Derivatives of 2-(Dipropylamino)tetralin: Effect of the C8-Substituent on the Interaction with 5-HT_{1A} Receptors

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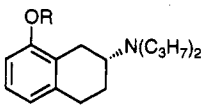
A series of 2-(dipropylamino)tetralin derivatives in which the C8 substituent is varied has been prepared and evaluated pharmacologically to explore the importance of the C8 substituent in the interaction of 2-aminotetralin-based ligands with serotonin (5-HT_{1A}) receptors. Enantiopure derivatives were prepared by facile palladium-catalyzed reactions of the triflates of the enantiomers of 8-hydroxy-2-(dipropylamino)tetralin (8-OH-DPAT, 1). The affinity of the compounds for the 5-HT_{1A} receptors was evaluated by competition experiments with [^{3}H]-8-OH-DPAT in rat hippocampal and cortical tissue. In addition, the compounds were evaluated for central 5-HT and dopamine receptor stimulating activity in vivo by use of biochemical and behavioral assays in rats. With the exception of the carboxy-substituted derivative which is devoid of 5-HT_{1A} receptor affinity, the compounds have moderate to high affinities (K_i values range from 0.7 to 130 nM) for 5-HT_{1A} receptors. Surprisingly, several of the derivatives do not produce any apparent effects in vivo although they have fairly high 5-HT_{1A} receptor affinities. However, the methoxycarbonyl- and acetyl-substituted derivatives are potent 5-HT_{1A} receptor agonists in vivo and exhibit in vitro affinities in the same range as the enantiomers of 1.

Introduction

8-Hydroxy-2-(dipropylamino)tetralin (8-OH-DPAT, 1) is a potent, efficacious, and centrally active 5-hydroxytryptamine (serotonin, 5-HT) receptor agonist with selectivity for 5-HT_{1A} receptors.[1,2] Since 1981, when its pharmacological profile was first reported, 1 has been frequently used as a pharmacological tool in the elucidation of serotonergic mechanisms and as a lead compound in studies on structure–activity relationships.[3,4] Reports on the potential clinical usefulness of (partial) 5-HT_{1A} receptor agonists in the treatment of anxiety and depression[5] have added further interest to medicinal chemistry based research on 1 and related compounds.



(*R*)-1: R = H
(*R*)-2: R = CH_3

A variety of structural modifications of 1 have been studied.[6] However, few studies on modifications of the C8 substituent of 1 have appeared in the literature.[7] We recently communicated that some C8-substituted 2-(dipropylamino)tetralin derivatives have high affinity for the 5-HT_{1A} receptor.[8] In the present report, which provides a full and extended account of that study, we describe several analogues of 1 with C8 substituents different from hydroxy which bind at least as potently as 1 to 5-HT_{1A} receptors.

The new analogues were synthesized by palladium-catalyzed methods using the triflates of (±)-, (*R*)-, or (*S*)-1 as key intermediates. The compounds were investigated pharmacologically in vitro using receptor binding techniques and in vivo by use of biochemical and behavioral tests in rats.

Chemistry

The syntheses of the derivatives of 1 are outlined in Scheme I, and physical data are presented in Table I. The synthetic strategy focused on the accessibility of the enantiopure antipodes of 1:[9] 50–100-g batches were prepared of the racemate and the enantiomers of 1 which were subsequently converted into the corresponding triflates [(±)-, (*R*)-, and (*S*)-3] by treatment with base and triflic anhydride.[10] The availability of enantiopure triflates of known stereochemistry was rewarding since the stereochemistry of the products from the palladium-catalyzed reactions follows directly from that of the starting materials. In addition, the palladium-catalyzed reaction should not cause racemization under the conditions used (unpublished observations). Therefore, the enantiopurities of the derivatives synthesized herein should be as high as those of (*S*)- and (*R*)-1, i.e., exceeding 99% ee.[9]

The enantiomers of deoxy derivative 4 were prepared from (*R*)- and (*S*)-3 by a Pd(II)-catalyzed reduction using formic acid as proton donor.[11] Methyl and phenyl substituents were introduced, producing 5 and 6, by coupling reactions with tetramethyltin and tributylphenyltin, respectively.[12] A Heck-type coupling[13] between 3 and (trimethylsilyl)acetylene followed by desilylation gave the ethynyl-substituted derivative 7. Methyl, butyl, and phenyl ketones 8-10 were produced from 3 and tetramethyltin, tetrabutyltin, or trimethylphenyltin by palladium-catalyzed carbonylations.[14] Alternatively, methyl ketone 8 was prepared by treatment of carboxylic acid 13 with methyllithium[15] or by palladium-catalyzed addition of 3 to butyl vinyl ether followed by hydrolysis.[16] Palladium-catalyzed carbonylation[17] of 3 in the presence of carbon monoxide and methanol produced methyl ester 11

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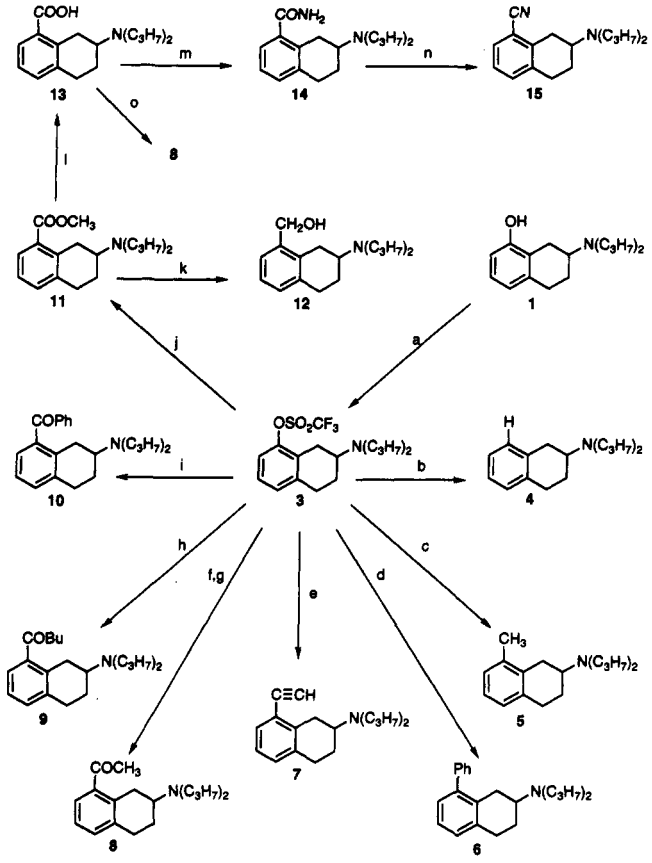
Scheme I



[a] Reagents: (a) Triflic anhydride, K_2CO_3, CH_2Cl_2; (b) $Pd(OAc)_2$, dppf, NEt_3, HCOOH, DMF; (c) $PdCl_2(Ph_3P)_2$, LiCl, Me_4Sn, 1,4-dioxane, DMF; (d) $Pd(Ph_3)_4$, $PhSnBu_3$, LiCl, 1,4-dioxane, DMF; (e) (i) $PdCl_2(Ph_3P)_2$, LiCl, (trimethylsilyl)acetylene, NEt_3, DMF, (ii) TBAF, THF; (f) $PdCl_2$(dppf), LiCl, Me_4Sn, CO, DMF; (g) (i) $Pd(OAc)_2$, dppp, butyl vinyl ether, NEt_3, DMF, (ii) 10% HCl; (h) $PdCl_2$(dppf), LiCl, Bu_4Sn, CO, DMF; (i) $PdCl_2$(dppf), LiCl, $PhSnMe_3$, CO, DMF; (j) $Pd(OAc)_2$, dppf, NEt_3, MeOH, DMSO, CO; (k) $LiAlH_4$, THF; (l) NaOH, H_2O, MeOH; (m) (i) $SOCl_2$, (ii) NH_4OH; (n) $POCl_3$, DMF; (o) (i) MeLi, ether, (ii) H_2O.

which was reduced with lithium aluminum hydride to produce the hydroxymethyl-substituted **12**. Compound **11** was hydrolyzed to the carboxylic acid **13** which was further transformed into the amide (**14**) and cyano (**15**) derivatives by standard reactions[18] (Scheme I).

Pharmacology

Stimulation of somatodendritic 5-HT_{1A} receptors on central 5-HT neurons with agonists such as **1** decreases the synthesis and release of 5-HT.[19] In the present study we have mainly used the ratio of the brain tissue concentrations of 5-hydroxyindoleacetic acid (5-HIAA) over 5-HT as a measurement of 5-HT turnover. Administration of a 5-HT_{1A} receptor agonist decreases this ratio because of the resulting decrease in 5-HT synthesis and release (Table II). The effects on dopamine (DA) turnover (the ratio of 3,4-dihydroxyphenylacetic acid, DOPAC, over DA) and on the accumulation of 5-hydroxytryptophan (5-HTP) and 3,4-dihydroxyphenylalanine (DOPA) following decarboxylase inhibition (NSD 1015) were also measured.

It is well-known that administration of (±)-**1** induces a complex behavioral syndrome in rats.[3b,20] It has also been established that 5-HT_{1A} receptor agonists decrease the body temperature in rats and reduce the number of animals leaving their cages after the cage lids have been removed (cage-leaving response).[21] Consequently, we studied the ability of the compounds to produce the behavioral syndrome, to induce hypothermia, and to inhibit the cage-leaving response. A protocol was followed (Table II) in which ex vivo biochemical and behavioral data were collected from each animal. In addition, we determined the affinity of the compounds for 5-HT_{1A} receptor binding sites using [^{3}H]-8-OH-DPAT as a ligand. The combination of in vivo and in vitro data allowed for a preliminary evaluation of the pharmacological profile of the compounds. Derivatives which exhibited affinity for 5-HT_{1A} receptors but did not produce effects in the initial in vivo assays were considered as putative antagonists. Consequently, their abilities to counteract selected effects of the full agonist (*R*)-**1** in vivo were evaluated.

Behavior. The enantiomers of **1** induce a clear-cut 5-HT motor syndrome (flat body posture, forepaw treading, hindlimb abduction) in both normal and reserpine-pretreated rats (Table II). (*R*)-**1** was more potent than (*S*)-**1**, but the intensity of the 5-HT syndrome was similar at high doses (1–10 μmol/kg, sc) of both compounds (data not shown). Subcutaneous administration of 32 μmol/kg of (*R*)-**2**,[3a,6b] (*S*)-**2**,[3a,6b] (±)-**4**, (*R*)-**4**, (*S*)-**7**, and (*R*)-**12**, of 10 μmol/kg of (*R*)-**11** and (*S*)-**11**, and of 1 μmol/kg of (*R*)-**8** and (*S*)-**8** produced flat body posture and forepaw treading in the rats. All of these compounds also elicited the syndrome in reserpine-pretreated rats except (*R*)-**2** and (*S*)-**2**, which were not tested in this model. Administration of (*S*)-**4**, (*R*)-**5**, (*S*)-**5**, and (*S*)-**12** produced only flat body posture in normal rats, but this behavior was counteracted by reserpine pretreatment. In contrast, the flat body posture induced by (*R*)-**7** and (*R*)-**10** was reserpine insensitive. Forepaw treading after (*R*)-**7** and (*R*)-**10** administration increased after reserpine pretreatment (Table II).

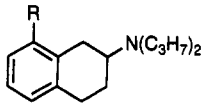
Compounds (±)-**8**, (±)-**9**, (±)-**11**, (±)-**12**, (±)-**14**, (±)-**15**, and (*S*)-**15** were only tested in reserpine-treated rats and produced the full 5-HT motor syndrome. The limited amount available of (*R*)-**15** and (±)-**7** allowed testing only at a dose of 10 μmol/kg. Compound (*R*)-**15** induced flat body posture but not the other components of the 5-HT syndrome, whereas (±)-**7** induced flat body posture in only one out of four rats.

No behavioral changes were observed after (±)-**3**, (*R*)-**3**, (*S*)-**3**, (±)-**6**, (*R*)-**6**, (*S*)-**6**, and (*S*)-**10** at a dose of 32 μmol/kg, indicating that they might be antagonists. However, when given 10 mm before (*R*)-**1**, neither (*R*)-**3**, (*S*)-**3**, (*R*)-**6**, (*S*)-**6**, nor (*S*)-**10** antagonized the behavioral syndrome induced by (*R*)-**1** (1.0 μmol/kg, sc). (*S*)-**4**, (*R*)-**5**, (*S*)-**5**, and (*S*)-**7** induced gnawing, biting, and chewing at the dose tested (data not shown), which indicated the presence of dopaminergic components in their behavioral profiles.

Cage-Leaving Response and Body Temperature. In agreement with previous observations, administration of low doses of (*R*)- or (*S*)-**1** prevented the rats from leaving their cages. In contrast, 75% of control rats treated with saline left their cages within 12 min (12–24 min after injection). Administration of (*R*)-**1**, (*S*)-**1**, (*R*)-**2**, (*S*)-**2**, (*S*)-**3**, (±)-**4**, (*R*)-**4**, (*S*)-**4**, (*R*)-**5**, (*S*)-**5**, (*R*)-**7**, (*S*)-**7**, (*R*)-**8**, (*S*)-**8**, (*R*)-**10**, (*R*)-**11**, (*S*)-**11**, (*R*)-**12**, and (*S*)-**12** inhibited the cage-leaving response whereas it was not changed after (*R*)-**3**, (*R*)-**6**, and (*S*)-**6**. Administration of (*S*)-**10** inhibited the cage-leaving response in two out of four rats (Table II).

Administration of (*R*)-**1** decreases body temperature in rats by about 2.6 °C after 30 min. In saline-treated animals,

Table I. Physical Data of Some Novel 2-Aminotetralin Derivatives



compd	R	prepn method[a]	mp, °C	yield, %	recrystn solvents[b]	formula	$[\alpha]^{D}_{22}$,[c] deg
(±)-3	OSO_2CF_3	I	128–130	91	A	$C_{17}H_{24}NF_3O_3S\cdot HCl$	
(*R*)-3	OSO_2CF_3	I	113–115	98	A	$C_{17}H_{24}NF_3O_3S\cdot HCl$	+59.6
(*S*)-3	OSO_2CF_3	I	114–116	94	A	$C_{17}H_{24}NF_3O_3S\cdot HCl$	−58.9
(±)-4	H	II	149–151[d]	87	D		
(*R*)-4	H	II	127–128	41	D	$C_{16}H_{25}N\cdot HCl$	+71.7
(*S*)-4	H	II	129–130	77	C	$C_{16}H_{25}N\cdot HCl$	−71.5
(±)-5	CH_3	III	153–154	41	B	$C_{17}H_{27}N\cdot HCl$	
(*R*)-5	CH_3	III	129–131	57	B	$C_{17}H_{27}N\cdot HCl$	+72.5
(*S*)-5	CH_3	III	129–131	56	B	$C_{17}H_{27}N\cdot HCl$	−68.9
(±)-6	C_6H_5	IV	162–163	89	A	$C_{22}H_{29}N\cdot C_2H_2O_4\cdot H_2O$	
(*R*)-6	C_6H_5	IV	115–116	83	F	$C_{22}H_{29}N\cdot C_2H_2O_4$	+24.1
(*S*)-6	C_6H_5	IV	115–117	88	F	$C_{22}H_{29}N\cdot C_2H_2O_4$	−25.2
(±)-7	C≡CH	V	186–189	49	B	$C_{18}H_{25}N\cdot HCl$	
(*R*)-7	C≡CH	V	211–213	31	C	$C_{18}H_{25}N\cdot HCl$	+69.4
(*S*)-7	C≡CH	V	213–216	33	C	$C_{18}H_{25}N\cdot HCl$	−69.8
(±)-8	$COCH_3$	VI (VII)	125–127	70 (56)	D	$C_{18}H_{27}NO\cdot HCl$	
(*R*)-8	$COCH_3$	VI	115–116	52	A	$C_{18}H_{27}NO\cdot HCl$	+122.7
(*S*)-8	$COCH_3$	VI (VIII)	114–116	44 (60)	A	$C_{18}H_{27}NO\cdot HCl$	−123.2
(±)-9	COC_4H_9	VI	106–108	71	A	$C_{21}H_{33}NO\cdot C_2H_2O_4$	
(±)-10	COC_6H_5	VI	147.5–150	52	A	$C_{23}H_{29}NO\cdot HCl$	
(*R*)-10	COC_6H_5	VI	65–67	65	C	$C_{23}H_{29}NO\cdot HCl\cdot{}^1/_2H_2O$	+95.6
(*S*)-10	COC_6H_5	VI	64–66	71	C	$C_{23}H_{29}NO\cdot HCl\cdot{}^1/_2H_2O$	−92.7
(±)-11	$COOCH_3$	IX	136–137	91	A	$C_{18}H_{27}NO_2\cdot HCl$	
(*R*)-11	$COOCH_3$	IX	148.5–150	71	A	$C_{18}H_{27}NO_2\cdot HCl$	+115.4
(*S*)-11	$COOCH_3$	IX	149–150	59	A	$C_{18}H_{27}NO_2\cdot HCl$	−115.1
(±)-12	CH_2OH	X	142–144	80	B	$C_{17}H_{27}NO\cdot HCl$	
(*R*)-12	CH_2OH	X	186–187.5	77	B	$C_{17}H_{27}NO\cdot HCl$	+65.3
(*S*)-12	CH_2OH	X	186–187	83	B	$C_{17}H_{27}NO\cdot HCl$	−64.8
(±)-13	COOH	*a*	245–247	97	B	$C_{17}H_{25}NO_2\cdot HCl$	
(±)-14	$CONH_2$	*a*	*e*	48[f]	C	$C_{17}H_{26}N_2O\cdot C_2H_2O_4$	
(±)-15	CN	*a*	176–178	71	B	$C_{17}H_{24}N_2\cdot HCl$	
(*R*)-15	CN	*g*	173–175	52[f]	A	$C_{17}H_{24}N_2\cdot HCl$	+82.3
(*S*)-15	CN	*g*	176–178	46[f]	A	$C_{17}H_{24}N_2\cdot HCl$	−82.0

[a] See the Experimental Section. [b] A: Chloroform/ether. B: Methanol/ether. C: Ether. D: Acetonitrile/ether. F: Acetone/ether. [c] MeOH, c = 1.0. [d] Previously reported, ref 31. [e] Hygroscopic. [f] The yield is calculated from 11. [g] Prepared directly from the corresponding enantiomer of 11 without isolation of intermediates.

the body temperature was increased by 0.5 °C after 30 min. Compounds (*R*)-1, (*S*)-1, (*R*)-2, (*R*)-2, (±)-4, (*R*)-4, (*S*)-4, (*R*)-5, (*S*)-5, (*R*)-6, (*R*)-7, (*S*)-7, (*R*)-8, (*S*)-8, (*R*)-10, (*R*)-11, (*S*)-11, and (*S*)-12 induced hypothermia at the doses administered (Table II). The hypothermia induced by the *R*-enantiomers of 1 and 8 was more pronounced than after the respective enantiomers. However, (*S*)-7 was more potent than the antipode. Compounds (*R*)-3, (*S*)-3, (*S*)-6, (*S*)-10, and (*R*)-12 did not affect the body temperature of the rats at 32 μmol/kg sc, but a lower dose of (*R*)-12 (3.2 μmol/kg sc) reduced the body temperature.

5-HT and DA Turnover. The 5-HT turnover in hippocampus was significantly lowered after (*R*)-1, (*S*)-1, (*R*)-2, (*S*)-2, (±)-4, (*R*)-4, (*R*)-5, (*R*)-7, (*S*)-7, (*R*)-8, (*S*)-8, (*R*)-10, (*R*)-11, (*S*)-11, (*R*)-12, and (*S*)-12 (Table II). (*S*)-3 and (*S*)-5 induced a nonsignificant decrease in 5-HT turnover whereas (*R*)-3, (*S*)-4, (*R*)-6, (*S*)-6, and (*S*)-10 did not change the 5-HT turnover. The DA turnover in corpus striatum was significantly lowered after administration of (*R*)-2, (±)-4, and (*S*)-4.

5-HTP and DOPA Accumulation. (*R*)-1 and (*S*)-1 decreased the accumulation of 5-HTP without affecting the DOPA accumulation at the doses tested (Table III). The enantiomers of 5, 7, and 12 and (*R*)-10 (32 μmol/kg) behaved as 5-HT_{1A} receptor agonists by inducing significant decreases in the 5-HTP accumulation. In contrast to the other derivatives tested in this assay, the acetylenic derivative (*R*)-7 produced a reduction in striatal DOPA accumulation, indicating a dopaminergic activity component. The racemic methyl ester derivative 11 (3.2 μmol/kg) behaved as a 5-HT_{1A} receptor agonist by producing a reduction in the 5-HTP accumulation without affecting the DOPA accumulation.

Antagonism of (*R*)-1-Induced Effects. The established 5-HT_{1A} receptor antagonist (*S*)-5-fluoro-8-hydroxy-2-(dipropylamino)tetralin [(*S*)-UH-301; 32 μmol/kg sc] is able to antagonize (*R*)-1-induced effects such as the 5-HT syndrome and the decrease in body temperature.[22] However, none of the new compounds tested ((*R*)-3, (*S*)-3, (*R*)-6, (*S*)-6, and (*R*)-10) were able to antagonize the (*R*)-1-induced effects at 32 μmol/kg sc (Table IV).

Affinity for 5-HT_{1A} Receptors in Vitro. The compounds were evaluated for their affinities for rat hippocampal and cortical 5-HT_{1A} receptors. It is noteworthy that, with the exception of carboxylic acid derivative (±)-13 (K_i > 300 nM), all C8 substitutions produced derivatives with appreciable affinity for 5-HT_{1A} receptors (K_i values range from 0.7 to 130 nM; Table II).

Discussion

On the basis of the screening data, it can be concluded that a number of the novel derivatives appear to be 5-HT_{1A} receptor agonists, with no apparent dopaminergic activity, thus, being similar in profile to the enantiomers of 1. This group of compounds produces a full-blown 5-HT syndrome in normal as well as in reserpine-treated animals, inhibits the cage-leaving response, and decreases body temperature and 5-HT turnover. This group includes the C8 unsub-

Table II. 2-(Dipropylamino)tetralins: Behavioral and Biochemical Effects and 5-HT_{1A} Receptor Affinities in Rats

compd	dose, μmol/kg	5-HT syndrome: normal[a,b]	5-HT syndrome: reserpine[b,c]	cage leaving[b]	change of body temperature[e]	5-HT turnover[f] hippocampus	DA turnover[f] striatum	5-HT_{1A} receptor binding: K_i, nM	range	n_H
control	0	0/45	0/10	35/45	0.5 ± 0.06	100	100			
(*R*)-1	1.0	42/42	15/15	0/42	−2.6 ± 0.08**	66 ± 7**	96 ± 6	1.3	1.1–1.5	0.97
(*S*)-1	10	4/4	5/5	0/4	−2.0 ± 0.16**	72 ± 5*	106 ± 12	1.8	1.6–2.0	0.89
(*R*)-2	32	4/4	NT[g]	0/4	−1.5 ± 0.11**	66 ± 6**	70 ± 3*	1.5	1.4–1.7	1.11
(*S*)-2	32	4/4	NT	0/4	−1.5 ± 0.19**	80 ± 3*	79 ± 7	2.8	2.7–3.0	0.96
(±)-3	32	NT	0/4	NT	NT	NT	NT			
(*R*)-3	32	0/4	NT	4/4	0.5 ± 0.09	106 ± 3	93 ± 2	3.8	2.8–5.7	0.79
(*S*)-3	32	0/4	NT	1/4	0.5 ± 0.03	84 ± 5	104 ± 2	9.5	7.4–13.2	0.83
(±)-4	32	4/4	4/4	0/4	−2.0 ± 0.03**	60 ± 2*	46 ± 2**	37	31–47	0.86
(*R*)-4	32	4/4	4/4	0/4	−1.4 ± 0.17**	51 ± 3**	77 ± 5	17	15–19	0.85
(*S*)-4	32	5/5[d]	0/4	1/5	−1.6 ± 0.12**	104 ± 13	62 ± 8**	56	46–71	0.83
(±)-5		NT	NT	NT	NT	NT	NT	42	39–46	0.99
(*R*)-5	32	4/4[d]	0/4	0/4	−2.1 ± 0.05**	69 ± 4*	88 ± 10	34	32–38	1.13
(*S*)-5	32	4/4[d]	0/4	0/4	−2.3 ± 0.51**	79 ± 4	80 ± 7	62	56–69	1.04
(±)-6	32	NT	0/4	NT	NT	NT	NT	12	11–13	0.95
(*R*)-6	32	0/4	0/4	3/4	−0.3 ± 0.21**	98 ± 4	85 ± 0	7.7	7.2–8.3	1.00
(*S*)-6	32	0/4	0/4	4/4	0.6 ± 0.09	98 ± 7	99 ± 0	24	22–26	1.04
(±)-7	10	NT	1/4[d]	NT	NT	NT	NT	4.0	3.6–4.6	0.95
(*R*)-7	32	4/4[d]	4/4	0/4	−1.6 ± 0.18**	73 ± 5**	78 ± 4	22	19–27	0.69
(*S*)-7	32	4/4	4/4	0/4	−2.8 ± 0.14**	66 ± 5**	82 ± 3	16	13–20	0.77
(±)-8	1.0	NT	4/4	NT	NT	NT	NT	0.9	0.7–1.1	0.88
(*R*)-8	1.0	4/4	4/4	0/4	−2.8 ± 0.11**	68 ± 1*	106 ± 14	1.8	1.6–2.0	0.96
(*S*)-8	1.0	4/4	4/4	0/4	−2.1 ± 0.14**	71 ± 9*	111 ± 10	0.7	0.6–1.0	0.92
(±)-9	32	NT	4/4	NT	NT	NT	NT	19	16–22	0.90
(±)-10		NT	NT	NT	NT	NT	NT	2.8	2.4–3.3	0.77
(*R*)-10[h]	32	4/4[d]	4/4	0/4	−3.3 ± 0.36**	74 ± 2*	122 ± 6	4.6	4.0–6.0	0.97
(*S*)-10[h]	32	0/4	NT	2/4	0.13 ± 0.1	112 ± 2	88 ± 9	16	14–20	0.67
(±)-11	3.2	NT	4/4	NT	NT	NT	NT	2.4	2.1–2.6	0.91
(*R*)-11	10	4/4	4/4	0/4	−2.3 ± 0.11**	63 ± 1*	90 ± 2	4.3	3.7–4.9	0.90
(*S*)-11	10	4/4	4/4	0/4	−2.5 ± 0.17**	59 ± 7**	98 ± 6	1.7	1.4–2.1	1.01
(±)-12	3.2	NT	3/4	NT	NT	NT	NT	25	23–30	0.90
(*R*)-12	32	4/4	4/4	0/4	0.3 ± 0.06	74 ± 1*	93 ± 3	23	20–26	0.82
	3.2	4/4	NT	0/4	−1.9 ± 0.17**	85 ± 18	88 ± 3			
(*S*)-12	32	4/4[d]	0/5	0/4	−2.2 ± 0.17**	75 ± 5*	121 ± 2	130	94–210	0.97
(±)-13		NT	NT	NT	NT	NT	NT	>300		
(±)-14	32	NT	4/4	NT	NT	NT	NT	6.0	5.7–6.3	0.89
(±)-15	32	NT	3/4	NT	NT	NT	NT	26	24–29	0.94
(*R*)-15	10	NT	3/4[d]	NT	NT	NT	NT	19	17–21	1.10
(*S*)-15	32	NT	4/4	NT	NT	NT	NT	37	31–42	0.98

[a] Not pretreated. [b] Shown are the number of the rats displaying the 5-HT syndrome or leaving the cage out of the number of rats tested. [c] Rats were pretreated with reserpine (5 mg/kg, sc) 18 h before test compound. [d] Rats only exhibited flat body posture. [e] The value (°C) is mean ± SEM (the number of the animals is the same as in cage-leaving test). [f] 5-HT turnover, 5-HIAA/5-HT; DA turnover, DOPAC/DA. [g] NT: not tested. [h] Tested as the oxalate instead of hydrochloride. The values are percent of control; means ± SEM (n = 5–7 and 4–6 in the control and experimental groups, respectively). Control levels for compounds **3**, **5**, **6**, **9** (5-HIAA/5-HT) 1.45 ± 0.1; (DOPAC/DA) 0.24 ± 0.01. Control levels for other compounds: (5-HIAA/5-HT) 1.1 ± 0.05; (DOPAC/DA) 0.14 ± 0.01. Statistics: ANOVA followed by the Tukey's studentized range test *$p < 0.05$; **$p < 0.01$ vs control.

stituted (*R*)-**4**, the hydroxymethyl-substituted (*R*)-**12** (the lack of body temperature reduction after high doses is probably due to the intense motor behavior; at lower doses, (*R*)-**12** induces hypothermia), the ethynyl-substituted (*S*)-**7**, as well as both enantiomers of the acetyl-substituted **8** and the methoxycarbonyl derivative **11**. This classification is supported by the decrease in hippocampal and striatal 5-HTP levels after administration of (*S*)-**7** and the enantiomers of **12**. In addition, we have recently studied in some detail the pharmacology of the enantiomers of **8**; both antipodes behave as 5-HT_{1A} receptor agonists, similar in potency to or slightly higher in potency than the enantiomers of **1**.[23]

The C8-methoxy-substituted **2** is the synthetic precursor of **1**.[18] Although exhibiting similar affinities for 5-HT_{1A} receptors, the enantiomers of **2** appear to be less selective than the enantiomers of **1** in that they decrease both 5-HT and DA turnover. In addition, the reduction in body temperature is smaller after the enantiomers of **2** although the doses are higher (Table II).

Due to lack of adequate quantities of substance, the butyl ketone (±)-**9**, the amide derivative (±)-**14**, and the cyano-substituted (±)-**15**, (*R*)-**15**, and (*S*)-**15** were only studied in a few assays. On the basis of their affinity for 5-HT_{1A} receptors and their ability to elicit the 5-HT syndrome in reserpine-treated animals, these compounds appear to be 5-HT_{1A} receptor agonists.

In a third group, consisting of (*R*)-**7** and (*R*)-**10**, the compounds behave as agonists in most assays, but they do not induce a full 5-HT syndrome; the animals only exhibit flat body posture at a dose of 32 μmol/kg. However, a full 5-HT syndrome was induced in reserpine-treated rats, and this may be a reflection of a low efficacy/potency of the compounds. (*R*)-**7** is apparently also lacking in selectivity since it reduces the striatal DOPA accumulation in normal animals (Table III).

The deoxy derivative (*S*)-**4**, the C8-methyl-substituted (*R*)-**5**, (*S*)-**5**, and the hydroxymethyl analogue (*S*)-**12** constitute a series of analogues which induces one component of the 5-HT syndrome, i.e. flat body posture, in normal but not in reserpine-treated animals. The affinity of these derivatives for the 5-HT_{1A} receptor is fairly low (Table II), but this does not explain why the flat body posture is absent in animals in which the 5-HT stores have been depleted. Even at higher doses (100 μmol/kg sc) of (*R*)-**5** and (*S*)-**5**, only flat body posture was produced

Table III. 2-(Dipropylamino)tetralins: Effects on 5-HTP and DOPA Accumulation in the Rat Brain[a]

compd	dose, μmol/kg	5-HTP hippocampus	5-HTP striatum	DOPA striatum
(*R*)-1	1.0	45 ± 2**	59 ● 3**	98 ± 9
	0.32	44 ± 4**	49 ● 3**	106 ± 4
(*S*)-1	0.32	NT[b]	54 ± 5**	94 ● 8
(*R*)-5	32	54 ± 4**	46 ± 2**	86 ± 4
(*S*)-5	32	64 ± 1**	52 ± 1**	119 ± 7
(*R*)-7	32	43 ± 4**	50 ± 4**	59 ± 8**
(*S*)-7	32	31 ± 1**	62 ± 6**	95 ± 4
(*R*)-10	32	56 ± 1**	56 ● 3**	69 ± 5
(*S*)-10	32	95 ● 3	102 ● 5	83 ● 4
(±)-11	3.2	NT[b]	59 ± 7**	81 ± 6
(*R*)-12	32	47 ± 2**	64 ● 5**	125 ● 12
(*S*)-12	32	58 ± 6**	66 ± 5**	101 ± 6

[a] The values are percent of control, means ● SEM (n = 15 and 5–6 in the control and tested groups, respectively). Animals were injected with test compounds sc, 60 min and NSD 1015 (287 μmol/kg) sc, 30 min before sacrifice. Control levels for (*S*)-1 (5-HTP ng/g tissue): striatum 104 ± 4.8 and (DOPA ng/g tissue) 1212 ± 39. Control levels for the other compounds (5-HTP ng/g tissue): hippocampus 139 ± 12, striatum 120 ± 12, and (DOPA ng/g tissue) 1250 ± 86. Statistics: ANOVA followed by the Tukey's studentized range test **$p < 0.01$ vs controls. [b] Not tested.

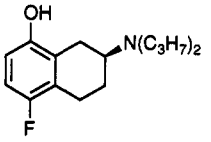
Table IV. Antagonism of (*R*)-1-Induced Effects on Behavior and Body Temperature[a]

compds	dose, μmol/kg	n	5-HT syndrome	body temperature[b]
saline + saline		7	0/7	0.20 ± 0.04
saline + (*R*)-1	1.0	8	8/8[c]	−2.61 ± 0.13[d]
(*S*)-UH-301[e] + saline	32 –	5	0/5	−0.02 ● 0.16
(*S*)-UH-301[e] + (*R*)-1	32 1.0	5	0/5	−0.76 ● 0.13[d,f]
(*R*)-3 + (*R*)-1	32 1.0	4	4/4[c]	−4.18 ± 0.11[d,f]
(*S*)-3 + (*R*)-1	32 1.0	4	4/4[c]	−3.18 ± 0.19[d]
(*R*)-6 + (*R*)-1	32 1.0	4	4/4[c]	−3.68 ± 0.22[d,f]
(*S*)-6 + (*R*)-1	32 1.0	4	4/4[c]	−2.58 ● 0.16[d]
(*S*)-10 + (*R*)-1	32 1.0	4	4/4[c]	−3.03 ± 0.08[d]

[a] Saline, test compounds and (*S*)-UH-301 were injected 10 min before (*R*)-1. Shown are number of rats displaying the behavior out of the number of rats tested, or change in body temperature compared with the preinjection value. Statistics: Fisher's exact probability test was used for the behavioral data and one-way ANOVA followed by Tukey's studentized range (HSD) test was used for body temperature values. [b] Temperature change in degrees Celcius. [c] $P < 0.005$. [d] $p < 0.01$ vs saline group. [e] See: ref 22. [f] $p < 0.01$ vs saline + (*R*)-1 group.

and no sign of forepaw treading was observed. Biting and chewing were observed over the dose range 32-100 μmol/kg of (*R*)- and (*S*)-5 (data not shown). A possible explanation for these results might be that these compounds act indirectly via release of endogeneous 5-HT in normal animals. The observation that the compounds within this group were able to decrease the body temperature of the rats and to inhibit the cage-leaving response would not be in conflict with this suggestion. The biochemical effects of the compounds do not simplify the characterization of their pharmacological profiles; (*R*)-5, (*S*)-5, and (*S*)-12 all reduced the 5-HT turnover and/or 5-HTP accumulation, indicating agonist actions at somatodendritic 5-HT_{1A} receptors. Compound (*S*)-4, in contrast to (*R*)-4, decreased the DA but not the 5-HT turnover. Thus, biochemically and behaviorally, (*R*)-4 behaves as selective 5-HT_{1A} receptor agonist, whereas (*S*)-4 displays both serotonergic and dopaminergic activities.

The triflates (*R*)-3 and (*S*)-3, the phenyl derivatives (*R*)-6 and (*S*)-6, as well as the benzoyl derivative (*S*)-10, constitute a group with a different profile; although these five derivatives had fairly high affinities for 5-HT_{1A} receptors, they were inactive in the in vivo behavioral or ex vivo biochemical assays. Since this might imply that the compounds are antagonists, we examined their ability to counteract the (*R*)-1-induced 5-HT syndrome and reduction in rat body temperature. However, in contrast to the established 5-HT_{1A} receptor antagonist (*S*)-UH-301,[22] none of these compounds counteracted the effects of (*R*)-1. Their inability to produce central effects may be related to pharmacokinetic factors such as extensive metabolism producing inactive metabolites or an inability to pass the blood–brain barrier.



(*S*)-UH-301

One of the aims of the present study was to investigate whether replacement of the C8-hydroxy group of 1 would lead to changes in the pharmacological profile. In contrast to results in a report discussing the effects of various C5 substituents on the 5-HT_{1A} receptor affinity of tryptamine derivatives,[24] which indicated that increasing steric bulk correlated with increased affinity; the affinity of the present derivatives does not appear to correlate with the electronic, lipophilic, or steric properties of the C8 substituent, or with combinations thereof ($R^2 < 0.16$; see the Experimental Section). This seems to indicate that the C5 substituent of the tryptamine derivatives and the C8 substituent of the 2-aminotetralin derivatives occupy different spacial positions in the binding site of the 5-HT_{1A} receptor.

In most derivatives, the *R*-enantiomer is the more potent antipode in terms of affinity. In contrast, in C8-acetyl- and methoxycarbonyl-substituted derivatives 8 and 11, the stereoselectivity is reversed, i.e., the *S*-enantiomers are more potent (Table II). It is noteworthy that several derivatives of 1 which do not have an oxygen atom directly connected to C8 have about the same affinity for 5-HT_{1A} receptors as 1 [cf. (*R*)-6, (*S*)- and (*R*)-8, (*R*)-10, (*S*)- and (*R*)-11]. Ongoing studies focus on the effects of introduction of various aromatic and heteroaromatic substituents in the C8-position of 2-(dipropylamino)tetralin.

Experimental Section

Chemistry. General Comments. Routine ^1H and ^{13}C NMR spectra were recorded at 90 and 22.5 MHz, respectively, on a JEOL FX 90Q spectrometer and were referenced to internal tetramethylsilane. IR spectra were obtained on a Perkin-Elmer 157 G spectrometer. All spectra were in accordance with the assigned structures. Melting points (uncorrected) were determined in open glass capillaries on a Thomas-Hoover apparatus. Optical rotations were obtained on a Perkin-Elmer 241 polarimeter. The elemental analyses (C, H, and N), which were performed by Micro Kemi AB, Uppsala, Sweden, were within 0.4% of the theoretical values. For purity tests, capillary GC

was performed on a Carlo Erba 4200 instrument equipped with an SE 54 fused-silica capillary column (10 m).

Synthesis. Below are given representative examples of the reactions presented in Table I.

(±)-8-[[(Trifluoromethyl)sulfonyl]oxy]-2-(dipropylamino)tetralin Hydrochloride [(±)-3]. Method I. A solution of trifluoromethanesulfonic anhydride (7.0 g, 24.8 mmol) in CH_2Cl_2 (20 mL) was added to a mixture of K_2CO_3 (3.4 g, 24.8 mmol) and (±)-8-hydroxy-2-(dipropylamino)tetralin [(±)-1;[1a] 3.06 g, 12.4 mmol] in CH_2Cl_2 (300 mL) kept at −78 °C. The cooling bath was removed, and stirring was continued until the temperature reached 0 °C. The mixture was extracted with ice-cold saturated aqueous K_2CO_3. The organic layer was dried (K_2CO_3), filtered, and concentrated. The residue was purified on an alumina column, eluting with ether/petroleum ether (1:8) to afford an oil that was converted into the hydrochloride. Recrystallization gave 5.01 g (97%) of pure (±)-3: ^1H NMR (methanol-d_4) δ 7.38–7.12 (m, 3 H), 3.93–3.66 (m, 1 H), 3.52–2.83 (m, 8 H), 2.56–2.24 (m, 1 H), 2.15–1.55 (m, 5 H), 1.05 (t, 6 H).

(S)-2-(Dipropylamino)tetralin Hydrochloride [(S)-4]. Method II. A mixture of the base of (S)-3 (250 mg, 0.66 mmol), triethylamine (200 mg, 2.0 mmol), $Pd(OAc)_2$ (7.4 mg, 0.033 mmol), 1,1′-bis(diphenylphosphino)ferrocene (36.6 mg, 0.066 mmol), and formic acid (61 mg, 1.3 mmol) in DMF (5 mL) was heated for 12 h at 60 °C under N_2. The reaction mixture was diluted with brine and extracted with ether (3 × 50 mL). The organic layer was dried (K_2CO_3), filtered, and concentrated. The residue was purified by chromatography on an alumina column, eluting with ether/petroleum ether (1:16). The pure base of 4 was converted into the hydrochloride (136 mg, 77%): ^1H NMR (methanol-d_4) δ 7.13 (s, 4 H), 3.87–3.56 (m, 1 H), 3.39–2.81 (m, 8 H), 2.50–2.19 (m, 1 H), 2.08–1.52 (m, 5 H), 1.04 (t, 6 H).

(R)-8-Methyl-2-(dipropylamino)tetralin Hydrochloride [(R)-5]. Method III. A mixture of the base of (R)-3 (500 mg, 1.32 mmol), tetramethyltin (500 mg, 2.8 mmol), bis(triphenylphosphine)palladium chloride(II) (46 mg, 0.066 mmol), LiCl (174 mg, 4.1 mmol), and 2,6-di-*tert*-butyl-4-methylphenol (a few grains) in dioxane (12 mL) and DMF (1.2 mL) was heated at 110 °C for 24 h in a sealed flask. The reaction mixture was filtered (Celite) and concentrated in vacuo. The residue was partitioned between aqueous saturated K_2CO_3 and ether. The organic layer was dried (K_2CO_3), filtered, and concentrated. The residue was purified on an alumina column, eluting with ether/petroleum ether (1:40). Conversion of the resulting oil into the hydrochloride gave 210 mg (57%) of (R)-5: ^1H NMR (methanol-d_4) δ 7.11–6.83 (s, 3 H), 3.96–3.53 (m, 1 H), 3.42–2.77 (m, 8 H), 2.48–2.14 (m, 1 H), 2.24 (s, 3 H), 2.13–1.57 (m, 5 H), 1.03 (t, 6 H).

(±)-8-Phenyl-2-(dipropylamino)tetralin Oxalate [(±)-6]. Method IV. A mixture of the base of (±)-3 (6.00 g, 15.8 mmol), tributylphenylstannane (6.97 g, 19 mmol), tetrakis(triphenylphosphine)palladium(0) (913 mg, 0.79 mmol), lithium chloride (2.1 g, 49 mmol) and 2,6-di-*tert*-butyl-4-methylphenol (radical inhibitor) in 10 mL of dimethylformamide and 30 mL of 1,4-dioxane was stirred at 120 °C for 24 h. The mixture was filtered (Celite), concentrated, and partitioned between saturated aqueous K_2CO_3 and ether. The organic layer was dried (K_2CO_3) and concentrated. The residue was chromatographed on an alumina column, eluting with ether/petroleum ether (1:40). The pure fractions were pooled and treated with ethereal oxalic acid, affording 5.60 (89%) of (±)-6: ^1H NMR (methanol-d_4) δ 7.50–6.99 (m, 8H), 3.88–3.51 (m, 1H), 3.35–3.21 (m, 2H), 3.18–2.88 (m, 6H), 2.50–2.10 (m, 2H), 2.08–1.39 (m, 4H), 0.93 (t, 6H).

(S)-8-Ethynyl-2-(dipropylamino)tetralin Hydrochloride [(S)-7]. Method V. A mixture of the base of (S)-3 (500 mg, 1.32 mmol), (trimethylsilyl)acetylene (200 mg, 1.98 mmol), bis(triphenylphosphine)palladium chloride(II) (28 mg, 0.04 mmol), triethylamine (0.8 mL, 5.8 mmol), and LiCl (168 mg, 3.96 mmol) in DMF (10 mL) was stirred at 90 °C for 1 h under N_2. The mixture was filtered and concentrated to provide an oil which was purified on a silica gel column eluting with ammonia saturated ether/petroleum ether (1:8). The resulting oil was dissolved in THF (20 mL), and a 1 M solution of tetrabutylammonium fluoride in THF (1.3 mL, 1.3 mmol) was added. The reaction mixture was stirred under N_2 for 1 h at room temperature. The volatiles were evaporated, and the residue was partitioned between aqueous saturated $NaHCO_3$ and ether. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified on a silica gel column eluting with ammonia-saturated ether/petroleum ether (1:8). The resulting oil was converted into 126 mg (33%) of pure (S)-7: ^1H NMR (methanol-d_4) δ 7.42–7.07 (m, 3 H), 3.88 (s, 1 H), 3.87–3.49 (m, 1 H), 3.48–2.83 (m, 8 H), 2.53–2.19 (m, 1 H), 2.16–1.58 (m, 5 H), 1.05 (t, 6 H); IR (neat) 3309, 2101 cm^{-1}.

(±)-8-Acetyl-2-(dipropylamino)tetralin Hydrochloride [(±)-8]. Method VI. A mixture of the base of (±)-3 (455 mg, 1.2 mmol), tetramethylstannane (257 mg, 1.44 mmol), LiCl (158 mg, 3.7 mmol), dichloro[1,1′-bis(diphenylphosphino)ferrocene]-palladium [$PdCl_2$(dppf);[14b] 61 mg, 0.07 mmol], molecular sieves (4 Å; 120 mg) and 2,6-di-*tert*-butyl-4-methylphenol (a few grains) in DMF (10 mL) was stirred under an atmosphere of CO for 14 h at 90 °C. The mixture was filtered (Celite), and the filtrate was concentrated and partitioned between water and ether. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography on an alumina column eluting with ether/petroleum ether (1:16). The resulting oil was treated with ethereal HCl to afford 258 mg (70%) of (±)-8: ^1H NMR (methanol-d_4) δ 7.82–7.61 (m, 1 H), 7.37–7.22 (m, 2 H), 3.82–3.55 (m, 1 H), 3.47–2.91 (m, 8 H), 2.61 (s, 3 H), 2.39–2.11 (m, 1 H), 2.08–1.54 (m, 5 H), 1.03 (t, 6 H); IR (neat) 1688 cm^{-1}.

(±)-8-Acetyl-2-(dipropylamino)tetralin Hydrochloride [(±)-8]. Method VII. A 5% solution of methyllithium in ether (0.6 mL, 0.96 mmol) was added to a chilled slurry of (±)-13 (100 mg, 0.32 mmol) in ether. The mixture was stirred at room temperature and under nitrogen for 3 days. Water was added carefully, and the mixture was extracted with ether. The organic layer was dried (K_2CO_3) and concentrated. The residue was purified by chromatography on an alumina column eluting with ether/petroleum ether (1:4). The pure fractions were pooled, concentrated, and converted into the hydrochloride. Recrystallization gave 55 mg (56%) of pure (±)-8.

(S)-8-Acetyl-2-(dipropylamino)tetralin Hydrochloride [(S)-8]. Method VIII. A mixture of the base of (S)-3 (500 mg, 1.32 mmol), butyl vinyl ether (661 mg, 6.6 mmol), palladium acetate (7.4 mg, 0.033 mmol), 1,3-bis(diphenylphosphino)propane (15 mg, 0.036 mmol), and triethylamine (267 mg, 2.64 mmol) in DMF (10 mL) was heated overnight at 120 °C in a sealed flask which was flashed with nitrogen several times before the reaction started. The catalysts were filtered off (Celite), and the solvent was removed. The residue was stirred with 10% aqueous hydrochloric acid at room temperature for 0.5 h. The reaction mixture was alkalinized with K_2CO_3 until pH ≈ 9 and partitioned between ether and water. The organic phase was dried (K_2CO_3), concentrated, and treated with ethereal HCl to afford 72 mg (60%) of (S)-8.

(±)-Methyl 2-(Dipropylamino)tetralin-8-carboxylate Hydrochloride [(±)-11]. Method IX. A mixture of the base of (±)-3 (2.28 g, 6.0 mmol), triethylamine (1.83 g, 18.4 mmol), $Pd(OAc)_2$ (40 mg, 0.18 mmol), 1,1′-bis(diphenylphosphino)ferrocene (200 mg, 0.36 mmol), and MeOH (3.72 g, 120 mmol) in DMSO (40 mL) was heated at 70 °C and stirred for 2 days under an atmosphere of CO. The mixture was partitioned between brine and ether. The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on an alumina column eluting with ether/petroleum ether (1:16). Pure fractions were pooled and concentrated. The resulting oil was converted into the hydrochloride. Recrystallization gave 1.79 g (91%) of pure (±)-11: ^1H NMR (methanol-d_4) δ 7.86–7.65 (m, 1 H), 7.41–7.12 (m, 2 H), 3.88 (s, 3 H), 3.71–3.50 (m, 1 H), 3.48–2.86 (m, 8 H), 2.39–2.18 (m, 1 H), 2.05–1.60 (m, 5 H), 1.05 (t, 6 H); IR (neat) 1724, 1262, 1138 cm^{-1}.

(S)-8-(Hydroxymethyl)-2-(dipropylamino)tetralin Hydrochloride [(S)-12]. Method X. A solution of (S)-11 (220 mg, 0.76 mmol) in THF (15 mL) was added during 15 min to a slurry of $LiAlH_4$ (250 mg, 6.6 mmol) in THF (10 mL). The reaction mixture was stirred for 12 h under N_2 and was then quenched by successive additions of water (0.25 mL), 5 M NaOH (0.25 mL), and water (0.5 mL). The organic layer was dried (K_2CO_3), filtered, and concentrated. The residue was purified on an alumina column by use of gradient elution (ether/petroleum ether → ether). Conversion of the resulting oil into the hydrochloride followed by recrystallization provided 188 mg (83%) of pure (S)-12: ^1H NMR (methanol-d_4) δ 7.22–7.05 (m, 3 H), 4.63 (s, 2 H),

3.88–3.58 (m, 1 H), 3.36–3.09 (m, 5 H), 3.06–2.82 (m, 3 H), 2.42–2.15 (m, 1 H), 2.09–1.59 (m, 5 H), 1.05 (t, 6 H); IR (KBr) 3330, 1051 cm^{-1}.

(±)-2-(Dipropylamino)tetralin-8-carboxylic Acid Hydrochloride [(±)-13]. A mixture of (±)-11 (1.5 g, 4.6 mmol), NaOH (736 mg, 18.4 mmol), MeOH (25 mL), and H_2O (4 mL) was stirred overnight at room temperature. The MeOH was evaporated, and concentrated HCl was added to a pH of about 6. The solution was extracted with $CHCl_3$. The organic layer was dried (Na_2SO_4) and concentrated to give 1.23 g (97%) of the pure base of (±)-13 which was converted into the hydrochloride: ^1H NMR (methanol-d_4) δ 7.88–7.71 (m, 1 H), 7.42–7.11 (m, 2 H), 3.82–3.45 (m, 1 H), 3.33–2.90 (m, 8 H), 2.50–2.21 (m, 1 H), 2.18–1.62 (m, 5 H), 1.04 (t, 6 H); IR(KBr) 2920, 1700, 1240 cm^{-1}.

(±)-8-Carbamoyl-2-(dipropylamino)tetralin Oxalate [(±)-14]. A mixture of (±)-13 (953 mg, 3.46 mmol) and thionyl chloride (10 mL) was stirred at 60 °C under N_2 for 3 h. The mixture was concentrated in vacuo, and aqueous concentrated NH_3 (10 mL) was added. The solution was stirred at room temperature for 2 h and was then extracted twice with ether. The organic layer was dried (K_2CO_3), filtered, and concentrated. The residue was purified on a silica gel column eluted with ammonia-saturated ethyl acetate. Pure fractions were pooled and treated with ethereal oxalic acid to afford 600 mg (48%) of (±)-14: ^1H NMR (methanol-d_4) δ 7.31–7.13 (m, 3 H), 3.90–3.58 (m, 1 H), 3.39–2.88 (m, 8 H), 2.38–2.16 (m, 1 H), 2,14–1.53 (m, 5 H), 1.03 (t, 6 H); IR (neat) 3360, 3200, 2960, 1655, 1420 cm^{-1}.

(±)-8-Cyano-2-(dipropylamino)tetralin Hydrochloride [(±)-15]. A solution of $POCl_3$ (2 mL, 21 mmol) in dry DMF (10 mL) was added to a solution of (±)-14 (200 mg, 0.64 mmol) in dry DMF (10 mL). The stirred reaction mixture was heated at 60 °C for 1 h under N_2. The mixture was concentrated to dryness, and the residue was partitioned between saturated aqueous Na_2CO_3 and CH_2Cl_2. The organic layer was dried (K_2CO_3), filtered, and concentrated. The resulting oil was chromatographed on an alumina column with ether/petroleum ether (1:16) as eluant. Pure fractions were pooled and converted into the hydrochloride which was recrystallized, affording 134 mg (71%) of (±)-15: ^1H NMR (methanol-d_4) δ 7.62–7.28 (m, 3 H), 4.12–3.70 (m, 1 H), 3.52–2.91 (m, 8 H), 2.66–2.37 (m, 1 H), 2.18–1.66 (m, 5 H), 1.06 (t, 6 H); IR (neat) 2211 cm^{-1}.

Pharmacology. General. Male Sprague–Dawley rats (ALAB, Stockholm) weighing 260–310 g were used. The animals were kept at room temperature (23 ± 1 °C) and were allowed food and water ad libitum with lights on between 06:00 and 18:00 for at least a week before the experiment. Each animal was used only once. All compounds were dissolved in 0.9% NaCl, occasionally with gentle warming in order to obtain complete dissolution, and injected subcutaneously (sc); injection volumes were 2 mL/kg. Control rats received the same number of saline injections at corresponding time points. All experiments were performed between 9:00 a.m. and 3:00 p.m.

Behavior, Cage-Leaving Response, and Body Temperature. Screening data were typically collected with a dose of 32 μmol/kg sc; occasionally other doses have been chosen, e.g., due to known high potency or limited availability of substance. On occasion, behavioral experiments were done with rats pretreated (18 h) with reserpine in order to disclose an indirect mode of action, e.g., an effect on the release of endogenous 5-HT. Reserpine-treated rats also constitute a more sensitive assay for directly acting 5-HT_{1A} receptor agonists. Some compounds showing no agonist activity were considered as potential 5-HT_{1A} receptor antagonists. These compounds (32 μmol/kg sc) were injected 10 min before a standard dose of (*R*)-1 (1.0 μmol/kg sc) with the objective of investigating the possible antagonism of the (*R*)-1-induced 5-HT syndrome and hypothermia. Rats were observed for 30 min after the (last) injection. Flat body posture, forepaw treading, and hindlimb abduction (the 5-HT syndrome) were scored as absent or present at 6–12 min and at 24–30 min after drug administration. The cage-leaving response was only studied in normal rats. Cages containing two rats were placed next to each other. The grid covers were removed from the cages at 12 min after injection, and the number of rats leaving their cages during the subsequent 12 min was noted. Body temperature was measured before and at 30 min postinjection using an electrical thermometer with the probe inserted into the colon, 3.5 cm from the anal orfice.

Biochemistry. Changes in the ratio of 5-hydroxyindoleacetic acid (5-HIAA) to 5-hydroxytryptamine (5-HT) and 3,4-dihydroxyphenylacetic acid (DOPAC) to dopamine (DA) were taken as an indication of changes in 5 HT and DA turnover. The rats were decapitated within 5–10 min after the last behavioral rating and body temperature measurement at 30 min after drug administration. Brain regions (hippocampus and corpus striatum) were rapidly dissected out and frozen until assayed. The 5-HT and DA syntheses were estimated by measuring the accumulation of 5-hydroxytryptophan (5-HTP) and 3,4-dihydroxyphenylalanine (DOPA), respectively, after inhibition of aromatic L-amino acid decarboxylase by use of NSD 1015.[25] Animals were injected with NSD 1015 (60 mg/kg; 287 μmol/kg sc) at 30 min after the administration of test compounds. The rats were decapitated after another 30 min. The hippocampus and the corpus striatum were dissected out and stored at −40 °C for not more than 1 week before being assayed. The frozen tissue samples were weighed and homogenized in 1 mL of 0.1 M perchloric acid, and α-methyl-5-hydroxytryptophan was added as an internal standard. After centrifugation (12 000 rpm, i.e. 18600*g*, 4 °C, 10 min) and filtration, 20 μL of the supernatant was injected into a high-performance liquid chromatograph with electrochemical detection (HPLC-EC) to analyze 5-HIAA, 5-HTP, 5-HT, DOPAC, DOPA, and DA. The HPLC system consisted of a PM-48 pump (Bioanalytical systems, BAS) with a CMA/240 autoinjector (injection volume: 20 μL), a precolumn (15 × 3.2 mm, RP-18 Newguard, 7 μm), a column (100 × 4.6 mm, SPHERI-5, RP-18, 5 μm), and an amperometric detector (LC-4B, BAS, equipped with an Ag/AgCl reference electrode and a MF-2000 cell) operating at a potential of +0.85 V. The mobile phase, pH 2.69, consisted of K_2HPO_4 and citric acid buffer (pH 2.5), 10% methanol, sodium octyl sulfate, 40 mg/L, and EDTA. The flow rate was 1 mL/min, and the temperature of the mobile phase was 35 °C.

5-HT_{1A} Receptor Binding Assay. Male Sprague–Dawley rats (weighing about 200 g) were decapitated, and cortex and hippocampus were dissected. The tissues (600–900 mg) from each rat were immediately homogenized in 15 mL of ice-cold 50 mM Tris-HCl buffer containing 4.0 mM $CaCl_2$ and 5.7 mM ascorbic acid, pH 7.5, with an Ultra Turrax (Janke and Kunkel, Staufen, FRG) for 10 s. After centrifugation for 12.5 min at 17 000 rpm (39800*g*) in a Beckman centrifuge with a chilled JA-17 rotor (Beckman, Palo Alto, CA), the pellets were resuspended in the same buffer and the homogenization and the centrifugation were repeated. The pellets from at least six rats were again suspended in the buffer, pooled, homogenized, and stored on ice for 1–4 h. The tissue homogenate was diluted to 10 mg/1.25 mL with the buffer, incubated for 10 min at 37 °C, and supplied with 10 μM pargylin (Sigma, St. Louis, MO) followed by reincubation for 10 min.

Incubation mixtures (2 mL) contained 1–300 nM test compound (diluted in 50 mM Tris-HCl containing 5.7 mM ascorbic acid, pH 7.5), 2 nM [^3H]-8-OH-DPAT ([^3H]-8-hydroxy-2-(di-*n*-propylamino)tetralin hydroxybromide), 31.60 Ci/mmol, New England Nuclear, Dreieich, Germany, and Research Biomedicals, Wayland, MA), 5 mg/mL tissue homogenate in 50 mM Tris-HCl buffer containing 4.0 mM $CaCl_2$, and 5.7 mM ascorbic acid, pH 7.5. Binding experiments were started by the addition of tissue homogenate and followed by incubation at 37 °C for 10 min. The incubation mixtures were filtered through Whatman GF/B glass filters with a Brandel Cell Harvester (Gaithersburg, MD). The filters were washed twice with 5 mL of ice-cold 50 mM Tris-HCl buffer, pH 7.5, and counted with 5 mL of Ultima Gold (Packard Instrument Co, IL) in a Beckman LS 3801 scintillation counter. Nonspecific binding was measured by the addition of 10 μM 5-HT·HCl to the reaction mixture. The binding data were processed by nonlinear least-squares computer analysis.[26] A K_d value of 1.4 nM for 8-OH-DPAT binding was obtained from the saturation experiment and was used to calculate the K_i values.

Correlation Studies. Four aromatic substituent descriptors were used to characterize the set of 12 enantiomeric pairs of C8-substituted compounds (1-8, 10-12, and 15): π, MR, σ_m, σ_p.[27-29] Attempts were made to correlate binding affinities from both enantiomers with each of the descriptors or with combinations

thereof (Cricket Graph Version 1.3.2).[30] The differences between binding data of the *R*- and *S*-enantiomers were also used in the correlation with all descriptors in order to expose the stereoselectivity. The chemical shifts from the ^{13}C NMR signal due to C8 were used as an additional descriptor. No correlation was observed between the binding affinity and the five descriptors (the correlation coefficient, R^2, was always less than 0.16).

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Supplementary Material Available: A table of ^{13}C NMR data of all test compounds (1 page). Ordering information is given on any current masthead page.

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