Synthesis and Biological Activity of *cis*-(3a*R*)-(−)-2,3,3a,4,5,9b-Hexahydro-3-propyl-1*H*-benz[*e*]indole-9-carboxamide: A Potent and Selective 5-HT$_{1A}$ Receptor Agonist with Good Oral Availability

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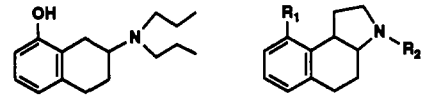
The synthesis and biological activity of *cis*-(3a*R*)-(−)-2,3,3a,4,5,9b-hexahydro-3-propyl-1*H*-benz[*e*]indole-9-carboxamide ((−)-**3a**), U93385, is described. The cis racemate and its enantiomer as well as the corresponding trans enantiomers were also synthesized and evaluated. The synthesis of these analogs was achieved via either a four-step conversion of the 9-hydroxy precursor into 9-carboxamide or an alternative synthesis using the (*R*)-α-methylbenzyl group as the chiral auxiliary. The cis racemate, (±)-**3a**, was found to be a selective and potent 5-HT$_{1A}$ receptor agonist with the activity residing in the *cis*-(3a*R*)-enantiomer, (−)-**3a**. The *cis*-(3a*S*)-enantiomer (+)-**3a** and *trans*-(3a*R*)-enantiomer (−)-**3b** displayed partial 5-HT$_{1A}$ agonist activity whereas the other *trans*-(3a*S*)-enantiomer (+)-**3b** showed no activity. The enantiomer (−)-**3a** was found to be selective in both in vitro and in vivo biochemical/behavioral assays. This compound potently reduced rectal temperature in mice, decreased the firing rate of rat midbrain serotonergic neurons, and suppressed rat brain 5-HT synthesis. This compound also reduced sympathetic nerve discharge and blood pressure in the anesthetized cat and showed activity in the forced swim assay in mice. It exhibited good oral activity in behavioral and biochemical assays and, in fact, had a 46% oral availability in the rat when comparing blood levels of parent drug after iv and po administration. This compound has demonstrated a potential for anxiolytic and antidepressant activity and is currently undergoing clinical evaluation.

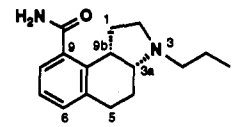
Introduction

Over 12 years ago, 8-hydroxy-2-(dipropylamino)tetralin (1,8-OH-DPAT) was synthesized and found to be a potent and selective serotonin receptor agonist.[1] This compound was later found to bind selectively to the 5-HT$_{1A}$ receptor in the brain.[2] Therapeutically, 5-HT$_{1A}$ receptor agonists are suggested to possess anxiolytic activity without the undesirable benzodiazepine-like side effects.[3] Buspirone, an aryl piperazine derivative with mixed 5-HT$_{1A}$ partial agonist and dopamine D$_2$ receptor antagonist activities, was the first agent to be approved for clinical use.[4] However, this compound is not optimal in terms of selectivity and pharmacokinetic properties and has a slow onset of action.[5] More selective 5-HT$_{1A}$ agonists with similar chemical structures, such as ipsapirone and gepirone, have been tested clinically for possible uses as anxiolytics and antidepressants.[3] Flesinoxan, a compound with higher intrinsic activity, is currently undergoing clinical evaluation.[6] At the present time, it is not clear whether a full or partial 5-HT$_{1A}$ agonist, or even an antagonist, would be an optimal therapeutic approach.

Although 8-OH-DPAT has been identified as the most selective and one of the most potent 5-HT$_{1A}$ agonists known, this compound suffers from poor oral availability and a short duration of action (see Table VI). Thus, considerable effort has been devoted to identify an agent in the 2-aminotetralin series with good pharmacological properties and improved pharmacokinetics.[7] These efforts have raised the realistic expectation of developing a therapeutically efficacious anxiolytic agent from this series of compounds. Our SAR work has been focused on the synthesis and identification of 8-OH-DPAT analogs with selectivity, potency, and acceptable oral availability.



1 (8-OH-DPAT) 2



cis-(3a*R*)-(−)-**3a**

In an earlier report, we described the SAR on rigid five-/six-fuxed angular tricyclic 2-aminotetralins, 2,3,3a,4,5,-9b-hexahydro-1*H*-benz[*e*]indole derivatives (**2**).[8] The analogs, where R$_1$ = OH or OMe and R$_2$ = propyl or allyl, were found to display potent 5-HT$_{1A}$ receptor agonist activity. Our study showed that the cis analogs are more potent than the corresponding trans analogs with 5-HT$_{1A}$ activity residing in the *cis*-(3a*R*)-enantiomer. However, these compounds displayed low metabolic stability in vitro when incubated with rat hepatocytes.[9]

Presumably, there are two major metabolic pathways possible within the hydroxylated 2-aminotetralin series. They are a direct glucuronidation and *N*-dealkylation, which would lead to a loss of metabolic stability and

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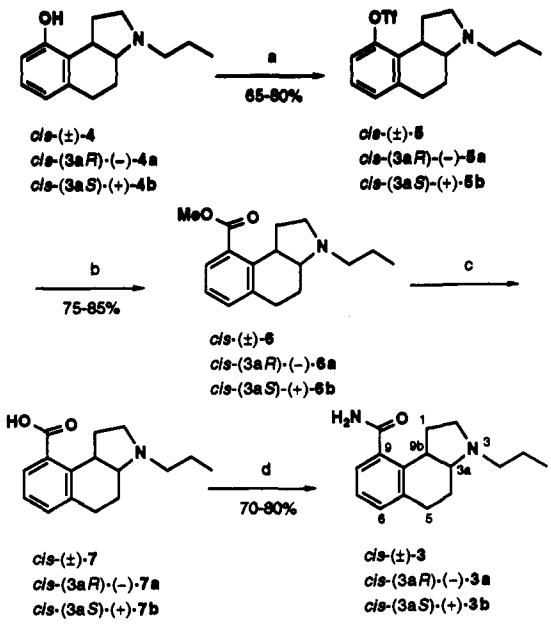
Scheme I[a]



[a] Reagents and conditions: (a) Tf_2O, pyr/CH_2Cl_2; (b) CO/$Pd(OAc)_2$, $Ph_2P(CH_2)_3PPh_2$/Et_3N, DMF/MeOH, 70 °C; (c) NaOH, MeOH/H_2O; (d) $(EtO)_2P(O)CN/NH_3$, Et_3N/DMF.

consequently low oral availability.[10] In previous SAR work on the 8-OH-DPAT (1) series, it was demonstrated that replacement of the hydroxyl group with a carboxamido group enhanced the compound's metabolic stability.[7h] Therefore, we decided to investigate whether the incorporation of the carboxamido group in the tricyclic series (2) would improve the metabolic stability of analogs while still maintaining potent 5-HT_{1A} agonist activity. The conversion could be easily achieved since the hydroxy precursors, *cis*-(±)-**4a**/*cis*-(3a*R*)-(-)-**4a**/*cis*-(3a*S*)-(+)-**4a** (Scheme I), were readily available.[8] We also wanted to evaluate all of the possible stereoisomers of these carboxamido analogs. We therefore developed an alternative synthesis designed to accommodate both pairs of cis and trans enantiomers. In this report we describe the synthesis of the racemate *cis*-(±)-**3a**, its enantiomers (-)-**3a** and (+)-**3a**, and the corresponding *trans*-enantiomers, (-)-**3b** and (+)-**3b**. All analogs were evaluated in in vitro 5-HT_{1A} and dopamine D_2 binding tests as well as in in vivo behavioral and biochemical assays.

Chemistry

An efficient synthesis of the racemate *cis*-(±)-**3a**, its enantiomers (-)-**3a** (U93385) and (+)-**3a**, was carried out by using the corresponding 9-hydroxy analogs[8] as the starting material. As shown in Scheme I, the hydroxy compounds *cis*-(±)-**4a**, *cis*-(3a*R*)-(-)-**4a**, and *cis*-(3a*S*)-(+)-**4a** were treated with triflic anhydride in pyridine/methylene chloride to yield 65–80% yield of the triflates (±)-**5a**, (-)-**5a**, and (+)-**5a**, respectively.[11] These triflates were then subjected to methoxycarbonylation catalyzed by palladium(II) acetate/1,3-bis(diphenylphosphino)propane/TEA in MeOH/DMF at 70 °C to afford the methyl esters (±)-**6a**, (-)-**6a**, and (+)-**6a** in 75–85% yield.[12] Hydrolysis of these esters with 2 equiv of sodium hydroxide in methanol yielded very insoluble amino acids (±)-**7a**, (+)-**7a**, and (+)-**7a** which were coupled with gaseous ammonia mediated by diethyl cyanophosphonate (DEPC)

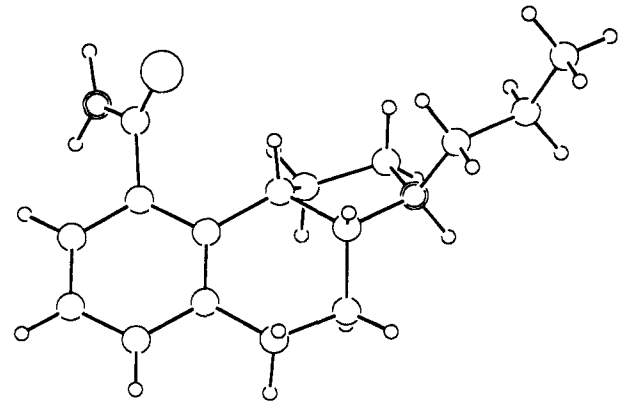


Figure 1. One of the two symmetry-independent molecules of (-)-**3a**.

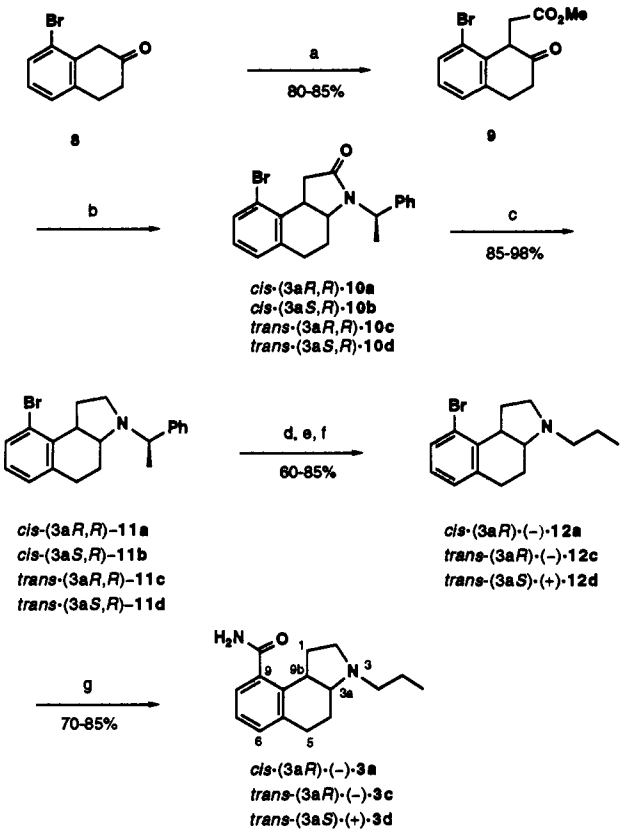
in TEA/DMF to yield the desired 9-carboxamides *cis*-(±)-**3a**, *cis*-(3a*R*)-(-)-**3a**, and *cis*-(3a*S*)-(+)-**3a** in 70–80% yield.[13]

X-ray crystallography of (-)-**3a**, as a 2:1 salt with (*R*,*R*)-dibenzoyl tartaric acid (see the Experimental Section), established the correct assignment of this compound as the *cis*-(3a*R*)-enantiomer (Figure 1). More than 20 different salt forms were attempted in an effort to produce a chemically stable, nonhygroscopic, and pharmacochemically acceptable salt.[14] In most cases a hygroscopic salt was formed. Fortunately, the 1:1 maleate salt of (-)-**3a**, U93385E, produced a crystalline form possessing excellent physicochemical properties suitable for drug formulation (see the Experimental Section).[15]

In the second synthesis, as outlined in Scheme II, 8-bromo-2-tetralone (8) was used as the starting material.[16] Regioselective alkylation of the C-1 position of tetralone 8 with methyl bromoacetate was carried out by using LDA as the base, yielding the keto ester **9** in 80–85% yield.[8] Reductive amination/cyclization of this keto ester **9** with (*R*)-α-methylbenzylamine afforded the mixture of diastereomeric lactams **10a**/**10b**.[17] The mixture of diastereomers was separated by chromatography using the Waters prep-500 HPLC. Interestingly, a 1:1 ratio of the cis/trans lactams was observed using 8-bromo keto ester **9** whereas a ratio of 10:1 was found when the 8-methoxy keto ester was reacted under the same conditions.[8] From the isolated cis lactams, we also found that the conversion had a diastereoselectivity favoring the desired diastereomer *cis*-(3a*R*,*R*)-**10a** over the undesired *cis*-(3a*S*,*R*)-**10a** in a 2:1 ratio. Both lactams were independently reduced with LAH/$AlCl_3$ (1:1) to yield the pyrrolidine derivatives, *cis*-(3a*R*,*R*)-**11a** and *cis*-(3a*S*,*R*)-**11a**, in 85–98% yield.[18] The trans lactams, (3a*R*,*R*)-**10b** and (3a*S*,*R*)-**10b**, were not separable at this stage. However, when the mixture was reduced under the same conditions, the diastereomers *trans*-(3a*R*,*R*)-**11b** and *trans*-(3a*S*,*R*)-**11b** became easily separable by column chromatography.

To confirm that the bromide *cis*-(3a*R*,*R*)-**11a** indeed was the precursor of the desired 9-carboxamide (-)-**3a**, the chiral α-methylbenzyl group was removed by refluxing this compound with 1-chloroethyl chloroformate in chlorobenzene followed by methanolysis.[19] The resulting crude HCl salt of the secondary amine was treated with excess propionaldehyde under reductive amination conditions[17] to yield *N*-propyl-9-bromo compound (-)-**12a** in 83% overall yield. In the final step, a lithium/halogen exchange using *tert*-butyllithium, followed by quenching with trimethylsilyl isocyanate, yielded the 9-carboxamide (-)-

Scheme II[a]



[a] Reagents and conditions: (a) LDA/$BrCH_2CO_2Me$, THF; (b) (*R*)-$H_2NCH(Me)Ph$, HOAc/$NaCNBH_3$, THF/MeOH; (c) LAH/$AlCl_3$, THF; (d) $ClCO_2CHClCH_3/C_6H_5Cl$, Δ; (e) MeOH, Δ; (f) EtCHO, HOAc/$NaCNBH_3$, THF/MeOH; (g) *t*-BuLi, Me_3SiNCO, THF.

3a in 85% yield.[20] The physical data of this 9-carboxamide were identical in every respect to those of (−)-**3a** obtained from *cis*-(3a*R*)-**4a** in the first synthesis. Since (+)-**3a** was already made available in the first synthesis, we did not proceed with the other bromide *cis*-(3a*S*,*R*)-**11a** to obtain (+)-**3a** via this route. The *trans*-9-bromo diastereomers (3a*R*,*R*)-**11b** and (3a*S*,*R*)-**11b** were also converted into the *trans*-9-carboxamides (−)-**3b** and (+)-**3b**, respectively, using the same three-step sequence (see Scheme II). As shown in Table I, both (−)-**3b** and (+)-**3b** showed identical physical properties except their equal but opposite optical rotations. These data indicate that they are enantiomers. The ^1H NMR spectra of both (−)-**3b** and (+)-**3b**, however, were different from those of the cis enantiomers (−)-**3a** and (+)-**3a**. On the basis of all available physical data, we assigned both (−)-**3b** and (+)-**3b** as a pair of trans enantiomers as opposed to (−)-**3a** and (+)-**3b**, which had already been firmly established as a pair of cis enantiomers.[21]

The analogs synthesized and biologically evaluated are listed in Table I, which includes the recrystallization solvent, the melting point, the optical rotations, and the molecular formula for each compound.

Pharmacology

As shown in Table II, the ability of the compounds to displace radioactively labeled ligands [^3H]-8-OH-DPAT or [^3H]-U86170 from 5-HT_{1A} or dopamine D_2 sites in the cloned CHO cells was assessed in vitro. These compounds were also tested in a broad binding assay.

Postsynaptic effects of the test compounds were assessed by the increase in 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 II).[22] 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 III, utilizes the well-established phenomenon of receptor-mediated feedback inhibition of the presynaptic neuron.[23] 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 dopaminergic and α-adrenergic receptors, respectively. Similarly, the synthesis rate of 5-HT is inhibited by 5-HT receptor agaonists.[24] 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 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.

The abilities of the test compounds to lower the body temperature in mice were assessed. As shown in Table IV, the mean maximum temperature drop 20 min following any dose was noted as an index of a compound's efficacy and an indirect estimate of intrinsic activity. Inhibition of firing rates of rat serotonergic neurons in the dorsal raphe nucleus was determined following intravenous injection of the test compounds. The cardiovascular effects were studied by measuring the change in blood pressure and sympathetic nerve activity in the anesthetized cat. These results are also listed in Table IV.

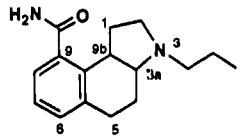
As shown in Table V, the compounds were screened in the despair model to determine whether they have potential in the treatment of depression. The swimming activity of the mice was monitored where increases in the measured swimming activity were considered indicative of antidepressant-like activity.

Finally, the oral availability was determined as the absolute oral availability by measuring the actual blood concentrations of parent compound by means of GC/MS after oral and intravenous administrations to rats. These results are listed in Table VI.

Results and Discussion

The racemate (±)-**3a** was found to be selective in vitro with high affinity for the 5-HT_{1A} receptor site (Table II).[25] The compound reversed reserpine-induced akinesia and induced a full-blown 5-HT_{1A} syndrome in rats indicative of a 5-HT_{1A} agonist with full intrinsic activity (Table II). The compound also selectively reduced 5-HTP accumulation and was approximately 20 times less potent than 8-OH-DPAT and 1.5 times less potent than flesinoxan after sc administration (Table III). Interestingly, (±)-**3a** reduced the blood pressure in the anesthetized cat but did

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



compd	confign at 3a,9b	recryst solvent	$[\alpha]^{a}_{D}$ (deg)	mp (°C)	formula	analyses
(±)-**3a**	*cis*	acetone		149	$C_{16}H_{22}N_2O$	C,H,N
(−)-**3a**	*cis*-(3a*R*)	acetone or hexane/EtOAc	−241	164–165	$C_{16}H_{22}N_2O$	C,H,N
(+)-**3a**	*cis*-(3a*S*)	acetone	+236	163–164	$C_{16}H_{22}N_2O$	C,H,N
(−)-**3b**	*trans*-(3a*R*)	acetone or hexane/EtOAc	−227	235–236	$C_{16}H_{22}N_2O$	C,H,N
(+)-**3b**	*trans*-(3a*S*)	acetone or hexane/EtOAc	+221	235–236	$C_{16}H_{22}N_2O$	C,H,N

[a] The optical rotations were measured in chloroform at 25 °C.

Table II. Affinities at 5-HT_{1A}[a] and D_2[b] Sites *in Vitro* and Effects on Motor Activity *in Vivo*

			motor activity		
compd	abs confign	binding 5-HT_{1A} K_i[c] (nM)	dose, μmol/kg	accumulated counts/30 min[d]	gross behavioral obsvns[e]
(±)-8-OH-DPAT (1)	(*RS*)	0.5 (±0.1)	0.2 sc	66 ± 17*	+5-HT
			10 po	17 ± 10*	+5-HT
			61 po	883 ± 453***	+5-HT
(+)-flesinoxan	(*R*)	2.9 (±0.9)	5 sc	84 ± 23***	+5-HT
			50 po	135 ± 35***	+5-HT
(±)-**3a**	*cis*	2.9 (±0.6)	12.5 sc	88 ± 18***	(+)-5-HT
(−)-**3a**	*cis*-(3a*R*)	1.9 (±0.2)	12.5 sc	249 ± 126***	+5-HT
			12.5 po	173 ± 68***	+5-HT
(+)-**3a**	*cis*-(3a*S*)	17 (±1.0)	50 sc	17 ± 4**	(+)-5-HT
(−)-**3b**	*trans*-(3a*R*)	28 (±3.5)	50 sc	16 ± 6	(+)-5-HT
(+)-**3b**	*trans*-(3a*S*)	>1441	50 sc	9 ± 4	no change

[a] [^{3}H]-8-OH-DPAT-labeled 5-HT_{1A} sites in cloned CHO cells. [b] Compounds (±)-**3**, (−)-**3a**, (+)-**3a**, (−)-**3b**, and (+)-**3b** all had D_2 binding affinities > 1629 nM when tested using [^{3}H]-U86170-labeled D_2 sites in cloned CHO cells. [c] K_i value followed by ±SEM. [d] Statistics according to Student's *t*-test where * indicates $p < 0.05$, ** indicates $p < 0.01$, and *** indicates $p < 0.001$. [e] The gross behavior was observed during the activity session, and +5-HT denotes a full-blown 5-HT syndrome and (+) 5-HT a partial response, mainly flat body posture.

Table III. Effects on Brain 5-HT and DA Synthesis Rates *in Vivo* after Subcutaneous and Oral Administration to Reserpinized Rats

		ED_{50},[a] μmol/kg					
		5-HTP accumuln			DOPA accumuln		
compd	route	limb	stri	hem	limb	stri	hem
(±)-8-OH-DPAT (1)	sc	0.052	0.052	0.063	I	I	I
	po	3	7.9	7.6	I	I	I
(+)-flesinoxan	sc	0.63	0.55	0.63	I	I	I
	po	0.36	0.27	0.36	P[b]	I	I
(±)-**3a**	sc	0.93	0.95	1.25	I	I	I
(−)-**3a**	sc	0.28	0.07	0.32	I	I	I
	po	0.23	<0.2	0.28	I	I	I
(+)-**3a**	sc	1.80	1.60	5.20	I	I	I
(−)-**3b**	sc	P[b]	P	P	I	I	I
(+)-**3b**	sc	I[c]	I	I	I	I	I

[a] Abbreviations: limb = limbic system, stri = corpus striatum, and hem = hemispheres. [b] P means a partial response at the highest dose tested (50 μmol/kg). 5-HT accumulations were 60–75% of those of the controls in the brain areas indicated. [c] I means inactive at the highest dose tested (50 μmol/kg).

not produce a maximal reduction in sympathetic nerve discharge (Table IV). It was also found to be active in the swim stress test, a putative model of antidepressive activity, at 12 μmol/kg, sc (Table V). This compound was found to be metabolically stable in an in vitro incubation with rat hepatocytes.[26] In accordance, the absolute oral availability was determined to be 70% when comparing blood levels of parent compound after iv and oral administration to the rat (Table VI).

As shown in Tables II and III, the serotonergic activity was essentially found to reside in the *cis*-(3a*R*)-enantiomer (−)-**3a**. The enantiomer (−)-**3a** displayed a potent affinity for the 5-HT_{1A} receptor with no appreciable affinity to the dopamine D_2 site (K_i > 1629 nM) and other dopamine and serotonin subtypes.[25] A potent reduction in 5-HTP accumulation was seen after both sc and oral administration (ED_{50}'s 0.28 and 0.23 μmol/kg, respectively). This would indicate that (−)-**3a** is approximately five times less potent than 8-OH-DPAT after sc administration, but it is at least 10 times more potent after oral administration. In behavioral experiments, (−)-**3a** elicited a full-blown 5-HT behavioral syndrome after both oral and sc doses. No DA-like mediated behavior was seen even after very high doses (50 μmol/kg, sc). The compound was also found to decrease rectal temperature in mice as well as to inhibit midbrain 5-HT cell firing rate in the rat (Table IV). Unlike the racemic (±)-**3**, (−)-**3a** produced a full inhibition of SND with a potency similar to flesinoxan and an efficacy similar to both 8-OH-DPAT and flesinoxan (Table IV). In addition, this compound was also found to be active in the swim stress test at 3.9 and 12 μmol/kg, sc, thus again equipotent to 8-OH-DPAT (Table V). Compound (−)-**3a** was also found to be active in animal behavioral models predictive of anxiolytic activity in man such as the male mouse isolation-induced aggression assay.[27] Other work[28] has suggested that (−)-**3a** demonstrated anxiolytic activity as defined by reducing the stress-induced increase in rat plasma corticosterone. This compound was expected to show good oral availability since it was active in behavioral and biochemical experiments after oral administration. In fact, (−)-**3a** has been shown to have the same metabolic stability in vitro as the racemate (±)-**3a** and a 46% absolute oral availability in the rat (Table VI). The half-life was approximately 2 h.

The *cis*-(3a*S*)-enantiomer (+)-**3a** was classified as a partial 5-HT_{1A} agonist due to the partial behavioral syndrome (abducted forepaws) and flat body posture that

Table IV. Effect of the Cis Analogs in the Hypothermia in Mice, 5-HT_{1A} Cell Firing Assays in the Rat, and on Arterial Blood Pressure/Sympathetic Nerve Activity (SND) in the Anesthetized Cat

	hypothermia				sympathetic nerve discharge			
	ED_{50}[a] (μmol/kg)	max drop (°F)	route	5-HT_{1A} cell firing ED_{50}[b] (μmol/kg)	ED_{50}[c] (μmol/kg)	max dec SND[d]	%BP at SND (ED_{50})	max dec BP[e]
(±)-8-OH-DPAT (1)	3 (1.6–5.5)	7.2	sc	0.006	0.03	2.0 (±0.5)	66 (±6)	57 (±3)
	30 (16–55)	7.5	po	(±0.02)				
(+)-flesinoxan	0.16 (0.04–0.66)	6.4	sc	0.16	0.14	2.0 (±0.7)	79 (±7)	55 (±4)
	1.6 (0.06–0.44)	4.5	po	(±0.06)				
(±)-**3a**	3.8 (1.2–12)	6.2	sc	0.009	0.1	33 (±12)	82 (±4)	63 (±5)
	28 (17–48)	5.5	po	(±0.002)				
(−)-**3a**	0.4 (0.13–1)	5.6	sc	0.023	0.049	0	83 (±2)	52 (±9)
	2.8 (1.2–6.6)	5.4	po	(±0.01)				
(+)-**3a**	8.9 (3.4–24)	6.5	sc	>1.2	NT[f]			
	28 (12–67)	2.4	po					

[a] ED_{50} values were followed by 95% confidence intervals. [b] ED_{50} values were followed by ±SEM. [c] Dose at which the SND has been reduced to 50% of the pretreatment value. [d] As percent of control. [e] Maximum decrease in blood pressure observed following 1 mg/kg dose. [f] NT = not tested.

Table V. Effects in the Swim Stress Test in Mice

compd	dose (μmol/kg, sc)	swimming activity (T/C)[a]
(±)-8-OH-DPAT (1)	1.2	0.9
	4.0	6.7***
	12	4.6***
	41	3.4***
(+)-flesinoxan	6.6	0.6
	39	3.3**
(±)-**3a**	3.9	1.2
	12	6.6**
	39	2.9
(−)-**3a**	1.2	1.5
	3.9	4.7***
	12	7.1***
	39	1.1
(+)-**3a**	1.2	1.0
	3.9	4.0***
	12	4.7***
	39	8.3***
(−)-**3b**	12	0.7
	39	1.7*
(+)-**3b**	12	1.2
	39	1.1

[a] T/C is the swimming activity of the treated mice divided by the control values. Statistic where * indicates $p < 0.05$, ** indicates $p < 0.01$, and *** indicates $p < 0.001$.

Table VI. Pharmacokinetics in the Rat

compd	oral availability (%)	half-life (min)
(±)-8-OH-DPAT (1)	2.4 (±0.9)[a]	60
(±)-**3a**	70 (±3)[b]	90
(−)-**3a**	46 (±8.5)[b]	120

[a] Obtained from blood plasma levels of parent compound following 1 μmol/kg, iv, and 20 μmol/kg, po administration. [b] Obtained from blood plasma levels of parent compounds following 5 μmol/kg, iv, and 40 μmol/kg, po administration. Calculated from total area from [C] *vs* time curves unless otherwise stated. SEM, $n = 4$.

was observed (Table II), even though it produced a maximal decrease in brain 5-HTP accumulation (Table III). Effects similar to this have been seen with other partial agonists such as buspirone. This compound was >20 times less potent than (−)-**3a** in decreasing body temperature in mice and was unable to inhibit cell firing rate at doses up to 1.2 μmol/kg, which is 50 times the ED_{50} of (−)-**3a** (Table IV). Interestingly, this enantiomer (+)-**3a** was found equipotent to (−)-**3a** and 8-OH-DPAT in the swim stress test in mice (Table V).

The *trans*-(3a*R*)-enantiomer (−)-**3b** was found to be a weak partial 5-HT_{1A} agonist with only a partial 5-HT syndrome and only a decrease in 5-HTP accumulation (40%) at 50 μmol/kg, sc (Tables II and III). The *trans*-(3a*S*)-enantiomer (+)-**3b** was inactive at 50 μmol/kg, sc. Again, a stereoselectivity for the binding site for one enantiomer is evident (Table II).

Conclusion

We have described herein the synthesis and biological activity of *cis*-(3a*R*)-(−)-2,3,3a,4,5,9b-hexahydro-3-propyl-1*H*-benz[*e*]indole-9-carboxamide ((−)-**3a**) and its stereoisomers. The cis racemate (±)-**3a** was found to be a selective and potent 5-HT_{1A} receptor agonist with serotonergic activity essentially residing in the *cis*-(3a*R*)-enantiomer (−)-**3a**. The *cis*-(3a*S*)-enantiomer (+)-**3a** and *trans*-(3a*R*)-enantiomer (−)-**3b** displayed partial 5-HT_{1A} agonist activity whereas the other *trans*-(3a*S*)-enantiomer (+)-**3b** showed no activity in the models used. The most active enantiomer (−)-**3a** was found to be a selective 5-HT_{1A} agonist with full intrinsic activity approximately five times less potent than 8-OH-DPAT (1) after sc administration but 10 times more potent after oral administration. This enantiomer (−)-**3a** potently reduced rectal temperature in mice, decreased the firing rate of rat midbrain serotonergic neurons, and suppressed the rat brain 5-HT synthesis. This compound also reduced sympathetic nerve discharge and blood pressure in the anesthetized cat and showed activity in the forced swim assay in mice. It exhibited good oral activity in behavioral and biochemical assays and possessed a good pharmacokinetic properties with an absolute oral bioavailability of 46% in the rat when comparing blood levels of parent compound after iv and po administration. This compound has demonstrated a potential for anxiolytic and antidepressant activity and is currently undergoing clinical evaluation.

Experimental Section

Synthesis. Analytical TLC was performed on Analtech 10-× 20-cm (250 μm) silica gel GF prescored glass plates which were developed in the solvent systems described. The plates were checked under ultraviolet light and developed by dipping in ammonium molybdate/cerium sulfate/10% sulfuric acid solution and heating on a hot plate. ^1H NMR spectra were obtained at 300 MHz on a Bruker Model AM-300 spectrometer in $CDCl_3$ solution unless noted otherwise. Chemical shifts (δ) are reported in parts per million relative to tetramethylsilane as an internal standard. 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 commerical chemicals were used as received from Aldrich unless noted otherwise. HPLC-grade methylene chloride, methanol, tetrahydrofuran, ethyl acetate, and hexane were used. All reactions were performed under a nitrogen atmosphere. Melting

points were determined in open capillary tubes on a Mettler FP-62 melting point apparatus and are uncorrected. The amine-based products were converted into the HCl salts by dissolving the free base in methanolic HCl solution.[29] 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 and optical rotations were performed by the Physical and Analytical Chemistry Unit of Upjohn Laboratories. The elemental analyses reported are within ±0.4% of the calculated values.

***cis*-(3a*R*)-(−)-2,3,3a,4,5,9b-Hexahydro-9-((trifluoromethanesulfonyl)oxy)-3-propyl-1*H*-benz[*e*]indole ((−)-5a), Enantiomer *cis*-(3a*S*)-(+)-5a, and Racemate *cis*-(±)-5a.** A solution of (−)-**4a** (0.23 g, 1 mmol) in a mixture of pyridine (3 mL) and methylene chloride (10 mL) was cooled to 0 °C. (*Note*: Since the starting material was not very soluble in methylene chloride, we found later that the reaction worked better in pure pyridine or pyridine/THF.) Triflic anhydride (0.5 mL, 3 mmol) dissolved in methylene chloride (1 mL) was added slowly over 10 min. The mixture was warmed to room temperature and stirred for 3 h. Methanol (2 mL) was then added and the mixture stirred for 10 min. The reaction was quenched with 10% sodium hydroxide (20 mL) and extracted with methylene chloride (2 × 500 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to yield a brown oil. The oil was purified by liquid chromatography on 100 g of silica gel, eluting with hexane/ethyl acetate (2:1). Homogeneous fractions were combined and concentrated to yield (−)-**5a** as a light yellow oil (0.28 g, 78%). This oil was converted into the HCl salt and recrystallized from ethyl acetate to afford a white solid: mp 207–208 °C; ^{1}H NMR δ 7.32–7.14 (m, 3 H), 4.18–1.92 (m, 14 H), 1.05 (t, J = 7.3 Hz, 3 H); IR (mull) ν_{max} 1617, 1574, 1463, and 1420 cm^{-1}; MS calcd for $C_{16}H_{20}F_3NO_3S$ 363.1116, found 363.1112; $[\alpha]^{25}_D$ −77° (*c* 0.95, $CHCl_3$). Anal. ($C_{16}H_{20}F_3NO_3S$·HCl) C, H, N.

Enantiomer *cis*-(3a*S*)-(+)-**5a** and racemate *cis*-(±)-**5a** were prepared by the same procedure from the hydroxy compounds (+)-**4a** and (±)-**4a**, respectively, in 65–80% yield. Both (+)-**5a** and (±)-**5a** were isolated as oils. ^{1}H NMR data were identical to those of (−)-**5a**.

***cis*-(3a*R*)-(−)-2,3,3a,4,5,9b-Hexahydro-9-carbomethoxy-3-propyl-1*H*-benz[*e*]indole ((−)-6a), Enantiomer *cis*-(3a*S*)-(+)-6a, and Racemate *cis*-(±)-6a.** A solution of (−)-**5a** (1.82 g, 5 mmol), triethylamine (1.5 mL, 11 mmol) in methanol (5 mL) and DMF (15 mL) was purged with nitrogen through a long needle syringe (10 min). Carbon monoxide gas was then introduced and the mixture bubbled for 10 min. During this time, a solution of palladium acetate (0.11 g, 0.5 mmol) and 1,3-bis(diphenylphosphino)propane (0.27 g, 0.65 mmol) dissolved in 5 mL of DMF/MeOH (3:1) was purged with nitrogen for 10 min. This solution was added to the reaction mixture and heated to 70 °C, and carbon monoxide was bubbled through the solution overnight. The mixture was purged with nitrogen, quenched with saturated $NaHCO_3$, and extracted with ethyl acetate (3 × 500 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to yield a brown oil. The oil was purified by liquid chromatography on 500 g of silica gel, eluting with hexane/ethyl acetate (4:1). Homogeneous fractions were combined and concentrated to yield pure (−)-**6a** as an oil (1.16 g, 85%). This oil was converted into the HCl salt and recrystallized from ethyl acetate/methanol to yield a white solid: mp 192–193 °C; ^{1}H NMR δ 7.86–7.74 (m, 1 H), 7.34 7.18 (m, 2 H), 4.75–4.52 (m, 1 H), 3.90 (s, 3 H), 4.10–1.62 (m, 13 H), 1.03 (t, J = 7.3 Hz, 3 H); IR (mull) ν_{max} 1719 and 1582 cm^{-1}; MS M$^+$ 273, other ions at m/z 244, 212, 183; $[\alpha]^{25}_D$ −101° (c 0.81, $CHCl_3$). Anal. ($C_{17}H_{23}NO_2$·HCl) C, H, N.

Enantiomer *cis*-(3a*S*)-(+)-**6a** and racemate *cis*-(±)-**6a** were prepared by the same procedure from the triflates (+)-**5a** and (±)-**5a**, respectively, in 80–85% yield. Both (+)-**6a** and (±)-**6** were isolated as an oil. ^{1}H NMR data were identical to those of (−)-**6a**.

***cis*-(3a*R*)-(−)-2,3,3a,4,5,9b-Hexahydro-9-3-propyl-1*H*-benz[*e*]indole-9-carboxamide ((−)-3a), Enantiomer *cis*-(3a*S*)-(+)-3a, and Racemate *cis*-(±)-3a.** A solution of (−)-**6a** (1.15 g, 4.2 mmol), 3 N NaOH (2.8 mL), and methanol (10 mL) was refluxed overnight (bath temp 70 °C). The mixture was neutralized with 6 N HCl (to pH 5). The solution was concentrated to dryness using methanol and toluene. A light yellow solid (−)-**7a** was obtained. A solution of this solid in DMF (15 mL) and triethylamine (1.8 mL, 12.6 mmol) was flushed with ammonia gas for 10 min and treated with diethyl cyanophosphonate (1.4 mL, 8.4 mmol). Ammonia gas was bubbled through the solution overnight at room temperature. The reaction mixture was concentrated in vacuo to dryness and dissolved in methanol. This solution was flash chromatographed (400 g of silica gel), eluting first with hexane/ethyl acetate (1:1) to remove the nonpolar impurities. This was followed by methylene chloride/methanol with 2.5 M NH_3 (95:5). Homogeneous fractions were combined and concentrated to yield a white solid (0.8 g, 74%). This solid was recrystallized from acetone (or hexane/ethyl acetate) to yield (−)-**3a** as a white solid: ^{1}H NMR δ 7.24 (d, J = 9.1 Hz, 1 H), 7.17 (d, J = 6.6 Hz, 1 H), 7.10 (t, J = 7.5 Hz, 1 H), 5.82 (br s, 1 H), 3.93 (q, J = 9.1 Hz, 1 H), 3.12–1.38 (m, 13 H), 0.93 (t, J = 7.3 Hz, 3 H); IR (mull) ν_{max} 3376, 1644, and 1586 cm^{-1}; MS M$^+$ 258, other ions at m/z 229, 212, 200; $[\alpha]^{25}_D$ −241° (c 0.43, $CHCl_3$). Anal. ($C_{16}H_{22}N_2O$) C, H, N. The 1:1 maleate of (−)-**3a** was prepared by dissolving (−)-**3a** (2.58 g, 10 mmol) and maleic acid (1.2 g, 10.5 mmol) in hot methanol (20 mL) and diluted with ethyl acetate (20 mL). The mixture was allowed to stand at room temperature for 3 h to yield a white solid (3.43 g): ^{1}H NMR (CD_3OD) δ 7.38 (m, 3 H), 6.25 (s, 2 H), 4.36–1.72 (m, 14 H), 1.05 (t, J = 7.3 Hz, 3 H); IR (mull) ν_{max} 3420, 3346, 3306, 3220, 1668, 1624, 1588, and 1576 cm^{-1}; $[\alpha]^{25}_D$ −119° (c 0.93, MeOH). Anal. ($C_{16}H_{22}N_2O$·$C_4H_4O_4$) C, H, N.

Enantiomer *cis*-(3a*S*)-(+)-**3a** and racemate *cis*-(±)-**3a** were prepared by the same procedure from the methyl esters (+)-**6b** and (±)-**6**, respectively, in 70–80% yield. The spectral data of both (+)-**3a** and (±)-**3a** were identical to those of (−)-**3a**. The optical rotation of *cis*-(3a*S*)-(+)-**3b** was: $[\alpha]^{25}_D$ +236° (c 0.82, $CHCl_3$). Anal. ($C_{16}H_{22}N_2O$) C, H, N.

(±)-1,2,3,4-Tetrahydro-8-bromo-2-oxo-1-naphthalene Acetic Acid Methyl Ester (9). An oven-dried, 5-L, three-neck flask, equipped with a dropping funnel and a mechanical stirrer, was charged with **8**[16] (71.73 g, 0.32 mol) and THF (2 L). The flask was cooled to −30 °C, and LDA (1.5 M, 234 mL, 0.35 mol) was added slowly over a 30 min period. Stirring was continued for 30 min more after addition was completed. Methyl bromoacetate (36.2 mL, 0.382 mol) in 500 mL of THF was added slowly over 45 min, and the dark brown solution was stirred for 4 h. The reaction was quenched with concentrated HCl (55 mL) to pH < 3. The solvent was removed in vacuo, and the concentrate was extracted with ethyl acetate (2 L). The organic layers were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated to yield a dark brown oil. This oil was purified by flash chromatography on 1 kg of silica gel, eluting first with hexane followed by 15% ethyl acetate/hexane. Fractions homogeneous by TLC were combined and concentrated in vacuo to give **9** as a brown oil (78 g, 82%): ^{1}H NMR δ 7.48 (d, J = 7.9 Hz, 1 H), 7.18 (d, J = 7.5 Hz, 1 H), 7.09 (t, J = 7.7 Hz, 1 H), 3.97 (t, J = 5.4 Hz, 1 H), 3.60 (s, 3 H), 3.57–3.45 (m, 1 H), 3.31–3.24 (m, 1 H), 3.09–2.91 (m, 2 H), 2.84–2.77 (m, 1 H), 2.61–2.49 (m, 1 H); IR (film) ν_{max} 1742, 1712, 1595, and 1563 cm^{-1}; MS M$^+$ 296, other ions at m/z 265, 236, 223, 217, 195, 175, 157, 144, 129, 115. Anal. Calcd for $C_{13}H_{13}BrO_3$: C, 52.55; H, 4.41. Found: C, 52.61; H, 4.45.

The Diastereomers of 1,3,3a,4,5,9b-Hexahydro-9-bromo-3-(1(*R*)-methylbenzyl)-2*H*-benz[*e*]indol-2-one (*cis*-(3a*R*,*R*)-10a, *cis*-(3a*S*,*R*)-10a, *trans*-(3a*R*,*R*)-10, and *trans*-(3a*S*,*R*)-10b). A solution of **9** (49.4 g, 0.166 mol) in 1 L of THF/MeOH (1:1) was treated with (*R*)-(+)-α-methylbenzylamine (107 mL, 0.83 mol) and cooled to −20 °C. Acetic acid (120 mL) was added to pH 4, and the mixture was stirred at −20 °C for 2 h. Sodium cyanoborohydride (10.4 g, 0.166 mol) was added, and stirring was continued for 3.5 h. A second equivalent of sodium cyanoborohydride (10.4 g, 0.166 mol) was added at −20 °C. The mixture was allowed to warm to room temperature and stirred for 3 days. The reaction was quenched with 300 mL of water and concentrated in vacuo. Sodium hydroxide (20%, 800 mL) was added to pH > 13, and the mixture was extracted with ethyl acetate (2 L). The organic layer was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated to give a tan oil (139 g). The oil was purified by flash chromatography on 1 kg

of silica gel, eluting with hexane/ethyl acetate (20:1). Less polar fractions were combined to give trans amino esters (18 g) (*Note*: when this amino ester was refluxed in acetic acid/toluene (1:10), the only products isolated (15.8 g, 25.7%) were a mixture of cyclized trans diastereomers (**10b**), indicating that this amino ester did not contain cis diastereomers), and more polar fractions afforded a mixture of cis and trans lactams (42 g). The mixture of these lactams was subjected to the Waters Prep LC system 500 eluting with 20% ethyl acetate/hexane. The sample solution was loaded onto the prep 500 in 35-mL portions (42 g was dissolved in 140 mL of methylene chloride). After each run, the mixed fractions were combined and the purification was repeated. The least polar fractions yielded a mixture of two trans diastereomers (3a*R*,*R*)-**10b** and (3a*S*,*R*)-**10b** which were not separable (6.3 g, 10.2%). (*Note*: The mixture became separable only after the LAH/$AlCl_3$ reduction.) The next polar fractions afforded the undesired cis diastereometer (3a*S*,*R*)-**10a** (7 g, 10.8%) as an oil whereas the most polar fractions yielded the desired cis diastereomer (3a*R*,*R*)-**10a** (14.8 g, 22%) as a solid. (*Note*: The isolated yield of *cis* diastereomer *cis*-(3a*R*,*R*)-**10a** varied from 22 to 26% depending on the run.)

Physical data for diastereomer *cis*-(3a*R*,*R*)-**10a**: mp 125–126 °C; ^{1}H NMR δ 7.39–7.30 (m, 6 H), 7.04–6.95 (m, 2 H), 5.53 (q, J = 7.2 Hz, 1 H), 3.58–3.46 (m, 2 H), 3.37–3.29 (m, 1 H), 2.89–1.72 (m, 5 H), 1.68 (d, J = 7.2 Hz, 3 H); IR (mull) ν_{max} 1681, 1639, 1603, 1593, and 1558 cm^{-1}; MS M$^+$ 369, other ions at m/z 354, 265, 161, 160, 146, 105; $[\alpha]^{25}_D$ −11.2° (*c* 1.3, $CHCl_3$). Anal. Calcd for $C_{20}H_{20}BrNO$: C, 64.87; H, 5.45; N, 3.78. Found: C, 64.85; H, 5.38; N, 3.74.

Physical data for diastereomer *cis*-(3a*S*,*R*)-**10a**: ^{1}H NMR δ 7.45–7.27 (m, 6 H), 6.97 (d, J = 5.0 Hz, 2 H), 5.54 (q, J = 7.2 Hz, 1 H), 3.97–3.89 (m, 1 H), 3.71–3.61 (m, 1 H), 3.34–3.25 (m, 1 H), 2.55–2.23 (m, 3 H), 1.69 (d, J = 7.2 Hz, 3 H), 1.50–1.16 (m, 2 H); $[\alpha]^{25}_D$ +235° (*c* 1.92, $CHCl_3$).

Physical data for diastereomers *trans*-(3a*R*,*R*)-**10b** and *trans*-(3a*S*,*R*)-**10b**: The characterization of these compounds was performed after LAH/$AlCl_3$ reduction and each diastereomer had been separated and purified.

***cis*-(3a*R*)-2,3,3a,4,5,9b-Hexahydro-9-bromo-3-(1(*R*)-methylbenzyl)-1*H*-benz[*e*]indole Hydrochloride (*cis*-(3a*R*,*R*)-11a) and Diastereomer *cis*-(3a*S*,*R*)-11a.** A suspension of lithium aluminum hydride (4.37 g, 115 mmol) in THF (600 mL) was cooled to −20 °C, and aluminum chloride (15.36 g, 115 mmol) was added slowly. The mixture was stirred for 15 min, a solution of *cis*-(3a*R*,*R*)-**10a** (21.3 g, 57 mmol) in THF (190 mL) was added slowly, and the resulting mixture was stirred at −20 °C for 1 h. The reaction was quenched with 20% NaOH to pH >13. Water was added, and the gray suspension was extracted with ethyl acetate (2 × 1 L). The combined organic layers were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated to yield an oil (22 g). This oil was purified by flash chromatography on 1 kg of silica gel, eluting with hexane/ethyl acetate (95:5) and collecting 100-mL fractions. Fractions homogeneous by TLC were combined to afford the desired product as a colorless oil (20.1 g, 98%). This oil was converted into the HCl salt and recrystallized from ethyl acetate/methanol to yield *cis*-(3a*R*,*R*)-**11a** as a white solid: mp 272–273 °C; ^{1}H NMR δ 7.82 (d, J = 8.1 Hz, 2 H), 7.54–7.46 (m, 4 H), 7.05–6.95 (m, 2 H), 4.36–4.02 (m, 2 H), 3.70–1.62 (m, 9 H), 1.97 (d, J = 6.9 Hz, 3 H); IR (mull) ν_{max} 1595, 1585, and 1563 cm^{-1}; MS M$^+$ 355, other ions at m/z 340, 270, 250, 235, 209, 128, 105; $[\alpha]^{25}_D$ +28° (*c* 1.32, $CHCl_3$). Anal. ($C_{20}H_{22}$BrN·HCl) C, H, N.

Diastereomer *cis*-(3a*S*,*R*)-**11a** was prepared from *cis*-(3a*R*,*S*)-**10a**, using the procedure described in the preparation of *cis*-(3a*R*,*R*)-**11a**. Recrystallization of the HCl salt from ethyl acetate/methanol yielded a white solid: mp 124–125 °C. The physical data revealed that the sample was contaminated with an unknown impurity: ^{1}H NMR δ 7.92, 7.78 (two d, J = 7.9 Hz, 1 H), 7.52–7.34 (m, 4 H), 7.12–6.94 (m, 2 H), 4.42–1.58 (m, 11 H), 2.02, 1.86 (two d, J = 6.8 Hz, 3 H); IR (mull) ν_{max} 3407, 1735, 1594, 1586, and 1561 cm^{-1}; $[\alpha]^{25}_D$ + 23.5° (*c* 1.07, $CHCl_3$). Repeated recrystallization did not eliminate this impurity which was shown by consistently low carbon analysis. Anal. Calcd for $C_{20}H_{22}$BrN·HCl: C, 61.16; H, 5.90; N, 3.57. Found: C, 59.16; H, 6.15; N, 3.37.

***trans*-(3a*R*)-2,3,3a,4,5,9b-Hexahydro-9-bromo-3-(1(*R*)-methylbenzyl)-1*H*-benz[*e*]indole Hydrochloride (*trans*-(3a*R*,*R*)-11b) and Diastereomer *trans*-(3a*S*,*R*)-11b.** Both diastereomers were prepared from the mixture of trans lactams (3a*R*,*R*)-**10b** and (3a*S*,*R*)-**10b** using the reduction procedure described in preparation of **11a**. The pure diastereomers were easily separated by chromatography, eluting with hexane/ethyl acetate (9:1). The less polar fraction was assigned as *trans*-(3a*S*,*R*)-**11b** and the more polar fraction as *trans*-(3a*R*,*R*)-**11b**. TLC analysis showed that both **11c** and **11d** are more polar than **11a** and **11b**. These diastereomers were then converted into the HCl salt and recrystallized from ethyl acetate/methanol to yield white solids.

Physical data for diastereomer *trans*-(3a*R*,*R*)-**11b**: mp 235–236 °C; ^{1}H NMR δ 7.34–7.22 (m, 6 H), 7.04 (d, J = 7.8 Hz, 1 H), 6.98 (t, J = 7.8 Hz, 1 H), 4.89–1.55 (m, 11 H), 1.97 (d, J = 6.9 Hz, 3 H); IR (mull) ν_{max} 1606, 1590, 1585, and 1558 cm^{-1}; MS M$^+$ 355, other ions at m/z 340, 329, 280, 250, 128, 105; $[\alpha]^{25}_D$ +15.4° (*c* 1.05, $CHCl_3$). Anal. ($C_{20}H_{22}$BrN·HCl) C, H, N.

Physical data for *trans*-(3a*S*,*R*)-**11b**: mp 246–247 °C; ^{1}H NMR δ 7.78–7.32 (m, 6 H), 6.98 (d, J = 7.8 Hz, 2 H), 4.24–1.12 (m, 11 H), 1.93 (d, J = 6.9 Hz, 3 H); IR (mull) ν_{max} 1606, 1594, 1586, and 1558 cm^{-1}; MS M$^+$ 355, other ions at m/z 340, 280, 250, 128, 105; $[\alpha]^{25}_D$ +102.6° (*c* 1.05, $CHCl_3$). Anal. ($C_{20}H_{22}$BrNO·HCl) C, H, N.

***cis*-(3a*R*)-(−)-2,3,3a,4,5,9b-Hexahydro-9-bromo-3-propyl-1*H*-benz[*e*]indole ((−)-12a).** A solution of *cis*-(3a*R*,*R*)-**11a** (22.5 g, 63 mmol) and 1-chloroethyl chloroformate (34 mL, 315 mmol) in chlorobenzene (200 mL) was refluxed for 24 h (bath temperature 130 °C). An additional 5 equiv of 1-chloroethyl chloroformate (34 mL, 315 mmol) was added, and refluxing was continued for an additional 24 h. The oil bath was cooled to 110 °C, and MeOH (200 mL) was added slowly. The solution was refluxed for 1 h. The solvent was removed in vacuo, and toluene was then added and again removed in vacuo to yield a tan/brown solid. This solid was dissolved in 600 mL of THF/MeOH (1:1) and treated with propionaldehyde (22.7 mL, 315 mmol) followed by acetic acid (20 mL) to pH 4–5. The solution was cooled to 0 °C, and sodium cyanoborohydride (7.92 g, 126 mmol) was added and stirred overnight at room temperature. The reaction was quenched with 20% NaOH, and solvents were removed in vacuo. The mixture was extracted with ethyl acetate (2 × 800 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The brown oil was purified by liquid chromatography on 600 g of silica gel, eluting with 4 L (9:1) and 10 L (4:1) of methylene chloride/ethyl acetate (4:1) to yield pure (−)-**12a** (15.4g, 83%) as a yellow oil: ^{1}H NMR δ 7.37 (d, J = 7.7 Hz, 1 H), 7.03 (d, J = 7.7 Hz, 1 H), 6.93 (t, J = 7.7 Hz, 1 H), 3.56 (q, J = 9.3 Hz, 1 H), 3.04 (t, J = 7.8 Hz, 1 H), 2.95–1.22 (m, 12 H), 0.94 (t, J = 7.4 Hz, 3 H); IR (film) ν_{max} 1593 and 1561 cm^{-1}; MS M$^+$ 293, other ions at m/z 264, 235, 207, 156, 128, 115, 92; $[\alpha]^{25}_D$ −167° (*c* 1.35, $CHCl_3$). Anal. ($C_{15}H_{20}$BrN) C, H, N.

***trans*-(3a*R*)-(−)-2,3,3a,4,5,9b-Hexahydro-9-bromo-3-propyl-1*H*-benz[*e*]indole ((−)-12b) and Enantiomer *trans*-(3a*S*)-(+)-12b.** Both (−)-**12b** and (+)-**12b** were prepared from *trans*-(3a*R*,*R*)-**11b** and *trans*-(3a*S*,*R*)-**11b**, respectively, using the procedure described in the preparation of (−)-**12a**. Compound (−)-**12b** was obtained in 73% yield as a yellow oil: ^{1}H NMR δ 7.35 (d, J = 7.7 Hz, 1 H), 7.07 (d, J = 7.7 Hz, 1 H), 6.94 (t, J = 7.7 Hz, 1 H), 3.43–3.37 (m, 1 H), 3.03–2.83 (m, 5 H), 2.26–1.54 (m, 8 H), 0.93 (t, J = 7.3 Hz, 3H); IR (film) ν_{max} 1591 and 1554 cm^{-1}; MS M$^+$ 293, other ions at m/z 264, 156, 128; $[\alpha]^{25}_D$ −91.3° (*c* 1.44, $CHCl_3$). Anal. ($C_{16}H_{20}$BrN). Compound (+)-**12b** was obtained in 63% yield as a yellow oil: ^{1}H NMR, IR, and MS were identical to those of (−)-**12b**: $[\alpha]^{25}_D$ +93.4° (*c* 1.44, $CHCl_3$). Anal. ($C_{16}H_{20}$BrN) C, H, N.

***cis*-(3a*R*)-(−)-2,3,3a,4,5,9b-Hexahydro-3-propyl-1*H*-benz[*e*]indole-9-carboxamide ((−)-3a).** An oven-dried flask was charged with THF (150 mL, distilled over ketyl) and cooled to −78 °C. *t*-BuLi (1.7 M) in pentane (61.7 mL, 105 mmol) was added slowly over 5 min to give a yellow solution. After the solution was stirred for 5–10 min, the bromide (−)-**12a** (14.7 g, 50 mmol) in THF (100 mL) was added over 10 min. The resulting brown mixture was stirred for 10 min, and trimethylsilyl isocyanate (10.2 mL, 75 mmol, freshly distilled over CaH) was added quickly by syringe at −78 °C. After 5 min, the dry ice/acetone bath was removed and the solution was allowed to warm

to room temperature over 1 h. The reaction was quenched with saturated aqueous ammonium chloride (100 mL), and THF was removed in vacuo. The mixture was treated with 20% NaOH until pH > 13, diluted with water, and extracted with methylene chloride (2 × 800 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to give a yellow solid. The solid was purified by liquid chromatography on 800 g of silica gel, eluting with acetone (4 L) and 10% 2-propanol/acetone (2 L). Fractions homogeneous by TLC were combined to yield (−)-**3a** as a solid (11.0 g, 85%) which was recrystallized from ethyl acetate/hexane. The physical data were identical to those of (−)-**3a** obtained from *cis*-(3a*R*)-(−)-**4a** *via* the first synthesis (see Scheme I): $[\alpha]^{25}_D$ −230° (*c* 1.22, $CHCl_3$), −234° (*c* 0.84, MeOH). A less polar compound (1.3 g, 12%) was isolated and identified as unsubstituted tricyclic analog **2** (R_1 = H, R_2 = propyl) as the side product from lithium/hydrogen exchange: ^{1}H NMR (as the HCl salt) δ 7.19–7.12 (m, 4 H), 4.12–1.60 (m, 14 H), 1.01 (t, *J* = 7.3 Hz, 3 H).

***trans*-(3a*R*)-(−)-2,3,3a,4,5,9b-Hexahydro-3-propyl-1*H*-benz[*e*]indole-9-carboxamide ((−)-3b) and Enantiomer *trans*-(3a*S*)-(+)-3b.** Both (−)-**3b** and (+)-**3b** were prepared in 70% yield from (−)-**12b** and (+)-**12b**, respectively, using the procedure described in the preparation of (−)-**3a** from (−)-**12a**. The physical data for both (−)-**3b** and (+)-**3b** were identical with an opposite optical rotation: ^{1}H NMR δ 7.24 (d, *J* = 9.1 Hz, 1 H), 7.17 (d, *J* = 6.6 Hz, 1 H), 7.10 (t, *J* = 7.5 Hz, 1 H), 5.82 (br s, 1 H), 3.93 (q, *J* = 9.1 Hz, 1H), 3.12–1.38 (m, 13 H), 0.93 (t, *J* = 7.3 Hz, 3 H); IR (mull) ν_{max} 3376, 1644, and 1586 cm^{-1}; MS M^+ at *m/z* 258, other ions at 229, 212, 200; $[\alpha]^{25}_D$ −227 ° (*c* 1.0, $CHCl_3$) for (−)-**3b** and $[\alpha]^{25}_D$ +221° (*c* 0.66, $CHCl_3$) for (+)-**3b**. Anal. ($C_{16}H_{22}N_2O$) C, H, N.

X-ray Crystallography of (−)-3a/(*R,R*)-dibenzoyltartrate. The absolute configuration of this compound was established on the basis of the known (*R,R*)-configuration of the (*R,R*)-dibenzoyltartaric acid. A solution of (−)-**3a** (258 mg, 1 mmol) and (*R,R*)-dibenzoyltartaric acid monohydrate (188 mg, 0.5 mmol) in methanol was azetroped with toluene. The resulting white solid was recrystallized from ethyl acetate/methanol to yield a white solid: mp 125–127 °C; ^{1}H NMR (CD_3OD) δ 7.96–6.88 (m, 16 H), 5.96 (s, 2 H), 0.82 (t, *J* = 7.3 Hz, 6H). These data indicate a 2:1 ratio of **3a** and dibenzoyl-L-tartaric acid.

Crystal data: $2(C_{16}H_{22}N_2O) \times C_{15}H_{14}O_8 \times H_2O \times 2.5$ (CH_3OH); formula weight = 1083.20; monoclinic; space group *C*2; *Z* = 4; *a* = 23.468(4) Å, *b* = 10.899(3) Å, *c* = 20.005(9) Å, β = 89.64(3)°; *V* = 5116.7(27) Å^3; calculated density = 1.41 g cm^{-3}, absorption coefficient μ = 0.6 mm^{-1}. Intensity data were collected at low temperature, −122 °C, on a Siemens P1bar diffractometer using graphite-monochromatized Cu Kα radiation, (λ(Cu Kα) = 1.5418 Å, with $2\theta_{max}$ = 135.° $\theta/2\theta$ step scans were used with scan widths ≥3.4° and scan rates of 4°/min. The data collection was repeated in another quadrant, and intensities were averaged; there were 4852 unique reflections. Ten reflections periodically monitored showed no trend toward deterioration; $\sigma^2(I)$ was approximated by $\sigma^2(I)$ from counting statistics + $(dI)^2$, where the coefficient of *I* was calculated from the variations in intensities of the monitored reflections and was 0.028. Cell parameters were determined by least-squares fit of Kα$_1$ 2θ values (λKα$_1$ = 1.5402) for 25 high 2θ reflections.[30]

A Lp correction appropriate for a monochromator with 50% perfect character was applied. A partial trial solution was obtained by direct methods using Multan80[31] and extended with successive Fourier syntheses. All hydrogens except those on the methanol and water molecules were found in difference maps close to generated positions; generated positions were used in the calculations and updated after each refinement. Temperature factors for hydrogens were assigned as one-half unit higher than the equivalent isotropic temperature factors for the attached carbon.

There are two molecules of (−)-**3a**, one molecule of (*R,R*)-dibenzoyl tartaric acid ((*R,R*)-DBTA), one water molecule, and 2.5 methanol molecules in the asymmetric unit. (One of the methanol molecules is in a special position, with carbon on the 2-fold axis and oxygen disordered.) Both amine nitrogens are protonated and make hydrogen bonds with DBTA oxygens. Most of the possible hydrogen bond donors and acceptors in the structure participate in hydrogen bonds; exceptions are the carbonyl oxygen on one of the two (−)-**3a** molecules and the carbonyl and ether oxygens in the DBTA molecule (all four carboxyl oxygens are involved in hydrogen bonds, however). Least-squares refinement included coordinates and anisotropic thermal parameters for non-hydrogen atoms except that the water oxygen and the methanol situated on the 2-fold axis were kept isotropic. The function minimized in the refinement was $\sum w(F_o^2 - F_c^2)^2$, where weights *w* were $1/\sigma^2(F_o^2)$. The absolute configuration of (−)-**3a** was determined from prior knowledge of the (*R,R*)-DBTA molecule to be *cis*-(3a*R*). Anomalous dispersion factors[32] were included in final refinement cycles; shifts in the final cycles were ≤0.2σ. The population factors for the special position methanol were 0.5 for the carbon on the 2-fold axis and 0.25 for each of the disordered oxygens. The final agreement index *R* was 0.073 for all 4852 reflections and 0.063 for the 4078 reflections with intensities >3σ. Atomic form factors were from Doyle and Turner[33] and, for hydrogen, from Stewart, Davidson, and Simpson.[34] The CRYM system of computer programs was used.[35]

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 am to 7 pm) 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 am and 1 pm.

Materials. (+)-**Flesinoxan** was synthesized at the Upjohn Company.[36] 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; pH 4).

5-HT$_{1A}$ and D$_2$ *in Vitro* Binding Assays. Competition binding experiments employed 11 dilutions of test compounds competing with [^{3}H]-8-OH-DPAT (85 Ci/mmol, 1.2 nM) or [^{3}H]-U86170[37] (62 Ci/mmol, 2 nM) for 5-HT$_{1A}$ and D$_2$ binding sites, respectively (Table II). In each case cloned mammalian receptors expressed in CHO-K1 cells were used.[38] 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.[39]

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.[40] Eighteen hours prior to the motility testing (carried out between 9 am and 1 pm), 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 or orally (*n* = 4). 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.[41] Separate dose–response curves based on four to six dose levels (*n* = 4) for each substance (sc and/or po administration) 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 % of controls, was as follows: limbic system −65%, striatum = −80%, and the hemispheres = −50%) and the 5-HTP (the maximal effect, expressed as % controls, was as follows: limbic system, striatum, and the hemispheres = −50%) levels were estimated separately (Table II). Reserpine pretreated control values for 5-HTP were (ng/g, mean ±SEM, *n* = 4) as follows: limbic system 163 ± 22, striatum = 125 ± 14, and the hemispheres 99 ± 13. DOPA (ng/g, mean ±SEM, *n* = 10); limbic system 808 ± 56, striatum 3653 ± 222, and the hemispheres 165 ± 11.

Hypothermia Assay. Charles River CF-1 mice (18–22 g, four per dose) were individually housed in clear plastic cages with sawdust bedding and perforated metal tops for 20 min prior to testing. After control rectal temperatures were measured, test compounds were given sc in 0.1 mL volume; 20 min later, rectal temperatures were again measured. A decrease of two or more °F was considered to be a positive hypothermic response. Drug doses started at 30 mg/kg and were decreased by half-log value until 0 out of 4 mice showed a positive hypothermic response. ED_{50}'s and 95% confidence intervals were determined by Spearman–Karber's method.[42] Oral dosing was similar to sc dosing except a rounded oral 18 ga hypodermic needle was used and the volume given was 0.2 mL. Regardless of the route of administration, the mean maximum temperature drop 20 min following any dose was noted as an index of drug efficacy and indirect estimate of intrinsic activity.

5-HT_{1A} Cell Firing. Charles River male Sprague–Dawley rats (280–330 g) were anesthetized with chloral hydrate (400 mg/kg ip). Supplemental doses were administered as needed to maintain anesthesia. The femoral artery and vein were cannulated for blood pressure and drug administration. The animal's head was held in a stereotaxic device and a small burr hole drilled at the appropriate location. Extracellular action potentials were recorded with a glass microelectrode (tip size <1 μm) filled with potamine sky blue dye in 2 M sodium chloride. Serotonergic neurons were identified by their large, biphasic positive–negative action potentials with slow and regular firing rates (approximately 0.8–2.5 spikes/s) as previously described.[43] The recording electrode was hydraulically advanced to reach the dorsal raphe nucleus (A 0.5–1.7 mm, L 0 mm, V 3.5–4.2 mm) according to the coordinates of Paxinos and Watson.[44] At the termination of each recording session, the location of the cell was identified by passing a 10-μA cathodic current for 10–20 min. The brain was then removed, sectioned, and stained and the pontamine sky blue deposit verified in each animal. Only those cells found to be in the appropriate area were included in the study. All drug solutions were made in distilled water. Each drug injection contained no more than 0.15 mL of a given concentration, followed by 0.2–0.4 mL of physiological saline to clean the catheter of any residual drug. Drug effects were measured as changes in firing rates as indicated by an integrated ratemeter output throughout the experiment. The dose required to depress neuronal firing by 50% was taken as the ED_{50}, measured by interpolation of the dose–response curve for each individual cell.

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

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

Swim Stress Test for Antidepressant-like Activity. To determine whether the test compounds have potential in the treatment of depressive disorders, they were screened in a swim stress paradigm adapted from the Porsolt behavioral despair assay.[45] This adaption involves the mechanization of the measurement of swimming behavior and the computer-assisted collection and analysis of the data.[46] Briefly, male CF-1 mice (28–31 g) were injected subcutaneously with solutions or suspensions of the test compounds in 0.25% aqueous methylcellulose at a volume dose of 10 mL/kg. Five mice were tested at each dose level, and typically several doses (e.g., 0.1 to 10 mg/kg) were tested. Testing involved placement of the mice (30 min after drug administration) individually into an enclosed aqueous environment. The swimming activity of the mice was monitored over the period of 8 min, and that during the last 3 min was compared to that of vehicle-treated animals. Significant increases ($p < 0.05$) in measured swimming activity were considered indicative of antidepressant-like activity.

Absolute Oral Bioavailability. Blood levels were measured by means of gas chromatography (Hewlett-Packard)–mass spectrometry (VG Trio II). The blood samples (150 μL) were collected from arterial catheters in male Sprague–Dawley rats (300 g, ALAB Sollentuna, Sweden) 24 h after operation. The duration of the sampling varied between 10 and 24 h. The samples were then diluted with 1 μL of water. Then 50 μL of internal standard [8-methoxy-2-(dicyclopropylmethylamino)tetralin], 10 pmol/μL, was added. The pH was adjusted to 11.0 by addition of 50 μL of saturated Na_2CO_3. After mixing, the samples were extracted with 4 mL of dichloromethane by shaking for 2 min. The organic layer was transferred to a smaller tube and evaporated to dryness under a stream of nitrogen. The reagent was evaporated under nitrogen, and the sample was redissolved in 40 μL of toluene for GC/MS analysis. A standard curve over the range 2–1000 pmol/mL was prepared by adding appropriate amounts of standard to blank blood samples. A set of control samples at two different concentrations (made up in bulk and kept frozen) were included in each assay. GC was performed on cross-linked PS 264 capillary column (15 m × 0.25 mm), and a 2-μL sample was injected in the splitless mode. The GC temperature was held at 90 °C for 1 min following injection and was then increased by 30 °C/min to the final temperature of 290 °C. Each sample was run in duplicate. The absolute oral availability of the compounds was assessed by comparing the areas under the curves (AUC) for po and iv administration ($n = 4$) in graphs where the blood concentrations of the compound were plotted against time. Rats treated orally with drug were starved 18 h before the experiment but had free access to water.

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Supplementary Material Available: The tables of fractional coordinates, bond lengths and angles, torsion angles, close intermolecular contacts, hydrogen bonds, and anisotropic thermal parameters (13 pages). Ordering information is given on any current masthead page.

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