Nonpeptide Angiotensin II Receptor Antagonists. 1. Synthesis and in Vitro Structure–Activity Relationships of 4-[[[(1H-Pyrrol-1-ylacetyl)amino]phenyl]methyl]imidazole Derivatives as Angiotensin II Receptor Antagonists

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A novel series of non-biphenylyltetrazole angiotensin II receptor antagonists which contain a 1H-pyrrol-1-ylacetyl residue in place of the benzoyl residue in EXP 6803 have been developed. The receptor binding activity of several members of this new series was in the 10^{-8} M range, which was better than that of EXP 6803. Introduction of a carboxylic acid moiety at the 2-position of the pyrrole ring enhanced the in vitro binding affinity at the receptor by 10-fold. Compounds containing an acetic acid (18) or a propionic acid residue (20) at the 5-position of the imidazole were more potent than the carboxylic acid analogue (24). The binding IC_{50} of the most potent compound 20 was 22 nM. Compounds 18, 20, and 24 in their best fit conformations were manually overlayed on that of the template conformation of EXP 6803 and EXP 8623, respectively. The synthesis and structure–activity relationship data are described.

Introduction

Recently, several nonpeptidic angiotensin II (AT₁) receptor antagonists have been reported,[1-7] and one of these, DuP 753[8] (losartan), is in phase III undergoing development as an antihypertensive. With the exception of SKF 108566 (Chart I),[7] the classes of antagonists, which are devoid of agonist activity, contain a common structural theme, a 1H-tetrazol-5-ylbiphenyl moiety or a slight variation thereof. By contrast, several variations of the imidazole moiety in DuP 753 have maintained high affinity for the AT₁ receptor. As part of an ongoing search to identify novel non-biphenylyltetrazole AT₁ receptor antagonists, we have explored the modification of the benzoyl moiety in EXP 6803, an early lead developed by Du Pont. Several variations of the "X" linkage, such as OCH₂, CH=CH (trans), CONH (reverse amide), O, S, CO, NHCONH, and a single bond (zero atom linker), between the two phenyl rings in EXP 6803 have been reported (Chart II).[9-12] The biphenyl derivative, EXP 7711, was a breakthrough into orally active compounds which eventually led to the discovery of DuP 753. We report herein our initial efforts in optimizing the receptor binding affinity of the EXP 6803 series by replacing the benzoyl group with novel 1H-pyrrol-1-yl-acetyl residues. This investigation led to several compounds with modest receptor binding affinity which contributed to the understanding of the structural requirements for optimal binding to the angiotensin receptor. The synthesis and in vitro structure–activity relationships are described.

Chemistry

Target compound esters 11–14 (Table II), 17, 19, 21, 23, and 27 (Table III), 29, 32, and 34 (Table IV) and 36, 38, 40, 42, 44, 46, and 48 (Table V) were prepared by coupling suitably substituted 1H-pyrroyl-1-ylacetic acids (Table I) with 1-(4-aminobenzyl)imidazole derivatives (Schemes III–V). Two procedures for the coupling reaction were used

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Chart I. Orally Active Angiotensin II Antagonists

DuP 753

(Losartan)

SKF-108566
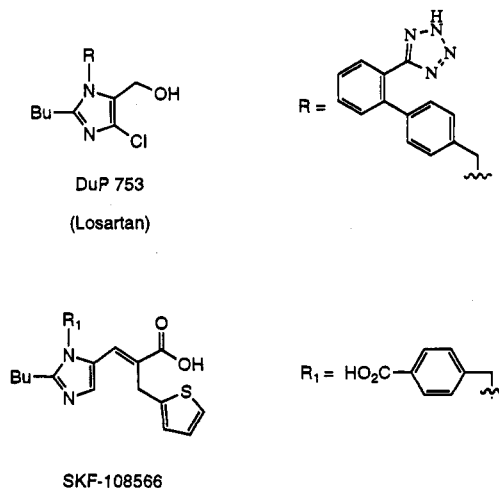
Chart II
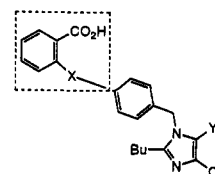
Compound	Y	X	AT₁ receptor binding IC_{50} (μM)
EXP 6803	CH₂CO₂CH₃	CONH-	0.14
EXP 7711	CH₂OH	bond	0.30
EXP 8623	CO₂H	bond	0.092

[DCC/HOBT, 30–40% (method A), and mixed anhydride,[13] 70–80% (method B), Scheme I]. Carboxylic acid derivatives 15, 18, 20, 22, 24, and 28 (Table III), 30, 31, 33, and 35 (Table IV), and 37, 39, 41, 43, and 45 (Table V) were obtained via saponification of the corresponding
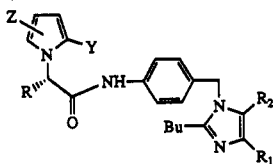
Table I. 1*H*-Pyrrole-1-acetic Acid Derivatives

compd	R[h]	Y	Z	mp, °C[a] (crystn solvent)	yield, %[b]	formula[c]	$[\alpha]_D^{22}$, deg (c, MeOH)
1	H	CO₂Me	H	131–132 (EtOAc)	65	$C_8H_9NO_4$	
2	Ph	CO₂Me	H	oil	10	$C_{14}H_{13}NO_4{}^e$	
3	Bu	CO₂Me	H	79–82 (EtOAc/hexane)	61.7	$C_{12}H_{17}NO_4$	1.1 (0.969)
4a	PhCH₂	CO₂Me	H	oil	41	$C_{15}H_{15}NO_4 \cdot 0.4AcOH$	−17.5 (1.0)
4b[d]	ThCH₂	CO₂Me	H	115–116 (EtOAc/hexane)	44	$C_{13}H_{13}NO_4S$	
4c	PhCH₂	H	H	90–93	80.9	$C_{13}H_{13}NO_2$	−57.7 (1.095)
4d	PhCH₂	Me	H	93–94 (hexane)	64.4	$C_{14}H_{15}NO_2$	−103.8 (1.002)
4e	PhCH₂	Me	3-CO₂Et	oil	42	$C_{17}H_{19}NO_4 \cdot 0.3AcOH^f$	−14.6 (1.212)
4f	PhCH₂	H	3-CO₂Et	oil	37.3	$C_{16}H_{17}NO_4{}^g$	−50.8 (0.875)
4g	ThCH₂	H	H	77–79° (hexane)	81.9	$C_{11}H_{11}NO_2S \cdot 0.1AcOH$	
4h	PhCH₂	Me	5-Me	119–122°	58	$C_{15}H_{17}NO_2$	−90.7 (1.058)

[a] Compounds were purified via chromatography. [b] Yields were not optimized. [c] All microanalytical values were within ±0.4% of the calculated values except for 2 and 4e. [d] Racemic. [e] C, N; H: calcd, 5.05; found, 5.91. [f] N, H; C: calcd, 66.19; found, 65.51. [g] Not analyzed. [h] Th = 2-thienyl.

Table II. [[[(1*H*-Pyrrolyl-1-acetyl)amino]phenyl]methyl]-3*H*-imidazoles

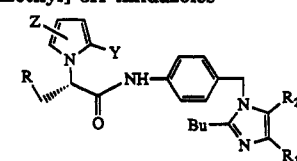| compd	Z	Y	R	R₂	R₁	mp, °C[a]	formula[c]	yield, %[b] (method)	receptor binding; IC_{50}, μM^d
11	H	CO₂Me	Ph	CH₂OH	Cl	e	$C_{29}H_{31}ClN_4O_4 \cdot 2.7H_2O$	20 (A)	1.12 ± 0.064
12	H	CO₂Me	Bu	CH₂OH	Cl	e	$C_{27}H_{35}ClN_4O_4$	34 (A)	0.59 ± 0.065
13	H	CO₂Me	H	CH₂OH	Cl	231–232	$C_{23}H_{27}ClN_4O_4 \cdot 0.14EtOAc$	38 (A)	8.37
14	H	CO₂Me	CH₂Ph	CH₂OH	Cl	e	$C_{30}H_{33}ClN_4O_4$	40 (A)	0.21 ± 0.058

[a] Compounds were purified by chromatography. [b] Yields were not optimized. [c] All microanalytical values were in agreement with assigned structures (within ±0.4%). [d] Concentration to inhibit binding of radiolabeled AII by 50%. IC_{50} values were obtained from a dose–response curve generated from at least five or six doses and are expressed as a mean ± SEM. [e] Foam.

esters (Scheme I). The hydrolysis step went smoothly with the exception of compounds in which Y = CO₂Me. In those cases the desired hydrolysis products were always contaminated with the isomeric acids (55–62, Table VII), which were separated via chromatography. Structures of these acids were proven from spectral data and analyses (see Experimental Section). Deschloro compounds 16, 25, and 26 were best prepared from the chloro esters 14 and 23 via catalytic reduction (5% Pd/C/KOAc) followed by hydrolysis (Scheme I).

The 1*H*-pyrrole-1-acetic acids (1–3, 4a–g, Table I) were prepared (40–80%) by reacting requisite amino acids with suitably substituted 2,5-dimethoxy-2,3,4,5-tetrahydro-furans (a) and 2,3-dihydrofurans (b) in AcOH (Scheme II).[14] The tetrahydrofuran derivatives (a) were in turn prepared via catalytic reduction of the corresponding 2,5-dihydrofurans.[15] Compound 4h was prepared by reacting L-phenylalanine with hexane 2,5-dione in AcOH under reflux (Scheme II). The 1*H*-indole-1-acetic acid ethyl ester derivative (5a, Scheme III) was synthesized via alkylation of 3-cyanoindole with ethyl 2-bromo-3-phenylpropionate in the presence of NaH. This procedure gave a mixture of N- and C-alkylation products (5a and 5b) which were separated by chromatography. Structures 5a and 5b were confirmed from spectral data and analyses. Compounds 5a,b were saponified to give desired acids 6a,b, respectively. Scheme IV outlines the synthetic routes to various
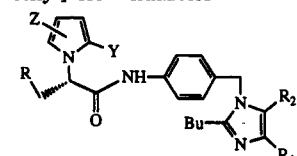
imidazole derivatives (7a–h). These compounds were prepared from a common intermediate, 2-butyl-4-chloro-5-imidazolemethanol (7) following literature methods.[16,17] Benzimidazoles (8a, 9a) and imidazo[4,5-*b*]pyridines (8b, 9b) were synthesized in two steps via alkylation of the requisite benzimidazole[18] and imidazo[4,5-*b*]pyridine[6,19,20] with *p*-nitrobenzyl bromide followed by catalytic reduction of the nitro derivatives (Scheme V). Compound (10, 10a,b) in which the chlorine at the 5-position of the imidazole was replaced with pyrrole were synthesized from the 4-aminoimidazole intermediate[21] as shown in Scheme VI. In general, *p*-nitrobenzylation of substituted imidazoles favored the desired N₁ isomers as the major product. The N₃ regioisomers, which were produced to a varying degree, were identified by TLC of the crude reaction mixtures but seldom isolated. The structures of the desired N₁ isomers, which were less polar and always moved faster on TLC plates, were proven from the ¹H NMR spectra and comparison with reference agents.[18] In some cases, structures were confirmed also by NOE experiments. For example, in the ¹H NMR spectra of 10b an NOE was observed between the protons at the α-positions of the phenyl ring, NCH₂ protons, and various protons at the close proximity (Figure 1).

Scheme VII outlines the synthesis of additional acyl-amino compounds (50–54, Table VI) which lacked the pyrrole ring. Compound 50 was obtained by reacting 7f

Table III. [[[(1H-Pyrrolyl-1-acetyl)amino]phenyl]methyl]-3H-imidazoles

compd	Z	Y	R^h	R_2	R_1	mp, °C^{a,b} (crystn solvent)	formula^c	receptor binding^d (% inhibit at 10^{-7} M)	rabbid aorta^e
								IC$_{50}$, μM	
14	H	CO$_2$Me	Ph	CH$_2$OH	Cl	f	C$_{30}$H$_{33}$ClN$_4$O$_4$	0.21 ± 0.058	
15	H	CO$_2$H	Ph	CH$_2$OH	Cl	f	C$_{29}$H$_{31}$ClN$_4$O$_4$·0.4H$_2$O	0.18 ± 0.009	17.0
16	H	CO$_2$H	Ph	CH$_2$OH	H	f	C$_{29}$H$_{32}$N$_4$O$_4$^{g}	1.1 ± 0.034	
17	H	CO$_2$Me	Ph	CH$_2$CO$_2$Me	Cl	186–188 (EtOAc/hexane)	C$_{32}$H$_{35}$ClN$_4$O$_5$	0.50 ± 0.025	
18	H	CO$_2$H	Ph	CH$_2$CO$_2$H	Cl	f	C$_{30}$H$_{31}$ClN$_4$O$_5$·0.5AcOH	0.027 ± 0.006	0.52
19	H	CO$_2$Me	Ph	(CH$_2$)$_2$CO$_2$Me	Cl	f	C$_{33}$H$_{37}$ClN$_4$O$_5$	0.21 ± 0.005	
20	H	CO$_2$H	Ph	(CH$_2$)$_2$CO$_2$H	Cl	106–107 dec	C$_{31}$H$_{33}$ClN$_4$O$_5$·0.2AcOH	0.022 ± 0.003	0.22
21	H	CO$_2$Me	Th	CH$_2$CO$_2$Me	Cl	171–172	C$_{30}$H$_{33}$ClN$_4$O$_5$S	0.80 ± 0.002	
22	H	CO$_2$H	Th	CH$_2$CO$_2$H	Cl	191–193	C$_{28}$H$_{29}$ClN$_4$O$_5$S	0.024 ± 0.004	
23	H	CO$_2$Me	Ph	CO$_2$Me	Cl	f	C$_{31}$H$_{33}$ClN$_4$O$_5$·0.2Et$_2$O	(15)	
24	H	CO$_2$H	Ph	CO$_2$H	Cl	116	C$_{29}$H$_{29}$ClN$_4$O$_5$·0.1cyclohexane·0.2H$_2$O	0.08 ± 0.006	0.55
25	H	CO$_2$Me	Ph	CO$_2$Me	H	174–175	C$_{31}$H$_{34}$N$_4$O$_5$	(33)	
26	H	CO$_2$H	Ph	CO$_2$H	H	211	C$_{29}$H$_{30}$N$_4$O$_5$·0.4CH$_2$Cl$_2$	0.02 ± 0.001	0.11
27	H	CO$_2$Me	Th	CO$_2$Me	Cl	f	C$_{29}$H$_{31}$ClN$_4$O$_5$S·0.1H$_2$O	(11)	
28	H	CO$_2$H	Th	CO$_2$H	Cl	f	C$_{27}$H$_{27}$ClN$_4$O$_5$S·2H$_2$O	0.18 ± 0.001	

^{a} Yields were in the range of 60–80% (esters) and 40–50% (acids). ^{b} Compounds were purified by chromatography. ^{c} All microanalytical values were in agreement with assigned structures (within ±0.4%) except for **16** (98%; HPLC t_R 2.73 min), **26** (96%; HPLC t_R 5.25 min), and **28** (94%; HPLC t_R 19.9 min). ^{d} Concentration to inhibit binding of radiolabeled AII by 50%. IC$_{50}$ values were obtained from a dose–response curve generated from at least five or six doses and are expressed as a mean ± SEM. Dup 753 IC$_{50}$ = 5 nM. ^{e} Determined on isolated rabbit aortic rings. Concentration to inhibit AII induced contraction by 50%. Data expressed as means of two separate experiments. ^{f} Foam. ^{g}N; C: calcd, 69.58; found, 67.62; H: calcd, 6.44; found, 5.85. ^{h} Th = 2-thienyl.

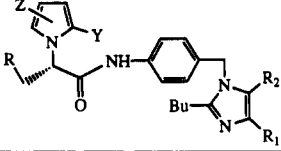**Table IV.** [[[(1H-Pyrrolyl-1-acetyl)amino]phenyl]methyl]-3H-imidazoles

compd	Z	Y	R	R_2	R_1	mp, °C^{a,b} (crystn solvent)	formula^c	receptor binding^d IC$_{50}$, μM
29	H	CO$_2$Me	Ph	CO$_2$Et	$-N\!\bigcirc$	e	C$_{36}$H$_{39}$N$_5$O$_5$·0.5H$_2$O	N
30	H	CO$_2$H	Ph	CO$_2$Et	$-N\!\bigcirc$	e	C$_{35}$H$_{37}$N$_5$O$_5$	2.5 ± 0.099
31	H	CO$_2$H	Ph	CO$_2$H	$-N\!\bigcirc$	e	C$_{33}$H$_{33}$N$_3$O$_5$·1.3CH$_2$Cl$_2$·1.2MeOH	0.34 ± 0.147
32	H	CO$_2$Me	Ph	(ring, Me)		202–203	C$_{34}$H$_{36}$N$_4$O$_3$·0.2H$_2$O	N
33	H	CO$_2$H	Ph	(ring, Me)		e	C$_{33}$H$_{34}$N$_4$O$_3$·0.6MeOH·0.6CH$_2$Cl$_2$	0.93 ± 0.093
34	H	CO$_2$Me	Ph	(N,Me ring, Me)		216–217 (EtOAc)	C$_{32}$H$_{33}$N$_5$O$_3$·0.1EtOAc	0.33 ± 0.068
35	H	CO$_2$H	Ph	(N,Me ring, Me)		e	C$_{31}$H$_{31}$N$_5$O$_3$·0.4CH$_2$Cl$_2$	0.06 ± 0.007

^{a} Yields were in the range of 60–80% (esters) and 40–50% (acids). ^{b} Compounds were purified by chromatography. ^{c} All microanalytical values were within ±0.4% of the calculated values. ^{d} Concentration to inhibit binding of radiolabeled AII by 50%. IC$_{50}$ values were obtained from a dose–response curve generated from at least five or six doses and are expressed as a mean ± SEM. N = Not tested. ^{e} Foam.

with 3-phenylpropionyl chloride in the presence of Et$_3$N and subsequent ester hydrolysis. Compounds **51** and **53** were similarly prepared via acylation of **7d** with benzoylformic acid and 2-cyano-3-phenylpropionic acid, respectively. Compound **52** was synthesized via treatment of **51** with NH$_2$OH. Compound **53** was reacted with a mixture of NaN$_3$/NH$_4$Cl in DMF to provide the tetrazole analogue **54**.
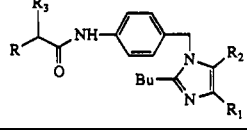
Biological Results and Discussion

Compounds in Tables II–VI were evaluated via an angiotensin receptor binding methodology. The method used was a conventional ligand binding assay based on the interaction of iodinated angiotensin II with a washed membrane fraction prepared from rat liver.[22] The IC$_{50}$ values of EXP compounds in Chart II were taken from

Table V. [[[(1*H*-Pyrrolyl-1-acetyl)amino]phenyl]methyl]-3*H*-imidazoles

compd	Z	Y	R[h]	R₂	R₁	mp, °C[a,b]	formula[c]	receptor binding[d] (% inhibn at 10⁻⁷ M)	rabbit aorta[e]
36	3-CO₂Et	H	Ph	CH₂CO₂Me	Cl	*g*	C₃₃H₃₇N₄O₅Cl·0.3TMA[f]	(7.2)	
37	3-CO₂Et	H	Ph	CH₂CO₂H	Cl	*g*	C₃₂H₃₅ClN₄O₅	0.24 ● 0.006	14.0
38	3-CO₂Et	Me	Ph	CH₂CO₂Me	Cl	84–85	C₃₄H₃₉ClN₄O₅	1.47 ± 0.190	
39	3-CO₂Et	Me	Ph	CH₂CO₂H	Cl	191–193 (EtOAc/hexane)	C₃₃H₃₇ClN₄O₅·1.8AcOH·1.0H₂O	0.14 ● 0.005	
40	H	Me	Ph	CH₂CO₂Me	Cl	*g*	C₃₁H₃₅ClN₄O₃·0.2H₂O	(14.8)	
41	H	Me	Ph	CH₂CO₂H	Cl	*g*	C₃₀H₃₃N₄O₃Cl·0.2H₂O	0.14 ± 0.001	6.4
42	H	H	Ph	CH₂CO₂Me	Cl	*g*	C₃₀H₃₃ClN₄O₃	1.92 ● 0.260	
43	H	H	Ph	CH₂CO₂H	Cl	*g*	C₂₉H₃₁ClN₄O₃·0.1H₂O	0.21 ± 0.003	6.3
44	H	H	Th	CO₂Me	Cl	*g*	C₂₇H₂₉N₄O₃ClS	(2.5)	
45	H	H	Th	CO₂H	Cl	*g*	C₂₆H₂₇ClN₄O₃S·0.4H₂O	0.67 ● 0.002	
46	H	H	Ph	CH₂OH	Cl	*g*	C₂₈H₃₁ClN₄O₂	(8.1)	
47	5-Me	Me	Ph	CH₂CO₂H	Cl	108–111	C₃₁H₃₅N₄ClO₃·0.64H₂O	0.37 ● 0.002	
48[i]	3-CN	H	Ph	CH₂CO₂Me	Cl	95–100	C₃₅H₃₄ClN₅O₃	N	
49[i]	3-CN	H	Ph	CH₂CO₂H	Cl	*g*	C₃₄H₃₂ClN₅O₃·0.87TFA·0.3H₂O	1.29 ● 0.381	

[a] Yields were in the range of 60–80% (esters) and 40–50% (acids). [b] Compounds were purified by chromatography. [c] All microanalytical values were within ±0.4% of calculated values. Compound 45 was 97% pure by HPLC, t_R 19.4 min. [d] Concentration to inhibit binding of radiolabeled AII by 50%. IC₅₀ values were obtained from a dose–response curve generated from at least five or six doses and are expressed as a mean ± SEM; DUP 753 IC₅₀ was 5 nM. N = Not tested. [e] Determinated on isolated rabbit aortic rings. Concentration to inhibit AII-induced contraction by 50%. Data expressed as means of two separate experiments. [f] TMA is trimethylacetic acid. [g] Foam. [h] Th = 2-thienyl. [i] Indole analogues.

Table VI. [[(Acylamino)phenyl]methyl]-3*H*-imidazoles

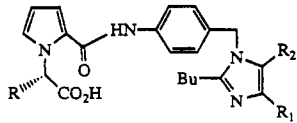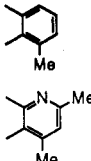| compd	R	R₁	R₂	R₃	mp, °C[b] (crystn solvent)	yield, %[a]	formula[c]	receptor binding; IC₅₀, μM[d] (% inhibn at 10⁻⁷ M)
50[f]	CH₂Ph	Cl	CH₂CO₂H	H	188–189	95	C₂₅H₂₈ClN₃O₃·0.2H₂O	(7.8)
51	Ph	Cl	CH₂OH	=O	162–163 (EtOAc/hexane)	82	C₂₃H₂₄ClN₃O₃·0.2H₂O	10.9 ± 2.44
52	Ph	Cl	CH₂OH	=NOH	197–199 dec (EtOAc/ether)	86	C₂₃H₂₅ClN₄O₃·0.7AcOH	3.25 ± 0.560
53	CH₂Ph	Cl	CH₂OH	CN	*e*	90	C₂₅H₂₇ClN₄O₂·0.4DMF	2.60 ± 0.119
54	CH₂Ph	Cl	CH₂OH	T[d]	*e*	30	C₂₅H₂₈ClN₇O₂·0.8HCl	2.6 ● 0.004

[a] Yields were not optimized. [b] Compounds were purified by chromatography. [c] All microanalytical values were within ±0.4% of the calculated values. [d] Concentration to inhibit binding of radiolabeled AII by 50%. IC₅₀ values were obtained from a dose–response curve generated from at least five or six doses and are expressed as a mean ● SEM. [e] Foam. [f] Isolated from water. [g] 2*H*-tetrazol-5-yl.

the literature.[12] DuP 753 was used as reference standard in this assay. The binding assay was followed with a functional assay for the ability of a compound to antagonize the AII-induced contraction of isolated rabbit aortic rings.[22] IC₅₀ values of selected compounds were determined in this test.
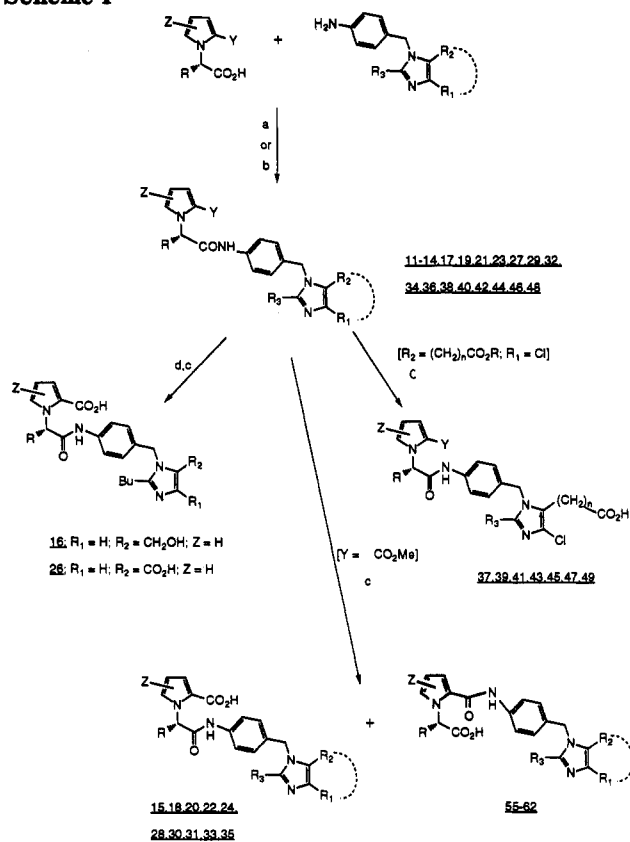
Our first aim was to define the side chain R which was critical to the binding to the angiotensin II receptor. With that objective in mind we prepared a small series of compounds varying the side chain R in the pyrroleacetic acid moiety which are listed in Table II. This data clearly indicates that a side chain is essential for activity and the benzyl group seems to be optimal at that position. Table III lists compounds wherein substitutions in the imidazole ring (R₁ and R₂) were modified. Compounds 14 and 15 bind to the receptor with very similar affinities which were comparable to that of EXP 6803 (Chart II).[12] The binding affinity of compound 17, wherein R₂ = CH₂CO₂Me, dropped to some extent whereas that of 19 (R₂ = CH₂-

CH₂CO₂Me) remained the same. The receptor affinity of diacids 18, 20, and 24 improved significantly with IC₅₀ values in the 10⁻⁸ M range. The relative order of potency was (CH₂)₂CO₂H > CH₂CO₂H > CO₂H > CH₂OH. The IC₅₀ of 24 was in the same range as that of compound EXP 8623 (Chart II). Compound 28, the thienyl analogue of the imidazole-5-carboxylic acid, was slightly less potent than 24 whereas compound 22, the corresponding analogue in the acetic acid series, maintained potency. Similar differences between series were observed with the de-schloro analogues. In the hydroxymethyl series (R₂ = CH₂-OH) the chloro compound seems to bind better than the hydrogen compound (compare 15 and 16) whereas in the carboxylic acid series the hydrogen analogue 26 improved the affinity by ca. 4-fold in comparison to 24 [IC₅₀ = 20 nM (26) vs 80 nM (24)]. Replacement of the 4-chloro residue with a more lipophilic group, such as pyrrole, gave 31, which led to a drop in the binding affinity (Table IV). Compounds wherein R₂ and R₁ were connected to form a

Table VII. 1*H*-Pyrrole-1-acetic Acid Derivatives

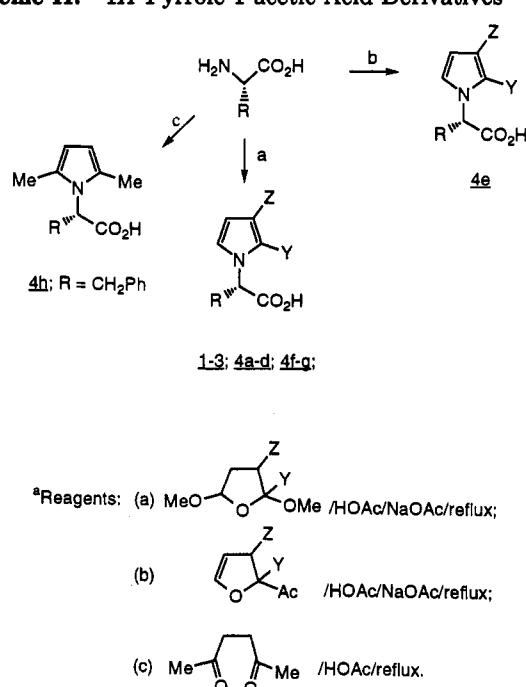| compd	R^d	R_2	R_1	formula[a-c]
55	H	CH_2OH	Cl	$C_{22}H_{25}ClN_4O_4 \cdot 1.8AcOH$
56	CH_2Ph	CH_2OH	Cl	$C_{29}H_{31}ClN_4O_4 \cdot 0.1CH_2Cl_2$
57	CH_2Ph	CH_2CO_2H	Cl	$C_{30}H_{31}ClN_4O_5 \cdot 0.7AcOH$
58	CH_2Th	CH_2CO_2H	Cl	$C_{28}H_{29}ClN_4O_5S \cdot 0.17AcOH$
59	CH_2Ph	$(CH_2)_2CO_2H$	Cl	$C_{31}H_{33}ClN_4O_5 \cdot 0.3EtOAc$
60	CH_2Ph			$C_{33}H_{34}N_4O_3 \cdot 0.43EtOAc$
61	CH_2Ph			$C_{31}H_{31}N_5O_3 \cdot 0.42CH_2Cl_2$
62	CH_2Ph	CO_2Et		$C_{35}H_{37}N_5O_5 \cdot 0.3CH_2Cl_2$

a Compounds were purified by chromatography and obtained as foams, except for 59 (mp 131 °C dec). *b* Yields were in the range 20–30%. *c* All microanalytical values were within ±0.4% of the calculated values. *d* Th = 2-thienyl.

Scheme I[a]

a Reagents: (a) DCC/HOBT (method A); (b) (CH₃)₃CCOCl/DMAP/THF (method B); (c) NaOH; (d) H₂/Pd-C/KOAc.

Scheme II.[a] 1*H*-Pyrrole-1-acetic Acid Derivatives

[a]Reagents: (a) MeO—⟨⟩—OMe /HOAc/NaOAc/reflux;

(b) ⟨⟩—Ac /HOAc/NaOAc/reflux;

(c) Me—CO—CO—Me /HOAc/reflux.

ring also had decreased affinity for the receptor. The contribution of the CH_2OH (or CO_2H) group was evident by the weak affinity of the benzimidazole analogue 33. The loss in the binding activity was regained by the imidazo[4,5-*b*]pyridine analogue 35.

Turning our attention to the substitution in the pyrrole ring, the data in Table V demonstrates that the 3-CO_2Et analogues 37 and 39 both retained modest affinity. It is of interest to note that the descarboxy compound 43 (R_2 = CH_2CO_2H; Y = H) retained modest binding affinity whereas compound 46 (R_2 = CH_2OH; Y = H) was significantly less potent in binding at the receptor. Similarly,

compound 41, the 2-methyl analogue of 43 retained the binding potency whereas 2,5-dimethyl analogue 47 suffered a slight loss in potency. Replacement of the pyrrole ring with an indole ring produced a significantly less potent compound (49; IC_{50} = 1.29 μM). In order to explore the role of the pyrrole ring, several compounds were investigated replacing the pyrrole ring with a diverse functional moieties ranging from a hydrogen to hydrogen-accepting groups (CO, C=NOH, CN) and acidic group (tetrazole). All these modifications gave compounds with very weak affinity (Table VI). The receptor binding affinities of the isomeric acids in Table VII were in the micromolar range (data not shown).

These compounds represent a novel series of potent and selective AT_1 antagonists (<20% inhibition at 1 μM for the AT_2 receptor). As seen from Tables II–V a good correlation exists between the receptor binding and the functional assay, although in general, a 10-fold decrease in IC_{50} was observed in the functional test. Like EXP

Scheme III.[a] 1*H*-Indole-1-acetic Acid Derivatives
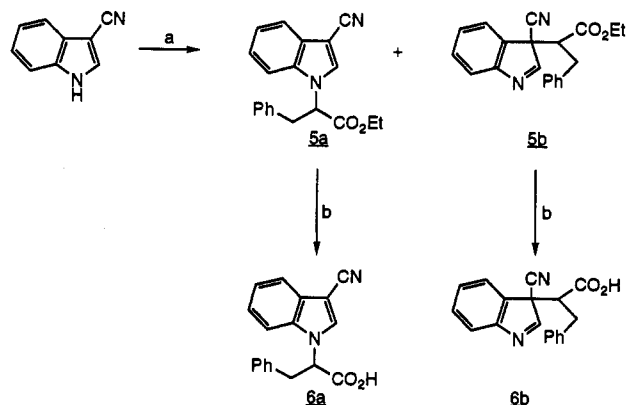
[a] Reagents: (a) PhCH₂CH(Br)CO₂Et/NaH; (b) NaOH.

Scheme IV.[a] 1-[(4-Aminophenyl)methyl]-3*H*-imidazole Derivatives
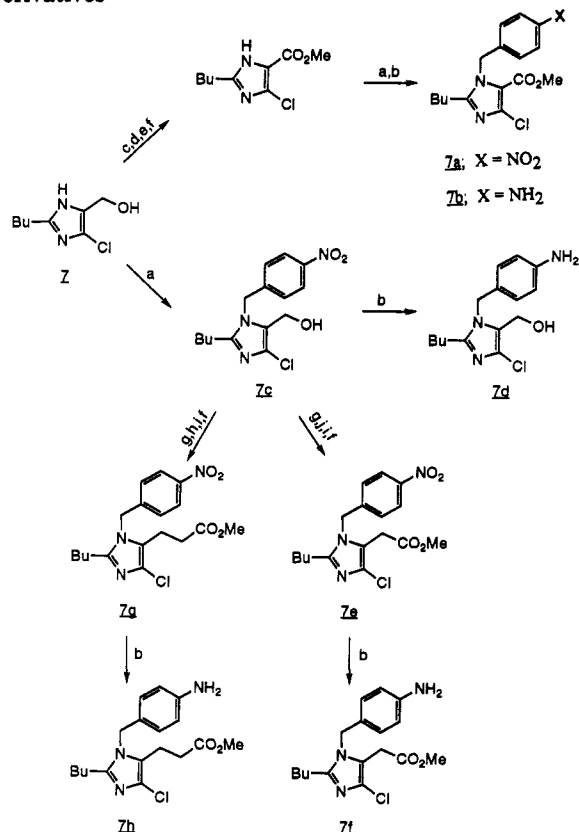
[a] Reagents: (a) p-NO₂BnBr/base; (b) H₂/Raney Ni; (c) MnO₂; (d) TMSCN; (e) CrO₃; (f) MeOH–H⁺; (g) SOCl₂; (h) CH₂(CO₂Me)₂/base; (i) HCl; (j) KCN.

6803 this series suffers from lack of in vivo activity after oral administration. For example, no blood pressure lowering effect was demonstrated with compound 18, even after dosing at 30 mg/kg in renal hypertensive rats.
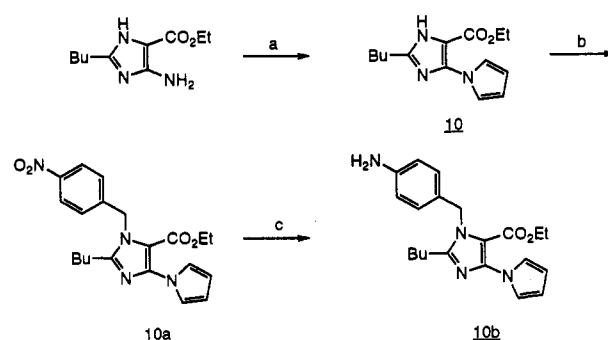
The two best compounds **20** and **24** in the "best-fit" conformations were manually overlayed on that of the template conformation of EXP 8623 (Figures 2 and 3). These figures depict that these molecules are able to mimic, to a reasonable extent, the spatial disposition of the imidazole and terminal carboxylic acid pharmacophore of these compounds. Figure 4 shows the close similarity in conformation of EXP 6803 and 18.
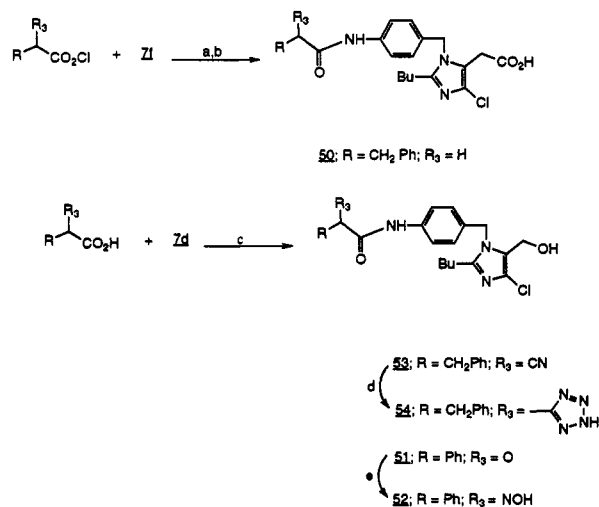
Summary

In summary, the data presented here demonstrates that replacement of the benzoyl group in EXP 6803 with a

Scheme V[a]

8a. 9a. R₁ = Bu; R = CH; R₂ = H; R₃ = Me

8b. 9b. R₁ = Et; R = N; R₂ = Me; R₃ = Me
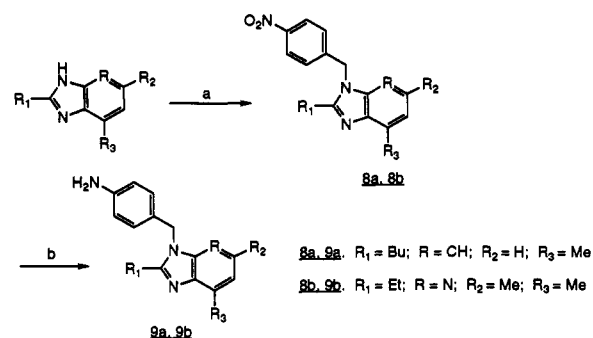
[a] Reagents: (a) p-NO₂BnBr/base; (b) H₂/Raney Ni.

Scheme VI[a]

[a]Reagents: (a) MeO⌐OMe/AcOH; (b) p-NO₂BnBr/Base; (c) H₂/Raney Ni

Scheme VII[a]

50; R = CH₂Ph; R₃ = H

53; R = CH₂Ph; R₃ = CN

54; R = CH₂Ph; R₃ = tetrazole

51; R = Ph; R₃ = O

52; R = Ph; R₃ = NOH

[a] Reagents: (a) Et₃N; (b) NaOH; (c) DCC/HOBT; (d) NaN₃/NH₄Cl; (e) NH₂OH.

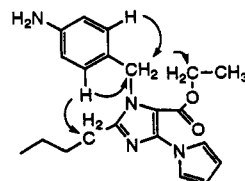**Figure 1.** The arrows indicate the NOE's observed between the NCH₂ protons and the various protons in close spatial proximity.

1*H*-pyrrol-1-ylacetyl group produced a novel series of potent and selective AT₁ receptor antagonists. The receptor binding affinity of several members of this series was in the 10⁻⁸ M range, which was better than EXP 6803. IC₅₀'s were also comparable to that of EXP 7711, which
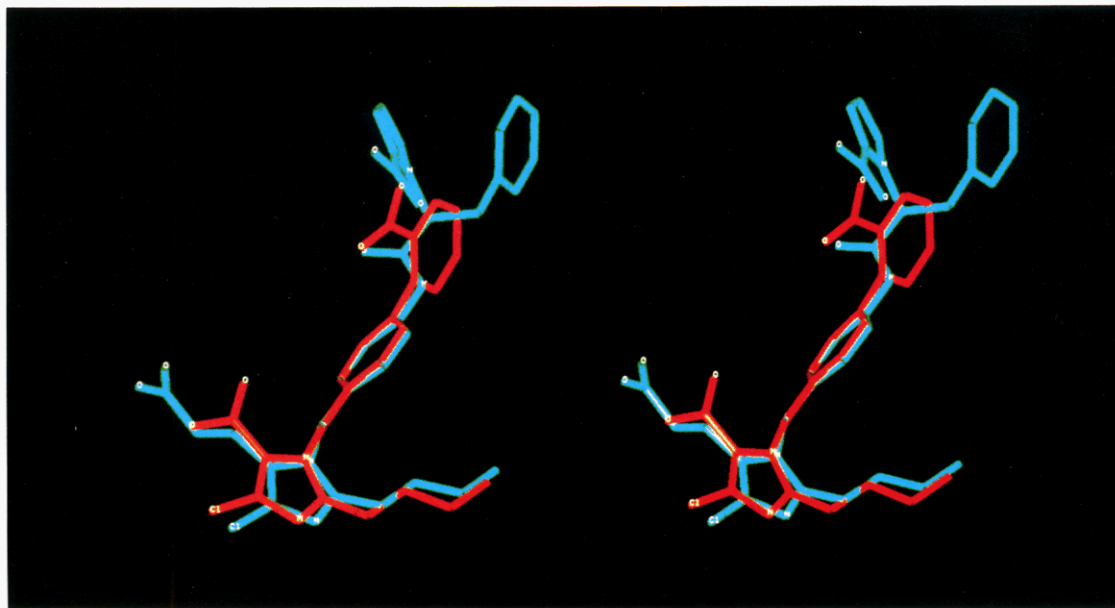
Figure 2. Possible overlap of low-energy structures for EXP 8623 (red) and **20** (blue).
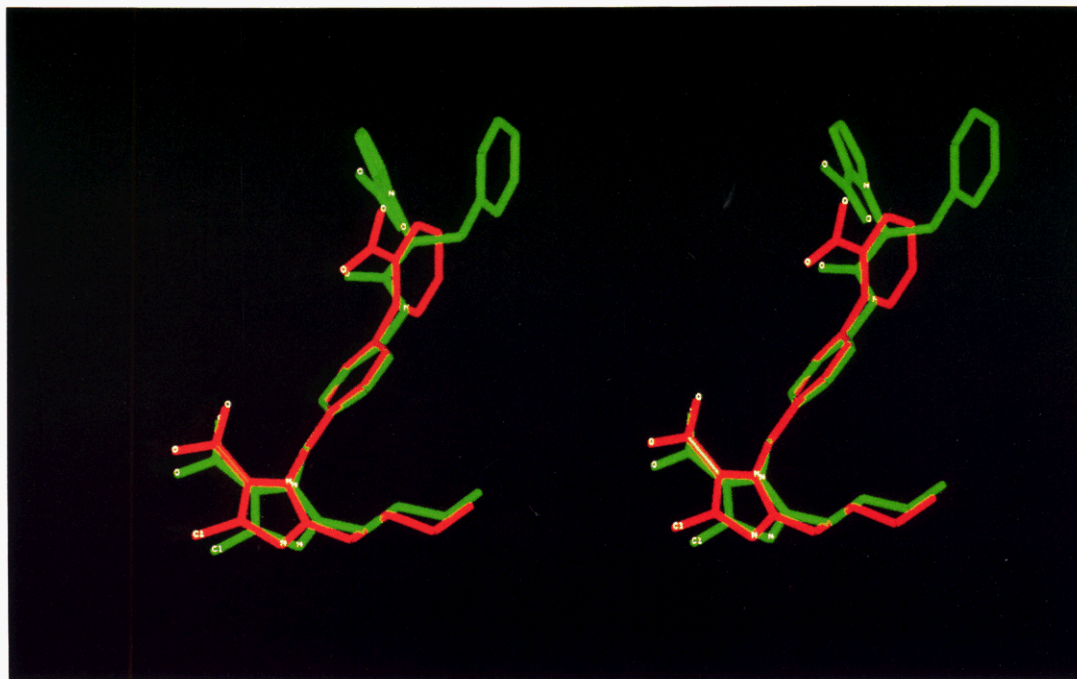

Figure 3. Possible overlap of low energy structures for EXP 8623 (red) and **24** (green).

has a more rigid conformation in the 2-carboxybiphenyl moiety. The structure–activity relationship data reported here are consistent with the widespread notions[10,17] that are summarized as follows: (a) at least one CO_2H group is essential for binding (binding site #1). (b) A hydrogen bonding site at the 5-position of the imidazole ring is present (binding site #2). (c) A CO_2H substitution afforded a more potent compound than the CH_2OH group; the position of the CO_2H group could be extended out with a $(CH_2)_2$ spacer. (d) The pyrrole ring is critical for binding and an ortho substitution on the pyrrole ring improves binding. (e) The phenylmethyl substituent adjacent to the amide group is projecting the pyrrole ring at a smaller angle with respect to the plane of the amide as a consequence of steric hindrance. This imparts a favorable and more rigid conformation to the pyrrole ring, which results in the enhancement of binding affinity. (f) In the

CH_2OH series, the presence of a carboxy group on the pyrrole ring is crucial for activity. By contrast, in the presence of a carboxy group on the imidazole ring, the pyrrole nitrogen is perhaps acting as a hydrogen-bonding group.

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 ^{1}H NMR spectra of all new compounds were consistent with the proposed structures (data for selected compounds are presented). ^{1}H NMR spectra were obtained in $CDCl_3$ (unless otherwise stated) on a Bruker AM 250 and are reported as δ values (ppm) relative to Me_4Si as internal standard. IR spectra were recorded on a Nicolet FTIR spectrophotometer in KBr.
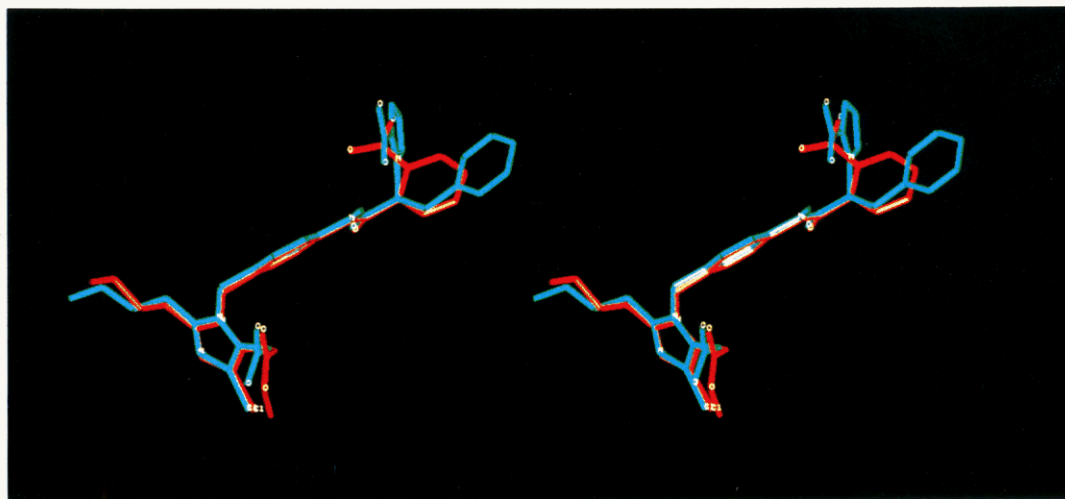
Figure 4. Sterioscopic molecular graphics show the close similarity in conformation of EXP 6803 (red) and 18 (blue).

Mass spectra were recorded on a VG 7070 E/HR mass spectrometer with an 11/250 data system. HPLC experiments were run on Ultrasphere C18 column using a mobile phase of 45/55/0.05 $H_2O/CH_3CN/Et_3N$ (pH 3.0) with a flow rate of 1.5 mL/min and detection at 214 nM. Elemental analyses were obtained on a Control Equipment Corp. Model 440 elemental analyzer. Molecular modeling was performed using the Sybyl[23] software on a Silicon Graphics 4D/35TG computer. Minimizations were carried out using molecular mechanics and the Tripos force field.

Compounds 7[16] and 7a[24] were prepared by following literature procedures. 2,5-Dihydro-2,5-dimethoxy-2-methylfuran was prepared according to the procedure of Clauson.[25] All target compounds were prepared via method B unless otherwise stated, and yields were not optimized. 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 IR, MS and ¹H NMR spectra and elemental analyses. Most compounds have a tendency to hold solvents, even upon drying under vacuum, which were quantitated from ¹H NMR spectra.

General Procedure for the Synthesis of 1H-pyrrole-1-acetic Acids (4a–h). (S)-2-(Methoxycarbonyl)-α-(phenylmethyl)-1H-pyrrole-1-acetic Acid (4a). To a warm solution of anhydrous NaOAc (30.7 g, 0.374 mmol) in HOAc (250 mL) was added L-phenylalanine (10.5 g, 0.0624 mmol) and the mixture heated until dissolution. Methyl 2,5-dimethoxytetrahydrofuran-5-carboxylate (11.87 g, 0.0624 mmol) was added followed by reflux of the mixture for 15–30 min. The reaction mixture was cooled and poured into ice–water and extracted with EtOAc. The EtOAc was washed with water and brine, dried, and stripped to give 14.5 g of a dark oil. It was purified via chromatography (CHCl₃/MeOH 8/2) to give 6.7 g of 4a as a light brown oil.

Compound 4e was similarly prepared from L-phenylalanine and ethyl 5-acetoxy-2-methyl-4,5-dihydrofuran-3-carboxylate.[26]

Compound 4h was similarly prepared from L-phenylalanine and 2,5-hexanedione.

3-Cyano-α-(phenylmethyl)-1H-indole-1-acetic Acid (6a). To a slurry of NaH (60%, 1.08 g, 27 mmol) in DMF (50 mL) was added a solution of 3-cyanoindole (2.56 g, 18 mmol) in DMF (50 mL). The reaction mixture was heated at 60 °C for 1 h and cooled to room temperature. A solution of ethyl 2-bromo-3-phenylpropionate[27] (5.7 g, 19.8 mmol) in DMF (40 mL) was added and the reaction mixture was stirred at room temperature for 18 h. DMF was distilled under vacuum and the residue was partitioned between EtOAc and water. The EtOAc layer was separated, washed with brine, dried, and evaporated. The crude material was chromatographed twice (SiO₂, CH₂Cl₂/hexane 1/4–EtOAc/hexane 1/10) to give two regioisomers.

Ethyl 3-Cyano-α-(phenylmethyl)-1H-indole-1-acetate (5a): 0.7 g; N-isomer; MS (FAB) m/z 318 (M); ¹H NMR δ 7.81–7.61 (m, 2 H), 7.35–7.10 (m, 8 H), 6.10 (t, 1 H), 4.18–3.99 (q, 2 H), 3.38–3.20 (d, 2 H), 1.19–0.99 (t, 3 H); IR 2215, 1733, 1728 cm⁻¹. Anal. Calcd for $C_{20}H_{18}N_2O_2$·0.1H_2O: C, 75.03, H, 5.73, N, 8.75. Found: C, 74.72; H, 5.73; N, 8.66.

Ethyl 3-cyano-α-(phenylmethyl)-3H-indole-3-acetate (5b): 0.7 g, C-isomer; MS (FAB) m/z 318 (M); ¹H NMR δ 7.78 (m, 2 H), 7.38–7.02 (m, 6 H), 7.01–6.92 (m, 2 H), 5.45–5.19 (dd, J = 8.8 Hz, 1 H), 4.28–4.10 (q, 2 H), 3.62–3.53 (dd, J = 6.47 Hz, 1 H), 3.51–3.32 (dd, J = 8.8 Hz, 1 H), 1.22–1.08 (t, 3 H); IR 2213, 1723 cm⁻¹. Anal. Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.30; H, 5.59; N, 8.80.

A solution of 5a (0.6 g, 1.9 mmol) in THF (20 mL) containing 2.1 mL of 0.1 N NaOH was stirred at room temperature for 18 h. Usual workup gave 0.46 g of the corresponding acid 6a: MS (FAB) m/z 308 (M); ¹H NMR δ 10.26 (s, 1 H), 7.87–7.53 (m, 2 H), 7.55–6.98 (m, 8 H), 6.03 (t, 1 H), 3.33 (d, 2 H). This was used as is for the coupling reaction.

Compound 6b was similarly prepared from 5b: MS (FAB) m/z 308 (M); ¹H NMR δ 9.26 (s, 1 H), 7.87–7.53 (m, 2 H), 7.40–7.05 (m, 6 H), 7.05–6.85 (m, 2 H), 5.45–5.15 (dd, J = 8.8 Hz, 1 H), 3.53 (dd, J = 6.47 Hz, 1 H), 3.45 (dd, J = 8.8 Hz, 1 H).

General Procedure. 3-[(4-Nitrophenyl)methyl]imidazole and 3-[(4-Aminophenyl)]methyl]imidazole Derivatives. Methyl 2-Butyl-5-chloro-3-[(4-nitrophenyl)methyl]-3H-imidazole-4-propanoate (7g). Thionyl chloride (2.82 mL, 39 mmol) was added to a solution of alcohol 7c (2.5 g, 7.7 mmol) in CHCl₃ (35 mL) at 0 °C. The solution was warmed to room temperature followed by heating at reflux for 3 h under N₂. It was evaporated to dryness and the residue was taken up in toluene. The toluene was distilled and this process was repeated once more to ensure complete removal of thionyl chloride and hydrochloric acid. The residue was dissolved in DMF (20 mL) and added dropwise to a solution of the anion of dimethyl malonate [prepared from 1.12 g, (8.5 mmol) of dimethyl malonate and 0.46 g (12 mmol) of 60% sodium hydride in 35 mL of DMF]. The reaction mixture was stirred at room temperature for 18 h under N₂. DMF was distilled under high vacuum and the residue was partitioned between EtOAc and water. The organic layer was separated, washed with water, dried, and stripped under reduced pressure. The residue was chromatographed (hexane/CH₂Cl₂ 1/4–EtOAc/CH₂Cl₂ 1/10) to give the desired diester as an oil (1.5 g): MS (EI) m/z 437 (M). Anal. Calcd for $C_{20}H_{24}ClN_3O_6$·0.17CH_2Cl_2: C, 53.56; H, 5.42; N, 9.29. Found: C, 53.95; H, 5.30; N, 9.09.

A suspension of 1.0 g of the above ester in 6 N HCl (25 mL) was heated under reflux for 3.5 h. The solution was cooled and extracted once with ether. The aqueous solution was adjusted to pH 3 with 1 N NaOH and extracted with EtOAc. The extract was dried and evaporated to yield 0.7 g of the desired acid: MS (EI) m/z 365 (M). Anal. Calcd for $C_{17}H_{20}ClN_3O_4$·0.09H_2O: C, 55.57; H, 5.57; N, 11.44. Found: C, 55.21; H, 5.42; N, 11.85.

This was converted to the methyl ester by refluxing a solution of the acid (0.7 g) in CH₃OH (25 mL) and concentrated H₂SO₄ (0.5 mL) for 2 h. Usual workup gave the ester as an oil (0.68 g): MS (EI) m/z 380 (M); ᴴ NMR δ 8.22 (d, 2 H), 7.18 (d, 2 H), 5.28 (s, 2 H), 3.65 (s, 3 H), 2.75 (t, 2 H), 2.52 (t, 4 H), 1.65 (m, 2 H), 1.32 (m, 2 H), 0.87 (t, 3 H). This material was used as is for the next step.

Methyl 3-[(4-Aminophenyl)methyl]-2-butyl-5-chloro-3H-imidazole-4-propanoate (7h). A solution of the above nitro compound (2.15 g) in THF (100 mL) was catalytically reduced with H$_2$/Raney Ni (50 psi) at 23 °C. The crude material, purified via chromatography (EtOAc/CH$_2$Cl$_2$ 1/4), afforded the corresponding amine (1.52 g, 78%): MS (CI) m/z 350 (M); ^{1}H NMR δ 8.12 (d, 2 H), 6.71 (d, 2 H), 5.25 (s, ~0.3 H, CH$_2$Cl$_2$), 4.92 (s, 2 H), 3.65 (s, 3 H), 3.55 (s, 2 H), 2.75 (t, 2 H), 2.52 (t, 4 H), 1.65 (m, 2 H), 1.32 (m, 2 H), 0.87 (t, 3 H). Anal. Calcd for C$_{18}$H$_{24}$-ClN$_3$O$_2$·0.12CH$_2$Cl$_2$: C, 60.45; H, 6.79; N, 11.67. Found: H, 6.56; N, 11.28.

Methyl 2-Butyl-5-chloro-3-[(4-nitrophenyl)methyl]-3H-imidazole-4-acetate (7e) was prepared from 7c.[16] Compound 7c (8.36 g, 0.026 mol) was converted to the corresponding chloride via treatment with SOCl$_2$ as described before. This was dissolved in CHCl$_3$ (80 mL) and the solution was treated with a solution of NaCN (7.11 g, 0.15 mol) and nBu$_4$NBr (0.97 g, 0.003 mol) in water (40 mL) over 5 min. This two-phase mixture was stirred vigorously at room temperature for 2 h. The layers were separated, and the aqueous layer was extracted with CH$_2$Cl$_2$. The combined organic layers were washed with water, dried, and evaporated to dryness. The residual solid was recrystallized from CH$_2$Cl$_2$/ether (1/4) to give 7.25 g of the corresponding nitrile: mp 121–125 °C; MS (CI) m/z 331 (M). Anal. Calcd for C$_{16}$H$_{17}$ClN$_4$O$_2$: C, 58.10; H, 4.57; N, 16.94; Cl, 10.72. Found: C, 57.75; H, 5.17; N, 16.64; Cl, 10.86.

A solution of the above nitrile (7.2 g) in 6 N HCl (100 mL) was heated under reflux for 3 h. The solution was cooled and adjusted to pH 1 with ice-cold 50% NaOH and stirred until it became filterable. The solid was filtered, washed with water, and pressed as dry as possible under suction. It was finally dried under high vacuum at 50 °C for 6 h to give 6.9 g of the crude acid; mp 210–212 °C. HCl(g) was bubbled to a stirred mixture of the above acid in CH$_3$OH (350 mL) and CH(OMe)$_3$ (18 mL) and the solution was heated under reflux for 3 h. It was evaporated to dryness under reduced pressure; the residue was triturated with EtOAc and filtered. The crude ester was recrystallized from EtOAc/Ether (1/1) to give 6.0 g of 7e: mp 101–103 °C; MS (CI) m/z 365 (M). Anal. Calcd for C$_{17}$H$_{20}$ClN$_3$O$_4$: C, 54.63; H, 5.16; N, 11.94; Cl, 10.08. Found: C, 54.72; H, 5.16; N, 11.90; Cl, 10.18.

Methyl 3-[(4-Aminophenyl)methyl]-2-butyl-5-chloro-3H-imidazole-4-acetate (7f) was obtained via catalytic reduction of 7e; MS (CI) m/z 336 (M).

2-Butyl-4-chloro-5-(hydroxymethyl)-1-[4-(nitrophenyl)-methyl]imidazole (7c) was prepared according to the procedure of Duncia et al.[10] This was reduced with H$_2$/Raney Ni to give 1-[4-(aminophenyl)methyl]-2-butyl-4-chloro-1H-imidazole-5-methanol (7d); MS (CI) m/z 293 (M).

Methyl 2-Butyl-5-chloro-3-[(4-aminophenyl)methyl]-3H-imidazole-5-carboxylate (7b). The starting material, methyl 2-butyl-4-chloroimidazole-5-carboxylate, was prepared from 7.[22] This was converted to 7b in two steps as described before.

Methyl 2-Butyl-4-chloro-3-[(4-nitrophenyl)methyl]-3H-imidazole-5-carboxylate (7a): MS (CI) m/z 352 (M). Anal. Calcd for C$_{16}$H$_{18}$ClN$_3$O$_4$: C, 54.63; H, 5.16; N, 11.94. Found: C, 54.67; H, 5.04; N, 11.85.

7b: MS (CI) m/z 322 (M). Anal. Calcd for C$_{16}$H$_{20}$ClN$_3$O$_2$: C, 59.72; H, 6.26; N, 13.06. Found: C, 60.12; H, 6.40; N, 12.79.

2-Butyl-4-methyl-1-[(4-nitrophenyl)methyl]-1H-benzimidazole (8a). The title compound was prepared (88%) in a manner analogous to that of 10a starting from 2-butyl-4-methylbenzimidazole:[18] mp 115–116 °C; MS (CI) m/z 323 (M); ^{1}H NMR δ 8.15 (d, 2 H), 7.18 (d, 2 H), 7.13–7.00 (m, 2 H), 6.98–6.85 (m, 1 H), 5.40 (s, 2 H), 2.84 (m, 2 H), 2.65 (s, 3 H), 1.72 (m, 2 H), 1.38 (m, 2 H), 0.85 (t, 3 H). Anal. Calcd for C$_{19}$H$_{21}$N$_3$O$_2$: C, 70.57; H, 6.55; N, 12.99. Found: C, 70.46; H, 6.64; N, 12.94.

2-Ethyl-5,7-dimethyl-3-[(4-nitrophenyl)methyl]-3H-imidazo[4,5-b]pyridine (8b) was prepared analogously to 8a starting from 5,7-dimethyl-2-ethylimidazo[4,5-b]pyridine:[19,20] mp 124–125 °C; MS (CI) 310 (m); ^{1}H NMR δ 8.15 (d, 2 H), 7.25 (d, 2 H), 6.90 (s, 1 H), 5.56 (s, 2 H), 2.74 (q, 2 H), 2.62 (s, 3 H), 2.56 (s, 3 H), 1.16 (t, 3 H). Anal. Calcd for C$_{17}$H$_{18}$N$_4$O$_2$·0.1H$_2$O: C, 65.41; H, 5.88; N, 17.95. Found: C, 65.26; H, 5.94; N, 17.99.

4-[(2-Butyl-4-methyl-1H-benzimidazol-1-yl)methyl]benzenamine (9a) was obtained from 8a via catalytic reduction with Raney Ni: mp 165–166 °C; MS (CI) m/z 293 (M); ^{1}H NMR

δ 7.12–6.92 (m, 3 H), 6.84 (d, 2 H), 6.59 (d, 2 H), 5.42 (s, 2 H), 3.62 (br, s, 2 H), 2.84 (m, 2 H), 2.65 (s, 3 H), 1.72 (m, 2 H), 1.38 (m, 2 H), 0.85 (t, 3 H). Anal. Calcd for C$_{19}$H$_{23}$N$_3$: C, 77.78; H, 7.90; N, 14.32. Found: C, 77.38; H, 7.90; N, 14.02.

4-[(2-Ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)-methyl]benzenamine (9b) was obtained from 8b via catalytic reduction with Raney Ni: mp 137–138 °C; MS (CI) m/z 280 (M); ^{1}H NMR δ 6.92 (s, 1 H), 6.83 (d, 2 H), 6.43 (d, 2 H), 5.22 (s, 2 H), 5.05 (s, 2 H), 2.74 (q, 2 H), 2.50 (s, 3 H), 2.48 (s, 3 H), 1.12 (t, 3 H). Anal. Calcd for C$_{17}$H$_{20}$N$_4$·0.3H$_2$O: C, 71.45; H, 7.27; N, 19.60. Found: C, 71.54; H, 7.07; N, 19.53.

Ethyl 2-Butyl-4-(1H-pyrrol-yl)imidazole-5-carboxylate (10). A mixture of ethyl 4-amino-2-butylimidazole-5-carboxylate[21] (2.7 g, 12.8 mmol), 2,5-dimethoxytetrahydrofuran (1.7 g, 12.8 mmol), and anhydrous NaOAc (6.4 g, 38.4 mmol) in HOAc (40 mL) was heated at reflux for 4 h. Acetic acid was distilled, the residue was poured into water, and the aqueous solution was extracted with EtOAc. The organic layer was washed successively with water, aqueous NaHCO$_3$, and brine, dried, and evaporated. The residue was chromatographed (CH$_2$Cl$_2$/EtOAc 9/1) to give a pale yellow solid (1.8 g, 67%): mp 74–77 °C; IR 1733 cm^{-1}; MS (CI) m/z 262 (M); ^{1}H NMR δ 9.75 (br, s, 1 H), 7.57 (t, 2 H), 7.26 (t, 2 H), 4.33 (q, 2 H), 4.05 (q, ~0.3 H, EtOAc), 2.73 (t, 2 H), 2.05 (s, ~0.5 H, EtOAc), 1.84–1.65 (m, 2 H), 1.43–1.37 (m, 5 H), 1.15 (t, ~0.5 H, EtOAc), 0.96 (t, 3 H). Anal. Calcd for C$_{14}$H$_{19}$N$_3$O$_2$·0.13EtOAc: C, 63.94; H, 7.41; N, 15.40. Found: C, 63.63; H, 7.02; N, 15.53.

Ethyl 2-Butyl-3-[(4-nitrophenyl)methyl]-4-(1H-pyrrol-1-yl)-3H-imidazole-5-carboxylate (10a). Sodium hydride (60%, 0.3 g, 7.3 mmol) was added to a solution of 10 (1.9 g, 7.3 mmol) in DMF (20 mL). The mixture was stirred at room temperature till the hydrogen evolution ceased. A solution of p-nitrobenzyl bromide (1.58 g, 7.3 mmol) in DMF (5 mL) was added and the reaction mixture was stirred for 6 h. DMF was distilled, the residue was treated with water, and the solution was extracted with EtOAc. The extract was washed with brine, dried, and evaporated. The residue was chromatographed (hexane/EtOAc 9/1-EtOAc) to give 1.4 g (66%) of the title compound as a pale yellow oil (10a): MS (CI) m/z 396 (M); ^{1}H NMR δ 8.21 (d, 2 H), 7.18 (m, 4 H), 6.22 (t, 2 H), 5.62 (s, 2 H), 4.12 (q, 2 H), 4.05 (q, ~0.4 H, EtOAc), 2.73 (t, 2 H), 2.05 (s, ~0.6 H, EtOAc), 1.76 (m, 2 H), 1.38 (m, 2 H), 1.15 (t, ~0.6 H, EtOAc), 1.12 (t, 3 H), 0.98 (t, 3 H). Anal. Calcd for C$_{21}$H$_{24}$N$_4$O$_4$·0.16EtOAc: C, 63.31; H, 6.21; N, 13.65. Found: C, 63.18; H, 6.04; N, 13.64.

Ethyl 3-[(4-Aminophenyl)methyl]-2-butyl-4-(1H-pyrrol-1-yl)-3H-imidazole-5-carboxylate (10b). An ethanolic (100 mL) solution of the above nitro compound 10a (1.4 g) was hydrogenated (0.1 g, 5% Pd/C) under 50 psi of hydrogen at 23 °C. After 4 h the gas was vented, and the solids were filtered through a bed of Celite. The filtrate was evaporated and the crude product was purified via chromatography (EtOAc/hexane 1/2) to obtain the amino compound as a viscous oil (10b, 1.0 g, 78%): MS (CI) m/z 366 (M); IR 3372, 3459 cm^{-1}; ^{1}H NMR δ 7.12 (t, 2 H), 6.21 (t, 2 H), 6.83 (d, 2 H), 6.63 (d, 2 H), 5.42 (s, 2 H), 4.17 (q, 2 H), 3.75 (br, 2 H), 2.74 (t, 2 H), 1.75 (m, 2 H), 1.38 (m, 2 H), 1.10 (t, 3 H), 0.98 (t, 3 H). Anal. Calcd for C$_{21}$H$_{26}$N$_4$O$_2$: C, 68.83; H, 7.15; N, 15.29. Found: C, 68.70; H, 7.13; N, 14.93.

Coupling Procedure. Method A. (S)-Methyl 2-Butyl-5-chloro-3-[[4-[[2-[2-(methoxycarbonyl)-1H-pyrroyl]-1-oxo-3-phenylpropyl]amino]phenyl]methyl]-3H-imidazole-4-acetate (17). To a mixture of methyl 3-[(4-aminophenyl)methyl]-2-butyl-5-chloro-3H-imidazole-4-acetate (7f; 1.0 g, 3.14 mmol) and 2-(methoxycarbonyl)-α-(phenylmethyl)-1H-pyrrole-1-acetic acid (4a; 0.87 g, 3.14 mmol) in DMF (15 mL) was added DCC (0.65 g, 3.14 mmol) and the mixture stirred at room temperature for 48 h (TLC indicated incomplete reaction). It was filtered and the filtrate evaporated under vacuum. The residue was diluted with EtOAc and filtered again. The mother liquor was concentrated to a small volume and chromatographed using EtOAc/hexane (1/1) as eluant to give 0.8 g (43%) of the title compound as an off-white material: mp 186–187 °C; MS (FAB) m/z 591 (M); IR 1702, 1742 cm^{-1}; ^{1}H NMR δ 8.67 (s, 1 H), 7.42 (d, J = 10 Hz, 2 H), 7.29–7.20 (m, 6 H), 6.97 (t, J = 2.5 Hz, 1 H), 6.83 (d, J = 10 Hz, 2 H), 6.22 (t, J = 2.5 Hz, 1 H), 5.99 (t, 1 H), 5.04 (s, 2 H), 3.84 (s, 3 H), 3.59 (s, 3 H), 3.65–3.73 and 3.20–3.25

(2 dd, J = 6.7, 13.5 Hz), 3.41 (s, 2 H), 2.52 (t, 2 H), 1.65–1.48 (m, 2 H), 1.37–1.28 (m, 2 H), 0.86 (t, 3 H).

Method B. (*RS*)-Methyl 2-Butyl-5-chloro-3-[[4-[[2-[2-(methoxycarbonyl)-1*H*-pyrrol-1-yl]-1-oxo-3-(2-thienyl)propyl]amino]phenyl]methyl]-3*H*-imidazole-4-acetate (21). Et₃N (0.56 g, 5.6 mmol) was added to an ice-cold solution of 2-(methoxycarbonyl)-α-(thienylmethyl)-1*H*-pyrrole-1-acetic acid (**4b**; 1.56 g, 5.6 mmol) in THF (10 mmol) followed by a solution of *tert*-butylacetyl chloride (0.74 g, 6.16 mmol). The mixture was stirred for 2 h followed by the addition of a solution of the above amine (**7f**; 1.85 g, 5.65 mmol) in THF (15 mL). The reaction mixture was allowed to warm up to room temperature and stirred for an additional 18 h. It was filtered and the filtrate was evaporated. The residue was taken up in EtOAc and the solution was washed with water, dried, and evaporated to yield a gum. It was chromatographed (CH₂Cl₂/EtOAc 9/1–EtOAc) to yield 2.3 g (70%) of a white solid: mp 171–172 °C; MS (FAB) *m/z* 598 (M); IR 1702, 1742 cm⁻¹; ¹H NMR δ 8.87 (s, 1 H), 7.42 (d, 2 H), 7.35 (s, 1 H), 7.15 (d, 1 H), 7.00 (t, 1 H), 6.92–6.84 (m, 3 H), 6.80 (t, 1 H), 6.27 (t, 1 H), 5.99 (t, 1 H), 5.04 (s, 2 H), 3.92 (m, 1 H), 3.84 (s, 3 H), 3.55 (s, 3 H), 3.45 (m, 1 H), 3.41 (s, 2 H), 2.52 (t, 2 H), 1.65–1.48 (m, 2 H), 1.37–1.28 (m, 2 H), 0.86 (t, 3 H).

Hydrolysis Procedure. (*S*)-2-Butyl-3-[[4-[[2-(2-carboxy-1*H*-pyrrol-1-yl)-1-oxo-3-phenylpropyl]amino]phenyl]methyl]-5-chloro-3*H*-imidazole-4-acetic Acid (18) and (*S*)-2-Butyl-1-[[4-[[[1-(1-carboxy-2-phenylethyl)-1*H*-pyrrol-3-yl]carbonyl]amino]phenyl]methyl]-4-chloro-1*H*-imidazole-5-acetic Acid (57). A solution of dilute NaOH [(0.15 g, 3.6 mmol) in 32 mL water] was added to a solution of the ester 17 (0.8 g, 1.35 mmol) in THF (72 mL) and the resulting mixture was stirred at room temperature for 18 h. THF was distilled and the residue was treated with water. The solution was adjusted to pH 3 and extracted with EtOAc. The extract was washed with brine, dried, and evaporated to yield a solid, TLC of which indicated a mixture. It was chromatographed (CH₂Cl₂/CH₃OH/AcOH 95/5/0.2) to give following fractions.

Faster moving fraction (18): 0.35 g (46%, foam); IR 1700 cm⁻¹; MS (FAB) *m/z* 563 (M); ¹H NMR (DMSO-*d₆*) δ 7.55 (d, 2 H), 7.44 (t, 1 H), 7.40–7.12 (m, 6 H), 7.02 (d, 2 H), 6.76 (t, 1 H), 6.09 (t, 1 H), 5.11 (s, 2 H), 3.47 (s, 3 H), 3.40–3.22 (m, 2 H), 2.46 (t, 2 H), 1.92 (s, 1.5 H, CH₃CO₂H), 1.46 (m, 2 H), 1.29–1.20 (m, 2 H), 0.80 (t, 3 H); HPLC (98%) t_R 4.4 min.

Slower moving fraction (57): 0.05 g (7%, foam); MS (FAB) *m/z* 563 (M); IR 1718 and 1733 cm⁻¹; ¹H NMR (DMSO-*d₆*) δ 7.63 (d, 2 H), 7.14–7.05 (m, 7 H), 7.10–6.85 (m, 3 H), 6.04 (t, 1 H), 5.12 (s, 2 H), 3.49 (s, 2 H), 3.42–3.33 (m, 2 H), 2.50 (m, 2 H), 2.01 (s, 2.5 H, CH₃CO₂H), 1.46 (m, 2 H), 1.29–1.20 (m, 2 H), 0.80 (t, 3 H); HPLC (94%) t_R 3.62 min.

(*S*)-Methyl 2-Butyl-1-[[4-[[2-(2-carbomethoxy-1*H*-pyrrol-1-yl)-1-oxo-3-phenylpropyl]amino]phenyl]methyl]-1*H*-imidazole-5-carboxylate (25). A solution of 4.6 g of 23 in THF/MeOH (1/1, 100 mL) containing 0.8 g of KOAc and 5% Pd/C (0.5 g) was hydrogenated under 16 psi of hydrogen. After 20 h the gas was vented, and the solids were filtered through a pad of Celite. The filtrate was evaporated, the residue was taken up in EtOAc, and the suspension was washed with water followed by brine. It was dried and evaporated and the residue purified via chromatography (CH₂Cl₂/acetone 5%) to yield 2.9 g (67%) of 25: mp 174–175 °C; MS (CI) *m/z* 543 (M); ¹H NMR δ 8.62 (br, s 1 H), 7.78 (s, 1 H), 7.40 (d, 2 H), 7.39–7.20 (m, 6 H), 6.96 (t, 1 H), 6.91 (d, 2 H), 6.22 (t, 1 H), 6.03 (t, 1 H), 5.46 (s, 2 H), 3.82 (s, 3 H), 3.77 (s, 3 H), 3.72 (m, 1 H), 3.20 (m, 1 H), 2.61 (m, 2 H), 1.72 (m, 2 H), 0.92 (t, 3 H).

This was hydrolyzed as before to give mixture of carboxylic acids which were chromatographed to give the desired acid 26: MS (FAB) *m/z* 471 (M – CO₂); HPLC (96%) t_R 5.25 min; ¹H NMR (DMSO-*d₆*) δ 12.5 (br, 2 H), 10.6 (s, 1 H), 7.652 (s, 1 H), 7.58 (d, 1 H), 7.45 (s, 1 H), 7.40–7.05 (m, 5 H), 6.98 (d, 2 H), 6.78 (t, 1 H), 6.38 (t, 1 H), 6.07 (t, 1 H), 5.47 (s, 2 H), 3.35 (m, 2 H), 2.60 (m, 2 H), 1.56 (m, 2 H), 1.32 (m, 2 H), 0.85 (t, 3 H).

3-[[4-[(Phenylpropionyl)amino]phenyl]methyl]-2-butyl-5-chloro-3*H*-imidazole-4-acetic Acid (50). A mixture of the amine 7f (0.5 g, 1.5 mmol), 3-phenylpropionyl chloride (0.25 g, 1.5 mmol), and Et₃N (0.2 g, 1.5 mmol) in CH₂Cl₂ (15 mL) was stirred at 23 °C for 18 h. The solution was diluted with an additional quantity of CH₂Cl₂ and the solution was washed with

water, dried, and evaporated to a small volume. This was filtered through a bed of silica gel, and the filtrate was evaporated to dryness to give the desired material (0.67 g, 97%): mp 134–135 °C; MS (CI) *m/z* 468 (M). Anal. Calcd for C₂₆H₃ClN₃O₃: C, 66.73; H, 6.46; N, 8.98. Found: C, 66.89; H, 6.52; N, 8.83.

A solution of the above ester (0.63 g) in THF (10 mL) was stirred with NaOH (2.7 mL, 0.23 N, 6.8 mmol) for 4 h. THF was distilled, the residue was dissolved in water, and the solution was acidified. The solid was filtered, washed with water, and dried to give the title acid (0.55 g, 90%): MS (FAB) *m/z* 454 (M); ¹H NMR (DMSO-*d₆*) δ 9.98 (s, 1 H), 7.54 (d, 2 H), 7.35–7.15 (m, 5 H), 6.95 (d, 2 H), 5.13 (s, 2 H), 3.45 (s, 3 H), 3.35 (br, H₂O), 2.88 (m, 2 H), 2.58 (t, 2 H), 2.48 (t, 2 H), 1.45 (m, 2 H), 1.21 (m, 2 H), 0.88 (t, 3 H).

N-[4-[[2-Butyl-4-chloro-5-(hydroxymethyl)-1*H*-imidazol-1-yl]methyl]phenyl]-α-oxobenzeneacetamide (51) was prepared from amine 7d and benzoylformic acid by DCC coupling (method A).

N-[4-[[2-Butyl-4-chloro-5-(hydroxymethyl)-1*H*-imidazol-1-yl]methyl]phenyl]-α-(hydroxyimino)-benzeneacetamide (52). A solution of 0.35 g of the above ketone 51 in EtOH (10 mL) was treated with a solution of NH₂OH·HCl (0.1 g) and NaOAc (0.15 g) in water (2 mL). The solution was heated under reflux for 18 h and evaporated. The residue was taken up in EtOAc and the solution was washed with water, dried, and stripped to yield a foam. This was triturated with Et₂O and filtered to give 0.31 g of the title compound.

N-[4-[[2-Butyl-4-chloro-5-(hydroxymethyl)-1*H*-imidazol-1-yl]methyl]phenyl]-α-cyanobenzenepropanamide (53) was prepared from 7d and 2-cyano-3-phenylpropionic acid[28] via DCC coupling.

N-[4-[[2-Butyl-4-chloro-5-(hydroxymethyl)-1*H*-imidazol-1-yl]methyl]phenyl]-α-(phenylmethyl)-1*H*-tetrazole-5-acetamide (54). A mixture of 53 (0.5 g, 1.11 mmol), NaN₃ (0.19 g, 2.9 mmol), and NH₄Cl (0.06 g, 1.12 mmol) in DMF (5 mL) was heated at 80 °C for 18 h. DMF was distilled under vacuum and the residue was partitioned between water and EtOAc. The aqueous solution was acidified with concentrated HCl and extracted with CH₂Cl₂. The organic layer was separated, washed with water, dried, and evaporated to yield 0.15 g (28%) of 54; MS (FAB) *m/z* 493 (M).

Biological Evaluation Procedures. Angiotensin Receptor Binding Methodology. Rat liver was obtained from male Long-Evans rats (200–500 g) sacrificed by decapitation. The tissues were disrupted in 10 volume 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 of HEPES buffer (as above and 10 mM MgCl₂) containing 10 mg of original tissue weight of homogenate and 0.5 nM [¹²⁵I]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 10 μM saralasin. The inhibitory concentration (IC₅₀) of an inhibitor that gave 50% displacement of the specifically bound iodinated angiotensin II (2nM) was 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 Methodology. 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, 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 FT03C 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 succeeding 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 of 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.

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