Derivatives of (*R*)- and (*S*)-5-Fluoro-8-hydroxy-2-(dipropylamino)tetralin: Synthesis and Interactions with 5-HT$_{1A}$ Receptors

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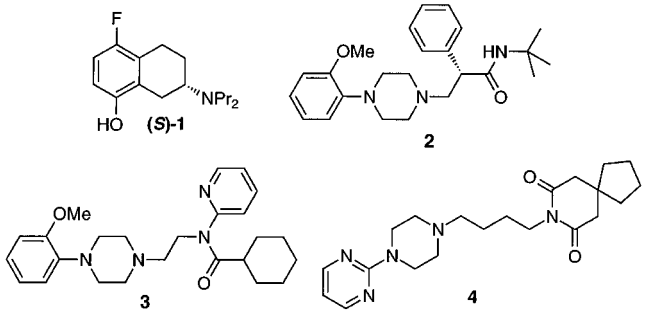
Analogs of the 5-HT$_{1A}$ receptor antagonist (*S*)-5-fluoro-8-hydroxy-2-(dipropylamino)tetralin [(*S*)-**1**, (*S*)-UH301] have been prepared. The C8-substituent has been varied, and in some derivatives one of the *N*-propyl groups has been exchanged for a 4-(8-aza-7,9-dioxospiro[4.5]decan-8-yl)-butyl group. The novel compounds have been evaluated for affinity to rat brain 5-HT$_{1A}$ receptors in competition experiments with [^{3}H]-8-OH-DPAT. In addition, the efficacy of the compounds was assessed by their ability to inhibit the VIP-stimulated cAMP formation in GH$_4$ZD10 cells expressing rat 5-HT$_{1A}$ receptors. Varying degrees of intrinsic activity was revealed among the compounds tested, i.e., the profiles ranged from full agonists to antagonists. All *R*-enantiomers are characterized as full agonists at 5-HT$_{1A}$ receptors, whereas partial agonists or antagonists were found among the corresponding *S*-enantiomers. Substitution of one of the *N*-propyl groups for a 4-(8-aza-7,9-dioxospiro[4.5]decan-8-yl)butyl group seems to increase efficacy as well as affinity for 5-HT$_{1A}$ receptors. A favorable interaction with an accessory binding site by the *N*-4-(8-aza-7,9-dioxospiro[4.5]decan-8-yl)butyl group may contribute to the increased affinity.

Introduction

Currently used antidepressants suffer from the shortcoming of having a very slow onset of action.[1] On the basis of pharmacological data, it has been hypothesized that the combination of a selective serotonin (5-HT) reuptake inhibitor (SSRI) with a 5-HT$_{1A}$ receptor antagonist might shorten the latency period.[2] A study in which the nonselective 5-HT$_{1A}$ receptor antagonist pindolol[3] was used in combination with a selective SSRI (paroxetin)[4] has provided additional support for this hypothesis since major clinical improvements were observed within 1 week.[5] However, no selective 5-HT$_{1A}$ receptor antagonists have been registered. In fact, despite the numerous reports on 5-HT$_{1A}$ receptor agonists and partial agonists during the past 15 years,[6] it was only fairly recently that the first selective 5-HT$_{1A}$ receptor antagonists were reported, (*S*)-UH301 [(*S*)-**1**],[7] (*S*)-WAY 100135 (**2**),[8] and WAY 100635 (**3**).[9]



Compound (*S*)-**1** may not be an ideal candidate for drug development because of a relatively low potency, a limited oral bioavailability, and a fairly short duration of action. In this study we explore the structure−activity relationships of a series of enantiopure analogs of (*S*)-**1** with the aim of finding additional and potentially more useful 5-HT$_{1A}$ receptor antagonists. We have studied the effect of substituting the hydroxyl group of (*R*)- and (*S*)-**1** with various other substituents. In addition, we have replaced one of the propyl groups with a 4-(8-aza-7,9-dioxospiro[4.5]decan-8-yl)butyl group because this group is part of the structure of the anxiolytic drug buspirone (**4**) and other arylpiperazines with high affinity for 5-HT$_{1A}$ receptors.[10] The novel compounds were evaluated *in vitro* for their affinities to [^{3}H]-8-OH-DPAT-labeled rat hippocampal 5-HT$_{1A}$ receptors. The efficacy of the derivatives was evaluated in a VIP-stimulated cAMP production assay using GH$_4$-ZD10 cells expressing rat 5-HT$_{1A}$ receptors. Several compounds showed appreciable affinity for 5-HT$_{1A}$ receptors, with the *N*-4-(8-aza-7,9-dioxospiro[4.5]decan-8-yl)butyl analogs having highest affinity. In addition, the compounds showed a varying degree of intrinsic activitiy, i.e., they ranged from full agonists to antagonists.

Chemistry

The syntheses of the novel derivatives of (*R*)- and (*S*)-**1** are outlined in Schemes 1 and 2, and their physical data are presented in Table 1. The synthetic strategies used were based on the accessability of the pure enantiomers of **1**[7a,l] (Scheme 1) and **12** (Scheme 2). The enantiomers of **12** were obtained from the secondary amines (*R*)- and (*S*)-**10**[7l] by *N*-alkylation with 8-(4-bromobutyl)-8-azaspiro-[4.5]decane-7,9-dione[11] to afford (*R*)- and (*S*)-**11**, respectively. Demethylation of the enantiomers of **11** using BBr_3[12] gave (*R*)- and (*S*)-**12** (Scheme 2).

Intermediates (*R*)- and (*S*)-**5** and (*R*)- and (*S*)-**13** were prepared from the corresponding enantiomers of **1** and **12** by treatment with triflic anhydride in the presence of base.[13] The enantiomeric triflates were then used in palladium-catalyzed reactions (Schemes 1 and 2): A

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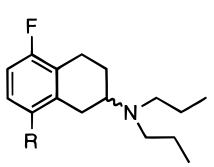
Table 1. Physical Data of the Novel Compounds



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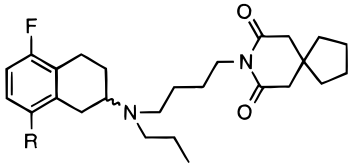
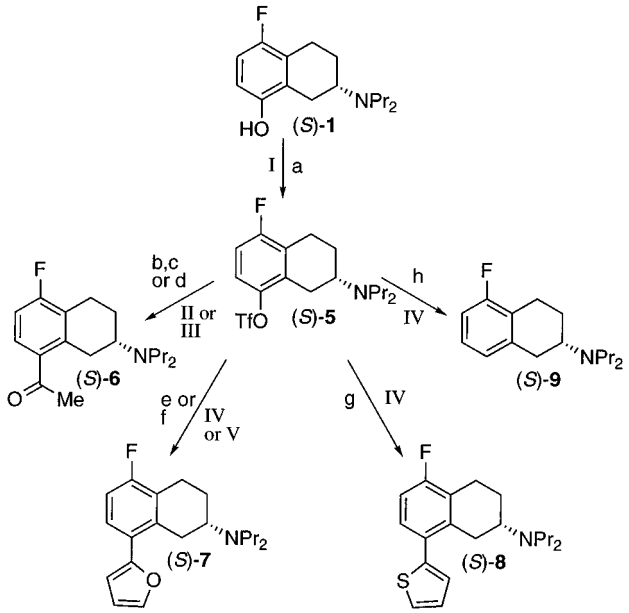


B

compd	general structure	R	method[a]	recryst solvents[b]	yield (%)	mp (°C)	$[\alpha]^{22}_D$ (deg) (*c* 1.0, MeOH)	formula
(*S*)-**5**	*A*	-OTf	I	A	71	145−146	−60.9	$C_{17}H_{23}F_4NOS\cdot HCl$
(*R*)-**5**	*A*	-OTf	I	A	69	146−147	+60.5	$C_{17}H_{23}F_4NOS\cdot HCl$
(*S*)-**6**	*A*	-COMe	II (III)	B	85 (54)	106−107	−123.6	$C_{18}H_{26}FNO\cdot HCl\cdot{}^1/_4H_2O$
(*R*)-**6**	*A*	-COMe	II	B	67	107.5−109	+124.6	$C_{18}H_{26}FNO\cdot HCl\cdot{}^1/_4H_2O$
(*S*)-**7**	*A*	2-furyl	IV (V)	C	75 (65)	159−160	−53.9	$C_{20}H_{26}FNO\cdot HCl$
(*R*)-**7**	*A*	2-furyl	IV	C	57	159−160	+53.0	$C_{20}H_{26}FNO\cdot HCl$
(*S*)-**8**	*A*	2-thienyl	IV	C	73	157−159	−19.4	$C_{20}H_{26}FNS\cdot HCl$
(*R*)-**8**	*A*	2-thienyl	IV	C	86	161−162	+18.5	$C_{20}H_{26}FNS\cdot HCl$
(*S*)-**9**	*A*	-H	VI	C	97	134−135	−70.9	$C_{16}H_{24}FNO\cdot HCl$
(*R*)-**9**	*A*	-H	VI	C	71	136−137	+70.9	$C_{16}H_{24}FNO\cdot HCl$
(*S*)-**11**	*B*	-OMe	VII	C	61	111−113	−49.5	$C_{27}H_{39}FN_2O_3\cdot HCl$
(*R*)-**11**	*B*	-OMe	VII	C	62	111−114	+50.2	$C_{27}H_{39}FN_2O_3\cdot HCl$
(*S*)-**12**	*B*	-OH	VIII	C	76	130−134	−50.8	$C_{26}H_{37}FN_2O_3\cdot HCl\cdot{}^1/_4H_2O$
(*R*)-**12**	*B*	-OH	VIII	C	69	130−134	+50.1	$C_{26}H_{37}FN_2O_3\cdot HCl\cdot{}^1/_2H_2O$
(*S*)-**13**	*B*	-OTf	I	C	67	144−145	−42.8	$C_{27}H_{36}F_4N_2O_5S\cdot HCl$
(*R*)-**13**	*B*	-OTf	I	C	75	144−145	+42.0	$C_{27}H_{36}F_4N_2O_5S\cdot HCl$
(*S*)-**14**	*B*	-COMe	II	B	80	110−112	−79.2	$C_{28}H_{39}FN_2O_3\cdot HCl\cdot{}^3/_4H_2O$
(*R*)-**14**	*B*	-COMe	II	B	71	110−112	+79.3	$C_{28}H_{39}FN_2O_3\cdot HCl\cdot{}^3/_4H_2O$
(*S*)-**15**	*B*	-2-furyl	IV		85[c]	70−73	−32.9	$C_{30}H_{39}FN_2O_3\cdot C_2H_2O_4\cdot H_2O$
(*R*)-**15**	*B*	-2-furyl	IV		63[c]	70−73	+31.1	$C_{30}H_{39}FN_2O_3\cdot C_2H_2O_4\cdot{}^3/_4H_2O$

[a] See the Experimental Section. [b] Recrystallization solvents: A, ether; B, ethyl acetate−ether; C, methanol−ether. [c] The yield is calculated for the amine.

Scheme 1[a]



[a] Reagents: (a) $(CF_3SO_2)_2O$, 2,4,6-trimethylpyridine, CH_2Cl_2; (b) butyl vinyl ether, $Pd(OAc)_2$, dppp, Et_3N, DMF; (c) aq HCl (5%); (d) Me_4Sn, CO, $PdCl_2$(dppf), LiCl, molecular sieves (4 Å), 2,6-di-*tert*-butyl-4-methylphenol, DMF; (e) Bu_3(2-furyl)Sn, $(Ph_3P)_4Pd$, LiCl, DMF; (f) (2-furan)$B(OH)_2$, $(Ph_3P)_4Pd$, LiCl, aq Na_2CO_3 (2 M), DME, EtOH; (g) Bu_3(2-thienyl)Sn, $(Ph_3P)_4Pd$, LiCl, DMF; (h) HCOOH, $Pd(OAc)_2$, dppf, Et_3N, DMF. Tf = CF_3SO_2−.

Heck reaction of (*R*)- and (*S*)-**5** with butyl vinyl ether followed by acid hydrolysis of the intermediate vinyl ether gave the acetyl derivatives (*R*)- and (*S*)-**6**.[14] Compound (*S*)-**6** was also obtained by a palladium-catalyzed carbonylative coupling reaction of (*S*)-**5** in the presence of carbon monoxide and tetramethylstannane.[15] The 8-heteroaryl substituents in **7** and **8** were introduced by palladium-catalyzed couplings of the corresponding tributylarylstannane with **5**.[16] In addition, (*S*)-**7** could also be obtained, although in lower yield, by a palladium-catalyzed coupling of 2-furanboronic acid with (*S*)-**5**.[17] A palladium-catalyzed reduction of the enantiomers of **5** using formic acid as the hydride donor[18] produced the deoxy derivatives (*R*)- and (*S*)-**9**.

The 8-acetyl derivatives (*R*)- and (*S*)-**14** and the 8-(2-furyl) derivatives (*R*)- and (*S*)-**15** were obtained from the corresponding enantiomers of **13** by using the Heck type reaction described above for the synthesis of **6** and the stannane-coupling reaction described for **7**, respectively (Scheme 2).

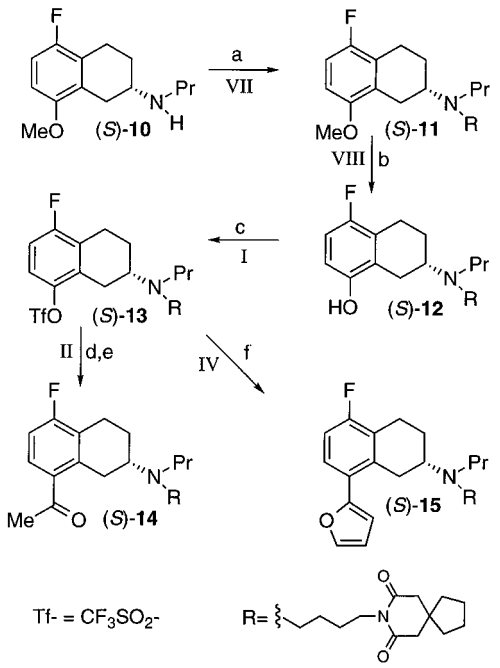
The availability of the enantiopure triflates **5** and **13**, together with the fact that palladium-catalyzed reactions on similar substrates do not cause racemization under the conditions used,[19] implies that the enantiopurity and the absolute configurations of the products should be the same as for (*R*)- and (*S*)-**1** and (*R*)- and (*S*)-**12**.

Pharmacological Results and Discussion

The ability of the *R*- and *S*-enantiomers of **5**−**9** and **11**−**15** to bind to and stimulate 5-HT$_{1A}$ receptors was studied (Table 2). In addition, the enantiomers of **1** were included in the biochemical studies for comparative purposes.

The affinity of the compounds to 5-HT$_{1A}$ receptors was determined in competition experiments using [^{3}H]-8-OH-DPAT and rat hippocampal 5-HT$_{1A}$ receptors, as previously described.[20] With the exception of the deoxy analog (*R*)-**9** and triflates (*S*)-**5** and (*S*)-**13**, the novel derivatives had fairly high 5-HT$_{1A}$ receptor affinities (K_i < 100 nM; Table 2). The highest affinities were found among *R*-enantiomers substituted with a spirocyclic side

Scheme 2[a]



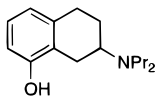
[a] Reagents: (a) RBr, K_2CO_3, MeCN; (b) BBr_3, CH_2Cl_2; (c) $(CF_3SO_2)_2O$, 2,4,6-trimethylpyridine, CH_2Cl_2; (d) butyl vinyl ether, $Pd(OAc)_2$, dppp, Et_3N, DMF; (e) aq HCl (5%); (f) Bu_3(2-furyl)Sn, $(Ph_3P)_4Pd$, LiCl, DMF.

chain [(*R*)-**11**−(*R*)-**15**]. In fact, the replacement of one *N*-propyl group with a *N*-4-(8-aza-7,9-dioxospiro[4.5]-decan-8-yl)butyl group increases the affinity throughout this series of compounds. With few exceptions,[21] previous studies of 2-aminotetralin-based 5-HT_{1A} receptor ligands have demonstrated that the *R*-enantiomers have higher affinity than the antipodes.[7a,19,22] In the present series, however, compounds **7** and **8** exhibited reversed enantiomeric affinity ratios, the *S*-enantiomers being more potent.

The efficacy of the novel derivatives was studied in a suspension of GH_4ZD10 cells expressing rat 5-HT_{1A} receptors by measuring the cAMP formation in the presence of vasoactive intestinal polypeptide (VIP), which stimulates cAMP formation.[23] It is well established that 5-HT_{1A} receptors are functionally coupled to G_i-proteins which inhibit the activity of adenylyl cyclase, the enzyme catalyzing the conversion of ATP into cAMP.[24] Thus, in this assay, 5-HT_{1A} receptor agonists, like 5-HT itself, inhibit the production of cAMP by coupling to G_i-proteins. Most of the new compounds were able to decrease the VIP-stimulated cAMP production. At the highest concentration used (10, 30, or 50 μM), several compounds inhibited about 60% of the cAMP formation [the *R*-enantiomers of **1**, **5**, **6**, **8**, and **11**−**15**, and (*S*)-**11**, and (*S*)-**13**]. Compounds (*R*)-**7**, (*S*)-**8**, and (*S*)-**12** and the enantiomers of **9** inhibited about 15−20%, whereas (*S*)-**1**, **6**, **7**, **14**, and **15** inhibited less than 10% of the cAMP formation.

Thus, certain compounds, (*S*)-**6**, (*S*)-**7**, (*S*)-**14**, and (*S*)-**15**, behaved as antagonists by not affecting the cAMP levels. In order to enable a tentative classification of the compounds as antagonists, partial agonists, or agonists, we studied their ability to reverse the 5-HT-induced reduction of the cAMP levels. An antagonist and a partial agonist would reverse (fully or partially) the cAMP levels, whereas an agonist would not. As expected, the 5-HT_{1A} receptor antagonist (*S*)-**1** did not affect the VIP-induced cAMP levels but blocked completely the 5-HT-induced reduction.

The majority of the novel compounds had affinity for 5-HT_{1A} receptors, produced reductions in the VIP-stimulated cAMP levels, and were unable to block the 5-HT-induced reduction in cAMP levels indicating that they are 5-HT_{1A} receptor agonists. Compounds (*S*)-**6**, (*S*)-**7**, and (*S*)-**14**, which did not affect the VIP-induced cAMP levels at a dose of 10 μM, were able to partially or fully reverse the 5-HT-induced reduction in cAMP levels. Hence, these compounds may be classified as putative 5-HT_{1A} receptor antagonists. The present data seem to indicate that the *S*-enantiomers of **8**, **9**, **12**, and **15** are weak antagonists or partial agonists. It should be noted that compounds such as (*S*)-**16** and **4** (Table 2) have been previously characterized as partial agonists.[23] However, additional studies are required to unambigously establish the pharmacological profiles of **8**, **9**, **12**, and **15**.



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Replacement of one of the *N*-propyl groups in the dipropylamino-substituted derivatives with a 4-(8-aza-7,9-dioxospiro[4.5]decan-8-yl)butyl group seems to increase affinity as well as efficacy of the compounds at 5-HT_{1A} receptors: For example, (*R*)-**1** (K_i = 19 nM) is a partial agonist, while (*R*)-**12** (K_i < 0.3 nM) is a full agonist, and the antagonists (*S*)-**1** (K_i = 24.8 nM) and (*S*)-**7** (K_i = 30.1 nM) are converted into the weak antagonists/partial agonists (*S*)-**12** (K_i = 18.2 nM) and (*S*)-**15** (K_i = 7.5 nM), respectively. It is most likely that the *N*-4-(8-aza-7,9-dioxospiro[4.5]decan-8-yl)butyl group contributes to the affinity for 5-HT_{1A} receptors by interacting favorably with an accessory agonist binding site.

It is not known how the interaction of the antagonist (*S*)-**1** with 5-HT_{1A} receptors differs from that of the potent 5-HT_{1A} receptor agonist 8-OH-DPAT (**16**)[25] Since a number of derivatives of **16** have been studied previously, we investigated if the different C8-substituents in the present series had the same effect on affinity as in the 8-OH-DPAT series (Table 3). In the two series of *R*-enantiomers, there is an excellent correlation (r^2 = 0.95), whereas the substituent-induced change in affinity is less well correlated in the corresponding *S*-enantiomers (r^2 = 0.69) (Figure 1). This comparison might indicate that the present *R*-derivatives may bind to 5-HT_{1A} receptors in a similar mode as the corresponding nonfluorinated derivatives whereas the *S*-enantiomers may display different binding modes. This would be consistent with the observation that several *S*-enantiomers in the present series display antagonist characteristics.

Experimental Section

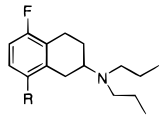
Chemistry. General Comments. Melting points (uncorrected) were determined in open glass capillaries on an Electrothermal melting point apparatus. All reactions were performed in an atmosphere of nitrogen. Routine ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on a JEOL FX 90Q spectrometer at 90, 22.5, and 84.2 MHz, respectively, on a JEOL EX-

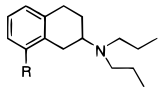
Table 2. Affinities of Novel 2-Aminotetralins for 5-HT$_{1A}$ Receptors Labeled with [^{3}H]-8-OH-DPAT and Their Effects on 5-HT$_{1A}$ Receptor-Mediated Inhibition of VIP-Stimulated cAMP Production

		VIP-stimulated cAMP production			
compd	K_i (nM)[a]	dose (μM)	(%)	dose (μM) + 1 μM 5-HT	(%)
(*S*)-**1**	24.8 ± 1.8	0.1	94 ± 8.9		57 ± 4.3
		1	100 ± 2.1	3	93 ± 2.9
		10	100 ± 1.9		
(*R*)-**1**	6.1[b]	0.1	86 ± 3.5		57 ± 4.3
		1	78 ± 10	3	64 ± 6.5
		10	61 ± 6.5		
(*S*)-**5**	490[c]				
(*R*)-**5**	18.5 ± 2.5	0.1	98 ± 2.1		60 ± 3.0
		1	91 ± 1.1	10	52 ± 2.4
		10	61 ± 4.6		
		30	48 ± 4.7		
(*S*)-**6**	13.6 ± 2.9	0.1	90 ± 3.1		57 ± 4.3
		1	98 ± 6.0	3	89 ± 7.9
		10	97 ± 6.1		
(*R*)-**6**	6.9 ± 0.1	0.01	99 ± 7.1		60 ± 3.0
		0.1	95 ± 2.9	50	63 ± 4.3
		1	63 ± 3.4		
		10	61 ± 9.4		
		30	62 ± 5.2		
(*S*)-**7**	30.1 ± 0.6	0.1	100 ± 3.6		56 ± 4.3
		1	98 ± 4.5	3	74 ± 3.9
		10	98 ± 5.1		
(*R*)-**7**	88.9 ± 24.5	0.01	106 ± 2.3		60 ± 3.0
		0.1	98 ± 4.0	10	61 ± 1.6
		1	97 ± 6.6		
		10	84 ± 1.7		
		30	79 ± 3.9		
(*S*)-**8**	32.7 ± 2.4	0.1	99 ± 6.2		57 ± 4.3
		1	96 ± 3.4	3	65 ± 5.0
		10	88 ± 7.9		
(*R*)-**8**	35.0 ± 8.3	0.1	98 ± 1.3		60 ± 3.0
		1	93 ± 2.6	10	58 ± 2.9
		10	79 ± 1.7		
		30	61 ± 1.6		
(*S*)-**9**	250[c]	0.05	85 ± 0.4		61 ± 2.2
		1	86 ± 2.8	50	73 ± 0.3
		50	86 ± 1.3		
(*R*)-**9**	136 ± 5	0.01	93 ± 7.2		60 ± 3.0
		0.1	98 ± 5.4	10	58 ± 2.8
		1	85 ± 5.7		
		10	81 ± 3.8		
		50	78 ± 3.4		
(*S*)-**11**	4.9 ± 0.3	0.05	87 ± 1.0		50 ± 4.8
		1	79 ± 5.5	50	41 ± 2.2
		50	39 ± 4.0		
(*R*)-**11**	<0.3	0.05	62 ± 6.7		56 ± 8.5
		1	56 ± 6.5	50	40 ± 11
		50	41 ± 9.0		
(*S*)-**12**	18.2 ± 0.9	0.05	95 ± 4.6		68 ± 1.3
		1	91 ± 6.1	50	77 ± 7.1
		50	82 ± 3.7		
(*R*)-**12**	<0.3	0.05	72 ± 4.0		68 ± 1.3
		1	66 ± 0.3	50	66 ± 13
		50	68 ± 9.1		
(*S*)-**13**	177 ± 15	0.05	98 ± 1.6		68 ± 1.3
		1	90 ± 2.8	50	55 ± 2.3
		50	65 ± 1.6		
(*R*)-**13**	0.9 ± 0.1	0.05	98 ± 8.6		68 ± 1.3
		1	73 ± 0.2	50	51 ± 2.0
		50	55 ± 1.6		
(*S*)-**14**	13.9 ± 0.5	0.05	104 ± 5.7		70 ± 1.3
		1	97 ± 4.8	1	91 ± 7.9
		10	109 ± 6.5	10	102 ± 13
		50	93 ± 5.6	50	91 ± 5.0
(*R*)-**14**	<0.3	0.05	50 ± 3.5		61 ± 4.5
		1	59 ± 5.5	50	55 ± 6.3
		50	48 ± 3.5		
(*S*)-**15**	7.5 ± 0.3	1	96 ± 2.0		62 ± 3.4
				0.1	58 ± 2.3
				1	66 ± 3.7
				10	68 ± 0.6
(*R*)-**15**	1.1 ± 0.03	1	60 ± 3.7		62 ± 3.4
				0.1	57 ± 7.5
				1	60 ± 8.7
				10	54 ± 7.8
(*S*)-**16**[d,e]	1.8	0.1	74 ± 3		43 ± 4
		1	61 ± 2	1	47 ± 5
		10	62 ± 3		
(*R*)-**16**[d,e]	1.3	0.1	53 ± 4		43 ± 4
		1	45 ± 3	1	41 ± 2
		10	47 ± 4		
4[e,f]	15	0.1	84 ± 3		43 ± 4
		1	75 ± 2	10	64 ± 2
		10	73 ± 1		

[a] The K_i values are means ± standard errors, $n = 2-3$. [b] From ref 7a. [c] $n = 1$, slightly modified method. [d] From ref 19a. [e] From ref 23. [f] From ref 30.

Table 3. Affinity to 5-HT$_{1A}$ Receptors of C8-Substituted Analogs of **1** and **16**





R	abs config	K_i (nM)	K_i (nM)	ref
H	*R*	136	17	19a
	S	250	56	19a
OH	*R*	6.1[a]	1.3	19a
	S	24.8	1.8	19a
OSO_2CF_3	*R*	18.5	3.8	19a
	S	490	9.5	19a
COMe	*R*	6.9	1.8	19a
	S	13.6	0.7	19a
2-furyl	*R*	88.9	9.3	22a
	S	30.1	1.8	22a
2-thienyl	*R*	35.0	8.4	22a
	S	32.7	5.5	22a

[a] From ref 7a.

270 spectrometer at 270 (^{1}H) or 67 (^{13}C) MHz, or on a JEOL EX400 spectrometer at 376.17 MHz (^{19}F) using CD_3OD solutions, which were referenced to internal tetramethylsilane or fluorotrichloromethane (^{19}F NMR). Infrared (IR) spectra were recorded on a Perkin-Elmer 298 infrared spectrophotometer or on a Perkin-Elmer 1600 Series FTIR. The spectra were all in accordance with the assigned structures. Optical rotation measurements were obtained on a Perkin-Elmer 241 polarimeter. Elemental analyses (C, H, and N) were performed by MikroKemi AB, Uppsala, Sweden, and were within 0.4% of the theoretical values. For all the compounds, only one spot [visualized by UV light, I_2 vapor, and Gibbs reagent (2,6-dichloroquinone-4-chloroimide, 4% in MeOH)] was obtained. Capillary GC was performed on a Carlo Erba 6000 instrument equipped with a DB-5 capillary column (25 m). Thin-layer chromatography (TLC) was performed by using aluminum sheets precoated with either silica gel 60 F_{254} or aluminum oxide 60 F_{254} E neutral (0.2 mm; E. Merck). For preparative TLC, plates precoated with either silica gel 60 F_{254} (2.0 mm) or aluminum oxide F_{254} T (1.5 mm) (E. Merck) was used. Column chromatography was performed on silica gel 60 (0.040−0.063 mm; E. Merck) silica gel 60 (0.015−0.040 mm; Merck) or aluminum oxide 90 (0.063−0.2 mm; E. Merck). Representative examples of the reactions presented in Table 1 are given below.

(*S*)-5-Fluoro-8-[(trifluoromethyl)sulfonyl]-2-(dipropylamino)tetralin Hydrochloride [(*S*)-5·HCl]. Method I. Trifluoromethanesulfonic anhydride (0.85 g, 3 mmol) in dichloromethane (CH_2Cl_2) (3 mL) was added to a solution of (*S*)-**1** (0.50 g, 1.9 mmol) and 2,4,6-trimethylpyridine (0.91 g, 7.5 mmol) in CH_2Cl_2 (10 mL) at −78 °C. After stirring for 1 h,

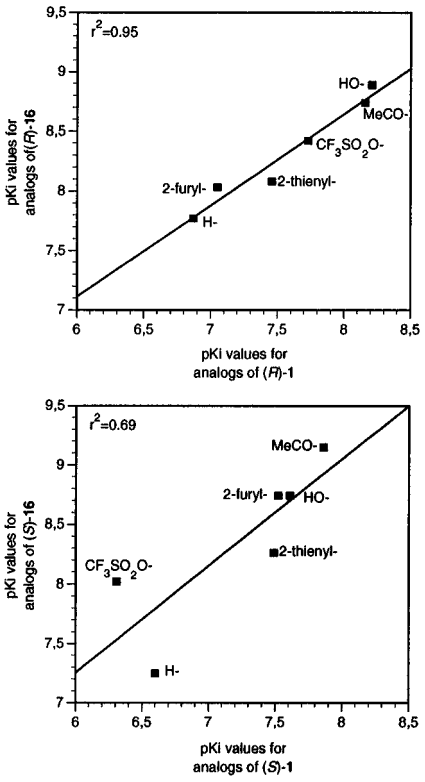


Figure 1. Correlation of pK_i for 5-HT$_{1A}$ receptors between 8-substituted analogs of (*R*)-**16** and (*R*)-**1** (top) and between 8-substituted analogs of (*S*)-**16** and (*S*)-**1** (bottom).

the cold bath was removed and ether was added. The organic phase was washed with saturated aqueous K_2CO_3 followed by water, dried (K_2CO_3), filtered, and concentrated. The residue was chromatographed [Al_2O_3; ether/light petroleum (1:20)]. The amine was converted into the hydrochloride salt to give 0.58 g (71%) of pure (*S*)-**5**·HCl: ^{1}H NMR δ 1.06 (t, 6H, J = 7.3 Hz), 1.78−2.05 (m, 5H), 2.39−2.47 (m, 1H), 2.79−2.93 (m, 1H), 3.00−3.11 (m, 1H), 3.16−3.38 (m, 6H), 3.78−4.00 (m, 1H), 7.16 (app t, 1H, J = 8.8 Hz), 7.30 (dd, 1H, J = 4.4, 9.0 Hz); ^{13}C NMR δ 11.3, 19.7, 22.8 (d, $J_{C,F}$ = 4.3 Hz), 23.0, 26.1, 54.2, 60.3, 115.5 (d, $J_{C,F}$ = 25.0 Hz), 120.0 (q, $J_{C,F}$ = 319.0 Hz), 121.9 (d, $J_{C,F}$ = 9.8 Hz), 127.3 (d, $J_{C,F}$ = 20.8 Hz), 130.1 (d, $J_{C,F}$ = 5.5 Hz), 144.9 (d, $J_{C,F}$ = 3.1 Hz), 160.8 (d, $J_{C,F}$ = 246.6 Hz); ^{19}F NMR δ −73.8, −115.7.

(*S*)-8-Acetyl-5-fluoro-2-(dipropylamino)tetralin Hydrochloride [(*S*)-6·HCl]. Method II. A mixture of Et_3N (0.2 g, 2.0 mmol), $Pd(OAc)_2$ (6 mg, 0.025 mmol), 1,3-bis(diphenylphosphino)propane (dppp) (11 mg, 0.027 mmol), and DMF (1.3 mL) was added to (*S*)-**5** (0.20 g, 0.50 mmol) followed by the addition of butyl vinyl ether (0.50 g, 5.0 mmol). The reaction flask was filled with nitrogen, sealed, and immersed in an oil bath, preheated to 90 °C. After 1 h, 5% aqueous HCl (2 mL) was added and the reaction mixture was allowed to reach room temperature. The mixture was alkalinized (solid $NaHCO_3$) and then extracted with ether. The combined organic layers was washed with water to neutral pH, dried (K_2CO_3), filtered, and concentrated. The crude residue was chromatographed [Al_2O_3; ether/light petroleum (1:8)], and the amine was converted into the hydrochloride salt, which was recrystallized to give 0.14 g (85%) of pure (*S*)-**6**·HCl: ^{1}H NMR δ 1.05 (t, 6H, J = 7.4 Hz), 1.78−2.01 (m, 5H), 2.33−2.43 (m, 1H), 2.59 (s, 3H), 2.73−2.88 (m, 1H), 3.10−3.35 (m, 6H), 3.52−3.61 (m, 1H), 3.65−3.77 (m, 1H), 7.10 (app t, 1H, J = 8.8 Hz), 7.89 (dd, 1H, J = 5.8, 8.7 Hz); ^{13}C NMR δ 11.3, 19.8, 22.7 (d, $J_{C,F}$ = 4.9 Hz), 22.9, 29.6, 29.9, 54.0, 61.3, 113.7 (d, $J_{C,F}$ = 22.0 Hz), 125.6 (d, $J_{C,F}$ = 18.3 Hz), 132.1 (d, $J_{C,F}$ = 9.7 Hz), 134.6 (d, $J_{C,F}$ = 3.7 Hz), 137.8 (d, $J_{C,F}$ = 4.9 Hz), 163.8 (d, $J_{C,F}$ = 251.5 Hz), 202.2; ^{19}F NMR δ −109.9; IR 1690 cm^{-1} (ν CO).

Method III. A mixture of (*S*)-**5** (0.1 g, 0.24 mmol), tetramethylstannane (0.2 g, 1.0 mmol), LiCl (30 mg, 0.74 mmol), [1,1′-bis(diphenylphosphino)ferrocene]palladium(II) chloride [$PdCl_2$(dppf)] (12 mg, 0.01 mmol), 4 Å molecular sieves (25 mg), and 2,6-di-*tert*-butyl-4-methylphenol (a few grains) in DMF (2 mL) was stirred under an atmosphere of CO at 90 °C for 16 h. The mixture was filtered (Celite) and concentrated. The residue was partitioned between ether and water, and the organic phase was dried (K_2CO_3), filtered, and concentrated. The crude product was chromatographed [Al_2O_3; ether/light petroleum (1:8)], and the amine was converted into the hydrochloride salt, which was recrystallized to give 42 mg (54%) of pure (*S*)-**6**·HCl.

(*S*)-5-Fluoro-8-(2-furyl)-2-(dipropylamino)tetralin Hydrochloride [(*S*)-7·HCl]. Method IV. Tributyl(2-furyl)-stannane (0.43 g, 1.2 mmol) in DMF (6 mL) was added to a mixture of (*S*)-**5** (0.40 g, 1 mmol), $(Ph_3P)_4Pd$ (23 mg, 0.02 mmol), and LiCl (0.13 g, 3 mmol) in DMF (10 mL). The flask was filled with nitrogen, sealed, and immersed in an oil bath, preheated to 120 °C. After 5 min the catalysts were filtered off (Celite) and the volatiles were evaporated *in vacuo*. The crude oil was dissolved in ether, washed with saturated aqueous K_2CO_3, dried (K_2CO_3), filtered, and concentrated. The residue was chromatographed [Al_2O_3; ether/light petroleum (1:20)], and the amine was converted into the hydrochloride salt, which was recrystallized to give 0.27 g (75%) of pure (*S*)-**7**·HCl: ^{1}H NMR δ 1.04 (t, 6H, J = 7.4 Hz), 1.71−2.04 (m, 5H), 2.37−2.43 (m, 1H), 2.77−2.90 (m, 1H), 3.15−3.37 (m, 7H), 3.69−3.81 (m, 1H), 6.56−6.58 (m, 1H), 6.62−6.63 (m, 1H), 7.03 (app t, 1H, J = 8.9 Hz), 7.51 (dd, 1H, J = 5.6, 8.5 Hz), 7.62−7.63 (m, 1H); ^{13}C NMR δ 11.4, 19.8, 22.9 (d, $J_{C,F}$ = 4.8 Hz), 23.1, 30.2 (d, $J_{C,F}$ = 2.4 Hz), 54.1, 61.7, 110.3, 112.5, 114.1 (d, $J_{C,F}$ = 21.9 Hz), 124.5 (d, $J_{C,F}$ = 18.4 Hz), 128.4 (d, $J_{C,F}$ = 3.6 Hz), 128.7 (d, $J_{C,F}$ = 9.8 Hz), 133.6 (d, $J_{C,F}$ = 4.9 Hz), 143.7, 153.4, 161.5 (d, $J_{C,F}$ = 245.4 Hz); ^{19}F NMR δ −117.3.

Method V. A mixture of (*S*)-**5** (0.10 g, 0.25 mmol), $(Ph_3P)_4$-Pd (7 mg, 0.006 mmol), LiCl (21 mg, 0,50 mmol), 2 M aqueous Na_2CO_3 (0.4 mL), 99% EtOH (0.75 mL), and 2-furanboronic acid[26] (36 mg, 0.38 mmol) in dimethoxyethane (DME; 3 mL) was refluxed for 3 h. The solvent was evaporated, and the residue was dissolved in ether. The ether solution was washed with saturated aqueous K_2CO_3 and brine, dried (K_2CO_3), filtered, and concentrated. The residue was chromatographed [Al_2O_3; ether/light petroleum (1:30)]. The amine was converted into the hydrochloride salt to give 60 mg (65%) of pure (*S*)-**7**·HCl.

(*S*)-5-Fluoro-8-(2-thienyl)-2-(dipropylamino)tetralin Hydrochloride [(*S*)-8·HCl]. This compound was prepared according to method IV from (*S*)-**5** (0.16 g, 0.40 mmol), tributyl-(2-thienyl)stannane (0.22 g, 0.60 mmol), $(Ph_3P)_4Pd$ (14 mg, 0.012 mmol), and LiCl (51 mg, 1.19 mmol) in DMF (3 mL) affording pure (*S*)-**8**·HCl (0.11 g, 73%): ^{1}H NMR δ 1.00 (t, 6H, J = 7.3 Hz), 1.63−1.85 (m, 4H), 1.87−2.02 (m, 1H), 2.33−2.42 (m, 1H), 2.78−2.91 (m, 1H), 3.10−3.32 (m, 7H), 3.63−3.77 (m, 1H), 7.01 (app t, 1H, J = 8.9 Hz), 7.09−7.11 (m, 1H), 7.12−7.15 (m, 1H), 7.27 (dd, 1H, J = 5.7, 8.5 Hz), 7.47−7.50 (m, 1H); ^{13}C NMR δ 11.3, 19.7, 19.8, 22.8 (d, $J_{C,F}$ = 4.9 Hz), 23.0, 30.4, 53.6, 54.4, 61.6, 113.9 (d, $J_{C,F}$ = 23.2 Hz), 124.5 (d, $J_{C,F}$ = 18.3 Hz), 127.1, 128.5 (2C:s), 131.3 (d, $J_{C,F}$ = 8.5 Hz), 131.9 (d, $J_{C,F}$ = 3.7 Hz), 135.0 (d, $J_{C,F}$ = 4.9 Hz), 141.9, 161.7 (d, $J_{C,F}$ = 245.4 Hz); ^{19}F NMR δ −117.4.

(*R*)-5-Fluoro-2-(dipropylamino)tetralin Hydrochloride [(*R*)-9·HCl]. Method VI. A solution of Et_3N (69 mg, 0.68 mmol), $Pd(OAc)_2$ (3 mg, 0.011 mmol), and 1,1′-bis(diphenylphosphino)ferrocene (dppf) (13 mg, 0.023 mmol) in DMF (1.7 mL) was added to (*R*)-**5** (90 mg, 0.23 mmol). Formic acid (98%, 21 mg, 0.45 mmol) was added, and the flask was filled with nitrogen, sealed, and immersed in an oil bath, preheated to 60 °C. After 15 min, the reaction mixture was diluted with ether. The ether solution was washed with saturated aqueous K_2CO_3 and brine, dried (K_2CO_3), filtered, and concentrated. The crude product was chromatographed [Al_2O_3; ether/light petroleum (1:20)], and the amine was converted into the hydrochloride salt, which was recrystallized to give 46 mg (71%) of pure (*R*)-**9**·HCl: ^{1}H NMR δ 1.05 (t, 6H, J = 7.3 Hz), 1.75−2.04 (m, 5H), 2.35−2.42 (m, 1H), 2.72−2.87 (m, 1H), 3.09−3.32 (m, 7H), 3.70−3.82 (m, 1H), 6.91 (app t, 1H, J = 8.9 Hz), 7.01 (d, 1H, J = 7.7 Hz), 7.14−7.22 (m, 1H); ^{13}C NMR δ 11.4, 19.7, 22.5 (d, $J_{C,F}$ = 4.9 Hz), 24.2, 30.3 (d, $J_{C,F}$ = 2.4

Hz), 53.9, 61.1, 113.8 (d, $J_{C,F}$ = 21.5 Hz), 123.6 (d, $J_{C,F}$ = 17.4 Hz), 126.0 (d, $J_{C,F}$ = 3.5 Hz), 128.7 (d, $J_{C,F}$ = 9.2 Hz), 136.6 (d, $J_{C,F}$ = 4.9 Hz), 162.0 (d, $J_{C,F}$ = 243.0 Hz); ^{19}F NMR δ −118.5.

(*S*)-5-Fluoro-8-methoxy-*N*-[4-(8-aza-7,9-dioxospiro[4.5]-decan-8-yl)butyl]-2-(propylamino)tetralin Hydrochloride [(*S*)-11·HCl]. Method VII. A mixture of (*S*)-**10**·HCl (2.0 g, 7 mmol), 8-(4-bromobutyl)-8-azaspiro[4.5]decane-7,9-dione (2.7 g, 9 mmol), K_2CO_3 (4.0 g, 29 mmol), and acetonitrile (15 mL) was heated to reflux under nitrogen for 36 h. Ether was added, and the reaction mixture was filtered and concentrated. The residue was chromatographed [SiO_2; ether/light petroleum (1:1) saturated with ammonia], and the amine was converted into the hydrochloride salt, which was recrystallized to give pure (*S*)-**11**·HCl (2.2 g, 61%): ^{1}H NMR δ 1.05 (t, 3H, J = 7.3 Hz), 1.48−1.53 (m, 4H), 1.60−1.99 (m, 11H), 2.30−2.38 (m, 1H), 2.65 (s, 4H), 2.71−2.84 (m, 2H), 3.04−3.41 (m, 6H), 3.67−3.77 (m, 1H), 3.79−3.84 (m, 2H), 3.82 (s, 3H), 6.78 (dd, 1H, J = 4.4, 9.0 Hz), 6.91 (app t, 1H, J = 9.1 Hz); ^{13}C NMR δ 11.4, 19.8, 22.9 (d, $J_{C,F}$ = 3.6 Hz), 23.6, 23.7, 25.2 (3C:s), 26.3, 38.5, 39.2, 40.7, 45.5, 52.1, 53.9, 56.3, 61.4, 109.4 (d, $J_{C,F}$ = 8.5 Hz), 113.6 (d, $J_{C,F}$ = 23.2 Hz), 124.2 (d, $J_{C,F}$ = 3.6 Hz), 124.7 (d, $J_{C,F}$ = 20.7 Hz), 154.7, 156.2 (d, $J_{C,F}$ = 236.8 Hz), 174.6; ^{19}F NMR δ −129.05; IR 1725, 1675 cm^{-1} (ν CO).

(*R*)-5-Fluoro-8-hydroxy-*N*-[4-(8-aza-7,9-dioxospiro[4.5]-decan-8-yl)butyl]-2-(propylamino)tetralin Hydrochloride [(*R*)-12·HCl]. Method VIII. BBr_3 (2.2 mL, 24 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a stirred solution of (*R*)-**11** (1.6 g, 3 mmol) in CH_2Cl_2 (30 mL) under nitrogen at −70 °C. After 1 h at room temperature, the reaction mixture was washed with saturated aqueous $NaHCO_3$. The organic layer was separated, dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed [SiO_2; CH_2Cl_2/MeOH (95:5)], and the amine was converted into the hydrochloride salt to give pure (*R*)-**12**·HCl (1.6 g, 69%): ^{1}H NMR δ 1.05 (t, 3H, J = 7.3 Hz), 1.47−1.53 (m, 4H), 1.63−1.96 (m, 11H), 2.31−2.37 (m, 1H), 2.65 (s, 4H), 2.72−2.82 (m, 2H), 3.06−3.34 (m, 6H), 3.65−3.78 (m, 1H), 3.82 (t, 2H, J = 6.7 Hz), 6.61 (dd, 1H, J = 4.5, 8.7 Hz), 6.76 (app t, 1H, J = 9.0 Hz); ^{13}C NMR δ 11.4, 19.8, 22.9 (d, $J_{C,F}$ = 3.7 Hz), 23.6, 23.9, 25.2, 25.4, 26.3, 38.5, 39.2, 40.7, 45.5, 52.1, 53.9, 61.5, 113.4 (d, $J_{C,F}$ = 8.5 Hz), 113.7 (d, $J_{C,F}$ = 23.6 Hz), 122.5 (d, $J_{C,F}$ = 3.6 Hz), 124.3 (d, $J_{C,F}$ = 19.5 Hz), 152.3 (d, $J_{C,F}$ = 2.4 Hz), 155.4 (d, $J_{C,F}$ = 234.4 Hz), 174.6; ^{19}F NMR δ −130.5; IR 1670, 1725 cm^{-1} (ν CO).

(*S*)-5-Fluoro-8-[(trifluoromethyl)sulfonyl]-*N*-[4-(8-aza-7,9-dioxospiro[4.5]decan-8-yl)butyl]-2-(propylamino)tetralin Hydrochloride [(*S*)-13·HCl]. This compound was prepared according to method I using (*S*)-**12** (0.97 g, 2.2 mmol), trifluoromethanesulfonic anhydride (1.34 g, 4.8 mmol), and 2,4,6-trimethylpyridine (1.2 mL, 8.7 mmol) in CH_2Cl_2 (30 mL). The crude product was chromatographed [Al_2O_3; ether/light petroleum (1:1)], and the amine was converted into the hydrochloride salt, which was recrystallized to give 0.90 g (67%) of pure (*S*)-**13**·HCl: ^{1}H NMR δ 1.06 (t, 3H, J = 7.3 Hz), 1.51−1.56 (m, 4H), 1.63−2.05 (m, 11H), 2.40−2.46 (m, 1H), 2.65 (s, 4H), 2.80−2.95 (m, 1H), 3.01−3.11 (m, 1H), 3.16−3.36 (m, 6H), 3.75−3.91 (m, 3H), 7.16 (app t, 1H, $^3J_{H,F} = J_{6,7}$ = 8.8 Hz), 7.30 (dd, 1H, J = 4.5, 9.1 Hz); ^{13}C NMR δ 11.4, 19.8, 22.9, 23.5, 25.2, 26.0, 26.2, 38.5, 39.1, 40.7, 45.4, 52.3, 54.1, 60.2, 115.5 (d, $J_{C,F}$ = 25.6 Hz), 120.0 (q, $J_{C,F}$ = 319.8 Hz), 121.9 (d, $J_{C,F}$ = 9.8 Hz), 127.3 (d, $J_{C,F}$ = 19.5 Hz), 130.2 (d, $J_{C,F}$ = 4.9 Hz), 144.9 (d, $J_{C,F}$ = 2.4 Hz), 160.8 (d, $J_{C,F}$ = 246.5 Hz), 174.6; ^{19}F NMR δ −73.8, −115.8; IR 1670, 1725 cm^{-1} (ν CO).

***(S)*-8-Acetyl-5-fluoro-*N*-[4-(8-aza-7,9-dioxospiro[4.5]-decan-8-yl)butyl]-2-(propylamino)tetralin Hydrochloride [(*S*)-14·HCl].** This compound was prepared according to method II using *(S)*-**13** (0.29 g, 0.5 mmol), Et_3N (0.2 g, 2.0 mmol), $Pd(OAc)_2$ (5.6 mg, 0.03 mmol), 1,3-bis(diphenylphosphino)propane (dppp) (11.4 mg, 0.03 mmol), and butyl vinyl ether (0.5 g, 5.0 mmol) in DMF (1.5 mL) and 5% aqueous HCl (2.0 mL). The crude product was chromatographed (Al_2O_3; ether) and the amine converted into the hydrochloride salt, which was recrystallized to give pure *(S)*-**14**·HCl (0.2 g, 80%): ^{1}H NMR δ 1.05 (t, 3H, J = 7.3 Hz), 1.48−1.53 (m, 4H), 1.62−1.98 (m, 11H), 2.34−2.42 (m, 1H), 2.59 (s, 3H), 2.65 (s, 4H), 2.74−2.88 (m, 1H), 3.12−3.35 (m, 6H), 3.52−3.60 (m, 1H), 3.64−3.76 (m, 1H), 3.81 (t, 2H, J = 6.7 Hz), 7.10 (app t, 1H, J = 8.8 Hz), 7.89 (dd, 1H, J = 5.7, 8.7 Hz); ^{13}C NMR δ 11.4, 19.8, 22.7 (d, $^3J_{C,F}$ = 4.9 Hz), 22.9, 23.6, 25.2, 26.2, 29.7, 29.8, 38.5, 39.2, 40.7, 45.4, 52.1, 54.0, 61.3, 113.7 (d, $J_{C,F}$ = 23.2 Hz), 125.6 (d, $J_{C,F}$ = 18.3 Hz), 132.0 (d, $J_{C,F}$ = 11.0 Hz), 134.7 (d, $J_{C,F}$ = 3.6 Hz), 137.8 (d, $J_{C,F}$ = 6.1 Hz), 163.8 (d, $J_{C,F}$ = 251.5 Hz), 174.6, 202.3; ^{19}F NMR δ −109.9; IR 1670, 1725 cm^{-1} (ν CO).

(*S*)-5-Fluoro-8-(2-furyl)-*N*-[4-(8-aza-7,9-dioxospiro[4.5]-decan-8-yl)butyl]-2-(propylamino)tetralin Oxalate [(*S*)-15·(COOH)$_2$]. This compound was prepared according to method IV using (*S*)-**13** (0.29 g, 0.5 mmol), tributyl(2-furyl)-stannane (0.22 g, 0.6 mmol), $(Ph_3P)_4Pd$ (12 mg, 0.01 mmol), and LiCl (0.06 g, 1.5 mmol) in DMF (10 mL). The crude product was chromatographed [Al_2O_3; ether/light petroleum (2:1)] to give pure (*S*)-**15** (0.21 g, 85%). The amine was converted into the oxalate salt (*S*)-**15**·$(COOH)_2$: ^{1}H NMR δ 1.02 (t, 3H, J = 7.3 Hz), 1.48−1.50 (m, 4H), 1.59−2.03 (m, 11H), 2.34−2.44 (m, 1H), 2.63 (s, 4H), 2.75−2.88 (m, 1H), 3.10−3.34 (m, 7H), 3.66−3.81 (m, 3H), 6.55−6.56 (m, 1H), 6.64 (d, 1H, J = 3.2 Hz), 7.02 (app t, 1H, J = 8.9 Hz), 7.52 (dd, 1H, J = 5.7, 8.7 Hz), 7.62 (m, 1H); ^{13}C NMR δ 11.4, 19.6, 22.9 (d, $J_{C,F}$ = 4.3 Hz), 23.2, 23.4, 25.2, 26.2, 30.3, 38.5, 39.2, 40.7, 45.4, 51.9, 53.9, 61.5, 110.4, 112.6, 114.1 (d, $J_{C,F}$ = 22.6 Hz), 124.5 (d, $J_{C,F}$ = 18.0 Hz), 128.4 (d, $J_{C,F}$ = 3.7), 128.6 (d, $J_{C,F}$ = 8.5 Hz), 133.7 (d, $J_{C,F}$ = 4.3 Hz), 143.7, 153.4, 161.5 (d, $J_{C,F}$ = 245.4 Hz, C-5), 167.2, 174.6; ^{19}F NMR δ −117.4; IR 1670, 1725 cm^{-1} (ν CO).

Pharmacology. 5-HT$_{1A}$ Receptor Binding Assay. The 5-HT$_{1A}$ receptor binding assays were performed as described previously, using [^{3}H]-8-OH-DPAT·HBr as radioligand.[20]

VIP-Stimulated cAMP Production Assay. GH_4ZD10 cells were obtained from Dr. Olivier Civelli (Vollum Institue for Advanced Biomedical Research, Oregon Health Sciences University, OR). Ham's F10 medium, Earle's balanced salt solution (EBSS) without Ca^{2+} and Mg^{2+}, and fetal calf serum (FCS), penicillin, streptomycin, and HEPES were obtained from Gibco Ltd., Paisley, Scotland, U.K. [^{3}H]-Adenosine 3′,5′-cyclic monophosphate ([^{3}H]cAMP) and cAMP were obtained from Amersham International plc, Amersham, U.K. Vasoactive intestinal polypeptide (VIP), theophylline, dithiothreitol, 3-isobutyl-1-methylxanthine (IBMX), Tris/HCl, Tris/base, geneticin, and 5-HT were obtained from Sigma Chemical Co., St. Louis, MO, and ascorbic acid was obtained from Merck, Darmstadt, Germany.

The cAMP assay, using cell suspensions, was carried out according to Dorflinger and Schonbrunn[27] with some minor modifications. Briefly, medium was removed, and the cells were detached from the culture flasks with EBSS supplemented with 1 mM EDTA (without Ca^{2+} or Mg^{2+}). Cells were then suspended in FCS-free Ham's medium. The suspension was centrifuged at ca. 250*g* for 5−7 min at room temperature and resuspended to a density of about 1 × 10^7 cells/mL in Ham's F10 medium containing 0.01% ascorbic acid and 0.1 mM IBMX. Cells were then preincubated in this solution for 1 h at 37 °C and then diluted with the same medium to a final density of 0.8−1.5 × 10^6 cells/mL. Aliquots (0.4 mL) of the cell suspension were added to Eppendorf tubes containing 0.1 mL of VIP (39 nM final concentration) along with the compounds and incubated for 20 min at 37 °C. Each sample was carried out in duplicate. Reactions were stopped by placing the assay tubes in boiling water for 4 min. The lysates were then centrifuged at 12 000 rpm for 4−5 min at 4 °C and supernatants frozen and stored at −20 °C until analyzed.

cAMP levels were determined in triplicate according to the method of Brown et al.[28] as modified by Nordstedt and Fredholm.[29] Results are given as percentage of the VIP-stimulated response (set to 100%). Statistical analysis was carried out using ANOVA followed by Scheffe's post hoc comparisons.

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