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

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A series of [2-(2-phenylethyl)phenoxy]ethylpyrrolidine derivatives were synthesized, and their affinity for serotonin-2 (5-HT_2) and dopamine-2 (D_2) receptors was examined. Among them, compound 17, (2*R*,4*R*)-4-hydroxy-2-[2-[2-[2-(3-methoxyphenyl)ethyl]phenoxy]ethyl]-1-methylpyrrolidine hydrochloride, showed high 5-HT_2 receptor affinity *in vitro*. This compound was a more potent inhibitor of *ex vivo* 5-HT-induced platelet aggregation than compound 3, which was previously shown to be more potent than ketanserin (1) and sarpogrelate (2a). However, compound 17 produced gastric irritation in rats. Therefore, we carried out a further derivatization of 17, and compound 45 (R-102444), a lauryl ester prodrug of compound 17, was found to be a promising candidate as an antithrombotic agent. Oral administration of R-102444 produced a marked inhibition of 5-HT-induced *ex vivo* platelet aggregation, and R-102444 did not cause any gastric irritation. The antiaggregatory effects of R-102444 were more potent than those of sarpogrelate (2a) and its active metabolite, M-1 (2b). In addition, R-102444 exhibited more potent antithrombotic effects than sarpogrelate in a rat photochemically-induced thrombosis model.

Key words serotonin-2 (5-HT_2) receptor; antiplatelet; R-102444; antagonist; [2-(2-phenylethyl)phenoxy]alkylamines

Platelet activation and vasoconstriction at the site of vascular injury play an important role in hemostasis and thrombosis.[2)] Platelets are activated by a variety of substances, including adenosine diphosphate (ADP), thromboxane A_2 (TXA_2), and serotonin (5-HT).[3—5)] Among them, 5-HT stored in the electrondense granules of platelets is released during platelet activation, and accelerates platelet aggregation.[6)] 5-HT is also a potent vasoconstrictor, and thus, released 5-HT constricts vascular vessels which accelerates thrombus formation.[7)] Since these responses of platelets and vascular muscles to 5-HT are mediated by the 5-HT_2 receptors on these tissues, 5-HT_2 antagonists are expected to be useful in the treatment of thrombosis.[8)]

Ketanserin (**1**), a 5-HT_2 receptor antagonist, inhibits 5-HT-induced platelet aggregation and vasoconstriction.[9)] However, this compound produces an antihypertensive action *via* its adrenergic (α_1) receptor antagonistic activity.[10,11)] Sarpogrelate (**2a**), a more selective 5-HT_2 antagonist, has been recently developed, and is now clinically available for the treatment of peripheral arterial occlusive disease in Japan.[12,13)]

We previously reported that [2-(2-phenylethyl)phenoxy]-alkylamine derivatives with a pyrrolidine or piperidine substructure show high 5-HT_2 but low D_2 receptor affinity.[14)] Among them, compound **3** was the most potent and selective to 5-HT_2 receptors in the binding assays. This compound inhibited the 5-HT-induced vasoconstriction *in vitro* and platelet aggregation both *in vitro* and *ex vivo*. However, this compound was irritant to the rat stomach. Thus, we examined modifications on the pyrrolidine moiety in compound **3**. A hydroxylation at the 4-position of the pyrrolidine ring in compound **3** successfully produced compound **17**. Some of the acyl derivatives of **17** exhibited an *ex vivo* antithrombotic effect in rats. Furthermore, lauryl ester **45** (R-102444) and palmitoyl ester **46** did not cause any gastric irritation. In this paper, we describe the synthesis and structure–activity relationships (SAR) of a series of these compounds. We also report a promising candidate, R-102444, as a prodrug-type 5-HT_2 antagonist in the cardiovascular system. Furthermore, the biological activities of R-102444 with those of sarpogrelate (**2a**) and its active metabolite, M-1 (**2b**) are compared.

Chemistry

The syntheses of the optically active pyrrolidine intermediates, (2*R*,4*R*)-**10** and its isomer (2*S*,4*R*)-**10**, are outlined in Chart 1. The tosylate, (2*R*,4*R*)-**10**, was prepared in eight steps starting from the commercially available (2*S*,4*R*)-4-benzyloxy-1-*tert*-butoxycarbonylproline (2*S*,4*R*)-**4**. The simultaneous esterification and deprotection of (2*S*,4*R*)-**4**, followed by re-protection by ethyl chloroformate gave a carbamate (2*S*,4*R*)-**5**. The carbamate was reduced with lithium borohydride ($LiBH_4$) to give an alcohol (2*S*,4*R*)-**6**. The alcohol was converted to (2*R*,4*R*)-**7** *via* a tosylate, and the following acidic ethanolysis of the resulting nitrile group gave an ester (2*S*,4*R*)-**8**. The ester was reduced with lithium aluminum hydride ($LiAlH_4$) under cooled conditions to give an alcohol (2*R*,4*R*)-**9**, which was then converted to the tosylate (2*R*,4*R*)-**10**. A diastereoisomer (2*S*,4*R*)-**10** was prepared in the same manner, from the carbamate (2*R*,4*R*)-**5**, which was derived from the commercially available *trans*-4-hydroxy-L-proline (2*S*,4*R*)-**11**, in three steps.

The synthetic routes of the compounds (**15**—**20**) listed in Table 3 are shown in Chart 2. The alkylation of phenols **12**[13,15)] with the tosylate (2*R*,4*R*)-**10** provided carbamates **13**, which were then hydrogenated to compounds **14**. The carbamate group of **14** was converted into an *N*-methyl group with $LiAlH_4$ to give 4-hydroxypyrrolidine derivatives **15**—**20**.

The synthetic pathways of three diastereomers of compound **17**, namely compound **22**, **25** and **27**, are illustrated in Chart 3. The (2*R*,4*S*) isomer, **22**, was prepared by means of the Mitsunobu inversion[16)] using **14a** and benzoic acid, followed by reduction of the resulting ester **21** with $LiAlH_4$. The (2*S*,4*R*) isomer, **25**, was synthesized from the phenol **12a** and

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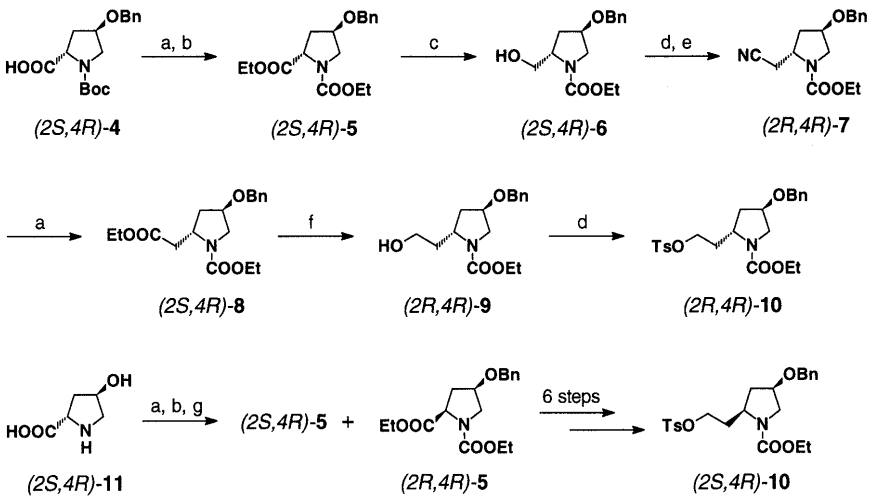
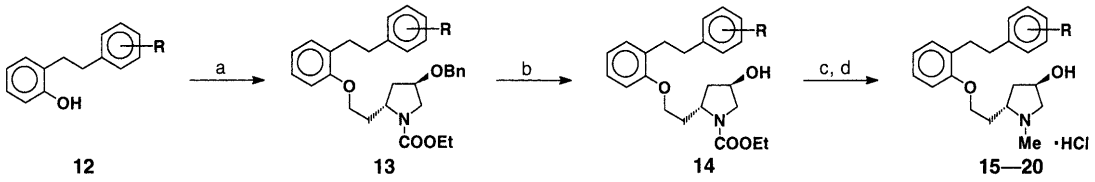


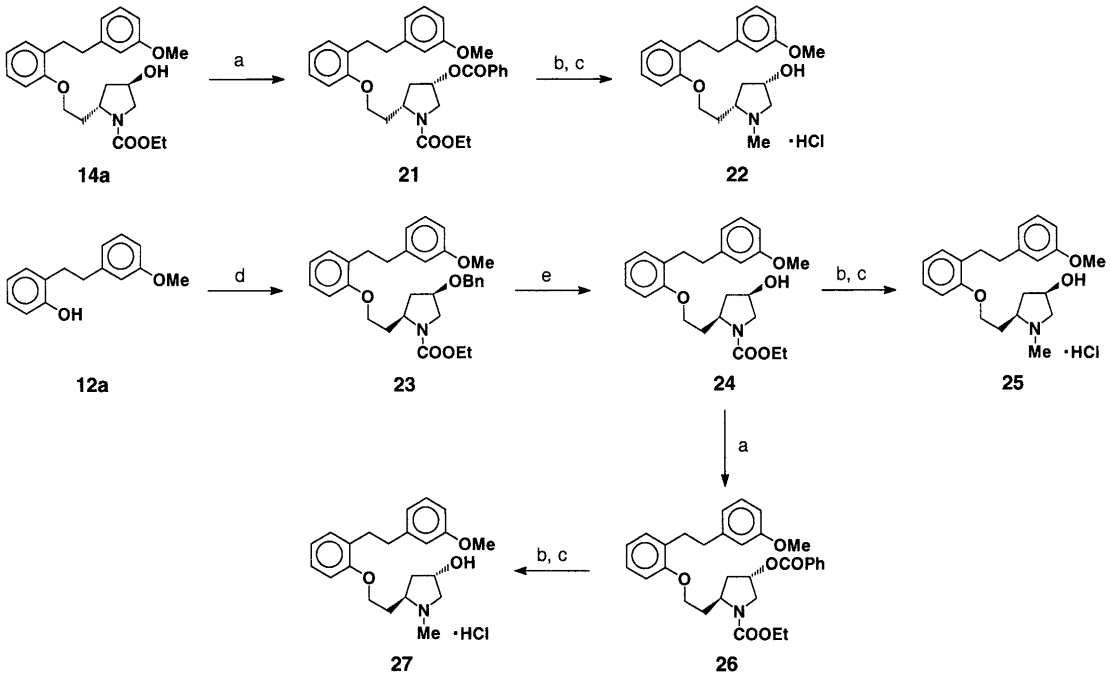
a) HCl (gas) / EtOH; b) ClCOOEt, Et_3N / acetone-H_2O; c) $LiBH_4$ / THF; d) Ts_2O, Et_3N / CH_2Cl_2; e) NaCN / DMF; f) $LiAlH_4$ / THF; g) BnBr, NaH, Bu_4NI / THF

Chart 1



a) *(2R,4R)*-**10**, *tert*-BuOK / DMA; b) H_2, Pd-C / EtOH; c) $LiAlH_4$ / THF; d) HCl / AcOEt or dioxane.

Chart 2



a) benzoic acid, PPh_3, DEAD / CH_2Cl_2; b) $LiAlH_4$ / THF; c) HCl / AcOEt or dioxane; d) *(2S,4R)*-**10**, *tert*-BuOK / DMA; e) H_2, Pd-C / EtOH.

Chart 3

(2*S*,4*R*)-**10** in the same manner as in the synthesis of **17**. The (2*S*,4*S*) isomer, **27**, was prepared from **24** similarly to the preparation of **22**. Each of the diastereomers was confirmed respectively by X-ray crystallographic analysis (Fig. 2).

Modifications at the 4-position of the pyrrolidine ring were achieved in the manner as shown in Chart 4. Oxopyrrolidine derivative **28** was prepared by Swern oxidation[17] of **17**. Reaction of **28** with hydroxylamine hydrochloride gave (*Z*)-

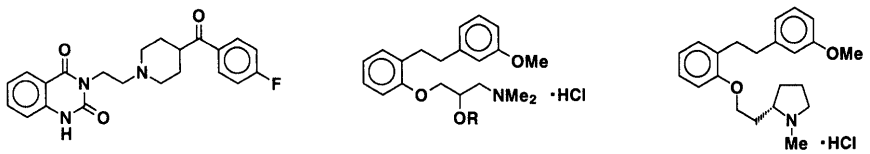


Fig. 1

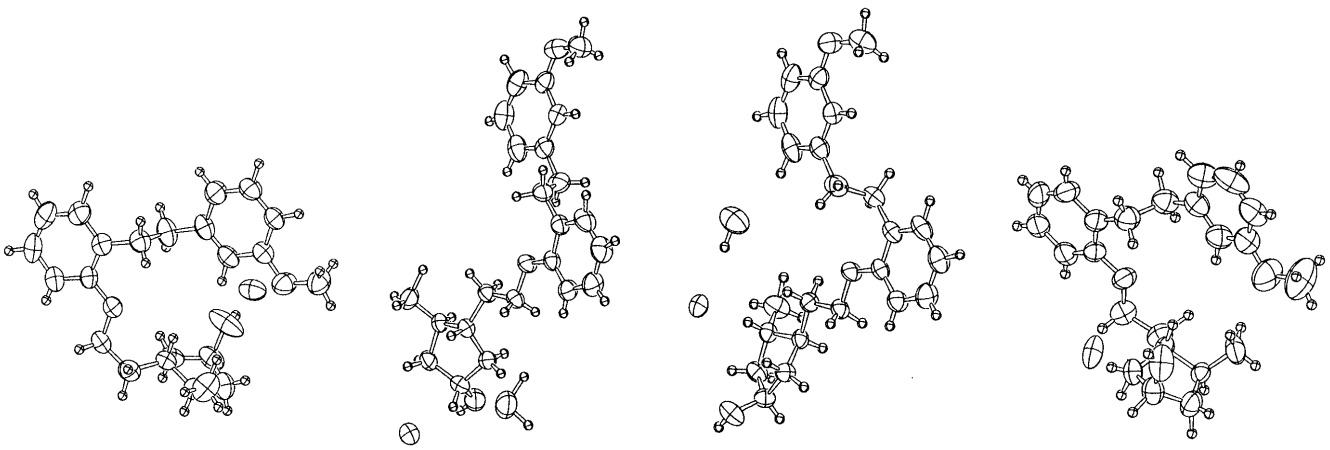
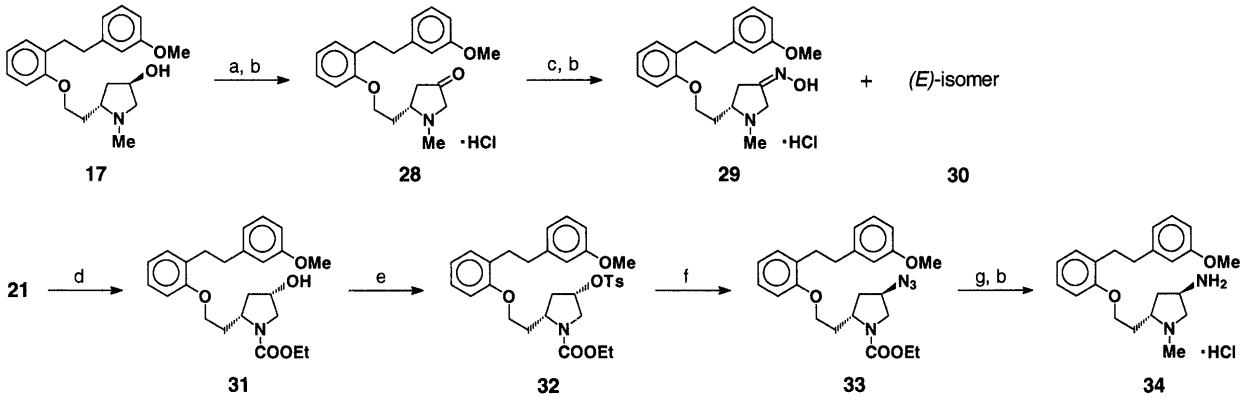


Fig. 2. ORTEP Drawing of Molecules **17**, **22**, **25**, and **27**



a) DMSO, $(COCl)_2$, Et_3N / CH_2Cl_2; b) HCl / AcOEt or dioxane; c) hydroxylamine hydrochloride, AcONa / MeOH; d) $LiBH_4$ / THF; e) Ts_2O, Et_3N / CH_2Cl_2; f) NaN_3 / DMF; g) $LiAlH_4$ / THF.

Chart 4

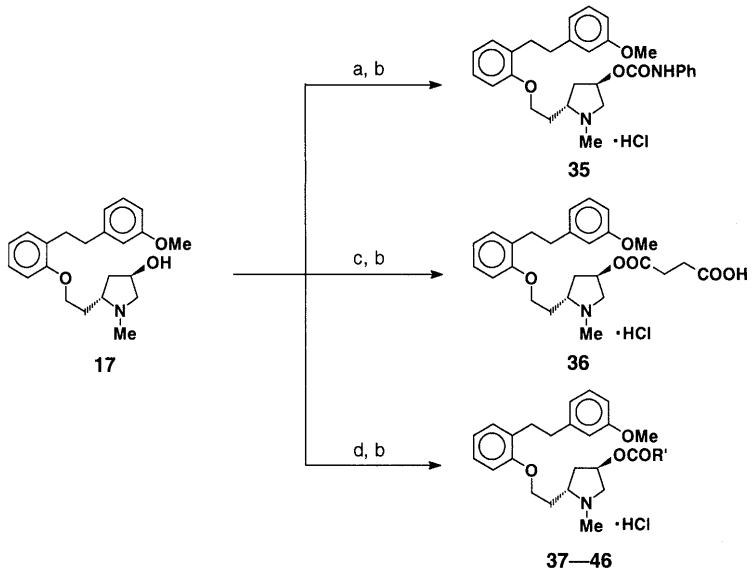
oxime **29** and (*E*)-oxime **30**, which were separated by silica gel column chromatography.[18] Aminopyrrolidine derivative **34** was synthesized as described below. Reduction of **21** with $LiBH_4$ gave an alcohol **31**, which was then converted to a tosylate **32**. The *SN*2 reaction of the tosylate **32** with sodium azide yielded an inverse azide **33**, which was then reduced with $LiAlH_4$ to give the desired product **34**.

The syntheses of the prodrug derivatives are outlined in Chart 5. Carbamate **35** was obtained from the treatment of **17** with phenyl isocyanate. Carbonates **37** and **38**, and esters (**36**, **39**—**46**) were prepared by the acylation of **17** with the corresponding acid anhydride or acyl chloride.

Results and Discussion

In the previous paper, we reported that (*S*)-2-[2-[2-[2-(3-methoxyphenyl)ethyl]phenoxy]ethyl]-1-methylpyrrolidine hydrochloride **3** has high affinity and specificity for 5-HT_2 receptors in the binding assays. Indeed, compound **3** was a potent inhibitor of *in vitro* 5-HT-induced vasoconstriction and of both *in vitro* and *ex vivo* platelet aggregation. However, oral administration of this compound caused gastric irritation in rats. Therefore, further modifications were made on the pyrrolidine moiety.

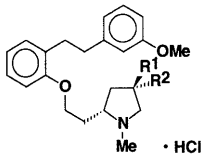
Although 5-HT_2 receptors are distributed both in the brain and peripheral tissues, 5-HT_2 receptor antagonists, as an antithrombotic agent, are expected to act solely on platelets and arterial walls. It is well known that lipophilic compounds are inclined to cross the blood brain barrier (BBB) more than hydrophilic compounds.[19] We reported that the D_2 receptor affinity depends on the lipophilicity around the amino moiety



a) phenyl isocyanate, Et_3N / CH_2Cl_2; b) HCl / AcOEt or dioxane; c) succinic anhydride / acetone; d) $(R'CO)_2O$ or R'COCl / pyridine

Chart 5

Table 1. Affinity of Compound **3** and Other Pyrrolidine Derivatives, Substituted at the 4-Position of the Pyrrolidine Ring for 5-HT_2 and D_2 Receptors



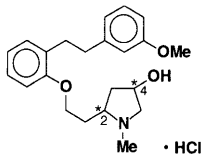
Compd.	R^1	R^2	IC_{50} (nM)[a]		Ratio[b]
			5-HT_2	D_2	D_2/5-HT_2
3	H	H	1.8	1100	610
34	NH_2	H	4.7	>5000	ND[c]
28	=O		49	>5000	ND[c]
29	=NOH (*Z*)		42	>5000	ND[c]
30	=NOH (*E*)		24	>5000	ND[c]
17	OH	H	2.2	2400	1100
Sarpogrelate (**2a**)			150	>5000	ND[c]
M-1 (**2b**)			16	>5000	ND[c]
Ketanserin (**1**)			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*) Not determined.

in a series of compounds.[14,20] Thus, we hypothesized that the selectivity in peripheral tissues depended on the hydrophilicity of the compounds, and we accordingly designed polar and/or hydrophilic modifications (amino (**34**), oxo (**28**), hydroxyimino (**29**, **30**), and hydroxy (**17**) derivatives) at the 4-position of the pyrrolidine ring. Binding assays of these compounds for 5-HT_2 and D_2 receptors showed that the modifications resulted in a reduction of the D_2 receptor binding (Table 1). All compounds shown in Table 1 exhibited low D_2 affinity with IC_{50} values of above 2400 nM. In addition, there was a small amount of ^{14}C-labeled **17** which was distributed in the brain after an intravenous administration to rats (data not shown).

In a 5-HT_2 receptor binding assay, compound **34** with an amino group exhibited a slightly lower affinity than **3**. An oxo compound (**28**) and hydroxyimino compounds (**29**, **30**) had significantly (thirteen-fold) less affinity than **3**. However, compound **17**, in which a hydroxy group was introduced, showed a similar high affinity for 5-HT_2 receptors, but lower D_2 receptor affinity compared to **3**. Among these compounds, **17** exhibited the largest D_2/5-HT_2 ratio (1100).

Table 2. Affinity of Compound **17** and Its Optical Isomers for 5-HT_2 Receptors



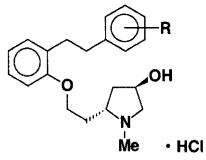
Compd.	Config.	IC_{50} (nM)[a]
17	(2*R*,4*R*)	2.2
22	(2*R*,4*S*)	36
25	(2*S*,4*R*)	64
27	(2*S*,4*S*)	51

a) Interaction of the compounds with rat brain 5-HT_2 was determined by conventional binding assay using [^{3}H]ketanserin.

Compound **17**, with high affinity and specificity to 5-HT_2 receptors, has two asymmetric carbon atoms at the 2- and 4-position of the pyrrolidine ring. Therefore, the other three optical isomers were prepared and their binding affinity for 5-HT_2 receptors were examined (Table 2). It was revealed that the compound with (2*R*, 4*R*) configuration, **17**, is the biologically active isomer. Compound **17** exhibited the highest affinity with an IC_{50} value of 2.2 nM, while the affinity of the other three optical isomers remarkably decreased by more than fifteen-fold compared with **17**. The configuration at the 2- and 4-position of the pyrrolidine ring was found to be important for high 5-HT_2 receptor affinity, which is consistent with the previous results of compound **3** and its enantiomer.[14]

The effect of substituents on the ω-phenyl group is summarized in Table 3. The methoxy-substituted compound at the 3-position (**17**) of the ω-phenyl ring showed higher 5-

Table 3. Affinity of Compound **17** and Its Derivatives for 5-HT$_2$ Receptors



Compd.	R	IC_{50} (nM)[a]
15	H	5.5
16	2-OMe	3.8
17	3-OMe	2.2
18	4-OMe	28
19	3,5-diOMe	5.2
20	3-OH	12

a) Interaction of the compounds with rat brain 5-HT$_2$ was determined by conventional binding assay using [^{3}H]ketanserin.

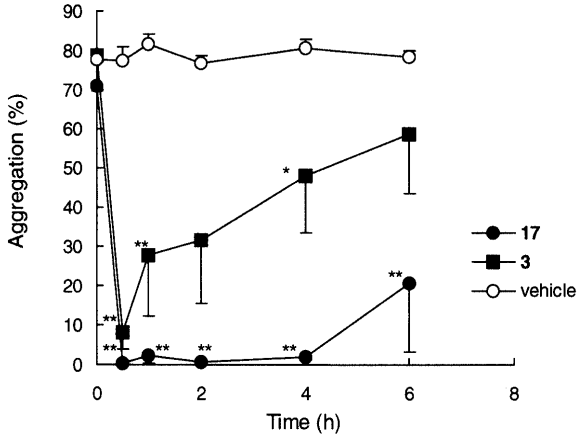


Fig. 3. *Ex Vivo* Antiplatelet Effects of Compound **3** and **17** in Cats

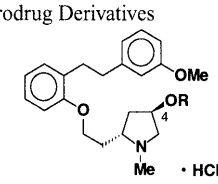
Data are represented as the mean±S.E.M. (n=4–6). * p<0.05, ** p<0.01 *vs.* vehicle (Dunnett's test).

HT$_2$ receptor affinity than those substituted at the 2- or 4-position (**16** or **18**). The 3,5-dimethoxy-substituted compound, **19**, exhibited slightly weaker activity than **17**. This result shows that the introduction of a bulky substituent decreases the affinity for 5-HT$_2$ receptors, which is consistent with that of (*RS*)-2-(2-pyrrolidinylethyl) compounds in the previous paper.[14] The de-methylation of the methoxy group of **17**, in the case of compound **20**, decreased the 5-HT$_2$ receptor affinity. In fact, a hydrophilic modification at the 3-position on the ω-phenyl ring resulted in the reduction of 5-HT$_2$ receptor binding affinity.

Our previous study[14] demonstrated that the *ex vivo* effects of compound **3** on platelet aggregation were more potent than those of ketanserin and sarpogrelate. In the present study, the inhibitory effects of compound **17** on 5-HT-induced platelet aggregation in cats were compared to those of compound **3** (Fig. 3). A single bolus administration of **17** (100 μg/kg, i.v.) produced a complete inhibition of platelet aggregation at 0.5 h postdose, which continued up to 4 h postdose. A marked inhibition (72%) was still evident even at 6 h. As shown in Fig. 3, compound **17** was more potent than compound **3**. These results suggest that **17** is a potent antiplatelet agent with a long duration of action *in vivo*.

The addition of **17** alone to platelet-rich plasma (PRP) did not cause any platelet aggregation up to 1 mM, as well as compound **3**. This compound also did not cause vasoconstriction, but inhibited 5-HT-induced vasoconstriction with an IC_{50} value of 1.8 nM. These results suggest that compound **17** is a 5-HT$_2$ receptor antagonist, and not an agonist.

Table 4. 5-HT$_2$ Receptor Affinity and *Ex Vivo* Antiplatelet Effects of Compound **17** and Its Prodrug Derivatives



Compd.	R	*In vitro*[a] IC_{50} (nM)	*Ex vivo*[b] inhibition (%)[c]
17	H	2.2	74.0±6.0 **
35	CONHPh	7.2	12.9±7.1
36	$CO(CH_2)_2COOH$	2.2	71.9±8.2 **
37	COOEt	3.0	NT[d]
38	COOPh	2.7	NT[d]
39	COPh	8.1	NT[d]
40	$COCH_3$	0.9	78.6±7.2 **
41	$CO(CH_2)_4CH_3$	2.2	74.3±3.7 **
42	$CO(CH_2)_5CH_3$	23	70.7±4.6 **
43	$CO(CH_2)_6CH_3$	43	70.2±7.3 **
44	$CO(CH_2)_8CH_3$	170	82.2±5.9 **
45 (R-102444)	$CO(CH_2)_{10}CH_3$	240	74.9±2.4 **
46	$CO(CH_2)_{14}CH_3$	310	79.2±6.2 **
Sarpogrelate (**2a**)			21.3±7.5[e]
			57.3±5.9 **[f]
M-1 (**2b**)			35.6±3.2 **[e]

a) Interaction of the compounds with rat brain 5-HT$_2$ was determined by conventional binding assay using [^{3}H]ketanserin. *b*) Inhibitory effects (%) of test compounds (1 mg/kg, *p.o.*) on 5-HT-induced platelet aggregation in rats. Platelet aggregation was measured 1 h after dosing. *c*) Data are represented as the mean±S.E.M. (n=6). * p<0.05, ** p<0.01 *vs.* vehicle (Dunnett's test). *d*) Not tested. *e*) Inhibitory effects (%) of sarpogrelate or M-1 (10 mg/kg, *p.o.*) on 5-HT-induced platelet aggregation in rats. *f*) Inhibitory effects (%) of sarpogrelate (100 mg/kg, *p.o.*) on 5-HT-induced platelet aggregation in rats.

The receptor binding specificity of **17** was further examined for other receptors (α_1, β, 5-HT$_1$, 5-HT$_3$). Compound **17** exhibited low affinity with IC_{50} values (nM) of 310 for α_1, 3700 for 5-HT$_1$, and over 5000 for β and 5-HT$_3$, respectively. This indicates that **17** is highly selective for 5-HT$_2$ receptors.

The *ex vivo* effects of test compounds (**17**, sarpogrelate, M-1) on 5-HT-induced platelet aggregation were examined in rats (Table 4). Oral administration of **17** (1 mg/kg) resulted in a marked inhibition (74%) of platelet aggregation at 1 h postdose. Sarpogrelate (10 and 100 mg/kg, *p.o.*) produced only moderate inhibition (21% and 57%, respectively), suggesting its weak potency. In addition, M-1 was found to be less potent than **17**. These results suggest that compound **17** exhibits more potent *ex vivo* antiaggregatory activity compared to that of sarpogrelate and M-1.

However, toxicology studies showed that compound **17** is an irritant to the rat stomach as much as compound **3**. The rat stomach has been shown to have 5-HT receptors including 5-HT$_{2A}$,[21] 5-HT$_{2B}$,[22] and 5-HT$_{2C}$.[23] Therefore, we hypothesized that the irritation is, at least in part, related to the 5-HT$_2$ receptor action. Thus, the prodrug derivatives (**35**—**46**), in which the hydroxy group at the 4-position of the pyrrolidine ring in **17** is protected, were prepared and examined *in vitro* for their 5-HT$_2$ receptor binding and *ex vivo* antiplatelet effects (Table 4). Carbamate **35** was slightly less potent than **17** *in vitro*, and **35** hardly inhibited platelet aggregation. Succinyl derivative **36** was as potent as **17** both *in vitro* and *ex*

Table 5. Physical Data for [2-(2-Phenylethyl)phenoxy]ethylpyrrolidine Derivatives

Compd.[a]	Formula	Yield (%)[b]	mp (°C)	$[\alpha]_D$ (MeOH)	Analysis (%) Calcd (Found)			
					C	H	N	Cl
15	$C_{21}H_{27}NO_2 \cdot HCl$	50	113—114	−13° (c=1.11)	69.69 (69.69)	7.80 (8.01)	3.87 (3.97)	9.80 (9.90)
16	$C_{22}H_{29}NO_3 \cdot HCl \cdot 0.35H_2O$	69	136—137	−11° (c=0.99)	66.35 (66.28)	7.77 (7.77)	3.52 (3.48)	8.90 (8.96)
17	$C_{22}H_{29}NO_3 \cdot HCl$	69	100—102	−12° (c=1.06)	67.42 (67.25)	7.72 (7.77)	3.57 (3.53)	9.05 (9.18)
18	$C_{22}H_{29}NO_3 \cdot HCl$	60	111—112	−11° (c=1.19)	67.42 (67.03)	7.72 (7.60)	3.57 (3.55)	9.05 (9.18)
19	$C_{23}H_{31}NO_4 \cdot HCl$	76	134—136	−12° (c=1.15)	65.47 (65.39)	7.64 (7.60)	3.32 (3.32)	8.40 (8.17)
20	$C_{21}H_{27}NO_3 \cdot HCl \cdot 0.50H_2O$	64	49—50	−15° (c=1.27)	65.19 (65.26)	7.55 (7.52)	3.62 (3.57)	9.16 (9.01)
22	$C_{22}H_{29}NO_3 \cdot HCl \cdot 0.50H_2O$	66	63—65	−24° (c=1.14)	65.90 (65.99)	7.79 (7.86)	3.49 (3.57)	8.84 (8.85)
25	$C_{22}H_{29}NO_3 \cdot HCl \cdot 0.30H_2O$	62	75—76	+24° (c=1.00)	66.50 (66.52)	7.76 (7.78)	3.53 (3.65)	8.92 (8.64)
27	$C_{22}H_{29}NO_3 \cdot HCl$	69	102—103	+12° (c=1.12)	67.42 (67.25)	7.72 (7.94)	3.57 (3.64)	9.05 (9.18)
28	$C_{22}H_{27}NO_3 \cdot HCl$	66	109—110	−72° (c=1.05)	67.77 (67.42)	7.24 (7.29)	3.59 (3.65)	9.09 (8.97)
29	$C_{22}H_{28}N_2O_3 \cdot HCl \cdot 0.10H_2O$	24	164—167	−53° (c=0.95)	64.97 (64.70)	7.24 (7.26)	6.89 (6.99)	8.72 (9.12)
30	$C_{22}H_{28}N_2O_3 \cdot HCl \cdot 0.15H_2O$	27	161—163	−52° (c=1.08)	64.82 (64.61)	7.24 (7.03)	6.87 (6.97)	8.70 (9.05)
34	$C_{22}H_{30}N_2O_2 \cdot 2HCl$	52	160—163	−11° (c=1.00)	61.82 (61.62)	7.55 (7.48)	6.55 (6.60)	16.59 (16.32)
35	$C_{29}H_{34}N_2O_4 \cdot HCl \cdot 0.80H_2O$	83	Oil	+2.0° (c=1.32)	66.29 (66.27)	7.02 (7.21)	5.33 (5.20)	6.75 (6.79)
36	$C_{26}H_{33}NO_6 \cdot HCl \cdot 0.75H_2O$	69	Oil	+1.2° (c=0.93)	61.77 (61.77)	7.08 (7.04)	2.77 (2.64)	7.01 (7.18)
37	$C_{25}H_{33}NO_5 \cdot HCl$	90	94—95	−5.9° (c=1.18)	64.71 (64.77)	7.39 (6.99)	3.02 (2.97)	7.64 (7.65)
38	$C_{29}H_{33}NO_5 \cdot HCl$	66	125—129	−6.6° (c=1.11)	68.03 (67.76)	6.69 (6.43)	2.74 (2.70)	6.92 (7.05)
39	$C_{29}H_{33}NO_4 \cdot HCl$	77	100—101	+10° (c=1.09)	70.22 (69.93)	6.91 (6.91)	2.82 (2.77)	7.15 (6.84)
40	$C_{24}H_{31}NO_4 \cdot HCl \cdot 0.35H_2O$	63	67—68	−3.8° (c=1.30)	65.47 (65.46)	7.49 (7.56)	3.18 (3.21)	8.05 (8.06)
41	$C_{28}H_{39}NO_4 \cdot HCl$	59	87—88	−3.2° (c=1.11)	68.62 (68.31)	8.23 (8.38)	2.86 (2.94)	7.23 (7.00)
42	$C_{29}H_{41}NO_4 \cdot HCl$	66	93—94	−2.6° (c=1.00)	69.10 (69.23)	8.40 (8.32)	2.78 (2.76)	7.03 (7.11)
43	$C_{30}H_{43}NO_4 \cdot HCl$	84	86—88	−2.6° (c=1.01)	69.54 (69.44)	8.56 (8.70)	2.70 (2.75)	6.84 (6.77)
44	$C_{32}H_{47}NO_4 \cdot HCl$	38	58—60	−2.0° (c=1.14)	70.37 (70.44)	8.86 (9.10)	2.56 (2.65)	6.49 (6.40)
45 (R-102444)	$C_{34}H_{51}NO_4 \cdot HCl$	73	73—74	−2.1° (c=1.19)	71.12 (70.87)	9.13 (9.08)	2.44 (2.48)	6.17 (6.13)
46	$C_{38}H_{59}NO_4 \cdot HCl \cdot 0.25H_2O$	86	Waxen Oil	−2.2° (c=1.06)	71.89 (71.84)	9.61 (9.54)	2.21 (2.21)	5.58 (5.68)

a) Compound **3** was reported in ref. 14. *b*) Yield not optimized.

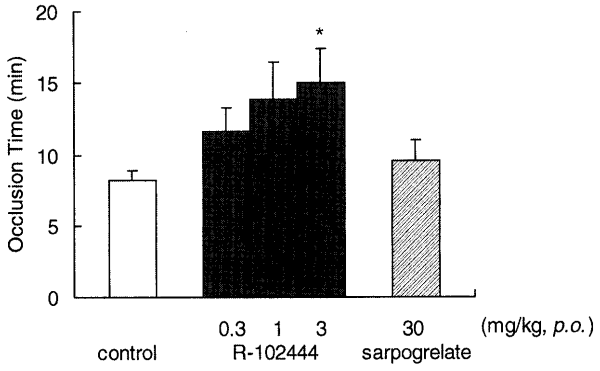


Fig. 4. Inhibitory Effects of R-102444 and Sarpogrelate on the Occlusion Time of the Rat Femoral Artery

Data are represented as the mean±S.E.M. (n=8−12). * $p<0.05$ *vs.* the control group (Dunnett's test).

vivo. Thus, *ex vivo* inhibitory effects of **35** and **36** were those of the compounds themselves; they did not function as prodrug derivatives. Carbonates **37** and **38** were also as potent as **17** for their 5-HT_2 receptor affinity. Benzoate **39**, acetate **40**, and hexanoic ester **41**, as the acyl moiety, also showed high affinity (IC_{50}<10 nM) *in vitro*. Since these seven compounds (**35**—**41**) with high affinity *in vitro* have a relatively small substituent at the 4-position of the pyrrolidine ring, the introduction of a more bulky substituent is presumably required to diminish the *in vitro* activity. Thus, we introduced higher carboxylic acids to the 4-position of the pyrrolidine ring. As expected, the introduction of higher carboxylic acids resulted in a reduction of the 5-HT_2 receptor affinity. The introduction of higher carboxylic acids, lauryl ester **45** (R-102444) and palmitoyl ester **46**, showed low affinity with IC_{50} values larger than 240 nM, indicating that these compounds are inactive *in vitro*. In contrast, these compounds orally administered to rats inhibited *ex vivo* platelet aggregation as potently as **17**. This result suggests that they were hydrolyzed at the acyl ester linkage after oral administration, and this newly formed **17** potently inhibited platelet aggregation. Furthermore, R-102444 and compound **46** did not cause gastric irritation in rats. R-102444 is obtained as a crystal form with a melting point of 73—74 °C, and compound **46**, as a waxen oil (Table 5). From the viewpoint of physical properties, R-102444 was selected for further study.

Figure 4 shows the antithrombotic effects of R-102444 and sarpogrelate in a rat photochemically-induced thrombosis model.[24] In the control group (0.5% gum tragachant-treatment), the femoral artery was completely occluded within 15 min (8.18±0.69 min, n=12) after the initiation of photochemical reaction (rose bengal injection). Pretreatment of R-102444 (0.3—3 mg/kg, *p.o.*) prolonged the time required for thrombotic occlusion of the artery in a dose-dependent manner. Statistically significant ($p<0.05$) prolongation was observed in the R-102444 (3 mg/kg)-treated group. In contrast, sarpogrelate even at 30 mg/kg produced only a moderate prolongation, which was not statistically significant ($p>0.05$). These results indicated that the antithrombotic effect of R-102444 is more potent than that of sarpogrelate.

In conclusion, we found that 4-hydroxypyrrolidine derivative, **17** with (2*R*, 4*R*) configuration, showed a similar high affinity for 5-HT_2 receptors, but lower D_2 receptor affinity compared to compound **3**. This compound was also efficacious in inhibiting 5-HT-induced *in vitro* vasoconstriction and *ex vivo* platelet aggregation. Although compound **17** was irritant to the rat stomach, its prodrug, R-102444 with potent

Table 6. Physical Data for [2-(2-Phenylethyl)phenoxy]ethylpyrrolidine Derivatives

Compd.[a]	^{1}H-NMR δ ($CDCl_3$)
15	1.98—2.16 (1H, m), 2.31—2.60 (2H, m), 2.36 (1H, dd, J=5.8, 14 Hz), 2.77—3.08 (1H, m), 2.84 (3H, s), 2.88 (4H, s), 3.75—4.23 (4H, m), 4.52—4.64 (1H, m), 6.83 (1H, d, J=8.1 Hz), 6.91 (1H, t, J=7.3 Hz), 7.08—7.35 (7H, m)
16	2.00—2.15 (1H, m), 2.28—2.63 (2H, m), 2.32 (1H, dd, J=5.8, 14 Hz), 2.79—3.04 (1H, m), 2.84 (3H, s), 2.87 (4H, s), 3.73—4.24 (4H, m), 3.79 (3H, s), 4.51—4.62 (1H, m), 6.77—6.96 (4H, m), 7.05—7.24 (4H, m)
17	2.02—2.14 (1H, m), 2.28—2.46 (1H, m), 2.34 (1H, dd, J=5.6, 14 Hz), 2.48—2.60 (1H, m), 2.76—2.95 (4H, m), 2.86 (3H, s), 2.99 (1H, d, J=12 Hz), 3.77 (3H, s), 3.82—4.22 (4H, m), 4.54—4.63 (1H, m), 6.70—6.80 (3H, m), 6.82 (1H, d, J=8.2 Hz), 6.91 (1H, t, J=7.4 Hz), 7.11—7.23 (3H, m)
18	2.00—2.17 (1H, m), 2.27—2.63 (2H, m), 2.33 (1H, dd, J=5.8, 14 Hz), 2.72—3.07 (5H, m), 2.85 (3H, s), 3.73—4.26 (4H, m), 3.78 (3H, s), 4.54—4.66 (1H, m), 6.78—6.96 (4H, m), 7.03—7.22 (4H, m)
19	2.04—2.18 (1H, m), 2.33 (1H, dd, J=5.9, 14 Hz), 2.36—2.49 (1H, m), 2.51—2.66 (1H, m), 2.72—3.05 (5H, m), 2.89 (3H, s), 3.76 (6H, s), 3.83—4.25 (4H, m), 4.56—4.65 (1H, m), 6.28—6.36 (3H, m), 6.83 (1H, d, J=8.0 Hz), 6.92 (1H, t, J=7.3 Hz), 7.12—7.24 (2H, m)
20	2.01—2.17 (1H, m), 2.23—2.55 (3H, m), 2.67—2.94 (4H, m), 2.87 (3H, s), 3.12 (1H, d, J=13 Hz), 3.76—4.08 (4H, m), 4.53—4.65 (1H, m), 6.62 (1H, d, J=7.4 Hz), 6.69 (1H, dd, J=1.7, 7.9 Hz), 6.75 (1H, d, J=7.9 Hz), 6.88—6.95 (2H, m), 7.06 (1H, t, J=7.9 Hz), 7.11—7.21 (2H, m)
22	2.08—2.22 (1H, m), 2.46—2.59 (2H, m), 2.63—2.96 (6H, m), 2.78 (3H, s), 3.21—3.36 (1H, m), 3.77 (3H, s), 3.79—4.00 (2H, m), 4.15—4.25 (1H, m), 4.44—4.55 (1H, m), 6.64—6.78 (3H, m), 6.83 (1H, d, J=7.3 Hz), 6.94 (1H, t, J=6.9 Hz), 7.13—7.25 (3H, m)
25	2.10—2.23 (1H, m), 2.48—2.62 (2H, m), 2.65—2.97 (6H, m), 2.79 (3H, s), 3.20—3.38 (1H, m), 3.77 (3H, s), 3.80—4.00 (1H, m), 4.14—4.26 (1H, m), 4.44—4.58 (1H, m), 6.64—6.78 (3H, m), 6.83 (1H, d, J=8.6 Hz), 6.94 (1H, t, J=7.6 Hz), 7.14—7.25 (3H, m)
27	2.05—2.21 (1H, m), 2.33 (1H, dd, J=5.3, 14 Hz), 2.36—2.69 (2H, m), 2.77—3.09 (5H, m), 2.88 (3H, s), 3.79 (3H, s), 3.81—4.28 (4H, m), 4.55—4.67 (1H, m), 6.70—6.82 (3H, m), 6.84 (1H, d, J=8.6 Hz), 6.93 (1H, t, J=7.9 Hz), 7.13—7.26 (3H, m)
28	2.53—3.02 (8H, m), 2.89 (3H, s), 3.11—3.28 (1H, m), 3.53—3.71 (1H, m), 3.75 (3H, s), 3.83—3.95 (1H, m), 4.08—4.24 (2H, m), 6.62—6.76 (3H, m), 6.80 (1H, d, J=8.6 Hz), 6.96 (1H, t, J=7.9 Hz), 7.12—7.25 (3H, m)
29[b]	2.13—2.32 (1H, m), 2.46—3.12 (7H, m), 2.90 (3H, s), 3.62—4.24 (4H, m), 3.71 (3H, s), 4.31 (1H, d, J=16 Hz), 6.70—6.82 (3H, m), 6.87 (1H, t, J=7.2 Hz), 6.97 (1H, d, J=8.2 Hz), 7.10—7.23 (3H, m)
30[b]	2.13—2.32 (1H, m), 2.46—3.12 (7H, m), 2.90 (3H, s), 3.64—4.20 (4H, m), 3.71 (3H, s), 4.32 (1H, d, J=16 Hz), 6.70—6.83 (3H, m), 6.87 (1H, t, J=7.4 Hz), 6.97 (1H, d, J=8.0 Hz), 7.10—7.24 (3H, m)
34[b]	2.07—2.32 (2H, m), 2.35—2.49 (2H, m), 2.72—2.98 (4H, m), 2.91 (3H, s), 3.12—3.28 (1H, m), 3.72 (3H, s), 3.83—4.10 (5H, m), 6.71—6.90 (4H, m), 6.96 (1H, d, J=7.3 Hz), 7.10—7.25 (3H, m)
35	2.28—2.43 (1H, m), 2.46—2.73 (3H, m), 2.78—2.99 (4H, m), 2.88 (3H, s), 3.06 (1H, d, J=13 Hz), 3.72—4.07 (2H, m), 3.76 (3H, s), 4.25—4.46 (2H, m), 5.35—5.45 (1H, m), 6.73—6.90 (4H, m), 6.94 (1H, t, J=7.0 Hz), 7.07 (1H, t, J=7.2 Hz), 7.14—7.32 (7H, m)
36	2.32—2.65 (8H, m), 2.78—2.94 (4H, m), 2.88 (3H, s), 3.00 (1H, d, J=14 Hz), 3.69—3.81 (1H, m), 3.77 (3H, s), 3.94—4.04 (1H, m), 4.17—4.26 (1H, m), 4.32 (1H, dd, J=4.8, 14 Hz), 5.26—5.33 (1H, m), 6.70—6.79 (3H, m), 6.84 (1H, d, J=7.7 Hz), 6.93 (1H, t, J=7.7 Hz), 7.13—7.23 (3H, m)
37	1.26 (3H, t, J=7.2 Hz), 2.27—2.42 (1H, m), 2.45—2.62 (3H, m), 2.76—2.96 (4H, m), 2.83 (3H, s), 3.00 (1H, d, J=13 Hz), 3.61—3.82 (1H, m), 3.73 (3H, s), 3.92—4.05 (1H, m), 4.10—4.26 (1H, m), 4.17 (2H, q, J=7.2 Hz), 4.35 (1H, dd, J=5.4, 13 Hz), 5.23—5.34 (1H, m), 6.68—6.80 (3H, m), 6.83 (1H, d, J=8.3 Hz), 6.93 (1H, t, J=7.7 Hz), 7.12—7.25 (3H, m)
38	2.35—2.50 (1H, m), 2.53—2.67 (3H, m), 2.78—2.99 (4H, m), 2.86 (3H, s), 3.10 (1H, d, J=13 Hz), 3.67—3.86 (1H, m), 3.74 (3H, s), 3.94—4.08 (1H, m), 4.15—4.29 (1H, m), 4.35—4.49 (1H, m), 5.34—5.44 (1H, m), 6.70—6.82 (3H, m), 6.85 (1H, d, J=8.1 Hz), 6.95 (1H, t, J=7.2 Hz), 7.09 (2H, d, J=7.9 Hz), 7.13—7.31 (4H, m), 7.37 (2H, t, J=7.9 Hz)
39	2.40—2.71 (4H, m), 2.75—2.95 (4H, m), 2.90 (3H, s), 3.09 (1H, d, J=13 Hz), 3.70 (3H, s), 3.76—3.93 (1H, m), 3.96—4.12 (1H, m), 4.21—4.34 (1H, m), 4.47 (1H, dd, J=5.6, 13 Hz), 5.53—5.62 (1H, m), 6.63—6.74 (3H, m), 6.86 (1H, d, J=8.1 Hz), 6.92 (1H, t, J=7.1 Hz), 7.08—7.25 (3H, m), 7.33 (2H, t, J=7.5 Hz), 7.54 (1H, t, J=7.5 Hz), 7.87 (2H, d, J=7.5 Hz)
40	1.93 (3H, s), 2.26—2.78 (4H, m), 2.76—3.00 (5H, m), 2.84 (3H, s), 3.63—3.82 (1H, m), 3.78 (3H, s), 3.93—4.06 (1H, m), 4.19—4.40 (2H, m), 5.27—5.37 (1H, m), 6.70—6.82 (3H, m), 6.85 (1H, d, J=7.9 Hz), 6.94 (1H, t, J=7.3 Hz), 7.13—7.26 (3H, m)
41	0.84 (3H, t, J=6.9 Hz), 1.10—1.33 (4H, m), 1.42—1.58 (2H, m), 2.14 (2H, t, J=7.6 Hz), 2.27—2.48 (2H, m), 2.51—2.70 (2H, m), 2.75—3.00 (5H, m), 2.85 (3H, s), 3.65—3.83 (1H, m), 3.77 (3H, s), 3.93—4.06 (1H, m), 4.19—4.30 (1H, m), 4.35 (1H, dd, J=5.7, 13 Hz), 5.29—5.37 (1H, m), 6.70—6.81 (3H, m), 6.85 (1H, d, J=8.1 Hz), 6.94 (1H, t, J=7.3 Hz), 7.13—7.26 (3H, m)
42	0.85 (3H, t, J=6.8 Hz), 1.10—1.33 (6H, m), 1.37—1.58 (2H, m), 2.14 (2H, t, J=7.5 Hz), 2.25—2.48 (2H, m), 2.50—2.67 (2H, m), 2.76—2.97 (5H, m), 2.85 (3H, s), 3.65—3.82 (1H, m), 3.77 (3H, s), 3.93—4.05 (1H, m), 4.19—4.30 (1H, m), 4.35 (1H, dd, J=5.5, 13 Hz), 5.28—5.39 (1H, m), 6.70—6.81 (3H, m), 6.85 (1H, d, J=7.9 Hz), 6.94 (1H, t, J=7.4 Hz), 7.13—7.25 (3H, m)
43	0.86 (3H, t, J=6.8 Hz), 1.11—1.34 (8H, m), 1.42—1.58 (2H, m), 2.14 (2H, t, J=7.6 Hz), 2.26—2.48 (2H, m), 2.50—2.67 (2H, m), 2.76—2.99 (5H, m), 2.85 (3H, s), 3.65—3.84 (1H, m), 3.77 (3H, s), 3.92—4.05 (1H, m), 4.18—4.30 (1H, m), 4.34 (1H, dd, J=5.4, 13 Hz), 5.30—5.38 (1H, m), 6.70—6.81 (3H, m), 6.85 (1H, d, J=7.9 Hz), 6.94 (1H, t, J=7.5 Hz), 7.13—7.26 (3H, m)
44	0.87 (3H, t, J=6.7 Hz), 1.10—1.35 (12H, m), 1.41—1.57 (2H, m), 2.14 (2H, t, J=7.6 Hz), 2.27—2.48 (2H, m), 2.50—2.68 (2H, m), 2.75—2.99 (5H, m), 2.85 (3H, s), 3.64—3.83 (1H, m), 3.77 (3H, s), 3.93—4.05 (1H, m), 4.18—4.30 (1H, m), 4.35 (1H, dd, J=5.5, 13 Hz), 5.29—5.38 (1H, m), 6.69—6.80 (3H, m), 6.85 (1H, d, J=8.1 Hz), 6.94 (1H, t, J=7.4 Hz), 7.12—7.25 (3H, m)
45 (R-102444)	0.88 (3H, t, J=6.8 Hz), 1.13—1.35 (16H, m), 1.43—1.57 (2H, m), 2.13 (2H, t, J=7.6 Hz), 2.27—2.46 (2H, m), 2.50—2.68 (2H, m), 2.76—2.96 (5H, m), 2.85 (3H, s), 3.65—3.83 (1H, m), 3.77 (3H, s), 3.94—4.05 (1H, m), 4.20—4.31 (1H, m), 4.34 (1H, dd, J=5.3, 13 Hz), 5.29—5.38 (1H, m), 6.70—6.80 (3H, m), 6.85 (1H, d, J=8.2 Hz), 6.94 (1H, t, J=7.4 Hz), 7.13—7.25 (3H, m)
46	0.88 (3H, t, J=6.6 Hz), 1.11—1.38 (24H, m), 1.41—1.57 (2H, m), 2.13 (2H, t, J=7.6 Hz), 2.24—2.48 (2H, m), 2.51—2.67 (2H, m), 2.75—2.97 (5H, m), 2.85 (3H, s), 3.63—3.82 (1H, m), 3.77 (3H, s), 3.92—4.07 (1H, m), 4.20—4.43 (2H, m), 5.28—5.40 (1H, m), 6.69—6.81 (3H, m), 6.85 (1H, d, J=7.9 Hz), 6.93 (1H, t, J=7.6 Hz), 7.12—7.28 (3H, m)

a) Compound **3** was reported in ref. 14. *b*) In DMSO-d_6.

ex vivo antiaggregatory effects, produced no gastric irritation. Moreover, R-102444 exhibited antithrombotic effect more potently than sarpogrelate in the photochemically-induced thrombosis model. R-102444 is currently under further evaluation in pharmacology and toxicology studies, and these data will be reported elsewhere.

Experimental

Melting points were determined with a Yanagimoto micro melting point apparatus and were uncorrected. ^{1}H- and ^{13}C-NMR spectra were obtained on a JEOL EX270 spectrometer and were reported as δ values relative to Me4Si 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. Optical rotations were measured on a Perkin-Elmer 141 spectrometer. Merck Silica gel 60 (230—400 mesh) was used in the column chromatography. Tetrahydrofuran, *N*,*N*-dimethylformamide *N*,*N*-dimethylacetamide, and dimethylsulfoxide are abbreviated as THF, DMF, DMA and DMSO, respectively.

(2*S*,4*R*)-4-Benzyloxy-1,2-diethoxycarbonylpyrrolidine ((2*S*,4*R*)-5) To a solution of (2*S*,4*R*)-4-benzyloxy-1-*tert*-butoxycarbonylproline (2*S*,4*R*)-**4** (15.0 g, 46.7 mmol) in EtOH (50 ml) was bubbled hydrogen chloride for 2 h. The resulting mixture was concentrated to give (2*S*,4*R*)-4-benzyloxy-2-ethoxycarbonylpyrrolidine as a colorless oil. To a solution of this oil in acetone (80 ml) and H_2O (80 ml) was added triethylamine (13.0 ml, 93.3 mmol) and the mixture was stirred at 0 °C for 10 min. Then ethyl chloroformate (4.89 ml, 51.4 mmol) was added to the solution. After stirring at room temperature for 3 h, the resulting mixture was concentrated and extracted with EtOAc. Then the extract was 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 (2*S*,4*R*)-**5** (13.4 g, 41.7 mmol, 89%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.17—1.31 (6H, m), 2.03—2.14 (1H, m), 2.36—2.48 (1H, m), 3.59—3.80 (2H, m), 4.04—4.24 (5H, m), 4.37—4.56 (3H, m), 7.24—7.38 (5H, m). $[\alpha]_D$ −53° (*c*=1.19, MeOH).

(2*S*,4*R*)-4-Benzyloxy-1-ethoxycarbonyl-2-hydroxymethylpyrrolidine ((2*S*,4*R*)-6) A solution of (2*S*,4*R*)-4-benzyloxy-1,2-diethoxycarbonylpyrrolidine (2*S*,4*R*)-**5** (10.2 g, 31.7 mmol) in THF (30 ml) was added dropwise to a suspension of $LiBH_4$ (2.07 g, 95.2 mmol) in THF (70 ml) at 0 °C. The mixture was stirred at room temperature for 7 h. 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 (hexane/EtOAc=2/3) to give (2*S*,4*R*)-**6** (8.05 g, 28.8 mmol, 91%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, t, *J*=7.3 Hz), 1.58—1.72 (1H, m), 2.14—2.28 (1H, m), 3.43 (1H, dd, *J*=4.3, 12 Hz), 3.51—3.65 (1H, m), 3.68—3.83 (2H, m), 4.01—4.24 (2H, m), 4.15 (2H, q, *J*=7.3 Hz), 4.51 (2H, s), 4.67—4.78 (1H, m), 7.22—7.41 (5H, m). $[\alpha]_D$ −48° (*c*=2.17, MeOH).

(2*R*,4*R*)-4-Benzyloxy-2-cyanomethyl-1-ethoxycarbonylpyrrolidine ((2*R*,4*R*)-7) To a solution of (2*S*,4*R*)-4-benzyloxy-1-ethoxycarbonyl-2-hydroxymethylpyrrolidine (2*S*,4*R*)-**6** (8.00 g, 28.6 mmol) and *p*-toluenesulfonic anhydride (Ts_2O) (10.28 g, 31.5 mmol) in CH_2Cl_2 (100 ml) was added triethylamine (4.39 ml, 31.5 mmol) at 0 °C 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 successively. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=13/7) to give (2*S*,4*R*)-4-benzyloxy-1-ethoxycarbonyl-2-(*p*-toluenesulfonyloxy)methylpyrrolidine (11.67 g, 26.9 mmol, 94%) as an oil. To a solution of this oil (11.53 g, 26.6 mmol) in DMF (80 ml) was added NaCN (1.30 g, 26.5 mmol) and the mixture was stirred at 80 °C for 2 h. The resulting mixture was diluted with EtOAc and washed with H_2O and brine successively. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=4/1) to give (2*R*,4*R*)-**7** (7.14 g, 24.8 mmol, 93%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, t, *J*=7.1 Hz), 1.95—2.12 (1H, m), 2.32—2.48 (1H, m), 2.70 (1H, dd, *J*=2.8, 17 Hz), 2.83, 3.15 (1H, dd, *J*=6.0, 17 Hz), 3.51 (1H, dd, *J*=4.2, 12 Hz), 3.74, 3.93 (1H, d, *J*=12 Hz), 4.07—4.27 (2H, m), 4.14 (2H, q, *J*=7.1 Hz), 4.51 (2H, s), 7.23—7.41 (5H, m). $[\alpha]_D$ −72° (*c*=1.94, MeOH).

(2*S*,4*R*)-4-Benzyloxy-1-ethoxycarbonyl-2-(ethoxycarbonylmethyl)-pyrrolidine ((2*S*,4*R*)-8) To a solution of (2*R*,4*R*)-4-benzyloxy-2-cyanomethyl-1-ethoxycarbonylpyrrolidine (2*R*,4*R*)-**7** (11.63 g, 40.3 mmol) in EtOH (20 ml) was bubbled hydrogen chloride for 2 h. The resulting mixture was concentrated *in vacuo*. The residue was diluted with EtOAc and washed with $NaHCO_3$ solution and brine successively. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=3/1) to give (2*S*,4*R*)-**8** (11.93 g, 35.6 mmol, 88%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (6H, t, *J*=7.3 Hz), 1.85—2.02 (1H, m), 2.28—2.53 (2H, m), 2.82—3.12 (1H, m), 3.37—3.50 (1H, m), 3.59—3.78 (1H, m), 4.03—4.37 (2H, m), 4.12 (4H, q, *J*=7.3 Hz), 4.50 (2H, d, *J*=4.6 Hz), 7.21—7.40 (5H, m). $[\alpha]_D$ −45° (*c*=1.30, MeOH).

(2*R*,4*R*)-4-Benzyloxy-1-ethoxycarbonyl-2-(2-hydroxyethyl)pyrrolidine ((2*R*,4*R*)-9) A solution of (2*S*,4*R*)-4-benzyloxy-1-ethoxycarbonyl-2-(ethoxycarbonylmethyl)pyrrolidine (2*S*,4*R*)-**8** (11.90 g, 35.5 mmol) in THF (50 ml) was added dropwise to a suspension of $LiAlH_4$ (1.35 g, 35.5 mmol) in THF (200 ml), vigorously stirring at −10 °C. After stirring at −10 °C for 30 min, Na_2SO_4 decahydrate was added slowly to the resulting suspension and the slurry was stirred for 1 h continuously. The insoluble material was filtered away and the filtrate was concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=1/3) to give (2*R*,4*R*)-**9** (8.86 g, 30.2 mmol, 85%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, t, *J*=6.9 Hz), 1.45—1.61 (1H, m), 1.66—1.93 (2H, m), 2.14—2.29 (1H, m), 3.43 (1H, dd, *J*=5.6, 12 Hz), 3.54—3.71 (3H, m), 3.84—3.96 (1H, m), 4.07—4.36 (2H, m), 4.15 (2H, q, *J*=6.9 Hz), 4.50 (2H, s), 7.25-7.42 (5H, m). $[\alpha]_D$ −36° (*c*=1.77, MeOH).

(2*R*,4*R*)-4-Benzyloxy-1-ethoxycarbonyl-2-[2-(*p*-toluenesulfonyloxy)-ethyl]pyrrolidine ((2*R*,4*R*)-10) To a solution of (2*R*,4*R*)-4-benzyloxy-1-ethoxycarbonyl-2-(2-hydroxyethyl)pyrrolidine (2*R*,4*R*)-**9** (8.83 g, 30.1 mmol) and Ts_2O (10.81 g, 33.1 mmol) in CH_2Cl_2 (300 ml) was added triethylamine (4.61 ml, 33.1 mmol) at 0 °C 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 successively. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=13/7) to give (2*R*,4*R*)-**10** (10.78 g, 24.1 mmol, 80%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, t, *J*=6.9 Hz), 1.71—1.90 (2H, m), 2.03—2.34 (2H, m), 2.44 (3H, s), 3.24—3.42 (1H, m), 3.57—3.90 (1H, m), 3.92—4.19 (6H, m), 4.48 (2H, s), 7.24—7.41 (7H, m), 7.78 (2H, d, *J*=7.9 Hz). $[\alpha]_D$ −22° (*c*=1.18, MeOH).

(2*R*,4*R*)-4-Benzyloxy-1-ethoxycarbonyl-2-[2-[2-[2-(3-methoxyphenyl)-ethyl]phenoxy]ethyl]pyrrolidine (13a: R=3-OMe) To a solution of 2-[2-(3-methoxyphenyl)ethyl]phenol **12a** (R=3-OMe) (500 mg, 2.19 mmol) in DMA (13 ml) was added *tert*-BuOK (270 mg, 2.41 mmol) and the mixture was stirred at 0 °C for 10 min. Then a solution of (2*R*,4*R*)-4-benzyloxy-1-ethoxycarbonyl-2-[2-(*p*-toluenesulfonyloxy)ethyl]pyrrolidine (2*R*,4*R*)-**10** (1.19 g, 2.66 mmol) in DMA (7 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 successively. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=4/1—3/1) to give **13a** (881 mg, 1.75 mmol, 80%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.10—1.34 (3H, m), 1.76—2.07 (2H, m), 2.23—2.57 (2H, m), 2.79—2.98 (4H, m), 3.43 (1H, dd, *J*=4.6, 12 Hz), 3.55—4.28 (7H, m), 3.75 (3H, s), 4.45 (2H, s), 6.68—6.92 (5H, m), 7.06—7.37 (8H, m). $[\alpha]_D$ −1.3° (*c*=1.20, MeOH).

(2*R*,4*R*)-1-Ethoxycarbonyl-4-hydroxy-2-[2-[2-[2-(3-methoxyphenyl)-ethyl]phenoxy]ethyl]pyrrolidine (14a: R=3-OMe) A solution of (2*R*,4*R*)-4-benzyloxy-1-ethoxycarbonyl-2-[2-[2-[2-(3-methoxyphenyl)ethyl]-phenoxy]ethyl]pyrrolidine **13a** (R=3-OMe) (853 mg, 1.69 mmol) in EtOH (6 ml) was hydrogenated over 5% Pd–C (84 mg) at 60 °C for 7 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=1/1) to give **14a** (654 mg, 1.58 mmol, 93%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.11—1.33 (3H, m), 1.72—2.25 (3H, m), 2.29—2.58 (1H, m), 2.80—2.98 (4H, m), 3.46 (1H, dd, *J*=4.6, 12 Hz), 3.50—3.75 (1H, m), 3.78 (3H, s), 3.95—4.29 (5H, m), 4.37—4.48 (1H, m), 6.70—6.93 (5H, m), 7.08—7.28 (3H, m). $[\alpha]_D$ −12° (*c*=0.73, MeOH).

(2*R*,4*R*)-4-Hydroxy-2-[2-[2-[2-(3-methoxyphenyl)ethyl]phenoxy]-ethyl]-1-methylpyrrolidine Hydrochloride (17: R=3-OMe) A solution of (2*R*,4*R*)-1-ethoxycarbonyl-4-hydroxy-2-[2-[2-[2-(3-methoxyphenyl)ethyl]-phenoxy]ethyl]pyrrolidine **14a** (R=3-OMe) (640 mg, 1.55 mmol) in THF (20 ml) was added dropwise to a suspension of $LiAlH_4$ (176 mg, 4.64 mmol) in THF (10 ml), vigorously stirring at room temperature. 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 stirred for 2 h continuously. 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*R*,4*R*)-4-hydroxy-2-[2-[2-[2-(3-methoxyphenyl)ethyl]-phenoxy]ethyl]-1-methylpyrrolidine (523 mg, 1.47 mmol, 95%) as a colorless oil. This oil was dissolved in dioxane (5 ml) and was treated with 4 N HCl in dioxane (1.10 ml, 4.40 mmol). The mixture was stirred at room temperature for 10 min, then concentrated. The oily residue was dissolved in a mixture of EtOAc/CH_2Cl_2=20/1, and the solution was allowed to stand at room temperature to give colorless crystals. The crystals were collected by filtration to give **17** (420 mg, 1.07 mmol, 73%).

Similarly, other 4-hydroxypyrrolidine derivatives, **15**, **16**, **18**—**20**, were prepared by the alkylation of phenols **12**[13,15] with the tosylate (2*R*,4*R*)-**10**, followed by catalytic hydrogenation and reduction with $LiAlH_4$.

(2*R*,4*S*)-4-Benzoyloxy-1-ethoxycarbonyl-2-[2-[2-[2-(3-methoxyphenyl)-

ethyl]phenoxy]ethyl]pyrrolidine (21) Diethyl azodicarboxylate (DEAD) (1.54 ml, 9.80 mmol) was added to a solution of (2*R*,4*R*)-1-ethoxycarbonyl-4-hydroxy-2-[2-[2-[2-(3-methoxyphenyl)ethyl]phenoxy]ethyl]pyrrolidine **14a** (R=3-OMe) (2.70 g, 6.53 mmol), benzoic acid (1.20 g, 9.83 mmol) and triphenylphosphine (2.57 g, 9.80 mmol) in CH_2Cl_2 (30 ml) at 0 °C and the mixture was stirred at room temperature for 1.5 h. The solvent was removed and the resulting residue was chromatographed on a silica gel column (hexane/EtOAc=3/1) to give **21** (3.20 g, 6.18 mmol, 95%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.06—1.34 (3H, m), 2.06—2.65 (4H, m), 2.78—2.97 (4H, m), 3.59—3.71 (1H, m), 3.74 (3H, s), 3.79—4.21 (5H, m), 4.23—4.35 (1H, m), 5.48—5.62 (1H, m), 6.66—6.91 (5H, m), 7.04—7.20 (3H, m), 7.31—7.46 (2H, m), 7.54 (1H, t, J=7.3 Hz), 7.99 (2H, d, J=7.9 Hz). $[\alpha]_D$ −3.7° (c=1.08, MeOH).

(2*R*,4*S*)-4-Hydroxy-2-[2-[2-[2-(3-methoxyphenyl)ethyl]phenoxy]ethyl]-1-methylpyrrolidine Hydrochloride (22) A solution of (2*R*,4*S*)-4-benzoyloxy-1-ethoxycarbonyl-2-[2-[2-[2-(3-methoxyphenyl)ethyl]phenoxy]ethyl]-pyrrolidine **21** (1.07 g, 2.07 mmol) in THF (7 ml) was added dropwise to a suspension of $LiAlH_4$ (234 mg, 6.17 mmol) in THF (13 ml), vigorously stirring at room temperature. 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 stirred for 2 h continuously. 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=17/3) to give (2*R*,4*S*)-4-hydroxy-2-[2-[2-[2-(3-methoxyphenyl)ethyl]phenoxy]ethyl]-1-methylpyrrolidine (662 mg, 1.86 mmol, 90%) as a colorless oil. This oil (638 mg, 1.79 mmol) was dissolved in dioxane (5 ml) and was treated with 4 N HCl in dioxane (1.35 ml, 5.40 mmol). The mixture was stirred at room temperature for 10 min, then concentrated. The oily residue was dissolved in a mixture of hexane/EtOAc=1/10, and the solution was allowed to stand at room temperature to give colorless crystals. The crystals were collected by filtration to give **22** (510 mg, 1.30 mmol, 73%).

Similarly, the other two optical isomers of compound **17** were synthesized. The (2*S*,4*R*) isomer, **25**, was synthesized from the phenol **12a** and (2*S*,4*R*)-**10**, in the same manner as in the synthesis of **17**. The (2*S*,4*S*) isomer, **27**, was prepared from **24** similarly to the preparation of **22**. The tosylate, (2*S*,4*R*)-**10**, was provided in the same manner as in the synthesis of (2*R*,4*R*)-**10** from the carbamate (2*R*,4*R*)-**5**, which was synthesized as described below.

(2*R*,4*R*)-4-Benzyloxy-1,2-diethoxycarbonylpyrrolidine ((2*R*,4*R*)-5) To a solution of (2*S*,4*R*)-4-hydroxyproline (2*S*,4*R*)-**11** (53.23 g, 406 mmol) in EtOH (250 ml) was bubbled hydrogen chloride for 3 h. The resulting mixture was concentrated to deposit colorless crystals. The crystals were collected by filtration to give (2*S*,4*R*)-2-ethoxycarbonyl-4-hydroxypyrrolidine hydrochloride (78.04 g, 399 mmol, 98%). To a solution of the crystals (10.0 g, 51.1 mmol) in acetone (80 ml) and H_2O (80 ml) was added triethylamine (15.0 ml, 108 mmol) and the mixture was stirred at 0 °C for 10 min. Then ethyl chloroformate (5.35 ml, 56.2 mmol) was added to the solution. After stirring at room temperature for 3 h, the resulting mixture was concentrated and extracted with EtOAc, and the extract was washed with brine. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=1/3) to give (2*S*,4*R*)-1,2-diethoxycarbonyl-4-hydroxypyrrolidine (11.3 g, 48.9 mmol, 96%) as a colorless oil. To a solution of this oil (10.6 g, 45.8 mmol) in THF (70 ml) was added NaH (2.41 g, 55.2 mmol, as a 55% w/w dispersion in mineral oil) and the mixture was stirred at 0 °C for 15 min. To the resulting solution was added benzyl bromide (6.57 ml, 55.2 mmol) and tetrabutylammonium iodide (Bu_4NI) (340 mg, 0.92 mmol) and the mixture was stirred at room temperature for 3 h. 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 (hexane/EtOAc=7/3) to give (2*S*,4*R*)-**5** (less polar: 6.64 g, 20.7 mmol, 45%) and (2*R*,4*R*)-**5** (more polar: 4.56 g, 14.2 mmol, 31%) as a colorless oil, respectively. ^{1}H-NMR ($CDCl_3$) δ: 1.15—1.32 (6H, m), 2.22—2.43 (2H, m), 3.55—3.74 (2H, m), 4.02—4.23 (5H, m), 4.35—4.53 (1H, m), 4.47 (2H, s), 7.22—7.39 (5H, m). $[\alpha]_D$ +34° (c=1.18, MeOH).

(*R*)-2-[2-[2-[2-(3-Methoxyphenyl)ethyl]phenoxy]ethyl]-1-methyl-4-oxopyrrolidine Hydrochloride (28) To a solution of DMSO (0.52 g, 6.66 mmol) in CH_2Cl_2 (10 ml) was added oxalyl chloride (0.58 ml, 6.65 mmol) and the mixture was stirred at −70 °C for 5 min. To the resulting solution was added a solution of (2*R*,4*R*)-4-hydroxy-2-[2-[2-[2-(3-methoxyphenyl)-ethyl]phenoxy]ethyl]-1-methylpyrrolidine (1.57 g, 4.42 mmol) in CH_2Cl_2 (5 ml) and the mixture was stirred at −70 °C for 1 h. Then triethylamine (1.85 ml, 13.3 mmol) was added to the mixture. After stirring at −70 °C for 1.5 h, the resulting solution was diluted with CH_2Cl_2 and washed with H_2O and brine successively. The organic layer was dried and concentrated, and the resulting residue was chromatographed on a silica gel column (hexane/EtOAc=1/1) to give (*R*)-2-[2-[2-[2-(3-methoxyphenyl)ethyl]phenoxy]ethyl]-1-methyl-4-oxopyrrolidine (1.30 g, 3.68 mmol, 83%) as an oil. This oil (485 mg, 1.37 mmol) was dissolved in dioxane (7 ml) and was treated with 4 N HCl in dioxane (1.03 ml, 4.12 mmol). The mixture was stirred at room temperature for 1 h, then concentrated. The oily residue was dissolved in a mixture of ether/EtOAc/MeOH=10/10/1, and the solution was allowed to stand at room temperature to give colorless crystals. The crystals were collected by filtration to give **28** (421 mg, 1.08 mmol, 79%).

(*S*)-(4*Z*)-Hydroxyimino-2-[2-[2-[2-(3-methoxyphenyl)ethyl]phenoxy]-ethyl]-1-methylpyrrolidine Hydrochloride (29) and (*S*)-(4*E*)-Hydroxyimino-2-[2-[2-[2-(3-methoxyphenyl)ethyl]phenoxy]ethyl]-1-methylpyrrolidine Hydrochloride (30) To a solution of (*R*)-2-[2-[2-[2-(3-methoxyphenyl)ethyl]phenoxy]ethyl]-1-methyl-4-oxopyrrolidine (797 mg, 2.25 mmol) and hydroxylamine hydrochloride (178 mg, 2.56 mmol) in MeOH (5 ml) was added sodium acetate (AcONa) (407 mg, 4.96 mmol), and the mixture was stirred at 0 °C for 2.5 h. 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 (MeOH/CH_2Cl_2/EtOAc=1/9/10) to give (*Z*)-oxime (less polar: 409 mg, 1.11 mmol, 49%) and (*E*)-oxime (more polar: 298 mg, 0.81 mmol, 36%) as a colorless solid, respectively. (*Z*)-oxime: ^{13}C-NMR ($CDCl_3$) δ: 32.2, 32.5, 35.8, 36.5, 40.0, 55.1, 56.2, 63.0, 65.0, 111.0, 111.1, 114.3, 120.6, 120.9, 127.3, 129.2, 130.1, 130.2, 144.0, 156.6, 159.6, 160.4. (*E*)-oxime: ^{13}C-NMR ($CDCl_3$) δ: 32.4 (2C), 33.2, 36.5, 40.1, 55.1, 58.7, 62.9, 64.9, 111.0, 111.1, 114.4, 120.6, 120.9, 127.2, 129.2, 130.0, 130.2, 144.0, 156.6, 159.6, 160.2.

(*Z*)-Oxime **29**: This oil (346 mg, 0.94 mmol) was dissolved in dioxane (5 ml) and was treated with 4 N HCl in dioxane (0.70 ml, 2.80 mmol). The resulting solution was concentrated. The oily residue was dissolved in a mixture of MeOH/CH_2Cl_2/EtOAc=1/10/10, and the solution was allowed to stand at room temperature to give colorless crystals. The crystals were collected by filtration to give **29** (188 mg, 0.46 mmol, 49%).

(*E*)-Oxime **30**: This oil (243 mg, 0.66 mmol) was dissolved in dioxane (5 ml) and was treated with 4 N HCl in dioxane (0.49 ml, 1.96 mmol). The resulting solution was concentrated. The oily residue was dissolved in a mixture of CH_2Cl_2/EtOAc=1/1, and the solution was allowed to stand at room temperature to give colorless crystals. The crystals were collected by filtration to give **30** (201 mg, 0.50 mmol, 75%).

(2*R*,4*S*)-1-Ethoxycarbonyl-4-hydroxy-2-[2-[2-[2-(3-methoxyphenyl)-ethyl]phenoxy]ethyl]pyrrolidine (31) A solution of (2*R*,4*S*)-4-benzoyloxy-1-ethoxycarbonyl-2-[2-[2-[2-(3-methoxyphenyl)ethyl]phenoxy]ethyl]-pyrrolidine **21** (3.15 g, 6.09 mmol) in THF (20 ml) was added dropwise to a suspension of $LiBH_4$ (398 mg, 18.3 mmol) in THF (10 ml), vigorously stirring at 0 °C. After stirring at room temperature for 18.5 h, $LiBH_4$ (265 mg, 12.2 mmol) was added, and the resulting mixture was stirred at 40 °C for 8 h. 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 (hexane/EtOAc=1/3) to give **31** (2.49 g, 6.02 mmol, 99%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.06—1.33 (3H, m), 1.93—2.30 (3H, m), 2.36—2.62 (1H, m), 2.81—2.98 (4H, m), 3.33—3.44 (1H, m), 3.55—3.85 (1H, m), 3.78 (3H, s), 3.95—4.23 (5H, m), 4.40—4.51 (1H, m), 6.70—6.93 (5H, m), 7.09—7.24 (3H, m). $[\alpha]_D$ +14° (c=1.22, MeOH).

(2*R*,4*S*)-1-Ethoxycarbonyl-2-[2-[2-[2-(3-methoxyphenyl)ethyl]phenoxy]ethyl]-4-(*p*-toluenesulfonyloxy)pyrrolidine (32) To a solution of (2*R*,4*S*)-1-ethoxycarbonyl-4-hydroxy-2-[2-[2-[2-(3-methoxyphenyl)ethyl]-phenoxy]ethyl]pyrrolidine **31** (2.44 g, 5.90 mmol) and Ts_2O (2.38 g, 7.07 mmol) in CH_2Cl_2 (50 ml) was added triethylamine (0.99 ml, 7.10 mmol) at 0 °C and the mixture was stirred at room temperature for 3 h. Then Ts_2O (995 mg, 2.96 mmol) and triethylamine (0.41 ml, 2.94 mmol) was added, and the resulting mixture was stirred continuously overnight at room temperature. The reaction mixture was diluted with CH_2Cl_2 and washed with H_2O and brine successively. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=13/7) to give **32** (2.99 g, 5.27 mmol, 83%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.00—1.34 (3H, m), 1.90—2.06 (1H, m), 2.09—2.52 (3H, m), 2.42 (3H, s), 2.76—2.98 (4H, m), 3.40—3.82 (2H, m), 3.76 (3H, s), 3.87—4.28 (5H, m), 5.02—5.11 (1H, m), 6.68—6.92 (5H, m), 7.05—7.23 (3H, m), 7.31 (2H, d, J=7.9 Hz), 7.76 (2H, d, J=7.9 Hz). $[\alpha]_D$ +4.9° (c=0.98, MeOH).

(2*S*,4*R*)-4-Azido-1-ethoxycarbonyl-2-[2-[2-[2-(3-methoxyphenyl)ethyl]-phenoxy]ethyl]pyrrolidine (33) To a solution of (2*R*,4*S*)-1-ethoxycarbonyl-2-[2-[2-[2-(3-methoxyphenyl)ethyl]phenoxy]ethyl]-4-(*p*-toluenesul-

fonyloxy)pyrrolidine **32** (1.00 g, 1.76 mmol) in DMF (20 ml) was added sodium azide (344 mg, 5.29 mmol) and the mixture was stirred at room temperature for 1 h and then 80 °C for 3 h. 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 (hexane/EtOAc=7/3) to give **33** (709 mg, 1.62 mmol, 92%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.10—1.35 (3H, m), 1.81—2.01 (1H, m), 2.03—2.16 (1H, m), 2.18—2.55 (2H, m), 2.80—2.98 (4H, m), 3.49 (1H, dd, J=5.3, 12 Hz), 3.54—3.82 (1H, m), 3.78 (3H, s), 3.95—4.24 (6H, m), 6.70—6.92 (5H, m), 7.07—7.27 (3H, m). $[\alpha]_D$ −12° (c=1.23, MeOH).

(2*S*,4*R*)-4-Amino-2-[2-[2-[2-(3-methoxyphenyl)ethyl]phenoxy]ethyl]-1-methylpyrrolidine Hydrochloride (34) A solution of (2*S*,4*R*)-4-azido-1-ethoxycarbonyl-2-[2-[2-[2-(3-methoxyphenyl)ethyl]phenoxy]ethyl]pyrrolidine **33** (681 mg, 1.55 mmol) in THF (7 ml) was added dropwise to a suspension of $LiAlH_4$ (177 mg, 4.66 mmol) in THF (13 ml), vigorously stirring at room temperature. After stirring at room temperature for 2 h, Na_2SO_4 decahydrate was added slowly to the resulting suspension and the slurry was stirred for 2 h continuously. 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=13/7) to give (2*S*,4*R*)-4-amino-2-[2-[2-[2-(3-methoxyphenyl)ethyl]phenoxy]ethyl]-1-methylpyrrolidine (310 mg, 0.87 mmol, 56%) as a colorless oil. This oil (291 mg, 0.82 mmol) was dissolved in dioxane (5 ml) and was treated with 4 N HCl in dioxane (0.61 ml, 2.44 mmol). The mixture was stirred at room temperature for 10 min, then concentrated. The oily residue was dissolved in a mixture of CH_2Cl_2/EtOAc=1/10, and the solution was allowed to stand at room temperature to give colorless crystals. The crystals were collected by filtration to give **34** (325 mg, 0.76 mmol, 93%).

(2*R*,4*R*)-2-[2-[2-[2-(3-Methoxyphenyl)ethyl]phenoxy]ethyl]-1-methyl-4-phenylcarbamoyloxypyrrolidine Hydrochloride (35) To a solution of (2*R*,4*R*)-4-hydroxy-2-[2-[2-[2-(3-methoxyphenyl)ethyl]phenoxy]ethyl]-1-methylpyrrolidine (500 mg, 1.41 mmol) and phenyl isocyanate (0.23 ml, 2.12 mmol) in CH_2Cl_2 (8 ml) was added triethylamine (0.22 ml, 1.58 mmol) at 0 °C and the mixture was stirred at room temperature for 6 h. 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 (CH_2Cl_2/MeOH=4/1) to give (2*R*,4*R*)-2-[2-[2-[2-(3-methoxyphenyl)ethyl]phenoxy]ethyl]-1-methyl-4-phenylcarbamoyloxypyrrolidine (578 mg, 1.22 mmol, 87%) as a colorless oil. This oil (543 mg, 1.14 mmol) was dissolved in dioxane (5 ml) and was treated with 4 N HCl in dioxane (0.86 ml, 3.44 mmol). The resulting solution was concentrated to give **35** (564 mg, 1.10 mmol, 96%) as an oil.

(2*R*,4*R*)-2-[2-[2-[2-(3-Methoxyphenyl)ethyl]phenoxy]ethyl]-1-methyl-4-succinyloxypyrrolidine Hydrochloride (36) A solution of (2*R*,4*R*)-4-hydroxy-2-[2-[2-[2-(3-methoxyphenyl)ethyl]phenoxy]ethyl]-1-methylpyrrolidine (500 mg, 1.41 mmol) and succinic anhydride (141 mg, 1.41 mmol) in acetone (8 ml) was refluxed for 4 h. The reaction mixture was cooled and then concentrated. The resulting residue 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 (CH_2Cl_2/MeOH=7/3) to give (2*R*,4*R*)-2-[2-[2-[2-(3-methoxyphenyl)ethyl]-phenoxy]ethyl]-1-methyl-4-succinyloxypyrrolidine (477 mg, 1.05 mmol, 75%) as a colorless oil. This oil (460 mg, 1.01 mmol) was dissolved in dioxane (7 ml) and was treated with 4 N HCl in dioxane (0.76 ml, 3.04 mmol). The resulting solution was concentrated to give **36** (462 mg, 0.94 mmol, 93%) as an oil.

(2*R*,4*R*)-4-Lauryloxy-2-[2-[2-[2-(3-methoxyphenyl)ethyl]phenoxy]-ethyl]-1-methylpyrrolidine Hydrochloride (45 (R-102444)) To a solution of (2*R*,4*R*)-4-hydroxy-2-[2-[2-[2-(3-methoxyphenyl)ethyl]phenoxy]ethyl]-1-methylpyrrolidine (388 mg, 1.09 mmol) and lauric anhydride (543 mg, 1.42 mmol) in pyridine (5 ml) was added 4-dimethylaminopyridine (DMAP) (40 mg, 0.33 mmol) and the mixture was stirred at room temperature for 4 h. The resulting solution was diluted with EtOAc and washed with 1 N HCl and brine successively. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (EtOAc) to give (2*R*,4*R*)-4-lauryloxy-2-[2-[2-[2-(3-methoxyphenyl)ethyl]phenoxy]ethyl]-1-methylpyrrolidine (549 mg, 1.02 mmol, 94%) as a colorless oil. This oil (535 mg, 0.99 mmol) was dissolved in dioxane (6 ml) and was treated with 4 N HCl in dioxane (0.75 ml, 3.00 mmol). The resulting solution was concentrated. The oily residue was dissolved in a mixture of ether/EtOAc=10/1, and the solution was allowed to stand at room temperature to give colorless crystals. The crystals were collected by filtration to give **45** (R-102444) (446 mg, 0.78 mmol, 78%).

Similarly, carbonates, **37**, **38**, and other esters, **39**—**44**, **46**, were prepared by the acylation of **17** with the corresponding acid anhydride or acyl chloride.

5-HT$_2$ Receptor Binding Assay The 5-HT$_2$ receptor binding assay of Leysen *et al.*[25] 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. 20.

D$_2$ Receptor Binding Assay The D$_2$ receptor binding assay of Köhler *et al.*[26] 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. 20.

α_1 Receptor Binding Assay The α_1 receptor binding assay of Greengrass and Bremner[27] was employed with modifications. It was performed using the α_1 antagonist, [^{3}H]prazosin, as the ^{3}H-ligand, and the cortex as reported in ref. 14.

β Receptor Binding Assay The β receptor binding assay of U'Prichard *et al.*[28] was employed with modifications. It was performed using the β antagonist, [^{3}H]dihydroalprenolol (DHA), as the ^{3}H-ligand, and the cortex as reported in ref. 14.

5-HT$_1$ Receptor Binding Assay The 5-HT$_1$ receptor binding assay of Middlemiss[29] was employed with modifications. It was performed using [^{3}H] 5-HT as the ^{3}H-ligand, and the cortex as reported in ref. 14.

5-HT$_3$ Receptor Binding Assay The 5-HT$_3$ receptor binding assay of Kilpatrick *et al.*[30] was employed with modifications. It was performed using the 5-HT$_3$ antagonist, [^{3}H]GR65630, as the ^{3}H-ligand and the cortex as reported in ref. 14.

5-HT-Induced Vasoconstriction Experiment The method involving contractions of the rat caudal arteries of Van Nueten *et al.*[31] was employed with some modifications as reported in ref. 20.

5-HT-Induced PRP Aggregation Preparation of platelets and measurements of platelet aggregation was reported in ref. 14.

***Ex Vivo* Platelet Aggregation** Groups of 5 male Sprague-Dawley rats (Japan SLC) were used in the experiments. Test compound suspended in 0.5% gum tragacanth solution was orally administered to rats in a volume of 1 ml/kg body weight, and, 1 h later, blood was collected from the abdominal aorta of rats under pentobarbital-anesthesia into a syringe containing 3.8% sodium citrate as an anticoagulant. The blood was centrifuged (3000 rpm, 15 min), and platelet-poor plasma (PPP) was obtained. Platelet counts in PRP were adjusted by the method of Born.[32] using a platelet aggregometer (PAM-6C, Mebanix). To PRP (0.24 ml) preincubated at 37 °C for 2 min was added 0.01 ml of ADP (final concentration: 1 μM) alone and in combination with 5-HT (final concentration: 10 μM), and platelet aggregation was monitored for 5 min. Aggregation responses were quantified as the area under the curve (AUC) of change in light transmission according to the method of Killam and Cohen.[33] The potentiation to 5-HT was calculated as the AUC measured after the ADP-induced aggregation subtracted from the AUC measured after the (5-HT+ADP)-induced aggregation. The antiaggregatory effect of the test compound was expressed as inhibition (%), which compared the potentiated AUC in the test compound-treated group to that in the control (0.5% gum tragacanth solution) group.

Photochemically-Induced Thrombosis Model in Femoral Artery A photochemically-induced thrombosis model was used according to the method established by Matsuno *et al.*[24] After anesthetizing male Sprague-Dawley rats (210—250 g) with pentobarbital (40 mg/kg, i.p.), a 5 mm segment of the left femoral artery distal to the inguinal ligament was separated carefully and a pulse Doppler flow probe (LMS) was attached to the vessel for monitoring the blood flow. The right femoral artery was canulated with a polyethylene tube for monitoring the blood pressure. After establishing the baseline blood flow, the femoral artery positioned about 5 mm proximal to the flow probe was irradiated with a green light (540 nm) using a Xenon lamp (Hamamatsu Photonics, Japan). Two min after irradiation, rose bengal (20 mg/kg, Wako) was injected into the right femoral vein. Arterial blood flow was continuously monitored for a maximum of 30 min on a thermal array recorder (Nihon Koden). Time to occlusion indicated by complete cessation of blood flow indicated thrombogenesis. If complete occlusion was not observed within 30 min after injection of rose bengal, the time to occlusion was taken to be 30 min. Test agents were orally administered to rats 1 h before rose bengal injection.

X-Ray Crystallographic Analysis The reflection data were collected on a Rigaku AFC-7R diffractometer with graphite-monochromated Cu$K\alpha$ radiation (λ=1.5418 Å). The structures were solved by direct methods using the SIR92 program[34] for **17** and **22**, and by heavy atom methods using the DIRDIF92 PATTY program[35] for **25** and **27**. The structures were then refined by the full-matrix least-squares procedure with anisotropic temperature factors for the non-hydrogen atoms and isotropic temperature factors for the

hydrogen atoms. Crystal data for **17**: $C_{22}H_{29}NO_3 \cdot HCl$; M=391.94; orthorhombic, space group $P2_12_12_1$, a=13.4470 (9) Å, b=21.317 (1) Å, c=7.7412 (9) Å; V=2219.0 (3) Å^3, D_c=1.173 g/cm^3, Z=4, R=0.031, R_w=0.045 for 1588 reflections with $I>3\sigma$ (I). Crystal data for **22**: $C_{22}H_{29}NO_3 \cdot HCl \cdot H_2O$; M=409.05; monoclinic, space group $C2$, a=13.170 (2) Å, b=7.464 (1) Å, c=22.622 (1) Å, β=94.400 (7)°; V=2217.3 (4) Å^3, D_c=1.228 g/cm^3, Z=4, R=0.031, R_w=0.045 for 1895 reflections with $I>3\sigma$ (I). Crystal data for **25**: $C_{22}H_{29}NO_3 \cdot HCl \cdot H_2O$; M=409.05; monoclinic, space group C2, a=13.162 (1) Å, b=7.4656 (7) Å, c=22.6077 (8) Å, β=94.441 (4)°; V=2214.8 (3) Å$_3$, D_c=1.229 g/cm^3, Z=4, R=0.028, R_w=0.042 for 1906 reflections with $I>3\sigma(I)$. Crystal data for **27**: $C_{22}H_{29}NO_3 \cdot HCl$; M=391.94; orthorhombic, space group $P2_12_12_1$, a=10.785 (1) Å, b=29.036 (2) Å, c=7.138 (2) Å; V=2235.3 (6) Å^3, D_c=1.165 g/cm^3, Z=4, R=0.048, R_w=0.070 for 1387 reflections with $I>3\sigma(I)$.

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18) The ^{13}C-NMR of **29** revealed a downfield methylene resonance (35.8 ppm) at 3-position of the pyrrolidine ring compared to the corresponding methylene resonance (33.2 ppm) of **30**. The ^{13}C-NMR of **29** also revealed a upfield methylene resonance (56.2 ppm) at 5-position compared to the corresponding methylene resonance (58.7 ppm) of **30**. According to these data, we determined that compound **29** is (*Z*)-oxime and compound **30** is (*E*)-oxime, respectively.
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