Nonpeptide Angiotensin II Receptor Antagonists: The Discovery of a Series of *N*-(Biphenylylmethyl)imidazoles as Potent, Orally Active Antihypertensives

David J. Carini,*[1] John V. Duncia,*[1] Paul E. Aldrich, Andrew T. Chiu, Alexander L. Johnson, Michael E. Pierce, William A. Price, Joseph B. Santella III, Gregory J. Wells, Ruth R. Wexler, Pancras C. Wong, Sung-Eun Yoo, and Pieter B. M. W. M. Timmermans

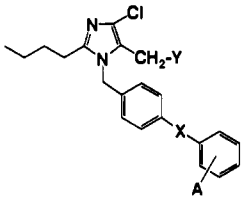
Medical Products Department, Pharmaceuticals Division, Experimental Station, E. I. du Pont de Nemours & Company, Inc., Wilmington, Delaware 19880-0402. *Received December 12, 1990*

A new series of nonpeptide angiotensin II (AII) receptor antagonists has been prepared. These *N*-(biphenylylmethyl)imidazoles, e.g. 2-butyl-1-[(2′-carboxybiphenyl-4-yl)methyl]-4-chloro-5-(hydroxymethyl)imidazole, differ from the previously reported *N*-(benzamidobenzyl)imidazoles and related compounds in that they produce a potent antihypertensive effect upon oral administration; the earlier series generally were active only when administered intravenously. It has been found that the acidic group at the 2′-position of the biphenyl is essential. Only ortho-substituted acids possess both high affinity for the AII receptor and good oral antihypertensive potency. The carboxylic acid group has been replaced with a variety of acidic isosteres, and the tetrazole ring has been found to be the most effective. The tetrazole derivative, DuP 753, is currently in development for the treatment of hypertension.

We have recently described the history behind the discovery of novel nonpeptide angiotensin II (AII) receptor antagonists.[2,3] All of the analogues discussed thus far lowered blood pressure intravenously; however, only in a few cases did we notice weak oral activity. We now report on the discovery of a series of potent, *orally active* AII receptor antagonists, which has led to a clinical candidate.

Discussion

Compounds with the core structure 1 have previously been found to be potent antagonists of the AII receptor and to be antihypertensive upon iv administration.[3] Replacement of the polar carboxylic acid group (A) with acid isosteres of greater lipophilicity, such as $NHSO_2CF_3$, resulted in some oral activity. However, none of these compounds when dosed orally produced an effect to compare with their intravenous antihypertensive effect.



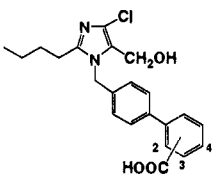
1

A = Acidic Functionality such as -COOH, -$NHSO_2CF_3$, -SO_3H, -CN_4H, etc.

X = One, two, and three atom linkages such as -O-, -S-, -CO-, -CONH-, -NHCO-, -NHCONH-, etc.

Y = Hydrogen bonding group such as COOH, OH, CH_2OCH_3.

The first breakthrough occurred when the X linkage of 1 was replaced with a carbon–carbon single bond generating a biphenyl system. Many of the compounds in this biphenyl series were found to be orally active as antihypertensives (see Tables I–VI). The isomeric compounds 2 and 3 have very similar binding affinities. Compound 3 is completely devoid of oral activity; however, compound 2 is orally active (ED_{30} = 11 mg/kg). Figure 1 shows the blood pressure lowering curve of biphenylcarboxylic acid 2. Apparently the carboxylic acid group in both isomers is oriented properly for relatively good binding to the AII receptor. Originally it was hypothesized that the carboxylic acid group of 2 is buried to a greater degree in the lipophilic mass of the biphenyl system than it is in 3, and that consequently 2 is overall more lipophilic than 3. The increased lipophilicity of 2 was felt to account for its bioavailability. However, it has been determined subsequently that the log *P* values of 2 and 3 are virtually identical.[4,5] Para isomer 4 does not bind well, presumably because the carboxylic acid is not oriented properly to allow for good interaction with the positive charge in the AII receptor.[6]



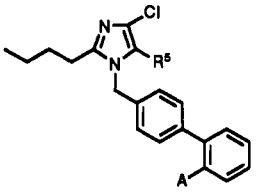
	Isomer	IC_{50} (μM)	ED_{30} (mg/kg p.o. RHR)
2	2-COOH	0.23	11
3	3-COOH	0.49	inactive
4	4-COOH	11.0	inactive

With the importance of the acid group (A) and of its position on the biphenyl both having been established, we concluded that further study of this key substituent was

(1) Coauthors to whom correspondence should be addressed at: DuPont Merck Pharmaceutical Company, P.O. Box 80402, Wilmington, DE 19880-0402.
(2) Part XII in a series. For part XI, see ref 14f.
(3) (a) Duncia, J. V.; Chiu, A. T.; Carini, D. J.; Gregory, G. B.; Johnson, A. L.; Price, W. A.; Wells, G. J.; Wong, P. C.; Calabrese, J. C.; Timmermans, P. B. M. W. M. *J. Med. Chem.* **1990**, *33*, 1312. (b) Carini, D. J.; Duncia, J. V.; Johnson, A. L.; Chiu, A. T.; Price, W. A.; Wong, P. C.; Timmermans, P. B. M. W. M. *J. Med. Chem.* **1990**, *33*, 1330.
(4) The log *P* values as determined by HPLC[5] for compounds 2 and 3 are 1.17 and 1.38, respectively.
(5) "A Rapid Method for Estimating log *P* for Organic Chemicals", U.S. Department of Commerce, National Technical Information Service, PB-284-386.
(6) Hsieh, K.; Marshall, G. R. *J. Med. Chem.* **1986**, *29*, 1968.
(7) Bordwell, F. G.; Algrim, D. *J. Org. Chem.* **1976**, *41*, 2507.
(8) (a) Exner, O.; Simon, W. *Collect. Czech. Chem. Commun.* **1965**, *30*, 4078. (b) Artemenko, A. I.; Anufriev, E. K.; Tikunova, I. V.; Trusevick, N. D. *Zhur. Obsch. Khim.* **1985**, *55*, 2645.
(9) Dulova, V. I.; Gordienko, N. S.; Dubina, V. L. *Zh. Fiz. Khim.* **1970**, *44*(10), 2640.
(10) Meresaar, V. *Acta Chem. Scand. A* **1974**, *28*, 656.
(11) Trepka, R. D.; Belisle, J. W.; Harrington, J. K. *J. Org. Chem.* **1974**, *39*, 1094.
(12) The pK_a of a 5-alkyl-substituted tetrazole is about 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*, 28.
(13) Tanaka, Y.; Velen, S. R.; Miller, S. I. *Tetrahedron* **1973**, *29*, 3271.

0022-2623/91/1834-2525$02.50/0

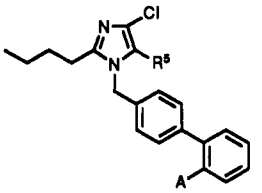
Table I. Angiotensin II Receptor Antagonists Containing "Amide-Type" Carboxylic Acid Isosteres

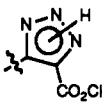
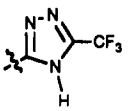
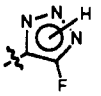


compd no.	R^5	A	est pK_a	IC_{50}[a] (μM)	in vivo activity iv (po)[b]	mp (°C)	elemental analysis
2	CH_2OH	COOH	5	0.23	3 (ED_{30} = 11)	171.0–172.0	C, H, Cl, N
5	CH_2OCH_3	COOH	5	0.099	10 (100)	166.5–169.0	C, H, N
6	CH_2OH	$CONH_2$	23[7]	35.0		155.0–157.0	C, H, Cl, N
7	CH_2OH	CONHOH	10.5[8a,b]	4.1	3 (>30)	glass	C, H, Cl, N
8	CH_2OH	$CONHOCH_3$	10.9[8a]	2.9	10 (inactive)	glass	C, H, Cl, N
9	CH_2OH	$CONHOCH_2Ph$	10.85[8a]	4.9	10 (inactive)	glass	C, H, Cl, N
10	CH_2OH	$CONHSO_2Ph$	8.44[9]	0.14	>3 (NA 30)	172.0–174.0	C, H, Cl, N
11	CH_2OCH_3	$CONHNHSO_2CF_3$	unknown	0.20	>3 (>30)	glass	C, H, Cl, F, N, S
12	CH_2OH	$NHCOCF_3$	9.5[10]	6.3	10 (inactive)	glass	C, H, N
13	CH_2OH	$NHSO_2CF_3$	4.5[11]	0.083	10 (100)	171.0–172.0	C, H, N
14	CH_2OCH_3	$NHSO_2CF_3$	4.5[11]	0.19	10 (100)	148.0–150.0	C, H, N

[a] Inhibition of specific binding of [^{3}H]angiotensin II (2 nM) to rat adrenal cortical microsomes. Intraassay and interassay variabilities of the IC_{50} values for a given compound are 5–10% and 15–30%, respectively (see the Experimental Section for further discussion of the IC_{50} data and method). [b] Iv and po (oral) blood pressure lowering activity in renal hypertensive rats. The tabulated values indicate doses (mg/kg) at which statistically significant drops in blood pressure were observed (>15 mmHg); values such as >3 designate that at this dose (mg/kg) no drop in blood pressure or a statistically insignificant drop in blood pressure was observed; inactive indicates a compound which failed to cause a significant drop in blood pressure even at 100 mg/kg; ED_{30} is the effective dose in mg/kg that lowers the blood pressure 30 mmHg (see the Experimental Section for further discussion of the in vivo data and method).

Table II. Angiotensin II Receptor Antagonists Containing "Azole-Type" COOH Isosteres



compd no.	R^5	A	est pK_a	IC_{50}[a] (μM)	in vivo activity iv (po)[b]	mp (°C)	elemental analysis
17	CH_2OH		5–6[12]	0.019	ED_{30} = 0.80 (ED_{30} = 0.59)	183.5–184.5	C, H, Cl
18	CH_2OCH_3		5–6[12]	0.032	1 (3)	glass	C, H, Cl
19	CH_2OH		unknown	0.28	>1 (>10)	glass	C, H, Cl
20	CH_2OH		7.0[13]	0.26	>1 (>10)	glass	C, H, Cl
21	CH_2OH		unknown	0.37	1 (10)	glass	C, H, Cl
22	CHO		unknown	13	>10 (inactive)	glass	C, H, Cl, F, N

[a,b] See Table I for an explanation of tabulated data.

well warranted. In an attempt to produce analogues of greater potency and bioavailability, the carboxylic acid group of 2 was replaced by a variety of isosteres of varying lipophilicity and increased metabolic stability. These compounds are listed in Tables I and II.

Table I summarizes the AII receptor blockers containing carboxylic acid isosteres that we classify as "amide-type" since all of them contain the carboxamide or sulfonamide functionality. We have previously shown that the greater the acidity of the "A" group (acidic group), the higher the binding affinity.[3a] Amide 6 is essentially nonacidic, and thus it does not have a good IC_{50} value. However, the acidity of the carboxamide group can be increased through substitution by electron-withdrawing heteroatoms such as

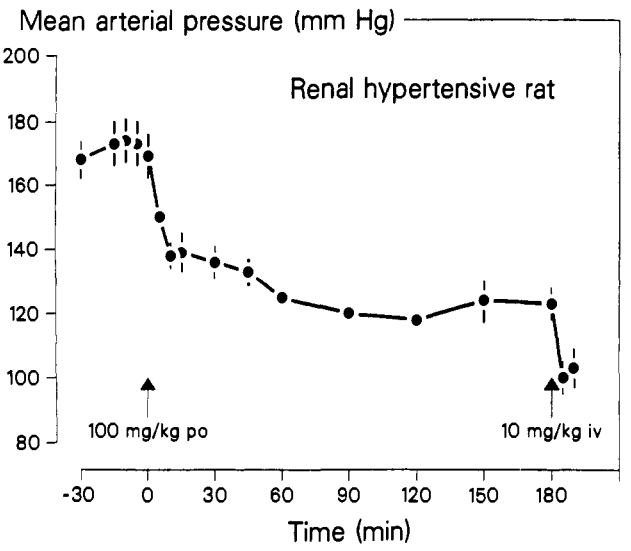


Figure 1. Effect of **2** at 100 mg/kg po and 10 mg/kg iv on mean arterial pressure in renal artery-ligated rats. Values represent the mean ± SEM (n = 6).

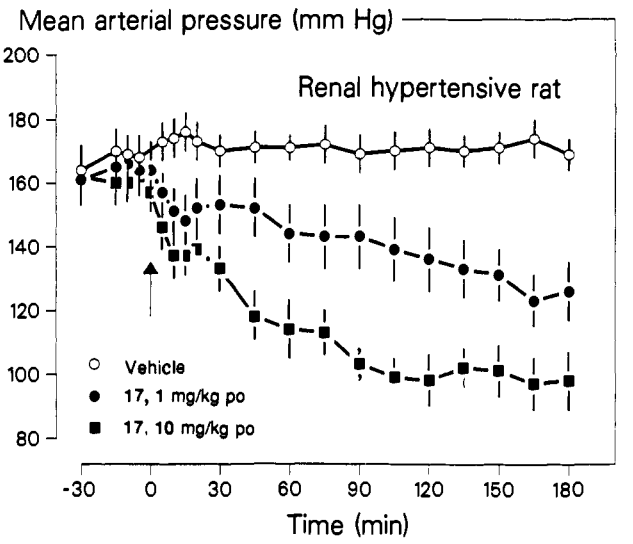
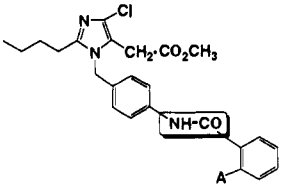


Figure 2. Effects of vehicle (n = 6) and **17** at 1 mg/kg po (n = 6) and 10 mg/kg po (n = 6) on mean arterial pressure in renal artery-ligated rats. Values represent the mean ± SEM.

found in the hydroxamic acids **7**, **8**, and **9**. Unfortunately these groups still were not acidic enough to allow for proper binding to the AII receptor. The more acidic sulfonyl amide **10** and trifluoromethanesulfonohydrazide **11** bind as well as the parent carboxylic acid **2**. Trifluoromethanesulfonohydrazide **11** contains a methoxymethyl group at the imidazole 5-position to simplify its synthesis. The methoxymethyl side chain has little effect on the binding affinity. This can be demonstrated by comparing the affinities of compounds **2** and **5**.

One may reverse the amide-type isosteres so that the amide nitrogen is linked directly to the terminal aromatic ring (compounds **12–14**). In these compounds, the acidic proton is located closer to the aromatic ring than in the carboxylic acid case. Trifluoroacetamide **12** is relatively nonacidic and as a result does not bind very well. However, trifluoromethanesulfonamides **13** and **14** are just as acidic as the parent carboxylic acid and have excellent binding affinities. Again, the methoxymethyl group of **14** reduces the binding affinity by only a factor of two when compared to **13**. Unfortunately, none of the compounds in Table I showed better oral activity than carboxylic acid **2**. This is in sharp contrast to compounds **15** and **16** from our earlier "amide-linked" series[3a] where trifluoromethanesulfonamide **16** showed some oral activity while carboxylic acid **15** was inactive.



"Amide-Linked Series"

15 A = -COOH
16 A = -NHSO2CF3

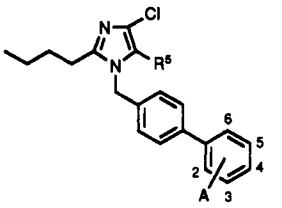
Table II summarizes the AII receptor antagonists containing what we have termed as "azole-type" carboxylic acid isosteres. The activity profile of tetrazole **17** is remarkable. It has a 1 order of magnitude greater binding affinity than carboxylic acid **2**. It has an iv ED_{30} of 0.80 mg/kg and an oral ED_{30} of 0.59 mg/kg.[14a-e] The increase in oral potency of **17** over that of **2** [ED_{30} (po) = 11.0 mg/kg] was greater than can be accounted for by the observed increase in binding affinity. The greater oral activity of **17** as compared to **2** may also be due in part to a greater oral bioavailability. Blood pressure lowering curves for **17** in the renal hypertensive rat are shown in Figure 2. Compound **17** is in development as its potassium salt (DuP 753). This development candidate is currently in phase II human clinical trials.

It is felt that besides mimicking the acidity of the carboxylic acid, the tetrazole, having four nitrogens, possesses a charge distribution that better interacts with the positive charge on the receptor. To test this hypothesis, it was decided to synthesize isosteres of the tetrazole. The triazole ring seemed to mimic a tetrazole with three of the four required nitrogens. However, a simple 1,2,3-triazole, for example, would not be sufficiently acidic, since it would have a pK_a of about 9.[15] However, substitution by electron-withdrawing groups, such as CN, CO_2Me, or CF_3, lowers the pK_a. As a result, the 1,2,3-triazoles **19** and **20** and the 1,2,4-triazole **21** possess binding affinities similar to that of the parent carboxylic acid **2**. These triazole groups do function as effective carboxylic acid isosteres. Unfortunately, none of the triazoles approached the binding affinity or oral activity of **17**. Most likely, the additional electron-withdrawing substituent on the triazole ring does not allow the triazole or the biphenyl or both to assume the proper conformation necessary for high binding affinity. Another possibility is that the extra substituent

(14) (a) Chiu, A. T.; McCall, D. E.; Price, W. A., Jr.; Wong, P. C.; Carini, D. J.; Duncia, J. V.; Wexler, R. R.; Yoo, S. E.; Johnson, A. L.; Timmermans, P. B. *J. Pharmacol. Exp. Ther.* **1990**, *252*, 711. (b) Wong, P. C.; Price, W. A., Jr.; Chiu, A. T.; Duncia, J. V.; Carini, D. J.; Wexler, R. R.; Johnson, A. L.; Timmermans, P. B. *J. Pharmacol. Exp. Ther.* **1990**, *252*, 719. (c) Wong, P. C.; Price, W. A., Jr.; Chiu, A. T.; Duncia, J. V.; Carini, D. J.; Wexler, R. R.; Johnson, A. L.; Timmermans, P. B. *J. Pharmacol. Exp. Ther.* **1990**, *252*, 726. (d) Wong, P. C.; Price, W. A., Jr.; Chiu, A. T.; Duncia, J. V.; Carini, D. J.; Wexler, R. R.; Johnson, A. L.; Timmermans, P. B. *Hypertension* **1990**, *15*, 459. (e) Wong, P. C.; Price, W. A., Jr.; Chiu, A. T., Carini, D. J.; Duncia, J. V.; Johnson, A. L.; Wexler, R. R.; Timmermans, P. B. *Hypertension* **1990**, *15*, 823. (f) Wong, P. C.; Price, W. A., Jr.; Chiu, A. T.; Duncia, J. V.; Carini, D. J.; Wexler, R. R.; Johnson, A. L.; Timmermans, P. B. *J. Pharmacol. Exp. Ther.* **1990**, *255*, 211.

(15) The pK_a of 4-phenyl-1,2,3-triazole is 9.2.[13]

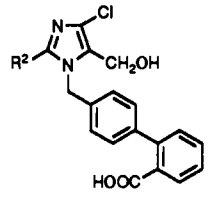
Table III. SAR around the Terminal Aromatic Ring



compd no.	R^5	A	IC_{50}[a] (μM)	in vivo activity iv (po)[b]	mp (°C)	elemental analysis
17	CH_2OH	CN_4H	0.019	ED_{30} = 0.80 (ED_{30} = 0.59)	183.5–184.5	C, H, Cl
23	CH_2OCH_3	2-CH_2CN_4H	0.30	10 (100)	149.5–152.5	C, H, Cl
24	CH_2OCH_3	2-CO-NH-CN_4H	0.70	10	169.0–173.0	C, H, Cl
25	CHO	2-CN_4H	0.02	0.3 (3)	154.0–155.0	C, H, N
26	CHO	3-CN_4H	>1	>10 (30)	157.0–159.0	C, H, N
27	CHO	4-CN_4H	>10	>3 (>30)	210.0–211.5	C, H, N
2	CH_2OH	2-COOH	0.23	3 (ED_{30} = 11)	171.0–172.0	C, H, Cl, N
3	CH_2OH	3-COOH	0.49	45 (100)	180.0–181.0	C, H, Cl
4	CH_2OH	4-COOH	11.0	>10 (inactive)	197.0–199.0	C, H, Cl, N
28	CH_2OH	3-CH_3-2-COOH	1.9	3 (10)	185.0–186.0	C, H, Cl, N
29	CH_2OH	6-OCH_3-2-COOH	3.0	10 (100)	167.0–170.0	C, H, Cl, N
30	CH_2OH	4-OCH_3-2-CN_4H	0.58	ED_{30} = 1.75 (>10)	glass	C, H, Cl, N
31	CH_2OH	5-OCH_3-2-CN_4H	0.12	ED_{30} = 6.03 (>10)	glass	C, H, Cl, N
32	CH_2OH	5-CN-2-CN_4H	0.51	3 (>30)	glass	C, H, Cl

[a,b] See Table I for an explanation of tabulated data.

Table IV. SAR at the Imidazole 2-Position



compd no.	R^2	IC_{50}[a] (μM)	in vivo activity iv (po)[b]	mp (°C)	elemental analysis
33	C_2H_5	1.70	10 (100)	153.0–156.0	C, H; HRMS[c]
34	C_3H_7	0.16	3 (30)	198.0–200.0	C, H, N
2	C_4H_9	0.23	3 (ED_{30} = 11)	171.0–172.0	C, H, Cl, N
35	C_5H_{11}	0.98	3 (30)	glass	C, H, N
36	C_6H_{13}	1.30	10 (inactive)	84.0–88.0	HRMS[a]
37	*trans*-CH_3CH_2CH=CH	0.08	ED_{30} = 1.0 (ED_{30} = 3.6)	198.5–199.5	C, H, Cl
38	phenyl	24	10 (100)	200.0–203.0	C, H, Cl, N

[a,b] See Table I for an explanation of tabulated data. [c] HRMS: high-resolution mass spectrum detects M^+ ion.

on the triazole ring interacts sterically with the receptor. Therefore in this case, where steric considerations around the tetrazole seem to be important, these triazoles represent poor isosteres for the tetrazole group. In contrast to the triazoles **19–21**, the 4-fluoro-1,2,3-triazole **22** has a remarkably poor binding affinity. The reason for this low affinity is uncertain; however, it is not due primarily to the substitution of the 5-aldehyde group for the 5-CH_2OH on the imidazole ring. For the compounds of this paper such a substitution results in a relatively small drop in binding affinity (compare **2** vs **66**, Table VI, and **17** vs **25**, Table III).

Binding affinity data defining the structure–activity relationships (SAR) for substituents around the terminal aromatic ring is summarized in Table III. Insertion of a one-atom or two-atom spacer between the tetrazole and the terminal phenyl ring, as in compounds **23** and **24**, respectively, lowers the binding affinities by more than 1 order of magnitude. Moving the acid group to the meta or para position on the terminal aromatic ring (**3**, **4**, **26**, and **27**) also lowers the binding affinity. However, the *m*-carboxylic acid **3** still binds fairly well compared to the *m*-tetrazole **26**, which is much less active. This represents one of the differences in SAR between the carboxylic acid and the tetrazole series. Substitution of a second functional group onto the terminal aromatic ring has led to lower binding affinities in all cases (compounds **28–32**). This roughly parallels the amide-linked series described previously[3a] in which substitution meta and para to the amide linkage led to lower binding affinities. These results suggest that the terminal aromatic ring may fit snuggly into a lipophilic pocket in which there is insufficient room for substituents on this phenyl ring.

The SAR at the imidazole 2-position is defined by the data summarized in Table IV. In contrast to the amide-linked compounds in which *n*-pentyl proved to be the optimum group for the imidazole 2-position [this generalization is based on a series of derivatives in which the imidazole 4- and 5-positions were occupied by hydrogens[3a]], the biphenyls show the highest binding affinity, for the saturated alkyl groups, when R^2 is *n*-propyl. The structure–activity relationship for alkyl substituents is graphically illustrated in Figure 3. The data suggests a hydrophobic pocket into which an aliphatic chain of the

Table V. SAR at the Imidazole 4-Position

compd no.	R^2	R^4	A	IC_{50}[a] (μM)	in vivo activity iv (po)[b]	mp (°C)	elemental analysis
2	*n*-butyl	Cl	COOH	0.23	3 (ED_{30} = 11)	171.0–172.0	C, H, Cl, N
39	*n*-butyl	Br	COOH	0.09	3 (30)	175.0–178.0	C, H, Br, N
40	*n*-butyl	I	COOH	0.061	10 (100)	163.0–165.0	C, H, I, N
41	*n*-butyl	H	COOH	0.27	10 (inactive)	glass	C, H, N
42	*n*-butyl	CF_3	COOH	0.062	3 (30)	198.0–199.5	C, H, F, N
43	*n*-butyl	NO_2	COOH	0.26	10 (inactive)	204.0–205.5	C, H, N
44	*n*-propyl	CH_3	COOH	1.8	ED_{30} = 1.3 (>30)	208.0–210.0	C, H, Cl, N (HCl salt)
17	*n*-butyl	Cl	CN_4H	0.019	ED_{30} = 0.80 (ED_{30} = 0.59)	183.5–184.5	C, H, Cl
45	*n*-butyl	Br	CN_4H	0.019	0.3 (3)	glass	C, H, Br, N
46	*n*-butyl	I	CN_4H	0.020	1 (10)	glass	C, H, I, N
47	*n*-butyl	H	CN_4H	0.029	NA (NA)	204.5–205.5	C, H, N
48	*n*-butyl	CF_3	CN_4H	0.012	ED_{30} = 0.53 (>3)	glass	C, H, F, N

[a,b] See Table I for an explanation of tabulated data.

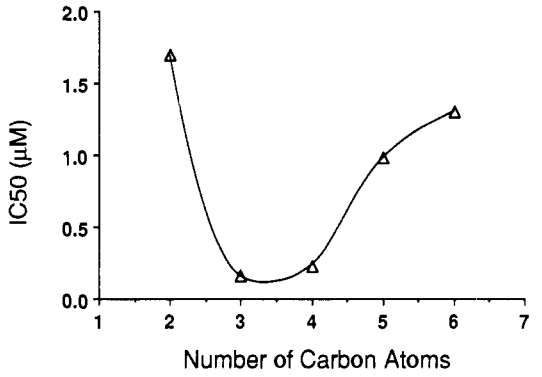


Figure 3. Binding affinity versus length of alkyl chain at the imidazole 2-position.

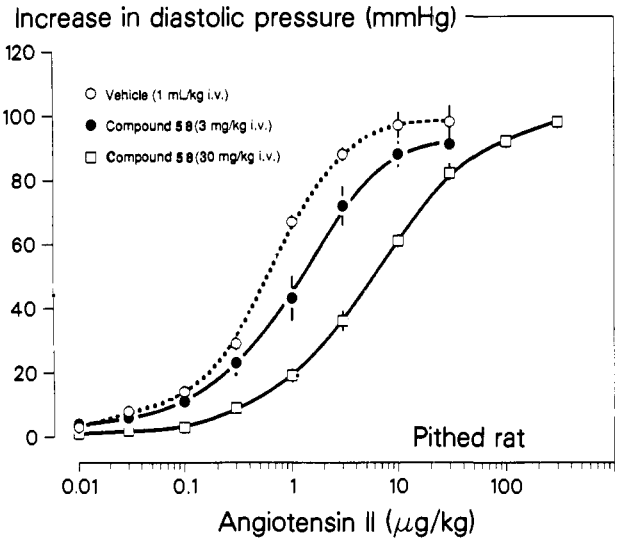


Figure 4. Effects of the vehicle (n = 4) and **58** at 3 mg/kg iv (n = 4) and 30 mg/kg iv (n = 3) on the log dose–pressor response curves for AII in the pithed rat.[16] Values represent the means ± SEM. The mean diastolic pressures for the vehicle-treated group and for the groups treated with 3 or 30 mg/kg each of **58** were 36 ± 1, 38 ± 2, and 29 ± 1 mmHg, respectively.

proper length fits tightly. The introduction of unsaturation into the imidazole side chain at position 2 (e.g. **37**) slightly increases binding affinity. From our amide-linked series,[3a] we discovered that only compounds with unbranched aliphatic chains at this position possess high affinity. Branched alkyl, cycloalkyl, and aromatic substituents give rise to compounds of lower binding affinity. The same is true in the biphenyl series. For example, compound **38** containing the 2-phenyl group is essentially inactive.

The SAR at the imidazole 4-position depends in part upon which acidic functional group is present on the biphenyl (as shown in Table V). In the carboxylic acid series (**2**, **39–44**), there seems to be a trend among the halogen substituents. We see that R^4 = I provides the highest binding affinity while R^4 = Cl affords the lowest. A large lipophilic and electron-withdrawing substituent seems to be favored here. This is supported by the good binding affinity of **42**, which contains a CF_3 group, and by the poor binding affinities of **43** and **44**, which contain a NO_2 and a CH_3 group, respectively. The SAR seen in the carboxylic acid series above holds true in the tetrazole series (**17**, **45–48**) in which the 4-CF_3 analogue is the most potent; however, the tetrazole series is relatively insensitive to small changes in steric bulk at this position.

The data in Table VI demonstrates that when A = COOH the imidazole 5-position can tolerate a wide range of substituents. Thus compounds **2**, **50–54**, **56–58**, and **63–66** have very similar binding affinities even though their 5-position substituents vary considerably in steric bulk. The exceptions include the poorly binding **49**, which contains a basic amino group, and the imidazole-5-carboxylic acid **63**, which binds unusually well. The naphthylurea **55** also binds relatively poorly as do the 5-carboxaldehyde **66** and the *N*,*N*-dimethyl-substituted 5-carboxamide **67**, for reasons that are not clear. In the tetrazole series (**17**, **59–62**), activity is more sensitive to substitution at the imidazole 5-position. Thus, the bulkier the side chain, the lower the binding affinity becomes. Anything larger than a CH_2OH group results in decreased binding affinity. Most likely, a large group at the imidazole 5-position prevents the biphenylyltetrazole portion from achieving the optimal conformation needed for good binding affinity.

In order to further investigate the range of functionality which could be tolerated at the imidazole 5-position in the biphenylcarboxylic acid series, we decided to attach another pharmacophore at this point. Thus the β-blocker pindolol was attached at this position via an amide linkage

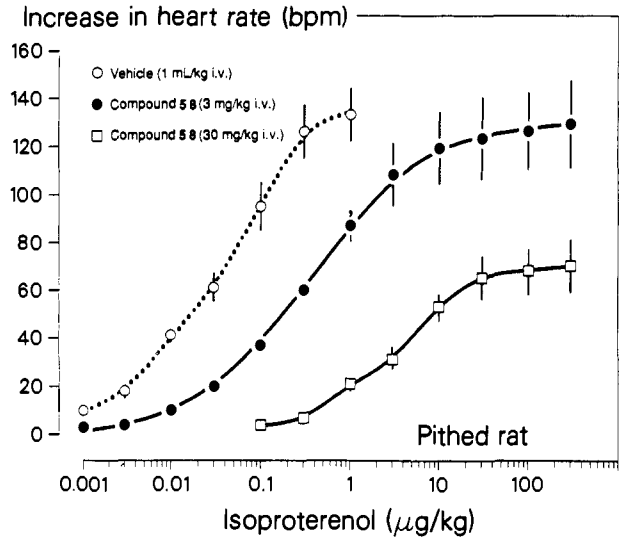
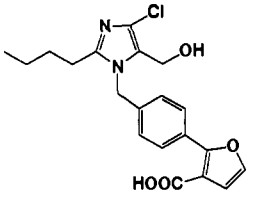


Figure 5. Effects of vehicle (n = 4) and **58** at 3 mg/kg iv (n = 4) and 30 mg/kg iv (n = 4) on the log dose–tachycardiac response curves for isoproterenol in the pithed rat.[16] Values represent the means ± SEM. The mean diastolic pressures for the vehicle-treated group and for the groups treated with 3 or 30 mg/kg each of **58** were 42 ± 3, 39 ± 3, and 32 ± 3 mmHg, respectively.

to yield compound **58**.[16,17] Remarkably this molecule exhibits both AII and β-adrenoreceptor antagonism, as shown in Figures 4 and 5, respectively.

Finally, replacement of the terminal phenyl ring of the biphenyl with a furan ring produces compound **68**, which exhibits a reduced binding affinity.



68

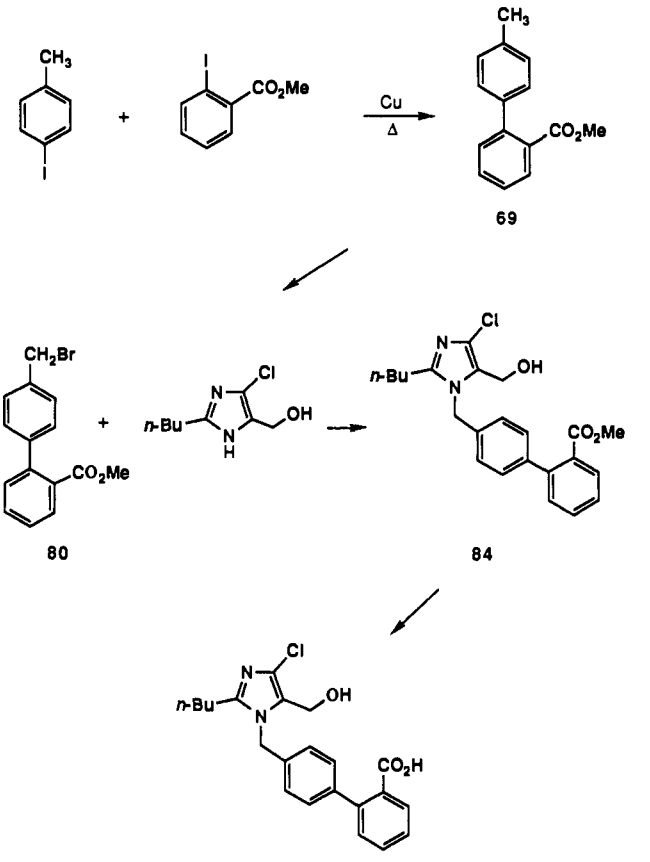
IC_{50} = 4.2 μM

Chemistry

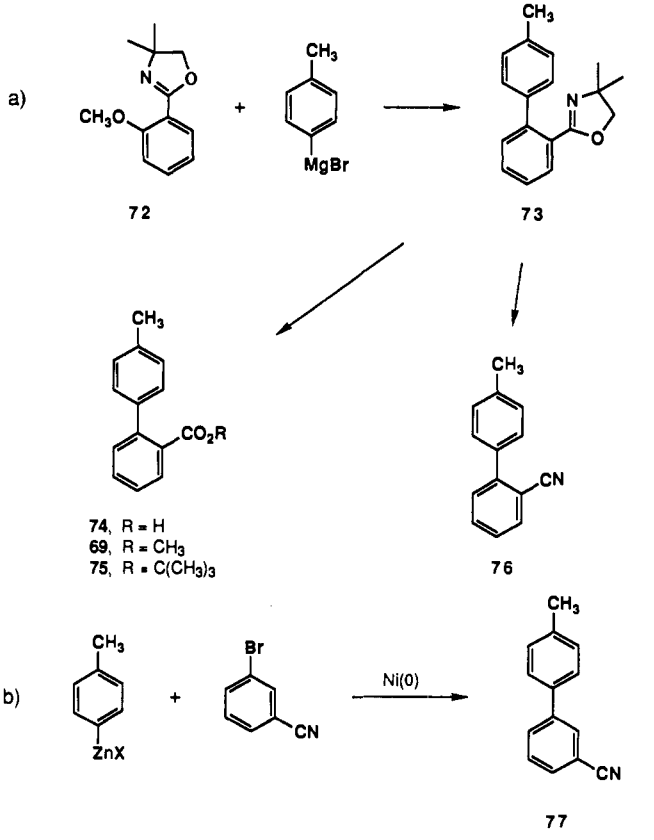
A general procedure employed in the preparation of most of the compounds in this paper is demonstrated in Scheme I for the preparation of **2**. The requisite biphenyl **69** was prepared by the Ullmann biaryl synthesis.[18] Bromination of **69** with *N*-bromosuccinimide provided **80**. Alkylation of 2-butyl-4(5)-chloro-5(4)-(hydroxymethyl)-imidazole[19] with **80** furnished an approximately 1:1 mixture of **84** and its regioisomer.[20] Saponification of **84** completed the procedure.

In addition to the Ullmann procedure another method which has been employed for the preparation of several of the biphenyl intermediates (e.g. **69**) utilizes the chemistry of Meyers (Scheme IIa).[21] The reaction of oxazoline **72** (with (4-methylphenyl)magnesium bromide afforded

Scheme I



Scheme II



(16) Carini, D. J.; Duncia, J. V. *U.S.* Patent 4916129, issued April 10, 1990. For the experimental protocol for Figures 4 and 5, see ref 14b.

(17) The β-blocker pindolol has been previously attached to an angiotensin converting enzyme (ACE) inhibitor moiety to result in a compound with those two respective activities: Allan, G.; Bull, D.; Lee, G. R. European Patent Application 0174162, published March 12, 1986.

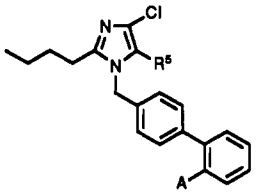
(18) Fanta, P. E. *Chem. Rev.* **1946**, *38*, 139; **1964**, *64*, 613.

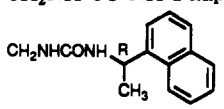
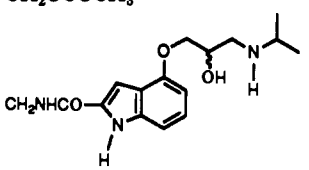
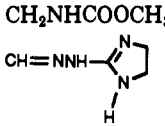
(19) Furukawa, Y.; Kishimoto, S.; Nishikawa, K. U.S. Patent 4340598, 1982.

(20) The regioisomers were assigned by analogy with the results of alkylations reported in (a) Furukawa, Y.; et al. U.S. Patent 4355040, 1982. (b) Reference 3a. The assignments were confirmed by X-ray crystallographic analysis of compound 17 and the regioisomer of **2**.

(21) Meyers, A. I.; Mihelich, E. D. *J. Am. Chem. Soc.* **1975**, *97*, 7383.

Table VI. SAR at the Imidazole 5-Position



compd no.	R^5	A	IC_{50}[a] (μM)	in vivo activity iv (po)[b]	mp (°C)	elemental analysis
2	CH_2OH	COOH	0.23	3 (ED_{30} = 11)	171.0–172.0	C, H, Cl, N
5	CH_2OCH_3	COOH	0.099	10 (100)	166.5–169.0	C, H, N
49	CH_2NH_2	COOH	3.2		glass	[c]
50	CH_2NH-$COOCH_3$	COOH	0.25	3 (30)	144.0–147.0	C, H, N
51	CH_2NH-$COOCH_2CH_3$	COOH	0.20	10 (100)	144.0–147.0	C, H, N
52	CH_2NH-$COOCH_2CH{=}CH_2$	COOH	0.39	10 (100)	139.5–142.0	C, H, N
53	CH_2NH-COO-adamantyl	COOH	0.60	3 (30)	170.0–172.0	C, H, N
54	CH_2NH-CO-$NHCH_3$	COOH	0.24	10 (inactive)	187.0–193.0	C, H, N
55	CH_2NH-CO-NH-1-naphthyl	COOH	3.0	10 (inactive)	169.0–175.0	C, H, N
56		COOH	0.70	>10 (inactive)	163.0–166.0	C, H, Cl
57	CH_2OCOCH_3	COOH	0.33	10 (100)	157.0–159.0	C, H, Cl, N
58		COOH	0.38	ED_{30} = 1.0	glass	C, H, N
17	CH_2OH	CN_4H	0.019	ED_{30} = 0.80 (ED_{30} = 0.59)	183.5–184.5	C, H, Cl
59	$CH_2NHCOOCH_3$	CN_4H	0.06	1 (>10)	202.0–204.5	C, H, Cl
60		CN_4H	0.29	3 (30)	224.0–227.5	C, H, Cl
61	$CH{=}NNHSO_2Ph$	CN_4H	0.66	3 (30)	227.5–230.0	C, H, Cl
62	CH(OH)Ph	CN_4H	0.41	3 (>30)	137.0–145.0	C, H, Cl
63	COOH	COOH	0.092	ED_{30} = 0.47 (>10)	185.0–189.0	C, H, Cl, N
64	$CONH_2$	COOH	0.15	10 (100)	200.0–202.0	C, H, Cl, N
65	CO_2CH_3	COOH	0.34	10 (100)	154.0–155.0	C, H, Cl, N
66	CHO	COOH	0.94	10 (ED_{30} = 1.7)	154.0–158.0 dec	C, H, Cl
67	$CON(CH_3)_2$	COOH	1.3	10 (10)	102.5–105.0	C, H, Cl, N

[a,b] See Table I for an explanation of tabulated data. [c] Intermediate to fully characterized compounds **50–56**.

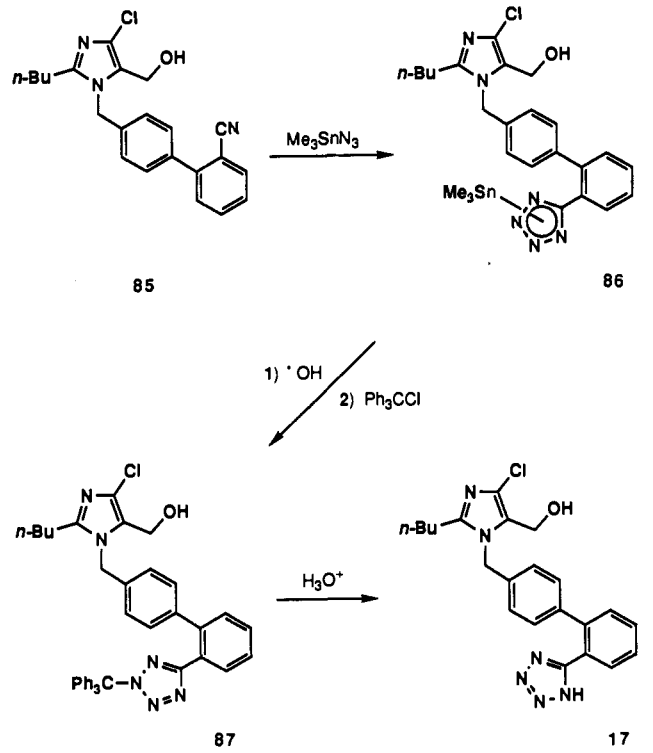
the biphenylyloxazoline **73**. The hydrolysis of **73** provided the biphenylcarboxylic acid **74**, and esterification of **74** afforded such key intermediates as **69** or the *tert*-butyl ester **75**. Alternatively the oxazoline ring can be fragmented employing phosphorus oxychloride[22] to furnish the nitrile **76**. A third method that has proven useful for the preparation of our biphenyl intermediates is the nickel(0)-catalyzed diaryl coupling,[23] which is exemplified in Scheme IIb for the synthesis of nitrile **77**.

An important class of compounds in this paper are the biphenylyltetrazoles (e.g. **17**). These compounds are prepared readily from the corresponding nitriles by employing trimethyltin azide.[24] For example, treatment of **85** with trimethyltin azide afforded the trimethyltin-substituted tetrazole **86** (Scheme III). The trimethyltin group was removed employing sodium hydroxide, and the product was isolated and purified most conveniently as the triphenylmethyl derivative **87**. Deprotection of **87** afforded the tetrazole **17**. Alternatively tributyltin azide was utilized to prepare the biphenylyltetrazole intermediate **79**[25] (see Scheme IV). The trimethyltin azide reagent is very effective for the conversion of hindered nitriles such as **85** to tetrazoles. The direct conversion of **85** to **17** under standard conditions employing sodium azide/ammonium chloride in DMF required 9 days at 100 °C to produce **17** in a yield of 32% as part of a complex mixture of products. ***Caution***: *Accelerated rate calorimetry (ARC) showed that at 115 °C volatile decomposition products begin to form with a relatively large heat of decomposition of –66 kcal/mol of starting nitrile. Therefore it is recommended that the trialkyltin azide procedures be used for the preparation of these tetrazoles.*

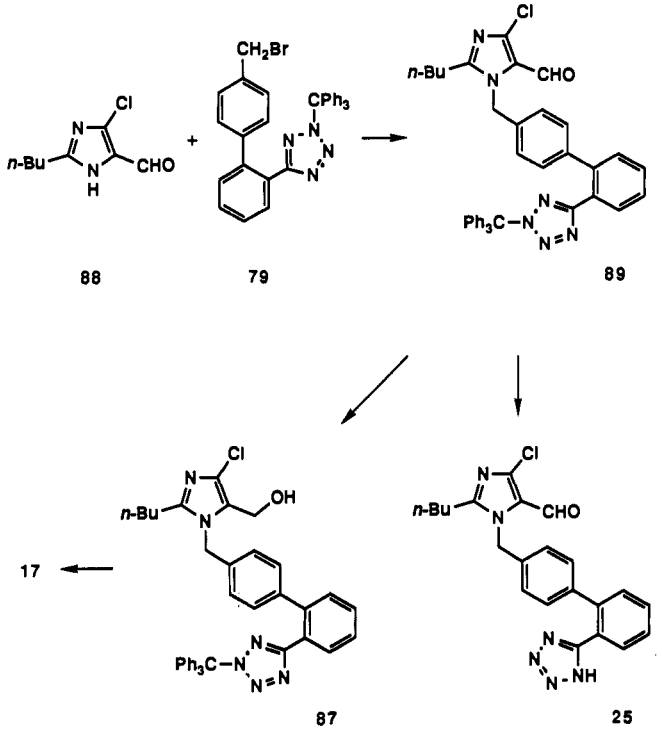
Imidazole-5-carboxaldehydes (e.g. **66**) and the imidazole-5-carboxylic acid **63** have been prepared by direct oxidation of the corresponding 5-(hydroxymethyl)imidazoles by employing such reagents as manganese dioxide and chromium trioxide, respectively. The ester **65** and the amides (e.g. **64**) were prepared from the aldehyde **66** by the chemistry of Corey and Gilman in which an aromatic

(22) Dordor, I. M.; Mellor, J. M. *Tetrahedron Lett.* **1983**, 1437.
(23) Negishi, E.-I.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821.
(24) For the use of trimethyltin azide to prepare tetrazoles, see: Sisido, K.; Nabika, K.; Isida, T.; Kozima, S. *J. Organomet. Chem.* **1971**, 337. For the preparation of trimethyltin azide or tributyltin azide, see: Luitjen, J. G.; Janssen, M. J.; Van Der Kerk, G. J. *Recl. Trav. Chim. Pays-Bas* **1963**, *81*, 286.
(25) Aldrich, P. E.; Duncia, J. V.; Pierce, M. E. U.S. Patent 4874867, 1989.

Scheme III



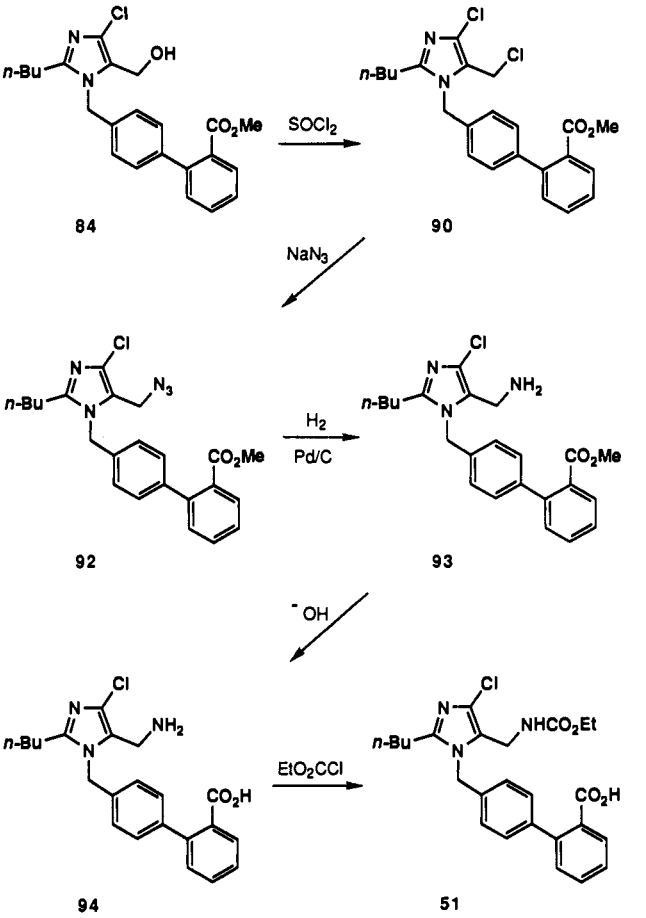
Scheme IV



aldehyde is treated with manganese dioxide/acetic acid/sodium cyanide in methanol[26] or with manganese dioxide/sodium cyanide in 2-propanol containing the appropriate amine.[27] A superior method for the preparation of the acid **63** was the saponification of the ester **65**.

Scheme IV demonstrates an alternative and frequently superior route to the imidazole-5-carboxaldehyde derivatives in which the imidazole aldehyde **88** was alkylated

Scheme V



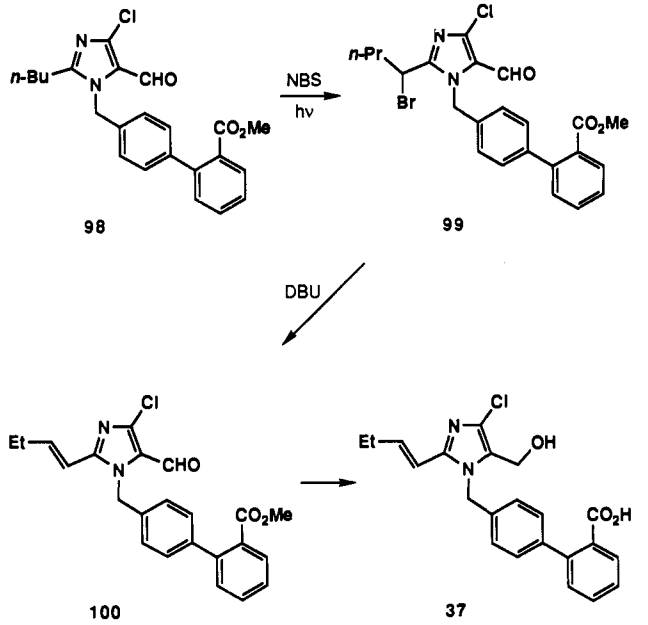
under relatively mild conditions to afford **89**. Deprotection of **89** furnished the desired aldehyde **25**. The main advantage to this synthetic route is that the direct alkylation of an imidazole aldehyde commonly provides the imidazole-5-carboxaldehyde as the major product.[28] For example, the alkylation of **88** furnished a 9:1 ratio of **89** and its regioisomer.[29] The alkylation shown in Scheme IV also was employed as part of an alternate preparation of the alcohol **17**. Reduction of **89** with sodium borohydride, followed by deprotection of **87**, afforded **17** in yields competitive with the chemistry shown in Scheme III. The chemistry shown in Scheme IV is generally applicable to the synthesis of most of the imidazole alcohols and aldehydes of this paper.

The aldehydes such as **89** and **25** can be utilized as intermediates in the preparation of a variety of other analogues. For examples, the addition of phenylmagnesium bromide to **89**, followed by removal of the triphenylmethyl protecting group, provided the secondary alcohol **62**, while the reaction of **25** with benzenesulfonylhydrazine afforded the hydrazone **61**.

The acetate **57** was prepared from the alcohol **2** by the standard procedure using acetic anhydride, triethylamine, and catalytic 4-(dimethylamino)pyridine. The ether **5**, the carbamates (e.g. **51**), the ureas (e.g. **55**), and the amide **58** were prepared by utilizing chemistry previously described by Duncia et al.[3a] and Carini et al.[3b] In the key steps a 5-(hydroxymethyl)imidazole derivative was converted with

(26) Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616.
(27) Gilman, N. W. *J. Chem. Soc., Chem. Commun.* **1971**, 733.
(28) Hoffmann, K. In *The Chemistry of Heterocyclic Compounds: Imidazole and Its Derivatives, Part I*; Weissberger, A., Ed.; Interscience: New York, 1953; Chapter III, p 58.
(29) The regioisomers were assigned by the conversion of aldehyde **89** to the alcohol **17**, see ref 20.

Scheme VI



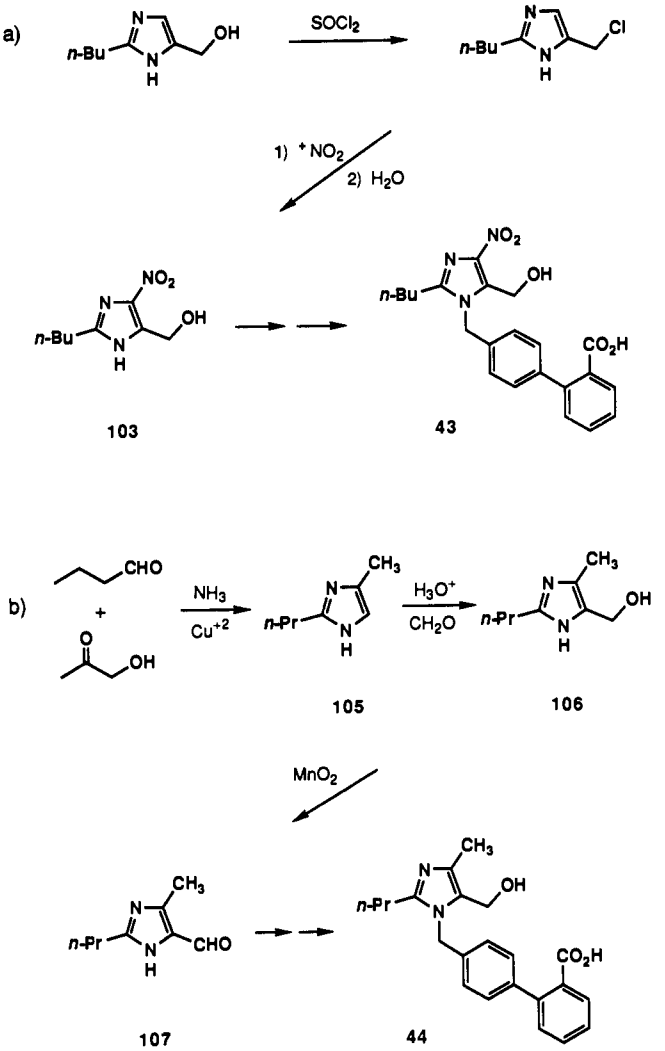
thionyl chloride to the intermediate 5-(chloromethyl)-imidazole; this intermediate was then allowed to react with an appropriate nucleophile. Scheme V demonstrates the application of this chemistry to the preparation of **51**.

When an imidazole bears an alkyl group at the 2-position the hydrogens on the α-carbon of the alkyl chain show remarkably high reactivity.[30] This is especially true when the imidazole also bears an electron-withdrawing group such as an aldehyde. In our compounds it has been possible to take advantage of this reactivity to selectively elaborate the 2-alkyl side chain. For example, the reaction of **98** with NBS under UV irradiation afforded the bromide **99** (Scheme VI). Treatment of **99** with DBU produced the *trans*-butenyl analogue **100**, and the reduction of **100**, followed by saponification, provided **37**.

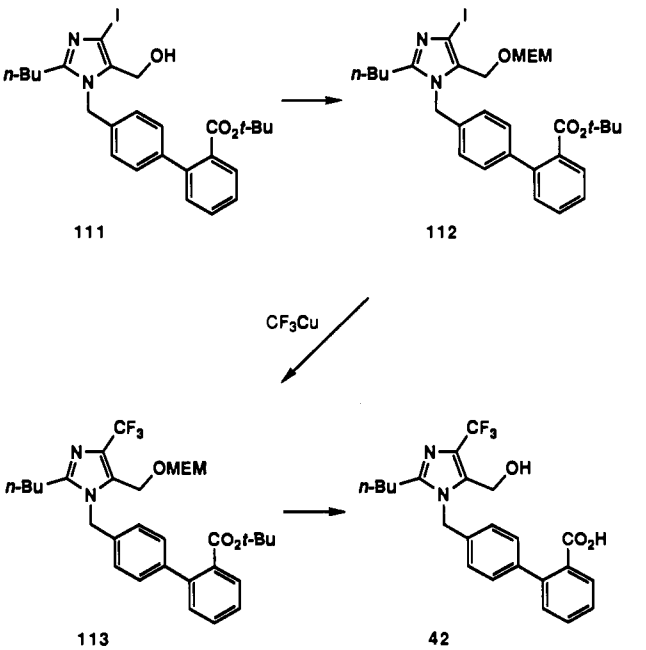
The 4-unsubstituted imidazole **41** was prepared by hydrodehalogenation of the 4-chloroimidazole **84** employing 10% palladium/carbon in methanol. The resulting dechlorinated imidazole **102** was saponified to afford **41**. The 4-nitroimidazole **43** and the 4-methylimidazole **44** were prepared from **103** and **107**, respectively, employing standard procedures described in the above schemes. The nitroimidazole **103** was prepared as shown in Scheme VIIa from 2-butyl-4(5)-(hydroxymethyl)imidazole.[31] In this procedure the hydroxymethyl group was protected during nitration as the chloromethyl group and was subsequently regenerated by hydrolysis. The preparation of 4(5)-methyl-2-propylimidazole-5(4)-carboxaldehyde (**107**) is described in Scheme VIIb. A variation of the Weidenhagen synthesis[32] was employed to produce the dialkylimidazole **105**. Hydroxymethylation[33] of **105** furnished **106**, and the oxidation of **106** produced **107**.

The key step in the synthesis of the 4-(trifluoromethyl)imidazole **42** utilized a (trifluoromethyl)copper reagent reported by Burton.[34] As shown in Scheme VIII,

Scheme VII



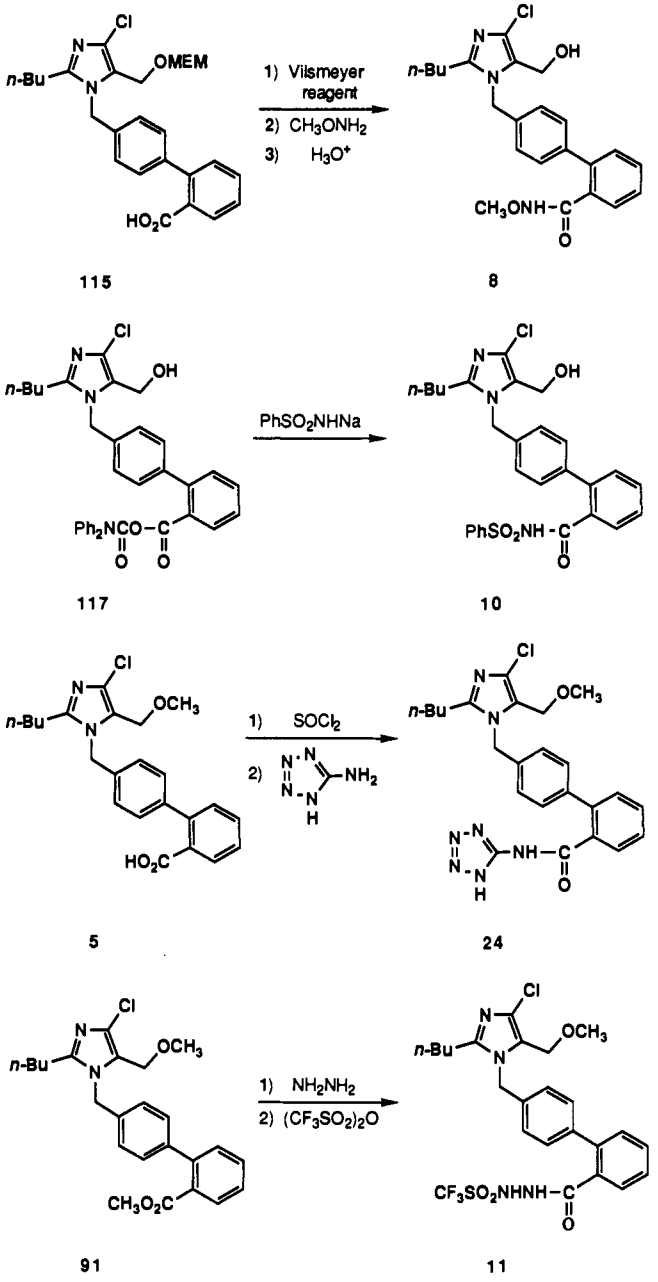
Scheme VIII



the alcohol **111** was protected as its MEM ether. Treatment of the 4-iodoimidazole **112** with the (trifluoromethyl)copper reagent in DMF/HMPA provided **113** in excellent yield. Exposure of **113** to aqueous tetrafluoroboric acid in acetonitrile removed the MEM ether pro-

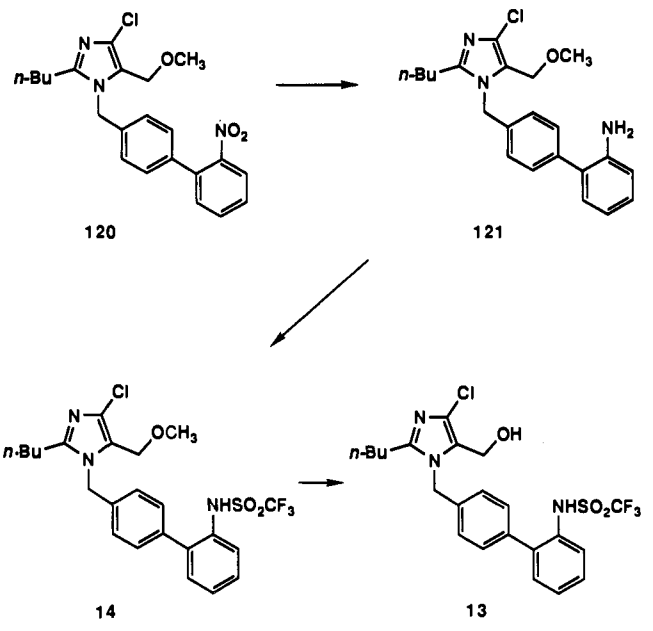
(30) Grimmett, M. R. In *Advances in Heterocyclic Chemistry, Vol. 27*; Katritzky, A. R., Boulton, A. J., Eds.; Academic: New York, 1980; pp 309–320.
(31) Dziuron, P.; Schunack, W. *Arch. Pharm.* **1974**, *307*, 470.
(32) Reiter, L. A. *J. Org. Chem.* **1987**, *52*, 2714.
(33) Kempe, U.; Dockner, T.; Frank, A. U.S. Patent 4278801, 1981.
(34) (a) Weimers, D. M.; Burton, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 832. (b) Burton, D. J.; Weimers, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 5014.

Scheme IX



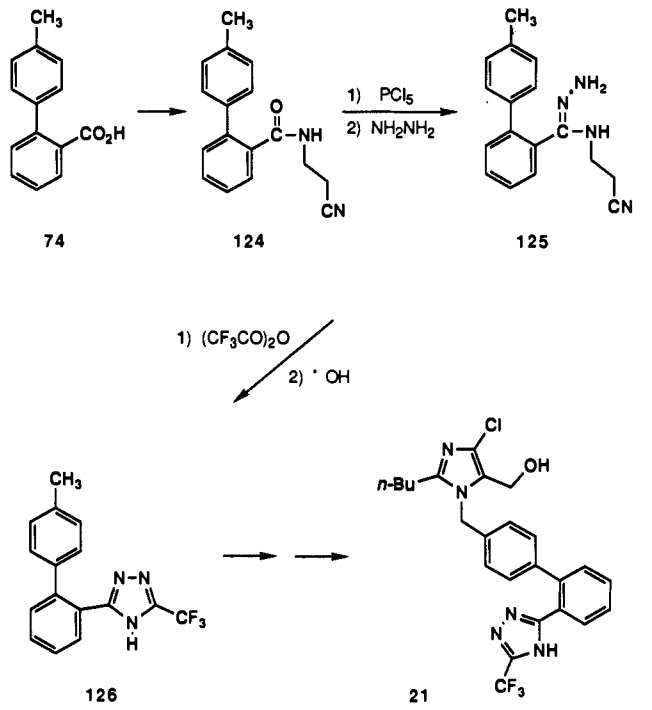
115 8 117 10 5 24 91 11

Scheme X



120 121 14 13

Scheme XI



74 124 125 126 21

tecting group and hydrolyzed the *tert*-butyl ester to afford **42**.

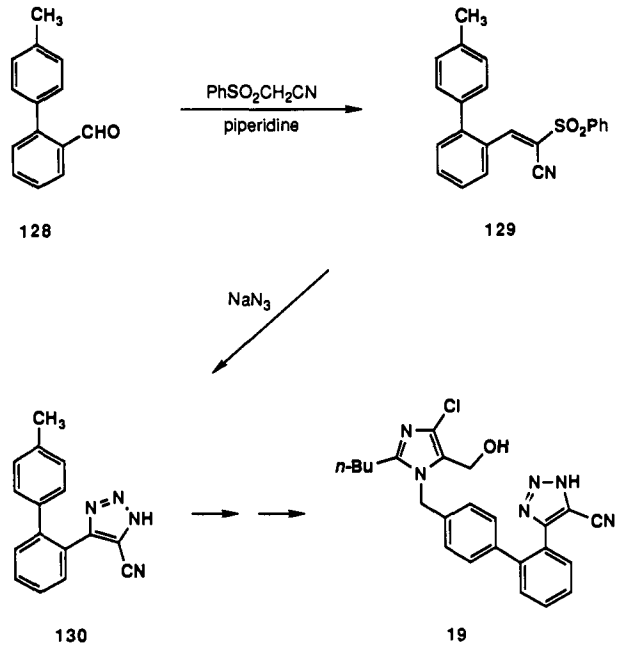
Several of the compounds in this paper represent analogues in which the carboxylic acid group or tetrazole ring on the biphenyl has been replaced with another acid isostere and these compounds can be divided into three categories. The first category, namely the amide derivatives, includes the hydroxamic acids (e.g. **8**),[35] the sulfonyl amide **10**,[36] the tetrazolyl amide **24**, and the acyl sulfonohydrazide **11**. These amides all were prepared by essentially the same chemistry in which the ester, active ester, or acid chloride of one of our biphenylcarboxylic acids was allowed to react with an appropriate amine derivative. The key steps in the preparation of each of these amides are shown in Scheme IX.

The trifluoromethanesulfonamides (**14** and **13**) were prepared as described in Scheme X. The nitrobiphenyl **120** was reduced to the aniline **121** with iron powder in acetic acid, and **121** was treated with trifluoromethanesulfonic anhydride to produce **14**. Hydrolysis of the methyl ether group of **14** then afforded the alcohol **13**.

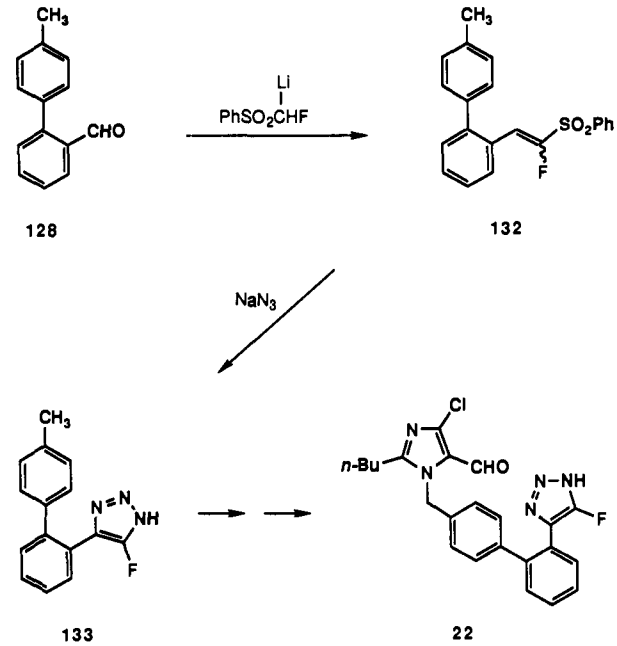
The last class of isosteres is represented by the acidic triazoles (**21**, **19**, and **22**). These triazoles were prepared from the biphenyl intermediates (**126**, **130**, and **133**). As shown in Scheme XI the 5-(trifluoromethyl)-1,2,4-triazole **126** was synthesized starting from the carboxylic acid **74**; this acid was converted, through its acid chloride, to the *N*-(cyanoethyl)amide **124**. The treatment of **124** with phosphorus pentachloride furnished an iminoyl chloride, which was allowed to react with hydrazine to provide the amidrazone **125**. The reaction of **125** with trifluoroacetic anhydride provided a triazole,[37] which was deprotected

(35) For the preparation of hydroxamic acids utilizing the Vilsmeier reagent, see: Nakonieczna, L.; et al. *Synthesis* **1985**, 929.
(36) For the preparation of sulfonyl amides, see: Brown, F. J.; Bernstein, P. R.; Yee, Y. K.; Matassa, V. G. Eur. Pat. Appl. 199543, 1986.

Scheme XII



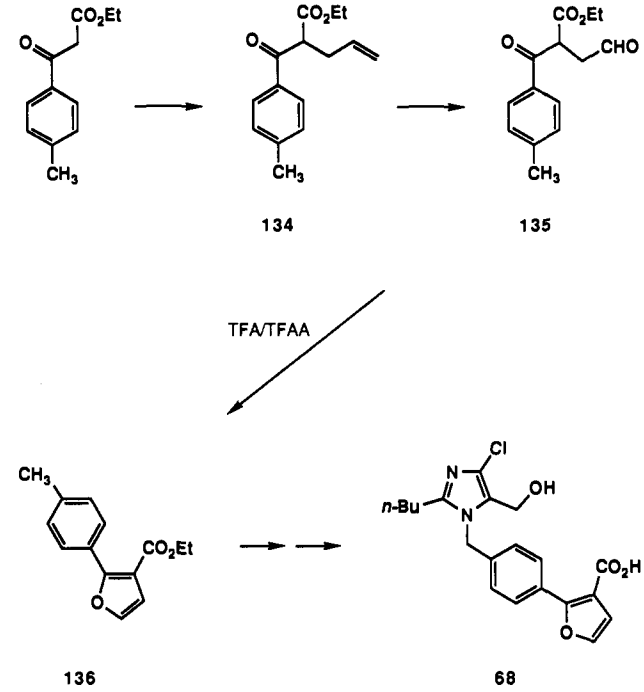
Scheme XIII



upon exposure to base to afford **126**. Tritylation, benzylic bromination, alkylation, and deprotection, as described for the tetrazole series, afforded **21**.

In Scheme XII is shown the synthetic route used to prepare the 5-cyano-1,2,3-triazole **130**. The condensation of the aldehyde **128** with benzenesulfonylacetonitrile furnished the acrylonitrile **129**, and the treatment of **129** with azide provided **130**.[38] The 5-fluoro-1,2,3-triazole **133** was prepared by employing chemistry analogous to that utilized for the synthesis of **130** (Scheme XIII). The requisite fluorovinyl sulfone **132** was produced by the addition of the lithium salt of fluoromethyl phenyl sulfone to **128**, followed by dehydration of the intermediate fluorohydrin.[39] The treatment of **132** with azide then produced **133**. To the best of our knowledge **133** represents the first preparation of the 5-fluoro-1,2,3-triazole ring system.

Scheme XIV



Finally, in Scheme XIV is described the preparation of the furan **68** in which the biphenyl group common to the compounds of this paper is replaced with a 2-phenylfuran moiety. This synthesis began with the alkylation of ethyl 3-(4-methylphenyl)-3-oxopropanoate[40] with allyl bromide to provide the olefin **134**. Oxidative cleavage of the olefin group with osmium tetroxide/sodium periodate furnished the aldehyde **135**, and the treatment of **135** with trifluoroacetic anhydride in the presence of catalytic trifluoroacetic acid provided the 4-(methylphenyl)furan **136**. The conversion of **136** to **68** was accomplished by employing the standard procedures described in Scheme I.

Conclusion

Through systematic modification of the linkage connecting the two phenyl rings in our AII receptor antagonists, we discovered that the biphenyl system can give rise to orally active compounds. The position of the acidic moiety on the biphenyl is very crucial. Only the ortho-substituted acids include compounds with good oral potency. Of all of the acidic isosteres investigated, the tetrazole-containing compounds had the greatest binding affinities and oral activities. Most likely, the tetrazole induces the correct biphenyl conformation. Having four heteroatoms that can support a negative charge, the tetrazole may have the necessary electronic distribution to better interact with a positive charge on the AII receptor.

The SAR around the imidazole ring demonstrates the need for an alkyl chain of 3–4 carbon atoms in length at the 2-position. The 4-position best tolerates a large, electronegative, lipophilic substituent. The 5-position generally prefers small H-bonding substituents such as alcohols, aldehydes, or carboxylic acids but will also tolerate a wide range of groups. With this information, we

(37) For the preparation of bis(perfluoroalkyl)-1,2,4-triazoles, see: (a) Brown, H. C.; Cheng, M. T. *J. Org. Chem.* **1962**, *27*, 3240. (b) Brown, H. C.; Pilipovich, D. *J. Am. Chem. Soc.* **1960**, *82*, 4700.

(38) Beck, G.; Gunther, D. *Chem. Ber.* **1973**, *106*, 2758.

(39) Inbasekaran, M.; Peet, N. P.; McCarthy, J. R.; LeTourneau, M. E. *J. Chem. Soc., Chem. Commun.* **1985**, 678.

(40) Wierenga, W.; Skulnick, H. I. *J. Org. Chem.* **1979**, *44*, 310.

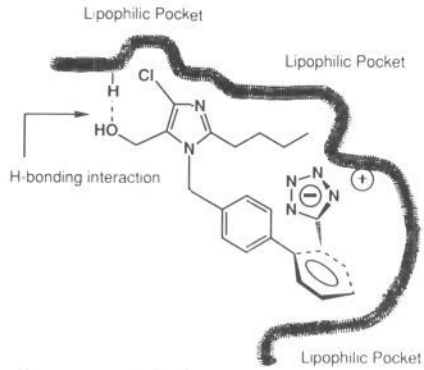


Figure 6. Summary of the key features of the *N*-(biphenylylmethyl)imidazole AII receptor antagonists and how they interact with a hypothetical model of the AII receptor.

can propose a hypothetical model for the AII receptor (Figure 6), as was attempted previously for the amide-linked series.[3a] As in the amide-linked series, the aromatic rings of the biphenyl moiety are nonplanar, thus placing the tetrazole anion in the right position to interact with a positive charge on the receptor. From the SAR developed for this series of antagonists, and from the SAR in the amide-linked series, we may conclude that there are three lipophilic pockets in the receptor as well as a hydrogen bonding moiety which interacts with the functionality at the imidazole 5-position.

It is anticipated that some of the compounds disclosed in this paper, in particular DuP 753, will eventually be useful for the treatment of hypertension. In addition, these compounds may become important pharmacological tools in the study of the AII receptor. We are currently working to further improve the potency of these compounds and to develop a model for how these nonpeptide antagonists mimic the hormone AII in their binding to the AII receptor.

Experimental Section

Physical Methods. IR spectra were obtained on a Perkin-Elmer 1710 Series FTIR or a Perkin-Elmer 1600 Series FTIR and were run as KBr pellets unless otherwise indicated. ^{1}H NMR spectra (200 MHz) were measured with an IBM/Bruker WP200SY spectrometer or a Varian Gemini 200 spectrometer; chemical shifts are expressed in ppm (δ) downfield from TMS as an internal standard. ^{19}F NMR spectra were measured with a Varian VXR500S spectrometer; chemical shifts are expressed in ppm (δ) upfield from fluorotrichloromethane as an internal standard. High-resolution mass spectra were determined 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., or Robertson Laboratory, Inc. Boiling points are uncorrected. Column chromatography was performed with E. Merck silica gel 60 (230–400 mesh).

Angiotensin II Receptor Binding Assay. 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.[41] and Gunther.[42]

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* 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 the filters were air-dried, the 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. Intraassay and interassay IC_{50} values for a given test compound may vary between 5–10% and 15–30%, respectively. For the potassium salt of compound **17** (DuP 753) the IC_{50} (nM) ±SEM is 24.5 ± 3 nM (n = 8).

Antihypertensive Effect in Conscious Renal Artery-Ligated Hypertensive Rats. Male Sprague–Dawley CD rats were anesthetized with hexobarbital (100 mg/kg, ip), and the left renal artery was completely ligated by means of a 4-0 silk suture, being careful not to damage the left kidney or left renal vein.[43] Six days after the ligation, the animals were anesthetized with hexobarbital (90 mg/kg, ip) and both the right jugular vein and carotid artery were cannulated. The catheters were passed subcutaneously to the dorsal side of the neck and exteriorized. After the animals had completely recovered from anesthesia (about 2.5 h after the surgery), the catheter was connected to a Gould pressure transducer (Gould Inc., Oxnard, CA) coupled to a polygraph (Grass Instrument Co., Quincy, MA) for monitoring arterial pressure. In a typical group of renal artery-ligated hypertensive rats the mean arterial pressure was 159 ± 4 mmHg (mean ±SEM, n = 6), whereas the mean arterial pressure of a group of normotensive rats was 100 ± 3 mmHg (n = 5).

To estimate the oral antihypertensive potency of the AII antagonists, groups of renal artery-ligated rats (n = 4–6 rats/dose) were dosed orally by gavage at different doses of the test compound; the range of doses tested was 1–100 mg/kg. The experiment was monitored for 3 h. The intravenous or oral ED_{30} of the test compound is the dose that decreased blood pressure by 30 mmHg and was calculated by linear regression using the mean maximal decreases in blood pressure determined at different doses (a minimum of three doses from the linear portion of the dose-response curve were used). As shown in Figure 2, blood pressure in the vehicle-treated group of renal artery-ligated rats (n = 6) was very stable for the experimental period. It varied from 169 ± 7 mmHg at the start of the experiment to 176 ± 6 mmHg, suggesting minimum blood pressure fluctuation. The data in Figure 2 is also indicative of the variation (SEM) in each of the individual blood pressure values measured throughout this study. The variation averages approximately 10–15%.

Methyl 4′-Methylbiphenyl-2-carboxylate (69). To a stirred solution of methyl 2-iodobenzoate (45.8 g, 173 mmol, 1.0 equiv) and 4-iodotoluene (38.2 g, 175 mmol, 1.0 equiv) at 180–190 °C was added copper powder (55.0 g, 865 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 for an additional hour. The mixture was allowed to cool to room temperature and was filtered, employing benzene as solvent; the resulting filtrate was concentrated under vacuum to provide the crude product. Column chromatography (elution: 50–100% benzene/hexane) followed by Kugelrohr distillation

(41) Glossmann, H.; Baukal, A.; Catt, K. A. *J. Biol. Chem.* **1974**, *240*, 825.

(42) Gunther, S.; Gimborne, M. A., Jr.; Alexander, R. W. *Circ. Res.* **1980**, *47*, 278.

(43) Cangiano, J. L.; Rodriquez-Sargent, C.; Martinez-Maldonado, M. *J. Pharmacol. Exp. Ther.* **1979**, *208*, 310.

(100–140 °C (0.025 Torr) furnished 4.50 g (11%) of **69** as a colorless oil: NMR ($CDCl_3$) δ 7.78 (d, 1 H, J = 8 Hz), 7.46 (d, 1 H, J = 8 Hz), 7.35 (t, 2 H, J = 8 Hz), 7.19 (s, 4 H), 3.64 (s, 3 H), 2.37 (s, 3 H); IR 1729 cm^{-1}.

Alternatively, the title compound was prepared by the following procedure: To a solution of 100 mL of methanol at 0 °C was added dropwise acetyl chloride (5.0 mL, 70 mmol), and the resulting solution was stirred at 0 °C for 0.25 h. To this solution was added 4′-methylbiphenyl-2-carboxylic acid (**74**, 5.00 g, 23.6 mmol), and the reaction mixture was refluxed for 4 h. After the mixture was cooled to room temperature, the solvent was removed under vacuum. The crude product was distilled as described above to afford 5.00 g (94%) of **69**.

2-Nitro-4′-methylbiphenyl (70). The title compound was prepared in 51% yield from 1-bromo-2-nitrobenzene by the procedure described for the preparation of **69**: NMR ($CDCl_3$) δ 7.80 (dd, 1 H, J = 8, 2.5 Hz), 7.57 (td, 1 H, J = 8, 2.5 Hz), 7.41 (m, 2 H), 7.19 (s, 4 H), 2.37 (s, 3 H).

2-Methoxybenzoyl Chloride (71). A solution of 2-methoxybenzoic acid (30 g, 200 mmol, 1.0 equiv) in thionyl chloride (50 mL, 690 mmol, 3.5 equiv) was stirred at 20 °C for 18 h, and then the excess thionyl chloride was removed under vacuum. The crude product was distilled to provide 32 g (95%) of **71** (bp 81–83 °C (0.7 Torr)) as a colorless liquid: NMR ($CDCl_3$) δ 8.06 (dd, 1 H, J = 8, 2 Hz), 7.57 (m, 1 H), 6.99 (m, 2 H), 3.84 (s, 3 H).

4,4-Dimethyl-2-(2-methoxyphenyl)oxazoline (72). To a solution of 2-amino-2-methyl-1-propanol (20.0 g, 224 mmol, 2.25 equiv) in 100 mL of methylene chloride at 0 °C was added dropwise a solution of **71** (17.0 g, 100 mmol, 1.00 equiv) in 50 mL of methylene chloride. Following the addition, the mixture was allowed to warm and then was stirred at 20 °C for 2 h. The solvent was removed under vacuum, and the residue was diluted with water. The resulting solids were filtered, washed with water, and dried to furnish 20.5 g of the crude amide as a colorless solid.

The amide (20.5 g, 92 mmol, 1.0 equiv) was dissolved in thionyl chloride (22 mL, 300 mL, 3.25 equiv), and the resulting solution was stirred at 25 °C for 1 h. At this point the reaction mixture was poured into diethyl ether, and the resulting solids were filtered, washed with diethyl ether, dried, and then dissolved in water. The solution was adjusted to pH 10 by employing 1.0 N aqueous sodium hydroxide solution and then extracted with diethyl ether. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, and concentrated under vacuum to afford 18.0 g (88% overall from **71**) of **72**[21] as a colorless solid: mp 70–72 °C; NMR ($CDCl_3$) δ 7.72 (dd, 1 H, J = 7.5, 2 Hz), 7.38 (m, 1 H), 6.95 (m, 2 H), 4.07 (s, 2 H), 3.86 (s, 3 H), 1.38 (s, 6 H).

4,4-Dimethyl-2-(4′-methylbiphenyl-2-yl)oxazoline (73). To a suspension of magnesium metal (2.50 g, 103 mmol, 2.10 equiv) in 200 mL of anhydrous tetrahydrofuran at 20 °C was added dropwise 4-bromotoluene (13.0 mL, 106 mmol, 2.20 equiv). Following the addition the mixture was stirred at 20 °C until the magnesium had entirely dissolved (1 h). The resulting reagent was added to a solution of **72** (10.0 g, 48.7 mmol, 1.00 equiv) in 100 mL of tetrahydrofuran at 20 °C, and the reaction mixture was stirred at 20 °C for 2 h. At this point the mixture was poured into saturated aqueous ammonium chloride solution, and the resulting emulsion was extracted with ethyl acetate. The combined organic phases were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to provide the crude product. Column chromatography on silica gel (elution: 35% ethyl acetate/hexane) provided 11.8 g (91%) of **73** as a colorless liquid: NMR ($CDCl_3$) δ 7.70 (dd, 1 H, J = 7.5, 1.5 Hz), 7.50–7.00 (m, 7 H), 3.80 (s, 2 H), 2.38 (s, 3 H), 1.30 (s, 6 H).

4′-Methylbiphenyl-2-carboxylic Acid (74). A solution of **73** (10.0 g, 38 mmol) in 200 mL of 4.5 N aqueous hydrochloric acid was refluxed for 12 h. The reaction mixture then was cooled to room temperature and extracted with diethyl ether. The combined diethyl ether extracts were concentrated to furnish 7.0 g (88%) of **74** as a colorless solid: mp 140–142 °C.

***tert*-Butyl 4′-Methylbiphenyl-2-carboxylate (75).** To a solution of **74** (42.4 g, 200 mmol, 1.0 equiv) in 200 mL of methylene chloride at 0 °C was added dropwise oxalyl chloride (20 mL, 230 mmol, 1.2 equiv). The reaction mixture was allowed to warm and then was stirred at 25 °C for 3 h. The solvent was removed under vacuum, and the residue was dissolved in benzene. The benzene then was removed under vacuum to provide 46.1 g of the crude acid chloride.

To a solution of the acid chloride (46.1 g, 200 mmol, 1.0 equiv) in 600 mL of anhydrous tetrahydrofuran at 0 °C was added potassium *tert*-butoxide (26.0 g, 230 mmol, 1.2 equiv) in portions such that the reaction temperature did not exceed 15–20 °C. The resulting mixture then was stirred at 25 °C for 1 h. Next the reaction mixture was poured into water, and the emulsion was extracted with diethyl ether. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Distillation afforded 49.5 g (92% overall from **74**) of **75** (bp 115–120 °C (0.05 Torr)): NMR ($CDCl_3$) δ 7.73 (dd, 1 H, J = 8, 3 Hz), 7.46–7.27 (m, 3 H), 7.18 (s, 4 H), 2.40 (s, 3 H), 1.30 (s, 9 H).

2-Cyano-4′-methylbiphenyl (76). To a solution of **73** (243.2 g, 917 mmol, 1.0 equiv) in 975 mL of pyridine at 10 °C was added dropwise phosphorus oxychloride (172 mL, 1840 mmol, 2.0 equiv) such that the reaction temperature did not exceed 15 °C. The reaction mixture then was stirred at 100 °C for 3 h. After being cooled to room temperature the mixture was quenched by addition of water, and the resulting emulsion was extracted with ethyl acetate. The combined organic phases were washed with water, 10% aqueous cupric sulfate solution, and brine. The solution then was dried over anhydrous magnesium sulfate, filtered, concentrated under vacuum, and recrystallized from heptane to furnish 169.6 g (96%) of **76** as a colorless solid: mp 48.0–49.5 °C; NMR (DMSO-d_6) δ 7.95 (d, 1 H, J = 8 Hz), 7.78 (t, 1 H, J = 8 Hz), 7.69–7.32 (m, 6 H), 2.39 (s, 3 H).

3-Cyano-4′-methylbiphenyl (77). To a dry 3-neck 1-L flask were added magnesium turnings (12.88 g, 0.53 mol, 1.86 equiv) and 120 mL of tetrahydrofuran. A solution of 4-bromotoluene (40.08 mL, 0.354 mol, 1.24 equiv) was then added at a rate such as to maintain the temperature at 50 °C. Once the reaction had finished, the solution of the Grignard reagent was allowed to cool to ambient temperature.

To a separate dry 3-neck 1-L flask was added freshly fused zinc chloride (35.50 g, 0.284 mol, 1 equiv). With stirring, the solution of Grignard reagent was added via cannula to the zinc chloride, while the temperature was maintained at 18 °C.

DIBAL (1.0 M in tetrahydrofuran, 13.0 mL, 13.0 mmol, 0.046 equiv) was added to a cold slurry (0 °C) of bis(triphenylphosphine)nickel(II) chloride (4.21 g, 6.4 mmol, 0.023 equiv) in 20 mL of tetrahydrofuran. The black mixture was allowed to warm to 20 °C when 3-bromobenzonitrile (3.18 g, 19.0 mmol, 0.067 equiv) was added, and the mixture was stirred for another 0.25 h at 20 °C. This mixture was then added to the cooled solution (6 °C) of toluylzinc chloride followed by a 3-bromobenzonitrile solution (44.55 g, 0.266 mol, 0.94 equiv) in 100 mL of tetrahydrofuran. The entire contents were stirred 16 h at 25 °C.

The mixture was diluted with ethyl acetate (400 mL) and washed with water (2 × 400 mL) and brine (1 × 400 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to provide 44.35 g of a white crystalline solid. Recrystallization from ethyl acetate afforded **77** (66%) in three crops: 22.30 g, mp 60.5–65.5 °C; 7.21 g, mp 59.5–63.0 °C; 6.44 g, mp 51.0–61.5 °C; NMR ($CDCl_3$) δ 7.85 (s, 1 H), 7.79 (dd, 1 H, J = 2, 9 Hz), 7.66–7.43 (m, 4 H), 7.28 (d, 2 H, J = 9 Hz), 2.43 (s, 3 H); IR (Nujol) 2230 cm^{-1}. Anal. ($C_{14}H_{11}N$) C, H, N.

***N*-(Triphenylmethyl)-5-(4′-methylbiphenyl-2-yl)tetrazole (78).** A solution of **76** (9.00 g, 46.6 mmol, 1.0 equiv), tributyltin chloride (16.4 g, 50.4 mmol, 1.1 equiv), sodium azide (3.00 g, 46.2 mmol, 1.0 equiv), and 35 mL of toluene was refluxed for 70 h. The mixture was diluted with an additional 35 mL of toluene and allowed to cool to 20 °C. To the reaction mixture was added 10 N aqueous sodium hydroxide solution (5.5 mL, 55 mmol, 1.2 equiv) and triphenylmethyl chloride (13.5 g, 48.4 mmol, 1.05 equiv), and the resulting mixture was stirred at 20 °C for 3 h. To the reaction mixture was added 35 mL of distilled water and 70 mL of heptane, and the resulting slurry was stirred at 0 °C for 1.5 h. The slurry was filtered, and the solids were washed with water and 1:1 heptane/toluene. The crude product was dissolved in methylene chloride, and the solution was washed with 0.4 N sodium hydroxide solution, water, and brine. The organic solution was dried over anhydrous sodium sulfate and then concentrated under vacuum to provide 15.1 g (68%) of **78**: mp 163–166 °C; NMR

($CDCl_3$) δ 8.10–6.80 (m, 23 H), 2.28 (s, 3 H).

***N*-(Triphenylmethyl)-5-[4′-(bromomethyl)biphenyl-2-yl]tetrazole (79).** A solution of **78** (31.0 g, 65 mmol, 1.00 equiv), *N*-bromosuccinimide (11.50 g, 65 mmol, 1.00 equiv), and dibenzoyl peroxide (1.10 g, 4.5 mmol, 0.07 equiv) in 390 mL of carbon tetrachloride was refluxed for 3 h, cooled to 40 °C, and then filtered. The filtrate was concentrated under vacuum to afford the crude product. The crude product is routinely used without further purification; however, trituration of the crude product with diisopropyl ether furnished 33.10 g (92%) of **79** as an off-white solid: mp 135–138 °C; NMR ($CDCl_3$) δ 8.20–6.70 (m, 23 H), 4.33 (s, 2 H).

Methyl 4′-(Bromomethyl)biphenyl-2-carboxylate (80). The title compound was prepared from **69** using the procedure described in the preparation of **79**: NMR ($CDCl_3$) δ 7.82 (d, 1 H, *J* = 8 Hz), 7.59–7.23 (m, 7 H), 4.52 (s, 2 H), 3.62 (s, 3 H).

4′-(Bromomethyl)-2-nitrobiphenyl (81). The title compound was prepared from **70** using the procedure described in the preparation of **79**: NMR ($CDCl_3$) δ 7.86 (dd, 1 H, *J* = 8, 2 Hz), 7.62 (td, 1 H, *J* = 8, 2 Hz), 7.53–7.21 (m, 6 H), 4.52 (s, 2 H).

***tert*-Butyl 4′-(Bromomethyl)biphenyl-2-carboxylate (82).** The title compound was prepared from **75** using the procedure described in the preparation of **79**: NMR ($CDCl_3$) δ 7.79 (d, 1 H, *J* = 8 Hz), 7.56–7.24 (m, 7 H), 4.51 (s, 2 H), 1.25 (s, 9 H).

4′-(Bromomethyl)-2-cyanobiphenyl (83). The title compound was prepared from **76** using the procedure described in the preparation of **79**: mp 114.5–120.0 °C; NMR ($CDCl_3$) δ 7.82–7.37 (m, 8 H), 4.50 (s, 2 H).

2-Butyl-1-[(2′-carbomethoxybiphenyl-4-yl)methyl]-4-chloro-5-(hydroxymethyl)imidazole (84). To a suspension of sodium methoxide (6.50 g, 120 mmol, 1.2 equiv) in 90 mL of dimethylformamide at 25 °C was added a solution of 2-butyl-4-(5)-chloro-5(4)-(hydroxymethyl)imidazole[19] (22.69 g, 120 mmol, 1.2 equiv) in 70 mL of dimethylformamide. The resulting mixture was stirred at 25 °C for 0.25 h, and then a solution of crude **80** (33.4 g, 100 mmol, 1.0 equiv) in 70 mL of dimethylformamide was added dropwise. The reaction mixture then was stirred at 40 °C for 4 h. After the mixture was cooled to room temperature 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 under vacuum. Column chromatography (elution: 5–25% ethyl acetate/benzene) furnished 13.80 g (34%) of **84**, the regioisomer of higher R_f:[20] mp 104–105 °C; NMR ($CDCl_3$) δ 7.84 (d, 1 H, *J* = 7.5 Hz), 7.58–7.26 (m, 5 H), 7.03 (d, 2 H, *J* = 8 Hz), 5.26 (s, 2 H), 4.52 (s, 2 H), 3.64 (s, 3 H), 2.37 (br s, 1 H), 2.60 (t, 2 H, *J* = 7 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-[(2′-carboxybiphenyl-4-yl)methyl]-4-chloro-5-(hydroxymethyl)imidazole (2). A solution of **84** (12.5 g, 30 mmol) in 400 mL of ethanol and 200 mL of 10% aqueous sodium hydroxide solution was refluxed for 14 h. After cooling to room temperature, the reaction mixture was filtered, and the solvents were removed under vacuum. The residue was dissolved in water, and the solution was adjusted to pH 3.5 with hydrochloric acid. The precipitated solids were recovered by filtration and recrystallized from ethyl acetate to provide 9.80 g (81%) of **2**: mp 171–172 °C; NMR (DMSO-d_6) δ 7.74 (d, 1 H, *J* = 8 Hz), 7.58 (t, 1 H, *J* = 8 Hz), 7.47 (t, 1 H, *J* = 8 Hz), 7.34 (m, 3 H), 7.12 (d, 2 H, *J* = 7.5 Hz), 5.30 (br s, 3 H), 4.37 (s, 2 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 1708 cm^{-1}. Anal. ($C_{22}H_{23}ClN_2O_3$) C, H, N, Cl.

2-Butyl-4-chloro-1-[(2′-cyanobiphenyl-4-yl)methyl]-5-(hydroxymethyl)imidazole (85). The title compound was prepared from 2-butyl-4(5)-chloro-5(4)-(hydroxymethyl)-imidazole[19] and **83** using the procedure described in the preparation of **84**: mp 153.5–155.5 °C; NMR ($CDCl_3$) δ 7.82–7.43 (m, 6 H), 7.12 (d, 2 H, *J* = 8 Hz), 5.32 (s, 2 H), 4.52 (s, 2 H), 2.62 (t, 2 H, *J* = 7 Hz), 1.70 (quint, 2 H, *J* = 7 Hz), 1.39 (sext, 2 H, *J* = 7 Hz), 0.90 (t, 3 H, *J* = 7 Hz). Anal. ($C_{22}H_{22}ClN_3O$) C, H, N.

2-Butyl-4-chloro-5-(hydroxymethyl)-1-[[2′-[(trimethylstannyl)tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole (86). A solution of **85** (7.66 g, 20 mmol, 1.0 equiv) and trimethyltin azide[24] (7.66 g, 39 mmol, 1.9 equiv) in 79 mL of xylene was stirred at 115 °C for 41 h. The resulting slurry was cooled to 80 °C and filtered, employing hot toluene. The solids were dried under vacuum to provide 10.7 g (94%) of **86**: mp 211–214 °C.

2-Butyl-4-chloro-5-(hydroxymethyl)-1-[[2′-[(triphenylmethyl)tetrazol-5-yl]biphenyl-4-yl]methyl]imidazole (87). To a suspension of **86** (10.5 g, 18 mmol, 1.0 equiv) in 50 mL of methylene chloride and 10 mL of tetrahydrofuran at 25 °C was added 10 N aqueous sodium hydroxide (1.9 mL, 19 mmol, 1.05 equiv), and the resulting mixture was stirred at 25 °C for 0.1 h. Triphenylmethyl chloride (5.30 g, 19 mmol, 1.05 equiv) was added, and the reaction mixture was stirred at 25 °C for 3 h. The mixture was diluted with water and extracted with methylene chloride. The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Recrystallization from toluene/hexane provided 9.60 g (80%) of **87**: mp 167–169 °C; NMR (DMSO-d_6) δ 7.80 (d, 1 H, *J* = 8 Hz), 7.65 (t, 1 H, *J* = 8 Hz), 7.55 (t, 1 H, *J* = 8 Hz), 7.50–7.25 (m, 10 H), 7.08 (d, 2 H, *J* = 8 Hz), 6.89 (m, 8 H), 5.25 (t, 1 H, *J* = 7 Hz), 5.20 (s, 2 H), 4.23 (d, 2 H, *J* = 7 Hz), 2.38 (t, 2 H, *J* = 7 Hz), 1.43 (quint, 2 H, *J* = 7 Hz), 1.16 (sext, 2 H, *J* = 7 Hz), 0.75 (t, 3 H, *J* = 7 Hz).

Alternatively, the title compound was prepared by the following procedure: To a mixture of **88** (3.57 g, 21 mmol, 1 equiv), tetrabutylphosphonium bromide (0.71 g, 2.1 mmol, 0.1 equiv), 10.00 N aqueous sodium hydroxide (4.2 mL, 42 mmol, 2 equiv), water (15 mL), and methylene chloride (70 mL) was added a solution of **79** (11.65 g, 21 mmol, 1 equiv) dissolved in methylene chloride (100 mL). The reaction mixture was stirred at 25 °C for 24 h. Sodium borohydride (0.79 g, 21 mmol, 1 equiv) was added, and the mixture was stirred another 24 h. Water (200 mL) was added, and the layers were separated. The organic layer was washed with water (2 × 200 mL), dried over anhydrous magnesium sulfate, and filtered, and the solvent was removed under vacuum to furnish 13.3 g of a yellow glass. The glass was crystallized from nitromethane to provide 7.52 g (54%) of **87** as an off-white powder.

2-Butyl-4-chloro-5-(hydroxymethyl)-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole (17). A solution of **87** (9.20 g, 13.8 mmol), 100 mL of 10% hydrochloric acid, and 200 mL of tetrahydrofuran was stirred at 25 °C for 4 h. To the solution was added excess 10% aqueous sodium hydroxide (~100 mL), and the solvents were removed under vacuum. The resulting residue was dissolved in water, and the mixture was filtered to remove the triphenylmethanol. The filtrate was adjusted to pH 3 employing hydrochloric acid, and the precipitate was recovered by filtration and dried. Recrystallization afforded 5.18 g (89%) of **17**: mp 183.5–184.5 °C; NMR (DMSO-d_6) δ 7.75–7.48 (m, 4 H), 7.07 (d, 2 H, *J* = 9 Hz), 7.04 (d, 2 H, *J* = 9 Hz), 5.24 (s, 2 H), 4.34 (s, 2 H), 2.48 (t, 2 H, *J* = 7 Hz), 1.48 (quint, 2 H, *J* = 7 Hz), 1.27 (sext, 2 H, *J* = 7 Hz), 0.81 (t, 3 H, *J* = 7 Hz). Anal. ($C_{22}H_{23}ClN_6O$) C, H, Cl.

2-Butyl-1-[(2′-carboxybiphenyl-4-yl)methyl]-4-chloroimidazole-5-carboxaldehyde (66). A mixture of **2** (1.46 g, 3.66 mmol), 7.30 g of activated manganese dioxide, and 40 mL of tetrahydrofuran was stirred at 25 °C for 120 h. The mixture was filtered through Celite, and the filtrate was concentrated under vacuum. Column chromatography (elution: 2–10% methanol/chloroform) followed by recrystallization from ethyl acetate provided 0.71 g (49%) of **66**: mp 154–158 °C dec; NMR (DMSO-d_6) δ 12.85 (br s, 1 H), 9.77 (s, 1 H), 7.77 (d, 1 H, *J* = 8 Hz), 7.62 (t, 1 H, *J* = 8 Hz), 7.50 (t, 1 H, *J* = 8 Hz), 7.40 (d, 1 H, *J* = 8 Hz), 7.26 (A_2B_2, 4 H, *J* = 8 Hz), 5.67 (s, 2 H), 2.70 (t, 2 H, *J* = 7 Hz), 1.56 (quint, 2 H, *J* = 7 Hz), 1.28 (sext, 2 H, *J* = 7 Hz), 0.83 (t, 3 H, *J* = 7 Hz): IR 1669, 1713 cm^{-1}. Anal. ($C_{22}H_{21}ClN_2O_3$) C, H, Cl.

2-Butyl-4(5)-chloroimidazole-5(4)-carboxaldehyde (88). To a solution of 2-butyl-4(5)-chloro-5(4)-(hydroxymethyl)imidazole[19] (50 g, 265 mmol, 1 equiv) in 150 mL of glacial acetic acid at 25 °C was added 1.0 N ceric ammonium nitrate/H_2O (595 mL, 595 mmol, 2.25 equiv) dropwise to maintain the temperature at 25–30 °C. The resulting solution was stirred at 25 °C for 3 h. The reaction mixture was cooled to 0 °C, and 50% sodium hydroxide solution (210 mL) was added; a precipitate resulted. The solution was adjusted to pH 6, and the solids were recovered by filtration and dried to provide 38.1 g (77%) of **88**: mp 92.5–93.5 °C; NMR ($CDCl_3$) δ 11.83 (br s, 1 H), 9.64 (s, 1 H), 2.85 (t, 2 H, *J* = 7 Hz), 1.78 (quint, 2 H, *J* = 7 Hz), 1.38 (sext, 2 H, *J* = 7 Hz), 0.93 (t, 3 H, *J* = 7 Hz).

2-Butyl-4-chloro-1-[[2'-[(triphenylmethyl)tetrazol-5-yl]-biphenyl-4-yl]methyl]imidazole-5-carboxaldehyde (89). A solution of **88** (3.27 g, 17.5 mmol, 1.0 equiv), **79** (10.73 g, 19.3 mmol, 1.1 equiv), potassium carbonate (4.83 g, 35 mmol, 2.0 equiv), and 100 mL of dimethylformamide was stirred at 25 °C for 24 h. The reaction mixture was filtered, and the filtrate was concentrated under vacuum. The residue was diluted with water, and the resulting mixture then was extracted with ethyl acetate. The combined organic phases were washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. Column chromatography (elution: ethyl acetate/toluene) afforded 5.69 g (49%) of **89**: NMR ($CDCl_3$) δ 9.73 (s, 1 H), 7.92 (m, 1 H), 7.51–6.81 (m, 22 H), 5.45 (s, 2 H), 2.49 (t, 2 H, J = 7 Hz), 1.64 (quint, 2 H, J = 7 Hz), 1.28 (sext, 2 H, J = 7 Hz), 0.86 (t, 3 H, J = 7 Hz).

2-Butyl-4-chloro-1-[[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]-methyl]imidazole-5-carboxaldehyde (25). The title compound was prepared from **89** by the procedure described for the preparation of **17**: mp 154–155 °C; NMR (DMSO-d_6) δ 9.68 (s, 1 H), 7.70–7.50 (m, 4 H), 7.05 (A_2B_2, 4 H, J = 8.5 Hz), 5.58 (s, 2 H), 2.63 (t, 2 H, J = 7 Hz), 1.51 (quint, 2 H, J = 7 Hz), 1.26 (sext, 2 H, J = 7 Hz), 0.81 (t, 3 H, J = 7 Hz). Anal. ($C_{22}H_{21}ClN_6O$) C, H, N.

Methyl 2-Butyl-1-[(2'-carboxybiphenyl-4-yl)methyl]-4-chloroimidazole-5-carboxylate (65). To a mixture of **66** (1.45 g, 3.65 mmol, 1.0 equiv) and sodium cyanide (0.91 g, 18.5 mmol, 5.0 equiv) in 20 mL of methanol at 25 °C was added dropwise glacial acetic acid (0.32 mL, 5.60 mmol, 1.5 equiv) followed by 7.25 g of manganese dioxide. The resulting mixture was stirred at 25 °C for 40 h. The reaction mixture was filtered through Celite, and the filtrate was diluted with water. The aqueous solution was adjusted to pH 3 by employing hydrochloric acid and then extracted with methylene chloride. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was recrystallized from diethyl ether to afford 0.90 g (58%) of **65**: mp 154–155 °C; NMR (DMSO-d_6) δ 12.75 (br s, 1 H), 7.73 (d, 1 H, J = 8 Hz), 7.58 (t, 1 H, J = 8 Hz), 7.46 (t, 1 H, J = 8 Hz), 7.34 (m, 3 H), 7.07 (d, 2 H, J = 8.5 Hz), 5.63 (s, 2 H), 3.78 (s, 3 H), 2.67 (t, 2 H, J = 7 Hz), 1.56 (quint, 2 H, J = 7 Hz), 1.29 (sext, 2 H, J = 7 Hz), 0.83 (t, 3 H, J = 7 Hz); IR 1713 cm^{-1}. Anal. ($C_{23}H_{23}ClN_2O_4$) C, H, N, Cl.

2-Butyl-1-[(2'-carboxybiphenyl-4-yl)methyl]-4-chloroimidazole-5-carboxamide (64). Anhydrous ammonia was bubbled into 40 mL of 2-propanol until the solvent was saturated. To this solution at 25 °C was added powdered sodium cyanide (0.49 g, 10 mmol, 5 equiv), followed by **66** (0.80 g, 2 mmol, 1 equiv), followed finally by 3.48 g of manganese dioxide. This mixture was stirred at 25 °C for 65 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated under vacuum. The residue was dissolved in water. The solution was adjusted to pH 3 with hydrochloric acid and then was extracted with methylene chloride. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography (elution: 0–10% 2-propanol/chloroform) provided 0.22 g (26%) of **64**: mp 200–202 °C; NMR (DMSO-d_6) δ 12.74 (br s, 1 H), 7.71 (d, 2 H, J = 8 Hz), 7.60–7.30 (m, 6 H), 7.09 (d, 2 H, J = 8.5 Hz), 5.57 (s, 2 H), 2.59 (t, 2 H, J = 7 Hz), 1.51 (quint, 2 H, J = 7 Hz), 1.26 (sext, 2 H, J = 7 Hz), 0.80 (t, 3 H, J = 7 Hz); IR 1668, 1703 cm^{-1}. Anal. ($C_{22}H_{22}ClN_3O_3 \cdot 0.5H_2O$) C, H, N, Cl.

2-Butyl-1-[(2'-carboxybiphenyl-4-yl)methyl]-4-chloroimidazole-5-carboxylic Acid (63). A solution of **65** (0.47 g, 1.1 mmol) in 80 mL of 5% aqueous sodium hydroxide was stirred at 25 °C for 18 h. The solution was adjusted to pH 3 by employing hydrochloric acid, and the resulting precipitate was recovered by filtration and dried to afford 0.28 g (62%) of **63**: mp 185–189 °C; NMR (DMSO-d_6) δ 12.97 (br s, 2 H), 7.68 (d, 1 H, J = 8 Hz), 7.53 (t, 1 H, J = 8 Hz), 7.41 (t, 1 H, J = 8 Hz), 7.34 (d, 1 H, J = 8 Hz), 7.28 (d, 2 H, J = 8.5 Hz), 7.02 (d, 2 H, J = 8.5 Hz), 5.61 (s, 2 H), 2.60 (t, 2 H, J = 7 Hz), 1.53 (quint, 2 H, J = 7 Hz), 1.27 (sext, 2 H, J = 7 Hz), 0.81 (t, 3 H, J = 7 Hz); IR 1698 cm^{-1}. Anal. ($C_{22}H_{21}ClN_2O_4$) C, H, N, Cl.

5-(Acetoxymethyl)-2-butyl-1-[(2'-carboxybiphenyl-4-yl)-methyl]-4-chloroimidazole (57). A solution of **2** (0.68 g, 1.7 mmol, 1.0 equiv), 4-(dimethylamino)pyridine (0.034 g, 0.28 mmol, 0.16 equiv), acetic anhydride (0.68 mL, 6.8 mmol, 4 equiv), and triethylamine (0.95 mL, 6.8 mmol, 4 equiv) in 50 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 then was acidified to pH 3 with hydrochloric acid and was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography (elution: 0–2% 2-propanol/chloroform) furnished 0.67 g (89%) of **57**: mp 157–159 °C; NMR (DMSO-d_6) δ 12.73 (br s, 1 H), 7.71 (d, 1 H, J = 7.5 Hz), 7.56 (t, 1 H, J = 7.5 Hz), 7.43 (t, 1 H, J = 7.5 Hz), 7.32 (m, 3 H), 7.02 (d, 2 H, J = 8 Hz), 5.29 (s, 2 H), 5.00 (s, 2 H), 2.59 (t, 2 H, J = 7 Hz), 1.76 (s, 3 H), 1.54 (quint, 2 H, J = 7 Hz), 1.28 (sext, 2 H, J = 7 Hz), 0.83 (t, 3 H, J = 7 Hz); IR 1712, 1739 cm^{-1}. Anal. ($C_{24}H_{25}ClN_2O_4$) C, H, N, Cl.

2-Butyl-1-[(2'-carbomethoxybiphenyl-4-yl)methyl]-4-chloro-5-(chloromethyl)imidazole Hydrochloride (90). A solution of **84** (10.00 g, 0.0242 mmol, 1 equiv), thionyl chloride (8.84 mL, 0.121 mmol, 5 equiv), and 100 mL of chloroform was stirred at 25 °C for 4 h. The solvent and excess thionyl chloride were removed under vacuum. Residual thionyl chloride was eliminated by dissolving the residue in toluene and then removing the toluene under vacuum. A solid was obtained that was slurried in toluene and filtered. The solid was further slurried in ether, filtered, and dried under high vacuum to yield 10.95 g (97 %) of **90** as a white solid: mp 160.0–162.5 °C; NMR ($CDCl_3$) δ 7.90 (d, 1 H, J = 7 Hz), 7.56 (t, 1 H, J = 7 Hz), 7.45 (t, 1 H, J = 7 Hz), 7.43–7.26 (m, 3 H), 7.12 (d, 2 H, J = 8 Hz), 5.47 (s, 2 H), 4.48 (s, 2 H), 3.70 (s, 3 H), 3.14 (t, 2 H, J = 7 Hz), 1.80 (quint, 2 H, J = 7 Hz), 1.44 (sext, 2 H, J = 7 Hz), 0.92 (t, 3 H, J = 7 Hz). Anal. ($C_{23}H_{24}Cl_2N_2O_2 \cdot HCl$) C, H, N.

2-Butyl-1-[(2'-carbomethoxybiphenyl-4-yl)methyl]-4-chloro-5-(methoxymethyl)imidazole (91). Sodium metal (0.54 g, 23.3 mmol, 2.2 equiv) was allowed to dissolve in 100 mL of methanol. To this solution at 0 °C was added **90** (4.97 g, 10.6 mmol, 1.0 equiv). The contents were allowed to warm to 25 °C and stirred for 18 h. The solvent was removed under vacuum, and water was added. The solution was adjusted to pH 5 with concentrated hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layers were collected, dried over anhydrous magnesium sulfate, and filtered, and the solvent was removed under vacuum to provide 4.77 g of **91** as an orange oil, which was used without further purification in the subsequent step: NMR ($CDCl_3$) δ 7.82 (d, 1 H, J = 7 Hz), 7.50 (t, 1 H, J = 7 Hz), 7.38 (t, 1 H, J = 7 Hz), 7.30 (d, 1 H, J = 7 Hz), 7.26 (d, 2 H, J = 10 Hz), 7.00 (d, 2 H, J = 10 Hz), 5.14 (s, 2 H), 4.32 (s, 2 H), 3.63 (s, 3 H), 3.28 (s, 3 H), 2.60 (t, 2 H, J = 7 Hz), 1.70 (quint, 2 H, J = 7 Hz), 1.36 (sext, 2 H, J = 7 Hz), 0.89 (t, 3 H, J = 7 Hz).

2-Butyl-1-[(2'-carboxybiphenyl-4-yl)methyl]-4-chloro-5-(methoxymethyl)imidazole (5). A solution of **91** (4.70 g, 11.0 mmol, 1 equiv), 0.5 N potassium hydroxide in methanol (33.03 mL, 16.5 mmol, 1.5 equiv), and 3 mL of water was refluxed for 6 h. An additional 10.0 mL of 0.5 N potassium hydroxide in methanol was added, and the reaction mixture was refluxed for 16 h. The solvent was removed under vacuum, and the residue was dissolved in water. The solution was acidified to pH 4 with concentrated hydrochloric acid. The resultant solids were filtered and dried under high vacuum to yield 3.89 g (90% overall from **90**) of **5** as a white solid: mp 166.5–169.0 °C; NMR (DMSO-d_6) δ 12.75 (m, 1 H), 7.81 (d, 1 H, J = 7 Hz), 7.55 (t, 1 H, J = 7 Hz), 7.43 (t, 1 H, J = 7 Hz), 7.35 (d, 1 H, J = 7 Hz), 7.29 (d, 2 H, J = 10 Hz), 7.08 (d, 2 H, J = 10 Hz), 5.24 (s, 2 H), 4.29 (s, 2 H), 3.20 (s, 3 H), 2.53 (t, 2 H, J = 7 Hz), 1.49 (quint, 2 H, J = 7 Hz), 1.25 (sext, 2 H, J = 7 Hz), 0.80 (t, 3 H, J = 7 Hz). Anal. ($C_{23}H_{25}ClN_2O_3 \cdot 0.2H_2O$) C, H, N.

5-(Azidomethyl)-2-butyl-1-[(2'-carbomethoxybiphenyl-4-yl)methyl]-4-chloroimidazole (92). A solution of **90** (3.31 g, 7.67 mmol, 1 equiv), sodium azide (1.50 g, 23.0 mmol, 3 equiv), and 100 mL of dimethyl sulfoxide was stirred at 25 °C for 16 h. Water was then added, and the aqueous mixture was extracted with ethyl acetate. The organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated to yield 3.48 g of

92 as an oil, which was suitable for further transformation: NMR ($CDCl_3$) δ 7.85 (d, 1 H, J = 7 Hz), 7.54 (t, 1 H, J = 7 Hz), 7.40 (t, 1 H, J = 7 Hz), 7.28 (d, 2 H, J = 8 Hz), 7.00 (d, 2 H, J = 8 Hz), 5.20 (s, 2 H), 4.23 (s, 2 H), 3.67 (s, 3 H), 2.63 (t, 2 H, J = 7 Hz), 1.73 (quint, 2 H, J = 7 Hz), 1.39 (sext, 2 H, J = 7 Hz), 0.91 (t, 3 H, J = 7 Hz); high-resolution MS calcd 438.1697, found 438.1669.

5-(Aminomethyl)-2-butyl-1-[(2′-carbomethoxybiphenyl-4-yl)methyl]-4-chloroimidazole (93). A mixture of **92** (3.48 g, 8.0 mmol), 10% palladium/carbon (0.5 g), and 100 mL of methanol was stirred at 25 °C under hydrogen (1 atm) for 1 h. The reaction mixture mixture was filtered through Celite, and the solvent was removed under vacuum to furnish 2.80 g (89% overall from **90**) of **93** as an oil: NMR ($CDCl_3$) δ 7.84 (d, 1 H, J = 7 Hz), 7.52 (t, 1 H, J = 7 Hz), 7.40 (t, 1 H, J = 7 Hz), 7.30 (d, 1 H, J = 7 Hz), 7.26 (d, 2 H, J = 8 Hz), 7.02 (d, 2 H, J = 8 Hz), 5.27 (s, 2 H), 3.74 (s, 2 H), 3.65 (s, 3 H), 2.60 (t, 2 H, J = 7 Hz), 1.67 (quint, 2 H, J = 7 Hz), 1.36 (sext, 2 H, J = 7 Hz), 0.86 (t, 3 H, J = 7 Hz). Anal. ($C_{23}H_{26}ClN_3O_2$·0.5DMSO) C, H, N.

5-(Aminomethyl)-2-butyl-1-[(2′-carboxybiphenyl-4-yl)methyl]-4-chloroimidazole (94). A solution of **93** (1.64 g, 3.98 mmol, 1 equiv), 0.5 N potassium hydroxide in methanol (11.96 mL, 5.98 mmol, 1.5 equiv), 1 mL of water, and 20 mL of methanol was refluxed for 18 h. The solution then was adjusted to neutrality with 1 N hydrochloric acid, and the solvents were removed under vacuum. The residue then was taken up in dimethylformamide, and the salts were filtered off. The dimethylformamide was removed under vacuum to afford 1.76 g of **94** as a glass suitable for further transformation: NMR (DMSO-d_6) δ 7.50 (d, 1 H, J = 7 Hz), 7.40–7.18 (m, 5 H), 6.92 (d, 2 H, J = 8 Hz), 6.50 (br m, 3 H), 5.26 (s, 2 H), 3.60 (s, 2 H), 2.55 (t, 2 H, J = 7 Hz), 1.51 (quint, 2 H, J = 7 Hz), 1.27 (sext, 2 H, J = 7 Hz), 0.81 (t, 3 H, J = 7 Hz).

2-Butyl-1-[(2′-carboxybiphenyl-4-yl)methyl]-4-chloro-5-[[(ethoxycarbonyl)amino]methyl]imidazole (51). To a solution of **94** (0.90 g, 2.26 mmol, 1 equiv), 1.000 N aqueous sodium hydroxide (2.26 mL, 2.26 mmol, 1 equiv), and tetrahydrofuran (enough to make a solution) at 0 °C was added, in five equal portions, ethyl chloroformate (0.22 mL, 2.26 mmol, 1 equiv) in 10 mL of tetrahydrofuran. Alternating with the portions of ethyl chloroformate was added, in five equal portions, 1.000 N aqueous sodium hydroxide (2.26 mL, 2.26 mmol, 1 equiv). The reaction mixture was allowed to stir for 16 h at 25 °C. Water was added, and the mixture was acidified to pH 3. The mixture was extracted with ethyl acetate (3×). The organic layers were collected, dried over anhydrous magnesium sulfate, and filtered, and the solvent was removed under vacuum to afford 0.77 g of a white glass. Crystallization from n-butyl chloride furnished 0.521 g (55% overall from **93**) of **51** as a white crystalline solid: mp 144.0–147.0 °C; NMR (DMSO-d_6) δ 12.74 (s, 1 H), 7.73 (d, 1 H, J = 7 Hz), 7.63–7.27 (m, 6 H), 7.03 (d, 2 H, J = 10 Hz), 5.27 (s, 2 H), 4.60 (br d, 2 H, J = 7 Hz), 3.90 (quart, 2 H, J = 7 Hz), 3.34 (s, 2 H), 2.47 (t, 2 H, J = 7 Hz), 1.48 (quint, 2 H, J = 7 Hz), 1.24 (sext, 2 H, J = 7 Hz), 1.06 (t, 3 H, J = 7 Hz), 0.78 (t, 3 H, J = 7 Hz). Anal. ($C_{25}H_{28}ClN_3O_4$·0.3H_2O) C, H, N.

2-Butyl-1-[(2′-carbomethoxybiphenyl-4-yl)methyl]-4-chloro-5-[[[(1-naphthylamino)carbonyl]amino]methyl]imidazole (95). A solution of **93** (1.00 g, 2.4 mmol, 1 equiv) and 1-naphthyl isocyanate (0.35 mL, 2,4 mmol, 1 equiv) in chloroform was stirred at 25 °C for 72 h. The solvent was removed under vacuum, and the residue was purified by column chromatography (elution: 1:1 hexane/ethyl acetate) to provide 0.77 g (55%) of **95** as a white glass: NMR ($CDCl_3$) δ 7.83 (d, 3 H, J = 6 Hz), 7.67 (d, 1 H, J = 6 Hz), 7.56–7.18 (m, 9 H), 6.97 (d, 2 H, J = 7 Hz), 6.74 (s, 1 H), 5.27 (s, 2 H), 4.74 (s, 1 H), 4.39 (d, 2 H, J = 7 Hz), 3.58 (s, 3 H), 2.60 (t, 2 H, J = 7 Hz), 1.43–1.21 (m, 4 H), 0.85 (t, 3 H, J = 7 Hz).

2-Butyl-1-[(2′-carboxybiphenyl-4-yl)methyl]-4-chloro-5-[[[(1-naphthylamino)carbonyl]amino]methyl]imidazole (55). The title compound was prepared from **95** by the procedure described for the preparation of **94**: mp 169.0–175.0 °C; NMR ($CDCl_3$) δ 8.45 (s, 1 H), 8.05–7.03 (m, 15 H), 6.97 (s, 1 H), 5.34 (s, 2 H), 4.30 (d, 2 H, J = 5 Hz), 2.52 (t, 2 H, J = 7 Hz), 1.48 (quint, 2 H, J = 7 Hz), 1.21 (sext, 2 H, J = 7 Hz), 0.85 (t, 3 H, J = 7 Hz). Anal. ($C_{33}H_{31}ClN_4O_3$·0.5H_2O) C, H, N.

[2-Butyl-4-chloro-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]imidazol-5-yl]phenylmethanol (62). A solution of phenylmagnesium chloride (2.0 M in tetrahydrofuran, 3.39 mL, 6.8 mmol, 1.5 equiv) was slowly added to a stirred solution of **89** (3.00 g, 4.5 mmol, 1 equiv) in 25 mL of dioxane at 0 °C. After 1 h, the reaction was quenched with methanol (5 mL), followed by water (25 mL). Trifluoroacetic acid (25 mL) was then added, and the mixture was stirred at 25 °C for 1 h. The solution was adjusted to pH 10 with 10 N aqueous sodium hydroxide, and the organic solvents were removed under vacuum, leaving behind solid triphenylmethanol and an aqueous phase containing the product. The triphenylmethanol was filtered, and the aqueous solution was acidified to pH 3 with concentrated hydrochloric acid, producing a precipitate. The solids were filtered, dried, and recrystallized from hexane/ethyl acetate to furnish 0.532 g (24%) of **62** as a white solid: mp 137–145 °C. NMR (DMSO-d_6) δ 7.77–7.46 (m, 4 H), 7.46–7.30 (m, 5 H), 6.94 (d, 2 H, J = 9 Hz), 6.76 (d, 2 H, J = 9 Hz), 6.37 (d, 1 H, J = 5 Hz), 5.97 (d, 1 H, J = 5 Hz), 5.09 (s, 2 H), 2.25 (t, 2 H, J = 7 Hz), 1.34 (quint, 2 H, J = 7 Hz), 1.17 (sext, 2 H, J = 7 Hz), 0.74 (t, 3 H, J = 7 Hz). Anal. ($C_{23}H_{27}ClN_6O$·0.5H_2O) C, H, Cl.

2-Butyl-4-chloro-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole-5-carboxaldehyde, Benzenesulfonylhydrazone (61). To a solution of **25** (1.00 g, 2.4 mmol, 1 equiv), 1.000 N aqueous sodium hydroxide (4.76 mL, 4.8 mmol, 2 equiv), and 10 mL of water was added benzenesulfonylhydrazide (0.41 g, 2.4 mmol, 1 equiv), and the solution was stirred for 18 h at 25 °C. The solution was acidified to pH 2.5 with concentrated hydrochloric acid. The resultant precipitate was filtered, dried, and recrystallized from ethyl acetate to yield 0.85 g (62%) of **61** as a solid: mp 227.5–230.0 °C dec; NMR (DMSO-d_6) δ 16.31 (br m, 1 H), 11.48 (br m, 1 H), 7.96 (s, 1 H), 7.78–7.39 (m, 9 H), 7.04 (d, 2 H, J = 7 Hz), 6.87 (d, 2 H, J = 7 Hz), 5.52 (s, 2 H), 2.51 (t, 2 H, J = 7 Hz), 1.45 (quint, 2 H, J = 7 Hz), 1.24 (sext, 2 H, J = 7 Hz), 0.79 (t, 3 H, J = 7 Hz). Anal. ($C_{28}H_{27}ClN_8O_2S$) C, H, Cl.

5-[[4-[[3-[*N*-(*tert*-Butoxycarbonyl)-*N*-isopropylamino]-2-hydroxypropyl]oxy]indole-2-carboxamido]methyl]-2-butyl-1-[(2′-carbomethoxybiphenyl-4-yl)methyl]-4-chloroimidazole (96). A solution of **93** (1.11 g, 2.7 mmol, 1 equiv), 4-[[3-[*N*-(*tert*-butoxycarbonyl)-*N*-isopropylamino]-2-hydroxypropyl]oxy]indole-2-carboxylic acid[17] (1.31 g, 2.7 mmol, 1 equiv), 1-hydroxybenzotriazole (0.38 g, 2.8 mmol, 1.05 equiv), dicyclohexylcarbodiimide (0.58 g, 2.8 mmol, 1.05 equiv), and 25 mL of dimethylformamide were mixed at 0 °C and then held at 0 °C in the refrigerator for 96 h. The dicyclohexylurea was filtered off, and the mixture was concentrated. Column chromatography (elution: 1:1 hexane/ethyl acetate) provided 1.59 g (75%) of **96** as a white solid: mp 157.5–160 °C; NMR (DMSO-d_6) δ 11.51 (s, 1 H), 8.83 (m, 1 H), 7.68 (m, 1 H), 7.44 (m, 2 H), 7.22–6.92 (m, 8 H), 6.43 (d, 1 H, J = 7 Hz), 5.34 (s, 2 H), 5.05 (d, 1 H, J = 7 Hz), 4.44 (m, 2 H), 3.97 (m, 4 H), 3.49 (s, 3 H), 3.05 (m, 1 H), 2.51 (t, 2 H, J = 7 Hz), 1.75–1.00 (m, 4 H), 1.35 (s, 9 H), 1.13 (d, 3 H, J = 7 Hz), 1.08 (d, 3 H, J = 7 Hz), 0.80 (t, 3 H, J = 7 Hz). Anal. ($C_{43}H_{52}ClN_5O_7$) C, H, Cl, N.

5-[[4-[[3-(*N*-Isopropylamino)-2-hydroxypropyl]oxy]indole-2-carboxamido]methyl]-2-butyl-1-[(2′-carbomethoxybiphenyl-4-yl)methyl]-4-chloroimidazole (97). To a solution of **96** (1.51 g, 1.9 mmol), tetrahydrofuran (7.5 mL), anisole (7.5 mL), and water (7.5 mL) was added trifluoroacetic acid (7.5 mL), and the resulting mixture was stirred at 25 °C for 7 h. Diethyl ether was added to precipitate a gum. The mother liquor was decanted, and the hygroscopic gum was dried under high vacuum overnight to afford 1.68 g of **97** as a hard glass: NMR (DMSO-d_6) δ 11.58 (s, 1 H), 8.80 (m, 1 H), 8.43 (m, 2 H), 7.70 (d, 1 H, J = 9 Hz), 7.48 (m, 2 H), 7.23–6.97 (m, 8 H), 6.52 (d, 1 H, J = 9 Hz), 5.37 (s, 2 H), 4.44 (d, 2 H, J = 5 Hz), 4.30–4.00 (m, 4 H), 3.50 (s, 3 H), 3.33 (m, 1 H), 3.12 (m, 2 H), 2.53 (t, 2 H, J = 7 Hz), 1.50 (quint, 2 H, J = 7 Hz), 1.32–1.15 (m, 8 H), 0.80 (t, 3 H, J = 7 Hz).

5-[[4-[[3-(*N*-Isopropylamino)-2-hydroxypropyl]oxy]indole-2-carboxamido]methyl]-2-butyl-1-[(2′-carboxybiphenyl-4-yl)methyl]-4-chloroimidazole (58). A solution of **97** (1.68 g), 25 mL of tetrahydrofuran, 75 mL of methanol, 5 mL of water, and 64 mL of 1.000 N aqueous sodium hydroxide was stirred at 50 °C for 24 h. The organic solvents were removed under vacuum when some of the sodium salt of the product precipitated from the remaining aqueous mixture. The solids were filtered and redissolved in water, and the solution was adjusted to pH

1 with concentrated hydrochloric acid. The aqueous mixture was extracted with ethyl acetate (3 × 100 mL). The organic layers were combined, dried over anhydrous magnesium sulfate, and filtered, and the solvent was removed under vacuum to provide 0.21 g of a white solid. The original aqueous layer was adjusted to pH 3–4 with 10 N aqueous sodium hydroxide; solids precipitated. The solids were filtered and dried, affording 0.497 g. The two batches of solids thus obtained were combined and dissolved in ethanol. Approximately 1.1 equiv of hydrogen chloride in 2-propanol (4.21 M) was added, followed by ether to precipitate the product as the hydrochloride salt. The resultant precipitate was filtered and dried under high vacuum to furnish 0.88 g (62% overall from **96**) of **58** as a colorless glass: NMR (DMSO-d_6) δ 12.72 (m, 1 H), 11.61 (s, 1 H, indole NH), 8.85 (m, 1 H, amide NH), 9.68 (m, 1 H, ammonium NH), 9.53 (m, 1 H, ammonium NH), 7.70 (m, 1 H), 7.45 (m, 2 H), 7.30–6.98 (m, 8 H), 6.55 (d, 1 H, J = 9 Hz), 5.91 (d, 1 H, J = 6 Hz), 5.36 (s, 2 H), 4.48 (d, 2 H, J = 7 Hz), 4.24 (m, 1 H), 4.13 (m, 2 H), 3.53–2.98 (m, 3 H), 2.57 (t, 2 H, J = 7 Hz), 1.54 (quint, 2 H, J = 7 Hz), 1.37–1.20 (m, 8 H), 0.84 (t, 3 H, J = 7 Hz). Anal. ($C_{37}H_{42}ClN_5O_5 \cdot 2HCl \cdot 2H_2O$) C, H, N.

2-Butyl-1-[(2′-carbomethoxybiphenyl-4-yl)methyl]-4-chloroimidazole-5-carboxaldehyde (98). A mixture of **84** (2.06 g, 5.0 mmol) and 3.08 g of manganese dioxide in 20 mL of methylene chloride was stirred at 25 °C for 40 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated under vacuum. Column chromatography (elution: ethyl acetate/benzene) provided 1.15 g (56%) of **98**: NMR ($CDCl_3$) δ 9.76 (s, 1 H), 7.83 (dd, 1 H, J = 8, 2 Hz), 7.52 (td, 1 H, J = 8, 2 Hz), 7.40 (td, 1 H, J = 8, 2 Hz), 7.31 (dd, 1 H, J = 8, 2 Hz), 7.17 (A_2B_2, 4 H, J = 8.5 Hz), 5.58 (s, 2 H), 3.63 (s, 3 H), 2.67 (t, 2 H, J = 7 Hz), 1.70 (quint, 2 H, J = 7 Hz), 1.38 (sext, 2 H, J = 7 Hz), 0.90 (t, 3 H, J = 7 Hz).

2-(1-Bromobutyl)-1-[(2′-carbomethoxybiphenyl-4-yl)methyl]-4-chloroimidazole-5-carboxaldehyde (99). A mixture of **98** (1.12 g, 2.75 mmol, 1.0 equiv) and *N*-bromosuccinimide (0.49 g, 2.75 mmol, 1.0 equiv) in 40 mL of carbon tetrachloride was irradiated (UV lamp, Pyrex filter) for 0.5 h. The reaction mixture was filtered, and the filtrate was concentrated. Column chromatography (elution: ethyl acetate/benzene) afforded 0.54 g (40%) of **99**: NMR ($CDCl_3$) δ 9.87 (s, 1 H), 7.86 (d, 1 H, J = 8 Hz), 7.54 (t, 1 H, J = 8 Hz), 7.46 (t, 1 H, J = 8 Hz), 7.30 (m, 3 H), 7.11 (d, 2 H, J = 8.5 Hz), 6.16 (d, 1 H, J = 16 Hz), 5.32 (d, 1 H, J = 16 Hz), 4.79 (t, 1 H, J = 7 Hz), 3.65 (s, 3 H), 2.32 (m, 2 H), 1.34 (sext, 2 H, J = 7 Hz), 0.83 (t, 3 H, J = 7 Hz); IR 1673, 1729 cm^{-1}.

2-(1-*trans*-Butenyl)-1-[(2′-carbomethoxybiphenyl-4-yl)methyl]-4-chloroimidazole-5-carboxaldehyde (100). A solution of **99** (0.54 g, 1.1 mmol, 1.0 equiv) and 1,8-diazabicyclo[5.4.0]-undec-7-ene (0.33 mL, 2.2 mmol, 2.0 equiv) in 10 mL of tetrahydrofuran was stirred at 25 °C for 18 h. The reaction mixture was diluted with diethyl ether, and the resulting solution was washed with 5% hydrochloric acid, water, and brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography (elution: ethyl acetate/benzene) furnished 0.26 g (58%) of **100**: NMR ($CDCl_3$) δ 9.75 (s, 1 H), 7.82 (d, 1 H, J = 8 Hz), 7.51 (t, 1 H, J = 8 Hz), 7.40 (t, 1 H, J = 8 Hz), 7.33–7.07 (m, 6 H), 6.27 (d, 1 H, J = 15 Hz), 5.62 (s, 2 H), 3.62 (s, 3 H), 2.30 (quint, 2 H, J = 7 Hz), 1.09 (t, 3 H, J = 7 Hz); IR 1657, 1724 cm^{-1}.

2-(1-*trans*-Butenyl)-1-[(2′-carbomethoxybiphenyl-4-yl)methyl]-4-chloro-5-(hydroxymethyl)imidazole (101). To a solution of **100** (0.26 g, 0.64 mmol, 1 equiv) in 10 mL of methanol at 0 °C was added sodium borohydride (0.24 g, 6.4 mmol, 10 equiv) portionwise over 0.5 h. The mixture was stirred at 0 °C for an additional 0.5 h and then was poured into 10% aqueous sodium hydroxide. The resulting mixture was extracted with ethyl acetate, and the combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography (elution: ethyl acetate/benzene) provided 0.23 g (88%) of **101**: NMR ($CDCl_3$) δ 7.84 (d, 1 H, J = 8 Hz), 7.53 (t, 1 H, J = 8 Hz), 7.40 (t, 1 H, J = 8 Hz), 7.29 (m, 3 H), 7.08 (d, 2 H, J = 8 Hz), 6.86 (dt, J = 15, 7 Hz), 6.17 (d, 1 H, J = 15 Hz), 5.30 (s, 2 H), 4.54 (br s, 1 H), 3.63 (s, 3 H), 2.23 (quint, 2 H, J = 7 Hz), 1.04 (t, 3 H, J = 7 Hz); IR 1724 cm^{-1}.

2-(1-*trans*-Butenyl)-1-[(2′-carboxybiphenyl-4-yl)methyl]-4-chloro-5-(hydroxymethyl)imidazole (37). The title compound was prepared from **101** by the procedure described for the preparation of **2**: mp 198.5–199.5 °C; NMR (DMSO-d_6) δ 7.71 (d, 1 H, J = 8 Hz), 7.56 (t, 1 H, J = 8 Hz), 7.44 (t, 1 H, J = 8 Hz), 7.32 (m, 3 H), 7.11 (d, 2 H, J = 8.5 Hz), 6.62 (d of t, 1 H, J = 15, 7 Hz), 6.39 (d, 1 H, J = 15 Hz), 5.38 (s, 2 H), 5.33 (br s, 1 H), 4.35 (s, 2 H), 2.18 (quint, 2 H, J = 7 Hz), 0.99 (t, 3 H, J = 7 Hz); IR 1703 cm^{-1}. Anal. ($C_{22}H_{21}ClN_2O_3$) C, H, Cl.

2-Butyl-1-[(2′-carbomethoxybiphenyl-4-yl)methyl]-5-(hydroxymethyl)imidazole (102). A mixture of **84** (2.00 g, 4.8 mmol) and 2.00 g of 10% palladium/carbon in 40 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 was concentrated under vacuum. Column chromatography (elution: 0–5% methanol/chloroform) afforded 1.45 g (79%) of **102**: NMR (DMSO-d_6) δ 7.74 (d, 1 H, J = 8 Hz), 7.60 (m, 2 H), 7.48 (t, 1 H, J = 8 Hz), 7.38 (d, 1 H, J = 8 Hz), 7.25 (A_2B_2, 4 H, J = 8 Hz), 5.88 (br s, 1 H), 5.57 (s, 2 H), 4.47 (s, 2 H), 3.55 (s, 3 H), 2.94 (t, 2 H, J = 7 Hz), 1.50 (quint, 2 H, J = 7 Hz), 1.24 (sext, 2 H, J = 7 Hz), 0.80 (t, 3 H, J = 7 Hz).

2-Butyl-1-[(2′-carboxybiphenyl-4-yl)methyl]-5-(hydroxymethyl)imidazole (41). A solution of **102** (1.45 g, 3.8 mmol), 40 mL of 10% aqueous sodium hydroxide, and 80 mL of ethanol was refluxed for 5 h. After cooling, the reaction mixture was filtered, and the solvents were removed under vacuum. The residue was dissolved in water, and the solution was adjusted to pH 6 by employing hydrochloric acid. The precipitate was recovered by filtration and dried to provide 0.96 g (69%) of **41**: NMR (DMSO-d_6) δ 7.69 (d, 1 H, J = 7.5 Hz), 7.54 (t, 1 H, J = 7.5 Hz), 7.43 (t, 1 H, J = 7.5 Hz), 7.33 (d, 1 H, J = 7.5 Hz), 7.16 (A_2B_2, 4 H, J = 8 Hz), 6.76 (s, 1 H), 5.24 (s, 2 H), 4.34 (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), 0.80 (t, 3 H, J = 7 Hz); IR 1705 cm^{-1}. Anal. ($C_{22}H_{24}N_2O_3 \cdot H_2O$) C, H, N.

2-Butyl-4(5)-(hydroxymethyl)-5(4)-nitroimidazole (103). To a solution of 2-butyl-4(5)-(hydroxymethyl)imidazole[31] (5.75 g, 37.3 mmol, 1 equiv) in 200 mL of aqueous methanol at 25 °C was added concentrated hydrochloric acid until the pH of the solution reached pH 3. The solvents were removed under vacuum, and the residue was dissolved in 100 mL of chloroform. To this solution at 25 °C was added dropwise thionyl chloride (15.0 mL, 205 mmol, 5.5 equiv), and the resulting solution was refluxed for 1 h. After cooling, the solution was concentrated under vacuum to provide a viscous yellow oil.

To a solution of 20 mL of concentrated sulfuric acid and 10 mL of concentrated nitric acid at −10 °C was added a solution of the above oil in 10 mL of concentrated sulfuric acid. The resulting solution was allowed to warm to ambient temperature and then was warmed gently on a steam bath for 2 h. After cooling the reaction mixture was poured onto water–ice, and the resulting emulsion was extracted with chloroform. The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting oil was dissolved in a mixture of 50 mL of 2-propanol and 50 mL of water. The solution was refluxed for 16 h, allowed to cool, and concentrated. Column chromatography (elution: methanol/chloroform) afforded 2.64 g (36%) of **103**: NMR (DMSO-d_6) δ 12.92 (br s, 1 H), 5.80 (br t, 1 H), 4.82 (d, 2 H, J = 5 Hz), 2.60 (t, 2 H, J = 7 Hz), 1.61 (quint, 2 H, J = 7 Hz), 1.25 (sext, 2 H, J = 7 Hz), 0.84 (t, 3 H, J = 7 Hz).

1-[[2′-(*tert*-Butoxycarbonyl)biphenyl-4-yl]methyl]-2-butyl-5-(hydroxymethyl)-4-nitroimidazole (104). The title compound was prepared from **82** and **103** by the procedure described for the preparation of **84**: NMR ($CDCl_3$) δ 7.79 (d, 1 H, J = 8 Hz), 7.45 (m, 2 H), 7.33 (d, 2 H, J = 8 Hz), 7.28 (d, 1 H, J = 8 Hz), 7.03 (d, 2 H, J = 8 Hz), 5.34 (s, 2 H), 4.87 (s, 2 H), 2.81 (br s, 1 H), 2.67 (t, 2 H, J = 7 Hz), 1.73 (quint, 2 H, J = 7 Hz), 1.37 (sext, 2 H, J = 7 Hz), 1.27 (s, 9 H), 0.90 (t, 3 H, J = 7 Hz); IR 1303, 1343, 1468, 1510, 1708 cm^{-1}.

2-Butyl-1-[(2′-carboxybiphenyl-4-yl)methyl]-5-(hydroxymethyl)-4-nitroimidazole (43). A solution of **104** (1.98 g, 4.25 mmol), 20 mL of trifluoroacetic acid, and 20 mL of methylene chloride was stirred at 25 °C for 1 h. The reaction mixture was poured into water. The resulting solution was adjusted to pH 3 with 10% aqueous sodium hydroxide and then was extracted with chloroform. The combined organic phasss were washed with

brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. Column chromatography (elution: methanol/chloroform) provided 1.49 g (86%) of **43**: mp 204–205.5 °C; NMR (DMSO-d_6) δ 7.71 (d, 1 H, J = 8 Hz), 7.56 (t, 1 H, J = 8 Hz), 7.43 (t, 1 H, J = 8 Hz), 7.32 (m, 3 H), 7.15 (d, 2 H, J = 8.5 Hz), 5.63 (br s, 1 H), 5.42 (s, 2 H), 4.83 (s, 2 H), 2.54 (t, 2 H, J = 7 Hz), 1.50 (quint, 2 H, J = 7 Hz), 1.24 (sext, 2 H, J = 7 Hz), 0.76 (t, 3 H, J = 7 Hz); IR 1717 cm^{-1}. Anal. ($C_{22}H_{23}N_3O_5$) C, H, N.

4(5)-Methyl-2-propylimidazole (105). To a well-stirred mixture of butyraldehyde (72 mL, 800 mmol, 1.9 equiv) and copper(II) acetate monohydrate (240 g, 1200 mmol, 2.8 equiv) in 100 mL of 25% aqueous ammonia at 0 °C was added acetol (32.8 mL, 430 mmol, 1.0 equiv) dropwise over 0.25 h. The mixture then was heated to 80–100 °C for 0.5 h. After allowing the reaction mixture to cool, the aqueous solution was decanted, and the residual material was triturated with aqueous ethanol. The resulting gray-green solid was recovered by filtration.

Into a suspension of the above solid in water at 80 °C was bubbled hydrogen sulfide gas for 0.5 h. The mixture then was filtered, while still hot, to remove the copper(I) sulfide. After cooling the filtrate was extracted with methylene chloride. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated to furnish 26.4 g (49%) of **105**: NMR ($CDCl_3$) δ 10.15 (br s, 1 H), 6.61 (s, 1 H), 2.64 (t, 2 H, J = 7 Hz), 2.20 (s, 3 H), 1.72 (sext, 2 H, J = 7 Hz), 0.92 (t, 3 H, J = 7 Hz).

4(5)-(Hydroxymethyl)-5(4)-methyl-2-propylimidazole (106). A solution of **105** (21.0 g, 170 mmol, 1 equiv), 37% aqueous formaldehyde 14.0 g, 170 mmol, 1 equiv), concentrated hydrochloric acid (76 g), and 100 mL of water was refluxed for 62 h. After cooling the mixture was diluted with water. The resulting aqueous solution was adjusted to pH 10 by employing 10% aqueous sodium hydroxide and then was extracted with 4:1 chloroform/2-propanol. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography (elution: 10% methanol/chloroform with 0.2% concentrated ammonia) followed by recrystallization from ethyl acetate provided 13.9 g (53%) of **106**: mp 138.5–139.5 °C; NMR (DMSO-d_6) δ 11.30 (br s, 1 H), 4.68 (br s, 1 H), 4.26 (s, 2 H), 2.46 (t, 2 H, J = 7 Hz), 2.06 (s, 3 H), 1.60 (sext, 2 H, J = 7 Hz), 0.88 (t, 3 H, J = 7 Hz).

4(5)-Methyl-2-propylimidazole-5(4)-carboxaldehyde (107). The title compound was prepared from **106** by the procedure described for the preparation of **88**: mp 128–128.5 °C; NMR (DMSO-d_6) δ 12.49 (br s, 1 H), 9.69 (s, 1 H), 2.53 (t, 2 H, J = 7 Hz), 2.38 (s, 3 H), 1.65 (sext, 2 H, J = 7 Hz), 0.87 (t, 3 H, J = 7 Hz); IR 1680 cm^{-1}.

1-[[2′-(*tert*-Butoxycarbonyl)biphenyl-4-yl]methyl]-4-methyl-2-propylimidazole-5-carboxaldehyde (108). The title compound was prepared from **82** and **107** by the procedure described for the preparation of **89**: NMR ($CDCl_3$) δ 9.77 (s, 1 H), 7.78 (d, 1 H, J = 8 Hz), 7.51–7.35 (m, 2 H), 7.27 (m, 3 H), 7.05 (d, 2 H, J = 8 Hz), 5.59 (s, 2 H), 2.64 (t, 2 H, J = 7 Hz), 2.50 (s, 3 H), 1.78 (sext, 2 H, J = 7 Hz), 0.97 (t, 3 H, J = 7 Hz).

1-[[2′-(*tert*-Butoxycarbonyl)biphenyl-4-yl]methyl]-5-(hydroxymethyl)-4-methyl-2-propylimidazole (109). To a solution of **108** (3.43 g, 8.2 mmol, 1 equiv) in 22 mL of methanol and 22 mL of tetrahydrofuran at 25 °C was added, in several portions, sodium borohydride (3.09 g, 82 mmol, 10 equiv). The reaction mixture was stirred at 25 °C for 1.5 h and then was poured into dilute aqueous sodium hydroxide solution. After stirring at 25 °C for 0.2 h this solution was extracted with chloroform. The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography (elution: ethyl acetate/benzene) afforded 3.32 g (96%) of **109** as a colorless glass: NMR ($CDCl_3$) δ 7.76 (d, 2 H, J = 8 Hz), 7.42 (m, 2 H), 7.28–7.24 (m, 3 H), 6.96 (d, 2 H, J = 8 Hz), 5.24 (s, 2 H), 4.47 (s, 2 H), 2.56 (t, 2 H, J = 7 Hz), 2.21 (s, 3 H), 1.71 (sext, 2 H, J = 7 Hz), 0.95 (t, 3 H, J = 7 Hz).

1-[(2′-Carboxybiphenyl-4-yl)methyl]-5-(hydroxymethyl)-4-methyl-2-propylimidazole Hydrochloride (44). A solution of **109** (3.32 g, 7.9 mmol) in 100 mL of 10% aqueous hydrochloric acid was stirred at 25 °C for 16 h. The solvent was removed under vacuum. The residue was dissolved into 10 mL of water. To this solution was added concentrated hydrochloric acid until a precipitate formed. The precipitate was recovered by filtration, washed with 10% hydrochloric acid, and dried to provide 2.22 g (70%) of **44**: mp 208–210 °C dec; NMR (DMSO-d_6) δ 12.92 (br s, 1 H), 7.74 (d, 1 H, J = 8 Hz), 7.58 (t, 1 H, J = 8 Hz), 7.47 (t, 1 H, J = 8 Hz), 7.34 (m, 3 H), 7.26 (d, 2 H, J = 8 Hz), 5.67 (br s, 1 H), 5.53 (s, 2 H), 4.42 (s, 2 H), 2.86 (t, 2 H, J = 7 Hz), 2.30 (s, 3 H), 1.54 (sext, 2 H, J = 7 Hz), 0.83 (t, 3 H, J = 7 Hz); IR 1718 cm^{-1}. Anal. ($C_{22}H_{24}N_2O_3$·HCl) C, H, N, Cl.

2-Butyl-4(5)-(hydroxymethyl)-5(4)-iodoimidazole (110). A solution of 2-butyl-4(5)-(hydroxymethyl)imidazole[31] (16.08 g, 104 mmol, 1 equiv), *N*-iodosuccinimide (24.65 g, 110 mmol, 1.05 equiv), 280 mL of 1,4-dioxane, and 240 mL of 2-methoxyethanol was stirred at 45 °C for 2 h. The solvents were reduced under vacuum until a thick slurry of precipitate had been produced. This slurry was diluted with water while being stirred vigorously. To this mixture was added a small portion of sodium bisulfite sufficient to remove any residual iodine. The resulting solids were recovered by filtration and dried to afford 25.1 g (86%) of **110**: mp 157.5–158.5 °C; NMR ($CDCl_3$) δ 12.11 (br s, 1 H), 5.10 (br s, 1 H), 4.29 (d, 2 H, J = 5 Hz), 2.55 (t, 2 H, J = 7 Hz), 1.57 (quint, 2 H, J = 7 Hz), 1.28 (sext, 2 H, J = 7 Hz), 0.88 (t, 3 H, J = 7 Hz).

1-[[2′-(*tert*-Butoxycarbonyl)biphenyl-4-yl]methyl]-2-butyl-5-(hydroxymethyl)-4-iodoimidazole (111). The title compound was prepared from **82** and **110** by the procedure described for the preparation of **84**: mp 125–126 °C; NMR ($CDCl_3$) δ 7.78 (d, 1 H, J = 7.5 Hz), 7.52–7.36 (m, 2 H), 7.28 (m, 3 H), 6.99 (d, 2 H, J = 8 Hz), 5.32 (s, 2 H), 4.50 (d, 2 H, J = 4 Hz), 2.60 (t, 2 H, J = 7 Hz), 1.83–1.57 (m, 3 H), 1.35 (sext, 2 H, J = 7 Hz), 1.25 (s, 9 H), 0.87 (t, 3 H, J = 7 Hz).

1-[[2′-(*tert*-Butoxycarbonyl)biphenyl-4-yl]methyl]-2-butyl-4-iodo-5-[[(2-methoxyethoxy)methoxy]methyl]imidazole (112). To a solution of *n*-butyllithium (1.6 M, 5.56 mL, 8.9 mmol, 1.5 equiv) in 80 mL of tetrahydrofuran at 0 °C was added dropwise *tert*-butyl alcohol (1.15 mL, 12.2 mmol, 2.0 equiv). To this solution was added **111** (3.28 g, 6.0 mmol, 1.0 equiv), followed by addition of (2-methoxyethoxy)methyl chloride (1.15 mL, 10.1 mmol, 1.68 equiv). The resulting solution was stirred at 25 °C for 16 h. The mixture was diluted with diethyl ether. The resulting solution was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography (elution: ethyl acetate/benzene) afforded 2.61 g (69%) of **112**: NMR ($CDCl_3$) δ 7.78 (d, 1 H, J = 8 Hz), 7.43 (m, 2 H), 7.28 (m, 3 H), 6.98 (d, 2 H, J = 8 Hz), 5.26 (s, 2 H), 4.69 (s, 2 H), 4.45 (s, 2 H), 3.68 (m, 2 H), 3.57 (m, 2 H), 3.37 (s, 3 H), 2.58 (t, 2 H, J = 7 Hz), 1.67 (quint, 2 H, J = 7 Hz), 1.34 (sext, 2 H, J = 7 Hz), 1.26 (s, 9 H), 0.87 (t, 3 H, J = 7 Hz).

1-[[2′-(*tert*-Butoxycarbonyl)biphenyl-4-yl]methyl]-2-butyl-5-[[(2-methoxyethoxy)methoxy]methyl]-4-(trifluoromethyl)imidazole (113). To a suspension of cadmium powder (22.4 g, 200 mmol, 2 equiv) in 50 mL of dimethylformamide at 25 °C was added dropwise bromochlorodifluoromethane (8.6 mL, 100 mmol, 1 equiv). The resulting mixture was stirred at 25 °C for 2 h and then was filtered through a course-fritted Schlenk funnel under nitrogen pressure, washing with an additional 10 mL of dimethylformamide, to provide a dark-brown solution of the (trifluoromethyl)cadmium reagent (1.0 M).

To a mixture of the above reagent (15 mL, 15 mmol, 3.6 equiv) and 20 mL of hexamethylphosphoric triamide at 0 °C was added copper(I) bromide (2.10 g, 15 mmol, 3.6 equiv) followed by **112** (2.61 g, 4.1 mmol, 1.0 equiv) in 5 mL of dimethyl formamide. The reaction mixture was stirred at 70–75 °C for 6 h. After cooling, the mixture was diluted with water and then was extracted with methylene chloride. The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography furnished 2.30 g (97%) of **113**: NMR ($CDCl_3$) δ 7.79 (d, 1 H, J = 8 Hz), 7.46 (m, 2 H), 7.28 (m, 3 H), 7.00 (d, 2 H, J = 8 Hz), 5.28 (s, 2 H), 4.71 (s, 2 H), 4.58 (s, 2 H), 3.66 (m, 2 H), 3.54 (m, 2 H), 3.38 (s, 3 H), 2.62 (t, 2 H, J = 7 Hz), 1.70 (quint, 2 H, J = 7 Hz), 1.36 (sext, 2 H, J = 7 Hz), 1.27 (s, 9 H), 0.88 (t, 3 H, J = 7 Hz).

2-Butyl-1-[(2′-carboxybiphenyl-4-yl)methyl]-5-(hydroxymethyl)-4-(trifluoromethyl)imidazole (42). A solution of **113** (2.30 g, 4.0 mmol) in 200 mL of 1.5 M tetrafluoroboric acid/acetonitrile was stirred at 25 °C for 18 h, and the mixture then was poured into water. The resulting solution was adjusted to pH 3 employing saturated sodium bicarbonate solution and then

was extracted with chloroform. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography (elution: methanol/chloroform) provided 1.38 g (80%) of **42**: mp 198–199.5 °C; NMR (DMSO-d_6) δ 7.75 (d, 1 H, J = 8 Hz), 7.54 (t, 1 H, J = 8 Hz), 7.43 (t, 1 H, J = 8 Hz), 7.32 (m, 3 H), 7.10 (d, 2 H, J = 8 Hz), 5.36 (s, 2 H), 4.51 (s, 2 H), 2.56 (t, 2 H, J = 7 Hz), 1.56 (quint, 2 H, J = 7 Hz), 1.30 (sext, 2 H, J = 7 Hz), 0.83 (t, 3 H, J = 7 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −57.8 (s, 3 F); IR 1702 cm^{-1}. Anal. ($C_{23}H_{23}F_3N_2O_3$) C, H, N, F.

2-Butyl-1-[(2′-carbamoylbiphenyl-4-yl)methyl]-4-chloro-5-(hydroxymethyl)imidazole (6). A solution of **85** (0.24 g, 0.63 mmol), 2 mL of 10% aqueous sodium hydroxide, and 4 mL of ethanol was refluxed for 100 h. After cooling, the mixture was diluted with water, and the resulting mixture extracted with ethyl acetate. The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography (elution: ethyl acetate/benzene) provided 0.17 g (68%) of **6**: mp 155–157 °C; NMR (DMSO-d_6) δ 7.63 (br s, 1 H), 7.46–7.27 (m, 7 H), 7.09 (d, 2 H, J = 8 Hz), 5.27 (s, 2 H), 5.24 (br s, 1 H), 4.33 (d, 2 H, J = 5 Hz), 2.50 (t, 2 H, J = 7 Hz), 1.49 (quint, 2 H, J = 7 Hz), 1.25 (sext, 2 H, J = 7 Hz), 0.80 (t, 3 H, J = 7 Hz); IR 1662 cm^{-1}. Anal. ($C_{22}H_{24}ClN_3O_2$) C, H, N, Cl.

2-Butyl-1-[(2′-carbomethoxybiphenyl-4-yl)methyl]-4-chloro-5-[[(2-methoxyethoxy)methoxy]methyl]imidazole (114). The title compound was prepared from **84** by the procedure described for the preparation of **112**: NMR ($CDCl_3$) δ 7.83 (d, 1 H, J = 8 Hz), 7.52 (t, 1 H, J = 8 Hz), 7.40 (t, 1 H, J = 8 Hz), 7.28 (m, 3 H), 7.00 (d, 2 H, J = 8 Hz), 5.19 (s, 2 H), 4.68 (s, 2 H), 4.48 (s, 2 H), 3.67 (m, 2 H), 3.64 (s, 3 H), 3.54 (m, 2 H), 3.37 (s, 3 H), 2.58 (t, 2 H, J = 7 Hz), 1.67 (quint, 2 H, J = 7 Hz), 1.34 (sext, 2 H, J = 7 Hz), 0.88 (t, 3 H, J = 7 Hz).

2-Butyl-1-[(2′-carboxybiphenyl-4-yl)methyl]-4-chloro-5-[[(2-methoxyethoxy)methoxy]methyl]imidazole (115). A solution of **114** (3.15 g, 6.3 mmol, 1 equiv) and potassium methanethiolate (2.77 g, 32 mmol, 5 equiv) in 125 mL of dimethylformamide was stirred at 125 °C for 4 h. After cooling the solvent was removed under vacuum, and the residue was dissolved in water. The resulting aqueous solution was washed with diethyl ether, adjusted to pH 3 by employing 10% hydrochloric acid, and extracted with methylene chloride. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was crystallized from 1-chlorobutane to afford 2.45 g (80%) of **115**; NMR ($CDCl_3$) δ 7.95 (d, 1 H, J = 8 Hz), 7.57 (t, 1 H, J = 8 Hz), 7.46 (t, 1 H, J = 8 Hz), 7.38 (m, 3 H), 7.05 (d, 2 H, J = 8 Hz), 5.22 (s, 2 H), 4.64 (s, 2 H), 4.48 (s, 2 H), 3.58 (m, 4 H), 3.40 (s, 3 H), 2.54 (t, 2 H, J = 7 Hz), 1.60 (quint, 2 H, J = 7 Hz), 1.32 (sext, 2 H, J = 7 Hz), 0.84 (t, 3 H, J = 7 Hz).

2-Butyl-4-chloro-1-[[2′-[(methoxyamino)carbonyl]biphenyl-4-yl]methyl]-5-[[(2-methoxyethoxy)methoxy]methyl]imidazole (116). A solution of oxalyl chloride (0.24 mL, 2.75 mmol, 1.1 equiv) in 5 mL of chloroform was added dropwise to a solution of 1 mL of dimethylformamide and 4 mL of chloroform at −20 °C. After this solution had been stirred at −20 °C for 0.35 h, *N*-methylmorpholine (0.28 mL, 2.50 mmol, 1.0 equiv) was added followed by **115** (1.21 g, 2.48 mmol, 1.0 equiv). After an additional 0.35 h at −20 °C, *N*-methylmorpholine (0.55 mL, 5.00 mmol, 2.0 equiv) and methoxyamine (1.35 mL, 25 mmol, 10 equiv) were added to the mixture. The reaction mixture was warmed slowly to 25 °C, stirred at 25 °C for 4 h, and then refluxed for 40 h. After cooling the mixture was diluted with ethyl acetate. The resulting solution was washed with 10% hydrochloric acid, water, 10% aqueous sodium bicarbonate solution, and brine. The solution then was dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography (elution: methanol/chloroform) furnished 0.21 g (16%) of **116**: NMR ($CDCl_3$) δ 7.85 (s, 1 H), 7.63 (d, 1 H, J = 8 Hz), 7.53–7.33 (m, 5 H), 7.05 (d, 2 H, J = 8 Hz), 5.20 (s, 2 H), 4.67 (s, 2 H), 4.47 (s, 2 H), 3.63 (m, 5 H), 3.55 (m, 2 H), 3.36 (s, 3 H), 2.56 (t, 2 H, J = 7 Hz), 1.67 (m, 2 H), 1.32 (m, 2 H), 0.87 (t, 3 H, J = 7 Hz); IR 1667 cm^{-1}.

2-Butyl-4-chloro-5-(hydroxymethyl)-1-[[2′-[(methoxyamino)carbonyl]biphenyl-4-yl]methyl]imidazole (8). The title compound was prepared from **116** by the procedure described for the preparation of **42**: NMR ($CDCl_3$) δ 11.31 (br s, 1 H), 7.48 (m, 1 H), 7.41–7.33 (m, 5 H), 7.09 (d, 2 H, J = 8 Hz), 5.27 (br s, 3 H), 4.32 (d, 2 H, J = 5 Hz), 3.44 (s, 3 H), 2.49 (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 1657 cm^{-1}. Anal. ($C_{23}H_{26}ClN_3O_3$) C, H, N, Cl.

2-Butyl-4-chloro-1-[[2′-[[(*N*,*N*-diphenylcarbamoyl)oxy]carbonyl]biphenyl-4-yl]methyl]-5-(hydroxymethyl)imidazole (117). A solution of **2** (3.99 g, 10 mmol, 1.0 equiv) and 1.00 N aqueous sodium hydroxide (10 mL, 10 mmol, 1.0 equiv) in 60 mL of methanol was added dropwise over 0.25 h to a solution of *N*-(*N*,*N*-diphenylcarbamoyl)pyridinium chloride[36] (3.73 g, 12 mmol, 1.2 equiv) in 30 mL of methanol at 25 °C. The resulting mixture was stirred at 25 °C for 0.75 h and then was diluted with ethyl acetate. This organic solution was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated to afford 6.55 g of crude **117**, which was used in the following reaction without further purification.

1-[[2′-(Benzenesulfonamidocarbonyl)biphenyl-4-yl]methyl]-2-butyl-4-chloro-5-(hydroxymethyl)imidazole (10). A solution of benzenesulfonamide (9.53 g, 60 mmol, 6.0 equiv) in 25 mL of dimethylformamide was added dropwise over 0.25 h to a suspension of oil-free sodium hydride (1.32 g, 55 mmol, 5.5 equiv) in 30 mL of dimethylformamide at 25 °C. The resulting mixture was stirred at 25 °C for 1 h. To the mixture was added a solution of crude **117** (6.55 g, 10 mmol, 1.0 equiv) in 15 mL of dimethylformamide. The reaction mixture then was stirred at 25 °C for 16 h. At this point the mixture was diluted with water, adjusted to pH 5 employing 10% hydrochloric acid, 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 (elution: 10% methanol/chloroform) furnished 1.54 g (29% overall from **2**) of **10**: mp 172–174 °C; NMR (DMSO-d_6) δ 12.55 (br s, 1 H), 7.82 (d, 1 H, J = 8 Hz), 7.62–7.33 (m, 7 H), 7.03 (d, 2 H, J = 8 Hz), 6.77 (d, 2 H, J = 8 Hz), 5.30 (br t, 1 H, J = 4 Hz), 5.23 (s, 2 H), 4.38 (d, 2 H, J = 4 Hz), 2.50 (t, 2 H, J = 7 Hz), 1.51 (quint, 2 H, J = 7 Hz), 1.27 (sext, 2 H, J = 7 Hz), 0.82 (t, 3 H, J = 7 Hz); IR 1170, 1352, 1708 cm^{-1}. Anal. ($C_{28}H_{28}ClN_3O_4S\cdot0.5H_2O$) C, H, N, Cl.

2-*n*-Butyl-4-chloro-5-(methoxymethyl)-1-[[2′-[[(1*H*-tetrazol-5-yl)amino]carbonyl]biphenyl-4-yl]methyl]imidazole (24). A solution of **5** (0.70 g, 1.7 mmol, 1 equiv), thionyl chloride (1.24 mL, 17 mmol, 10 equiv), and 10 mL of chloroform was refluxed for 2.5 h. The solvent and excess thionyl chloride were removed under vacuum, and the residue was concentrated twice from toluene to afford 0.82 g of the acid chloride as a brown oil: IR 1784 cm^{-1}.

The above acid chloride was dissolved in 50 mL of tetrahydrofuran, and the resulting solution was dripped into a solution of 5-aminotetrazole (0.175 g, 1.7 mmol, 1 equiv) in 1.000 N aqueous sodium hydroxide (3.40 mL, 3.40 mmol, 2 equiv) at 0 °C. The resulting mixture was stirred for 16 h at 25 °C. Another 1 equiv of 5-aminotetrazole in 1.000 N aqueous sodium hydroxide was then added, and the solution was stirred for another 24 h. The solution was adjusted to pH 3 with concentrated hydrochloric acid and then was extracted with ethyl acetate (1X). The organic layer was washed with water (3X) and brine (1X) and dried over anhydrous magnesium sulfate, and the solvent was removed under vacuum to provide 0.84 g of a yellow glass. Column chromatography (0–100% ethyl acetate/ethanol) furnished 0.39 g of a tan glass. Recrystallization from 1-chlorobutane provided 0.104 g (13%) of **24**: mp 169.0–173.0 °C; NMR (DMSO-d_6) δ 7.73–7.30 (m, 6 H), 7.00 (d, 2 H, J = 7 Hz), 5.18 (s, 2 H), 4.23 (s, 2 H), 2.55 (t, 2 H, J = 7 Hz), 1.63 (quint, 2 H, J = 7 Hz), 1.31 (sext, 2 H, J = 7 Hz), 0.84 (t, 3 H, J = 7 Hz). Anal. ($C_{24}H_{26}ClN_7O_2\cdot0.5H_2O\cdot0.1C_4H_9Cl$) C, H, Cl.

2-Butyl-4-chloro-1-[[2′-(hydrazinocarbonyl)biphenyl-4-yl]methyl]-5-(methoxymethyl)imidazole (118). A solution of **91** (2.00 g, 4.7 mmol, 1 equiv), hydrazine (1.5 mL, 46.8 mmol, 10 equiv), and 30 mL of methanol was refluxed for 72 h, after which 1.5 mL of additional hydrazine was added and the reaction mixture was refluxed for another 24 h. Once again hydrazine (1.5 mL) was added, and the reaction was refluxed for a final 24 h. The reaction was worked up by first removing the hydrazine and methanol under vacuum, followed by dissolving the residue in ethyl acetate (200 mL) and washing it with water (3 × 100 mL).

The organic layer was dried over anhydrous magnesium sulfate, and the solvent was removed under vacuum to afford 1.37 g (62%) of **118** as a white glass: NMR ($CDCl_3$) δ 7.67–7.32 (m, 4 H), 7.40 (d, 2 H, J = 9 Hz), 7.03 (d, 2 H, J = 9 Hz), 7.56 (br s, 1 H), 5.17 (s, 2 H), 4.27 (s, 2 H), 3.25 (s, 3 H), 2.57 (t, 2 H, J = 7 Hz), 1.70 (quint, 2 H, J = 7 Hz), 1.34 (sext, 2 H, J = 7 Hz), 0.86 (t, 3 H, J = 7 Hz). Anal. ($C_{23}H_{27}ClN_4O_2$) C, H, N.

2-Butyl-4-chloro-5-(methoxymethyl)-1-[[2′-[[(trifluoromethanesulfonyl)hydrazo]carbonyl]biphenyl-4-yl]methyl]imidazole (11). A solution of trifluoromethanesulfonic anhydride (0.42 mL, 2.5 mmol, 1.5 equiv) in 2 mL of methylene chloride was slowly dripped into a stirred solution at −78 °C of **118** (0.71 g, 1.7 mmol, 1 equiv), triethylamine (0.35 mL, 2.5 mmol, 1.5 equiv), and 5 mL methylene chloride. The solution was stirred at −78 °C for 1 h and then was allowed to warm to 25 °C. After 2 h at 25 °C, water (100 mL) was added, the solution adjusted to pH 5, and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The organic layers were dried over anhydrous magnesium sulfate and filtered, the solvent was removed under vacuum, and the residue was purified by column chromatography (elution: 50–100% ethyl acetate/hexane) to afford 0.38 g (40%) of **11** as a light yellow glass: NMR ($CDCl_3$) δ 7.82–7.15 (m, 8 H), 6.94 (d, 2 H, J = 8 Hz), 5.13 (s, 2 H), 4.25 (s, 2 H), 3.17 (s, 3 H), 2.53 (t, 2 H, J = 7 Hz), 1.69 (quint, 2 H, J = 7 Hz), 1.27 (sext, 2 H, J = 7 Hz), 0.81 (t, 3 H, J = 7 Hz); FABMS calcd 559.15, found 559.15. Anal. ($C_{24}H_{26}ClF_3N_4O_4S{\cdot}0.5H_2O{\cdot}0.4C_4H_8O_2$) C, H, N, Cl, F, S.

2-Butyl-4-chloro-5-(hydroxymethyl)-1-[(2′-nitrobiphenyl-4-yl)methyl]imidazole (119). The title compound was prepared from 2-butyl-4(5)-chloro-5(4)-(hydroxymethyl)-imidazole[19] and **81** by the procedure described for the preparation of **84**: NMR ($CDCl_3$) δ 7.82 (d, 1 H, J = 8 Hz), 7.58 (t, 1 H, J = 8 Hz), 7.44 (t, 1 H, J = 8 Hz), 7.35 (d, 1 H, J = 8 Hz), 7.27 (d, 2 H, J = 8 Hz), 7.05 (d, 2 H, J = 8 Hz), 5.21 (s, 2 H), 4.46 (s, 2 H), 2.57 (t, 2 H, J = 7 Hz), 1.65 (quint, 2 H, J = 7 Hz), 1.33 (sext, 2 H, J = 7 Hz), 0.86 (t, 3 H, J = 7 Hz).

2-Butyl-4-chloro-5-(methoxymethyl)-1-[(2′-nitrobiphenyl-4-yl)methyl]imidazole (120). A solution of **119** (4.30 g, 10.8 mmol), concentrated hydrochloric acid (0.85 mL), and 200 mL of methanol was refluxed for 20 h. After cooling the solvent was removed under vacuum, and the residue was dissolved in water. This aqueous solution was adjusted to pH 7 with aqueous sodium bicarbonate solution and then was extracted with methylene chloride. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated to furnish 4.40 g (99%) of **120**: NMR ($CDCl_3$) δ 7.88 (d, 1 H, J = 8 Hz), 7.63 (t, 1 H, J = 8 Hz), 7.50 (t, 1 H, J = 8 Hz), 7.42 (d, 1 H, J = 8 Hz), 7.30 (d, 2 H, J = 8.5 Hz), 7.05 (d, 2 H, J = 8.5 Hz), 5.20 (s, 2 H), 4.30 (s, 2 H), 3.27 (s, 3 H), 2.59 (t, 2 H, J = 7 Hz), 1.67 (quint, 2 H, J = 7 Hz), 1.35 (sext, 2 H, J = 7 Hz), 0.87 (t, 3 H, J = 7 Hz).

1-[(2′-Aminobiphenyl-4-yl)methyl]-2-butyl-4-chloro-5-(methoxymethyl)imidazole (121). A mixture of **120** (4.40 g, 10.6 mmol, 1.0 equiv), iron powder (2.10 g, 37.6 mmol, 3.5 equiv), glacial acetic acid (4.25 mL, 74.2 mmol, 7 equiv), and 200 mL of methanol was refluxed for 5 h. After cooling the solvent was removed under vacuum, and the residue was dissolved in ethyl acetate. The precipitated iron salts were removed by filtration through Celite, and the filtrate was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography (elution: 10–30% ethyl acetate/benzene) provided 2.95 g (72%) of **121**: NMR ($CDCl_3$) δ 7.43 (d, 1 H, J = 8 Hz), 7.19–7.04 (m, 4 H), 6.80 (m, 2 H), 5.19 (s, 2 H), 4.33 (s, 2 H), 3.70 (br s, 1 H), 3.28 (s, 3 H), 2.59 (t, 2 H, J = 7 Hz), 1.67 (quint, 2 H, J = 7 Hz), 1.34 (sext, 2 H, J = 7 Hz), 0.87 (t, 3 H, J = 7 Hz).

2-Butyl-4-chloro-5-(methoxymethyl)-1-[[2′-(trifluoromethanesulfonamido)biphenyl-4-yl]methyl]imidazole (14). To a solution of **121** (2.95 g, 7.68 mmol, 1.0 equiv) and triethylamine (1.07 mL, 7.68 mmol, 1.0 equiv) in 30 mL of methylene chloride at −78 °C was added trifluoromethanesulfonic anhydride (2.59 mL, 15.4 mmol, 2.0 equiv) dropwise so as to maintain the reaction temperature below −50 °C. Following the addition, the reaction mixture was allowed to warm slowly to 25 °C. At this point the mixture was poured into dilute aqueous acetic acid. The resulting suspension was stirred vigorously for several minutes and then was extracted with methylene chloride. The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography (elution: 20–50% ethyl acetate/benzene) afforded 0.80 g (20%) of **14**: mp 148–150 °C; NMR ($CDCl_3$) δ 7.60 (d, 1 H, J = 8 Hz), 7.44–7.27 (m, 5 H), 7.07 (d, 2 H, J = 8 Hz), 5.20 (s, 2 H), 4.29 (s, 2 H), 3.27 (s, 3 H), 2.57 (t, 2 H, J = 7 Hz), 1.65 (quint, 2 H, J = 7 Hz), 1.35 (sext, 2 H, J = 7 Hz), 0.88 (t, 3 H, J = 7 Hz); IR 1206, 1376 cm^{-1}. Anal. ($C_{23}H_{25}ClF_3N_3O_3S$) C, H, N.

2-Butyl-4-chloro-5-(hydroxymethyl)-1-[[2′-(trifluoromethanesulfonamido)biphenyl-4-yl]methyl]imidazole (13). A solution of **14** (0.46 g, 0.9 mmol), 0.5 mL of concentrated sulfuric acid, 5 mL of glacial acetic acid, 5 mL of water, and 10 mL of tetrahydrofuran was refluxed for 8 h. After cooling the solvent was removed under vacuum, and the residue was dissolved in water. This aqueous solution was adjusted to pH 7 by employing aqueous sodium bicarbonate solution and then was extracted with methylene chloride. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography (elution: methanol/chloroform) furnished 0.26 g (58%) of **13**: mp 171–172 °C; NMR (DMSO-d_6/$CDCl_3$) δ 10.60 (br s, 1 H), 7.56 (m, 1 H), 7.42–7.32 (m, 5 H), 7.09 (d, 2 H, J = 8 Hz), 5.30 (s, 2 H), 4.85 (br s, 1 H), 4.45 (d, 2 H, J = 4 Hz), 2.56 (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 1206, 1375 cm^{-1}. Anal. ($C_{22}H_{23}ClF_3N_3O_3S{\cdot}0.5H_2O$) C, H, N.

2-Butyl-4-chloro-1-[[2′-(hydroxymethyl)biphenyl-4-yl]methyl]-5-(methoxymethyl)imidazole (122). To a solution of **91** (5.62 g, 13 mmol, 1 equiv) in tetrahydrofuran was slowly added a 1.0 M lithium aluminum hydride solution in tetrahydrofuran (39.5 mL, 39 mmol, 3 equiv). The resultant mixture was refluxed for 2 h and worked up by the Steinhardt procedure (Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; John Wiley and Sons: New York, 1967; p 584) to furnish 4.68 g (90%) of **122** as a light yellow oil that slowly crystallized: NMR ($CDCl_3$) δ 7.57 (br d, 1 H, J = 7 Hz), 7.47–7.20 (m, 5 H), 7.03 (d, 2 H, J = 9 Hz), 5.18 (s, 2 H), 4.58 (s, 2 H), 4.32 (s, 2 H), 3.28 (s, 3 H), 2.60 (t, 2 H, J = 7 Hz), 1.67 (quint, 2 H, J = 7 Hz), 1.35 (sext, 2 H, J = 7 Hz), 0.86 (t, 3 H, J = 7 Hz). Anal. ($C_{23}H_{27}ClN_2O_2$) C, H, Cl.

2-Butyl-4-chloro-1-[[2′-(cyanomethyl)biphenyl-4-yl]methyl]-5-(methoxymethyl)imidazole (123). A solution of **122** (4.68 g, 12.0 mmol, 1 equiv), thionyl chloride (4.38 mL, 60 mmol, 5 equiv), and 100 mL of chloroform was stirred at 25 °C for 2 h. The solvent and excess thionyl chloride were removed under vacuum, and the residue was concentrated twice from toluene. The residue was dissolved in 100 mL of DMSO, and sodium cyanide (3.53 g, 72 mmol, 6 equiv) was added. The mixture was stirred for 24 h at 25 °C. Water (250 mL) was added, and the solution was extracted with ethyl acetate (3X). The organic layers were combined, dried over anhydrous magnesium sulfate, and filtered, and the solvent was removed under vacuum to provide 5.20 g of **123** as a brown oil, which was used without purification in the next step: NMR ($CDCl_3$) δ 7.54 (m, 1 H), 7.40 (m, 2 H), 7.28 (m, 3 H), 7.08 (d, 2 H, J = 10 Hz), 5.23 (s, 2 H), 4.33 (s, 2 H), 3.63 (s, 2 H), 3.30 (s, 3 H), 2.60 (t, 2 H, J = 7 Hz), 1.70 (quint, 2 H, J = 7 Hz), 1.37 (sext, 2 H, J = 7 Hz), 0.90 (t, 3 H, J = 7 Hz); high-resolution MS calcd 407.1764, found 407.1778.

2-Butyl-4-chloro-1-[[2′-[(1*H*-tetrazol-5-yl)methyl]biphenyl-4-yl]methyl]-5-(methoxymethyl)imidazole (23). A mixture of **123** (5.20 g, 13.0 mmol, 1 equiv), sodium azide (2.49 g, 38 mmol, 3 equiv), ammonium chloride (2.03 g, 38 mmol, 3 equiv), and dimethylformamide was heated at 100 °C for 48 h. The reaction was cooled to room temperature, and 1 equiv each of sodium azide and ammonium chloride were added; heating was resumed for another 24 h. The reaction was cooled to room temperature, the inorganic salts were filtered, and the dimethylformamide was removed under vacuum. The residue was taken up in water and ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate (2X). The organic layers were collected, dried over anhydrous magnesium sulfate, and filtered. The solvent was removed under vacuum, and the residue was purified by column chromatography (elution: 1:1 hexane/ethyl acetate to 1:1 ethyl acetate/2-propanol) to afford 3.13 g (58% overall from **122**) of **23** as a light yellow solid: mp 149.0–152.5 °C; NMR ($CDCl_3$) δ 7.37–7.15 (m, 6 H), 6.96 (d, 2 H,

J = 9 Hz), 5.18 (s, 2 H), 4.30 (s, 2 H), 4.24 (s, 2 H), 3.27 (s, 3 H), 2.57 (t, 2 H, J = 7 Hz), 1.56 (quint, 2 H, J = 7 Hz), 1.28 (sext, 2 H, J = 7 Hz), 0.77 (t, 3 H, J = 7 Hz). Anal. ($C_{24}H_{27}ClN_6O$) C, H, Cl.

N-(2-Cyanoethyl)-4'-methylbiphenyl-2-carboxamide (124). A solution of **74** (50.00 g, 236 mmol, 1 equiv), thionyl chloride (87.5 mL, 1200 mmol, 5.1 equiv), and 500 mL of chloroform was refluxed for 4 h. The solvent was removed under vacuum, and the residue was concentrated twice from toluene to remove traces of thionyl chloride. The acid chloride thus obtained was dissolved in 250 mL of tetrahydrofuran. This solution was added dropwise in five equal portions, alternating with five equal portions of 1.000 N aqueous sodium hydroxide (236 mL, 236 mmol, 1 equiv), into a solution of 2-aminopropionitrile fumarate (30.25 g, 236 mmol, 1 equiv) in 1.000 N aqueous sodium hydroxide (236 mL, 236 mmol, 1 equiv) at 0 °C. After 12 h at 25 °C, water (250 mL) was added, and the mixture was extracted with ethyl acetate (3 × 500 mL). The organic layers were collected, dried over anhydrous magnesium sulfate, and filtered, and the solvent was removed under vacuum. The residue was recrystallized from methylcyclohexane to furnish 53.50 g (86%) of **124** as a white solid: mp 102.0–103.5 °C. NMR ($CDCl_3$) δ 7.68 (d, 1 H, J = 7 Hz), 7.56–7.19 (m, 7 H), 5.65 (br m, 1 H), 3.43 (quart, 2 H, J = 7 Hz), 2.39 (t, 2 H, J = 7 Hz). Anal. ($C_{17}H_{16}N_2O$) C, H, N.

N^3-(2-Cyanoethyl)-4'-methylbiphenyl-2-carboxamidrazone (125). A mixture of **124** (35.5 g, 126.7 mmol, 1 equiv) and phosphorus pentachloride (29.01 g, 139.3 mmol, 1.1 equiv) was gently heated under water-aspirator vacuum with a heat gun to maintain a slow but constant evolution of gas. After gas evolution had stopped (15–30 min), the resultant oil was dissolved in 300 mL of dioxane, and hydrazine (20.09 mL, 633.7 mmol, 5 equiv) was slowly added thereto. The resultant biphasic mixture was stirred for 16 h at 25 °C. The solvent was removed under vacuum, and the residue was partitioned between water and ethyl acetate. The organic layers were combined, dried over anhydrous magnesium sulfate, and filtered, and the solvent was removed under vacuum to provide an orange glass. Slurrying this glass in 1:1 hexane/ethyl acetate afforded 16.14 g (46%) of **125** as a light pink solid: mp 146.5–147.0 °C; NMR ($CDCl_3$) δ 7.60–7.16 (m, 10 H), 6.15 (m, 1 H), 2.98 (quart, 2 H, J = 7 Hz), 2.40 (s, 3 H), 1.93 (t, 2 H, J = 7 Hz). Anal. ($C_{17}H_{18}N_4 \cdot 0.1N_2H_4$) C, H, N.

3-(4'-Methylbiphenyl-2-yl)-5-(trifluoromethyl)-1,2,4-triazole (126). To 600 mL of trifluoroacetic anhydride at 0 °C was added **125** (14.91 g, 53.6 mmol). The mixture was allowed to warm to 25 °C and was stirred at 25 °C for 18 h. The solvent was removed under vacuum, and the residue was taken up in ethyl acetate. The solution was washed with 1 N aqueous sodium hydroxide (3×) and brine, dried over anhydrous magnesium sulfate, and filtered, and the solvent was removed under vacuum to provide 18.0 g (50.6 mmol) of a pink solid. This solid, without purification, was dissolved in 300 mL of tetrahydrofuran to which was added 1.000 N aqueous sodium hydroxide (55.6 mL, 55.6 mmol, 1 equiv). The mixture was allowed to stir at 25 °C for 5 h. The solvents were removed under vacuum, and water was added. This mixture was extracted with ethyl acetate (3×). The organic layers were combined, dried over anhydrous magnesium sulfate, and filtered, and the solvent was removed under vacuum to afford 15.8 g of an orange oil, which subsequently crystallized. These solids were dissolved in 1 N aqueous sodium hydroxide, the insoluble matter was filtered, and the clear filtrate was acidified to pH 1. The filtrate was extracted with ethyl acetate (3×). The organic layers were combined, dried over anhydrous magnesium sulfate, and filtered, and the solvent was removed under vacuum to furnish 13.5 g (83%) of **126** as a clear colorless oil, which subsequently crystallized: mp 113.5–115.5 °C; NMR ($CDCl_3$) δ 9.86 (m, 1 H), 8.53 (m, 2 H), 8.28 (m, 1 H), 7.37 (m, 1 H), 7.34 (d, 2 H, J = 9 Hz), 2.42 (s, 3 H). Anal. ($C_{16}H_{12}F_3N_3$) C, H, N.

3-(4'-Methylbiphenyl-2-yl)-5-(trifluoromethyl)-N-(triphenylmethyl)-1,2,4-triazole (127). A solution of **126** (10.9 g, 35.9 mmol, 1 equiv), triphenylmethyl bromide (11.62 g, 35.9 mmol, 1 equiv), triethylamine (5.00 mL, 35.9 mmol, 1 equiv), 150 mL of methylene chloride, and 100 mL of dimethylformamide was stirred at 25 °C for 18 h. The solvent was removed under vacuum, and the residue was dissolved in ethyl acetate. The resulting solution was washed with 1 N aqueous sodium hydroxide (2×), dried over anhydrous magnesium sulfate, and filtered, and the solvent was removed under vacuum. The residue was chromatographed (elution: 5% ethyl acetate/hexane) to afford 17.24 g of a white solid. Recrystallization of the solid from methylcyclohexane provided 13.41 g (68%) of **127**: mp 171.0–174.5 °C; NMR ($CDCl_3$) δ 7.32–6.93 (m, 17 H), 6.66 (d, 6 H, J = 9 Hz), 2.55 (s, 3 H). Anal. ($C_{35}H_{26}N_3F_3$) C, H, N.

2-Butyl-4-chloro-5-(hydroxymethyl)-1-[[2'-[5-(trifluoromethyl)-1,2,4-triazol-3-yl]biphenyl-4-yl]methyl]imidazole (21). The title compound was prepared from **127** and 2-butyl-4(5)-chloro-5(4)-(hydroxymethyl)imidazole[19] by the procedures described for the preparations of **79**, **84**, and **17**: NMR ($CDCl_3$) δ 12.67 (br s, 1 H), 7.88 (d, 1 H, J = 9 Hz), 7.55 (t, 1 H, J = 9 Hz), 7.47 (t, 1 H, J = 9 Hz), 7.37 (d, 1 H, J = 9 Hz), 7.10 (d, 2 H, J = 9 Hz), 6.92 (d, 2 H, J = 9 Hz), 5.16 (s, 2 H), 4.39 (s, 2 H), 2.45 (t, 2 H, J = 7 Hz), 1.53 (quint, 2 H, J = 7 Hz), 1.25 (sext, 2 H, J = 7 Hz), 0.82 (t, 3 H, J = 7 Hz). Anal. ($C_{24}H_{23}ClF_3N_5O$) C, H, Cl.

4'-Methylbiphenyl-2-carboxaldehyde (128). To a solution of **69** (49.5 g, 217 mmol, 1.0 equiv) in toluene at −78 °C was added dropwise over 0.5 h diisobutylaluminum hydride (1.0 M in toluene, 544 mL, 544 mmol, 2.5 equiv) such that the reaction temperature remained below −70 °C. Following the addition, the mixture was stirred at −78 °C for 0.25 h, after which methanol was added cautiously (24.7 mL). When gas evolution had ceased, the mixture was poured into a solution of aqueous potassium sodium tartrate (247 mL of saturated solution + 1482 mL of water). The mixture was stirred until an extractable solution was obtained. The layers were separated, and the aqueous layer was extracted with diethyl ether (2×). The combined organic layers were dried over anhydrous magnesium sulfate and filtered, and the solvent was removed under vacuum to afford 42.55 g of the alcohol as a light yellow oil which crystallized overnight: mp 54.0–57.0 °C; NMR ($CDCl_3$) δ 7.56–7.16 (m, 8 H), 4.59 (s, 2 H), 2.40 (s, 3 H), 1.74 (s, 1 H).

This alcohol intermediate was subsequently oxidized by treatment with pyridinium chlorochromate (69.39 g, 320 mmol, 1.5 equiv) in 400 mL of methylene chloride at 25 °C for 0.5 h. The solvent was decanted, and the residual tar was washed with several portions of ethyl ether. The organic portions were combined, filtered through a pad of Florisil, dried over anhydrous magnesium sulfate, and filtered, and the solvent was removed under vacuum. Column chromatography (elution: 10% ethyl acetate/hexane) to provided 38.8 g (91%) of **128** as a light yellow oil, which was of sufficient purity to be used in the next step: NMR ($CDCl_3$) δ 9.98 (s, 1 H), 8.01 (d, 1 H, J = 7 Hz), 7.64 (t, 1 H, J = 7 Hz), 7.53–7.38 (m, 2 H), 7.28–7.17 (m, 4 H), 2.43 (s, 3 H).

2-(4'-Methylbiphenyl-2-yl)-1-(benzenesulfonyl)acrylonitrile (129). A solution of **128** (6.00 g, 30.6 mmol, 1 equiv), (benzenesulfonyl)acetonitrile[38] (5.54 g, 30.6 mmol, 1 equiv), piperidine (0.5 mL), dimethylformamide, and 40 mL of benzene was refluxed in a Dean–Stark apparatus for 18 h. The solvents were removed under vacuum, and the residue was chromatographed (elution: 25% ethyl acetate/hexane) to provide 9.86 g (90%) of **129** as a light yellow solid: mp 91.0–93.0 °C; NMR ($CDCl_3$) δ 8.20 (s, 1 H), 8.08 (d, 1 H, J = 9 Hz), 7.95 (d, 2 H, J = 9 Hz), 7.77–7.17 (m, 8 H), 7.08 (d, 2 H, J = 9 Hz), 2.42 (s, 3 H). Anal. ($C_{22}H_{17}NO_2S$) C, H, S.

5-Cyano-4-(4'-methylbiphenyl-2-yl)-1,2,3-triazole (130). A solution of **129** (8.51 g, 23.7 mmol, 1 equiv), sodium azide (1.53 g, 23.7 mmol, 1 equiv), and dimethylformamide was stirred at 100 °C for 2.5 h. After cooling, the reaction mixture was poured into water, and the resulting mixture was extracted with ethyl acetate (3×). The aqueous layer then was saturated with sodium chloride and reextracted with ethyl acetate (2×). The ethyl acetate layers were combined, dried over anhydrous magnesium sulfate, and filtered, and the solvent was removed under vacuum. Column chromatography (elution: ethyl acetate) furnished 6.21 g of a clear, colorless oil, which subsequently crystallized. Recrystallization from acetonitrile afforded 3.59 g (58%) of **130** as white crystals: mp 170.5–172.0 °C; NMR (DMSO-d_6) δ 7.72–7.49 (m, 4 H), 7.15 (d, 2 H, J = 9 Hz), 6.98 (d, 2 H, J = 9 Hz), 2.29 (s, 3 H). Anal. ($C_{16}H_{12}N_4$) C, H, N.

2-Butyl-4-chloro-1-[[2'-(5-cyano-1,2,3-triazol-4-yl)biphenyl-4-yl]methyl]-5-(hydroxymethyl)imidazole (19). The

title compound was prepared from **130** and 2-butyl-4(5)-chloro-5(4)-(hydroxymethyl)imidazole[19] by the procedures described for the preparations of **127**, **79**, **84**, and **17**: NMR ($CDCl_3$) δ 7.66–7.44 (m, 4 H), 7.15 (d, 2 H, J = 9 Hz), 6.95 (d, 2 H, J = 9 Hz), 5.25 (s, 2 H), 4.50 (s, 2 H), 2.55 (t, 2 H, J = 7 Hz), 1.55 (quint, 2 H, J = 7 Hz), 1.27 (sext, 2 H, J = 7 Hz), 0.80 (t, 3 H, J = 7 Hz). Anal. ($C_{24}H_{23}ClN_6O$) C, H, Cl.

2-[2-Fluoro-1-hydroxy-2-(benzenesulfonyl)ethyl]-4′-methylbiphenyl (131). Fluoromethyl phenylsulfone[39] (5.00 g, 28.7 mmol, 1 equiv) was dissolved in 25 mL of tetrahydrofuran, and the solution was cooled to −78 °C. n-Butyllithium (2.5 M in hexane, 11.48 mL, 28.7 mmol, 1 equiv) was added dropwise, and the reaction mixture turned dark brown. The mixture was stirred for 2 h at −78 °C, **128** (5.63 g, 28.7 mmol, 1 equiv) was added, and the reaction mixture was stirred at −78 °C for another 2 h. Methanol (20 mL) was added as a quench, followed by ethyl acetate (200 mL) and water (200 mL). The layers were separated. The organic layer was washed with water (2 × 200 mL) and dried over anhydrous magnesium sulfate, and the solvent was removed under vacuum to furnish 10.66 g of **131** as an amber oil, which was used in the next step without further purification: NMR (DMSO-d_6) δ 8.00–7.00 (m, 13 H), 6.20–4.90 (m, 3 H), 2.42 (s, $^1/_2$ × 3 H), 2.38 (s, $^1/_2$ × 3 H).

2-[2-Fluoro-2-(benzenesulfonyl)ethen-1-yl]-4′-methylbiphenyl (132). A solution of **131** (10.66 g, 28.8 mmol, 1 equiv), methanesulfonyl chloride (2.45 mL, 31.7 mmol, 1.1 equiv), triethylamine (10.03 mL, 71.9 mmol, 2.5 equiv), and methylene chloride (25 mL) was stirred at 25 °C. A sudden increase in reaction temperature was observed, and a precipitate formed almost immediately. After 24 h, ethyl acetate (200 mL) was added, and this mixture was rinsed with 1 N hydrochloric acid (3 × 200 mL). The organic layer was dried over anhydrous magnesium sulfate, and the solvent was removed under vacuum to afford a dark amber oil. Flash chromatography (elution: 0–25% ethyl acetate/pentane) provided 7.72 g of an off-white oil. Trituration of the oil with pentane furnished 5.26 g of **132** as a white solid. A second crop afforded an additional 0.43 g of **132** (total yield 56%): mp 83.0–90.0 °C; NMR (DMSO-d_6) δ 7.93 (d, 2 H, J = 8 Hz), 7.90–7.40 (m, 7 H), 7.31 (d, 2 H, J = 8 Hz), 7.20 (d, 2 H, J = 8 Hz), 7.10 (s, $^1/_2$ × 1 H), 7.00 (s, $^1/_2$ × 1 H), 2.40 (s, 3 H). Anal. ($C_{21}H_{17}FO_2S$) C, H, N, F.

5-Fluoro-4-(4′-methylbiphenyl-2-yl)-1,2,3-triazole (133). A solution of **132** (5.32 g, 15.1 mmol, 1 equiv), sodium azide (1.96 g, 30.2 mmol, 2 equiv), and dimethylformamide (30 mL) was heated at 100 °C with stirring for 70 h. After cooling, ethyl acetate (300 mL) was added, and the mixture was washed with water (3 × 200 mL). The organic layer was dried over anhydrous magnesium sulfate, and the solvent was removed under vacuum to provided 0.58 g (15%) of **133** as a yellow oil: NMR ($CDCl_3$) δ 7.62 (d, 1 H, J = 8 Hz), 7.58–7.35 (m, 3 H), 7.15 (d, 2 H, J = 8 Hz), 2.37 (s, 3 H). Anal. ($C_{15}H_{12}N_3F$) C, H, N, F.

2-Butyl-4-chloro-1-[[2′-(5-fluoro-1,2,3-triazol-4-yl)biphenyl-4-yl]methyl]imidazole-5-carboxaldehyde (22). The title compound was prepared from **88** and **133** by the procedures described for the preparations of **127**, **79**, **89**, and **17**: NMR ($CDCl_3$) δ 11.25 (br s, 1 H), 9.78 (s, 1 H), 7.60 (d, 1 H, J = 8 Hz), 7.58–7.35 (m, 3 H), 7.18 (d, 2 H, J = 8 Hz), 7.00 (d, 2 H, J = 8 Hz), 5.58 (s, 2 H), 2.65 (t, 2 H, J = 7 Hz), 1.68 (quint, 2 H, J = 7 Hz), 1.36 (sext, 2 H, J = 7 Hz), 0.90 (t, 3 H, J = 7 Hz). Anal. ($C_{23}H_{21}ClFN_5O\cdot0.8H_2O\cdot0.1C_4H_8O_2$) C, H, N, Cl, F.

Ethyl 3-(4-Methylphenyl)-3-oxo-2-(2-propenyl)propanoate (134). Sodium metal (7.43 g, 323 mmol, 1.05 equiv) was allowed to dissolve in 250 mL of ethanol. To this solution was added ethyl 3-(4-methylphenyl)-3-oxopropanoate[40] (63.66 g, 309 mmol, 1.00 equiv). The ethanol was removed under vacuum, and the residue was dissolved in 250 mL of dimethylformamide. Allyl bromide (29.3 mL, 338 mmol, 1.10 equiv) and then sodium iodide (4.56 g, 304 mmol, 1.00 equiv) were added, and the contents were stirred for 18 h at 25 °C. The dimethylformamide was removed under vacuum. The residue was diluted with water, and the mixture was extracted with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate and filtered, and the solvent was removed under vacuum to afford 74.21 g (98%) of **134** as an amber oil: NMR ($CDCl_3$) δ 7.81 (d, 2 H, J = 10 Hz), 7.30 (d, 2 H, J = 10 Hz), 5.96–5.72 (m, 1 H), 5.21–5.00 (m, 2 H), 4.41 (t, 1 H, J = 7 Hz), 4.16 (quart, 2 H, J = 7 Hz), 2.78 (t, 2 H, J = 7 Hz), 2.42 (s, 3 H), 1.18 (t, 3 H, J = 7 Hz). Anal. ($C_{15}H_{18}O_3$) C, H.

3-Carbethoxy-4-(4-methylphenyl)-4-oxobutanal (135). A mixture of **134** (74.21 g, 301 mmol, 1.0 equiv), catalytic osmium tetroxide (0.10 g), sodium metaperiodate (141.8 g, 663 mmol, 2.2 equiv), 500 mL of diethyl ether, and 1000 mL of water was stirred at 25 °C. After 24 h additional osmium tetroxide (0.11 g) was added, and, after another 24 h, osmium tetroxide (0.20 g) and sodium metaperiodate (190 g, 888 mmol, 3.0 equiv) were added. After an additional 96 h the layers were separated, and the organic layer was washed with aqueous sodium bisulfite (1 × 500 mL) and brine (1 × 300 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to provide 64.99 g of a dark brown oil. Column chromatography (elution: 20% ethyl acetate/hexane) furnished 37.5 g (50%) of **135** as an amber oil: NMR ($CDCl_3$) δ 9.79 (s, 1 H), 7.93 (d, 2 H, J = 9 Hz), 7.27 (d, 2 H, J = 9 Hz), 4.87 (t, 1 H, J = 7 Hz), 4.13 (quart, 2 H, J = 7 Hz), 3.37–3.08 (AB multiplet, 2 H), 2.40 (s, 3 H), 1.14 (t, 3 H, J = 7 Hz). Anal. ($C_{14}H_{16}O_4$) C, H.

3-Carbethoxy-2-(4-methylphenyl)furan (136). To a solution of **135** (10.0 g, 40 mmol) and 50 mL of trifluoroacetic anhydride at 0 °C was added catalytic trifluoroacetic acid (2 drops), and the mixture then was allowed to warm to 25 °C. After 3 h at 25 °C, additional trifluoroacetic anhydride (50 mL) together with trifluoroacetic acid (2 drops) were added. After another 18 h at 25 °C, the solvent was removed under vacuum, and the residue was partitioned between 1 N aqueous sodium hydroxide (200 mL) and ethyl acetate (200 mL). The layers were separated, and the organic layer was washed with 1 N aqueous sodium hydroxide (2 × 200 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to afford 9.95 g of a brown oil which was chromatographed (elution: 1% ethyl acetate/hexane) to provide 2.57 g (28%) of **136** as an off-white solid: mp 79.0–80.5 °C; NMR ($CDCl_3$) δ 7.88 (d, 2 H, J = 9 Hz), 7.42 (d, 1 H, J = 2 Hz), 7.26 (d, 2 H, J = 9 Hz), 6.83 (d, 1 H, J = 2 Hz), 4.34 (quart, 2 H, J = 7 Hz), 2.40 (s, 3 H), 1.34 (t, 3 H, J = 7 Hz); high-resolution MS calcd 230.0943, found 230.0938.

2-Butyl-1-[4-(3-carboxyfuran-2-yl)benzyl]-4-chloro-5-(hydroxymethyl)imidazole (68). The title compound was prepared from **136** and 2-butyl-4(5)-chloro-5(4)-(hydroxymethyl)imidazole[19] by the procedures described for the preparations of **79**, **84**, and **2**: mp 158.5–160.0 °C; NMR (DMSO-d_6) δ 12.80 (br s, 1 H), 7.92 (d, 2 H, J = 9 Hz), 7.82 (d, 1 H, J = 2 Hz), 7.17 (d, 2 H, J = 9 Hz), 6.84 (d, 1 H, J = 2 Hz), 5.30 (m, 3 H), 4.34 (s, 2 H), 2.47 (t, 2 H, J = 7 Hz), 1.47 (quint, 2 H, J = 7 Hz), 1.24 (sext, 2 H, J = 7 Hz), 0.74 (t, 3 H, J = 7 Hz). Anal. ($C_{20}H_{21}ClN_2O_4$) C, H, N.

Acknowledgment. We wish to thank Arthur Vatvars for kindly determining the log P values for compounds **2** and **3**.

Registry No. **2**, 114798-27-5; **3**, 114798-90-2; **4**, 126938-11-2; **5**, 114799-01-8; **6**, 126938-12-3; **7**, 114799-42-7; **8**, 114822-96-7; **9**, 114799-41-6; **10**, 124751-02-6; **11**, 124750-05-6; **12**, 114799-43-8; **13**, 114799-22-3; **14**, 114799-21-2; **17**, 114798-26-4; **18**, 114798-94-6; **19**, 125573-80-0; **20**, 124750-21-6; **21**, 124750-23-8; **22**, 133909-85-0; **23**, 114799-34-7; **24**, 114799-33-6; **25**, 114798-36-6; **26**, 133909-86-1; **27**, 133909-87-2; **28**, 114799-05-2; **29**, 133909-88-3; **30**, 133909-89-4; **31**, 133909-90-7; **32**, 124750-26-1; **33**, 114799-06-3; **34**, 114799-07-4; **35**, 114799-08-5; **36**, 114799-09-6; **37**, 114798-32-2; **38**, 133909-91-8; **39**, 114799-03-0; **40**, 114822-94-5; **41**, 114799-00-7; **42**, 114798-96-8; **43**, 114798-95-7; **44**, 124750-09-0; **45**, 124749-81-1; **46**, 124749-89-9; **47**, 133909-92-9; **48**, 124749-78-6; **49**, 114799-97-2; **50**, 114798-28-6; **51**, 114799-23-4; **52**, 133909-93-0; **53**, 114799-27-8; **54**, 114799-32-5; **55**, 114799-31-4; **56**, 133909-94-1; **57**, 114799-14-3; **58**, 133909-95-2; **59**, 114799-28-9; **60**, 124750-14-7; **61**, 124750-13-6; **62**, 124751-01-5; **63**, 114799-75-6; **64**, 114799-17-6; **65**, 114799-16-5; **66**, 114798-30-0; **67**, 114799-20-1; **68**, 114799-39-2; **69**, 114772-34-8; **70**, 70680-21-6; **71**, 21615-34-9; **72**, 57598-33-1; **73**, 84392-32-5; **74**, 7148-03-0; **75**, 114772-36-0; **76**, 114772-53-1; **77**, 133909-96-3; **78**, 133909-97-4; **79**, 133051-88-4; **80**, 114772-38-2; **81**, 114772-39-3; **82**, 114772-40-6; **83**, 114772-54-2; **84**, 114772-43-9; **85**, 114772-55-3; **86**, 133909-98-5; **87**, 133909-99-6; **88**, 83857-96-9; **89**, 133910-00-6; **90**, 114772-71-3; **91**, 114772-50-8; **92**, 114772-72-4; **93**, 114772-73-5; **94**, 114799-97-2; **95**, 133910-01-7; **96**, 133910-02-8; **97**, 133910-03-9; **98**, 114772-66-6; **99**, 114772-67-7; **100**, 114772-68-8; **101**, 114772-69-9; **102**,

114772-45-1; **103**, 114772-60-0; **104**, 124750-36-3; **105**, 37455-55-3; **106**, 68282-41-7; **107**, 68282-59-7; **108**, 124750-54-5; **109**, 124750-55-6; **110**, 133379-10-9; **111**, 114772-46-2; **112**, 114772-62-2; **113**, 114772-63-3; **114**, 114772-83-7; **115**, 114772-84-8; **116**, 114772-85-9; **117**, 124779-26-6; **118**, 114772-77-9; **119**, 124750-43-2; **120**, 114772-51-9; **121**, 114772-70-2; **122**, 114772-75-7; **123**, 114772-76-8; **124**, 120568-15-2; **125**, 120568-16-3; **126**, 124750-65-8; **127**, 133910-04-0; **128**, 16191-28-9; **129**, 124750-63-6; **130**, 124750-64-7; **131**, 133910-05-1; **132**, 133910-06-2; **133**, 133910-07-3; **134**, 124750-42-1; **135**, 114772-81-5; **136**, 114772-82-6; methyl 2-iodobenzoate, 610-97-9; 4-iodotoluene, 624-31-7; 1-bromo-2-nitrobenzene, 577-19-5; 2-methoxybenzoic acid, 579-75-9; 2-amino-2-methyl-1-propanol, 124-68-5; 4-bromotoluene, 106-38-7; 3-bromobenzonitrile, 6952-59-6; 2-butyl-4(5)-chloro-5(4)-(hydroxymethyl)imidazole, 79047-41-9; 4-[[3-[*N*-(*tert*-butoxycarbonyl)-*N*-isopropylamino]-2-hydroxypropyl]oxy]indole-2-carboxylic acid, 103221-84-7; 2-butyl-4(5)-(hydroxymethyl)-imidazole, 68283-19-2; butyraldehyde, 123-72-8; acetol, 116-09-6; (phenylsulfonyl)acetonitrile, 7605-28-9; ethyl 3-(4-methylphenyl)-3-oxopropanoate, 7116-41-8; allyl bromide, 106-95-6.

GABA-Uptake Inhibitors: Construction of a General Pharmacophore Model and Successful Prediction of a New Representative

Victor N'Goka,[†] Gilbert Schlewer,*[,†] Jean-Michel Linget,[†] Jean-Pierre Chambon,[‡] and Camille-Georges Wermuth[†]

Laboratoire de Pharmacochimie Moléculaire, Centre de Neurochimie du CNRS, 5, rue Blaise Pascal, 67084 Strasbourg Cedex, France, and Sanofi Recherche, Rue du Professeur J. Blayac, 34082 Montpellier Cedex, France. *Received March 18, 1991*

A model for the pharmacophore of GABA-uptake inhibitors was established using published structure–activity data and molecular modeling. The model accounted for the activities of different classes of GABA-uptake inhibitors. Analogues of guvacine substituted at position 6 were synthesized in order to confirm the model. 6-(3,3-Diphenylpropyl)guvacine (**30f**), which fit well with the pharmacophore, had an in vitro IC_{50} of 0.1 μM. This value is as good as those of the best GABA-uptake inhibitors known today.

γ-Aminobutyric acid (GABA, 1) is a major neurotransmitter in mammals.[1-9] Dysfunctioning of GABA-ergic synapses has been invoked for diseases such as Parkinson's disease,[10-13] Huntington's chorea,[14] epilepsy,[15,16] and some forms of schizophrenia.[17-19] One of the possible ways to palliate GABA deficiency lies in the inhibition of uptake mechanisms of this neurotransmitter.[20-24] Taking in account the results of various studies devoted to this GABA-ergic regulation approach[25-27] allowed us to establish a model pharmacophore by means of computer modeling. The validity of the model pharmacophore was confirmed through its ability to rationalize the activity of some newly described uptake inhibitors and to guide the design of a novel, potent GABA uptake inhibitor.

Identification and Construction of the Pharmacophore

Studies on GABA-uptake inhibitors have been developed in several directions. Analogues of GABA itself have been prepared in order to modulate the chain length or to introduce substituents or unsaturation. Although these modifications yielded active compounds, only 2-fluoro-GABA (2)[28] (Figure 1) showed uptake-inhibitory potency comparable to that of GABA itself. Most of these acyclic GABA analogues are not selective for GABA-uptake inhibition but also possess agonist properties.

Conformationally restricted cyclic GABA analogues have also been studied, e.g., where the methylenes have been incorporated into homocyclic systems such as cyclopropyl,[29] cyclobutyl,[29] cyclopentyl,[30] cyclopentenyl,[30] cyclohexyl,[29,31] cyclohexenyl,[29] and cyclohexadienyl[29] rings. The best activities were found for cyclopentyl and cyclopentenyl rings, and high stereoselectivity was observed for the (+)-4(*S*)- versus the (−)-4(*R*)-aminocyclopentene-1-carboxylic acids[30] **3** and **4**, respectively (Figure 1). Some heterocyclic amino acids were also described as GABA-uptake inhibitors, especially in the pyrrolidine[29] and pi-

[†] Laboratoire de Pharmacochimie Moléculaire, Centre de Neurochimie du CNRS.
[‡] Sanofi Recherche.

(1) Roberts, E., Chase, T. R., Tower, D. B., Eds. *GABA in Nervous System Function*; Raven Press: New York, 1976, 554 pp.
(2) Awapara, J.; Landau, A. UJ.; Fuerst, R.; Seale, B. Free γ-aminobutyric acid in brain. *J. Biol. Chem.* **1950**, *187*, 35–39.
(3) Roberts, E.; Frankel, S. γ-Aminobutyric acid in brain: Its formation from glutamic acid. *J. Biol. Chem.* **1950**, *187*, 55–64.
(4) Udenfriend, S. Identification of γ-aminobutyric acid in brain by the isotope derivative method.
(5) Oja, S. S.; Kontro, P.; Lähdesmäki, P. Amino Acids as Inhibitory Neurotransmitters. *Progress in Pharmacology*; G. Fischer Verlag: Stuttgart, 1977; Vol. 1, No. 3, 120 pp.
(6) Curtis, D. R.; Johnston, G. A. R. Amino acid transmitters in the mammalian nervous system. *Ergeb. Physiol, Biol. Chem. Exp. Pharmakol.* **1974**, *69*, 97–188.
(7) Enna, S. J.; Gallaghe, J. P. Biochemical and electrophysiological characteristics of mammalian GABA receptors.
(8) Okada, Y.; Ozawa, S. The concentration of GABA required for its inhibitory action in the hippocampal pyramidal cell in vitro. *Excerpta Med., Sect. 1* **1982**, *565*, 87–95.
(9) Olsen, R. W.; Yang, J.; King, R. G.; Dilber, A.; Stauber, G. B.; Ransom, R. W. Barbiturate and benzodiazepine modulation of GABA receptor-binding and function. *Life Sci.* **1986**, *39*, 1969–1976.
(10) McGeer, P. L.; McGeer, E. G. Enzymes associated with penetration of catecholamines, acetylcholine and GABA in human controls and patients with Parkinson's disease and Huntington's chorea. *J. Neurochem.* **1976**, *261*, 65–76.
(11) Lloyd, K. G.; Möhler, H.; Heitz, P.; Bartholini, G. Distribution of choline acetyltransferase and glutamate decarboxylase within substantia nigra and in other brain-regions from control and Parkinson's patients. *J. Neurochem.* **1975**, *25*, 789–795.
(12) Lloyd, K. G.; Shemen, L.; Hornykiewicz, O. Distribution of high affinity sodium-independent [^{3}H]gamma aminobutyric acid [^{3}H]GABA binding in human brain. Alteration in Parkinson's disease. *Brain Res.* **1977**, *127*, 269–278.
(13) Tower, D. B. GABA and seizures. Clinical correlates in man. In *GABA in Nervous System Function*; Roberts, E., Chase, T. R., Tower, D. B., Eds.; Raven: New York, 1976; pp 461–478.
(14) Lloyd, K. G.; Dreksler, S.; Bird, E. D. Alteration in [^{3}H]GABA binding in Huntington's chorea. *Life Sci.* **1977**, *21*, 747–754.

0022-2623/91/1834-2547$02.50/0