Eur. J. Med. Chem. 34 (1999) 487–503

Original article

cis- and *trans*-2,3,3a,4,5,9b-Hexahydro-1*H*-benz[*e*]indoles: synthesis and evaluation of dopamine D_2 and D_3 receptor binding affinity

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(Received 7 August 1998; accepted 25 November 1998)

Abstract – *cis*- and *trans*-2,3,3a,4,5,9b-Hexahydro-1*H*-benz[*e*]indoles were synthesized as conformationally rigid analogues of 3-phenylpyrrolidine and evaluated for dopamine (DA) D_{2S} and D_3 receptor binding affinity. The tricyclic benz[*e*]indole nucleus was constructed by a previously reported reductive amination-cyclization procedure. Several unexpected side products were isolated and characterized using the general method. The *trans*-diastereoisomers exhibited greater affinities for the DA D_3 receptor than the corresponding *cis*-isomers. In both the *cis*- and *trans*- series the greatest affinity for DA D_3 receptors was shown by compounds substituted with *N*-*n*-propyl or *N*-allyl groups. The *cis*-(±)-*N*-allyl derivative **21e** demonstrated a D_{2S}/D_3 selectivity of 290. Resolution of *cis*-(±)-**5** and *trans*-(±)-**21c** into individual enantiomers showed that in both series the more active isomer had 3a*R* absolute configuration. These novel ligands may be useful tools for gaining additional information about the DA D_3 receptor. © Elsevier, Paris

dopamine / D_{2S} receptor / D_3 receptor / *cis*- and *trans*-2,3,3a,4,5,9b-hexahydro-1*H*-benz[e]indoles / receptor binding affinity

1. Introduction

Recent advances in molecular cloning techniques have led to the characterization of at least five DA receptor subtypes, designated D_1–D_5 [1]. Based on similarities in functional and pharmacological properties, ligand binding, and sequence homologies, the receptors can be divided into two major classes: the D_1-family (D_1 and D_5) and the D_2-family (D_2, D_3 and D_4) [2, 3]. Considerable interest has recently been focused on the D_3 receptor due to its possible role in schizophrenia [4]. The D_3 receptor is expressed mainly in the areas of the brain such as the nucleus accumbens and the islands of Calleja. These regions are believed to be involved in thought and emotional processes, whereas the caudate in which D_2 receptors are highly expressed may effect motor control [5].

The 2-aminotetralin, [*R*-(+)-7-OH-DPAT, **1**, *figure 1*], was shown to exhibit preference for the D_3 receptor [6, 7]; however, the apparent selectivity of *R*-(+)-7-OH-DPAT in radioligand binding studies is dramatically reduced using in vitro functional tests to evaluate D_3 receptor stimulation [8, 9]. Initial binding studies in CHO-K1 cells using [^{3}H]spiperone as the radioligand showed that the DA agonists *R*-(+)-7-OH-DPAT and PD 128907 (**2**, *figure 1*) exhibited selectivity for D_3 versus D_{2L} receptors [5, 10]. These studies, however, were carried out under conditions which favour binding to

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Abbreviations: DA (dopamine), R-(+)-7-OH-DPAT [R-(+)-7-hydroxy-2-(N,N-di-n-propylamino)tetralin], PD 128907 [R-(+)-trans-3,4,4a,10b-tetrahydro-4-n-propyl-2H,5H-1-benzopyrano[4,3-b]-1,4-oxazin-9-ol], cis-(±)-8-OH-PBZI [cis-(±)-2,3,3a,4,5,9b-hexa hydro-8-hydroxy-3-n-propyl-1H-benz[e]indole], LDA (lithium diisopropylamide), SAR (structure-activity relationships), QUIN (quinpirole), Bz (benzyl), LAH (lithium aluminium hydride), THF (tetrahydrofuran).

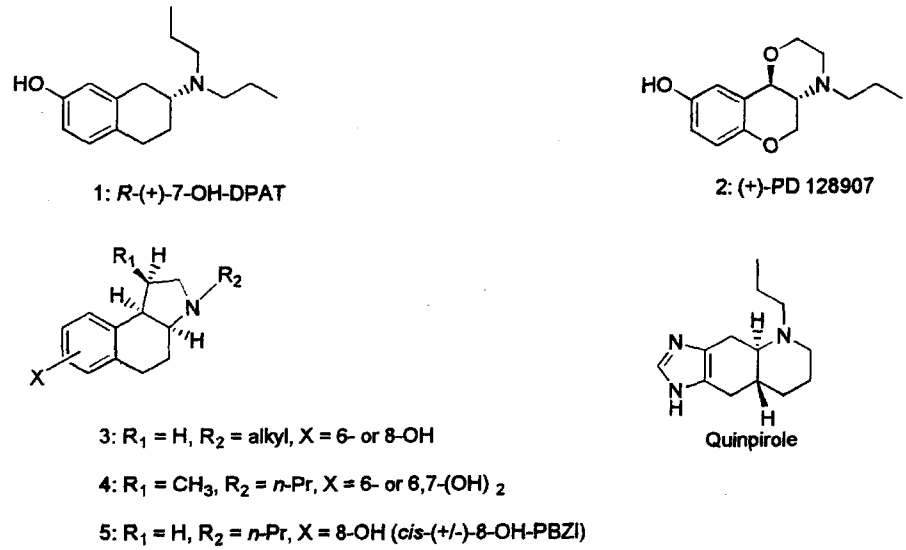


Figure 1. Structures of dopamine agonists **1–5.**

GTP-insensitive, D_{2L} receptor sites with low affinity for agonists. When binding studies were performed using [^{3}H]N-0437, an agonist ligand, only binding to the high affinity site of the D_{2L} receptor was measured. The selectivities of *R*-(+)-7-OH-DPAT and PD 128907 at D_3 versus D_2 receptors using these assay conditions were only 24- and 18-fold, respectively [5, 10].

Previous studies on 3-phenylpyrrolidines have shown that these compounds exhibit dopaminergic activity in several behavioural and biochemical tests [11–13]. Additionally, several of these derivatives were shown to have moderate affinity for D_1 and D_2 receptors in rat striatal tissue [14]. In an effort to incorporate the 3-phenylpyrrolidine nucleus into a more rigid framework, *cis*-(±)-2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]indoles (**3,** *figure 1*) [15] and *cis*-(±)-1-methyl-2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]indoles (**4,** *figure 1*) [16] were synthesized and evaluated for in vitro binding affinity at D_1 and D_2 receptors. The results of the binding studies indicated that these compounds exhibited only weak affinity at D_1 and D_2 receptors.

Lin et al. [17] described the synthesis and SAR of a series of *cis*- and *trans*-6- and 9-hydroxy-2,3,3a,4,5,9b-hexahydro-1*H*- benz[*e*]indoles at D_2 and $5HT_{1A}$ receptors. Compounds having 6-hydroxy or 6-methoxy-substitution were shown to have D_2 antagonistic activity. In the *cis*-series, only the *N*-allyl analogues displayed D_2 receptor affinity. Surprisingly, the 6-hydroxy derivative was less potent than the 6-methoxy analogue. In the *trans*-series, the *N*-(*n*-propyl) derivatives showed slightly higher binding affinities than the corresponding *N*-allyl derivatives. In contrast to the *cis*-diastereoisomers, the *trans*-6-hydroxy derivatives exhibited greater affinities than the 6-methoxy derivatives at D_2 receptors. As part of a program to identify ligands selective for DA receptor subtypes, *cis*-(±)-8-OH-PBZI (**5,** *figure 1*) was found to exhibit high selectivity for the DA D_3 receptor [18]. This compound was previously found to exhibit only weak binding affinity at D_1 and D_2 receptors in rat striatal tissue [15]. Additional studies on *cis*-(±)-8-OH-PBZI showed that this compound exhibits a pharmacological profile typical of antipsychotic agents; however, the compound lacks motor side effects often produced by classical antipsychotics. These studies further suggest that *cis*-(±)-8-OH-PBZI demonstrates its in vivo effects by a postsynaptic DA D_3 agonist mechanism of action [19]. Because *cis*-(±)-8-OH-PBZI represents a novel DA D_3 agonist, the structural modification of this lead compound was of interest. Since the report by Lin et al. [17] showed that *trans*-*N*-(*n*-propyl)-and *N*-allyl-6-hydroxy-hexahydrobenz[*e*]indoles exhibited potent binding affinity at DA D_2 receptors, the synthesis and evaluation of *trans*-8-hydroxy-2,3,3a,4,5,9b-hexahydrobenz[*e*] indoles at DA D_3 receptors were major objectives of this investigation. The previous report by Lin et al. [17] showed that in the *cis*-series the 3a*R*-(-)-enantiomers were more potent. Thus, resolution and testing of the individual enantiomers of *cis*- and *trans*-2,3,3a,4,5, 9b-hexahydro-8-hydroxy-3-*n*-propyl-1*H*-benz[*e*]indoles were carried out. An additional objective was to deter-

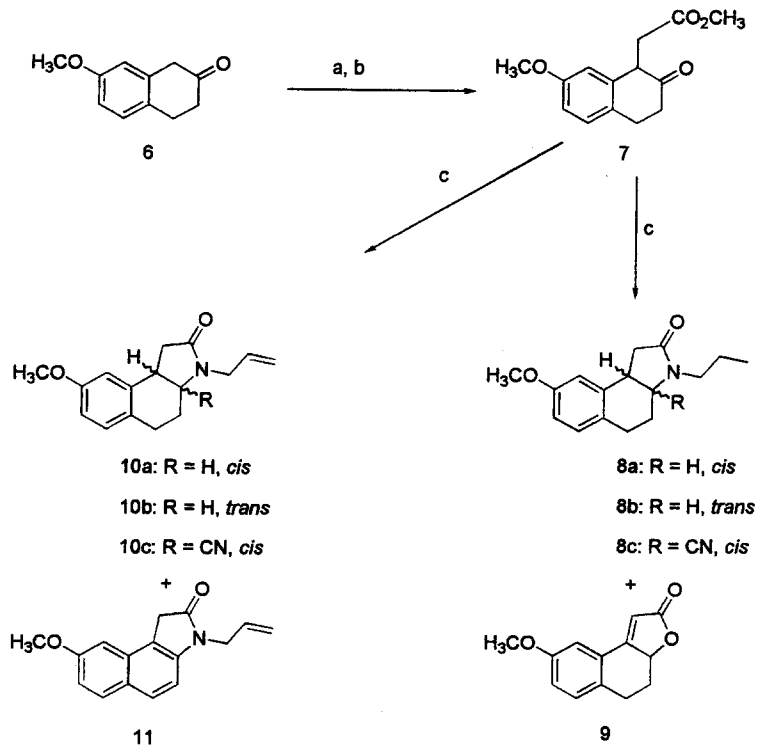


Figure 2. (a) p-$CH_3C_6H_4SO_2OH$/pyrrolidine, (b) i. $BrCH_2CO_2CH_3/CH_3OH$, ii. H_2O, reflux, (c) n-propylamine or allylamine/HOAc/$NaBH_3CN/CH_3OH$.

mine the effect of replacement of the *N*-(*n*-propyl) substituent by hydrogen, methyl, or allyl groups [15, 17]. Although substitution at the 1-position of 6-hydroxy or 6,7-dihydroxy-2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]indoles decreased D_1 and D_2 receptor binding affinity [16], we were interested in determining the effect of small (methyl) or large (benzyl) groups at this position and evaluating the effect on D_3 receptor binding affinity.

2. Chemistry

In our earlier reports, construction of the 2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]indole system was accomplished by catalytic or metal hydride reduction of either 1,2,4,5-tetrahydro-3*H*-benz[*e*]indoles or 1,3,3a,4,5,9b-hexa-hydro-2*H*-benz[*e*]indol-2-ones [15, 16]. Analysis of the reduction products by HPLC and ^1H and ^{13}C NMR revealed the presence of only one diastereoisomer. X-ray crystallography established the (3a,9b)-stereochemistry as *cis* [15, 16]. Since a major goal of this investigation was to compare the D_3 receptor binding affinities of *trans*-2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]indoles with the corresponding *cis*-diastereoisomers, an alternate synthetic route was needed that would yield at least some of the *trans*-isomer. A reductive amination-cyclization procedure developed by Lin et al. [17] was employed to build the requisite tricyclic ring system (*figures 2* and *3*).

Conversion of 7-methoxy-2-tetralone (**6**) to a pyrrolidine enamine [20] followed by reaction with methyl bromoacetate afforded the ketoester **7**. Using the reductive amination-cyclization procedure, a complex mixture of the *cis*- and *trans*-lactams **8a** and **8b**, the *cis*-3a-cyano lactam **8c**, and the unsaturated lactone **9** was obtained (*figure 2*). The lactone apparently results from a keto-enol tautomerization of **7** followed by cyclization and isomerization of the double bond to the 1,9b-position. The NMR spectrum confirmed the presence of an olefinic proton at δ 6.09. The *cis*-3a-cyano lactam **8c** appears to be generated by attack of cyanide ion on the imminium ion at C-2 followed by cyclization. Although fresh sodium cyanoborohydride was utilized in the reaction, some hydrolysis occurs under the reaction conditions to generate hydrogen cyanide. The structural assignment of the *cis*-cyano lactam was confirmed by single crystal X-ray

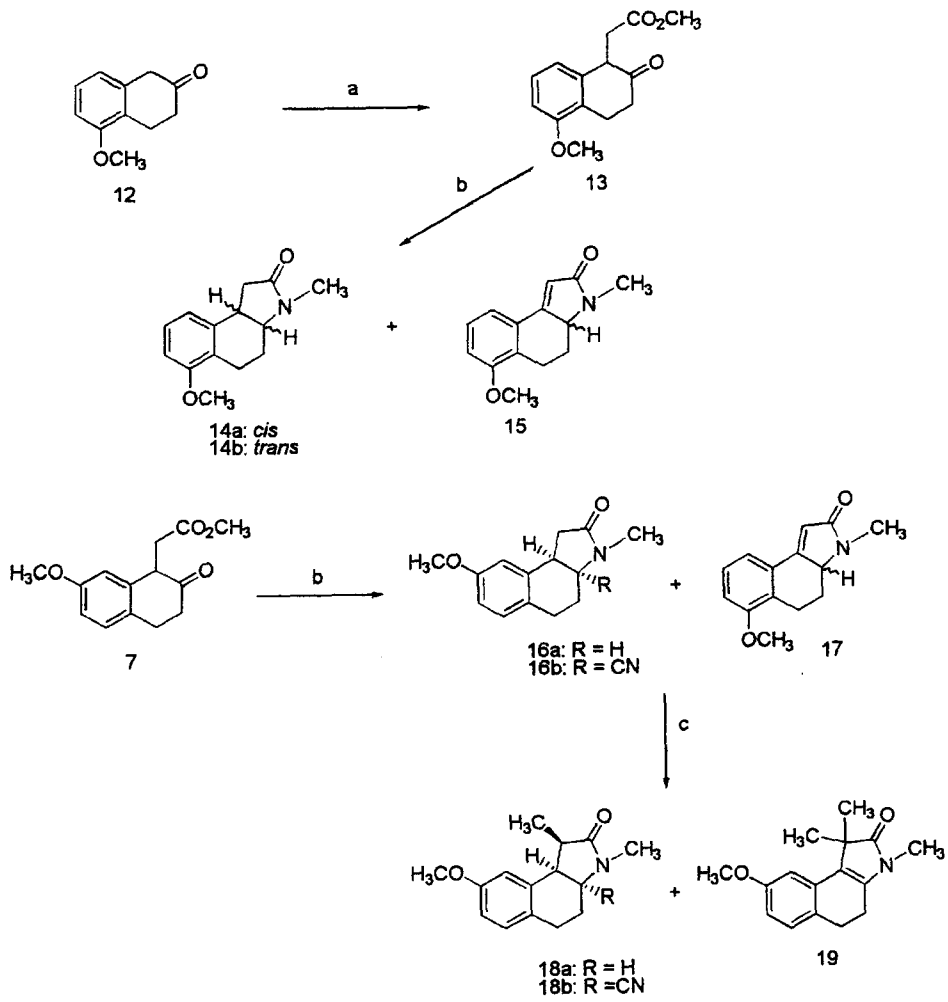


Figure 3. (a) p-$CH_3C_6H_4SO_2OH$/pyrrolidine, (b) $CH_3NH_2.HCl/Et_3N$/HOAc/MeOH, (c) LDA/THF/CH_3I.

crystallography *(figure 4)*. The molecule crystallized with four molecules in the unit cell. The arbitrary numbering system for **8c** is shown in *figure 4*. The orientation of the hydrogen atom at C3 (9b-position) and the cyano group at C12 (3a-position) are *cis* with respect to the C3–C12 bond. There are no unusual intramolecular close contacts. Based on previous work [15–17], the major product of this reaction was the *cis*-lactam **8a**. Reaction of the ketoester **7** with allylamine under the same conditions also gave a complex mixture *(figure 2)*. Flash chromatography on silica gel using ethyl acetate-hexane (2:1) yielded the *cis*- and *trans*-lactams **10a** and **10b**, the *cis*-3a-cyano lactam **10c**, and the 1,3-dihydro-2*H*-benz[*e*]indol-2-one **11**. The formation of **11** could be explained by imine/enamine tautomerization followed by ring closure to give a 1,3,4,5-tetrahydro-2*H*- benz[*e*] indol-2-one. Aromatization of this intermediate yields the lactam **11**.

The 6- and 8-methoxy-1,3,3a,4,5,9b-hexahydro-3-methyl-2*H*- benz[*e*]indoles were synthesized as shown in *figures 3, 5* and *6*. Although earlier work had shown that D_2 activity was maximal with *n*-propyl or *n*-butyl [15], the *N*-methyl derivatives were prepared for inclusion in the D_3 receptor binding assay. Reaction of the 8-methoxy ketoester **7** with methylamine hydrochloride in the presence of triethylamine using the typical reaction conditions gave the *cis*-lactam **16a**, the *cis*-3a-cyano lactam **16b**, and the unsaturated lactam **17**. The *trans*-diastereoisomer of **16a** was not isolated from the reaction mixture. In contrast, reaction of the 6-methoxy ketoester

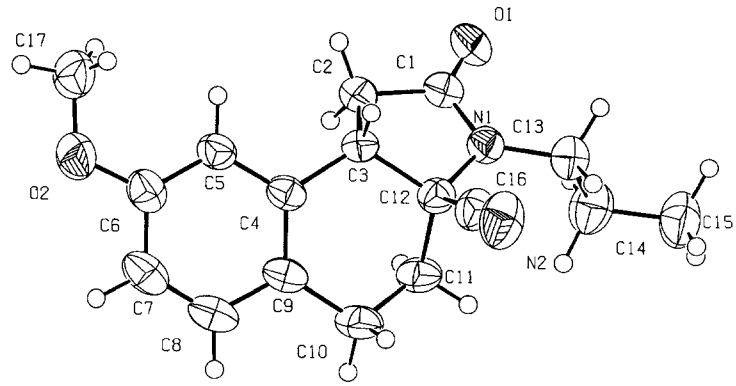
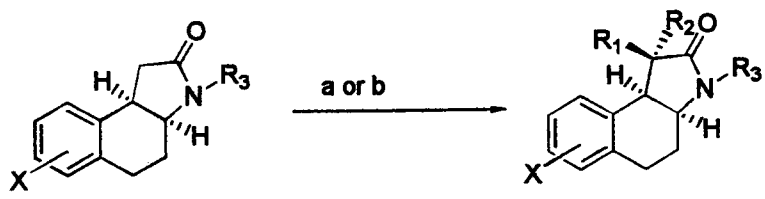


Figure 4. ORTEP diagram of **8c**. C3 and C12 correspond to C9b and C3a of the benz[*e*]indole nucleus.

13 under the same reaction conditions afforded the *cis*- and *trans*-lactams **14a** and **14b** and the unsaturated lactam **15** *(figure 3)*. Our previous studies with 3-phenylpyrrolidines showed that introduction of a *trans*-4-methyl substituent drastically reduced D_1 and D_2 receptor binding affinity; whereas, a *cis*-4-methyl group increased D_1 selectivity [14]. Studies with 6-hydroxy-2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]indoles indicated that introduction of a 1-methyl group reduced binding at D_1 and D_2 receptors [16]. Since earlier studies demonstrated considerable differences in receptor binding when a methyl group was substituted on the five-membered pyrrolidine ring, the effect on D_3 receptor binding affinity of small (1-methyl) and large (1-benzyl) substituents on the benz[*e*]indole nucleus was evaluated in this investigation. Due to the difficulty in separating **16b** and **17**, the complex mixture was alkylated with methyl iodide in the presence of LDA at –60 °C to readily afford the 1-methyl lactams **18a** and **18b**, respectively. Based on previous work [16] utilizing X-ray crystallography, the 1-methyl group was shown to be oriented in the opposite direction of the hydrogen at C-9b. Thus, the hydrogens at the 1,3a, and 9b-positions were on the same side, and the 1-methyl lactams **18a** and **18b** were designated the *cis-syn*-diastereoisomers. After deprotonation at C-3a of the unsaturated lactam **17**, the resonance stabilized anion undergoes alkylation at the C-1 position. Subsequently, a proton is removed from the C-1 position, and the resulting anion undergoes reaction with methyl iodide to yield the 1,1-dimethyl lactam **19**. The separation of the mixture of lactams generated in the reaction was accomplished by silica gel chromatography. The 1-methyl (**20a**) and 1-benzyl (**20d**) lactams were prepared in a similar manner as shown in *figure 5*; however, alkylation of *cis*-(±)-1,3,3a,4,5,9b-hexahydro-2*H*-benz[*e*]indol-2-one (**14a**) with methyl iodide gave a mixture of the dimethyl (**20b**) and monomethyl (**20c**) lactams, respectively. The target 6- and 8-hydroxy-2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]indoles were obtained by reduction of the corresponding lactams with lithium aluminum hydride followed by *O*-demethylation with either 48% hydrobromic acid or diphenylphosphine and *n*-butyllithium in tetrahydrofuran *(figure 6)* [17]. The *cis*- and *trans*-8-methoxy-*N*-(*n*-propyl) derivatives **21a** and **21b** and the *cis*- and *trans*-8-methoxy-*N*-allyl **21d** and **21f** derivatives were purified and tested as the hydrochloride salts. All other intermediate 6-methoxy-2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]indoles were not isolated and purified. These intermediates were directly demethylated and characterized as the hydrochloride or hydrobromide salts of the corresponding phenols. Resolution of *cis*-(±)-2,3,3a,4,5,9b-hexahydro-8-hydroxy-3-(*n*-propyl)-1*H*-benz[*e*]indole (±)-(**5**) was accomplished by isocratic HPLC on a chiral resin to yield *cis*-(+)-(**5**) and *cis*-(-)-**5**. HPLC using a chiral column showed that the optical purity of *cis*-(+)-**5** was 100% ee and *cis*-(-)-**5** was > 99.6% ee, respectively. X-ray crystallography *(figure 7)* of *cis*-(+)-**5** established the absolute configuration as 3a*S*, 9b*R*. In a similar manner, resolution of *trans*-(±)-2,3,3a,4,5,9b-hexahydro-8-hydroxy-3-(*n*-propyl)-1*H*-benz[*e*]indole (±)-**21c** gave *trans*-(+)-(**21c**) (99.6% ee) and *trans*-(-)-**21c** (100.0% ee). As shown in *figure 8*, X-ray crystallography of *trans*-(-)-**21c** established the absolute configuration as 3a*S*, 9b*S*.

3. Pharmacology

The direct interaction of the *cis*- and *trans*-hexahydrobenz[*e*]indoles with the human DA D_{2S} and D_3 receptor binding sites were studied in detail by in vitro radioligand binding displacement studies [18]. All assays



8a: X = 8–OCH_3, R_3 = *n*-Pr

14a: X = 6–OCH_3, R_3 = CH_3

20a: X = 8–OCH_3, R_1 = CH_3, R_2 = H, R_3 = *n*-Pr

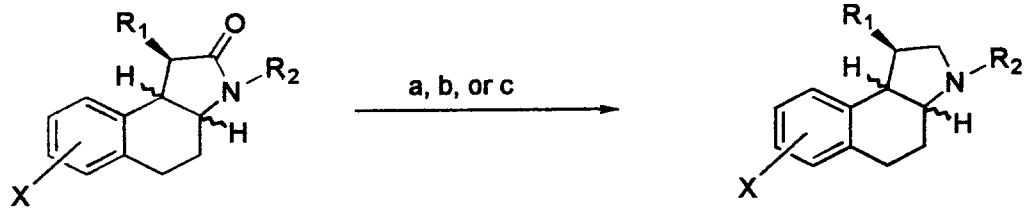
20b: X = 6–OCH_3, R_1 = R_2 = R_3 = CH_3

20c: X = 6–OCH_3, R_1 = CH_3, R_2 = H, R_3 = CH_3

20d: X = 6–OCH_3, R_1 = CH_2Ph, R_2 = H, R_3 = CH_3

Figure 5. (a) LDA/THF/CH_3I, (b) LDA/THF/BzBr.

were configured using radioligands selective for the target receptor. Assays were configured so that preferential binding to the G-protein coupled receptor state (with high affinity for agonists) was measured. Under these conditions the assay does not exhibit a preference for antagonists over agonists, and the use of a radiolabelled antagonist or agonist should not influence the results. Membrane preparations from clonal cells expressing D_{2S} (Ltk^- cells) and D_3 (BHK 21tk^- cells) were used in these studies. The data from the competition binding studies utilizing [^{3}H]spiperone (D_{2S}) and [^{3}H]*R*-(+)-7-OH-DPAT (D_3) as the radioligands revealed that several hexahydro-8-hydroxybenz[*e*]indoles have high affinities and selectivities for the DA D_3 receptor *(table 1)*.



cis-**8a:**	R_1 = H,	R_2 = *n*-Pr,	X = 8-OCH_3	*cis*-**21a:**	R_1 = H,	R_2 = *n*-Pr,	X = 8-OCH_3
trans-**8b:**	R_1 = H,	R_2 = *n*-Pr,	X = 8-OCH_3	*cis*-**5:**	R_1 = H,	R_2 = *n*-Pr,	X = 8-OH
cis-**10a:**	R_1 = H,	R_2 = allyl,	X = 8-OCH_3	*cis*-**21b:**	R_1 = H,	R_2 = *n*-Pr,	X = 8-OCH_3
trans-**10b:**	R_1 = H,	R_2 = allyl,	X = 8-OCH_3	*trans*-**21c:**	R_1 = H,	R_2 = *n*-Pr,	X = 8-OH
trans-**14b:**	R_1 = H,	R_2 = CH_3,	X = 6-OCH_3	*cis*-**21d:**	R_1 = H,	R_2 = allyl,	X = 8-OCH_3
cis-**18a:**	R_1 = CH_3,	R_2 = CH_3,	X = 8-OCH_3	*cis*-**21e:**	R_1 = H,	R_2 = allyl,	X = 8-OH
cis-**20a:**	R_1 = CH_3,	R_2 = *n*-Pr,	X = 8-OCH_3	*trans*-**21f:**	R_1 = H,	R_2 = allyl,	X = 8-OCH_3
cis-**20c:**	R_1 = CH_3,	R_2 = H,	X = 6-OCH_3	*trans*-**21g:**	R_1 = H,	R_2 = allyl,	X = 8-OH
cis-**20d:**	R_1 = Bz,	R_2 = CH_3,	X = 6-OCH_3	*cis*-**21h:**	R_1 = CH_3,	R_2 = CH_3,	X = 8-OH
				cis-**21i:**	R_1 = CH_3,	R_2 = *n*-Pr,	X = 8-OH
				cis-**21j:**	R_1 = Bz,	R_2 = CH_3,	X = 6-OH
				trans-**21k:**	R_1 = H,	R_2 = CH_3,	X = 5-OH
				cis-**21l:**	R_1 = CH_3,	R_2 = H,	X = 6-OH

Figure 6. (a) LAH/THF, (b) 48 % HBr or BuLi/Ph_2P/THF, (c) i. LAH/THF, ii. 48 % HBr.

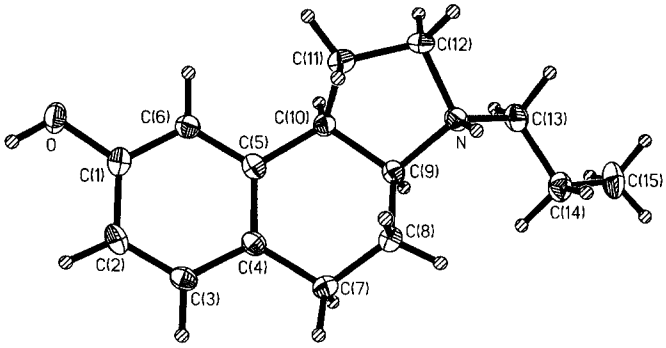


Figure 7. ORTEP diagram of *cis*-(+)-**5**. C10 and C9 correspond to C9b and C3a of the benz[*e*]indole nucleus.

The *trans*-analogues exhibited greater affinities at the DA D_3 receptor than the corresponding *cis*-isomers; however, their selectivities for this receptor were decreased. With the exception of the 6-hydroxy derivative (±)-**21k**, only compounds bearing a 8-hydroxy substituent demonstrated appreciable D_3 affinity. The *trans*-(+)-*N*-*n*-propyl (±)-**21c** and (±)-*N*-allyl (**21g**) derivatives exhibited the greatest affinities for the D_3 receptor (K_i = 2.1 nM and 1.7 nM, respectively) with D_{2S}/D_3 selectivities of 73 and 34, respectively. Resolution of (±)-**21c** into its enantiomeric forms showed that the D_3 affinity resided mainly in the (+)-3a*R*, 9b*R* enantiomer.

In the *cis*-series the 8-hydroxy-*N*-allyl derivative (±)-**21e** exhibited the greatest D_3 affinity (K_i = 10 nM) and D_{2S}/D_3 selectivity (290) of any compound evaluated in this study. The *cis*-(±)-*N*-allyl (**21e**) derivative showed about 4-fold greater affinity for the D_3 receptor than the corresponding *N*-*n*-Pr (±)-**5** derivative. Resolution of (±)-**5** into its individual enantiomers showed that the (-)-3a*R*, 9b*S* isomer exhibited most of the D_3 receptor

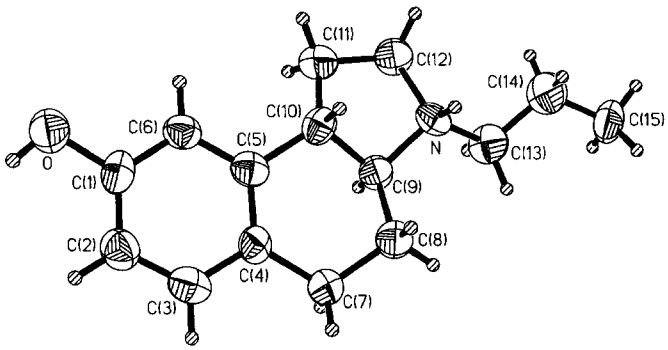


Figure 8. ORTEP diagram of *trans*-(-)-**21c**. C10 and C9 correspond to C9b and C3a of the benz[*e*]indole nucleus.

binding affinity. Compared with the more active *trans*-*N*-*n*-Pr (+)-**21c** enantiomer, (-)-**5** exhibited about a 6-fold lower affinity for the DA D_3 receptor and a slightly greater selectivity for this receptor. Introduction of a 1β-CH_3 group led to decreased D_3 receptor affinity in both the 8-OH and 6-OH series [compare compounds (±)-**5** and (±)-**21i** and compounds (±)-**21l** and (±)-**23**].

4. Conclusions

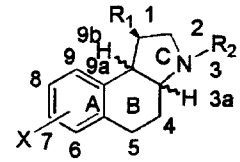
Conformationally constrained *cis*- and *trans*-2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]indoles were synthesized by employing a key reductive amination-cyclization step previously reported by Lin et al. [17]. Unlike the earlier report, several side products were isolated and characterized. Several 8-hydroxyhexahydro- benz[*e*]indoles exhibited potent binding affinity at DA D_3 receptors. The *trans*-diastereoisomers demonstrated greater affinities at D_3 receptors than the corresponding *cis*-isomers. The most potent derivatives in both series were substituted with an *N*-*n*-Pr or *N*-allyl group with the greatest D_{2S}/D_3 selectivity found with the *cis*-(±)-*N*-allyl derivative (±)-**21e**. The *cis*-and *trans*-(±)-8-hydroxy-2,3,3a,4,5,9b-hexahydro-3-(*n*-propyl)-1*H*-benz[*e*]indoles were resolved into their corresponding enantiomers, and the absolute configuration at the 3a and 9b-positions was determined by single crystal X-ray analysis. In the *cis*-series the more active enantiomer was the 3a*R*, 9b*S*-isomer while in the *trans*-series the 3a*R*, 9b*R*-enantiomer exhibited greater D_3 affinity. Introduction of a 1β-substituent (methyl or benzyl) resulted in dramatically decreased DA D_3 receptor affinity. These conformationally constrained 8-hydroxy-2,3,3a,4,5,9-hexahydro-benz[*e*]indoles may be useful probes for exploring the DA D_3 receptor. Additionally, these compounds may have therapeutic potential in a variety of central nervous system disorders involving abnormalities of DA neurotransmission [19].

5. Experimental protocols

5.1. Chemistry

Melting points were determined on a Thomas-Hoover melting points 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, a JEOL Eclipse 400 MHz spectrometer, or a Bruker 400 MHz spectrometer. Chemical shifts were reported in parts per million (δ) relative to tetramethyl-

Table I. In vitro binding at D_{2S} and D_3 receptors[a].



Compound	R_1	R_2	X	B/C Ring	D_{2S}[c]	D_3[d]	D_{2S}/D_3[e]
(±)-**21a**	H	*n*-Pr	8-OCH_3	*cis*	5070 ± 357	1500 ± 158	3
(±)-**5**	H	*n*-Pr	8-OH	*cis*	1576 ± 237[f]	39.2 ± 3.0[f]	40
(+)-**5**	H	*n*-Pr	8-OH	*cis*[g]	5476 ± 1194	296 ± 12	19
(-)-**5**	H	*n*-Pr	8-OH	*cis*[h]	1007 ± 45	14.7 ± 4.3	69
(±)-**21b**	H	*n*-Pr	8-OCH_3	*trans*	8417 ± 1338	368 ± 66	23
(±)-**21c**	H	*n*-Pr	8-OH	*trans*	147 ± 21	2.1 ± 1.9	73
(+)-**21c**	H	*n*-Pr	8-OH	*trans*[i]	105 ± 21	2.3 ± 1.9	46
(-)-**21c**	H	*n*-Pr	8-OH	*trans*[j]	2100 ± 569	156 ± 2.5	14
(±)-**21d**	H	allyl	8-OCH_3	*cis*	3630 ± 201	553 ± 0.5	7
(±)-**21e**	H	allyl	8-OH	*cis*	2907 ± 34	10 ± 1	290
(±)-**21f**	H	allyl	8-OCH_3	*trans*	2760 ± 429	158 ± 43	18
(±)-**21g**	H	allyl	8-OH	*trans*	57 ± 4	1.7 ± 0.2	34
(±)-**21h**	CH_3	CH_3	8-OH	*cis*	3276 ± 513	351 ± 44	9
(±)-**21i**	CH_3	*n*-Pr	8-OH	*cis*	3717 ± 966	452 ± 57	8
(±)-**21j**	Bz	CH_3	6-OH	*cis*	2475 ± 383	898 ± 128	3
(±)-**21k**	H	CH_3	6-OH	*trans*	5.3 ± 1.8	44 ± 24	0.12
(±)-**21l**	CH_3	H	6-OH	*cis*	3615 ± 44	1238 ± 7	3
(±)-**22**[k]	CH_3	*n*-Pr	6-OH	*cis*	3624 ± 770	1245 ± 30	3
(±)-**23**[l]	H	H	6-OH	*cis*	1379 ± 451	101 ± 1	14
(±)-**24**[k]	CH_3	*n*-Pr	6,7-$(OH)_2$	*cis*	4496 ± 830	264 ± 48	17
2					202 ± 123	0.4 ± 0.3	505
Quin[f]					80 ± 42	1.2 ± 0.8	67

[a]Competitive displacement studies were performed using membrane preparations from clonal cells expressing D_{2S} (Ltk^- cells) and D_3 (BHK 21tk^- cells) receptors, respectively. [b]K_i values were calculated from the Cheng-Prusoff equation [18], using IC_{50} values obtained from competitive displacement studies with at least 5 different ligand concentrations. The results shown represent the mean ± SD of 2–8 separate experiments. The K_D values used in the calculations were established in independent binding experiments for each receptor subtype. [c][^{3}H]Spiperone (0.1 nM) was used to label D_{2S} receptors. [d][^{3}H]*R*-(+)-7-OH-DPAT (0.1 nM) was used to label D_3 receptors. [e]D_3 selectivity D_{2S} $(K_i)/D_3$ (K_i). [f]Reference [18]. [g]Absolute configuration (3a*S*, 9b*R*). [h]Absolute configuration (3a*R*, 9b*S*). [i]Absolute configuration (3a*R*, 9b*R*). [j]Absolute configuration (3a*S*, 9b*S*). [k]Reference [16]. [l]Reference [15].

silane. Mass spectra were recorded on a Finnigan MAT TSQ 4510 spectrometer. TLC was performed on precoated plastic silica gel sheets (5 × 20 cm) with fluorescent indicator UV_{254} (EM Industries). Flash chromatography was performed using silica gel (40 μm) purchased from J. R. Baker Chemical Company. Analytical data were obtained from Oneida Research Services, Inc., Whitesboro, NY.

5.1.1. (±)-1,2,3,4-Tetrahydro-7-methoxy-2-oxo-1-naphthaleneacetic acid methyl ester **7**

The 2-tetralone **6** (60.0 g, 341 mmol) was dissolved in dry toluene (800 mL) under a nitrogen atmosphere. The reaction mixture was treated with *p*-toluenesulfonic acid monohydrate (2.72 g, 14.3 mmol) followed by the dropwise addition of pyrrolidine (48.4 g, 681 mmol) [20]. The mixture was refluxed overnight with water being removed via a Dean Stark trap. After cooling, the toluene was removed under reduced pressure to afford a brown oil. The oil was dissolved in dry MeOH (800 mL), charged into a dry flask, and treated dropwise with methyl bromoacetate (104.2 g, 681 mmol) under nitrogen. After refluxing overnight, water (270 mL) was added, and the mixture was refluxed for 3 h. The reaction mixture was concentrated under reduced pressure, and the crude product was extracted with CH_2Cl_2 (3 × 300 mL). The CH_2Cl_2 extracts were washed with water (3 × 400 mL), dried (Na_2SO_4), filtered, and evaporated to yield a brown oil. Vacuum distillation gave 57.5 g (68%) of **7** as a colourless oil: b.p. 170–174 °C; (0.4 mm); IR (neat)

1 734 (C=O, ketone), 1 717 (C=O, ester) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.54 (t, J = 5 Hz, 2 H, H-4), 2.98 (d, J = 6 Hz, 2 H, CH_2COOCH_3), 3.01 (t, J = 5 Hz, 2 H, H-3), 3.65 (s, 3 H, $COOCH_3$), 3.74 (s, 3 H, OCH_3), 3.88 (t, J = 6 Hz, 1 H, H-1), 6.91 (m, 3 H, ArH); ^{13}C NMR δ 27.2, 32.9, 37.7, 48.8, 51.8, 55.2, 111.9, 128.6, 129.4, 136.8, 158.8, 172.3, 209.5. Due to its instability, this compound was kept in the freezer under nitrogen without obtaining an elemental analysis.

5.1.2. cis-(±)-1,3,3a,4,5,9b-Hexahydro-8-methoxy-3-n-propyl-2H-benz[e]indol-2-one **8a**, *trans-(±)-1,3,3a,4,5,9b-Hexahydro-8-methoxy-3-n-propyl-2H-benz[e]indol-2-one* **8b**, *cis-(±)-3a-Cyano-1,3,3a,4,5,9b-hexahydro-8-methoxy-3-n-propyl-2H-benz[e]indol-2-one* **8c**, *and (±)-4,5-Dihydro-8-methoxynaphtho[2,1-b]furan-2(3aH)-one* **9**

A solution of *n*-propylamine (23.2 g, 282 mmol) in dry MeOH (100 mL) was treated dropwise with the ketoester **7** (10.0 g, 40.3 mmol) in MeOH (25 mL) followed by the addition of glacial acetic acid (16.2 mL) and $NaBH_3CN$ (7.59 g, 121 mmol). The reaction mixture was stirred overnight at room temperature under nitrogen. The solvent was removed under reduced pressure, and the resulting residue was acidified (pH 2) with 1 N HCl and stirred for 30 min. The mixture was extracted with CH_2Cl_2 (3 × 200 mL), and the combined extracts were washed with water (3 × 200 mL), dried (Na_2SO_4), and evaporated under vacuum to afford a light yellow oil. The resulting mixture was flash chromatographed on silica gel using ethyl acetate/hexane (4:1). Identical fractions as determined by TLC were combined and evaporated under reduced pressure.

The least polar compound was obtained as a yellow solid. Recrystallization from ethyl acetate/hexane gave 1.10 g (13%) of **9**: m.p. 144–145 °C; ^1H NMR ($CDCl_3$) δ 2.07 (m, 2 H, H-4), 3.04 (t, 2 H, H-5), 3.84 (s, 3 H, OCH_3), 5.07 (m, 1 H, H-3a), 6.09 (d, 1 H, H-3a), 7.10 (m, 3 H, ArH); ^{13}C NMR ($CDCl_3$) δ 26.9, 30.4, 55.5, 80.2, 109.6, 110.5, 118.6, 128.1, 130.3, 158.5, 166.2; MS (EI) m/z 217 $(M + 1)^+$. Anal. ($C_{13}H_{12}O_3$) C, H.

A second compound was obtained as a light yellow solid which gave 0.92 g (8%) of **8c** after recrystallization from EtO_2/petroleum ether: m.p. 99.5–100.5 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, J = 7.4 Hz, 3 H, $NCH_2CH_2CH_3$), 1.78 (m, 2 H, $NCH_2CH_2CH_3$), 2.20 (m, 2 H), 2.43 (dd, 1 H), 2.80 (m, 2 H), 3.06 (dd, 1 H), 3.37 (m, 2H), 3.78 (s, 3 H, OCH_3), 3.89 (t, J = 9.7 Hz, 1 H, H-9b), 6.62 (d, J = 3.6 Hz, 1 H), 6.77 (dd, 1 H), 7.17 (d, J = 8.5 Hz, 1 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 11.0, 21.1, 23.9, 29.6, 37.8, 40.6, 42.7, 54.9, 59.9, 112.9, 113.0, 119.4, 125.4, 129.3, 134.6, 158.2, 172.1; MS (EI) m/z 284 M^+. Anal. ($C_{17}H_{20}N_2O_2$) H, N, C: calcd 71.80; found 72.26.

A third compound was obtained as a yellow solid. Recrystallization from ethyl acetate/hexane gave 1.8 g (18%) of **8b**: m.p. 94–95 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 11.0, 20.9, 25.9, 26.0, 34.6, 41.7, 43.0, 54.9, 60.3, 110.1, 111.5, 126.7, 129.1, 137.6, 157.5, 175.0; MS (EI) m/z 259 M^+. Anal. ($C_{16}H_{21}NO_2$) C, H, N.

The most polar compound was obtained as a light yellow solid. Recrystallization from ethyl acetate/hexane yielded 5.43 g (52%) of **8a**: m.p. 69–70 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, J = 7.4 Hz, 3 H), 1.57 (m, 2 H), 1.87 (m, 2 H), 2.43 (dd, 1 H), 2.66 (m, 2 H), 2.88 (dd, 1 H), 3.32 (m, 3 H), 3.78 (s, 3 H, OCH_3), 3.89 (m, 1 H, H-3a), 6.65 (d, J = 2.6 Hz, 1 H), 6.71 (dd, 1 H), 7.02 (d, J = 8.4 Hz, 1 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 10.9, 20.3, 25.0, 35.0, 38.8, 41.5, 54.8, 56.6, 111.8, 113.2, 127.8, 128.9, 138.0, 157.8, 173.0; MS (EI) m/z 259 M^+. Anal. ($C_{16}H_{21}NO_2$) C, H, N.

5.1.3. cis-(±)-1,3,3a,4,5,9b-Hexahydro-8-methoxy-3-(2-propenyl)-2H-benz[e]indol-2-one **10a**, *trans-(±)-1,3,3a,4,5,9b-Hexahydro-8-methoxy-3-(2-propenyl)-2H-benz[e]-indol-2-one* **10b**, *cis-(±)-3a-Cyano-1,3,3a,4,5,9b-hexahydro-8-methoxy-3-(2-propenyl)-2H-benz[e]indol-2-one* **10c**, *1,3-Dihydro-8-methoxy-3-(2-propenyl)-2H- benz[e]-indol-2-one* **11**

In a similar manner as described above, the ketoester **7** (20.0 g, 80.6 mmol), allylamine (32.1 g, 564 mmol), glacial acetic acid (32 mL), and $NaBH_3CN$ (15.2 g, 242 mmol) in MeOH (325 mL) yielded an oil. The reaction mixture was flash chromatographed on silica gel using ethyl acetate/hexane (2:1) as the solvent. The impure fractions were rechromatographed using the same solvent system. Identical fractions as determined by TLC were combined and evaporated under reduced pressure.

The least polar compound was obtained as a light yellow oil. Recrystallization from diethyl ether/petroleum ether gave 3.63 g (18%) of **11**: m.p. 140.0–140.5 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 3.73 (s, 2 H, H-1), 3.92 (s, 3 H, OCH_3), 4.41 (dd, 2 H), 5.24 (m, 2 H), 5.89 (m, 1 H), 6.81 (d, J = 2.3 Hz, 1 H), 6.98 (m, 2 H), 7.69 (d, J = 8.9 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 34.9, 42.4, 55.4, 100.4, 107.9, 117.0, 117.4, 125.5, 128.4, 130.7, 130.9, 131.8, 142.4, 158.8, 175.3. Anal. ($C_{16}H_{15}NO_2$) C, H, N.

A second non-polar product was obtained as a light yellow solid. Recrystallization from diethyl ether/petroleum ether afforded 1.12 g (5%) of **10c**: m.p. 98–99 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.16 (m, 2 H, H-4), 2.48 (dd, 1 H), 2.78 (m, 2 H, H-5), 3.07 (dd, 1 H), 3.77 (s, 3 H, OCH_3), 3.89 (t, 1 H, H-9b), 4.11 (m, 2 H),

5.33 (dd, 2 H), 5.91 (m, 1 H), 6.62 (d, 1 H), 6.77 (dd, 1 H), 7.04 (d, 1 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 24.4, 30.4, 38.2, 41.2, 44.1, 55.5, 60.7, 113.4, 113.6, 119.3, 119.5, 126.0, 129.9, 132.5, 135.1, 158.8, 172.4; MS (EI) m/z 282 M^+. Anal. ($C_{17}H_{18}N_2O$) C, H, N.

A third compound was obtained as a yellow oil which solidified upon standing. Recrystallization from diethyl ether/petroleum ether gave 1.23 g (6%) of **10b**: m.p. 108.5–109.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.05 (m, 2 H), 2.63 (m, 2H), 3.00 (m, 2 H), 3.08 (m, 1 H, H-9b), 3.35 (m, 1 H, H-3a), 3.79 (s, 3 H, OCH_3), 3.97 (m, 2 H), 5.19 (m, 2 H), 5.75 (m, 1 H), 6.56 (d, J = 2.3 Hz, 1 H), 6.73 (dd, 1 H), 7.03 (d, J = 8.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 26.3, 35.0, 43.3, 55.4, 60.9, 78.5, 110.6, 112.0, 117.4, 127.2, 129.6, 133.1, 138.0, 158.0, 175.4; MS (EI) m/z 257 M^+. Anal. ($C_{16}H_{19}NO_2$) C, H, N.

The most polar compound was obtained as a yellow oil which solidified upon standing. Recrystallization from diethyl ether/petroleum ether yielded 12.5 g (60%) of **10a**: m.p. 79–80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.86 (m, 2 H), 2.65 (m, 2 H), 2.67 (m, 2 H), 3.78 (s, 3 H, OCH_3), 3.88 (m, 1 H, H-3a), 4.04 (m, 3 H), 5.23 (m, 2 H), 5.80 (m, 1 H), 6.65 (d, J = 2.5 Hz, 1 H), 7.02 (d, J = 8.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 24.9, 25.4, 34.9, 38.6, 42.8, 54.8, 56.4, 111.8, 113.3, 117.3, 127.8, 129.0, 132.3, 137.9, 157.8, 172.8; MS (EI) m/z 257 M^+. Anal. ($C_{16}H_{19}NO_2$) H, N, C: calcd 74.68; found 74.11.

5.1.4. (±)-1,2,3,4-Tetrahydro-5-methoxy-2-oxo-1-naphthaleneacetic acid methyl ester **13**

Following the procedure described for the synthesis of **7**, the 2-tetralone **12** (28.0 g, 159 mmol), *p*-toluenesulfonic acid monohydrate (1.36 g, 7.2 mmol), pyrrolidine (22.6 g, 318 mmol), and methyl bromoacetate (48.6 g, 318 mmol) yielded a dark green oil. Vacuum distillation gave 21.7 g (55%) of **13** as a colourless oil: b.p. 175–190 °C (0.6 mm; reference [17] no reported b.p.); IR (neat) 1 736 (C=O, ketone), 1 719 (C=O, ester) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.87 (m, 6 H), 3.67 (s, 3 H, $COOCH_3$), 3.84 (s, 3 H, OCH_3), 3.90 (t, 1 H, H-1), 7.17 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 20.6, 33.9, 37.1, 48.6, 51.7, 55.6, 109.1, 118.3, 125.8, 127.7, 137.6, 156.5, 172.3.

5.1.5. cis-(±)-1,3,3a,4,5,9b-Hexahydro-6-methoxy-3-methyl-2H-benz[e]indol-2-one **14a**, *trans-(±)-1,3,3a,4,5,9b-Hexahydro-6-methoxy-3-methyl-2H-benz[e]indol-2-one* **14b**, *and (±)-3,3a,4,5-Tetrahydro-6-methoxy-3-methyl-2H- benz[e]indol-2-one* **15**

Using the general reductive amination-cyclization procedure, the ketoester **13** (4.61 g, 18.6 mmol), methylamine hydrochloride (12.5 g, 186 mmol), triethylamine (18.8 g, 186 mmol), glacial acetic acid (7.5 mL), and $NaBH_3CN$ (3.51 g, 55.8 mmol) in absolute ethanol (270 mL) afforded an oil which solidified upon standing. Recrystallization from ethyl acetate/hexane gave 0.22 g (5%) of **15**: m.p. 174.5–175.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.30 (m, 4 H), 3.05 (s, 3 H, NCH_3), 3.85 (s, 3 H, OCH_3), 4.02 (m, 1 H, H-3a), 6.22 (d, 1 H), 7.02 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 21.9, 27.0, 28.1, 55.5, 62.3, 111.0, 117.0, 117.8, 121.0, 125.9, 127.4, 156.8, 172.0. Anal. ($C_{14}H_{15}NO_2$) C, H, N.

The filtrate remaining from the recrystallization of **15** was concentrated under reduced pressure and flash chromatographed on silica gel using ethyl acetate/hexane (9:1) as the solvent. Fractions determined to be identical by TLC were combined and concentrated under reduced pressure. The less polar product was obtained as a white solid which afforded 0.34 g (8%) of **14b** after recrystallization from ethyl acetate/hexane: m.p. 163–164 °C; ^{1}H NMR ($CDCl_3$) δ 2.43 (m, 8 H), 2.86 (s, 3 H, NCH_3), 3.83 (s, 3 H, OCH_3), 6.96 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 22.1, 26.2, 27.1, 35.3, 43.4, 55.3, 62.0, 108.4, 117.0, 123.7, 126.9, 137.9, 157.2, 176.0. Anal. ($C_{14}H_{17}NO_2$) C, H, N.

The more polar compound was obtained as a light yellow solid. Recrystallization from ethyl acetate/hexane gave 1.72 g (40%) of **14a**: m.p. 117–118 °C; ^{1}H NMR ($CDCl_3$) δ 2.73 (m, 8 H), 2.91 (s, 3 H, NCH_3), 3.82 (s, 3 H, OCH_3), 6.95 (m, 3 H, ArH); ^{13}C NMR ($CDCl_3$) δ 19.3, 24.5, 27.6, 35.2, 39.3, 55.5, 59.2, 107.8, 121.1, 125.5, 127.1, 138.8, 156.8, 173.7. Anal. ($C_{14}H_{17}NO_2$) N, C: calcd 72.70; found 72.28, H: calcd 7.41; found 6.94.

5.1.6. cis-(±)-1,3,3a,4,5,9b-Hexahydro-8-methoxy-3-methyl-2H-benz[e]indol-2-one **16a** *and cis-(±)-3a-Cyano-1,3,3a,4,5,9b-hexahydro-8-methoxy-3-methyl-2H-benz[e]indol-2-one* **16b**

Using the general reductive amination-cyclization procedure, methylamine hydrochloride (29.7 g, 440 mmol), triethylamine (31.8 g, 314 mmol), the ketoester **7** (15.6 g, 62.8 mmol), glacial acetic acid (25 mL), and $NaBH_3CN$ (11.8 g, 189 mmol) in dry methanol (200 mL) gave, after the standard work-up, a light yellow oil. The oil was flash chromatographed on silica gel using ethyl acetate as the solvent. Fractions determined to be identical by TLC were combined and concentrated under reduced pressure. The less polar compound was obtained as a light yellow solid after trituration with diethyl ether/hexane. Recrystallization from CH_2Cl_2/hexane afforded 1.60 g (11%) of **16b**: m.p. 148–149 °C; ^{1}H NMR ($CDCl_3$) δ 2.86 (s, 7 H), 2.98 (s, 3 H, OCH_3), 6.93 (s, 3 H, ArH); ^{13}C NMR ($CHCl_3$) δ 23.9, 26.2, 29.4, 38.5, 40.3, 55.4, 60.8, 113.4, 119.1, 126.1, 129.7, 135.3, 158.8, 172.7. Anal. ($C_{15}H_{16}N_2O_2$) H, N, C: calcd 70.29; found 69.89.

The more polar compound was obtained as a white solid after trituration with water. Recrystallization from CH_2Cl_2/hexane yielded 8.89 g (61%) of **16a**: m.p. 119–120 °C; ^{1}H NMR ($CDCl_3$) δ 2.34 (m, 6 H), 2.89 (s, 3 H), 3.71 (m, 2 H), 3.76 (s, 3 H), 6.89 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 25.3, 25.5, 27.6, 35.1, 39.2, 55.3, 59.3, 112.2, 113.7, 128.3, 129.4, 138.6, 158.3, 173.5. Anal. ($C_{14}H_{17}NO_2$) C, H, N.

5.1.7. cis-syn-(±)-1,3,3a,4,5,9b-Hexahydro-8-methoxy-1,3-dimethyl-2H-benz[e]indol-2-one **18a**, *cis-syn-(±)-3a-Cyano-1,3-dimethyl-1,3,3a,4,5,9b-hexahydro-8-methoxy-2H-benz[e]indol-2-one* **18b**, *and 8-Methoxy-1,3,4,5-tetrahydro-1,1,3-trimethyl-2H-benz[e]indol-2-one* **19**

Using the procedure described above, the ketoester **7** (5.00 g, 21.1 mmol), methylamine hydrochloride (9.52 g, 141 mmol), triethylamine (10.2 g, 101 mmol), glacial acetic acid (8.1 mL), and $NaBH_3CN$ (3.80 g, 60.4 mmol) in dry methanol (70 mL) afforded a mixture of **16a**, **16b**, and **17**. Since the separation was difficult, the entire mixture was used directly in the next step without further purification. The oil was dissolved in dry THF (400 mL), cooled to –60 °C under a nitrogen atmosphere, and treated with LDA (16.9 mL, 25.3 mmol, 1.5 M in cyclohexane) for 5 min. The mixture was stirred for 2 h, and methyl iodide (3.59 g, 25.3 mmol) was added dropwise. After warming to room temperature, the mixture was stirred for 20 h and quenched with 3 N HCl (pH < 3). The reaction mixture was evaporated under reduced pressure, and the remaining residue was extracted with CH_2Cl_2 (3 × 100 mL). The combined CH_2Cl_2 extracts were washed with water (3 × 200 mL), dried (Na_2SO_4), filtered, and evaporated to yield a brown oil. The oil was flash chromatographed on silica gel using ethyl acetate/hexane (4:1) as the solvent system.

The least polar compound was obtained as a yellow solid. Recrystallization from hexane gave 0.21 g (4%) of **19**: m.p. 154.5–155.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 6 H), 2.75 (m, 4 H), 3.09 (s, 3 H, NCH_3), 3.79 (s, 3 H, OCH_3), 6.88 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 20.3, 23.3, 26.3, 27.2, 45.8, 55.2, 108.0, 119.9, 124.9, 128.4, 132.6, 139.2, 158.5, 183.7. Anal. ($C_{16}H_{19}NO_2$) C, H, N.

A second compound was obtained as a yellow solid. Recrystallization from ethyl acetate/hexane gave 0.82 g (15%) of **18b**: m.p. 147–148 °C; ^{1}H NMR ($CDCl_3$) δ 1.49 (d, J = 7 Hz, 3 H, 1-CH_3), 2.70 (m, 6 H), 3.02 (s, 3 H, NCH_3), 3.79 (s, 3 H, OCH_3), 6.88 (m, 3 H, ArH); ^{13}C NMR ($CDCl_3$) δ 16.3, 24.6, 26.4, 30.1, 44.3, 49.5, 55.4, 113.5, 113.9, 119.4, 126.5, 129.8, 135.2, 158.9, 174.8. Anal. ($C_{16}H_{18}N_2O_2$) H, N, C: calcd 71.09; found 72.84.

The most polar product was obtained as a yellow oil which solidified upon standing. Recrystallization from diethyl ether/hexane gave 2.62 g (53%) of **18a**: m.p. 97–98 °C; ^{1}H NMR ($CDCl_3$) δ 1.40 (d, J = 7 Hz, 3 H, 1-CH_3), 2.38 (m, 7 H), 2.92 (s, 3 H, NCH_3), 3.79 (s, 3 H, OCH_3), 6.88 (m, 3 H, ArH); ^{13}C NMR ($CDCl_3$) δ 16.4, 25.9, 44.5, 44.7, 55.4, 57.8, 112.4, 114.1, 128.9, 129.4, 138.5, 158.5, 175.9. Anal. ($C_{15}H_{19}NO_2$) C, H, N.

5.1.8. cis-syn-(±)-1,3,3a,4,5,9b-Hexahydro-8-methoxy-1-methyl-3-n-propyl-2H-benz[e]indol-2-one **20a**

In a similar manner as described above, **8a** (1.50 g, 5.78 mmol), LDA (4.63 mL, 6.94 mmol, 1.5 M in cyclohexane), methyl iodide (0.98 g, 6.94 mmol) in dry THF (95 mL) gave a brown oil. The oil was flash chromatographed on a silica gel column using ethyl acetate/hexane (4:1) as the eluent. Identical fractions as determined by TLC were combined and concentrated under reduced pressure to give a yellow solid. Recrystallization from hexane afforded 1.22 g (77%) of **20a**: m.p. 192–193 °C; ^{1}H NMR ($CDCl_3$) δ 0.94 (t, 3 H, J = 7 Hz, $NCH_2CH_2CH_3$), 1.42 (d, J = 7 Hz, 3 H, 1-CH_3), 2.56 (m, 11 H), 3.80 (s, 3 H, OCH_3), 6.90 (m, 3 H, ArH); ^{13}C NMR ($CDCl_3$) δ 11.4, 16.3, 20.9, 25.8, 26.2, 42.2, 44.4, 44.6, 55.3, 112.1, 113.9, 128.6, 129.4, 138.3, 158.1, 175.9.

5.1.9. cis-(±)-1,3,3a,4,5,9b-Hexahydro-6-methoxy-1,1,3-trimethyl-2H-benz[e]indol-2-one **20b** *and cis-syn-(±)-1,3-Dimethyl-1,3,3a,4,5,9b-hexahydro-6-methoxy-2H-benz[e]indol-2-one* **20c**

Using the method described for the synthesis of **20a**, **14a** (0.40 g, 1.74 mmol), LDA (1.75 mL, 2.62 mmol, 1.5 M in cyclohexane), and methyl iodide (0.50 g, 3.49 mmol) in THF (20 mL) gave a yellow semi-solid. The reaction mixture was flash chromatographed on a silica gel column using ethyl acetate/hexane (3:2) as the solvent. Identical fractions as determined by TLC were combined and concentrated under reduced pressure.

The less polar compound was obtained as an oil which afforded a solid upon trituration with hexane. Recrystallization from methanol/water gave 0.10 g (20%) of **20b**: m.p. 200–202 °C; ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 6 H, $(CH_3)_2$), 3.09 (s, 3 H, NCH_3), 3.25 (m, 6 H), 3.83 (s, 3 H, OCH_3), 7.08 (m, 3 H, ArH); ^{13}C NMR ($CDCl_3$) δ 19.3, 20.0, 23.3, 23.9, 46.0, 55.5, 108.0, 114.0, 123.0, 127.1, 138.5, 156.9, 183.8. Anal. ($C_{16}H_{21}NO_3$) C, H, N.

The more polar compound was obtained as an oil which was triturated with hexane to afford **20c** as a brown solid: m.p. 81–82 °C; ^{1}H NMR ($CDCl_3$) δ 1.41 (d, J = 7 Hz, 3 H, 1-CH_3), 2.66 (m, 7 H), 2.92 (s, 3 H, NCH_3), 3.82 (s, 3 H, OCH_3), 6.96 (m, 3 H, ArH).

5.1.10. cis-syn-(±)-1-Benzyl-1,3,3a,4,5,9b-hexahydro-6-methoxy-3-methyl-2H-benz[e]indol-2-one **20d**

Following the procedure described above, **14a** (0.91 g, 3.93 mmol), LDA (3.95 mL, 5.92 mmol, 1.5 M in cyclohexane), and benzyl bromide (0.81 g, 4.72 mmol) in THF (45 mL) gave a light yellow oil. The reaction mixture was flash chromatographed on a silica gel column using ethyl acetate/hexane (3:2) as the solvent. Removal of the solvent under reduced pressure gave a white solid which was recrystallized from diethyl ether/hexane to yield 0.70 g (39%) of **20d**: m.p. 128–129 °C; ^{1}H NMR ($CDCl_3$) δ 2.68 (m, 9 H), 2.84 (s, 3 H, NCH_3), 3.78 (s, 3 H, OCH_3), 6.83 (m, 8 H, ArH); ^{13}C NMR ($CDCl_3$) δ 17.2, 24.3, 27.5, 36.6, 38.5, 53.5, 55.3, 56.6, 107.3, 120.7, 125.5, 126.6, 126.9, 128.5, 129.7, 138.7, 138.8, 156.2, 175.9. Anal. ($C_{21}H_{23}NO_2$) C, H, N.

5.1.11. cis-(±)-2,3,3a,4,5,9b-Hexahydro-8-methoxy-3-n-propyl-1H-benz[e]indole hydrochloride **21a**

A solution of **8a** (1.00 g, 3.90 mmol) in THF (40 mL) was added to a stirred suspension of LAH (1.57 g, 41.4 mmol) in THF (25 mL) under a nitrogen atmosphere. The mixture was refluxed for 24 h, cooled to room temperature, and treated dropwise with water to decompose the excess LAH. The mixture was filtered and evaporated under reduced pressure. The resulting residue was partitioned between CH_2Cl_2 (100 mL) and water (100 mL), and the organic layer was separated, dried (Na_2SO_4), filtered, and evaporated to yield a yellow oil. The crude product was flash chromatographed on silica gel using ethyl acetate/hexane/triethylamine (100:50:1.5) as the solvent. Evaporation of the solvents gave a light yellow oil. Formation of the hydrochloride salt gave 0.90 g (83%) after recrystallization from diethyl ether/isopropanol: m.p. 147.5–148 °C; ^{1}H NMR (DMSO-d_6) δ 0.93 (t, J = 7 Hz, 3 H, $NCH_2CH_2CH_3$), 2.78 (m, 14 H), 3.72 (s, 3 H, OCH_3), 6.89 (m, 3 H, ArH); ^{13}C NMR (DMSO-d_6) δ 10.9, 18.1, 24.3, 25.7, 31.9, 39.1, 52.7, 55.0, 55.7, 65.0, 112.0, 113.2, 127.9, 128.9, 137.2, 157.8. Anal. ($C_{16}H_{24}ClNO$) C, N, H: calcd 8.58; found 7.97.

5.1.12. trans-(±)-2,3,3a,4,5,9b-Hexahydro-8-methoxy-3-n-propyl-1H-benz[e]indole hydrochloride **21b**

According to the method for the synthesis of **21a**, **8b** (0.65 g, 2.5 mmol) and LAH (0.29 g, 7.6 mmol) in dry THF (40 mL) gave a yellow oil which was purified by flash chromatography on silica gel using a solvent system of ethyl acetate/hexane/triethylamine (50:50:1). Evaporation of the solvents afforded an oil. A hydrochloride salt was prepared and recrystallized from diethyl ether/isopropanol to afford 0.57 g (80%) of **21b**: m.p. 204–205 °C; ^{1}H NMR (DMSO-d_6) δ 0.94 (t, J = 7 Hz, 3 H, $NCH_2CH_2CH_3$), 2.50 (m, 14 H), 3.72 (s, 3 H, OCH_3), 6.89 (m, 3 H, ArH); ^{13}C NMR (DMSO-d_6) δ 10.9, 18.1, 22.5, 24.9, 26.8, 43.0, 52.2, 53.3, 55.0, 67.6, 111.1, 112.5, 126.6, 129.1, 137.2, 157.5. Anal. ($C_{16}H_{24}ClNO$) H, N, C: calcd 68.19; found 66.49.

5.1.13. cis-(±)-2,3,3a,4,5,9b-Hexahydro-8-methoxy-3-(2-propenyl)-1H-benz[e]indole hydrochloride **21d**

Following the procedure for the preparation of **21a**, **10a** (6.00 g, 23.3 mmol) and LAH (2.69 g, 70.9 mmol) in dry THF (350 mL) yielded a yellow oil. The reaction mixture was flash chromatographed on silica gel using ethyl acetate/hexane/triethylamine (20:10:0.3) as the solvent. The solvents were evaporated to afford an oil. The hydrochloride was prepared and recrystallized from diethyl ether/isopropanol to give 5.68 g (87%) of **21d**: m.p. 144.5–145.0 °C; ^{1}H NMR (DMSO-d_6) δ 2.76 (m, 12 H), 3.76 (s, 3 H, OCH_3), 5.52 (m, 2 H, $NCH_2CH{=}CH_2$), 6.18 (m, 1 H, $NCH_2CH{=}CH_2$), 6.90 (m, 3 H, ArH); ^{13}C NMR (DMSO-d_6) δ 24.1, 25.6, 31.9, 39.4, 52.0, 55.0, 55.9, 64.0, 112.0, 113.2, 123.9, 127.9, 128.6, 128.9, 137.2, 157.8. Anal. ($C_{16}H_{22}ClNO$) C, H, N.

5.1.14. trans-(±)-2,3,3a,4,5,9b-Hexahydro-8-methoxy-3-(2-propenyl)-1H-benz[e]indole hydrochloride **21f**

In a similar manner as described for the synthesis of **21a**, **10b** (2.50 g, 9.7 mmol) and LAH (1.12 g, 29.5 mmol) in dry THF (150 mL) yielded a yellow oil which was flash chromatographed on a silica gel column using a solvent system of ethyl acetate/hexane/triethyl amine (50:50:1). Evaporation of the solvents afforded a yellow oil. The hydrochloride was prepared and recrystallized from diethyl ether/isopropanol to give 2.25 g (83%) of **21f**: m.p. 190.5–191.5 °C; ^{1}H NMR (DMSO-d_6) δ 2.94 (m, 12 H), 3.73 (s, 3 H, OCH_3), 5.51 (m, 2 H), 6.05 (m, 1 H), 6.93 (m, 3 H, ArH); ^{13}C NMR (DMSO-d_6) δ 22.4, 24.9, 26.7, 43.1, 51.6, 53.5, 54.9, 66.9, 110.0, 112.4, 123.5, 126.5, 128.2, 129.0, 137.1, 157.4. Anal. ($C_{16}H_{22}ClNO$) C, H, N.

5.1.15. cis-(±)-2,3,3a,4,5,9b-Hexahydro-8-hydroxy-3-n-propyl-1H-benz[e]indole hydrobromide **5**

The free base of **21a** was prepared as previously described from **8a** (4.93 g, 19.0 mmol) and LAH (2.19 g, 57.8 mmol) to yield an oil. The oil was dissolved in 48% HBr (50 mL) into which nitrogen was bubbled, and the solution was refluxed for 3 h. Evaporation of the reaction mixture afforded an oil. After azeotropic distillation with absolute ethanol to remove the remaining water, the oil was triturated with diethyl ether/isopropanol to produce a yellow solid. Recrystallization from diethyl ether/isopropanol afforded 3.86 g (65%) of **5**: m.p. 213.5–214.5 °C; ([15], m.p. 214–215 °C); ^{1}H NMR (DMSO-

d_6) δ 0.93 (t, J = 7 Hz, 3 H), 3.71 (m, 14 H), 6.78 (m, 3 H, ArH), 9.22 (s, 1 H, ArOH), 9.50 (br s, 1 H, NH^+); ^{13}C NMR (DMSO-d_6) δ 10.9, 18.3, 24.4, 25.7, 25.8, 31.9, 52.8, 55.7, 65.3, 113.5, 114.5, 125.8, 128.8, 136.8, 155.8.

5.1.16. trans-(±)-2,3,3a,4,5,9b-Hexahydro-8-hydroxy-3-n-propyl-1H-benz[e]indole hydrobromide **21c**

In a similar manner as described above, **8b** (0.80 g, 3.1 mmol) and LAH (0.36 g, 9.4 mmol) in dry THF (50 mL) yielded a yellow oil. Methyl ether cleavage with 48% HBr (15 mL) gave a yellow solid. Recrystallization from ethanol/diethyl ether afforded 0.69 g (72%) of **21c**: m.p. 245.0–245.5 °C; ^1H NMR (DMSO-d_6) δ 0.95 (t, J = 7 Hz, 3 H), 2.70 (m, 14 H), 6.71 (m, 3 H, ArH), 9.25 (s, 1 H, ArOH), 10.50 (br s, 1 H, NH^+); ^{13}C NMR (DMSO-d_6) δ 10.9, 18.1, 22.8, 24.9, 26.8, 43.0, 52.5, 53.5, 67.9, 112.1, 113.9, 124.6, 129.0, 136.8, 155.4. Anal. ($C_{15}H_{22}BrNO$) C, H, N.

5.1.17. cis-(±)-2,3,3a,4,5,9b-Hexahydro-8-hydroxy-3-(2-propenyl)-1H-benz[e]indole hydrochloride **21e**

A solution of diphenylphosphine (4.78 g, 25.7 mmol) in THF (85 mL) was treated with *n*-butyllithium (21.4 mL, 34.2 mmol, 1.6 M in hexane) at 0 °C [17]. After stirring for 10 min, the deep red solution was treated with **21d** (free base, 2.22 g, 9.12 mmol) in THF (35 mL) and refluxed for 24 h. Water was added to quench the reaction, and the mixture was concentrated under reduced pressure. The resulting residue was extracted with CH_2Cl_2 (3 × 100 mL), and the combined extracts were washed with water (100 mL) and brine (100 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give an oil. The oil was purified by flash chromatography on a silica gel column, eluting with ethyl acetate/hexane/triethylamine (30:10:0.4). Evaporation of the solvents gave a light yellow oil. Formation of the hydrochloride salt and recrystallization from diethyl ether/isopropanol gave 1.80 g (85%) of **21e**: m.p. 195.5–196.5 °C; ^1H NMR (DMSO-d_6) δ 2.77 (m, 12 H), 5.51 (m, 2 H), 6.10 (m, 1 H), 6.75 (s, 3 H, ArH), 9.29 (s, 1 H, ArOH); ^{13}C NMR (DMSO-d_6) δ 24.1, 25.6, 31.7, 39.0, 52.0, 55.9, 64.1, 113.5, 114.4, 124.0, 125.8, 128.4, 128.8, 136.8, 155.8. Anal. ($C_{15}H_{20}ClNO$) H, N, C: calcd 67.78; found 67.00.

5.1.18. trans-(±)-2,3,3a,4,5,9b-Hexahydro-8-hydroxy-3-(2-propenyl)-1H-benz[e]indole hydrochloride **21g**

Using the method for the synthesis of **21e**, diphenylphosphine (1.84 g, 9.9 mmol), *n*-butyllithium (8.22 mL, 13.2 mmol, 1.6 M in hexane), and **21f** (0.80 g, 3.3 mmol) in THF (50 mL) yielded an oil. The oil was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexane/triethylamine (50:50:1). Evaporation of the solvents afforded an oil. A hydrochloride was prepared and recrystallized form ethanol/diethyl ether to afford 0.60 g (79%) of **21g**: m.p. 251–251.5 °C; ^1H NMR (DMSO-d_6) δ 2.90 (m, 12 H), 5.52 (m, 2 H), 6.04 (s, 1 H), 6.74 (m, 3 H, ArH), 9.31 (s, 1 H, ArOH); ^{13}C NMR (DMSO-d_6) δ 22.7, 25.0, 26.8, 43.1, 51.8, 53.6, 67.1, 112.1, 114.0, 123.7, 124.7, 128.3, 129.0, 137.0, 155.5. Anal. ($C_{15}H_{20}ClNO$) C, H, N.

5.1.19. cis-syn-(±)-1,3-Dimethyl-2,3,3a,4,5,9b-hexahydro-8-hydroxy-1H-benz[e]indole hydrobromide **21h**

In a similar manner as described for **21a**, **18a** (3.34 g, 13.4 mmol) and LAH (1.57 g, 41.4 mmol) in THF (210 mL) afforded an oil. Vacuum distillation gave 2.67 g (85%) of a clear oil. This compound was used directly in the next step. As described for the preparation of **5**, the oil was refluxed in 48% HBr (30 mL) for 3 h. Standard work-up gave a light yellow solid which was recrystallized from diethyl ether/isopropanol to yield 3.18 g (74%) of **21h**: m.p. 209–210 °C; ^1H NMR (DMSO-d_6) δ 1.14 (d, J = 6 Hz, 3 H, 1-CH_3), 2.50 (m, 9 H), 2.91 (s, 3 H, NCH_3), 6.75 (m, 3 H, ArH), 9.23 (s, 1 H, ArOH); ^{13}C NMR (DMSO-d_6) δ 14.8, 24.2, 24.5, 46.8, 59.6, 66.6, 113.5, 114.7, 126.8, 129.0, 136.0, 155.6. MS (EI) m/z 218 (M^+-Br). Anal. ($C_{14}H_{20}BrNO$) C, H, N.

5.1.20. cis-syn-(±)-2,3,3a,4,5,9b-Hexahydro-8-hydroxy-1-methyl-3-n-propyl-1H-benz[e]indole hydrochloride **21i**

A solution of *cis*-**8a** (1.50 g, 5.78 mmol) in THF (65 mL) was cooled to –60 °C under a nitrogen atmosphere, and LDA (4.63 mL, 6.94 mmol, 1.5 M in cyclohexane) was added slowly for 5 min. The mixture was stirred for 2 h, and methyl iodide (0.98 g, 6.94 mmol) in THF (30 mL) was added dropwise. After warming to room temperature, the mixture was stirred for 20 h and quenched with 3 N HCl to pH < 3. The reaction mixture was concentrated under reduced pressure and extracted with CH_2Cl_2 (3 × 50 mL). The combined CH_2Cl_2 extracts were washed with water (3 × 50 mL), dried (Na_2SO_4), filtered, and evaporated to yield a brown oil. The oil was chromatographed on a silica gel column using ethyl acetate/hexane (4:1) as the eluent. Fractions homogeneous by TLC were combined and concentrated under reduced pressure to give a yellow solid. Recrystallization from hexane afforded 1.22 g (77%) of the mono-methyl lactam: m.p. 192–193 °C; ^1H NMR ($CDCl_3$) δ 0.94 (t, J = 7 Hz, 3 H, $NCH_2CH_2CH_3$), 1.42 (d, J = 7 Hz, 3 H, 1-CH_3), 2.56 (m, 11 H), 3.80 (s, 3 H, OCH_3), 6.90 (m, 3 H, ArH); ^{13}C NMR ($CDCl_3$) δ 11.4, 16.3, 20.9, 25.8, 26.2, 42.2, 44.4, 44.6, 55.3, 112.1, 113.9, 128.6, 129.4, 138.3, 158.1, 175.9.

In a similar manner as described for **21a**, a portion of the above mono-methyl lactam (1.00 g, 3.1 mmol) and LAH (0.36 g, 9.4 mmol) in THF (60 mL) yielded a light yellow oil. The oil was dissolved in 48% HBr (20 mL) and was refluxed for 18 h under nitrogen. The mixture was cooled to room temperature and treated with 20% NaOH until the pH > 9. The mixture was extracted with CH_2Cl_2 (3 × 100 mL), and the combined extracts were washed with brine, dried (Na_2SO_4), filtered, and evaporated to give a tan solid. A hydrochloride salt was prepared and recrystallized from ethanol/diethyl ether to yield 0.76 g (74%) of **21i:** m.p. 212.5–213.5 °C; ^{1}H NMR (DMSO-d_6) δ 0.93 (t, J = 7 Hz, 3 H), 1.10 (d, J = 6 Hz, 3 H, 1-CH_3), 2.62 (m, 13 H), 6.76 (m, 3 H), 9.29 (s, 1 H, ArOH), 10.49 (br s, 1 H, NH^+); ^{13}C NMR (DMSO-d_6) δ 10.9, 14.6, 18.1, 24.9, 25.6, 46.4, 55.8, 57.8, 66.1, 113.5, 115.0, 126.8, 135.6, 138.9, 155.5. Anal. ($C_{16}H_{24}ClNO$) N, C: calcd 68.19; found 67.70, H: calcd 8.58; found 8.05.

5.1.21. cis-syn-(±)-1-Benzyl-2,3,3a,4,5,9b-hexahydro-6-hydroxy-3-methyl-1H-benz[e]indole hydrobromide **21j**

Using the procedure described for **21a**, **20d** (0.63 g, 1.96 mmol) and LAH (0.25 g, 6.66 mmol) in dry THF (50 mL) yielded an oil. Methyl ether cleavage was carried out in the typical manner to afford, after recrystallization from diethyl ether/ isopropanol, 0.42 g (57%) of **21j**: m.p. 143–144 °C; ^{1}H NMR (DMSO-d_6) δ 2.65 (m, 9 H), 3.36 (s, 3 H, NCH_3), 7.00 (m, 8 H), 9.49 (s, 1 H, ArOH); ^{13}C NMR (DMSO-d_6) δ 17.6, 23.0, 37.3, 39.3, 44.8, 47.1, 58.5, 66.4, 112.9, 119.2, 123.2, 126.4, 126.6, 128.6, 136.6, 139.2, 154.2. Anal. ($C_{20}H_{24}BrNO_2$) H, N, C: calcd 64.20; found 63.72.

5.1.22. trans-(±)-2,3,3a,4,5,9b-Hexahydro-6-hydroxy-3-methyl-1H-benz[e]indole hydrochloride **21k**

In a similar manner as described for **21a**, **14b** (220 mg, 0.95 mmol) and LAH (110 mg, 2.90 mmol) in THF (25 mL) gave an oil. The oil was dissolved in 48% HBr (30 mL) and refluxed for 3 h. Typical work-up gave 224 mg (84%) of **21k** after recrystallization from diethyl ether/isopropanol: m.p. 315–316 °C; ^{1}H NMR (DMSO-d_6) δ 2.79 (m, 11 H), 2.87 (s, 3 H, NCH_3), 6.83 (m, 3 H), 9.46 (s, 1 H, ArOH); ^{13}C NMR (DMSO-d_6) δ 21.8, 22.7, 25.1, 37.4, 43.1, 54.9, 68.0, 112.7, 116.1, 121.0, 126.4, 137.0, 154.5. Anal. ($C_{20}H_{24}BrNO$) C, H, N.

5.1.23. cis-syn-(±)-2,3,3a,4,5,9b-Hexahydro-6-hydroxy-1-methyl-1H-benz[e]indole hydrobromide **21l**

A suspension of **20c** [16] (0.94 g, 4.06 mmol) and LAH (0.46 g, 12.0 mmol) was reacted in the standard manner to afford an oil. The oil was dissolved in 48% HBr (10 mL) and refluxed for 2 h to yield 0.31 g (26%) of **21l** after recrystallization from ethanol/diethyl ether: m.p. 188–189 °C; ^{1}H NMR (CD_3OD) δ 0.82 (d, J = 7 Hz, 3 H), 2.80 (m, 9 H), 6.83 (m, 3 H); ^{13}C NMR (CD_3OD) δ 16.0, 21.0, 26.4, 38.1, 44.4, 52.3, 59.6, 113.7, 122.1, 125.1, 128.0, 135.3, 155.8. Anal. ($C_{13}H_{18}BrNO$) C, H, N.

*5.1.24. Enantiomeric separation of cis-(±)-2,3,3a,4,5,9b-Hexahydro-8-hydroxy-3-n-propyl-1H-benz[e]indole cis-(±)-***5**

cis-(±)-**5** HCl was dissolved in *n*-heptane/ isopropanol/diethylamine (57:43:0.5) and fractionated by HPLC (13 runs) using a 20 × 250 mm Chiralcel OD column (Daicel Chemical Industries, Inc.). The column was eluted isocratically with *n*-heptane/isopropanol/ diethylamine (85:15:0.1) at a flow rate of 5 mL/min and fractions collected corresponding to 1 min/fraction. The eluting enantiomers were detected spectroscopically by measuring absorbance at a wavelength of 225 nm. Two eluting peaks were detected, corresponding to fractions 18–21 (*cis*-(±)-**5**) and 23–26 (*cis*-(-)-**5**). Fractions from the different runs corresponding to these peaks were separately pooled to yield 43 mg of each enantiomer. *cis*-(+)-**5**: $[\alpha]_D^{20°}$= +101.4° (*c*0.5, MeOH); NMR (300 MHz, $CDCl_3$) δ 0.95 (t, 3 H, CH_3), 1.55–1.88 (m, 5 H), 2.29 (m, 1 H), 2.40–2.62 (m, 3 H), 2.66–2.83 (m, 2 H), 2.98 (m, 1 H), 3.13 (t, 1 H), 3.31 (q, 1 H), 6.58 (m, 2 H), 6.92 (d, 1 H). *cis*-(-)-**5**: $[\alpha]_D^{20°}$= –97.7° (*c*0.5, MeOH); NMR (300 MHz, $CDCl_3$) identical to that of *cis*-(+)-**5**. The enantiomeric excess was determined by HPLC using a 4.6 × 250 mm Chiralcel OD column eluting with *n*-heptane/isopropanol/diethylamine (90:10:0.1). The flow rate was 0.5 mL/min, and the eluting sample was monitored spectroscopically at 225 and 280 nm. The peak retention times for *cis*-(+)-**5** (ee 100%) and *cis*-(-)-**5** (ee > 99.6%) were 9.2 min and 10.6 min, respectively.

*5.1.25. Enantiomeric separation of trans-(±)-2,3,3a,4,5,9b-Hexahydro-8-hydroxy-3-n-propyl-1H-benz[e]indole (±)-***21c**

trans-(±)-**21c** HBr was dissolved in 3 mL *n*-heptane/isopropanol/diethylamine (50:50:0.8) and fractionated by HPLC (3 runs) using a 20 × 250 mm Chiralcel-OD column. The column was eluted isocratically with *n*-heptane/isopropanol/diethylamine (90:10:0.1) at a flow rate of 5 mL/min and fractions collected corresponding to 1 min/fraction. The eluting enantiomers were detected spectroscopically by measuring absorbance at a wavelength of 225 nm. Two eluting peaks were detected, corresponding to fractions 26–29 (*trans*-(-)-**21c**) and 35–40 (*trans*-(+)-**21c**). Fractions from the different runs corresponding to these peaks were separately pooled to yield 8.6 mg of *trans*-(+)-**21c**. The separated enantiomers

(free bases) were precipitated from acetone/HCl (130:1) and recrystallized as the HCl salts from acetone/methanol (3:1) to afford 4 mg of (-)-**21c** and 3.3 mg of (+)-**21c**, respectively. *trans*-(-)-**21c** HCl: m.p. 263–266 °C; $[\alpha]_D^{20°}$= –53° (*c*0.24, MeOH); NMR (300 MHz, CD_3OD) δ 1.08 (t, 3 H, CH_3), 1.83 (m, 2 H), 2.03 (m, 2 H), 2.48 (m, 1 H), 2.63 (m, 1 H), 2.90–3.20 (m, 5 H), 3.35–3.60 (m, 2 H), 3.90 (q, 1 H), 6.58 (d, 1 H), 6.65 (dd, 1 H), 7.00 (d, 1 H). *trans*-(+)-**21c** HCl: m.p. 263–266 °C; $[\alpha]_D^{20°}$= +45.0° (*c*0.24, MeOH); NMR (300 MHz, CD_3OD) spectrum identical to that obtained for *trans*-(-)-**21c**. The enantiomeric excess for the two enantiomers were determined by HPLC using a 4.6 × 250 mm Chiralcel OD column eluting with *n*-heptane/isopropanol/diethylamine (92:8:0.1). The flow rate was 0.7 mL/min, and the eluting sample was monitored spectroscopically at 225 and 280 nm. The peak retention times for *trans*-(-)-**21c** (ee 100%) and *trans*-(+)-**21c** (ee > 99.6%) were 11.3 min and 15.6 min, respectively.

5.2. X-ray crystallography

A single crystal of **8c** with dimensions of 1.00 × 0.75

the "International Tables for X-ray Crystallography" [24]. The final fractional coordinates, bond angles, and bond distances for **8c** are on file with the editor. A colourless crystal of *cis*-(+)-**5** was mounted on an Enraf Nonius CAD 4F diffractometer with a Cu target X-ray tube (λ = 1.5418 Å). The crystal was cooled to 120 K using Cryostream nitrogen gas system [25]. The compound was found to crystallize in space group $P2_12_12_1$ with unit cell dimensions of a = 7.279(3), b = 11.972(3), c = 16.455(5) Å and V = 1438.0(8) Å^3. The calculated density was 1.24 g/cm^3 of Z = 4 and a formula weight of 267.79 g/mol. The intensity data were collected in the ω scan mode. A total of 2 482 unique reflections were collected to a $(\sin\theta/\lambda)_{max}$ of 0.60 Å^{-1}. Data were corrected for Lorenz and polarization effects. Four standards were measured every 4 h, and no fading was observed. The structure was solved by direct methods and refined by a full-matrix least squares technique. The hydrogen atoms were all located from electron density maps. The non-hydrogen atoms were refined anisotropically and the hydrogen atoms were refined isotropically. The origin was fixed by use of least-squares restraints [26]. The Flack x-parameter is 0.02(2), indicating

nates, bond angles, and bond distances for *trans*-(-)-**21c** are on file with the editor. The crystallographic computations were performed with SHELXS86 [28] and SHELXL93 [29]. The atomic scattering factors were taken from the literature [24]. SHELXTL was used for the illustrations [30]. The orientation of the hydrogen atoms at C9 (position 3a) and C10 (position 9b) in (+)-**5** are *cis* with respect to the C9–C10 bond, whereas they are *trans* in (-)-**21c**. In both structures the chloride ions are involved in hydrogen bonds. In *cis*-(+)-**5** the N–H···Cl bond is 3.087(3) Å (with H···Cl = 2.18(3) Å) and the O··· Cl (–1/2 + x, ½ – y, –z) bond is 3.089(3) Å (with H··· Cl = 2.20(5) Å). In *trans*-(-)-**21c** the N··· Cl (– x, ½ + y, 1 – z) bond is 3.113(5) Å and the O··· Cl bond is 3.095(4) Å (with H··· Cl = 2.279(4) Å.

5.3. Dopamine receptor-expressing cell lines

The human DA D_3 receptor was recloned by rt-PCR and stably expressed as described in a recent report [18]. The human DA D_2 receptor was stably expressed in Ltk^- cells as described by Bunzow et al. [31]. Cell lines were propagated in Dulbeccos modified Eagles media (DMEM) supplemented with foetal calf serum (10%, v/v), penicillin/streptomycin (20 μg/mL) and either 0.5 mg/mL of G418 (D_{2S}) or 5 μM methotrexate (DA D_3). G418 and methotrexate were added to cell cultures as selection factors maintaining expression of the transfected gene, D_{2S} and D_3, respectively. The plasmid DNA containing the receptor sequence also contains G418 and methotrexate resistant genes. Clonal cells losing the plasmid are then susceptible to selection with these agents. The cell membranes used in radioligand binding experiments were prepared from clonal cell lines expressing individual receptor subtypes by hypotonic lysis, essentially as described by Scheideler and Zukin [32]. Membrane protein concentrations were estimated using a modified Lowry method [33].

5.4. Specific radioligand binding to dopamine receptor subtypes

Cell membranes (3–40 μg, final membrane protein concentration) were resuspended in assay buffer (20 mM Hepes, pH 7.4, containing 2 mM $MgCl_2$) and incubated with 0.5 nM [^{3}H]*R*-(+)-7-OH-DPAT (DA D_3) or 0.1 nM [^{3}H]spiperone (DA D_{2S}) for 45 min at 25 °C. Free and bound ligand were separated by rapid filtration through Whatman GF/B filters, the filters were then washed with 8 mL of assay buffer containing 100 mM NaCl, and the filter-bound radioactivity determined by scintillation counting. Non-specific binding was assessed in the presence of 5 μM of (-)-QUIN (DA D_3) or 3 μM (+)-butaclamol (DA D_{2S}).

Acknowledgements

The authors are very appreciative of a grant from the Louisiana Education Quality Support Fund with matching funds provided by the School of Pharmacy and Northeast Louisiana University to purchase the 400 MHz NMR spectrometer.

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