Eur J Med Chem (1995) 30, 943–948

Short communication

Synthesis and evaluation of *cis*-1-methyl-3-*n*-propyl-2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]indoles for *in vitro* dopamine D_1 and D_2 receptor binding affinity

D Ghosh[1,2], CL Klein[3], B Garner[3], PH Andersen[4], AM Crider[1]*

[1]*School of Pharmacy, Northeast Louisiana University, Monroe, LA 71209;*
[2]*Purdue University, School of Pharmacy and Pharmacal Sciences, West Lafayette, IN 47907;*
[3]*Department of Chemistry, Xavier University of Louisiana, New Orleans, LA 70125, USA;*
[4]*Molecular Pharmacology, Bioscience, Novo Nordisk, DK-2880, Bagsvaerd, Denmark*

(Received 27 February 1995; accepted 20 July 1995)

Summary — *cis-syn*-1-Methyl-3-*n*-propyl-2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]indoles **6** and **7** were synthesized as conformationally rigid analogs of 4-methyl-3-(3,4-dihydroxyphenyl)-1-(*n*-propyl)pyrrolidine **1** and evaluated for dopamine D_1 and D_2 receptor binding affinity. The target compounds **6** and **7** were obtained from the key tricyclic lactams **10** and **11**, respectively. The stereochemistry was confirmed by single crystal X-ray analysis. Compounds **6** and **7** demonstrated low *in vitro* binding affinity at D_1 and D_2 receptors using [3H]SCH 23390 and [3H]spiperone as the D_1 and D_2 receptor radioligands, respectively. These data suggest that the 1-methyl group may interfere with the binding of **6** and **7** at D_1 and D_2 receptors. Molecular modeling studies revealed that unlike the 4-methyl group of **1**, the 1-methyl group of **6** and **7** was directed toward the so-called 'steric occlusion site' of the dopamine receptor.

dopamine / D_1 receptor / D_2 receptor / binding affinity / hexahydro-1*H*-benz[*e*]indole / dopaminergic activity

Introduction

Dopamine (DA) has been implicated in the pathophysiology of several disease conditions. In our ongoing quest to understand the dopamine pharmacophore, we previously [1] reported that 3-(3,4-dihydroxy)phenyl-1-(*n*-propyl)pyrrolidine exhibited DA agonist activity in several behavioral tests. Studies with 4-methyl derivatives of 3-(3,4-dihydroxy)phenyl-1-(*n*-propyl)pyrrolidine demonstrated that the DA receptor binding affinity resided mainly with the *cis*-4-methyl derivative **1** (fig 1) [2, 3]. *In vitro* binding studies using rat striatal tissue showed that **1** had moderate affinity for the DA D_1 and D_2 receptors [4]. In contrast, the *trans*-4-methyl derivative **2** had little affinity for DA receptors. Replacement of the *n*-propyl substituent of **1** by *n*-butyl **3** resulted in decreased DA receptor binding affinity [4].

In a recent report, Cruse *et al* [5] synthesized and evaluated 2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]indoles as semirigid analogs of the 3-phenylpyrrolidines. The rigidification of the 3-phenylpyrrolidine nucleus was accomplished by joining the phenyl group and the pyrrolidine ring by an ethylene bridge. Previous work [5] showed that a catechol nucleus was not essential for binding affinity at DA receptors. The 6-hydroxy derivative **4** exhibited greater affinity at DA D_1 and D_2 receptors than the 8-hydroxy derivative **5**. In fact, compound **5** was essentially devoid of affinity for D_1 receptors having an $IC_{50} > 10\,000$ nM (table I).

Several studies have examined octahydrobenzo[*f*]-quinolines in a variety of assays to determine DA

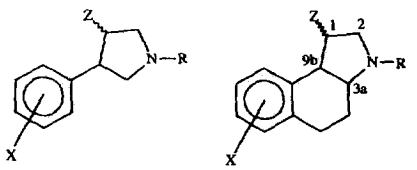


Fig 1. Structures of 2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]-indoles and 3-phenylpyrrolidines **1**–**7**. **1** X = 3,4-$(OH)_2$; R = *n*-Pr; Z = CH_3(*cis*); **2** X = 3,4-$(OH)_2$; R = *n*-Pr; Z = CH_3(*trans*); **3** X = 3,4-$(OH)_2$; R = *n*-Bu; Z = CH_3(*cis*); **4** X = 6-OH, R = *n*-Pr; Z = H; **5** X = 8-OH; R = *n*-Pr; Z = H; **6** X = 6-OH; R = *n*-Pr; Z = CH_3; **7** X = 6,7-$(OH)_2$; R = *n*-Pr; Z = CH_3.

*Correspondence and reprints

Table I. *In vitro* binding at D_1 and D_2 receptors.

Compound	*D_1 K_i (nM)*	*D_2 K_i (nM)*
1[a]	503	1250
2[a]	4120	6700
3[a]	4890	1249
4[b]	1994	575
5[b]	> 10 000[c]	1230
6	> 3000[c]	> 3000
7	> 3000[c]	> 3000[c]
SKF 38393[d]	18	9300

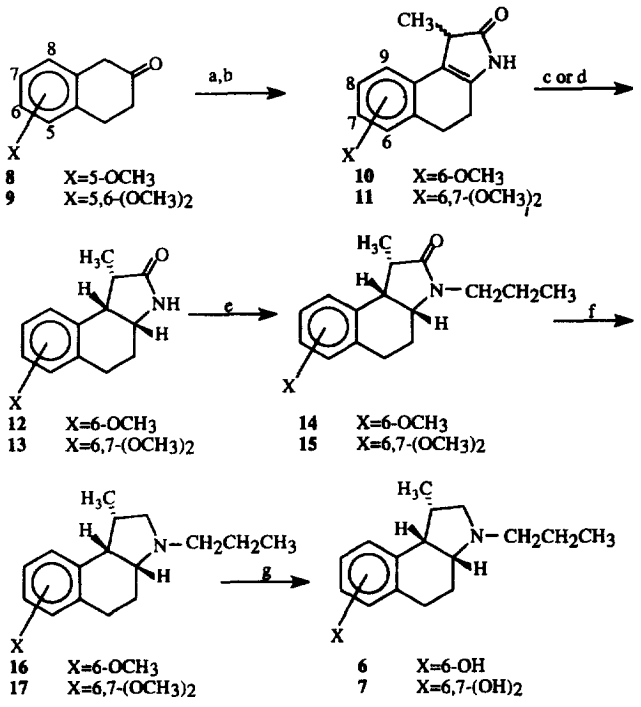
[a]Reference [4]; [b]reference [5]; [c]IC_{50}; [d]reference [24].

activity [6–10]. Activity in these compounds occurs with the *trans* isomers. Octahydrobenzo[*f*]quinolines with *trans* stereochemistry are planar, rigid structures in which the dopamine moiety is in an antiperiplanar conformation. However, in the *cis*-octahydrobenzo[*f*]-quinolines 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 important in ligand–DA receptor interactions [11, 12]. *trans*-7,8-Dihydroxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinolines demonstrated greater DA agonist activity than the corresponding 9-hydroxy or 8,9-dihydroxy derivatives [13].

Since *cis*-4-methyl-3-phenylpyrrolidines had exhibited increased selectivity at DA D_1 receptors [4] and only the 6-hydroxybenz[*e*]indoles had demonstrated D_1 receptor binding affinity [5], the synthesis of 6-hydroxy- and 6,7-dihydroxybenz[*e*]indoles was initiated. The incorporation of the 4-methyl-3-phenylpyrrolidine nucleus into the more rigid 2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]indole ring system was expected to enhance DA D_1 receptor binding.

Chemistry

The initial attempt to synthesize 1-methyl derivatives of 2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]indoles **6** and **7** using the reported methods [14, 15] was unsuccessful. The synthesis of the target compound was accomplished as depicted in scheme 1. The tetralones **8** and **9** were converted to pyrrolidine enamines by refluxing with pyrrolidine and then alkylated with 2-bromopropionamide in methanol. Hydrolysis of the intermediate imminium salts gave in low yields the key intermediate tricyclic lactams **10** and **11**, respectively. The double bond in **10** and **11** was expected to be at the 1,9b position of the ring system due to the conjugation with the C-2 carbonyl group and the phenyl ring. However, the presence of a doublet for the C-1



Scheme 1. (a) (i) Pyrrolidine, (ii) 2-bromopropionamide; (b) hydrolysis; (c) Et_3SiH/CF_3COOH; (d) H_2/Pd-C; (e) NaH/*n*-propyl iodide; (f) LAH/THF; (g) 48% HBr.

methyl group at δ 2.07 (for **10**) and 1.95 (for **11**) in the ^{1}H-NMR spectrum confirmed the presence of a double bond at the 3a,9b position. If the double bond of **10** or **11** had been at the 1,9b position, the C-1 methyl group would have exhibited a singlet in the ^{1}H-NMR spectrum. Reduction of the double bond of **10** and **11** with triethylsilane and trifluoroacetic acid or by catalytic (palladium on carbon) hydrogenation afforded only 3a,9b-*cis* isomers **12** and **13**. High pressure liquid chromatography (reverse phase, C-18, methanol/water) of the reaction mixture indicated the presence of only one diastereomer. A nuclear Overhauser effect (NOE) experiment using 400 MHz NMR spectrometry indicated that the hydrogens of **12** at the 1, 3a and 9b positions were on the same side of the ring (*cis-syn*). The addition of hydrogens to the 3a,9b double bond occurred from the sterically less hindered side of the ring to produce the *cis-syn* configuration in **12** and **13**. X-ray crystallography was used to determine the stereochemistry of **12** (fig 2).

The lactams **12** and **13** were alkylated with *n*-propyl iodide in the presence of sodium hydride in dimethylformamide to yield **14** and **15**. Reduction of **14** and **15** with lithium aluminum hydride followed by *O*-demethylation afforded the desired 6-hydroxy **6** and

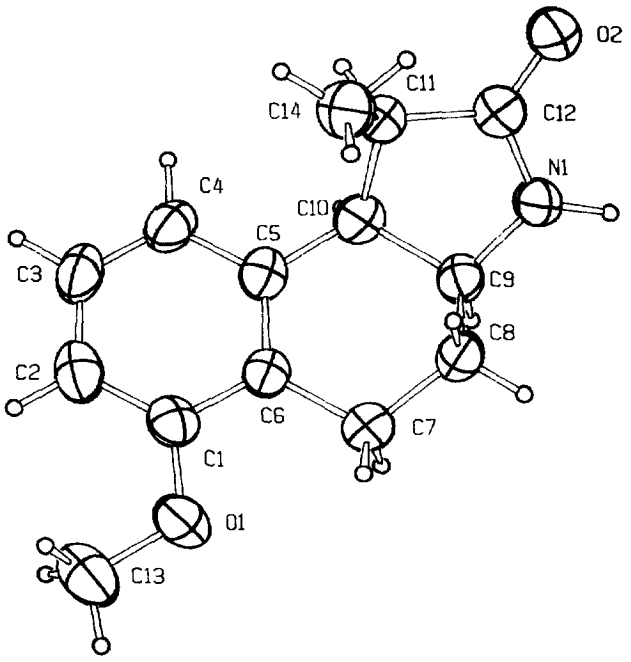


Fig 2. Ortep diagram of **12** drawn at a 50% probability level. C-9 and C-10 correspond to C-3a and C-9b of the benz[*e*]indole nucleus.

6,7-dihydroxy **7** derivatives, respectively. Since previous work [5] had shown that these procedures did not alter the configuration at 1, 3a or 9b, the stereochemistry for the final products, **6** and **7**, is assumed to be *cis-syn*.

Results and discussion

The *in vitro* binding affinity of **6** and **7** at DA D_1 and D_2 receptors was evaluated in rat striatal tissue using [^{3}H]SCH23390 and [^{3}H]spiperone as the D_1 and D_2 radioligands, respectively (table I). These compouds were essentially devoid of affinity for the DA D_1 and D_2 receptors (IC_{50} values > 3000 nM). Molecular modeling studies (fig 3) with the energy minimized conformation of *cis*-3-(3,4-dihydroxyphenyl)-4-methyl-1-(*n*-propyl)pyrrolidine **1** and *cis-syn*-6,7-dihydroxy-1-methyl-3-(*n*-propyl)-2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]indole **7** revealed that the methyl group of the latter could be directed towards the so-called 'steric hindrance region' of DA receptor models [16, 17]. However, the 4-methyl group of **1** may be directed towards an accessory region [18]. These data suggest that the orientation of 4-methyl-3-phenylpyrrolidine **1** at the receptor site would be different from the orientation of the benz[*e*]indole **6** or **7**.

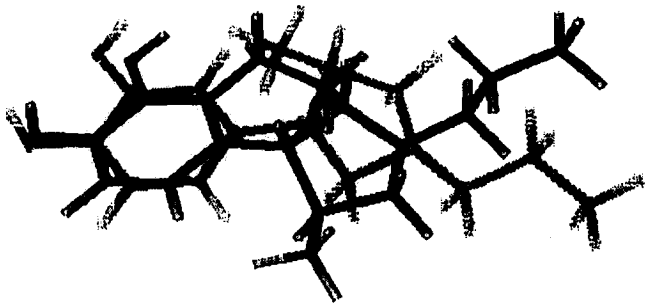


Fig 3. Three-point superimposition of 3-phenylpyrrolidine **1** (shaded) and 2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]indole **7** (dark).

Despite the structural similarities between the 3-phenylpyrrolidine **1** and the conformationally rigid 1-methyl-hexahydro-1*H*-benz[*e*]indoles **6** and **7**, steric hindrance might be forcing the tricyclic molecules to attain the unfavorable orientation at the receptor site.

The hexahydrobenz[*e*]indoles exhibit differences in DA receptor binding affinities from the corresponding octahydrobenzo[*f*]quinolines. Unlike the *cis*-octahydrobenzo[*f*]quinolines [6], the *cis*-hexahydrobenz[*e*]indoles exhibit activity at DA D_1 and D_2 receptors [5, 19]. The torsion angle of *cis*-hexahydrobenz[*e*]indoles (Ar-C_1-C_{9b}-C_{3a}-N) is 151° [5]. Thus, the lower affinity of *cis*-hexahydrobenz[*e*]indoles may be due to an inability to attain a *trans* (antiperiplanar) conformation. This conformation is preferred by most DA agonists [11, 20]. The torsion angle (Ar-C_1-C-C-N) in the *trans* conformation for DA approaches 180°.

Molecular modeling of the hexahydro-1*H*-benz[*e*]-indoles showed a more planar conformation for the *trans* isomers than the *cis* isomers [5]. Since DA receptors more readily accommodate compounds with a more planar conformation, the 3a,9b-*trans*-hexahydrobenz[*e*]indoles could exhibit greater affinity for DA receptors. A recent report with *trans*-hexahydrobenz[*e*]indoles [19] indicated that *trans*-3-allyl-6-hydroxy-2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]indole exhibited potent binding affinity at DA D_2 receptors [19].

The information regarding the spatial orientation of the 1-methyl group of **6** and **7**, as was found from this investigation, could be useful for future research to develop probes for DA receptors.

Experimental protocols

Chemistry

Melting points were determined on a Thomas–Hoover melting point apparatus and were not corrected. The IR spectra were recorded as potassium bromide pellets or as liquid films on

a Nicolet 5MX FT spectrometer. The NMR spectra were recorded on a JEOL FX 90Q spectrometer or on a Bruker 400 MHz spectrometer. Chemical shifts were reported in parts per million (δ) relative to tetramethylsilane (1%). Mass spectra were recorded on a Finnigan MAT TQS 4510 spectrometer. HPLC analyses were performed on an ISCO Model V40 with a UV-vis absorbance detector. Ultraviolet spectral measurements were performed with a Gilford 'Response' spectrophotometer. Precoated plastic TLC sheets (5 x 20 cm, 0.2 mm aluminum oxide M/UV_{254}) and silica gel (0.25 mm with fluorescent indicator UV_{254}) were purchased from the Brinkmann Instruments Co. Silica gel (40 μm) for flash chromatography was obtained from the JR Baker Chemical Company. All reagents and solvents were used without purification except where indicated. Analytical data were obtained from Oneida Research Services, Inc, Whitesboro, New York.

6-Methoxy-1-methyl-1,3,4,5-tetrahydro-2H-benz[e]indol-2-one ***10***

Following the method of Cornforth [21], 5-methoxy-2-tetralone **8** was prepared. Under nitrogen, a mixture of **8** (11.2 g, 64 mmol), dry toluene (100 mL), and *p*-toluenesulfonic acid (0.50 g, 2.6 mmol) was refluxed for 15 min. The solution was cooled and pyrrolidine (6.8 g, 96 mmol) was added *via* a syringe through a rubber septum. A Dean–Stark trap was fitted to the reaction flask, and water was removed over a period of 3 h. The reaction mixture was cooled, evaporated under vacuum, and transferred to a clean reaction flask with methanol (100 mL). The solution of the enamine was treated with 2-bromopropionamide (11.2 g, 74 mmol) and refluxed under nitrogen for 10 h. The reaction mixture was quenched with water (30 mL) and was stirred at room temperature for 30 h. The white crystalline solid that precipitated was filtered, and the residue was air dried. The filtrate was extracted with dichloromethane (200 mL), and the dichloromethane was dried (sodium sulfate) and evaporated to a semisolid mass. Trituration of the residue with ethyl acetate/hexane afforded a solid which was combined with the precipitated solid to give 2.6 g (17%) of white crystalline **10**. Recrystallization from ethyl acetate gave an analytical sample: mp 225–226°C; IR (KBr) 1668 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 2.07 (d, 3H, CH_3), 2.40 (m, 4H), 3.82 (s, 3H, OCH_3), 4.12 (m, 1H, H-1), 7.35 (m, 3H, ArH); ^{13}C-NMR (DMSO-d_6) δ 9.6 (1-CH_3), 21.7, 29.2, 54.9 (C-1), 55.4 (OCH_3), 110.6, 119.1, 124.9, 125.3, 127.0, 131.0, 148.9, 156.8, 173.5 (C-2). Anal $C_{14}H_{15}NO_2$ (C, H, N).

6,7-Dimethoxy-1-methyl-1,3,4,5-tetrahydro-2H-benz[e]indol-2-one ***11***

Using the literature procedure [22], 5,6-dimethoxy-2-tetralone **9** was prepared. Following the method of preparation of **10**, **9** (5.70 g, 28 mmol), pyrrolidine (3.92 g, 55 mmol), and 2-bromopropionamide (4.73 g, 31 mmol) gave a white solid. Recrystallization from methanol yielded 705 mg (10%) of **11**; mp 229–230°C; IR (KBr) 1688 (lactam, C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.95 (d, 3H, CH_3), 2.70 (m, 4H, $ArCH_2CH_2$), 3.75 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.11 (m, 1H, H-1), 7.20 (m, 2H, ArH); ^{13}C-NMR (DMSO-d_6) δ 9.5, 21.9, 29.8, 54.9, 55.6, 59.3, 110.9, 122.8, 123.2, 123.5, 131.2, 145.9, 149.0, 152.5, 173.7. Anal $C_{15}H_{17}NO_3$ (C, H, N).

cis-syn-6-Methoxy-1-methyl-1,3,3a,4,5,9b-hexahydro-2H-benz[e]indol-2-one ***12***

Method A. Hydrogenation of ***10*** *with palladium on carbon.* A mixture of **10** (602 mg, 2.6 mmol) and 10% palladium on carbon (400 mg) in absolute ethanol (100 mL) was shaken on a Parr hydrogenator at an initial pressure of 46 psi. After the theoretical amount of hydrogen had been absorbed, the catalyst was filtered, and the solvent was removed under reduced pressure to afford 467 mg (78%) of **12** as a white powder. Analytically pure **12** was obtained by recrystallization of a small sample from acetonitrile: mp 201–203°C; IR (KBr) 1709 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.95 (d, 3H, J = 7.7 Hz, CH_3), 1.65 (m, 1H, H-5), 2.02 (m, 1H, H-5), 2.43 (m, 1H, H-4), 2.85 (m, 1H, H-4), 2.90 (m, 1H, H-9b), 3.81 (s, 3H, OCH_3), 3.82 (m, 1H, H-3a), 3.93 (m, 1H, H-1), 6.70 (m, 2H, ArH), 7.15 (m, 1H, ArH), 7.24 (s, 1H, NH); ^{13}C-NMR ($CDCl_3$) δ 14.8 (CH_3), 19.6 (C-4), 29.3 (C-5), 40.1 (C-9b), 40.2 (C-3a), 52.7 (C-1), 55.2 (OCH_3), 107.3 (C-9), 122.1 (C-7), 126.3 (C-8), 126.5 (C-9a), 135.4 (C-5a), 156.7 (C-6), 180.8 (C-2); MS (EI) *m/z* 231 (M^+). Anal $C_{14}H_{17}NO_2$ (C, H, N).

Method B. Ionic hydrogenation of ***10*** *with triethylsilane in trifluoroacetic acid.* Following the method of Cannon *et al* [23], triethylsilane (1.4 g, 12 mmol) was added to a solution of **10** (274 mg, 1.2 mmol) in dichloromethane (3 mL) at room temperature. Trifluoroacetic acid (2.8 mL) was added dropwise at 10°C over 10 min. After stirring for 24 h, the solvents were evaporated and dichloromethane (50 mL) was added to dissolve the solid that remained. The dichloromethane was washed with aqueous saturated sodium bicarbonate (25 mL) and with water (25 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated to yield 120 mg (40%) of a white solid.

TLC (silica gel) indicated that the reduction product was identical to the product obtained by reduction of **10** with palladium on carbon. The NMR spectra of the reduction product was also identical. HPLC analysis of this compound showed the presence of **12** only.

cis-syn-6,7-Dimethoxy-1-methyl-1,3,3a,4,5,9b-hexahydro-2H-benz[e]indol-2-one ***13***

Using *Method A*, **11** (350 mg, 1.3 mmol) and 10% palladium on carbon (450 mg) gave 250 mg (74%) of **13** as a white solid. Recrystallization from methanol gave an analytical sample: mp 168–170°C; IR (KBr) 1673 (C=O) cm^{-1}; ^{1}H-NMR (CD_3OD) δ 0.84 (d, J = 8 Hz, 3H, 1-CH_3), 2.55 (m, 7H), 3.75 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 6.88 (s, 2H, ArH); ^{13}C-NMR (CD_3OD) δ 14.9, 20.6, 30.0, 41.0, 41.9, 54.2, 56.3, 60.6, 111.9, 127.1, 128.7, 133.1, 147.2, 152.0, 182.9. Anal $C_{15}H_{19}NO_3$ (C, H, N).

cis-syn-6-Methoxy-1-methyl-3-(n-propyl)-1,3,3a,4,5,9b-hexahydro-2H-benz[e]indol-2-one ***14***

Sodium hydride (355 mg, 8.4 mmol) as a 60% mineral oil dispersion was washed with hexane (3 x 25 mL), suspended in dry dimethylformamide (DMF) (50 mL), and charged in a reaction flask under nitrogen. The stirred suspension was treated dropwise with a solution of **12** (1.36 g, 6.0 mmol) in DMF (10 mL). After the addition had been completed, the reaction mixture was heated at 80°C for 3 h and allowed to cool to room temperature. A solution of *n*-propyl iodide (1.05 g, 6.0 mmol) in DMF (15 mL) was added, and the solution was heated at 80°C for 10 h. The reaction mixture was cooled, treated with absolute ethanol (5 mL), and evaporated under reduced pressure to afford an oil. The residue was partitioned between diethyl ether (25 mL) and water (15 mL), and the diethyl ether layer was separated, dried (Na_2SO_4), filtered, and evaporated to yield a semisolid. Flash chromatography (silica gel, ethyl acetate/hexane 50:50) gave 491 mg (31%) of **14** as a white solid. Recrystallization from 2-propanol/water gave an analytical sample: mp 68–70°C; IR (KBr) 1690 (C=O)

cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.94 (t, 3H, CH_2CH_3), 1.47 (d, 2H, $CHCH_3$), 2.60 (br m, 10H), 3.82 (s, 3H, OCH_3), 6.95 (m, 3H, ArH); ^{13}C-NMR ($CDCl_3$) δ 11.4, 16.1, 20.0, 21.0, 24.8, 42.2, 44.4, 55.0, 55.4, 107.9, 121.0, 126.7, 138.2, 156.8, 176.0. Anal $C_{17}H_{23}NO_2$ (C, H, N).

cis-syn-6,7-Dimethoxy-1-methyl-3-(n-propyl)-1,3,3a,4,5,9b-hexahydro-2H-benz[e]indol-2-one ***15***

Using the method described for **14**, **13** (440 mg, 1.7 mmol), 60% sodium hydride (92 mg, 2.3 mmol), and *n*-propyl iodide (280 mg, 1.7 mmol) in DMF (80 mL) gave 305 mg (60%) of **15** as a semisolid mass: IR (KBr) 1684 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.93 (t, J = 7 Hz, 3H, $CH_2CH_2CH_3$), 1.39 (d, J = 7 Hz, 2H, 1-CH_3), 2.55 (m, 9H), 3.60 (t, 2H, NCH_2), 3.79 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 6.90 (m, 2H, ArH); ^{13}C-NMR ($CDCl_3$) δ 11.4, 16.0, 20.3, 20.9, 24.9, 42.2, 43.9, 44.6, 55.2, 55.8, 60.2, 110.6, 124.0, 130.3, 130.7, 146.1, 151.0, 176.0. Anal $C_{18}H_{25}NO_3$ (C, H, N); C: calc 71.25; found 69.76.

cis-syn-6-Hydroxy-1-methyl-3-(n-propyl)-2,3,3a,4,5,9b-hexahydro-1H-benz[e]indole ***6***

A suspension of lithium aluminum hydride (806 mg, 21.2 mmol) in dry THF (150 mL) was treated with **14** (294 mg, 1.06 mmol) in THF (10 mL) through a rubber septum. The reaction mixture was refluxed for 7 h, cooled to room temperature, and treated carefully with water to decompose the excess lithium aluminum hydride. The reaction mixture was filtered, and the solvent was removed under reduced pressure. The residue was partitioned between dichloromethane (25 mL) and water (25 mL). The dichloromethane solution was separated, dried (Na_2SO_4), filtered, and evaporated to yield **16** as an oil: ^{1}H-NMR (CD_3OD) δ 0.67 (d, 3H, J = 7 Hz, CH_3), 2.40 (m, 9H), 3.81 (s, 3H, OCH_3), 6.95 (m, 3H, ArH); ^{13}C-NMR (CD_3OD) δ 16.8, 20.3, 29.0, 30.5, 45.8, 54.0, 55.4, 57.0, 107.1, 122.3, 122.8, 125.5, 126.0, 127.6.

The crude 6-methoxy derivative **16** was demethylated in refluxing 48% hydrobromic acid (15 mL) to afford 250 mg (77%) of **6** after recrystallization from absolute ethanol/diethyl ether: mp 209–211°C (dec); ^{1}H-NMR (CD_3OD) δ 1.05 (t, 3H, CH_2CH_3), 1.18 (d, 3H, 1-CH_3), 2.95 (m, 13H), 6.81 (m, 3H, ArH); ^{13}C (CD_3OD) δ 11.4, 15.4, 19.8, 20.2, 26.5, 41.7, 48.3, 58.4, 60.2, 69.0, 114.3, 121.2, 124.2, 128.0, 136.7, 155.7. Anal $C_{16}H_{24}BrNO$ (C, H, N).

cis-syn-6,7-Dihydroxy-1-methyl-3-(n-propyl)-2,3,3a,4,5,9b-hexahydro-1H-benz[e]indole ***7***

According to the method described for the synthesis of **16**, **15** (306 mg, 1 mmol) and lithium aluminum hydride (805 mg, 21 mmol) gave **17** as an oil: ^{1}H-NMR ($CDCl_3$) δ 0.92 (t, 3H, CH_2CH_3), 1.10 (d, 3H, 1-CH_3), 2.25 (m, 13H), 3.78 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 6.76 (m, 2H, ArH). Methyl ether cleavage was accomplished by refluxing **17** with 48% hydrobromic acid (10 mL) under nitrogen to give a solid. Recrystallization from absolute ethanol/diethyl ether gave 160 mg (60%) of **7** as the hydrobromide salt: mp 278–280°C (dec); ^{1}H-NMR (CD_3OD) δ 1.03 (t, 3H, J = 7 Hz, CH_2CH_3), 1.17 (d, 3H, J = 6.5 Hz, 1-CH_3), 2.95 (m, 16H), 6.62 (m, 2H, ArH); ^{13}C-NMR (CD_3OD) δ 11.4, 15.3, 20.2, 26.6, 41.7, 49.2, 50.2, 58.4, 60.1, 69.0, 114.2, 116.1, 120.8, 127.0, 143.6, 145.0. Anal $C_{16}H_{24}BrNO_2$ (C, H, N).

Pharmacology

The *in vitro* binding affinity of **6** and **7** at dopamine D_1 and D_2 receptors was evaluated using rat striatal tissue following the reported method [24]. K_i values were calculated from the expression, $K_i = IC_{50}/(1 + [L]/K_d)$, where IC_{50} is the concentration of the compound causing 50% inhibition of specific binding, L is the concentration of the radioligand used, and K_d is the dissociation constant of the radioligand ([^{3}H]SCH 23390, 0.14 nM; [^{3}H]spiperone 0.08 nM). The results are the means of two/three experiments with three to six concentrations for each assay.

Molecular modeling

All computations were performed using a Tektronix CAChe work system (CAChe Version 3.0, Tektronix Inc, 1993). The minimum energy of **1** and **7** was calculated as 1.2437 kcal/mole and 5.1775 kcal/mole, respectively. The energy minimized structures were superimposed using three points.

X-ray crystallography

A single colorless crystal of **12** 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 = 5.802(1), b = 29.209(3), c = 7.356(2) Å, β = 105.77(1)°, and V = 1199.7 Å^3. The calculated density was 1.275 g/cm^3 of z = 4 and a formula weight of 230.29 g/mol. Three-dimensional intensity data were collected in the ω: 2θ scan mode. A total of 2333 reflections were collected to a sin $(\theta/\lambda)_{max}$ of 0.58 Å^{-1}. Data were corrected for Lorentz and polarization effects. Absorption as a function of ψ was corrected empirically (minimum transmittance 97.11%). Three standard reflections measured every 2 h showed only minor fluctuations in intensity.

The structure was solved by direct methods using the MULTAN [25] series of programs that revealed the positions of most of the non-hydrogen atoms on the initial E-maps. Subsequent Fourier synthesis revealed the locations of the remaining non-hydrogen atoms. All hydrogen atoms were calculated on the basis of sp^2 or sp^3 geometry and a C-H bond length of 0.95 Å. The structure was refined by full-matrix least-squares minimization of the function $\Sigma w(|F_o| - |F_c|)^2$, with anisotropic thermal parameters for all non-hydrogen atoms, and with hydrogen atom positions and temperature factors fixed, 1183 independent, observed reflections [$I > 3\sigma(I)$] led to a final R = 0.052 and R_w = 0.074. Conventional reliability indices, $R = \Sigma(|F_o| - |F_c|)/\Sigma|F_o|$ and $R_w = (\Sigma w(|F_o| - |F_c|)^2/\Sigma w F_o^2)^{1/2}$ with $w = 1/\sigma(F)^2$, where $\sigma(F)$ is the estimated standard deviation in F_o. F_o and F_c are observed and calculated structure factors, respectively. There were no significant peaks in the final difference map.

All computer programs used for data collection and refinement are part of the CAD4-molEN package [26]. Scattering factors were taken from the *International Tables for X-ray Crystallography* [27] and included corrections for anomalous scattering contributions.

The final fractional coordinates for **12** are given in table II. Tables giving bond lengths, bond angles, and general anisotropic displacement parameter expressions for **12** are on file with the authors.

The compound crystallized with four molecules in the unit cell. The orientation of the hydrogen atoms at C9 and C10 (C-3a and C-9b, fig 3) are *cis* with respect to the C9-C10 bond. There are no unusual intra- or intermolecular bond lengths.

Table II. Positional parameters and their estimated standard deviations.

Atom	*x*	*y*	*z*	*B(A2)*
O1	0.4343(5)	0.78970(9)	0.0618(4)	4.62(6)
O2	–0.2624(4)	1.01698(8)	0.2115(3)	4.00(6)
N1	–0.3222(5)	0.9482(1)	0.0570(4)	3.50(7)
C1	0.3921(6)	0.8126(1)	0.2128(5)	3.42(8)
C2	0.5272(7)	0.8066(1)	0.3977(5)	4.20(9)
C3	0.4688(7)	0.8314(1)	0.5391(5)	4.40(9)
C4	0.2828(7)	0.8617(1)	0.4977(5)	4.03(9)
C5	0.1455(6)	0.8679(1)	0.3121(5)	3.25(8)
C6	0.2010(6)	0.8435(1)	0.1668(5)	3.07(8)
C7	0.0588(7)	0.8498(1)	–0.0365(5)	3.69(9)
C8	–0.0691(6)	0.8954(1)	–0.0711(5)	3.52(8)
C9	–0.2179(6)	0.9031(1)	0.0671(5)	3.30(8)
C10	–0.0648(6)	0.9006(1)	0.2743(5)	3.16(7)
C11	–0.0068(6)	0.9508(1)	0.3303(5)	3.04(7)
C12	–0.2102(6)	0.9762(1)	0.1967(5)	3.25(8)
C13	0.6297(8)	0.7588(2)	0.0980(7)	5.7(1)
C14	0.2352(6)	0.9689(1)	0.3134(5)	3.90(9)

Acknowledgments

This research was supported by the School of Pharmacy and Health Sciences, Northeast Louisiana University and completed in collaboration with Novo Nordisk, Bagsvaerd, Denmark, and Xavier University of Louisiana at New Orleans. The authors are grateful to DE Nichols of Purdue University for the access to the CAChe Work station.

References

1 Crider AM, Hemdi TF, Hassan MN, Fahn S (1984) *J Pharm Sci* 73, 1585–1587
2 Crider AM, Sylvestri SC, Tschappat KD, Dick RM, Leader WG (1988) *J Heterocycl Chem* 25, 1407–1412
3 Tschappat KD, Crider AM, Hassan MN, Fahn S (1987) *J Heterocycl Chem* 24, 673–676
4 Crider AM, Andersen PH, Cruse SF, Ghosh D, Harpalani A (1992) *Eur J Med Chem* 27, 407–411
5 Cruse SF, Lear J, Klein CL, Andersen PH, Dick RM, Crider AM (1993) *J Pharm Sci* 82, 334–339
6 Cannon JG, Suarez-Guiterrez C, Lee T *et al* (1979) *J Med Chem* 22, 341–347
7 Cannon JG, Lee T, Goldman HC *et al* (1980) *J Med Chem* 23, 1–5
8 Wikström H, Sanchez D, Lindberg P *et al* (1982) *J Med Chem* 25, 925–931
9 Findell PK, Torkelson SM, Craig JC, Weiner RI (1988) *Mol Pharmacol* 33, 78–83
10 Craig JC, Torkelson SM, Findell PR, Weiner RI (1989) *J Med Chem* 32, 961–968
11 Hacksell U, Arvidsson LE, Svensson U *et al* (1981) *J Med Chem* 24, 1475–1482
12 Wikström H, Andersson B, Sanchez D *et al* (1985) *J Med Chem* 28, 215–225
13 Cannon JG (1985) *In: Progress in Drug Research* (Jucker E, ed), Birkhauser Verlag, Basel, 304–414
14 Kavadidas G, Velkof S, Belleau B (1979) *Can J Chem* 57, 1852–1860
15 Reimann E, Bracher F (1988) *Arch Pharm (Weinheim)* 321, 185–188
16 McDermed JD, Freeman HS, Ferris RM (1984) *In: Catecholamines: Basic and Clinical Frontiers* (Usdin E, Kopin IJ, Barchas J, ed) Pergamon Press, New York, 568–570
17 Nichols DE (1983) *In: Dopamine Receptors* (Kaiser C, Kebabian JW, eds), ACS Symposium Series 224, American Chemical Society, Washington, DC, 201–218
18 Brewster WK, Nichols DE, Riggs RM *et al* (1990) *J Med Chem* 33, 1756–1764
19 Lin CH, Haadsma-Svensson R, Lahti RA *et al* (1993) *J Med Chem* 36, 1053–1068
20 Cannon JG (1983) *Ann Rev Pharmacol Toxicol* 23, 103–129
21 Cornforth JW, Cornforth RH (1942) *J Chem Soc* 689–691
22 Horn AS, Dijkstra J, Feenstra MGP, Grol CJ, Rollema H, Westernik BHC (1980) *Eur J Med Chem* 15, 387–392
23 Cannon JG, Chang Y, Amoo VE, Kathleen AW (1986) *Synthesis* 494–496
24 Andersen PH, Jansen JA (1990) *Eur J Pharmacol* 188, 335–347
25 Main P, Fiske SJ, Hull SE *et al* (1982) A system of computer programs for the automatic solution of crystal structures for X-ray diffraction data, MULTAN 82, Universities of York, UK, and Louvain, Belgium
26 Fair CK (1990) Enraf-Nonius structure determination system, Delft Instruments, The Netherlands
27 Anon (1974) *International Tables for X-ray Crystallography*, Kynoch, Birmingham, UK, vol 45