Derivatives of 5-[[1-(4′-Carboxybenzyl)imidazolyl]methylidene]hydantoins as Orally Active Angiotensin II Receptor Antagonists[1,2]

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A series of 5-[[1-(4′-carboxybenzyl)imidazolyl]methylidene]hydantoins have been prepared and evaluated as in vitro and in vivo angiotensin II (Ang II) antagonists. Variation of substituents on the hydantoin ring leads to potent and selective Ang II antagonists with nanomolar IC_{50} values at the AT_1 receptor and negligible affinity for the AT_2 receptor. Preferred substituents include an *n*-butyl at R_1 and an alkyl or heteroarylmethyl substituent at R_2. The selection of the R_2 substituent was guided in part by the calculation of its log *P* since a significant correlation was observed between CLOGP and AT_1 binding affinity. The biphenyl tetrazole pharmacophore, common to a number of AT_1 antagonists, could be replaced by, for example, a 4-carbomethoxyphenyl substituent resulting in potent Ang II antagonists both in vitro and in vivo. A representative compound of this series is **57**, which reduced the mean arterial blood pressure of renal hypertensive rats by 40% at 30 mg/kg po and by 25% at 10 mg/kg po. In addition this compound was efficacious in the salt-deplete normotensive monkey model maximally decreasing blood pressure 27% at 10 mg/kg po. In summary, these compounds belong to a novel class of Ang II antagonists that lack the biphenyl tetrazole moiety yet display appreciable and long lasting oral activity.

Introduction

The renin angiotensin system plays an important role in the regulation of blood pressure in addition to electrolyte homeostasis.[3,4] The kidney responds to a reduction of blood pressure by the release of renin from the juxtaglomerular cells surrounding the afferent arterioles.[5] This enzyme cleaves angiotensinogen to angiotensin I which is in turn converted to the potent vasoconstrictor angiotensin II (Ang II) by the nonspecific carboxydipeptidase angiotensin-converting enzyme (ACE).[6] As a vasoconstrictor and stimulator of aldosterone release, Ang II increases peripheral resistance and expands blood volume as dual mechanisms for restoring blood pressure. In renin dependent hypertension, this blood pressure-regulating mechanism is compromised resulting in abnormal cardiac output and peripheral resistance.[7]

The renin angiotensin system offers several pharmacologically distinct approaches for antihypertensive therapy. These approaches include inhibitors of renin release[8] as well as those of the enzyme renin.[9] Although a number of renin inhibitors have entered clinical trials to date, their poor bioavailability has thus far precluded further development.[10] A particularly successful pharmacologic approach, however, has involved the inhibition of the ACE.[11,12] Inhibitors such as captopril and enalapril have been shown to be clinically efficacious in the treatment of hypertension and, more recently, congestive heart failure.[13] These ACE inhibitors are not without side effects,[14–16] and as a result, recent efforts have focused upon the discovery of Ang II receptor antagonists.[17]

Saralasin, a specific Ang II antagonist, lowered blood pressure in patients with elevated renin levels but, in addition, exhibited partial agonist effects in vivo and poor bioavailability.[18,19] This peptide, however, has served to demonstrate the usefulness of Ang II blockade and hence established several research programs directed toward the discovery of nonpeptide Ang II antagonists.[20–25] The first orally active, nonpeptide Ang II receptor antagonist, DuP 753 (Cozaar), has recently been marketed for the clinical treatment of hypertension.[26]

We have previously described aspects of our research programs relating to both AT_1[27] and AT_2[28] specific ligands and now describe a novel series of potent AT_1 ligands. One of our strategies for developing an alternate series of Ang II antagonists required an investigation of the notion that the biphenyl tetrazole moiety of most Ang II antagonists is a requirement for oral activity.[29] In fact recent reports have demonstrated that the biphenyl tetrazole moiety of L-158,809[30] could be replaced with acylsulfonamides[31] or (dialkylphenoxy)-phenylacetic acids[32] while still retaining excellent oral activity. Furthermore, several reports from the SKF group[33–36] describing the structure–activity relationship (SAR) of a series of 1-(carboxybenzyl)imidazole-5-acrylic acids, exemplified by SKF 108566 (**1**), was particularly interesting since this series lacked the biphenyl tetrazole moiety. We considered that a suitably substituted hydantoin could replace the acrylic acid of SKF 108566 and allow the appropriate positioning of hydrogen bond donor and hydrophobic functionality as previously dictated by SAR studies.[27,37–39] The present paper describes the synthesis and SAR of a series of 5-[[1-(4′-carboxybenzyl)imidazolyl]methylidene]hydantoins **2** that resulted from this analysis (Figure 1).

Chemistry

Our initial synthetic route to prepare the requisite alkylidenehydantoins involved a base-catalyzed conden-

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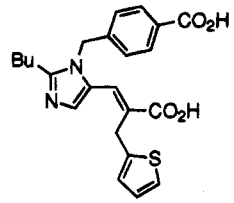

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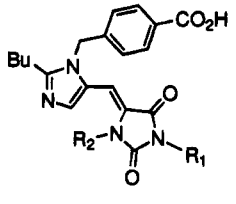
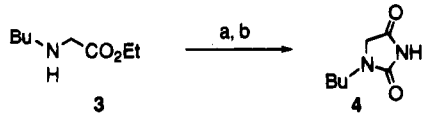


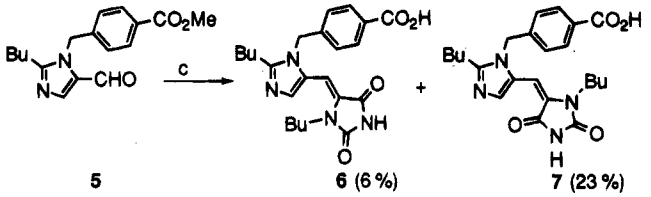
2

Figure 1. SKF 108566 (1) and 5-[[1-(4'-carboxybenzyl)-imidazolyl]methylidene]hydantoins **2**.

Scheme 1.[a] Synthesis of Isomeric Mixture of (*Z*)- and (*E*)-Methylidenehydantoins[a]



3 4



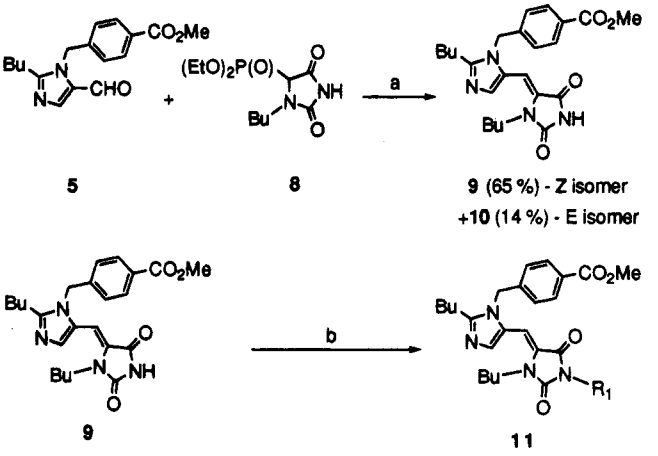
5 6 (6%) 7 (23%)

[a] Reagents: (a) 1.1 equiv of HCl, KNCO, H_2O; (b) concentrated HCl or NaOMe, MeOH; (c) **4**, $(Me)_4NOH$, MeOH, H_2O, 100–120 °C.

sation of an alkyl-substituted hydantoin with methyl 4-[(2-butyl-5-formyl-1*H*-imidazol-1-yl)methyl]benzoate (**5**). The intermediate hydantoins **4** were prepared in a two-step process, starting from the appropriately N-substituted-glycine ester (Scheme 1).[40] For example, treatment of **3** with dilute aqueous HCl and KNCO provided an intermediate urea. Cyclization to 1-butyl-2,4-imidazolidinedione (1-butylhydantoin,[41] **4**) was affected either with hot concentrated HCl or by treatment with NaOMe in MeOH. The condensation of **4** with **5** was initially performed under strongly basic conditions using $(Me)_4NOH$ in alcohol–water mixtures at 100–120 °C. These conditions led to a mixture of regioisomeric products with the *E* isomer predominating and caused hydrolysis of the methyl ester to afford the corresponding acid. These *Z* and *E* regioisomeric products **6** and **7**, respectively (**97–105**), were then separated with some difficulty by crystallization or chromatography. The *Z* isomer was distinguished from the *E* isomer via a nuclear Overhauser effect. Particularly characteristic of the *E* isomer was the cross enhancement that was observed upon irradiating the methylene of the NCH_2R substituent and the vinylic proton of the methylidenehydantoin. In addition it was routinely observed that the imidazole proton of the *E* isomer exhibited a downfield shift attributable to the anisotropic deshielding by the π electrons in the carbonyl group.

An alternative method of condensation that offered greater control of regiochemistry about the double bond involved the use of diethyl (2,5-dioxo-3-butyl-4-imidazolyl)phosphonate (**8**) (Scheme 2).[42,43] Thus **8** was condensed with the aldehyde **5** in the presence of 1,8-diazabicyclo[4.4.0]undec-7-ene (DBU) in methylene chloride to afford predominantly the required *Z* isomer **9**. The small amount of the corresponding *E* isomer **10** was separated through chromatography. These alkylidenehydantoins were then alkylated in excellent yield by

Scheme 2.[a] Procedure for the Regioselective Synthesis of Methylidenehydantoins and Subsequent Alkylation[a]

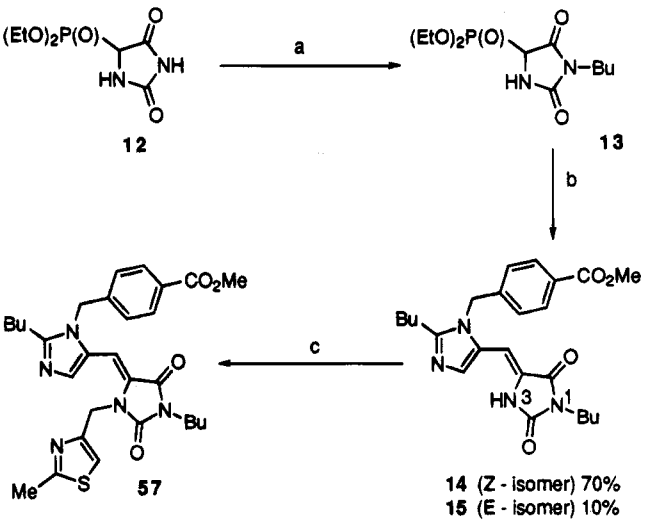


5 8 9 (65%) - Z isomer
+10 (14%) - E isomer

9 11

[a] Reagents: (a) DBU, CH_2Cl_2; (b) R_1-X, K_2CO_3, DMF.

Scheme 3.[a] Synthetic Route Allowing Functionalization of Hydantoin N_1 and N_3[a]



12 13 14 (Z - isomer) 70%
15 (E - isomer) 10%
57

[a] Reagents: (a) BuI, K_2CO_3, DMF, room temperature; (b) **5**, DBU, CH_2Cl_2; (c) 2-methyl-4-(chloromethyl)thiazole, K_2CO_3, DMF.

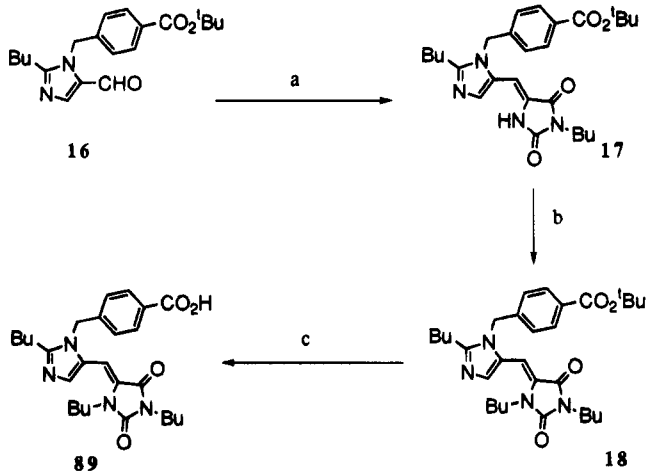
treatment with an alkyl iodide and potassium carbonate in DMF to afford, for example, **11**.

Once preliminary SAR studies established that the preferred substituent at R_1 was butyl, we modified the synthetic route to allow alkylation of R_2 as the final synthetic step. As outlined in Scheme 3 the intermediate aldehyde **5** was condensed with the hydantoin phosphonate **13** to afford the useful intermediate **14** in good yield. Although this condensation afforded some corresponding *E* isomer, typically ca. 10%, as evident by NMR of the crude reaction mixture, the *Z* isomer could be isolated directly by crystallization of the reaction mixture after workup.

The phosphonate **13** was prepared, in excellent yield, by the treatment of **12** with butyl iodide and potassium carbonate in DMF. In fact this was a general procedure with the reaction tolerant of a number of electrophiles. In the case of less reactive electrophiles such as SEM-Cl, MOM-Cl, and MEM-Cl and some alkyl bromides, it was necessary to employ NaH in THF or DMF to afford good yields of the required products **80–88**.

This intermediate **14** was then reacted with a variety of electrophiles to afford the majority of compounds used to explore the SAR described herein. Again K_2CO_3 or NaH was employed as base, and only 1 equiv of the

Scheme 4.[a] Synthesis of 5-[[1-(4′-Carboxybenzyl)imidazolyl]methylidene]hydantoins[a]



[a] Reagents: (a) **13**, DBU, CH_2Cl_2; (b) BuI, K_2CO_3, DMF, room temperature; (c) TFA, CH_2Cl_2.

electrophile was added to prevent quarternization of the substituted imidazole. The final products **38–79** were simply isolated as their hydrochloride salts which allowed direct crystallization from the reaction mixture (Scheme 3).

During the attempted saponification of the esters, we noted that only partial hydrolysis was affected by dilute aqueous hydrochloric acid and that with concentrated acid substantial *Z* to *E* isomerization occurred. Basic saponification was equally fruitless due to competing urea formation as a result of hydantoin ring cleavage.

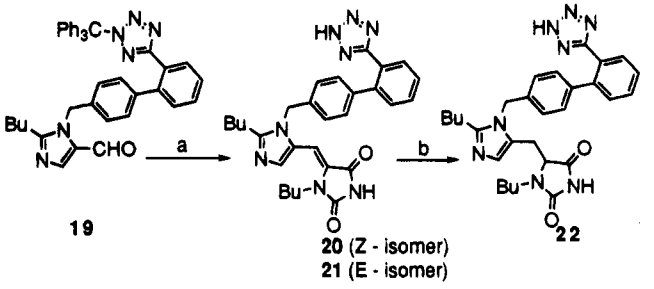
The problem of saponification was overcome by the use of *tert*-butyl benzoate esters (Scheme 4). These esters behaved similarly to the corresponding methyl esters during the reaction with the hydantoin phosphonates and the alkylation procedure but, in addition, allowed facile deesterification with trifluoroacetic acid in methylene chloride without concomitant *Z* to *E* isomerization to afford the required products **89–96** and **107–110**.

Scheme 5 outlines the chemistry used to prepare a number of alkylidenehydantoins that incorporate a variety of benzoate ester surrogates. The aldehydes **19**,[21,44] **23**,[33] **27**,[45] **30**,[46] and **35**[47] underwent condensation with the hydantoin phosphonates in the expected fashion. In these cases the *Z* isomers were typically separated by chromatography in good yield. Fortunately detritylation of the protected tetrazoles, with citric or acetic acid, occurred without significant *Z* to *E* isomerization to afford **20**, **21** and **33**, **34**.

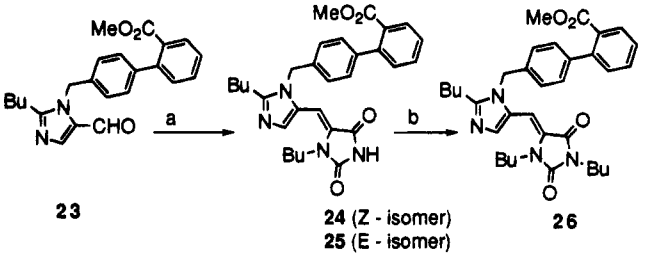
Biological Assays

The alkylidenehydantoins were evaluated as Ang II antagonists by a combination of in vitro AT_1 receptor binding and isolated vascular ring contraction assays as previously described.[48] Selected compounds were also evaluated in an AT_2 binding assay, using membranes isolated from the rabbit uterus, and were consistently found to lack significant binding activity at this receptor subtype. The AT_1 binding assay, which evaluated the ability of the test compounds to displace [^{125}I]Ang II in a rat liver membrane preparation, was used to select compounds for a functional assay. This functional assay studied the ability of the test compound to inhibit Ang II-induced vasoconstriction in isolated

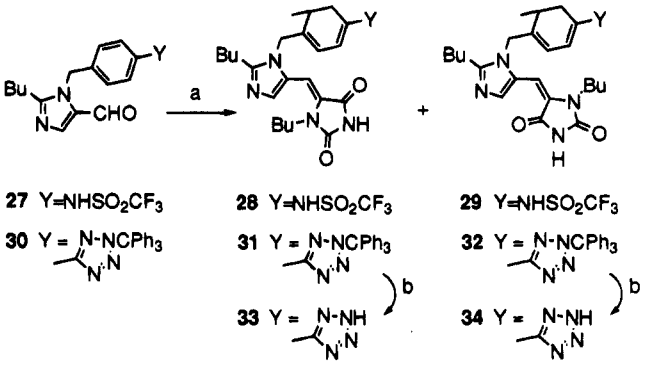
Scheme 5. Analogs Incorporating Benzoate Ester Surrogates



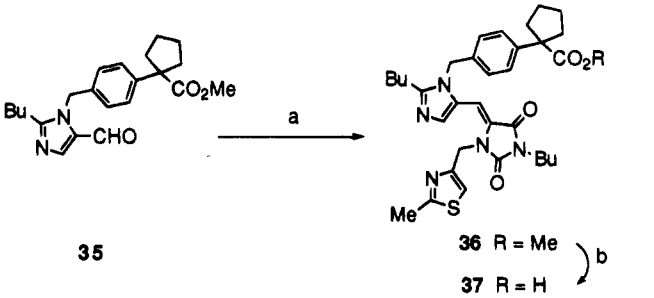
Reagents: (a) **8**, NaH, MeOH; CH_3CO_2H, MeOH
(b) Trityl-**20**, H_2, Pd/C; CH_3CO_2H, MeOH



Reagents: (a) **8**, NaH, MeOH; (b) BuI, K_2CO_3, DMF



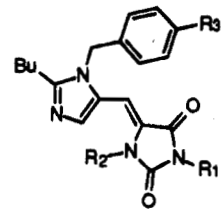
Reagents: (a) **8**, NaH, MeOH; (b) Citric acid, MeOH, reflux



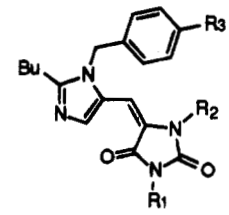
Reagents: (a) **13**, NaH, MeOH; **2-methyl-4-(chloromethyl)thiazole**, K_2CO_3, DMF; (b) 2N HCl, reflux

rabbit aorta rings (RAR). Compounds which displayed good activity in these in vitro screens were then evaluated in two in vivo screens. The majority of the potent compounds were examined in conscious, renal hypertensive rats, and the decrease in blood pressure was monitored over a period of 20 h.[27] A compilation of the activities of these hydantoins is given in Table 1. Finally selected compounds were tested in conscious, high-renin, normotensive male cynomolgus monkey model.[49]

Table 1. Compilation of Rat Liver Membrane Binding (AT_1), Inhibition of Ang-II Induced Rabbit Aortic Ring Contraction (RAR), and Oral Antihypertensive Activity in Renal Hypertensive Rats (RHR) of Substituted Alkylidenehydantoins[a]



Z-isomer



E-isomer

compd	R_1	R_2	R_3	isomer	IC_{50} (nM) AT_1	IC_{50} (nM) RAR	RHR % max 30 mg/kg	RHR % max 10 mg/kg
9	H	butyl	CO_2Me	Z	3.5	30	−11	NT
20	H	butyl	2-(1*H*-tetrazol-5-yl)phenyl	Z	1.4	40	IA	NT
21	H	butyl	2-(1*H*-tetrazol-5-yl)phenyl	E	2.7	NT	NT	NT
24	H	butyl	2-carbomethoxy)phenyl	Z	15.9	NT	NT	NT
25	H	butyl	2-carbomethoxy)phenyl	E	9.9	NT	NT	NT
26	Butyl	butyl	2-carbomethoxy)phenyl	Z	29.6	NT	NT	NT
28	H	butyl	trifluoromethanesulfonamido	Z	3.3	120	−11	NT
29	H	butyl	trifluoromethanesulfonamido	E	4.2	NT	NT	NT
33	H	butyl	1*H*-tetrazol-5-yl	Z	7.1	40	IA	NT
34	H	butyl	1*H*-tetrazol-5-yl	E	2.5	NT	NT	NT
36	butyl	(2-methyl-4-thiazolyl)methyl	1-(methoxycarbonyl)cyclopent-1-yl	Z	8.0	NT	NT	NT
37	butyl	(2-methyl-4-thiazolyl)methyl	1-carboxycyclopent-1-yl	Z	1.9	NT	−16	NT
38	butyl	(4-aminophenyl)methyl	CO_2Me	Z	3.0	NT	NT	NT
39	butyl	(3,4-dihydroxyphenyl)methyl	CO_2Me	Z	4.9	NT	NT	NT
40	butyl	(4-methoxyphenyl)methyl	CO_2Me	Z	9.8	NT	NT	NT
41	butyl	(4-cyanophenyl)methyl	CO_2Me	Z	11.1	NT	NT	NT
42	butyl	phenylmethyl	CO_2Me	Z	12.4	NT	NT	NT
43	butyl	[4-methoxycarbonyl)phenyl]methyl	CO_2Me	Z	14.3	NT	NT	NT
44	butyl	(4-nitrophenyl)methyl	CO_2Me	Z	16.9	NT	NT	NT
45	butyl	(4-chlorophenyl)methyl	CO_2Me	Z	17.6	500	−15	NT
46	butyl	(4-methylphenyl)methyl	CO_2Me	Z	34.6	NT	NT	NT
47	butyl	[4-(trifluoromethyl)phenyl]methyl	CO_2Me	Z	159.0	NT	NT	NT
48	butyl	butyl	CO_2Me	Z	8.5	460	−27	NT
49	butyl	hexyl	CO_2Me	Z	40.2	NT	NT	NT
50	butyl	(2-naphthalenyl)methyl	CO_2Me	Z	104.0	NT	NT	NT
51	butyl	diphenylmethyl	CO_2Me	Z	884.0	NT	NT	NT
52	butyl	c-hexylmethyl	CO_2Me	Z	3.3	NT	NT	NT
53	butyl	pentyl	CO_2Me	Z	6.1	NT	NT	NT
54	butyl	4,4,4-trifluorobutyl	CO_2Me	Z	6.4	NT	NT	NT
55	butyl	$CH{=}CMe_2$	CO_2Me	Z	11.1	NT	NT	NT
56	butyl	(2-thienyl)methyl	CO_2Me	Z	3.4	370	−28	NT
57	butyl	(2-methyl-4-thiazolyl)methyl	CO_2Me	Z	3.8	350	−40	−25
58	butyl	(3-thienyl)methyl	CO_2Me	Z	4.8	NT	−36	NT
59	butyl	phenethyl	CO_2Me	Z	31.0	NT	NT	NT
60	butyl	(5-bromo-2-thienyl)methyl	CO_2Me	Z	17.8	NT	NT	NT
61	butyl	(3-methyl-2-thienyl)methyl	CO_2Me	Z	23.9	NT	NT	NT
62	butyl	(4-bromo-2-thienyl)methyl	CO_2Me	Z	21.9	NT	NT	NT
63	butyl	(2-amino-4-thiazolyl)methyl	CO_2Me	Z	1.2	290	−37	−39
64	butyl	(3,5-dimethyl-4-isoxazolyl)methyl	CO_2Me	Z	198.0	NT	NT	NT
65	butyl	(3-thienyl)ethyl	CO_2Me	Z	14.6	NT	NT	NT
66	butyl	(2-thienyl)ethyl	CO_2Me	Z	14.5	NT	NT	NT
67	butyl	(2-pyridinyl *N*-oxide)methyl	CO_2Me	Z	260.0	NT	NT	NT
68	butyl	(2-pyridinyl)methyl	CO_2Me	Z	5.8	490	−20	NT
69	butyl	(5-bromo-3-thienyl)methyl	CO_2Me	Z	25.4	NT	NT	NT
70	butyl	(5-isoxazolyl)methyl	CO_2Me	Z	10.1	>100	−23	NT
71	butyl	(4-thiazolyl)methyl	CO_2Me	Z	8.0	NT	NT	NT
72	butyl	(1*H*-tetrazol-5-yl)methyl	CO_2Me	Z	41.7	NT	NT	NT
73	butyl	(1*H*-imidazol-5-yl)methyl	CO_2Me	Z	54.5	NT	NT	NT
74	butyl	(5-methyl-3-ioxazolyl)methyl	CO_2Me	Z	8.5	NT	NT	NT
75	butyl	(3-chlorophenyl)methyl	CO_2Me	Z	117.0	NT	NT	NT
76	butyl	(2-methyl-4-imidazolyl)methyl	CO_2Me	Z	245.0	NT	NT	NT
77	butyl	(3-methylphenyl)methyl	CO_2Me	Z	18.5	NT	NT	NT
78	butyl	(3-furanyl)methyl	CO_2Me	Z	8.3	>100	−22	NT
79	butyl	[5-methoxycarbonyl)-2-thienyl]methyl	CO_2Me	Z	4.2	NT	NT	NT
80	methyl	(2-methyl-4-thiazolyl)methyl	CO_2Me	Z	16.6	NT	NT	NT
81	ethyl	(2-methyl-4-thiazolyl)methyl	CO_2Me	Z	11.1	NT	NT	NT
82	propyl	(2-methyl-4-thiazolyl)methyl	CO_2Me	Z	9.0	NT	NT	NT
83	hexyl	(2-methyl-4-thiazolyl)methyl	CO_2Me	Z	5.3	>100	−34	NT
84	hydroxymethyl	(2-methyl-4-thiazolyl)methyl	CO_2Me	Z	35.7	NT	NT	NT
85	3-hydroxypropyl	(2-methyl-4-thiazolyl)methyl	CO_2Me	Z	47.9	NT	NT	NT
86	methoxymethyl	(2-methyl-4-thiazolyl)methyl	CO_2Me	Z	47.8	NT	NT	NT
87	(thiomethyl)ethyl	(2-methyl-4-thiazolyl)methyl	CO_2Me	Z	9.6	NT	NT	NT
88	trifluorobutyl	(2-methyl-4-thiazolyl)methyl	CO_2Me	Z	70.0	NT	NT	NT
89	butyl	butyl	CO_2H	Z	1.3	14	−45	−21
90	butyl	butyl	CO_2H	E	0.5	NT	NT	IA
91	butyl	(2-thienyl)methyl	CO_2H	Z	0.7	13	-28	NT
92	butyl	(2-thienyl)methyl	CO_2H	E	0.6	NT	NT	NT

Table 1 (Continued)

compd	R_1	R_2	R_3	isomer	IC_{50} (nM) AT_1	IC_{50} (nM) RAR	RHR % max 30 mg/kg	RHR % max 10 mg/kg
93	butyl	(2-amino-4-thiazolyl)methyl	CO_2H	Z	0.6	2.9	IA	NT
94	butyl	(2-amino-4-thiazolyl)methyl	CO_2H	E	0.5	NT	NT	NT
95	butyl	(2-methyl-4-thiazolyl)methyl	CO_2H	Z	1.2	2.6	−34	NT
96	butyl	(2-methyl-4-thiazolyl)methyl	CO_2H	E	1.7	NT	NT	NT
97	H	butyl	CO_2H	Z	2.8	28	−17	NT
98	H	butyl	CO_2H	E	2.4	44	IA	NT
99	H	3-methylbutyl	CO_2H	Z	6.6	32	NT	NT
100	H	3-methylbutyl	CO_2H	E	4.9	74	NT	NT
101	H	phenylmethyl	CO_2H	Z	4.0	35	NT	NT
102	H	phenylmethyl	CO_2H	E	3.4	>100	NT	NT
103	H	(2-thienyl)methyl	CO_2H	Z	2.3	18	−21	NT
104	H	(2-thienyl)methyl	CO_2H	E	2.6	NT	IA	NT
105	H	(4-chlorophenyl)methyl	CO_2H	Z	3.0	28	−17	NT
106	H	(2-thienyl)methyl	CO_2Me	Z	7.1	28	−19	NT
107	butyl	(5-methyl-2-thienyl)methyl	CO_2H	Z	0.6	5.3	−22	NT
108	butyl	(4-methyl-2-thienyl)methyl	CO_2H	Z	1.5	21	−16	NT
109	butyl	(5-methyl-3-thienyl)methyl	CO_2H	Z	0.7	9.2	−23	−28
110	butyl	(3-thienyl)methyl	CO_2H	Z	0.9	10	−42	−28

[a] NT, not tested; IA, inactive (% max < 10%).

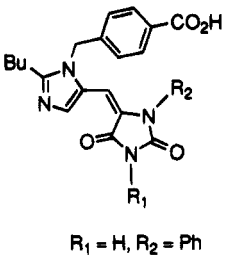


Figure 2. Initial chemical lead.

Results and Discussion

With the discovery of our initial lead, (*E*)-4-[[2-butyl-5-[(2,5-dioxo-3-phenyl-4-imidazolidinylidene)methyl]-1*H*-imidazol-1-yl]methyl]benzoic acid (AT_1 IC_{50} = 0.5 μM) (Figure 2) we chose to optimize in vitro activity by a three-stage approach. Our first step was to vary the substituents at R_1 and R_2 guided in part by the physiochemical characteristics of the substituents, SAR of SKF 108566, and peptide analogs of Ang II.[50,51] Secondly, we investigated the in vitro activity of the *Z* and *E* geometrical isomers of the more potent analogs. Finally we replaced the 4-carboxybenzyl substituent with a number of substituents of varying pK_a and steric requirements.[52]

The selection of an optimal R_2 hydantoin substituent was pursued by a combination of three approaches. One of these involved the incorporation of a number of substituted aromatics at R_2 while targeting the *Z* isomer with an *n*-butyl substituent at R_1 (**38**–**47**). The *Z* isomer was pursued initially since it corresponded to the orally active geometrical isomer from the SKF 108566 series, and an *n*-butyl substituent was incorporated at R_1 for synthetic simplicity. Our selection of aromatic substituents was guided by correlating the σ (electronic) and Π (hydrophobic) values of the substituent with in vitro activity.[53] As an initial approach we attempted to correlate the in vitro activity of the derivatives via the Topliss[54,55] approach and by employing Craig plots.[56] Both the Topliss and Craig approaches indicated that substituents with both a negative σ and Π were optimal for in vitro activity (**38**, **39**). However, at this point we could not determine whether the in vitro activity was a result of the electronic or lipophilic nature of the substituent. We therefore compared the in vitro activity via regression analysis

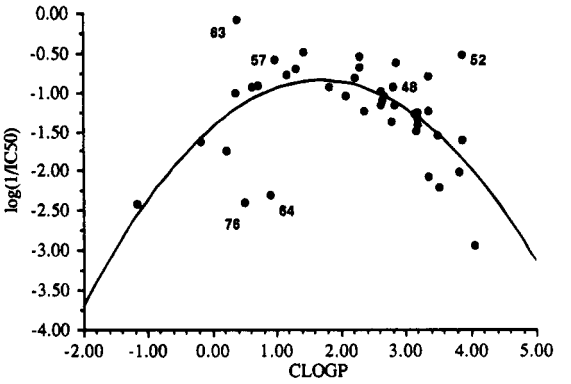


Figure 3. Comparison of the in vitro AT_1 receptor binding affinity of compounds **38**–**79** with calculated log *P* of the substituent R_2.

with the σ, Π, MR (molecular refractivity), *F* (field inductive), and *R* (resonance) values for the aromatic substituents. Significant correlation was only readily apparent with Π, indicating that the lipophilicity of the substituent was crucial in determining activity.[57] Furthermore by measuring the HPLC retention times of each of the derivatives (**38**–**47**), under isocratic conditions, we observed the excellent correlation[58] between experimentally measured HPLC retention time and Π.[59] This data prompted the interesting conclusion that in vitro binding activity could be predicted by simply observing the HPLC retention time of the derivative.

Concomitantly to the synthesis of benzyl substituents at R_2, we also investigated the binding affinity of analogs which were alkyl substituted at R_2 (**48**, **49**, **52**–**55**). Interestingly these analogs also demonstrated excellent in vitro activity, and in the light of the results of the above analysis, this was not surprising due to the similarity in the CLOGP[60] values for the alkyl substituents and benzyl substituents (**42**, **48**). However, although in vitro activity compared favorably with the lipophilicity of the substituent, the unexpected potent in vitro activity of compound **52** demonstrates a limitation of simply relying on the CLOGP values to predict activity (Figure 3).

As an extension of this correlation of in vitro activity with lipophilicity of the R_2 substituent, we then investigated a variety of heterocycles[61,63] (**56**–**79**) which were calculated to have CLOGP values that expanded upon the range of the alkyl and substituted benzyls previously

examined. Although we realized that many problems exist in calculating log P values for heterocycles due to hidden steric and electronic properties, we were simply looking for a semiquantitative guide to aid in the selection of appropriate heterocycles.

In fact as can be seen from Table 1 and Figure 3, a remarkable number of heterocycles afforded potent in vitro compounds, the most potent of which tended to be substituted thiazole and thiophene heterocycles (**57**, **58**). Furthermore Figure 3 demonstrates a parabolic dependence ($P < 0.005$) between the in vitro activity and the lipophilic nature of the substituent, although it should be pointed out that calculating an optimal log P is hindered by the apparent spread ($R^2 = 0.35$) of compounds. Two compounds, **64** and **76**, in particular showed surprisingly poor IC_{50}'s based on their calculated log P. This may be the result of unusual electronic or steric effects of the substituents and hence an unfavorable association with the receptor. Of particular interest was the excellent activity of **63**. This unexpected level of activity, based upon its corresponding log P, may be the result of the known inherent problems associated with calculating the log P of substituents that contain basic residues. However, in order to address the question of whether the calculated log P values are truly reflective of the measured log P we selected several representative compounds (**42**, **48**, **49**, **52**, **56–58**, **60**, **61**) and measured their log P by the octanol/water partition method. Gratifyingly the regression analysis indicated an excellent correlation[64] between the calculated and measured log P and furthermore demonstrated the usefulness of the CLOGP algorithm in calculating the log P of at least some of the heteroaryl substituents studied here.

Having studied the SAR's for the R_2 position, we then systematically studied the effect of the R_1 substituent to investigate whether a butyl substituent was optimal for activity. We uniformly increased the alkyl chain length at R_1, in addition to introducing a number of alkyl chains containing heteroatoms, while incorporating one of the more potent heterocycles in the form of (2-methyl-4-thiazolyl)methyl at the R_2 position (**57**, **80–88**). From this analysis we determined that optimal in vitro binding affinity was indeed afforded by a four-carbon alkyl chain at R_1.

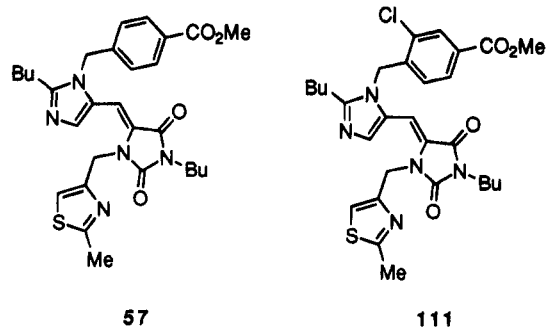
At this point then, we felt assured that the R_1 and R_2 substituents had been adequately explored, and hence we turned our attention to some secondary considerations. The first of these was the excellent in vitro activity of the corresponding E isomers. As can be seen in Table 1, the in vitro activity was maintained in both the E and Z isomers **89–104**. Furthermore although only a limited number of these E isomers (**98**, **100**, **102**) were evaluated in the RAR assay, it was apparent that they inhibited the contraction of isolated rabbbit aorta rings but to a lesser extent than the corresponding Z isomers (**97**, **99**, **101**). It soon became apparent that despite such good in vitro activity, the E isomers **90**, **98**, and **104** were devoid of oral activity in the renal hypertensive rat (RHR) despite the fact that the corresponding Z isomers (**89**, **97**, **103**) displayed reasonable oral activity in the same assay. We were further surprised to find that the saturated analog of **97** or **98** had relatively poor in vitro activity.[65] One possible explanation for the lack of oral activity of the E isomer may be a preferential metabolic deactivation by Michael addition to the E isomer.[66] Clearly it is difficult to draw definitive conclusions concerning the oral activity of the E isomers due to the lack of metabolic studies and the relatively few E isomers that were tested orally.

In our final approach to optimizing in vitro activity, we examined a variety of benzoic acid replacements (**20**, **21**, **24–26**, **28**, **29**, **33**, **34**, **36**, **37**). Although these compounds displayed excellent in vitro activity, their lack of in vivo activity and lengthy synthesis precluded further study.

Compounds which showed appreciable inhibition of [^{125}I]Ang II in rat liver membrane preparations (AT_1) were generally also evaluated for antagonism of Ang-II induced contraction of rabbit aortic rings (RAR). The results of this assay clearly demonstrated that the acids were more potent antagonists than the corresponding esters and usually confirmed the potency of the most active analogs. However, the critical test was the determination of oral activity in renal hypertensive rats. Due to the intensive nature of this assay, we limited the test to compounds that displayed in vitro activity (AT_1) better than a threshold value of 20 nM and/or showed significant activity in RAR. Initially compounds were tested at a single dose to demonstrate oral activity, and then the most active analogs were tested at multiple doses to demonstrate a dose–response relationship. Compounds **9** and **48**, **56** and **106**, **89** and **97**, and **91** and **103** demonstrate the trend toward enhanced in vivo activity afforded by an alkyl chain at R_1. Furthermore, although the in vitro activity was generally slightly superior for the analogs incorporating an acid at R_3 (**9** and **97**, **48** and **89**, **56** and **91**, **57** and **95**), the in vivo activity of the acids and esters were similar, yet there was a notable exception (**63**, **93**). Due to the inherent variability associated with measuring blood pressure responses after oral dosing, it is difficult to speculate as to why certain analogs show relatively poor oral activity in light of potent in vitro activity. Obviously such factors as absorption, distribution, metabolism, and elimination are important, and the correlation of these parameters with oral activities is better addressed by studies which determine the pharmacokinetics and pharmacodynamics of the compounds under study, which is beyond the scope of this report.

Although all of the compounds previously described were competitive antagonists, we discovered that slight modification of the benzoic acid pharmacophore by the introduction of a 2-chloro substituent[67] at R_4 afforded an insurmountable antagonist,[68] **111** (Figure 4), as has been previously seen in the SKF 108566 series of compounds. The increased lipophilicity afforded by the chloro substitution presumably causes a receptor–ligand interaction that leads to a partial but constant suppression of the maximal contraction of the rabbit aortic ring induced by Ang II.[69] However, when dosed orally, **111** demonstrated a sustained and rapid reduction in blood pressure at doses of 3 and 10 mg/kg, which was similar to the effect seen with **57** (Figures 5 and 6).

To this point all of the alkylidenehydantoins had been tested in tissues isolated from rat and rabbit and the oral activity of the compounds assayed in the renal



57 111

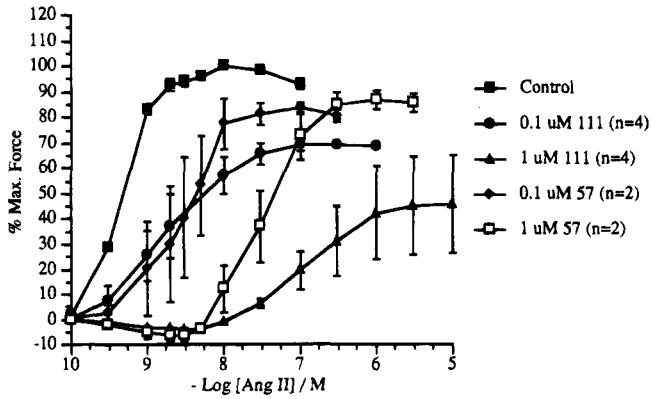


Figure 4. Surmountable (**57**) and insurmountable (**111**) AT_1 receptor antagonists in rabbit aorta.

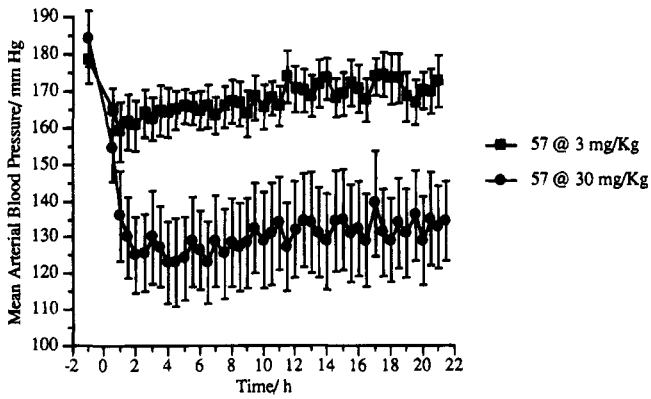


Figure 5. Effect of compound **57** at 3 mg/kg po (n = 7) and 30 mg/kg po (n = 9) on mean arterial blood pressure in renal hypertensive rats.

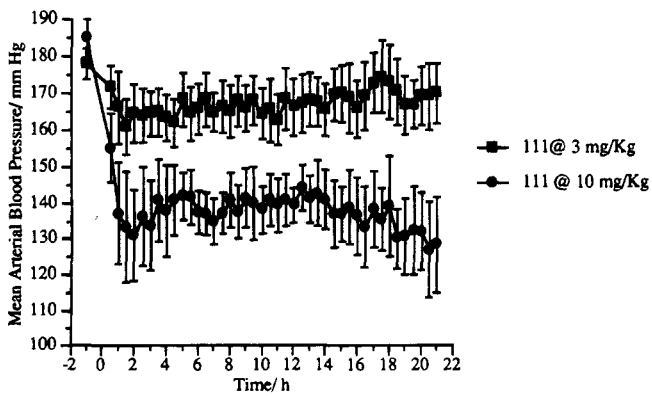


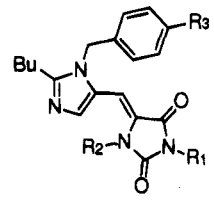
Figure 6. Effect of compound **111** at 10 mg/kg po (n = 4) and 3 mg/kg po (n = 5) on mean arterial blood pressure in renal hypertensive rats.

hypertensive rat. We therefore considered that a primate model of hypertension would be a reasonable extension of the previous studies and hence provide some insight to the suitability of these compounds for clinical studies. Gratifyingly compounds **57** and **111**, when dosed orally in a primate model of renin dependent hypertension, caused a reduction in blood pressure that was evident up to 4.5 h (Table 2).

Table 2. Effect of Compounds **57** and **111** at 10 mg/kg on Salt-Deplete Normotensive Monkeys

	blood pressure (mm/Hg)		
compd	baseline	min.	at 4.5 h
57	101 ± 8	74 ± 6	88 ± 5
111	100 ± 4	80 ± 2	85 ± 6

Table 3. Comparison of AT_1 and AT_2 Binding Affinities of Representative [(Benzylimidazolyl)alkylidene]hydantoins



				IC_{50} (nM)	
compd	R_1	R_2	R_3	AT_1	AT_2
20	H	butyl	2-(1*H*-tetrazol-5-yl)phenyl	1.4	789
37	butyl	(2-methyl-4-thiazolyl)methyl	1-carboxycyclopent-1-yl	1.9	549
48	butyl	butyl	methoxycarbonyl	8.5	5870

Finally the selectivity of these Ang II antagonists for the AT_1 receptor subtype was evaluated (Table 3). From this analysis it was determined that modifcation of the benzyl 4-substituent afforded compounds with modest AT_2 binding affinity. In fact this trend has been observed previously[70-72] and suggests that further modification of the R_3 substituent would also be a fruitful avenue of exploration in the design of dual AT_1/AT_2 ligands for this series of compounds.

Conclusion

This report describes a series of novel substituted 5-[[1-(4′-carboxybenzyl)imidazolyl]methylidene]-hydantoins that are potent orally active angiotensin II (AT_1) receptor antagonists. The in vitro potency was demonstrated to closely correlate with the lipophilicity of the R_2 substituent. A good agreement was observed between the calculated log P, the log P measured by the octanol/water partition protocol, and the log P calculated by the HPLC for a variety of R_2 substituents, which further indicated that the CLOGP algorithm is a useful tool for predicting in vitro activity. A butyl substituent at R_1 was optimal for in vitro activity and furthermore enhanced the antihypertensive activity in renal hypertensive rats. A 4-carboxybenzyl substituent generally afforded the most potent compounds, although the corresponding esters were also orally active. Rather surprisingly replacement of the carboxylic acid with a tetrazole, (trifluoromethyl)sulfonamide, or tetrazolylphenyl substituent, although displaying excellent in vitro activity, afforded orally inactive compounds when tested in the renal hypertensive rat.

This class of compounds is represented by compound **57** which displayed a dose-related lowering of blood pressure, and the effect (−25% at 10 mg/kg po) was sustained for at least a period of 24 h in the renal hypertensive rat. This compound also caused a maximal blood pressure reduction of 27% (at 10 mg/kg po)

and a 13% reduction at 4.5 h in salt-deplete normotensive monkeys. This profile of activity and duration of action makes these compounds suitable candidates for antihypertensive therapy.

Experimental Section

Melting points are uncorrected and were determined on a Thomas-Hoover capillary melting point apparatus. Infrared (IR) spectra were determined in KBr on a Mattson Cygnus 100 or a Nicolet MX1 FTIR spectrophotometer. Proton magnetic resonance (NMR) were recorded on either a Varian XL-200 or XL-300, Unity-400, or Bruker AM250 instrument; shifts are reported in δ units relative to internal tetramethylsilane. Mass spectra were obtained on a Finnigan 4500 or a VG analytical 7070 E/HF spectrometer. Elemental analyses were performed on a CEC Model 240 elemental analyzer, and all compounds prepared had analytical results within 0.4% of the theoretical values, unless otherwise noted. Column chromatography was performed using E. Merck silica gel 60 (230–400 mesh). Thin layer chromatography was performed with glass-backed silica gel (60 F 254) plates employing either UV light or iodine vapor for visualization. Purity of compounds was assayed by analytical HPLC employing a Beckman Ultrasphere C18 column (0.46 cm × 25 cm) with a mobile phase consisting of MeCN/H_2O and a flow rate of 1.5 mL/min detecting at 214 or 254 nm; in all cases the purity exceeded 98%.

1-Butyl-2,4-imidazolidinedione (1-Butylhydantoin, 4). To a solution of ethyl *N*-butylglycinate (31.80 g, 0.20 mol) in 1 N HCl (220 mL) was added potassium cyanate (24.4 g, 0.30 mol) in portions. The resulting solution was warmed to 90 °C and held at this temperature for 10 min. Concentrated HCl (250 mL) was added cautiously and the mixture heated at 90–100 °C for 30 min. After concentrating to dryness, the residue was extracted with 1:1 ethanol/methylene chloride (400 mL). The extract was evaporated in vacuo and then triturated with water (100 mL). Filtration afforded pure product (21.22 g, 68%): ^{1}H NMR ($CDCl_3$) 0.95 (t, J = 7.24 Hz, 3H), 1.33 (m, 2H), 1.52 (m, 2H), 3.37 (t, J = 7.35 Hz, 2H), 3.91 (s, 2H), 8.73 (brs, 1H). Anal. ($C_7H_{12}N_2O_2$) C, H, N.

(*Z*)-4-[[2-Butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1*H*-imidazol-1-yl]methyl]benzoic Acid (6). A mixture of methyl 4-[(2-butyl-5-formyl-1*H*-imidazol-1-yl)methyl]benzoate (**5**) (3.44 g, 0.012 mol), 1-butylhydantoin (**4**) (2.40 g, 0.016 mol), 25% tetramethylammonium hydroxide in methanol (25.92 g, 0.071 mol), and water (12 mL) was heated in an open flask at an oil bath temperature of 135–150 °C which caused the methanol to distill over. A yellow solution formed during this process, and the mixture was maintained at an oil bath temperature of 135–150 °C for a total of 45 min. The solution was cooled, and glacial acetic acid (5.04 g, 0.084 mol) and water (100 mL) were added. The precipitate was collected and washed with water to afford the title compound as a mixture of *Z* and *E* isomers (3.60 g, 70%). Crystallization from methanol and dichloromethane readily afforded the *E* isomer (1.16 g, 23%). The pure *Z* isomer (0.300 g, 6%) was obtained by repeated crystallization from ethyl acetate and hexane: ^{1}H NMR (DMSO) 0.63 (m, 3H), 0.84 (m, 7H), 1.28 (m, 2H), 1.60 (m, 2H), 2.68 (t, J = 7.33 Hz, 2H), 3.65 (brt, 2H), 5.38 (s, 2H), 6.25 (s, 1H) 7.10 (d, J = 8.55 Hz, 2H), 7.12 (s, 1H), 7.89 (d, J = 8.55 Hz, 2H), 11.42 (s, 1H), 13.00 (brs, 1H). Anal. ($C_{23}H_{28}N_4O_4$) C, H, N.

(*E*)-4-[[2-Butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1*H*-imidazol-1-yl]methyl]benzoic acid (7): ^{1}H NMR (DMSO) 0.64 (m, 3H), 0.84 (t, J = 7.31 Hz, 3H), 0.98 (m, 4H), 1.33 (m, 2H), 1.60 (m, 2H), 2.72 (t, J = 7.36 Hz, 2H), 3.45 (brs, 2H), 5.54 (s, 2H), 5.86 (s, 1H), 7.07 (d, J = 8.25 Hz, 2H), 7.91 (d, J = 8.25 Hz, 2H), 8.24 (s, 1H), 11.22 (s, 1H), 13.00 (brs, 1H). Anal. ($C_{23}H_{28}N_4O_4 \cdot 0.25H_2O$) C, H, N.

Diethyl (2,5-Dioxo-3-butyl-4-imidazolyl)phosphonate (8). To a solution of 1-butylhydantoin (**4**) (5.25 g, 0.034 mol) in acetic acid (45 mL), under nitrogen, at 90–100 °C was added a solution of bromine (1.86 mL) in acetic acid (15 mL) dropwise over 5 min. The mixture was maintained at this temperature for 90 min. At this time an aliquot revealed the reaction to be complete as judged by NMR. The solution was cooled, concentrated, and then evaporated again from toluene (50 mL). This oil was dissolved in ether (70 mL) and treated with triethyl phosphite (5.0 mL, 0.029 mol). After stirring for 16 h the mixture was concentrated in vacuo. The oil was dissolved in chloroform and filtered through a pad of silica gel. Concentration in vacuo afforded the product as a viscous, colorless oil (7.69 g, 80%): ^{1}H NMR ($CDCl_3$) 0.93 (t, J = 7.00 Hz, 3H), 1.26–1.43 (m, 8H), 1.55 (m, 2H), 3.39 (m, 1H), 3.78 (m, 1H), 4.26 (m, 4H), 4.35 (d, J = 15.00 Hz, 1H), 8.40 (brs, 1H). Anal. ($C_{11}H_{21}N_2O_5P$) C, H, N.

Methyl (*Z*)-4-[[2-Butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1*H*-imidazol-1-yl]methyl]benzoate (9). To a suspension of diethyl (3-butyl-2,5-dioxo-4-imidazolyl)phosphonate (**8**) (0.59 g, 1.85 mmol) and LiCl (0.160 g, 3.72 mmol) in acetonitrile (5 mL) was added DBU (0.554 mL, 3.70 mmol). After stirring for 5 min, methyl 4-[(2-butyl-5-formyl-1*H*-imidazol-1-yl)methyl]benzoate (**5**) (0.461 g, 1.54 mmol) was added in one portion. This wine-red solution was stirred for 16 h and evaporated in vacuo. Silica gel chromatography, eluting with chloroform, afforded the *Z* isomer (0.441 g, 65%): ^{1}H NMR ($CDCl_3$) 0.74 (t, J = 6.83 Hz, 3H), 0.89 (t, J = 7.27 Hz, 3H), 1.11 (m, 4H), 1.36 (m, 2H), 1.73 (m, 2H), 2.64 (t, J = 7.78 Hz, 2H), 3.78 (m, 2H), 3.90 (s, 3H), 5.19 (s, 2H), 6.31 (s, 1H) 7.03 (d, J = 8.12 Hz, 2H), 7.16 (s, 1H), 7.98 (d, J = 8.18 Hz, 2H), 8.60 (bs, 1H). Anal. ($C_{24}H_{30}N_4O_4$) C, H, N.

The more polar *E* isomer was then eluted from the column (0.096 g, 14%). **Methyl (*E*)-4-[[2-butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1*H*-imidazol-1-yl]methyl]benzoate (10):** ^{1}H NMR ($CDCl_3$) 0.75 (t, J = 6.83 Hz, 3H), 0.90 (t, J = 7.27 Hz, 3H), 1.14 (m, 4H), 1.40 (m, 2H), 1.72 (m, 2H), 2.74 (t, J = 7.78 Hz, 2H), 3.38 (m, 2H), 3.91 (s, 3H), 5.25 (s, 2H), 5.61 (s, 1H), 7.06 (d, J = 8.12 Hz, 2H), 8.04 (d, J = 8.18 Hz, 2H), 8.45 (s, 1H) (NH absent). Anal. ($C_{24}H_{30}N_4O_4$) C, H, N.

Diethyl (1-Butyl-2,5-dioxo-4-imidazolyl)phosphonate (13). To a solution of diethyl (2,5-dioxo-4-imidazolyl)phosphonate (**12**) (6.00 g, 0.025 mol) in DMF (15 mL), under N_2, were added K_2CO_3 (17.5 g, 0.127 mol) and 1-iodobutane (2.9 mL, 0.025 mol). The mixture was stirred at room temperature for 16 h and then filtered and the solid washed with ethyl acetate. The filtrate was concentrated in vacuo to afford a yellow oil which was redissolved in ethyl acetate, washed with water and brine, and then dried over $MgSO_4$. Evaporation of solvents under high vacuum afforded the required product as a viscous yellow oil which solidified on standing (6.45 g, 88%): ^{1}H NMR ($CDCl_3$) 0.92 (t, J = 7.26 Hz, 3H), 1.29–1.42 (m, 8H), 1.59 (m, 2H), 3.51 (t, J = 7.17 Hz, 2H), 4.26 (m, 4H), 4.38 (d, J = 15.00 Hz, 1H) 6.80 (brs, 1H). Anal. ($C_{11}H_{21}N_2O_5P$) C, H, N.

Methyl (*Z*)-4-[[2-Butyl-5-[(1-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1*H*-imidazol-1-yl]methyl]benzoate (14). To a solution of diethyl (1-butyl-2,5-dioxo-4-imidazolyl)phosphonate (**13**) (0.37 g, 1.28 mmol) in methylene chloride (5 mL) at room temperature were added DBU (0.38 mL, 2.54 mmol) and then methyl 4-[(2-butyl-5-formyl-1*H*-imidazol-1-yl)methyl]benzoate (**5**) (0.3 g, 1.00 mmol). This mixture was stirred for 16 h, diluted with ethyl acetate, and washed with brine. After drying over $MgSO_4$, the product was isolated, by chromatography eluting with 1% methanol in chloroform, as a yellow solid (0.305 g, 70%). A sample was recrystallized from ethyl acetate: ^{1}H NMR ($CDCl_3$) 0.83 (t, J = 7.07 Hz, 3H), 0.90 (t, J = 7.07 Hz, 3H), 1.22–1.40 (m, 4H), 1.62 (m, 4H), 2.67 (t, J = 7.36 Hz, 2H), 3.58 (t, J = 7.17 Hz, 2H), 3.91 (s, 3H), 5.23 (s, 2H), 6.29 (s, 1H), 7.00 (d, J = 8.12 Hz, 2H), 7.56 (s, 1H), 8.00 (d, J = 8.12 Hz, 2H), 9.28 (brs, 1H). Anal. ($C_{24}H_{30}N_4O_4$) C, H, N.

A small amount (10% yield) of the *E* isomer was isolated as well. **Methyl (*E*)-4-[[2-butyl-5-[(1-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1*H*-imidazol-1-yl]methyl]benzoate (15):** ^{1}H NMR ($CDCl_3$) 0.86 (t, J = 7.27 Hz, 3H), 0.90 (t, J = 7.27 Hz, 3H), 1.28–1.38 (m, 4H), 1.62–1.80 (m, 4H), 2.65 (t, J = 7.26 Hz, 2H), 3.58 (t, J = 7.08 Hz, 2H), 3.89 (s, 3H), 5.21 (s, 2H), 5.90 (s, 1H), 7.00 (d, J = 8.12 Hz, 2H), 8.00 (d, J = 8.12 Hz, 2H), 8.10 (brs, 1H), 8.45 (s, 1H). Anal. ($C_{24}H_{30}N_4O_4 \cdot 0.33H_2O$) C, H, N.

1,1-Dimethylethyl (*Z*)-4-[[2-Butyl-5-[(1-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1*H*-imidazol-1-yl]methyl]benzoate (17). To a solution of diethyl (1-butyl- 2,5-dioxo-

4-imidazolyl)phosphonate **(13)** (1.42 g, 4.86 mmol) in dichloromethane (10 mL), at −78 °C, was added DBU (0.731 mL, 4.88 mmol). After stirring for 15 min, a solution of 1,1-dimethylethyl 4-[(2-butyl-5-formyl-1*H*-imidazol-1-yl)methyl]-benzoate **(16)** (1.39 g, 4.06 mmol) in dichloromethane (5 mL) was added dropwise. This mixture was allowed to warm to room temperature and stirred for 16 h. The mixture was diluted with dichloromethane (30 mL) and washed with brine. After drying over $MgSO_4$, the solvents were removed in vacuo to afford a yellow solid which was collected and washed with ether to afford the title compound (1.307 g, 67%). ^1H NMR revealed 8% of the corresponding *E* isomer (characteristic ^1H signals at δ 5.38, 6.07, 8.24) which could not be separated by chromatography: ^1H NMR (DMSO) 0.83 (t, J = 7.38 Hz, 3H), 0.86 (t, J = 7.41 Hz, 3H), 1.27 (m, 4H), 1.52 (s, 9H), 1.54 (m, 4H), 2.65 (t, J = 7.27 Hz, 2H), 3.42 (t, J = 6.62 Hz, 2H), 5.46 (s, 2H), 6.22 (s, 1H), 7.05 (d, J = 8.16 Hz, 2H), 7.75 (s, 1H), 7.87 (d, J = 8.22 Hz, 2H), 10.40 (s, 1H). Anal. ($C_{27}H_{36}N_4O_4 \cdot 0.2H_2O$) C, H, N.

2-Butyl-1-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-5-formylimidazole (19). A solution of 2-butyl-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-4-chloro-5-formylimidazole (3.90 g, 5.89 mmol) in THF (100 mL), potassium acetate (0.6 g, 6.12 mmol), and Pd/C (10%) (0.5 g) was hydrogenated for 19 h. The solvents were removed in vacuo, and the product was purified by chromatography eluting with 30−50% ethyl acetate in hexanes. Unreacted starting material was recovered (0.700 g, 18%) and then the title compound eluted (2.43 g, 66%): ^1H NMR ($CDCl_3$) 0.87 (t, J = 7.26 Hz, 3H), 1.32 (m, 2H), 1.70 (m, 2H), 2.57 (t, J = 7.27 Hz, 2H), 5.49 (s, 2H), 6.80−7.50 (m, 22H), 7.79 (s, 1H), 7.95 (m, 1H), 9.67 (s, 1H). Anal. ($C_{41}H_{36}N_6O$) C, H, N.

(*Z*)-1-Butyl-5-[[2-butyl-3-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methylene]-3*H*-imidazol-4-yl]methylene]-2,4-imidazolidinedione (20). To a solution of diethyl (3-butyl-2,5-dioxo-4-imidazolyl)phosphonate **(8)** (0.770 g, 2.73 mmol) in methanol (20 mL) was added sodium hydride (0.16 g, 5.33 mmol), and the mixture was stirred for 5 min. A solution of 2-butyl-1-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]-methyl]-5-formylimidazole **(19)** (1.15 g, 1.83 mmol) in methylene chloride (100 mL) was then added. The mixture was stirred for 16 h. The solvents were removed in vacuo and ethyl acetate (100 mL) and methylene chloride (10 mL) added. The solution was washed with saturated NH_4Cl and brine. After drying over Na_2SO_4, the *Z* isomer (0.815 g, 58%) and *E* isomer (0.550 g, 39%) were purified by chromatography eluting with 1% methanol in chloroform. The *Z* isomer (0.800 g, 1.04 mmol) was added to methanol (100 mL) and 5% aqueous citric acid (5 mL). This white heterogenous mixture was refluxed for 3 h in which time a solution formed. The solution was cooled to room temperature and diluted with water (10 mL) and hexanes (100 mL). The aqueous methanol fraction was evaporated in vacuo and then dissolved in a mixture of ethyl acetate and water. After drying the organic fraction over Na_2SO_4, the product was precipitated by the addition of ether to a methylene chloride solution of the product (0.440 g, 46% overall): ^1H NMR (DMSO) 0.61 (m, 3H), 0.85 (m, 7H), 1.18 (m, 2H), 1.59 (m, 2H), 2.76 (t, J = 7.94 Hz, 2H), 3.60 (s, 2H), 5.35 (s, 2H), 6.26 (s, 1H), 6.99 (d, J = 7.73 Hz, 2H), 7.07 (d, J = 8.07 Hz, 2H), 7.35 (s, 1H), 7.47 (d, J = 7.94 Hz, 2H), 7.6−7.70 (m, 3H), 11.55 (s, 1H); HPLC eluant 55% 0.1% TFA in H_2O:45% MeCN, t_R 2.98 (99%); MS (CI) 525 (M + 1).

1-Butyl-5-[[2-butyl-3-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-3*H*-imidazol-4-yl]methyl]-2,4-imidazolidinedione (22). To 1-butyl-5-[[2-butyl-3-[[2′-[*N*-(triphenylmethyl)tetrazol-5-yl][1,1′-biphenyl]-4-yl]methyl]-3*H*-imidazol-4-yl]methyl]-2,4-imidazolidinedione (0.080 g, 0.10 mmol) were added methanol (30 mL) and glacial acetic acid (0.06 mL). This white heterogenous mixture was refluxed for 5 h in which time a solution formed. The solution was cooled to room temperature and diluted with water (10 mL) and hexanes (50 mL). The aquous methanol fraction was evaporated in vacuo and then dissolved in a minimal amount of methanol. Ether was added to precipitate a white solid: ^1H NMR (DMSO) 0.83 (m, 6H), 1.17−1.52 (m, 8H), 2.51 (m, 1H), 2.92 (m, 4H), 3.40 (m, 1H), 4.34 (s, 1H), 5.21 (s, 2H), 6.68 (s, 1H), 6.89 (d, J = 7.80 Hz, 2H), 7.08 (d, J = 7.80 Hz, 2H), 7.47−7.63 (m, 4H), 10.90 (s, 1H) (NH absent); HPLC eluant 67% 0.1% TFA in H_2O:33% MeCN, t_R 5.4 (98%). Anal. ($C_{29}H_{34}N_8O_2 \cdot H_2O$) C, H; N: calcd, 20.57; found, 20.07.

Methyl (*E*)- and (*Z*)-4′-[[2-Butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1*H*-imidazol-1-yl]methyl]-[1,1′-biphenyl]-2-carboxylate (24 and 25). To a solution of diethyl (3-butyl-2,5-dioxo-4-imidazolyl)phosphonate **(8)** (0.540 g, 1.91 mmol) in methanol (15 mL) was added NaH (80% in oil, 0.115 g, 3.83 mmol). The solution was stirrred for 5 min, and then 2-butyl-1-[(2′-carbomethoxy[1,1′-biphenyl]-4-yl)methyl]-1*H*-imidazole-5-carboxaldehyde **(23)** (0.515 g, 1.37 mmol) was added. The yellow solution was stirred for 16 h at room temperature and then diluted with ethyl acetate and saturated ammonium chloride. The organic fraction was washed with brine and then dried over Na_2SO_4. Chromatography separated the *Z* (0.304 g, 43%) and *E* (0.280 g, 40%) isomers, eluant 0−2% methanol in chloroform.

Methyl (*Z*)-4′-[[2-butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1*H*-imidazol-1-yl]methyl][1,1′-biphenyl]-2-carboxylate (24): ^1H NMR ($CDCl_3$) 0.71 (t, J = 6.50 Hz, 3H), 0.89 (t, J = 7.17 Hz, 3H), 1.18 (m, 4H), 1.34 (m, 2H), 1.73 (m, 2H), 2.71 (t, J = 7.60 Hz, 2H), 3.61 (s, 3H), 3.77 (m, 2H), 5.17 (s, 2H), 6.38 (s, 1H), 6.99 (d, J = 8.12 Hz, 2 H), 7.20−7.52 (m, 5H), 7.30 (s, 1H), 7.80 (d, J = 7.60 Hz, 1H), 10.50 (brs, 1H). Anal. ($C_{30}H_{34}N_4O_4$) H, N; C: calcd, 70.02; found, 69.58.

Methyl (*E*)-4′-[[2-butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1*H*-imidazol-1-yl]methyl][1,1′-biphenyl]-2-carboxylate (25): ^1H NMR ($CDCl_3$) 0.81 (t, J = 6.93 Hz, 3H), 0.92 (t, J = 7.17 Hz, 3H), 1.20−1.45 (m, 6H), 1.76 (m, 2H), 2.79 (t, J = 7.27 Hz, 2H), 3.43 (m, 2H), 3.66 (m, 3H), 5.23 (s, 2H), 5.78 (s, 1H), 7.02 (d, J = 8.11 Hz, 2H), 7.25−7.52 (m, 5H), 7.84 (d, J = 7.60 Hz, 1H), 8.35 (brs, 1H), 8.45 (s, 1H). Anal. ($C_{30}H_{34}N_4O_4$) C, H, N.

(*Z*)-*N*-[4-[[2-Butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1*H*-imidazol-1-yl]methyl]phenyl]-1,1,1-trifluoromethanesulfonamide (28). To a solution of diethyl (3-butyl-2,5-dioxo-4-imidazolyl)phosphonate **(8)** (1.48 g, 5.06 mmol) in ethanol (10 mL) was cautiously added sodium hydride batchwise (1.0 g, 25 mmol). The cloudy solution was stirred for 30 min, and then 2-butyl-1-[[4-(1,1,1-trifluoromethanesulfonamido)phenyl]methyl]-5-formylimidazole **(27)** (0.68 g, 1.75 mmol) in ethanol (10 mL) was added over 30 min. This solution was heated at reflux for 2 h. The reaction mixture was cooled to room temperature and treated with glacial acetic acid (2 mL). Evaporation in vacuo afforded a thick gel. Chromatography eluting with 0−4% methanol in chloroform afforded the required *Z* isomer which was triturated with ether/hexanes to afford the title compound as an amorphous solid (0.565 g, 61%). The more polar *E* isomer was then eluted: ^1H NMR (DMSO) 0.62 (t, J = 6.5 Hz, 3H), 0.84 (m, 7H), 1.30 (m, 2H), 1.58 (m, 2H), 2.88 (t, J = 7.4 Hz, 2H), 3.53 (brs, 2H), 5.31 (s, 2H), 6.26 (s, 1H), 6.95 (d, J = 8.4 Hz, 2H), 7.04 (d, J = 8.4 Hz, 2H), 7.51 (s, 1H), 11.75 (s, 1H) (NH absent). Anal. ($C_{23}H_{28}N_5O_4F_3S$) C, H, N.

(*E*)-*N*-[4-[[2-Butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1*H*-imidazol-1-yl]methyl]phenyl]-1,1,1-trifluoromethanesulfonamide (29): 0.11 g, 12%; ^1H NMR (DMSO) 0.80 (t, J = 7.0 Hz, 3H), 0.86 (t, J = 7.2 Hz, 3H), 0.95 (m, 2H), 1.19 (m, 2H), 1.31 (m, 2H), 1.61 (m, 2H), 2.96 (t, J = 8.0 Hz, 2H), 3.51 (brs, 2H), 5.48 (s, 2H), 5.98 (s, 1H), 6.91 (d, J = 8.5 Hz, 2H), 7.04 (d, J = 8.5 Hz, 2H), 8.32 (s, 1H), 11.45 (s, 1H) (NH absent). Anal. ($C_{23}H_{28}N_5O_4F_3S \cdot 0.25H_2O$) C, H, N.

(Z)- and (*E*)-1-Butyl-5-[[2-butyl-3-[[4-(1*H*-tetrazol-5-yl)-phenyl]methyl]-3*H*-imidazol-4-yl]methylene]-2,4-imidazolidinedione (33 and 34). To a solution of diethyl (3-butyl-2,5-dioxo-4-imidazolyl)phosphonate **(8)** (0.240 g, 0.86 mmol) in ethanol (10 mL) was added sodium hydride (0.072 g, 1.80 mmol), and the mixture was stirred for 15 min. A solution of 2-butyl-1-[[4-[1-(triphenylmethyl)tetrazol-5-yl]phenyl]methyl]-5-formylimidazole **(30)** (0.400 g, 0.72 mmol) in methylene chloride (5 mL) was then added. The mixture was stirred for 16 h. The solvents were removed in vacuo and the *Z* and *E* isomers purified by chromatography eluting with 20% ethyl acetate in methylene chloride. The *Z* isomer **31** (0.36 g, 72%) and the *E* isomer **32** (0.09 g, 18%) were each separately

dissolved in methanol (5 mL) containing a 10% aqueous solution of citric acid (0.5 mL). The reaction mixture was refluxed overnight. Water (20 mL) was added and the mixture extracted with hexane. The aqueous fraction was then extracted with ethyl acetate, washed with brine, and dried over $MgSO_4$. After evaporating in vacuo, the residue was crytallized from a combination of hexane, ethyl acetate, and methanol. This procedure afforded **33** (0.06 g, 17%): ^{1}H NMR (DMSO) 0.61 (m, 3H), 0.88 (m, 7H), 1.34 (m, 2H), 1.62 (m, 2H), 2.74 (t, J = 7.3 Hz, 2H), 3.64 (brs, 2H), 5.41 (s, 2H), 6.28 (s, 1H), 7.18 (s, 1H), 7.23 (d, J = 8.23 Hz, 2H), 8.00 (d, J = 8.23 Hz, 2H), 11.44 (s, 1H) (NH absent). Anal. ($C_{23}H_{28}N_8O_2S\cdot0.9H_2O$) C, H, N.

34: ^{1}H NMR (DMSO) 0.61 (m, 3H), 0.86 (t, J = 7.24 Hz, 3H), 1.05 (m, 4H), 1.35 (m, 2H), 1.62 (m, 2H), 2.76 (t, J = 7.3 Hz, 2H), 3.47 (brs, 2H), 5.49 (s, 2H), 5.96 (s, 1H), 7.09 (d, J = 8.20 Hz, 2H), 7.98 (d, J = 8.20 Hz, 2H), 8.24 (s, 1H), 11.24 (s, 1H) (NH absent). Anal. ($C_{23}H_{28}N_8O_2S\cdot1.67H_2O$) C, H, N.

Methyl (*Z*)-1-[4-[[2-Butyl-5-[[1-butyl-3-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1*H*-imidazol-1-yl]methyl]phenyl]cyclopentanecarboxylate Monohydrochloride (36). Methyl (*Z*)-1-[4-[[2-butyl-5-[[1-butyl-2,5-dioxo-4-imidazolidinylidene]methyl]-1*H*-imidazol-1-yl]methyl]phenyl]cyclopentanecarboxylate (1.00 g, 1.97 mmol) and 4-(chloromethyl)-2-methylthiazole monohydrochloride (0.363 g, 1.97 mmol) were dissolved in DMF (10 mL). K_2CO_3 (3.0 g, 21.7 mmol) was added and the mixture stirred for 16 h. The mixture was filtered and evaporated. The residue was added to water, and the gum that formed was dissolved in ether. After washing the ethereal fraction with water and drying over K_2CO_3, the product was purified by chromatography: eluant 0.5–3% methanol in chloroform. The appropriate fraction was dissolved in ether and treated with ethereal HCl to afford the required product (0.64 g, 48%). A small amount of the corresponding *E* isomer (10%) was also collected: ^{1}H NMR (DMSO) 0.77 (t, J = 7.10 Hz, 3H), 0.90 (t, J = 7.25 Hz, 3H), 1.15–1.85 (m, 14H), 2.51 (m, 2H), 2.56 (s, 3H), 2.93 (t, J = 7.23 Hz, 2H), 3.54 (brt, J = 7.0 Hz, 2H), 3.51 (s, 3H), 4.82 (s, 2H), 5.20 (s, 2H), 6.08 (s, 1H), 7.00 (s, 1H), 7.02 (d, J = 8.33 Hz, 2H), 7.29 (d, J = 8.33 Hz, 2H), 7.78 (s, 1H). Anal. ($C_{34}H_{43}N_5O_4S\cdot HCl\cdot H_2O$) C, H, N.

(*Z*)-1-[4-[[2-Butyl-5-[[1-butyl-3-[(2-methyl-4-thiazoly)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1*H*-imidazol-1-yl]methyl]phenyl]cyclopentanecarboxylic Acid (37). Methyl (*Z*)-1-[4-[[2-butyl-5-[[1-butyl-2,5-dioxo-3-[(2-methyl-4-thiazoly)methyl]-4-imidazolidinylidene]methyl]-1*H*-imidazol-1-yl]methyl]phenyl]cyclopentanecarboxylate monohydrochloride **(36)** (0.340 g, 0.506 mmol) and 2 N HCl (15 mL) were heated at reflux for 2 h. After evaporation in vacuo, the residue was dissolved in methanol and treated with saturated aqueous NaOAc to precipitate a gum. This gum crystallized from ethyl acetate and was then recrystallized from methanol/ether to afford the title compound (0.153 g, 50%): ^{1}H NMR (DMSO) 0.79 (t, J = 7.34 Hz, 3H), 0.88 (t, J = 7.39 Hz, 3H), 1.15–1.77 (m, 14H), 2.50 (m, 2H), 2.55 (s, 3H), 2.56 (t, J = 6.15 Hz, 2H), 3.51 (brt, J = 6.83 Hz, 2H), 4.96 (s, 2H), 5.01 (s, 2H), 6.27 (s, 1H), 6.73 (s, 1H), 6.80 (d, J = 8.29 Hz, 2H), 7.12 (s, 1H), 7.24 (d, J = 8.29 Hz, 2H) (CO_2H absent). Anal. ($C_{33}H_{41}N_5O_4S$) C, H, N.

Methyl (*Z*)-4-[[2-Butyl-5-[[1-butyl-2,5-dioxo-3-(phenylmethyl)-4-imidazolidinylidene]methyl]-1*H*-imidazol-1-yl]methyl]benzoate Monohydrochloride (42). To a solution of methyl (*Z*)-4-[[2-butyl-5-[(1-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1*H*-imidazol-1-yl]methyl]benzoate **(14)** (0.509 g, 1.16 mmol) in DMF (6 mL) was added K_2CO_3 (0.800 g, 5.80 mmol). After stirring for 5 min, benzyl bromide (0.150 mL, 1.26 mmol) was added. The mixture was stirred for 16 h, diluted with ethyl acetate, washed with water and brine, and then dried over $MgSO_4$. A viscous oil (0.525 g, 86%) was obtained upon chromatography on silica gel (eluant 1% methanol in chloroform) and evaporation of the solvents in vacuo. This yellow oil was dissolved in ether and treated with ethereal HCl to afford a foamy solid upon evaporation in vacuo. This foam was crystallized from 2-propanol and ether: ^{1}H NMR ($CDCl_3$) 0.84 (t, J = 7.2 Hz, 3H), 0.96 (t, J = 7.2 Hz, 3H), 1.35 (m, 4H), 1.65 (m, 4H), 2.76 (t, J = 7.7 Hz, 2H), 3.68 (t, J = 7.2 Hz, 2H), 3.91 (s, 3H), 4.32 (s, 2H), 4.90 (s, 2H), 5.84 (s, 1H), 6.70 (m, 2H), 6.82 (d, J = 7.92 Hz, 2H), 7.28 (m, 3H), 7.30 (s, 1H), 7.98 (d, J = 7.92, 2H). Anal. ($C_{31}H_{36}N_4O_4\cdot HCl\cdot 1.25H_2O$) C, H, N.

Methyl (*Z*)-4-[[2-Butyl-5-[(1,3-dibutyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1*H*-imidazol-1-yl]methyl]benzoate Monohydrochloride (48). To a solution of methyl (*Z*)-4-[[2-butyl-5-[(1-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1*H*-imidazol-1-yl]methyl]benzoate **(14)** (0.140 g, 0.32 mmol) in DMF (2 mL) was added K_2CO_3 (0.200 g, 1.44 mmol). After stirring for 5 min, 1-iodobutane (0.050 mL, 0.44 mmol) was added. The mixture was stirred for 16 h, diluted with ethyl acetate, washed with water and brine, and then dried over $MgSO_4$. A viscous oil was obtained by evaporation of the solvents in vacuo. This yellow oil was dissolved in ether and treated with ethereal HCl to precipitate a gummy solid. This gum was crystallized from 2-propanol/ether to afford the title compound (0.130 g, 82%): ^{1}H NMR (DMSO) 0.62 (t, J = 6.8 Hz, 3H), 0.86 (m, 8H), 1.23–1.75 (m, 10H), 2.50 (brs, 2H), 3.11 (t, J = 7 Hz, 2H), 3.49 (m, 2H), 3.83 (s, 3H), 5.66 (s, 2H), 6.26 (s, 1H), 7.34 (d, J = 8.21 Hz, 2H), 7.92 (d, J = 8.21 Hz 2H), 7.95 (s, 1H). Anal. ($C_{28}H_{38}N_4O_4\cdot HCl$) C, H, N.

Methyl (*Z*)-4-[[2-Butyl-5-[[1-butyl-3-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1*H*-imidazol-1-yl]methyl]benzoate Dihydrochloride (57). To a solution of methyl (*Z*)-4-[[2-butyl-5-[(1-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1*H*-imidazol-1-yl]methyl]benzoate hydrochloride (prepared by treating **14** with ethereal HCl and crystallization from 2-propanol/ether) (3.00 g, 6.3 mmol) in DMF (20 mL) was added K_2CO_3 (10.0 g, 72 mmol). After stirring for 5 min, 2-methyl-4-(chloromethyl)thiazole hydrochloride (1.33 g, 7.2 mmol) was added. An additional amount of DMF (10 mL) was added after a period of 4 h to aid stirring. The mixture was stirred for 3 days and then filtered. The filtrate was concentrated in vacuo and added to water (20 mL). The gum was separated, dissolved in ether (50 mL), washed with water, and dried over K_2CO_3 and charcoal. A viscous oil was obtained by evaporation of the solvents in vacuo which was dissolved in ether, treated with ethereal HCl, and then evaporated in vacuo to afford a solid foam. Recrystallization from 2-propanol/ether afforded the title compound (2.90 g, 73%): ^{1}H NMR (DMSO) 0.80 (t, J = 7.34 Hz, 3H), 0.88 (t, J = 7.37 Hz, 3H), 1.25 (m, 4H), 1.54 (m, 4H), 2.56 (s, 3H), 2.96 (brt, J = 7.65 Hz, 2H), 3.52 (brt, J = 6.84 Hz, 2H), 3.86 (s, 3H), 4.84 (s, 2H), 5.36 (s, 2H), 5.98 (s, 1H), 7.05 (s, 1H), 7.20 (d, J = 8.24 Hz, 2H), 7.84 (s, 1H), 7.92 (d, J = 8.26 Hz, 2H). Anal. ($C_{29}H_{35}N_5O_4S\cdot 2HCl\cdot 0.5H_2O$) C, H, N.

Methyl (*Z*)-4-[[2-Butyl-5-[[1-butyl-3-[(2-amino-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1*H*-imidazol-1-yl]methyl]benzoate Dihydrochloride (63). To a solution of methyl (*Z*)-4-[[2-butyl-5-[(1-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1*H*-imidazol-1-yl]methyl]benzoate hydrochloride (**14**·HCl) (3.70 g, 7.8 mmol) in DMF (30 mL) was added K_2CO_3 (15.0 g, 0.1 mol). After stirring for 5 min, 2-amino-4-(chloromethyl)thiazole hydrochloride (1.85 g, 10.0 mmol) was added. The mixture was stirred for 72 h and then diluted with ethyl acetate and filtered. The filtrate was concentrated in vacuo and added to water (50 mL). The brown solid that formed was dissolved in methylene chloride (100 mL), washed with water, and dried over K_2CO_3 and charcoal. A viscous oil (4.5 g) was obtained by evaporation of the solvents in vacuo. This oil was dissolved in ether and treated with ethereal HCl to precipitate a gum which was collected by decantation. This gum was recrystallized from 2-propanol/ether to afford the title compound as a white solid (3.20 g, 62%): ^{1}H NMR (DMSO) 0.82 (t, J = 7.20 Hz, 3H), 0.88 (t, J = 7.30 Hz, 3H), 1.28 (m, 4H), 1.55 (m, 4H), 3.00 (brt, J = 7.4 Hz, 2H), 3.50 (brt, J = 6.6 Hz, 2H), 3.86 (s, 3H), 4.67 (s, 2H), 5.47 (s, 2H), 6.00 (s, 1H), 6.38 (s, 1H), 7.27 (d, J = 8.02 Hz, 2H), 7.77 (s, 1H), 7.96 (d, J = 8.02 Hz, 2H) (NH_2 absent). Anal. ($C_{28}H_{34}N_6O_4S\cdot 2HCl\cdot 2H_2O$) C, H, N.

(*Z*)-4-[[2-Butyl-5-[(1,3-dibutyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1*H*-imidazol-1-yl]methyl]benzoic Acid (89). To a solution of 1,1-dimethylethyl (*Z*)-4-[[2-butyl-5-[(1-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1*H*-imidazol-1-yl]methyl]benzoate **(17)** (2.04 g, 4.25 mmol) in DMF (20 mL) were added K_2CO_3 (2.93 g, 5 equiv) and 1-iodobutane (1.70 g, 2 equiv). The mixture was stirred for 16 h and then evapo-

rated in vacuo. The ethyl acetate extract was washed with brine, dried over $MgSO_4$, and then evaporated in vacuo. The yellow oil that resulted (2.33 g) was used directly in the subsequent reaction. 1,1-Dimethylethyl (*Z*)-4-[[2-butyl-5-[(1,3-dibutyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1*H*-imidazol-1-yl]methyl]benzoate **(18)** (2.33 g, assume 4.25 mmol) was dissolved in methylene chloride (20 mL) and trifluoroacetic acid (15 mL). After stirring for 4 h, the reaction mixture was evaporated in vacuo. The yellow residue was dissolved in dichloromethane (50 mL) and washed with aqueous NaOAc (10%, 60 mL) and brine. A yellow foam was obtained upon evaporation of the organic extract after drying over $MgSO_4$. This foam solidified upon trituration with ether. The required *Z* isomer (1.085 g, 52%) was separated from the *E* isomer **90** (12%) by chromatography, eluting with 2–3% methanol in dichloromethane: ^{1}H NMR (DMSO) 0.63 (m, 3H), 0.86 (m, 8H), 1.22 (m, 2H), 1.30 (m, 2H), 1.50 (m, 2H), 1.61 (m, 2H), 2.69 (t, J = 7.60 Hz, 2H), 3.33 (m, 2H), 3.44 (t, J = 7.2 Hz, 2H), 3.70 (m, 2H), 5.40 (s, 2H), 6.37 (s, 1H), 7.10 (d, J = 8.40 Hz, 2H), 7.15 (s, 1H), 7.88 (d, J = 8.40 Hz, 2H), 13.00 (brs, 1H). Anal. ($C_{27}H_{36}N_4O_4$) C, H, N.

(*Z*)-4-[[2-Butyl-5-[[1-butyl-3-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1*H*-imidazol-1-yl]methyl]benzoic Acid (95). A mixture of methyl (*Z*)-4-[[2-butyl-5-[[1-butyl-3-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1*H*-imidazol-1-yl]methyl]-benzoate **(57)** (0.428 g, 0.65 mmol) and 2 N HCl (12 mL) was refluxed for 1 h in which time all the solid dissolved. The solvents were removed in vacuo, and the mixture was evaporated from ethanol (5 mL) three times. The solid that resulted was treated with 5% aqueuos sodium acetate (10 mL) and water (10 mL) to precipitate a gummy solid which was dissolved in methylene chloride (30 mL). The organic layer was dried over Na_2SO_4 and then evaporated in vacuo. The residue was recrystallized from hot ethyl acetate/hexane to afford the title compound (0.279 g, 80%): ^{1}H NMR (DMSO) 0.80 (t, J = 7.27 Hz, 3H), 0.88 (t, J = 7.29 Hz, 3H) 1.27 (m, 4H), 1.53 (m, 4H), 2.54 (s, 3H), 2.55 (t, J = 7.35 Hz, 2H), 3.50 (t, J = 6.75 Hz, 2H), 4.95 (s, 2H), 5.15 (s, 2H), 6.22 (s, 1H), 6.73 (s, 1H), 6.94 (d, J = 8.13 Hz, 2H), 7.15 (s, 1H), 7.84 (d, J = 8.11 Hz, 2H), 13.00 (brs, 1H). Anal. ($C_{28}H_{33}N_5O_4S$) C, H, N.

Isomerization of (*Z*)-4-[[2-Butyl-5-[[1-butyl-3-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]-methyl]-1*H*-imidazol-1-yl]methyl]benzoic Acid (95) to (*E*)-4-[[2-Butyl-5-[[1-butyl-3-[(2-methyl-4-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1*H*-imidazol-1-yl]methyl]benzoic Acid (96). Methyl (*Z*)-4-[[2-butyl-5-[[1-butyl-3-[(4-methyl-2-thiazolyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1*H*-imidazol-1-yl]methyl]benzoic acid **(95)** (0.25 g, 0.46 mmol) was dissolved in concentrated HCl (15 mL) and the mixture refluxed for 4 h. The mixture was concentrated in vacuo and aqueous sodium acetate added. The precipitate was collected and washed with water. This solid was dissolved in methanol (2 mL), treated with charcoal, and then filtered and concentrated in vacuo. The residue was recrystallized from hot ethyl acetate to afford the title compound (0.04 g, 16%): ^{1}H NMR (DMSO) 0.80 (t, J = 7.27 Hz, 3H), 0.89 (t, J = 7.29 Hz, 3H), 1.27 (m, 4H), 1.54 (m, 4H), 2.47 (s, 3H), 2.62 (t, J = 7.31 Hz, 2H), 3.52 (t, J = 6.85 Hz, 2H), 4.85 (s, 2H), 5.42 (s, 2H), 6.17 (s, 1H), 6.92 (d, J = 8.20 Hz, 2H), 6.95 (s, 1H), 7.82 (d, J = 8.21 Hz, 2H), 8.29 (s, 1H) (CO_2H absent). Anal. ($C_{28}H_{33}N_5O_4S$·0.25H_2O) C, H, N.

Hydrogenation of 98 To Afford 4-[[2-Butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinyl)methyl]-1*H*-imidazol-1-yl]-methyl]benzoic Acid. To a solution of (*E*)-4-[[2-butyl-5-[(3-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1*H*-imidazol-1-yl]methyl]benzoic acid **(98)** (0.84 g, 2.00 mmol) in 1 N NaOH (2.04 mL, 2.04 mmol) and water (500 mL) was added PtO_2 (0.200 g), and then a hydrogen balloon was attached. The mixture was stirred for 3 h, 1 N HCl (2.04 mL, 2.04 mmol) was added, and then the mixture was concentrated at reduced pressure. Ethanol (50 mL) was added and the mixture filtered. The filtrate was evaporated in vacuo, and the residue (0.700 g, 90% pure) was purified by crystallization and chromatography eluting with 5–15% methanol in chloroform: ^{1}H NMR (DMSO) 0.78 (t, J = 7.39 Hz, 3H), 0.81 (t, J = 7.20 Hz, 3H), 1.25–1.48 (m, 8H), 2.50 (brt, 2H), 2.86 (m, 2H), 3.40 (m, 2H), 4.31 (brt, 1H), 5.25 (s, 2H), 6.58 (s, 1H), 6.98 (d, J = 8.21 Hz, 2H), 7.89 (d, J = 8.21 Hz, 2H) (CO_2H and NH absent). Anal. ($C_{23}H_{30}N_4O_4S$·H_2O) C, H, N.

(*Z*)-4-[[2-Butyl-5-[[1-butyl-3-[(5-methyl-3-thienyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1*H*-imidazol-1-yl]methyl]benzoic Acid (109). To a solution of 1,1-dimethylethyl (*Z*)-4-[[2-butyl-5-[(1-butyl-2,5-dioxo-4-imidazolidinylidene)methyl]-1*H*-imidazol-1-yl]methyl]benzoate **(17)** (1.00 g, 2.08 mmol) in THF (15 mL) was added NaH (0.11 g, 2.75 mmol). This mixture was stirred for 15 min to afford a yellow solution. 4-(Bromomethyl)-2-methylthiophene (0.65 g, 3.39 mmol) in THF (5 mL) was added dropwise over 30 min. After 3 h potassium iodide (0.5 g, 3 mmol) was added, and then the mixture was stirred for 16 h. The mixture was filtered, and the solvents were removed in vacuo. The product was isolated, by chromatography eluting with 0–8% acetone in dichloromethane (0.78 g, 64%). The 1,1-dimethylethyl (*Z*)-4-[[2-butyl-5-[[1-butyl-3-[(5-methyl-3-thienyl)methyl]-2,5-dioxo-4-imidazolidinylidene]methyl]-1*H*-imidazol-1-yl]methyl]benzoate (0.78 g, 1.32 mmol) was disolved in methylene chloride (14 mL) and trifluoroacetic acid (10 mL). After stirring for 2 h, the reaction mixture was evaporated in vacuo. After chromatography, eluant 0–6% methanol in dichloromethane, the foam was dissolved in ethyl acetate, washed with 10% aqueous NaOAc and brine, and then dried over $MgSO_4$. Crystallization from ether afforded **109** (0.319 g, 45%): ^{1}H NMR (DMSO) 0.81 (t, J = 7.31 Hz, 3H), 0.87 (t, J = 7.18 Hz, 3H), 1.26 (m, 4H), 1.53 (m, 4H), 2.34 (s, 3H), 2.58 (t, J = 7.33 Hz, 2H), 3.49 (t, J = 6.75 Hz, 2H), 4.84 (s, 2H), 5.13 (s, 2H), 6.21 (s, 1H), 6.31 (s, 1H), 6.44 (s, 1H), 6.96 (d, J = 8.11 Hz, 2H), 7.16 (s, 1H), 7.84 (d, J = 8.02 Hz, 2H) (CO_2H absent). Anal. ($C_{29}H_{34}N_4O_4S$) C, H, N.

Biological Assays. Angiotensin Receptor Binding Assay (AT1). Methods for the preparation of rat liver membranes have been reported previously in detail.[17] Solutions (10 mM) of the test compounds were diluted to the appropriate concentration and added to 1 mg of rat liver membrane homogenate, 1 mg of wheat germ agglutinin (WGA)-coated scintillation proximity assay (SPA) beads, and 50 pM [^{125}I]angiotensin II. After an incubation of 180 min at 25 °C, the light emitted by the stimulated SPA bead was measured. Nonspecific binding was defined as radioactivity retained on the beads in the presence of 10 μM saralasin. The inhibitory concentration (IC_{50}) of an inhibitor that gave 50% displacement of the specifically bound [^{125}I]angiotensin II was then calculated. Concentrations of the test compound were tailored to adequately span the concentration inhibiting binding by 50%. Typically IC_{50}'s were determined via nonlinear regression curve fitting employing seven points and in duplicate. Individual points were determined with an average error of ±5%. For comparison, using this protocol, reference values for antagonists were DuP 753,[21] 9.2 nM; L-158809,[30] 0.8 nM; and SKF 108566,[36] 2.8 nM.

For assessing AT_2 receptor binding, a similar protocol was employed except rabbit uterine membranes were used.

Angiotensin II-Induced Contraction in Isolated Vascular Tissue (RAR). Details for the rabbit thoracic aorta ring preparation have been reported previously.[17] Briefly the aortic rings were connected to a pressor transducer, and the tissue preparation was allowed to equilibrate at a mechanically induced tension of 4 g for 1.5 h before use. A control–response curve to exogenous Ang II was recorded. The test compound in DMSO was added to the bath (Krebs-bicarbonate solution gassed continuously with 5% CO_2 in oxygen) at several concentrations that were expected to span the IC_{50}, as predicted from receptor binding studies. The tissue preparation was allowed to equilibrate for 10 min. For each concentration of antagonist, the pressor response to 10 nM Ang II was recorded. The preparation was then allowed to equilibrate for 1 h between Ang II challenges. The IC_{50} of the test compounds represents the mean concentration of antagonist that inhibited by 50% the contractile response to Ang II for two rings within the same bath.

Evaluation of the Test Compound in Conscious Renal Hypertensive Rats (RHR). The protocol was similar to that

previously described.[17] Briefly young male Sprague–Dawley rats underwent bilateral renal artery clipping to afford rats with mean blood pressure of greater than 150 mmHg. The test compounds were administered in 0.5% methocel in water by oral gavage in a volume of 2 mL/kg, and the blood pressure was measured by a cannula inserted in the abdominal aorta. Data reported represent the maximum percent reduction in blood pressure relative to base line and were averaged over three to four animals. Standard error mean was typically <5% in control and <8% in drug-treated animals. Heart rate did not vary significantly from base line.

Evaluation of the Test Compound in Sodium-Deplete Normotensive Monkeys. The protocol was similar to that previously described.[49] Briefly animals were rendered renin dependent by a combination of a sodium-restricted diet and pretreatment with the diuretic furosemide. In this model saralasin (20 μg/kg/min) infusion reduced mean arterial blood pressure by 23 ± 2 mmHg. The test compounds were administered in 0.5% methocel in water by oral gavage in a volume of 2 mL/kg, and the blood pressure was measured via an arterial vascular access port. Data reported represent the maximum percent reduction in blood pressure relative to base line and were averaged over two animals. Heart rate did not vary significantly from base line.

Supporting Information Available: Tables of HPLC retention times, log *P* measured by octanol/water partition method, analytical data, blood pressure effect of compounds on renal hypertensive rats, and inhibition of Ang II-induced pressor responses in normotensive rats (9 pages). Ordering information is given on any current masthead page.

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