Potent Nonpeptide Angiotensin II Receptor Antagonists. 2.[1] 1-(Carboxybenzyl)imidazole-5-acrylic Acids

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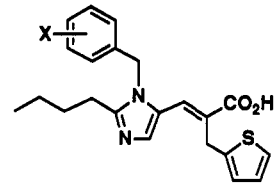
The further evolution of the imidazole-5-acrylic acid series of nonpeptide angiotensin II receptor antagonists is detailed (for Part 1, see: *J. Med. Chem.* **1992**, *35*, 3858). Modifications of the *N*-benzyl ring substitution were undertaken in an effort to mimic the Tyr[4] residue of angiotensin II. Introduction of a *p*-carboxylic acid on the *N*-benzyl ring resulted in the discovery of compounds with nanomolar affinity for the receptor and good oral activity. SAR studies of these potent antagonists revealed that the thienyl ring, the (*E*)-acrylic acid, and the imidazole ring in addition to the two acid groups were important for high potency. Also, overlay comparisons of the parent diacid with both angiotensin II and a representative biphenylyltetrazole nonpeptide angiotensin II receptor antagonist are presented. The parent diacid analog, SK&F 108566 or (*E*)-3-[2-butyl-1-(4-carboxybenzyl)-1*H*-imidazol-5-yl]-2-[(2-thienyl)methyl]propenoic acid, is currently in clinical development for the treatment of hypertension.

Recently, a number of groups have reported the discovery of potent nonpeptide angiotensin II (AII) receptor antagonists.[2,3] In a previous paper, we described the discovery of a novel class of nonpeptide AII receptor antagonists distinguished by a substituted acrylic acid side chain attached to an imidazole nucleus.[1] An important aspect of the development of this novel series of compounds was the use of a peptide pharmacophore model of AII to help formulate design hypotheses and guide our synthetic efforts. The lead antagonist in this series, the imidazole-5-acrylic acid 1, had submicromolar affinity for the receptor and showed a measure of oral activity in antagonizing AII induced hypertension in vivo. An overlay comparison of the nonpeptide with AII suggested that the newly introduced structural elements of this series, the thiophene ring and the (*E*)-acrylic acid, mimicked the carboxy-terminal region of the octapeptide.

We now report our research on the investigation of the SAR of other structural features of the imidazoleacrylic acids, most notably the *N*-benzyl ring. This effort has culminated with the discovery of novel nonpeptide AII receptor antagonists with nanomolar affinity for the receptor and demonstrated in vivo oral activity. One compound from this series, 2 (SK&F 108566),[4] is currently in clinical development for the treatment of hypertension. In addition to a discussion of the SAR around lead compound 2, a proposal on how it overlays the C-terminus of our peptide pharmacophore model as well as an overlay comparison with another representative nonpeptide AII receptor antagonist are presented.



1 (X = 2-Cl)

2 (X = 4-CO_2H)

Strategy

In the development of 1, the improvement in activity over a benzylimidazole reported in the patent literature[5] could largely be attributed to modifications introduced on the imidazole C-5 acid side chain.[1] The remaining positions on the imidazole ring remained to be investigated in depth. To help formulate design hypotheses for structural modifications to 1 to further improve activity, we examined an overlay of the nonpeptide on our pharmacophore model (Figure 1), a strategy which had proven successful in the initial design of the substituted acrylic acid antagonists.[1] In the overlay comparison, the thiophene ring and acrylic acid of 1 can align with the C-terminal phenyl ring and carboxylic acid of AII. Also, the butyl chain attached to the imidazole 2-position lies near the hydrophobic region of Ile[5]. The 2-chlorobenzyl ring of 1 is positioned to overlay the aromatic region near Tyr[4] of AII. The modeling comparison suggested that increasing the resemblance of the *N*-benzyl ring to the tyrosine by introducing polar substituents which may more closely mimic the phenol may be one avenue to increase the affinity of 1. Therefore, our initial chemical strategy for generating acrylic acid antagonists with increased potency focused on modifying the *N*-benzyl ring substitution pattern.

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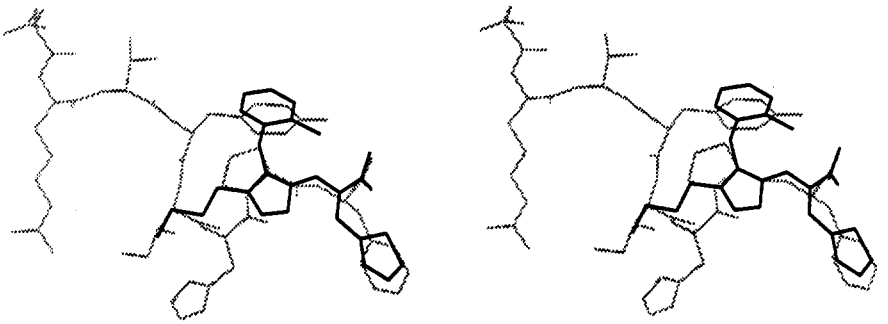


Figure 1. Stereoplot of an overlay of 1 (solid) on a postulated pharmacophore model (shaded) of angiotensin II (Asp-Arg-Val-Tyr-Ile-His-Pro-Phe).

Results and Discussion

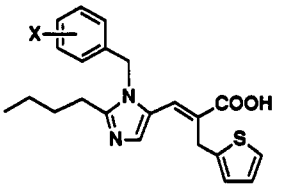
Biological Assays. As in the previous study,[1] the compounds were evaluated for activity using two different in vitro screens: competitive binding vs. radiolabelled AII in a rat mesenteric artery receptor preparation, and inhibition of AII induced vasoconstriction in isolated rabbit aorta strips.[6] Since 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 present SAR study as well. These two assays did not always correlate, and the reasons for the lack of complete correlation remain unclear. Nevertheless, the most potent compounds exhibited good activity in both assays. Finally, the more potent compounds were also examined in the conscious normotensive rat for inhibition of the in vivo pressor effect of exogenously administered AII.

***N*-Benzyl Ring Substitution.** Altering the substitution pattern on the *N*-benzyl aromatic ring proved to be a fruitful area of research. A variety of different groups were investigated and a number were found to be effective replacements for the 2-Cl in 1 (Table 1). Introduction of a hydroxy group (4) to mimic the tyrosine phenol resulted in a 10-fold improvement in binding affinity. However, analogs containing nonprotic groups such as 2,3-Cl_2 (5), 2-CN (7), and 2-NO_2 (8) also showed a similar order of magnitude increase in binding affinity. In spite of the improved in vitro binding affinity, no improvement in in vivo potency was observed for these compounds. Interestingly, substituting at the 2-position with a carboxylic acid (10), which is isoelectronic with the nitro group but has an overall negative charge, resulted in a comparatively inactive compound. Also, simple alteration of the position of a substituent on the *N*-benzyl ring appeared to profoundly influence activity, as exemplified by the difference in activity between the isomeric 2- and 3-substituted methoxy analogs (11 vs 12). This observation encouraged us to also investigate various substituents at the 4-position of the *N*-benzyl ring.

Not unexpectedly, a different pattern of activity emerged at the 4-position. Whereas the hydroxy analog 14 was still potent, the nitro analog 16 had poor activity. The 4-methoxy analog 15 exhibited improved activity in comparison to the 2- and 3-methoxy compounds. However, the most significant increase in activity was observed on attaching a carboxylic acid at the 4-position of the *N*-benzyl ring. The 4-CO_2H analog 2 (SK&F 108566) displayed nanomolar affinity for the receptor, equivalent to AII in vitro. Importantly, this dramatic increase in activity carried over in vivo, where 2 showed both enhanced potency and good oral activity in both rats and dogs.[6,7] In the carboxy-substituted series, activity decreased going from 4- to 3- to 2-substitution (cf. 2, 17, and 10), whereas the opposite trend was apparent in the isoelectronic nitro-substituted analogs (cf. 8, 9, and 16).

Some additional modifications of the *N*-benzyl ring substitution of the basic diacid structure are presented in Table II. Since an increase in affinity on going from 2-chlorobenzyl to 4-carboxybenzyl had been observed in the parent acetic acid series,[8] we attached the biphenylcarboxylic acid group which led to high affinity analogs in the Du Pont series[9] in hopes of seeing a corresponding improvement in the acrylic acid system. However, activity dropped off for this analog (20), indicating that the biphenylcarboxylate of this class of nonpeptide antagonists may not interact with the same site on the receptor as the

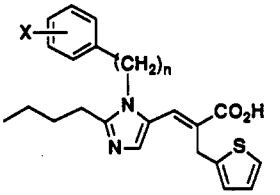
Table I. *N*-Benzyl Substitution



no.	X	IC_{50} (nM)[a]	K_b (nM)[b]	in vivo ID_{50} iv (mg/kg)[c]	mp (°C)[d]	synthetic method[e]
1	2-Cl	440	51	3.6	177–179	A + D
3	H	4530	268	NT	194–197	C + E
4	2-OH	34	90	NT	189–190	*f*
5	2,3-Cl_2	46	79	2.8	184–185	A + E
6	2-CF_3	260	51	3.4	202–203	A + D
7	2-CN	22	20	NT	210–212	B + E
8	2-NO_2	31	57	2.6	205–206	B + D
9	3-NO_2	210	47	7.0	182–184	A + D
10	2-CO_2H	6000	2250	NT	209–210	B + E
11	2-OMe	7350	870	15	186–187	A + D
12	3-OMe	180	120	8	170–171	A + D
13	2-NO_2, 3-OMe	130	24	NT	213–215	A + D
14	3-Me, 4-OH	21	33	NT	150–152	*f*
15	3-Me, 4-OMe	66	70	NT	140–141	B + D
16	4-NO_2	620	50	NT	198–200	B + D
17	3-CO_2H	3.3	11	NT	243–244	B + D
2	4-CO_2H	1.0	0.21	0.08	260–261	C + D
18	4-CN	118	230	NT	190–192	C + D
19	4-I	1035	1050	NT	190–191	A + E

[a] Inhibition of [^{125}I]AII specific binding to rat mesenteric arteries, n = 3–5, as described in ref 1. [b] Inhibition of AII-induced vasoconstriction of the rabbit aorta, n = 3–5, as described in ref 1. [c] Dose that produced 50% inhibition of the pressor response to AII in conscious normotensive rats, n = 3–4, as described in ref 1. An NT means the compound was not tested in this assay. [d] A d denotes decomposition. [e] Letter refer to procedures (Schemes I–III) for synthesis of the aldehyde + unsaturated ester intermediates. The esters were converted to the acrylic acid analogs via standard base hydrolysis unless otherwise noted. See the Experimental Section for specific details. [f] Prepared by BBr_3 hydrolysis of the corresponding methoxy compound.

Table II. 4-CO_2H Analogs



no.	X	n	IC_{50} (nM)[a]	K_b (nM)[b]	in vivo ID_{50} iv (mg/kg)[c]	mp (°C)[d]	synthetic method[e]
2	4-CO_2H	1	1.0	0.21	0.08	260–261	C + D
20	4-(2'-CO_2H-C_6H_4)	1	6.6	1.6	0.62	189–192	C + E
21	2-Cl, 4-CO_2H	1	1.45	0.02	0.06	230–231	B + E
22	3-Cl, 4-CO_2H	1	1.0	0.13	0.12	245–246	B + E
23	2,5-Cl_2, 4-CO_2H	1	35	1.6	0.68	145–146	B + E
24	3-Ph, 4-CO_2H	1	2.5	2.5	0.18	158–161	C + D
25	2-NO_2, 4-CO_2H	1	0.15	0.85	0.06	163–164	B + E
26	3-OH, 4-CO_2H	1	0.59	1.8	0.15	192–194	C + D[f]
27	3,4-$(CO_2H)_2$	1	4.6	11	0.12	204–205	C + D
28	4-CH_2CO_2H	1	60	4.8	0.84	169–171	C + E
29	4-CO_2H	2	63	74	NT	256–259d	C + E
30	4-CO_2H	0	250	26	NT	260–261	C[g] + E

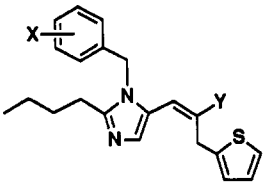
[a–e] See Table I for an explanation of tabulated data. [f] The phenol, which was protected as its MOM ether throughout the synthesis, was liberated with HCl/MeOH prior to base hydrolysis of the esters. [g] The potassium salt of 2-butylimidazole was reacted with methyl 4-fluorobenzoate to generate the *N*-phenyl-substituted imidazole. Treatment with formaldehyde then oxidation with MnO_2 furnished the requisite aldehyde.

N-benzyl carboxylate of the imidazoleacrylic acids. Retention of high affinity was sensitive to chain length at this positon as either extending the acid chain by one carbon (**28**), inserting a second methylene unit between the benzoic acid and imidazole rings (**29**), or removing a carbon (**30**) led to a dropoff in activity. On the other hand, the aromatic ring could be substituted with additional functionality with no loss of activity. The combination of the 4-carboxy with a 2-chloro (**21**) or 2-nitro (**25**) led to extremely potent compounds in both the in vitro and in vivo assays. Since in the imidazole-5-acetic acid series, the 2-chloro group on the *N*-benzyl ring caused the benzyl ring to favor an orthogonal relationship with the imidazole ring,[4] the potent imidazole-5-acrylic acids such as **2** may adopt a similar conformation at the receptor.

Acid Replacements. A number of acid replacements were investigated at both acid groups of **2** (Table III). In general, the imidazole-5-acrylic acid proved more sensitive to replacement than the benzoic acid. On the *N*-benzyl ring, the 4-carboxamide analog **31** exhibited good binding, but the corresponding esters **33** and **34** lost affinity, suggesting a polar group at the para position enhanced affinity. Conversion to the 4-tetrazole (**35**) did not generate any increase in in vivo potency when administered intravenously or orally (data not shown) although high binding affinity was retained. This acid replacement caused a 10-fold improvement in binding affinity and a remarkable improvement in oral potency in the biphenylylimidazole series,[9] revealing another divergence in the SAR for the imidazole *N*-benzyl substituents in the two series of antagonists. On the imidazole 5-side chain, both the acrylamide analog **37** and the tetrazole **40** displayed lower affinity. Whereas conversion to the bis-amide **38** led to an even larger dropoff in activity, high binding affinity returned for the bis-tetrazole **41**. Replacement of the acrylic acid with a tetrazole was also examined in analogs containing different substituents on the *N*-benzyl ring and either no change or a loss of activity was observed.

2-Alkyl Group Modifications. An examination of the SAR at the 2-position of the imidazole ring was undertaken in three different *N*-benzyl series (Table IV). In the 2-Cl series, the slight improvement in binding affinity for the

Table III. Acid Replacements



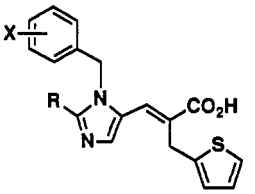
no.	X	Y	IC_{50} (nM)[a]	K_b (nM)[b]	in vivo ID_{50} iv (mg/kg)[c]	mp (°C)[d]
2	4-CO_2H	CO_2H	1.0	0.21	0.08	260–261
31	4-$CONH_2$	CO_2H	0.56	12	NT	210–212
32	4-SO_2NH_2[e]	CO_2H	4.5	25	>3.0	264–266
33	4-CO_2Me	CO_2H	39	250	NT	217–220
34	4-CO_2Et	CO_2H	27.6	13	NT	129–131
35	4-CN_4H	CO_2H	0.4	0.25	0.2	246–248
36	4-CO_2Et	CO_2Et	1270	420	NT	120–124
37	4-CO_2H	$CONH_2$	21	NT	NT	192–194
38	4-$CONH_2$	$CONH_2$	94.2	180	NT	183–185d
39	4-CO_2H	CO-Gly	4.81	1.22	NT	223–224
40	4-CO_2H	CN_4H	0.30	61.2	0.70	227–230d[f]
42	2-Cl	CN_4H	310	500	8.0	188–190[f]
43	2,3-Cl_2	CN_4H	1300	520	8.0	204–205
44	2-CF_3	CN_4H	4770	590	8.0	206–208
45	2-NO_2	CN_4H	230	360	3.5	231–234d

[a–d] See Table I for an explanation of tabulated data. [e] The sulfonamide, which was protected with a diphenylmethyl group throughout the synthesis (procedures B + E), was liberated in the final step with TFA in phenol. [f] HCl salt.

propyl (**46**) and hexyl (**47**) analogs was offset by reduced in vivo activity. Also, introduction of unsaturation (**48**) did not increase activity. Similar results were observed in the 2-NO_2 series. In the 4-carboxybenzyl series, no improvement in activity was seen for the simple propyl (**51**) or hexyl (**52**) analogs. The branched (**53**, **54**) or phenyl ring (**55**) terminated side chains, which were synthesized to hinder potential metabolism at the terminus of the alkyl side chain, showed significantly reduced affinity for the receptor.

Additional SAR. The SAR of the group appended to the acrylic acid side chain in the 4-carboxybenzyl series was generally consistent with what was observed in the less potent 2-chlorobenzyl series[1] (Table V). First, the

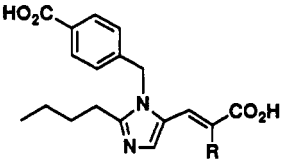
Table IV. 2-Substituted Analogs

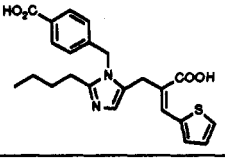


no.	R	X	IC_{50} (nM)[a]	K_b (nM)[b]	in vivo ID_{50} iv (mg/kg)[c]	mp (°C)[d]
1	*n*-butyl	2-Cl	440	51	3.6	177–79
46	*n*-propyl	2-Cl	127	90	8.1	200–202
47	*n*-hexyl	2-Cl	123	30	5.7	161–163
48	(*E*)-2-butenyl	2-Cl	570	140	NT	224–226
8	*n*-butyl	2-NO_2	31	57	2.6	205–206
49	*n*-propyl	2-NO_2	15	220	NT	225d
50	*n*-hexyl	2-NO_2	43	110	NT	187–189
2	*n*-butyl	4-CO_2H	1.0	0.21	0.08	260–261
51	*n*-propyl	4-CO_2H	5.0	3.8	0.16	250d
52	*n*-hexyl	4-CO_2H	0.80	3.2	0.60	210–212
53	isopentyl	4-CO_2H	33.6	1.61	NT	251–252
54	isobutyl	4-CO_2H	163	4.3	2.00	280–281
55	phenethyl	4-CO_2H	NT	1400	NT	213–214

[a–d] See Table I for an explanation of tabulated data.

Table V. Acrylic Acid Side Chain SAR

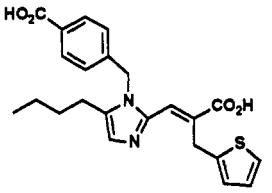


no.	R	IC_{50} (nM)[a]	K_b (nM)[b]	in vivo ID_{50} iv (mg/kg)[c]	mp (°C)[d]
2	CH_2-2-thienyl	1.0	0.1	0.08	260–261
56	H	391	97.3	NT	204–206
57	*n*-butyl	23.2	0.57	0.33	263–265
58	CH_2-2-(tetrahydrothienyl)	33.8	10.6	NT	259–264d
59	CH_2-phenyl	4.26	0.44	NT	265–267
60	CH_2CH_2-2-thienyl	3.25	0.75	0.24	244–246d
61	$C(CH_3)_3$-2-thienyl	416	53.7	NT	237–240
62[e]	CH_2-2-thienyl	363	2460	NT	
63[f]	CH_2-2-thienyl	6000	3860	NT	201–202
64[g]	CH_2-2-thienyl	53	8.7	0.24	175–176
65		470	263	>3.0	

[a–d] See Table I for an explanation of tabulated data. [e] (*Z*)-Olefin isomer. [f] Acrylic acid side chain attached to C-4 of imidazole ring. [g] Saturated olefin.

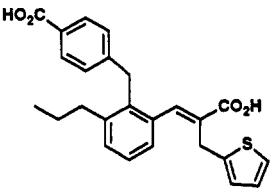
dropoff in affinity and potency for **56**, an analog lacking any substituent on the acrylic acid side chain, indicated that the 2-thienylmethyl group remained crucial for good activity in the potent diacid series. Second, analogs containing an aryl substituent on the acid side chain displayed enhanced affinity as compared to the alkyl substituted compounds. The diminished activity for the tetrahydrothienyl compound **58** demonstrated the importance of the aromatic ring at this position. Also, the one carbon extended thiophene analog **60** showed slightly diminished activity as in the 2-chlorobenzyl series. Finally, the saturated derivative **64** and the isomeric olefins **62**, **63**, and **65** all displayed lower activity, demonstrating the necessity of the rigid (*E*)-acrylic acid at C-5 of the imidazole.

The extent to which the imidazole ring contributed to the potency of the acrylic acid antagonists was investigated via the synthesis of two key analogs. The first, the isomeric imidazole **66**, in which the substituted acrylic acid is attached at C-2 and the butyl chain appended onto C-5, displayed sharply reduced binding affinity and potency in the rabbit aorta. The second, an analog in which the core imidazole was replaced by a phenyl ring (**67**), had no detectable affinity for the receptor and vastly diminshed potency. These two results taken together implicate the imidazole ring as one of the important binding groups in the potent acrylic acid series of nonpeptide AII antagonists.



66

IC_{50} = 248 nM K_b = 6.8 nM



67

IC_{50} = >10 μM K_b = 323 nM

Pharmacology. Although the pharmacology of **2** has been published in detail,[6] a few salient aspects which distinguish the imidazoleacrylic acids from other nonpeptides deserve mention. Consistent with the earlier imidazoleacrylic acid antagonists such as **1**,[1] compound **2** exhibits high selectivity for the AT-1 angiotensin receptor subtype, which is similar to the *N*-biphenylyltetrazole–imidazole class of nonpeptide AII antagonists such as DuP 753 (**68**),[9] but different than the spinacine[10] series which shows selectivity for the AT-2 receptor. Compound **2** has also been shown to be a long-acting antihypertensive agent in both the rat and dog.[7] Moreover, **2** is a purely competitive antagonist, lacking the "insurmountable" antagonism characteristic of the biphenyltetrazoles such as EXP 3174, the active metabolite associated with the prolonged duration of action of **68** observed in rats.[11]

Molecular Modeling. At the outset of our research on nonpeptide AII receptor antagonists, we proposed that the *N*-benzyl ring and carboxylic acid of the small molecules overlaid positions 4 and 8 of AII,[1] which were known to be important regions for receptor binding as well as key determinants of agonist versus antagonist activity for the octapeptides. Consistent with the fundamental premise of our original modeling hypothesis, the potent small molecule diacid **2** can be positioned to overlay the Tyr^4 and Phe^8 residues of AII (Figure 2). By slightly opening the χ^1 angle of Tyr^4 in the pharmacophore model of AII[12] the tyrosine phenol in AII can align with the *p*-carboxylic acid of **2**, which suggests that this polar group in **2** may be interacting with the same residue on the receptor as the Tyr^4 phenol in AII. The general preference for polar para substituents on the *N*-benzyl ring in the acrylic acid series is reminiscent of AII peptide agonists at Tyr^4, as methylating the tyrosine phenol is known to generate peptide antagonists.[13] The proposed overlay of **2** on this modified pharmacophore model of AII at the C-terminus remains unaffected. The acid and thiophene ring of **2** maintain their alignment with the corresponding elements of Phe^8–possibly mimicking a peptide antagonist conformation adopted by AII peptide antagonists containing a D-aryl amino acid at position 8.[1] According to this hypothesis, the acrylic acid may overlay

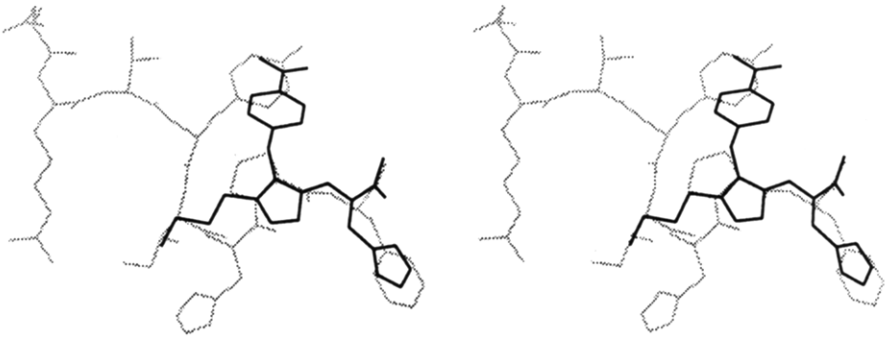


Figure 2. Stereoplot of an overlay of **2** (solid) on a postulated pharmacophore model (shaded) of angiotensin II (Asp-Arg-Val-Tyr-Ile-His-Pro-Phe).

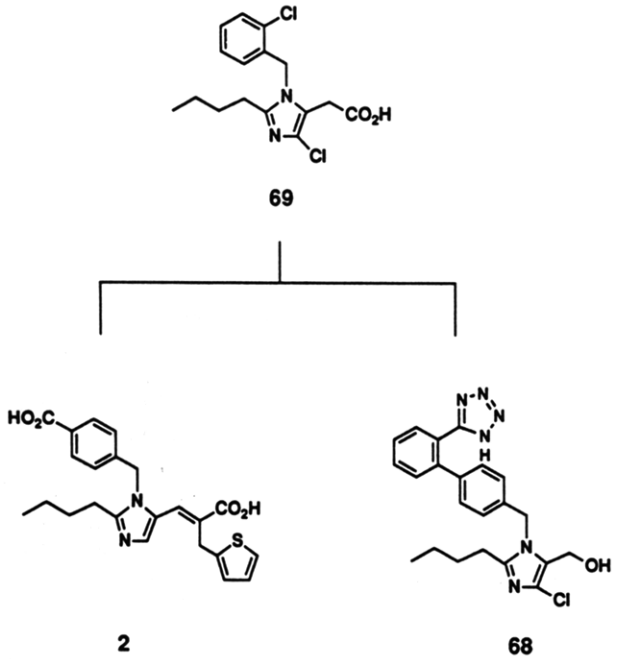


Figure 3. Comparison of **2** and **68** depicting the relationship to their common ancestor **69**.

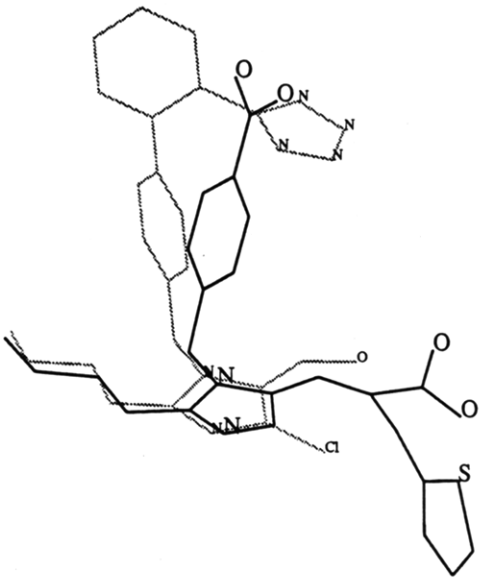


Figure 4. Overlay of butylimidazole portions of **2** (solid) and **68** (shaded).

the octapeptide in an agonist conformation at Tyr[4] and yet mimic an antagonist conformation at Phe[8]. The butyl chain of **2** extends into the hydrophobic region near Ile[5], and the imidazole ring of **2**, which was demonstrated to be crucial for high affinity, may be mimicking a binding interaction of the carbonyl of the His[6]–Pro[7] peptide bond. Thus, there are are number of possible areas of overlap with AII which may account for the observed potency of the small molecule acrylic acids.

The acrylic acids such as **2** represent a novel class of nonpeptide AII receptor antagonists, structurally distinct from the number of recently reported nonpeptide AII antagonists which contain a biphenylyltetrazole-type side chain attached to a heterocyclic core.[2,3] In addition to overlaying **2** on the native peptide AII, it is also interesting to compare it to **68**, the structural prototype of the more common biphenylyltetrazole-containing nonpeptides. Interestingly, both compounds were developed through modification of the same benzylimidazole **69** (Figure 3) originally reported in the patent literature.[5,14] One possible overlay comparison of **2** with **68** (Figure 4) is generated by lining up the butylimidazole portions of each molecule, the structural feature leftover from their common ancestor **69**. In this overlay, the benzoic acid of **2** and the tetrazole of **68** can be superimposed, and the acrylic acid of **2** and the hydroxymethyl of **68** point in the same general direction. Taking into account the known in vivo oxidation of the hydroxymethyl group of **68** to the corresponding carboxylic acid to yield an active metabolite responsible for much of the pharmacology[11] increases its resemblance to **2**. However, in this overlay comparison, **68** lacks functionality in the vicinity of the thiophene ring of **2**, and **2** likewise does not overlay the outer phenyl ring of **68**.

Another overlay comparison emphasizes the similarities in the gross structural modifications done to **69** in the development of these two distinct classes of AII receptor antagonists. In spite of clearly different design strategies by the two research groups,[15] in each series high potency was acheived by attaching an extension onto the original imidazole nucleus which contains a carboxylic acid equivalent and an aryl ring. Overlaying the two structurally related extensions, the *N*-biphenylyltetrazole of **68** and the thienylmethyl-substituted acrylic acid of **2**, furnishes the overlay depicted in Figure 5. According to this overlay, the benzoic acid portion of **2** can also be superimposed on the imidazole ring of **68**, which is substituted with a hydroxymethyl group serving as a latent carboxylic acid. This overlay comparison suffers because it does not allow the alignment of the common butyl side chains of each molecule. However, this hydrophobic portion of each molecule may interact with a large hydrophobic pocket in the AII receptor, such as the one which provides a space for the alternating hydrophobic residues of AII: Val[3], Ile[5], and Pro[7].

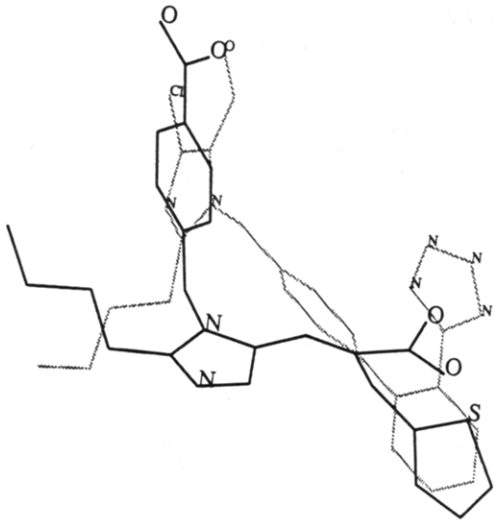
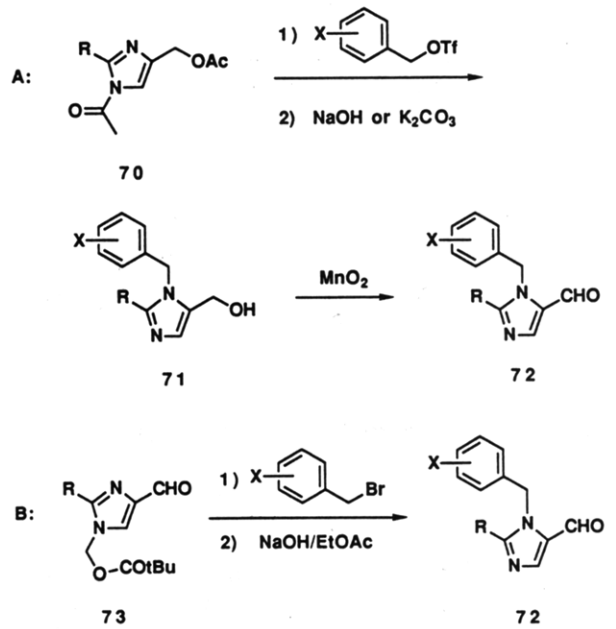


Figure 5. Overlay of extended acid side chains of **2** (solid) and **68** (shaded).

The second overlay proposal may better explain the divergence in SAR for the two structurally similar series of nonpeptide antagonists. Thus, at the para position of the *N*-benzyl ring, a second phenyl ring containing an acid or tetrazole led to improved activity in the biphenylyltetrazole series, but the 4-carboxybenzyl group proved superior in the acrylic acid series. Conversely, the thienylmethyl group attached to the imidazole-5-acrylic acid side chain is crucial for high affinity, but a simple alcohol or carboxylic acid is sufficient at this postion in the biphenylyltetrazole series. Also, if **68** aligns with **2** as in Figure 5, it could overlay our pharmacophore model of the peptide AII in an analogous fashion at the C-terminus. The tetrazole and the phenyl ring to which it is attached may mimic the Phe[8] carboxylic acid and phenyl ring, and the hydroxymethyl group on the imidazole can align with the Tyr[4] phenol. The many other nonpeptide antagonists which incorporate similar biphenylyltetrazoles attached to a heterocyclic core may align similarly with **2** and AII.

In spite of the successful use of overlay hypotheses in the development of these potent AII antagonists, it is important to recognize the limitations of such peptide pharmacophore modeling. Although the prediction by the modeling that an additional aryl ring to mimic the C-terminal phenylalanine would enhance activity proved accurate, the modeling could not predict which aryl ring system would prove most effective. It was left to synthesis of a variety of aryl ring systems to discover that the thienylmethyl-substituted acrylic acid provided the best combination of in vitro activity and in vivo potency.[1] Similarly, the discovery of the *p*-carboxylic acid on the *N*-benzyl ring was a result of an intensive analog effort around *N*-benzyl ring substituents under the general goal to mimic the tyrosine phenol. Thus, the molecular modeling proved most effective when used in conjunction with the synthesis of numerous compounds. Finally, although a provocative recent report of an X-ray crystal structure of angiotensin II bound to a high-affinity monoclonal antibody does provide some qualitative support for our pharmacophore model,[16] no conclusive physical evidence exists to support the hypothesis that the nonpeptides and the peptide interact with the same surface region of the receptor or that any of the models utilized represents an actual bioactive conformation of AII.

Scheme I. Procedures A and B for Synthesis of Imidazole-5-carboxaldehydes

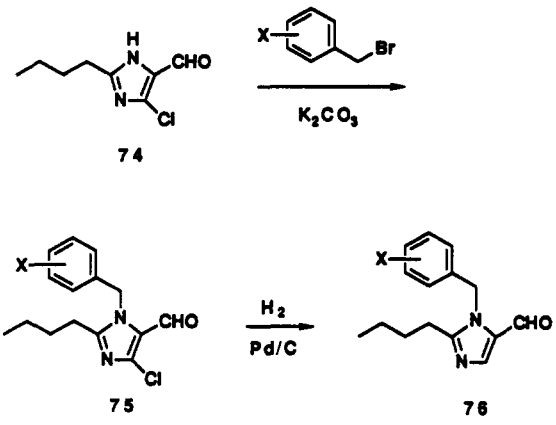


Chemistry

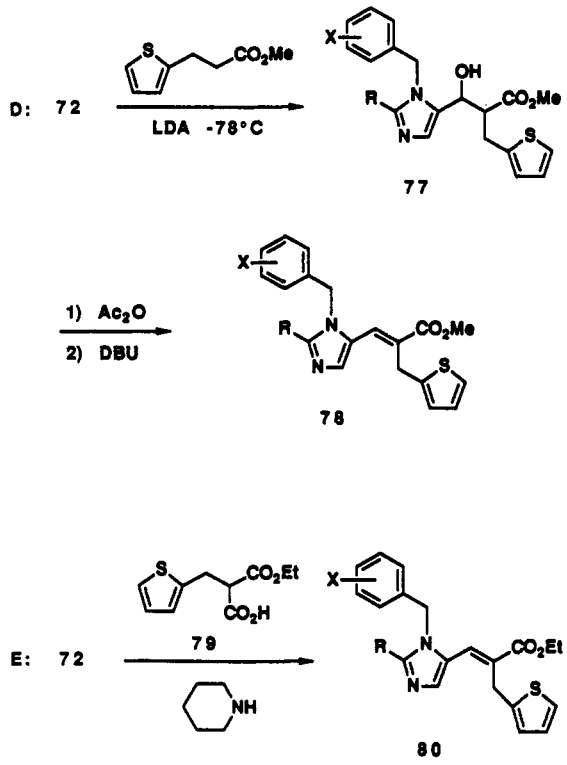
Modification of the substituents on the *N*-benzyl ring of the imidazoleacrylic acid antagonists as described in this paper required the synthesis of a variety of 1,2-disubstituted imidazole-5-carboxaldehydes. These key intermediates were obtained by regioselective N-alkylation of the imidazole ring using any of three general synthetic routes. The first two involved benzylation of an N-3 protected imidazole followed by hydrolysis of the resultant quaternary salt (Scheme I). For example, the reaction of diacetyl imidazole **70** with a benzyl triflate or mesylate[17] (procedure A), which has been described for the synthesis of *N*-(2-chlorobenzyl)-substituted imidazoles,[1] could be extended to the synthesis of other *N*-benzyl analogs. In the case of compounds containing an ester group on the benzyl ring, a mild K_2CO_3 hydrolysis was employed to selectively cleave the primary acetate intermediate. Oxidation of the resultant imidazole methyl alcohol **71** furnished the aldehyde. In a related method, the (pivaloyloxy)methyl (POM) substituted imidazolecarboxaldehyde **73** was fused with the desired benzyl bromide to form an imidazolium salt, which was treated with aqueous base to generate the properly substituted imidazolecarboxaldehyde directly (procedure B). The third route involved regioselective alkylation of the 4-chloroimidazole-5-carboxaldehyde **74** at N-1,[5,9] followed by dehalogenation (procedure C, Scheme II). Reduction of the imidazole 4-Cl could be accomplished selectively in the presence of other chloro groups on the *N*-benzyl ring. For all three of these methods, NOE measurements supported the assigned imidazole regiochemistry. Due to the ready availability of numerous benzyl halide or alcohol starting materials via conventional routes, the combined use of all of these methods provided access to a variety of *N*-benzyl ring analogs.

The imidazole-5-carboxaldehydes were converted into the corresponding acrylate esters using two different methods (Scheme III). The first (procedure D), reaction with an ester enolate followed by dehydration, has been previously described.[1] The second method (procedure E), direct condensation of the imidazole-5-carboxaldehyde

Scheme II. Procedure C



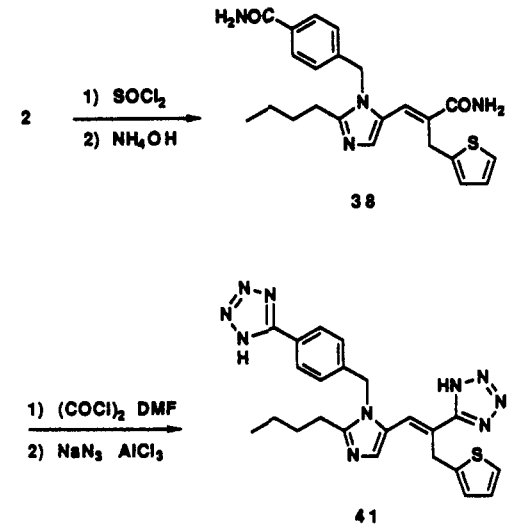
Scheme III. Procedures D and E for the Synthesis of (*E*)-Acrylic Acids



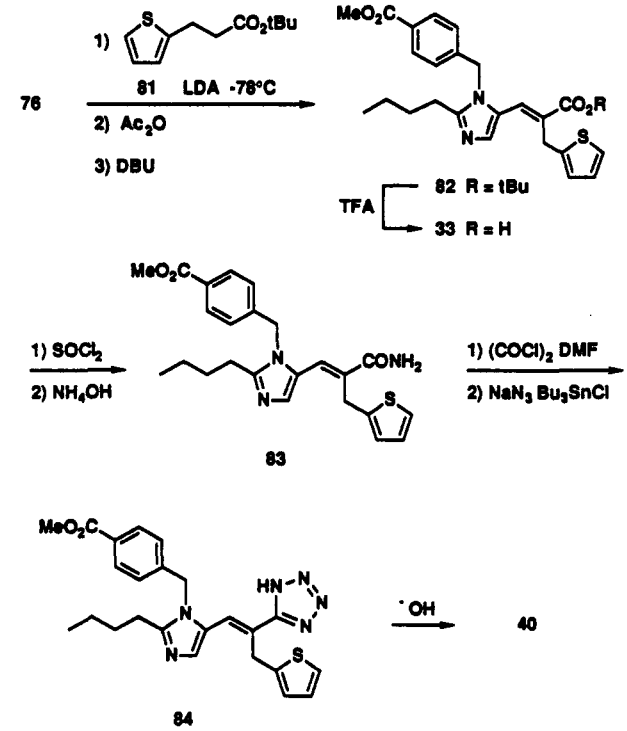
with an excess of the half-acid of ethyl (2-thienylmethyl)malonate (**79**), provided the (*E*)-acrylate in a single step. This route proved especially useful for synthesizing a variety of analogs containing the desired 2-thienylmethyl substituent. Finally, the target imidazoleacrylic acid antagonists were obtained by standard base hydrolysis of the esters.

A number of strategies were employed to synthesize the acid replacements shown in Table III. The diacid **2** was converted to the bis-acid chloride and reacted with ammonia to furnish the bis-amide **38** (Scheme IV). Dehydration with thionyl chloride/DMF gave the bis-nitrile, and heating with sodium azide and aluminum choride, the procedure normally employed for the synthesis of the other tetrazoles, yielded the bis-tetrazole **41**. In order to modify the acrylic acid in the presence of the benzoic acid, the *tert*-butyl ester **82** was synthesized (Scheme V). However, some overreaction of the *tert*-butyl ester enolate on the benzyl ring ester took place, a result not observed with the corresponding methyl ester enolate. The troublesome side product could be separated following

Scheme IV



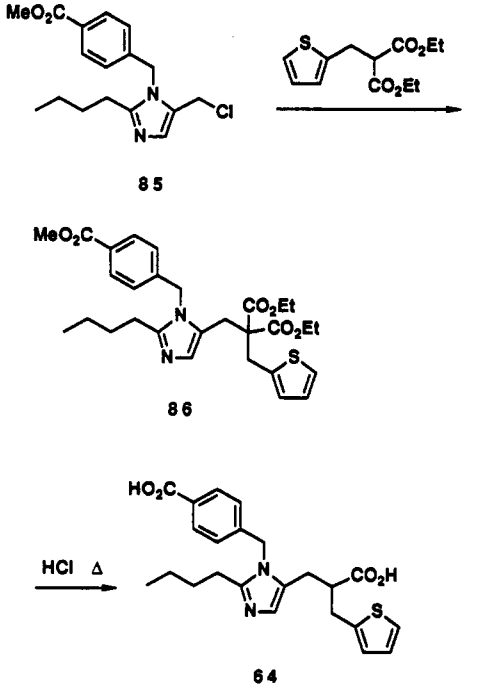
Scheme V



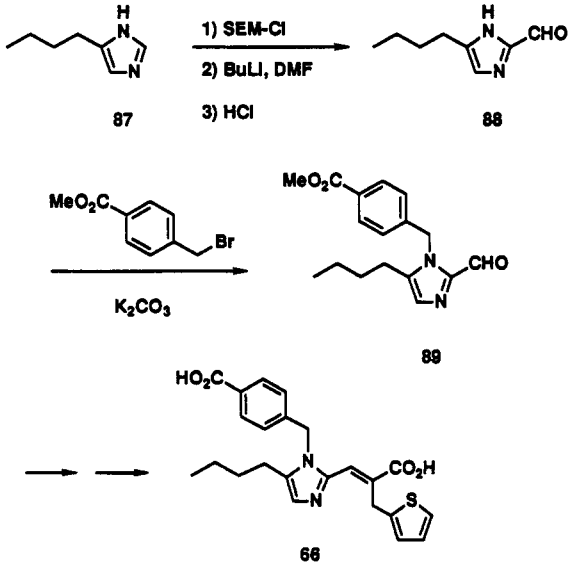
TFA hydrolysis of the *tert*-butyl ester, enabling synthesis of the monoamide and monotetrazole analogs of the acrylic acid. In this tetrazole synthesis, the use of the less reactive tributyltin azide over prolonged reaction time was required to avoid a side reaction with the methyl ester. Use of the appropriate benzyl halide starting material provided acrylic acid analogs containing selective modifications of the *N*-benzyl ring carboxylic acid. For example, the 4-carboxamide and 4-tetrazole analogs were both prepared from the benzonitrile intermediate used in the synthesis of **18**.

For the 2-substituted analogs in Table IV, the different 2-alkyl-4(5)-(hydroxymethyl)imidazoles were synthesized via a literature method[18] and converted into the requisite imidazole-5-carboxaldehyde via either procedure A or B shown in Scheme I. The 2-butenyl analog **48** was made by treatment of the 2-butylimidazole-5-carboxaldehyde with NBS followed by elimination with DBU as previously reported.[9]

Scheme VI. Synthesis of Saturated Analog



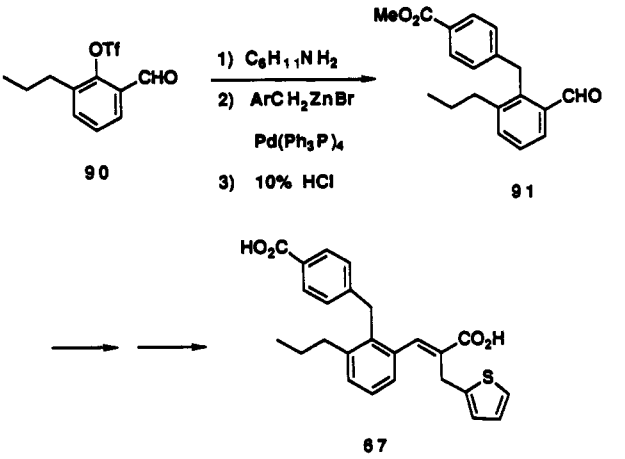
Scheme VII. Synthesis of Imidazole Regioisomer



The compounds containing various replacements for the 2-thienylmethyl group in Table V were synthesized from the appropriate ester and 2-butyl-1-(4-carbomethoxybenzyl)imidazole 5-carboxaldehyde **76** by one of the routes shown in Scheme III. The isomeric (*Z*)-acrylic acid **62** was obtained by photoisomerization of the (*E*)-acrylic acid **2** as described in the experimental section. The imidazole C-4 regioisomer **63** was made by taking on the minor product from alkylation procedure C (Scheme II). The saturated analog **64** was synthesized via the malonate intermediate **86** (Scheme VI), and the olefin regioisomer **65** was isolated from a mixture of products resulting from base hydrolysis of an acrylonitrile intermediate as described in the Experimental Section.

The reverse imidazole **66** was made by alkylation of 4(5)-*n*-butylimidazole-2-carboxaldehyde (**88**) as shown in Scheme VII. In this case, the desired 1,2,5-trisubstituted imidazole **89** was obtained as the minor component in a 4:1 mixture of regioisomers. Reaction of **89** with malonate

Scheme VIII



79 as in procedure E (Scheme III) and hydrolysis of the esters provided the target compound. NOE measurements on the intermediate diester supported the assigned 1,2,5-trisubstitued imidazole regiochemistry and (*E*)-olefin geometry. Finally, the phenyl analog **67** was made via a palladium-catalyzed coupling of the benzylzinc reagent with the aromatic triflate **90** to afford the benzaldehyde intermediate **91** in low yield (Scheme VIII). Conversion to the acrylic acid was accomplished using prodedure D (Scheme III) followed by standard ester hydrolysis.

Conclusion

Previously, investigating the proposal that the small molecule AII receptor antagonists may be overlaying both the Tyr[4] and Phe[8] regions of the peptide, we had demonstrated how extension of the acid side chain and attachment of an additional aryl residue on a literature compound to more closely resemble the phenylalanine C-terminus of AII led to the discovery of **1**. In a continuation of that study, this paper has shown how alteration of the *N*-benzyl ring substitution of **1** in an effort to more closely resemble the tyrosine of AII resulted in the discovery of the diacid **2**, an extremely potent nonpeptide angiotensin II receptor antagonist. Compound **2** has nanomolar affinity for the AT-1 angiotensin receptor, is a purely competitive antagonist, displaying none of the "insurmountable" antagonism characterisitic of other nonpeptide AII antagonists, and has good oral activity. In addition to the two acidic groups, the (*E*)-acrylic acid and the thiophene and imidazole rings of **2** have all been shown to be important for high potency. An overlay comparison of **2** with a representative biphenylylimidazole nonpeptide antagonist suggests that these two apparently similar series of antagonists may in fact be binding in a different fashion. Finally, in spite of acknowledged limitations, thinking about the relationship of the peptide and various nonpeptides in terms of overlay hypotheses has proven very helpful in accomplishing the objective of designing potent nonpeptide receptor antagonists. The work presented herein on the discovery of potent angiotensin II receptor antagonists may serve as a model for the use of peptide pharmacophore modeling in future drug design efforts.

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. Gas chromatography was performed on a CarloErba Fractovap 4160 capillary GC, using J&W DB-5 columns, with helium carrier gas, and FID detectors. Chromatography refers to flash chromatography using Kieselgel 60, 230–400-mesh silica gel.

Procedure A. (a) 1-Acetyl-4-(acetoxymethyl)-2-(2-methylpropyl)imidazole (70). 2-(2-Methylpropyl)-4(5)-(hydroxymethyl)imidazole (34.1 g, 0.22 mol) was mixed with acetic anhydride (105 mL, 1.1 mol) at 0 °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 removed under reduced pressure. The residue was taken up in ethyl acetate, washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated to give 50.9 g (97%) of **70**. NMR ($CDCl_3$): 7.23 (s, 1H), 5.02 (s, 2H), 2.92 (d, 2H, J = 7.9), 2.56 (s, 3H), 2.10 (s, 3H), 2.10 (m, 1H), 0.96 (d, 6H, J = 7.3).

(b) 2-(2-Methylpropyl)-1-[(4-carbomethoxyphenyl)methyl]-5-(hydroxymethyl)imidazole (71). To a solution of triflic anhydride (4.2 mL, 25.0 mmol) in CH_2Cl_2 (30 mL) at −78 °C was added a solution of diisopropylethylamine (4.5 mL, 25.6 mmol) and 4-carbomethoxybenzyl alcohol (4.15 g, 24.5 mmol) in CH_2Cl_2 (20 mL) over 10 min. After the mixture was stirred for an additional 30 min at −78 °C, a solution of the diacetate **70** (5.75 g, 24.1 mmol) in CH_2Cl_2 (16 mL) was added slowly. The cooling bath was removed, and the reaction mixture was stirred at room temperature for 18 h and then concentrated. The residue was dissolved in EtOAc, washed with saturated $NaHCO_3$, 5% HCl, and brine, dried (Na_2SO_4), and concentrated. The crude acetate was dissolved in MeOH (125 mL) and water (20 mL) and treated with K_2CO_3 (5.68 g, 41.1 mmol) at room temperature for 1 h. The reaction mixture was filtered, the filter cake was rinsed with MeOH, and the filtrates were concentrated. The residue was taken up in EtOAc, washed with water and brine, dried (Na_2SO_4), and concentrated. Chromatography (EtOAc/MeOH) provided the title compound (4.20 g, 58%). NMR ($CDCl_3$): 7.99 (d, 2H, J = 8.3), 7.03 (d, 2H, J = 8.3), 6.88 (s, 1H), 5.30 (s, 2H), 4.46 (s, 1H), 3.90 (s, 3H), 2.41 (d, 2H, J = 7.2), 2.03 (m, 1H), 0.88 (d, 6H, J = 7.0).

(c) 2-(2-Methylpropyl)-1-[(4-carbomethoxyphenyl)methyl]imidazole-5-carboxaldehyde (72). To the alcohol **71** (4.12 g, 13.6 mmol) in CH_2Cl_2 (150 mL) was added MnO_2 (13.4 g, 154 mmol) followed by 30-mL CH_2Cl_2 rinses. The black heterogeneous solution was stirred for 19 h at room temperature, filtered through Celite, and concentrated to afford 4.1 g (100%) of the aldehyde **72**. NMR ($CDCl_3$): 9.67 (s, 1H), 7.98 (d, 2H, J = 8.5), 7.83 (s, 1H), 7.05 (d, 2H, J = 8.5), 5.63 (s, 2H), 3.90 (s, 3H), 2.52 (d, 2H, J = 7.3), 2.13 (m, 1H), 0.92 (d, 6H, J = 6.6).

Procedure B. (a) 2-Butyl-1-[(pivaloyloxy)methyl]-1*H*-imidazole-4-carboxaldehyde (73). To a solution of 2-butyl-4(5)-(hydroxymethyl)imidazole[19] (20.0 g, 130 mmol) in CH_2Cl_2 (800 mL) was added MnO_2 (60.0 g, 690 mmol). The black heterogeneous solution was stirred for 24 h at room temperature, filtered through Celite with CH_2Cl_2 rinses, and concentrated to afford 16.2 g (82%) of the aldehyde. The aldehyde (16.2 g, 106 mmol) was suspended with K_2CO_3 (18.1 g, 131 mmol) in dry DMF (150 mL) under argon and treated with chloromethyl pivalate (Aldrich, 20.6 g, 137 mmol). The mixture was stirred at 25 °C for 22 h. The reaction mixture was filtered, and the filter cake was washed with Et_2O. The Et_2O soution was washed with H_2O (2×) and brine (1×), dried ($MgSO_4$), and concentrated to give the title compound (28 g, 99%) which was used without further purification. NMR ($CDCl_3$): 9.83 (s, 1H), 7.72 (s, 1H), 5.84 (s, 2H), 2.80 (d, 2H, J = 7.6), 1.80 (quint, 2H, J = 7.4), 1.44 (sextet, 2H, J = 7.3), 1.19 (s, 9H), 0.97 (t, 3H, J = 7.3).

(b) 2-Butyl-1-[(4-nitrophenyl)methyl]-1*H*-imidazole-5-carboxaldehyde (72). The aldehyde **73** (2.74 g, 10.3 mmol) and 4-nitrobenzyl bromide (Eastman, 2.22 g, 10.3 mmol) were heated to 100 °C to produce a freely stirring liquid solution. After 2.5 h, a solid had formed and the reaction mixture was cooled to room temperature. The solid was rinsed with ether and dried to yield 4.30 g (87%). The crude quaternary salt was taken up in water (70 mL) and EtOAc (30 mL) and treated with aqueous NH_4OH (4 mL). The EtOAc layer was washed with brine, the aqueous layers were extracted once with EtOAc, and the combined EtOAc layers were dried ($MgSO_4$) and concentrated. Chromatography (EtOAc/hexanes) provided 1.04 g (35%) of the title aldehyde. NMR ($CDCl_3$): 9.67 (s, 1H), 8.19 (d, 2H, J = 8.6), 7.84 (s, 1H), 7.17 (d, 2H, J = 8.8), 5.67 (s, 2H), 2.66 (t, 2H, J = 7.7), 1.72 (quint, 2H, J = 7.9), 1.37 (sextet, 2H, J = 7.6), 0.90 (t, 3H, J = 7.3).

Procedure C. (a) 2-Butyl-4-chloro-1-[(4-carbomethoxyphenyl)methyl]-1*H*-imidazole-5-carboxaldehyde (75). A mixture of the imidazole **74** (9.90 g, 53.0 mmol) and finely pulverized anhydrous K_2CO_3 (10.26 g, 74.2 mmol) in DMF was stirred at ambient temperature for 20 min, (4-carbomethoxyphenyl)methyl bromide (12.76 g, 55.7 mmol) was added all at once, and the mixture was heated at 70 °C in an oil bath for 1 h, cooled, and filtered. The filter cake was rinsed with ether, and the combined ethereal and DMF filtrates were washed with water (3 x 140 mL) and then with brine, dried (Na_2SO_4), and concentrated to a solid. Trituration of the solid provided 15.86 (89%) of product, mp 92–94 °C.

(b) 2-Butyl-1-[(4-carbomethoxyphenyl)methyl]-1*H*-imidazole-5-carboxaldehyde (76). A mixture of chloroaldehyde **75** (18.34 g, 54.8 mmol), 3.70 g of 10% Pd/C, KOAc (6.17 g, 62.9 mmol), and MeOH (200 mL) was hydrogenated at 40 psi on a Parr shaker for 1.25 h. The mixture was filtered through a Celite pad and then concentrated. The residue was partitioned in EtOAc–H_2O, and the pH of the mixture was adjusted to pH 8–9 with 5% aqueous Na_2CO_3. The EtOAc phase was separated, washed with water and brine, dried (Na_2SO_4), and concentrated to provide 15.74 g of the deschloro aldehyde along with some of the overreduced alcohol. The mixture was back oxidized with activated MnO_2 (31.15 g, 358 mmol) in 300 mL of refluxing CH_2Cl_2. The MnO_2 was removed by filtration, and the filtrate was evaporated to a syrup (14.50 g, 88%) which could be recrystallized from Et_2O/*n*-hexane: mp 58–60 °C. NMR ($CDCl_3$): 9.67 (s, 1H), 7.98 (d, 2H, J = 8.4), 7.81 (s, 1H), 7.06 (d, 2H, J = 8.3), 5.63 (s, 2H), 3.90 (s, 3H), 2.63 (t, 2H, J = 7.7), 1.66 (quint, 2H, J = 7.8), 1.35 (sextet, 2H, J = 7.6), 0.88 (t, 3H, J = 7.3).

Procedure D. Methyl (*E*)-3-[2-Butyl-1-[(4-carbomethoxyphenyl)methyl]imidazol-5-yl]-2-(2-thienylmethyl)-2-propenoate (78). To a solution of diisopropylamine (4.9 mL, 35 mmol) in THF (150 mL) at −78 °C under argon was added a 2.5 M solution of *n*-butyllithium in hexane (13 mL, 32.5 mmol). After 15 min, methyl 3-(2-thienyl)propionate[1] (5.7 g, 33.5 mmol) was added dropwise as a solution in THF (7 mL plus 2 × 2-mL flask rinses). The ester enolate was allowed to form over 60 min before addition of aldehyde **76** (7.44 g, 24.8 mmol) in 10 mL THF (followed by 2 × 5 mL THF flask rinses) at −78 °C via cannula. 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 once with brine. The combined aqueous layers were extracted once with ether, and the combined ether layers were dried (Na_2SO_4) and evaporated. The crude mixture of alcohols **77** was dissolved in CH_2Cl_2 (180 mL) and treated with acetic anhydride (14 mL, 148 mmol) and (dimethylamino)pyridine (1.22 g, 9.89 mmol) for 19 h under argon. Saturated aqueous $NaHCO_3$ (250 mL) was added, and the biphasic reaction mixture was stirred for approximately 15 min (until bubbling ceased). The aqueous layer was washed twice with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and evaporated. The crude acetate mixture was dissolved in toluene (180 mL) and treated with DBU (9.0 mL, 59 mmol). The reaction was heated to 100 °C under argon for 60 min, cooled to room temperature, and concentrated. The dark brown residue was taken up in ethyl acetate, washed with aqueous NH_4Cl, water, and brine, dried (Na_2SO_4), and evaporated. The residue was purified via flash chromatography (ethyl acetate/hexane) to afford 9.61 g (86%) of the diester **78**. NMR ($CDCl_3$): 8.01 (d, 2H, J = 8.6), 7.45 (s, 1H), 7.43 (s, 1H), 7.10 (dd, 1H, J = 1.1, 5.1), 7.03 (d, 2H, J = 8.7), 6.89 (dd, 1H, J = 3.4, 5.0), 6.80 (dd, 1H, J = 1.1, 3.6), 5.23 (s, 2H), 4.10 (s, 2H), 3.91 (s, 3H), 3.73 (s, 3H), 2.63 (t, 2H, J = 7.5), 1.69 (quint, 2H, J = 7.6), 1.35 (sextet, 2H, J = 7.5), 0.88 (t, 3H, J = 7.3).

(*E*)-3-[2-Butyl-1-[(4-carboxyphenyl)methyl]imidazol-5-yl]-2-(2-thienylmethyl)-2-propenoic Acid (2). The diester (8.50 g, 18.8 mmol) was dissolved in ethanol (260 mL), treated with 10% NaOH solution (100 mL) for 17 h at room temperature, diluted with water (200 mL), and acidified to pH ~5 with 10%

HCl. The white solid was collected and washed with water. Further workup of the mother liquors yielded additional solid. The two batches were combined and recrystallized (MeOH) to give 5.59 g (70%) of the diacid 2. An X-ray structural analysis confirmed the assigned imidazole regiochemistry and olefin stereochemistry. NMR ($CDCl_3$ containing CD_3OD): 7.98 (d, 2H, J = 8.3), 7.51 (s, 1H), 7.28 (s, 1H), 7.13 (dd, 1H, J = 1.0, 5.1), 7.07 (d, 2H, J = 8.3), 6.87 (dd, 1H , J = 3.5, 5.0), 6.76 (dd, 1H, J = 1.0, 3.5), 5.37 (s, 2H), 4.05 (s, 2H), 2.70 (t, 2H, J = 7.7), 1.59 (quint, 2H, J = 7.6), 1.31 (sextet, 2H, J = 7.5), 0.85 (t, 3H, J = 7.3). Anal. ($C_{23}H_{24}N_2O_4S$) C, H, N.

Procedure E. (a) 2-Carbethoxy-3-(2-thienyl)propanoic Acid (79). Diethylmalonate (146.1 g, 912.3 mmol), 2-thiophenecarboxaldehyde (101.4 g, 885.7 mmol), piperidine (11.99 mL), benzoic acid (0.23 g), and cyclohexane (630 mL) were refluxed in a flask fitted with a water separator until water ceased to be formed (20 h). The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in 300 mL of ether, washed with 3 × 75 mL 10% HCl, then with 3 × 75 mL saturated $NaHCO_3$, and finally with brine, dried (Na_2SO_4), and evaporated to provide 208.6 g (93%) of diethyl 2-thenylidenemalonate. The product was used in the next step without further purification. A stirred solution of diethyl 2-thenylidenemalonate (34.10 g, 134.0 mmol) in EtOH (150 mL) cooled to 0 °C was treated with $NaBH_4$ (2.65 g, 70.0 mmol) added in small portions over a 10-min period. The reaction was almost instantaneous. The mixture was adjusted to pH 6.0 with glacial acetic acid and filtered to remove a small amount of solid. The filtrate was concentrated, and the residue was partitioned in an Et_2O–H_2O mixture. The ethereal phase was separated, washed with water and brine, dried (Na_2SO_4), and evaporated to a syrup providing clean diethyl (2-thienylmethyl)malonate (31.60 g, 92%). NMR ($CDCl_3$), 7.15 (d, 1H, J = 5.1), 6.90 (m, 2H), 4.18 (q, 4H, J = 7.0), 3.64 (t, 1H, J = 7.2), 3.42 (d, 2H, J = 7.6), 1.24 (t, 6H, J = 7.1). A solution of 87.5% pure KOH (3.37 g, 52.28 mmol) in EtOH (80 mL) was added dropwise over 1 h to a stirred solution of diethyl (2-thienylmethyl)malonate (13.69 g, 52.58 mmol) in EtOH (40 mL). The mixture was stirred at ambient temperature for 48 h and concentrated. The residue was dissolved in water (40 mL), washed with ether, and then acidified (pH 1.0) with 2 N H_2SO_4. The product was extracted with ether, washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo to a syrup 11.12 g (91%). NMR ($CDCl_3$): 7.15 (d, 1H, J = 5.1), 6.92 (m, 2H), 4.18 (q 2H, J = 7.0), 3.63 (t, 1H, J = 7.3), 3.42 (d, 2H, J = 7.6), 1.24 (t, 3H, J = 7.1).

(b) Ethyl (*E*)-3-[2-Butyl-1-[(4-carbomethoxyphenyl)methyl]imidazol-5-yl]-2-(2-thienylmethyl)-2-propenoate (80). 2-Butyl-1-[(2-carbomethoxyphenyl)methyl]-1*H*-imidazole-5-carboxaldehyde (2.16 g, 7.47 mmol), **79** (5.12 g, 22.4 mmol), piperidine (0.51 g, 5.98 mmol), and a trace of benzoic acid in toluene (100 mL) were heated to reflux for 18 h under argon, using a Dean–Stark trap to remove water. The mixture was concentrated under reduced pressure, and the residue was chromatographed to provide the desired acrylate ester (1.34 g, 40%). NMR ($CDCl_3$): 8.12 (dd, 1H, J = 7.4, 1.3), 7.46, (s, 1H), 7.37 (m, 2H), 7.33 (s, 1H), 7.09 (d, 1H, J = 5.1), 6.88 (dd, 1H, J = 3.5, 5), 6.81 (d, 1H, J = 3.5), 6.35 (d, 1H, J = 7.2), 5.60 (s, 2H), 4.15 (q, 2H, J = 7.1), 4.11 (s, 2H), 3.98 (s, 3H), 2.55 (t, 2H, J = 7.7), 1.66 (quint, 2H, J = 7.8), 1.23 (sext, 2H, J = 7.5), 1.17 (t, 3H, J = 7.1), 0.85 (t, 3H, J = 7.4).

(*E*)-3-[2-Butyl-1-[(4-carboxamidophenyl)methyl]imidazol-5-yl]-2-(2-thienylmethyl)-2-propenamide (38). To a suspension of the diacid 2 (0.81 g, 1.91 mmol) in benzene (10 mL) was added thionyl chloride (1.63 g, 13.7 mmol). The resultant mixture was heated to 55 °C for 2.5 h and then evaporated to an oily residue. The residue was twice taken up in hexanes and evaporated again. The solid acid chloride was added to concentrated NH_4OH (40 mL), broken up with a spatula, and the suspension was stirred for 1.5 h at room temperature. The solid was filtered, washed with water, and dried to yield 0.81 g (100%) of the bis-amide 38. NMR ($CDCl_3$ containing CD_3OD): 7.86 (d, 2H, J = 8.5), 7.26 (s, 1H), 7.22 (s, 1H), 7.20 (dd, 1H, J = 1.0, 5.1), 7.08 (d, 2H, J = 8.3), 6.93 (dd, 1H, J = 3.5, 5.0), 6.83 (dd, 1H, J = 1.0, 3.5), 5.36 (s, 2H), 4.11 (s, 2H), 2.68 (t, 2H, J = 7.4), 1.63 (quint, 2H, J = 7.6), 1.35 (sextet, 2H, J = 7.5), 0.87 (t, 3H, J = 7.4). Anal. ($C_{23}H_{26}N_4O_2S \cdot {}^1/_4H_2O$) C, H, N.

(*E*)-3-[2-Butyl-1-[[4-(tetrazol-5-yl)phenyl]methyl]imidazol-5-yl]-1-(2-thienyl)-2-(5-tetrazoyl)-2-propene (41). To a solution of DMF (0.62 mL, 8.00 mmol) in acetonitrile (15 mL) was added oxalyl chloride (0.66 mL, 7.41 mmol) at 0 °C under argon. Bubbling was observed, followed by formation of a white precipitate. Three minutes later, a solution of the bis-amide 38 (0.81 g, 1.91 mmol) in DMF (8 mL) was added via cannula, followed by 2 × 1-mL flask rinses, and the reaction became homogeneous. Five minutes later, pyridine (1.20 mL, 14.8 mmol) was added; the reaction mixture was stirred for an additional 5 min at 0 °C and then partitioned between ethyl acetate and 50% aqueous NH_4Cl. The ethyl acetate layer was washed with water and brine. The combined aqueous layers were extracted once with ethyl acetate. The ethyl acetate extracts were combined, dried (Na_2SO_4), and concentrated. Flash chromatography (ethyl acetate/hexanes) afforded 0.70 g (95%) of the bis-nitrile. NMR ($CDCl_3$): 7.67 (d, 2H, J = 8.3), 7.41 (s, 1H), 7.22 (dd, 1H, J = 1.3, 5.0), 7.03 (d, 2H, J = 8.6), 6.95 (m, 2H), 6.76 (s, 1H), 5.21 (s, 2H), 3.97 (s, 2H), 2.64 (t, 2H, J = 7.4), 1.70 (quint, 2H, J = 7.8), 1.36 (sextet, 2H, J = 7.6), 0.89 (t, 3H, J = 7.3). $AlCl_3$ (0.94 g, 7.05 mmol) was added at 0 °C with stirring to a mixture of the bis-nitrile (0.70 g, 1.80 mmol) in THF (10 mL). NaN_3 (2.11 g, 32.1 mmol) was added all at once, followed by a 2-mL THF rinse, and the reaction was heated to 65 °C for 20 h and then cooled to room temperature. The reaction mixture was diluted with ethyl acetate (20 mL) and treated with 10% HCl (20 mL) with vigorous stirring for 5 min. The ethyl acetate layer was washed with water and brine. The combined aqueous layers were extracted once with ethyl acetate. The ethyl acetate layers were combined, dried (Na_2SO_4), and concentrated. The solid residue was recrystallized (ethyl acetate/methanol) to furnish 0.39 g (42%) of the tetrazole hydrochloride 41. NMR ($CDCl_3$ containing CD_3OD): 8.04 (d, 2H, J = 8.4), 7.69 (d, 1H, J = 0.9), 7.50 (d, 1H, J = 0.8), 7.38 (d, 2H, J = 8.4), 7.18 (dd, 1H, J = 1.1, 5.1), 6.85 (dd, 1H, J = 3.4, 5.1), 6.72 (dd, 1H, J = 1.1, 3.4), 5.68 (s, 2H), 4.39 (s, 2H), 3.11 (t, 2H, J = 7.4), 1.70 (quint, 2H, J = 7.8), 1.43 (sextet, 2H, J = 7.6), 0.94 (t, 3H, J = 7.3). Anal. ($C_{23}H_{24}N_{10}S \cdot HCl$) C, H, N.

***tert*-Butyl 3-(2-Thienyl)propanoate (81).** To a suspension of NaH (2.55 g, 103 mmol) in DME (200 mL) was added *tert*-butyl *P,P*-dimethylphosphonoacetate (Fluka, 25 g, 106 mmol) at 0 °C. The mixture stirred at room temperature for 30 min as the bubbling gradually ceased before addition of 2-thiophenecarboxaldehyde (Aldrich, 11.5 g, 101 mmol). After 2.5 h, the heterogeneous reaction mixture was poured into 400 mL of ice and stirred vigorously for 5 min. The aqueous layer was diluted with brine and extracted with ethyl acetate. The combined ethyl acetate extracts were dried ($MgSO_4$) and concentrated. Chromatography (ether/hexanes) furnished the unsaturated ester (18.6 g, 88%), which was dissolved in EtOAc (150 mL), treated with 10% Pd/C (1.6 g), and hydrogenated on the Paar apparatus at 50 psi for 6 h. 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), treated with 10% Pd/C (1.3 g), and hydrogenated for 12 h as before. Filtration and concentration gave 18.0 g (96%) of the title compound. NMR ($CDCl_3$): 7.13 (dd, 1H, J = 1.0, 5.1), 6.90 (dd, 1H, J = 3.5, 5), 6.82 (dd, 1H, J = 1.0, 3.5), 3.12 (t, 2H, J = 7), 2.59 (t, 2H, J = 7).

(*E*)-3-[2-Butyl-1-[(4-carbomethoxyphenyl)methyl]imidazol-5-yl]-2-(2-thienylmethyl)-2-propenoic Acid (33). To a solution of diisopropylamine (2.0 mL, 14.3 mmol) in THF (75 mL) was added a 2.5 M solution of *n*-BuLi in hexanes (5.4 mL, 13.5 mmol) at −78 °C. After 15 min, a solution of ester 81 (2.87 g, 13.5 mmol) in THF (8 mL) was added dropwise via cannula over 15 min and rinsed in with 2 mL of THF. The ester enolate was allowed to form for 30 min at −78 °C, and then a solution of aldehyde **76** (3.76 g, 12.5 mmol) in THF (14 mL) was added rapidly. The reaction was stirred an additional 5 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 the aldol product along with traces of starting aldehyde. The crude residue was dissolved in CH_2Cl_2 (100 mL) and treated with acetic anhydride (6.0 mL, 63.6 mmol) and DMAP (0.62 g, 5.0 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 (100 mL) and treated with DBU (4.6 mL, 30.1 mmol). The reaction was heated to 110 °C for 40 min, cooled to room temperature, and concentrated. The dark brown residue was taken up in EtOAc and washed with water and brine. The EtOAc layer was dried (Na_2SO_4) and concentrated. Chromatography (EtOAc/hexanes) yielded 3.44 g of the desired diester **82** contaminated with the product of further attack of the *tert*-butyl ester enolate on the benzoate ester. The crude diester **82** was dissolved in CH_2Cl_2 (65 mL) and treated with TFA (22 mL) for 5 h at room temperature. The reaction mixture was concentrated and taken up in CH_2Cl_2 and 5% $NaHCO_3$. After the bubbling had ceased, the aqueous layer was neutralized with 10% HCl and washed repeatedly with CH_2Cl_2. The organic washes were dried (Na_2SO_4) and concentrated to leave 2.61 g of crude solid. Recrystallization from EtOH afforded 1.18 g (22% overall from the aldehyde) of pure monoester **33**. NMR ($CDCl_3$ containing CD_3OD): 8.02 (d, 2H, J = 8.5), 7.53 (s, 1H), 7.31 (s, 1H), 7.18 (dd, 1H, J = 1.0, 5.1), 7.11 (d, 2H, J = 8.3), 6.89 (dd, 1H, J = 3.5, 5), 6.79 (dd, 1H, J = 1.0, 3.5), 5.39 (s, 2H), 4.06 (s, 2H), 3.90 (s, 3H), 2.72 (t, 2H, J = 7.4), 1.62 (quint, 2H, J = 7.3), 1.35 (sextet, 2H, J = 7.5), 0.88 (t, 3H, J = 7.4). Anal. ($C_{25}H_{28}N_2O_2S \cdot 0.75H_2O$) C, H, N.

(*E*)-3-[2-Butyl-1-[(4-carbomethoxyphenyl)methyl]imidazol-5-yl]-2-(2-thienylmethyl)-2-propenamide (83). To a suspension of the acid **33** (1.18 g, 2.7 mmol) in benzene (35 mL) was added thionyl chloride (4.89 g, 41 mmol). The resultant mixture was heated to 55 °C for 2.5 h and then evaporated to an oily residue. The residue was taken up in hexanes and evaporated again. The solid acid chloride was added to concentrated NH_4OH (30 mL) and broken up with a spatula, and the suspension was stirred for 1 h at room temperature. The solid was filtered, washed with water, and dried to yield 1.15 g (98%) of the ester amide **83**. NMR ($CDCl_3$ containing CD_3OD): 8.00 (d, 2H, J = 8.5), 7.49 (s, 1H), 7.40 (s, 1H), 7.20 (dd, 1H, J = 1.0, 5.1), 7.02 (d, 2H, J = 7.3), 6.93 (dd, 1H, J = 3.5, 5.0), 6.86 (dd, 1H, J = 1.0, 3.5), 5.54 (bs, 2H), 5.23 (s, 2H), 4.09 (s, 2H), 3.91 (s, 3H), 2.62 (t, 2H, J = 7.4), 1.68 (quint, 2H, J = 7.3), 1.37 (sextet, 2H, J = 7.5), 0.87 (t, 3H, J = 7.4). Basic hydrolysis of the methyl ester with 10% NaOH in EtOH furnished the acid amide **37** in 40% yield. Anal. ($C_{23}H_{25}N_3O_3S \cdot 0.25H_2O$) C, H, N.

(*E*)-3-[2-Butyl-1-[(4-carboxyphenyl)methyl]imidazol-5-yl]-1-(2-thienyl)-2-(5-tetrazolyl)-2-propene (40). To a solution of DMF (0.44 mL, 5.68 mmol) in acetonitrile (20 mL) was added the oxalyl chloride (0.46 mL, 5.17 mmol) at 0 °C under argon. Bubbling was observed, followed by formation of a white precipitate. Three minutes later, a solution of the amide **83** (1.14 g, 2.61 mmol) in DMF (25 mL) was added via cannula, followed by 2 × 2-mL flask rinses, and the reaction became homogeneous. Five minutes later, pyridine (0.85 mL, 10.5 mmol) was added; the reaction mixture was stirred for an additional 5 min at 0 °C and then partitioned between ethyl acetate and 50% aqueous NH_4Cl. The ethyl acetate layer was washed with water and brine. The combined aqueous layers were extracted once with ethyl acetate. The ethyl acetate extracts were combined, dried (Na_2SO_4) and concentrated. Flash chromatography (ethyl acetate/hexanes) afforded 0.86 g (78%) of the nitrile. NMR ($CDCl_3$): 8.04 (d, 2H, J = 8.5), 7.39 (s, 1H), 7.12 (dd, 1H, J = 1.0, 5.1), 6.96 (m, 4H), 6.81 (s, 1H), 5.20 (s, 2H), 3.98 (s, 2H), 3.95 (s, 3H), 2.67 (t, 2H, J = 7.7), 1.71 (quint, 2H, J = 7.5), 1.38 (sextet, 2H, J = 7.4), 0.89 (t, 3H, J = 7.5). To a solution of NaN_3 (234 mg, 3.60 mmol) in toluene (2 mL) was added tributyltin chloride (1.20 g, 3.54 mmol) dropwise at room temperature. After 10 min, a solution of the nitrile (416 mg, 0.99 mmol) in toluene (4 mL) was added, and the reaction mixture was heated to 100 °C for 6 days, cooled to room temperature, treated with 10:1 MeOH/1N HCl (8 mL) for 2 h, diluted with ethyl acetate, washed with water and brine, dried (Na_2SO_4), and concentrated. The crude solid residue was rinsed with ether (3×) and then ethyl acetate to afford the ester–tetrazole **84** (413 mg, 83%). Ester hydrolysis with 10% aqueous NaOH in EtOH gave the title acid–tetrazole **40** in 50% yield. NMR ($CDCl_3$ containing CD_3OD): 8.00 (d, 2H, J = 8.5), 7.49 (s, 1H), 7.48 (s, 1H), 7.16 (m, 3H), 6.86 (dd, 1H, J = 3.5, 5.0), 6.74 (dd, 1H, J = 1.0, 3.5), 5.50 (s, 2H), 4.39 (s, 2H), 2.73 (t, 2H, J = 7.7), 1.62 (quint, 2H, J = 7.5), 1.37 (sextet, 2H, J = 7.4), 0.89 (t, 3H, J = 7.5). Anal. ($C_{23}H_{24}N_6O_2S \cdot 0.25H_2O$) C, H, N.

(*Z*)-3-[2-Butyl-1-[(4-carboxyphenyl)methyl]imidazol-5-yl]-2-(2-thienylmethyl)-2-propenoic Acid (62). A solution of 1.0 g (2.3 mmol) of diacid **2** in methanol (220 mL) was irradiated with a 100-W medium-pressure mercury lamp housed in a water-cooled Pyrex vessel. The reaction was followed by HPLC. After 1 h, the reaction mixture contained a 2:1 mixture of **2** and **62**. Continued irradiation did not change the isomer ratio. The solvent was removed, affording 1.0 g of an orange solid which was treated with diazomethane to form a mixture of methyl esters. Chromatography (ethyl acetate/hexanes) followed by standard base hydrolysis resulted in the isolation of **62**. NMR ($CDCl_3$): 7.95 (d, 2H), 7.65 (s, 1H), 7.34 (d, 1H), 7.14 (d, 2H), 6.91 (m, 1H), 6.70 (d, 1H), 6.64 (s, 1H), 5.44 (s, 2H), 3.84 (s, 2H), 2.72 (t, 2H), 1.58 (m, 2H), 1.33 (m, 2H), 0.87 (t, 3H).

2-Butyl-1-[(4-carbomethoxyphenyl)methyl]-5-(chloromethyl)imidazole Hydrochloride (85). Thionyl chloride (7.5 mL, 103 mmol) was added cautiously (exothermic reaction) to 2-butyl-1-[(4-carbomethoxyphenyl)methyl]-5-(hydroxymethyl)imidazole (**71**) (1.51 g, 49.9 mmol). The mixture was heated for 45 min on a steam bath, cooled, diluted with Et_2O (30 mL), and then concentrated. The Et_2O treatment was repeated twice. The resulting solid was collected by filtration and air-dried to provide 1.76 g (99%) of product: mp 151–153 °C. NMR ($CDCl_3$): 8.08 (d, 2H, J = 8.2), 7.56 (s, 1H), 7.13 (d, 1H, J = 8.2), 5.51 (s, 2H), 4.53 (s, 2H), 3.94 (s, 3H), 3.04 (dd, 2H, J = 8.1, 7.6), 1.75 (quint, 2H, J = 8.0), 1.36 (sextet, 2H, J = 7.5), 0.87 (t, 3H, J = 7.2).

(*R,S*)-Ethyl 3-[2-Butyl-1-[(4-carbomethoxyphenyl)methyl]-1*H*-imidazol-5-yl]-2-(2-thienylmethyl)-2-carbethoxypropanoate (86). Diethyl (2-thienylmethyl)malonate (2.68 g, 10.45 mmol) was added over a 5-min period to a stirred suspension of 97% sodium hydride (0.245 g, 10.21 mmol) in anhydrous DMF (25 mL) under argon. The mixture was stirred for 2 h at ambient temperature, and then a solution of (chloromethyl)imidazole hydrochloride **85** (1.76 g, 499 mmol) in anhydrous DMF (10 mL) was added over a 10-min period. After 18 h the mixture was filtered to remove the NaCl. The NaCl cake was washed with ether and combined with the DMF filtrate (total volume 130 mL). This mixture was washed with 3 × 50 mL of water to remove the DMF and then extracted with 4 × 25 mL of 6 N HCl. The aqueous extract was washed with ether, cooled in an ice bath, and adjusted to pH 9–10 with 50% NaOH. The product was extracted with ether, washed with water and brine, dried (Na_2SO_4), and concentrated to provide the malonic ester **86** (2.28 g, 84%) as a syrup. NMR ($CDCl_3$): 7.94 (d, 2H, J = 8.5), 7.10 (d, 1H, J = 5.1), 6.86 (s, 1H), 6.85 (d, 2H, J = 8.3), 6.82 (m, 1H), 6.60 (d, 1H, J = 3.4), 5.00 (s, 2H), 4.18 (q, 4H, J = 7.4), 3.90 (s, 3H), 2.97 (s, 2H), 2.54 (t, 2H, J = 7.4), 1.66 (quint, 2H, J = 7.3), 1.33 (sextet, 2H, J = 7.3), 1.22 (t, 6H, J = 7.2), 0.87 (t, 3H, J = 7.3).

(*R,S*)-3-[2-Butyl-1-[(4-carboxyphenyl)methyl]-1*H*-imidazol-5-yl]-2-(2-thienylmethyl)propanoic Acid (64). The malonic ester **86** (1.03 g, 19.05 mmol) and concentrated HCl (25 mL) were heated to reflux for 24 h and then concentrated to a foam. The foam was dissolved in acetone and evaporated to dryness (2×), and then the material was triturated in ether to give 0.88 g of the hydrochloride salt, which formed a foam. The salt was redissolved in water, adjusted to pH 10 with 10% aqueous NaOH, and then readjusted, carefully, to pH 4.0 with 6 N HCl to precipitate the diacid, which was collected by filtration to give 0.53 g (65%) of the title compound. NMR (DMSO-d_6): 7.94 (d, 2H, J = 8.3), 7.30 (d, 1H, J = 5.1), 6.99 (d, 2H, J = 8.3), 6.87 (dd, 1H, J = 3.3, 5.1), 6.74 (d, 1H, J = 3.4), 6.67 (s, 1H), 5.17 (s, 2H), 2.97–2.51 (m, 3H), 1.50 (quint, 2H, J = 7.3), 1.25 (sextet, 2H, J = 7.3), 0.78 (t, 3H, J = 7.3). Anal. ($C_{23}H_{26}N_2O_4S$) C, H, N.

(*Z*)-2-[[2-Butyl-1-[(4-carboxyphenyl)methyl]imidazol-5-yl]methyl]-3-(2-thienyl)-2-propenoic Acid (65). Reaction of aldehyde **76** with 2-(thienylmethyl)cyanoacetic acid according to procedure E as described for the synthesis of **80** gave a mixture of (*E*)- and (*Z*)-cyano olefins. A solution of this mixture (10.0 g, 23.9 mmol) in MeOH (480 mL) was treated with 25% NaOH (240 mL) over 15 min and refluxed for 18 h. The mixture was

cooled, washed with EtOAc (500 mL) and acidified to pH = 3 with 6N HCl. The products were extracted from the aqueous layer with EtOAc (2 × 500 mL) and the organic extracts were washed with brine, dried ($MgSO_4$) and concentrated to a mixture of **2** and **65**. The mixture was treated with diazomethane and the diester isomers were separated by chromatography (EtOAc/hexanes) to afford the desired dimethyl ester (4.9 g, 45%). Base hydrolysis and recrystallization (EtOAc) afforded the title compound. NMR ($CDCl_3$): 7.87 (s, 1H), 7.81 (d, 2H), 7.53 (d, 1H), 7.22 (d, 1H), 7.17 (d, 2H), 7.01 (s, 1H), 6.94 (t, 1H), 5.50 (s, 2H), 3.58 (s, 2H), 2.83 (t, 2H), 1.42–1.35 (m, 2H), 1.20–1.10 (m, 2H), 0.63 (t, 3H).

4(5)-*n*-Butylimidazole (87). Bromine (122.60 g, 767 mmol) was added dropwise (1.5 h) to a stirred solution of hexanal (76.07 g, 759 mmol) and dioxane (2.59 mL, 30.4 mmol) in Et_2O (300 mL) cooled to 0 °C.[20] The bromine was consumed instantly forming a colorless solution, and toward the end of the addition a yellow color persisted. The mixture was neutralized with a saturated aqeuous Na_2CO_3 solution. The ethereal portion was separated, dried (Na_2SO_4), and concentrated to provide 126.09 (93%) of product as a pale yellow liquid. The material was used in the next step with further purification. A heterogeneous mixture of 2-bromohexanal (126.0 g, 704 mmol) and formamide (240 mL) was heated at 185 °C for 8 h in an oil bath.[21] The excess formamide was distilled at aspirator pressure (bp 100–106 °C). Water (900 mL) was added to the cooled residue, the pH was adjusted to 8–9 with solid Na_2CO_3, and the product was extracted with EtOAc. The EtOAc extract was washed with water and brine, dried (Na_2SO_4), and concentrated under reduced pressure to an amber syrup (62.6 g, 72%) of crude product. Kugelrohr distillation provided 24.7 g of product: bp (0.1 mm) 110–115 °C, which solidified into a waxy solid. NMR ($CDCl_3$): 7.56 (s, 1H), 6.78 (s, 1H), 2.62 (t, 2H, J = 7.8), 1.62 (quint, 2H, J = 7.5), 1.34 (sextet, 2H, J = 7.1), 0.91 (t, 3H, J = 7.1).

4(5)-*n*-Butylimidazole-2-carboxaldehyde (88). A solution of 4(5)-*n*-butylimidazole (5.54 g, 44.61 mmol) in dry THF (20 mL) was added slowly to a stirred suspension of dry NaH (1.18 g, 49.07 mmol) in dry THF (20 mL), under argon. The mixture was stirred at ambient temperature until gas evolution ceased (~1 h). The mixture was cooled to 0 °C in an ice bath, and SEM-Cl (7.81 g; 46.84 mmol) was added dropwise over a 20 min period. The mixture was stirred for 0.5 h in the cold and then at ambient temperature for 1 h, evaporated in vacuo, and the residue was partitioned in Et_2O–H_2O mixture. The ethereal phase was separated, washed with water and brine, dried (Na_2SO_4), and concentrated to provide crude product consisting of a mixture of the two regioisomers. Combination with another run and distillation afforded 6.63 g of a fraction: bp (0.05 mm) 97–100 °C, consisting of a 5:1 mixture of 4-butyl- and 5-butyl-1-[[2-(trimethylsilyl)ethoxy]methyl]imidazoles which was used without separation. A solution of 2.5 M *n*-butyllithium in hexane (10.3 mL, 25.9 mmol) was added over a 15-min period to a stirred solution of the mixture of 4- and 5-butyl-1-[[2-(trimethylsilyl)-ethoxy]methyl]imidazoles (6.58 g, 25.9 mmol) in anhydrous THF (100 mL) at −40 °C under argon. The light orange mixture was stirred for 20 min, and then anhydrous DMF (1.89 g, 20 mL, 25.9 mmol) was added over a 15-min period. The reaction was stirred for 18 h at ambient temperature, quenched with 60 mL of saturated NH_4Cl, stirred vigorously for a few minutes, and then separated into two phases. The aqueous phase was extracted with Et_2O, and the Et_2O extract was combined with the organic phase and concentrated. The residue was dissolved in Et_2O, washed with water and brine, dried (Na_2SO_4), and concentrated to provide 7.18 g (98%) of crude product. Chromatography (85:15 *n*-hexane–EtOAc) provided 5.95 g (81%) of a 5:1 mixture of 4-butyl- and 5-butyl-1-[[2-(trimethylsilyl)ethoxy]methyl]imidazole-2-carboxaldehydes which was used without separation. A stirred solution of the mixture of imidazole-2-carboxaldehydes (4.36 g, 15.4 mmol) in 50 mL of 3 N HCl and 20 mL of MeOH was heated at 80 °C in an oil bath for 2.5 h and concentrated, and the residue was partitioned in EtOAc–H_2O. Aqueous Na_2CO_3 (5%) was added to adjust the pH to 8–9. The organic phase was separated, washed with water and brine, dried (Na_2SO_4), and concentrated to provide 2.26 g (96%) of the title compound as a powdery solid. NMR (DMSO-d_6 with D_2O): 9.45 (s, 1H), 7.10 (s, 1H), 2.50 (t, 2H, J = 7.8), 1.46 (quint, 2H, J = 7.5), 1.20 (sextet, 2H, J = 7.2), 0.79 (t, 3H, J = 7.3).

5-*n*-Butyl-1-[(4-carbomethoxyphenyl)methyl]imidazole-2-carboxaldehyde (89). The aldehyde was alkylated as described in procedure C with 4-(carbomethoxyphenyl)methyl bromide providing a 5.93 g (92%) of a mixture of regioisomers. Chromatography (*n*-hexane–EtOAc, 8:2) provided 4.06 g of the 4-butyl isomer and 1.12 g of the desired 5-butyl isomer. NMR ($CDCl_3$): 9.77 (s, 1H), 7.99 (d, 2H, J = 8.5), 7.23 (d, 2H, J = 8.6), 6.92 (s, 1H), 5.62 (s, 2H), 3.90 (s, 3H), 2.62 (t, 2H, J = 7.3), 1.65 (quint, 2H, J = 7.3), 1.36 (sextet, 2H, J = 7.5), 0.93 (t, 3H, J = 7.8).

3-Propyl-2-[(trifluoromethyl)sulfonoxy]benzaldehyde (90). A mixture of 3-allylsalicylaldehyde (Lancaster, 7.67 g, 45.9 mmol) and 5% Pd/C (0.79 g) in MeOH (100 mL) was hydrogenated on the Parr apparatus at 40 psi for 10 min. The reaction mixture was filtered through Celite with EtOAc rinses and concentrated. TLC and NMR analysis indicated a trace of overreduction to the benzyl alcohol. The mixture was dissolved in CH_2Cl_2 (120 mL), treated with MnO_2 (19.1 g, 220 mmol) for 19 h at room temperature, filtered through Celite, and concentrated to furnish 6.58 g (87%, 40.1 mmol) of 3-propyl-2-hydroxybenzaldehyde. To a solution of this aldehyde in THF (200 mL) was added NaH (1.03 g, 41.6 mmol) portionwise at room temperature, and the mixture was stirred for 30 min as bubbling gradually ceased. *N*-Phenyltriflimide (14.6 g, 40.5 mmol) was added all at once and the reaction mixture was stirred for 3 h, then diluted with ether, and washed with saturated NH_4Cl, water, and brine. The ether layer was dried (Na_2SO_4) and concentrated. Chromatography (ether/hexanes) yielded the title compound (6.80 g, 57%). NMR ($CDCl_3$): 10.26 (s, 1H), 7.86 (dd, 1H, J = 2.0, 7.5), 7.62 (dd, 1H, J = 1.9, 7.7), 7.48 (t, 1H, J = 7.7), 2.79 (t, 2H, J = 7.8), 1.70 (sextet, 2H, J = 7.5), 0.99 (t, 3H, J = 7.3).

3-Propyl-2-[(4-carboxyphenyl)methyl]benzaldehyde (91). To a solution of the aldehyde **90** (3.17 g, 10.7 mmol) in benzene (20 mL) was added cyclohexylamine (1.14 g, 11.7 mmol) at room temperature.[22] The reaction mixture was heated to reflux for 3.5 h and then concentrated to afford the imine (4.01 g, 99%). The imine, which was used without further purification, was dissolved in THF (20 mL) and treated with LiCl (780 mg, 18.4 mmol), $Pd(Ph_3P)_4$ (1.0 g, 0.86 mmol), and a solution of (4-carbomethoxybenzyl)zinc bromide in THF (10 mL), prepared from methyl 4-(bromomethyl)benzoate (3.72 g, 15.9 mmol, Aldrich), zinc metal (1.28 g, 19.6 mmol), and dibromoethane (0.068 mL, 0.78 mmol) according to the method of Knochel.[23] The reaction mixture was heated to reflux for 20 h, cooled, diluted with ether, washed with 5% HCl, 5% $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. The crude residue was dissolved in THF (100 mL) and treated with 10% HCl (30 mL) to remove the imine. After 90 min at room temperature, the reaction mixture was diluted with ether, washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. Chromatography (ether/hexanes) yielded a fraction containing a mixture of the title compound and bibenzyl contaminant. To aid separation, the mixture was treated with $NaBH_4$ at 0 °C in MeOH for 30 min and worked up with aqueous HCl. Rechromatography (ethyl acetate/hexanes) provided the desired benzyl alcohol (233 mg). To a solution of the alcohol (233 mg, 0.78 mmol) in CH_2Cl_2 (10 mL) was added MnO_2 (410 mg, 4.7 mmol). The reaction was stirred at room temperature for 20 h, filtered through Celite, and concentrated to yield the title aldehyde (195 mg, 6% overall from the starting aldehyde). NMR ($CDCl_3$): 10.16 (s, 1H), 7.89 (d, 2H, J = 8.5), 7.76 (dd, 1H, J = 1.3, 7.2), 7.45 (m, 2H), 7.07 (d, 2H, J = 8.5), 4.59 (s, 2H), 3.88 (s, 3H), 2.60 (t, 2H, J = 7.8), 1.53 (sextet, 2H, J = 7.5), 0.92 (t, 3H, J = 7.3).

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