Studies on Antihypertensive Agents with Antithrombotic Activity. 2.[1] Syntheses and Pharmacological Evaluation of Pyrrolo[2,3-*c*]azepine Derivatives

Akira MIZUNO,* Mikiko MIYA, Tomoe KAMEI, Makoto SHIBATA, Toshio TATSUOKA, Kyoko NAKANISHI, Chikako TAKIGUCHI, Toshinori HIDAKA, Akira YAMAKI, and Norio INOMATA

Suntory Institute for Biomedical Research, 1–1–1, Wakayamadai, Shimamoto-cho, Mishima-gun, Osaka 618–8503, Japan.
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As an extension of our previous investigation,[1] a series of 7-aminoalkylpyrrolo[2,3-*c*]azepine derivatives was synthesized and evaluated as α_1-adrenergic- and serotonin 2 (5-HT_2)-receptor antagonists, with the aim of finding a novel potent antihypertensive agent with both activities. Among the compounds obtained in this study, (*E*)-1-ethyl-7-[3-[4-(4-fluorophenyl)piperazin-1-yl]propyl]-4-hydroxyimino-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepin-8-one (16d) displayed potent α_1-adrenoceptor blocking activity (pA_2=7.83±0.20) and 5-HT_2-receptor blocking activity (pA_2=9.47±0.17) in isolated guinea pig arteries. At 3 mg/kg oral administration, compound 16d exhibited antihypertensive activity more potent than that of doxazosin in deoxycorticosterone acetate (DOCA)-salt hypertensive dogs. Furthermore, this compound reduced the rate of mouse acute pulmonary thromboembolitic death induced by collagen and serotonin at oral doses of 0.3 mg/kg or more, and its effect lasted for at least 6 h at 3 mg/kg.

Key words α_1-adrenoceptor antagonist; serotonin 2 receptor antagonist; pyrrolo[2,3-*c*]azepine; antihypertension; antiplatelet aggregation

Hypertension is an important risk factor for various cardiovascular disorders,[2] and it has been recognized that antihypertensive agents are useful in reducing the incidence of ischemic heart disease in addition to providing satisfactory blood pressure control.[3] Among the numerous antihypertensive drugs with various pharmacological profiles, the α_1-adrenoceptor blocking agents, such as doxazosin (**1**) and prazosin (**2**, Fig. 1), have not only an antihypertensive effect[4] but also a beneficial effect on plasma lipids.[5] These drugs are therefore first-choice agents in the clinical setting,[6] and especially doxazosin has been widely used in treatment of hypertension.

In an experimental hypertension model, serotonin-induced contractile response of arteries by 5-HT_2-receptors is augmented.[7] In addition, it has been reported that several aspects of platelet function, such as adhesiveness and aggregation, are abnormal in patients with essential hypertension,[8] and that plasma concentration of serotonin in patients with hypertension or peripheral vascular diseases is increased.[9]

Aggregating platelets release stored serotonin, resulting in the augmentation of platelet aggregation and clotting process induced by various substances including adenosine diphosphate (ADP), epinephrine and collagen,[10] as well as the exacerbation of vasoconstriction induced by various vasoactive substances.[11] Among the factors released from aggregating platelets in injured endothelium region including ADP, thromboxane A_2 (TXA_2) and serotonin, serotonin is reported to induce vasoconstriction more markedly than TXA_2.[12] Therefore, it is thought that a drug possessing both α_1-adrenoceptor blocking action and 5-HT_2-receptor blocking action would be beneficial in preventing circulatory diseases that involve vasoconstriction and platelet aggregation as well as controlling blood pressure.[13]

Ketanserin (**3**, Fig. 1) was developed as an antihypertensive agent,[14] and it has also been shown to be useful in the treatment of some circulatory diseases.[15] Although ketanserin has both α_1-adrenoceptor blocking activity and serotonin 2 (5-HT_2)-receptor blocking activity, its α_1 blocking activity is weak in comparison with doxazosin. On the basis of the above-mentioned considerations, we have attempted to find a novel compound possessing both the potent α_1-adrenoceptor blocking activity of doxazosin as well as the potent 5-HT_2-receptor blocking action of ketanserin to develop an antihypertensive drug with a potent antiplatelet aggregating effect.

Previously, we reported the syntheses and structure-activity relationships (SAR) of 1-aminoalkylpyrrolo[2,3-*c*]-azepine derivatives, remarking on the similarity of chemical reactivities between the nitrogen atom at the 1-position of 1,4,5,6,7,8-tetrahydropyrrolo[2,3-*c*]azepine-4,8-dione (**4**) and the nitrogen atom at the 3-position of 2,4(1*H*,3*H*)-quinazolinedione (**5**).[1] In the previous study, we found that the pyrrolo[2,3-*c*]azepine ring system was a useful component in eliciting α_1- and/or 5-HT_2-receptor blocking activities, and that some compounds, especially (*E*)-1-[4-[4-(4-fluorobenzoyl)piperidino]butyl]-4-hydroxyimino-7-methyl-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepin-8-one (**6**, SUN9221), were potent antihypertensive agents with potent α_1- and 5-HT_2-receptor blocking activities. We were therefore interested in the syntheses and pharmacological profiles of 7-aminoalkylpyrrolo[2,3-*c*]azepine derivatives (I, Fig. 1), because of the structural similarities of the amide portions between **4** and **5**.

Here, we describe the synthesis, pharmacological evaluation and SAR of compound I.

Chemistry

Synthetic pathways for preparation of the intermediates (**10**) are shown in Chart 1. 1-Alkylpyrrole-2-carboxylic acids (**7**) were condensed with β-alanine benzyl ester *p*-toluenesulfonate in the presence of diethyl phosphorocyanidate (DEPC),[16] followed by hydrogenolysis of the benzyl group,

* To whom correspondence should be addressed. e-mail: Akira_Mizuno@suntory.co.jp

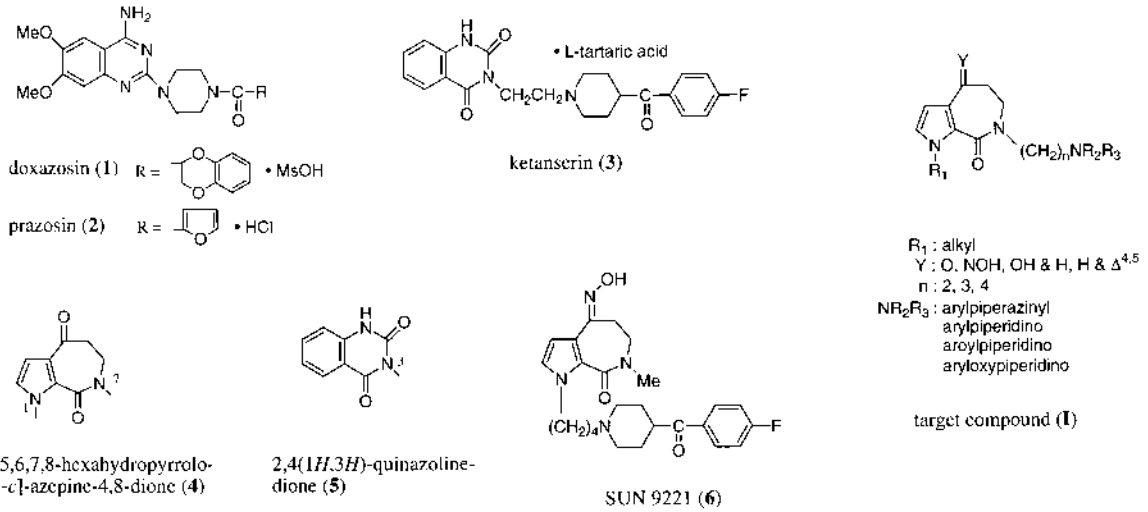


Fig. 1

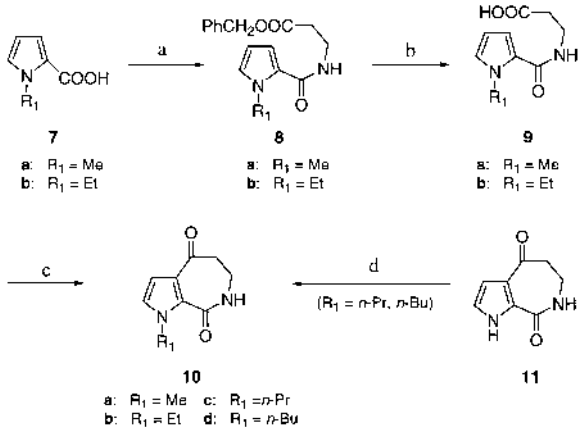


Chart 1

producing 3-[2-(1-alkylpyrrole)carboxamido]propionic acids (**9**) in good yields. Cyclization of the resultant **9** with 80% polyphosphoric acid (PPA) at 100 °C afforded 1-alkyl-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepine-4,8-diones (**10**) in good yields. Compounds **10c** and **10d** were prepared by facile alkylation of the *N*-unsubstituted compound (**11**).[1)]

The target compounds listed in Tables 1—3 were prepared as outlined in Chart 2. The reaction of the sodium salt of **10** with α,ω-dihaloalkane afforded 7-(ω-haloalkyl) compounds (**12**), and then treatment of **12** with the appropriate amine in the presence of base (K_2CO_3, $NaHCO_3$) gave the desired 7-aminoalkyl compounds (**13a**—**i**, **13k**) (Method A). As an alternative method, treatment of **10** with NaH, followed by alkylation with *N*-(ω-chloroalkyl)amine, directly afforded **13j** and **13l**—**m** (Method B).

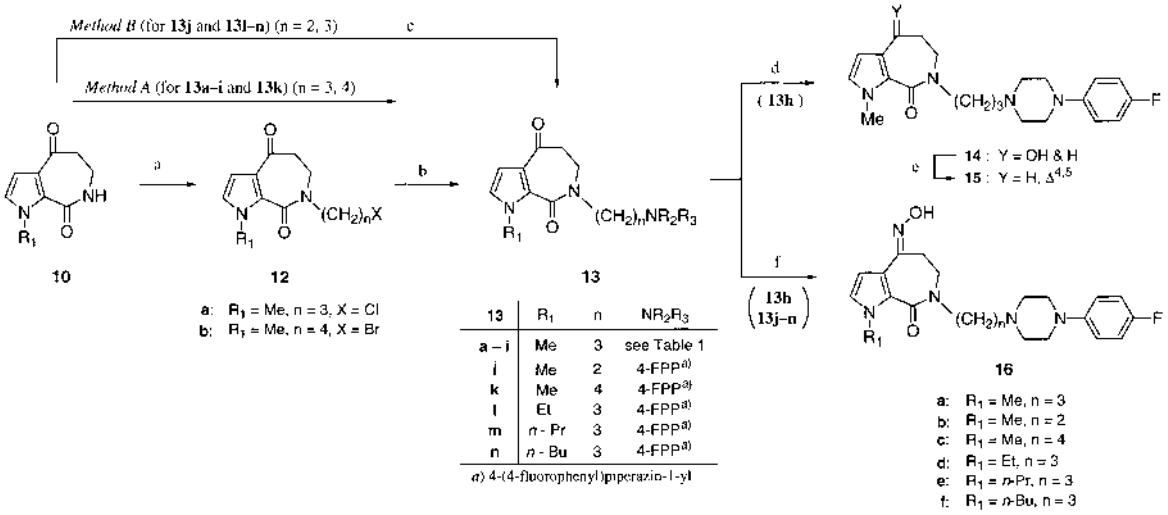
Reduction of **13h** with $NaBH_4$ afforded the 4-hydroxy compound (**14**), which was dehydrated to give the 4,5-unsaturated compound (**15**). Treatment of **13h** and **13j**—**n** with hydroxylamine hydrochloride in basic medium afforded the (*E*)-oximes (**16**) accompanied by very small amounts (2% in the case of **13h**) of the geometric isomers (**16′**) of the oxime moiety, which could be easily separated by column chromatography.[17)]

The chemical structures of the synthesized compounds were confirmed from spectroscopic data (IR, ^{1}H-NMR, MS) and elemental analyses. The structure of **16d** was further substantiated by X-ray crystallography, which showed that the geometry at the 4-position was the (*E*)-configuration (Fig. 2).

Results and Discussion

It has been reported that the contractions induced by norepinephrine (NE) and serotonin in the isolated aorta and mesenteric artery of the guinea pig are mainly caused by activation of α_1-adrenergic receptors and 5-HT_2-receptors, respectively.[18)] Therefore, the antagonist effects of the compounds on α_1-adrenergic receptors and 5-HT_2-receptors were evaluated in terms of the ability to block 10^{-5} M NE-induced contractions and 10^{-5} M serotonin-induced contractions of isolated guinea pig arteries, respectively. α_1- and 5-HT_2-receptor blocking activities of each compound were compared with those of doxazosin and ketanserin.

Initially, we investigated the effects of the amine moieties at the 7-position side-chain of 1-methyl-4-keto-pyrroloazepine derivatives on both activities. The results of this study are shown in Table 1. Compound **13a**, having the same amine moiety as ketanserin, exhibited less potent α_1- and 5-HT_2-receptor blocking activities than ketanserin, in contrast to the case of 1-aminoalkylpyrroloazepine derivatives.[1)] While the compounds with 4-(4-fluorophenoxypiperidine) (**13b**), 4-phenylpiperidine (**13c**) and 1-phenylpiperazine (**13d**) did not show sufficient α_1-adrenoceptor blocking activity, compounds **13e** and **13h** had α_1-adrenoceptor blocking activity almost similar to that of ketanserin. In contrast to compound **13e**, a shift of the methoxy substituent from the *o*-position to the *m*- or *p*-position led to loss of α_1-blocking activity (**13f**, **13g**). This result is in agreement with previous studies suggesting that the introduction of an *o*-methoxy group on the phenylpiperazine moiety gives the highest affinity for the α_1-adrenoceptor.[19)] Some of the compounds with arylpiperazine (**13d**, **13h**, **13i**) showed considerable 5-HT_2-receptor blocking activity. Among compounds **13a**—**i**, the



a) i) NaH, ii) X-$(CH_2)_n$-X; b) R_2R_3NH, K_2CO_3 or $NaHCO_3$, (NaI); c) i) NaH, ii) Cl$(CH_2)_nNR_2R_3$; d) $NaBH_4$; e) MsCl, Et_3N; f) $NH_2OH \cdot HCl$, AcONa.

Chart 2

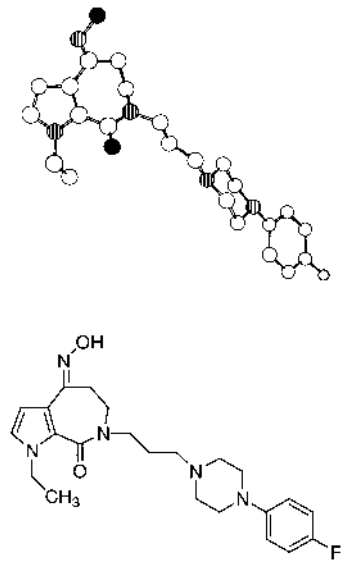


Fig. 2. Molecular Structure of Compound **16d** as Determined by X-Ray Crystallography

compound with 1-(4-fluorophenyl)piperazine at the amine moiety (**13h**) was preferable with regard to both activities.

In the next step, we investigated the effects of the various groups at the 4-position, maintaining the optimal amine moiety of **13h**. As shown in Table 2, both α_1- and 5-HT_2-receptor blocking activities were largely affected by the nature of this group. Introduction of the hydroxy group at the 4-position (**14**) resulted in marked enhancement of the 5-HT_2-receptor blocking activity, but the α_1-adrenoceptor blocking activity was almost completely abolished. Both α_1- and 5-HT_2-receptor blocking activities were slightly reduced in the 4,5-unsaturated compound (**15**) compared with **13h**. Introduction of an (*E*)-hydroxyimino group (**16a**) led to marked improvement of both α_1- and 5-HT_2-receptor blocking activities. These results revealed that α_1-adrenoceptor blocking activity might be related to the steric and/or electronic factors of the pyrroloazepine ring, and reduction in the electron density might be preferable to elicit potent α_1-blocking activity.

Next, the effects of the alkylene chain length (*n*) at the 7-position and the substituent at the 1-position of the 7-aminoalkylpyrroloazepine derivatives were examined. The results of this study are summarized in Table 3. The length of the alkyl side-chain between the pyrrolo[2,3-*c*]azepine ring system and 4-(4-fluorophenyl)piperazine moiety seemed to have little effect on α_1-adrenoceptor blocking activity, but to be an important factor for 5-HT_2-receptor blocking activity. The best result was obtained with $n=3$ (**16a**—**c**).

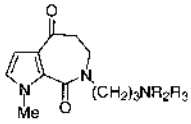
Subsequently, the effects of the substituent at the 1-position were investigated. No distinct relationship was observed between the alkyl group and 5-HT_2-receptor blocking activity. In contrast, introduction of a larger group such as a *n*-propyl (**16e**) or *n*-butyl (**16f**) group at this position resulted in a decrease in the α_1-adrenoceptor blocking activity, suggesting some steric effects around this position. The best result was obtained with compound **16d** with an ethyl group at the 1-position.

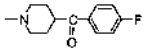
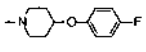
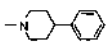
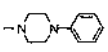
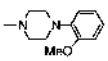
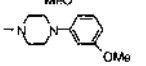
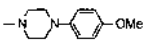
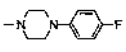
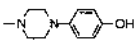
The α_1- and 5-HT_2-receptor blocking activities of compound **16d** in the isolated guinea pig artery were compared with those of reference compounds. The results are summarized in Table 4. Compound **16d** showed α_1-adrenoceptor blocking activity equivalent to that of doxazosin, and 2.5-fold stronger activity than ketanserin. In addition, compound **16d** showed approximately 1.8-fold 5-HT_2-receptor blocking activity in comparison with an active control, ketanserin. 7-Aminoalkylpyrrolo[2,3-*c*]azepine was characterized by more potent 5-HT_2-receptor blocking activity rather than α_1-adrenoceptor blocking activity, as compared with 1-aminoalkyl derivative, SUN9221.

In the 7-aminoalkylpyrrolo[2,3-*c*]azepine derivative series, (*E*)-1-ethyl-7-[3-[4-(4-fluorophenyl)piperazin-1-yl]propyl]-4-hydroxyimino-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepin-8-one (**16d**), which displayed both the potent α_1-adrenoceptor blocking activity of doxazosin as well as the potent 5-HT_2-receptor blocking action of ketanserin, was selected for further pharmacological evaluation.

Antihypertensive activity was evaluated by oral adminis-

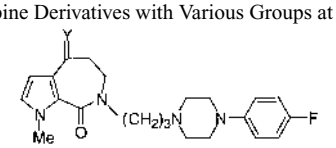
Table 1. α_1-Adrenergic- and 5-HT$_2$-Receptor Blocking Activities of Pyrrolo[2,3-*c*]azepine Derivatives with Various Amine Moieties



Compound	–NR$_2$R$_3$	α_1-blocking activity[a] (% inhibition)		5-HT$_2$-blocking activity[b] (% inhibition)	
		10^{-8} M	10^{-7} M	10^{-7} M	10^{-6} M
13a		2	27	24	60
13b		2	24	3	30
13c		1	15	8	62
13d		0	15	47	84
13e		6	41	7	28
13f		0	0	29	32
13g		0	0	NT[c]	12
13h		2	36	45	94
13i		0	7	28	83
1		3	78	5	3
3		3	47	93	100

a) % inhibition of 10^{-5} M norepinephrine-induced contraction in guinea pig aorta. *b*) % inhibition of 10^{-5} M serotonin-induced contraction in guinea pig mesenteric artery. *c*) Not tested.

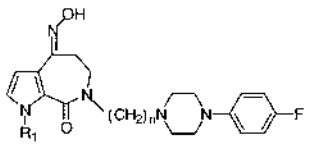
Table 2. α_1-Adrenergic- and 5-HT$_2$-Receptor Blocking Activities of Pyrrolo[2,3-*c*]azepine Derivatives with Various Groups at the 4-Position



Compound	Y	α_1-blocking activity[a] (% inhibition)		5-HT$_2$-blocking activity[b] (% inhibition)	
		10^{-8} M	10^{-7} M	10^{-7} M	10^{-6} M
13h	O	2	36	45	94
14	–OH, H	0	6	76	88
15	–H, $\Delta^{4,5}$	3	27	36	75
16a	(*E*)-NOH	10	60	75	94
1		3	78	5	3
3		3	47	93	100

a), *b*) See corresponding footnotes of Table 1.

Table 3. α_1-Adrenergic- and 5-HT$_2$-Receptor Blocking Activities of Pyrrolo[2,3-*c*]azepine Derivatives **16a**—**f**



Compound	R$_1$	*n*	α_1-blocking activity[a] (% inhibition)		5-HT$_2$-blocking activity[b] (% inhibition)	
			10^{-8} M	10^{-7} M	10^{-7} M	10^{-6} M
16a	Me	3	10	60	75	94
16b	Me	2	14	52	0	6
16c	Me	4	4	56	47	94
16d	Et	3	13	59	96	96
16e	*n*-Pr	3	3	26	75	94
16f	*n*-Bu	3	2	32	83	—[c]
1			3	78	5	3
3			3	47	93	100

a), *b*) See corresponding footnotes of Table 1. *c*) Data was not obtained, because the time of the effect was too long.

tration of **16d** and the reference compound to conscious deoxycorticosterone acetate (DOCA)-salt hypertensive dogs. The results are shown in Fig. 3. Oral administration of **16d** at doses of 1 and 3 mg/kg reduced the blood pressure in a dose-dependent manner (Fig. 3A). The hypotensive effect with changes of more than 20% lasted for longer than four hours after administration at a dose of 3 mg/kg. This effect was more potent than that by the same dose of doxazosin (Fig. 3B), and was almost equipotent to that produced by the same dose of ketanserin. In addition, at a lower dose of 1 mg/kg, compound **16d** induced a more potent hypotensive effect than ketanserin during the several hours after dosing (Fig. 3C).

Subsequently, the anti-thrombotic effects due to antiplatelet action were investigated. The results are shown in Fig. 4. In the acute pulmonary thromboembolic death model by intravenously injected collagen and serotonin in mice,[20] **16d** inhibited the mortality rate dose-dependently by oral administration at doses of 0.3 mg/kg or more, one hour before

Table 4. α_1-Adrenergic- and 5-HT_2-Receptor Blocking Activities of **16d** and Reference Compounds in Isolated Guinea Pig Arteries[a)]

Compound	α_1-blocking activity[b)]		5-HT_2-blocking activity[c)]	
	pA_2	Slope	pA_2	Slope
16d	7.83±0.20	0.94±0.09	9.47±0.17	1.36±0.08
1	7.81±0.20	1.23±0.18	<5	—
3	7.44±0.20	0.98±0.16	9.21±0.23	1.46±0.17
SUN 9221 (**6**)	8.98±0.21	0.98±0.04	8.74±0.22	1.18±0.20

a) Each value indicates the mean±S.E. of pA_2 value and slope value, determined from Schild plots of more than three experiments. *b*) Determined by antagonism of norepinephrine-induced contraction in mesenteric arteries. *c*) Determined by antagonism of serotonin-induced contraction in femoral arteries.

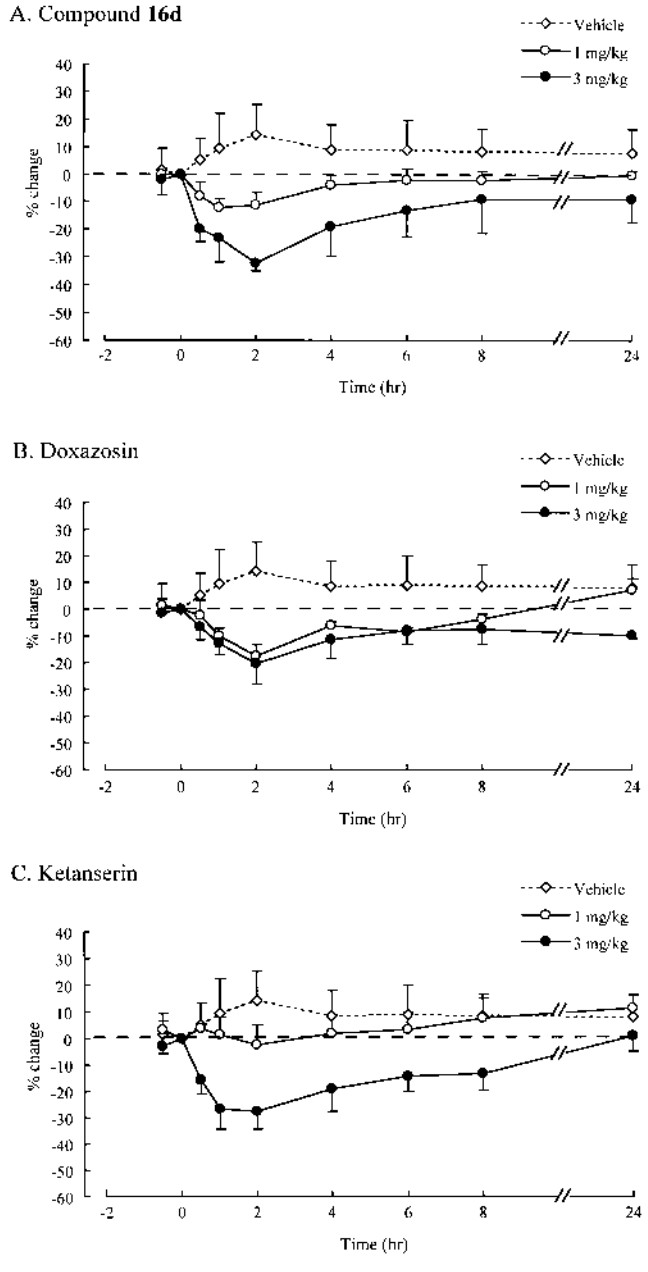


Fig. 3. Antihypertensive Effects of Compound **16d** in Conscious DOCA-salt Hypertensive Dogs

(A) Effects of oral administration of **16d** (1, 3 mg/kg) and vehicle on mean blood pressure. (B) Effects of oral administration of doxazosin (1, 3 mg/kg) and vehicle on mean blood pressure. (C) Effects of oral administration of ketanserin (1, 3 mg/kg) and vehicle on mean blood pressure. Each value indicates the mean±S.E. percent change in blood pressure relative to the control just before drug application in three dogs for compound **16d** and four dogs for doxazosin, ketanserin and vehicle.

induction of platelet aggregation, and its effect was almost equipotent to that of the same doses of ketanserin. In addition, prazosin and ticlopidine at doses of 10 and 30 mg/kg did not show a marked inhibitory effect, while aspirin showed an inhibitory effect only at a high dose of 100 mg/kg. Even 6 hours after the administration of 3 mg/kg of compound **16d**, the mortality rate was markedly decreased to 20%.

In conclusion, some of the 7-aminoalkylpyrrolo[2,3-*c*]azepine derivatives exhibited α_1- and 5-HT_2-receptor blocking activities. Introduction of various substituents at the 4-position of the pyrrolo[2,3-*c*]azepine ring significantly affected both activities, with compounds containing an (*E*)-hydroxyimino group showing the greatest activity. Compound **16d** displayed both α_1-adrenoceptor blocking activity ($pA_2=7.83\pm0.20$) and 5-HT_2-receptor blocking activity ($pA_2=9.47\pm0.17$) in an *in vitro* assay. At 3 mg/kg oral administration, this compound also exhibited more potent antihypertensive activity than doxazosin in DOCA-salt hypertensive dogs, as well as showing a potent antiplatelet aggregation effect on pulmonary thromboembolic death in mice. These results indicated that the pyrrolo[2,3-*c*]azepine ring system is a useful component for eliciting potent α_1-adrenoceptor blocking activity as well as 5-HT_2-receptor blocking activity.

Evaluation of effectiveness in various cardiovascular disease models and the side effect profile of these compounds is necessary to facilitate further development.

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 are expressed in δ (ppm) values with tetramethylsilane as an internal standard. IR spectra were recorded on a Hitachi 260-10 or 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 or obtained at the Analytical Center of Tokyokasei Kogyo Co. Ltd. at Tokyo, Japan.

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: 1-(4-hydroxyphenyl)piperazine hydrobromide[21]; 1-(2-chloroethyl)-4-(4-fluorophenyl)piperazine[22]; 1-(3-chloropropyl)-4-(4-fluorophenyl)piperazine[22]; 4-(4-fluorophenoxy)piperidine hydrochloride.[23] Methyl pyrrole-2-carboxylate was prepared according to a procedure similar to that described in the literature.[24]

1-Ethylpyrrole-2-carboxylic Acid (7b) i) The method of Guida and Mathre[25] was employed with minor modification. To a stirred suspension of potassium *tert*-butoxide (17.5 g, 156 mmol) and 18-crown-6 (3.44 g, 13 mmol) in Et_2O (250 ml) was added a solution of methyl pyrrole-2-carboxylate (16.3 g, 130 mmol) in Et_2O (20 ml) at 0 °C. To the resultant suspension was added dropwise a solution of EtI (30.4 g, 195 mmol) in Et_2O (30 ml) under vigorous stirring and ice-cooling, followed by stirring at room temperature for 17 h. The reaction mixture was poured into 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 (bp_{38} 113.0—116.0 °C) to afford methyl 1-ethylpyrrole-2-carboxylate (18.3 g, 92%) as a colorless oil. This material was immediately used in the next step without further purification. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (3H, t, J=7.3 Hz), 3.81 (3H, s), 4.36 (2H, q, J=7.3 Hz), 6.12 (1H, m), 6.86 (1H, t, J=2.0 Hz), 6.94 (1H, m).

ii) A mixture of methyl 1-ethylpyrrole-2-carboxylate (18.0 g, 118 mmol)

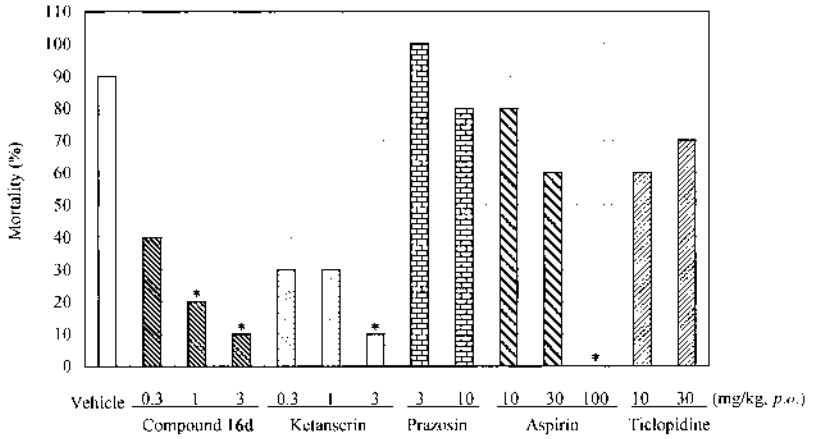


Fig. 4. Effects of Compound **16d**, Ketanserin, Prazosin, Aspirin and Ticlopidine on Pulmonary Thromboembolic Death in Mice

Each column indicates the mortality rate due to pulmonary embolism induced by intravenous administration of collagen (1 mg/kg) and serotonin (5 mg/kg) one hour after oral administration of test drugs. *, $p<0.05$ *vs.* vehicle group (Fisher's exact test). $n=10$ per each group.

and 2 N NaOH (118 ml) was stirred at 60 °C for 11 h, and then cooled down to 0 °C. The reaction mixture was acidified with 6 N HCl under ice-cooling, saturated with NaCl, and extracted with EtOAc (200 ml, 2×100 ml). The combined extracts were washed with brine (100 ml), dried, and concentrated to give **7b** as a solid (15.2 g, 93%). The material was sufficiently pure to be used without further purification in the next step. An analytical sample was obtained by recrystallization. mp 79.0—81.0 °C (hexane) (lit.,[26] 80—81 °C). IR (KBr): 3200—2800, 1672, 1534 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, t, J=7.2 Hz), 4.36 (2H, q, J=7.2 Hz), 6.16 (1H, dd, J=2.1, 3.9 Hz), 6.92 (1H, t, J=2.1 Hz), 7.11 (1H, dd, J=2.1, 3.9 Hz), 11.50 (1H, br s).

1-Methyl-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepine-4,8-dione (10a) i) To a stirred solution of **7a** (38.9 g, 311 mmol) and β-alanine benzyl ester *p*-toluenesulfonate (131 g, 373 mmol) in *N*,*N*-dimethylformamide (DMF) (400 ml) at 0 °C were added dropwise and successively a solution of DEPC (60.9 g, 373 mmol) in DMF (50 ml) and a solution of Et_3N (75.5 g, 746 mmol) in DMF (150 ml). After stirring at room temperature for 19 h, the reaction mixture was concentrated. The residue was dissolved in EtOAc–benzene (3 : 1 v/v, 1 l), washed successively with saturated K_2CO_3, water, 5% HCl, water and brine (500 ml each). The organic layer was dried and concentrated to give a solid, which was recrystallized from EtOAc–diisopropyl ether (IPE) to afford benzyl 3-[2-(1-methylpyrrole)carboxamido]propionate (**8a**) (80.9 g, 91%) as colorless crystals. mp 61.0—62.0 °C. IR (KBr): 3324, 1736, 1633, 1552, 1519 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.66 (2H, t, J=6.0 Hz), 3.64 (2H, q, J=6.0 Hz), 3.91 (3H, s), 5.14 (2H, s), 6.05 (1H, m), 6.42—6.52 (2H, m), 6.69 (1H, m), 7.30—7.40 (5H, m). *Anal.* Calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78. Found: C, 67.16; H, 6.34; N, 9.77.

ii) A suspension of **8a** (40.0 g, 140 mmol) and 5% Pd/C (2.00 g, 5% wt eq) in tetrahydrofuran (THF) (600 ml) was vigorously stirred under an atmosphere of hydrogen for 15 h at room temperature. The catalyst was filtered through Celite and washed thoroughly with THF. The combined filtrate and washings were concentrated to give a solid, which was recrystallized from EtOAc to afford 3-[2-(1-methylpyrrole)carboxamido]propionic acid (**9a**) (26.0 g, 95%) as colorless crystals. mp 131.0—132.5 °C. IR (KBr): 3399, 3200—2800, 1720, 1595, 1558, 1516 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.48 (2H, m), 3.37 (2H, m), 3.82 (3H, s), 5.99 (1H, m), 6.73 (1H, m), 6.87 (1H, m), 8.02 (1H, m), 12.23 (1H, br s). *Anal.* Calcd for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.16; N, 14.28. Found: C, 55.20; H, 6.16; N, 14.22.

iii) A mixture of **9a** (23.2 g, 118 mmol) and approximately 80% PPA (1.15 kg) was mechanically stirred at 100 °C for 30 min. The reaction mixture was poured into ice-water, and the pH of the solution was adjusted to 5 with NaOH. The precipitate was collected and washed with water. The filtrate was saturated with NaCl, and extracted with THF (3×500 ml). The extracts were washed with brine, dried, and concentrated to give a solid. The combined precipitate and solid were purified by column chromatography (eluent, $CHCl_3$: MeOH=97 : 3) to give a solid, which was recrystallized from $CHCl_3$–IPE to afford **10a** (17.9 g, 85%) as colorless crystals. mp 196.0—198.0 °C. IR (KBr): 3336, 1634, 1530 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.83 (2H, m), 3.53 (2H, m), 3.97 (3H, s), 6.29 (1H, br s), 6.73 (1H, d, J=2.6 Hz), 6.79 (1H, d, J=2.6 Hz). *Anal.* Calcd for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.70; H, 5.62; N, 15.70.

Compound **10b** was synthesized from **7b** using the 3-step procedure described above.

1-Ethyl-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepine-4,8-dione (**10b**): 63% overall yield, colorless crystals, mp 156.5—157.5 °C (EtOAc–IPE). IR (KBr): 3275, 1643, 1528 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (3H, t, J=7.3 Hz), 2.83 (2H, m), 3.53 (2H, m), 4.41 (2H, q, J=7.3 Hz), 6.35 (1H, br s), 6.74 (1H, d, J=2.6 Hz), 6.86 (1H, d, J=2.6 Hz). *Anal.* Calcd for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.57. Found: C, 62.58; H, 6.29; N, 14.55.

1-*n*-Propyl-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepine-4,8-dione (10c) A suspension of **11**[1] (1.64 g, 10 mmol), 1-iodopropane (5.10 g, 30 mmol) and K_2CO_3 (4.15 g, 30 mmol) in 2-butanone (50 ml) was stirred under reflux. After 16 h, 1-iodopropane (3.40 g, 20 mmol) was added and the resultant mixture was stirred under reflux for an additional 7 h. The reaction mixture was filtered, the residue was washed with EtOAc, and the combined filtrate and washings were concentrated. The residue was purified by column chromatography (eluent, EtOAc : hexane=2 : 1) to afford **10c** (1.82 g, 88%). An analytical sample was obtained by recrystallization. mp 68.0—69.0 °C (EtOAc–IPE), colorless crystals. IR (KBr): 3202, 1655, 1526 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, t, J=7.3 Hz), 1.83 (2H, m), 2.82 (2H, m), 3.53 (2H, m), 4.34 (2H, t, J=7.3 Hz), 6.72 (1H, d, J=2.6 Hz), 6.84 (1H, d, J=2.6 Hz), 7.15 (1H, br s). *Anal.* Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.13; H, 6.86; N, 13.58.

Compound **10d** was prepared similarly.

1-*n*-Butyl-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepine-4,8-dione (**10d**): 91% yield, colorless crystals, mp 63.0—64.5 °C (EtOAc–IPE). IR (KBr): 3208, 1660, 1530 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, t, J=7.3 Hz), 1.34 (2H, m), 1.78 (2H, m), 2.82 (2H, m), 3.53 (2H, m), 4.36 (2H, t, J=7.3 Hz), 6.72 (1H, d, J=2.9 Hz), 6.84 (1H, d, J=2.9 Hz), 6.88 (1H, br s). *Anal.* Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.44; H, 7.35; N, 12.71.

7-(3-Chloropropyl)-1-methyl-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]-azepine-4,8-dione (12a) To a stirred suspension of NaH (3.00 g of a 60% oil dispersion, 75 mmol) in DMF (250 ml) was added a solution of **10a** (13.4 g, 75 mmol) in DMF (125 ml) at 0 °C, and stirring was continued at 0 °C for 30 min and then at room temperature for 2 h. A solution of 1,3-dichloropropane (33.9 g, 300 mmol) in DMF (125 ml) was added to the reaction mixture at 0 °C and stirring was continued at room temperature for 16 h. The reaction mixture was concentrated, and the residue was diluted with 10% citric acid (200 ml) and extracted with EtOAc (2×700 ml). The combined extracts were washed with brine, dried, and concentrated to give an oil, which was purified by column chromatography (eluent, EtOAc : hexane=1 : 1) to afford **12a** (10.9 g, 57%). An analytical sample was obtained by recrystallization. mp 78.5—80.0 °C (IPE), colorless crystals. IR (KBr): 1658, 1638, 1492 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.15 (2H, m), 2.79 (2H, m), 3.63 (2H, t, J=6.3 Hz), 3.66—3.85 (4H, m), 3.93 (3H, s), 6.64 (1H, d, J=3.0 Hz), 6.75 (1H, d, J=3.0 Hz). *Anal.* Calcd for $C_{12}H_{15}ClN_2O_2$: C, 56.58; H, 5.94; N, 11.00. Found: C, 56.77; H, 5.81; N, 10.85.

Compound **12b** was similarly prepared from **10a** and 1,4-dibromobutane.

7-(4-Bromobutyl)-1-methyl-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepine-4,8-dione (**12b**): 58% yield, colorless crystals, mp 78.0—79.5 °C

(EtOAc–IPE). IR (KBr): 1657, 1630, 1526, 1492 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.82 (2H, m), 1.94 (2H, m), 2.80 (2H, m), 3.48 (2H, t, J=6.4 Hz), 3.64 (2H, t, J=7.2 Hz), 3.69 (2H, m), 3.93 (3H, s), 6.64 (1H, d, J=2.8 Hz), 6.75 (1H, d, J=2.8 Hz). *Anal.* Calcd for $C_{13}H_{17}BrN_2O_2$: C, 49.85; H, 5.47; N, 8.94. Found: C, 49.96; H, 5.31; N, 8.76.

7-[3-[4-(4-Fluorobenzoyl)piperidino]propyl]-1-methyl-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepine-4,8-dione (13a) A mixture of chloride **12a** (254 mg, 1 mmol), 4-(4-fluorobenzoyl)piperidine hydrochloride (4-FBP·HCl) (244 mg, 1 mmol), $NaHCO_3$ (336 mg, 4 mmol) and NaI (300 mg, 2 mmol) in CH_3CN (25 ml) was stirred under reflux for 14 h. After evaporation of the solvent, the residue was diluted with half-saturated K_2CO_3 (50 ml), and then extracted with $CHCl_3$ (3×50 ml). The combined extracts were washed with brine, dried, and concentrated to give an oil, which was purified by column chromatography (eluent, $CHCl_3$: MeOH=93 : 7) to afford **13a** (402 mg, 94%) as a pale brown oil. IR (film): 1676, 1661, 1632, 1597, 1491 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.75—1.95 (6H, m), 2.13 (2H, m), 2.45 (2H, t, J=7.3 Hz), 2.80 (2H, m), 3.01 (2H, m), 3.21 (1H, m), 3.63 (2H, t, J=7.3 Hz), 3.71 (2H, m), 3.93 (3H, s), 6.64 (1H, d, J=2.8 Hz), 6.74 (1H, d, J=2.8 Hz), 7.14 (2H, t, J=8.6 Hz), 7.98 (2H, m). HR-FAB-MS Calcd for $C_{24}H_{29}FN_3O_3$ $[MH]^+$ 426.2193. Found 426.2177.

Compounds **13f** and **13g** were similarly synthesized from **12a** (1 eq), $NaHCO_3$ (6 eq) and NaI (2 eq) with 1-(3-methoxyphenyl)piperazine dihydrochloride (1 eq) and 1-(4-methoxyphenyl)piperazine succinate (1 eq), respectively. Compounds **13h** and **13k** were similarly synthesized from **12a** (1 eq) and **12b** (1 eq), respectively, with 1-(4-fluorophenyl)piperazine (1.5 eq), K_2CO_3 (1.5 eq) and NaI (2 eq). Compound **13i** was prepared by the same manner as described for **13a**, except that 1-(4-hydroxyphenyl)piperazine·HBr was used instead of 4-FBP·HCl.

7-[3-[4-(3-Methoxyphenyl)piperazin-1-yl]propyl]-1-methyl-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepine-4,8-dione (**13f**): 84% yield, colorless oil. IR (film): 1661, 1633, 1493 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.90 (2H, quintet, J=7.3 Hz), 2.49 (2H, t, J=7.3 Hz), 2.62 (4H, m), 2.79 (2H, m), 3.21 (4H, m), 3.65 (t, J=7.3 Hz) and 3.70 (m) (total 4H), 3.79 (3H, s), 3.93 (3H, s), 6.42 (1H, dd, J=1.9, 7.9 Hz), 6.46 (1H, m), 6.53 (1H, dd, J=1.9, 7.9 Hz), 6.64 (1H, d, J=2.7 Hz), 6.74 (1H, d, J=2.7 Hz), 7.17 (1H, t, J=7.9 Hz). HR-FAB-MS Calcd for $C_{23}H_{31}N_4O_3$ $[MH]^+$ 411.2396. Found 411.2411.

7-[3-[4-(4-Methoxyphenyl)piperazin-1-yl]propyl]-1-methyl-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepine-4,8-dione (**13g**): 91% yield, colorless oil. IR (KBr): 1657, 1623, 1515 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.89 (2H, m), 2.48 (2H, m), 2.62 (4H, m), 2.80 (2H, m), 3.10 (4H, m), 3.65 (2H, t, J=7.3 Hz), 3.71 (2H, m), 3.76 (3H, s), 3.93 (3H, s), 6.64 (1H, d, J=2.7 Hz), 6.73 (1H, d, J=2.7 Hz), 6.84 (2H, m), 6.90 (2H, m). *Anal.* Calcd for $C_{23}H_{30}N_4O_3$: C, 67.29; H, 7.37; N, 13.65. Found: C, 67.43; H, 7.41; N, 13.62.

7-[3-[4-(4-Fluorophenyl)piperazin-1-yl]propyl]-1-methyl-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepine-4,8-dione (**13h**): 95% yield, colorless crystals, mp 123.0—124.0 °C (EtOAc–IPE). IR (KBr): 1653, 1635 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.89 (2H, quintet, J=7.3 Hz), 2.48 (2H, t, J=7.3 Hz), 2.62 (4H, m), 2.80 (2H, m), 3.13 (4H, m), 3.65 (2H, t, J=7.3 Hz), 3.71 (2H, m), 3.94 (3H, s), 6.64 (1H, d, J=2.7 Hz), 6.75 (1H, d, J=2.7 Hz), 6.84—6.92 (2H, m), 6.93—7.00 (2H, m). *Anal.* Calcd for $C_{22}H_{27}FN_4O_2$: C, 66.31; H, 6.83; N, 14.06. Found: C, 66.33; H, 6.79; N, 14.14.

7-[3-[4-(4-Hydroxyphenyl)piperazin-1-yl]propyl]-1-methyl-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepine-4,8-dione (**13i**): 72% yield, colorless crystals, mp 155.5—156.5 °C (EtOAc–hexane). IR (KBr): 3530, 1640, 1616 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.86 (2H, t, J=7.3 Hz), 2.48 (2H, t, J=7.3 Hz), 2.62 (4H, m), 2.80 (2H, m), 3.08 (4H, m), 3.64 (2H, t, J=7.3 Hz), 3.69 (2H, m), 3.93 (3H, s), 6.64 (1H, d, J=3.3 Hz), 6.71—6.89 (5H, m). *Anal.* Calcd for $C_{22}H_{28}N_4O_3$: C, 66.64; H, 7.12; N, 14.13. Found: C, 66.34; H, 7.12; N, 13.99.

7-[4-[4-(4-Fluorophenyl)piperazin-1-yl]butyl]-1-methyl-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepine-4,8-dione (**13k**): 100% yield, colorless crystals, mp 137.0—138.5 °C (EtOAc–IPE). IR (KBr): 1660, 1634, 1509 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.60 (2H, m), 1.72 (2H, m), 2.45 (2H, t, J=7.3 Hz), 2.60 (4H, m), 2.79 (2H, m), 3.12 (4H, m), 3.62 (2H, t, J=7.3 Hz), 3.68 (2H, m), 3.93 (3H, s), 6.64 (1H, d, J=2.8 Hz), 6.73 (1H, d, J=2.8 Hz), 6.83—6.91 (2H, m), 6.92—6.99 (2H, m). *Anal.* Calcd for $C_{23}H_{29}FN_4O_2$: C, 66.97; H, 7.09; N, 13.58. Found: C, 67.00; H, 7.00; N, 13.57.

7-[3-(4-Phenylpiperazin-1-yl)propyl]-1-methyl-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepine-4,8-dione (13d) A suspension of **12a** (1.05 g, 4.12 mmol), 1-phenylpiperazine (2.01 g, 12.4 mmol) and K_2CO_3 (1.71 g, 12.4 mmol) in DMF (80 ml) was stirred at 80 °C for 10 h. The mixture was diluted with EtOAc–benzene (3 : 1 v/v, 400 ml), and washed successively with water (3×300 ml) and brine (300 ml). The organic layer was dried and concentrated to give an oil, which was purified by column chromatography (eluent, $CHCl_3$: MeOH=97 : 3) to afford **13d** (770 mg, 49%) as a pale yellow solid. An analytical sample was obtained by recrystallization. mp 116.5—118.0 °C (EtOAc), pale yellow crystals. IR (KBr): 1651, 1634 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.89 (2H, quintet, J=7.3 Hz), 2.47 (2H, t, J=7.3 Hz), 2.61 (4H, m), 2.79 (2H, m), 3.20 (4H, m), 3.59—3.78 (4H, m), 3.92 (3H, s), 6.63 (1H, d, J=3.3 Hz), 6.73 (1H, d, J=3.3 Hz), 6.84 (1H, t, J=7.3 Hz), 6.92 (2H, d, J=7.3 Hz), 7.25 (2H, t, J=7.3 Hz). *Anal.* Calcd for $C_{22}H_{28}N_4O_2$: C, 69.45; H, 7.42; N, 14.73. Found: C, 69.45; H, 7.54; N, 14.68.

Compounds **13b**, **13c** and **13e** were prepared similarly except that in the synthesis of **13b**, NaI (1 eq) was added.

7-[3-[4-(4-Fluorophenoxy)piperidino]propyl]-1-methyl-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepine-4,8-dione (**13b**): 66% yield, yellow oil, IR (film): 1661, 1633, 1504 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.69—2.05 (6H, m), 2.28 (2H, m), 2.43 (2H, t, J=7.3 Hz), 2.65—2.84 (4H, m), 3.62 (2H, t, J=7.3 Hz), 3.70 (2H, m), 3.92 (3H, s), 4.21 (1H, m), 6.61 (1H, d, J=3.3 Hz), 6.74 (1H, d, J=3.3 Hz), 6.78—6.90 (2H, m), 6.94 (2H, t, J=8.6 Hz). HR-FAB-MS Calcd for $C_{23}H_{29}FN_3O_3$ $[MH]^+$ 414.2193. Found 414.2195.

1-Methyl-7-[3-(4-phenylpiperidino)propyl]-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepine-4,8-dione (**13c**): 34% yield, colorless oil, IR ($CHCl_3$): 1655, 1625, 1485 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.75—2.00 (6H, m), 2.10 (2H, m), 2.48 (t, J=7.3 Hz) and 2.63 (m) (total 3H), 2.80 (2H, m), 3.08 (2H, m), 3.65 (t, J=7.3 Hz) and 3.71 (m) (total 4H), 3.93 (3H, s), 6.64 (1H, d, J=2.7 Hz), 6.74 (1H, d, J=2.7 Hz), 7.15—7.35 (5H, m). HR-FAB-MS Calcd for $C_{23}H_{30}N_3O_2$ $[MH]^+$ 380.2338. Found 380.2358.

7-[3-[4-(2-Methoxyphenyl)piperazin-1-yl]propyl]-1-methyl-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepine-4,8-dione (**13e**): 29% yield, colorless oil. IR ($CHCl_3$): 1660, 1635, 1495 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.92 (2H, quintet, J=7.3 Hz), 2.53 (2H, t, J=7.3 Hz), 2.70 (4H, m), 2.80 (2H, m), 3.12 (4H, m), 3.65 (t, J=7.3 Hz) and 3.70 (m) (total 4H), 3.86 (3H, s), 3.93 (3H, s), 6.64 (1H, d, J=2.7 Hz), 6.74 (1H, d, J=2.7 Hz), 6.80—7.05 (4H, m). HR-FAB-MS Calcd for $C_{23}H_{31}N_4O_3$ $[MH]^+$ 411.2396. Found 411.2404.

7-[3-[4-(4-Fluorophenyl)piperazin-1-yl]propyl]-4-hydroxy-1-methyl-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepin-8-one (14) To a stirred solution of **13h** (1.00 g, 2.5 mmol) in EtOH (50 ml) was added portionwise $NaBH_4$ (836 mg, 22.1 mmol) at 0 °C, and stirring was continued at 0 °C for 1 h and at room temperature for 18 h. Water (50 ml) was added, and the resulting mixture was stirred at room temperature for 2 h. After evaporation of the solvent, the residue was taken up in EtOAc (150 ml), washed with water and brine (50 ml each), dried, and concentrated. The residue was purified by column chromatography (eluent, $CHCl_3$: MeOH=19 : 1) to afford **14** (906 mg, 90%). An analytical sample was obtained by recrystallization. mp 133.5—134.5 °C (EtOAc), colorless crystals. IR (KBr): 3500—3200, 1601, 1508, 1495 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.85 (2H, quintet, J=7.3 Hz), 2.03—2.31 (3H, m), 2.47 (2H, dt, J=2.0, 7.3 Hz), 2.63 (4H, m), 3.12 (4H, m), 3.35 (1H, ddd, J=3.3, 7.3, 14.9 Hz), 3.48—3.63 (3H, m), 3.87 (3H, s), 4.91 (1H, t, J=5.3 Hz), 6.16 (1H, d, J=2.6 Hz), 6.71 (1H, d, J=2.6 Hz), 6.82—7.03 (4H, m). *Anal.* Calcd for $C_{22}H_{29}FN_4O_2$: C, 65.98; H, 7.30; N, 13.99. Found: C, 65.96; H, 7.29; N, 14.03.

7-[3-[4-(4-Fluorophenyl)piperazin-1-yl]propyl]-1-methyl-1,6,7,8-tetrahydropyrrolo[2,3-*c*]azepin-8-one (15) To a stirred solution of **14** (300 mg, 0.75 mmol) and Et_3N (759 mg, 7.5 mmol) in CH_2Cl_2 (25 ml) was added dropwise a solution of methanesulfonyl chloride (172 mg, 1.5 mmol) in CH_2Cl_2 (5 ml) at 0 °C, and stirring was continued at 0 °C for 30 min and at room temperature for 24 h. The mixture was diluted with CH_2Cl_2 (30 ml), washed with saturated $NaHCO_3$, water and brine (30 ml each), dried and concentrated. The residue was purified by column chromatography (eluent, $CHCl_3$: MeOH=19 : 1) to afford **15** (270 mg, 94%). An analytical sample was obtained by recrystallization. mp 85.5—86.5 °C (EtOAc–IPE), colorless crystals. IR (KBr): 1615, 1514, 1495 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.82 (2H, quintet, J=7.3 Hz), 2.42 (2H, t, J=7.3 Hz), 2.59 (4H, m), 3.12 (4H, m), 3.59 (2H, t, J=7.3 Hz), 3.69 (2H, d, J=6.5 Hz), 3.96 (3H, s), 5.94 (1H, m), 6.09 (1H, d, J=2.5 Hz), 6.72—6.78 (2H, m), 6.86 (2H, m), 6.95 (2H, t, J=8.6 Hz). *Anal.* Calcd for $C_{22}H_{27}FN_4O$: C, 69.09; H, 7.12; N, 14.65. Found: C, 69.04; H, 7.16; N, 14.65.

(*E*)-7-[3-[4-(4-Fluorophenyl)piperazin-1-yl]propyl]-4-hydroxyimino-1-methyl-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepin-8-one (16a) and (*Z*)-7-[3-[4-(4-Fluorophenyl)piperazin-1-yl]propyl]-4-hydroxyimino-1-methyl-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepin-8-one (16a′) A solution of **13h** (398 mg, 1 mmol), hydroxylamine hydrochloride (139 mg, 2 mmol) and sodium acetate (164 mg, 2 mmol) in MeOH (15 ml) was stirred under reflux for 16 h. After evaporation of the solvent, the residue was diluted with half-saturated K_2CO_3 (40 ml), and then extracted with $CHCl_3$ (2×40 ml). The combined extracts were washed with brine, dried, and concentrated to give an oil, which contained **16a** (*Rf* 0.40, $CHCl_3$: MeOH=9 : 1) for the

most part and a trace amount of its isomer (**16a′**) (*Rf* 0.27, $CHCl_3$: MeOH= 9 : 1). The mixture was subjected to column chromatography (eluent; EtOAc : MeOH = 9 : 1) to give (*E*)-oxime (**16a**) (382 mg, 92%) as a colorless solid from the first fraction. The second fraction yielded (*Z*)-oxime (**16a′**) (8.1 mg, 2%). **16a**; mp 167.5—169.5 °C (EtOH), colorless crystals. IR (KBr): 3450—3200, 1610, 1597, 1508 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.89 (2H, quintet, *J*=7.3 Hz), 2.48 (2H, t, *J*=7.3 Hz), 2.65 (4H, m), 2.98 (2H, m), 3.13 (4H, m), 3.50—3.63 (4H, m), 3.87 (3H, s), 6.33 (1H, d, *J*=2.6 Hz), 6.67 (1H, d, *J*=2.6 Hz), 6.82—7.03 (4H, m), 9.54 (1H, br s). *Anal.* Calcd for $C_{22}H_{28}FN_5O_2$: C, 63.90; H, 6.83; N, 16.94. Found: C, 63.75; H, 6.94; N, 16.97. **16a′**; pale yellow oil. IR (film): 3450—3100, 1622, 1510 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.89 (2H, m), 2.48 (2H, m), 2.65 (4H, m), 2.84 (2H, m), 3.14 (4H, m), 3.50—3.68 (4H, m), 3.88 (3H, s), 6.76 (1H, d, *J*=2.7 Hz), 6.87 (2H, m), 6.95 (2H, m), 7.10 (1H, d, *J*=2.7 Hz), 9.05 (1H, br s). HR-FAB-MS Calcd for $C_{22}H_{29}FN_5O_2$ $[MH]^+$ 414.2305. Found 414.2311.

Compound **16c** was similarly synthesized from **13k**.

(*E*)-7-[4-[4-(4-Fluorophenyl)piperazin-1-yl]butyl]-4-hydroxyimino-1-methyl-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepin-8-one (**16c**): 94% yield, colorless crystals, mp 186.0—187.5 °C (EtOH). IR (KBr): 3000—2600, 1627, 1511 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.52—1.75 (4H, m), 2.45 (2H, t, *J*=7.3 Hz), 2.60 (4H, m), 2.95 (2H, m), 3.13 (4H, m), 3.50—3.58 (4H, m), 3.87 (3H, s), 6.36 (1H, d, *J*=2.8 Hz), 6.68 (1H, d, *J*=2.8 Hz), 6.82—6.90 (2H, m), 6.91—6.99 (2H, m), 8.36 (1H, br s). *Anal.* Calcd for $C_{23}H_{30}FN_5O_2$: C, 64.62; H, 7.07; N, 16.38. Found: C, 64.64; H, 7.04; N, 16.41.

(*E*)-1-Ethyl-7-[3-[4-(4-fluorophenyl)piperazin-1-yl]propyl]-4-hydroxyimino-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepin-8-one (16d) i) To a stirred suspension of NaH (1.52 g of 60% oil dispersion, 38 mmol) in DMF (50 ml) was added dropwise a solution of **10b** (6.04 g, 31 mmol) in DMF (90 ml) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and at 40 °C for 1.5 h, and then cooled again to 0 °C. A solution of 1-(3-chloropropyl)-4-(4-fluorophenyl)piperazine (12.1 g, 47 mmol) in DMF (60 ml) was added to the reaction mixture at 0 °C, and stirring was continued at room temperature for 23 h. After evaporation of the solvent, the residue was diluted with half-saturated K_2CO_3 (200 ml), and then extracted with EtOAc (2×250 ml). The combined extracts were washed with brine, dried, and concentrated. The residue was subjected to column chromatography (eluent, EtOAc, then $CHCl_3$: MeOH = 97 : 3) to afford 1-ethyl-7-[3-[4-(4-fluorophenyl)piperazin1-yl]propyl]-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepine-4,8-dione (**13l**) (10.6 g) as a yellow oil. This material was used immediately in the next step without further purification. An analytical sample was obtained by further purification by column chromatography (eluent, $CHCl_3$: MeOH = 97 : 3). IR (film): 1660, 1631, 1509, 1486 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.44 (3H, t, *J*=7.2 Hz), 1.89 (2H, quintet, *J*=7.3 Hz), 2.48 (2H, t, *J*=7.3 Hz), 2.62 (4H, m), 2.79 (2H, m), 3.12 (4H, m), 3.65 (2H, t, *J*=7.3 Hz), 3.71 (2H, m), 4.36 (2H, q, *J*=7.2 Hz), 6.65 (1H, d, *J*=2.8 Hz), 6.81 (1H, d, *J*=2.8 Hz), 6.87 (2H, m), 6.95 (2H, m). HR-FAB-MS Calcd for $C_{23}H_{30}FN_4O_2$ $[MH]^+$ 413.2353. Found 413.2358.

ii) Compound **13l** (10.6 g) was reacted with hydroxylamine hydrochloride (3.61 g, 52 mmol) and sodium acetate (4.27 g, 52 mmol) in MeOH (300 ml) in the same manner as described for the preparation of **16a** to afford **16d** (7.88 g, 59% overall yield from **10b**). mp 149.5—150.5 °C (EtOH), colorless crystals. IR (KBr): 2900—2600, 1631, 1511 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (3H, t, *J*=7.3 Hz), 1.89 (2H, m), 2.48 (2H, m), 2.64 (4H, m), 2.97 (2H, m), 3.16 (4H, m), 3.43—3.68 (4H, m), 4.29 (2H, t, *J*=7.3 Hz), 6.35 (1H, d, *J*=3.0 Hz), 6.75 (1H, d, *J*=3.0 Hz), 6.81—7.04 (4H, m), 9.13 (1H, br s). *Anal*. Calcd for $C_{23}H_{30}FN_5O_2$: C, 64.62; H, 7.07; N, 16.38. Found: C, 64.66; H, 7.08; N, 16.49.

Compounds **16b**, **16e** and **16f** were similarly prepared using the 2-step procedure described above, starting from **10a**, **10c** and **10d**, respectively. In the synthesis of **16b**, 1-(2-chloroethyl)-4-(4-fluorophenyl)piperazine was used instead of 1-(3-chloropropyl)-4-(4-fluorophenyl)piperazine.

(*E*)-7-[2-[4-(4-Fluorophenyl)piperazin-1-yl]ethyl]-4-hydroxyimino-1-methyl-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepin-8-one (**16b**): 23% overall yield from **10a**, colorless crystals, mp 149.5—150.5 °C (EtOH). IR (KBr): 2900—2600, 1619, 1509 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.66 (2H, t, *J*=6.6 Hz), 2.71 (4H, m), 3.01 (2H, m), 3.12 (4H, m), 3.59 (2H, m), 3.71 (2H, t, *J*=6.6 Hz), 3.87 (3H, s), 6.36 (1H, d, *J*=2.7 Hz), 6.69 (1H, d, *J*=2.7 Hz), 6.89 (2H, m), 6.95 (2H, m), 8.52 (1H, br s). *Anal.* Calcd for $C_{21}H_{26}FN_5O_2$: C, 63.14; H, 6.56; N, 17.53. Found: C, 62.96; H, 6.57; N, 17.26.

(*E*)-7-[3-[4-(4-Fluorophenyl)piperazin-1-yl]propyl]-4-hydroxyimino-1-*n*-propyl-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepin-8-one (**16e**): 51% overall yield from **10c**, colorless crystals, mp 153.5—154.5 °C (EtOAc–hexane). IR (KBr): 3450—3200, 1601, 1510 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, *J*=7.3 Hz), 1.76 (2H, m), 1.90 (2H, m), 2.49 (2H, m), 2.65 (4H, m), 2.97 (2H, m), 3.17 (4H, m), 3.50—3.65 (4H, m), 4.23 (2H, t, *J*=7.1 Hz), 6.33 (1H, d, *J*=2.7 Hz), 6.73 (1H, d, *J*=2.7 Hz), 6.89 (2H, m), 6.96 (2H, m), 9.39 (1H, br s). *Anal.* Calcd for $C_{24}H_{32}FN_5O_2$: C, 65.28; H, 7.30; N, 15.86. Found: C, 65.13; H, 7.42; N, 15.93.

(*E*)-1-*n*-Butyl-7-[3-[4-(4-fluorophenyl)piperazin-1-yl]propyl]-4-hydroxyimino-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepin-8-one (**16f**): 49% overall yield from **10d**, colorless crystals, mp 164.5—165.5 °C (EtOAc–hexane). IR (KBr): 3450—3200, 1600, 1509 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, t, *J*=7.3 Hz), 1.29 (2H, m), 1.74 (2H, m), 1.89 (2H, m), 2.48 (2H, m), 2.64 (4H, m), 2.97 (2H, m), 3.16 (4H, m), 3.50—3.65 (4H, m), 4.27 (2H, t, *J*=7.1 Hz), 6.33 (1H, d, *J*=2.8 Hz), 6.74 (1H, d, *J*=2.8 Hz), 6.90 (2H, m), 6.96 (2H, m), 9.10 (1H, br s). *Anal.* Calcd for $C_{25}H_{34}FN_5O_2$: C, 65.91; H, 7.52; N, 15.37. Found: C, 65.81; H, 7.60; N, 15.36.

X-Ray Crystallographic Analysis of 16d Diffraction measurements were performed on a Rigaku AFC-5R diffractometer using graphite monochromated CuK_α radiation (λ =1.54178 Å). Crystals of **16d** were grown from EtOH and subjected to crystallographic analysis when they were found to belong to the monoclinic space group $P2_1/a$ with the following unit cell parameters; a=17.028(2) Å, b=14.027(4) Å, c=9.902(2) Å, β =75.78(2)°, V=2292.4(8) Å^3, Z=4. The final *R*-factor and weighted *R*-factor were 0.111 and 0.128, respectively, based on 3590 refrections with $F>3\sigma(F)$.

α_1-Adrenergic and Serotonin (5-HT$_2$)-Receptor Antagonist Activity The functional α_1-adrenergic and serotonin (5-HT$_2$)-receptor antagonist activity against NE and serotonin, respectively, was determined in isolated guinea pig aorta and mesenteric artery, respectively. In brief, a male Hartley strain guinea pig was anesthetized with pentobarbital Na (50 mg/kg, i.p.) and sacrificed by decapitation. The aorta and mesenteric arterial bed 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 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 a 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 aortic or mesenteric arterial preparation was contracted continuously with NE (10^{-5} M) or transiently with serotonin (10^{-5} M), respectively. Test samples at final concentrations of 10^{-8} and 10^{-7} M were added under continuous contraction induced by NE or five minutes before transient contraction induced by serotonin. The functional α_1-adrenergic or serotonin (5-HT$_2$)-receptor antagonist activity against NE or serotonin was determined as the reduction in peak contraction using more than two preparations.

Regarding the selected compounds, the pA_2 values were determined to measure the potency of their antagonism of α_1- or 5-HT$_2$-receptors. In brief, cumulative concentration–response curves for NE or serotonin were constructed by the method of stepwise addition of the agonist, using helical strips of isolated mesenteric or femoral guinea pig arteries, respectively. NE or serotonin 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 NE or serotonin was obtained again. The pA_2 values were determined from Schild plots.

Measurement of Blood Pressure Male and female mongrel dogs, weighing about 10 kg, were anesthetized with pentobarbital Na (50 mg/kg, i.p.) and unilaterally nephrectomized under sterile conditions. From one week after the operation, the dogs were administered 25 mg/kg of DOCA subcutaneously once a week, and were given drinking water containing 0.5% potassium chloride and 0.5% saccharose to induce hypertension. Approximately one month after the nephrectomy, the dogs received implants into the abdominal artery *via* the left femoral artery to measure blood pressure. The blood pressure was measured with a telemetry system (Multitelemeter 511, Nihon Denki Sanei) under conscious, unrestricted conditions. Dogs with a mean blood pressure higher than 120 mmHg were used for the experiments. Compound **16d** and reference drugs were suspended with distilled water containing 0.5% carboxymethylcellulose and administered orally.

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. Compound **16d** and reference drugs were dissolved in saline containing 10% dimethylsulfoxide, and were administered orally 1 h prior to the injection of serotonin and collagen. Compound **16d** was also additionally administered orally 0.5, 2, 4, 6 h prior to injection of the inducer. Ten mice

were used for each group. Results are expressed as mortality rate in animal number and percentage.

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