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

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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 \( \alpha_1 \)-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 \( \alpha_1 \)-adrenoceptor blocking activity (\( \text{pA}_2 \) = 7.83 \pm 0.20) and 5-HT\(_2\)-receptor blocking activity (\( \text{pA}_2 \) = 9.47 \pm 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 thromboembolic 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 \( \alpha_1 \)-adrenoceptor antagonist; serotonin 2 receptor antagonist; pyrrolo[2,3-c]azepine; antihypertension; antiplatelet aggregation

Hypertension is an important risk factor for various cardiovascular disorders,3 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 \( \alpha_1 \)-adrenoceptor blocking drugs, such as doxazosin (1) and prazosin (2, Fig. 1), have not only an antihypertensive effect 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 adheriveness 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,9 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 \( \Lambda_2 \) (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 \( \alpha_1 \)-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 \( \alpha_1 \)-adrenoceptor blocking activity and serotonin 2 (5-HT\(_2\))-receptor blocking activity, its \( \alpha_1 \) 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 \( \alpha_1 \)-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-tetrahydroxyazeprolo[2,3-c]azepine-4,8-dione (4) and the nitrogen atom at the 3-position of 2,4(1H,3H)-quinazolinedione (5).11 In the previous study, we found that the pyrrolo[2,3-c]azepine ring system was a useful component in eliciting \( \alpha_1 \)- 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 \( \alpha_1 \)- 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 (1, 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 1.

Chemistry

Synthetic pathways for preparation of the intermediates (10) are shown in Chart 1. 1-Alkylpyrrolole-2-carboxylic acids (7) were condensed with \( \beta \)-alanine benzyl ester \( p \)-toluenesulfonate in the presence of diethyl phosphorocyanidate (DEPC),16 followed by hydrogenolysis of the benzyl group,
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 a,α-dihaloalkane afforded 7-(α-haloalkyl) compounds (12), and then treatment of 12 with the appropriate amine in the presence of base (K₂CO₃, NaHCO₃) 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-(α-chloroalkyl)amine, directly afforded 13j and 13l—m (Method B).

Reduction of 13h with NaBH₄ 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, ¹H-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 noradrenaline (NE) and serotonin in the isolated aorta and mesenteric artery of the guinea pig are mainly caused by activation of α₁-adrenergic receptors and 5-HT₂-receptors, respectively.18) Therefore, the antagonist effects of the compounds on α₁-adrenergic receptors and 5-HT₂-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. α₁- and 5-HT₂-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 α₁-and 5-HT₂-receptor blocking activities than ketanserin, in contrast to the case of 1-aminoalkylpyrroloazepine derivatives. While the compounds with 4-(4-fluorophenoxypiperidine) (13b), 4-phenylpiperidine (13c) and 1-phenylpiperazine (13d) did not show sufficient α₁-adrenoceptor blocking activity, compounds 13e and 13h had α₁-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 α₁-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 α₁-adrenoceptor.19) Some of the compounds with arylpiperazine (13d, 13h, 13i) showed considerable 5-HT₂-receptor blocking activity. Among compounds 13a—i, the
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 $\alpha_1$- and 5-HT2-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-HT2-receptor blocking activity, but the $\alpha_1$-adrenoceptor blocking activity was almost completely abolished. Both $\alpha_1$- and 5-HT2-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 $\alpha_1$- and 5-HT2-receptor blocking activities. These results revealed that $\alpha_1$-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 $\alpha_1$-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 and 4-(4-fluorophenyl)piperazine moiety seemed to have little effect on $\alpha_1$-adrenoceptor blocking activity, but to be an important factor for 5-HT2-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-HT2-receptor blocking activity. In contrast, introduction of a larger group such as an $n$-propyl (16e) or $n$-butyl (16f) group at this position resulted in a decrease in the $\alpha_1$-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 $\alpha_1$- and 5-HT2-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 $\alpha_1$-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-HT2-receptor blocking activity in comparison with an active control, ketanserin. 7-Aminoalkylpyrrolo[2,3-c]azepine was characterized by more potent 5-HT2-receptor blocking activity rather than $\alpha_1$-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-hydroxyiminomino-1,4,5,6,7,8-hexahydropyrrolo[2,3-c]azepin-8-one (16d), which displayed both the potent $\alpha_1$-adrenoceptor blocking activity of doxazosin as well as the potent 5-HT2-receptor blocking action of ketanserin, was selected for further pharmacological evaluation.

Antihypertensive activity was evaluated by oral adminis-
tration of 16d and the reference compound to conscious de-
oxycorticosterone 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 an-
tiplatelet 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 ad-
ministration at doses of 0.3 mg/kg or more, one hour before

Table 1. α₁-Adrenergic- and 5-HT₂-Receptor Blocking Activities of Pyrrolo[2,3-c]azepine Derivatives with Various Amine Moieties

<table>
<thead>
<tr>
<th>Compound</th>
<th>–NR₂R₃</th>
<th>α₁-blocking activity*a (10⁻⁸ M)</th>
<th>α₁-blocking activity*a (10⁻⁷ M)</th>
<th>5-HT₂-blocking activity*b (10⁻⁸ M)</th>
<th>5-HT₂-blocking activity*b (10⁻⁷ M)</th>
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<tbody>
<tr>
<td>13a</td>
<td></td>
<td>2</td>
<td>27</td>
<td>24</td>
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</tr>
<tr>
<td>13b</td>
<td></td>
<td>2</td>
<td>24</td>
<td>3</td>
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<td>13c</td>
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<td></td>
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<tr>
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<td></td>
<td>2</td>
<td>36</td>
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<td>94</td>
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<tr>
<td>13i</td>
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<td>3</td>
<td></td>
<td>3</td>
<td>47</td>
<td>93</td>
<td>100</td>
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</tbody>
</table>

*a) % inhibition of 10⁻⁷ M norepinephrine-induced contraction in guinea pig aorta.  
b) % inhibition of 10⁻⁷ M serotonin-induced contraction in guinea pig mesenteric artery.  
c) Not tested.

Table 2. α₁-Adrenergic- and 5-HT₂-Receptor Blocking Activities of Pyrrolo[2,3-c]azepine Derivatives with Various Groups at the 4-Position

<table>
<thead>
<tr>
<th>Compound</th>
<th>Y</th>
<th>α₁-blocking activity*a (10⁻⁸ M)</th>
<th>α₁-blocking activity*a (10⁻⁷ M)</th>
<th>5-HT₂-blocking activity*b (10⁻⁸ M)</th>
<th>5-HT₂-blocking activity*b (10⁻⁷ M)</th>
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<tr>
<td>13h</td>
<td>O</td>
<td>2</td>
<td>36</td>
<td>45</td>
<td>94</td>
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<tr>
<td>14</td>
<td>–OH, H</td>
<td>0</td>
<td>6</td>
<td>76</td>
<td>88</td>
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<tr>
<td>15</td>
<td>–H, α₄⁺⁻⁵⁻</td>
<td>3</td>
<td>27</td>
<td>36</td>
<td>75</td>
</tr>
<tr>
<td>16a</td>
<td>(E)-NOH</td>
<td>10</td>
<td>60</td>
<td>75</td>
<td>94</td>
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<tr>
<td>1</td>
<td></td>
<td>3</td>
<td>78</td>
<td>5</td>
<td>3</td>
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<td>3</td>
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<td>3</td>
<td>47</td>
<td>93</td>
<td>100</td>
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</tbody>
</table>

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

Table 3. α₁-Adrenergic- and 5-HT₂-Receptor Blocking Activities of Pyrrolo[2,3-c]azepine Derivatives 16a—f

<table>
<thead>
<tr>
<th>Compound</th>
<th>R₁, n</th>
<th>α₁-blocking activity*a (10⁻⁸ M)</th>
<th>α₁-blocking activity*a (10⁻⁷ M)</th>
<th>5-HT₂-blocking activity*b (10⁻⁸ M)</th>
<th>5-HT₂-blocking activity*b (10⁻⁷ M)</th>
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<tbody>
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<td>16a</td>
<td>Me 3</td>
<td>10</td>
<td>60</td>
<td>75</td>
<td>94</td>
</tr>
<tr>
<td>16b</td>
<td>Me 2</td>
<td>14</td>
<td>52</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>16c</td>
<td>Me 4</td>
<td>4</td>
<td>56</td>
<td>47</td>
<td>94</td>
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<td>16d</td>
<td>Et 3</td>
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<td>59</td>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td>16e</td>
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<td>26</td>
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<td>94</td>
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<tr>
<td>16f</td>
<td>n-Bu 3</td>
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<td>32</td>
<td>83</td>
<td>–*</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>3</td>
<td>78</td>
<td>5</td>
<td>3</td>
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<tr>
<td>3</td>
<td></td>
<td>3</td>
<td>47</td>
<td>93</td>
<td>100</td>
</tr>
</tbody>
</table>

*a), b) See corresponding footnotes of Table 1.  
c) Data was not obtained, because the time of the effect was too long.
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 \( \alpha_1 \)- 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 \( \alpha_1 \)-adrenoceptor blocking activity (\( pA_2 = 7.83 \pm 0.20 \)) and 5-HT\(_2\)-receptor blocking activity (\( pA_2 = 9.47 \pm 0.17 \)) 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 \( \alpha_1 \)-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 Bruker ARX 400 FT NMR spectrometer, and the chemical shifts are expressed in ppm 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\(^{22}\); 1-(3-chloropropyl)-4-(4-fluorophenyl)piperazine\(^{22}\); 4-(4-fluorophenyl)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 Mathie\(^{25}\) 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\(_2\)O (250 ml) was added a solution of methyl pyrrole-2-carboxylate (16.3 g, 130 mmol) in Et\(_2\)O (20 ml) at 0 °C. To the resultant suspension was added dropwise a solution of Et\(_3\)N (30.4 g, 195 mmol) in Et\(_2\)O (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\(_2\)O (2×50 ml). The combined organic layers were washed with brine, dried, and evaporated to give an oil, which was distilled (bp 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\(_3\)) \( \delta \): 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)

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### Table 4. \( \alpha_1 \)-Adrenergic- and 5-HT\(_2\)-Receptor Blocking Activities of 16d and Reference Compounds in Isolated Guinea Pig Arteries\(^{a}\)

<table>
<thead>
<tr>
<th>Compound</th>
<th>( \alpha_1 )-blocking activity ( pA_2 )</th>
<th>Slope</th>
<th>5-HT(_2)-blocking activity ( pA_2 )</th>
<th>Slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>16d</td>
<td>7.83 ± 0.20</td>
<td>0.94 ± 0.09</td>
<td>9.47 ± 0.17</td>
<td>1.36 ± 0.08</td>
</tr>
<tr>
<td>1</td>
<td>7.81 ± 0.20</td>
<td>1.23 ± 0.18</td>
<td>&lt;5</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>7.44 ± 0.20</td>
<td>0.98 ± 0.16</td>
<td>9.21 ± 0.23</td>
<td>1.46 ± 0.17</td>
</tr>
<tr>
<td>SUN 9221 (6)</td>
<td>8.98 ± 0.21</td>
<td>0.98 ± 0.04</td>
<td>8.74 ± 0.22</td>
<td>1.18 ± 0.20</td>
</tr>
</tbody>
</table>

\( a \) 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.

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**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. of 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.
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 268—81 °C). IR (KBr): 3424, 1720, 1518, 1495 cm−1. 

1-Methyl-1,4,5,6,7,8-hexahydropyrrolo[2,3-e]azepine-4,8-dione (10a)  

i) To a stirred solution of 7a (38.9 g, 311 mmol) and β-diene benzyl ester p-toluene sulfonate (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 Et3N (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 K2CO3, 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]propionic acid (10a) (26.0 g, 95%) as colorless crystals. mp 131.0—132.5 °C. IR (KBr): 3324, 1736, 1633, 1552, 1519 cm−1. 

<image>

**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.

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

1-1H-NMR (CDCl3): 3324, 1736, 1633, 1552, 1519 cm−1. 1H-NMR (CDCl3) d 1.41 (3H, t, J=7.2 Hz), 3.6 (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-e]azepine-4,8-dione (10a)  

To a solution of 7a (38.9 g, 118 mmol) and approximately 80% PPA (196.0—198.0 °C. IR (KBr): 3336, 1634, 1530 cm−1. 1H-NMR (CDCl3) d 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 C9H12N2O3: C, 64.13; H, 6.86; N, 13.58. Found: C, 64.13; H, 6.84; N, 13.58.

Compound 10d was prepared similarly. 

1-Butyl-1,4,5,6,7,8-hexahydropyrrolo[2,3-e]azepine-4,8-dione (10d): 91% yield, colorless crystals, mp 63.0—64.5 °C (EtOAc–IPE). IR (KBr): 3208, 1660, 1530 cm−1. 1H-NMR (CDCl3) d 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 C15H20N2O2: 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-e]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. 1H-NMR (CDCl3) d 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 C15H19ClN2O2: 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-e]azepine-4,8-dione (12b): 58% yield, colorless crystals, mp 78.0—79.5 °C.
8.67. After evaporation of the solvent, the residue was diluted with half-saturated K₂CO₃ (50 ml), and then extracted with CHCl₃ (2 ml). The combined extracts were washed with brine, dried, and concentrated to give an oil, which was purified by column chromatography (elucent, CHCl₃; MeOH = 97:3) to afford 13f (770 mg, 49%) as a pale yellow solid. An analytical sample was obtained by recrystallization. mp 155.5—156.5 °C (EtOAc–hexane). IR (KBr): 1.75—1.95 (6H, m), 2.10 (2H, 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), 3.48 (2H, t, J = 2.7 Hz), 3.71 (2H, m), 3.93 (3H, s), 6.64 (1H, d, J = 3.7 Hz), 2.53 (2H, t, J = 7.3 Hz), 6.82—7.03 (4H, m). HR-FAB-MS Calcd for C₂₃H₂₉FN₂O₂ [MH⁺]: 411.2396. Found 411.2404.

7-[3-[4-(Fluorobenzoyl)piperidin-1-yl]propyl-1-methyl-1,4,5,6,7,8-hexahydropropolo[2,3-c]azepine-4,8-dione (18) A solution of chloride (254 mg, 1 mmol), 4-(4-fluorobenzoyl)piperidine hydrochloride (1.05 g, 4.12 mmol) and Et₃N (4.12 mmol) in CH₂Cl₂ (25 ml) was stirred at room temperature for 2 h. After evaporation of the solvent, the residue was diluted with half-saturated K₂CO₃ (40 ml), and then extracted with CHCl₃ (770 mg, 49%) as a pale yellow solid. An analytical sample was obtained by recrystallization. mp 155.5—156.5 °C (EtOAc–hexane). IR (KBr): 1.75—1.95 (6H, m), 2.10 (2H, 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), 3.48 (2H, t, J = 2.7 Hz), 3.71 (2H, m), 3.93 (3H, s), 6.64 (1H, d, J = 3.7 Hz), 2.53 (2H, t, J = 7.3 Hz), 6.82—7.03 (4H, m). HR-FAB-MS Calcd for C₂₃H₂₉FN₂O₂ [MH⁺]: 411.2396. Found 411.2404.

7-[3-[4-(Fluorobenzoyl)piperidin-1-yl]propyl-1-methyl-1,4,5,6,7,8-hexahydropropolo[2,3-c]azepine-4,8-dione (18) A solution of chloride (254 mg, 1 mmol), 4-(4-fluorobenzoyl)piperidine hydrochloride (1.05 g, 4.12 mmol) and Et₃N (4.12 mmol) in CH₂Cl₂ (25 ml) was stirred at room temperature for 2 h. After evaporation of the solvent, the residue was diluted with half-saturated K₂CO₃ (40 ml), and then extracted with CHCl₃ (770 mg, 49%) as a pale yellow solid. An analytical sample was obtained by recrystallization. mp 155.5—156.5 °C (EtOAc–hexane). IR (KBr): 1.75—1.95 (6H, m), 2.10 (2H, 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), 3.48 (2H, t, J = 2.7 Hz), 3.71 (2H, m), 3.93 (3H, s), 6.64 (1H, d, J = 3.7 Hz), 2.53 (2H, t, J = 7.3 Hz), 6.82—7.03 (4H, m). HR-FAB-MS Calcd for C₂₃H₂₉FN₂O₂ [MH⁺]: 411.2396. Found 411.2404.
most part and a trace amount of its isomer (16a′) (Rf’0.27, CHCl3; 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, 1601, 1510 cm

2900—2600, 1619, 1509 cm

IR: 3450—3200, 1619, 1509 cm

16a′: pale yellow oil. IR (film): 1660, 1631, 1509, 1486 cm

16b: mp 164.5—165.5 °C (EtOAc–hexane). IR (KBr): 3450—3200, 1619, 1509 cm

H-NMR (CDCl 3): 1.18—1.75 (4H, m), 2.45 (2H, t, 2.7 Hz), 2.67 (4H, m), 3.50—3.68 (4H, m), 3.88 (3H, s), 6.76 (1H, d, 7.3 Hz), 6.87 (2H, m), 6.95 (2H, m), 7.10 (1H, d, 7.3 Hz).

16c: mp 164.5—165.5 °C (EtOAc–hexane). IR (KBr): 3450—3200, 1619, 1509 cm

H-NMR (CDCl 3): 0.74 (3H, t, 7.3 Hz), 1.26 (3H, t, 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=7.2 Hz), 6.89 (2H, m), 6.92 (2H, m), 9.39 (1H, brs).

Anal. Calcd for C18H18F2NO 2: C, 64.00; H, 4.00; N, 13.82. Found: C, 64.13; H, 7.42; N, 15.93.

16d: mp 149.5—150.5 °C (EtOH). IR (KBr): 3450—3200, 1619, 1509 cm

H-NMR (CDCl 3): 1.35 (3H, s), 1.72 (2H, t, J=6.1 Hz), 2.48 (2H, m), 2.63 (4H, m), 2.75 (1H, d, J=7.2 Hz), 6.40 (1H, d, J=6.8 Hz), 6.68 (1H, d, J=7.2 Hz), 6.73 (1H, d, J=6.1 Hz), 6.89 (2H, m), 6.92 (2H, m), 7.20 (1H, d, J=7.2 Hz), 7.50 (1H, d, J=7.2 Hz).
were used for each group. Results are expressed as mortality rate in animal number and percentage.

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References and Notes

17) The geometry of the oxime moiety of 16 and 16’ was determined by comparison of the ‘H-NMR data of both isomers. For instance, the signal of the C-3 methine proton of 16a appeared at δ 7.10, and this was shifted to a lower field compared to that of 16a (δ 6.33) by the anisotropic effect of the oxygen atom of the oxime moiety.