Nonpeptide Angiotensin II Receptor Antagonists. 1. Synthesis and in Vitro Structure–Activity Relationships of 4-[[[(1*H*-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 1*H*-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 (AT_1) 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 1*H*-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 AT_1 receptor. As part of an ongoing search to identify novel non-biphenylyltetrazole AT_1 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 OCH_2, 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 1*H*-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.

Chart I. Orally Active Angiotensin II Antagonists

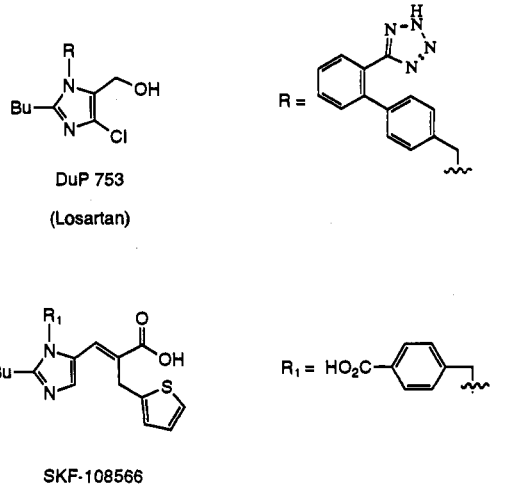
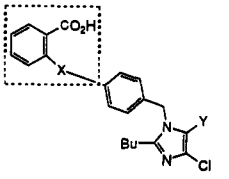


Chart II



Compound	Y	X	AT_1 receptor binding IC_{50} (μM)
EXP 6803	$CH_2CO_2CH_3$	CONH-	0.14
EXP 7711	CH_2OH	bond	0.30
EXP 8623	CO_2H	bond	0.092

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 1*H*-pyrroyl-1-ylacetic acids (Table I) with 1-(4-aminobenzyl)imidazole derivatives (Schemes III–V). Two procedures for the coupling reaction were used [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

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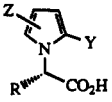
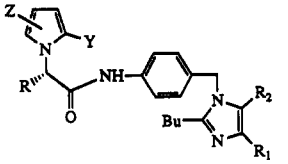
Table I. 1*H*-Pyrrole-1-acetic Acid Derivatives



compd	R[h]	Y	Z	mp, °C[a] (crystn solvent)	yield, %[b]	formula[c]	$[\alpha]_D^{22}$, deg (c, MeOH)
1	H	CO_2Me	H	131–132 (EtOAc)	65	$C_8H_9NO_4$	
2	Ph	CO_2Me	H	oil	10	$C_{14}H_{13}NO_4$[e]	
3	Bu	CO_2Me	H	79–82 (EtOAc/hexane)	61.7	$C_{12}H_{17}NO_4$	1.1 (0.969)
4a	$PhCH_2$	CO_2Me	H	oil	41	$C_{15}H_{15}NO_4$·0.4AcOH	−17.5 (1.0)
4b[d]	$ThCH_2$	CO_2Me	H	115–116 (EtOAc/hexane)	44	$C_{13}H_{13}NO_4S$	
4c	$PhCH_2$	H	H	90–93	80.9	$C_{13}H_{13}NO_2$	−57.7 (1.095)
4d	$PhCH_2$	Me	H	93–94 (hexane)	64.4	$C_{14}H_{15}NO_2$	−103.8 (1.002)
4e	$PhCH_2$	Me	3-CO_2Et	oil	42	$C_{17}H_{19}NO_4$·0.3AcOH[f]	−14.6 (1.212)
4f	$PhCH_2$	H	3-CO_2Et	oil	37.3	$C_{18}H_{17}NO_4$[g]	−50.8 (0.875)
4g	$ThCH_2$	H	H	77–79° (hexane)	81.9	$C_{11}H_{11}NO_2S$·0.1AcOH	
4h	$PhCH_2$	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	R_2	R_1	mp, °C[a]	formula[c]	yield, %[b] (method)	receptor binding; IC_{50}, μM[d]
11	H	CO_2Me	Ph	CH_2OH	Cl	e	$C_{29}H_{31}ClN_4O_4$·2.7H_2O	20 (A)	1.12 ± 0.064
12	H	CO_2Me	Bu	CH_2OH	Cl	e	$C_{27}H_{35}ClN_4O_4$	34 (A)	0.59 ± 0.065
13	H	CO_2Me	H	CH_2OH	Cl	231–232	$C_{23}H_{27}ClN_4O_4$·0.14EtOAc	38 (A)	8.37
14	H	CO_2Me	CH_2Ph	CH_2OH	Cl	e	$C_{30}H_{33}ClN_4O_4$	40 (A)	0.21 ± 0.058

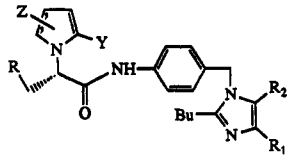
[a] Compounds were purified by chromatography. [b] Yields were not optimized. [c] All microanalytical values were in agreement with assigned structures (within ±0.4%). [d] Concentration to inhibit binding of radiolabeled AII by 50%. IC_{50} values were obtained from a dose–response curve generated from 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 = CO_2Me. 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-tetrahydrofurans (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 N_1 isomers as the major product. The N_3 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 N_1 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, NCH_2 protons, and various protons at the close proximity (Figure 1).

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

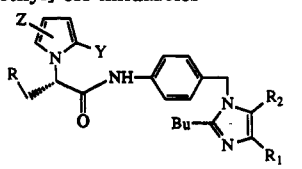
Table III. [[[(1*H*-Pyrrolyl-1-acetyl)amino]phenyl]methyl]-3*H*-imidazoles



compd	Z	Y	R[b]	R_2	R_1	mp, °C[a,b] (crystn solvent)	formula[c]	IC_{50}, μM: receptor binding[d] (% inhibit at 10^{-7} M)	IC_{50}, μM: rabbid aorta[e]
14	H	CO_2Me	Ph	CH_2OH	Cl	*f*	$C_{30}H_{33}ClN_4O_4$	0.21 ± 0.058	
15	H	CO_2H	Ph	CH_2OH	Cl	*f*	$C_{29}H_{31}ClN_4O_4 \cdot 0.4H_2O$	0.18 ± 0.009	17.0
16	H	CO_2H	Ph	CH_2OH	H	*f*	$C_{29}H_{32}N_4O_4$[g]	1.1 ± 0.034	
17	H	CO_2Me	Ph	CH_2CO_2Me	Cl	186–188 (EtOAc/hexane)	$C_{32}H_{35}ClN_4O_5$	0.50 ± 0.025	
18	H	CO_2H	Ph	CH_2CO_2H	Cl	*f*	$C_{30}H_{31}ClN_4O_5 \cdot 0.5AcOH$	0.027 ± 0.006	0.52
19	H	CO_2Me	Ph	$(CH_2)_2CO_2Me$	Cl	*f*	$C_{33}H_{37}ClN_4O_5$	0.21 ± 0.005	
20	H	CO_2H	Ph	$(CH_2)_2CO_2H$	Cl	106–107 dec	$C_{31}H_{33}ClN_4O_5 \cdot 0.2AcOH$	0.022 ± 0.003	0.22
21	H	CO_2Me	Th	CH_2CO_2Me	Cl	171–172	$C_{30}H_{33}ClN_4O_5S$	0.80 ± 0.002	
22	H	CO_2H	Th	CH_2CO_2H	Cl	191–193	$C_{29}H_{29}ClN_4O_5S$	0.024 ± 0.004	
23	H	CO_2Me	Ph	CO_2Me	Cl	*f*	$C_{31}H_{33}ClN_4O_5 \cdot 0.2Et_2O$	(15)	
24	H	CO_2H	Ph	CO_2H	Cl	116	$C_{29}H_{29}ClN_4O_5 \cdot 0.1cyclohexane \cdot 0.2H_2O$	0.08 ± 0.006	0.55
25	H	CO_2Me	Ph	CO_2Me	H	174–175	$C_{31}H_{34}N_4O_5$	(33)	
26	H	CO_2H	Ph	CO_2H	H	211	$C_{29}H_{30}N_4O_5 \cdot 0.4CH_2Cl_2$	0.02 ± 0.001	0.11
27	H	CO_2Me	Th	CO_2Me	Cl	*f*	$C_{29}H_{31}ClN_4O_5S \cdot 0.1H_2O$	(11)	
28	H	CO_2H	Th	CO_2H	Cl	*f*	$C_{27}H_{27}ClN_4O_5S \cdot 2H_2O$	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. [[[(1*H*-Pyrrolyl-1-acetyl)amino]phenyl]methyl]-3*H*-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_2Me	Ph	CO_2Et		*e*	$C_{36}H_{39}N_5O_5 \cdot 0.5H_2O$	N
30	H	CO_2H	Ph	CO_2Et		*e*	$C_{35}H_{37}N_5O_5$	2.5 ± 0.099
31	H	CO_2H	Ph	CO_2H		*e*	$C_{33}H_{33}N_3O_5 \cdot 1.3CH_2Cl_2 \cdot 1.2MeOH$	0.34 ± 0.147
32	H	CO_2Me	Ph			202–203	$C_{34}H_{36}N_4O_3 \cdot 0.2H_2O$	N
33	H	CO_2H	Ph			*e*	$C_{33}H_{34}N_4O_3 \cdot 0.6MeOH \cdot 0.6CH_2Cl_2$	0.93 ± 0.093
34	H	CO_2Me	Ph			216–217 (EtOAc)	$C_{32}H_{33}N_5O_3 \cdot 0.1EtOAc$	0.33 ± 0.068
35	H	CO_2H	Ph			*e*	$C_{31}H_{31}N_5O_3 \cdot 0.4CH_2Cl_2$	0.06 ± 0.007

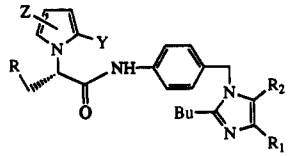
[a] Yields were in the range of 60–80% (esters) and 40–50% (acids). [b] Compounds were purified by chromatography. [c] All microanalytical values were within ±0.4% of the calculated values. [d] Concentration to inhibit binding of radiolabeled AII by 50%. IC_{50} values were obtained from a dose–response 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_3N 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_2OH. Compound **53** was reacted with a mixture of NaN_3/NH_4Cl 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

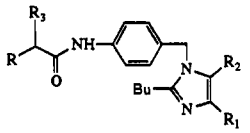
Table V. [[[(1*H*-Pyrrolyl-1-acetyl)amino]phenyl]methyl]-3*H*-imidazoles



compd	Z	Y	R[b]	R_2	R_1	mp, °C[a,b]	formula[c]	IC_{50}, μM: receptor binding[d] (% inhibn at 10^{-7} M)	IC_{50}, μM: rabbit aorta[e]
36	3-CO_2Et	H	Ph	CH_2CO_2Me	Cl	*g*	$C_{33}H_{37}N_4O_5Cl$·0.3TMA[f]	(7.2)	
37	3-CO_2Et	H	Ph	CH_2CO_2H	Cl	*g*	$C_{32}H_{35}ClN_4O_5$	0.24 ± 0.006	14.0
38	3-CO_2Et	Me	Ph	CH_2CO_2Me	Cl	84–85	$C_{34}H_{39}ClN_4O_5$	1.47 ± 0.190	
39	3-CO_2Et	Me	Ph	CH_2CO_2H	Cl	191–193 (EtOAc/hexane)	$C_{33}H_{37}ClN_4O_5$·1.8AcOH·1.0H_2O	0.14 ± 0.005	
40	H	Me	Ph	CH_2CO_2Me	Cl	*g*	$C_{31}H_{35}ClN_4O_3$·0.2H_2O	(14.8)	
41	H	Me	Ph	CH_2CO_2H	Cl	*g*	$C_{30}H_{33}N_4O_3Cl$·0.2H_2O	0.14 ± 0.001	6.4
42	H	H	Ph	CH_2CO_2Me	Cl	*g*	$C_{30}H_{33}ClN_4O_3$	1.92 ± 0.260	
43	H	H	Ph	CH_2CO_2H	Cl	*g*	$C_{29}H_{31}ClN_4O_3$·0.1H_2O	0.21 ± 0.003	6.3
44	H	H	Th	CO_2Me	Cl	*g*	$C_{27}H_{29}N_4O_3ClS$	(2.5)	
45	H	H	Th	CO_2H	Cl	*g*	$C_{29}H_{27}ClN_4O_3S$·0.4H_2O	0.67 ± 0.002	
46	H	H	Ph	CH_2OH	Cl	*g*	$C_{29}H_{31}ClN_4O_2$	(8.1)	
47	5-Me	Me	Ph	CH_2CO_2H	Cl	108–111	$C_{31}H_{35}N_4ClO_3$·0.64H_2O	0.37 ± 0.002	
48[i]	3-CN	H	Ph	CH_2CO_2Me	Cl	95–100	$C_{35}H_{34}ClN_5O_3$	N	
49[i]	3-CN	H	Ph	CH_2CO_2H	Cl	*g*	$C_{34}H_{32}ClN_5O_3$·0.87TFA·0.3H_2O	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%. 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} 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



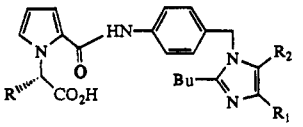
compd	R	R_1	R_2	R_3	mp, °C[b] (crystn solvent)	yield, %[a]	formula[c]	receptor binding; IC_{50}, μM[d] (% inhibn at 10^{-7} M)
50[f]	CH_2Ph	Cl	CH_2CO_2H	H	188–189	95	$C_{25}H_{28}ClN_3O_3$·0.2H_2O	(7.8)
51	Ph	Cl	CH_2OH	=O	162–163 (EtOAc/hexane)	82	$C_{23}H_{24}ClN_3O_3$·0.2H_2O	10.9 ± 2.44
52	Ph	Cl	CH_2OH	=NOH	197–199 dec (EtOAc/ether)	86	$C_{23}H_{25}ClN_4O_3$·0.7AcOH	3.25 ± 0.560
53	CH_2Ph	Cl	CH_2OH	CN	*e*	90	$C_{25}H_{27}ClN_4O_2$·0.4DMF	2.60 ± 0.119
54	CH_2Ph	Cl	CH_2OH	T[g]	*e*	30	$C_{25}H_{28}ClN_7O_2$·0.8HCl	2.6 ± 0.004

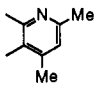
[a] Yields were not optimized. [b] Compounds were purified by chromatography. [c] All microanalytical values were within ±0.4% of the calculated values. [d] Concentration to inhibit binding of radiolabeled AII by 50%. IC_{50} values were obtained from a dose–response curve generated from at least five or six doses and are expressed as a mean ± SEM. [e] Foam. [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] IC_{50} 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 (R_1 and R_2) 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 R_2 = CH_2CO_2Me, dropped to some extent whereas that of **19** (R_2 = CH_2CO_2Me) remained the same. The receptor affinity of diacids **18**, **20**, and **24** improved significantly with IC_{50} values in the 10^{-8} M range. The relative order of potency was $(CH_2)_2CO_2H$ > CH_2CO_2H > CO_2H > CH_2OH. The IC_{50} 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 deschloro analogues. In the hydroxymethyl series (R_2 = CH_2OH) 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** [IC_{50} = 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 R_2 and R_1 were connected to form a

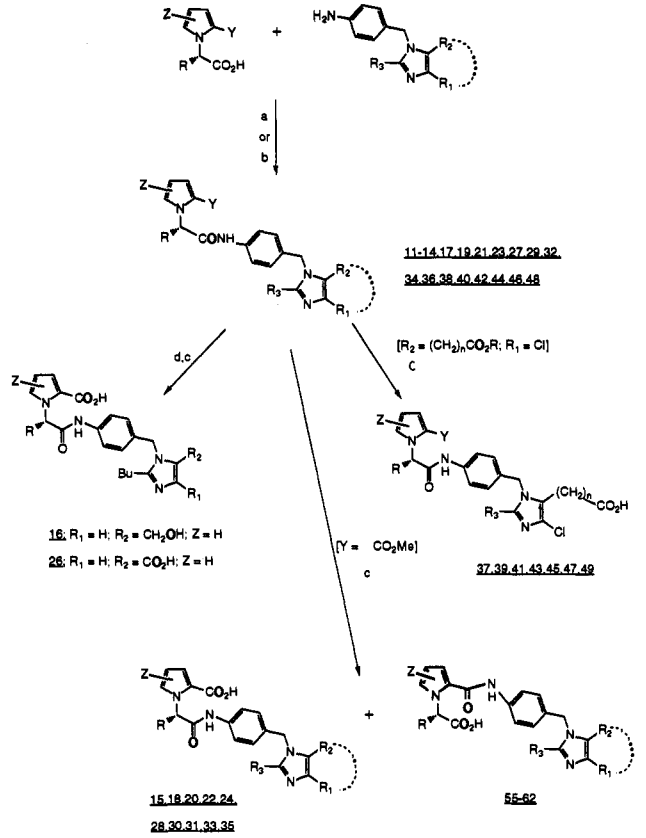
Table VII. 1*H*-Pyrrole-1-acetic Acid Derivatives



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	$C_{29}H_{29}ClN_4O_5S \cdot 0.17AcOH$
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		$C_{25}H_{37}N_5O_5 \cdot 0.3CH_2Cl_2$

[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]

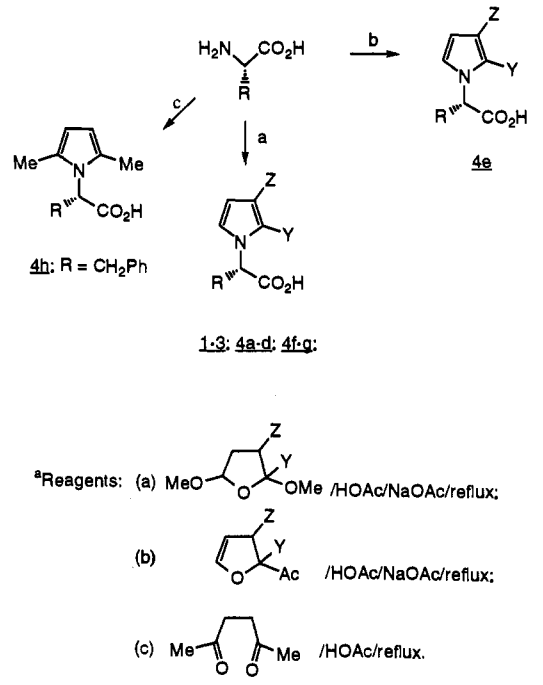


[a] Reagents: (a) DCC/HOBT (method A); (b) $(CH_3)_3CCOCl$/DMAP/THF (method B); (c) NaOH; (d) H_2/Pd-C/KOAc.

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,

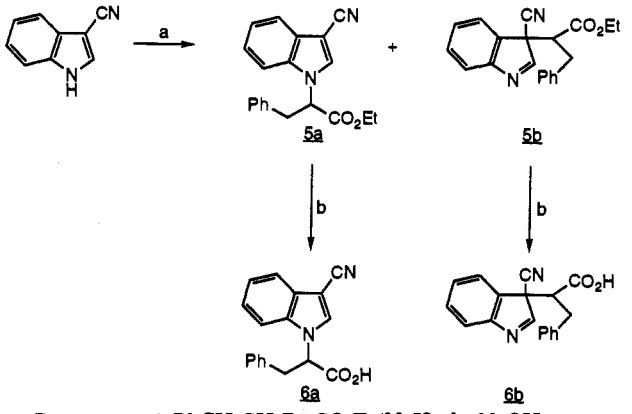
Scheme II.[a] 1*H*-Pyrrole-1-acetic Acid Derivatives



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).

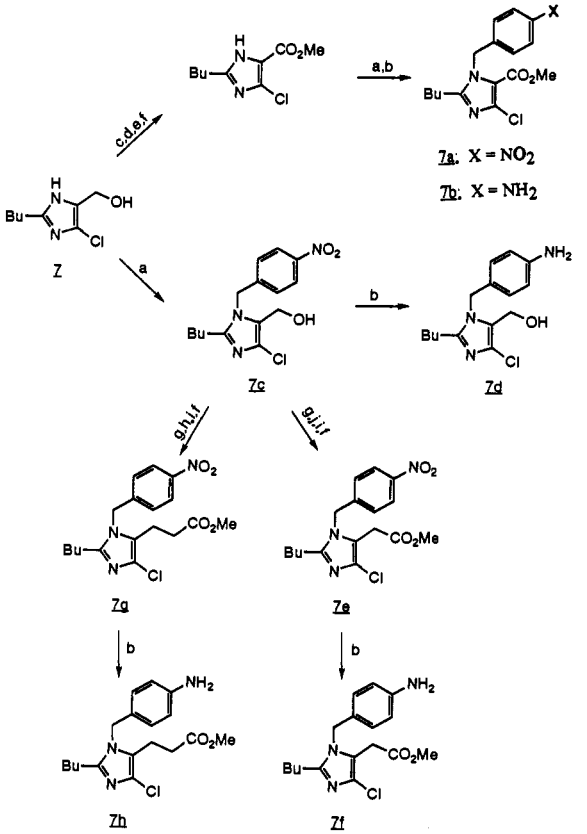
These compounds represent a novel series of potent and selective AT_1 antagonists (<20% inhibition at 1 μM for the AT_2 receptor). As seen from Tables II–V a good correlation exists between the receptor binding and the functional assay, although in general, a 10-fold decrease in IC_{50} was observed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

Scheme III.[a] 1*H*-Indole-1-acetic Acid Derivatives



[a] Reagents: (a) $PhCH_2CH(Br)CO_2Et/NaH$; (b) NaOH.

Scheme IV.[a] 1-[(4-Aminophenyl)methyl]-3*H*-imidazole Derivatives



[a] Reagents: (a) p-NO_2BnBr/base; (b) H_2/Raney Ni; (c) MnO_2; (d) TMSCN; (e) CrO_3; (f) MeOH–H^+; (g) $SOCl_2$; (h) $CH_2(CO_2Me)_2$/base; (i) HCl; (j) KCN.

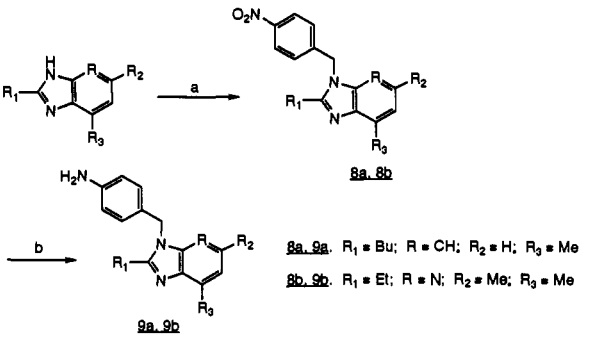
6803 this series suffers from lack of in vivo activity after oral administration. For example, no blood pressure lowering effect was demonstrated with compound **18**, even after dosing at 30 mg/kg in renal hypertensive rats.

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

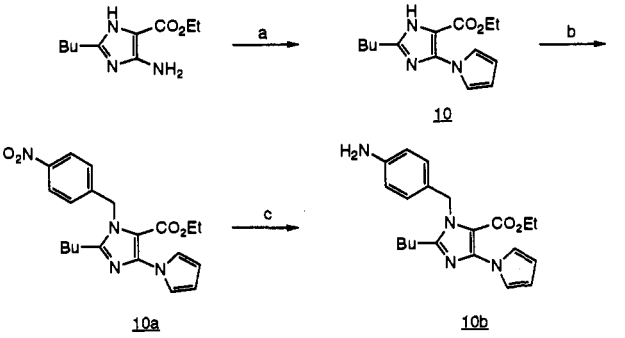
In summary, the data presented here demonstrates that replacement of the benzoyl group in EXP 6803 with a 1*H*-pyrrol-1-ylacetyl group produced a novel series of potent and selective AT_1 receptor antagonists. The receptor binding affinity of several members of this series was in the 10^{-8} M range, which was better than EXP 6803. IC_{50}'s were also comparable to that of EXP 7711, which

Scheme V[a]



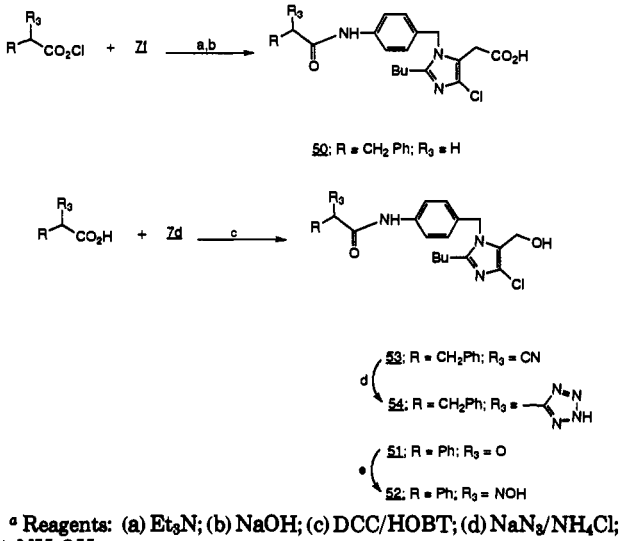
[a] Reagents: (a) p-NO_2BnBr/base; (b) H_2/Raney Ni.

Scheme VI[a]



[a] Reagents: (a) MeO–(THF)–OMe/AcOH; (b) p-NO_2BnBr/Base; (c) H_2/Raney Ni

Scheme VII[a]



[a] Reagents: (a) Et_3N; (b) NaOH; (c) DCC/HOBT; (d) NaN_3/NH_4Cl; (e) NH_2OH.

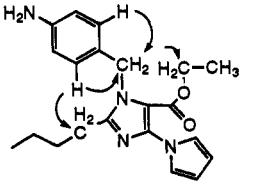


Figure 1. The arrows indicate the NOE's observed between the NCH_2 protons and the various protons in close spatial proximity.

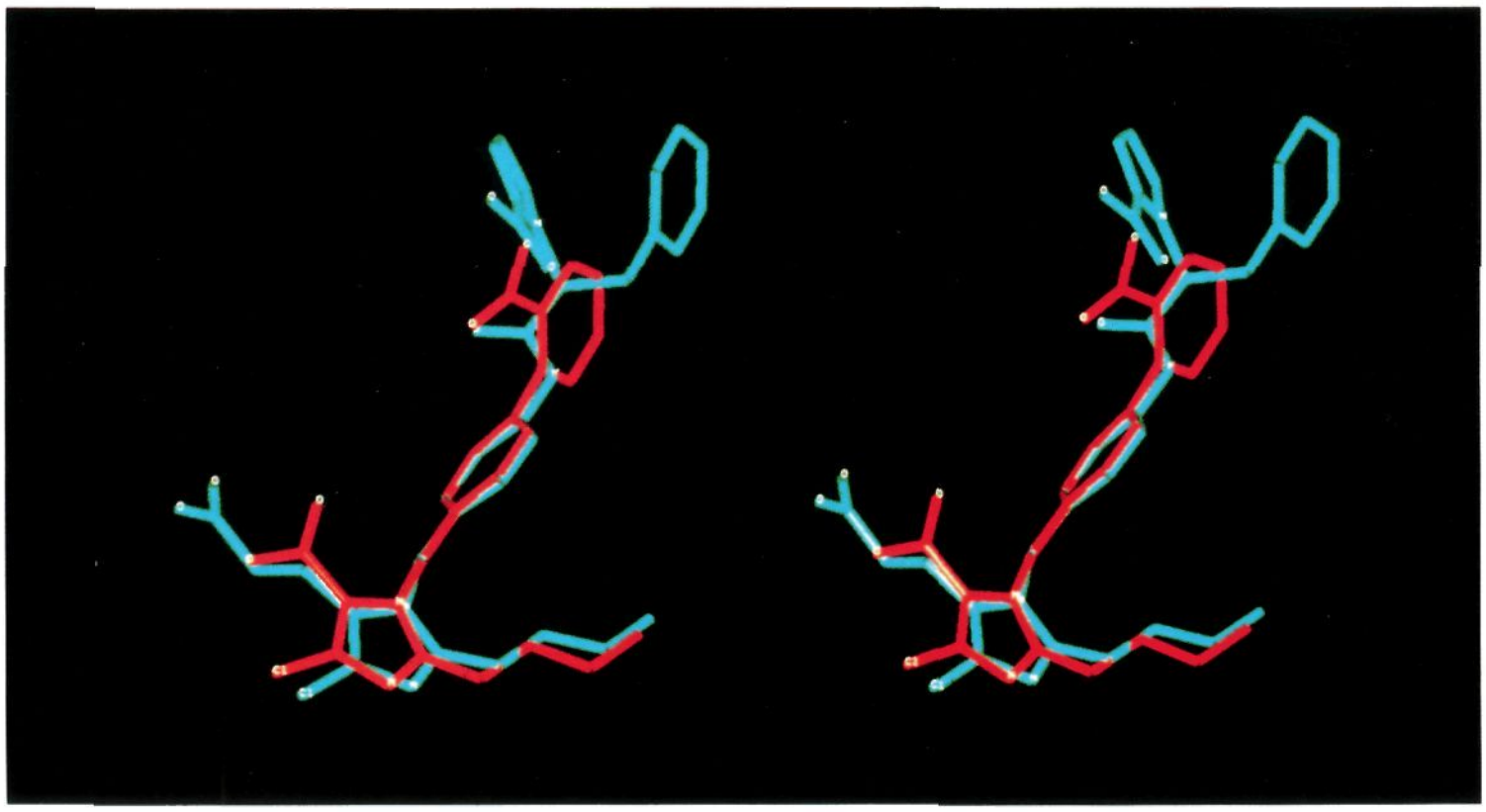


Figure 2. Possible overlap of low-energy structures for EXP 8623 (red) and **20** (blue).

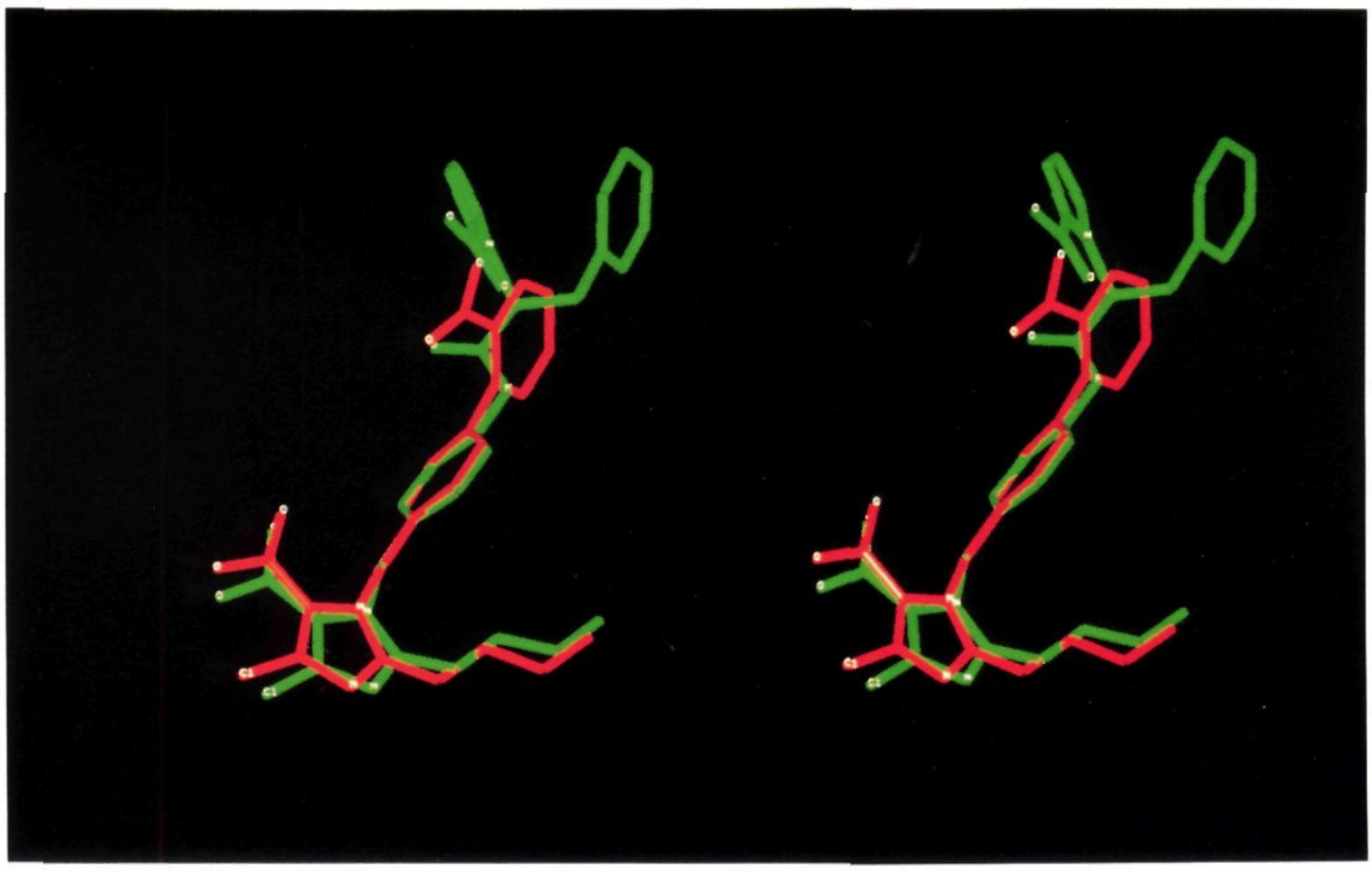


Figure 3. Possible overlap of low energy structures for EXP 8623 (red) and **24** (green).

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 ^1H NMR spectra of all new compounds were consistent with the proposed structures (data for selected compounds are presented). ^1H 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.

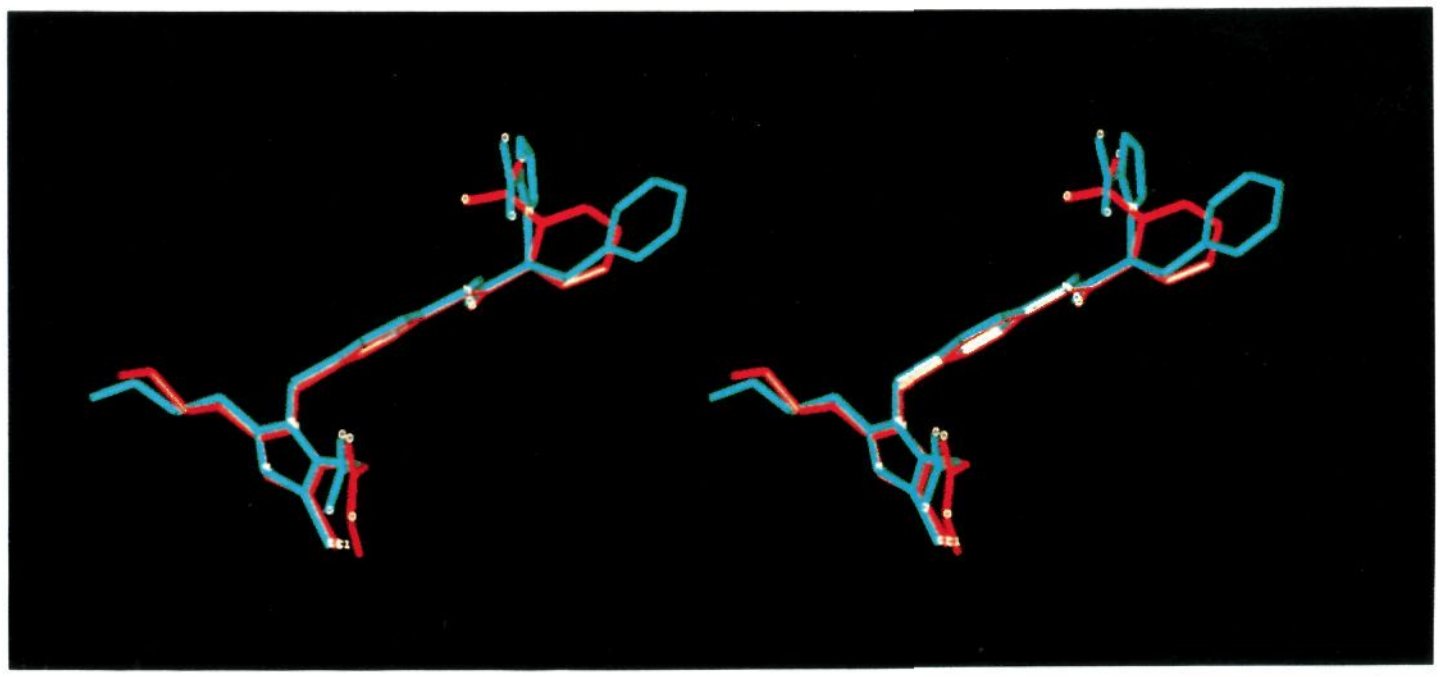


Figure 4. Sterioscopic molecular graphics show the close similarity in conformation of EXP 6803 (red) and 18 (blue).

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 1*H*-pyrrole-1-acetic Acids (4a–h). (*S*)-2-(Methoxycarbonyl)-α-(phenylmethyl)-1*H*-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 ($CHCl_3$/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)-1*H*-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 (SiO_2, CH_2Cl_2/hexane 1/4–EtOAc/hexane 1/10) to give two regioisomers.

Ethyl 3-Cyano-α-(phenylmethyl)-1*H*-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 $C_{20}H_{18}N_2O_2 \cdot 0.1H_2O$: C, 75.03, H, 5.73, N, 8.75. Found: C, 74.72; H, 5.73; N, 8.66.

Ethyl 3-cyano-α-(phenylmethyl)-3*H*-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]-3*H*-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 $CHCl_3$ (35 mL) at 0 °C. The solution was warmed to room temperature followed by heating at reflux for 3 h under N_2. 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 N_2. 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/CH_2Cl_2 1/4–EtOAc/CH_2Cl_2 1/10) to give the desired diester as an oil (1.5 g): MS (EI) *m/z* 437 (M). Anal. Calcd for $C_{20}H_{24}ClN_3O_6 \cdot 0.17CH_2Cl_2$: 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 $C_{17}H_{20}ClN_3O_4 \cdot 0.09H_2O$: 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 CH_3OH (25 mL) and concentrated H_2SO_4 (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-3*H*-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_2Cl_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_2Cl_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 $C_{18}H_{24}ClN_3O_2 \cdot 0.12CH_2Cl_2$: 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]-3*H*-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_4NBr (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_2Cl_2. The combined organic layers were washed with water, dried, and evaporated to dryness. The residual solid was recrystallized from CH_2Cl_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 $C_{16}H_{17}ClN_4O_2$: 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_3OH (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 $C_{17}H_{20}ClN_3O_4$: 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-3*H*-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-1*H*-imidazole-5-methanol (7d)**; MS (CI) *m/z* 293 (M).

Methyl 2-Butyl-5-chloro-3-[(4-aminophenyl)methyl]-3*H*-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]-3*H*-imidazole-5-carboxylate (7a): MS (CI) *m/z* 352 (M). Anal. Calcd for $C_{16}H_{18}ClN_3O_4$: 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 $C_{16}H_{20}ClN_3O_2$: 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]-1*H*-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 $C_{19}H_{21}N_3O_2$: 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]-3*H*-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 $C_{17}H_{18}N_4O_2 \cdot 0.1H_2O$: C, 65.41; H, 5.88; N, 17.95. Found: C, 65.26; H, 5.94; N, 17.99.

4-[(2-Butyl-4-methyl-1*H*-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-3*H*-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 $C_{17}H_{20}N_4 \cdot 0.3H_2O$: C, 71.45; H, 7.27; N, 19.60. Found: C, 71.54; H, 7.07; N, 19.53.

Ethyl 2-Butyl-4-(1*H*-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_2Cl_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 $C_{14}H_{19}N_3O_2 \cdot 0.13$EtOAc: 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-(1*H*-pyrrol-1-yl)-3*H*-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 $C_{21}H_{24}N_4O_4 \cdot 0.16$EtOAc: 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-(1*H*-pyrrol-1-yl)-3*H*-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 $C_{21}H_{28}N_4O_2$: 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)-1*H*-pyrroyl]-1-oxo-3-phenylpropyl]amino]phenyl]methyl]-3*H*-imidazole-4-acetate (17). To a mixture of methyl 3-[(4-aminophenyl)methyl]-2-butyl-5-chloro-3*H*-imidazole-4-acetate (**7f**; 1.0 g, 3.14 mmol) and 2-(methoxycarbonyl)-α-(phenylmethyl)-1*H*-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). Et_3N (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 (CH_2Cl_2/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}; ^{1}H 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 (CH_2Cl_2/CH_3OH/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); ^{1}H NMR (DMSO-d_6) 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, CH_3CO_2H), 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}; ^{1}H NMR (DMSO-d_6) 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, CH_3CO_2H), 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 (CH_2Cl_2/acetone 5%) to yield 2.9 g (67%) of **25**: mp 174–175 °C; MS (CI) m/z 543 (M); ^{1}H 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 – CO_2); HPLC (96%) t_R 5.25 min; ^{1}H NMR (DMSO-d_6) 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 Et_3N (0.2 g, 1.5 mmol) in CH_2Cl_2 (15 mL) was stirred at 23 °C for 18 h. The solution was diluted with an additional quantity of CH_2Cl_2 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 $C_{26}H_3ClN_3O_3$: 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); ^{1}H NMR (DMSO-d_6) 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, H_2O), 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 NH_2OH·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 Et_2O 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), NaN_3 (0.19 g, 2.9 mmol), and NH_4Cl (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 CH_2Cl_2. 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 50000g 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 $MgCl_2$) containing 10 mg of original tissue weight of homogenate and 0.5 nM [^{125}I]angiotensin II. Test compounds were dissolved at 10 mM in DMSO, and diluted in DMSO to 100 times the final incubation concentration. Control incubations received an equal volume (10 μL) of DMSO. The resulting concentration of DMSO had no effect on binding. Incubation was initiated by agitating the rack of tubes on a vortex mixer. Tubes were then placed in a 25 °C shaking water bath for 60 min. Incubations were terminated by filtration through Whatman GF/B glass-fiber filter sheets which had been presoaked in 50 mM Tris buffer, pH 7.7 containing 100 mM bacitracin using a Brandel 48R cell harvester. Filters were washed with three 4-mL rinses of 50 mM Tris buffer. The filtration was completed within 25 s. Filters were transferred to scintillation vials in which 8 mL of Formula 963 scintillation fluid was added, and the vials were left overnight, shaken, and then counted in a liquid scintillation counter.

Specific binding was defined as total binding minus nonspecific binding, which was determined in the presence of 10 μM saralasin. The inhibitory concentration (IC_{50}) 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 FTO3C 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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