Imidazole-5-acrylic Acids: Potent Nonpeptide Angiotensin II Receptor Antagonists Designed Using a Novel Peptide Pharmacophore Model[1]

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A series of novel nonpeptide angiotensin II receptor antagonists containing a substituted (*E*)-acrylic acid has been developed. The overlay of **1**, an imidazole-5-acetic acid found in the patent literature, on a novel pharmacophore model of AII suggested that extension of the acid side chain and attachment of a second aryl residue to mimic the C-terminal phenylalanine region of AII would lead to increased activity. A study of extended acid side chains at C-5 of the imidazole nucleus led to the discovery of the (*E*)-acrylic acid **5** as a promising starting point for further exploration. As predicted by the modeling, substitution of a benzyl group on the acrylic acid side chain to mimic the phenylalanine gave increased potency. An extensive study of the SAR of the newly introduced aromatic ring revealed that electron-rich heteroaryl rings provided improved activity, most notably in the in vivo rat models. Compound **40**, (*E*)-3-[2-butyl-1-[(2-chlorophenyl)methyl]imidazol-5-yl]-2-[(2-thienyl)methyl]-2-propenoic acid, has been shown to be a potent, competitive, and orally active small molecule AT-1 receptor antagonist. It exhibits a 2 orders of magnitude increase in binding affinity and a 10-fold improvement in in vivo potency as compared to compound **1** and represents an important milestone in the development of even more potent nonpeptide angiotensin II receptor antagonists.

Blockade of the renin–angiotensin system (RAS) with angiotensin converting enzyme (ACE) inhibitors has been shown to be effective in the treatment of hypertension, congestive heart failure, and possibly chronic renal failure.[2] These compounds exert their beneficial therapeutic effects via inhibition of the synthesis of the octapeptide angiotensin II (AII), a powerful vasoconstrictor. The success of the ACE inhibitors has sparked an interest in the development of alternate methods of specifically interrupting the RAS. Ideally, the most direct approach to interfere with the RAS would be to inhibit the binding of the effector hormone angiotensin II at the receptor level. Competitive AII receptor antagonists are expected to have similar therapeutic effects and indications as the ACE inhibitors without the unwanted side effects associated with inhibition of other ACE-mediated pathways, such as bradykinin metabolism. Initial research in this area led to the discovery of peptide analogs, such as saralasin ([Sar^1,Ala^8]-AII), which displayed potent and selective AII receptor antagonist activity both in vitro and in vivo. However, these peptides had limited therapeutic utility due to partial agonist activity, short duration of action, and lack of appreciable oral bioavailability.[3] Only in recent years have a number of nonpeptide AII antagonists that show promise as inhibitors of the RAS been reported.[4] We recently disclosed the development and pharmacology of the extremely potent, highly selective and competitive nonpeptide antagonist, SK&F 108566.[5] Herein, we elaborate on the design of the distinguishing structural feature of this novel class of nonpeptide AII receptor antagonists: the substituted acrylic acid portion attached to the imidazole nucleus. This research was highlighted by the

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(1) This paper is dedicated to Professor Ralph Hirschmann on the occasion of his 70th birthday.

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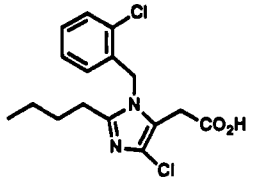
use of a unique pharmacophore model of AII[6] as a template to assist in small molecule optimization. Incorporation of structural modifications suggested by the overlay of compound 1, a weak benzylimidazole antagonist found in the patent literature,[7] on a peptide pharmacophore model of AII helped in the development of potent nonpeptide analogs. The success of this endeavor attests to the significance of peptide pharmacophore modeling in peptidomimetic drug design.

Overlay Hypothesis

Pharmacological evaluation of benzylimidazole 1, a compound described as an AII antagonist in the patent literature,[7] showed it to be a specific, competitive AII receptor antagonist which displayed modest levels of activity both in vitro and in vivo (Table I). Our strategy to improve upon this activity hypothesized that elements of the benzylimidazole antagonist mimicked portions of the octapeptide AII at the receptor. Therefore, modification of 1 to more closely resemble AII could lead to more potent analogs. In this theory, the small molecule could either mimic octapeptide agonists such as AII, but lack the necessary size or critical structural features to elicit agonist activity, or overlay structurally related octapeptide receptor antagonists such as saralasin. We felt that an intimate knowledge of the SAR of peptide AII analogs together with an analysis of the structure of the nonpeptide lead could be used to generate a pharmacophore model of AII. Molecular modeling of 1 on the peptide pharmacophore model may suggest structural modifications to the small molecule which could lead to enhanced potency. Thus, consideration of both peptide and nonpeptide SAR could be instrumental in the design of high affinity nonpeptide AII receptor antagonists.



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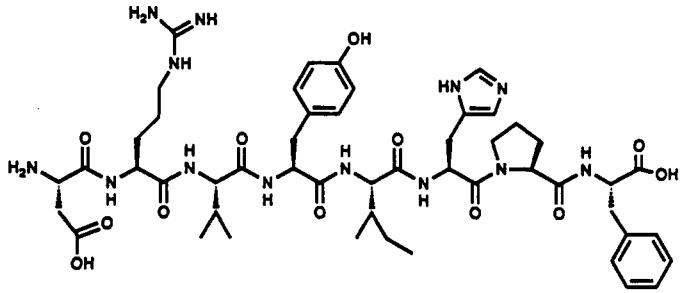
As an initial exercise, structural features of the small molecule and the peptide were examined for regions of potential overlay. For example, the core imidazole ring in 1 could be positioned over the imidazole ring found at His[6] in AII, an approach utilized by the DuPont group.[4a] Similarly, the carboxylic acid of 1 could align with either Asp[1] or the C-terminal carboxylate of AII. Finally, the *N*-benzyl ring of 1 could in theory mimic any of three aromatic rings in AII: Tyr[4], His[6], or Phe[8]. The lipophilic butyl side chain of 1 may similarly overlay any of three hydrophobic residues in AII: Val[3], Ile[5], or Pro[7]. Thus, the benzylimidazole 1 and the octapeptide AII shared a number of common structural elements, which suggested a myriad of possible overlay hypotheses.



angiotensin II

Careful examination of existing AII peptide SAR[8] helped refine our overlay hypothesis. At the six position in AII, there was a marked preference for side chains with unsubstituted five-membered heterocyclic rings, thus discounting an overlay of either the tetrasubstituted imidazole ring or *N*-benzyl of 1 at this position. The imidazole ring in the small molecule could instead be serving as a template which holds the critical binding elements in the proper orientation.[9] In addition, the retention of activity observed with residue 2–8 heptapeptides (i.e., AIII) and Sar[1]-substituted analogs of AII,[8] both of which lack the N-terminal Asp residue, favored the C-terminal carboxylate as the more likely region of potential overlay for the carboxylic acid of 1. In fact, the C-terminal region of AII has been identified as crucial for both receptor recognition and activation.[8,10] For example, the single replacement of L-Phe at position eight with D-Phe or aliphatic amino acids converted potent agonists to potent antagonists. Also, esterification or reduction of this acid in AII caused a loss of activity,[11] as was observed in the imidazoleacetic acid series.[7] Although we considered a number of possible overlay hypotheses,[6] including the alignment of the phenyl ring and carboxylic acid of 1 with the corresponding elements of Phe,[8] we were intrigued by

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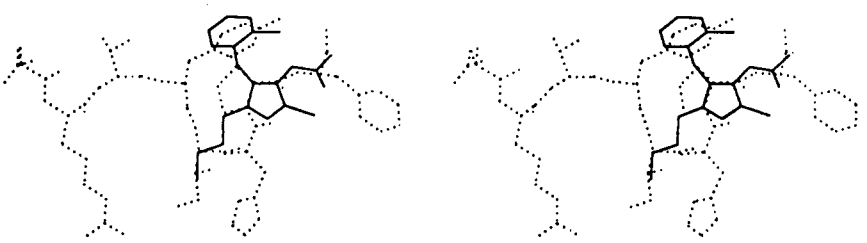


Figure 1. Stereoplot of an overlay of 1 (solid) on a postulated pharmacophore model of angiotensin II (dotted).

the possibility that the phenyl group of 1 may instead mimic the Tyr[4] aromatic region while the carboxyl of 1 maintains an overlap with the terminal carboxylate of AII. In the octapeptide series, aromatic analogs which lack the hydrophilic phenol of tyrosine at position four have lost agonist activity, but are potent AII antagonists. Thus, the overlay of the phenyl ring and carboxylic acid of 1 with positions four and eight of AII, which have been identified as important regions for receptor binding as well as key determinants of agonist versus antagonist activity for the octapeptides, became the focus of our molecular modeling efforts.

The existing models for the conformation of AII[12] could not adequately support the hypothesis that the *N*-benzyl of 1 could overlay the Tyr[4] aromatic region while the carboxyl maintains its alignment with the C-terminus of AII. From SAR studies on numerous peptide analogs containing conformationally constrained amino acids,[13] a set of allowed ϕ/ψ angles for each residue in AII had been determined. Starting from a literature model,[14] it was possible to place AII in a conformation, consistent with the acceptable ϕ/ψ angles, which positioned Tyr[4] and the C-terminal carboxylate of AII in close proximity to better accommodate the proposed overlay with the phenyl ring and carboxylic acid of 1, as shown in Figure 1.[6] In addition, the butyl side chain on the imidazole ring in 1 extended into the lipophilic region near Ile[5] of AII. This model of AII, which originated from consideration of both peptide and small molecule SAR, has served as a valuable template guiding the design of a series of potent small molecule receptor antagonists.[15]

According to this theory, the small molecule covered the Tyr[4] aromatic ring, Ile[5] side chain, and the Phe[8] carboxylate of AII but failed to reach other important binding regions of the octapeptide, such as the Arg[2] and His[6] side chains and Phe[8] aromatic ring. We felt that overlay of at least one more key binding region would be necessary for improving the affinity of a small molecule antagonist. In the present overlay, the region around Phe[8] appeared most accessible, and structural modifications to 1 were suggested which would increase its resemblance to the Phe[8] region and possibly enhance potency. First, the chain connecting the acid to the imidazole ring of 1 could be lengthened to better approximate the separation between the aromatic ring of Tyr[4] and the C-terminal carboxylate. In addition, attaching a substituent to the acid side chain of 1 to interact with the binding pocket for the octapeptide's C-terminal side chain could lead to more potent analogs. For example, another aryl group would mimic either an agonist ([L-Phe[8]]-AII) or antagonist ([D-Phe[8]]-AII) at position eight. Alternatively, a new aliphatic substituent would more closely resemble potent octapeptide antagonists such as saralasin or [Sar[1],Ile[8]]-AII. This paper describes our research on modifying the acetic acid side chain of 1 to better fit the proposed pharmacophore model and the evolution of substituted imidazole-5-acrylic acids as a new class of potent small molecule AII receptor antagonists.

Biological Assays

The compounds which were synthesized as part of our research on nonpeptide angiotensin II receptor antagonists were evaluated for activity using two different in vitro screens: competitive binding vs radiolabeled AII in a rat mesenteric artery receptor preparation (this tissue has since been shown to consist largely of the AT-1 receptor subtype[5b]); and inhibition of AII-induced vasoconstriction in isolated rabbit aorta strips. The competitive binding assay measured the intrinsic affinity of a particular compound for the AII receptor while the rabbit aorta assay verified the results obtained in the receptor binding screen as well as tested the compound's ability to counteract the effects of AII in a physiologically relevant system. As we were interested in both a compound's intrinsic affinity and its ability to functionally antagonize AII, both assays were monitored for improvement in potency in the SAR study. Although the relative order of activity for the two in vitro screens did not always agree, the most potent compounds exhibited good activity in both assays. Currently, we do not have a good explanation for the discrepancy between the two assays, although a number of factors, such as different receptor subtype populations, variations in tissue distribution, or species difference may account for some of the observed lack of correlation. Finally, the more potent compounds were also examined in the conscious normotensive rat for inhibition of the in vivo pressor effect of AII.

Results and Discussion

Extended Acid Side Chains. At the time we initiated our research, little data was available concerning different carboxylic acid chain lengths in the small molecule imidazole series.[7] Therefore, as a preliminary investigation of our overlay hypothesis, we examined longer tethers connecting the imidazole ring and the carboxylic acid, varying the rigidity of the chain in addition to its length. Also, the chlorine atom found at C-4 in 1 was replaced with hydrogen, since preliminary experiments had shown

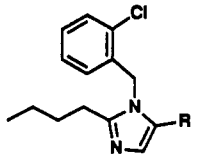
(12) See reference 4a for a comprehensive bibliography of proposed models of AII.

(13) Samanen, J.; Cash, T.; Narindray, D.; Brandeis, E.; Adams, W.; Weideman, H.; Yellin, T.; Regoli, D. An Investigation of Angiotensin II Agonist and Antagonist Analogues with 5,5-Dimethylthiazolidine-4-carboxylic Acid and Other Constrained Amino Acids. *J. Med. Chem.* **1991**, *34*, 3036–3043.

(14) Premilat, S.; Maigret, B. Statistical Molecular Models for Angiotensin II and Enkephalin Related to NMR Coupling Constants. *J. Phys. Chem.* **1980**, *84*, 293–99.

(15) As potency has increased in the small molecules, the original model of AII has necessarily undergone some minor revisions. Nevertheless, the original premise involving the concomitant overlay of both the Tyr[4] and Phe[8] regions of AII by the small molecule imidazole antagonists has remained intact.

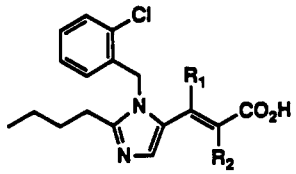
Table I. Acid Side Chain Study



no.	R	IC_{50} (μM)[a]	K_b (μM)[b]	in vivo ID_{50} iv (mg/kg)[c]	mp (°C)[d]
1[e]	CH_2CO_2H	43	2.7	30	167–169[f]
2	CH_2CO_2H	12	1.8	22.5	158–161[f]
3	$(CH_2)_2CO_2H$	16.5	2.8	NT	163–164[g]
4	(*Z*)-(CH=CH)CO_2H	124	14	NT	183–184
5	(*E*)-(CH=CH)CO_2H	8.9	0.81	15	178–179
6	$(CH_2)_3CO_2H$	>10	15	NT	119–121[g]
7	$(CH_2)_4CO_2H$	17	11	NT	190–191[g]
8	(*E,E*)-$(CH{=}CH)_2CO_2H$	22	2.5	NT	219–220
9	$(CH_2)_5CO_2H$	19	7.0	NT	144–145[g]
10	*p*-$C_6H_4CO_2H$	23.5	3.5	NT	238 d[g]
11	*m*-$C_6H_4CO_2H$	33.9	4.8	NT	165–168[g]
12	*o*-$C_6H_4CO_2H$	>100	17.2	NT	224–226[g]

[a] Inhibition of [^{125}I]AII specific binding to rat mesenteric arteries, n = 3–5, as described in the Experimental Section. [b] Inhibition of AII-induced vasoconstriction of the rabbit aorta, n = 3–5, as described in the Experimental Section. [c] Dose that produced 50% inhibition of the pressor response to AII in conscious normotensive rats, n = 3–4, as described in the Experimental Section. An NT means the compound was not tested in this assay. [d] A d denotes decomposition. [e] Imidazole ring substituted with a 4-Cl. [f] Reference 5a. [g] HCl salt.

Table II. Substituted *trans*-Acrylic Acids

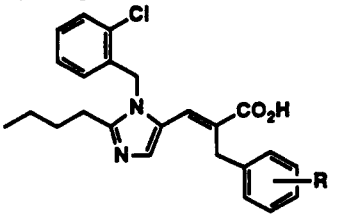


no.	R_1	R_2	IC_{50} (μM)[a]	K_b (μM)[b]	method[c]	mp (°C)[d]
5	H	H	8.9	0.81	A	178–179
13	H	Me	22.3	0.97	A	228–229
14	H	*n*Bu	6.9	0.16	A	179–181
15	H	Ph	20.1	0.60	B	210–212
16	H	β-naphth	127	>100	B	271–273[d]
17	H	CH_2Ph	2.6	0.064	A	177–178
17c[e]	H	CH_2Ph	38	8.7	A	95–97[f]
18	H	CH_2CH_2Ph	2.9	0.42	A	189–190
19	H	CH_2(β-naphth)	21.9	14.6	A	164–165
20	Me	H	3.6	0.66	A	198–199[g]
21	*n*Bu	H	12.0	0.73	D	131–132
22	CH_2Ph	H	9.8	0.33	D	92–94 d[g]
23	Me	CH_2Ph	28.4	0.76	D	206–207[g]
24	H	CH(Me)Ph	4.6	0.24	A	180–186

[a] Inhibition of [^{125}I]AII specific binding to rat mesenteric arteries, n = 3–5, as described in the Experimental Section. [b] Inhibition of AII-induced vasoconstriction of the rabbit aorta, n = 3–5, as described in the Experimental Section. [c] Method refers to general route to unsaturated esters. The esters were converted to the acrylic acid analogs via standard basic hydrolysis unless otherwise noted. See the Experimental Section for specific details. [d] A d denotes decomposition. [e] (*Z*)-isomer. [f] Sodium salt. [g] HCl salt.

that this chloro group was not essential for activity.[5a] The other substituents on the imidazole ring were held constant to determine the effects of alterations only in the C-5 acid side chain. The data presented in Table I indicate that although extended acid side chains of varying length could be accommodated by the receptor, the best activity was observed with the (*E*)-olefin compound **5**. This extended analog was more active than the (*Z*)-acrylic acid **4** or the saturated derivative **3** of the same length. In the aryl

Table III. Phenyl Ring Substitution



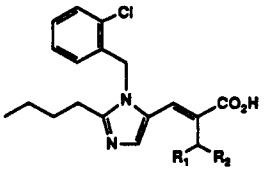
no.	R	IC_{50} (μM)[a]	K_b (μM)[b]	in vivo ID_{50} iv (mg/kg)[c]	method[d]	mp (°C)[e]
17	H	2.6	0.06	14	A	177–178
25	4-OMe	0.81	0.12	9.0	A	158–159
26	3-OMe	0.81	0.27	10.0	A	173–174
27	3,4-(OCH_2O)	0.47	0.13	9.4	C	160–165
28	3,4-$(OMe)_2$	6.8	0.62	NT	C	162–165[f]
29	3,4,5-$(OMe)_3$	1.9	1.7	NT	C	165–167
30	3-OPh	10	18.1	NT	A	164–165
31	4-OH	0.12	0.47	NT	C	255 d
32	3,4-$(OH)_2$	0.058	0.14	20[g]	*h*	>260 d
33	4-NH_2	3.0	0.32	NT	*i*	191–192
34	4-$N(Me)_2$	14.6	0.59	NT	C	171–172
35	2-Me	5.0	1.14	NT	A	190–191
36	3,4-Cl_2	25.6	13.7	NT	A	177–718
37	4-NO_2	0.40	0.31	NT	C[j]	207–208[f]

[a] Inhibition of [^{125}I]AII specific binding to rat mesenteric arteries, n = 3–5, as described in the Experimental Section. [b] Inhibition of AII-induced vasoconstriction of the rabbit aorta, n = 3–5, as described in the Experimental Section. [c] Dose that produced 50% inhibition of the pressor response to AII in conscious normotensive rats, n = 3–4, as described in the Experimental Section. An NT means the compound was not tested in this assay. [d] Method refers to general route to unsaturated esters. The esters were converted to the acrylic acid analogs via standard basic hydrolysis unless otherwise noted. See the Experimental Section for specific details. [e] A d denotes decomposition. [f] HCl salt. [g] Dosed intraduodenally. [h] Prepared by acid hydrolysis of methylenedioxy group of compound **26**. [i] Prepared by $Na_2S_2O_3$ reduction of nitro group of the methyl ester of compound **36**, followed by standard base hydrolysis. [j] Ester intermediate hydrolyzed with 6 N HCl.

series, the para and meta isomers **11** and **12** displayed more potency than the ortho analog **13**. Taken together, these results suggest that the carboxylate prefers to extend away from the imidazole core of the molecule when interacting with the receptor, as suggested by the molecular modeling. The rigid (*E*)-acrylic acid **5**, which lengthened the acid side chain in a conformationally restricted manner while maintaining potency, represented a promising lead for further exploration. Further investigation of substituted (*E*)-acrylic acids is the focus of the remainder of this report.

Substituted Acrylic Acids. The retention of activity observed upon extending the acetic acid side chain encouraged us to investigate the second aspect of the overlay hypothesis: attachment of a substituent to the (*E*)-acrylic acid **5** to interact with the binding pocket for the C-terminal side chain. The results are presented in Table II. Gratifyingly, addition of an arylmethyl appendage α to the carboxylic acid to mimic Phe[8] led to a notable increase in potency, as predicted by the overlay hypothesis. The benzyl analog **17** containing a one-carbon tether displayed better overall activity than the phenyl (**15**)- or phenethyl (**18**)-substituted compounds, most notably in the rabbit aorta assay. As in the unsubstituted series, the (*E*)-acrylic acid **17** was more active than its (*Z*)-isomer **17c**. Compounds containing simple alkyl groups such as methyl (**13**) or butyl (**14**) at this position were less potent, and the naphthyl analogs **16** and **19** displayed diminished activity. Conversely, at the position

Table IV. Heteroaryl Analogs



no.	R_1	R_2	IC_{50} (μM)[a]	K_b (μM)[b]	in vivo ID_{50} iv (mg/kg)[c]	method[d]	mp (°C)[e]
38	H	2-furyl	1.2	0.05	NT	A	180–182
38c[f]	H	2-furyl	>100	14.4	NT	A	134–136
39	H	3-furyl	0.36	0.03	NT	A	168–169
40	H	2-thienyl	0.44	0.05	3.6	C	177–179
41	H	3-thienyl	0.33	0.17	6.4	C	192–193
42	H	2-(5-Me)thienyl	0.70	0.13	7.6	C	169–170
43	H	2-(3-Me)thienyl	0.73	0.28	NT	C	174–175
44	H	2-(5-OMe)thienyl	0.09	0.03	NT	C	184–185
45	H	2-(4-OMe)thienyl	0.30	0.03	NT	C	170–711
46	H	CH_2-2-thienyl	0.86	0.14	NT	C	184–185
47	benzyl	2-thienyl	5.2	0.61	NT	C	200–202
48	phenyl	2-thienyl	2.4	2.3	NT	C	204–206
49	butyl	2-thienyl	18.7	3.1	NT	C	161–163
50	H	2-pyridyl	0.82	2.9	NT	C	156–160 d
51	H	3-pyridyl	0.30	0.18	9.8	C	161–164 d
52	H	4-pyridyl	0.15	0.17	5.9	C	178–182 d
53	H	4(5)-imidazoyl	0.25	0.31	11.0	C[g]	230–231[h]

[a] Inhibition of [^{125}I]AII specific binding to rat mesenteric arteries, n = 3–5, as described in the Experimental Section. [b] Inhibition of AII-induced vasoconstriction of the rabbit aorta, n = 3–5, as described in the Experimental Section. [c] Dose that produced 50% inhibition of the pressor response to AII in conscious normotensive rats, n = 3–4, as described in the Experimental Section. An NT means the compound was not tested in this assay. [d] Method refers to general route to unsaturated esters. The esters were converted to the acrylic acid analogs via standard basic hydrolysis unless otherwise noted. See the Experimental Section for specific details. [e] A d denotes decomposition. [f] Z isomer. [g] During synthesis, imidazole nitrogen was protected with trityl group which was removed during acid hydrolysis of methyl ester intermediate. [h] Dihydrochloride salt.

β to the carboxylic acid, the methyl-substituted analog **20** exhibited comparable activity to the benzyl compound **22**. However, the combination of α-benzyl with β-methyl (**23**) led to decreased affinity for the receptor. In addition, substitution at the benzylic carbon (**24**) led to no further increases in potency.

Aryl Ring Modifications. The overlay hypothesis had correctly predicted that attachment of an aryl ring would increase potency. Further synthesis of a variety of aryl analogs led to the discovery of even more potent AII receptor antagonists. A number of substituents on the newly introduced phenyl ring were examined in the α-benzyl acrylic acid series (Table III). Two general trends were observed. First, addition of electron-rich groups such as hydroxy or methoxy, especially at the para position (**25**, **31**), led to enhanced affinity. Second, increased bulkiness caused a dropoff in activity. For example, the 3,4-methylenedioxy derivative **27** was more potent than the more sterically demanding 3,4-dimethoxy compound **28**. Similarly, the free amine or phenolic compounds displayed more potency than their larger methylated counterparts (cf. **33** vs **34**, **31** vs **25**, or **32** vs **28**).

The general preference for electron-rich groups as well as the intolerance for increased bulk was also observed in a series of acrylic acid antagonists with heterocyclic rings at this position. In addition to having submicromolar affinity for the receptor, the heterocyclic compounds exhibited increased potency in the in vivo rat model (Table IV). As potency increased, the difference in activity between the (*Z*)- and (*E*)-acrylic acid analogs became more pronounced (cf. **38** vs **38c**). In the pyridyl series, a stepwise increase in activity was observed going from the 2- to 3- to 4-substituted analogs (**50–52**). Also, addition of a methoxy group to the thiophene ring (**44**) led to increased affinity, as in the phenyl ring study. One-carbon homologation of the connecting chain to furnish the thienylethyl analog **46** did not improve activity. The branched analogs **47–49**, which were examined to investigate whether the SAR was revealing two distinct binding pockets in the receptor, one of which selected for heteroaryl analogs, and the other for aromatic or aliphatic groups, also had lower affinity.

The 2-thienylmethyl acrylic acid analog **40** provided the best overall combination of high receptor affinity and enhanced in vivo potency. Compound **40** inhibited binding of AII in several tissues containing largely the AT-1 receptor, including rat aorta smooth muscle cells (IC_{50} = 0.21 μM) and rat kidney tubule (IC_{50} = 0.23 μM). This compound showed no affinity (IC_{50} > 10 μM) for the AT-2 receptor found in bovine ovary. As AT-1 receptor-specific compounds, the imidazole-5-acrylic acids are similar to the biphenylimidazole[4a,b] class of nonpeptide AII antagonists, but different than the spinacine[4d] series which appear to be specific for the AT-2 receptor. Unlike their peptide counterparts,[3] the imidazole-5-acrylic acid AII receptor antagonists have shown no evidence of agonist activity. Also, **40** had no effect on ACE activity or on vasoconstriction induced by norepinephrine, KCl, or endothelin-1, suggesting that the observed pharmacological effects are due solely to AII receptor antagonism. In contrast to other nonpeptide AII antagonists,[4c] **40** exhibited purely competitive AII antagonism, producing parallel shifts in the dose–response curves in the rabbit aorta assay with no attenuation of the maximum response. In the normotensive rat, **40** inhibited the pressor response to AII when administered both iv (ID_{50} = 3.6 mg/kg) and id (ID_{50} = 4.8 mg/kg). In addition, **40** exhibited dose-dependent reduction of blood pressure in the renin-dependent hypertensive rat model (Figure 2). Thus, the 2-thienylmethyl-substituted imidazoleacrylic acid **40** has been

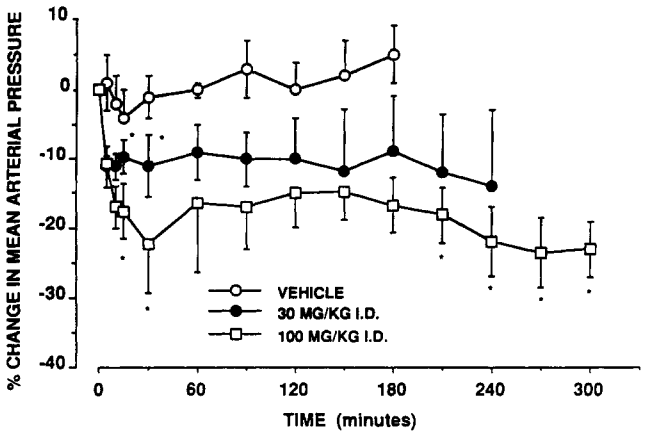


Figure 2. Effect of **40** at 30 mg/kg (n = 4) and 100 mg/kg (n = 3) dosed intraduodenally (id) on mean arterial pressure (MAP) of renin-dependent hypertensive rats (* denotes significant ($p \leq 0.05$) change in blood pressure).

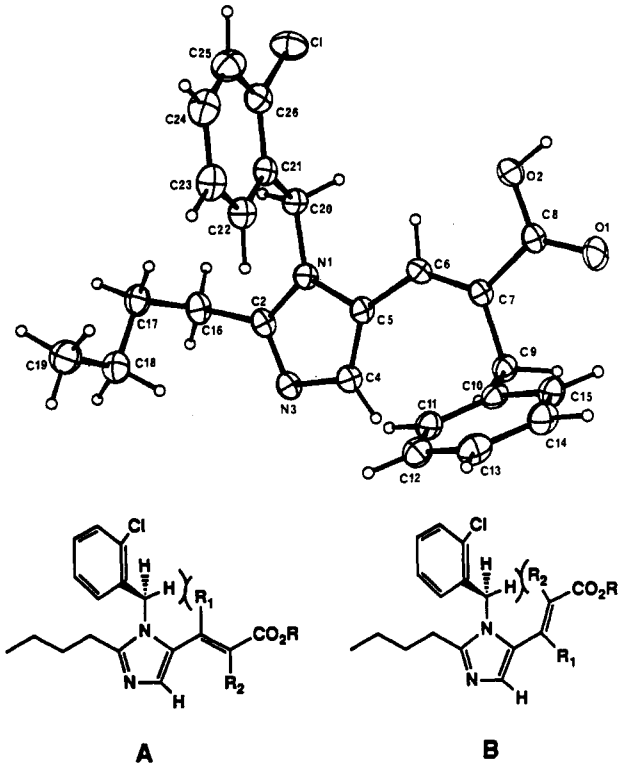
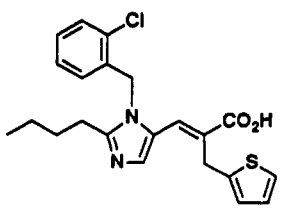


Figure 3. ORTEP drawing of X-ray structure of **17** and comparison of different conformers of substituted acrylic acids.

shown to be a potent, competitive, and orally active small molecule AII-1 receptor antagonist.



40

Molecular Modeling. An X-ray structure of **17** (Figure 3) showed the acid coplanar with the imidazole and the acrylic acid side chain in a conformer (Figure 3, A) in which the benzyl group (R_2) lay closer to the C-4 hydrogen on the imidazole, presumably to avoid steric interaction with the benzylic hydrogens at N-1, as in the 180° opposite rotamer B, Figure 2. Interestingly, NOE studies and energy minimization calculations on compounds **20**, **21**, and **22** showed that a single substituent R_1 on the β position led to a predominance of rotamer B in which R_1 avoided the negative interaction with the benzylic hydrogens at N-1 found in rotamer A. The increase in activity of **20** (R_1 = Me, R_2 = H) as compared to **5** suggests that rotamer B may represent an important binding conformation for the acrylic acid in the absence of an α substituent. However, the general increase in potency observed for compounds containing arylmethyl R_2 substituents suggests that rotamer A may be the preferred conformation of the small molecule for optimal binding of both of the aromatic rings and the acid group. The decreased activity exhibited by **23** (R_1 = Me, R_2 = CH_2Ph) may be due to a destabilization of the more favorable arrangement of binding groups presented by rotamer A.

The overlay of the α-thienylmethyl acrylic acid analog **40** on the proposed pharmacophore model of AII is depicted in Figure 4. The appended thiophene ring and acrylic acid of the imidazole antagonist align with the phenyl ring and carboxylate of the C-terminal phenylalanine of AII. The butyl chain attached at C-2 of the imidazole and the 2-chlorophenyl group in **40** maintain their respective overlays with the hydrophobic region near Ile^5 and the Tyr^4 aromatic ring in AII. Interestingly, in their preferred conformation (rotamer A, Figure 3), the aryl-substituted acrylic acids cannot mimic the agonist conformation at the C-terminus of AII proposed by Marshall,[16] where the position eight phenylalanine aromatic ring lies over the plane of the Pro^7-Phe^8 amide bond. To accommodate the rigid thienylmethyl-substituted acrylic acid **40**, the phenylalanine aromatic ring is instead swung away from the adjacent Pro^7-Phe^8 peptide bond as shown. This may represent an antagonist conformation reminiscent of AII peptide antagonists containing a D-aryl amino acid at position eight. The weaker affinity of the simple alkyl-substituted acrylic acid analogs as compared to the benzyl-substituted compounds argues against a proposed overlay on AII peptide antagonists containing alkyl amino acid residues at position eight.[6]

Chemistry

The imidazole-5-carboxaldehyde **56**, a key intermediate in the synthesis of a large number of analogs, was conveniently prepared on a large scale via the sequence in Scheme I. Treatment of the diacetate **54**, obtained from acetylation of 2-butyl-4(5)-(hydroxymethyl)imidazole,[17] with 2-chlorobenzyl triflate at low temperature[18] and then aqueous base afforded the (hydroxymethyl)imidazole **55**, which was oxidized to the desired aldehyde.

Acid Side Chain Study. In our study of the acid side chain at C-5 of the imidazole, a variety of extended acid side chains was synthesized. The imidazole carboxylic acids containing an aryl linker were synthesized via a

(16) Marshall, G. R. Determination of the Receptor Bound Conformation of Angiotensin. *Dtsch. Apoth. Ztg.* **1986**, *85*, 2783–85.

(17) Dziuron, P.; Shunack, W. Imidazol-4-carbinole aus Iminoestern und Dihydroxyaceton. *Arch. Pharm. (Weinheim, Ger)* **1974**, *307*, 470.

(18) (a) Kamijo, T.; Yamamoto, R.; Harada, H.; Iizuka, K. An Improved Procedure for the Synthesis of 1-Substituted Imidazoles. *Chem. Pharm. Bull.* **1983**, *31*, 1213–1221. (b) Hodges, J. C. Regiospecific Synthesis of 3-Substituted Histidines. *Synthesis* **1987**, 20–24.

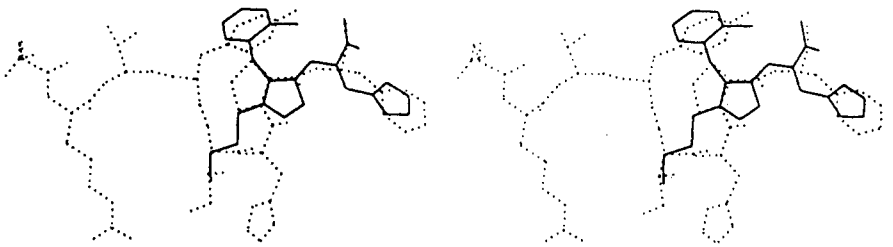
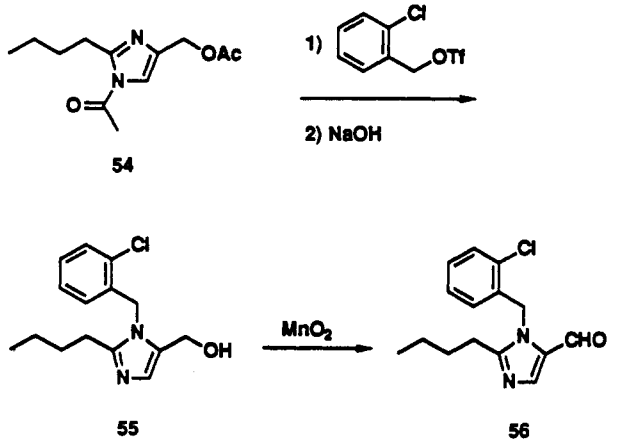
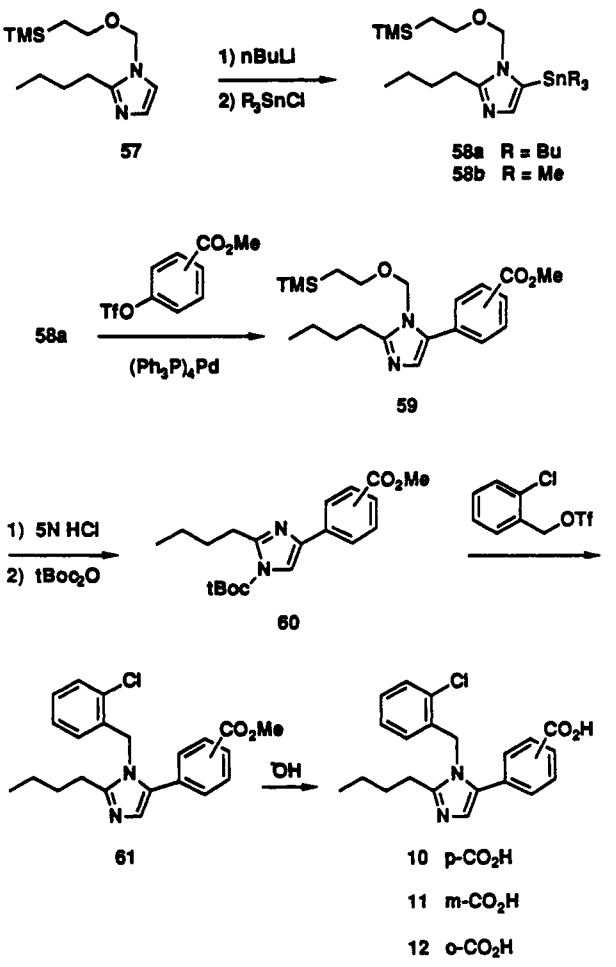


Figure 4. Stereoplot of an overlay of 40 (solid) on a postulated pharmacophore model of angiotensin II (dotted)

Scheme I. Synthesis of Imidazole-5-carboxyaldehyde



Scheme II. Synthesis of Imidazole Benzoic Acids



palladium-catalyzed coupling of the SEM-protected 5-stannyl imidazole **58a**[19] and aromatic triflates (Scheme II). The SEM protecting group was exchanged for the desired benzyl substituent via a three-step sequence[18b] to afford the desired 1,2,5-trisubstituted imidazole **61**. A series of three-carbon chain acid derivatives was prepared as in Scheme III. To synthesize the (*Z*)-acrylic acid **4**, a related palladium-catalyzed coupling route was employed (Scheme IIIc). Reaction of stannylimidazole **58b** with a mixture of (*Z*)- and (*E*)-methyl-3-bromopropenoate[20] in the presence of catalytic $(Ph_3P)_4Pd$ furnished both acrylate isomers. The product mixture contained largely the (*Z*)-acrylate **63** along with a lesser amount of the (*E*)-isomer, reflecting the predominance of the (*Z*)-isomer in the starting vinyl bromide. Replacement of the SEM with 2-chlorobenzyl was accomplished as described in Scheme II. The syntheses of analogs with an acid chain containing four, five, or six carbon atoms are shown in Scheme IV. Palladium-catalyzed coupling of 5-bromoimidazole **64** and methyl 4-(tributylstannyl)-3-butenoate[21] gave the butenoate ester **66** and avoided the extra steps required by the use of the SEM protecting group. Phosphorus ylide chemistry on the aldehyde **56** furnished the five- and six-carbon side chain intermediates **67** and **68**. In each of these examples, olefin hydrogenation and/or ester hydrolysis as in Scheme IIIb provided the target chain-extended acids.

Substituted Acrylic Acids. Substituted acrylic acid analogs were synthesized by a variety of methods.[22]

Condensation reactions on the imidazole-5-carboxaldehyde **56** using substituted Horner–Emmons reagents (Scheme V) furnished a chromatographically separable mixture of (*E*)- and (*Z*)-acrylates, with the (*E*)-isomer **69** being the major product. Differences between the two isomers were apparent in their NMR spectra. In the (*E*)-products, the neighboring ester group caused the resonance of the olefinic proton to be shifted downfield as compared to the (*Z*)-ester isomers. Likewise, a similar downfield shift was evident in the signal for the allylic protons in the (*E*)-products, indicating an effect of the nearby imidazole ring. NOE measurements supported the structure assignments. The required substituted phosphonate reagents **71** were synthesized by alkylation of the parent trimethyl phosphonoacetate using sodium hydride in DME. In the case of the methyl ketone **72**, reaction with trimethyl phospho-

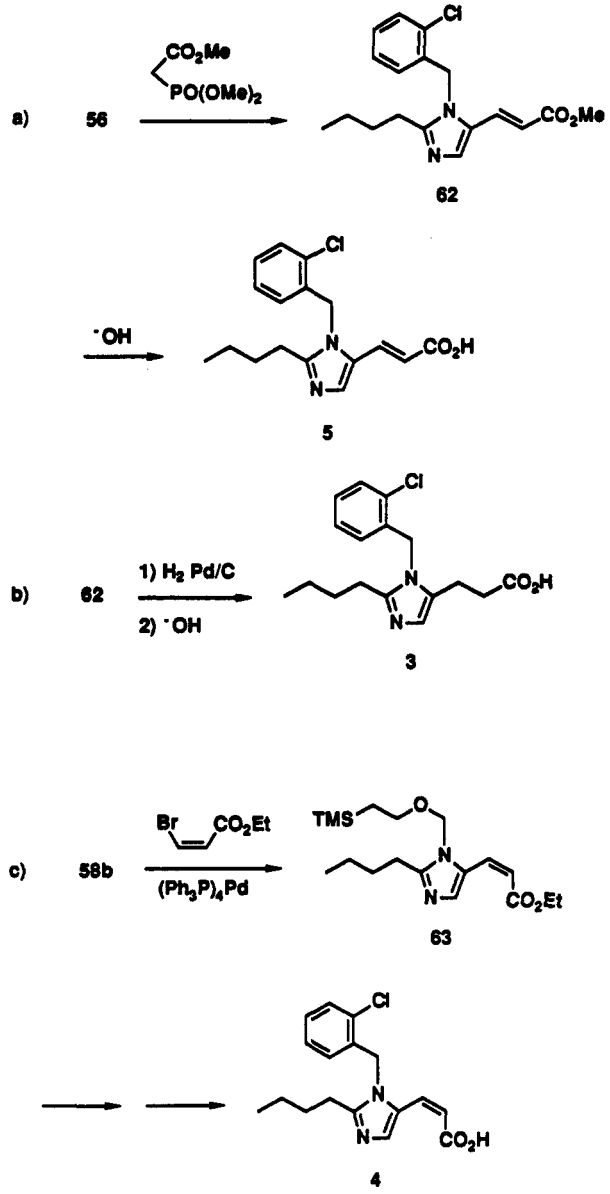
(19) The 5-stannyl derivative of 1,2-dimethyl imidazole had been reported: Iddon, B.; Lim, B. L. Reactions of 1,2-Dimethylimidazole, Particularly its Metallation. *J. Chem. Soc., Perkin Trans. 1* **1983**, 271.

(20) MacInnes, I.; Schorstein, D. E.; Suckling, C. J.; Wrigglesworth, R. Latent inhibitors. Part 2. Allylic Inhibitors of Alcohol Dehydrogenase. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1103–1108.

(21) Collins, P. W.; Kramer, S. W.; Gasiecki, A. F.; Weier, R. M.; Jones, P. H.; Gullikson, G. W.; Bianchi, R. G.; Bauer, R. F. Synthesis and Gastrointestinal Pharmacology of a 3*E*,5*Z* Diene Analogue of Misoprostol. *J. Med. Chem.* **1987**, *30*, 193–197.

(22) A preliminary account of this chemistry has been presented: Finkelstein, J. A.; Gaitanopoulos, D.; Keenan, R. M. Synthetic Routes to Imidazole-5-acrylic Acids: Potent Small Molecule Angiotensin II Receptor Antagonists: Abstracts of the 4th Chemical Congress of North America, New York, N.Y., August 25–30, 1991, ORGN 119.

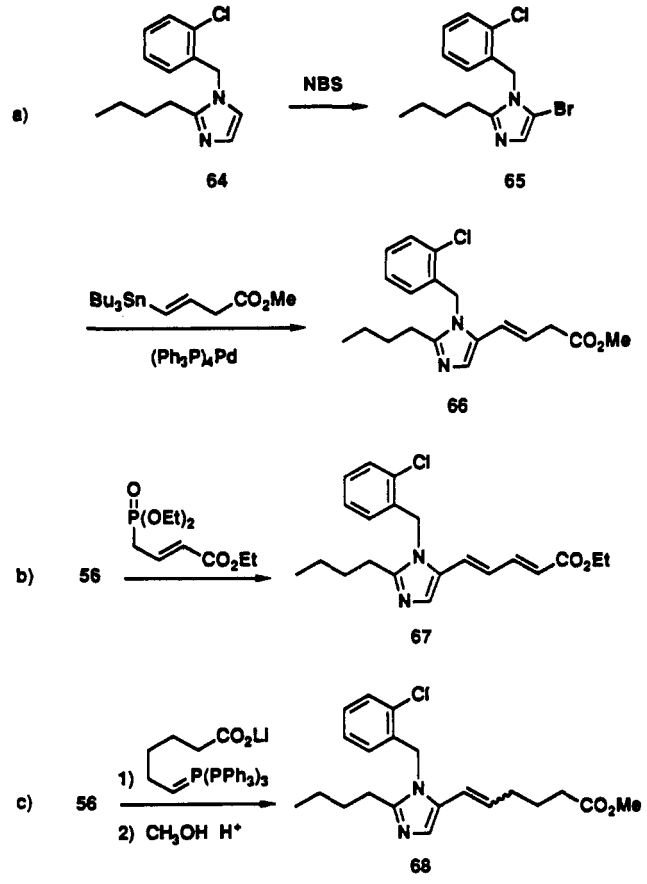
Scheme III. Synthesis of Three-Carbon Acid Side Chains



noacetate proceeded in low yield to furnish the β-methylacrylate. A related reaction provided acrylic acid analogs **15** and **16** in which the olefin was directly substituted with an aryl ring (Scheme VI).

An alternate route which introduced the (*E*)-olefin stereospecifically involved treating the aldehyde **56** with the lithium enolate of a methyl propionate at low temperature, affording an approximately 1:1 mixture of aldol diastereoisomers **73** (Scheme VII). Chromatography proved unnecessary as acetylation of the mixture followed by elimination with DBU afforded exclusively the (*E*)-acrylate **74** in high overall yield. Interestingly, if the DBU reaction were stopped before complete conversion to product, an analysis of the recovered starting material revealed an unchanged 1:1 ratio of acetate isomers. Although the reasons for this selectivity remain unclear, invoking a common intermediate resulting from loss of acetate would provide an avenue for either diastereomer to proceed to the same (*E*)-olefin. The 3-(2-thienyl)-propionate esters **76** containing additional substitution at the β position were synthesized by conjugate addition of an organocuprate to methyl 3-(2-thienyl)acrylate **75**.[23]

Scheme IV. Synthesis of Four-, Five-, and Six-Carbon Acid Side Chains

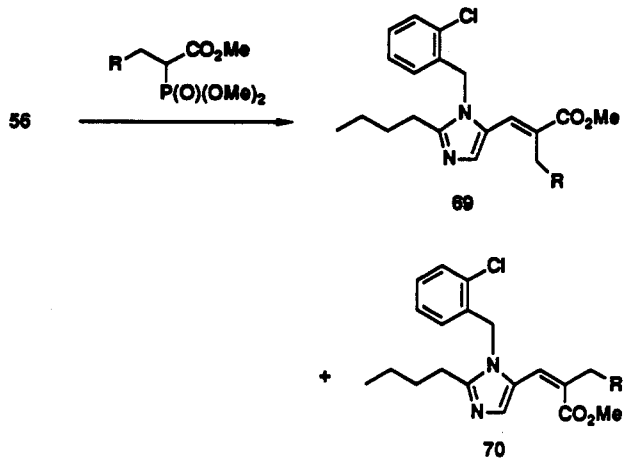


A route employing a palladium-catalyzed coupling reaction was utilized to synthesize β-substituted acrylic acid derivatives (Scheme VIII). (*E*)-Vinyl triflates **79** underwent palladium-catalyzed coupling with a SEM-protected imidazole organometallic to afford the imidazole acrylates **78**. Although the stannylimidazole derivative **58a** was used initially, a more convenient procedure employing the imidazole–zinc intermediate avoided the purification problems associated with the presence of organotin impurities in the reaction mixture. Whereas none of the (*Z*)-isomer was observed in the reaction with the β-butyl or β-benzyl triflates **79a** and **79b**, the coupling with the α-benzyl-β-methylvinyl triflate **79c** generated a 1:1 mixture of olefin isomers, indicating that additional bulk at the α position led to loss of stereochemical integrity at some point during the coupling procedure.[24] Exchange of SEM for benzyl as in Scheme II furnished the *N*-benzyl acrylate esters. The requisite (*E*)-vinyl triflates **79** could be synthesized with high selectivity from readily available β-keto esters by deprotonation with sodium hydride in DMF followed by treatment with *N*-phenyl triflimide.

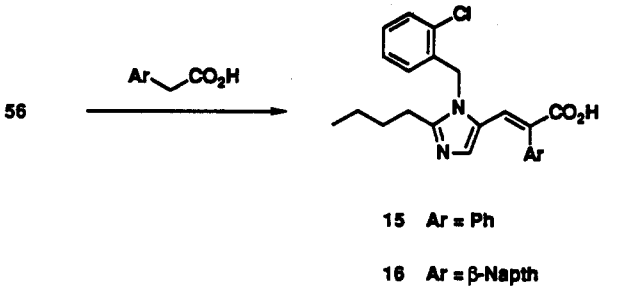
(23) For the phenyl- and butyl-substituted analogs **47** and **48**, higher order cuprate reagents were employed to make the requisite propionate ester. See the following: Lipshutz, B. H. Conjugate Addition Reactions of α,β-Unsaturated Esters with Higher Order Cuprates $R_2Cu(CN)Li_2$. *Tetrahedron Lett.* **1983**, *24*, 127–130. A mixed cuprate was used in the synthesis of the benzyl analog **46**. See the following: Behforouz, M.; Curran, T. T.; Bolan, J. L. Regiospecific Addition of Organocopper Reagents to α,β-Unsaturated Esters. *Tetrahedron Lett.* **1986**, *27*, 3107–110.

(24) An analogous palladium-catalyzed coupling of an organotin with a similar vinyl triflate has also been reported to yield a mixture of cis and trans olefinic products. See the following: Houpis, I. N. Palladium(II)-Catalyzed Coupling of 2-Carboxyethyl Enol Triflates with Organostannanes. *Tetrahedron Lett.* **1991**, *32*, 6675.

Scheme V. Method A



Scheme VI. Method B



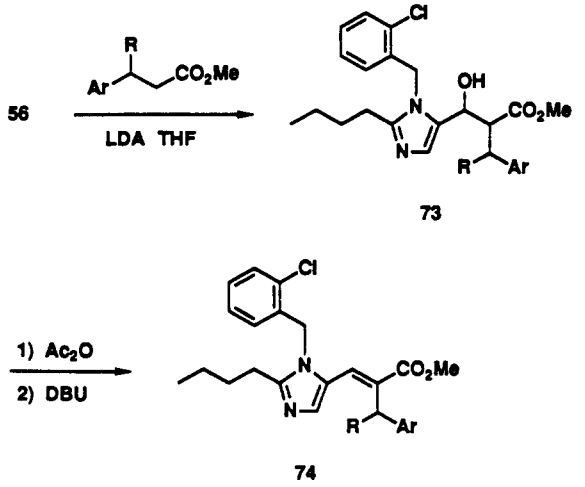
Interestingly, simply switching the reaction solvent to THF led to a predominance of the isomeric (*Z*)-vinyl triflate.[25]

Conclusion

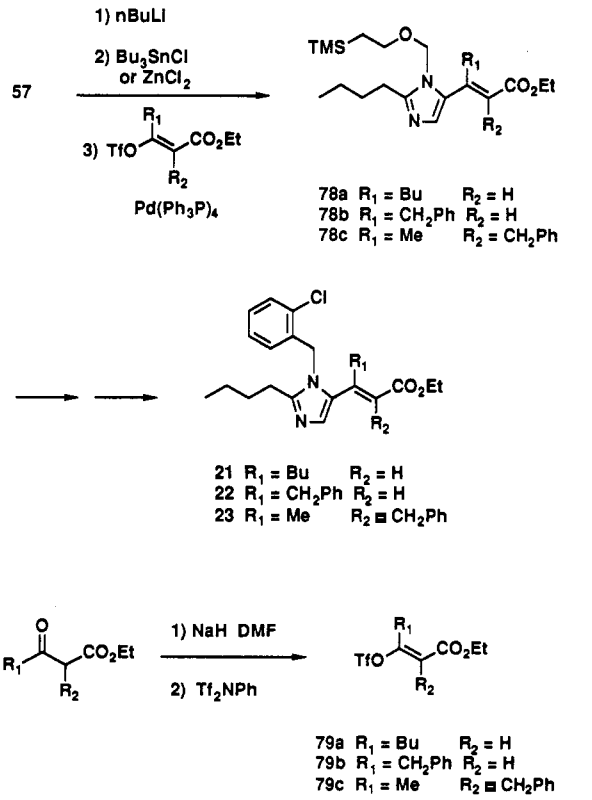
In summary, a series of potent and specific small molecule AII receptor antagonists containing a substituted acrylic acid attached to an imidazole nucleus has been discovered. Overlaying the small molecule 1 on a novel pharmacophore model of angiotensin II suggested that extension of the acid side chain and attachment of a second aryl residue to mimic the C-terminal phenylalanine region of AII would lead to increased activity. An extensive study

(25) A preliminary account of this chemistry has been presented: Morgan, T.; Keenan, R. M. Regio- and Stereoselective Synthesis of Vinyl Triflates from β-Ketoesters. *Abstracts of Papers*, 200th American Chemical Society National Meeting, Washington, D.C., August 26–31, 1990; American Chemical Society: Washington, DC, 1990; ORGN 61.

Scheme VII. Method C



Scheme VIII. Method D



of the SAR of the newly introduced aromatic ring revealed that electron-rich heteroaryl rings provided improved activity, most notably in the in vivo models. Compound **40**, an imidazole-5-acrylic acid containing a 2-thienylmethyl substituent on the acid side chain, has been shown to be a potent, competitive, and orally active small molecule AT-1 receptor antagonist. It exhibited a 2 orders of magnitude increase in binding affinity and a 10-fold improvement in in vivo potency as compared to compound **1**. Thus peptide pharmacophore modeling, which pointed to the acid side chain as a promising place to alter the original molecule, played a key role in the design of a novel class of nonpeptide antagonists. Finally, although not nearly as potent as other reported nonpeptide antagonists,[4] **40** represents an important milestone in the development of more potent compounds. The distinguishing structural feature of **40**, the thienylmethyl-substituted acrylic acid, is retained in extremely potent nonpeptide antagonists exemplified by SK&F 108566.[5] Future reports from these laboratories will detail the further evolution of the imidazole-5-acrylic acid class of nonpeptide angiotensin II antagonists which resulted in the discovery of SK&F 108566.

Experimental Section

General. Melting points were measured with a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H NMR spectra were obtained with a Bruker AM-250 spectrometer and are reported as ppm downfield from Me_4Si with multiplicity, number of protons, and coupling constant(s) in hertz indicated parenthetically. Elemental analyses were obtained using a Perkin-Elmer 240C elemental analyzer. Chromatography refers to flash chromatography using Kieselgel 60, 230–400 mesh silica gel.

1-Acetyl-4-(acetoxymethyl)-2-butylimidazole (54). 2-Butyl-4(5)-(hydroxymethyl)imidazole (253 g, 1.53 mol) was mixed with acetic anhydride (1 L, 10.6 mol) at −15 °C, and the reaction mixture was allowed to warm slowly to room temperature with stirring and then stirred an additional 19 h. The acetic anhydride was evaporated at reduced pressure. The residue was taken up in methylene chloride, washed with 5% $NaHCO_3$ and water, dried (Na_2SO_4), and concentrated to give 323 g (83%) of **54**: NMR ($CDCl_3$) 7.23 (s, 1 H), 5.00 (s, 2 H), 3.02 (t, 2 H, J = 7.9), 2.56 (s, 3 H), 2.10 (s, 3 H), 1.71 (quint, 2 H, J = 7.7), 1.42 (sext, 2 H, J = 7.4), 0.94 (t, 3 H, J = 7.3).

2-Butyl-1-[(2-chlorophenyl)methyl]-5-(hydroxymethyl)-imidazole (55). To a solution of triflic anhydride (120 mL, 0.71 mol) in methylene chloride (200 mL) at −78 °C was added a solution of diisopropylethylamine (128 mL, 0.73 mol) and 2-chlorobenzyl alcohol (104 g, 0.72 mol) in methylene chloride (350 mL) over 20 min. After stirring for an additional 20 min at −78 °C, a solution of **54** (146 g, 0.61 mol) in methylene chloride (300 mL) was added over 20 min. The cooling bath was removed, the reaction mixture was stirred at room temperature for 18 h, and the solvents were evaporated to yield crude 2-*n*-butyl-5-(acetoxymethyl)-1-[(2-chlorophenyl)methyl]imidazole. The residue was dissolved in MeOH (200 mL) and treated with 10% NaOH solution (0.7 L, 1.75 mol) and the mixture heated on a steam bath for 4 h. After cooling, the reaction mixture was extracted with methylene chloride (3×), and the combined organic phases were washed with water, dried (Na_2SO_4), and concentrated. A similar procedure was carried out on another 151 g (0.63 mol) of 1-acetyl-4-(acetoxymethyl)-2-*n*-butylimidazole. The two batches of crude material were combined for purification. The residue was dissolved in ether, cooled, and seeded to give the crude product as a light-brown solid. Repeated recrystallizations from EtOAc gave a total of 246 g (71%) of clean **55**: mp 138–140 °C; NMR ($CDCl_3$) 7.39 (dd, 1 H, J = 7.8, 1), 7.17 (m, 2 H), 6.89 (s, 1 H), 6.37 (d, 1 H, J = 7.5), 5.28 (s, 2 H), 4.46 (s, 2 H), 4.19 (m, 1 H), 2.47 (t, 2 H, J = 7.8), 1.59 (quint, 2 H, J = 7.8), 1.25 (sext, 2 H, J = 7.4), 0.82 (t, 3 H, J = 7.3).

2-Butyl-1-[(2-chlorophenyl)methyl]imidazole-5-carboxaldehyde (56). To the alcohol **55** (44.4 g, 159 mmol) in CH_2Cl_2 (550 mL) was added MnO_2 (133 g, 1.53 mol) followed by 200-mL CH_2Cl_2 rinses. The black heterogeneous solution was stirred for 19 h at room temperature, filtered through Celite, and concentrated to afford 40.9 g (93%) of the aldehyde **56**: NMR ($CDCl_3$) 9.67 (s, 1 H), 7.82 (s, 1 H), 7.40 (dd, 1 H, J = 7.8, 1), 7.16 (m, 2 H), 6.40 (d, 1 H, J = 7.3), 5.66 (s, 2 H), 2.58 (t, 2 H, J = 7.7), 1.66 (quint, 2 H, J = 7.8), 1.31 (sext, 2 H, J = 7.4), 0.86 (t, 3 H, J = 7.3).

2-Butyl-1-[[2-(trimethylsilyl)ethoxy]methyl]imidazole (57). A solution of 2-butylimidazole[26] (5.45 g, 43.9 mmol) in DMF (14 mL) was added to a slurry of sodium hydride (1.45 g, 48.3 mmol, 80% in oil) in DMF (65 mL) at room temperature. Stirring was continued for 1 h and SEM-Cl (8.41 mL, 46.1 mmol) was then added, and the reaction mixture was stirred for 19 h at room temperature. The reaction was poured into ice–water and extracted three times with ethyl acetate (100 mL), and the combined organic extracts were washed with water and brine and then dried with sodium sulfate and filtered. The solvent was removed, and the oil was purified by column chromatography (EtOAc/hexane) to give the product as an oil (10.8 g, 96%): NMR ($CDCl_3$) 6.94 (d, 1 H, J = 1.4), 6.89 (d, 1 H, J = 1.4), 5.20 (s, 2 H), 3.47 (t, 2 H, J = 8.0), 2.72 (t, 2 H, J = 7.7), 1.76 (quint, 2 H, J = 7.8), 1.44 (sext, 2 H, J = 7.5), 0.94 (t, 3 H, J = 7.3), 0.89 (t, 2 H, J = 8.2), −0.02 (s, 9 H).

2-Butyl-1-[[2-(trimethylsilyl)ethoxy]methyl]-5-(tributylstannyl)imidazole (58a). A solution of *n*BuLi in hexanes (2.5 M) was added to the imidazole (3.96 g, 15.6 mmol) in ether (100 mL) at room temperature. After 1 h, during which time the lithiated imidazole had precipitated, Bu_3SnCl (5.3 g, 16.3 mmol) was added via syringe. The precipitate cleared up immediately. The reaction was stirred for 18 h at room temperature and diluted with ether, and the ether layer was washed with saturated NH_4Cl and brine, dried (Na_2SO_4), and concentrated. Flash chromatography (ether/hexanes, 1:2) afforded the desired product (6.83 g, 81%): NMR ($CDCl_3$) 6.94 (s, 1 H), 5.18 (s, 2 H), 3.40 (t, 2 H, J = 8.4), 2.73 (t, 2 H, J = 7.8), 1.77 (quint, 2 H, J = 7.6), 1.61–0.86 (m, 34 H), 0.02 (s, 9 H).

2-Butyl-1-[[2-(trimethylsilyl)ethoxy]methyl]-5-(trimethylstannyl)imidazole (58b). A solution of *n*BuLi in hexanes (1.6 M) was added to the imidazole **58** (8.4 g, 33.0 mmol) in ether (210 mL) at room temperature. After 1 h, during which time the lithiated imidazole had precipitated, a solution of Me_3SnCl (7.0 g, 34.7 mmol) in ether (15 mL) was added via cannula. The precipitate cleared up immediately. The reaction was stirred for 20 h at room temperature and diluted with ether, and the ether layer was washed with saturated NH_4Cl and brine, dried (Na_2SO_4), and solvents evaporated under vacuum to yield 13.5 g (98%). The product, which was approximately 80% pure by NMR with the remainder being recovered starting material, was used without further purification: NMR ($CDCl_3$) 6.95 (s, 1 H), 5.22 (s, 2 H), 3.43 (t, 2 H, J = 8.4), 2.76 (t, 2 H, J = 7.8), 1.75 (quint, 2 H, J = 7.6), 1.44 (m, 2 H), 0.99–0.90 (m, 5 H), 0.33 (s, 9 H), −0.01 (s, 9 H).

Methyl 4-[2-Butyl-1-[[2-(trimethylsilyl)ethoxy]methyl]-imidazol-5-yl]benzoate (59). $Pd(Ph_3P)_4$ (74 mg, 0.064 mmol) was added to a solution of stannylimidazole **58a** (2.01 g, 3.7 mmol), methyl 4-[(trifluoromethyl)sulfonoxy]benzoate[27] (0.91 g, 3.2 mmol), and LiCl (0.40 g, 9.6 mmol) in dioxane (18 mL) at room temperature. A spatula tipful of a radical scavenger, 2,6-di-*tert*-butyl-4-methylphenol, was added and the reaction was heated to 100 °C for 3.5 h. The reaction was cooled to room temperature and treated with a 1:1 mixture of ether and 30% aqueous KF solution for 17 h. The mixture was suction-filtered through a pad of Celite with ether rinses and the filtrate washed with water and brine, dried ($MgSO_4$), and concentrated. Chromatography (EtOAc/hexanes) gave 0.86 g (60%) of **59**: NMR ($CDCl_3$) 8.10 (d, 2 H, J = 8.6), 7.56 (d, 2 H, J = 8.6), 7.11 (s, 1 H), 5.20 (s, 2

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H), 3.96 (s, 3 H), 3.48 (t, 2 H, J = 8.4), 2.82 (t, 2 H, J = 7.6), 1.86 (quint, 2 H, J = 7.7), 1.49 (sext, 2 H, J = 7.6), 1.00 (t, 3 H, J = 7.5), 0.91 (t, 2 H, J = 8.5), 0.01 (s, 9 H). The 2- and 4-isomers were prepared in similar fashion from methyl 2-iodobenzoate and methyl 3-[(trifluoromethyl)sulfonoxy]benzoate,[27] respectively.

Methyl [1-(*tert*-Butoxycarbonyl)-2-butylimidazol-4-yl]benzoate (60). HCl (5 N, 26 mL) was added to a solution of **59** (2.09 g, 5.30 mmol) in methanol (13 mL), and the reaction was heated for 3.5 h at 60–65 °C. The ethyl alcohol was removed by evaporation, and the reaction was carefully adjusted to slightly basic with 10% sodium hydroxide and extracted 3 times with ethyl acetate (50 mL). The ethyl acetate was washed with water and brine, dried (Na_2SO_4), filtered, and evaporated to an oil. The oil was dissolved in methanol (20 mL), triethylamine (1.65 g, 16.3 mmol) was added followed by *t*-Boc anhydride (3.4 g, 15.6 mmol), and the solution was stirred for 18 h at 25 °C. TLC analysis indicated that the reaction was incomplete; therefore the reaction mixture was concentrated, dissolved in methanol (20 mL), and treated again with triethylamine (1.65 g, 16.3 mmol) and *t*-Boc anhydride (3.4 g, 15.6 mmol) for 4 h. The solvent was evaporated at reduced pressure, and product was purified by chromatography (EtOAc/hexane) to give an oil (0.91 g, 65%): NMR ($CDCl_3$) 8.06 (d, 2 H, J = 8.6), 7.86 (d, 2 H, J = 8.6), 7.66 (s, 1 H), 3.94 (s, 3 H), 3.06 (t, 2 H, J = 7.6), 1.79 (quint, 2 H, J = 7.7), 1.65 (s, 9 H), 1.49 (sext, 2 H, J = 7.6), 0.97 (t, 3 H, J = 7.5). The 2- and 3-isomers were prepared in similar fashion.

Methyl 4-[2-Butyl-1-[(2-chlorophenyl)methyl]imidazol-5-yl]benzoate (61). To a stirred solution of triflic anhydride (0.50 mL, 2.80 mmol) in CH_2Cl_2 (20 mL) at −78 °C was added a solution of 2-chlorobenzyl alcohol (0.40 g, 2.80 mmol) and diisopropylethylamine (0.60 mL, 3.4 mmol) in CH_2Cl_2 (30 mL) over a period of 3 min. After stirring for 20 min at −78 °C, a solution of imidazole **60** (0.91 g, 2.3 mmol) in dichloromethane (8 mL) was added over 10 min and the reaction was allowed to warm to room temperature for 18 h. A solution of sodium bicarbonate (5%) was added, and the mixture was vigorously stirred for 20 min. The aqueous layer was washed twice with CH_2Cl_2; the combined organic layers were dried (Na_2SO_4), filtered, and concentrated to an oil. The oil was purified by column chromatography (EtOAc/hexane) to give the product as an oil (0.63 g, 71%): NMR ($CDCl_3$) 8.10 (d, 2 H, J = 8.5), 7.41 (d, 1 H, J = 7.6), 7.28 (d, 2 H, J = 8.5), 7.23 (s, 1 H), 7.22 (m, 2 H), 6.56 (d, 1 H, J = 7.4), 5.20 (s, 2 H), 3.90 (s, 3 H), 2.56 (t, 2 H, J = 7.8), 1.75 (quint, 2 H, J = 7.7), 1.38 (sext, 2 H, J = 7.6), 0.89 (t, 3 H, J = 7.3). The 2- and 3-isomers were prepared in similar fashion.

4-[2-Butyl-1-[(2-chlorophenyl)methyl]imidazol-5-yl]benzoic Acid (10). Basic hydrolysis of ester **61** following the procedure for compound **5** provided the benzoic acid analog **10**: NMR (CD_3OD) 8.03 (d, 2 H, J = 8.5), 7.71 (s, 1 H), 7.47 (d, 2 H, J = 8.5), 7.39 (dd, 1 H, J = 1.3, 7.6), 7.27 (m, 2 H), 6.82 (dd, 1 H, J = 1.4, 7.6), 5.52 (s, 2 H), 3.02 (t, 2 H, J = 7.8), 1.71 (quint, 2 H, J = 7.7), 1.41 (sext, 2 H, J = 7.6), 0.92 (t, 3 H, J = 7.3). Anal. ($C_{21}H_{21}ClN_2O_2 \cdot HCl \cdot {}^3/_4H_2O$) C, H, N. Similar procedures were employed to prepare the benzoic acid analogs **11** and **12**.

Methyl (*E*)-3-[2-Butyl-1-[(2-chlorophenyl)methyl]imidazol-5-yl]-2-propenoate (62). Trimethyl phosphonoacetate (Aldrich, 98%, 2.91 mL, 17.6 mmol) was added dropwise to a suspension of sodium hydride (0.432 g, 18.0 mmol) in dry DME (50 mL). After stirring for 30 min at 45 °C, aldehyde **56** (3.32 g, 12.0 mmol) was added rapidly and the mixture was stirred for 45 min at 50 °C. The reaction was poured into 100 mL of ice–water and extracted with ethyl acetate (2 × 100 mL). The ethyl acetate solution was washed with water and brine, dried with Na_2SO_4, filtered, and evaporated to an oil. The oil was triturated with hexane, and the product was isolated as a solid (3.21 g, 80%): NMR ($CDCl_3$) 7.53 (s, 1 H), 7.48 (dd, 1 H, J = 7.7, 1.0), 7.31 (d, 1 H, J = 15.8), 7.22 (m, 2 H), 6.38 (dd, 1 H, J = 7.5, 1.1), 6.17 (d, 1 H, J = 15.8), 5.24 (s, 2 H), 3.72 (s, 3 H), 2.60 (t, 2 H, J = 7.8), 1.69 (quint, 2 H, J = 7.8), 1.34 (sext, 2 H, J = 7.4), 0.88 (t, 3 H, J = 7.3).

(*E*)-3-[2-Butyl-1-[(2-chlorophenyl)methyl]imidazol-5-yl]-2-propenoic Acid (5). To a solution of **62** (969 mg, 2.91 mmol) in ethyl alcohol (16 mL) was added 10% sodium hydroxide (3.5 mL), and the reaction was stirred at 25 °C for 2 h. The solution was neutralized to pH 4.5 with hydrochloric acid (3 N) while cooling in ice. A white solid precipitated and was filtered, washed with water, and dried to give the title compound (728 mg, 78%): NMR ($CDCl_3$) 7.59 (s, 1 H), 7.44 (dd, 1 H, J = 7.9, 1.3), 7.35 (d, 1 H, J = 15.9), 7.21 (m, 2 H), 6.38 (dd, 1 H, J = 7.7, 1.4), 6.19 (d, 1 H, J = 15.9), 5.25 (s, 2 H), 2.62 (t, 2 H, J = 7.6), 1.65 (quint, 2 H, J = 7.8), 1.33 (sext, 2 H, J = 7.7), 0.85 (t, 3 H, J = 7.3). Anal. ($C_{17}H_{19}ClN_2O_2$) C, H, N.

3-[2-Butyl-1-[(2-chlorophenyl)methyl]imidazol-5-yl]propanoic Acid (3). A solution of ester **62** (2.00 g, 6.0 mmol) and PtO_2 (0.20 g, 0.8 mmol) in EtOH (60 mL) was placed under hydrogen baloon for 2 h. The reaction mixture was filtered through Celite with EtOH rinses and evaporated to yield 2.0 g (100%) of the saturated ester. Basic hydrolysis as in the preparation of compound **5** furnished 0.64 g (34%) of the title compound: NMR ($CDCl_3$) 7.49 (dd, 1 H, J = 7.7, 1.0), 7.34 (s, 1 H), 7.30 (m, 2 H), 6.52 (dd, 1 H, J = 7.5, 1.1), 5.35 (s, 2 H), 2.92 (t, 2 H, J = 7.8), 2.78 (m, 4 H), 1.68 (quint, 2 H, J = 7.8), 1.37 (sext, 2 H, J = 7.4), 0.86 (t, 3 H, J = 7.3). Anal. ($C_{17}H_{21}ClN_2O_2$) C, H, N.

Ethyl (*Z*)-3-[2-Butyl-1-[[2-(trimethylsilyl)ethoxy]methyl]imidazol-5-yl]-2-propenoate (63). The stannylimidazole **58b** (13.4 g, ~80% pure, 26 mmol) and ethyl 3-bromoacrylate (6.41 g, 35.8 mmol) were dissolved in *m*-xylene, treated with $(Ph_3P)_4Pd$ (790 mg, 0.68 mmol), and heated to 120 °C for 20 h. The xylene was removed under vacuum, and the residue was dissolved in EtOAc, washed once each with water, 10% NH_4OH, water, and brine, dried ($MgSO_4$), and concentrated. Column chromatography (EtOAc/hexanes 1:4–1:2) afforded, in order of elution, 3.66 g (40%) of the (*Z*)-acrylate **63** and 2.32 g (26%) of the (*E*)-isomer. **63**: NMR ($CDCl_3$) 8.36 (s, 1 H), 6.94 (d, 1 H, J = 12.8), 5.73 (d, 1 H, J = 12.8), 5.20 (s, 2 H), 4.15 (q, 2 H, J = 7.1), 3.49 (t, 2 H, J = 8.1), 2.69 (t, 2 H, J = 7.9), 1.71 (quint, 2 H, J = 7.8), 1.38 (sext, 2 H, J = 7.4), 1.27 (t, 3 H, J = 7.1), 0.91 (t, 3 H, J = 7.3), 0.87 (t, 2 H, J = 8.1), −0.05 (s, 9 H).

(*Z*)-3-[2-Butyl-1-[(2-chlorophenyl)methyl]imidazol-5-yl]-2-propenoic Acid (4). The SEM protecting group of **63** was exchanged for (2-chlorophenyl)methyl following the procedure for the conversion of **59** (via **60**) to **61** to provide the desired ester in an overall yield of 30% after chromatography. To a solution of the ester (302 mg, 0.87 mmol) in ethyl alcohol (5 mL) was added 10% sodium hydroxide (1.0 mL), and the reaction was stirred at 25 °C for 3 h. The solution was neutralized to pH 3.5 with hydrochloric acid (3 N) while cooling in ice. The product was filtered, washed with water, and dried to give a solid (121 mg, 44%): NMR ($CDCl_3$ with a drop of CD_3OD) 8.25 (s, 1 H), 7.46 (dd, 1 H, J = 1.1, 7.9), 7.28 (dt, 1 H, J_d = 7.8, J_t = 1.2), 7.20 (dt, 1 H, J_d = 7.8, J_t = 1.1), 6.42 (dd, 1 H, J = 1.1, 7.9), 6.35 (d, 1 H, J = 12.8), 5.76 (d, 1 H, J = 12.8), 5.25 (s, 2 H), 2.67 (t, 2 H, J = 7.8), 1.63 (quint, 2 H, J = 7.7), 1.34 (sext, 2 H, J = 7.5), 0.87 (t, 3 H, J = 7.4). Anal. ($C_{17}H_{19}ClN_2O_2$) C, H, N.

2-Butyl-1-[(2-chlorophenyl)methyl]imidazole (64). To a suspension of sodium hydride (97%, 3.47 g, 0.14 mmol) in 150 mL of DMF was added 2-butylimidazole[28] (14.8 g, 0.12 mmol) in 50 mL of DMF over 20 min. After 80 min at room temperature, 2-chlorobenzyl chloride (20.4 g, 0.127 mmol) was added. After 2.5 h, the reaction mixture was diluted with EtOAc and quenched with water. The aqueous layer was extracted 3× with EtOAc. Combined EtOAc layers were washed once each with water and brine, dried (Na_2SO_4), and concentrated. Chromatography (EtOAc/hexanes, 1:1) yielded 28.7 g (97%): NMR ($CDCl_3$) 7.42 (dd, 1 H, J = 7.7, 1.4), 7.21 (m, 2 H), 7.06 (s, 1 H), 6.42 (dd, 1 H, J = 7.8, 1.5), 5.22 (s, 2 H), 2.55 (t, 2 H, J = 7.5), 1.64 (quint, 2 H, J = 7.8), 1.32 (sext, 2 H, J = 7.4), 0.86 (t, 3 H, J = 7.3).

2-Butyl-1-[(2-chlorophenyl)methyl]-5-bromoimidazole (65). To a solution of **64** (8.99 g, 36.1 mmol) in 170 mL of THF was added NBS (97%, 6.59 g, 35.9 mmol). The reaction was stirred at room temperature for 1.75 h, then diluted with ether, and washed with water (3×) and brine. The aqueous layers were extracted once with ether; the combined ether layers were dried (Na_2SO_4) and concentrated. Chromatography (EtOAc/hexanes, 1:5) afforded 5.62 g (48%) of the desired 5-bromoimidazole **65** as well as smaller amounts of the 4-bromo and dibromo products. **65**: NMR ($CDCl_3$) 7.42 (dd, 1 H, J = 7.7, 1.4), 7.21 (m, 2 H), 7.06 (s, 1 H), 6.42 (dd, 1 H, J = 7.8, 1.5), 5.22 (s, 2 H), 2.55 (t, 2 H, J = 7.5), 1.64 (quint, 2 H, J = 7.8), 1.32 (sext, 2 H, J = 7.4), 0.86 (t, 3 H, J = 7.3).

Methyl (*E*)-4-[2-Butyl-1-[(2-chlorophenyl)methyl]imidazol-5-yl]-3-butenoate (66). To a solution of **65** (5.53 g, 16.9 mmol) and methyl (*E*)-4-(tributylstannyl)-3-butenoate (7.62 g, 19.6 mmol) in 90 mL toluene were added $(Ph_3P)_4Pd$ (0.99 g, 0.86 mmol) and a few crystals of 2,6-di-*tert*-butyl-4-methylphenol. The reaction mixture was heated to 110 °C for 5.5 h, cooled, diluted with EtOAc, washed with water and brine, dried ($MgSO_4$), and concentrated. The residue was dissolved in 150 mL of EtOAc and treated with 150 mL of 30% aqueous KF at room temperature for 16 h. The white solid was filtered off and the filtrate diluted with ether, washed with water, 50% aqueous NH_4OH (3×), and brine, dried ($MgSO_4$), and concentrated. Chromatography furnished 4.76 g (81%) of **66** as an oil: NMR ($CDCl_3$) 7.43 (dd, 1 H, J = 7.7, 1), 7.22 (m, 2 H), 7.20 (s, 1 H), 6.43 (d, 1 H, J = 7.5), 6.06 (m, 2 H), 5.15 (s, 2 H), 3.68 (s, 3 H), 3.14 (d, 2 H, J = 6.8), 2.56 (t, 2 H, J = 7.8), 1.67 (quint, 2 H, J = 7.8), 1.34 (sext, 2 H, J = 7.4), 0.87 (t, 3 H, J = 7.3).

4-[2-Butyl-1-[(2-chlorophenyl)methyl]imidazol-5-yl]butanoic Acid (6). A mixture of ester **66** (134 mg, 0.39 mmol) and 10% Pd/C (21 mg) in 7 mL of EtOH was stirred at room temperature under H_2 (1 atm) for 1 h. The reaction mixture was filtered through Celite with EtOAc rinses and concentrated. Chromatography (EtOAc/hexanes, 2:1–4:1) gave 53 mg (39%) of the saturated ester. A solution of the saturated ester (53 mg, 0.15 mmol) in 4 mL of 5 N HCl was heated to 100 °C for 22 h and then concentrated to dryness. The residue was purified by trituration with MeOH/ether to afford 52 mg (93%) of **6** as a white solid: NMR ($CDCl_3$ with a drop of CD_3OD) 7.52 (dd, 1 H, J = 1.3, 7.9), 7.34 (m, 2 H), 7.30 (s, 1 H), 6.59 (d, 1 H, J = 7.5), 5.41 (s, 2 H), 2.90 (t, 2 H, J = 7.8), 2.62 (t, 2 H, J = 7.7), 2.40 (t, 2 H, J = 6.8), 1.94 (quint, 2 H, J = 7.6), 1.64 (quint, 2 H, J = 7.7), 1.36 (sext, 2 H, J = 7.5), 0.89 (t, 3 H, J = 7.3). Anal. ($C_{18}H_{23}ClN_2O_2 \cdot {}^3/_4HCl$) C, H, N.

Methyl (*E,E*)-5-[2-Butyl-1-[(2-chlorophenyl)methyl]imidazol-5-yl]-2,4-pentadienoate (67). Trimethyl 4-phosphonocrotonate (0.78 g, 3.75 mmol) was added dropwise at 0 °C to a suspension of sodium hydride (0.11 g, 4.5 mmol) in DME (10 mL) resulting in gas evolution. The mixture was stirred at 25 °C for 30 min, aldehyde **56** was added, and the reaction mixture was stirred at 40 °C for 1 h. The reaction was quenched with water (20 mL) and extracted three times with ether (40 mL). The ether solution was washed with water and brine and dried ($MgSO_4$). The ether was removed, and the resulting oil was triturated with ether to give the low melting solid **67** (330 mg). Flash chromatography of the filtrate (hexane/ethyl acetate 1:1) gave an additional 181 mg giving a total yield of 511 mg (38%): NMR ($CDCl_3$) 7.45 (dd, 1 H, J = 7.7, 1.5), 7.43 (s, 1 H), 7.24 (m, 3 H), 6.63 (dd, 1 H, J = 11.1, 15.4), 6.41 (dd, 1 H, J = 7.7, 1.5), 6.41 (d, 1 H, J = 15.3), 5.85 (d, 1 H, J = 15.3), 5.20 (s, 2 H), 3.72 (s, 3 H), 2.61 (t, 2 H, J = 7.8), 1.69 (quint, 2 H, J = 7.8), 1.36 (sext, 2 H, J = 7.4), 0.88 (t, 3 H, J = 7.3).

(*E,E*)-5-[2-Butyl-1-[(2-chlorophenyl)methyl]imidazol-5-yl]-2,4-pentadienoic Acid (8). Basic hydrolysis of **67** as in the preparation of **5** afforded the title compound (75%) as a white solid. Anal. ($C_{19}H_{21}ClN_2O_2$) C, H, N.

5-[2-Butyl-1-[(2-chlorophenyl)methyl]imidazol-5-yl]pentanoic Acid (7). Hydrogenation of ester **67** to the saturated ester followed by basic hydrolysis as for the preparation of compound **3** furnished the title compound: NMR (CD_3OD) 7.55 (dd, 1 H, J = 7.5, <1), 7.37 (m, 4 H), 6.72 (dd, 1 H, J = 7.5, <1), 5.53 (s, 2 H), 2.93 (t, 2 H, J = 7.5), 2.54 (t, 2 H, J = 7.5), 2.27 (t, 2 H, J = 7.5), 1.66 (m, 6 H), 1.33 (m, 2 H), 0.88 (t, 3 H, J = 7.5). Anal. ($C_{19}H_{25}ClN_2O_2 \cdot HCl$) C, H, N.

Methyl (*E/Z*)-6-[2-Butyl-1-[(2-chlorophenyl)methyl]imidazol-5-yl]-5-hexenoate (68). A 2.5 M solution of *n*-butyllithium in hexane (3.7 mL, 9.17 mmol) was added dropwise to a suspension of (4-carboxybutyl)triphenylphosphonium bromide (2.1 g, 4.7 mmol) (Aldrich) in THF (100 mL) maintained at 0 °C under an argon atmosphere. The resulting dark red solution was stirred 15 min, and a solution of aldehyde **56** (1.0 g, 3.61 mmol) in THF (50 mL) was added dropwise. The mixture was stirred for 1 h at 0 °C and then at ambient temperature for 72 h. After filtration the volatiles were removed at reduced pressure and the residue dissolved in 5% aqueous Na_2CO_3. The solution was extracted with ethyl ether (3 × 30 mL) and the aqueous phase acidified to pH 3 and extracted with ethyl acetate (2 × 30 mL) (discarded). The pH of the aqueous phase was adjusted to 4.5 and again extracted with ethyl acetate (2 × 30 mL). The extract was dried ($MgSO_4$) and filtered, and the solvent was removed to give 0.6 g (46%) of alkene acid product. Without further purification, the alkenoic acid was dissolved in CH_3OH (25 mL) and ethereal HCl added (25 mL). The mixture was stirred at ambient temperature for 72 h and the solvent evaporated. The residue was dissolved in CH_2Cl_2, washed with 5% aqueous $NaHCO_3$, dried ($MgSO_4$), and filtered, and the solvent was removed at reduced pressure. Chromatography of the residue on SiO_2 eluting with 1:1 ethyl acetate/hexane gave 0.24 g (39%) of the title alkene methyl ester as an approximately 1:1 mixture of olefin isomers.

6-[2-Butyl-1-[(2-chlorophenyl)methyl]imidazol-5-yl]hexanoic Acid (9). Hydrogenation of ester **68** to the saturated ester followed by basic hydrolysis as for the preparation of compound **3** furnished the crude title compound. Recrystallization from acetone/ethyl ether gave the pure acid as the hydrochloride salt: NMR ($CDCl_3$) 7.52 (dd, 1 H, J = 7.5, <1.0), 7.32 (m, 4 H), 6.43 (d, 1 H, J = 7.5), 5.27 (s, 2 H), 2.96 (t, 2 H, J = 7.5), 2.44 (t, 2 H, J = 7.5), 2.35 (t, 2 H, J = 7.5), 1.73 (t, 2 H, J = 7.5), 1.63 (m, 4 H), 1.35 (m, 4 H), 0.84 (t, 3 H, J = 7.5). Anal. ($C_{20}H_{27}ClN_2O_2 \cdot HCl$) C, H, N.

Method A. (a) Trimethyl 2-Benzylphosphonoacetate (71). Trimethyl phosphonoacetate (18.2 g, 100 mmol) was added dropwise to a suspension of sodium hydride (2.76 g, 115 mmol) in dry DME (120 mL). After stirring for 60 min at 25 °C, benzyl bromide (21.4 g, 125 mmol) was added and the mixture was stirred for 1.5 h at 60 °C. The reaction mixture was poured into 200 mL of ice–water and extracted with ethyl acetate (3 × 100 mL). The ethyl acetate solution was washed with water and brine, dried with Na_2SO_4, filtered, and evaporated to an oil which was purified by flash column chromatography (hexane/EtOAc) to give the product as an oil (22.2 g, 82%): NMR ($CDCl_3$) 7.25 (m, 5 H), 3.84–3.51 (6 s, 9 H), 3.26 (m, 3 H).

(b) Methyl (*E*)- and (*Z*)-3-[2-Butyl-1-[(2-chlorophenyl)methyl]imidazol-5-yl]-2-benzyl-2-propenoate (69, 70). Trimethyl 2-benzylphosphonoacetate (**71**) (15.5 g, 56.9 mmol) in dry DME (10 mL) was added dropwise over 20 min to a suspension of sodium hydride (1.37 g, 56.9 mmol) in dry DME (80 mL). After stirring for 15 min at 50 °C and then 15 min at 25 °C, a solution of aldehyde **56** (9.00 g, 32.5 mmol) in DME (10 mL) was added rapidly and the mixture was stirred for 2 h at 70 °C and 18 h at 25 °C. The reaction was poured into 200 mL of ice–water and extracted with ether (3 × 150 mL). The ether solution was washed with water and brine, dried with Na_2SO_4, filtered, and evaporated to an oil. The isomers were purified by flash column chromatography (hexane/EtOAc) with the (*E*)-isomer **69** (5.75 g, 42%) eluting before the (*Z*)-isomer **70** (1.12 g, 8%). This order of elution was observed for all of the (*E*)/(*Z*)-ester mixtures. **69**: NMR ($CDCl_3$) 7.48 (s, 1 H), 7.45 (dd, 1 H, J = 1.1, 7.9), 7.21 (m, 8 H), 6.39 (dd, 1 H, J = 1.2, 7.6), 5.25 (s, 2 H), 4.01 (s, 2 H), 3.70 (s, 3 H), 2.59 (t, 2 H, J = 7.5), 1.68 (quint, 2 H, J = 7.4), 1.34 (hex, 2 H, J = 7.4), 0.88 (t, 3 H, J = 7.3). **70**: NMR ($CDCl_3$) 7.87 (s, 1 H), 7.38 (dd, 1 H, J = 1.2, 7.8), 7.26 (m, 7 H), 6.76 (s, 1 H), 6.48 (dd, 1 H, J = 1.1, 7.6), 5.09 (s, 2 H), 3.76 (s, 3 H), 3.55 (s, 2 H), 2.55 (t, 2 H, J = 7.6), 1.68 (quint, 2 H, J = 7.4), 1.37 (hex, 2 H, J = 7.4), 0.88 (t, 3 H, J = 7.3).

2-Butyl-1-[(2-chlorophenyl)methyl]-5-acetylimidazole (72). To a solution of aldehyde **56** (1.10 g, 3.97 mmol) in THF (15 mL) was added a solution of methyllithium (1.2 M in ether, 3.64 mL, 4.37 mmol) at −78 °C. After 75 min, the reaction was quenched with aqueous NH_4Cl, diluted with EtOAc, and allowed to warm to room temperature. The aqueous layer was extracted once with EtOAc, and the combined organic extracts were washed with brine, dried with Na_2SO_4, filtered, and evaporated to an oil. Flash chromatography afforded 1.07 g (92%) of the desired alcohol. A solution of the alcohol (1.07 g, 3.65 mmol) in toluene (4 mL) was treated with activated MnO_2 at 100 °C for 30 min and then at 60–90 °C for 90 h. Filtration through Celite, concentration, and purification via flash chromatography provided 0.63 g (59%) of the ketone **72**: NMR ($CDCl_3$) 7.85 (s, 1 H), 7.40 (dd, 1 H, J = 7.8, 1.2), 7.18 (m, 2 H), 6.34 (d, 1 H, J = 7.3), 5.68 (s, 2 H), 2.58 (t, 2 H, J = 7.7), 2.43 (s, 3 H), 1.67 (quint, 2 H, J = 7.8), 1.34 (sext, 2 H, J = 7.4), 0.87 (t, 3 H, J = 7.3).

(*E*)-3-[2-Butyl-1-[(2-chlorophenyl)methyl]imidazol-5-yl]-2-butenoic Acid (20). Following the same procedure as described for **62**, the methyl ester of **21** was isolated from ketone **73** in 37% yield. Basic hydrolysis of the ester as in the preparation of compound **5** furnished the title compound in 41% yield: NMR ($CDCl_3$ with a drop of DMSO-d_6) 7.56 (s, 1 H), 7.50 (d, 1 H, J = 7.9), 7.38 (t, 1 H, J = 7.7), 7.30 (t, 1 H, J = 7.8), 6.69 (d, 1 H, J = 7.7), 5.92 (d, 1 H, J = 1.1), 5.46 (s, 2 H), 2.96 (t, 2 H, J = 7.8), 2.28 (d, 3 H, J = 1.1), 1.72 (quint, 2 H, J = 7.7), 1.38 (sext, 2 H, J = 7.5), 0.90 (t, 3 H, J = 7.5). Anal. ($C_{18}H_{21}ClN_2O_2$·HCl) C, H, N.

Method B. (*E*)-3-[2-Butyl-1-[(2-chlorophenyl)methyl]-imidazol-5-yl]-2-phenyl-2-propenoic Acid (15). Aldehyde **56** (0.55 g, 2.0 mmol), phenylacetic acid (0.31 g, 2.28 mmol), potassium carbonate (0.126 g, 0.914 mmol), and acetic anhydride (1 mL) were combined and heated at 140 °C for 6 h. The reaction mixture was cooled in ice and diluted with water, and the water was decanted from the residual oil. The oil was triturated with ether, and the title compound was isolated after recrystallization from methanol–ethyl acetate to give a solid (0.143 g, 18%): NMR (CD_3OD) 7.57 (dd, 1 H, J = 1.1, 7.9), 7.38 (m, 5 H), 7.37 (s, 1 H), 7.15 (d, 2 H, J = 7.4), 6.38 (dd, 1 H, J = 1.1, 7.9), 5.90 (s, 1 H), 5.38 (s, 2 H), 2.53 (t, 2 H, J = 7.8), 1.48 (quint, 2 H, J = 7.7), 1.22 (sext, 2 H, J = 7.5), 0.78 (t, 3 H, J = 7.4). Anal. ($C_{23}H_{23}ClN_2O_2$) C, H, N.

Method C. (a) Methyl 3-(2-Thienyl)-2-propenoate (75). To a suspension of 3-(2-thienyl)acrylic acid (25.6 g, Aldrich, 98%) in MeOH (350 mL) was added a 1 M solution of ethereal HCl (70 mL). The mixture was stirred at room temperature for 17 h and then at 50 °C for 6 h. The solvents were evaporated, and the residue was taken up in ether, washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. The material was dissolved in ether and filtered through a plug of silica and reconcentrated. The residue was triturated with hexanes to afford 24.0 g (88%) of the ester **75** as a tan solid: NMR ($CDCl_3$) 7.79 (d, 1 H, J = 15), 7.37 (d, 1 H, J = 5.1), 7.24 (d, 1 H, J = 3.5), 7.05 (dd, 1 H, J = 3.5, 5), 6.23 (d, 1 H, J = 15), 3.80 (s, 3 H).

(b) Methyl 3-(2-Thienyl)heptanoate (76). To a suspension of CuCN (1.23 g, 13.7 mmol) in ether (25 mL) was added a 2.5 M solution of *n*-BuLi in hexanes (10.5 mL, 26.2 mmol) at −78 °C. The reaction mixture was warmed to −25 °C for 20 min and recooled to −78 °C, and ester **75** in ether (20 mL) was added. The reaction was stirred at −78 °C for 40 min, at −25 °C for 60 min, and then diluted with ether and washed twice with a 9:1 mixture of NH_4OH and saturated NH_4Cl. The ether layer was washed with brine, dried (Na_2SO_4), and concentrated. Chromatography (ether/hexanes) provided 1.74 g (65%) of the title compound: NMR ($CDCl_3$) 7.15 (d, 1 H, J = 5.1), 6.92 (dd, 1 H, J = 3.5, 5), 6.81 (d, 1 H, J = 3.5), 3.62 (s, 3 H), 3.44 (quint, 1 H), 2.64 (m, 2 H), 1.67 (m, 2 H), 1.26 (m, 4 H), 0.84 (t, 3 H).

(b) Methyl 3-(2-Thienyl)propanoate (77). A solution of ester **75** in EtOAc (150 mL) was treated with 10% Pd/C (3.46 g) and hydrogenated at ~45 psi on a Parr hydrogenator for 5 h at room temperature. The catalyst was removed by filtration and the residue concentrated. GC analysis indicated that the reaction was ~75% complete. The residue was redissolved in EtOAc (150 mL), treatd with 10% Pd/C (3.20 g), and hydrogenated for 6 h as before. Filtration and concentration gave 35.0 g (98%) of the title compound: NMR ($CDCl_3$) 7.12 (d, 1 H, J = 5.1), 6.91 (dd, 1 H, J = 3.5, 5), 6.82 (d, 1 H, J = 3.5), 3.69 (s, 3 H), 3.17 (t, 2 H, J = 7), 2.70 (t, 2 H, J = 7).

(c) Methyl (*E*)-3-[2-Butyl-1-[(2-chlorophenyl)methyl]imidazol-5-yl]-2-[(2-thienyl)methyl]-2-propenoate (74). To a solution of diisopropylamine (29 mL, 207 mmol) in THF (350 mL) was added a 2.5 M solution of *n*-BuLi in hexanes (80 mL, 200 mmol) at −78 °C. After 15 min, methyl 3-(2-thienyl)-propanoate (**77**) (32.7 g, 192 mmol) was added dropwise via cannula over 15 min and rinsed in with 10 mL of THF. The ester enolate was allowed to form for 60 min at −78 °C, and then a solution of aldehyde **55** (40.9 g, 148 mmol) in THF (60 mL) was added rapidly. The reaction was stirred an additional 10 min at −78 °C before quenching into a 1:1 mixture of ether and saturated aqueous NH_4Cl with ether rinses. The ether layer was washed with brine. The combined aqueous layers were extracted with ether, and the combined ether layers were dried (Na_2SO_4) and concentrated to afford aldol product **73** along with traces of starting ester **77**. The crude residue was dissolved in CH_2Cl_2 (400 mL) and treated with acetic anhydride (140 mL, 1.48 mmol) and (dimethylamino)pyridine (6.32 g, 51.2 mmol) for 16 h. Saturated aqueous $NaHCO_3$ was added cautiously, and the biphasic reaction mixture was stirred for approximately 30 min (until bubbling ceased). The aqueous layer was washed twice with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated. The crude acetate was dissolved in toluene (420 mL) and treated with DBU (55.0 mL, 360 mmol). The reaction was heated to 100 °C under argon for 60 min, cooled to room temperature, and concentrated in vacuo. The dark brown residue was taken up in ether, treated with silica gel, and filtered with ether rinses. The filtrate was evaporated and purified via chromatography (EtOAc/hexane) to provide 52.4 g (83% from the aldehyde **56**) of the unsaturated ester **74**: NMR ($CDCl_3$) 7.44 (s, 1 H), 7.43 (dd, 1 H, J = 7.4, 1.3), 7.39 (s, 1 H), 7.21 (m, 2 H), 7.12 (d, 1 H, J = 5.1), 6.90 (dd, 1 H, J = 3.5, 5), 6.81 (d, 1 H, J = 3.5), 6.39 (dd, 1 H, J = 7.2, 1.2), 5.22 (s, 2 H), 4.12 (s, 2 H), 3.72 (s, 3 H), 2.60 (t, 2 H, J = 7.7), 1.68 (quint, 2 H, J = 7.8), 1.34 (sext, 2 H, J = 7.5), 0.86 (t, 3 H, J = 7.4).

Method D. (a) Ethyl (*E*)-3-[[(Trifluoromethyl)sulfonyl]-oxy]-2-heptenoate (79a). To a suspension of NaH (97%, 357 mg, 14.4 mmol) in DMF at room temperature was added ethyl 3-oxoheptanoate (2.07 g, 12.0 mmol) dropwise. After stirring for 30 min, *N*-phenyltriflamide (4.97 g, 13.8 mmol) was added in one portion and the reaction mixture was stirred for an additional 2 h, then diluted with ether, washed with saturated NH_4Cl, water, and brine, dried (Na_2SO_4), and concentrated. Chromatography (EtOAc/hexanes) gave **79a** in 94% yield: NMR ($CDCl_3$) 5.93 (s, 1 H), 4.22 (q, 2 H, J = 7.1), 2.92 (t, 2 H, J = 7.6), 1.60 (quint, 2 H, J = 7.4), 1.39 (m, 2 H), 1.31 (t, 3 H, J = 7.2), 0.94 (t, 3 H, J = 7.2).

(b) Ethyl (*E*)-3-[2-Butyl-2-[[2-(trimethylsilyl)ethoxy]-methyl]imidazol-5-yl]-2-heptenoate (78a). A solution of stannylimidazole **58a** (1.973 g, 3.63 mmol) and triflate **79a** (1.1 g, 3.62 mmol) in THF (5 mL) was added to a mixture of lithium chloride (470 mg, 11.1 mmol) and $(Ph_3P)_4Pd$ (88 mg, 0.076 mmol) in THF (10 mL). The reaction was heated to reflux under argon for 22 h, cooled, and diluted with ether, and the ether layer was washed with water, 10% ammonium hydroxide solution, and brine. The extract was dried with sodium sulfate and concentrated. The crude product was chromatographed (EtOAc/hexane) to give 1.09 g (74%) of the title compound: NMR ($CDCl_3$) 7.11 (s, 1 H), 5.97 (s, 1 H), 5.14 (s, 2 H), 4.19 (q, 2 H, J = 7.1), 3.54 (t, 2 H, J = 8.3), 2.94 (t, 2 H, J = 7.6), 1.78 (m, 4 H), 1.43 (m, 6 H), 1.30 (t, 3 H, J = 7.1), 0.94 (m, 8 H), 0.02 (s, 9 H).

(c) (*E*)-3-[2-Butyl-1-[(2-chlorophenyl)methyl]imidazol-5-yl]-2-heptenoic Acid (21). The SEM protecting group of **78a** was exchanged for (2-chlorophenyl)methyl following the procedure for the conversion of **59** (via **60**) to **61** to provide the desired ester in an overall yield of 20% after chromatography: NMR ($CDCl_3$) 7.48 (dd, 1 H, J = 7.7, 1.3), 7.28 (m, 3 H), 6.51 (dd, 1 H, J = 7.4, 1.4), 5.67 (s, 1 H), 5.28 (s, 2 H), 4.18 (q, 2 H, J = 7.1), 2.89 (t, 2 H, J = 7.5), 2.59 (t, 2 H, J = 7.7), 1.76 (quint, 2 H, J = 7.8), 1.37 (m, 6 H), 1.29 (t, 3 H, J = 7.1), 0.94 (t, 3 H, J = 7.4), 0.88 (t, 3 H, J = 7.6). Basic hydrolysis following the procedure for compound **5** provided the title compound (51%): NMR ($CDCl_3$) 7.44 (dd, 1 H, J = 7.7, 1.3), 7.23 (m, 3 H), 6.48 (d, 1 H, J = 7.7), 5.68 (s, 1 H), 5.24 (s, 2 H), 2.84 (t, 2 H, J = 7.5), 2.61 (t, 2 H, J = 7.7), 1.71 (quint, 2 H, J = 7.8), 1.33 (m, 6 H), 0.87 (t, 3 H, J = 7.4), 0.81 (t, 3 H, J = 7.6). Anal. ($C_{21}H_{27}ClN_2O_2$) C, H, N.

Ethyl (*E*)-2-Benzyl-3-[[(trifluoromethyl)sulfonyl]oxy]-2-butenoate (79c). Following the same procedure as described for **79a**, the title compound was isolated from ethyl 2-benzylacetoacetate in 85% yield along with 15% of its (*Z*)-isomer: **79c**: NMR ($CDCl_3$) 7.22 (m, 5 H), 4.13 (q, 2 H, J = 7.1), 3.81 (s, 2 H), 2.47 (s, 3 H), 1.15 (t, 3 H, J = 7.2).

Ethyl (*E*)-3-[2-Butyl-1-[[2-(trimethylsilyl)ethoxy]methyl]imidazol-5-yl]-2-benzyl-2-butenoate (78c). According to the procedure of **78a** starting with stannylimidazole **58a** and triflate **79c**, the title compound was obtained in 28% yield as an oil. Also, 33% of the (*Z*)-olefin isomer was isolated. **78c**: NMR ($CDCl_3$) 7.21 (m, 3 H), 7.06 (d, 2 H, J = 7.1), 6.80 (s, 1 H), 4.91 (s, 2 H), 4.17 (q, 2 H, J = 7.1), 3.55 (s, 2 H), 3.42 (t, 2 H, J = 8.1),

2.71 (t, 2 H, J = 7.6), 2.21 (s, 3 H), 1.78 (quint, 2 H, J = 7.4)), 1.41 (hex, 2 H), 1.18 (t, 3 H, J = 7.1), 0.90 (m, 5 H), 0.03 (s, 9 H).

(*E*)-3-[2-Butyl-1-[(2-chlorophenyl)methyl]imidazol-5-yl]-2-benzyl-2-butenoic Acid (23). The SEM protecting group of **78c** was exchanged for (2-chlorophenyl)methyl following the procedure for the conversion of **59** (via **60**) to **61** to provide the desired ester in an overall yield of 57% after chromatography. Basic hydrolysis following the procedure for compound **5**, followed by trituration with EtOAc/ether provided the title compound (52%) as the white hydrochloride salt: NMR ($CDCl_3$) 7.43 (dd, 1 H, J = 1.1, 8.0), 7.32 (t, 2 H, J = 7.6), 7.14 (m, 6 H), 7.01 (dd, 2 H, J = 1.1, 7.3), 6.57 (d, 1 H, J = 7.6), 4.66 (s, 2 H), 3.48 (s, 2 H), 2.80 (t, 2 H, J = 7.5), 1.91 (s, 3 H), 1.72 (quint, 2 H, J = 7.4), 1.35 (hex, 2 H, J = 7.4), 0.89 (t, 3 H, J = 7.3). Anal. ($C_{23}H_{27}ClN_2O_2$·HCl) C, H, N.

Procedure 2: Use of Imidazole–Zinc Intermediate. (a) Ethyl (*E*)-4-Phenyl-3-[[(trifluoromethyl)sulfonyl]oxy]-2-butenoate (79b). According to the procedure for **79a**, the title compound was isolated in 88% yield along with 9% of its (*Z*)-isomer. **79a**: NMR ($CDCl_3$) 7.28 (m, 5 H), 6.03 (s, 1 H), 4.26 (s, 2 H), 4.23 (q, 2 H, J = 7.1), 1.28 (t, 3 H, J = 7.2).

(b) Ethyl (*E*)-3-[2-Butyl-1-[[2-(trimethylsilyl)ethoxy]methyl]imidazol-5-yl]-4-phenyl-2-butenoate (78b). To a solution of **57** (1.8 g, 5.32 mmol) in ethyl ether (16 mL) was added *n*-BuLi in hexane (6.5 mmol) at a slow rate. After an additional 1 h of stirring at 25 °C, a solution of zinc chloride in ether (6.5 mL of 1.0 M) was added followed by THF (15 mL). After an additional 75 min of stirring, the zinc chloride–imidazole adduct solution was transferred under argon to a solution of ethyl 4-phenyl-3-[[(trifluoromethyl)sulfonyl]oxy]butenoate (1.63 g, 6.41 mmol) and $(Ph_3P)_4Pd$ (317 mg) in THF (30 mL). The reaction mixture was stirred at 25 °C for 20 h and worked up by dilution with ether and washing with aqueous NH_4Cl and brine. The ether layer was dried over $MgSO_4$ and concentrated. The crude product was chromatographed over silica gel with a gradient of EtOAc in hexane to give 1.77 g (75%) of **78b**: NMR ($CDCl_3$) 7.21 (m, 5 H), 7.09 (s, 1 H), 6.13 (s, 1 H), 5.01 (s, 2 H), 4.35 (s, 2 H), 4.21 (q, 2 H, J = 7.1), 3.42 (t, 2 H, J = 8.1), 2.67 (t, 2 H, J = 7.6), 1.75 (quint, 2 H, J = 7.4), 1.39 (m, 2 H), 1.30 (t, 3 H, J = 7.1), 0.92 (m, 5 H), 0.01 (s, 9 H).

(c) (*E*)-3-[2-Butyl-1-[(2-chlorophenyl)methyl]imidazol-5-yl]-4-phenyl-2-butenoic Acid (22). The SEM protecting group of **78b** was exchanged for (2-chlorophenyl)methyl following the procedure for the conversion of **59** (via **60**) to **61** to provide the desired ester in an overall yield of 57% after chromatography. The ester was dissolved in ethanol and 5 N hydrochloric acid solution, and the solution was slowly heated at 100 °C with evaporation of the alcohol. After being heated at 100 °C for 6 h, the reaction was cooled and the white precipitate was collected, air-dried, and then triturated with ether/methanol to afford 65% of **22** as the white hydrochloride salt: NMR ($CDCl_3$) 7.35 (dd, 1 H, J = 1.1, 8.0), 7.15 (m, 6 H), 6.95 (dt, 2 H, J = 1.0, 7.6), 6.03 (d, 1 H, J = 7.2), 5.79 (bs, 1 H), 5.11 (s, 2 H), 4.31 (s, 2 H), 2.44 (t, 2 H, J = 7.5), 1.58 (quint, 2 H, J = 7.4), 1.25 (hex, 2 H, J = 7.4), 0.80 (t, 3 H, J = 7.3). Anal. ($C_{24}H_{25}ClN_2O_2$·HCl) C, H, N.

X-ray Crystallography. Crystals of **17** were grown by slow evaporation from ethyl acetate. A plate of approximate dimensions 0.30 × 0.40 × 0.20 mm was mounted on a glass fiber with epoxy cement. Lattice parameters were obtained from the setting angles of 25 reflections well distributed in reciprocal space and measured on an Enraf Nonius CAD4 diffractometer using graphite monochromated copper radiation ($\lambda k\alpha$ = 1.54184 Å). The space group is $P1$ with a = 11.634 (4) Å, b = 11.971 (5) Å, c = 8.961 (3) Å, α = 96.40 (3)°, β = 112.04 (3)°, γ = 61.47 (3)°, V = 1012.8 (10) Å^3, Z = 2 at 174 K for $C_{24}H_{25}ClN_2O_2$, M_r = 408.93, ρ = 1.341 g cm^{-1}, μ = 18.528 cm^{-1}. Intensity data, also measured on the diffractometer, were collected using variable speed ω–2θ scans, 2θ max = 136° and index ranges $-14 \le h,k \le 14$, $0 \le l \le 10$. Intensities (3936 collected) were corrected for Lorentz and polarization effects and for absorption (0.727 min., 1.202 max correction factors). Symmetry equivalent observations were averaged (r_{int} = 0.020). Three intensity standards monitored every 3 h of exposure time showed a maximum change of ±1%. Of the unique set of 3680 data, 3315 were considered observed with $I \ge 3\sigma(I)$.

The structure was solved with MULTAN80[28] and refined by standard full matrix least squares techniques. Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atom positions, located from difference Fourier maps, were refined with isotropic temperature factors. The function minimized was $\sum w(|F_o| - |F_c|)^2$ with the weights, w, defined as $4F_o^2/\sigma(F_o^2)$ and $\sigma(F_o^2) = [\sigma^2(I_c) + 0.009I_c^2)]$. The refinement converged (max Δ/σ = 0.03) to values of the conventional crystallographic residuals R = 0.051, wR = 0.072 for 3315 observations and 363 variables. Maximum excursions in a final difference Fourier map were within ±0.51 e Å^{-3}. Neutral atom scattering factors were used.[29] Fractional atomic coordinates are listed in the supplementary material. The molecule displays a shape which resembles a "broken cup" with the imidazole ring acting as the cup bottom and the substituents closing off three-quarters of the cylindrical side. The *o*-chlorophenyl ring sits perpendicular to the imidazole ring (the dihedral angle between ring planes is 95°) with the chlorine atom pointing away from the imidazole ring center. The acrylic acid moiety is virtually coplanar with the imidazole ring. One intermolecular hydrogen bond exists with distances and an angle of O2···N3 2.618 (2) Å, H14···N3 1.39 (4) Å, O2–H14···N3 164 (4)°.

Biological Assays. The radioligand binding assay, the rabbit aorta assay, and the normotensive rat in vivo assay have been described in detail.[5b] A brief description of each method follows.

The radioligand binding assay was a modification of a method previously described.[30] A particulate fraction from rat mesenteric arteries was incubated in Tris buffer with 80 pM of [^{125}I]-angiotensin II with or without angiotensin II antagonists for 1 h at 25 °C. The incubation was terminated by rapid filtration, and receptor-bound [^{125}I]angiotensin II trapped on the filter was quantified with a γ counter. The potency of angiotensin II antagonists was expressed as the IC_{50}, which is the concentration of antagonist to displace 50% of the total specifically bound angiotensin II.

The ability of the compounds to antagonize angiotensin II induced vasoconstriction was examined in the rabbit aorta. Ring segments were cut from the rabbit thoracic aorta and suspended in organ baths containing physiological salt solution. The ring segments were mounted over metal supports and attached to force displacement transducers which were connected to a recorder. Cumulative concentration–response curves to angiotensin II were performed in the absence of antagonist or following a 30-min incubation with antagonist. Antagonist dissociation constants (K_b) were calculated by the dose-ratio method using the mean effective concentrations.

For the in vivo data, rats were prepared with indwelling femoral arterial and venous catheters.[31] Two to three days following surgery the rats were placed in a restrainer, and blood pressure was continuously monitored from the arterial catheter with a pressure transducer and recorded on a polygraph. The change in mean arterial pressure in response to intravenous injections of 250 ng/kg angiotensin II was compared at various time points prior to and following the administration of the compounds intravenously at doses of 0.3–300 mg/kg. The dose of compound needed to produce 50% inhibition of the control pressor response to angiotensin II (ID_{50}) was used to estimate the potency of the compounds.

For the conscious renin-dependent hypertensive rat data (Figure 4), male Sprague-Dawley rats (250–300 g) were anesthetized with ketamine hydrochloride (60 mg/kg, im) and sodium pentobarbital (20 mg/kg, ip). Catheters were placed in the abdominal aorta and vena cava via a femoral artery and vein,

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respectively. An additional Tygon tubing was sewn into the duodenum for intraduodenal administration of drugs. All tubing was tunneled under the skin and exited in the midscapular region. When not in use, the vascular catheters were filled with a 1:1 mixture of 50% dextrose and heparin (1 000 units/mL), the duodenal tube was filled with sterile saline, and all were sealed under pressure with stainless steel pins. The animals were accustomed to a restraining cage prior to surgery and during the 7–10-day recovery period. After base line blood pressure measurements had been recorded, renin-dependent hypertension was established by partial renal artery ligation of one kidney. This method results in an approximately 5-fold increase in plasma renin activity (Edwards et al., unpublished observations). Animals were anesthetized as above, and via a flank incision two of the three blood vessels to the left kidney were ligated. Rats were placed in the restrainer, and arterial pressure was measured before and after the intraduodenal administration of various doses of **40**.

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Supplementary Material Available: Tables (with standard deviations) of positional parameters, equivalent isotropic temperature factors and their estimated standard deviations, listings of H-atom coordinates, anisotropic displacement parameters for nonhydrogen atoms, and bond distances and angles for **17** (9 pages). Ordering information is given on any current masthead page.