Nonpeptide Angiotensin II Receptor Antagonists. 2. Design, Synthesis, and Structure–Activity Relationships of 2-Alkyl-4-(1*H*-pyrrol-1-yl)-1*H*-imidazole Derivatives: Profile of 2-Propyl-1-[[2′-(1*H*-tetrazol-5-yl)-[1,1′-biphenyl]-4-yl]-methyl]-4-[2-(trifluoroacetyl)-1*H*-pyrrol-1-yl]-1*H*-imidazole-5-carboxylic Acid (CI-996)[1]

Ila Sircar,*,† John C. Hodges,† John Quin III,† Amy M. Bunker,† R. Thomas Winters,† Jeremy J. Edmunds,† Catherine R. Kostlan,† Cleo Connolly,† Stephen J. Kesten,† James M. Hamby,† John G. Topliss,† Joan A. Keiser,‡ and Robert L. Panek‡

Departments of Chemistry and Pharmacology, Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, Ann Arbor, Michigan 48105

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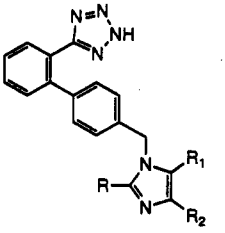
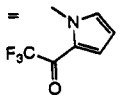
A novel series of nonpeptide angiotensin II (AII) receptor antagonists containing a 1*H*-pyrrol-1-yl moiety at the 4-position of the imidazole have been developed. The pyrrole group occupies the same lipophilic pocket at the receptor as the chloro group in DuP 753 (**68**) and EXP 3174 (**69**) and the pentafluoro group in DuP 532 (**70**), respectively. The impetus for its selection came from bioisosteric considerations based on hydrophobic and electronic substituent constants. An extensive study of the structure–activity relationships revealed several highly potent AII receptor antagonists. An acyl substitution at the 2-position of the pyrrole ring improved activity, most notably in the in vivo rat model. In addition, the 2-substituted pyrrole compounds improved chemical stability toward extremely facile decarboxylation reaction associated with unsubstituted pyrrole analogues, thus facilitating development of these agents. The IC_{50}'s of **18**, **20**, and **42** (<1 nM) were better than the reference compounds **69** and **70**, respectively. These compounds were selective AII antagonists that compete at the AT_1 receptor and showed no affinity at the AT_2 receptor at concentrations up to 10 μM. Upon intravenous administration in a normotensive rat model, compound **18** inhibited the AII-induced responses with ED_{50} of 6 μg/kg per min. In a renal hypertensive rat model, the antihypertensive potency of compound **18**, at a dose of 10 mg/kg, was very similar to those **68** and **69**, respectively. Compound **18** demonstrated a dose-related (3–30 mg/kg) decrease in blood pressure that was sustained for greater than 24 h. On the basis of its profile, compound **18**, designated as CI-996, has been selected for in-depth studies. The design, synthesis, in vitro, and in vivo structure–activity relationships are described.

Introduction

The renin–angiotensin system (RAS) is an important physiological mechanism in the regulation of blood pressure and fluid and electrolyte homeostasis in normal and various pathophysiological states via its effector peptide, angiotensin II (AII).[2] AII is a potent vasoconstrictor and stimulator of aldosterone secretion. These actions of AII are mediated through specific receptors on the cell surface, which can be blocked by selective receptor antagonists.[3-6] The discovery of the first orally active, nonpeptide, AII receptor antagonist, DuP 753 (losartan),[7-9] has opened an exciting new phase of research on the RAS and generated tremendous interest in pharmaceutical industry to develop AT_1[10]-selective agents for the treatment of hypertension. The development of DuP 753 (**68**) and related AII antagonists provides some unusual structure–activity relationships (SAR).[11,12] All compounds of this class are devoid of partial agonist activity. Interestingly, there is a subclass that is distinguished by its competitive (surmountable) mode of action and another subclass that includes compounds with a free carboxylic group at the 5-position of the imidazole ring, such as EXP 3174 (**69**),[13] Dup 532 (**70**),[14] and EXP 3892 (**71**)[15] (Chart I), that are more potent and noncompetitive (unsurmountable) antagonists. Dup 532 (**70**) is the prototype of the noncompetitive subclass chosen for clinical trial. Additional SAR studies for related compounds also suggest that the chloro and the carboxy substituents on the imidazole ring of **69** are not essential for in vitro activity and can be replaced successfully by a fused benzene ring[16,17] or a fused pyridine ring.[18] The fused pyridine ring modification gave highly

Chart I



68; DuP 753 (losartan);	R = Bu;	R_2 = Cl;	R_1 = CH_2OH
69; EXP 3174;	R = Bu	R_2 = Cl;	R_1 = CO_2H
70; DuP 532;	R = Pr;	R_2 = CF_2CF_3;	R_1 = CO_2H
71; EXP 3892;	R = Pr;	R_2 = CF_3	R_1 = CO_2H
18; CI-966;	R = Pr;	R_2 = 	R_1 = CO_2H

† Department of Chemistry.
‡ Department of Pharmacology.

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Table I. Bioisosteric Relationship of Chloro and 1*H*-Pyrrol-1-yl Substituents[a]

substitution	π	F	R
chloro	0.71	0.41	−0.15
1*H*-pyrrol-1-yl	0.95	0.50	−0.09

[a] Physicochemical constants: hydrophobic (π); electronic (F and R; inductive and resonance, respectively).

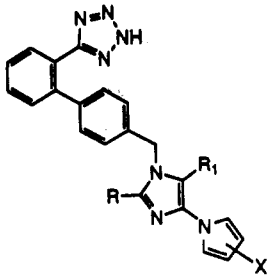
potent antagonist L-158809.[18] At the onset of our work, no systematic SAR study at these positions of the imidazole was reported, although several examples of 4-substituted imidazoles including an aromatic and heteroaromatic ring attached via a carbon atom,[19,20] thioalkyl and thioaryl group,[21] sulfonamides and carboxamides,[22] and spirocyclopentyl derivatives[23] have appeared in the patent literature since then. In seeking new series of AII antagonists, we chose to focus on the contribution of the lipophilic and electron-withdrawing substituent at the 4-position and henceforth designed a series of 4-(1*H*-pyrrol-1-yl)imidazoles related to EXP 3174 (**69**). The general concept of bioisosterism based on the physicochemical substituent constants were first put forward by Hansch.[24] The impetus for the exploration of a 4-(1*H*-pyrrol-1-yl)imidazole type substituent in our work was the bioisosteric relationship of chloro and 1*H*-pyrrol-1-yl substituents based on their hydrophobic and electronic substituent constants (Table I).[25] It has been well-established that the presence of a chloro substituent at the 4-position of the imidazole nucleus in this class of compounds imparts favorable activity characteristics.[8] Thus, if the controlling factors with respect to the effect on the activity of substituents at the 4-position of the imidazole ring are hydrophobic and electronic, one would expect to see favorable activity characteristics with the 1*H*-pyrrol-1-yl substituent. In this paper, the synthesis and structure–activity relationships data are presented. On the basis of the profile, compound 18 (designated as CI-996) was selected for further studies.

Chemistry

Synthesis of Target Compounds, Table II. Compounds in their trityl protected form (R_3 = CN, CO_2R, CHO, COPh) were prepared by reacting suitably substituted imidazoles (Table III) with trityl-protected (bromomethyl)biphenyl compound **67**[7,26] in the presence of anhydrous base (KO^{t}Bu, NaH, K_2CO_3, Cs_2CO_3) in DMF at room temperature (Scheme I). The preferred base, in our hands, was Cs_2CO_3, which typically gave the cleanest reaction and highest yield. This reaction resulted in favor of the desired N_1-regioisomer as the major product which was always admixed with the N_3-isomer. These isomers were separated by flash chromatography and almost invariably the N_1-isomer, being less polar, moved faster on the column. The structure of the N_1- and N_3-isomers was confirmed from the ^{1}H NMR spectra (higher chemical shift of NCH_2 for 1-isomer vs 3-isomer) and NOE experiments (see Experimental Section for details). The ratio of the two isomers was dependent upon steric and electronic properties of substituents at the 4- and 5-positions of the imidazole. In general, the highest ratio of N_1- vs N_3-isomer was obtained with unsubstituted pyrrole bearing a CHO or CN at the 5-position of the imidazole ring. Acidic (citric acid/MeOH–H_2O) cleavage of the trityl protecting group yielded the free tetrazoles (**2, 4, 5, 7, 9, 11, 13, 16, 19, 21, 23, 26, 27, 33, 34, 37, 39, 41**). Compounds bearing a CO_2R group at the imidazole 5-position were saponified to give the corresponding CO_2H compounds (**6, 8, 18, 20, 22, 24, 32, 35, 36, 38, 40, 42**). The saponification reaction occurs under exceedingly mild condition for the N_1-regioisomer, hence enabling selective transformation of ester to acid even in the presence of base-sensitive groups on the pyrrole ring, such as, compounds **16** (X = 2-$COCF_3$), **23** (X = 2-Me, 3-CO_2Me), and **26** (X = 3-CO_2Et). Under strongly basic conditions the corresponding dicarboxylic acid analogues **17, 25,** and **28** were obtained (Scheme II). The fact that the CO_2Me group on the product of N_1-benzylation was saponified under very mild conditions compared to that of the product of N_3-benzylation was of critical importance to the success of the above coupling reaction, requiring the use of anhydrous conditions. Moisture in the presence of base under the reaction conditions degrades the desired product, reducing the yield and giving the appearance of lesser N_1-regioselectivity. The CO_2H compounds (**1, 8**) were obtained also from the corresponding nitriles (**2, 9**). Compounds **1** and **8** with an unsubstituted pyrrole ring were prone to thermal decarboxylation, which proved to be a problem in routine purification. Usual workup and recrystallization led to substantial decarboxylated materials (**3** and **10**, Scheme II), necessitating purification by reverse-phase chromatography and low-temperature solvent removal. Addition of either electron-withdrawing (**6, 18, 32**) or -donating (**20, 22, 35, 42**) groups at the pyrrole 2-position substantially increased stability toward decarboxylation. This would imply that the effect of 2-substituents on the pyrrole ring in inhibiting decarboxylation was not related to their electronic properties but rather to steric interactions that twist the pyrrole ring out of the plane with the imidazole ring and thus reducing the possibilities for resonance stabilization of developing charges in the decarboxylation reaction. Compounds **12** and **31** were prepared from **11** and **18** via $NaBH_4$ reduction while compound **30**, bearing a CH_2OH group at the imidazole 5-position, was best obtained from **19** by $LiAlH_4$ reduction (Scheme III). Compounds wherein R_3 was an aldehyde were transformed to the corresponding vinylogous esters at the trityl-protected stage and were subsequently treated with citric acid to generate free tetrazole compounds **36** (Et ester, not isolated), **37**, and **39**. These were transformed to the corresponding acids **36, 38,** and **40** via saponification (Scheme IV). It is noteworthy that benzylation of imidazoles **65** and **66**, containing a vinylogous ester at the 5-position with the requisite benzyl bromide **67**, gave exclusively the N_3-isomers of **37** and **39** (**37a** and **39a**), respectively (Scheme IV).

Synthesis of 4-(1*H*-Pyrrol-1-yl)imidazoles (Table III). 4-(1*H*-Pyrrol-1-yl)imidazoles **43–45, 47, 51,** and **61** were prepared from requisite 4-aminoimidazoles by a modification of the Knorr pyrrole synthesis utilizing 2,5-dimethoxytetrahydrofuran under acidic conditions (Scheme V).[30–32] The 2,5-dialkylpyrrole analogues **50, 53–54,** and **64** were prepared by reacting the aminoimidazole with the requisite dicarbonyl compounds. Additional substituents on the pyrrole are either introduced as part of the tetrahydrofuran intermediate (**49, 59, 60**; Scheme V)[33,34] or by subsequent electrophilic substitution reactions on the pyrrole ring (Scheme VI).[35] Compounds **46, 48,** and **52** were obtained by reacting the corresponding unsubstituted pyrroles **44, 47,** and **51** with $(CF_3CO)_2O$. Introduction of an aldehyde moiety (**62**) was accomplished via Vilsmeier reaction [$(COCl)_2$/DMF] on **51**. Chlorination of **61** with NCS provided the 2,5-dichloro analogue **63**. Compounds **56** and **58** were obtained by MnO_2 oxidation

Table II. Structure-Activity Data of 4-(1*H*-Pyrrol-1-yl)-1-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1*H*-imidazole Derivatives



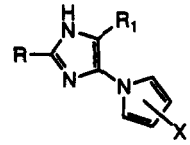
compd	R	R_1	X	mp, °C[b]	formula[c]	IC_{50}, nM[d] receptor binding[d]	IC_{50}, nM[d] rabbit aorta[e]
1[f]	Bu	CO_2H	H	122–124 dec	$C_{26}H_{25}N_7O_2$·0.13EtOAc 0.04 Et_2O; 0.43H_2O	1.57 ± 0.10	7.0
2	Bu	CN	H	85–100	$C_{26}H_{24}N_8$·0.5 isooctane	209 ± 4	>100
3	Bu	H	H	136–137.0	$C_{25}H_{25}N_7$	27.0 ± 0	400
4	Bu	COPh	H	*a*	$C_{32}H_{29}N_7O$·0.4EtOAc	23.3 ± 0.0	5400
5	Bu	CO_2Me	2-$COCF_3$	99–102	$C_{29}H_{26}F_3N_7O_3$	3.57 ± 0.01	52 (44–62)
6	Bu	CO_2H	2-$COCF_3$	160–173	$C_{28}H_{24}F_3N_7O_3$·0.5cyclohexane	2.37 ± 0.01	4.0 (3.4–4.7)
7	Pr	CO_2Et	H	160–163	$C_{27}H_{27}N_7O_2$	12.2 ± 0.0	330
8	Pr	CO_2H	H	122–125	$C_{25}H_{23}N_7O_2$	1.71 ± 0.06	5.4
9	Pr	CN	H	178–180	$C_{25}H_{22}N_8$·0.1MeO^{i}Pr	332 ± 12	1500
10	Pr	H	H	122–125	$C_{24}H_{23}N_7$·0.5H_2O	5.6 ± 1.6	3500
11	Pr	CN	2-$COCF_3$	160 dec	$C_{27}H_{21}F_3N_8O$·0.25(^{i}Pr)$_2O$	171 ± 0	780
12[g]	Pr	CN	2-CH(OH)CF_3	97–103	$C_{27}H_{23}F_3N_8O$	233 ± 3	2200
13[h]	Pr	CN	2-CO_2Me	85–90	$C_{27}H_{24}N_8O_2$·0.5 *c*-hexane	53.3 ± 1.6	2400
14	Pr	CN	2-CO_2H	140–146	$C_{26}H_{22}N_8O_2$·0.8H_2O; 0.1cyclohexane	103 ± 13	NT
15	Pr	$CONH_2$	2-CO_2H	*a*	$C_{26}H_{24}N_8O_3$·1.3H_2O; 0.4cyclohexane	8.76 ± 1.69	57 (54–59)
16	Pr	CO_2Me	2-$COCF_3$	128–131	$C_{28}H_{24}F_3N_7O_3$	3.64 ± 0.11	73 (72–74)
17	Pr	CO_2H	2-CO_2H	157–160 dec	$C_{26}H_{23}N_7O_4$·1.78H_2O	11.2 ± 1.1	19 (20–23)
18	Pr	CO_2H	2-$COCF_3$	184–188	$C_{27}H_{22}F_3N_7O_3$·0.5benzene	0.58 ± 0.00	3.8 (3.5–4.1)
19	Pr	CO_2Me	2,5-Me_2	*a*	$C_{28}H_{29}N_7O_2$·0.5H_2O	20.9 ± 0.0	150
20	Pr	CO_2H	2,5-Me_2	*a*	$C_{27}H_{27}N_7O_2$·1.3CH_2Cl_2·CH_3OH	0.82 ± 0.06	2.35 (1.9–2.8)
21	Pr	CO_2Me	2-Pr, 5-Me	95–101	$C_{30}H_{33}N_7O_2$·0.1EtOAc	15.1 ± 0.0	>100
22	Pr	CO_2H	2-Pr, 5-Me	155 (dec)	$C_{29}H_{31}N_7O_2$·1.1H_2O	0.9 ± 0.0	4.5 (4.0–5.2)
23	Pr	CO_2Me	2-Me, 3-CO_2Me	*a*	$C_{29}H_{29}N_7O_4$·0.17CH_2Cl_2	18.8 ± 1.4	>100
24	Pr	CO_2H	2-Me, 3-CO_2Me	*a*	$C_{28}H_{27}N_7O_4$·1.5H_2O	1.37 ± 0.06	8.2 (5.2–18)
25	Pr	CO_2H	2-Me, 3-CO_2H	*a*	$C_{27}H_{25}N_7O_4$·1.5H_2O·1.1HOAc	11.0 ± 1.0	9.0 (5.6–19)
26	Pr	CO_2Me	3-CO_2Et	80.2–81.6	$C_{29}H_{29}N_7O_4$	158 ± 4	>100
27	Pr	CO_2H	3-CO_2Et	154.0–155.4	$C_{28}H_{27}N_7O_4$·0.38CH_2Cl_2	22.0 ± 0.6	NT
28	Pr	CO_2H	3-CO_2H	156.2–157.8	$C_{26}H_{23}N_7O_4$·0.9H_2O·0.1EtOAc	25.1 ± 0.3	NT
29	Pr	CHO	2,5-Me_2	*a*	$C_{27}H_{27}N_7O$·0.2H_2O	13.7 ± 0.0	71 (45–140)
30	Pr	CH_2OH	2,5-Me_2	*a*	$C_{27}H_{29}N_7O$·0.4H_2O·0.1Et_2O	23.8 ± 1.2	39 (28–56)
31	Pr	CO_2H	2-CH(OH)CF_3	142–144 dec	$C_{27}H_{24}N_7F_3O_3$·0.4Et_2O·0.25H_2O	1.04 ± 0.11	2.9 (2.2–3.7)
32	Pr	CO_2H	2-CHO	178–180	$C_{26}H_{23}N_7O_3$·0.4H_2O·0.1EtOAc	0.8 ± 0.00	2.6 (2.5–7.8)
33	Pr	CN	2,5-Me_2	*a*	$C_{27}H_{26}N_8$	188 ± 0	NT
34	c-Pr	CO_2Me	2,5-Me_2	116–128	$C_{28}H_{27}N_7O_2$	65.5 ± 3.5	>100
35	c-Pr	CO_2H	2,5-Me_2	167–182	$C_{27}H_{25}N_7O_2$	2.81 ± 0.28	4.8 (2.7–6.6)
36	Pr	CH=$CHCO_2H$	H	120 dec	$C_{27}H_{25}N_7O_2$	4.0 ± 0.2	34 (32–36)
37	Pr	CH=$CHCO_2Me$	2,5-Me_2	212–213	$C_{30}H_{31}N_7O_2$	21.6 ± 0.2	NT
38	Pr	CH=$CHCO_2H$	2,5-Me_2	144–150	$C_{29}H_{29}N_7O_2$·0.7H_2O	3.32 ± 0.24	21 (12–29)
39	Pr	CH=$C(CH_3)CO_2Et$	H	89–91	$C_{30}H_{31}N_7O_2$·H_2O	2.8 ± 0.5	>100
40	Pr	CH=$C(CH_3)CO_2H$	H	>200	$C_{28}H_{27}N_7O_2$·H_2O	2.5 ± 0.0	18 (15–26)
41	Pr	CO_2Et	2,5-Cl_2	*a*	$C_{27}H_{25}Cl_2N_7O_2$·0.7H_2O	3.93 ± 0.02	430
42	Pr	CO_2H	2,5-Cl_2	156–157	$C_{25}H_{21}Cl_2N_7O_2$·0.5H_2O·0.3EtOAc	0.14 ± 0.00	3.3 (3.0–3.6)

[a] Compounds were isolated as foams. [b] Yields of compounds were in the range 60–75% (R_1 = CO_2Me/CO_2Et), 80–90% (R_1 = CO_2H), and 80–90% (R_1 = CHO) respectively. See Experimental Section for all other compounds. [c] All compounds gave satisfactory analysis for C,H,N except **12**, **13**, **33** (89.7% by HPLC), and **36** (84% by HPLC). [d] Concentration required to inhibit [^{125}I]AII binding to the rat liver by 50%. IC_{50} values (without BSA) were obtained from a dose–response curve generated from at least five or six doses and are expressed as mean ± SEM. [e] Concentration required to inhibit [^{125}I]AII-induced contraction of the rabbit aorta by 50%. Data expressed as means of two separate experiments. Values in parenthesis indicate the range of IC_{50}s. [f] Attempts to remove solvents from compared **1** by heating at 60 °C under vacuum gave rise to significant decarboxylation. [g] H: calcd, 4.35; found, 4.83; N: calcd 21.04; found, 19.41. [h] N: calcd, 20.96; found, 20.05.

of the corresponding alcohols **55** and **57**, which, in turn, were prepared from the carboxylic esters **53** and **51** via $LiAlH_4$ reduction. Compounds **56** and **58** were transformed to the vinylogous esters **65** and **66**, respectively, by the treatment with (carbomethoxymethylene)triphenylphosphorane in toluene (Scheme IV).

Several synthetic routes (Scheme VII, methods A–C) were utilized for the preparation of the key intermediate 2-alkyl-4-aminoimidazoles bearing either a nitrile or an ester group at the 5-position. Method A involved treatment of the requisite imidate with aminomalononitrile (or aminocyanoacetic acid ester) in the presence of mild base, such as, KOAc.[27] Method B, which was very similar to the method A, involved reaction of the requisite orthoester in place of the imidate with aminomalononitrile in the presence of base to give a substituted imidate which was, in turn, treated with ammonia in MeOH to give the desired 4-amino-imidazoles. This latter method was mostly used for the 4-amino-5-cyano-imidazoles. The alternative method C[28,29] utilized reaction of the imidate

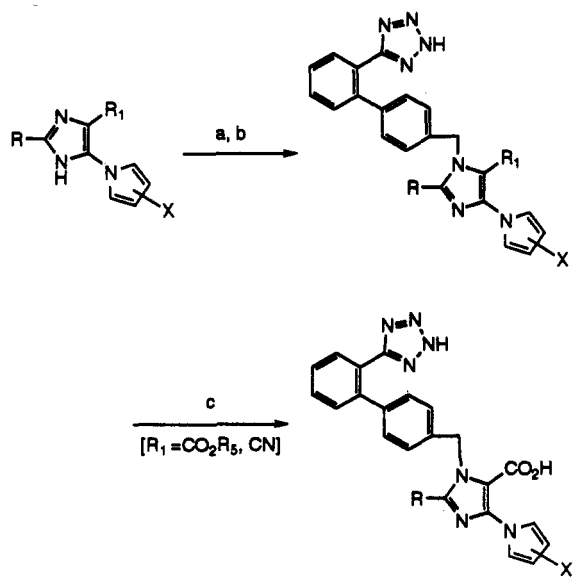
Table III. 4-(Substituted-1*H*-pyrrol-1-yl)-1*H*-imidazoles: Physical Data



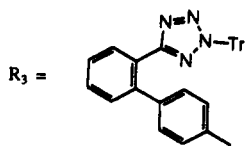
compd	R	R_1	X	mp, °C[a] (recrystn solvent)	yield, %[b]	formula[c]
43	Bu	CN	H	oil	93	$C_{12}H_{14}N_4 \cdot 0.23H_2O$
44	Bu	CO_2Me	H	oil	80	$C_{13}H_{17}N_3O_2$
45	Bu	COPh	H	118–120	64	$C_{18}H_{19}N_3O$
46	Bu	CO_2Me	2-$COCF_3$	100–102 (D)	96	$C_{15}H_{16}F_3N_3O_3$
47	Pr	CN	H	75–78	88	$C_{11}H_{12}N_4 \cdot 0.06EtOAc$
48	Pr	CN	2-$COCF_3$	104–105 (A)	81	$C_{13}H_{11}F_3N_4O$
49	Pr	CN	2-CO_2Me	oil		$C_{14}H_{14}F_3N_3O_3$
50	Pr	CN	2,5-Me_2	134–137	89	$C_{13}H_{16}N_4 \cdot 0.2H_2O$
51	Pr	CO_2Me	H	135–138 (A)	46	$C_{12}H_{15}N_3O_2$
52	Pr	CO_2Me	2-$COCF_3$	158–159 (B)	62	$C_{14}H_{14}N_3F_3O_3$
53	Pr	CO_2Me	2,5-Me_2	176–177.5 (A)	71	$C_{14}H_{19}N_3O_2$
54	Pr	CO_2Me	2-Me, 5-Pr	foam	65	$C_{16}H_{23}N_3O_2$
55	Pr	CH_2OH	2,5-Me_2	foam	90	$C_{13}H_{19}N_3O$
56	Pr	CHO	2,5-Me_2	119–121	75	$C_{13}H_{17}N_3O$
57	Pr	CH_2OH	H	155–158 (C)	81	$C_{11}H_{15}N_3O_1$
58	Pr	CHO	H	118.5–120 (D)	55	$C_{11}H_{13}N_3O_1$
59	Pr	CO_2Me	3-CO_2Et	101–102 (A)	49	$C_{15}H_{19}N_3O_4$
60	Pr	CO_2Me	2-Me, 3-CO_2Me	161–162 (D)	44	$C_{15}H_{19}N_3O_4$
61	Pr	CO_2Et	H	126–128 (D)	41	$C_{13}H_{17}N_3O_2$
62	Pr	CO_2Me	2-CHO	oil	84	$C_{13}H_{15}N_3O_3$
63	Pr	CO_2Et	2,5-Cl_2	133–133.5	72	$C_{13}H_{15}Cl_2N_3O_2$
64	c-Pr	CO_2Me	2,5-Me_2	121–141	95	$C_{14}H_{17}N_3O_2$
65	Pr	$CH{=}CHCO_2Me$	2,5-Me_2	foam	81	$C_{16}H_{21}N_3O_2$
66	Pr	$CH{=}C(Me)CO_2Et$	H	127–130	78	$C_{16}H_{21}N_3O_2$

[a] A (ether/hexane), B (ether), C (heptane/EtOAc), D (hexane/EtOAc). [b] Yield was not optimized and represents the last step. [c] Most of these compounds were characterized by ^1H NMR spectra. Satisfactory elemental analysis were obtained for all compounds except **44**, **49**, **54**, **55**, and **65**.

Scheme I[a]

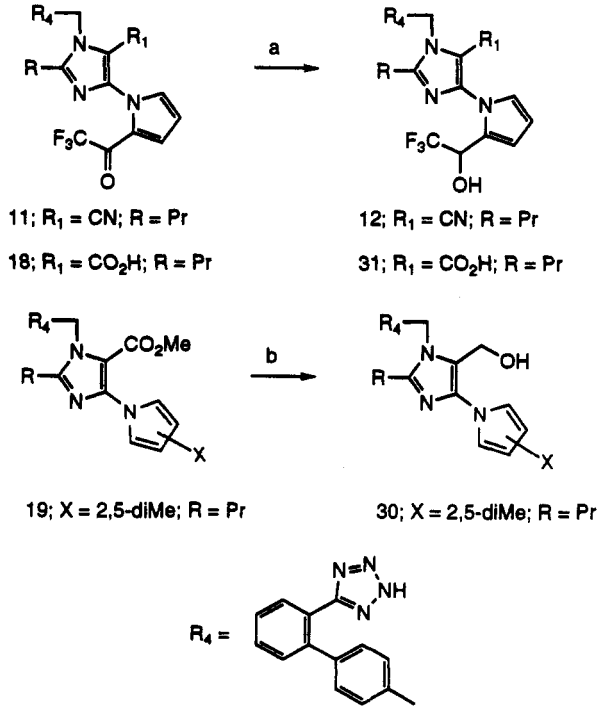


[a] Reagents: (a) R_3CH_2Br (67)/Cs_2CO_3/DMF (60–75%), (b) citric acid/MeOH–H_2O/Δ (80–90%), (c) K_2CO_3/H_2O/DMF (89%).



with cyanamide to give the cyanoimidate which was converted to the desired amino compound in two steps [(i) NH_2CH_2COR (R = OMe, OEt and Ph); (ii) NaOMe].

Scheme II[a]



11; R_1 = CN; R = Pr

12; R_1 = CN; R = Pr

18; R_1 = CO_2H; R = Pr

31; R_1 = CO_2H; R = Pr

19; X = 2,5-diMe; R = Pr

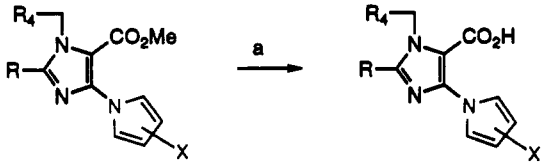
30; X = 2,5-diMe; R = Pr

[a] Reagents: (a) 2 N NaOH/reflux (89%), (b) toluene/Δ.

Results and Discussions

In Vitro AII Antagonism. Receptor Binding Assay. Compounds in Table II were evaluated for activity using two different in vitro screens: (i) a radioligand binding assay involving displacement of [^{125}I]AII[36] from rat liver membrane preparation which corresponds to the AT_1 receptor subtype and (ii) inhibition of AII-induced vas-

Scheme III[a]



16; X = 2-$COCF_3$; R = Pr

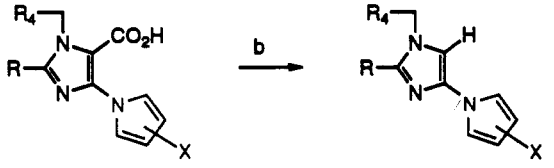
23; X = 2-Me, 3-CO_2Me; R = Pr

26; X = 3-CO_2Et; R = Pr

17; X = 2-CO_2H; R = Pr

25; X = 2-Me, 3-CO_2H; R = Pr

28; X = 3-CO_2H; R = Pr

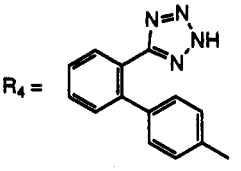


1; X = H; R = Bu

8; X = H; R = Pr

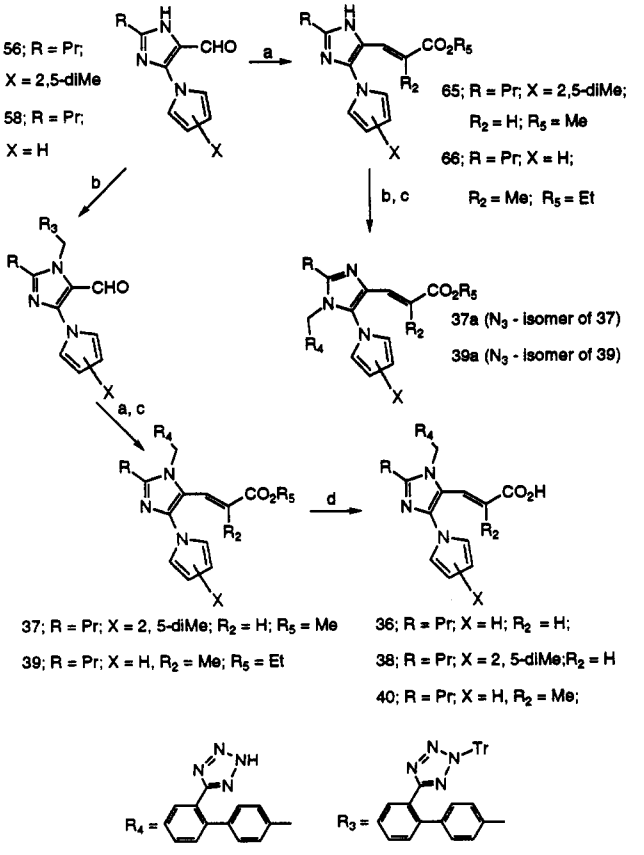
3; X = H; R = Bu

10; X = H; R = Pr



[a] Reagents (a) $NaBH_4$/MeOH (67%), (b) LAH/THF (80%).

Scheme IV[a]



56; R = Pr; X = 2,5-diMe

58; R = Pr; X = H

65; R = Pr; X = 2,5-diMe; R_2 = H; R_5 = Me

66; R = Pr; X = H; R_2 = Me; R_5 = Et

37a (N_3 - isomer of 37)

39a (N_3 - isomer of 39)

37; R = Pr; X = 2, 5-diMe; R_2 = H; R_5 = Me

39; R = Pr; X = H, R_2 = Me; R_5 = Et

36; R = Pr; X = H; R_2 = H;

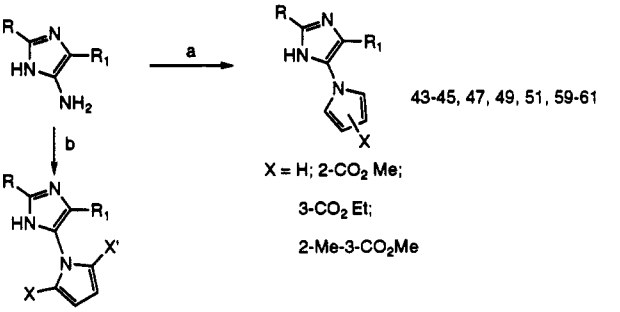
38; R = Pr; X = 2, 5-diMe; R_2 = H

40; R = Pr; X = H, R_2 = Me;

[a] Reagents: (a) $Ph_3{=}C(R_2)CO_2R_2$/toluene/reflux, (b) R_3CH_2Br (67)/Cs_2CO_3/DMF, (c) citric acid/MeOH–H_2O/Δ, (d) LiOH.

oconstriction in isolated rabbit aorta strips. The N_3-isomers showed less affinity at the AT_1 receptor compared to the N_1-isomers (data not shown). IC_{50} values for reference compounds **68–70** are included for comparison.

Scheme V[a]



43-45, 47, 49, 51, 59-61

X = H; 2-CO_2 Me; 3-CO_2 Et; 2-Me-3-CO_2Me

50; R = Pr; R_1 = CN; X = X' = Me

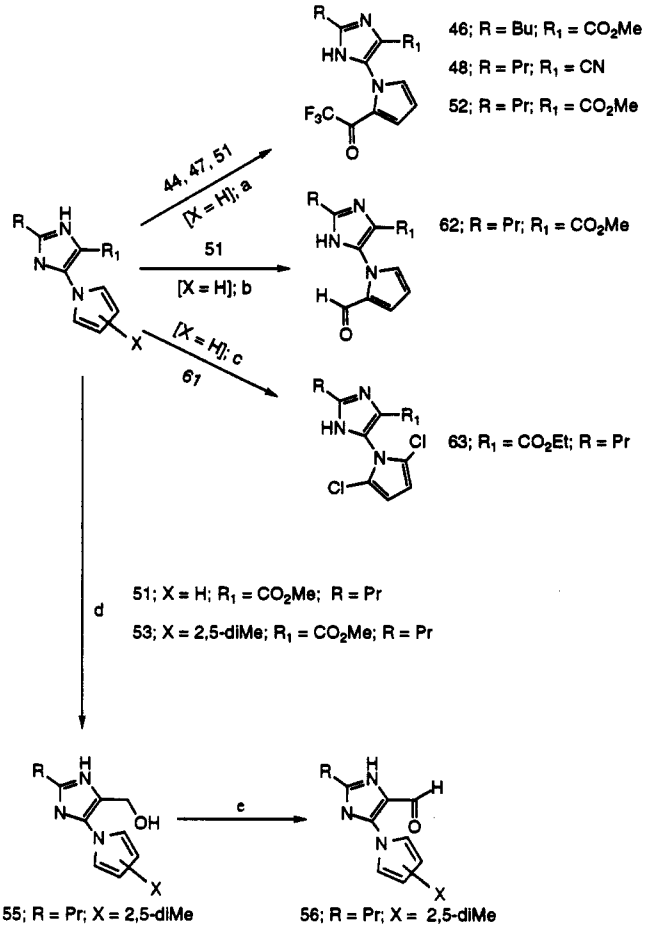
53; R = Pr; R_1 = CO_2Me; X = X' = Me

54; R = Pr; R_1 = CO_2Me; X = Me; X' = Pr

64; R = cPr; R_1 = CO_2Me; X = X' = Me

[a] Reagents: (a)  /HOAc/KOAc/Δ, (b) XC(O)-$CH_2CH_2C(O)X'$/AcOH/EtOH/Δ.

Scheme VI[a]



46; R = Bu; R_1 = CO_2Me

48; R = Pr; R_1 = CN

52; R = Pr; R_1 = CO_2Me

62; R = Pr; R_1 = CO_2Me

63; R_1 = CO_2Et; R = Pr

51; X = H; R_1 = CO_2Me; R = Pr

53; X = 2,5-diMe; R_1 = CO_2Me; R = Pr

55; R = Pr; X = 2,5-diMe

57; R = Pr; X = H

56; R = Pr; X = 2,5-diMe

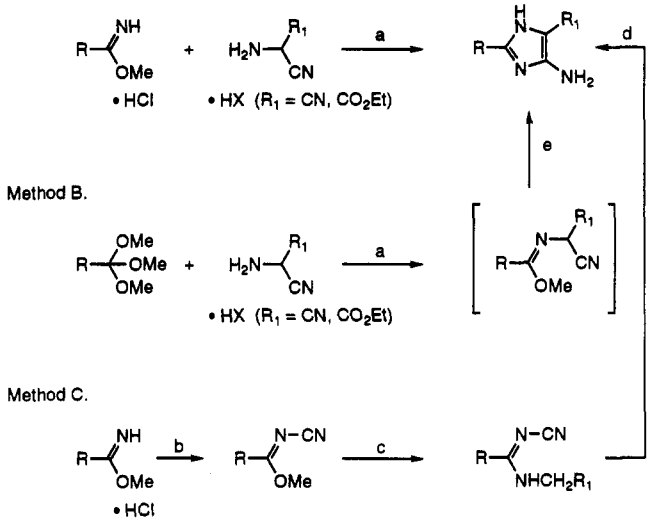
58; R = Pr; X = H

[a] Reagents: (a)$(CF_3CO)_2O/CH_2Cl_2$, (b) $(COCl)_2$/DMF, (c) NCS, (d) LAH/THF (80%), (e) MnO_2/THF/Δ.

We first turned our attention to the contribution of the pyrrole moiety to the binding affinity of Dup 753 (**68**) and EXP 3174 (**69**). We were pleased to find that the AT_1 receptor binding affinity of **68**, **69**, and **70**[14] (IC_{50}'s of 5.0, 1.6, and 3.4 nM, respectively) were largely maintained in the unsubstituted pyrrole compounds **1** and **8** (IC_{50}'s of 1.57 and 1.71 nM, respectively).

The role of substituents on the pyrrole ring was next examined. For most of the compounds, the binding affinity

Scheme VII[a]



[a] Reagents: (a) KOAc/MeOH, (b) H_2NCN/Na_2HPO_4, (c) HCl·$H_2NCH_2R_1$ (R_1 = CO_2Me, CO_2Et and COPh)/Et_3N, (d) NaOMe/MeOH, (e) NH_3/MeOH; Hx = p-toluenesulfonic acid

of 2-substituted and 2,5-disubstituted analogues was enhanced (compare IC_{50}'s of **18**, **20**, **22**, **31**, **32**, **42** with that of **8**). The two most effective substitutions were (i) 2,5-dichloro and (ii) 2-$COCF_3$ producing **42** and **18** with IC_{50}'s of 0.14 and 0.58 nM, respectively. The hydroxy-2,2,2-trifluoroethyl analogue **31** (1 nM) also retained potency similar to **18**. The exception was with the pyrrole-2-carboxylic acid analogue **17**, which had decreased potency. The 3-ethyl ester and carboxylic acid analogues **27** and **28** also had reduced potency by 13–15-fold.

Modifications of functionality at the 5-position of the imidazole ring were next evaluated to find out the critical contribution of the carboxyl group to the binding affinity. As shown in Table II, when X = H, activity is best with R_1 = CO_2H (**8**, 1.7 nM), compared to CH=C(Me)CO_2H (**40**, 2.5 nM), CH=C(Me)CO_2Et (**39**, 2.8 nM), CH=$CHCO_2H$ (**36**, 4 nM), H (**10**, 5.6 nM), CO_2Et (**7**, 12.2 nM), and CN (**9**, 332 nM) at that position. It is interesting to note that the removal of 5-CO_2H moiety of **8**, to give **10**, led to a 3-fold drop in potency while the vinylogous acid derivatives **36**, **39**, and **40** retained potency. The carbonitrile derivative **9** was the least active of all. Similar structure–activity relationships (SAR) were demonstrated with substituted pyrrole compounds. With 2,5-dimethylpyrrole the following relative order of potency was observed: R_1 = CO_2H (**20**, 0.82 nM) > CH=$CHCO_2H$ (**38**, 3.32 nM) > CHO (**29**, 13.7 nM) > CO_2Me (**19**, 20.9 nM) > CH=$CHCO_2Me$ (**37**, 21.6 nM) > CH_2OH (**30**, 24 nM) > CN (**33**, 188 nM). Comparison between ester and acid at R_1 indicated that the acids were consistently better bound than the corresponding esters. The potency differences between esters and acids were marginal (1–7-fold) with compounds in which X = H, 3-CO_2Et, and 2-$COCF_3$ groups. For examples, compare **5** vs **6**, **7** vs **8**, **16** vs **18**, **26** vs **27**, and **39** vs **40**. In contrast, with the exception of **37** and **38**, the potency differences became significant in the 2,5-disubstituted pyrrole series (compare **19** vs **20**, **21** vs **22**, **34** vs **35**, and **41** vs **42**). The reason for this discrepancy is not clear. One possible explanation could be variable amounts of enzyme-catalyzed ester hydrolysis under the assay conditions. In vitro AII receptor binding SAR for the imidazole 2-position shows R = nBu ≥ nPr > cPr. Replacement of the 1-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl] moiety with 1-[[[4-(1*H*-tetrazol-5-yl)-phenyl]-4-yl]methyl] produced significantly lower affinity compounds (data not shown).[1]

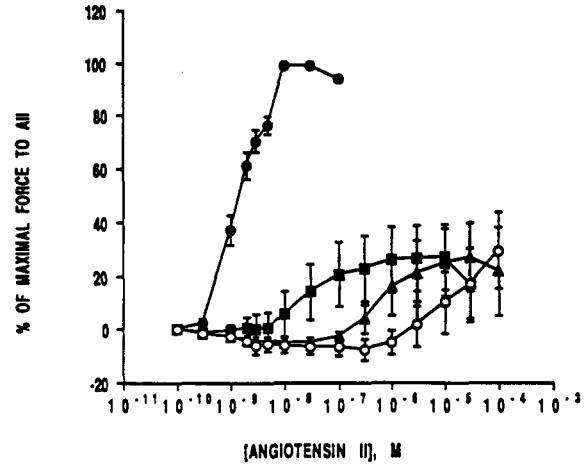


Figure 1. Effects of increasing concentrations of compound **18** on angiotensin II-induced contractile responses in rabbit aortic ring preparations. Maximal responses to angiotensin II in control tissues were 3.8 ± 0.2 g. Values represent the mean with SE bars (n = 4): ●, control; ■, 1 nM; ▲, 10 nM; ○, 100 nM.

Rabbit Aorta Functional Assay. Compounds were evaluated for antagonism of AII-induced contraction of rabbit aortic ring. This assay verified the results obtained in the receptor binding screen as well as tested the compound's ability to counteract the effects of AII in a physiologically relevant system. Although the relative order of activity for the two in vitro screens did not always agree, qualitatively the most potent compounds exhibited good activity in both assays. The data in Table II clearly demonstrates the importance of a carboxylic acid at the 5-position of the imidazole ring. The corresponding esters were significantly less potent. Hepatic metabolism of esters to acids in the rat liver membrane binding assay is believed responsible for the disparity between binding and functional potencies. The most potent compounds were **20** (2.4 nM), **31** (2.9 nM), **42** (3.3 nM), **18** (3.8 nM), **6** (4 nM), **22** (4.5 nM), **35** (4.8 nM), **8** (5.4 nM), and **1** (7 nM). Correlation between binding affinity and functional antagonism was seen for most of the compounds (a 2–10-fold difference was commonly observed) with few exceptions. For example, compound **10** (X = H) showed nanomolar potency in the binding assay whereas micromolar-range potency was observed in the functional assay. Although we do not have a good explanation for the discrepancy between the two assays, variations in tissue distribution, receptor subtype population, or species difference may account for some of the observed lack of correlation. The more potent compounds also demonstrated insurmountable antagonism in this assay.[37] Figure 1 shows data for compound **18**, which fits with the general observation of insurmountable antagonism associated with AII antagonists containing an imidazole-5-carboxylic acid moiety.

In Vivo Pharmacological Evaluation. Selected compounds listed in Table IV were evaluated for AII antagonism in vivo by determining their intravenous ED_{50} values for inhibition of the pressor response induced by infusion of AII in conscious, normotensive rats. The potency did not strictly follow the relative affinities determined in the binding assay. The most potent compound, **18**, gave ED_{50} = 6.23 μg/kg per min whereas the corresponding unsubstituted pyrrole analogue **8** gave an ED_{50} value of 27 μg/kg per min. In this assay compound **18** was twice as potent as compound **69**. Potent compounds were evaluated orally in the renal hypertensive rat (RHR) model (see Experi-

Table IV. Correlation of Rat Liver Binding, Rabbit Aorta Contraction, and in Vivo Profile of Selected Compounds

compd	IC_{50}, nM: rat liver binding[a]	IC_{50}, nM: rabbit aorta contraction[b]	in vivo, iv ED_{50}, (μg/kg per min)[c]	in vivo, oral % change in bp[d]
1	1.6	7.0	38	-27 ± 16
5	3.6	52	NT	-19 ± 8
6	2.4	4.0	NT	-16 ± 6
7	12	330	NT	-22 ± 5
8	1.7	5.4	27	-25 ± 4
16	3.6	73	36	-28 ± 4
18	0.58	3.8	6.23	-29 ± 10
19	21	150	NT	-8 ± 4
20	0.82	2.4	NT	-26 ± 2
22	0.9	4.5	NT	-6 ± 6
35	2.8	4.8	NT	-11 ± 4
38	3.3	21	16.4	-8 ± 1
39	2.8	>100	NT	-12 ± 3
68	5.0	89	75.9	-27 ± 6
69	1.6	1.8	13.6	-22 ± 1

[a] See Table I. [c] Dose that produces 50% inhibition of the pressor response to AII in conscious, normotensive rats (n = 3–4). A 15-min infusion was used. [d] Effect of compounds on mean arterial pressure after oral dosing at 10 mg/kg to renal, hypertensive rats. Data represent the mean ± SE (n = 5–6); NT = not tested.

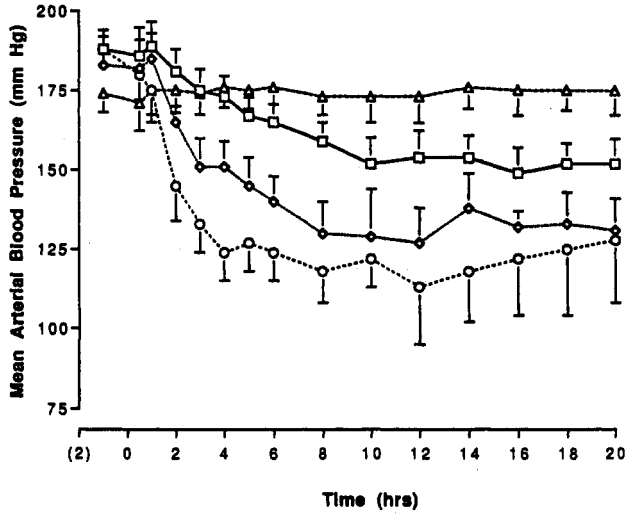


Figure 2. Effects of compound 18 on mean arterial blood pressure after oral dosing to renal hypertensive, conscious rats. Data shown as mean with SE bars (n = 5/6): □, 3 mg/kg; ◇, 10 mg/kg; ○, 30 mg/kg. △, vehicle (0.1% methocel, 2 mL/kg, n = 9).

mental Section for methods). As seen from Table IV, the antihypertensive potency of these compounds in vivo are very susceptible to substituent effects. In the 2-propylimidazole series, the potency of the ester/acid pair 7 and 8 (X = H) was comparable to the corresponding analogues 16 and 18 (X = 2-$COCF_3$), respectively. The 2-butylimidazole analogues 1, 5, and 6 behaved differently, however. Compound 1 retained the potency of the propyl compound 8 whereas 5 and 6 had decreased potency relative to 16 and 18. Compounds in which X = 2,5-dialkyls were not as effective as the corresponding hydrogen analogues in reducing the blood pressure. The relative order of potency was 8 (X = H) = 18 (X = 2-$COCF_3$) >20 (X = 2,5-Me_2) >22 (X = 2-Pr, 5-Me). Vinylogous compounds 38 and 39 were extremely weak in decreasing blood pressure in this model in spite of their excellent in vitro affinity for the receptor. Based on this initial profile, compound 18 was chosen for in depth studies. Figure 2 shows dose-related blood pressure lowering effect with this compound in RHR model. Following oral administration, compound 18 produced rapid reductions in blood pressure at doses ranging from 3 to 30 mg/kg. Maximum reductions in blood pressure were observed between 4 and 8 h postdose. Blood pressure remained decreased for greater than 24 h after a single oral dose; there was little or no return toward baseline at any of the doses examined. The highest dose of compound 18 tested, 30 mg/kg, normalized blood pressure in these renal hypertensive rats. Compound 18 also showed similar efficacy when evaluated orally in renal hypertensive monkeys.[1] Detailed pharmacological studies including primate evaluation will be reported elsewhere.

Compound 18, designated CI-996, is thus a potent, insurmountable, and orally active AII antagonist lacking agonist activity. On the basis of this profile, it has been selected for further studies as a clinical candidate for the treatment of hypertension.

Summary

This report describes a novel series of potent, nonpeptide receptor antagonists derived from 4-(1*H*-pyrrol-1-yl)-substituted imidazoles. The data presented here indicates that the 1*H*-pyrrol-1-yl moiety can successfully replace the chloro substituent at the 4-position of the imidazole with retention of activity. This unusual bioisosteric replacement has not been previously reported to our knowledge. In the in vitro binding assay using rat liver membrane preparation, several compounds in this series exhibited IC_{50} values in the range 0.3–10 nM. Structure–activity relationship data showed the R_1= CO_2R (R = H or Me) moiety to be optimal for receptor binding and functional response. A variety of substituents was introduced on the pyrrole ring with a small enhancement in binding leading to compounds 18, 20, 32, and 42 with subnanomolar potency. More importantly, the contributions of 2-substituents on the pyrrole moiety were, however, evident in stabilizing the compounds from decarboxylation at the 5-imidazole position. Upon intravenous administration in normotensive rats, compound 18 inhibited the AII-induced pressor response with an ED_{50} of 6 μg/kg per min. [ED_{50} (69) = 13.6 μg/kg]. Several compounds demonstrated good oral activity in the renal hypertensive rat model although correlations between the in vitro potency and oral antihypertensive efficacy were not very good. In this model compound 18 showed a dose-related (3–30 mg/kg) lowering of blood pressure; the effect (-28% at 10 mg/kg) was sustained for a period of at least 24 h. On the basis of its profile, compound 18, designated CI-996, has been selected for clinical evaluation.

Experimental Section

Melting points are uncorrected and were taken on a Thomas-Hoover capillary melting point apparatus. Each analytical sample was homogeneous by TLC performed on silica gel (60 F 254) plates, which were visualized with UV light or iodine vapor. Flash chromatography was performed on silica gel 60 (230–400 mesh). IR and ^1H NMR spectra of all new compounds were consistent with proposed structures. ^1H NMR spectra were obtained in DMSO-d_6 (unless otherwise stated) on a Bruker AM 250 instrument and are reported as values (ppm) downfield from Me_4Si. IR spectra were recorded on a Nicolet FTIR spectrophotometer with KBr disks. Mass spectra were recorded on a VG 7070 E/HR mass spectrometer with an 11/250 data system. Analytical HPLC experiments were performed using a Beckman Ultrasphere C_{18} column (4.6 mm × 25 cm) with a flow rate of 1.5 mL/min and detection either at 214 or 254 nm. Elemental analyses were obtained using a Control Equipment Corporation, Model 440 elemental analyzer.

Compound 67 was prepared by following literature methods.[6,26]

All operations were carried out at ambient temperature unless otherwise stated. Anhydrous $MgSO_4$ was used as a drying agent

and all evaporations were carried out at below 50 °C by using a rotary evaporator. All compounds were characterized via elemental analyses, and MS, IR, and 1H NMR spectral data. Most compounds retained solvents, even on drying under vacuum, which were quantitated from ^{1}H NMR spectra. Purity of the final compounds were assessed by HPLC. Yields were not optimized.

2-Butyl-4-(1*H*-pyrrol-1-yl)-1-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1*H*-imidazole-5-carbonitrile (2). A solution of **43** (1.7 g, 7.94 mmol) in THF (20 mL) was treated with a solution of KO^{t}Bu (0.97 g, 8.66 mmol) in dry THF (20 mL) and the mixture was stirred for 5 min. A solution of **67** (6.0 g) in dry THF (20 mL) was added and the reaction mixture was stirred under N_2 for 18 h. The resulting suspension was filtered and evaporated. The residue was purified by flash chromatography ($CHCl_3$/hexane, 90:10) to give **2** (5.8 g) in its trityl-protected form. The protecting group was removed by refluxing a methanolic (80 mL) solution of the above compound containing citric acid (10%, 5.2 mL) for 24 h. Evaporation gave a residue that was purified by chromatography eluting with a gradient of EtOAc/hexane (50:50) to EtOAc. Upon evaporation of solvents a gum was obtained that was redissolved in CH_2Cl_2 diluted with 2,2,4-trimethylpentane and evaporated to give **2** (2.8 g, 70%) as a solid: MS (FAB) *m/e* 470 (M + Na − 1), 448 (M); ^{1}H NMR ($CDCl_3$) 8.01 (d, 1 H), 7.55 (m, 2 H), 7.38 (m, 3 H), 7.18 (m, 4 H), 6.30 (t, 2 H), 5.19 (s, 2 H), 2.70 (t, 2 H), 1.73 (m, 2.5 H, part isooctane), 1.38 (m, 2 H), 1.11 (d, 1 H, isooctane), 0.90 (m, 10.5 H, part isooctane).

Compound 9 was prepared in a similar fashion.

2-Butyl-4-(1*H*-pyrrol-1-yl)-1-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1*H*-imidazole-5-carboxylic Acid (1). A mixture of **2** (1.4 g, 2.3 mmol) and 2 N NaOH (75 mL, 150 mmol) was heated at reflux for 24 h. The cooled solution was acidified to pH 3.5 by portionwise addition of citric acid. The solid was filtered and rinsed well with water. It was purified by C_{18} reverse-phase chromatography eluting with CH_3CN/H_2O (40:60). CH_3CN was evaporated from the pure fractions under reduced pressure, keeping the temperature below 30 °C. The remaining aqueous portion was extracted with EtOAc and the extract was dried and evaporated to a syrup that was dissolved in Et_2O, which itself was evaporated to give **1** (0.4 g, 37%) as a colorless powder: MS (FAB) *m/e* 468 (M + 1), 424 (M − CO_2 + 1); ^{1}H NMR ($CDCl_3$ and DMSO-d_6) 7.70 (d, 1 H), 7.58 (t, 1 H), 7.46 (m, 2 H), 7.28 (t, 1 H), 7.11 (d, 2 H), 6.98 (d, 2 H), 6.21 (t, 2 H), 5.60 (s, 2 H), 4.13 (q, 0.25 H, EtAc), 3.45 (q, 0.15 H, Et_2O), 2.64 (t, 2 H), 2.04 (s, 0.38 H, EtOAc), 1.68 (m, 2 H), 1.38 (m, 2 H), 1.20 (m, ~0.5 H, EtOAc, Et_2O), 0.89 (t, 3 H). Attempts to remove solvents by heating at 50 °C under vacuum gave rise to significant decarboxylation. HPLC (0.1% TFA/CH_3CN, 50/50; t_R 5.60 min). The only significant byproduct was identical to **3** below by HPLC (0.1% TFA/CH_3CN, 50/50; t_R 3.46 min).

Compound 8 was prepared in a similar fashion from **9**.

2-Butyl-4-(1*H*-pyrrol-1-yl)-1-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1*H*-imidazole (3). A suspension of **1** (50 mg) in toluene (10 mL) was heated under reflux for 1 h. Evaporation gave a gummy solid that was redissolved in Et_2O and evaporated again to give **3** as a white powder: MS (FAB) *m/e* 424 (M + 1); ^{1}H NMR ($CDCl_3$) 7.91 (d, 1 H), 7.65 (m, 2 H), 7.43 (d, 2 H), 7.16 (d, 2 H), 6.92 (d, 2 H), 6.84 (s, 2 H), 6.55 (s, 1 H), 6.13 (s, 2 H), 5.04 (s, 2 H), 2.43 (t, 2 H), 1.67 (m, 2 H), 1.32 (m, 2 H), 0.90 (t, 3 H).

2-Propyl-1-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]-methyl]-4-[2-(trifluoroacetyl)-1*H*-pyrrol-1-yl]-1*H*-imidazole-5-carbonitrile (11). A suspension of **48** (0.89 g, 3 mmol), **67** (2.1 g, 3 mmol), and anhydrous K_2CO_3 (0.5 g, 3.6 mmol) in DMF (10 mL) was stirred at room temperature under N_2 for 24 h. EtOAc (50 mL) was added, and inorganic solids were removed by filtration. The filtrate was evaporated under reduced pressure and the major product was isolated by flash chromatography (toluene/CH_3CN, 96:4) to afford 1.3 g of **11** in its trityl-protected form. It was dissolved in CH_3OH (50 mL), treated with aqueous 10% citric acid (1.5 mL), and heated at reflux for 90 min. After cooling to room temperature, water (10 mL) and hexane (100 mL) were added, and the mixture was shaken vigorously. The methanol layer was separated, washed again with hexane, and evaporated. The residue was diluted with water and extracted with EtOAc. The EtOAc layer was dried and evaporated and the residue was crystallized from ^{t}BuOMe/^{i}Pr$_2$O to give 0.65 g (41% from **48**) of **11**: MS (CI) *m/e* 531 (M + 1); ^{1}H NMR 7.85 (m, 1 H), 7.70 (m, 2 H), 7.58 (m, 2 H), 7.17 (s, 4 H), 6.66 (m, 1 H), 5.46 (s, 2 H), 3.58 (m, 0.5 H, ^{i}Pr$_2$O), 2.70 (t, 2 H), 1.58 (m, 2 H), 1.03 (d, 3 H, ^{i}Pr$_2$O), 0.87 (t, 3 H).

1-[5-Cyano-2-propyl-1-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1*H*-imidazol-4-yl]-1*H*-pyrrole-2-carboxylic Acid (14) and 1-[5-(aminocarbonyl)-2-propyl-1-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1*H*-imidazol-4-yl]-1*H*-pyrrole-2-carboxylic Acid (15). In a manner analogous to that used to prepare **11**, compound **49** was reacted with **67** and detritylated to give **13**. A solution of compound **13** (0.54 g, 1.09 mmol) in THF/MeOH (2:1, 30 mL) was treated with 0.2 N NaOH (11 mL, 2.2 mmol) and the solution was heated at reflux for 20 h. The reaction mixture was cooled to room temperature and acidified with 1 N HCl (2.2 mL, 2.2 mmol). It was partitioned between EtOAc and brine. The organic layer was separated, dried, and stripped to give a semisolid residue. It was triturated with ^{i}Pr$_2$O and filtered. HPLC showed two products, which were separated by reverse-phase flash chromatography (H_2O/CH_3CN 80:20–60:40 gradient). The fast-eluting component was identified as **15** (40 mg, 30%): MS (FAB) *m/e* 497 (M + 1). ^{1}H NMR ($CDCl_3$) 7.78 (d, 1 H), 7.56 (t, 1 H), 7.46 (d,1 H), 7.40 (t, 1 H), 6.97 (m, 6 H), 6.23 (t, 1 H), 5.85 (br, 2 H), 5.49 (s, 2 H), 3.70 (br, 2.6 H, H_2O), 2.62 (t, 2 H), 1.69 (m, 2 H), 1.42 (s, 4.8 H, c-hexane), 0.92 (t, 3 H). HPLC (0.1% TFA/CH_3CN 50:50; 98.2%, t_R 3 min). The slow-eluting component, **14** (0.225 g, 68%), was 98.6% pure by HPLC (0.1% TFA/CH_3CN 50:50; t_R 7 min): MS (FAB) *m/e* 479 (M + 1); ^{1}H NMR ($CDCl_3$) 7.96 (d, 1 H), 7.50 (m, 2 H), 7.39 (d, 1 H), 7.18 (m, 5 H), 7.14 (m, 1 H), 6.28 (m, 1 H), 5.75–6.75 (br, H_2O), 5.22 (s, 2 H), 2.78 (t, 2 H), 1.78 (m, 2 H), 1.42 (s, 1.2 H, c-hexane), 1.01 (t, 3 H).

Methyl 2-Propyl-1-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-4-[2-(trifluoroacetyl)-1*H*-pyrrol-1-yl]-1*H*-imidazole-5-carboxylate (16). Cs_2CO_3 (32.9 g, 0.1 mol) was added to a solution of **52** (15 g, 0.046 mol) in DMF (500 mL). After 5 min, compound **67** (26.9 g, 0.048 mol) was added and the reaction mixture stirred for 6 h. It was filtered to remove inorganics and the DMF was distilled under high vacuum. The residue was partitioned between EtOAc (150 mL) and water (50 mL). The organic layer was extracted with brine, dried, and evaporated, and the residue was chromatographed eluting with a gradient of EtOAc/hexane (1:4) to EtOAc/hexane (1:1) to afford 25 g (67%) of the N_1-isomer in its trityl-protected form: MS (FAB) *m/e* 807 (M + 1); ^{1}H NMR 5.7 (s, 2 H, NCH_2). Differential ^{1}H NMR NOE experiments showed NOE's between N_1CH_2 protons and the protons at the close proximity, namely, 5-CO_2CH_3 and 2-CH_2-CH_2CH_3 protons. Further elution with EtOAc gave 6.2 g of the corresponding N_3-isomer, methyl 2-propyl-1-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl-4-[2-(trifluoroacetyl)-1*H*-pyrrol-1-yl]-1*H*-imidazole-4-carboxylate, in its trityl-protected form: MS (FAB) *m/e* 807 (M + 1); ^{1}H NMR 5.2 (s, 2 H, NCH_2).

The protecting group was removed by refluxing a solution of the above higher R_f compound in methanol (280 mL) containing 10% aqueous citric acid (28 mL) for 4 h. The reaction mixture was diluted with water (100 mL) and the milky solution extracted several times with hexane. The aqueous layer was extracted with EtOAc, the extract was washed with brine and dried, and the solvent was removed. The residue was recrystallized using hexane/EtOAc (1:1) to afford 13.4 g (52% from **52**) of the title compound: MS (FAB) *m/e* 564 (M + 1); ^{1}H NMR 7.67 (m, 3H), 7.56 (t, 2 H), 7.45 (t, 1 H), 7.18 (q, 4 H), 6.53 (q, 1 H), 5.69 (s, 2 H), 3.43 (s, 3 H), 2.58 (t, 2 H), 1.57 (m, 2 H), 0.85 (t, 3 H).

Compounds 4, 5, 7, 10, 19, 21, 23, 26, 29, 34, 41 were prepared in similar fashion.

2-Propyl-1-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]-methyl]-4-[2-(trifluoroacetyl)-1*H*-pyrrol-1-yl]-1*H*-imidazole-5-carboxylic Acid (18). K_2CO_3 (4.0 g) was added to a solution of **16** (2.55 g, 4.4 mmol) in DMF (15 mL) and water (0.5 mL) and the reaction mixture stirred for 48 h (TLC at this time showed complete reaction). The insoluble materials were filtered and washed with DMF. A 10% citric acid solution (100 mL) was added slowly to the filtrate and the resulting mixture extracted with EtOAc/hexane (2:1). The organic layer was washed with water, dried, and evaporated, and the residual oil was dissolved in a few milliliters of benzene to induce crystallization, affording 2.6 g of (98%) of **18**: MS (FAB) *m/e* 550.3 (M + 1); ^{1}H NMR 7.67

(m, 3 H), 7.57 (t, 2 H), 7.37 (s, 3 H, benzene), 7.08 (q, 4 H), 6.53 (q, 1 H), 5.69 (s, 2 H), 2.58 (t, 2 H), 1.57 (m, 2 H), 0.85 (t, 3 H).

Compounds 6, 20, 22, 24, 25, 27, 28, 32, 35, 42 were prepared in an analogous manner.

4-[2,5-Dichloro-1*H*-pyrrol-1-yl]-2-propyl-1-[[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl] methyl]-1*H*-imidazole-5-carboxylic Acid (42). A solution of **41** (0.18 g, 0.37 mmol) and LiOH (0.14 g, 3.7 mmol) in a mixture of 2:1 THF/H_2O (7.5 mL) was stirred overnight at room temperature under N_2. The solution was diluted with water and extracted with ether. The aqueous solution was acidified to pH 2 and extracted with ether. The extract was dried, evaporated, and flash chromatographed ($CHCl_3$/MeOH 4:1) to yield 0.17 g of a white foam: MS (FAB) *m/e* 522.1 (M); ^{1}H NMR 7.85–7.45 (m, 4 H), 7.25–7.05 (d, 2 H), 7.05–6.85 (d, 2 H), 6.27 (s, 2 H), 5.69 (s, 2 H), 3.35 (m, H_2O and CH_2 from EtOAc), 2.61 (t, 2 H), 12.08 (s, 1 H, from EtOAc), 0.62 (t, 2 H), 1.15 (t, ~1 H, from EtOAc), 0.85 (t, 2 H). HPLC (94.2%; 0.1% TFA/CH_3CN, 45/55; t_R 4.81 min).

Compounds 27 and 40 were prepared in an analogous manner.

4-(2-Carboxy-1*H*-pyrrol-1-yl)-2-propyl-1-[[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1*H*-imidazole-5-carboxylic Acid (17). A solution of **16** (0.8 g, 1.42 mmol) was dissolved in an aqueous solution of NaOH (1.68 g, 42 mmol) in 14 mL of H_2O and the resulting solution refluxed overnight. After cooling in an ice bath, the pH of the solution was adjusted to 4 with concentrated HCl. The precipitate was filtered, washed several times with water, and dried under high vacuum for 18 h to afford 0.6 g (85%) of **17**: MS (FAB) *m/e* 498 (M + 1); ^{1}H NMR 7.82–7.56 (m, 4 H), 7.18–7.10 (m, 1 H), 7.10–6.95 (m, 4 H), 6.92–6.82 (m, 1 H), 6.35 (m, 1 H), 5.72 (s, 2 H), 2.61 (t, 2 H), 1.71–1.48 (m, 2 H), 0.91 (t, 3 H).

Compounds 25 and 28 were analogously prepared.

4-[2-(1-Hydroxy-2,2,2-trifluoroethyl)-1*H*-pyrrol-1-yl]-2-propyl-1-[[2'-(1*H*-tetrazol-5 yl)[1,1'-biphenyl]-4-yl]methyl]-1*H*-imidazole-5-carboxylic Acid (31). $NaBH_4$ (0.11 g, 2.9 mmol) was added to a solution of **18** (0.27 g, 0.5 mmol) in methanol (15 mL) and the reaction was stirred for 6 h. Acetone (2 mL) was added and the reaction was stirred for 10 min. The solvent was evaporated, the residue dissolved in water and the aqueous solution was acidified with 10% citric acid. The precipitate was filtered and the residue washed with a small volume of ether and dried to give 0.19 g (67%) of **31**: MS (FAB) *m/e* 574 (M + Na), 552 (M + 1), 534 (M – OH); ^{1}H NMR ($CDCl_3$) 7.79–7.35 (m, 4 H), 7.35–6.92 (m, 5 H), 6.43 (t, 1 H), 6.18 (t, 1 H), 5.66 [dd, 2 H (s, 2 H, in DMSO-d_6)], 5.04 (q, 1 H), 3.45 (q, ~2 H, Et_2O), 2.62 (t, 2 H), 1.91–1.63 (m, 2 H), 1.18 (t, 3 H, Et_2O), 0.90 (t, 3 H).

Compound 12 was similarly prepared.

4-(2,5-Dimethyl-1*H*-pyrrol-1-yl)-2-propyl-1-[[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1*H*-imidazole-5-carboxaldehyde (29). The following compounds were prepared starting from **56** (4.0 g, 17.4 mmol) by following methodology similar to that for compound **16**. The crude product was separated by flash chromatography (hexane/EtOAc, 3:1) to give N_1- and N_3-regioisomers.

High R_f regioisomer, 4-(2,5-dimethyl-1*H*-pyrrol-1-yl)-2-propyl-1-[[2'-[1-(triphenylmethyl)-1*H*-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1*H*-imidazole-5-carboxaldehyde (oil, 5.62 g): MS (FAB) *m/e* 708 (M + 1); ^{1}H NMR 5.62 (s, 2 H, NCH_2). Anal. Calcd for $C_{46}H_{41}N_7O$: C, 78.05; H, 5.84; N, 13.85. Found: C, 77.64; H, 5.65; N, 3.65.

Low R_f regioisomer, 5-(2,5-dimethyl-1*H*-pyrrol-1-yl)-2-propyl-1-[[2'-[1-(triphenylmethyl)-1*H*-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1*H*-imidazole-4-carboxaldehyde (oil, 0.8 g): MS (FAB) *m/e* 708 (M + 1); ^{1}H NMR 4.83 (s, 2 H, NCH_2). Anal. Calcd for $C_{46}H_{41}N_7O$; C, 78.05; H, 5.84; N, 13.85. Found; C, 77.89; H, 5.77; N, 13.84.

A solution of the high R_f isomer (1.0 g) in CH_3OH (100 mL) and 10% aqueous citric acid (20 mL) was heated at reflux for 30 min. The reaction mixture was cooled, diluted with 20 mL of water, and extracted with hexane. The aqueous layer was concentrated to 50 mL, diluted with water, and extracted with EtOAc. The EtOAc layer was washed with water, dried, stripped, and chromatographed (EtOAc/hexane, 50:50–90:10) to give **29**: MS (FAB) *m/e* 466 (M + 1); ^{1}H NMR 9.98 (s, 1 H), 7.72 (m, 2 H), 7.61 (t, 2 H), 7.13 (m, 2 H), 7.06 (t, 2 H), 5.78 (s, 2 H), 5.38 (s, 2 H), 3.32 (br, H_2O), 2.46 (t, 2 H), 1.95 (s, 6 H), 1.55 (m, 2 H), 0.87 (t, 2 H).

4-(2,5-Dimethyl-1*H*-pyrrol-1-yl)-2-propyl-1-[[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1*H*-imidazole-5-methanol (30). To a solution of **19** in its trityl-protected form, methyl 4-(2,5-dimethyl-1*H*-pyrrol-1-yl)-2-propyl-1-[[2'-(1-triphenylmethyl)-1*H*-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1*H*-imidazole-5-carboxylate (1.0 g, 1.36 mmol), in THF (12 mL) was added dropwise a solution of $LiAlH_4$ in ether (1 M, 1.5 mL). The reaction mixture was stirred overnight then quenched with aqueous saturated $(NH_4)_2SO_4$. The resulting suspension was filtered and the insoluble material washed with hot EtOAc. The EtOAc layer was separated and the aqueous layer extracted with additional EtOAc. The combined organic layer was washed with brine, dried, and evaporated and the crude product was purified by flash chromatography (CH_2Cl_2/acetone, 5%) to afford 0.4 g of **30** in its trityl-protected form: mp 185–186 °C; MS (FAB) *m/e* 710 (M + 1). Anal. Calcd for $C_{46}H_{43}N_7O$: C, 77.83; H, 6.11; N, 13.81. Found: C, 77.43; H, 6.02; N, 13.50. The trityl group was removed by heating a solution of the above in MeOH/citric acid mixture to give compound **30** (0.16 g, 59%) as a foam: MS (FAB) *m/e* 468 (M + 1), 450 (M – OH); ^{1}H NMR 7.72 (m, 2 H), 7.61 (t, 2 H), 7.13 (m, 2 H), 7.06 (t 2 H), 5.78 (s, 2 H), 5.38 (s, 2 H), 5.21 (br, 1H), 4.08 (s, 2 H), 3.38 (q, ~0.4 H, Et_2O), 2.46 (t, 2 H), 1.95 (s, 6 H), 1.55 (m, 2 H), 1.12 (t, ~0.6 H, Et_2O), 0.87 (t, 2 H).

Methyl (E)-3-[4-(2,5-Dimethyl-1*H*-pyrrol-1-yl)-2-propyl-1-[[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1*H*-imidazol-5-yl]-2-propenoate (37). A solution of **29** in its trityl form (the high R_f isomer from experiment **29**, 5 g, 10.7 mmol) and (carbomethoxymethylene)triphenylphosphorane (13 g, 38.9 mmol) in toluene (50 mL) was heated at reflux for 30 min. The reaction mixture was cooled, filtered and the filtrate was evaporated. Purification of the residue by flash chromatography (hexane/EtOAc, 2:1) gave **37** in its trityl-protected form (2.7 g) as an oil: MS (FAB) *m/e* 764 (M + 1). Anal. Calcd for $C_{49}H_{45}N_7O_2$: C, 77.04; H, 5.94; N, 12.83. Found: C, 77.02; H, 5.76; N, 12.70. A solution of this compound (1.0 g) in CH_3OH (100 mL) and 10% aqueous citric acid (20 mL) was heated at reflux for 30 min. The reaction mixture was cooled, diluted with 20 mL water, and extracted with hexane. The aqueous layer was concentrated to 50 mL, diluted with water, and filtered. The residue was washed with water, air-dried, and recrystallized from isopropyl ether to give **37** (0.49 g, 24%): MS (FAB) *m/e* 522 (M + 1); ^{1}H NMR 7.65 (d, 2 H), 7.60 (t, 2 H), 7.37 (d, J = 15 Hz, 2 H), 7.16 (d, 2 H), 6.96 (d, 2 H), 5.92 (s, 2 H), 5.53 (s, 2 H), 4.90 (d, *J* = 15 Hz, 1 H), 3.62 (s, 3 H), 3.32 (br, H_2O), 2.73 (t, 2 H), 1.92 (s, 6 H), 1.65 (m, 2 H), 0.90 (t, 2 H).

Compound 39 was prepared in a manner analogous to that used for **37** starting from **58**.

Ethyl (*E*)-3-[2-propyl-5-(1*H*-pyrrol-1-yl)-1-[[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1*H*-imidazol-4-yl]-2-methyl-2-propenoate (39a) was obtained in a manner analogous to that used to prepare **11** in two steps from **66**: MS (EI) *m/e* 521 (M); ^{1}H NMR ($CDCl_3$) 4.89 (s, 2H, NCH_2). Anal. Calcd for $C_{30}H_{31}N_7O_2$: C, 69.08; H, 5.99; N, 18.80. Found: C, 68.37; H, 5.93; N, 18.84.

Methyl (*E*)-3-[5-(2,5-Dimethyl-1*H*-pyrrol-1-yl)-2-propyl-1-[[2'-[1-(triphenylmethyl)-1*H*-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1*H*-imidazole-4-yl]-2-propenoate (37a). This trityl-protected derivative was prepared in a manner analogous to that of **39a** from **65**. MS (FAB) *m/e* 764 (M + 1); ^{1}H NMR 4.81 (s, 2H, NCH_2).

(*E*)-3-[4-(2,5-Dimethyl-1*H*-pyrrol-1-yl)-2-propyl-1-[[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1*H*-imidazol-5-yl]-2-propenoic Acid (38). A solution of **37** (1.55 g, 3 mmol) and potassium trimethylsilanoate (0.96 g, 7.5 mmol) in dry THF (80 mL) was stirred for 3 h under N_2. The resulting precipitate was filtered; the residue was air-dried and then dissolved in water (50 mL). The free acid was precipitated by the addition of 1 N HCl and collected by filtration. It was washed with water and air-dried to give the desired acid **38** (1.3 g, 83%): MS (FAB) *m/e* 508 (M + 1); ^{1}H NMR 7.68 (d, 2 H), 7.62 (d, 2 H), 7.37 (d, *J* = 15 Hz, 2 H), 7.16 (d, 2 H), 7.01 (d, 2 H), 5.92 (s, 2 H), 5.45 (s, 2 H), 5.01 (d, *J* = 15 Hz, 1 H), 4.89 (br, H_2O), 2.78 (t, 2 H), 1.96 (s, 6 H), 1.65 (m, 2 H), 0.90 (t, 2 H).

Compounds 20, 24, and 35 were prepared in similar fashion from the corresponding methyl esters.

2-Alkyl-4-(1*H*-pyrrol-1-yl)-1*H*-imidazole-5-carboxylates and Related Compounds (Table III, Schemes V and VI) from 2-alkyl-4-amino-1*H*-imidazole intermediates (Scheme VII). Methyl 4-amino-2-propyl-1*H*-imidazole-5-carboxylate (Scheme VII, Method C). Hydrogen chloride gas was bubbled through an ether (500 mL) solution of butyronitrile (275.4 g) and methanol (160 g) for a period of 3 h. The temperature during the addition rose from −4 to 4 °C, and the reaction mixture was stirred at 0 °C for 1 h and then stored at −25 °C for 16 h. The resulting suspension was stirred at −10 °C and ether (1.8 L) added over a period of 40 min and stirred for an additional hour at 0 °C. It was filtered under N_2, the residue was washed with ether and dried to afford 280 g of methyl butyrimidate hydrochloride. The filtrate was cooled to 5 °C for 30 min and filtered, and the residue was washed with ether to afford an additional 42 g of title product: mp 80–81 °C; MS (EI) *m/e* 102 (M + 1). The butyrimidate salt (322 g, 2.34 mol) was dissolved in a 50% aqueous solution of NH_2CN (236 g, 2.81 mol) and cooled in an ice bath. Na_2HPO_4 (164 g, 1.15 mol) was added over a period of 1 h. The resulting suspension was stirred at room temperature for 2 h and the liquid decanted from the reaction mixture. The remaining solid was diluted with water (2 L) and extracted with ether (3 × 600 mL). The combined organic layers were washed with water, dried, and evaporated under reduced pressure. The residue was distilled under high vacuum (bp 85–90 °C/5 mmHg) to afford 258 g of methyl *N*-cyanobutyrimidate: MS (EI) *m/e* 127 (M + 1).

Et_3N (211 g, 2.09 mol) was added to an ice-cold methanolic solution (1.5 L) of the above imidate (240 g, 1.90 mol) and methyl glycinate hydrochloride (250 g, 1.99 mol) over a period of 15 min. The resulting solution was stirred at 20 °C for 17 h and then concentrated under reduced pressure to an oily–solid residue (690 g). The residue was taken up in EtOAc, and the insoluble salts were removed by filtration. The filtrate was washed with water followed by 10% aqueous NaCl solution. The organic layer was dried and evaporated to dryness to give the product methyl *N*-(*N'*-cyanobutyrimidoyl)glycinate (370 g) which was used in the next step without further purification.

A solution of the glycinate derivative (344 g, 1.9 mol) in methanol (600 mL) was added to a solution of NaOMe (108 g, 2.0 mol) in MeOH (1 L) at 0 °C over a period of 30 min. The resulting orange solution was allowed to warm to room temperature over a period of 1 h and then refluxed for 1 h. The dark solution was evaporated to dryness under reduced pressure and the residue was partitioned between water and EtOAc. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried, and evaporated. The residue was recrystallized from EtOAc to afford 131 g (38% yield) of methyl 4-amino-2-propyl-1*H*-imidazole-5-carboxylate: mp 133–136 °C; MS (EI) *m/e* 184 (M + 1).

4-Amino-5-benzoyl-2-propyl-1*H*-imidazole was obtained in a similar fashion by replacing methyl glycinate hydrochloride with 2-aminoacetophenone hydrochloride in the above reaction sequence.

Methyl 2-Propyl-4-(1*H*-pyrrol-1-yl)-1*H*-imidazole-5-carboxylate (51, Scheme V). 2,5-Dimethoxytetrahydrofuran (117 g, 0.885 mol) was added to a mixture of the above amine (145 g, 0.798 mol) and NaOAc (388 g, 4.73 mol) in HOAc (1.5 L) at 80 °C with stirring. The resulting dark solution was refluxed for 20 min, cooled, and poured onto ice. The gummy mixture was extracted with CH_2Cl_2, and the combined organic layers were washed with water, dried, and concentrated to give a dark solid. The residue was dissolved in CH_2Cl_2 (2 L) and the solution was filtered through a bed of silica gel (300 g), eluting with CH_2Cl_2. The filtrate was evaporated to dryness and the crude product recrystallized from ether/hexane (2:1) to provide **51** (86 g, 46%). MS (EI) *m/e* 234 (M + 1). ^{1}H NMR ($CDCl_3$) 10.07 (br, 1 H), 7.40 (t, 2 H), 6.34 (t, 2 H), 3.75 (s, 3 H), 2.68 (t, 2 H), 1.78 (m, 2 H), 0.99 (t, 3 H).

5-Amino-2-propyl-1*H*-imidazole-4-carbonitrile (Scheme VII, Method B). A mixture of KOAc (8.8 g, 90 mmol), aminomalononitrile p-toluenesulfonate (22.8 g, 90 mmol), trimethyl orthobutyrate (25 g, 169 mmol) in anhydrous CH_3OH (90 mL) was stirred at room temperature under N_2 for 18 h. Solids were removed by filtration, and the residue was rinsed with CH_3OH. The combined filtrate and washings were evaporated at reduced pressure and the residual gum was treated with saturated methanolic ammonia (250 mL) at room temperature. A mildly exothermic reaction ensued and after 1.5 h the solution was evaporated. The residue was partitioned between 10% K_2CO_3 (200 mL), saturated NaCl (50 mL), and EtOAc (250 mL). The aqueous layer was washed three times with EtOAc (250 mL each), and the combined EtOAc layers were dried over a mixture of $MgSO_4$ and activated charcoal, filtered, and evaporated. Filtration through a bed of silica gel eluting with EtOAc/hexane (60:40 to 90:10) removed colored impurities. After evaporation of the solvents, the purified product was taken up in $CHCl_3$ with gentle warming (~40 °C) and evaporated to give the title compound as a tan solid (10.8 g, 80%): mp 117–119 C; ^{1}H NMR ($CDCl_3$ and DMSO-d_6) 9.05 (br, 1H), 6.54–7.23 (br, 2H), 2.50 (t, 2H), 1.67 (m, 2H), 0.93 (t, 3H).

2-Propyl-5-(1*H*-pyrrol-1-yl)-1*H*-imidazole-4-carbonitrile (47, Scheme V). The above aminoimidazole (10 g, 66.7 mmol) was dissolved in HOAc (70 mL), treated with KOAc (20 g, 204 mmol), and heated to reflux. 2,5-Dimethoxytetrahydrofuran (10.3 mL, 79.5 mmol) was added as rapidly as possible and the reaction was held at reflux for 1 min further before cooling in an ice bath. The resulting solution was concentrated at 0.5 mmHg and the residual gum was partitioned between EtOAc (400 mL) and 10% K_2CO_3 (400 mL). The organic layer was dried and evaporated. Flash chromatography (EtOAc/hexane 10–30% gradient) gave pure product (11.7 g, 88%) upon evaporation of solvents and drying at 0.5 mmHg at room temperature overnight: mp 75–78C; ^{1}H NMR ($CDCl_3$) 10.07 (br, 1 H), 7.40 (t, 2 H), 6.34 (t, 2 H), 2.68 (t, 2 H), 2.20 (s, ~0.1 H, EtOAc), 1.78 (m, 2 H), 0.99 (t, 3 H); MS (EI) *m/e* 201 (M + 1), 200 (M), 172 (m − C_2H_4).

5-Amino-2-butyl-1*H*-imidazole-4-carbonitrile (Scheme VII, Method A). A mixture of the butyrimidate salt (1.5 g, 10 mmol), aminomalononitrile p-toluenesulfonate salt (2.5 g, 10 mmol) and anhydrous NaOAc (2.46 g, 30 mmol) in absolute EtOH (15 mL) was stirred at 23 °C for 6 h. The reaction mixture was filtered and the filtrate was evaporated to dryness. The residue was triturated with EtOAc to give a solid which was filtered off. The filtrate was evaporated to dryness and the residue flash chromatographed (CH_2Cl_2/MeOH, 5%) to give 0.6 g (36%) of the desired product: mp 115–116 °C; ^{1}H NMR ($CDCl_3$) 9.05 (br, 1 H), 4.24 (br, 2 H), 2.60 (t, 2 H), 1.67 (m, 2 H), 1.33 (m, 2 H), 0.93 (t, 3 H).

This was converted to **43** in a manner analogous to that of **47**.

Methyl 2-Propyl-5-[2-(trifluoroacetyl)-1*H*-pyrrol-1-yl]-1*H*-imidazole-4-carboxylate (52). Trifluoroacetic anhydride (46.61 mL, 0.33 mol) was added to a stirred solution of **51** (26 g, 0.11 mol) in CH_2Cl_2 (500 mL) at room temperature and the resulting solution was stirred for 18 h. The reaction mixture was cooled to 5 °C and a saturated aqueous solution of $NaHCO_3$ (100 mL) was added slowly and the mixture stirred for 10 min. The organic layer was separated, washed with additional $NaHCO_3$ solution, dried, and evaporated to dryness. The residue was triturated with ether to afford the product, which was collected by filtration (23 g, 62%): MS (EI) *m/e* 329 (M^+); ^{1}H NMR ($CDCl_3$) 9.07 (br, 1 H), 7.40 (t, 1 H), 7.52 (d, 1 H), 6.45 (t, 1 H), 3.76 (s, 3 H), 2.68 (t, 2 H), 1.78 (m, 2 H), 0.99 (t, 3 H).

Methyl 5-(2,5-Dimethyl-1*H*-pyrrol-1-yl)-2-propyl-1*H*-imidazole-4-carboxylate (53). A solution of the above amino compound (4 g, 21.83 mmol) and hexane-2,5-dione (2.5 g, 21.85 mM) in a mixture of EtOH/AcOH (10 mL each) was heated under reflux for 6 h. The residue was triturated with a small volume of hexane/ether to give a solid which was filtered and washed with hexane and dried to give 4 g (70%) of **52**: MS (EI) *m/e* 261 (M); ^{1}H NMR ($CDCl_3$) 10.07 (br, 1 H), 5.90 (s, 2 H), 3.76 (s, 3 H), 2.75 (t, 2 H), 2.03 (s, 6 H), 1.90–1.70 (m, 2 H), 0.98 (t, 3 H).

5-(2,5-Dimethyl-1*H*-pyrrol-1-yl)-2-propyl-1*H*-imidazole-4-carboxaldehyde (56). A solution of $LiAlH_4$ (1 M, 2.1 mL, 7.7 mmol) was added dropwise to a solution of **53** (0.5 g, 1.91 mmol) in THF (15 mL) at room temperature. The reaction mixture stirred for 18 h and quenched by the addition of saturated aqueous $(NH_4)_2SO_4$. The suspension was filtered and the residue washed thoroughly with EtOAc. The combined organic solutions were dried and evaporated to give 5-(2,5-dimethyl-1*H*-pyrrol-1-yl)-2-propyl-1H-imidazole-4-methanol (**55**, 0.2 g, 45%), which was used without purification in the next step: MS (EI) *m/e* 233 (M + 1); ^{1}H NMR 12.05 (br, 1 H), 5.68 (s, 2 H), 5.02 (t, 1 H), 4.12 (d, 2 H), 2.55 (t, 2 H), 1.95 (s, 6 H), 1.65 (m, 2 H), 0.88 (t, 3 H).

Active MnO_2 (11.2 g, 0.13 mol) was added to a solution of **55** (6.0 g, 26 mmol) in dry THF (125 mL) and the reaction mixture refluxed for 4 h under N_2. It was cooled and filtered through Celite and the resulting filtrate evaporated to give a solid. Purification by flash chromatography (hexane/EtOAc, 2:1) gave 4.5 g (75%) of the aldehyde **56**. MS (CI) *m/e* 231 (M); ^{1}H NMR 12.05 (br, 1 H), 9.95 (s, 1 H), 5.68 (s, 2 H), 2.55 (t, 2 H), 1.95 (s, 6 H), 1.65 (m, 2 H), 0.88 (t, 3 H).

Methyl 5-[3-(Methoxycarbonyl)-2-methyl-1*H*-pyrrol-1-yl]-2-propyl-1*H*-imidazole-4-carboxylate (60). This compound was prepared in a manner analogous to that of **51** from methyl 5-amino-2-propyl-1*H*-imidazole-4-carboxylate and methyl 5-(acetyloxy)-2-methyl-4,5-dihydrofuran-3-carboxylate:[29] MS (CI) *m/e* 305 (M); ^{1}H NMR ($CDCl_3$) 10.07 (br, 1 H), 6.68 (d, 1 H), 6.61 (d, 1 H), 3.83 (s, 3 H), 3.76 (s, 3 H), 2.75 (t, 2 H), 2.40 (s, 3 H), 1.90–1.70 (m, 2 H), 0.98 (t, 3 H).

Methyl 5-(2-Formyl-1*H*-pyrrol-1-yl)-2-propyl-1*H*-imidazole-4-carboxylate (62). A solution of DMF (2 mL) in CH_2Cl_2 (5 mL) was added dropwise with stirring to a solution of oxalyl chloride (0.55 mL, 6.3 mmol) in CH_2Cl_2 (45 mL) at −30 °C. The reaction mixture was stirred for an additional 15 min followed by the addition of a solution of **51** (1.4 g, 6 mmol) in DMF (8 mL). It was stirred for 2.5 h at that temperature and gradually warmed to the ambient temperature. The solvent was removed under high vacuum and the residue was partitioned between a 0.2 M solution of NaOAc and EtOAc. The organic layer was separated and the aqueous solution was extracted with EtOAc. The combined organic extract was washed with brine, dried, and evaporated to give 1.44 g (92%) of **62**: MS (CI) *m/e* 261 (M); ^{1}H NMR ($CDCl_3$) 9.52 (s, 1 H), 7.42–7.18 (m, 2 H), 6.65 (m, 1 H), 3.65 (s, 3 H); 2.65 (t, 2 H), 1.93–1.65 (m, 2 H), 0.95 (t, 3 H).

Ethyl 5-(2,5-Dichloro-1*H*-pyrrol-1-yl)-2-propyl-1*H*-imidazole-4-carboxylate (63). *N*-Chlorosuccinimide (1.08 g, 8.09 mmol) was added to a solution of **61** (1.0 g, 4.05 mmol) in THF (20 mL) at 0 °C. The reaction mixture was allowed to warm to the ambient temperature and stirred for 18 h. The solvent was evaporated, the residue treated with ether and filtered. The filtrate was evaporated and the residue chromatographed (CH_2Cl_2/EtOAc, 8:2) to give **63** (0.92 g, 72%) as a white solid. MS (CI) *m/e* 316 (M); ^{1}H NMR ($CDCl_3$) 10.07 (br, 1 H), 6.13 (s, 2 H), 4.16 (q, 2 H), 2.75 (t, 2 H), 1.90–1.70 (m, 2 H), 1.12 (t, 3 H), 0.98 (t, 3 H).

Methyl (*E*)-3-[5-(2,5-Dimethyl-1*H*-pyrrol-1-yl)-2-propyl-1*H*-imidazol-4-yl]-2-propenoate (65, Scheme IV). A solution of **56** (0.3 g, 1.3 mM) and (carbomethoxymethylene)triphenylphosphorane (0.87 g, 2.6 mM) in toluene (50 mL) was heated under reflux for 6 h. Toluene was evaporated and the solution was chromatographed (EtOAc/hexane, 1:1) to give cis- and trans-isomers. Cis-isomer (0.1 g, 27%): MS (EI) *m/e* 287 (M); ^{1}H NMR 12.25 (br, 1 H), 6.26 (d, 1 H, J = 12.3 Hz), 5.86 (s, 2 H), 5.77 (d, 1 H, J = 12.3 Hz), 3.75 (s, 3 H), 2.75 (t, 2 H), 1.85 (s, 6 H), 1.75 (m, 2 H), 0.97 (t, 3 H). Trans-isomer (0.2 g, 54%); MS (EI) *m/e* 287 (M); ^{1}H NMR 12.61 (br, 1 H), 6.95 (d, 1 H, J = 16 Hz), 5.99 (d, 1 H, J = 16 Hz), 5.81 (s, 2 H), 3.64 (s, 3 H), 2.65 (t, 2 H), 1.85 (s, 6 H), 1.75 (m, 2 H), 0.97 (t, 3 H).

Biological Assays

Angiotensin (AT_1) receptor binding: Rat liver was obtained from male Long–Evans rats (200–500 g) sacrificed by decapitation. The tissues were disrupted in 10 volumes of ice-cold 10 mM HEPES buffer (pH 7.4, containing 10 μM leupeptin, bestatin, pepstatin A, and captopril) and 100 μM PMSF for 20 s in a Brinkmann Polytron PT-10 at setting 7. The suspension was centrifuged at 50000*g* for 10 min, and the pellet was resuspended in 10 volume of HEPES as above, centrifuged, and resuspended at 1 g/5 mL. Aliquots of the membrane suspension were stored frozen at −70 °C up to 1 month until required. Incubations were performed with a final volume of 1 mL HEPES buffer (as above and 10 mM $MgCl_2$) containing 10 mg of original tissue weight of homogenate and 0.5 nM [^{125}I]angiotensin II. Test compounds were dissolved at 10 mM in DMSO and diluted in DMSO to 100 times the final incubation concentration. Control incubations received an equal volume (10 μL) of DMSO. The resulting concentration of DMSO had no effect on binding. Incubation was initiated by agitating the rack of tubes on a vortex mixer. Tubes were then placed in a 25 °C shaking water bath for 60 min. Incubations were terminated by filtration through Whatman GF/B glass-fiber filter sheets which had been presoaked in 50 mM Tris buffer, pH 7.7 containing 100 mM bacitracin using a Brandel 48R cell harvester. Filters were washed with three 4-mL rinses of 50 mM Tris buffer. The filtration was completed within 25 s. Filters were transferred to scintillation vials in which 8 mL of Formula 963 scintillation fluid was added, and the vials were left overnight, shaken, and then counted in a liquid scintillation counter.

Specific binding was defined as total binding minus nonspecific binding which was determined in the presence of 1.0 μM saralasin. The inhibitory concentration (IC_{50}) of an inhibitor that gave 50% displacement of the specifically bound [^{125}I]angiotensin II were calculated by weighing nonlinear regression curve-fitting to the mass-action equation using the Enzfitter computer program.

Angiotensin II-induced contraction in isolated vascular tissue: Rabbits (New Zealand white, 3–4 kg) were killed by cranial–vertebral dislocation. The thoracic aorta was rapidly removed and placed in room-temperature physiological salt solution [PSS composition: NaCl (118.2 mM), KCl (4.6 mM), KH_2PO_4 (1.2 mM), $NaHCO_3$ (24.8 mM), $MgSO_4$ (1.2 mM), $CaCl_2$ (2.5 mM), EDTA (0.026 mM) and dextrose (10 mM)]. Tissues were gently cleaned of fat and connective tissue and cut into 4–5 mm wide circular segments. The bath chambers were maintained at 37 °C, aerated with 95% O_2/5% CO_2. Contractions of the rings were measured isometrically with a Grass FTO_3C force-displacement transducer and recorded on a Gould oscillograph as changes in grams of force. Tissues were allowed to equilibrate for 1.5 h before the experimental protocol was initiated. After the equilibration period, the aortic segments were contracted with KCl (122 mM) and maintained for 5 min, and the successive washout was continued until baseline force was achieved. The tissues were then contracted to a plateau with 10^{-8} M AII (0.001 N HCl). Following a washout, the AII challenge was repeated a second time and then washed out. The test compound (in 20 μL DMSO) was added to the bath and allowed to incubate for 10 min before repeating the concentration–response curve to AII. The strength of this AII contraction was compared to the average of two control contractions. The AII response in the presence of test compound was expressed as a percent of the AII response in the absence of the test compound. The IC_{50} estimate for an antagonist was obtained graphically from the concentration–response curve generated for inhibition of the AII-induced contractions.

Antagonism of Angiotensin II-Induced Pressor Responses in Conscious, Normotensive Rats. Male Sprague–Dawley normotensive rats weighing between 250 and 300 g were anesthetized with 50 mg/kg sodium pentobarbital delivered intraperitoneally. Both jugular veins were cannulated; one cannula was used for administration of the test compound and the other for AII administration. A single carotid artery was cannulated (PE 50) and the cannula was connected to a pressor transducer for the measurement of arterial blood pressure. The pressure signal was amplified and conditioned by a transducer coupler and input simultaneously to a chart

recorder and a computer data-acquisition system. Maximum change in mean blood pressure (MBP) was calculated using a baseline control taken immediately prior to an AII challenge and the maximum increase in MBP during that challenge interval. The rat was tracheotomized with PE 240. After the rats were surgically prepared, ganglionic blockade was induced with mecamylamine (1.25 mg/mL per kg). This resulted in a 20–50 mmHg drop in arterial blood pressure. After the blood pressure stabilized, the animal was challenged with a 0.1 μg/0.1 mL per kg iv bolus of AII. Subsequent AII challenges were administered at 15-min intervals. Compounds were tested at five rising half-log doses in a cumulative fashion with each dose infused for 15 min at a constant rate of 18 μL/min. The constant infusion of drug was started 10 min prior to AII challenges to provide time for clearing cannula dead space and time for a 5-min prechallenge delivery of compound. The infusion was continued another 5 min during and after the AII challenge. To test for antagonist specificity, a phenylephrine challenge (3 μg/mL per kg iv bolus) was administered at the end of the experiment. Effects of the antagonist on angiotensin responses were expressed as percentage inhibition of the control AII response.

Blood Pressure Lowering Activity in Renal Hypertensive Rats: Male Sprague–Dawley rats underwent bilateral renal artery clipping at 5 weeks of age using aseptic techniques. Postsurgically prepared rats were returned to the animals colony and maintained on a fixed light cycle with free access to normal rat chow and water for an additional 10–12 weeks. All experiments were performed in accordance with the NIH guidelines for Laboratory Animals according to the protocol approved by the Parke-Davis Animal Care and Use Committee.

For blood pressure determinations animals were anesthetized and a cannula was implanted in the abdominal aorta and routed subcutaneously to exit at the neck. Each animal was fitted with a harness/swivel apparatus and individually housed. Animals were given a 48 h postsurgical recovery period. The blood pressure signal was amplified and conditioned by a transducer coupler input to a wave form. Both blood pressure and heart rate were recorded continuously; data were averaged at 30-min intervals. Animals with a mean blood pressure of less than 150 mmHg were excluded from further study.

The blood pressure lowering activity of each compound was examined after oral administration to groups of five or six conscious rats. Compounds were suspended in 0.5% methocel in water and administered by oral gavage at a 10 mg/kg dose in a volume of 2 mL/kg. Baseline blood pressure was determined by averaging the 60-min period immediately prior to dosing. Data are presented as the maximum percent reduction in blood pressure relative to baseline within each animal.

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