Synthesis and Serotonin 2 (5-HT_2) Receptor Antagonist Activity of 5-Aminoalkyl-Substituted Pyrrolo[3,2-*c*]azepines and Related Compounds

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Received November 1, 1999; accepted January 28, 2000

A series of 5-aminoalkylpyrrolo[3,2-*c*]azepine derivatives was synthesized and their serotonin 2 (5-HT_2) receptor antagonist and antiplatelet aggregation activities were evaluated. 5-HT_2 receptor antagonist activity was largely determined by the nature of the substituent at the 8-position as well as the aminoalkyl group at the 5-position of the pyrrolo[3,2-*c*]azepine ring.

Compound 18a, 5-[3-[4-(4-fluorophenyl)piperazin-1-yl]propyl]-8-hydroxy-1-methyl-1,4,5,6,7,8-hexahydropyrrolo[3,2-*c*]azepin-4-one, was recognized as having potent 5-HT_2 receptor antagonist activity with weak α_1 adrenoceptor blocking activity and no significant D_2 receptor binding affinity, while the corresponding isomeric pyrrolo[3,4-*c*]azepine derivative (22) displayed only weak 5-HT_2 receptor antagonist activity. After racemic 18a was resolved directly *via* diastereomeric salt formation, each enantiomer was evaluated precisely. The 5-HT_2 receptor antagonist activity of 18a was found to reside primarily in (−)-18a (which was about 14-fold more potent than (+)-18a in isolated guinea pig arteries). Consequently, (*S*)-(−)-18a (SUN C5174) displayed the overall best profile with potent 5-HT_2 receptor antagonist activity (pA_2=8.98±0.06) and high selectivity *versus* other receptors.

SUN C5174 showed a marked inhibitory effect on the platelet aggregation induced by serotonin in combination with collagen and adenosine diphosphate (ADP) in canine or human platelet-rich plasma (IC_{50}=6.5 to 16 nM). Moreover, this compound significantly inhibited the mortality rate in mouse acute pulmonary thromboembolitic death induced by collagen and serotonin at oral doses of 0.3 mg/kg or higher.

SUN C5174 is currently undergoing clinical evaluation.

Key words serotonin 2 receptor antagonist; pyrrolo[3,2-*c*]azepine; SUN C5174; antiplatelet aggregation

Arterial thromboembolic events and their ischemic complications give rise to a variety of vasoocculusive disorders such as unstable angina, myocardial infarction, stroke, or peripheral arterial diseases.[1] As such diseases still remain the leading cause of human morbidity and mortality,[2] new antithrombotic therapeutic agents are needed.

Serotonin is accumulated into platelets, stored, and later released from platelets activated by collagen, norepinephrine (NE), thromboxan A_2 (TXA_2), adenosine diphosphate (ADP) and other endogenous products. Serotonin only weakly induces platelet aggregation, but synergistically potentiates the effects of the above vasoactive and platelet aggregative substances.[3]

Since these activities have been demonstrated to be mediated through the serotonin 2 (5-HT_2) receptor,[4] 5-HT_2 receptor selective antagonists are expected to be useful in the treatment of peripheral circulatory disorders involving vasoconstriction and platelet aggregation.[5]

The 5-HT_2 receptor antagonist ketanserin (**1**, Fig. 1) has been shown to be beneficial in the treatment of some circulatory diseases.[4a,6] It is well known that this compound has not only potent 5-HT_2 receptor antagonist activity but also considerable α_1-adrenoceptor blocking activity which has been confirmed to be responsible for the blood pressure reduction.[7] Due to adverse effects such as hypotension based on α_1-adrenoceptor blocking activity, compounds with less potent α_1 blocking activity are preferable. The selective 5-HT_2 receptor antagonist, sarpogrelate (**2a**), was recently reported as a therapeutic agent for treatment of peripheral circulatory disturbance.[8]

We are interested in preparing agents with new pharmacological profiles based on utilization of unique skeletons. Previously, we reported the structure–activity relationships (SAR) of pyrrolo[2,3-*c*]azepine derivatives containing a unique bicyclic ring found in certain marine sponges.[9] The ring system was found to be a useful component in eliciting α_1- and/or 5-HT_2-receptor antagonist activities, which were markedly affected by the nature of the functional group at the 4-position of the pyrroloazepine ring. Certain compounds, especially (*E*)-1-[4-[4-(4-fluorobenzoyl)piperidino]butyl]-4-

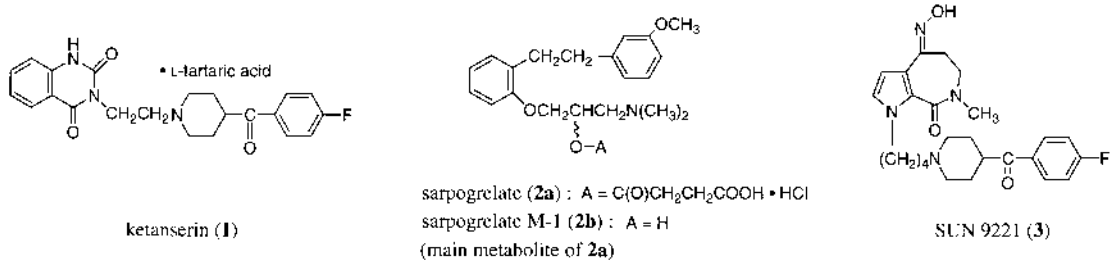

Fig. 1

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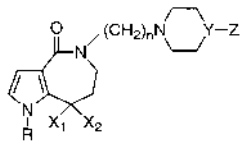
hydroxyimino-7-methyl-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepin-8-one (**3**, SUN9221), were potent antihypertensive agents with potent α_1- and 5-HT_2-receptor antagonist activities. These results suggested that further modification of this ring may produce a selective 5-HT_2 receptor antagonist, and therefore we synthesized and evaluated pyrrolo[3,2-*c*]azepine derivatives (Fig. 2, I) and related compounds.

In this paper, we describe the SAR within a series of these compounds that led to the discovery of SUN C5174 (compound (−)-**18a**), a potent and selective 5-HT_2 receptor antagonist.

Chemistry Synthetic pathways for preparation of the key intermediates (**7**, **12** and **13**) are shown in Chart 1. (1-Substituted)-3-pyrrolecarboxylic acids (**4**) were condensed with β-alanine benzyl ester *p*-toluenesulfonate in the presence of diethyl phosphorocyanidate (DEPC),[10] followed by hydrogenolysis of the benzyl group affording 3-(3-pyrrolecarboxamido)propionic acids (**6**) in good yields. Cyclization of the resultant **6** with 80% polyphosphoric acid (PPA) at 100 °C produced predominantly pyrrolo[3,2-*c*]azepine compounds (**7**) over pyrrolo[3,4-*c*]azepine compounds (**8**) in the range of approximately 2.3 : 1, and whose structures were determined by comparison of NMR data of both compounds (method A).[11] Compounds **7c** and **7d** were prepared by alkylation of **7a** in high yields (method B). Subsequently, the reaction of **7** with α-bromo-ω-chloroalkane in the presence of *tert*-BuOK afforded the ω-chloro derivatives (**12**), but yields were poor (method C). As this route was not satisfactory, a more expedient route was investigated. Condensation of **4** with *N*-substituted β-alanine ester derivative (**9**), followed by alkaline hydrolysis of the ester group and cyclization with a mixture of methanesulfonic acid and P_2O_5, directly afforded predominantly the pyrrolo[3,2-*c*]azepine derivatives (**12**) in better yields accompanied by small amounts of isomeric **13** (method D).

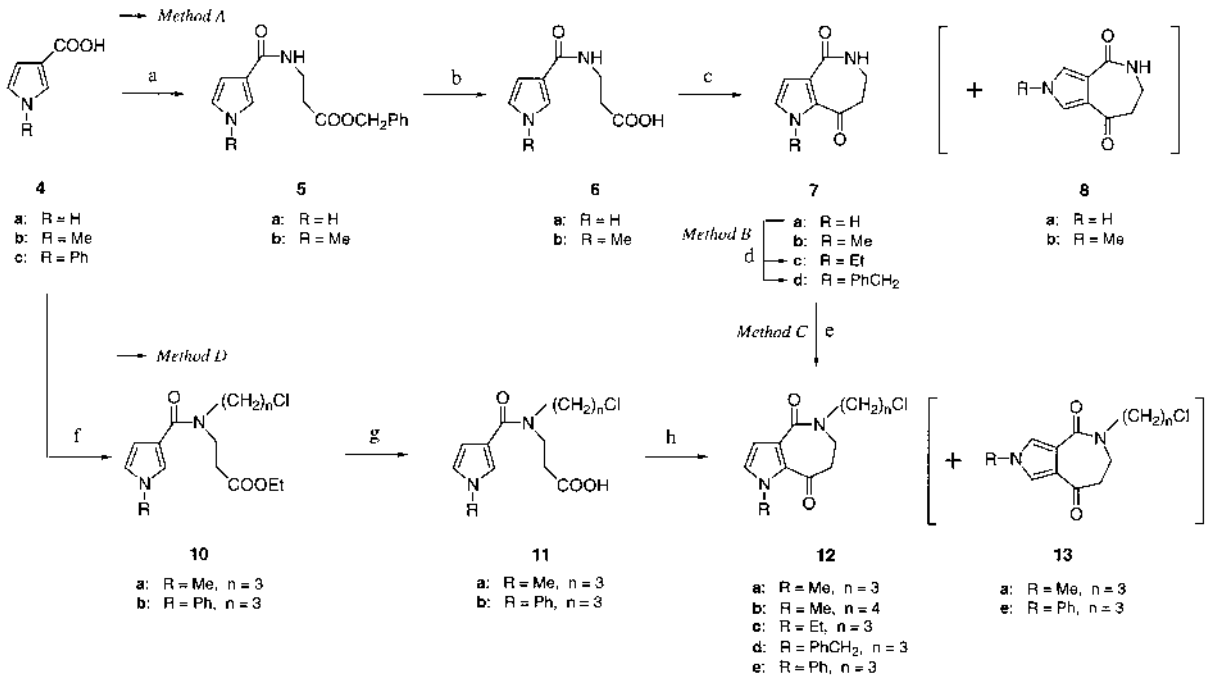
The target compounds indicated in Tables 1—4 were synthesized as outlined in Charts 2—3. The ω-chloro derivatives (**12**) were reacted with the appropriate amine in the presence of base (K_2CO_3 or $NaHCO_3$) and NaI to give the 8-aminoalkyl compounds (**14**) in good yields (method E). As introduction of the chloroethyl group into **7b** by method C was unsuccessful, an alternative approach was adopted for preparation of **14n**. Direct introduction of an aminoethyl moiety into the 5-position of **7b** using 1-(2-chloroethyl)-4-(4-fluorophenyl)piperazine in the presence of NaH gave **14n** in 18% yield (method F). Reduction of **14** with $NaBH_4$ afforded the desired 8-hydroxy compounds (**18**) (method G). Compound **18b**, with a carbonyl group in the amino moiety at the 5-position, was prepared by initial reduction of **12** and subsequent replacement of chlorine atom by amination (method H) (Chart 2). The derivatives (**15**, **16**, **19** and **20**) with various groups at the 8-position were synthesized from **14a** and **18a**. Treatment of **14a** with hydroxylamine hy-



R : alkyl, aryl, aralkyl
X_1, X_2 : =O, =NOH, OH & H *etc.*
n : 2, 3, 4
Y : CH, N
Z : aryl, aroyl *etc.*

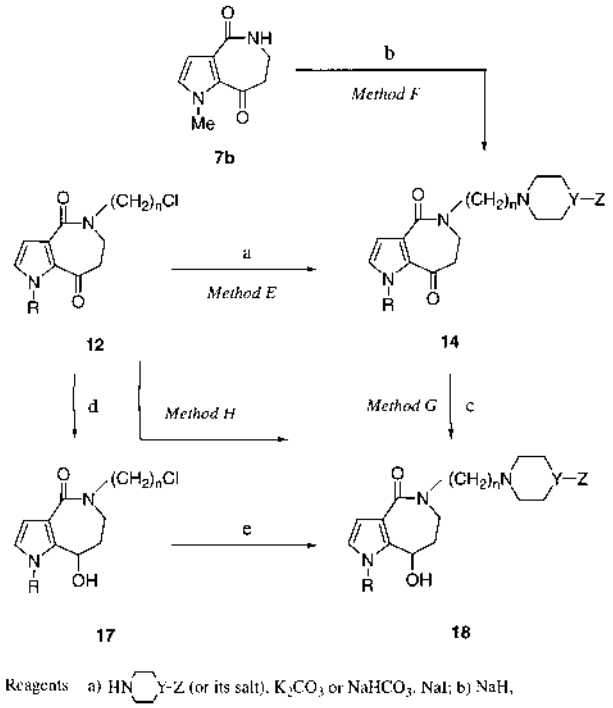
target compound (I)

Fig. 2



Reagents a) $NH_2CH_2CH_2COOCH_2Ph \cdot TsOH$, DEPC, Et_3N; b) H_2, 5% Pd–C; c) 80% PPA; d) RI (for **7c**) or RBr (for **7d**), K_2CO_3; e) *tert*-BuOK, $Br(CH_2)_nCl$; f) $Cl(CH_2)_3NHCH_2CH_2COOEt \cdot HCl$ (**9**), WSCD · HCl, Et_3N, 4-DMAP; g) i) aq.–NaOH, ii) dil.–HCl; h) MsOH, P_2O_5

Chart 1



*Compounds **14** and **18***

14, 18	R	n	Y	Z
a	Me	3	N	4-F-Ph
b [a]	Me	3	CH	4-F-benzoyl
c	Me	3	CH	Ph
d	Me	3	N	Ph
e	Me	3	N	2-F-Ph
f	Me	3	N	3-F-Ph
g	Me	3	N	4-Cl-Ph
h	Me	3	N	4-OH-Ph
i	Me	3	N	4-NO_2-Ph
j	Me	3	N	4-MeO-Ph
k	Me	3	N	Ph_2CH
l	Me	3	N	2-pyrimidinyl
m	Me	3	N	3-(1,2-BIT) [b]
n	Me	2	N	4-F-Ph
o	Me	4	N	4-F-Ph
p	Et	3	N	4-F-Ph
q	$PhCH_2$	3	N	4-F-Ph
r	Ph	3	N	4-F-Ph

a) **14b** is absent, as Method H was used
b) 3-(1,2-benzisothiazolyl)

Chart 2

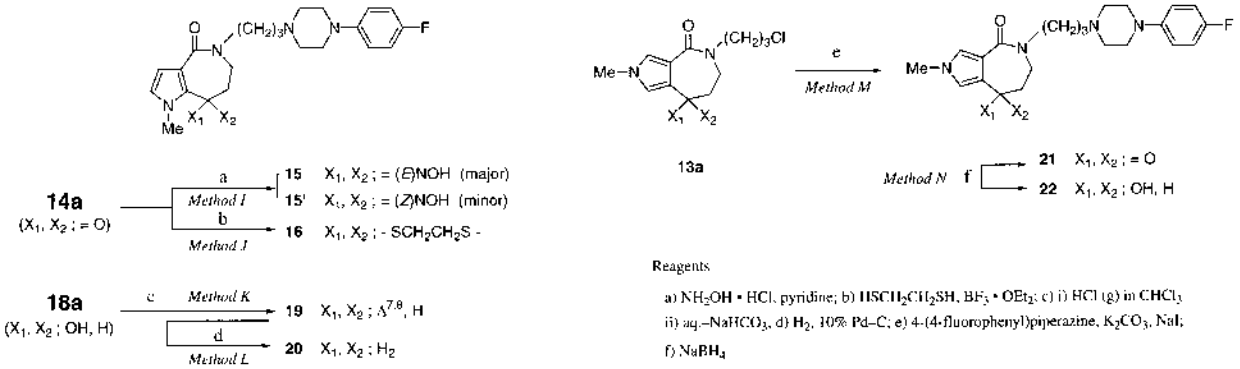


Chart 3

drochloride in basic medium afforded exclusively the (*E*)-oxime (**15**) accompanied by a very small amount of the (*Z*)-oxime (**15′**), which could be easily separated by column chromatography (method I).[12] Thioacetal compound (**16**) was obtained by reaction of **14a** with ethanedithiol and boron trifluoride etherate (method J). Compound **18a** was dehydrated with hydrogen chloride in $CHCl_3$ to give the 7,8-unsaturated compound (**19**) (method K), which was reduced by catalytic hydrogenation on Pd on carbon to give the 8-methylene compound (**20**) (method L). The isomeric pyrrolo[3,4-*c*]azepine derivatives (**21** and **22**) were prepared from **13a** in a manner similar to preparation of **14a** and **18a**, respectively (methods M, N) (Chart 3).

Optical resolution of **18a** was performed by diastereomeric salt formation with optically active tartaric acid, followed by fractional recrystallization. Treatment of the resolved-amine tartaric acid salts with aqueous NaOH and subsequent recrystallization produced free bases, (−)-**18a** and (+)-**18a** (Chart 4). The enantiomeric purities of (−)-**18a** and (+)-**18a** were over 99% ee, as determined by HPLC using a chiral column. The absolute configuration of (−)-**18a** was established as 8*S* on the basis of X-ray crystallographic analysis of (−)-**18a**·L-(+)-tartaric acid salt (Fig. 3).

The chemical structures of the synthesized compounds were confirmed from spectroscopic data (IR, ^{1}H-NMR, MS) and elemental analyses.

Results and Discussion

It has been reported that the contractions induced by serotonin and NE in the isolated mesenteric artery and aorta of the guinea pig are mainly caused by activation of 5-HT_2 receptors and α_1-adrenergic receptors, respectively.[13] Therefore, antagonistic effects of compounds on 5-HT_2 receptors and α_1-adrenergic receptors were evaluated in terms of the ability to block 10^{-5} M serotonin-induced contractions and 10^{-5} M NE-induced contractions of isolated guinea pig arter-

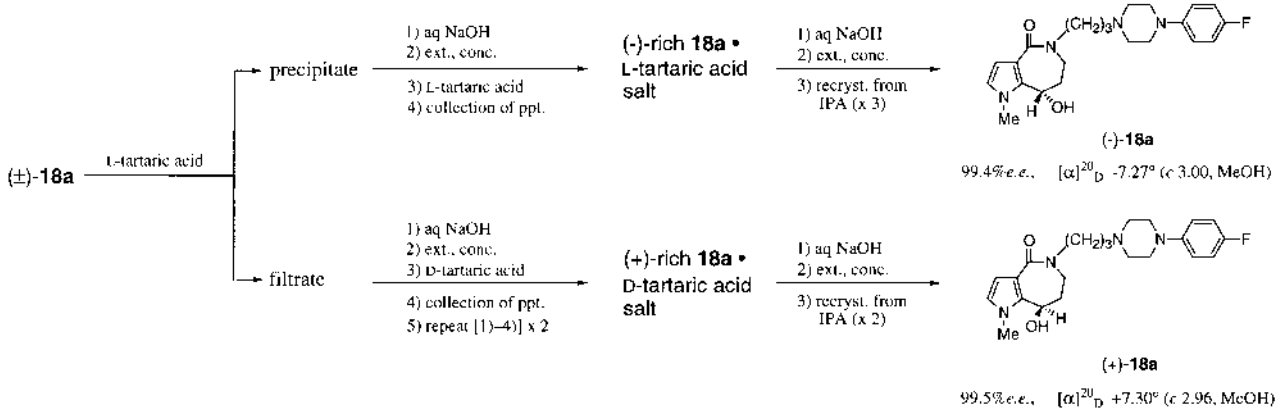


Chart 4

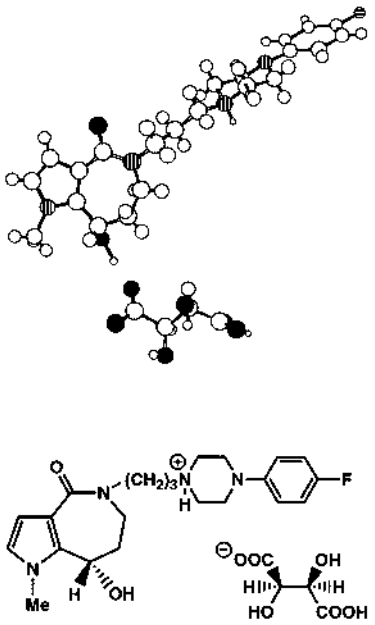


Fig. 3. Molecular Structure of Compound (−)-**18a**·L-(+)-Tartrate as Determined by X-Ray Crystal Analysis

ies, respectively. Details concerning the test methods are described in the Experimental Section.

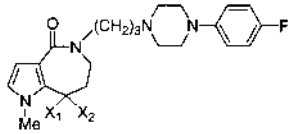
Initially, we investigated the influence of various groups at the 8-position of 1-methylpyrrolo[3,2-*c*]azepine derivatives, as shown in Table 1. 5-HT_2 receptor antagonist activity and selectivity were largely affected by the nature of this group. While a carbonyl derivative (**14a**) and a (*E*)-hydroxyimino compound (**15**) exhibited only weak 5-HT_2 receptor antagonist activity, the hydroxy compound (**18a**) showed very potent activity. Compounds **16** and **19** had potent 5-HT_2 receptor antagonist activity comparable to that of **18a**, but at the expense of higher α_1 blocking and D_2 receptor binding activities. Furthermore, methylene compound (**20**) exhibited the same or slightly more potent 5-HT_2 receptor antagonist activity, but had low selectivity since α_1 blocking activity was rather more potent than that of **18a**. The hydroxy group must be an important factor for manifestation of the potent and selective 5-HT_2 receptor antagonist activity.

Subsequently, the effects of various amines were examined with compounds containing a hydroxy group at the 8-position. As shown in Table 2, the amine moieties markedly affected the 5-HT_2 blocking activity. The compounds with a "ketanserin side chain" (**18b**) and 4-phenylpiperidine (**18c**) did not exhibit potent activity. Compound **18d**, which has a piperazine moiety instead of piperidine, showed improved potency, but the selectivity was not sufficient. The effects of substituents on the benzene ring on activity were further explored in a piperazine series. 4-Fluoro substitution (**18a**) led to marked improvement of both 5-HT_2 receptor antagonist activity and selectivity, whereas 2-fluoro (**18e**) or 3-fluoro (**18f**) substitution diminished the activity, in comparison with the unsubstituted compound **18d**. 4-Chloro (**18g**) and 4-hydroxy (**18h**) compounds exhibited less potent activity than the 4-fluoro compound (**18a**), and comparably weak α_1 blocking and D_2 receptor binding activities as the 4-fluoro compound. The results with compounds **18a** and **18d**—**h** suggested that the presence of a substituent in the 4-position of the benzene ring was important for suppressing α_1 blocking activity and D_2 receptor binding affinity. Both 4-nitro (**18i**) and 4-methoxy (**18j**) compounds showed negligible 5-HT_2 receptor antagonist activity. These observations suggested that the 5-HT_2 receptor antagonist activity was influenced by both the electronic and steric effects of the substituents at the 4-position. Larger groups such as methoxy and nitro groups at the 4-position interfere with the interaction, and serve to reduce activity. Replacement of the phenyl group with other groups such as a benzhydryl (**18k**), 2-pyrimidinyl (**18l**) and 3-(1,2-benzisothiazolyl) group (**18m**) markedly diminished activity.

The next step was optimization of the alkylene chain length (*n*) at the 5-position and the substituent at the 1-position of the pyrrolo[3,2-*c*]azepine skeleton, whilst maintaining the optimal amine moiety of **18a**. The results of this study are summarized in Table 3. Alteration of the alkyl chain between the 5-position of pyrrolo[3,2-*c*]azepine and the 4-(4-fluorophenyl)piperazine moiety from propylene (**18a**) to either ethylene (**18n**) or tetramethylene (**18o**), reduced the 5-HT_2 receptor antagonist activity by more than 10-fold. The length of the alkyl side chain was critical for selectivity against α_1 blocking activity as well as 5-HT_2 receptor antagonist activity, and was optimal with $n=3$.

Subsequently, the effects of the substituent at the 1-position were examined. Substitution of the methyl group by larger groups such as an ethyl (**18p**), benzyl (**18q**) and

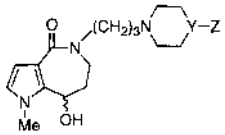
Table 1. Biological Activities of Pyrrolo[3,2-*c*]azepine Derivatives with Various Groups at the 8-Position



Compound	X_1, X_2	5-HT_2-blocking activity[a] (% inhibition)			α_1-blocking activity[b] (% inhibition)		D_2 receptor binding affinity[c] IC_{50} (nM)
		10^{-8} M	10^{-7} M	10^{-6} M	10^{-8} M	10^{-7} M	
14a	=O		23	74	1	9	3260
15	=NOH(*E*)		13	52	14	40	1410
16	–SCH_2CH_2S–	25	79		3	24	721
18a	–OH, H	45	88	93	1	10	3110
19	$\Delta^{7,8}$, H	44	79		38	79	1710
20	H_2	65	92		12	62	3900
Ketanserin (**1**)		43	93	100	3	47	831
Sarpogrelate (**2a**)			12	27	1	3	>10000
Sarpogrelate M-1 (**2b**)			23	69	3	7	8660

a) % inhibition of 10^{-5} M serotonin-induced contraction in guinea pig mesenteric artery. *b*) % inhibition of 10^{-5} M norepinephrine-induced contraction in guinea pig aorta. *c*) IC_{50} value in [^{3}H]-raclopride binding to rat striatum membrane preparations.

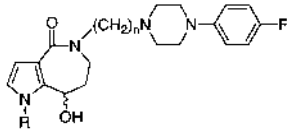
Table 2. Biological Activities of 8-Hydroxypyrrolo[3,2-*c*]azepine Derivatives with Various Amine Moieties (**18**)



Compound	Y	Z	5-HT_2-blocking activity[a] (% inhibition)			α_1-blocking activity[b] (% inhibition)		D_2 receptor binding affinity[c] IC_{50} (nM)
			10^{-8} M	10^{-7} M	10^{-6} M	10^{-8} M	10^{-7} M	
18a	N	4-F-Ph	45	88	93	1	10	3110
18b	CH	4-F-benzoyl		28	75	2	30	>10000
18c	CH	Ph	9	45	85	1	6	3010
18d	N	Ph	33	84		3	27	2000
18e	N	2-F-Ph		30	81	5	36	2590
18f	N	3-F-Ph		52	88	1	28	2400
18g	N	4-Cl-Ph	18	53	93	1	7	5800
18h	N	4-OH-Ph		59	89	1	12	8560
18i	N	4-NO_2-Ph		2	11	2	5	>10000
18j	N	4-MeO-Ph		2	16	2	5	>10000
18k	N	benzhydryl		12	48	0	0	6420
18l	N	2-Pyrimidinyl		7	13	1	2	>10000
18m	N	3-(1,2-BIT)[d]		49	89	5	68	1100

a)—*c*) see corresponding footnotes of Table 1. *d*) 3-(1,2-benzisothiazolyl).

Table 3. Biological Activities of 8-Hydroxypyrrolo[3,2-*c*]azepine Derivatives **18n**—**r**



Compound	R	*n*	5-HT_2-blocking activity[a] (% inhibition)			α_1-blocking activity[b] (% inhibition)		D_2 receptor binding affinity[c] IC_{50} (nM)
			10^{-8} M	10^{-7} M	10^{-6} M	10^{-8} M	10^{-7} M	
18a	Me	3	45	88	93	1	10	3110
18n	Me	2		10	52	3	29	8490
18o	Me	4		22	62	1	41	162
18p	Et	3	15	70		14	53	4470
18q	$PhCH_2$	3		49	89	5	68	483
18r	Ph	3		26	63	4	61	993

a)—*c*) see corresponding footnotes of Table 1.

phenyl (**18r**) groups resulted in a decrease in the 5-HT_2 receptor antagonist activity, suggesting some steric effects around this position. The best result was obtained with compound **18a** with the methyl group at the 1-position.

We prepared the isomeric pyrrolo[3,4-*c*]azepine analog of **18a** in order to clarify the pharmacological significance of the pyrrolo[3,2-*c*]azepine skeleton. As shown in Table 4, the isomeric compound **22** exhibited less than one tenth of the 5-HT_2 receptor antagonist activity of the corresponding compound **18a**, indicating that combination of the pyrrolo[3,2-*c*]azepine skeleton and the 8-hydroxy group of **18a** is important for manifestation of the potent 5-HT_2 receptor antagonist activity.

Consequently, we selected compound **18a** for further studies. Compound **18a** was a racemic compound possessing an asymmetric center at the 8-position in the pyrroloazepine ring. Since Pfeiffer's rule states that highly potent chiral compounds display a large difference in potency between their enantiomers,[14] we resolved **18a** *via* a diastereomeric salt to separate (+)-**18a** and (−)-**18a**, and subsequently elucidated their pharmacological properties. In the experiment using isolated guinea pig arteries, the 5-HT_2 receptor antagonist activity of **18a** was found to reside primarily in (−)-**18a**, which was about 14-fold more potent than that of (+)-**18a**. In contrast, the α_1 blocking activity of (−)-**18a** was equivalent to or less than that of (+)-**18a** (Table 5). (−)-**18a** displayed high 5-HT_2 receptor binding affinity (IC_{50}=4.26 nM), which was 60-fold or more than 100-fold higher than its affinity for α_1 receptors (IC_{50}=254 nM) or 5-HT_{1A} receptors (IC_{50}=480 nM) respectively, and more than 400-fold higher for other receptors such as α_2 (IC_{50}=2380 nM), β (IC_{50}>10000 nM), D_2 (IC_{50}=2380 nM), muscarinic cholinergic (mACh) (IC_{50}> 10000 nM), H_1 (IC_{50}=1730 nM) and H_2 (IC_{50}=7790 nM) receptors in receptor binding assays.

In human and canine platelet-rich plasma (PRP), collagen- or ADP-induced platelet aggregation potentiated by serotonin was markedly inhibited by (−)-**18a** (IC_{50}=6.5—16 nM) (Table 6). This antiplatelet aggregation effect by (−)-**18a** was more than 20-fold stronger than that by (+)-**18a**, and more than 2- and 100-fold stronger than those by ketanserin and sarpogrelate, respectively.

Next, we evaluated both enantiomers in an *in vivo* study. In the acute pulmonary thromboembolic death model in mice, (−)-**18a** (0.03 to 1 mg/kg) inhibited the mortality in a dose-dependent manner by oral administration before induction of platelet aggregation, and its inhibitory effect was significant at doses of 0.3 mg/kg or higher (Fig. 4). In addition, (+)-**18a** and ketanserin significantly inhibited mortality at 3 and 1 mg/kg, respectively. In contrast, sarpogrelate showed no significant inhibitory effect even at 30 mg/kg. From the results of *in vitro* and *in vivo* experiments, it was suggested that (−)-**18a** showed much more potent and selective 5-HT_2 receptor antagonist activity than (+)-**18a**.

In conclusion, several 5-aminoalkylpyrrolo[3,2-*c*]azepine derivatives showed potent 5-HT_2 receptor antagonist activity. Among these, (*S*)-(−)-5-[3-[4-(4-fluorophenyl)piperazin-1-

Table 4. Biological Activities of Pyrrolo[3,2-*c*]azepine Derivatives (**14a**, **18a**) and Pyrrolo[3,4-*c*]azepine Derivatives (**21**, **22**)

Compound	5-HT_2-blocking activity[a] (% inhibition)			α_1-blocking activity[b] (% inhibition)		D_2 receptor binding affinity[c] IC_{50} (nM)
	10^{-8} M	10^{-7} M	10^{-6} M	10^{-8} M	10^{-7} M	
14a		23	74	1	9	3260
18a	45	88	93	1	10	3110
21		31	75	2	19	NT[d]
22		20	75	1	7	6340

a)—*c*) see corresponding footnotes of Table 1. *d*) Not tested.

Table 5. Comparison of Biological Activities of Racemic and Optically Active **18a**

Compound	5-HT_2-blocking activity[a] (% inhibition)						α_1-blocking activity[b] (% inhibition)					D_2 receptor binding affinity[c]
	10^{-9} M	3×10^{-9} M	10^{-8} M	10^{-7} M	10^{-6} M	pA_2[d]	10^{-9} M	10^{-8} M	10^{-7} M	10^{-6} M	pA_2[d]	IC_{50} (nM)
(±)-**18a**		11	45	88	93	8.65±0.05	0	1	10	59	6.59±0.08	3110
(−)-**18a** (SUN C5174)	7	31	58	91		8.98±0.06	0	0	7	54	6.51±0.12	2380
(+)-**18a**			18	38	88	7.83±0.07	0	0	8	59	6.76±0.04	4750

a)—*c*) see corresponding footnotes of Table 1. *d*) Each value indicates the mean±S.E. of 3—5 experiments.

Table 6. Antiplatelet Aggregation Effects of (−)-**18a** and Reference Drugs in Canine and Human Platelet-rich Plasma

	Species	Dog		Human	
	Compound/inducer	Collagen (0.3—1 μg/ml)+ Serotonin (1 μM)	ADP (0.3—2 μM)+ Serotonin (1 μM)	Collagen (0.03—0.1 μg/ml) +Serotonin (1 μM)	ADP (0.5—1 μM)+ Serotonin (10 μM)
IC_{50} (nM)	(−)-**18a** (SUN C5174)	6.5	13	6.6	16
	(+)-**18a**	305	274	617	2559
	Ketanserin	19	29	54	43
	Sarpogrelate	>1000	1679	>1000	>10000
	Sarpogrelate M-1	218	159	356	2259

IC_{50} is the mean concentration that produced 50% inhibition estimated from the concentration-response curve in 4—6 experiments.

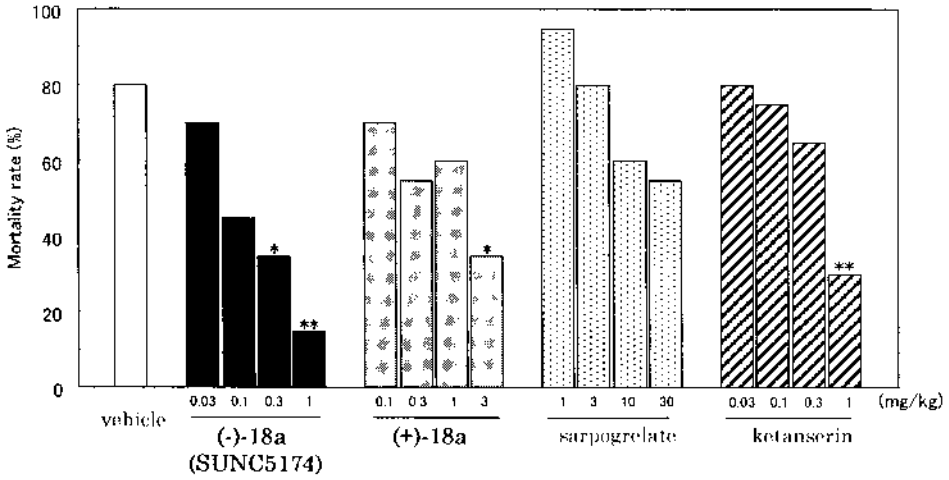


Fig. 4. Inhibitory Effects of Oral (−)-**18a** and Reference Drugs on Pulmonary Thromboembolic Death in Mice

Each column shows the percentage mortality rate due to pulmonary embolism induced by the intravenous dosing of collagen (5 mg/kg) and serotonin (1 mg/kg) 1 h after oral administration of the test drugs. Twenty mice were used in each group. Statistical differences in the results between vehicle control group and test drug treatment groups were analyzed using Fisher's exact test. *, $p<0.05$; **, $p<0.01$.

yl]propyl]-8-hydroxy-1-methyl-1,4,5,6,7,8-hexahydropyrrolo[3,2-*c*]azepin-4-one ((−)-**18a**, SUN C5174) displayed the best overall profile with potent and selective 5-HT_2 receptor antagonist activity. This property was confirmed by *in vivo* evaluation. These results indicated that the pyrrolo[3,2-*c*]azepine ring system is a useful scaffold for 5-HT_2 receptor antagonists.

Compound (−)-**18a** (SUN C5174) is currently undergoing clinical evaluation for treatment of peripheral circulatory diseases. Further pharmacological evaluation of (−)-**18a** will be reported elsewhere.

Experimental

Melting points were determined in open capillaries with a Büchi 535 digital melting point apparatus, and are uncorrected. The ^{1}H-NMR spectra were recorded on a JEOL JNM-GX270 or Brucker ARX 400 FT NMR spectrometer, and the chemical shifts were expressed in δ (ppm) values with tetramethylsilane as an internal standard. IR spectra were recorded on a Perkin-Elmer 1640 instrument. High resolution fast atom bombardment mass spectra (HR-FAB-MS) were measured on a JEOL JMS-HX110A instrument. Elemental analyses were performed on a Perkin-Elmer 240B elemental analyzer. Optical rotations were measured on a JASCO DIP-360 polarimeter.

In general, all organic extracts were dried over anhydrous sodium sulfate and the solvent was removed with a rotary evaporator under reduced pressure. Analytical TLC was carried out using Silica gel 60 F_{254} plates (Merck Art 5715). Column chromatography was performed on Silica gel 60 (Merck Art 9385, 230—400 mesh).

The following known materials were prepared as described in the literature: methyl pyrrole-3-carboxylate;[15] pyrrole-3-carboxylic acid;[15b] 1-phenyl-1*H*-pyrrole-3-carboxylic acid;[16] 1-(4-hydroxyphenyl)piperazine hydrobromide;[17] 1-(1,2-benzisothiazol-3-yl)piperazine;[18] 1-(2-chloroethyl)-4-(4-fluorophenyl)piperazine.[19] 1-(3-Fluorophenyl)piperazine was prepared according to a procedure similar to that described in the literature.[17]

Methyl 1-Methyl-1*H*-pyrrole-3-carboxylate The method of Guida and Mathre[20] was employed with minor modification. Potassium *tert*-butoxide (49.8 g, 444 mmol) and 18-crown-6 (7.82 g, 29.6 mmol) were added successively to a stirred solution of methyl pyrrole-3-carboxylate (37.0 g, 296 mmol) in Et_2O (370 ml) at 0 °C. To the resultant suspension was added dropwise a solution of MeI (84.0 g, 592 mmol) in Et_2O (30 ml) under vigorous stirring and ice-cooling, followed by stirring at room temperature for 1 h. The reaction mixture was poured into half-saturated NaCl (200 ml), and the layers were separated. The aqueous layer was extracted with Et_2O (2×50 ml). The combined organic layers were washed with brine, dried, and evaporated to give an oil, which was distilled to afford the title compound (32.1 g, 78%) as a colorless oil, bp_4 93.0—96.0 °C. IR (film): 1705 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.65 (3H, s), 3.78 (3H, s), 6.51—6.58 (2H, m), 7.22 (1H, m).

1-Methyl-1*H*-pyrrole-3-carboxylic Acid (4b) A mixture of methyl 1-methyl-1*H*-pyrrole-3-carboxylate (13.0 g, 93.4 mmol), 1 N NaOH (156 ml) and MeOH (156 ml) was stirred under reflux for 6 h. The reaction mixture was concentrated, and the residue was partitioned between water and Et_2O (150 ml each). The aqueous layer was acidified with 6 N HCl and extracted with EtOAc (3×150 ml). The combined extracts were washed with brine (150 ml), dried, and concentrated to give a solid which was recrystallized from EtOAc–diisopropyl ether (IPE) to afford **4b** (9.29 g, 79%) as pale brown crystals, mp 144.0—145.5 °C (lit.,[21] 145.0—145.5 °C). IR (KBr): 3300—2200, 1671 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.68 (3H, s), 6.56 (1H, m), 6.62 (1H, m), 7.31 (1H, m).

Ethyl 3-(3-Chloropropyl)aminopropionate Hydrochloride (9) 3-Chloropropylamine hydrochloride (130 g, 1 mol) was added to a stirred solution of 5 N NaOH (200 ml) at 0 °C. To the resultant solution was added *N*,*N*-dimethylformamide (DMF) (400 ml) and ethyl acrylate (120 g, 1.20 mol) successively below 10 °C. After stirring at room temperature for 16 h, the reaction mixture was poured into water (600 ml) and then extracted with EtOAc (4×200 ml). The combined extracts were washed with water (3×200 ml) and brine (200 ml), dried, and concentrated to afford a yellow oil (195 g). 4 N hydrogen chloride solution in EtOAc (252 ml) was added dropwise to a solution of the resultant oil in EtOAc (974 ml) below 15 °C under stirring, and stirring was continued at 0 °C for 30 min. The precipitates were filtered and washed twice with EtOAc to give **9** (148 g, 64%), mp 138.0—141.0 °C (acetone), colorless crystals. IR (KBr): 2850—2600, 1724 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7.1 Hz), 2.41 (2H, m), 3.02 (2H, t, J=7.2 Hz), 3.19 (2H, m), 3.30 (2H, t, J=7.2 Hz), 3.72 (2H, m), 4.19 (2H, q, J=7.1 Hz), 9.75 (2H, br s). *Anal.* Calcd for $C_8H_{16}ClNO_2\cdot HCl$: C, 41.75; H, 7.45; N, 6.09. Found: C, 41.85; H, 7.46; N, 6.21.

Method A: 1-Methyl-1,4,5,6,7,8-hexahydropyrrolo[3,2-*c*]azepine-4,8-dione (7b) and 2-Methyl-2,4,5,6,7,8-hexahydropyrrolo[3,4-*c*]azepine-4,8-dione (8b) To a stirred solution of **4b** (9.29 g, 74.2 mmol) and β-alanine benzyl ester *p*-toluenesulfonate (31.3 g, 89.1 mmol) in DMF (400 ml) at 0 °C were added dropwise and successively a solution of DEPC (14.5 g, 89.1 mmol) in DMF (50 ml) and a solution of Et_3N (18.0 g, 178 mmol) in DMF (50 ml). After stirring at room temperature for 16 h, the reaction mixture was concentrated. The residue was dissolved in EtOAc–benzene (2 : 1 v/v, 600 ml), washed successively with half-saturated K_2CO_3, water, 10% citric acid, water and brine (300 ml each). The organic layer was dried and concentrated to give a brown solid, which was recrystallized from EtOAc–hexane to afford **5b** (19.1 g, 90%) as colorless crystals. This material was used immediately in the next step, mp 109.0—110.0 °C. IR (KBr): 3270, 1732, 1623, 1558 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.66 (2H, t, J=5.9 Hz), 3.64 (3H, s), 3.66 (2H, m), 5.14 (2H, s), 6.28 (1H, dd, J=2.0, 2.6 Hz), 6.33 (1H, br s), 6.53 (1H, dd, J=2.0, 2.6 Hz), 7.11 (1H, t, J=2.0 Hz), 7.29—7.41 (5H, m).

A suspension of **5b** (19.0 g, 66.4 mmol) and 5% Pd–C (1.90 g, 10% wt eq) in tetrahydrofuran (THF) (500 ml) was vigorously stirred under an atmos-

phere of hydrogen for 21 h at room temperature. The catalyst was filtered through celite and washed thoroughly with MeOH. The combined filtrate and washings were concentrated to give a solid, which was recrystallized from CH_3CN to afford **6b** (12.3 g, 95%) as colorless crystals. This material was used immediately in the next step, mp 136.0—138.5 °C. IR (KBr): 3357, 1715, 1574 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.44 (2H, t, J=7.2 Hz), 3.35 (2H, m), 3.61 (3H, s), 6.39 (1H, m), 6.66 (1H, m), 7.21 (1H, m), 7.54 (1H, t, J=5.5 Hz).

A mixture of **6b** (11.0 g, 56.1 mmol) and approximately 80% PPA (550 g) was mechanically stirred at 100 °C for 1 h and then 120 °C for 10 min. The reaction mixture was poured into ice-water, and the pH of the solution was adjusted to 4 with K_2CO_3. The resultant solution was extracted with $CHCl_3$ (2×1 l, 2×500 ml). The extracts were washed with brine, dried, and concentrated to give a solid, which contained **7b** and **8b**. The mixture was subjected to column chromatography (eluent, EtOAc : MeOH=97 : 3, then $CHCl_3$: MeOH=19 : 1) to give **7b** (6.29 g, 63%) from the first fraction. The second fraction yielded **8b** (2.58 g, 26%). **7b**: mp 174.0—176.0 °C (CH_3CN), colorless crystals. IR (KBr): 3349, 1652, 1522 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.86 (2H, m), 3.52 (2H, m), 3.97 (3H, s), 6.78 (1H, d, J=2.6 Hz), 6.87 (1H, d, J=2.6 Hz), 7.98 (1H, br s). *Anal.* Calcd for $C_9H_{10}N_2O_2$: C, 60.67; H, 5.66; N, 15.72. Found: C, 60.79; H, 5.61; N, 15.97. **8b**: mp 218.0—222.0 °C (CH_3CN–IPE), colorless crystals. IR (KBr): 3176, 1652, 1547, 1519 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.82 (2H, m), 3.52 (2H, m), 3.74 (3H, s), 6.90 (1H, br s), 7.34—7.36 (2H, m). *Anal.* Calcd for $C_9H_{10}N_2O_2$: C, 60.67; H, 5.66; N, 15.72. Found: C, 60.67; H, 5.63; N, 15.90.

Compounds **7a** and **8a** were synthesized from **4a** using the 3-step procedure described above. **7a**: 52% overall yield, colorless crystals, mp >250 °C (MeOH–IPE). ^{1}H-NMR ($CDCl_3$) δ: 2.71 (2H, m), 3.33 (2H, m), 6.57 (1H, s), 7.11 (1H, d, J=2.4 Hz), 8.29 (1H, br s), 12.13 (1H, br s). *Anal.* Calcd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.06. Found: C, 58.23; H, 4.86; N, 16.89. **8a**: 23% overall yield, colorless crystals, mp >250 °C (MeOH–IPE). ^{1}H-NMR ($CDCl_3$) δ: 2.65 (2H, m), 3.29 (2H, m), 7.34 (1H, s), 7.43 (1H, s), 7.80 (1H, br s), 11.97 (1H, br s). *Anal.* Calcd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.06. Found: C, 58.38; H, 4.92; N, 16.90.

Method B: 1-Ethyl-1,4,5,6,7,8-hexahydropyrrolo[3,2-*c*]azepine-4,8-dione (7c) A suspension of **7a** (164 mg, 1 mmol), iodoethane (312 mg, 2 mmol) and K_2CO_3 (276 mg, 2 mmol) in 2-butanone (40 ml) was stirred under reflux for 15 h. The reaction mixture was filtered, the residue was washed with $CHCl_3$, and the combined filtrate and washings were concentrated. The residue was purified by column chromatography (eluent, $CHCl_3$: MeOH=9 : 1) to afford **7c** (184 mg, 96%), which was used immediately in the next step. A pure sample was obtained by recrystallization, mp 155.0—156.0 °C (EtOAc–IPE), colorless crystals. IR (KBr): 3185, 1668, 1643, 1526 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, t, J=7.1 Hz), 2.87 (2H, m), 3.50 (2H, m), 4.39 (2H, q, J=7.1 Hz), 6.29 (1H, br s), 6.82 (1H, d, J=2.7 Hz), 6.94 (1H, d, J=2.7 Hz). *Anal.* Calcd for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.57. Found: C, 62.53; H, 6.28; N, 14.52.

Compound **7d** was prepared in a similar manner to that described for **7c**, and used immediately in the next step. **7d**: 93% yield, colorless crystals, mp 170.5—171.5 °C (EtOAc–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.83 (2H, m), 3.49 (2H, m), 5.60 (2H, s), 6.78 (1H, br s), 6.87 (1H, d, J=2.7 Hz), 6.97 (1H, d, J=2.7 Hz), 7.11 (2H, m), 7.24—7.34 (3H, m).

Method C: 5-(3-Chloropropyl)-1-methyl-1,4,5,6,7,8-hexahydropyrrolo[3,2-*c*]azepine-4,8-dione (12a) To a stirred solution of potassium *tert*-butoxide (1.68 g, 15 mmol) in THF (40 ml) was added **7b** (1.34 g, 7.5 mmol) at 0 °C followed by stirring at the same temperature for 1 h. A solution of 1-bromo-3-chloropropane (5.90 g, 37.5 mmol) in THF (40 ml) was added dropwise to the reaction mixture at 0 °C and stirring was continued at room temperature for 93 h. An aqueous solution of citric acid (1.58 g, 8.2 mmol) was then added, and the mixture was concentrated. The residue was diluted with water (100 ml), and extracted with $CHCl_3$ (2×100 ml). The combined extracts were washed with brine, dried, and concentrated to give an oil, which was purified by column chromatography (eluent, EtOAc : hexane=2 : 1) to afford **12a** (628 mg, 33%), which was used immediately in the next step. A pure sample was obtained by recrystallization, mp 116.5—118.0 °C (EtOAc–IPE), colorless crystals. IR (KBr): 1660, 1626, 1524 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.14 (2H, quintet, J=6.7 Hz), 2.85 (2H, dd, J=4.0, 6.6 Hz), 3.62 (2H, t, J=6.7 Hz), 3.69 (2H, m), 3.75 (2H, t, J=6.7 Hz), 3.95 (3H, s), 6.77 (1H, d, J=2.6 Hz), 6.84 (1H, d, J=2.6 Hz). *Anal.* Calcd for $C_{12}H_{15}ClN_2O_2$: C, 56.59; H, 5.94; N, 11.00. Found: C, 56.68; H, 5.90; N, 11.04.

Compounds **12b**—**d** were prepared in a similar manner to that described for **7c**, and was used without further purification. **12b**: 49% yield, colorless crystals, mp 100.0—102.0 °C (EtOAc–hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.76—1.91 (4H, m), 2.83 (2H, dd, J=4.0, 6.4 Hz), 3.57—3.69 (6H, m), 3.95 (3H, s), 6.76 (1H, d, J=2.6 Hz), 6.83 (1H, d, J=2.6 Hz). **12c**: 29% yield, colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (3H, t, J=7.1 Hz), 2.14 (2H, quintet, J=6.7 Hz), 2.85 (2H, m), 3.61 (2H, t, J=6.7 Hz), 3.68 (2H, m), 3.74 (2H, t, J=6.7 Hz), 4.36 (2H, q, J=7.1 Hz), 6.78 (1H, d, J=2.7 Hz), 6.92 (1H, d, J=2.7 Hz). **12d**: 22% yield, colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 2.13 (2H, m), 2.81 (2H, m), 3.61 (2H, t, J=6.4 Hz), 3.66 (2H, m), 3.74 (2H, t, J=6.9 Hz), 5.57 (2H, s), 6.83 (1H, d, J=2.7 Hz), 6.95 (1H, d, J=2.7 Hz), 7.10 (2H, m), 7.23—7.34 (3H, m).

Method D: 5-(3-Chloropropyl)-1-methyl-1,4,5,6,7,8-hexahydropyrrolo[3,2-*c*]azepine-4,8-dione (12a) and 5-(3-Chloropropyl)-2-methyl-2,4,5,6,7,8-hexahydropyrrolo[3,4-*c*]azepine-4,8-dione (13a) To a stirred solution of **4b** (12.5 g, 100 mmol) and **9** (27.6 g, 120 mmol) in CH_2Cl_2 (450 ml) at 0 °C were added successively a solution of Et_3N (12.1 g, 120 mmol) in CH_2Cl_2 (50 ml), powdered 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSCD·HCl) (23.0 g, 120 mmol) and powdered 4-dimethylaminopyridine (4-DMAP) (2.93 g, 24 mmol). After stirring at room temperature for 5 h, the reaction mixture was washed sequentially with water, 1 N HCl, water, half-saturated $NaHCO_3$, water and brine (250 ml each), dried, and concentrated. The residue was purified by column chromatography (eluent, EtOAc : hexane=1 : 1) to afford **10a** (26.1 g, 87%) as a colorless oil. IR (film): 1730, 1611, 1540 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7.1 Hz), 2.12 (2H, m), 2.68 (2H, t, J=7.3 Hz), 3.57 (2H, t, J=6.4 Hz), 3.62—3.68 (5H, m), 3.80 (2H, t, J=7.3 Hz), 4.15 (2H, q, J=7.1 Hz), 6.33 (1H, m), 6.54 (1H, t, J=2.5 Hz), 7.05 (1H, m). HR-FAB-MS Calcd for $C_{14}H_{22}{}^{35}ClN_2O_3$: 301.1319 $[MH]^+$. Found: 301.1322.

To a stirred solution of ester **10a** (1.50 g, 5 mmol) in THF (2.6 ml) was added dropwise 2 N NaOH (2.6 ml, 5.2 mmol) under ice-cooling followed by stirring at room temperature for 30 min. The resultant solution was acidified (pH *ca.* 3) with 6 N HCl under ice-cooling, and then extracted with CH_2Cl_2 (3×50 ml). The combined extracts were washed with brine, dried, and concentrated to afford crude carboxylic acid **11a** (1.36 g). This material was immediately used in the next step without further purification.

To crude **11a** (1.36 g) was added a solution (5.82 g) which was prepared by stirring a mixture of P_2O_5 and methanesulfonic acid (1 : 6.1 w/w) at 90 °C until homogeneity (approximately 2 h) in another vessel, and the resultant mixture was stirred at 90 °C for 30 min. The reaction mixture was poured into ice-water, and extracted with $CHCl_3$ (3×100 ml). The organic extracts were washed with brine, dried, and concentrated to give a solid, which contained **12a** and **13a**. The mixture was subjected to column chromatography (eluent, EtOAc) to give **12a** (945 mg, 74%) as colorless crystals from the first fraction. The second fraction yielded **13a** (107 mg, 8.4%). **12a**: Physical data were identical with those of the compound prepared by method C. **13a**: mp 123.0—124.5 °C (EtOAc), colorless crystals. IR (KBr): 1653, 1625, 1520 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.13 (2H, quintet, J=6.6 Hz), 2.80 (2H, m), 3.62 (2H, t, J=6.6 Hz), 3.66 (2H, m), 3.71 (2H, t, J=6.6 Hz), 3.73 (3H, s), 7.28—7.31 (2H, m). *Anal.* Calcd for $C_{12}H_{15}ClN_2O_2$: C, 56.59; H, 5.94; N, 11.00. Found: C, 56.54; H, 6.00; N, 10.83.

Compounds **12e** and **13e** were synthesized from **4c** in a similar manner described for **12a** and **13a**, and used immediately in the next step. **12e**: 51% overall yield, mp 97.0—98.5 °C (EtOAc–hexane), colorless crystals. ^{1}H-NMR ($CDCl_3$) δ: 2.16 (2H, m), 2.81 (2H, m), 3.64 (2H, t, J=6.4 Hz), 3.75—3.81 (4H, m), 6.92 (1H, d, J=2.8 Hz), 6.99 (1H, d, J=2.8 Hz), 7.22—7.27 (2H, m), 7.40—7.46 (3H, m). **13e**: 5.8% overall yield, mp 116.5—118.0 °C (EtOAc–hexane), colorless crystals. ^{1}H-NMR ($CDCl_3$) δ: 2.16 (2H, m), 2.87 (2H, m), 3.64 (2H, t, J=6.4 Hz), 3.71—3.79 (4H, m), 7.37—7.52 (5H, m), 7.73 (1H, d, J=2.6 Hz), 7.75 (1H, d, J=2.6 Hz).

Method E: 5-[3-[4-(4-Fluorophenyl)piperazin-1-yl]propyl]-1-methyl-1,4,5,6,7,8-hexahydropyrrolo[3,2-*c*]azepine-4,8-dione (14a) A mixture of chloride **12a** (611 mg, 2.4 mmol), 1-(4-fluorophenyl)piperazine (649 mg, 3.6 mmol), K_2CO_3 (498 mg, 3.6 mmol) and NaI (720 mg, 4.8 mmol) in CH_3CN (30 ml) was stirred under reflux for 38 h. After the solvent was removed, the residue was diluted with half-saturated K_2CO_3 (50 ml), and then extracted with $CHCl_3$ (2×100 ml). The combined extracts were washed with brine, dried, and concentrated to give an oil, which was purified by column chromatography (eluent, EtOAc : MeOH=9 : 1) to afford **14a** (960 mg, quant.) as a pale yellow oil. IR (film): 1654, 1624 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.88 (2H, quintet, J=7.3 Hz), 2.48 (2H, t, J=7.3 Hz), 2.62 (4H, m), 2.84 (2H, m), 3.12 (4H, m), 3.58—3.74 (4H, m), 3.95 (3H, s), 6.77 (1H, d, J=2.6 Hz), 6.81—7.02 (5H, m). HR-FAB-MS Calcd for $C_{22}H_{28}FN_4O_2$: 399.2196 $[MH]^+$. Found: 399.2220.

Compounds **14c**—**m** and **14o**—**r** were prepared in a similar manner to

14a, except that in the syntheses of **14c**, **14i**, **14k** and **14m**, amine (1 eq) and $NaHCO_3$ (2 eq) were used instead of amine (1.5 eq) and K_2CO_3 (1.5 eq): in the syntheses of **14e** and **14g**, amine hydrochloride (1 eq) and $NaHCO_3$ (4 eq) were used: in the syntheses of **14f** and **14h**, amine hydrobromide (1 eq) and $NaHCO_3$ (4 eq) were used: in the syntheses of **14j** and **14l**, amine dihydrochloride (1 eq) and $NaHCO_3$ (6 eq) were used. These compounds were immediately transformed to the corresponding alcohol **18** by method G.

Method F: 5-[2-[4-(4-Fluorophenyl)piperazin-1-yl]ethyl]-1-methyl-1,4,5,6,7,8-hexahydropyrrolo[3,2-*c*]azepine-4,8-dione (14n) To a stirred suspension of NaH (1.92 g of a 60% oil dispersion, 48 mmol) in DMF (100 ml) was added a solution of **7b** (7.13 g, 40 mmol) in DMF (150 ml) at 0 °C over a period of 30 min. The mixture was stirred at 0 °C for 30 min and at room temperature for 90 min, and then cooled again to 0 °C. A solution of 1-(2-chloroethyl)-4-(4-fluorophenyl)piperazine (14.6 g, 60 mmol) in DMF (150 ml) was added to the mixture over a period of 30 min, and stirring was continued at room temperature for 16 h. The title compound **14n** (2.77 g, 18%) was obtained as a yellow oil by the same work-up and purification procedure as described for the preparation of **14a**. IR (film): 1652, 1626 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.63—2.72 (6H, m), 2.93 (2H, m), 3.10 (4H, m), 3.67 (2H, m), 3.78 (2H, m), 3.95 (3H, s), 6.77 (1H, d, J=2.6 Hz), 6.83 (1H, d, J=2.6 Hz), 6.85 (2H, m), 6.95 (2H, m). HR-FAB-MS Calcd for $C_{21}H_{26}FN_4O_2$: 385.2039 $[MH]^+$. Found: 385.2032.

Method G: 5-[3-[4-(4-Fluorophenyl)piperazin-1-yl]propyl]-8-hydroxy-1-methyl-1,4,5,6,7,8-hexahydropyrrolo[3,2-*c*]azepin-4-one (18a) To a stirred solution of ketone **14a** (797 mg, 2 mmol) in EtOH (30 ml) was added portionwise $NaBH_4$ (757 mg, 20 mmol) at 0 °C, and stirring was continued at 0 °C for 1 h and at room temperature for 16 h. Water (20 ml) was added, and the resultant mixture was stirred at room temperature for 1 h. After the solvent was removed, the residue was diluted with brine (100 ml) and then extracted with $CHCl_3$ (3×100 ml). The combined extracts were washed with brine, dried, and concentrated. The residue was purified by column chromatography (eluent, EtOAc : MeOH=4 : 1) to afford **18a** (710 mg, 89%) as colorless crystals. Compound **18n** was synthesized similarly from **14n**. Compounds **18c**—**m** and **18o**—**r** were prepared by amination of chloride **12** (method E) and successive reduction of crude **14** (method G) in a similar manner to that described above. The physical data for compounds **18a** and **18c**—**r** are listed in Table 7.

Method H: 5-[3-[4-(4-Fluorobenzoyl)piperidino]propyl]-8-hydroxy-1-methyl-1,4,5,6,7,8-hexahydropyrrolo[3,2-*c*]azepin-4-one (18b) To a stirred suspension of ketone **12a** (255 mg, 1 mmol) in EtOH (10 ml) was added portionwise $NaBH_4$ (85 mg, 2.25 mmol) at 0 °C, followed by stirring at room temperature for 6 h. The work-up was performed in a similar manner to that described in method G to give crude **17** (256 mg) as a colorless solid. This material was sufficiently pure to be used without further purification in the next step. A pure sample was obtained by recrystallization from EtOAc–hexane, mp 107.0—108.5 °C, colorless crystals. IR (KBr): 3328, 1586, 1542, 1513 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.05 (2H, quintet, J=6.7 Hz), 2.22 (2H, m), 2.61 (1H, d, J=7.8 Hz), 3.33 (1H, m), 3.52—3.69 (5H, m), 3.72 (3H, s), 4.85—4.93 (1H, m), 6.60 (1H, d, J=2.9 Hz), 6.66 (1H, d, J=2.9 Hz). *Anal.* Calcd for $C_{12}H_{17}ClN_2O_2$: C, 56.14; H, 6.67; N, 10.91. Found: C, 56.08; H, 6.73; N, 10.86.

A suspension of crude **17** (256 mg), 4-(4-fluorobenzoyl)piperidine hydrochloride (244 mg, 1 mmol), $NaHCO_3$ (336 mg, 4 mmol) and NaI (300 mg, 2 mmol) in CH_3CN (15 ml) was stirred under reflux for 15 h. The work-up and purification was performed in a similar manner to that described in method E to afford **18b** (335 mg, 78% overall) as colorless crystals. The physical data for **18b** are listed in Table 7.

Method I: (*E*)-5-[3-[4-(4-Fluorophenyl)piperazin-1-yl]propyl]-8-hydroxyimino-1-methyl-1,4,5,6,7,8-hexahydropyrrolo[3,2-*c*]azepin-4-one (15) and (*Z*)-5-[3-[4-(4-Fluorophenyl)piperazin-1-yl]propyl]-8-hydroxyimino-1-methyl-1,4,5,6,7,8-hexahydropyrrolo[3,2-*c*]azepin-4-one (15′) A solution of **14a** (797 mg, 2 mmol) and hydroxylamine hydrochloride (556 mg, 8 mmol) in pyridine (40 ml) was stirred at 90 °C for 17 h. After the reaction mixture was evaporated to dryness, the residue was diluted with half-saturated K_2CO_3 (80 ml), and then extracted with $CHCl_3$ (2×100 ml). The combined extracts were washed with brine, dried, and concentrated to give an oil, which contained mainly **15** (Rf 0.46, $CHCl_3$: MeOH=9 : 1) and a trace amount of the isomer **15′** (Rf 0.35, $CHCl_3$: MeOH=9 : 1). The mixture was subjected to column chromatography (eluent, $CHCl_3$: MeOH=19 : 1) to give (*E*)-oxime **15** (816 mg, 99%) as a colorless oil from the first fraction. The second fraction yielded (*Z*)-oxime **15′** (11 mg, 1%) as a colorless oil. **15**: IR (film): 3177, 1615, 1506 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.89 (2H, m), 2.50 (2H, m), 2.67 (4H, m), 3.05 (2H, m), 3.18 (4H, m), 3.53 (2H, m), 3.61 (2H, t, J=6.9 Hz), 3.67 (3H, s), 6.60 (1H, d, J=3.0 Hz), 6.64 (1H, d, J=3.0 Hz), 6.86 (2H, m), 6.96 (2H, m). HR-FAB-MS Calcd for $C_{22}H_{29}FN_5O_2$: 414.2305 $[MH]^+$. Found: 414.2294. **15′**: IR (film): 3190, 1614, 1505 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.86 (2H, m), 2.46 (2H, m), 2.63 (4H, m), 2.93 (2H, m), 3.13 (4H, m), 3.51—3.57 (4H, m), 3.62 (3H, s), 6.59 (1H, d, J=2.8 Hz), 6.70 (1H, d, J=2.8 Hz), 6.87 (2H, m), 6.96 (2H, m). HR-FAB-MS Calcd for $C_{22}H_{29}FN_5O_2$: 414.2305 $[MH]^+$. Found: 414.2310.

Method J: 5-[3-[4-(4-Fluorophenyl)piperazin-1-yl]propyl]-1-methyl-1,4,5,6,7,8-hexahydropyrrolo[3,2-*c*]azepin-4-one-8-spiro-2′-(1′,3′-dithiolane) Dihydrochloride (16) To a stirred solution of **14a** (398 mg, 1 mmol) and 1,2-ethanedithiol (168 μl, 2 mmol) in acetic acid (15 ml) was added dropwise boron trifluoride etherate (246 μl, 2 mmol), followed by stirring at room temperature. After 24 h, 1,2-ethanedithiol (1.5 ml, 18 mmol) and boron trifluoride etherate (1.97 ml, 18 mmol) were added and the resultant mixture was stirred for an additional 48 h. The reaction mixture was then made basic with 2 N NaOH and extracted with $CHCl_3$ (2×50 ml). The combined extracts were washed with brine, dried, and concentrated. The residue was purified by column chromatography (eluent, EtOAc : MeOH=9 : 1) to afford **16′** (free base) (373 mg, 79%) as a pale yellow oil. IR (film): 1608 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.82 (2H, quintet, J=7.3 Hz), 2.45 (2H, t, J=7.3 Hz), 2.60 (4H, m), 2.69 (2H, d, J=9.1 Hz), 3.11 (4H, m), 3.41—3.70 (8H, m), 3.99 (3H, s), 6.64 (1H, d, J=2.9 Hz), 6.70 (1H, d, J=2.9 Hz), 6.86 (2H, m), 6.94 (2H, m). The free base **16′** was dissolved in $CHCl_3$ and treated with a solution of hydrogen chloride in Et_2O to give a solid, which was recrystallized from EtOH–Et_2O to afford **16** as pale yellow crystals, mp 196 °C (dec.). *Anal.* Calcd for $C_{24}H_{31}FN_4OS_2 \cdot 2HCl \cdot 1/2H_2O$: C, 51.79; H, 5.98; N, 10.07. Found: C, 51.88; H, 6.30; N, 9.98.

Method K: 5-[3-[4-(4-Fluorophenyl)piperazin-1-yl]propyl]-1-methyl-1,4,5,6-tetrahydropyrrolo[3,2-*c*]azepin-4-one (19) To a stirred solution of **18a** (1.60 g, 4 mmol) in $CHCl_3$ (20 ml) was added a saturated solution of hydrogen chloride in $CHCl_3$ (120 ml) at room temperature, and stirring was continued at room temperature for 2 h. The mixture was washed with saturated $NaHCO_3$ (100 ml) and brine (50 ml), dried and concentrated. The residue was purified by column chromatography (eluent, $CHCl_3$: MeOH=97 : 3) to give a solid which was recrystallized from CH_2Cl_2–hexane to afford **19** (1.36 g, 89%) as colorless crystals, mp 175.5—177.0 °C (CH_2Cl_2–hexane). IR (KBr): 2822, 1594 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.82 (2H, quintet, J=7.3 Hz), 2.43 (2H, t, J=7.3 Hz), 2.59 (4H, m), 3.11 (4H, m), 3.60 (2H, t, J=7.3 Hz), 3.61 (3H, s), 3.71 (2H, d, J=6.9 Hz), 6.09 (1H, m), 6.64—6.69 (2H, m), 6.75 (1H, d, J=2.9 Hz), 6.86 (2H, m), 6.94 (2H, m). *Anal.* Calcd for $C_{22}H_{27}FN_4O$: C, 69.09; H, 7.12; N, 14.65. Found: C, 68.80; H, 7.11; N, 14.62.

Method L: 5-[3-[4-(4-Fluorophenyl)piperazin-1-yl]propyl]-1-methyl-1,4,5,6,7,8-hexahydropyrrolo[3,2-*c*]azepin-4-one (20) A suspension of **19** (210 mg, 0.55 mmol), 10% Pd–C (50 mg) and acetic acid (5 drops) in EtOH (30 ml) was vigorously stirred under an atmosphere of hydrogen at room temperature for 20 h. The catalyst was filtered through celite and washed with $CHCl_3$. After the combined filtrate and washings were concentrated, the residue was diluted with $NaHCO_3$ (50 ml) and extracted with $CHCl_3$ (3×50 ml). The extracts were washed with brine, dried, and concentrated to give an oil, which was purified by column chromatography (eluent, EtOAc : MeOH=5 : 1) to afford **20** (210 mg, quant.) as a pale yellow oil. IR (film): 1604, 1509 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.83 (2H, m), 2.11 (2H, m), 2.46 (2H, m), 2.61 (4H, m), 2.78 (2H, t, J=6.9 Hz), 3.12 (4H, m), 3.44 (2H, m), 3.49 (3H, s), 3.58 (2H, t, J=7.3 Hz), 6.54 (1H, d, J=3.0 Hz), 6.68 (1H, d, J=3.0 Hz), 6.82—6.90 (2H, m), 6.90—6.98 (2H, m). HR-FAB-MS Calcd for $C_{22}H_{30}FN_4O$: 385.2403 $[MH]^+$. Found: 385.2392.

Method M: 5-[3-[4-(4-Fluorophenyl)piperazin-1-yl]propyl]-2-methyl-2,4,5,6,7,8-hexahydropyrrolo[3,4-*c*]azepine-4,8-dione (21) The title compound was prepared from chloride **13a** by the same procedure as described for the preparation of **14a**, 93% yield, mp 140.0—141.0 °C, colorless crystals (EtOAc–IPE). IR (KBr): 1654, 1615, 1547 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.87 (2H, quintet, J=7.3 Hz), 2.47 (2H, t, J=7.3 Hz), 2.62 (4H, m), 2.79 (2H, m), 3.12 (4H, m), 3.60—3.68 (4H, m), 3.72 (3H, s), 6.87 (2H, m), 6.95 (2H, m), 7.27—7.29 (2H, m). *Anal.* Calcd for $C_{22}H_{27}FN_4O_2$: C, 66.31; H, 6.83; N, 14.06. Found: C, 66.26; H, 6.88; N, 14.13.

Method N: 5-[3-[4-(4-Fluorophenyl)piperazin-1-yl]propyl]-8-hydroxy-2-methyl-2,4,5,6,7,8-hexahydropyrrolo[3,4-*c*]azepin-4-one (22) The title compound was prepared from **21** by the same procedure as described for the preparation of **18a**. 99% yield, mp 95.0—97.0 °C, colorless crystals (toluene). IR (KBr): 3500—3200, 1599, 1537 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.84 (2H, quintet, J=7.3 Hz), 2.06—2.26 (3H, m), 2.46 (2H, m), 2.61 (4H,

Table 7. Physical and Spectral Data for Compounds **18a**—**r**

Compd. No.	Yield (%)[a]	mp (°C) (solvent)[b]	Formula	Analysis (%) or HRMS Calcd (Found)			^{1}H-NMR ($CDCl_3$) δ	IR (cm^{-1})
				C	H	N		
18a	89	166.0—167.5 (EA)	$C_{22}H_{29}FN_4O_2$	65.98 (65.92	7.30 7.37	13.99 14.04)	1.82 (2H, quintet, *J*=7.3 Hz), 2.15—2.32 (3H, m), 2.44 (2H, t, *J*=7.3 Hz), 2.60 (4H, m), 3.11 (4H, m), 3.34 (1H, m), 3.52 (1H, m), 3.59—3.70 (2H, m), 3.72 (3H, s), 4.91 (1H, br s), 6.61 (1H, d, *J*=2.9 Hz), 6.70 (1H, d, *J*=2.9 Hz), 6.87 (2H, m), 6.95 (2H, m)	3258, 1595, 1509[e]
18b	78	175.5—178.0 (dec.) (IPA–IPE)	$C_{24}H_{30}FN_3O_3$	67.43 (67.14	7.07 7.14	9.83 9.74)	1.72—1.87 (6H, m), 2.07 (2H, m), 2.21 (2H, m), 2.38 (2H, m), 2.98 (2H, m), 3.18 (1H, m), 3.30 (1H, m), 3.44 (1H, m), 3.56 (1H, m), 3.63 (1H, m), 3.72 (3H, s), 4.88 (1H, t, *J*=4.8 Hz), 6.58 (1H, d, *J*=2.9 Hz), 6.65 (1H, d, *J*=2.9 Hz), 7.13 (2H, m), 7.96 (2H, m)	1677, 1600, 1508[e]
18c	79	—[c]	$C_{23}H_{31}N_3O_2$	382.2494 $[MH]^+$ (382.2529 $[MH]^+$)[d]			1.82—1.93 (6H, m), 2.10—2.31 (4H, m), 2.44—2.59 (3H, m), 3.12 (2H, d, *J*=11.3 Hz), 3.33 (1H, m), 3.46—3.69 (3H, m), 3.72 (3H, s), 4.90 (1H, t, *J*=4.6 Hz), 6.59 (1H, d, *J*=2.9 Hz), 6.66 (1H, d, *J*=2.9 Hz), 7.17—7.25 (3H, m), 7.25—7.33 (2H, m)	3312, 1591, 1540, 1511[f]
18d	89	167.5—170.0 (IPA–IPE)	$C_{22}H_{30}N_4O_2$	69.08 (68.99	7.91 8.07	14.65 14.50)	1.81 (2H, quintet, *J*=7.3 Hz), 2.22 (2H, m), 2.44 (2H, m), 2.61 (4H, m), 3.20 (4H, m), 3.33 (1H, m), 3.48 (1H, m), 3.63 (2H, m), 3.72 (3H, s), 4.89 (1H, t, *J*=4.3 Hz), 6.59 (1H, d, *J*=2.9 Hz), 6.64 (1H, d, *J*=2.9 Hz), 6.84 (1H, d, *J*=7.3 Hz), 6.91 (2H, d, *J*=8.1 Hz), 7.25 (2H, m)	3278, 1598, 1508[e]
18e	73	138.0—140.0 (EA)	$C_{22}H_{29}FN_4O_2$	65.98 (65.81	7.30 7.30	13.99 13.88)	1.82 (2H, quintet, *J*=7.3 Hz), 2.23 (2H, m), 2.46 (2H, m), 2.63 (4H, m), 3.11 (4H, m), 3.34 (1H, m), 3.52 (1H, m), 3.59—3.70 (2H, m), 3.72 (3H, s), 4.90 (1H, t, *J*=4.5 Hz), 6.61 (1H, d, *J*=2.9 Hz), 6.70 (1H, d, *J*=2.9 Hz), 6.88—7.08 (4H, m)	3312, 1587, 1540, 1501[e]
18f	81	163.5—168.5 (EA–H)	$C_{22}H_{29}FN_4O_2$	65.98 (65.88	7.30 7.30	13.99 13.91)	1.80 (2H, m), 2.22 (2H, m), 2.43 (2H, m), 2.58 (4H, m), 3.19 (4H, m), 3.32 (1H, m), 3.48 (1H, m), 3.57—3.69 (2H, m), 3.72 (3H, s), 4.89 (1H, t, *J*=4.4 Hz), 6.51 (1H, dt, *J*=1.9, 8.2 Hz), 6.57 (1H, m), 6.60 (1H, d, *J*=2.9 Hz), 6.66 (1H, m), 6.68 (1H, d, *J*=2.9 Hz), 7.17 (1H, m)	3273, 1596, 1509[e]
18g	89	181.0—183.0 (C–EA)	$C_{22}H_{29}ClN_4O_2$	63.38 (63.29	7.01 7.03	13.44 13.50)	1.82 (2H, m), 2.22 (2H, m), 2.43 (2H, m), 2.59 (4H, m), 3.15 (4H, m), 3.33 (1H, m), 3.50 (1H, m), 3.56—3.69 (2H, m), 3.72 (3H, s), 4.89 (1H, m), 6.61 (1H, d, *J*=2.9 Hz), 6.69 (1H, d, *J*=2.9 Hz), 6.82 (2H, m), 7.19 (2H, m)	3236, 1582, 1538, 1500[e]
18h	49	—[c]	$C_{22}H_{30}N_4O_3$	399.2396 $[MH]^+$ (399.2412 $[MH]^+$)[d]			1.83 (2H, quintet, *J*=7.3 Hz), 2.21 (2H, m), 2.44 (2H, t, *J*=7.3 Hz), 2.60 (4H, m), 3.07 (4H, m), 3.34 (1H, m), 3.57—3.71 (3H, m), 3.72 (3H, s), 4.91 (1H, m), 6.63 (1H, d, *J*=2.6 Hz), 6.72 (1H, d, *J*=2.6 Hz), 6.75—6.84 (4H, m)	3250, 1585, 1513[f]
18i	87	177.0—178.5 (C–IPE)	$C_{22}H_{29}N_5O_4$	61.81 (61.59	6.84 6.79	16.38 16.26)	1.81 (2H, quintet, *J*=7.3 Hz), 2.13—2.31 (3H, m), 2.45 (2H, m), 2.59 (4H, m), 3.33 (1H, m), 3.41 (4H, m), 3.50—3.71 (3H, m), 3.72 (3H, s), 4.91 (1H, br s), 6.62 (1H, d, *J*=2.9 Hz), 6.70 (1H, d, *J*=2.9 Hz), 6.81 (2H, m), 8.11 (2H, m)	3299, 1599, 1509[e]
18j	84	155.0—158.0 (C–IPE)	$C_{23}H_{32}N_4O_3 \cdot 1/4H_20$	66.24 (66.29	7.73 7.80	13.43 13.39)	1.81 (2H, quintet, *J*=7.3 Hz), 2.22 (2H, m), 2.44 (2H, m), 2.61 (4H, m), 3.09 (4H, m), 3.33 (1H, m), 3.51 (1H, m), 3.57—3.69 (2H, m), 3.72 (3H, s), 3.76 (3H, s), 4.89 (1H, t, *J*=4.6 Hz), 6.60 (1H, d, *J*=2.9 Hz), 6.69 (1H, d, *J*=2.9 Hz), 6.83 (2H, m), 6.89 (2H, m)	3304, 1597, 1513[e]
18k	67	—[c]	$C_{29}H_{36}N_4O_2$	473.2916 $[MH]^+$ (473.2901 $[MH]^+$)[d]			1.76 (2H, m), 2.19 (2H, m), 2.32—2.57 (10H, m), 3.28 (1H, m), 3.47 (1H, m), 3.53—3.66 (2H, m), 3.71 (3H, s), 4.22 (1H, s), 4.88 (1H, t, *J*=4.5 Hz), 6.59 (1H, d, *J*=2.9 Hz), 6.67 (1H, d, *J*=2.9 Hz), 7.16 (2H, t, *J*=7.3 Hz), 7.26 (4H, m), 7.40 (4H, m)	3319, 1590, 1540, 1509[f]
18l	80	169.0—172.5 (EA–H)	$C_{20}H_{28}N_6O_2$	62.48 (62.48	7.34 7.33	21.86 21.89)	1.81 (2H, quintet, *J*=7.3 Hz), 2.22 (2H, m), 2.42 (2H, m), 2.49 (4H, m), 3.33 (1H, m), 3.49 (1H, m), 3.59—3.70 (2H, m), 3.72 (3H, s), 3.81 (4H, m), 4.89 (1H, t, *J*=4.4 Hz), 6.46 (1H, d, *J*=4.8 Hz), 6.60 (1H, d, *J*=2.9 Hz), 6.68 (1H, d, *J*=2.9 Hz), 8.29 (2H, d, *J*=4.8 Hz)	3250, 1610, 1584, 1546, 1508[e]
18m	85	170.0—170.5 (C–EA)	$C_{23}H_{29}N_5O_2S$	62.84 (62.74	6.65 6.60	15.93 15.94)	1.83 (2H, m), 2.23 (2H, m), 2.37 (1H, br s), 2.49 (2H, m), 2.68 (4H, m), 3.35 (1H, m), 3.51 (1H, m), 3.55 (4H, m), 3.60—3.70 (2H, m), 3.73 (3H, s), 4.91 (1H, m), 6.61 (1H, d, *J*=2.9 Hz), 6.69 (1H, d, *J*=2.9 Hz), 7.35 (1H, m), 7.46 (1H, m), 7.80 (1H, d, *J*=8.2 Hz), 7.89 (1H, d, *J*=8.2 Hz)	3226, 1583, 1541, 1515[e]

Table 7. (continued)

Compd. No.	Yield (%)[a]	mp (°C) (solvent)[b]	Formula	Analysis (%) or HRMS Calcd (Found) C	H	N	^{1}H-NMR ($CDCl_3$) δ	IR (cm^{-1})
18n	97[g]	185.5—187.5 (IPA)	$C_{21}H_{27}FN_4O_2$	65.27 (65.24	7.04 7.12	14.50 14.54)	2.31 (2H, m), 2.53—2.65 (3H, m), 2.69—2.84 (3H, m), 3.09 (4H, m), 3.31 (1H, m), 3.47 (1H, m), 3.57 (1H, m), 3.68 (3H, s), 4.03 (1H, br s), 4.22 (1H, m), 4.91 (1H, m), 6.57 (1H, d, J=2.9 Hz), 6.63 (1H, d, J=2.9 Hz), 6.83 (2H, m), 6.92 (2H, m)	3282, 1582, 1512[e]
18o	85	197.0—198.5 (EtOH)	$C_{23}H_{31}FN_4O_2$	66.64 (66.56	7.54 7.59	13.52 13.53)	1.50—1.65 (4H, m), 2.21 (2H, m), 2.42 (2H, m), 2.59 (4H, m), 3.10 (4H, m), 3.28 (1H, m), 3.47 (1H, m), 3.58 (1H, m), 3.71 (3H, s), 4.88 (1H, t, J=4.6 Hz), 6.59 (1H, d, J=2.9 Hz), 6.66 (1H, d, J=2.9 Hz), 6.82—6.91 (2H, m), 6.94 (2H, m)	3316, 1582, 1512[e]
18p	58	146.0—147.0 (C–H)	$C_{23}H_{31}FN_4O_2 \cdot 1/4H_2O$	65.93 (65.94	7.46 7.52	13.37 13.23)	1.43 (3H, t, J=7.3 Hz), 1.83 (2H, quintet, J=7.3 Hz), 2.23 (2H, m), 2.45 (2H, t, J=7.3 Hz), 2.60 (4H, m), 3.11 (4H, m), 3.34 (1H, m), 3.52—3.71 (3H, m), 3.98—4.16 (2H, m), 4.93 (1H, t, J=4.4 Hz), 6.70 (1H, d, J=3.0 Hz), 6.75 (1H, d, J=3.0 Hz), 6.86 (2H, m), 6.94 (2H, m)	3298, 1583, 1512[e]
18q	80	—[c]	$C_{28}H_{33}FN_4O_2$	477.2666 $[MH]^+$ (477.2685 $[MH]^+$)[d]			1.82 (2H, m), 2.15 (2H, m), 2.45 (2H, m), 2.60 (4H, m), 3.11 (4H, m), 3.31 (1H, m), 3.53 (1H, m), 3.58—3.73 (3H, m), 4.76 (1H, t, J=4.3 Hz), 5.15 (1H, d, J=16.1 Hz), 5.43 (1H, d, J=16.1 Hz), 6.69 (1H, d, J=2.9 Hz), 6.78 (1H, d, J=2.9 Hz), 6.86 (2H, m), 6.95 (2H, m), 7.04 (2H, m), 7.25—7.35 (3H, m)	3310, 1590, 1540, 1508[f]
18r	92	190.5—192.0 (C–EE)	$C_{27}H_{31}FN_4O_2$	70.11 (69.74	6.75 6.71	12.11 12.05)	1.86 (2H, m), 2.18 (2H, m), 2.48 (2H, m), 2.61 (4H, m), 3.11 (4H, m), 3.37 (1H, m), 3.63 (2H, t, J=7.2 Hz), 3.78 (1H, m), 4.88 (1H, t, J=4.1 Hz), 6.78 (1H, d, J=3.0 Hz), 6.83—6.90 (3H, m), 6.95 (2H, m), 7.39—7.53 (5H, m)	3111, 1610, 1509[e]

a) Overall yield from **12** unless otherwise noted. *b*) Recrystallization solvents: C=chloroform, EA=ethyl acetate, EE=diethyl ether, H=hexane. *c*) Obtained as an oil. *d*) Determined by high-resolution mass spectrometry. *e*) KBr. *f*) Film. *g*) Based on **14n**.

m), 3.12 (4H, m), 3.33 (1H, m), 3.57 (2H, t, J=7.3 Hz), 3.59 (1H, m), 3.63 (3H, s), 4.94 (1H, t, J=5.3 Hz), 6.64 (1H, d, J=2.6 Hz), 6.83—6.98 (4H, m), 7.22 (1H, d, J=2.6 Hz). *Anal.* Calcd for $C_{22}H_{29}FN_4O_2 \cdot H_2O$: C, 63.14; H, 6.98; N, 13.39. Found: C, 63.10; H, 7.32; N, 13.34.

Optical Resolution of Racemic 5-[3-[4-(4-Fluorophenyl)piperazin-1-yl]propyl]-8-hydroxy-1-methyl-1,4,5,6,7,8-hexahydropyrrolo[3,2-*c*]azepin-4-one [Preparation of (−)-18a and (+)-18a] To a warm solution of racemic **18a** (20.0 g, 50 mmol) in MeOH (160 ml) was added L-(+)-tartaric acid (7.50 g, 50 mmol). After the mixture was stirred at room temperature overnight and then at 0 °C for 1 h, the precipitate was collected and dried, yielding 12.5 g of a colorless powder. 2 N NaOH (56.5 ml, 113 mmol) was added to this solid, and extracted with $CHCl_3$ (3×100 ml). The extracts were washed with brine, dried, and evaporated to give the (−)-rich free form. The operations described above, *i.e.* formation of a salt with L-(+)-tartaric acid (1 eq), collection of precipitate, neutralization, extraction and evaporation, were repeated once more. The obtained solid was recrystallized from 2-propanol (IPA) (1 ml/1 g-solid) three times to afford optically pure (−)-**18a** (5.78 g, 29%, 99.4% ee). The filtrate from the first precipitate was concentrated and converted to the free base to give 10.2 g of (+)-rich free form as a colorless solid. The operations described as for (−)-**18a**, *i.e.* formation of a salt with D-(−)-tartaric acid (1 eq), collection of precipitate, neutralization, extraction and evaporation, were repeated three times. The obtained solid was recrystallized from IPA (1 ml/1 g-solid) twice to afford optically pure (+)-**18a** (5.36 g, 27%, 99.5% ee). (−)-**18a**: mp 168.5—170.0 °C, colorless crystals. The IR and ^{1}H-NMR spectra were identical with those of racemic **18a**, $[\alpha]_D^{20}$ (c=3.00, MeOH)=−7.27°. *Anal.* Calcd for $C_{22}H_{29}FN_4O_2$: C, 65.98; H, 7.30; N, 13.99. Found: C, 66.18; H, 7.39; N, 13.99. (+)-**18a**: mp 168.5—170.0 °C, colorless crystals. The IR and ^{1}H-NMR spectra were identical with those of racemic **18a**. $[\alpha]_D^{20}$ (c=2.96, MeOH)=+7.30°. *Anal.* Calcd for $C_{22}H_{29}FN_4O_2$: C, 65.98; H, 7.30; N, 13.99. Found: C, 65.97; H, 7.49; N, 14.06. The enantiomeric purities of (−)-**18a** and (+)-**18a** were determined by HPLC under the following conditions: column, CHIRALPAK AD (DAICEL, 4.6 mm i.d.×250 mm); column temperature, 40 °C; mobile phase, hexane–MeOH–EtOH–diethylamine (70 : 20 : 10 : 0.1); flow rate, 1.0 ml/min; detector, UV at 254 nm; retention time, (−)-**18a**, 5.6 min; (+)-**18a**, 6.7 min.

Preparation of (−)-18a L-(+)-Tartrate A mixture of (−)-**18a** (200 mg, 0.5 mmol) and L-(+)-tartaric acid (75 mg, 0.5 mmol) in MeOH (7 ml) was gently heated until a clear solution was obtained. The solution was allowed to stand at room temperature for 24 h. The crystals that formed were collected and washed with cold MeOH to afford the title compound (180 mg, 65%). *Anal.* Calcd for $C_{26}H_{35}FN_4O_8$: C, 56.72; H, 6.41; N, 10.18. Found: C, 56.88; H, 6.35; N, 10.15.

X-Ray Crystallographic Analysis of (−)-18a·L-(+)-Tartrate Diffraction measurements were performed on a Rigaku AFC-7R diffractometer using graphite monochromated CuK_α radiation (λ=1.54178 Å). Crystals of (−)-**18a**·L-(+)-tartrate were subjected to crystallographic analysis and were found to belong to the orthorhombic space group $P2_12_12_1$ with the following unit cell parameters; a=18.828(4) Å, b=18.829(5) Å, c=7.490(6) Å, V=2655(2) Å^3, Z=4. The final R-factor and weighted R-factor were 0.048 and 0.072, respectively, based on 1765 reflections with $I>3\sigma(I)$.

Serotonin (5-HT$_2$)- and α_1-Adrenergic-Receptor Antagonist Activity The functional serotonin (5-HT$_2$)- and α_1-adrenergic-receptor antagonist activities against serotonin and NE, respectively, were determined in the isolated guinea pig mesenteric artery and aorta, respectively.[13] Briefly, male Hartley strain guinea pigs were anesthetized with pentobarbital Na (50 mg/kg, i.p.) and killed by decapitation. The mesenteric arterial bed and aorta were rapidly dissected out. Helical strips (2 mm in width, 20 mm in length) of the arteries were prepared using forceps and mounted vertically in a Magnus chamber, filled with warm (37 °C) and oxygenated (95% O_2 and 5% CO_2 gas mixture) Tyrode's solution with the following composition (in mM): NaCl 137, KCl 5.4, $CaCl_2$ 2.7, $MgCl_2$ 0.5, $NaHPO_4$ 0.45, $NaHCO_3$ 11.9, glucose 5.5. The upper side of the tissue was connected to a force-displacement transducer (Shinkoh U gage, UL-10G) using silk thread. The isometric tension was recorded continuously using a pen-recorder (National, VP-6537). After a 1-h equilibration period with a resting tension of 0.5 g, the mesenteric arterial or aortic preparation was contracted transiently with serotonin (10^{-5} M) or continuously with NE (10^{-5} M), respectively. Test samples at final concentrations of 10^{-9} and 10^{-6} M were added before transient contraction induced by serotonin or under continuous contraction induced by NE. The functional serotonin (5-HT$_2$)- or α_1-antagonist activities against serotonin or NE were determined as the reduction in peak contraction.

For selected compounds, the pA_2 values were determined to measure the potency of their antagonistic action against 5-HT$_2$- or α_1-receptors. Briefly,

cumulative concentration–response curves for serotonin and NE were constructed by stepwise addition of the agonist, using helical strips of isolated femoral or mesenteric guinea pig arteries, respectively. Serotonin or NE was then washed out several times during a 1-h period. The strips were incubated with various concentrations of compounds for 10 min, and a concentration-response curve for serotonin or NE was obtained again. The pA_2 values were determined from Schild plots.

Receptor Binding Assays 5-HT_2 receptor,[22] α_1-adrenoceptor,[23] 5-HT_{1A} receptor,[24] α_2-adrenoceptor,[25] β-adrenoceptor,[26] D_2-dopamine receptor,[27] mACh receptor,[28] H_1-histamine receptor[29] and H_2-histamine receptor[30] binding assays were performed as previously described with slight modifications.

5-HT_2 Receptor Binding Assay Aliquots (90 μg of protein) of rat frontal cortex membranes were incubated at 25 °C for 45 min with 1 nM [^{3}H]ketanserin and various concentrations of test compounds in 50 mM Tris–HCl buffer (pH 7.7) with a final incubation volume of 250 μl. Specific binding was defined as that displaceable by 1 μM ketanserin.

α_1-Adrenoceptor Binding Assay Aliquots (90 μg of protein) of rat cerebral cortex membranes were incubated at 25 °C for 30 min with 0.3 nM [^{3}H]prazosin and various concentrations of test compounds in 50 mM Tris–HCl buffer (pH 7.7), 0.01% ascorbic acid with a final incubation volume of 250 μl. Specific binding was defined as that displaceable by 10 μM prazosin.

5-HT_{1A} Receptor Binding Assay Aliquots (80 μg of protein) of rat hippocampus membranes were incubated at 25 °C for 30 min with 0.4 nM [^{3}H]8-hydroxy-DPAT and various concentrations of test compounds in 50 mM Tris–HCl buffer (pH 7.7), 10 μM pargyline, 4 mM $CaCl_2$, 0.1% ascorbic acid with a final incubation volume of 250 μl. Specific binding was defined as that displaceable by 100 μM serotonin.

α_2-Adrenoceptor Binding Assay Aliquots (90 μg of protein) of rat striatum membranes were incubated at 25 °C for 30 min with 2 nM [^{3}H]rauwolscine and various concentrations of test compounds in 20 mM HEPES-Na buffer (pH 7.4) with a final incubation volume of 250 μl. Specific binding was defined as that displaceable by 10 μM yohimbine.

β-Adrenoceptor Binding Assay Aliquots (100 μg of protein) of rat cerebral cortex membranes were incubated at 25 °C for 30 min with 1.5 nM [^{3}H]dihydroalprenolol and various concentrations of test compounds in 50 mM Tris–HCl buffer (pH 7.7) with a final incubation volume of 250 μl. Specific binding was defined as that displaceable by 100 μM propranolol.

D_2-Dopamine Receptor Binding Assay Aliquots (90 μg of protein) of rat striatum membranes were incubated at 25 °C for 60 min with 1 nM [^{3}H]raclopride and various concentrations of test compounds in 50 mM Tris–HCl buffer (pH 7.4), 0.01% ascorbic acid, 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$ with a final incubation volume of 250 μl. Specific binding was defined as that displaceable by 1 μM spiperone.

mACh Receptor Binding Assay Aliquots (9 μg of protein) of rat cerebral cortex membranes were incubated at 37 °C for 60 min with 0.3 nM [^{3}H]quinuclidinyl benzilate and various concentrations of test compounds in 50 mM Na-phosphate buffer (pH 7.4), 100 mM NaCl, 1 mM $MgCl_2$ with a final incubation volume of 250 μl. Specific binding was defined as that displaceable by 10 μM atropine.

H_1-Histamine Receptor Binding Assay Aliquots (80 μg of protein) of guinea pig cerebellum membranes were incubated at 25 °C for 30 min with 4 nM [^{3}H]pyrilamine and various concentrations of test compounds in 50 mM Na-K-phosphate buffer (pH 7.5) with a final incubation volume of 250 μl. Specific binding was defined as that displaceable by 2 μM triprolidine.

H_2-Histamine Receptor Binding Assay Aliquots (310 μg of protein) of guinea pig cerebral cortex membranes were incubated at 25 °C for 30 min with 3 nM [^{3}H]tiotidine and various concentrations of test compounds in 50 mM Na-K-phosphate buffer (pH 7.5) with a final incubation volume of 250 μl. Specific binding was defined as that displaceable by 100 μM cimetidine.

For all binding assays, incubation was terminated by rapid filtration under vacuum, and the filters were processed for radioactivity determination. The inhibition of binding by the test compound was analyzed to estimate the IC_{50} (the concentration of the test compound causing 50% inhibition of binding) using Multicalc™ Advanced (wallac, Finland).

Measurement of Platelet Aggregation The platelet donors were five healthy volunteers aged 25—35 years who took no medication that might alter platelet function for at least two weeks before the start of the study. Canine platelets were prepared from six adult Beagle dogs. Venous blood was mixed with a one-tenth volume of trisodium citrate (0.1 M, pH 7.35), and PRP was then obtained by centrifugation at 200×g for 5 min at room temperature. It was adjusted to a platelet count of about 300000 μl^{-1} with autologous platelet-poor plasma, prepared by centrifugation at 900×g for 20 min. Platelet aggregation was measured by turbidometry in two dual-chamber channel platelet aggregometers (Mevanix, PAM-8C). PRP (200 μl) was incubated in the aggregation cuvette for 2 min with test sample (10^{-9}—10^{-5} M) and $CaCl_2$ (1 mM). Serotonin (1 or 10 μM) in combination with collagen (0.03—1 μg/ml) or ADP (0.3—2 μM) was then added. The final volume of PRP+agonist/test samples was 250 μl. The concentration of serotonin was chosen because it produced a submaximal potentiation effect, and when used alone it caused less than 10% aggregation. The concentrations of collagen and ADP were determined in each preparation as the maximum concentrations that caused less than 10% aggregation. The degree of aggregation at 10 min after the addition of agonists was measured as the percentage of the difference in light transmission between PRP and platelet-poor plasma.

Acute Pulmonary Thromboembolic Death in Mice Male ddY mice weighing about 25 g (5 to 6 weeks-old) were used after overnight fasting. Acute pulmonary thromboembolism was induced by rapid injection of a mixture (0.1 ml/10 g body weight) of serotonin (1 mg/kg) and collagen (5 mg/kg) into the tail vein and the mortality of mice within 10 min was determined. With the exception of sarpogrelate, all compounds were dissolved in saline containing 10% dimethylsulfoxide. Sarpogrelate was dissolved in 0.5% tragacanth in water according to Hara *et al.*[31] Compounds were administered orally one hour prior to the injection of serotonin and collagen. Twenty mice were used for each group. Results are expressed as mortality rate in animal numbers and percentage. The dose (ED_{50}) producing 50% reduction of mortality was estimated from the dose-response curve.

Acknowledgments We thank Drs. F. Satoh, T. Tanaka, S. Tanaka and T. Nakanishi for their encouragement throughout this study, and Dr. H. Fukami for useful suggestions during the preparation of this manuscript. We are grateful to Dr. M. Shiro, Rigaku Corporation, Mr. S. Matsuki and Mr. Y. Oyama for X-ray crystallographic analyses. Thanks are also due to Mr. T. Fujita and Dr. H. Naoki, Suntory Institute for Bioorganic Research, for the measurement of HR-FAB-MS.

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same position, and were lower than those of **7**.
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