Nonpeptide Angiotensin II Receptor Antagonists: Synthesis, Biological Activities, and Structure−Activity Relationships of Imidazole-5-carboxylic Acids Bearing Alkyl, Alkenyl, and Hydroxyalkyl Substituents at the 4-Position and Their Related Compounds

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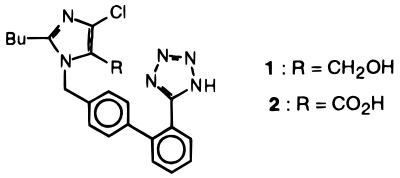
A series of imidazole-5-carboxylic acids bearing alkyl, alkenyl, and hydroxyalkyl substituents at the 4-position and their related compounds were prepared and evaluated for their antagonistic activities to the angiotensin II (AII) receptor. Among them, the 4-(1-hydroxyalkyl)-imidazole derivatives had strong binding affinity to the AII receptor and potently inhibited the AII-induced pressor response by intravenous administration. Various esters of these acids showed potent and long-lasting antagonistic activity by oral administration. The most promising compounds were (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl (CS-866) and (pivaloyloxy)-methyl esters of 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[(2′-1*H*-tetrazol-5-ylbiphenyl-4-yl)-methyl]imidazole-5-carboxylic acid (**26c**). A study involving stereochemical comparison of **26c** with the acetylated C-terminal pentapeptide of AII was also undertaken.

Introduction

The great success of angiotensin-converting enzyme (ACE) inhibitors:[1] captopril, enalapril, and others, which inhibit the formation of angiotensin II (AII) from angiotensin I (AI) in the renin-angiotensin system (RAS),[2] in treatment of hypertension and congestive heart failure, led to recognition of the important role of the RAS in homeostasis of the cardiovascular system. Agents, that block the RAS at steps other than the one blocked by ACE inhibitors have also been studied during the last few decades. They have been expected to lack adverse effects[3] observed with the use of ACE inhibitors, such as dry cough and angioedema, caused by the potentiation of bradykinin, substance P, and other biologically active peptides.[4] Renin inhibitors,[5] which interrupt the formation of AI, showed highly specific and potent inhibitory activity for human renin, but they have not yet been used in the clinical stage because of poor bioavailability and metabolic instability. On the other hand, AII receptor antagonists,[6] which suppress the final stage of the RAS, look promising. AII analogue peptides,[7] such as saralasin[8] and sarmesin,[9] are known to be potent antagonists and to lower blood pressure in humans, when administered intravenously.[10] However, these peptides have been limited in clinical use because of ineffectiveness orally, metabolic instability, and their partial agonist activity.[11] The first nonpeptide AII antagonists, 1-benzylimidazole-5-acetic acid derivatives, were reported by the Takeda group.[12] Unfortunately, they did not have sufficient potency for clinical purposes. The DuPont group pursued a study in this field and developed losartan (DuP 753), **1**, [13] which is orally effective and metabolized to the more potent full antagonist EXP 3174, **2**.[14] Since then, numerous new antagonists have been reported by various research groups.[15] Losartan (**1**), now used in the clinical stage, and other antagonists in clinical trials selectively block the AT_1 receptor, which is one of the two major subtypes



of the AII receptor, AT_1 and AT_2, and is responsible for most of the presently known pharmacological functions.[16]

Structure−activity relationships (SAR) of the imidazole antagonists have been reported.[13c,17] Lipophilic substituents, like a biphenylylmethyl group at the 1-position and a linear alkyl group at the 2-position, which will associate with hydrophobic pockets of the receptor, and an acidic group, like tetrazole, CO_2H, or $NHSO_2CF_3$, on the biphenylyl group at the 1-position, which will bind to a basic position of the receptor, are required for potent antagonistic activity. Furthermore, a nitrogen atom at the 3-position enhances the activity through hydrogen bonding to the receptor.[18] However, the functions of substituents at the 4- and 5-positions on the imidazole ring in relation to the antagonistic activity had remained ambiguous at the time starting our study. The DuPont group[13c] recommended a lipophilic and electron-withdrawing group, such as iodine or CF_3, as a substituent at the 4-position and a small-sized group, such as CH_2OH, CH_2OMe, or CO_2H, which is capable of forming a hydrogen bond, as a substituent at the 5-position. Later, they reported on the SAR of alkyl- and (perfluoroalkyl)imidazoles[17c,e] and found that the imidazoles, which have ethyl and pentafluoroethyl groups at the 4-position, have highly antihypertensive potencies upon oral administration. On the other hand, the antagonist SK&F108566 (**3**),[19] developed by Smith-Kline Beecham, has a large substituent, thienylmethyl acrylate group, at the 5-position, which mimics Phe[8] of AII. Similarly, the 1,2,4-triazole antagonist **4**, bearing a (2-carboxybenzyl)thio group at the 5-position, had

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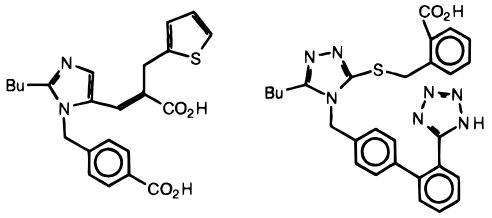
potent binding affinity.[20] These results suggested that the receptor would have a hydrophobic pocket and an ionic or a hydrogen-bonding site corresponding to the places near the 5-position of the imidazole nuclei. On the contrary, Thomas et al.[18] suggested that chlorine and CH_2OH in **1** would not be critical to binding, since the benzimidazole **5** had an antagonistic potency comparable to **1**.



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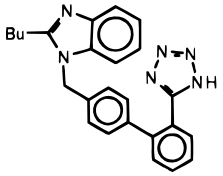

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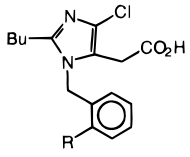
Molecular modeling and stereochemical comparison studies on imidazole antagonists and AII have been discussed by a few groups in order to understand a role of functional groups in antagonists.[17a,19] The first attempt was done by the DuPont group.[17a] They overlayed the imidazole ring and the carboxy group of **6**, which is one of the first nonpeptide antagonists reported by the Takeda group,[12] upon the His^6 imidazole ring and the C-terminal carboxy group of AII, respectively, and directed the benzyl group toward the N-terminus of AII. The SmithKline Beecham group[19] suggested that the imidazole ring might not only mimic the peptide amide bond of AII but also act as a scaffold, locating the pharmacophores in favorable positions. They supposed that the butyl, carboxy, and 2-chlorobenzyl groups of **7**[12] might correspond to the alkyl chain of Ile^5, C-terminal carboxylic acid, and the side chain of Tyr^4 in AII, respectively. Furthermore, the benzylcarboxylate and thienylmethyl acrylate moieties in **3** could overlay the side chain of Tyr^4 and the C-terminal Phe^8, respectively. On the other hand, the Glaxo group suggested that the carboxy group at the 5-position on the imidazole ring would not work as an ionic interaction with the AII receptor but as a hydrogen-bonding interaction.[21]

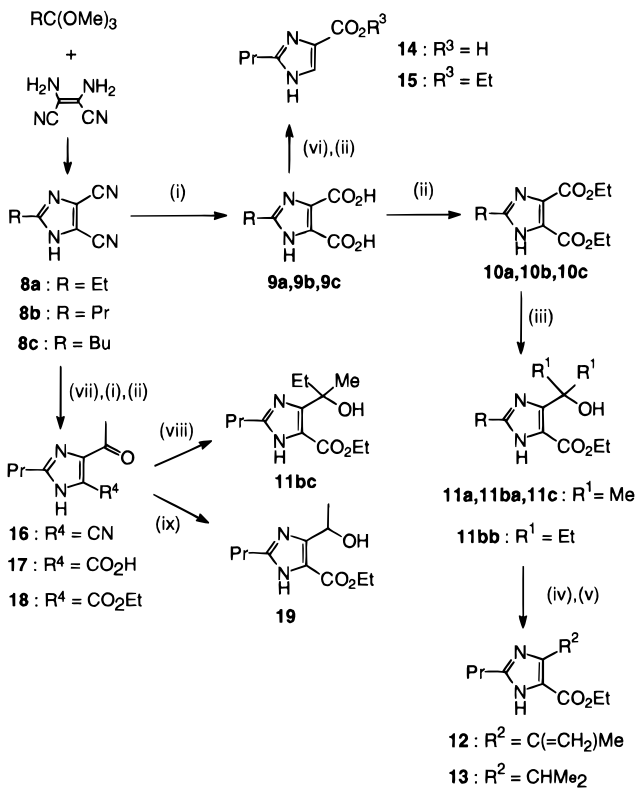


6 : R = H

7 : R = Cl

In a previous paper,[22] we reported that imidazoles that had hydroxymethyl and carboxy groups at the 4- and 5-positions, respectively, possessed potent antagonistic activity, which would be caused by hydrogen bonding or hydrophilicity of the hydroxymethyl group. Here we report on the synthesis of the imidazole antagonists possessing alkyl, alkenyl, and hydroxyalkyl substituents at the 4-position, their biological evaluation (SAR), and stereochemical comparison with the C-terminal pentapeptide of AII.

Scheme 1[a]



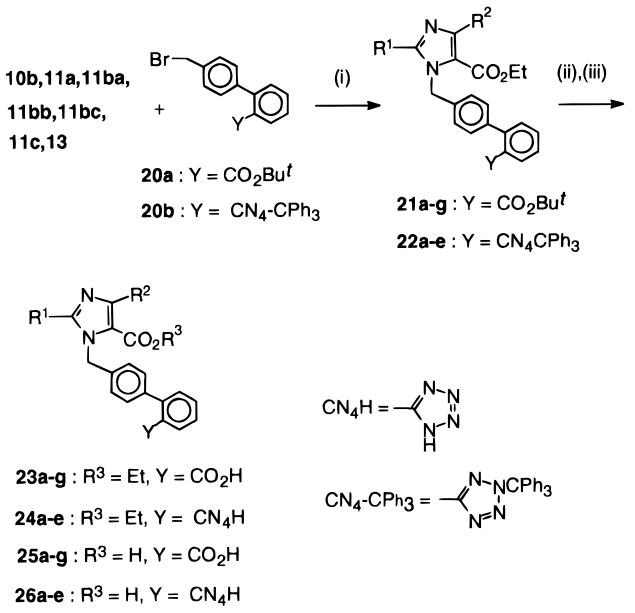
[a] Reagents: (i) 6 N HCl; (ii) HCl/EtOH; (iii) $R^1MgX/Et_2O/CH_2Cl_2$; (iv) $POCl_3$/pyridine/benzene; (v) H_2/Pd−C/MeOH; (vi) Ac_2O; (vii) MeMgBr/THF; (viii) EtMgCl/THF/CH_2Cl_2; (ix) $NaBH_4$/EtOH.

Chemistry

All the imidazole moieties referred to in this paper were derived from the imidazole-4,5-dicarbonitriles **8a**−**c**, which were easily prepared by heating ortho esters with diaminomaleonitrile, as shown in Scheme 1. Acid hydrolysis of **8a**−**c** in 6 N HCl gave the dicarboxylic acids **9a**−**c**. After esterification of **9a**−**c** in ethanol in the presence of hydrogen chloride, the diesters **10a**−**c** obtained were treated with 4 equiv of MeMgBr or EtMgCl, to afford the 4-(1-hydroxyalkyl)imidazoles **11a**,**ba**,**bb**,**c** in 76−95% yields. Dehydration of **11ba** with phosphoryl chloride and pyridine gave the 4-isopropenylimidazole **12**, which was converted to the 4-isopropylimidazole **13** by hydrogenation on Pd−C. Decarboxylation[23] of **9b** was carried out by boiling in Ac_2O, to give the monocarboxylic acid **14**, which was esterified with HCl−ethanol to give **15**. Grignard reaction of **8b** with 3 equiv of MeMgBr afforded the 4-acetylimidazole **16**. Acid hydrolysis of **16**, followed by esterification, gave **18**. Reaction of **18** with EtMgBr afforded **11bc**. Reduction of **18** with $NaBH_4$ provided the 4-(1-hydroxyethyl)imidazole **19**.

Alkylation of **10b** with the biphenyl **20a**[13c] furnished the (biphenylylmethyl)imidazole **21a**, as shown in Scheme 2. Similarly, alkylation of **11a**,**ba**,**bb**,**bc**,**c** and **13** with **20a** afforded **21b**−**g**, and alkylation of **10b**, **11a**,**ba**,**c** and **13** with **20b**[13c] gave **22a**−**e**. Removal of the *tert*-butyl group in **21a**−**g** with 4 N HCl in dioxane, followed by alkaline hydrolysis, afforded the target dicarboxylic acids **25a**−**g**. Detritylation of **22a**−**e** with 25% aqueous AcOH, followed by alkaline hydrolysis, provided the desired compounds **26a**−**e**.

Scheme 2[a]



21 ~ 26

a ; R^1 = Pr , R^2 = CO_2Et (**21~24**) , R^2 = CO_2H (**25,26**) :

b ; R^1 = Et, R^2 = CMe_2OH : **c** ; R^1 = Pr , R^2 = CMe_2OH ;

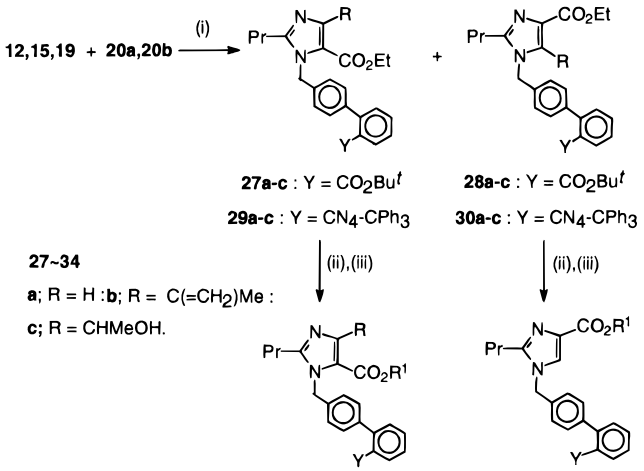
d , R^1 = Bu , R^2 = CMe_2OH : **e** ; R^1 = Pr , R^2 = $CHMe_2$:

f ; R^1 = Pr , R^2 = CMeEtOH : **g** ; R^1 = Pr , R^2 = CEt_2OH .

[a] Reagents: (i) $Bu^tOK/AcNMe_2$; (ii) **21a**−**g** → **23a**−**g**, 4 N HCl/dioxane; **22a**−**e** → **24a**−**e**, 25% aqueous AcOH; (iii) LiOH/dioxane/H_2O.

Alkylation of the imidazole **15**, bearing no substituent at the 5-position, with **20a** yielded a mixture of the regioisomers **27a** and **28a**, in a ratio of 1:3, as shown in Scheme 3. Alkylation of **12** and **19**, which have isopropenyl and 1-hydroxyethyl groups at the 4-position, respectively, afforded predominantly **27b**,**c** with minor products **28b**,**c**. Similar results were obtained on alkylation of **12**, **15**, and **19** with **20b**: i.e., **15** afforded **29a** and **30a** in a ratio of 1:3, and **12** and **19** provided predominantly **29b**,**c** with minor products **30b**,**c**. Removal of the protecting groups of **27a**−**c**, **28a**, **29a**−**c**, and **30a** gave the target compounds **33a**−**c**, **37**, **34a**−**c**, and **38**, respectively, by the same procedure described in Scheme 2. The structures of the alkylated imidazoles in Schemes 2 and 3 were determined by proton NMR spectra and X-ray analysis. The methylene protons of the biphenylylmethyl groups of the imidazole-5-carboxylates **21a**−**g**, **22a**−**e**, **27a**−**c**, and **29a**−**c** were observed at δ 5.3−5.7. On the other hand, the methylene protons of the imidazole-4-carboxylates **28a**−**c** and **30a**−**c** were at δ 5.0−5.3. The 0.3−0.5 ppm downfield shifts observed in the imidazole-5-carboxylates, in comparison with the imidazole-4-carboxylates, are caused by the anisotropic effect of the 5-ester group. The structure of **22c** was assuredly confirmed by X-ray analysis of **26c**, which was obtained from **22c** as described above. The X-ray-determined structure is shown in Figure 1a. The X-ray analysis showed a protonation of the nitrogen atom at the 3-position on the imidazole ring, a carboxylate anion form of the carboxy group at the 5-position, and the presence of an intramolecular hydrogen bond between the hydroxy group at the 4-position and the 5-carboxylate anion.

Scheme 3[a]



[a] Reagents: (i) $Bu^tOK/AcNMe_2$; (ii) 4 N HCl/dioxane or 25% aqueous AcOH; (iii) LiOH/dioxane/H_2O.

Modifications[22] of the ester groups on the imidazole rings are illustrated in Scheme 4. Reduction of **21a** and **22a** with diisobutylaluminum hydride (DIBAH) gave 4-(hydroxymethyl)imidazoles **39** and **40**, respectively. On the other hand, reduction of **21a** with lithium tri-*tert*-butoxyaluminohydride afforded predominantly 5-(hydroxymethyl)imidazole **45**, with minor product **39**, in a ratio of 6.6:1, and **22a** provided **46** and **40** in a ratio of 9.5:1.[24] The structure of **39** was determined by X-ray analysis; the result is shown in Figure 1b. The X-ray analysis showed the presence of an intermolecular hydrogen bond between the hydroxy group at the 4-position and the nitrogen atom at the 3-position. The structures of the other reduced products were deduced by proton NMR spectra, that is, the methylene protons of the biphenylylmethyl groups of **39** and **40** were observed at δ 5.61 and 5.47, respectively, whereas those of **45** and **46** were shown at higher fields, δ 5.26 and 5.08, respectively, as observed in the products of Schemes 2 and 3. Further reduction of **45** with DIBAH gave the diol **51**. Removal of the protecting groups in **39**, **40**, **45**, **46**, and **51** afforded the objective compounds **43**, **44**, **49**, **50**, and **52**, respectively.

The 4-methyl- and -ethylimidazoles **57a**,**b** and **58a**,**b** were prepared by dehydroxylation of **27c**, **29c**, **39**, and **40**, as shown in Scheme 5. Esterification of **39** with ethyl chloroglyoxylate, followed by heating with tributyltin hydride, gave the dehydroxylated imidazole **53a**, which was converted to **57a** by removal of the protecting groups. The same procedure was done on **27c**, **29c**, and **40** to give the desired compounds **57b** and **58a**,**b**.

Preparation of prodrugs **63a**−**d**, **64a**,**b**, and **68**, which were expected to improve bioavailability, is illustrated in Scheme 6. Alkaline hydrolysis of **21c** and **22c** gave the imidazole-5-carboxylic acids **59** and **60**, respectively. Esterification of **59** and **60** with appropriate alkyl halides, followed by removal of the *tert*-butyl or trityl group, gave **63a**−**d** and **64a**,**b** which are the prodrugs of the carboxy group at the 5-position on the imidazole ring. The X-ray-determined structure of **64a** (CS-866), which is one of the most promising compounds, is shown

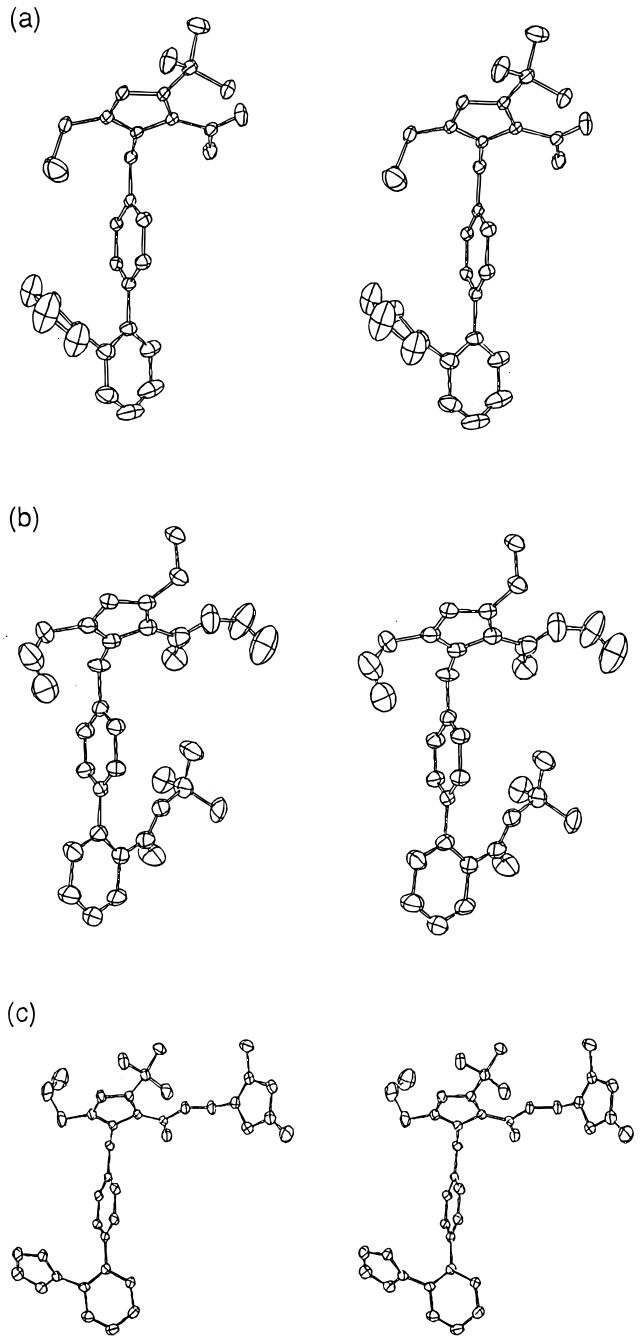


Figure 1. X-ray-determined structures of **26c** (a), **39** (b), and **64a** (c).

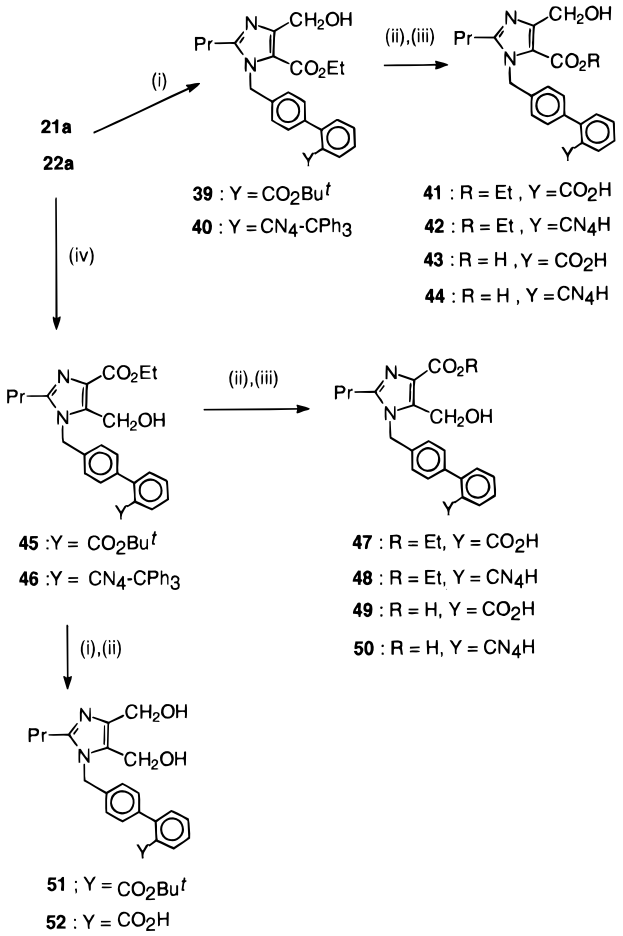
in Figure 1c. The prodrug **68** of the carboxybiphenyl moiety was prepared as follows. Benzylation of **59**, followed by removal of the *tert*-butyl group, gave **66**. Pivaloyloxymethylation of **66** with (pivaloyloxy)methyl chloride, followed by removal of the benzyl group by hydrogenolysis, afforded **68**.

Biological Activities

Binding Affinities to AII (AT_1) Receptor (in Vitro Activities) and Antagonistic Activities by Intravenous Administration (in Vivo Activities). Compounds prepared in Schemes 2−5 were evaluated for in vitro and in vivo AII antagonistic activities. The in vitro activities were determined by a conventional ligand-binding assay on a bovine adrenal cortex using [^{125}I]AII and are expressed as IC_{50} values. The in vivo activity was determined by the inhibition of the pressor response induced by infusion of AII in anesthetized normotensive rats. Compounds were administered intravenously, and inhibitory effects were estimated at 2 min after administration of the test compounds. The potency is expressed in terms of ID_{50} values. The resulting in vitro and in vivo activities are shown in Table 1, in which the activities are compared with those of **1** and **2** and their carboxybiphenyl analogues **69** and **70**.

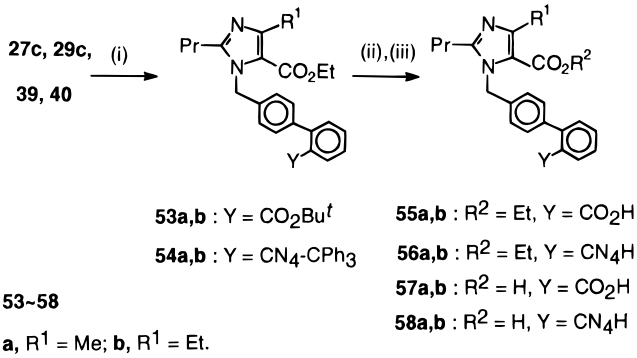
Antagonistic Activities by Oral Administration. In order to evaluate for oral activities, **25c**, **26c**, **34c**, and **44**, which showed potent antagonistic activities by

Scheme 4[a]



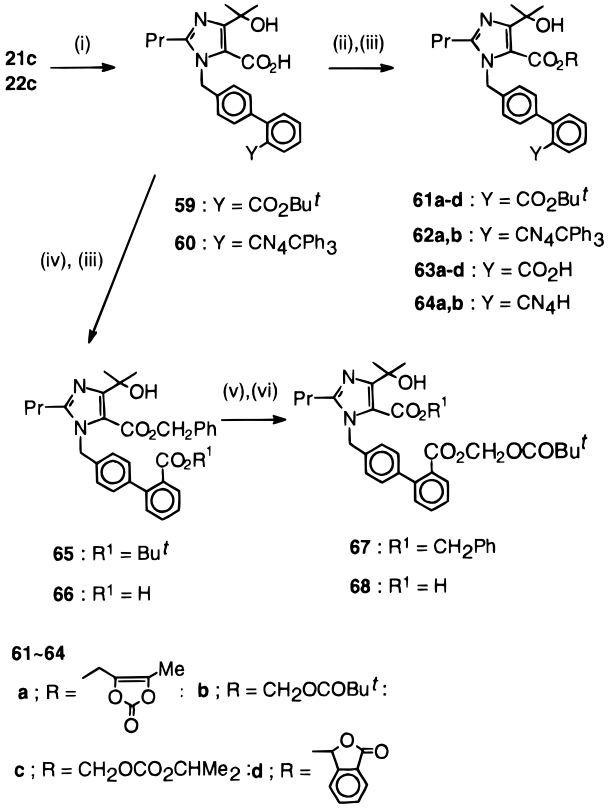
[a] Reagents: (i) Bu^i_2AlH/toluene; (ii) 4 N HCl/dioxane or 25% aqueous AcOH; (iii) LiOH/dioxane/H_2O; (iv) $LiAl(OBu^t)_3H$/THF.

Scheme 5[a]



[a] Reagents: (i) $ClCOCO_2Et/Et_3N/CH_2Cl_2$ then Bu_3SnH/toluene; (ii) 4 N HCl/dioxane or 25% aqueous AcOH; (iii) NaOH/dioxane/H_2O.

Scheme 6[a]



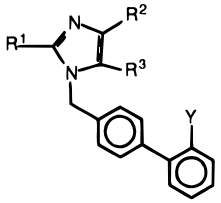
[a] Reagents: (i) LiOH/dioxane/H_2O; (ii) RCl/K_2CO_3/$AcNMe_2$; (iii) 4 N HCl/dioxane or 25% aqueous AcOH; (iv) $PhCH_2Br/K_2CO_3$/$AcNMe_2$; (v) $Bu^tCO_2CH_2Cl/K_2CO_3/AcNMe_2$; (vi) H_2/Pd−C/EtOH.

intravenous administration, and the prodrugs[26] of **25c** and **26c** were orally administered to conscious normotensive rats. After administration of the test compounds, AII was administered repeatedly at appropriate intervals and the AII pressor responses were measured. The inhibitory effects, recorded at 1, 3, and 6 h after oral administrarion of the test compounds, are shown in Table 2 and are compared with those of **1** and **2**.

Molecular Modeling

Conformational Analysis of 26c. Calculation on **26c** was carried out on structure **71**, in which the carboxy group and imidazole ring take the forms of a carboxylate anion and a protonated imidazole ring, respectively, as was found in the X-ray-determined structure (Figure 1a), and the tetrazole group is in an anion form in order to reduce the computational burden by introducing C_2 symmetry into the ring. Geometry optimization of **71** was carried out using the PM3 method of the MOPAC program.[27] First, the three-dimensional structures of **72** and **73** were examined to find the stable substructure conformations of **71**. The torsional angles of $\tau_1-\tau_8$ were incremented by 30°, 120°, 30°, 120°, 30°, 30°, 30°, and 30°, respectively, in the generation of initial conformations. After the geometry optimization, 43 and 2 distinct conformers with a relative energy (difference from the lowest) of $\Delta E < 7.0$ kcal/mol were obtained for **72** and **73**, respectively. As for the torsional angle of τ_2 to locate the hydroxyl hydrogen, only the most preferable angles were taken into account. Initial conformations of **71** were then generated by combining the preferred torsional angles of $\tau_1-\tau_8$ obtained above. Geometry optimization of those structures gave 28 stable conformers with the $\Delta E < 7$ kcal/mol. These conformers were classified into six groups, neglecting the conformations of the propyl substituent at the 2-position. The most stable conformations of each group are listed in Table 3.

Table 1. In Vitro and in Vivo AII Antagonist Properties of Imidazoles

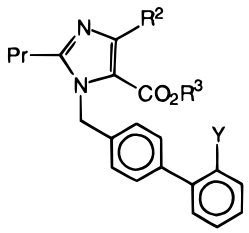


compd	R^1	R^2	R^3	Y	in vitro IC_{50}[a] (nM)	in vivo ID_{50}[b] (mg/kg)
33a	Pr	H	CO_2H	CO_2H	60	0.22
57a	Pr	Me	CO_2H	CO_2H	110	0.096
57b	Pr	Et	CO_2H	CO_2H	100	0.27
25e	Pr	$CHMe_2$	CO_2H	CO_2H	360	0.14
33b	Pr	$C(=CH_2)Me$	CO_2H	CO_2H	270	0.37
43	Pr	CH_2OH	CO_2H	CO_2H	58	0.069
33c	Pr	CHMeOH	CO_2H	CO_2H	28	0.062
25c	Pr	CMe_2OH	CO_2H	CO_2H	28	0.056
25f	Pr	CMeEtOH	CO_2H	CO_2H	51	0.074
25g	Pr	CEt_2OH	CO_2H	CO_2H	110	0.11
41	Pr	CH_2OH	CO_2Et	CO_2H	840	1.5
23c	Pr	CMe_2OH	CO_2Et	CO_2H	600	1.2
37	Pr	CO_2H	H	CO_2H	45 000	8.2
25a	Pr	CO_2H	CO_2H	CO_2H	320	0.67
49	Pr	CO_2H	CH_2OH	CO_2H	20 000	8.8
52	Pr	CH_2OH	CH_2OH	CO_2H	2700	2.1
25b	Et	CMe_2OH	CO_2H	CO_2H	37	0.30
25d	Bu	CMe_2OH	CO_2H	CO_2H	30	0.066
34a	Pr	H	CO_2H	Tz[c]	9.1	0.018
58a	Pr	Me	CO_2H	Tz	11	0.028
58b	Pr	Et	CO_2H	Tz	12	0.019
26e	Pr	$CHMe_2$	CO_2H	Tz	46	0.014
34b	Pr	$C(=CH_2)Me$	CO_2H	Tz	50	0.012
44	Pr	CH_2OH	CO_2H	Tz	6.9	0.0062
34c	Pr	CHMeOH	CO_2H	Tz	4.9	0.0063
26c	Pr	CMe_2OH	CO_2H	Tz	8.1	0.0079
24c	Pr	CMe_2OH	CO_2Et	Tz	200	0.32
38	Pr	CO_2H	H	Tz	14 000	2.4
26a	Pr	CO_2H	CO_2H	Tz	100	0.031
50	Pr	CO_2H	CH_2OH	Tz	4600	1.7
26b	Et	CMe_2OH	CO_2H	Tz	5.3	0.019
26d	Bu	CMe_2OH	CO_2H	Tz	9.5	0.017
1	Bu	Cl	CH_2OH	Tz	120[d]	0.30
2	Bu	Cl	CO_2H	Tz	22[d]	0.10
69	Bu	Cl	CH_2OH	CO_2H	490[d]	2.3
70	Bu	Cl	CO_2H	CO_2H	130[d]	0.21

[a] IC_{50} values were determined by a radioligand-binding assay using [^{125}I]AII (0.1 nM) and bovine adrenal cortex. [b] ID_{50} values were determined by inhibitory activity to the AII-induced pressor response. Test compounds were intravenously administered. [c] Tetrazol-5-yl. [d] See ref 25.

Conformational Analysis of Acetylated C-Terminal Pentapeptide of AII. Considering the computational ease, calculations were performed on the acetyl derivative of the C-terminal pentapeptide of AII, Ac-Tyr-Ile-His-Pro-Phe-CO_2^- (**74**), which is considered to be the target sequence of nonpeptide antagonists as mentioned below. The two initial conformations of **74** were taken from TAA[28] (Tyr^{145}-Phe-His-Pro-Phe^{149}) and AK3[29] (Trp^{127}-Ile-His-Pro-Gly^{131}) which were selected by the sequence homology search of Protein Data Bank[30] at Brookhaven National Laboratory. After mutation of those two structures into **74**, energy minimization was performed using the QUANTA/CHARMm program.[31] The pentapeptide is yet so flexible with 17 rotatable

Table 2. Inhibition of the AII-Induced Pressor Response by Imidazole Derivatives in Conscious, Normotensive Rats by Oral Administration



compd	R^2	R^3	Y	dose (mg/kg)	inhibition (%) at 1 h	at 3 h	at 6 h
25c	CMe_2OH	H	CO_2H	1	50	42	12
				3	78	67	48
				10	88	70	56
23c	CMe_2OH	Et	CO_2H	3	26	28	25
				10	40	70	75
63a	CMe_2OH	MDO[a]	CO_2H	1	72	70	70
63b	CMe_2OH	POM[b]	CO_2H	0.3	43	32	35
				1	52	61	75
				3	85	85	87
63c	CMe_2OH	IPM[c]	CO_2H	1	71	71	71
63d	CMe_2OH	PHT[d]	CO_2H	1	73	77	74
68	CMe_2OH	H	CO_2POM	1	20	35	40
44	CH_2OH	H	Tz[e]	0.3	76	75	65
34c	CHMeOH	H	Tz	0.3	80	78	69
26c	CMe_2OH	H	Tz	0.3	83	77	78
				1	98	98	93
24c	CMe_2OH	Et	Tz	1	70	72	76
64a	CMe_2OH	MDO	Tz	0.03	32	39	55
				0.1	66	77	83
				0.3	78	88	92
64b	CMe_2OH	POM	Tz	0.03	29	41	43
				0.1	75	84	70
				0.3	76	85	90
1	Cl	(CH_2OH)	Tz	1	12	12	32
				3	38	35	65
				10	69	77	85
2	Cl	H	Tz	1	74	72	70
				3	81	81	81
				10	89	93	89

[a] (5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl. [b] (Pivaloyloxy)methyl. [c] [(Isopropoxycarbonyl)oxy]methyl. [d] Phthalidyl. [e] Tetrazol-5-yl.

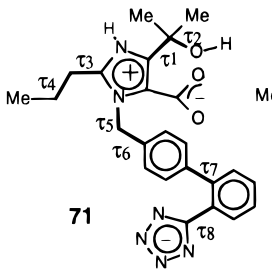
Table 3. Representative Stable Conformers of **71** with ΔE < 7.0 kcal/mol

conformer no.	torsional angles (deg) τ_1	τ_2	τ_3	τ_4	τ_5	τ_6	τ_7	τ_8	ΔE (kcal/mol)
1	138	58	80	180	53	−117	−89	160	0.0
2	−138	−56	80	180	53	63	84	19	0.6
3	−138	−58	−83	−179	−53	117	88	22	1.5
4	139	56	−83	−179	−51	118	90	18	2.1
5	13	159	82	180	54	62	84	21	3.2
6	11	159	−84	−179	−53	118	90	18	4.9

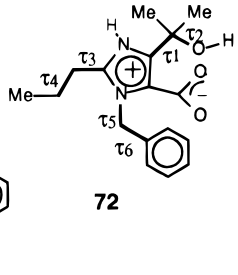
bonds, shown as thick lines, that the random sampling approach was employed using the "filter search" option of the QUANTA/CHARMm program. Starting from the two conformations derived from TAA and AK3, 100 stable conformations were obtained from each initial conformation. The conformational energies of those conformers ranged from −65.7 to −38.5 kcal/mol.

Results and Discussion

SAR: (i) In Vitro Activities. In the carboxybiphenyl series (Y = CO_2H), the imidazole-5-carboxylic acid **33a** (IC_{50} = 60 nM), which has no substituent at the 4-position, had a 2-fold stronger binding affinity than



71



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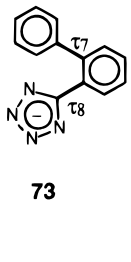
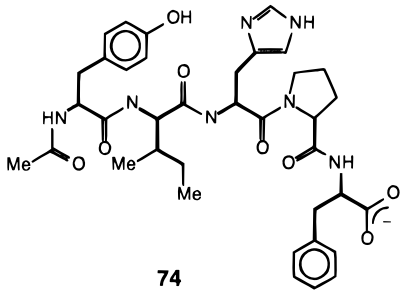


73



74

1 and **70** but was less potent than **2**. Introduction of alkyl or alkenyl groups at the 4-position lowered the binding affinity. The relative order of binding affinities to the receptor was H (**33a**) > Me (**57a**) = Et (**57b**) > C(=CH_2)Me (**33b**) > $CHMe_2$ (**25e**), showing that a bulky alkyl or alkenyl group is unfavorable for binding to the receptor. Replacement of the alkyl group with a hydroxyalkyl group at the 4-position led to an improvement of the activity as seen in **43**, **33c**, and **25c**. A higher improvement ratio was observed in bulkier R^2 [Me (**57a**) vs CH_2OH (**43**), 1.9-fold; Et (**57b**) vs CHMeOH (**33c**), 3.6-fold; $CHMe_2$ (**25e**) vs CMe_2OH (**25c**), 13-fold], which means that the hydroxy group plays an important role in the binding affinity and compensates the disadvantage of lipophilicity of the bulky alkyl group. The hydroxymethyl derivative **43**, which is smaller than **33c**, and compounds **25f**,**g**, having bulky substituents at the 4-position compared with **25c**, had weak binding affinities compared with **33c** and **25c**. These results show that a medium-sized hydroxyalkyl group, such as CHMeOH and CMe_2OH, is favorable for the substituent at the 4-position. Esterification (**23c**, **41**) of the carboxy groups at the 5-position of **25c** and **43** markedly decreased the activity, indicating that an ionizable group is favorable for the binding affinity. Imidazole-4-carboxylic acids **37**, **25a**, and **49** showed poor activities, which suggests that a polar group, such as CO_2H, is unfavorable at the 4-position. Imidazole-4,5-dimethanol **52**, which has a hydroxymethyl group at the 4-position instead of the chlorine atom of **69**, had a weak binding affinity compared with **69**. It is interesting that the hydroxyalkyl substituent at the 4-position with the carboxy group at the 5-position, not with the ester and hydroxymethyl group, contributes to potentiation of activity. This contribution may be brought about by the intramolecular hydrogen bond between the hydroxyalkyl group and the carboxy group as seen in the X-ray-determined structure of Figure 1a. Shortening (**25b**) or elongating (**25d**) the alkyl group at the 2-position of **25c** resulted in a slight loss of antagonistic activities. The 2-butylimidazole **25d**, which is the 4-(1-hydroxy-1-methylethyl) analogue of **70**, had a 4-fold greater potent binding affinity than **70**.

Replacement of the carboxybiphenyl group with a tetrazolylbiphenyl group (Y = tetrazolyl group) resulted

in an improved antagonistic activity; i.e., imidazole-5-carboxylic acid **34a** showed a 6.6-fold more potent binding affinity than the corresponding biphenylylcarboxylic acid **33a** [**34a** (IC_{50} = 9.1 nM) vs **33a** (IC_{50} = 60 nM)]. Alkylation (**58a**,**b**, **26e**) or alkenylation (**34b**) at the 4-position reduced the binding affinity. The bulky alkyl substituents seemed to be disadvantageous for activity as observed in the carboxybiphenyl series. Introduction of a hydroxy group on the 4-alkyl group enhanced the activity. The bulkier substituent brought on higher improvement ratio on the activity [Me (**58a**) vs CH_2OH (**44**), 1.6-fold; Et (**58b**) vs CHMeOH (**34c**), 2.4-fold; $CHMe_2$ (**26e**) vs CMe_2OH (**26c**), 5.7-fold]. This tendency was consistent with that in the carboxybiphenyl series. The ethyl ester **24c** showed only one-twenty-fifth the binding activity of **26c**, and imidazole-4-carboxylic acids **26a**, **38**, and **50** had poor activities as observed in the carboxybiphenyl series. Replacement of the propyl group at the 2-position of **26c** with an ethyl group (**26b**) improved the binding affinity. The 2-butyl derivative **26d**, which is a 4-(1-hydroxy-1-methylethyl) analogue of **2**, was less potent than **26c** but more potent than **2**.

Compound **26c** did not show antagonism against the AT_2 receptor prepared from the cerebrum membrane at a concentration of 0.1 mM, which implies that **26c** is the AT_1 selective antagonist.

(ii) In Vivo Activities. SAR on in vivo activities is expected to be different from that on in vitro activities because of the effect of metabolism and pharmacokinetics of test compounds.

In the carboxybiphenyl series, **33a**, bearing no substituent at the 4-position, had the same activity as **70**, which has a chlorine atom at the 4-position. Although alkylation (**57a**, **57b**, **25e**) of **33a** reduced the in vitro activities, their in vivo activities were comparable with or more potent than that of **33a**. The most active derivative **57a** (R^2 = Me) suppressed the AII-induced pressor response by twice as much as **33a**. These results are presumably caused by metabolic instability of **33a** and a high affinity of the alkyl antagonists toward the target organ. Isopropenylation (**33b**) reduced the potency by almost one-half that of **33a**. The hydroxyalkyl derivatives (**43**, **33c**, **25c**) had more potent activities than the corresponding alkyl compounds [Me (**57a**) vs CH_2OH (**43**), 1.4-fold; Et (**57b**) vs CHMeOH (**33c**), 4.3-fold; $CHMe_2$ (**25e**) vs CMe_2OH (**25c**), 2.5-fold], which is in agreement with their potent in vitro activities. More bulky hydroxyalkyl substituents (**25f**,**g**) diminished the potencies as seen in the in vitro activities. The weak in vivo activities of ethyl esters **41** and **23c**, 4-carboxy compounds **37**, **25a**, and **49**, and the 4,5-dihydroxymethyl derivative **52** were consistent with their weak in vitro activities. The 2-ethyl derivative **25b** had only one-fifth potency of **25c**, while the 2-butyl derivative **25d** showed almost the same potency as **25c**.

Replacement of the carboxybiphenyl group with a tetrazolylbiphenyl group led to a drastic increase in the in vivo activity. Compound **34a**, bearing no substituent at the 4-position, inhibited the AII pressor response by 1 order of magnitude and is, therefore, more potent than the corresponding biphenylcarboxylic acid **33a**. Alkylation (**58a**,**b**, **26e**) and isopropenylation (**34b**) at the 4-position of **34a** kept the in vivo activities at the level of **34a**. Introduction of a hydroxy group (**44**, **34c**, **26c**) to the alkyl group of **58a**,**b** and **26e** led to an enhancement in the activities by a 1.8−4.5-fold range as observed in the carboxybiphenyl series. These compounds had the most potent antagonistic activities in the compounds prepared. Esterification (**24c**) markedly diminished the activity. Except for **26a**, 4-carboxy derivatives **38** and **50** had weak activities as predicted from their in vitro activities. The ethyl (**26b**) and butyl (**26d**) derivatives at the 2-position were less potent than **26c**.

Oral Activities. One of the pharmacological requirements of an antihypertensive agent is that it must be orally effective. Sometimes, agents, which have potent in vitro activities and significantly reduce blood pressure by intravenous administration, do not show sufficient efficacy by oral administration because of their low bioavailability, liability to metabolism, and high clearance.

Compound **25c**, which was the most potent compound in the carboxybiphenyl series, showed maximal suppression within 1 h after oral administration. Its potency was more than that of **1** but less than that of **2**. The ID_{50} values of **25c** by iv and po administrations were 0.056 and 1 mg/kg, respectively. The large ID_{50} value by po administration would be caused by poor bioavailability of **25c**. In order to improve the bioavailability, **25c** was esterified and these esters were evaluated for their ability to suppress the AII pressor response. Compound **25c** has two carboxy groups on the imidazole ring and the biphenyl moiety. At first, the esters of the imidazole carboxy group were examined. The ethyl ester **23c** suppressed the AII-induced pressor response less potently than **25c**. This result means that the ethyl ester is not converted to the parent carboxylic acid in vivo by the esterase. The (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl (MDO) (**63a**), (pivaloyloxy)-methyl (POM) (**63b**), [(isopropoxycarbonyl)oxy]methyl (**63c**), and phthalidyl (**63d**) esters, whose ester residues are known to be useful as prodrug residues of the β-lactam antibiotics,[32] showed potent and long-lasting suppression of the AII-induced pressor response. Their potencies were the same as that of **2** and 3-fold more potent than that of **25c**. On the other hand, the POM ester **68** at the carboxybiphenyl moiety gave poor inhibitory activity.

In the tetrazolylbiphenyl series, imidazole-5-carboxylic acids **44**, **34c**, and **26c**, which showed strong binding affinities and potent suppressive activities on the AII-induced pressor response by intravenous administration, showed potent and long-lasting suppression of the AII-induced pressor response orally. These compounds suppressed the AII-induced pressor response in a range of 76−83% at a dose of 0.3 mg/kg. The time courses for suppression of these compounds are shown in Figure 2. Of these three compounds, **26c** showed the most prolonged effect, which may be caused by its metabolic stability due to the hindrance of the tertiary alcohol and by its large lipophilicity compared with **34c** and **44**. Hereupon, the most favorable acid (**26c**) was esterified in order to improve bioavailability. Though the ethyl ester **24c** was less active than the parent compound **26c**, the MDO (**64a**) (CS-866) and POM (**64b**) esters had the most potent and durable inhibitory activities among the compounds tested by oral administration. Their poten-

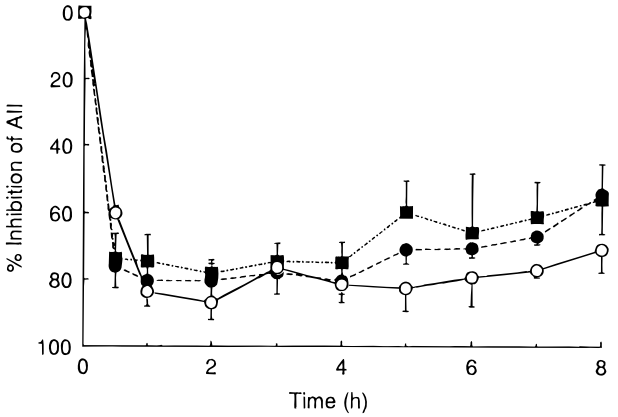


Figure 2. Time courses of **26c** (○), **34c** (●), and **44** (■) for inhibition of the AII (50 ng/kg, iv)-induced pressor response in conscious normotensive rats ($n = 3-5$). The compounds were administered orally at a dose of 0.3 mg/kg.

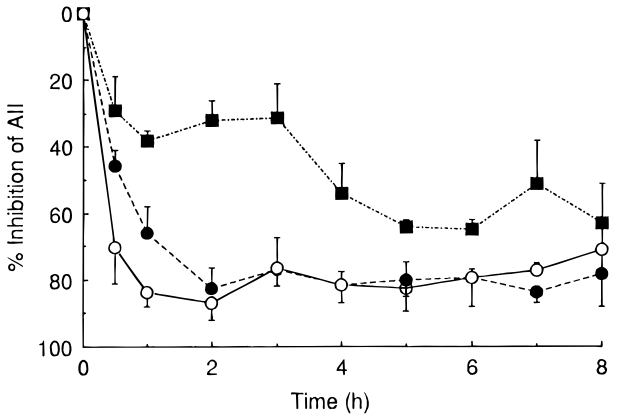


Figure 3. Time courses of **1** (3 mg/kg, po, ■), **26c** (0.3 mg/kg, po, ○), and **64a** (0.1 mg/kg, po, ●) for inhibition of the AII (50 ng/kg, iv)-induced pressor response in conscious normotensive rats ($n = 3-5$).

cies at 0.1 mg/kg dose were comparable to that at 0.3, 3, and 10 mg/kg doses of **26c**, **2**, and **1**, respectively. The time course for inhibition of **64a** (0.1 mg/kg, po) in comparison with **1** (3 mg/kg, po) and **26c** (0.3 mg/kg, po) is shown in Figure 3.

Superposition of 26c upon Acetylated C-Terminal Pentapeptide of AII. For the purpose of understanding the role of the 1-hydroxy-1-methylethyl group at the 4-position of **26c** from the standpoint of stereochemistry, we studied stereochemical comparison of **26c** with AII.

The conformation bound to the receptor has not been determined definitely on account of its gross flexibility.[33] In the early overlay studies[17a,19] of the nonpeptide antagonists **6**, **7**, and **3** with AII, these antagonists overlapped with the C-terminal pentapeptide of AII, Tyr^4-Ile^5-His^6-Pro^7-Phe^8. Garcia et al. reported the three-dimensional structure of the AII−Fab complex, in which the central AII sequence, Tyr^4-Ile^5-His^6-Pro^7, located in the deepest region of the combining site, and the terminal Phe^8 were important residues for binding to the receptor.[34] Consequently, studying the conformation of the C-terminal pentapeptide of AII, instead of AII, can be considered a logical approach to the overlay study. In practice, the acetyl derivative **74** of the C-terminal pentapeptide of AII was adopted for a molecular modeling study, in order to simplify the calculations.

Each conformation of **74**, obtained by the molecular modeling study, was examined graphically to determine whether it could be superposed on any of the six conformers of **71** listed in Table 3, with the tetrazole ring of **71** overlapped on either the C-terminal carboxy group or the phenolic hydroxy group of Tyr in **74**. These acidic moities are supposed to be one of the most important pharmacophores. Several pairs that appeared to be well-superposed upon each other were selected and then subjected to a more unbiased superposition to maximize the overlap of the van der Waals volume of hydrophobic groups, i.e., carbon atoms and hydrogen atoms attached to them. Two kinds of superposed structures, A and B, with the most reasonable correspondence of functional groups are shown in Figure 4.

Conformers 4 and 3 of **71** in Table 3 were employed in superpositions A and B, respectively. In the case of superposition A, the acidic moieties, tetrazole and carboxy groups, of **71** correspond to the phenolic hydroxy group of Tyr and the C-terminal carboxy group, respectively, and the hydrophobic moieties, the propyl, isopropyl, and terminal phenyl groups, agree with the alkylene chain of Pro, the phenyl group of Phe, and the phenyl group of Tyr, respectively. The imidazole ring of **71** has no directly corresponding group in **74** but seems to serve as a junction of the pharmacophore groups. In contrast with superposition A, the tetrazole and carboxy groups of superposition B correspond to the C-terminal carboxy group and the carbonyl group of Ile in **74**, respectively. The propyl, isopropyl, terminal phenyl, and internal benzyl groups can be overlayed on the alkylene chain of Pro, the alkyl group of Ile, the phenyl group of Phe, and the imidazolylmethyl group of His, respectively. The nitrogen atom at the 3-position on the imidazole ring, which would interact with the AII receptor through hydrogen bonding,[18] is located near the carbonyl oxygen of His. It is interesting in the superposition B that the 1-hydroxy-1-methylethyl group of **71** is positioned where the alkyl side chain and the peptide backbone carbonyl group of Ile are located. The hydrogen bond between the hydroxy group in the 4-substituent and the neighboring carboxy group in **71** seems to change the nature of the carboxy group to that of the corresponding carbonyl group of Ile from the electostatic point of view and to direct the isopropyl group toward the position occupied by the side chain of Ile. These speculations might account for the potent activities of **26c** and the compounds having a hydroxyalkyl group at the 4-position.

In superposition B we suppose that **71** would bind to the AII receptor through the following interactions: (i) hydrophobic bindings of the propyl chain at the 2-position, the isopropyl group at the 4-position, the terminal phenyl group of the substituent at the 1-position, and the benzyl group at the 1-position, which correspond to the alkylene group of Pro, the alkyl chain of Ile, the phenyl group of Phe, and the imidazolylmethyl group of His in AII, respectively, with lipophilic pockets of the receptor, (ii) an ionic bonding between the tetrazole group, corresponding to the C-terminal carboxy group of AII, and a cationic group of the receptor, and (iii) a hydrogen bonding between the carboxy group at the 5-position, corresponding to the carbonyl group of Ile, and a proton donor of the receptor. Hydrophobic

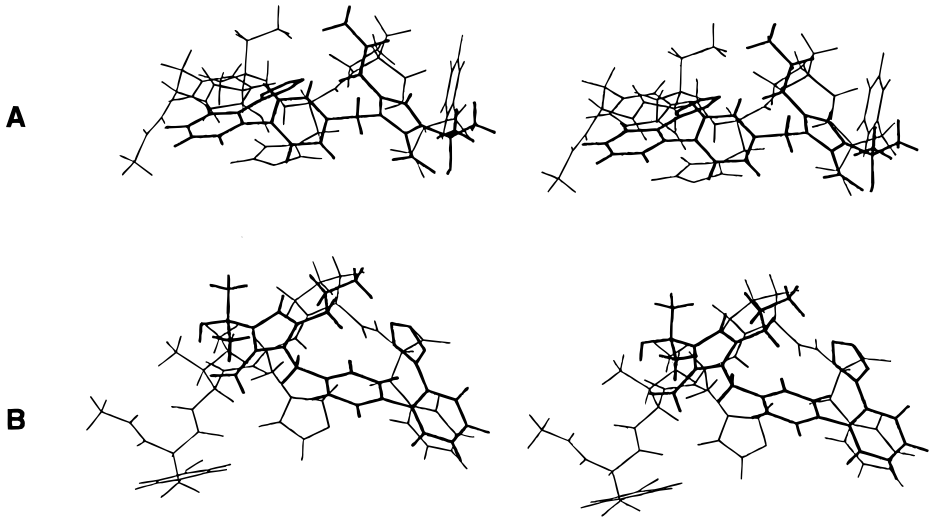


Figure 4. Stereoviews of superposition structures A and B. Thick lines indicate **71**, and thin lines indicate **74**. (a) Superposition A: The overlapped van der Waals volume of hydrophobic groups is 172 Å^3. (b) Superposition B: The overlapped van der Waals volume of hydrophobic groups is 186 Å^3.

interaction between the substituent at the 4-position and a postulated secondary lipophilic pocket in the AII receptor was proposed by the Searle group.[35] A few groups[17d,36] suggested that a character of the substituent at the 5-position as a hydrogen-bonding acceptor is favorable for binding to the receptor. These proposed interactions are well-consistent with our results. Furthermore, the conformation of **71** in superposition B is in fair agreement with that of a potent, conformationally restricted imidazole antagonist[36b] which would be the active conformation for interaction with the receptor.

Conclusion

2-Alkyl-1-[[2′-carboxy(or tetrazol-5-yl)biphenyl-4-yl]-methyl]imidazole-5-carboxylic acids bearing alkyl, alkenyl, and hydroxyalkyl substituents at the 4-position have been synthesized and evaluated for in vitro and in vivo antagonisic activities on the AII receptor. In the carboxybiphenyl series, the most active compound, **25c**, has propyl, 1-hydroxy-1-methylethyl, and carboxy groups at the 2-, 4-, and 5-positions, respectively. The low oral bioavailability of **25c** was improved by esterification of the 5-carboxy group with MDO, POM, [(isopropoxycarbonyl)oxy]methyl, and phthalidyl groups. Replacement of the carboxybiphenyl group with a tetrazolylbiphenyl group enhanced the antagonistic activity. The most potent imidazoles were hydroxymethyl (**44**), 1-hydroxyethyl (**34c**), and (1-hydroxy-1-methyl)ethyl (**26c**) derivatives, which had 2.7−4.5 times stronger binding affinity than **2** and 15−24 times stronger affinity than **1**, and they inhibited the AII-induced pressor response 13−16 times more potently than **2** by intravenous administration. Among them, **26c** showed the most lasting antagonistic activity, when administered orally. The MDO (**64a**) (CS-866) and POM (**64b**) esters of **26c** were the most promising antagonists prepared in the present study. These compounds suppressed the AII-induced pressor response 3 times more potently than **26c** and 100 times more potently than **1** by oral administration. Stereochemical comparison of **26c** with the acetylated C-terminal pentapeptide **74** of AII gave two reasonable superposition structures, A and B. Superposition B suggested that the substituent suitable for the 4-position would be a medium-sized hydrophobic group having a hydroxy group which forms a hydrogen bond with the carboxy group at the 5-position. This hydrogen bonding would change the nature of the carboxy group at the 5-position to that of the carbonyl group of Ile and direct the isopropyl group toward the alkyl chain of Ile.

The conformational analysis of the pentapeptide is incomplete in the following views: (i) the pentapeptide in AII was utilized in the computational modeling, (ii) the conformations of the pentapeptide sequences of TAA and AK3 were utilized in the conformational study of the pentapeptide of AII, and (iii) no solvents were taken into account in all the calculations. Despite such limitations, however, we are confident that our results would serve as a future working model for synthetic study of the next-generation antagonists.

Experimental Section

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Recrystallization solvents for analytical samples are described in parentheses after melting points. Proton NMR spectra were obtained on a JEOL EX270 instrument and are reported as δ values relative to Me_4Si as the internal standard. The following abbreviations are used to describe peak patterns whenever appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, qi = quintet, sx = sextet, sp = septet, m = multiplet. IR spectra were taken on a JASCO FT/IR-8900 spectrometer. The abbreviations sh and wk indicate shoulder and weak, respectively. Elemental analyses were performed by the Institute of Science and Technology, Inc., and the results obtained are within ±0.4% of the theoretical values unless indicated otherwise. Flash column chromatography was done on Merck silica gel 60 (230−400 mesh). Isopropyl ether, tetrahydrofuran, *N*,*N*-dimethylformamide, *N*,*N*-dimethylacetamide, and dimethyl sulfoxide are abbreviated as IPE, THF, DMF, DMA, and DMSO, respectively.

2-Propylimidazole-4,5-dicarbonitrile (8b).[37] A mixture of diaminomaleonitrile (24.1 g, 0.162 mol) and trimethyl orthobutyrate (15.95 g, 0.148 mol) in CH_3CN (95 mL) was stirred under reflux for 5 h. After the solvent was evaporated in vacuo, the residue was diluted with xylene (87 mL) and the solution was refluxed for 7 h. After cooling in an ice bath, the precipitates were collected by filtration: yield 18.7 g (96%); mp 141−144 °C.

Similarly, **8a**,**c** were prepared using trimethyl orthopropionate and trimethyl orthovalerate, respectively, instead of trimethyl orthobutyrate. **8a**: 97%; mp 179−181 °C.[38] **8c**: 79%; mp 111−112 °C. Anal. ($C_9H_{10}N_4$) C,H,N.

2-Propylimidazole-4,5-dicarboxylic Acid (9b).[39] A solution of **8b** (39.5 g, 0.247 mol) in 6 N HCl (360 mL) was refluxed for 8 h. After cooling, the precipitates were collected by filtration and washed with water and acetone: yield 39.3 g (80%); mp 261−263 °C.

Similarly, **9a**,**c** were prepared. **9a**: 55%; mp 265−268 °C.[40] **9c**: 69%; mp 261−263 °C.[40]

Diethyl 2-Propylimidazole-4,5-dicarboxylate (10b). To a suspension of **9b** (120 g, 0.606 mol) in EtOH (1.3 L) was bubbled HCl gas at room temperature for 3 h. The resulting solution was allowed to stand overnight at room temperature and concentrated in vacuo. The residue was dissolved in EtOAc and aqueous $NaHCO_3$ and neutralized with powdered $NaHCO_3$. The organic phase was separated, dried over $MgSO_4$, and concentrated in vacuo to give crystalline **10b**, which was washed with IPE−hexane: yield 147.8 g (86%); mp 84−86 °C (EtOAc−IPE); NMR ($CDCl_3$) 0.97 (3H, t, J = 7.5 Hz), 1.38 (6H, t, J = 7 Hz), 1.79 (2H, sx, J = 7.5 Hz), 2.78 (2H, t, J = 7.5 Hz), 4.39 (4H, q, J = 7 Hz); IR (KBr) 2609, 1749, 1724 (sh) cm^{-1}. Anal. ($C_{12}H_{18}N_2O_4$) C,H,N.

Similarly, **9a**,**c** and **14** were esterified to afford **10a**,**c** and **15**, respectively. **10a**: 85%; mp 88−90 °C (EtOAc−IPE).[38] **10c**: 85%; mp 83−84 °C. Anal. ($C_{13}H_{20}N_2O_4$) C,H,N. **15**: 56%; mp 108−110 °C. Anal. ($C_9H_{14}N_2O_2$) C,H,N.

Ethyl 4-(1-Hydroxy-1-methylethyl)-2-propylimidazole-5-carboxylate (11ba). To a stirred solution of 3 M MeMgBr in Et_2O (250 mL, 0.75 mol) was added a solution of **10b** (45.7 g, 0.18 mol) in CH_2Cl_2 (120 mL) at 0−10 °C under N_2. The mixture was stirred at 10−15 °C for 1 h and then diluted with EtOAc (0.5 L) and aqueous NH_4Cl (0.3 L), successively. The organic phase was separated, washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give a syrup, which was crystallized in IPE−hexane: yield 40.9 g (95%); mp 101−102 °C (IPE); NMR ($CDCl_3$) 0.97 (3H, t, J = 7.5 Hz), 1.36 (3H, t, J = 7 Hz), 1.62 (6H, s), 1.74 (2H, sx, J = 8 Hz), 2.68 (2H, t, J = 8 Hz), 4.36 (2H, q, J = 7 Hz); IR (KBr) 3373, 1718 (sh), 1676 cm^{-1}. Anal. ($C_{12}H_{20}N_2O_3$) C,H,N.

Similarly, **11a**,**bb**,**c** were prepared. **11a**: 76%; mp 191−192 °C (EtOAc). Anal. ($C_{11}H_{18}N_2O_3$) C,H,N. **11bb**: 83%; syrup. Anal. ($C_{14}H_{24}N_2O_3 \cdot {}^1/_2H_2O$) C,H,N. **11c**: 78%; syrup. Anal. ($C_{13}H_{22}N_2O_3$) C,H,N.

Ethyl 4-Isopropenyl-2-propylimidazole-5-carboxylate (12). To a solution of **11ba** (10.0 g, 41.6 mmol) in benzene (200 mL) was dropwise added $POCl_3$ (8.53 mL, 91.5 mmol), and the mixture was refluxed for 1 h. Pyridine (10.0 mL, 124 mmol) was added to the reaction mixture at room temperature, and the mixture was refluxed for 1 h. After removal of the solvent by evaporation in vacuo, the residue was dissolved in EtOAc and aqueous $NaHCO_3$ and neutralized with powdered $NaHCO_3$. The organic phase was separated, washed with aqueous NaCl, dried over Na_2SO_4, and concentrated in vacuo to give a crystalline residue, which was washed with IPE: yield 8.39 g (91%); mp 131−131.5 °C (EtOAc); NMR ($CDCl_3$) 0.99 (3H, t, J = 7.5 Hz), 1.36 (3H, t, J = 7.5 Hz), 1.77 (2H, sx, J = 7.5 Hz), 2.19 (3H, s), 2.70 (2H, t, J = 7.5 Hz), 4.35 (2H, q, J = 7.5 Hz), 5.31−5.32 (2H, m), 5.55 (1H, br s); IR (KBr) 1714 cm^{-1}. Anal. ($C_{12}H_{18}N_2O_2$) C,H,N.

Ethyl 4-Isopropyl-2-propylimidazole-5-carboxylate (13). A mixture of **12** (5.39 g, 24.2 mmol) and 10% Pd−C (0.54 g) in MeOH (50 mL) was stirred at room temperature under a hydrogen atmosphere for 3 h. The catalyst was filtered off, and the filtrate was concentrated in vacuo to give crystalline **13**, which was washed with IPE: yield 5.04 g (93%); mp 133−136 °C (EtOAc−hexane); NMR ($CDCl_3$) 0.96 (3H, t, J = 7.5 Hz), 1.29 (6H, d, J = 7 Hz), 1.34 (3H, t, J = 7 Hz), 1.75 (2H, sx, J = 7.5 Hz), 2.72 (2H, t, J = 7.5 Hz), 3.66 (1H, sp, J = 7 Hz), 4.32 (2H, q, J = 7 Hz); IR (KBr) 1708, 1699 cm^{-1}. Anal. ($C_{12}H_{20}N_2O_2$) C,H,N.

2-Propylimidazole-4-carboxylic Acid (14). A suspension of **9b** (24.0 g, 0.121 mol) in Ac_2O (700 mL) was stirred under reflux for 33 h. After removal of the solvent by evaporation in vacuo, the residue was mixed with H_2O (250 mL), and the mixture was refluxed for 3 h. The solvent was evaporated to give a crystalline residue, which was washed with EtOH−Et_2O: yield 14.5 g (78%); mp 242−244 °C dec (EtOH); NMR (DMSO-d_6) 0.88 (3H, t, J = 7.5 Hz), 1.58−1.74 (2H, m), 2.59 (2H, t, J = 7.5 Hz), 7.54 (1H, s), 9.70−12.00 (1H, br s); IR (KBr) 1638 cm^{-1}. Anal. ($C_7H_{10}N_2O_2$) C,H,N.

4-Acetyl-2-propylimidazole-5-carbonitrile (16). To a solution of **8b** (10.0 g, 64.2 mmol) in THF (100 mL) was dropwise added a solution of 1 M MeMgBr in THF (194 mL, 194 mmol) at 10−15 °C under N_2. After stirring at 10−15 °C for 0.5 h, the reaction mixture was diluted with EtOAc (200 mL) and saturated aqueous NH_4Cl (200 mL), successively, and then acidified with aqueous $KHSO_4$. The organic phase was separated, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexane, 1:1) to give crystalline **16**: yield 9.18 g (81%); mp 93−94 °C (IPE−hexane); NMR ($CDCl_3$) 1.00 (3H, t, J = 7.5 Hz), 1.81 (2H, sx, J = 7.5 Hz), 2.72 (3H, s), 2.79 (2H, t, J = 7.5 Hz), 10.70 (1H, br s); IR (KBr) 3430, 2238, 1680 cm^{-1}. Anal. ($C_9H_{11}N_3O$) C,H,N.

Ethyl 4-Acetyl-2-propylimidazole-5-carboxylate (18). A solution of **16** (4.00 g, 23.2 mmol) in 6 N HCl (60 mL) was refluxed for 8 h. After evaporation of the solvent in vacuo followed by removal of a trace of H_2O by codistillation with EtOH, the residual solid **17** was dissolved in EtOH (60 mL). To the solution was bubbled HCl gas at room temperature for 20 min. After standing at room temperature for 16 h, the solution was concentrated in vacuo. The residue was dissolved in EtOAc and aqueous $NaHCO_3$ and neutralized with powdered $NaHCO_3$. The organic phase was separated, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexane, 1:1) to give crystalline **18**: yield 3.07 g (59%); mp 80.5−82 °C (IPE−hexane); NMR ($CDCl_3$) 0.98 (3H, t, J = 7.5 Hz), 1.43 (3H, t, J = 7 Hz), 1.79 (2H, sx, J = 7.5 Hz), 2.76 (3H, s), 2.77 (2H, t, J = 7.5 Hz), 4.45 (2H, q, J = 7 Hz), 10.44 (1H, br s); IR (KBr) 3426, 1725, 1665 cm^{-1}. Anal. ($C_{11}H_{16}N_2O_3$) C,H,N.

Ethyl 4-(1-Hydroxy-1-methylpropyl)-2-propylimidazole-5-carboxylate (11bc). To a solution of **18** (460 mg, 2.05 mmol) in THF (5 mL) was added a solution of 2 M EtMgCl in THF (2.25 mL, 4.5 mmol) at −45 to −40 °C under N_2. After stirring at −40 °C for 2.5 h, EtOAc and saturated aqueous NH_4Cl were added, and then the mixture was stirred for 0.5 h. The organic phase was separated, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (MeOH/CH_2Cl_2, 1:30) to give **11bc** as a syrup: yield 357 mg (69%); NMR ($CDCl_3$) 0.86 (3H, t, J = 7.5 Hz), 0.92 (3H, t, J = 7.5 Hz), 1.28 (3H, t, J = 7.5 Hz), 1.59 (3H, s), 1.72 (2H, sx, J = 7.5 Hz), 1.77−1.90 (1H, m), 1.90−2.05 (1H, m), 2.66 (2H, t, J = 7.5 Hz), 4.31 (2H, q, J = 7.5 Hz), 6.06 (1H, br s); IR (liquid film) 3196, 1711 (sh), 1676 cm^{-1}. Anal. ($C_{13}H_{22}N_2O_3$) H,N; C: calcd, 61.39; found, 60.88.

Ethyl 4-(1-Hydroxyethyl)-2-propylimidazole-5-carboxylate (19). To a solution of **18** (1.50 g, 6.69 mmol) in EtOH (15 mL) was added $NaBH_4$ (125 mg, 3.30 mmol), and the mixture was stirred at room temperature for 0.5 h. After adding acetone (2 mL), followed by stirring for 10 min, the reaction solution was concentrated in vacuo. The residue was purified by flash column chromatography (MeOH/CH_2Cl_2, 1:10) to give crystalline **19**: yield 1.32 g (87%); mp 149−150.5 °C (EtOAc−IPE); NMR ($CDCl_3$) 0.97 (3H, t, J = 7.5 Hz), 1.37 (3H, t, J = 7.5 Hz), 1.53 (3H, d, J = 6.5 Hz), 1.75 (2H, sx, J = 7.5 Hz), 2.69 (2H, t, J = 7.5 Hz), 4.36 (2H, q, J = 7.5 Hz), 5.23 (1H, q, J = 6.5 Hz); IR (KBr) 3101, 1706 cm^{-1}. Anal. ($C_{11}H_{18}N_2O_3$) C,H,N.

Diethyl 1-[[2′-(*tert*-Butoxycarbonyl)biphenyl-4-yl]-methyl]-2-propylimidazole-4,5-dicarboxylate (21a). After adding $KOBu^t$ (561 mg, 5 mmol) to a solution of **10b** (1.27 g, 5 mmol) in DMA (13 mL) under ice cooling, followed by stirring for 10 min, a solution of *tert*-butyl 4′-(bromomethyl)biphenyl-2-carboxylate (**20a**) (2.08 g, 6 mmol) in DMA (20 mL) was added, and the mixture was stirred at room temperature for 1 h. EtOAc and H_2O were added. The organic phase was separated, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexane, 1:2) to give **21a**: yield 2.61 g (quantitative); mp 65−67 °C (IPE−hexane); NMR ($CDCl_3$) 0.96 (3H, t, J = 8 Hz), 1.26 (9H, s), 1.27 (3H, t, J = 7.5 Hz), 1.39 (3H, t, J = 7.5 Hz), 1.76 (2H, sx, J = 8 Hz), 2.67 (2H, t, J = 8 Hz), 4.27 (2H, q, J = 7.5 Hz), 4.39 (2H, q, J = 7.5 Hz), 5.47 (2H, s), 7.03 (2H, d, J = 8

Hz), 7.25−7.73 (3H, m), 7.42 (1H, t, J = 7.5 Hz), 7.47 (1H, t, J = 7.5 Hz), 7.77 (1H, d, J = 7.5 Hz); IR (KBr) 1709 cm^{-1}. Anal. ($C_{30}H_{36}N_2O_6$) C,H,N.

Similarly, **21b**−**g** and **22a**−**e** were prepared. **21b**: 80%; mp 88−89 °C (IPE). Anal. ($C_{29}H_{36}N_2O_5$) C,H,N. **21c**: 85%; mp 91 °C (hexane). Anal. ($C_{30}H_{38}N_2O_5$) C,H,N. **21d**: 71%; mp 94−96 °C (hexane). Anal. ($C_{31}H_{40}N_2O_5$) C,H,N. **21e**: syrup; quantitative. Anal. ($C_{30}H_{38}N_2O_4$) C,H,N. **21f**: syrup; 97%. Anal. ($C_{31}H_{40}N_2O_5$) C,H,N. **21g**: syrup; 71%. Anal. ($C_{32}H_{42}N_2O_5$) C,N; H: calcd, 7.92; found, 7.37. **22a**: 89%; mp 144−145 °C (EtOAc). Anal. ($C_{45}H_{42}N_6O_4$) C,H,N. **22b**: 81%; mp 152−153 °C dec (EtOAc). Anal. ($C_{44}H_{42}N_6O_3$) C,H,N. **22c**: 80%; mp 165−166 °C dec (IPE−hexane). Anal. ($C_{45}H_{44}N_6O_3$) C,H,N. **22d**: 88%; mp 118−121 °C dec (IPE). Anal. ($C_{46}H_{46}N_6O_3$) C,H,N. **22e**: 69%; mp 122−124 °C (IPE−hexane). Anal. ($C_{45}H_{44}N_6O_2$) C,H,N.

Ethyl 1-[[2′-(*tert*-Butoxycarbonyl)biphenyl-4-yl]methyl]-2-propylimidazole-5-carboxlate (27a) and Ethyl 1-[[2′-(*tert*-Butoxycarbonyl)biphenyl-4-yl]methyl]-2-propylimidazole-4-carboxlate (28a). By the same procedure as described in the preparation of **21a**, **15** (1.00 g, 5.49 mmol) was alkylated with **20a** (2.29 g, 6.59 mmol). The products were subjected to flash column chromatography (EtOAc/hexane, 1:1) to give the following fractions. Faster moving fraction **27a**: syrup; yield 602 mg (24%); NMR ($CDCl_3$) 0.98 (3H, t, J = 7.5 Hz), 1.22 (9H, s), 1.32 (3H, t, J = 7.5 Hz), 1.72−1.88 (2H, m), 2.66 (2H, t, J = 7.5 Hz), 4.25 (2H, q, J = 7.5 Hz), 5.63 (2H, s), 7.01 (2H, d, J = 8.5 Hz), 7.23−7.30 (3H, m), 7.34−7.51 (2H, m), 7.77 (1H, d,d, J = 1.5, 7.5 Hz), 7.78 (1H, s); IR (liquid film) 1710 cm^{-1}. Anal. ($C_{27}H_{32}N_2O_4$) C,H,N.

Slower moving fraction **28a**: syrup; yield 1.83 g (74%); NMR ($CDCl_3$) 0.98 (3H, t, J = 7.5 Hz), 1.27 (9H, s), 1.37 (3H, t, J = 7.5 Hz), 1.70−1.90 (2H, m), 2.69 (2H, t, J = 7.5 Hz), 4.36 (2H, q, J = 7.5 Hz), 5.14 (2H, s), 7.12 (2H, d, J = 8.5 Hz), 7.26−7.53 (5H, m), 7.54 (1H, s), 7.79 (1H, d,d, J = 1.5, 7.5 Hz); IR (liquid film) 1709 cm^{-1}. Anal. ($C_{27}H_{32}N_2O_4$) C,H,N.

Similarly, **27b**,**c**, **28b**,**c**, **29a**−**c**, and **30a**−**c** were prepared. **27b**: syrup; 72%. Anal. ($C_{30}H_{36}N_2O_4$) C,H,N. **28b**: gum; 18%. Anal. ($C_{30}H_{36}N_2O_4 \cdot 0.7H_2O$) C,H,N. **27c**: 87%; syrup. Anal. ($C_{29}H_{36}N_2O_5$) C,H,N. **28c**: 6%; mp 168−169 °C (IPE). Anal. ($C_{29}H_{36}N_2O_5$) C,H,N. **29a**: 22%; mp 169−171 °C dec (IPE). Anal. ($C_{42}H_{38}N_6O_2$) C,H,N. **30a**: 67%; mp 187−189 °C dec (EtOAc). Anal. ($C_{42}H_{38}N_6O_2$) C,H,N. **29b**: 63%; amorphous solid. Anal. ($C_{45}H_{42}N_6O_2$) C,H,N. **30b**: 29%; amorphous solid. Anal. ($C_{45}H_{42}N_6O_2$) C,H,N. **29c**: 81%; mp 135−137 °C (EtOAc−IPE). Anal. ($C_{44}H_{42}N_6O_3$) C,H,N. **30c**: 5%; mp 195−196.5 °C (IPE). Anal. ($C_{44}H_{42}N_6O_3 \cdot {}^1/_2H_2O$) C,H,N.

Diethyl 1-[(2′-Carboxybiphenyl-4-yl)methyl]-2-propylimidazole-4,5-dicarboxylate (23a). A solution of **21a** (2.04 g, 3.92 mmol) in 4 N HCl in dioxane (10 mL) was allowed to stand at room temperature for 16 h. The solvent was removed by evaporation in vacuo to give the HCl salt of **23a** as an amorphous powder: yield 1.96 g (quantitative). The HCl salt (0.30 g, 0.60 mmol) was dissolved in H_2O (10 mL) and EtOAc (10 mL). To the solution was added $NaHCO_3$ (0.27 g, 3.2 mmol), and then the mixture was adjusted to pH 3.0 with 1 N HCl. The organic phase was separated, dried over $MgSO_4$, and concentrated in vacuo to give **23a**: yield 0.27 g (96%); mp 166−169 °C (EtOAc−IPE); NMR (DMSO-d_6) 0.88 (3H, t, J = 7.5 Hz), 1.16 (3H, t, J = 7 Hz), 1.27 (3H, t, J = 7 Hz), 1.63 (2H, sx, J = 7.5 Hz), 2.65 (2H, t, J = 7.5 Hz), 4.19 (2H, q, J = 7 Hz), 4.24 (2H, q, J = 7 Hz), 5.46 (2H, s), 7.07 (2H, d, J = 8 Hz), 7.31 (2H, d, J = 8 Hz), 7.34 (1H, d,d, J = 1, 8 Hz), 7.45 (1H, d,t, J = 1, 8 Hz), 7.56 (1H, d,t, J = 1, 8 Hz), 7.72 (1H, d,d, J = 1, 8 Hz); IR (KBr) 3429, 2616, 2498, 1729, 1697 cm^{-1}. Anal. ($C_{26}H_{28}N_2O_6$) C,H,N.

Similarly, **23b**−**g**, **31a**−**c**, and **35** were prepared from the corresponding *tert*-butyl esters. **23b**: 96%; mp 206−207 °C. Anal. ($C_{25}H_{28}N_2O_5$) C,H,N. **23c**: 92%; mp 167−168 °C (EtOAc−IPE). Anal. ($C_{26}H_{30}N_2O_5$) C,H,N. **23d**: 99%; mp 148−150 °C (EtOAc−IPE). Anal. ($C_{27}H_{32}N_2O_5$) C,H,N. **23e**: 82%; mp 178−179 °C. Anal. ($C_{26}H_{30}N_2O_4$) C,H,N. **23f**: 78%; mp 158−160 °C (EtOAc). Anal. ($C_{27}H_{32}N_2O_5$) C,H,N. **23g**: 92%; mp 165−167 °C (EtOAc−IPE). Anal. ($C_{28}H_{34}N_2O_5$) C,H,N. **31a**: 94%; mp 200−204 °C (EtOH−Et_2O). Anal. ($C_{23}H_{24}N_2O_4$) C,H,N. **31b**: 92%; mp 181−182 °C (EtOAc). Anal. ($C_{26}H_{28}N_2O_4$) C,H,N. **31c**: obtained as HCl salt; 94%; mp 166−168 °C (EtOAc−IPE). Anal. ($C_{25}H_{29}ClN_2O_5$) C,H,N. **35**: 90%; mp 220−224 °C (EtOH). Anal. ($C_{23}H_{24}N_2O_4$) C,H,N.

Diethyl 2-Propyl-1-[(2′-1*H*-tetrazol-5-ylbiphenyl-4-yl)-methyl]imidazole-4,5-dicarboxylate (24a). A solution of **22a** (1.01 g, 1.38 mmol) in 25% aqueous AcOH (20 mL) was stirred at 80 °C for 2.5 h. To the reaction solution was added H_2O (15 mL), and the mixture was cooled in an ice bath. The precipitates were filtered off and washed with 50% aqueous AcOH. The filtrate was concentrated to give the amorphous powder **24a**, which was washed with IPE: yield 492 mg (72%); NMR ($CDCl_3$) 0.89 (3H, t, J = 7.5 Hz), 1.24 (3H, t, J = 7.5 Hz), 1.29 (3H, t, J = 7.5 Hz), 1.64 (2H, sx, J = 7.5 Hz), 2.62 (2H, t, J = 7.5 Hz), 4.25 (2H, q, J = 7.5 Hz), 4.26 (2H, q, J = 7.5 Hz), 5.40 (2H, s), 6.94 (2H, d, J = 8 Hz), 7.13 (2H, d, J = 8 Hz), 7.39 (1H, d, J = 7 Hz), 7.52 (1H, t, J = 7.5 Hz), 7.58 (1H, d,t, J = 1, 7.5 Hz), 7.93 (1H, d,d, J = 1, 7.5 Hz); IR (KBr) 3428, 1717 cm^{-1}. Anal. ($C_{26}H_{28}N_6O_4$) C,H; N: calcd, 17.20; found, 16.78.

Similarly, **24b**−**e**, **32a**−**c**, and **36** were prepared from the corresponding trityl derivatives. **24b**: 95%; mp 170−172 °C dec (EtOAc). Anal. ($C_{25}H_{28}N_6O_3$) C,H,N. **24c**: 92%; mp 162−164 °C (EtOAc). Anal. ($C_{26}H_{30}N_6O_3$) C,H,N. **24d**: 77%; mp 140−142 °C (EtOAc−IPE). Anal. ($C_{27}H_{32}N_6O_3$) C,H,N. **24e**: 93%; 119−122 °C (EtOAc). Anal. ($C_{26}H_{30}N_6O_2$) C,H,N. **32a**: 84%; mp 173−175 °C (EtOAc). Anal. ($C_{23}H_{24}N_6O_2$) C,H,N. **32b**: 94%; mp 180−181.5 °C (EtOAc). Anal. ($C_{26}H_{28}N_6O_2$) C,H,N. **32c**: 92%; mp 151−153 °C (EtOAc−Et_2O). Anal. ($C_{25}H_{28}N_6O_3$) C,H,N. **36**: 86%; mp 120−123 °C (EtOAc). Anal. ($C_{23}H_{24}N_6O_2$) C,H,N.

1-[(2′-Carboxybiphenyl-4-yl)methyl]-2-propylimidazole-4,5-dicarboxylic Acid (25a). After stirring a suspension of **23a** (1.50 g, 2.72 mmol) and $LiOH \cdot H_2O$ (684 mg, 16.3 mmol) in dioxane (15 mL) and H_2O (15 mL) at room temperature for 5 h, dioxane was removed by distillation in vacuo. To the residual solution was added 1 N HCl (16.3 mL) to give precipitates which were collected by filtration: yield 1.11 g (quantitative); mp 201−202 °C (EtOH−EtOAc); NMR (DMSO-d_6) 0.81 (3H, t, J = 7.5 Hz), 1.48 (2H, sx, J = 7.5 Hz), 2.90 (2H, t, J = 7.5 Hz), 6.00 (2H, s), 7.20 (2H, d, J = 8 Hz), 7.29−7.36 (3H, m), 7.45 (1H, t, J = 8 Hz), 7.57 (1H, t, J = 7 Hz), 7.72 (1H, d, J = 8.5 Hz); IR (KBr) 2641, 2566, 1703, 1675 cm^{-1}. Anal. ($C_{22}H_{20}N_2O_6 \cdot {}^1/_4H_2O$) C,H,N.

Similarly, **25b**−**g**, **26a**−**e**, **33a**−**c**, **34a**−**c**, **37**, and **38** were prepared from the corresponding ethyl esters. **25b**: 88%; mp 195 °C. Anal. ($C_{23}H_{24}N_2O_5$) C,H,N. **25c**: 91%; mp 180−182 °C (EtOH). Anal. ($C_{24}H_{26}N_2O_5 \cdot {}^1/_2H_2O$) C,H,N. **25d**: 81%; mp 190−192 °C dec (EtOH). Anal. ($C_{25}H_{28}N_2O_5$) C,H,N. **25e**: quantitative; mp 222−224 °C. Anal. ($C_{24}H_{26}N_2O_4$) C,H,N. **25f**: 77%; mp 181−182 °C (MeOH). Anal. ($C_{25}H_{28}N_2O_5$) C,H,N. **25g**: 95%; mp 155−158 °C (EtOH−EtOAc). Anal. ($C_{26}H_{30}N_2O_5 \cdot H_2O$) C,H,N. **26a**: 76%; mp 229.5−232 °C (MeOH). Anal. ($C_{22}H_{20}N_6O_4$) C,H,N. **26b**: 96%; mp 184−187 °C (soften), 188−189 °C (melt). Anal. ($C_{23}H_{24}N_6O_3 \cdot H_2O$) C,H,N. **26c**: 94%; mp 199−201 °C (EtOH). Anal. ($C_{24}H_{26}N_6O_3$) C,H,N. **26d**: 56%; mp 178−181 °C (EtOH). Anal. ($C_{25}H_{28}N_6O_3 \cdot {}^1/_2C_2H_5OH$) C,H,N. **26e**: 89%; mp 167 °C (soften). Anal. ($C_{24}H_{26}N_6O_2 \cdot {}^1/_4H_2O$) C,H,N. **33a**: 72%; mp 226−228 °C dec (EtOH). Anal. ($C_{21}H_{20}N_2O_4$) C,H,N. **33b**: 94%; mp 206−207 °C. Anal. ($C_{24}H_{24}N_2O_4$) C,H,N. **33c**: 85%; mp 165−169 °C (MeOH−Et_2O). Anal. ($C_{23}H_{24}N_2O_5 \cdot {}^1/_2H_2O$) C,H,N. **34a**: 87%; mp 232−233 °C dec. Anal. ($C_{21}H_{20}N_6O_2$) C,H,N. **34b**: 85%; mp 179−182 °C (soften), 184 °C (melt). Anal. ($C_{24}H_{24}N_6O_2 \cdot {}^1/_3H_2O$) C,H,N. **34c**: 77%; mp 229−232 °C (MeOH). Anal. ($C_{23}H_{24}N_6O_3$) C,H,N. **37**: 76%; mp 173−175 °C dec (EtOH−EtOAc). Anal. ($C_{21}H_{20}N_2O_4 \cdot {}^1/_2C_2H_5OH$) C,H,N. **38**: 62%; mp 208−210 °C dec. Anal. ($C_{21}H_{20}N_6O_2 \cdot {}^1/_2C_2H_5OH$) C,H,N.

Ethyl 1-[[2′-(*tert*-Butoxycarbonyl)biphenyl-4-yl]methyl]-4-(hydroxymethyl)-2-propylimidazole-5-carboxylate (39). To a solution of **21a** (1.94 g, 3.73 mmol) in THF (15 mL) was added a 1.5 M solution of diisobutylaluminum hydride in toluene (5.22 mL, 7.83 mmol) at −30 to −20 °C under N_2 atmosphere. The mixture was allowed to stand at −5 °C for 20 h. After adding aqueous NH_4Cl and EtOAc, the mixture was stirred at room temperature for 2 h. The precipitates were

filtered off through a Celite pad. The organic phase was separated, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (MeOH/CH_2Cl_2, 1:15) to give crystalline **39** which was washed with IPE: yield 1.47 g (82%); mp 113 °C (EtOAc−IPE); NMR ($CDCl_3$) 0.99 (3H, t, J = 7.5 Hz), 1.24 (9H, s), 1.31 (3H, t, J = 7 Hz), 1.80 (2H, sx, J = 7.5 Hz), 2.69 (2H, t, J = 7.5 Hz), 3.63 (1H, br s), 4.27 (2H, q, J = 7 Hz), 4.88 (2H, s), 5.61 (2H, s), 7.00 (2H, d, J = 8 Hz), 7.27 (2H, d, J = 8 Hz), 7.27 (1H, d,d, J = 1, 7 Hz), 7.39 (1H, d,t, J = 1, 7.5 Hz), 7.48 (1H, d,t, J = 1, 7.5 Hz), 7.77 (1H, d,d, J = 1, 7.5 Hz); IR (KBr) 3234, 1706, 1698 cm^{-1}. Anal. ($C_{28}H_{34}N_2O_5$) C,H,N.

Similarly, **40** and **51** were prepared from **22a** and **45. 40**: 69%; mp 134−136 °C (EtOAc). Anal. ($C_{43}H_{40}N_6O_3$) C,H,N. **51**: 77%; mp 176−177 °C. Anal. ($C_{26}H_{32}N_2O_4$) H,N; C: calcd, 71.53; found, 71.12.

Ethyl 1-[(2′-Carboxybiphenyl-4-yl)methyl]-4-(hydroxymethyl)-2-propylimidazole-5-carboxylate (41). By the same procedure as described in the preparation of **23a**, **39** (0.84 g, 1.76 mmol) was treated with 4 N HCl in dioxane (10 mL) to give **41** (0.69 g, 93%): mp 224−226 °C (EtOH); NMR (DMSO-d_6) 0.89 (3H, t, J = 7.5 Hz), 1.22 (3H, t, J = 7.5 Hz), 1.64 (2H, sx, J = 7.5 Hz), 2.62 (2H, t, J = 7.5 Hz), 4.19 (2H, q, J = 7.5 Hz), 4.60 (2H, d, J = 5 Hz), 4.75 (1H, t, J = 5 Hz), 5.58 (2H, s), 7.01 (2H, d, J = 8.5 Hz), 7.29 (2H, d, J = 8.5 Hz), 7.34 (1H, d, J = 7.5 Hz), 7.44 (1H, t, J = 7.5 Hz), 7.55 (1H, t, J = 7.5 Hz), 7.71 (1H, d, J = 7.5 Hz), 12.74 (1H, s); IR (KBr) 3410, 2452, 1701 cm^{-1}. Anal. ($C_{24}H_{26}N_2O_5$) C,H,N.

Similarly, **47** and **52** were prepared. **47**: quantitative; mp 215 °C (soften), 230 °C (melt) (EtOH). Anal. ($C_{24}H_{26}N_2O_5$) C,H,N. **52**: obtained as HCl salt; quantitative; mp 200 °C (color), 217 °C (melt). Anal. ($C_{22}H_{24}N_2O_4 \cdot HCl \cdot {}^1/_3H_2O$) C,H, Cl,N.

Ethyl 4-(Hydroxymethyl)-2-propyl-1-[(2′-1*H*-tetrazol-5-ylbiphenyl-4-yl)methyl]imidazole-5-carboxylate (42). By the same procedure as described in the preparation of **24a**, **40** (700 mg, 1.02 mmol) was treated with 25% aqueous AcOH to give crystalline **42** (293 mg, 64%): mp 160−162 °C (EtOAc−IPE); NMR (DMSO-d_6) 0.87 (3H, t, J = 7.5 Hz), 1.20 (3H, t, J = 7 Hz), 1.59 (2H, sx, J = 7.5 Hz), 2.57 (2H, t, J = 7.5 Hz), 4.17 (2H, q, J = 7 Hz), 4.58 (2H, s), 4.74 (1H, br s), 5.53 (2H, s), 6.92 (2H, d, J = 8 Hz), 7.05 (2H, d, J = 8 Hz), 7.51−7.58 (2H, m), 7.63−7.69 (2H, m); IR (KBr) 1710 cm^{-1}. Anal. ($C_{24}H_{26}N_6O_3$) C,H,N.

Similarly, **48** was prepared. **48**: quantitative; mp 128 °C (soften). Anal. ($C_{24}H_{26}N_6O_3$) C,H,N.

1-[(2′-Carboxybiphenyl-4-yl)methyl]-4-(hydroxymethyl)-2-propylimidazole-5-carboxylic Acid (43). By the same procedure as described in the preparation of **25a**, **41** (584 mg, 1.38 mmol) was hydrolyzed with $LiOH \cdot H_2O$ (232 mg, 5.54 mmol) to give **43** (520 mg, 96%): mp 216−218 °C dec (MeOH); NMR (DMSO-d_6) 0.88 (3H, t, J = 7.5 Hz), 1.62 (2H, sx, J = 7.5 Hz), 2.57 (2H, t, J = 7.5 Hz), 4.62 (2H, s), 5.64 (2H, s), 7.04 (2H, d, J = 8 Hz), 7.29 (2H, d, J = 8 Hz), 7.35 (1H, d, J = 7.5 Hz), 7.44 (1H, t, J = 7.5 Hz), 7.55 (1H, d,t, J = 1, 7.5 Hz), 7.70 (1H, d, J = 7.5 Hz); IR (KBr) 2610, 2499, 1717, 1634, 1599 cm^{-1}. Anal. ($C_{22}H_{22}N_2O_5$) C,H,N.

Similarly, **44**, **49**, and **50** were obtained by hydrolysis of **42**, **47**, and **48**, respectively. **44**: 95%; mp 223−224 °C dec (EtOH). Anal. ($C_{22}H_{22}N_6O_3$) C,H,N. **49**: quantitative; mp 210−212 °C dec (EtOH). Anal. ($C_{22}H_{22}N_2O_5 \cdot {}^1/_2C_2H_5OH$) C,H,N. **50**: quantitative; mp >270 °C. Anal. ($C_{22}H_{22}N_6O_3$) C,H,N.

Ethyl 1-[[2′-(*tert*-Butoxycarbonyl)biphenyl-4-yl]methyl]-5-(hydroxymethyl)-2-propylimidazole-4-carboxylate (45). A mixture of **21a** (5.87 g, 11.3 mmol) and $LiAlH(OBu^t)_3$ (5.73 g, 22.6 mmol) in THF (59 mL) was stirred at room temperature for 5 days. During the above reaction period, two portions of additional $LiAl(OBu^t)_3$ (1.43 g × 2, 11.3 mmol) were added to the reaction mixture, respectively, on the second and third days. MeOH (10 mL) was added under ice cooling, and the mixture was stirred for 10 min. The solvent was removed by distillation in vacuo, and the residue was dissolved in EtOAc and H_2O. After removal of the precipitates by filtration through a Celite pad, the organic phase was separated, dried over Na_2SO_4, and concentrated in vacuo. The residue was subjected to flash column chromatography (EtOAc/CH_2Cl_2, 1:1) to give the following fractions. Faster moving fraction **45**: yield 3.55 g (66%); mp 123−124.5 °C (IPE); NMR ($CDCl_3$) 0.96 (3H, t, J = 8 Hz), 1.26 (9H, s), 1.43 (3H, t, J = 7 Hz), 1.73 (2H, sx, J = 8 Hz), 2.67 (2H, t, J = 8 Hz), 3.73 (1H, t, J = 6.5 Hz), 4.44 (2H, q, J = 7 Hz), 4.72 (2H, d, J = 6.5 Hz), 5.26 (2H, s), 6.97 (2H, d, J = 8.5 Hz), 7.26−7.31 (3H, m), 7.42 (1H, t, J = 7 Hz), 7.49 (1H, t, J = 7 Hz), 7.78 (1H, d, J = 6.5 Hz); IR (KBr) 3310, 1715 cm^{-1}. Anal. ($C_{28}H_{34}N_2O_5$) C,H,N.

Slower moving fraction **39** was obtained as a mixture of **39** and **45**: yield 0.45 g (10%).

Similarly, **22a** was reduced with $LiAlH(OBu^t)_3$ to give **46** and **40. 46**: 79%; mp 162−164 °C (color), 174−177 °C (melt). Anal. ($C_{43}H_{40}N_6O_3$) C,H,N. **40**: 8.3% (as a mixture of **22a** and **40**).

Ethyl 1-[[2′-(*tert*-Butoxycarbonyl)biphenyl-4-yl]methyl]-4-methyl-2-propylimidazole-5-carboxylate (53a). To a solution of **39** (479 mg, 1.00 mmol) and Et_3N (0.35 mL, 2.52 mmol) in CH_2Cl_2 (6 mL) was added $ClCOCO_2Et$ (165 mg, 1.21 mmol) under ice cooling and N_2. After stirring at room temperature for 0.5 h, the reaction mixture was diluted with EtOAc and washed with aqueous $NaHCO_3$. The organic phase was dried over $MgSO_4$ and concentrated in vacuo to give the 4-ethoxyglyoxylyl ester of **39** as a syrup (590 mg, quantitative): NMR ($CDCl_3$) 0.98 (3H, t, J = 7.5 Hz), 1.23 (9H, s), 1.29 (3H, t, J = 7.5 Hz), 1.36 (3H, t, J = 7 Hz), 1.78 (2H, sx, J = 7.5 Hz), 2.67 (2H, t, J = 7.5 Hz), 4.27 (2H, q, J = 7 Hz), 4.35 (2H, q, J = 7.5 Hz), 5.53 (2H, s), 5.62 (2H, s), 7.02 (2H, d, J = 8 Hz), 7.25−7.29 (3H, m), 7.39 (1H, t, J = 7.5 Hz), 7.48 (1H, t, J = 7.5 Hz), 7.77 (1H, d, J = 7.5 Hz).

To a solution of the above ester (544 mg, 0.92 mmol) in toluene (10 mL) were added Bu_3SnH (600 mg, 2.06 mmol) and 2,2′-azobis(isobutyronitrile) (20 mg, 0.12 mmol), and the mixture was refluxed for 1.5 h under N_2. The reaction solution was concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexane, 1:1) to give **53a** as a syrup (282 mg, 61%): NMR ($CDCl_3$) 0.97 (3H, t, J = 7.5 Hz), 1.22 (9H, s), 1.31 (3H, t, J = 7.5 Hz), 1.76 (2H, sx, J = 7.5 Hz), 2.52 (3H, s), 2.63 (2H, t, J = 7.5 Hz), 4.24 (2H, q, J = 7.5 Hz), 5.58 (2H, s), 6.99 (2H, d, J = 8 Hz), 7.25 (2H, d, J = 8 Hz), 7.28 (1H, d, J = 8 Hz), 7.38 (1H, t, J = 8 Hz), 7.47 (1H, t, J = 8 Hz), 7.76 (1H, d, J = 8 Hz); IR (liquid film) 1703 cm^{-1}. Anal. ($C_{28}H_{34}N_2O_4$) C,H,N.

Similarly, **53b** and **54a**,**b** were prepared from **27c**, **40**, and **29c**, respectively. **53b**: 45%; syrup. Anal. ($C_{29}H_{36}N_2O_4$) C,H,N. **54a**: 87%; mp 178.5−179 °C dec (MeCN−EtOAc). Anal. ($C_{43}H_{40}N_6O_2$) C,H,N. **54b**: 52%; mp 139−141 °C (IPE−hexane). Anal. ($C_{44}H_{42}N_6O_2$) C,H,N.

Ethyl 1-[(2′-Carboxybiphenyl-4-yl)methyl]-4-methyl-2-propylimidazole-5-carboxylate (55a). By the same procedure as described in the preparation of **23a**, **53a** (1.30 g, 2.80 mmol) was treated with 4 N HCl in dioxane to give **55a** (1.02 g, 89%): mp 186−188 °C (EtOH−EtOAc); NMR (DMSO-d_6) 0.87 (3H, t, J = 7.5 Hz), 1.21 (3H, t, J = 7 Hz), 1.62 (2H, sx, J = 7.5 Hz), 2.39 (3H, s), 2.58 (2H, t, J = 7.5 Hz), 4.18 (2H, q, J = 7 Hz), 5.56 (2H, s), 6.99 (2H, d, J = 8 Hz), 7.28 (2H, d, J = 8 Hz), 7.34 (1H, d,d, J = 1, 7.5 Hz), 7.44 (1H, d,t, J = 1, 7.5 Hz), 7.55 (1H, d,t, J = 1, 7.5 Hz), 7.71 (1H, d,d, J = 1, 7.5 Hz), 12.75 (1H, br s); IR (KBr) 2438, 1704 cm^{-1}. Anal. ($C_{24}H_{26}N_2O_4$) C,H,N.

Similarly, **55b** was prepared. **55b**: 89%; mp 181−182 °C (EtOAc). Anal. ($C_{25}H_{28}N_2O_4$) C,H,N.

Ethyl 4-Methyl-2-propyl-1-[(2′-1*H*-tetrazol-5-ylbiphenyl-4-yl)methyl]imidazole-5-carboxylate (56a). By the same procedure as described in the preparation of **24a**, **54a** (1.15 g, 1.71 mmol) was treated with 25% aqueous AcOH to give **56a** (710 mg, 96%): mp 179.5−180.5 °C (EtOAc); NMR ($CDCl_3$) 0.84 (3H, t, J = 7.5 Hz), 1.18 (3H, t, J = 7.5 Hz), 1.54 (2H, sx, J = 7.5 Hz), 1.93 (3H, s), 2.18 (2H, t, J = 7.5 Hz), 4.14 (2H, q, J = 7.5 Hz), 5.40 (2H, s), 6.70 (2H, d, J = 8 Hz), 7.03 (2H, d, J = 8 Hz), 7.44 (1H, d,d, J = 1.5, 7.5 Hz), 7.52−7.62 (2H, m), 7.87 (1H, d,d, J = 1.5, 7.5 Hz); IR (KBr) 1705 cm^{-1}. Anal. ($C_{24}H_{26}N_6O_2$) C,H,N.

Similarly, **56b** was prepared. **56b**: 95%; mp 182−183 °C (EtOAc−Et_2O). Anal. ($C_{25}H_{28}N_6O_2$) C,H,N.

1-[(2′-Carboxybiphenyl-4-yl)methyl]-4-methyl-2-propylimidazole-5-carboxylic Acid (57a). By a procedure

similar to the preparation of **25a**, **55a** (570 mg, 1.40 mmol) was hydrolyzed with NaOH (304 mg, 7.6 mmol) at 70 °C for 5 h to give **57a** (498 mg, 94%): mp 197−199 °C; NMR (DMSO-d_6) 0.87 (3H, t, J = 7.5 Hz), 1.61 (2H, sx, J = 7.5 Hz), 2.41 (3H, s), 2.61 (2H, t, J = 7.5 Hz), 5.63 (2H, s), 7.03 (2H, d, J = 8 Hz), 7.29 (2H, d, J = 8 Hz), 7.35 (1H, d,d, J = 1, 7.5 Hz), 7.44 (1H, d,t, J = 1, 7.5 Hz), 7.55 (1H, d,t, J = 1, 7.5 Hz), 7.71 (1H, d,d, J = 1, 7.5 Hz), 12.85 (2H, br s); IR (KBr) 1713, 1638 (wk) cm^{-1}. Anal. ($C_{22}H_{22}N_2O_4 \cdot {}^1/_2H_2O$) C,H,N.

Similarly, **57b** and **58a**,**b** were prepared. **57b**: 94%; mp 220−222 °C dec. Anal. ($C_{23}H_{24}N_2O_4$) C,H,N. **58a**: 97%; mp 202.5−204 °C dec. Anal. ($C_{22}H_{22}N_6O_2$) C,H,N. **58b**: 98%; mp 198−199 °C dec (EtOH−Et_2O). Anal. ($C_{23}H_{24}N_6O_2 \cdot {}^1/_3H_2O$) C,H,N.

1-[[2′-(*tert*-Butoxycarbonyl)biphenyl-4-yl]methyl]-4-(1-hydroxy-1-methylethyl)-2-propylimidazole-5-carboxylic Acid (59). After stirring a mixture of **21c** (7.5 g, 14.8 mmol) and LiOH·H_2O (3.10 g, 73.8 mmol) in dioxane (39 mL) and H_2O (65 mL) at room temperature for 20 h, dioxane was removed by distillation in vacuo. To the concentrate was dropwise added 1 N HCl (73.6 mL) under ice cooling to give **59** as precipitates, which were collected by filtration and washed with H_2O and IPE: yield 7.09 g (quantitative); mp 148−150 °C (EtOAc−IPE); NMR ($CDCl_3$) 0.89 (3H, t, J = 7.5 Hz), 1.24 (9H, s), 1.62 (2H, sx, J = 7.5 Hz), 1.69 (6H, s), 2.96 (2H, t, J = 7.5 Hz), 5.88 (2H, s), 7.09 (2H, d, J = 8 Hz), 7.21−7.26 (3H, m), 7.38 (1H, d,t, J = 1, 7.5 Hz), 7.45 (1H, d,t, J = 1, 7.5 Hz), 7.76 (1H, d,d, J = 1, 7.5 Hz); IR (KBr) 2498, 1708, 1625, 1590 cm^{-1}. Anal. ($C_{28}H_{34}N_2O_5$) C,H,N.

(5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 1-[[2′-(*tert*-Butoxycarbonyl)biphenyl-4-yl]methyl]-4-(1-hydroxy-1-methylethyl)-2-propylimidazole-5-carboxylate (61a). To a mixture of **59** (1.00 g, 2.09 mmol) and K_2CO_3 (0.60 g, 4.34 mmol) in DMA (10 mL) was added a solution of 4-(chloromethyl)-5-methyl-2-oxo-1,3-dioxole (74% purity, 621 mg, 3.10 mmol) in DMA (6 mL) dropwise. The mixture was stirred at room temperature for 1 h and then at 50 °C for 2 h. EtOAc and H_2O were added. The organic phase was separated, washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give crystalline **61a** (964 mg, 78%) which was washed with EtOAc−hexane (1:1). The mother solution was concentrated in vacuo, and the residue was subjected to flash column chromatography (EtOAc/hexane, 1:1) to give further **61a** (140 mg, 11%): 152−155 °C (EtOAc−IPE); 0.98 (3H, t, J = 7.5 Hz), 1.27 (9H, s), 1.63 (6H, s), 1.76 (2H, sx, J = 7.5 Hz), 2.07 (3H, s), 2.68 (2H, t, J = 7.5 Hz), 4.89 (2H, s), 5.46 (2H, s), 5.57 (1H, s), 6.90 (2H, d, J = 8 Hz), 7.28 (2H, d, J = 8 Hz), 7.32 (1H, d, J = 7.5 Hz), 7.39 (1H, t, J = 7.5 Hz), 7.50 (1H, t, J = 7.5 Hz), 7.76 (1H, d, J = 7.5 Hz); IR (KBr) 3435, 1828, 1742 (sh), 1705, 1673 cm^{-1}. Anal. ($C_{33}H_{38}N_2O_8$) C,H,N.

Similarly, **61b**−**d** and **65** were prepared. **61b**: 98%; mp 104−106 °C (IPE). Anal. ($C_{34}H_{44}N_2O_7$) C,H,N. **61c**: 85%; mp 89−92 °C (IPE−hexane). Anal. ($C_{33}H_{42}N_2O_8$) C,H,N. **61d**: 95%; mp 143−146 °C (EtOAc−IPE). Anal. ($C_{36}H_{38}N_2O_7$) C,H,N. **65**: 96%; mp 97−98 °C (IPE). Anal. ($C_{35}H_{40}N_2O_5$) C,H,N.

(5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 1-[(2′-Carboxybiphenyl-4-yl)methyl]-4-(1-hydroxy-1-methylethyl)-2-propylimidazole-5-carboxylate (63a). By the same procedure as described in the preparation of **23a**, **61a** (0.87 g, 1.47 mmol) was treated with 4 N HCl in dioxane to give **63a** (0.79 g, quantitative): mp 171−172 °C (EtOAc−IPE); NMR (DMSO-d_6) 0.91 (3H, t, J = 7.5 Hz), 1.49 (6H, s), 1.64 (2H, sx, J = 7.5 Hz), 2.08 (3H, s), 2.65 (2H, t, J = 7.5 Hz), 5.07 (2H, s), 5.23 (1H, s), 5.47 (2H, s), 6.96 (2H, d, J = 8 Hz), 7.27 (2H, d, J = 8 Hz), 7.36 (1H, d, J = 7.5 Hz), 7.44 (1H, t, J = 7.5 Hz), 7.56 (1H, t, J = 7.5 Hz), 7.71 (1H, d, J = 7.5 Hz), 12.73 (1H, br s); IR (KBr) 3431, 2613, 2501, 1825, 1735 (sh), 1711 (sh), 1687 cm^{-1}. Anal. ($C_{29}H_{30}N_2O_8$) C,H,N.

Similarly, **63b**−**d** and **66** were prepared. **63b**: quantitative; mp 156 °C (EtOAc−IPE). Anal. ($C_{30}H_{36}N_2O_7$) C,H,N. **63c**: 95%; mp 147−149 °C (EtOAc−IPE). Anal. ($C_{29}H_{34}N_2O_8$) C,H,N. **63d**: quantitative; mp 187−188 °C (EtOAc−IPE). Anal. ($C_{32}H_{30}N_2O_7$) C,H,N. **66**: quantitative; mp 147−149 °C (EtOAc−IPE). Anal. ($C_{31}H_{32}N_2O_5$) C,H,N.

(5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 4-(1-Hydroxy-1-methylethyl)-2-propyl-1-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole-5-carboxylate (62a). After stirring a mixture of **22c** (30.0 g, 41.8 mmol) and LiOH·H_2O (2.65 g, 63.1 mmol) in dioxane (344 mL) and H_2O (158 mL) at 5−10 °C for 20 h, the reaction solution was concentrated in vacuo to a volume of about 100 mL. EtOAc (0.6 L) and NaCl were added. The organic phase was separated, dried over Na_2SO_4, and concentrated in vacuo. The residual gum, the lithium salt of **60**, was dried at 50 °C in vacuo and then dissolved in DMA (160 mL). To the solution were added powdered K_2CO_3 (6.08 g, 44 mmol) and a solution of 4-(chloromethyl)-5-methyl-2-oxo-1,3-dioxole (74% purity, 11.2 g, 55.8 mmol) in DMA (16 mL) dropwise, successively. The mixture was stirred at room temperature for 1 h and at 50 °C for 3 h. EtOAc and H_2O were added. The organic phase was separated, dried over $MgSO_4$, and concentrated in vacuo. The residual crystals were washed with EtOAc−IPE to give **62a** (29.3 g, 88%): mp 102−104 °C (EtOAc−IPE); NMR ($CDCl_3$) 0.89 (3H, t, J = 7.5 Hz), 1.62 (6H, s), 1.60−1.75 (2H, m), 1.97 (3H, s), 2.54 (2H, t, J = 8 Hz), 4.70 (2H, s), 5.30 (2H, s), 5.61 (1H, s), 6.68 (2H, d, J = 7.5 Hz), 6.90−7.52 (20H, m), 7.87 (1H, d, J = 7.5 Hz); IR (KBr) 3420, 1825, 1738 (wk), 1707, 1678 cm^{-1}. Anal. ($C_{48}H_{44}N_6O_6$) C,H,N.

Similarly, **62b** was prepared. **62b**: 96%; amorphous powder. Anal. ($C_{49}H_{50}N_6O_5$) C,H,N.

(5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 4-(1-Hydroxy-1-methylethyl)-2-propyl-1-[(2′-1*H*-tetrazol-5-ylbiphenyl-4-yl)methyl]imidazole-5-carboxylate (64a) (CS-866). By the same procedure as described in the preparation of **24a**, **62a** (29.3 g, 36.6 mmol) was treated with 25% aqueous AcOH to afford **64a** (16.6 g, 81%): mp 180−182 °C dec (EtOH); NMR (DMSO-d_6) 0.88 (3H, t, J = 7.5 Hz), 1.47 (6H, s), 1.58 (2H, sx, J = 7.5 Hz), 2.08 (3H, s), 2.60 (2H, t, J = 7.5 Hz), 5.05 (2H, s), 5.20 (1H, s), 5.42 (2H, s), 6.86 (2H, d, J = 8.5 Hz), 7.04 (2H, d, J = 8.5 Hz), 7.52−7.70 (4H, m); IR (KBr) 3291, 1833, 1740 (sh), 1708 cm^{-1}. Anal. ($C_{29}H_{30}N_6O_6$) C,H,N.

Similarly, **64b** was prepared. **64b**: 89%; amorphous powder. Anal. ($C_{30}H_{36}N_6O_5$) C,H,N.

Benzyl 4-(1-Hydroxy-1-methylethyl)-1-[[2′-[[(pivaloyloxy)methoxy]carbonyl]biphenyl-4-yl]methyl]-2-propylimidazole-5-carboxylate (67). By the same procedure as the preparation of **61a**, **66** (1.07 g, 2.08 mmol) was esterified with $ClCH_2OCOBu^t$ (0.47 g, 3.12 mmol) to give **67** (1.30 g, quantitative) as a syrup: NMR ($CDCl_3$) 0.96 (3H, t, J = 7.5 Hz), 1.19 (9H, s), 1.62 (6H, s), 1.72 (2H, sx, J = 7.5 Hz), 2.65 (2H, t, J = 7.5 Hz), 5.17 (2H, s), 5.40 (2H, s), 5.78 (2H, s), 5.79 (1H, s), 6.77 (2H, d, J = 8 Hz), 7.19−7.24 (3H, m), 7.28 (2H, d, J = 8 Hz), 7.25−7.33 (2H, m), 7.33 (1H, d, J = 7.5 Hz), 7.43 (1H, t, J = 7.5 Hz), 7.58 (1H, t, J = 7.5 Hz), 7.89 (1H, d, J = 7.5 Hz); IR (liquid film) 3437, 1754, 1705, 1603 cm^{-1}. Anal. ($C_{37}H_{42}N_2O_7$) C,H,N.

4-(1-Hydroxy-1-methylethyl)-1-[[2′-[[(pivaloyloxy)-methoxy]carbonyl]biphenyl-4-yl]methyl]-2-propylimidazole-5-carboxylic Acid (68). A mixture of **67** (970 mg, 1.55 mmol) and 5% Pd−C (100 mg) in MeOH (15 mL) was stirred under a hydrogen atmosphere at room temperature for 3 h. The catalyst was removed by filtration, and the filtrate was concentrated in vacuo to give a syrup which was crystallized in EtOAc−IPE: yield 0.64 g (77%); mp 146−148 °C (EtOAc−IPE); NMR (DMSO-d_6) 0.88 (3H, t, J = 7.5 Hz), 1.12 (9H, s), 1.53 (6H, s), 1.59 (2H, sx, J = 7.5 Hz), 2.60 (2H, t, J = 7.5 Hz), 5.70 (2H, s), 5.73 (2H, s), 7.02 (2H, d, J = 8.5 Hz), 7.25 (2H, d, J = 8.5 Hz), 7.43 (1H, d,d, J = 1, 7.5 Hz), 7.50 (1H, d,t, J = 1, 7.5 Hz), 7.65 (1H, d,t, J = 1, 7.5 Hz), 7.74 (1H, d,d, J = 1, 7.5 Hz); IR (KBr) 3426, 3211, 2623, 1753, 1633, 1597 cm^{-1}. Anal. ($C_{30}H_{36}N_2O_7$) C,H,N.

AII Receptor (AT_1) Binding Assay. Membrane fractions of bovine adrenal cortex were prepared by modifications of the method of Maeda et al.[41] The freshly isolated bovine adrenal cortex was homogenized in ice-cold medium containing 10 mM sodium phosphate buffer (pH 7.4), 30 mM NaCl, 1 mM $MgCl_2$, 0.1 mM EDTA, 1 mM dithiothreitol (DTT), 1 μM (*p*-amidinophenyl)methanesulfonyl fluoride HCl (*p*-APMSF), and 0.02% NaN_3. The homogenate was layered on a 41% sucrose solution and centrifuged at 95000*g* for 60 min. The interfacial band

Table 4. Experimental Data and Final Refinement Results for **26c**, **39**, and **64a**

	26c	**39**	**64a**
molecular formula	$C_{24}H_{25}N_6O_3$	$C_{28}H_{34}N_2O_5$	$C_{29}H_{30}N_6O_6$
formula weight	446.51	478.59	558.59
space group	*P*21/*c*	*P*21/*n*	*P*21/*c*
crystal system	monoclinic	monoclinic	monoclinic
a (Å)	10.067 (3)	19.756 (2)	12.404 (2)
b (Å)	17.992 (2)	16.569 (2)	21.256 (2)
c (Å)	14.214 (5)	8.200 (1)	10.969 (1)
β (deg)	91.39 (5)	101.31 (1)	101.56 (1)
V (Å^3)	2573.6 (5)	2632.1 (8)	2833.1 (5)
Z	4	4	4
D_{calcd} (g cm^{-3})	1.15	1.21	1.31
radiation	Cu Kα	Cu Kα	Cu Kα
wave length (Å)	1.541 78	1.541 78	1.541 78
crystal size (mm)	0.3 × 0.3 × 0.3	0.3 × 0.3 × 0.2	0.4 × 0.3 × 0.3
F(000)	944	1024	1176
$2\theta_{max}$ (deg)	128	128	128
reflections measured	4311	4098	4776
reflections $F_o \geq 3\sigma F_o$	2976	2144	3543
weighting scheme, *w*	$1/[1 + [(F_o - 35)/45]^2]$	$1/[1 + [(F_o - 15/70]^2]$	1.0
final *R*	0.045	0.064	0.061
final R_w	0.043	0.063	0.059
Fourier excursions (eÅ^{-3})	0.10, −0.14	0.6, −0.16	0.20, −0.28

between the supernatant and the sucrose portion was collected. The membrane fraction was washed by centrifugation at 95000*g* for 20 min. The pellet obtained was used as the source of AII receptor.

Binding of [^{125}I]AII to membranes was performed at 22 °C for 120 min in 96-well plates. Each 200 μL incubated solution contained the following (final concentration): 20 mM Tris HCl (pH 7.4), 120 mM NaCl, 5 mM $MgCl_2$, 0.05% bovine serum albumin (BSA), 1 μM *p*-APMSF, 0.5 mM EDTA, 0.1 mM DTT, 0.1 nM [^{125}I]AII (specific activity 2200 Ci/mmol), the test compound (appropriate concentration), and membrane preparations (10 μg of protein/well). At the end of the incubation, bound complex was trapped on filters (GF/C) and washed with cold Tris buffer (pH 7.4; 3 × 250 μL). Filter disks were dried, punched out, and counted in a γ-counter. Specific binding was defined as total binding minus nonspecific binding, which was estimated in the presence of 1 μM unlabeled AII. The IC_{50} of an inhibitor was determined as the concentration that displaced the specifically bound [^{125}I]AII by 50%.

Antagonism of AII-Induced Pressor Response by Intravenous Administration. Male Wistar−Imamichi rats weighing 300−400 g were anesthetized with inactin (100 mg/kg, ip). An animal was surgically prepared with an aortic cannula inserted via the left femoral artery for measuring blood pressure and with a caval cannula inserted via the left femoral vein for injecting AII and a test compound. The aortic cannula was connected to a pressure transducer (TP-200T, Nihon Kohden), and mean blood pressure and heart rate were continuously recorded on a pen-writing recorder (WT-685G, Nihon Kohden). AII (50 ng/kg) was intravenously administered via the cannula at intervals of 10 min, and the pressor response (about 50 mmHg) was observed. After constant pressor responses to AII were obtained, a test compound was intravenously administered. Two minutes later, AII (50 ng/kg) was again injected, and the inhibitory effect of the test compound was estimated. The percent inhibitions of the pressor response to AII with progressive increases of the test compound were used to calculate the value of ID_{50}, which was determined as the dose that inhibited the AII-induced pressor response by 50%. AII and the test compound were dissolved in 0.5% BSA and DMSO, respectively.

Antagonism of AII-Induced Pressor Response by Oral Administration. Male Wistar−Imamichi rats weighing 300−400 g were anesthetized with sodium pentobarbital (50 mg/kg, ip), and two cannulae were placed by the same procedure described above. The other end of the venous cannula was led under the skin and exteriorized at the back of the neck. A rat was placed in an individual cage after surgery and fasted for 24 h. On the next day, the aortic cannula was connected to a pressure transducer (TP-200T, Nihon Kohden), and mean blood pressure and heart rate were continuously recorded on a pen-writing recorder (WT-685G, Nihon Kohden). After blood pressure and heart rate were stabilized, AII was administered at a dose of 50 ng/kg *via* the venous cannula. Intravenous administration of AII was repeated until a constant response was obtained, and then the test compound was orally administered. Intravenous administrations of AII (50 ng/kg) were repeated at appropriate intervals for 8 h. The pressor responses were recorded, and the inhibitory effect of the test compound was expressed as the percentage of the inhibition of the AII pressor response. AII and the test compound were dissolved in 0.5% BSA and 50% aqueous DMF, respectively.

X-ray Structural Analysis of 26c, 39, and 64a. Compounds **26c**, **39**, and **64a** were crystallized from EtOH, IPE, and EtOH diffusion systems, respectively. Lattice constants were determined by least-squares fit of angular settings of 20 reflections with the range 20° < 2θ < 50°. Intensity data were obtained on a Rigaku AFC-5R diffractometer, using the ω−2θ scan technique. All intensities were corrected for Lorentz and polarization effects but not for absorption. Three structures of **26c**, **39**, and **64a** were solved by the direct methods using MULTAN 78[42] and refined by the block-diagonal least-squares technique with anisotropic thermal parameters. Hydrogen atoms were located on a difference Fourier synthesis and refined isotropically. A difference Fourier map revealed two positions of the terminal methyl group of the propyl group of **39**, which were included with population parameters of 0.75 and 0.25. Atomic scattering factors were taken from the Revised and Supplementary Tables.[43] Calculations were carried out with the DIRECT-SEARCH program system.[44] The experimental data and final refinement results for **26c**, **39**, and **64a** are presented in Table 4. Full crystallographic details are available as supporting information.

Molecular Modeling. All calculations were performed on a microVAX 4200 and an IRIS workstation. Geometry optimization of **71** in the form of a carboxylate anion, a protonated imidazole ring, and a tetrazole anion was carried out using the PM3 method of the MOPAC program. The torsional angles of τ_1−τ_8 were incremented by 30°, 120°, 30°, 120°, 30°, 30°, 30°, and 30°, respectively, in the generation of initial conformations. Conformational analysis of **74** in the carboxylate anion form of the C-terminal was performed with the QUANTA/CHARMm program. Stable conformations of **74** were searched using the random perturbation of 17 rotatable bonds with the window of 120° starting from the two kinds of initial conformations. Perturbed conformations with lower energies <5000 kcal/mol were filtered and energy-minimized with the adopted-basis Newton−Raphson method with a distance dependent dielectric of *r*. Superposition of stable conformers of **71** and **74** was initially examined graphically with QUANTA. Several promising pairs were then selected and subjected to the superposition to maximize the overlap of the van der Waals

volume of hydrophobic groups, i.e., carbon atoms and hydrogen atoms attached to them while keeping the functional groups of the tetrazole ring, the carboxylate, the phenyl group, and the isopropyl group of **71** in the proximity of the corresponding functional groups of **74**. The van der Waals volume was evaluated by the number of grid points of 0.5 Å within the van der Waals sphere of atoms.

Supporting Information Available: X-ray crystallographic data for compounds **26c**, **39**, and **64a** (12 pages). Ordering information is given on any current masthead page.

References

(1) Wyvratt, M. J.; Patchett, A. A. Recent Developments in the Design of Angiotensin-Converting Enzyme Inhibitors. *Med. Res. Rev.* **1985**, *5*, 483−531.

(2) (a) Vollotton, M. B. The Renin-Angiotensin System. *Trends Pharmacol. Sci.* **1987**, *8*, 69−74. (b) Johnson, C. I. Biochemistry and Pharmacology of the Renin-angiotensin System. *Drugs* **1990**, *39* (Suppl. 1), 21−31.

(3) (a) Coulter, D. M.; Edwards, I. R. Cough Associated with Captopril and Enalapril. *Br. Med. J.* **1987**, *294*, 1521−1523. (b) McEwan, J. R.; Fuller, R. W. Angiotensin Converting Enzyme Inhibitors and Cough. *J. Cardiovasc. Pharmacol.* **1989**, *13* (Suppl. 3), S67−S69. (c) Lindgren, B. R.; Andersson, R. G. G. Angiotensin-Converting Enzyme Inhibitors and Their Influence on Inflammation, Bronchial Reactivity and Cough. *Med. Toxicol. Adverse Drug Exp.* **1989**, *4*, 369−380. (d) Chin, H. L.; Buchan, D. A. Severe Angioedema after Long-Term Use of an Angiotensin-Converting Enzyme Inhibitor. *Ann. Intern. Med.* **1990**, *112*, 312−313.

(4) Erdös, E. G.; Skidgel, R. A. The Unusual Substrate Specificity and the Distribution of Human Angiotensin I Converting Enzyme. *Hypertension* **1986**, *8* (Suppl. I), I-34−I-37.

(5) (a) Greenlee, W. J. Renin Inhibitors. *Med. Res. Rev.* **1990**, *10*, 173−236. (b) Kleinert, H. D. Recent Developments in Renin Inhibitors. *Exp. Opin. Invest. Drugs* **1994**, *3*, 1087−1104.

(6) (a) Hodges, J. C.; Hamby, J. M.; Blankley, C. J. Angiotensin II Receptor Binding Inhibitors. *Drugs Future* **1992**, *17*, 575−593. (b) Timmermans, P. B. M. W. M.; Wong, P. C.; Chiu, A. T.; Herblin, W. F.; Benfield, P.; Carini, D. J.; Lee, R. J.; Wexler, R. R.; Saye, J. A. M.; Smith, R. D. Angiotensin II Receptors and Angiotensin II Receptor Antagonists. *Pharmacol. Rev.* **1993**, *45*, 205−251.

(7) (a) Khosla, M. C.; Smeby, R. R.; Bumpus, F. M. Structure-Activity Relationship in Angiotensin II Analogs; Angiotensin. *Handb. Exp. Pharmacol.* **1974**, *37*, 126−161. (b) Türker, R. K.; Page, I. H.; Bumpus, F. M. Antagonists of Angiotensin II. Angiotensin. *Handb. Exp. Pharmacol.* **1974**, *37*, 162−169.

(8) Pals, D. T.; Masucci, F. D.; Denning, G. S., Jr.; Sipos, F.; Fessler, D. C. Role of the Pressor Action of Angiotensin II in Experimental Hypertension. *Circ. Res.* **1971**, *29*, 673−681.

(9) Matsoukas, J. M.; Goghari, M. H.; Scanlon, M. N.; Franklin, K. J.; Moore, G. J. Synthesis and Biological Activities of Analogues of Angiotensin II and III Containing *O*-Methyltyrosine and D-Tryptophan. *J. Med. Chem.* **1985**, *28*, 780−783.

(10) (a) Brunner, H. R.; Gavras, H.; Laragh, J. H.; Keenan, R. Angiotensin-II Blockade in Man by Sar^1-Ala^8-Angiotensin II for Understanding and Treatment of High Blood-pressure. *Lancet* **1973**, 1045−1048. (b) Streeten, D. H. P.; Anderson, G. H., Jr.; Dalakos, T. G. Angiotensin Blockade: Its Clinical Significance. *Am. J. Med.* **1976**, *60*, 817−824. (c) Ogihara, T.; Yamamoto, T.; Kumahara, Y. Clinical Applications of Synthetic Angiotensin II Analogue. *Jpn. Circ. J.* **1974**, *38*, 997−1003. (d) Hata, T.; Ogihara, T.; Mikami, H.; Nakamaru, M.; Maruyama, A.; Mandai, T.; Kumahara, Y. Comparison of the Biological Effects of Two Angiotensin II Analogues in Hypertensive Patients with Sodium Depletion. *Life Sci.* **1978**, *22*, 1955−1962.

(11) Streeten, D. H. P.; Anderson, G. H., Jr. Angiotensin-Receptor Blocking Drugs; Clinical Pharmacology of Antihypertensive Drugs. In *Handbook of Hypertension*; Doyle, A. E., Ed.; Elsevier: Amsterdam, 1984; Vol. 5, pp 246−271.

(12) Furukawa, Y.; Kishimoto, S.; Nishikawa, K. Hypotensive Imidazole-5-acetic Acid Derivatives. Jpn. Patent 56-71,073, 1981, and 56-71,674, 1981; U.S. Patent 4,340,598, 1982, and 4,355, 040, 1982.

(13) (a) Chiu, A. T.; McCall, D. E.; Price, W. A.; Wong, P. C.; Carini, D. J.; Duncia, J. V.; Wexler, R. R.; Yoo, S. E.; Johnson, A. L.; Timmermans, P. B. M. W. M. Nonpeptide Angiotensin II Receptor Antagonists. VII. Cellular and Biochemical Pharmacology of DuP 753, an Orally Active Antihypertensive Agent. *J. Pharmacol. Exp. Ther.* **1990**, *252*, 711−718. (b) Duncia, J. V.; Carini, D. J.; Chiu, A. T.; Johnson, A. L.; Price, W. A.; Wong, P. C.; Wexler, R. R.; Timmermans, P. B. M. W. M. The Discovery of DuP 753, A Potent Orally Active Nonpeptide Angiotensin II Receptor Antagonist. *Med. Res. Rev.* **1992**, *12*, 149−191. (c) Carini, D. J.; Duncia, J. V.; Aldrich, P. E.; Chiu, A. T.; Johnson, A. L.; Pierce, M. E.; Price, W. A.; Sautella, J. B., III; Wells, G. J.; Wexler, R. R.; Wong, P. C.; Yoo, S. E.; Timmermans, P. B. M. W. M. Nonpeptide Angiotensin II Receptor Antagonists: The Discovery of a Series of *N*-(Biphenylmethyl)imidazoles as Potent, Orally Active Antihypertensives. *J. Med. Chem.* **1991**, *34*, 2525−2547.

(14) 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. Nonpeptide Angiotensin II Receptor Antagonists. XI. Pharmacology of EXP 3174: An Active Metabolite of DuP 753, An Orally Active Antihypertensive Agent. *J. Pharmacol. Exp. Ther.* **1990**, *255*, 211−217.

(15) (a) Greenlee, W. L.; Siegl, P. K. S. Angiotensin/renin Modulators. *Annu. Rep. Med. Chem.* **1991**, *26*, 63−72. (b) Greenlee, W. L.; Siegl, P. K. S. Angiotensin/renin Modulators. *Annu. Rep. Med. Chem.* **1992**, *27*, 59−68. (c) Buchholz, R. A.; Lefker, B. A.; Kiron, M. A. R. Hypertension Therapy: What Next? *Annu. Rep. Med. Chem.* **1993**, *28*, 69−78. (d) Ashton, W. T. Nonpeptide Angiotensin II Receptor Antagonists. *Exp. Opin. Invest. Drugs* **1994**, *3*, 1105−1142.

(16) (a) Whitebread, S.; Mele, M.; Kamber, B.; de Gasparo, M. Preliminary Biochemical Characterization of two Angiotensin II Receptor Subtypes. *Biochem. Biophys. Res. Commun.* **1989**, *163*, 284−291. (b) Chiu, A. T.; Herblin, W. F.; McCall, D. E.; Ardecky, R. J.; Carini, D. J.; Duncia, J. V.; Pease, L. J.; Wong, P. C.; Wexler, R. R.; Johnson, A. L.; Timmermans, P. B. M. W. M. Identification of Angiotensin II Receptor Subtypes. *Biochem. Biophys. Res. Commun.* **1989**, *165*, 196−203. (c) Bumps, F. M.; Catt, K. J.; Chiu, A. T.; DeGasparo, M.; Goodfriend, T.; Husain, A.; Peach, M. J.; Taylor, D. G., Jr.; Timmermans, P. B. M. W. M. Nomenclature for Angiotensin Receptors: A Report of the Nomenclature Committee of the Council for High Blood Pressure Research. *Hypertension* **1991**, *17*, 720−721.

(17) (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. The Discovery of Potent Nonpeptide Angiotensin II Receptor Antagonists: A New Class of Potent Antihypertensives. *J. Med. Chem.* **1990**, *33*, 1312−1329. (b) Carini, D. J.; Duncia, J. V.; Johnson, A. L.; Chiu, A. T.; Price, W. A.; Wong, P. C.; Timmermans, P. B. M. W. Nonpeptide Angiotensin II Receptor Antagonists: *N*-[(Benzyloxy)benzyl]imidazoles and Related Compounds as Potent Antihypertensives. *J. Med. Chem.* **1990**, *33*, 1330−1336. (c) Carini, D. J.; Chiu, A. T.; Wong, P. C.; Johnson, A. L.; Wexler, R. R.; Timmermans, P. B. M. W. M. The Preparation of (Perfluoroalkyl)imidazoles as Nonpeptide Angiotensin II Receptor Antagonists. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 895−898. (d) Dowle, M. D.; Judd, D. B.; Middlemiss, D.; Scopes, D. I. C.; Ross, B. C.; Pass, M.; Tranquillini, E.; Jack, T. I.; Hobson, J. E.; Panchal, T. A.; Stuart, P. G.; Drew, G. M.; Robertson, M. J.; Hilditch, A.; Clark, K. L.; Travers, A.; Hunt, A. A. E.; Manchee, G. R.; Walker, D. G.; Eddershaw, P. J.; Donnelly, M.; Bayliss, M. K. Benzofuran Based Angiotensin II Antagonists Related to GR117289: Part III; GR138950, A Triflamide with High Oral Bioavalability. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2047−2050. (e) Carini, D. J.; Ardecky, R. J.; Ensinger, C. L.; Pruitt, J. R.; Wexler, R. R.; Wong, P. C.; Huang, S.-M.; Aungst, B. J.; Timmermans, P. B. M. W. M. Nonpeptide Angiotensin II Receptor Antagonists: The Discovery of DMP 581 and DMP 811. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 63−68.

(18) Thomas, A. P.; Allott, C. P.; Gibson, K. H.; Major, J. S.; Masek, B. B.; Oldham, A. A.; Ratcliffe, A. H.; Roberts, D. A.; Russell, S. T.; Thomason, D. A. New Nonpeptide Angiotensin II Receptor Antagonists. 1. Synthesis, Biological Properties, and Structure-Activity Relationships of 2-Alkyl Benzimidazole Derivatives. *J. Med. Chem.* **1992**, *35*, 877−885.

(19) (a) Weinstock, J.; Keenan, R. M.; Samanen, J.; Hempel, J.; Finkelstein, J. A.; Franz, R. G.; Gaitanopoulos, D. E.; Girard, G. R.; Gleason, J. G.; Hill, D. T.; Morgan, T. M.; Peishoff, C. E.; Aiyar, N.; Brooks, D. P.; Fredrickson, T. A.; Ohlstein, E. H.; Ruffolo, R. R., Jr.; Stack, E. J.; Sulpizio, A. C.; Weidley, E. F.; Edwards, R. M. 1-(Carboxybenzyl)imidazole-5-acrylic Acids: Potent and Selective Angiotensin II Receptor Antagonists. *J. Med. Chem.* **1991**, *34*, 1514−1517. (b) Keenan, R. M.; Weinstock, J.; Finkelstein, J. A.; Franz, R. G.; Gaitanopoulos, D. E.; Girard, G. R.; Hill, D. T.; Morgan, T. M.; Samanen, J. M.; Hempel, J.; Eggleston, D. S.; Aiyar, N.; Griffin, E.; Ohlstein, E. H.; Stack, E. J.; Weiley, E. F.; Edwards, R. Imidazole-5-acrylic Acids: Potent Nonpeptide Angiotensin II Receptor Antagonists Designed Using a Novel Peptide Pharmacophore Model. *J. Med. Chem.* **1992**, *35*, 3858−3872.

(20) Ashton, W. T.; Cantone, C. L.; Chang, L. L.; Hutchins, S. M.; Strelitz, R. A.; MacCoss, M.; Chang, R. S. L.; Lotti, V. J.; Faust, K. A.; Chen, T.-B.; Bunting, P.; Schorn, T. W.; Kivlighn, S. D.; Siegl, P. S. Nonpeptide Angiotensin II Antagonists Derived from 4*H*-1,2,4-Triazoles and 3*H*-Imidazo[1,2-b][1,2,4]triazoles. *J. Med. Chem.* **1993**, *36*, 591−609.

(21) Middlemiss, D.; Watson, S. P.; Ross, B. C.; Dowle, M. D.; Scopes, D. I. C.; Montana, J. G.; Hirst, G. C.; Panchal, T. A.; Paton, J. M. S.; Hubbard, T.; Stuart, G.; Drew, G. M.; Hilditch, A.; Travers,

A.; Robertson, M. J.; Hunt, A. A. E.; Palmer, E.; Manchee, G. R. Benzofuran Based Angiotensin II Antagonists Related to GR117289: Part II; Amino Acid Amides. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2043−2046.

(22) Yanagisawa, H.; Amemiya, Y.; Kanazaki, T.; Fujimoto, K.; Shimoji, Y.; Fujimoto, Y.; Sada, T.; Mizuno, M.; Koike, H. Angiotensin II Receptor Antagonists: Imidazoles and Pyrroles Bearing Hydroxymethyl and Carboxy Substituents. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 177−184.

(23) Davis, D. P.; Kirk, K. L.; Cohen, L. A. New Synthesis of 2-Nitroimidazoles. *J. Heterocycl. Chem.* **1982**, *19*, 253−256.

(24) Reduction of the corresponding dimethyl ester of **22a** with lithium tri-*tert*-butoxyaluminohydride was reported to afford the methyl esters corresponding to **46** and **40** in a ratio of 6:1. Carini, D. J.; Duncia, J. J. V.; Wong, P. C. B. Angiotensin II Receptor Blocking Imidazoles. US Patent 5,138,069, 1992; example 279.

(25) IC_{50} values of **1**, **69**, and **70** were reported to be 19, 230, and 92 nM, respectively, in ref 13c, and IC_{50} values of **1** and **2** were 26 and 37 nM, respectively, in ref 14 at rat adrenal cortical microsomes. The relative inhibitory potency of **1** was reported to be lower by 1 order of magnitude at bovine adrenal cortex than at rat adrenal cortex. (a) Ball, T.; Baukal, A. J.; Eng, S.; Catt, K. J. Angiotensin II Receptor Subtypes and Biological Responses in the Adrenal Cortex and Medulla. *Mol. Pharmacol.* **1991**, *40*, 401−406. (b) Kubo, K.; Inada, Y.; Kohara, Y.; Sugiura, Y.; Ojima, M.; Itoh, K.; Furukawa, Y.; Nishikawa, K.; Naka, T. Nonpeptide Angiotensin II Receptor Antagonists. Synthesis and Biological Activity of Benzimidazoles. *J. Med. Chem.* **1993**, *36*, 1772−1784.

(26) After completing our study, prodrugs of AII receptor antagonists have been reported; see: (a) Zydowsky, T. M.; Winn, M.; De, B.; Altenbach, R. J.; Rosenberg, S. H.; Kerkman, D. J.; DeBernardis, J. F.; Buckner, S. A.; Lee, J.; Brune, M.; Morse, P.; Warner, R. B.; Marsh, K.; Srivatsa, G. S.; Bauch, J. 4-Aminopyrimidine-5-carboxylic Acid Prodrugs as Angiotensin II Antagonists. Presented at the 204th National Meeting of the American Chemical Society, Washington, DC, August 23−28, 1992; MEDI 27. (b) Kubo, K.; Kohara, Y.; Yoshimura, Y.; Inada, Y.; Shiboura, Y.; Furukawa, Y.; Kato, T.; Nishikawa, K.; Naka, T. Nonpeptide Angiotensin II Receptor Antagonists. Synthesis and Biological Activity of Potential Prodrugs of Benzimidazole-7-carboxylic Acids. *J. Med. Chem.* **1993**, *36*, 2343−2349. (c) Kim, K. S.; Qian, L.; Bird, J. E.; Dickinson, K. E. J.; Moreland, S.; Schaeffer, T. R.; Waldron, T. L.; Delaney, C. L.; Weller, H. N.; Miller, A. V. Quinoxaline N-Oxide Containing Potent Angiotensin II Receptor Antagonists: Synthesis, Biological Properties, and Structure-Activity Relationships. *J. Med. Chem.* **1993**, *36*, 2335−2342. (d) Middlemiss, D.; Watson, S. P.; Ross, B. C.; Dowle, M. D.; Scopes, D. I. C.; Montana, J. G.; Stah, P.; Hirst, G. C.; Panchal, T. A.; Paton, J. M. S.; Pass, M.; Hubbard, T.; Hamblett, J.; Cardwell, K. S.; Jack, T. I.; Stuart, G.; Coote, S.; Bradshaw, J.; Drew, G. M.; Hilditch, A.; Clark, K. L.; Robertson, M. J.; Bayliss, M. K.; Donnelly, M.; Palmer, E.; Manchee, G. R. M. Benzofuran Based Angiotensin II Antagonists Related to GR117289: Enhancement of potency *in vitro* and Oral Activity. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 589−594. (e) Carini, D. J.; Ardecky, R. J.; Ensinger, C. L.; Pruitt, J. R.; Wexler, R. R.; Wong, P. C.; Huang, S.-M.; Aungst, B. J.; Timmermans, P. B. M. W. M. Nonpeptide Angiotensin II Receptor Antagonists: The Discovery of DMP581 and DMP811. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 63−68. (f) Ryono, D. E.; Poss, M. A.; Bird, J. E.; Buote, J.; Chong, S.; Dejneka, T.; Dickinson, K. E. J.; Gu, Z.; Mathers, P.; Moreland, S.; Morrison, R. A.; Petrillo, E. W.; Powell, J. R.; Shaeffer, T.; Spitzmiller, E. R.; White, R. E. Orally Active Prodrugs of Quinoline-4-carboxylic Acid Angiotensin II Receptor Antagonists. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 201−206.

(27) Stewert, J. J. MOPAC Ver. 6. *QCPE Bull.* **1989**, *9*, 10. Revised as Ver. 6.01 by T. Hirano, University of Tokyo, for HITAC and UNIX machines (*JCPE Newslett.* **1989**, *1*, 10).

(28) Diederichs, K.; Schulz, G. E. Three-dimensional Structure of the Complex between the Mitochondrial Matrix Adenylate Kinase and Its Substrate AMP. *Biochemistry* **1990**, *29*, 8138−8144.

(29) Matsuura, Y.; Kusunoki, M.; Harada, W.; Kakudo, M. Structure and Possible Catalytic Residues of Taka-Amilase A. *J. Biochem. (Tokyo)* **1984**, *95*, 697−702.

(30) (a) Bernstein, F. C.; Koetzle, T. F.; Williams, G. J. B.; Meyer, E. F., Jr.; Brice, M. D.; Rodgers, J. R.; Kennard, O.; Shimanouchi, T.; Tasumi, M. Protein Data Bank: A Computer-based Archival File for Macromolecular Structures. *J. Mol. Biol.* **1977**, *112*, 535−542. (b) Abola, E. E.; Bernstein, F. C.; Bryant, S. H.; Koetzle, T. F.; Weng, J. Protein Data Bank. In *Crystallographic Database-Information Content, Software Systems, Scientific Applications*; Allen, F. H., Bergerhoff, G., Sievers, R., Eds.; Data Commission of the International Union of Crystallography: Bonn/Cambridge/Chester, 1987; pp 107−132.

(31) This program has been developed by Molecular Simulation Inc.

(32) (a) Herres, H. Pro-drugs of β-Lactam Antibiotics. *Drugs Today* **1983**, *19*, 499−538. (b) Sakamoto, F.; Ikeda, S.; Tsukamoto, G. Studies on Prodrugs. II. Preparation and Characterization of (5-substituted 2-oxo-1,3-dioxolen-4-yl)methyl esters of ampicillin. *Chem. Pharm. Bull.* **1984**, *32*, 2241−2248. (c) v. Daehne, W.; Frederiksen, E.; Gundersen, E.; Lund, F.; Mørch, P.; Petersen, H. J.; Roholt, K.; Tybring, L.; Godtfredsen, W. O. Acyloxymethyl Esters of Ampicillin. *J. Med. Chem.* **1970**, *13*, 607−612. (d) Fujimoto, K.; Ishihara, S.; Yanagisawa, H.; Ide, J.; Nakayama, E.; Nakao, H.; Sugawara, S.; Iwata, M. Studies on Orally Active Cephalosporin Esters. *J. Antibiot.* **1987**, *40*, 370−384. (e) Shiobara, Y.; Tachibana, A.; Sasaki, H.; Watanabe, T.; Sado, T. Phthalidyl D-α-Aminobenzylpenicillinate Hydrochloride (PC-183), a New Orally Active Ampicillin Ester I. Absorption, Excretion and Metabolism of PC-183 and Ampicillin. *J. Antibiot.* **1974**, *27*, 665−673.

(33) See footnote 9 in ref 17a.

(34) Garcia, K. C.; Ronco, P. M.; Verroust, P. J.; Brünger, A. T.; Amzel, L. M. Three Dimensional Structure of an Angiotensin II-Fab Complex at 3 Å: Hormone Recogniton by an Anti-Idiotypic Antibody. *Science* **1992**, *257*, 502−507.

(35) Reiz, D. V.; Garland, D. J.; Norton, M. B.; Collins, J. T.; Reinhard, E. J.; Manning, R. E.; Olins, G. M.; Chen, S. T.; Palomo, M. A.; McMahon, E. G.; Koehler, K. F. N1-Sterically Hindered 2H-Imidazol-2-one Angiotensin II Receptor Antagonists: The Conversion of Surmountable Antagonists to Insurmountable Antagonists. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1055−1060.

(36) (a) Yanagisawa, T.; Ueyama, N.; Kawai, T.; Sonegawa, M.; Baba, H.; Mochizuki, S.; Kozakai, K.; Tomiyama, T. 4,5,6,7-Tetrahydro-8-oxocycloheptimidazoles: A New Class of Potent Nonpeptide Angiotensin II Receptor Antagonists. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1559−1564. (b) Huang, H.-C.; Chamberlain, T. S.; Olins, G. M.; Corpus, V. M.; Chen, S. T.; McMahon, E. G.; Palomo, M. A.; Blaine, E. H.; Manning, R. E. Discovery of Nonpeptide, Potent Conformationally Restricted Angiotensin II Receptor Antagonists. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2591−2596.

(37) Begland, R. W.; Hartter, D. R.; Jones, F. N.; Sam, D. J.; Sheppard, W. A.; Webster, O. W.; Weigert, F. J. Hydrogen Cyanide Chemistry. VIII. New Chemistry of Diaminomaleonitrile. Heterocyclic Synthesis. *J. Org. Chem.* **1974**, *39*, 2341−2350.

(38) Tamamushi, Y. Synthesis of 2-Ethylimidazole Derivatives. Synthesis of 2-Ethyl-4,5-diaminomethylimidazole. *J. Pharm. Soc. Jpn.* **1937**, *57*, 1023−1028.

(39) Ivanov, V. A. *Zh. Prikl. Khim.* **1979**, *52*, 1655−1656; *Chem. Abstr.* **1979**, *91*, 211325b.

(40) Fargher, R. G.; Pyman, F. L. Nitro-, Arylazo-, and Aminoglyoxalines. *J. Chem. Soc.* **1919**, *115*, 217−260.

(41) Maeda, T.; Balakrishnan, K.; Mehdi, S. Q. A Simple and Rapid Method for the Preparaton of Plasma Membranes. *Biochim. Biophys. Acta* **1983**, *731*, 115−120.

(42) Main, P.; Hull, S. E.; Lessinger, L.; Germain, G.; Declercq, J. P.; Woolfson, M. M. *MULTAN 78. A System of Computer Programs for the Automatic Solution of Crystal Structure from X-Ray Diffraction Data*; University of York: England, and Louvain, Belgium, 1978.

(43) Revised and Supplementary Tables. *International Tables for X-Ray Crystallography. Vol. IV*; Ibers, J. S., Hamilton, W. C., Eds.; Kynoch Press: Birmingham, England, 1974.

(44) Koyama, Y.; Okada, K. Automation of the Crystal Structure Analysis. *Acta Crystallogr., Sect. A* **1975**, *A31*, S18.02.2−18.

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