Centrally Acting Serotonergic and Dopaminergic Agents. 1. Synthesis and Structure–Activity Relationships of 2,3,3a,4,5,9b-Hexahydro-1*H*-benz[*e*]indole Derivatives

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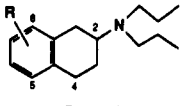
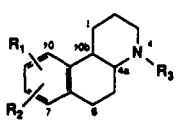
The synthesis and structure–activity relationships (SAR) of 2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]-indole derivatives (**3**) are described. These compounds are conformationally restricted, angular tricyclic analogs of 2-aminotetralin. The synthesis was achieved in several steps from the corresponding 2-tetralones. The enantiomers of the cis analogs were obtained from either fractional recrystallizations of the diastereomeric salts of di-*p*-toluoyl-L-(or D)-tartaric acid or an asymmetric synthesis using chiral (*R*)-α-methylbenzylamine. All analogs were evaluated in the in vitro 5-HT_{1A} and D_2 binding assays and selected analogs were investigated further in biochemical and behavioral tests. Analogs with 9-methoxy substitution (R_1 in **3**) showed mixed 5-HT_{1A} agonist and dopamine antagonist activities whereas the corresponding 9-hydroxy analogs displayed selective 5-HT_{1A} agonist activity. The cis analogs were found to be more potent than the corresponding trans analogs and in the cis series, the (3a*R*)-(−)-enantiomers displayed higher potency. Nitrogen substitution (R_2 in **3**) with either an *n*-propyl or an allyl group produced similar activities whereas replacement with a bulky α-methylbenzyl group resulted in loss of activity. Analogs without aromatic substitution (R_1 = H in **3**) still showed good 5-HT_{1A} agonist activity, although less potent than the 9-methoxy series. In this case, the trans analogs possessed equal or higher in vitro 5-HT_{1A} affinity than the corresponding cis analogs. Analogs with either 6-methoxy or 6-hydroxy substitution (R_1 in **3**) were found to display dopamine antagonist properties. However, only *N*-allyl analogs showed this activity. In the 6-methoxy-*N*-allyl series, the cis analog was found to be more potent than the trans analog. Again, between the pair of cis enantiomers, the (3a*R*)-(−)-enantiomer showed higher potency. Incorporation of an additional methyl group into 9-methoxy cis analogs at C-2 resulted in retention of potent 5-HT_{1A} agonist activity.

Introduction

The neurotransmitters serotonin and dopamine have been implicated in various central nervous system (CNS) related disorders such as anxiety, depression, schizophrenia, and Parkinson's disease. A series of 2-aminotetralins was found to exert a variety of centrally acting pharmacological effects. In 1976, 5-hydroxy-2-(di-*n*-propylamino)-tetralin (**1a**, 5-OH-DPAT) was shown to have highly active



1a, R=5-OH
1b, R=8-OH



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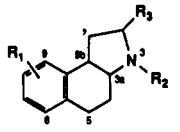

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dopamine receptor agonist activity.[1] Later, the closely related 8-hydroxy analog **1b** (8-OH-DPAT) was found to be a potent 5-HT receptor agonist devoid of dopamine receptor stimulation.[2] In 1983, it was established that 8-OH-DPAT selectively binds to the 5-HT_1 receptor subtype.[3] These relatively simple 2-aminotetralins have attracted considerable attention in the search for therapeutically useful agents derived from these compounds.[4] In addition, these compounds have become important pharmacological tools toward understanding the functional role of these neurotransmitters. 5-HT_{1A} receptor agonists were later implicated in playing an important role in the control of anxiety and depression without a hallucinogenic effect[5] and may also be involved in the regulation of sympathetic nerve activity and blood pressure.[6] On the other hand, dopamine receptor agonists may be involved in several psychiatric and neurological illnesses such as schizophrenia, Parkinson's disease, and drug addiction.[7]

Selective serotonin and/or dopamine agonists may prove to have useful therapeutic applications. Thus, in an effort to provide agents with high potency and selectivity, we have elected to construct conformationally restricted analogs of 2-aminotetralin. Attention in this area has been focused on the semirigid, angularly annelated 1,2,3,4,-4a,5,6,10b-octahydrobenzo[*f*]quinolines, as represented by the generic structure **2**. For example, Cannon et al. reported the synthesis and biological properties of the 7,8-dihydroxy, 8,9-dihydroxy, 7-hydroxy-8-methyl, and 7,10-dimethoxy analogs of **2** in which the nitrogen substitution is hydrogen, methyl, ethyl or *n*-propyl.[8] Most of these analogs display moderate to potent dopamine agonist activity with *n*-propyl substitution showing the optimum

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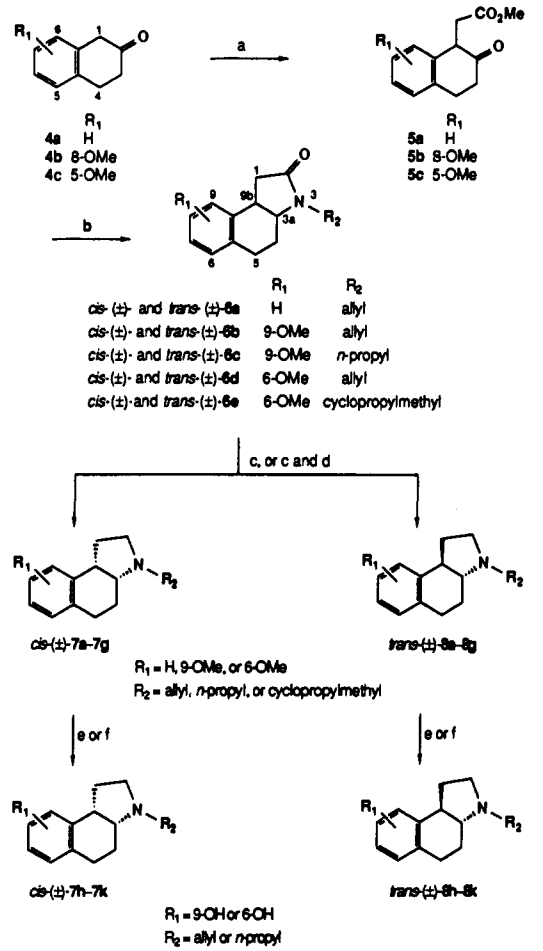
potency. On the same ring system, Wikström et al. showed that the 10-hydroxy isomer is a centrally acting serotonin receptor agonist devoid of dopaminergic activity whereas its corresponding 7-, 8-, and 9-hydroxy analogs exert dopaminergic effects.[9] These authors found that the trans isomers were consistently more potent than their corresponding cis isomers with respect to their actions on 5-HT receptors (10-hydroxy analogs) and DA receptors (7-, 8-, and 9-hydroxy analogs).[9a] These results demonstrate, similar to **1a** and **1b**,[2a] that the position of the hydroxyl group determines the serotonergic or dopaminergic activity. Also, after examining the resolved *cis*-10-hydroxy-*N*-*n*-propyl analogs of **2**, they concluded that the serotonergic activity resides in the cis-(4a*R*,10b*S*)-enantiomer of **2**.[9c]

We envisioned that five/six fused ring analogs 2,3,3a,4,5,-9b-hexahydro-1*H*-benz[*e*]indole derivatives (**3**)[10] would be even more conformationally restricted and could possibly lead to more selective and potent analogs. Therefore, we became interested in examining the potential biological activities of cis and trans analogs of **3** and the differences in activity displayed by the enantiomers. We also wanted to investigate the effects of aromatic ring methoxy or hydroxy substitution (R_1) at C-9 or C-6 on serotonergic or dopaminergic activity. The selection of the nitrogen substitution (R_2) was based on previous SAR work reported by Arvidsson et al.[4a] in the 8-OH-DPAT series. These authors reported that the optimum activity was found with *n*-propyl substitution on the nitrogen of 2-aminotetralins. We therefore decided to limit the nitrogen substitution in **3** to an *n*-propyl or a similar substituent such as an allyl or cyclopropylmethyl group. These same authors noted that when there is steric bulk around the vicinity of nitrogen in the 8-OH-DPAT series, the potency is considerably reduced. For example, the analog with mono-*N*-isopropyl substitution was found to be 16 times less potent than 8-OH-DPAT, which has an *N*,*N*-di-*n*-propyl substitution. To test this steric effect on the tricyclic system **3**, we decided to incorporate an additional methyl group (R_3) at the C-2 position on the pyrrolidine ring. The presence of this methyl group on the rigid five/six fused ring system may cause a pronounced effect on the biological activity. Herein we describe an efficient synthesis and resolution of a series of analogs represented by generic structure **3**. All analogs were evaluated in the in vitro 5-HT_{1A} and D_2 binding assays, and those with interesting binding properties were selected and investigated further in biochemical and behavioral tests.

Chemistry

An efficient synthetic method toward 2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]indole derivatives **3** was developed using easily accessible 2-tetralone derivatives.[11] Two key steps involved the regiospecific introduction of the alkyl side chain at the C-1 position and subsequent ring closure of this side chain with the C-2 nitrogen to form lactam derivatives (steps a and b in Scheme I). In earlier work,[12] we established that selective alkylation occurs at the C-1 position of 2-tetralones using a base at low temperature followed by treatment with an appropriate substituted halide. Thus, using LDA as the base and methyl bromoacetate as the halide, various alkylated 2-tetralones such as **5a**, **5b**, and **5c** were prepared in 67–82% yields from the corresponding 2-tetralones, **4a**, **4b**, and **4c**, respectively.

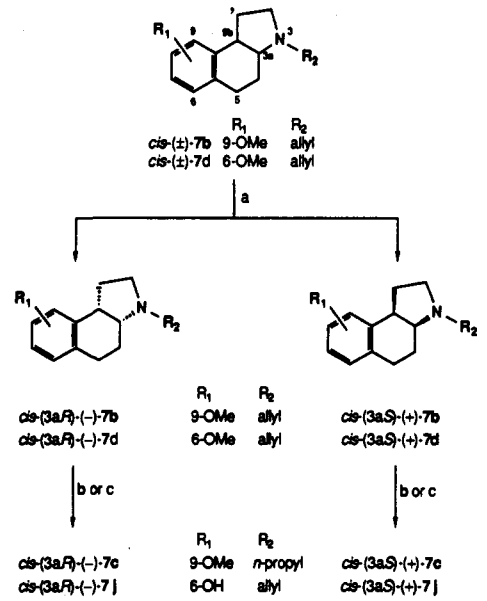
Scheme I[a]



[a] Reagents and conditions: (a) LDA, $BrCH_2CO_2Me$, THF; (b) allylamine, *n*-propylamine, or (aminomethyl)cyclopropane, HOAc, $NaCNBH_3$, THF/MeOH; (c) LAH/THF, Δ; (d) H_2, Pd/C, MeOH; (e) Ph_2PH, *n*-BuLi, THF, Δ; (f) 48% HBr, Δ.

Keto esters **5a**, **5b**, and **5c** were then allowed to react with allylamine, *n*-propylamine, or (aminomethyl)cyclopropane (Scheme I), using the well-established Borch reductive amination procedure ($NaCNBH_3$/HOAc in THF/MeOH).[13] The reaction was carried out at room temperature for 24–48 h, yielding a mixture of *cis*-(±)- and *trans*-(±)-lactams via reductive amination/cyclization in 55–75% yield. We found that in the case of (±)-**6a**, (±)-**6b**, and (±)-**6c**, the mixture of *cis*-(±)- and *trans*-(±)-lactams was not separable by chromatography. However, the lactams *cis*-(±)-**6d**/*trans*-(±)-**6d** and *cis*-(±)-**6e**/*trans*-(±)-**6e**, obtained from 5-methoxy keto ester **5c**, were readily separable by chromatography (Scheme I). Assignment of the major product as *cis*-(±)-**6d** (62%) and the minor product as *trans*-(±)-**6d** (14%) was based on 500-MHz ^1H NMR decoupling experiments (see the Experimental Section). The decoupling of *trans*-(±)-**6d** clearly showed the coupling constant for C-3a (δ 3.40–3.32) and C-9b protons to be 10.3 Hz, indicating they are diaxial, assigning this compound as the trans product. The decoupling of *cis*-(±)-**6d** did not resolve the peaks but it showed a small coupling constant for C-3a (δ 3.90–3.82) and C-9b protons, indicating they are equatorial–axial, assigning this compound as the cis product. The correct assignment of the cis configuration was later confirmed by X-ray crystallography when *cis*-(±)-**6d** was converted to the pyrrolidine derivatives (±)-**7d** and resolved into a pair of enantiomers *cis*-(−)-**7d** and *cis*-(+)-**7d** (see Schemes I and II and Figure 1). On the basis of this result the major product was

Scheme II[a]



[a] Reagents and conditions: (a) di-*p*-toluoyl-L(or D)-tartaric acid, MeOH or 2-PrOH; (b) H_2, Pd/C, MeOH; (c) Ph_2PH, *n*-BuLi, THF, Δ.

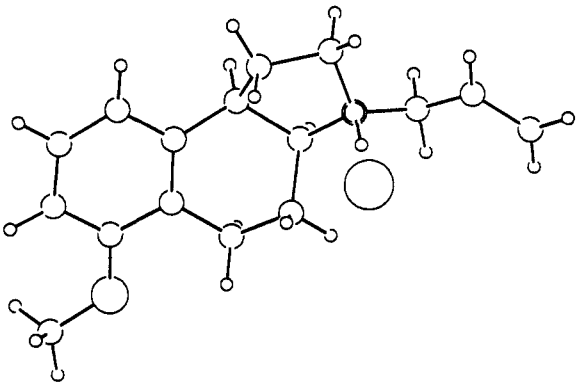


Figure 1. The X-ray crystallographic structure of (+)-**7d**, confirmed as *cis*-(3a*S*)-(+)-2,3,3a,4,5,9b-hexahydro-6-methoxy-3-(2-propenyl)-1*H*-benz[*e*]indole hydrochloride.

assigned as the cis isomer whereas the minor product as the trans isomer for all compounds obtained from this reductive amination/cyclization procedure. The predominant formation of the cis product from this reductive amination is consistent with mechanistic considerations in which the iminium ion is reduced from the less hindered side by sodium cyanoborohydride.[13]

The lactams were then converted into the desired pyrrolidine derivatives by refluxing with lithium aluminum hydride in THF (Scheme I). When the inseparable lactams *cis*-(±)- and *trans*-(±)-**6a/6b** were deoxygenated under these conditions, the *cis*-(±)-**7a/7b** and *trans*-(±)-**8a/8b** isomers became readily separable by chromatography. The ratio of cis/trans products in this case was found to be about 10:1. Although the *n*-propyl analog *cis*-(±)-**7c** was obtained by the same procedure, no attempt was made to isolate the *trans*-(±)-**8c** in this case. The separable lactams *cis*-(±)-**6d/6e** and *trans*-(±)-**6d/6e** were also independently converted into the pyrrolidine derivatives *cis*-(±)-**7d/7e** and *trans*-(±)-**8d/8e**, respectively, by the same procedure. Alternatively, the *n*-propyl analogs can be prepared from the corresponding allyl analogs via hydrogenation using palladium on carbon as the catalyst. Thus, the allyl analogs *cis*-(±)-**7a/7d** and *trans*-(±)-**8a/8d** were converted into the corresponding *n*-propyl analogs *cis*-(±)-**7f/7g** and *trans*-(±)-**8f/8g**, respectively. As listed in Table I, pure cis-(±)-analogs **7a–g** and trans-(±)-analogs **8a–g** (as the HCl salt) were synthesized in this manner. Since the peaks on the ^1H NMR of these pyrrolidine derivatives were even more complicated than those of the lactams, the decoupling experiments on these compounds were not carried out.

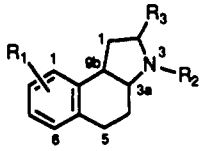
As shown in Scheme I, two methods were utilized to prepare the phenolic derivatives. Analogs with a simple *N*-*n*-propyl substitution, *cis*-(±)-**7c** and *trans*-(±)-**8g**, were refluxed in 48% HBr to yield the corresponding phenolic analogs, *cis*-(±)-**7i** and *trans*-(±)-**8k**, respectively. Since analogs with an *N*-allyl group react with HBr, an alternative method was required for the demethylation. Thus, O-demethylation of *cis*-(±)-**7b** and *trans*-(±)-**8b** was accomplished in high yield by refluxing with 3 equiv of lithium diphenylphosphide in THF[14] to afford phenolic analogs *cis*-(±)-**7h** and *trans*-(±)-**8h**, respectively. Similar conversions afforded phenolic analogs *cis*-(±)-**7j** and *trans*-(±)-**8j** from the corresponding methoxy analogs *cis*-(±)-**7d** and *trans*-(±)-**8d**. The phenolic *n*-propyl analog *cis*-(±)-**7k** was obtained from the catalytic hydrogenation of the corresponding allylic analog *cis*-(±)-**7j**. As listed in Table I, all phenolic analogs were also purified as the HCl salts.

The resolution of 6-methoxy-*N*-allyl analog *cis*-(±)-**7d** was achieved efficiently utilizing the fractional recrystallization of the diastereomeric salts. As shown in Scheme II, a 1:1 mixture of *cis*-(±)-**7d** and di-*p*-toluoyl-L(or D)-tartaric acid was recrystallized from methanol. Only two or three recrystallizations were needed to obtain >95% pure diastereomeric salts, as determined by 300-MHz ^1H NMR, in excellent yield (37–38% out of 50% maximum yield). Each diastereomeric salt was then converted into the free base to yield the pure enantiomers *cis*-(3a*R*)-(-)-**7d** and *cis*-(3a*S*)-(+)-**7d**. X-ray crystallography of one of the enantiomers, *cis*-(3a*S*)-(+)-**7d** (Figure 1), confirmed the assigned absolute configuration of both enantiomers. The methoxy analogs (-)-**7d** and (+)-**7d** were then converted into the corresponding phenolic analogs *cis*-(3a*R*)-(-)-**7j** and *cis*-(3a*S*)-(+)-**7j**, respectively, via the lithium diphenylphosphide procedure.[14]

The resolution of 9-methoxy-*N*-allyl analog *cis*-(±)-**7b** using di-*p*-toluoyl-L(or D)-tartaric acid was less efficient. Since these diastereomeric salts failed to crystallize from methanol, 2-propanol was used as the solvent. After two or three recrystallizations and free basing, both *cis*-(3a*R*)-(-)-**7b** and *cis*-(3a*S*)-(+)-**7b** were isolated in only 13–15% yield for each salt. The X-ray crystallography of one of the enantiomers, *cis*-(3a*R*)-(-)-**7b** (Figure 2), confirmed the assigned absolute configuration of both enantiomers.

Although catalytic hydrogenation of 9-methoxy-*N*-allyl enantiomers (-)-**7b** and (+)-**7b** led to the corresponding 9-methoxy-*N*-*n*-propyl enantiomers (-)-**7c** and (+)-**7c**, respectively, we decided to obtain these enantiomers via an alternative approach. As shown in Scheme III, reductive amination/cyclization of the keto ester **5b** with (*R*)-(+)-methylbenzylamine afforded lactam **9**. This lactam was then reduced with LAH in THF to yield a mixture of diastereomers *cis*-(3a*R*,*R*)-**10a** and *cis*-(3a*S*,*R*)-**10b**. After chromatographic separation, pure diastereomers **10a** and **10b** were obtained in 40% and 20% yields, respectively. The diastereomers **10a/10b**, obtained in 2:1 ratio, indicated that some degree of diastereoselectivity was achieved in this transformation. The purity of these diastereomers (>95%) was determined by 300-MHz ^1H NMR using integration of the distinctive peaks for each

Table I. Physical Properties of 2,3,3a,4,5,9b-Hexahydro-1*H*-benz[*e*]indole Derivatives



compd	R_1	R_2	R_3	config at 3a,9b	recryst solvent	mp (°C)	formula[a]
(±)-7a	H	allyl	H	*cis*-(±)	EtOAc/MeOH	170–172	$C_{15}H_{19}N$·HCl
(±)-7b	9-OMe	allyl	H	*cis*-(±)	EtOAc/MeOH	152–154	$C_{16}H_{21}NO$·HCl
(−)-7b	9-OMe	allyl	H	*cis*-3a*R*-(−)	EtOAc/MeOH	195–196	$C_{16}H_{21}NO$·HCl
(+)-7b	9-OMe	allyl	H	*cis*-3a*S*-(+)	EtOAc/MeOH	195–196	$C_{16}H_{21}NO$·HCl
(±)-7c	9-OMe	*n*-propyl	H	*cis*-(±)	EtOAc/MeOH	153–156	$C_{16}H_{23}NO$·HCl
(−)-7c	9-OMe	*n*-propyl	H	*cis*-3a*R*-(−)	hexane/EtOAc/MeOH	150–151	$C_{16}H_{23}NO$·HCl
(+)-7c	9-OMe	*n*-propyl	H	*cis*-3a*S*-(+)	hexane/EtOAc/MeOH	150–151	$C_{16}H_{23}NO$·HCl
(±)-7d	6-OMe	allyl	H	*cis*-(±)	EtOAc/MeOH	173–174	$C_{16}H_{21}NO$·HCl
(−)-7d	6-OMe	allyl	H	*cis*-3a*R*-(−)	EtOAc/MeOH	201–202	$C_{16}H_{21}NO$·HCl
(+)-7d	6-OMe	allyl	h	*cis*-3a*S*-(+)	EtOAc/MeOH	201–202	$C_{16}H_{21}NO$·HCl
(±)-7e	6-OMe	cpm[b]	H	*cis*-(±)	EtOAc/MeOH	201–202	$C_{17}H_{23}NO$·HCl
(±)-7f	H	*n*-propyl	H	*cis*-(±)	hexane/EtOAc/MeOH	166–167	$C_{15}H_{21}N$·HCl
(±)-7g	6-OMe	*n*-propyl	H	*cis*-(±)	EtOAc/MeOH	197–198	$C_{16}H_{23}NO$·HCl
(±)-7h	9-OH	allyl	H	*cis*-(±)	EtOAc/MeOH	205–206	$C_{15}H_{19}NO$·HCl
(±)-7i	9-OH	*n*-propyl	H	*cis*-(±)	EtOAc/MeOH	223–224	$C_{15}H_{21}NO$·HCl
(−)-7i	9-OH	*n*-propyl	H	*cis*-3a*R*-(−)	EtOAc/MeOH	183–184	$C_{15}H_{21}NO$·HCl
(+)-7i	9-OH	*n*-propyl	H	*cis*-3a*S*-(+)	EtOAc/MeOH	183–184	$C_{15}H_{21}NO$·HCl
(±)-7j	6-OH	allyl	H	*cis*-(±)	EtOAc/MeOH	234–235	$C_{15}H_{19}NO$·HCl
(−)-7j	6-OH	allyl	H	*cis*-3a*R*-(−)	EtOAc/MeOH	238–240	$C_{15}H_{19}NO$·HCl
(+)-7j	6-OH	allyl	H	*cis*-3a*S*-(+)	EtOAc/MeOH	239–240	$C_{15}H_{19}NO$·HCl
(±)-7k	6-OH	*n*-propyl	H	*cis*-(±)	hexane/EtOAc/MeOH	244–245	$C_{15}H_{21}NO$·HCl
(±)-8a	H	allyl	H	*trans*-(±)	EtOAc/MeOH	236–238	$C_{15}H_{19}N$·HCl
(±)-8b	9-OMe	allyl	H	*trans*-(±)	EtOAc/MeOH	231–232	$C_{16}H_{21}NO$·HCl
(±)-8d	6-OMe	allyl	H	*trans*-(±)	EtOAc/MeOH	234–235	$C_{16}H_{21}NO$·HCl
(±)-8e	6-OMe	cpm[b]	H	*trans*-(±)	EtOAc/MeOH	268–270	$C_{17}H_{26}NO$·HCl
(±)-8f	H	*n*-propyl	H	*trans*-(±)	hexane/EtOAc/MeOH	192–193	$C_{15}H_{21}N$·HCl
(±)-8g	6-OMe	*n*-propyl	H	*trans*-(±)	hexane/EtOAc/MeOH	220–221	$C_{16}H_{23}NO$·HCl
(±)-8h	9-OH	allyl	H	*trans*-(±)	EtOAc/MeOH	287–288	$C_{15}H_{19}NO$·HCl
(±)-8j	6-OH	allyl	H	*trans*-(+)	EtOAc/MeOH	>300	$C_{15}H_{19}NO$·HCl
(±)-8k	6-OH	*n*-propyl	H	*trans*-(±)	hexane/EtOAc/MeOH	>300	$C_{15}H_{21}NO$·HCl
10a	9-OMe	mbz[c]	H	*cis*-3a*R*	EtOAc/MeOH	167–169	$C_{21}H_{25}NO$·HCl
10b	9-OMe	mbz[c]	H	*cis*-3a*S*	EtOAc/MeOH	219–220	$C_{21}H_{25}NO$·HCl
(±)-12a	9-OMe	*n*-propyl	2α-Me	*cis*-(3aα,9bα)-(±)	hexane/EtOAc	177–178	$C_{17}H_{25}NO$·HCl
(±)-12b	9-OMe	*n*-propyl	2β-Me	*cis*-(3aα,9bα)-(±)	hexane/EtOAc	206–207	$C_{17}H_{25}NO$·HCl

[a] The elementary analyses are within ±0.4% of the theoretical values. [b] Cyclopropylmethyl group. [c] (*R*)-(+)-α-Methylbenzyl group.

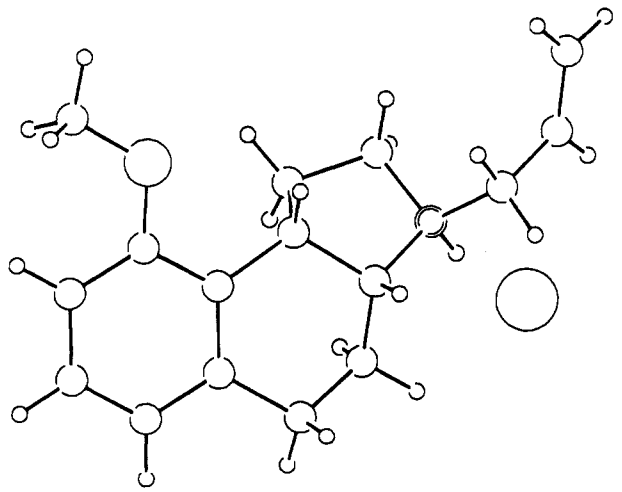


Figure 2. The X-ray crystallographic structure of (−)-**7b**, confirmed as *cis*-(3a*R*)-(−)-2,3,3a,4,5,9b-hexahydro-9-methoxy-3-(2-propenyl)-1*H*-benz[*e*]indole hydrochloride.

diastereomer. Each diastereomer was then converted into the *n*-propyl analogs *cis*-(3a*R*)-(−)-**7c** and *cis*-(3a*S*)-(+)-**7c** via a four-step sequence: (a) refluxing with 1-chloroethyl chloroformate in chlorobenzene,[15] (b) methanolysis, (c) addition of propionyl chloride/triethylamine in methylene chloride, and (d) reaction with LAH/$AlCl_3$ (1:1) in THF.[16] The absolute configurations of (−)-**7c** and (+)-**7c** were confirmed when the optical rotations were compared to those obtained from the hydrogenation of the resolved allyl analogs (−)-**7b** and (+)-**7b** (see the Experimental Section). The absolute configuration of (−)-**7b** was already established by X-ray crystallography as described earlier. The methoxy analogs (−)-**7c** and (+)-**7c** were then converted into the corresponding phenolic analogs *cis*-(3a*R*)-(−)-**7i** and *cis*-(3a*S*)-(+)-**7i** by the lithium diphenylphosphide procedure.[14]

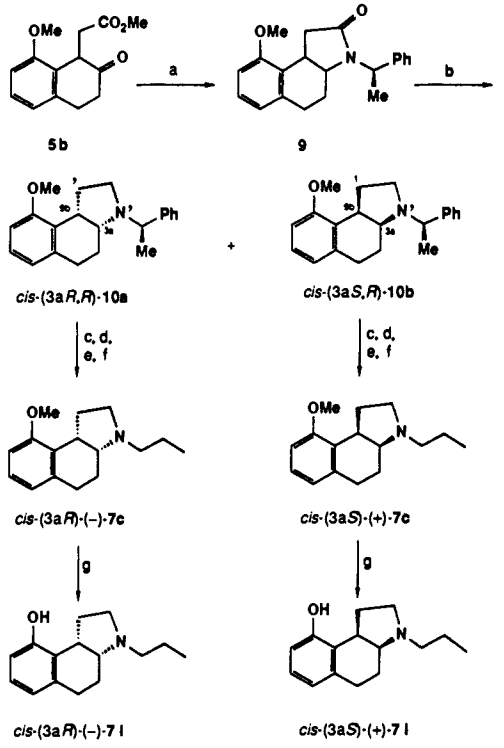
To complete our SAR work on this series, a pair of racemic 2-methyl analogs *cis*-(±)-**12a** and *cis*-(±)-**12b** was synthesized for biological evaluation. As shown in Scheme IV, *cis*-(±)-1-allyl-*N*-*n*-propyl analog **11**[12] was subjected to amino mercuration.[17] The less polar product (48%) was assigned as *cis*-(2α,3aα,9bα)-(±)-**12a** and the more polar product (9%) as *cis*-(2β,3aα,9bα)-(±)-**12b**. No attempt was made to resolve these compounds. Although ^{1}H NMR decoupling experiments were less clear in determining the stereochemistry of the C-2 methyl group in **12a** and **12b**, a definitive assignment was achieved by X-ray crystallography on analog **12a** as shown in Figure 3.

All analogs synthesized and biologically evaluated, within the scope of generic structure **3**, are listed in Table I. The table includes the solvent used for recrystallization of the HCl salt, the melting point, and the molecular formula for each analog.

Pharmacological Results and Discussion

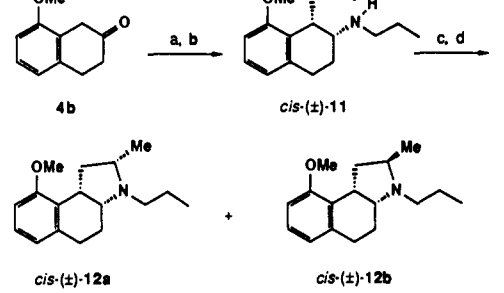
The compounds were evaluated for their in vitro binding affinity at 5-HT_{1A} receptors using [^{3}H]-8-OH-DPAT in

Scheme III[a]



[a] Reagents and conditions: (a) (*R*)-$H_2NCH(Me)Ph$, HOAc, $NaCNBH_3$, THF/MeOH; (b) LAH/THF, Δ; (c) $ClCO_2CHClCH_3$, PhCl, Δ; (d) MeOH, Δ; (e) ClCOEt, Et_3N, CH_2Cl_2; (f) LAH/$AlCl_3$, THF; (g) Ph_2PH, *n*-BuLi, THF, Δ.

Scheme IV[a]



[a] Reagents and conditions: (a) LDA, allyl bromide, THF; (b) *n*-propylamine, HOAc, $NaCNBH_3$, THF/MeOH; (c) $Hg(OAc)_2$, MeOH; (d) NaOH, MeOH, $NaBH_4$.

either homogenate of bovine hippocampus or cloned CHO cells and at dopamine D_2 receptors using either [^{3}H]-raclopride in rat striatum or [^{3}H]U86170 in cloned CHO cells (Table II). Analogs which displayed selective activity in the 5-HT_{1A} binding screen were evaluated for their ability to produce hypothermia in mice (Table II). Intrinsic activity determinations were made by in vitro tests on compounds that were active at the dopamine D_2 receptor (Table III).[18] Interactions with brain serotonin and dopamine receptors in vivo were evaluated by the effects on the synthesis rates of serotonin and dopamine in rats (represented by 5-HTP and DOPA accumulation, Table IV). Inhibition of firing rates of serotonergic neurons in the dorsal raphe nucleus or dopaminergic neurons in the substantia nigra pars compacta was determined following intravenous injection of the test compounds in rats (Table V).

A compound's anxiolytic potential was evaluated in the face-to-face and isolation-induced aggression assays, behavioral paradigms in mice (Table VI). A compound's ability to stimulate or antagonize dopaminergic systems

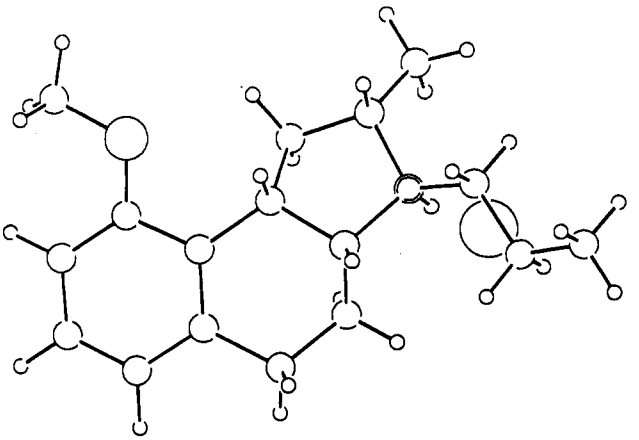


Figure 3. The X-ray crystallographic structure of (±)-**12a**, confirmed as (2α,3aα,9bα)-(±)-2,3,3a,4,5,9b-hexahydro-9-methoxy-2-methyl-3-*n*-propyl-1*H*-benz[*e*]indole hydrochloride.

was measured by effects on locomotor activity in normal or reserpinized mice (Table VII). Cardiovascular effects were also studied by measuring the change in blood pressure and sympathetic nerve activity in the anesthetized cat (Table VIII).

5-HT_{1A} Receptor Agonists. Analogs with 9-methoxy aromatic substitution showed potent 5-HT_{1A} affinity in vitro; however, they were also found active at D_2 receptors both in vitro and in vivo (see Tables II and IV). For example, *cis*-(±)-**7b** and its active enantiomer *cis*-(3a*R*)-(−)-**7b** showed no selectivity in vivo with decreases in 5-HTP and increases in DOPA accumulation. The racemate (±)-**7b** effectively reduced the firing rate of serotonergic neurons and its enantiomer (−)-**7b** was able to antagonize the inhibitory effects of *d*-amphetamine on the dopamine neuronal firing rate at very low doses (ED_{50} = 0.04 μmol/kg iv; Table V). When tested in the isolation-induced aggregation assay, (−)-**7b** was active at 11 and 36 μmol/kg po (Table VI). These data suggest that (±)-**7b** and (−)-**7b** are mixed 5-HT_{1A} receptor agonists and DA receptor antagonists. In the locomotor activity assays (Table VII), (±)-**7b** and (−)-**7b** blocked both *d*-amphetamine- and apomorphine-induced hyperactivity and did not stimulate behavior on reserpinized mice when given alone. This is a further indication of their DA receptor antagonist properties. The other enantiomer, *cis*-(3a*S*)-(+)-**7b**, is 500 and 100 times less potent than (−)-**7b** in vitro at 5-HT_{1A} and D_2 sites, respectively (see Table II). It is also interesting to note that the trans analog (±)-**8b** is active as a mixed 5-HT_{1A} agonist and DA antagonist, with activity at 0.4, 4, and 36 μmol/kg ip in the antagonism of *d*-amphetamine-induced hyperactivity (Table VII).

Analogs with 9-hydroxy aromatic substitution showed selective 5-HT_{1A} receptor agonist activity. The *cis*-*N*-allyl analog (±)-**7h** is not only more potent in vitro (5-HT_{1A} K_i = 0.3 nM) than the corresponding methoxy analog (±)-**7b** (5-HT_{1A} K_i = 1.2 nM), but is also selective for the 5-HT_{1A} site both in vitro and in vivo. Similarly the hydroxy *N*-*n*-propyl enantiomer *cis*-(3a*R*)-(−)-**7i** was found to be a selective 5-HT_{1A} agonist (K_i = 0.1 nM) whereas the corresponding methoxy analog, *cis*-(3a*R*)-(−)-**7c**, is active on both D_2 (K_i = 67 nM) and 5-HT_{1A} (K_i = 0.2 nM) binding affinities.

The racemic 9-methoxy *cis*-analogs with an additional methyl group at C-2 on the pyrrolidine ring, *cis*-(3α,3aα,-9bα)-(±)-**12a** and *cis*-(2β,3aα,9bα)-(±)-**12b**, were also found to be selective 5-HT_{1A} agonists both in vitro and in vivo (Tables II, IV, and V). Furthermore, (±)-**12a** de-

Table II. Affinities at Central 5-HT_{1A} and D_2 Sites in Vitro and Effects on Hypothermia in the Mouse

	K_i[c] (nM)		mouse hypothermia assay		
compd	5-HT_{1A} binding affinity[a]	D_2 binding affinity[b]	ED_{50} (μmol/kg)[g]	max temp decrease	route
8-OH-DPAT	1.6 (±0.3)	>1000	1.0 (0.5–1.8)	7.2	sc
		86 (±8)[e]	9.7 (5.2–18)	7.5	po
apomorphine	NT[j]	26 (±6)[e]	NT[j]		
chlorpromazine	673 (±98)[d]	3.0 (±1.6)[e]	NT[j]		
(±)-7a	31 (±10)	>1000[f]	22[i]	4.4	sc
			69 (28–174)	4.0	po
(±)-7b	1.2 (±0.1)	>1000[f]	8.2 (4–19)	4.2	sc
	0.4 (±0.1)[d]	7.0 (±3)[e]	101[i]	3.6	po
(−)-7b	<1	5.3 (±1)	NT[j]		
	0.2 (±0.1)[d]	6.7 (±1)[e]			
(+)-7b	49 (±13)	270 (±174)	62[i]	3.9	sc
	100 (±18)[d]	77 (±6)[e]			
(±)-7c	4.4 (±2.5)	>1000	20[i]	1.5	sc
			109 (55–126)	6.0	po
(−)-7c	0.2 (±0.01)	67 (±15)	NT[j]		
(+)-7c	186 (±72)	>1000	NT[j]		
(±)-7d	252 (±50)	42 (±12)	>107[h]		sc
	>333[d]	78 (±10)[e]			
(−)-7d	236 (±28)	25 (±6)	NT[j]		
		18 (±6)[e]e			
(+)-7d	>333[d]	>339[e]	NT[j]		
(±)-7e	>1000	>10000	NT[j]		
(±)-7f	37 (±7)[d]	548 (±98)[e]	NT[j]		
(±)-7g	>1000	>1000	NT[j]		
(±)-7h	0.3 (±0.1)[d]	153 (±71)[e]	NT[j]		
(±)-7i	1.4 (±0.4)	>1000[f]	2.1[i]	8.8	sc
			154 (85–227)	2.6	po
(−)-7i	0.1 (±0.01)	>1000[f]	0.3 (0.1–0.8)	5.5	sc
			4.9 (2–12)	7.3	po
(+)-7i	3.0 (±1.0)	>1000[f]	0.05 (0.01–0.2)	8.5	sc
			21 (8–51)	5.5	po
(±)-7j	923 (±88)	198 (±98)	NT[j]		
		75 (±13)[e]			
(−)-7j	54 (±17)	49 (±12)	NT[j]		
		108 (±36)[e]			
(+)-7j	>1000	259 (±139)	NT[j]		
		59 (±5)[e]			
(±)-7k	>1000[f]	>1000	NT[j]		
		218 (±40)[e]			
(±)-8a	11 (±3)	>1000[f]	45 (26–77)	4.5	sc
(±)-8b	4.7 (±0.9)	13 (±4)	40 (24–69)	4.5	sc
		8.5 (±2)[e]			
(±)-8d	16 (±7)	99 (±60)	>107[h]	3.4	sc
	3.7 (±2.2)[d]	50 (±4)[e]			
(±)-8e	66 (±33)	>10000	NT[j]		
(±)-8f	44 (±12)[d]	>1000[f]	NT[j]		
(±)-8g	66 (±14)	63 (±36)	34 (18–64)	3.9	sc
(±)-8h	4.9 (±0.7)[d]	25 (±6)[e]	NT[j]		
(±)-8j	16 (±2)	54 (±14)	113[i]	2.1	sc
		4.1 (±1.4)[e]			
(±)-8k	338 (±140)	33 (±15)	NT[j]		
		93 (±31)[e]			
10a	>442[d]	>339[e]	NT[j]		
10b	317 (±162)[d]	392 (±28)[e]	NT[j]		
(±)-12a	1.0 (±0.3)	>1000[f]	14 (6–33)	6.8	sc
			338[i]	3.0	po
(±)-12b	16 (±3)	>1000[f]	19 (9–41)	5.2	sc
			104 (53–206)	2.4	po

[a] [^{3}H]-8-OH-DPAT-labeled 5-HT_{1A} sites in bovine hippocampus. [b] [^{3}H]-raclopride-labeled D_2 sites in rat striatum. [c] K_i values followed by SEM. [d] [^{3}H]-8-OH-DPAT-labeled 5-HT_{1A} sites in cloned CHO cells. [e] [^{3}H]U86170-labeled D_2 sites in cloned CHO cells. [f] IC_{50}'s in nM were estimated from a single point experiment; compound was run at one μM. [g] ED_{50}'s followed by 95% confidence intervals. [h] As approximate ED_{50}'s; higher doses were not tested to determine 95% confidence intervals. [i] Dose–response curve was too steep to calculate 95% confidence intervals. [j] Not tested.

creased sympathetic nerve discharge (ED_{50} = 0.17 μmol/kg) whereas the other isomer, (±)-**12b**, was inactive (Table VIII). Compound (±)-**12b** is active at 34 μmol/kg ip in the isolation-induced aggression assay and the face-to-face test (Table VI). These data suggest that there is a configurational preference for the *cis*-(2α,3a*R*,9b*S*)-isomer over the *cis*-(2β,3aα,9bα)-isomer toward 5-HT_{1A} receptor.

Nitrogen substitution with either an *n*-propyl or an allyl group in the 9-methoxy series was found to give similar biological activity. For example, the *n*-propyl analog (−)-**7c** has essentially the same profile as the allyl analog (−)-**7b**. However, when the substituent was changed to a bulky α-methylbenzyl group (**10a** and **10b**), binding affinity to both the 5-HT_{1A} and D_2 receptors was lost. In the present study, the cis analogs with 9-methoxy or 9-hydroxy substitution were found to be more potent in the 5-HT_{1A} binding assay than the corresponding trans analogs. For example, *cis*-(±)-**7b** is 4 times more potent than the *trans*-(±)-**8b**. These results are opposite to the findings in the octahydrobenzo[*f*]quinoline series (**2**), where 10-hydroxy-4-*n*-propyl trans analogs are more potent than the corresponding cis analogs in serotonergic activity.[9a] These

Table III. Predicted Intrinsic Activity from GTP Shift

Dopamine Intrinsic Activity			
compd	% intrinsic activity	compd	% intrinsic activity
apomorphine	73	(±)-7j	29
chlorpromazine	5	(−)-7j	22
(−)-3PPP	34	(+)-7j	50
(±)-7b	15	(±)-7k	1
(−)-7b	24	(±)-8b	0
(+)-7b	17	(±)-8d	0
(−)-7c	37	(±)-8g	0
(±)-7d	0	(±)-8h	13
(−)-7d	0	(±)-8j	44
(±)-7h	7	(±)-8k	28
(+)-7l	0		

Table IV. Effects of Selected Compounds on the Synthesis Rates of Dopamine and Serotonin (DOPA and 5-HTP Accumulation) in the Rat Ventral Limbic Brain Region

	accumulation		
compd	dose (μmol/kg)	DOPA[a]	5-HTP[a]
8-OH-DPAT	3.0	3	−47*
	0.3	16	−37*
apomorphine	3.7	−55*	17
haloperidol	2.7	144*	−7
(±)-7a	12.0	20	−46*
(±)-7b	3.6	48	−52*
(−)-7b	3.6	54*	−28
(±)-7d	10.7	147*	−4
(−)-7d	3.6	63*	3
(±)-7e	10.2	−15	−7
(±)-7g	10.6	34	7
(±)-7h	3.8	16	−44*
(±)-7j	3.8	51*	1
(−)-7j	3.8	45	−0.3
(±)-8a	4.0	26*	−7
(±)-8b	3.6	158*	−28*
(±)-8d	10.7	95*	−51*
(±)-8j	3.8	73*	−12
(±)-12a	3.4	7	−42*
(±)-12b	3.4	−1	−43*

[a] As a percent change from the control value. *$p < 0.05$.

Table V. Effects on Inhibition of 5-HT_{1A} and DA Cell Firing in the Rat

	Cell Firing ED_{50}[a] (μmol/kg)	
compd	5-HT_{1A}	DA
8-OH-DPAT	0.005 (±0.02)	2.25 (±1.4)[b]
apomorphine		0.03 (±0.001)
haloperidol		0.019 (±0.005)[b]
		0.018 (±0.006)[c]
(±)-7a	0.12 (±0.03)	
(±)-7b	0.04 (±0.01)	
(−)-7b	0.007 (±0.02)	0.04 (±0.01)[b]
(±)-7d		0.42 (±0.17)[b]
		0.88 (±0.19)[c]
(−)-7d		0.24 (±0.09)[b]
		0.91 (±0.18)[c]
(+)-7d		>3.6
(+)-7j		2.82 (±0.94)[b]
(±)-8j		0.97 (±0.31)[c]
(±)-8k		0.43 (±0.12)[b]
(±)-12b	0.10 (±0.01)	1.70 (±0.16)[b]

[a] ED_{50} value followed by SEM. [b] Tested as an antagonist versus amphetamine. [c] Tested as an antagonist versus apomorphine.

data suggest that the stereochemical environment of a six/six fused ring (**2**) versus a six/five ring (**3**) has a subtle effect on the compound's affinity toward 5-HT_{1A} receptor. In the cis series, the serotonergic activity was found to reside in the (3a*R*)-(−)-enantiomer, which is consistent with the findings in the octahydrobenzo[*f*]quinoline series (**2**).[9c]

Although the 9-methoxy or 9-hydroxy substitution is believed to be critical for serotonergic activity, the compounds without aromatic substitution (R_1 = H in **3**), derivatives such as *N*-allyl analogs *cis*-(±)-**7a**/*trans*-(±)-**8a** and *N*-*n*-propyl analogs *cis*-(±)-**7f**/*trans*-(±)-**8f**, still displayed 5-HT_{1A} receptor agonist activity. For example, analog (±)-**7a** was found to be a selective serotonergic agent in the brain biochemistry with a decrease in 5-HTP accumulation and no significant effect on the accumulation of DOPA (Table IV). This compound is approximately 3 times less potent than the corresponding 9-methoxy analog (±)-**7b** in inhibiting the 5-HT_{1A} neuronal firing rate (ED_{50} = 0.12 μmol/kg; Table V). Analog (±)-**7a** also displayed weak activity in the sympathetic nerve discharge model (ED_{50} = 0.36 μmol/kg; Table VIII) and a slight hypothermic effect (4.4 °F maximum temperature drop; Table II). In this series, the trans analogs seem to possess equal or higher in vitro 5-HT_{1A} affinity than the corresponding cis analogs. This is demonstrated by the *N*-allyl cis/trans pair **7a**/**8a**, where the 5-HT_{1A} affinity was found to be 3 times higher for the trans analog. On the other hand, the *N*-*n*-propyl cis/trans pair **7f**/**8f** showed about equal potency (Table II).

Table VI. Effects of Selected Compounds in the Face-to-Face and Isolation-Induced-Aggression Behavioral Assays in the Mouse

	behavior					
	face-to-face			isolation-induced aggression		
compd	dose (μmol/kg)	route	time (s)	dose (μmol/kg)	route	time (s)
8-OH-DPAT[a]	0.0	sc	1.1	0.0	ip	6
	0.3	sc	1.6	0.3	ip	11
	3.0	sc	5.0*	0.9	ip	20
	30	sc	4.4*			
				0.0	ip	177
				3.0	ip	310*
				9.1	ip	437*
				30	ip	351*
(−)-7b[a]	0.0	po	1.2	0.0	po	18
	0.4	po	0.9	3.6	po	85+
	3.6	po	1.3	11	po	40*
	36	po	1.4			
				0.0	po	27
				36	po	236*
(+)-7b	0.0	po	0.8	0.0	po	27
	0.4	po	0.9	36	po	21
	3.6	po	0.6			
	36	po	1.0			
(±)-12b[a]	0.0	sc	0.6	0.0	ip	9
	34	sc	1.5**	3.4	ip	17
				10	ip	8
				34	ip	469*
				0.0	po	82
				34	po	49

[a] Compound was tested on two occasions, using different doses or different routes of administration. *$p < 0.05$. **$p < 0.10$.

DA Receptor Antagonists. Analogs with 6-methoxy or 6-hydroxy substitution on the aromatic ring are dopamine receptor antagonists. For example, 6-methoxy-*N*-allyl analog *cis*-(±)-**7d** displays potent D_2 receptor binding activity (D_2 K_i = 42 nM) with a predicted intrinsic activity of 0% (Table III). Compound (±)-**7d** induces a substantial increase in DOPA accumulation (147%) without affecting 5-HTP accumulation (Table IV). This compound also decreases locomotor hyperactivity induced by apomorphine and *d*-amphetamine but no stimulation in reserpinized mice (Table VII). Neither *cis*-(±)-**7d** nor *trans*-(±)-**8d** have any effect on sympathetic nerve discharge (Table VIII). These data suggest that (±)-**7d** is a selective dopaminergic antagonist. The dopaminergic activity was found to reside in the *cis*-(3a*R*)-enantiomer (−)-**7d** as demonstrated by a selective increase in DOPA accumulation and antagonist activity in the locomotor

Table VII. Locomotor Activity in Mice

compd	dose[a]	reserpinized mice: stimulation (mean counts)	reserpinized mice: antagonism of apomorphine[b]	antagonism of amphetamine[c]: 0–10 min	antagonism of amphetamine[c]: 10–20 min
Apo[d]	0.03	22	119	78	86
	0.3	150*	135	73	96
	3.2	1777*	139	52**	42*
	32	1184*	113	69	66
Hal[e]	0.3	9	58	94	71
	2.7	1	10*	72	28*
(±)-7b	0.4	6	55**	96	94
	3.6	37	6*	121	94
	36	70	4*	54*	45*
(−)-7b	0.4	7	50**	29*	45*
	3.6	79	14*	52*	49*
	36	52	11*	24*	18*
(+)-7b	0.4	8	103	83	92
	3.6	12	114	73	77
	36	18	115	54*	67*
(−)-7c	0.4	19	41*	60**	93
	3.5	36	6*	72**	67**
	35	69	9*	49*	51*
(±)-7d	0.4	15	73	91	92
	3.6	9	27*	112	59
	36	9	1*	33*	17*
(−)-7d	0.4	17	78	164**	120
	3.6	5	62	130**	105
	36	3	21*	52*	38*
(±)-7f	0.4	15	128	56*	76
(±)-7h	0.4	135	46	56*	62*
	3.8	63*	8*	78	68*
	38	32	11*	54*	69*
(±)-7j	0.4	0	130	101	111
	3.8	8	111	88	111
	38	12	21*	32*	52*
(−)-7j	0.4	73	54	110	105
	3.8	8	62	97	115
	38	3	7*	22*	23*
(+)-7j	0.4	11	79	50*	76
	3.8	42	62*	54*	90
	38	17	62**	20*	37*
(±)-8b	0.4	36	140	65**	65**
	3.6	11	30*	65**	57*
	36	48	5*	40*	32*
(±)-8d	0.4	4	156*	78	106
	3.6	81	142	76	116
	36	49	13*	42*	54*
(±)-8f	0.4	22	55	41*	61*
	4.0	15	48	22*	46*
(±)-8g	0.4	1	188*	87	123
	3.5	6	122	64*	98
	35	27	53**	10*	34*
(±)-8h	0.4	26	73	46*	66*
	3.8	5	5*	71	53*
	38	1	9*	49*	33*
(±)-8j	0.4	12	109	65**	83**
	3.8	4	67**	29*	82**
	38	53	6*	5*	8*
(±)-8k	0.4	63	72	54*	86**
	3.7	2	46*	34*	47*
	37	162	4*	6*	5*

[a] Dose in μmol/kg ip. [b] Mean percent of apomorphine control. [c] Mean percent of amphetamine control. [d] Apomorphine. [e] Haloperidol. *$p < 0.05$. **$p < 0.10$.

assay (Tables IV and VII). O-Demethylation of (±)-7d yielded the less potent 6-hydroxy analog (±)-7j (D_2 K_i = 198 nM). When its enantiomers were examined, (−)-7j showed both 5-HT_{1A} (K_i = 54 nM) and D_2 (K_i = 49 nM) binding affinities whereas its antipod, (+)-7j, showed only a weak D_2 affinity (K_i = 259 nM). Both (±)-7j and (−)-7j showed activity only at the highest doses tested (38 μmol/kg ip) as antagonists in the locomotor assay (Table VII). Interestingly, *cis*-(3a*S*)-(+)-7j produced antagonism at all doses tested (0.4, 3.8, and 38 μmol/kg ip) against *d*-amphetamine-induced hyperactivity even though it has relatively low D_2 binding affinity (K_i = 259 nM).

Table VIII. Effect of Selected Compounds on Arterial Blood Pressure (BP) and Sympathetic Nerve Activity (SND) in the Anesthetized Cat

compd	SND[a] ED_{50} (μmol/kg)	max decrease SND (% control)	% BP (at SND ED_{50})	max decrease BP[b] (% control)
DPAT	0.03	2 (±0.5)	66 (±6)	57 (±3)
(±)-7a	0.36	0 (±0)	76 (±12)	60 (±12)
(±)-7b	IA[c]	189 (±52)		59 (±7)
(−)-7b	IA[c]	385 (±14)		55 (±1)
(±)-7d	IA[c]	132 (±3)		98 (±0.4)
(±)-8d	IA[c]	105 (±17)		61 (±6)
(±)-12a	0.17	42 (±7)	82 (±4)	73 (±4)
(±)-12b	IA[c]	250 (±47)		65 (±7)

[a] Dose at which the SND has been reduced to 50% of the pretreatment value. [b] Maximum decrease observed following 1 mg/kg dose. [c] Inactive.

It is interesting to note that, in this series of compounds, substitution on the nitrogen must be limited to an allyl group for dopamine antagonist activity to be displayed. The other cis-fused racemic analogs with either a cyclopropylmethyl (**7e**) or an *n*-propyl group (**7g**) are inactive both in the in vitro dopamine D_2 binding and in the in vivo biochemical assays (Tables II and IV). The 6-hydroxy-*N*-*n*-propyl analog (±)-**7k** was also found to be inactive in the dopamine binding assay.

In the 6-methoxy-*N*-allyl series, the cis analog (±)-**7d** was found to be more potent and selective than the corresponding trans analog (±)-**8d**. The trans analog (±)-**8d** does not display selectivity and actually has a preference for the 5-HT_{1A} receptor both in vitro and in the in vivo biochemical assay. This analog (±)-**8d**, as well as its corresponding *N*-*n*-propyl analog (±)-**8g**, displayed antagonist activity in the locomotor assay (Table VII). In the 6-hydroxy-*N*-allyl series, however, the trans analog (±)-**8j** displayed higher 5-HT_{1A} and D_2 affinities than the corresponding cis analog (±)-**7j**. Both 6-hydroxy-*N*-allyl analog (±)-**8j** and *N*-*n*-propyl analog (±)-**8k** were found to be very active in the antagonism of apomorphine and *d*-amphetamine-induced hyperactivity (0.4, 4, and 37 μmol/kg ip; see Table VII). This was rather unexpected since they are relatively less active in the D_2 binding assay (K_i = 54 and 33 nM, respectively). It is again interesting to note that, in the octahydrobenzo[*f*]quinoline series, the 7-hydroxy trans analogs are potent DA receptor agonists whereas the 7-hydroxy cis analogs are antagonists.[9a]

Conclusion

The synthetic methodology described herein gives an easy access to a novel class of conformationally restricted analogs, 2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]indoles, as represented by the generic structure **3**. The structure–activity relationships of this series of compounds have led to the identification of potent mixed 5-HT_{1A} receptor agonist/DA receptor antagonists, selective 5-HT_{1A} receptor agonists, and selective DA receptor antagonists. Analogs with 9-methoxy substitution (R_1) on the aromatic ring showed mixed 5-HT_{1A} receptor agonist and dopamine receptor antagonist properties whereas the corresponding 9-hydroxy analogs displayed selective 5-HT_{1A} receptor agonist activity. In this series, the cis analogs were found to be more potent than the corresponding trans analogs. Among the cis enantiomers examined, the activity was found to reside in the (3a*R*)-(−)-enantiomers. Nitrogen substitution (R_2) with either an *n*-propyl group or an allyl group produced good activity whereas replacement with a bulky α-methylbenzyl group resulted in loss of activity. Analogs without aromatic substitution (R_1 = H), although less potent than the 9-methoxy series, still showed good

5-HT_{1A} receptor agonist activity. In this case, however, the trans analogs were found to be either equal to or more potent than the corresponding cis analogs in the in vitro 5-HT_{1A} binding assay. Analogs with either 6-methoxy or 6-hydroxy substitution (R_1) on the aromatic ring were found to display dopamine receptor antagonist properties. However, only *N*-allyl analogs showed this activity. In the 6-methoxy-*N*-allyl series, the cis analog was found to be more potent than the corresponding trans analog, and in the cis series, the activity was also found to reside in the (3a*R*)-(−)-enantiomer. Incorporation of an additional methyl group (R_3) into the 9-methoxy *cis*-(±)-analog at C-2 on the pyrrolidine ring resulted in retention of 5-HT_{1A} agonist activity. These conformationally restricted analogs, represented by the generic structure **3**, have displayed interesting pharmacological profiles and proven to be valuable tools for molecular modeling[19] in the search for selective serotonin and dopamine ligands.

Experimental Section

Synthesis. Analytical TLC was performed on Analtech 10 × 20 cm (250 μm) silica gel GF prescored glass plates which were developed in the solvent systems described. The plates were checked under ultraviolet light and developed by dipping in ammonium molybdate/cerium sulfate/10% sulfuric acid solution and heating on a hot plate. ^{1}H NMR spectra were obtained at 300 MHz on a Bruker Model AM-300 spectrometer in $CDCl_3$ solution unless noted otherwise. Chemical shifts (δ) are reported in parts per million relative to internal tetramethylsilane. Flash column chromatography and medium-pressure liquid chromatography were performed with 400 g–1 kg silica gel 60 (230–400 mesh) purchased from EM Science. All commercial chemicals were used as received from Aldrich unless noted otherwise. HPLC-grade methylene chloride, methanol, tetrahydrofuran, ethyl acetate, and hexane were used. All reactions were performed under a nitrogen atmosphere. Melting points were determined in open capillary tubes on a Mettler FP-62 melting point apparatus and are uncorrected. The amine-based products were converted into the HCl salts by dissolving the free base in methanolic HCl solution.[20] The solvent was removed and azeotroped with toluene in vacuo, followed by recrystallization from an appropriate solvent. Other physical data, such as IR, MS, elemental analyses, and optical rotations, were performed by the Physical and Analytical Chemistry Unit of Upjohn Laboratories. The elemental analyses reported are within ±0.4% of the calculated values.

(±)-1,2,3,4-Tetrahydro-2-oxo-1-naphthaleneacetic Acid Methyl Ester (5a). A solution of 2-tetralone (**4a**, 6.6 mL, 55 mmol) in THF (100 mL) was cooled to −30 °C and LDA in cyclohexane (36.6 mL, 55 mmol) was added slowly over 5 min. The mixture was stirred for 30 min and methyl bromoacetate (5.7 mL, 60 mmol) was added. The solution was allowed to warm to 0 °C and stirred for 1 h. The reaction was quenched with 3 N HCl to pH < 3. THF was removed in vacuo and the concentrate was extracted with methylene chloride (2 × 500 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to yield a yellow oil. This oil was purified by medium-pressure liquid chromatography on 560 g of silica gel, eluting with hexane/ethyl acetate (4:1). Fractions homogeneous by TLC were combined and concentrated in vacuo to yield **5a** (8.22 g, 75.4%) as a near colorless oil: ^{1}H NMR δ 7.28–7.09 (m, 4 H), 3.96 (t, J = 7 Hz, 1 H), 3.68 (s, 3 H), 3.58–2.42 (m, 6 H); IR (film) ν_{max} 1738, 1719, 1605, 1582 cm^{-1}; MS, M$^+$ m/z 218, other ions at m/z 187, 158, 145, 130, 115. Since this keto ester was found to be unstable at room temperature, the oil was stored in a freezer under nitrogen.

(±)-1,2,3,4-Tetrahydro-8-methoxy-2-oxo-1-naphthaleneacetic Acid Methyl Ester (5b). This compound was prepared from 8-methoxy-2-tetralone (**4b**, 1.76 g, 10 mmol), using the alkylation procedure described in the preparation of **5a**. The reaction was run at room temperature for 2 h after the addition of methyl bromoacetate. The crude product was purified by medium-pressure liquid chromatography on 400 g of silica gel, eluting with hexane/acetone (4:1). Fractions homogeneous by TLC were combined and concentrated to yield the desired product **5b** (1.96 g, 82%) as yellow oil: ^{1}H NMR δ 7.19 (t, J = 7.9 Hz, 1 H), 6.82 (d, J = 7.6 Hz, 1 H), 6.75 (d, J = 8.2 Hz), 3.85 (t, J = 5.1 Hz, 1 H), 3.83 (s, 3 H), 3.81 (t, J = 7 Hz), 3.56 (s, 3 H), 3.49–2.57 (m, 6 H); IR (film) ν_{max} 1741, 1713, 1601, 1587 cm^{-1}; MS, M$^+$ m/z 248, other ions at m/z 216, 188, 174, 147. Since this keto ester was also found to be unstable at room temperature, this oil was stored in a freezer under nitrogen.

(±)-1,2,3,4-Tetrahydro-5-methoxy-2-oxo-1-naphthaleneacetic Acid Methyl Ester (5c). This compound was prepared from 5-methoxy-2-tetralone (**4c**, 5.3 g, 30 mmol), using the alkylation procedure described in the preparation of **5a**. The crude product was purified by medium-pressure liquid chromatography on 400 g of silica gel, eluting with 500 mL of hexane followed by hexane/ethyl acetate (9:1). Fractions homogeneous by TLC were combined and concentrated to yield the desired product **5c** (5.0 g, 67%) as a colorless oil: ^{1}H NMR δ 7.2 (t, J = 8.0 Hz, 1 H), 6.80 (d, J = 8.2 Hz, 1 H), 6.73 (d, J = 7.8 Hz, 1 H), 3.94 (t, J = 6.0 Hz, 1 H), 3.85 (s, 3 H), 3.68 (s, 3 H), 3.32–2.42 (m, 6 H); IR (film) ν_{max} 1729, 1717, 1686, 1600, 1588 cm^{-1}; MS, M$^+$ m/z 248, other ions at m/z 216, 188, 174, 147. This keto ester was found to be unstable and this oil was stored in a freezer under nitrogen.

***cis*-(±)- and *trans*-(±)-1,3,3a,4,5,9b-Hexahydro-3-(2-propenyl)-2*H*-benz[*e*]indol-2-one (6a).** A solution of keto ester **5a** (7.9 g, 36 mmol) and allylamine (13.5 mL, 180 mmol) in 144 mL of MeOH/THF (1:1) was treated with acetic acid to pH 4–5 (about 23 mL) at 0–5 °C. The mixture was stirred for 30 min and sodium cyanoborohydride (4.5 g, 72 mmol) was added. The resulting solution was stirred at room temperature for 1–3 days. The reaction was quenched with 20% sodium hydroxide and the solvent was removed in vacuo. The concentrate was extracted with methylene chloride (3 × 500 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by medium-pressure liquid chromatography on 900 g of silica gel, eluting with hexane/acetone (3:1). Fractions homogeneous by TLC were combined and concentrated to yield **6a** (4.5 g, 55%) as a yellow oil: ^{1}H NMR δ 7.20–7.00 (m, 4 H), 5.80–5.20 (m, 3 H), 4.40 (m, 1 H), 3.90–1.70 (m, 9 H). In this case, the *cis*- and *trans*-lactams were not separable by chromatography. The mixture was used in the next step without further attempts to isolate the isomers or to obtain the analytical data.

***cis*-(±)- and *trans*-(±)-1,3,3a,4,5,9b-Hexahydro-9-methoxy-3-(2-propenyl)-2*H*-benz[*e*]indol-2-one (6b).** These lactams were prepared from **5b** (1.94 g, 7.8 mmol), using the reductive amination/cyclization procedure described in the preparation of **6a**. The crude product was purified by medium-pressure liquid chromatography on 900 g of silica gel, eluting with hexane/acetone (3:1). Fractions homogeneous by TLC were combined and concentrated to yield **6b** (1.15 g, 57%) as a yellow oil: ^{1}H NMR δ 7.13 (t, J = 7.9 Hz, 1 H), 6.77–6.67 (m, 2 H), 5.87–5.22 (m, 3 H), 4.42–4.10 (m, 1 H), 3.82 (s, 3 H), 3.85–1.58 (m, 9 H). Similar to **6a**, the *cis*- and *trans*-lactams were not separable by chromatography. The mixture was used in the next step without further attempts to isolate the isomers or to obtain the analytical data.

***cis*-(±)- and *trans*-(±)-1,3,3a,4,5,9b-Hexahydro-9-methoxy-3-*n*-propyl-2*H*-benz[*e*]indol-2-one (6c).** The keto ester **5b** (11.3 g, 45.5 mmol) was reacted with *n*-propylamine (18.7 mL, 227.5 mmol), by the reductive amination/cyclization procedure described in the preparation of **6a**. The crude product was purified by flash chromatography on 1 kg of silica gel, eluting with hexane/ethyl acetate (2:1). Fractions homogeneous by TLC were combined to yield the lactam **6c** (6.3 g, 54%) as a yellow oil: ^{1}H NMR δ 7.13 (t, J = 7.9 Hz, 1 H), 6.73 (d, J = 7.6 Hz, 1 H), 6.72 (d, J = 8.2 Hz, 1 H); MS M$^+$ m/z 259, other ions at m/z 244, 230, 216, 202, 188, 173.

***cis*-(±)- and *trans*-(±)-1,3,3a,4,5,9b-Hexahydro-6-methoxy-3-(2-propenyl)-2*H*-benz[*e*]indol-2-one [*cis*-(±)-6d and *trans*-(±)-6d].** These compounds were prepared from the keto ester **5c** (4.6 g, 18.5 mmol), using the reductive amination/cyclization procedure described in the preparation of **6a**. The crude product was purified by medium-pressure liquid chromatography on 900 g of silica gel, eluting with hexane/acetone (3:1). Fractions homogeneous by TLC were combined and concentrated in vacuo.

The less polar product was obtained as a yellow oil which was

recrystallized from hexane/ethyl acetate to yield the lactam (0.92 g, 14.3%) as a white solid: mp 137–138 °C; ^{1}H NMR δ 7.17 (t, J = 7.9 Hz, 1 H), 6.75 (d, J = 8.3 Hz, 1 H), 6.65 (d, J = 7.6 Hz, 1 H), 5.86–5.12 (m, 3 H), 4.22–4.12 (m, 1 H), 3.82 (s, 3 H), 3.83–3.72 (m, 1 H), 3.40–3.32 (m, 1 H), 3.15–1.62 (m, 7 H); the decoupling experiments (500 MHz ^{1}H NMR) determined the coupling constant for C-3a (δ 3.40–3.32) and C-9b protons to be 10.3 Hz, indicating they are diaxial, confirming this compound as *trans*-(±)-**6d**; IR (mull) ν_{max} 1686, 1645, 1603, 1582 cm^{-1}; MS, M$^+$ m/z 257, other ions at m/z 242, 228. Anal. ($C_{16}H_{19}NO_2$) C, H, N.

The more polar product was obtained as a yellow oil which was recrystallized from hexane/ethyl acetate to give another lactam (2.93 g, 61.6%) as a white solid: mp 89–90 °C; ^{1}H NMR δ 7.16 (t, J = 7.9 Hz), 6.75 (d, J = 7.7 Hz), 6.70 (d, J = 8.2 Hz), 5.88–5.18 (m, 3 H), 4.43–4.32 (m, 1 H), 3.90–3.82 (m, 1 H), 3.82 (s, 3 H), 3.68–3.60 (m, 2 H), 3.02–1.62 (m, 6 H); the decoupling experiments did not resolve the peaks, but they showed a small coupling constant for C-3a (δ 3.90–3.82) and C-9b protons, indicating they are equatorial–axial, assigning this product as *cis*-(±)-**6d**; IR (mull) ν_{max} 1684, 1641, 1601, 1584 cm^{-1}; MS, M$^+$ m/z 257, other ions at m/z 242, 228. Anal. ($C_{16}H_{19}NO_2$) C, H, N.

***cis*-(±)-1,3,3a,4,5,9b-Hexahydro-6-methoxy-3-(cyclopropylmethyl)-2*H*-benz[*e*]indol-2-one [*cis*-(±)-6e and *trans*-(±)-6e].** These compounds were prepared from **5c** (4.97 g, 20 mmol), using the reductive amination/cyclization procedure described in the preparation of **6a**. The crude product was purified by medium-pressure liquid chromatography on 400 g of silica gel, eluting with hexane/ethyl acetate (1:2). Fractions homogeneous by TLC were combined and concentrated in vacuo.

The less polar product (0.72 g, 13%), assigned as *trans*-(±)-**6e**, was obtained as a white solid: mp 134–135 °C; ^{1}H NMR δ 7.18 (t, J = 7.9 Hz, 1 H), 6.76 (d, J = 8.2 Hz, 1 H), 6.67 (d, J = 7.5 Hz, 1 H), 3.83 (s, 3 H), 3.54–3.46 (m, 1 H), 3.16–1.75 (m, 9 H), 1.05–0.18 (m, 5 H); IR (mull) ν_{max} 1689, 1600, 1582 cm^{-1}; MS, M$^+$ m/z 271, other ions at m/z 256, 242, 216, 173. Anal. ($C_{17}H_{21}NO_2$) C, H, N.

The more polar product (2.78 g, 51%), assigned as *cis*-(±)-**6e**, was obtained as a white solid: mp 81–82 °C; ^{1}H NMR δ 7.18 (t, J = 7.9 Hz, 1 H), 6.76 (d, J = 7.7 Hz, 1 H), 6.69 (d, J = 8.1 Hz, 1 H), 4.06–3.99 (m, 1 H), 3.82 (s, 3 H), 3.67–1.60 (m, 9 H), 1.08–0.18 (m, 5 H); IR (mull) ν_{max} 1686, 1602, 1584 cm^{-1}; MS, M$^+$ m/z 271, other ions at m/z 256, 242, 216, 173. Anal. ($C_{17}H_{21}NO_2$) C, H, N.

***cis*-(±)-2,3,3a,4,5,9b-Hexahydro-3-(2-propenyl)-1*H*-benz[*e*]indole Hydrochloride (7a) and *trans*-(±)-2,3,3a,4,5,9b-Hexahydro-3-(2-propenyl)-1*H*-benz[*e*]indole Hydrochloride (8a).** To a suspension of lithium aluminum hydride (4.95 g, 130 mmol) in THF (150 mL) at 0 °C was added slowly to a solution of the **6a** (7.4 g, 32.6 mmol) in THF (10 mL). The mixture was refluxed for 4 h and cooled to room temperature. The gray suspension was then transferred into an Erlenmeyer flask and quenched at 0 °C by slow addition of saturated aqueous sodium sulfate with vigorous stirring. The mixture was diluted with 1 L ethyl acetate and dried over anhydrous sodium sulfate. Filtration through a layer of Celite was followed by concentration of the filtrate in vacuo. The crude product was then purified by flash chromatography on 1 kg of silica gel, eluting with hexane/ethyl acetate (1:1). Fractions homogeneous by TLC were combined and concentrated in vacuo.

The less polar product (4.09 g, 58.9%) was obtained as an oil. Conversion into the HCl salt and recrystallization afforded (±)-**7a** as a white solid: ^{1}H NMR δ 7.18–7.10 (m, 4 H), 6.42–5.44 (m, 3 H), 4.10–1.60 (m, 12 H); IR (mull) ν_{max} 1598 cm^{-1}; MS, M$^+$ m/z 213, other ions at m/z 186, 143, 129, 128, 115. Anal. ($C_{15}H_{19}N$·HCl) C, H, N.

The more polar product (0.4 g, 5.8%) was also obtained as an oil. Conversion into the HCl salt and recrystallization afforded (±)-**8a** as a white solid: ^{1}H NMR δ 7.23–7.05 (m, 4 H), 6.24–5.44 (m, 3 H), 4.12–1.82 (m, 12 H); IR (mull) ν_{max} 1598 cm^{-1}; MS, M$^+$ m/z 213, other ions at m/z 186, 143, 129, 128, 115. Anal. ($C_{15}H_{19}N$·HCl) C, H, N.

The assignment of the major product (±)-**7a** as the cis isomer and the minor product (±)-**8a** as the trans isomer was based on the *cis*-lactam as the major component in the starting material **6a**. This was based on analogy to the separation of *cis*- and *trans*-lactams, *cis*-(±)-**6d** and *trans*-(±)-**6d**, in which cis isomer was found to be the major product.

***cis*-(±)-2,3,3a,4,5,9b-Hexahydro-9-methoxy-3-(2-propenyl)-1*H*-benz[*e*]indole Hydrochloride (7b) and *trans*-(±)-2,3,3a,4,5,9b-Hexahydro-9-methoxy-3-(2-propenyl)-1*H*-benz[*e*]indole Hydrochloride (8b).** These compounds were prepared from **6b** (8 g, 31.1 mmol), using the reduction procedure described in the preparation of *cis*-(±)-**7a** and *trans*-(±)-**8a**. The crude product was purified by flash chromatography on 1 kg of silica gel, eluting with hexane/ethyl acetate (1:1). Fractions homogeneous by TLC were combined and concentrated.

The less polar product (4.64 g, 61%) was obtained as an oil. Conversion into the HCl salt and recrystallization yielded *cis*-(±)-**7b** as a white solid: ^{1}H NMR δ 7.06 (t, J = 7.9 Hz, 1 H), 6.70 (d, J = 7.2 Hz, 1 H), 6.68 (d, J = 7.9 Hz, 1 H), 6.08–5.05 (m, 3 H), 3.80 (s, 3 H), 3.58–1.32 (m, 12 H); IR (mull) ν_{max} 1603, 1585 cm^{-1}; MS, M$^+$ m/z 243, other ions at m/z 228, 216, 202, 187, 173, 159. Anal. ($C_{16}H_{21}NO$·HCl) C, H, N.

The more polar product (0.4 g, 5.3%) was also obtained as an oil. Conversion into the HCl salt and recrystallization afforded *trans*-(±)-**8b** as a white solid: ^{1}H NMR δ 7.13 (t, J = 7.9 Hz, 1 H), 6.72 (d, J = 7.7 Hz, 1 H), 6.67 (d, J = 8.2 Hz, 1 H), 6.25–5.40 (m, 3 H), 3.80 (s, 3 H), 3.99–1.32 (m, 12 H); IR (mull) ν_{max} 1599, 1579 cm^{-1}; MS, M$^+$ m/z 243, other ions at m/z 228, 216, 202, 187, 173, 159. Anal. ($C_{16}H_{21}NO$·HCl) C, H, N.

Similar to **7a** and **8a**, the major product **7b** was assigned as the cis isomer whereas the minor product **8b** was assigned as the trans isomer.

***cis*-(±)-2,3,3a,4,5,9b-Hexahydro-9-methoxy-3-(*n*-propyl)-1*H*-benz[*e*]indole Hydrochloride (7c).** The lactam **6c** (5.9 g, 23.7 mmol) was reacted with LAH (3.63 g, 95.7 mmol), using the reduction procedure described in the preparation of **7a** and **8a**. The crude product was purified by flash chromatography on 1 kg of silica gel, eluting with hexane/ethyl acetate (4:1). Fractions homogeneous by TLC were combined and concentrated to yield the desired product (4.64 g, 83%) as an oil. Conversion into the HCl salt and recrystallization yielded *cis*-(±)-**7c** as a white solid: ^{1}H NMR δ 7.15 (t, J = 7.9 Hz, 1 H), 6.82 (d, J = 8.3 Hz, 1 H), 6.75 (d, J = 7.7 Hz, 1 H), 3.83 (s, 3 H), 4.10–1.50 (m, 14 H), 1.06 (t, J = 7.4 Hz, 3 H); IR (mull) ν_{max} 1601, 1585 cm^{-1}; MS, M$^+$ m/z 245, other ions at m/z 216, 187, 176, 159. Anal. ($C_{16}H_{23}NO$·HCl) C, H, N.

Note: No attempt was made to isolate the minor product, *trans*-(±)-**8c**.

***cis*-(±)-2,3,3a,4,5,9b-Hexahydro-6-methoxy-3-(2-propenyl)-1*H*-benz[*e*]indole Hydrochloride (7d).** This compound was prepared from *cis*-(±)-**6d** (2.7 g, 10.5 mmol), using the reduction procedure described in the preparation of (±)-**7a** and (±)-**8a**. The crude product was purified by medium-pressure liquid chromatography on 400 g of silica gel, eluting with hexane/acetone (4:1). Fractions homogeneous by TLC were combined and concentrated to give the desired product (2.37 g, 93%) as an oil. Conversion into the HCl salt and recrystallization yielded *cis*-(±)-**7d** as a white solid: ^{1}H NMR δ 7.16 (t, J = 8.0 Hz, 1 H), 6.75–6.66 (m, 2 H), 6.42–5.44 (m, 3 H), 3.82 (s, 3 H), 4.02–1.50 (m, 12 H); IR (mull) ν_{max} 1591 cm^{-1}; MS, M$^+$ m/z 243, other ions at m/z 228, 216, 174, 160. Anal. ($C_{16}H_{21}NO$·HCl) C, H, N.

***trans*-(±)-2,3,3a,4,5,9b-Hexahydro-6-methoxy-3-(2-propenyl)-1*H*-benz[*e*]indole Hydrochloride (8d).** This compound was prepared from *trans*-(±)-**6d** (0.58 g, 2.25 mmol), using the reduction procedure described in the preparation of (±)-**7a** and (±)-**8a**. The crude product was purified by medium-pressure liquid chromatography on 400 g of silica gel, eluting with hexane/acetone (4:1). Fractions homogeneous by TLC were combined and concentrated to yield the desired product (0.38 g, 69%) as an oil. Conversion into the HCl salt and recrystallization yielded *trans*-(±)-**8d** as a white solid: ^{1}H NMR δ 7.18 (t, J = 8.0 Hz, 1 H), 6.75 (d, J = 8.3 Hz, 1 H), 6.67 (d, J = 7.7 Hz, 1 H), 6.25–6.45 (m, 3 H), 3.82 (s, 3 H), 4.10–1.82 (m, 12 H); IR (mull) ν_{max} 1587 cm^{-1}; MS, M$^+$ m/z 243, other ions at m/z 228, 216, 173, 159. Anal. ($C_{16}H_{21}NO$·HCl) C, H, N.

***cis*-(±)-2,3,3a,4,5,9b-Hexahydro-6-methoxy-3-(cyclopropylmethyl)-1*H*-benz[*e*]indole Hydrochloride (7e).** This compound was prepared from *cis*-(±)-**6e** (2.45 g, 9 mmol) and LAH (1.02 g, 27 mmol), using the reduction procedure described in the preparation of (±)-**7a** and (±)-**8a**. The crude product was purified by medium-pressure liquid chromatography on 400 g of silica gel, eluting with hexane/ethyl acetate (3:2). Fractions homogeneous by TLC were combined and concentrated to yield

the desired product (2.0 g, 88%) as an oil. Conversion into the HCl salt and recrystallization yielded *cis*-(±)-**7e** as a white solid: ^{1}H NMR δ 7.17 (t, J = 8.0 Hz, 1 H), 6.82–6.68 (m, 2 H), 3.82 (s, 3 H), 4.18–1.90 (m, 12 H), 1.62–0.38 (m, 5 H); IR (mull) ν_{max} 1599, 1588 cm^{-1}; MS, M$^+$ m/z 257, other ions at m/z 242, 228, 216, 173, 159. Anal. ($C_{17}H_{23}NO$·HCl) C, H, N.

***trans*-(±)-2,3,3a,4,5,9b-Hexahydro-6-methoxy-3-(cyclopropylmethyl)-1*H*-benz[*e*]indole Hydrochloride (8e).** This compound was prepared from *trans*-(±)-**6e** (0.48 g, 1.8 mmol), using the reduction procedure described in the preparation of (±)-**7a** and (±)-**8a**. The crude product was purified by medium-pressure liquid chromatography on 400 g of silica gel, eluting with hexane/ethyl acetate (3:2). Fractions homogeneous by TLC were combined and concentrated to yield the desired product (0.37 g, 81%) as an oil. Conversion into the HCl salt and recrystallization yielded *trans*-(±)-**8e** as a white solid: ^{1}H NMR δ 7.17 (t, J = 8.0 Hz, 1 H), 6.75 (d, J = 8.2 Hz, 1 H), 6.68 (d, J = 7.7 Hz, 1 H), 3.82 (s, 3 H), 4.30–1.40 (m, 12 H), 1.42–0.38 (m, 5 H); IR (mull) ν_{max} 1599, 1583 cm^{-1}; MS, M$^+$ m/z 257, other ions at m/z 242, 228, 216, 173, 159. Anal. ($C_{17}H_{23}NO$·HCl) C, H, N.

***cis*-(±)-2,3,3a,4,5,9b-Hexahydro-3-*n*-propyl-1*H*-benz[*e*]indole Hydrochloride (7f).** A mixture of compound *cis*-(±)-**7a** (0.5 g, 2.0 mmol) and 10% Pd/C (0.1 g) in 40 mL of methanol was hydrogenated in a Parr shaker at 40 psi for 3 h at room temperature. The mixture was then filtered through a layer of Solka Floc and concentrated in vacuo. Conversion into the HCl salt and recrystallization yielded *cis*-(±)-**7f** (0.43 g, 86%) as a white solid: ^{1}H NMR δ 7.21–7.08 (m, 5 H), 4.12–1.50 (m, 14 H), 1.04 (t, J = 7.3 Hz, 3 H); IR (mull) ν_{max} 1604, 1582 cm^{-1}; MS, M$^+$ m/z 215, other ion at m/z 202, 186, 143, 129. Anal. ($C_{16}H_{23}NO$·HCl) C, H, N.

***trans*-(±)-2,3,3a,4,5,9b-Hexahydro-3-*n*-propyl-1*H*-benz[*e*]indole Hydrochloride (8f).** This compound was prepared from *trans*-(±)-**8a** (0.19 g, 0.8 mmol), using the hydrogenation procedure described in the preparation of (±)-**7f**. Conversion into the HCl salt and recrystallization yielded *trans*-(±)-**8f** (0.14 g, 56%) as a white solid: ^{1}H NMR δ 7.20–7.01 (m, 5 H), 4.22–1.72 (m, 14 H), 1.04 (t, J = 7.3 Hz, 3 H); IR (mull) ν_{max} 1603, 1578 cm^{-1}; MS, M$^+$ m/z 215, other ion at m/z 202, 186, 143, 129. Anal. ($C_{16}H_{23}NO$·HCl) C, H, N.

***cis*-(±)-2,3,3a,4,5,9b-Hexahydro-6-methoxy-3-*n*-propyl-1*H*-benz[*e*]indole Hydrochloride (7g).** This compound was prepared from (±)-**7d** (0.56 g, 2.0 mmol), using the hydrogenation procedure described in the preparation of (±)-**7f**. Conversion into the HCl salt and recrystallization yielded *cis*-(±)-**7g** (0.42 g, 75%) as a white solid: ^{1}H NMR δ 7.16 (t, J = 8.0 Hz, 1 H), 6.75–6.62 (m, 2 H), 4.10–1.90 (m, 14 H), 1.03 (t, J = 7.3 Hz, 3 H); IR (mull) ν_{max} 1660, 1590 cm^{-1}; MS, M$^+$ m/z 245, other ion at m/z 216, 185, 173, 159. Anal. ($C_{16}H_{23}NO$·HCl) C, H, N.

***trans*-(±)-2,3,3a,4,5,9b-Hexahydro-6-methoxy-3-*n*-propyl-1*H*-benz[*e*]indole Hydrochloride (8g).** This compound was prepared from (±)-**8d** (0.14 g, 0.5 mmol), using the hydrogenation procedure described in the preparation of (±)-**7f**. Conversion into the HCl salt and recrystallization yielded *trans*-(±)-**8g** (0.13 g, 92%) as a white solid: ^{1}H NMR δ 7.17 (t, J = 8.0 Hz, 1 H), 6.74 (d, J = 8.3 Hz, 1 H), 6.66 (d, J = 7.7 Hz, 1 H), 3.82 (s, 3 H), 4.24–1.72 (m, 14 H), 1.36 (t, J = 7.3 Hz, 3 H); IR (mull) ν_{max} 1603, 1586 cm^{-1}; MS, M$^+$ m/z 245, other ions at m/z 216, 187, 173, 159. Anal. ($C_{16}H_{23}NO$·HCl) C, H, N.

***cis*-(±)-2,3,3a,4,5,9b-Hexahydro-9-hydroxy-3-(2-propenyl)-1*H*-benz[*e*]indole Hydrochloride (7h).**[14] A solution of diphenylphosphine (0.28 mL, 1.5 mmol) in THF (5 mL) was treated with 1.6 M *n*-butyllithium in hexane (1.3 mL, 2.0 mmol) at 0 °C. The resulting red solution was stirred for 10 min, at which time starting material *cis*-(±)-**7b** (0.14 g, 0.5 mmol) in THF (2 mL) was added and refluxed for 24 h. The reaction was quenched with water and extracted with methylene chloride (2 × 500 mL). The combined organic layers were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to yield a colorless oil. The oil was purified by medium-pressure liquid chromatography on 200 g of silica gel, eluting with methylene chloride (500 mL) followed by methylene chloride/acetone (1:1). Fractions homogeneous by TLC were combined and concentrated in vacuo to give a colorless oil. Conversion into the HCl salt and recrystallization yielded *cis*-(±)-**7h** (0.1 g, 80%) as a white solid: ^{1}H NMR ($CDCl_3$ + 10% CD_3OD) δ 7.01 (t, J = 7.9 Hz, 1 H), 6.68 (t, J = 7.6 Hz, 2 H), 6.28–5.52 (m, 3 H), 3.98–1.82 (m, 12 H); IR (mull) ν_{max} 3260, 3230, 1605, 1586 cm^{-1}; MS, M$^+$ m/z 229, other ions at m/z 214, 159, 145, 115. Anal. ($C_{15}H_{19}NO$·HCl) C, H, N.

***trans*-(±)-2,3,3a,4,5,9b-Hexahydro-9-hydroxy-3-(2-propenyl)-1*H*-benz[*e*]indole Hydrochloride (8h).** This compound was prepared from *trans*-(±)-**8b** (0.42 g, 1.5 mmol), using the demethylation procedure described in the preparation of (±)-**7h**. Conversion into the HCl salt and recrystallization yielded *trans*-(±)-**8h** (0.26 g, 63%) as a white solid: ^{1}H NMR δ 7.01 (t, J = 8.1 Hz, 1 H), 6.65 (t, J = 8.2 Hz, 2 H), 6.16–5.53 (m, 3 H), 4.12–1.92 (m, 12 H); IR (mull) ν_{max} 3267, 3133, 1608, 1583 cm^{-1}; MS, M$^+$ m/z 229, other ion at m/z 214, 159, 145, 115. Anal. ($C_{16}H_{23}NO$·HCl) C, H, N.

***cis*-(±)-2,3,3a,4,5,9b-Hexahydro-9-hydroxy-3-*n*-propyl-1*H*-benz[*e*]indole Hydrochloride (7i).** A solution of the methoxy compound *cis*-(±)-**7c** (1.0 g, 3.5 mmol) in 48% hydrobromic acid (15 mL) was refluxed (bath temperature, 120 °C) for 18 h. The mixture was cooled to room temperature and treated with 20% sodium hydroxide until pH >9. The mixture was extracted with methylene chloride (3 × 500 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to give a tan solid. Conversion into the HCl salt and recrystallization yielded *cis*-(±)-**7i** (0.5 g, 54%) as a white solid: ^{1}H NMR δ 6.92 (t, J = 7.8 Hz, 1 H), 6.51 (d, J = 7.5 Hz, 2 H), 3.50–1.50 (m, 14 H), 1.01 (t, J = 7.2 Hz, 3 H); IR (mull) ν_{max} 3172, 1609, 1587 cm^{-1}; MS, M$^+$ m/z 231, other ions at m/z 202, 173, 145, 131, 115. Anal. ($C_{15}H_{21}NO$·HCl) C, H, N.

***cis*-(±)-2,3,3a,4,5,9b-Hexahydro-6-hydroxy-3-(2-propenyl)-1*H*-benz[*e*]indole Hydrochloride (7j).** This compound as prepared from *cis*-(±)-**7d** (1.6 g, 6.5 mmol), using the demethylation procedure described in the preparation of (±)-**7h**. The crude product was purified by medium-pressure liquid chromatography on 400 g of silica gel, eluting with hexane/acetone (2:1). Fractions homogeneous by TLC were combined and concentrated to yield an oil. Conversion into the HCl salt and recrystallization yielded *cis*-(±)-**7j** (0.8 g, 51%) as a white solid: ^{1}H NMR ($CDCl_3$ + 10% CD_3OD) δ 6.69 (t, J = 7.9 Hz, 1 H), 6.34 (d, J = 7.9 Hz, 2 H), 5.88–5.18 (m, 3 H), 3.62–1.50 (m, 12 H); IR (mull) ν_{max} 3165, 1588 cm^{-1}; MS, M$^+$ m/z 229, other ions at m/z 214, 202, 188, 159, 145. Anal. ($C_{15}H_{19}NO$·HCl) C, H, N.

***trans*-(±)-2,3,3a,4,5,9b-Hexahydro-6-hydroxy-3-(2-propenyl)-1*H*-benz[*e*]indole Hydrochloride (8j).** This compound was prepared from *trans*-(±)-**8d** (0.98 g, 3.5 mmol), using the demethylation procedure described in the preparation of (±)-**7h**. The crude product was purified by medium-pressure liquid chromatography on 400 g of silica gel, eluting with hexane/acetone (2:1). Fractions homogeneous by TLC were combined and concentrated to yield a colorless oil. Conversion into the HCl salt and recrystallization yielded *trans*-(±)-**8j** (0.75 g, 80%) as a white solid: ^{1}H NMR (CD_3OD) δ 7.02 (t, J = 7.9 Hz, 1 H), 6.67 (d, J = 8.0 Hz, 1 H), 6.63 (d, J = 7.6 Hz, 1 H), 6.12–5.50 (m, 3 H), 4.14–1.85 (m, 12 H); IR (mull) ν_{max} 3133, 1605, 1582 cm^{-1}; MS, M$^+$ m/z 229, other ions at m/z 214, 202, 188, 159, 145. Anal. ($C_{15}H_{19}NO$·HCl) C, H, N.

***cis*-(±)-2,3,3a,4,5,9b-Hexahydro-6-methoxy-3-*n*-propyl-1*H*-benz[*e*]indole Hydrochloride (7k).** This compound was prepared from *cis*-(±)-**7j** (0.13 g, 0.5 mmol), using the hydrogenation procedure described in the preparation of (±)-**7f**. Conversion into the HCl salt and recrystallization yielded *cis*-(±)-**7k** (0.095 g, 71%) as a white solid: ^{1}H NMR (CD_3OD) δ 7.01 (t, J = 7.9 Hz, 1 H), 6.71 (d, J = 7.7 Hz, 1 H), 6.63 (d, J = 8.0 Hz, 1 H), 3.94–1.72 (m, 14 H), 1.06 (t, J = 7.4 Hz, 3 H); IR (mull) ν_{max} 3168, 1610, 1588 cm^{-1}; MS, M$^+$ m/z 231, other ions at m/z 202, 173, 115. Anal. ($C_{15}H_{21}NO$·HCl) C, H, N.

***trans*-(±)-2,3,3a,4,5,9b-Hexahydro-6-hydroxy-3-*n*-propyl-1*H*-benz[*e*]indole Hydrochloride (8k).** This compound was prepared from *trans*-(±)-**8g** (0.6 g, 2 mmol), using the procedure described in the preparation of (±)-**7i**. Conversion into the HCl salt and recrystallization yielded *trans*-(±)-**8k** (0.26 g, 49%) as a white solid: ^{1}H NMR (CD_3OD) δ 6.98 (t, J = 7.9 Hz, 1 H), 6.61 (t, J = 9.0 Hz, 1 H), 3.92–1.64 (m, 14 H), 1.02 (t, J = 7.4 Hz, 3 H); IR (mull) ν_{max} 3547, 3473, 1607, 1584 cm^{-1}; MS, M$^+$ m/z 231, other ions at m/z 202, 115. Anal. ($C_{15}H_{21}NO$·HCl) C, H, N.

Resolution of *cis*-(±)-2,3,3a,4,5,9b-Hexahydro-6-methoxy-3-(2-propenyl)-1*H*-benz[*e*]indole (7d) into Its Enantiomers, *cis*-(3a*R*)-(−)-7d and *cis*-(3a*S*)-(+)-7d. A mixture of free base of *cis*-(±)-**7d** (6.1 g, 25 mmol) and (−)-di-*p*-toluoyl-L-tartaric acid monohydrate (10.6 g, 26.3 mmol) (Aldrich, D21,960-6) was

dissolved in hot methanol (200 mL) and concentrated to about 100 mL. The solution was allowed to stand at room temperature for 2–3 days. The crystals were isolated (11.0 g) and ^{1}H NMR showed the enhancement of the vinyl protons at δ 5.36 (d) and 5.28 (d), indicating the enrichment of one diastereomeric salt. The ^{1}H NMR of the mother liquor showed the enhancement of the vinyl protons at δ 5.29 (d) and 5.18 (d), indicating the other diastereomeric salt remained in the solution. Two additional recrystallizations afforded **(−)-7d/di-*p*-toluoyl-L-tartaric acid salt** (5.85 g, 37.2%). ^{1}H NMR analysis indicated that the salt was >95% pure: mp 167–168 °C; ^{1}H NMR ($CDCl_3$ + 5% CD_3OD) δ 7.99 (d, J = 8.2 Hz, 4 H), 7.16 (d, J = 8.0 Hz, 4 H), 7.07 (t, J = 7.9 Hz, 1 H), 6.66 (d, J = 7.7 Hz, 1 H), 6.59 (d, J = 7.7 Hz, 1 H), 6.04–5.89 (m, 1 H), 5.95 (s, 2 H), 5.36 (d, J = 16.2 Hz, 1 H), 5.28 (d, J = 10.5 Hz, 1 H), 3.80 (s, 3 H), 2.37 (s, 6 H), 3.75–1.48 (m, 12 H). This salt was free-based by refluxing in a mixture of 15 mL of 20% sodium hydroxide and 150 mL of methanol overnight. The methanol was removed in vacuo, extracted with ether (2 × 600 mL), washed with brine, dried ($MgSO_4$), filtered, and concentrated to yield a colorless oil (2.1 g) as the free base of (−)-**7d**. A small amount of this oil was converted into the HCl salt and recrystallized to yield (−)-**7d** as a white solid: ^{1}H NMR, IR, and MS were identical to those of (±)-**7d**. Since compound (+)-**7d** (see below) was determined by X-ray crystallography to be the *cis*-(3a*S*)-(+)-enantiomer, compound (−)-**7d** was therefore the *cis*-(3a*R*)-(−)-enantiomer: $[\alpha]^{25}_D$ −43° (*c* 0.99, MeOH). Anal. ($C_{16}H_{21}NO$·HCl) C, H, N.

To purify the other enantiomer, the combined mother liquors were free-based by the same method described above to yield an oil. This oil (3.54 g, 14.5 mmol) was then combined with (+)-di-*p*-toluoyl-D-tartaric acid (5.78 g, 15.2 mmol) (Aldrich 30,281-3) and dissolved in hot methanol (400 mL) and concentrated to 100 mL in volume. After allowing the solution to stand at room temperature for 2–3 days, the crystals were isolated to give the diastereomeric salt. Two additional recrystallizations afforded **(+)-7d/di-*p*-toluoyl-D-tartaric acid salt** (5.95 g, 37.8%): mp 167–168 °C; ^{1}H NMR was identical to that of (+)-**7d**/di-*p*-toluoyl-L-tartaric acid salt. This salt was free-based by the same method as described above to yield a colorless oil (2.1 g) as the free base of (+)-**7d**. A small amount of this oil was converted into the HCl salt and recrystallized to yield (+)-**7d** as a white solid: ^{1}H NMR, IR, and MS were identical to (±)-**7d**. Compound (+)-**7d** was determined by X-ray crystallography (Figure 1) as the *cis*-(3a*S*)-(+)-enantiomer: $[\alpha]^{25}_D$ +43° (*c*, 1.0, MeOH). Anal. ($C_{16}H_{21}NO$·HCl) C, H, N.

Resolution of *cis*-(±)-2,3,3a,4,5,9b-Hexahydro-9-methoxy-3-(2-propenyl)-1*H*-benz[*e*]indole (7b) into Its Enantiomers, *cis*-(3a*R*)-(−)-7b and *cis*-(3a*S*)-(+)-7b. The resolution was carried out in the same manner as the resolution of (±)-**7d** described above. A mixture of the free base of (±)-**7b** (6.1 g, 25 mmol) and di-*p*-toluoyl-L-tartaric acid (10.2 g, 26.3 mmol) was recrystallized twice from 2-propanol (100 mL) to give pure **(+)-7b/di-*p*-toluoyl-L-tartaric acid salt** (2.31 g, 14.9%). This salt was free-based, converted into the HCl salt, and recrystallized to yield (+)-**7b** (0.83 g) as a white solid: ^{1}H NMR was identical to that of (±)-**7b**. Since compound (−)-**7b** (see below) was determined by X-ray crystallography to be the *cis*-(3a*R*)-(−)-enantiomer, compound (+)-**7b** was therefore the *cis*-(3a*S*)-(+)-enantiomer: $[\alpha]^{25}_D$ +52° (*c* 0.64, $CHCl_3$). Anal. ($C_{16}H_{21}NO$·HCl) C, H, N.

To purify the other enantiomer, the combined mother liquor was free-based the same way described above to give an oil. A mixture of this oil (3.78 g, 15.6 mmol) and di-*p*-toluoyl-D-tartaric acid (6.3 g, 16.3 mmol) was recrystallized twice from 2-propanol to give **(−)-7b/di-*p*-toluoyl-D-tartaric acid salt** (2.1 g, 13.3%). This salt was free-based, converted into the HCl salt, and recrystallized to yield (−)-**7b** as a white solid: ^{1}H NMR was identical to that of (±)-**7b**. Compound (−)-**7b** was determined by X-ray crystallography (Figure 2) as the *cis*-(3a*R*)-(−)-enantiomer: $[\alpha]^{25}_D$ −54° (*c* 0.91, $CHCl_3$). Anal. ($C_{16}H_{21}NO$·HCl) C, H, N.

***cis*-(3a*R*)-(−)-2,3,3a,4,5,9b-Hexahydro-6-hydroxy-3-(2-propenyl)-1*H*-benz[*e*]indole (7j).** This compound was prepared from (−)-**7d** (2.24 g, 9.2 mmol), using the demethylation procedure described in the preparation of (±)-**7h**. The crude product was purified by medium-pressure liquid chromatography on 400 g of silica gel, eluting with hexane/acetone (2:1). Fractions homogeneous by TLC were combined and concentrated to yield an oil. Conversion into the HCl salt and recrystallization yielded *cis*-(−)-**7j** (2.0 g, 95%) as a white solid: ^{1}H NMR, IR, and MS were identical to those of (±)-**7j**: $[\alpha]^{25}_D$ −43° (*c* 0.43, MeOH). Anal. ($C_{15}H_{19}NO$·HCl) C, H, N.

***cis*-(3a*S*)-(+)-2,3,3a,4,5,9b-Hexahydro-6-hydroxy-3-(2-propenyl)-1*H*-benz[*e*]indole (7j).** This compound was prepared from (+)-**7d** (2.28 g, 9.4 mmol), using the demethylation procedure described in the preparation of (±)-**7h**. The crude product was purified by medium-pressure liquid chromatography on 400 g of silica gel, eluting with hexane/acetone (2:1). Fractions homogeneous by TLC were combined and concentrated to yield an oil. Conversion into the HCl salt and recrystallization yielded *cis*-(+)-**7j** (2.0 g, 93%) as a white solid: ^{1}H NMR, IR, and MS were identical to those of (±)-**7j**: $[\alpha]^{25}_D$ +41° (*c* 0.46, MeOH). Anal. ($C_{15}H_{19}NO$·HCl) C, H, N.

***cis*-(±)-1,3,3a,4,5,9b-Hexahydro-9-methoxy-3-(2(*R*)-methylbenzyl)-2*H*-benz[*e*]indol-2-one (9).** This compound was prepared from **5b** (15.9 g, 64 mmol) and (*R*)-(+)-α-methylbenzylamine (41.3 mL, 320 mmol), using the reductive amination/cyclization procedure described in the preparation of **6a**. The crude product was purified by flash chromatography on 1 kg of silica gel, eluting with hexane/ethyl acetate (3:1). Fractions homogeneous by TLC were combined and concentrated to give a mixture of lactam **9** (11.2 g, 54%) as an oil: ^{1}H NMR δ 7.43–7.27 (m, 5 H), 7.09 (t, J = 7.9 Hz, 1 H), 6.68–6.62 (m, 2 H), 5.54 (t, J = 7.3 Hz, 1 H), 3.78 (s, 3 H), 3.42–1.52 (m, 8 H), 1.64 (d, J = 7.3 Hz, 3 H). The *cis*- and *trans*-lactams and their diastereomers were not separable by chromatography. The mixture was used in the next step without any further attempt to isolate the diastereomers.

***cis*-2,3,3a*R*,4,5,9b-Hexahydro-9-methoxy-3-(2(*R*)-methylbenzyl)-1*H*-benz[*e*]indole (10a) and *cis*-2,3,3a*S*,4,5,9b-Hexahydro-9-methoxy-3-(2(*R*)-methylbenzyl)-1*H*-benz[*e*]indole (10b).** These compounds were prepared from **9** (11.2 g, 34.8 mmol), using the reduction procedure described in the preparation of **6a** and **7a**. The crude product was chromatographed on 1 kg of silica gel, eluting with hexane/ethyl acetate (4:1). The diastereomers were separated and collected in three portions (less polar diastereomer A, mixture A + B, and more polar diastereomer B). The mixed fractions were purified again on 1 kg of silica gel, eluting with hexane/ethyl acetate (12:1). The homogeneous fractions were combined to yield pure diastereomers A and B. The less polar product (diastereomer A; 2.1 g, 19.6%) was assigned as the *cis*-(3a*S*,*R*)-isomer **10b** whereas the more polar product (diastereomer B, 4.4 g, 41.1%) was assigned as the *cis*-(3a*R*,*R*)-isomer **10a**. The assignment was confirmed later by converting these compounds into *n*-propyl analogs *cis*-(3a*R*)-(−)-**7c** and *cis*-(3a*S*)-(+)-**7c**. The optical rotations of these analogs were then compared with the hydrogenation products of the resolved allyl analogs *cis*-(3a*R*)-(−)-**7b** and *cis*-(3a*S*)-(+)-**7b**.

A small amount of diastereomer A was converted into the HCl salt and recrystallized from ethyl acetate/methanol to yield **10b** as a white solid: ^{1}H NMR (as a free base) δ 7.38–7.19 (m, 5 H), 7.04 (t, J = 7.9 Hz, 1 H), 6.67 (t, J = 7.6 Hz, 2 H), 3.82 (q, J = 6.7 Hz, 1 H), 3.78 (s, 3 H), 3.35 (q, J = 8.3 Hz, 1 H), 2.99–1.62 (m, 8 H), 1.44 (d, J = 6.7 Hz, 3 H); IR (mull) ν_{max} 1599, 1474, 1281 cm^{-1}; MS, M$^+$ m/z 307, other ions at m/z 292, 230, 202, 187, 173, 105; $[\alpha]^{25}_D$ +46° (*c* 1.21, MeOH). Anal. ($C_{21}H_{25}NO$·HCl) C, H, N.

A small amount of diastereomer B was converted into the HCl salt and recrystallized from ethyl acetate/methanol to yield **10a** as a white solid: ^{1}H NMR (as a free base) δ 7.41–7.22 (m, 5 H), 7.08 (t, J = 7.9 Hz, 1 H), 6.67 (dd, J = 8.1 and 2.3 Hz, 2 H), 3.79 (s, 3 H), 3.35 (q, J = 8.0 Hz, 1 H), 3.19 (q, J = 7.5 Hz, 1 H), 2.82–1.40 (m, 8 H), 1.42 (d, J = 6.6 Hz, 3 H); IR (mull) ν_{max} 1599, 1466, 1251 cm^{-1}; MS, M$^+$ m/z 307, other ions at m/z 292, 230, 202, 187, 173, 105; $[\alpha]^{25}_D$ +9.31° (*c* 1.02, MeOH). Anal. ($C_{21}H_{25}NO$·HCl) C, H, N.

***cis*-(3a*R*)-(−)-2,3,3a,4,5,9b-Hexahydro-9-methoxy-3-*n*-propyl-1*H*-benz[*e*]indole Hydrochloride (7c).**[15] A solution of **10a** (4.98 g, 16.2 mmol) and 1-chloroethyl chloroformate (16 mL, 148 mmol) in chlorobenzene (100 mL) was refluxed (bath temperature, 140 °C) for 2 days. The mixture was concentrated in vacuo to half of its original volume. Methanol (80 mL) was added and refluxed (bath temperature, 80 °C) for 1 h. The solvent was removed in vacuo to yield a brown oil. This oil was dissolved in

methylene chloride (80 mL) and treated with triethylamine (13.5 mL, 97.2 mmol) followed by propionyl chloride (2.8 mL, 32.4 mmol) at room temperature. After stirring for 2 h, methanol (2 mL) was added and the mixture stirred for additional 1 h. The reaction was quenched with 10% sodium hydroxide and extracted with methylene chloride (2 × 600 mL). The combined organic layers were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to give a brown oil. This oil was purified by medium-pressure liquid chromatography on 400 g of silica gel, eluting with hexane/acetone (2:1). Fractions homogeneous by TLC were combined and concentrated to yield propionamide (3.4 g) as a light brown oil.

A suspension of lithium aluminum hydride (0.95 g, 25 mmol) in THF (100 mL) was cooled to −20 °C and treated with aluminum chloride (3.3 g, 25 mmol) via a powder funnel over 5 min.[16] The mixture was stirred for 10 min and a solution of propionamide in THF (25 mL) was added slowly over 30 min. The mixture was allowed to warm to room temperature over 1 h, quenched with 10% sodium hydroxide, diluted with water (500 mL), and extracted with methylene chloride (2 × 1 L). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to yield an oil. This oil was purified by medium-pressure liquid chromatography on 400 g of silica gel, eluting with hexane/acetone (2:1). Fractions homogeneous by TLC were combined and concentrated to yield the free base of (−)-**7c** (2.42 g, 79%). A small amount of this oil was converted into the HCl salt and recrystallized to yield (−)-**7c** as a white solid: ^{1}H NMR, IR, and MS were identical to those of (±)-**7c**. Compouund (−)-**7c** was determined as the *cis*-(3a*R*)-(−)-enantiomer: $[\alpha]^{25}_D$ −37.3° (*c* 0.55, $CHCl_3$) (see experiment below).

Compound (−)-**7c** was also prepared from *cis*-(3a*R*)-(−)-**7d** (0.2 g, 0.7 mmol), using the hydrogenation procedure described in the preparation of (±)-**7f**. The crude product was converted into the HCl salt and recrystallized to yield (−)-**7c** (0.11 g, 55%) as a white solid: ^{1}H NMR, IR, and MS were identical to those of (±)-**7c**. The optical rotations of *cis*-(3a*R*)-(−)-**7c** showed $[\alpha]^{25}_D$ −81° (*c* 0.39, MeOH) and −38.4° (*c* 1.14, $CHCl_3$). Anal. ($C_{16}H_{23}NO$·HCl) C, H, N.

***cis*-(3a*S*)-(+)-2,3,3a,4,5,9b-Hexahydro-9-methoxy-3-*n*-propyl-1*H*-benz[*e*]indole Hydrochloride (7c).** This compound was prepared from **10b** (3.38 g, 11 mmol), using the same procedure described in the preparation of (−)-**7c**. The crude product was purified by medium-pressure liquid chromatography on 400 g of silica gel, eluting with hexane/acetone (2:1). Fractions homogeneous by TLC were combined and concentrated to yield the free base of (+)-**7c** (2.46 g, 86%) as an oil. A small amount of this oil was converted into the HCl salt and recrystallized to yield (+)-**7c** as a white solid: $[\alpha]^{25}_D$ +36.5° (*c* 0.57, $CHCl_3$).

This compound was also prepared from *cis*-(3a*S*)-(+)-**7b** (0.2 g, 0.7 mmol) and 10% Pd/C (0.2 g), using the hydrogenation procedure described in the preparation of **8a**. The crude product was converted into the HCl salt and recrystallized to yield (+)-**7c** (0.11 g, 55%) as a white solid: ^{1}H NMR, IR, and MS were identical to those of (±)-**7c**. The optical rotations of *cis*-(3a*S*)-(+)-**7c** showed $[\alpha]^{25}_D$ +78° (*c* 0.42, MeOH) and +37° (*c* 0.9, $CHCl_3$). Anal. ($C_{16}H_{23}NO$·HCl) C, H, N.

***cis*-(3a*R*)-(−)-2,3,3a,4,5,9b-Hexahydro-9-hydroxy-3-*n*-propyl-1*H*-benz[*e*]indole Hydrochloride (7i).** This compound was prepared from (−)-**7c** (2.3 g, 9.4 mmol), using the demethylation procedure described in the preparation of (±)-**7h**. The crude product was purified by medium-pressure liquid chromatography on 400 g of silica gel, eluting with methylene chloride/acetone (1:1). Fractions homogeneous by TLC were combined and concentrated to yield the free base of (−)-**7i** (2.13 g, 98%) as a yellow oil. Conversion into the HCl salt and recrystallization yielded (−)-**7i** as a white solid: ^{1}H NMR, IR, and MS were identical to those of (±)-**7i**; $[\alpha]^{25}_D$ −58.7° (*c* 0.61, $CHCl_3$). Anal. ($C_{15}H_{21}NO$·HCl) C, H, N.

***cis*-(3a*S*)-(+)-2,3,3a,4,5,9b-Hexahydro-9-hydroxy-3-*n*-propyl-1*H*-benz[*e*]indole Hydrochloride (7i).** This compound was prepared from (+)-**7c** (3.06 g, 12.5 mmol), using the demethylation procedure as described in the preparation of (±)-**7h**. The crude product was purified by medium-pressure liquid chromatography on 400 g of silica gel, eluting with methylene chloride/acetone (1:1). Fractions homogeneous by TLC were combined and concentrated to yield the free base of (+)-**7i** (2.83 g, 98%) as a yellow oil. Conversion into the HCl salt and recrystallization yielded (+)-**7i** as a white solid: ^{1}H NMR, IR, and MS were identical to those of (±)-**7i**; $[\alpha]^{25}_D$ −58° (*c* 0.52, $CHCl_3$). Anal. ($C_{15}H_{21}NO$·HCl) C, H, N.

(2α,3aα,9bα)-(±)-2,3,3a,4,5,9b-Hexahydro-9-methoxy-2-methyl-3-*n*-propyl-1*H*-benz[*e*]indole Hydrochloride (12a) and (2β,3aα,9bα)-(±)-2,3,3a,4,5,9b-Hexahydro-9-methoxy-2-methyl-3-*n*-propyl-1*H*-benz[*e*]indole Hydrochloride (12b).[17] A mixture of **11** (5.2 g, 20 mmol) and mercuric acetate (19 g, 60 mmol) in methanol (1 L) was stirred at room temperature for 3 days. The greenish gray mixture was then treated with a solution containing sodium borohydride (3.0 g, 80 mmol) in 20% sodium hydroxide (80 mL). After stirring of the mixture vigorously for 3 h, methanol was removed in vacuo and the concentrate was extracted with methylene chloride (2 × 1 L). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting oil was purified by medium-pressure liquid chromatography on 800 g of silica gel, eluting with hexane/acetone (9:1). The fractions homogeneous by TLC were combined and concentrated.

The less polar product was obtained as an oil (2.48 g, 48%). This oil was converted into the HCl salt and recrystallized to yield (±)-**12a** as a white solid: ^{1}H NMR δ 7.16 (t, *J* = 7.9 Hz, 1 H), 6.73 (t, *J* = 8.6 Hz, 2 H), 3.83 (s, 3 H), 3.78–1.72 (m, 13 H), 1.74 (d, *J* = 6.5 Hz, 3 H), 1.04 (t, *J* = 7.3 Hz, 3 H); IR (mull) ν_{max} 1603, 1586 cm^{-1}; MS, M$^+$ *m/z* 259, other ions at *m/z* 244, 230, 159, 115. Anal. ($C_{17}H_{25}NO$·HCl) C, H, N.

The more polar product was obtained as an oil (0.48 g, 9%). This oil was converted into the HCl salt and recrystallized to yield (±)-**12b** as a white solid: ^{1}H NMR δ 7.13 (t, *J* = 7.9 Hz, 1 H), 6.69 (d, *J* = 7.9 Hz, 2 H), 3.79 (s, 3 H), 4.23–1.54 (m, 13 H), 1.70 (d, *J* = 6.8 Hz, 3 H), 1.03 (t, *J* = 7.4 Hz, 3 H); IR (mull) ν_{max} 1609, 1587 cm^{-1}; MS, M$^+$ *m/z* 259, other ions at *m/z* 244, 230, 159, 115. Anal. ($C_{17}H_{25}NO$·HCl) C, H, N.

X-ray crystallography on compound (±)-**12a** (see Figure 3) confirmed the correct assignment for the configuration of the C-2 methyl group on the pyrrolidine ring in both isomers.

X-ray Crystallography of (+)-7d, (−)-7b, and (±)-12a. Graphite-monochromatized Cu Kα radiation was used, (λ(Cu Kα) = 1.5418 Å), with $2\theta_{max}$ = 134° for (+)-**7d** and (−)-**7b** and 137° for (±)-**12a**. $\theta/2\theta$ scans were used with scan widths ≥ 3.2° [≥3.4° for (−)-**7b**] and scan rates of 2°/min. The total time spent counting background, half at each end of the scan, was equal to the time spent scanning. Ten reflections periodically monitored showed no trend toward deterioration; $\sigma^2(I)$ was approximated by $\sigma^2(I)$ from counting statistics +(d*I*)^2, where the coefficient of *I* was calculated from the variations in intensities of the monitored reflections, and was 0.077 for (+)-**7d** and 0.028 for (±)-**12a**. For (−)-**7b**, d was set at 0.03. The monitored reflections in the data for (±)-**12a** showed a step function with lower intensities in the middle part of the data collection; this was corrected by scaling with a time-dependent polynomial function with six terms. Cell parameters were determined by least squares fit of $K\alpha_1$ 2θ values ($\lambda_{K\alpha 1}$ = 1.5402) for 25 high 2θ reflections.[21] An *Lp* correction appropriate for a monochromator with 50% perfect character was applied, and the data were corrected for absorption.[22]

The structures were solved by direct methods, using DIREC[23] for (−)-**7b** and (±)-**12a** and MULTAN80[24] for (+)-**7d**. Hydrogens in all three structures were found in difference maps close to generated positions; generated positions were used except for the methoxy hydrogens in the unprimed molecule in (+)-**7d**, which was rotated +11° to match found hydrogen positions. Least-squares refinement included coordinates and anisotropic thermal parameters for nonhydrogen atoms; hydrogen coordinates were also included in the (−)-**7b** refinement. The function minimized in the refinement was $\sum w(F_o^2 - F_c^{*2})^2$, where weights *w* were $1/\sigma^2(F_o^2)$ and, for (−)-**7b** and (±)-**12a**, F_c^{*2} was as defined by Larson.[25] [In the (+)-**7d** refinement, F_c was not corrected for secondary extinction.] In the final refinements of (+)-**7d** and (−)-**7b**, anomalous dispersion factors[26] were included; shifts in the final cycles of all refinements were ≤0.3σ. The absolute configuration of (+)-**7d** and of (−)-**7b** were determined by the method of Bijvoet;[27] accurate measurements of reflections which were very strongly influenced by anomalous dispersion were compared, each one being measured at all accessible symmetry-related positions [for (+)-**7d**, 15 reflections, 30 Friedel pairs were measured; for (−)-**7b**, 12 reflections, 21 Friedel pairs were measured.] In each case there was unamimous agreement among

the measured pairs, the comparisons indicated unequivocally that (+)-**7d** has the cis-(3a*S*) configuration, and (−)-**7b** has the cis-(3a*R*) configuration. Atomic form factors were from Doyle and Turner[28] and, for hydrogen, from Stewart, Davidson, and Simpson.[29] The CRYM system of computer programs was used.[22]

The atomic coordinates and thermal parameters are deposited at the Cambridge Crystallographic Data Centre. In addition, these tables and tables of bond lengths and angles, torsion angles, and close intermolecular contacts are available as supplementary material.

Crystal data specific for (+)-7d: $2(C_{16}H_{21}NO{\cdot}HCl)$; formula wt = 2(243.3 + 36.5); monoclinic; space group *C*2; $Z = 8$, a = 31.244 (4) Å, b = 13.652 (2) Å, c = 7.025 (1) Å, β = 103.15 (1)°; V = 2917.9 (6) Å^3; calculated density = 1.27 g cm^{-3}; absorption coefficient μ = 2.1 mm^{-1}. Intensity data were collected at low temperature, −120 °C, on a thin clear plate, 0.01 × 0.12 × 0.20 mm, mounted on a glass fiber on a Siemens $P2_1$ diffractometer. The final agreement index R was 0.104 for all 2196 reflections and 0.075 for the 1339 reflections having $F_o^2 \geq 3\sigma$. The standard deviation of fit was 1.5. The symmetry independent molecules are approximately related by $x' \sim x$; $y' \sim y + {}^1/_2$; $z' \sim z - {}^1/_2$. The amine nitrogens are protonated and are hydrogen bonded with the chlorines; the N to Cl distances are 3.106 (8) and 3.069 (8) Å.

Crystal data specific for (−)-7b: $C_{16}H_{21}NO{\cdot}HCl$; formula wt = 243.3 + 36.5; monoclinic; space group $P2_1$; $Z = 2$; a = 6.987 (1) Å, b = 9.274 (2) Å, c = 11.707 (1) Å, β = 103.12 (1)°; V = 738.8 (2) Å^3; calculated density = 1.26 g cm^{-3}; absorption coefficient μ = 2.1 mm^{-1}. Intensity data were collected at low temperature, −120 °C, on a clear thick plate, 0.05 × 0.15 × 0.42 mm, mounted on a glass fiber on a Siemens $P2_1$ diffractometer. The final agreement index R was 0.039 for all 1388 reflections and 0.038 for the 1362 reflections having $F_o^2 \geq 3\sigma$. The standard deviation of the fit was 3.1. The amine nitrogen is protonated and makes a hydrogen bond with the chlorine; the N to Cl distance is 3.039 (2) Å.

Crystal data specific for (±)-12a: $C_{17}H_{25}NO{\cdot}HCl$; formula wt = 259.3 + 36.5; monoclinic; space group $P2_1/c$; $Z = 4$; a = 11.351(2), b = 10.946(2), and c = 13.464(4) Å, β = 96.40(4)°; V = 1662(1) Å^3; calculated density = 1.18 g cm^{-3}, absorption coefficient m = 1.9 mm^{-1}. Intensity data were collected at room temperature on a clear prism of 0.01 × 0.14 × 0.15 mm mounted on a glass fiber on a Siemens $P\bar{1}$ diffractometer. The final agreement index R was 0.077 for all 2113 reflections, and 0.043 for the 1210 reflections having $F_o^2 \geq 3\sigma$. The standard deviation of fit was 1.4. The amine nitrogen is protonated and is hydrogen bonded with the chlorine; the N to Cl distance is 3.123(2) Å.

Serotonin and Dopamine Binding Assays. 5-HT_{1A} receptor bindings were measured by using [^{3}H]-8-OH-DPAT (sp act. 85 Ci/mmol, NEN) labeled 5-HT_{1A} site in homogenates of bovine hippocampus prepared with a Polytron and diluted 1:400.[30] Samples were incubated for 1 h at room temperature and then filtered over SS no. 24 filters (pretreated with 0.05% PEI) and rinsed three times with 0.5 mL of 50 mM TRIS pH 7.4 buffer. Nonspecific binding was determined using serotonin (1 μM). IC_{50} and K_i values were calculated by log-probit analysis, using at least four concentrations of the drug, in triplicate. D_2 dopamine receptor bindings were measured by using either [^{3}H]raclopride (sp act. 80 Ci/mmol, NEN) labeled D_2 site in homogenates of rat striata prepared with a Polytron and diluted 1:300.[31] Samples were incubated for 1 h at room temperature and then filtered over SS no. 24 filters (pretreated with 0.05% PEI) and rinsed three times with 0.5 mL of 50 mM TRIS pH 7.4 buffer. Filters were counted using standard liquid scintillation techniques. Nonspecific binding was determined using haloperidol (1 μM). IC_{50} and K_i values were calculated by log-probit analysis, using at least four concentrations of the drug, in triplicate. The bindings using CHO cells were measured by competition binding experiments employing eleven dilutions of test sample with [^{3}H]-8-OH-DPAT (85 Ci/mmol, 1.2 nM) or [^{3}H]-U86170[32] (62 Ci/mmol, 2 nM) for 5-HT_{1A} and D_2 binding sites, respectively. In each case cloned mammalian receptors expressed in CHO-K1 cells were used.[33] IC values were estimated by fitting the data to a one-site model by nonlinear least squares minimization. K_i values were calculated with the Cheng–Prushoff equation.[34]

Hypothermia Assay. Charles River CF-1 mice (18–22 g, 4 per dose) were individually housed in clear plastic cages with sawdust bedding and perforated metal tops for 20 min prior to testing. After control rectal temperatures were measured, test compounds were given sc in 0.1-mL volume; 20 min later, rectal temperatures were again measured. A decrease of 2 or more °F was considered to be a positive hypothermic response. Drug doses started at 30 mg/kg and were decreased by half-log value until 0 out of 4 mice showed a positive hypothermic response. ED_{50}'s and 95% confidence intervals were determined by Spearman–Karber's method.[35] Oral dosing was similar to sc dosing, except a rounded oral 18-ga hypodermic needle was used and the volume given was 0.2 mL. Regardless of the route of administration, the mean maximum temperature drop 20 min following any dose was noted as an index of drug efficacy and indirect estimate of intrinsic activity.

Dopamine Intrinsic Activity Measurements. Intrinsic activity was determined using membranes from CHO cells stably transfected with the dopamine D_2 receptor as previously described by Lahti et al.[18] Briefly, this method uses the ratio of the affinity of a compound for the low- and high-affinity states of the receptor to determine the intrinsic activity. The affinity for the low-affinity agonist state is determined using [^{3}H]raclopride + GTP and the affinity for the high affinity state is determined using the dopamine agonist ligand [^{3}H]U-86170.[32]

Amine Synthesis and Metabolism. Brain levels of DOPA and 5-HTP in the rat were determined as described previously.[36] Briefly, male Sprague–Dawley rats were injected sc with test drug or vehicle at time zero. Fifteen minutes later the rats received an aromatic decarboxylase inhibitor (NSD 1015 at 100 mg/kg ip). The rats were sacrificed 30 min later, and the tissues in the ventral limbic brain area were removed and frozen for later analysis. Tissues were weighed and extracted in 0.1 N perchloric acid containing an internal standard of dihydroxybenzylamine (2 μg/mL). The extract was then analyzed by HPLC using a Bioanalytical Systems ODS column. DOPA and 5-HTP were detected electrochemically and quantified by peak integration using Waters Maxima(R) software. Biochemical differences were compared between a control (N = 6) and a test group (N = 6) by unpaired t-test.

Recordings from Dopaminergic and Serotonergic Neurons. Charles River male Sprague–Dawley rats (280–330 g) were anesthetized with chloral hydrate (400 mg/kg ip). Supplemental doses were administered as needed to maintain anesthesia. The femoral artery and vein were cannulated for blood pressure and drug administration. The animal's head was held in a stereotaxic device and a small burr hole drilled at the appropriate location. Extracellular action potentials were recorded with a glass microelectrode (tip size <1 μm) filled with pontamine sky blue dye in 2 M sodium chloride. Dopaminergic neurones were identified by their long duration action potential (>2.5 ms), shape and firing pattern (>12 spikes/s) as previously described.[37] The recording electrode was hydraulically lowered into the substantia nigra pars compacta area (P 5.0–6.0 mm, L 2.0–2.2 mm, V 7.0–8.0 mm) according to the coordinates of Paxinos and Watson.[38] Serotonergic neurons were identified by their large, biphasic positive-negative action potentials with slow and regular firing rates (approximately 0.8–2.5 spikes/s) as previously described.[39] The recording electrode was hydraulically advanced to reach the dorsal raphe nucleus (A 0.5–1.7 mm, L 0 mm, V 3.5–4.2 mm) according to the coordinates of Paxinos and Watson.[36] At the termination of each recording session, the location of the cell was identified by passing a 10-μA cathodic current for 10–20 min. The brain was then removed, sectioned, and stained, and the pontamine sky blue deposit verified in each animal. Only those cells found to be in the appropriate area were included in the study. All drug solutions were made in distilled water. Each drug injection contained no more than 0.15 mL of a given concentration, followed by 0.2–0.4 mL of physiological saline to clean the catheter of any residual drug. Drug effects were measured as changes in firing rates as indicated by an integrated ratemeter output throughout the experiment. The dose required to depress neuronal firing by 50% was taken as the ED_{50}, measured by interpolation of the dose–response curve for each individual cell.

Face to Face Test for Anxiolytics (a Social Interaction Test in Mice). When two mice are placed together from separate cages into a small chamber, they investigate each other as well as the environment. The prior administration of anxiolytic drugs

increases the amount of social interaction, including the amount of face to face interaction. This test is a simplified version of Sandra File's social interaction test in rats.[40] Male CF-1 mice (Charles River, 19–29 g, 8 pairs/dose) were injected subcutaneously (sc) or orally (po). Compounds were dissolved or suspended in 0.25% methylcellulose or 0.1% citric acid. During the 30-min absorption time, mice were housed 2/cage with a familiar partner (i.e., a mouse from the same home cage). Pairs of mice from different home cages were then placed together into a small plastic cage (7 in. × 5½ in.) with a cardboard lid and with fresh wood litter on the floor. Duration of face to face interaction was measured visually for 3 min. Groups were compared by Wilcoxon's rank sum (two-tailed). A significant increase ($p < 0.05$) above the daily control value was interpreted as an anxiolytic effect.

Isolation-Induced Aggregation Test for Anxiolytic Activity in Mice. Aggressiveness in adult male mice increases following a period of social isolation. Anxiolytic compounds and sedatives suppress the aggressiveness (i.e., increase the latency to fighting). Male CF-1 mice (20–22 g) were obtained from Charles River or Harlan, and separated into two groups. Isolated "resident" mice were housed singly for at least 1 month. Group-housed "intruder" mice were housed 4–6/cage. Food and water were available ad libitum. Mice weighed 28–30 g at the time of the first tests. Compounds were dissolved or suspended in 0.25% methylcellulose or 0.1% citric acid. Drugs were tested blindly, with 6 mice/treatment group ($n = 12$ for vehicle). Each isolated "resident" mouse was injected intraperitoneally (ip) or orally with drug 30 min before introduction of an untreated, group-housed "intruder" mouse into the resident's home cage. The number of seconds until fighting began was recorded, and the intruder was removed as soon as fighting began. The isolated resident mice were allowed a minimum of 3 days recovery before reuse. Groups were compared statistically by Wilcoxon's rank sum. Mice which failed to fight within 10 min were arbitrarily assigned 600 s.

Locomotor Activity. (1) Reserpinized Mice. (A) Stimulation. Harlan male NSA (CF-1) mice, 13–19 g, were injected with 5 mg/kg reserpine subcutaneously (sc) 18–24 h before testing and with 300 mg/kg DL-α-methyl-*p*-tyrosine intraperitoneally (ip) 1–5 h before testing. Test drug was given ip 15 min before mice were placed singly into 8-in. × 8-in. cages (Omnitech Digiscan Monitors). Locomotor activity was recorded for 10 min, as horizontal activity counts. Control mice (given reserpine and DL-α-methyl-*p*-tyrosine) were nearly motionless. Groups were compared by Student's *t*-test, or by least significant difference, and each point represented six mice. **(B) Antagonism of Apomorphine.** Immediately afterward, all mice were injected with 1 mg/kg apomorphine HCl sc and were returned to the cages to record locomotor activity for 10 min, as percent of control counts (for apomorphine alone, which stimulated activity in these reserpinized mice).

(2) Antagonism of Amphetamine. Drug-naive Harlan male B6C3F1 mice, 23–27 g, were placed singly into 8-in. × 8-in. cages (Omnitech Digiscan Monitors) for 20 min to partially habituate them to the cages. Then the mice were given *d*-amphetamine sulfate 3 mg/kg sc plus test drug ip. Locomotor activity (horizontal activity) was recorded for two 10-min intervals, as percent of control (for amphetamine alone, which stimulated activity in mice). Data were analyzed by Student's *t*-test, or by least significant difference, and each point represented six mice.

Sympathetic Nerve Activity. Adult cats (2.5–4.0 kg) were anesthetized by intramuscular injection of ketamine (11 mg/kg), followed by intravenous injection of chloralose (80 mg/kg). This dose of anesthetic was sufficient to maintain an appropriate level of anesthesia for the duration of the experiments. Each animal was placed in a stereotaxic apparatus, and a femoral artery and vein were cannulated for recording blood pressure and for peripheral drug administration, respectively. Heart rate was recorded continuously with a Grass 7P4 tachograph triggered by the electrocardiogram. A glass tracheal cannula was inserted, and, following surgery, the animals were artificially ventilated and paralyzed with gallamine (4 mg/kg iv). Rectal temperature was maintained between 37 and 38 °C using a heating pad.

Sympathetic nerve discharge (SND) was recorded from the central end of the sectioned left inferior cardiac nerve. The nerve was located distal to its exit from the stellate ganglion and was isolated outside the pleural cavity after removal of the vertebral portion of the first rib. Nerve activity was recorded under mineral oil using a bipolar platinum electrode with capacity coupled preamplification at low and high frequency half-amplitude responses of 1 and 500 Hz, respectively. Sympathetic activity was quantitated using cumulative integration. Cumulative intravenous doses of a compound were tested at 20-min intervals.

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Supplementary Material Available: A table of C, H, N analyses and high resolution mass spectrum results as well as tables of fractional coordinates, bond lengths and angles, close intermolecular contacts, hydrogen bonds, and anisotropic thermal parameters (17 pages). Ordering information is given on any current masthead page.

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