6,7,8,9-Tetrahydro-*N*,*N*-di-*n*-propyl-3*H*-benzindol-8-amines. Derivatives as Potent and Orally Active Serotonin 5-HT$_{1A}$ Receptor Agonists

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Derivatives and isosteric derivatives of the potent 5-HT$_{1A}$ agonist 8-(di-*n*-propylamino)-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole-1-carbaldehyde (**5**) were prepared and evaluated *in vivo* and *in vitro* for serotonergic and dopaminergic activity. The 1-cyano analog **8** was found to be almost equipotent to **5** and the previously described 2-cyano derivative **6**, while a 1-chloro and 1-(1,1,1-trifluoroethyl) substituent (**9** and **10**, respectively) formed less potent derivatives. The isosteric 6,7,8,9-tetrahydro-1*H*-benz[*g*]indoles **4** and **12**–**15** showed surprisingly low affinity or activity at both serotonergic and dopaminergic systems. The interpretations of these results by means of drug–receptor interactions at the 5-HT$_{1A}$ subtype are discussed. Compounds **6** and **8** were found to have high oral bioavailability in the rat (63% and 54%, respectively).

Introduction

The indole NH moiety can be regarded as a bioisostere of the hydrogen-bonding H donor properties of the phenolic OH group. This approach has been useful for determining the nature of the hydrogen bonding between phenol-containing ligands and receptor proteins.[1–4] For example Asselin et al.[1] demonstrated that the "indolic" aminotetralin **2a** (Figure 1) showed dopaminergic effects and thus mimicked the action of 7-hydroxy-2-(*N*,*N*-dipropylamino)-1,2,3,4-tetrahydronaphthalene (7-OH-DPAT, **1b**). It was pointed out that, since the lone pairs in the indole nitrogen of **2a** cannot participate in a H-bond (due to its contribution to the aromaticity), the indole NH moiety can only participate as a H-bond donor (electron-pair acceptor). In a subsequent paper, Nichols et al.[5] showed that the linear indolic aminotetralin **3**, with the NH moiety in the same position as **2a** but with a NH vector pointing orthogonal to that of **2a**, had a much lower dopamine activity in the prolactin release model. This was recently confirmed by us in a biochemical test model.[6] This gave an indication of the direction of a possible H-bond of 7-OH-DPAT (**1b**) in the dopamine site of the D_2 receptor even though the possibility that compound **3** is poorly active by steric interference cannot be outruled. Later Wikström et al.[7] showed that compound **2b**, the dimethyl analog of **2a**, possesses considerable 5-HT$_{1A}$ agonist properties in addition to its dopaminergic activity, reported by Asselin et al.[1] It was speculated that the high electron density in the indole 3-position (corresponding to 1-position of **2b**), resembled the 8-oxygen in 8-hydroxy-2-(*N*,*N*-dipropylamino)-1,2,3,4-tetrahydronaphthalene (8-OH-DPAT, **1a**), the well-studied standard serotonin 5-HT$_{1A}$ agonist.[8–15] If one considers hydrogen bond attraction to the receptor protein, it is possible that in the case of **2b** the partial negative charge of the π-electron cloud

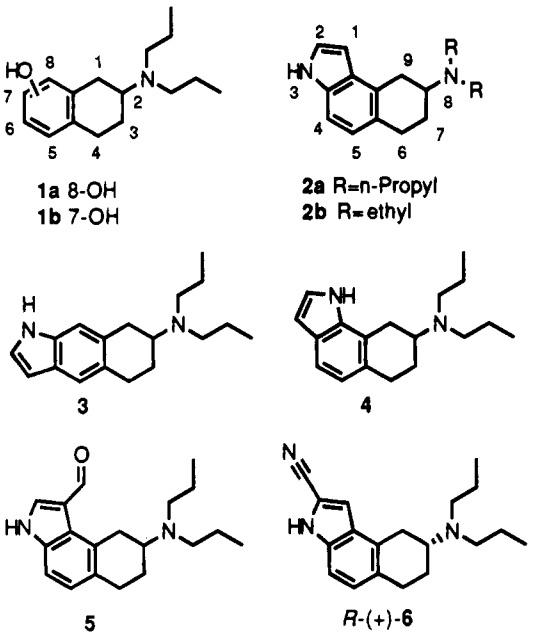

Figure 1. Structures discussed.

nearby C1 serves as a hydrogen bond acceptor, since the hydrogen at C1 presumably is poor as a donor.[16] However, the relatively low binding (compared to 8-OH-DPAT) of the dimethyl compound **2b** indicated that a better probe for this hypothesis would be compound **2a**. In our recent publication[6] we demonstrated that compound **2a** is indeed a very potent 5-HT$_{1A}$ agonist with high affinity for the 5-HT$_{1A}$ receptor, in addition to its dopaminergic activity. It was also shown that introduction of a formyl group in the 1-position of **2a**, resulting in compound **5** (OSU191), enhanced the 5-HT$_{1A}$-stimulating properties and decreased the dopaminergic activity. This selectivity was more pronounced in the (−)-*S*-enantiomer. In another paper by Romero et al.,[17] the 2-cyano analog *R*-(+)-**6** was reported to possess considerable 5-HT$_{1A}$ affinity. These results have prompted us to go further with this investigation and produce analogs of compound **5** and its enantiomers. We also

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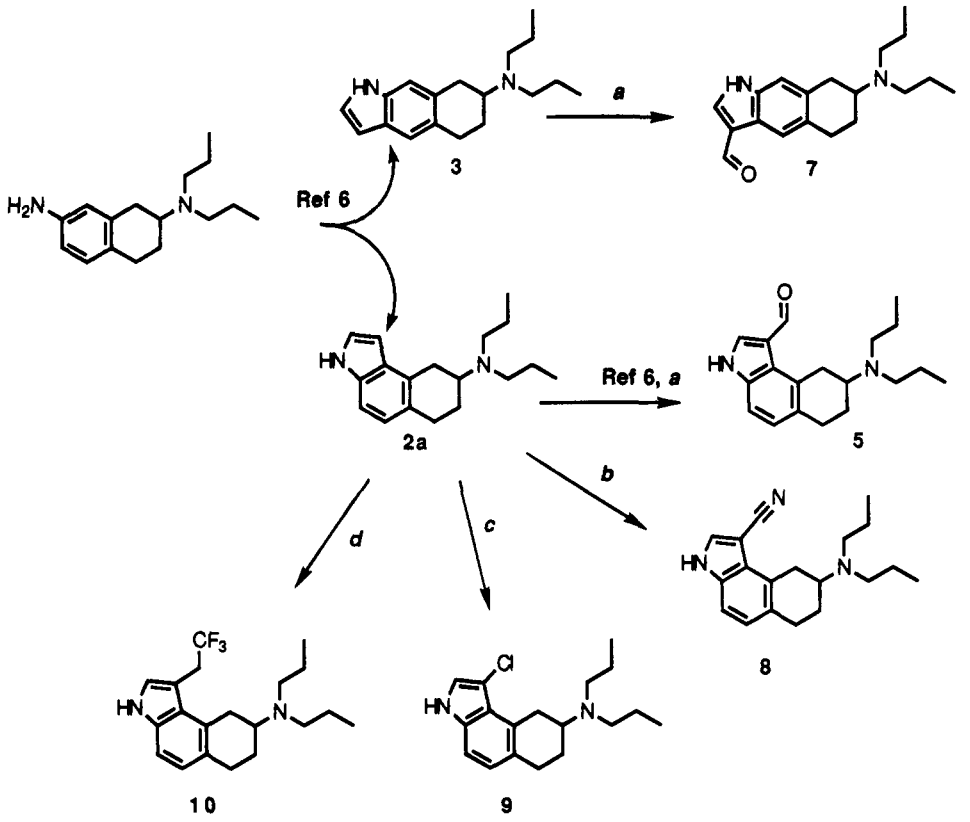
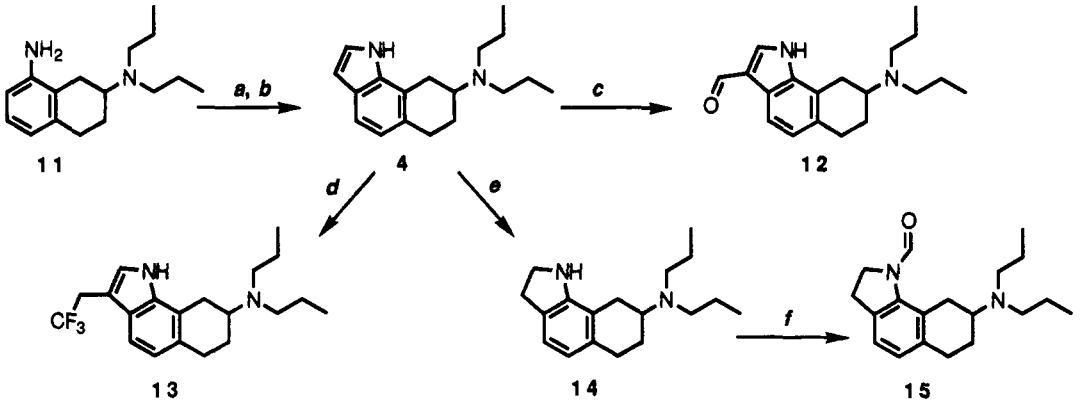
Scheme 1[a]



[a] Reagents: (a) DMF, $POCl_3$, 50 °C; (b) (1) $ClSO_2NCO$, MeCN, rt, (2) MeCN, DMF, rt; (c) NCS, THF, rt; (d) (1) BzCl, NaH, DMF, rt, (2) TFAA, CH_2Cl_2, rt, (3) LAH, THF, reflux.

Scheme 2[a]



[a] Reagents: (a) (1) chloral hydrate, $HONH_2$·HCl, Na_2SO_4, H_2O, reflux, (2) 90% H_2SO_4, 25–80 °C; (b) LAH, diethyl ether, rt; (c) DMF, $POCl_3$; (d) (1) TFAA, Me_3N, CH_2Cl_2, rt, (2) LAH, THF/diethyl ether, rt; (e) Et_3SiH/TFA, MeCN, rt; (f) EtOOCH, 100 °C.

wanted to investigate analogs of regioisomers **3** and **4**. Compound **4** represents a structural class where the indole NH moiety is in the same position as the phenolic hydroxy group in 8-OH-DPAT. In analogy to the pharmacological resemblance between 8-OH-DPAT (**1a**) and the formylindole **5**, we wanted to compare 7-OH-DPAT (**1b**), by means of dopaminergic responses, with the 3-formyl derivative of **4**. This compound would have the indoloformyl moiety in the "same aminotetralin position" as **1b** has its phenolic moiety.

Chemistry

Compounds **2a** and **3** were prepared from 7-NH_2-DPAT as previously reported by Stjernlöf et al.[6,18] Vilsmeyer formylation of **3** yielded **7**.[19] The syntheses of 1-cyano derivatives **8**, *R*-(+)-**8**, and *S*-(−)-**8** were accomplished by the use of chlorosulfonyl isocyanate from the corresponding racemic or resolved material.[6,20] The 1-chloro derivative **9** was prepared by chlorination using *N*-chlorosuccinimide[21] and the 1,1,1-trifluoroethyl derivative **10** via *N*-benzylation, trifluoroacetylation, and subsequent lithium aluminium hydride reduction (Scheme 1).

The isomeric (to compound **2**) ring system where the indole nitrogen is in the 1-position was synthesized by a similar technique (Scheme 2). Thus, the aminotetralin **11**[18] was converted to the indole **4** as outlined for compound **2a**.[1,6] This compound was subjected to Vilsmeyer formylation in the 3-position as before to yield the formyl derivative **12**. Trifluoroacetylation of compound **4** and subsequent reduction (lithium aluminium hydride) afforded the 1,1,1-trifluoroethylated compound

Table 1. Effects of Rat Brain DA and 5-HT Synthesis Rates *in Vivo*

	ED_{50}, μmol/kg (pED_{50}, mol/kg)					
	DOPA accumulation[a]			5-HTP accumulation[a]		
compd[b]	limb.	stri	hem.	limb.	stri	hem.
1a[c]	I (45)	I (45)	I (45)	0.052	0.052	0.063
1b[c]	0.027	0.030	I (11)	I (11)	I (11)	I (11)
3[f]	P (50)[e]	P (50)	I (50)	P (50)	I (50)	I (50)
4	P (50)[e]	P (50)	I (50)	I (50)	I (50)	P (50)
5[f]	0.30[i]	3.3[i]	I (12.5)	0.11	0.067	0.13
	(6.52 ± 0.64)	(5.48 ± 0.08)		(6.95 ± 0.29)	(7.18 ± 0.39)	(6.88 ± 0.30)
R-(+)-**5**[f]	I (3.1)	I (3.1)	I (3.1)	0.072[i]	0.12[i]	0.45
				(7.14 ± 0.33)	(6.91 ± 0.44)	(6.34 ± 0.20)
S-(−)-**5**[f]	4.33[i]	I (12.5)	I (12.5)	0.11	0.052	0.032
	(5.36 ± 0.50)			(6.94 ± 0.81)	(8.28 ± 1.04)	(7.49 ± 0.49)
R−(+)-**6**[g]	2.01[i]	3.36[i]	I (12.5)	0.21	0.079	0.28
	(5.69 ± 0.29)	(5.47 ± 0.07)		(6.67 ± 0.17)	(7.10 ± 0.46)	(6.56 ± 0.46)
R-(+)-**6** po	P (3.1)	P (3.1)	I (3.1)	0.38[i]	0.46[i]	0.38[i]
				(5.42 ± 0.15)	(6.34 ± 0.23)	(6.42 ± 0.14)
7	27.8[i]	16.7[i]	I (50)	13	18	14
(14.56 ± 0.15)	(4.78 ± 0.20)			(4.88 ± 0.14)	(4.74 ± 0.48)	(4.87 ± 0.46)
8	1.05	3.2[i]	5.2[i]	0.17	0.22	0.45
	(5.98 ± 0.20)	(5.49 ± 0.12)	(5.29 ± 0.16)	(6.77 ± 0.21)	(6.65 ± 0.33)	(6.35 ± 0.46)
R-(+)-**8**	1.65[i]	I (3.1)	I (3.1)	0.092	0.036	0.14
	(5.78 ± 0.53)			(7.03 ± 0.33)	(7.44 ± 0.91)	(6.85 ± 0.30)
S-(−)-**8**	42[i]	52[i]	I (50)	0.12	0.089	0.15
	(4.37 ± 0.50)	(4.29 ± 0.52)		(7.93 ± 0.22)	(7.05 ± 0.28)	(6.81 ± 0.32)
9	3.7	3.4	P (50)	1.4	1.7	1.4
	(5.43 ± 0.22)	(5.47 ± 0.16)		(5.86 ± 0.65)	(5.78 ± 0.49)	(5.85 ± 0.60)
10	I (50)	P (50)	I (50)	I (50)	I (50)	I (50)
12	I (50)	I (50)	I (50)	I (50)	I (50)	I (50)
13	I (50)	I (50)	I (50)	I (50)	I (50)	I (50)
14	P (50)	P (50)	I (50)	I (50)	I (50)	I (50)
15	P (50)	P (50)	I (50)	I (50)	I (50)	I (50)

[a] Abbreviations: limb., limbic system; hem., hemispheres, and stri, corpus striatum. ED_{50} values were calculated by fitting a sigmoidal curve to the dose responses. Given are ED_{50} values in μmol/kg and in parentheses are pED_{50} values (95% confidence limits). [b] Subcutaneous administration unless otherwise stated. [c] Data from refs 6 and 9. [d] I = Inactive in the highest dose tested (dose in parentheses). [e] P = Partial response, with significance at least to the 95% level, at the highest dose tested (dose in parentheses). [f] Data from ref 6. Recalculated by sigmoidal curve fitting (see footnote *i*). [g] Other biological data are presented in ref 8. [i] Dose−response curve not fully covered. In these cases either the slope or the max decrease values were fixed in order to obtain an ED_{50} with confidence limits.

13. Reducing indole **4** by means of triethylsilane/trifluoroacetic acid gave the indoline **14**, which was N-formylated using ethyl formate to give a N-formylated derivative, compound **15**.

Pharmacology

Biochemistry. The *in vivo* biochemical test utilizes the well-established phenomenon of receptor-mediated feedback inhibition of the presynaptic neuron.[22] Dopamine DA and noradrenaline (NA) have the same general biosynthetic pathway, and the synthesis rate of the catecholamines DA and NA is decreased by agonists (and increased by antagonists) at dopaminergic and α-adrenergic presynaptic receptors, respectively. Similarly, the synthesis rate of 5-HT is inhibited by 5-HT autoreceptor agonists.[13,23,24] 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 1). In addition, the DOPA accumulation was used as an indicator of the DA synthesis rate in the DA-rich areas (i.e. limbic system and corpus striatum) and the NA synthesis rate in the NA-rich hemispheres (mainly cortex). For this study we used reserpine-pretreated rats (5 mg/kg sc, 18 h), in which the synthesis rate of especially DOPA is raised via feedback regulation. This behavioral and biochemical model is designed to detect directly acting agonists at central monoamine receptors.

Locomotor Activity and Behavior. 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 stereotyped behavior, such as sniffing and licking. Selective 5-HT_{1A} receptor agonists induce the so-called 5-HT-syndrome (flat body posture and reciprocal forepaw treading).

Motor activity recordings were carried out as previously described with the use of motility meters (Table 2).[25] The behavior of the animals was observed through semitransparent glass windows.

***In Vitro* Binding.** The abilities of the test compounds to displace the radioactively labeled ligands [^{3}H]-spiperone and [^{3}H]-8-OH-DPAT from D_2- and 5-HT_{1A} receptor sites, respectively, in homogenized rat brain tissue were assessed in vitro.[26]

Oral Bioavailability. The oral availability was determined both as the *in vivo* response ratio of oral and subcutaneous administration and as the absolute oral availability by means of analysis of the actual plasma concentrations after oral and intravenous or subcutaneous administration (Table 3).

Results and Discussion

Introduction of a formyl substituent in the 1-position of the indole/aminotetralin skeleton, as in compound **5** switched the pharmacological profile from a mixed 5-HT_{1A}/D_2 agonist to a selective 5-HT_{1A} agonist with full intrinsic activity.[6] For comparison, we tested the corresponding 2-nitrile *R*-(+)-**6**[17,27] in our pharmacological models. This compound is also a potent 5-HT_{1A} agonist

Table 2. *In Vitro* Binding and *in Vivo* Behavioral Data

	in vitro binding,[a] K_i, nM		motor activity and behavior[b]		
compd	5-HT_{1A}	D_2	dose (sc), μmol/kg	counts/30 min, dpm	behavior
1a[c]	8.7 ± 5.8	1357 ± 275	0.02	66 ± 17	5-HT
1b[c]	2810	54 ± 12	3.5	170 ± 7	DA
2a[d]	12 ± 4.2	156 ± 30	12.5	177 ± 39***	5-HT, DA
R-(+)-**2a**[d]	7.0 ± 0.7	100 ± 14	0.8	82 ± 18***	5-HT, DA
S-(+)-**2a**[d]	14 ± 3.2	146 ± 42	0.8	29 ± 6*	5-HT, DA
3	570[e]	350[e]	50	51 ± 18*	5-HT, DA
4	220[e]	145[e]	50	119 ± 41*	DA
5[d]	1.3[e]	120[e]	12.5	231 ± 60***	5-HT
R-(+)-**5**[d]	1.4 ± 0.3	382 ± 68	3.1	162 ± 53***	5-HT
S-(+)-**5**[d]	2.0 ± 0.5	3592 ± 136	12.5	413 ± 227*	5-HT
R-(+)-**6**	1.7 ± 0.2	538 ± 67	12.5	194 ± 71**	5-HT
7	4720[e]	700[e]	50	172 ± 26***	5-HT, DA
8	1.8 ± 0.3	439 ± 85	12.4	317 ± 102*	5-HT
R-(+)-**8**	2.7 ± 0.5	419 ± 108	NT	NT	
S-(+)-**8**	2.9 ± 0.8	8015 ± 2657	3.1	300 ± 34***	5-HT
9	12.6 ± 2.1	317 ± 24	NT	NT	
10	182 ± 12	796 ± 147	50	10 ± 5	–
12	6720[e]	>16000[e]	50	7 ± 3	–
13	8800[e]	2330[e]	50	74 ± 28**	–
14	410[e]	650[e]	NT	NT	–
15	550[e]	>16000[e]	50	NT	5-HT, DA

[a] Ligands used were [^{3}H]spiperone (D_2 antagonist) and [^{3}H]-8-OH-DPAT (5-HT_{1A} agonist). Values with SEM are from 3 to 7 experiments were each concentration were run in triplicate unless otherwise stated. [b] Motor activity values are given with SEM ($n = 4$) for the actual dose. ***, **, and * designate $p = 0.005$, 0.05, and 0.5, respectively. The 5-HT behavioral response in reserpine-pretreated animals consists of 5-HT syndrome (flat body posture, extended extremeties, and reciprocal forepaw treading), whereas the dopamine agonist mediated effects (DA) include increased locomotor activity and stereotypical behavior (sniffing, licking, and rearing). [c] Values from ref 9 (included for comparison). [d] Binding values from ref 6 (included for comparison). [e] Single experiment run in triplicates.

Table 3. Pharmacokinetics

compd	dose, μmol/kg	AUC, pmol/g h	C_{max}, pmol/mL	t_{max}, min	$t_{1/2}$, iv, h	F (po/iv),[b] %	ED_{50} ratio[a] (sc/po), %
1c	iv 1.0	213 ± 53	344 ± 93	3 ± 1	1.2	2.4 ± 0.9[d]	2
	po 2.0	104 ± 36	63 ± 32	29 ± 9			
R-(+)-**5**[c]	iv 2.0	431 ± 14	712 ± 38	2 ± 0	1.5	46 ± 16[e]	15
	po 10.0	848 ± 276	108 ± 63	150 ± 82			
S-(−)-**5**[c]	iv 2.0	607 ± 65	849 ± 35	2 ± 0	1.0	72 ± 12[f]	18
	po 10.0	2224 ± 371	606 ± 80	48 ± 17			
R-(+)-**6**	iv 4.0	1817 ± 252	2566 ± 528	4 ± 2	1.5	63 ± 7	55
	po 10.0	2857 ± 300	1116 ± 171	75 ± 42			
8	iv 5.0	1115 ± 94	1733 ± 138	2 ± 0	1.5	54 ± 13[e]	NT
	po 40.0	4849 ± 1182	1504 ± 406	135 ± 15			

[a] Determined as the ratio of the 5-HTP-accumulation decrease in limbic regions after oral and subcutaneous administration (see Table 1). [b] Blood plasma levels in rats. Calculated from total area from [C] *vs* time curves unless otherwise stated. [c] Data from ref 6. [d] SEM, $n = 5$. [e] SEM, $n = 4$. [f] SEM, $n = 6$. All other values are given with SEM, $n = 4$–6.

with full intrinsic activity, equipotent to 8-OH-DPAT (**1a**) and compound **5** (Tables 1 and 2). It displays weak effects at dopaminergic, and also adrenergic, neurons as reflected by the decrease in DOPA accumulation in the various brain regions. The binding profile (Table 2) is similar to that of 8-OH-DPAT and **5**. Notable is the difference in 5-HT_{1A}-binding affinity using brain homogenate (*R*-(+)-**6** *Ki* = 1.7 nM, Table 2) and CHO-cells (*R*-(+)-**6** *Ki* = 0.1 nM[17]). This is true also for other compounds such as 8-OH-DPAT (**1a**) and **5** (see refs 6 and 8). Interestingly, the pharmacological differences between the positional isomers *R*-(+)-**6** and *R*-(+)-**8** are very small. There is likely considerable accomodation of different hydrogen-bonding trajectories.

An introduction of a halogen in the **1**-position of compound **2a** (**9**) results in a lower 5-HT_{1A} receptor binding affinity and a higher dopamine receptor D_2 affinity compared to compounds **5**, *R*-(+)-**6**, and **8**. In addition, the trifluroethyl-substituted compound **10** was prepared with the intention to investigate how an electron-withdrawing group spaced **1** atom further away from the aromatic system of the molecule would influence the pharmacological profile. Compounds **5**, *R*-(+)-**6**, and **8** possess electron-withdrawing groups (**1**-CHO, 2-CN, and 1-CN, respectively), conjugated with the aromatic system and thus extending the π-system. The 5-HT_{1A}-binding affinity of compound **10** is about a 100-fold lower than that of compounds **5**, *R*-(+)-**6**, and **8**. It also showed poor D_2 receptor binding affinity. Furthermore, it did not display any activity at the highest dose tested in the *in vivo* biochemical models. Both nitrile-substituted analogs **8** and *R*-(+)-**6** showed good oral bioavailability ($F = 54$ and 63%, respectively, Table 3). This is comparable to the oral bioavailability of the enantiomers of compound **5** and superior to the oral bioavailability of 8-OH-DPAT (2.4%).[6] The relatively high *in vivo* response in the 5-HTP accumulation assay after oral administration of *R*-(+)-**6**, as compared to subcutaneous administration, also indicates a favorable oral bioavailability (Tables **1** and 3).

The NH moiety of the isomeric "indolic" aminotetralin **4** is situated in the same position as the phenol group in 8-OH-DPAT. Hypothetically, if 8-OH-DPAT would interact with a hydrogen bond as a H-bond donor with the hydrogen pointing "northeast", compound **4** would possess considerable 5-HT_{1A} activity, if one assumes that the indole NH moiety is a good mimic of the H-donor properties of the phenol group. The 5-HT_{1A}

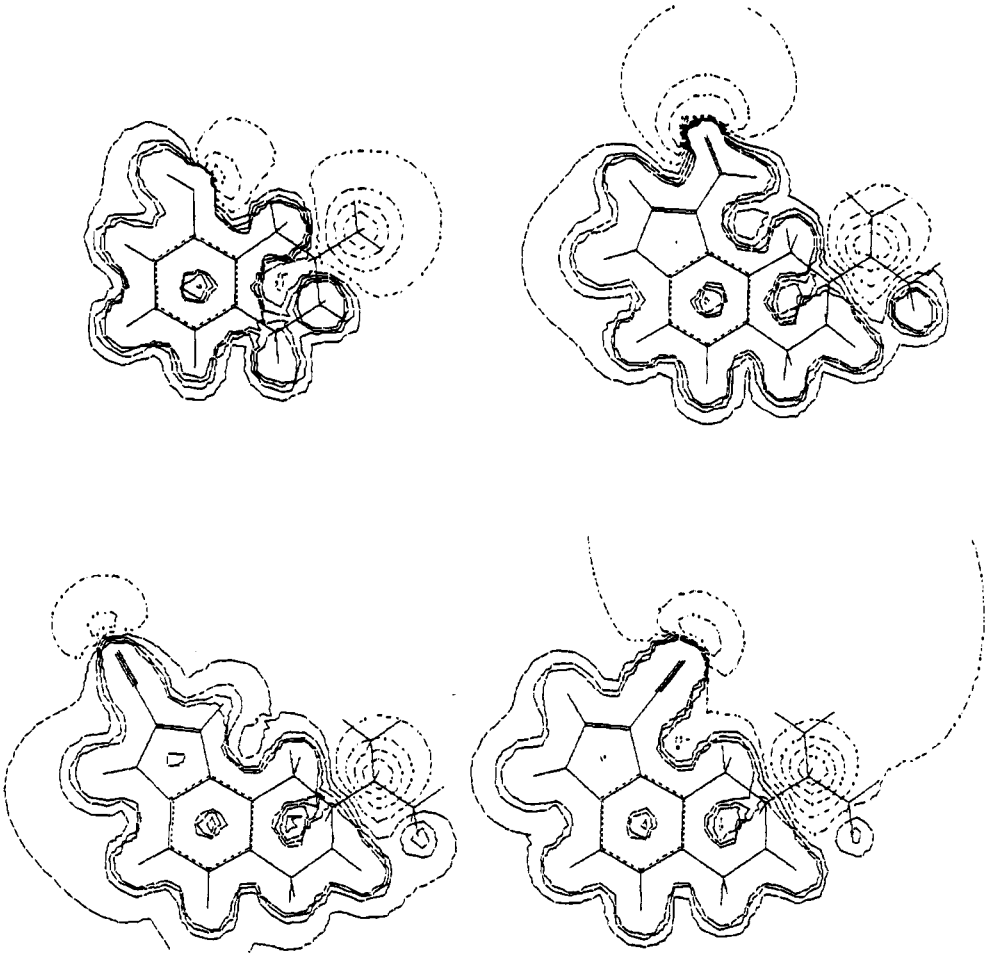


Figure 2. Electrostatic potential maps of the global energy minimum of compounds *R*-(+)-**1a** (top left), *R*-(+)-**5** (top right), *R*-(+)-**6** (bottom left), and *R*-(+)-**8** (bottom right). The grid plane was chosen 0.5 Å below the plane defined by the aromatic rings, where the negative contour plots (dotted lines) were most clear.

binding affinity of compound **4** is very low, as compared to 8-OH-DPAT and other potent compounds in this series. In addition, it is inactive at the highest dose tested in the 5-HTP accumulation assay and shows no dopaminergic activity. Compound **14**, having an anilinic NH moiety, could also serve as a probe of this assumption. This compound shows even lower affinity in the binding assays and only partial *in vivo* responses at the highest dose tested in the DOPA accumulation assay. The N-formylated indoline compound **15** can possibly be regarded as a bioisostere to compound **5** without the aromatic conjugation possibilities. However, this compound shows poor *in vitro* and *in vivo* responses.

Compound **4** was also derivatized in the 3-position to yield the formyl derivative **12** and the trifluoroethyl compound **13**. These compounds were devoid of affinity and activity in the assays used and did not to any extent mimic 7-OH-DPAT (**1b**) as in the case of the resemblance between 8-OH-DPAT (**1a**) and the formyl compound **5**. The linear indole formyl derivative **7** displayed very poor affinity for both 5-HT_{1A} and D_2 receptors. Interestingly, this compound is moderately potent but still a full agonist in the *in vivo* 5-HTP accumulation assay. The 5-HT syndrome is very weak. This profile may be compatible with the interpretation that compound **7** is a presynaptic 5-HT agonist. Although not investigated, metabolic activation of compound 7 may be required for *in vivo* 5-HT_{1A} agonist activity.

This SAR study has revealed some important prerequisites for good 5-HT_{1A} receptor affinity and potency. Presuming that the molecule possesses a suitable shape including an aromatic moiety and a basic nitrogen and is substituted with suitable N-alkyl groups, the next important quality seems to be a negative charge (δ^-) positioned somewhere in a quite large area outside the 2-aminotetralin 8 position. From the electrostatic potential maps of the potent agonists *R*-(+)-**8**, *R*-(+)-**6**, and *R*-(+)-**5**, it is quite clear that there is a negative potential center "north" of the aromatic ring system (Figure 2). It seems important, however, that this negative charge is connected (e.g. by resonance) to the aromatic system. This is reflected by the poor activity of compound **10**, which possesses a δ^- at the CF_3 group, not directly connected to the aromatic system. Also, the fact that the formamide **15**, which is almost inactive, possesses a similar shape (compared to **5**), but has no resonance connection from the formyl group to the aromatic system, may support this. Whether this phenomenon is due to the receptor preferring planarity in this region or if there are electrostatic implications remains to be investigated. While the pyrrolo and formyl moieties in compound **5** probably lie in the aromatic ring plane, molecular mechanics calculations[28] performed on compound **15** reveal that the formyl group lies somewhat out of the aromatic ring plane due to the sp3 hybridization of N1 and due to the fact that C2 is forced somewhat out of the plane. Additionally, the

hydrogens of C2 and C3 in **15** are of course pointing out of the plane, which makes this compound less planar in this region compared to compounds **5**, **6**, and **8**. Additionally, it may be speculated that for compound **2a** and its derivatives the ligand receptor complex is stabilized by an additional interaction with the receptor defined by the indole NH moiety. This type of interaction would not be present for the isomeric indole series.

The poor activity of especially compound **4**, but also its derivatives, may also be explained from a hydrogen bond point of view apart from the possibility of unfavorable steric interactions of C2 and C3. If one accepts that the indole NH moiety is a good mimic of the phenol group, the conformation of 8-OH-DPAT, when the OH-hydrogen is pointing "northeast" in the aromatic plane (toward the cyclohexene ring) can be outruled as a part of a 5-HT_{1A} receptor pharmacophore, but only if the H-bond donor properties are considered. The H-bond acceptor properties of this conformation are still to be considered. In fact, this conformation, which has an energy of only 0.4 kcal higher than the global energy minimum (the corresponding "northwest" OH-conformation) also shows a negative center, here pointing "northwest". This conformation would mimic the action of compounds **5** and **8**. It has been shown that *o*-fluorinated 8-OH-DPAT (7-fluoro-8-hydroxy-2-(di-*n*-propylamino)-1,2,3,4-tetrahydronaphthalene) is equipotent to 8-OH-DPAT (**1a**).[29] In this case an internal hydrogen bond between the OH-hydrogen and the fluorine stabilizes the rotamer, in which the OH group is pointing "northwest" (from the cyclohexene ring).[30] In this conformation it is likely that the H-bond donor properties are used in the interaction with the receptor protein, competing with the H···F-bond. Upon considering these findings altogether, it may be speculated that the interaction between 8-OH-DPAT and the 5-HT_{1A} receptor is promoted both by its H-bond donor properties when OH is pointing "northwest" and by its H-bond acceptor properties when the OH is pointing "northeast". Presuming that this part of the ligand is interacting with a serine (or threonine unit) in the receptor protein, this may be more easily accepted since the OH of the serine unit also possesses the complementary H-bond donor/acceptor possibilities. In fact, this interpretation of the drug–receptor interaction may shed further light upon the previously mentioned steric freedom of the 5-HT_{1A} receptor for the area outside the aminotetralin 8-position. If one superimposes the potent cyano derivatives **6** and **8**, it is obvious that there must be quite a high degree of steric acceptance in this part of the 5-HT_{1A} receptor. From this observation, also some drug–receptor interaction conclusions may be drawn, if one considers a H-bond attraction to the cyano moieties to be preferable. In fact, serine[198] and threonine[199] of transmembranal region 5 of the 5-HT_{1A} receptor have by mutation studies been suggested to be specifically involved in the ligand–receptor interactions.[31] In Figure 3 is shown schematically two possible interpretations of the similar pharmacological profile of compounds **6** and **8**. The first explanation (A) is that compounds **6** and **8** use different OH moieties (Ser[198] and Thr[199]) from the receptor protein in their respective CN···H hydrogen bonds. The second explanation (B) is more an account of the dynamics of the receptor protein and attributed to the possibility that only one CH_nOH from the receptor protein can be involved in the CN···H bond. Theoretically, if an CH_nOH (Ser or Thr) group has the ability to rotate along the C–C axis, the hydrogen-bonding possibilities would be found (depending on the steric acceptance of the rest of the protein) along the perifery of this circular movement. This would explain some of the difficulties previous authors[32–34] have had to make their models more specific when many structurally different types of 5-HT_{1A} receptor agonists are used to find a universal pharmacophore. Especially since in the traditional way of receptor mapping it is presupposed that the binding site accomodates one single pharmacophore, which encourages mapping of ligand conformations on each other with the lowest root mean square values possible. In contrast, this suggests that the binding site of a receptor accomodates several "types" of slightly different pharmacophores, depending on the rotational freedom of the functional groups of the amino acids involved in the drug–receptor complex, which makes it difficult to use the ligand mapping approach. With this reasoning, compounds **6** and **8** would represent slightly different modes of interaction where, for instance, compounds **1a** and **5** fit better to the binding mode described by compound **8**. Several studies discuss which amino acid residues may be involved in 5-HT_{1A} receptor binding.[31,35–37] In Figure 3 is also included an aspartate residue which is supposed to interact with the amine nitrogen of ligands. However, before interactions are further defined, this "rotational freedom" approach may open a way to investigate the 3D-structure and dynamics of receptor binding sites.

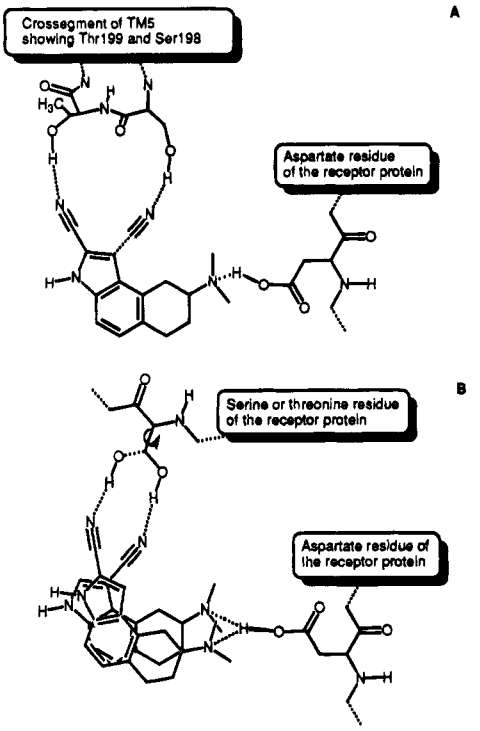


Figure 3. Compounds **6** and **8** overlapped in two sketches showing possible modes of interactions with the receptor protein. In part A a cross-segment of transmembranal region 5 (TM5)[47] containing Ser[198] and Thr[199] is shown. In part B the possible interaction between the respective cyano groups of compounds **6** and **8** and one freely rotating serine (or threonine) residue of the receptor protein is shown. Aspartate residues have also been discussed in the interaction between the receptor and the amino group of 5-HT_{1A} ligands.[31]

Experimental Section

Chemistry. Nuclear magnetic resonance spectroscopy was performed on a Varian VXR4000 300 MHz spectrometer, using tetramethylsilane as the internal standard. ^{13}C-Spectral peaks 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 HP 5700A gas chromatograph. Elemental analyses (C, H, N) for the new substances were within 0.4% of the theoretical values (Mikrokemi AB) unless otherwise stated. Melting points were determined using a Reichert Thermovar microscope and are uncorrected. All physical data analyses (except for mp and elemental analysis) of the amines were performed on the free bases. Chromatography on silica was performed using the flash chromatography technique. Yields were not optimized.

7-(Di-*n*-propylamino)-5,6,7,8-tetrahydro-1*H*-benz[*f*]indole-3-carbaldehyde (7). An ice cold solution of phosphorus oxychloride (0.35 mL) in dimethylformamide (20 mL) was added to an ice cold solution of *N,N*-di-*n*-propyl-5,6,7,8-tetrahydro-1*H*-benz[*f*]indol-7-ylamine (**3**,[6] 300 mg, 1.11 mmol) in dimethylformamide (10 mL). The reaction mixture was stirred at 0 °C for 10 min and at 50 °C for 1.5 h. After pouring the mixture on ice, it was basified (15% sodium hydroxide) and quickly heated to 50 °C. The aqueous mixture was extracted three times (dichloromethane) and the organic solution was dried (magnesium sulfate), filtered, and evaporated several times after addition of 99% ethanol. The raw product (220 mg, 60%) was further purified on a silica column using methanol as the eluant to yield 70 mg (21%) of the desired material. Prior to elemental analysis and pharmacological testing, the fumarate salt was prepared and recrystallized from methanol/diethyl ether (mp 196–201 °C, $^1/_2$ fumarate): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 6H), 1.50 (sext, 4H), 1.65 (oct, 1H), 2.05 (br d, 1H), 2.50 (t, 4H), 2.80–3.15 (m, 5H), 7.14 (s, 1H), 7.74 (s, 1H), 8.0 (s, 1H), 9.70 (br s, 1H), 9.95 (s, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 11.9 (CH_3), 22.0 (CH_2), 25.8 (CH_2), 30.0 (CH_2), 33.2 (CH_2), 52.7 (CH_2), 57.1 (CH), 111.4 (CH), 119.0 (C), 120.8 (CH), 122.9 (C), 132.2 (C), 133.8 (C), 135.8 (C), 136.3 (CH), 185.2 (CH); MS *m/e* 298 (M^+, 22), 198 (100), 269 (60), 170 (53), 126 (31). Anal. ($C_{21}H_{28}N_2O_3$) C, H, N.

8-(Di-*n*-propylamino)-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole-1-carbonitrile (8). To an ice-cooled solution of *N,N*-di-*n*-propyl-6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-8-ylamine (**2a**,[6] 500 mg, 1.85 mmol) in acetonitrile (10 mL), in an inert atmosphere, was added dropwise a solution of 360 mg (2.50 mmol) of chlorosulfonyl isocyanate in acetonitrile (1.5 mL). After stirring for 20 min, a solution of 154 mg of dimethylformamide in acetonitrile (10 mL) was added dropwise and the resulting mixture was stirred for 1 h. The mixture was poured on ice and basified using dilute ammonia. After extraction six times with dichloromethane, the organic solution was dried (magnesium sulfate), filtered, and evaporated. Methanol was added until most of the material was dissolved. After filtration of the solid undissolved material (40 mg of product, 90% purity), the volume of the solution was reduced to one-half by evaporation. The precipitated product was filtered off (180 mg of pure product). From the mother liquor additional material (220 mg) was recovered, giving a total yield of 80%: mp 218–220 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.9 (t, 6H), 1.45 (q, 4H), 1.6 (m, 1H), 1.95 (br d, 1H), 2.45 (m, 4H), 2.9 (m, 4H), 3.4 (solvent hidden, "1"), 6.95 (d, 1H), 7.25 (d, 1H), 8.15 (s, 1H), 12.0 (br s, 1H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 11.78 (CH_3), 21.71 (CH_2), 28.64 (CH_2), 29.38 (CH_2), 52.02 (CH_2), 56.18 (CH), 83.13 (C), 110.43 (CH), 118.20 (C), 124.66 (CH), 125.07 (C), 127.61 (C), 128.86 (C), 133.43 (C), 134.50 (CH); MS *m/e* 295 (M^+, 6), 195 (100), 266 (50), 193 (20), 179 (15), 196 (15). Anal. ($C_{20}H_{24}N_3{}^1/_2H_2O$) C, H, N.

***R*-(+)-8-(Di-*n*-propylamino)-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole-1-carbonitrile (*R*-(+)-8).** This compound was prepared from (*R*)-(+)-*N,N*-di-*n*-propyl-5,6,7,8-tetrahydro-1*H*-benz[*f*]indol-7-ylamine (*R*-(+)-**3**)[6] in a manner similar to that of the racemic compound **8**: mp 175–178 °C; $[\alpha]^{20}_D = 104°$ (*c* 0.5, methanol). Anal. ($C_{20}H_{24}N_3{}^1/_2H_2O$) C, H, N.

***S*-(−)-8-(Di-*n*-propylamino)-6,7,8,9-tetrahydro-3*H*-benz[*e*]indole-1-carbonitrile (*S*-(−)-8).** This compound was prepared from (*S*)-(−)-*N,N*-di-*n*-propyl-5,6,7,8-tetrahydro-1*H*-benz[*f*]indol-7-ylamine (*S*-(−)-**3**)[6] in a similar manner as for the racemic compound **8**: mp 177–180 °C $[\alpha]^{20}_D = -104°$ (*c* 0.5, methanol). Anal. ($C_{20}H_{24}N_3{}^1/_2H_2O$) C, H, N.

***N,N*-Di-*n*-propyl-1-chloro-6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-8-ylamine (9).** A solution of *N*-chlorosuccinimide (180 mg, 1.35 mmol) and *N,N*-di-*n*-propyl-6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-8-ylamine[6] (382 mg, 0.26 mmol) in tetrahydrofuran (20 mL) was stirred in room temperature for 2 h. The solution was washed (saturated sodium carbonate solution), dried (magnesium sulfate), filtered, and evaporated to yield 350 mg of a crude product that was purified on a silica column using a mixture of butanol, acetic acid, and water (4:1:1) as eluant to give 184 mg (43%) of the desired material. Analytical and biological samples were recrystallized from ethanol (99%): mp 161–165 °C; ^{1}H NMR (75.4 MHz, $CDCl_3$) δ 0.90 (t, 6H), 1.50 (sixt, 4H), 1.65 (m, 1H), 2.05 (br d, 1H), 2.55 (t, 4H), 2.8–3.2 (m:s, 4H), 3.75 (d, 1H), 6.92 (d, J = 8.3 Hz, 1H), 7.10 (two d, 2H), 8.1 (br s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 11.69 (CH_3),19.85 (CH_2), 25.38 (CH_2), 29.37 (CH_2), 29.67 (CH_2), 52.37 (CH_2), 58.60 (CH), 105.80 (C), 110.21 (CH), 121.59 (CH), 122.24 (C), 124.08 (CH), 126.89 (C), 127.68 (CH), 133.63 (C); MS *m/e* 306 (7, M^+), 304 (20, $M^+ - 2$(isotope)), 204 (100), 275 (77), 169 (44), 177 (20). Anal. ($C_{18}H_{25}ClN_2{}^1/_2H_2O$) C, H, N.

***N,N*-Di-*n*-propyl-1-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-8-ylamine (10).** To a solution of *N,N*-di-*n*-propyl-6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-8-ylamine[6] (200 mg, 0.74 mmol) in dimethylformamide (4 mL) was added sodium hydride (55% mineral oil dispersion, 40 mg, 0.86 mmol) at ambient temperature. After a few minutes, benzyl chloride (100 mg, 0.80 mmol) was added. The progress of the reaction was monitored by GLC. After stirring for 2 h, the reaction had stopped. Another 10 mg (0.21 mmol) of sodium hydride dispersion and benzyl chloride (25 mg, 0.20 mmol) was added consecutively and the reaction was completed within 30 min. Triethyl amine (10 mL) was added and the reaction mixture was stirred for 15 min and then poured on water/diethyl ether, shaken, and separated. The aqueous phase was extracted once more with diethyl ether. The combined ether extracts were dried (magnesium sulfate), filtered, and evaporated under reduced pressure. Ethanol (99%) was added and evaporated again. This procedure was repeated until no dimethylformamide was left and yielded 284 mg (107%) of the intermediate *N,N*-di-*n*-propyl-3-benzyl-6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-8-ylamine, of which 270 mg (0.75 mmol) was brought to solution in triethylamine (0.5 mL) and dichloromethane (5 mL). Trifluoroacetic acid anhydride (206 mg, 307 mL, 0.98 mmol) was added and the stirred mixture was kept at room temperature overnight. Water was added and the mixture was stirred for several hours. The organic layer was evaporated and the raw product (533 mg) was chromatographed on a silica column using acetone as eluant to yield 350 mg (102%) of 3-benzyl-8-(di-*n*-propylamino)-6,7,8,9-tetrahydro-3*H*-benz[*e*]indol-1-yl trifluoromethyl ketone. A mixture of this material (0.338 mg, 0.74 mmol) and lithium aluminium hydride (230 mg, 6.0 mmol) in tetrahydrofuran (20 mL, refluxed and distilled from potassium) was refluxed for 3 days and then cooked to dryness and refilled with tetrahydrofuran. The remaining lithium aluminium hydride was destroyed: 0.3 mL of water, 0.3 mL of 15% sodium hydroxide, and 0.9 mL of water was cautiously added consecutively. The resulting precipitate was filtered off and the filtrate was evaporated to yield 190 mg (73%) of a raw product which was chromatographed on a silica column using methanol as eluant. The pure fractions were collected, and the solvent was evaporated, yielding 44 mg (17%) of an oil, which was converted to the hydrochloride salt with HCl-saturated ether: mp 124–127 °C (HCl salt); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.9 (t, 6H), 1.50 (sext, 4H), 1.65 (m, 1H), 2.05 (br d, 1H), 2.55 (t, 4H), 2.95 (m, 2H), 3.05 (m, 1H), 3.25–3.4 (br d, 1H), 4.75 (d q, J = 10.6 Hz (F-coupl), 2H), 6.9 (d, J = 8.3 Hz, 1H), 7.11 (s, 1H), 7.14 (d, J = 8.5 Hz, 1H), 8.15 (br s, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 11.9 (CH_3), 22.1 (CH_2), 25.6 (CH_2), 30.1 (CH_2), 30.5 (CH_2), 32.1 (F-coupl, 0.4

Hz, q, CH_2), 52.8 (CH_2), 57.1 (CH), 104.8 (C), 109.2 (CH), 124.0 (CH), 124.7 (CH), 125.4 (C), 127.6 (F-coupl, 2.0 Hz, q, CF_3), 128.0 (C), 128.6 (C), 134.5 (C); MS *m/e* 352 (17, M^+), 252 (100), 323 (34), 225 (17), 167 (16). Anal. ($C_{20}H_{29}ClF_3N_2 \cdot H_2O$) C, H, N.

N,N-Di-*n*-propyl-6,7,8,9-tetrahydro-1*H*-benz[*g*]indol-8-ylamine (4). To a solution of di-*n*-propyl-5,6,7,8-tetrahydro-1,7-naphthalenediamine dihydrochloride[18] (2.25 g, 7.05 mmol) in water (25 mL) was added chloral hydrate (1.3 g, 7.9 mmol) followed by hydroxylamine hydrochloride (1.6 g, 23 mmol) and sodium sulfate (8 g, 56 mmol). The mixture was refluxed under an inert atmosphere for 1 h, cooled, basified (dilute ammonia), and extracted three times with ethyl acetate. After drying (magnesium sulfate) and filtering, the solution was evaporated to a residue of 2.2 g. This material (freezer cold) was subjected to a freezer cold solution of water in concentrated sulfuric acid (1:9, 100 mL). The temperature was slowly raised to 80 °C and stirred for 1 h. After cooling, the mixture was poured on ice/water. Ethyl acetate was added and the aqueous solution was basified (33% ammonia) under stirring. The phases were separated and two additional extractions were performed. The combined organic phases were dried (magnesium sulfate), filtered, and evaporated to yield 1.83 g of a raw product. This material was purified on a silica column using dichloromethane/methanol (19:1) as eluant and yielded 1.56 g of the intermediate isatine (8-(di-*n*-propylamino)-6,7,8,9-tetrahydro-1*H*-benz[*g*]indole-2,3-dione) (74%) as an orange solid (mp >260 °C, dec). This intermediate (1.0 g, 3.33 mmol) was dissolved in dry diethyl ether (175 mL) and slowly added to a suspension of 1.4 g (37 mmol) lithium aluminium hydride in dry diethyl ether (350 mL). The mixture was stirred for 4 h. Water (1.4 mL), 15% sodium hydroxide (1.4 mL), and water (4.2 mL) were cautiously added in consecutive order. After stirring for 10 min the precipitated inorganic material was filtered off on Celite and evaporated to a residue of 0.75 g (83%). The HCl salt was prepared from saturated hydrochloric acid in methanol and recrystallized from ethanol/diethyl ether: mp 264–268 °C (HCl); ^{1}H NMR (22.5 MHz, $CDCl_3$) δ 0.90 (t, 6H), 1.53 (sixt, 4H), 1.7 (oct, 1H), 2.10 (br d, 1H), 2.55 (t, 4H), 2.75–3.10 (m, 3H), 3.15 (d of d of t, J = 2.6, 5.3, 11.3 Hz, 1H), 6.52 (d of d, J = 2.0, 3.2 Hz, 1H), 6.90 (d, J = 8.1 Hz, 1H), 7.16 (t, J = 2.6 Hz, 1H), 7.42 (d, J = 8.1 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 12.0 (CH_3), 23.3 (CH_2), 25.7 (CH_2), 27.2 (CH_2), 30.1 (CH_2), 52.8 (CH_2), 56.9 (CH), 103.0 (CH), 118.1 (CH), 118.9 (C), 121.1 (CH), 123.2 (CH), 125.1 (C), 129.8 (C), 135.3 (C); MS *m/e* 270 (M^+, 24), 170 (100), 143 (50), 241 (38), 168 (31). Anal. ($C_{18}H_{27}ClN_2$) C, H, N.

8-(Di-*n*-propylamino)-6,7,8,9-tetrahydro-1*H*-benz[*g*]indole-3-carboxaldehyde (12). In the same manner as described for compound **7**, *N,N*-di-*n*-propyl-6,7,8,9-tetrahydro-1*H*-benz[*g*]indol-8-ylamine (**4**, 120 mg, 0.44 mmol) was converted to 60 mg (46%) of the desired material as a solid after purification on silica (methanol): mp 187–190 °C (free base); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 6H), 1.60 (sext, 4H), 1.70 (oct, 1H), 1.95 (br s, 1H), 2.10 (br d, 1H), 2.50t (4), 2.75–3.20 (m, 4H), 7.05 (d, J = 8.3 Hz, 1H), 7.80 (s, 1H), 8.05 (d, J = 8.0 Hz, 1H), 8.90 (br s, 1H), 10.0 (s, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 11.9 (CH_3), 22.3 (CH_2), 25.4 (CH_2), 27.2 (CH_2), 30.1 (CH_2), 52.7 (CH_2), 56.6 (CH), 119.1 (CH), 119.6 (C), 120.2 (C), 121.8 (C), 124.2 (CH), 132.6 (C), 134.5 (CH), 136.2 (C), 185.3 (CH); MS *m/e* 298 (M^+, 42), 198 (100), 269 (90), 170 (56), 168 (51), 98 (37). Anal. ($C_{19}H_{26}N_2O$) C, H, N.

N,N-Di-*n*-propyl-3-(2,2,2-trifluoroethyl)-6,7,8,9-tetrahydro-1*H*-benz[*g*]indol-8-ylamine (13). A mixture of *N,N*-di-*n*-propyl-6,7,8,9-tetrahydro-1*H*-benz[*g*]indol-8-ylamine (4, 100 mg, 0.37 mmol), trimethylamine (340 mg, 5.8 mmol), and trifluoroacetic anhydride (540 mg, 2.5 mmol) in dichloromethane (5 mL) was stirred for 5 h at room temperature. The mixture was poured into dichloromethane (25 mL) and 10% sodium carbonate (10 mL) and stirred. The organic phase was separated, dried (sodium sulfate), and evaporated to a residue, which was redissolved in dry diethyl ether (10 mL) and dry tetrahydrofuran (10 mL). Lithium aluminium hydride (0.3 g, 7.8 mmol) was added and the resulting mixture was refluxed for 2 days. After cooling, the mixture was diluted with diethyl ether (25 mL). Water (0.3 mL), 15% sodium hydroxide (0.3 mL), and water (0.9 mL) were added consecutively. After 10 min, the inorganic salts were filtered off (Celite) and the solution was evaporated to yield 145 mg of a colorless oil. This material was chromatographed on silica (flash chromatography, dichloromethane/methanol 9:1), giving 50 mg (38%) of the purified product as an oil (hygroscopic): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 6H), 1.5 (sixt, 4H), 1.7 (m, 2H), 2.1 (br d, 1H), 2.5 (t, 4H), 2.7–3.2 (m's, 4H), 3.5 (q, 2H), 6.9 (d, J = 8.1 Hz, 1H), 7.1 (d, J = 2.5 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 8.1 (br s, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 11.9 (CH_3), 22.3 (CH_2), 25.6 (CH_2), 27.1 (CH_2), 30.0 (CH_2), 30.6, 52.7 (CH_2), 56.8 (CH), 105.3 (C), 116.2 (CH), 119.1 (C), 121.4 (CH), 123.2 (CH), 124.7 (C), 130.4 (C), 135.4 (C); MS *m/e* 352 (M^+, 29), 252 (100), 323 (56), 167 (32), 225 (28), 251 (26). High Res MS ($C_{20}H_{27}N_2F_3$) calc 352.212634, found 352.2139.

N,N-Di-*n*-propyl-2,3,6,7,8,9-Hexahydro-1*H*-benz[*g*]indole-8-ylamine (14). A solution of *N,N*-di-*n*-propyl-6,7,8,9-tetrahydro-1*H*-benz[*g*]indol-8-ylamine (4, 134 mg, 0.5 mmol) in acetonitrile (5 mL) was added to a solution of triethylsilane (2.0 g, 17.2 mmol) in trifluoroacetic acid (5 mL). The mixture was stirred overnight, evaporated, and redissolved in water. After washing 2 times with diethyl ether, the aqueous phase was basified (1 g sodium carbonate) and extracted three times (diethyl ether). The organic solution was dried (sodium sulfate) and evaporated to a residue of 124 mg which was purified on silica (flash chromatography, diethyl ether) to yield 105 mg (78%) of a colorless oil. Prior to biological testing, the dihydrochloride salt was prepared as an oil, which did not solidify in any solvent tested: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.9 (t, 6H), 1.5 (sext, 4H), 1.60 (oct, 1H), 2.0 (br d, 1H), 2.5 (t, 4H), 2.3–2-9 (m:s, 6H), 3.0 (t, 2H), 3.4 (s, 1H), 3.55 (t, 2H), 6.50 (d, J = 7.6 Hz, 1H), 6.90 (d, J = 7.4 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 11.9 (CH_3), 21.9 (CH_2), 25.5 (CH_2), 27.1 (CH_2), 29.8 (CH_2), 30.0 (CH_2), 47.5 (CH_2), 50.4 (CH), 52.7 (CH_2), 57.0 (CH), 118.3 (C), 118.9 (CH), 121.6 (CH), 125.7 (C), 135.3 (C), 150.0 (C); MS *m/e* 272 (M^+, 24), 172 (100), 145 (44), 243 (32), 170 (22), 144 (21). Anal. ($C_{18}H_{30}Cl_2N_2 \cdot H_2O$) C, H, N.

8-(Di-*n*-propylamino)-2,3,6,7,8,9-hexahydro-1*H*-benz[*g*]-indole-1-carbaldehyde (15). A solution of *N,N*-di-*n*-propyl-2,3,6,7,8,9-hexahydro-1*H*-benz[*g*]indole-8-ylamine (**14**, 105 mg, 0.38 mmol) in ethyl formate (25 mL) was stirred in a sealed tube at 100 °C under an inert atmosphere for several days. The progress of the reaction was followed by GLC. When the reaction was complete, the solvent was removed by evaporation and the residue subjected to a silica column and eluted by flash chromatography (dichloromethane/methanol 19:1) to yield 101 mg (86%) of pure solid product: mp 78–80 °C; ^{1}H NMR (75.4 MHz, $CDCl_3$) δ 0.90 (t, 6H), 1.50 (sixt, 4H), 1.65 (oct, 1H), 2.05 (br d, 1H), 2.45 (m, 4H), 2.6–3.2 (m, 7H), 3.80 (q, 1H), 4.45 (d of t, 1H), 6.80 (d, J = 7.7 Hz, 1H), 7.0 (d, J = 7.6 Hz, 1H), 8.95 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 11.9 (CH_3), 22.2 (CH_2), 25.5 (CH_2), 27.6 (CH_2), 30.3 (CH_2), 30.9 (CH_2), 45.8 (CH_2), 52.6 (CH_2), 57.2 (CH), 123.0 (CH), 125.0 (CH), 130.7 (C), 136.9 (C), 139.9 (C), 160.8 (CH); MS *m/e* 300 (M^+, 5), 200 (100), 271 (44), 201 (23), 172 (19). Anal. ($C_{19}H_{28}N_2O$) C, H, N.

Computational Methods. The conformations of the molecules calculated are of the low-energy conformations calculated with Hyperchem software, developed by Hypercube Inc.,[38] using the extended MM2 force field[39]called MM+. To be able to create electrostatic potential contour plots, semiempirical single point calculations were performed using the AM1 method,[40] which calculates the wave function and the distribution of charges and electron of the molecule. In order to display the results from the single point calculation, each molecule was placed in the plane of the screen and a grid system built from 45 horizontal and 45 vertical points with its center at the center of the mass of the molecule. The grid plane could be chosen at any offset distance from the plane of the molecule (i.e. perpendicular or unperpendicular to the molecular plane). In each grid point the electrostatic potential was calculated and displayed as contour isopotential lines connecting grid points with similar potentials. Positive and negative potentials are here displayed as lines and dashed lines, respectively. For simplicity, the substituents on the 8-nitrogen are truncated to methyl groups.

Minimizations were also made using MacMimic[28] interfaced with the MM2 force field.

Pharmacology. Animals. Male rats used in the biochemical and motor activity experiments were of the Sprague-Dawley strain (ALAB, Sollentuna, Sweden), weighing 200–300 g. The rats were kept five per cage with free access to water and food, 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 determinations of DOPA and 5-HTP by means of HPLC with electrochemical detection were performed according to a modification of a previously described method.[41,42] Separate dose–response curves based on four to six 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 and the 5-HTP levels was obtained (Table 1). The maximal effect, expressed as percent of controls, was normally as follows: for DOPA, limbic system = −65%, striatum = −80%, hemispheres = −50% and, for 5-HTP, limbic system, striatum, and hemispheres = −50%. Control values were as follows: for 5-HTP (ng/g, mean ± SEM, $n = 10$), limbic system = 192 ± 18, striatum = 129 ± 14, and hemispheres = 131 ± 14 and, for DOPA (ng/g, mean ± SEM, $n = 10$), limbic system = 808 ± 56, striatum = 3653 ± 222, and hemispheres = 156 ± 11.

The dose–response curves were obtained by nonlinear curve-fitting to a sigmoidal function based on chemical equilibrium, but with variable slope. The software used was Kaleidagraph,[43] where the methods are predominantly based on the recipes described by Press et al.[44] As the coefficient of variation rather than the standard deviation is constant in this type of measurements, the fit was performed using the logarithms of the measured values. All parameters were also determined as logarithmic values to make the parameter error estimates represent factors rather than differences. The curve equation was

$$y = \log\left(10^{k_1} + \frac{10^{k_2} - 10^{k_1}}{1 + 10^{(k_4 - x)10k_3}}\right)$$

were k_1 = log(control level), k_2 = log(full effect level), k_3 = log slope, k_4 = log ED_{50} and x and y are the dose and response, respectively, expressed in log units. Under ideal circumstances, all the parameters (k_1–k_4) were obtained with confidence limits of 95%. In some cases, however, the dose–response curve was not fully covered. In these cases one or two of the parameters (k_2 and/or k_3) were set to fixed values (on the basis of experiences from earlier experiments, see above). In Table 1 only the ED_{50} values are mentioned.

Motor Activity. The motor activity was measured by means of photocell recordings (M/P 40 Fc electronic motility meter, Motron Products, Stockholm, Sweden) as previously described.[25] 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/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 2). 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 brain stem 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 of 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 20000g 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 219–221 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 (Brandels 48 sample harvester). The tubes were rinsed with 4 mL, and the filters (Whatman GF/B) 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 31%) 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} values (the concentation of drug required to displace 50% of the labeled ligand) were calculated by a semilog plot and linear regression analysis. The inhibition constants (K_i) of the various compounds were calculated using the formula of Cheng and Prusoff:[45] $K_i = IC_{50}/(1+[L/K_d])$, 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 24 Ci/mmol) binding was carried out as described by Hyttel and Arnt.[26] 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 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 by gas chromatography (Hewlett Packard)/mass spectrometry (VG Trio II). Male Sprague-Dawley rats treated orally with drug were starved for 18 h before the experiment. The blood samples (100–250 μL) were collected at various time intervals up to 12 h after drug injection.

Plasma Levels of Compounds *R*-(+)-6 and 8. The weighed samples were diluted with 1 mL of water. Then 25 ng of the internal standard 8-methoxy-2-[(dicyclopropylmethyl)amino]-1,2,3,4-tetra-hydronaphthalene[46] was added. The pH was adjusted to 11.0 by addition of saturated sodium carbonate (50 μL). 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 standard to blank blood samples. Gas chromatography was performed on a cross-linked PS 264 capillary column (15 m × 0.25 mm) and 2 μL of 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 availability 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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References

(1) Asselin, A. A.; Humber, L. G.; Voith, K.; Metcalf, G. Drug Design via Pharmacophore Identification. Dopaminergic Activity of 3H-Benz[*e*]indol-8-amine and Their Mode of Interaction with the Dopamine Receptor. *J. Med. Chem.* **1986**, *29*, 648–654.

(2) Asselin, A. A.; Humber, L. G.; Crosilla, D.; Oshiro, G.; Wojdan, A.; Grimes, D.; Heaslip, R. J.; Rimele, T. J.; Shaw, C.-C. Indole-Phenol Bioisosterism. Synthesis and Antihypertensive Activity of a Pyrrolo Analogue of Labetalol. *J. Med. Chem.* **1986**, *29*, 1009–1015.

(3) Dionne, G.; Humber, L. G.; Asselin, A. A.; McQuillan, J.; Treasurywala, A. M. Ligand-Receptor Interactions vio Hydrogen-Bond Formation. Synthesis and Pharmacological Evaluation of Pyrrolo and Pyrido Analogues of the Cardiotonic Agent 7-Hydroxycyclindole. *J. Med. Chem.* **1986**, *29*, 1452–1457.

(4) Soll, R. M.; Humber, L. G.; Deininger, D.; Asselin, A. A.; Chau, T. T.; Weichman, B. M. Synthesis and Analgesic Evaluation of 4-(2-Heptyloxy)-7-[(Z)-(3-hydroxycyclohexyl]indole: A Caveat on Indole-Phenol Bioisosterism. *J. Med. Chem.* **1986**, *29*, 1457–1460.

(5) Nichols, D. E.; Cassady, J. M.; Persons, P. E.; Yeung, M. C.; Clemens, J. A.; Smalstig, E. B. Synthesis and Evaluation of N,N-Di-n-propyltetrahydronenz[*f*]indol-7-amine and Related Congeners as Dopamine Agonists. *J. Med. Chem.* **1989**, *32*, 2128–2134.

(6) Stjernlöf, P.; Gullme, M.; Elebring, T.; Andersson, B.; Wikström, H.; Lagerquist, S.; Ekman, A.; Carlsson, A.; Sundell, S. *S*-and-*R* -Di-n-propyl amino-6,7,8,9-tetrahydro-3*H*-benzo[*e*]indole-1-carbaldehyde: A New Class of Orally active 5-HT_{1A}-Receptor Agonists. *J. Med. Chem.* **1993**, *36*, 2059–2065.

(7) Wikström, 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-3H-benz[e]indol-8-amine: Central Dopamine and Serotonin Receptor Properties. *J. Med. Chem.* **1989**, *32*, 2273–2276.

(8) Arvidsson, L.-E.; Hacksell, U.; Nilsson, J. L. G.; Hjorth, S.; Carlsson, A.; Lindberg, P.; Sanchez, D.; Wikström, H. 8-Hydroxy-2-(di-n-propylamino)tetralin, a New Centrally acting 5-Hydroxytryptamine Receptor Agonist. *J. Med. Chem.* **1981**, *24*, 921–923.

(9) Arvidsson, L.-E.; Hacksell, U.; Johansson, A. M.; Nilsson, J. L. G.; Lindberg, P.; Sanchez, D.; Wikström, H.; Svensson, K.; Hjorth, S.; Carlsson, A. 8-Hydroxy-2-(alkylamino)tetralins and Related Compounds as Central 5-Hydroxytryptamine Receptor Agonists. *J Med. Chem.* **1984**, *27*, 45–51.

(10) Arvidsson, L.-E. Brain 5-HT_{1A} Receptors; Ellis Horwood Ltd.: Chichester, England, 1987; pp 19–26.

(11) Feenstra, M.; Rollema, H.; Dijkstra, D.; Grol, C. J.; Horn, A. S.; Westerink, B. H. C. Effect of Non-Catecholic 2-Aminotetralin Derivatives on Dopamine Metabolism in the Rat Striatum. *Naunyn-Schmied. Arch. Pharmacol.* **1980**, *313*, 213–219.

(12) Gozlan, H.; El Mestkawy, S.; Pichat, L.; Glowinski, J.; Hamon, M. Identification of presynaptic serotonin autoreceptors using a new ligand: ^{3}H-PAT. *Nature* **1983**, *305*, 140–142.

(13) Hjorth, S.; Carlsson, A.; Lindberg, P.; Sanchez, D.; Wikström, H.; Arvidsson, L.-E.; Hacksell, U.; Nilsson, J. L. G. 8-Hydroxy-2-di-n-propylaminotetralin, 8-OH-DPAT: A Potent and Selective Simplified Ergot Congener with Central 5-HT Receptor Stimulating Activity. *J. Neural Transm.* **1982**, *55*, 169–188.

(14) Hjorth, S.; Carlsson, A.; Magnusson, T.; Arvidsson, L.-E. In vivo biochemical characterization of 8-OH-DPAT. Evidence for 5-HT receptor selectivity and agonist action in the rat CNS. *Brain 5-HT_{1A} Receptors*; Ellis Horwood Ltd.: Chichester, England, 1987; pp 94–105.

(15) Middlemiss, D. N.; Foxard, J. R. 8-Hydroxy-2-(Di-n-Propylamino)-tetralin discriminates between subtypes of the 5-HT_1 recognition site. *Eur. J. Pharmacol.* **1983**, *90*, 151–153.

(16) The high electron density of the indole C3-position is well-established, as well as the possibility for hydrogen bonding to π-systems [see for instance (a) Remers, W. A.; Brown, R. K. In *The Chemistry of Heterocyclic Compounds. Indoles*; Houlihan, W. J., Ed.; Wiley-Interscience, Inc.: New York, 1972, Part 1. (b) Legon, A. C.; Millen, D. J. Angular Geometries and Other Properties of Hydrogen-Bonded Dimers: A Simple Electrostatic Interpretation of the Success of the Electron-Pair Model. *Chem. Soc. Rev.* **1987**, 467–498. (c) Pimentel, G. C.; McClellan, A. L. In *The Hydrogen Bond*; W. H. Freeman and Co.: San Fransisco, 1960, and references cited therein]. Semiempirical calculations (AM1, Hyperchem. Unpublished results from Dr. Lars O. Hansson, this laboratory) show that the preferred site of protonation (gaseous phase) in indole is the C3-position with a proton affinity in the same range as for N-protonation of pyridine [(d) Dewar, M. J. S; Dieter, K. M. Evaluation of AM1 Calculated Proton Affinities and Deprotonation Enthalpies. *J. Am. Chem. Soc.* **1986**, *108*, 8075–8086]. The ability for hydrogen bond acceptance has been shown to approximately follow the basicity (proton affinity) [(e) March, J. *Advanced Organic Chemistry*, 3rd ed.; John Wiley and Sons: New York, 1985, and references cited therein].

(17) Romero, A. G.; Leiby, J. A.; McCall, R. B.; Piercey, M. F.; Smith, M. W.; Han, F. Novel 2-Substituted Tetrahydro-3*H*-benzo[*e*]-indole Amines: Highly Potent and Selective Agonists Acting at the 5-HT_{1A} Receptor as Possible Anxiolytics and Antidepressants. *J. Med. Chem.* **1993**, *36*, 2066–2074.

(18) Stjernlöf, P.; Elebring, T.; Andersson, B.; Svensson, A.; Ekman, A.; Svensson, K.; Carlsson, A.; Wikström, H. 5-, 6-, 7-, and 8-Amino-2-(N,N-di-n-propylamino)-1,2,3,4-tetrahydronaphtalenes: Centrally acting DA and 5-HT_{1A} agonists. *Eur. J. Med. Chem.* **1993**, *28*, 693–701.

(19) James, P. D.; Snyder, H. R. Indole-3-aldehyde *Organic Synthesis, Collect. Vol. IV*, Wiley: New York, pp 539–432.

(20) Mehta, G.; Dhar, D. N.; Suri, S. C. Reaction of Indoles with Chlorosulphonyl Isocyanate; A Versatile Route to 3-Substituted Indoles. *Synthesis* **1978**, 374–376.

(21) Comins, D. L.; Killpack, M. O. N-Methyl lithiation of N-methylindoles directed by α-aminoalkoxides. *Tetrahedron Lett.* **1989**, *30*, 4337–4340.

(22) Andén, N.-E.; Carlsson, A.; Häggendal, J. Adrenergic Mechanisms. *Annu. Rev. Pharmacol.* **1961**, *9*, 119–134.

(23) Aghajanian, G. K.; Bunney, B. S.; Kuhar, M. J. *Proceedings of the Symposium on Drug Abuse, Metabolism, and Regulatory Neurotransmitters*; Plenum Press: New York, 1972; pp 115–134.

(24) Neckers, L. M.; Neff, N. H.; Wyatt, R. J. Increased serotonin turnover in corpus striatum following an injection of kainic acid: Evidence for neuronal feedback regulation of synthesis. *Naunyn Schmiedberg's Arch. Pharmacol.* **1979**, *306*, 173–177.

(25) Hacksell, U.; Svensson, U.; Nilsson, J. L. G.; Hjorth, S.; Carlsson, A.; Wikström, H.; Lindberg, P.; Sanchez, D. N-Alkylated 2-aminotetralins: Central Dopamine-receptor stimulating activity. *J. Med. Chem.* **1979**, *22*, 1469–1475.

(26) Hyttel, J.; Arnt, J. Charcterization of binding of 3H-SCH 23390 to dopamine D1 receptors. Correlation to other D-1 and D-2 measures and effect of selective leasions. *J. Neural Transm.* **1987**, *68*, 171–189.

(27) Compound R-(+)-**6** was generously supplied by Dr. Arthur G. Romero, Medicinal Chemistry Research, Upjohn Laboratories, The Upjohn Company, Kalamazoo, MI 49001. See also ref 17.

(28) MM2 calculations were made using MM2-91 supported by MacMimic (InStar Software, Ideon Research Park, S223 70 Lund, Sweden). A similar result was obtained when the structure was minimized in Sybyl with the Tripos force field.

(29) Wikström, H. Ortho-Fluorinated 5- and 8-Hydroxy-2-(di-n-propylamino)tetralin: Central Dopamine and Serotonin Receptor Stimulating Properties. *Neurology Neurobiology, 42A (Progress in Catecholamine Resesrch, Part. A: Basic Aspects and Mechanisms)*; Alan R. Liss, Inc: New York, 1988; 409–414.

(30) Information concerning intramolecular hydrogen bonds between halogen and a phenolic OH has been summarized: Joesten, M. D.; Schaad, L. J. *Hydrogen Bonding*; Marcel Dekker, Inc.: New York, 1974; Chapter 5.

(31) Ho, B. H.; Karschin, A.; Branchek, t.; Davidsson, N.; Lester, H. A. The role of conserved aspartate and serine residues in ligand binding and in function of the 5-HT_{1A} receptor: A site directed mutation study. *FEBS Lett.* **1992**, *312*, 259–262.

(32) Mellin, C.; Vallgårda, J.; Nelson, D. L.; Björk, L.; Yu, H.; Andén, N.-E.; Csöregh, I.; Arvidsson, L.-E.; Hacksell, U. A 3-D-Model for 5-HT1A-Receptor Agonists Based on Stereoselective Methyl-Substituted and Conformationally Restricted Analogues of 8-Hydroxy-2-(dipropylamino)tetralin. *J. Med. Chem.* **1991**, *34*, 497–510.

(33) Westkaemper, R. B.; Glennon, R. A. Approaches to Molecular Modeling Studies and Specific Application to Serotonin Ligands and Receptors. *Pharmacol. Biochem. Behav.* **1991**, *40*, 1019–1031.

(34) Chidester, C. G.; Lin, C.-H.; Lahti, R. A.; Haadsma-Svensson, S. R.; Smith, M. W. Comparision of 5-HT_{1A} and Dopamine D_2 Pharmacophores. X-Ray Structures and Affinities of Conformationally Constrained Ligands. *J. Med. Chem.* **1993**, *36*, 1301–1315.

(35) Hartig, P. R. Molecular biology of 5-HT receptors. *Trends Pharmacol. Sci.* **1989**, *10*, 64–69.

(36) Shih, J. C.; Yang, W.; Chen, K.; Gallaher, T. Molecular Biology of Serotonin (5-HT) Receptors. *Pharmacol. Biochem. Behav.* **1991**, *40*, 1053–1058.
(37) Trumpp-Kallmeyer, S.; Hoflack, J.; Bruinvels, A.; Hibert, M. Modeling of G-Protein-Coupled Receptors: Application to Dopamine, Adrenaline, Serotonin, Acetylcholine and Mammalian Opsin Receptors. *J. Med. Chem.* **1992**, *35*, 3448–3462.
(38) Hyperchem release 3 for windows, 1993, Hypercube Inc. and Autodesk Inc.
(39) Burkert, U.; Allinger, N. L. *Molecular Mechanics*; *ACS Monograph 177*; American Chemical Society: Washington, DC, 1982.
(40) Dewar, M. J. S.; Zoebish, E. G.; Healy, E. F.; Stewart, J. J. P. AM1: A New General Purpose Quantum Mechanical Molecular Model. *J. Am. Chem. Soc.* **1985**, *107*, 3902–3909.
(41) Shum, A.; Sole, M. J.; van Loon, G. R. Simultaneous measurement of 5-hydroxytryptophan and L-dihydroxyphenylalanine by high performance liquid chromatography with electrochemical detection. Measurement of serotonin and catecholamine turnover in discrete brain regions. *J. Chromatogr.* **1982**, *228*, 123–130.
(42) Svensson, K. *Dopamine autoreceptor antagonists. A new class of central stimulants*; University of Göteborg: Sweden, 1986 (ISBN 91-7900-078-9).
(43) Calculated by Kaleidagraph Version 3.0.1 available from Synergy Software (PCS Inc.), 2457 Perkionen Avenue, Reading, PA 19606.
(44) Press, W. H.; Teukolsky, S. A.; Vetterling, W. T.; Flamery, B. P. *Numerical Recipes in C*; Cambridge University Press: Cambridge, 1992.
(45) Cheng, Y. C.; Prusoff, W. H. Relation Between the Inhibition Constant *Ki* and the Concentration of Inhibitor which causes Fifty per Cent Inhibition (IC50) of an Enzymatic Reaction. *Biochem. Pharmacol.* **1973**, *22*, 3099–3108.
(46) Andersson, B. R.; Carlsson, P. E. A.; Svensson, K. A. I.; Wikström, H. V. Preparation of 8-methoxy-2-aminotetralins as therapeutics for the central nervous system disorders. *Eur. Pat.Appl.* 1989, *EP334538*,
(47) The transmembranal region 5 of the 5-HT1A receptor was minimized to an α-helical structure in MM+ (Hyperchem; see ref 38) using the amino acid sequence reported in ref 37. The cross-segment containing Ser198 and Thr199 was examined and it was found that the distances between the two OH groups closely fitted the distance between the cyano groups in compounds **6** and **8** when they were overlapped as shown by Figure 3A.