Studies on Nonpeptide Angiotensin II Receptor Antagonists. IV.[1] Synthesis and Biological Evaluation of 4-Acrylamide-1*H*-imidazole Derivatives

Toshio OKAZAKI,* Toshihiro WATANABE, Kazumi KIKUCHI, Akira SUGA, Masayuki SHIBASAKI, Akira FUJIMORI, Osamu INAGAKI, and Isao YANAGISAWA[2]

Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co., Ltd., 21 Miyukigaoka, Tsukuba, Ibaraki 305–8585, Japan. Received December 11, 1997; accepted January 26, 1998

A novel series of nonpeptide angiotensin II antagonists containing the acrylamide group at the 4-position of the imidazole ring was synthesized and their antagonistic activity was examined by functional assay in rabbit aorta. The acrylamide group was selected as a large lipophilic surrogate for the chloro group of EXP3174. A structure–activity relationship study of the acrylamide moiety has shown that substitution at the 4-position with the *N*-methyl-3,3-dimethylacrylamide group resulted in the optimal compound, 2-butyl-4-[(3,3-dimethylacryloyl)methylamino]-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-imidazole-5-carboxylic acid (1), which was superior to EXP3174 *in vitro*. Since 1 showed only poor activity against angiotensin II-induced pressor response in rats after oral administration, the carboxylic acid function of 1 was converted into prodrug esters (13). Among these, the 1-[(ethoxycarbonyl)oxy]ethyl ester (13a) showed the most potent and longest-lasting activity when given orally to rats. When administered orally to conscious furosemide-treated dogs, 13a showed an approximately 3-fold increased hypotensive activity in comparison with DuP 753. These data suggest that 13a may be an useful agent for the treatment of angiotensin II-dependent diseases, such as hypertension.

Key words nonpeptide angiotensin II antagonist; *N*-methyl-3,3-dimethylacrylamide; prodrug; antihypertensive

Angiotensin II (AII), an octapeptide produced by the renin–angiotensin system (RAS), plays an important role in the regulation of blood pressure, fluid volume homeostasis, and salt retention.[3] Blockade of the RAS *via* the use of angiotensin converting enzyme (ACE) inhibitors has been shown to provide therapeutic benefit in the treatment of hypertension and congestive heart failure.[4] However, the inherent side effects associated with ACE inhibitors, such as dry cough and angioedema, occur as a result of nonspecific effects of ACE on substrates other than angiotensin I.[5] Thus, antagonism of the AII receptor has long been recognized to offer another approach to intervention in the RAS without these undesirable side effects. Although many peptide AII antagonists have been available for a number of years, intravenous application is necessary due to their poor bioavailability.[6] Therefore, the discovery of the first potent and orally active nonpeptide AII antagonist, DuP753 (losartan, Cozaar®),[7] has stimulated extensive research interest in this area, and numerous patents and publications on AII antagonists have appeared over the last few years.[8]

On the basis of published studies,[7,9] some structure–activity relationships (SARs) are apparent for the 4- and 5-positions of the imidazole ring of DuP 753: 1) The chloro substituent at 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 a large lipophilic substituent such as a bromo, iodo or perfluoroalkyl group. 2) In addition to the hydroxymethyl group, a function such as a carboxyl group or a methoxycarbonyl group at the 5-position of the imidazole ring, which is capable of hydrogen-bonding interaction with the AII receptor, enhances the binding affinity. Compounds such as EXP3174[10] and DuP 532[11] with a carboxyl group at the 5-position show enhanced potency relative to DuP 753 and prolonged duration of action. EXP3174, the major active metabolite resulting from the oxidation of DuP 753 *in vivo* in rats, is believed to play a significant role in the antihypertensive effect of DuP 753.[12]

Looking for a new series of AII antagonists, we focused our attention on the nature of the substituents at the 4-position of the imidazole AII antagonists. We selected the amide group as a large lipophilic surrogate for the chloro group of EXP3174. It was assumed that the amide group, bearing R^c and R^d groups as lipophilic substituents, is able to participate effectively in interaction with the receptor (Fig. 1). Among these moieties, we selected the acrylamide group and evaluated the ability of its derivatives to antagonize AII *in vitro* and *in vivo*.[13] Herein, we report an SAR study of a series of acrylamide derivatives which led to the identification of compound **1**. In addition, we report enhanced oral potency of **1** in the form of prodrugs.

Chemistry The synthetic procedures for the key ethyl ester intermediates (**10**), which were also evaluated *in vitro*, are shown in Chart 1. The imidate hydrochlorides (**2**) were reacted with cyanamide in ethanol to give the *N*-cyanoimidates (**3**),[14] which were converted to the *N*-(*N*′-cyanoimidolyl)glycine derivatives (**4**) by treatment with glycine ethyl ester hydrochloride in ethanol in the presence of triethylamine.[15] Alkylation of **4** in *N*,*N*-dimethylformamide (DMF) with *N*-triphenylmethyl-5-[4′-(bromomethyl)biphenyl-2-yl]tetrazole[7] using sodium hydride as a base gave the intermediate *N*-cyanoamidines (**5**), which were cyclized to the 4-amino-1*H*-imidazole derivatives (**6**) by treatment of 0.5 eq of sodium hydride in DMF.[13] Compounds **6** were acylated with the acryloyl chloride derivatives (**7**) in pyridine (method A) or in dichloromethane with triethylamine as a base (method B) to afford the amide derivatives (**8**). Alkylation of **8** with alkyl iodides (R^2I) in DMF in the presence of sodium

* To whom correspondence should be addressed.

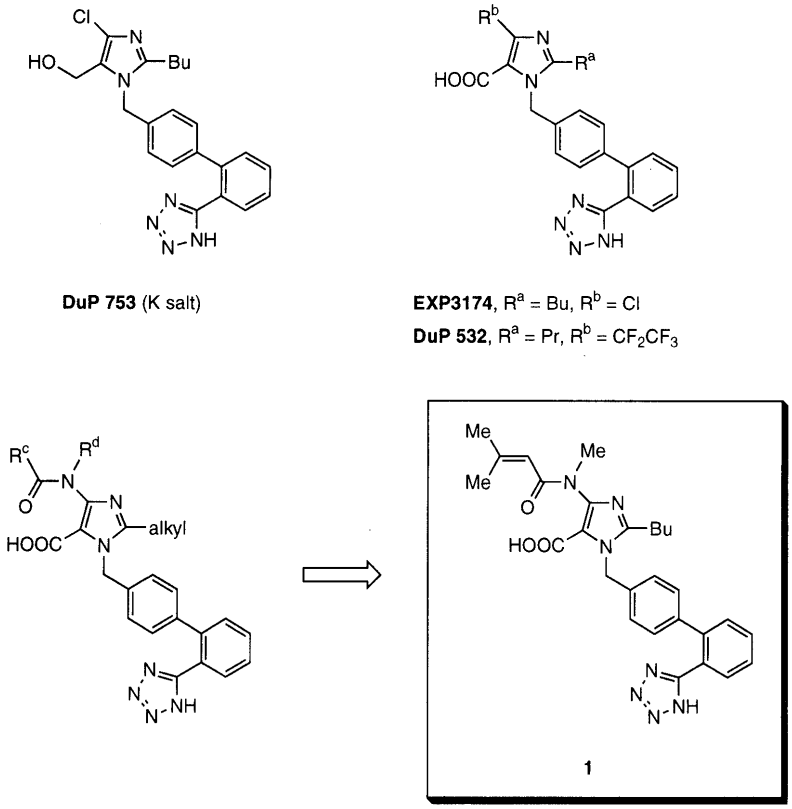


Fig. 1

hydride led to the *N*-alkylated compounds (**9**). Trityl-deprotection of **8** or **9** provided the ester derivatives **10a**—**m**.

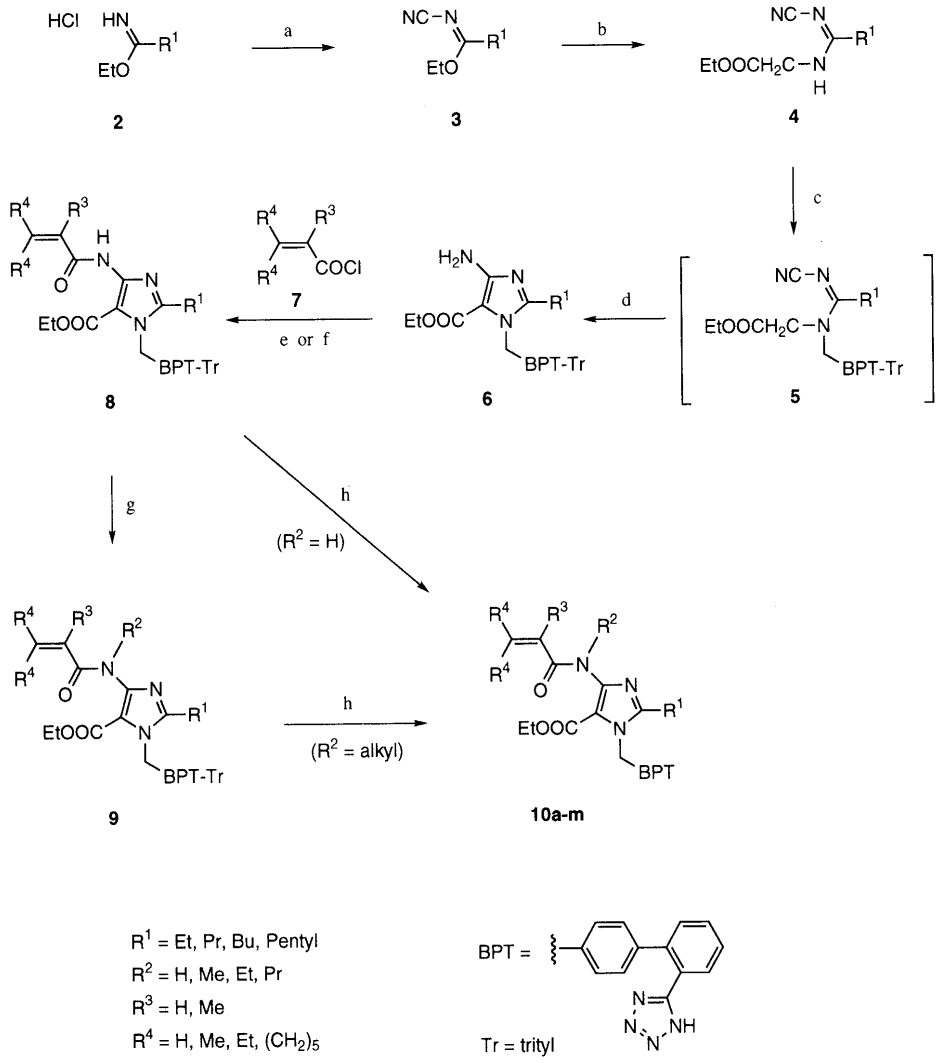
The synthesis of the acid **1** and its prodrugs (**13**) is summarized in Chart 2. Alkaline hydrolysis of the ester derivative **10h** gave the acid **1**, which was alkylated at the tetrazole ring with trityl chloride to give the trityl derivative **11**. The prodrugs **13a**—**d** were obtained by the reaction of the potassium salt of compound **11** with appropriate alkyl halides (R^5X) in acetone or DMF, followed by removal of the trityl group.

Results and Discussion

To identify the optimum acrylamide group at the 4-position of the imidazole ring, the ethyl esters **10** were tested *in vitro* for the ability to inhibit the AII-induced contraction of rabbit thoracic strips. The pA_2 values were determined in order to compare the relative potencies of the antagonists (pA_2; see experimental section and Table 1). The ethoxycarbonyl group at the 5-position of the imidazole ring would have a beneficial effect on the *in vitro* activity,[1b] and it was assumed that the best acrylamide group in the ethyl esters **10** is also the most favorable substituent for the biologically active carboxylic acid derivative.

First, it appeared that the *N*-methylacrylamide derivatives **10a** and **10f** showed potent antagonistic activity with pA_2 values of 8.54 and 9.15, respectively. Introduction of a methyl as R^3 resulted in an approximately 4-fold decrease of potency (**10a** *vs.* **10b**, and **10f** *vs.* **10g**). In contrast, the activity increased approximately 2-fold when two methyl groups were introduced at the terminal position (R^4) of the acryloyl moiety (**10a** *vs.* **10c**, and **10f** *vs.* **10h**). Larger substituents at the R^4 position, such as the diethyl (**10d**) and cyclic pentylene (**10e**) groups, were acceptable. In the DuP 532 series,[9b,c] there was an optimal size for the perfluoroalkyl substituent at the 4-position of imidazole ring: the pentafluoroethyl group is optimal for high AII antagonistic activity, and the activity declines with further increase in the length of the perfluoroalkyl chain. The results for **10d**, **e** may suggest that the perfluoroalkyl group of the DuP 532 series and the large acryloyl group of this series of compounds orient to different regions in the extensive lipophilic pocket. The activity of this series of compounds varied with the length of the alkyl chain at the imidazole 2-position, as previously reported for the 4-chloroimidazole series,[7,9a] and the order was butyl (**10h**) > propyl (**10c**) > pentyl (**10j**) > ethyl (**10i**).

Comparison of compounds (pA_2: 9.38 (**10h**), 9.09 (**10l**), and 8.63 (**10m**)) with the corresponding *N*-dealkylated derivative (pA_2: 8.01 (**10k**)) demonstrated that the *N*-alkyl group is critical for the activity of these compounds, while methyl was the optimal *N*-alkyl group (methyl (**10h**) > ethyl (**10l**) > propyl (**10m**)). Previously,[1a] we have reported that ethyl is the optimal length at the 7-position of the 2,7-dialkylpyrazolo[1,5-*b*][1,2,4]triazole derivatives, in which the 7-position corresponds to the 4-position of the imidazole derivatives such as DuP 753 and DuP 532. We speculate that the *N*-methyl moiety of this series of compounds corresponds to the pentafluoroethyl group of DuP 532 and the ethyl group at the 7-position of the pyrazolo[1,5-*b*][1,2,4]triazole derivative, and that these substituents with the length of two atoms (C, N) fit into the same region in the lipophilic pocket. The other possible



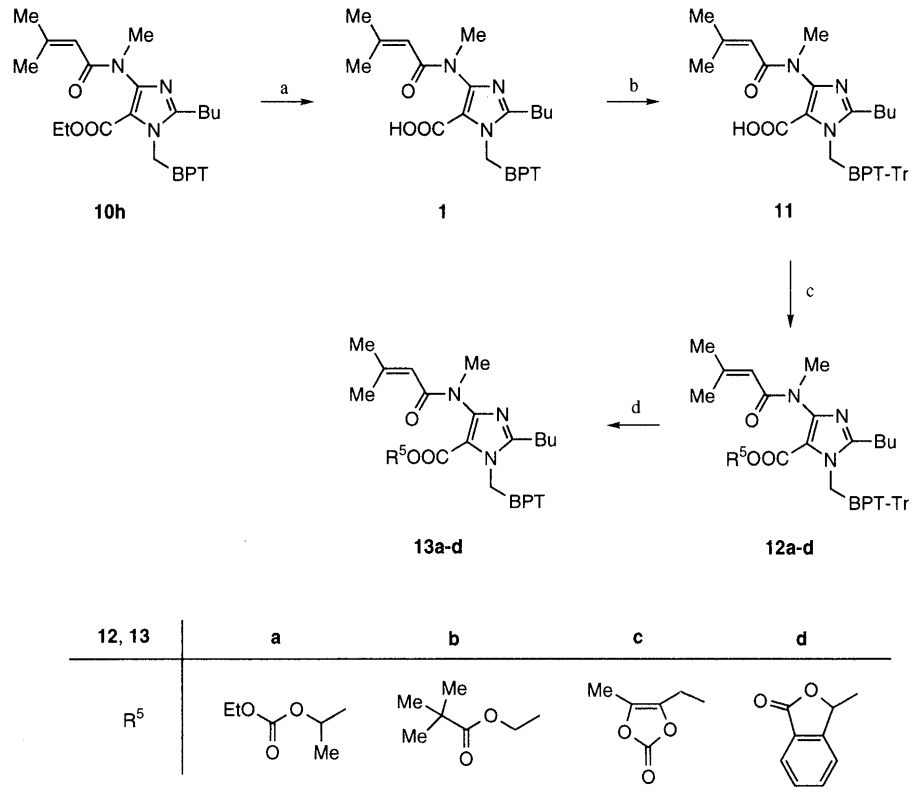
(a) NH_2CN, EtOH; (b) $NH_2CH_2COOEt \cdot HCl$, Et_3N, EtOH; (c) *N*-triphenylmethyl-5-[4'-(bromomethyl)biphenyl-2-yl]tetrazole, NaH, DMF; (d) 0.5 eq NaH, DMF; (e) pyridine (Method A); (f) CH_2Cl_2, Et_3N (Method B); (g) R^2I, NaH, DMF; (h) AcOH, EtOH, reflux

Chart 1

explanation of the potency of **10h** is that the conformation of the imidazole moiety, which consists of the amide group and the neighboring ester group, is influenced in a beneficial way by *N*-methylation. Fig. 2 shows the result of X-ray crystallographic analysis of the *N*-dealkylated derivative **10k**. The amide hydrogen at the 4-position forms a hydrogen bridge to the carbonyl group at the 5-position. The distance between the amide hydrogen and the carbonyl oxygen is 2.05 Å. As a result, the 3,3-dimethylacryloyl group and the ethoxy group, respectively, point upward and downward in the molecule. This may be an unfavorable arrangement for approach of **10k** to the receptor site. In contrast, as shown in Fig. 3, the carbonyl group at the 5-position of the imidazole ring of the *N*-methyl derivative **10h** points downward, and the 3,3-dimethylacryloyl group and the *N*-methyl group of **10h** respectively stick out opposite to the plane of the imidazole ring.

Among the ester derivatives, **10h** was selected (pA_2: 9.38) and converted to the carboxylic acid **1**. In the rabbit aorta, compound **1** caused nonparallel shifts to the right of the concentration–response curve for AII and reduced the maximal response to AII (insurmountable antagonism), as reported with EXP3174.[10] The pD'_2 value of **1** was three times greater than that of EXP3174 (pD'_2; see experimental section and Table 1). In order to confirm the lipophilicity of the substituent at the 4-position of the imidazole ring, log *P* values were calculated for **1** and EXP3174.[16] Calculation showed that **1** has an indistinguishable *C*log *P* value from EXP3174 (**1**, 4.95 *vs.* EXP3174, 4.93). These results imply that the *N*-methyl-3,3-dimethylacrylamide group of **1** would interact effectively with the lipophilic pocket.

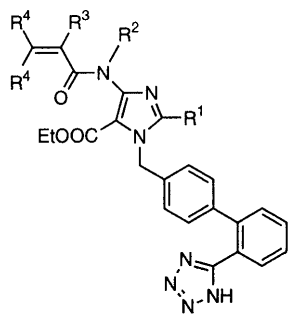
Compound **1** was tested for the ability to inhibit AII-induced pressor response in conscious normotensive rats (Fig. 4). After oral administration, 1 showed a dose-dependent inhibitory effect. At 30 mg/kg, the potency of **1** was higher than that of EXP3174. In this model, EXP3174 and compound **1** were characterized by rapid onset of the activity. In contrast, the onset of the activity was



(a) NaOH, EtOH; (b) Ph_3CCl, Et_3N, DMF; (c) KOH–EtOH; then R^5X, acetone or DMF; (d) AcOH, EtOH, reflux

Chart 2

Table 1. Physical Properties and *in Vitro* AII Antagonistic Potencies of Compounds **10** and **1**



Compd.	R^1	R^2	R^3	R^4	Method	Yield (%)[a]	mp (°C)	Formula[b]	pA_2	pD'_2
10a	Propyl	Methyl	H	H	B	51	192—193	$C_{27}H_{29}N_7O_3$	8.54	
10b	Propyl	Methyl	Methyl	H	A	14	152—154	$C_{28}H_{31}N_7O_3$	8.02	
10c	Propyl	Methyl	H	Methyl	A	68	174—175	$C_{29}H_{33}N_7O_3 \cdot 0.3H_2O$	8.85	
10d	Propyl	Methyl	H	Ethyl	A	32	173—175	$C_{31}H_{37}N_7O_3$	8.42	
10e	Propyl	Methyl	H	$-(CH_2)_5-$	A	34	213—215	$C_{32}H_{37}N_7O_3$	8.76	
10f	Butyl	Methyl	H	H	B	26	Powder	$C_{28}H_{31}N_7O_3 \cdot 0.5H_2O$	9.15	
10g	Butyl	Methyl	Methyl	H	A	23	132—134	$C_{29}H_{33}N_7O_3$	8.57	
10h	Butyl	Methyl	H	Methyl	A	47	184—185	$C_{30}H_{35}N_7O_3$	9.38	
10i	Ethyl	Methyl	H	Methyl	A	13	107—110	$C_{28}H_{31}N_7O_3 \cdot 0.7H_2O$	8.03	
10j	Pentpyl	Methyl	H	Methyl	A	25	197—199	$C_{31}H_{37}N_7O_3$	8.66	
10k	Butyl	H	H	Methyl	A	27	113—115	$C_{29}H_{33}N_7O_3 \cdot 0.8H_2O$	8.01	
10l	Butyl	Ethyl	H	Methyl	A	52	139—141	$C_{31}H_{37}N_7O_3$	9.09	
10m	Butyl	Propyl	H	Methyl	A	44	144—146	$C_{32}H_{39}N_7O_3$	8.63	
1 (5-COOH)	Butyl	Methyl	H	Methyl			156—158	$C_{28}H_{31}N_7O_3 \cdot 0.3H_2O$		9.67
EXP3174										9.13

a) Yield calculated from 4-amino-1*H*-imidazoles **6**. *b*) Analytical results were within ±0.4% of the theoretical values.

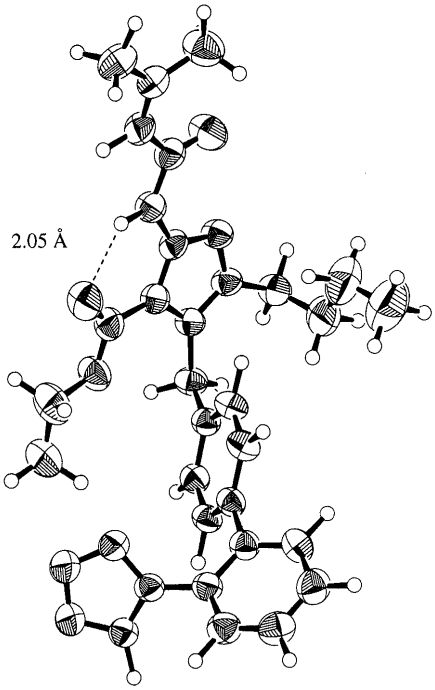


Fig. 2. An ORTEP Drawing of the Molecule of **10k**

Methanol solvent of crystallization was eliminated to simplify the figure.

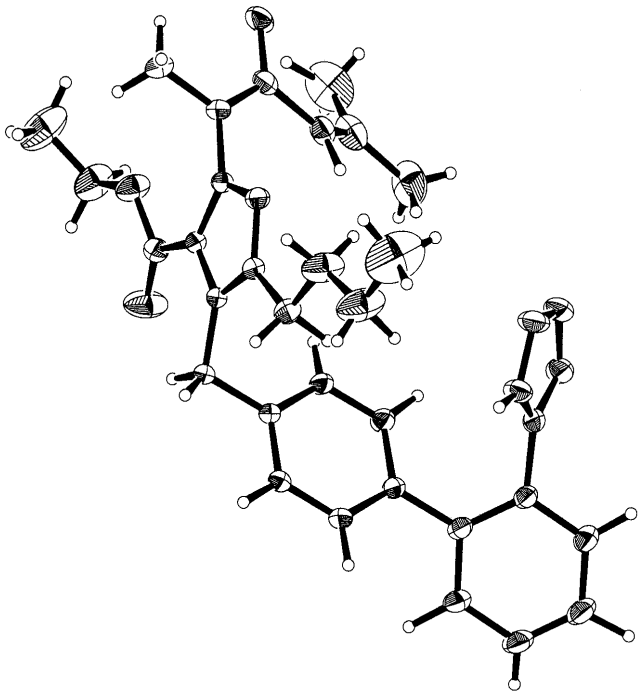


Fig. 3. An ORTEP Drawing of the Molecule of **10h**

slower with DuP 753, presumably due to the delay incurred in the metabolism of DuP 753 to its active component, EXP3174. As a result, EXP3174 and compound **1** (30 mg/kg) were less potent than DuP 753 at 1—8 h and 3—8 h, respectively, postdose. These results suggest that the carboxylic acid derivative EXP3174 has poor bioavailability as compared to DuP 753,[8] and that this tendency is similar to that of the carboxylic acid derivative **1**.

In order to enhance the oral potency of the carboxylic

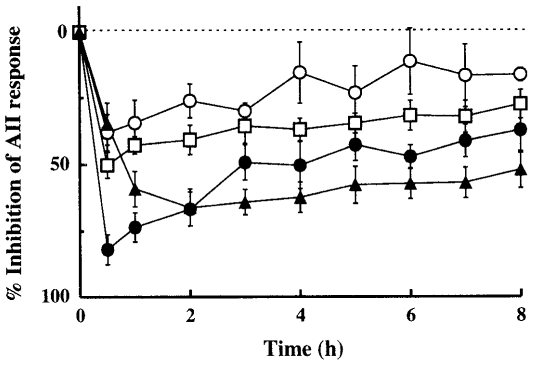


Fig. 4. Oral Inhibitory Activity on AII-induced Pressor Response in Conscious Normotensive Rats

SEM are indicated for each point. —○— **1**, 10 mg/kg, $n=3$; —●— **1**, 30 mg/kg, $n=5$; —□— EXP3174, 30 mg/kg, $n=7$; —▲— DuP 753, 30 mg/kg, $n=6$.

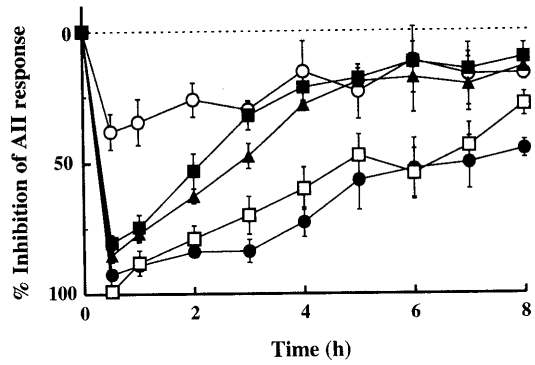


Fig. 5. Oral Inhibitory Activity on AII-induced Pressor Response in Conscious Normotensive Rats

SEM are indicated for each point. —●— **13a**, 10 mg/kg, $n=4$; —□— **13b**, 10 mg/kg, $n=3$; —▲— **13c**, 10 mg/kg, $n=3$; —■— **13d**, 10 mg/kg, $n=4$; —○— **1**, 10 mg/kg, $n=3$.

acid derivative **1**, prodrugs (**13a—d**) were prepared. The ester residues of **13a—d** have been employed to improve the oral absorption of the β-lactam antibiotic, Ampicillin, by masking the highly polar character of its carboxyl group.[17] As shown in Fig. 5, improvement of the oral potency of **1** was obtained with all these prodrugs, whereas the activities of the cyclic carbonate **13c** and the phthalidyl ester **13d** were transient. Of the four prodrugs, the 1-[(ethoxycarbonyl)oxy]ethyl ester **13a** gave the best result. Compound **13a** showed a good inhibitory effect, over 70%, 4 h after administration at a dose of 10 mg/kg, and after 5 h, its potency was comparable to that of a 30 mg/kg dose of DuP 753.

The oral hypotensive effect of compound **13a** was evaluated in furosemide-treated dogs (Fig. 6). In this dog model, compound **13a** also showed good potency as compared to that of DuP 753, which was used as a positive control. The maximal decreases in mean arterial pressure (MBP) were 25 and 27 mmHg for **13a** (10 mg/kg) and DuP 753 (30 mg/kg), respectively. These results indicated that **13a** was approximately 3-fold more potent than DuP 753.

In conclusion, we have identified a novel series of acrylamide derivatives **10** as potent AII antagonists. SAR studies of this series have led to the conclusion that the *N*-methyl-3,3-dimethylacrylamide derivative **10h** is the optimal compound. Hydrolysis of the ethyl ester moiety of **10h** gave the acid **1**, which was an approximately 3-fold

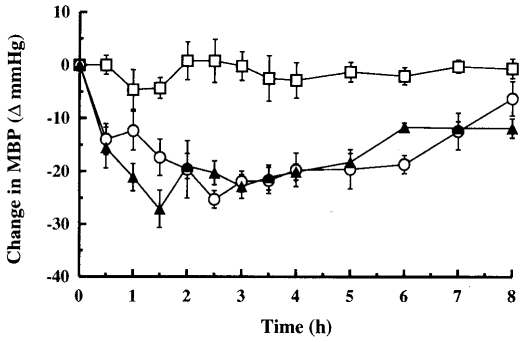


Fig. 6. Oral Hypotensive Activity in Furosemide-Treated Sodium-Depleted Dogs

SEM is indicated for each point. —□— vehicle, $n=4$; —○— **13a**, 10 mg/kg, $n=3$; —▲— DuP 753, 30 mg/kg, $n=4$.

more potent *in vitro* than EXP3174. In order to improve the oral activity of **1**, the prodrugs **13** were examined. Among these, **13a** displayed the most potent and the longest-lasting activity when given orally to rats. In a dog model, **13a** showed an increased oral hypotensive effect as compared to DuP 753. These results suggest that **13a** will be useful 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 (EI) or a JEOL JMS DX-300 (FAB) mass spectrometer. Elemental analysis was performed with a Yanaco MT-5. X-Ray diffraction measurements were made with a Rigaku AFC5R diffractometer using Cu*K*α radiation. Column chromatography was performed on silica gel (Merck Kieselgel 60, 70—230 mesh). The 4-amino-1*H*-imidazole derivatives **6** were synthesized by the following general method.[13-15]

General Method for the Synthesis of 4-Amino-1*H*-imidazole Derivatives (6) Ethyl 4-Amino-2-butyl-1-[[2′-[*N*-(triphenylmethyl)tetrazol-5-yl]-biphenyl-4-yl]methyl]-1*H*-imidazole-5-carboxylate Cyanamide (5.87 g, 0.14 mol) was added to a solution of ethyl valerimidate hydrochloride (22.0 g, 0.13 mol) in EtOH (110 ml), and the mixture was stirred overnight at room temperature. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was partitioned between water and AcOEt. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo* to give the crude ethyl *N*-cyanovalerimidate (17.9 g, 87%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.84—1.02 (3H, m), 1.20—1.87 (7H, m), 2.69 (2H, t, $J=7.4$ Hz), 4.29 (2H, q, $J=7.1$ Hz). EI-MS *m/z*: 154 (M^+).

Triethylamine (35.1 g, 0.35 mol) was added dropwise to a solution of ethyl *N*-cyanovalerimidate (17.8 g, 0.12 mol) and glycine ethyl ester hydrochloride (19.4 g, 0.14 mol) in EtOH (85 ml) under ice-cooling, and the mixture was allowed to warm to room temperature. It was stirred overnight, then concentrated under reduced pressure. Water was added to the residue and the whole was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo* to give the crude *N*-(*N*′-cyanovalerimidolyl)glycine ethyl ester (10.6 g, 43%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, $J=7.0$ Hz), 1.23—1.82 (7H, m), 2.66 (2H, t, $J=7.7$ Hz), 4.07 (2H, d, $J=4.6$ Hz), 4.27 (2H, q, $J=7.2$ Hz), 6.10—6.40 (1H, m). EI-MS *m/z*: 211 (M^+).

Sodium hydride (60% in mineral oil, 2.11 g, 52.8 mmol) was added to a solution of *N*-(*N*′-cyanovalerimidolyl)glycine ethyl ester (10.6 g, 50.2 mmol) in DMF (100 ml) under ice-cooling, and the mixture was stirred for 5 min. *N*-Triphenylmethyl-5-[4′-(bromomethyl)biphenyl-2-yl]tetrazole (29.6 g, 53.1 mmol) was added and the stirring was continued for 2 h at room temperature. Further sodium hydride (60% in mineral oil, 1.06 g, 26.5 mmol) was added to the reaction mixture under ice-cooling, and stirring was continued for 3 h at room temperature. The mixture was concentrated under reduced pressure and the residue was partitioned between water and AcOEt. The organic layer was washed with water, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (AcOEt : *n*-hexane = 1 : 1) to give a crystalline product, which was washed with AcOEt–*n*-hexane (1 : 1) to give the title compound (12.2 g, 35%). ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, t, $J=7.3$ Hz), 1.16—1.31 (5H, m), 1.60 (2H, m), 2.42 (2H, t, $J=7.6$ Hz), 4.16 (2H, q, $J=6.9$ Hz), 5.32 (2H, s), 6.81 (2H, d, $J=8.5$ Hz), 6.94 (6H, d, $J=7.9$ Hz), 7.07 (2H, d, $J=8.5$ Hz), 7.24—7.49 (12H, m), 7.87—7.89 (1H, m). FAB-MS *m/z*: 688 $(M+H)^+$.

Using this procedure, the following 4-amino-1*H*-imidazole derivatives were synthesized.

Ethyl 4-Amino-2-ethyl-1-[[2′-[*N*-(triphenylmethyl)tetrazol-5-yl]biphenyl-4-yl]methyl]-1*H*-imidazole-5-carboxylate: ^{1}H-NMR ($CDCl_3$) δ: 1.14 (3H, t, $J=7.7$ Hz), 1.22 (3H, t, $J=7.2$ Hz), 2.41 (2H, t, $J=7.7$ Hz), 4.18 (2H, q, $J=7.2$ Hz), 5.31 (2H, s), 6.81 (2H, d, $J=8.1$ Hz), 6.91—6.94 (6H, m), 7.08 (2H, d, $J=8.1$ Hz), 7.23—7.50 (12H, m), 7.88—7.90 (1H, m). FAB-MS *m/z*: 660 $(M+H)^+$.

Ethyl 4-Amino-2-propyl-1-[[2′-[*N*-(triphenylmethyl)tetrazol-5-yl]-biphenyl-4-yl]methyl]-1*H*-imidazole-5-carboxylate: ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, $J=7.3$ Hz), 1.16—1.24 (3H, m), 1.65 (2H, m), 2.40 (2H, t, $J=7.6$ Hz), 4.16 (2H, q, $J=7.0$ Hz), 5.32 (2H, s), 6.81 (2H, d, $J=8.2$ Hz), 6.94 (6H, d, $J=7.9$ Hz), 7.08 (2H, d, $J=8.2$ Hz), 7.21—7.50 (12H, m), 7.87—7.89 (1H, m). FAB-MS *m/z*: 674 $(M+H)^+$.

Ethyl 4-Amino-2-pentyl-1-[[2′-[*N*-(triphenylmethyl)tetrazol-5-yl]-biphenyl-4-yl]methyl]-1*H*-imidazole-5-carboxylate: ^{1}H-NMR ($CDCl_3$) δ: 0.83 (3H, t, $J=7.0$ Hz), 1.16—1.40 (7H, m), 1.54—1.66 (2H, m), 2.41 (2H, t, $J=7.9$ Hz), 4.16 (2H, q, $J=6.7$ Hz), 5.32 (2H, s), 6.81 (2H, d, $J=8.2$ Hz), 6.94 (6H, d, $J=7.9$ Hz), 7.07 (2H, d, $J=8.2$ Hz), 7.24—7.48 (12H, m), 7.88 (1H, d, $J=7.3$ Hz). FAB-MS *m/z*: 702 $(M+H)^+$.

Ethyl 2-Butyl-4-[(3,3-dimethylacryloyl)amino]-1-[[2′-[*N*-(triphenylmethyl)tetrazol-5-yl]biphenyl-4-yl]methyl]-1*H*-imidazole-5-carboxylate (8h) (Chart 1, Method A) 3,3-Dimethylacryloyl chloride (1.30 g, 11.0 mmol) was added dropwise to a solution of ethyl 4-amino-2-butyl-1-[[2′-[*N*-(triphenylmethyl)tetrazol-5-yl]biphenyl-4-yl]methyl]-1*H*-imidazole-5-carboxylate (5.00 g, 7.27 mmol) in pyridine (50 ml) under ice-cooling, and the mixture was stirred for 90 min at the same temperature, then concentrated under reduced pressure. The residue was partitioned between water and $CHCl_3$. The organic layer was washed with water, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (AcOEt : *n*-hexane = 1 : 1) to give a crystalline product, which was washed with Et_2O to give the title compound (4.05 g, 72 %). ^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, t, $J=7.3$ Hz), 1.17 (3H, t, $J=7.1$ Hz), 1.31 (2H, m), 1.67 (2H, m), 1.92 (3H, s), 2.24 (3H, s), 2.63—2.74 (2H, m), 4.17 (2H, q, $J=7.1$ Hz), 5.39 (2H, s), 5.95 (1H, br), 6.78 (2H, d, $J=8.1$ Hz), 6.90—6.96 (6H, m), 7.11 (2H, d, $J=8.1$ Hz), 7.23—7.52 (12H, m), 7.88—7.91 (1H, m). FAB-MS *m/z*: 770 $(M+H)^+$.

Ethyl 2-Butyl-4-[(3,3-dimethylacryloyl)methylamino]-1-[[2′-[*N*-(triphenylmethyl)tetrazol-5-yl]biphenyl-4-yl]methyl]-1*H*-imidazole-5-carboxylate (9h) Sodium hydride (60% in mineral oil, 0.32 g, 8.00 mmol) was added to a solution of **8h** (4.00 g, 5.20 mmol) and methyl iodide (1.51 g, 10.6 mmol) in DMF (40 ml) under ice-cooling, and the mixture was stirred overnight at room temperature, then concentrated under reduced pressure. The residue was partitioned between water and AcOEt. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was subjected to silica gel column chromatography. The AcOEt–*n*-hexane (1 : 1) eluate gave an oily product, which was crystallized from Et_2O to give **9h** (2.90 g, 71%). 1H-NMR ($CDCl_3$) δ: 0.86 (3H, t, $J=7.3$ Hz), 1.23 (3H, t, $J=7.1$ Hz), 1.28 (2H, m), 1.60—1.70 (5H, m), 2.07 (3H, s), 2.54 (2H, t, $J=7.6$ Hz), 3.24 (3H, s), 4.14 (2H, q, $J=7.1$ Hz), 5.44—5.53 (3H, m), 6.76 (2H, d, $J=7.9$ Hz), 6.94 (6H, d, $J=7.9$ Hz), 7.10 (2H, d, $J=7.9$ Hz), 7.24—7.50 (12H, m), 7.91 (1H, d, $J=7.3$ Hz). FAB-MS *m/z*: 784 $(M+H)^+$.

Ethyl 2-Butyl-4-[(3,3-dimethylacryloyl)methylamino]-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-imidazole-5-carboxylate (10h) A solution of **9h** (2.90 g, 3.70 mmol) and acetic acid (4 ml) in EtOH (76 ml) was refluxed for 3 h and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography. The $CHCl_3$–MeOH (20 : 1) eluate gave an oily product, which was crystallized from Et_2O to give **10h** (1.81 g, 91%). mp 184—185 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, $J=7.3$ Hz), 1.23 (3H, t, $J=7.2$ Hz), 1.36 (2H, m), 1.62 (3H, s), 1.70 (2H, m), 1.98 (3H, s), 2.62—2.74 (2H, m), 3.13 (3H, s), 4.10—4.27 (2H, m), 5.41 (1H, s), 5.58 (2H, s), 6.96 (2H, d, $J=7.6$ Hz), 7.16 (2H, d, $J=7.6$ Hz), 7.39—7.60 (3H, m), 7.97 (1H, d, $J=7.3$ Hz).

FAB-MS *m/z*: 542 $(M+H)^+$. *Anal.* Calcd for $C_{30}H_{35}N_7O_3$: C, 66.52; H, 6.51; N, 18.10. Found: C, 66.50; H, 6.51; N, 18.05.

Ethyl 4-(Acryloylamino)-2-butyl-1-[[2′-[*N*-(triphenylmethyl)tetrazol-5-yl]biphenyl-4-yl]methyl]-1*H*-imidazole-5-carboxylate (8f) (Chart 1, Method B) Acryloyl chloride (0.15 g, 1.66 mmol) was added dropwise to a solution of ethyl 4-amino-2-butyl-1-[[2′-[*N*-(triphenylmethyl)-tetrazol-5-yl]biphenyl-4-yl]methyl]-1*H*-imidazole-5-carboxylate (1.00 g, 1.45 mmol) and triethylamine (0.33 g, 3.26 mmol) in CH_2Cl_2 (12 ml) under ice-cooling, and the mixture was stirred for 6 h at room temperature. The reaction mixture was washed successively with 5% aqueous citric acid solution, diluted aqueous $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (AcOEt : *n*-hexane = 1 : 1) to give 0.61 g (57%) of **8f** as a foam. ^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, t, J=7.4 Hz), 1.17 (3H, t, J=7.2 Hz), 1.29 (2H, m), 1.67 (2H, m), 2.53—2.68 (2H, m), 4.17 (2H, q, J=7.2 Hz), 5.36 (2H, s), 5.79 (1H, d, J=11.7 Hz), 6.41—6.50 (1H, m), 6.77 (2H, d, J=8.1 Hz), 6.92—6.97 (6H, m), 7.09 (2H, d, J=8.1 Hz), 7.23—7.52 (12H, m), 7.86—7.89 (1H, m). FAB-MS *m/z*: 742 $(M+H)^+$.

8f was led to **10f** in a similar manner to that described for the preparation of **10h**.

10f: Yield 47%, powder. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, t, J=7.3 Hz), 1.20 (3H, t, J=7.2 Hz), 1.38 (2H, m), 1.71 (2H, m), 2.65 (2H, t, J=8.0 Hz), 3.19 (3H, s), 4.15 (2H, q, J=7.2 Hz), 5.45 (1H, d, J=10.4 Hz), 5.57 (2H, s), 6.02 (1H, dd, J=10.4, 17.0 Hz), 6.21 (1H, d, J=17.0 Hz), 7.00 (2H, d, J=7.9 Hz), 7.20 (2H, d, J=7.9 Hz), 7.42—7.61 (3H, m), 8.00 (1H, d, J=7.9 Hz). FAB-MS *m/z*: 514 $(M+H)^+$. *Anal.* Calcd for $C_{28}H_{31}N_7O_3 \cdot 0.5H_2O$: C, 64.35; H, 6.17; N, 18.76. Found: C, 64.38; H, 6.20; N, 18.90.

All compounds of formula **10** were prepared from the corresponding 4-amino-1*H*-imidazole derivatives **6** in a similar manner to that described for **10h** or **10f**, and are listed in Tables 1 and 2.

2-Butyl-4-[(3,3-dimethylacryloyl)methylamino]-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-imidazole-5-carboxylic Acid (1) A solution of **10h** (2.0 g, 3.69 mmol), 1 N aqueous NaOH (11 ml) and EtOH (15 ml) was stirred overnight at room temperature. The mixture was neutralized with 1 N hydrochloric acid (11 ml) and extracted with AcOEt (150 ml × 2). The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The resulting residue was crystallized from acetone to give **1** (1.38 g, 73%). mp 156—158 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.79 (3H, t, J=7.4 Hz), 1.23 (2H, m), 1.51 (2H, m), 1.61 (3H, s), 1.94 (3H, s), 2.57 (2H, t, J=7.4 Hz), 3.06 (3H, s), 5.41 (1H, s), 5.60 (2H, s), 6.91 (2H, d, J=8.2 Hz), 7.06 (2H, d, J=8.2 Hz), 7.52—7.69 (4H, m). FAB-MS *m/z*: 514 $(M+H)^+$. *Anal.* Calcd for $C_{28}H_{31}N_7O_3 \cdot 0.3H_2O$: C, 64.80; H, 6.13; N, 18.89. Found: C, 64.93; H, 6.16; N, 18.81.

2-Butyl-4-[(3,3-dimethylacryloyl)methylamino]-1-[[2′-[*N*-(triphenylmethyl)tetrazol-5-yl]biphenyl-4-yl]methyl]-1*H*-imidazole-5-carboxylic Acid (11) The title compound was prepared from **1** using a conventional method (trityl chloride/triethylamine/DMF). Yield 86%. ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, t, J=7.3 Hz), 1.26 (2H, m), 1.58—1.74 (5H, m), 2.03 (3H , br s), 2.53 (2H, t, J=7.6 Hz), 3.25 (3H, br s), 5.40—5.57 (3H, m), 6.72—6.96 (8H, m), 7.08 (2H, d, J=7.8 Hz), 7.23—7.49 (12H, m), 7.90—7.93 (1H, m). FAB-MS *m/z*: 756 $(M+H)^+$.

1-[(Ethoxycarbonyl)oxy]ethyl 2-Butyl-4-[(3,3-dimethylacryloyl)methylamino]-1-[[2′-[*N*-(triphenylmethyl)tetrazol-5-yl]biphenyl-4-yl]methyl]-1*H*-imidazole-5-carboxylate (12a) A mixture of 1-chloroethyl ethyl carbonate (3.03 g, 19.9 mmol) and sodium iodide (8.93 g, 59.6 mmol) in acetonitrile (80 ml) was stirred for 45 min at 60—70 °C, and then concentrated under reduced pressure. To the residue was added diethyl ether, and the mixture was filtered. The filtrate was evaporated to give crude ethyl 1-iodoethyl carbonate, which was used without further purification. Next, 0.1 N ethanolic KOH (69.5 ml) was added to a solution of compound **11** (5.00 g, 6.61 mmol) in EtOH (200 ml), and the solvent was removed *in vacuo*. To a fine suspension of the resulting residue in acetone (200 ml) was added dropwise a solution of the crude ethyl 1-iodoethyl carbonate in acetone (30 ml), then the mixture was stirred overnight at room temperature. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (AcOEt : *n*-hexane = 1 : 1) to give **12a** (4.25 g, 74%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.72—0.98 (3H, m), 1.17—1.76 (16H, m), 2.09 (3H , s), 2.55 (2H, t, J=7.6 Hz), 3.23 (3H, s), 4.17 (2H, q, J=7.2 Hz), 5.39—5.57 (3H, m), 6.70—7.95 (24H, m). FAB-MS *m/z*: 872 $(M+H)^+$.

(Pivalolyloxy)methyl 2-Butyl-4-[(3,3-dimethylacryloyl)methylamino]-1-[[2′-[*N*-(triphenylmethyl)tetrazol-5-yl]biphenyl-4-yl]methyl]-1*H*-imidazole-5-carboxylate (12b) A 0.1 N ethanolic KOH solution (69.5 ml) was added to a solution of compound **11** (5.00 g, 6.61 mmol) in EtOH (200 ml), and the solvent was removed *in vacuo*. To a fine suspension of the resulting residue in acetone (200 ml) were added chloromethyl pivalate (1.54 g, 10.2 mmol) and 10% aqueous NaI solution (20 ml). The mixture was refluxed for 8 h and concentrated under reduced pressure. The residue was dissolved in AcOEt and water, and the organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (AcOEt : *n*-hexane = 1 : 1) to give 3.80 g (66%) of **12b** as a foam. ^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, t, J=7.3 Hz), 1.15 (9H, s), 1.25—1.29 (2H, m), 1.48—1.72 (5H, m), 2.06 (3H , s), 2.52—2.60 (2H, m), 3.22 (3H, s), 5.42—5.51 (3H, m), 5.75 (2H, s), 6.74 (2H, d, J=7.8 Hz), 6.94 (6H d, J=7.8 Hz), 7.09 (2H, d, J=7.8 Hz), 7.24—7.49 (12H, m), 7.92 (1H, d, J=7.3 Hz). FAB-MS *m/z*: 870 $(M+H)^+$.

Compound **12c** was prepared from (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl bromide[17c] in a similar manner to that described for **12b**.

(5-Methyl-2-oxo-1,3-dioxolen-4-yl)methyl 2-Butyl-4-[(3,3-dimethylacryloyl)methylamino]-1-[[2′-[*N*-(triphenylmethyl)tetrazol-5-yl]biphenyl-4-yl]methyl]-1*H*-imidazole-5-carboxylate (**12c**): Yield 63%, foam. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=7.1 Hz), 1.22—1.36 (2H, m), 1.52—1.75 (5H, m), 2.07 (6H , br s), 2.56 (2H, t, J=7.6 Hz), 3.21 (3H, br s), 4.81 (2H, s), 5.44 (2H, s), 5.47 (1H, s), 6.70—6.78 (2H, m), 6.92—6.98 (6H, m), 7.11 (2H, d, J=8.3 Hz), 7.25—7.52 (12H, m), 7.91 (1H, d, J=7.3 Hz). FAB-MS *m/z*: 867 (M^+).

Phthalidyl 2-Butyl-4-[(3,3-dimethylacryloyl)methylamino]-1-[[2′-[*N*-(triphenylmethyl)tetrazol-5-yl]biphenyl-4-yl]methyl]-1*H*-imidazole-5-carboxylate (12d) A 0.1 N ethanolic KOH solution (69.5 ml) was added to a solution of compound **11** (5.00 g, 6.61 mmol) in EtOH (200 ml), and the solvent was removed *in vacuo*. To a solution of the resulting residue in DMF (200 ml), were added 3-bromophthalide[18] (2.85 g, 13.4 mmol) and NaI (0.30 g, 2.00 mmol) under ice-cooling. The mixture was stirred for 3 h at the same temperature and concentrated under reduced pressure. The residue was dissolved in AcOEt and water, and the organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (AcOEt : *n*-hexane = 2 : 1) to give 5.12 g (87%) of **12d** as a foam. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=6.8 Hz), 1.23—1.34 (2H, m), 1.50—1.70 (5H, m), 1.91 (3H, br s), 2.54—2.65 (2H, m), 3.04 (3H, br s), 5.36—5.54 (3H, m), 6.77—7.93 (28H, m). FAB-MS *m/z*: 888 $(M+H)^+$.

1-[(Ethoxycarbonyl)oxy]ethyl 2-Butyl-4-[(3,3-dimethylacryloyl)methylamino]-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-imidazole-5-carboxylate (13a) A solution of **12a** (2.00 g, 2.29 mmol) and acetic acid (4 ml) in EtOH (76 ml) was refluxed overnight and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography. The $CHCl_3$–MeOH (50 : 1) eluate gave a oily product, which was crystallized from Et_2O to give **13a** (0.98 g, 68%). mp 112—114 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, t, J=7.3 Hz), 1.21 (3H, t, J=7.3 Hz), 1.39 (2H, m), 1.50 (3H, d, J=5.4 Hz), 1.64 (3H, s), 1.73 (2H, m), 2.04 (3H, s), 2.67—2.82 (2H, m), 3.18 (3H, s), 4.04—4.18 (2H, m) 5.43 (1H, s), 5.54 (2H, s), 6.70—6.83 (1H, m), 6.88—7.00 (2H, m), 7.10—7.20 (2H, m), 7.42—7.61 (3H, m), 8.01 (1H, d, J=7.3 Hz). FAB-MS *m/z*: 630 $(M+H)^+$. *Anal.* Calcd for $C_{33}H_{39}N_7O_6 \cdot 0.6H_2O$: C, 61.88; H, 6.33; N, 15.31. Found: C, 61.70; H, 6.17; N, 15.32.

The following compounds of formula **13** were prepared in a similar manner to that described for **13a**.

(Pivalolyloxy)methyl 2-Butyl-4-[(3,3-dimethylacryloyl)methylamino]-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-imidazole-5-carboxylate (**13b**): Yield 77%, mp 141—142 °C (crystallized from Et_2O). ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, t, J=7.3 Hz), 1.24 (9H, s), 1.40 (2H, m), 1.58—1.82 (5H, m), 2.03 (3H, s), 2.70—2.90 (2H, m), 3.23 (3H, br s), 5.44 (1H, br s), 5.56 (2H, s), 5.79 (2H, s), 6.92—7.02 (2H, m), 7.12—7.20 (2H, m), 7.41—7.61 (3H, m), 8.05 (1H, d, J=7.3 Hz). FAB-MS *m/z*: 628 $(M+H)^+$. *Anal.* Calcd for $C_{34}H_{41}N_7O_5 \cdot 0.3H_2O$: C, 64.50; H, 6.62; N, 15.49. Found: C, 64.59; H, 6.60; N, 15.40.

(5-Methyl-2-oxo-1,3-dioxolen-4-yl)methyl 2-Butyl-4-[(3,3-dimethylacryloyl)methylamino]-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-imidazole-5-carboxylate (**13c**): Yield 61%, mp 139—140 °C (crystallized from Et_2O). ^{1}H-NMR ($CDCl_3$) δ: 0.90, (3H, t, J=7.3 Hz), 1.37 (2H, m), 1.58—1.78 (5H, m), 2.00 (3H , s), 2.15 (3H, s), 2.62—2.80 (2H, m), 3.16 (3H, br s), 4.93 (2H, s), 5.42 (1H, br s), 5.52 (2H, br s), 6.88 (2H, d, J=7.8 Hz), 7.16—7.20 (2H, m), 7.34—7.63 (3H, m), 7.88 (1H, d, J=7.3 Hz). FAB-MS *m/z*: 626 $(M+H)^+$. *Anal.* Calcd for $C_{33}H_{35}N_7O_6$: C, 63.35; H, 5.64; N, 15.67. Found: C, 63.16; H, 5.65; N, 15.67.

Phthalidyl 2-Butyl-4-[(3,3-dimethylacryloyl)methylamino]-1-[[2′-

Table 2. Physical Data for Compounds **10**

Compd.	^{1}H-NMR δ (in $CDCl_3$, J in Hz)	MS m/z $(M+H)^+$	Analysis (%) Calcd (Found)		
			C	H	N
10a	0.86 (3H, t, J=7.3), 1.11 (3H, t, J=7.1), 1.60 (2H, m), 2.60 (2H, t, J=7.3), 3.13 (3H, s), 4.09 (2H, q, J=7.1), 5.54—5.58 (3H, m), 6.04 (1H, dd, J=10.4, 17.1), 6.12 (1H, dd, J=2.5, 17.1), 6.97 (2H, d, J=7.9), 7.09 (2H, d, J=7.9), 7.53—7.69 (4H, m)[a]	500	64.91 (64.72	5.85 5.85	19.63 19.39)
10b	0.94 (3H, t, J=7.3), 1.28 (3H, t, J=7.4), 1.68—1.84 (5H, m), 2.62 (2H, t, J=7.7), 3.21 (3H, br s), 4.16—4.26 (2H, m), 4.96—5.04 (2H, m), 5.55 (2H, br s), 6.94 (2H, d, J=7.9), 7.12—7.22 (2H, m), 7.53—8.10 (4H, m)	514	65.48 (65.25	6.08 6.20	19.09 18.91)
10c	0.94 (3H, t, J=7.4), 1.21 (3H, t, J=7.1), 1.61 (3H, s), 1.71 (2H, m), 1.95 (3H, s), 2.59 (2H, t, J=7.6), 3.07 (3H, s), 4.15 (2H, q, J=7.1), 5.39 (1H, s), 5.56 (2H, s), 6.92 (2H, d, J=7.8), 7.14 (2H, d, J=7.8), 7.40—7.60 (3H, m), 7.90 (1H, m)	528	65.35 (65.37	6.35 6.43	18.39 18.23)
10d	0.79 (3H, t, J=7.6), 0.96—1.04 (6H, m), 1.26 (3H, t, J=7.1), 1.76 (2H, m), 1.95 (2H, q, J=7.3), 2.48 (2H, q, J=7.3), 2.66 (2H, t, J=7.6), 3.19 (3H, s), 4.18 (2H, q, J=7.1), 5.42 (1H, s), 5.59 (2H, s), 7.03 (2H, d, J=7.8), 7.20 (2H, d, J=7.8), 7.40—7.62 (3H, m), 8.13 (1H, d, J=7.3)	556	67.01 (66.78	6.71 6.64	17.64 17.56)
10e	0.96 (3H, t, J=7.3), 1.25 (3H, t, J=7.1), 1.38—1.53 (6H, m), 1.74 (2H, m), 1.90 (2H, m), 2.53—2.68 (4H, m), 3.13 (3H, s), 4.17 (2H, q, J=7.1), 5.34 (1H, s), 5.58 (2H, s), 6.96 (2H, d, J=7.8), 7.16 (2H, d, J=7.8), 7.40—7.61 (3H, m), 8.01 (1H, d, J=7.3)	568	67.70 (67.65	6.57 6.49	17.27 17.27)
10f	0.91 (3H, t, J=7.3), 1.20 (3H, t, J=7.2), 1.38 (2H, m), 1.71 (2H, m), 2.65 (2H, t, J=8.0), 3.19 (3H, s), 4.15 (2H, q, J=7.2), 5.45 (1H, d, J=10.4), 5.57 (2H, s), 6.02 (1H, dd, J=10.4, 17.0), 6.21 (1H, d, J=17.0), 7.00 (2H, d, J=7.9), 7.20 (2H, d, J=7.9), 7.42—7.61 (3H, m), 8.00 (1H, d, J=7.9)	514	64.35 (64.38	6.17 6.20	18.76 18.90)
10g	0.90 (3H, t, J=7.3), 1.28 (3H, t, J=7.1), 1.35 (2H, m), 1.68 (2H, m), 1.76 (3H, s), 2.67 (2H, t, J=7.6), 3.23 (3H, br s), 4.16—4.28 (2H, m), 5.02 (2H, br s), 5.55 (2H, s), 6.94 (2H, d, J=7.8), 7.12—7.22 (2H, m), 7.40—7.61 (3H, m), 8.03 (1H, d, J=7.8)	528	66.02 (66.05	6.30 6.41	18.58 18.36)
10h	0.90 (3H, t, J=7.3), 1.23 (3H, t, J=7.2), 1.36 (2H, m), 1.62 (3H, s), 1.70 (2H, m), 1.98 (3H, s), 2.62—2.74 (2H, m), 3.13 (3H, s), 4.10—4.27 (2H, m), 5.41 (1H, s), 5.58 (2H, s), 6.96 (2H, d, J=7.6), 7.16 (2H, d, J=7.6), 7.39—7.60 (3H, m), 7.97 (1H, d, J=7.3)	542	66.52 (66.50	6.51 6.51	18.10 18.05)
10i	1.20—1.27 (6H, m), 1.62 (3H, s), 1.98 (3H, s), 2.66 (2H, q, J=7.3), 3.10 (3H, s), 4.16 (2H, q, J=6.8), 5.40 (1H, s), 5.57 (2H, s), 6.93 (2H, d, J=7.6), 7.14 (2H, d, J=7.6), 7.39—7.60 (3H, m), 7.92 (1H, d, J=7.3)	514	63.91 (63.89	6.21 6.07	18.63 18.36)
10j	0.87 (3H, t, J=7.1), 1.20—1.34 (7H, m), 1.62 (3H, s), 1.71 (2H, m), 1.98 (3H, s), 2.61 (2H, t, J=7.8), 3.10 (3H, s), 4.16 (2H, q, J=7.2), 5.41 (1H, s), 5.57 (2H, s), 6.94 (2H, d, J=8.3), 7.16 (2H, d, J=8.3), 7.40—7.60 (3H, m), 7.99 (1H, d, J=7.3)	556	67.01 (67.09	6.71 6.69	17.64 17.50)
10k	0.83 (3H, t, J=7.3), 1.13 (3H, t, J=7.1), 1.26 (2H, m), 1.57 (2H, m), 1.87 (3H, s), 2.07 (3H, s), 2.25—2.34 (2H, m), 4.16 (2H, q, J=7.1), 5.36 (2H, s), 5.68 (1H, br s), 6.82 (2H, d, J=7.8), 7.11 (2H, d, J=7.8), 7.36—7.56 (3H, m), 7.87 (1H, d, J=7.3), 8.78 (1H, br s)	528	64.26 (64.33	6.43 6.32	18.09 17.94)
10l	0.91 (3H, t, J=7.3), 1.10 (3H, t, J=7.1), 1.23 (3H, t, J=7.0), 1.36 (2H, m), 1.61 (3H, s), 1.69 (2H, m), 2.01 (3H, s), 2.64 (2H, t, J=7.9), 3.73 (2H, q, J=7.1), 4.10—4.20 (2H, m), 5.40 (1H, s), 5.58 (2H, br s), 6.96 (2H, d, J=8.2), 7.18 (2H, d, J=8.2), 7.39—7.60 (3H, m), 8.03 (1H, d, J=7.9)	556	67.01 (66.89	6.71 6.77	17.64 17.62)
10m	0.88 (3H, t, J=7.3), 0.91 (3H, t, J=7.3), 1.24 (3H, t, J=7.3), 1.37 (2H, m), 1.50—1.63 (5H, m), 1.69 (2H, m), 2.02 (3H, s), 2.66 (2H, t, J=7.8), 3.58—3.70 (2H, m), 4.12—4.20 (2H, m), 5.42 (1H, s), 5.58 (2H, br s), 6.97 (2H, d, J=8.3), 7.18 (2H, d, J=8.3), 7.39—7.61 (3H, m), 8.07 (1H, d, J=7.3)	570	67.46 (67.83	6.90 7.06	17.21 16.96)

a) Measured in DMSO-d_6.

(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-imidazole-5-carboxylate (**13d**): Yield 72%, mp 202—203 °C (crystallized from Et_2O). ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J=7.3 Hz), 1.38 (2H, m), 1.50—1.80 (5H, m), 1.87 (3H, br s), 2.70—2.88 (2H, m), 3.09 (3H, br s), 5.32—5.60 (3H, br m), 6.78—6.86 (2H, m), 7.03—7.15 (2H, m), 7.40—7.92 (9H, m). FAB-MS m/z: 646 $(M+H)^+$. *Anal.* Calcd for $C_{36}H_{35}N_7O_5$: C, 66.96; H, 5.46; N, 15.18. Found: C, 66.82; H, 5.47; N, 14.99.

X-Ray Crystallographic Analysis of 10h Suitable crystals ($C_{30}H_{35}N_7O_3$) for X-ray diffraction studies were obtained from EtOH–AcOEt. Crystal data: crystal system, monoclinic; space group, $P2_1/c$(#14); lattice parameters, a=9.061(4) Å, b=18.826(2) Å, c=18.209(2) Å, β=96.40(2)°, V=3086(1) A°^{3}; $D_{calc.}$, 1.165 g/cm^3; Z value, 4; F_{000}, 1152.00; final R value, R=0.056, R_W=0.096.

X-Ray Crystallographic Analysis of 10k Suitable crystals ($C_{29}H_{33}N_7O_3 \cdot MeOH$) for X-ray diffraction studies were obtained from MeOH. Crystal data: crystal system, monoclinic; space group, $P2_1/a$(#14); lattice parameters, a=25.431(2) Å, b=14.693(3) Å, c=7.944(2) Å, β=94.04(1)°, V=2961.1(8) Å^3; $D_{calc.}$, 1.183 g/cm^3; Z value, 4; F_{000}, 1120.00; final R value, R=0.069, R_W=0.124.

Antagonism Assay with 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 strips 3 mm wide and 30 mm long. 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 testing 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 2 times 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 a 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]). As EXP3174 and **1** were found to exert insurmountable AII antagonism, the pD'_2 values, *i.e.*, the negative logarithm values of the concentration of the compound which inhibits the maximum response by 50%, were calculated.

Inhibition of Pressor Response to AII in Conscious Normotensive Rats Male Wistar rats aged 16 to 24 weeks were anesthetized with sodium pentobarbital (60 mg/kg, i.p.) and the left carotid artery and vein were cannulated with polyethylene tubing for the measurement of blood pressure and the intravenous administration of AII, respectively. The catheter was passed subcutaneously, exteriorized at the neck, and filled with saline containing heparin. The animals were allowed to recover from surgery for at least 3 to 4 d before the beginning of the experiment. The catheter was connected to a pressure transducer (Nihon Kohden, Japan) and the blood pressure was monitored with a polygraph (Nihon Kohden, Japan). To determine the effect of the compound on the AII-induced pressor response, AII (1 μg/kg) was injected i.v. before the oral administration of the test compound and subsequently at set times. The pressor responses to AII after the administration of the test compound were expressed as percent inhibition of the pressor response before the treatment.

Hypotensive Effect in Furosemide-Treated Sodium-Depleted Dogs Beagle dogs of either sex weighing 8.0 to 13.5 kg were used. The animals were anesthetized with sodium thiopental (30 mg/kg, i.v.). Anesthesia was maintained with 0.5% to 1% halothane in oxygen and room air during surgical operation. Under sterile surgical procedures, the right femoral artery was exposed. The abdominal aorta was cannulated with polyvinyl tubing *via* the femoral artery. The catheter was passed subcutaneously, exteriorized *via* the neck, and filled with saline containing heparin. The skin incision was closed and the dog was allowed to recover from surgery for at least 3 to 4 d. The dogs received an intramuscular dose and intravenous dose of furosemide (10 mg/kg) at 16 and 2 h before the administration of a test compound, respectively. The animals were deprived of water from 18 h before to 8 h after dosing. The arterial catheter was connected to a pressure transducer (Nihon Kohden, Japan), and MBP was recorded with a polygraph (Nihon Kohden, Japan). MBP were measured before and after oral administration of **13a** (10 mg/kg) or DuP 753 (30 mg/kg).

Acknowledgments We are grateful to the staff of the Division of Molecular Chemistry Research Laboratory for measurement of ^{1}H-NMR, MS and elemental analyses. We are also indebted to Mr. H. Nakahara and Dr. H. Kurihara for X-ray diffraction studies.

References and Notes

1) *a*) Part I: Okazaki T., Suga A., Watanabe T., Kikuchi K., Kurihara H., Shibasaki M., Fujimori A., Inagaki O., Yanagisawa I., *Chem. Pharm. Bull.*, **46**, 69—78 (1998); *b*) Part II: *Idem*, *ibid.*, **46**, 287—293 (1998); *c*) Part III: Okazaki T., Kikuchi K., Watanabe T., Suga A., Shibasaki M., Fujimori A., Inagaki O., Yanagisawa I., *ibid.*, **46**, 777—781 (1998).
2) Present address: *Corporate Planning Department, Yamanouchi Pharmaceutical Co., Ltd., 2–3–11, Nihonbashi-Honcho, Chuo-ku, Tokyo 103–8411, Japan.*
3) Vallotton M. B., *Trends Pharmacol. Sci.*, **8**, 69—74 (1987).
4) *a*) Ondetti M. A., Rubin B., Cushman D. W., *Science*, **196**, 441—444 (1977); *b*) Patchett A. A., Harris E., Tristram E. W., Wyvratt M. J., Wu M. T., Taub D., Peterson E. R., Ikeler T. J., ten Broeke J., Payne L. G., Ondeyka D. L., Thorsett E. D., Greenlee W. J., Lohr N. S., Hoffsommer R. D., Joshua H., Ruyle W. V., Rothrock J. W., Aster S. D., Maycock A. L., Robinson F. M., Hirschmann R., Sweet C. S., Ulm E. H., Gross D. M., Vassil T. C., Stone C. A., *Nature* (London), **288**, 280—283 (1980); *c*) The Consensus Trial Study Group, *New Engl. J. Med.*, **316**, 1429—1435 (1987).
5) *a*) Erdos E. G., Skidgel R. A., *Hypertension*, **8** (Suppl. I), I-34—I-37 (1986); *b*) Williams G. H., *New Eng. J. Med.*, **319**, 1517—1525 (1988).
6) *a*) Brunner H. R., Gavras H., Laragh J. H., Keenan R., Lancet, **2**, 1045—1048 (1973); *b*) Ogihara T., Yamamoto T., Kumahara Y., *ibid.*, **1**, 219 (1974); *c*) Streeten D. H. P., Anderson G. H., Jr., "Handbook of Hypertension," Vol 5, ed. by Doyle A. E., Clinical Pharmacology of Antihypertensive Drugs, Elsevier Science Publisher, 1984, pp. 246—271.
7) Carini D. J., Duncia J. V., Aldrich P. E., Chiu A. T., Johnson A. L., Pierce M. E., Price W. A., Santella J. B., III, Wells G. J., Wexler R. R., Wong P. C., Yoo S.-E., Timmermans P. B. M. W. M., *J. Med. Chem.*, **34**, 2525—2547 (1991).
8) *a*) Ashton W. T., *Exp. Opin. Invest. Drugs*, **3**, 1105—1142 (1994); *b*) Wexler R. R., Greenlee W. J., Irvin J. D., Goldberg M. R., Prendergast K., Smith R. D., Timmermans P. B. M. W. M., *J. Med. Chem.*, **39**, 625—656 (1996).
9) *a*) Duncia J. V., Chiu A. T., Carini D. J., Gregory G. B., Johnson A. L., Price W. A., Wells G. J., Wong P. C., Calabrese J. C., Timmermans P. B. M. W. M., *J. Med. Chem.*, **33**, 1312—1329 (1990); *b*) Carini D. J., Chiu A. T., Wong P. C., Johnson A. L., Timmermans P. B., Wexler R. R., Abstract of Papers, 201st National Meeting of the American Chemical Society, Atlanta, GA, April 14—19, 1991; American Chemical Society, Atlanta, GA, 1991; MEDI No. 55; *c*) Carini D. J., Chiu A. T., Wong P. C., Johnson A. L., Wexler R. R., Timmermans P. B. M. W. M., *Bioorg. Med. Chem. Lett.*, **3**, 895—898 (1993).
10) Wong P. C., Price W. A., Jr., Chiu A. T., Duncia J. V., Carini D. J., Wexler R. R., Johnson A. L., Timmermans P. B. M. W. M., *J. Pharmacol. Exp. Ther.*, **255**, 211—217 (1990).
11) Chiu A. T., Carini D. J., Duncia J. V., Leung K. H., McCall D. E., Price W. A., Jr., Wong P. C., Smith R. D., Wexler R. R., Timmermans P. B. M. W. M., *Biochem. Biophys. Res. Commun.*, **117**, 209—217 (1991).
12) Sweet C. S., Nelson E. B., *J. Hypertension*, **11** (Suppl. 3), S63—S67 (1993).
13) Amide derivatives of another type have been reported; see: Chakravarty P. K., Patchett A. A., Schoen W., Greenlee W. J., Mantlo N. B., Walsh T. F., Eur. Pat. Appl. EP 401 030 (1990) [*Chem. Abstr.*, **114**, 207257*g* (1991)].
14) Huffman K. R., Schaefer F. C., *J. Org. Chem.*, **28**, 1816—1821 (1963).
15) Edenhofer A., *Helv. Chim. Acta*, **58**, 2192—2209 (1975).
16) SYBYL software, Tripos Inc., St. Louis, MO, U.S.A.
17) *a*) Ekstrom B., Forsgren U., Jalar L.-P., Magni L., Sjoberg B., Sjovall J., *Drugs Exp. Clin. Res.*, **3**, 3—10 (1977); *b*) Daehne W. V., Frederiksen E., Gundersen E., Lund F., Mørch P., Petersen H. J., Roholt K., Tybring L., Godtfredsen W. O., *J. Med. Chem.*, **13**, 607—612 (1970); *c*) Sakamoto F., Ikeda S., Tsukamoto G., *Chem., Pharm. Bull.*, **32**, 2241—2248 (1984); *d*) Isaka I., Nakano K., Kashiwagi T., Koda A., Horiguchi H., Matsui H., Takahashi K., Murakami M., *ibid.*, **24**, 102—107 (1976); *e*) Kubo K., Kohara Y., Yoshimura Y., Inada Y., Shibouta Y., Furukawa Y., Kato T., Nishikawa K., Naka T., *J. Med. Chem.*, **36**, 2343—2349 (1993).
18) Shriner R. L., Wolf F. J., "Organic Syntheses," Coll. Vol. II, ed. by Blatt A. H., John Wiley and Sons, Inc., New York, 1955, pp. 737—740.