Derivatives of *cis*-2-Amino-8-hydroxy-1-methyltetralin: Mixed 5-HT$_{1A}$-Receptor Agonists and Dopamine D$_2$-Receptor Antagonists

Ye Liu,[†] Hong Yu,[‡] Nina Mohell,[§] Gunnar Nordvall,[†] Tommy Lewander,[‡] and Uli Hacksell*,[†]

Department of Organic Pharmaceutical Chemistry, Box 574, Uppsala Biomedical Centre, Uppsala University, S-751 23 Uppsala, Sweden, Department of Psychiatry, Ulleråker, Uppsala University, S-750 17 Uppsala, Sweden, and Department of Neuropharmacology, CNS Preclinical R&D, Astra Arcus, AB, S-151 85 Södertälje, Sweden

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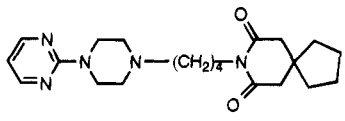
(1*S*,2*R*)-8-Hydroxy-1-methyl-2-(dipropylamino)tetralin [(1*S*,2*R*)-**3**] has been previously characterized as a selective and potent but partial 5-HT$_{1A}$-receptor agonist. In the present study, we have prepared derivatives of (1*S*,2*R*)- and (1*R*,2*S*)-**3** in which various C8-substituents have been introduced. In addition, the enantiomers of the *N*-isopropyl-*N*-*n*-propylamino derivative of **3** were prepared. The new derivatives were tested *in vivo* by use of behavioral and biochemical tests in rats. In addition, the affinity of the compounds was studied by competition experiments with [^{3}H]-8-OH-DPAT in rat brain tissue. The only new derivative which behaved like a selective 5-HT$_{1A}$-receptor agonist was the C8-carboxamide derivative (1*S*,2*R*)-**13**. The other active derivatives, including (1*S*,2*R*)-**3**, have more complicated pharmacological profiles and may be best characterized as mixed 5-HT$_{1A}$-receptor agonists/dopamine D$_2$-receptor antagonists.

Introduction

The neurotransmitter serotonin (5-hydroxytryptamine; 5-HT) is involved in a variety of physiological processes including the regulation of mood, sexual and feeding behaviors, and the sleep–wake cycle.[1] During the past 6 years, a steadily growing number of 5-HT-receptors has been characterized by use of pharmacological and molecular biological techniques. Presently, the diversity of 5-HT-receptors appears to be best described in terms of seven subgroups: 5-HT$_1$-, 5-HT$_2$-, and 5-HT$_4$–5-HT$_7$-receptors, which are G protein-coupled, and 5-HT$_3$-receptors, which are ligand-gated ion channels.[2] The 5-HT$_1$-receptor subfamily is characterized functionally by being negatively coupled to adenylyl cyclase. Thus, stimulation of a 5-HT$_1$-receptor decreases intracellular cAMP levels. The 5-HT$_{1A}$-receptor subtype, which is present postsynaptically in relation to the 5-HT neuron but also presynaptically, as a somatodendritic autoreceptor, is a novel target for putative antidepressants and anxiolytics. Interest in this area was fueled by the discovery that the anxiolytic agent buspirone (1) displays high affinity for 5-HT$_{1A}$-receptors.[3,4]



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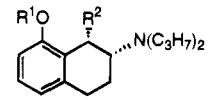

(*R*)-**2**: R^1=H, R^2=H
(1*S*,2*R*)-**3**: R^1=H, R^2=CH$_3$
(1*S*,2*R*)-**4**: R^1=R^2=CH$_3$

8-Hydroxy-2-(dipropylamino)tetralin (8-OH-DPAT; **2**), which was reported by Arvidsson et al.[5] to be a potent centrally active 5-HT-receptor agonist, is a selective 5-HT$_{1A}$-receptor ligand.[6–8] It has served as a lead compound in the search for compounds with similar pharmacological profiles but with improved pharmacokinetic properties (see, for example, refs 9 and 10) as well as for 5-HT$_{1A}$-receptor antagonists.[11] A large variety of 2-aminotetralin derivatives has been synthesized and characterized pharmacologically, and several indirect models which describe observed structure–activity relationships (SAR) have been deduced.[12–15]

One of the key derivatives in our indirect model for 5-HT$_{1A}$-receptor agonists[13] was the potent agonist (1*S*,2*R*)-ALK-3 [(1*S*,2*R*)-**3**].[16] Compound (1*S*,2*R*)-**3** has a limited conformational flexibility as compared to **2**,[12] and the selectivity and high 5-HT$_{1A}$-receptor affinity of **2** appeared to be retained in (1*S*,2*R*)-**3**.[16,17] A more detailed pharmacological evaluation has demonstrated that (1*S*,2*R*)-**3** may be best characterized as a partial 5-HT$_{1A}$-receptor agonist.[17] Similarly, (*S*)-**2** appears to be a partial 5-HT$_{1A}$-receptor agonist, whereas (*R*)-**2** behaves as a full agonist.[17] In contrast to the enantiomers of **2**, which display little stereoselectivity,[18] (1*S*,2*R*)-**3** behaves as a potent 5-HT$_{1A}$-receptor agonist in *ex vivo* biochemical and behavioral tests, whereas the 1*R*,2*S*-enantiomer is inactive.[16] In terms of 5-HT$_{1A}$-receptor affinity, the stereoselectivity of **3** is larger than 1000-fold whereas that of **2** is less than 2-fold.[17] This drastic increase in stereoselectivity which is achieved by introducing a *cis*-C1-methyl substituent in **2** has been ascribed to the steric bulk of the pseudoaxial methyl group which appears to prevent (1*R*,2*S*)-**3** from interacting optimally with an anchoring Asp-derived carboxylate of the 5-HT$_{1A}$-receptor.[13]

In the present report we describe the synthesis and pharmacological evaluation of some differently C8-substituted derivatives of **3**. The aim of the study was to increase our knowledge of the SAR of 2-aminotetralin derivatives interacting with 5-HT$_{1A}$-receptors. Specifically, we wanted to explore whether (a) the high affinity and stereoselectivity of **3** could be modified by a change of the C8-substituent and (b) the effect of the C8-substituent in **3** would be similar to that observed in **2**. In addition, we replaced one of the two *N*-propyl groups of **3** and the methoxy derivative **4** with an isopropyl group in order to evaluate the effect of *N*-alkyl group

[†] Department of Organic Pharmaceutical Chemistry, Uppsala University.
[‡] Department of Psychiatry, Uppsala University.
[§] CNS Preclinical R&D.
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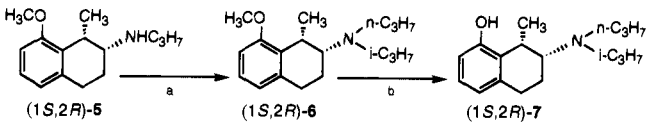
Scheme 1[a]



[a] Reagents: (a) *i*-PrI, K_2CO_3, $(i\text{-Pr})_2NEt$; (b) 48% HBr.

modification on the interaction with the 5-HT_{1A}-receptor. The new derivatives were investigated pharmacologically by use of behavioral and biochemical tests in rats. In addition, the affinities of the compounds for rat 5-HT_{1A}-receptors and human dopamine (DA) D_{2A}-receptors (selected compounds) were studied *in vitro*.

Chemistry

Our synthetic strategy was based on the accessability of the enantiopure antipodes of **5** (Scheme 1).[16] Following the procedure developed by Arvidsson,[16] we methylated 8-methoxy-2-tetralone and subsequently performed a reductive amination, the stereoselectivity (the cis/trans ratio was improved from 74:26[16] to 84:16) and yield (improvement from 38%[16] to 53%) of which were better than previously published. Racemic **5** was resolved into the enantiomers using the published protocol.[16]

Each of the enantiomers of **5** were readily converted into the corresponding enantiomer of the *N*-isopropyl-substituted methoxy and hydroxy derivatives **6** and **7** (Scheme 1). The enantiomers of **4** were prepared from those of **5** by treatment with base and iodopropane. A subsequent demethylation afforded the antipodes of hydroxyl compound **3**.[16] The enantiomers of the key intermediate **8** were synthesized from those of **3** in the presence of triflic anhydride and base according to the standard conditions.

The C8-substituent of the enantiopure triflates (1*S*,2*R*)- and (1*R*,2*S*)-**8** was converted into other groups by palladium-catalyzed reactions (Scheme 2). 2-Furyl derivative (1*S*,2*R*)-**9** was obtained by palladium-catalyzed coupling[19a] of (1*S*,2*R*)-**8** with 2-furylboronic acid.[19b] Phenyl ketone (1*S*,2*R*)-**10** was prepared from (1*S*,2*R*)-**8** by use of a palladium-catalyzed carbonylation in which trimethylphenyltin provided the phenyl group.[20] Methyl ketone (1*S*,2*R*)-**11** was produced by a Heck coupling of (1*S*,2*R*)-**8** with butyl vinyl ether followed by acid-catalyzed hydrolysis of the resulting enol ether.[21,22]

Palladium-catalyzed carbonylation of (1*S*,2*R*)-**8** in the presence of carbon monoxide and methanol or isopropylamine produced (1*S*,2*R*)-**12** and (1*S*,2*R*)-**13**, respectively.[23,24] However, these two reactions suffered from poor yields since equal amounts of the reduced side product (1*S*,2*R*)-**14** and the desired product were formed. This side reaction was not affected by a change of ligand from 1,3-bis(diphenylphosphino)propane (dppp) to 1,1'-bis(diphenylphosphino)ferrocene (dppf). It is likely that the steric bulk of the pseudoaxial C1-methyl group decreases the rate of the insertion of CO into the palladium−carbon bond or the subsequent transmetalation step since this would favor a palladium-catalyzed reduction. The hydride being donated may originate from the triethylamine present in the reaction mixture.[25] Protium derivative (1*S*,2*R*)-**14**, which is an interesting test compound as well as a side product in the carbonylation reactions, was prepared in a preparative scale from (1*S*,2*R*)-**8** by a Pd(II)-catalyzed reduction using formic acid as the proton donor.[26,27]

Although the enantiopurities of the target compounds were not determined experimentally, it is most likely that the high enantiopurities of the enantiomers of **3** are retained in the products of the palladium-catalyzed reactions since no epimerization, which would lead to readily detected trans derivatives, was observed. The unlikely process of racemization would require inversion of the stereogenic centres at both C1 and C2. Physical data of the novel compounds are presented in Table 1.

Pharmacology

Stimulation of somatodendritic 5-HT_{1A}-receptors on central 5-HT neurons with agonists such as **2** decreases the synthesis and release of 5-HT.[28] In the present study we have used the ratio of the brain tissue concentrations of 5-hydroxyindoleacetic acid (5-HIAA) over 5-HT as a measure of 5-HT turnover. Administration of a 5-HT_{1A}-agonist decreases this ratio because of the resulting decrease in 5-HT synthesis and release. The effects on brain DA turnover were also investigated by measuring DA and its acid metabolites, 3-methoxy-4-hydroxyphenylacetic acid [homovanillic acid (HVA)] and 3,4-dihydroxyphenylacetic acid (DOPAC), and the DOPAC over DA ratio.

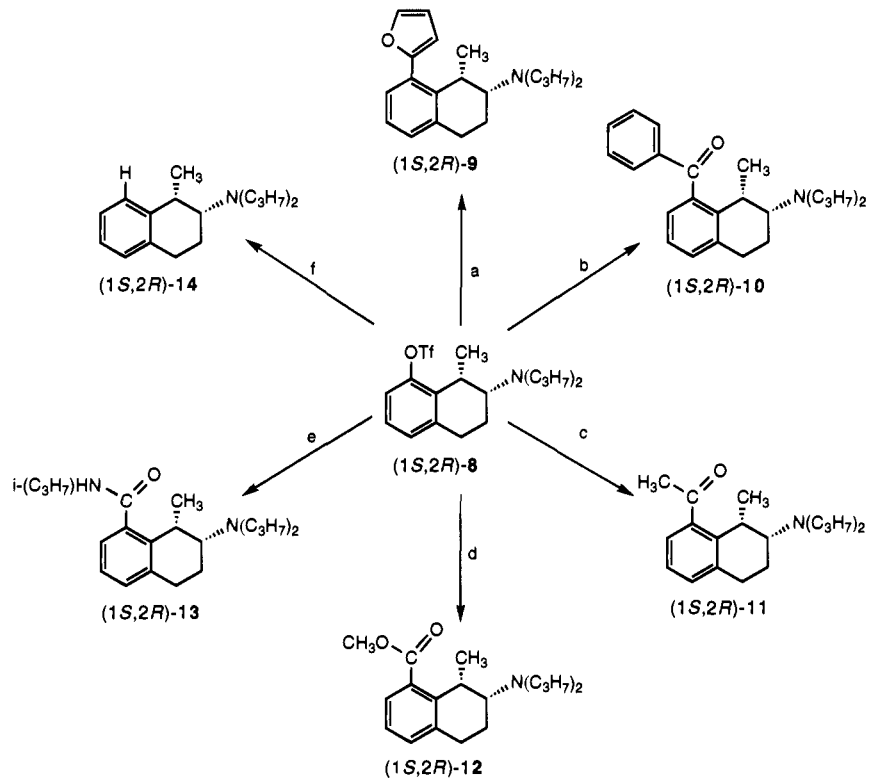
It is well-known that administration of 5-HTP or (±)-**2** induces a complex behavioral syndrome in rats (the serotonin, or 5-HT, syndrome).[29,30] 5-HT_{1A}-receptor agonists also decrease the body temperature[31] in rats and reduce the number of animals leaving their cages (cage-leaving response).[32] Therefore, we have studied the ability of the compounds to produce the behavioral syndrome, induce hypothermia, and inhibit the cage-leaving response. We have also determined the affinity of the compounds for 5-HT_{1A}-receptors using [^{3}H]-8-OH-DPAT as the radioligand. In addition, some of the compounds were evaluated for their affinities for human DA D_{2A}-receptors using [^{3}H]raclopride as the radioligand. The combination of these *in vivo* and *in vitro* data (Tables 2 and 3) allows for a preliminary evaluation of the pharmacological profile of the compounds.

Behavior, Body Temperature and Biochemistry *in Vivo*. Rats receiving the 5-HT_{1A}-receptor agonist (*R*)-**2** (1.0 μmol/kg sc; positive controls) exhibited the 5-HT syndrome (flat body posture and forepaw treading) between 4 and 25 min postinjection. The cage-leaving response was inhibited, and the body temperature was reduced by 2.6 °C. The 5-HT turnover (5-HIAA:5-HT) was decreased by 39% as compared to the saline-treated group, and the DA turnover (DOPAC:DA) was unaffected.

All test compounds were administered subcutaneously (sc) in a dose of 32 μmol/kg, if not stated otherwise. The previously studied[16] 8-hydroxy-substituted (1*S*,2*R*)-**3** induced the 5-HT syndrome and inhibited the cage-leaving response but induced only a weak hypothermia. The 5-HT turnover was decreased, and the DA turnover was increased. In contrast, (1*R*,2*S*)-**3** did not produce any significant effects *in vivo*.

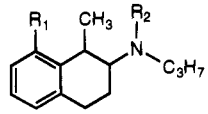
The C8-methoxy-substituted (1*S*,2*R*)-**4** induced the 5-HT syndrome and hypothermia (−2.5 °C) and inhibited the cage-leaving response. In addition, (1*S*,2*R*)-**4** significantly decreased 5-HT turnover and increased DA turnover. Whereas (1*R*,2*S*)-**4** neither induced the 5-HT syndrome nor reduced the 5-HT turnover, it induced hypothermia (−1.2 °C) and inhibited the cage-leaving response. The DA turnover and the levels of HVA were

Scheme 2[a]



[a] Reagents: (a) 2-furylboronic acid, $Pd(Ph_3)_4$, LiCl, 2 M Na_2CO_3, DMF; (b) $PhSnMe_3$, LiCl, $PdCl_2$(dppf), CO, DMF; (c) (1) butyl vinyl ether, $Pd(OAc)_2$, dppp, NEt_3, DMF; (2) 10% HCl; (d) $Pd(OAc)_2$, dppf, MeOH, NEt_3, CO, DMSO; (e) $Pd(OAc)_2$, dppp, NEt_3, *i*-$PrNH_2$, CO, DMF; (f) $Pd(OAc)_2$, dppf, NEt_3, HCOOH, DMF.

Table 1. Physical Data of Some 2-Amino-1-methyltetralin Derivatives



compound	R_1	R_2	mp (°C)	yield (%)	recrystn solvent[a]	$[\alpha]^{22}_D$	formula[b]
(1*S*,2*R*)-**6**	OCH_3	*i*-Pr	140–142	49	A	+34.5	$C_{18}H_{29}NO{\cdot}HCl{\cdot}H_2O$
(1*R*,2*S*)-**6**	OCH_3	*i*-Pr	141–143	38	A	−33.4	$C_{18}H_{29}NO{\cdot}HCl$
(1*S*,2*R*)-**7**	OH	*i*-Pr	255–257	98	B	+31.0	$C_{17}H_{27}NO{\cdot}HCl$
(1*R*,2*S*)-**7**	OH	*i*-Pr	255–257	98	B	−32.2	$C_{17}H_{27}NO{\cdot}HCl$
(1*S*,2*R*)-**8**	OTf	*n*-Pr	145–147	93	C	+4.3	$C_{18}H_{26}NO_3SF_3{\cdot}HCl$
(1*R*,2*S*)-**8**	OTf	*n*-Pr	145–147	96	C	−2.8	$C_{18}H_{26}NO_3SF_3{\cdot}HCl$
(1*S*,2*R*)-**9**	2-furyl	*n*-Pr	164–165	42	A	+40.1	$C_{21}H_{29}NO{\cdot}HCl$
(1*R*,2*S*)-**9**	2-furyl	*n*-Pr	165–167	47	A	−40.2	$C_{21}H_{29}NO{\cdot}HCl$
(1*S*,2*R*)-**10**	COPh	*n*-Pr	180–182	47	B	−33.1	$C_{24}H_{31}NO{\cdot}HCl$
(1*R*,2*S*)-**10**	COPh	*n*-Pr	179–180	54	B	+35.0	$C_{24}H_{31}NO{\cdot}HCl$
(1*S*,2*R*)-**11**	$COCH_3$	*n*-Pr	132–133	49	B	+7.7	$C_{19}H_{29}NO{\cdot}C_2H_2O_4$
(1*R*,2*S*)-**11**	$COCH_3$	*n*-Pr	130–131	41	A	−7.9	$C_{19}H_{29}NO{\cdot}C_2H_2O_4$
(1*S*,2*R*)-**12**	$COOCH_3$	*n*-Pr	161–162	26	B	+17.5	$C_{19}H_{29}NO_2{\cdot}HCl$
(1*R*,2*S*)-**12**	$COOCH_3$	*n*-Pr	161–163	18	B	−17.7	$C_{19}H_{29}NO_2{\cdot}HCl$
(1*S*,2*R*)-**13**	CONH(*i*-Pr)	*n*-Pr	210–212	23	B	−4.8	$C_{21}H_{34}N_2O{\cdot}HCl{\cdot}{}^1/_2H_2O$
(1*R*,2*S*)-**13**	CONH(*i*-Pr)	*n*-Pr	212–214	20	B	+4.8	$C_{21}H_{34}N_2O{\cdot}HCl$
(1*S*,2*R*)-**14**	H	*n*-Pr	179–180	62	C	+57.6	$C_{17}H_{27}N{\cdot}HCl$
(1*R*,2*S*)-**14**	H	*n*-Pr	179–180	20[c]	C	−56.9	$C_{17}H_{27}N{\cdot}HCl$

[a] A: ether. B: methanol/ether. C: acetonitrile/ether. [b] Elemental analyses were within 0.4% of the theoretical values. [c] Obtained as side product from the reaction for (1*R*,2*S*)-**13**.

significantly decreased by 31% and 47%, respectively, after administration of (1*R*,2*S*)-**4**. None of the enantiomers of the C8-trifluorosulfonyl- and -benzoyl-substituted analogues **8** and **10** induced the 5-HT syndrome, and the cage-leaving response and body temperature were unaffected. However, (1*S*,2*R*)-**10** but not (1*R*,2*S*)-**10** induced the 5-HT syndrome and hypothermia after iv administration (32 μmol/kg) (data not shown). None of the enantiomers of **8** and **10** changed the 5-HT or DA turnover.

The C8-substituted acetyl and carboxamide derivatives (1*S*,2*R*)-**11** and (1*S*,2*R*)-**13** behaved as 5-HT_{1A}-receptor agonists by inducing the 5-HT syndrome, inhibiting the cage-leaving response, and producing hypothermia. Interestingly, (1*S*,2*R*)-**11** had no effect at all on 5-HT turnover, whereas (1*S*,2*R*)-**13** induced the expected reduction. DA turnover as well as HVA and DOPAC levels were significantly increased by (1*S*,2*R*)-**11** but not by (1*S*,2*R*)-**13**. The (1*R*,2*S*)-enantiomers of **11** and **13** were inactive with respect to serotonergic

Table 2. *cis*-2-Amino-1-methyltetralin Derivatives: Affinities for 5-HT_{1A}- and D_{2A}-Receptors and Effects on Behavior and Body Temperature in Rats[a]

compound	5-HT_{1A}-receptor affinity			D_{2A}-receptor affinity			behavior			change of body[b] temperature (°C)
	K_i (nM)	SEM/range	n	K_i (nM)	SEM	n	FPT	FBP	cage leaving	
saline	–	–		–			0/7	0/7	6/7	0.1 ± 0
(*R*)-**2**	4.1[c]						7/7[d]	7/7[d]	0/7	−2.6 ± 0.2**
(1*S*,2*R*)-**3**	2.9[c]			30.0	±4.0	3	4/4[d]	4/4[d]	0/4	−0.2 ± 0.1
(1*R*,2*S*)-**3**	2920[c]						0/4	0/4	2/4	−0.3 ± 0.2
(1*S*,2*R*)-**4**	6.0	±0.05[e]	2	33.9	±7.7	3	4/4[d]	4/4[d]	0/4	−2.5 ± 0.2**
(1*R*,2*S*)-**4**	285	±35[e]	2	1050	±260	3	0/4	0/4	1/4	−1.2 ± 0.2**
(1*S*,2*R*)-**6**	116	104−131[f]	1				0/4	0/4	2/4	0.1 ± 0
(1*R*,2*S*)-**6**	1420	±643[e]	3				0/4	0/4	2/4	0.0 ± 0.1
(1*S*,2*R*)-**7**	81	72−93[f]	1	614	±67	2	0/5	0/5	4/5	−0.3 ± 0.1
(1*R*,2*S*)-**7**	6650	4055−1838[f]	1				0/5	0/5	4/5	−0.1 ± 0.1
(1*S*,2*R*)-**8**	6.7	5.25−9.06[f]	1	124	±14	3	0/5	0/5	4/5	0.0 ± 0
(1*R*,2*S*)-**8**	236	185−326[f]	1				0/5	0/5	3/5	0.1 ± 0
(1*S*,2*R*)-**9**	>1000		1				0/4	0/4	3/4	0.1 ± 0
(1*R*,2*S*)-**9**	44.0	39−52[f]	1				0/4	0/4	3/4	0.1 ± 0
(1*S*,2*R*)-**10**	2.6						0/5	0/5	4/5	0.1 ± 0
(1*R*,2*S*)-**10**	7.6	±0.4[e]	2				0/5	0/5	4/5	0.0 ± 0
(1*S*,2*R*)-**11**	0.56	±0.01[e]	2	40	±7.9	3	5/5[d]	5/5[d]	0/5	−1.7 ± 0.1**
(1*R*,2*S*)-**11**	138	±9.2[e]	2				0/4	0/4	3/4	0.1 ± 0.1
(1*S*,2*R*)-**12**	18	12−40[f]	1	58.8	±11	3	5/5[d]	5/5[d]	0/5	−2.7 ± 0.1**
(1*R*,2*S*)-**12**	417	±177[e]	3				0/5	0/5	2/5	−0.1 ± 0
(1*S*,2*R*)-**13**	38	33−45[f]	1				5/5[d]	5/5[d]	0/5	−2.5 ± 0.2**
(1*R*,2*S*)-**13**	>1000		1				0/5	0/5	4/5	0.0 ± 0
(1*S*,2*R*)-**14**	49	42−61[f]	1	87	±10	3	0/5	3/5[g]	1/5	−0.7 ± 0.1**
(1*R*,2*S*)-**14**	>1000		1				0/5	0/5	3/5	−0.1 ± 0.1

[a] Shown is the number of rats displaying the behavior out of the number of rats tested or the change of body temperature from the preinjection value. Compounds were given at a dose of 32 μmol/kg sc except (*R*)-**2** (1.0 μmol/kg sc). Abbreviations: FPT, forepaw treading; FBP, flat body posture. Statistics: Fisher's exact probability test was used for the behavioral data. [b] Tukey's studentized range (HSD) test was used for changes of body temperature values. **$p \leq 0.01$ vs saline-treated animals. [c] From ref 17. [d] $p \leq 0.005$ vs saline-treated animals. [e] SEM. [f] Range. [g] $p \leq 0.05$ vs saline-treated animals.

effects *in vivo*. Compound (1*R*,2*S*)-**13** reduced the DOPAC levels and induced biting and chewing, which are typical dopaminergic behaviors.

The enantiomers of the 2-furyl-substituted compound **9** were inactive in most of the assays. The 5-HIAA levels were significantly increased after (1*R*,2*S*)-**9**, but this change was not large enough to affect the 5-HT turnover.

The methyl ester (1*S*,2*R*)-**12** behaved as a 5-HT_{1A}-receptor agonist. In addition, DA turnover was significantly increased. The 1*R*,2*S*-enantiomer, however, increased 5-HT turnover but had neither other serotonergic nor dopaminergic actions.

The deoxy analogue (1*S*,2*R*)-**14** behaved as a weak 5-HT agonist with regard to behavior and body temperature. However, (1*S*,2*R*)-**14** did not reduce 5-HT turnover. Instead, it increased DA turnover and the levels of DOPAC and HVA. The 1*R*,2*S*-enantiomer did not induce any serotonergic or dopaminergic actions.

The *N*-isopropyl-*N*-propyl-substituted **6** and **7** were inactive in the various models at the doses tested with the exception of (1*S*,2*R*)-**7**. Compound (1*S*,2*R*)-**7** significantly reduced the DA levels by about 26% and increased the DA turnover by 55% and HVA levels by about 125%.

The 5-HT_{1A}-receptor binding data are shown in Table 2. In most cases, compounds with high to moderate affinity for the 5-HT_{1A}-receptors were also active *in vivo*. However, there were some notable exceptions. Thus, whereas (1*S*,2*R*)-**8**, (1*R*,2*S*)-**9**, and (1*S*,2*R*)- and (1*R*,2*S*)-**10** were inactive as 5-HT_{1A}-receptor agonists *in vivo* in the dose tested, they all displayed fair *in vitro* affinity for the 5-HT_{1A}-receptors (K_i = 2.6−44 nM). In contrast, (1*R*,2*S*)-**12** increased 5-HT turnover but only possessed fairly low affinity (K_i = 143 nM) for the 5-HT_{1A}-receptor.

Six compounds, (1*S*,2*R*)-**3**, -**4**, -**7**, -11, -**12**, and -**14**, increased the DA turnover; consequently, the affinities of these compounds for DA D_2-receptors were determined (K_i = 27−614 nM).

Discussion

The present series of C8-substituted derivatives exhibits pharmacological characteristics which makes it distinctly different from the corresponding C1-unsubstituted analogues.[33−35] It is of particular interest that the pharmacology of the lead compound (1*S*,2*R*)-**3** is more complicated than previously believed.[16,36] In reserpinized rats, (1*S*,2*R*)-**3** potently decreases brain 5-HTP accumulation without affecting DOPA accumulation following decarboxylase inhibition and induces a 5-HT syndrome although not as potently as **2**.[16] Further, (1*S*,2*R*)-**3** has been characterized as a partial postsynaptic 5-HT_{1A}-receptor agonist because it was able to attenuate the behavioral effects of racemic **2**.[36]

In the present study we used normal and non-reserpine-pretreated[16] animals in the *in vivo* assays. As expected from a 5-HT_{1A}-receptor agonist, (1*S*,2*R*)-**3** produced the 5-HT behavior, inhibited the cage-leaving response, and decreased the rat brain 5-HT turnover (Tables 2 and 3). However, in contrast to the full agonist (*R*)-**2**, which is a potent hypothermic agent, (1*S*,2*R*)-**3** did not induce a significant decrease in body temperature at a dose of 32 μmol/kg sc. This is noteworthy because (1*S*,2*R*)-**3** has high affinity for 5-HT_{1A}-receptors and the dose of (1*S*,2*R*)-**3** was much higher than that of (*R*)-**2**. The present study showed that (1*S*,2*R*)-**3** significantly and markedly increased DA turnover, which was unaffected by (*R*)-**2** at the dose tested.

An increase in DA turnover may reflect DA D_2-receptor antagonism, and such a pharmacological profile is not revealed in reserpinized animals. In fact, when the affinity of (1*S*,2*R*)-**3** for [^{3}H]raclopride-labeled human DA D_{2A}-receptors was measured, it turned out to

Table 3. Effects of the *cis*-2-Amino-1-methyltetralin Derivatives on Metabolism and Turnover of 5-HT and DA in the Rat Brain *in Vivo*[a]

		hippocampus			striatum			
compound	*n*	5-HIAA	5-HT	5-HIAA/5-HT	HVA	DOPAC	DA	DOPAC/DA
(*R*)-**2**	12	80 ± 3	130 ± 3*	61 ± 1**	105 ± 3	109 ± 4	108 ± 4	102 ± 5
(1*S*,2*R*)-**3**	4	88 ± 3	121 ± 7	72 ± 2**	196 ± 3**	225 ± 5**	83 ± 1	275 ± 7**
(1*R*,2*S*)-**3**	4	104 ± 6	109 ± 7	95 ± 5	96 ± 4	118 ± 6	107 ± 7	112 ± 6
(1*S*,2*R*)-**4**	4	76 ± 4	108 ± 3	70 ± 4**	121 ± 11	134 ± 13	89 ± 4	151 ± 7**
(1*R*,2*S*)-**4**	4	79 ± 7	81 ± 5	96 ± 9	53 ± 5	80 ± 4	118 ± 7	69 ± 2*
(1*S*,2*R*)-**6**	4	104 ± 3	86 ± 2	116 ± 6	105 ± 11	102 ± 9	99 ± 6	102 ± 4
(1*R*,2*S*)-**6**	4	110 ± 4	87 ± 4	124 ± 5	90 ± 6	96 ± 3	103 ± 4	94 ± 4
(1*S*,2*R*)-**7**	6	93 ± 2	96 ± 3	97 ± 3	225 ± 5**	116 ± 6	74 ± 3	155 ± 6**
(1*R*,2*S*)-**7**	5	79 ± 9	97 ± 6	80 ± 5	100 ± 4	86 ± 9	110 ± 5	77 ± 6
(1*S*,2*R*)-**8**	5	87 ± 2	105 ± 2	82 ± 3	102 ± 4	105 ± 4	108 ± 3	97 ± 2
(1*R*,2*S*)-**8**	5	91 ± 9	97 ± 6	80 ± 5	99 ± 4	107 ± 7	107 ± 4	99 ± 7
(1*S*,2*R*)-**9**	4	111 ± 9	110 ± 5	101 ± 11	107 ± 7	116 ± 6	91 ± 3	128 ± 11
(1*R*,2*S*)-**9**	4	121 ± 7*	108 ± 6	107 ± 3	109 ± 4	102 ± 10	103 ± 4	98 ± 6
(1*S*,2*R*)-**10**	5	92 ± 12	101 ± 7	89 ± 8	111 ± 6	117 ± 9	105 ± 6	110 ± 4
(1*R*,2*S*)-**10**	5	114 ± 2	93 ± 3	123 ± 5	97 ± 5	112 ± 8	102 ± 7	109 ± 5
(1*S*,2*R*)-**11**	5	96 ± 4	99 ± 2	97 ± 2	203 ± 6**	192 ± 14**	95 ± 4	200 ± 12**
(1*R*,2*S*)-**11**	4	93 ± 7	99 ± 3	93 ± 5	93 ± 9	103 ± 6	95 ± 7	110 ± 1
(1*S*,2*R*)-**12**	5	78 ± 6	122 ± 6	64 ± 3**	194 ± 12**	167 ± 12**	112 ± 7	152 ± 10**
(1*R*,2*S*)-**12**	5	112 ± 4	86 ± 2	131 ± 4*	104 ± 7	97 ± 8	96 ± 7	103 ± 3
(1*S*,2*R*)-**13**	3	66 ± 1**	123 ± 1	54 ± 1**	94 ± 5	74 ± 5	99 ± 6	76 ± 1
(1*R*,2*S*)-**13**	4	97 ± 15	104 ± 8	92 ± 8	76 ± 4	59 ± 4*	82 ± 7	74 ± 3
(1*S*,2*R*)-**14**	5	92 ± 3	94 ± 4	98 ± 2	168 ± 6**	152 ± 7*	95 ± 5	164 ± 11**
(1*R*,2*S*)-**14**	4	112 ± 10	107 ± 1	104 ± 8	111 ± 9	92 ± 4	113 ± 6	81 ± 4

[a] The values are percentages of controls, means ± SEM. Control levels for compounds **7**–**10** and **12**–**14**: hippocampus, 5-HIAA = 387 ± 18 ng/g, 5-HT = 455 ± 12 ng/g; striatum, DA = 13.2 ± 0.8 μg/g, DOPAC = 1938 ± 188 ng/g, HVA = 1215 ± 63 ng/g. Control level for compounds **2**–**4**, **6**, and 11: hippocampus, 5-HIAA = 508 ± 25 ng/g, 5-HT = 560 ± 33 ng/g; striatum, DA = 10.9 ± 0.1 μg/g, DOPAC = 1780 ± 193 ng/g, HVA = 1110 ± 41 ng/g. Statistics: ANOVA followed by Tukey's studentized range (HSD) test. *$P \leq 0.05$; **$p \leq 0.01$ vs control.

have a rather high affinity for this receptor (Table 2), the affinity being only slightly lower than that of the established DA D_2-receptor antagonist (1*S*,2*R*)-UH-232.[37-39] Thus, the profile of (1*S*,2*R*)-**3** is not that of a selective, partial 5-HT_{1A}-receptor agonist. Instead, (1*S*,2*R*)-**3** may be best characterized as a mixed partial 5-HT_{1A}-receptor agonist/DA D_2-receptor antagonist. This interpretation is supported by an *in vivo* microdialysis study[36b] in which (1*S*,2*R*)-**3** induced a dose-dependent increase in hippocampal DOPAC output and a decrease in 5-HT and 5-HIAA output.

In a previous study,[16] the racemate of the C8-methoxy-substituted **4** was shown to potently decrease the accumulation of 5-HTP in reserpinized rats. In addition, it decreased the accumulation of DOPA in limbic and striatal rat brain regions, indicating that **4** had DA-receptor-stimulating properties. In the present study, (1*S*,2*R*)-**4** behaved essentially as the phenolic (1*S*,2*R*)-**3**. It induced an increase in DA turnover, but (1*S*,2*R*)-**4** produced hypothermia whereas (1*S*,2*R*)-**3** did not. Thus, (1*S*,2*R*)-**4** appears to be a mixed 5-HT_{1A}-receptor agonist/DA D_2-receptor antagonist. This interpretation was supported by the fairly high affinity of (1*S*,2*R*)-**4** for 5-HT_{1A}- (K_i = 6 nM) and DA D_{2A}- (K_i = 34 nM) receptors.

As noted previously, the stereoselectivity of **3** is very high, the 1*R*,2*S*-enantiomer being inactive in the assays performed. In contrast, the 1*R*,2*S*-enantiomer of **4**, which has much lower affinity for 5-HT_{1A}-receptors than the antipode, induced a weak hypothermia but did not induce any behavioral and biochemical effects in the rats. It did, however, decrease the DA turnover although its affinity for DA D_{2A}-receptors is low (K_i = 1050 nM). The hypothermia may be related to its dopaminergic action. Although our data does not allow a final pharmacological classification, (1*S*,2*R*)-**3**, (1*S*,2*R*)-**4**, and the methyl ester (1*S*,2*R*)-**12** produce similar effects in the various assays and thus appear to have similar pharmacological profiles.

The C8-acetyl derivative (1*S*,2*R*)-**11** behaves as a 5-HT_{1A}-receptor agonist in the behavioral and biochemical assays, but it does not affect 5-HT turnover. The lack of ability of (1*S*,2*R*)-**11** to induce changes in 5-HIAA and 5-HT levels is surprising since it has high affinity for 5-HT_{1A}-receptors. In contrast, the affinity of (1*S*,2*R*)-**11** for DA D_{2A}-receptors (K_i = 40 nM) is reflected in an increased DA turnover, indicating that it may be a DA-receptor antagonist. Also (1*S*,2*R*)-**14** appears to be best characterized as a DA D_{2A}-receptor antagonist as it shows a moderate affinity for DA D_{2A}-receptors and induces an increase in DA turnover. However, it also binds to 5-HT_{1A}-receptors, induces a weak decrease in body temperature, and produces flat body posture in some rats, indicating that the lack of response in some models may be related to low 5-HT_{1A}-receptor agonist potency. The only C1-substituted compound in the present study which behaves like a selective and potent 5-HT_{1A}-receptor agonist, without concomitant dopaminergic effects, is the carboxamide derivative (1*S*,2*R*)-**13**. The 5-HT_{1A}-receptor affinity of this derivative is, however, considerably lower than that of (*R*)-**2**.

As noted above, the increase in DA turnover induced by (1*S*,2*R*)-**3**, (1*S*,2*R*)-**4**, (1*S*,2*R*)-**7**, (1*S*,2*R*)-**11**, (1*S*,2*R*)-**12**, and (1*S*,2*R*)-**14** (Table 3) and their affinity for DA D_{2A}-receptors (Table 2) indicate that this series of compounds acts as DA D_{2A}-receptor antagonists. It is noteworthy that addition of a *cis*-C1-methyl substituent to (*R*)-**2**, a compound which is a very weak DA D_{2A}-receptor agonist, considerably increases the DA D_{2A}-receptor affinity and appears to abolish efficacy.

In this context it is of interest to compare the structure of (1*S*,2*R*)-**4** with that of the DA D_2-receptor antagonist (1*S*,2*R*)-UH-232[38,39] and that of (*R*)-**2** with the DA D_2-receptor agonist (*R*)-7-OH-DPAT[40] (Figure 1). The four compounds have the same absolute con-

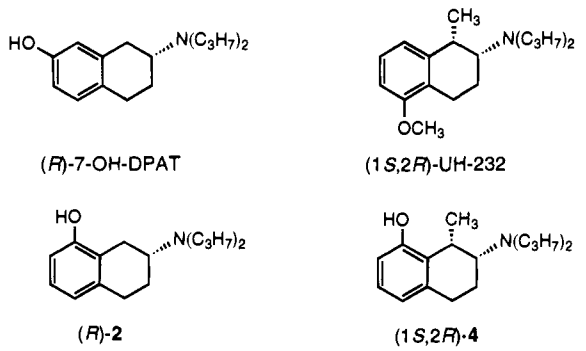


Figure 1. Structural comparison of four compounds with different pharmacological profiles. (*R*)-7-OH-DPAT and (*R*)-**2** are potent and selective DA- and 5-HT_{1A}-receptor agonists, respectively. In addition, (*R*)-**2** has low affinity for D_2-receptors. The methyl-substituted (1*S*,2*R*)-UH-232 and (1*S*,2*R*)-**4** act as antagonists on D_2-receptors and, in addition, (1*S*,2*R*)-**4** is a potent 5-HT_{1A}-receptor agonist.

figuration at C2, and the antagonists differ from the agonists in having a cis-positioned methyl group in the C1-position of the tetralin moiety. As indicated by docking experiments in which agonists and antagonists were allowed to interact with a model of the binding site of the DA D_{2A}-receptor,[41] these structural similarities and differences are reflected in different modes of DA D_2-receptor interactions of the agonists and antagonists.

The ability of the 5-HT_{1A}-receptor agonist (*R*)-**2** to stimulate and bind with low affinity to DA D_2-receptors is indicated by docking experiments (Figure 2); an edge to face interaction between the aromatic ring of the ligand and Phe 390 is essential for agonist activity, and the aromatic ring of (*R*)-**2** readily forms such an interaction, while the protonated nitrogen interacts favorably with Asp 114. The distance from the hydroxyl group of (*R*)-**2** to Ser 193 is, however, too long (5.3 Å) for the formation of a strong hydrogen bond, and this rationalizes the low affinity of (*R*)-**2** for DA D_2-receptors.

The partial but potent 5-HT_{1A}-receptor agonist (1*S*,2*R*)-**4** does not fit into the agonist binding site of the DA D_2-receptor because the steric bulk of the C1-methyl group prevents a proper interaction of the protonated nitrogen with Asp 114. Instead, (1*S*,2*R*)-**4** binds in the same mode to the receptor as the DA D_2-receptor antagonist (1*S*,2*R*)-UH-232.[39,41] In this mode of interaction (Figure 3), the aromatic ring can not interact with Phe 390 but another aromatic interaction, with His 393, is favorable. Further, in the antagonist mode of binding of (1*S*,2*R*)-**4**, the C1-methyl group is located in a lipophilic pocket, the borders of which are defined by Val 111, Leu 171, Phe 110, and Asp 114.

Experimental Section

Chemistry. General Comments. Routine ^1H and ^{13}C NMR spectra were recorded on JEOL FX 90Q or JNM-EX270 spectrometers and 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 analysis (C, H, and N), wich 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 1 (Schemes 1 and 2). Identical conditions were used for the preparation of both enantiomers.

(1*S*,2*R*)-8-Methoxy-1-methyl-2-(*N*-isopropyl-*N*-propylamino)tetralin Hydrochloride [(1*S*,2*R*)-6]. A mixture of (1*S*,2*R*)-8-methoxy-1-methyl-2-(propylamino)tetralin [(1*S*,2*R*)-**5**][16] (500 mg, 2.15 mmol), 2-iodopropane (400 mg, 2.35 mmol), K_2CO_3 (322 mg, 2.35 mmol), and diisopropylethylamine (280 mg, 2.35 mmol) in a few drops of CH_3CN was heated at 80 °C for 2 weeks. Ether was added, and the solid K_2CO_3 was filtered off. The filtrate was concentrated and purified by chromatography on alumina eluted with ether/petroleum ether (1:8). The eluted fractions were concentrated and purified further on a silica gel column eluted with ammonia-saturated ether/petroleum ether (1:4). Pure fractions were pooled and treated with ethereal HCl to give (1*S*,2*R*)-**6**. ^1H NMR (CD_3OD): δ 7.14 (t, 1H, *J* = 7.9 Hz), 6.79 (d, 1H, *J* = 7.9 Hz), 6.72 (d, 1H, *J* = 7.9 Hz), 4.00–3.92 (m, 1H), 3.84 (s, 3H), 3.71–3.54 (m, 2H), 3.41–3.22 (m, 1H), 3.20–3.08 (m, 1H), 3.07–3.02 (m, 2H), 2.26–2.04 (m, 2H), 1.92–1.76 (m, 2H), 1.46–1.36 (m, 6H), 1.29 (d, 3H, *J* = 6.9 Hz), 1.05 (t, 3H, *J* = 7.3 Hz). ^{13}C NMR (CD_3OD): δ 157.63, 135.82, 128.69, 128.57, 121.90, 108.80, 66.74, 63.78, 55.84, 51.73, 30.91, 29.40, 21.49, 20.63, 17.02, 16.37, 15.44, 11.43.

(1*S*,2*R*)-8-Hydroxy-1-methyl-2-(*N*-isopropyl-*N*-propylamino)tetralin Hydrochloride [(1*S*,2*R*)-7]. A solution of (1*S*,2*R*)-**6** (160 mg, 0.51 mmol) in 30 mL of 48% hydrobromic acid was heated at 120 °C under nitrogen for 2 h. The reaction mixture was concentrated and then partitioned between a saturated aqueous $NaHCO_3$ solution and CH_2Cl_2. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography on silica gel using ammonia-saturated ether/petroleum ether (1:1) as eluent. Pure fractions were pooled and treated with ethereal hydrogen chloride to give the corresponding hydrochloride which was recrystallized to afford (1*S*,2*R*)-**7**. ^1H NMR (CD_3OD): δ 6.97 (dd, 1H), 6.62–6.59 (m, 2H), 4.02–3.90 (m, 1H), 3.68–3.50 (m, 2H), 3.38–3.24 (m, 1H), 3.18–3.08 (m, 1H), 3.03–2.98 (m, 2H), 2.30–2.12 (m, 2H), 1.88–1.78 (m, 2H), 1.45–1.36 (m, 6H), 1.31 (d, 3H, *J* = 6.6 Hz), 1.06 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (CD_3OD): δ 155.56, 135.88, 128.48, 127.28, 120.74, 113.30, 64.26, 55.92, 51.81, 31.21, 29.52, 21.62, 20.90, 17.11, 16.35, 15.02, 11.43.

(1*R*,2*S*)-1-Methyl-2-(dipropylamino)-8-[[(trifluoromethyl)sulfonyl]oxy]tetralin Hydrochloride [(1*R*,2*S*)-8]. A solution of triflic anhydride (5.76 g, 20.4 mmol) in CH_2Cl_2 (20 mL) was slowly added under nitrogen to a precooled (−78 °C) mixture of (1*R*,2*S*)-8-hydroxy-1-methyl-2-(dipropylamino)-tetralin[16] [(1*R*,2*S*)-**3**; 2.67 g, 10.2 mmol], collidine (1.24 g, 10.2 mmol), and K_2CO_3 (2.82 g, 20.4 mmol) in CH_2Cl_2 (30 mL). The cooling was interrupted, the reaction mixture was concentrated, and the residue was partitioned between saturated aqueous K_2CO_3 and CH_2Cl_2. The organic layer was dried (K_2CO_3), filtered, and concentrated. The residue was chromatographed on an alumina column eluted with ether/petroleum ether (1:20). Pure fractions were pooled and concentrated to afford (1*R*,2*S*)-**8** which was converted into the hydrochloride and recrystallized. ^1H NMR ($CDCl_3$; base): δ 7.09 (m, 3H), 3.52–3.21 (m, 1H), 3.10–2.46 (m, 7H), 2.09–1.78 (m, 2H), 1.71–1.29 (m, 4H), 1.14 (d, 3H, *J* = 6.9 Hz), 0.88 (t, 6H). ^{13}C NMR ($CDCl_3$; base): δ 147.96, 138.95, 135.70, 128.82, 126.84, 118.41, 118.72 (q, *J* = 320 Hz, CF_3), 58.99, 52, 84, 31.13, 29.71, 21.00, 20.63, 15.23, 11.80.

(1*R*,2*S*)-8-Furyl-1-methyl-2-(dipropylamino)tetralin Hydrochloride [(1*R*,2*S*)-9]. A mixture of (1*R*,2*S*)-**8** (500 mg, 1.27 mmol), tetrakis(triphenylphosphino)palladium (37 mg, 32 μmol), 2-furylboronic acid[19] (183 mg, 1.9 mmol), LiCl (108 mg, 2.54 mmol), and 2 M aqueous $NaHCO_3$ (1.9 mL, 3.81 mmol) in EtOH (3 mL) and ether (12 mL) was heated at 95 °C under nitrogen for 1 day. The reaction mixture was concentrated and partitioned between ether and saturated aqueous K_2CO_3. The organic layer was dried (K_2CO_3), filtered, and concentrated. The residue was purified by column chromatography on alumina with ether/petroleum ether (1:12) as eluent. Pure fractions were pooled and treated with ethereal hydrogen chloride. After standing overnight in ether, crystals of (1*R*,2*S*)-**9** formed. ^1H NMR (CD_3OD): δ 7.64 (m, 1H), 7.43–7.11 (m, 3H),

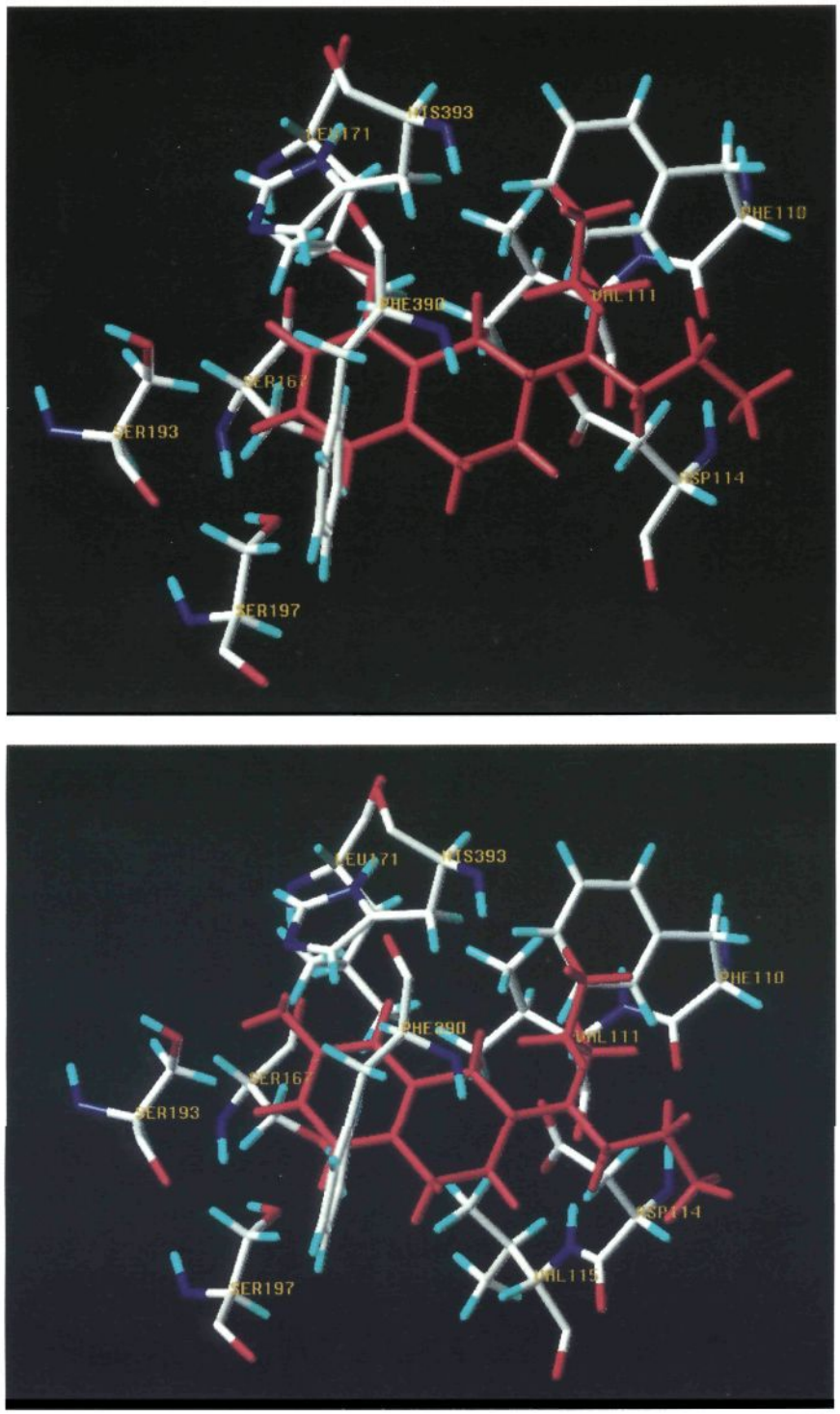


Figure 2. Docking of the weakly binding (*R*)-**2** (top) and the potent DA D_2-receptor agonist (*R*)-7-OH-DPAT (bottom) with a model of the DA D_2-receptor binding site.[41] (*R*)-7-OH-DPAT but not (*R*)-**2** forms a hydrogen bond with Ser 193.

6.59 (m, 2H), 4.08−3.84 (m, 1H), 3.81−3.49 (m, 1H), 3.41−3.00 (m, 6H), 2.46−2.11 (m, 2H), 1.99−1.52 (m, 4H), 1.22 (d, 3H, J = 6.9 Hz), 1.11−0.89 (m, 6H). ^{13}C NMR (CD_3OD): δ 154.92, 143.99, 138.52, 136.11, 131.39, 130.62, 128.73, 128.36, 112.77, 110.26, 65.08, 53.90, 53.07, 32.62, 29.13, 20.21, 18.76, 18.05, 16.38, 11.56.

(1*R*,2*S*)-8-Benzoyl-1-methyl-2-(dipropylamino)tetralin Hydrochloride [(1*R*,2*S*)-10]. A mixture of (1*R*,2*S*)-**8** (210 mg, 0.52 mmol), phenyltrimethylstannane (154 mg, 0.64 mmol), LiCl (70 mg, 1.64 mmol), and dichloro[1,1′-bis(diphenylphosphino)ferrocene]palladium(II)[42] (18 mg, 21 μmol) in DMF (5 mL) was stirred under an atmosphere of carbon monoxide at 110 °C for 18 h. The reaction mixture was filtered (Celite), concentrated, and chromatographed on an alumina column eluted with ether/petroleum ether (1:16). Further purification on a silica column eluted with ammonia-saturated ether/petroleum ether (1:4) gave pure fractions, which were treated with ethereal HCl to give (1*R*,2*S*)-**10** which was recrystallized. ^{1}H NMR (oxalate in CD_3OD): δ 7.94−7.00 (m, 8H), 3.91−3.51 (m, 2H), 3.44−2.93 (m, 6H), 2.48−2.07 (m, 2H), 1.94−1.38 (m, 4H), 1.30−1.11 (m, 3H), 1.08−0.81 (m, 6H). ^{13}C NMR (oxalate in CD_3OD): δ 200.23, 164.74, 139.73, 139.08, 139.01, 136.58, 135.40, 132.53, 131.36, 130.22, 127.87, 64.19, 53.13, 31.94, 28.94, 20.03, 17.92, 16.37, 11.47.

(1*S*,2*R*)-8-Acetyl-1-methyl-2-(dipropylamino)tetralin Oxalate [(1*S*,2*R*)-11]. A solution of palladium acetate (6 mg,

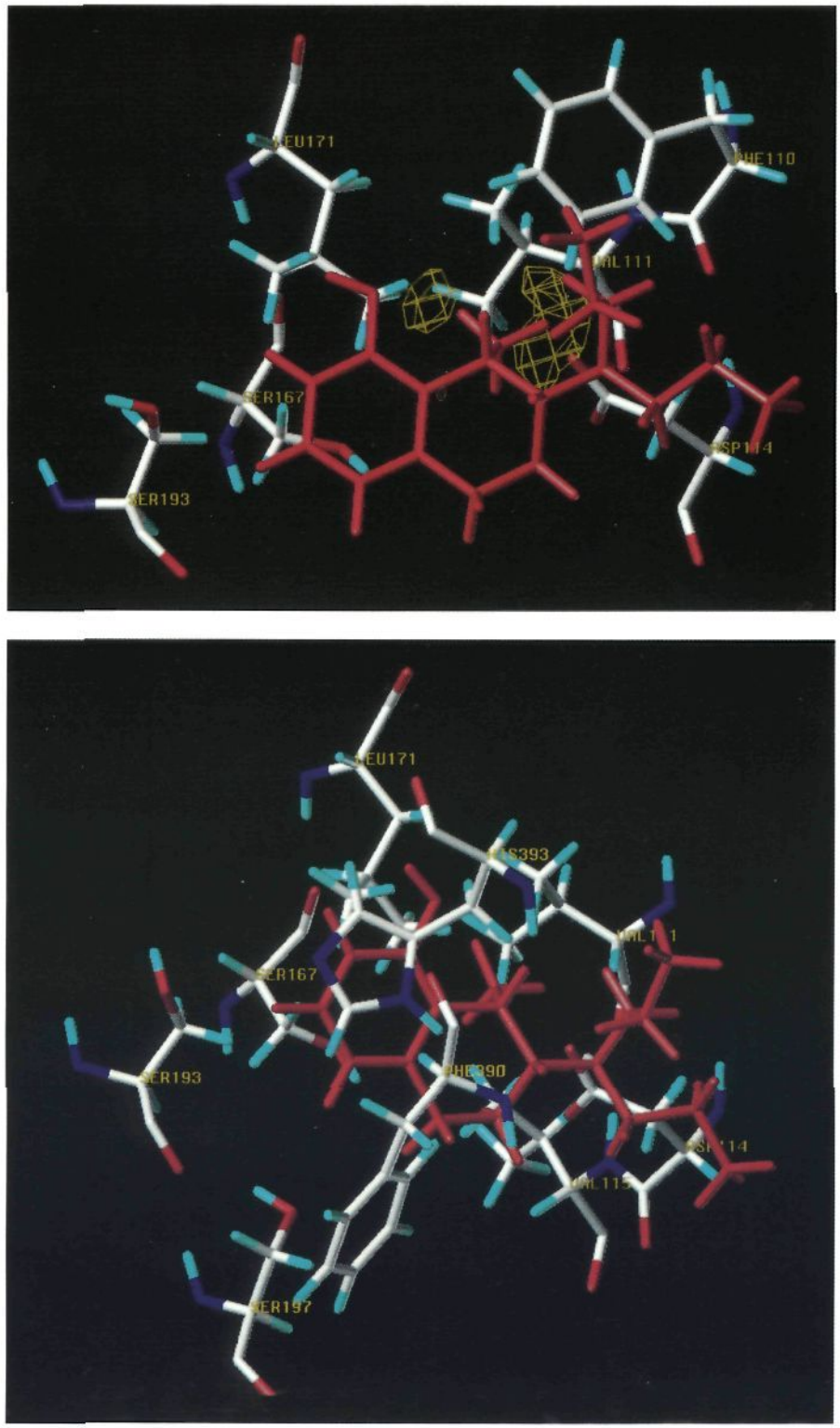


Figure 3. Docking of (1*S*,2*R*)-**4** with the DA D_2-receptor. (1*S*,2*R*)-**4** can not bind as an agonist because of strong steric repulsion (in yellow) between the C1-methyl group and parts of Asp 114 and Val 111 (top). Therefore, (1*S*,2*R*)-**4** binds (bottom) as the DA D_2-receptor antagonist (1*S*,2*R*)-UH-232 (see ref 41).

26.6 μmol) and 1,3-bis(diphenylphosphino)propane (12.5 mg, 30.4 μmol) in DMF (2 mL) was added to a mixture of (1*S*,2*R*)-**8** (300 mg, 0.76 mmol), butyl vinyl ether (380 mg, 3.8 mmol), and triethylamine (154 mg, 1.52 mmol) in DMF (4 mL) kept under nitrogen. The reaction mixture was heated at 130 °C in a sealed flask for 24 h and then filtered through Celite. The resulting mixture was concentrated, and the residue was treated with 10% aqueous HCl (5 mL). The acidic solution was stirred at room temperature for 0.5 h and then partitioned between aqueous saturated K_2CO_3 and CH_2Cl_2. The organic layer was dried (K_2CO_3), filtered, and concentrated. The residue was chromatographed on an alumina column eluted with ether/petroleum ether (1:20). Pure fractions were pooled and treated with ethereal oxalic acid to afford (1*S*,2*R*)-**11** which was recrystallized. ^{1}H NMR (CD_3OD): δ 7.25−7.66 (m, 1H), 7.35−7.20 (m, 2H), 4.40−4.30 (m, 1H), 3.62−3.54 (m, 1H), 3.27−2.98 (m, 6H), 2.61 (s, 3H), 2.39−2.12 (m, 2H), 1.85−1.66 (m, 4H), 1.23 (d, 3H, J = 6.9 Hz), 1.05 (t, 6H). ^{13}C NMR (hydrochloride in CD_3OD): δ 204.39, 139.84, 137.93, 136.48, 133.76, 129.19, 127.77, 64.33, 53.46, 52.53, 30.70, 30.51, 28.72,

19.73, 18.13, 17.91, 17.02, 11.30. IR (liquid film of free base): 2960, 1690, 1257 cm^{-1}.

Methyl (1*S*,2*R*)-1-Methyl-2-(dipropylamino)tetralin-8-carboxylate Hydrochloride [(1*S*,2*R*)-12]. A mixture of (1*S*,2*R*)-**8** (500 mg, 1.27 mmol), palladium acetate (8.6 mg, 38 μmol), 1,1'-bis(diphenylphosphino)ferrocene (42 mg, 76 μmol), triethylamine (386 mg, 3.81 mmol), and CH_3OH (813 mg, 25.4 mmol) in DMSO (10 mL) was stirred at 110 °C under an atmosphere of carbon monoxide for 4 days. The reaction mixture was filtered (Celite) and concentrated, and the residue was partitioned between saturated aqueous K_2CO_3 and ether. The organic layer was dried (K_2CO_3), filtered, and concentrated. The residue was chromatographed on an alumina column eluted with a gradient of ether/petroleum ether (1:20–1:8) to separate the ester from the byproduct (1*S*,2*R*)-**14**. Pure fractions were pooled and treated with ethereal HCl. The resulting hydrochloride was recrystallized from methanol/ether to give 110 mg (26%) of (1*S*,2*R*)-**12**. ^1H NMR (CD_3OD): δ 7.76 (d, 1H, *J* = 7.6 Hz), 7.36 (d, 1H, *J* = 7.2 Hz), 7.27 (dd, 1H, *J* = 7.9, 7.2 Hz), 4.54 (m, 1H), 3.89 (s, 3H), 3.68–3.59 (m, 1H), 3.36–3.00 (m, 6H), 2.33–2.13 (m, 2H), 1.91–1.72 (m, 4H), 1.29 (d, 3H, *J* = 6.6 Hz), 1.13–0.97 (m, 6H). ^{13}C NMR (CD_3OD): δ 169.25, 141.67, 136.35, 134.34, 130.26, 130.08, 127.87, 64.58, 53.60, 52.74, 31.36, 28.91, 19.82, 18.19, 16.96, 11.29.

(1*R*,2*S*)-8-[(Isopropylamino)carbonyl]-1-methyl-2-(dipropylamino)tetralin Hydrochloride [(1*R*,2*S*)-13]. A solution of palladium acetate (9 mg, 38 μmol) and 1,3-bis(diphenylphosphino)propane (31 mg, 76 μmol) in DMF (2 mL) was added to a mixture of (1*R*,2*S*)-**8** (500 mg, 1.27 mmol), isopropylamine (1.5 g, 25.4 mmol), and triethylamine (386 mg, 3.81 mmol) in DMF (2 mL) kept under an atmosphere of carbon monoxide. The reaction mixture was heated under an atmosphere of carbon monoxide at 120 °C for 3 days. After filtration (Celite), the mixture was partitioned between ether and 10% aqueous $NaHCO_3$. The organic layer was dried (K_2CO_3), filtered, and concentrated. The residue was purified by chromatography on silica gel using THF/hexane (1:2) as eluent to afford two major fractions (A and B), each of which was further chromatographed on a silica column eluted with ether/petroleum ether (1:4 and 1:1, respectively) and concentrated. The purified residue from fraction A was treated with ethereal HCl to afford 70 mg (20%) of (1*R*,2*S*)-**14**. The purified residue from fraction B was converted into the hydrochloride which was recrystallized, affording 90 mg (20%) of (1*R*,2*S*)-**13**. ^1H NMR (CD_3OD): δ 7.22 (m, 3H), 4.24–4.10 (m,), 4.07–3.90 (m, 1H), 3.70–3.53 (m, 1H), 3.41–2.92 (m, 6H), 2.41–2.09 (m, 2H), 1.80 (m, 4H), 1.41–1.14 (m, 9H), 1.13–0.92 (m, 6H). ^{13}C NMR (CD_3OD): δ 171.77, 137.89, 137.77, 135.85, 131.57, 127.98, 126.68, 64.53, 53.67, 52.99, 43.02, 31.52, 28.98, 22.59, 22.46, 19.95, 18.26, 16.98, 11.36.

(1*S*,2*R*)-1-Methyl-2-(dipropylamino)tetralin Hydrochloride [(1*S*,2*R*)-14]. A mixture of (1*S*,2*R*)-**8** (210 mg, 0.53 mmol), palladium acetate (86 mg, 27 μmol), 1,1'-bis(diphenylphosphino)ferrocene (29 mg, 53 μmol), triethylamine (161 mg, 1.59 mmol), and formic acid (49 mg, 1.06 mmol) in DMF (5 mL) was stirred at 60 °C under nitrogen for 0.5 h. The reaction mixture was filtered (Celite), concentrated, and chromatographed on an alumina column eluted with ether/light petroleum (1:8). Pure fractions were pooled and treated with ethereal hydrogen chloride to give (1*S*,2*R*)-**14** which was recrystallized. ^1H NMR (CD_3OD): δ 7.21–7.04 (m, 4H), 3.74–3.65 (m, 1H), 3.51–3.40 (m, 1H), 3.35–3.11 (m, 4H), 3.08–2.91 (m, 2H), 2.34–2.04 (m, 2H), 1.90–1.72 (m, 4H), 1.34 (d, 3H, *J* = 6.9 Hz), 1.11–0.98 (m, 6H). ^{13}C NMR (CD_3OD): δ 140.52, 134.89, 130.13, 129.67, 128.03, 127.51, 64.85, 53.40, 35.62, 29.31, 20.27, 18.72, 18.11, 11.29.

Computational Methods. Conformational energies and energy-minimized geometries of the unprotonated amines were obtained on a Macintosh IIfx or Macintosh Centris 650 computer using the molecular mechanics program MM2(87)[43] or MM2(91)[44] developed by Allinger and co-workers. Conformational energy curves were calculated by using the driver option implemented in MM2(87) with an angle increment of 10° and with full energy minimization except for the dihedral angle(s) used as driving angle(s). The structural modeling was performed by use of the interactive computer graphics program MacMimic, version 2.1, InStar Software, IDEON Research Park, S-233 70 Lund, Sweden.

Receptor Modeling. Receptor models were constructed using Sybyl 5.5 (TRIPOS Associates Inc., 1699 S. Hanley Rd., Suite 303, St. Louis, MO). The coordinates for bacteriorhodopsin were obtained from Hederson et al.[45] The amino acid sequences for the human D_{2A}- and D_3-receptors were obtained from published sequences.[46–48] The receptor models of the human D_{2A}- and D_3-receptors were constructed in a similar way according to a strategy previously described for the muscarinic m1 receptor.[49] In short, the models are based on a presumed homology in three-dimensional structure between bacteriorhodopsin and the GPC receptors. α-Helices were constructed from the primary structure of the D_{2A}- and D_3-receptors. Transmembrane regions (TM) were determined by examining hydropathy plots and multiple sequence alignments of a number of GPC receptors. The relative rotations of the helices were estimated by considering conserved amino acids and hydrophobic moment plots. The α-helices ($\phi = -55.02$ and $\psi = -50.43$) were constructed from the amino acid sequences of the TMs, and proline kinks were taken into account. Side chain conformations from rotamer libraries were used. The helices were energy minimized using the AMBER all-atom force field. Fitting of the backbone of these helices onto the backbone of bacteriorhodopsin produced the TM bundle of the receptors. The loop regions were not included in the modeling. The side chains were adjusted manually to avoid overlap produced by the fitting procedure. The resulting TM bundle was energy minimized using the AMBER united-atom force field (2000 iterations) and the all-atom force field (500 iterations) with no restriction of the backbone and a distance-dependent dielectric constant of 4.0 and nonbonded cutoff of 9.0 Å.

A DA-receptor-excluded volume[50] was used to probe a common binding site for the agonists. The docking procedure done in Sybyl involved manual docking of the receptor-excluded volume into the homology-based receptor model using one of the oxygens in Asp114 (TM 3) as an anchoring point. Bond lengths and angles of attractive interactions were optimized, and repulsive van der Waals interactions were minimized during the docking. In addition, the conformations of the side chains forming the putative binding site were changed manually to minimize overlap between the homology-based receptor models and the receptor-excluded volume (using the Sybyl command mvolume). After definition of the binding site model by use of the indirect model, we performed manual docking experiments with individual ligands to achieve optimal interactions with each ligand.

Pharmacology. General. Male Sprague–Dawley rats (ALAB, Stockholm) weighing 260–310 g were used. The animals were kept at room temperature (23 ± 1 °C) for at least a week before the experiment and allowed food and water *ad libitum* with lights on between 06:00 and 18:00. Each animal was used only once. All compounds were dissolved in 0.9% NaCl, occasionally with gentle warming in order to obtain complete dissolution. Control rats received the same number of saline injections at corresponding time intervals. Injection volumes were 2 mL/kg sc. 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 for test compounds and 1 μmol/kg for (*R*)-**2**. The rats were observed with the objective of investigating the possible 5-HT syndrome and hypothermia for 30 min after the administration of test compounds. Attention was paid to flat body posture, forepaw treading, and hind limb abduction (the 5-HT syndrome). These behaviors were rated as absent or present. Cage-leaving response was measured 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 were noted. Body temperature was measured before and at 30 min postinjection using an electrical thermometer with the probe inserted in the rectum 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 an indication of changes in 5-HT and DA turnover, respectively. 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 frozen 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 supernatant was injected into a high-performance liquid chromatography column with electrochemical detection (HPLC-EC) to analyze 5-HIAA, 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), an amperometric detector (LC-4B, BAS) with Ag/AgCl reference electrode, and a MF-2000 cell (BAS) operating at a potential of 0.85 V. The mobile phase, pH 2.69, consisted of K_2HPO_4, citric acid buffer (pH 2.5), 10% methanol, sodium octyl sulfate (40 mg/L), and EDTA; flow rate, 1 mL/min, and temperature of mobile phase, 35 °C.

5-HT$_{1A}$-Receptor Binding Assay. Male Sprague–Dawley rats (weighing about 200 g) were decapitated, and the cortex and hippocampus were dissected out. 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 instrument (Janke and Kunkel, Staufen, FRG) for 10 s. After centrifugation for 12.5 min at 17 000 rpm (39800*g*; Beckman centrifuge, Palo Alto, CA), 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 μM pargyline (Sigma, St. Louis, MO) 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]-8-OH-DPAT ([^{3}H]-8-hydroxy-2-(di-*n*-propylamino)tetralin·HBr; New England Nuclear, Dreieich, Germany, and Research Biomedicals, Wayland, MA), and 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. Nonspecific 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). 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. The binding data were analyzed by nonlinear regression using the LIGAND program.[51]

DA D$_{2A}$-Receptor Binding Assay. The D_{2A}-receptor binding assay was performed essentially as previously described.[37] Mouse fibroblast (Ltk$^-$) cells expressing human D_{2A}-receptors were obtained from Dr. O. Civelli (Vollum Institute, OR). All tissue culture reagents were obtained from GIBCO Ltd. (Paisley, Scotland, U.K.) except streptomycin sulfate (Sigma Chemicals Co., St. Louis, MO) and benzylpenicillin K (Astra).

The D_{2A} cells were grown in 225 cm^2 flasks with ventilated caps (Costar) in 5% CO_2 in air at 37 °C. They were cultured in DMEM (Dulbecco's modified eagles medium) supplemented with 10 mM HEPES, 10% fetal calf serum (heat-inactivated), and PeSt (70 μg/mL benzylpenicillin K and 100 μg/mL streptomycin sulfate) and selected with Geneticin (G-418, 0.7 mg/mL). The cells were detached with 0.05% trypsin and 0.02% EDTA in PBS (phosphate-buffered saline). Upon harvesting, the cells were centrifuged (300*g* for 10 min), washed in DMEM two additional times, and homogenized (Dounce homogenizer) in 10 mM Tris-HCl and 5 mM $MgSO_4$, pH 7.4. The homogenate was washed twice in binding buffer (see below) by centrifugation (43500*g* for 10 min) and stored in aliquots at −70 °C.

The frozen cell membranes were thawed, homogenized with a Branson 450 sonifier, and suspended in binding buffer (in mM: 50 Tris-HCl, 120 NaCl, 5 KCl, 1.5 $CaCl_2$, 4 $MgCl_2$, 1 EDTA; pH 7.4 at 22 °C). The binding assays were performed in duplicate in a total volume of 0.5 mL with a receptor concentration of 80–100 pM (5–25 μg of protein/tube). The binding reaction with [^{3}H]raclopride was initiated by the addition of membranes and carried out at 22 ± 1 °C for 60 min. Nonspecific binding was defined with 1 μM (+)-butaclanol. The incubations were terminated by rapid filtration through Whatman GF/B filters and subsequent washing with cold buffer (50 mM Tris-HCl, pH 7.4) using a cell harvester (Brandel cell harvester). Scintillation cocktail (Packard Ultima Gold; 3 mL) was added and the radioactivity determined in a Packard 2200CA liquid scintillation analyzer at 50% efficiency. The data were analyzed as above.

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