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C8-Substituted derivatives of 2-(dipropylamino)tetralin: exploration of the effect of C8-aryl and heteroaryl substituents on the interaction with 5-HT_{1A}-receptors

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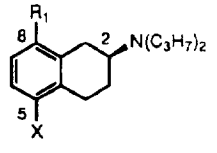
Summary — In order to further explore the structure–activity relationships of serotonergic 2-aminotetralin derivatives, a total of 12 aryl and heteroaryl substituents have been introduced in the C8-position of 2-(dipropylamino)tetralin. The affinity of the compounds was studied by competition experiments with [^{3}H]-8-OH-DPAT in rat-brain tissue. In addition, the effects of the compounds were assessed *in vivo* using biochemical and behavioral tests in rats. Although all the novel derivatives had fairly high affinities for the 5-HT_{1A} receptors, several compounds failed to produce biochemical or behavioral effects indicative of 5-HT_{1A}-receptor stimulation. In addition, they did not appear to be 5-HT_{1A}-receptor antagonists. Hence, the apparent inactivity *in vivo* may be due to pharmacokinetic factors such as extensive metabolism or poor ability to pass the blood–brain barrier. However, a few compounds in the present series, such as (*S*)-8-(2-furyl)-2-(dipropylamino)tetralin, did produce most of the *in vivo* pharmacological actions typical of 5-HT_{1A} receptor agonists.

5-HT_{1A} agonist / 5-HT_{1A} antagonist / 8-OH-DPAT / SAR

Introduction

The observation that buspirone has high affinity for serotonin 5-HT_{1A} receptors indicated that the well-characterized 5-HT_{1A} receptor [1–3] may be an interesting target for novel anxiolytic and antidepressant agents [4–6]. As a result, numerous 5-HT_{1A} receptor agonists and putative 5-HT_{1A} receptor antagonists have been synthesized and evaluated pharmacologically. We have been focusing on studies of analogues of the potent and selective 5-HT_{1A} receptor agonist 8-hydroxy-2-(dipropylamino)tetralin (8-OH-DPAT; **1**) [7–9]. These efforts have led to the identification of an array of interesting 5-HT_{1A} receptor agonists [10–12] and to the development of (*S*)-UH-301 **2** [13–16], the first 5-HT_{1A} receptor antagonist.



(*S*)-**1**: X = H, R_1 = OH
(*S*)-**2**: X = F, R_1 = OH
(*S*)-**3**: X = H, R_1 = $COCH_3$
(*S*)-**4**: X = H, R_1 = Ph

Although derivatives of **1** have been of interest for more than 10 years, only fairly recent studies have addressed the role of the C8-substituent [17–21]. On the basis of these studies, it appears that the C8-hydroxyl substituent of **1** can be substituted with a variety of groups without much loss in 5-HT_{1A} receptor affinity. In fact, the enantiomers of the C8-acetyl-substituted LY-41 **3** are equipotent or slightly more potent than the enantiomers of **1** [22]. Even introduction of a phenyl substituent in the C8-position of **1**, affording LY-49 **4**, gives a compound with high affinity for the 5-HT_{1A} receptor [19, 21]. In order to further explore the structure–activity relationships of the serotonergic 2-aminotetralins we have now prepared and evaluated pharmacologically a series of enantiopure C8-aryl- and heteroaryl-substituted 2-(dipropylamino)tetralin derivatives. Target compounds were selected on the basis of a combination of synthetic feasibility and information content. The compounds have been investigated pharmacologically *in vitro* using receptor-binding techniques and *in vivo* by use of biochemical and behavioral tests in rats. Physical data of the new compounds are presented in table I and test results are given in tables II–V.

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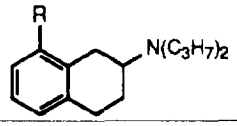
Table I. Physical data of some novel 2-aminotetralin derivatives*.



(±)-4	phenyl	I[e]	162-163	89	A		$C_{22}H_{29}N \cdot C_2H_2O_4 \cdot H_2O$
(*R*)-4	phenyl	I[e]	115-116	83	F	+24.1	$C_{22}H_{29}N \cdot C_2H_2O_4$
(*S*)-4	phenyl	I[e]	115-117	88	F	-25.2	$C_{22}H_{29}N \cdot C_2H_2O_4$
(±)-6	fluorophenyl	I	197-199	68	B		$C_{22}H_{28}NF \cdot C_2H_2O_4$
(*R*)-6	fluorophenyl	I	136-138	60	C	+26.8	$C_{22}H_{28}NF \cdot C_2H_2O_4 \cdot 1/4H_2O$
(*S*)-6	fluorophenyl	I	137-138	65	A	-27.2	$C_{22}H_{28}NF \cdot C_2H_2O_4$
(±)-7	methoxyphenyl	I	172-174	85	C		$C_{23}H_{31}NO \cdot HCl$
(*R*)-7	methoxyphenyl	I	141-142	78	C	+14.2	$C_{23}H_{31}NO \cdot C_2H_2O_4$
(*S*)-7	methoxyphenyl	I	140-141	82	C	-14.7	$C_{23}H_{31}NO \cdot C_2H_2O_4$
(±)-8	hydroxyphenyl	II	164-167	87	A		$C_{22}H_{29}NO \cdot HCl \cdot H_2O$
(*R*)-8	hydroxyphenyl	II	f	95	C	+13.1	$C_{22}H_{29}NO \cdot C_2H_2O_4$
(*S*)-8	hydroxyphenyl	II	f	98	C	-13.3	$C_{22}H_{29}NO \cdot C_2H_2O_4 \cdot 3/4H_2O$
(±)-9	g	III	137-139	64	A		$C_{23}H_{28}NO_3F_3 \cdot HCl$
(*R*)-9	g	III	163-164	66	A	+18.1	$C_{23}H_{28}NO_3F_3 \cdot HCl$
(*S*)-9	g	III	163-165	70	A	-19.6	$C_{23}H_{28}NO_3F_3 \cdot HCl$
(±)-10	acetylphenyl	IV	168-169	63	A		$C_{24}H_{31}NO \cdot HCl \cdot 1/2H_2O$
(*R*)-10	acetylphenyl	IV	99-101	56	A	+14.1	$C_{24}H_{31}NO \cdot C_2H_2O_4 \cdot 1/2H_2O$
(*S*)-10	acetylphenyl	IV	97-99	70	A	-15.8	$C_{24}H_{31}NO \cdot C_2H_2O_4 \cdot 1/4H_2O$
(±)-11	2-furyl	V	113-114	63	B		$C_{20}H_{27}NO \cdot C_2H_2O_4$
(*R*)-11	2-furyl	V	107-109	83	F	+40.1	$C_{20}H_{27}NO \cdot C_2H_2O_4$
(*S*)-11	2-furyl	V	109-110	70	F	-39.4	$C_{20}H_{27}NO \cdot C_2H_2O_4$
(±)-12	2-thienyl	V	161-162	24	F		$C_{20}H_{27}NS \cdot HCl$
(*R*)-12	2-thienyl	V	182-183	33	B	+16.8	$C_{20}H_{27}NS \cdot HCl$
(*S*)-12	2-thienyl	V	182-184	59	B	-17.4	$C_{20}H_{27}NS \cdot HCl$
(±)-13	3-furyl	V	169-171	40	F		$C_{20}H_{27}NO \cdot HCl$
(*R*)-13	3-furyl	V	163-164	60	F	+36.6	$C_{20}H_{27}NO \cdot HCl$
(*S*)-13	3-furyl	V	164-165	61	F	-36.4	$C_{20}H_{27}NO \cdot HCl$
(±)-14	3-thienyl	V	f	34	C		$C_{20}H_{27}NS \cdot HCl$
(*R*)-14	3-thienyl	V	143-145	47	C	+27.8	$C_{20}H_{27}NS \cdot HCl$
(*S*)-14	3-thienyl	V	143-145	39	C	-27.8	$C_{20}H_{27}NS \cdot HCl$
(±)-15	2-benzofuryl	I	63-66	48	C		$C_{24}H_{29}NO \cdot C_2H_2O_4 \cdot H_2O$
(±)-17	h	VI	168-170	69	F		$C_{19}H_{27}N_3O \cdot HCl \cdot 1/2H_2O$

[a]See *Experimental protocols*. [b]A: chloroform/ether; B: methanol/ether; C: ether; D: acetonitrile/ether; F: acetone/ether. [c]MeOH, c = 1.0. [d]Elemental analysis were within 0.4% of calculated values. [e]Previously reported [9, 11]. [f]Very hygroscopic. [g]4-[(Trifluoromethanesulfonyl)oxy]phenyl. [h]5-(3-Methyl-1,2,4-oxadiazole)yl. *Fluorophenyl = 4-fluorophenyl; methoxyphenyl = 4-methoxyphenyl; hydroxyphenyl = 4-hydroxyphenyl; acetylphenyl = 4-acetylphenyl.

Chemistry

The difference in intrinsic activity between (*R*)- and (*S*)-**1** [23] and the reversed stereoselectivity of the C8-acetyl-substituted **3** [22] emphasizes the importance of testing the enantiomers of 2-aminotetralin derivatives. Consequently, we wanted to prepare both antipodes of most of the substances in the present series.

The pure enantiomers of **1**, which may be prepared on the 100-g scale by a facile method [24], served as key intermediates. The enantiomers of **1** were conveniently converted into triflates (*S*)- or (*R*)-**5** by treatment with triflic anhydride in the presence of pyridine and potassium carbonate [19, 21]. Palladium-catalyzed couplings [25] of the enantiomers of **5** with the appropriate tributyl(aryl)stannanes in a mixture of 1,4-dioxane and dimethylformamide afforded the corresponding enantiomers of the substituted **4**, **6** and **7** (scheme 1). The coupling of triflate **5** with tributyl(4-acetylphenyl)stannane proved to be very sluggish and did not yield any desired product. In order to obtain the 4-acetylphenyl derivative **10**, we demethylated the 4-methoxyphenyl-substituted **7** and converted the resulting phenol (**8**) into triflate **9**. Compound **10** was readily obtained from **9** by a palladium-catalyzed carbonylation [26] in the presence of tetramethyltin and an atmosphere of carbon monoxide (scheme 2).

The heteroaromatic derivatives **11–14** were prepared from triflate **5** by palladium-catalyzed reactions with the appropriate tributylheteroarylstannanes in dimethylformamide. However, in the preparation of **15**, a mixture of dimethylformamide and 1,4-dioxane was used to couple tributyl(2-benzofuranyl)stannane with **5** (scheme 1).

The oxadiazole derivative **17** was prepared from the ester **16** [19, 21] by reaction with acetamide oxime and sodium ethoxide in refluxing ethanol (scheme 3) [27, 28].

Pharmacology

It is well known that administration of (±)-**1** induces a complex behavioral syndrome (forepaw treading, flat body posture and hindlimb abduction) in rats [8, 29, 30]. It has also been established that 5-HT_{1A} receptor agonists decrease the body temperature in rats [31] and inhibit the so-called cage-leaving response [32]. We have therefore studied the ability of the compounds to produce these actions in rats. The data are presented in table II.

Stimulation of central somatodendritic 5-HT_{1A} receptors with agonists such as **1** decreases the synthesis and release of 5-HT [33–35]. The novel compounds were therefore also evaluated in biochemical assays *in vivo* (tables III and IV). The ratio of the brain tissue concentrations of 5-hydroxyindoleacetic acid (5-HIAA) over 5-HT was used as a measure of 5-HT turnover; 5-HT_{1A} receptor agonists decrease this ratio because the inhibition of 5-HT synthesis and release results in decreased levels of 5-HIAA, the acid metabolite of 5-HT, and increased levels of 5-HT. The effects on dopamine (DA) turnover (the ratio of the DA metabolite 3,4-dihydroxyphenylacetic acid over DA) was studied as an indicator of DA-receptor stimulation.

In addition, we measured the effects of selected analogues on the accumulation of 5-hydroxytryptophan (5-HTP) and 3,4-dihydroxyphenylalanine (DOPA) following decarboxylase inhibition by means of NSD1015 (benzylhydrazine hydrochloride). Throughout, 32 μmol/kg of the test compounds were administered subcutaneously (sc) to the rats.

Behavior, cage-leaving response and body temperature

A positive control group that received (*R*)-**1** (1 μmol/kg, sc) exhibited the 5-HT syndrome (flat body posture and forepaw treading) during 4–25 min post-injection. None of the rats displayed the cage-leaving response and the body temperature was reduced by 2.6°C.

(*S*)-**11** was the only new compound that produced a 5-HT syndrome identical to that elicited by (*R*)-**1** (1 μmol/kg, sc). Several of the other derivatives, *ie* (*R*)- and (*S*)-**8**, (*S*)-**10**, (*R*)-**11**, and (*S*)- and (*R*)-**13**, only induced a flat body posture in the dose tested, which probably corresponds to a partially developed syndrome in the rats.

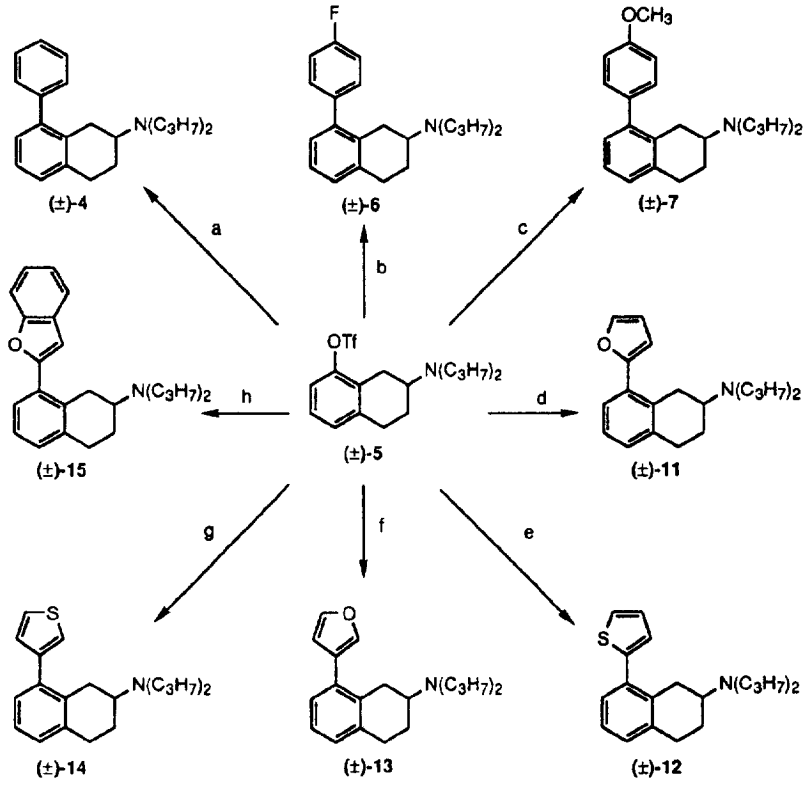
Rats treated with (*R*)-**7**, (*S*)- and (*R*)-**8**, (*R*)-**9**, and (*S*)-and (*R*)-**11** did not produce the cage-leaving response. Some compounds produced a partial cage-leaving response, *ie* only one out of four rats ((*S*)-**9**, (*S*)-**10**, and (*S*)- and (*R*)-**13**) or two out of four rats ((*S*)- and (*R*)-**12**, and (*S*)-**14**) responded.

Seven compounds in the new series ((*S*)- and (*R*)-**8**, (*S*)-**10**, (*S*)- and (*R*)-**11**, and (*S*)- and (*R*)-**13**) produced a significant decrease in rat body temperature, another indication of 5-HT_{1A} receptor stimulation.

To evaluate if the *in vivo* effects of the compounds were due to a direct stimulation of postsynaptic 5-HT_{1A} receptors, the enantiomers of **8**, **11** and **13**, and (*R*)-**9** and (*S*)-**10** were evaluated also in reserpine-pretreated rats (table IV). The compounds induced a flat body posture in the reserpine-treated animals which was more pronounced than that observed in the unpretreated rats. Apparently, reserpine pretreatment makes the rats more prone to exhibit this particular aspect of the 5-HT syndrome. However, it is noteworthy that none of the compounds could induce forepaw treading at the dose tested.

5-HT and DA turnover

The efficacious 5-HT_{1A} receptor agonist (*R*)-**1** (1 μmol/kg, sc) inhibited the 5-HT turnover by 33% compared with saline-treated controls whereas the DA turnover was unaffected. The new compounds did not induce significant changes in DA turnover but (*R*)-**8** and (*S*)- and (*R*)-**11** produced a significant decrease in the 5-HT turnover.



Scheme 1. Reagents: a. $Pd(Ph_3P)_4$, $PhSnBu_3$, LiCl, 1,4-dioxane, DMF; b. $Pd(Ph_3P)_4$, LiCl, 1,4-dioxane, DMF, tributyl(4-fluorophenyl)stannane; c. $Pd(Ph_3P)_4$, LiCl, 1,4-dioxane, DMF, tributyl(4-methoxyphenyl)stannane; d. $Pd(Ph_3P)_4$, LiCl, DMF, tributyl(2-furyl)stannane; e. $Pd(Ph_3P)_4$, LiCl, DMF, tributyl(2-thienyl)stannane; f. $Pd(Ph_3P)_4$, LiCl, DMF, tributyl(3-furyl)stannane; g. $Pd(Ph_3P)_4$, LiCl, DMF, tributyl(3-thienyl)stannane; h. $Pd(Ph_3P)_4$, LiCl, 1,4-dioxane, DMF, trimethyl(2-benzofuryl)stannane.

5-HTP and DOPA accumulation

5-HT_{1A} receptor agonists like (*R*)- or (*S*)-**1** decrease the accumulation of 5-HTP without affecting the DOPA levels. In reserpine-treated rats, both enantiomers of **8** and **13** as well as (*S*)-**10** induced a significant decrease in the 5-HTP accumulation without affecting the accumulation of DOPA (table IV). (*R*)-**9** reduced the striatal but not the hippocampal 5-HTP levels.

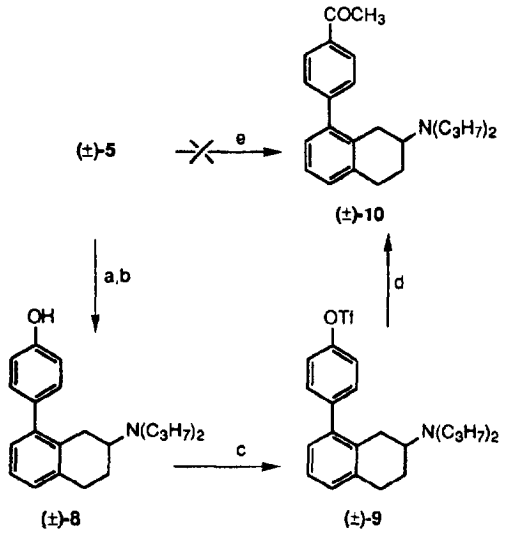
The effect of the enantiomers of **11** on the accumulations of 5-HTP and DOPA in the striatum was studied in nonpretreated rats. The enantiomers significantly decreased the 5-HTP accumulation without affecting the DOPA accumulation.

Affinity for 5-HT_{1A} receptors in vitro

The compounds tested showed high to moderate affinities for the 5-HT_{1A} receptors (table V). None of the compounds except (*S*)-**7** has K_i values above 50 nM and the K_i values of the enantiomers of **4, 6, 8,** and **10–14** are below 25 nM. The difference in affinity between pairs of enantiomers is rather small throughout the series, thus paralleling the moderate stereoselectivity observed previously among most derivatives of **1** which lack alkyl substituents in the non-aromatic ring [36].

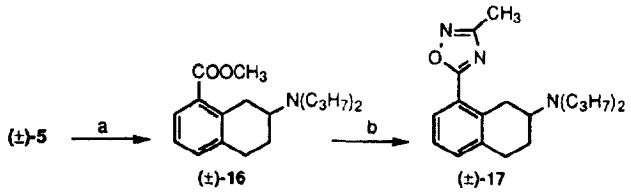
Results and discussion

On the basis of the data presently available, it may be concluded that the enantiomers of the 2- and 3-furyl-substituted derivatives **11** and **13**, the enantiomers of the 4-hydroxyphenyl-substituted **8**, and the 4-acetylphenyl-substituted (*S*)-**10** are 5-HT_{1A} receptor agonists, similar in profile but of lower potency than the hydroxy-substituted (*S*)- and (*R*)-**1**. These novel



Scheme 2. Reagents: a. Tributyl(4-methoxyphenyl)stannane, $Pd(Ph_3P)_4$, LiCl, 1,4-dioxane, DMF; b. 48% HBr; c. $(F_3CSO_2)_2O$, K_2CO_3, CH_2Cl_2; d. $(CH_3)_4Sn$, $PdCl_2$(dppf), LiCl, DMF, CO; e. $Pd(Ph_3P)_4$, LiCl, tributyl(4-acetylphenyl)stannane, 1,4-dioxane, DMF.

compounds have lower affinities for the 5-HT_{1A} receptor than (*S*)- and (*R*)-**1** but induce (a) biochemical effects indicative of 5-HT_{1A} receptor stimulation, (b) hypothermia, and (c) a flat body posture in normal as well as in reserpine-pretreated animals. Since the biochemical and behavioral effects occur both in normal and in reserpine-treated rats, they appear to be independent of the presence of endogenous 5-HT. Hence, the compounds may be classified as directly acting 5-HT_{1A} receptor agonists. We cannot, however, explain the inability of these analogues to induce forepaw treading in reserpine-treated rats, a behavior



Scheme 3. Reagents: a. $Pd(OAc)_2$, dppf, CH_3OH, DMSO, CO [19, 21]; b. $CH_3(C{=}NOH)NH_2$, $NaOC_2H_5$, 99.5% EtOH.

considered to be an integral part of the 5-HT behavioral syndrome. The ability of (*S*)-**11** to induce the complete 5-HT syndrome in normal but not in reserpine-treated animals is particularly enigmatic as reserpine-treated rats are usually more sensitive to 5-HT_{1A} receptor agonists.

(*S*)-**8**, (*S*)-**10** and (*R*)- and (*S*)-**13** did not inhibit the turnover of 5-HT but they significantly decreased the accumulation of 5-HTP. This complicates the evaluation of the pharmacological profiles but appears to suggest that inhibition of 5-HTP accumulation might be a more sensitive indicator of 5-HT_{1A} receptor agonism.

The triflate (*R*)-**9** induced biochemical changes suggestive of 5-HT_{1A} receptor stimulation. However, the inability of (*R*)-**9** to induce hypothermia and a 5-HT syndrome clearly distinguishes its profile from that of a potent 5-HT_{1A} receptor agonist.

Although all of the new analogues of **1** had fairly high affinities for the 5-HT_{1A} receptors, several compounds, including the enantiomers of the phenyl-, 4-fluorophenyl-, 4-methoxyphenyl-, and the 2- and 3-thienyl-substituted derivatives, failed to produce biochemical or behavioral effects in rats at the dose tested. The lack of agonist-related *in vivo* effects of the enantiomers of **4**, which suggests that they might be antagonists or very weak partial agonists, has been addressed previously and it was shown that neither enantiomer is a 5-HT_{1A} receptor antagonist [21]. Both (*S*)- and (*R*)-**4**, however, as well as the enantiomers of **11**, behave as potent agonists *in vitro* in a forskoline-stimulated adenylyl cyclase assay (AR Martin, personal communication). Thus, the inability of (*S*)- and (*R*)-**4**, as well as that of several other derivatives in the present series, to produce serotonergic effects *in vivo* may be related to pharmacokinetic factors such as extensive metabolism.

In most derivatives of **1**, the (*R*)-enantiomers are more potent in terms of affinity than the (*S*)-antipodes [10–12, 21, 37–41]. In the present series, four derivatives, *ie* the 4-hydroxyphenyl-substituted **8**, the 2- and 3-furyl-substituted **11** and **13**, and the 2-thienyl-substituted **12**, demonstrate a reversed stereoselectivity, the (*S*)-enantiomers having the higher affinity. In general, however, it is apparent from this work and previously published [21] studies of C8-substituted derivatives that different substituents have a relatively small effect on 5-HT_{1A} receptor affinity. As suggested by a referee, this seems to imply that a region of bulk tolerance exists in the receptor.

In conclusion, this study has demonstrated that C8-aryl or heteroaryl substitution may lead to potent 5-HT_{1A} receptor ligands. However, in order to provide a better understanding of the pharmacology of some of the compounds, pharmacokinetic and extended pharmacological studies have to be performed.

Table II. Novel 2-aminotetralin derivatives: effects on behavior and body temperature in rats[a].

Compound	Behavior		Cage-leaving	Change of body temperature (°C)
	FPT	FBP		
saline	0/9	0/9	7/9	0.17 ± 0.01
(*R*)-**1**	8/8[b]	8/8[b]	0/8	-2.64 ± 0.08**
(*R*)-**4**	0/4	0/4	3/4	0.28 ± 0.03
(*S*)-**4**	0/4	0/4	4/4	0.25 ± 0.1
(*R*)-**6**	0/4	0/4	4/4	-0.13 ± 0.20
(*S*)-**6**	0/4	0/4	3/4	0.13 ± 0.05
(*R*)-**7**	0/4	1/4	0/4	-0.08 ± 0.11
(*S*)-**7**	0/4	0/4	3/4	-0.03 ± 0.05
(*R*)-**8**	0/4	4/4[b]	0/4	-2.43 ± 0.05**
(*S*)-**8**	0/4	3/4[c]	0/4	-0.95 ± 0.18**
(*R*)-**9**	0/4	0/4	0/4	-0.20 ± 0.28
(*S*)-**9**	0/4	0/4	1/4	0.11 ± 0.04
(*R*)-**10**	0/4	0/4	3/4	-0.13 ± 0.05
(*S*)-**10**	0/4	3/4[c]	1/4	-1.48 ± 0.23**
(*R*)-**11**	0/5	5/5[b]	0/5	-2.78 ± 0.09**
(*S*)-**11**	5/5[b]	5/5[b]	0/5	-2.55 ± 0.09**
(*R*)-**12**	0/4	0/4	2/4	0.30 ± 0.01
(*S*)-**12**	0/4	0/4	2/4	0.23 ± 0.06
(*R*)-**13**	0/4	3/4[c]	1/4	-1.83 ± 0.57**
(*S*)-**13**	0/4	2/4	1/4	-1.68 ± 0.19**
(*R*)-**14**	0/4	0/4	3/4	0.05 ± 0.05
(*S*)-**14**	0/4	0/4	2/4	0.00 ± 0.08

[a]Compounds were given at the dose of 32 μmol/kg, sc except compound **1** (1 μmol/kg, sc). Shown are the number of rats displaying the behavior out of the number of rats tested, or change of body temperature compared with the pre-injection value. Abbreviations: FPT = forepaw treading; FBP = flat body posture. Statistics: Fisher's exact probability test was used for the behavioral data. [b] ≤ 0.005, [c] ≤ 0.05. Anova followed by the Tukey's studentized range (HSD) test was used for changes of body temperature.

Experimental protocols

Chemistry

Routine ^{1}H- and ^{13}C-NMR spectra were recorded at 90 MHz 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. Analysis indicated by the symbols of the elements 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). Tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$] (Merck products) was used as received.

Synthesis

Preparation of organostannanes

The following organostannanes were prepared according to literature procedures: tributyl(4-methoxyphenyl)stannane [42], tributyl(2-furyl)stannane [43], tributyl(3-furyl)stannane [43], tributyl(2-thienyl)stannane [43] and tributyl(3-thienyl)stannane [43].

Tributyl(4-fluorophenyl)stannane

A solution of *p*-fluorobromobenzene (5 g, 28.6 mmol) in ether (15 ml) was added to freshly ground magnesium with stirring under nitrogen. The reaction mixture was heated to reflux until the magnesium dissolved. A solution of tributyltin chloride (7.8 g, 24 mmol) in ether (10 ml) was added to the Grignard reagent and the reaction was interrupted after reflux for 3 d. The reaction mixture was diluted with an aqueous saturated ammonium chloride solution and partitioned between ether and water. The organic layer was dried (magnesium sulfate), filtered and concentrated. The residue was distilled under vacuum to give 7.1 g (68%) of tributyl(4-fluorophenyl)stannane, bp 117–134°C/1 mmHg. ^{1}H-NMR ($CDCl_3$) δ 7.45–7.37 (m, 2H), 7.07–6.99 (m, 2H), 1.59–0.84 (m, 27H). ^{13}C-NMR ($CDCl_3$) δ 162.93 (C4', d, J = 246 Hz), 137.55 (C2'), 136.42 (C1'), 114.77 (C3', d, J = 18 Hz), 28.77 (C3), 27.05 (C2), 13.30 (C4), 9.31 (C1). Signals due to C-Sn couplings were observed but are not indicated. Anal $C_{18}H_{31}FSn$ (C, H).

(4-Acetylphenyl)tributylstannane

Trifluoromethylsulfonic anhydride (6.8 ml, 40.4 mmol) was slowly added to a solution of *p*-acetylphenol (5 g, 36.8 mmol) in pyridine (18.8 ml) at 0°C under nitrogen. The reaction was complete after 3 d of stirring at room temperature. The reaction mixture was poured into 10 ml water and was partitioned between water and ether. The organic layer was washed successively with water, 10% aqueous hydrochloric acid, and water. The ether solution was dried (magnesium sulfate), filtered and concentrated. The residue was chromatographed on an alumina column with ethylacetate/hexane 1:20 as eluent. Pure fractions were pooled and concentrated to afford 6.7 g of 4-acetylphenyl trifluoromethanesulfonate as a colorless oil, which was sufficiently pure for the next reaction step.

A mixture of the above 4-acetylphenyl trifluoromethanesulfonate (5.3 g, 19.8 mmol), hexabutylditin (12.6 g, 21.8 mmol), tetrakis(triphenylphosphine)palladium(0) (545 mg, 0.4 mmol), lithium chloride (2.6 g, 61.4 mmol) and 2.6-di-*t*-butyl-4-methylphenol (catalyst) in 1.4-dioxane (90 ml) was heated overnight at 100°C under nitrogen. The catalyst was filtered (Celite) and the filtrate was concentrated. The residue was purified by chromatography on silica gel eluted with ethylacetate/hexane 1:50. Pure fractions were pooled and concentrated to give 2.95 g (36%) of tributyl(4-acetylphenyl)stannane. ^{1}H-NMR ($CDCl_3$) δ 7.88 (d, 2H, J = 8 Hz), 7.59 (d, 2H, J = 8 Hz), 2.59 (s, 3H), 1.72–0.84 (m, 27H). ^{13}C-NMR ($CDCl_3$) δ 198.46 (C=O), 150.17 (C4'), 136.57 (C3'), 127.04 (C2'), 28.98 (C3), 27.26 (C2), 26.43 (CH_3), 13.58 (C4), 9.62 (C1). The signal due to C1' was obscured and signals from C-Sn couplings were observed but are not indicated. Anal $C_{20}H_{34}OSn$ (C, H).

Example of method I. (±)-8-(4'-Methoxyphenyl)-2-(dipropylamino)tetralin hydrochloride (±)-7

A mixture of (±)-2-(dipropylamino)-8-[(trifluoromethylsulfonyl)oxy]tetralin [21] ((±)-**5**; 1.0 g, 2.5 mmol), tributyl(4-methoxyphenyl)stannane (1.2 g, 3.02 mmol), tetrakis(triphenylphosphine)palladium(0) (87 mg, 0.075 mmol), and lithium chloride (330 mg, 7.75 mmol) in 1,4-dioxane (15 ml) and dimethylformamide (2 ml) was stirred at 120°C in a sealed

Table III. Novel 2-aminotetralin derivatives: effects on 5-HT and DA turnover in the rat brain.

Compound[a]	n	Hippocampus (%)			Striatum (%)		
		5-HIAA	5-HT	5-HIAA/5-HT	DOPAC	DA	DOPAC/DA
(*R*)-**1**	6	77±4**	118±5*	66±4**	107±6	94±6	115±7
(*R*)-**4**	4	92±11	107±5	86±5	119±9	122±6	98±9
(*S*)-**4**	4	72±6	83±6	85±6	102±12	116±8	89±13
(*R*)-**6**	4	108±4	82±6	127±7	105±7	98±5	118±
(*S*)-**6**	4	81±6	80±4	102±9	120±9	106±6	112±3
(*R*)-**7**	4	115±8	114±7	104±7	80±6	95±5	84±5
(*S*)-**7**	4	131±18	108±13	118±5	88±9	100±10	88±2
(*R*)-**8**	4	77±2**	102±6	74±4**	100±7	95±3	103±5
(*S*)-**8**	4	89±3	102±6	86±4	85±3	104±3	82±4
(*R*)-**9**	4	82±2**	105±2	80±1	92±16	105±15	87±7
(*S*)-**9**	4	102±1	101±2	104±2	80±5	90±5	88±4
(*R*)-**10**	4	113±5	109±2	97±4	92±6	100±3	92±6
(*S*)-**10**	4	100±8	112±5	88±6	90±6	108±3	84±6
(*R*)-**11**	4	78±10	119±5	63±7*	116±10	125±8	92±3
(*S*)-**11**	4	79±5	138±23	59±6*	94±9	105±9	90±3
(*R*)-**12**	4	97±4	102±4	96±3	99±9	94±6	105±7
(*S*)-**12**	3	98±3	113±2	87±1	104±6	101±1	101±6
(*R*)-**13**	4	84±2	102±3	83±3	123±7	104±4	120±2
(*S*)-**13**	4	92±4	104±6	89±6	79±8	108±5	74±6
(*R*)-**14**	4	76±8	90±3	83±7	79±6	100±8	81±4
(*S*)-**14**	4	92±3	93±2	98±4	119±5	92±3	131±5

[a]Compounds shown above were given at the dose 32 μmol/kg, sc except (*R*)-**1** (1 μmol/kg, sc). The values (means ± SEM) are percentages of control. Control levels for 5-HIAA, 5-HT and 5-HT turnover in hippocampus were respectively: 462 ± 43, 529 ± 26 and 1.24 ± 0.04 ng/g tissue ((*R*)-**1**, **4** and **11–14**), and 533 ± 17, 489 ± 19 and 1.09 ± 0.02 ng/g tissue (for the rest). Control levels for DOPAC, DA and DA turnover in striatum were respectively: 2076 ± 166, 9584 ± 596 and 0.22 ± 0.02 ng/g tissue ((*R*)-**1**, **4**, and **11–14**), and 2515 ± 122, 10219 ± 45 and 0.23 ± 0.01 ng/g tissue (for the rest). Statistics: Anova followed by the Tukey's studentized range test. $^*p \leq 0.05$, $^{**}p \leq 0.01$ *vs* control.

flask for 20 h. The catalyst was filtered off (Celite) and the filtrate was concentrated. The resulting residue was purified by means of chromatography on an alumina column with ether/light petroleum 1:20 as eluent. Pure fractions were pooled and concentrated. An ether solution of the product was treated with ethereal hydrogen chloride and allowed to stand at room temperature overnight affording 793 mg (85%) of (±)-**7** as a white solid. ^{1}H-NMR (CD_3OD) δ 7.28–6.89 (m, 7H), 3.82 (s, 3H), 3.77–3.62 (m, 1H), 3.35–2.92 (m, 8H), 2.39–2.29 (m, 1H), 2.05–1.58 (m, 5H), 1.06–0.87 (m, 6H). ^{13}C-NMR (CD_3OD) δ 160.50, 143.34, 136.89, 131.39, 131.32, 129.05, 128.55, 127.64, 114.91, 62.21, 55.83, 29.92, 29.56, 24.29, 19.66, 11.29.

Example of method II. (R)-8-(4'-Hydroxyphenyl)-2-(dipropylamino)tetralin oxalate (R)-8

A solution of (*R*)-**7** (1.67 g, 3.9 mmol) in freshly distilled 48% aqueous hydrobromic acid (80 ml) was heated at 120°C under nitrogen for 2 h. The reaction mixture was concentrated and partitioned between ice-cold aqueous saturated sodium bicarbonate and dichloromethane. The organic layer was dried (sodium sulfate), filtered and concentrated. The residue was treated with ethereal oxalic acid and the salt was crystallized from ether to afford 1.53 g (95%) of (*R*)-**8**. ^{1}H-NMR (CD_3OD) δ 7.21–6.73 (m, 7H), 3.79–3.58 (m, 1H), 3.36–2.79 (m, 8H), 2.41–1.49 (m, 6H), 1.03–0.82 (m, 6H). ^{13}C-NMR (CD_3OD) δ 157.88, 143.52, 136.75, 133.26, 131.35, 131.26, 128.97, 128.29, 127.52, 116.15, 62.08, 51.82, 29.86, 29.49, 24.21, 19.61, 11.27.

Example of method III. (±)-2-(Dipropylamino)-8-[4'-(trifluoromethanesulfonyloxy)phenyl]tetralin hydrochloride (±)-9

A solution of trifluoromethylsulfonic anhydride (295 mg, 1.04 mmol) in dichloromethane (5 ml) was added to a mixture of the base of (±)-**8** (225 mg, 0.69 mmol) and potassium carbonate (200 mg, 1.46 mmol) in dichloromethane (10 ml) kept at –78°C under nitrogen. The reaction temperature was allowed to reach 0°C over 1 h and the reaction was quenched by addition of an ice-cold aqueous saturated potassium carbonate solution. The mixture was partitioned between dichloromethane and water, and the organic layer was dried (potassium carbonate), filtered and concentrated. The residue was chromatographed on an alumina column eluted with ether/light petroleum 1:4. Pure fractions were collected, concentrated and treated with ethereal hydrogen chloride to give 220 mg (64%) of (±)-**9**. ^{1}H-NMR (CD_3OD) δ 7.62–6.98 (m, 7H), 3.88–3.52 (m, 1H), 3.35–2.90 (m, 8H), 2.52–1.44 (m, 6H), 1.09–0.88 (m, 6H). ^{13}C-NMR (CD_3OD) δ 152.35, 140.58, 136.17, 132.83, 129.74, 127.27, 124.40, 124.21, 110.13, 107.88, 56.15, 51.73, 30.36. 29.62, 24.24, 21.25, 10.90.

Table IV. Novel 2-aminotetralin derivatives: effects on behavior and 5-HTP and DOPA accumulation in reserpine-pretreated rats[a].

	Behavior[b]		5-HTP[c]		DOPA[c]
Compound	FPT	FBP	Hippocampus	Striatum	Striatum
Control	0/8	0/8			
(*R*)-**1**[d,e]	5/5	5/5	45 ± 2**	59 ± 3**	98 ± 9
(*R*)-**8**	0/5	5/5	60 ± 3**	65 ± 5**	104 ± 7
(*S*)-**8**	0/5	4/5	61 ± 3**	63 ± 6**	88 ± 6
(*R*)-**9**	0/5	2/5	79 ± 6	70 ± 3*	82 ± 8
(*S*)-**10**	0/4	4/4	61 ± 7**	60 ± 12**	96 ± 2
(*R*)-**11**	0/4	4/4	-	51 ± 5**,e	97 ± 6e
(*S*)-**11**	2/4	4/4	-	51 ± 3**,e	86 ± 7e
(*R*)-**13**	0/5	4/5	65 ± 3**	62 ± 5**	98 ± 5
(*S*)-**13**	0/5	5/5	61 ± 6**	64 ± 7**	98 ± 2

[a]The rats were pretreated with reserpine (5 mg/kg, sc) 18 h before the administration of test compounds (32 μmol/kg, sc). [b]The numbers of rats displaying the behavior out of the number of rats tested. FPT: forepaw treading; FBP: flat body posture. [c]The values (means ± SEM) are percentages of control. Control levels after pretreatment of reserpine were 168 ± 7.8 ng/g tissue (hippocampus) and 163 ± 6.7 ng/g tissue (striatum) for 5-HTP and 4327 ± 130 ng/g tissue (striatum) for DOPA. Control levels without pretreatment of reserpine were 146 ± 8 ng/g tissue (striatum) for 5-HTP and 1919 ± 99 ng/g tissue (striatum) for DOPA. [d]1.0 μmol/kg, sc. [e]Not reserpine pretreated.

Example of method IV. (±)-8-(4-Acetylphenyl)-2-(dipropylamino)tetralin hydrochloride (±)-10

A mixture of the base of (±)-**9** (100 mg, 0.22 mmol), tetramethyltin (51 mg, 0.29 mmol), dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) (8 mg, 0.009 mmol), lithium chloride (29 mg, 0.68 mmol), 2,6-di-*t*-butyl-4-methylphenol (catalyst) and molecular sieve (4 Å, 40 mg) in dimethylformamide (3 ml) was heated overnight at 120°C under an atmosphere of carbon monoxide with vigorous stirring. The catalyst was filtered off (Celite) and the filtrate was partitioned between a saturated aqueous potassium carbonate solution and ether. The ether layer was dried (potassium carbonate), filtered and concentrated. The residue was purified by chromatography on an alumina column eluted with ether/light petroleum 1:4 and subsequently on a silica-gel column eluted with ammonia-saturated ether/light petroleum 1:4. Pure fractions were pooled and converted into the hydrochloride which was recrystallized to afford 56 mg (63%) of (±)-**10**. ^{1}H-NMR (CD_3OD) δ 8.07 (d, 2H, *J* = 7.9 Hz), 7.49 (d, 2H, *J* = 8.2 Hz), 7.32–7.00 (m, 3H), 3.81–3.66 (m, 1H), 3.39–2.88 (m, 8H), 2.63 (s, 3H), 2.42–2.25 (m, 1H), 2.05–1.87 (m, 1H), 1.82–1.54 (m, 4H), 0.96 (t, 6H). ^{13}C-NMR (CD_3OD) δ 200.02, 147.56, 142.55, 137.25, 137.04, 131.09, 130.69, 129.65, 129.54, 128.66, 127.83, 62.10, 54.32, 53.57, 29.81, 29.58, 26.79, 24.17, 19.69, 11.29.

Example of method V. (S)-8-(2-Furyl)-2-(dipropylamino)tetralin oxalate (S)-11

A mixture of (*S*)-**5** (3.5 g, 9.22 mmol), tetrakis(triphenylphosphine)palladium(0) (426 mg, 0.37 mmol), lithium chloride (1.17 g, 27.7 mmol), tributyl(2-furyl)stannane (3.62 g, 10.14 mmol) in 140 ml dimethylformamide was stirred at 110°C for 20 min under nitrogen. The catalyst was filtered off (Celite) and the mixture was concentrated. The residue was diluted with ether and the ether solution was washed with a saturated aqueous potassium carbonate solution and with brine, dried (potassium carbonate) and concentrated. The residue was purified by chromatography on an alumina column with ether/petroleum ether 1:20 as eluent. The pure fractions were pooled and treated with a saturated ethereal solution of oxalic acid affording 2.50 g (70%) of (*S*)-**11**. ^{1}H-NMR ($CDCl_3$; free base) δ 7.59–7.33 (m, 2H), 7.26–6.88 (m, 2H), 6.56–6.37 (d,

Table V. Novel 2-aminotetralin derivatives: affinities for 5-HT_{1A} receptors.

Compound	5-HT_{1A}-Receptor affinity (K_i, nM)[a]	
	(R)-Enantiomer	(S)-Enantiomer
1[b]	1.3 (1.1-1.5)	1.8 (1.6-2.0)
4	7.9 (7.7-8.3)	24 (22-26)
6	10.8 (9.5-12,5)	13.1 (12-15)
7	20 (17-25)	59 (53-68)
8	12 (10-15)	8.8 (7.5-11)
9	18 (7.0-24)	46 (19-65)
10	12 (10-14)	24 (22-26)
11	9.3 (8.0-11)	1.8 (1.6-2.0)
12	8.4 (7.3-9.9)	5.5 (5.0-6.4)
13	6.6 (5.5-8.3)	5.6 (4.8-6.1)
14	5.7 (4.8-7.2)	13.8 (12-17)
(±)-**15**	30 (27-33)	
(±)-**17**	29 (27-32)	

[a]Range in parenthesis, *N* = 2. [b]From reference [21].

2H), 3.12–2.63 (m, 4H), 2.60–2.31 (m, 4H), 2.24–1.84 (m, 1H), 1.75–1.09 (m, 6H), 1.03–0.71 (t, 6H). ^{13}C-NMR ($CDCl_3$; free base) δ 152.35, 140.58, 136.17, 132.83, 129.74, 127.27, 124.40, 124.21, 110.13, 107.88, 56.15, 51.73, 30.36, 29.62, 24.24, 21.25, 10.90. IR (liquid film): 3060, 2958, 1450, 1375, 773, 730 cm^{-1}.

Example of method VI. (±)-8-[5-(3-Methyl-1,2,4-oxadiazole)-yl]-2-(dipropylamino)tetralin hydrochloride (±)-17
Pieces of sodium (32 mg, 1.39 mmol) were added to a suspension of 4 Å molecular sieve (100 mg) in 2.5 ml of 99.5% ethanol under nitrogen. Acetamide oxime (100 mg, 1.36 mmol) was added after the sodium had dissolved and (±)-methyl 2-(dipropylamino)tetralin-8-carboxylate (**16**) [21] (100 mg, 0.3 mmol) was added. The reaction mixture was refluxed under nitrogen for 30 h. The molecular sieve was filtered off and the solvent was removed under reduced pressure. The residue was partitioned between dichloromethane and water. The organic layer was washed with water, dried over magnesium sulfate, filtered and concentrated. The resulting residue was treated with ethereal HCl and the formed salt was recrystallized from acetone/ether to afford 67 mg (69%) of (±)-**17**. ^{1}H-NMR (CD_3OD) δ 7.98–7.90 (m, 1H), 7.49–7.33 (m, 2H), 3.91–3.76 (m, 1H), 3.48–2.97 (m, 8H), 2.45 (s, 3H), 2.47–2.33 (m, 1H), 2.06–1.75 (m, 5H), 1.06 (t, 6H). ^{13}C-NMR (CD_3OD) δ 177.32, 169.45, 139.21, 134.98, 134.84, 130.20, 128.77, 125.28, 62.24, 54.75, 30.71, 30.35, 24.49, 20.39, 12.24, 11.98.

Pharmacology

Male Sprague–Dawley rats (B & K, Stockholm) weighing 260–310 g were used. The animals were kept at room temperature (23 ± 1°C) with lights on between 06:00 and 18:00 h for at least a week before the experiment and were allowed food and water *ad libitum*. Each animal was only used once. All compounds were dissolved in 0.9% NaCl, occasionally with gentle warming in order to obtain complete dissolution, and injected subcutaneously (sc). The injection volume was 2 ml/kg. Control rats received the same number of saline injections at corresponding time intervals. Throughout, (*R*)-**1**·HCl (1.0 μmol/kg) was used as a positive control. All experiments were performed between 09:00 and 15:00 h.

Behavior, cage-leaving and body temperature
Screening data were typically collected with a dose of 32 μmol/kg, sc; occasionally other doses were chosen, *eg*, due to the known high potency of (*R*)-**1**. The rats were observed for 30 min after the injection of test compounds. Attention was paid to flat body posture and forepaw treading (5-HT motor syndrome). These behaviors were rated as absent or present. Cages containing two nonpretreated rats were placed next each other. The grid-covers were removed 12 min after injection of the tested compounds and the number of rats leaving their cages during the next 12 min were noted (cage-leaving response) [32]. Body temperature was measured before and at 30 min after the injection using an electric thermometer with the probe inserted into the colon, 3.5 cm from the anal orifice.

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 indications of changes in the 5-HT and DA turnover. Within 5–10 min after the last behavioral rating and body temperature measurement, the rats were decapitated (35–45 min after injection). Brain regions (hippocampus and corpus striatum) were rapidly dissected out and frozen until assayed. The accumulation of 5-hydroxytryptophan (5-HTP) and 3,4-dihydroxyphenylalanine (DOPA) were measured after NSD 1015 for estimation of the 5-HT and DA synthesis [44]. At 18 h after reserpine pretreatment, animals were first injected with test compounds, followed by injection of an inhibitor of aromatic L-amino acid decarboxylase, NSD 1015 (60 mg/kg, *ie* 287 μmol/kg, sc), and decapitated at 30 min thereafter. The hippocampus and corpus striatum were rapidly dissected out and frozen. The frozen samples were stored for no longer than one week. They 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, *ie* 18 600 *g*, 4°C, 10 min) and filtration, 20 μl supernatant was injected into a high-performance liquid chromatography with electrochemical detection (HPLC-EC) to analyze 5-HIAA, 5-HTP, 5-HT, DOPAC, DOPA and DA. The HPLC system consisted of PM-48 pump (Bioanalytical systems, BAS) with a CMA/240 autoinjector (injection volumes: 20 μl), a precolumn (15 x 3.2 mm, RP-18 Newguard, 7 μ), a column (100 x 4.6 mm, spheri-5, RP-18, 5 μ), an amperometric detector (LC-4B, BAS) with Ag/AgCl reference electrode and MF-2000 cell (BAS) 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 octylsulfate (40 mg/l) and 10% 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 out. The tissues (600–900 mg) from each rat were immediately homogenized in 15 ml 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 (39 800 *g*; Beckman centrifuge Palo Alto, CA, USA), the pellets were resuspended in the same buffer and homogenization and centrifugation repeated. The tissue homogenate was diluted to 8 mg/ml with the buffer, incubated for 10 min at 37°C and supplied with 10 mM pargyline (Sigma, Saint Louis, MO, USA) followed by reincubation for 10 min.

Incubation mixtures (2 ml) contained various concentrations of test compound (diluted in 50 mM Tris-HCl containing 5.7 mM ascorbic acid, pH 7.5), 2 nM [^{3}H]-**1** ([^{3}H]-8-hydroxy-2-(di-*n*-propylamino)tetralin·HBr, New England Nuclear, Dreieich, Germany and Research Biomedicals, Wayland, MA, USA), 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. Non-specific binding was measured by the addition of 10 μM 5-HT·HCl to the reaction mixture. 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 fiber filters with a Brandel Cell Harvester (Gaithersburg, MD, USA). The filters were washed twice with 5 ml ice-cold 50 mM Tris-HCl buffer, pH 7.5, and counted with 5 ml Ultima Gold (Packard Instrument Co, IL, USA) in a Beckman LS 3801 scintillation counter. The binding data were analyzed by non-linear regression using the Ligand program [45]. 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.

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