# Synthesis and Pharmacological Evaluation of Pyrroloazepine Derivatives as Potent Antihypertensive Agents with Antiplatelet Aggregation Activity

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Received September 17, 1998; accepted November 2, 1998

**A series of 1-aminoalkyl-pyrrolo[2,3-*c*]azepin-8-one derivatives was synthesized and evaluated as $\alpha_1$ adrenergic and serotonin 2 (5-HT$_2$) receptor antagonists, with the aim of finding a novel antihypertensive agent potently exhibiting both activities. Some compounds with a 4-[4-(4-fluorobenzoyl)piperidino]butyl group at the 1-position exhibited both activities, and varied significantly in terms of the substituents at the 4-position of the pyrroloazepine ring. Among the compounds obtained in this study, (*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 (15a, SUN9221) displayed potent $\alpha_1$-adrenergic antagonistic activity (pA$_2$=8.89±0.21) and 5-HT$_2$ antagonistic activity (pA$_2$=8.74±0.22) in isolated guinea pig arteries. This compound exhibited antihypertensive activity and a duration of action equivalent to orally administered prazosin or doxazosin, 3 mg/kg, in conscious spontaneously hypertensive rats, as well as potent antiplatelet aggregation activity.**

**Key words** $\alpha_1$-adrenergic antagonist; serotonin 2 antagonist; pyrrolo[2,3-*c*]azepine; antihypertension; antiplatelet aggregation; SUN9221

Hypertension is an important risk factor for various cardiovascular disorders,[1] and it has been recognized that antihypertensive agents are needed to reduce the incidence of ischemic heart disease in addition to providing satisfactory blood pressure control.[2] Among numerous antihypertensive drugs with various pharmacological profiles, the $\alpha_1$-adrenoceptor blocking agents, such as prazosin (**1**) and doxazosin (**2**), have not only an antihypertensive effect[3] but also a beneficial effect on plasma lipids.[4] These drugs are therefore first-choice agents in a clinical setting.[5]

In patients with essential hypertension, several aspects of platelet function, such as adhesiveness and aggregation, have been reported to be abnormal.[6] Blood platelets possess a specific uptake mechanism and intracellular storage organelles for serotonin. Following its local release from platelets at sites of vascular injury, serotonin activates serotonin 2 (5-HT$_2$) receptors on the vascular wall and on platelets and so induces vasoconstriction and further platelet aggregation.[7] In addition, serotonin acts indirectly to amplify the platelet aggregation and vasoconstriction induced by other biologically active substances, such as norepinephrine (NE), thromboxane A$_2$ (TXA$_2$), adenosine diphosphate (ADP), and collagen.[8] Therefore, it is thought that 5-HT$_2$ receptor antagonists would be beneficial in preventing circulatory diseases which involve vasoconstriction and platelet aggregation.[9]

Ketanserin (**3**) was developed and launched as an antihypertensive agent,[10] and it has also been shown to be useful in the treatment of some circulatory diseases.[7,11] Although this compound has potent 5-HT$_2$ antagonist activity and weak $\alpha_1$-adrenoceptor blocking activity, its hypotensive activity is weak in comparison with prazosin.[12] On the basis of abovementioned considerations, we have attempted to find a novel compound possessing both the potent $\alpha_1$-adrenoceptor blocking activity of prazosin as well as the potent 5-HT$_2$ blocking action of ketanserin in order to develop an antihy-

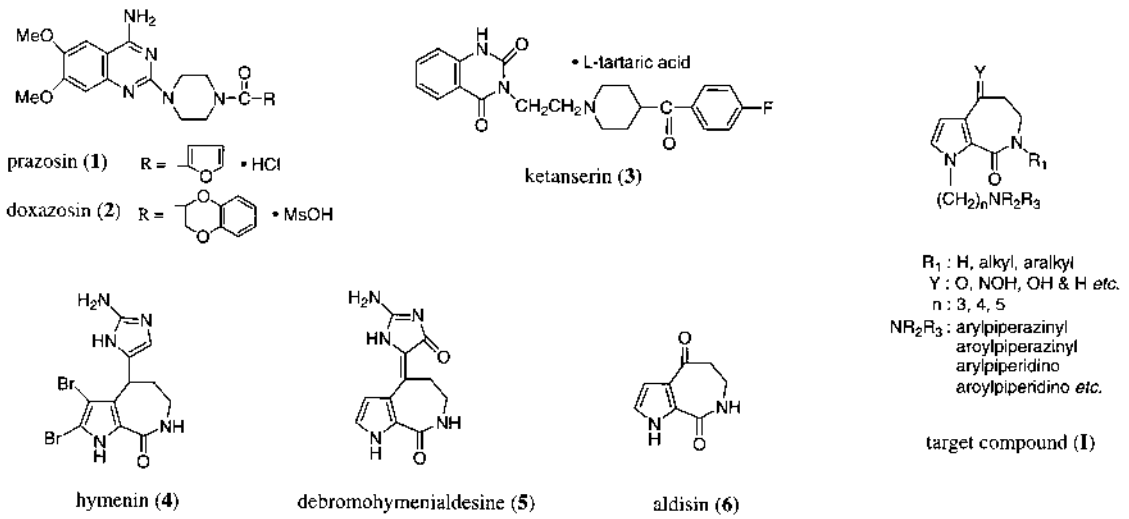


Fig. 1

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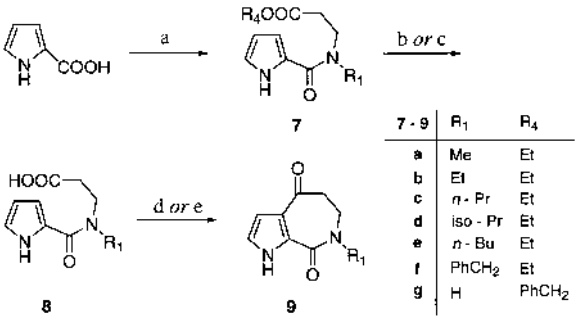
pertensive drug with a potent antiplatelet aggregating effect.

Considerable progress has been made in structure–activity relationship (SAR) studies on $\alpha_1$-adrenoceptor blocking agents containing 2,4(1*H*,3*H*)-quinazolinedione (*e.g.* ketanserin, SGB-1534[13]) and its related ring systems, such as pyrimido[5,4-*b*]indole-2,4-dione,[14] 2,3-dihydroimidazo[1,2-*c*]quinazolin-5(6*H*)-one[15] and thienopyrimidine-2,4-diones[16]. A series of compounds which possess a pyrrolo[2,3-*c*]-azepine skeleton, such as hymenin (**4**),[17] debromohymenialdisine (**5**)[18] and aldisin (**6**),[19] have been obtained from certain marine sponges. Biological evaluation of these compounds showed that compound **4** has $\alpha_1$-adrenoceptor blocking activity,[17] but this skeleton has not been used as a drug, to our knowledge. As far as compound **6** is concerned, the nitrogen atom at the 1-position is connected to a carbonyl group and the carboxamide group through a conjugated system and, therefore, is similar to that of the nitrogen atom at the 3-position of 2,4(1*H*,3*H*)-quinazolinedione. In fact, the nitrogen atoms in both skeletons are easily alkylated[20] and their reactivities are similar. Since we were interested in the pyrrolo[2,3-*c*]azepine skeleton because of its structural uniqueness, we tried to synthesize a number of pyrrolo[2,3-*c*]azepin-8-one derivatives. Their general structure (I) is shown in Fig. 1.

We describe here the syntheses, pharmacological evaluation and SAR of compound I.

## Chemistry

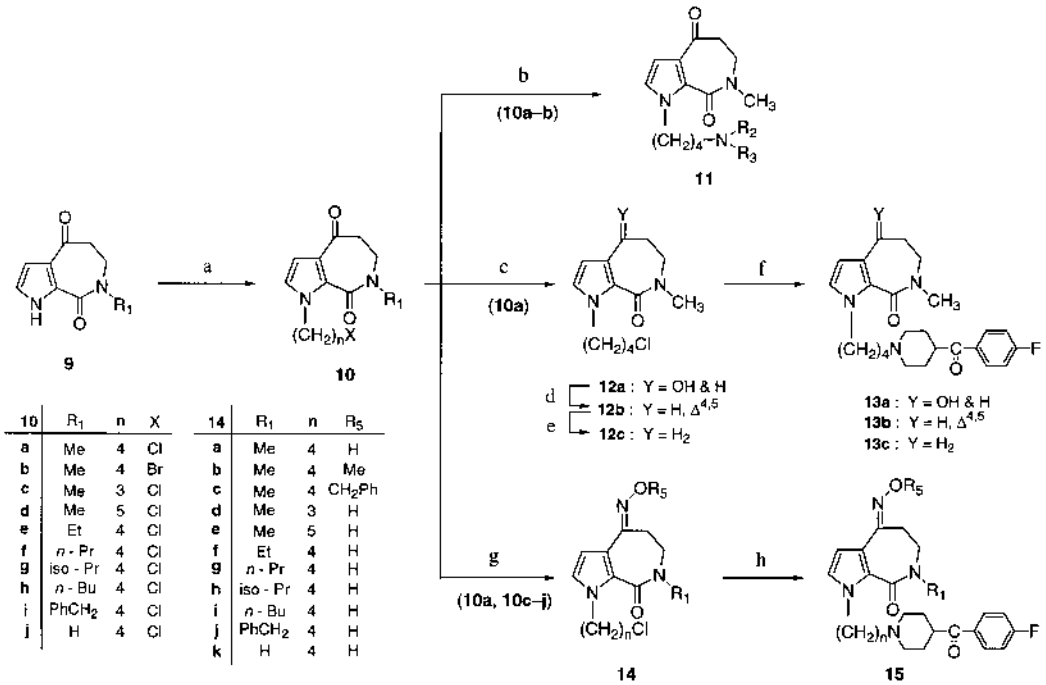
Synthetic routes to the intermediate (**9**) are shown in Chart 1.[21] 2-Pyrrolecarboxylic acid was condensed with appropriate 3-aminopropionic acid esters in the presence of diethyl phosphorocyanidate (DEPC),[22] followed by deesterification by alkaline hydrolysis or hydrogenolysis, producing 3-(2-pyrrolecarboxamido)propionic acid (**8**) in good yield. Cyclization of the resultant **8** with 80% polyphosphoric acid (PPA) at 100 °C afforded (7-substituted-)1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepine-4,8-diones (**9**) in fairly good yield except when $R_1$ was a benzyl group. The alternative method of conversion of **8** to **9** was achieved by transforming **8** into its acid chloride, followed by a Friedel–Crafts reaction catalyzed by $AlCl_3$ (Chart 1).[23] The target compounds were prepared as outlined in Chart 2. The reaction of **9** with $\alpha,\omega$-dihaloalkane in the presence of $K_2CO_3$ afforded **10**, and then treatment of **10** with the appropriate amine gave the desired 4-keto compounds (**11**). The *N*-methyl derivative, **10a**, was successively transformed by the usual procedures to **12a**, **12b** and **12c**, which reacted with 4-(4-fluorobenzoyl)piperidine (4-FBP)·HCl in the presence of $K_2CO_3$ and NaI to give **13a**, **13b** and **13c**, respectively. Reaction of **10** with hydroxylamine hydrochloride or *O*-substituted hydroxylamine hydrochloride in basic medium afforded predominantly the (*E*)-oxime (**14**) accompanied by a very small amount (<2% in the case of **14a′**) of the geometric isomers (**14′**) of the oxime moiety, which could be easily separated by column chromatography on silica-gel.[24] Subsequent amination of **14** pro-




| 7 - 9 | $R_1$ | $R_4$ |
|---|---|---|
| a | Me | Et |
| b | Et | Et |
| c | *n* - Pr | Et |
| d | iso - Pr | Et |
| e | *n* - Bu | Et |
| f | $PhCH_2$ | Et |
| g | H | $PhCH_2$ |

a: $R_1NHCH_2CH_2COOR_4$, DEPC, $Et_3N$; b: i) aq–NaOH ii) dil–HCl (for **a**—**f**); c: $H_2$, 5% Pd/C (for **g**); d: 80% PPA; e: i) $(COCl)_2$, DMF ii) $AlCl_3$.

Chart 1




| 10 | $R_1$ | n | X |
|---|---|---|---|
| a | Me | 4 | Cl |
| b | Me | 4 | Br |
| c | Me | 3 | Cl |
| d | Me | 5 | Cl |
| e | Et | 4 | Cl |
| f | *n* - Pr | 4 | Cl |
| g | iso - Pr | 4 | Cl |
| h | *n* - Bu | 4 | Cl |
| i | $PhCH_2$ | 4 | Cl |
| j | H | 4 | Cl |

| 14 | $R_1$ | n | $R_5$ |
|---|---|---|---|
| a | Me | 4 | H |
| b | Me | 4 | Me |
| c | Me | 4 | $CH_2Ph$ |
| d | Me | 3 | H |
| e | Me | 5 | H |
| f | Et | 4 | H |
| g | *n* - Pr | 4 | H |
| h | iso - Pr | 4 | H |
| i | *n* - Bu | 4 | H |
| j | $PhCH_2$ | 4 | H |
| k | H | 4 | H |

a: $X(CH_2)_nX$, $K_2CO_3$; b: $R_2R_3NH$ ($Et_3N$ or $K_2CO_3$, NaI); c: $NaBH_4$; d: HCl (g) in $CHCl_3$; e: $H_2$, 10% Pd/C; f: 4-FPB·HCl, $K_2CO_3$, NaI; g: $NH_2OR_5$·HCl, NaOAc or pyridine; h: 4-FPB or 4-FPB·HCl, $Et_3N$ or $K_2CO_3$, NaI.

Chart 2

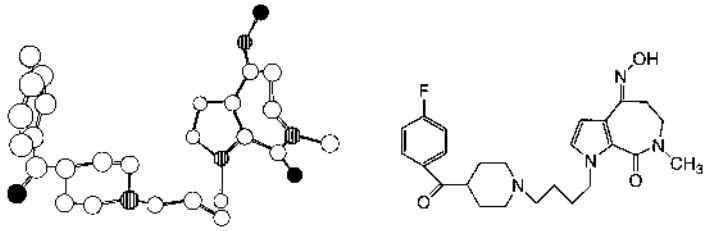
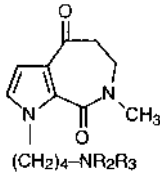
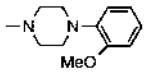
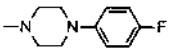
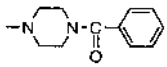
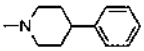
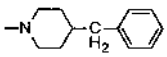
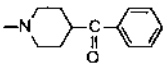
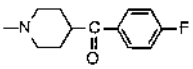


Fig. 2. Molecular Structure of Compound **15a** as Determined by X-Ray Crystal Analysis

Table 1. $\alpha_1$- and 5-$HT_2$-Blocking Activities of Compounds **11a**—**g**



| Compound | $-NR_2R_3$ | $\alpha_1$-Blocking activity[a] (% inhibition) | | 5-$HT_2$-Blocking activity[b] (% inhibition) | |
|---|---|---|---|---|---|
| | | $10^{-8}$ M | $10^{-7}$ M | $10^{-7}$ M | $10^{-6}$ M |
| **11a** |  | 48 | 85 | 1 | 11 |
| **11b** |  | 4 | 50 | 15 | 65 |
| **11c** |  | 1 | 2 | 12 | 35 |
| **11d** |  | 3 | 50 | 25 | 27 |
| **11e** |  | 7 | 30 | 3 | 5 |
| **11f** |  | 33 | 69 | 3 | 43 |
| **11g** |  | 56 | 80 | 37 | 88 |
| Prazosin (**1**) | | 46 | 86 | 0 | 1 |
| Doxazosin (**2**) | | 3 | 78 | 5 | 3 |
| Ketanserin (**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.

duced the desired 4-imino compounds (**15**) in a similar manner (Chart 2).

The chemical structures of the synthesized compounds were confirmed from spectroscopic data (IR, $^1$H-NMR, mass) and elemental analyses. The structure of **15a** 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 NE and serotonin in the isolated aorta and mesenteric artery of the guinea pig are mainly caused by activation of $\alpha_1$-adrenergic receptors and 5-$HT_2$ receptors, respectively.[25] Therefore, the antagonist effects of the compounds on $\alpha_1$-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. The pharmacological profile of each compound was compared with those of prazosin, doxazosin and ketanserin.

We first investigated the effects of various amine moieties at the 1-position side-chain of the 7-methyl-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepine-4,8-dione derivatives on both activities, as shown in Table 1. Compound **11a** exhibited a potent $\alpha_1$ blocking effect comparable with that of prazosin, but no 5-$HT_2$ blocking activity. In contrast, compound **11b**

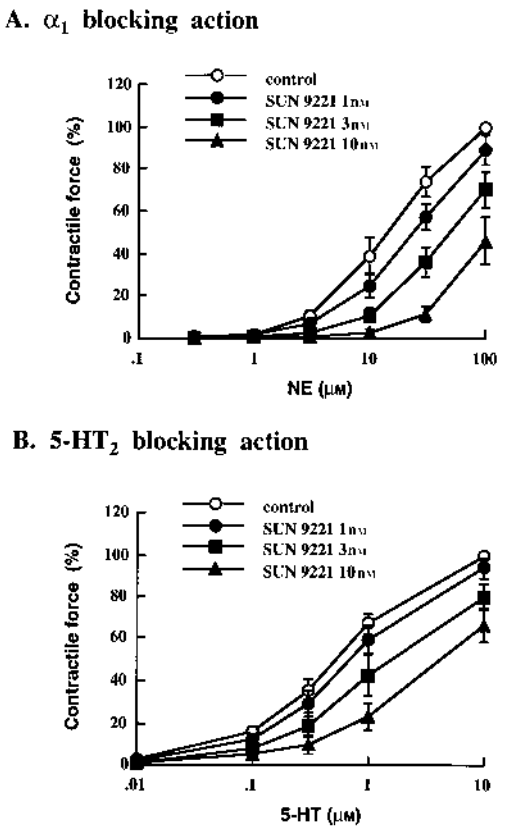


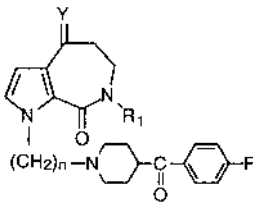

Fig. 3. The Effect of Compound **15a** (SUN9221) on the Norepinephrine-Induced Contractile Response in Mesenteric Arteries (A) and Serotonin-Induced Contractile Response in Femoral Arteries (B)

Values from four experiments presented as mean±S.E., expressed as a percentage of the maximal contraction of the control.

showed weak 5-$HT_2$ blocking activity. Compound **11f**, possessing a benzoylpiperidine moiety, showed considerable $\alpha_1$ blocking activity, whereas substitution of this moiety by benzoylpiperazine (**11c**), phenylpiperidine (**11d**) and benzylpiperidine moieties (**11e**) diminished this activity. The introduction of a fluorine atom at the 4-position of the benzene ring of **11f** resulted in not only an enhancement of $\alpha_1$ blocking activity but also the induction of 5-$HT_2$ blocking activity (**11g**).

The next step was to maintain the optimal amine moiety of **11g** and investigate the effects of the functional group at the 4-position, the alkylene chain length (*n*) at the 1-position, and the substituent at the 7-position of the pyrrolo[2,3-*c*]azepine skeleton. The results of this study are summarized in Table 2. The $\alpha_1$ blocking activity was markedly reduced in compounds **13a**—**c** compared with **11g**, while the 5-$HT_2$ blocking activity was not substantially affected. Introduction of an (*E*)-hydroxyimino group at the 4-position (**15a**) resulted in a marked enhancement of the 5-$HT_2$ blocking activity, while retaining the potent $\alpha_1$ blocking activity of **11g**. Compound **15a** showed stronger $\alpha_1$ blocking activity ($pA_2$=8.89±0.21, slope=0.98±0.04, mean±S.E. of four experiments) (Fig. 3A) than prazosin ($pA_2$=8.59±0.24, slope=1.01±0.16), doxazosin ($pA_2$=7.81±0.20, slope=1.23±0.18) and ketanserin ($pA_2$=7.44±0.20, slope=0.98±0.16), and slightly less potent 5-$HT_2$ blocking activity ($pA_2$=8.74±0.22, slope=1.18±0.20) (Fig. 3B) than ketanserin ($pA_2$=9.21±0.23, slope=1.46±0.17). Replacement of the hydrogen atom on the oxime moiety at the 4-position of **15a** by a methyl (**15b**) or benzyl group (**15c**) markedly diminished the $\alpha_1$ blocking activity. This result suggests that, in a series of 4-imino compounds, the presence of a hydrogen atom is cru-

Table 2. $\alpha_1$- and 5-$HT_2$-Blocking Activities of Compounds **13a**—**c** and **15a**—**k**




| Compound | $R_1$ | *n* | Y | $\alpha_1$-Blocking activity[a] (% inhibition) | | 5-$HT_2$-Blocking activity[b] (% inhibition) | |
|---|---|---|---|---|---|---|---|
| | | | | $10^{-8}$ M | $10^{-7}$ M | $10^{-7}$ M | $10^{-6}$ M |
| **13a** | Me | 4 | –OH, H | 24 | 59 | 15 | 72 |
| **13b** | Me | 4 | –H, $\Delta^{4,5}$ | 14 | 49 | 27 | 74 |
| **13c** | Me | 4 | $H_2$ | 8 | 39 | 33 | 79 |
| **15a** | Me | 4 | (*E*)-NOH | 55 | 79 | 88 | 96 |
| **15b** | Me | 4 | (*E*)-$NOCH_3$ | 3 | 26 | 74 | 90 |
| **15c** | Me | 4 | (*E*)-$NOCH_2Ph$ | 0 | 0 | 8 | NT[c] |
| **15d** | Me | 3 | (*E*)-NOH | 3 | 34 | 44 | 69 |
| **15e** | Me | 5 | (*E*)-NOH | 24 | 70 | 44 | 85 |
| **15f** | H | 4 | (*E*)-NOH | 35 | 58 | 53 | 95 |
| **15g** | Et | 4 | (*E*)-NOH | 81 | 90 | 80 | 96 |
| **15h** | *n*-Pr | 4 | (*E*)-NOH | 63 | 82 | 87 | 92 |
| **15i** | iso-Pr | 4 | (*E*)-NOH | 29 | 59 | 67 | 97 |
| **15j** | *n*-Bu | 4 | (*E*)-NOH | 85 | 93 | 48 | 83 |
| **15k** | $PhCH_2$ | 4 | (*E*)-NOH | 81 | 90 | 22 | 93 |
| Prazosin (**1**) | | | | 46 | 86 | 0 | 1 |
| Doxazosin (**2**) | | | | 3 | 78 | 5 | 3 |
| Ketanserin (**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.

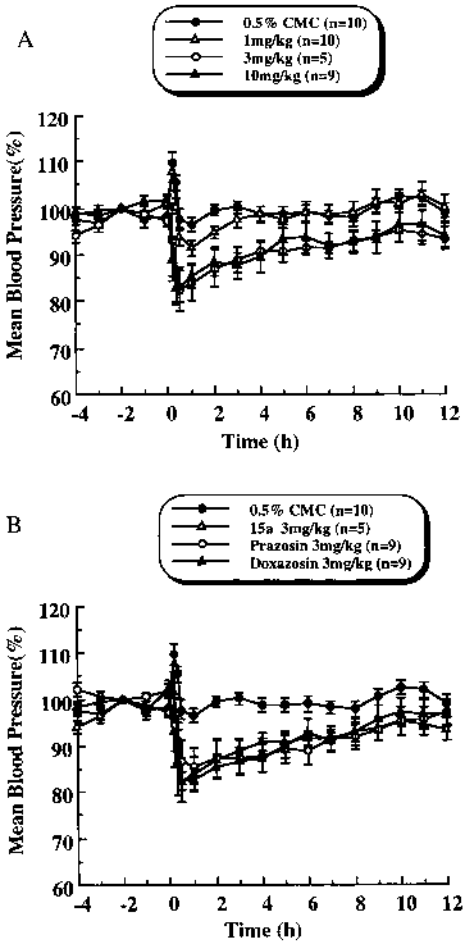



Fig. 4. Antihypertensive Effect of Compound **15a** in Conscious Spontaneously Hypertensive Rats

(A) Effect of oral administration of **15a** (1, 3, 10 mg/kg) on mean blood pressure. (B) Effect of **15a**, prazosin and doxazosin on mean blood pressure at an oral dose of 3 mg/kg. Each value indicates mean±S.E. % of control blood pressure just before drug application.

cial for potent $\alpha_1$ blocking activity, and the hydrogen atom might interact with the hydrophilic site of the $\alpha_1$ receptor. In contrast, only a smaller substituent, as in **15b**, produced acceptable 5-$HT_2$ blocking activity. This led us to presume that the C=N–O– structure was indispensable and larger substituents might create steric bulk which could not fit the 5-$HT_2$ receptor site. The length of the alkyl side-chain between the pyrrolo[2,3-*c*]azepine ring system and the 4-FBP moiety seemed to be critical for both activities, and it was optimal at $n=4$ (**15a**, **15d**, **15e**). This result is in agreement with the situation of ketanserin, which has also four atoms between the benzene ring of the quinazolinedione moiety and the nitrogen atom of 4-FBP.

Subsequently, the effect of substitution at the 7-position was examined. Whereas no distinct relationship was observed between substitution at the 7-position and $\alpha_1$ blocking activity (**15a**, **15f**—**k**), introduction of a larger group at this position showed a tendency to reduce 5-$HT_2$ blocking activity (**15j**, **15k**). The compounds with a methyl (**15a**), ethyl (**15g**), and *n*-propyl group (**15h**) at the 7-position were preferable as far as both activities were concerned.

In the series of 1-aminoalkyl-pyrrolo[2,3-*c*]azepin-8-one derivatives, (*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 (**15a**, SUN9221), which showed not only the most potent 5-$HT_2$ receptor blocking activity, equipotent with **15g** and **15h**, but also sufficient $\alpha_1$ blocking activity, was selected for further pharmacological evaluation.

Table 3. Antiplatelet Aggregation Effect of **15a** in Human PRP

| Compound | $IC_{50}$ (nM) | | |
|---|---|---|---|
| | ADP ($10^{-6}$ M) + Serotonin ($10^{-5}$ M) | Collagen (0.1 $\mu$g/ml) + Serotonin ($10^{-5}$ M) | Epinephrine ($10^{-6}$ M) + Serotonin ($10^{-5}$ M) |
| **15a** (SUN9221) | 35 | 10 | 14 |
| Ketanserin | 84 | 28 | 37 |
| Doxazosin | >1000 | >1000 | >1000 |

$IC_{50}$ is the mean concentration which produces 50% inhibition estimated from the concentration–response curve involving 3—8 experiments.

Antihypertensive activity was evaluated by orally administering **15a** and reference compounds to conscious spontaneously hypertensive rats (SHR). The results are shown in Fig. 4. Oral administration of **15a** at doses of 1, 3, 10 mg/kg reduced the blood pressure in a dose-dependent manner (Fig. 4A). The hypotensive effect lasted for more than twelve hours at 3 mg/kg, and this effect was almost equipotent to that produced by the same dose of prazosin or doxazosin (Fig. 4B).

In addition, in human platelet-rich plasma (PRP), the potentiation of collagen-, ADP- and epinephrine-induced platelet aggregation by serotonin was markedly inhibited by **15a**. This antiplatelet aggregation effect of **15a** was more potent than that of ketanserin. Doxazosin did not show any inhibitory effect on platelet aggregation (Table 3).

In conclusion, some compounds with a 4-[4-(4-fluorobenzoyl)piperidino]butyl group at the 1-position of the pyrrolo-[2,3-*c*]azepin-8-one moiety exhibited $\alpha_1$ receptor and 5-$HT_2$ receptor antagonist activity. 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 **15a** (SUN9221) displayed potent $\alpha_1$-adrenergic antagonist activity ($pA_2=8.89\pm0.21$) and 5-$HT_2$ antagonist activity ($pA_2=8.74\pm0.22$) in an *in vitro* assay. This compound also exhibited antihypertensive activity equal to that of orally administered prazosin and doxazosin, at 3 mg/kg, in SHR, as well as a potent antiplatelet aggregation effect. These results show that the pyrrolo[2,3-*c*]azepine ring system is a useful moiety for eliciting potent $\alpha_1$ blocking activity as well as 5-$HT_2$ blocking activity.

Evaluation of the side-effect profile and selectivity of these compounds is necessary to assist further development

**Experimental**

Melting points were determined on a Yanagimoto micro-melting point apparatus or 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 $\delta$ (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.

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: ethyl 3-methylaminopropionate;[26] ethyl 3-ethylaminopropionate;[27] ethyl 3-*n*-butylaminopropionate;[28] ethyl 3-benzylaminopropionate;[29] 1-benzoylpiperazine;[30] 1-benzoylpiperidine.[31] Ethyl 3-*n*-propylaminopropionate and ethyl 3-isopropylaminopropionate were prepared according to a procedure similar to that described in the literature.[28]

**3-(*N*-Ethyl-2-pyrrolecarboxamido)propionic Acid (8b)** i) To a stirred solution of pyrrole-2-carboxylic acid (44.44 g, 400 mmol) and ethyl 3-ethylaminopropionate (63.89 g, 440 mmol) in *N*,*N*-dimethylformamide (DMF) (300 ml) at 0 °C were added dropwise and successively a solution of DEPC (71.81 g, 440 mmol) in DMF (100 ml) and a solution of $Et_3N$ (44.52 g, 440 mmol) in DMF (50 ml). After stirring at room temperature for 20 h, the reaction mixture was concentrated. The residue was dissolved in EtOAc–benzene (2 : 1 v/v, 600 ml), washed successively with half-saturated $K_2CO_3$ (300 ml), water (300 ml), 5% HCl (300 ml), water (300 ml) and saturated NaCl (300 ml). The organic layer was dried and concentrated to afford a brown oil, which was solidified by triturating with diisopropyl ether (IPE)–hexane. The solid was collected and washed with hexane to afford ethyl 3-(*N*-ethyl-2-pyrrolecarboxamido)propionate (**7b**) (84.50 g, 89%) as pale brown crystals. This material was sufficiently pure to be used without further purification in the next step. A pure sample as colorless crystals was obtained by recrystallization from IPE. mp 50.5—52.5 °C. IR (KBr): 3265, 2978, 1721, 1595, 1548 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$ 1.21—1.39 (6H, m), 2.73 (2H, t, $J$=7.3 Hz), 3.67 (2H, m), 3.83 (2H, m), 4.16 (2H, q, $J$=7.2 Hz), 6.26 (1H, m), 6.57 (1H, m), 6.93 (1H, m), 10.18 (1H, br).

ii) A suspension of **7b** (59.79 g, 250 mmol) in 2 N NaOH (625 ml) was stirred at room temperature for 18 h. The resultant solution was acidified (pH *ca*. 2—3) with 3 N HCl under ice-cooling. The precipitate formed was collected by filtration and washed with water to give **8b** (50.02 g, 85% overall yield from pyrrole-2-carboxylic acid). mp 146.0—147.0 °C (EtOAc), colorless crystals. IR (KBr): 3400—3200, 1699, 1561 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$ 1.17 (3H, t, $J$=7.0 Hz), 2.59 (2H, t, $J$=7.4 Hz), 3.55 (2H, m), 3.66 (2H, m), 6.12 (1H, m), 6.48 (1H, m), 6.88 (1H, m), 11.36 (1H, br), 12.30 (1H, br).

Compounds **8a** and **8c**—**f** were prepared similarly. **8a**: 75% yield, colorless crystals, mp 125.0—127.0 °C (EtOAc). $^1$H-NMR (DMSO-$d_6$) $\delta$ 2.54 (2H, t, $J$=7.3 Hz), 3.13 (3H, s), 3.68 (2H, t, $J$=7.3 Hz), 6.11 (1H, m), 6.53 (1H, m), 6.87 (1H, m), 11.27 (1H, br s), 12.29 (1H, br).[21] **8c**: 83% yield, colorless crystals, mp 121.5—122.5 °C (EtOAc). $^1$H-NMR ($CDCl_3$) $\delta$ 0.97 (3H, t, $J$=7.2 Hz), 1.76 (2H, m), 2.75 (2H, t, $J$=7.2 Hz), 3.56 (2H, m), 3.84 (2H, m), 6.25 (1H, m), 6.55 (1H, m), 6.95 (1H, m), 8.02 (1H, br), 10.50 (1H, br s). **8d**: 53% yield, colorless crystals, mp 101.0—103.0 °C (EtOAc–IPE). $^1$H-NMR ($CDCl_3$) $\delta$: 1.30 (6H, d, $J$=6.6 Hz), 2.77 (2H, t, $J$=7.3 Hz), 3.71 (2H, m), 4.87 (1H, m), 6.26 (1H, m), 6.60 (1H, m), 6.96 (1H, m), 10.16 (1H, br s). **8e**: 87% yield, colorless crystals, mp 115.0—120.0 °C. $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.90 (3H, t, $J$=7.3 Hz), 1.28 (2H, m), 1.57 (2H, m), 2.56 (2H, t, $J$=7.3 Hz), 3.47 (2H, m), 3.66 (2H, m), 6.12 (1H, m), 6.43 (1H, m), 6.86 (1H, m), 11.39 (1H, s). **8f**: 96% yield, colorless crystals, mp 146.0—147.5 °C (EtOAc–IPE). $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.62 (2H, t, $J$=7.3 Hz), 3.68 (2H, m), 4.82 (2H, s), 6.07 (1H, m), 6.34 (1H, m), 6.90 (1H, m), 7.21—7.46 (5H, m), 11.52 (1H, s), 12.36 (1H, br).

**3-(2-Pyrrolecarboxamido)propionic Acid (8g)** i) Pyrrole-2-carboxylic acid (5.34 g, 48.1 mmol) was allowed to react with $\beta$-alanine benzyl ester *p*-toluenesulfonate (18.59 g, 52.9 mmol), DEPC (9.42 g, 57.7 mmol) and $Et_3N$ (11.68 g, 115.4 mmol) in DMF (140 ml), in a similar manner to that described for compound **7b**. After an analogous work-up to that used to prepare **7b**, the resultant residue was subjected to column chromatography. Elution with EtOAc–hexane (1 : 1) gave a crystalline product, which was recrystallized from $CHCl_3$–IPE to afford benzyl 3-(2-pyrrolecarboxamido)propionate (**7g**) (11.65 g, 89%) as colorless crystals, mp 82.0—83.0 °C. IR (KBr): 3394, 3276, 1732, 1613, 1567, 1529 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.68 (2H, t, $J$=6.9 Hz), 3.69 (2H, m), 5.14 (2H, s), 6.20 (1H, m), 6.50 (1H, m), 6.55 (1H, m), 7.30—7.40 (5H, m), 9.95 (1H, br).

ii) A suspension of **7g** (10.0 g, 36.7 mmol) and 5% Pd/C (2.0 g, 20% wt eq) in tetrahydrofuran (THF) (300 ml) was vigorously stirred in a stream of hydrogen gas for 4 h. The reaction mixture was filtered through celite, and the filtrate was concentrated to give a crystalline product, which was recrystallized from $CH_3CN$ to afford **8g** (5.61 g, 84%) as colorless crystals, mp 148.0—150.0 °C. IR (KBr): 3600—3200, 1674, 1576 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.48 (2H, m), 3.42 (2H, m), 6.05 (1H, m), 6.74 (1H, m), 6.82 (1H, m), 8.01 (1H, t, $J$=5.3 Hz), 11.38 (1H, s), 12.17 (1H, br).[21]

**7-Methyl-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepine-4,8-dione (9a)**[21] A mixture of **8a** (7.00 g, 35.7 mmol) and approximately 80% PPA (250 g) was mechanically stirred at 100 °C for 30 min. The reaction mixture was poured into ice-water, and extracted with $CHCl_3$ (4×200 ml). The organic layer was washed with saturated NaCl, dried, and concentrated to afford **9a** (5.58 g, 88%). mp 175.0—177.0 °C ($CHCl_3$–IPE), colorless crystals. IR (KBr): 3400—3050, 1668, 1646, 1615, 1552 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.89 (2H, m), 3.27 (3H, s), 3.73 (2H, m), 6.77 (1H, t, $J$=2.6 Hz), 6.94 (1H, t, $J$=2.6 Hz), 10.84 (1H, br).

Compounds **9c**—**g** were prepared similarly. **9c**: 79% yield, colorless crystals, mp 144.0—148.0 °C (EtOAc). $^1$H-NMR ($CDCl_3$) $\delta$: 0.99 (3H, t, $J$=7.5 Hz), 1.68 (2H, m), 2.87 (2H, m), 3.61 (2H, t, $J$=7.2 Hz), 3.70 (2H, m), 6.78 (1H, t, $J$=2.6 Hz), 6.94 (1H, t, $J$=2.6 Hz), 10.64 (1H, br). **9d**: 89% yield, colorless crystals, mp 155.0—158.0 °C (EtOAc). $^1$H-NMR ($CDCl_3$) $\delta$: 1.24 (6H, d, $J$=6.6 Hz), 2.82 (2H, m), 3.58 (2H, m), 5.05 (1H, m), 6.77 (1H, m), 6.94 (1H, t, $J$=2.7 Hz), 10.42 (1H, br). **9e**: 91% yield, pale brown crystals, mp 115.0—118.0 °C (EtOAc). $^1$H-NMR ($CDCl_3$) $\delta$: 0.97 (3H, t, $J$=7.3 Hz), 1.41 (2H, m), 1.64 (2H, m), 2.86 (2H, m), 3.64 (2H, t, $J$=7.3 Hz), 3.69 (2H, m), 6.78 (1H, m), 6.93 (1H, m), 10.42 (1H, br s). **9f**: 47% yield, colorless crystals, mp 176.0—179.0 °C ($CHCl_3$–hexane). $^1$H-NMR ($CDCl_3$) $\delta$: 2.74 (2H, m), 3.67 (2H, m), 4.87 (2H, s), 6.77 (1H, m), 6.89 (1H, t, $J$=2.6 Hz), 7.22—7.44 (5H, m), 11.24 (1H, br). **9g**: 68% yield, pale brown powder, mp >250 °C. $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.71 (2H, m), 3.37 (2H, m), 6.56 (1H, m), 6.99 (1H, m), 8.32 (1H, t, $J$=4.6 Hz), 12.16 (1H, br s).[21]

**7-Ethyl-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepine-4,8-dione (9b)** Oxalyl chloride (1.52 g, 12 mmol) and DMF (1 drop, a catalytic amount) were added successively to a stirred solution of **8b** (2.10 g, 10 mmol) in THF (30 ml) at room temperature, and the mixture was stirred for 3 h. After evaporation of the solvent, the residue was dissolved in 1,2-dichloroethane (100 ml). To this solution was added aluminum chloride (4.00 g, 30 mmol) at room temperature, and the mixture was stirred at 50 °C for 2 h, and then at room temperature for 20 h. The mixture was poured into ice-water (300 g) and the layers were separated. The aqueous layer was extracted with $CHCl_3$ (2×200 ml). The combined organic layer was washed with saturated NaCl, dried and evaporated. The residue was purified by column chromatography (eluent; EtOAc : hexane = 3 : 2) to give **9b** (1.54 g, 80%). mp 131.0—133.0 °C (isopropanol (IPA)), colorless crystals. IR (KBr): 3400—3000, 1634, 1550 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.27 (3H, t, $J$=7.3 Hz), 2.88 (2H, m), 3.60—3.82 (4H, m), 6.77 (1H, t, $J$=2.6 Hz), 6.94 (1H, m), 11.00 (1H, br).

**1-(4-Chlorobutyl)-7-methyl-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepine-4,8-dione (10a)** A suspension of **9a** (2.67 g, 15 mmol), 1,4-dichlorobutane (7.62 g, 60 mmol) and $K_2CO_3$ (8.29 g, 60 mmol) in DMF (150 ml) was heated at 80 °C for 5 h. The reaction mixture was poured into 5% HCl (200 ml) and diluted with EtOAc–benzene (2 : 1 v/v, 500 ml). The organic layer was washed with water (3×200 ml) and saturated NaCl, dried and concentrated. The residue was purified by column chromatography (eluent; EtOAc : hexane = 1 : 1) to give **10a** (3.91 g, 97%). Recrystallization from EtOAc–hexane afforded colorless crystals, mp 59.0—60.5 °C. IR ($CHCl_3$): 2945, 1660, 1635, 1520 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.80 (2H, m), 1.98 (2H, m), 2.79 (2H, m), 3.21 (3H, s), 3.54 (2H, t, $J$=6.6 Hz), 3.71 (2H, m), 4.36 (2H, t, $J$=7.2 Hz), 6.65 (1H, d, $J$=2.6 Hz), 6.80 (1H, d, $J$=2.6 Hz).

Compounds **10b**—**j** were prepared similarly. **10b**: 69% yield, colorless crystals, mp 81.5—83.0 °C (IPE). $^1$H-NMR ($CDCl_3$) $\delta$: 1.80—2.07 (4H, m), 2.79 (2H, m), 3.21 (3H, s), 3.40 (2H, t, $J$=6.3 Hz), 3.72 (2H, m), 4.36 (2H, t, $J$=7.0 Hz), 6.65 (1H, d, $J$=2.6 Hz), 6.80 (1H, d, $J$=2.6 Hz). **10c**: 85% yield, colorless crystals, mp 85.0—87.0 °C (EtOAc). $^1$H-NMR ($CDCl_3$) $\delta$: 2.32 (2H, m), 2.80 (2H, m), 3.21 (3H, s), 3.53 (2H, t, $J$=6.0 Hz), 3.71 (2H, m), 4.48 (2H, t, $J$=6.6 Hz), 6.67 (1H, t, $J$=2.7 Hz), 6.86 (1H, d, $J$=2.7 Hz). **10d**: 90% yield, colorless oil. $^1$H-NMR ($CDCl_3$) $\delta$: 1.47 (2H, m), 1.75—1.90 (4H, m), 2.77 (2H, dd, $J$=3.9, 6.6 Hz), 3.21 (3H, s), 3.53 (2H, t, $J$=6.6 Hz), 3.71 (2H, m), 4.33 (2H, t, $J$=7.3 Hz), 6.64 (1H, d, $J$=2.7 Hz), 6.79 (1H, d, $J$=2.7 Hz). **10e**: 94% yield, colorless crystals, mp 58.0—59.0 °C (IPE). $^1$H-NMR ($CDCl_3$) $\delta$: 1.25 (3H, t, $J$=7.0 Hz), 1.80 (2H, m), 1.97 (2H, m), 2.79 (2H, m), 3.53 (2H, t, $J$=6.6 Hz), 3.57—3.77 (4H, m), 4.38 (2H, t, $J$=7.3 Hz), 6.64 (1H, d, $J$=3.3 Hz), 6.80 (1H, d, $J$=3.3 Hz). **10f**: 98% yield, colorless oil. $^1$H-NMR ($CDCl_3$) $\delta$: 0.98 (3H, t, $J$=7.3 Hz), 1.66 (2H, m), 1.81 (2H, m), 1.96 (2H, m), 2.78 (2H, m), 3.50—3.58 (4H, m), 3.68 (2H, m), 4.37 (2H, t, $J$=7.3 Hz), 6.64 (1H, d, $J$=3.0 Hz), 6.80 (1H, d, $J$=3.0 Hz). **10g**: 88% yield, colorless oil. $^1$H-NMR ($CDCl_3$) $\delta$: 1.22 (6H, d, $J$=7.3 Hz), 1.77 (2H, m), 1.97 (2H, m), 2.75 (2H, m), 3.50—3.59 (4H, m), 4.38 (2H, t, $J$=7.0 Hz), 5.04 (1H, m), 6.64 (1H, d, $J$=3.0 Hz), 6.79 (1H, d, $J$=3.0 Hz). **10h**: 98% yield, colorless oil. $^1$H-NMR ($CDCl_3$) $\delta$: 0.97 (3H, t, $J$=7.2 Hz), 1.42 (2H, m), 1.62 (2H, m), 1.81 (2H, m), 1.96 (2H, m), 2.78 (2H, m), 3.52 (2H,

t, $J$=6.5 Hz), 3.58 (2H, m), 3.59 (2H, t, $J$=7.2 Hz), 4.37 (2H, t, $J$=7.3 Hz), 6.65 (1H, d, $J$=3.0 Hz), 6.79 (1H, d, $J$=3.0 Hz). **10i**: 76% yield, colorless oil. $^1$H-NMR ($CDCl_3$) $\delta$: 1.82 (2H, m), 2.00 (2H, m), 2.63 (2H, m), 3.56 (2H, t, $J$=6.6 Hz), 3.65 (2H, m), 4.43 (2H, t, $J$=7.0 Hz), 4.80 (2H, s), 6.65 (1H, d, $J$=2.7 Hz), 6.82 (1H, d, $J$=2.7 Hz), 7.28—7.42 (5H, m). **10j**: 77% yield, colorless crystals, mp 77.0—78.0 °C (EtOAc–hexane). $^1$H-NMR ($CDCl_3$) $\delta$: 1.79 (2H, m), 1.98 (2H, m), 2.83 (2H, m), 3.42—3.67 (4H, m), 4.42 (2H, t, $J$=7.0 Hz), 6.74 (1H, d, $J$=3.0 Hz), 6.85 (1H, d, $J$=3.0 Hz), 7.10 (1H, br t).

**1-(4-Chlorobutyl)-4-hydroxy-7-methyl-1,4,5,6,7,8-hexahydropyrrolo-[2,3-*c*]azepin-8-one (12a)** To a stirred solution of **10a** (2.84 g, 10.6 mmol) in EtOH (100 ml) was added portionwise $NaBH_4$ (1.51 g, 40 mmol) at 0 °C, and stirring was continued at 0 °C for 1 h, and then at room temperature for 40 h. After the solvent was removed *in vacuo*, the residue was diluted with water (150 ml) and then extracted with $CH_2Cl_2$ (3×100 ml). The combined organic extracts were washed with saturated NaCl, dried, and concentrated to give an oil, which was purified by column chromatography (eluent; EtOAc : hexane=4 : 1) to give **12a** (2.85 g, 100%) as a colorless oil. IR (film): 3399, 2944, 1612, 1535 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.76 (2H, m), 1.91 (2H, m), 2.01 (1H, m), 2.08—2.33 (2H, m), 3.11 (3H, s), 3.33 (1H, m), 3.45—3.58 (3H, m), 4.30 (2H, m), 4.87 (1H, m), 6.17 (1H, d, $J$=2.6 Hz), 6.76 (1H, d, $J$=2.6 Hz).

**1-(4-Chlorobutyl)-7-methyl-1,6,7,8-tetrahydropyrrolo[2,3-*c*]azepin-8-one (12b)** To a stirred solution of **12a** (286 mg, 1.06 mmol) in $CHCl_3$ (15 ml) was added a saturated solution of hydrogen chloride in $CHCl_3$ (1 ml) under ice-cooling. The mixture was stirred at room temperature for 1 h, and concentrated. The residue was purified by column chromatography (eluent; EtOAc : hexane=1 : 1) to give **12b** (252 mg, 94%) as a colorless oil. IR (film): 2953, 1620, 1523 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.80 (2H, m), 1.97 (2H, m), 3.12 (3H, s), 3.52 (2H, t, $J$=6.6 Hz), 3.67 (2H, d, $J$=6.6 Hz), 4.39 (2H, t, $J$=7.3 Hz), 5.98 (1H, dt, $J$=6.6, 9.2 Hz), 6.10 (1H, d, $J$=2.9 Hz), 6.75 (1H, d, $J$= 9.2 Hz), 6.80 (1H, d, $J$=2.9 Hz).

**1-(4-Chlorobutyl)-7-methyl-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepin-8-one (12c)** A suspension of **12b** (803 mg, 3.18 mmol) and 10% Pd/C (80 mg, 10% wt eq) in THF (30 ml) was vigorously stirred under an atmosphere of hydrogen for 16 h at room temperature. The catalyst was filtered through celite and washed with $CHCl_3$. The combined filtrate and washings were concentrated to give **12c** (735 mg, 91%) as a colorless oil. IR (film): 2938, 1624 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.73 (2H, m), 1.82—2.10 (4H, m), 2.70 (2H, t, $J$=7.3 Hz), 3.10 (3H, s), 3.35 (2H, t, $J$=6.0 Hz), 3.50 (2H, t, $J$=6.6 Hz), 4.24 (2H, t, $J$=6.6 Hz), 5.92 (1H, s), 6.68 (1H, s).

**(*E*)-1-(4-Chlorobutyl)-4-hydroxyimino-7-methyl-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepin-8-one (14a) and (*Z*)-1-(4-Chlorobutyl)-4-hydroxyimino-7-methyl-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepin-8-one (14a′)** A solution of **10a** (755 mg, 2.81 mmol), hydroxylamine hydrochloride (391 mg, 5.62 mmol) and sodium acetate (461 mg, 5.62 mmol) in MeOH (20 ml) was stirred under reflux for 5 h. The reaction mixture was concentrated, and the residue was taken up in EtOAc (30 ml), washed with half-saturated $K_2CO_3$ (15 ml) and saturated NaCl (15 ml), dried and then concentrated to give a crystalline product, which contained **14a** (*Rf* 0.28/EtOAc : hexane=2 : 1) for the most part and a trace amount of its isomer (**14a′**) (*Rf* 0.10/EtOAc : hexane=2 : 1). The mixture was subjected to column chromatography eluting with EtOAc–hexane (2 : 1) to give (*E*)-oxime (**14a**) (749 mg, 94%) as colorless crystals from the first fraction. The second fraction yielded (*Z*)-oxime (**14a′**) (11 mg, 1.4%) as colorless crystals. **14a**: mp 118.0—119.0 °C (EtOAc). IR (KBr): 3234, 1604, 1531 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.76 (2H, m), 1.93 (2H, m), 2.97 (2H, m), 3.13 (3H, s), 3.51 (2H, t, $J$=6.5 Hz), 3.57 (2H, m), 4.31 (2H, t, $J$=7.1 Hz), 6.39 (1H, d, $J$=2.7 Hz), 6.76 (1H, d, $J$=2.7 Hz), 8.70 (1H, br s). **14a′**: mp 116.0—117.0 °C (EtOAc). IR (KBr): 3280, 1619, 1601, 1523 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.77 (2H, m), 1.94 (2H, m), 2.87 (2H, m), 3.13 (3H, s), 3.51 (2H, t, $J$=6.5 Hz), 3.55 (2H, m), 4.31 (2H, t, $J$=7.0 Hz), 6.82 (1H, d, $J$=2.4 Hz), 7.04 (1H, d, $J$=2.4 Hz), 8.72 (1H, br).

Compounds **14c** and **14i** were prepared similarly. In the syntheses of **14c**, *O*-benzylhydroxylamine hydrochloride was used, instead of hydroxylamine hydrochloride. **14c**: 87% yield, colorless crystals, mp 62.0—64.0 °C (IPE). $^1$H-NMR ($CDCl_3$) $\delta$: 1.76 (2H, m), 1.92 (2H, m), 2.94 (2H, m), 3.10 (3H, s), 3.46—3.59 (4H, m), 4.30 (2H, t, $J$=6.9 Hz), 5.18 (2H, s), 6.43 (1H, d, $J$=3.0 Hz), 6.75 (1H, d, $J$=3.0 Hz), 7.26—7.45 (5H, m). **14i**: 86% yield, pale brown crystals, mp 133.0—136.0 °C (EtOH). $^1$H-NMR ($CDCl_3$) $\delta$: 0.96 (3H, t, $J$=7.3 Hz), 1.39 (2H, m), 1.61 (2H, m), 1.78 (2H, m), 1.92 (2H, m), 2.96 (2H, m), 3.50 (4H, t, $J$=6.6 Hz), 3.54 (2H, m), 4.32 (2H, t, $J$=7.0 Hz), 6.38 (1H, d, $J$=2.6 Hz), 6.75 (1H, d, $J$=2.6 Hz), 7.26 (1H, br s).

**(*E*)-1-(4-Chlorobutyl)-7-ethyl-4-hydroxyimino-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepin-8-one (14f)** A solution of **10e** (1.41 g, 5 mmol) and hydroxylamine hydrochloride (1.74 g, 25 mmol) in pyridine (30 ml) was stirred at room temperature for 17 h. The solvent was evaporated, and the last traces of pyridine were coevaporated with toluene. The residue was dissolved with 10% citric acid (200 ml) and then extracted with $CHCl_3$ (3×100 ml). The combined organic extracts were washed with saturated NaCl (100 ml), dried, and concentrated to give an oil which was purified by column chromatography (eluent; $CHCl_3$ : MeOH=19 : 1) to give **14f** (1.45 g, 97%) as a colorless oil. IR ($CHCl_3$): 3570, 3250, 2940, 1625 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.23 (3H, t, $J$=7.0 Hz), 1.75 (2H, m), 1.91 (2H, m), 2.99 (2H, m), 3.40—3.68 (6H, m), 4.32 (2H, t, $J$=7.2 Hz), 6.39 (1H, d, $J$=3.3 Hz), 6.75 (1H, d, $J$=3.3 Hz), 9.56 (1H, br s).

Compounds **14b**, **14d**—**h**, **14j** and **14k** were prepared similarly. In the syntheses of **14b**, *O*-methylhydroxylamine hydrochloride was used, instead of hydroxylamine hydrochloride.

**14b**: 47% yield, a brown oil. $^1$H-NMR ($CDCl_3$) $\delta$: 1.78 (2H, m), 1.93 (2H, m), 2.90 (2H, m), 3.11 (3H, s), 3.49—3.56 (4H, m), 3.94 (3H, s), 4.30 (2H, t, $J$=7.2 Hz), 6.43 (1H, d, $J$=3.0 Hz), 6.76 (1H, d, $J$=3.0 Hz). **14d**: 86% yield, colorless crystals, mp 158.0—161.0 °C (EtOAc). $^1$H-NMR ($CDCl_3$) $\delta$: 2.28 (2H, m), 2.98 (2H, m), 3.13 (3H, s), 3.51 (2H, t, $J$=6.6 Hz), 3.57 (2H, m), 4.42 (2H, t, $J$=6.6 Hz), 6.40 (1H, d, $J$=3.0 Hz), 6.82 (1H, d, $J$=3.0 Hz), 7.94 (1H, br s). **14e**: 87% yield, colorless crystals, mp 113.0—115.0 °C (EtOAc). $^1$H-NMR ($CDCl_3$) $\delta$: 1.44 (2H, m), 1.73—1.86 (4H, m), 2.97 (2H, m), 3.13 (3H, s), 3.52 (2H, t, $J$=6.6 Hz), 3.58 (2H, m), 4.28 (2H, t, $J$=7.3 Hz), 6.38 (1H, d, $J$=2.6 Hz), 6.76 (1H, d, $J$=2.6 Hz), 8.55 (1H, br s). **14g**: 64% yield, colorless crystals, mp 93.0—95.0 °C (EtOH–IPE). $^1$H-NMR ($CDCl_3$) $\delta$: 0.96 (3H, t, $J$=7.3 Hz), 1.56—1.85 (4H, m), 1.93 (2H, m), 2.97 (2H, m), 3.43—3.63 (6H, m), 4.32 (2H, t, $J$=7.2 Hz), 6.39 (1H, d, $J$=2.7 Hz), 6.76 (1H, d, $J$=2.7 Hz), 8.54 (1H, br s). **14h**: 68% yield, colorless crystals, mp 111.0—113.0 °C (IPE). $^1$H-NMR ($CDCl_3$) $\delta$: 1.20 (6H, t, $J$=6.6 Hz), 1.74 (2H, m), 1.89 (2H, m), 2.93 (2H, m), 3.46 (2H, m), 3.50 (2H, t, $J$=6.6 Hz), 4.33 (2H, t, $J$=6.6 Hz), 4.93 (1H, m), 6.38 (1H, d, $J$=3.0 Hz), 6.76 (1H, d, $J$=3.0 Hz), 8.52 (1H, br s). **14j**: 96% yield, colorless crystals, mp 160.0—162.0 °C ($CHCl_3$–hexane). $^1$H-NMR ($CDCl_3$) $\delta$: 1.80 (2H, m), 1.95 (2H, m), 2.82 (2H, m), 3.42—3.61 (4H, m), 4.37 (2H, t, $J$=7.0 Hz), 4.73 (2H, s), 6.39 (1H, d, $J$=2.7 Hz), 6.78 (1H, d, $J$=2.7 Hz), 7.25—7.42 (5H, m), 8.87 (1H, br s). **14k**: 87% yield, colorless crystals, mp 158.5—159.5 °C ($CHCl_3$–hexane). $^1$H-NMR ($CDCl_3$) $\delta$: 1.77 (2H, m), 1.93 (2H, m), 2.97 (2H, m), 3.42 (2H, m), 3.52 (2H, t, $J$=6.6 Hz), 4.35 (2H, t, $J$=7.0 Hz), 6.44 (1H, d, $J$=2.7 Hz), 6.82 (1H, d, $J$=2.7 Hz), 7.06 (1H, d, $J$=5.9 Hz), 9.89 (1H, s).

**1-[4-[4-(2-Methoxyphenyl)piperazin-1-yl]butyl]-7-methyl-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepine-4,8-dione (11a)** A suspension of bromide **10b** (313 mg, 1 mmol), 1-(2-methoxyphenyl)piperazine (385 mg, 2 mmol) and $K_2CO_3$ (276 mg, 2 mmol) in DMF (10 ml) was stirred at 80 °C for 16 h. The mixture was diluted with EtOAc–benzene (3 : 1 v/v, 100 ml), and washed with saturated $K_2CO_3$, water (×2) and saturated NaCl. 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 **11a** (390 mg, 92%) as colorless crystals.

Compounds **11c′** (free base), **11e** and **11g** were prepared in the same manner as **11a**, except that for **11g**, **10a** was used instead of **10b**. **11c′** was converted into the hydrochloride and recrystallized to give **11c** as colorless crystals. Compound **11f** was similarly synthesized from **10a** (1 eq), 4-benzoylpiperidine hydrochloride (1.5 eq) and $K_2CO_3$ (3 eq). The physical data for compounds **11a**, **11c** and **11e**—**g** are listed in Table 4.

**7-Methyl-1-[4-(4-phenylpiperidino)butyl]-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepine-4,8-dione Hydrochloride (11d)** A suspension of chloride **10a** (806 mg, 3 mmol), 4-phenylpiperidine (1.94 g, 12 mmol) and NaI (4.50 g, 30 mmol) in DMF (70 ml) was stirred at 80 °C for 5 h. The work-up and purification was performed in a similar manner to that described for compound **11a** to give **11d′** (free base) (1.11 g, 94%) as a pale yellow oil, which was converted to the hydrochloride and recrystallized from IPA–IPE to give **11d** as pale yellow crystals. Compounds **11b** was prepared similarly. The physical data for compounds **11b** and **11d** are listed in Table 4.

**1-[4-[4-(4-Fluorobenzoyl)piperidino]butyl]-4-hydroxy-7-methyl-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepin-8-one (13a)** A suspension of **12a** (542 mg, 2 mmol), 4-FPB·HCl (487 mg, 2 mmol), NaI (600 mg, 4 mmol) and $K_2CO_3$ (1.11 g, 8 mmol) in $CH_3CN$ (30 ml) was stirred under reflux for 17 h. After the solvent was removed *in vacuo*, the residue was diluted with half-saturated $K_2CO_3$ (100 ml) and then extracted with $CH_2Cl_2$ (3×100 ml). The combined organic extracts were washed with saturated NaCl, dried, and concentrated to give a solid which was purified by column chromatography (eluent; $CHCl_3$ : MeOH=9 : 1) to give **13a** (627 mg, 71%)

Table 4. Physical and Spectral Data for Compounds **11a**—**g**, **13a**—**c** and **15a**—**k**

| Compd. No. | Yield (%)[a] | mp (°C) (Solvent)[b] | Formula | *Anal.* (%) Calcd (Found) C | H | N | $^1$H-NMR ($CDCl_3$) $\delta$ | IR ($cm^{-1}$) |
|---|---|---|---|---|---|---|---|---|
| **11a** | 92 | 142.5—144.5 (EA–H) | $C_{24}H_{32}N_4O_3$ | 425.2553 [MH]$^+$ (425.2538 [MH]$^+$)[d] | | | 1.57 (2H, m), 1.85 (2H, m), 2.45 (2H, m), 2.52—2.74 (4H, m), 2.79 (2H, dd, *J*=4.0, 6.6 Hz), 2.97—3.18 (4H, m), 3.21 (3H, s), 3.70 (2H, m), 3.86 (2H, s), 4.36 (2H, t, *J*=7.3 Hz), 6.64 (1H, d, *J*=3.0 Hz), 6.81 (1H, d, *J*=3.0 Hz), 6.83—7.06 (5H, m) | 2955, 1660, 1628[f] |
| **11b** | 96 | 115.0—116.0 (EA–H) | $C_{23}H_{29}FN_4O_2$ | 66.97 (66.92 | 7.09 7.09 | 13.58 13.46) | 1.55 (2H, m), 1.86 (2H, m), 2.41 (2H, t, *J*=7.3 Hz), 2.57 (4H, dd, *J*=4.6, 5.3 Hz), 2.78 (2H, m), 3.11 (4H, d, *J*=4.6, 5.3 Hz), 3.20 (3H, s), 3.72 (2H, m), 4.35 (2H, t, *J*=7.3 Hz), 6.64 (1H, d, *J*=3.3 Hz), 6.77—7.02 (m) and 6.81 (d, *J*=7.3 Hz) (total 5H) | 2930, 1655, 1630[g] |
| **11c** | 85 | 178.0—183.0 (M–EA–IPE) | $C_{24}H_{30}N_4O_3$ ·HCl | 62.80 (62.60 | 6.81 6.85 | 12.21 11.99) | 1.52 (2H, m), 1.85 (2H, m), 2.23—2.60 (m) and 2.39 (t, *J*=7.3 Hz) (total 6H), 2.78 (2H, dd, *J*=4.0, 6.0 Hz), 3.20 (3H, s), 3.30—3.90 (6H, m), 4.33 (2H, t, *J*=7.3 Hz), 6.63 (1H, d, *J*=3.0 Hz), 6.79 (1H, d, *J*=3.0 Hz), 7.32—7.49 (5H, m)[e] | 2938, 1667, 1629[f] |
| **11d** | 94 | 208.0—210.0 (IPA–IPE) | $C_{24}H_{31}N_3O_2$ ·HCl | 67.04 (66.79 | 7.50 7.55 | 9.77 9.70) | 1.56 (2H, m), 1.69—1.93 (6H, m), 2.04 (2H, dt, *J*=4.0, 11.2 Hz), 2.40 (2H, m), 2.49 (1H, m), 2.79 (2H, m), 3.02 (2H, m), 3.21 (3H, s), 3.71 (2H, m), 4.35 (2H, t, *J*=7.2 Hz), 6.64 (1H, d, *J*=2.6 Hz), 6.81 (1H, d, *J*=2.6 Hz), 7.13—7.35 (5H, m)[e] | 2940, 1655, 1620[f] |
| **11e** | 65 | —[c] | $C_{25}H_{33}N_3O_2$ | 408.2651 [MH]$^+$ (408.2635 [MH]$^+$)[d] | | | 1.35 (2H, m), 1.41—1.70 (5H, m), 1.70—1.98 (4H, m), 2.32 (2H, t, *J*=7.6 Hz), 2.53 (2H, d, *J*=6.6 Hz), 2.78 (2H, m), 2.89 (2H,m), 3.20 (3H, s), 3.70 (2H, m), 4.32 (2H, t, *J*=7.3 Hz), 6.62 (1H, d, *J*=2.6 Hz), 6.78 (1H, d, *J*=2.6 Hz), 7.07—7.35 (5H, m) | 2910, 1650, 1625[g] |
| **11f** | 61 | —[c] | $C_{25}H_{31}N_3O_3$ | 422.2443 [MH]$^+$ (422.2444 [MH]$^+$)[d] | | | 1.45—1.60 (2H, m), 1.75—1.90 (6H, m), 2.00—2.17 (2H, m), 2.38 (2H, t, *J*=7.5 Hz), 2.78 (2H, m), 2.87—3.01 (2H, m), 3.20 (3H, s), 3.24 (1H, m), 3.71 (2H, m), 4.34 (2H, t, *J*=7.3 Hz), 6.62 (1H, d, *J*=3.0 Hz), 6.80 (1H, d, *J*=3.0 Hz), 7.40—7.60 (3H, m), 7.92 (2H, d, *J*=7.9 Hz) | 2940, 1680, 1660, 1635, 1600[g] |
| **11g** | 86 | 107.0—109.0 (E–IPE) | $C_{25}H_{30}FN_3O_3$ | 68.32 (68.40 | 6.88 6.90 | 9.56 9.53) | 1.53 (2H, m), 1.72—1.92 (6H, m), 1.97—2.17 (2H, m), 2.38 (2H, t, *J*=7.3 Hz), 2.77 (2H, m), 2.96 (2H, m), 3.10—3.30 (m) and 3.21 (s) (total 4H), 3.72 (2H, m), 4.35 (2H, t, *J*=7.3 Hz), 6.63 (1H, d, *J*=2.6 Hz), 6.80 (1H, d, *J*=2.6 Hz), 7.13 (2H, t, *J*=8.6 Hz), 7.96 (2H, m) | 2930, 1660, 1635, 1600[g] |
| **13a** | 71 | 119.0—120.5 (EA–H) | $C_{25}H_{32}FN_3O_3$ | 68.01 (67.91 | 7.30 7.28 | 9.52 9.52) | 1.48 (2H, m), 1.72—1.88 (6H, m), 1.91—2.07 (3H, m), 2.27 (1H, m), 2.35 (2H, m), 2.95 (2H, m), 3.12 (3H, s), 3.18 (1H, m), 3.36 (1H, m), 3.51 (1H, m), 4.29 (2H, m), 4.91 (1H, dd, *J*=4.8, 6.1 Hz), 6.15 (1H, d, *J*=2.7 Hz), 6.76 (1H, d, *J*=2.7 Hz), 7.13 (2H, t, *J*=8.6 Hz), 7.95 (2H, m) | 3363, 2946, 1676, 1594[f] |
| **13b** | 99 | —[c] | $C_{25}H_{30}FN_3O_2$ | 424.2401 [MH]$^+$ (424.2393 [MH]$^+$)[d] | | | 1.52 (2H, m), 1.71—1.92 (6H, m), 2.10 (2H, m), 2.39 (2H, m), 2.97 (2H, m), 3.12 (3H, s), 3.20 (1H, m), 3.67 (2H, d, *J*=6.6 Hz), 4.37 (2H, t, *J*=7.3 Hz), 5.97 (1H, dt, *J*=6.6, 9.6 Hz), 6.08 (1H, d, *J*=2.7 Hz), 6.74 (1H, d, *J*=6.6 Hz), 6.81 (1H, d, *J*=2.7 Hz), 7.13 (2H, m), 7.96 (2H, m) | 2945, 1682, 1620[h] |
| **13c** | 79 | 76.0—78.5 (EA–IPE) | $C_{25}H_{32}FN_3O_2$ | 70.56 (70.44 | 7.58 7.60 | 9.87 9.80) | 1.50 (2H, m), 1.69—1.90 (6H, m), 1.95—2.15 (4H, m), 2.37 (2H, m), 2.70 (2H, t, *J*=7.9 Hz), 2.96 (2H, m), 3.10 (3H, s), 3.19 (1H, m), 3.35 (2H, m), 4.23 (2H, t, *J*=7.3 Hz), 5.91 (1H, d, *J*=2.6 Hz), 6.69 (1H, d, *J*=2.6 Hz), 7.16 (2H, m), 7.96 (2H, m) | 2932, 1673, 1622, 1596[f] |
| **15a** | 67 | 168.0—169.5 (E–W) | $C_{25}H_{31}FN_4O_3$ | 66.06 (65.90 | 6.87 6.89 | 12.33 12.27) | 1.54 (2H, m), 1.67—2.00 (6H, m), 2.13 (2H, m), 2.40 (2H, t, *J*=7.6 Hz), 2.80—3.08 (4H, m), 3.12 (3H, s), 3.21 (1H, quint, *J*=7.3 Hz), 3.56 (2H, m), 4.28 (2H, t, *J*=6.9 Hz), 6.35 (1H, d, *J*=2.6 Hz), 6.75 (1H, d, *J*=2.6 Hz), 7.13 (2H, t, *J*=6.9 Hz), 7.96 (2H, dd, *J*=5.6, 8.6 Hz), 10.16 (1H, br s) | 2936, 1670, 1629[f] |
| **15b** | 67 | —[c] | $C_{26}H_{33}FN_4O_3$ | 469.2615 [MH]$^+$ (469.2596 [MH]$^+$)[d] | | | 1.50 (2H, m), 1.75—1.88 (6H, m), 1.97—2.13 (2H, m), 2.35 (2H, m), 2.85—3.03 (4H, m), 3.11 (3H, s), 3.18 (1H, m), 3.54 (2H, m), 3.94 (3H, s), 4.28 (2H, m), 6.41 (1H, d, *J*=2.7 Hz), 6.76 (1H, d, *J*=2.7 Hz), 7.13 (2H, t, *J*=8.6 Hz), 7.96 (2H, m), | 2945, 1680, 1625, 1600[g] |
| **15c** | 78 | —[c] | $C_{32}H_{37}FN_4O_3$ | 545.2928 [MH]$^+$ (545.2936 [MH]$^+$)[d] | | | 1.48 (2H, m), 1.70—1.92 (6H, m), 2.03 (2H, m), 2.35 (2H,m), 2.87—3.02 (4H, m), 3.10 (3H, s), 3.16 (1H, m), 3.53 (2H, m), 4.28 (2H, t, *J*=7.3 Hz), 5.18 (2H, s), 6.41 (1H, d, *J*=2.6 Hz), 6.76 (1H, d, *J*=2.6 Hz), 7.13 (2H, m), 7.24—7.43 (5H, m), 7.95 (2H, m) | 2942, 1680, 1631, 1597[h] |
| **15d** | 69 | 194.0—197.0 (M) | $C_{24}H_{29}FN_4O_3$ | 65.44 (65.40 | 6.64 6.66 | 12.72 12.61) | 1.77—1.95 (4H, m), 1.90—2.18 (4H, m), 2.36 (2H, t, *J*=7.3 Hz), 2.90—3.02 (4H, m), 3.12 (3H, s), 3.20 (1H, m), 3.55 (2H, m), 4.31 (2H, m), 6.35 (1H, d, *J*=2.6 Hz), 6.78 (1H, d, *J*=2.6 Hz), 7.13 (2H, t, *J*=8.6 Hz), 7.95 (2H, m), 10.10 (1H, br s) | 3570, 2940, 1680, 1625, 1600[g] |

Table 4. (continued)

| Compd. No. | Yield (%)[a] | mp (°C) (Solvent)[b] | Formula | *Anal.* (%) Calcd (Found) C | H | N | $^1$H-NMR ($CDCl_3$) $\delta$ | IR ($cm^{-1}$) |
|---|---|---|---|---|---|---|---|---|
| **15e** | 93 | 167.0—170.0 (M) | $C_{26}H_{33}FN_4O_3$ | 66.65 (66.80 | 7.10 7.22 | 11.96 11.88) | 1.25—1.40 (2H, m), 1.46—1.62 (2H, m), 1.83—1.95 (6H, m), 2.02—2.17 (2H, m), 2.34 (2H, m), 2.90—3.08 (4H, m), 3.13 (3H, s), 3.14 (1H, m), 3.55 (2H, m), 4.25 (2H, m), 6.35 (1H, d, $J$=2.5 Hz), 6.74 (1H, d, $J$=2.5 Hz), 7.13 (2H, t, $J$=8.6 Hz), 7.96 (2H, dd, $J$=5.3, 8.6 Hz), 8.58 (1H, br s) | 3570, 2940, 1680, 1630, 1600[g] |
| **15f** | 85 | 99.0—104.0 (E) | $C_{24}H_{29}FN_4O_3$ | 65.44 (65.40 | 6.64 6.66 | 12.72 12.74) | 1.52 (2H, m), 1.66—1.98 (6H, m), 2.06 (2H, m), 2.37 (2H, t, $J$=7.3 Hz), 2.85—3.09 (4H, m), 3.18 (1H, quint, $J$=7.2 Hz), 3.40 (2H, m), 4.32 (2H, t, $J$=7.3 Hz), 6.42 (1H, d, $J$=2.6 Hz), 6.69 (1H, t, $J$=6.0 Hz), 6.80 (1H, d, $J$=2.6 Hz), 7.12 (2H, t, $J$=8.6 Hz), 7.95 (2H, dd, $J$=5.3, 8.6 Hz), 10.02 (1H, br s) | 3550, 2900, 1675, 1640, 1590[g] |
| **15g** | 69 | 158.0—160.0 (E) | $C_{26}H_{33}FN_4O_3$ | 66.65 (66.74 | 7.10 7.24 | 11.96 11.83) | 1.22 (3H, t, $J$=7.2 Hz), 1.51 (2H, m), 1.66—1.97 (6H, m), 2.08 (2H, m), 2.37 (2H, t, $J$=7.6 Hz), 2.80—3.08 (4H, m), 3.18 (1H, quint, $J$=7.3 Hz), 3.38—3.70 (4H, m), 4.30 (2H, t, $J$=6.9 Hz), 6.35 (1H, d, $J$=2.6 Hz), 6.74 (1H, d, $J$=2.6 Hz), 7.13 (2H, t, $J$=8.6 Hz), 7.95 (2H, dd, $J$=5.3, 8.6 Hz), 9.27 (1H, br s) | 3560, 2920, 1675, 1615, 1595[g] |
| **15h** | 57 | 157.0—159.0 (E) | $C_{27}H_{35}FN_4O_3$ | 67.20 (67.06 | 7.31 7.37 | 11.61 11.53) | 0.95 (3H, t, $J$=7.3 Hz), 1.40—2.15 (12H, m), 2.35 (2H, t, $J$=7.5 Hz), 2.80—3.05 (4H, m), 3.18 (1H, m), 3.40—3.60 (4H, m), 4.30 (2H, t, $J$=7.0 Hz), 6.35 (1H, d, $J$=2.9 Hz), 6.75 (1H, d, $J$=2.9 Hz), 7.13 (2H, m), 7.95 (2H, m), 8.85 (1H, br s) | 2936, 1670, 1628, 1595[f] |
| **15i** | 75 | 151.5—152.5 (E) | $C_{27}H_{35}FN_4O_3$ | 67.20 (66.93 | 7.31 7.26 | 11.61 11.45) | 1.20 (6H, d, $J$=7.3 Hz), 1.49 (2H, m), 1.70—1.88 (6H, m), 2.04 (2H, m), 2.34 (2H, m), 2.85—3.00 (4H, m), 3.17 (1H, m), 3.44 (2H, m), 4.31 (2H, m), 4.93 (1H, m), 6.35 (1H, d, $J$=2.6 Hz), 6.75 (1H, d, $J$=2.6 Hz), 7.12 (2H, m), 7.95 (2H, m), 8.35 (1H, br s) | 3560, 2930, 1680, 1615, 1600[g] |
| **15j** | 78 | 115.0—117.0 (E) | $C_{28}H_{37}FN_4O_3$ | 67.72 (67.80 | 7.51 7.57 | 11.28 11.22) | 0.95 (3H, t, $J$=7.3 Hz), 1.38 (2H, m), 1.50 (2H, m), 1.60 (2H, m), 1.65—1.95 (6H, m), 2.06 (2H, m), 2.35 (2H, t, $J$=7.5 Hz), 2.85—3.05 (4H, m), 3.18 (1H, m), 3.40—3.60 (4H, m), 4.30 (2H, t, $J$=7.0 Hz), 6.35 (1H, d, $J$=2.6 Hz), 6.74 (1H, d, $J$=2.6 Hz), 7.13 (2H, t, $J$=8.6 Hz), 7.95 (2H, dd, $J$=5.3, 8.6 Hz), 8.86 (1H, br s) | 2935, 1671, 1637, 1600[f] |
| **15k** | 52 | 182.0—185.0 (E–EE) | $C_{31}H_{35}FN_4O_3$ | 70.17 (70.12 | 6.65 6.81 | 10.56 10.48) | 1.52 (2H, m), 1.64—1.97 (6H, m), 2.06 (2H, m), 2.37 (2H, t, $J$=7.3 Hz), 2.80 (2H, m), 2.96 (2H, m), 3.17 (1H, quint, $J$=7.3 Hz), 3.50 (2H, m), 4.35 (2H, t, $J$=6.9 Hz), 4.72 (2H, s), 6.36 (1H, d, $J$=2.6 Hz), 6.78 (1H, d, $J$=2.6 Hz), 7.13 (2H, t, $J$=8.6 Hz), 7.20—7.41 (5H, m), 7.95 (2H, dd, $J$=5.3, 8.6 Hz), 9.13 (1H, br s) | 3575, 2940, 1680, 1625, 1600[g] |

*a*) Yield of amination step. *b*) Recrystallization solvent: EA=ethyl acetate, H=hexane, M=methanol, E=ethanol, W=water, EE=ethyl ether. *c*) Obtained as an oil. *d*) Determined by high-resolution mass spectrometry. *e*) Spectral data of the free base. *f*) KBr. *g*) $CHCl_3$. *h*) film.

as colorless crystals. Compounds **13b** and **13c** were synthesized similarly from **12b** and **12c**, respectively. The physical data for compounds **13a**—**c** are listed in Table 4.

**(*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 (15a)** A suspension of **14a** (2.84 g, 10 mmol), 4-FPB·HCl (2.44 g, 10 mmol), $Et_3N$ (2.02 g, 20 mmol) and NaI (3.00 g, 20 mmol) in $CH_3CN$ (30 ml) was refluxed for 22 h. After the solvent was removed *in vacuo*, the residue was diluted with 3.2% $K_2CO_3$ (150 ml) and then extracted with $CH_2Cl_2$ (3×100 ml). The combined organic extracts were washed with saturated NaCl (100 ml), dried, and concentrated. The residue was chromatographed using $CHCl_3$–MeOH (9 : 1) as eluent to give crude **15a** (4.24 g), which was recrystallized from EtOH–$H_2O$ using activated carbon to afford **15a** (3.05 g, 67%) as colorless crystals. The physical data for compound **15a** are listed in Table 4.

**(*E*)-1-[4-[4-(4-Fluorobenzoyl)piperidino]butyl]-4-methoxyimino-7-methyl-1,4,5,6,7,8-hexahydropyrrolo[2,3-*c*]azepin-8-one (15b)** A suspension of **14b** (100 mg, 0.34 mmol), 4-FPB·HCl (98 mg, 0.40 mmol), $Et_3N$ (101 mg, 1 mmol) and NaI (95 mg, 0.67 mmol) in DMF (5 ml) was stirred at 80 °C for 18 h. The mixture was diluted with EtOAc–benzene (3 : 1 v/v, 250 ml), and washed with half-saturated $K_2CO_3$, water (×2) and saturated NaCl . 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 **15b** (106 mg, 67%).

Compound **15c** was synthesized from **14c** in a similar manner, except that the reaction was carried out in $CH_3CN$ at reflux temperature. Compounds **15d** and **15e** were prepared from **14d** and **14e**, respectively, with 4-FPB·HCl (1.2 eq), $K_2CO_3$ (2.2 eq) and NaI (1 eq), and compounds **15f**—**k** were prepared from corresponding **14** with 4-FPB (1.2 eq), $Et_3N$ (2 eq) and NaI (2 eq) in a similar manner. The physical data for compounds **15b**—**k** are listed in Table 4.

**X-Ray Crystallographic Analysis of 15a** Diffraction measurements were performed on a Rigaku AFC-5R diffractometer using graphite monochromated $CuK_\alpha$ radiation ($\lambda$=1.54178 Å). Crystals of **15a** were grown from EtOAc and subjected to crystallographic analysis when they were found to belong to the orthorhombic space group *P*cab with the following unit cell parameters; $a$=11.110(1) Å, $b$=40.622(16) Å, $c$=10.680(1) Å, $\alpha=\beta=\gamma$=90°, $V$=4820.1(20) Å$^3$, $Z$=8. The final *R*-factor and weighted *R*-factor was 0.141 and 0.145, respectively.

**$\alpha_1$-Adrenergic and Serotonin (5-HT$_2$)-Receptor Antagonist Activity** The functional $\alpha_1$-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 killed 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

before transient contraction induced by serotonin. The functional $\alpha_1$- or serotonin (5-$HT_2$)-antagonist activity against NE or serotonin was determined as the reduction in peak contraction.

Regarding the selected compounds, the $pA_2$ values were determined to measure the potency of their antagonism of $\alpha_1$- 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** The blood pressure of conscious, unrestricted SHR was measured with a telemetry system according to the method reported by Schnell and Wood.[32] In brief, a male SHR (12-week-old) anesthetized with pentobarbital Na (50 mg/kg, i.p.) was shaved in the suprapubic region and scrubbed with polividoneiodine, and care was taken to maintain sterility throughout the operative procedure. With the aid of a microscope, the descending aorta was exposed through a midline incision in the abdomen. A sensor catheter (TA11PA-C40, Data Sciences) was placed in the aorta below the renal artery, pointing upstream. It was secured at the site of entry into the vessel with tissue adhesive (Vetbond, 3M). To prevent free movement of the transmitter, a tab fixed to it was sutured to the inner abdominal wall using a continuous suture with polyester thread. Immediately after surgery, the animal was given penicillin (50000 U/animal, Meiji-seika) intramuscularly and, after recovery, was returned to its cage. The animals were allowed to recover for a week before the start of data collection. One receiver (model RA1310, Data Sciences) was placed under each cage. The biotelemetry receivers were connected to a multiplexer (RMX 10, Data Sciences), and the digital signal was transferred *via* a consolidation matrix (BCM 100, Data Sciences) located in the animal room to a computer-based data acquisition system (Dataquest IV, version 1.21, Data Sciences). The computer was configured to record in cyclic runs of 1 min. During the cycles, each rat was measured for 5 s with a sampling rate of 250 Hz. The average values of systolic, diastolic and mean blood pressure were then computed and stored.

**Measurement of Platelet Aggregation** The platelet donors were five healthy volunteers aged 25—35 years who denied taking any medication which might alter platelet function for at least two weeks before the start of the study. Venous blood was mixed with one-tenth the volume of trisodium citrate (0.1 M, pH 7.35), and PRP was then obtained by centrifugation at $200\times\boldsymbol{g}$ for 5 min at room temperature. It was adjusted to a platelet count of about 300000 $\mu l^{-1}$ with autologous platelet-poor plasma, prepared by centrifugation at $900\times\boldsymbol{g}$ for 20 min. Platelet aggregation was measured by turbidometry in two dual-chamber channel platelet aggregometers (Mevanix, PAM-8C). PRP (200 $\mu$l) was incubated in the aggregation cuvette for 2 min with a test sample ($10^{-9}$—$10^{-6}$ M) and $CaCl_2$ (1 mM). Serotonin ($10^{-6}$ or $10^{-5}$ M) in combination with collagen (0.1 $\mu$g/ml), ADP ($10^{-6}$ M) or epinephrine ($10^{-6}$ M) was then added. The final volume of PRP+ agonists/test samples was 250 $\mu$l. 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, ADP and epinephrine were determined as the maximum concentrations which 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.

**Acknowledgments** We thank Drs. F. Satoh and T. Kanai for their encouragement throughout this work, and Dr. H. Fukami for useful suggestions during the preparation of this manuscript. Mr. T. Fujita and Dr. H. Naoki, Suntory Institute for Bioorganic Research, are gratefully acknowledged for the measurement of HR-FAB-MS. Thanks are also due to Mr. S. Matsuki and Mr. Y. Oyama for the X-ray crystallographic analyses.

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