cis-1,2,3a,4,5,9b-Hexahydro-3*H*-benz[e]indoles: Synthesis and In Vitro Binding Affinity at Dopamine D1 and D2 Receptors

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Abstract □ *cis*-1,2,3a,4,5,9b-Hexahydro-3*H*-benz[e]indoles were synthesized and evaluated for in vitro dopamine D1 and D2 receptor binding affinity. The target compounds **21–25** were readily prepared by reduction of the air-sensitive tricyclic enamines **10–14**. Reduction of **10–14** with sodium borohydride, sodium cyanoborohydride, palladium on carbon in ethanol, and platinum oxide in ethanol or acetic acid gave only the *cis* **(3a,9b)** 1,2,3a,4,5,9b-hexahydro-3*H*-benz[e]indoles. The stereochemistry was confirmed by single-crystal X-ray analysis. In the 6-hydroxy series, the binding affinity at D1 and D2 receptors was of the order **22** (*N*-*n*-butyl) > **21** (*N*-*n*-propyl) > **23** (*N*-H). The compounds demonstrated greater binding affinity at D2 receptors than at D1 binding sites. In contrast, 8-OH derivatives exhibited affinity only for D2 receptors, with **25** (*N*-*n*-butyl) having slightly greater affinity than **24** (*N*-*n*-propyl).

Compounds containing the 3-phenylpyrrolidine nucleus have been extensively evaluated in a variety of behavioral and biochemical tests to determine dopaminergic activity.[1–3] The in vitro binding affinity of the 3-phenylpyrrolidines at dopamine D1 and D2 receptors was recently investigated.[4] Maximal binding affinity at D1 and D2 receptors was demonstrated with a catechol nucleus and an *n*-pentyl group on the ring nitrogen. Introduction of a *trans* 4-methyl group drastically reduces binding to both D1 and D2 receptors. However, a *cis* 4-methyl substituent increases D1 selectivity in some cases. Compounds having only a *meta*-hydroxyl group on the 3-phenyl substituent exhibit both D1 and D2 receptor affinity when a *n*-butyl group is present on the pyrrolidine ring nitrogen (**1a**, Table I). Apparently, the *n*-butyl substituent has a greater influence on binding at both D1 and D2 receptors than the presence of a catechol nucleus (**1b**, Table I) in this series of compounds.

As a continuation of our work on the dopaminergic activity of 3-phenylpyrrolidines, the synthesis of more rigid analogues of these compounds was of interest. Octahydrobenzo[f]quinolines have been evaluated in numerous tests to determine dopaminergic activity.[5–9] Dopaminergic activity in these compounds occurs only with the *trans* (**4a,10b**) isomers. Octahydrobenzo[f]quinolines having the *trans* stereochemistry are planar, rigid structures in which the dopamine moiety is in an antiperiplanar conformation. However, in the *cis* (**4a,10b**) isomers, the piperidine ring is almost perpendicular to the plane of the other two rings. Coplanarity of the nitrogen atom with the phenyl ring is thought to be an important

Table I—*cis*-1,2,3a,4,5,9b-Hexahydro-3*H*-benz[e]indoles

Compound	mp, °C	Method	Yield, %	Recrystallization Solvent[a]	Formula[b]	DA Receptor Binding[c] D1 K_i, nM[d]	DA Receptor Binding[c] D2 K_i, nM[d]
15	195–196[e]	C, D, E, F	50[f,g]	A	$C_{16}H_{24}ClNO$	—[h]	—
16	123–124[i]	D	48[g]	B	$C_{17}H_{26}ClNO$	—	—
17	206–207[j]	C, D, E	53[f,g]	B	$C_{20}H_{24}ClNO$	—	—
18	233–234	H	46	A	$C_{13}H_{18}ClNO$	—	—
19	142–143[k]	C, G	50[g,l]	B	$C_{16}H_{24}ClNO$	—	—
20	152–153[m]	C	63[g]	C	$C_{17}H_{26}ClNO$	—	—
21	228–230	I	24	D	$C_{15}H_{22}BrNO$	1994	575
22	225–226	I	65	D	$C_{16}H_{24}BrNO$	1730	308
23	269–270	I	49	D	$C_{12}H_{16}BrNO$[n]	>3000	2125
24	214–215	I	60	A	$C_{15}H_{22}BrNO$	>10 000[o]	1230
25	220–222	I	72	C	$C_{16}H_{24}BrNO$	>10 000[o]	1000
1a	—	—	—	—	—	540[p]	241[p]
1b	—	—	—	—	—	362[p]	95[p]
R(+)3-PPP	—	—	—	—	—	3740[q]	1300[q]
S(−)3-PPP	—	—	—	—	—	>1000[q]	190[q]
Quinpirole	—	—	—	—	—	>5000[q]	720[q]
SKF 38393	—	—	—	—	—	18[q]	9300[q]

[a] A = 2-Propanol, B = 2-propanol/Et_2O, C = 95% EtOH, D = absolute EtOH. [b] All compounds gave acceptable C, H, N analyses ± 0.4% of the calculated values, except where indicated. [c] [^{3}H]SCH 23390 and [^{3}H]spiperone were used as the D1 and D2 ligands, respectively. [d] K_i values were calculated from the expression, $K_i = IC_{50}/(1 + [L]/K_D)$, where IC_{50} is the concentration of compound causing 50% inhibition of specific binding, L is the concentration of the radioligand used, and K_D is the dissociation constant[23] of the radioligand ([^{3}H]SCH 23390, 0.14 nM; [^{3}H]spiperone, 0.08 nM); the results are the means of 2–3 experiments with 3–6 concentrations in each assay. [e] The bp of the free base, 145–150 °C at 0.7 mmHg. [f] Method C. [g] Yield of the free base. [h] —, Not determined. [i] The bp of the free base is 165–169 °C at 1.0 mmHg. [j] The bp of the free base is 170–173 °C at 0.3 mmHg. [k] The bp of the free base is 135–140 °C at 1.0 mmHg. [l] Method G. [m] The bp of the free base is 154–156 °C at 0.4 mmHg. [n] Calcd for C, 53.33; found, 52.33. [o] IC_{50}. [p] Reference 4. [q] Reference 24.

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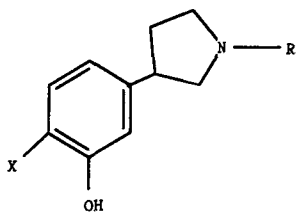
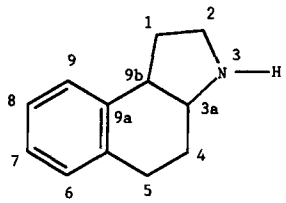


1a: X-H, R-$CH_2CH_2CH_2CH_3$

1b: X-OH, R-$CH_2CH_2CH_2CH_3$



2

determinant in dopamine receptor interactions.[10,11]

The benz[e]indole nucleus **2** is a ring-condensed analogue of the benzo[f]quinoline ring system. Synthesis of derivatives of **2** would allow incorporation of the 3-phenylpyrrolidine nucleus into a semirigid ring system. Although the benz[e]indole ring system has been synthesized, in most cases, substitution is present at the 9b position.[12–17]

This study was initiated to synthesize derivatives of **2** for in vitro dopamine D1 and D2 receptor binding affinity studies with [^{3}H]SCH 23390 (7-chloro-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3benzazepin-8-ol; Amersham, U.K.) and [^{3}H]spiperone as the D1 and D2 radioligands, respectively. Several structure–activity relationships were to be explored in this investigation. Because *cis* (**4a,10b**) benzo[f]quinolines lack dopaminergic activity, the synthesis of both *cis* (**3a,9b**) and *trans* (**3a,9b**) benz[e]indoles was of interest. A second objective of this work was to synthesize 6- and 8-monohydroxy derivatives of **2**. The related 7- and 9-hydroxybenzo[f]quinolines exhibit potent dopaminergic activity.[7,11] Also, *meta*-hydroxyphenylpyrrolidines were previously shown to exhibit potent binding affinity for D1 and D2 receptors (Table I).[4]

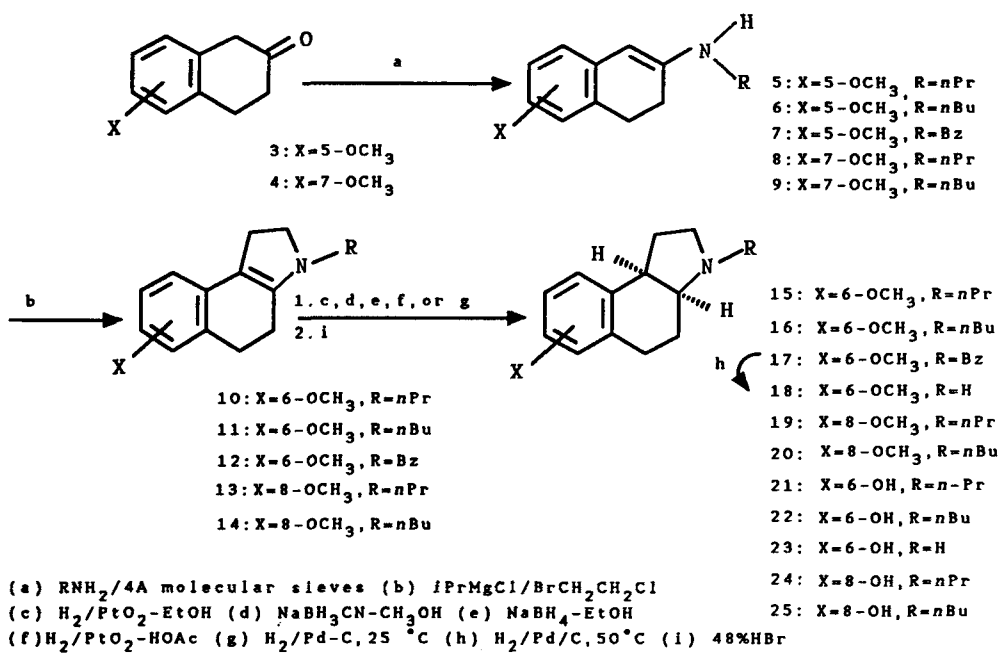
A final objective was to determine the effect of alkyl substitution on the ring nitrogen of 6- and 8-hydroxybenz[e]-indoles. A dopamine receptor model has been proposed in which two directions of the *N*-alkyl group are possible.[11] Similarly, Seiler and Markstein[18] proposed a rotamer-based model that defines both small and large alkyl binding sites. When fitted to either of these models, the *n*-butyl group of 9-hydroxybenzo[f]quinolines is directed toward a sterically restricted *N*-alkyl binding site that can maximally accommodate an *n*-propyl substituent. However, in the 7-hydroxybenzo[f]quinolines, replacement of the *n*-propyl group by an *n*-butyl group on the ring nitrogen leads to an increase in dopaminergic activity.[11] In this series, the *N*-alkyl substituent is directed upwards toward a sterically less restricted area on the dopamine receptor. Thus, evaluation of the dopamine D1 and D2 receptor binding affinity of 3-*n*-propyl- and 3-*n*-butylbenz[e]indole derivatives may add insight into the mode of binding of this series of compounds.

Results and Discussion

Chemistry—The synthesis of the desired hexahydro-3*H*-benz[e]indoles **21–25** was accomplished as shown in Scheme I, and the physicochemical properties are given in Table I. The key step in this reaction sequence involved the preparation of the tricyclic enamines **10–14** by the procedures of Evans et al.[12] and Kavadias et al.[13] The only products isolated in this reaction were the tricyclic enamines **10–14** in which the double bond is in the six-membered ring in conjugation with the benzene ring. If the double bond had been elsewhere, an olefinic proton would have been observed in the ^{1}H NMR spectra.[13] The 1,2,4,5-tetrahydro-3*H*-benz[e]indoles **10–14** were extremely air sensitive oils and could not be distilled. However, these compounds were stable under a nitrogen atmosphere when stored at 0 °C and were used directly in the synthesis of **15–20** without purification.

Reduction of the tricyclic enamines **10–14** was expected to give mixtures of the *cis*- and *trans*-hexahydrobenz[e]indoles. The only known report concerning the stereochemistry of the reduction of 1,2,4,5-tetrahydro-3*H*-benz[e]indoles dealt with compounds having 9b-alkyl substitution. In this case, catalytic hydrogenation with platinum oxide gave only the *cis* isomers.[15]

The related hexahydrobenzo[f]quinolines have been reduced by various methods to give mixtures of *cis*- and *trans*-octahydrobenzo[f]quinolines. Catalytic reduction with platinum oxide or palladium on carbon in ethanol gave predominately *cis* stereochemistry,[19] whereas reduction with



Scheme I

sodium borohydride or sodium cyanoborohydride gave equal mixtures of *cis* and *trans* or mixtures with mostly *trans* stereochemistry.[9,19] Higher percentages of the *trans* isomers were produced with platinum oxide in acetic acid.[19]

Based on the ^{13}C NMR spectra, catalytic and metal hydride reduction (methods C–G) of the tricyclic enamines **10–14** consistently gave only one isomer. The stereochemistry of the hexahydro-3*H*-benz[e]indoles **15–20** could not be established by examination of the bridgehead protons (*3a,9b*). In the octahydrobenzo[f]quinolines, the ^1H NMR of the *N*-benzyl derivatives produced spectra that were consistent with spectra obtained with octahydrobenzo[g]quinolines.[19,20] The methylene protons of the *N*-benzyl substituent gave an AB quartet with a large chemical shift difference in the *trans* isomers (48–60 Hz). In the *cis* isomers, the methylene protons produced singlets or an AB quartet with a small chemical shift difference (1–24 Hz). The ^1H NMR spectrum of the 3-benzyl-1,2,3a,4,5,9b-hexahydro-3*H*-benz[e]indole **17** produced an AB quartet with a chemical shift difference of 61 Hz, suggesting *trans* geometry.

A single-crystal X-ray study of **17** was used to determine the stereochemistry of the ring junction. The arbitrary numbering system for **17** is shown in Figure 1, and the final fractional coordinates are given in Table II. This compound crystallizes as the hydrochloride salt with four molecules in the unit cell. The nitrogen atom is protonated, and hydrogen is bonded to the chloride [N . . . Cl, 3.019(2) Å; N-H . . . Cl, 161.9(1.7)°]. The orientation of the hydrogen atoms at C9 and C10 are *cis* with respect to the C9-C10 bond.[21] There are no unusual intramolecular bond distances or angles.[22]

Molecular models reveal that the *cis*-1,2,3a,4,5,9b-hexahydro-3*H*-benz[e]indoles are more flexible structures than the corresponding *trans*-diastereoisomers. Thus, reduction of 1,2,4,5-tetrahydro-3*H*-benz[e]indoles leads to the conformationally less restrained *cis*-diastereoisomers. Because all reduction methods (methods C–G) gave only one diastereoisomer, the stereochemistry for the final products (**21–25**) is assumed to be *cis*.

Pharmacology—The in vitro binding affinity of the 6- and 8-hydroxyhexahydro-3*H*-benz[e]indoles **21–25** at dopamine D1 and D2 receptors was evaluated in rat striatal tissue with [^3H]*SCH 23390* and [^3H] spiperone as the D1 and D2 radioligands, respectively (Table I).[23,24] The 6-hydroxyhexahydro-3*H*-benz[e]indoles **21** and **22** exhibited greater affinity for both D1 and D2 receptors than the corresponding 8-hydroxy isomers **24** and **25**. Replacement of the *N*-*n*-propyl substituent (**21**) with *n*-butyl (**22**) slightly increased D1 and D2 binding affinity in the 6-hydroxy series. The same trend was seen with 8-hydroxy derivatives at D2 receptors. However, **24** and **25** were essentially inactive at D1 receptors. The binding affinity of *R*(+)[3-(3-hydroxy)phenyl-1-*N*-*n*-propylpiperidine], *S*(−)-[3-(3-hydroxy)phenyl-1-*N*-*n*-propylpiperidine] quinpirole, and SKF 38393 (7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine) at D1 and D2 receptors is given in Table I for comparison.[24]

The hexahydrobenz[e]indoles exhibit significant differences in binding at D1 and D2 binding sites from the corresponding 7 and 9-hydroxybenzo[f]quinolines. In contrast to the 9-hydroxybenzo[f]quinolines, replacement of the 3-*n*-propyl group in **24** by a *n*-butyl group (**25**) does not lead to a decrease in activity.[11] A second major difference is that in the benz[e]indoles, unlike the benzo[f]quinolines, affinity for dopamine receptors is demonstrated in compounds with the *cis* stereochemistry.

The torsion angles of the *cis*- and *trans*-octahydrobenzo[f]quinolines (Ar-C_1-C_{10b}-C_{4a}-N) and *cis*-hexahydro-3*H*-benz[e]indoles (Ar-C_1-C_{9b}-C_{3a}-N) are 152, 173, and 151°, respectively.[25] Thus, the low affinity of *cis*-1,2,3a,4,5,9b-hexahydro-3*H*-benz[e]indoles for dopamine D1 and D2 receptors may be due to the inability to attain a *trans* (antiperiplanar) conformation. This conformation is preferred by most dopamine agonists.[10,26] In the *trans* conformation for dopamine, the torsion angle (Ar-C_1-C-C-N) approaches 180°.

Incorporation of the 3-phenylpyrrolidine nucleus into the more rigid *cis*-hexahydrobenz[e]indole ring system does not result in greater affinity for D1 and D2 receptors. A comparison of the 3-*n*-butyl derivative **22** with the monohydroxyphenylpyrrolidine **1a** indicates that **1a** has ~3.2 and 1.3 times the affinity at D1 and D2 receptors, respectively. The catechol derivative **1b**, with an *N*-*n*-butyl substituent, has even greater affinity than **22** at D1 and D2 binding sites. Further studies involving biochemical and behavioral tests are necessary to completely describe the pharmacological activity of these benz[e]indole derivatives.

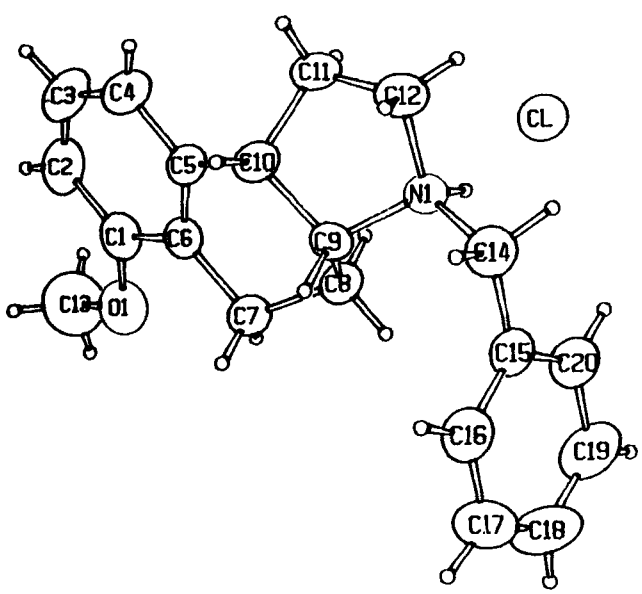


Figure 1—ORTEP diagram of 3-benzyl-6-methoxy-1,2,3a,4,5,9b-hexahydro-3*H*-benz[e]indole hydrochloride (**17**) drawn at 50% probability level.

Experimental Section

Chemistry—All reagents and solvents were purchased and used as received. Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. IR spectra were recorded as KBr pellets or as liquid films on a Nicolet 5MX FT spectrometer. The ^1H and ^{13}C NMR spectra were recorded at 89.55 and 22.49 MHz on a JEOL FX 90Q spectrometer or at 300 and 75 MHz on a Varian VXR 300 MHz spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane or, in the case of D_2O, relative to sodium 2,2-dimethyl-2-silapentane-5-sulfonate. (Elemental analyses are available upon request from the author.)

Method A: Synthesis of *N*-Substituted 3,4-Dihydronaphthalenes (5–9)—*5-Methoxy-2-(N-propylamino)-3,4-dihydronaphthalene (5)*—Under N_2, the 2-tetralone **3**[27] (1.76 g, 10 mmol), dissolved in a minimum amount of Et_2O (10 mL), was added in a dropwise manner to a solution of *n*-propylamine (0.72 g, 12 mmol) in Et_2O (10 mL) containing 4A molecular sieves (4 g).[28] With occasional shaking, the reaction was followed by IR spectroscopy to monitor the disappearance of the C=O peak at ~1715 cm^{-1} and the appearance of the C=C—N peak at ~1635 cm^{-1}. The mixture was filtered, and the solvent was removed under reduced pressure to yield an oil. Vacuum distillation gave 1.6 g (73%) of **5**, bp 157–161 °C (0.6 mmHg; lit.[29] no reported bp); IR (neat): 1634 (C=C—N) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.97 (t, 3 H, CH_3), 1.61 (m, 2 H, CH_2CH_3), 2.22–3.10 (m, 6 H, $ArCH_2CH_2$ and NCH_2), 3.78 (s, 3 H, OCH_3), 5.19 (s, 1 H, ArCH=C), 6.77 (m, 3 H, ArH); MS: m/z 217 (M^+). The elemental analyses of the bicyclic enamines **5–9** were not performed because of their air

Table II—Positional Parameters and Their Estimated Standard Deviations[a]

Atom	x	y	z	B, Å^2
Cl	−0.02249(4)	0.28920(4)	0.45756(4)	4.07(1)
O1	0.4243(1)	0.0564(1)	0.26147(9)	4.80(3)
N1	0.2137(1)	0.1999(1)	0.61135(9)	2.80(3)
C1	0.3716(2)	−0.0111(2)	0.3152(1)	3.69(4)
C2	0.3358(2)	−0.1225(2)	0.2901(2)	4.80(5)
C3	0.2824(2)	−0.1822(2)	0.3488(2)	5.18(6)
C4	0.2650(2)	−0.1334(2)	0.4322(2)	4.34(5)
C5	0.3021(2)	−0.0218(1)	0.4592(1)	3.17(4)
C6	0.3551(1)	0.0402(2)	0.4002(1)	3.05(4)
C7	0.3899(2)	0.1623(2)	0.4249(1)	3.31(4)
C8	0.3042(2)	0.2176(1)	0.4726(1)	3.16(4)
C9	0.3110(1)	0.1557(1)	0.5697(1)	2.80(3)
C10	0.2850(2)	0.0278(2)	0.5540(1)	3.16(4)
C11	0.1543(2)	0.0153(2)	0.5563(1)	3.90(4)
C12	0.1503(2)	0.0990(2)	0.6356(1)	3.88(4)
C13	0.4301(3)	0.0148(3)	0.1672(2)	7.19(7)
C14	0.2583(2)	0.2822(2)	0.6991(1)	3.65(4)
C15	0.3246(2)	0.3811(2)	0.6755(1)	3.30(4)
C16	0.4507(2)	0.3885(2)	0.7199(2)	4.44(5)
C17	0.5127(2)	0.4781(2)	0.6984(2)	6.11(6)
C18	0.4486(2)	0.5605(2)	0.6317(2)	6.71(7)
C19	0.3228(2)	0.5559(2)	0.5883(2)	5.39(6)
C20	0.2607(2)	0.4662(2)	0.6103(1)	3.89(4)

[a] Anisotropically refined atoms are given in the form of the isotropic equivalent displacement parameter defined as follows: (4/3) · [a2 · B(1,1) + b2 · B(2,2) + c2 · B(3,3) + ab(cos gamma) · B(1,2) + ac(cos beta) · B(1,3) + bc(cos alpha) · B(2,3)].

sensitivity. These compounds were used directly in the synthesis of **10–14** (method B). The following compounds were synthesized by method A.

*2-(*N*-Butylamino)-5-methoxy-3,4-dihydronaphthalene (6)*—The tetralone **3** (7.35 g, 42 mmol) and *n*-butylamine (3.7 g, 50 mmol) afforded 4.75 g (49%) of **6**, bp 173–176 °C (1.3 mm) (lit.[29] no reported bp); IR (neat): 1632 (C=C—N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.96 (t, 3 H, CH_3), 2.50–3.09 (m, 10 H, ring CH_2 and $NCH_2CH_2CH_2$), 3.79 (s, 3 H, OCH_3), 5.19 (s, 1 H, ArCH=C), 6.76 (m, 3 H, ArH).

*2-(*N*-Benzyl)-5-methoxy-3,4-dihydronaphthalene (7)*—The 2-tetralone **3** (9.5 g, 54 mmol) and benzylamine (5.8 g, 54 mmol) gave 10.3 g (72%) of **7** as an oil (lit.[30] no reported bp); IR (neat): 1630 (C=C—N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.28 (m, 2 H, $ArCH_2CH_2$), 2.87 (m, 2 H, $ArCH_2CH_2$), 3.77 (s, 3 H, OCH_3), 4.24 (m, 2 H, $ArCH_2N$), 5.28 (s, 1 H, ArCH=C), 6.47–7.32 (m, 8 H, ArH).

*7-Methoxy-2-(*N*-propylamino)-3,4-dihydronaphthalene (8)*—Following the general procedure, 4[9] (4.9 g, 28 mmol) and *n*-propylamine (1.97 g, 33 mmol) gave 3.7 g (61%) of **8**, bp 162–172 °C (0.7 mmHg; lit.[11] no reported bp); IR (neat): 1635 (C=C—N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.99 (t, 3 H, CH_3), 1.63 (m, 2 H, CH_2CH_3), 2.24 (m, 2 H, $ArCH_2CH_2$), 2.76 (m, 2 H, $ArCH_2CH_2$), 3.03 (t, 2 H, NCH_2), 3.76 (s, 3 H, OCH_3), 6.65 (m, 3 H, ArH).

*2-(*N*-Butylamino)-7-methoxy-3,4-dihydronaphthalene (9)*—The tetralone **4** (12.5 g, 71 mmol) and *n*-butylamine (6.4 g, 104 mmol) yielded 13.3 g (81%) of **9**, bp 164–170 °C (0.8 mmHg; lit.[11] no reported bp); IR (neat): 1635 (C=C—N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.90 (m, 3 H, CH_3), 1.43–2.99 (m, 10 H, ring CH_2 and $NCH_2CH_2CH_2$), 5.10 (s, 1 H, ArCH=C), 6.57 (m, 3 H, ArH).

Method B: Synthesis of *N*-Substituted 1,2,4,5-Tetrahydro-3*H*-benz[e]indoles (10–14)—*6-Methoxy-3-(*n*-propyl)-1,2,4,5-tetrahydro-3*H*-benz[e]indole (10)*—With the method of Kavadias et al.,[13] a solution of **5** (6.0 g, 28 mmol) in tetrahydrofuran (THF, 10 mL) was placed into a flask equipped with a reflux condenser, septum cap, and an addition funnel under a N_2 atmosphere. A solution of 2 M *i*-propylmagnesium chloride (17.4 mL, 35 mmol) in THF was added slowly with a syringe at such a rate as to maintain gentle refluxing. Then, $BrCH_2CH_2Cl$ (5.07 g, 35 mmol) was added to the stirred solution in a dropwise manner while maintaining controlled refluxing. The reaction mixture was cooled in an ice bath, and 1 M ethylenediaminetetraacetic acid tetrasodium salt (45 mL) was added slowly with vigorous stirring. A 1:1 mixture of Et_2O and benzene (100 mL) was added, and the aqueous phase was extracted with Et_2O (100 mL). The combined organic phase was washed with H_2O (2 × 10 mL), dried (Na_2SO_4), and evaporated to give 6.8 g (100%) of **10** as a dark oil; IR (neat): 1638 (C=C—N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.93 (t, 3 H, CH_3), 1.54 (m, 2 H, CH_2CH_3), 2.21–3.39 (m, 10 H, ring CH_2 and NCH_2), 3.79 (s, 3 H, OCH_3), 6.79 (m, 3 H, ArH). Due to the extreme air sensitivity of **10–14**, elemental analyses were not obtained (with the exception of **12**) and the compounds were used directly in the synthesis of **15–20**.

*3-(*n*-Butyl)-6-methoxy-1,2,4,5-tetrahydro-3*H*-benz[e]indole (11)*—Compound **6** (4.75 g, 21 mmol), 2 M *i*-propylmagnesium chloride (20 mL, 40 mmol), and $BrCH_2CH_2Cl$ (3.8 g, 21 mmol) afforded 5.2 g (98%) of **11** as an oil; IR (neat): 1628 (C=C—N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.94 (t, 3 H, CH_3), 1.42–3.72 (m, 14 H, ring CH_2 and $NCH_2CH_2CH_2$), 3.81 (s, 3 H, OCH_3), 6.80 (m, 3 H, ArH).

*3-Benzyl-6-methoxy-1,2,4,5-tetrahydro-3*H*-benz[e]indole (12)*—The bicyclic enamine **7** (10.3 g, 38.7 mmol), 2 M *i*-propylmagnesium chloride (29 mL, 58 mmol), and $BrCH_2CH_2Cl$ (6.9 g, 38.7 mmol) gave 10.4 g (92%) of **12** as an oil; IR (neat): 1630 (C=C—N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.39–3.38 (m, 8 H, ring CH_2), 3.80 (s, 3 H, OCH_3), 4.12 (s, 2 H, $CH_2C_6H_5$), 6.86 (m, 8 H, ArH).

Anal.—Calcd for $C_{20}H_{21}NO$: H, N, C (calcd, 82.47; found 81.61).

*8-Methoxy-3-(*n*-propyl)-1,2,4,5-tetrahydro-3*H*-benz[e]indole (13)*—The enamine **8** (3.7 g, 17 mmol), 2 M *i*-propylmagnesium chloride (16.0 mL, 32 mmol), and $BrCH_2CH_2Cl$ (3.0 g, 21 mmol) yielded 3.8 g (93%) of **13**; IR (neat): 1630 (C=C—N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.93 (t, 3 H, CH_3), 1.55 (m, 2 H, CH_2CH_3), 2.21–3.42 (m, 10 H, ring CH_2 and NCH_2), 3.77 (s, 3 H, OCH_3), 6.67 (m, 3 H, ArH).

*3-(*n*-Butyl)-8-methoxy-1,2,4,5-tetrahydro-3*H*-benz[e]indole (14)*—Compound **9** (13.3 g, 57.7 mmol), 2 M *i*-propylmagnesium chloride (54 mL, 109 mmol), and $BrCH_2CH_2Cl$ (10.2 g, 71 mmol) afforded 14.8 g (98%) of **14** as a dark brown oil; IR (neat): 1628 (C=C—N) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.94 (m, 3 H, CH_3), 1.43–3.41 (m, 14 H, ring CH_2 and $NCH_2CH_2CH_2$), 3.77 (s, 3 H, OCH_3), 6.66 (m, 3 H, ArH).

Method C: Synthesis of *cis*-6-Methoxy-3-(*n*-propyl)-1,2,3a,4,5,9b-hexahydro-3*H*-benz[e]indole (15) with Platinum Oxide in Ethanol—The enamine **10** (6.8 g, 28 mmol) and Pt_2O (266 mg) in EtOH (60 mL) was hydrogenated overnight on a Parr apparatus at 50 psi.[31] The catalyst was filtered, and the solvent was evaporated under reduced pressure to afford an oil. Vacuum distillation gave 3.4 g (50%) of **15**; ^{1}H NMR ($CDCl_3$): δ 0.92 (t, 3 H, CH_3), 1.42–3.49 (m, 14 H, ring CH, ring CH_2, and NCH_2), 3.79 (s, 3 H, OCH_3), 6.68 (m, 3 H, ArH); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 12.2 ($NCH_2CH_2CH_3$), 19.1 (C-5), 22.0 ($NCH_2CH_2CH_3$), 25.5 (C-4), 33.6 (C-1), 41.0 (C-9b), 52.9 (C-2), 56.7 (NCH_2), 62.1 (C-3a), 106.8 (C-7), 120.9 (C-9), 126.2 (C-8), 126.3 (C-5a), 142 (C-9a), and 156.4 (C-6); MS: *m/z* 245 (M^+).

An analytical sample was prepared by formation of the hydrochloride salt. The following compounds were synthesized by method C.

*cis-3-Benzyl-6-methoxy-1,2,3a,4,5,9b-hexahydro-3*H*-benz[e]indole (17)*—Compound **12** (15.0 g, 52 mmol) and PtO_2 (0.5 g) in EtOH (100 mL) gave, after vacuum distillation, 8.1 g (53%) of **17**; ^{1}H NMR

($CDCl_3$): δ 1.44–3.36 (m, 10 H, ring CH and CH_2), 3.37 (d, 1 H, J = 13 Hz, NCH_2), 3.79 (s, 3 H, OCH_3), 4.05 (d, 1 H, J = 13 Hz, NCH_2), 6.98 (m, 8 H, ArH); ^{13}C NMR ($CDCl_3$); δ 18.6, 25.7, 33.9, 41.4, 53.2, 55.6, 58.5, 62.0, 107.3, 121.3, 126.4, 127.1, 128.4, 129.1, 140.4, 142.6, and 157.0.

An analytical sample was prepared by formation of the hydrochloride salt.

*cis-8-Methoxy-3-(*n*-propyl)-1,2,3a,4,5,9b-hexahydro-3*H*-benz[e]indole (19)*—Compound **13** (7.7 g, 32 mmol) and PtO_2 (314 mg) yielded 2.1 g (27%) of **19**; ^1H NMR ($CDCl_3$): δ 0.92 (m, 3 H, CH_3), 1.43–3.36 (m, 12 H, ring CH, ring CH_2, and NCH_2CH_2), 3.76 (s, 3 H, OCH_3), 6.75 (m, 3 H, ArH); ^{13}C NMR ($CDCl_3$): δ 12.1, 22.1, 25.9, 27.2, 34.1, 41.9, 53.2, 55.4, 62.7, 111.6, 114.0, 129.1, 130.4, 141.9, and 158.4.

The hydrochloride salt was prepared to yield an analytical sample.

*cis-3-(*n*-Butyl)-8-methoxy-1,2,3a,4,5,9b-hexahydro-3*H*-benz[e]indole (20)*—The enamine **14** (14.8 g, 58 mmol) and PtO_2 (0.56 g) gave 9.5 g of **20**; ^1H NMR ($CDCl_3$): δ 0.93 (t, 3 H, CH_3), 1.46–3.36 (m, 16 H, ring CH, ring CH_2, and $NCH_2CH_2CH_2$), 3.76 (s, 3 H, OCH_3), 6.82 (m, 3 H, ArH); ^{13}C NMR ($CDCl_3$): δ 14.2, 21.0, 25.9, 27.3, 31.2, 34.1, 41.8, 53.2, 54.6, 55.5, 62.7, 111.3, 114.0, 129.1, 130.4, 142.1, and 158.3.

The preparation of the hydrochloride gave analytically pure **20** · HCl.

Method D: Synthesis of *cis*-3-(*n*-Butyl)-6-methoxy-1,2,3a,4,5,9b-hexahydro-3*H*-benz[e]indole (16) with Sodium Cyanoborohydride—The enamine **11** (4.7 g, 18 mmol) was dissolved in Et_2O (300 mL) and etheral hydrogen chloride was added until precipitation was complete.[9] The mixture was placed in the freezer for 15 min, and the Et_2O was decanted. The residue was dissolved in a mixture of MeOH (92 mL) and THF (275 mL), cooled to −30 °C, and treated with $NaBH_3CN$ (2.1 g, 33 mmol) under N_2 while maintaining the temperature at −25 °C. The reaction mixture was stirred for 2 h, allowed to warm to room temperature, poured into H_2O, and basified with solid Na_2CO_3. The mixture was extracted with CH_2Cl_2 (3 × 100 mL), and the combined extracts were dried (Na_2SO_4), filtered, and evaporated. Removal of the solvent under reduced pressure gave an oil. Vacuum distillation afforded 2.2 g (48%) of **16**; ^1H NMR ($CDCl_3$): δ 0.92 (t, 3 H, CH_3), 1.24–3.38 (m, 16 H, ring CH, ring CH_2, and $NCH_2CH_2CH_2$), 3.81 (s, 3 H, OCH_3), 6.87 (m, 3 H, ArH); ^{13}C NMR ($CDCl_3$): δ 13.9, 19.0, 20.8, 25.7, 31.0, 33.6, 41.4, 53.0, 54.3, 55.4, 62.3, 107.3, 121.1, 126.2, 126.6, 142.3, and 157.0.

A hydrochloride salt was prepared to yield analytically pure **16** · HCl.

Compounds **15** and **17** were also synthesized by this method. For **15**, the enamine **10** (5.0 g, 21 mmol) and $NaBH_3CN$ (6.1 g, 97 mmol) were combined to yield 2.25 g (38%) of **15**, bp 124–126 °C (0.5 mmHg). The ^1H and ^{13}C NMR spectra of the HCl salt were identical to those of the HCl salt of **15** prepared by method C. For **17**, **12** (1.5 g, 5.15 mmol) and $NaBH_3CN$ (1.5 g, 23.4 mmol) were combined to yield 0.7 g (45%) of **17**. The ^1H and ^{13}C NMR spectra were identical to those obtained for **17** synthesized by method C.

Method E: Reduction of 10 with Sodium Borohydride in Ethanol—The enamine **10** (3.3 g, 13.6 mmol) was dissolved in absolute EtOH (200 mL), and $NaBH_4$ (0.54 g, 14.2 mmol) was added under a N_2 atmosphere.[19] After stirring for 3 h, the reaction mixture was cooled and acidified with HOAc. The solvents were evaporated, and the residue was basified with saturated $NaHCO_3$ solution. The basic solution was extracted with Et_2O (3 × 100 mL). The combined Et_2O extracts were washed with H_2O (1 × 100 mL), dried (Na_2SO_4), filtered, and evaporated. Vacuum distillation gave 1.8 g (53%) of **15** bp 151–156 °C (1 mmHg). The ^1H and ^{13}C NMR spectra were identical to those obtained for **15** prepared by method C.

Synthesis of 17 by Method E—Compound **12** (4.3 g, 14.8 mmol) and $NaBH_4$ (0.6 g, 15.5 mmol) gave, after flash chromatography on SiO_2 with CH_2Cl_2:hexane (25:75) as the solvent, 1.0 g (23%) of **17**. The ^1H and ^{13}C NMR spectra were identical to those obtained for **17** prepared by method C.

Method F: Reduction of 10 with Platinum Oxide in Acetic Acid—Compound **10** (3.0 g, 12 mmol) in HOAc (50 mL) was shaken overnight on a Parr hydrogenator at 50 psi in the presence of PtO_2 (120 mg).[19] The catalyst was filtered, and the reaction mixture was treated with saturated $NaHCO_3$ and then with 40% NaOH solution to adjust the pH to 9–10. The solution was extracted with CH_2Cl_2 (3 × 50 mL), and the combined CH_2Cl_2 extracts were washed with H_2O (1 × 100 mL), dried (Na_2SO_4), filtered, and evaporated. Vacuum distillation of the residue gave 1.3 g (44%) of **15**, bp 150–155 °C (1 mmHg). The ^1H and ^{13}C NMR spectra were identical to those for **15** synthesized by method C.

Method G: Reduction of 13 with Palladium on Carbon—*Synthesis of* cis-*8-Methoxy-3-(*n*-propyl)-1,2,3a,4,5,9b-hexahydro-3*H*-benz[e]indole (19)*—A mixture of **13** (3.8 g, 16 mmol) and 10% Pd/C (380 mg) in EtOH (100 mL) was shaken for 24 h on a Parr hydrogenator at an initial pressure of 50 psi. The catalyst was filtered, and the solvent was evaporated under reduced pressure to give 1.9 g of **19**; ^1H NMR ($CDCl_3$): δ 0.92 (t, 3 H, CH_3), 1.43–3.36 (m, 12 H, ring CH, ring CH_2, and NCH_2CH_2), 3.76 (s, 3 H, OCH_3), 6.75 (m, 3 H, ArH); ^{13}C NMR ($CDCl_3$): δ 12.1, 22.1, 25.9, 27.2, 34.1, 41.9, 53.2, 55.4, 56.9, 62.7, 111.5, 114.0, 129.1, 130.4, 142.0, and 158.4.

A hydrochloride salt was prepared to afford an analytical sample.

Method H: Synthesis of *cis*-6-Methoxy-1,2,3a,4,5,9b-hexahydro-3*H*-benz[e]indole Hydrochloride (18)—A mixture of **17** (6.0 g, 18 mmol) and 10% palladium on carbon (3.0 g) in ethanolic HCl (100 mL) was shaken overnight on a Parr hydrogenator at 50 psi and 50 °C. The catalyst was filtered, and the solvent was evaporated to afford a solid. Recrystallization produced 2.0 g of **18**; ^1H NMR (CD_3OD): δ 1.81–4.39 (m, 10 H, including s at 3.99, OCH_3), 7.36 (m, 3 H, ArH); ^{13}C NMR ($CDCl_3$, free base): δ 20.2, 27.8, 35.6, 42.3, 45.8, 55.5, 56.5, 107.2, 121.7, 125.9, 126.5, 141.2, and 156.8.

Method I: Methyl Ether Cleavage—*Synthesis of* cis-*6-Hydroxy-3-(*n*-propyl)-1,2,3a,4,5,9b-hexahydro-3*H*-benz[e]indole Hydrobromide (21)*—A mixture of **15** (2.0 g, 8 mmol) and 48% HBr (20 mL) was refluxed under N_2 for 2 h. Evaporation of the solvent followed by azeotropic distillation with absolute EtOH afforded a brown solid. Recrystallization gave 0.6 g of **21**; ^1H NMR (CD_3OD): δ 1.26 (t, 3 H, CH_3), 1.92–4.27 (m, 14 H, ring CH, ring CH_2, and NCH_2CH_2), 6.96 (m, 3 H, ArH). The following compounds were synthesized by method I.

*cis-3-(*n*-Butyl)-6-hydroxy-1,2,3a,4,5,9b-hexahydro-3*H*-benz[e]indole Hydrobromide (22)*—Compound **16** (1.0 g, 3.9 mmol) and 48% HBr (10 mL) afforded 0.8 g of **22**; ^1H NMR (CD_3OD): δ 1.08 (t, 3 H, CH_3), 1.42–3.96 (m, 16 H), 6.92 (m, 3 H, ArH).

*cis-6-Hydroxy-1,2,3a,4,5,9b-hexahydro-3*H*-benz[e]indole Hydrobromide (23)*—Compound **18**) (1.5 g, 7.39 mmol) and 48% HBr (15 mL) gave 1.1 g of **23**; ^1H NMR (CD_3OD): δ 1.79–4.23 (m, 10 H), 6.94 (m, 3 H, ArH); MS: *m/z* 189 (M^+, free base).

*cis-8-Hydroxy-3-(*n*-propyl)-1,2,3a,4,5,9b-hexahydro-3*H*-benz[e]indole Hydrobromide (24)*—Compound **19** (1.0 g, 4.12 mmol) and 48% HBr (10 mL) gave 0.8 g of **24**; ^1H NMR (CD_3OD): δ 1.03 (t, 3 H, CH_3), 1.68–3.96 (m, 14 H, ring CH, ring CH_2, and NCH_2CH_2), 6.74 (m, 3 H, ArH).

*cis-3-(*n*-Butyl)-8-hydroxy-1,2,3a,4,5,9b-hexahydro-3*H*-benz[e]indole Hydrobromide (25)*—Compound **20** (1.0 g, 3.9 mmol) and 48% HBr (10 mL) yielded 0.9 g of **25**; ^1H NMR (D_2O): δ 1.09 (t, 3 H, CH_3), 1.41–4.06 (m, 16 H), and 6.87 (m, 3 H, ArH).

[^{3}H] SCH 23390 Binding—Male Wistar rats weighing 130–200 g (Molleggaards Breeding Labs., Lille Skensved, Denmark) were used for all in vitro binding studies. Rat striatal tissue was processed as previously described.[23,24] Briefly, the tissue was homogenized gently by hand with a glass-teflon homogenizer (10 strokes) in 100 volumes of 10 mM imidazole · HCl (pH 7.4 to 25 °C) containing 2 mM EDTA and centrifuged at 25 000 × *g* for 20 min at 4 °C. The pellet was resuspended in 100 volumes of the same buffer and the homogenization/centrifugation step was repeated a total of three times. The final pellet was resuspended in 100 volumes of 2 mM imidazole · HCl (pH 7.4 at 25 °C) containing 2 mM EDTA and used immediately for the binding assays. A mixture of 100 μL of the rat striatal tissue suspension, 600 μL of 16.67 mM imidazole · HCl (pH 7.4 at 25 °C) containing 16.67 mM theophylline, 1 mM ethylene glycol-bis(β-aminoethyl ether)-*N,N,N',N'*-tetraacetic acid (EGTA), and 10 mM $MgSO_4$, 100 μL of [^{3}H]SCH 23390 (Amersham, U.K., 73.4 Ci/mmol, final concentration 0.2 nM), and 200 μL of H_2O, test compound, or 1 μM *cis*-flupentixol (for control, compound testing, or nonspecific binding studies, respectively) was incubated at 30 °C for 60 min followed by rapid filtration through Whatman GF/B filters under reduced pressure. The filters were washed with 2 × 10 mL of 0.9% NaCl, and the radioactivity was determined in 4 mL of scintillation fluid by counting in a conventional counter. Binding data were fitted using the EBDA-scarfit software package obtained from Elsevier Biosoft.

[^{3}H]Spiperone Binding—As previously described,[23,24] rat striatal tissue was homogenized in 2 × 10 mL of 50 mM Tris HCl (pH 7.4 at 30 °C) containing 120 mM NaCl and 4 mM $MgCl_2$ with a polytron homogenizer and centrifuged for 10 min at 40 000 × *g*. The pellet was resuspended in 1000 volumes (original wet weight) and used imme-

diately for the D2 binding assay. The assay mixture consisted of 2.5 mL of tissue suspension, 25 μL of [^{3}H]spiperone (New England Nuclear, Boston, MA; final concentration 0.05 nm), 25 μL of H_2O, test compound or 100 nM domperidone (for control, compound testing, or nonspecific binding studies, respectively). Incubation was carried out at 30 °C for 20 min, followed by 10 min on ice. The reaction was terminated by rapid filtration through Whatman GF/B filters, followed by a 2 × 10-mL wash with 0.9% NaCl. Radioactivity trapped on the filters was measured by conventional scintillation counting.

Crystallography—A single colorless crystal with dimensions 0.40 × 0.35 × 0.50 mm was mounted on an Enraf-Nonius CAD4 diffractometer with a Mo target X-ray tube (λ = 0.70930 Å) and a graphite crystal monochromator. The compound was found to crystallize in space group $P2_1/n$, with unit cell dimensions of a = 11.569(2), b = 11.821(3), c = 13.881(2) Å, β = 110.13(1)°, and V = 1782.3 Å^3. The calculated density, D_x, was 1.23 g/mL for Z = 4 and a formula weight of 328.66 g/mol. Three-dimensional intensity data were collected in the ω:2Θ scan mode. A total of 3447 reflections were collected to a sin Θ/λ maximum of 0.59 Å^{-1}. Data were corrected for Lorentz and polarization effects. Absorption as a function of psi was corrected empirically (minimum transmittance 95.63%). Three standard reflections measured every 2 h during data collection showed a small amount (2.9%) of decay, which was corrected with a linear decay model.

The structure was solved by direct methods with the MULTAN[32] series of programs that revealed the location of 22 atoms on the initial E map. A subsequent Fourier map revealed the location of one remaining atom. All hydrogen atoms were calculated on the basis of sp^2 or sp^3 geometry and a C—H bond distance of 0.95 Å. The structure was refined by least-squares minimization of the function $\Sigma w(F_o - F_c)^2$, with anisotropic thermal parameters for all nonhydrogen atoms, and with hydrogen atom positions and temperature factors refined. With 2124 independent, observed reflections [$I > 3\sigma(I)$] led to a final R of 0.033 and R_w of 0.042.[33] There were no peaks > 0.23 e/Å^3 on the final difference Fourier map.

All computer programs used for data collection and refinement are part of the CAD4-MOlen package.[34] Scattering factors were taken from the *International Tables for X-ray Crystallography*[35] and included corrections for anomalous scattering contributions.

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