Studies on Nonpeptide Angiotensin II Receptor Antagonists. III.[1] Synthesis and Biological Evaluation of 5-Alkylidene-3,5-dihydro-4*H*-imidazol-4-one Derivatives

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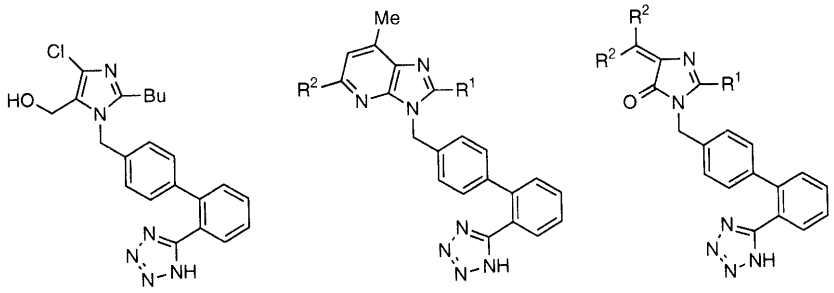
5-Alkylidene-3,5-dihydro-4*H*-imidazol-4-one derivatives were synthesized and evaluated for activity as angiotensin II receptor antagonists. Substitutions at C-2 and C-5, respectively, with a propyl group and a 1-methylethylidene group resulted in the optimal compound, 3,5-dihydro-5-(1-methylethylidene)-2-propyl-3-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-4*H*-imidazol-4-one (2b), with a pA_2 value of 8.85 in rabbit aorta. When administered orally to rats, 2b showed a greater inhibitory effect on angiotensin II-induced pressor response than DuP 753. Compound 2b also showed a good antihypertensive effect when administered orally to conscious sodium-depleted spontaneously hypertensive rats, with a duration of action of 24 h. These data suggest that 2b may be a useful agent for the treatment of angiotensin II-dependent diseases such as hypertension.

Key words angiotensin II; nonpeptide angiotensin II antagonist; dihydroimidazole; antihypertensive

The octapeptide angiotensin II (AII) is the primary component of the renin-angiotensin system (RAS) and plays an important role in the regulation of blood pressure, volume homeostasis, and salt retention.[3] Blockade of RAS with angiotensin converting enzyme (ACE) inhibitor has been shown to be beneficial in the treatment of hypertension or congestive heart failure.[4] The ACE, however, inhibits not only the generation of AII, but also the degradation of bradykinin and substance P, leading to adverse effects such as dry cough and angioedema.[5] Use of AII receptor antagonists may be a more specific approach to suppress the effect of the RAS.[6] Thus, the discovery of the first potent and orally active nonpeptide AII antagonist DuP 753 (losartan, Cozaar®)[7] has stimulated extensive research interest in this area.[8]

On the basis of the published work,[7,9] the structure–activity relationships (SAR) around the imidazole ring of DuP 753 are clear. First, the biphenyl acid, especially biphenylyltetrazole (BPT), linked to imidazole by a methylene group is essential for strong binding and oral potency. Second, a small alkyl group at the 2-position of the imidazole ring is necessary for high binding affinity. Third, the chloro and hydroxymethyl groups, respectively, at the 4- and 5-position are not essential for the activity. The substituent in the 4-position interacts with the receptor by occupying a lipophilic pocket, and the binding affinity of DuP 753 derivatives could be improved by replacing the chloro group with large lipophilic substituents, such as the bromo group and the perfluoroalkyl group. In addition to the hydroxymethyl group, functional groups such as a carboxylic acid group and a methoxycarbonyl group at the imidazole 5-position, which are capable of hydrogen-bonding interaction with the AII receptor, enhance the binding affinity. Similar SAR have also been demonstrated for imidazopyridines (**1** and L-158 809),[10] in which the methyl group at the 7-position is considered to be accepted by the same lipophilic pocket as the chloro group of DuP 753,[1a] and the pyridine nitrogen mimics the hydrogen-bonding activity.

Looking for a novel series of AII antagonists, our attention was focused on the nature of the substituents at the imidazole 4- and 5-position of DuP 753. We newly designed 5-alkylidene-3,5-dihydro-4*H*-imidazol-4-one as the head (compounds **2**) and examined their ability to antagonize AII *in vitro* and *in vivo*. The alkylidene group and the oxo group of **2** were respectively expected to mimic



DuP 753 (K salt)

1, R^1 = Pr, R^2 = H

L-158 809, R^1 = Et, R^2 = Me

2

R^1 = alkyl, alkylthio

R^2 = alkyl

Fig. 1

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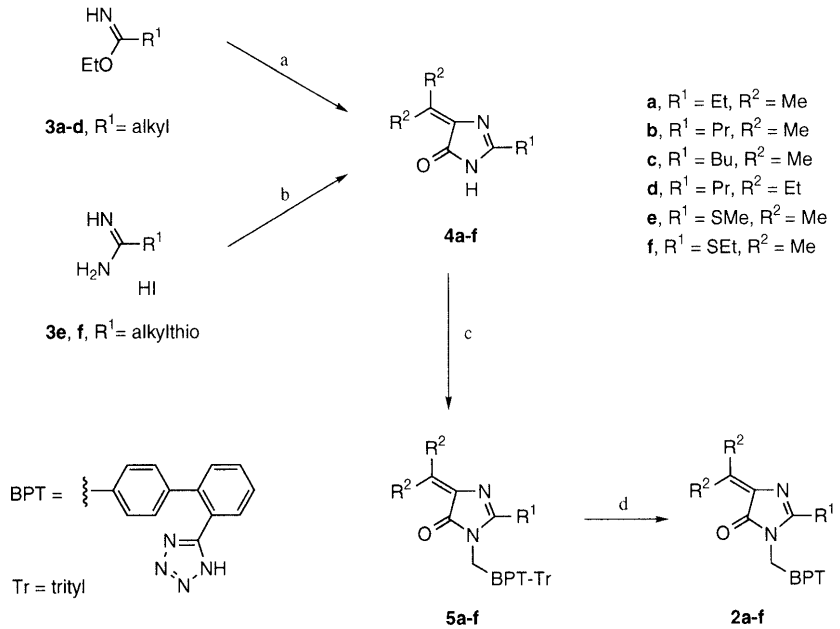


(a) NH_2CH_2COOEt, $(R^2)_2$ CO, reflux; (b) $BrCH_2COOEt$, acetone, Et_3N, reflux; (c) *N*-triphenylmethyl-5-[4′(bromomethyl)biphenyl-2-yl]tetrazole, *tert*-BuOK, DMF; (d) AcOH, MeOH, reflux.

Chart 1

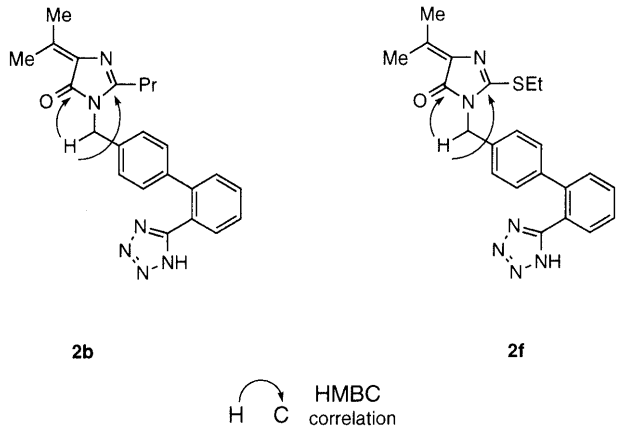


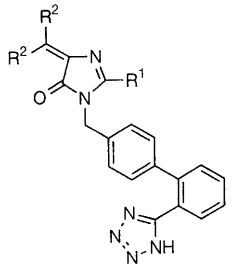
Fig. 2. HMBC Observations for Compounds **2b, f**

the lipophilic substituent and the hydrogen-bonding substituent. In this paper, we describe the synthesis and biological properties of this series of compounds.

Chemistry

The synthetic routes to the target compounds **2** are shown in Chart 1. 2-Alkyldihydroimidazole derivatives (**4a—d**) were obtained from the alkylimidates (**3a—d**) according to the literature method.[11] 2-Alkylthiodihydroimidazole derivatives (**4e, f**) were prepared by heating 2-alkylisothioureas hydroiodide (**3e, f**) with ethyl bromoacetate and triethylamine in acetone. Alkylation of **4a—f** in *N*,*N*-dimethylformamide (DMF) with *N*-triphenylmethyl-5-[4′-(bromomethyl)biphenyl-2-yl]tetrazole[7] using potassium *tert*-butoxide as a base gave the *N*(3)-isomers (**5a—f**) as major products. The trityl group of **5a—f** was cleaved by treatment with acetic acid in methanol to yield the final compounds (**2a—f**). The regiochemistry of the *N*(3)-isomers could be confirmed by heteronuclear multiple bond correlation (HMBC) experiments on the representative final compounds **2b, f** (Fig. 2).

Table 1. Physical Properties and *in Vitro* AII Antagonistic Potencies of Compounds **2a—f**



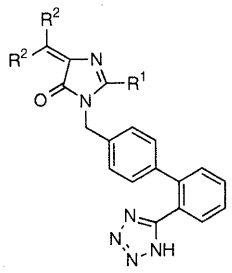
Compd.	R^1	R^2	Yield (%)[a]	mp (°C)	Formula[b]	pA_2
Dup 753						8.30
2a	Ethyl	Methyl	25	201—202	$C_{22}H_{22}N_6O \cdot 0.15H_2O$	8.37
2b	Propyl	Methyl	25	157—158	$C_{23}H_{24}N_6O$	8.85
2c	Butyl	Methyl	11	156—157	$C_{24}H_{26}N_6O$	8.60
2d	Propyl	Ethyl	18	Powder	$C_{25}H_{28}N_6O$[c]	8.51
2e	SMe	Methyl	13	199—200	$C_{21}H_{20}N_6OS$	7.99
2f	SEt	Methyl	25	184—185	$C_{22}H_{22}N_6OS$	8.68

a) Yield calculated from the intermediates **4a—f**. *b*) Analytical results were within ±0.3% of the theoretical values unless otherwise noted. *c*) Determined by HR-SIMS; $[M+H]^+$ (Calcd, 429.2403; Found, 429.2396).

Results and Discussion

The compounds were tested *in vitro* for the ability to inhibit the AII-induced contraction of rabbit thoracic strips. The compounds shifted the AII curve to the right in a parallel fashion (surmountable antagonism), and the pA_2 values were determined in order to compare the relative potencies. The pharmacological results are summarized in Table 1. First, it appeared that compound **2b**, which has a 1-methylethylidene group at the 5-position of the dihydroimidazole ring, showed potent antagonistic activity with a pA_2 value of 8.85. The pA_2 value of **2b** was about 3 times greater than that of DuP 753, which was used as a control compound. The high potency of **2b**

Table 2. *In Vivo* AII Antagonistic Potencies of Compounds **2a**—**f** and Oral Antihypertensive Activity of **2b**



Compd.	R^1	R^2	Inhibition[a] (%)	Antihypertensive activity[b,c] maximum decrease in blood pressure (%)			
				0—6 (h)	6—12 (h)	12—18 (h)	18—24 (h)
Dup 753			51	15	13	25	26
2a	Ethyl	Methyl	65				
2b	Propyl	Methyl	89	14	24	25	22
2c	Butyl	Methyl	51				
2d	Propyl	Ethyl	86				
2e	SMe	Methyl	43				
2f	SEt	Methyl	46				

a) Percent inhibition of AII-induced pressor response in pithed rats at 1 h after oral administration of test compounds (30 mg/kg). *b*) Effects of **2b** (30 mg/kg *p.o.*, $n=3$) and DuP 753 (30 mg/kg *p.o.*, $n=6$) on mean blood pressure in conscious sodium-depleted spontaneously hypertensive rats. *c*) Blank space, not tested.

suggests that the 1-methylethylidene group and the oxo group of the dihydroimidazole ring strongly contribute to the interaction with the AII receptor. Replacement of the 1-methylethylidene group of **2b** with the 1-ethylpropylidene group resulted in a 2-fold decrease in the activity (**2d**), suggesting that the volume of the substituent at the 5-position of the dihydroimidazole ring is critical in this series of compounds.[12] It is known that in the DuP 753 series, the *in vitro* activity varies markedly depending on the length of the alkyl chain at the 2-position of the imidazole ring.[7,9] Among these 2-alkyldihydroimidazole derivatives, the activity order was propyl (**2b**) > butyl (**2c**) > ethyl (**2a**). The alkyl group at the 2-position of the dihydroimidazole ring could be satisfactorily replaced by the alkylthio group from the viewpoint of *in vitro* activity, while the ethylthio group (**2f**) showed more potent activity than the methylthio group (**2e**).

The compounds were orally evaluated for the inhibition of AII-induced pressor response in pithed rats. The pharmacological results are summarized in Table 2. The oral potency depends on the substituent at the 2-position of the dihydroimidazole ring. In the 2-alkyl series, the order of activity was propyl (**2b** and **2d**) > ethyl (**2a**) > butyl (**2c**). 2-Alkylthio derivatives **2e**, **f** showed poor oral potency as compared to 2-alkyl derivatives **2a**—**d**, demonstrating that the substitution of the 2-position of the dihydroimidazole ring also affects the oral potency in this series of compounds. Compound **2b**, the most potent compound of this series in the *in vitro* and the *in vivo* tests, showed a greater inhibitory effect than DuP 753.

For measurement of antihypertensive effects, compound **2b** was given orally to conscious salt-depleted spontaneously hypertensive rats (SHRs), and the mean blood pressure (MBP) was monitored for 24 h (Table 2). Compound **2b** decreased MBP by 14—25% with a 24 h duration of action, and its potency was comparable to or better than that of DuP 753 at 0—18 h postdose. In this model, the onset of the activity was slower with DuP 753, presumably due to the delay incurred in the metabolism of DuP 753 to its active component, EXP3174.[13]

In conclusion, we have identified a novel series of 5-alkylidene-3,5-dihydro-4*H*-imidazol-4-one derivatives as potent AII antagonists. SAR studies of this series have led to the conclusion that **2b** is the optimal compound. In a rat model, **2b** showed a good oral antihypertensive effect, suggesting that **2b** may be applicable in the treatment of AII-related diseases such as hypertension.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a JEOL FX-90, a JNM-LA 300, a JNM-EX 400 or a JNM-GX 500 spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a Hitachi M-80 (electron impact (EI)), a JEOL JMS DX-300 (FAB) or a VG ZAD-SE (high resolution (HR)-MS) mass spectrometer. Elemental analysis was performed with a Yanaco MT-5. Column chromatography was performed on silica gel (Merck Kieselgel 60, 70—230 mesh). 2-Alkyl-5-alkylidene-1,5-dihydro-4*H*-imidazol-4-one derivatives **4a**—**d** were prepared as reported.[11]

1,5-Dihydro-5-(1-methylethylidene)-2-methylthio-4*H*-imidazol-4-one (4e)[14] A solution of 2-methylisothiourea hydroiodide (5.00 g, 22.9 mmol), ethyl bromoacetate (3.82 g, 22.9 mmol) and triethylamine (4.64 g, 45.8 mmol) in acetone (50 ml) was refluxed overnight. After filtration to remove the salt, the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography ($CHCl_3$: AcOEt = 10 : 1) to give a crystalline product, which was washed with *n*-hexane to give 0.74 g (19%) of **4e**, mp 155—158 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.22 (3H, s), 2.34 (3H, s), 2.60 (3H, s). EI-MS *m/z*: 170 (M^+). *Anal.* Calcd for $C_7H_{10}N_2OS$: C, 49.39; H, 5.92; N, 16.46; S, 18.84. Found: C, 49.10; H, 6.10; N, 16.28; S, 18.53.

1,5-Dihydro-2-ethylthio-5-(1-methylethylidene)-4*H*-imidazol-4-one (4f) Compound **4f** was prepared from 2-ethylisothiourea hydroiodide in a similar manner to that described for **4e**. Yield 21%, mp 117—118 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, t, $J=7.4$ Hz), 2.21 (3H, s), 2.34 (3H, s), 3.20 (2H, q, $J=7.4$ Hz). EI-MS *m/z*: 184 (M^+). *Anal.* Calcd for $C_8H_{12}N_2OS \cdot 0.1H_2O$: C, 51.64; H, 6.61; N, 15.06; S, 17.23. Found: C, 51.73; H, 6.89; N, 15.01; S, 17.21.

3,5-Dihydro-5-(1-methylethylidene)-2-propyl-3-[[2′-[*N*-(triphenylmethyl)tetrazol-5-yl]biphenyl-4-yl]methyl]-4*H*-imidazol-4-one (5b) Potassium *tert*-butoxide (182 mg, 1.62 mmol) was added portionwise to a solution of compound **4b** (270 mg, 1.62 mmol) and *N*-triphenylmethyl-5-[4′-(bromomethyl)biphenyl-2-yl]tetrazole (1.00 g, 1.79 mmol) in dry DMF (20 ml) at 0—10 °C under argon gas. The mixture was stirred for 2 h under ice-cooling, then poured into saturated aqueous NaCl solution and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (CH_2Cl_2 : AcOEt = 50 : 1—15 : 1) to give 0.47 g (45%) of **5b** as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, $J=7.4$ Hz), 1.62 (2H, m), 2.27—2.31 (5H, m), 2.44 (3H, s), 4.65 (2H, s), 6.91—6.97 (8H, m), 7.09 (2H, d, $J=7.8$ Hz), 7.23—7.52 (12H, m), 7.90—7.93 (1H, m). FAB-MS *m/z*: 643 $(M+H)^+$.

3,5-Dihydro-5-(1-methylethylidene)-2-propyl-3-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-4*H*-imidazol-4-one (2b) A solution of **5b** (0.46 g, 0.72 mmol) and acetic acid (3 ml) in MeOH (57 ml) was refluxed for 2 h and concentrated under reduced pressure. Toluene was added to the residue and evaporated *in vacuo*, and this was repeated 3 times. The residue was subjected to silica gel column chromatography. The $CHCl_3$–MeOH (23 : 2) eluate gave an oily product, which was crystallized from acetone–Et_2O to give **2b** (0.16 g, 56%), mp 157—158 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, t, $J=7.4$ Hz), 1.59 (2H, m), 2.13 (3H, s), 2.29—2.32 (5H, m), 4.72 (2H, s), 7.08 (2H, d, $J=8.8$ Hz), 7.10 (2H, d, $J=8.8$ Hz), 7.40—7.90 (4H, m). FAB-MS *m/z*: 401 $(M+H)^+$. *Anal.* Calcd for $C_{23}H_{24}N_6O$: C, 68.98; H, 6.04; N, 20.98. Found: C, 68.84; H, 5.82; N, 21.01.

The preparation of **2a**, **c**—**f** was carried out from the corresponding dihydroimidazole derivatives **4** according to the procedure described for **2b**.

3,5-Dihydro-2-ethyl-5-(1-methylethylidene)-3-[[2′-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]methyl]-4*H*-imidazol-4-one (2a) Yield 25% from **4a**. mp 201—202 °C (crystallized from acetone–Et_2O). ^{1}H-NMR ($CDCl_3$) δ: 1.09 (3H, t, J=7.5 Hz), 2.11 (3H, s), 2.30 (3H, s), 2.35 (2H, t, J=7.5 Hz), 4.69 (2H, s), 7.03 (2H, d, J=8.8 Hz), 7.05 (2H, d, J=8.8 Hz), 7.39—7.80 (4H, m), 12.86 (1H, br). FAB-MS m/z: 387 $(M+H)^+$. *Anal.* Calcd for $C_{22}H_{22}N_6O \cdot 0.15H_2O$: C, 67.90; H, 5.78; N, 21.60. Found: C, 68.13; H, 6.01; N, 21.32.

2-Butyl-3,5-dihydro-5-(1-methylethylidene)-3-[[2′-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]methyl]-4*H*-imidazol-4-one (2c) Yield 11% from **4c**. mp 156—157 °C (crystallized from acetone–Et_2O). ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, t, J=6.4 Hz), 1.10—1.80 (4H, m), 2.15 (3H, s), 2.20—2.50 (5H, m), 4.72 (2H, s), 7.11 (4H, s), 7.34—7.98 (4H, m). FAB-MS m/z: 415 $(M+H)^+$. *Anal.* Calcd for $C_{24}H_{26}N_6O$: C, 69.54; H, 6.32; N, 20.27. Found: C, 69.42; H, 6.37; N, 20.27.

3,5-Dihydro-5-(1-ethylpropylidene)-2-propyl-3-[[2′-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]methyl]-4*H*-imidazol-4-one (2d) Yield 18% from **4d**. ^{1}H-NMR (DMSO-d_6) δ: 0.88 (3H, t, J=7.4 Hz), 1.04—1.10 (6H, m), 1.54 (2H, m), 2.37 (2H, t, J=7.4 Hz), 2.61 (2H, q, J=8.0 Hz), 2.83 (2H, q, J=7.2 Hz), 4.74 (2H, s), 7.07 (2H, d, J=8.4 Hz), 7.12 (2H, d, J=8.4 Hz), 7.53—7.68 (4H, m). HR-MS m/z: 429.2396 $(M+H)^+$ (Calcd for $C_{25}H_{29}N_6O$: 429.2403).

3,5-Dihydro-5-(1-methylethylidene)-2-methylthio-3-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-4*H*-imidazol-4-one (2e) Yield 13% from **4e**. mp 199—200 °C (crystallized from AcOEt). ^{1}H-NMR (DMSO-d_6) δ: 2.17 (3H, s), 2.31 (3H, s), 2.55 (3H, s), 4.68 (2H, s), 7.07 (2H, d, J=7.9 Hz), 7.16 (2H, d, J=7.9 Hz), 7.53—7.70 (4H, m). FAB-MS m/z: 405 $(M+H)^+$. *Anal.* Calcd for $C_{21}H_{20}N_6OS$: C, 62.36; H, 4.98; N, 20.78; S, 7.93. Found: C, 62.24; H, 5.08; N, 20.63; S, 7.65.

3,5-Dihydro-2-ethylthio-5-(1-methylethylidene)-3-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-4*H*-imidazol-4-one (2f) Yield 25% from **4f**. mp 184—185 °C (crystallized from AcOEt). ^{1}H-NMR (DMSO-d_6) δ: 1.33 (3H, t, J=7.4 Hz), 2.17 (3H, s), 2.31 (3H, s), 3.18 (2H, q, J=7.4 Hz), 4.67 (2H, s), 7.07 (2H, d, J=8.3 Hz), 7.15 (2H, d, J=8.3 Hz), 7.53—7.70 (4H, m). FAB-MS m/z: 419 $(M+H)^+$. *Anal.* Calcd for $C_{22}H_{22}N_6OS$: C, 63.14; H, 5.30; N, 20.08; S, 7.66. Found: C, 62.97; H, 5.36; N, 19.99; S, 7.60.

Antagonism of AII-Contracted Rabbit Aorta Strips The thoracic aorta was isolated from male New Zealand White male rabbits weighing 2.0 to 4.5 kg. The aorta was cleaned of adherent fat and connective tissue, and cut into 3 mm wide and 30 mm long strips. The vascular endothelium was removed by gently rubbing the intimal surface of the vessel. Preparations were mounted in 30 ml organ baths containing Krebs–Henseleit solution (NaCl 118.4, KCl 4.7, $MgSO_4 \cdot 7H_2O$ 1.2, KH_2PO_4 1.2, $CaCl_2 \cdot 2H_2O$ 2.5, $NaHCO_3$ 25.0, and glucose 11.1 mM) maintained at 37 °C and bubbled with a 95% O_2, 5% CO_2 gas. Under a resting tension of 1.5 g, isometric tension changes were recorded on a polygraph (Rikadenki Kogyo, Japan) through a force displacement transducer (Nihon Kohden, Japan). After equilibration for 1 h, a single contractile–response curve to the cumulative addition of AII was constructed. The strips were then washed twice and allowed to relax to the baseline tension. Each strip was then incubated for 30 min with several concentrations of the test compounds and the concentration–response curves for AII were again obtained. The results are expressed as a percentage of the maximal AII response obtained with the first curve, which served as the control. EC_{50}s (AII concentration that contracted the strip to half the control maximum) for each curve were calculated. Potency data for each compound tested are expressed as the pA_2 (defined as $-\log K_B$, where K_B=(molar concentration of antagonist)/[(EC_{50} with antagonist/EC_{50} without antagonist)−1]).

Inhibition of Pressor Response to AII in Pithed Rats Male Wistar rats weighing 250 to 400 g (12 to 22 weeks old) were given an oral dose of test compounds (30 mg/kg). At set times after dosing, the rats were anesthetized with ether and pithed by inserting a steel rod through the orbit and foramen magnus down into the spinal canal. Immediately after pithing, the rats were vagotomized bilaterally at the neck and artificially ventilated with room air with a tidal volume of 1 ml/100 g body weight at a rate of 50 breaths/min using a rodent respirator (Shinano, Japan). Blood pressure was measured at the left carotid artery *via* a pressure transducer (Nihon Kohden, Japan) and recorded on a polygraph recorder (Nihon Kohden, Japan). The left femoral vein was cannulated for intravenous administration of AII (1 μg/kg). The pressor response to AII was measured at set times. One animal was used once for each drug. In a separate experiment, the control response to AII was obtained in untreated animals. Percent inhibition was calculated by means of the following formula: [(control response−response at set time)/(control response)] × 100.

Antihypertensive Effect in Conscious Sodium-Depleted SHRs Blood pressure was measured by a telemetry system. The system consists of 4 parts: a battery-operated transmitter, a receiver, a pressure reference module and data acquisition software (Data Sciences Inc., U.S.A.) running on an IBM PC/AT compatible computer. Male spontaneously hypertensive rats weighing 250 to 300 g were anesthetized with sodium pentobarbital (60 mg/kg, i.p.). A catheter which refers pressure to a sensor consisting of an implantable transmitter was inserted and secured in the abdominal aorta for continuous recording of the blood pressure. The rats were housed in individual cages after surgery. Each cage was placed on a receiver panel connected to the personal computer (Kyocera, Japan) to allow data storage. After the recovery periods from surgery (at least 10 d), rats were fed with a sodium-deficient diet (0.14 g/100 g NaCl diet, Oriental Bio-service Kanto, Japan). The antihypertensive activity of each compound was examined after oral administration to groups of three or six conscious rats. The mean blood pressure of each rat was recorded from 6 h before to 24 h after dosing; data in each group were averaged at 30-min intervals. Baseline blood pressure was determined by averaging data prior to dosing. Data in Table 2 are presented as the maximum percent decrease in mean blood pressure relative to the baseline.

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References and Notes

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