Articles

(S)- and (R)-8-(Di-n-propylamino)-6,7,8,9-tetrahydro-3H-benz[e]indole-1-carbaldehyde: A New Class of Orally Active 5-HT$_{1A}$-Receptor Agonists

Peter Stjernlöf,*,† Maria Gullme,† Thomas Elebring,†,‡ Bengt Andersson,† Håkan Wikström,†,§ Sören Lagerquist,‖ Kjell Svensson,‖ Agneta Ekman,‖ Arvid Carlsson,‖ and Staffan Sundell⊥

Medicinal Chemistry Unit, Department of Pharmacology, University of Göteborg, Medicinaregatan 7, S-413 90 Göteborg, Sweden, Department of Pharmacology, University of Göteborg, Medicinaregatan 7, S-413 90 Göteborg, Sweden, and Structural Chemistry Unit, Department of Medicinal Biochemistry, Medicinaregatan 9, University of Göteborg, S-413 90 Göteborg, Sweden

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The enantiomers of 6,7,8,9-tetrahydro-*N*,*N*-di-*n*-propyl-3*H*-benz[*e*]indol-8-amine (*S*-(−)-**2b** and *R*-(+)-**2b**) and their corresponding 1-formyl analogs (*S*-(−)-**6** and *R*-(+)-**6**) were prepared and evaluated pharmacologically for serotonergic and dopaminergic activity. The introduction of a formyl group in the 1-position shifted the pharmacological profile of **2b** from a mixed D_2/5-HT$_{1A}$ agonists to a selective 5-HT$_{1A}$ agonist (**6**). The enantiomers of **6** were agonists with full intrinsic activity and had an affinity comparable to that of 8-hydroxy-2-(di-*n*-propylamino)tetrahydronaphthalene (8-OH-DPAT). In contrast to 8-OH-DPAT, the enantiomers of compound **6** were found to have good oral availability.

Serotonin receptor agonists such as buspirone (Figure 1) with selectivity for 5-hydroxytryptamine 1A (5-HT$_{1A}$) receptors have proved to be useful for the treatment of anxiety and depression.[1] The widely used 5-HT$_{1A}$ reference compound, 8-OH-DPAT (**1**) is very potent and selective.[2] It has, however, a very poor oral bioavailability in rats (see Table II). It was recently shown that 8-OH-DPAT is extensively glucuronidated and depropylated in rats.[3] Hence, new analogs of **1**, with reduced propensity for metabolic inactivation are warranted. Recent work by Wikström *et al.* describes the enantiomers of the 6,7,8,9-tetrahydro-*N*,*N*-dimethyl-3*H*-benz[*e*]indol-8-amine (**2a**).[4] It was found that *R*-(+)-**2a** possesses both serotonergic and dopaminergic properties in rats. It was suggested that the dopaminergic properties of this compound emanate from the indole–NH moiety, a bioisostere of the hydroxyl group in the potent aminotetralin (+)-*R*-7-OH-DPAT (**3**). The 5-HT$_{1A}$ effect was speculated to be an effect of the high electron density in the 1-position, which is equivalent to the 8-position of the 2-aminotetralin.

Compound **2b** has been synthesized by Asselin *et al.* and was reported to be an orally active dopamine agonist.[5] The aim of this study was to investigate the effects of the introduction of an electron-withdrawing formyl group in the 1-position of *R*-(+)-**2b** and *S*-(−)-**2b**. This substitution alters the electron distribution of the indole ring system. The compounds were tested both *in vitro* and *in vivo* and were compared with 8-OH-DPAT (**1**). The findings from this paper have also led to the preparation of 2-substituted

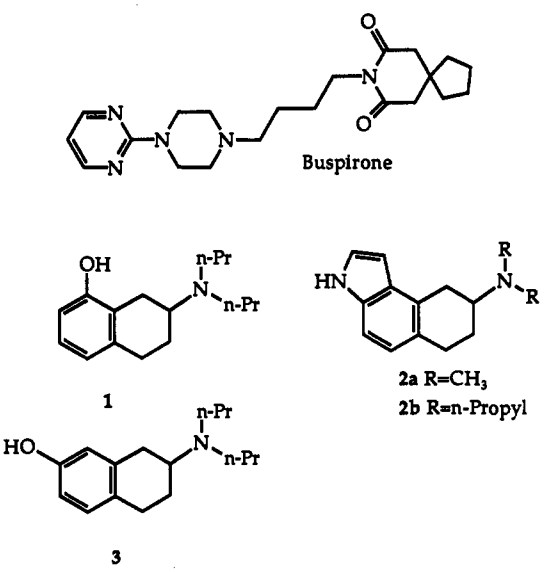

Figure 1. Structures discussed.

derivatives of **2b**, whose synthesis and pharmacology are presented in this issue.[6]

Chemistry

The key intermediate 7-NH_2-DPAT (**4**) was prepared by a route in publication by Stjernlöf *et al.* (Scheme I).[7] This compound was further subjected to the isatin synthesis and reduction (Scheme II) according to Asselin *et al.* to give the regioisomers **2b** and **5** (the latter was not reported by Asselin *et al.*).[5] Compound **5** had been synthesized earlier using another route by Nichols *et al.*[8] Compound **2b** was resolved *via* classical recrystallization of diastereomeric salt using *p*-toluoyltartaric acid. The enantiomeric purities were assessed by ^{1}H NMR of the free bases with the addition of the chemical shift reagents "Pirkle's alcohols" ((+)- and (−)-1-anthryl-2,2,2-trifluo-

† Medicinal Chemistry Unit, Department of Pharmacology.
‖ Department of Pharmacology.
⊥ Structural Chemistry Unit, Department of Medicinal Biochemistry.
‡ Present address: Astra-Hässle AB, Kärragatan 5, S-43183 Mölndal, Sweden.
§ Present address: University Centre for Pharmacy, Department of Medicinal Chemistry, University of Groningen, Antonius Deusinglaan 2, NL-9713AW Groningen, The Netherlands.

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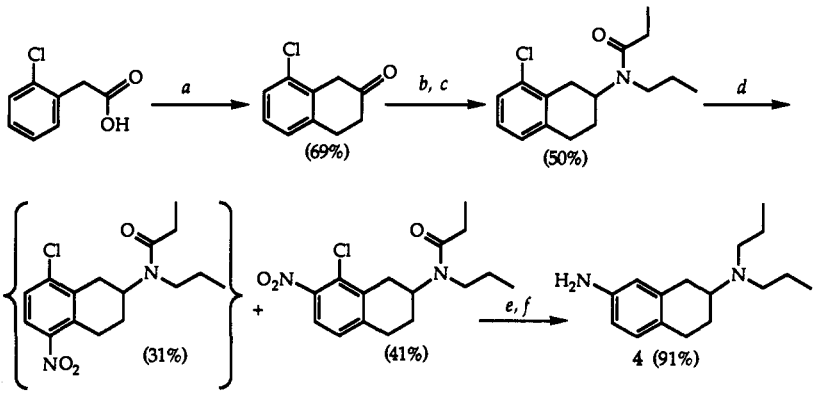
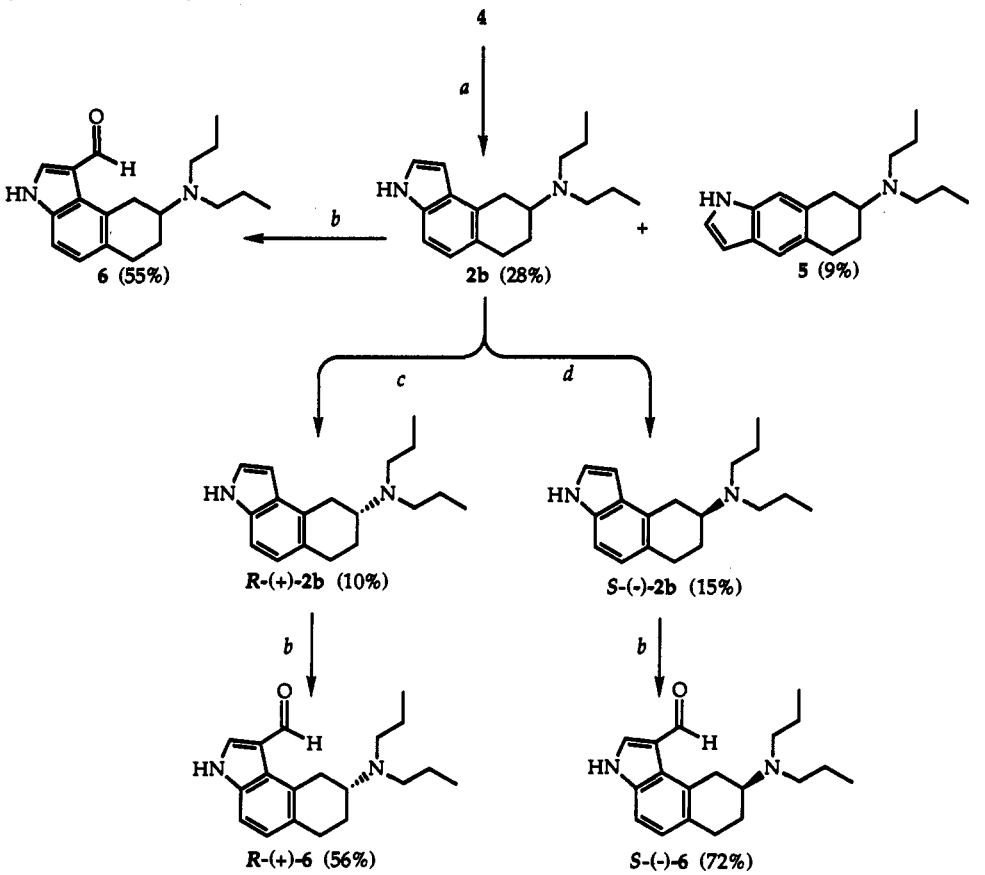
Scheme I. Preparation of 7-NH_2-DPAT (4) according to Stjernlöf *et al.*[7]



[a] (a) (1) $SOCl_2$, CH_2Cl_2, reflux, 1.5 h. (2) $AlCl_3$, CH_2Cl_2, ethylene, −5 to 25 °C, 2 h. (b) (1) *n*-$PrNH_2$, $NaCNBH_4$, MeOH, room temperature, 15 h. (2) Aqueous HCl. (c) EtCOCl, Et_3N, CH_2Cl_2, room temperature, 10 min. (d) HNO_3/H_2SO_4, $MeNO_2$, −5 °C, 1 h. (e) NH_4OOCH, Pd/C, MeOH, room temperature. (f) $LiAlH_4$, ether, room temperature, 15 h.

Scheme II. Preparation of Compounds *R*-(+)-6 and *S*-(−)-6[a]



[a] (a) (1) Chloral hydrate, hydroxylamine hydrochloride, and sodium sulfate, H_2O, reflux, 1 h. (2) 90% H_2SO_4, 25–80 °C, 0.5 + 0.5 h. (3) LAH, diethyl ether, room temperature, 1 h. (b) $POCl_3$, DMF, 0–50 °C, 1–2 h, purification on silica (MeOH). (c) (−)-*p*-Toluoyltartaric acid, 5% ethanol in ethyl acetate. (d) (+)-*p*-Toluoyltartaric acid, 5% ethanol in ethyl acetate.

roethanol).[4,9] Single-crystal X-ray analysis confirmed the (+)-enantiomer to have the *R* configuration and possessing a half-chair conformation of the aminotetralin moiety with the amino nitrogen in a pseudoequatorial position (Figures 2 and 3). Both racemic **2b** and its enantiomers were formylated by the Vilsmeyer–Hack formylation using phosphorus oxychloride in dimethyl formamide to give (*rac*)-, *R*-(+)-, and *S*-(−)-6, respectively (Scheme II).[10]

Pharmacology

Biochemistry (Table I). The *in vivo* biochemical test utilizes the well-established phenomenon of receptor-mediated feedback inhibition of the presynaptic neuron.[11] Dopamine (DA) and noradrenaline (NA) have the same general biosynthetic pathway, and the synthesis rate of the catecholamines DA and NA are 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 agonists.[12] The 5-HTP accumulation, following decarboxylase inhibition by means of 3-(hydroxybenzyl)hydrazine (NSD 1015), was used as an indicator of the 5-HT synthesis rate in three different brain areas (Table I). In addition, the accumulation of L-dihydroxyphenylalanine (DOPA) 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 NA synthesis rate in the NA-rich hemispheres (mainly

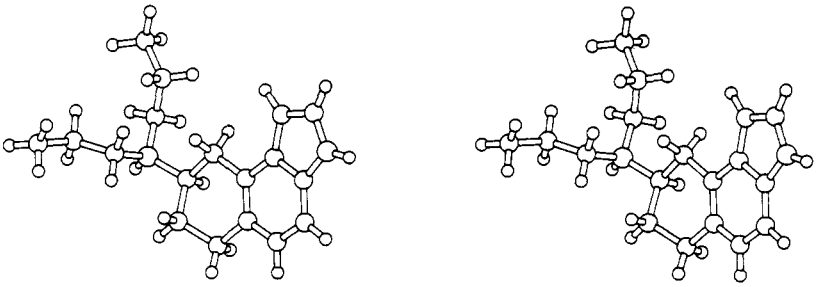


Figure 2. Stereodrawing of the X-ray structure of compound *R*-(+)-**2b**. The ditoluoyltartaric acid part of the structure has been omitted for clarity.

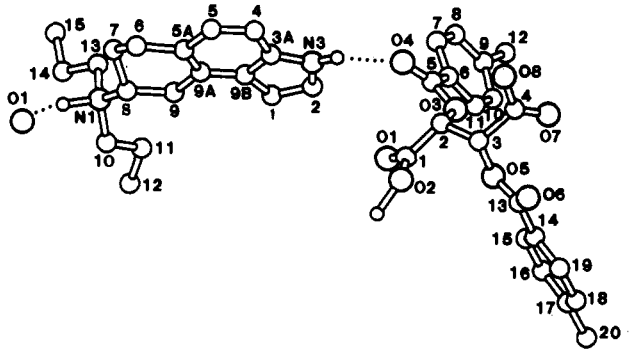


Figure 3. Segment of the unit cell showing hydrogen bonds (dotted lines), molecular structure and atom numbering scheme for *R*-(+)-**2b** and di-*p*-toluoyl-D-tartrate. The oxygen atom O1 at the left is part of a second di-p-toluoyl-D-tartrate molecule. Only hydrogen atoms connected to heteroatoms are shown.

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* feed-back regulation. This behavioral and biochemical model is designed to detect directly acting agonists at central monoamine receptors.

Behavior (Table I). Postsynaptic agonistic effects of the test compounds were assessed by the increase in locomotor activity (reversal of reserpine-induced hypokinesia). DA receptor agonists induce locomotor stimulation and at high doses also stereotypies, such as sniffing and licking. Selective 5-HT$_{1A}$ receptor agonists induce the 5-HT syndrome (flat body posture and reciprocal forepaw treading).

***In Vitro* Binding (Table I).** The abilities of the test compounds to displace the radioactively labeled ligands [^{3}H]spiperone and [^{3}H]-8-OH-DPAT from dopamine D$_2$ and serotonin 5-HT$_{1A}$ receptor sites, respectively, in homogenized rat brain tissue were assessed *in vitro*.[13]

Oral Bioavailability. The oral bioavailability was determined both as the *in vivo* response ratio of oral and subcutaneous administration and as the absolute oral bioavailability by means of analysis of the actual plasma concentrations after oral and intravenous or subcutaneous administration (Table II).

Results and Discussion

As can be seen in Table I, the *N,N*-di-*n*-propyl analog **2b** indeed shows much higher *in vivo* activity and *in vivo* affinity at 5-HT$_{1A}$ receptors than its *N,N*-dimethyl analog **2a**. This potency relationship between **2b** and **2a** is true also regarding their dopamine D$_2$ receptor agonist activity. Introduction of a formyl group in the 1-position of **2b** yielding compound **6** alters the binding profile from a mixed D$_2$/5-HT$_{1A}$ agonist to a selective and very potent 5-HT$_{1A}$-receptor agonist. The two enantiomers of **6** have almost equally high affinity for 5-HT$_{1A}$-receptor sites (in Table I are for these compounds given binding data from both brain homogenate and CHO-cells). The (−)-*S*-enantiomer seems to be more selective 5-HT$_{1A}$ receptors *versus* D$_2$ receptors. (The D$_2$/5-HT$_{1A}$ binding affinity ratio is about 2600, brain homogenate.) At the present time we have no explanation for the possible synergistic effects of the two enantiomers of compound **6** at dopamine receptors. This phenomenon seems to be present not only for compound **6** but also for **2b** in the *in vivo* biochemical test model (DOPA accumulation). The reduced D$_2$ activity and enhanced 5-HT$_{1A}$ activity of compounds **6** as compared to **2b** may depend on the additional electron withdrawal (by conjugation) from the indole nitrogen toward the carbonyl moiety. From a drug-receptor interaction point of view, this has interesting molecular modeling implications. A hydrogen bond in the drug–receptor interaction with the 5-HT$_{1A}$ receptor of compound **6** is likely to be provided by the formyl oxygen atom, as compared to the 8-oxygen in 8-OH-DPAT. This implies that there may be a higher degree of steric freedom in the region of the 8-position in aminotetralin-like structures than was previously believed. Molecular mechanics calculations suggest that the two possible low-energy conformations of the conjugating formyl group (*i.e.* s-cis and s-trans) has an energy difference of about 1 kcal in favor of the s-cis conformation with an average energy barrier between the two of 4 kcal.[14] This may be a result of steric hindrance of the oxygen to be in the s-trans conformation. The low dopamine activity of *S*-(−)-**6** compared to its enantiomer fits well into the receptor concept of McDermed, where it was shown that the dopamine activity of 7-OH-DPAT (**3**) resides in the *R*-enantiomer.[15] The unsubstituted *N,N*-dimethyl analog **2a** and the *N,N*-dipropyl compound **2b** also follows this pattern; the latter however only *in vivo*. From Figure 3 it can be noted that the indole N–H moiety forms an (for the crystal packing) important H bond with the ester carbonyl oxygen (O4, Figure 3) of the counterion. This suggests that for this class of compounds this hydrogen bonding ability may play an important role not only for the dopamine D$_2$ binding affinity but possibly also for the 5-HT$_{1A}$ binding affinity in the respective drug–receptor interaction.

The linear indolic compound **5** showed only weak responses in the *in vivo* biochemical tests and fairly low affinity for both 5-HT$_{1A}$ and D$_2$ sites. This confirms the finding of Nichols *et al.* that this compound has lower dopaminergic activity than compound **2b**.[8] These compounds have the indole NH moiety in the same position but with the possible hydrogen bonding vector orthogonal to each other.

The data in Tables I and II reveals that oral administration of the enantiomers of **6** is only 5–6 times less efficient (limbic regions) as compared to subcutaneous

Table I. *In Vitro* and *in Vivo* Pharmacological Data on Compounds Discussed

	biochemistry ED_{50}, μmol/kg							
	DOPA accumulation[c]			5-HTP accumulation[c]			behavioral	*in vitro* binding:[b] K_i, nM[d]
compd[a]	limb	stri	hem	limb	stri	hem	response[a]	D2	5-HT_{1A}
(±)-1[f]	I (45)[g]	I (45)	I (45)	0.052	0.052	0.063	+5-HT	1357 ± 275	8.7 ± 5.8 (2.1[i])
(±)-1 (po)	$P_{35\%}$ (61)[h]	$P_{43\%}$ (61)	I (61)	3.0 (0.9–7.5)	7.9 (5.7–12)	7.9 (5.4–15)	+5-HT		
R-(+)-1[f]	I (50)	I (50)	I (50)	0.036	0.047	0.050	+5-HT	826 ± 56	3.1 ± 0.2 (1.1[i])
S-(−)-1[f]	I (50)	I (50)	I (50)	0.061	0.065	0.077	+5-HT	5072 ± 249	8.4 ± 1.1 (1.9[i])
(±)-**2a**[j]	0.30 (0.24–0.38)	0.40 (0.28–0.48)	$P_{34\%}$ (4.0)	0.30 (0.13–0.39)	0.30 (0.20–0.40)	0.40 (0.20–0.65)	mix. DA, 5-HT	300	66
R-(+)-**2a**[j]	0.30 (0.18–0.35)	0.40 (0.39–0.49)	$P_{30\%}$ (2.0)	0.40 (0.31–0.65)	0.10 (0.07–0.25)	0.40 (0.31–0.50)	mix. DA, 5-HT	170	25
S-(−)-**2a**[j]	4.2 (3.2–4.8)	8.0 (5.0–11.0)	13.0 (8.0–20.0)	3.9 (3.1–4.5)	3.9 (2.8–5.5)	2.7 (2.3–3.0)	no change	1580	190
(±)-**2b**	0.18 (0.13–0.23)	0.28 (0.25–0.3)	$P_{22\%}$ (12.5)	0.1 (0.075–0.14)	0.08 (0.05–0.13)	0.11 (0.05–0.13)	mix. DA, 5-HT	156 ± 30	12 ± 4.2
R-(+)-**2b**	$P_{37\%}$ (3.1)	0.16 (0.12–0.21)	I (3.1)	0.20 (0.10–0.32)	0.25 (0.14–0.50)	0.41 (0.22–0.65)	mix. DA, 5-HT	100 ± 14	7.0 ± 0.7
S-(−)-**2b**	$P_{31\%}$ (3.1)	$P_{37\%}$ (3.1)	I (3.1)	0.16 (0.1–0.25)	0.30 (0.12–0.75)	0.20 (0.12–0.31)	mix. DA, 5-HT	146 ± 42	14 ± 3.2
5	$P_{30\%}$ (50)	$P_{51\%}$ (50)	I (50)	I (50)	I (50)	$P_{35\%}$ (50)	mix. DA, 5-HT	350[k]	570[k]
(±)-**6**	0.47	1.8	I (12.5)	0.060 (0.03–0.1)	0.054 (0.035–0.08)	0.067 (0.038–0.12)	+5-HT	120[k] 40 ± 6[l]	1.3[k] 0.2 ± 0.03[m]
R-(+)-**6**	I (3.1)	I (3.1)	I (3.1)	0.14 (0.10–0.20)	0.095 (0.05–0.19)	0.16 (0.13–0.18)	+5-HT	382 ± 68 17 ± 3[l]	1.4 ± 0.3 0.2 ± 0.02[m]
R-(+)-**6** (po)	$P_{31\%}$ (25)	I (25)	I (25)	0.96 (0.65–1.3)	1.5 (0.95–2.0)	0.95 (0.70–1.2)	+5-HT		
S-(−)-**6**	$P_{37\%}$ (12.5)	$P_{25\%}$ (12.5)	I (12.5)	0.09 (0.065–0.14)	0.08 (0.06–0.13)	0.095 (0.06–0.12)	+5-HT	3592 ± 136 423 ± 92[l]	2.0 ± 0.5 0.2 ± 0.01[m]
S-(−)-**6** (po)	I (12.5)	I (12.5)	I (12.5)	0.50 (0.32–1.0)	1.10 (0.4–2.3)	1.10 (0.5–2.2)	+5-HT		

[a] In reserpine pretreated rats the 5-HT behavioral response consists of the 5-HT syndrome (flat body posture, extended extremities, and reciprocal forepaw treading). Dopamine agonist mediated effects (DA) include locomotor activity and stereotypies (sniffing, licking, and rearing). [b] Ligands used are [^{3}H]spiperone (D_2 antagonist) and [^{3}H]-8-OH-DPAT (5-HT_{1A} agonist) unless otherwise stated. Values with SEM are from 3–7 triplicate experiments unless otherwise stated. [c] Abbreviations: limb, limbic system; stri, corpus striatum; and hem, hemispheres. ED_{50} values with graphically estimated deviation below based on SEM for each dose. [d] Inhibition constants (K_i) were calculated as described by Cheng and Prusoff.[22] [e] Subcutaneous administration unless otherwise stated. [f] *In vivo* data from ref 2a. [g] I = Inactive at the highest dose tested (dose in paratheses). [h] P = Partial response. Shown is the maximal reduction obtained in per cent at the highest dose tested (dose in parantheses). [i] *In vitro* data from ref 2d. [j] *In vitro* and *in vivo* data from ref 4. *In vivo* data somewhat recalculated. [k] Single experiment. [l] Binding experiments (D_2, [^{3}H]Raclopride, CHO-cells) as described in ref 6.[25] [m] Binding experiments (5-HT_{1A}, [^{3}H]-8-OH-DPAT, CHO-cells) as described in ref 6.[25]

Table II. Pharmacokinetics

compd	dose, μmol/dg	AUC, pmol/g h	C_{max}, pmol/mL	t_{max} min	$t_{1/2}$ (iv), h	F (iv/po),[b] %	ED_{50} ratio[a] (sc/po)
1	1.0 (iv)	213 ± 53	344 ± 93	3 ± 1	1.2	2.4 ± 0.9[c]	2
	20.0 (po)	104 ± 36	63 ± 32	29 ± 9			
R-(+)-**6**	2.0 (iv)	431 ± 14	712 ± 38	2 ± 0	1.5	46 ± 16[d]	15
	10.0 (po)	848 ± 276	108 ± 63	150 ± 82			
S-(−)-**6**	2.0 (iv)	607 ± 65	849 ± 35	2 ± 0	1.0	72 ± 12[e]	18
	10.0 (po)	2224 ± 371	606 ± 80	48 ± 17			

[a] 5-HTP accumulation in limbic regions (see Table I). [b] Blood plasma levels in rats. Calculated from total area from [C] versus time curves unless otherwise stated. [c] SEM, $n = 5$. [d] SEM, $n = 4$. [e] SEM, $n = 6$. All other values are given with SEM, $n = 4$–6.

administration. This is a considerable improvement, as compared to the poor oral activity (60 times less efficient po *versus* sc) of 8-OH-DPAT (**1**). The difference in blood plasma levels is even more dramatic. Here it is shown that the enantiomers of **6** have an absolute oral availability of 46% (*R*-(+)-**6**) and 72% (*S*-(−)-**6**), while 8-OH-DPAT (**1**) shows an oral availability of less than 3%. Notably, there is a tendency to other pharmacokinetic differences between the enantiomers of compound **6**, as shown by the more extended concentration *versus* time curve for the *R*-(+)-enantiomer (*i.e.* differences in $t_{1/2}$, t_{max}, and C_{max}). Unfortunately, it was found in the preclinical development of this series of compounds that both *R*-(+)-**6** and *S*-(−)-**6** are positive in the Ames test, implying that these compounds may be mutagenic in animals and humans.[16]

Experimental Section

Chemistry. Magnetic resonance spectra were performed on a Varian VXR4000 300-MHz spectrometer using tetramethylsilane as the internal standard. ^{13}C spectra were assigned in most of the cases with the use of the attached proton test (APT). Mass spectra were recorded on a HP5970A mass-selective detector working at 70 eV and interfaced with a HP5700A gas chromatograph. Elemental analysis (C, H, N) for new and biologically tested substances were within 0.4% of the theoretical values (Mikrokemi AB). Melting points were determined using a Reichert Thermovar microscope and are uncorrected. All physical data (except for melting points and elemental analysis) on amines were performed on the free bases. Yields are not optimized.

Di-*n*-propyl(6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-8-yl)amine (2b) and Di-*n*-propyl(5,6,7,8-tetrahydro-1*H*-benzo[*f*]indol-7-yl)amine (5). To a solution of 16.7 g (62 mmol) of 7-amino-2-(*N*,*N*-di-*n*-propylamino)-1,2,3,4-tetrahydronaphthalene hydrochloride (**4**) (prepared according to ref 7) in water (275 mL) were added chloral hydrate (12.1 g, 73 mmol), hydroxylamine hydrochloride (14.8 g, 0.21 mmol), and sodium sulfate (75 g, 530 mmol). The solution was refluxed for 1 h in an inert atmosphere. After the solution was cooled to ambient temperature diluted ammonia was added and a dark brown oil separated. The oil was

taken up in ethyl acetate by extraction five times. After drying (sodium sulfate), filtration, and evaporation of the solvent, the remaining oil was refrigerated and subjected to cooled aqueous sulfuric acid (350 mL conc H_2SO_4/35 mL water). The resulting solution was stirred in an inert atmosphere at ambient temperature for 30 min and then at 80 °C for 30 min. After cooling to room temperature, the solution was poured on ice. The solution was basified (diluted ammonia) and extracted (ethyl acetate) 5 times. The organic solution was dried (sodium sulfate), filtered, and evaporated to yield a raw product (17.5 g, 86%) of isatins that were dissolved in dry diethyl ether (100 mL) and slowly added to a suspension of 12 g (315 mmol) of lithium aluminum hydride in dry diethyl ether (500 mL) and stirred at room temperature for 1 h. Water (12 mL), 15% sodium hydroxide (12 mL), and additional water (36 mL) were cautiously added dropwise. After 10 min of stirring, the inorganic salts were filtered off and the solution was evaporated to a residue of 14.2 g (86%) of the raw product as an oil. Purification on silica (petroleum ether/diethyl ether, 1:3) afforded 4.7 g (28%) of **2b** and 1.5 g (9%) of the isomer **5** and 2.5 g (15%) of a mixture that could be recycled in another batch. Analytical and biological samples were treated with fumaric acid and recrystallized from ethanol/diethyl ether.

2b: mp 168–172 °C (1 fumarate salt); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 6 H), 1.50 (sixt, 4 H), 1.70 (oct, 1 H), 2.10 (br d, 1 H), 2.52 (t, 4 H), 2.80–3.00 (m, 3 H), 3.0–3.20 (m, 2 H), 6.53 (t, 1 H), 6.93 (d, 1 H), 7.14–7.20 (two d, 2 H), 8.15 (br s, 1 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 11.99 (CH_3), 22.37 (CH_2), 26.17 (CH_2), 29.21 (CH_2), 30.05 (CH_2), 52.83 (CH_2), 57.04 (CH), 100.45 (CH), 108.65 (CH), 123.25 (CH), 123.54 (CH), 127.01 (C), 127.56 (C), 128.07 (C), 133.58 (C); MS (90 eV) *m/e* 270 (M^+, 18), 170 (100), 143 (44), 241 (40), 168 (27). Anal. ($C_{22}H_{30}N_2O_4$) C, H, N.

5: mp 205–210 °C (1/2 fumar. salt); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 6 H), 1.50 (sixt, 4 H), 1.70 (m, 1 H), 2.05 (br d, 1 H), 2.50 (t, 4 H), 2.80–3.10 (m, 5 H), 6.42 (s, 1 H), 7.10 (s, 2 H), 7.34 (s, 1 H), 7.98 (br s, 1 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 12.0 (CH_3), 22.2 (CH_2), 26.5 (CH_2), 30.1 (CH_2), 33.0 (CH_2), 52.8 (CH_2), 57.4 (CH), 101.8 (CH), 110.6 (CH), 119.4 (CH), 124.0 (CH), 126.6 (C), 128.7 (C), 131.4 (C), 134.9 (C); MS *m/e* 270 (M^+, 21), 170 (100), 143 (39), 241 (36), 169 (26). Anal. ($C_{20}H_{28}N_2O_2$) C, H, N.

(*R*)-(+)-Di-*n*-propyl(6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-8-yl)amine (*R*-(+)-2b). Racemic di-*n*-propyl(6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-8-yl)amine (**2b**) (1.70 g, 6.30 mmol) and 2.43 g (6.30 mmol) of (−)-di-*p*-toluoyltartaric acid were dissolved in ethanol and evaporated. The residue was recrystallized from 5% ethanol in ethyl acetate. The progress in resolution was monitored by measuring changes in optical rotation of the diastereomeric salt. After four additional recrystallizations, there was no change in optical rotation (at $[\alpha]^{20}_D$ = −41.2°, *c* 1.0, methanol). The base was liberated by basification (10% sodium carbonate), extraction (ethyl acetate), drying (magnesium sulfate), filtering, and evaporation of the solvent to yield 170 mg of (+)-di-*n*-propyl(6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-8-yl)amine (*R*-(+)-**2b**) with an optical purity of >98%. Analytical and biological samples were treated with fumaric acid and recrystallized from ethanol/diethyl ether. NMR and MS spectra matched the spectra of the racemic material: mp 200–202 °C (1 fumarate) $[\alpha]^{20}_D$ +91.4° (*c* 1.0, methanol). Anal. ($C_{22}H_{30}N_2O_4$) C, H, N.

(*S*)-(−)-Di-*n*-propyl(6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-8-yl)amine (*S*-(−)-2b). The mother liquors from the resolution of the (+)-enantiomer where combined, evaporated, and worked up as above to yield 1.20 g (4.4 mmol) of the enriched (−)-isomer, which was treated as above with 1.7 g (4.4 mmol) (+)-di-*p*-toluoyltartaric acid. After four recrystallizations no change in optical rotation of the diastereomeric salt was registered (at $[\alpha]^{20}_D$ = +41.5°, *c* 1.0, methanol). The free base was liberated as described above to give 260 mg of (−)-di-*n*-propyl(6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-8-yl)amine (*S*-(−)-**2b**) with an enantiomeric purity of >98%. Analytical and biological samples were treated with fumaric acid and recrystallized from ethanol/diethyl ether. NMR and MS spectra matched the spectra of the racemic material: mp 202–205 °C (1 fumarate), $[\alpha]^{20}_D$ −90.9° (*c* 1.0, methanol). Anal. ($C_{22}H_{30}N_2O_4$) C, H, N.

8-(Di-*n*-propylamino)-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole-1-carbaldehyde (6). To an ice-cooled solution of phosphoroxy chloride (1.0 mL, 0.63 g, 4.0 mmol) in dimethylformamide (30 mL) was added di-*n*-propyl(6,7,8,9-tetrahydro-3*H*-benz[*e*]-indol-8-yl)amine (**2b**) (0.92 g, 3.4 mmol) in dimethylformamide (10 mL). The solution was stirred at ambient temperature for 10 min and thereafter at 50 °C for 1 h. The solution was poured on ice and basified (5% sodium hydroxide). After extraction three times (dichloromethane) the organic solution was dried (magnesium sulfate) and filtered, and the solvent was evaporated. The raw product was chromatographed on a silica column eluting with methanol to yield 0.56 g (55%) of pure **6**. Analytical and biological samples were treated with fumaric acid and recrystallized from ethanol/diethyl ether: mp 177–182 °C (1 fumarate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, 6 H), 1.53 (sixt, 4 H), 1.72 (oct, 1 H), 2.10 (br s, 1 H), 2.60 (t, 4 H), 2.90–3.05 (m, 2 H), 3.05–3.25 (m, 2 H), 4.55 (q, 1 H), 7.05 (d, 1 H), 7.21 (d, 1 H), 7.95 (s, 1 H), 9.50 (br s, 1 H), 10.22 (s, 1 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 11.97 (CH_3), 22.03 (CH_2), 26.24 (CH_2), 30.48 (CH_2), 32.09 (CH_2), 52.78 (CH_2), 57.15 (CH), 109.59 (CH), 121.01 (C), 124.49 (C), 125.25 (CH), 130.03 (C), 130.82 (C), 133.93 (CH), 135.24 (C), 185.73 (CH); MS *m/e* 298 (M^+, 12), 198 (100), 269 (82), 170 (56), 154 (18). Anal. ($C_{23}H_{30}N_2O_5$) C, H, N.

(*R*)-(+)-8-(Di-*n*-propylamino)-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole-1-carbaldehyde (*R*-(+)-6). This compound was prepared from 0.47 g (1.74 mmol) *R*-(+)-di-*n*-propyl(6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-8-yl)amine (*R*-(−)-**2b**) according to the preparation of the racemic material to yield 0.30 g (56%) after purification on silica eluting with methanol. NMR and MS spectra were identical to that of the racemic material. Prior to biological testing the fumaric acid salt was prepared and recrystallized from ethanol/diethyl ether: mp 165–170 °C (1 fumarate), $[\alpha]^{20}_D$ +112° (*c* = 1.0, methanol, free base). Anal. ($C_{23}H_{30}N_2O_5$) C, H, N.

(*S*)-(−)-8-(Di-*n*-propylamino)-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole-1-carbaldehyde (*S*-(−)-6). This compound was prepared from 0.50 g (1.85 mmol) (*S*)-(−)-di-*n*-propyl(6,7,8,9-tetrahydro-3*H*-benzo[*e*]indol-8-yl)amine (*S*-(−)-**2b**) according to the preparation of the racemic material and the (+)-enantiomer to yield 0.40 g (72%) of the desired compound after purification on silica (methanol). NMR and MS spectra were identical to that of the racemic material. Prior to biological testing the fumaric acid salt was prepared and recrystallized from ethanol/diethyl ether: mp 164–168 °C (1 fumarate), $[\alpha]^{20}_D$ −112° (*c* = 1, methanol, free base). Anal. ($C_{23}H_{30}N_2O_5$) C, H, N.

Determination of Optical Purity. The optical purity of *R*-(+)-**2b** and *S*-(−)-**2b** were determined by the use of (−)- and (+)-1-anthryl-2,2,2-trifluoroethanol respectively (Pirkles alcohol). With the addition of 5 molar equiv of the alcohol to a 10 mg/mL solution of **2b** in $CDCl_3$, two well-separated signals at δ 6.41 and δ 6.45 (1-CH resonance) were exhibited in the ^{1}H NMR spectrum. No traces of the corresponding enantiomer could be detected for either of the enantiomers. The detection limit for the corresponding enantiomer was estimated to be lower than 2%. Therefore the enantiomeric purity was established to be >98% for both *R*-(+)-**2b** and *S*-(−)-**2b**.

X-ray Analysis of *R*-(+)-2b Ditoluoyl Tartaric Acid Salt. The salts obtained in the resolution step of **2b** was used and a crystal with the dimension 0.36 × 0.29 × 0.05 mm was selected for data collection with an Enraf-Nonius CAD4F-11 diffractometer. The angular settings of 25 reflections ($25° < \theta < 49°$) were measured to calculate the lattice parameters, *c.f.* Table V (supplementary) for crystal material data. Intensity data for one unique set of reflections with $\theta = 60°$ ($0 \le h \le 9$, $0 \ge k \ge 15$, $0 \ge l \ge 32$) were collected by the $\omega/2\theta$ scan method using monochromatized Cu Kα radiation. Three intensity control reflections, which were measured every 2 h, indicated no significant decay. A total of 2896 reflections were recorded and of these 2163 reflections with $I > 2.5\sigma(I)$ were observed. All intensities were corrected for Lorentz and polarization effects but not for absorption or extinction.

The structure was solved by direct methods with MITHRIL[17] which provided the non-hydrogen atom positions. The position of H atoms connected to methyl carbon, nitrogen or oxygen atoms were determined from $\Delta\rho$ maps. Remaining hydrogen atoms were included at calculated positions. Refinement was carried out by the full-matrix least-squares method using anisotroipic temperature factor equal to the U_{eq} value of the parent atom. The hydrogen atom parameters were not refined. The absolute

configuration of (+)-2b was established from the known configuration of the counterion. After refinement the R value was $R = 0.046$ (unit weights, $S = 0.79$, $\Delta/\sigma < 0.01$, $-0.17 < \Delta\rho < 0.23$ e Å^{-3}). All calculations have been performed using mainly the program NRVAX.[18] The molecular conformation and the atom labeling scheme are shown in Figure 3.

Pharmacology. 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 5 per cage with free access to water and food, for at least one week from arrival until used in the experiments.

Materials. All substances to be tested were dissolved in saline immediately before use, occasionally with the addition of a few drops of glacial acetic acid and/or moderate heating in order to obtain complete dissolution. Reserpine was dissolved in a few drops of glacial acetic acid and made up to volume with 5.5% glucose solution. Injection volumes were 5 mL/kg, and all solutions had neutral pH at the time of injection (except for the solutions of reserpine; pH ≈ 4).

Biochemistry. The biochemical experiments and the determinations of DOPA and 5-HTP by means of HPLC with electrochemical detection were performed according to a modification of a previously described method.[19,20] Separate dose–response curves based on 4–6 dose levels ($n = 4$) for each substance (sc administration) and each brain area were constructed. From these curves, the dose of the drug yielding a half-maximal decrease (ED_{50} value) of the DOPA (the maximal effect, expressed as % of controls, was limbic system, −65%; striatum, −80%; and the hemispheres, −50%) and the 5-HTP (the maximal effect, expressed as % of controls limbic system, striatum, and the hemispheres, 50%) levels were estimated separately (Table I). Control values were for 5-HTP (ng/g, mean ± SEM, $n = 10$): limbic system, 192 ± 18; striatum, 129 ± 14, and the hemispheres, 131 ± 14. Control values were for DOPA (ng/g, mean ± SEM, $n = 10$): limbic system, 808 ± 56; striatum, 3653 ± 222; and the hemispheres, 156 ± 11.

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.[21] Eighteen hours prior to the motility testing (carried out between 9 a.m. and 1 p.m.), the rats were subcutaneously injected in the neck region with reserpine (5 mg/kg). The different test compounds were also administered subcutaneously in the neck region ($n = 4$). Immediately after drug administration, the rats were placed in the test cages (one rat per cage) and put into the motility meters. Motor activity was then followed and recorded for the subsequent 30 min (control values 3 ± 1 counts/30 min, mean ± SEM; $n = 13$) (Table I). Observations of gross behavior were made throughout the activity sessions through semitransparent mirrors.

5-HT$_{1A}$ Radioligand Binding. Male Sprague–Dawley rats (160–225 g) were killed by decapitation, and the whole brain with the exception of the brainstem and cerebellum was rapidly removed, weighed, and chilled in ice-cold 0.9% sodium chloride. Each brain was homogenized (Ultra-Turrax, 20 s) in 10 mL ice-cold 50 mM Tris buffer (pH 8.0 at 25 °C) containing 120 mM sodium chloride, 4 mM calcium chloride and 4 mM magnesium chloride and centrifuged at 20 000 g at 4 °C for 10 min. Pellets were resuspended in 10 mL of fresh buffer and preincubated for 10 min in a 37 °C water bath and then recentrifuged. Final pellets were homogenized in 100 volumes (w/v) of Tris buffer (as described above) containing 10 μM pargyline. The incubation tubes were kept on ice in triplicates and received 100 μL of drug solution in water (or water for total binding) and 1000 μL of membrane suspension (corresponds to 10 mg of original tissue). The binding experiment was initiated by addition of 100 μL of [^{3}H]-8-OH-DPAT (specific activity 219–240 Ci/mmol) in ascorbic acid (the final incubation concentration was 1 nM [^{3}H]-8-OH-DPAT in 0.1% ascorbic acid). After incubation for 15 min at 37 °C the reaction was terminated by separation of the free radioligand from bound by rapid vacuum filtration using a cell harvester equipment (O.M. Teknik, Denmark). The tubes were rinsed with 4 mL of ice-cold 0.9% sodium chloride, and the filters (Whatman GF/F 25 mm) were washed twice with 4 mL of ice-cold 0.9% sodium chloride.

The radioactivity of the filters was measured in a liquid scintillation counter (efficiency 41%) in 5 mL of Ready Safe (Beckman). Specific binding (70–75% of total binding) was defined as the radioactivity displaced by 10 μM 5-HT. IC_{50} value (the concentration of drug required to displace 50% of the labeled ligand) was calculated by semi-log plot and linear regression analysis. The inhibition constants (K_i) of the various compounds were calculated using the formula of Cheng and Prusoff:[22] $K_i = IC_{50}/(1 + [L/K_d])$, where L = concentration of labeled ligand and K_d = its affinity constant.

D$_2$ Radioligand Binding. Preparation of rat striatal membranes for [^{3}H]spiperone (specific activity 28 Ci/mmol) binding was carried out as described by Hyttel and Arnt.[13] The final pellets were homogenized in 1300 volumes of 50 mM potassium phosphate buffer and the membrane suspension was incubated with 0.5 nM [^{3}H]spiperone in a final volume of 4.2 mL (3 mg of original tissue) for 10 min at 37 °C. Specific binding was 70–80% of total binding and was obtained by adding 10 μM 6,7-ADTN to the membrane suspension.

Absolute Oral Bioavailability. Blood plasma levels were analyzed either by HPLC technique using a Kontron 420 HPLC pump equipped with a Jasco 821 FP fluorescence detector ($\lambda_{ex} = 285$, $\lambda_{em} = 365$) or by gas chromatography (Hewlett Packard)/mass spectrometry (VG Trio II). Male Sprague–Dawley rats treated orally with drug were starved 18 h before the experiment. The blood samples (100–250 μL) were collected from arterial catheters in rats (300 g). The experiment started 24 h after operation and blood samples were collected at various time intervals up to 12 h after drug injection.

Compound 6. The weighed blood samples were diluted with water (0.5 mL). Internal standard was added. Here the chromane analog with the oxygen in 6-position of 6 (8-(di-*n*-propylamino)-3,7,8,9-tetrahydropyrano[3,2-*e*]indole-1-carbaldehyde) was used as internal standard.[23] The sample was then buffered with saturated sodium carbonate (50 μL) and extracted with dichloromethane (4 mL) for 30 min. The organic phase was evaporated to dryness and the residue was dissolved in methanol (25 μL). In order to obtain a fluorescent material, compound 6 together with the internal standard were reduced to the corresponding alcohols by the addition of a freshly prepared aqueous solution of 0.1 M sodium borohydride (50 μL). The samples were allowed to react over night and were then injected into a HPLC LiChrosphere 60 RP-selectB (5 μm, 125 length × 4 mm i.d.) column using gradient elution (A, 25 mM acetic acid, 25 mM sodium acetate, 5 mM diethyl amine; B, methanol). A calibration curve was constructed by adding compound 6 (0.5–150 ng) to blank blood samples using 12 different concentrations in duplicate. Included were also blank blood samples, blanks with internal standard, and reagent blanks. The assay was linear over the concentration range and the detection limit in blood samples was estimated to about 1 ng/mL. The bioavailability was determined as the ratio between the integrals of per oral and intravenous drug concentration/time curves. The half life was estimated from the corresponding log [C] curves.

Compound 1. The weighed samples were diluted with 1 mL water. Then 25 ng of internal standard 8-methoxy-2-[(dicyclopropylmethyl)amino)]-1,2,3,4-tetrahydronaphthalene[24] was added. The pH was adjusted to 11.0 by addition of 50 mL of saturated sodium carbonate. After mixing, the samples were extracted with 4 mL of dichloromethane by shaking for 30 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 1 standard to blank blood samples. Gas chromatography 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 290 °C. The absolute oral bioavailability of the compound was assessed by comparing the areas under the curves (AUC), for po ($n = 5$) and iv ($n = 3$) administration, in graphs where the blood concentrations of the compound were plotted against time.

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Supplementary Material Available: Elemental analysis protocol, crystal data, positional and thermal parameters, bond lengths, bond angles, observed and calculated structure factors, and a steroview of unit cell (9 pages). Ordering information is given on any current masthead page.

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