The Discovery of Potent Nonpeptide Angiotensin II Receptor Antagonists: A New Class of Potent Antihypertensives

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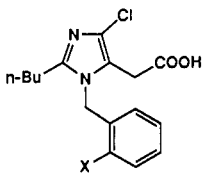
A new class of potent antihypertensives has been discovered that exert their effect through blockade of the angiotensin II (AII) receptor. Most AII antagonists reported so far are peptide mimics of the endogenous vasoconstrictor octapeptide angiotensin II. The compounds of this paper are nonpeptides and therefore constitute a new class of potent AII receptor antagonists. Based on the overlap of a conformation of AII with literature lead **3**, a hypothesis was developed suggesting the need for an additional acidic functionality to increase the lead's potency. The substitution of an additional carboxylic acid resulted in a *10-fold* increase in binding affinity observed for diacid **4**. The binding affinities for subsequent compounds were eventually increased *1000-fold* over that of the literature leads through a systematic SAR study. Thus the AII receptor binding affinity [IC_{50} (μM)] of 15 μM for literature lead **1**, for example, was increased to 0.018 and 0.012 μM for compounds **33** and **53**. A structure–affinity relationship has been found requiring the presence of four key elements for good activity: (1) an additional phenyl ring at the *N*-benzyl para position of the benzylimidazole nucleus, (2) an acidic functionality at the ortho position of the terminal aromatic ring, (3) a lipophilic side chain at the imidazole 2-position of three to five carbon atoms in length, and (4) a group at the imidazole 5-position capable of hydrogen bonding. The synthesis as well as the pharmacological activity of the compounds in this new series of AII receptor antagonists are presented.

Since the discovery of angiotensin converting enzyme inhibitors for the treatment of hypertension,[1] there has been a flurry of activity aimed toward the blockade of other parts of the renin–angiotensin system (Figure 1).[1c] This is evidenced, for example, by the large volume of recent work on renin inhibitors.[2] Both of these classes of enzyme inhibitors exert an antihypertensive effect by lowering the plasma concentrations of the powerful vasoconstrictor octapeptide angiotensin II (AII). AII receptor antagonists, such as saralasin[3] ([Sar[1],Ala[8]]AII), also show antihypertensive action. However, all potent AII receptor antagonists so far have been peptides which are orally ineffective and have short plasma half-lives, and many exhibit partial agonism.[4] We now report on the history of the development of our potent, competitive, nonpeptide AII receptor antagonists.[5a,b]

The discovery of captopril by Cushman and Ondetti[1a] is the classic example of the kind of strategy where a peptide is used as a lead. We were not able to find a shorter but still potent peptide fragment of AII that could be made into a nonpeptide analogue. Therefore, we turned our attention to the only reported nonpeptide AII antagonist leads in the literature.[6] We found these lead compounds, **1–3**, to impart, at very high concentrations, a small decrease in blood pressure via selective blockade of the AII receptor.[7a,b]



	X	IC_{50} (μM)[7a, 7b, 7c]
1	NO_2	15
2	Cl	40
3	H	150

To improve the potency of these lead compounds, we theorized that they bound to the AII receptor, but were rather small compared to the endogenous peptide and therefore had to be enlarged. The C-terminal carboxylic acid of AII seems to be required for binding to the receptor, since C-terminal esterification or amidation significantly reduced the biological activity.[8a,b] We further hypothesized that the carboxylic acid in lead compounds **1–3** was playing a similar role to that of the C-terminal carboxylic acid of AII. By using Dreiding models and computer modeling[9] to aid in visualization, we aligned the carboxyl group of **3** with the C-terminal carboxyl group of AII as

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closely as possible. Both of these COOH groups (anions at physiological pH) were aimed at a hypothetical positive charge on the receptor. Then the imidazole nitrogens of **3** were aligned with those of the histidine residue of AII. The benzyl group of **3**, being the most accessible for analoging, was pointed toward the N-terminus of AII. The resultant picture (Figure 2) showed that the para position of the benzyl group of **3** held the most promise for systematic extension of the molecule toward the N-terminus of AII.

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(9) We gratefully acknowledge J. M. Blaney and W. C. Ripka of the Molecular Modeling Laboratory (Medical Products Department) for providing a computer-generated picture of the overlap of **3** with AII. At the time of this work (1982), there were several conformational models for AII reported in the literature. We chose the conformation reported in Smeby, R. R.; Fermandjian, S. Conformation of Angiotensin II. *Chemistry and Biochemistry of Amino Acids, Peptides and Proteins, 5*; Weinstein, B., Ed.; Marcel Dekker, Inc.: New York, 1978; p 117, since the model had good support from spectroscopic and biological SAR data. Other references pertaining to the conformation of AII are as follows: Vesterman, B. G.; Betins, J.; Nikiforovich, G. V. *Biofizika* **1988** *33* (6), 932–8. Fowler, P. W.; Moore, G. J. *Biochem. Biophys. Res. Commun.* **1988**, *153* (3), 1296–300. Surewicz, W. K.; Mantsch, H. H. *J. Am. Chem. Soc.* **1988**, *110* (13), 4412–14. Matsoukas, J. M.; Goghari, M. 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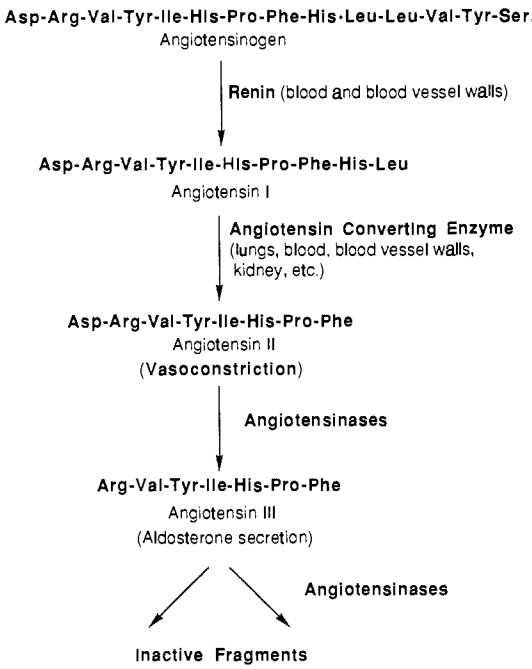
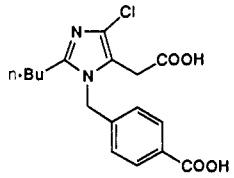


Figure 1. The renin–angiotensin system.

Discussion

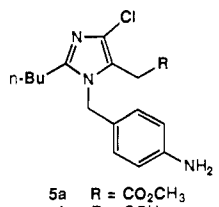
We decided to investigate the effect of introducing a second acidic functional group, such as a carboxylic acid, into the para position of the phenyl ring of lead compound **3**. We believed that an acidic group at physiological pH would provide a negative charge in the area of space where the acidic Tyr^4 phenolic OH and the Asp^1 β-carboxylic acid[10] of AII reside (see Figure 2). To our delight, dicarboxylic acid **4** showed a 10-fold increase in binding



4 IC_{50} (μM) = 1.2

affinity to the AII receptor over the early literature leads. Compound **4** as well as all subsequent compounds turned out to be pure AII antagonists.[5a,b] Given the success of achieving an increase in potency of 1 order of magnitude, we continued to enlarge the molecules at the para position of the benzyl group, as our hypothesis would suggest, all the while incorporating a carboxylic acid group.

Anilines **5a–c** served as intermediates from which a wide variety of carboxylic acid containing analogues could be quickly and easily made by reaction with an appropriate cyclic anhydride. A few analogues that did not contain a carboxyl group in the vicinity of the para position of the *N*-benzyl group were also made to check the absolute necessity for this acidic functionality. These are summarized in Table I with their corresponding binding affinities for the AII receptor.



5a R = CO_2CH_3
b R = OCH_3
c R = OH

From Table I, we see that it was possible to take weakly active compounds that had IC_{50} values in the 10^{-5} M range and increase their binding affinities by 3 orders of magnitude to the 10^{-8} M range.

A carboxylic acid is needed in the para position on the benzene ring for an increase in the first order of magnitude (compounds **4**, **7**, and **9**) over the literature compounds as was discussed earlier. A second order of magnitude comes about from the introduction of a second phenyl ring as in phthalamic acids **22–24**.[11] The phenyl group locks the carboxyl group in a cisoid relationship with the amide bond's carbonyl group (see Figure 3, cis amide–acid arrangement) so that the acid group is now rigidly held near the para position of the benzyl group. Thus compounds **20** and **21** bind poorly even with an additional phenyl group because the carboxyl group is allowed too many degrees of freedom. Extending the carboxyl group away from the para position of the benzyl group of the original lead compound **4** decreases the binding affinity as seen with compounds **10**, **17**, **18** and **19**. The cisoid configuration coupled with an additional aromatic group are key to the 2 orders of magnitude increase in binding affinity (Figure 3).

Additional substitution on the terminal aromatic ring meta to either the amide or the carboxyl groups leads to decreased binding affinities. Thus compounds **26**, **28**, and **29** have lower binding affinities than the unsubstituted phthalamic acid **22** due to increased steric interactions between this region of the terminal aromatic ring and the receptor site (Figure 3).

The increase in the final 1 order of magnitude in binding affinity is achieved by substitution ortho to the amide bond on the terminal aromatic ring (compounds **31–34**). The nitrobenzoic acid derivative **30** is about as potent as the unsubstituted phthalamic acid **22** due to the nitro group being ortho to the carboxyl group. Therefore, in the dichlorophthalamic acids **33** and **34**, it is the chlorine ortho to the amide linkage that enhances the binding affinity. The presence of ortho substituents on benzamide, for ex-

(10) The evidence for the relative importance of the β-carboxyl of Asp^1 of AII is mixed. For example, replacement of the β-carboxyl with a neutral amide group results in the reduction of the contractile response in rabbit aorta strips.[10a] However, in vivo, there is no change observed in the pressor activity.[10a] When Asp^1 is replaced with Gly^1, so that the acidic side chain is replaced by a hydrogen atom, the pressor activity drops to 40% of that of AII.[10a] Complete removal of Asp^1 results in the C-terminal heptapeptide of AII which possesses about 15–50% of the pressor activity of AII.[10a] When the β-carboxyl of Asp^1 is replaced by a positively charged guanidine group, the pressor activity drops to 33% of that of AII. Replacement of Asp^1 with pyroglutamic acid results in an enhancement of the pressor activity (150%). Replacement of Asp^1 with Sar^1 in AII results in an enhancement of the pressor (150%) and myotropic (180%) effects. These Sar-induced effects are explained by increases in intrinsic activity and stability to metabolism.[10b] The effects observed for the other peptides could also be a combination of the effects of changes in intrinsic activity and metabolism. The disparity in the SAR around the β-COOH group of Asp^1 of AII encouraged us even more to see what effect the substitution of a carboxyl group would have on compound **3**. (a) Khosla, M. C.; Smeby, R. R.; Bumpus, F. M. Structure–Activity Relationship in Angiotensin II Analogues. *Handbook of Experimental Pharmacology*; Page, I. H., Bumpus, F. M., Eds.; Springer Verlag: New York, 1974; Vol. 37, p 127. (b) Hall, M. M.; Khosla, M. C.; Khairallah, P. A.; Bumpus, F. M. *Int. Res. Commun. System No. 3-0-1*, April, 1973. Hall, M. M.; Khosla, M. C.; Khairallah, P. A.; Bumpus, F. M. *J. Pharmacol. Exp. Ther.* **1974**, *188*, 222.

(11) For those compounds lacking a carboxyl group, the presence of a second phenyl ring at the para position of the benzyl group also increases the binding affinity by 1 order of magnitude, i.e. compound **25** vs 11.

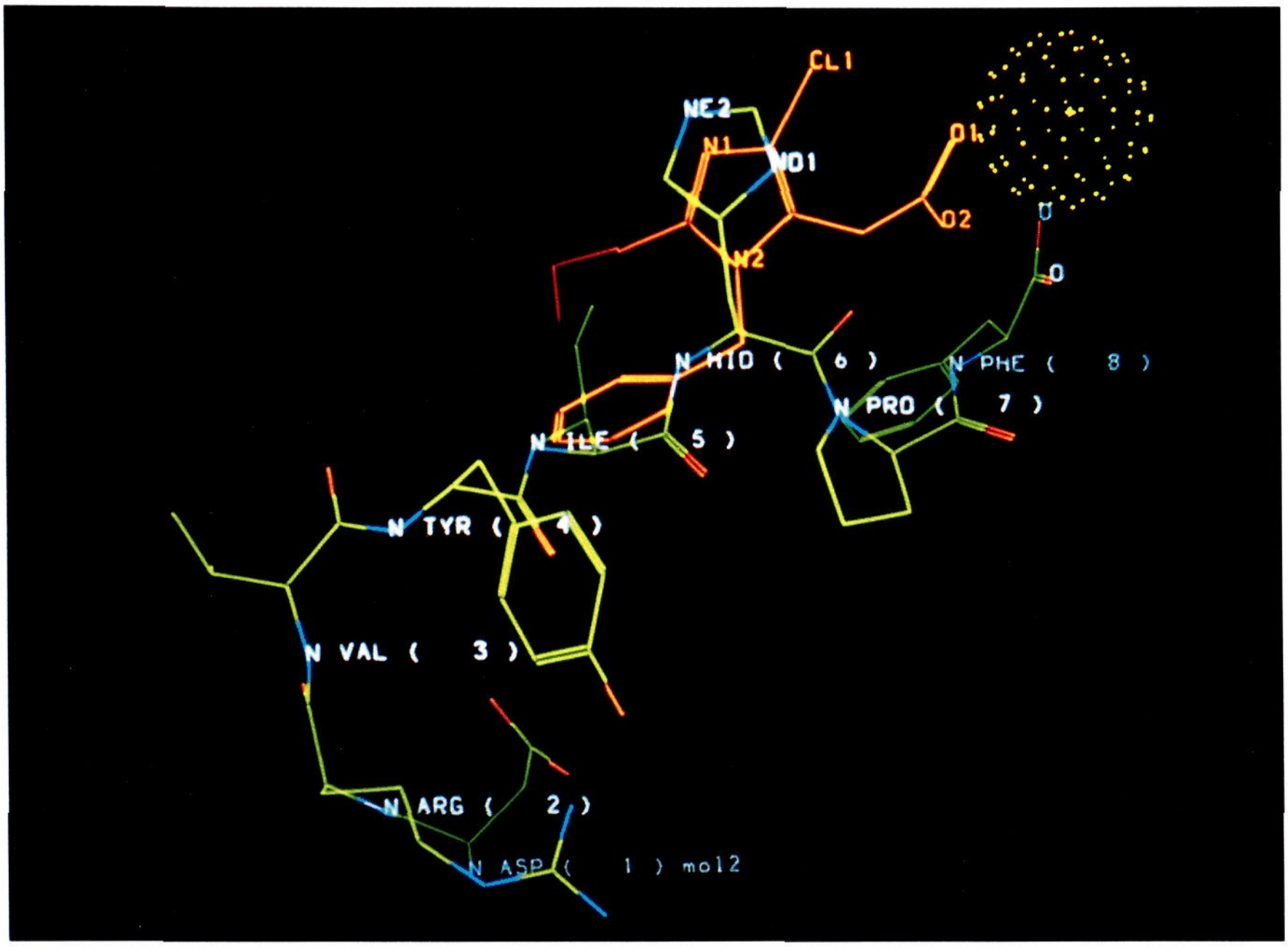


Figure 2. Overlap of lead compound **3** (orange) with the structure of AII (green).[9] The gold sphere represents a positively charged site on the receptor (courtesy of Jeff M. Blaney and William C. Ripka of the Molecular Modeling Laboratory, Medical Products Department, Du Pont).

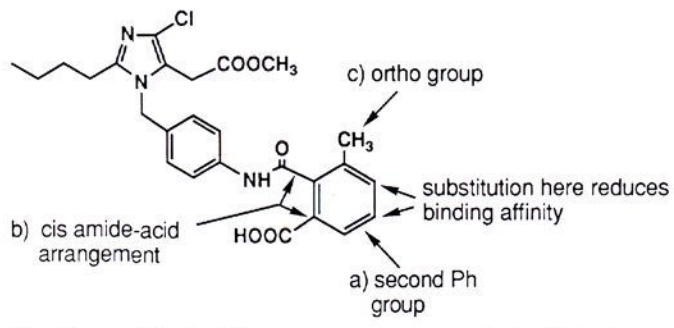


Figure 3. Cis amide/acid arrangement coupled with the presence of an additional phenyl group increases the binding affinity 10-fold. The presence of the ortho substituent to the amide bond further increases the binding affinity.

ample, is known to force the benzoyl phenyl out of the plane of the amide as a consequence of steric hindrance, while at the same time increasing the amide bond's rotational barrier.[12a,b] The ortho substituent thus imparts a favorable and more rigid conformation to the terminal aromatic ring to result in the enhancement of binding affinity. It remains unclear as to whether the amide is cis or trans on the receptor.[13] However in the X-ray crystal structure of **40** (see Chemistry section and Figure 8), the amide bond is trans.

N-Methylation of the amide nitrogen, on the other hand, drastically lowers the binding affinity by 2 orders of magnitude (**35** vs **34**). Apparently, the tertiary amide imparts an unfavored conformation for binding or there is need for a H-bonding interaction of the amide bond with the receptor.

In the synthesis of these AII receptor antagonists, the imidazole alkylation step (see Chemistry section) always leads to two regioisomeric products. The 4-chloro regioisomer always has the greater binding affinity for the AII receptor compared to the 5-chloro regioisomer (**4** vs **6**, **7** vs **8**, and **22** vs **23**).

Diphenic acid derivative **36** possesses the good binding affinity of its phthalamic acid counterpart **22**. One may imagine how the nonplanar biphenyl rings might orient the carboxyl group in a way to mimic the phthalamic acid when the amide and phenyl groups are out of plane with respect to one another.

It is unclear why the tetrafluorophthalamic acid **27** is a less potent binder than its unhalogenated counterpart **22**.

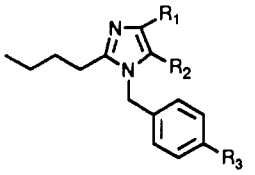
In vitro binding affinities translate well into in vivo blood pressure lowering activity.[5a,b] For example, the ED_{30}s of **4**, **22**, and **53** (Table II) are 10, 11, and 0.2 mg/kg cum iv in the renal hypertensive rat.[5a,b]

We next turned our attention to introducting oral activity into our carboxylic acid AII blockers since all of them

(12) (a) Lewin, A. H.; Frucht, M. *Tetrahedron Lett.* **1970**, 1079. (b) Hirota, M.; Todokoro, K. *Chem. Lett.* **1974**, 777.

(13) Secondary benzamides may adopt cis or trans conformations in solution. The conformation is solvent, concentration, and temperature dependent: Stewart, W. E.; Siddall, J. H. *Chem. Rev.* **1970**, *70*, 517.

Table I. Binding Affinities of COOH Containing *N*-Benzylimidazole AII Receptor Antagonists



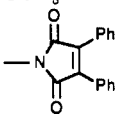
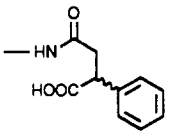
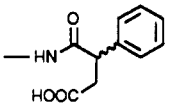
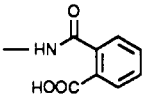
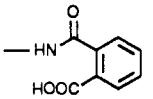
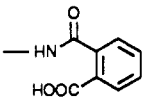
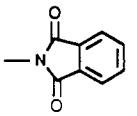
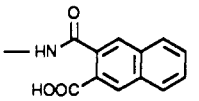
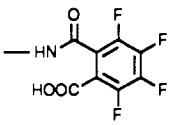
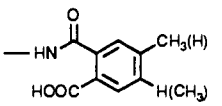
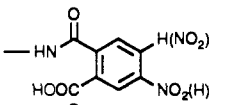
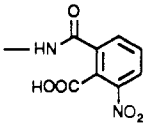
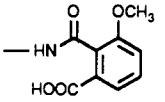
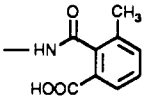
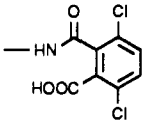
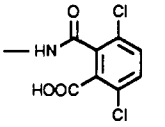
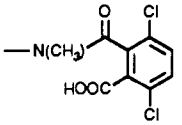
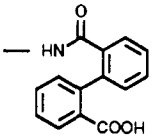
compd	R_1	R_2	R_3	IC_{50}, μM	mp, °C	anal.
4	Cl	CH_2COOH	COOH	1.6	170.0–174.0	C,H,Cl,N
5a	Cl	CH_2COOCH_3	NH_2	100	87.5–88.5	C,H,Cl,N
6	CH_2COOH	Cl	COOH	19	203.5–204.5	C,H,N
7	Cl	CH_2OH	COOH	1.7	165.0–166.0	C,H,Cl,N
8	CH_2OH	Cl	COOH	100	171.0–172.0	C,H,N
9	Cl	CH_2OAc	COOH	5.3	oil	C,H,N
10	Cl	CH_2COOH	CH_2COOH	13	156.0–157.0	C,H,N
11	Cl	CH_2COOCH_3	NO_2	100	97.5–100.0	C,H,Cl,N
12	Cl	CH_2COOCH_3	$NHCH_2Ph$	40	oil	*a*
13	Cl	CH_2OH	CHO	28	89.0–90.0	*a*
14	Cl	CH_2OH	CH=NOH	>100	188.0–188.5	C,H,Cl
15	Cl	CH_2OH	OCH_3	100	88.0–91.0	C,H,Cl,N
16	Cl	CH_2COOCH_3		>10	54.0–61.0	C,H,Cl,N
17	Cl	CH_2COOCH_3	$NHCO(CH_2)_2COOH$	46	145.0–146.0	C,H,Cl,N
18	Cl	CH_2COOCH_3	$NHCO(CH_2)_3COOH$	32	112.0–113.0	C,H,Cl,N
19	Cl	CH_2COOCH_3	NHCOCH=CHCOOH (cis)	11	138.0–139.5	C,H,Cl,N
20	Cl	CH_2OCH_3		2.8	b	C,H,Cl,N
21	Cl	CH_2OCH_3		7.5	b	C,H,Cl,N
22	Cl	CH_2COOCH_3		0.14	109.5–112.5	C,H,Cl,N
23	CH_2COOCH_3	Cl		0.42	150.5–152.5	C,H,N
24	Cl	CH_2OCH_3		0.28	153.5–155.5	C,H,Cl
25	Cl	CH_2COOCH_3		3.1	141.5–143.0	C,H,Cl
26	Cl	CH_2COOCH_3		5.8	172.5–173.0	C,H,N
27	Cl	CH_2COOCH_3		0.79	169.0–170.5	C,H,N
28	Cl	CH_2COOCH_3		0.38	129.0–131.0	C,H,N
29	Cl	CH_2COOCH_3		6.9	148.0–151.0	C,H,N
30	Cl	CH_2COOCH_3		0.40	184.0–186.0	C,H,N

Table I (Continued)

compd	R_1	R_2	R_3	IC_{50}, μM	mp, °C	anal.
31	Cl	CH_2COOCH_3		0.08	151.0–153.0	C,H,N
32	Cl	CH_2COOCH_3		0.032	119.0–121.0	C,H,N
33	Cl	CH_2COOCH_3	 (DCHA salt)[c]	0.018	199.0–200.0	C,H,Cl
34	Cl	CH_2OCH_3		0.042	116.0–118.0	C,H,Cl,N
35	Cl	CH_2OCH_3		5.70	120.0–123.5	C,H,Cl
36	Cl	CH_2COOCH_3		0.19	130.0–134.0	C,H,Cl,N

[a] Intermediate to a fully characterized compound. MS detects M^+. [b] The product mixture containing **20** and **21** was separated by HPLC as the dicyclohexylamine salts, **21** being the major isomer (3:1 mixture): Zorbax-NH2; 1:1 A:B, A = 500:1 $CHCl_3$–HOAc, B = MeOH. [c] DCHA = dicyclohexylamine.

show in vivo activity via iv administration only. The replacement of the polar carboxyl group with other, perhaps more lipophilic and/or metabolically more stable acidic isosteres, yielded compounds that showed glimmers of oral activity. Two such isosteres with pK_a values similar to that of the carboxylic acid group are the trifluoromethanesulfonamide[14] and tetrazole[15] groups. These analogues are listed in Table II.

The structure–affinity relationship of the compounds in Table II match those of the phthalamic acids in Table I. Overall, the trifluoromethanesulfonamides show a slightly lower binding affinity than their phthalamic acid counterparts (**37** vs **4**, **40** vs **22**). The tetrazole, however, appears to mimic a carboxylic acid quite well (**39** vs **4**).

Placement of a methyl group ortho to the acidic trifluoromethanesulfonamido group slightly enhances the binding affinity (**49** vs **40**). Substituents meta and para to the CF_3SO_2NH group (**43–48**) lower binding affinity as seen previously in the phthalamic acid series. This also accounts for the low binding affinity of the acidic dinitrophenol **52**.[16] Compounds **38**, **42**, **50**, and **51** have pK_a values higher[16] than that of **37** or **40** and therefore have lower binding affinities. Alkylation of the amide nitrogen as in **41** reduced the binding affinity in a similar fashion as in the phthalamic acid series. The effect of the sulfonic acid on binding affinity (**53** vs **40**) is striking and is possibly due to a more hydrophilic[18] or to a more acidic COOH isostere.[16]

The trifluoromethanesulfonamide and tetrazole groups did impart some oral activity to the AII blockers, and these results are shown in Figures 4–6.

Table III summarizes the effects of moving the acid functionality around the aromatic ring. In the simple monophenyl cases (**4**, **54**, **55**, **39**, and **56**) the para position always shows the highest binding affinity. For the trifluoromethanesulfonamidobenzamide series (**40**, **57**, and **58**), the acid moiety must be ortho to the amide bond for

(14) The pK_a of $PhNHSO_2CF_3$ is 4.45. The log *P* values of $PhNHSO_2CF_3$ and PhCOOH are 3.05 and 1.87, respectively. Trepka, R. D.; Harrington, J. K.; Belisle, J. W. *J. Org. Chem.* **1974**, *39*, 1094.

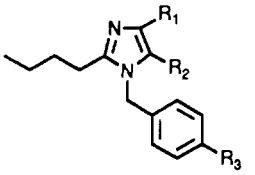
(15) The pK_a of a 5-alkyl-substituted tetrazole is ca. 6: Lednicer, D.; Mitscher, L. A. *The Organic Chemistry of Drug Synthesis*; John Wiley and Sons: New York, 1980; Vol. 2, pp 301 and 345. The tetrazole group is believed to be metabolically more stable than the COOH group: Holland, G. F.; Pereira, J. N. *Experientia* **1967**, *23*, 88.

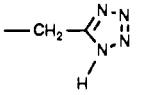
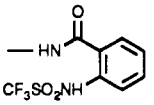
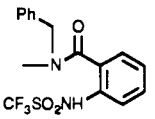
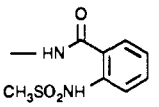
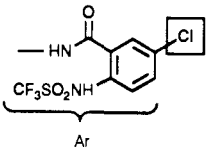
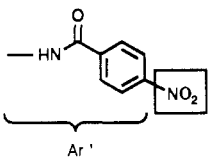
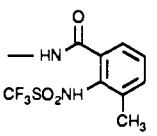
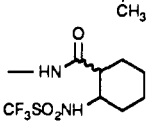
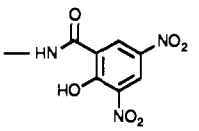
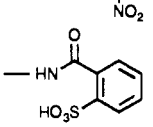
(16) The pK_a of 2,4-dinitrophenol is 4.3–5.5, depending on the solvent: Barrette, W. C., Jr.; Johnson, H. W., Jr.; Sawyer, D. T. *Anal. Chem.* **1984**, 1890. The pK_a of $PhNHSO_2CH_3$ is 8.85 (ref 14). The pK_a of **50** and **51** should be similar to that of $CH_3NHSO_2CF_3$, namely 7.56 (ref 14). The pK_a of $CF_3CONHPh$ is ca. 9.5; Meresaar, V. *Acta Chem. Scand. A* **1974**, *28*, 656. The pK_a of benzenesulfonic acid is −6.65: Crumrine, D. S.; Shankweiler, J. M.; Hoffman, R. V. *J. Org. Chem.* **1986**, *51*, 5013. Cerfontain, H.; Schnitzer, B. W. *Recl. Trav. Chim. Pays-Bas* **1972**, *91*, 199.

(17) The imidazole 4-position may be substituted by either Cl or H to yield compounds of essentially equivalent binding affinity. See part 6 in this series: Carini, D. J.; Et al. *J. Med. Chem.*, following paper in this issue.

(18) The π value for COOH is −0.32.[18a] For a 1-substituted tetrazole the π value is −1.04[18a] (more hydrophilic). The 5-substituted tetrazole, as in the case of our compounds, should be even more hydrophilic. The estimated π value for SO_3H is −1.86.[18b] (a) Hansch, C.; Leo, A. *Substituent Constants for Correlation Analysis in Chemistry and Biology*; John Wiley and Sons: New York, 1979. (b) Estimated by the Pomona College Medicinal Chemistry Project CLOGP version 3.53 (1988), Pomona College, Claremont, CA.

Table II. Binding Affinities of AII Receptor Antagonists Containing COOH Isosteres



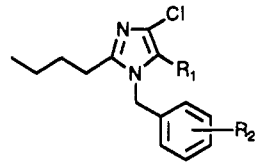
compd	R_1	R_2	R_3	estimated pK_a (refs 14–16)	IC_{50}, μM	mp, °C	anal.
37	Cl	CH_2COOCH_3	$NHSO_2CF_3$	4.5	2.1	154.0–157.0	C,H,Cl,N
38	Cl	CH_2COOCH_3	$NHCOCF_3$	9.5	27	122.0–124.0	C,H,N
39	Cl			4–5	1.2	229.0–230.0	C,H,N
40	Cl	CH_2COOCH_3		4.5	0.5	151.0–152.0	C,H,N
41	Cl	CH_2COOCH_3		4.5	2.7	oil	C,H,N
42	Cl	CH_2COOCH_3		8.9	2.3	74.0–79.5	C,H,N
43	Cl	CH_2COOCH_3		4.5	5.9	195.0–197.0	C,H,N
44	Cl	CH_2COOCH_3	Ar–Br	4.5	40	214.0–216.0	C,H,N
45	Cl	CH_2COOCH_3	Ar–I	4.5	3.4	226.0–228.0	C,H,N
46	Cl	CH_2COOCH_3	Ar–CH_3	4.5	0.81	188.5–189.5	C,H,N
47	Cl	CH_2COOCH_3		4.5	>10	100.0–110.0	C,H,N
48	Cl	CH_2COOCH_3	Ar′–Cl	4.5	11	136.0–140.0	C,H,N
49	Cl	CH_2COOCH_3		4.5	0.19	153.0–156.0	C,H,N
50	Cl	CH_2COOCH_3		7.6	3.9[a]	*b*	C,H
51	Cl	CH_2COOCH_3	isomer of 50	7.6	4.5[a]	*b*	C,H,N
52	Cl	CH_2COOCH_3		4.3–5.5	>30	226.0–230.0	C,H,N
53	Cl	CH_2OCH_3		−6.6	0.012	>275	C,H,Cl,N

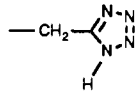
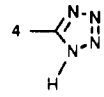
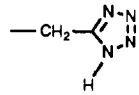
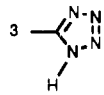
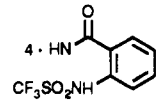
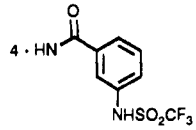
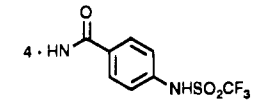
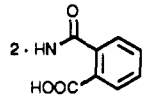
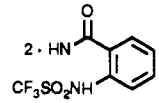
[a] Compounds **50** and **51** are cis and trans isomers which could be separated chromatographically. However, their structural assignments could not be made. [b] Amorphous solid.

the greatest binding affinity, while meta followed by para substitution decreases in affinity, in that order. Finally, locating the amide bond at the ortho position of the benzyl group as in compounds **59** and **60** causes loss of activity.

Table IV shows the effect of varying the alkyl chain (R_1) at the 2-position of the imidazole ring on binding affinity. We find that the optimal length of R_1 is five carbons when R_2 and R_3 are H. The structure–affinity relationship is

Table III. Effect of Ring Position of the Acidic Moiety on Binding Affinity



compd	R_1	R_2	IC_{50}, μM	mp, °C	anal.
4	CH_2COOH	4-COOH	1.2	170.0–174.0	C,H,Cl,N
54	CH_2COOH	3-COOH	100	219.5–221.5	C,H,N
55	CH_2COOH	2-COOH	38	190.0–191.0	C,H,Cl,N
39			1.2	229.0–230.0	C,H,N
56			3.8	258.0 dec	C,H,N
40	CH_2COOCH_3		0.5	151.0–152.0	C,H,N
57	CH_2COOCH_3		1.3	*a*	C,H,N
58	CH_2COOCH_3		84	88.0 dec	C,H,N
59	CH_2COOCH_3		100	142.0–143.5	C,H,N
60	CH_2COOCH_3		>100	66.0–70.5	C,H,N

[a] Amorphous solid.

very well defined at this position and is summarized graphically in Figure 7.

The presence of the aryl groups on the R_1 side chain lowers the binding affinity (**69**, **70**, and **73**). Removal of the R_1 side chain removes all binding affinity (compound **74**)[17] and suggests the presence of a lipophilic pocket in this area of the AII receptor. Removal of the R_3 side chain (**65** vs **22** or **24**)[17] reduces the binding affinity by slightly less than 1 order of magnitude and thereby denotes a hydrogen-bonding pocket in this area of the AII receptor.

Reversal of the amide linkage, wherein the carbonyl group is now attached to the phenyl ring of the *N*-benzyl group, gave rise to generally less potent binders to the AII receptor (Table V). However, the structure–affinity relationship follows the same trends seen earlier. Thus again, placement of a methyl group ortho to the acid group (**76**) raises the binding affinity by 1 order of magnitude as in the sulfonamide series (**49**). The marked effect of the tetrazole isostere **77** over that of the carboxylic acid **75** is also striking and is reminiscent of the effect the sulfonic acid **53** had over the phthalamic acid **24**. Increased hydrophilicity of these groups compared to that of the carboxyl group[18] in this region of the molecule could be responsible for the enhanced binding affinity. Finally, the selectivity for the L-amino acid analogues **78** and **80** over the D-amino acid analogues **79** and 81 corresponds well with the fact that incorporation of D-amino acid residues into synthetic variations of AII octapeptides in many cases leads to loss of binding affinity.[19]

Chemistry

Compounds in Table I were synthesized by the routes depicted in Scheme I. Alkylation of imidazole **82**[6] with a substituted benzyl bromide yields **83**, **13**, **15**, and their minor regioisomers **84**, which can be easily separated by flash chromatography. The major isomer is always the faster moving spot by TLC (silica gel) and eventually leads to the isomer exhibiting the higher receptor binding affinity (compare the binding affinities of **4** with **6**, **7** with **8**, and **22** with **23**). The correlation of structure with TLC behavior was established absolutely in the case of compound **40** (Table II) by an X-ray crystal-structure determination (Figure 8). Compound **40** was prepared via several steps from the major regioisomer **83a**. Apparently, the hydroxyl group of the minor regioisomer **84a** can in-

(19) [Asn[1],D-Arg[2]]AII, [Asn[1],D-Tyr[4],Val[5]]AII, [Asn[1],Val[5],D-His[6]]AII, and [D-Phe[8]]AII have consistently lower in vivo pressor effects than their L-amino acid counterparts (4, 0.025, 1.0, and 0.1% of the in vivo pressor activity of AII, respectively). The all L counterparts [Asn[1]]AII and [Asn[1],Val[5]]AII exhibit 100% of the pressor activity of AII. [D-Phe[8]]AII is also a very weak antagonist of the AII receptor (see ref 10 and references therein). Substitution of D-Pro[7] for its L isomer has also led to analogues with greatly diminished agonist and antagonist activities: Moore, G. J. In *Peptides Structure and Function. Proceedings of the Seventh American Peptide Symposium*; Rich, D. H., Gross, E., Eds.; Pierce Chemical Co.: Rockford, IL, 1981; p 245.

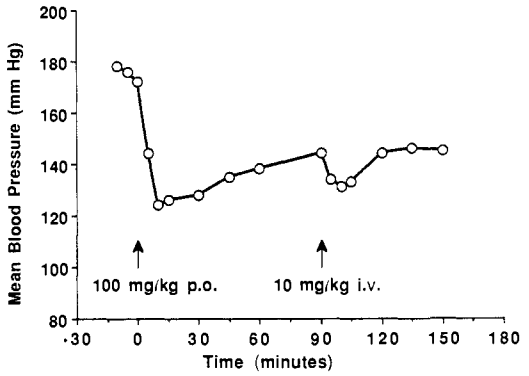


Figure 4. Oral activity of trifluoromethanesulfonamide **37** in the renal hypertensive rat.[5b,7a,b]

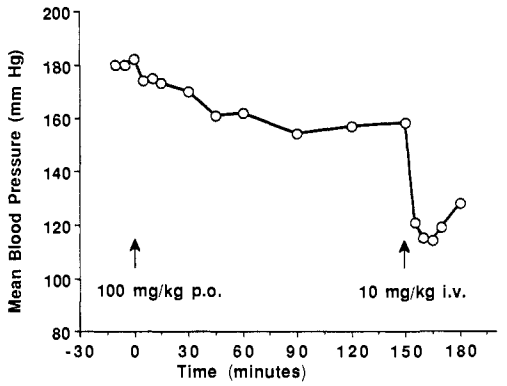
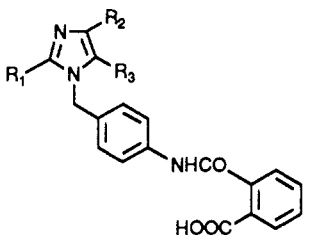


Figure 5. Oral activity of bistetrazole **39** in the renal hypertensive rat.[5b,7a,b]

Table IV. Effect of the Imidazole 2-Substituent (R_1) on Binding Affinity



compd	R_1	R_2	R_3	IC_{50}, μM	mp, °C	anal.
61	H	H	H	100	169.0–171.5	C,H,N
62	CH_3	H	H	100	188.0–189.0	C,H,N
63	CH_3CH_2	H	H	8.5	188.5–189.5	C,H,N
64	$CH_3(CH_2)_2$	H	H	3.7	181.5–183.0	C,H,N
65	$CH_3(CH_2)_3$	H	H	0.62	188.5–189.5	C,H,N
66	$CH_3(CH_2)_4$	H	H	0.24	170.5–171.5	C,H,N
67	$CH_3(CH_2)_5$	H	H	0.35	171.0–171.5	C,H,N
68	$CH_3(CH_2)_6$	H	H	1.1	181.0–182.0	C,H,N
69	$PhCH_2CH_2$	H	H	9.4	149.0–153.0	C,H,N
70	4-CH_3OPhCH_2	H	H	2.5	149.0–153.0	C,H,N
71	cyclohexyl-CH_2	H	H	2.8	150.0–152.0	C,H,N
72	$(CH_3)_2CH$	H	H	12	195.0–196.0	C,H,N
73	$Ph(CH_2)_3$	Cl	CH_2OH	80	129.0–132.0	C,H,N
74	H	H	CH_2OH	>100	157.0–159.0	C,H,N

teract to a greater extent with silica gel than that of the major regioisomer **83a** where the CH_2OH group is shielded by the adjacent functionality.

(Hydroxymethyl)imidazoles **83a–c** may be converted into key aniline intermediates **5a–d** by the simple transformations shown in Scheme I. Reduction of the corresponding formamide intermediate or reductive amination with benzaldehyde converts **5a** and **5b** into **12** and **88**, respectively. Aniline derivatives **5a,b,d** and **88** react with a wide variety of cyclic anhydrides to produce the amide–acids **90a–c**. For example, mixing together chloroform

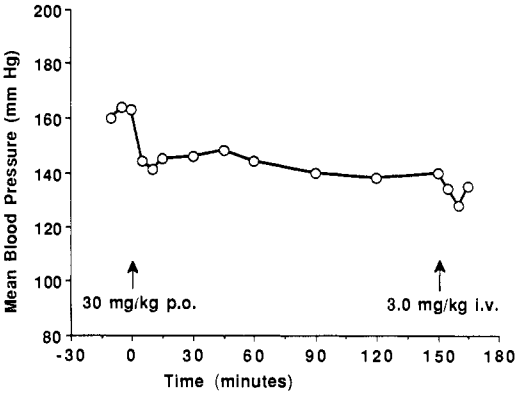


Figure 6. Oral activity of trifluoromethanesulfonamide **40** in the renal hypertensive rat.[5b,7a,b]

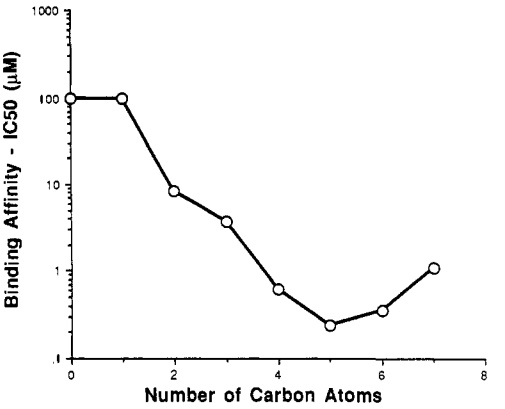


Figure 7. Binding affinity versus number of carbon atoms in the imidazole 2-side chain.

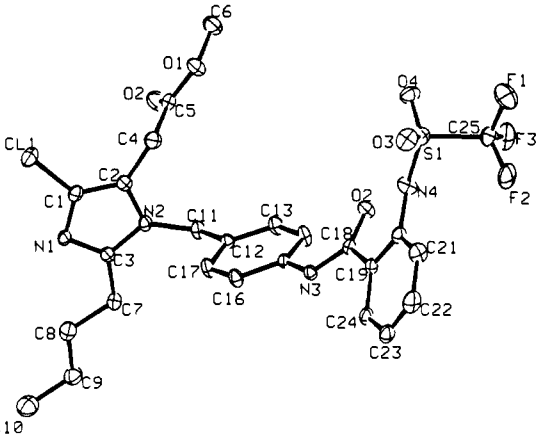


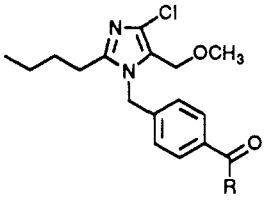
Figure 8. X-ray crystal structure of **40**.

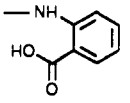
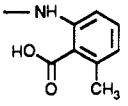
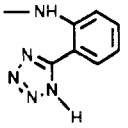
solutions of **5a** and phthalic anhydride yields a solution which after a few minutes slowly begins to precipitate the product phthalamic acid **22** in 86% yield.[20] *The simplicity of this reaction coupled with the commercial availability of a wide variety of cyclic anhydrides permitted the rapid synthesis of a large number of compounds (summarized in Table I), leading quickly to the development of a SAR.*

3-Substituted phthalic anhydrides react regiospecifically with aniline derivative **5a** to yield only one detectable isomer by ^1H NMR spectroscopy,[21c–f] namely, **30**, **31**, and **32**. The reaction of aniline itself with 3-nitro- and 3-methylphthalic anhydride is also regiospecific, yielding

(20) For the original reaction of aniline with phthalic anhydride, see: Sherrill, M. L.; Schaeffer, F. L.; Shoyer, E. P. *J. Am. Chem. Soc.* **1928**, *50*, 474.

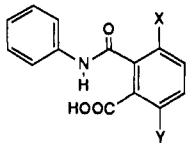
Table V. Binding Affinities of "Reversed Amide Linkage" AII Receptor Antagonists



compd	R	IC_{50}, μM	mp, °C	anal.
75		8.0	oil	C,H,Cl
76		0.50	a	C,H,Cl
77		0.57	a	C,H,Cl
78	L-Phe	6.1	149.0–152.0	C,H,N
79	D-Phe	22	150.0–151.5	C,H,N
80	L-Pro	6.4	134.5–136.0	C,H,N
81	D-Pro	120	134.0–136.0	C,H,N

[a] Amorphous solid.

compounds **91** and **92** whose structures were determined by X-ray crystallography (Figures 9 and 10).



91 X = H; Y = NO_2
92 X = CH_3; Y = H

Assuming that aniline derivative **5a** reacts in a similar fashion to aniline itself, then adduct **30** should possess the regiochemistry observed in **91**, and **32** should possess that of **92**. The 3-methoxyphthalic anhydride adduct **31** possesses greater binding affinity than that of the unsubstituted phthalamic acid **22**, as is the case for **32** and not **30**. Therefore, the regiochemistry of **31** must be the same as that of **32**. In addition, the transition states for both the 3-methoxy- and 3-methylphthalic anhydride reactions should be similar and different from that of the 3-nitrophthalic anhydride reaction (see subsequent discussion). Reaction of aniline derivative **5a** with **4** or 5-substituted phthalic anhydrides, however, led to mixtures of regioisomers as in compounds **28** and **29**.[22]

The regioselectivity may be explained through the trajectory of the nucleophile and the subsequent transition state pictured in Figure 11. We assume that the aniline

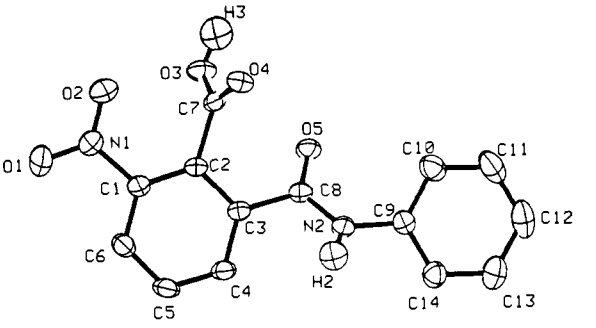


Figure 9. X-ray crystal structure of **91**.

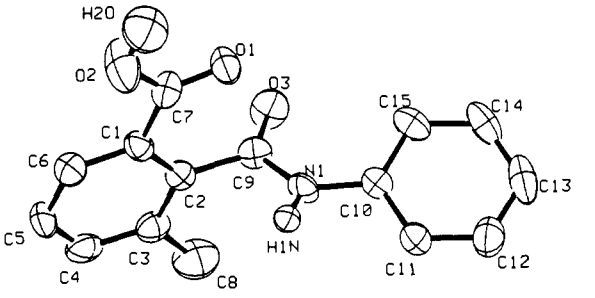


Figure 10. X-ray crystal structure of **92**.

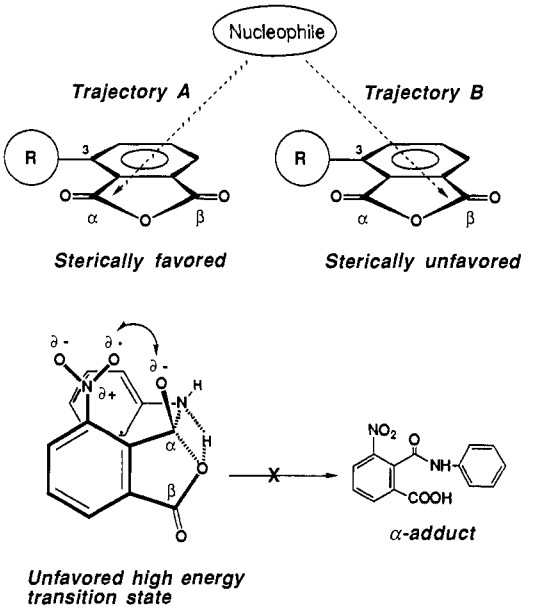
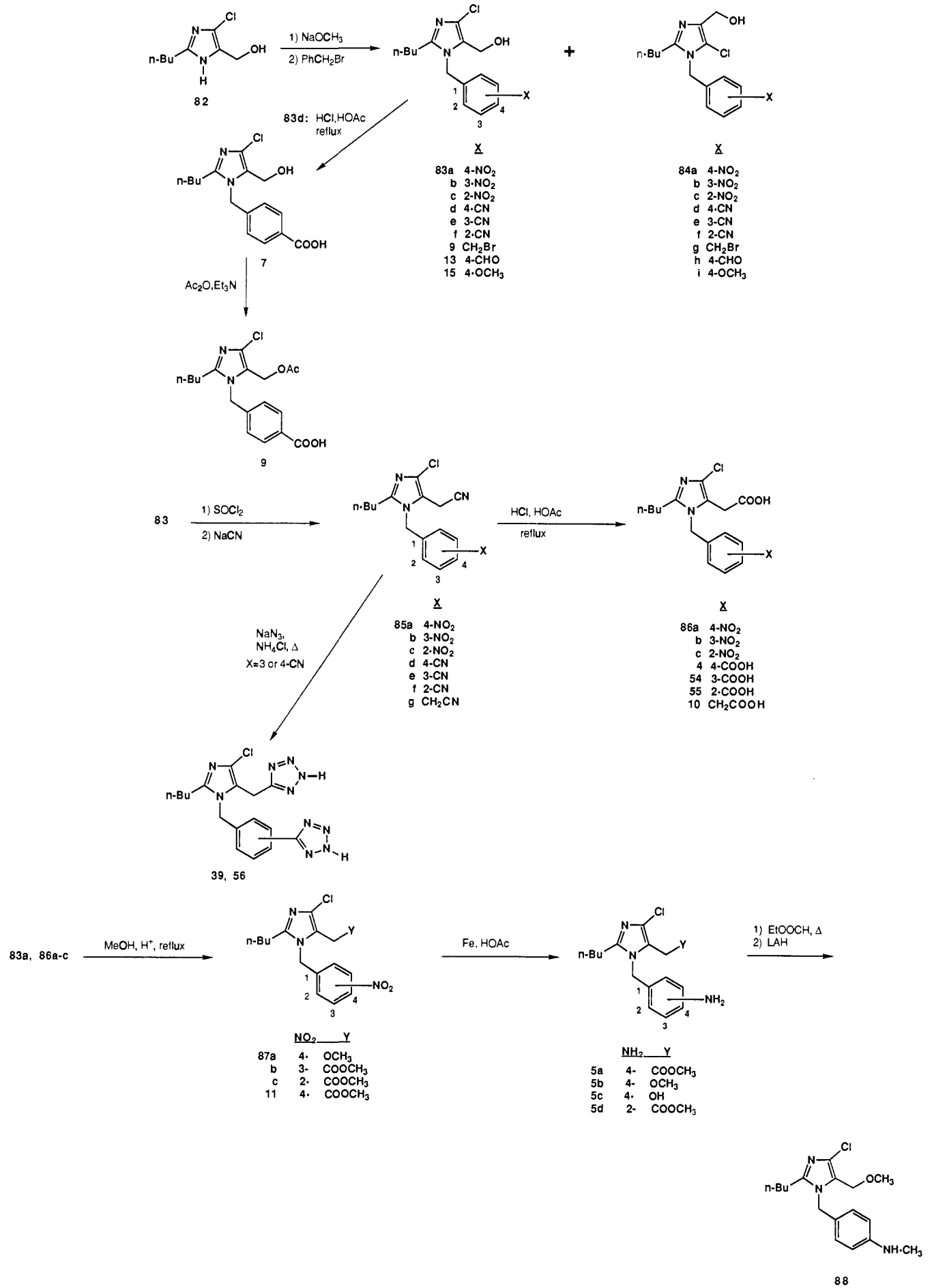


Figure 11. Sterically unencumbered trajectory A favors addition of a nucleophile to the α-carbonyl group of 3-methyl- and 3-methoxyphthalic anhydrides. The high-energy transition state for the addition of anilines to the α-carbonyl of 3-nitrophthalic anhydride accounts for the observed preference for the β-carbonyl addition adduct.

amino group approaches the α- and β-carbonyl groups of phthalic anhydride via the Bürgi–Dunitz trajectories as shown.[21a,b] Only trajectory A avoids any steric interaction with the substituent at the 3-position. Therefore, trajectory A is always favored, and as a result, the α-carbonyl group of 3-methyl and 3-methoxyphthalic anhydride reacts with aniline. However, in the case of 3-nitrophthalic anhydride, the developing negative charge on the reacting α-carbonyl oxygen in the transition state interacts unfavorably with the electron density on the nitro group's oxygens. Apparently, the transition state is so high in energy that the approach over the nitro group by the aniline to react with the β-carbonyl group is much more energetically favored. In addition, for 3-methylphthalic

(21) For theoretical approaches to the reaction of carbonyl groups, see: (a) Bürgi, H. B.; Dunitz, J. D.; Shefter, E. *J. Am. Chem. Soc.* **1973**, *95*, 5065. (b) Houk, K. N.; Paddon-Row, M. N.; Rondan, N. G.; Wu, Y. D.; Brown, F. K.; Spellmayer, D. C.; Metz, J. T.; Li, Y.; Loncharich, R. J. *Science* **1986**, *231*, 1108. For examples of regioselectivity in the reaction of Grignard, aryllithium, and metal hydride reagents with 3-substituted phthalic anhydrides, see: (c) Soucy, C.; Favreau, D.; Kayser, M. M. *J. Org. Chem.* **1987**, *52*, 129. (d) Braun, M.; Veith, R.; Moll, G. *Chem. Ber.* **1985**, *118*, 1058. (e) Braun, M. *Liebigs Ann. Chem.* **1981**, 2247. (f) Taub, D.; Girotra, N. N.; Hoffsommer, R. D.; Kuo, C. H.; Slates, H. L.; Weber, S.; Wendler, N. L. *Tetrahedron* **1968**, *24*, 2443.

Scheme I



X	
83a	4-NO_2
b	3-NO_2
c	2-NO_2
d	4-CN
e	3-CN
f	2-CN
9	CH_2Br
13	4-CHO
15	4-OCH_3

X	
84a	4-NO_2
b	3-NO_2
c	2-NO_2
d	4-CN
e	3-CN
f	2-CN
g	CH_2Br
h	4-CHO
i	4-OCH_3

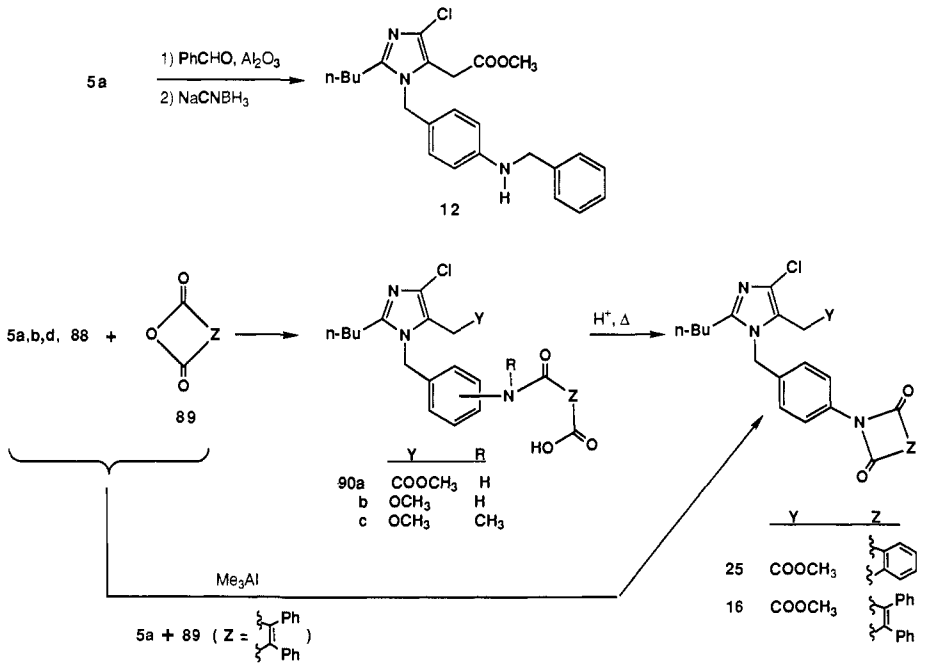
X	
85a	4-NO_2
b	3-NO_2
c	2-NO_2
d	4-CN
e	3-CN
f	2-CN
g	CH_2CN

X	
86a	4-NO_2
b	3-NO_2
c	2-NO_2
4	4-COOH
54	3-COOH
55	2-COOH
10	CH_2COOH

NO_2	Y	
87a	4-	OCH_3
b	3-	$COOCH_3$
c	2-	$COOCH_3$
11	4-	$COOCH_3$

NH_2	Y	
5a	4-	$COOCH_3$
5b	4-	OCH_3
5c	4-	OH
5d	2-	$COOCH_3$

Scheme I (Continued)



anhydride, the relief of steric strain between the 3-methyl group and the α-carbonyl group in the transition state[23] also favors regiospecific reaction to the α-carbonyl group.

Ring closure and dehydration of **90a** (Scheme I) yields phthalimide **25**. Diphenylmaleic anhydride fails to react with aniline **5a** as mentioned previously. Trimethylaluminum promotes the reaction, but dehydration occurs to directly yield the diphenylmaleimide **16**.

Scheme II details the synthesis of the CF_3SO_2NH, CF_3CONH, 2,4-dinitrophenol, and SO_3H isostere containing compounds. The synthesis of **93**, described in the literature,[24] was applied to the other CF_3SO_2NH-containing compounds. The amide linkages were formed by coupling aniline **5a** with the corresponding acid chlorides in the presence of an acid scavenger such as sodium bicarbonate. The fully saturated analogues **50** and **51** (cis and trans isomers) were made by the above procedure starting with 2-aminocyclohexanecarboxylic acid.[25] Sulfonic acid **53** was made by coupling of aniline **5b** with *o*-sulfobenzoic acid anhydride (**96**).

The 2-alkylimidazoles in Table IV were prepared by the same procedures described in Scheme I. The imidazole starting materials were commercially available or were prepared by a literature procedure.[26]

Compound **74** having only a 5-hydroxylmethyl substituent on the imidazole was prepared from the corresponding 2-mercapto-1-nitrobenzyl precursor **98** as shown in Scheme III by the Marckwald imidazole synthesis.[27]

The reversed amide bond analogues in Table V were made by the procedures shown in Scheme IV. Coupling of the acid chloride of **101** with various amino acids under Schotten–Baumann type conditions yielded products **75–81**. The optical rotations of the L and D amino acid coupled products **78–81** were equal and opposite. 2-(5-Tetrazolyl)aniline used to make **77** was synthesized from the corresponding anthranilonitrile and sodium azide.

Conclusion

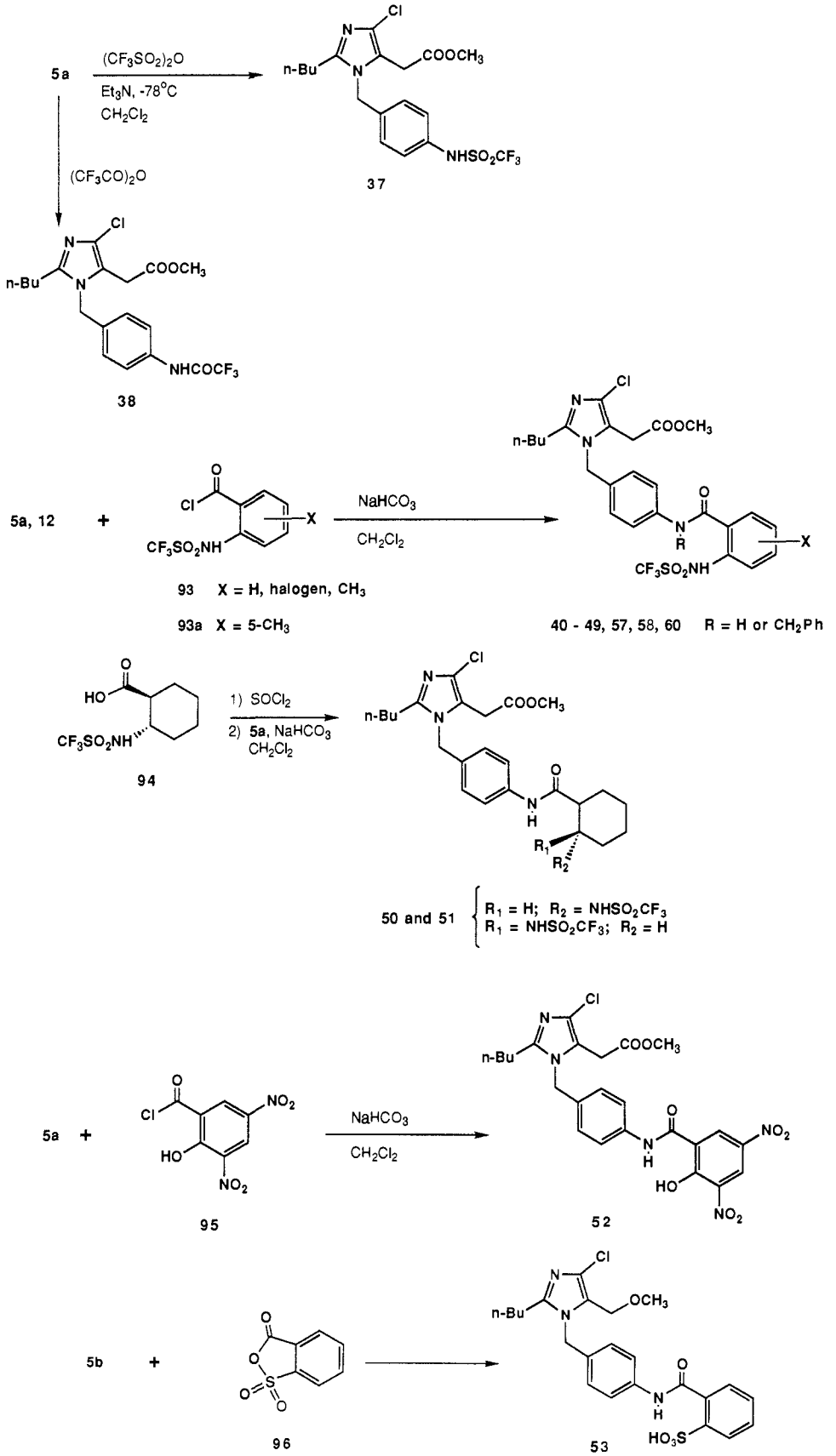
The initial working hypothesis, which suggested the need for an additional acidic functionality for lead compounds **1–3**, has led to the discovery of potent nonpeptide antagonists for the AII receptor. Unfortunately, the model for the overlap between AII and literature lead **3**, which so successfully led to dicarboxylic acid **4**, cannot explain the good binding affinities observed for the nonacidic side chain containing compounds (imidazole 5-position side chains such as alcohols, esters, and ethers). The fit of our more potent AII antagonists onto AII is currently being reevaluated, and will be reported in the near future.

By using one of the simplest reactions in organic chemistry, namely the reaction of an amine with an anhydride, we were able to efficiently make compounds that contained an additional acid group. Capitalizing on the large variety of commercially available cyclic anhydrides, we quickly discovered a series of AII blockers that were 3 orders of magnitude more potent than the initial leads. We also successfully substituted COOH isosteres, such as the tetrazole and CF_3SO_2NH groups, which not only retained good in vitro binding affinity but began to show glimmers of oral activity.

From the structure–affinity relationships discussed, we can draw a hypothetical model for the AII receptor as shown in Figure 12. The key features are the positively charged site on the receptor binding to the negatively charged acid group of the ligand (at the physiological pH), the two lipophilic pockets, and the hydrogen bond acceptor group. Since reversal or alkylation of the amide linkage leads to a loss in binding affinity, there might also be an additional hydrogen-bonding interaction of the amide bond with the receptor. The other possibility is that N-alkylation prevents the best conformer from binding. The conformation of the terminal aromatic ring seems to be important for good binding affinity, since ortho substitution to the amide linkage yielded the most potent compounds in this series.

(22) Regioisomeric amide N*H* resonances of the 4-substituted phthalic anhydride adducts are readily detectable by 200-MHz NMR spectroscopy.
(23) Reference 21d, p 1063.
(24) Kiroyuki, K.; Shunichi, H.; Hiromichi, O. EP38636A2, Oct. 28, 1981 (CA96: 103561z).
(25) Moriconi, E. J.; Mazzochi, P. H. *J. Org. Chem.* **1966**, *31*, 1372.
(26) Kirk, K. L. *J. Org. Chem.* **1978**, *43*, 4381.
(27) Marckwald, W. *Chem. Ber.* **1892**, *25*, 2354.

Scheme II



We hope that the compounds disclosed in this paper will become important pharmacological tools in the future study of the AII receptor. Work is currently in progress aimed toward further improving the oral activity and binding affinities of these angiotensin II receptor blockers.

Experimental Section

Physical Methods. Melting points (uncorrected) were determined in an open capillary with a Thomas-Hoover melting point apparatus. IR spectra were determined with either a

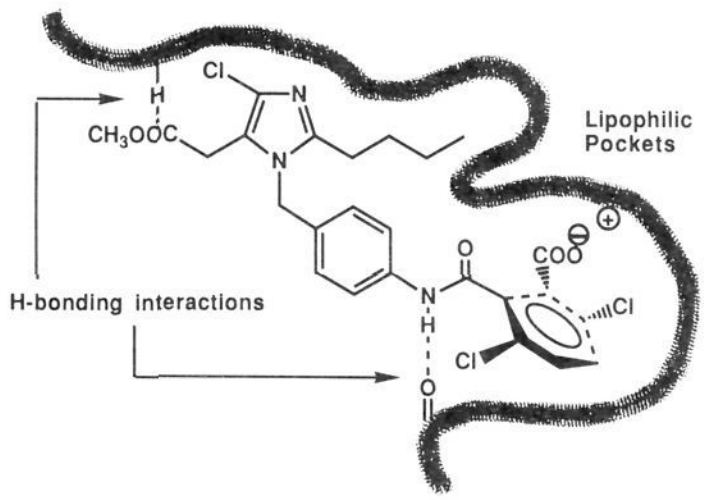
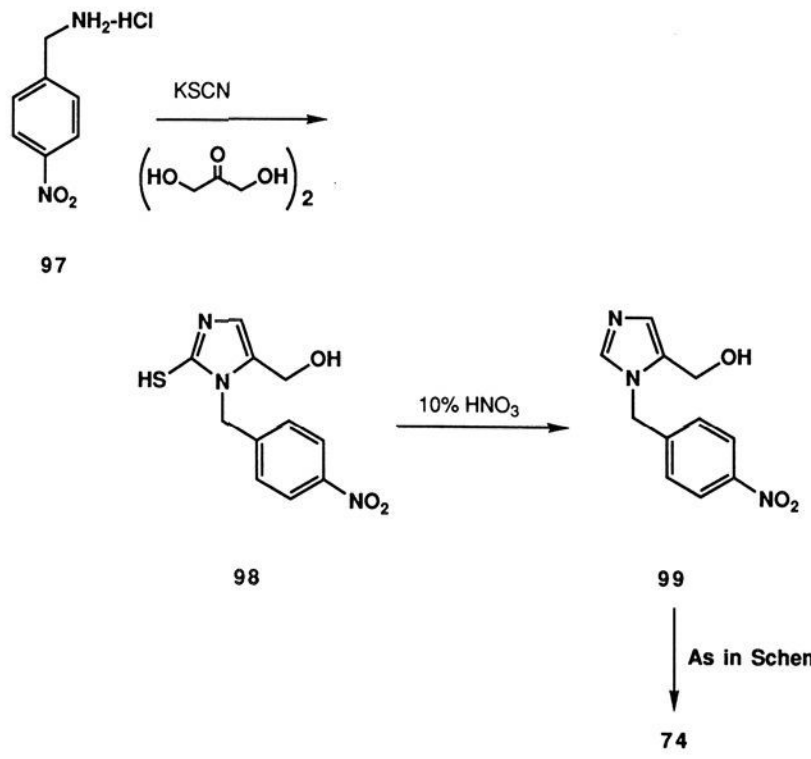


Figure 12. Summary of the key features of the AII receptor. Compounds with an ortho substituent (such as Cl, Me, or OMe) to the amide linkage are the most potent.

Scheme III

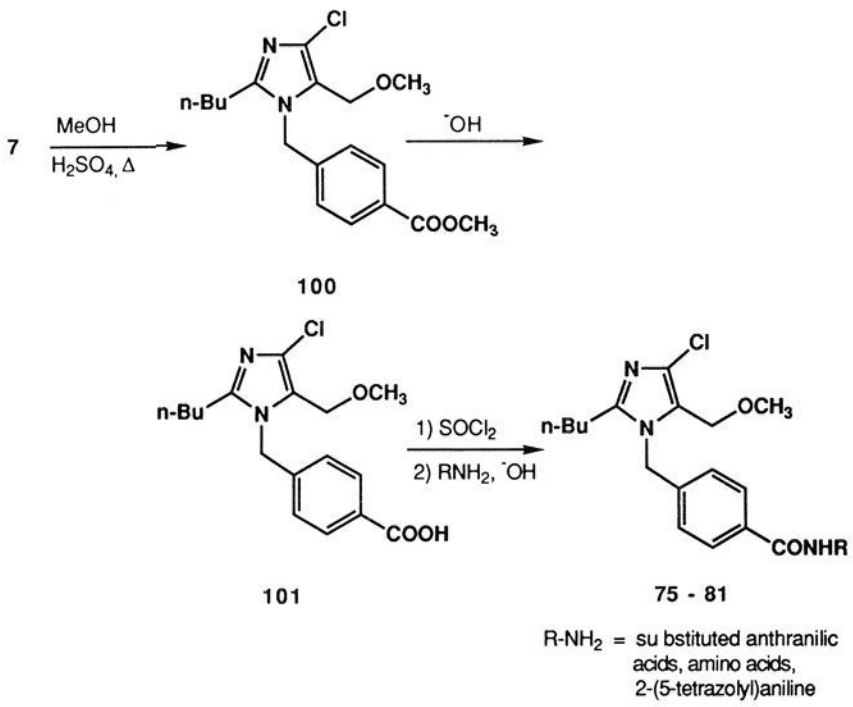


Perkin-Elmer 1600 Series FTIR spectrophotometer or a Perkin-Elmer 1710 FTIR spectrophotometer. NMR spectra were determined with a IBM/Bruker 200SY (200 MHz) spectrometer containing tetramethylsilane as internal standard. Optical rotations were run on a Perkin-Elmer Model 241 polarimeter. Microanalyses were performed by Micro-analysis, Inc., Wilmington, DE, by Spang Microanalytical Laboratory, Eagle Harbor, MI, or by Robertson Laboratory, Inc., Madison, NJ, and were within 0.4% of the calculated values. High-resolution mass spectra were obtained on a VG Instrument Co. Model ZAB-2F spectrometer. FAB mass spectra were obtained on a VG Instrument Co. Model ZAB-2E spectrometer. [^{3}H]AII was obtained from Du Pont NEN Products (Boston, MA). Chromatography was done by using the medium-flash method.[28]

Angiotensin II Receptor Binding Assay.[7b] Male Sprague–Dawley CD rats (300–400 g) were obtained from Charles River Breeding Laboratories (Kingston, NY) and kept on standard laboratory chow. AII receptors from adrenal cortical microsomes were prepared by modifications of the methods of Glossmann et al.[29] and Gunther.[30]

Briefly, adrenals were obtained after cervical dislocation and kept in ice-cold sucrose buffer containing 0.2 M sucrose, 1 mM EDTA, and 10 mM Tris (pH 7.4). After removal of the medulla, the cortices were minced, rinsed, and homogenized in a chilled ground glass tissue grinder. The homogenate was spun at 3000*g*

Scheme IV



for 10 min, and supernatant was decanted through cheesecloth. Combined supernatants were spun at 12000*g* for 13 min. The final supernatant was then centrifuged at 102000*g* for 60 min. All of the previous steps were carried out at 4 °C. The pellet was resuspended in assay buffer containing 0.25% BSA, 5 mM $MgCl_2$, and 50 mM Tris, pH 7.2 at 25 °C.

Binding assays were performed by incubating aliquots of freshly prepared particulate fraction (0.02–0.03 mg of protein) with [^{3}H]AII (2 nm) with or without varying concentrations of inhibitor in 12 × 75 mm polystyrene tubes in a final volume of 0.5 mL of assay buffer. After incubation in a shaking incubator for 60 min at 25 °C, the reaction was terminated by addition of 3 mL of cold assay buffer and the bound and free radioactivity was rapidly passed through glass-fiber filters (Reeves Angel 934 AH, Gaithersburg, MD) prewetted with assay buffer. After rinsing, the filters were air-dried, and trapped radioactivity was determined by scintillation counting. Assays were performed in duplicate. All data presented are specific binding, defined as that displaceable by 1 μM unlabeled AII added to the mixture. The inhibitory concentration (IC_{50}) of an inhibitor that gave 50% displacement of the specific binding of labeled AII (2 nM) was estimated from the linear portion of the displacement curve.

Antihypertensive Effect in Conscious Renal Artery Ligated Hypertensive Rats.[5a,b] Male CD Sprague–Dawley rats (300–350 g) (Charles River Laboratories) were anesthetized with hexobarbital (100 mg/kg ip), and the left renal artery was completely ligated by means of 4-0 silk suture being careful not to damage the left kidney or left renal vein.[31] Six days after ligation, the animals were anesthetized with hexobarbital (90 mg/kg ip), and both the right jugular vein and carotid artery was cannulated. The catheters were passed subcutaneously to the dorsal side of the neck and exteriorized. After the animals had completely recovered from anesthesia (at least 2–2.5 h after the surgery), the carotid catheter was connected to a Gould pressure transducer coupled to a Grass polygraph for monitoring mean arterial pressure. Heart rate was recorded by the Grass tachygraph.

Compounds **37** and **39** were suspended in 0.25% Methocel and given at 100 mg/kg po in a volume of 5 mL/kg. Compound **40** (its sodium salt) was dissolved in water and given at 30 mg/kg po in a volume of 5 mL/kg.

2-*n*-Butyl-4-chloro-5-(hydroxymethyl)-1-[(4-nitrophenyl)methyl]imidazole (83a) and Its Regioisomer (84a). 2-*n*-Butyl-4-chloro-5-(hydroxymethyl)imidazole[6] (**82**) (30.0 g, 159 mmol, 1 equiv) was added to a stirred solution of sodium methoxide in methanol (3.66 g of Na, 159 mmol, 1 equiv in 150 mL of methanol) at 0 °C. The solvent was removed in vacuo and the residue dissolved in DMF (150 mL). 4-Nitrobenzyl bromide (37.8 g, 175 mmol, 1.1 equiv) was added and the solution stirred at 25

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(30) Gunther, S.; Gimborne, M. A., Jr.; Alexander, R. W. *Circ. Res.* **1980**, *47*, 278.
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°C overnight. The solvent was removed in vacuo, and the residue partitioned between ethyl acetate (200 mL) and water (200 mL). The aqueous layer was extracted twice with ethyl acetate (2 × 200 mL). The organic layers were combined and dried ($MgSO_4$), and the solvent was removed in vacuo. Flash chromatography in 1:1 hexane–ethyl acetate over silica gel yielded a faster eluting isomer, **83a** (22.4 g, 44%), and a slower eluting isomer, **84a** (10.3 g, 20%).

83a: mp 104.0–105.5 °C (*n*-BuCl); NMR ($CDCl_3$) δ 8.22 (d, 2 H, J = 9 Hz), 7.20 (d, 2 H, J = 9 Hz), 5.36 (s, 2 H), 4.51 (s, 2 H), 2.52 (t, 2 H, J = 7 Hz), 1.64 (m, 2 H), 1.32 (m, 2 H), 0.88 (t, 3 H, J = 7 Hz); IR 3200 br, 1710, 1520, 1349 (NO_2) cm^{-1}. Anal. ($C_{15}H_{18}ClN_3O_3$) C, H, Cl, N.

84a: mp 109.5–110.5 °C (*n*-BuCl); NMR ($CDCl_3$) δ 8.25 (d, 2 H, J = 7 Hz), 7.21 (d, 2 H, J = 7 Hz), 5.22 (s, 2 H), 4.64 (s, 2 H), 3.22 (m, 1 H), 2.60 (t, 2 H, J = 7 H), 1.66 (t of t, 2 H, J = 7, 7 Hz), 1.37 (t of q, 2 H, J = 7, 7 Hz), 0.88 (t, 3 H, J = 7 Hz); IR (Nujol) 3210 br, 1599, 1110, 1080, 1019, 857, 828, 732 cm^{-1}. Anal. ($C_{15}H_{18}ClN_3O_3$) C, H, Cl, N.

2-*n*-Butyl-4-chloro-5-(cyanomethyl)-1-[(4-nitrophenyl)methyl]imidazole (85a). Imidazolemethanol **83a** (13.9 g, 43 mmol, 1 equiv) was mixed and stirred with thionyl chloride (15.6 mL, 214 mmol, 5 equiv) in chloroform (150 mL) initially at 0 °C followed by warming to room temperature. After 2 h, the mixture was evaporated and the residue taken up in toluene (100 mL). The toluene was evaporated and the residue was again treated with toluene to remove traces of thionyl chloride. The residue was dissolved in DMSO (200 mL) and sodium cyanide (12.6 g, 257 mmol, 6 equiv) was added. After stirring overnight, the mixture was diluted with water (500 mL) and extracted with ethyl acetate (3 × 500 mL). The organic layers were combined and dried ($MgSO_4$), and the solvent was removed in vacuo to yield 16.3 g of a tarry oil. Flash chromatography in 4:1 hexane–ethyl acetate over silica gel yielded 7.1 g (45%) of a burgundy oil which was suitable for further transformation. A 0.5-g sample was recrystallized (hexane–ethyl acetate), yielding 0.25 g of a white solid: mp 118.0–119.0 °C; NMR ($CDCl_3$) δ 8.26 (d, 2 H, J = 8 Hz), 7.19 (d, 2 H, J = 8 Hz), 5.32 (s, 2 H), 3.55 (s, 2 H), 2.62 (t, 2 H, J = 7 Hz), 1.70 (m, 2 H), 1.38 (m, 2 H), 0.91 (t, 3 H, J = 7 Hz); IR (neat) 2263, 1347 cm^{-1}. Anal. ($C_{16}H_{17}ClN_4O_2$) C, H, Cl, N.

2-*n*-Butyl-4-chloro-1-[(4-nitrophenyl)methyl]imidazole-5-acetic Acid (86a). 2-Butyl-4-chloro-5-(cyanomethyl)-1-[(4-nitrophenyl)methyl]imidazole (**85a**) (7.08 g) and a 1:1 mixture of 12 N HCl and glacial acetic acid (175 mL) were mixed and refluxed for 6 h. The solvents were removed by rotary evaporation, and water (300 mL) was then added to the residue. After a few minutes, the product precipitated and was collected and dried to yield 7.35 g (98%) of a white solid: mp 207.0–210.0 °C; NMR (DMSO-d_6/$CDCl_3$) δ 8.20 (d, 2 H, J = 10 Hz), 7.22 (d, 2 H, J = 10 Hz), 5.28 (s, 2 H), 3.42 (s, 2 H), 2.52 (t, 2 H, J = 7 Hz), 1.64 (m, 2 H), 1.34 (m, 2 H), 0.86 (t, 3 H, J = 7 Hz); IR (neat) 3440 br, 1710 br, 1349 cm^{-1}. Anal. ($C_{16}H_{18}ClN_3O_4$) C, H, Cl, N.

Methyl 2-*n*-Butyl-4-chloro-1-[(4-nitrophenyl)methyl]-imidazole-5-acetate (11). The imidazoleacetic acid (**86a**) (7.35 g, 20.9 mmol, 1 equiv), 3.1 M HCl in dioxane (34.0 mL, 105.4 mmol, 5 equiv), and 100 mL of methanol were mixed and refluxed for 7.5 h. The solvents were removed by rotary evaporation, and the residue was taken up in methylene chloride and 1 N NaOH (300 mL each). The layers were separated, and the organic layer was washed two more times with 1 N NaOH (300 mL each), dried, and concentrated to yield 5.43 g (71%) of a white solid: mp 97.5–100.0 °C; NMR (DMSO-d_6) δ 8.23 (d, 2 H, J = 9 Hz), 7.33 (d, 2 H, J = 9 Hz), 5.50 (s, 2 H), 3.73 (s, 2 H), 3.40 (s, 3 H), 2.66 (t, 2 H, J = 7 Hz), 1.53 (m, 2 H), 1.22 (m, 2 H), 0.76 (t, 3 H, J = 7 Hz); IR 3400, 1742, 1171, 1015, 860, 841, 798, 735 cm^{-1}. Anal. ($C_{17}H_{20}ClN_3O_4$) C, H, Cl, N.

Methyl 1-[(4-Aminophenyl)methyl]-2-*n*-butyl-4-chloro-imidazole-5-acetate (5a). The nitro ester 11 (5.00 g, 13.7 mmol, 1 equiv), iron (2.67 g, 47.8 mmol, 3.5 equiv), glacial acetic acid (5.47 mL, 95.3 mmol, 7 equiv), and methanol (250 mL) were combined and refluxed for 5.5 h. The solvent was removed by rotary evaporation. The residue was diluted with water (300 mL) and extracted five times with 300-mL portions of ethyl acetate. The organic layers were dried ($MgSO_4$) and concentrated. The residue was flash chromatographed in 75:25 hexane–ethyl acetate over silica gel to yield 4.53 g (98%) of a golden yellow oil which crystallized after standing for several days: mp 87.5–88.5 °C; NMR ($CDCl_3$) δ 6.72 (d, 2 H, J = 7 Hz), 6.60 (d, 2 H, J = 7 Hz), 4.99 (s, 2 H), 3.61 (s, 3 H), 3.47 (s, 2 H), 2.60 (t, 2 H, J = 7 Hz), 1.68 (m, 2 H), 1.35 (m, 2 H), 0.86 (t, 3 H, J = 7 Hz); IR 3400 br, 1732 cm^{-1}. Anal. ($C_{17}H_{22}ClN_3O_2$) C, H, Cl, N.

Methyl 2-*n*-Butyl-4-chloro-1-[[4-(diphenylmaleimidyl)-phenyl]methyl]imidazole-5-acetate (16). Aniline derivative **5a** (0.5 g, 1.5 mmol, 1 equiv) and α,β-diphenylmaleic anhydride (0.37 g, 1.5 mmol, 1 equiv) were mixed and stirred in chloroform. No reaction occurred. Trimethylaluminum (1.12 mL of a 2 M solution in toluene, 2.24 mmol, 1.5 equiv) was then slowly dripped into the solution (CH_4 evolution!) and the contents allowed to stir for 48 h. The reaction was cautiously poured into a 5% NaH_2PO_4 (aq) solution (200 mL) followed by extraction of the aqueous with ethyl acetate (3 × 100 mL). The organic layers were dried ($MgSO_4$) and evaporated, and the residue was flash chromatographed over silica gel in 75:25 hexane–ethyl acetate to yield 300 mg (35%) of a glass: mp 54–61 °C; NMR ($CDCl_3$) δ 7.59–7.35 (m, 12), 7.07 (d, 2, J = 8 Hz), 5.17 (s, 2), 3.61 (s, 3), 3.52 (s, 2), 2.62 (t, 2, J = 7 Hz), 1.74 (t of t, 2, J = 7, 7 Hz), 1.39 (t of q, 2, J = 7, 7 Hz), 0.94 (t, 3, J = 7 Hz); IR 1739, 1710, 795, 759, 690 cm^{-1}. Anal. ($C_{33}H_{30}ClN_3O_4$) C, H, Cl, N.

Methyl 2-*n*-Butyl-1-[[4-(2-carboxybenzamido)phenyl]-methyl]-4-chloroimidazole-5-acetate (22). A chloroform solution of amino ester **5a** (500 mg, 1.5 mmol, 1 equiv) was mixed with a chloroform solution (10 mL) of phthalic anhydride (221 mg, 1.5 mmol, 1 equiv). After 5 min of stirring at room temperature, product began to precipitate. After 24 h, the product was filtered, washed with a minimum amount of $CHCl_3$, and dried to yield 400 mg of a white solid. After some evaporation, the mother liquor yielded an additional 220 mg of product, both crops having identical melting points (yield 86%): mp 109.5–112.5 °C; NMR (DMSO-d_6) δ 10.37 (s, 1 H), 7.85 (d, 2 H, J = 8 Hz), 7.71–7.50 (m, 5 H), 6.96 (d, 2 H, J = 10 Hz), 5.12 (s, 2 H), 3.60 (s, 2 H), 3.49 (s, 3 H), 2.55 (t, 2, J = 7 Hz), 1.52 (m, 2 H), 1.27 (m, 2 H), 0.83 (t, 3 H, J = 7 Hz); IR 3300, 1740, 1680, 790, 757, 710 cm^{-1}. The carboxylic acid could be titrated with 1 equiv of 1.000 N NaOH to form the sodium salt. Anal. ($C_{25}H_{26}ClN_3O_5$) C, H, Cl, N.

Methyl 2-*n*-Butyl-4-chloro-1-[(4-phthalimidophenyl)-methyl]imidazole-5-acetate (25). Phthalamic acid **22** (1.00 g), methanol (50 mL), and 3.6 mL of 3.1 N HCl in dioxane were refluxed for 6 days. The solvent was removed in vacuo and the residue taken up in ethyl acetate (100 mL). The organic phase was washed with 1 N NaOH (2 × 100 mL) and brine (1 × 100 mL), dried ($MgSO_4$), and concentrated. The residue was flash chromatographed over silica gel in 75:25 hexane–ethyl acetate to yield 400 mg (42%) of an oil which eventually crystallized: mp 141.5–143.0 °C; NMR ($CDCl_3$) δ 7.92 (m, 2 H), 7.80 (m, 2 H), 7.43 (d, 2 H, J = 10 Hz), 7.08 (d, 2 H, J = 10 Hz), 5.17 (s, 2 H), 3.62 (s, 3 H), 3.50 (s, 2 H), 2.62 (t, 2 H, J = 7 Hz), 1.71 (t of t, 2 H, J = 7, 7 Hz), 1.36 (t of q, 2 H, J = 7, 7 Hz), 0.89 (t, 3 H, J = 7 Hz); IR 1719, 720 cm^{-1}. Anal. ($C_{25}H_{24}ClN_3O_4$) C, H, Cl.

2-*n*-Butyl-4-chloro-5-(methoxymethyl)-1-[(4-nitrophenyl)methyl]imidazole (87a). Imidazolemethanol **83a** (10.5 g, 32.4 mmol, 1 equiv), concentrated sulfuric acid (26 mL), and methanol (300 mL) were mixed and refluxed overnight. The solvent was removed in vacuo and the residue taken up in water (about 300 mL). The pH was adjusted to 5 with 1 N NaOH and the aqueous portion extracted with ethyl acetate (3 × 250 mL). The organic layers were collected and dried ($MgSO_4$) and the solvent removed in vacuo to yield 11.57 g of an amber oil which was suitable for further transformation: NMR ($CDCl_3$) δ 8.22 (d, 2 H, J = 8 Hz), 7.15 (d, 2 H, J = 8 Hz), 5.26 (s, 2 H), 4.25 (s, 2 H), 3.23 (s, 3 H), 2.52 (t, 2 H, J = 7 Hz), 1.64 (t of t, 2 H, J = 7, 7 Hz), 1.28 (t of q, 2 H, J = 7, 7 Hz), 0.81 (t, 3 H, J = 7 Hz); IR 2873, 1346, 799, 659 cm^{-1}. Anal. ($C_{16}H_{20}ClN_3O_3 \cdot (H_2O)_{0.5}$ C, H, Cl.

1-[(4-Aminophenyl)methyl]-2-*n*-butyl-4-chloro-5-(methoxymethyl)imidazole (5b). (Nitrobenzyl)imidazole **87a** (11.22 g) was carefully added to a mixture of methanol (100 mL) containing 1.0 g of 10% palladium on carbon. Hydrogen gas was then bubbled through the solution for 4 h. The solution was filtered through Celite and the solvent removed in vacuo to yield 9.23 g of an amber oil. Flash chromatography in 1:1 hexane–ethyl acetate over silica gel followed by recrystallization from hexane–*tert*-butyl

methyl ether yielded 5.40 g (56.5% from **87a**) of an orange solid: mp 79.5–81.5 °C; NMR ($CDCl_3$) δ 7.99 (s, 1 H), 6.78 (d of d, 4 H, J = 5, 5 Hz), 5.05 (s, 2 H), 4.24 (s, 2 H), 3.27 (s, 3 H), 2.59 (t, 2 H, J = 7 Hz), 1.62 (t of t, 2 H, J = 7, 7 Hz), 1.32 (t of q, 2 H, J = 7, 7 Hz), 0.84 (t, 3 H, J = 7 Hz); IR 3350, 2605, 820, 778 cm^{-1}. Anal. ($C_{16}H_{22}ClN_3O$) C, H, Cl, N.

2-*n*-Butyl-1-[[4-(2-carboxybenzamido)phenyl]methyl]-4-chloro-5-(methoxymethyl)imidazole (24). Aniline derivative **5b** (3.00 g, 9.7 mmol, 1 equiv) and phthalic anhydride (1.44 g, 9.7 mmol, 1 equiv) were reacted by the procedure for compound **22**. Workup yielded 1.71 g of an off-white powder, which was washed with acetonitrile. The insoluble material was filtered and dried to yield 1.17 g of a white powder (26%): mp 165.5–166.5 °C; NMR (DMSO-d_6) δ 13.01 (m, 1 H), 10.39 (s, 1 H), 7.87 (d, 1 H, J = 7 Hz), 7.75–7.46 (m, 5 H), 7.03 (d, 2 H, J = 8 Hz), 5.16 (s, 2 H), 4.30 (s, 2 H), 3.20 (s, 3 H), 2.54 (t, 2 H, J = 7 Hz), 1.54 (t of t, 2 H, J = 7, 7 Hz), 1.30 (t of q, 2 H, J = 7, 7 Hz), 0.83 (t, 3 H, J = 7 Hz); IR 3288 br, 1694 w, 1658 s, 1088, 803, 709 cm^{-1}. Anal. ($C_{24}H_{26}ClN_3O_4$) C, H, Cl.

2-*n*-Butyl-4-chloro-1-[(4-cyanophenyl)methyl]-5-(hydroxymethyl)imidazole (83d and Its Regioisomer 84d). The title compound was prepared by the method described for **83a** starting with 4-(bromomethyl)benzonitrile (8.60 g, 44 mmol, 1.1 equiv). The crude product was flash chromatographed over silica gel in 1:1 hexane–ethyl acetate to yield 6.83 g (56%) of one regioisomer (**83d**) as a white solid: mp 124.5–127.5 °C; NMR ($CDCl_3$) δ 7.65 (d, 2 H, J = 8 Hz), 7.13 (d, 2 H, J = 8 Hz), 5.30 (s, 2 H), 4.46 (s, 2 H), 2.49 (t, 2 H, J = 7 Hz), 1.59 (m, 2 H), 1.28 (m, 2 H), 0.84 (t, 3 H, J = 7 Hz); IR 2227 cm^{-1}. Anal. ($C_{16}H_{18}ClN_3O$) C, H, N.

Continued elution yielded 3.56 g (29%) of the second regioisomer (**84d**) as a white solid: mp 98.0–100.0 °C; NMR ($CDCl_3$) δ 7.67 (d, 2 H, J = 9 Hz), 7.12 (d, 2 H, J = 9 Hz), 5.17 (s, 2 H), 4.62 (s, 2 H), 2.57 (t, 2 H, J = 7 Hz), 1.60 (t of t, 2 H, J = 7, 7 Hz), 1.31 (t of q, 2 H, J = 7, 7 Hz), 0.86 (t, 3 H, J = 7 Hz); IR 3190, 2230, 1030, 810, 549 cm^{-1}. Anal. ($C_{16}H_{18}ClN_3O$) C, H, N.

2-*n*-Butyl-4-chloro-5-(hydroxymethyl)-1-[(4-carboxyphenyl)methyl]imidazole (7). 2-*n*-Butyl-4-chloro-5-(hydroxymethyl)-1-[(4-cyanophenyl)methyl]imidazole (**83d**) (1.00 g, 3.3 mmol, 1 equiv), 1.000 N NaOH (9.88 mL, 9.9 mmol, 3 equiv), and ethylene glycol (20 mL) were mixed and refluxed under N_2 for 24 h. Water was added (50 mL) and the pH adjusted to 2 with concentrated HCl. The mixture was extracted once (50 mL) with ethyl acetate. The organic layer was washed with water (3 × 50 mL) and dried ($MgSO_4$) and the solvent removed in vacuo to yield 0.89 g of a white glass. Recrystallization from hexane–ethyl acetate yielded 0.78 g. Recrystallization a second time from ethyl acetate yielded 0.58 g (55%) of a white solid: mp 165.0–166.0 °C; NMR ($CDCl_3$ + DMSO-d_6) δ 7.96 (d, 2 H, J = 8 Hz), 7.13 (d, 2 H, J = 8 Hz), 5.33 (s, 2 H), 4.40 (s, 2 H), 2.50 (t, 2 H, J = 7 Hz), 1.57 (t of t, 2 H, J = 7, 7 Hz), 1.27 (t of q, 2 H, J = 7, 7 Hz), 0.85 (t, 3 H, J = 7 Hz); IR 3400 br, 1700 br, 750 br cm^{-1}. Anal. ($C_{16}H_{19}ClN_2O_3$) C, H, Cl, N.

5-(Acetoxymethyl)-2-*n*-butyl-1-[(4-carboxyphenyl)methyl]-4-chloroimidazole (9). The imidazolemethanol **7** (2.00 g, 6.2 mmol, 1 equiv), acetic anhydride (1.46 mL, 15.5 mmol, 2.5 equiv), triethylamine (2.59 mL, 18.6 mmol, 3 equiv), and THF (50 mL) were mixed and stirred for 3 days. Water (200 mL) was added to the solution and the mixture was stirred for 0.5 h. The pH was lowered to 5 with concentrated HCl and the mixture extracted with ethyl acetate (3 × 100 mL). The organic layers were dried ($MgSO_4$) and concentrated to yield 2.47 g of a brown oil. This product (2.16 g) was dissolved in a minimum of ethyl acetate and dicyclohexylamine (DCHA) (1.18 mL, 1 equiv) was added. The solution was allowed to slowly evaporate overnight. The DCHA salt thus obtained (1.43 g) was subsequently taken up in ethyl acetate (100 mL) and washed with 1 N HCl (3 × 100 mL), followed by brine. The organic layer was dried ($MgSO_4$) and concentrated to yield a light yellow oil (670 mg) (30%): NMR ($CDCl_3$) δ 8.09 (d, 2 H, J = 10 Hz), 7.05 (d, 2 H, J = 10 Hz), 5.20 (s, 2 H), 4.98 (s, 2 H), 2.58 (t, 2 H, J = 7 Hz), 1.82 (t of t, 2 H, J = 7, 7 Hz), 1.33 (t of q, 2 H, J = 7, 7 Hz), 0.86 (t, 3, J = 7 Hz); IR 1741, 1715, 750 cm^{-1}. Anal. ($C_{18}H_{21}ClN_2O_4$) C, H, N.

2-*n*-Butyl-4-chloro-5-(cyanomethyl)-1-[(4-cyanophenyl)methyl]imidazole (85d). Thionyl chloride (3.60 mL, 49 mmol, 5 equiv) was slowly dripped into a solution of 2-*n*-butyl-4-chloro-1-[(4-cyanophenyl)methyl]-5-(hydroxymethyl)imidazole (**83d**) (3.0 g, 9.9 mmol, 1 equiv) in a minimum of $CHCl_3$. The mixture was stirred for 2 h at 25 °C after which the solvent was removed in vacuo and the residue suspended in toluene (200 mL). The toluene was removed on the rotary evaporator and this procedure was repeated again to remove all traces of thionyl chloride. The chloride was then dissolved in DMSO (minimum to dissolve) and added to a solution of sodium cyanide (2.90 g, 59 mmol, 6 equiv) in DMSO (200 mL). The solution was stirred overnight under N_2 at room temperature after which 500 mL of H_2O was added and the aqueous layer was extracted with ethyl acetate (3 × 300 mL). The organic layers were dried and concentrated, and the residue was flash chromatographed in 4:1 hexane–ethyl acetate over silica gel to yield 1.62 g (52%) of a light yellow solid: mp 109.5–113.0 °C; NMR ($CDCl_3$) δ 7.70 (d, 2 H, J = 10 Hz), 7.12 (d, 2 H, J = 10 Hz), 3.51 (s, 2 H), 2.60 (t, 2 H, J = 7 Hz), 1.70 (m, 2 H), 1.40 (m, 2 H), 0.90 (t, 3 H, J = 7 Hz); IR 3040, 2261, 2230 cm^{-1}. Anal. ($C_{17}H_{17}ClN_4$) C, H, Cl, N.

2-*n*-Butyl-1-[(4-carboxyphenyl)methyl]-4-chloroimidazole-5-acetic Acid (4). The bisnitrile **85d** (4.3 g) and a solution of 1:1 12 N HCl–glacial acetic acid (100 mL) were mixed and refluxed for 6 h. The solvents were removed in vacuo, and the residue was flash chromatographed on silica gel in methanol. The product was dissolved in 1 N NaOH (200 mL), the solids were filtered, and the clear filtrate was acidified to pH 2–3 with concentrated HCl. A gummy precipitate was obtained. Ethyl acetate (200 mL) was added to dissolve the gum, and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 200 mL). The organic layers were combined and dried ($MgSO_4$), and the solvent was removed in vacuo to yield 1.39 g of a light yellow glass. The filtered solids were dissolved in a 1:1 mixture of H_2O and ethyl acetate (200 mL). While the mixture was stirred, the pH was adjusted to 2 with concentrated HCl. The insoluble matter was filtered, and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 100 mL), the organic layers were combined and dried ($MgSO_4$), and the solvent was removed in vacuo to yield 630 mg of a white glass. Recrystallization of the glasses (hexane–ethyl acetate) yielded 1.82 g (38%) of a white solid: mp 170.0–174.0 °C; NMR (DMSO-d_6) δ 7.90 (d, 2 H, J = 9 Hz), 7.14 (d, 2 H, J = 9 Hz), 5.27 (s, 2 H), 3.49 (s, 2 H), 2.50 (t, 2 H, J = 7 Hz), 1.49 (t of t, 2 H, J = 7, 7 Hz), 1.25 (t of q, 2 H, J = 7, 7 Hz), 0.80 (t, 3 H, J = 7 Hz); IR (Nujol) 1684 (br), 1199, 748 cm^{-1}. Anal. ($C_{17}H_{19}ClN_2O_4$) C, H, Cl, N.

Methyl 2-*n*-Butyl-4-chloro-1-[[4-(trifluoromethanesulfonamido)phenyl]methyl]imidazole-5-acetate (37). A solution of triflic anhydride (0.88 mL, 5.2 mmol, 1 equiv) in methylene chloride (5 mL) was dripped into a solution of methyl 2-butyl-1-[(4-aminophenyl)methyl]-4-chloroimidazole-5-acetate (**5a**) (1.74 g, 5.2 mmol, 1 equiv) and triethylamine (1.44 mL, 10.4 mmol, 2 equiv) in 20 mL of methylene chloride at −78 °C. The solution was kept at −78 °C for 1 h after which it was allowed to warm to room temperature. After 24 h, the reaction was quenched with water (100 mL) and the pH adjusted to 5 with concentrated HCl and the aqueous extracted with methylene chloride (5 × 100 mL). The organic layers were dried ($MgSO_4$) and concentrated, and the residue was flash chromatographed in 1:1 hexane–ethyl acetate on silica gel. The crystalline product which formed in the 1:1 hexane–ethyl acetate solution while the crude product was being applied to the column was isolated (1.03 g). Chromatography of the mother liquor yielded an additional 1.03 g (42%) of the title compound as a white solid: mp 154.0–157.0 °C; the product could be titrated with 1 equiv of 1.000 N NaOH: NMR ($CDCl_3$) δ 7.32 (d, 2 H, J = 10 Hz), 6.91 (d, 2 H, J = 10 Hz), 5.15 (s, 2 H), 3.62 (s, 3 H), 3.46 (s, 2 H), 2.55 (t, 2 H, J = 7 Hz), 1.56 (m, 2 H), 1.26 (m, 2 H), 0.72 (t, 3 H, J = 7 Hz); IR 1747, 1373, 1214, 1145, 812, 634, 600 cm^{-1}. Anal. ($C_{18}H_{21}ClF_3N_3O_4S$) C, H, N.

2-*n*-Butyl-4-chloro-5-[(1*H*-tetrazol-5-yl)methyl]-1-[[4-(1*H*-tetrazol-5-yl)phenyl]methyl]imidazole (39). 2-Butyl-4-chloro-1-[(4-cyanophenyl)methyl]-5-(cyanomethyl)imidazole (**85d**) (2.00 g, 6.4 mmol, 1 equiv), ammonium chloride (0.91 g, 17 mmol, 2.7 equiv), sodium azide (1.11 g, 17 mmol, 2.7 equiv), and DMF (25 mL) were mixed and stirred at 80 °C for 24 h. The mixture was filtered and the solvent removed by rotary evaporation. The residue was dissolved in water (100 mL) and methylene chloride

(100 mL). The layers were separated, and the aqueous layer was extracted again with methylene chloride (2 × 100 mL). The aqueous layer was acidified with concentrated HCl to pH of 3. The solid which precipitated was collected and dried to yield 430 mg (17%) of the title compound as a tan solid: mp 228 °C (dark), 229.0–230.0 °C dec. The product when titrated with 1.000 N NaOH showed the presence of exactly two acidic functionalities. NMR (DMSO-d_6) δ 7.95 (d, 2 J = 7 Hz), 7.13 (d, 2, J = 7 Hz), 5.34 (s, 2), 4.23 (s, 2), 2.53 (t, 2 J = 7 Hz), 1.50 (t of t, 2, J = 7, 7 Hz), 1.26 (t of q, 2, J = 7 Hz), 0.79 (t, 3, J = 7 Hz); IR 3420 br, 1930 br, 740 cm^{-1}. Anal. ($C_{17}H_{19}ClN_{10}$) C, H, N.

Methyl 2-*n*-Butyl-4-chloro-1-[[4-[2-(trifluoromethanesulfonamido)benzamido]phenyl]methyl]imidazole-5-acetate (40). Aniline derivative **5a** (1.00 g, 2.98 mmol, 1 equiv) and 2-(trifluoromethanesulfonamido)benzoyl chloride (described in EP 38636A2)[24] (0.86 g, 2.99 mmol, 1 equiv) were mixed and stirred in 50 mL of methylene chloride (acid chloride was added last) at 25 °C. After 2.5 h the reaction was filtered, the solvent was removed in vacuo, and the residue was recrystallized from ethyl acetate–hexane to yield 1.07 g (61%) of light yellow crystals: mp 151.0–152.0 °C; NMR ($CDCl_3$) δ 9.32 (s, 1 H), 8.02 (d, 1 H, J = 10 Hz), 7.79 (d, 1 H, J = 10 Hz), 7.56 (d of d, 2 H, J = 10, 10 Hz), 7.50 (d, 2 H, J = 10 Hz), 7.78 (d of d, 1 H, J = 10, 10 Hz), 6.86 (d, 2 H, J = 10 Hz), 5.10 (s, 2 H), 3.58 (s, 3 H), 3.45 (s, 2 H), 2.45 (t, 2 H, J = 7 Hz), 1.52 (t of t, 2 H, J = 7, 7 Hz), 1.22 (t of q, 2 H, J = 7, 7 Hz), 0.75 (t, 3 H, J = 7 Hz). Titration of the product with 1.000 N NaOH shows the presence of exactly one acidic functionality. IR 1750, 1641, 1601, 1543, 1519, 1498, 1462, 1260, 1227, 814, 754 cm^{-1}. Anal. ($C_{25}H_{26}ClF_3N_4O_5S$) C, H, N.

Methyl 2-*n*-Butyl-4-chloro-1-[[4-[*N*-(phenylmethyl)-*N*-[2-(trifluoromethanesulfonamido)benzoyl]amino]phenyl]methyl]imidazole-5-acetate (41). Part A. Methyl 2-*n*-Butyl-4-chloro-1-[[4-(*N*-(phenylmethyl)amino)phenyl]methyl]imidazole-5-acetate (12). A mixture of aniline **5a** (1.00 g, 3.0 mmol, 1 equiv), benzaldehyde (0.30 mL, 3.0 mmol, 1 equiv), 4A powdered molecular sieves (enough to make a slurry), and 40 mL of THF was stirred overnight at room temperature. The next day, more benzaldehyde (0.2 mL) and acidic Al_2O_3 (activity 1, 1 g) were added, and the slurry was stirred another 24 h. The solids were filtered, and the solvent from the filtrate was removed in vacuo. The residue was dissolved in methanol (10 mL) and sodium cyanoborohydride was added (0.19 g, 3.0 mmol, 1 equiv). The mixture was stirred for 24 h, after which the solvent was removed in vacuo to yield a green oil which was flash chromatographed over silica gel in 70:30 hexane–ethyl acetate to yield 740 mg (58%) of product as an oil which was suitable for further transformation: NMR ($CDCl_3$) δ 7.42–7.24 (m, 5 H), 6.74 (d, 2 H, J = 7 Hz), 6.56 (d, 2 H, J = 7 Hz), 4.98 (s, 2 H), 4.31 (s, 2 H), 3.61 (s, 3 H), 3.48 (s, 2 H), 2.60 (t, 2 H, J = 7 Hz), 1.67 (t of t, 2 H, J = 7, 7 Hz), 1.35 (t of q, 2 H, J = 7, 7 Hz), 0.89 (t, 3 H, J = 7 Hz); IR 1740, 1687, 1667, 820, 721 cm^{-1}; MS m/e calcd for $C_{24}H_{28}ClN_3O_2$ 425.1868, found 425.1853.

Part B (41). Aniline derivative **12** (700 mg, 1.6 mmol, 1 equiv), 2-(trifluoromethanesulfonamido)benzoyl chloride (0.47 g, 1.6 mmol, 1 equiv), sodium bicarbonate (0.41 g, 4.9 mmol, 3 equiv), and methylene chloride (25 mL) were mixed and stirred at 25 °C. After 24 h, 0.25 equiv more of the acid chloride was added. After an additional 24 h, 0.25 equiv more of the acid chloride was added. The following day, the reaction was worked up by slowly adding 1 N HCl to pH 5 followed by extraction with ethyl acetate (3 × 150 mL). The organic layers were combined and dried ($MgSO_4$), and the solvent was removed in vacuo and the residue flash chromatographed in 75:25 hexane–ethyl acetate to yield 900 mg (81%) of a light yellow oil: NMR ($CDCl_3$) δ 7.59 (d, 1, J = 10 Hz), 7.33–7.16 (m, 6), 6.89 (d, 2, J = 10 Hz), 6.76 (d, 2, J = 10 Hz), 6.93–6.70 (m, 2 H), 5.12 (s, 2), 5.02 (s, 2), 3.55 (s, 3), 3.39 (s, 2), 2.47 (t, 2, J = 7 Hz), 1.64 (t of t, 2, J = 7, 7 Hz), 1.30 (t of q, 2, J = 7, 7 Hz), 0.88 (t, 3, J = 7 Hz); IR 3440, 1741, 1203 (s), 1146, 753, 700, 603 cm^{-1}. Anal. ($C_{32}H_{32}ClF_3N_4O_5S$) C, H, N.

Methyl 2-*n*-Butyl-4-chloro-1-[[4-[5-methyl-2-(trifluoromethylsulfonamido)benzamido]phenyl]methyl]imidazole-5-acetate (46). Part A. 5-Methyl-2-(trifluoromethanesulfonamido)benzoyl Chloride (93a). Trifluoromethanesulfonic anhydride (11.1 mL, 66.6 mmol, 2 equiv) was added dropwise to a stirred solution under N_2 of methyl 2-amino-5-methylbenzoate[32] (5.5 g, 33.3 mmol, 1 equiv) and triethylamine (4.7 mL, 33.3 mmol, 1 equiv) in methylene chloride (50 mL) at −78 °C. The reaction was kept below −40 °C for 3 h after which the pH was adjusted first to 8 with 1 N NaOH, followed by 2 with concentrated HCl. The layers were separated, and the organic layer was washed with water (3×). The organic layer was dried ($MgSO_4$) and the solvent removed in vacuo to yield 7.00 g (70%) of a wax. The product (methyl 5-methyl-2-(trifluoromethanesulfonamido)benzoate) was suitable for further transformation: NMR ($CDCl_3$) δ 11.14 (m, 1 H), 7.85 (s, 1 H), 7.63 (d, 1 H, J = 9 Hz), 7.35 (d, 1 H, J = 9 Hz), 3.98 (s, 3 H), 2.38 (s, 3 H).

The above ester (7.00 g, 23.5 mmol, 1 equiv) and 1 M NaOH (50.0 mL, 50 mmol, 2.1 equiv) were mixed and refluxed under N_2 for 2 h. The pH was adjusted to 3 with 1 N HCl and the resultant precipitate was filtered and dried under high vacuum overnight to yield 6.30 g (95%) of the corresponding carboxylic acid as a white powder: mp 172.0–174.0 °C; NMR (DMSO-d_6) δ 11.1 (bm, 2 H), 7.33 (s, 1 H), 7.42 (d, 1 H, J = 9 Hz), 7.32 (d, 1 H, J = 9 Hz), 2.33 (s, 3 H). This acid (6.3 g, 22.3 mmol, 1 equiv) was refluxed with thionyl chloride (16.2 mL, 222 mmol, 10 equiv) for 3 h. The excess thionyl chloride was removed in vacuo and the residue azeotroped with toluene. Kugelrohr distillation (92 °C at 0.6 mm) yielded 5.9 g (88%) of the corresponding acid chloride as an oil: IR 1713 cm^{-1}.

Part B (46). The acid chloride (0.90 g, 3.0 mmol, 1 equiv) was dissolved in 10 mL of methylene chloride and added to a stirred mixture of aniline **5a** (1.00 g, 3.0 mmol, 1 equiv), sodium bicarbonate (1.25 g, 14.9 mmol, 5 equiv) in methylene chloride (25 mL) at 25 °C. After 24 h, the solids were filtered, and the filtrate was evaporated to a glass. Subsequent crystallization from *n*-butyl chloride yielded 1.10 g (61%) of a white solid: mp 188.5–189.5 °C; NMR (DMSO-d_6) δ 11.40 (m, 1 H), 7.69 (d, 2 H, J = 9 Hz), 7.63 (s, 1 H), 7.33 (s, 2 H), 7.05 (d, 2 H, J = 9 Hz), 5.22 (s, 2 H), 3.69 (s, 2 H), 3.50 (s, 3 H), 2.66 (t, 2 H, J = 7 Hz), 2.36 (s, 3 H), 1.55 (t of t, 2 H, J = 7, 7 Hz), 1.30 (t of q, 2 H, J = 7, 7 Hz), 0.84 (t, 3 H, J = 7 Hz); IR 3231, 1748, 967, 929 cm^{-1}. Anal. ($C_{26}H_{28}ClF_3N_4O_5S·H_2O$) C, H, N.

Methyl 2-*n*-Butyl-4-chloro-1-[[4-[*trans*-2-(trifluoromethanesulfonamido)cyclohexanecarboxamido]phenyl]methyl]imidazole-5-acetate and Its Cis Isomer (50 and 51). Part A. *trans*-2-(Trifluoromethanesulfonamido)cyclohexanecarboxylic Acid (94). The entitled compound was synthesized from ethyl *trans*-2-aminocyclohexanecarboxylate[25] by the procedure described for compound **46**, part A: mp (*n*-BuCl) 114.5–118.5 °C; NMR (DMSO-d_6) δ 12.47 (bs, 1 H), 9.52 (bs, 1 H), 2.35 (d of d of d, 1 H, J = 10, 10, 4 Hz), 2.10–1.13 (m, 9 H); IR 3300, 1709, 1381, 1232, 1185, 1150, 1069, 612 cm^{-1}. Anal. ($C_8H_{12}F_3NO_4S$) C, H, N.

Part B (50 and 51). Carboxylic acid **94** (500 mg, 1.82 mmol, 1 equiv) and thionyl chloride (2.30 mL, 31.5 mmol, 17.3 equiv) were mixed and refluxed for 2 h. The excess thionyl chloride was removed in vacuo and the residue suspended in toluene. The toluene was removed by rotary evaporation and the procedure repeated to remove traces of thionyl chloride. Final rotary evaporation yielded 460 mg of a white crystalline acid chloride product which was used without further purification (IR 1789 cm^{-1}).

Aniline **5a** (530 mg, 1.57 mmol, 1 equiv), *trans*-2-(trifluoromethanesulfonamido)cyclohexanoyl chloride (460 mg, 1.57 mmol, 1 equiv), and sodium bicarbonate (400 mg, 4.70 mmol, 3 equiv) were mixed and stirred in chloroform (20 mL) overnight. Water (100 mL) was then added, and the pH was adjusted to 4 with 1 N HCl. The aqueous was extracted with methylene chloride (3 × 100 mL), and the organic layers were dried ($MgSO_4$) and concentrated. Gradient flash chromatography of the residue in 60:40 hexane–ethyl acetate to 100% ethyl acetate over silica gel yielded two isomers; both were isolated as glasses, the faster eluting product being the minor isomer (170 mg) while the slower, the major isomer (520 mg) (64%).

Minor isomer **50**: NMR ($CDCl_3$) δ 7.94 (s, 1 H), 7.42 (d, 2 H, J = 10 Hz), 6.88 (d, 2 H, J = 10 Hz), 6.52 (bd, 2 H, J = 8 Hz),

(32) Obtained from 2-amino-5-methylbenzoic acid through the esterification procedure described in Dougherty, C. M.; Baumgarten, R. L.; Sweeny, A., Jr.; Concepcion, E. *J. Chem. Ed.* **1977**, *54* (10), 643–4. Mp 62.5–64.0 °C (lit.[33] mp 58 °C).

5.11 (s, 2 H), 3.75 (m, 1 H), 3.63 (s, 3 H), 3.48 (s, 2 H), 2.56 (t, 2 H, J = 7 Hz), 2.29–1.25 (m, 13 H), 0.86 (t, 3 H, J = 7 Hz); IR 3440 (br), 1739, 1670, 1603, 1190, 604 cm^{-1}; MS m/e calcd for $C_{25}H_{32}ClF_3N_4O_5S$ 592.1734, found 592.1689. Anal. ($C_{25}H_{32}ClF_3N_4O_5S$) C, H.

Major isomer **51**: ($CDCl_3$) δ 8.18 (s, 1 H), 7.42 (d, 2 H, J = 10 Hz), 6.84 (d, 2 H, J = 10 Hz), 6.47 (bd, 1 H, J = 8 Hz), 5.07 (s, 2 H), 3.72 (m, 1 H), 3.57 (s, 3 H), 3.47 (s, 2 H), 2.53 (t, 2 H, J = 7 Hz), 2.24–1.12 (m, 13 H), 0.82 (t, 3 H, J = 7 Hz); IR 3440 br, 1739, 1667, 1604, 1192, 610 cm^{-1}. Anal. ($C_{25}H_{32}ClF_3N_4O_5S$) C, H, N.

2-*n*-Butyl-1-[[4-[[(2-carboxyphenyl)amino]carbonyl]-phenyl]methyl]-4-chloro-5-(methoxymethyl)imidazole (75). Part A. 2-*n*-Butyl-4-chloro-1-[(4-carbomethoxyphenyl)-methyl]-5-(methoxymethyl)imidazole (100). Hydroxy acid **7** (17.6 g), methanol (500 mL), and concentrated sulfuric acid (50 mL) were mixed and refluxed overnight. Potassium carbonate (100 g) was then carefully added to the solution which was cooled over ice. The reaction mixture was stirred for 2.5 h. The solvent was removed in vacuo and the residue dissolved in water (1 L). This aqueous mixture was extracted with ethyl acetate (3 × 400 mL). The organic layers were combined and dried ($MgSO_4$), and the solvent was removed in vacuo to yield 15.2 g (79%) of an oil: NMR (DMSO-d_6) δ 8.46 (d, 2 H, J = 9 Hz), 7.68 (d, 2 H, J = 9 Hz), 5.82 (s, 2 H), 4.80 (s, 2 H), 4.37 (s, 3 H), 3.66 (s, 3 H), 3.02 (t, 2 H, J = 7 Hz), 2.01 (t of t, 2 H, J = 7, 7 Hz), 1.77 (t of q, 2 H, J = 7, 7 Hz), 1.33 (t, 3 H, J = 7 Hz); IR 1724 cm^{-1}. Anal. ($C_{18}H_{23}ClN_3O_3$) C, H, N.

Part B. 2-*n*-Butyl-4-chloro-1-[(4-carboxyphenyl)-methyl]-5-(methoxymethyl)imidazole (101). Ester **100** (15.2 g, 43.3 mmol, 1 equiv), 0.5 N KOH in methanol (130 mL, 65.0 mmol, 1.5 equiv), water (10 mL), and methanol (50 mL) were mixed and refluxed for 4 h. The solvent was removed in vacuo and the residue dissolved in water (300 mL). The pH was adjusted to 4 with concentrated HCl and this aqueous mixture extracted with ethyl acetate (3 × 300 mL). The organic layers were combined and dried ($MgSO_4$), and the solvent was removed in vacuo and the crude residue recrystallized from hexane–butyl chloride to yield 9.6 g (66%) of a white solid: mp 126.5–127.5 °C; NMR (DMSO-d_6) δ 12.95 (bs, 1 H), 7.93 (d, 2 H, J = 9 Hz), 7.16 (d, 2 H, J = 9 Hz), 5.30 (s, 2 H), 4.31 (s, 2 H), 3.19 (s, 3 H), 2.50 (t, 2 H, J = 7 Hz), 1.49 (t of t, 2 H, J = 7, 7 Hz), 1.24 (t of q, 2 H, J = 7, 7 Hz), 0.80 (t, 3 H, J = 7 Hz). Anal. ($C_{17}H_{21}ClN_2O_3$) C, H, N.

Part C (75). Carboxylic acid **101** (6.00 g, 17.8 mmol, 1 equiv), thionyl chloride (13.0 mL, 178 mmol, 10 equiv), and chloroform (100 mL) were mixed and refluxed for 6 h. The solvent was removed in vacuo, and the residue was dissolved in toluene. The solvent was removed on the rotary evaporator and the evaporation from toluene repeated to remove all of the thionyl chloride. This yielded 6.0 g of acid chloride as an amber gum. IR 1776, 1745 cm^{-1}. Anthranilic acid (0.737 g, 5.36 mmol, 1 equiv) was dissolved in 1.000 N NaOH (10.75 mL, 10.7 mmol, 2 equiv) and water (100 mL) and cooled over ice. The aforementioned acid chloride (1.91 g, 5.36 mmol, 1 equiv), dissolved in THF (50 mL), was slowly added via a dropping funnel to the stirred and cooled anthranilic acid solution. The following day more anthranilic acid (74 mg, 0.536 mmol, 0.1 equiv) was added to bring the reaction to completion. After 1.5 h, the solution was acidified to pH 5 with 1 N HCl and extracted with ethyl acetate (1 × 100 mL). The ethyl acetate layer was washed with water (3 × 50 mL) and brine (1 × 50 mL) and dried ($MgSO_4$), and the solvent was removed in vacuo to yield 2.28 g of a brown glass. This glass was dissolved in a minimum amount of ethyl acetate and dicyclohexylamine (1 equiv) was added. The salt did not crystallize and therefore was flash chromatographed over silica gel, starting in 100% ethyl acetate and finishing in 1:1 ethyl acetate–2-propanol, to yield 1.44 g of an oil. This oil was dissolved in ethyl acetate (100 mL) and a minimum of methanol and washed with 1 N HCl (2 × 50 mL). The ethyl acetate layer was dried ($MgSO_4$) and the solvent removed in vacuo to yield 0.52 g (21%) of an amber oil: NMR ($CDCl_3$) δ 12.53 (s, 1 H), 8.91 (d, 1 H, J = 8 Hz), 8.23 (d, 1 H, J = 7 Hz), 8.08 (d, 3 H, J = 7 Hz), 7.62 (t, 1 H, J = 6 Hz), 7.11 (t, 2 H, J = 7 Hz), 5.30 (s, 2 H), 4.30 (s, 2 H), 3.30 (s, 3 H), 2.72 (t, 2 H, J = 7 Hz), 1.72 (t of t, 2 H, J = 7, 7 Hz), 1.31 (t of q, 2 H, J = 7, 7 Hz), 0.83 (t, 3 H, J = 7 Hz); IR 1670 br, 762 cm^{-1}. Anal. ($C_{25}H_{25}ClN_3O_4$) C, H, N.

2-*n*-Butyl-4-chloro-5-(methoxymethyl)-1-[[4-(methylamino)phenyl]methyl]imidazole (88). 1-[(4-Aminophenyl)-methyl]-2-*n*-butyl-4-chloro-5-(methoxymethyl)imidazole (**5b**) (10.94 g) and ethyl formate (150 mL) were mixed and refluxed overnight. The excess ethyl formate was removed in vacuo and another 150 mL added and the mixture was refluxed overnight again. The excess ethyl formate was removed in vacuo and the residue flash chromatographed over silica gel in 1:1 hexane–ethyl acetate to yield 9.52 g of a golden oil which slowly crystallized after several days. This oil (9.40 g, 28 mmol, 1 equiv) was dissolved in THF and to it LAH (1 M in THF, 84.0 mL, 84 mmol, 3 equiv) was slowly added via syringe under N_2. After stirring for 1 h, the mixture was worked up by the Steinhardt procedure[34] to yield 8.47 g (73%) of an orange oil: NMR ($CDCl_3$) δ 6.84 (d, 2 H, J = 10 Hz), 6.55 (d, 2 H, J = 10 Hz), 5.02 (s, 2 H), 4.26 (s, 2 H), 3.27 (s, 3 H), 2.81 (s, 3 H), 2.58 (t, 2 H, J = 7 Hz), 1.67 (t of t, 2 H, J = 7, 7 Hz), 1.35 (t of q, 2 H, J = 7, 7 Hz), 0.87 (t, 3 H, J = 7 Hz). Anal. ($C_{17}H_{24}ClN_3O$) C, H, N.

2-(Hydroxymethyl)-1-[(4-nitrophenyl)methyl]imidazole (99). Part A. Preparation of 5-(Hydroxymethyl)-2-mercapto-1-[(4-nitrophenyl)methyl]imidazole (98). A mixture of 4-nitrobenzylamine hydrochloride (75 g, 0.40 mol), 1,3-dihydroxyacetone dimer (32.1 g, 0.17 mol), and potassium thiocyanate (51.9 g, 0.53 mol) in 1-butanol (250 mL) and glacial acetic acid (40 mL) was stirred vigorously at room temperature for 48 h. The mixture was suction filtered and the solid was washed with water (3 × 300 mL) followed by ether (3 × 300 mL), before being dried overnight under vacuum to yield 70.9 g (75%) of a yellow tan powder: mp 214.0–215.0 °C dec; NMR (DMSO-d_6) δ 12.25 (s, 1 H; absent in D_2O shake), 8.20 (d, 2 H, J = 8 Hz), 7.40 (d, 2 H, J = 8 Hz), 6.90 (s, 1 H), 5.40 (s, 2 H), 5.25 (t, 1 H, J = 5 Hz; absent in D_2O shake), 4.15 (d, 2 H, J = 5 Hz; s in D_2O); MS m/e 265.

Part B. To 200 mL of 10% HNO_3 was added 5-(hydroxymethyl)-2-mercapto-1-[(4-nitrophenyl)methyl]imidazole (**98**) (10 g, 37.7 mmol) with vigorous stirring. The mixture was briefly contained in an ice bath (5 min) to moderate the mild exotherm and evolution of reddish gas. The mixture was stirred further for 2 h at 25 °C and suction filtered through a course fritted filter funnel (to remove solids), and the filtrate was basified with 4 N NaOH to precipitate the product. This mixture was cooled in an ice bath and the solid was collected by suction filtration, washed with water, and dried in vacuo to yield 6.9 g (78%) of a light brown solid: mp 203.0–206.0 °C dec; NMR (DMSO-d_6) δ 8.20 (d, 2 H, J = 6 Hz), 7.75 (s, 1 H), 7.40 (d, 2 H, J = 6 Hz), 6.80 (s, 1 H), 5.40 (s, 2 H), 5.20 (t, 1 H, J = 5 Hz, absent in D_2O), 4.30 (d, 2 H, J = 5 Hz, singlet in D_2O); MS m/e 233.

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