Nonpeptide Angiotensin II Receptor Antagonists: *N*-[(Benzyloxy)benzyl]imidazoles and Related Compounds as Potent Antihypertensives[1,2]

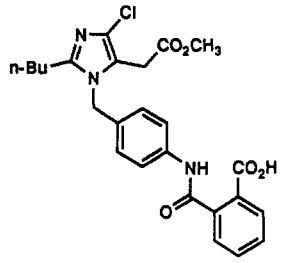
David J. Carini,* John V. Duncia, Alexander L. Johnson, Andrew T. Chiu, William A. Price, Pancras C. Wong, and Pieter B. M. W. Timmermans

Medicinal Chemistry and Cardiovascular Pharmacology Sections, Medical Products Department, Experimental Station, E. I. du Pont de Nemours and Co., Inc., Wilmington, Delaware 19880. *Received July 19, 1989*

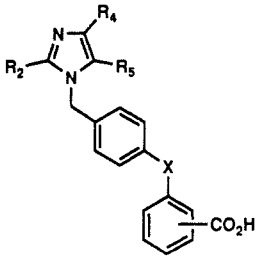
A series of compounds has been synthesized and demonstrated to be antagonists of the angiotensin II (AII) receptor. These compounds are structurally related to the *N*-(benzamidobenzyl)imidazoles and extend the scope of this new class of nonpeptide AII antagonists. It has been found that the amide linkage (X = NHCO) in the *N*-(benzamidobenzyl)imidazoles can be replaced successfully by a variety of groups (X = single bond, O, S, CO, OCH_2, CH=CH, NHCONH); linkers of 0–1 atoms in length are most effective. When administered intravenously to awake renal hypertensive rats, these compounds are potent antihypertensives.

Angiotensin II (AII), an octapeptide produced by the renin–angiotensin system, is a powerful endogenous vasopressor.[3] Drugs that inhibit the renin–angiotensin system, such as Squibb's captopril or Merck's enalapril, have been shown to be effective for the treatment of human hyptension.[4] These angiotensin converting enzyme (ACE) inhibitors work by blocking the production of angiotensin II from angiotensin I. An alternative and possibly superior approach would be to block the action of AII at the level of its receptor. While there are numerous peptides known to antagonize AII, few nonpeptide antagonists of angiotensin II have been described.[5,6]

Our group at Du Pont has reported a series of novel *N*-(benzamidobenzyl)imidazoles (e.g. **1**) to be potent AII receptor antagonists.[7] In this paper we extend the scope of this new class of nonpeptide AII antagonists. The compounds (**2**–**8**) have been found to be antagonists of the AII receptor and, as such, are potent antihypertensives.



1



2, X = single bond
3, = CO
4, = O
5, = S
6, = OCH_2
7, = CH=CH (trans)
8, = NHCONH

Chemistry

A general procedure used to prepare many of the compounds in this paper is demonstrated in Scheme I for the synthesis of **2a**. The requisite biphenyl **9** was prepared by the Ullmann biaryl synthesis.[8] Bromination of **9** with NBS provided **10**. Alkylation of 2-butyl-4(5)-chloro-5-(4)-(hydroxymethyl)imidazole (**11**)[9,10] with **10** furnished the ester **12**, and saponification of **12** completed the procedure. Compounds **4** and **5** were prepared by essentially the route described in Scheme I. For these syntheses the diaryl ether and the diaryl sulfide employed in place of biphenyl **9** were produced by variations of the Ullmann diaryl ether synthesis.[11]

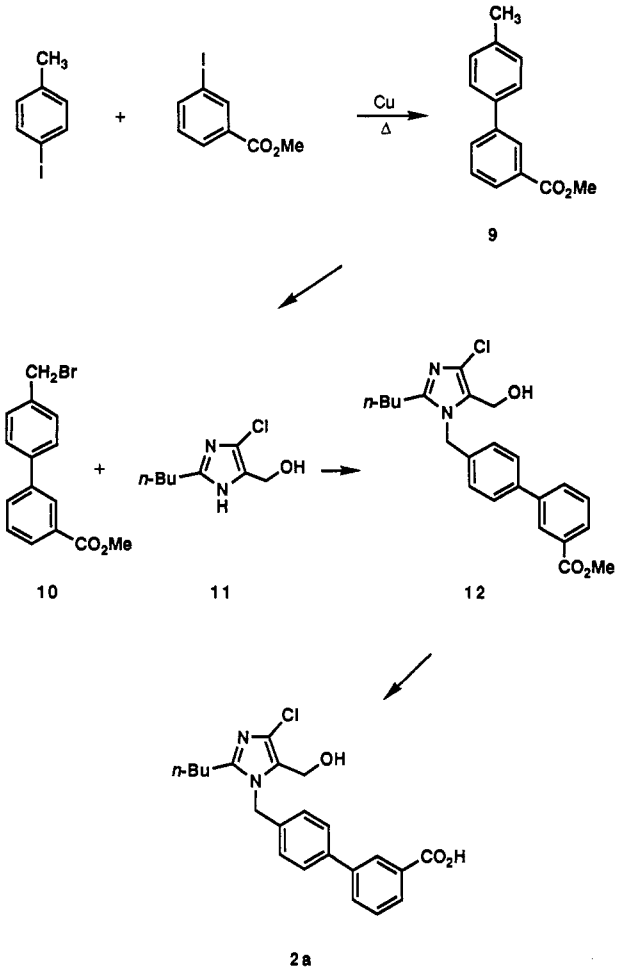
The *N*-[(benzyloxy)benzyl]imidazole **6a** was prepared as shown in Scheme II. The phenol **21** was prepared either by catalytic hydrogenolysis of **20** or by heating **20** in trifluoroacetic acid. Alkylation of **21** with 2-cyanobenzyl bromide furnished **22**, and hydrolysis of **22** produced **6a**. The corresponding (alkylthio)imidazole **6e** was synthesized as described in Scheme III. Intermediate **27** was prepared by a modification of the procedure reported by W. Schaub and H. Gerhards.[12] The preparation of **6e** was completed employing the chemistry described in Scheme II for the preparation of **6a**.

The 4-unsubstituted imidazoles (**2b** and **6b**) were prepared by hydrodehalogenation of an appropriate chloroimidazole intermediate (e.g. **12**) employing 10% palladium/carbon in methanol. The resulting dechlorinated imidazoles were converted to **2b** and **6b** by employing the chemistry described above for the preparations of **2a** and **6a**. Attempts to prepare **6b** directly by alkylation of 2-butyl-4(5)-(hydroxymethyl)imidazole furnished only the 4-(hydroxymethyl)imidazole regioisomer. The acetates (**2c**, **3c**, and **6c**) were produced from the corresponding alcohols by the standard procedure using acetic anhydride, triethylamine, and catalytic 4-(dimethylamino)pyridine. The ethers (**2d**, **3e**, and **6d**) and the carbamate **3d** were prepared by utilizing chemistry described by Duncia et al.[7]

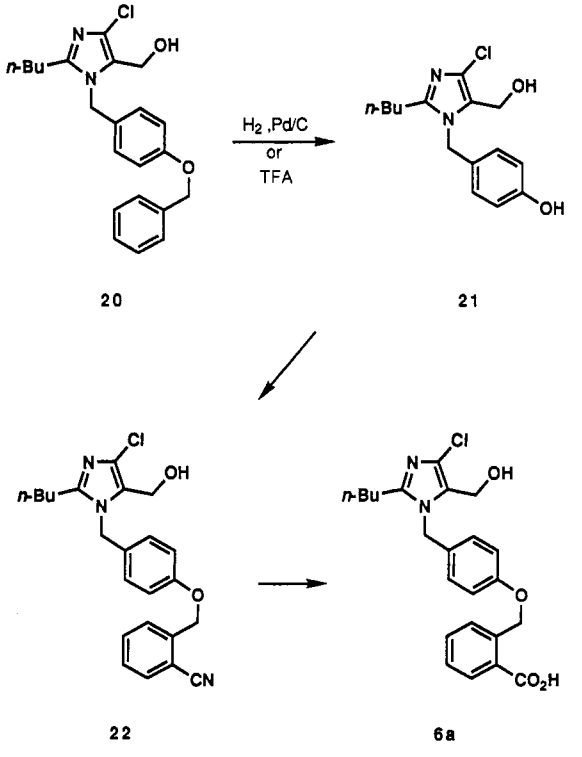
(1) This paper is part 6 in the series; for part 5, see ref 7.
(2) These compounds were initially disclosed in Carini, D. J.; Duncia, J. J. V. Eur. Pat. Appl. 253310, 1988, and were reported in part at the 197th National Meeting of the American Chemical Society, Dallas, TX, April 1989; MEDI 64.
(3) Vallotton, M. B. *Trends Pharmacol. Sci.* **1987**, *8*, 69.
(4) Johnson, C. I. In *Handbook of Hypertension, Vol. 5: Clinical Pharmacology of Antihypertensive Drugs*; Doyle, A. E., Ed.; Elsevier: Amsterdam, 1984; p 272.
(5) (a) Furukawa, Y.; Nishikawa, K. Eur. Pat. Appl. 103647, 1984. (b) Furukawa, Y.; et al. U.S. Patent 4355040, 1982. (c) U.S. Patent 4340598, 1982.
(6) Blankley, C. J.; et al. Eur. Pat. Appl. 245637, 1987.
(7) Duncia, J. V.; et al. *J. Med. Chem.*, preceding paper in this issue. Reported in part at the 197th National Meeting of the American Chemical Society, Dallas, TX, April 1989; MEDI 63 and 65.
(8) Fanta, P. E. *Chem. Rev.* **1946**, *38*, 139; **1964**, *64*, 613.
(9) Prepared as described in ref 5c.
(10) The regioisomers were assigned by analogy with the results of alkylations reported in ref 5b, 5c, and 7.
(11) Moroz, A. A.; Shvartsberg, M. S. *Russ. Chem. Rev.* **1974**, *43*, 679.
(12) Schaub, W.; Gerhards, H. Ger. Offen, 2618370, 1978.

0022-2623/90/1833-1330$02.50/0

Scheme I

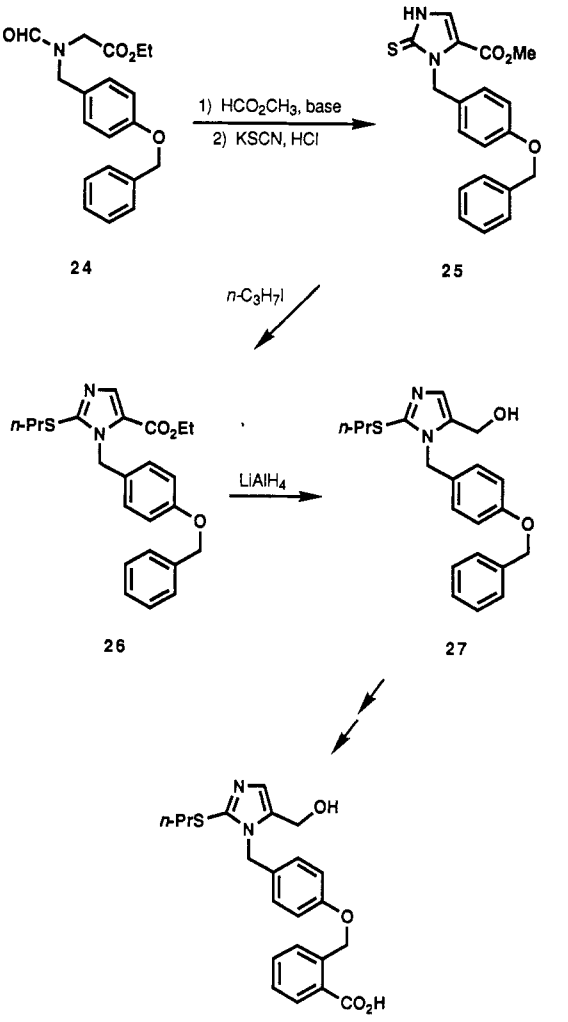


Scheme II



In the key steps a 5-(hydroxymethyl)imidazole derivative is converted with thionyl chloride to the intermediate 5-(chloromethyl)imidazole; this intermediate is then treated with an appropriate nucleophile. Scheme IV

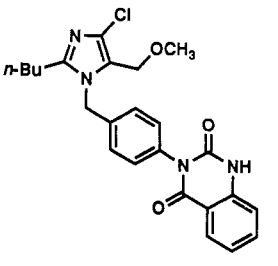
Scheme III



demonstrates the application of this chemistry to the preparation of **3e**.

The key step in the preparation of stilbene **7** was the Wittig olefination of aldehyde **30**, which itself was prepared by diisobutylaluminum hydride reduction of the corresponding nitrile **29** (Scheme V). Hydrolysis of the nitrile **31** with aqueous base afforded **7**. The stereochemistry of the double bond in **31** was assigned as trans based on a ^{1}H NMR coupling constant of 16.3 Hz between the olefinic hydrogens.

Finally, the urea **8** was synthesized as shown in Scheme VI. The trifluoromethanesulfonamido group in **8** was employed as an isosteric replacement for the carboxyl group. The parent carboxylic acid could not be isolated because of its tendency to rapidly cyclize to **35**.

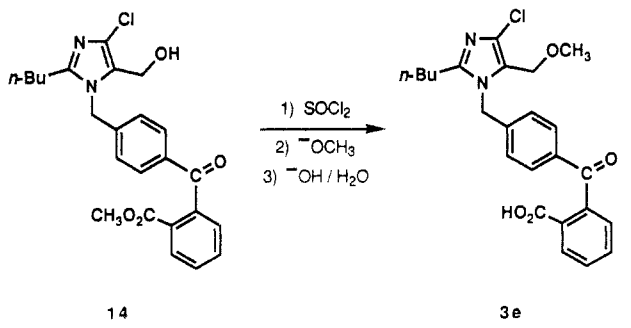


35

Discussion

The compounds **2–8** were tested primarily for their affinity for the AII receptor as measured by their ability to

Scheme IV



14 3e

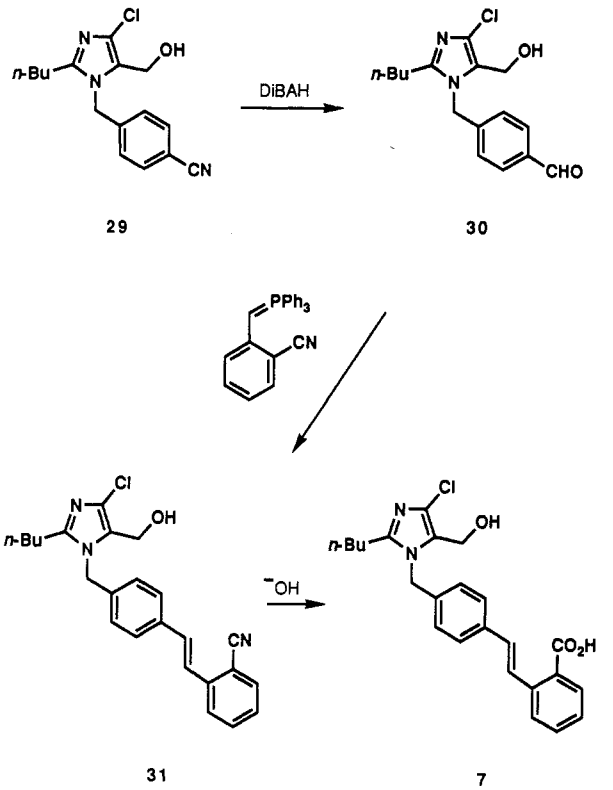
displace [^{3}H]-AII (2 nM) from its specific binding sites in rat adrenal cortical microsomes; the data are reported in Table I. Direct comparison of the IC_{50} values for **2a**, **3a**, **4**, **5**, **6a**, **7**, and **8** demonstrates that activity in this series is optimal when the linking group, X, is 0–1 atoms in length. The biphenyl **2a**, benzophenone **3a**, diaryl ether **4**, and diaryl sulfide **5** (IC_{50}'s = 0.16–0.49 μM) are essentially equipotent with the *N*-(benzamidobenzyl)imidazoles (e.g. **1**, IC_{50} = 0.14 μM).[7] The [(benzyloxy)benzyl]imidazole **6a**, with a two-atom linker, was prepared as a close structural analogue of **1**. However, when the amide linking group in **1** was replaced with the more conformationally flexible $-OCH_2-$ linker of **6a** (IC_{50} = 0.92 μM), a significant loss of affinity was observed. On the basis of the hypothesis that the amide group in **1** would possess a planar transoid conformation, the *trans*-stilbene derivative **7** was prepared. Remarkably, **7** (IC_{50} = 5.4 μM) is 50-fold less potent than **1**. Finally, the urea **8** (IC_{50} = 2.4 μM) demonstrates poor affinity for the AII receptor when compared with the amide **1**. This loss of affinity is not believed to be due to the trifluoromethanesulfonamido group, which has been shown to be an excellent isostere of the carboxylic acid group in the (benzamidobenzyl)imidazole series.[7]

Comparison of binding affinities within a class of compounds (**2a–d**, **3a–d**, or **6a–d**) indicates that this series of AII receptor antagonists is relatively insensitive to the nature of the substituent at the 5-position of the imidazole ring. A variety of functional groups including alcohols, ethers, esters, and carbamates have been employed with only minor variations in potency. Comparison of compounds **2a** and **6a** with the corresponding dechlorinated imidazoles **2b** and **6b** demonstrates that the chlorine is not critical to the binding affinity of these compounds. Therefore, the affinity of this series of compounds for the AII receptor apparently is not dependent on the pK_a of the imidazole. However, when the alkyl substituent at the 2-position on the imidazole ring is replaced by a alkylthio group (i.e. **6e–f**), the result is a significant drop in affinity. This result reaffirms an observation in our (benzamidobenzyl)imidazole series that activity is critically dependent on the nature of the substituent at the imidazole 2-position.[7]

The compounds reported in this paper have failed to demonstrate oral antihypertensive activity. However, several of these compounds have been administered intravenously to renal hypertensive rats;[13] doses of 10–45 mg/kg have been observed to reduce blood pressure in these rats by >30 mmHg. The compounds are therefore potent antihypertensives.

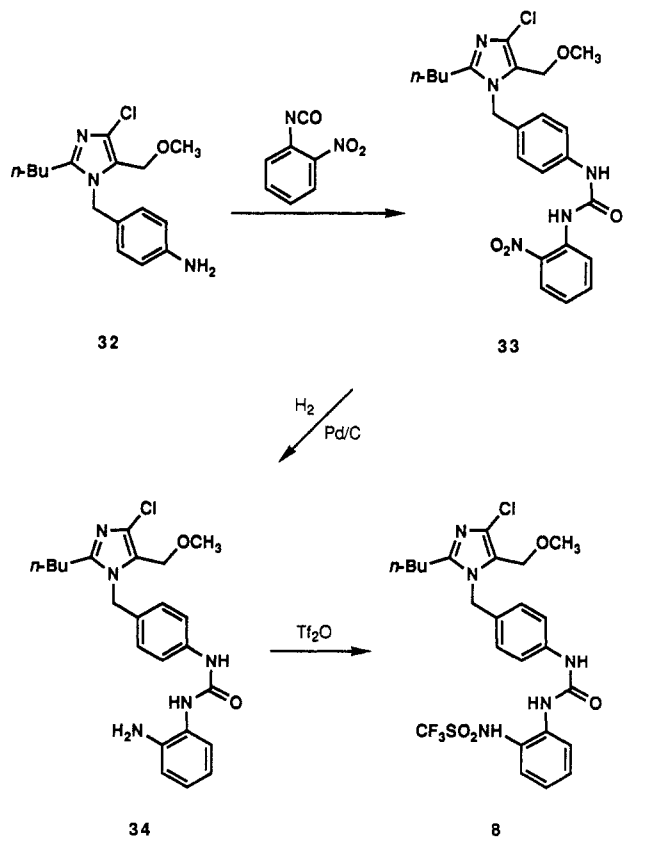
(13) The renal hypertensive rats employed in this screen were awake rats made hypertensive by ligation of the left renal artery; see ref 18.

Scheme V



29 30 31 7

Scheme VI

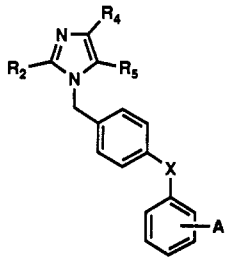


32 33 34 8

Experimental Section

IR spectra were obtained on a Perkin-Elmer 1710 Series FTIR and were run as KBr pellets. ^{1}H NMR (200 MHz) spectra were measured with an IBM/Bruker WP200SY spectrometer. Chemical shifts are expressed in ppm (δ) downfield from TMS as an internal standard. High-resolution mass spectra were determined

Table I. Angiotensin II Receptor Antagonists



no.	R^2	R^4	R^5	X	A	mp,[a] °C	receptor affinity:[e] IC_{50}, μM
1	n-C_4H_9	Cl	$CH_2CO_2CH_3$	NHCO	2-CO_2H		0.14[f]
2a	n-C_4H_9	Cl	CH_2OH	single bond	3-CO_2H	180–181	0.49
2b	n-C_4H_9	H	CH_2OH	single bond	3-CO_2H	154–155	1.1
2c	n-C_4H_9	Cl	CH_2OCOCH_3	single bond	3-CO_2H	172–173	2.5
2d	n-C_4H_9	Cl	CH_2OCH_3	single bond	3-CO_2H	167.5–168.5	2.9
3a	n-C_4H_9	Cl	CH_2OH	CO	2-CO_2H	90–95[b]	0.16[f]
3b	n-C_4H_9	CH_2OH	Cl	CO	2-CO_2H	214–216	0.34[f]
3c	n-C_4H_9	CH_2OCOCH_3	Cl	CO	2-CO_2H	152.5–154	1.4
3d	n-C_4H_9	Cl	$CH_2NHCO_2CH_3$	CO	2-CO_2H	*d*	0.27[f]
3e	n-C_4H_9	Cl	CH_2OCH_3	CO	2-CO_2H	210–211.5	0.15[f]
4	n-C_4H_9	Cl	CH_2OH	O	2-CO_2H	178–180	0.40
5	n-C_4H_9	Cl	CH_2OH	S	2-CO_2H	166–167	0.40
6a	n-C_4H_9	Cl	CH_2OH	OCH_2	2-CO_2H	57–62	0.92
6b	n-C_4H_9	H	CH_2OH	OCH_2	2-CO_2H	115–116	0.31
6c	n-C_4H_9	Cl	CH_2OCOCH_3	OCH_2	2-CO_2H	139.5–141.5	1.8
6d	n-C_4H_9	Cl	CH_2OCH_3	OCH_2	2-CO_2H	126.5–128	1.2
6e	n-C_3H_7S	H	CH_2OH	OCH_2	2-CO_2H	161–163	5.9
6f	n-C_2H_5S	H	CH_2OH	OCH_2	2-CO_2H	152–155	12
7	n-C_4H_9	Cl	CH_2OH	*trans*-CH=CH	2-CO_2H	165–166[c]	5.4
8	n-C_4H_9	Cl	CH_2OCH_3	NHCONH	2-$NHSO_2CF_3$	155–157.5	2.4

[a] All compounds exhibited NMR, IR, and mass spectra consistent with structure. Except where indicated, satisfactory analyses (±0.4%) were obtained for either C, H, N or C, H, Cl. [b] Satisfactory analysis was obtained for C, H. [c] Elemental analysis was not obtained. Compound gave satisfactory analysis by high-resolution mass spectroscopy. [d] Melting point was not determined as the compound sublimed without melting. [e] Compounds were tested for their ability to displace [^{3}H]-AII (2 nM) from its specific binding sites in a rat adrenal cortical microsome preparation; see ref 18. [f] Compound was evaluated as the sodium salt.

on a Finnegan MAT 8230. Melting points are uncorrected and were measured with a Thomas-Hoover Unimelt apparatus. Elemental analyses were within ±0.4% of theoretical values and were determined by Micro-Analysis, Inc. Boiling points are uncorrected. Column chromatography was performed with E. Merck silica gel 60 (230–400 mesh).

Methyl 4′-Methylbiphenyl-3-carboxylate (9). To a stirred solution of methyl 3-iodobenzoate (25.2 g, 96 mmol, 1.0 equiv) and 4-iodotoluene (21.0 g, 96 mmol, 1.0 equiv) at 180–190 °C under nitrogen was added copper powder (30.3 g, 477 mmol, 5.0 equiv) in portions over 1 h. When approximately one-third of the copper had been added, the reaction initiated, and the temperature increased spontaneously to 240 °C. The mixture was allowed to cool to 210 °C and was held at 210 °C during the addition of the remaining copper and then for an additional hour. The mixture was allowed to cool to room temperature and was filtered with benzene as solvent; the resulting filtrate was concentrated under vacuum to provide the crude product. Column chromatography on silica gel (elution: 50–100% benzene/hexane) followed by distillation furnished 7.60 g (35%) of **9** (bp 114–115 °C (0.025 Torr)) as a colorless oil: NMR ($CDCl_3$) δ 8.27 (s, 1 H), 7.99 (d, 1 H, J = 8 Hz), 7.77 (d, 1 H, J = 8 Hz), 7.54–7.44 (m, 3 H), 7.26 (d, 2 H, J = 7 Hz), 3.94 (s, 3 H), 2.41 (s, 3 H).

Methyl 4′-(Bromomethyl)biphenyl-3-carboxylate (10). A solution of **9** (7.31 g, 32 mmol, 1.0 equiv), *N*-bromosuccinimide (5.75 g, 32 mmol, 1.0 equiv) azobisisobutyronitrile (0.125 g, 0.76 mmol, 0.025 equiv), and 500 mL of carbon tetrachloride was refluxed for 3 h. After cooling to room temperature, the resulting suspension was filtered and then concentrated under vacuum to provide 9.90 g (86%, 85% purity) of crude **10**, which was used in the subsequent reaction without further purification: NMR ($CDCl_3$) δ 8.28 (s, 1 H), 8.05 (d, 1 H, J = 8 Hz), 7.79 (d, 1 H, J = 8 Hz), 7.67–7.48 (m, 5 H), 4.55 (s, 2 H), 3.98 (s, 3 H).

2-Butyl-1-[(3′-carbomethoxybiphenyl-4-yl)methyl]-4-chloro-5-(hydroxymethyl)imidazole (12). To a suspension of sodium methoxide (1.43 g, 26.5 mmol, 1.0 equiv) in 20 mL of dimethylformamide at 25 °C was added a solution of 2-butyl-4-(5)-chloro-5(4)-(hydroxymethyl)imidazole (**11**, 5.00 g, 26.5 mmol, 1.0 equiv)[9] in 15 mL of dimethylformamide. The resulting mixture was stirred at 25 °C for 0.25 h, and then to this mixture was added dropwise a solution of crude **10** (9.90 g, 27.5 mmol, 1.05 equiv) in 15 mL of dimethylformamide. Finally, the reaction mixture was stirred at 40 °C for 4 h. After cooling to 25 °C, the solvent was removed under vacuum. The residue was dissolved in ethyl acetate, and this solution was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography on silica gel (elution: 10–25% ethyl acetate/benzene) afforded 3.85 g (35%) of **12**, the regioisomer of higher R_f:[10] mp 162–163 °C; NMR ($CDCl_3$) δ 8.24 (s, 1 H), 8.03 (d, 1 H, J = 8 Hz), 7.76 (d, 1 H, J = 8 Hz), 7.52 (t, 1 H, J = 8 Hz), 7.33 (A_2B_2, 4 H, J = 7 Hz), 5.27 (s, 2 H), 4.52 (d, 2 H, J = 6.5 Hz), 3.93 (s, 3 H), 2.60 (t, 2 H, J = 7 Hz), 1.89 (t, 1 H, J = 6.5 Hz), 1.67 (quint, 2 H, J = 7 Hz), 1.35 (sext, 2 H, J = 7 Hz), 0.88 (t, 3 H, J = 7 Hz).

2-Butyl-1-[(3′-carboxybiphenyl-4-yl)methyl]-4-chloro-5-(hydroxymethyl)imidazole (2a). A solution of **12** (0.30 g, 0.73 mmol) in 16 mL of ethanol and 8 mL of 10% aqueous sodium hydroxide was refluxed for 5 h. After cooling, the reaction mixture was filtered, and the solvent was removed under vacuum. The residue was dissolved in water, and the solution was acidified to pH 3.5 with hydrochloric acid. The precipitated solid was recovered by filtration and recrystallized from aqueous ethanol to furnish 0.24 g (83%) of **2a**: mp 180–181 °C; NMR ($CDCl_3$/DMSO-d_6) δ 8.26 (s, 1 H), 8.04 (d, 1 H, J = 8 Hz), 7.77 (d, 1 H, J = 8 Hz), 7.52 (t, 1 H, J = 8 Hz), 7.36 (A_2M_2, 4 H, J = 8 Hz), 5.30 (s, 2 H), 4.48 (s, 2 H), 2.57 (t, 2 H, J = 7 Hz), 1.64 (quint, 2 H, J = 7 Hz), 1.34 (sext, 2 H, J = 7 Hz), 0.87 (t, 3 H, J = 7 Hz); IR 1705 cm^{-1}. Anal. ($C_{22}H_{23}ClN_2O_3$) C, H, Cl.

2-Butyl-1-[(3′-carbomethoxybiphenyl-4-yl)methyl]-5-(hydroxymethyl)imidazole (13). A mixture of 1.00 g of 10% palladium/carbon and **12** (1.00 g, 2.4 mmol) in 20 mL of methanol was stirred at 25 °C for 5 min. Hydrogen gas was bubbled into

the solution, and the mixture was stirred under H_2(g) (1 atm) at 25 °C for 3.5 h. The mixture was filtered and the filtrate concentrated under vacuum. Column chromatography (elution: 0–5% methanol/chloroform) furnished 0.33 g (36%) of **13**: NMR (DMSO-d_6) δ 8.20 (s, 1 H), 7.98 (d, 2 H, J = 8 Hz), 7.65 (t, 1 H, J = 8 Hz), 7.41 (A_2M_2, 4 H, J = 8 Hz), 6.80 (s, 1 H), 5.30 (s, 2 H), 5.12 (t, 1 H, J = 5 Hz), 4.37 (d, 2 H, J = 5 Hz), 3.90 (s, 3 H), 2.52 (t, 2 H, J = 7 Hz), 1.51 (quint, 2 H, J = 7 Hz), 1.27 (sext, 2 H, J = 7 Hz), 0.80 (t, 3 H, J = 7 Hz).

2-Butyl-1-[(3′-carboxybiphenyl-4-yl)methyl]-5-(hydroxymethyl)imidazole (2b). A solution of **13** (0.33 g, 0.87 mmol), 20 mL of ethanol, and 10 mL of 10% aqueous sodium hydroxide was refluxed for 4.5 h. After cooling, the reaction mixture was filtered, and the solvent was removed under vacuum. The residue was dissolved in water, and the solution was acidified to pH 6 with hydrochloric acid. The precipitate was recovered by filtration and dried under vacuum to afford 0.17 g (54%) of **2b**: mp 154–155 °C; NMR (DMSO-d_6) δ 8.14 (s, 1 H), 7.90 (m, 2 H), 7.68–7.53 (m, 3 H), 7.12 (d, 2 H, J = 7 Hz), 6.77 (s, 1 H), 5.27 (s, 2 H), 4.35 (s, 2 H), 2.50 (t, 2 H, J = 7 Hz), 1.49 (quint, 2 H, J = 7 Hz), 1.25 (sext, 2 H, J = 7 Hz), 0.79 (t, 3 H, J = 7 Hz). Anal. ($C_{22}H_{24}N_2O_3 \cdot 0.5H_2O$) C, H, N.

5-(Acetoxymethyl)-2-butyl-1-[(3′-carboxybiphenyl-4-yl)methyl]-4-chloroimidazole (2c). A solution of **2a** (0.10 g, 0.25 mmol, 1.0 equiv), 4-(dimethylamino)pyridine (0.005 g, 0.04 mmol, 0.16 equiv), acetic anhydride (0.10 mL, 1.0 mmol, 4 equiv), and triethylamine (0.14 mL, 1.0 mmol, 4 equiv) in 8 mL of tetrahydrofuran was stirred for 4.5 h at 25 °C. The reaction mixture was poured into water, and aqueous sodium hydroxide was added until the pH of the solution remained in the range of pH 8–9. The solution was then acidified to pH 3.5 with hydrochloric acid and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, and concentrated. Column chromatography on silica gel (elution: 0–0.5% isopropanol/chloroform) furnished 0.065 g (59%) of **2c**: mp 172–173 °C; NMR (DMSO-d_6) δ 8.17 (s, 1 H), 7.93 (t, 2 H, J = 8 Hz), 7.61 (t, 1 H, J = 8 Hz), 7.43 (A_2M_2, 4 H, J = 8 Hz), 5.32 (s, 2 H), 4.99 (s, 2 H), 2.60 (t, 2 H, J = 7 Hz), 1.76 (s, 3 H), 1.53 (quint, 2 H, J = 7 Hz), 1.28 (sext, 2 H, J = 7 Hz), 0.82 (t, 3 H, J = 7 Hz); IR 1747, 1703 cm^{-1}. Anal. ($C_{24}H_{25}ClN_2O_4 \cdot 0.25H_2O$) C, H, Cl.

2-Butyl-1-[4-(2-carbomethoxybenzoyl)benzyl]-4-chloro-5-(hydroxymethyl)imidazole (14). The title compound was prepared from methyl 2-p-toluoylbenzoate[14] by using the procedures described in the preparations of **10** and **12**: NMR ($CDCl_3$) δ 8.03 (d, 1 H, J = 7 Hz), 7.67 (m, 4 H), 7.36 (d, 1 H, J = 7 Hz), 7.05 (d, 2 H, J = 7 Hz), 5.28 (s, 2 H), 4.43 (s, 2 H), 3.63 (s, 3 H), 2.53 (t, 2 H, J = 7 Hz), 1.60 (quint, 2 H, J = 7 Hz), 1.30 (sext, 2 H, J = 7 Hz), 0.87 (t, 3 H, J = 7 Hz).

2-Butyl-1-[4-(2-carboxybenzoyl)benzyl]-4-chloro-5-(hydroxymethyl)imidazole (3a). The title compound was prepared from **14** by the procedure described for the preparation of **2a**: mp 90–95 °C; NMR ($CDCl_3$) δ 8.05 (d, 1 H, J = 7 Hz), 7.75–7.48 (m, 4 H), 7.37 (d, 1 H, J = 7 Hz), 7.00 (d, 2 H, J = 7 Hz), 5.20 (s, 2 H), 4.40 (s, 2 H), 2.45 (t, 2 H, J = 7 Hz), 1.50 (quint, 2 H, J = 7 Hz), 1.25 (sext, 2 H, J = 7 Hz), 0.79 (t, 3 H, J = 7 Hz); IR 1710, 1673 cm^{-1}. Anal. ($C_{23}H_{23}ClN_2O_4 \cdot CH_3OH$) C, H.

5-(Azidomethyl)-2-butyl-1-[4-(2-carbomethoxybenzoyl)benzyl]-4-chloroimidazole (16). Thionyl chloride (4.13 mL, 56.6 mmol, 5.0 equiv) was added dropwise over 0.2 h to a solution of **14** (5.00 g, 11.3 mmol, 1.0 equiv) in 50 mL of chloroform at 25 °C. The reaction mixture was stirred at 25 °C for 4 h, and then the solvent and excess thionyl chloride were removed under vacuum. The residue was dissolved in toluene, and the volume of solvent was reduced under vacuum until a precipitate formed. This solid was recovered by filtration to furnish 2.91 g (52%) of crude 2-butyl-1-[4-(2-carbomethoxybenzoyl)benzyl]-4-chloro-5-(chloromethyl)imidazole hydrochloride (**15**): mp 139–143.5 °C.

A solution of **15** (0.84 g, 1.83 mmol, 1.0 equiv), sodium azide (0.24 g, 3.66 mmol, 2.0 equiv), and 25 mL of dimethyl sulfoxide was stirred for 5 h at 25 °C. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic phases were dried over anhydrous magnesium sulfate, filtered, and concentrated. The resulting crude solid was washed with diethyl ether to provide 0.54 g (63%) of **16**: mp 127–129.5 °C; NMR ($CDCl_3$) δ 8.05 (d, 1 H, J = 8 Hz), 7.75 (d, 2 H, J = 8 Hz), 7.65 (t, 1 H, J = 8 Hz), 7.56 (t, 1 H, J = 8 Hz), 7.36 (d, 1 H, J = 8 Hz), 7.03 (d, 2 H, J = 8 Hz), 5.19 (s, 2 H), 4.18 (s, 2 H), 3.68 (s, 3 H), 2.56 (t, 2 H, J = 7 Hz), 1.81 (quint, 2 H, J = 7 Hz), 1.36 (sext, 2 H, J = 7 Hz), 0.90 (t, 3 H, J = 7 Hz); IR 2150, 1713, 1671 cm^{-1}.

2-Butyl-1-[4-(2-carbomethoxybenzoyl)benzyl]-4-chloro-5-[[(methoxycarbonyl)amino]methyl]imidazole (17). To a solution of **16** (4.24 g, 9.10 mmol, 1.0 equiv) in 40 mL of acetone and 13 mL of water at 25 °C was added chromium(II) chloride (6.75 g, 54.7 mmol, 6.0 equiv), and the mixture was stirred at 25 °C. When nitrogen evolution had stopped, the reaction mixture was diluted with saturated aqueous sodium bicarbonate and then extracted with ethyl acetate. The combined organic phases were dried over anhydrous magnesium sulfate, filtered, and concentrated. The resulting solid was washed with diethyl ether to afford 2.92 g of a white solid: mp 178.5–181 °C.

To a solution of the above solid (0.50 g, 1 equiv) and 1.00 N aqueous sodium hydroxide (1.14 mL, 1.14 mmol, 1.0 equiv) in 10 mL of water at 0 °C was added dropwise, in five equal portions, a solution of methyl chloroformate (0.18 mL, 2.3 mmol, 2.0 equiv) in 5 mL of tetrahydrofuran. Alternating with the portions of methyl chloroformate was added five equal portions of 1.00 N aqueous sodium hydroxide (total: 1.14 mL, 1.14 mmol, 1.0 equiv). After the additions were completed, the mixture was stirred for 4 h at 25 °C. The reaction mixture was diluted with water, adjusted to pH 5 with 1 N hydrochloric acid, and then extracted with ethyl acetate. The combined organic phases were dried over anhydrous magnesium sulfate, filtered, and concentrated. Column chromatography (elution: 0–100% 2-propanol/ethyl acetate) furnished 0.28 g (34% overall) of **17** as an oil: NMR ($CDCl_3$) δ 8.10 (d, 1 H, J = 7 Hz), 7.75 (d, 2 H, J = 7 Hz), 7.75–7.56 (m, 2 H), 7.39 (d, 1 H, J = 7 Hz), 7.02 (d, 2 H, J = 7 Hz), 5.32 (s, 2 H), 4.83 (m, 1 H), 4.28 (d, 2 H, J = 7 Hz), 3.70 (s, 3 H), 3.57 (s, 3 H), 2.58 (t, 2 H, J = 7 Hz), 1.72 (quint, 2 H, J = 7 Hz), 1.37 (sext, 2 H, J = 7 Hz), 0.92 (t, 3 H, J = 7 Hz).

2-Butyl-1-[4-(2-carboxybenzoyl)benzyl]-4-chloro-5-[[(methoxycarbonyl)amino]methyl]imidazole (3d). A solution of **17** (0.27 g, 0.54 mmol, 1.0 equiv), 0.5 N potassium hydroxide in methanol (1.19 mL, 0.60 mmol, 1.1 equiv), and 1.0 mL of water was refluxed for 4 h. After cooling, the solvents were removed under vacuum, and the residue was dissolved in water. The solution was adjusted to pH 3 with hydrochloric acid, and the resulting precipitate was recovered by filtration to provide 0.20 g (76%) of **3d** as a white solid: solid sublimes; NMR (DMSO-d_6) δ 13.17 (br s, 1 H), 7.97 (d, 1 H, J = 7 Hz), 7.71 (t, 1 H, J = 7 Hz), 7.63 (t, 1 H, J = 7 Hz), 7.56 (d, 2 H, J = 10 Hz), 7.50 (m, 1 H), 7.36 (d, 1 H, J = 7 Hz), 7.03 (d, 2 H, J = 10 Hz), 5.31 (s, 2 H), 4.06 (d, 2 H, J = 7 Hz), 2.46 (t, 2 H, J = 7 Hz), 1.48 (quint, 2 H, J = 7 Hz), 1.22 (sext, 2 H, J = 7 Hz), 0.78 (t, 3 H, J = 7 Hz); IR 1709 (br), 1673 cm^{-1}. Anal. ($C_{25}H_{26}ClN_3O_5$) C, H, N.

2-Butyl-1-[4-(2-carboxybenzoyl)benzyl]-4-chloro-5-(methoxymethyl)imidazole (3e). Sodium metal (0.10 g, 4.36 mmol, 2.0 equiv) was allowed to dissolve in 25 mL of methanol. To this solution at 25 °C was added **15** (1.00 g, 2.18 mmol, 1.0 equiv), and the mixture was stirred at 25 °C for 24 h. The mixture was diluted with water, adjusted to pH 4 with hydrochloric acid, and extracted with ethyl acetate. The combined organic phases were dried over anhydrous magnesium sulfate, filtered, and concentrated. This crude product was saponified by employing the procedure used in the preparation of **2a** to afford 0.66 g (69%) of **3e**: mp 210–211.5 °C; NMR (DMSO-d_6) δ 12.15 (br s, 1 H), 7.95 (d, 1 H, J = 7 Hz), 7.62 (t, 1 H, J = 7 Hz), 7.55 (d, 2 H, J = 8 Hz), 7.34 (d, 1 H, J = 7 Hz), 7.10 (d, 2 H, J = 8 Hz), 5.25 (s, 2 H), 4.22 (s, 2 H), 3.09 (s, 3 H), 2.46 (t, 2 H, J = 7 Hz), 1.45 (quint, 2 H, J = 7 Hz), 1.20 (sext, 2 H, J = 7 Hz), 0.75 (t, 3 H, J = 7 Hz). Anal. ($C_{24}H_{25}ClN_2O_4 \cdot 0.5H_2O$) C, H, N.

2-(4-Methylphenoxy)benzoic Acid (18). To a solution of p-cresol (5.95 g, 55 mmol, 1.1 equiv) and 2-chlorobenzoic acid (7.83 g, 50 mmol, 1.0 equiv) in 50 mL of dimethylformamide at 25 °C was added, in portions, anhydrous potassium carbonate (14.50 g, 105 mmol, 2.1 equiv). The resulting mixture was heated to 80 °C, and copper (I) iodide (0.10 g, 0.5 mmol, 0.01 equiv) was added. The reaction mixture then was refluxed for 16 h. While still hot the mixture was poured onto water–ice. The resulting suspension was filtered, and the filtrate was adjusted to pH 3.0 with aqueous

(14) Risinger, G. E.; Thompson, J. A. *Recl. Trav. Chim. Pays-Bas* 1963, *82*, 801.

hydrochloric acid. The precipitate was recovered by filtration. The crude solid was dissolved in aqueous sodium hydroxide. This solution was acidified to pH 6.0 with hydrochloric acid, filtered, and then acidified to pH 3.0. Filtration provided 5.67 g (50%) of **18**,[15] which was employed in the following reaction without further purification: NMR ($CDCl_3$) δ 8.15 (d of d, 1 H, J = 1.5, 8 Hz), 7.42 (d of t, 1 H, J = 1.5, 8 Hz), 7.23–7.12 (m, 3 H), 6.97 (d, 2 H, J = 8 Hz), 6.80 (d, 1 H, J = 8 Hz), 2.37 (s, 3 H).

Methyl 2-(4-Methylphenoxy)benzoate (19). A solution of **18** (37.70 g, 165 mmol) and 12.0 mL of concentrated sulfuric acid in 500 mL of methanol was refluxed for 14 h. After cooling, the reaction mixture was concentrated under vacuum, and the residue was added to a mixture of methylene chloride and water. The organic phase was separated, washed with saturated sodium bicarbonate solution and brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was distilled by Kugelrohr (120–135 °C/0.025 Torr) to furnish 35.08 g (88%) of **19**[16] as a colorless oil which crystallized on standing: mp 31–34 °C; NMR ($CDCl_3$) δ 7.87 (d of d, 1 H, J = 2, 8 Hz), 7.39 (t of d, 1 H, J = 2, 8 Hz), 7.11 (m, 3 H), 6.88 (m, 3 H), 3.81 (s, 3 H), 2.30 (s, 3 H).

2-Butyl-1-[4-(2-carboxyphenoxy)benzyl]-4-chloro-5-(hydroxymethyl)imidazole (4). The title compound was prepared from **19** by the procedures described in the preparations of **10**, **12**, and **2a**: mp 178–180 °C; NMR (DMSO-d_6) δ 7.79 (d, 1 H, J = 7.5 Hz), 7.53 (t, 1 H, J = 7.5 Hz), 7.23 (t, 1 H, J = 7.5 Hz), 7.07 (d, 2 H, J = 7.5 Hz), 6.96–6.85 (m, 3 H), 5.18 (s, 2 H), 4.32 (s, 2 H), 2.47 (t, 2 H, J = 7 Hz), 1.46 (quint, 2 H, J = 7 Hz), 1.23 (sext, 2 H, J = 7 Hz), 0.78 (t, 3 H, J = 7 Hz); IR 1709 cm^{-1}. Anal. ($C_{22}H_{23}ClN_2O_4$) C, H, Cl.

1-[4-(Benzyloxy)benzyl]-2-butyl-4-chloro-5-(hydroxymethyl)imidazole (20). To a suspension of sodium methoxide (1.43 g, 26.5 mmol, 1.0 equiv) in 20 mL of dimethylformamide at 25 °C was added a solution of 2-butyl-4(5)-chloro-5(4)-(hydroxymethyl)imidazole (**11**, 5.00 g, 26.5 mmol, 1.0 equiv)[9] in 15 mL of dimethylformamide. The resulting mixture was stirred at 25 °C for 0.25 h, and then to this mixture was added, dropwise, a solution of 4-(benzyloxy)benzyl chloride (7.40 g, 31.8 mmol, 1.2 equiv) in 15 mL of dimethylformamide. The reaction mixture was stirred at 40 °C for 4 h. After cooling, the solvent was removed under vacuum. The residue was dissolved in ethyl acetate, and this solution was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography on silica gel (elution: 10–25% ethyl acetate/benzene) afforded 3.27 g (32%) of **20**: mp 115–116 °C; NMR ($CDCl_3$) δ 7.39 (m, 5 H), 6.94 (s, 4 H), 5.15 (s, 2 H), 5.04 (s, 2 H), 4.47 (br s, 2 H), 2.56 (t, 2 H, J = 7 Hz), 2.07 (br s, 1 H), 1.63 (quint, 2 H, J = 7 Hz), 1.32 (sext, 2 H, J = 7 Hz), 0.87 (t, 3 H, J = 7 Hz).

2-Butyl-4-chloro-1-(4-hydroxybenzyl)-5-(hydroxymethyl)imidazole (21). A mixture of **20** (0.50 g, 1.30 mmol), 0.50 g of 10% palladium/carbon, and 40 mL of tetrahydrofuran was stirred at room temperature under hydrogen gas (1 atm) for 6 h. The mixture was filtered through Celite under nitrogen, and the resulting solution was concentrated under vacuum. The crude product was extracted with hot chloroform. After cooling, the chloroform mixture was concentrated under vacuum, and the resulting solid was washed with hexane to afford 0.16 g (42%) of **21**: NMR (DMSO-d_6) δ 9.43 (s, 1 H), 6.81 (A_2B_2, 4 H, J = 10 Hz), 5.21 (t, 1 H, J = 5 Hz), 5.10 (s, 2 H), 4.33 (d, 2 H, J = 5 Hz), 2.47 (t, 2 H, J = 7 Hz), 1.44 (quint, 2 H, J = 7 Hz), 1.23 (sext, 2 H, J = 7 Hz), 0.79 (t, 3 H, J = 7 Hz).

2-Butyl-4-chloro-1-[4-[(2-cyanobenzyl)oxy]benzyl]-5-(hydroxymethyl)imidazole (22). To a solution of **21** (1.00 g, 3.4 mmol, 1.0 equiv) in 15 mL of dimethylformamide at 25 °C was added sodium methoxide (0.185 g, 3.4 mmol, 1.0 equiv), and the resulting mixture was stirred at 25 °C for 0.25 h. To this mixture was then added a solution of α-bromo-o-tolunitrile (0.80 g, 4.1 mmol, 1.2 equiv) in 5 mL of dimethylformamide. The reaction mixture was stirred at 25 °C for 16 h. The solvent was removed under vacuum, and the residue was dissolved in ethyl acetate. This solution was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Column chromatography on silica gel (elution: 10–25% ethyl acetate/benzene) provided 0.76 g (55%) of **22**: NMR ($CDCl_3$) δ 7.73–7.59 (m, 3 H), 7.44 (m, 1 H), 6.96 (s, 4 H), 5.23 (s, 2 H), 5.14 (s, 2 H), 4.50 (d, 2 H, J = 4.5 Hz), 2.57 (t, 2 H, J = 7 Hz), 1.66 (quint, 2 H, J = 7 Hz), 1.33 (sext, 2 H, J = 7 Hz), 0.87 (t, 3 H, J = 7 Hz).

2-Butyl-1-[4-[(2-carboxybenzyl)oxy]benzyl]-4-chloro-5-(hydroxymethyl)imidazole (6a). A solution of **22** (0.20 g, 0.50 mmol) and 6 mL of 10% aqueous sodium hydroxide in 14 mL of ethylene glycol was refluxed for 14 h. After cooling, the reaction mixture was filtered, and the solvent then was removed under vacuum. The residue was dissolved in water, and the solution was acidified to pH 3.5 with hydrochloric acid. The precipitated solid was recovered by filtration to afford 0.17 g (81%) of **6a** as a white solid: mp 57–62 °C; NMR (DMSO-d_6) δ 7.91 (d, 1 H, J = 8 Hz), 7.58 (m, 2 H), 7.42 (m, 1 H), 6.98 (A_2B_2, 4 H, J = 7.5 Hz), 5.42 (s, 2 H), 5.15 (s, 2 H), 4.32 (s, 2 H), 2.48 (t, 2 H, J = 7 Hz), 1.44 (quint, 2 H, J = 7 Hz), 1.23 (sext, 2 H, J = 7 Hz), 0.79 (t, 3 H, J = 7 Hz); IR 1702 cm^{-1}. Anal. ($C_{23}H_{25}ClN_2O_4 \cdot 2H_2O$) C, H, N.

***N*-[4-(Benzyloxy)benzyl]glycine Ethyl Ester (23).** To a suspension of glycine ethyl ester hydrochloride (11.0 g, 79 mmol, 2.0 equiv) in 100 mL of dimethylformamide at 25 °C was added triethylamine (22.0 mL, 158 mmol, 4.0 equiv). To the resulting milky suspension was added 4-(benzyloxy)benzyl chloride (9.08 g, 39 mmol, 1.0 equiv) in 50 mL of dimethylformamide dropwise over 0.5 h. The mixture was stirred for 16 h at 25 °C. The reaction mixture was diluted with diethyl ether and then filtered to remove the precipitated triethylamine hydrochloride. The resulting solution was concentrated under vacuum, and the residue was dissolved in ethyl acetate. The solution was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Kugelrohr distillation provided 5.90 g (51%) of **23**: bp 160–180 °C (0.015 Torr); NMR ($CDCl_3$) δ 7.43–7.27 (m, 5 H), 7.06 (A_2B_2, 4 H, J = 8 Hz), 5.01 (s, 2 H), 4.14 (quart, 2 H, J = 7 Hz), 3.71 (s, 2 H), 3.36 (s, 3 H), 2.01 (br s, 1 H), 1.24 (t, 3 H, J = 7 Hz).

1-[4-(Benzyloxy)benzyl]-5-carbomethoxy-2(3*H*)-imidazolethione (25). A solution of **23** (5.83 g, 19.5 mmol, 1.0 equiv), formic acid (0.86 mL, 22.8 mmol, 1.2 equiv), and 20 mL of xylene was refluxed for 2 h under a Dean–Stark trap. After cooling, the reaction mixture was washed sequentially with 20% aqueous formic acid, water, saturated sodium bicarbonate solution, water, and brine. Finally the mixture was dried over anhydrous sodium sulfate and filtered, and the filtrate was concentrated to furnish 6.23 g of crude *N*-[4-(benzyloxy)benzyl]-*N*-formylglycine ethyl ester (**24**).

To a suspension of sodium methoxide (1.10 g, 20 mmol, 1.05 equiv) in 35 mL of tetrahydrofuran at 10 °C was added, in one portion, a solution of **24** (6.23 g, 19 mmol, 1.0 equiv) and methyl formate (3.46 mL, 56 mmol, 3.0 equiv) in 15 mL of tetrahydrofuran. The mixture was stirred at 10 °C for 1 h and then at 25 °C for 16 h. The solvent was removed under vacuum, and the residue was dissolved in 36 mL of methanol. To this solution was added concentrated hydrochloric acid (3.57 mL, 43 mmol, 2.3 equiv), and the mixture was stirred at 40 °C for 0.5 h. A solution of potassium thiocyanate (2.80 g, 29 mmol, 2.0 equiv) in 6 mL of water was added, and the resulting mixture was stirred for 16 h at 40 °C. Finally, 40 mL of water was added, and the mixture was allowed to cool to 25 °C. The precipitated solid was recovered by filtration to afford 3.60 g (52%) of **25**: NMR ($CDCl_3$) δ 11.25 (br s, 1 H), 8.05 (s, 1 H), 7.39 (m, 5 H), 7.03 (A_2B_2, 4 H, J = 7 Hz), 5.06 (s, 2 H), 4.56 (s, 2 H), 3.81 (s, 3 H).

1-[4-(Benzyloxy)benzyl]-5-carbethoxy-2-(propylthio)-imidazole (26). To 60 mL of ethanol at 25 °C was added sodium metal (0.30 g, 13 mmol, 1.3 equiv). After the sodium metal dissolved, **25** (3.54 g, 10 mmol, 1.0 equiv) was added followed immediately by 1-iodopropane (2.24 mL, 23 mmol, 2.3 equiv). The mixture was stirred at 25 °C for 3 h. At this point, the solvent was removed under vacuum and the residue was dissolved in methylene chloride. This solution was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated to furnish 3.46 g of crude **26**, used in the subsequent reaction without further purification: NMR ($CDCl_3$) δ 7.77 (s, 1 H), 7.45–7.32 (m, 5 H), 7.03 (A_2B_2, 4 H, J = 8 Hz), 5.49 (s, 2 H), 5.03 (s, 2 H), 4.28 (quart, 2 H, J = 7 Hz), 3.20 (t, 2 H, J = 7 Hz), 1.32 (t, 3 H, J = 7 Hz), 1.02 (t, 3 H, J = 7 Hz).

1-[4-(Benzyloxy)benzyl]-5-(hydroxymethyl)-2-(propylthio)imidazole (27). A solution of **26** (2.05 g, 5.0 mmol, 1.0 equiv)

(15) Agranat, I.; Tapuhi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 665. Ullmann, F.; Zlokasaff, M. *Chem. Ber.* **1905**, *38*, 2112.
(16) Cella, J. A. *J. Org. Chem.* **1988**, *53*, 2099.

in 10 mL of tetrahydrofuran was added dropwise to 1 M lithium aluminum hydride/tetrahydrofuran (10 mL, 10 mmol, 2.0 equiv) at 0 °C such that the reaction temperature remained below 5 °C. The resulting solution then was stirred at 0 °C for 1 h. At this point, the reaction mixture was quenched by sequential dropwise addition of 0.40 mL of water, 0.40 mL of 15% aqueous sodium hydroxide, and 1.20 mL of water. The resulting suspension was filtered and washed with diethyl ether, and the filtrate was concentrated to furnish 1.55 (84%) of **27**: NMR ($CDCl_3$) δ 7.41–7.29 (m, 5 H), 7.03–6.86 (m, 5 H), 5.22 (s, 2 H), 5.01 (s, 2 H), 4.45 (s, 2 H), 3.01 (t, 2 H, J = 7 Hz), 2.32 (br s, 1 H), 1.66 (sext, 2 H, J = 7 Hz), 0.97 (t, 3 H, J = 7 Hz).

1-(4-Hydroxybenzyl)-5-(hydroxymethyl)-2-(propylthio)-imidazole (28). A solution of **27** (1.40 g, 3.8 mmol) in 15 mL of trifluoroacetic acid was refluxed for 0.25 h. After cooling, the reaction was poured into water containing an excess of sodium bicarbonate, and the resulting emulsion was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography on silica gel (elution: 0–5% methanol/chloroform) afforded 0.28 g (27%) of **28**: NMR (DMSO-d_6) δ 9.41 (s, 1 H), 6.88 (s, 1 H), 6.79 (A_2B_2, 4 H, J = 9 Hz), 5.14 (t, 1 H, J = 5 Hz), 5.07 (s, 2 H), 4.33 (d, 2 H, J = 5 Hz), 2.89 (t, 2 H, J = 7 Hz), 1.54 (sext, 2 H, J = 7 Hz), 0.88 (t, 3 H, J = 7 Hz).

1-[4-[(2-Carboxybenzyl)oxy]benzyl]-5-(hydroxymethyl)-2-(propylthio)imidazole (6e). The title compound was prepared from **28** by using the alkylation and saponification procedures employed for the preparation of **22** and **6a**: mp 161–163 °C; NMR (DMSO-d_6) δ 13.12 (br s, 1 H), 7.93 (d, 1 H, J = 7 Hz), 7.58 (m, 2 H), 7.45 (m, 1 H), 6.99 (A_2B_2, 4 H, J = 8 Hz), 6.98 (s, 1 H), 5.42 (s, 2 H), 5.25 (br s, 1 H), 5.17 (s, 2 H), 4.35 (s, 2 H), 2.92 (t, 2 H, J = 7 Hz), 1.54 (sext, 2 H, J = 7 Hz), 0.89 (t, 3 H, J = 7 Hz); IR 1674 cm^{-1}. Anal. ($C_{22}H_{24}N_2O_4S·H_2O$) C, H, N.

2-Butyl-4-chloro-1-(4-formylbenzyl)-5-(hydroxymethyl)-imidazole (30). To a solution of 2-butyl-4-chloro-1-(4-cyanobenzyl)-5-(hydroxymethyl)imidazole (**29**, 5.05 g, 16.6 mmol, 1.0 equiv) in 350 mL of benzene at 25 °C was added dropwise 1.5 M diisobutylaluminum hydride in toluene (22.8 mL, 34.2 mmol, 2.05 equiv). The mixture was warmed to 45 °C and stirred for 16 h. After cooling, the reaction mixture was poured into ice-cold 20% aqueous sulfuric acid. This solution was allowed to warm to 25 °C and then stirred for 2 h. The solution was cooled to 0 °C, neutralized with aqueous sodium hydroxide, and extracted with ethyl acetate. The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography on silica gel (elution: 0–20% ethyl acetate/benzene) provided 3.60 g (71%) of **30**: mp 89–90 °C; NMR ($CDCl_3$) δ 9.96 (s, 1 H), 7.86 (d, 2 H, J = 8 Hz), 7.17 (d, 2 H, J = 8 Hz), 5.26 (s, 2 H), 4.42 (s, 2 H), 2.54 (t, 2 H, J = 7 Hz), 1.64 (quint, 2 H, J = 7 Hz), 1.32 (sext, 2 H, J = 7 Hz), 0.86 (t, 3 H, J = 7 Hz).

2-Butyl-4-chloro-1-[(2′-cyano-*trans*-stilben-4-yl)-methyl]-5-(hydroxymethyl)imidazole (31). To a solution of α-bromo-*o*-tolunitrile (0.98 g, 5.0 mmol, 1.0 equiv) in 25 mL of dimethylformamide at 25 °C was added triphenylphosphine (1.40 g, 5.4 mmol, 1.1 equiv). The mixture was stirred at 80 °C for 3 h and then treated with **30** (1.53 g, 5.0 mmol, 1.0 equiv), followed immediately by sodium methoxide (0.54 g, 10.0 mmol, 2.0 equiv). The mixture then was stirred at 80 °C for 3 h. After cooling, the mixture was diluted with water and extracted with benzene. The organic phases were combined, washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography on silica gel (elution: 0–20% ethyl acetate/benzene) afforded 0.45 g (22%) of **31**: NMR ($CDCl_3$) δ 8.01 (d, 1 H, J = 8.5 Hz), 7.85 (d, 1 H, J = 8.5 Hz), 7.73 (t, 1 H, J = 8.5 Hz), 7.47 (t, 1 H, J = 8.5 Hz), 7.44 (AB, 2 H, J = 16.3 Hz), 7.38 (A_2B_2, 4 H, J = 8 Hz), 5.28 (s, 2 H), 5.24 (t, 1 H, J = 4.5 Hz), 4.34 (d, 2 H, J = 4.5 Hz), 2.49 (t, 2 H, J = 7 Hz), 1.47 (quint, 2 H, J = 7 Hz), 1.24 (sext, 2 H, J = 7 Hz), 0.79 (t, 3 H, J = 7 Hz).

2-Butyl-1-[(2′-carboxy-*trans*-stilben-4-yl)methyl]-4-chloro-5-(hydroxymethyl)imidazole (7). The title compound was prepared from **31** by the procedure described for the preparation of **6a**: mp 165–166 °C; NMR ($CDCl_3$) δ 8.08–8.00 (m, 2 H), 7.71 (d, 1 H, J = 8.5 Hz), 7.57–7.47 (m, 3 H), 7.34 (t, 1 H, J = 7.5 Hz), 7.01–6.92 (m, 3 H), 5.21 (s, 2 H), 4.50 (s, 2 H), 2.60 (t, 2 H, J = 7 Hz), 1.62 (quint, 2 H, J = 7 Hz), 1.31 (sext, 2 H, J = 7 Hz), 0.83 (t, 3 H, J = 7 Hz); IR 1703 cm^{-1}; high-resolution MS calcd 424.1554, found 424.1557.

***N*-[4-[[2-Butyl-4-chloro-5-(methoxymethyl)imidazol-1-yl]methyl]phenyl]-*N*′-(2-nitrophenyl)urea (33).** A solution of 1-(4-aminobenzyl)-2-butyl-4-chloro-5-(methoxymethyl)imidazole (**32**, 1.00 g, 3.24 mmol, 1.0 equiv)[17] and 2-nitrophenyl isocyanate (0.53 g, 3.24 mmol, 1.0 equiv) in 40 mL of chloroform was stirred at 25 °C for 24 h and then refluxed for 8 h. The reaction mixture was cooled to 25 °C and the precipitate recovered by filtration. The filtrate was concentrated under vacuum, and the residue was triturated with diethyl ether. The resulting solids were filtered, combined with the initial precipitate, and recrystallized from acetonitrile to afford 1.11 g (73%) of **33** as a yellow solid: mp 199–200 °C; NMR (DMSO-d_6) δ 9.93 (s, 1 H), 9.63 (s, 1 H), 8.25 (d, 1 H, J = 9 Hz), 8.07 (d, 1 H, J = 9 Hz), 7.70 (t, 1 H, J = 9 Hz), 7.47 (d, 2 H, J = 9 Hz), 7.21 (t, 1 H, J = 9 Hz), 7.02 (d, 2 H, J = 9 Hz), 5.13 (s, 2 H), 4.29 (s, 2 H), 3.20 (s, 3 H), 2.52 (t, 2 H, J = 7 Hz), 1.49 (quint, 2 H, J = 7 Hz), 1.25 (sext, 2 H, J = 7 Hz), 0.81 (t, 3 H, J = 7 Hz); IR 1712 cm^{-1}.

***N*-(2-Aminophenyl)-*N*′-[4-[[2-butyl-4-chloro-5-(methoxymethyl)imidazol-1-yl]methyl]phenyl]urea (34).** A mixture of **33** (1.05 g, 2.22 mmol) and 0.50 g of 10% palladium/carbon in 75 mL of methanol and 50 mL of tetrahydrofuran at 25 °C was hydrogenated in a Parr shaker (3 atm) for 2 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated under vacuum. Column chromatography (elution: 60% ethyl acetate/hexane) provided 0.52 g (54%) of **34**: NMR (DMSO-d_6) δ 8.82 (s, 1 H), 7.73 (s, 1 H), 7.43 (d, 2 H, J = 9 Hz), 7.33 (d, 1 H, J = 9 Hz), 6.98 (d, 2 H, J = 9 Hz), 6.85 (t, 1 H, J = 9 Hz), 6.74 (d, 1 H, J = 9 Hz), 6.56 (t, 1 H, J = 9 Hz), 5.12 (s, 2 H), 4.78 (s, 2 H), 4.30 (s, 2 H), 3.22 (s, 3 H), 2.50 (t, 2 H, J = 7 Hz), 1.51 (quint, 2 H, J = 7 Hz), 1.27 (sext, 2 H, J = 7 Hz), 0.83 (t, 3 H, J = 7 Hz); IR 1658 cm^{-1}.

***N*-[4-[[2-Butyl-4-chloro-5-(methoxymethyl)imidazol-1-yl]methyl]phenyl]-*N*′-[2-(trifluoromethanesulfonamido)-phenyl]urea (8).** To a solution of **34** (0.48 g, 1.09 mmol, 1.0 equiv) and triethylamine (0.17 mL, 1.20 mmol, 1.1 equiv) in 15 mL of methylene chloride at −78 °C was added dropwise over 0.5 h a solution of trifluoromethanesulfonic anhydride (0.20 mL, 1.20 mmol, 1.1 equiv) in 2 mL of methylene chloride. The solution was stirred at −78 °C for 1 h, warmed to 25 °C over several hours, and stirred to 25 °C for 12 h. The solvent was removed under vacuum, and the residue was dissolved in water. The aqueous solution was adjusted to pH 11 with 10 N aqueous sodium hydroxide, washed with diethyl ether, adjusted to pH 3 with concentrated hydrochloric acid, and extracted with ethyl acetate. The combined ethyl acetate extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated. Recrystallization from 1-chlorobutane furnished 0.32 g (56%) of **8**: mp 155–157.5 °C; NMR (DMSO-d_6) δ 9.54 (s, 1 H), 8.28 (s, 1 H), 8.00 (d, 1 H, J = 9 Hz), 7.46 (d, 2 H, J = 9 Hz), 7.34–7.16 (m, 2 H), 7.06 (d, 1 H, J = 9 Hz), 7.01 (d, 2 H, J = 9 Hz), 5.13 (s, 2 H), 4.27 (s, 2 H), 3.18 (s, 3 H), 2.52 (t, 2 H, J = 7 Hz), 1.48 (quint, 2 H, J = 7 Hz), 1.25 (sext, 2 H, J = 7 Hz), 0.80 (t, 3 H, J = 7 Hz); IR 1689 cm^{-1}. Anal. ($C_{24}H_{27}ClF_3N_5O_4S·0.5H_2O$) C, H, N.

Registry No. **1**, 114822-88-7; **2a**, 114798-90-2; **2b**, 114798-99-1; **2c**, 114798-92-4; **2d**, 114798-91-3; **3a**, 114799-50-7; **3b**, 114799-51-8; **3c**, 125848-44-4; **3d**, 114799-56-3; **3e**, 114822-98-9; **4**, 114822-97-8; **5**, 114799-44-9; **6a**, 114799-48-3; **6b**, 114799-46-1; **6c**, 114799-49-4; **6d**, 114799-47-2; **6e**, 114799-61-0; **6f**, 125848-45-5; **7**, 114799-60-9; **8**, 125848-40-0; **9**, 114772-33-7; **10**, 114772-37-1; **11**, 79047-41-9; **12**, 114772-41-7; **13**, 114772-42-8; **14**, 114772-97-3; **15**, 114772-98-4; **16**, 114773-01-2; **17**, 114773-04-5; **18**, 21905-69-1; **19**, 21905-72-6; **20**, 114799-98-3; **21**, 125848-41-1; **22**, 114772-91-7; **23**, 15917-88-1; **24**, 114773-14-7; **25**, 114773-15-8; **26**, 114773-16-9; **27**, 114773-17-0; **28**, 114773-18-1; **29**, 114799-90-5; **30**, 114773-11-4; **31**, 114773-12-5; **32**, 114772-10-0; **33**, 125848-42-2; **34**, 125848-43-3; angiotensin II, 11128-99-7; *p*-cresol, 106-44-5; 2-chlorobenzoic acid, 26264-09-5; glycine ethyl ester hydrochloride, 623-33-6; 4-(benzyloxy)benzyl chloride, 836-42-0; α-bromo-*o*-tolunitrile, 22115-41-9; triphenylphosphine, 603-35-0; 2-nitrophenyl isocyanate, 3320-86-3; trifluoromethyl sulfonic anhydride, 358-23-6.

(17) Prepared as described in ref 7.

(18) Chiu, A. T.; et al. *Eur. J. Pharmacol.* **1988**, *157*, 13.