a-hexahydrobenzo[5,6]cyclohepta[1,2,3-*ij*]isoquinoline **5a** and the 5,6-dihydroxy analogue **6a** showed D_2 agonist activity. This was proved by their effects on prolactin release from primary cultures of rat anterior pituitary cells. Molecular modeling studies showed that the geometric parameters (namely the distances from *meta* and *para* hydroxyl oxygens to the nitrogen and the height of nitrogen from the hydroxylated phenyl ring plane) of the dopaminergic pharmacophore embedded in our compounds have lower values in comparison with those observed in D_1 and D_2 selective ligands.

Introduction

Dopamine-mediated neurotransmission plays an important role in several psychiatric and neurological disorders. For this reason great interest has been focused on the search for novel dopamine (DA) receptor agonists and antagonists. DA receptors are classified into two families: D_1-like (D_1 and D_5) and D_2-like (D_2, D_3, and D_4), on the basis of amino acid sequences and of their ability to activate or inhibit the enzyme adenylyl cyclase, respectively.[1] DA antagonists are used for treating schizophrenia, mania, delirium and Huntington's disease. Clinical applications of central DA agonists include the treatment of Parkinson's disease and neuroendocrine disorders.

R-(−)-Apomorphine (**1**; Fig. 1) is a D_1 and D_2 DA receptor agonist. This compound has been the subject of extensive SAR studies with regard to its interactions with DA receptors.[2] The apomorphine tetracyclic system incorporates the 1-benzyltetrahydroisoquinoline moiety that is embedded also in the D_1 selective antagonists 1-(2,5-dimethoxy-4-propylbenzyl)-6-chloro-7-hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**2**),[3] and 1-(2-bromo-4,5-dimethoxybenzyl)-7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetra-hydroisoquinoline (**3**).[4]

In a previous work, we described the synthesis of some 5-hydroxy-2,3,12,12a-tetrahydro-1H-[1]benzoxepino[2,3,4*ij*]isoquinolines as monophenolic ligands for DA receptors.[5] The *N*-methyl derivative **4** bound to the D_2-like receptors with the same affinity as DA and showed D_2 agonist activity. As an extension of our research in this field, here we report the synthesis of 5-hydroxy- and 5,6-dihydroxy-1,2,3,7,12,12a-hexahydrobenzo[5,6]cyclo-

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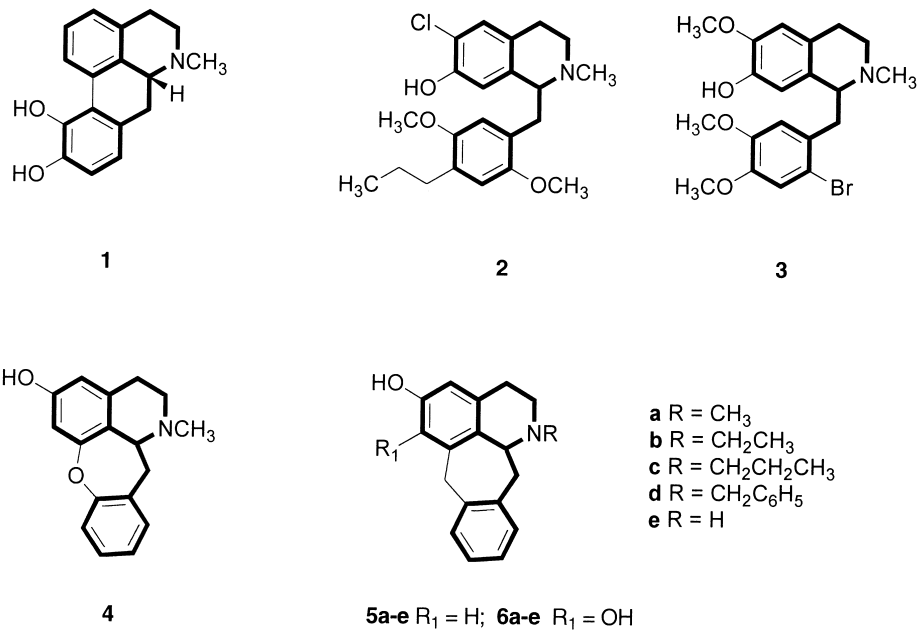
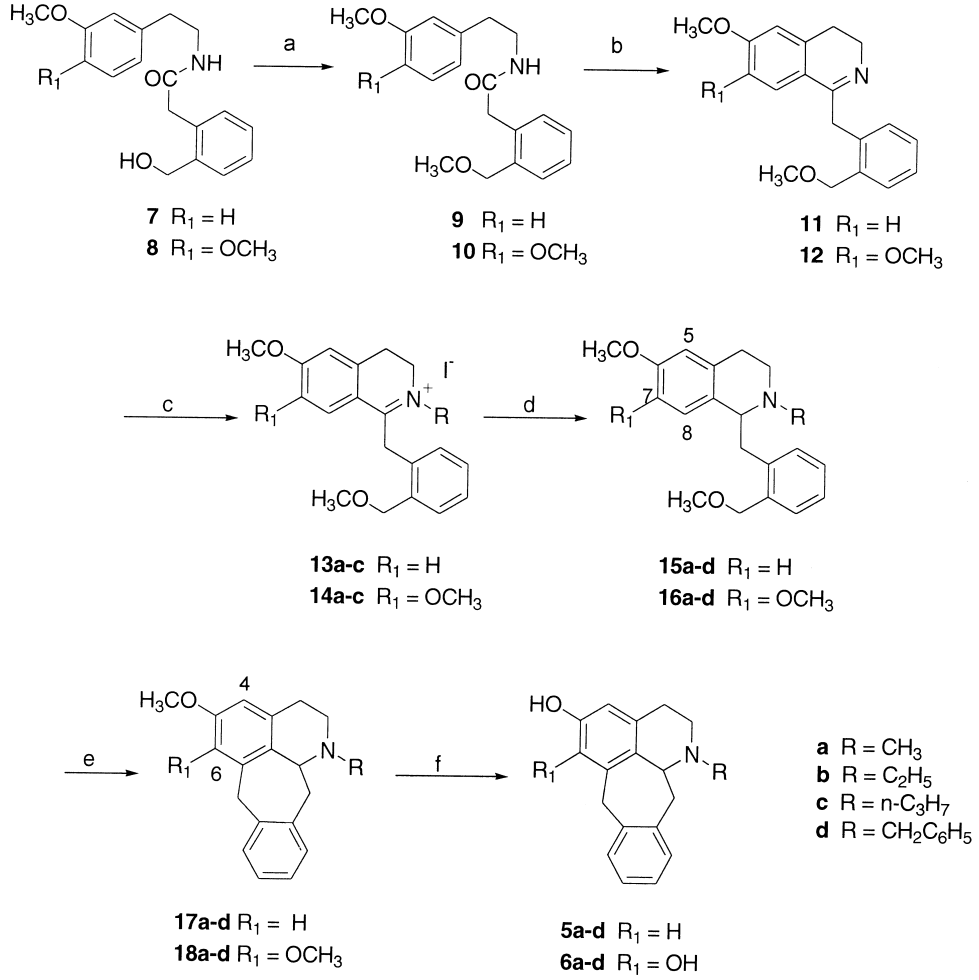
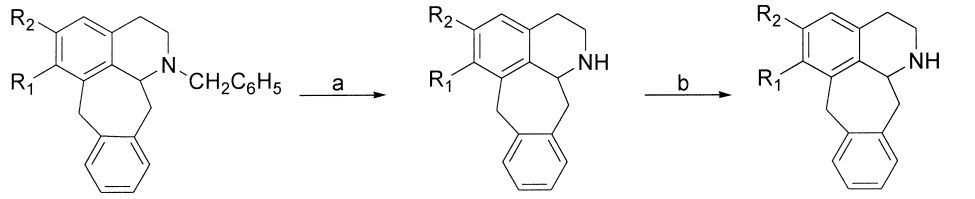


Figure 1. Structures of R-(−)-apomorphine (**1**), tetrahydrobenzylisoquinolines (**2**, **3**), tetrahydrobenzoxepinoisoquinoline (**4**), and hexahydrobenzocycloheptaisoquinolines (**5a–e**, **6a–e**).



Scheme 1. Reagents: (a) $(CH_3)_2SO_4$, tetrabutylammonium bromide, CH_2Cl_2, NaOH 10%; (b) $POCl_3$, CH_3CN, reflux; (c) RX, CH_3CN; (d) $NaBH_4$, $CHCl_3$, CH_3OH; (e) H_2SO_4 98%, −40 °C; (f) CH_3SO_3H, methionine, rt.



Scheme 2. Reagents: (a) H_2, Pd/C 10%, CH_3COOH; (b) CH_3SO_3H, methionine, rt.

hepta[1,2,3-*ij*]isoquinoline derivatives (**5a–e** and **6a–e**), a new class of rigid congeners of 1-benzyltetrahydroisoquinoline. The new compounds are isosteres of previously reported tetrahydrobenzoxepino [2,3,4-*ij*]isoquinolines,[5] and were synthesized with the aim to verify whether the isosteric replacement of oxygen with a methylene could affect the affinity and selectivity for DA receptors. The monohydroxy derivatives were prepared in order to develop monophenolic ligands for DA receptors and to compare their affinities with catechol compounds which, as a rule, show higher affinities and D_1 selectivity. Isoquinoline nitrogen was substituted with methyl, ethyl, *n*-propyl, and benzyl groups in view of the fact that they can modulate the D_1 and D_2 affinities.

Results and Discussion

The 5-hydroxy- and 5,6-dihydroxyhexahydrobenzo[5,6]cyclohepta[1,2,3-*ij*]isoquinolines **5a–e** and **6a–e** were synthesized successfully as illustrated in Schemes 1 and 2. The hydroxyamides **7** and **8** were prepared in good yields from 2-[(3-methoxy- or 3,4-dimethoxy)phenyl] ethylamine and 3-isochromanone in refluxing xylene, by a modification of the method previously described.[6] Then, the benzylic hydroxy group was protected by methylation with dimethylsulphate in a two-phase system according to the Merz procedure.[7]

The amides **9** and **10** were subjected to Bischler–Napieralski cyclization with phosphorus oxychloride in dry acetonitrile. The resulting 3,4-dihydroisoquinolines **11** and **12** were alkylated with the appropriate alkyl iodide (methyl, ethyl, propyl iodide) or benzyl bromide to give the corresponding dihydroisoquinolinium salts **13a–d** and **14a–d**. Reduction with sodium borohydride in $CHCl_3$/CH_3OH afforded the tetrahydroisoquinolines **15a–d** and **16a–d**. The hexahydrobenzo[5,6]cyclohepta[1,2,3-*ij*]isoquinolines **17a–d** and **18a–d** were obtained by intramolecular cyclization in concentrated sulfuric acid at low temperature under nitrogen. The hydroxy derivatives **5a–e** and **6a–e** were obtained by demethylation with methanesulfonic acid and methionine.[8] Catalytic hydrogenation of benzyl derivatives **17d** and **18d** in glacial acetic acid in presence of 10% Pd/C, followed by *O*-demethylation, produced the unsubstituted derivatives **5e** and **6e** (Scheme 2).

The cyclization of 1-(2-methoxymethylbenzyl)-5-methoxy-1,2,3,4-tetrahydroisoquinolines to benzo[5,6]cyclohepta[1,2,3-*ij*]isoquinolines was established on the basis of ^1H NMR spectra.

Tetrahydroisoquinoline **15a** (Scheme 1) showed three signals in the aromatic area ascribed to the hydrogens at C-5, C-7, and C-8. The signal of the hydrogen at C-5 ($\delta = 6.85$) appeared as a doublet with a coupling constant of 2.64 Hz. This hydrogen is coupled to the hydrogen on C-7 and the constant value is consistent with a *meta* coupling. The hydrogen at C-7 gave a double doublet ($\delta = 6.50$) with two coupling constants of 2.64 and 8.45 Hz. This hydrogen is coupled to the hydrogens on C-5 ($J = 2.64$ Hz) and on C-8 (*ortho* coupling, $J = 8.45$ Hz). At δ 6.18 a doublet with a coupling constant of 8.45 Hz was present and was ascribed to the hydrogen on C-8. The spectrum of hexahydrocycloheptaisoquinoline **17a** showed two doublets at δ 6.85 and 6.74. The coupling constants value was 2.61, thus indicating a *meta* coupling between the hydrogen at C-4 and C-6.

NMR spectra of the oxalate salts **5a–e** and **6a–e** showed a very broad signal (basically a deformation of the baseline). These signals disappeared after D_2O addition, and they can be assigned to hydroxy and ammonium groups.

Table 1 gives the binding affinities for the novel hydroxybenzocycloheptaisoquinolines (**5a–e**, **6a–e**) and methoxylated precursors (**17a–e**, **18a–e**) determined in DA D_1 and D_2 receptor assays. Affinities are referred to D_1-like and D_2-like families of DA receptors. Porcine striatal membranes were 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.

Furthermore, the compound **5a** and the dihydroxy analogue **6a** 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 indicated 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.[9,10]

As far as the affinities for D_1 receptor are concerned, all compounds show lower binding affinity than DA or R-(−)-apomorphine. Substituents on the nitrogen atom

seem to affect the D_1 affinities. Bulky groups decrease the affinity. The *N*-ethyl, the *N*-methyl and the unsubstituted derivatives are the most active. Methoxy groups demethylation does not significantly increase the affinity. A slight increase is observed in the catechol **6b** and in the monophenolic derivative **5e** that is the most active in the series.

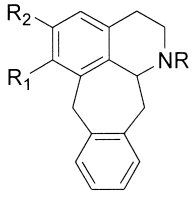
Data obtained for D_2 receptor did not differ substantially from those for D_1 receptor. The dimethoxy *N*-benzyl derivative **18d** showed D_2 affinity similar to that of DA, while all the others were less potent than DA or R-(−)-apomorphine. As regards the in vitro effects on PRL release from primary cultures of rat anterior pituitary cells, the compounds **5a** and **6a** at low concentrations stimulated, and at higher concentrations inhibited PRL release (Fig. 2). Both compounds showed agonist activity at D_2 receptors.

The dihydroxy derivative **6a** stimulates PRL release at a concentration of 1 nM and is more effective than **5a**. It can be hypothesized that the PRL-stimulating activity demonstrated by **5a** and **6a** is due to the higher affinity to 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, which has been shown to stimulate PRL release only at low concentrations (1–100 pM).[11]

From a comparison of binding affinities of 5-hydroxy-1-methyl-2,3,12,12a-tetrahydro-1H-[1]benzoxepino[2,3,4-*ij*]isoquinoline **4** (Fig. 1, D_1, $K_i = 2.88\,\mu M$; D_2, $K_i = 0.27\,\mu M$) and 5-hydroxy-1-methyl-2,3,12,12a-hexahydrobenzo[5,6]cyclohepta[1,2,3-*ij*]isoquinoline **5a** (D_1, $K_i = 6.4\,\mu M$; D_2, $K_i = 8.9\,\mu M$) it is evident that the isosteric replacement of oxygen with a methylene decreases both affinity and selectivity.

Binding data obtained with our compounds indicated that the presence of a phenol or a catechol group did not modify the affinity for D_1 and D_2 receptor. Moreover, the affinities of methoxy derivatives did not differ significantly from those of hydroxy derivatives. These results suggest that all compounds have weak interactions with the receptors. A similar trend was observed with the previously synthesized 5-hydroxy- and 10-hydroxy-2,3,12,12a-tetrahydro-1H-[1]benzoxepino[2,3,-4-*ij*]isoquinolines which showed low affinity and selectivity at both the D_1-like and D_2-like receptors.[5] In these compounds the lack of the catechol nucleus could not be invoked as the only factor responsible for affinity to D_1 and D_2 receptors. Indeed, the findings presented in the present paper confirmed that the catechol nucleus

Table 1. Inhibition of [^{3}H]SCH 23390 (D_1-like) and [^{3}H]Spiperone (D_2-like) binding to porcine striatal membranes of the hexahydrobenzo-[5,6]cyclohepta[1,2,3-*ij*]isoquinoline derivatives



Compound	R	R_1	R_2	K_i (μM)[a]		Ratio
				D_1-like	D_2-like	D_1-like/D_2-like
5a	CH_3	H	OH	6.4±0.4	8.9±0.6	0.72
5b	C_2H_5	H	OH	21.8±1.8	14.8±1.1	1.47
5c	*n*-C_3H_7	H	OH	29.8±1.2	40.3±3.1	0.74
5d	$CH_2C_6H_5$	H	OH	41.9±2.2	32.3±2.0	1.29
5e	H	H	OH	3.7±0.1	22.1±1.7	0.16
6a	CH_3	OH	OH	8.6±0.3	8.2±0.4	1.06
6b	C_2H_5	OH	OH	6.6±0.2	9.7±0.5	0.68
6c	*n*-C_3H_7	OH	OH	11.6±0.8	13.7±0.7	0.85
6d	$CH_2C_6H_5$	OH	OH	21.6±1.2	6.4±0.4	3.38
6e	H	OH	OH	6.3±0.3	18.9±0.9	0.33
17a	CH_3	H	OCH_3	6.1±0.3	14.7±1.1	0.41
17b	C_2H_5	H	OCH_3	8.3±0.4	16.5±1.2	0.50
17c	*n*-C_3H_7	H	OCH_3	22.3±1.7	6.7±0.2	3.33
17d	$CH_2C_6H_5$	H	OCH_3	55.4±2.1	17.4±1.3	3.18
17e	H	H	OCH_3	10.8±1.3	8.0±0.5	1.35
18a	CH_3	OCH_3	OCH_3	7.2±0.5	23.3±1.5	0.31
18b	C_2H_5	OCH_3	OCH_3	27.4±1.8	28.2±2.0	0.97
18c	*n*-C_3H_7	OCH_3	OCH_3	72.2±4.1	13.9±0.8	5.19
18d	$CH_2C_6H_5$	OCH_3	OCH_3	61.8±3.2	4.9±0.2	12.6
18e	H	OCH_3	OCH_3	4.3±0.2	13.1±0.9	0.33
dopamine				1.22±0.1	4.38±0.2	0.28
apomorphine				0.36±0.02	0.18±0.01	2.0

[a]The K_i values are means±S.E.M. of at least three experiments.

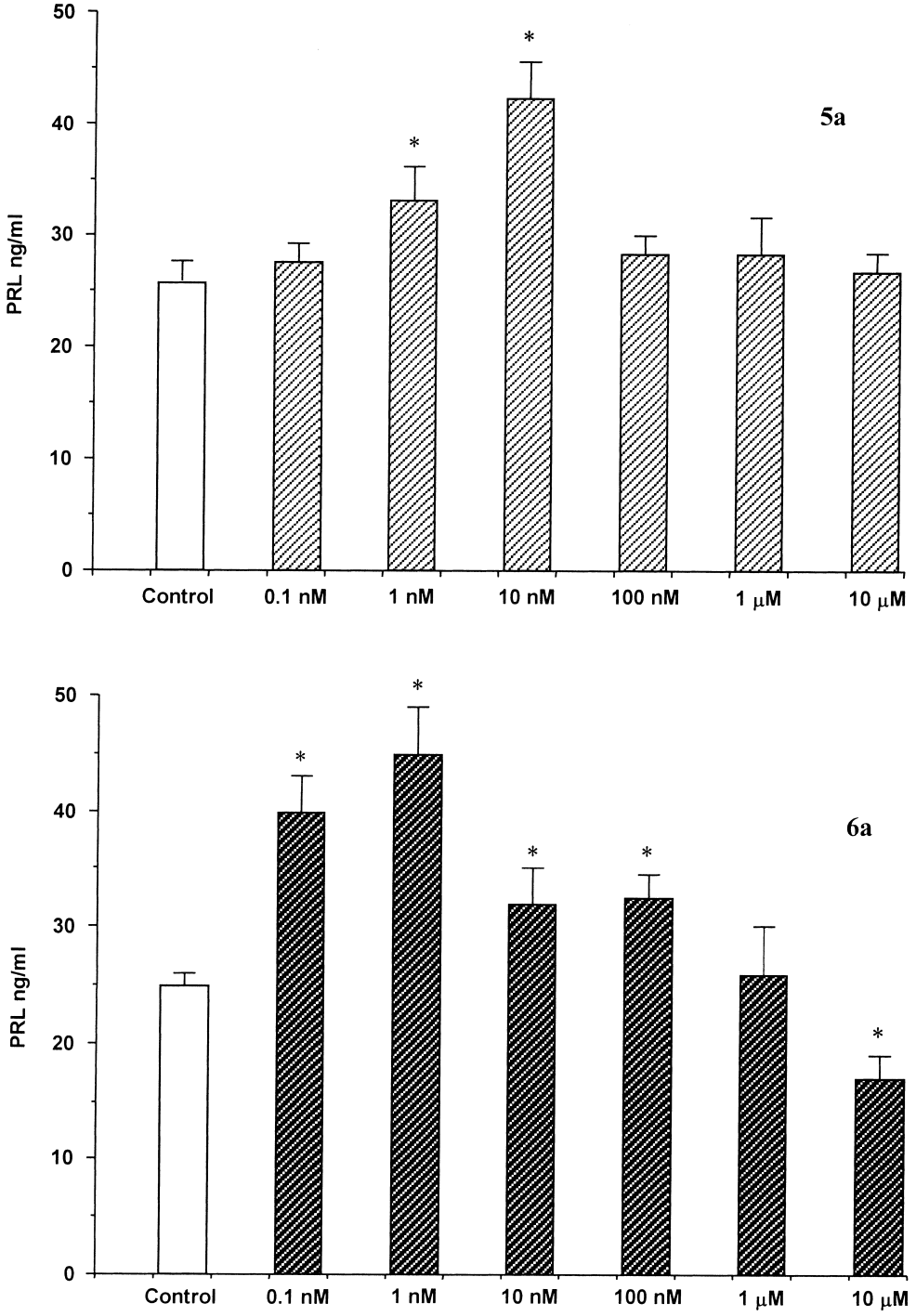


Figure 2. Effect of **5a** and **6a** on PRL release from anterior pituitary cell cultures in vitro after a 1 h incubation. Group means ± SEM, $n = 6$–8, $^*p < 0.02$ versus control.

was an important but not a sufficient feature to display high affinity at D_1 receptor (see compound **6a**, Table 1).

In order to identify the molecular features responsible for the low affinity and selectivity toward D_1 and D_2 receptors, molecular modeling studies were performed on the representative compounds **4**, **5a** and **6a** (Fig. 1). Although highly congeneric, these compounds alternatively displayed all the pharmacophore features required for the binding of an agonist to both the D_1 and D_2 receptors, namely one or both the hydroxyl groups, and the cationic nitrogen.

MACROMODEL 6.5[12] was used for the compounds modeling reported in the present study. Initial structures, built in their protonated forms, were energy minimized within the MM2* force field,[13] using the Steepest Descendent minimizer, allowing for 1000 iterations per structure, until a gradient of 0.05 kJ/Å was reached.

Table 2. ΔE and geometry calculations values of the representative structures of the most populated and energetically accessible conformationally related families of **4**, **5a** and **6a**

Compound	Conformation	ΔE	Times[a]	Distance (Å)		Height[d] (Å)
				1[b]	2[c]	
4	1	0.00	63	6.48		0.07
	2	0.42	42	6.46		0.17
	3	0.65	44	6.45		0.37
	4	4.85	41	6.41		0.88
5a	1	0.00	72	6.48		0.02
	2	0.92	47	6.46		0.30
	3	1.26	73	6.46		0.30
	4	4.36	39	6.43		0.85
6a	1	0.00	23	6.48	6.21	0.01
	2	0.85	23	6.46	6.18	0.31
	3	1.75	20	6.45	6.21	0.29
	4	4.45	26	6.44	6.21	0.31

[a]Times number that each conformation was found.
[b]Distance between nitrogen and oxygen of 5-OH.
[c]Distance between nitrogen and oxygen of 6-OH.
[d]Height of the nitrogen from the phenyl ring plane.

In general, the compounds acting on the same receptors are likely to have a common topology for the pharmacophore moieties. In our case, the accuracy in finding their common pharmacophore conformations was facilitated by the use of highly congeneric rigid compounds. Since the ligands probably do not bind to the receptor in their global minimum conformations, we were interested in finding families of candidate conformations of each compound which were within the region of conformational space energetically accessible ($\Delta E = 5$ kcal/mol).

To search conformational space, a molecular simulation following a stochastic approach, called Monte Carlo,[14] was performed. This approach is based on exploring the energy surface by randomly probing the geometry of a molecular system. This led us to reach a more realistic picture of the molecules, which is likely far from the static, idealized image provided by molecular mechanics but where all the atoms are in constant motion. The Monte Carlo searching algorithm was used in combination with an energy minimization procedure to explore the energetically accessible conformations.

Thus the Monte Carlo/energy minimization protocol of the MACROMODEL[12] program was used until a number of 500 final structures ($\Delta E = 50$ kcal/mol) was collected. The ring closure bonds were used by the protocol in six- and seven-membered non-aromatic rings to allow torsion angles within these rings to be varied as well. The energy minimization convergence criterion was set to an RMS gradient of 0.05 kJ/Å. All the heavy atoms were superimposed in order to eliminate duplicate conformations, and thus the output of this protocol application is an ensemble of representative structures of conformationally related families (Table 2).

The search results were filtered on energy ($\Delta E \leq 5.0$ kcal/mol). The representative structures of the conformationally related families were taken into account to evaluate and compare geometric parameters of the pharmacophore patterns. The parameters referring to the pharmacophore patterns were in accordance with those used by other authors: (a) the distances between the cationic nitrogen and the hydroxyl oxygens *meta* and *para* to the ethylamine chain; (b) the height of the nitrogen above the plane of the ring to which the oxygens are bonded.[15,16]

The pharmacophore map which had been hypothesized by Wilcox et al.[16] for both the D_1 and D_2 receptors had highlighted a distinction between these two receptors in terms of the pharmacophore geometric parameters values. For high affinity and selective D_1 ligands, such as 3-allyl-6-bromo-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine (Br-APB), these authors reported: (a) a distance between the nitrogen and *meta* and *para* hydroxyl oxygens of the catechol ring of around 7.0 and 6.7 Å, respectively; (b) a height of the nitrogen above the plane of the catechol ring around 1.28 Å. In the pharmacophore map for D_2 agonists, the distances reported for *N*-*n*-propylnorapomorphine (NPA), a high affinity and selective D_2 ligand, were 7.6 Å for *N*-*m*-OH and 6.4 Å for *N*-*p*-OH; the height of the nitrogen above the plane of the catechol ring was 1.83 Å.

Interestingly, we found that the low energy conformations of the least selective derivatives **4**, **5a** and **6a** had lower values for the postulated pharmacophore geometry parameters, compared with those observed in D_1 and D_2 selective ligands. In fact, for any low energy conformation, the distances between the *meta* and *para* hydroxyl group (5-OH and 6-OH) and nitrogen atom (Fig. 3) were around 6.5 Å (lower compared to the values of 7 and 7.6 Å found in D_1 and D_2 selective ligands, respectively), and 6.2 Å (lower compared to the values 6.7 and 6.4 Å found in D_1 and D_2 selective ligands, respectively).

The nitrogen atoms were nearly coplanar with the phenyl ring, approximately 0.01–0.9 Å away from the phenyl ring plane; these values are lower than the 1.28 and 1.83 Å found for D_1 and D_2 ligands, such as Br-APB and NPA. Consequently, the differences between D_1 and D_2 selective ligands and D_1/D_2 unselective ligands lie in the pharmacophore patterns geometry.

The combination of these differences, in terms of geometry pharmacophore features, could play a crucial role in defining D_1/D_2 receptor selectivity. Since the unselective ligands present lower distance values compared to those found in the pharmacophore patterns of D_1 and D_2 selective ligands, it is reasonable to assume that these geometry parameters values allow ligands to be recognized by both receptors. Thus, these pharmacophore parameters values could help in understanding the low affinity and selectivity at D_1 and D_2 receptors displayed by compounds **4**, **5a**, **6a**. Finally, these parameters could be important for designing new selective ligands.

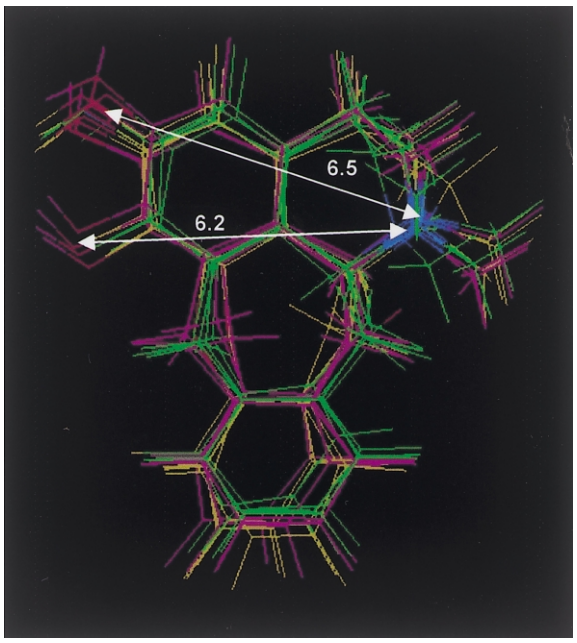


Figure 3. Superimposed candidate pharmacophore conformations of low selective compounds **4** (shown in green), **5a** (shown in magenta) and **6a** (shown in yellow). The oxygen atoms are shown in red and the nitrogen in blue. The arrows highlight the distances (Å) between cationic nitrogen and hydroxyl oxygen at position 5 and 6.

Experimental

Chemistry

Melting points were measured on a Büchi 510 apparatus and are uncorrected. Microanalyses were performed on a 1106 Carlo Erba CHN Analyzer. Analyses indicated by the symbols of the elements were within ±0.4% of the calculated values.

^{1}H NMR spectra were recorded on a Varian VXR 200-MHz spectrometer. Chemical shift values 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 analyses and NMR data. TLC was performed with Merck 60 F_{254} precoated silica on glass. 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 with the reported solvent. Oxalate salts were formed by dissolving the base in ether and adding 1 equivalent of oxalic acid dissolved in a small amount of ether.

2-[2-(Hydroxymethyl)phenyl]-*N*-(3-methoxyphenethyl)-acetamide 7. A mixture of 2-(3-methoxyphenyl) ethylamine (0.54 g, 3.60 mmol) and 3-isochromanone (0.56 g, 3.80 mmol) in xylene (2 mL) was refluxed under N_2 for 2 h with azeotropic removal of water. Solvent was removed under vacuum. The residue was purified by silica gel column chromatography (eluent AcOEt) and recrystallized from $CHCl_3$/cyclohexane. Yield 56%, mp 103–105 °C. IR (film) ν (cm^{-1}) 3275 (NH), 3185 (OH), 1630 (C=O). ^{1}H NMR ($CDCl_3$) δ 7.25 (m, 5H, ArH), 6.76 (m, 1H, ArH), 6.62 (m, 2H, ArH), 6.20 (br s, 1H, NH), 4.61 (s, 2H, CH_2O), 3.68 (s, 3H, OCH_3), 3.59 (s, 2H, CH_2CO), 3.49 (q, J = 6.85 Hz, 2H, CH_2N), 2.72 (t, J = 6.85 Hz, 2H, $ArCH_2CN$), 2.65 (br s, 1H, OH). Anal. calcd for ($C_{18}H_{21}NO_3$): C, 72.22; H, 7.07; N, 4.68; found: C, 71.95; H, 6.91; N, 4.84.

General procedure for the preparation of compounds 9 and 10. The two-phase system consisting of (a) a solution of the amides 7 or 8 (2.20 mmol) and tetrabutylammonium bromide (0.005 g, 0.016 mmol) in CH_2Cl_2 (2.7 mL) and (b) 50% NaOH (0.5 mL) was equilibrated by vigorous stirring for 15–30 min. Dimethylsulfate (0.25 mL, 2.60 mmol) was then added dropwise with cooling. The mixture was stirred for 3 h at room temperature and, after addition of 30% NH_4OH (0.1 mL), for a further 30 min. The mixture was poured into water and the organic phase was separated, washed with water, dried, and evaporated under reduced pressure.

2-[2-(Methoxymethyl)phenyl]-*N*-(3-methoxyphenethyl)-acetamide 9. The crude product was purified by chromatography on silica gel (eluent AcOEt/cyclohexane 6:4) to obtain an oily residue in 58% yield. ^{1}H NMR ($CDCl_3$) δ 7.29 (m, 4H, ArH), 7.13 (m, 1H, ArH), 6.72 (m, 1H, ArH), 6.60 (m, 2H, ArH), 6.12 (br s, 1H, NH), 4.38 (s, 2H, CH_2O), 3.76 (s, 3H, OCH_3), 3.58 (s, 2H, CH_2CO), 3.40 (q, J = 6.6 Hz, 2H, CH_2N), 3.26 (s, 3H, OCH_3), 2.67 (t, J = 6.6 Hz, 2H, $ArCH_2CN$). Anal. calcd for ($C_{19}H_{23}NO_3$): C, 72.82; H, 7.39; N, 4.47; found: C, 72.64; H, 7.58; N, 4.23.

2-[2-(Methoxymethyl)phenyl]-N-(3,4-dimethoxyphenethyl) acetamide 10. The residue was purified by silica-gel column chromatography (eluent AcOEt) and then recrystallized from cyclohexane. Yield 63%, mp 93–95 °C. ^{1}H NMR ($CDCl_3$) δ 7.27 (m, 4H, ArH), 6.68 (m, 1H, ArH), 6.55 (m, 2H, ArH), 6.10 (br s, 1H, NH), 4.38 (s, 2H, CH_2O), 3.82 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.56 (s, 2H, CH_2CO), 3.40 (q, J = 6.65 Hz, 2H, CH_2N), 3.29 (s, 3H, OCH_3), 2.62 (t, J = 6.65 Hz, 2H, $ArCH_2CN$). Anal. calcd for ($C_{20}H_{25}NO_4$): C, 69.95; H, 7.34; N, 4.08; found: C, 70.19; H, 7.51; N, 4.26.

General procedure for the preparation of dihydroisoquinolines 11 and 12. The amide **9** or **10** (1.28 mmol) in dry acetonitrile (6.4 mL) was treated with phosphoryl chloride (0.39 g, 2.57 mmol) and refluxed under N_2 for 15 min. Solvent and excess of reagent were removed in vacuo. A solution of the residue in $CHCl_3$ (10 mL) was rapidly washed with 1 N NaOH, dried, and evaporated under reduced pressure. The residue was converted to the oxalate salt which was recrystallized from EtOH/Et_2O.

6-Methoxy-1-[2-(methoxymethyl)benzyl]-3,4-dihydroisoquinoline oxalate 11. Yield 90%, mp 175–177 °C. ^{1}H NMR (DMSO-d_6) δ 7.80 (d, J = 8.79 Hz, 1H, ArH), 7.26 (m, 4H, ArH), 7.06 (s, 1H, ArH), 6.96 (d, J = 8.79 Hz, 1H, ArH), 4.51 (s, 2H, CH_2O), 3.87 (s, 3H, OCH_3), 3.75 (t, J = 7.70 Hz, 2H, CH_2N^+), 3.29 (s, 3H, OCH_3), 3.00 (t, J = 7.70 Hz, 2H, $ArCH_2CN$). Anal. calcd for ($C_{19}H_{21}NO_2 \cdot H_2C_2O_4$): C, 65.44; H, 6.02; N, 3.63; found: C, 65.21; H, 6.19; N, 3.81.

6,7-Dimethoxy-1-[2-(methoxymethyl)benzyl)-3,4-dihydroisoquinoline oxalate 12. Yield 83%, mp 197–198 °C. ^{1}H NMR (DMSO-d_6) δ 7.30 (m, 5H, ArH), 7.10 (s, 1H, ArH), 4.51 (s, 2H, CH_2O), 3.86 (s, 3H, OCH_3), 3.80 (t, J = 7.49 Hz, 2H, CH_2N^+), 3.68 (s, 3H, OCH_3), 3.30 (s, 3H, OCH_3), 3.04 (t, J = 7.49 Hz, 2H, $ArCH_2CN$). Anal. calcd for ($C_{20}H_{23}NO_3H_2C_2O_4$): C, 63.60; H, 6.07; N, 3.37; found: C, 63.78; H, 5.87; N, 3.13.

General procedure for the preparation of alkyliodides 13a–c and 14a–c. The appropriate alkyl iodide (methyl iodide, ethyl iodide, propyl iodide) (4.37 mmol) was added to a solution of the base **11** or **12** (2.20 mmol) in dry acetonitrile. The mixture was refluxed for 3 h. The solvent was removed to give a yellow solid which was recrystallized.

6-Methoxy-1-[2(methoxymethyl)benzyl]-2-methyl-3,4-dihydroisoquinolinium iodide 13a. Recrystallized from *i*-PrOH/Et_2O. Yield 60%, mp 172–174 °C. ^{1}H NMR (DMSO-d_6) δ 7.83 (d, J = 8.79 Hz, 1H, ArH), 7.48 (d, J = 6.96 Hz, 1H, ArH), 7.20 (m, 2H, ArH), 7.15 (d, J = 2.28 Hz, 1H, ArH), 7.02 (dd, J = 2.28, 8.79 Hz, 1H, ArH), 6.88 (d, J = 6.96 Hz, 1H, ArH), 4.64 (s, 4H, $ArCH_2O$, $ArCH_2C{=}N^+$), 4.20 (t, J = 7 Hz, 2H, CH_2N^+), 3.90 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.40 (s, 3H, N^+CH_3), 3.25 (t, J = 7 Hz, 2H, $ArCH_2CN^+$). Anal. calcd for ($C_{20}H_{24}INO_2$): C, 54.93; H, 5.53; N, 3.20; found: C, 55.11; H, 5.64; N, 3.44.

2-Ethyl-6-methoxy-1-[2(methoxymethyl)benzyl]-3,4-dihydroisoquinolinium iodide 13b. Recrystallized from EtOH/Et_2O. Yield 80%, mp 135–137 °C. ^{1}H NMR (DMSO-d_6) δ 7.82 (d, J = 8.76 Hz, 1H, ArH), 7.45 (m, 1H, ArH), 7.30 (m, 2H, ArH), 7.14 (d, J = 2.27 Hz, 1H, ArH), 7.02 (dd, J = 2.27, 8.76 Hz, 1H, ArH), 6.85 (d, J = 6.92 Hz, 1H, ArH), 4.69 (s, 2H, $ArCH_2O$), 4.60 (s, 2H, $ArCH_2C{=}N$), 4.19 (t, J = 7 Hz, 2H, CH_2N^+), 3.94 (m, 5H, N^+CH_2C, OCH_3), 3.39 (s, 3H, OCH_3), 3.21 (t, J = 7 Hz, 2H, $ArCH_2CN^+$), 1.50 (t, J = 7.04 Hz, 3H, N^+-C-CH_3). Anal. calcd for ($C_{21}H_{26}INO_2$): C, 55.88; H, 5.81; N, 3.10; found: C, 55.82; H, 5.93; N, 2.92.

6-Methoxy-1-[2(methoxymethyl)benzyl]-2-propyl-3,4-dihydroisoquinolinium iodide 13c. Recrystallized from EtOH/Et_2O. Yield 78%, mp 162–164 °C. ^{1}H NMR (DMSO-d_6) δ 7.88 (d, J = 8.75 Hz, 1H, ArH), 7.48 (m, 1H, ArH), 7.29 (m, 2H, ArH), 7.15 (d, J = 2.3 Hz, 1H, ArH), 7.01 (dd, J = 2.3, 8.75 Hz, 1H, ArH), 6.85 (d, J = 6.94 Hz, 1H, ArH), 4.69 (s, 2H, $ArCH_2O$), 4.62 (s, 2H, $ArCH_2C{=}N$), 4.20 (t, J = 7.12 Hz, 2H, CH_2N^+), 3.88 (m, 5H, N^+CH_2CC, OCH_3), 3.40 (s, 3H, OCH_3), 3.23 (t, J = 7.12 Hz, 2H, $ArCH_2CN^+$), 1.78 (m, 2H, N^+CCH_2C), 0.90 (t, J = 7.3 Hz, 3H, N^+CCCH_3). Anal. calcd for ($C_{22}H_{28}INO_2$): C, 56.78; H, 6.06; N, 3.01; found: C, 57.05; H, 5.81; N, 2.82.

6,7-Dimethoxy-1-[2(methoxymethyl)benzyl]-2-methyl-3,4-dihydroisoquinolinium iodide 14a. Recrystallized from *i*-PrOH. Yield 83%, mp 192–194 °C. ^{1}H NMR (DMSO-d_6) δ 7.45 (m, 1H, ArH), 7.30 (m, 3H, ArH), 7.18 (s, 1H, ArH), 6.92 (d, J = 6.9 Hz, 1H, ArH), 4.70 (s, 2H, $ArCH_2C{\doteq}N$), 4,60 (s, 2H, $ArCH_2O$), 4.15 (t, J = 7.21 Hz, 2H, CH_2N^+), 3.90 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.60 (s, 3H, OCH_3), 3.38 (s, 3H, N^+CH_3), 3.20 (t, J = 7.21 Hz, 2H, $ArCH_2CN^+$). Anal. calcd for ($C_{21}H_{26}INO_3$): C, 53.97; H, 5.61; N, 3.00; found: C, 53.83; H, 5.42; N, 3.13.

6,7-Dimethoxy-2-ethyl-1-[2(methoxymethyl)benzyl]-3,4-dihydroisoquinolinium iodide 14b. Recrystallized from *i*-PrOH. Yield 60%, mp 181–183 °C. ^{1}H NMR (DMSO-d_6) d 7.48 (m, 1H, ArH), 7.30 (m, 3H, ArH), 7.20 (s, 1H, ArH), 6,90 (m, 1H, ArH), 4.72 (s, 2H, $ArCH_2C{=}N$), 4.60 (s, 2H, $ArCH_2O$), 4.18 (t, J = 7.08 Hz, 2H, CH_2N^+), 4.02 (q, J = 7.12 Hz, 2H, N^+CH_2C), 3.92 (s, 3H, OCH_3), 3.52 (s, 3H, OCH_3), 3.41 (s, 3H, OCH_3), 3.20 (t, J = 7.08 Hz, 2H, $ArCH_2CN^+$), 1.34 (t, J = 7.12 Hz, 3H, N^+CCH_3). Anal. calcd for ($C_{22}H_{28}INO_3$): C, 54.89; H, 5.86; N, 2.91; found: C, 54.66; H, 5.91; N, 2.97.

6,7-Dimethoxy-1-[2(methoxymethyl)benzyl]-2-propyl-6,7-dimethoxy-3,4-dihydroisoquinolinium iodide 14c. Recrystallized from *i*-PrOH. Yield 51%, mp 190–192 °C. ^{1}H NMR (DMSO-d_6) δ 7.45 (m, 1H, ArH), 7.28 (m, 3H, ArH), 7.20 (s, 1H, ArH), 6.88 (m, 1H, ArH), 4.75 (s, 2H, $ArCH_2C{=}N$), 4.60 (s, 2H, $ArCH_2O$), 4.15 (t, J = 7.21 Hz, 2H, CH_2N^+), 3.90 (m, 5H, N^+CH_2CC, OCH_3), 3.60 (s, 3H, OCH_3), 3.38 (s, 3H, OCH_3), 3.20 (t, J = 7.21 Hz, 2H, $ArCH_2CN^+$), 1.79 (m, 2H, N^+CCH_2C), 0.92 (t, J = 7.4 Hz, 3H, N^+CCCH_3). Anal. calcd for ($C_{23}H_{30}INO_3$): C, 55.76; H, 6.10; N, 2.83; found: C, 56.01; H, 5.89; N, 2.92.

General procedure for the preparation of *N*-alkyltetrahydroisoquinoline 15a–c and 16a–c. Sodium borohydride (0.048 g, 1.27 mmol) was added in portion to a stirred solution of the appropriate alkyliodide **13a–c** or **14a–c** (1.27 mmol) in $CHCl_3$ (1.5 mL) and CH_3OH (7 mL). The mixture was stirred for 30 min at room temperature. After evaporation of solvent, water and $CHCl_3$ were added. The organic phase was separated, dried, and evaporated. The residue was converted to the oxalate salt.

6-Methoxy-1-[2-(methoxymethyl)benzyl]-2-methyl-1,2,3,4-tetrahydroisoquinoline oxalate 15a. Recrystallized from EtOH/Et_2O. Yield 84%, mp 130–132 °C. ^{1}H NMR (DMSO-d_6) δ 10.93 (br s, 1H, NH^+), 7.28 (m, 3H, ArH), 7.10 (m, 1H, ArH), 6.85 (d, J = 2.64 Hz, 1H, ArH), 6.50 (dd, J = 2.64, 8.45 Hz, 1H, ArH), 6.18 (d, J = 8.45 Hz, 1H, ArH), 4.45 (m, 1H, CHN^+), 4.20 (d, J = 11.8 Hz, 1H, ArCHO), 4.00 (d, J = 11.8 Hz, 1H, ArCHO), 3.72 (m, 5H, CH_2N^+, OCH_3), 3.40 (m, 2H, $ArCH_2$), 3.22 (s, 3H, OCH_3), 3.06 (m, 2H, $ArCH_2CN^+$) 2.80 (s, 3H, N^+CH_3). Anal. calcd for ($C_{20}H_{25}NO_2H_2C_2O_4$): C, 65.82; H, 6.78; N, 3.49; found: C, 63.66; H, 6.63; N, 3.27.

2-Ethyl-6-methoxy-1-[2-(methoxymethyl)benzyl]-1,2,3,4-tetrahydroisoquinoline oxalate 15b. Recrystallized from i-PrOH. Yield 80%, mp 140–141 °C. ^{1}H NMR (DMSO-d_6) δ 10.05 (br s, 1H, NH^+), 7.28 (m, 3H, ArH), 7.06 (m, 1H, ArH), 6.86 (d, J = 2.51 Hz, 1H, ArH), 6,51 (dd, J = 2.51, 8.40 Hz, 1H, ArH), 6.10 (d, J = 8.40 Hz, 1H, ArH), 4.46 (m, 1H, CHN^+), 4.30 (d, J = 12 Hz, 1H, ArCHO), 4.02 (d, J = 12 Hz, 1H, ArCHO), 3.71 (m, 5H,

CH_2N^+, OCH_3), 3.40 (m, 2H, CH_2N^+), 3.22 (s, 3H, OCH_3), 3.02 (m, 4H, two $ArCH_2CN^+$), 1.23 (t, $J=7.3$ Hz, 3H, N^+CCH_3). Anal. calcd for ($C_{21}H_{27}NO_2 \cdot H_2C_2O_4$): C, 66.49; H, 7.03; N, 3.37; found: C, 66.21; H, 7.24; N, 3.16.

6-Methoxy-1-[2-(methoxymethyl)benzyl]-2-propyl-1,2,3,-4-tetrahydroisoquinoline oxalate 15c. Recrystallized from EtOH/Et_2O. Yield 71%, mp 161–163 °C. ^1H NMR (DMSO-d_6) δ 10.40 (br s, 1H, NH^+), 7.26 (m, 3H, ArH), 7.02 (m, 1H, ArH), 6.81 (d, $J=2.71$ Hz, 1H, ArH), 6.51 (dd, $J=2.71$, 8.56 Hz, 1H, ArH), 6.10 (d, $J=8.56$ Hz, 1H, ArH), 4.44 (m, 1H, CHN^+), 4.29 (d, $J=12.3$ Hz, 1H, ArCHO), 4.15 (d, $J=12.3$ Hz, 1H, ArCHO), 3.70 (m, 5H, CH_2N^+, OCH_3), 3.39 (m, 2H, $ArCH_2$), 3.25 (s, 3H, OCH_3), 2.92 (m, 4H, two $ArCH_2CN^+$), 1.69 (m, 2H, N^+CCH_2C), 0.82 (t, $J=7.51$ Hz, 3H, N^+CCCH_3). Anal. calcd for ($C_{22}H_{29}NO_2H_2C_2O_4$): C, 67.11; H, 7.28; N, 3.26; found: C, 67.24; H, 7.37; N, 3.09.

6,7-Dimethoxy-1-[2-(methoxymethyl)benzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline oxalate 16a. Recrystallized from EtOH/Et_2O. Yield 73%, mp 119–121 °C. ^1H NMR (DMSO-d_6) δ 9.90 (br s, 1H, NH^+), 7.28 (m, 3H, ArH), 7.10 (m, 1H, ArH), 6.80 (s, 1H, ArH), 5.52 (s, 1H, ArH), 4.40 (m, 1H, CHN^+), 4.25 (d, $J=12.41$ Hz, 1H, ArCHO), 3.98 (d, $J=12.41$ Hz, 1H, ArCHO), 3.68 (m, 5H, OCH_3, CH_2N^+), 3.41 (m, 2H, $ArCH_2$), 3.22 (s, 3H, OCH_3), 3.20 (s, 3H, OCH_3), 3.03 (m, 2H, $ArCH_2CN^+$), 2.80 (s, 3H, N^+CH_3). Anal. calcd for ($C_{21}H_{27}NO_3H_2C_2O_4$): C, 64.02; H, 6.77; N, 3.25; found: C, 63.87; H, 6.53; N, 3.06.

6,7-Dimethoxy-2-ethyl-1-[2-(methoxymethyl)benzyl]-1,2,3,4-tetrahydroisoquinoline oxalate 16b. Recrystallized from *i*-PrOH. Yield 87%, mp 146–147 °C. ^1H NMR (DMSO-d_6) δ 9.80 (br s, 1H, NH^+), 7.29 (m, 3H, ArH), 7.06 (m, 1H, ArH), 6.83 (s, 1H, ArH), 5.52 (s, 1H, ArH), 4.49 (m, 1H, CHN^+), 4.30 (d, 1H, $J=12.25$ Hz, ArCHO), 4.00 (d, $J=12.25$ Hz, 1H, ArCHO), 3.73 (s, 3H, OCH_3), 3.48 (m, 2H, CH_2N^+), 3.30–2.91 (m, 12H, two OCH_3, two $ArCH_2CN^+$, N^+CH_2C), 1.30 (t, $J=7.4$ Hz, 3H, N^+CCH_3). Anal. calcd for ($C_{22}H_{29}NO_3H_2C_2O_4$): C, 64.71; H, 7.01; N, 3.14; found: C, 64.58; H, 6.95; N, 3.29.

6,7-Dimethoxy-1-[2-(methoxymethyl)benzyl]-2-propyl-1,2,3,4-tetrahydroisoquinoline oxalate 16c. Recrystallized from EtOH/Et_2O. Yield 71%, mp 75–78 °C (dec). ^1H NMR (DMSO-d_6) δ 9.90 (br s, 1H, NH^+), 7.28 (m, 3H, ArH), 7.07 (m, 1H, ArH), 6.72 (s, 1H, ArH), 5.51 (s, 1H, ArH), 4.46 (m, 1H, CHN^+), 4.30 (d, $J=12.3$ Hz, 1H, ArCHO), 4.00 (d, $J=12.3$ Hz, 1H, ArCHO), 3.70 (s, 3H, OCH_3), 3.48 (m, 2H, CH_2N^+), 3.22 (s, 3H, OCH_3), 3.20 (s, 3H, OCH_3), 2.98 (m, 6H, two $ArCH_2$, N^+CH_2CC), 1.75 (m, 2H, N^+CCH_2C), 0.90 (t, $J=7.42$ Hz, 3H, N^+CCCH_3). Anal. calcd for ($C_{23}H_{31}NO_3 \cdot H_2C_2O_4$): C, 65.34; H, 7.24; N, 3.05; found: C, 65.46; H, 7.03; N, 2.91.

General procedure for the preparation of the benzyltetrahydroisoquinolines oxalate 15d and 16d. A solution of amide **9** or **10** (1.60 mmol) and phosphoryl chloride (0.3 mL, 3.20 mmol) in dry acetonitrile (7 mL) was refluxed, under N_2, for 15 min. The solvent and the excess of reagent were removed under reduced pressure. A solution of the residue in $CHCl_3$ (10 mL) was rapidly washed with 1 N NaOH, dried and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent AcOEt). After removal of the solvent a mixture of the product, KI (0.87 g, 5.26 mmol), benzyl bromide (0.28 g, 1.66 mmol) and dry acetone (36 mL) was heated at 70 °C, under N_2, for 2 days. The solvent was removed under vacuum. The residue was dissolved in CH_3OH (22 mL) containing a trace of H_2O, and $NaBH_4$ (0.045 g, 1.19 mmol) was added, under stirring, in small portions over 30 min at room temperature. Stirring was maintained for an additional 60 min. The solvent was removed, the residue was diluted with H_2O and extracted with CH_2Cl_2. The organic extracts were dried and evaporated. The residue was purified by column chromatography on silica gel (eluent AcOEt). Evaporation of pure fractions gave a oily residue. This was converted to the oxalate salt which was recrystallized from EtOH/Et_2O.

2-Benzyl-6-methoxy-1-[2-(methoxymethyl)benzyl]-1,2,3,-4-tetrahydroisoquinoline oxalate 15d. Yield 30%, mp 192–194 °C. ^1H NMR (DMSO-d_6) δ 10.90 (br s, 1H, NH^+), 7.24 (m, 8H, ArH), 7.04 (m, 1H, ArH), 6.80 (d, $J=2.1$ Hz, 1H, ArH), 6.60 (dd, $J=2.1$, 8.5 Hz, 1H, ArH), 6.42 (d, $J=8.5$ Hz, 1H, ArH), 4.33–3.40 (m, 6H, $ArCH_2O$, CHN^+, OCH_3), 3.23–2.60 (m, 11H, two $ArCH_2$, two CH_2N^+, OCH_3). Anal. calcd for ($C_{26}H_{29}NO_2 \cdot H_2C_2O_4$): C, 70.42; H, 6.54; N, 2.93; found: C, 70.16; H, 6.71; N, 2.78.

2-Benzyl-5,6-dimethoxy-1-[2-(methoxymethyl)benzyl]-1,2,3,4-tetrahydroisoquinoline oxalate 16d. Yield 25%, mp 175–177 °C. ^1H NMR (DMSO-d_6) δ 7.28 (m, 8H, ArH), 7.02 (m, 1H, ArH), 6.80 (s, 1H, ArH), 5.85 (s, 1H, ArH), 4.02 (m, 5H, $ArCH_2O$, $ArCH_2N^+$, CHN^+), 3.75 (s, 3H, OCH_3), 3.68–2.62 (m, 9H, two $ArCH_2$, CH_2N^+, OCH_3). Anal. calcd for ($C_{27}H_{31}NO_3 \cdot H_2C_2O_4$): C, 68.62; H, 6.55; N, 2.76; found: C, 68.51; H, 6.76; N, 2.92.

General procedure for the preparation of methoxybenzo[5,6]cyclohepta[1,2,3-*ij*]isoquinolines 17a–d and 18a–d. The appropriate 2-alkyl-1-[2-(methoxymethyl)benzyl]-6-methoxy- (or 6,7-dimethoxy)-1,2,3,4-tetrahydroisoquinoline (2.12 mmol) was added in portions to cold 98% sulfuric acid (50 mL) at −40 °C, under N_2, with vigorous mechanical stirring. After the addition, the reaction mixture was stirred at −10 °C for 2 h. Then, the mixture was poured into crushed ice and left stirring for 2 h. The solution was made alkaline with 2 N NaOH and extracted with $CHCl_3$. The extracts were dried and evaporated under vacuum. The oil was treated with ethereal oxalic acid and the oxalate salt was recrystallized from EtOH/Et_2O.

5-Methoxy-1-methyl-1,2,3,7,12,12a-hexahydrobenzo-[5,6]cyclohepta[1,2,3-*ij*]isoquinoline oxalate 17a. Yield 35%, mp 128–130 °C. ^1H NMR (DMSO-d_6) δ 8.20 (br s, 1H, NH^+), 7.18 (m, 4H, ArH), 6.85 (d, $J=2.61$, 1H,

ArH), 6.74 (d, $J=2.61$ Hz, 1H, ArH), 5.08 (dd, $J=4.03$, 12.09 Hz, 1H, CHN^+), 4.32 (d, $J=15.02$ Hz, 1H, ArCHAr), 3.79 (d, $J=15.02$ Hz, 1H, ArCHAr), 3.72 (s, 3H, OCH_3), 3.47 (m, 4H, two $ArCH_2$), 3.01 (m, 2H, CH_2N^+), 2.90 (s, 3H, N^+CH_3). Anal. calcd for ($C_{19}H_{21}NO{\cdot}H_2C_2O_4$): C, 68.28; H, 6.28; N, 3.79; found: C, 68.55; H, 6.47; N, 3.73.

1-Ethyl-5-methoxy-1,2,3,7,12,12a-hexahydrobenzo[5,6]-cyclohepta[1,2,3-*ij*]isoquinoline oxalate 17b. Yield 28%, mp 102–105 °C. ^{1}H NMR (DMSO-d_6) δ 8.40 (br s, 1H, NH^+), 7.18 (m, 4H, ArH), 6.85 (d, $J=2.49$ Hz, 1H, ArH), 6.73 (d, $J=2.49$ Hz, 1H, ArH), 5.12 (dd, $J=4.2$, 11.7 Hz, 1H, CHN^+), 4.48 (d, 1H, $J=14.7$ Hz, ArCHAr), 3.74–2.80 (m, 12H, ArCHAr, OCH_3, two $ArCH_2$, CH_2N^+, N^+CH_2C), 1.32 (t, $J=7.5$ Hz, 3H, N^+CCH_3). Anal. calcd for ($C_{20}H_{23}NO{\cdot}H_2C_2O_4$): C, 68.92; H, 6.57; N, 3.65; found: C, 68.67; H, 6.76; N, 3.58.

5-Methoxy-1-propyl-1,2,3,7,12,12a-hexahydrobenzo[5,6]-cyclohepta[1,2,3-*ij*]isoquinoline oxalate 17c. Yield 14%, mp 115–118 °C. ^{1}H NMR (DMSO-d_6) δ 10.21 (br s, 1H, NH^+), 7.18 (m, 4H, ArH), 6.82 (d, $J=2.2$ Hz, 1H, ArH), 6.73 (d, $J=2.2$ Hz, 1H, ArH), 5.10 (m, 1H, CHN^+), 4.46 (d, $J=15.2$ Hz, 1H, ArCHAr), 3.87–2.85 (m, 12H, ArCHAr, OCH_3, two $ArCH_2$, CH_2N^+, N^+CH_2CC), 1.80 (m, 2H, N^+CCH_2C), 0.95 (t, $J=7.3$ Hz, 3H, N^+CCCH_3). Anal. calcd for ($C_{21}H_{25}NO{\cdot}H_2C_2O_4$): C, 69.50; H, 6.85; N, 3.52; found: C, 69.64; H, 7.01; N, 3.73.

1-Benzyl-5-methoxy-1,2,3,7,12,12a-hexahydrobenzo[5,6]-cyclohepta[1,2,3-*ij*]isoquinoline oxalate 17d. Yield 22%, mp 174–176 °C.^{1}H NMR (DMSO-d_6) δ 10.40 (br s, 1H, NH^+), 7.24 (m, 9H, ArH), 6.85 (d, $J=2.15$ Hz, 1H, ArH), 6.70 (d, $J=2.15$ Hz, 1H, ArH), 4.80 (m, 1H, CHN^+), 4.30 (d, $J=14.8$ Hz, 1H, ArCHAr), 3.76–2.62 (m, 12H, ArCHAr, OCH_3, two $ArCH_2$, two CH_2N^+). Anal. calcd for ($C_{25}H_{25}NO{\cdot}H_2C_2O_4$): C, 72.79; H, 6.11; N, 3.14; found: C, 72.64; H, 6.05; N, 2.92.

5,6-Dimethoxy-1-methyl-1,2,3,7,12,12a-hexahydrobenzo[5,6]cyclohepta[1,2,3-*ij*]isoqui-noline oxalate 18a. Yield 54%, mp 181–183 °C. ^{1}H NMR (DMSO-d_6) δ 9.25 (br s, 1H, NH^+), 7.18 (m, 4H, ArH), 6.85 (s, 1H, ArH), 5.10 (dd, $J=4.4$, 12.45 Hz, 1H, CHN^+), 4.15 (d, $J=14.1$ Hz, 1H, ArCHAr), 4.05 (d, $J=14.1$ Hz, 1H, ArCHAr), 3.75 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.60–2.92 (m, 6H, two $ArCH_2$, CH_2N^+), 2.85 (s, 3H, N^+CH_3). Anal. calcd for ($C_{20}H_{23}NO_2H_2C_2O_4$): C, 66.15; H, 6.31; N, 3.51; found: C, 66.32; H, 6.16; N, 3.34.

5,6-Dimethoxy-1-ethyl-1,2,3,7,12,12a-hexahydrobenzo-[5,6]cyclohepta[1,2,3-*ij*]isoqui-noline oxalate 18b. Yield 42%, mp 103–105 °C. ^{1}H NMR (DMSO-d_6) δ 7.15 (m, 4H, ArH), 6.86 (s, 1H, ArH), 6.25 (br s, 1H, NH^+), 5.12 (dd, $J=4.5$, 12.28 Hz, 1H, CHN^+), 4.21 (d, $J=14.3$ Hz, 1H, ArCHAr), 4.06 (d, $J=14.3$ Hz, 1H, ArCHAr), 3.78 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.60–2.80 (m, 8H, two $ArCH_2$, two N^+CH_2), 1.32 (t, $J=7.24$ Hz, 3H, N^+CCH_3). Anal. calcd for ($C_{21}H_{25}NO_2{\cdot}H_2C_2O_4$): C, 66.81; H, 6.58; N, 3.39; found: C, 66.59; H, 6.42; N, 3.35.

5,6-Dimethoxy-1-propyl-1,2,3,7,12,12a-hexahydrobenzo[5,6]cyclohepta[1,2,3-*ij*]isoquino-line oxalate 18c. Yield 41%, mp 104–106 °C. ^{1}H NMR (DMSO-d_6) δ 8.75 (br s, 1H, NH^+), 7.12 (m, 4H, ArH), 6.81 (s, 1H, ArH), 5.08 (dd, $J=4.35$, 12.5 Hz, 1H, CHN^+), 4.20 (d, $J=14.6$ Hz, 1H, ArCHAr), 4.02 (d, $J=14.6$ Hz, 1H, ArCHAr), 3.80 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.66–2.75 (m, 8H, two $ArCH_2$, two N^+CH_2), 1.78 (m, 2H, N^+CCH_2C), 0.92 (t, $J=7.32$ Hz, 3H, N^+CCH_3). Anal. calcd for ($C_{22}H_{27}NO_2{\cdot}H_2C_2O_4$): C, 67.43; H, 6.84; N, 3.28; found: C, 67.22; H, 6.71; N, 3.09.

1-Benzyl-5,6-dimethoxy-1,2,3,7,12,12a-hexahydrobenzo[5,6]cyclohepta[1,2,3-*ij*]isoquino-line oxalate 18d. Yield 26%, mp 149–151 °C. ^{1}H NMR (DMSO-d_6) δ 10.60 (br s, 1H, NH^+), 7.42 (m, 5H, ArH), 7.15 (m, 4H, ArH), 6.80 (s, 1H, ArH), 4.82 (dd, $J=4.3$, 12.65 Hz, 1H, CHN^+), 4.15 (s, 2H, $ArCH_2N^+$), 4.05 (m, 2H, $ArCH_2Ar$), 3.80 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.60–2.60 (m, 6H, two $ArCH_2$, CH_2N^+). Anal. calcd for ($C_{26}H_{27}NO_2{\cdot}H_2C_2O_4$): C, 70.72; H, 6.15; N, 2.95; found: C, 70.66; H, 6.04; N, 2.81.

General procedure for the demethylation

A mixture of the appropriate 1-alkyl-1,2,3,7,12,12a-hexahydro-5-methoxy- (or 5,6-dimethoxy-)benzo[5,6]cyclohepta[1,2,3-*ij*]isoquinoline (0.40 mmol), methanesulfonic acid (7.1 g, 74 mmol), H_2O (0.3 mL), and methionine (0.69 g, 4.6 mmol) was stirred at 40 °C for 4 days. The solution was poured into ice–H_2O and adjusted to pH 8.0 with 15% NH_4OH. The mixture was extracted with AcOEt. The organic extracts, washed with aqueous $NaHSO_3$ and H_2O, were dried and evaporated. The oil was treated with ethereal oxalic acid or EtOH/HCl and the salt was recrystallized from EtOH/Et_2O.

5-Hydroxy-1-methyl-1,2,3,7,12,12a-hexahydrobenzo-[5,6]cyclohepta[1,2,3-*ij*]isoquinoline oxalate 5a. Yield 29%, mp 150–152 °C. ^{1}H NMR (DMSO-d_6) δ 7.18 (m, 4H, ArH), 6.62 (d, $J=2.28$ Hz, 1H, ArH), 6.52 (d, J = 2.28 Hz, 1H, ArH), 5.02 (dd, $J=3.7$, 11.6 Hz, 1H, CHN^+), 4.30 (d, $J=15.1$ Hz, 1H, ArCHAr), 3.72 (d, $J=15.1$ Hz, 1H, ArCHAr), 3.40 (m, 4H, two $ArCH_2$), 2.92 (m, 2H, N^+CH_2), 2.88 (s, 3H, N^+CH_3). Anal. calcd for ($C_{18}H_{19}NO{\cdot}H_2C_2O_4$): C, 67.59; H, 5.96; N, 3.94; found: C, 67.32; H, 6.17; N, 3.71.

1-Ethyl-5-hydroxy-1,2,3,7,12,12a-hexahydrobenzo[5,6]-cyclohepta[1,2,3-*ij*]isoquinoline oxalate 5b. Yield 66%, mp 144–146 °C. ^{1}H NMR (DMSO-d_6) δ 7.18 (m, 4H, ArH), 6.62 (d, $J=2.25$ Hz, 1H, ArH), 6.52 (d, $J=2.25$ Hz, 1H, ArH), 5.20 (dd, $J=3.4$, 11.8 Hz, 1H, CHN^+), 4.40 (d, $J=14.8$ Hz, 1H, ArCHAr), 3.60 (d, $J=14.8$ Hz, 1H, ArCHAr), 3.59–2.74 (m, 8H, two $ArCH_2$, two N^+CH_2), 1.30 (t, $J=7.9$ Hz, 3H, N^+CCH_3). Anal. calcd for ($C_{19}H_{21}NO{\cdot}H_2C_2O_4$): C, 68.28; H, 6.28; N, 3.79; found: C, 68.47; H, 6.13; N, 3.95.

5-Hydroxy-1-propyl-1,2,3,7,12,12a-hexahydrobenzo[5,6]-cyclohepta[1,2,3-*ij*]isoquinoline oxalate 5c. Yield 44%, mp 133–135 °C (dec). ^{1}H NMR (DMSO-d_6) δ 8.80 (br s,

1H, NH^+), 7.18 (m, 4H, ArH), 6.64 (d, $J=2.6$ Hz, 1H, ArH), 6.53 (d, $J=2.6$ Hz, 1H, ArH), 5.00 (dd, $J=3.5$, 11.3 Hz, 1H, CHN^+), 4.39 (d, $J=14.3$ Hz, 1H, ArCHAr), 3.69 (d, $J=14.3$ Hz, 1H, ArCHAr), 3.45 (m, 4H, two $ArCH_2$), 2.98 (m, 4H, two N^+CH_2), 1.77 (m, 2H, N^+CCH_2C), 0.92 (t, $J=7.45$ Hz, 3H, N^+CCCH_3). Anal. calcd for ($C_{20}H_{23}NO{\cdot}H_2C_2O_4$): C, 68.91; H, 6.57; N, 3.65; found: C, 69.12; H, 6.36; N, 3.78.

1-Benzyl-5-hydroxy-1,2,3,7,12,12a-hexahydrobenzo[5,6]-cyclohepta[1,2,3-*ij*]isoquinoline oxalate 5d. Yield 22%, mp 125–127 °C. ^{1}H NMR (DMSO-d_6) δ 7.48 (m, 5H, ArH), 7.14 (m, 4H, ArH), 6.60 (d, $J=2.4$ Hz, 1H, ArH), 6.50 (d, $J=2.4$ Hz, 1H, ArH), 4.76 (dd, $J=3.2$, 11.3 Hz, 1H, CHN^+), 4.28 (d, $J=13.9$ Hz, 1H, ArCHAr), 4.15 (s, 2H, N^+CH_2Ar), 3.60 (d, $J=13.9$ Hz, 1H, ArCHAr), 3.50–2.62 (m, 6H, two $ArCH_2$, N^+CH_2). Anal. calcd for ($C_{24}H_{23}NO{\cdot}H_2C_2O_4$): C, 72.37; H, 5.84; N, 3.25; found: C, 72.14; H, 5.62; N, 3.32.

5-Hydroxy-1,2,3,7,12,12a-hexahydrobenzo[5,6]cyclohepta[1,2,3-*ij*]isoquinoline oxalate 5e. Yield 52%, mp 126–128 °C (hygroscopic solid). ^{1}H NMR (DMSO-d_6) δ 7.22 (m, 4H, ArH), 6.68 (d, $J=2.6$ Hz, 1H, ArH), 6,58 (d, $J=2.6$ Hz, 1H, ArH), 4.67 (dd, $J=3.4$, 11.2 Hz, 1H, CHN^+), 4.09 (m, 2H, $ArCH_2Ar$), 3.61–2.72 (m, 6H, two $ArCH_2$, N^+CH_2). Anal. calcd for ($C_{17}H_{17}NO{\cdot}H_2C_2O_4$): C, 66.85; H, 5.62; N, 4.10; found: C, 67.11; H, 5.43; N, 4.27.

1-Methyl-5,6-dihydroxy-1,2,3,7,12,12a-hexahydrobenzo[5,6]cyclohepta[1,2,3-*ij*]isoquino-line hydrochloride 6a. Yield 25%, mp 159–161 °C (hygroscopic solid). ^{1}H NMR (DMSO-d_6) δ 11.30 (m, 1H, NH^+), 9.58 (s, 1H, OH), 8.50 (s, 1H, OH), 7.12 (m, 4H, ArH), 6.57 (s, 1H, ArH), 5.18 (dd, $J=3.2$, 11.6 Hz, 1H, CHN^+), 4.14 (d, $J=13.7$ Hz, 1H, ArCHAr), 4.02 (d, $J=13.7$ Hz, 1H, ArCHAr), 3.70–3.12 (m, 4H, two $ArCH_2$), 2.85 (m, 5H, N^+CH_2, N^+CH_3). Anal. calcd for ($C_{18}H_{19}NO_2HCl$): C, 68.03; H, 6.34; N, 4.41; found: C, 67.81; H, 6.22; N, 4.33.

1-Ethyl-5,6-dihydroxy-1,2,3,7,12,12a-hexahydrobenzo[5,6]cyclohepta[1,2,3-*ij*]isoquino-line oxalate 6b. Yield 25%, mp 176–178 °C. ^{1}H NMR (DMSO-d_6) δ 8.75 (br s, 3H, two OH, NH^+), 7.10 (m, 4H, ArH), 6.48 (s, 1H, ArH), 4.90 (dd, $J=3.1$, 11.4 Hz, 1H, CHN^+), 4.12 (d, $J=14.1$ Hz, 1H, ArCHAr), 4.00 (d, $J=14.1$ Hz, 1H, ArCHAr), 3.50–2.51 (m, 8H, two $ArCH_2$, two N^+CH_2), 1.26 (t, $J=7.9$ Hz, 3H, N^+CCH_3). Anal. calcd for ($C_{19}H_{21}NO_2{\cdot}H_2C_2O_4$): C, 65.44; H, 6.02; N, 3.63; found: C, 65.65; H, 5.86; N, 3.89.

5,6-Dihydroxy-1-propyl-1,2,3,7,12,12a-hexahydrobenzo[5,6]cyclohepta[1,2,3-*ij*]isoquino-line oxalate 6c. Yield 41%, mp 149–151 °C. ^{1}H NMR (DMSO-d_6) δ 8.90 (br s, 3H, two OH, NH^+), 7.12 (m, 4H, ArH), 6.52 (s, 1H, ArH), 5.01 (dd, $J=3.35$, 11.6 Hz, 1H, CHN^+), 4.12 (d, $J=13.9$ Hz, 1H, ArCHAr), 4.02 (d, $J=13.9$ Hz, 1H, ArCHAr), 3.65–2.60 (m, 8H, two $ArCH_2$, two N^+CH_2), 1.78 (m, 2H, N^+CCH_2C), 0.98 (t, $J=7.25$ Hz, 3H, N^+CCCH_3). Anal. calcd for ($C_{20}H_{23}NO_2{\cdot}H_2C_2O_4$): C, 66.15; H, 6.31; N, 3.51; found: C, 66.05; H, 6.53; N, 3.77.

1-Benzyl-5,6-dihydroxy-1,2,3,7,12,12a-hexahydrobenzo[5,6]cyclohepta[1,2,3-*ij*]isoquino-line oxalate 6d. Yield 70%, mp 165–167 °C. ^{1}H NMR (DMSO-d_6) δ 7.90 (br s, 3H, two OH, NH^+), 7.45 (m, 5H, ArH), 7.12 (m, 4H, ArH), 6.52 (s, 1H, ArH), 4.78 (dd, $J=3.2$, 11.5 Hz, 1H, CHN^+), 4.16 (s, 2H, $ArCH_2N^+$), 4.12 (d, $J=13.64$ Hz, 1H, ArCHAr), 3.86 (d, $J=13.64$ Hz, 1H, ArCHAr), 3.58–2.48 (m, 6H, two $ArCH_2$, N^+CH_2). Anal. calcd for ($C_{24}H_{23}NO_2{\cdot}H_2C_2O_4$): C, 69.79; H, 5.63; N, 3.13; found: C, 69.88; H, 5.41; N, 2.92.

5,6-Dihydroxy-1,2,3,7,12,12a-hexahydrobenzo[5,6]cyclohepta[1,2,3-*ij*]isoquinoline oxalate 6e. Yield 60%, mp 130–132 °C. ^{1}H NMR (DMSO-d_6) δ 8.10 (br s, 4H, two OH, NH_2^+), 7.12 (m, 4H, ArH), 6.55 (m, 1H, ArH), 4.82 (dd, $J=3.28$, 11.66 Hz, 1H, CHN^+), 4.10 (s, 2H, $ArCH_2Ar$), 3.50–2.69 (m, 6H, two $ArCH_2$, N^+CH_2). Anal. calcd for ($C_{17}H_{17}NO_2H_2C_2O_4$): C, 63.86; H, 5.36; N, 3.92; found: C, 63.58; H, 5.13; N, 4.11.

General procedure for the preparation of the compounds 17e and 18e. A mixture of **17d** or **18d** (0.20 mmol), acetic acid (10 mL), and 10% Pd/C (100 mg) was shaken under 25 psi of H_2, in a Parr flask at room temperature for 3 h. After filtration, the solvent was evaporated under reduced pressure. The residue was dissolved in water. The solution was basified with 15% NH_4OH to pH 9 and extracted with $CHCl_3$. The extracts were dried and evaporated. The residue was converted to the oxalate, and the salt was recrystallized from $EtOH/Et_2O$.

5-Methoxy-1,2,3,7,12,12a-hexahydrobenzo[5,6]cyclohepta[1,2,3-*ij*]isoquinoline oxalate 17e. Yield 79%, mp 123–125 °C. ^{1}H NMR (DMSO-d_6) δ 8.55 (br s, 2H, NH_2^+), 7.20 (m, 4H, ArH), 6.85 (d, $J=2.61$ Hz, 1H, ArH), 6.75 (d, $J=2.61$ Hz, 1H, ArH), 4.70 (dd, $J=6.06$, 10.1 Hz, 1H, CHN^+), 4.17 (d, $J=14.8$ Hz, 1H, ArCHAr), 4.04 (d, $J=14.8$ Hz, 1H, ArCHAr), 3.75 (s, 3H, OCH_3), 3.51–2.80 (m, 6H, two $ArCH_2$, N^+CH_2). Anal. calcd for ($C_{18}H_{19}NO{\cdot}H_2C_2O_4$): C, 67.59; H, 5.96; N, 3.94; found: C, 67.41; H, 6.12; N, 3.69.

5,6-Dimethoxy-1,2,3,7,12,12a-hexahydrobenzo[5,6]cyclohepta[1,2,3-*ij*]isoquinoline oxalate 18e. Yield 75%, mp 123–125 °C. ^{1}H NMR (DMSO-d_6) δ 7.70 (br s, 2H, NH_2^+), 7.21 (m, 4H, ArH), 6.88 (s, 1H, ArH), 4.93 (dd, $J=5.28$, 11.2 Hz, 1H, CHN^+), 4.14 (s, 2H, $ArCH_2Ar$), 3.78 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 3.54–2.83 (m, 6H, two $ArCH_2$, N^+CH_2). Anal. calcd for ($C_{19}H_{21}NO_2{\cdot}H_2C_2O_4$): C, 65.44; H, 6.02; N, 3.63; found: C, 65.67; H, 6.24; N, 3.45.

Pharmacological methods

Binding assays: dopamine D_1 and D_2 receptors. [^{3}H]SCH 23390 (86 Ci/mmol) and [^{3}H]Spiperone (96 Ci/mmol) were purchased from Amersham International (England), dopamine HCl from Sigma, R-(−)-apomorphine HCl and ketanserin tartrate from Research Biochemicals Inc. All other reagents were obtained from commercial suppliers.

Striatal tissue was isolated from porcine brains. The striatum membranes were prepared as previously described.[17]

In brief, tissue was homogenised in 20 volumes of ice-cold 50 mM Tris–HCl buffer at pH 7.4 (buffer T), containing protease inhibitors (20 μg/mL soybean trypsin inhibitor, 200 μg/mL, and 160 μg/mL benzamidine), using an Ultra-Turrax TP-1810 (3×20 s). The homogenate was centrifuged for 10 min at 50,000 *g* at 4 °C. The resulting pellet was then washed once by resuspension in fresh buffer T and by centrifugation as before. The final pellet was frozen at −20 °C until the time of assay.

For D_1 and D_2 dopamine binding assay, the porcine striatal pellets were suspended in the incubation buffer 50 mM Tris–HCl buffer at pH 7.4. [^{3}H]SCH 23390 binding to D_1 receptors was assayed in a final incubation volume of 500 μL, which contained crude membranes (~0.2 mg of protein), radioligand (~0.5 nM; $K_d = 1.3$ nM) and the tested compound in the range 10^{-8}–10^{-3} M.

[^{3}H]Spiperone binding for D_2 receptors was assayed in a final incubation volume of 500 μL. Porcine striatal membranes (~0.2 mg of protein) were incubated with radioligand (~0.3 nM, $K_d = 0.71$ nM), 50 nM Ketanserin, to prevent binding of radioligand to 5-HT_{2A} receptors, and various concentrations (10^{-8}–10^{-3} M) of the tested compound. All assays were performed in duplicate. Dopamine was essayed in presence of the monoamine oxidase inhibitor pargyline (10 μM).

For both radioligand binding assays, the incubation was at 37 °C for 60 min and was terminated by dilution to 5 mL with ice-cold buffer T, followed immediately by rapid filtration through glass fibre Whatman GF/C filters. The filters were then washed (3×5 mL) with buffer T, and the amount of radioactivity retained on the filters was determined by Packard 1600 TR liquid scintillation counter at 66% efficiency. Non specific binding was defined in the presence of 2.5 mM dopamine.

The compounds were routinely dissolved in ethanol. The level of ethanol did not exceed 1% and was maintained constant in all tubes. For the active compounds, the IC_{50} values were determined and K_i values were derived according to the equation of Cheng and Prusoff.[18] Protein concentration was assayed by the method of Lowry et al.[19]

PRL release from anterior pituitary cell cultures. The assay was performed as previously described.[20] PRL concentrations were measured by a radioimmunoassay kit supplied by NIDDK's National Hormone and Pituitary Program, USA. The sensitivity of the assay was 50 pg/tube.

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