(*R*)-(+)-2-[[[3-(Morpholinomethyl)-2*H*-chromen-8-yl]oxy]methyl]morpholine Methanesulfonate: A New Selective Rat 5-Hydroxytryptamine$_{1B}$ Receptor Antagonist

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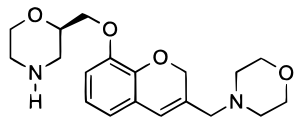
Received December 1, 1997

In the search for new 5-hydroxytryptamine (5-HT) receptor antagonists it was found that the compound (*R*)-(+)-2-[[[3-(morpholinomethyl)-2*H*-chromen-8-yl]oxy]methyl]morpholine methanesulfonate, (*R*)-**25**, is a selective rat 5-hydroxytryptamine$_{1B}$ (r5-HT$_{1B}$) receptor antagonist. The binding profile showed a 13-fold preference for r5-HT$_{1B}$ (K_i = 47 ± 5 nM; n = 3) vs bovine 5-HT$_{1B}$ (K_i = 630 nM; n = 1) receptors. The compound had very low affinity for other monoaminergic receptors examined. The r5-HT$_{1B}$ receptor antagonism was demonstrated by the potentiation of the K^+-stimulated release of [^{3}H]-5-HT from superfused rat brain slices in vitro, an effect that was antagonized by addition of 5-HT to the superfusion fluid. (*R*)-**25** at 20 mg/kg sc enhanced the 5-HT turnover in four rat brain regions (hypothalamus, hippocampus, striatum, and frontal cortex) with about 40% measured as the 5-HTP accumulation after decarboxylase inhibition with 3-hydroxybenzylhydrazine. At 3 mg/kg sc (*R*)-**25** produced a significant increase in the number of wet dog shakes in rats, a 5-HT$_{2A}$/5-HT$_{2C}$ response that was abolished by depletion of 5-HT after pretreatment with the tryptophan hydroxylase inhibitor *p*-chlorophenylalanine. These observations show that (*R*)-**25**, by inhibiting terminal r5-HT$_{1B}$ autoreceptors, increases the 5-HT turnover and the synaptic concentration of 5-HT.

Introduction

Of the many 5-hydroxytryptamine (5-HT, serotonin) receptors discovered,[1] two subtypes of the 5-HT$_1$ receptor group appear to play important roles in the feedback regulation of the activity in 5-HT neurons. Inhibitory somatodendritic 5-HT$_{1A}$ receptors in the raphé nuclei sense the concentration of 5-HT around the cell bodies. Through these receptors the impulse propagation in the 5-HT neuron is regulated and thereby also the amount of 5-HT being released at the nerve terminals.[2] 5-HT$_{1B}$ autoreceptors located on the nerve terminals regulate the synaptic concentration of 5-HT by controlling the exocytotic release of 5-HT.[3,4] The influence of the somatodendritic 5-HT$_{1A}$ receptors on 5-HT neurotransmission has been extensively studied with electrophysiological and neurochemical techniques[5−8] using selective 5-HT$_{1A}$ receptor agonists and antagonists. However, the lack of selective ligands for the 5-HT$_{1B}$ receptors has hampered studies of the functional role of the terminal autoreceptors in the regulation of release of 5-HT. Another impeding factor has been the species difference in the terminal 5-HT autoreceptors between rodents and most other species including man. Although the rodent 5-HT$_{1B}$ (r5-HT$_{1B}$) receptor displays more than 90% homology with the human h5-HT$_{1B}$ receptor, their pharmacology is quite different.[9] During recent years an increasing interest has therefore been focused on development of agonists and antagonists of the h5-HT$_{1B}$ receptor, resulting in selective agonists, e.g., sumatriptan,[10] and antagonists, e.g., GR 127935.[11] It was observed earlier that some but not all β-adrenoceptor antagonists, e.g., (−)-pindolol, (−)-cyanopindolol, (−)-propranolol, and (−)-alprenolol, also antagonize the 5-HT$_{1A}$ and r5-HT$_{1B}$ receptors but have low affinities for other 5-HT receptors.[12] Other β-adrenoceptor antagonists with high affinity for r5-HT$_{1B}$ are (−)-penbutulol[13] and isamoltane.[14,15]

Chart 1



•CH_3SO_3H•H_2O

((*R*)-**25**)

During our synthesis and screening for new selective antagonists of the terminal 5-HT$_{1B}$ autoreceptor with potential for antidepressive effect, we discovered that one compound, *R*-(+)-2-[[[3-(morpholinomethyl)-2*H*-chromen-8-yl]oxy]methyl]morpholine methanesulfonate, NAS-181 ((*R*)-**25**) (Chart 1), is a selective r5-HT$_{1B}$ receptor antagonist with interesting in vitro and in vivo properties in rats.

Chemistry

Two key intermediates, described by the general formula **A** and **B** (Scheme 5), were prepared and used in the synthesis of (*R*)-(+)-2-[[[3-(morpholinomethyl)-2*H*-chromen-8-yl]oxy]methyl]morpholine methanesulfonate ((*R*)-**25**) and its analogues.

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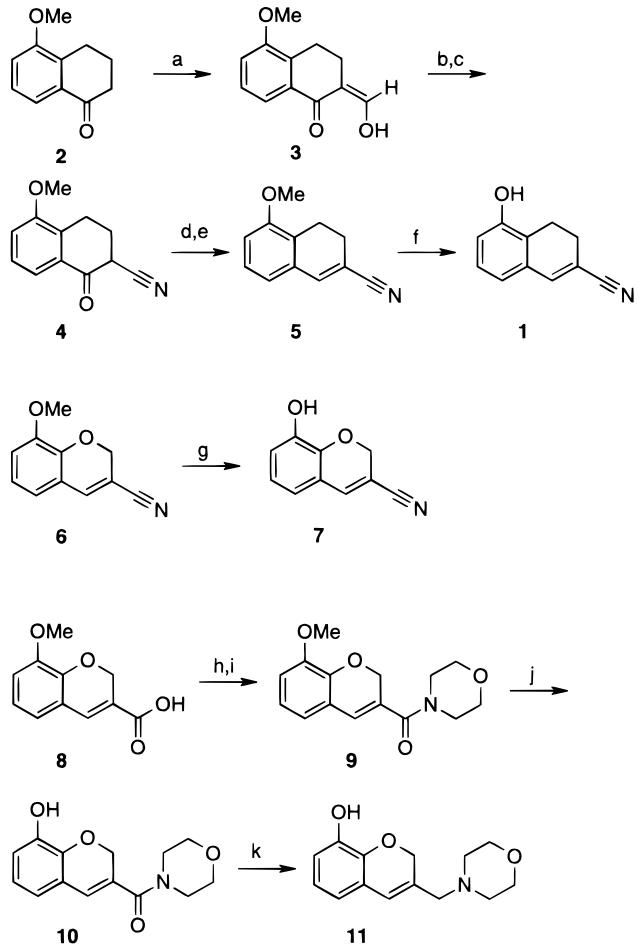
S0022-2623(97)00806-6 CCC: $15.00
Published on Web 04/29/1998

Scheme 1[a]

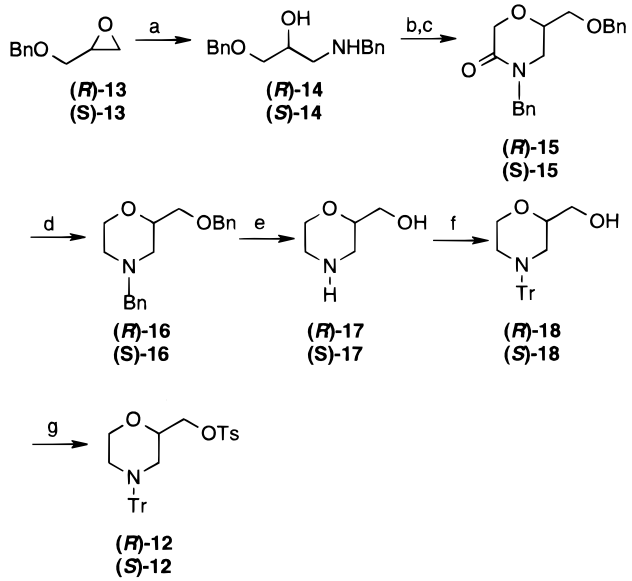


[a] Reagents and conditions: (a) $NaOCH_3$, ethyl formate, MeOH; (b) $H_2NOH{\cdot}HCl$, HOAc, Δ; (c) $NaOCH_3$, MeOH, 0 °C; (d) $NaBH_4$, MeOH; (e) PTS, toluene, Δ; (f) BBr_3, CH_2Cl_2, rt; (g) BBr_3, CH_2Cl_2, −20 °C; (h) $SOCl_2$, toluene, Δ; (i) morpholine, dioxane; (j) BBr_3, CH_2Cl_2, −20 °C; (k) LAH, $AlCl_3$, THF, 0 °C.

The synthesis of the phenols **1**, **7**, **10** and **11** (**A** intermediates in Scheme 5) is outlined in Scheme 1. 6-Cyano-7,8-dihydro-1-naphthol (**1**) was synthesized starting from the commercially available 5-methoxy-1-tetralone (**2**) which was transformed into the 2-hydroxymethylene derivative **3** by treatment with ethyl formate and sodium methoxide. Treatment with hydroxylamine hydrochloride in acetic acid at reflux followed by stirring in methanol in the presence of sodium methoxide gave the nitrile **4**. The keto group was reduced with sodium borohydride, whereupon the formed alcohol was dehydrated using a Dean−Stark trap. The above synthesis was carried out by a slight modification of a procedure previously described.[16] The methoxy group in derivative **5** was cleaved with boron tribromide at room temperature to give the phenol **1** in high yield.

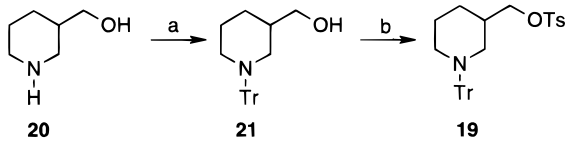
The corresponding chromene **7** was prepared in one step by demethylation of 8-methoxy-3-cyano-2*H*-chromene (**6**)[17] with boron tribromide at −20 °C in 92% yield. 8-Hydroxy-3-(*N*-morpholinomethyl)-2*H*-chromene (**11**) was synthesized starting from 8-methoxy-2*H*-chromene-3-carboxylic acid (**8**)[17] which was converted to the acid chloride by reaction with thionyl chloride. The acid chloride was then reacted with morpholine to form the amide **9** which was subsequently treated with boron tribromide at −20 °C to give the phenol **10**. The amide function in compound **10** was initially reduced with lithium aluminum hydride in low yields, but it was found that aluminum hydride[18,19] was a superior reducing agent giving compound **11** in 96% yield.

Scheme 2[a]



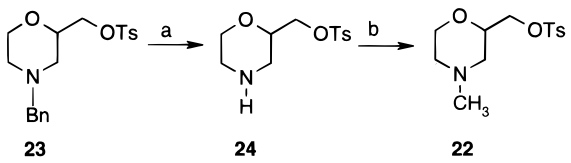
[a] Reagents and conditions: (a) benzylamine; (b) chloroacetyl chloride, TEA, CH_2Cl_2; (c) $NaOCH_3$, methanol, Δ; (d) LAH, diethyl ether; (e) Pd/C, H_2, EtOH/HOAc, Δ; (f) trityl chloride, TEA, CH_2Cl_2; (g) *p*-tosyl chloride, pyridine, CH_2Cl_2.

Scheme 3[a]



[a] Reagents and conditions: (a) trityl chloride, TEA, CH_2Cl_2; (b) *p*-tosyl chloride, pyridine, CH_2Cl_2.

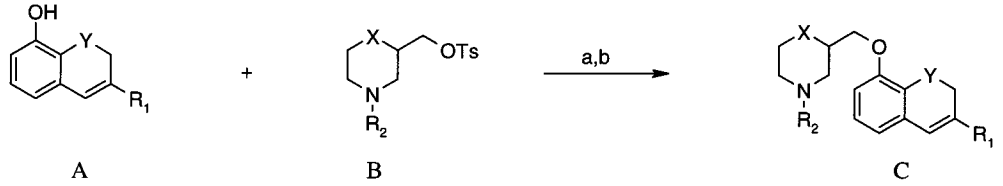
Scheme 4[a]



[a] Reagents and conditions: (a) Pd/C, H_2, HOAc; (b) iodomethane, DMF.

The syntheses of the key intermediates **12**, **19** and **22** (**B** intermediates in Scheme 5) are shown in Schemes 2−4, and they were performed as follows: The synthesis of the enantiomers of (*R*,*S*)-2-[[(*p*-tolylsulfonyl)oxy]methyl]-4-(triphenylmethyl)morpholine[20] ((*R*,*S*)-**12**), (*R*)-**12** and (*S*)-**12**, starts with a nucleophilic ring opening of the glycidyl ether (*R*)-**13** or (*S*)-**13** using an excess of benzylamine (Scheme 2). The amino alcohols **14** were acylated using chloroacetyl chloride, and the formed product was cyclized in methanol at reflux using sodium methoxide to give the lactam **15** in approximately 90% yield. The lactam **15** was reduced to the morpholine compound **16** with lithium aluminum hydride in diethyl ether at room temperature in high yield followed by removal of the benzyl groups by hydrogenation over palladium on activated carbon at 55−60 °C to give

Scheme 5[a]



A B C

No	Y	R_1	No	X	R_2	No	Y	R_1	X	R_2
11	O	CH_2-morpholino	(*R,S*)-12	O	Tr	(*R,S*)-25	O	CH_2-morpholino	O	H
11			(*R*)-12	O	Tr	(*R*)-25	O	CH_2-morpholino	O	H
11			(*S*)-12	O	Tr	(*S*)-25	O	CH_2-morpholino	O	H
1	CH_2	CN	(*R,S*)-12	O	Tr	(*R,S*)-26	CH_2	CN	O	H
7	O	CN	(*R,S*)-12	O	Tr	(*R,S*)-27	O	CN	O	H
7			22	O	CH_3	(*R,S*)-28	O	CN	O	CH_3
7			19	CH_2	Tr	(*R,S*)-29	O	CN	CH_2	H
10	O	CO-morpholino	(*R,S*)-12	O	Tr	(*R,S*)-30	O	CO-morpholino	O	H

[a] Reagents and conditions: (a) DMF, K_2CO_3, Δ; (b) where applicable HOAc/H_2O.

Table 1. Affinities of New Compounds for the r5-HT_{1B} Receptor in Membranes of Rat Cerebral Cortex Using [^{125}I]Iodocyanopindolol as Ligand

compd	K_i, nM (±SEM)	*n*
(*R,S*)-**25**	60 ± 14	5
(*R*)-**25**	47 ± 5	3
(*S*)-**25**	275 ± 38	3
(*R,S*)-**26**	445	1
(*R,S*)-**27**	250 ± 50	3
(*R,S*)-**28**	3600	1
(*R,S*)-**29**	1400	1
(*R,S*)-**30**	240	1

compound **17** in a moderate yield. Protection of the morpholine nitrogen with triphenylmethyl chloride gave compound **18**, and subsequent conversion of the alcohol group to the tosylate gave compound **12** in good yield.

(*R,S*)-3-[[(*p*-Tolylsulfonyl)oxy]methyl]-1-(triphenylmethyl)piperidine (**19**) was synthesized from the commercially available (*R,S*)-3-(hydroxymethyl)piperidine (**20**) which was reacted with triphenylmethyl chloride to give compound **21** and then finally tosylated (Scheme 3).

(*R,S*)-4-Methyl-2-[[(*p*-tolylsulfonyl)oxy]methyl]morpholine (**22**) was prepared in two steps from (*R,S*)-4-benzyl-2-[[(*p*-tolylsulfonyl)oxy]methyl]morpholine[21] (**23**) (Scheme 4). The benzyl group was removed by catalytic hydrogenation at room temperature. Methylation of compound **24** with iodomethane gave **22** in 71% yield.

The syntheses of the final compounds **25**−**30** (**C**) are shown in Scheme 5. The phenols **1**, **7**, **10**, and **11** were alkylated with the tosylates (*R,S*)-**12**, (*S*)-**12**, (*R*)-**12**, **21**, and **22** yielding the desired products. In the cases where applicable, the alkylation was followed by hydrolysis of the trityl group in acetic acid.

Pharmacology

Radioligand binding studies, using [^{125}I]iodocyanopindolol as ligand for the r5-HT_{1B} receptor, showed that compound (*R*)-**25** had the highest affinity for this receptor (Table 1). The other enantiomer, (*S*)-**25**, and (*R,S*)-**27** and (*R,S*)-**30** were 4−5 times less active as (*R*)-**25**. The other compounds tested ((*R,S*)-**26**, (*R,S*)-**28**, and (*R,S*)-**29**) were even less potent. (*R*)-**25** was therefore chosen for further studies in order to elucidate its selectivity and its in vivo properties.

Table 2. Receptor Binding Profile of (*R*)-**25** and Its Antipode

		affinity, K_i, nM	
receptor	ligand	(*R*)-**25**	(*S*)-**25**
5-HT_{1A}	[^{3}H]-8-OH-DPAT	>10 000	>10 000
b5-HT_{1B} + 5-HT_{1D}	[^{3}H]-5-HT	630	>10 000
5-HT_6	[^{3}H]-5-HT	>3 000	
5-HT_7	[^{3}H]-5-HT	>3 000	
5-HT_{2A}	[^{3}H]ketanserin	>10 000	>10 000
5-HT_{2C}	[^{3}H]mesulergine	>10 000	>10 000
α_1-adrenoceptor	[^{3}H]prazosin	>10 000	>10 000
α_2-adrenoceptor	[^{3}H]RX821002	>10 000	>10 000
β-adrenoceptor	[^{3}H]dihydroalprenolol	>10 000	10 000
dopamine D_1	[^{3}H]SCH 23390	>10 000	>10 000
dopamine D_2	[^{3}H]raclopride	>10 000	>10 000
σ	[^{3}H]DTG	>10 000	>10 000
muscarinic	[^{3}H]QNB	>1 000	

Table 3. Potentiation of K^+-Stimulated Release of [^{3}H]-5-HT from Brain Slices by (*R*)-**25**

concn, nM	*n*	S_2/S_1 (mean ± SEM)	S_2/S_1, % of control	*P*[a]
0	6	0.99 ± 0.03		
10	4	1.11 ± 0.09	115 ± 3	>0.05
100	3	1.23 ± 0.11	131 ± 2	<0.05
1000	8	1.44 ± 0.06	153 ± 6	<0.05

[a] Versus the appropriate control (Student's *t*-test).

The affinity of (*R*)-**25** for the 5-HT_{1D} receptors in calf caudate membranes (mainly constituting the homologous bovine 5-HT_{1B} receptor) was more than 10 times less than that for the rat r5-HT_{1B} receptor. (*R*)-**25** had very low affinities for all other receptors examined, including 5-HT_{2A}, 5-HT_{2C}, 5-HT_6, and 5-HT_7, α_1-, α_2-, and β-adrenoceptors, and dopamine D_1 and D_2 (Table 2).

The r5-HT_{1B} antagonistic property of (*R*)-**25** was characterized in the K^+-stimulated release of [^{3}H]-5-HT from preloaded rat occipital cortical slices. As shown in Table 3 (*R*)-**25** dose-dependently potentiated the [^{3}H]-5-HT release in the concentration range 10−1000 nM. Furthermore, the potentiation of the release caused by (*R*)-**25** was antagonized at 1000 nM but not at 100 nM of unlabeled 5-HT into the superfusion fluid (Table 4), which indicates competition between these two compounds.

The effect of (*R*)-**25** on the 5-HT turnover in rat brain in vivo was determined by using the 5-HTP accumulation technique. At 20 mg/kg sc (*R*)-**25**, the 5-HTP

Table 4. Antagonism of the (*R*)-**25**-Induced Potentiation of K$^+$-Stimulated [^{3}H]-5-HT Release from Brain Slices by 5-HT

expt	treatment	concn, nM	*n*	S_2/S_1 (mean ± SEM)	% of control (mean ± SEM)
1	control		4	0.86 ± 0.04	
	(*R*)-**25**	1000	4	1.28 ± 0.03	149 ± 3
	5-HT	100	6	0.71 ± 0.02	83 ± 2
	(*R*)-**25** + 5-HT	1000 + 100	5	1.39 ± 0.07	161 ± 8
2	control		4	0.75 ± 0.02	
	(*R*)-**25**	1000	4	1.12 ± 0.03	149 ±4
	5-HT	1000	6	0.60 ± 0.02	80 ± 3
	(*R*)-**25** + 5-HT	1000 + 1000	6	0.80 ± 0.02	107 ± 3[a]

[a] $P < 0.05$ vs (*R*)-**25** and 5-HT (Dunnett's *t*-test following ANOVA).

Table 5. Effect of (*R*)-**25**, 20 mg/kg sc, on the 5-HT Turnover in Four Rat Brain Regions

region	treatment	5-HTP, nmol/g of tissue	5-HT, nmol/g of tissue	5-HIAA, nmol/g of tissue	5-HTP, % of control	5-HIAA/5-HT, % of control
hypothalamus	saline	1.21 ± 0.06	5.05 ± 0.27	2.73 ± 0.12		
	(*R*)-**25**	1.69 ± 0.07	4.36 ± 0.17	3.91 ± 0.11	140 ± 5[a]	166 ± 6[a]
hippocampus	saline	0.47 ± 0.03	1.79 ± 0.13	1.64 ± 0.09		
	(*R*)-**25**	0.67 ± 0.02	1.68 ± 0.07	2.30 ± 0.07	148 ± 3[a]	142 ± 5[a]
frontal cortex	saline	0.37 ± 0.02	2.77 ± 0.11	1.05 ± 0.07		
	(*R*)-**25**	0.53 ± 0.02	2.42 ± 0.11	1.47 ± 0.07	142 ± 5[a]	161 ± 10[a]
striatum	saline	0.43 ± 0.03	2.01 ± 0.13	2.43 ± 0.18		
	(*R*)-**25**	0.62 ± 0.02	1.87 ± 0.09	3.27 ± 0.12	142 ± 5[a]	145 ± 5[a]

[a] $P < 0.05$ vs control (Dunnett's *t*-test following ANOVA). (*R*)-**25** or saline was injected 30 min before 3-hydroxybenzylhydrazine dihydrochloride, 100 mg/kg sc, and the rats were sacrificed 30 min thereafter. The brain regions were rapidly dissected, frozen on dry ice, and analyzed with HPLC technique.

Table 6. Effect of (*R*)-**25** on the Wet Dog Shake Response (WDS) in Rats

pretreatment[a]	compd	dose, mg/kg sc	*n*	no. of WDS/60 min[b] (mean ± SEM)
	saline		30	6.0 ± 0.2
saline	(*R*)-**25**	3	10	17 ± 1.6[c]
pCPA	(*R*)-**25**	3	9	9.2 ± 0.8
saline	quipazine	1	8	36 ± 3.0
pCPA	quipazine	1	8	30 ± 3.0

[a] pCPA, 200 mg/kg ip, or saline was injected 72 and 48 h before the test compound. [b] The number of WDS was counted from 5 to 65 min after the injection of the test compounds. [c] $P < 0.05$ vs saline control and pCPA + (*R*)-**25** (Dunnett's *t*-test following ANOVA).

accumulation was significantly increased (40%) compared with saline-treated controls in all four brain regions analyzed (Table 5). The ratio 5-HIAA/5-HT in these brain regions was even more elevated (40−60%).

An enhanced release of 5-HT leading to increased synaptic concentration of 5-HT was strongly supported by the observation that (*R*)-**25** induced wet dog shake behavior in rats (Table 6). The effect was abolished by pretreatment of the rats with the tryptophan hydroxylase inhibitor *p*-chlorophenylalanine (pCPA), indicating the presynaptic 5-HT origin of the effect. When the wet dog shake behavior was evoked by the 5-HT$_{2A}$/5-HT$_{2C}$ receptor agonist quipazine, there was no significant reduction by the pCPA treatment (Table 6).

Discussion

The receptor profile of (*R*)-**25** shows that this compound is a selective r5-HT$_{1B}$ receptor ligand with moderate to high potency. Since (*R*)-**25** has low affinity for the 5-HT$_{1D}$ receptor in calf caudate, which mainly appears to consist of the bovine 5-HT$_{1B}$ receptor,[22,23] the receptor profile of (*R*)-**25** differs from that of 2′-methyl-4′-(5-methyl[1,2,4]oxadiazol-3-yl)biphenyl-4-carboxylic acid [4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]amide (GR127,935) which has high affinity for the two homologous forms of the 5-HT$_{1B}$ receptor and also has high affinity for the 5-HT$_{1D}$ receptor.[24] The affinity of (*R*)-**25** for the latter receptor type remains to be elucidated.

The potentiation of the K$^+$-stimulated [^{3}H]-5-HT release from superfused slices of rat occipital cortex and the competition between (*R*)-**25** and 5-HT in this in vitro model showed that (*R*)-**25** is an antagonist at this receptor. Moreover, (*R*)-**25** markedly increased the 5-HTP accumulation in all four brain regions examined in 3-hydroxybenzylhydrazine-treated rats and increased the 5-HIAA/5-HT ratio in the brain even more. These findings suggest that the 5-HT turnover was increased in these 5-HT terminal regions, supposedly due to the increased 5-HT release from the terminals. The induction of wet dog shake behavior by (*R*)-**25** is in strong accordance with this notion since the response was abolished by depletion of 5-HT in the brain with pCPA. These observations indicate that, under normal conditions, the terminal 5-HT$_{1B}$ receptors have a functional role in determining the amount of 5-HT released from the terminals.

Since (*R*)-**25** is a selective r5-HT$_{1B}$ receptor antagonist, this compound may become a valuable tool for studies of the functional role of the r5-HT$_{1B}$ receptors in rodents.

Experimental Section

Chemistry. ^{1}H and ^{13}C NMR spectra were measured on a Varian Gemini-300 (300 MHz), Varian Unity-400 (400 MHz), or JEOL FX200 (200 MHz) spectrometer using Me_4Si as an internal standard. Mass spectra were recorded on a Finnigan UNICAM Automass or Finnigan MAT SSQ 710 instrument. Melting points were determined on a Mettler FP61 or FP62 instrument and are not corrected. Elemental analyses were within ±0.4% of theoretical values unless otherwise stated. Thin-layer chromatography was performed on silica gel plates (Merck No. 1.05719) with fluorescent indicator, and the plates were visualized with light at 254 and 365 nm. Column chromatography was performed on silica gel (Merck 60, 230−400 mesh ASTM). Tetrahydrofuran was distilled from sodium/benzophenone. Diethyl ether was dried over sodium, and methanol, *N*,*N*-dimethylformamide, and dioxane were dried over 3-Å molecular sieves.

2-(Hydroxymethylene)-5-methoxy-3,4-dihydro-2*H*-naphthalen-1-one (3). To a suspension of sodium methoxide (prepared from sodium (5.7 g, 0.25 mol) and anhydrous methanol and the excess of methanol removed in vacuo) in anhydrous benzene (80 mL) was added a solution of ethyl formate (20 mL, 0.26 mol), dissolved in anhydrous benzene (120 mL). The mixture was stirred at 0 °C, and 5-methoxy-1-tetralone (24.8 g, 0.14 mol), dissolved in anhydrous benzene (120 mL), was added dropwise over a period of 2 h. After stirring at 0 °C for an additional 2 h, the reaction mixture was stirred at ambient temperature for 15 h. Water (50 mL) was added carefully, and the phases were separated. The organic phase was extracted with a 2 M aqueous solution of sodium hydroxide, and the combined water phases were cooled on an ice bath and acidified with a 2 M aqueous solution of hydrochloric acid. The acidified water phase was extracted, twice, with methylene chloride, and the combined organic phases were dried (Na_2SO_4), filtered, and evaporated in vacuo to afford 24.8 g (86% yield) of a brown oil that crystallized on standing: mp 68−69 °C (lit.[25] mp 68−69 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (br s, 1 H), 7.60 (d, J = 8 Hz, 1 H), 7.30 (t, J = 8 Hz, 1 H), 7.02 (d, J = 8 Hz, 1 H), 3.86 (s, 3 H), 2.88 (t, J = 7 Hz, 2 H), 2.53 (t, J = 7 Hz, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 182.6, 176.7, 156.3, 132.7, 130.3, 127.3, 118.3, 114.5, 108.5, 55.8, 22.3, 21.1; EIMS (70 eV) *m*/*z* (relative intensity) 204 (M^+, 100), 187 (47), 175 (41), 160 (29), 131 (23), 115 (38), 77 (39). Anal. ($C_{12}H_{12}O_3$) C, H, N.

2-Cyano-5-methoxy-3,4-dihydro-2*H*-naphthalen-1-one (4). To a solution of 2-(hydroxymethylene)-5-methoxy-3,4-dihydro-2*H*-naphthalen-1-one (24.3 g, 0.12 mol) in glacial acetic acid (480 mL) was added hydroxylamine hydrochloride (16.5 g, 0.24 mol), and the reaction mixture was heated at reflux for 30 min. The acetic acid was evaporated in vacuo, and the residue was dissolved in water (300 mL) and extracted, twice, with diethyl ether. The phases were separated, and the combined organic phases were washed with a saturated aqueous sodium hydrogen carbonate solution and then with water. The ether phase was dried (Na_2SO_4), filtered, and evaporated in vacuo to afford 27 g of crude isoxazole (MS (CI) *m*/*z* (relative intensity) 202 (100, M + 1)).

To an ice-cold solution of the crude isoxazole in diethyl ether (400 mL) was added dropwise a solution of sodium methoxide (prepared from sodium; 5.5 g, 0.24 mol) in anhydrous methanol (125 mL) over a period of 45 min. The reaction mixture was stirred at 0 °C for 2 h, and water (250 mL) was then added carefully. The phases were separated, and the water phase was extracted with methylene chloride. The phases were separated, and the organic phase was dried (Na_2SO_4), filtered, and evaporated in vacuo to afford 19 g (79% yield) of the title compound as light-brown crystals: mp 126−128 °C (lit.[26] mp 130−132 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (dd, J = 8, 1 Hz, 1 H), 7.33 (t, J = 8 Hz, 1 H), 7.09 (dd, J = 8, 1 Hz, 1 H), 3.88 (s, 3 H), 3.73 (dd, J = 12, 4 Hz, 1 H), 3.21 (app dt, J = 18, 4 Hz, 1 H), 2.90−2.77 (m, 1 H), 2.58 (dq, J = 13, 4 Hz, 1 H), 2.47−2.32 (m, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 188.3, 156.8, 132.1, 131.4, 127.7, 119.6, 116.9, 115.5, 55.9, 40.6, 27.0, 21.6; EIMS (70 eV) *m*/*z* (relative intensity) 201 (M^+, 100), 148 (93), 120 (70), 105 (21), 90 (57), 77 (51). Anal. ($C_{12}H_{11}NO_2$) C, H, N.

2-Cyano-5-methoxy-3,4-dihydronaphthalene (5). To an ice-cold solution of 2-cyano-5-methoxy-1-tetralone (4 g, 20 mmol) in anhydrous methanol (150 mL) was added sodium borohydride (3.6 g, 95 mmol) portionwise. The reaction mixture was stirred at ambient temperature for 35 min, and the reaction was then quenched by the addition of a 1 M aqueous solution of hydrochloric acid (25 mL). The methanol was evaporated in vacuo, and the remaining suspension was diluted with water (50 mL) and extracted, twice, with methylene chloride. The combined organic phases were dried (Na_2SO_4), filtered, and evaporated in vacuo affording 3.9 g of a brown solid.

The residue was dissolved in toluene (100 mL), and a catalytic amount of *p*-toluenesulfonic acid was added. The reaction was refluxed for 10 h, and water was continuously removed using a Dean−Stark trap. The solution was cooled and washed with a saturated aqueous sodium hydrogen carbonate solution and water. The organic phase was dried (Na_2SO_4), filtered, and evaporated in vacuo. Purification on a silica gel column using hexane/ethyl acetate, 3:1, as the eluent gave 2.3 g (62% yield) of the title compound as colorless crystals: mp 43−44 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.18 (app t, J = 8 Hz, 1 H), 7.11 (t, J = 2 Hz, 1 H), 6.87 (d, J = 8 Hz, 1 H), 6.75 (d, J = 8 Hz, 1 H), 3.83 (s, 3 H), 2.87 (t, J = 9 Hz, 2 H), 2.48 (br t, J = 8 Hz, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 156.2, 141.6, 132.0, 127.4, 123.2, 120.6, 119.4, 112.7, 109.8, 55.6, 24.2, 19.1; EIMS (70 eV) *m*/*z* (relative intensity) 185 (M^+, 100), 170 (48), 154 (44), 145 (25), 129 (20), 115 (41). Anal. ($C_{12}H_{11}NO$) C, H, N.

6-Cyano-7,8-dihydro-1-naphthol (1). A solution of boron tribromide (7.7 g, 31 mmol) in methylene chloride (30 mL) was added to a solution of 2-cyano-5-methoxy-3,4-dihydronaphthalene (1.9 g, 10 mmol) in methylene chloride (30 mL) at −50 °C. The reaction solution was allowed to reach room temperature and stirring was continued for 1.5 h. The reaction was quenched with ice−water, the phases were separated, and the organic phase was dried (Na_2SO_4), filtered, and evaporated in vacuo. Purification on a silica gel column using hexane/ethyl acetate as an eluent gave 1.5 g (85% yield) of the title compound as white crystals: mp 162−164 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (t, J = 2 Hz, 1 H), 7.10 (t, J = 8 Hz, 1 H), 6.81 (dd, J = 8, 1 Hz, 1 H), 6.76 (d, J = 7 Hz, 1 H), 5.29 (s, 1 H), 2.89 (t, J = 9 Hz, 2 H), 2.55 (app dt, J = 9, 2 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6, 141.9, 132.5, 127.5, 121.1, 121.0, 119.7, 117.9, 109.5, 24.0, 19.0; EIMS (70 eV) *m*/*z* (relative intensity) 171 (M^+, 100), 170 (77), 156 (22), 142 (20), 131 (47), 115 (33). Anal. ($C_{11}H_9NO$) C, H, N.

3-Cyano-8-hydroxy-2*H*-chromene (7). A solution of 8-methoxy-3-cyano-2*H*-chromene (6.4 g, 34 mmol) in methylene chloride (150 mL) was cooled to −20 °C, and a solution of boron tribromide (9.9 mL, 103 mmol) in methylene chloride (100 mL) was added dropwise. After the addition, the reaction mixture was stirred at −20 °C for another 17 h. The reaction was quenched by the careful addition of water during 20 min. The phases were separated, and the organic phase was dried (Na_2SO_4), filtered, and evaporated in vacuo to give a crude product. Purification on a silica gel column using hexane/ethyl acetate (3:1) as the eluent gave 5.4 g (92% yield) as white crystals: mp 120−121 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (t, J = 1 Hz, 1 H), 6.96 (dd, J = 8, 2 Hz, 1 H), 6.89 (t, J = 8 Hz, 1 H), 6.70 (dd, J = 7, 2 Hz, 1 H), 5.43 (br s, 1 H), 4.87 (dd, J = 1 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.3, 140.7, 138.9, 122.7, 120.2, 119.9, 119.2, 116.3, 103.4, 64.7; EIMS (70 eV) *m*/*z* (relative intensity) 173 (M^+, 100), 145 (54), 130 (25), 117 (63), 89 (53), 63 (33). Anal. ($C_{10}H_7NO_2$) C, H, N.

8-Methoxy-3-(morpholinocarbonyl)-2*H*-chromene (9). To a suspension of 8-methoxy-2*H*-chromene-3-carboxylic acid (3.0 g, 15 mmol) in toluene (40 mL) was added thionyl chloride (1.1 mL, 15 mmol), and the reaction mixture was heated at reflux for 3 h. The clear solution was evaporated in vacuo, and the residue was dissolved in anhydrous dioxane (40 mL) and cooled on an ice bath. To the ice-cooled solution of the acid chloride was added morpholine (3.2 g, 36 mmol), dissolved in anhydrous dioxane (20 mL), dropwise, and the reaction mixture was allowed to stir at room temperature for 40 min. The solvent was evaporated in vacuo, and the crude product was partitioned between methylene chloride and water. The phases were separated, and the organic phase was dried (Na_2SO_4), filtered, and evaporated in vacuo to give a crude product. Purification on a silica gel column using ethyl acetate as the eluent gave 3.1 g (77% yield) of the title compound as light-yellow crystals: mp 96−97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91−6.84 (m, 2 H), 6.72 (dd, J = 7, 2 Hz, 1 H), 6.60 (t, J = 2 Hz, 1 H), 4.94 (d, J = 2 Hz, 2 H), 3.88 (s, 3 H), 3.70 (br s, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$, 50 °C) δ 167.5, 148.3, 143.5, 127.1, 126.9, 122.2, 122.1, 120.3, 114.0, 67.0, 66.3, 56.4, 45.3; EIMS (70 eV) *m*/*z* (relative intensity) 275 (M^+, 60), 189 (100), 161 (54), 118 (41), 114 (9), 86 (27). Anal. ($C_{15}H_{17}NO_4$) C, H, N.

8-Hydroxy-3-(morpholinocarbonyl)-2*H*-chromene (10). The compound was prepared as described for **1** starting from **9** (17 g, 63 mmol). Purification on a silica gel column using chloroform/ethanol (100:0.5) as the eluent gave 6.7 g (41% yield) of the title compound as colorless crystals: mp 170−172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (dd, J = 8, 2 Hz, 1 H), 6. 83 (app t, J = 8 Hz, 1 H), 6.65 (dd, J = 8, 2 Hz, 1 H), 6.59 (t, J = 2 Hz, 1 H), 5.52 (br s, 1 H), 4.94 (d, J = 2 Hz, 2 H), 3.70 (br s, 8 H); ^{13}C NMR (50 MHz, $CDCl_3$, 50 °C) δ 167.5, 144.6, 141.0, 126.7, 126.5, 122.2, 121.5, 119.4, 117.3, 67.1, 66.5, 45.4; EIMS (70 eV) *m*/*z* (relative intensity) 261 (M^+, 98), 175 (100), 147 (60), 91 (90), 86 (47). Anal. ($C_{14}H_{15}NO_4$) C, H, N.

8-Hydroxy-3-(morpholinomethyl)-2*H*-chromene (11). To a suspension of lithium aluminum hydride (0.63 g, 16 mmol) in anhydrous tetrahydrofuran (350 mL) was carefully added anhydrous aluminum chloride (0.73 g, 5.5 mmol) portionwise. After stirring for 1 h at ambient temperature, the suspension was filtered through Celite, and the clear solution was cooled on an ice bath. To the cooled solution of aluminum hydride was added 8-hydroxy-3-(morpholinocarbonyl)-2*H*-chromene (2.3 g, 8.8 mmol), and the reaction mixture was stirred on an ice bath for 20 min. The reaction was quenched by the careful addition of a mixture of water and tetrahydrofuran (1:1) and was then poured into methylene chloride (300 mL). The crystals were filtered and dried in vacuo to afford 2.1 g (96% yield) of the title compound as white crystals. An analytical sample was crystallized from ethyl acetate which gave white needles: mp 149−150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79−6.74 (m, 2 H), 6.55 (dd, J = 7, 3 Hz, 1 H), 6.33 (app t, J = 2 Hz, 1 H), 5.43 (s, 1 H), 4.82−4.81 (m, 2 H), 3.70 (app t, J = 4 Hz, 4 H), 3.05 (br s, 2 H), 2.43 (app t, J = 4 Hz, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.5, 140.2, 131.7, 122.9, 122.7, 121.9, 118.2, 115.7, 68.1, 67.2, 62.3, 53.8; EIMS (70 eV) *m*/*z* (relative intensity) 247 (M^+, 13), 161 (36), 160 (100), 132 (9.4), 115 (7), 100 (16). Anal. ($C_{14}H_{17}NO_3$), C, H, N.

(*R*)-(+)-1-(*N*-Benzylamino)-3-(benzyloxy)propan-2-ol ((*R*)-14). To benzylamine (300 mL, 2.8 mol) was added benzyl (*S*)-glycidyl ether (70 g, 0.43 mol), and the reaction mixture was stirred for 65 h at room temperature. The excess benzylamine was removed in vacuo, and the crude yellow oil was purified by distillation to give 92 g (80% yield) of the title compound as a viscous oil: bp 176−178 °C (0.01 mmHg); $[\alpha]^{21}_D$ +12° (*c* 1.4, methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.18 (m, 10 H), 4.54 (s, 2 H), 3.95−3.70 (m, 3 H), 3.55−3.40 (m, 2 H), 2.80−2.60 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.5, 138.3, 128.9, 128.6, 128.2, 127.5, 73.7, 73.1, 69.2, 54.0, 51.6; EIMS (70 eV) *m*/*z* (relative intensity) 271 (M^+, 0.4), 180 (21), 150 (8), 120 (100), 106 (72), 91 (99), 65 (70). Anal. ($C_{17}H_{21}NO_2$) C, H, N.

(*S*)-(−)-1-(*N*-Benzylamino)-3-(benzyloxy)propan-2-ol ((*S*)-14). The compound was prepared as described for its antipode (*R*)-**14**. The spectroscopic data were in full accordance with its enantiomer: yield 70%; $[\alpha]^{21}_D$ −12° (*c* 1.1, methanol). Anal. ($C_{17}H_{21}NO_2$) C, H, N.

(*R*)-(+)-4-*N*-Benzyl-6-[(benzyloxy)methyl]-2,3,5,6-tetrahydro-1,4-oxazin-3-one ((*R*)-15). To an ice-cooled solution of (*R*)-**14** (91 g, 0.34 mol) and triethylamine (51 mL, 0.37 mol) in methylene chloride (1000 mL) was added dropwise a solution of chloroacetyl chloride (38 g, 0.34 mol) in methylene chloride (200 mL). After the addition, the reaction mixture was stirred at ambient temperature for 2.5 h. The reaction mixture was washed with a 1 M aqueous solution of hydrochloric acid. The organic phase was dried (Na_2SO_4), filtered, and evaporated in vacuo which gave 116 g of a crude solid residue: CIMS *m*/*z* 348 (M + 1).

The residue, dissolved in methanol (300 mL), was added to a solution of sodium (8.3 g, 0.36 mol) in methanol (1500 mL), and the reaction mixture was stirred at reflux for 4 h. The solvent was evaporated in vacuo, and the residue was partitioned between diethyl ether and a 1 M aqueous solution of hydrochloric acid. The phases were separated, and the ether phase was washed with water, dried (Na_2SO_4), filtered, and evaporated in vacuo to give 94 g (90% yield) of the title compound as a colorless oil. An analytical sample was purified on a silica gel column using hexane/ethyl acetate (3:1) as the eluent: $[\alpha]^{21}_D$ +41° (*c* 1.4, methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.25 (m, 10 H), 4.71 (d, J = 15 Hz, 1 H), 4.51 (d, J = 15 Hz, 1 H), 4.52 (s, 2 H), 4.41 (d, J = 17 Hz, 1 H), 4.26 (d, J = 17 Hz, 1 H), 3.96−3.88 (m, 1 H), 3.55 (dd, J = 16, 5 Hz, 1 H), 3.46 (dd, J = 10, 5 Hz, 1 H), 3.29 (app t, J = 11 Hz, 1 H), 3.12 (dd, J = 12, 3 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 137.5, 136.1, 128.8, 128.5, 128.3, 127.9, 127.8, 127.8, 73.6, 72.5, 69.8, 67.7, 49.5, 47.5; EIMS (70 eV) *m*/*z* (relative intensity) 311 (M^+, 8), 220 (11), 190 (17), 146 (10), 91 (100), 65 (37). Anal. ($C_{19}H_{21}NO_3$) C, H, N.

(*S*)-(−)-4-*N*-Benzyl-6-[(benzyloxy)methyl]-2,3,5,6-tetrahydro-1,4-oxazin-3-one ((*S*)-15). The compound was prepared as described for its antipode (*R*)-**15**. The spectroscopic data were in full accordance with its enantiomer: yield 93%; $[\alpha]^{21}_D$ −38° (*c* 1.0, methanol). Anal. ($C_{19}H_{21}NO_3$) C, H, N.

(*R*)-(−)-4-(Benzylamino)-2-[(benzyloxy)methyl]morpholine ((*R*)-16). To a stirred solution of (*R*)-**15** (39 g, 0.12 mol) in anhydrous diethyl ether (850 mL) was added portionwise lithium aluminum hydride (9.4 g, 0.25 mmol). After stirring at room temperature for 40 min, the reaction was quenched by the addition of water (9.4 mL) followed by a 15% aqueous solution of sodium hydroxide (9.4 mL) and again water (28 mL). After stirring for 20 min, the reaction mixture was filtered, dried (Na_2SO_4), filtered, and evaporated in vacuo to give 36 g (97% yield) of the title compound as a colorless oil. An analytical sample was purified on a silica gel column using hexane/ethyl acetate (3:1) as the eluent: $[\alpha]^{21}_D$ −14° (*c* 1.5, methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.21 (m, 10 H), 4.56 (d, J = 12 Hz, 1 H), 4.50 (d, J = 12 Hz, 1 H), 3.91−3.83 (m, 1 H), 3.82−3.73 (m, 1 H), 3.70 (dt, J = 11, 2 Hz, 1 H), 3.48 (s, 2 H), 3.47 (dd, J = 10, 6 Hz, 1 H), 3.39 (dd, J = 10, 4 Hz, 1 H), 2.76−2.61 (m, 2 H), 2.17 (dt, J = 11, 3 Hz, 1 H), 1.96 (app t, J = 11 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 137.7, 129.2, 128.4, 128.3, 127.7, 127.6, 127.1, 74.8, 73.3, 71.4, 66.7, 63.2, 55.3, 52.9; EIMS (70 eV) *m*/*z* (relative intensity) 297 (M^+, 0.3), 206 (100), 191 (99), 190 (69), 146 (100), 120 (43), 100 (82), 91 (99), 65 (99). Anal. ($C_{19}H_{23}NO_2$) C, H, N.

(*S*)-(+)-4-(Benzylamino)-2-[(benzyloxy)methyl]morpholine ((*S*)-16). The compound was prepared as described for its antipode (*R*)-**16**. The spectroscopic data were in full accordance with its enantiomer: yield 98%; $[\alpha]^{21}_D$ +17° (*c* 1.5, methanol). Anal. ($C_{19}H_{23}NO_2$) C, H, N.

(*R*)-(−)-2-(Hydroxymethyl)morpholine ((*R*)-17). A solution of (*R*)-**16** (86 g, 0.29 mol) in ethanol (800 mL) was acidified by the dropwise addition of concentrated hydrochloric acid (30 mL). Palladium (10%) on activated carbon (6 g) was added, and the mixture was hydrogenated at 55−60 °C and atmospheric pressure for 4 h. The catalyst was filtered off, and the solvent was evaporated in vacuo. The remaining solid was dissolved in water (75 mL) and cooled with an ice bath. The solution was alkalized with a 40% aqueous solution of sodium hydroxide, and the solvent was evaporated in vacuo. The remaining solid was dissolved in methylene chloride, filtered, and evaporated in vacuo which gave 17 g (52% yield) of the title compound as a colorless oil. An analytical sample was purified by distillation: bp 78−80 °C (0.6 mmHg); $[\alpha]^{21}_D$ −2.6° (*c* 2, methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.30−3.85 (m, 1 H), 3.68−3.51 (m, 4 H), 2.92−2.80 (m, 3 H), 2.71−2.46 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 77.0, 67.5, 63.5, 47.2, 45.4; EIMS (70 eV) *m*/*z* (relative intensity) 117 (M^+, 9), 99 (37), 86 (52), 71 (52), 57 (99), 56 (100). Anal. ($C_5H_{11}NO_2$) C, H, N.

(*S*)-(−)-2-(Hydroxymethyl)morpholine ((*S*)-17). The compound was prepared as described for its antipode (*R*)-**17**. The spectroscopic data were in full accordance with its enantiomer: yield 22%; $[\alpha]^{21}_D$ +1.7° (*c* 1.1, methanol). Anal. ($C_5H_{11}NO_2$) C, H, N.

(*R*)-(+)-2-(Hydroxymethyl)-4-(triphenylmethyl)morpholine ((*R*)-18). To an ice-cooled solution of (*R*)-**17** (9.5 g, 81 mmol) and triethylamine (14 mL, 98 mmol) in methylene chloride (100 mL) was added dropwise a solution of triphenylmethyl chloride (23 g, 81 mmol). After the addition, the

reaction mixture was stirred at ambient temperature for 2 h. The reaction mixture was washed with water, the phases were separated, and the organic phase was dried (Na_2SO_4), filtered, and evaporated in vacuo to give the crude product. Purification on a silica gel column using chloroform as the eluent gave 17 g (58% yield) of the title compound as a viscous oil: $[\alpha]^{21}_D$ +17° (*c* 2, methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (br d, J = 7 Hz, 6 H), 7.26 (t, J = 7 Hz, 6 H), 7.15 (t, J = 7 Hz, 3 H), 4.00−3.80 (m, 3 H), 3.56−3.36 (m, 2 H), 2.91 (t, J = 9 Hz, 2 H), 2.03 (br s, 1 H), 1.69 (app t, J = 10 Hz, 1 H), 1.47 (t, J = 11 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.4, 127.7, 126.2, 76.9, 76.8, 67.1, 64.2, 49.6, 48.1; EIMS (70 eV) *m*/*z* (relative intensity) 359 (M^+, 1), 244 (27), 243 (100), 165 (58). Anal. ($C_{24}H_{25}NO_2$) C, H, N.

(*S*)-(−)-2-(Hydroxymethyl)-4-(triphenylmethyl)morpholine ((*S*)-18). The compound was prepared as described for its antipode (*R*)-**18**. The spectroscopic data were in full accordance with its enantiomer: yield 36%; $[\alpha]^{21}_D$ −16° (*c* 1.1, methanol). Anal. ($C_{24}H_{25}NO_2$) C, H, N.

(*R*)-(+)-2-[[(*p*-Tolylsulfonyl)oxy]methyl]-4-(triphenylmethyl)morpholine ((*R*)-12). To a cooled (−10 °C) solution of (*R*)-**18** (17 g, 47 mmol) and pyridine (4.2 mL, 51 mmol) in methylene chloride (60 mL) was added portionwise *p*-tolylsulfonyl chloride (9.8 g, 51 mmol). After the addition, the reaction mixture was stirred at ambient temperature for 17 h. The product precipitated, and the crystals were filtered and washed with cold methylene chloride. Purification on a silica gel column using chloroform as the eluent gave 17 g (70% yield) of the title compound as white crystals: mp 211−212 °C; $[\alpha]^{21}_D$ +20° (*c* 0.5, methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 8 Hz, 2 H), 7.40 (br app d, J = 7 Hz, 6 H), 7.30−7.22 (m, 8 H), 7.17 (t, J = 7 Hz, 3 H), 4.07−3.73 (m, 5 H), 2.85 (app t, J = 12 Hz, 2 H), 2.43 (s, 3 H), 1.70−1.25 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.8, 132.9, 129.8, 129.4, 128.0, 127.7, 126.4, 78.0, 73.5, 70.3, 67.0, 49.8, 47.8, 21.5; EIMS (70 eV) *m*/*z* (relative intensity) 513 (M^+, 0.1), 244 (20), 243 (100), 241 (13), 166 (12), 165 (51), 99 (13), 91 (11), 56 (11). Anal. ($C_{31}H_{31}NO_4S$) C, H, N.

(*S*)-(−)-2-[[(*p*-Tolylsulfonyl)oxy]methyl]-4-(triphenylmethyl)morpholine ((*S*)-12). The compound was prepared as described for its antipode (*R*)-**12**. The spectroscopic data were in full accordance with its enantiomer: yield 46%; $[\alpha]^{21}_D$ −22° (*c* 0.11, methanol); mp 221−223 °C. Anal. ($C_{31}H_{31}NO_4S$) C, H, N.

(*R*,*S*)-3-(Hydroxymethyl)-1-(triphenylmethyl)piperidine (21). The compound was prepared as described for (*R*)-**18** starting from (*R*,*S*)-3-(hydroxymethyl)piperidine: yield 95% of a viscous oil; ^{1}H NMR (400 MHz, DMSO, 100 °C) δ 7.40 (app d, J = 8 Hz, 6 H), 7.27 (t, J = 8 Hz, 6 H), 7.14 (t, J = 8 Hz, 3 H), 3.98−3.95 (m, 1 H), 3.30−3.24 (m, 1 H), 3.19−3.13 (m, 1 H), 2.79 (br d, J = 10 Hz, 1 H), 1.96−1.91 (m, 1 H), 1.79−1.60 (m, 3 H), 1.42 (app dd, 1 H), 1.21 (t, J = 10 Hz, 1 H), 0.82−0.78 (m, 1 H); ^{13}C NMR (100 MHz, DMSO, 100 °C) δ 142.2, 128.4, 126.8, 125.2, 76.8, 63.9, 51.6, 48.7, 27.1, 24.5; EIMS (70 eV) *m*/*z* (relative intensity) 357 (M^+, 4), 280 (4), 244 (28), 243 (100), 165 (54), 91 (5). Anal. ($C_{25}H_{27}NO$) C, H, N.

(*R*,*S*)-3-[[(*p*-Tolylsulfonyl)oxy]methyl]-1-(triphenylmethyl)piperidine (19). The compound was prepared as described for (*R*)-**12**: yield 45% of white crystals; mp 209−210 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8 Hz, 2 H), 7.39 (br d, J = 7 Hz, 6 H), 7.28−7.22 (m, 8 H), 7.14 (t, J = 7 Hz, 3 H), 4.00−3.76 (m, 2 H), 3.00−2.54 (br signal, 2 H), 2.45 (s, 3 H), 2.27−2.15 (m, 1 H), 1.82−1.58 (m, 3 H), 1.48−1.07 (br signal, 1 H), 0.95−075 (br signal, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 133.1, 129.7, 129.2, 127.8, 127.4, 126.0, 77.4, 72.9, 51.3, 49.0, 36.7, 27.3, 25.0, 21.6; EIMS (70 eV) *m*/*z* (relative intensity) 511 (M^+, 1), 434 (2), 244 (29), 243 (100), 165 (36), 91 (9). Anal. ($C_{32}H_{33}NO_3S$) C, H, N.

(*R*,*S*)-2-[[(*p*-Tolylsulfonyl)oxy]methyl]morpholine (24). (*R*,*S*)-4-Benzyl-2-[[(*p*-tolylsulfonyl)oxy]methyl]morpholine (**23**;[21] 4.0 g, 11 mmol) was dissolved in acetic acid (150 mL) and hydrogenated over palladium (10%) on activated carbon (0.60 g) at room temperature and atmospheric pressure until H_2 uptake ceased (3 h). The catalyst was filtered off and the solvent evaporated in vacuo. The remaining solid was dissolved in water (100 mL) and cooled with an ice bath. The solution was alkalized with an aqueous solution of 2 M sodium hydroxide and extracted with methylene chloride. The phases were separated, and the organic phase was dried (Na_2SO_4), filtered, and evaporated in vacuo. Purification on a silica gel column using chloroform/ethanol saturated with NH_3 (100:4) as the eluent gave 1.7 g (57% yield) of the title compound as a viscous colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J = 8 Hz, 2 H), 7.35 (d, J = 8 Hz, 2 H), 4.02−3.92 (m, 2 H), 3.80 (app dt, J = 12, 2 Hz, 1 H), 3.70−3.62 (m, 1 H), 3.53 (ddd, J = 11, 9, 5 Hz, 1 H), 2.86 (dd, J = 12, 2 Hz, 1 H), 2.81−2.76 (m, 2 H), 2.57 (dd, J = 12, 10 Hz, 1 H), 2.44 (s, 3 H), 5.00 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.9, 132.7, 129.8, 127.9, 73.6, 70.1, 67.5, 47.2, 45.2, 21.4; EIMS (70 eV) *m*/*z* (relative intensity) 271 (M^+, 1), 155 (4), 99 (64), 91 (26), 71 (63), 56 (100). Anal. ($C_{12}H_{17}NO_4S$) C, H, N.

(*R*,*S*)-4-Methyl-2-[[(*p*-tolylsulfonyl)oxy]methyl]morpholine (22). To a solution of **24** (0.75 g, 2.8 mmol) and potassium carbonate (0.57 g, 4.1 mmol) in anhydrous *N*,*N*-dimethylformamide (35 mL) was added a solution of iodomethane (170 mL, 2.8 mmol) in anhydrous *N*,*N*-dimethylformamide (5 mL) dropwise during 30 min. After the addition, the reaction mixture was stirred for another 30 min and filtered, and the solvent was evaporated in vacuo. Purification on a silica gel column using chloroform/ethanol saturated with NH_3 (100:2) as the eluent gave 0.56 g (71% yield) of the title compound as a viscous colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J = 8 Hz, 2 H), 7.75 (d, J = 8 Hz, 2 H), 4.03 (dd, J = 10, 6 Hz, 1 H), 3.97 (dd, J = 10, 5 Hz, 1 H), 3.82 (ddd, J = 11, 3, 2 Hz, 1 H), 3.72 (m, 1 H), 3.59 (dt, J = 11, 3 Hz, 1 H), 2.68 (app dt, J = 11, 2 Hz, 1 H), 2.58 (app dq, J = 12, 4, 2 Hz, 1 H), 2.45 (s, 3 H), 2.26 (s, 3 H), 2.08 (dt, J = 11, 3 Hz, 1 H), 1.86 (dd, J = 11, 10 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.0, 132.8, 129.9, 128.0, 72.3, 70.2, 66.5, 56.3, 54.4, 46.1, 21.5; EIMS (70 eV) *m*/*z* (relative intensity) 285 (M^+, 8), 228 (13), 155 (4), 130 (5), 114 (100), 91 (21), 71 (23). Anal. ($C_{13}H_{19}NO_4S$) C, H, N.

(*R*)-(+)-2-[[[3-(Morpholinomethyl)-2*H*-chromen-8-yl]oxy]methyl]morpholine Methanesulfonate ((*R*)-25). To a solution of **11** (1.7 g, 7 mmol) and (*R*)-**12** (3.6 g, 7 mmol) in dimethylformamide (60 mL) was added potassium carbonate (1.5 g, 11 mmol), and the reaction mixture was stirred at 100 °C for 10 h. The reaction mixture was filtered and evaporated in vacuo, and the crude product was partitioned between methylene chloride and water. The phases were separated, and the organic phase was dried (Na_2SO_4), filtered, and evaporated in vacuo to give a crude product which was purified on a silica gel column using hexane/ethyl acetate (3:1) as the eluent. The residue was dissolved in acetic acid diluted to 30% with water (100 mL in total), and the reaction mixture was allowed to stir at ambient temperature for 20 min. The solvent was evaporated in vacuo, the mixture was partitioned between water and diethyl ether, the phases were separated, and the water layer was cooled with an ice bath. After alkalization with a 2 M aqueous solution of sodium hydroxide, the mixture was extracted, twice, with methylene chloride. The combined organic phases were dried (Na_2SO_4), filtered, and evaporated in vacuo. Purification on a silica gel column using chloroform/methanol/NH_3 (95:5:1) as the eluent gave 1.1 g (46% yield) of the title compound as a colorless oil: $[\alpha]^{21}_D$ −1.3° (*c* 1.6, methanol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67−6.60 (m, 2 H), 6.48 (dd, J = 7, 2 Hz, 1 H), 6.15 (br s, 1 H), 4.66 (br s, 2 H), 3.89 (dd, J = 10, 6 Hz, 1 H), 3.79 (dd, J = 10, 5 Hz, 1 H), 3.78−3.68 (m, 2 H), 3.53 (app t, J = 5, 4 Hz, 4 H), 3.48 (dd, J = 11, 3 Hz, 1 H), 2.92 (dd, J = 12, 2 Hz, 1 H), 2.7 (s, 2 H), 2.74 (app dt, J = 12, 3 Hz, 1 H), 2.65 (br d, J = 11 Hz, 1 H), 2.56 (dd, J = 10, 12 Hz, 1 H), 2.27 (br s, 4 H), 1.84 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.3, 143.6, 132.0, 123.9, 122.5, 121.3, 119.9, 115.2, 75.2, 71.1, 68.3, 67.8, 67.2, 62.1, 53.8, 48.6, 46.0; EIMS (70 eV) *m*/*z* (relative intensity) 346 (M^+, 2), 260 (24), 259 (100), 161 (36), 160 (55), 131 (28), 115 (22), 100 (86), 98 (87), 86 (11), 72 (41), 70 (13), 57(13), 56 (96).

The mesylate precipitated out of tetrahydrofuran/diethyl ether: yield 1.3 g (42%) of off-white crystals; mp 139−141 °C; $[\alpha]^{21}_D$ +2.3° (*c* 1.7, methanol); HPLC purity 99.4% (Novapak C18 (3.9 × 150 mm), 0.05 M phosphate buffer (pH 4.6)/acetonitrile, 9:1, v/v). Anal. ($C_{19}H_{26}N_2O_4 \cdot CH_3SO_3H \cdot H_2O$) C, H, N.

(*S*)-(−)-2-[[[3-(Morpholinomethyl)-2*H*-chromen-8-yl]oxy]methyl]morpholine Hydrochloride ((*S*)-25). The compound was prepared as described for its antipode (*R*)-**25**. The spectroscopic data were in accordance with its enantiomer: $[\alpha]^{21}_D$ +1.1° (*c* 1.2, methanol). The hydrochloride precipitated out of tetrahydrofuran: mp 156−158 °C; $[\alpha]^{21}_D$ −1.6° (*c* 1.2, methanol). Anal. ($C_{19}H_{26}N_2O_4 \cdot HCl \cdot 1.5H_2O$) C, H; N: calcd, 7.4; found, 6.9.

(*R,S*)-2-[[[3-(Morpholinomethyl)-2*H*-chromen-8-yl]oxy]methyl]morpholine Oxalate ((*R,S*)-25). The compound was prepared as described for (*R*)-**25**. The spectroscopic data were in accordance with its enantiomers. The oxalate precipitated out of tetrahydrofuran: yield 32%; mp 116 °C (sinters). Anal. ($C_{19}H_{26}N_2O_4 \cdot C_2H_2O_4 \cdot H_2O$) C, H, N.

(*R,S*)-2-[[(2-Cyano-3,4-dihydro-5-naphthyl)oxy]methyl]morpholine Hydrochloride ((*R,S*)-26). The compound was prepared as described for (*R*)-**25** (yield 92%). An analytical sample was converted into the hydrochloride and was recrystallized from ethanol to give the title compound as white crystals: mp 185−187 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20−7.12 (m, 2 H), 6.87 (d, J = 8 Hz, 1 H), 6.78 (d, J = 8 Hz, 1 H), 4.06−3.83 (m, 4 H), 3.69 (app dt, J = 11, 3 Hz, 1 H), 3.05−2.86 (m, 5 H), 2.78 (app dd, J = 12, 10 Hz, 1 H), 2.50 (app dt, J = 8, 2 Hz, 2 H), 2.07 (br s, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.3, 141.4, 132.0, 127.3, 123.5, 120.9, 119.6, 113.9, 109.7, 74.9, 69.6, 68.0, 48.4, 45.8, 24.1, 19.1; EIMS (70 eV) *m/z* (relative intensity) 270 (M^+, 52), 115 (11), 100 (100), 86 (26), 70 (30). Anal. ($C_{16}H_{18}N_2O_2 \cdot HCl \cdot {}^1/_2H_2O$) C, H, N.

(*R,S*)-2-[[(3-Cyano-2*H*-chromen-8-yl)oxy]methyl]morpholine Hydrochloride ((*R,S*)-27). The compound was prepared as described for (*R*)-**25**. The crude product was purified on a silica gel column using ethyl acetate/methanol/ammonium hydroxide (80:20:1) as the eluent to give the base as a viscous oil: yield 92%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (t, J = 1 Hz, 1 H), 6.96 (dd, J = 8, 2 Hz, 1 H), 6.89 (t, J = 8 Hz, 1 H), 6.75 (dd, J = 8, 2 Hz, 1 H), 4.85 (d, J = 1 Hz, 2 H), 4.04 (dd, J = 10, 6 Hz, 1 H), 3.98−3.82 (m, 3 H), 3.66 (dt, J = 11, 3 Hz, 1 H), 3.05 (dd, J = 12, 2 Hz, 1 H), 2.97−2.80 (m, 2 H), 2.73 (dd, J = 12, 10 Hz, 1 H), 1.74 (br s, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 147.4, 138.9, 122.2, 121.1, 118.1, 116.5, 103.5, 74.9, 71.0, 68.0, 64.5, 48.3, 45.8; EIMS (70 eV) *m/z* (relative intensity) 272 (M^+, 50), 173 (4), 116 (6), 100 (49), 70 (18), 56 (100). The hydrochloride salt precipitated out of tetrahydrofuran: mp 158−159 °C. Anal. ($C_{15}H_{16}N_2O_3 \cdot HCl$) C, H, N.

(*R,S*)-2-[[(3-Cyano-2*H*-chromen-8-yl)oxy]methyl]-4-*N*-methylmorpholine Hydrochloride ((*R,S*)-28). The compound was prepared as described for (*R*)-**25**. The crude product was purified on a silica gel column using chloroform/ethanol saturated with NH_3 (95:5) as the eluent, and the amine was converted into the hydrochloride in tetrahydrofuran to give the title compound as white crystals: yield 40%; mp 198−200 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (t, J = 1 Hz, 1 H), 6.96 (dd, J = 8, 2 Hz, 1 H), 6.89 (t, J = 8 Hz, 1 H), 6.75 (dd, J = 7, 2 Hz, 1 H), 4.85 (d, J = 1 Hz, 2 H), 4.15−3.88 (m, 4 H), 3.71 (app dt, J = 11, 2 Hz, 1 H), 2.85 (app dt, J = 11, 2 Hz, 1 H), 2.66 (app dq, J = 3, 11 Hz, 1 H), 2.32 (s, 3 H), 2.17 (dt, J = 11, 3 Hz, 1 H), 2.00 (dd, J = 11, 10 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.8, 144.5, 139.4, 122.6, 121.5, 121.4, 118.4, 117.0, 103.8, 74.1, 71.1, 67.0, 64.6, 57.3, 54.9, 46.5; EIMS (70 eV) *m/z* (relative intensity) 286 (M^+, 71), 114 (100), 89 (22), 84 (18), 72 (43), 71 (34), 70 (32). Anal. ($C_{16}H_{18}N_2O_3 \cdot HCl$) C, H, N.

(*R,S*)-3-[[(3-Cyano-2*H*-chromen-8-yl)oxy]methyl]piperidine Hydrochloride ((*R,S*)-29). The compound was prepared as described for (*R*)-**25**. The crude product was purified on a silica gel column using methylene chloride/ethanol saturated with NH_3 (100:15) as the eluent, and the amine was converted into the hydrochloride from diethyl ether/methylene chloride to give the title compound as white crystals: yield 33%; mp 199−200 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (t, J = 2 Hz, 1 H), 6.92−6.87 (m, 2 H), 6.73 (dd, J = 6, 3 Hz, 1 H), 4.84 (d, J = 1 Hz, 2 H), 3.90−3.80 (m, 2 H), 3.24 (app dd, J = 12, 3 Hz, 1 H), 3.03 (app dt, J = 12, 4 Hz, 1 H), 2.61 (dt, J = 12, 3 Hz, 1 H), 2.47 (dd, J = 12, 10 Hz, 1 H), 2.11−1.97 (m, 2 H), 1.95−1.84 (m, 1 H), 1.76−1.65 (m, 1 H), 1.59−1.43 (m, 1 H), 1.32−1.17 (m, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 147.4, 143.8, 138.8, 122.0, 120.8, 120.4, 117.3, 116.3, 103.2, 72.3, 64.2, 49.3, 46.4, 36.4, 27.4, 25.2; EIMS (70 eV) *m/z* (relative intensity) 270 (M^+, 94), 172 (11), 116 (13), 98 (100), 89 (29), 69 (35). Anal. ($C_{16}H_{18}N_2O_2 \cdot HCl$) C, H, N.

(*R,S*)-2-[[(3-(Morpholinocarbonyl)-2*H*-chromen-8-yl]oxy]methyl]morpholine Oxalate ((*R,S*)-30). The compound was prepared as described for (*R*)-**25**. The crude product was purified on a silica gel column using methylene chloride/methanol/ammonium hydroxide (95:5:0.5) as the eluent, and the amine was converted into the oxalate from diethyl ether/tetrahydrofuran to give the title compound as white crystals: yield 28%; mp 118 °C (sinters); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90 (dd, J = 8, 2 Hz, 1 H), 6.85 (t, J = 8 Hz, 1 H), 6.73 (dd, J = 7, 2 Hz, 1 H), 6.58 (t, J = 1 Hz, 1 H), 4.91 (d, J = 1 Hz, 2 H), 4.06 (dd, J = 10, 6 Hz, 1 H), 3.98−3.83 (m, 3 H), 3.74−3.61 (m, 9 H), 3.07 (dd, J = 12, 2 Hz, 1 H), 2.97−2.79 (m, 2 H), 2.73 (dd, J = 12, 10 Hz, 1 H), 1.82 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$, 50 °C) δ 167.9, 147.8, 144.5, 127.0, 126.9, 122.2, 122.0, 121.2, 116.8, 75.1, 71.1, 68.2, 67.1, 66.2, 48.5, 46.0, 45; EIMS (70 eV) *m/z* (relative intensity) 360 (M^+, 100), 261 (42), 176 (14), 175 (12), 100 (42), 86 (17), 70 (23), 56 (84). Anal. ($C_{19}H_{24}N_2O_5 \cdot C_2H_2O_4 \cdot {}^1/_2H_2O$) C, H, N.

Pharmacology. 1. Radioligand Binding Studies. Affinities for the following receptors were determined as described by Jackson et al.[27] (the radioligand and tissue in parentheses): 5-HT$_{1A}$ ([^{3}H]OH-DPAT, rat hippocampus), α_1-adrenoceptors ([^{3}H]prazosin, rat cortex), α_2-adrenoceptors ([^{3}H]-RX821002 ((1,4-[6,7-^{3}H]benzodioxan-2-methoxy-2-yl)-2-imidazoline hydrochloride), rat cortex), β-adrenoceptors ([^{3}H]dihydroalprenolol, rat cortex), dopamine D$_1$ ([^{3}H]SCH-23390, rat striatum); dopamine D$_2$ ([^{3}H]raclopride, cell (LtkhD$_{2A}$) membranes). The following receptors were determined as described by Johansson et al.:[28] 5-HT$_{2A}$ ([^{3}H]ketanserin, rat cortex), 5-HT$_{2C}$ ([^{3}H]mesulergine, rat cortex), 5-HT$_6$ ([^{3}H]-5-HT, cell (CHOr5-HT$_6$) membranes), 5-HT$_7$ ([^{3}H]-5-HT, cell (CHOr5-HT$_7$) membranes). [^{125}I]Iodocyanopindolol was used as the ligand for r5-HT$_{1B}$ receptors in rat cerebral cortical membranes in the presence of 60 μM isoproterenol in order to avoid binding to β-adrenoceptors as described by Hoyer et al.[29] Membranes from calf caudate were used for the assay of 5-HT$_{1D}$ receptors with [^{3}H]-5-HT in the presence of 8-OH-DPAT, 100 nM, and mesulergine, 100 nM, to avoid binding to 5-HT$_{1A}$ and 5-HT$_{2C}$ receptors according to the method of Heuring and Peroutka;[30] 5-HT, 10 μM, was used in these three assays to determine the specific binding. Binding to σ recepors in membranes from whole rat brains was assayed with [^{3}H]DTG (*N,N′*-di(*o*-tolyl)-guanidine) as described by Ross.[31]

2. Potassium-Stimulated [^{3}H] Overflow from Rat Cortical Slices Preloaded with [^{3}H]-5-HT. The method described by Rényi et al.[15] was used. Slices from occipital cortex (0.3 × 0.3 mm) preloaded with [^{3}H]-5-HT were superfused with freshly oxygenated Krebs-Henseleit's buffer, pH 7.4, containing 2.5 μM citalopram at a flow rate of 0.4 mL/min. After a 50 min washing, 4-min fractions were collected, and after 62 min a buffer solution containing 25 mM KCl was administered for 4 min followed by superfusion with the original buffer. The slices were superfused with the test compound at appropriate concentrations in the buffer for 72 min. A second addition of 25 mM KCl and the test compound were administered for 4 min beginning at 98 min, and the superfusion was continued and stopped at 122 min. The radioactivities in the fractions and remaining activities in the slices were counted by liquid scintillation, and the percentage of fractional release for each fraction was determined. The

ratio of release in the presence of the test compound after the second stimulation (S_2) to that after the first stimulation (S_1) was determined and expressed as a percentage of the corresponding ratio in the controls without test compound. To evaluate the intrinsic activity, the test compound and 5-HT were administered in the same solution.

3. 5-HT Turnover in Various Brain Regions. The rate of 5-HT turnover in hypothalamus, hippocampus, frontal cortex, and striatum in rats was determined as the accumulation of 5-hydroxytryptophan (5-HTP) after treatment with the 5-HTP decarboxylase inhibitor 3-hydroxybenzylhydrazine dihydrochloride (NSD 1015), 100 mg/kg sc. The test compound was injected sc 30 min before NSD 1015, and the rats were killed 30 min after. The various brain regions were rapidly dissected out, frozen on dry ice, and stored at −70 °C. 5-HTP, 5-HT, and 5-hydroxyindoleacetic acid (5-HIAA) were analyzed by HPLC.[32]

4. Determination of Wet Dog Shake Behavior. The number of wet dog shakes, including whole body shake and head shake, was determined during 60 min, starting 5 min after the injection of the test compound.[15] Groups of 8−10 rats were used and compared with saline-treated rats ($n = 30$).

Acknowledgment. We thank Charlotte Ahlgren, Gunilla Ericsson, Ingrid Fagervall, Eva Jerning, Susanne Rosqvist, and Maria Sällemark at Astra Arcus AB and Björn Svensson at Astra Pain Control, Södertälje, for some of the binding values and Sverker Hansson, Rolf Johansson, and Carina Stenfors at Astra Arcus AB for valuable discussions of the manuscript.

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JM970806I