C-9 and N-Substituted Analogs of *cis*-(3a*R*)-(−)-2,3,3a,4,5,9b-Hexahydro-3-propyl-1*H*-benz[*e*]indole-9-carboxamide: 5-HT_{1A} Receptor Agonists with Various Degrees of Metabolic Stability

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Closely related analogs of the 5-HT_{1A} receptor agonist *cis*-(3a*R*)-(−)-2,3,3a,4,5,9b-hexahydro-3-propyl-1*H*-benz[*e*]indole-9-carboxamide (**1**, U93385) were synthesized and pharmacologically evaluated. 9-Carboxamide analogs with varied nitrogen substitution (R_2) were synthesized, and their serotonergic activity was evaluated in vitro and in vivo. Many of these compounds were incubated in the presence of rat hepatocytes, and the metabolic stability in vitro was compared to that of compound **1**. Only the *N*-methyl and *N*-ethyl analogs ((−)-**5a** and (−)-**5b**) were more stable than compound **1**, indicating that N-dealkylation is a major route of metabolism in this series. In addition, these analogs were found to be partial 5-HT_{1A} receptor agonists in vivo. Modifications were also made to the carboxamide functionality of compound **1** (R_1 in **2**) to yield substituted amides or ketones. Among these analogs, the methyl ketone (−)-**15a** was found to be a 5-HT_{1A} agonist with full intrinsic activity in vivo and was approximately 20 times more potent than compound **1** and 5 times more potent than 8-OH-DPAT.

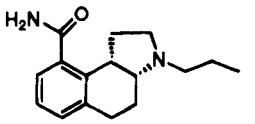
Introduction

In a recent report, the carboxamide **1** [*cis*-(3a*R*)-(−)-2,3,3a,4,5,9b-hexahydro-3-(*n*-propyl)-1*H*-benz[*e*]indole-9-carboxamide, U93385] was described as a selective 5-HT_{1A} receptor agonist with good oral availability having potential anxiolytic and antidepressant properties.[1] It displayed potent activity in animal models such as the stress-induced increase in corticosterone,[2] the isolation-induced aggression assay,[3] and stress-swim test.[1] These paradigms are believed to be predictive of anxiolytic or antidepressant activity in humans.

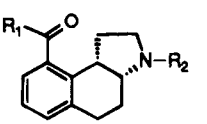
When it is intended that clinical drug administration will be via the oral route, one of the key determinants governing drug candidate selection is acceptable oral bioavailability (*F*). *F* may be determined for selected compounds in the species used for pharmacological and toxicological investigations. However, such studies are time- and resource-consuming, and, during the drug discovery phase where many "active" compounds are being considered, some preliminary assessment of likely bioavailability is very useful to aid selection of compounds for in vivo investigation. Work in our laboratories with selected compounds from the same series as those currently under discussion has indicated that extensive first-pass metabolism rather than poor absorption following oral administration is the major determinant of *F* (unpublished data). Earlier work, with 2-aminotetralins, showed a good correlation between metabolites produced during incubation with rat hepatocytes and those seen in rat urine following oral dosing.[4] We have demonstrated similar good relationships between in vitro and in vivo metabolites of certain compounds described in this paper (data not shown).

Assuming hepatic metabolism predominates in vivo, metabolic stability measured in vitro during incubation in the presence of freshly prepared hepatocytes should be a useful predictor of *F*. Where this logic holds, a comparison of the metabolic stabilities of two compounds measured in vitro using the same hepatocyte preparation should allow approximate prediction of *F* for one compound if *F* has been experimentally determined for the other. This approach can provide useful information enabling structure/metabolism relationships to be investigated for a large number of compounds and ensures metabolic/pharmacokinetic, as well as pharmacological, input into the choice of compounds for in vivo investigation and subsequent selection of drug development candidates. This approach is particularly relevant where the intended clinical administration is via the oral route and has proved useful in the evaluation of other aminotetralin analogs.[5] We believe that the use of intact cells as the in vitro system confers advantages over alternative subcellular models. It is difficult to optimize cofactor concentrations, necessary for incubations with the latter systems, when dealing with a large number of test compounds, and with intact cells, only those compounds whose physicochemcial characteristics allows passage across a cell membrane are granted access to drug metabolizing enzymes.

In this report, we describe the synthesis and biological evaluation of compounds represented by generic formula **2**. Initially, a large number of analogs with a variety



1, U93385



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of nitrogen substitution (R_2) were synthesized to evalu-

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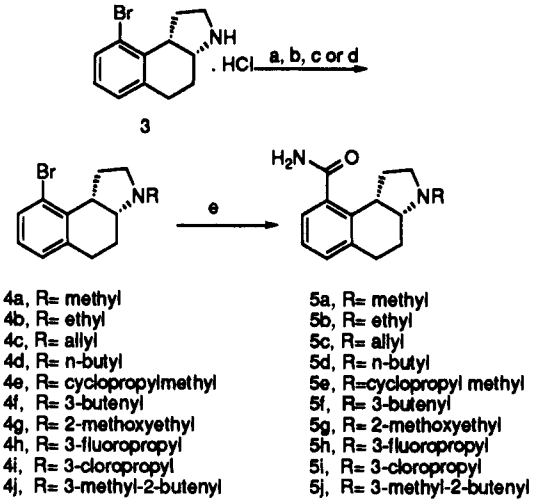
Scheme 1[a]



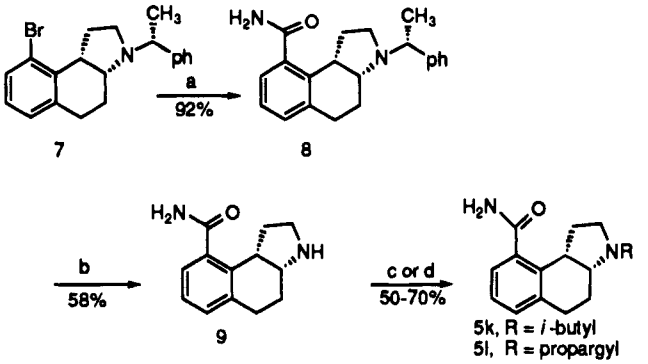
[a] Reagents and conditions: (a) aldehyde, HOAc, $NaCNBH_3$, THF/MeOH or CH_3CN; (b) acid chloride, py/CH_2Cl_2 followed by LAH/$AlCl_3$, THF; (c) bromide, Et_3N/DMF; (d) bromide, Na_2CO_3/CH_3CN, Δ; (e) *t*-BuLi/TMSNCO, THF.

ate the influence of this group on the serotonergic response and metabolic stability in vitro. Secondly, compounds with substitutions in the 9-carboxamide region (R_1 in **2**) were investigated. Previously published 2-aminotetralins substituted with a ketone functionality demonstrated high affinity for the 5-HT_{1A} sites.[6] Therefore, we were interested in evaluating the effect of a carbonyl substituent on this tricyclic ring system in terms of both serotonergic activity and metabolic stability.

Chemistry

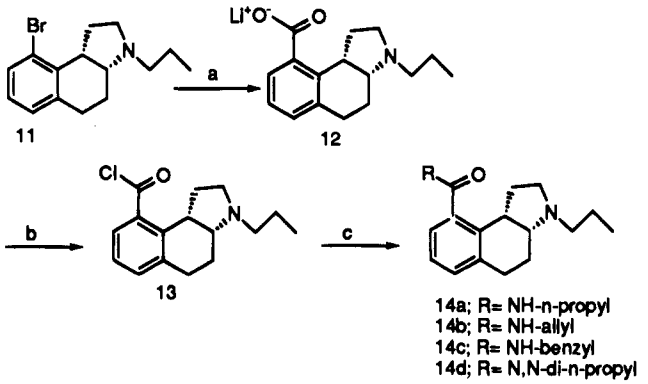
Two synthetic approaches were utilized to obtain the analogs with various nitrogen substitution (R_2 in **2**). As shown in Scheme 1, the first approach utilized bromide **3** as the starting material.[1] Depending on the nature of the substituent, we found that different alkylation methods were required. For example, when **3** was reacted with paraformaldehyde under reductive amination conditions,[7] the desired methyl analog was obtained in 90% yield. However, when **3** was reacted with acetaldehyde under the same conditions, the desired ethyl analog **4b** was obtained in very low yield (<30%). In order to synthesize larger quantities of **4b**, it was necessary to acylate **3** (acetyl chloride, pyridine/methylene chloride) followed by reduction of the acetamide with LAH/$AlCl_3$ in 93% overall yield.[8] Refluxing **3** with ethyl iodide in acetonitrile in the presence of sodium carbonate failed to give any of the desired product **4b**. Presumably, the reaction resulted in the formation of a quaternary salt. Similar results were observed when allyl bromide was reacted under the same conditions. Therefore, the allylation was changed to milder conditions by stirring allyl bromide with **3** in the presence of triethylamine in DMF at room temperature. This modification resulted in 95% yield of the allyl analog **4c**. The remaining analogs **4d**–**j** were obtained by either acylation/reduction or alkylation in 80–90% yield. In the process of preparing the chloropropyl intermediate **4i**, the alkylation of **3** with 3-bromo-1-chloropropane (Na_2CO_3/CH_3CN, 90 °C) resulted in the formation of dimer **6** as the major product (eq 1). By lowering the reaction temperature to 60 °C, the dimerization could be minimized and the desired product **4i** was obtained in 60% yield. The N-substituted aryl bromides **4a**–**j** were then subjected to lithium/halogen exchange using *tert*-butyllithium followed by quenching with trimethylsilyl isocyanate (TMSNCO) to yield the 9-carboxamide analogs **5a**–**j** in good yield.[9]

Scheme 2[a]

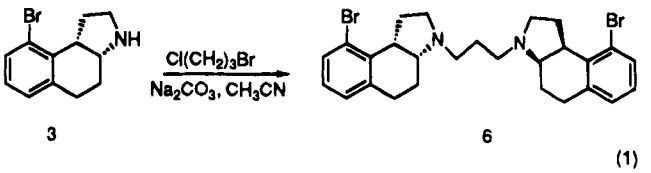


[a] Reagents and conditions: (a) *t*-BuLi/TMSNCO, THF; (b) $NH_4^+CO_2^-$, Pd/C, MeOH; (c) isobutylraldehyde, HOAc, $NaCNBH_3$, THF/MeOH; (d) propargyl chloride, Et_3N, DMF.

Scheme 3[a]



[a] Reagents and conditions: (a) *t*-BuLi, THF, CO_2; (b) $(ClCO)_2$, DMF, THF/CH_2Cl_2; (c) amine, CH_2Cl_2/THF.



(1)

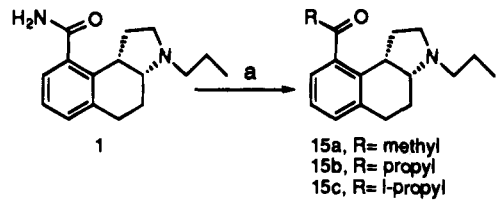
By reacting the 9-carboxamide 1 by reacting

Analogs **5k** and **5l** were synthesized via a second approach illustrated in Scheme 2. Bromide **7**[1] was converted into carboxamide **8** via the *t*-BuLi/TMSNCO procedure previously described.[9] This amide was then subjected to hydrogenolysis ($NH_4^+CO_2^-$, Pd/C, MeOH)[10] to remove the chiral α-methylbenzyl auxiliary. Reductive amination with isobutyraldehyde afforded analog **5k** whereas mild alkylation described earlier using propargyl chloride in TEA/DMF yielded analog **5l**.

Substituted carboxamide analogs and carbonyl analogs were also synthesized. As shown in Scheme 3, bromide **11**[1] was converted into the acid chloride **13** (*t*-BuLi/CO_2 followed by oxalyl chloride/DMF). The acid chloride could then be condensed with a variety of amines to yield the substituted amides **14a**–**d** in 30–40% overall yield.

In addition, the 9-carbonyl analogs **15a**–**c** were obtained directly from the 9-carboxamide 1 by reacting

Scheme 4[a]



[a] Reagents and conditions: (a) (1) RMgBr or RMgCl, ether, Δ, (2) HCl, Δ.

with the appropriate grignard reagent in refluxing ether (Scheme 4).[11] We were unable to synthesize the *tert*-butyl ketone using *tert*-butylmagnesium chloride in refluxing THF.

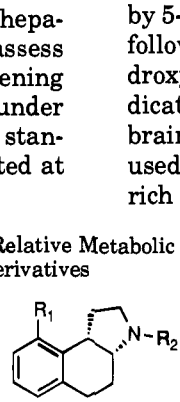
Pharmacology

As shown in Table 1, the ability of the compounds to displace radioactively labeled ligands [^{3}H]-8-OH-DPAT or [^{3}H]U86170 from 5-HT$_{1A}$ or D$_2$ sites, respectively, in cloned CHO cells was assessed in vitro.[12] The metabolic stability of the test compounds was evaluated after incubation in the presence of freshly isolated rat hepatocytes in vitro. This procedure was used to assess likely metabolism in vivo from the in vitro screening model. The rates of metabolism of a compound under this test were determined by HPLC, which was standardized to that of a reference compound incubated at the same time.

Postsynaptic effects of the test compounds were assessed by the increase in the locomotor activity (reversal of reserpine induced hypokinesia). Motor-activity recordings were carried out as previously described with the use of motility meters (see also Table 2).[13] The gross behavior of the animals was observed during the motility recordings. The DA-mediated behavior was characterized by hyperlocomotion, sniffing, and licking, whereas the 5-HT-mediated behavior consisted of a flat body posture, abducted hind- and forelegs, and forepaw treading, the so-called "5-HT behavioral syndrome".

The in vivo biochemical test, as illustrated in Table 2, utilizes the well-established phenomenon of receptor mediated feedback inhibition of the presynaptic neuron.[14] Dopamine (DA) and noreprinephrine (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.[15] The 5-HTP accumulation, following decarboxylase inhibition by means of 3-hydroxybenzylhydrazine (NSD1015), was used as an 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

Table 1. Binding Affinities at 5-HT$_{1A}$ and D$_2$ Sites and Relative Metabolic Stability in Vitro of *cis*-(3a*R*)-(−)-2,3,3a,4,5,9b-Hexahydro-1*H*-benz[*e*]indole Derivatives



compd	R_1	R_2	affinity K_i, nM (SEM) 5-HT$_{1A}$ binding[a]	affinity K_i, nM (SEM) D$_2$ binding[b]	relative metabolic stability[d]
8-OH-DPAT			0.5 (±0.1)	86 (±8)	0.16
(−)-**1**	$CONH_2$	propyl	1.9 (±0.2)	>1629	1
(−)-**4a**	Br	methyl	24 (±0.8)	41 (±9)	NT
(−)-**4b**	Br	ethyl	11 (±1)	34 (±5)	NT
(−)-**4c**	Br	allyl	1 (±0.1)	3.2 (±0.4)	NT
(−)-**4d**	Br	n-butyl	45 (±6)	75 (±15)	NT
(−)-**4e**	Br	cpm[e]	4.7 (±0.5)	119 (±12)	NT
(−)-**4f**	Br	3-butenyl	34 (±2)	55 (±15)	NT
(−)-**4g**	Br	2-methoxyethyl	97 (±8)	252 (±15)	NT
(−)-**4h**	Br	3-fluoropropyl	4.7 (±0.4)	47 (±3)	NT
(−)-**4i**	Br	3-chloropropyl	12 (±0.1)	73 (±11)	NT
(−)-**4j**	Br	3-methyl-2-butenyl	266 (±20)	18 (±2)	0.21
(−)-**5a**	$CONH_2$	methyl	41(±2)	>1000[c]	4.9
(−)-**5b**	$CONH_2$	ethyl	23 (±3)	>1000[c]	1.5
(−)-**5c**	$CONH_2$	allyl	1.5 (±0.1)	>1000[c]	1.0
(−)-**5d**	$CONH_2$	*n*-butyl	83 (±11)	>1000[c]	0.3
(−)-**5e**	$CONH_2$	cpm[e]	8.3 (±0.7)	>1000[c]	0.5
(−)-**5f**	$CONH_2$	3-butenyl	82 (±10)	>1000[c]	0.33
(−)-**5g**	$CONH_2$	2-methoxyethyl	129 (±10)	>1000[c]	0.58
(−)-**5h**	$CONH_2$	3-fluoropropyl	3.9 (±0.4)	>1000[c]	0.68
(−)-**5i**	$CONH_2$	3-chloropropyl	15 (±0.9)	>1000[c]	0.22
(−)-**5j**	$CONH_2$	3-methyl-2-butenyl	271 (±22)	>1000[c]	NT
(−)-**5k**	$CONH_2$	isobutyl	42 (±3)	>1000[c]	0.23
(−)-**5l**	$CONH_2$	propargyl	48 (±5)	>1000[c]	0.37
(−)-**14a**	CONHPr	propyl	52 (±6)	>1000[c]	NT
(−)-**14b**	CONHallyl	propyl	2.2 (±0.5)	>1000[c]	0.40
(−)-**14c**	CONHBz	propyl	22 (±4)	>1000[c]	0.16
(−)-**14d**	$CON(Pr)_2$	propyl	434 (±61)	>1000[c]	NT
(−)-**15a**	$COCH_3$	propyl	0.4 (±0.03)	91 (±7)	0.13
(−)-**15b**	$CO(CH_2)_2CH_3$	propyl	0.7 (±0.04)	22 (±1)	0.05
(−)-**15c**	$COCH(CH_3)_2$	propyl	1.2 (±0.1)	62 (±6)	0.80

[a] [^{3}H]-8-OH-DPAT labeled 5-HT$_{1A}$ sites in cloned CHO cells. [b] [^{3}H]U86170-labeled D$_2$ sites in cloned CHO cells. [c] IC$_{50}$'s in nM were estimated from a single point experiment; compound was run at 1 μM. [d] In vitro metabolic stabilites are expressed relative to the stability of compound **1**. [e] cpm = cyclopropylmethyl.

Table 2. Behavioral Observations, Effects on Locomotor Activity, and Effects on Brain 5-HT and DA Synthesis Rates in Vivo after Subcutaneous Administration to Reserpinized Rats

compd	behavioral observations[a]	locomotor activity[b]	DOPA acc[c]		5-HTP acc[c]
			stri	cort	limb
8-OH-DPAT	++5HT	66 ± 17* (0.2)	$I(45)^d$	$I(45)$	0.052
1	++5HT	249 ± 126** (12.5)	$I(50)$	$I(50)$	0.28
5a	(+)5HT	23 ± 7* (50)	$I(50)$	$I(50)$	17.6
5b	(+)5HT	13 ± 6* (12.5)	$I(100)$	$I(100)$	2.0
5c	+5HT	215 ± 69*** (12.5)	$I(12.5)$	$I(12.5)$	0.04
5e	(+)5HT	32 ± 10 (50)	$I(50)$	$I(50)$	1.0
14a	(+)5HT (+)DA	58 ± 10*** (10)	$I(50)$	$I(50)$	4.0
14b	(+)5HT +DA	82 ± 45** (50)	$I(50)$	$I(50)$	0.8
14c	(+)5HT	41 ± 19** (12.5)	$I(50)$	$I(50)$	7.0
15a	++5HT	115 ± 22*** (0.8)	$I(2.1)$	$I(2.1)$	0.0125
15b	++5HT	631 ± 93*** (3.1)	$I(3.1)$	$I(3.1)$	0.260
15c	++5HT	450 ± 118* (3.1)	$I(3.1)$	$I(3.1)$	0.025

[a] The animals' gross behavior was observed 30 min after injection (dose shown in brackets in the locomotor activity studies). 5HT denotes the serotonin behavioral syndrome, i.e., flat body posture and reciprocal forepaw treading while DA denotes dopamine mediated behavior such as locomotion and sniffing. The symbols ++ and (+) denote the intensity of the behavioral effects. [b] The locomotor activity was measured during a 30 min period after sc administration using photocell motility meters. Data are expressed as accumulated counts per 30 min (mean ± SEM, $n = 4$) at the dose shown in parentheses. Reserpinized control values = 3 ± 1, $n = 13$. Statistics according to Student's t test where * indicates $p < 0.05$, ** indicates $p < 0.01$ and *** indicates $p < 0.001$. [c] ED_{50} values, μmol/kg, sc. Abbreviations: limb = limbic system, stri = corps striatum, and hem= hemishpheres. [d] I means inactive at the highest dose tested in parentheses.

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.

The 5-HT behavioral syndrome (flat body posture and reciprocal forepaw treading) was scored in non-pretreated rats in order to evaluate the intrinsic activity elicited by a compound (for results see Figure 1a,b). Full 5-HT_{1A} agonists are known to produce a full behavioral syndrome whereas a partial agonist does not.

Results and Discussion

All the 9-bromo-3-substituted analogs (**4a–j**) displayed affinity to both the serotonin 1A (5-HT_{1A}) and dopamine (DA) D_2 receptors in vitro (see Table 1). Interestingly, **4j** (3-methyl-butenyl) showed a 26-fold preference for the D_2 receptor (K_i = 18 nM) but had only a weak affinity for the 5-HT_{1A} receptor site (K_i = 266 nM). Another analog that displayed weak affinity in the binding assay was **4g**, the 2-methoxyethyl derivative (K_i = 97 nM).

As shown in Table 1, the 9-carboxamido-3-substituted derivatives **5a–l** displayed high selectivity with varying degrees of affinity for the 5-HT_{1A} receptor site. The allyl analog **5c** was equipotent to compound **1**, and the cyclopropylmethyl (**5e**) and 3-fluoropropyl (**5h**) analogs were 2–4 times less potent than **1**. These results are in agreement with earlier work in the aminotetralin area. Arvidsson *et al.*[16] reported that the propyl group exhibits optimal serotonergic activity in the 2-aminotetralin area. However, from the present work one can see that the allyl and cyclopropylmethyl groups also show potent in vitro activity. Other compounds (**5a, 5b, 5d, 5f, 5i, 5k,** and **5l**) were found to be 10–40 times less potent than U93385 in the binding assay. Two analogs (**5g** and **5j**) displayed very weak binding affinities for the 5-HT_{1A} receptor site. From the binding data it can be seen that as the nitrogen substituent becomes more bulky, the binding affinity is decreased.

Although the methyl (**5a**) and ethyl (**5b**) analogs vary only slightly in structure from compound **1**, they produced only a maximal reduction in 5-HTP accumulation in reserpinized rats with low potency (Table 2). During behavioral observations, these compounds did not produce a full behavioral syndrome even at high doses. In addition, one can note that they also did not induce locomotor activity to the extent of the full agonists (compare **5a** or **5b** to **1** or **5c** for example). This indicates partial agonist effects at 5-HT_{1A} receptors. In order to closely evaluate the intrinsic activity of these compounds, they were tested in a behavioral scoring paradigm. Full agonists are known to produce a full 5-HT_{1A} behavioral syndrome which includes a pronounced straub tail, forepaw treading (piano playing), and flat body posture. However, compounds which have a lower intrinsic acitivity, for example buspirone, do not show full efficacy in this model (i.e., they show only flat body posture). It was found that both **5a** and **5b** induced flat body posture (Figure 1a) while **5b** only induced weak forepaw treading and **5a** was inactive in this respect (Figure 1b). This confirms that **5b** and especially **5a** possess low intrinsic efficacy in vivo.

In contrast, compounds **5c** (allyl) and **5e** (cyclopropylmethyl) were found to be full agonists *in vivo* (see Table 2). However, at high doses, both compounds showed a trend toward a reduction in DOPA accumulation, albeit not significant, indicating some weak dopaminergic agonist activity. Compound **5c** has similar potency and efficacy to compound **1** in inducing the 5-HT behavioral syndrome (Figures 1a and 1b).

The substituted amides **14a–d** had good binding affinity for the 5-HT_{1A} receptor site with the exception of the di-*n*-propyl derivative **14d** (K_i = 434 nM). In addition, compound **14b** was found to display approximately 20 times higher affinity than **14a** and 10 times that of **14c**. In vivo, the compounds all seemed to exhibit partial agonist activity with a good separation from dopaminergic activity (see Table 2). The allyl derivative **14b** was approximately 4 times more potent than the propyl analog **14a** in decreasing 5-HTP accumulation. The benzyl analog **14c** was 7 times less potent. Recently, a chroman analog with an isopropyl-substituted amide was published as a selective 5-HT_{1A} agonist.[17] The authors also noted that these compounds has good bioavailability (17–21%) in dogs.

The ketones **15a–c** displayed potent 5-HT_{1A} agonist activity (see Tables 1 and 2). In fact, the methyl ketone

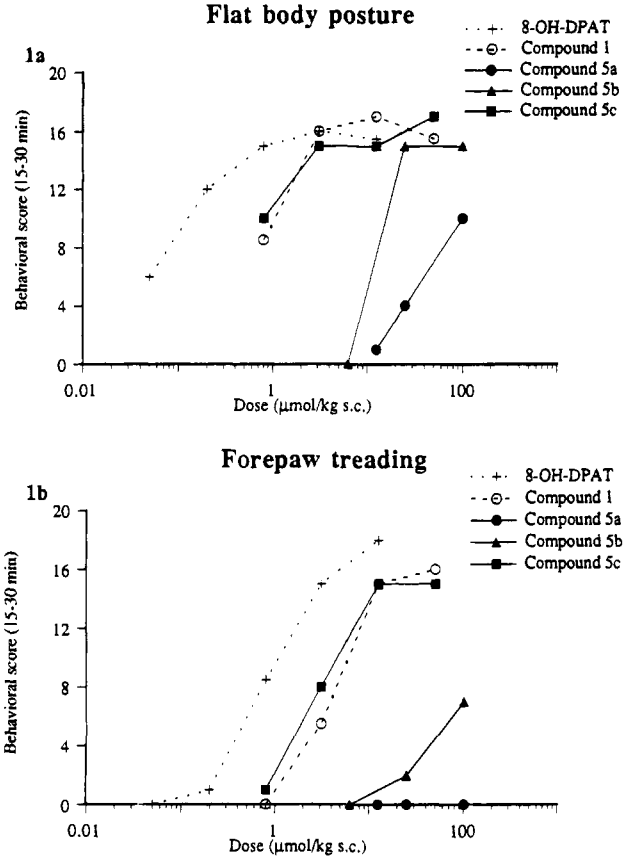


Figure 1. Effects of selected test compounds on the 5-HT behavioral syndrome in rats. Shown are the median values (n = 5) of the flat body posture (a) and forepaw treading (b).

15a was found to be the most potent 5-HT_{1A} agonist tested thus far. As shown in Table 2, **15a** was 20 times more potent than compound **1** and 5 times more potent than 8-OH-DPAT in reducing brain 5-HTP accumulation (ED_{50} = 0.0125 μmol/kg, sc). It displays a full intrinsic activity with a full behavioral syndrome including a pronounced straub tail, piano playing (forepaw treading), and flat body posture as low as 0.050 μmol/kg, sc. No dopaminergic effects were seen up to 3.1 μmol/kg (>168 times its ED_{50}). The propyl ketone (**15b**) and isopropyl ketone (**15c**) were approximately equipotent to compound **1** in vivo as 5-HT_{1A} agonists with full intrinsic activity (Table 2). The data generated so far on the 9-keto derivatives are consistent with the results published on 8-acyl aminotetralin derivatives.[18] The methyl ketone, in that study, was found to be much more active than the propyl ketone. However, the isopropyl ketone was found to show the longest duration of action following oral administration. In our hands the isopropyl analog was quite potent and up to the highest dose tested (3.1 μmol/kg) did not show any dopaminergic activity. It should also be noted that in the in vitro DA D_2 binding assay, all the 9-keto derivatives displayed moderate binding affinities (20–90-fold); however, no dopaminergic effects were seen in the in vivo biochemical assay.

Several compounds show reasonably high binding affinities but in many instances their metabolic stabilities vary widely (e.g., compounds **15a**, **15b**, and **15c**). The metabolic data obtained are shown in Table 1. The stabilities of all compounds tested are expressed relative to that of compound **1**. These data indicate the value of investigating the metabolic stabilities of a large number of compounds as part of the decision making process for drug candidate selection. In the case of the primary amides (**1** and **5a–l**), tertiary amine N-dealkylation is the most likely route of metabolism. This is known to be so for compounds **1**, **5a**, **5b**, and **5d** for which the secondary amine (**9**) was the major metabolite as detected by mass spectroscopy (data not shown). Hydroxylation of one of the aliphatic carbon atoms of the amine side chains may be important in the cases of the butyl and butenyl analogs (**5d** and **5f**). The increased stabilities of the methyl, ethyl, and allyl analogs (**5a, 5b**, and **5c**) would be predicted on the basis of the greater resistance of such groups to N-dealkylation relative to a propyl group as in compound **1**. The substituted amides **14b** and **14c** were also found to be unstable in this preparation.

In addition, the isopropyl ketone **15c** was much more stable (0.8 relative to compound **1**) than the corresponding methyl ketone **15a** (0.13) and propyl ketone **15b** (0.05). This would be consistent with the Lilly findings that the isopropyl ketone deriviative of DPAT had the longest duration of action in the 8-acylaminotetralin series.[18]

In conclusion, we find that 9-carboxamido derivatives with modification of the nitrogen substituent retain largely the selective 5-HT_{1A} receptor binding but are in most cases less potent than the propyl substituted analog. The N-allyl analog **5c** was found to be equipotent and stable to compound **1**. The intrinsic activity was lowered by the replacement of the N-propyl with a methyl or ethyl group. One of the most interesting compounds in this series is the N-ethyl analog **5b** which was found to be partial agonist with high metabolic stability. The substituted amides still retained agonist activity, even with the bulky N-benzylcarboxamide **14c**. The 9-keto derivatives are extremely potent full 5-HT_{1A} receptor agonists. The methyl ketone **15a** was found to be approximately 20 times more potent than compound **1** but considerably less stable in the in vitro assays.

Experimental Section

Synthesis. Analytical TLC was performed on Analtech 10 × 20 cm (250 μm) silica gel prescored glass plates which were developed in the solvent systems described. The plates were checked under ultraviolet light and developed by dipping in ammonium molybdate/cerium sulfate/10% sulfuric acid solution and heating on a hot plate or in an iodide chamber. ^1H NMR spectra were obtained at 300 MHz on a Bruker Model AM-300 spectrometer or a Varian XL 300 spectrometer in $CDCl_3$ solution unless noted otherwise. Chemical shifts (δ) are reported in parts per million relative to internal tetramethylsilane. The aliphatic protons in this tricyclic series consisted of multiple peaks, which have been listed as a range of chemical shifts. GC was performed with a Hewlett-Packard 5380A instrument with a flame-ionization detector. A fused silica column (11 m, 0.22 mm i.d.) coated with cross-linked SE54 (film thickness 0.3 mm, He gas, flow 40 cm/s) was used throughout. The program run on the GC was with initial temperature 150 °C, initial time = 0 and rate = 30 deg/min to 300 °C final temperature unless otherwise noted. GC/MS spectra were recorded on a HP5970A mass selective detector working at 70 eV and interfaced with a HP5700 gas chromatograph (fused silica column as previously described). Flash column chromatography and medium-pressure liquid chromatography were performed with 400 g to 1 kg of silica gel 60 (230–400 mesh) purchased from EM Science. All commercial chemicals were used as received from Aldrich unless noted otherwise. HPLC-grade methylene chloride, methanol, tetrahydrofuran, ethyl acetate, and hexane were used. All reactions were performed under nitrogen atmosphere. Melting

points were determined in open capillary tubes on a Mettler FP-62 melting point apparatus and are uncorrected. The amine-based products were converted into the HCl salts by dissolving the free base in a methanolic HCl solution.[19] The solvent was removed and azeotroped with toluene in vacuo followed by recrystallization from an appropriate solvent. Other physical data, such as IR (infrared spectra), MS (mass spectra), and elemental analyses were performed by the Physical and Analytical Chemistry Unit of the Upjohn Laboratories. The elemental analyses reported are within 0.4% of the calculated values.

***cis*-(3a*R*)-2,3,3a,4,5,9b-Hexahydro-9-bromo-3-methyl-1*H*-benz[*e*]indole (4a).** To a solution of **3** (5.77 g, 20 mmol), formaldehyde (37%, 15 mL), and HOAc (to pH <5) in THF/acetonitrile (3:1, 200 mL) was added sodium cyanoborohydride (2.5 g, 40 mmol). After 24 h of stirring at room temperature, the reaction was quenched with 20% NaOH and extracted with ethyl acetate (2 × 800 mL). The combined organic layers were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated to give a light yellow oil. The oil was purified by LC on 400 g of silica gel, eluting with hexane/acetone (3:1) and collecting 40 mL fractions afforded pure product as a solid (4.82 g, 90%). A small amount was converted into the HCl salt and recrystallized from ethyl acetate/ethanol to give a white solid: mp 199–200 °C; ^{1}H NMR δ 7.43 (d, J = 7.4 Hz, 1H), 7.14–7.04 (m, 2H), 2.99 (s, 3H), 4.18–1.60 (m, 10H); IR (mull) ν_{max} 1612 and 1592 cm^{-1}; MS, M$^+$ 265, other ions at m/z 208, 186, 128; $[\alpha]^{25}_D$ −120° (c 0.91, MeOH). Anal. ($C_{13}H_{16}$BrN·HCl) C, H, N.

***cis*-(3a*R*)-2,3,3a,4,5,9b-Hexahydro-9-bromo-3-ethyl-1*H*-benz[*e*]indole (4b).** A solution of **3** (2.0 g, 7 mmol) and triethylamine (8.8 mL, 63 mmol) in methylene chloride (50 mL) was stirred at room temperature. Acetyl chloride (1.5 mL, 21 mmol) was added slowly over 5 min. The yellow mixture was stirred at room temperature for 2 h. Then, methanol (5 mL) was added and stirred for 30 min. The reaction was quenched with saturated $NaHCO_3$ and extracted with methylene chloride (2 × 500 mL). The combined organic layers were washed with water, brine, dried ($MgSO_4$), filtered and concentrated. The crude yellow oil was purified by LC on 400 g of silica gel, eluting with hexane/acetone (1:1). Homogeneous fractions were collected to yield a yellow oil (1.86 g, 100%). LAH (0.53 g, 14 mmol) was suspended in THF (40 mL) and cooled to −20 °C followed by the slow addition of $AlCl_3$ (1.87 g, 14 mmol). The mixture was stirred at −20 °C for 10 min, followed by the addition of the amide dissolved in 10 mL THF over 5 min. The mixture was allowed to warm to room temperature, stirred for 2 h, and then diluted with 200 mL of THF while cooling to 0 °C. Saturated Na_2SO_4 was added dropwise until the solution became white. The mixture was transferred to a 2 L Erlenmeyer flask, diluted with ethyl acetate (1 L) and methanol (50 mL), and dried ($MgSO_4$). After stirring for 1 h, the solution was filtered and concentrated to give a light yellow oil. The crude oil was purified by LC on 400 g of silica gel, eluting with hexane/acetone (4:1) to give a light yellow oil (1.82 g, 93%). A small amount of this oil was converted into the HCl salt and recrystallized from ethyl acetate/hexane/methanol to yield an off-white solid: mp 161–162 °C; ^{1}H NMR δ 7.43 (d, J = 7.5 Hz, 1H), 7.11–7.09 (m, 2H), 4.18–1.52 (m, 12H), 1.61 (t, J = 7.3 Hz, 3H); IR (mull) ν_{max} 1610 and 1590 cm^{-1}; MS, M$^+$ 279, other ions at m/z 264, 178; $[\alpha]^{25}_D$ −97° (c 0.98, MeOH). Anal. ($C_{14}H_{18}$BrN·HCl) C, H, N.

***cis*-(3a*R*)-2,3,3a,4,5,9b-Hexahydro-9-bromo-3-allyl-1*H*-benz[*e*]indole (4c).** A solution of **3** (5.77 g, 20 mmol) and triethylamine (15 mL, 100 mmol) in DMF (160 mL) was treated with allyl bromide (3.3 mL, 40 mmol) at room temperature. The mixture was stirred at room temperature for 2 h, diluted with water (500 mL), and extracted with t-BuOMe (2 × 500 mL). The combined organic layers were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated to give a light yellow oil. The oil was purified by LC on 400 g of silica gel, eluting with hexane/ethyl acetate (9:1). Homogeneous fractions were collected and concentrated to yield a nearly colorless oil (5.52 g, 95%). A small amount of this oil was converted into the HCl salt and recrystallized from ethyl acetate/hexane/methanol to give a white solid: mp 178–179 °C; ^{1}H NMR δ 7.43 (d, J = 7.6 Hz, 1H), 7.13–7.04 (m, 2H) 6.52–5.48 (m, 3H), 4.24–1.58 (m, 12H); IR (mull) ν_{max} 1593 cm^{-1}; MS, M$^+$ 291, other ions at m/z 264, 128; $[\alpha]^{25}_D$ −95° (c 0.83, MeOH). Anal. ($C_{15}H_{18}$BrN·HCl) C, H, N.

***cis*-(3a*R*)-2,3,3a,4,5,9b-Hexahydro-9-bromo-3-*n*-butyl-1*H*-benz[*e*]indole (4d).** Compound **3** was reacted under the same conditions as in the preparation of **4b** using butyl chloride to afford the title compound in 91% yield. A small amount of the oil was converted to the HCl salt and but failed to recrystallize: ^{1}H NMR δ 7.38 (d, J = 7.8 Hz, 1H), 7.02 (d, J = 7.4 Hz, 1H), 6.93 (t, J = 8.3 Hz, 1H), 3.59 (q, J = 9.1 Hz, 1H), 3.12–1.28 (m, 16H), 0.93 (t, J = 9.3 Hz, 3H); IR (film) ν_{max} 1593 cm^{-1}; MS, M$^+$ 307, other ions at m/z 264, 128; $[\alpha]^{25}_D$ −161° (c 1.02, MeOH). Anal. ($C_{16}H_{22}$BrN) C, H, N.

***cis*-(3a*R*)-2,3,3a,4,5,9b-Hexahydro-9-bromo-3-(cyclopropylmethyl)-1*H*-benz[*e*]indole (4e).** Compound **3** was reacted under the same conditions as in the preparation of **4b** using cyclopropanecarbonyl chloride to afford the title compound in 85% yield as an oil. A small amount of the oil was converted into the HCl salt and recrystallized from ethyl acetate/hexane to give an off-white solid: mp 82–84 °C; ^{1}H NMR δ 7.43 (d, J = 8.7 Hz, 1H), 7.15–7.00 (m, 2H), 4.20–1.46 (m, 12H), 0.92–0.24 (m, 5H); IR (mull) ν_{max} 1593 cm^{-1}; MS, M$^+$ 305, other ions at m/z 264, 250, 128, 55; $[\alpha]^{25}_D$ −157° (c 1.06, MeOH). Anal. ($C_{16}H_{20}$BrN·HCl) C, H, N.

***cis*-(3a*R*)-2,3,3a,4,5,9b-Hexahydro-9-bromo-3-(3-butenyl)-1*H*-benz[*e*]indole (4f).** A mixture of **3** (2.88 g, 10 mmol), 4-bromo-1-butene (3 mL, 30 mmol), and Na_2CO_3 (4.23 g, 40 mmol) in acetonitrile (40 mL) was heated at 90 °C for 24 h. The mixture was filtered and rinsed with methylene chloride, and the filtrate was diluted with methylene chloride (to 800 mL). The organic layer was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated. The resulting yellow oil was purified by LC on 400 g of silica gel, eluting with hexane/acetone (9:1). Homogeneous fractions yielded a light yellow oil (1.84 g, 60%). A small amount was converted into the HCl salt and recrystallized from ethyl acetate/methanol to yield an off-white solid: mp 155–156 °C; ^{1}H NMR δ 7.42 (d, J = 7.8 Hz, 1H), 7.14–7.00 (m, 2H), 5.82–5.14 (m, 3H), 4.22–1.55 (m, 14H); IR (mull) ν_{max} 1599 cm^{-1}; MS, ions at m/z 264, 184, 128; $[\alpha]^{25}_D$ −89° (c 0.33, MeOH). Anal ($C_{16}H_{20}$BrN·HCl) C, H, N.

***cis*-(3a*R*)-2,3,3a,4,5,9b-Hexahydro-9-bromo-3-(2-methoxyethyl)-1*H*-benz[*e*]indole (4g).** Compound **3** was reacted under the same conditions as in the preparation of **4f** using 2-bromoethyl methyl ether to afford the title compound **4g** in 84% yield as an oil. A small amount was converted into the HCl salt and recrystallized from ethyl acetate/methanol to yield a white solid: mp 132–133 °C; ^{1}H NMR δ 7.43 (d, J = 6.8 Hz, 1H), 7.13–7.00 (m, 2H), 3.41 (s, 3H), 4.04–1.80 (m, 14H); IR (mull) ν_{max} 1589, 1557 cm^{-1}; MS, M$^+$ 309, other ions at m/z 264, 128; $[\alpha]^{25}_D$ −79° (c 1.03, MeOH). Anal. ($C_{15}H_{20}$BrNO·HCl) C, H, N.

***cis*-(3a*R*)-2,3,3a,4,5,9b-Hexahydro-9-bromo-3-(3-fluoropropyl)-1*H*-benz[*e*]indole (4h).** Compound **3** was reacted under the same conditions as in the preparation of **4f** using 1-bromo-3-fluoropropane to afford the title compound **4h** in 90% yield as a colorless oil. This oil failed to crystallize as the HCl salt: ^{1}H NMR δ 7.38 (d, J = 7.8 Hz, 1H), 7.03 (d, J = 7.4 Hz, 1H), 6.94 (t, J = 7.7 Hz, 1H), 4.68–4.42 (m, 2H), 3.62 (q, J = 9.0 Hz, 1H), 3.12–1.22 (m, 13H); IR (film) ν_{max} 1593, 1561 cm^{-1}; MS, M$^+$ 311 , other ions at m/z 264, 128; $[\alpha]^{25}_D$ −168° (c 0.96, MeOH). Anal. ($C_{15}H_{19}$BrFN) C, H, N.

***cis*-(3a*R*)-2,3,3a,4,5,9b-Hexahydro-9-bromo-3-(3-chloropropyl)-1*H*-benz[*e*]indole (4i) and Bis[(3a*R*-*cis*)-2,3,3a,4,5,-9b-hexahydro-9-bromo-1*H*-benz[*e*]indolyl]-1,3-propane (6).** Compound **3** was reacted under the same conditions as in the preparation of **4f** using 1-bromo-3-chloropropane to afford the title compound **4i** in 23% yield as a colorless oil. A small amount was converted into the HCl salt and recrystallized from ethyl acetate/methanol to give a white solid: mp 142–143 °C; ^{1}H NMR δ 7.44 (d, J = 7.4 Hz, 1H), 7.12–7.07 (m, 2H), 3.71 (t, J = 6.1 Hz, 2H), 4.18–1.62 (m, 13H); IR (mull) ν_{max} 1593 cm^{-1}; MS, a mixture of chlorobromo (M$^+$ 327) and dibromo (M$^+$ 313); $[\alpha]^{25}_D$ −80° (c 0.95, MeOH). Anal ($C_{15}H_{19}$BrClN·HCl): C, 45.75, H, N. Note: Product **4i** was contaminated with the 3-bromopropyl analog as indicated by the CHN and MS analysis. A second product, dimer **6**, was

also obtained and recrystallized from ethyl acetate/hexane to give a white solid (0.75 g): mp 100–101 °C; ^{1}H NMR δ 7.39 (d, J = 7.8 Hz, 2H), 7.04 (d, J = 7.4 Hz, 2H), 6.94 (t, J = 7.7 Hz, 2H), 3.68–3.52 (q, J = 9.1 Hz, 2H), 3.12–1.24 (m, 26H); IR (mull) ν_{max} 1592 and 1561 cm^{-1}; MS, M$^+$ 542, other ions at m/z 291, 264, 128. Anal. ($C_{27}H_{32}BrN_2$) C, H, N. Note that the dimerization could be lessened by heating at 60 °C for 4 h.

***cis*-(3a*R*)-2,3,3a,4,5,9b-Hexahydro-9-bromo-3-(3-methyl-2-butenyl)-1*H*-benz[*e*]indole (4j).** Compound **3** was reacted under the same conditions as in the preparation of **4c** using 4-bromo-2-methyl-2-butene to afford the title compound **4j** in 92% yield as a colorless oil. A small amount was converted into the HCl salt and recrystallized from EtOAc/MeOH to give a white solid: mp 152–153 °C; ^{1}H NMR δ 7.43 (d, J = 7.6 Hz, 1H), 7.15–7.00 (m, 2H), 5.61 (t, J = 7.7 Hz, 1H), 1.89 (s, 3H), 1.78 (s, 3H), 3.92–1.78 (m, 12H); IR (mull) ν_{max} 1595, 1563 cm^{-1}; MS, M$^+$ 319, other ions at m/z 304, 276, 251, 69; $[\alpha]^{25}_D$ −92° (c 0.98, MeOH). Anal. ($C_{17}H_{22}BrN$·HCl) C, H, N.

***cis*-(3a*R*)-2,3,3a,4,5,9b-Hexahydro-3-methyl-1*H*-benz[*e*]indole-9-carboxamide (5a).** A three-neck round-bottomed flask containing THF (20 mL) was cooled to −78 °C, and *t*-BuLi (10 mL, 16.8 mmol, 1.7 M in pentane) was added dropwise over 5 min. The resulting yellow solution was stirred for 10 min, and **4a** (2.13 g, 8 mmol, in 10 mL of THF) was added over 10 min. The mixture was stirred for 10 min, and TMSNCO (1.6 mL, 12 mmol, freshly distilled over CaH) was added *via* syringe. The mixture was allowed to warm to room temperature, stirred for 1 h, quenched with saturated NH_4Cl, and treated with 20% NaOH to pH >13. The mixture was extracted with methylene chloride (2 × 500 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to give an off-white solid. The solid was recrystallized from ethyl acetate (0.7 g). The mother liquor was purified by LC on 400 g of silica gel, eluting with methylene chloride/methanol and 4 M ammonia (9:1). Homogeneous fractions were combined and concentrated to yield a solid which was recrystallized from ethyl acetate/hexane to give a white solid. The two solids were combined together and dried in the vacuum oven (1.6 g, 87%): mp 191–192 °C; ^{1}H NMR δ 7.25 (d, J = 5.4 Hz, 1H), 7.18 (d, J = 7.1 Hz, 1H), 7.10 (t, J = 7.4 Hz, 1H), 3.99 (q, J = 9.1 Hz, 1H), 3.08–1.38 (m, 10H), 2.39 (s, 3H); IR (mull) ν_{max} 3382, 3309, 1642, 1611, 1585 cm^{-1}; MS, M$^+$ 230, other ions at m/z 212, 198, 170, 128, 115; $[\alpha]^{25}_D$ −241° (c 0.94, MeOH). Anal. ($C_{14}H_{18}N_2O$) C, H, N.

***cis*-(3a*R*)-2,3,3a,4,5,9b-Hexahydro-3-ethyl-1*H*-benz[*e*]indole-9-carboxamide (5b).** This compound was prepared from **4b** (1.6 g, 5.8 mmol), using the same procedure described in the preparation of **5a** to yield a solid (0.85 g, 60.7%): mp 172–173 °C; ^{1}H NMR δ 7.25 (d, J = 6.6 Hz, 1H), 7.17 (d, J = 7.1 Hz, 1H), 7.13 (t, J = 7.4 Hz, 1H), 3.99 (q, J = 9.1 Hz, 1H), 3.18–1.42 (m, 12H), 1.15 (t, J = 7.3 Hz, 3H); IR (mull) ν_{max} 3381, 3301, 1644, 1612, 1586 cm^{-1}; MS, M$^+$ 244, other ions at m/z 229, 212, 198, 170, 128, 115; $[\alpha]^{25}_D$ −220° (c 0.87, MeOH). Anal. ($C_{15}H_{20}N_2O$) C, H, N.

***cis*-(3a*R*)-2,3,3a,4,5,9b-Hexahydro-3-(2-propenyl)-1*H*-benz[*e*]indole-9-carboxamide (5c).** This compound was prepared from **4c** (2.34 g, 8 mmol), using the same procedure described in the preparation of **5a** to yield a solid (1.72 g, 84%): mp 170–171 °C; ^{1}H NMR δ 7.24 (d, J = 7.6 Hz, 1H), 7.17 (d, J = 7.1 Hz, 1H), 7.10 (t, J = 7.4 Hz, 1H), 6.05–5.02 (m, 3H), 3.94 (q, J = 9.0 Hz, 1H), 3.54–1.35 (m, 12H); IR (mull) ν_{max} 3272, 3297, 1647, 1622, 1587 cm^{-1}; MS, M$^+$ 256, other ions at m/z 229, 198, 170, 128, 115; $[\alpha]^{25}_D$ −221° (c 0.86, MeOH). Anal. ($C_{16}H_{20}N_2O$) C, H, N.

***cis*-(3a*R*)-2,3,3a,4,5,9b-Hexahydro-3-*n*-butyl-1*H*-benz[*e*]indole-9-carboxamide (5d).** This compound was prepared from **4d** (1.85 g, 6 mmol), using the same procedure described in the preparation of **5a** to yield a solid (1.4 g, 86%): mp 165–166 °C; ^{1}H NMR d 7.24 (d, J = 8.7 Hz, 1H), 7.17 (d, J = 6.8 Hz, 1H), 7.10 (t, J = 7.4 Hz, 1H), 3.92 (q, J = 9.1 Hz, 1H), 3.12–1.24 (m, 16H), 0.93 (t, J = 7.3 Hz, 3H); IR (mull) ν_{max} 3311, 3208, 1638, 1633, 1586 cm^{-1}; MS, M$^+$ 272, other ions at m/z 254, 229, 212, 200, 183, 155, 129; $[\alpha]^{25}_D$ −219° (c 0.68, MeOH). Anal. ($C_{17}H_{24}N_2O$) C, H, N.

***cis*-(3a*R*)-2,3,3a,4,5,9b-Hexahydro-3-(methylcyclopropyl)-1*H*-benz[*e*]indole-9-carboxamide (5e).** This compound was prepared from **4e** (1.84 g, 6 mmol), using the same procedure described in the preparation of **5a** to yield a solid (1.42 g, 89%): mp 180–181 °C; ^{1}H NMR δ 7.24 (d, J = 8.0 Hz, 1H), 7.17 (d, J = 6.9 Hz, 1H), 7.10 (t, J = 7.4 Hz, 1H), 3.93 (q, J = 9.1 Hz, 1H), 3.28–1.42 (m, 12H), 1.02–0.12 (m, 5H); IR (mull) ν_{max} 3394, 3289, 1627, 1609, 1583 cm^{-1}; MS, M$^+$ 270, other ions at m/z 252, 229, 198, 184, 170, 155; $[\alpha]^{25}_D$ −210° (c 0.9, MeOH). Anal. ($C_{17}H_{22}N_2O$) C, H, N.

***cis*-(3a*R*)-2,3,3a,4,5,9b-Hexahydro-3-(3-butenyl)-1*H*-benz[*e*]indole-9-carboxamide (5f).** This compound was prepared from **4f** (1.53 g, 5 mmol) using the same procedure described in the preparation of **5a** to yield a solid (1.2 g, 89%): mp 166–167 °C; ^{1}H NMR δ 7.24 (d, J = 8.2 Hz, 1H), 7.17 (d, J = 7.0 Hz, 1H), 7.10 (t, J = 7.4 Hz, 1H), 5.92–4.92 (m, 3H), 3.93 (q, J = 9.1 Hz, 1H), 3.14–1.40 (m, 14H); IR (mull) ν_{max} 3313, 3293, 1645, 1621, 1587 cm^{-1}; MS, M$^+$ 270, other ions at m/z 229, 200, 183, 171, 155; $[\alpha]^{25}_D$ −228° (c 0.98, MeOH). Anal. ($C_{17}H_{22}N_2O$) C, H, N.

***cis*-(3a*R*)-2,3,3a,4,5,9b-Hexahydro-3-(2-methoxyethyl)-1*H*-benz[*e*]indole-9-carboxamide (5g).** This compound was prepared from **4g** (2.3 g, 7.5 mmol) using the same procedure in the preparation of **5a** to yield a solid (1.74 g, 84%): mp 174–175 °C; ^{1}H NMR δ 7.24 (d, J = 8.1 Hz, 1H), 7.17 (d, J = 6.7 Hz, 1H), 7.09 (t, J = 8.2 Hz, 1H), 3.93 (q, J = 9.1 Hz, 1H), 3.38 (s, 3H), 3.62–1.42 (m, 13H); IR (mull) ν_{max} 3376, 3198, 1639, 1628, 1608, 1583 cm^{-1}; MS, M$^+$ 274, other ions at m/z 229, 212, 200, 183, 171, 155; $[\alpha]^{25}_D$ −201° (c 1.12, MeOH). Anal. ($C_{16}H_{22}N_2O_2$) C, H, N.

***cis*-(3a*R*)-2,3,3a,4,5,9b-Hexahydro-3-(3-fluoropropyl)-1*H*-benz[*e*]indole-9-carboxamide (5h).** This compound was prepared from **4h** (2.0 g, 6.4 mmol) using the same procedure described in the preparation of **5a** to yield a solid (1.5 g, 85%): mp 134–135 °C; ^{1}H NMR δ 7.25 (d, J = 7.6 Hz, 1H), 7.17 (d, J = 6.7 Hz, 1H), 7.12 (t, J = 7.5 Hz, 1H), 4.72–4.42 (m,2H), 3.95 (q, J = 9.1 Hz, 1H), 3.12–1.42 (m, 13H); IR (mull) ν_{max} 3386, 3201, 1638, 1626, 1582 cm^{-1}; MS, M$^+$ 276, other ions at m/z 229, 212, 200, 183, 170, 155; $[\alpha]^{25}_D$ −219° (c 0.78, MeOH). Anal. ($C_{16}H_{21}FN_2O$) C, H, N.

***cis*-(3a*R*)-2,3,3a,4,5,9b-Hexahydro-3-(3-chloropropyl)-1*H*-benz[*e*]indole-9-carboxamide (5i).** This compound was prepared from **4i** (2.0 g, 6 mmol), using the same procedure described in the preparation of **5a** to yield a solid (1.2 g, 68%): mp 140–141 °C; ^{1}H NMR δ 7.24 (d, J = 7.6 Hz, 1H), 7.17 (d, J = 6.7 Hz, 1H), 7.12 (t, J = 7.5 Hz, 1H), 3.92 (q, J = 9.1 Hz, 1H), 3.72–3.58 (m, 2H), 3.12–1.38 (m, 13H); IR (mull) ν_{max} 3380, 3292, 1647, 1627, 1607, 1583 cm^{-1}; MS, M$^+$ 292, other ions at m/z 229, 212, 200, 183, 155; $[\alpha]^{25}_D$ −235° (c 0.42, MeOH). Anal. ($C_{16}H_{21}ClN_2O$) C, H, N.

***cis*-(3a*R*)-2,3,3a,4,5,9b-Hexahydro-3-(3-methyl-2-butenyl)-1*H*-benz[*e*]indole-9-carboxamide (5j).** This compound was prepared from **4j** (2.4 g, 7.5 mmol), using the same procedure described in the preparation of **5a** to yield a solid (1.8 g, 85%) : mp 144–145 °C; ^{1}H NMR δ 7.24 (d, J = 7.6 Hz, 1H), 7.13 (d, J = 6.7 Hz, 1H), 7.11 (t, J = 7.6 Hz, 1H), 5.25 (m, 1H), 3.95 (q, J = 9.1 Hz, 1H), 1.74 (s, 3H), 1.68 (s, 3H), 3.52–1.42 (m, 11H); IR (mull) ν_{max} 3387, 3285, 1646, 1618, 1587 cm^{-1}; MS, M$^+$ 284, other ions at m/z 269, 241, 229, 216, 198, 187, 170, 155. ; $[\alpha]^{25}_D$ −202° (c 0.95, MeOH). Anal. ($C_{18}H_{24}N_2O$) C: calcd, 76.02; found, 75.56; H, N.

***cis*-(3a*R*)-2,3,3a,4,5,9b-Hexahydro-3-(1(*R*)-methylbenzyl)-1*H*-benz[*e*]indole-9-carboxamide (8).** This compound was prepared from **7** (3.92 g, 11.0 mmol), using the same procedure described in the preparation of **5a**. The crude yellow oil was purified by LC on 400 g of silica gel eluting with hexane/acetone (1:1) and collecting 40 mL fractions. Homogeneous fractions were combined and concentrated to give a light yellow oil (3.24 g, 92%): ^{1}H NMR δ 7.94–7.05 (m, 8H), 6.19/5.92 (broad s, 2H), 4.00–1.50 (m, 11H), 1.44 (d, J = 6.7 Hz, 3H); IR (mull) ν_{max} 3424, 3331, 1656, 1608, 1587 cm^{-1}; MS, M$^+$ 320, other ions at m/z 305, 243, 215, 198, 105; $[\alpha]^{25}_D$ −75° (c 0.91, MeOH). Anal. ($C_{21}H_{24}N_2O$) C: calcd, 78.71; found, 76.21; H, N: calcd, 8.74; found, 8.10.

***cis*-(3a*R*)-2,3,3a,4,5,9b-Hexahydro-1*H*-benz[*e*]indole-9-carboxamide (9).** A mixture of **8** (1.92 g, 6 mmol), $NH_4^+CO_2^-$ (1.9 g, 30 mmol), and Pd/C (10%, 1.0 g) in methanol (60 mL)

was stirred at room temperature for 48 h. The reaction did not proceed, so the mixture was filtered and restarted. After 24 h, the mixture was filtered through a layer of SolkaFloc and concentrated. The resulting yellow solid was recrystallized from ethyl acetate/methanol to give an off-white solid (0.75g, 58%): mp 179–180 °C; ^{1}H NMR (CD_3OD) δ 7.28–7.12 (m, 3H), 3.88–1.48 (m, 10H); IR (mull) ν_{max} 3359, 3313, 1687, 1643, 1630, 1607, 1583 cm^{-1}; MS, M$^+$ 216, other ions at m/z 199, 198, 187, 170, 156, 128.

***cis*-(3a*R*)-2,3,3a,4,5,9b-Hexahydro-3-isobutyl-1*H*-benz[*e*]indole-9-carboxamide (5k).** Compound **9** (2.5 mmol) was reacted under the same conditions as in the preparation of **4a** using isobutyrlaldehyde to afford the title compound in 47% yield. The maleic acid salt was made and recrystallized from ethyl acetate/methanol to give a white solid: mp 202–203 °C; ^{1}H NMR (CD_3OD) δ 7.38–7.18 (m, 3H), 6.24 (s, 2H), 4.32–1.72 (m, 13H), 1.12, 1.11, 1.10, 1.09 (dd, J = 7.4 Hz, 6H); IR (mull) ν_{max} 1586 and 1577 cm^{-1}; MS, M$^+$ 272, other ions at m/z 229, 212, 200, 183, 171, 155; $[\alpha]^{25}_D$ −108° (c 0.94, MeOH). Anal. ($C_{17}H_{24}N_2O{\cdot}C_4H_4O_4$) C, H, N.

***cis*-(3a*R*)-2,3,3a,4,5,9b-Hexahydro-3-propargyl-1*H*-benz[*e*]indole-9-carboxamide (5l).** A solution of **9** (0.7 g, 2.1 mmol), propargyl chloride (0.74 mL, 10.2 mmol), and triethylamine (2.8 mL, 20.4 mmol) in DMF (5 mL) was heated at 60 °C for 1 h. The excess reagent was removed *in vacuo*, and then treated with 10% NaOH (10 mL) and water (200 mL), and extracted with methylene chloride (2 × 400 mL). The combined organic layers were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated. The resulting oil was purified by LC on 200 g of silica gel, eluting with ca. 1 L of methylene chloride followed by methylene chloride/methanol (20:1). Homogeneous fractions were combined and concentrated to yield an off-white solid (0.36 g, 67%). The solid was recrystallized from ethyl acetate/hexane to give an off-white solid: mp 152–153 °C; ^{1}H NMR δ 7.26 (d, J = 7.5 Hz, 1H), 7.18 (d, J = 7.5 Hz, 1H), 7.10 (t, J = 7.5 Hz, 1H), 5.75 (bs, 2H), 3.97 (q, J = 9.2 Hz, 1H), 3.55 (q of d, J = 16.8 and 2.4 Hz, 2H), 3.12–2.42 (m, 6H), 2.21 (t, J = 2.4 Hz, 1H), 1.95–1.42 (m, 2H); IR (mull) ν_{max} 3299, 3290, 3312, 2122, 2102, 1650, 1624, 1586 cm^{-1}; M$^+$ 254, other ions at m/z 236, 226, 215, 198, 187, 170, 155; $[\alpha]^{25}_D$ −231° (c 1.0, MeOH) Anal. ($C_{16}H_{18}N_2O$) C, H, N.

***cis*-(3a*R*)-2,3,3a,4,5,9b-Hexahydro-3-*n*-propyl-1*H*-benz[*e*]indole-9-carboxylic Acid Lithium Salt (12).** To a dry three-neck round-bottomed flask was added THF (40 mL), and the solution was cooled to −78 °C. A solution of *tert*-butyllithium (24 mL, 40.8 mmol, 1.7 M in pentane, Aldrich) was added (yellow color), and the mixture was stirred for ca. 10 min. A precipitate fell out of the reaction mixture. A solution of 11 (6 g, 20.4 mmol) in THF (60 mL) was added dropwise, and the mixture was stirred for an additional 20 min. Gaseous CO_2 was bubbled through the solution with a constant flow for 30 min. The reaction was quenched with methanol (5 mL), warmed to room temperature, and concentrated *in vacuo* to yield a pale solid (12 g). The material was used as is in the next reaction.

***cis*-(3a*R*)-2,3,3a,4,5,9b-Hexahydro-3-*n*-propyl-1*H*-benz[*e*]indole-9-carboxylic Acid Chloride (13).** In a 250 mL round-bottomed flask, was dissolved **12** (5.41 g, 20.4 mmol) in THF (25 mL), methylene chloride (75 mL), and DMF (5 drops). Oxalyl chloride (3.56 mL, 20.8 mmol) was added (gas evolution), and the mixture was stirred for 4 h (milky solution). The solution was concentrated *in vacuo*. The crude material from this reaction was separated into four portions and reacted with the appropriate amines (see procedures for **14a–d**).

***cis*-(3a*R*)-2,3,3a,4,5,9b-Hexahydro-3-*n*-propyl-1*H*-benz[*e*]indole-9-N-*n*-propylcarboxamide (14a).** To a solution of **13** (1.4 g, 5.1 mmol, assuming 100% conversion to 13) in methylene chloride/THF (1:1, 50 mL) was added propylamine (1.67 mL, 20.4 mmol). There was a color change of brown to yellow. The mixture was stirred at room temperature overnight. The solution was quenched with 1 N NaOH and extracted with methylene chloride (3 × 100 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to yield an oily yellow solid (1.72 g). From flash chromatography (100 g of silica gel), eluting with methylene chloride/methanol (95:5), three main fractions were collected. First were some mixed fractions of product and the 9H compound (0.67 g, 43%), followed by the desired product (630 mg, 41%): mp 98–99 °C; ^{1}H NMR δ 7.15–7.04 (m, 3H), 5.97 (bs, 1H), 3.94–3.85 (q, J = 9.0 Hz, 1H), 3.37–3.29 (m, 2H), 3.16–3.11 (t, J = 7.6 Hz, 1H), 2.93–2.70 (m, 3H), 2.57–2.54 (t, J = 4.2 Hz, 0.5 H), 2.51–2.49 (t, J = 4.2 Hz, 0.5 H), 2.40–2.23 (m, 3H), 1.96–1.90 (m, 1H), 1.64–1.46 (m, 6H), 0.97–0.88 (m, 6H); IR (mull) ν_{max} 3300, 2767, 2743, 1636, 1587, 1534 cm^{-1}; MS M$^+$ 300, other ions at m/z 271, 257, 242, 212, 200, 184, 169, 155, 141, 128, 11, 106, 41; $[\alpha]^{25}_D$ −184° (c 0.464, MeOH). Anal. ($C_{19}H_{28}N_2O$) C, H, N.

***cis*-(3a*R*)-2,3,3a,4,5,9b-Hexahydro-3-*n*-propyl-1*H*-benz[*e*]indole-9-(2-propenyl)carboxamide (14b).** Compound **13** (1.4 g, 5.1 mmol) was reacted under the same conditions as in the preparation of **14a** using allylamine to afford the title compound in 30% yield which was a solid after concentration: mp 85–86 °C; ^{1}H NMR δ 7.20–7.07 (m, 3H), 5.99–5.87 (m, 2H), 5.30–5.17 (m, 2H), 4.12–3.90 (m, 3H), 3.15 (m, 1H), 2.91–2.71 (m, 3H), 2.57–2.51 (m, 1H), 2.36–2.33 (m, 3H), 1.93 (m, 1H), 1.62–1.52 (m, 4H), 0.96–0.91 (t, J = 7.3 Hz, 3H); IR (mull) ν_{max} 3311, 1650, 1640, 1591, 1536 cm^{-1}; MS M$^+$ 298, other ions at m/z 269, 240, 212, 198, 183, 169, 155, 141, 128, 115; $[\alpha]^{25}_D$ −138° (c 0.7392, MeOH).

***cis*-(3a*R*)-2,3,3a,4,5,9b-Hexahydro-3-*n*-propyl-1*H*-benz[*e*]indole-9-*N*-benzylcarboxamide (14c).** Compound **13** (1.4 g, 5.1 mmol) was reacted under the same conditions as in the preparation of **14a** using benzylamine to afford the title compound in 41% yield which was a solid after concentration: mp 122–124 °C; ^{1}H NMR δ 7.39–7.08 (m, 8H), 6.1 (bs, 1H), 4.65–4.61 (t, J = 5.8 Hz, 2H), 3.90–3.83 (q, J = 9.0 Hz, 1H), 3.1–1.4 (m, 13H), 0.97–0.92 (t, J = 7.3 Hz, 3H); IR (mull) ν_{max} 3319, 1641, 1527, 1496 cm^{-1}; MS, M$^+$ 348, other ions at m/z 319, 290, 257, 240, 212, 91; $[\alpha]^{25}_D$ −132° (c 0.6911, MeOH).

***cis*-(3a*R*)-2,3,3a,4,5,9b-Hexahydro-3-*n*-propyl-1*H*-benz[*e*]indole-9-*N*,*N*-di-*n*-propylcarboxamide (14d).** Compound **13** (1.4 g, 5.1 mmol) was reacted under the same conditions as in the preparation of **14a**, using di-*n*-propylamine to afford the title compound in 30% yield as an oil: ^{1}H NMR δ 7.09–6.98 (m, 3H), 3.8–3.5 (m, 1H), 3.3–2.6 (m, 7H), 2.54–2.40 (m, 1H), 2.3–2.0 (m, 2H), 1.95–1–85 (m, 1H), 1.73–1.41 (m, 8H), 1.01–0.9 (m, 6H), 0.78–0.65 (dt, J = 7.3 Hz, 3H); IR (liq) ν_{max} 2873, 1635, 1592, 1456, 1420 cm^{-1}; MS, M$^+$ 342, other ions at m/z 313, 299, 284, 258, 242, 212, 198, 184, 171, 155, 142, 128, 107; $[\alpha]^{25}_D$ −132° (c 0.468, MeOH).

***cis*-(3a*R*)-2,3,3a,4,5,9b-Hexahydro-3-*n*-propyl-1*H*-benz[*e*]indole-9-yl Methyl Ketone (15a).** To a solution of 1 (500 mg, 1.9 mmol) in diethyl ether (20 mL) at 40 °C was added methylmagnesium bromide (3.87 mL, 11.61 mmol, 3 M solution in ether, Aldrich). The color changed to yellow, and a precipitate began to crash out of the solution. The mixture was refluxed for 56 h. The reaction was quenched by adding water dropwise and 10% HCl, followed by 1 N NaOH, and extracted with ethyl acetate (4 × 75 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and evaporated to yield an oil (480 mg). This oil was confirmed to be the imine ($CH_3C{=}NH$). The imine was hydrolyzed using 6 N HCl by gently warming on a stirplate to form the methyl ketone **15a**. The mixture was basified and extracted to yield the product as an yellow oil (382 mg, 78%): ^{1}H NMR δ 7.45–7.43 (d, J = 6.0 Hz, 1H), 7.23–7.12 (m, 2H), 4.04–3.95 (q, J = 9.0 Hz, 1H), 3.19–1.26 (m, 13H), 2.58 (s, 3H), 0.96–0.91 (t, J = 7.3 Hz, 3H); ^{13}C NMR δ 203.4, 140.1, 140.0, 138.5, 131.6, 126.6, 124.8, 62.1, 56.7, 52.7, 38.4, 34.4, 30.5, 27.0, 26.5, 21.8, 12.2; MS, M$^+$ 257, other ions at m/z 228, 181, 128, 106; $[\alpha]^{25}_D$ −209° (c 1.8, MeOH); GC t_R = 2.75 min (98%).

***cis*-(3a*R*)-2,3,3a,4,5,9b-Hexahydro-3-*n*-propyl-1*H*-benz[*e*]indol-9-yl *n*-Propyl Ketone (15b).** Compound 1 (500 mg, 1.9 mmol) was reacted under the same conditions as in the preparation of **15a** using propylmagnesium chloride to afford the title compound in 83% yield as a brown oil: ^{1}H NMR δ 7.39–7.33 (d, 7.8 Hz, 1H), 7.17–7.12 (m, 2H), 3.92–3.85 (q, J = 9.1 Hz, 1H), 3.04 (t, J = 9.0 Hz, 1H), 2.9–1.3 (m, 16H), 0.98 (t, J = 7.4 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C NMR δ 206.3, 140.1, 139.5, 139.2, 125.7, 124.8, 62.1, 56.7, 52.7, 44.6, 38.4, 34.7, 27.1, 26.6, 21.8, 17.7, 13.9, 12.1; MS, M$^+$ 285, other ions at m/z 256, 227, 209, 184, 167, 128, 115; $[\alpha]^{25}_D$ −184° (c 2.04, MeOH): GC t_R = 3.36 min (99%).

***cis*-(3a*R*)-2,3,3a,4,5,9b-Hexahydro-3-*n*-propyl-1*H*-benz[*e*]indol-9-yl Isopropyl Ketone (15c).** Compound 1 (500 mg, 1.9 mmol) was reacted under the same conditions as in the preparation of **15a** using isopropylmagnesium chloride to afford the title compound in 66% yield as a brown oil: ^{1}H NMR δ 7.34–7.14 (m, 3H), 3.85–3.79 (t, J = 9.0 Hz, 1H), 3.38–1.34 (m, 15H), 1.21–1.17 (m, 6H), 0.98–0.93 (t, J = 7.4 Hz, 3H); ^{13}C NMR δ 206.4, 140.3, 139.8, 138.6, 130.9, 125.4, 124.8, 62.2, 56.8, 52.7, 39.3, 38.5, 35.1, 27.4, 26.7, 21.8, 19.1, 18.6, 12.1; MS M^+ 285, other ions at m/z 256, 209, 184, 167, 155, 141, 128, 115; $[\alpha]^{25}_D$ −170° (c 2.14, MeOH); GC t_R = 3.24 min (97%).

Animals. Animals used in the biochemical and motor activity experiments were male rats of the Sprague–Dawley strain (ALAB, Sollentuna, Sweden), weighing 200–300 g. The rats were kept five per cage under controlled environmental conditions (22 °C, 55% relative humidity with lights on 5 a.m. to 7 p.m.) and with free access to water and food, at least 1 week from arrival until used in the experiments. The experiments were performed between 9 a.m. and 1 p.m.

Materials. 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 solution had neutral pH at the time of injection (except for the solutions of reserpine; pH 4).

5-HT$_{1A}$ and D$_2$ Binding Assays in Vitro. Competition binding experiments employed 11 dilutions of test compounds competing with the 5-HT$_{1A}$ agonist [^{3}H]-8-OH-DPAT (85 Ci/mmol, 1.2 nM) or the D$_2$ agonist [^{3}H]U86170[20] (62 Ci/mmol, 2 nM) for 5-HT$_{1A}$ and D$_2$ binding sites, respectively (Table 1). In each cloned mammalian receptors expressed in CHO-K1 cells were used.[21] IC$_{50}$ values were estimated by fitting the data to a one-site model by nonlinear least squares minimization. K_i values were calculated with the Cheng–Prushoff equation.[22]

Determination of in Vitro Metabolic Stability. Rat hepatocytes were prepared by a modification of the collagenase perfusion method.[23] In vitro clearance (CL$_{int}$) was assessed following incubation of each compound at three concentrations in rat hepatocyte suspensions (5 million cells mL^{-1}). The initial rate of metabolism at each substrate concentration was calculated from each concentration/time curve and values of the apparent V_{max} and K_m of metabolism of each compound were obtained from application of the initial rate data to the direct linear plot procedure.[24] V_{max}/K_m = intrinsic clearance (CL$_{int}$). A standard compound (1) was incubated on each occasion and the metabolic stability of each test compound was compared to that of the standard (CL$_{int}$ standard/CL$_{int}$ test compound = relative metabolic stability). Using this procedure results obtained on different days could be compared.

Motor Activity. The motor activity was measured by means of photocell recordings (M/P 40 Fc Electronic Motility Meter, Motron Products, Stockholm) as previously described.[12] Eighteen hours prior to the motility testing (carried out between 9 a.m. and 1 p.m.), the rats were subcutaneously injected in the neck region with reserpine (5 mg/kg). The different test compounds were also administered subcutaneously in the neck region. Immediately after drug administration, the rats were placed in the test cages (one rat/cage) and put into the motility meters. Motor activity was then followed and recorded for the subsequent 30 min (control values 3 ± 1 accumulated counts /30 min, mean ± SEM, n = 13). Observations of gross behavior were made throughout the activity sessions through semitransparent mirrors.

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.[25] 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 (ED50 value) of the DOPA (the maximal effect, expressed as percent of controls, was limbic system −65%, striatum = −80% and the hemispheres = −50%) and the 5-HTP (the maximal effect, expressed as percent of controls, was limbic −50%) levels were estimated separately (Table 2). The control value for 5-HTP in the limbic system was 163 ± 22 (ng/g, mean ± SEM, n = 4) and for DOPA in the striatum and the cortex were 3653 ± 222 and 165 ± 11, respectively (ng/g, mean ± SEM, n = 10).

Scoring of the 5-HT Behavioral Syndrome. The 5-HT behavioral syndrome (flat body posture and reciprocal forepaw treading) was scored in non-pretreated rats according to the procedure described by Tricklebank et al.[26] Briefly, the animals were injected with test drugs subcutaneously, and the behavior was scored 15 min thereafter by one person blind to the treatment. The flat body posture and forepaw treading was then scored every 3 min for the subsequent 15 min. The rating scale was: 0 = absent, 1 = weak, 2 = present, 3 = strong. The total scores during the 15 min period were added. Shown are the median values. Saline levels were 1 for flat body posture and 0 for forepaw treading (n = 5).

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Supplementary Material Available: High-resolution mass spectroscopy and CHN analyses (2 pages). Ordering information is given on any current masthead page.

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