Structure–Activity Relationships in the 8-Amino-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole Ring System. 2. Effect of 8-Amino Nitrogen Substitution on Serotonin Receptor Binding and Pharmacology

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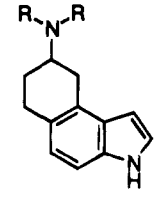
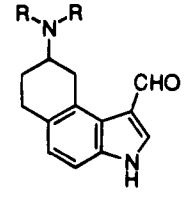
A series of analogs of the potent and selective 5-HT_{1A} agonist 8-(di-*n*-propylamino)-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole-1-carbaldehyde (**2b**) (OSU191) was prepared in which the dipropylamino group was modified to bear a variety of substituents. These compounds were evaluated for both *in vitro* and *in vivo* effects, including the establishment of a receptor binding profile for these analogs at the 5-HT_{1A}, dopamine D-2, dopamine D-3, 5-$HT_{1D\alpha}$, and 5-$HT_{1D\beta}$ sites. Several of the analogs were evaluated for their biochemical effects in reserpinized rats, specifically with regard to *in vivo* changes in brain levels of 5-HTP and DOPA. Nearly all of the compounds prepared for this study were exceedingly potent at the 5-HT_{1A} receptor, although most also displayed significant affinity for the dopamine D-2 receptor. A strong preference for the 5-$HT_{1D\alpha}$ over the 5-$HT_{1D\beta}$ receptor was also apparent. An analog bearing a butylglutarimide side chain, *S*-**7k**, was extremely selective for the 5-HT_{1A} receptor. Although this compound possessed a K_i of 0.6 nM, it elicited only modest changes in 5-HTP brain levels. However, this compound did not appear as an antagonist when tested in a cyclic-AMP-based intrinsic activity assay.

Introduction

The search for orally available, selective serotonin-1A (5-HT_{1A}) agonists is fueled by their therapeutic potential as antidepressive and anxiolytic agents.[1,2] Although hydroxylated 2-aminotetralins have proven remarkable in their selectivity and potency at both serotonin and dopamine receptors,[3,4] the poor pharmacokinetics of this structural class has led to the development of related, more complex molecules. The 3*H*-benz[*e*]indol-8-amino ring system was first described by Asselin et al. in 1986.[5] These authors prepared the methyl and propyl analogs **1a**,**b** in order to test the hypothesis that a pyrrolo moiety could replace a phenolic hydroxyl as an essential pharmacophore for dopamine agonists. These compounds did in fact possess potent dopaminergic properties. However, Wikström et al. later showed that **1a** possessed both dopaminergic and serotonergic activities.[6] Recently, Stjernlöf et al. have demonstrated that introduction of a formyl group at the indole C-1 position (as in **2b**, OSU191) greatly attenuates the dopamine properties of this structural class and leads to selective and potent serotonergic agents.[7] We have already reported an efficient asymmetric synthesis of OSU191 (**2b**), the prototypical member of this family of compounds.[8] In the preceding paper, we described a series of analogs in which the formyl moiety was systematically replaced by other functionalities.[9] In this work, we will describe variations at the amino substituent and their effects on the *in vitro* receptor binding and the *in vivo* pharmacology of this interesting class of potent serotonin/dopamine agents.



1a (R=CH_3)
b (R=*n*-Pr)



2a (R=CH_3)
b (R=*n*-Pr) **OSU191**

The analogs prepared for this study fall into three main structural types, illustrated generically by compounds **6**, **9**, and **16**. Each of these are representatives of the 6,7,8,9-tetrahydro-3*H*-benz[*e*]indole tricyclic skeleton and differ only in the nature of the position 8 substituent. Both **6** and **9** represent structures containing an 8-amino functionality in which the nitrogen substituents are either separate (**6**) or joined together in a ring (**9**). Compounds related to the generic structure **16** have an amino group attached to the tetrahydrobenzindole framework through a methylene spacer. These analogs were motivated from a consideration of the potent serotonergic activity of the related indolodioxans such as **12**.[10] For each of these three structural types also exists a corresponding analog which bears a formyl group at the indole C-1 position. These formylated compounds are generically represented by structures **7**, **10**, and **17**. The compounds prepared for this study were evaluated for their ability to bind to a variety of central nervous system receptors. Highlighted in this work will be the 5-HT_{1A}, dopamine D-2, dopamine D-3,

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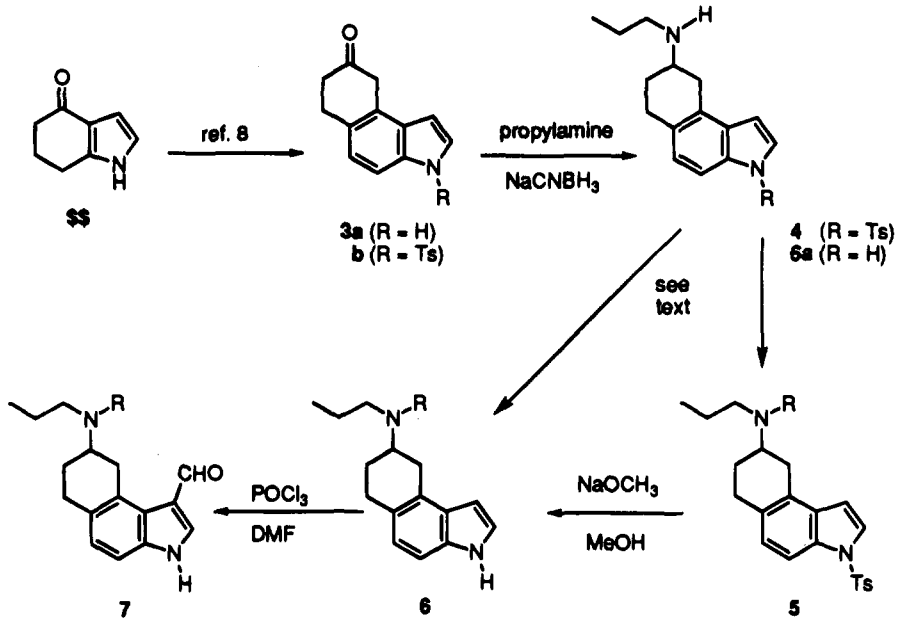
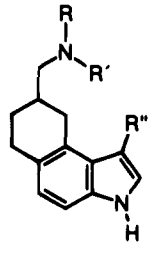
Scheme 1



5-$HT_{1D\alpha}$, and 5-$HT_{1D\beta}$ receptors. Further characterization of these compounds will include an *in vivo* biochemical assay. Measurements of 5-HTP and DOPA accumulation in differing brain regions will be used to assess the degree of serotonin and/or dopamine agonism.



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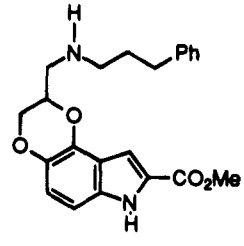

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Chemistry

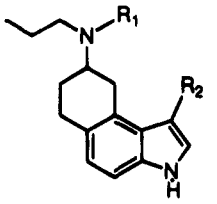
The majority of the analogs prepared for this study were synthesized by the route shown in Scheme 1. We have already described the transformation of commercially available 4-oxo-4,5,6,7-tetrahydroindole into either enantiomer of the advanced intermediate **4** via a ring annulation, aromatization, and reductive amination sequence.[8] Detosylation was performed either at this stage (yielding **6a**) or following N-substitution. Alkylation of **4** (or **6a**) with alkyl halides in refluxing acetonitrile in the presence of sodium carbonate afforded the tertiary amines **5** (or **6**). Alternatively, **4** (or **6a**) could be acylated with an acid chloride (for **6i**, the corresponding carboxylic acid was used and coupled with dicyclohexylcarbodiimide) and the resulting amides reduced to **5** (or **6**) using lithium aluminum hydride (for *R*-(+)-**6d**, alane was used for this reduction). For the preparation of the *N*-methyl derivative **6b**, a reductive amination procedure using formaldehyde and sodium triacetoxyborohydride was applied to **6a**. Treatment of **5** with methanolic sodium methoxide resulting in removal of the *N*-tosyl group to give the deprotected indoles **6**. Vilsmeier–Haack reactions on **6** then provided the formylated products **7**. Listed in Table 1 are the compounds prepared for this study by this synthetic sequence.

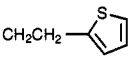
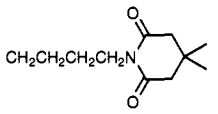
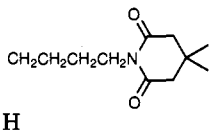
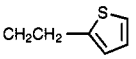
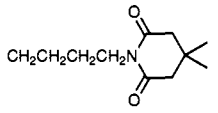
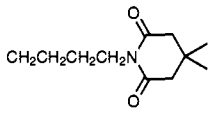
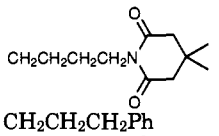
A few compounds in which the C-8 amino substituents were joined together to form a ring were prepared as illustrated in Scheme 2. Reductive amination of **3b** with either pyrrolidine or homopiperidine afforded the tertiary amines **8**. As before, tosyl removal provided the indoles **9**, and subsequent Vilsmeier–Haack reaction gave the formylated derivatives **10**. The compounds prepared by this route are listed in Table 2. Finally, a small number of analogs were prepared in which the amino substituent was separated from the tricyclic framework by a single methylene spacer. These compounds are structurally related to the potent serotonergic agent **12**[10] and are represented generically by **11**. These compounds were prepared as depicted in Scheme 3. Treatment of **3b** with diethyl cyanophosphonate gave predominately the phosphorylated cyanohydrin **13** accompanied by a small amount of the corresponding enol phosphonate.[11] This mixture (ca. 83:17) was reduced using *in situ* generated samarium diiodide to give the nitrile **14** in 69% overall yield from **3b**. Reduction of **14** with diisobutyl aluminum hydride afforded the aldehyde **15**, from which the analogs **16a,b** were obtained through standard reductive amination chemistry. Finally, compound **17** was prepared from **16b** by a Vilsmeier–Haack formylation. The homologated compounds prepared by this sequence are listed in Table 3.

Biological Results and Discussion

The *in vivo* biochemical test, as illustrated in Table 5, utilizes the well-established phenomenon of receptor-mediated feedback inhibition of the presynaptic neuron.[12] Dopamine (DA) and norepinephrine (NE) have the same general biosynthetic pathway, and the synthesis rate of the catecholamines DA and NE is decreased by agonists (and increased by antagonists) at the dopaminergic and α-adrenergic receptors, respectively. Similarly, the synthesis rate of 5-HT is inhibited by 5-HT receptor agonists.[4,13,14] The 5-HTP accumulation, following decarboxylase inhibition by means of (3-hydroxybenzyl)hydrazine (NSD1015), was used as an

Table 1. 8-Amino-3*H*-benz[e]indoles **6** (R_2 = H) and **7** (R_2 = CHO)



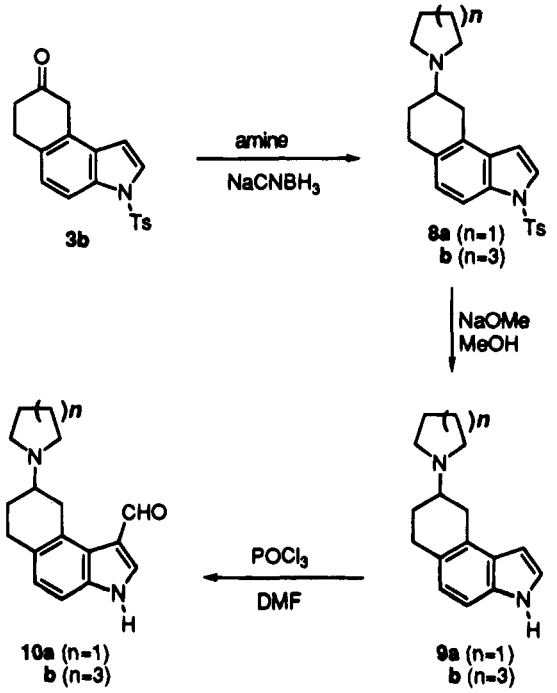
compd	R_1	R_2	formula	mp, °C[a]	anal.[b]
6a	H	H	$C_{15}H_{20}N_2 \cdot 0.75C_4H_4O_4$	245–248	C, H, N
6b	CH_3	H	$C_{16}H_{22}N_2$	72–75	HRMS[c]
6c	$CH_2CH{=}CH_2$	H	$C_{18}H_{24}N_2 \cdot C_4H_4O_4 \cdot 0.67H_2O$	180–185	C, H, N
***R*-6d**	$CH_2CH(Me)_2$	H	$C_{19}H_{28}N_2 \cdot C_4H_4O_4$	116–117	C, H, N
6e	CH_2c-Pr	H	$C_{19}H_{26}N_2 \cdot C_4H_4O_4 \cdot 0.25H_2O$	205–219	C, H, N
6f	CH_2Ph	H	$C_{22}H_{26}N_2 \cdot 0.5C_4H_4O_4 \cdot 0.87H_2O$	165–169	C, H, N
6g	CH_2CH_2Ph	H	$C_{23}H_{28}N_2$	–	C, H, N
6h		H	$C_{21}H_{26}N_2S \cdot 0.5C_4H_4O_4$	108–112	C, H, N
6i	$CH_2CH_2CH_2Ph$(o-MeO)	H	$C_{25}H_{32}N_2O_2$	130–131	HRMS
6j	$CH_2CH_2CH_2OPh$(*m*-Cl)	H	$C_{24}H_{29}N_2OCl$	137–139	HRMS
6k		H	$C_{26}H_{37}N_3O_2 \cdot HCl \cdot 1.5H_2O$	152–153	C, H, N
***R*-6k**		H	$C_{26}H_{37}N_3O_2 \cdot 0.5H_2O$	–	C, H, N
7a	H	CHO	$C_{16}H_{20}N_2O \cdot C_4H_4O_4$	>230 dec	C, H, N
7b	CH_3	CHO	$C_{17}H_{22}N_2O \cdot C_4H_4O_4 \cdot H_2O$	205–207	C, H, N
7c	$CH_2CH{=}CH_2$	CHO	$C_{19}H_{24}N_2O \cdot 0.25C_4H_4O_4 \cdot 0.5H_2O$	167–171	C, H, N
***R*-7d**	$CH_2CH(Me)_2$	CHO	$C_{20}H_{28}N_2O \cdot C_4H_4O_4 \cdot 0.25H_2O$	97–99	C, H, N
7e	CH_2c-Pr	CHO	$C_{20}H_{26}N_2O \cdot 0.5C_4H_4O_4 \cdot H_2O$	199–202	C, H, N
7f	CH_2Ph	CHO	$C_{23}H_{26}N_2O \cdot C_4H_4O_4 \cdot 0.5H_2O$	206–210	C, H, N
7g	CH_2CH_2Ph	CHO	$C_{24}H_{28}N_2O \cdot 0.75H_2O$		C, H, N
7h		CHO	$C_{22}H_{26}N_2OS \cdot 0.5C_4H_4O_4 \cdot 0.25H_2O$	185–188	C, H, N
7i	$CH_2CH_2CH_2Ph$(o-MeO)	CHO	$C_{26}H_{32}N_2O_2 \cdot HCl \cdot 0.5H_2O$	196–197	C, H, N
7j	$CH_2CH_2CH_2OPh$(*m*-Cl)	CHO	$C_{25}H_{29}N_2O_2 \cdot HCl \cdot 0.5H_2O$	155–160	C, H, N
7k		CHO	$C_{27}H_{37}N_3O_3 \cdot 0.75H_2O$	–	C, H, N
***R*-7k**		CHO	$C_{27}H_{37}N_3O_3 \cdot C_4H_4O_4 \cdot H_2O$	104–106	C, H, N
***S*-7k**		CHO	$C_{27}H_{37}N_3O_3 \cdot C_4H_4O_4 \cdot H_2O$	88–90	C, H, N
7l	$CH_2CH_2CH_2Ph$	CHO	$C_{25}H_{30}N_2O \cdot HCl \cdot 0.25H_2O$	202–204	C, H, N
***R*-7l**	$CH_2CH_2CH_2Ph$	CHO	$C_{25}H_{30}N_2O \cdot 0.5C_4H_4O_4 \cdot 0.33H_2O$	165–167	C, H, N

[a] Where the melting point value is indicated as a dash, elemental analysis was performed on an oil. [b] Analyses for the indicated elements were within ±0.40% of the calculated values. [c] Satisfactory HRMS to within 0.004 mass unit of the calculated value was obtained.

indicator of the 5-HT synthesis rate in three different brain areas. In addition, the DOPA accumulation was used as an indicator of the DA synthesis rate in the DA rich areas (i.e., the limbic system and the corpus striatum) and the NE synthesis rate in the NE rich hemispheres (mainly cortex). For this study we used reserpine-pretreated rats (5 mg/kg sc, 18 h), in which the synthesis rate of especially DOPA is raised via feedback regulation. This behavioral and biochemical model is designed to detect directly acting agonists at central monoamine receptors.

Listed in Table 4 are the binding affinities for the compounds prepared in this study. Nearly all of these analogs displayed excellent affinity for the 5-HT_{1A} receptor, with over one-half of the compounds possessing sub-nanomolar inhibition constants. A wide variety of N-substituents is well-tolerated at the 5-HT_{1A} site, ranging from very small alkyl substituents such as methyl (**7b**, K_i 0.7 nM) to the bulky 4-butylglutarimide moiety (**7k**, K_i 1.3 nM). Only the unformylated (dipropylamino)methyl analog **16b** displayed poor binding affinity for the 5-HT_{1A} receptor (K_i > 200 nM) relative to the other compounds of this study. However, the formylated derivative **17** displayed a K_i of 42 nM for this receptor. The enhancement of affinity for 5-HT_{1A} by addition of a formyl moiety at the indole C-1 position

Scheme 2



is a general observation within this series of analogs and typically results in a 10−20-fold decrease in K_i. For example, compare the 5-HT_{1A} affinities of the analog pair **6j** and **7j**, which possess K_i's of 12 and 0.8 nM, respectively. Two compounds which lack the indole formyl group yet nevertheless display excellent affinity at 5-HT_{1A} are **6g,h**. Both of these analogs contain a nitrogen substituent comprised of an aromatic ring and a two-carbon tether. In addition, incorporation of the indole C-1 formyl group attenuates binding to the dopamine D-2 site, although this effect is less pronounced than the potentiation of serotonin affinity. Overall, the formyl group at the indole C-1 position is a key structural component for gaining affinity and selectivity for the 5-HT_{1A} receptor. These observations are in agreement with earlier findings of Stjernlöf et al. in the original studies of OSU191 (**2b**).[7]

Although most of the compounds prepared for this study were racemates, a few representative examples were synthesized in optically pure form to examine the effects of stereochemistry on binding profiles and *in vivo* activities. In general, the greater binding affinity for all the receptors tested resided in the *R*-isomer. This is illustrated by examining the binding profiles for **1a**, **2a**, and **7k**, where the *R*-enantiomers possessed equal or lower inhibition constants for all serotonin and dopamine receptors. However, the enantiomers of the formylated derivative **2b** showed no difference in 5-HT_{1A} receptor binding, although this particular analog was among the most potent prepared in this study (K_i 0.2 nM). In contrast, however, the *S*-isomer of the unformylated analog **1b** displayed better affinity for the 5-HT_{1A} receptor than its corresponding *R*-isomer (K_i's of 1.4 and 5.2 nM, respectively). This compound was also the only analog for which the *S*-isomer bound with greater affinity for the dopamine D-3 site. Clearly, the influence of absolute stereochemistry of the C-8 carbon is dependent upon the nature of the nitrogen substituents. However, in all cases the *S*-isomer had significantly lower affinity for the dopamine D-2 receptor than the corresponding *R*-isomer.

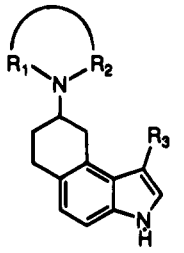
Table 4 also provides binding information for the dopamine D-3 receptor. This site is thought to be involved in the inhibition of locomotor activity.[15] Selective agents for the D-3 receptor have been difficult to identify due to the similarity in compound preference between D-2 and D-3 agents. Recently, some selective D-3 antagonists have been reported.[16] The compounds in this study possess good affinity for the D-3 site which in general parallels that for the D-2 receptor. However, these compounds are generally slightly better ligands at D-2 than at D-3, and none show a preference for the latter receptor.

Another receptor pair which we have chosen to examine with the compounds of this study are the 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ sites.[17,18] The antimigraine drug sumatriptan binds well to both of these receptors (K_i's 4.6 and 9.4 nM, respectively) but poorly at either the 5-HT_{1A} or D-2 sites.[19] It has recently been reported that mRNA encoding for only the 5-$HT_{1D\beta}$ receptor subtype was expressed by vascular smooth muscle of the central nervous system,[20] while that for the 5-$HT_{1D\alpha}$ subtype was exclusively found in postmortem human trigeminal ganglia.[21] These findings suggest that a selective 5-$HT_{1D\alpha}$ agent may be an effective antimigraine treatment free of undesired cardiovascular side effects. As can be seen from the Table 4, many of the compounds prepared in this study displayed excellent affinity for the 5-$HT_{1D\alpha}$ receptor, although in general these affinities were poorer than those for 5-HT_{1A}. However, two of the compounds prepared, **6i,j**, were equipotent at the 5-$HT_{1D\alpha}$ and 5-HT_{1A} receptors. For **6i**, the inhibition constants at these receptors were 2.5 and 2.9 nM, respectively, while for **6j** they were 13 and 12 nM, respectively. It is a general observation that this class of pyrroloaminotetralins shows a strong selectivity for the 5-$HT_{1D\alpha}$ over the 5-$HT_{1D\beta}$ site, often favoring the former receptor by 20−30-fold. None of the analogs described in this study showed a preference for the 5-$HT_{1D\beta}$ receptor.

Many of the compounds prepared for this study, especially the 1-formyl derivatives, were evaluated for *in vivo* effects. As a marker of *in vivo* activity, we assayed biochemical changes in different regions of the brains of reserpinized rats. It is well known that dopamine agonists reduce the synthesis rate of dopamine by a feedback inhibition mechanism and that this reduction is determined by a decrease in DOPA, the biosynthetic precursor to dopamine. In a similar manner, serotonin agonists decrease the synthesis rate of 5-HT as reflected by a decrease in the levels of 5-HTP. The results of the biochemical changes induced by the compounds of this study are shown in Table 5.

As expected from the *in vitro* binding results, the enantiomers of the nonformylated compound **1b** showed equivalent *in vivo* activity in both the dopamine and serotonin systems. Interestingly, the closely related isobutyl analog *R*-**6d** showed no *in vivo* dopaminergic activity despite its excellent affinity for the D-2 receptor. Also binding well at the D-2 receptor but without dopaminergic effects *in vivo* was the 3-phenylpropyl derivative *R*-**7l**. The rest of the compounds tested were inactive in the dopaminergic system as would be an-

Table 2. Dimethylamines **2a** and Cyclic Amines **9** (R_3 = H) and **10** (R_3 = CHO)



compd	R_1	R_2	R_3	formula	mp, °C	anal.[a]
R-**2a**	CH_3	CH_3	CHO	$C_{15}H_{18}N_2O{\cdot}0.75C_4H_4O_4$	188–191	C, H, N
S-**2a**	CH_3	CH_3	CHO	$C_{15}H_{18}N_2O{\cdot}0.5C_4H_4O_4$	188–191	C, H, N
9a	$-CH_2(CH_2)_2CH_2-$		H	$C_{16}H_{20}N_2$	185–187	HRMS[b]
9b	$-CH_2(CH_2)_4CH_2-$		H	$C_{18}H_{24}N_2$	80–83	HRMS
10a	$-CH_2(CH_2)_2CH_2-$		CHO	$C_{17}H_{20}N_2O$	>100 dec	HRMS
10b	$-CH_2(CH_2)_4CH_2-$		CHO	$C_{19}H_{24}N_2O$	200–201 dec	HRMS

[a] Analyses for the indicated elements were within ±0.40% of the calculated values. [b] Satisfactory HRMS to within 0.004 mass unit of the calculated value was obtained.

Scheme 3

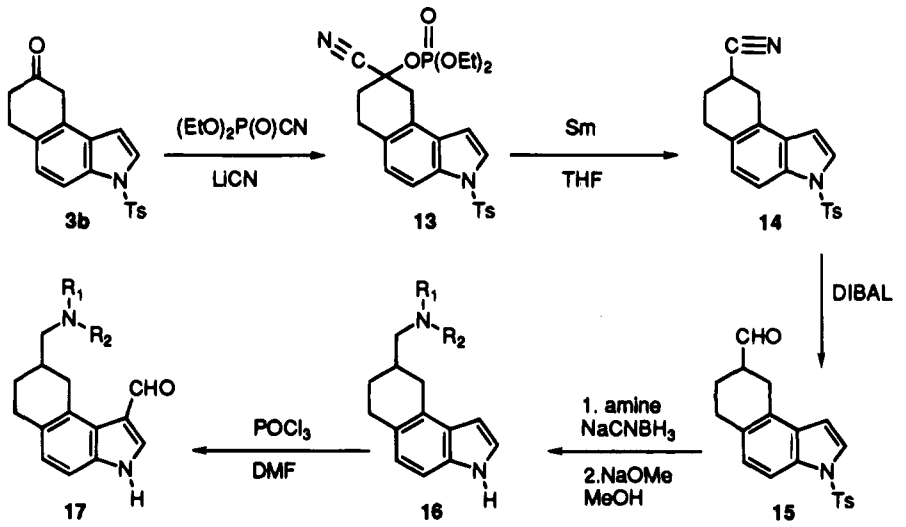
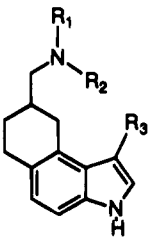


Table 3. 8-Aminomethyl derivatives **16** (R_3 = H) and **17** (R_3 = CHO)



compd	R_1	R_2	R_3	formula	mp, °C[a]	anal.[b]
16a	$CH_2CH_2CH_2Ph$	H	H	$C_{22}H_{26}N_2{\cdot}HCl{\cdot}0.25H_2O$	139–141	C, H, N
16b	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	H	$C_{19}H_{28}N_2$	160–161	HRMS[c]
17	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	CHO	$C_{20}H_{28}N_2O{\cdot}0.75H_2O$	–	C, H, N

[a] Where the melting point value is indicated as a dash, elemental analysis was performed on an oil. [b] Analyses for the indicated elements were within ±0.40% of the calculated values. [c] Satisfactory HRMS to within 0.004 mass unit of the calculated value was obtained.

ticipated from their structure (1-formyl derivatives) and/or lack of significant affinity for the D-2 receptor.

As can be seen from Table 5, nearly all of the compounds tested were active *in vivo* as serotonin agonists. Exceedingly potent was the prototype compound **2b**. In this case, the *S*-isomer was clearly more potent *in vivo* than the corresponding *R*-isomer. Also very potent in this assay were the allyl (**7c**), cyclopropylmethyl (**7e**), 2-(thiopheneyl)ethyl (**7h**), and 3-phenylpropyl (**7l**) derivatives. The potent *in vivo* activity displayed by these compounds correlates well with their high affinity for the 5-HT_{1A} receptor. It is interesting to compare the difference in serotonergic *in vivo* activity of the enantiomers of the 4-glutarimidylbutyl derivative **7k**. Although both isomers possess excellent affinity for 5-HT_{1A}, only *R*-**7k** appears as an agonist *in vivo*. It is difficult to reconcile the extremely high affinity of *S*-**7k** for the 5-HT_{1A} receptor (K_i 1.5 nM) with

Table 4. *In Vitro* Receptor Binding Profile

	K_i, nM				
compd	5-HT_{1A}	D-2	D-3	5-$HT_{1D\alpha}$	5-$HT_{1D\beta}$
1a	15 ± 3	24 ± 4	383 ± 93	12 ± 2	270 ± 180
R-**1a**	15 ± 4	15 ± 2	270 ± 78	15 ± 6	228 ± 55
S-**1a**	137 ± 25	377 ± 79	I[a]	228 ± 60	1690 ± 460
1b	3.3 ± 0.5	15 ± 0.8	37 ± 5	39 ± 14	349 ± 125
R-**1b**	5.2 ± 0.8	7.4 ± 0.9	30 ± 4	16 ± 6	139 ± 62
S-**1b**	1.4 ± 0.2	17 ± 2	22 ± 2	441 ± 65	2275 ± 246
R-**2a**	1.5 ± 0.1	13 ± 4	265 ± 62	1.6 ± 0.1	20 ± 2
S-**2a**	18 ± 2	250 ± 22	I	19 ± 1	ND[b]
2b	0.2 ± 0.03	40 ± 6	70 ± 17	ND	ND
R-**2b**	0.2 ± 0.02	17 ± 3	51 ± 6	ND	ND
S-**2b**	0.2 ± 0.01	423 ± 92	751 ± 116	ND	ND
6a	3.2 ± 0.6	48 ± 8	115 ± 21	69 ± 9	483 ± 86
6b	14 ± 1	33 ± 4	113 ± 5	170 ± 11	I
6c	4.6 ± 0.2	42 ± 2	77 ± 9	35 ± 2	I
R-**6d**	3.6 ± 0.5	5.7 ± 2	18 ± 7	35 ± 3	219 ± 40
6e	2.5 ± 0.2	33 ± 2	50 ± 4	75 ± 6	I
6f	1.9 ± 0.9	22 ± 4	43 ± 7	192 ± 43	4605 ± 1162
6g	0.7 ± 0.2	5.5 ± 1.2	18 ± 9	7.4 ± 0.6	249 ± 72
6h	0.6 ± 0.1	5.5 ± 0.5	5.5 ± 0.1	13 ± 2	I
6i	2.9 ± 0.6	4.8 ± 2	10 ± 1	2.5 ± 0.6	40 ± 6
6j	12 ± 4	15 ± 5	20 ± 1	13 ± 3	243 ± 48
6k	1.9 ± 0.8	15 ± 4	29 ± 5	26 ± 3	224 ± 40
R-**6k**	0.2 ± 0.03	6.5 ± 2.0	ND	ND	ND
7a	1 ± 0.1	60 ± 17	I	27 ± 1	227 ± 21
7b	0.7 ± 0.1	151 ± 11	258 ± 40	16 ± 2	109 ± 12
7c	0.3 ± 0.1	59 ± 2	130 ± 6	ND	49 ± 4
R-**7d**	1.1 ± 0.3	28 ± 0.2	100 ± 43	6.5 ± 0.4	ND
7e	0.6 ± 0.1	228 ± 30	164 ± 10	24 ± 2	196 ± 17
7f	2.7 ± 0.3	90 ± 4	115 ± 25	33 ± 3	992 ± 73
7g	0.04 ± 0.005	62 ± 6	81 ± 4	2.8 ± 0.5	56 ± 4
7h	0.1 ± 0.02	25 ± 3	48 ± 5	2 ± 0.2	46 ± 3
7i	1.2 ± 0.6	14 ± 4	84 ± 18	3.4 ± 0.4	11 ± 1
7j	0.8 ± 0.4	28 ± 3	159 ± 36	5.1 ± 0.7	187 ± 23
7k	2.8 ± 1.4	136 ± 27	450 ± 113	9.8 ± 1.2	115 ± 15
R-**7k**	0.6 ± 0.1	62 ± 4	154 ± 25	5.0 ± 0.4	119 ± 12
S-**7k**	1.5 ± 0.8	859 ± 162	1270 ± 69	250 ± 19	1617 ± 499
7l	0.6 ± 0.3	13 ± 4	42 ± 9	2 ± 0.2	11 ± 1
R-**7l**	<0.02[c]	5.8 ± 1.1	19 ± 2	0.9 ± 0.2	14 ± 1
9a	0.8 ± 0.1	94 ± 12	I	77 ± 5	I
9b	15 ± 1	100 ± 5	I	340 ± 47	I
10a	0.07[c]	>1000	I	ND	ND
10b	0.24[c]	>1000	ND	ND	ND
16a	3.4 ± 0.9	32 ± 5	199 ± 24	63 ± 4	228 ± 29
16b	>200	>1000	ND	ND	ND
17	42 ± 6	**1**	ND	ND	ND

[a] I = inactive, defined as less that 45% inhibition of test ligand binding at 10^{-6} M. [b] ND = not determined. [c] Value determined using calf caudate hippocampus.

its weak *in vivo* biochemical effects without considering a possible role for *S*-**7k** as a serotonin antagonist. However, when *R*-**7k** and *S*-**7k** were evaluated in a cyclic-AMP-based intrinsic activity assay, they both appeared as partial agonists.[22] The difference between these two isomers could be due to a stereochemical requirement for *in vivo* activity which is not present for the *in vitro* binding assay, although this is not supported by the results with either **1b** or **2b**. Another possibility is the contribution of the 5-HT_{1D} receptors (or 5-HT_{1B}) to the inhibition of 5-HT synthesis. The *R*-isomer of **7k** binds quite well to 5-HT_{1D}, especially 5-$HT_{1D\alpha}$ (K_i 5.0), whereas *S*-**7k** displays a much weaker affinity at these sites. Notable also are the pyrrolidine analogs where, in contrast to the binding results, the nonformylated compound **9a** seems to be more potent *in vivo* than the corresponding formylated compound **10a**.

In this and the preceding article, we have synthesized a number of structural analogs of the 6,7,8,9-tetrahydrobenz[*e*]indole nucleus. Nearly all of the analogs in this study displayed excellent affinity for the 5-HT_{1A} receptor and good selectivity for serotonin over dopamine sites. As previously mentioned, the incorporation of an aldehyde moiety at the indole 1-position attenuates dopamine binding with little or no concomitant reduction in 5-HT_{1A} affinity. This study has also demonstrated that a surprisingly wide variety of functionalities is well-tolerated at the C-8 nitrogen position (*R* in **6** and **7**) of this framework. Indeed, such divergent groups as methyl (**7a**) and (*m*-chlorophenoxy)propyl (**7j**) impart nearly identical affinities at 5-HT_{1A} (1.0 and 0.8 nM, respectively). However, there exists a demonstrable effect of absolute stereochemistry on the overall binding profiles of these analogs, wherein the *R*-isomer generally possess the superior receptor affinity. However, this stereochemical dependence of binding is manifest for the 5-HT_{1A} site to a lesser extent than the other receptors studied. For example, the most selective compound in the present study was *S*-**7k**, which displayed excellent affinity and selectivity for 5-HT_{1A}. In general, those analogs possessing good affinity for 5-HT_{1A} also displayed clear agonist pharmacology as reflected by the *in vivo* biochemical results.

As previously reported, members of this family of benzindoles have displayed a mutagenic potential by testing positive in the Ames assay.[7] However, the preparation of a large number of compounds based upon this heterocycle has permitted an in-depth structure–activity relationship (SAR) to be defined. In a future article, the results from these studies will be analyzed using a partial least squares (PLS) regression protocol. From this analysis has emerged some of the structural features of this family of molecules crucial for good affinity for the 5-HT_{1A} receptor. In addition, the conclusions from this analysis will allow for the prediction of both *in vitro* and *in vivo* activities upon the basis of calculated physical parameters of specific substituents.

Experimental Section

Chemistry. Proton and carbon magnetic resonance spectra were recorded on a Bruker Aspect 3000 spectrometer and are reported in ppm on the δ scale from internal tetramethylsilane. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. When necessary, solvents and reagents were dried prior to use. Anhydrous tetrahydrofuran refers to material that was distilled from sodium metal/benzophenone ketyl. Dichloromethane was dried over activated 4 Å molecular sieves. Thin-layer chromatography was carried out using Analtech 250 μm silica gel GF plates. Flash chromatography was performed using EM Reagents silica gel 60 (230–400 mesh). Unless otherwise noted, all nonaqueous reactions were carried out under an atmosphere of dry nitrogen using oven-dried glassware.

General Procedure for Indole Detosylation. A 0.1–0.3 M solution of the *N*-tosylindole in THF/MeOH (ranging from 1:2 to 2:1) was treated with 25% sodium methoxide in MeOH (5–10 equiv) and refluxed until TLC indicated complete conversion (typically 18 h). The reaction mixture was cooled and poured into water, and the volatiles were removed in vacuo. The resulting aqueous phase was extracted with dichloromethane (3×), and the combined organics layers were washed with water and brine and dried over $MgSO_4$. The solution was filtered and concentrated to a crude product which was purified as indicated.

General Procedure for Vilsmeier–Haack Formylation. A solution of the indole and phosphorus oxychloride (1.1–2.7 equiv) in DMF (0.1–0.5 M) was heated to 50–80 °C for 1.5–3.0 h, at which point it was cooled and added to water (4–5 reaction volumes). After adjusting the pH to >13 with NaOH (aqueous), the resulting mixture was extracted with an organic solvent (typically ethyl acetate or dichloromethane).

Table 5. 5-HTP and DOPA Accumulation in Reserpinized Rats, ED_{50}, mmol/kg (pED_{50})[a]

	DOPA, (μmol/kg)			5-HTP (μmol/kg)		
compd	limb	stri	hem	limb	stri	hem
R-**1b**	0.15 (6.81 ± 0.43)	0.18 (6.75 ± 0.22)	I[b](3.1)	0.21 (6.69 ± 0.31)	0.17 (6.77 ± 0.41)	0.28 (6.55 ± 0.42)
S-**1b**	0.51 (6.29 ± 0.60)	0.82 (6.09 ± 0.75)	I(3.1)	0.21 (6.69 ± 0.38)	0.34 (6.46 ± 0.78)	0.23 (6.63 ± 0.46)
R-**2a**	P[c](12.5)	P(12.5)	I(12.5)	2.90 (5.50 ± 0.32)	0.95 (6.02 ± 0.42)	0.56 (6.25 ± 0.51)
S-**2a**	I(50)	I(50)	I(50)	13.1 (4.9 ± 1.0)	12.1 (4.90 ± 0.6)	15.3 (4.8 ± 3.0)
R-**2b**	I(3.1)	I(3.1)	I(3.1)	0.072 (7.14 ± 0.33)	0.12 (6.91 ± 0.44)	0.45 (6.34 ± 0.20)
S-**2b**	P(12.5)	P(12.5)	I(12.5)	0.11 (6.94 ± 0.81)	0.0052 (8.28 ± 1.04)	0.032 (7.49 ± 0.49)
6c	I(12.5)	0.97 (6.01 ± 0.40)	I(12.5)	P(12.5)	0.18 (6.74 ± 0.40)	I(12.5)
R-**6d**	I(12.5)	I(12.5)	I(12.5)	1.80 (5.74 ± 0.34)	1.23 (5.91 ± 0.36)*	3.59 (5.45 ± 0.52)
6e	1.18 (5.93 ± 0.44)	1.40 (5.85 ± 0.20)	I(12.5)	0.11 (6.95 ± 0.30)	0.11 (6.98 ± 0.30)	0.18 (6.75 ± 0.40)
6f	8.10 (5.1 ± 0.40)	8.77 (5.05 ± 0.22)	I(50)	7.58 (5.12 ± 0.36)	6.87 (5.16 ± 0.30)	6.72 (5.17 ± 0.22)
7c	P(12.5)	I(12.5)	I(12.5)	0.19 (6.72 ± 0.27)	0.16 (6.8 ± 1.1)	0.19 (6.72 ± 0.27)
7e	I(3.1)	I(3.1)	I(3.1)	0.23 (6.64 ± 0.24)*	0.33 (5.48 ± 0.26)	0.34 (6.47 ± 0.26)
7f	I(3.1)	I(3.1)	I(3.1)	I(3.1)	I(3.1)	I(3.1)
7h	P(12.5)	P(12.5)	I(12.5)	0.082 (7.08 ± 0.19)	0.044 (7.35 ± 0.41)	0.11 (6.95 ± 0.20)
7j	I(50)	I(50)	I(50)	4.79 (5.31 ± 0.28)*	4.01 (5.40 ± 0.06)	5.12 (5.29 ± 0.22)*
R-**7k**	I(12.5)	I(12.5)	I(12.5)	3.78 (5.42 ± 0.22)	2.98 (5.53 ± 0.56)	4.63 (5.53 ± 0.26)
S-**7k**	I(25)	I(25)	I(25)	I(25)	I(25)	I(25)
R-**7l**	P(12.5)	P(12.5)	I(12.5)	0.66 (6.18 ± 0.32)	0.43 (6.36 ± 0.23)	0.75 (6.12 ± 0.24)
9a	1.57 (5.81 ± 0.26)	3.26 (5.49 ± 0.14)	I(50)	0.092 (7.03 ± 0.26)	0.066 (7.18 ± 0.22)	0.051 (7.29 ± 0.22)
10a	P(12.5)	P(12.5)	P(12.5)	0.58 (6.24 ± 0.48)	0.58 (6.24 ± 0.42)	0.86 (6.07 ± 0.30)
16a	I(50)	I(50)	I(3.1)	19 (4.72 ± 2.3)	34 (4.46 ± 8.1)	I(3.1)
17	I(50)	I(50)	I(50)	P(50)	P(50)	P(50)

[a] ED_{50} values calculated as described in ref 30. The pED_{50} values are given with the 95% confidence intervals. An asterisk indicates fixed values were introduced for the slope. [b] I = inactive at the highest dose (in parentheses) tested. [c] P = partial effects in the highest dose (in parentheses) tested.

The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to a crude product which was purified by flash chromatography on silica gel.

(*S*)-(−)-8-(*N*,*N*-Dimethylamino)-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole-1-carbaldehyde (*S*-(−)-2a). The title compound was prepared from *S*-(−)-**1a**[6] (58 mg, 0.27 mmol) according to the general formylation procedure. In this manner was obtained 50 mg of crude product. This material was chromatographed on prewashed (methanol) silica gel using methanol as the eluant to yield *S*-(−)-**2a** (41 mg, 63%). The fumarate salt was prepared and recrystallized from ethanol/diethyl ether: mp 188−191 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 9.80 (s, 1H), 8.10 (s, 1H), 7.25 (d, 1H), 7.05 (d, 1H), 3.95 (d of d, 1H), 2.9−3.4 (m, 4H), 2.70 (s, 6H), 2.30 (br d, 1H), 1.70 (oct, 1H); MS *m*/*e* 242 (33, M^+), 170 (100), 143 (56), 199 (48), 198 (28); $[\alpha]^{20}_D$ −95° (c 1.0, methanol, free base). Anal. ($C_{15}H_{18}N_2O{\cdot}0.5C_4H_4O_4$) C, H, N.

(*R*)-(+)-8-(*N*,*N*-Dimethylamino)-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole-1-carbaldehyde (*R*-(+)-2a). The title compound was prepared from *R*-(+)-**1a**[6] (120 mg, 0.56 mmol) according to the general formylation procedure. In this manner was obtained 110 mg of crude product which after purification yielded *R*-(+)-**2a** (82 mg, 60%). The fumarate salt was prepared and recrystallized from ethanol/diethyl ether: mp 188−191°C; $[\alpha]^{20}_D$ +97.3° (*c* 1.0, methanol, free base). Anal. ($C_{15}H_{18}N_2O{\cdot}0.75C_4H_4O_4$) C, H, N.

***N*-Propyl-*N*-(6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-8-yl)-amine (6a).** A solution of **3b**[8] (8.8 g, 25.9 mmol), propylamine (10.5 mL, 129 mmol), and *p*-toluenesulfonic acid (0.49 g, 2.6 mmol) in toluene (200 mL) was refluxed overnight with azeotropic removal of water by a Dean−Stark trap. After cooling, the reaction mixture was evaporated to dryness, and the resulting residue was dissolved in THF/methanol (200 mL, 1:1). Sodium cyanoborohydride (9.0 g, 143 mmol) was added, and the reaction mixture was stirred at room temperature overnight, at which point it was concentrated in vacuo and redissolved in ethyl acetate/water. After stirring for 1 h, the phases were separated and the organic layer was washed with 15% NaOH (aqueous), dried over Na_2SO_4, filtered, and concentrated. The residue thus obtained (10.6 g) was dissolved in THF/methanol (130 mL, 2:1) and treated with sodium methoxide (30% solution in MeOH, 63 mL, 350 mmol). After heating to reflux for 2 h, the reaction mixture was cooled and concentrated. The product was partitioned between water and dichloromethane (2×), and the combined organic phases were washed once with brine, dried over $MgSO_4$, filtered, and concentrated to yield 5.8 g of crude product. This material was purified by chromatography on silica gel using methanol as the eluant to give 2.8 g (47%) of **6a**. The fumaric acid salt was prepared and recrystallized from 99% ethanol: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (br s, 1H), 7.20 (d, *J* = 8.3 Hz, 1H), 7.15 (s, 1H), 6.95 (d, *J* = 8.3 Hz, 1H), 6.50 (m, 1H), 3.30 (d of d, *J* = 15.9, 5.1 Hz, 1H), 2.80−3.15 (m, 5H), 2.75 (t, 2H), 2.15 (m, 1H), 1.65 (m, 1H), 1.55 (sxt, 2H), 1.00 (t, 3H); MS *m*/*e* 228 (M^+, 29), 143 (100), 169 (31), 168 (31), 170 (27), 115 (14), 199 (13), 154 (12). Anal. ($C_{15}H_{20}N_2{\cdot}0.75C_4H_4O_4$) C, H, N.

N-Methyl-N-propyl-N-(6,7,8,9-tetrahydro-3H-benz[e]indol-8-yl)amine (6b). To a solution of **6a** (119 mg, 0.52 mmol), formaldehyde (37% aqueous solution, 0.5 mL), and acetic acid (approximately 100 mL) in tetrahydrofuran (10 mL) was added in one portion sodium triacetoxyborohydride (214 mg, 1.0 mmol). After stirring for 10 min, water and diethyl ether were added. Layers were separated, and the aqueous phase was extracted twice more with diethyl ether. The combined ethereal extracts were dried ($MgSO_4$), filtered, and evaporated to a residue (98 mg). This material was purified on silica gel using dichloromethane/methanol (4:1) to yield 72 mg (57%) of **6b** as a solid: mp 72–75 °C (free base); ^1H NMR (300 MHz, $CDCl_3$) δ 8.40 (br s, 1H), 7.2 (m, 2H), 6.92 (d, J = 8.4 Hz, 1H), 6.48 (m, 1H), 3.5–3.2 (m, 3H), 3.15–2.95 (m, 4H), 2.87 (t, 2H), 2.65 (s, 3H), 2.4 (br d, 1H), 1.82 (m, 3H), 1.0 (t, 3H); MS m/e 242 (M^+, 75), 170 (100), 143 (77), 213 (65), 168 (30); HRMS m/e 242.1794 ($C_{16}H_{22}N_2$ requires 242.1783).

N-Allyl-N-propyl-N-(6,7,8,9-tetrahydro-3H-benz[e]indol-8-yl)amine (6c). A mixture of **6a** (53 mg, 0.23 mmol) and potassium carbonate (500 mg) in acetonitrile (5 mL) was treated with allyl bromide (31 mL, 0.37 mmol) and stirred overnight. The reaction mixture was concentrated and partitioned between dichloromethane and 10% Na_2CO_3. The organic phase was dried ($MgSO_4$), filtered, and evaporated to a residue of 48 mg. This crude material was purified on silica gel (methanol) to yield **6c** (37 mg, 59%). The fumaric acid salt was prepared and recrystallized from MeOH/diethyl ether: mp 180–185 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.15 (br s, 1H), 7.16 (m, 2H), 6.92 (d, J = 8.2 Hz, 1H), 6.52 (s, 1H), 5.95 (m, 1H), 5.24 (d of q, J = 17.1, 1.5 Hz, 1H), 5.09 (d of d, J = 10.2, 1.6 Hz, 1H), 3.40–3.05 (m's, 5H), 2.95 (m, 2H), 2.55 (m, 2H), 2.1 (br d, 1H), 1.75 (oct, 1H), 1.53 (sxt, 2H), 0.90 (t, 3H); MS m/e 268 (M^+, 6), 143 (100), 170 (97), 168 (46), 239 (34), 124 (30). Anal. ($C_{18}H_{24}N_2 \cdot C_4H_4O_4 \cdot 0.67H_2O$) C, H, N.

(R)-(+)-N-Isobutyl-N-propyl-N-(6,7,8,9-tetrahydro-3H-benz[e]indol-8-yl)amine (R-(+)-6d). A solution of *R*-(+)-**4**[8] (1.26 g, 3.0 mmol) and triethylamine (1.7 mL, 12 mmol) in methylene chloride (60 mL) was treated with isobutyryl chloride (0.63 mL, 6.0 mmol). The mixture was stirred at room temperature for 2 h and the reaction quenched with methanol (4 mL). After stirring for 1 h, the mixture was treated with 10% NaOH and extracted with methylene chloride. The organic layer was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated to give a yellow oil. The oil was purified by liquid chromatography, eluting with hexane/acetone (2:1) to give the expected amide as an oil which later solidified (1.26 g, 97%): ^1H NMR δ 7.82–6.56 (m, 8H), 4.82–4.64/4.23–4.10 (m, 1H), 3.32–1.53 (m, 10H), 2.33 (s, 3H), 1.25–1.11 (two d, 6H), 0.95–0.85 (two t, 3H); IR (mull) n_{max} 1638, 1597, 1529 cm^{-1}; MS no M^+, other ions at m/z 323, 168, 91. Anal. Calcd for $C_{26}H_{32}N_2O_3S$: C, 69.00; H, 7.13; N, 6.19. Found: C, 68.63; H, 7.30; N, 6.09.

Lithium aluminum hydride (0.32 g, 8.4 mmol) was suspended in THF (28 mL) and cooled to −20 °C. Aluminum chloride (1.1 g, 8.4 mmol) was added through a powder funnel over 5 min. After the mixture was stirred for 10 min, the amide obtained above (1.27 g, 2.8 mmol) in THF (5 mL) was added. The mixture was allowed to warm to room temperature over 1 h. The reaction was quenched at 0 °C with 20% NaOH (10 mL) and the mixture diluted with water (100 mL). The mixture was extracted with methylene chloride (2 × 500 mL), and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by liquid chromatography, eluting with hexane/acetone (4:1) to give a yellow oil (1.2 g, 98%). The oil was converted into the HCl salt and crystallized from ethyl acetate/methanol to give *R*-(+)-**5d** as a white solid: mp 186–187 °C; ^1H NMR (CD_3OD) δ 7.79–6.79 (m, 8H), 3.95–3.72 (m, 1H), 3.48–1.78 (m, 13H), 2.32 (s, 3H), 1.10/1.08 (d, 6H), 1.04 (t, 3H); IR (mull) n_{max} 1595 cm^{-1}; M^+ 438, other ions at m/z 395, 324, 298, 283, 240, 168, 154, 142.

The title compound was prepared from *R*-(+)-**5d** (1.14 g, 2.6 mmol) according to the general detosylation procedure to give *R*-(+)-**6d** (0.56 g, 76%) as a light yellow oil following chromatography (33% hexane/acetone). The oil was converted into the fumarate and crystallized from ether/2-propanol to give a white solid: mp 116–117 °C; ^1H NMR (CD_3OD) δ 7.23–6.45 (m, 4H), 6.68 (s, 2H), 3.96–3.82 (m, 1H), 3.50–1.78 (m, 13H), 1.12/1.09 (dd, 6H), 1.06 (t, 3H); IR (mull) n_{max} 3075, 3024, 1718, 1703, 1640, 1589 cm^{-1}; $[\alpha]^{25}_D$ 71° (*c* 0.26, MeOH); HRMS m/e 284.2261 ($C_{19}H_{28}N_2$ requires 284.2252).

N-(Cyclopropylmethyl)-N-propyl-N-(6,7,8,9-tetrahydro-3H-benz[e]indol-8-yl)amine (6e). To a solution of **6a** (180 mg, 0.79 mmol) and triethylamine (0.3 mL) in dichloromethane (5 mL) was added cyclopropanecarboxylic acid chloride (125 mL, 144 mg, 1.38 mmol) in portions over a 3 h period. Sodium carbonate (10%) was added, and the mixture was shaken. The organic phase was dried ($MgSO_4$), filtered, and evaporated to a residue of 240 mg of the desired amide. This crude product was dissolved in tetrahydrofuran (10 mL), treated with lithium aluminum hydride (450 mg, 11.9 mmol), and stirred overnight. Water (0.45 mL), 5% NaOH (0.45 mL), and water (1.35 mL) were added consecutively. After a few minutes, inorganic material was filtered off and the solution was evaporated to a residue which was purified on silica gel (CH_2Cl_2/methanol, 19:1) to give 195 mg (88%) of **6e**. The fumaric acid salt was prepared and recrystallized from MeOH/diethyl ether: mp 205–210 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.25–7.10 (m, 2H), 6.65 (d, 1H), 6.48 (s, 1H), 3.5 (br s or m, 1H), 3.25 (d of d, 1H), 2.95 (m, 2H), 2.9–2.6 (m, 4H), 2.27 (br d, 1H), 1.9–1.6 (m, 4H), 1.10 (br s, 1H), 0.95 (t, 3H), 0.62 (d, 2H), 0.25 (d, 2H); MS m/e 282 (24), 170 (100), 143 (63), 253 (47), 168 (31), 169 (30). Anal. ($C_{19}H_{26}N_2 \cdot C_4H_4O_4 \cdot 0.25H_2O$) C, H, N.

N-Benzyl-N-propyl-N-(6,7,8,9-tetrahydro-3H-benz[e]indol-8-yl)amine (6f). A mixture of **6a** (100 mg, 0.44 mmol), benzyl chloride (111 mg, 0.88 mmol), and potassium carbonate (1 g) in acetonitrile (5 mL) was heated to 80 °C overnight. After cooling, the reaction mixture was concentrated in vacuo and the resulting residue was partitioned between CH_2Cl_2 and 3 M NaOH (aqueous). The organic layer was dried ($MgSO_4$), filtered, and concentrated to a residue which was purified by chromatography on silica gel (5% ethyl acetate/hexane) to give 57 mg (41%) of **6f.** The fumarate salt was prepared and recrystallized from MeOH/diethyl ether: mp 165–169 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 (br s, 1H), 7.42 (d, J = 6.9 Hz, 1H), 7.35–7.05 (m, 6H), 6.90 (d, J = 8.4 Hz, 1H), 6.02 (sept, 1H), 3.75 (2 d, 2H), 3.20–3.05 (m, 2H), 3.05–2.80 (m, 3H), 2.57 (oct, 2H), 2.10 (br d, 1H), 1.72 (oct, 1H), 1.50 (sxt, 2H), 0.88 (t, 3H); MS m/e 318 (M^+, 17), 170 (100), 143 (60), 91 (50), 289 (30), 168 (26). Anal. ($C_{22}H_{26}N_2 \cdot 0.5C_4H_4O_4 \cdot 0.87H_2O$) C, H, N.

N-(2-Phenylethyl)-N-propyl-N-(6,7,8,9-tetrahydro-3H-benz[e]indol-8-yl)amine (6g). A mixture of **4b** (756 mg, 2.0 mmol), powdered Na_2CO_3 (1.06 g, 10.0 mmol), and (2-bromoethyl)benzene (0.82 mL, 6.0 mmol) in acetonitrile (20 mL) was refluxed under N_2 for 48 h. After cooling, the reaction mixture was poured into water and volatiles were removed in vacuo. The resulting aqueous phase was extracted with dichloromethane (2 × 40 mL), and the combined organic layers were washed once with brine, dried over $MgSO_4$, filtered, and concentrated to a yellow oil. This material was purified by chromatography on 80 g of silica gel using 30% ethyl acetate/hexane to give **5g** (866 mg, 89%) as a light tan, tacky solid: R_f 0.38 (30% ethyl acetate/hexane); IR (neat) 1373, 1188, 1178, 1157, 1144, 1132, 1089, 701, 671, 616 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (m, 3H, aromatic), 7.52 (d, J = 3.7 Hz, 1H, indole), 7.20 (m, 7H, aromatic), 7.00 (d, J = 8.5 Hz, 1H, aromatic), 6.60 (d, J = 3.7 Hz, 1H, indole), 3.01–2.73 (m, 9H, phenyl-CH_2's & N-CH_2 & methine), 2.56 (t, J = 7.4 Hz, 2H, N-CH_2), 2.32 (s, 3H, tosyl-CH_3), 2.02 (m, 1H, N-C(H)-CH_{2a}), 1.52 (m, 3H, N-C(H)-CH_{2b} & CH_3-CH_2), 0.90 (t, J = 7.3 Hz, 3H, CH_3); FAB HRMS calcd (M^+H) 487.2432, found 487.2419.

The title compound was prepared from **5g** (800 mg, 1.65 mmol) according to the general detosylation procedure to give **6g** (468 mg, 85%) as a clear colorless syrup following chromatography (30% ethyl acetate/hexane). A 135 mg portion of this material was dissolved in diethyl ether (15 mL) and treated with gaseous HCl to give a white solid. Free base: R_f 0.38 (30% ethyl acetate/hexane); IR (neat) 3411, 2955, 2931, 2871, 2838, 1489, 1453, 759, 719, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.12 (br s, 1H, NH), 7.23 (m, 7H, aromatic & indole), 6.94 (d, J = 8.3 Hz, 1H, aromatic), 6.50 (t, J = 2.2 Hz, 1H, indole), 3.16 (m, 2H, methine & phenyl-CH_{2a}), 2.96–2.78 (m,

7H, phenyl-CH_2's & phenyl-CH_{2b} & N-CH_2), 2.63 (dd J = 9.3, 7.5 Hz, 2H, N-CH_2), 2.06 (m, 1H, N-C(H)-CH_{2a}), 1.59 (m, 3H, N-C(H)-CH_{2b} & CH_3-CH_2), 0.92 (t, J = 7.3 Hz, 3H, CH_3). Anal. ($C_{23}H_{28}N_2$) C, H, N.

N-Propyl-N-[2-(2-thiopheneyl)ethyl]-N-(6,7,8,9-tetrahydro-3H-benz[e]indol-8-yl)amine (6h). To a solution of **6a** (60 mg, 0.26 mmol) and triethylamine (0.1 mL) in dichloromethane (5 mL) was added thiophene-2-ylacetic acid chloride (43 mL, 56 mg, 0.34 mmol). After stirring overnight, the solution was washed (10% Na_2CO_3), dried ($MgSO_4$), filtered, and concentrated to yield 92 mg of the expected amide. This crude product was dissolved in dry diethyl ether (15 mL), treated with lithium aluminum hydride (150 mg, 4 mmol), and stirred overnight. Water (0.15 mL), 10% NaOH (0.15 mL), and water (0.45 mL) were added consecutively, the precipitated inorganic material was filtered off, and the resulting solution was evaporated to a residue of 77 mg (88%). Chromatography on silica gel (petroleum ether/diethyl ether, 3:1) gave 38 mg (47%) of **6h**. The fumaric acid salt was prepared and recrystallized from MeOH/diethyl ether: mp 108–112 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (br s, 1H), 7.18 (d, J = 2.7 Hz, 1H), 7.16 (d, J = 2.4 Hz, 1H), 7.12 (d of d, J = 1.2, 5.1 Hz, 1H), 6.94 (d, J = 3.5 Hz, 1H), 6.92 (d, J = 3.4 Hz, 1H), 6.83 (d, J = 3.3 Hz, 1H), 6.50 (t, 1H), 3.25–3.05 (m, 2H), 3.05–2.80 (m, 7H), 2.60 (t, 2H), 2.10 (br d, 1H), 1.70 (m, 1H), 1.53 (sext, 2H), 0.95 (t, 3H); MS m/e 241 (M^+ − 97, 41, M − thiophenemeth), 170 (100), 155 (14), 168 (14), 143 (11). Anal. ($C_{21}H_{26}N_2S$·$0.5C_4H_4O_4$) C, H, N

N-[3-(o-Methoxyphenyl)propyl]-N-propyl-N-(6,7,8,9-tetrahydro-3H-benz[e]indol-8-yl)amine (6i). A solution of compound 4 (735 mg, 1.9 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C and treated sequentially with 3-(2-methoxyphenyl)-propanoic acid (865 mg, 4.8 mmol), DCC (435 mg, 2.1 mmol), and 4-DMAP (49 mg, 0.4 mmol). The ice bath was removed after 0.5 h and the mixture allowed to stir at room temperature for 48 h. The reaction mixture was washed once with 50 mL of saturated aqueous $NaHCO_3$. The aqueous solution was back-extracted with CH_2Cl_2, and the combined organics were filtered through a pad of Celite. The filtrate was concentrated, and the resulting crude product was purified by flash chromatography on 150 g of silica gel with (a) 25% ethyl acetate in hexane and (b) 40% ethyl acetate in hexane to give the desired amide: R_f 0.23 (40% ethyl acetate in hexane); IR (mull) 2956, 2921, 2870, 2855, 1638, 1464, 1460, 1374, 1178, 671 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78–7.71 (m, 3H, aromatic H's), 7.52 (d of d, J_a = 3.7 Hz, J_b = 9.7 Hz, 1H, aromatic H), 7.20 (d, J = 8.1 Hz, 3H, aromatic H's), 7.14 (q, J = 7.7 Hz, 1H, aromatic H), 7.02 (d of d, J_a = 4.3 Hz, J_b = 8.5 Hz, 1H, aromatic H), 6.93–6.82 (m, 1.5H, aromatic H), 6.65 (d, J = 8.0 Hz, 0.5H, aromatic H), 6.56 (t, J = 3.8 Hz, 1H, aromatic H), 4.68 (m, 0.5H), 4.09 (m, 0.5H), 3.85 (s, 1.5H), 3.49 (s, 1.5H), 3.23 (m, 0.5H), 3.14–2.83 (several m, 8H), 2.62 (t, J = 8.2 H, 2H), 2.33 (s, 3H), 1.94–1.85 (m, 2H), 1.65–1.57 (m, 2H), 0.91–0.84 (m, 3H); HRMS m/e 544.2406 ($C_{32}H_{36}N_2O_4S$ requires 544.2396).

A 0.1 M THF solution of this amide (1.43 mmol) was then added to lithium aluminum hydride (10 equiv 1 M in THF), and the resulting mixture was refluxed for 18 h. The reaction mixture was worked up using the Fieser and Fieser protocol to provide 532 mg (99%) of **6i** as a clear oil: R_f 0.32 (40% ethyl acetate in n-hexane); IR (mull) 2954, 2927, 2868, 2855, 2617, 1494, 1463, 1377, 1244, 761 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (br s, 1H, N-H), 7.19–7.14 (m, 4H, aromatic H's), 6.94–6.82 (2 m, 3H, aromatic H's), 6.52 (quintet, J = 0.8 Hz, 1H, aromatic H), 3.80 (s, 3H, OC-H_3), 3.17–3.09 (m, 2H), 2.93–2.88 (m, 3H), 2.68–2.62 (m, 4H), 2.57–2.52 (m, 2H), 2.10–2.05 (m, 1H), 1.85–1.45 (several m, 5H), 0.91 (t, J = 7.3 Hz, 3H, CH_2CH_2C-H_3). The HCl salt was prepared by using the AcCl method (>1 equiv of acetyl chloride in 1 mL of MeOH and 15 mL of diethyl ether) to give the product as a tan solid: mp 130–131 °C; HRMS m/e 376.2502 ($C_{25}H_{32}N_2O$ requires 376.2502).

N-[3-(m-Chlorophenoxy)propyl]-N-propyl-N-(6,7,8,9-tetrahydro-3H-benz[e]indol-8-yl)amine (6j). A mixture of **4** (1.2 g, 3.15 mmol), 3-(m-chlorophenoxy)propyl bromide (2.36 g, 9.45 mmol), and freshly crushed Na_2CO_3 (1.67 g, 15.75 mmol) in CH_3CN (9 mL) was refluxed for 3 days under argon and then cooled to room temperature and diluted with H_2O (50 mL), and the organics were removed in vacuo. The aqueous residue was extracted two times with CH_2Cl_2 (60 mL); the extracts were combined, dried with Na_2SO_4, filtered, and concentrated to a crude oil which was purified by flash chromatography on 150 g of silica gel using 30% ethyl acetate in hexane to give **5j** (1.55 g, 89%): R_f 0.29 (25% ethyl acetate in hexane); IR (neat) 1595, 1473, 1373, 1284, 1188, 1178, 1157, 1143, 672, 616 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (t, J = 8.5 Hz, 3H, aromatic H's), 7.48 (d, J = 3.7 Hz, 1H, aromatic H), 7.18 (d of d, J_a = 8.2 Hz, J_b = 10.0 Hz, 3H, aromatic H's), 7.01 (d, J = 8.5 Hz, 1H, aromatic H), 6.93–6.88 (m, 2H, aromatic H's), 6.77 (d of d, J_a = 2.5 Hz, J_b = 8.4 Hz, 1H, aromatic H), 6.41 (d, J = 3.7 Hz, 1H, aromatic H), 4.13–3.86 (3 m, 2H), 2.95–2.50 (several m, 9H), 2.32 (s, 3H), 2.02 (m, 1H), 1.88 (m, 2H), 1.62 (m, 1H), 1.45 (q, J = 7.3 Hz, 2H), 0.87 (t, J = 7.3 Hz, 3H); HRMS m/e 550.2050 ($C_{31}H_{35}N_2O_3SCl$ requires 550.2057).

The title compound was prepared from **5j** (1.43 g, 2.6 mmol) according to the general detosylation procedure to give **6j** (892 mg, 86%) as an oil following chromatography (40% ethyl acetate/hexane): R_f 0.25 (25% ethyl acetate in n-hexane); IR (mull) 2953, 2924, 2870, 2855, 2621, 2511, 1594, 1580, 1468, 1232 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (br s, 1H, N-H), 7.20–7.14 (m, 3H, aromatic H's), 6.94–6.90 (m, 3H, aromatic H's), 6.79 (q of d, J_a = 1.0 Hz, J_b = 8.4 Hz, 1H, aromatic H), 6.38 (heptet, J = 0.8 Hz, 1H, aromatic H), 4.13–3.99 (m, 2H), 3.10–3.05 (m, 2H), 2.95–2.66 (several m, 5H), 2.55 (d of d, J_a = 7.2 Hz, J_b = 8.9 Hz, 1H), 2.07–2.03 (m, 1H), 1.92 (quintet, J = 6.3 Hz, 2H), 1.75–1.62 (m, 1H), 1.56–1.44 (quintet, J = 7.4 Hz, 2H), 0.90 (t, J = 7.3 Hz, 3H, NCH_2CH_2C-H_3). The HCl salt was prepared by using the AcCl method described above to give the product as a pale lilac solid: mp 137–139 °C; HRMS m/e 396.1963 ($C_{24}H_{29}N_2OCl$ requires 396.1968).

N-4-[(3,3-Dimethylglutarimidyl)butyl]-N-propyl-N-(6,7,8,9-tetrahydro-3H-benz[e]indol-8-yl)amine (6k). A mixture of **4** (1.56 g, 4.08 mmol), 4-(3,3-dimethylglutarimidyl)-butyl iodide (3.96 g, 12.24 mmol), and freshly crushed Na_2CO_3 (2.16 g, 20.40 mmol) in CH_3CN (20 mL) was refluxed for 18 h under argon. The reaction mixture was cooled to room temperature and diluted with H_2O (50 mL), and the organics were removed in vacuo. The aqueous residue was extracted two times with CH_2Cl_2 (60 mL); the extracts were combined, dried over Na_2SO_4, filtered, and concentrated to a crude oil which was purified by flash chromatography on 150 g of silica gel using a gradient solvent system starting with 40% ethyl acetate in hexane and increasing to 100% ethyl acetate to give **5k** (1.93 g, 82%): R_f 0.43 (ethyl acetate); IR (neat) 2957, 1674, 1372, 1362, 1157, 1188, 1178, 1130, 672, 616 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (t, J = 8.4 Hz, 3H), 7.52 (d, J = 3.7 Hz, 1H), 7.20 (d, J = 8.2 Hz, 2H), 7.01 (d, J = 8.5 Hz, 1H), 6.65 (d, J = 3.4 Hz, 1H), 3.77 (t, J = 6.9 Hz, 2H), 3.00–2.69 (several m, 5H), 2.54–2.43 (m, 8H), 2.32 (s, 3H), 2.04–1.99 (m, 1H), 1.62–1.43 (m, 7H), 1.06 (s, 6H), 0.87 (t, J = 7.2 Hz, 3H); HRMS m/e 577.2978 ($C_{33}H_{43}N_3O_4S$ requires 577.2974).

The title compound was prepared from **5k** (1.74 g, 3.01 mmol) according to the general detosylation procedure to give **6k** (682 mg, 54%) as an oil following chromatography (1:2:2 acetone/dichloromethane/hexane): R_f 0.50 (100% ethyl acetate); IR (mull) 2954, 2923, 2870, 2855, 1669, 1465, 1458, 1372, 1366, 1352 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (br s, 1H), 7.17–7.15 (2 m, 2H, aromatic H's), 6.92 (d, J = 8.3 Hz, 1H, aromatic H), 6.52 (t, J = 2.0 Hz, 1H, aromatic H), 3.80 (t, J = 6.8 Hz, 2H), 3.14–2.48 (3 m and s at 2.48, 13H), 2.05 (m, 1H), 1.68 (m, 1H), 1.51 (m, 6H), 1.06 (s, 6H), 0.90 (t, J = 7.3 Hz, 3H). The HCl salt was prepared from ethereal HCl to give a white solid: mp 152–153 °C; HRMS m/e 423.2897 ($C_{26}H_{37}N_3O_2$ requires 423.2886).

R-(+)-N-4-[(3,3-dimethylglutarimidyl)butyl]-N-propyl-N-(6,7,8,9-tetrahydro-3H-benz[e]indol-8-yl)amine (R-(+)-6k). A solution of R-(+)-**4**[8] (1.68 g, 4.0 mmol) in acetonitrile (75 mL) was treated with powdered Na_2CO_3 (2.04 g, 19.2 mmol) and 4-(3,3-dimethylglutarimidyl)butyl iodide (3.73 g, 11.5 mmol), and the mixture was refluxed under N_2 overnight. After cooling to room temperature, the reaction mixture was

poured into water and the volatiles were removed in vacuo. The resulting aqueous phase was extracted with dichloromethane (2 × 100 mL), and the combined organic layers were washed once with brine, dried over $MgSO_4$, filtered, and concentrated to a light brown oil. This material was purified by chromatography on 145 g of silica gel using 60% ethyl acetate/hexane to give *R*-(+)-**5k** (2.11 g, 91%) as an off-white solid: IR (mull) 2956, 2925, 2870, 2856, 1673, 1374, 1365, 1178, 1130, 671 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (m, 3H, aromatic), 7.52 (d, J = 3.7 Hz, 1H, indole), 7.20 (d, J = 8.3 Hz, 2H, aromatic), 7.01 (d, J = 8.5 Hz, 1H, aromatic), 6.65 (dd, J = 3.7, 0.6 Hz, 1H, indole), 3.77 (br t, J = 6.9 Hz, 2H, O=C-N-CH_2), 2.84 (m, 5H, phenyl-CH_2's & N-CH), 2.50 (m, 8H, O=C-CH_2's & N-CH_2's), 2.32 (s, 3H, tosyl-CH_3), 2.02 (m, 1H, N-C(H)-CH_{2a}), 1.62−1.41 (m, 7H, N-C(H)-CH_{2b} & N-(CH_2)-CH_2's), 1.06 (s, 6H, gem-CH_3's), 0.87 (t, J = 7.2 Hz, 3H, propyl-CH_3); $[\alpha]_D$ +49.2° (c 1.005, methanol). Anal. Calcd for $C_{33}H_{43}N_3O_4S_1 \cdot 0.25H_2O$: C, 68.07; H, 7.53; N, 7.22. Found: C, 68.15; H, 7.57; N, 7.26.

The title compound was prepared from *R*-(+)-**5k** (2.03 g, 3.5 mmol) according to the general detosylation procedure to give *R*-(+)-**6k** (818 mg, 55%) as a light green solid following chromatography (75% ethyl acetate/hexane): R_f 0.25 (75% ethyl acetate/hexane); IR (mull) 2956, 2930, 2870, 1724, 1670, 1370, 1350, 1333, 1272, 1127 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.18 (br s, 1H, NH), 7.16 (m, 2H, aromatic & indole), 6.92 (d, J = 8.3 Hz, 1H, aromatic), 6.52 (t, J = 2.2 Hz, 1H, indole), 3.80 (t, J = 6.8 Hz, 2H, O=N-CH_2), 3.14−2.86 (m, 5H, phenyl-CH_2's & N-CH), 2.54 (m, 8H, O=C-CH_2's & N-CH_2's), 2.03 (m, 1H, N-C(H)-CH_{2a}), 1.50 (m, 7H, N-C(H)-CH_{2b} & N-(CH_2)-CH_2's), 1.06 (s, 6H, gem-CH_3's), 0.89 (t, J = 7.3 Hz, 3H, propyl-CH_3); $[\alpha]_D$ +62° (c 1.035, methanol). Anal. ($C_{26}H_{37}N_3O_2 \cdot 0.5H_2O$) C, H, N.

8-(*N*-Propylamino)-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole-1-carbaldehyde (7a). The title compound was prepared from propyl (6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-8-yl)ammonium acetate (**6a**·HOAc) (122 mg, 0.53 mmol) according to the general formylation procedure. In this manner was obtained 64 mg of crude product which was purified on silica gel (methanol) to yield 40 mg (29%) of **7a** as a powder. The fumarate salt was prepared and recrystallized from methanol/diethyl ether: mp >230 °C dec (fumarate); ^1H NMR (300 MHz, $CDCl_3$) δ 10.12 (s, 1H), 9.55 (br s, 1H), 7.90 (s, 1H), 7.20 (d, J = 8.3 Hz, 1H), 7.05 (d, J = 8.3 Hz, 1H), 3.75 (m, 2H), 3.2−2.9 (m, 4H), 2.75 (t, 2H), 2.15 (br d, 1H), 1.7 (m, 1H), 1.6 (sxt, 2H), 1.0 (t, 3H); MS m/e 256 (M^+, 58), 198 (100), 170 (97), 143 (61), 227 (55). Anal. ($C_{16}H_{20}N_2O \cdot C_4H_4O_4$) C, H, N.

8-(*N*-Methyl-*N*-propylamino)-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole-1-carbaldehyde (7b). The title compound was prepared from **6b** (237 mg, 0.98 mmol) according to the general formylation procedure. In this manner was obtained 261 mg of crude product. Purification on silica gel afforded 102 mg (39%) of **7b**. The fumarate salt was prepared and recrystallized from methanol/diethyl ether: mp 205−207 °C (fumarate); ^1H NMR (300 MHz, $CDCl_3$) δ 11.1 (br s, 1H), 9.67 (s, 1H), 7.75 (s, 1H), 7.23 (d, J = 8.8 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 4.0 (br d, 1H), 3.4−2.8 (m, 6H), 2.80 (s, 3H), 2.4 (br d, 1H), 1.95 (m, 1H), 1.83 (m, 2H), 1.02 (t, 3H); MS m/e 270 (M^+, 40), 198 (100), 241 (80), 170 (56), 199 (35), 143 (20). Anal. ($C_{17}H_{22}N_2O \cdot C_4H_4O_4 \cdot H_2O$) C, H, N.

8-(*N*-Allyl-*N*-propylamino)-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole-1-carbaldehyde (7c). The title compound was prepared from **6c** (29 mg, 0.11 mmol) according to the general formylation procedure. In this manner was obtained 27 mg of a crude product which was purified by chromatography on silica gel (methanol) to provide 16 mg (50%) of **7c**. The fumarate salt was prepared and recrystallized from methanol/diethyl ether: mp 167−171 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 10.20 (s, 1H), 9.95 (br s, 1H), 7.95 (s, 1H), 7.21 (d, J = 18.3 Hz, 1H), 7.02 (d, J = 18.3 Hz, 1H), 5.95 (m, 1H), 5.24 (d of d, J = 17.1, 1.4 Hz, 1H), 5.10 (d of d, J = 10.1, 1.1 Hz, 1H), 3.60 (q, 1H), 3.30 (d, 2H), 3.15 (q, 2H), 2.95 (m, 2H), 2.60 (t, 2H), 2.1 (br d, 1H), 1.75 (m, 1H), 1.55 (sxt, 2H), 0.90 (t, 3H); MS m/e 296 (M^+, 16), 198 (100), 170 (60), 267 (58), 197 (43), 143 (21). Anal. ($C_{19}H_{24}N_2O \cdot 0.5C_4H_4O_4 \cdot 0.5H_2O$) C, H, N.

(*R*)-(+)-8-(*N*-Isobutyl-*N*-propylamino)-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole-1-carbaldehyde (*R*-(+)-7d). The title compound was prepared from *R*-**6d** (0.28 g, 1 mmol) according to the general formylation procedure. In this manner was obtained a crude product which was purified by liquid chromatography, eluting with hexane/acetone (2:1). Fractions homogeneous by TLC were combined and concentrated to give *R*-(+)-**7d** as an oil (0.23 g, 74%). The oil was converted into the fumarate and crystallized from diethyl ether/2-propanol to give a white solid: mp 97−99 °C; ^1H NMR (CD_3OD) δ 9.76 (s, 1H), 8.13 (s, 1H), 7.32−7.02 (2 d, 2H), 6.68 (s, 1H), 4.24−1.80 (m, 14H), 1.14/1.12 (2 d, 6H), 1.07 (t, 3H); IR (mull) n_{max} 3076, 3040, 2731, 2700, 2652, 1704, 1663, 1573 cm^{-1}; MS calcd for $C_{20}H_{28}N_2O$ 312.2202, found 312.2206; $[\alpha]^{25}_D$ 79° (c 0.29, MeOH). Anal. ($C_{20}H_{28}N_2O \cdot C_4H_4O_4 \cdot 0.25H_2O$) C, H, N.

8-[*N*-(Cyclopropylmethyl)-*N*-propylamino]-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole-1-carbaldehyde (7e). The title compound was prepared from **6e** (195 mg, 0.69 mmol) according to the general formylation procedure. In this manner was obtained 90 mg (42%) of **7e** after purification on silica gel using methanol. The half-fumaric salt was prepared and recrystallized from methanol/diethyl ether: mp 199−202 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 10.25 (s, 1H), 9.10 (br s, 1H), 7.95 (s, 1H), 7.21 (d, J = 8.3 Hz, 1H), 7.04 (d, J = 8.3 Hz, 1H), 2.90−3.60 (m, 4H), 2.65 (t, 2H), 2.55 (m, 2H), 2.10 (br d, 1H), 1.70 (m, 2H), 1.55 (sext, 2H), 0.92 (t, 4H), 0.50 (q, 2H), 0.15 (q, 2H). Anal. ($C_{20}H_{26}N_2O \cdot 0.5C_4H_4O_4 \cdot H_2O$) C, H, N.

8-(*N*-Benzyl-*N*-propylamino)-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole-1-carbaldehyde (7f). The title compound was prepared from **6f** (25 mg, 0.078 mmol) according to the general formylation procedure. In this manner was obtained 20 mg of crude product which was chromatographed on silica gel (dichloromethane/methanol, 9:1) to give 17 mg (63%) of **7f**. The fumarate salt was prepared and recrystallized from methanol/diethyl ether: mp 206−210 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 10.22 (s, 1H), 9.0 (br s, 1H), 7.94 (d, 1H), 7.44 (d, 1H), 7.4−7.1 (m, 5H), 7.02 (d, 1H), 3.82 (s, 2H), 3.55 (m, 1H), 3.3−2.8 (m's, 4H), 2.52 (sxt, 2H), 2.45 (oct, 2H), 2.10 (br d, 1H), 1.90 (m, 1H), 0.95 (t, 3H); MS m/e 346 (M^+, 9), 198 (100), 91 (97), 317 (76), 170 (68), 148 (48). Anal. ($C_{23}H_{26}N_2O_2 \cdot C_4H_4O_4 \cdot 0.67H_2O$) C, H, N.

8-(*N*-Phenethyl-*N*-propylamino)-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole-1-carbaldehyde (7g). The title compound was prepared from **6g** (287 mg, 0.86 mmol) according to the general formylation procedure. In this manner was obtained a yellow-orange oil. This material was purified by chromatography on 31 g of silica gel using 25% acetone/hexane to give **7g** (185 mg, 60%) as a light yellow/orange tacky solid. A 153 mg portion of this material was dissolved in diethyl ether (15 mL) and treated with gaseous HCl to give a light pink/red solid. Free base: R_f 0.20 (25% acetone/hexane); IR (neat) 2956, 2931, 1651, 1509, 1495, 1467, 1403, 1395, 749, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.16 (s, 1H, O=C-H), 9.27 (br s, 1H, NH), 7.92 (d, J = 2.6 Hz, 1H, indole), 7.21 (m, 6H, aromatic), 7.00 (d, J = 8.3 Hz, 1H, aromatic), 3.54 (m, 1H, methine), 3.12 (m, 2H, phenyl-CH_2), 2.96 (m, 2H, N-CH_2), 2.87 (m, 4H, phenyl-$CH_{2a\&b}$ & phenyl-CH_2), 2.66 (t, J = 7.5 Hz, 2H, N-CH_2), 2.07 (m, 1H, N-C(H)-CH_{2a}), 1.59 (m, 1H, N-C(H)-CH_{2b}) 1.52 (sx, J = 7.4 Hz, 2H, C(H)$_3$-CH_2), 0.92 (t, J = 7.3 Hz, 3H, CH_3). Anal. ($C_{24}H_{28}N_2O_1 \cdot 0.75H_2O$) C, H, N.

8-[*N*-Propyl-*N*-(2-thiophene-2-ylethyl)amino]-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole-1-carbaldehyde (7h). The title compound was prepared from **6h** (24 mg, 0.071 mmol) according to the general formylation procedure. In this manner was obtained 27 mg of a crude product which upon purification on silica gel (methanol) provided 15 mg (58%) of **7h**. The fumarate was prepared and recrystallized from methanol/diethyl ether: mp 185−188 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 10.12 (s, 1H), 9.55 (br s, 1H), 8.02 (d, J = 2.2 Hz, 1H), 7.20 (d, J = 8.3 Hz, 1H), 7.12 (d of d, J = 1.2, 5.1 Hz, 1H), 6.99 (d, J = 8.3 Hz, 1H), 6.92 (d of d, J = 3.4, 5.1 Hz, 1H), 6.84 (d, J = 2.8 Hz, 1H), 3.60 (q, 1H), 3.30−2.85 (m, 8H), 2.70 (t, 2H), 2.10 (br d, 1H), 1.70 (m, 1H), 1.53 (sext, 2H), 0.95 (t, 3H); MS m/e 269 (M^+ − 97, 100, M^+ − thiophenemeth), 198 (57), 168 (28), 72 (27), 270 (27), 155 (23). Anal. ($C_{22}H_{26}N_2OS \cdot 0.5C_4H_4O_4 \cdot 0.25H_2O$) C, H, N.

3-[*N*-[(*o*-Methoxyphenyl)propyl]-*N*-propylamino]-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole-1-carbaldehyde (7i). The title compound was prepared from **6i** (380 mg, 1.01 mmol) according to the general formylation procedure. In this manner was obtained after purification 351 mg (86%) of **7i** as an oil: R_f 0.38 (ethyl acetate); IR (mull) 2951, 2928, 2871, 2855, 1668, 1495, 1465, 1443, 1406, 1243 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.25 (s, 1H), 9.25 (br s, 1H), 7.95 (s, 1H, aromatic H), 7.17 (q, J = 8.2 Hz, 3H, aromatic H's), 7.02 (d, J = 8.3 Hz, 1H, aromatic H), 6.86 (q, J = 8.6 Hz, 2H, aromatic H's), 3.80 (s, 3H, OC-H_3), 3.55 (br q, 1H), 3.11 (br q, J = 10.7 Hz, 2H), 2.97 (m, 3H), 2.71–2.56 (several m, 6H), 2.05 (m, 1H), 1.80 (m, 3H), 1.51 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H, CH_2CH_2C-H_3); HRMS *m/e*, 404.2462 ($C_{26}H_{32}N_2O_2$ requires 404.2464). The HCl salt was prepared from ethereal HCl to give a purple solid: mp 196–197 °C. Anal. ($C_{26}H_{32}N_2O_2$·HCl·0.25H_2O) C, H, N.

8-[*N*-[(*m*-Chlorophenoxy)propyl]-*N*-propylamino]-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole-1-carbaldehyde (7j). The title compound was prepared from **6j** (738 mg, 1.86 mmol) according to the general formylation procedure. In this manner was obtained after purification **7j** (640 mg, 81%) as an oil: R_f 0.07 (40% ethyl acetate in hexane); IR (mull) 2950, 2929, 2869, 2855, 1674, 1595, 1467, 1406, 1394, 1244 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.20 (s, 1H), 8.9 (br s, 1H), 7.93 (d, J = 3.2 Hz, 1H, aromatic H), 7.21–7.15 (m, 2H, aromatic H's), 7.03 (d, J = 8.3 Hz, 1H, aromatic H), 6.91–6.88 (m, 2H, aromatic H's), 6.79 (t of d, J_a = 1.7 Hz, J_b = 8.4 Hz, 1H, aromatic H), 4.06 (t, J = 6.2 Hz, 2H), 3.54 (d, J = 11.56 Hz, 1H), 3.18–2.89 (several m, 4H), 2.78 (t, J = 6.8 Hz, 2H), 2.58 (d of d, J_a = 6.6 Hz, J_b = 8.2 Hz, 2H), 2.03 (m, 1H), 1.94 (t, J = 6.5 Hz, 2H), 1.72 (m, 1H), 1.50 (sextet, J = 7.2 Hz, 2H), 0.90 (t, J = 7.3 Hz, 3H); HRMS *m/e* 424.1908 ($C_{25}H_{29}N_2O_2Cl$ requires 424.1917). The HCl salt was prepared from ethereal HCl to give a white solid: mp 155–160 °C. Anal. ($C_{25}H_{29}N_2O_2$-Cl·HCl·0.5H_2O) C, H, N.

8-[*N*-[(3,3-Dimethylglutarimidyl)butyl]-*N*-propylamino]-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole-1-carbaldehyde (7k). The title compound was prepared from **6k** (250 mg, 0.59 mmol) according to the general formylation procedure. In this manner was obtained after purification **7k** (144 mg, 54%) as an oil: R_f 0.19 (10% methanol in ethyl acetate); IR (mull) 2954, 2925, 2869, 2856, 1671, 1465, 1394, 1372, 1350, 1127 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.74 (br s, 1H), 10.10 (s, 1H), 7.92 (s, 1H, aromatic H), 7.18 (d, J = 8.3 Hz, 1H, aromatic H), 6.96 (d, J = 8.4 Hz, 1H, aromatic H), 3.80 (t, 7.3 Hz, 2H), 3.52 (m, 1H), 3.12–3.04 (m, 2H), 2.98–2.90 (m, 2H), 2.65–2.53 (m, 4H), 2.47 (s, 3H), 2.04 (m, 1H), 1.65–1.48 (m, 7H), 1.04 (s, 6H), 0.89 (t, J = 7.2 Hz, 3H); HRMS *m/e* 451.2834 ($C_{27}H_{37}N_3O_3$ requires 451.2835). The HCl salt was prepared from ethereal HCl to give a purple solid. Anal. ($C_{27}H_{37}N_3O_3$·0.75H_2O) C, H, N.

(*R*)-(+)-8-[*N*-[(3,3-Dimethylglutarimidyl)butyl]-*N*-propylamino]-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole-1-carbaldehyde (*R*-(+)-7k). The title compound was prepared from *R*-(+)-**6k** (401 mg, 0.94 mmol) according to the general formylation procedure. In this manner was obtained *R*-(+)-**7k** (342 mg, 80%) as a pale yellow oil after chromatography (74:25:1 ethyl acetate/hexane/triethylamine). A 212 mg portion of this material was converted to the fumarate salt by treatment with isopropyl alcohol (15 mL) and fumaric acid (55 mg, 1.0 equiv) by recrystallization from ethyl acetate/IPA to afford 240 mg of a light peach solid: mp 103.5–105.5 °C; IR (mull) 2954, 2925, 2870, 2855, 1669, 1466, 1397, 1374, 1368, 1353 cm^{-1}; ^1H NMR (free base; 300 MHz, $CDCl_3$) δ 10.14 (s, 1H, CHO), 9.92 (br s, 1H, NH), 7.91 (s, 1H, indole), 7.18 (d, J = 8.3 Hz, 1H, aromatic), 6.98 (d, J = 8.3 Hz, 1H, aromatic), 3.80 (t, J = 6.8 Hz, 2H, O=C-N-CH_2), 3.47 (br m, 1H, phenyl-CH_{2a}), 3.08–2.90 (m, 4H, phenyl-CH_2's & N-CH), 2.57 (m, 4H, N-CH_2's), 2.49 (s, 4H, O=C-CH_2's), 2.05 (m, 1H, N-C(H)-CH_{2a}), 1.51 (m, 7H, N-C(H)-CH_{2b} & N-(CH_2)-CH_2's), 1.06 (s, 6H, gem-CH_3's), 0.89 (t, J = 7.2 Hz, 3H, propyl-CH_3); $[\alpha]^{20}_D$ 49° (*c* 0.862, methanol). Anal. ($C_{27}H_{37}N_3O_3$·1.0$C_4H_4O_4$·1.0H_2O) C, H, N.

(*S*)-(−)-8-[*N*-[(3,3-Dimethylglutarimidyl)butyl]-*N*-propylamino]-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole-1-carbaldehyde (*S*-(−)-7k). The title compound was prepared from *S*-(−)-**6k** (254 mg, 0.6 mmol) according to the general formylation procedure. In this manner was obtained *S*-(−)-**7k** (220 mg, 81%) as light yellow solid after chromatography (40:59:1 ethyl acetone/hexane/triethylamine). This material displayed identical NMR data as *R*-(+)-**7k**. This material was converted to the fumarate salt by treatment with isopropyl alcohol (15 mL) and fumaric acid (52 mg, 1.0 equiv) by recrystallization from ethyl acetate/IPA to afford 269 mg of a light tan solid: $[\alpha]^{20}_D$ −50° (*c* 0.750, methanol). Anal. ($C_{27}H_{37}N_3O_3$·1.0$C_4H_4O_4$·1.0H_2O) C, H, N.

8-[*N*-(3-Phenylpropyl)-*N*-propylamino]-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole-1-carbaldehyde (7l). A solution of **4** (3.20 g, 8.4 mmol) in acetonitrile (20 mL) was treated with powdered Na_2CO_3 (4.66 g, 5 equiv) and 3-phenylpropyl bromide (4.0 mL, 3.0 equiv), and the mixture was refluxed under N_2 overnight. After cooling to room temperature, the reaction mixture was poured into water and volatiles were removed in vacuo. The resulting aqueous phase was extracted with dichloromethane (3 × 100 mL), and the combined organic layers were washed once with brine, dried over $MgSO_4$, filtered, and concentrated to a yellow oil (7.75 g). This material was purified by chromatography on 350 g of silica gel using 20% ethyl acetate/hexane (column loaded with CH_2Cl_2) to give **5l** (4.01 g, 95%) as a white solid: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.73 (t, J = 7.6 Hz, 3H, aromatic H), 7.52 (d, J = 4.3 Hz, 1H, indole H), 7.28–7.13 (m, 7H, aromatic H), 7.00 (d, J = 7.6 Hz, 1H, aromatic H), 6.61 (d, J = 4.3 Hz, 1H, indole H), 3.08–2.45 (m, 11H, NCH + benzylic H's), 2.32 (s, 3H, tosyl-CH_3), 2.00 (br s, 1H, ring CH_2), 1.78 (quint, J = 7.5 Hz, 2H, propyl CH_2), 1.61 (m, 1H, ring CH_2), 1.45 (quint, J = 7.5 Hz, 2H, propyl CH_2), 0.88 (t, J = 7.6 Hz, 3H, propyl CH_3).

This material (4.00 g, 8.0 mmol) was detosylated according to the general procedure to give **6l** (2.49 g, 90%) as a thick oil following chromatography (25% ethyl acetate/hexane): ^1H NMR ($CDCl_3$, 500 MHz) δ 8.13 (br s, 1H, indole NH), 7.30–7.14 (m, 7H, aromatic), 6.92 (d, J = 7.7 Hz, 1H, aromatic), 6.51 (m, 1H, indole H), 3.19–2.49 (m, 11H, NCH + benzylic H's), 2.09 (br m, 1H, ring CH_2), 1.83 (quint, J = 7.6 Hz, 2H, propyl CH_2), 1.68 (m, 1H, ring CH_2), 1.51 (quint, J = 7.6 Hz, 2H, propyl CH_2), 0.91 (t, J = 7.6 Hz, 3H, propyl CH_3).

The title compound was prepared from **6l** (2.5 g) according to the general formylation procedure to give racemic **7l**: ^1H NMR ($CDCl_3$, 300 MHz) δ 10.22 (s, 1H, CHO), 9.22 (br s, 1H, NH), 7.93 (d, J = 2.1 Hz, 1H, indole C-H), 7.29–7.16 (m, 6H, aromatic), 7.02 (d, J = 7.7 Hz, 1H, aromatic), 3.51 (br q, J = 10.2 Hz, 1H, NCH), 3.14–2.92 (m, 4H, NCH_2), 2.67 (m, 4H, ring benzylic H's), 2.57 (t, J = 7.5 Hz, 2H, $PhCH_2$), 2.06 (br m, 1H, ring CH_2), 1.90–1.77 (m, 2H, Ph-C-CH_2), 1.69 (m, 1H, ring CH_2), 1.58–1.42 (m, 2H, propyl CH_2), 0.91 (t, J = 7.6 Hz, 3H, CH_3). Anal. ($C_{25}H_{30}N_2O$·HCl·0.25H_2O) C, H, N.

(*R*)-(+)-8-[*N*-(3-Phenylpropyl)-*N*-propylamino]-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole-1-carbaldehyde (*R*-(+)-7l). The (+)-isomer *R*-(+)-**5l** was prepared on a 2.07 mmol scale starting with (+)-**4** exactly as describe above for the racemic **5l**. The desired product was thus obtained in 91% yield after purification by chromatography. The (+)-isomer *R*-(+)-**6l** was prepared on a 1.88 mmol scale starting with (+)-**5l** exactly as describe above for the racemic isomer **6l**. The desired product was thus obtained in 85% yield and provided spectra identical to those of **6l**: $[\alpha]^{20}_D$ +59° (*c* 0.47, CH_2Cl_2). Anal. ($C_{24}H_{30}N_2$) C, H, N.

The title compound was prepared from *R*-(+)-**6l** (448 mg, 1.3 mmol) according to the general formylation procedure. In this manner was obtained *R*-(+)-**7l** (380 mg, 78%) as a slightly colored oil after chromatography (75% ethyl acetate/hexane). The half-fumaric acid salt was prepared from hot 2-propanol and isolated as the hemihydrate. NMR and MS data were identical to that of **7l**: $[\alpha]^{20}_D$ +64.4° (*c* 0.815, MeOH). Anal. ($C_{27}H_{32}N_2O_3$·0.5$C_4H_4O_4$·0.33H_2O) C, H, N.

8-Pyrrolidin-1-yl-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole (9a). A solution of 2 g (5.89 mmol) of **3b**,[8] 9.83 mL (117.80 mmol) of pyrrolidine, and 11.2 mg (0.05 mmol) of *p*-toluenesulfonic acid in 150 mL of toluene was refluxed for 8 h (bath temperature 120–125 °C) using a Dean–Stark reflux condenser for the azeotropic removal of water. Toluene was removed in vacuo, and the solid was dissolved in 150 mL of

MeOH/THF (1:1). At 0 °C, acetic acid (to pH 4–5) and 740 mg (11.78 mmol) of $NaCNBH_3$ were added. The reaction mixture stirred overnight at room temperature. The reaction was quenched with 1 N NaOH and the mixture extracted with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to yield a brown oil. The compound was purified by flash chromatography using 400 g of silica gel 60 (230–400 mesh) eluting with 95:5 methylene chloride/methanol with NH_3 (3 M). Homogeneous fractions were combined and concentrated to yield 2.04 g (88%) of **8a** as a solid: mp 144–146 °C; IR (mull) n_{max} 2332, 1596 cm^{-1}; MS M^+ at *m/z* 394, other ions at 323, 297, 239, 168, 155, 142, 97, 96, 91, 70.

The title compound was prepared from **8a** (2.04 g, 5.17 mmol) according to the general detosylation procedure to give **9a** (1.50 g, 73%) as a tan solid following chromatography: mp 185–187 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.20–7.18 (m, 2H), 6.94–6.92 (d, 1H), 6.50 (m, 1H), 3.34–3.32 (dd, 1H), 2.98–2.88 (m, 7H), 2.7–2.6 (m, 1H), 2.28 (m, 1H), 1.92 (m, 6H); IR (mull) n_{max} 3225, 3205, 1350 cm^{-1}; R_f 0.40 in 95:5 methylene chloride/methanol with NH_3 (3 M); HRMS *m/e* 240.1622 ($C_{16}H_{20}N_2$ requires 240.1626).

8-Perhydroazepin-1-yl-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole (9b). A solution of 2 g (5.89 mmol) of **3b**,[8] 1.99 mL (17.67 mmol) of hexamethyleneimine, and 11.2 mg (0.05 mmol) of *p*-toluenesulfonic acid in 150 mL of toluene was refluxed overnight (bath temperature 120–125 °C) using a Dean–Stark trap for the azeotropic removal of water. Toluene was removed in vacuo, and the solid was dissolved in 150 mL of MeOH/THF (1:1). At 0 °C, acetic acid (to pH 4–5) and 740 mg (11.78 mmol) of $NaCNBH_3$ were added. The reaction mixture stirred overnight at room temperature. The reaction was quenched with 1 N NaOH and the mixture extracted with methylene chloride (emulsion formed) and ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to yield a solid. The compound was purified by flash chromatography using 400 g of silica gel 60 (230–400 mesh) eluting with 95:5 methylene chloride/methanol with NH_3 (3 M). Homogeneous fractions were combined and concentrated to yield 1.56 g (63%) of **8b** as a pale brown solid: mp 139–141 °C; ^1H NMR ($CDCl_3$TMS) δ 7.75–7.73 (m, 3H), 7.53–7.52 (d, 1H), 7.22–7.19 (d, 2H), 7.03–7.00 (d, 1H), 6.64–6.63 (d, 1H), 3.2–1.6 (m, 22H); IR (mull) n_{max} 3117, 3073, 2658, 1597, 1453, 1365 cm^{-1}; MS M^+ at *m/z* 422, other ions at 323, 297, 267, 168, 142, 124; R_f 0.55 in 95:5 methylene chloride/methanol with NH_3 (3 M).

The title compound was prepared from **8b** (1.50 g, 3.5 mmol) according to the general detosylation procedure to give **9b** (1.37 g, 95%) as a tan solid following chromatography (95:5 dichloromethane/MeOH with 3 M NH_3): mp 80–83 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 8.39 (s, 1H), 7.22–7.18 (m, 2H), 6.92–6.89 (d, 1H), 6.49–6.47 (t, 1H), 3.37–3.33 (d, 2H), 3.11–2.96 (m, 7H), 2.39 (m, 1H), 1.91–1.72 (m, 9H); IR (mull) n_{max} 3390, 3219, 2710, 2619, 1586 cm^{-1}; MS M^+ at *m/z* 268, other ions at 169, 154, 143, 124; R_f 0.26 in 95:5 methylene chloride/methanol with NH_3 (3 M); HRMS *m/e* 269.2014 ($C_{18}H_{24}N_2$ requires 269.2018).

8-Pyrrolidin-1-yl-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole-1-carbaldehyde (10a). The title compound was prepared from **9a** (480 mg, 2 mmol) according to the general formylation procedure. In this manner was obtained **10a** (500 mg, 93%) as a tan solid: mp >100 °C dec; ^1H NMR (300 MHz, $CDCl_3$) δ 10.16 (s, 1H), 7.89 (s, 1H), 7.20–7.17 (d, 1H), 7.04–7.01 (d, 1H), 3.8–3.7 (dd, 1H), 3.6 (q, 1H), 2.97 (m, 2H), 2.77–1.6 (m, 12H); IR (mull) n_{max} 3365, 3136, 1663, 1631, 1587, 1509, 1495 cm^{-1}; R_f 0.32 in 95:5 CH_2Cl_2/MeOH with NH_3 (3 M); HRMS m/e 268.1584 ($C_{17}H_{20}N_2O$ requires 268.1576).

8-Perhydroazepin-1-yl-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole-1-carbaldehyde (10b). The title compound was prepared from **9b** (268 mg) according to the general formylation procedure. In this manner was obtained **10b** (180 mg, 61%) as a solid after chromatography (95:5 methylene chloride/methanol with 3 M NH_3). The fumarate was made and recrystallized from 2-propanol/ether to yield a yellow solid: mp 200–201 °C dec; ^1H NMR (CD_3OD, TMS) δ 9.96 (s, 1H), 8.31 (s, 1H), 7.50–7.47 (d, 1H), 7.28–7.25 (d, 2H), 6.86 (s, 2H), 4.4–2.9 (m, 19H), IR (mull) n_{max} 3202, 1966, 1927, 1696, 1675, 1657, 1511 cm^{-1}; R_f 0.33 in 95:5 methylene chloride/methanol with NH_3 (3 M); HRMS *m/e* 296.1877 ($C_{19}H_{24}N_2O$ requires 296.1889).

Diethyl 8-Cyano-*N*-(tolylsulfonyl)-6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-8-yl) Phosphate (13). To a solution of **3b**[8] (5.43 g, 16.0 mmol) in THF (320 mL) and diethyl cyanophosphonate (7.3 mL, 48.0 mmol) was added lithium cyanide (1.58 g, 48.0 mmol). The reaction mixture was stirred under nitrogen for 30 min and poured into 300 mL of water, and the volatiles were removed in vacuo. The aqueous residue was extracted with ethyl acetate (2 × 300 mL), and the combined organics were washed with water (1 × 100 mL) and brine (1 × 100 mL), dried over $MgSO_4$, filtered, and concentrated to a yellow oil. This material was determined by ^1H NMR to be a 83:17 ratio of desired product **13** and an enol–phosphonate derivative and was used directly for the next step without further purification: ^1H NMR (free base; 300 MHz, $CDCl_3$) δ 6.66 (d, J = 3.7 Hz, 0.205H, indole-C_3H of enol–phosphonate), 6.61 (d, J = 3.8 Hz, 1H, indole-C_3H of desired product).

3-*N*-(Tolylsulfonyl)-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole-8-carbonitrile (14). To a suspension of samarium powder in tetrahydrofuran (320 mL) was added diiodoethane (13.53 g, 48.0 mmol), resulting in gas evolution and an exotherm. The mixture was stirred for 1 h and then treated dropwise with a solution of **13** (9.0 g, 17 mmol theory) in THF (160 mL) and *tert*-butyl alcohol (1.6 mL, 17 mmol). The reaction mixture was stirred for an additional hour and then the reaction quenched with 600 mL of 10% HCl, and the volatiles were removed in vacuo. The aqueous residue was extracted with CH_2Cl_2 (2 × 800 mL), and the combined organics were washed with 5% $Na_2S_2O_3$ (1 × 500 mL) and brine (1 × 500 mL), dried over $MgSO_4$, filtered, and concentrated to a yellow oil. This material was purified by chromatography on 360 g of silica gel using 30% ethyl acetate/hexane to give **14** (4.11 g, 69%) as a white solid: mp 192.5–194 °C dec; R_f 0.57 (50% ethyl acetate/hexane); IR (mull) 2954, 2943, 2923, 2855, 1364, 1180, 1159, 1137, 1127, 673 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (m, 3H, aromatic), 7.54 (d, J = 3.7 Hz, 1H, indole), 7.22 (m, 2H, aromatic), 7.03 (d, J = 8.6 Hz, 1H, aromatic), 6.57 (dd, J = 3.7, 0.7 Hz, 1H, indole), 3.26–2.82 (m, 5H, phenyl-CH_2's & methine), 2.32 (s, 3H, CH_3), 2.12 (m, 2H, phenyl-C(H_2)-CH_2); HRMS *m/e* 350.1080 ($C_{20}H_{18}N_2O_2S$ requires 350.1089).

3-*N*-(Tolylsulfonyl)-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole-8-carbaldehyde (15). A solution of **14** (4.04 g, 11.5 mmol) in CH_2Cl_2 (80 mL) was cooled to 0 °C and treated dropwise with diisobutylaluminum hydride (12.7 mL, 12.7 mmol). The reaction mixture was stirred for 2 h at which point it was treated with 10% NH_4Cl (300 mL, aqueous) and extracted twice with CH_2Cl_2 (300 mL). The combined organics were washed once with water (150 mL) and once with brine (150 mL), dried over $MgSO_4$, filtered, and concentrated to an off-white solid. This material was purified by chromatography on 400 g of silica gel using 100% dichloromethane to give **15** (3.33 g, 82%) as a white solid: mp 162.0–163.0 °C; R_f 0.14 (10% acetone/hexane); IR (mull) 2954, 2925, 2869, 2855, 1366, 1180, 1158, 1141, 1129, 673 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.81 (s, 1H, O=C-H), 7.74 (m, 3H, aromatic), 7.55 (d, J = 3.7 Hz, 1H, indole), 7.19 (d, J = 8.5 Hz, 2H, aromatic), 7.02 (d, J = 8.5 Hz, 1H, aromatic), 6.66 (dd, J = 3.7, 0.6 Hz, 1H, indole), 3.09–2.91 (m, 4H, phenyl-CH_2's), 2.75 (m, 1H, methine), 2.33 (s, 1H, CH_3), 2.24 (m, 1H, phenyl-C(H_2)-CH_{2a}), 1.80 (m, 1H, phenyl-C(H_2)-CH_{2b}); HRMS *m/e* 353.1090 ($C_{20}H_{19}NO_3S$ requires 353.1086).

***N*-Propyl-*N*-[(6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-8-yl)-methyl]amine (16a).** A solution of **15** (844 mg, 2.5 mmol) in THF/MeOH (14 mL, 1:1) was cooled to 0 °C and treated with 3-phenyl-1-propylamine (1.8 mL, 12.5 mmol) and acetic acid (3 mL). The reaction mixture was stirred for 30 min, and then a single portion of sodium cyanoborohydride (314 mg, 5.0 mmol) was added (some foaming occurred). The reaction was warmed to room temperature for 16 h, at which time it was treated with 2 N NaOH (40 mL) and extracted with dichloromethane (2 × 40 mL). The combined organics were washed once with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated to a light yellow syrup. This material was purified by chromatography on 120 g of silica gel using 75%

ethyl acetate/hexane to 913 mg (77%) of a thick yellow syrup: IR (neat) 2921, 1473, 1372, 1188, 1178, 1157, 1141, 701, 671, 616 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (m, 3H, aromatic), 7.51 (d, J = 3.7 Hz, 1H, indole), 7.21 (m, 7H, aromatic), 7.01 (d, J = 8.5 Hz, 1H, aromatic), 6.63 (d, J = 3.7 Hz, 1H, indole), 3.02 (m, 1H, phenyl-CH_{2a}-C(H)), 2.85 (m, 2H, phenyl-CH_2), 2.65 (m, 6H, N-CH_2's & phenyl-CH_2), 2.49 (m, 1H, phenyl-CH_{2b}-C(H)), 2.32 (s, 3H, CH_3), 1.84 (m, 4H, N-C(H_2)-CH_2 & N-C(H_2)-C(H)-CH_{2a} & methine), 1.40 (m, 1H, N-C(H_2)-C(H)-CH_{2b}). Anal. Calcd for $C_{29}H_{32}N_2O_2S_1$: C, 73.70; H, 6.83; N, 5.93. Found: C, 73.71; H, 6.95; N, 5.93.

This material (870 mg, 1.84 mmol) was detosylated according to the general procedure to give **16a** (471 mg, 80%) as a tan syrup following chromatography (74:25:1 ethyl acetate/hexane/triethylamine). A 200 mg portion of this material was dissolved in diethyl ether (15 mL) and treated with a HCl solution (90 mL of acetyl chloride, 0.25 mL of methanol, and 15 mL of diethyl ether) to give a tan solid. Free base: R_f 0.29 (99% ethyl acetate/triethylamine); IR (mull) 3243, 3024, 2949, 2924, 2854, 2784, 1495, 1454, 762, 728 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.18 (br s, 1H, indole NH), 7.21 (m, 7H, aromatic), 6.93 (d, J = 8.3 Hz, 1H, aromatic), 6.51 (m, 1H, indole), 3.13 (dd, J = 16.7, 5.4 Hz, 1H, phenyl-CH_{2a}-C(H)), 2.89 (m, 2H, phenyl-CH_2), 2.70 (m, 7H, N-CH_2's & phenyl-CH_{2b}-C(H) & phenyl-CH_2), 2.01 (m, 2H, N-C(H_2)-C(H)-CH_{2a} & methine), 1.87 (qnt, J = 7.7 Hz, 2H, N-C(H_2)-CH_2), 1.48 (m, 1H, N-C(H_2)-C(H)-CH_{2b}). Anal. ($C_{22}H_{26}N_2$·HCl·0.25H_2O) C, H, N, Cl.

***N,N*-Dipropyl-*N*-[(6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-8-yl)methyl]amine (16b).** A solution of **15** (844 mg, 2.5 mmol) in THF/MeOH (14 mL, 1:1) was cooled to 0 °C and treated with di-*n*-propylamine (1.7 mL, 12.5 mmol) and acetic acid (3 mL). The reaction mixture was stirred for 30 min, and a single portion of sodium cyanoborohydride (314 mg, 5.0 mmol) was added (some foaming occurred). The reaction was warmed to room temperature for 2 h, at which time it was treated with 1 N NaOH (35 mL) and extracted with dichloromethane (3 × 30 mL). The combined organics were washed once with 1 N NaOH (30 mL) and once with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated to a light yellow oil. This material was purified by chromatography on 100 g of silica gel using 20% acetone/hexane to give 847 mg (77%) of a white solid: mp 95.5–97.5 °C; R_f 0.32 (20% acetone/hexane); IR (mull) 2955, 2924, 2856, 1370, 1367, 1185, 1172, 1157, 1139, 1131 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (m, 3H, aromatic), 7.51 (d, J = 3.7 Hz, 1H, indole), 7.18 (d, J = 8.3 Hz, 2H, aromatic), 7.01 (d, J = 8.5 Hz, 1H, aromatic), 6.65 (d, J = 3.7 Hz, 1H, indole), 3.05 (m, 1H, phenyl-CH_{2a}-C(H)), 2.84 (m, 2H, phenyl-CH_2's), 2.32 (m, 10H, N-CH_2's & tosyl-CH_3 & phenyl-CH_{2b}-C(H)), 2.00 (m, 2H, C(H)-CH_2-C(H_2)), 1.42 (m, 5H, N-C(H_2)-CH_2's & methine), 0.86 (t, J = 7.3 Hz, 6H, CH_3's). Anal. Calcd for $C_{26}H_{34}N_2O_2S_1$: C, 71.20; H, 7.81; N, 6.39. Found: C, 71.14; H, 7.82; N, 6.41.

This white solid (674 mg, 1.51 mmol) was detosylated according to the general procedure to give **16b** (390 mg, 91%) as a clear colorless oil following chromatography (20% acetone/hexane). A 90 mg portion of this material was dissolved in diethyl ether (15 mL) and treated with a HCl solution (34 mL of acetyl chloride, 2 mL of methanol, and 4 mL of diethyl ether) to give a purple solid: mp 160.0–161.0 °C. Free base: R_f 0.34 (20% acetone/hexane). HCl salt: IR (mull) 3185, 2950, 2922, 2857, 2854, 2632, 2521, 1458, 1423, 1377 cm^{-1}. Free base: ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 (br s, 1H, NH), 7.16 (m, 2H, indole & aromatic), 6.94 (d, J = 8.3 Hz, 1H, aromatic), 6.53 (m, 1H, indole), 3.15 (m, 1H, phenyl-CH_{2a}-C(H)), 2.89 (m, 2H, phenyl-CH_2's), 2.56–2.35 (m, 7H, N-CH_2's & phenyl-CH_{2b}-C(H)), 2.06 (m, 2H, C(H)-CH_2-C(H_2)), 1.46 (m, 5H, N-C(H_2)-CH_2's & methine), 0.89 (t, J = 7.3 Hz, 6H, CH_3's); HRMS m/e 284.2260 ($C_{19}H_{28}N_2$ requires 284.2252).

8-[(*N,N*-Dipropylamino)methyl]-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole-1-carbaldehyde (17). The title compound was prepared from **16b** (300 mg, 1.05 mmol) according to the general formylation procedure. In this manner was obtained **17** (202 mg, 62%) as a light tan oil after chromatography (25% acetone/hexane). This material was dissolved in diethyl ether (30 mL) and treated with a HCl solution (91 mL of acetyl chloride, 1 mL of methanol, and 15 mL of diethyl ether) to give a purple solid. Free base: R_f 0.21 (25% acetone/hexane); IR (mull) 3122, 2952, 2914, 2854, 1664, 1508, 1464, 1425, 1403, 1378 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.27 (s, 1H, O=C-H), 9.35 (br s, 1H, NH), 7.95 (s, 1H, indole), 7.20 (d, J = 8.3 Hz, 1H, aromatic), 7.03 (d, J = 8.3 Hz, 1H, aromatic), 3.46 (dd, J = 17.0, 5.1 Hz, 1H, phenyl-CH_{2a}-C(H)), 2.93 (m, 2H, phenyl-CH_2), 2.76 (dd, J = 17.1, 10.1 Hz, 1H, phenyl-CH_{2b}-C(H)), 2.43 (m, 6H, N-CH_2's), 2.08 (m, 2H, phenyl-C(H_2)-CH_{2a} & methine), 1.45 (m, 5H, N-C(H_2)-CH_2's & phenyl-C(H_2)-CH_{2b}), 0.88 (t, J = 7.3 Hz, 6H, CH_3's). Anal. ($C_{20}H_{28}N_2O_1$·0.75H_2O) C, H, N.

***In Vitro* Binding.** Competition radioligand binding experiments employed 11 drug concentrations run in duplicate. Radioligands used were [^{3}H]U-86170[23](D-2 dopamine, 62 Ci/mmol, 2 nM), [^{3}H]spiperone (123 Ci/mmol, 0.3 nM, D-2 dopamine, or 0.5 nM, D-3 dopamine), [^{3}H]-8-OH-DPAT (5-HT_{1A}, 147 Ci/mmol, 1 nM), and [^{3}H]serotonin (5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$, 69 Ci/mmol, 1.7 nM). Nonspecific binding (75–95% of total) was defined with the following cold compounds added in excess: haloperidol (D-2 and D-3), lisuride (5-HT_{1A}), and serotonin (5-HT_{1D}). Total binding was determined with buffer. Buffers (pH 7.4) used were 50 mM Tris, 5 mM $MgCl_2$ (5-HT_{1A}), the same with 0.1% ascorbic acid (5-HT_{1D}), 20 mM HEPES, 10 mM $MgSO_4$ (D-2 using [^{3}H]U-86170 as radioligand), and 20 mM HEPES, 10 mM $MgCl_2$, 150 mM NaCl, 1 mM EDTA (D-3 and D-2 using [^{3}H]spiperone as radioligand). Cloned mammalian receptors permanently expressed in CHO cells were the source of all binding sites.[24,25] Membranes were prepared by mechanical disruption of cell pellets in ice cold 50 mM Tris, 5 mM EDTA, 5 mM EGTA, pH 7.4, followed by low (1000g), medium (20000g) and high (80000g) speed centrifugation steps. Binding mixtures were made in deep 96-well titer dishes by the addition of 50 μL of drug dilution, 50 μL of radioligand, and 800 μL of membranes (20–60 μg of protein) in binding buffer. After room temperature incubation for 1 h (5-HT_{1D} reactions were protected from light), reactions were stopped by vacuum filtration with a TomTec harvester. Counting was with a 1205 β-plate scintillation counter using Meltilex as scintillant. IC_{50} values were estimated by fitting the data to a one-site competition model:

$$Y = T/(1 + 10^{\log(X)-\log(IC_{50})})$$

where Y is the specific CPM's bound at concentration X and T is the specific CPM's bound in the absence of competitor. Inhibition constants (K_i) were calculated with the Cheng–Prushoff equation.[28]

Pharmacology. Male rats used in the biochemical experiments were of the Sprague–Dawley strain (ALAB, Sollentuna, Sweden) weighing 200–300 g. The rats were kept 5/cage with free access to water and food at least 1 week from arrival until used in the experiments. All substances to be tested were dissolved in saline immediately before use, occasionally with the addition of a few drops of glacial acetic acid and/or moderate heating in order to obtain complete dissolution. Reserpine was dissolved in a few drops of glacial acetic acid and made up to volume with 5.5% glucose solution. Injection volumes were 5 mL/kg, and all solutions had neutral pH at the time of injection (except for the solutions of reserpine, which had a pH of ca. 4).

Biochemistry. The biochemical experiments and the determinations of DOPA and 5-HTP by means of HPLC with electrochemical detection were performed according to a modification of a previously described method.[29] Separate dose–response curves based on four to six dose levels (n = 4) for each substance and each brain area were constructed. From these curves, the dose of the drug yielding a half-maximal decrease (ED_{50} value) of the DOPA and 5-HTP levels was determined. The maximal effect, expressed as percent of controls, for DOPA was normally limbic system, −65%; striatum, −80%; and the hemispheres, −50%; and for 5-HTP was limbic system, striatum, and the hemispheres, −50%. Control values for 5-HTP were (ng/g, mean ± SEM, n = 10) limbic system, 192 ± 18; striatum, 129 ± 14; and the hemispheres, 131 ± 14. Control values for DOPA were (ng/g, mean ± SEM,

$n = 10$) limbic system, 808 ± 56; striatum, 3653 ± 222; and the hemispheres, 156 ± 11. The dose–response curves were obtained by nonlinear curve fitting to a sigmoidal function as previously described.[30]

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Supplementary Material Available: ^{13}C NMR and FAB HRMS data (4 pages). Ordering information is given on any current masthead page.

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