Novel 2-Substituted Tetrahydro-3*H*-benz[*e*]indolamines: Highly Potent and Selective Agonists Acting at the 5-HT_{1A} Receptor as Possible Anxiolytics and Antidepressants

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The synthesis of (+)-(*R*)-2-cyano-*N*,*N*-dipropyl-8-amino-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole [(*R*)-14, U92016A], a potent 5-HT_{1A} agonist, and related analogs is described. *In vitro* binding studies show that the (*R*)-enantiomers of this series possess the highest potency for the 5-HT_{1A} receptor. *In vivo* hypothermia correlates with this, with the (*R*)-enantiomers causing a greater temperature drop than the (*S*)-enantiomers. The most active compound in 5-HT_{1A} binding and in the *in vivo* models was (*R*)-14, which was found to be highly potent as an agonist in single cell firing studies, as well as potent and of very high intrinsic activity in mouse hypothermia and the sympathetic nerve discharge (SND) models. An *in vivo* duration of action study, following SND, showed (*R*)-14 to possess a long duration of action. The synthesis *via* a nitrene insertion, determination of absolute configuration, and biological activities of this series is described.

Introduction

The involvement of serotonin (5-hydroxytryptamine, 5-HT) in the etiology and treatment of anxiety and depression has been the subject of intensive investigations. This was prompted by the discovery that buspirone and other agonists of the 5-HT_{1A} receptor subtype possess clinical efficacy as novel anxiolytics and antidepressants.[1] Classical tricyclic antidepressants act on 5-HT transmission through a nonselective blockade of 5-HT uptake[2] while newer "atypical" antidepressants drugs (i.e. fluoxetine and fluvoxamine) act selectively to inhibit 5-HT uptake.[3] The net effect of both of these classes of antidepressants is to increase the concentration of 5-HT at the synapse of 5-HT neurons. Recently, it has been shown that 5-hydroxytryptophan (5-HTP), the biochemical precursor to 5-HT, as well as 5-HT uptake inhibitors are effective in the treatment of generalized anxiety and panic disorders.[4] The recent discovery that buspirone and other 5-HT_{1A} receptor agonists produce anxiolytic and antidepressant activity has directed attention to the 5-HT_{1A} receptor as the possible site of all of these anxiolytic and antidepressant effects.

In the central nervous system (CNS), the 5-HT_{1A} receptor is broadly distributed, occurring as a somatodendritic autoreceptor on 5-HT cell bodies located in the raphe nuclei, and postsynaptically in other areas such as the hippocampus.[5] Unlike the benzodiazepines, 5-HT_{1A} agonists have been reported to produce little sedation, do not potentiate the effects of ethanol, and do not show potential for dependence or abuse.[6] While the arylpiperazine 5-HT_{1A} agent buspirone is clinically utilized for the treatment of anxiety, it possesses less intrinsic activity and is a partial agonist at the 5-HT_{1A} receptor, in contrast to the prototypical 5-HT_{1A} ligand 8-hydroxy-*N*,*N*-di-*n*-propylaminotetralin (8-OH-DPAT, Figure 1), which is a full agonist.[7] Also, the clinical efficacy of this arylpiperazine is limited, requiring a 2-week delay before the onset of anxiolytic activity.[8] The reason for this delay is unknown. Interestingly, patients with a history of benzodiazepine use frequently respond poorly.[9] There is speculation as to whether a 5-HT_{1A} receptor full agonist would possess greater clinical utility and this is the basis of this research, the synthesis and evaluation of potent, high intrinsic activity 5-HT_{1A} receptor agonists (Table I).

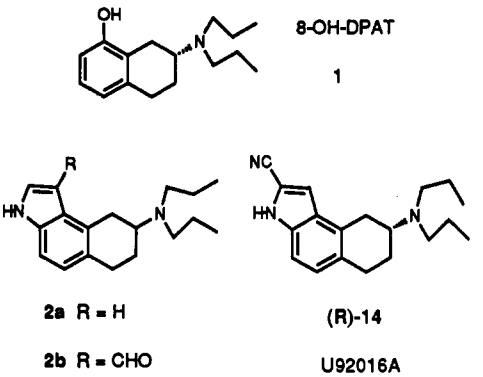

Figure 1.

It has been reported that, while 8-aminotetrahydro-3*H*-benz[*e*]indole **2a** possessed affinity for the 5-HT_{1A} receptor,[10] it was nonselective and equipotent at the dopamine D_2 receptor.[11] After Carlsson's group brought the much more selective 1-formyl analog **2b** to our attention,[12] we became interested in synthesizing analogs with functional groups substituted on the pyrrole portion of the molecule, with the desire to continue to improve the selectivity for the 5-HT_{1A} receptor. The ring system of these analogs was synthesized by a nitrene insertion reaction, induced by pyrolyzing a vinyl azide, to generate the heterocycle portion of an indole subunit. This allowed the synthesis of optically active (+)-(*R*)-14, also known as U92016A, in 11 steps. The absolute configuration of the congeners described herein was determined by X-ray analysis to aid in the determination of the 5-HT_{1A} receptor SAR. Besides receptor binding profiles, the compounds were tested in three models of intrinsic activity: single cell (5-HT) firing (rat), hypothermia (mouse), and sympathetic nerve discharge (SND) (cat).

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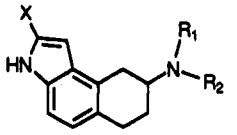
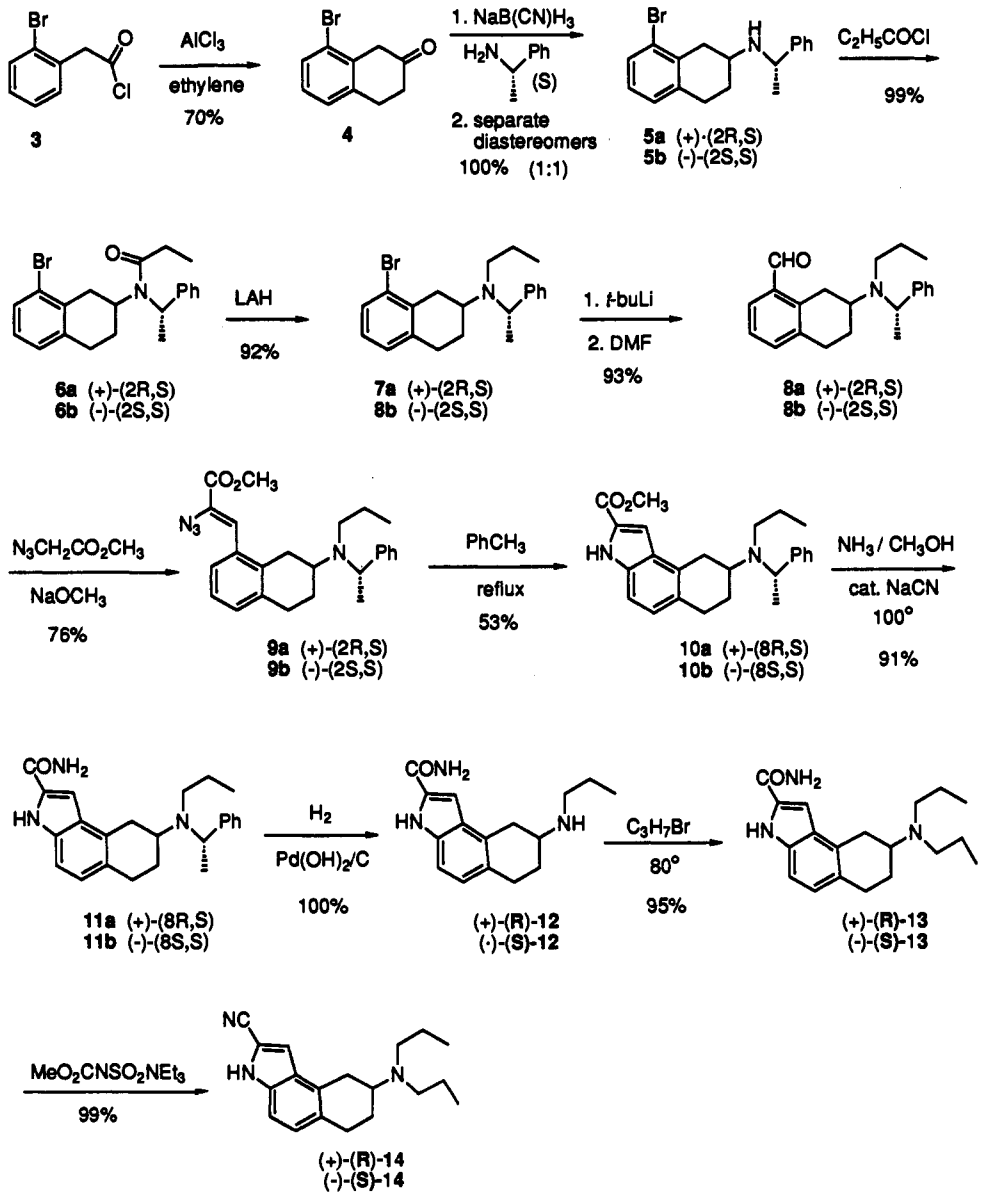
Table I. Physical Properties of 8-Aminotetrahydro-3*H*-benz[*e*]indole Derivatives



cmpd	R_1	R_2	X	$[\alpha]^{25}_D$, deg (c values, MeOH)	formula[a]	mp, °C
(*R*)-12	H	*n*-propyl	$CONH_2$	+69.4 (0.535)	$C_{19}H_{21}N_3O$	230–231
(*S*)-12	H	*n*-propyl	$CONH_2$	−70.1 (0.874)	$C_{19}H_{21}N_3O$	230–231
(*R*)-13	*n*-propyl	*n*-propyl	$CONH_2$	+88.0 (0.835)	$C_{19}H_{27}N_3O\cdot HCl$	302 dec
(*S*)-13	*n*-propyl	*n*-propyl	$CONH_2$	−86.9 (2.525)	$C_{19}H_{27}N_3O\cdot HCl$	302 dec
(*R*)-14	*n*-propyl	*n*-propyl	CN	+104 (1.500)	$C_{19}H_{25}N_3\cdot HCl$	134–135
(*S*)-14	*n*-propyl	*n*-propyl	CN	−105 (0.740)	$C_{19}H_{25}N_3\cdot HCl$	134–135
(*R*)-15	*n*-propyl	*c*-prop-methyl[b]	$CONH_2$	+138 (0.515)	$C_{20}H_{25}N_3\cdot HCl$	309 dec
(*S*)-15	*n*-propyl	*c*-prop-methyl[b]	$CONH_2$	−136 (0.550)	$C_{20}H_{25}N_3\cdot HCl$	308 dec
(*R*)-16	*n*-propyl	imide butyl[c]	$CONH_2$	+64.8 (0.720)	$C_{27}H_{38}N_4O_3\cdot HCl$	210 dec
(*S*)-16	*n*-propyl	imide butyl[c]	$CONH_2$	−65.6 (0.720)	$C_{27}H_{38}N_4O_3\cdot HCl$	210 dec
(*R*)-17	*n*-propyl	imide butyl[c]	CN	+71.2 (0.527)	$C_{27}H_{38}N_4O_2\cdot HCl$	220–221
(*S*)-17	*n*-propyl	imide butyl[c]	CN	−73.9 (1.23)	$C_{27}H_{36}N_4O_2\cdot HCl$	220–221

[a] Analyses were within ±0.40% of the calculated values. [b] Cyclopropylmethyl. [c] 4-(4,4-dimethyl-2,6-dioxopiperidin-1-yl)butyl.

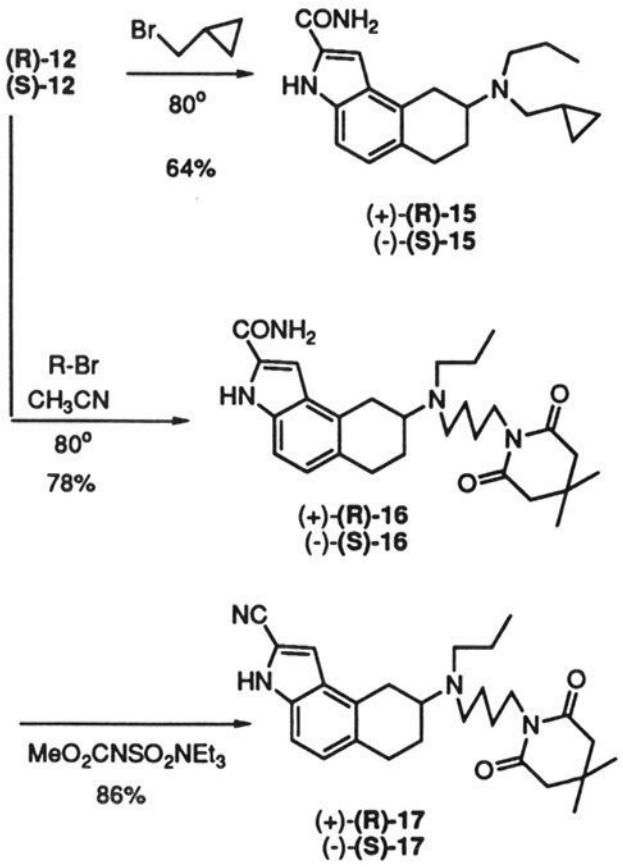
Scheme I



Results

Chemistry. 8-Bromo-2-tetralone was obtained in a tandem Friedel–Crafts reaction utilizing 2-bromophenylacetyl chloride and ethylene (Scheme I).[13] The aminotetralins were synthesized and resolved into their optical antipodes at an early stage through the use of (−)-*S*-α-methylbenzylamine in a reductive amination. Both Borch[14] ($HOAc/NaCNBH_3$) and $TiCl_4/NaCNBH_3$[15] con-

Scheme II



ditions provided the diastereomers (+)-(2*R*,*S*)-**5a** and (−)-(2*S*,*S*)-**5b** in a 1:1 ratio in very high yield. These could be easily separated by flash chromatography to afford the optically pure diastereomeric secondary amines, which were carried on separately. Attempts to alkylate the sterically hindered amine contained in **5** with *n*-iodopropane in refluxing acetonitrile to give tertiary amine **7** were unsuccessful. To circumvent this problem, **5** was acylated with propionyl chloride to give the amide **6**, which was then reduced with LAH to give **7**. A metal–halogen exchange reaction followed by formylation with DMF gave aldehyde **8**. Aldehyde **8** underwent condensation with methyl azidoacetate[16] to afford the (*Z*)-azido substituted cinnamic acid derivative **9** in very good yield. Compound **9** underwent a facile thermolysis via a nitrene insertion to afford indole **10**. This indole-containing adduct was heated with methanolic ammonia in the presence of catalytic sodium cyanide[17] to afford the carboxamide **11** in excellent yield. Hydrogenation over Pearlman's catalyst afforded secondary amine **12**, which was alkylated with various alkyl halides. The carboxamide was smoothly dehydrated to the corresponding nitrile using Burgess' reagent (Scheme II).[18]

Absolute Configuration. The absolute configuration of this series was determined by performing an X-ray diffraction experiment with (−)-(2*S*,*S*)-**6b**. The X-ray-determined structure is shown in Figure 2. The known absolute configuration of the chiral auxiliary (*S*) allows the stereochemistry of the 2-aminotetralin bond to be assigned unambiguously (*S*). Details of the structure determination are in the Experimental Section. It is convenient to note that throughout this series the (+)-enantiomer/diastereomer contains the (*R*)-2-aminotetralin stereochemistry, whereas the (−)-enantiomer/diastereomer contains the (*S*)-2-aminotetralin stereochemistry.

Biology. Table II shows that all of the analogs, including buspirone and 8-OH-DPAT, exhibited high affinity and selectivity for the 5-HT_{1A} receptor relative to the D_2-dopamine receptor. Of the analogs evaluated, (*R*)-**14** possessed the greatest potency, 0.1 nM. Stereoselectivity at the 5-HT_{1A} receptor was evident, the (*R*)-enantiomers having higher affinity than the (S)-enantiomers, particularly for the (*R*)-**12**/(*S*)-**12**, (*R*)-**16**/(*S*)-**16**, and (*R*)-**17**/(*S*)-**17** pairs. Stereoselectivity was also evident at the D_2-dopamine receptor. Only (*R*)-**14**, (*R*)-**16**, and (*R*)-**17** were found to possess significant D_2-dopamine affinity, but even these expressed a high degree of receptor selectivity (D2/5-HT1A = 357, 64, and 219, respectively). Examination of Figure 3 shows why this is not surprising. Assuming that the ligands bind to the receptor in the ground-state conformation with the amino group pseudoequatorial, both the (*R*)- and (*S*)-enantiomers have similar, but not identical, overlap of the essential pharmacophore structural features (amino and aryl). This observation that antipodes can possess differential but similar affinity for the 5-HT_{1A} receptor is documented and has been included in the development of receptor-fit structure–activity relationship models.[19]

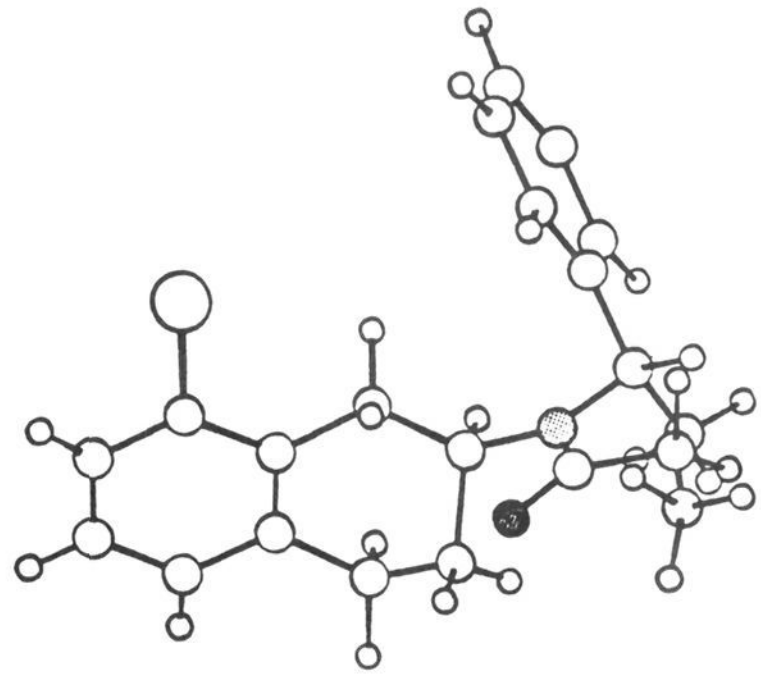


Figure 2. X-ray structure determination of the absolute configuration of (−)-(2*S*,*S*)-**6b**.

Single cell firing was obtained for only selected compounds (Table III). (*R*)-**14** exhibited high potency in shutting off 5-HT neurons (acting as agonists at the presynaptic 5-HT_{1A} autoreceptor), with ED_{50}'s on the order of 3 μg. It is interesting to contrast the lack of activity of enantiomeric amides (*S*)-**13** and (*R*)-**13** to the very potent, structurally homologous nitrile (*R*)-**14**, in the single cell firing model. While the amides both possess high affinity for the 5-HT_{1A} receptor, they are inactive in single cell firing.

Hypothermia has been used to evaluate 5-HT_{1A} agonists for their potential as antidepressants and anxiolytics[20] and is used to measure the intrinsic activity of compounds acting on 5-HT_{1A} receptors located on presynaptic 5-HT sites as agonists.[21,22] Supporting this is a study where chronic administration of the tryptophan 5-hydroxylase inhibitor *p*-chlorophenylalanine (*p*-CPA) or the 5-HT neurotoxin 5,7-dihydroxytryptamine (5,7-DHT) abolished the hypothermic effect of 8-OH-DPAT by depleting the synapse of 5-HT.[23] However, hypothermia is a nonspecific *in vivo* endpoint that is sensitive to both D_2 and 5-HT_{1A} agonists. Since all of the compounds in Table III had much higher affinity for the 5-HT_{1A} receptor than the D_2 receptor, it is likely that the hypothermic response in Table III is due to 5-HT_{1A} agonist activity. For (*R*)-**14**, which was one of the most hypothermic agents, the selective binding to the 5-HT_{1A} receptor was reflected in selective depression of 5-HT neurons when compared to dopamine neurons in single cell firing (Table III). It is of value to note that the (*R*)-enantiomers, without exception, induced

Table II. 5-HT_{1A} and D_2 Receptor Binding Affinities, Hypothermia, and Sympathetic Nerve Discharge (SND)

compound	binding affinity[a] K_i ± SEM (nM) 5-HT_{1A}	D_2-dopamine	hypothermia (mouse) max[c] temp decrease, °C	ED_{50},[d] mg/kg sc	SND[b] (cat) max[e] effect, % control	ED_{50},[f] mg/kg iv
buspirone	3.1 ± 1.0	13 ± 1.4	1.9	3.0 (1.6–6.1)	43 (±0)	0.08 (0.05–0.14)
8-OH-DPAT	0.1 ± 0.1	93 ± 10	4.0	1.0 (0.5–1.8)	0 (±0)	0.01 (0.007–0.15)
(*R*)-12	7.6 ± 1.0	857 ± 85	2.4	2.3 (1.0–5.5)	NT[g]	NT
(*S*)-12	103 ± 7	>1667	1.8	17.3 (17.3–17.3)	NT	NT
(*R*)-13	1.6 ± 0.2	215 ± 12	3.3	0.6 (0.3–1.2)	0 (±0)	0.19 (0.12–0.36)
(*S*)-13	1.9 ± 0.2	>1000[h]	2.2	1.0 (0.5–1.8)	10 (±10)	0.19 (0.15–0.29)
(*R*)-14	0.1 ± 0.1	35 ± 2.5	7.2	0.04 (0.01–0.12)	0 (±0)	0.017 (0.011–0.035)
(*S*)-14	0.4 ± 0.3	896 ± 91	6.3	1.3 (0.8–2.2)	0 (±0)	0.15 (0.08–0.29)
(*R*)-15	2.7 ± 0.3	389 ± 23	4.0	2.3 (1.3–4.2)	43 (±2)	0.9 (0.6–1.3)
(*S*)-15	5.3 ± 0.6	>1000[h]	3.3	9.7 (5.2–18.4)	14 (±3)	0.4 (0.1–0.9)
(*R*)-16	0.6 ± 0.1	38 ± 3.3	2.8	9.7 (4.4–21.6)	22 (±7)	0.41 (0.1–0.9)
(*S*)-16	108 ± 32	914 ± 97	2.2	4.1 (1.7–9.8)	NT	NT
(*R*)-17	0.2 ± 0.0	44 ± 1.3	6.8	0.13 (0.06–0.31)	0 (±0)	0.01 (0.007–0.15)
(*S*)-17	2.8 ± 1.5	>333	3.9	3.1 (1.6–6.1)	NT	NT

[a] All compounds displayed <50% inhibition when tested at 1 μM at the α_1-, α_2-, and β-adrenergic, opioid, 5-HT_2, and cholinergic receptors using standard ^{3}H-labeled ligands; [^{3}H]-8-OH-DPAT binding to bovine hippocampal membranes and [^{3}H]U-86170 binding to D2-dopamine receptors expressed in CHO K-1 cells. [b] n = 3 for all compounds except buspirone (n = 6), 8-OH-DPAT (n = 8), (*R*)-14 (n = 6), and (*S*)-13 (n = 2). [c] Maximum obtaintable hypothermic effect, up to 30 mg/kg dose. [d] ED_{50} values are followed by 95% confidence intervals. [e] Maximum decrease in SND (±SEM) observed at a 1 mg/kg dose. [f] Dose required to reduce SND to 50% of the pretreatment value, followed by 95% confidence intervals. [g] Not tested. [h] IC_{50} value, determined from a single experiment.

Figure 3. MM2 conformational analysis showing the similar spatial planar geometry of the amine and the aryl ring (substituents X, R_1, and R_2 omitted for clarity).

Table III. Electrophysiological Data for Selected Compounds

compd	ED_{50} ± SEM,[a] μg/kg iv, rat (n) 5-HT cells	DA cells
buspirone	15.4 ± 5.5 (6)	11.3 ± 4.3 (5)[b]
8-OH-DPAT	1.6 ± 0.6 (7)	740 ± 470 (6)[b]
(*R*)-13	>100	NT[c]
(*S*)-13	>100	NT
(*R*)-14	3.4 ± 0.7 (4)	84 ± 12 (3)[b]

[a] Dose to reduce neuronal firing by 50%. [b] Antagonist. [c] Not tested.

a greater hypothermia response than the (*S*)-enantiomers. This is consistent with the greater 5-HT_{1A} receptor binding affinity of the (*R*)-enantiomers, and may imply a higher intrinsic activity for structurally similar (*R*)-enantiomers, which is supported by the recent discovery that (*R*)-8-OH-DPAT is a full agonist while (*S*)-OH-DPAT is only a partial agonist with an intrinsic activity of 0.5.[24-26] Furthermore, the 5-fluoro analog of (*R*)-8-OH-DPAT acts at the 5-HT_{1A} site as an agonist whereas the (*S*)-antipode appears to be an antagonist.[27]

(*R*)-14 and (*R*)-17, both (*R*)-nitriles, were shown to have profound hypothermic effects, causing temperature depressions of 7.2 and 6.8 °C, respectively. (*R*)-14 was also the most potent compound in this model, with a greater than 10 times increased potency than all of the other compounds in Table III, with the exception of the related nitrile (*R*)-17. Neither of the analogous amides (*R*)-13 nor (*S*)-13 showed good 5-HT_{1A} or D_2 potency *in vivo*, when measured on the single cell firing assay (*vide supra*). This suggests that the hypothermic activity (which is allowed a longer time to develop) of these two compounds may have been due to either metabolic activation into a 5-HT_{1A} or D_2 agonist or, just as likely, blood–brain barrier pharmakokinetics. Indeed, the carboxamide-substituted analogs are all quite lipophobic, and may be slow to get into the brain. Thus our approach to measuring single cell activity very soon after injection of drug may discriminate against compounds with slow rates of brain penetration, while the design used in the *in vivo* models in Table III allows more time for drug to accumulate in the brain.

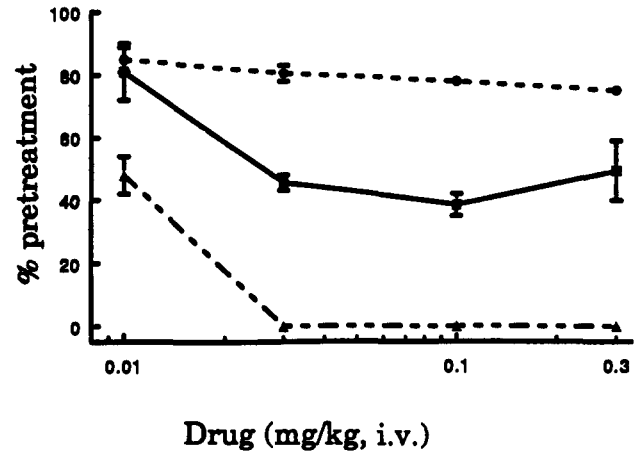


Figure 4. Dose–response curve (±SEM) for (*R*)-14's effect on sympathetic nerve discharge (- - -), mean arterial pressure (—), and heart rate (- -) in the intact cat (n = 6).

Sympathetic nerve discharge (SND) is affected by the tonic excitatory input that 5-HT neurons provides to central sympathetic neurons.[28] Thus, monitoring SND as well as SND inhibition's effects on mean arterial pressure (MAP) and heart rate (HR), provides a measure of the efficacy of 5-HT_{1A} receptor agonists to inhibit sympathetic nerve activity, a means of determining the intrinsic activity at the 5-HT_{1A} receptor. (*R*)-14 was again the most potent, with an ED_{50} value of 17 μg/kg. Figure 4 shows that (*R*)-14 was able to completely shut off SND at a dose of 0.03 mg/kg (iv). Furthermore, following the time course of SND inhibition with (*R*)-14 *vs* 8-OH-DPAT shows that (*R*)-14 possesses a much greater pharmacological half-life, far surpassing that of the prototypical 5-HT_{1A} agonist 8-OH-DPAT (Figure 5).

Conclusion

We have reported the synthesis of (*R*)-14 (U92016A), a potent, high intrinsic activity 5-HT_{1A} agonist. Related 2-substituted tetrahydro-3*H*-benz[*e*]indolamines possess

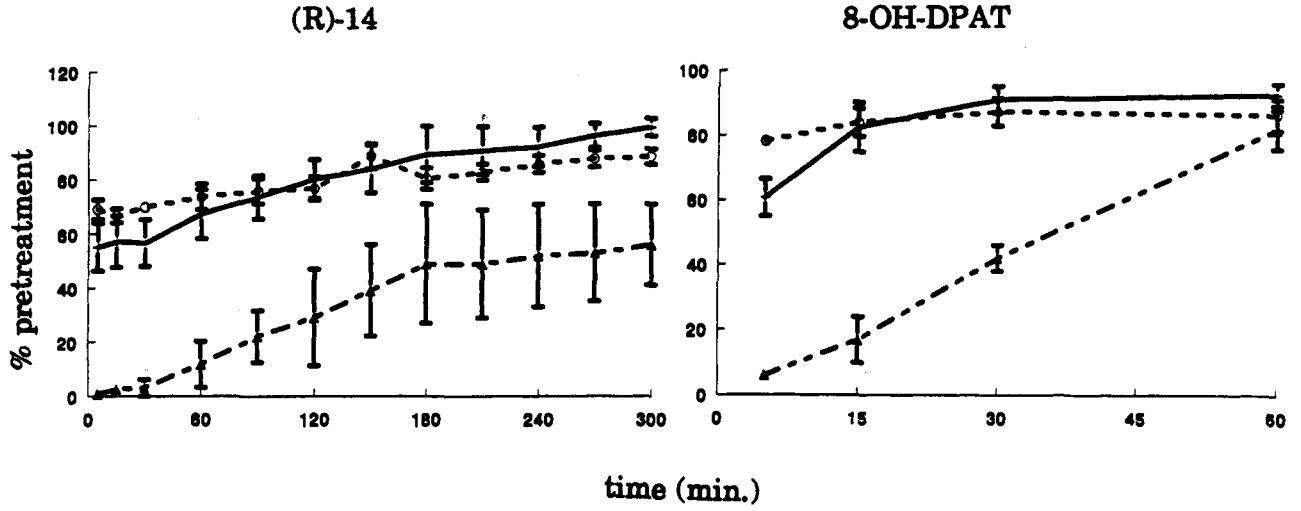


Figure 5. Comparison of efficacy (±SEM) and duration of action of (*R*)-14 and 8-OH-DPAT on sympathetic nerve discharge (- - -), mean arterial pressure (—), and heart rate (- -) in the intact cat ($n = 4$). Equally effective doses ((*R*)-14, 100 μg/kg; 8-OH-DPAT, 30 μg/kg iv) were given. Note the difference in the time coordinate scale.

high affinity and selectivity for the 5-HT_{1A} receptor. Several possess exceedingly high potency and efficacy in the *in vivo* models. This was especially true for (*R*)-14. The 5-HT_{1A} receptor, in both binding affinity and the *in vivo* hypothermia model, prefers the (*R*)-analogs, with the nitrile-substituted congeners usually possessing significantly greater efficacy. The preference for nitrile over carboxamide functional groups may be due to a lipophilic pocket in the binding site. These benz[*e*]indoles also show favorable pharmacokinetics, with good resistance to metabolism[29] and excellent *in vivo* duration of action results in the SND and hypothermia models. High intrinsic activity 5-HT_{1A} agonists such as (*R*)-14 may be effacaceous in the treatment of anxiety and depression.

Experimental Section

Chemistry. Proton and carbon magnetic resonance spectra were recorded on a Bruker Aspect 3000 spectrometer and are reported in ppm from trimethylsilane; coupling constants are reported in hertz. Infrared spectra were obtained using a Digilab Model FTS-40 spectrophotometer. Mass spectra were obtained with a Varian MAT CH5-DF spectrophotometer. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Optical rotations were taken with a Perkin-Elmer 241 polarimeter.

All reactions were carried out under an atmosphere of nitrogen. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Other solvents were used from freshly opened bottles. Thin-layer chromatography was performed using Analtech 250 μm silica gel GF plates. Flash chromatography was carried out on EM Reagents silica gel (230–400 mesh).

8-Bromo-2-tetralone (4). Aluminum trichloride (456 g, 3.4 mol) was suspended in methylene chloride (3000 mL) and cooled to −10 °C with an ice/salt bath. 2-Bromophenylacetyl chloride (200 g, 856 mmol) was added over 1 h. Gaseous ethylene (approximately 170 g, 6 mol) was bubbled into the solution over 1 h while being stirred rapidly. The solution was stirred for 15 min more, and then 6 N aqueous hydrochloric acid and ice were added slowly to quench the reaction. The solution was extracted and separated, and the organic layer was washed with 2 N aqueous hydrochloric acid, water, saturated aqueous sodium bicarbonate, and brine. Drying over sodium sulfate followed by solvent removal *in vacuo* afforded 273 g of a solid which was pure enough for further use, if desired. To rid the crude material of the polymeric hydrocarbon material (polyethylene) present, the crude material was recrystallized from hexane with a trace of toluene added. The first crop gave 134 g (70% yield) of off-white crystals (mp 73 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, 1H, $J = 9$), 7.19 (d, 1H, $J = 7$), 7.09 (t, 1H, $J = 9$), 3.67 (s, 2H), 3.09 (t, 2H, $J = 6$), 2.60 (t, 2H, $J = 7$); IR (mineral oil mull) 2950, 1706, 1563, 1446 cm^{-1}; MS *m/e* (rel intensity, 70 eV) 226 (M, 80), 224 (M, 82), 184 (95), 182 (100); high resolution calcd 223.9837, found 223.9844. Anal. ($C_{10}H_9OBr$) C, H.

(±)-8-Bromo-*N*-[(*S*)-α-methylbenzyl]-2-aminotetralin Diastereomers (5a and 5b). 8-Bromo-2-tetralone (25 g, 111.1 mmol), (*S*)-(−)-α-methylbenzylamine (71.5 mL, 555.5 mmol), acetic acid (80 mL), 4 A molecular sieves (15 mL), THF (125 mL), and methanol (125 mL) were introduced into a flask and cooled to 0 °C. Sodium cyanoborohydride (15.1 g, 222.2 mmol) was added in portions over a 15-min period. The slurry was allowed to stir for 3 h. The slurry was filtered and the solvent reduced to a syrup by evaporation in vacuo. The residue was partitioned between ether and 2 N aqueous sodium hydroxide. The ether layer was washed with water (3×) and brine. After drying over anhydrous sodium sulfate the solvent was removed in vacuo. The viscous oil was placed on a flash silica gel column (5 cm × 50 cm) and eluted with ethyl acetate/hexane (8%) to separate the higher R_f (+)-(2*R*,*S*)-diastereomer (**5a**), which solidifies upon standing to a waxy solid (17 g, 46% yield), mp 59 °C. The solvent was changed to ethyl acetate/hexane (12%) to elute the lower R_f (−)-(2*S*,*S*)-diastereomer (**5b**) (an oil, 16 g, 44% yield). (+)-(2*R*,*S*)-Diastereomer: $[\alpha]^{25}_D = +49.75$ °C ($c = 1.980$, methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 6H), 6.95 (m, 2H), 4.04 (dd, 1H, $J = 13.2, 6.6$), 2.97–2.68 (m, 4H), 2.43 (dd, 1H, $J = 16.9, 9$), 2.07 (m, 1H), 1.53 (m, 1H), 1.35 (d, 3H, $J = 6.6$), 1.33 (m, 1H); IR (thin film) 3082, 2924, 1561, 1491, 1439 cm^{-1}; MS *m/e* (rel. intensity, 70 eV) 331 (M, 50), 224 (30), 209 (42), 130 (95), 129 (100); high resolution calcd 329.0780, found 329.0766. (−)-(2*S*,*S*)-Diastereomer: $[\alpha]^{25}_D = -197.96$ °C ($c = 1.370$, methanol); ^{1}H NMR (300 MHz, $CDCl_3$) 7.37–7.23 (m, 6H), 6.99–6.90 (m, 2H), 4.09 (m, 1H), 3.15 (dd, 1H, $J = 16.9, 5$), 2.8–2.6 (m, 3H), 2.43 (dd, 1H, $J = 16.9, 9$), 1.83 (m, 1H), 1.52 (m, 1H), 1.38 (d, 3H, $J = 6.6$), 1.37 (m, 1H); IR (thin film) 3059, 3024, 2959, 1561, 1491, 1439, 1124, 736, 701 cm^{-1}; high resolution calcd 329.0780, found 329.0774. Anal. ($C_{18}H_{20}NBr$) C, H, N.

(+)-8-Bromo-*N*-[(*S*)-α-methylbenzyl]-2(*R*)-propionamidotetralin [(+)-6a]. (+)-8-Bromo-*N*-[(*S*)-α-methylbenzyl]-2(*R*)-aminotetralin [(+)-**5a**] (86.5 g, 262 mmol) was dissolved in methylene chloride (600 mL) with triethylamine (40 mL, 287 mmol) and cooled to 0 °C. Propionyl chloride (25 mL, 288 mmol) was added and the solution stirred for 1 h. The reaction was washed with water, 2 N aqueous hydrochloric acid, water, aqueous sodium bicarbonate, and brine and then dried over anhydrous sodium sulfate. Solvent removal in vacuo afforded 100 g (99% yield) of a yellow solid: mp 124 °C; $[\alpha]^{25}_D = +25.1$ °C ($c = 1.06$, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.26 (m, 5H), 6.93 (m, 3H), 5.16 (m, 1H), 3.29 (m, 1H), 3.25 (m, 1H), 2.87–2.3 (m, 6H), 1.70 (d, 3H, $J = 6.6$), 1.3 (m, 1H), 1.21 (t, 3H, $J = 7.3$); IR (mineral oil) 2783, 1641, 1444, 1437, 1384, 1376, 1277 cm^{-1}; MS *m/e* (rel intensity, 70 eV) 386 (M, 8), 210 (45), 210 (45), 178 (100),

129 (50), 105 (95); high resolution calcd 385.1042, found 385.1047. Anal. ($C_{21}H_{24}NOBr$) C, H, N.

(-)-8-Bromo-N-[(S)-α-methylbenzyl]-2(S)-propionamidotetralin [(-)-6b]. (-)-8-Bromo-N-[(S)-α-methylbenzyl]-2(S)-aminotetralin [(-)-**5b**] (69.9 g, 212 mmol) was acylated using the procedure described above to yield a solid (79 g, 96% yield): mp 94 °C; $[\alpha]^{25}_D$ = -96.4 °C (methanol, c = 1.07); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.2 (m, 5H), 7.0–6.8 (m, 3H), 5.16 (m, 1H), 3.35 (m, 2H), 2.95–2.3 (m, 6H), 1.8 (m, 1H), 1.67 (d, 3H, J = 6.8), 1.20 (t, 3H, J = 7.1); IR (mineral oil) 2924, 1648, 1438, 1278, 1168, 1025 cm^{-1}; MS m/e (rel intensity, 70 eV) 387 (M, 8), 385 (M, 8), 416 (3), 314 (3), 210 (45), 208 (45), 178 (100), 129 (49), 105 (100); high resolution calcd 385.1042, found 385.1050. Anal. ($C_{21}H_{24}$-NOBr) C, H, N.

(+)-8-Bromo-N-[(S)-α-methylbenzyl]-N-propyl-2(R)-aminotetralin [(+)-7a]. (+)-8-Bromo-N-[(S)-α-methylbenzyl]-2(R)-propionamidotetralin [(+)-**6a**] (100 g, 259 mmol) in THF (500 mL) was added to a slurry of LAH (9.8 g, 257 mmol) in THF (100 mL). The slurry was refluxed for 3 h and then cooled. Water (10 mL) was cautiously added, followed by 15% aqueous sodium hydroxide (10 mL) and water again (29 mL). The slurry was filtered through diatomaceous earth and the solvent removed *in vacuo* to afford a viscous oil (88.6 g, 92% yield): $[\alpha]^{25}_D$ = +72.3 °C (c = 1.03, hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (m, 2H), 7.35–7.15 (m, 4H), 7.05–6.85 (m, 2H), 4.08 (dd, 1H, J = 13.5, 6.7), 2.9 (m, 1H), 2.8–2.5 (m, 6H), 1.95 (m, 1H), 1.7–1.45 (m, 4H), 1.42 (d, 3H, J = 6.8), 0.86 (t, 3H, J = 7.0); ^{13}C NMR (partial, 75 MHz, $CDCl_3$) 58.3 (CH), 54.4 (CH), 48.1 (CH_2), 34.9 (CH_2), 30.5 (CH_2), 26.1 (CH_2), 24.1 (CH_2), 19.5 (CH_3), 11.7 (CH_3); IR (thin film) 2960, 1600, 1491, 1438, 1268 cm^{-1}; MS m/e (rel intensity, 70 eV) 373 (M, 8), 371 (M, 8), 358 (5), 356 (5), 344 (14), 342 (14), 293 (9), 264 (10), 240 (15), 238 (15), 105 (100); high resolution calcd 371.1249, found 371.1260. Anal. ($C_{21}H_{26}NBr$) C, H, N.

(-)-8-Bromo-N-[(S)-α-methylbenzyl]-N-propyl-2(S)-aminotetralin [(-)-7b]. (-)-8-Bromo-N-[(S)-α-methylbenzyl]-2(S)-propionamidotetralin [(-)-**6b**] (79 g, 204 mmol) was reduced in the manner described above to yield 48 g (63% yield) of an oil: $[\alpha]^{25}_D$ = -109.3 °C (c = 1.27, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.15 (m, 6H), 7.1–6.8 (m, 2H), 4.04 (m, 1H), 3.05–2.5 (m, 7H), 1.65 (m, 1H), 1.55–1.4 (m, 2H), 1.43 (d, 3H, J = 6.9), 1.25 (m, 1H), 0.85 (t, 3H, J = 7.1); ^{13}C NMR (partial, 75 MHz, $CDCl_3$) δ 57.7 (CH), 54.4 (CH), 47.7 (CH_2), 34.2 (CH_2), 30.6 (CH_2), 27.3 (CH_2), 24.1 (CH_2), 18.0 (CH_3), 11.7 (CH_3); IR (thin film) 2959, 1559, 1492, 1438, 1367, 1077 cm^{-1}; MS m/e (rel intensity, 70 eV) 373 (M, 4), 371 (M, 4), 358 (3), 356 (3), 344 (10), 342 (10), 240 (13), 238 (13), 228 (10), 226 (10), 210 (16), 208 (16); high resolution calcd 371.1249, found 371.1226. Anal. ($C_{21}H_{26}NBr$) C, H, N.

(+)-8-Formyl-N-[(S)-α-methylbenzyl]-N-propyl-2(R)-aminotetralin [(+)-8a]. (+)-8-Bromo-N-[(S)-α-methylbenzyl]-N-methylbenzyl]-N-propyl-2(R)-aminotetralin [(+)-**7a**] (30 g, 80 mmol) and THF (200 mL) were cooled to -78 °C. *tert*-Butyllithium (102.9 mL of a 1.7 M solution in pentane) was added over 5 min. The dark solution was stirred for 5 min more and then quenched with dimethylformamide (30 g, 410 mmol). The solution was allowed to warm to 0 °C, whereupon it was quenched with water. The reaction was partitioned between ether and water, by washing the ether layer with water (4×). The solution was washed with brine and dried over anhydrous sodium sulfate. Solvent removal in vacuo afforded the product as an oil (24 g, 93% yield): $[\alpha]^{25}_D$ = +101.5 °C (c = 3.725, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.27 (s, 1H), 7.60 (m, 1H), 7.38–7.20 (m, 5H), 7.06 (m, 2H), 4.04 (m, 1H), 3.4 (m, 1H), 3.1–2.9 (m, 1H), 2.85–2.5 (m, 4H), 1.7 (m, 1H), 1.65–1.4 (m, 4H), 1.41 (t, 3H, J = 6.8), 0.83 (dd, 3H, J = 13.9, 7.2); IR (thin film) 2960, 1698, 1582, 1452, 1369 cm^{-1}; MS m/e (rel intensity, 70 eV) 321 (M, 8), 306 (8), 293 (40), 278 (15), 264 (45), 251 (10), 236 (12), 188 (70), 105 (100). Anal. ($C_{22}H_{27}NO$) C, H, N.

(-)-8-Formyl-N-[(S)-α-methylbenzyl]-N-propyl-2(S)-aminotetralin [(-)-8b]. (-)-8-Bromo-N-[(S)-α-methylbenzyl]-N-propyl-2(S)-aminotetralin [(-)-**7b**] (30 g, 80 mmol) was formylated using the procedure described above to give an oil (25.5 g, 99% yield): $[\alpha]^{25}_D$ = -110.7 °C (c = 3.84, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.24 (s, 1H), 7.6 (d, 1H, J = 6), 7.43 (m, 2H), 7.31–7.18 (m, 4H), 7.0 (m, 1H), 4.1 (m, 1H), 3.2 (m, 1H), 3.05–2.7 (m, 4H), 2.7–2.5 (m, 2H), 2.0 (m, 1H), 1.7 (m, 1H), 1.6–1.45 (m, 2H), 1.42 (d, 3H, J = 6.9), 0.86 (t, 3H, J = 7.1); IR (thin film) 2960, 1698, 1582, 1452, 1369, 1229; MS m/e (rel intensity, 70 eV) 321 (M, 5), 306 (5), 293 (35), 278 (8), 264 (50), 251 (7), 236 (10); high resolution calcd 321.2093, found 321.2086. Anal. ($C_{22}H_{27}NO$) C, H, N.

(+)-8-[(Z)-2-Azido-3-methoxy-3-oxopropenyl]-N-[(S)-α-methylbenzyl]-N-propyl-2(R)-aminotetralin [(+)-9a]. (+)-8-Formyl-N-[(S)-α-methylbenzyl]-N-propyl-2(R)-aminotetralin [(+)-**8a**] (32 g, 99.7 mmol), methyl azidoacetate (46 g, 400 mmol), ether (50 mL), and methanol (300 mL) were cooled to -5 °C. Sodium methoxide (91.1 mL, 400 mmol, of a 25% w/w solution in methanol) was slowly added. The reaction was allowed to warm slowly in a 25 °C water bath. After 1 h at 25 °C, the solution was cooled to 0 °C and saturated aqueous ammonium chloride added. The reaction was rapidly partitioned between ether and 10% aqueous sodium carbonate (to neutralize the ammonium chloride). The ether layer was washed with water (5×) and brine. The solution was dried over anhydrous sodium sulfate and stripped of solvent in vacuo to afford a liquid. This was simply filtered through a flash silica gel column (4 cm × 50 cm) with ethyl acetate/hexane (15:85). The title compound (31.6 g, 76% yield) was obtained as a viscous oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, 1H, J = 8), 7.4–7.2 (m, 5H), 7.11 (m, 2H), 7.01 (d, 1H, J = 8.1), 4.05 (m, 1H), 3.95 (s, 3H), 3.0 (m, 1H), 2.75–2.5 (m, 5H), 1.65 (m, 1H), 1.6–1.48 (m, 2H), 1.43 (d, 3H, J = 6.6), 1.28 (m, 2H), 0.86 (t, 3H, J = 7.1); IR (thin film) 2995, 2150, 1718, 1600, 1500, 1390 cm^{-1}; MS m/e (rel intensity, FAB) 419 (M + H, 28), 418 (M, 5), 389 (6), 332 (4), 287 (7), 257 (6), 105 (100).

(-)-8-[(Z)-2-Azido-3-methoxy-3-oxopropenyl]-N-[(S)-α-methylbenzyl]-N-propyl-2(S)-aminotetralin [(-)-9b]. (-)-8-Formyl-N-[(S)-α-methylbenzyl]-N-propyl-2(S)-aminotetralin [(-)-**8b**] (26.4 g, 82 mmol) was condensed with methyl azidoacetate in the manner described above. The title compound was obtained as an oil (22.8 g, 67% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, 1H, J = 7.5), 7.42 (d, 2H, J = 7.4), 7.31–7.17 (m, 3H), 7.10 (t, 1H, J = 7.2), 7.02 (d, 1H, J = 7.2), 7.00 (s, 1H), 4.08 (m, 1H), 3.95 (s, 3H), 3.0 (m, 1H), 2.9–2.7 (m, 2H), 2.7–2.55 (m, 4H), 2.0 (m, 1H), 1.65 (m, 1H), 1.55–1.4 (m, 2), 1.41 (d, 3H, J = 7.1), 0.86 (t, 3H, J = 7.2); IR (thin film) 2995, 2150, 1710, 1600, 1425, 1380 cm^{-1}; MS m/e (rel intensity, FAB) 419 (M + H, 32), 391 (5), 362 (4), 294 (30).

(+)-2-Carbomethoxy-N-[(S)-α-methylbenzyl]-N-propyl-8(R)-amino-6,7,8,9-tetrahydro-3H-benz[e]indole [(+)-10a]. (+)-8-[(Z)-2-Azido-3-methyl-3-oxopropenyl]-N-[(S)-α-methylbenzyl]-N-propyl-2(R)-aminotetralin [(+)-**9a**] (36 g, 86 mmol) and toluene (800 mL) were brought to reflux for 1.5 h. The solution was cooled and stripped of solvent. The residue was crystallized from cyclohexane to obtain a white solid (17.7 g, 53% yield): mp 115 °C; $[\alpha]^{25}_D$ = +125.03 °C ($CHCl_3$, c = 1.92); ^{1}H NMR (300 MHz, $CDCl_3$) 8.8 (bs, 1H), 7.41 (d, 2H, J = 7.1), 7.35–7.15 (m, 5H), 6.99 (d, 1H, J = 8.4), 4.1 (dd, 1H, J = 13, 7), 3.94 (s, 3H), 3.2–2.5 (m, 7H), 1.78 (m, 1H), 1.72–1.55 (m, 3H), 1.44 (d, 3H, J = 7.1), 0.86 (t, 3H, J = 7.1); IR (mineral oil mull) 3170, 2995, 1697, 1500, 1250, 1204 cm^{-1}; MS m/e (rel intensity, 70 eV) 390 (M, 50), 375 (5), 361 (45), 285 (32), 257 (50), 105 (100). Anal. ($C_{25}H_{30}N_2O_2$) C, H, N.

(-)-2-Carbomethoxy-N-[(S)-α-methylbenzyl]-N-propyl-8-(S)-amino-6,7,8,9-tetrahydro-3H-benz[e]indole [(-)-10b]. (-)-8-[(Z)-2-azido-3-methoxy-3-oxopropenyl]-N-[(S)-α-methylbenzyl]-N-propyl-2(S)-aminotetralin [(-)-**9b**] (22 g, 52 mmol) was thermolyzed using the conditions described above. The product was obtained as a white solid (10.1 g, 50% yield): mp 122 °C; $[\alpha]^{25}_{589}$ = -168.1 °C (c = 1.13, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.8 (bs, 1H), 7.5–7.4 (m, 2H), 7.35–7.0 (6H), 4.11 (m, 1H), 3.93 (s, 3H), 3.05 (m, 1H), 2.95–2.75 (m, 3H), 2.74–2.5 (m, 3H), 2.05 (m, 1H), 1.85 (m, 1H), 1.55–1.4 (m, 2H), 1.43 (d, 3H, J = 6.8), 0.88 (t, 3H, J = 7.1); IR (mineral oil mull) 3350, 2995, 1704, 1505, 1200 cm^{-1}; MS m/e (rel intensity, 70 eV) 390 (M, 53), 375 (5), 361 (48), 285 (24), 257 (35), 228 (40), 105 (100); high resolution calcd 390.2307, found 390.2305. Anal. ($C_{25}H_{30}N_2O_2$) C, H, N.

(+)-2-Carbamoyl-N-[(S)-α-methylbenzyl]-N-propyl-8(R)-amino-6,7,8,9-tetrahydro-3H-benz[e]indole [(+)-11a]. (+)-2-Carbomethoxy-N-[(S)-α-methylbenzyl]-N-propyl-8(R)-amino-6,7,8,9-tetrahydro-3H-benz[e]indole [(+)-**10a**] (70 g, 179 mmol) dissolved in THF (15 mL) was added to a saturated solution of ammonia in methanol (100 mL) containing sodium cyanide (219 mg, 0.03 mol equiv). This solution was heated in a pressure reactor at 95 °C for 5 days. The solution was cooled and the

solvent removed in vacuo. Flash chromatography (230–400 mesh silica gel) with ethyl acetate/hexane afforded a white powder (61 g, 91% yield): mp 235 °C; $[\alpha]^{25}_D$ = +107.3 °C (c = 1.95, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) 9.45 (bs, 1H), 7.40 (d, 2H, J = 6.8), 7.3–7.1 (m, 4H), 6.96 (d, 1H, J = 7.0), 6.89 (s, 1H), 6.02 (bs, 2H), 4.09 (m, 1H), 3.2–3.05 (m, 1H), 3.05–2.5 (m, 6H), 1.7 (m, 1H), 1.65–1.55 (m, 1H), 1.55–1.47 (m, 2H), 1.44 (d, 3H, J = 7.1), 0.86 (t, 3H, J = 7.2); IR (mineral oil mull) 3322, 1658, 1599, 1444, 1418, 1345 cm^{-1}; MS m/e (rel intensity, 70 eV) 375 (M, 52), 360 (7), 346 (40), 270 (29), 253 (10), 242 (55); high resolution calcd 375.2310, found 275.2310. Anal. ($C_{24}H_{29}N_3O$) C, H, N.

(–)-2-Carbamoyl-*N*-[(*S*)-α-methylbenzyl]-*N*-propyl-8(*S*)-amino-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole [(–)-11b]. (–)-2-Carbomethoxy-*N*-[(*S*)-α-methylbenzyl]-*N*-propyl-8(*S*)-amino-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole [(–)-**10b**] (14.3 g, 36.7 mmol) was treated with ammonia using the procedure described above. The amide was obtained as needles (12 g, 87% yield): mp 140 °C; $[\alpha]^{25}_D$ = –206.17 °C (c = 0.875, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.56 (bs, 1H), 7.48 (d, 2H, J = 7.3), 7.3–7.15 (m, 4H), 6.97 (d, 1H, J = 8.5), 6.82 (s, 1H), 6.09 (bs, 2H), 4.12 (dd, 1H, J = 13, 6.7), 3.08 (m, 1H), 2.85 (m, 4H), 2.75–2.67 (m, 1H), 2.65–2.5 (m, 1H), 2.07 (m, 1H), 1.75 (m, 1H), 1.6–1.55 (m, 2H), 1.44 (d, 3H, J = 7.1), 0.88 (t, 3H, J = 7.2); IR (mineral oil mull) 3214, 2922, 1652, 1618, 1589, 1441, 1417, 1346 cm^{-1}; MS m/e (rel intensity; 70 eV) 375 (M, 60), 360 (9), 346 (45), 270 (30), 253 (10), 242 (50), 213 (35), 105 (100). Anal. ($C_{24}H_{29}N_3O$) C, H, N.

(+)-(*R*)-2-Carbamoyl-*N*-propyl-8-amino-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole [(*R*)-12]. (+)-2-Carbamoyl-*N*-[(*S*)-α-methylbenzyl]-*N*-propyl-8(*R*)-amino-6,7,8,9-tetrahydro-3*H*-benz[*e*]-indole [(+)-**11a**] (12 g, 32 mmol), 12 N aqueous hydrochloric acid (2.66 mL, 32 mmol), 10% palladium/carbon (2.5 g), 20% palladium hydroxide/carbon (0.5 g), water (10 mL), THF (20 mL), and methanol (150 mL) were placed in a Parr bottle and hydrogenated at 50 psi for 12 h. Diatomaceous earth was added and the slurry was filtered. Sodium hydroxide (1.33 g, 33.2 mmol) was added. Most of the solvent was removed in vacuo. Water (100 mL) was added and again most of the solvent was removed in vacuo. This procedure was repeated again, the water being stripped off until 250 mL remained. The white powder was filtered, washed with water, and then dried in vacuo to afford a white solid which was recrystallized from methanol/hexane (8.9 g, 100% yield): mp 230 °C; $[\alpha]^{25}_{589}$ = +69.4 °C (c = 0.535, methanol); ^{1}H NMR (300 MHz, CD_3OD) δ 7.19 (d, 1H, J = 8.4), 7.10 (s, 1H), 6.95 (d, 1H, J = 8.1), 3.25 (m, 1H), 3.0–2.7 (m, 3H), 2.69 (t, 2H, J = 7), 2.55 (m, 1H), 2.12 (m, 1H), 1.65–1.5 (m, 3H), 0.98 (t, 3H, J = 7.1); IR (mineral oil mull) 3320, 3150, 3080, 1672, 1619, 1526, 1429, 1345 cm^{-1}; MS m/e (rel intensity, 70 eV) 271 (M, 100), 254 (5), 242 (42), 228 (18), 213 (31), 195 (50), 186 (70); high resolution calcd 271.1685, found 271.1682. Anal. ($C_{16}H_{21}N_3O$) C, H, N.

(+)-(*R*)-2-Carbamoyl-*N*,*N*-dipropyl-8-amino-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole [(*R*)-13]. (+)-(*R*)-2-Carbamoyl-*N*-propyl-8-amino-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole [(*R*)-**12**] (40 g, 148 mmol) was mixed with sodium carbonate (31.3 g, 377 mmol), bromopropane (53 mL, 583 mmol), acetonitrile (300 mL), and DMF (100 mL) and heated to reflux for 18 h. The slurry was cooled and poured into methylene chloride and washed with water (2×) and brine. The organic layer was dried over anhydrous sodium sulfate and the solvent removed in vacuo to afford a white solid (44 g, 95% yield), which crystallized from methanol/ether as the hydrochloride salt: mp 302 °C dec; $[\alpha]^{25}_{589}$ = +88.0 °C (c = 0.835 methanol); ^{1}H NMR (300 MHz, $CDCl_3$) 7.21 (d, 1H, J = 8.4), 6.99 (d, 1H, J = 8.2), 6.93 (s, 1H), 3.12 (m, 2H), 2.9 (m, 3H), 2.57 (dd, 4H, J = 14, 6.3), 2.1 (m, 1H), 1.68 (m, 1H), 1.5 (m, 4H), 0.91 (t, 6H, J = 7.3); ^{13}C NMR (partial, 75 MHz, $CDCl_3$) δ 135.0 (C), 129.0 (C), 127.6 (C), 126.3 (CH), 109.8 (CH), 101.9 (CH), 56.7 (CH), 52.8 (CH_2), 29.9 (CH_2), 28.9 (CH_2), 25.9 (CH_2), 22.0 (CH_2), 11.9 (CH_3); IR (mineral oil mull) 3220, 2995, 1654, 1602, 1528, 1347 cm^{-1}; MS m/e (rel intensity, 70 eV) 313 (M, 45), 284 (100), 213 (40), 196 (23). Anal. ($C_{19}H_{27}N_3O$·HCl·0.5H_2O) C, H, N.

(+)-(*R*)-2-Cyano-*N*,*N*-dipropyl-8-amino-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole [(*R*)-14]. (+)-(*R*)-2-Carbamoyl-*N*,*N*-dipropyl-8-amino-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole [(*R*)-**13**] (1.5 g, 4.8 mmol) was dissolved in THF (25 mL). Burgess' reagent (2.9 g, 12 mmol) was added in portions over a 20-min period. The reaction was allowed to stir for 3 h. The reaction was partitioned between 10% aqueous sodium carbonate and ether. The ether layer was washed with water and brine. After drying over anhydrous sodium sulfate the solvent was removed in vacuo to afford a white solid (1.4 g, 99% yield), m.p. 134 °C. Freebase: $[\alpha]^{25}_{589}$ = +104 °C (c = 1.50, methanol). The product was crystallized as the hydrochloride salt from methanol/ether: mp 308 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.1 (bs, 1H), 7.17 (d, 1H, J = 7.7), 7.15 (s, 1H), 7.08 (d, 1H, J = 7.6), 3.07 (m, 2H), 2.91 (m, 3H), 2.55 (t, 4H, J = 7.5), 2.1 (m, 1H), 1.65 (m, 1H), 1.5 (m, 4H), 0.92 (t, 6H, J = 7.3); IR (mineral oil mull) 3131, 2813, 2213, 1462, 1364, 1254 cm^{-1}; MS m/e (rel intensity, 70 eV), 295 (M, 30), 266 (100), 252 (4), 195 (65). Anal. ($C_{19}H_{25}N_3$·HCl) C, H, N.

(+)-(*R*)-2-Carbamoyl-*N*(cyclopropylmethyl)-*N*-propyl-8-amino-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole [(*R*)-15]. (+)-(*R*)-2-Carbamoyl-*N*-propyl-8-amino-6,7,8,9-tetrahydro-3*H*-benz[*e*]-indole [(*R*)-**12**] (2.2 g, 8.2 mmol) was alkylated with (bromomethyl)cyclopropane (2.3 mL, 24.6 mmol) in refluxing acetonitrile (15 mL), with sodium carbonate (680 mg, 8.2 mmol), affording 1.69 g (64% yield) of product. The hydrochloride salt was crystallized from methanol/ether: mp 309 °C dec; $[\alpha]^{25}_{589}$ = +138.45 °C (c = 0.515, methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.65 (bs, 1H), 7.21 (d, 1H, J = 8.4), 7.02 (d, 1H, J = 8.2), 6.90 (s, 1H), 6.15 (bs, 2H), 3.25 (m, 1H), 3.11 (m, 1H), 2.93 (m, 3H), 2.62–2.42 (m, 4H), 2.08 (m, 1H), 1.59–1.51 (m, 3H), 0.90 (m, 1H), 0.92 (t, 3H, J = 7.1), 0.52 (m, 2H), 0.14 (m, 2H); IR (mineral oil mull) 3280, 2990, 1670, 1600, 1510 cm^{-1}; MS m/e (rel intensity 70 eV) 325 (M, 55), 296 (100), 270 (8), 253 (5), 213 (30). Anal. ($C_{20}H_{27}N_3O$·HCl·0.5H_2O) C, H, N.

(+)-(*R*)-2-Carbamoyl-*N*-[4-(4,4-dimethyl-2,6-dioxopiperidin-1-yl)butyl]-*N*-propyl-8-amino-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole [(*R*)-16]. (+)-(*R*)-2-Carbamoyl-N-propyl-8-amino-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole [(*R*)-**12**] (2.2 g, 8.2 mmol) was alkylated with 4-(4,4-dimethyl-2,6-dioxopiperidin-1-yl)-*n*-butyl iodide (5.06 g, 15.6 mmol) in refluxing acetonitrile (20 mL) with sodium carbonate (1.29 g, 15.5 mmol). The product was obtained as an oil (2.97 g, 78% yield). The hydrochloride salt was crystallized from 2-propanol/ether: mp = 210 °C dec; $[\alpha]^{25}_{589}$ = +64.8 °C (c = 0.72, methanol); ^{1}H NMR (300 MHz, CD_3OD) δ 7.18 (d, 1H, J = 8.5), 7.11 (s, 1H), 6.92 (d, 1H, J = 8.2), 3.77 (t, 2H, J = 6.8), 3.15–2.7 (m, 5H), 2.65–2.52 (m, 4H), 2.50 (s, 4H), 2.08 (m, 1H), 1.65–1.45 (m, 7H), 1.00 (s, 6H), 0.92 (t, 3H, J = 7.3); IR (mineral oil mull) 3267, 2925, 1723, 1663, 1604, 1349, 1272. MS m/e (rel intensity, 70 eV) 466 (M, 30), 437 (60), 284 (100), 253 (8), 213 (70), 196 (50). Anal. ($C_{27}H_{38}N_4O_3$HCl) C, H, N.

(+)-(*R*)-2-Cyano-*N*-[4-(4,4-dimethyl-2,6-dioxopiperidin-1-yl)butyl]-*N*-propyl-8-amino-6,7,8,9-tetrahydro-3*H*-benz[*e*]-indole [(*R*)-17]. (+)-(*R*)-2-Carbamoyl-*N*-[4-(4,4-dimethyl-2,6-dioxopiperidin-1-yl)butyl]-*N*-propyl-8-amino-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole [(*R*)-**16**] (1.53 g, 3.30 mmol) was dehydrated with Burgess' reagent (1.95 g, 8.19 mmol) in methylene chloride (10 mL) and THF (6 mL) at 25 °C. The organic layer was washed with saturated aqueous sodium bicarbonate, water, and brine. Drying over sodium sulfate and solvent removal *in vacuo* afforded a foam. This was purified using flash chromatography (230–400 mesh silica gel), eluting with ethyl acetate/hexane (1:1) to afford a foam (1.32 g, 86% yield). The product was crystallized as the hydrochloride salt from methanol/ether: mp 220 °C; $[\alpha]^{25}_D$ = +71.2 °C (c = 0.527, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) 8.75 (bs, 1H), 7.18 (s, 1H), 7.16 (d, 1H, J = 8.1), 7.08 (d, 1H, J = 8.2), 3.80 (t, 2H, J = 6.7), 3.1–2.95 (m, 2H), 2.9–2.7 (m, 3H), 2.6–2.5 (m, 4H), 2.51 (s, 4H), 1.7–1.4 (m, 7H), 1.07 (s, 6H), 0.89 (t, 3H); IR (mineral oil mull) 3295, 2221, 1724, 1663, 1437, 1361, 1272, 1128. MS m/e (rel intensity, 70 eV) 448 (M, 20), 419 (55), 226 (100), 195 (67). Anal. ($C_{27}H_{37}N_4O_2Cl$·HCl) C, H, N.

X-ray single-crystal structure determination of (–)-(2*S*,*S*)-6b: $C_{21}H_{24}NOBr$; space group, $P2_12_12_1$, cell parameters, a = 7.125(3) Å, b = 14.664(3) Å, c = 17.790(2) Å; molecular weight = 615.33; Z = 4; calculated density = 1.3735 g/cm^3; R = 0.042 for the final least squares refinement.

A clear, prism-shaped crystal (0.15 × 0.15 × 0.3 mm) was selected and mounted on a glass fiber. The data was collected on a Simens $P2_1$ X-ray diffractometer controlled by a Harris computer, at low temperature (–130 °C), with graphite-monochromatized Cu Kα radiation [λ(Cu Kα) = 1.5405 Å]. All 1832 unique reflections were measured to a $2\theta_{max}$ of 138 °C for Laue

group mmm; 1730 intensities were >3σ. The $\theta/2\theta$ step-scan technique was used with a scan speed of 4.0 °C/min and a scan width of >3.4 °C. Ten reflections periodically monitored showed no trend toward deterioration. Standard deviations in the intensities were approximated from the following equation: $\sigma^2(I) = \sigma^2(I)_{\text{counting statistics}} + (0.0116I)^2$, where the coefficient I was calculated from the variation in intensities of the monitored reflections. Cell parameters were determined by least-squares fit of Cu Kα_1 2θ values [λ(Cu Kα_1) = 1.5402 Å] for 25 high-2θ reflections. *Lp* corrections appropriate for a monochromator with 50% perfect character were applied. The calculated overall absorption coefficient was 1.3/mm.

The structure was solved by direct methods, using RANTAN. The trial solution obtained the Br atomic position. Subsequent Fourier transform found the rest of the 23 nonhydrogen atoms. A total of 19 of 24 hydrogen atoms were clearly shown in difference Fourier maps. The remaining five hydrogens were generated according to the molecular geometry. Least-squares refinement included coordinates and anisotropic thermal parameters of all non-hydrogen atoms. No hydrogen atoms were refined. The function minimized in the refinement was $\sum w(F_o^2 - F_c^2)^2$, where weights w were $1/\sigma^2(F_o^2)$. Atomic form factors were from Doyle and Turner[30] and, for hydrogen, from Stewart, Davidson, and Simpson.[31] In the final refinement cycle, all shifts were <0.04σ for non-hydrogen atoms. R = 0.42, S = 4.24, w_R = 0.103; final difference Fourier peaks were 0.54 e Å^{-3}. Centrosymmetrically related pairs of 15 enantiomer sensitive reflections were measured, and all data confirmed the assignment of the absolute configuration, The CRYM system of computer programs was used. Coordinates for the X-ray structure are in the supplementary material.

Receptor Binding. IC_{50} values were estimated from a nonlinear single site fit to data obtained from competition binding experiments employing at least 10 drug concentrations run in duplicate. The radioligands used were [^{3}H]-8-OH-DPAT (164.5 Ci/mmol, 1 nM) and [^{3}H]U-86170 (86.1 Ci/mmol, 1.7 nM). 5-HT$_{1A}$ receptors were assayed in bovine hippocampal preparations. D2-dopamine receptors were either from human clones expressed in CHO K1 cells[32] or from rat striatal membranes. Dissociation constants (K_i) were calculated with the Cheng and Prusoff equation.[33] The data in Table I are in nM ± SEM.

Electrophysiology. Upjohn male Sprague–Dawley rats, 250–350 g were anesthetized with chloral hydrate (400 mg/kg).[34] Extracellular action potentials were recorded with a glass microelectrode (tip size < 1 μm) filled with pontamine sky blue dye in 2 M NaCl. Standard electrophysiological techniques were used to record firing rates of 5HT cells in the dorsal raphe (DR)[35] and DA cells in the substantia nigra pars compacta (SNPC).[36] At the termination of each recording session, the location of each cell was identified by passing 10 μA cathodic current through the recording electrode for 10–20 min. The brain was then removed, fixed in 10% formalin, sectioned, and stained, and the location of the pontamine sky blue mark within DR, MnR, LC, or SNPC was determined for each animal. The dose required to inhibit neuronal activity by 50% is defined as the ED_{50}.

Hypothermia. Rectal temperatures were measured in Charles River mice, 18–22 g, individually housed in clear plastic chambers, following 0.1-mL sc drug injections. Dose–response curves were measured by noting how many of four mice had >1.1 °C decreases with each dose (half-log intervals) 20 min following injection. Spearman–Karber statistics[37] were used to estimate ED_{50}'s. The mean maximum temperature drop recorded at 20 min was noted as a crude index of drug efficacy and indirect measure of intrinsic activity.

Sympathetic Nerve Discharge. Mongrel cats (2.5–4.0 kg) were anesthetized with an intravenous injection of chloralose (80 mg/kg) and placed in a stereotaxic apparatus. The femoral artery and vein were cannulated in order to monitor arterial blood pressure and for intravenous drug injections, respectively. A glass trachea tube was inserted and rectal temperature was maintained using a heating pad and/or lamp. Animals were allowed to breath spontaneously. Sympathetic nerve discharge (SND) was recorded under mineral oil from the isolated left inferior cardiac nerve using a bipolar platinum electrode with capacity coupled preamplification at low and high frequency half-amplitude responses at 1 and 500 Hz, respectively. Sympathetic nerve discharge was quantitated using cumulative integration (i.e. summation of voltage contained in sympathetic slow waves). Mean arterial pressure (MAP), HR, and SND were allowed to equilibrated for 1 h after surgery. Pretreatment values for sympathetic nerve discharge were averaged over the last 10 min of the equilibration period. A cumulative dose–response curve was constructed to determine the effects of a compound on SND. The starting dose of a compound was 0.01 mg/kg iv, and the cumulative dose of the drug being tested was increased every 20 min to achieve total cumulative dose of 0.03, 0.1, 0.3, and 1.0 mg/kg iv. The effects of the compound on SND were determined 15–20 min after each dose. Following the last dose of an agent, the 5-HT$_{1A}$ antagonist spiperone was administered intravenously at a dose of 1 mg/kg.

Supplementary Material Available: A table of C, H, N analyses and high resolution mass spectrum data, as well as X-ray-determined tables of fractional coordinates, bond lengths and angles, and anisotropic thermal parameters are available (3 pages). Ordering information is given on any current masthead page.

References

(1) Reviews: (a) Glennon, R. A. *Neurosci. Biohehav. Rev.* **1990**, *14*, 35. (b) Kostowski, W.; Plaznik, A.; Archer, T. Possible implications of 5-HT function for the etiology and treatment of depression. *New Trends Exp. Clin. Psychiatry* **1989**, *5*, 91–116. (c) Soubrie, P. 5-HT$_{1A}$ receptors: A bridge between anxiety and depression. In *Behavioral Pharmacology of 5-HT*; Bevan, P., Cools, A., Archer, T., Eds.; Lawrence Erlbaum Assoc.: Hilldale, NJ, 1989; pp 337–352. (d) Traber, J.; Glaser, T. 5-HT receptor-related anxiolytics. *Trends Pharmacol. Sci.* **1987**, *8*, 432–437.

(2) Andersson, J. L. Serotonin receptor changes after chronic antidepressant treatments: Ligand binding, electrophysiological, and behavioral studies. *Life Sci.* **1983**, *32*, 1791–1801.

(3) Boyer, W. F.; Feighner, J. P. Update on the selective serotonin reuptake inhibitors. In *New Pharmacological Approahces to Depression and Anxiety, International Coference on Antidepressant and Anxiolytic Drugs. Conference Documentation.* IBC Technical Services, Ltd.: London, 1989, p 1–14.

(4) Westenberg, H. G.; den Boer, J. A.; Kahn, R. S. Psychopharmacology of anxiety disorders: on the role of serotonin in the treatment of anxiety states and phobic disorders. *Psychopharmacol. Bull.* **1987**, *23*, 145–149. Kahn, R. S.; Westenberg, H. G. L-5-Hydroxytryptophan in the treatment of anxiety disorders. *J. Affective Disord.* **1985**, *8*, 197–200. Den Boer, J. A.; Westenberg, H. G. Effect of a serotonin and noradrenalin uptake inhibitor in panic disorder: a double blind comparative study with fluvoxamine and maprotiline. *Int. Clin. Psychopharmacol.* **1988**, *3*, 59–74.

(5) Van der Maelen, C. P.; Matheson, G. K.; Wilderman, R. C.; Patterson, L. A. Inhibitor of serotoninergic dorsal raphe' neurons by systemic and iontophoretic administration of buspirone, a non-benzodiazepine anxiolytic drug. *Eur. J. Pharmacol.* **1986**, *129*, 123–130. Sprouse, J. C.; Aghajanian, G. K. Responses of hippocampal pyrimidal cells to putative serotonin 5-HT$_{1A}$ and 5-HT$_{1B}$ agonists: a comparitive study with dorsal raphe' neurons. *Neuropharmacology* **1988**, *27*, 707–715.

(6) Feighner, J. P.; Boyer, W. F. Serotonin 1A anxiolytics: An overivew. *Psychopathology*, **1989(b)**, *22* (suppl. 1), 21–26.

(7) Andrade, R.; Nicoll Novel anxiolytics discriminate between postsynaptic serotonin receptors mediating different physiological responses on single neurons of the rat hippocampus. *Naunyl-Schmeideberg's Arch. Pharmacol.* **1987**, *336*, 5–10.

(8) Tyrer, P.; Murphey, S.; Owen, R. T. The risk of pharmacological dependence with buspirone. *Br. J. Clin. Pract.*, **1985**, *39*, 91–93.

(9) Schweizer, E. E.; Rickels, K.; Lucki, I. Resistance to the anti-anxiety effect of buspirone in patients with a history of benzodiazepine use. *N. Engl. J. Med.* **1986**, *314*, 719–720.

(10) Wikstrom, H.; Andersson, B.; Svensson, A.; Humber, L. G.; Asselin, A. A.; Svensson, K.; Ekman, A.; Carlsson, A.; Nilsson, I.; Chidester, C. Resolved 6,7,8,9-tetrahydro-N,N-dimethyl-3*H*-benz[*e*]-indol-8-amine: Central dopamine and serotonin receptor stimulating properties. *J. Med. Chem.* **1989**, *32*, 2273–2276.

(11) Asselin, A. A.; Humber, L. G.; Voith, K.; Metcalf, G. Drug design via pharmacophore identification. Dopaminergic activity of 3*H*-benz[*e*]indol-8-amines and their mode of interaction with the dopamine receptor. *J. Med. Chem.* **1986**, *29*, 648–654.

(12) Stjernlöf, P.; Gullme, M.; Elebring, T.; Andersson, B.; Wikström, H.; Lagerquist, S.; Svensson, K.; Ekman, A.; Carlsson, A.; Sundell, S. (*S*)- And (*R*)-8-(Di-*n*-propylamino)-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole-1-carbaldehyde: A new class of orally active 5-HT$_{1A}$ receptor agonists. *J. Med. Chem.*, previous paper in this issue.

(13) Burckhalter, J. H.; Campbell, J. R. Ethylene and phenylacetyl chloride in the Friedel–Crafts reaction. Novel synthesis of 2-tetralones and benzofuranones. *J. Org. Chem.* **1961**, *26*, 4232–4235.

(14) Borch, R. F.; Bernstein, M. D.; Durst, H. D. The cyanoborohydride anion as a selective reducing agent. *J. Am. Chem. Soc.* **1971**, *93*, 2897–2904.
(15) Barney, C. H.; Huber, E. W.; McCarthy, J. R. A convenient synthesis of hindered amines and α-trifluoromethylamines from ketones. *Tetrahedron Lett.* **1990**, 5547–5550.
(16) Henn, L.; Hickey, D. M. B.; Moody, C. J.; Rees, C. W. Formation of indoles, isoquinolines, and other fused pyridines from azidoacrylates. *J. Chem. Soc. Perkin Trans. 1* **1984**, 2189–2196.
(17) Hogberg, T.; Strom, P.; Ebner, M.; Ramsby, S. Cyanide as an Efficient and Mild Catalyst in the Aminolysis of Esters. *J. Org. Chem.* **1987**, *52*, 2033–2036.
(18) Claremon, D. A.; Phillips, B. T. An efficient chemoselective synthesis of nitriles from primary amides. *Tetrahedron Lett.* **1988**, 2155–2158.
(19) Mellin, C.; Vallgarda, J.; Nelson, D. L.; Bjork, L.; Yu, H.; Anden, N.-E.; Csoregh, I.; Arvidsson, L.-E.; Hacksell, U. A 3-D model for 5-HT_{1A} receptor agonists based on stereoselective methyl-substituted and conformationally restricted analogs of 8-hydroxy-2-(dipropylamino)tetralin. *J. Med. Chem.* **1991**, *34*, 497–509. Cornfield, L. J.; Lambert, G.; Arvidsson, L.-E.; Mellin, C.; Vallgarda, J.; Hacksell, U.; Nelson, D. L. Intrinsic activity of enantiomers of 8-hydroxy-2-(di-*n*-propylamino)tetralin and its analogs at 5-hydroxytryptamine$_{1A}$ receptors that are negatively coupled to adenylate cyclase. *Mol. Pharmacol.* **1991**, *39*, 780–787.
(20) Martin, K. F.; Phillips, I.; Hearson, M.; Prow, M. P.; Heal, D. J. Characterization of 8-OH-DPAT-induced hypothermia in mice as a 5-HT_{1A} autoreceptor response and its evaluation as a model to selectively identify antidepressants. *Br. J. Pharmacol.* **1992**, *107*, 15–21. Kostowski, W.; Dyr, W.; Krzascik, P.; Jarbe, T.; Archer, T. 5-Hydroxytryptamine$_{1A}$ receptor agonists in animal models of depression and anxiety. *Pharmacol. Toxicol.* **1992**, *71*, 24–30.
(21) Martin, K. F.; Heal, D. J. 8-OH-DPAT-Induced hypothermia in rodents. A specific model of 5-HT_{1A} autoreceptor function? In *Serotonin: Molecular Biology, Receptors and Functional Effects*; Fozard, J. R., Saxena, P. R., Eds.; Birkhäuser Verlag, Basel, Switzerland, 1991; pp 483–490.
(22) Green, A. R.; Goodwin, G. M. The pharmacology of the hypothermic response of rodents to 8-OH-DPAT administration and the effects of psychotropic drug administration on this response. In *Brain 5-HT_{1A} Receptors*; Dourish, C. T., Ahlenius, S., Hutson, P. H., Eds.; Ellis Horwood Ltd.: Chichester, England, 1987; Chapter 14.
(23) Goodwin, G. M.; De Souze, R. J.; Green, A. R. The pharmacology of the hypothermic response in mice to 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT): A model of presynaptic 5-HT_1 function. *Neuropharmacology* **1985**, *24*, 1187–1194.
(24) Nelson, D. L. Structure-Activity Relationships at 5-HT_{1A} Receptors: Binding Profiles and Intrinsic Activity. Combined Southeast/Southwest Regional ACS Meeting, New Orleans, LA, 1990, p 137 (abstract).
(25) Seiler, M. P.; Stoll, A.; Hagenbach, A.; Florsheim, P.; Fozard, J. R.; Kalkman, H.; Mir, A. K.; Siegl, H.; Schoeffter, P.; Hoyer, D. Novel Approaches to Drugs Acting on "5-HT_1-like" Receptors. Medicinal Chemistry Meeting, Jerusalem, September 1990.
(26) Cornfield, L. J.; Lambert, G.; Arvidsson, L. E.; Mellin, C.; Vallgarda, J.; Hacksell, U.; Nelson, D. L. Intrinsic activity of enantiomers of 8-hydroxy-2-(di*n*-propylamino)tetralin and its analogs at 5-HT_{1A} receptors that are negatively coupled to adenylate cyclase. *Mol. Pharmacol.* **1991**, *39*, 780–787.
(27) Hillver, S.-E.; Bjork, L.; Li, Y.-L.; Svensson, B.; Ross, S.; Anden, N.-E.; Hacksell, U. (S)-5-Fluoro-8-hydroxy-2-(dipropylamino)-tetralin: A putative 5-HT_{1A} receptor antagonist. *J. Med. Chem.* **1990**, *33*, 1541–1544.
(28) McCall, R. B.; Patel, B. N.; Harris, L. T. Effects of serotonin$_1$ and serotonin$_2$ receptor agonists and antagonists on blood pressure, heart rate and sympathetic nerve activity. *J. Pharm. Exp. Ther.* **1987**, *242*, 1152–1159.
(29) Duncan, J. N.; Rees, S., Upjohn Labs, U.K. Stability to rat hepatocytes, unpublished data.
(30) Doyle, P. A.; Turner, P. S. Relativistic Hartree-Fock X-Ray and electron scattering factors. *Acta Crystallogr.* **1968**, *A24*, 390–397.
(31) Stewart, R. F.; Davidson, E. R.; Simpson, W. T. Coherent X-Ray scattering for the hydrogen atom in the hydrogen molecule. *J. Chem. Phys.* **1965**, *42*, 3175–3187.
(32) Chio, C. L.; Hess, C. S.; Graham, R. S.; Huff, R. M. A second molecular form of D_2 dopamine receptor in rat and bovine caudate nucleus. *Nature* **1990**, *434*, 266–269.
(33) Cheng, Y.; Prusoff, W. H. Relationship between the inhibition constant (K_I) and the concentration of inhibitor which causes 50 per cent inhibition (I_{50}) of an enzymatic reaction. *Biochem. Pharmacol.* **1973**, *22*, 3099–3108.
(34) Piercey, M. F.; Lum, J. T.; Palmer, J. R. Effects of methylenedioxymethamphetamine (MDMA, "ecstasy") on serotonergic, dopaminergic, and noradrenergic neurons. *Brain Res.* **1990**, *526*, 203–206.
(35) Aghajanian, G. K.; Foote, W. E.; Sheard, M. H. Action of psychotogenic drugs on single midbrain raphe neurons. *J. Pharmacol. Exp. Ther.* **1970**, *137*, 178–187.
(36) Bunney, B. S.; Aghajanian, G. K. Antipsychotic drugs and central dopaminergic neurons: a model for predicting therapeutic efficacy and incidence of extrapyramidal side effects. In *Predictability in Phychopharmacology: Preclinical and Clinical Correlates*; Subilovsky, A., Gershon, S., Beers, B., Eds.; Reven Press, New York, 1975; pp 225–245.
(37) Finney, D. J. *Statistical Method in Biological Assay*; Hafner Pub. Co.: New York, 1964, p 524.