[2-(ω-Phenylalkyl)phenoxy]alkylamines II: Synthesis and Selective Serotonin-2 Receptor Binding

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Received August 23, 1999; accepted November 2, 1999

A series of [2-(ω-phenylalkyl)phenoxy]alkylamines was synthesized and their receptor binding affinity was examined *in vitro*. These compounds showed an affinity for serotonin-2 (5-HT_2) and dopamine-2 (D_2) receptors. [2-(2-phenylethyl)phenoxy]alkylamine derivatives with a pyrrolidine or piperidine moiety in the structure showed higher affinity for 5-HT_2 receptors but lower affinity for D_2 receptors. Among these compounds, (*S*)-2-[2-[2-[2-(3-methoxyphenyl)ethyl]phenoxy]ethyl]-1-methylpyrrolidine, (*S*)-27, exhibited the most potent and selective affinity for 5-HT_2 receptors. Furthermore, (*S*)-27 was effective in inhibiting 5-HT-induced vasoconstriction *in vitro* and platelet aggregation both *in vitro* and *ex vivo*.

Key words serotonin-2 (5-HT_2) receptor; antiplatelet; antagonist; [2-(2-phenylethyl)phenoxy]alkylamines

Serotonin (5-hydroxytryptamine; 5-HT) produces a wide variety of biological activities on many organ systems including the central nervous, gastrointestinal, and cardiovascular systems. These responses to 5-HT are mediated by its receptors on the cell membranes. To date, there are at least 16 identified subtypes of 5-HT receptors, which are now categorized into five main classes (5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4, and 5-HT_7).[2,3)] The most well-characterized of these receptor subtypes is the 5-HT_2 receptor, due to the availability of reasonably selective agonists and antagonists.[4—7)] 5-HT_2 receptors are located both centrally and peripherally. Peripheral 5-HT_2 receptors are located on blood vessels and platelets, and are intimately involved in hemostasis and thrombosis.[8—11)]

Ketanserin, a 5-HT_2 receptor antagonist, shows high affinity for 5-HT_2 receptors on platelets and inhibits 5-HT-induced platelet aggregation and vasoconstriction.[12)] However, this compound shows relatively high affinity for adrenergic (α_1) receptors, in addition to 5-HT_2 receptors.[13,14)] Sarpogrelate, a more selective 5-HT_2 antagonist, has been developed, and is now clinically available for the treatment of peripheral arterial occlusive diseases.[15,16)]

We previously reported that [2-(4-phenylbutyl)phenoxy]alkylamine derivatives have high affinity for both 5-HT_2 and dopamine-2 (D_2) receptors.[17)] In the course of a study of [2-(ω-phenylalkyl)phenoxy]alkylamine derivatives, [2-(2-phenyllethyl)phenoxy]alkylamine derivatives with a pyrrolidine or piperidine moiety in the structure showed relatively potent and selective affinity for 5-HT_2 receptors. Thus, we have attempted to synthesize highly potent and selective antagonists for peripheral 5-HT_2 receptors on blood vessels and platelets. In this paper, we describe the synthesis and structure–activity relationships (SAR) of these compounds. We also report biological activities of (*S*)-**27**, the most active compound as a peripheral 5-HT_2 antagonist, in comparison with ketanserin and sarpogrelate.

Chemistry The phenol derivatives **4**—**8** were synthesized as shown in Chart 1. Aldehydes **1** and phosphonium chloride **2** were subjected to the Wittig reaction to give the corresponding olefins **3**, which were then converted to the phenol derivatives **4**—**8** by catalytic hydrogenation.

The syntheses of the racemic cyclic amino derivatives having an ω-phenyl ring **11**—**43** are outlined in Chart 2. Piperidine (X=CH_2) and morpholine (X=O) derivatives (**11**—**17**, **20**—**26**, **29**, **30**) were synthesized as described below. Compounds **10** were prepared by the alkylation of **4**—**8** with tosylates (**9**: R^2=OTs) (method A), or by means of the Mitsunobu reaction[18)] between **4**—**8** and a hydroxy derivative (**9**: R^2=OH) (method B). The resulting compounds **10** were reduced with lithium aluminum hydride to give *N*-methylated (*N*-Me) compounds (**11**—**17**, **21**, **23**, **25**, **29**, **30**). *N*-nonalkylated (*N*-H) compounds (**20**, **22**, **24**, **26**) were prepared by the treatment of **10** with HCl. *N*-Methylpyrrolidine derivatives (**18**, **19**, **27**, **31**—**43**) were prepared by alkylation of **4** or **6** with 2-(2-chloroethyl)-1-methylpyrrolidine hydrochloride (method C), or by means of the Mitsunobu reaction[18)] between **4** or **6** and 1-methyl-2-pyrrolidineethanol (method D). *N*-H compound **28** was prepared by alkylation of **4** with 1-*tert*-buthoxycarbonyl-2-[2-(*p*-toluenesulfonyloxy)ethyl]-pyrrolidine followed by the treatment with HCl.

The synthesis of the *N*-methylpyrrolidine derivative having an ω-cyclohexane, **48**, is shown in Chart 3. 2-Benzyloxybenzylchloride **44** was converted to the corresponding Grignard reagent and the Grignard reagent was treated with cyclohexanecarboxaldehyde to afford **45**. The hydroxy group of **45** was replaced with a chlorine atom by thionyl chloride, and the chlorine atom was replaced with a hydrogen atom by tributyltin hydride to provide **46**. Removal of the benzyl group by catalytic hydrogenation afforded phenol **47**, which was then treated with 2-(2-chloroethyl)-1-methylpyrrolidine hydrochloride in the presence of *tert*-BuOK to give **48**.

The syntheses of the optically active pyrrolidine intermediates ((*S*)-**51**, (*R*)-**55**, (*S*)-**55**, and (*S*)-**60**) are outlined in Charts 4—6. They were performed as follows: The tosylate (*S*)-**51** was synthesized from the commercially available 2-pyrrolidinemethanol (*S*)-**49** through protection by ethyl chloroformate to give carbamate (*S*)-**50**, and tosylation (Chart 4).

The tosylate (*R*)-**55** was prepared in four steps starting from the tosylate (*R*)-**51** (Chart 5). The one carbon elongation of (*R*)-**51** with sodium cyanide provided (*R*)-**52**, and the resulting nitrile group was hydrolyzed in an acidic condition

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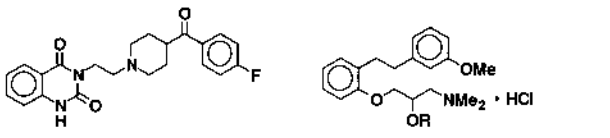
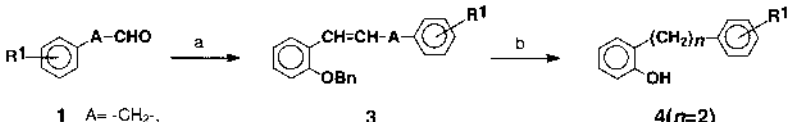


ketanserin sarpogrelate (R=CO(CH$_2$)$_2$COOH)
M-1 (R=H)



1 A= -CH$_2$-, -CH=CHCH$_2$-, *etc.* 3 4(*n*=2) 5(*n*=3) 6(*n*=4) 7(*n*=5) 8(*n*=6)

a) 2-benzyloxybenzyltriphenylphosphonium chloride **2**, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) / CH$_3$CN; b) H$_2$, Pd-C / EtOH.

Chart 1

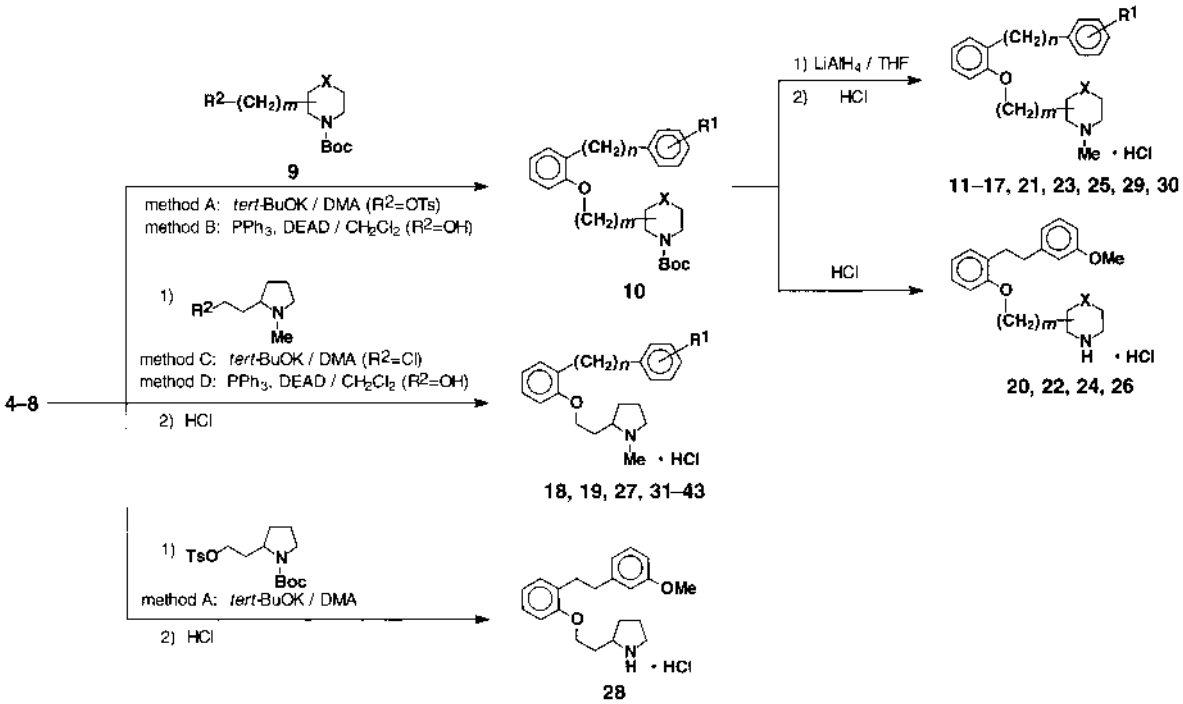
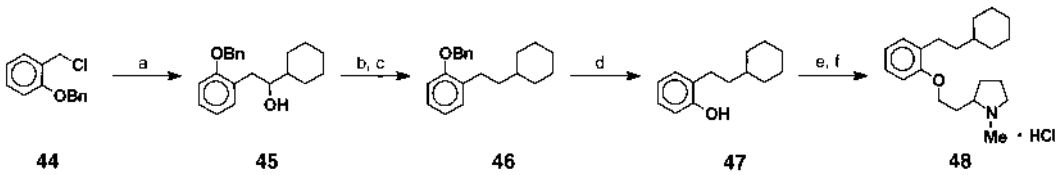


Chart 2



44 45 46 47 48

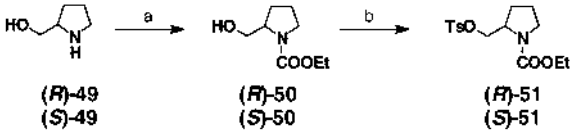
a) Mg / THF, then cyclohexanecarboxaldehyde; b) SOCl$_2$, Et$_3$N / THF; c) Bu$_3$SnH, AIBN / toluene; d) H$_2$, Pd-C / EtOH; e) 2-(2-chloroethyl)-1-methylpyrrolidine hydrochloride, *tert*-BuOK / DMA; f) HCl.

Chart 3

to give an ester (*R*)-**53**. The ester (*R*)-**53** was reduced with lithium aluminum hydride to give an alcohol (*R*)-**54**, which was then converted to the tosylate (*R*)-**55**. The enantiomer of (*R*)-**55**, (*S*)-**55** was prepared in the same manner.

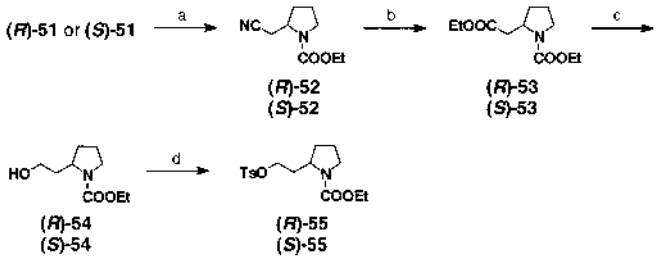
The tosylate (*S*)-**60** was prepared in five steps starting from the alcohol (*S*)-**50** (Chart 6). The Swern oxidation[19] of the alcohol (*S*)-**50** provided an aldehyde (*S*)-**56**, which was then subjected to the Wittig reaction to give an α,β-unsaturated ester (*S*)-**57**. The ester (*S*)-**57** was hydrogenated, and the following reduction of the saturated ester (*S*)-**58** with lithium aluminum hydride gave an alcohol (*S*)-**59**, which was then converted to the tosylate (*S*)-**60**.

The syntheses of the target compounds ((*R*)-**27**, (*S*)-**27**, (*S*)-**62**, and (*S*)-**63**) are shown in Chart 7. The phenol **4a** (R^1=3-OMe) was alkylated with the tosylates ((*S*)-**51**, (*R*)-**55**, (*S*)-**55**, and (*S*)-**60**) to give carbamates, which were then reduced with lithium aluminum hydride to give the desired products. This was followed by their corresponding salt formation.



a) ClCOOEt, Et_3N / CH_2Cl_2; b) Ts_2O, Et_3N / CH_2Cl_2.

Chart 4



a) NaCN / DMF; b) H_2SO_4 / EtOH; c) $LiAlH_4$ / THF; d) Ts_2O, Et_3N / CH_2Cl_2.

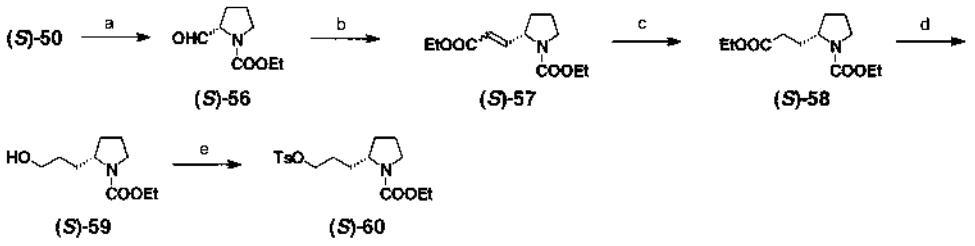
Chart 5

Results and Discussion

All compounds have diphenylalkylene structures connecting two phenyl parts in this series. In the previous paper, we reported the relationship between the alkylene chain length and D_2 receptor binding of 3-dimethylamino-1-(ω-phenylalkylphenoxy)-2-propanol derivatives.[17] Only the tetramethylene derivative showed D_2 receptor affinity, and the tetramethylene derivatives with a piperidine moiety, including compound **13**, exhibited high affinity for 5-HT_2 and D_2 receptors. Thus, we examined the influence of the alkylene chain length in the diphenylalkylene moiety of compound **13** (Table 1). The compounds in Table 1 exhibited high affinity for 5-HT_2 receptors with their IC_{50} values between 1.9 and 31 nM. Among them, the dimethylene derivative **11** and the tetramethylene derivative **13** were highly potent; their IC_{50} values were smaller than that of M-1, the active metabolite of sarpogrelate. In the D_2 receptor binding studies, the tetramethylene derivative **13** exhibited high affinity with an IC_{50} of 9.2 nM, while other compounds had markedly reduced activity (IC_{50}s >150 nM). This is consistent with the results reported for 3-dimethylamino-1-(ω-phenylalkylphenoxy)-2-propanol derivatives.[17]

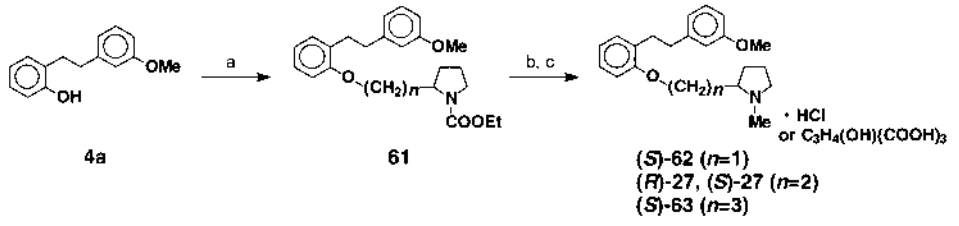
Among the [2-(ω-phenylalkyl)phenoxy]alkylamine derivatives with a piperidine or pyrrolidine moiety, the dimethylene and tetramethylene derivatives (**16**—**19**) were examined in 5-HT_2 and D_2 receptor binding assays (Table 2). The dimethylene derivatives **16** and **18** showed higher 5-HT_2 and lower D_2 receptor affinity compared with the corresponding tetramethylene derivatives, **17** and **19**, respectively. Thus, the dimethylene chain was suitable for selectivity of the 5-HT_2 receptor.

The dimethylene derivatives with a cyclic amino group were examined in 5-HT_2 and D_2 receptor binding assays (Table 3). The introduction of a 3-methoxy group on the ω-phenyl ring increased the affinity for the 5-HT_2 receptor (**16** *vs*. **21**, **18** *vs*. **27**), which is consistent with our previous re-



a) DMSO, $(COCl)_2$, Et_3N / CH_2Cl_2; b) PPh_3=CHCOOEt / CH_3CN; c) H_2, Pd-C / EtOH; d) $LiAlH_4$ / THF; e) Ts_2O, Et_3N / CH_2Cl_2.

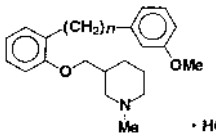
Chart 6



a) (*S*)-**51** or (*R*)-**55** or (*S*)-**55** or (*S*)-**60**, *tert*-BuOK / DMA; b) $LiAlH_4$ / THF; c) HCl or $C_3H_4(OH)(COOH)_3$.

Chart 7

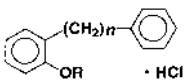
Table 1. Affinity of 3-[2-[ω-(3-Methoxyphenyl)alkyl]phenoxymethyl]-1-methylpiperidine Derivatives for 5-HT_2 and D_2 Receptors



Compd.	n	IC_{50} (nM)[a]		Ratio[b] D_2/5-HT_2
		5-HT_2	D_2	
11	2	1.9	150	79
12	3	17	490	29
13[c]	4	2.2	9.2	4.2
14	5	31	270	8.7
15	6	28	1800	64
Sarpogrelate		150	>5000	ND[d]
M-1		16	>5000	ND[d]
Ketanserin		5.3	940	180

a) Interaction of the compounds with rat brain 5-HT_2 and D_2 receptors was determined by conventional binding assay using [^{3}H]ketanserin and [^{3}H]raclopride. *b*) Ratio: the IC_{50} values for D_2 *vs.* 5-HT_2 receptors. *c*) Data from reference 17. *d*) Not determined.

Table 2. Affinity of Dimethylene and Tetramethylene Derivatives with a 2-(ω-phenylalkyl)phenoxy Group for 5-HT_2 and D_2 Receptors

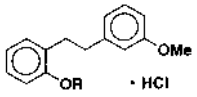


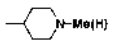
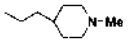
Compd.	R	n	IC_{50} (nM)[a]		Ratio[b] D_2/5-HT_2
			5-HT_2	D_2	
16		2	4.7	470	100
17[c]		4	11	40	3.6
18		2	6.1	760	120
19[c]		4	32	28	0.88

a) Interaction of the compounds with rat brain 5-HT_2 and D_2 receptors was determined by conventional binding assay using [^{3}H]ketanserin and [^{3}H]raclopride. *b*) Ratio: the IC_{50} values for D_2 *vs.* 5-HT_2 receptors. *c*) Data from reference 17.

sults.[17] Among this series of compounds, the 5-HT_2 and D_2 receptor affinity of *N*-Me compounds (**11**, **21**, **23**, **25**, **27**) were higher than those of the corresponding *N*-H compounds (**20**, **22**, **24**, **26**, **28**). Compound **21**, which has a 2-(2-piperidinylethyl) structure, showed high affinity for 5-HT_2 receptors. However, **21** also showed high affinity for D_2 receptors, and its D_2/5-HT_2 ratio was smaller than that of **11**. The D_2 receptor affinity of compound **23** was six-fold lower than that of **11**, and its 5-HT_2 receptor affinity was also slightly lower than **11**. It is interesting to note that these three compounds (**11**, **21**, **23**) with potent affinity (IC_{50} <10 nM) for 5-HT_2 receptors, have three carbon atoms between the piperidine nitrogen and the etheral oxygen. In contrast, the other piperidine derivatives such as **29** with five carbon atoms and **30** with two carbon atoms between the piperidine nitrogen and etheral oxygen, respectively, were less active. In the previous paper, we reported that the D_2 receptor affinity depends on the lipophilicity around the amino moiety in a series of compounds.[17] Morpholine derivative **25**, which has an oxygen instead of a methylene group at the 4-position of piperidine, was prepared in an attempt to reduce the D_2 receptor

Table 3. Affinity of Cyclic Amino Derivatives with a 2-[2-(3-Methoxyphenyl)ethyl]phenoxy Group for 5-HT_2 and D_2 Receptors



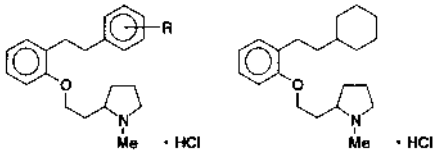
Compd.[a]	R[a]	IC_{50} (nM)[a,b]		Ratio[c] D_2/5-HT_2
		5-HT_2	D_2	
11		1.9	150	79
(20)		(5.0)	(890)	(180)
21		3.6	120	33
(22)		(55)	(>3000)	(ND[d])
23		7.7	1000	130
(24)		(32)	(>3000)	(ND[d])
25		11	1600	150
(26)		(17)	(>3000)	(ND[d])
27		2.0	670	340
(28)		(39)	(>3000)	(ND[d])
29		46	230	5.0
30		77	>5000	(ND[d])

a) *N*-H compounds are described in parentheses. *b*) Interaction of the compounds with rat brain 5-HT_2 and D_2 receptors was determined by conventional binding assay using [^{3}H]ketanserin and [^{3}H]raclopride. *c*) Ratio: the IC_{50} values for D_2 *vs.* 5-HT_2 receptors. *d*) Not determined.

affinity by decreasing the lipophilicity around the amino moiety. As expected, the D_2 receptor affinity of **25** was lower than that of the piperidine derivative, **11**. However, the 5-HT_2 receptor affinity of **25** also decreased in parallel. Compound **27**, which has a pyrrolidine ring instead of a piperidine ring, was as potent as **11** and **21** for its 5-HT_2 receptor affinity, but less potent for its D_2 receptor affinity compared to **11** and **21**. Among these three compounds, **27** exhibited the highest D_2/5-HT_2 ratio (340), suggesting a high selectivity. The pyrrolidine derivatives, therefore, seemed superior to the piperidine derivatives as selective 5-HT_2 antagonists.

The effect of the substituent on the ω-phenyl group was examined (Table 4). Most compounds show high affinity for 5-HT_2 receptors, regardless of the type of the substituent. Compounds substituted at the 3-position (**27**, **34**, **37**) of the ω-phenyl ring showed higher affinity than those substituted at the 2- or 4-position (**31**, **33**, **36** or **32**, **35**, **38**). The methoxy-substituted compounds showed slightly more potent activity than their corresponding ethoxy compounds. Compounds **37** and **39**, having a chlorine and a fluorine atom, respectively, on the ω-phenyl ring also showed more potent activity than the bromo analog **40**. These results show that the introduction of a bulky substituent decreases the affinity for 5-HT_2 receptors. The introduction of a hydrophilic hydroxy group (**43**) instead of the etheral *O*-methyl group of **27** also decreased the 5-HT_2 receptor affinity. The reduction of the ω-phenyl ring, which leads to an ω-cyclohexane in compound **48**, maintained the 5-HT_2 receptor affinity. In the case of 2-(1-methyl-2-pyrrolidinylethyl) derivatives, as indicated in Table 4, all of the compounds showed low activity for D_2 receptors (IC_{50}s >460 nM). However, compounds with a

Table 4. Affinity of 1-Methyl-2-[2-[2-(2-phenylethyl)phenoxy]ethyl]-pyrrolidine Derivatives and 2-[2-[2-(2-Cyclohexylethyl)phenoxy]ethyl]-1-methylpyrrolidine Derivative for 5-HT_2 and D_2 Receptors

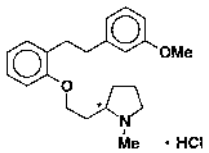


48

Compd.	R	IC_{50} (nM)[a]		Ratio[b] D_2/5-HT_2
		5-HT_2	D_2	
18	H	6.1	760	120
31	2-OMe	3.5	1100	310
27	3-OMe	2.0	670	340
32	4-OMe	6.1	780	130
33	2-OEt	10	1700	170
34	3-OEt	6.7	640	96
35	4-OEt	12	460	38
36	2-Cl	15	1100	73
37	3-Cl	4.5	660	150
38	4-Cl	7.9	1200	150
39	3-F	4.4	600	140
40	3-Br	8.7	960	110
41	3-CN	5.4	610	110
42	3-Me	5.0	700	140
43	3-OH	17	1500	88
48		4.8	530	110

a) Interaction of the compounds with rat brain 5-HT_2 and D_2 receptors was determined by conventional binding assay using [^{3}H]ketanserin and [^{3}H]raclopride. *b*) Ratio: the IC_{50} values for D_2 *vs.* 5-HT_2 receptors.

Table 5. Affinity of (*RS*)-**27** and Its Optically Active Compounds for 5-HT_2 and D_2 Receptors



Compd.	IC_{50} (nM)[a]		Ratio[b] D_2/5-HT_2
	5-HT_2	D_2	
(*RS*)-**27**	2.0	670	340
(*S*)-**27**	1.8	1100	610
(*R*)-**27**	6.4	490	77

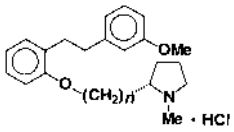
a) Interaction of the compounds with rat brain 5-HT_2 and D_2 receptors was determined by conventional binding assay using [^{3}H]ketanserin and [^{3}H]raclopride. *b*) Ratio: the IC_{50} values for D_2 *vs.* 5-HT_2 receptors.

changed substituent on the ω-phenyl ring were not as potent and selective for 5-HT_2 receptors as **27**.

Although **27** had potent and selective affinity for 5-HT_2 receptors, this compound has the asymmetric carbon atom at the 2-position of the pyrrolidine ring. Therefore, each of the enantiomers was prepared to examine its binding affinity for 5-HT_2 and D_2 receptors (Table 5). The compound with (*S*) configuration, (*S*)-**27**, exhibited higher 5-HT_2 receptor affinity and lower D_2 receptor affinity than racemic **27**. These results indicate that (*S*)-**27** is the active enantiomer in 5-HT_2 receptor affinity.

Table 6 shows the effect of the alkylene chain attached to the 2-position of pyrrolidine. Among these compounds, (*S*)-**27** (n=2) showed the highest affinity for 5-HT_2 receptors. Compared with (*S*)-**27**, (*S*)-**62** (n=1) and (*S*)-**63** (n=3) showed lower affinity. These results show that the 5-HT_2 receptor affinity was the highest for pyrrolidine derivatives with three carbon atoms between the pyrrolidine nitrogen and etheral oxygen. This is consistent with results in the study of the piperidine derivatives.

Table 6. Affinity of (*S*)-**27** and Its Analogs for 5-HT_2 and D_2 Receptors



Compd.	n	IC_{50} (nM)[a]		Ratio[b] D_2/5-HT_2
		5-HT_2	D_2	
(*S*)-**62**	1	6.4	>3000	ND[c]
(*S*)-**27**	2	1.8	1100	610
(*S*)-**63**[d]	3	20	2500	130

a) Interaction of the compounds with rat brain 5-HT_2 and D_2 receptors was determined by conventional binding assay using [^{3}H]ketanserin and [^{3}H]raclopride. *b*) Ratio: the IC_{50} values for D_2 *vs.* 5-HT_2 receptors. *c*) Not determined. *d*) Citrate.

Table 7. 5-HT-Induced Human PRP Aggregation (*in Vitro*)

Compd.	IC_{50} (μM)[a]
(*S*)-**27**	0.057 (0.049—0.066)
Sarpogrelate	>100
M-1	3.6 (2.8—4.7)
Ketanserin	0.14 (0.083—0.24)

a) Data are expressed as the mean values and 95% confidence limits in parentheses.

Table 7 shows the IC_{50} values (μM) for the test compounds ((*S*)-**27**, ketanserin, sarpogrelate, and M-1, the active metabolite of sarpogrelate) against *in vitro* human platelet aggregation. (*S*)-**27** inhibited platelet aggregation in a concentration-dependent manner with an IC_{50} value of 0.057 μM. Ketanserin and M-1 also inhibited platelet aggregation, but these agents were less potent than (*S*)-**27**. Sarpogrelate produced the minimum inhibition on platelet aggregation. These results clearly indicate that (*S*)-**27** has more potent *in vitro* antiaggregatory activity compared to those of sarpogrelate, M-1, and ketanserin.

The *ex vivo* effects of 5-HT_2 antagonists, (*S*)-**27**, ketanserin and sarpogrelate on 5-HT-induced platelet aggregation were examined in cats (Fig. 1). Single bolus administration of (*S*)-**27** (100 μg/kg, i.v.) resulted in a marked inhibition (90%) of platelet aggregation at 0.5 h postdose. The inhibition disappeared gradually, but was still evident even at 6 h (29% inhibition). Ketanserin (100 μg/kg, i.v.) also showed an inhibition (61%) at 0.5 h postdose, but the extent of the inhibition was smaller than (*S*)-**27**. In addition, the effect of ketanserin disappeared at 4 h postdose. Sarpogrelate even at the highest dose (1000 μg/kg, i.v.) failed to inhibit platelet aggregation, indicating weak efficacy of this agent. These results suggest that (*S*)-**27** is a potent antiplatelet agent with long duration of action *in vivo*.

The addition of (*S*)-**27** alone to platelet-rich plasma (PRP) did not cause any platelet aggregation up to 1 mM. Thus, this

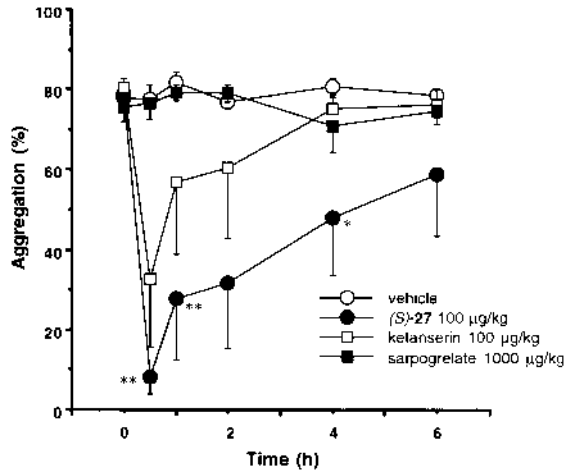


Fig. 1. *Ex Vivo* Antiplatelet Effects of (*S*)-**27**, Ketanserin and Sarpogrelate in Cats

Data are represented as the mean±S.E.M. (n=4-6).* $p<0.05$, ** $p<0.01$ *vs.* vehicle (Dunnett's test).

compound is unlikely to have any agonistic activity for 5-HT_2 receptors. (*S*)-**27** also did not cause vasoconstriction, but inhibited 5-HT-induced vasoconstriction with an IC_{50} value of 2.2 nM. These results suggest that (*S*)-**27** is a 5-HT_2 receptor antagonist and not an agonist.

The binding affinity of (*S*)-**27** was further examined for other receptors (α_1, β, 5-HT_1, and 5-HT_3). (*S*)-**27** exhibited low affinity with IC_{50}s (nM) of 490 for α_1 and over 5000 for β, 5-HT_1, and 5-HT_3, respectively. This clearly indicates that (*S*)-**27** is highly selective for 5-HT_2 receptors.

In conclusion, we found that new [2-(2-phenylethyl)phenoxy]alkylamine derivatives with a pyrrolidine or piperidine moiety in their structure have high affinity for 5-HT_2 receptors but low affinity for D_2 receptors. Among these compounds, (*S*)-**27** exhibited the highest selectivity and potency for 5-HT_2 receptors in the binding assays. This compound was also effective in inhibiting 5-HT-induced vasoconstriction *in vitro* and platelet aggregation both *in vitro* and *ex vivo.*

Experimental

Melting points were determined with a Yanagimoto micro melting point apparatus and were uncorrected. ^{1}H-NMR spectra were obtained on a JEOL EX270 spectrometer and were reported as δ values relative to Me_4Si as the internal standard. Abbreviations of the ^{1}H-NMR peak patterns are as follows: br=broad, s=singlet, d=doublet, t=triplet, q=quartet, and m=multiplet. IR spectra were taken on a JASCO FT/IR-8900 spectrometer. Merck Silica gel 60 (230—400 mesh) was used in the column chromatography. Tetrahydrofuran, *N*,*N*-dimethylacetamide, and dimethylsulfoxide are abbreviated as THF, DMA, and DMSO, respectively.

1-*tert*-Butoxycarbonyl-3-[2-[2-(3-methoxyphenyl)ethyl]phenoxymethyl]piperidine (10: m=1, n=2, R^1=3-OMe, X=CH_2) (Method A) To a solution of 2-[2-(3-methoxyphenyl)ethyl]phenol[16] **4a** (R^1=3-OMe) (790 mg, 3.46 mmol) in DMA (8 ml) was added *tert*-BuOK (388 mg, 3.46 mmol) and the mixture was stirred at 0 °C for 10 min. Then a solution of 1-*tert*-butoxycarbonyl-3-(*p*-toluenesulfonyloxymethyl)piperidine **9** (m=1, X=CH_2) (1.28 g, 3.46 mmol) in DMA (7 ml) was added and the mixture was stirred overnight at room temperature. The resulting suspension was diluted with EtOAc and washed with H_2O and brine. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=5/1—4/1) to give **10** (m=1, n=2, R^1=3-OMe, X=CH_2) (1.09 g, 2.56 mmol, 74%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.12—1.79 (3H, m), 1.43 (9H, s), 1.85—2.12 (2H, m), 2.71—3.03 (6H, m), 3.79 (3H, s), 3.85 (2H, d, J=5.9 Hz), 3.88—4.25 (2H, m), 6.70—6.94 (5H, m), 7.08—7.31 (1H, m).

3-[2-[2-(3-Methoxyphenyl)ethyl]phenoxy]methyl-1-methylpiperidine Hydrochloride (11) A solution of 1-*tert*-butoxycarbonyl-3-[2-[2-(3-methoxyphenyl)ethyl]phenoxymethyl]piperidine **10** (m=1, n=2, R^1=3-OMe, X=CH_2) (850 mg, 2.00 mmol) in THF (6 ml) was added to a suspension of $LiAlH_4$ (113 mg, 2.98 mmol) in THF (10 ml) at room temperature. The mixture was stirred at room temperature for 2 h and then refluxed for 2.5 h. The mixture was cooled, and to the mixture Na_2SO_4 decahydrate was added slowly and the slurry was then stirred for 30 min. The insoluble material was filtered away, and the filtrate was concentrated. The resulting residue was chromatographed on a silica gel column (CH_2Cl_2/MeOH=20/1—10/1) to give 3-[2-[2-(3-methoxyphenyl)ethyl]phenoxy]methyl-1-methylpiperidine (520 mg, 1.53 mmol, 77%) as a colorless oil. This oil was dissolved in EtOAc (5 ml) and was treated with 4 N HCl in dioxane (1.15 ml, 4.59 mmol). The mixture was stirred at room temperature for 10 min and concentrated. The oily residue was dissolved in a mixture of EtOAc/CH_2Cl_2=9/1, and the solution was allowed to stand at room temperature. The precipitate formed was collected by filtration to give **11** (443 mg, 1.18 mmol, 77%) as colorless crystals.

3-[2-[2-(3-Methoxyphenyl)ethyl]phenoxy]methylpiperidine Hydrochloride (20) A solution of 1-*tert*-butoxycarbonyl-3-[2-[2-(3-methoxyphenyl)-ethyl]phenoxymethyl]piperidine **10** (m=1, n=2, R^1=3-OMe, X=CH_2) (240 mg, 0.564 mmol) in EtOAc (4 ml) was treated with 4 N HCl in dioxane (4 ml) and the mixture was stirred at room temperature for 3 h and then concentrated. The oily residue was dissolved in EtOAc, and the solution was allowed to stand at room temperature. The precipitate formed was collected by filtration to give **20** (183 mg, 0.506 mmol, 90%) as colorless crystals.

Similarly, the morpholine derivatives **25** and **26** and other piperidine derivatives **11**—**16**, **20**—**22**, and **29** were prepared by alkylation of phenol derivatives **4**—**8**[20] with tosylates, followed by a treatment with lithium aluminum hydride or HCl as described in method A.

1-*tert*-Butoxycarbonyl-4-[2-[2-(3-methoxyphenyl)ethyl]phenoxy]-piperidine (10: m=0, n=2, R^1=3-OMe, X=CH_2) (Method B) Diethyl azodicarboxylate (DEAD) (1.05 ml, 6.67 mmol) was added to a solution of 2-[2-(3-methoxyphenyl)ethyl]phenol **4a** (R^1=3-OMe) (456 mg, 2.00 mmol), 1-*tert*-butoxycarbonyl-4-hydroxypiperidine (1.20 g, 5.96 mmol) and triphenylphosphine (1.73 g, 6.60 mmol) in CH_2Cl_2 (30 ml) and the mixture was stirred at room temperature for 3 h. The solvent was removed and the resulting residue was chromatographed on a silica gel column (hexane/EtOAc=4/1) to give **10** (m=0, n=2, R^1=3-OMe, X=CH_2) (379 mg, 0.92 mmol, 46%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.47 (9H, s), 1.71—2.03 (4H, m), 3.36—3.52 (2H, m), 3.60—3.73 (2H, m), 3.78 (3H, s), 4.46—4.59 (1H, m), 6.70—6.92 (5H, m), 7.10—7.29 (1H, m).

4-[2-[2-(3-Methoxyphenyl)ethyl]phenoxy]-1-methylpiperidine Hydrochloride (23) A solution of 1-*tert*-butoxycarbonyl-4-[2-[2-(3-methoxyphenyl)ethyl]phenoxy]piperidine **10** (m=0, n=2, R^1=3-OMe, X=CH_2) (482 mg, 1.17 mmol) in THF (5 ml) was treated with a suspension of $LiAlH_4$ (44.5 mg, 1.17 mmol) in THF (5 ml) under cooling. The resulting mixture was refluxed for 1 h and then cooled. To the resulting suspension was slowly added Na_2SO_4 decahydrate and the mixture was stirred for 30 min. The insoluble material was filtered away and the filtrate was concentrated. The resulting residue was chromatographed on a silica gel column (CH_2Cl_2/MeOH=20/1—10/1) to give 4-[2-[2-(3-methoxyphenyl)ethyl]phenoxy]-1-methylpiperidine (220 mg, 0.68 mmol, 58%) as a light yellow oil. This oil was dissolved in EtOAc (5 ml) and was treated with 4 N HCl in dioxane (0.25 ml, 1.00 mmol). The resulting solution was concentrated. The oily residue was dissolved in EtOAc (20 ml), and the solution was allowed to stand at room temperature. The precipitate formed was collected by filtration to give **23** (170 mg, 0.47 mmol, 69%) as colorless crystals.

Similarly, other piperidine derivatives **17**, **24**, and **30** were prepared by means of the Mitsunobu reaction[18] between the phenol derivatives **4**—**8**[20] and a hydroxy derivative (**9**), followed by a treatment with lithium aluminum hydride or HCl as described in method B.

1-Methyl-2-[2-[2-(2-phenylethyl)phenoxy]ethyl]pyrrolidine Hydrochloride (18) (Method C) To a solution of 2-(2-phenylethyl)phenol **4b** (R^1=H) (1.00 g, 5.04 mmol) in DMA (10 ml) was added *tert*-BuOK (566 mg, 5.04 mmol) and the mixture was stirred at room temperature for 10 min. Then a solution of 2-(2-chloroethyl)-1-methylpyrrolidine hydrochloride (928 mg, 5.04 mmol) in DMA (10 ml) was added, and stirring continued at room temperature for 3 h and at 60 °C for 3 h. The resulting solution was diluted with EtOAc and washed with H_2O and brine. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (CH_2Cl_2/MeOH=20/1—10/1) to give 1-methyl-2-[2-[2-(2-phenylethyl)phenoxy]ethyl]pyrrolidine (480 mg, 1.55 mmol, 31%) as a col-

Table 8. Physical Data for [2-(ω-Phenylalkyl)phenoxy]alkylamines

Compd.[a]	Formula	Yield (%)[b]	mp (°C)	Analysis (%) Calcd (Found)			
				C	H	N	Cl
11	$C_{22}H_{29}NO_2 \cdot HCl$	59	191—193	70.29 (69.99)	8.04 (8.15)	3.73 (3.74)	9.43 (9.38)
12	$C_{23}H_{31}NO_2 \cdot HCl$	75	106—107	70.84 (70.84)	8.27 (8.33)	3.59 (3.63)	9.09 (9.02)
14	$C_{25}H_{35}NO_2 \cdot HCl$	58	90—91	71.83 (71.65)	8.68 (8.61)	3.35 (3.32)	8.48 (8.75)
15	$C_{26}H_{37}NO_2 \cdot HCl$	63	100	72.28 (72.00)	8.87 (8.84)	3.24 (3.22)	8.32 (8.53)
16	$C_{22}H_{29}NO \cdot HCl$	48	128—130	73.41 (73.42)	8.40 (8.54)	3.89 (3.92)	9.85 (9.70)
18	$C_{21}H_{27}NO \cdot HCl$	7.5	154—156	72.92 (72.56)	8.16 (8.32)	4.05 (4.01)	10.25 (10.21)
20	$C_{21}H_{27}NO_2 \cdot HCl$	90	155—157	69.69 (69.35)	7.80 (7.81)	3.87 (3.87)	9.80 (9.67)
21	$C_{23}H_{31}NO_2 \cdot HCl$	37	115—117	70.84 (70.72)	8.27 (8.31)	3.59 (3.75)	9.09 (9.03)
22	$C_{22}H_{29}NO_2 \cdot HCl$	33	102—104	70.29 (70.12)	8.04 (7.93)	3.73 (3.75)	9.43 (9.42)
23	$C_{21}H_{27}NO_2 \cdot HCl \cdot 0.15H_2O$	40	147—148	69.18 (69.26)	7.82 (7.85)	3.84 (3.95)	9.72 (9.60)
24	$C_{20}H_{25}NO_2 \cdot HCl \cdot 0.15H_2O$	91	121—122	68.52 (68.48)	7.56 (7.55)	4.00 (3.99)	10.11 (10.23)
25	$C_{21}H_{27}NO_3 \cdot HCl$	65	174—176	66.74 (66.43)	7.47 (7.41)	3.71 (3.82)	9.38 (9.30)
26	$C_{20}H_{25}NO_3 \cdot HCl \cdot 0.15H_2O$	26	110—112	65.53 (65.58)	7.23 (7.14)	3.82 (3.83)	9.67 (9.70)
27	$C_{22}H_{29}NO_2 \cdot HCl$	28	109—110	70.29 (69.98)	8.04 (8.06)	3.73 (3.76)	9.43 (9.26)
28	$C_{21}H_{27}NO_2 \cdot HCl$	61	86—87	69.69 (69.36)	7.80 (7.81)	3.87 (3.98)	9.80 (10.13)
29	$C_{21}H_{31}NO_2 \cdot HCl$	56	97—99	70.84 (70.46)	8.27 (8.38)	3.59 (3.61)	9.09 (9.12)
30	$C_{21}H_{27}NO_2 \cdot HCl$	49	158—160	69.69 (69.44)	7.80 (7.73)	3.87 (3.96)	9.80 (9.73)
31	$C_{22}H_{29}NO_2 \cdot HCl \cdot 0.35H_2O$	11	143—145	69.13 (69.05)	8.10 (8.13)	3.66 (3.70)	9.27 (9.45)
32	$C_{22}H_{29}NO_2 \cdot HCl \cdot 0.20H_2O$	20	136—138	69.62 (69.56)	8.31 (8.09)	3.54 (3.71)	8.97 (9.07)
33	$C_{23}H_{31}NO_2 \cdot HCl \cdot 0.30H_2O$	24	148—150	69.87 (70.25)	8.27 (7.93)	3.58 (3.65)	9.09 (8.59)
34	$C_{23}H_{31}NO_2 \cdot HCl$	18	120—121	70.84 (70.61)	8.27 (7.47)	3.58 (3.60)	9.09 (9.16)
35	$C_{23}H_{31}NO_2 \cdot HCl$	50	133—134	70.84 (70.65)	8.27 (8.24)	3.58 (3.61)	9.09 (9.15)
36	$C_{21}H_{26}ClNO \cdot HCl$	26	187—188	66.31 (66.01)	7.16 (7.09)	3.68 (3.71)	18.64 (18.56)
37	$C_{21}H_{26}ClNO \cdot HCl$	32	119—121	66.31 (66.24)	7.16 (7.37)	3.68 (3.65)	18.64 (18.32)
38	$C_{21}H_{26}ClNO \cdot HCl$	21	145—146	66.31 (66.34)	7.16 (7.15)	3.68 (3.72)	18.64 (18.42)
39[c]	$C_{21}H_{26}FNO \cdot HCl$	35	135—136	69.31 (69.40)	7.48 (7.44)	3.85 (3.81)	9.74 (9.86)
40[d]	$C_{21}H_{26}BrNO \cdot HCl$	26	127—129	59.38 (59.13)	6.41 (6.32)	3.30 (3.35)	8.35 (8.29)
41	$C_{22}H_{26}N_2O \cdot HCl \cdot 0.30H_2O$	24	101	70.22 (70.21)	7.39 (7.52)	7.44 (7.45)	9.42 (9.38)
42	$C_{22}H_{29}NO \cdot HCl \cdot 0.15H_2O$	5.1	128—130	72.87 (72.86)	8.42 (8.25)	3.86 (3.85)	9.78 (9.67)
43	$C_{21}H_{27}NO_2 \cdot HCl$	38	68—70	69.69 (69.66)	7.80 (7.86)	3.87 (3.91)	9.80 (10.00)
48	$C_{21}H_{33}NO \cdot HCl \cdot 0.62H_2O$	28	101—102	69.46 (69.84)	9.78 (9.96)	3.86 (4.04)	9.76 (9.36)
(*S*)-**27**	$C_{22}H_{29}NO_2 \cdot HCl$	85	133—135	70.29 (70.14)	8.04 (8.24)	3.73 (3.81)	9.43 (9.75)
(*R*)-**27**	$C_{22}H_{29}NO_2 \cdot HCl$	67	133—136	70.29 (70.21)	8.04 (8.07)	3.73 (3.83)	9.43 (9.65)
(*S*)-**62**	$C_{21}H_{27}NO_2 \cdot HCl$	18	124—126	69.69 (69.40)	7.80 (7.83)	3.87 (3.91)	9.80 (9.64)
(*S*)-**63**	$C_{29}H_{39}NO_9 \cdot 0.50H_2O$	87	Oil	62.80 (62.78)	7.27 (7.44)	2.53 (2.45)	

a) Compounds **13**, **17**, and **19** were reported in reference 17. *b*) Yield not optimized. *c*) *Anal*. Calcd: F, 5.22. Found: F, 5.09. *d*) *Anal.* Calcd: Br, 18.81. Found: Br, 19.18.

Table 9. Physical Data for [2-(ω-Phenylalkyl)phenoxy]alkylamines

Compd.[a]	^{1}H-NMR δ ($CDCl_3$)
11	1.44—2.07 (3H, m), 2.22—2.98 (8H, m), 2.75 (3H, s), 3.38—3.58 (2H, m), 3.79 (3H, s), 3.85—4.03 (2H, m), 6.72—6.87 (4H, m), 6.94 (1H, t, *J*=7.6 Hz), 7.13—7.31 (3H, m)
12	1.35—1.58 (1H, m), 1.81—2.04 (4H, m), 2.22—2.95 (8H, m), 2.72 (3H, s), 3.36—3.59 (2H, m), 3.79 (3H, s), 3.77—4.03 (2H, m), 6.68—6.85 (4H, m), 6.92 (1H, t, *J*=7.9 Hz), 7.11—7.30 (3H, m)
14	1.32—1.73 (7H, m), 1.77—2.06 (2H, m), 2.25—2.97 (8H, m), 2.67 (3H, s), 3.29—3.58 (2H, m), 3.79 (3H, s), 3.80—4.02 (2H, m), 6.65—6.82 (4H, m), 6.91 (1H, t, *J*=7.6 Hz), 7.10—7.25 (3H, m)
15	1.23—1.75 (9H, m), 1.83—2.05 (2H, m), 2.21—2.97 (4H, m), 2.57 (4H, t, *J*=7.6 Hz), 2.72 (3H, s), 3.38—3.60 (2H, m), 3.79 (3H, s), 3.82—4.04 (2H, m), 6.68—6.85 (4H, m), 6.91 (1H, t, *J*=6.9 Hz), 7.10—7.26 (3H, m)
16	1.22—2.40 (7H, m), 2.44—2.65 (2H, m), 2.74 (3H, s), 2.81—3.20 (5H, m), 3.22—3.59 (1H, m), 3.96—4.20 (2H, m), 6.84 (1H, d, *J*=7.9 Hz), 6.92 (1H, t, *J*=7.3 Hz), 7.10—7.33 (7H, m)
18	1.88—2.13 (2H, m), 2.15—2.37 (2H, m), 2.39—2,62 (2H, m), 2.68—2.98 (5H, m), 2.75 (3H, s), 3.19—3.37 (1H, m), 3.82—4.03 (2H, m), 4.16—4.28 (1H, m), 6.85 (1H, d, *J*=7.9 Hz), 6.93 (1H, t, *J*=7.6 Hz), 7.11—7.37 (7H, m)
20	1.40—2.21 (4H, m), 2.45—2.62 (1H, m), 2.72—2.98 (6H, m), 3.40—3.59 (2H, m), 3.76 (3H, s), 3.86 (2H, d, *J*=4.6 Hz), 6.64—6.83 (4H, m), 6.89 (1H, t, *J*=7.3 Hz), 7.07—7.29 (3H, m)
21	1.27—2.15 (5H, m), 2.18—2.42 (2H, m), 2.45—2.72 (2H, m), 2.75 (3H, s), 2.77—3.13 (5H, m), 3.40—3.55 (1H, m), 3.78 (3H, s), 3.96—4.19 (2H, m), 6.66—6.80 (3H, m), 6.84 (1H, d, *J*=7.9 Hz), 6.93 (1H, t, *J*=7.3 Hz), 7.12—7.33 (3H, m)
22	1.27—2.08 (6H, m), 2.10—2.32 (1H, m), 2.47—2.69 (1H, m), 2.70—2.96 (5H, m), 3.15—3.34 (1H, m), 3.40—3.53 (1H, d, *J*=13 Hz), 3.77 (3H, s), 4.02—4.24 (2H, m), 6.68—6.95 (5H, m), 7.07—7.32 (3H, m)
23	2.02—2.25 (2H, m), 2.48—2.78 (2H, m), 2.73 (3H,s), 2.81—3.09 (6H, m), 3.17—3.40 (2H, m), 3.76 (3H, s), 4.60—4.79 (1H, m), 6.65—6.85 (4H, m), 6.95 (1H, t, *J*=7.3 Hz), 7.16—7.30 (3H, m)
24	2.05—2.21 (2H, m), 2.24—2.42 (2H, m), 2.80—2.99 (4H, m), 3.21—3.38 (4H, m), 3.76 (3H, s), 4.56—4.68 (1H, m), 6.60—6.81 (4H, m), 6.92 (1H, t, *J*=7.3 Hz), 7.11—7.27 (3H, m)
25	2.77 (3H, s), 2.68—3.06 (6H, m), 3.40 (2H, t, *J*=12 Hz), 3.79 (3H, s), 4.01—4.20 (3H, m), 4.32—4.47 (1H, m), 4.51—4.64 (1H, m), 6.72—6.88 (4H, m), 6.95 (1H, t, *J*=7.6 Hz), 7.15—7.32 (3H, m)
26	2.78—2.97 (4H, m), 3.02—3.18 (2H, m), 3.36 (1H, d, *J*=13 Hz), 3.48 (1H, d, *J*=13 Hz), 3.76 (3H, s), 3.98—4.15 (4H, m), 4.24—4.37 (1H, m), 6.68—6.96 (5H, m), 7.08—7.31 (3H, m)
27	1.89—2.14 (2H, m), 2.16—2.35 (2H, m), 2.37—2.63 (2H, m), 2.77 (3H, s), 2.69—3.00 (5H, m), 3.21—3.40 (1H, m), 3.78 (3H, s), 3.80—4.09 (2H, m), 4.15—4.29 (1H, m), 6.65—6.98 (5H, m), 7.11—7.30 (3H, m)
28	1.72—2.13 (3H, m), 2.16—2.32 (2H, m), 2.42—2.59 (1H, m), 2.75—2.98 (4H, m), 3.18—3.42 (2H, m), 3.65—3.82 (1H, m), 3.76 (3H, s), 3.98—4.17 (2H, m), 6.65—6.92 (5H, m), 7.06—7.25 (3H, m)
29	1.75—2.14 (7H, m), 2.56 (2H, t, *J*=11 Hz), 2.70 (3H, s), 2.78—2.97 (4H, m), 3.47 (2H, d, *J*=11 Hz), 3.79 (3H, s), 4.02 (2H, t, *J*=5.9 Hz), 6.71—6.96 (5H, m), 7.10—7.30 (3H, m)
30	1.42—1.65 (1H, m), 1.93—2.12 (1H, m), 2.23—2.57 (3H, m), 2.59—2.79 (1H, m), 2.81—2.98 (4H, m), 2.82 (3H, s), 3.38—3.70 (2H, m), 3.78 (3H, s), 4.93—5.17 (1H, m), 6.68—6.82 (3H, m), 6.94 (1H, t, *J*=7.3 Hz), 7.00—7.29 (4H, m)
31	1.85—2.63 (6H, m), 2.77—2.94 (5H, m), 2.74 (3H, s), 3.25—3.41 (1H, m), 3.75—3.89 (1H, m), 3.80 (3H, s), 3.91—4.05 (1H, m), 4.17—4.28 (1H, m), 6.80—6.97 (4H, m), 7.05—7.27 (4H, m)
32[b]	1.90—2.14 (2H, m), 2.16—2.37 (2H, m), 2.40—2.63 (2H, m), 2.70—2.95 (5H, m), 2.78 (3H, s), 3.19—3.37 (1H, m), 3.79 (3H, s), 3.82—4.08 (2H, m), 4.15—4.29 (1H, m), 6.77—6.88 (3H, m), 6.92 (1H, t, *J*=7.6 Hz), 7.01—7.24 (4H, m)
33	1.40 (3H, t, *J*=7.3 Hz), 1.86—2.13 (2H, m), 2.15—2.36 (2H, m), 2.39—2.62 (2H, m), 2.65—2.99 (5H, m), 2.71 (3H, s), 3.21—3.40 (1H, m), 3.79—4.10 (2H, m), 4.02 (2H, q, *J*=7.3 Hz), 4.15—4.32 (1H, m), 6.78—6.98 (4H, m), 7.04—7.25 (4H, m)
34	1.39 (3H, t, *J*=7.3 Hz), 1.90—2.14 (2H, m), 2.17—2.38 (2H, m), 2.40—2.64 (2H, m), 2.68—2.97 (5H, m), 2.78 (3H, s), 3.22—3.41 (1H, m), 3.80—4.08 (2H, m), 4.00 (2H, q, *J*=7.3 Hz), 4.16—4.30 (1H, m), 6.65—6.79 (3H, m), 6.84 (1H, d, *J*=7.9 Hz), 6.93 (1H, t, *J*=7.9 Hz), 7.11—7.28 (3H, m)
35	1.40 (3H, t, *J*=7.2 Hz), 1.89—2.14 (2H, m), 2.17—2.38 (2H, m), 2.41—2.65 (2H, m), 2.70—2.99 (5H, m), 2.76 (3H, s), 3.18—3.37 (1H, m), 3.82—4.09 (2H, m), 4.01 (2H, q, *J*=7.2 Hz), 4.15—4.31 (1H, m), 6.76—6.88 (3H, m), 6.92 (1H, t, *J*=7.3 Hz), 7.04 (2H, d, *J*=8.6 Hz), 7.10—7.25 (2H, m)
36	1.91—2.13 (2H, m), 2.17—2.35 (2H, m), 2.38—2.60 (2H, m), 2.72—3.07 (5H, m), 2.78 (3H, s), 3.29—3.48 (1H, m), 3.82—4.03 (2H, m), 4.10—4.22 (1H, m), 6.82 (1H, d, *J*=7.9 Hz), 6.94 (1H, t, *J*=7.6 Hz), 7.04—7.25 (5H, m), 7.31—7.40 (1H, m)
37	1.93—2.15 (2H, m), 2.19—2.38 (2H, m), 2.41—2.63 (2H, m), 2.72—2.97 (5H, m), 2.79 (3H, s), 3.18—3.37 (1H, m), 3.81—4.06 (2H, m), 4.15—4.29 (1H, m), 6.84 (1H, d, *J*=7.9 Hz), 6.93 (1H, t, *J*=7.9 Hz), 6.95—7.05 (1H, m), 7.10—7.28 (5H, m)
38	1.92—2.14 (2H, m), 2.17—2.37 (2H, m), 2.41—2.65 (2H, m), 2.71—2.95 (1H, m), 2.77 (3H, s), 2.86 (4H, s), 3.13—3.31 (1H, m), 3.82—4.07 (2H, m), 4.12—4.28 (1H, m), 6.82 (1H, d, *J*=8.6 Hz), 6.92 (1H, t, *J*=7.6 Hz), 7.00—7.13 (3H, m), 7.16—7.31 (3H, m)
39	1.91—2.15 (2H, m), 2.19—2.38 (2H, m), 2.41—2.63 (2H, m), 2.70—2.98 (1H, m), 2.78 (3H, s), 2.88 (4H, s), 3.20—3.39 (1H, m), 3.82—4.06 (2H, m), 4.13—4.29 (1H, m), 6.77—6.98 (5H, m), 7.08—7.30 (3H, m)
40	1.92—2.16 (2H, m), 2.19—2.40 (2H, m), 2.44—2.68 (2H, m), 2.74—3.10 (5H, m), 2.79 (3H, s), 3.19—3.43 (1H, m), 3.82—4.10 (2H, m), 4.15—4.33 (1H, m), 6.85 (1H, d, *J*=7.9 Hz), 6.93 (1H, t, *J*=7.3 Hz), 7.05 (1H, t, *J*=7.3 Hz), 7.11—7.42 (5H, m)
41	1.96—2.19 (2H, m), 2.21—2.42 (2H, m), 2.47—2.65 (2H, m), 2.77—2.99 (1H, m), 2.83 (3H, s), 2.90 (4H, s), 3.20—3.38 (1H, m), 3.85—4.09 (2H, m), 4.14—4.28 (1H, m), 6.85 (1H, d, *J*=7.9 Hz), 6.91 (1H, t, *J*=7.3 Hz), 7.06 (1H, d, *J*=7.3 Hz), 7.21 (1H, t, *J*=7.9 Hz), 7.30—7.44 (3H, m), 7.50 (1H, d, *J*=6.9 Hz)
42	1.88—2.14 (2H, m), 2.15—2.39 (2H, m), 2.33 (3H, s), 2.41—2.65 (2H, m), 2.68—2.97 (5H, m), 2.75 (3H, s), 3.20—3.41 (1H, m), 3.78—4.09 (2H, m), 4.18—4.30 (1H, m), 6.82—7.09 (5H, m), 7.13—7.32 (3H, m)
43	1.92—2.58 (6H, m), 2.65—3.10 (5H, m), 2.83 (3H, s), 3.16—3.43 (1H, m), 3.60—4.09 (3H, m), 6.57 (1H, d, *J*=7.3 Hz), 6.68—6.81 (2H, m), 6.92 (1H, t, *J*=7.3 Hz), 7.00 (1H, s), 7.05 (1H, t, *J*=7.9 Hz), 7.12—7.25 (2H, m)
48	0.84—1.02 (2H, m), 1.10—1.35 (4H, m), 1.40—1.50 (2H, m), 1.60—1.84 (5H, m), 2.02—2.68 (8H, m), 2.78—3.01 (1H, m), 2.86 (3H, s), 3.32—3.52 (1H, m), 3.83—4.07 (2H, m), 4.19—4.30 (1H, m), 6.83 (1H, d, *J*=8.3 Hz), 6.92 (1H, t, *J*=7.4 Hz), 7.13—7.22 (2H, m)
(*S*)-**27**	1.91—2.12 (2H, m), 2.15—2.36 (2H, m), 2.40—2.61 (2H, m), 2.67—2.99 (5H, m), 2.76 (3H, s), 3.20—3.37 (1H, m), 3.78 (3H, s), 3.79—4.04 (2H, m), 4.15—4.30 (1H, m), 6.65—6.78 (3H, m), 6.84 (1H, d, *J*=7.9 Hz), 6.93 (1H, t, *J*=7.9 Hz), 7.13—7.30 (3H, m)
(*R*)-**27**	1.89—2.14 (2H, m), 2.16—2.37 (2H, m), 2.40—2.63 (2H, m), 2.70—2.98 (5H, m), 2.77 (3H, s), 3.21—3.40 (1H, m), 3.77 (3H, s), 3.79—4.06 (2H, m), 4.15—4.30 (1H, m), 6.65—6.80 (3H, m), 6.84 (1H, d, *J*=7.9 Hz), 6.93 (1H, t, *J*=7.3 Hz), 7.13—7.31 (3H, m)
(*S*)-**62**[c]	1.75—2.16 (3H, m), 2.20—2.40 (1H, m), 2.74—3.01 (4H, m), 2.95 (3H, s), 3.03—3.22 (1H, m), 3.49—3.68 (1H, m), 3.72 (3H, s), 3.75—3.95 (1H, m), 4.23—4.46 (2H, m), 6.70—6.85 (3H, m), 6.91 (1H, t, *J*=7.3 Hz), 7.00 (1H, d, *J*=7.9 Hz), 7.13—7.28 (3H, m)
(*S*)-**63**	1.74—2.39 (8H, m), 2.58—3.20 (13H, m), 3.76 (3H, s), 3.67—4.11 (3H, m), 6.67—6.95 (5H, m), 7.06—7.25 (3H, m)

a) Compounds **13**, **17**, and **19** were reported in reference 17. *b*) In $CDCl_3+D_2O$. *c*) In DMSO-d_6.

orless oil. This oil was dissolved in EtOAc (5 ml) and was treated with 4 N HCl in dioxane (0.63 ml, 2.52 mmol). The resulting solution was concentrated. The oily residue was dissolved in EtOAc (10 ml), and the solution was allowed to stand at room temperature. The precipitate formed was collected by filtration to give **18** (130 mg, 0.38 mmol, 24%) as colorless crystals.

Other pyrrolidine derivatives (**19**, **31**—**43**) were similarly prepared with the exceptions of **27** which was prepared by method D, and **28** which was prepared by method A.

2-[2-[2-[2-(3-Methoxyphenyl)ethyl]phenoxyl]ethyl]-1-methylpyrrolidine Hydrochloride (27) (Method D) DEAD (10.2 ml, 65 mmol) was added to a solution of 2-[2-(3-methoxyphenyl)ethyl]phenol **4a** (R^1=3-OMe) (10.6 g, 46.4 mmol), 1-methyl-2-pyrrolidineethanol (8.4 g, 65 mmol) and triphenylphosphine (17 g, 65 mmol) in CH_2Cl_2 (200 ml) and the mixture was stirred overnight at room temperature. The resulting solution was concentrated. The resulting residue was chromatographed on a silica gel column (CH_2Cl_2/MeOH=10/1) to give 2-[2-[2-[2-(3-methoxyphenyl)ethyl]phenoxyl]ethyl]-1-methylpyrrolidine (5.7 g, 16.8 mmol, 36%) as a yellow oil. This oil was dissolved in EtOAc (100 ml) and was treated with 4 N HCl in dioxane (5.0 ml, 20 mmol). The resulting solution was concentrated. The oily residue was dissolved in EtOAc (150 ml), and the solution was allowed to stand at room temperature. The precipitate formed was collected by filtration to give **27** (4.88 g, 13.0 mmol, 77%) as colorless crystals.

2-[2-[2-[2-(3-Methoxyphenyl)ethyl]phenoxyl]ethyl]pyrrolidine Hydrochloride (28) (Method A) To a solution of 2-[2-(3-methoxyphenyl)-ethyl]phenol **4a** (R^1=3-OMe) (680 mg, 2.98 mmol) in DMA (5 ml) was added *tert*-BuOK (340 mg, 3.03 mmol) and the mixture was stirred at 0 °C for 10 min. Then 1-*tert*-butoxycarbonyl-2-[2-(*p*-toluenesulfonyl)oxyethyl]-pyrrolidine (1.20 g, 3.25 mmol) was added and the whole was stirred at 50 °C for 1 h. The resulting suspension was diluted with EtOAc and washed with H_2O and brine. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (benzene/EtOAc=10/1) to give 1-*tert*-butoxycarbonyl-2-[2-[2-[2-(3-methoxyphenyl)-ethyl]phenoxyl]ethyl]pyrrolidine (910 mg, 2.14 mmol, 72%) as a colorless oil. This oil was dissolved in dioxane (5 ml) and treated with 4 N HCl in dioxane (5 ml). The mixture was stirred at room temperature for 3 h and the resulting solution was concentrated. The resulting residue was chromatographed on a silica gel column (CH_2Cl_2/EtOAc=10/1) to give 2-[2-[2-[2-(3-methoxyphenyl)ethyl]phenoxyl]ethyl]pyrrolidine (510 mg, 1.57 mmol, 73%) as a colorless oil. This oil was dissolved in dioxane (5 ml) and treated with 4 N HCl in dioxane (0.50 ml, 2.0 mmol). The resulting solution was concentrated. The oily residue was dissolved in EtOAc (10 ml), and the solution was allowed to stand at room temperature. The precipitate formed was collected by filtration to give **28** (344 mg, 0.95 mmol, 61%) as colorless crystals.

2-(2-Benzyloxybenzyl)-1-cyclohexylethane-1-ol (45) A solution of 2-benzyloxybenzylchloride **44** (41.5 g, 178 mmol) in THF (50 ml) was added to a suspension of Mg (4.33 g, 178 mmol) and I_2 (trace) in THF (300 ml). The mixture was stirred under reflux for 2 h, and cooled to room temperature. Then cyclohexanecarboxaldehyde (10 g, 89 mmol) was added, and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried and evaporated. The resulting residue was chromatographed on a silica gel column (EtOAc/hexane=1/19—3/17) to give **45** (17.9 g, 57.7 mmol, 65%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 0.97—1.32 (5H, m), 1.35—1.48 (1H, m), 1.56—1.93 (6H, m), 2.64 (1H, dd, J=9.2, 14 Hz), 3.01 (1H, dd, J=3.0, 14 Hz), 3.58—3.70 (1H, m), 5.09 (2H, s), 6.89—6.98 (2H, m), 7.16—7.47 (7H, m).

1-Benzyloxy-2-(2-cyclohexylethyl)benzene (46) Triethylamine (4.36 ml, 31.3 mmol) was added to a solution of 2-(2-benzyloxybenzyl)-1-cyclohexylethane-1-ol **45** (8.10 g, 26.1 mmol) in THF (200 ml) and the mixture was stirred at room temperature for 15 min. Then thionyl chloride (2.23 ml, 31.3 mmol) was added, the reaction mixture was stirred overnight at room temperature, and was poured in water and extracted with EtOAc. The organic layer was washed with brine, dried and evaporated. The resulting residue was chromatographed on a silica gel column (EtOAc/hexane=3/97) to give 2-(2-benzyloxyphenyl)-1-chloro-1-cyclohexylethane (5.93 g, 18.0 mmol, 69%) as a colorless oil. To a solution of this compound (5.60 g, 17.0 mmol) and 2,2′-azobisisobutyronitrile (AIBN) (140 mg, 0.85 mmol) in toluene (50 ml) was added dropwise a solution of tributyltin hydride (5.95 g, 20.4 mmol) in toluene (10 ml). The reaction mixture was stirred under reflux for 1 h, and then the solvent was removed. The resulting residue was chromatographed on a silica gel column (hexane) to give **46** (4.51 g, 15.3 mmol, 90%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 0.81—0.99 (2H, m), 1.05—1.36 (4H, m), 1.40—1.82 (7H, m), 2.61—2.74 (2H, m), 5.08 (2H, s), 6.85—6.95 (2H, m), 7.14 (2H, t, J=7.6 Hz), 7.26—7.49 (5H, m).

2-(2-Cyclohexylethyl)phenol (47) A solution of 1-benzyloxy-2-(2-cyclohexylethyl)benzene **46** (4.51 g, 15.3 mmol) in EtOH (50 ml) was hydrogenated over 5% Pd–C (450 mg) at 60 °C for 4 h with stirring. The catalyst was filtered away, and the filtrate was concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=19/1—9/1) to give **47** (2.92 g, 14.3 mmol, 93%) as a colorless solid. ^{1}H-NMR ($CDCl_3$) δ: 0.83—1.05 (2H, m), 1.09—1.39 (4H, m), 1.43—1.56 (2H, m), 1.60—1.87 (5H, m), 2.54—2.66 (2H, m), 4.69 (1H, s), 6.75 (1H, d, J=7.9 Hz), 6.86 (1H, t, J=7.9 Hz), 7.01—7.14 (2H, m).

2-[2-[2-(2-Cyclohexylethyl)phenoxy]ethyl]-1-methylpyrrolidine Hydrochloride (48) To a solution of 2-(2-cyclohexylethyl)phenol **47** (500 mg, 2.45 mmol) in DMA (10 ml) was added *tert*-BuOK (549 mg, 4.89 mmol) and the mixture was stirred at room temperature for 30 min. 2-(2-Chloroethyl)-1-methylpyrrolidine hydrochloride (450 mg, 2.44 mmol) was added, and the mixture was stirred at 60 °C for 5 h. 2-(2-Chloroethyl)-1-methylpyrrolidine hydrochloride (80 mg, 0.43 mmol) was then added, and the mixture was stirred overnight at room temperature. The resulting solution was diluted with EtOAc and washed with H_2O and brine. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (CH_2Cl_2/MeOH=97/3) to give 2-[2-[2-(2-cyclohexylethyl)phenoxy]ethyl]-1-methylpyrrolidine (350 mg, 1.11 mmol, 45%) as a colorless oil. This oil was dissolved in dioxane (4 ml) and was treated with 4 N HCl in dioxane (0.83 ml, 3.32 mmol). The resulting solution was concentrated. The oily residue was dissolved in EtOAc (10 ml), and the solution was allowed to stand at room temperature. The precipitate formed was collected by filtration to give **48** (243 mg, 0.69 mmol, 62%) as colorless crystals.

(*S*)-1-Ethoxycarbonyl-2-hydroxymethylpyrrolidine ((*S*)-50) To a solution of (*S*)-2-pyrrolidinemethanol (*S*)-**49** (13.86 g, 137 mmol) in acetone (80 ml) and H_2O (80 ml) was added triethylamine (19.10 ml, 137 mmol) and the mixture was stirred at 0 °C for 15 min. Then ethyl chloroformate (14.35 ml, 151 mmol) was added and the whole was stirred at room temperature for 6 h. The resulting mixture was concentrated and extracted with EtOAc and washed with brine. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=3/7) to give (*S*)-**50** (20.31 g, 117 mmol, 86%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7.3 Hz), 1.48—1.67 (1H, m), 1.71—2.12 (3H, m), 3.27—3.43 (1H, m), 3.46—3.74 (3H, m), 3.86—4.07 (1H, m), 4.16 (2H, q, J=7.0 Hz), 4.46—4.65 (1H, m). $[\alpha]_D$ −53 ° (c=1.60, $CHCl_3$).

(*S*)-1-Ethoxycarbonyl-2-(*p*-toluenesulfonyloxymethyl)pyrrolidine ((*S*)-51) To a solution of (*S*)-1-ethoxycarbonyl-2-hydroxymethylpyrrolidine (*S*)-**50** (20.84 g, 120 mmol) and *p*-toluenesulfonic anhydride (Ts_2O) (49.58 g, 152 mmol) in CH_2Cl_2 (160 ml) was added triethylamine (21.17 ml, 152 mmol) and the mixture was stirred at room temperature for 2.5 h. The resulting mixture was diluted with CH_2Cl_2 and washed with H_2O and brine. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=13/7) to give (*S*)-**51** (34.51 g, 105 mmol, 90%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.05—1.32 (3H, m), 1.70—2.09 (4H, m), 2.45 (3H, s), 3.23—3.48 (2H, m), 3.82—4.24 (5H, m), 7.27—7.42 (2H, m), 7.77 (2H, d, J=8.6 Hz). $[\alpha]_D$ −48 ° (c=1.45, MeOH).

(*S*)-2-(Cyanomethyl)-1-ethoxycarbonylpyrrolidine ((*S*)-52) To a solution of (*S*)-1-ethoxycarbonyl-2-(*p*-toluenesulfonyloxymethyl)pyrrolidine (*S*)-**51** (33.96 g, 104 mmol) in DMF (200 ml) was added NaCN (5.08 g, 104 mmol) and the mixture was stirred at 80 °C for 4.5 h. The resulting mixture was diluted with EtOAc and washed with H_2O and brine. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=3/1—13/7) to give (*S*)-**52** (16.87 g, 92.6 mmol, 89%) as a yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7.3 Hz), 1.76—2.30 (4H, m), 2.48—2.94 (2H, m), 3.35—3.61 (2H, m), 3.97—4.28 (3H, m). $[\alpha]_D$ −103 ° (c=1.54, MeOH).

(*S*)-1-Ethoxycarbonyl-2-(ethoxycarbonylmethyl)pyrrolidine ((*S*)-53) To a solution of (*S*)-2-(cyanomethyl)-1-ethoxycarbonylpyrrolidine (*S*)-**52** (16.84 g, 92.4 mmol) in EtOH (20 ml) was added conc. H_2SO_4 (7.78 ml, 139 mmol) and the mixture was stirred at 80 °C for 8 h. The resulting mixture was diluted with EtOAc and washed with H_2O, $NaHCO_3$ solution, and brine. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=3/1) to give (*S*)-**53** (11.19 g, 48.8 mmol, 53%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (6H, t, J=7.3 Hz), 1.70—1.96 (3H, m), 2.00—2.16 (1H, m), 2.31 (1H, dd, J=9.9, 15 Hz), 2.74—3.03 (1H, m), 3.32—3.51 (2H, m), 4.05—4.26 (1H, m), 4.13 (4H, q, J=7.3 Hz). $[\alpha]_D$ −49 ° (c=1.47, MeOH).

(*S*)-1-Ethoxycarbonyl-2-(2-hydroxyethyl)pyrrolidine ((*S*)-54) A solution of (*S*)-1-ethoxycarbonyl-2-(ethoxycarbonylmethyl)pyrrolidine (*S*)-**53** (11.15 g, 48.6 mmol) in THF (20 ml) was added dropwise to a suspension of $LiAlH_4$ (1.85 g, 48.7 mmol) in THF (30 ml) at −10 °C. The mixture was stirred at −10 °C for 1 h. To the resulting suspension was slowly added Na_2SO_4 decahydrate and the slurry was then stirred for 30 min. The insoluble material was filtered away and the filtrate was concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=3/7) to give (*S*)-**54** (7.07 g, 37.8 mmol, 78%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.28(3H, t, J=7.3 Hz), 1.40—1.57 (1H, m), 1.59—1.80 (2H, m), 1.83—2.08 (3H, m), 3.29—3.44 (2H, m), 3.51—3.70 (2H, m), 4.06—4.27 (4H, m). $[\alpha]_D$ −41 ° (c=1.64, MeOH).

(*S*)-1-Ethoxycarbonyl-2-[2-(*p*-toluenesulfonyloxy)ethyl]pyrrolidine ((*S*)-55) To a solution of (*S*)-1-ethoxycarbonyl-2-(2-hydroxyethyl)pyrrolidine (*S*)-**54** (7.05 g, 37.7 mmol) and Ts_2O (15.98 g, 49.0 mmol) in CH_2Cl_2 (60 ml) was added triethylamine (6.82 ml, 48.9 mmol) and the mixture was stirred at room temperature for 2 h. It was then diluted with CH_2Cl_2 and washed with H_2O and brine. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=3/2) to give (*S*)-**55** (10.08 g, 29.5 mmol, 78%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, t, J=6.9 Hz), 1.55—2.23 (6H, m), 2.45 (3H, s), 3.24—3.50 (2H, m), 3.78—3.92 (1H, m), 3.97—4.18 (4H, m), 7.35 (2H, d, J=8.6 Hz), 7.79 (2H, d, J=7.9 Hz). $[\alpha]_D$ −18 ° (c=0.97, MeOH).

(*S*)-1-Ethoxycarbonyl-2-[2-[2-[2-(3-methoxyphenyl)ethyl]phenoxy]-ethyl]pyrrolidine ((*S*)-61) (n=2) To a solution of 2-[2-(3-methoxyphenyl)ethyl]phenol **4a** (R^1=3-OMe) (4.86 g, 21.3 mmol) in DMA (30 ml) was added *tert*-BuOK (2.63 g, 23.4 mmol) and the mixture was stirred at 0 °C for 15 min. Then a solution of (*S*)-1-ethoxycarbonyl-2-[2-(*p*-toluenesulfonyloxy)ethyl]pyrrolidine (*S*)-**55** (8.0 g, 23.4 mmol) in DMA (20 ml) was added and the whole was stirred at room temperature for 4 h. The resulting suspension was diluted with EtOAc and washed with H_2O and brine. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=3/1—13/7) to give (*S*)-**61** (n=2) (7.56 g, 19.0 mmol, 89%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.08—1.33 (3H, m), 1.75—2.09 (5H, m), 2.15—2.40 (1H, m), 2.80—2.98 (4H, m), 3.30—3.57 (2H, m), 3.78 (3H, s), 3.93—4.21 (5H, m), 6.69—6.92 (5H, m), 7.06—7.25 (3H, m). $[\alpha]_D$ +4.4 ° (c=1.33, MeOH).

(*S*)-2-[2-[2-[2-(3-Methoxyphenyl)ethyl]phenoxyl]ethyl]-1-methylpyrrolidine Hydrochloride ((*S*)-27) A solution of (*S*)-1-ethoxycarbonyl-2-[2-[2-[2-(3-methoxyphenyl)ethyl]phenoxy]ethyl]pyrrolidine (*S*)-**61** (n=2) (9.10 g, 22.9 mmol) in THF (50 ml) was added dropwise to a suspension of $LiAlH_4$ (2.61 g, 48.7 mmol) in THF (50 ml). The mixture was refluxed for 1 h and then cooled. To the resulting suspension was slowly added Na_2SO_4 decahydrate and the slurry was then stirred for 1 h. The insoluble material was filtered away and the filtrate was concentrated. The resulting residue was chromatographed on a silica gel column (CH_2Cl_2/MeOH=9/1) to give 2-[2-[2-[2-(3-methoxyphenyl)ethyl]phenoxyl]ethyl]-1-methylpyrrolidine (7.35 g, 21.7 mmol, 95%) as a colorless oil. This oil (7.19 g, 21.2 mmol) was dissolved in dioxane (35 ml) and was treated with 4 N HCl in dioxane (15.9 ml, 63.6 mmol). The mixture was stirred at room temperature for 10 min, then concentrated. The oily residue was dissolved in EtOAc, and the solution was allowed to stand at room temperature. The precipitate formed was collected by filtration to give colorless crystals (7.11 g, 18.9 mmol, 89%). $[\alpha]_D$ −41 ° (c=1.64, MeOH).

(*S*)-1-Ethoxycarbonyl-2-formylpyrrolidine ((*S*)-56) To a solution of DMSO (6.85 ml, 96.5 mmol) in CH_2Cl_2 (120 ml) was added oxalyl chloride (8.42 ml, 97 mmol) and the mixture was stirred at −60 °C for 5 min. (*S*)-1-Ethoxycarbonyl-2-hydroxymethylpyrrolidine (*S*)-**50** (11.14 g, 64.3 mmol) in CH_2Cl_2 (30 ml) was then added and the mixture was stirred at −60 °C for 1 h. To the resulting solution was added triethylamine (26.89 ml, 193 mmol) and the mixture was stirred at −60 °C for 1 h. The resulting solution was diluted with CH_2Cl_2 and washed with H_2O and brine. The organic layer was dried and concentrated, and the resulting residue was chromatographed on a silica gel column (hexane/EtOAc=13/7) to give (*S*)-**56** (8.67 g, 50.6 mmol, 79%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.22, 1.29 (each 3H, t, J=6.9 Hz), 1.72—2.23 (4H, m), 3.41—3.67 (2H, m), 4.05—4.32 (3H, m), 9.51, 9.59 (each 1H, s). $[\alpha]_D$ −80 ° (c=1.46, MeOH).

(*S*)-1-Ethoxycarbonyl-2-(2-ethoxycarbonyl-1-ethenyl)pyrrolidine ((*S*)-57) A solution of (*S*)-1-ethoxycarbonyl-2-formylpyrrolidine (*S*)-**56** (4.00 g, 23.4 mmol) and (carbethoxymethylene)triphenylphosphorane (8.95 g, 25.7 mmol) in CH_3CN (60 ml) was refluxed for 1 h. The resulting mixture was cooled and then concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=3/1—7/3) to give (*S*)-**57** (5.51 g, 22.8 mmol, 98%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.12—1.38 (6H, m), 1.70—1.95 (3H, m), 1.97—2.20 (1H, m), 3.33—3.59 (2H, m), 4.01—4.26 (4H, m), 4.38—4.61 (1H, m), 5.74—5.95 (1H, m), 6.73—6.93 (1H, m). $[\alpha]_D$ −96 ° (c=1.57, MeOH).

(*S*)-1-Ethoxycarbonyl-2-(2-ehtoxycarbonylethyl)pyrrolidine ((*S*)-58) A solution of (*S*)-1-ethoxycarbonyl-2-(2-ethoxycarbonyl-1-ethenyl)pyrrolidine (*S*)-**57** (5.48 g, 22.7 mmol) in EtOH (35 ml) was hydrogenated over 5% Pd–C (550 mg) at 60 °C for 5 h with stirring. The catalyst was filtered away, and the filtrate was concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=3/1) to give (*S*)-**58** (5.09 g, 20.9 mmol, 92%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (6H, t, J=7.3 Hz), 1.29—1.39 (1H, m), 1.43—2.12 (5H, m), 2.23—2.44 (2H, m), 3.07—3.55 (2H, m), 3.70—3.96, 4.55—4.71 (each 1H, m), 4.13 (4H, q, J=7.3 Hz). $[\alpha]_D$ −33 ° (c=1.39, MeOH).

(*S*)-1-Ethoxycarbonyl-2-(3-hydroxypropyl)pyrrolidine ((*S*)-59) A solution of (*S*)-1-ethoxycarbonyl-2-(2-ethoxycarbonylethyl)pyrrolidine (*S*)-**58** (5.06 g, 20.8 mmol) in THF (20 ml) was added dropwise to a suspension of $LiAlH_4$ (789 mg, 20.8 mmol) in THF (40 ml) at −10 °C. The mixture was stirred at −10 °C for 1 h. To the resulting suspension was slowly added Na_2SO_4 decahydrate and the slurry was then stirred for 2 h. The insoluble material was filtered off and the filtrate was concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=1/1) to give (*S*)-**59** (2.85 g, 14.2 mmol, 68%) as a colorless oil. ^{1}H-NMR ($CDCl_3$ +D_2O) δ: 1.26 (3H, t, J=7.3 Hz), 1.33—2.05 (8H, m), 3.29—3.54 (2H, m), 3.58—4.01 (3H, m), 4.04—4.27 (2H, m). $[\alpha]_D$ −57 ° (c=1.01, MeOH).

(*S*)-1-Ethoxycarbonyl-2-[3-(*p*-toluenesulfonyloxy)propyl)pyrrolidine ((*S*)-60) To a solution of (*S*)-1-Ethoxycarbonyl-2-(3-hydroxypropyl)pyrrolidine (*S*)-**59** (2.83 g, 14.1 mmol) and Ts_2O (5.96 g, 18.3 mmol) in CH_2Cl_2 (35 ml) was added triethylamine (2.55 ml, 18.3 mmol) and the mixture was stirred at room temperature for 2.5 h. The resulting mixture was diluted with CH_2Cl_2 and washed with brine. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=13/7) to give (*S*)-**60** (4.81 g, 13.5 mmol, 96%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7.3 Hz), 1.30—1.48 (1H, m), 1.52—2.01 (7H, m), 2.45 (3H, s), 3.23—3.54 (2H, m), 3.66—3.89 (1H, m), 3.94—4.22 (4H, m), 7.35 (2H, d, J=7.9 Hz), 7.79 (2H, d, J=8.6 Hz). $[\alpha]_D$ −35 ° (c=1.35, MeOH).

(*S*)-1-Ethoxycarbonyl-2-[3-[2-[2-(3-methoxyphenyl)ethyl]phenoxy]-propyl]pyrrolidine ((*S*)-61) (n=3) To a solution of 2-[2-(3-methoxyphenyl)ethyl]phenol **4a** (R^1=3-OMe) (800 mg, 3.50 mmol) in DMA (15 ml) was added *tert*-BuOK (433 mg, 3.86 mmol) and the mixture was stirred at 0 °C for 15 min. A solution of (*S*)-1-ethoxycarbonyl-2-[3-(*p*-toluenesulfonyloxy)propyl)pyrrolidine (*S*)-**60** (1.37 g, 3.85 mmol) in DMA (7 ml) was then added and the whole was stirred at room temperature for 3.5 h. The resulting suspension was diluted with EtOAc and washed with H_2O and brine. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=4/1) to give (*S*)-**61** (n=3) (1.30 g, 3.16 mmol, 90%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.11—1.32 (3H, m), 1.47—2.07 (8H, m), 2.79—2.96 (4H, m), 3.26—3.56 (2H, m), 3.78 (3H, s), 3.84—4.17 (5H, m), 6.70—6.92 (5H, m), 7.06—7.25 (3H, m). $[\alpha]_D$ −31 ° (c=1.09, MeOH).

(*S*)-2-[3-[2-[2-(3-Methoxyphenyl)ethyl]phenoxyl]propyl]-1-methylpyrrolidine Citrate ((*S*)-63) A solution of (*S*)-1-ethoxycarbonyl-2-[3-[2-[2-(3-methoxyphenyl)ethyl]phenoxy]propyl]pyrrolidine (*S*)-**61** (n=3) (1.27 g, 3.09 mmol) in THF (20 ml) was added dropwise to a suspension of $LiAlH_4$ (350 mg, 9.22 mmol) in THF (15 ml). The mixture was refluxed for 1 h and then cooled. To the resulting suspension was slowly added Na_2SO_4 decahydrate and the slurry was then stirred for 2 h. The insoluble material was filtered away and the filtrate was concentrated. The resulting residue was chromatographed on a silica gel column (CH_2Cl_2/MeOH=9/1) to give 2-[3-[2-[2-(3-methoxyphenyl)ethyl]phenoxyl]propyl]-1-methylpyrrolidine (996 mg, 2.82 mmol, 91%) as a colorless oil. To a solution of this oil (880 mg, 2.49 mmol) in EtOH (5 ml) was added citric acid (523 mg, 2.49 mmol) and the mixture was stirred at room temperature for 2 h, then concentrated. The oily residue was dissolved in EtOAc, and the solution was allowed to stand at room temperature. The precipitate formed was collected by filtration to give colorless crystals (1.30 g, 2.38 mmol, 96%). $[\alpha]_D$ −12 ° (c=1.30, MeOH).

5-HT$_2$ Receptor Binding Assay The 5-HT$_2$ receptor binding assay of Leysen *et al.*[21] was employed with some modifications. It was performed using the 5-HT$_2$ antagonist, [^{3}H]ketanserin, as the ^{3}H-ligand and the cortex as reported in ref 17.

D$_2$ Receptor Binding Assay The D$_2$ receptor binding assay of Köhler *et al.*[22] was employed with some modifications. It was performed using the D$_2$ antagonist, [^{3}H]raclopride, as the ^{3}H-ligand and the striatum as reported in

ref 17.

α_1 Receptor Binding Assay The α_1 receptor binding assay of Greengrass and Bremner[23] was employed with modifications. It was performed in a similar manner to the 5-HT_2 receptor binding assay, except for the use of the α_1 antagonist, [^{3}H]prazosin, as the ^{3}H-ligand.

β Receptor Binding Assay The β receptor binding assay of U'Prichard *et al*.[24] was employed with modifications. It was performed in a similar manner to the 5-HT_2 receptor binding assay, except for the use of the β antagonist, [^{3}H]dihydroalprenolol (DHA), as the ^{3}H-ligand.

5-HT_1 Receptor Binding Assay The 5-HT_1 receptor binding assay of Middlemiss[25] was employed with modifications. It was performed in a similar manner to the 5-HT_2 receptor binding assay, except for the use of the [^{3}H] 5-HT as the ^{3}H-ligand.

5-HT_3 Receptor Binding Assay The 5-HT_3 receptor binding assay of Kilpatrick *et al*.[26] was employed with modifications. It was performed in a similar manner to the 5-HT_2 receptor binding assay, except for the use of the 5-HT_3 antagonist, [^{3}H]GR65630, as the ^{3}H-ligand.

5-HT-Induced Vasoconstriction Experiment Contractions of the rat caudal arteries of Van Nueten *et al*.[27] were employed with some modifications as reported in ref 17.

5-HT-Induced PRP Aggregation Preparation of Platelets: For *in vitro* experiments, human blood was withdrawn by venepuncture from normal volunteers, who had not taken any medication for a period of at least 10 d. For *ex vivo* experiments, blood was withdrawn from the left carotid artery of pentobarbital (40 mg/kg, i.p.)-anesthetized male cats (American Shorthair, Kasho, 2.5—3.6 kg) before and 0.5, 1, 2, 4 and 6 h after intravenous administration of test compounds. Blood samples were collected into plastic syringes containing 3.8% trisodium citrate (1 : 9, v/v). The blood was centrifuged, to obtain PRP, at $150\times g$ (human) and $120\times g$ (cat) for 15 min at room temperature. Platelet-poor plasma (PPP) was obtained by centrifugation of the remaining blood at $2000\times g$ for 10 min. Platelet counts in PRP were adjusted to 3×10^8/ml (human) and 2.5×10^8/ml (cat) by adding PPP.

Measurements of Platelet Aggregation: All aggregation studies were performed in a 6-channel aggregometer (NKK, Tokyo, Japan). The PRP was incubated at 37 °C for 1.5 min in the aggregometer, with stirring (1000 rpm), followed by stimulation with 5-HT (10 μM) combined with collagen (0.125 μg/ml) for human platelets and 5-HT alone (4—8 μM) for cat platelets. Changes in light transmission were recorded for 10 min after the stimulation. The extent of aggregation was estimated by the percent of maximum increase in light transmission, with the PPP representing 100% transmittance. In human platelet studies, test compounds dissolved in saline were added to the PRP before agonist stimulation, and results were expressed as IC_{50} values (μM), the concentration produced a 50% inhibition.

Acknowledgments We wish to thank Miss Takako Nagasawa[28] for the biological data, and Mrs. Megumi Akamatsu for the syntheses.

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