

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

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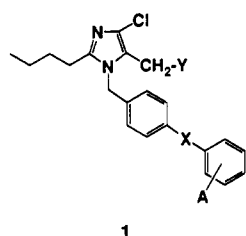
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A new series of nonpeptide angiotensin II (AII) receptor antagonists has been prepared. These *N*-(biphenylmethyl)imidazoles, e.g. 2-butyl-1-[(2'-carboxybiphenyl-4-yl)methyl]-4-chloro-5-(hydroxymethyl)imidazole, differ from the previously reported *N*-(benzamido-benzyl)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.<sup>2,3</sup> 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.<sup>3</sup> Replacement of the polar carboxylic acid group (A) with acid isosteres of greater lipophilicity, such as  $\text{NH}\text{SO}_2\text{CF}_3$ , resulted in some oral activity. However, none of these compounds when dosed orally produced an effect to compare with their intravenous antihypertensive effect.



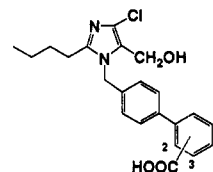
A = Acidic Functionality such as  $-\text{COOH}$ ,  $-\text{NH}\text{SO}_2\text{CF}_3$ ,  $-\text{SO}_3\text{H}$ ,  $-\text{CN}_4\text{H}$ , etc.

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

Y = Hydrogen bonding group such as  $\text{COOH}$ ,  $\text{OH}$ ,  $\text{CH}_2\text{OCH}_3$ .

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 ( $\text{ED}_{30} = 11 \text{ mg/kg}$ ). 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.<sup>4,5</sup> 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.<sup>6</sup>



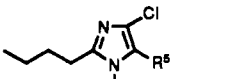
Isomer	$\text{IC}_{50}$ ( $\mu\text{M}$ )	$\text{ED}_{30}$ (mg/kg p.o. RHR)
2	0.23	11
3	0.49	inactive
4	11.0	inactive

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

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- (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<sup>5</sup> for compounds 2 and 3 are 1.17 and 1.38, respectively.
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**Table I. Angiotensin II Receptor Antagonists Containing "Amide-Type" Carboxylic Acid Isosteres**



compd no.	R <sup>5</sup>	A	est pK <sub>a</sub>	IC <sub>50</sub> <sup>a</sup> (μM)	in vivo activity iv (po) <sup>b</sup>	mp (°C)	elemental analysis
2	CH <sub>2</sub> OH	COOH	5	0.23	3 (ED <sub>50</sub> = 11)	171.0–172.0	C, H, Cl, N
5	CH <sub>2</sub> OCH <sub>3</sub>	COOH	5	0.099	10 (100)	166.5–169.0	C, H, N
6	CH <sub>2</sub> OH	CONH <sub>2</sub>	23 <sup>7</sup>	35.0		155.0–157.0	C, H, Cl, N
7	CH <sub>2</sub> OH	CONHOH	10.5 <sup>8a,b</sup>	4.1	3 (>30)	glass	C, H, Cl, N
8	CH <sub>2</sub> OH	CONHOCH <sub>3</sub>	10.9 <sup>8a</sup>	2.9	10 (inactive)	glass	C, H, Cl, N
9	CH <sub>2</sub> OH	CONHOCH <sub>2</sub> Ph	10.85 <sup>8a</sup>	4.9	10 (inactive)	glass	C, H, Cl, N
10	CH <sub>2</sub> OH	CONHSO <sub>2</sub> Ph	8.44 <sup>9</sup>	0.14	>3 (NA 30)	172.0–174.0	C, H, Cl, N
11	CH <sub>2</sub> OCH <sub>3</sub>	CONHNHSO <sub>2</sub> CF <sub>3</sub>	unknown	0.20	>3 (>30)	glass	C, H, Cl, F, N, S
12	CH <sub>2</sub> OH	NHCOCF <sub>3</sub>	9.5 <sup>10</sup>	6.3	10 (inactive)	glass	C, H, N
13	CH <sub>2</sub> OH	NHSO <sub>2</sub> CF <sub>3</sub>	4.5 <sup>11</sup>	0.083	10 (100)	171.0–172.0	C, H, N
14	CH <sub>2</sub> OCH <sub>3</sub>	NHSO <sub>2</sub> CF <sub>3</sub>	4.5 <sup>11</sup>	0.19	10 (100)	148.0–150.0	C, H, N

<sup>a</sup> Inhibition of specific binding of [<sup>3</sup>H]angiotensin II (2 nM) to rat adrenal cortical microsomes. Intraassay and interassay variabilities of the IC<sub>50</sub> values for a given compound are 5–10% and 15–30%, respectively (see the Experimental Section for further discussion of the IC<sub>50</sub> data and method). <sup>b</sup> 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<sub>30</sub> 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

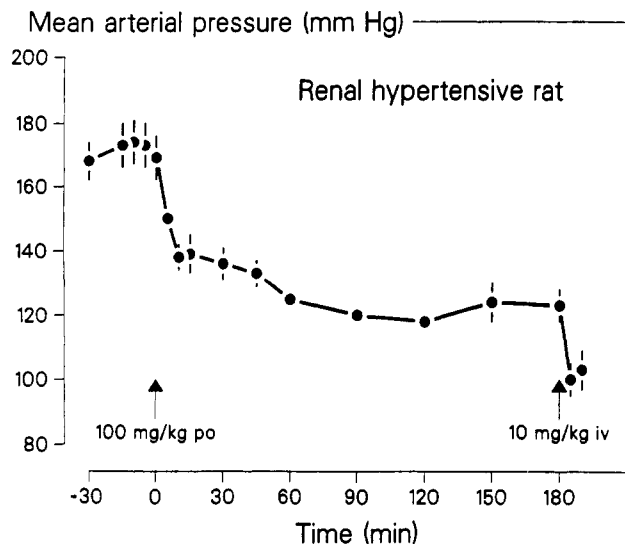
compd no.	R <sup>5</sup>	A	est pK <sub>a</sub>	IC <sub>50</sub> <sup>a</sup> (μM)	in vivo activity iv (po) <sup>b</sup>	mp (°C)	elemental analysis
17	CH <sub>2</sub> OH		5-6 <sup>12</sup>	0.019	ED <sub>30</sub> = 0.80 (ED <sub>30</sub> = 0.59)	183.5-184.5	C, H, Cl
18	CH <sub>2</sub> OCH <sub>3</sub>		5-6 <sup>12</sup>	0.032	1 (3)	glass	C, H, Cl
19	CH <sub>2</sub> OH		unknown	0.28	>1 (>10)	glass	C, H, Cl
20	CH <sub>2</sub> OH		7.0 <sup>13</sup>	0.26	>1 (>10)	glass	C, H, Cl
21	CH <sub>2</sub> OH		unknown	0.37	1 (10)	glass	C, H, Cl
22	CHO		unknown	13	>10 (inactive)	glass	C, H, Cl, F, N

<sup>a, b</sup> 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.<sup>3a</sup> Amide 6 is essentially nonacidic, and thus it does not have a good IC<sub>50</sub> 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  $\pm$  SEM ( $n = 6$ ).

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<sup>3a</sup> where trifluoromethanesulfonamide **16** showed some oral activity while carboxylic acid **15** was inactive.

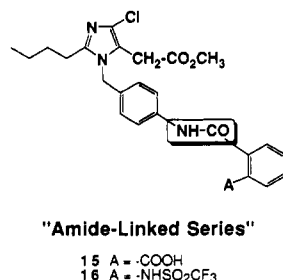
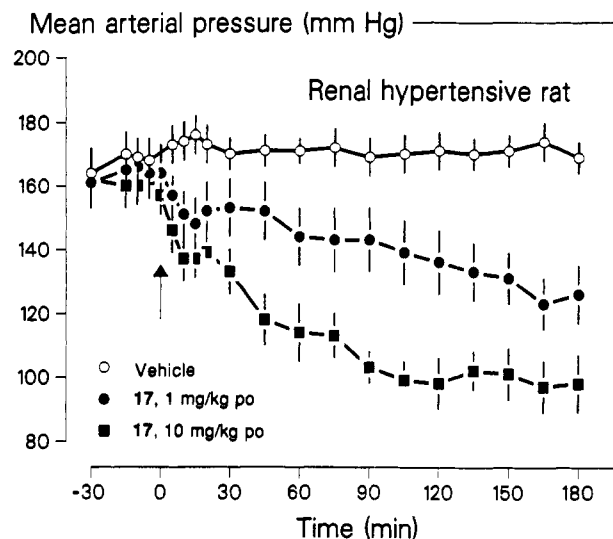


Table II summarizes the AII receptor antagonists containing what we have termed as "azole-type" carboxylic acid isosteres. The activity profile of tetrazole **17** is remarkable. It has a 1 order of magnitude greater binding affinity than carboxylic acid **2**. It has an iv ED<sub>50</sub> of 0.80 mg/kg and an oral ED<sub>50</sub> of 0.59 mg/kg.<sup>14a-e</sup> The increase



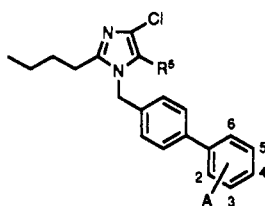
**Figure 2.** Effects of vehicle ( $n = 6$ ) and **17** at 1 mg/kg po ( $n = 6$ ) and 10 mg/kg po ( $n = 6$ ) on mean arterial pressure in renal artery-ligated rats. Values represent the mean  $\pm$  SEM.

in oral potency of **17** over that of **2** [ED<sub>50</sub> (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.

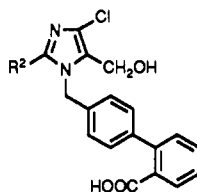
It is felt that besides mimicking the acidity of the carboxylic acid, the tetrazole, having four nitrogens, possesses a charge distribution that better interacts with the positive charge on the receptor. To test this hypothesis, it was decided to synthesize isosteres of the tetrazole. The triazole ring 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<sub>a</sub> of about 9.<sup>15</sup> However, substitution by electron-withdrawing groups, such as CN, CO<sub>2</sub>Me, or CF<sub>3</sub>, lowers the pK<sub>a</sub>. 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

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- (15) The pK<sub>a</sub> of 4-phenyl-1,2,3-triazole is 9.2.<sup>13</sup>

**Table III.** SAR around the Terminal Aromatic Ring

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

<sup>a,b</sup> See Table I for an explanation of tabulated data.**Table IV.** SAR at the Imidazole 2-Position

compd no.	R <sup>2</sup>	IC <sub>50</sub> <sup>a</sup> (μM)	in vivo activity iv (po) <sup>b</sup>	mp (°C)	elemental analysis
33	C <sub>2</sub> H <sub>5</sub>	1.70	10 (100)	153.0–156.0	C, H; HRMS <sup>c</sup>
34	C <sub>3</sub> H <sub>7</sub>	0.16	3 (30)	198.0–200.0	C, H, N
2	C <sub>4</sub> H <sub>9</sub>	0.23	3 (ED <sub>30</sub> = 11)	171.0–172.0	C, H, Cl, N
35	C <sub>5</sub> H <sub>11</sub>	0.98	3 (30)	glass	C, H, N
36	C <sub>6</sub> H <sub>13</sub>	1.30	10 (inactive)	84.0–88.0	HRMS <sup>c</sup>
37	<i>trans</i> -CH <sub>3</sub> CH <sub>2</sub> CH=CH	0.08	ED <sub>30</sub> = 1.0 (ED <sub>30</sub> = 3.6)	198.5–199.5	C, H, Cl
38	phenyl	24	10 (100)	200.0–203.0	C, H, Cl, N

<sup>a,b</sup> See Table I for an explanation of tabulated data. <sup>c</sup>HRMS: high-resolution mass spectrum detects M<sup>+</sup> 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<sub>2</sub>OH 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<sup>3a</sup> 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 snugly 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<sup>3a</sup>], the biphenyls show the highest binding affinity, for the saturated alkyl groups, when R<sup>2</sup> 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 <sup>2</sup>	R <sup>4</sup>	A	IC <sub>50</sub> <sup>a</sup> (μM)	in vivo activity iv (po) <sup>b</sup>	mp (°C)	elemental analysis
2	<i>n</i> -butyl	Cl	COOH	0.23	3 (ED <sub>30</sub> = 11)	171.0–172.0	C, H, Cl, N
39	<i>n</i> -butyl	Br	COOH	0.09	3 (30)	175.0–178.0	C, H, Br, N
40	<i>n</i> -butyl	I	COOH	0.061	10 (100)	163.0–165.0	C, H, I, N
41	<i>n</i> -butyl	H	COOH	0.27	10 (inactive)	glass	C, H, N
42	<i>n</i> -butyl	CF <sub>3</sub>	COOH	0.062	3 (30)	198.0–199.5	C, H, F, N
43	<i>n</i> -butyl	NO <sub>2</sub>	COOH	0.26	10 (inactive)	204.0–205.5	C, H, N
44	<i>n</i> -propyl	CH <sub>3</sub>	COOH	1.8	ED <sub>30</sub> = 1.3 (>30)	208.0–210.0	C, H, Cl, N (HCl salt)
17	<i>n</i> -butyl	Cl	CN <sub>4</sub> H	0.019	ED <sub>30</sub> = 0.80 (ED <sub>30</sub> = 0.59)	183.5–184.5	C, H, Cl
45	<i>n</i> -butyl	Br	CN <sub>4</sub> H	0.019	0.3 (3)	glass	C, H, Br, N
46	<i>n</i> -butyl	I	CN <sub>4</sub> H	0.020	1 (10)	glass	C, H, I, N
47	<i>n</i> -butyl	H	CN <sub>4</sub> H	0.029	NA (NA)	204.5–205.5	C, H, N
48	<i>n</i> -butyl	CF <sub>3</sub>	CN <sub>4</sub> H	0.012	ED <sub>30</sub> = 0.53 (>3)	glass	C, H, F, N

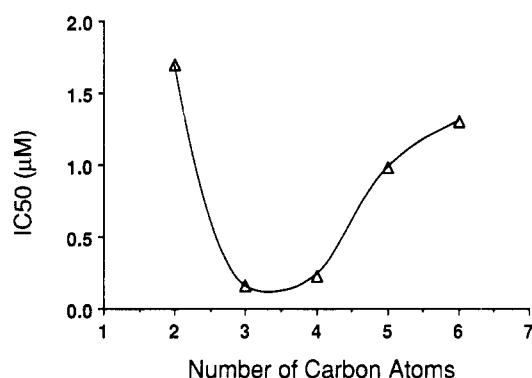
<sup>a,b</sup> See Table I for an explanation of tabulated data.

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

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,<sup>3a</sup> 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<sup>4</sup> = I provides the highest binding affinity while R<sup>4</sup> = 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<sub>3</sub> group, and by the poor binding affinities of 43 and 44, which contain a NO<sub>2</sub> and a CH<sub>3</sub> 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<sub>3</sub> 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

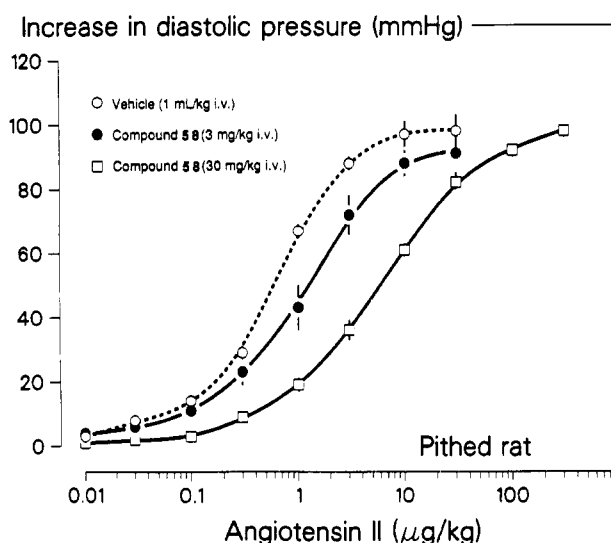
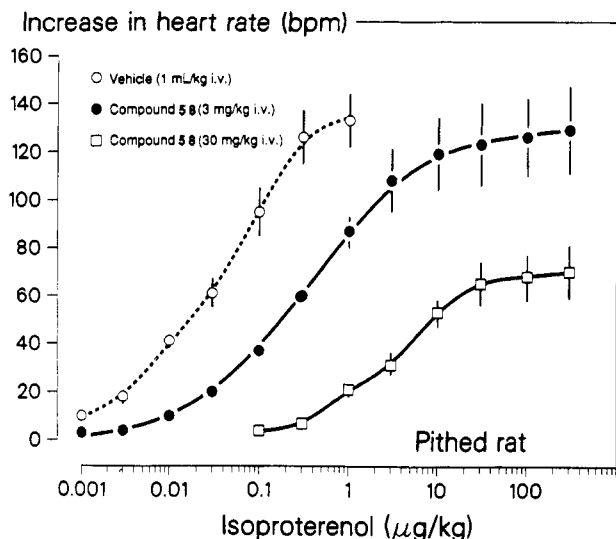


Figure 4. Effects of the vehicle ( $n = 4$ ) and 58 at 3 mg/kg iv ( $n = 4$ ) and 30 mg/kg iv ( $n = 3$ ) on the log dose-pressor response curves for AII in the pithed rat.<sup>16</sup> Values represent the means  $\pm$  SEM. The mean diastolic pressures for the vehicle-treated group and for the groups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

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<sub>2</sub>OH group results in decreased binding affinity. Most likely, a large group at the imidazole 5-position prevents the biphenyltetrazole portion from achieving the optimal conformation needed for good binding affinity.

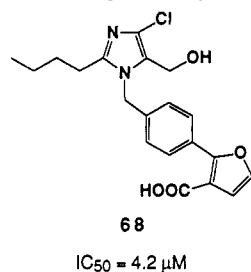
In order to further investigate the range of functionality which could be tolerated at the imidazole 5-position in the biphenylcarboxylic acid series, we decided to attach another pharmacophore at this point. Thus the  $\beta$ -blocker pindolol was attached at this position via an amide linkage



**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.<sup>16</sup> Values represent the means  $\pm$  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  $42 \pm 3$ ,  $39 \pm 3$ , and  $32 \pm 3$  mmHg, respectively.

to yield compound 58.<sup>16,17</sup> Remarkably this molecule exhibits both AII and  $\beta$ -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.

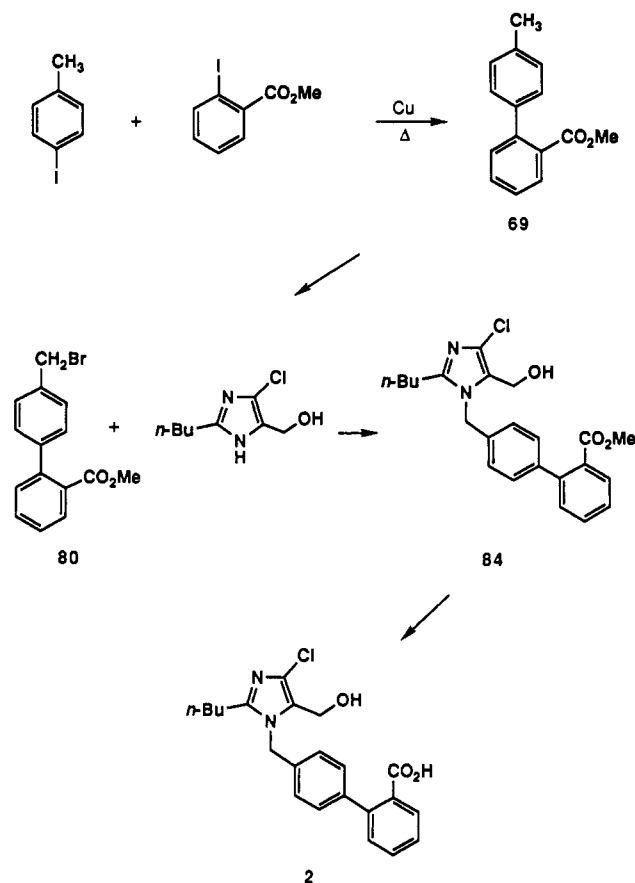


## Chemistry

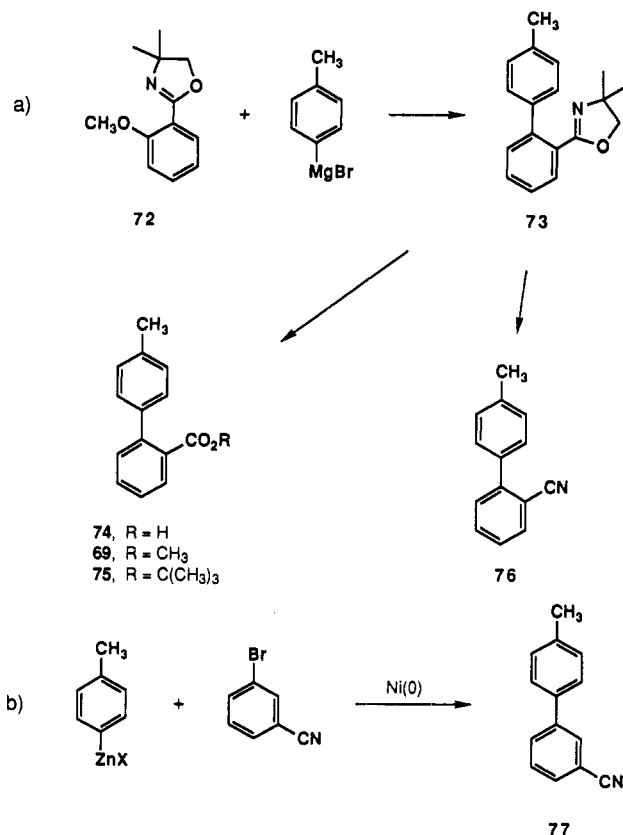
A general procedure employed in the preparation of most of the compounds in this paper is demonstrated in Scheme I for the preparation of 2. The requisite biphenyl 69 was prepared by the Ullmann biaryl synthesis.<sup>18</sup> Bromination of 69 with *N*-bromosuccinimide provided 80. Alkylation of 2-butyl-4(5)-chloro-5(4)-(hydroxymethyl)imidazole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

**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  $\beta$ -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.

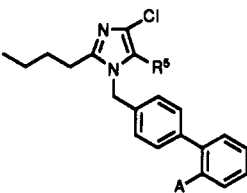
(19) Furukawa, Y.; Kishimoto, S.; Nishikawa, K. U.S. Patent 4340598, 1982.

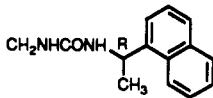
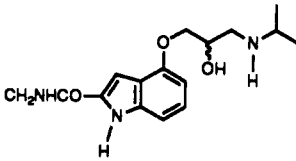
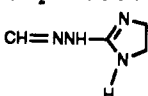
(20) The regioisomers were assigned by analogy with the results of alkylations reported in (a) Furukawa, Y.; et al. U.S. Patent 4355040, 1982. (b) Reference 3a. The assignments were confirmed by X-ray crystallographic analysis of compound 17 and the regioisomer of 2.

istry of Meyers (Scheme IIa).<sup>21</sup> The reaction of oxazoline 72 (with (4-methylphenyl)magnesium bromide afforded

(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 <sup>5</sup>	A	IC <sub>50</sub> <sup>a</sup> (μM)	in vivo activity iv (po) <sup>b</sup>	mp (°C)	elemental analysis
2	CH <sub>2</sub> OH	COOH	0.23	3 (ED <sub>30</sub> = 11)	171.0–172.0	C, H, Cl, N
5	CH <sub>2</sub> OCH <sub>3</sub>	COOH	0.099	10 (100)	166.5–169.0	C, H, N
49	CH <sub>2</sub> NH <sub>2</sub>	COOH	3.2		glass	c
50	CH <sub>2</sub> NH-COOCH <sub>3</sub>	COOH	0.25	3 (30)	144.0–147.0	C, H, N
51	CH <sub>2</sub> NH-COOCH <sub>2</sub> CH <sub>3</sub>	COOH	0.20	10 (100)	144.0–147.0	C, H, N
52	CH <sub>2</sub> NH-COOCH <sub>2</sub> CH=CH <sub>2</sub>	COOH	0.39	10 (100)	139.5–142.0	C, H, N
53	CH <sub>2</sub> NH-COO-adamantyl	COOH	0.60	3 (30)	170.0–172.0	C, H, N
54	CH <sub>2</sub> NH-CO-NHCH <sub>3</sub>	COOH	0.24	10 (inactive)	187.0–193.0	C, H, N
55	CH <sub>2</sub> NH-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 <sub>2</sub> OCOCH <sub>3</sub>	COOH	0.33	10 (100)	157.0–159.0	C, H, Cl, N
58		COOH	0.38	ED <sub>30</sub> = 1.0	glass	C, H, N
17	CH <sub>2</sub> OH	CN <sub>4</sub> H	0.019	ED <sub>30</sub> = 0.80 (ED <sub>30</sub> = 0.59)	183.5–184.5	C, H, Cl
59	CH <sub>2</sub> NHCOOCH <sub>3</sub>	CN <sub>4</sub> H	0.06	1 (>10)	202.0–204.5	C, H, Cl
60		CN <sub>4</sub> H	0.29	3 (30)	224.0–227.5	C, H, Cl
61	CH=NNHSO <sub>2</sub> Ph	CN <sub>4</sub> H	0.66	3 (30)	227.5–230.0	C, H, Cl
62	CH(OH)Ph	CN <sub>4</sub> H	0.41	3 (>30)	137.0–145.0	C, H, Cl
63	COOH	COOH	0.092	ED <sub>30</sub> = 0.47 (>10)	185.0–189.0	C, H, Cl, N
64	CONH <sub>2</sub>	COOH	0.15	10 (100)	200.0–202.0	C, H, Cl, N
65	CO <sub>2</sub> CH <sub>3</sub>	COOH	0.34	10 (100)	154.0–155.0	C, H, Cl, N
66	CHO	COOH	0.94	10 (ED <sub>30</sub> = 1.7)	154.0–158.0 dec	C, H, Cl
67	CON(CH <sub>3</sub> ) <sub>2</sub>	COOH	1.3	10 (10)	102.5–105.0	C, H, Cl, N

<sup>a,b</sup> See Table I for an explanation of tabulated data. <sup>c</sup> Intermediate to fully characterized compounds 50–56.

the biphenyloxazoline 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<sup>22</sup> 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,<sup>23</sup> which is exemplified in Scheme IIb for the synthesis of nitrile 77.

An important class of compounds in this paper are the biphenyltetrazoles (e.g. 17). These compounds are prepared readily from the corresponding nitriles by employing trimethyltin azide.<sup>24</sup> 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 tri-

phenylmethyl derivative 87. Deprotection of 87 afforded the tetrazole 17. Alternatively tributyltin azide was utilized to prepare the biphenyltetrazole intermediate 79<sup>25</sup> (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

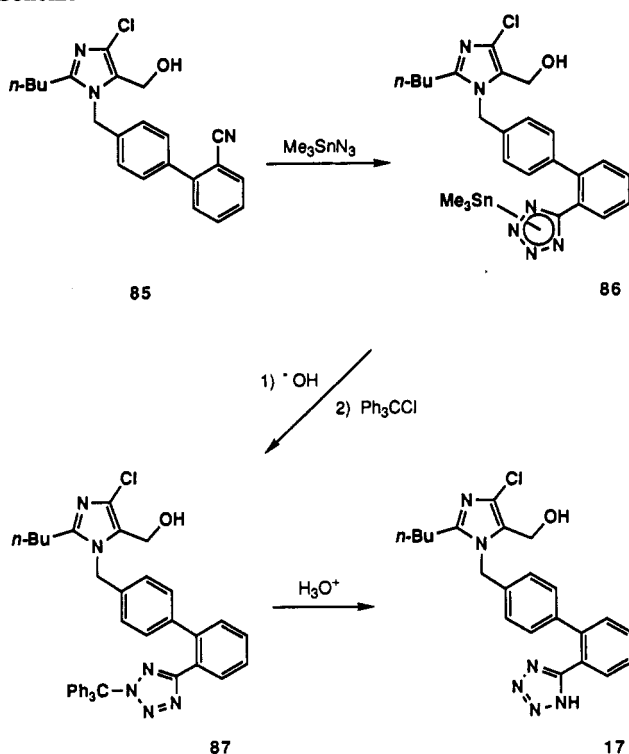
(22) Dordor, I. M.; Mellor, J. M. *Tetrahedron Lett.* 1983, 1437.

(23) Negishi, E.-I.; King, A. O.; Okukado, N. *J. Org. Chem.* 1977, 42, 1821.

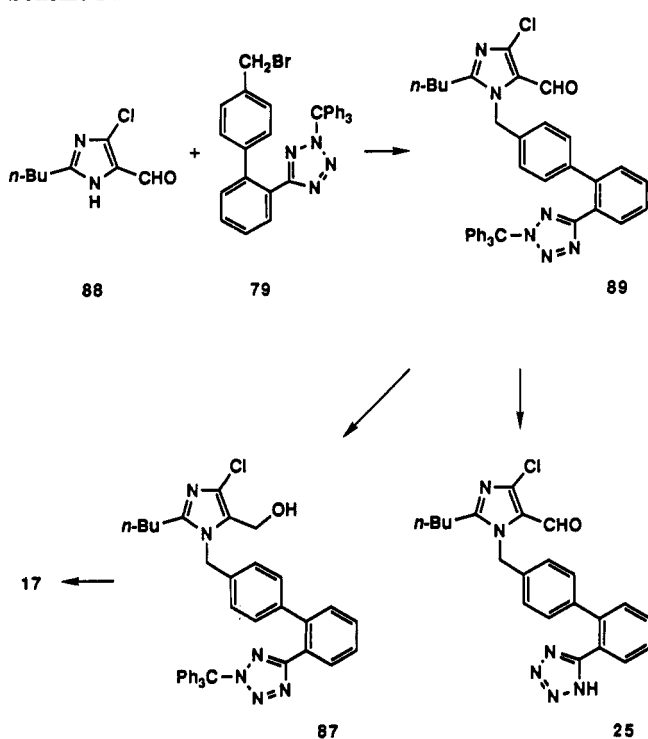
(24) For the use of trimethyltin azide to prepare tetrazoles, see: Sisido, K.; Nabika, K.; Isida, T.; Kozima, S. *J. Organomet. Chem.* 1971, 337. For the preparation of trimethyltin azide or tributyltin azide, see: Luitjen, J. G.; Janssen, M. J.; Van Der Kerk, G. J. *Recl. Trav. Chim. Pays-Bas* 1963, 81, 286.

(25) Aldrich, P. E.; Duncia, J. V.; Pierce, M. E. U.S. Patent 4874867, 1989.

Scheme III



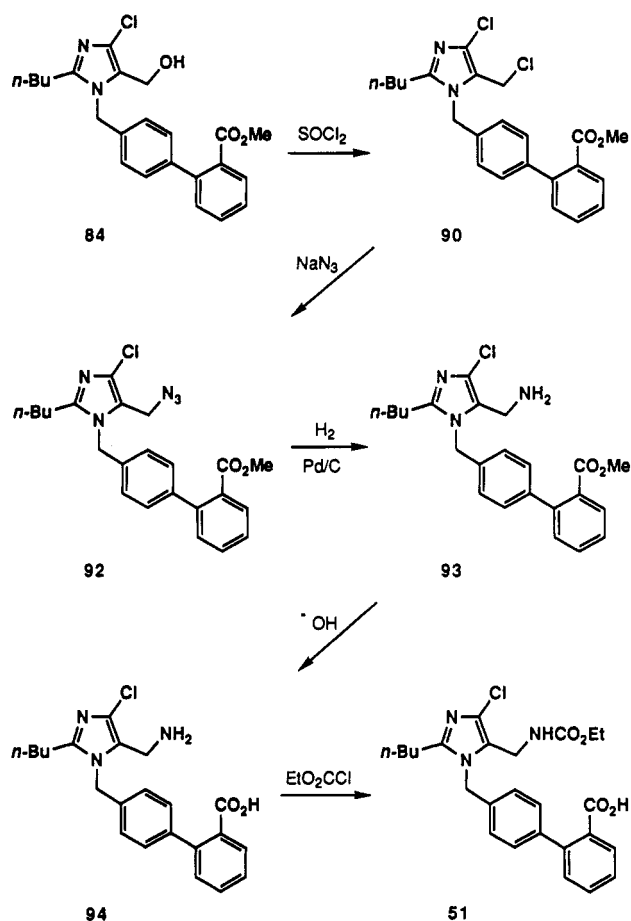
Scheme IV



aldehyde is treated with manganese dioxide/acetic acid/sodium cyanide in methanol<sup>26</sup> or with manganese dioxide/sodium cyanide in 2-propanol containing the appropriate amine.<sup>27</sup> 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.<sup>28</sup> For example, the alkylation of 88 furnished a 9:1 ratio of 89 and its regioisomer.<sup>29</sup> 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 benzene-sulfonylhydrazine 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.<sup>3a</sup> and Carini et al.<sup>3b</sup> 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.

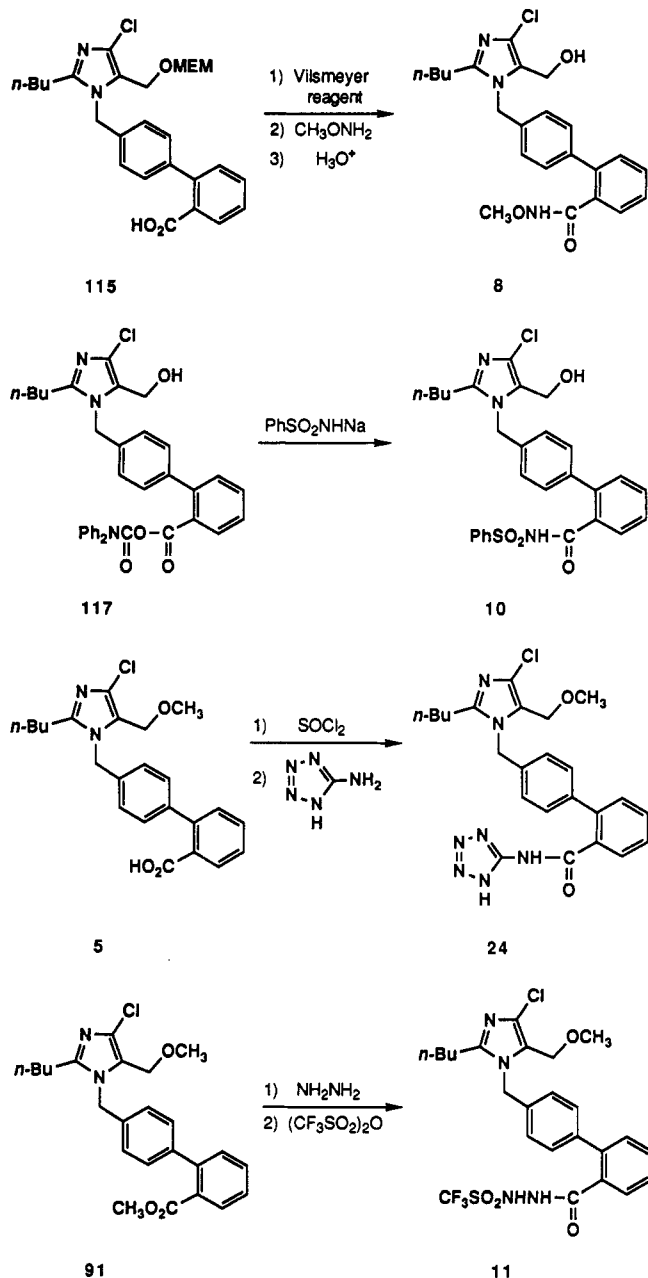
(28) Hoffmann, K. In *The Chemistry of Heterocyclic Compounds: Imidazole and Its Derivatives, Part I*; Weissberger, A., Ed.; Interscience: New York, 1953; Chapter III, p 58.

(29) The regioisomers were assigned by the conversion of aldehyde 89 to the alcohol 17, see ref 20.





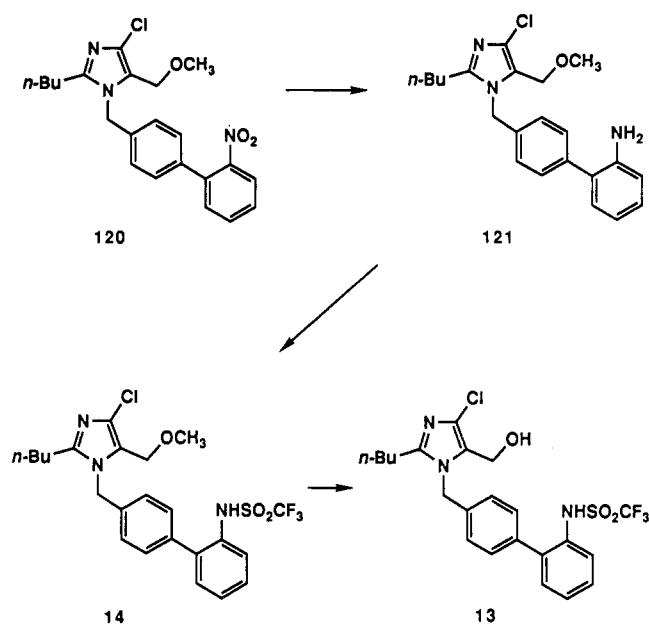
## Scheme IX



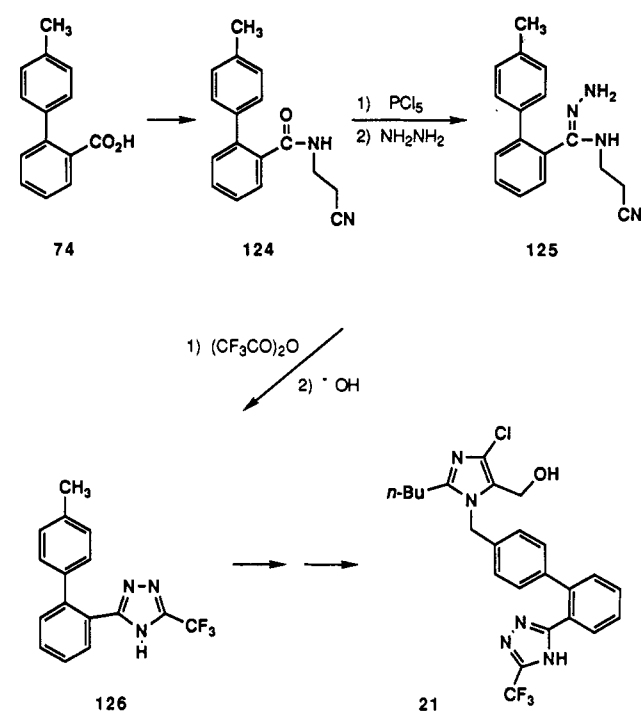
protecting group and hydrolyzed the *tert*-butyl ester to afford 42.

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),<sup>35</sup> the sulfonyl amide 10,<sup>36</sup> 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.

## Scheme X



## Scheme XI



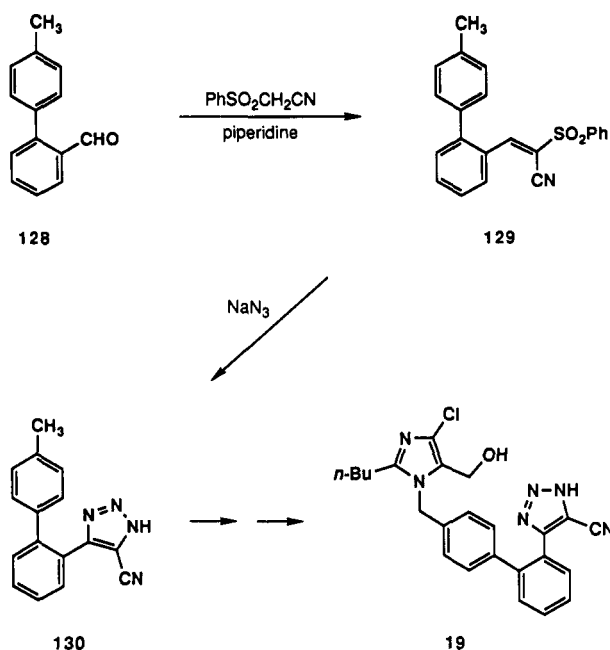
The trifluoromethanesulfonamides (14 and 13) were prepared as described in Scheme X. The nitrobiphenyl 120 was reduced to the aniline 121 with iron powder in acetic acid, and 121 was treated with trifluoromethanesulfonyl anhydride to produce 14. Hydrolysis of the methyl ether group of 14 then afforded 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,<sup>37</sup> which was deprotected

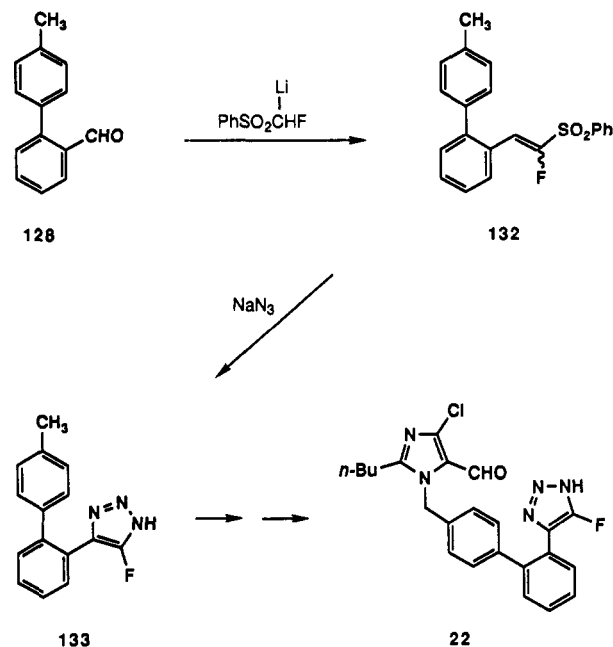
(35) For the preparation of hydroxamic acids utilizing the Vilsmeier reagent, see: Nakonieczna, L.; et al. *Synthesis* 1985, 929.

(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



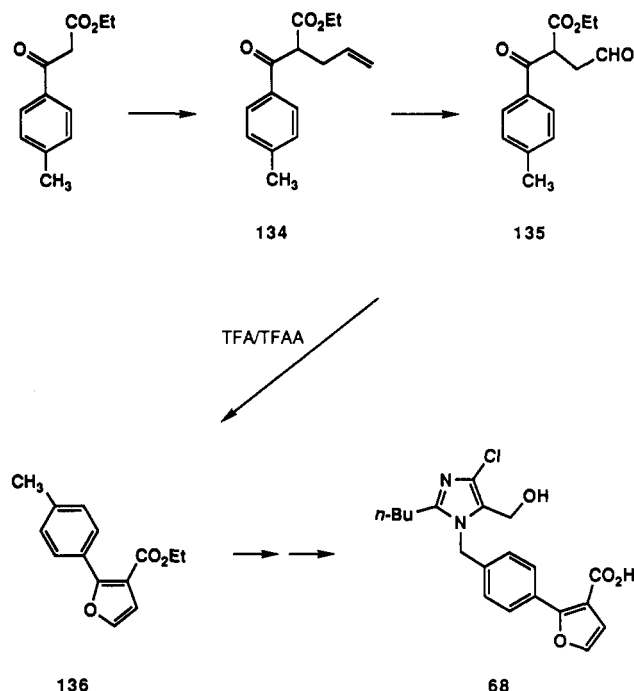
## Scheme XIII



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.<sup>38</sup> 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 fluo-

## Scheme XIV



rohydrin.<sup>39</sup> 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.

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<sup>40</sup> 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

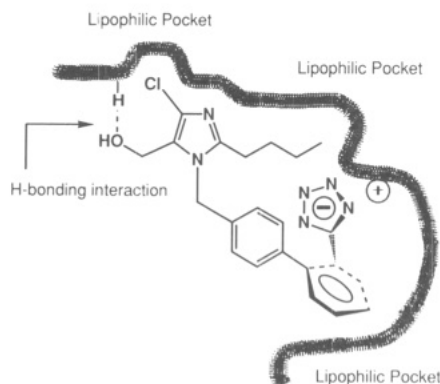
(37) For the preparation of bis(perfluoroalkyl)-1,2,4-triazoles, see: (a) Brown, H. C.; Cheng, M. T. *J. Org. Chem.* 1962, 27, 3240.

(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*-(biphenylmethyl)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.<sup>3a</sup> 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. <sup>1</sup>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 ( $\delta$ ) downfield from TMS as an internal standard. <sup>19</sup>F NMR spectra were measured with a Varian VXR500S spectrometer; chemical shifts are expressed in ppm ( $\delta$ ) 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  $\pm 0.4\%$  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.<sup>41</sup> and Gunther.<sup>42</sup>

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 3000g

for 10 min, and supernatant was decanted through cheesecloth. Combined supernatants were spun at 12000g for 13 min. The final supernatant was then centrifuged at 102000g 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<sub>2</sub>, 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 [<sup>3</sup>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  $\mu$ M unlabeled AII added to the mixture. The inhibitory concentration (IC<sub>50</sub>) 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<sub>50</sub> 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<sub>50</sub> (nM)  $\pm$ SEM is 24.5  $\pm$  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.<sup>43</sup> 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  $\pm$  4 mmHg (mean  $\pm$ SEM,  $n$  = 6), whereas the mean arterial pressure of a group of normotensive rats was 100  $\pm$  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<sub>30</sub> 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  $\pm$  7 mmHg at the start of the experiment to 176  $\pm$  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

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(100–140 °C (0.025 Torr) furnished 4.50 g (11%) of **69** as a colorless oil: NMR (CDCl<sub>3</sub>)  $\delta$  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<sup>-1</sup>.

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<sub>3</sub>)  $\delta$  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<sub>3</sub>)  $\delta$  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**<sup>21</sup> as a colorless solid: mp 70–72 °C; NMR (CDCl<sub>3</sub>)  $\delta$  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<sub>3</sub>)  $\delta$  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<sub>3</sub>)  $\delta$  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*<sub>6</sub>)  $\delta$  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<sub>3</sub>)  $\delta$  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<sup>-1</sup>. Anal. (C<sub>14</sub>H<sub>11</sub>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<sub>3</sub>)  $\delta$  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<sub>3</sub>)  $\delta$  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<sub>3</sub>)  $\delta$  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<sub>3</sub>)  $\delta$  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<sub>3</sub>)  $\delta$  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<sub>3</sub>)  $\delta$  7.82–7.37 (m, 8 H), 4.50 (s, 2 H).

**2-Butyl-1-[(2'-carboxymethoxybiphenyl-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<sup>19</sup> (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<sub>f</sub>*<sup>20</sup> mp 104–105 °C; NMR (CDCl<sub>3</sub>)  $\delta$  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*<sub>6</sub>)  $\delta$  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<sup>-1</sup>. Anal. (C<sub>22</sub>H<sub>23</sub>ClN<sub>2</sub>O<sub>3</sub>) 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<sup>19</sup> and 83 using the procedure described in the preparation of 84: mp 153.5–155.5 °C; NMR (CDCl<sub>3</sub>)  $\delta$  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<sub>22</sub>H<sub>22</sub>ClN<sub>2</sub>O) 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<sup>24</sup> (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*<sub>6</sub>)  $\delta$  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*<sub>6</sub>)  $\delta$  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<sub>22</sub>H<sub>23</sub>ClN<sub>2</sub>O) 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*<sub>6</sub>)  $\delta$  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<sub>2</sub>B<sub>2</sub>, 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<sup>-1</sup>. Anal. (C<sub>22</sub>H<sub>21</sub>ClN<sub>2</sub>O<sub>3</sub>) 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<sup>19</sup> (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<sub>2</sub>O (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<sub>3</sub>)  $\delta$  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<sub>3</sub>)  $\delta$  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'-(1H-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*<sub>6</sub>)  $\delta$  9.68 (s, 1 H), 7.70–7.50 (m, 4 H), 7.05 (A<sub>2</sub>B<sub>2</sub>, 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<sub>22</sub>H<sub>21</sub>ClN<sub>5</sub>O) 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*<sub>6</sub>)  $\delta$  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<sup>-1</sup>. Anal. (C<sub>23</sub>H<sub>23</sub>ClN<sub>2</sub>O<sub>4</sub>) 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*<sub>6</sub>)  $\delta$  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<sup>-1</sup>. Anal. (C<sub>22</sub>H<sub>22</sub>ClN<sub>3</sub>O<sub>3</sub>·0.5H<sub>2</sub>O) 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*<sub>6</sub>)  $\delta$  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<sup>-1</sup>. Anal. (C<sub>22</sub>H<sub>21</sub>ClN<sub>2</sub>O<sub>4</sub>) 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*<sub>6</sub>)  $\delta$  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<sup>-1</sup>. Anal. (C<sub>24</sub>H<sub>25</sub>ClN<sub>2</sub>O<sub>4</sub>) 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<sub>3</sub>)  $\delta$  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<sub>23</sub>H<sub>24</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub>·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<sub>3</sub>)  $\delta$  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*<sub>6</sub>)  $\delta$  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<sub>23</sub>H<sub>25</sub>ClN<sub>2</sub>O<sub>3</sub>·0.2H<sub>2</sub>O) 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 ( $\text{CDCl}_3$ )  $\delta$  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 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 ( $\text{CDCl}_3$ )  $\delta$  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. ( $\text{C}_{23}\text{H}_{26}\text{ClN}_3\text{O}_2 \cdot 0.5\text{DMSO}$ ) 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 ( $\text{DMSO}-d_6$ )  $\delta$  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 $\times$ ). 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 ( $\text{DMSO}-d_6$ )  $\delta$  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. ( $\text{C}_{25}\text{H}_{28}\text{ClN}_5\text{O}_4 \cdot 0.3\text{H}_2\text{O}$ ) 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 ( $\text{CDCl}_3$ )  $\delta$  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 ( $\text{CDCl}_3$ )  $\delta$  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. ( $\text{C}_{33}\text{H}_{31}\text{ClN}_4\text{O}_3 \cdot 0.5\text{H}_2\text{O}$ ) C, H, N.

**[2-Butyl-4-chloro-1-[[2'-(1H-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 ( $\text{DMSO}-d_6$ )  $\delta$  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. ( $\text{C}_{28}\text{H}_{27}\text{ClN}_5\text{O} \cdot 0.5\text{H}_2\text{O}$ ) C, H, Cl.

**2-Butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]imidazole-5-carboxaldehyde, Benzenesulfonylhydrazide (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 ( $\text{DMSO}-d_6$ )  $\delta$  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. ( $\text{C}_{28}\text{H}_{27}\text{ClN}_5\text{O}_2\text{S}$ ) 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<sup>17</sup> (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 ( $\text{DMSO}-d_6$ )  $\delta$  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. ( $\text{C}_{43}\text{H}_{52}\text{ClN}_5\text{O}_7$ ) 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 ( $\text{DMSO}-d_6$ )  $\delta$  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- $d_6$ )  $\delta$  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<sub>3</sub>)  $\delta$  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<sub>2</sub>B<sub>2</sub>, 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<sub>3</sub>)  $\delta$  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<sup>-1</sup>.

**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<sub>3</sub>)  $\delta$  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<sup>-1</sup>.

**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<sub>3</sub>)  $\delta$  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<sup>-1</sup>.

**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- $d_6$ )  $\delta$  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<sup>-1</sup>. 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<sub>2</sub>(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- $d_6$ )  $\delta$  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<sub>2</sub>B<sub>2</sub>, 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- $d_6$ )  $\delta$  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<sub>2</sub>B<sub>2</sub>, 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<sup>-1</sup>. 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<sup>31</sup> (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- $d_6$ )  $\delta$  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<sub>3</sub>)  $\delta$  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<sup>-1</sup>.

**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 phases 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- $d_6$ )  $\delta$  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  $\text{cm}^{-1}$ . Anal. ( $\text{C}_{22}\text{H}_{23}\text{N}_3\text{O}_5$ ) 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 ( $\text{CDCl}_3$ )  $\delta$  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- $d_6$ )  $\delta$  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- $d_6$ )  $\delta$  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  $\text{cm}^{-1}$ .

**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 ( $\text{CDCl}_3$ )  $\delta$  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 ( $\text{CDCl}_3$ )  $\delta$  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- $d_6$ )  $\delta$  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  $\text{cm}^{-1}$ . Anal. ( $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_3\text{HCl}$ ) C, H, N, Cl.

**2-Butyl-4(5)-(hydroxymethyl)-5(4)-iodoimidazole (110).** A solution of 2-butyl-4(5)-(hydroxymethyl)imidazole<sup>31</sup> (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 ( $\text{CDCl}_3$ )  $\delta$  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 ( $\text{CDCl}_3$ )  $\delta$  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]methylimidazole (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 ( $\text{CDCl}_3$ )  $\delta$  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 coarse-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 ( $\text{CDCl}_3$ )  $\delta$  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- $d_6$ )  $\delta$  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);  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ )  $\delta$  -57.8 (s, 3 F); IR 1702  $\text{cm}^{-1}$ . Anal. ( $\text{C}_{23}\text{H}_{23}\text{F}_3\text{N}_2\text{O}_3$ ) 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- $d_6$ )  $\delta$  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  $\text{cm}^{-1}$ . Anal. ( $\text{C}_{22}\text{H}_{24}\text{ClN}_3\text{O}_2$ ) C, H, N, Cl.

**2-Butyl-1-[(2'-carboxymethoxybiphenyl-4-yl)methyl]-4-chloro-5-[(2-methoxyethoxy)methoxy]methylimidazole (114).** The title compound was prepared from 84 by the procedure described for the preparation of 112: NMR ( $\text{CDCl}_3$ )  $\delta$  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]methylimidazole (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 ( $\text{CDCl}_3$ )  $\delta$  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]methylimidazole (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 ( $\text{CDCl}_3$ )  $\delta$  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  $\text{cm}^{-1}$ .

**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 ( $\text{CDCl}_3$ )  $\delta$  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  $\text{cm}^{-1}$ . Anal. ( $\text{C}_{23}\text{H}_{26}\text{ClN}_3\text{O}_3$ ) 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*-diphenylcarbamoylpyridinium chloride<sup>36</sup> (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- $d_6$ )  $\delta$  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  $\text{cm}^{-1}$ . Anal. ( $\text{C}_{28}\text{H}_{28}\text{ClN}_3\text{O}_4\text{S}\cdot 0.5\text{H}_2\text{O}$ ) 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  $\text{cm}^{-1}$ .

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- $d_6$ )  $\delta$  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. ( $\text{C}_{24}\text{H}_{26}\text{ClN}_7\text{O}_2\cdot 0.5\text{H}_2\text{O}\cdot 0.1\text{C}_4\text{H}_9\text{Cl}$ ) 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  $\times$  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<sub>3</sub>)  $\delta$  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<sub>23</sub>H<sub>27</sub>ClN<sub>4</sub>O<sub>2</sub>) 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  $\times$  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<sub>3</sub>)  $\delta$  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<sub>24</sub>H<sub>28</sub>ClF<sub>3</sub>N<sub>4</sub>O<sub>4</sub>S-0.5H<sub>2</sub>O-0.4C<sub>4</sub>H<sub>8</sub>O<sub>2</sub>) 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<sup>19</sup> and 81 by the procedure described for the preparation of 84: NMR (CDCl<sub>3</sub>)  $\delta$  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<sub>3</sub>)  $\delta$  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<sub>3</sub>)  $\delta$  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<sub>3</sub>)  $\delta$  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<sup>-1</sup>. Anal. (C<sub>23</sub>H<sub>26</sub>ClF<sub>3</sub>N<sub>3</sub>O<sub>3</sub>S) 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*<sub>6</sub>/CDCl<sub>3</sub>)  $\delta$  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<sup>-1</sup>. Anal. (C<sub>22</sub>H<sub>23</sub>ClF<sub>3</sub>N<sub>3</sub>O<sub>3</sub>S-0.5H<sub>2</sub>O) 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 Steinhart 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<sub>3</sub>)  $\delta$  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<sub>23</sub>H<sub>27</sub>ClN<sub>2</sub>O<sub>2</sub>) 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<sub>3</sub>)  $\delta$  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<sub>3</sub>)  $\delta$  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 ( $CDCl_3$ )  $\delta$  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<sup>3</sup>-(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 ( $CDCl_3$ )  $\delta$  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 ( $CDCl_3$ )  $\delta$  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 ( $CDCl_3$ )  $\delta$  7.32–6.93 (m, 17 H), 6.66 (d, 6 H,  $J = 9$  Hz), 2.55 (s, 3 H). Anal. ( $C_{35}H_{28}N_3F_3$ ) 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<sup>19</sup> by the procedures described for the preparations of 79, 84, and 17: NMR ( $CDCl_3$ )  $\delta$  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. ( $C_{24}H_{25}ClF_3N_5O$ ) 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 ( $CDCl_3$ )  $\delta$  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) 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 ( $CDCl_3$ )  $\delta$  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<sup>38</sup> (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 ( $CDCl_3$ )  $\delta$  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 ( $DMSO-d_6$ )  $\delta$  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<sup>19</sup> by the procedures described for the preparations of 127, 79, 84, and 17: NMR (CDCl<sub>3</sub>)  $\delta$  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<sub>24</sub>H<sub>23</sub>ClN<sub>3</sub>O) C, H, Cl.

**2-[2-Fluoro-1-hydroxy-2-(benzenesulfonyl)ethyl]-4'-methylbiphenyl (131).** Fluoromethyl phenylsulfone<sup>39</sup> (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  $\times$  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*<sub>6</sub>)  $\delta$  8.00–7.00 (m, 13 H), 6.20–4.90 (m, 3 H), 2.42 (s,  $1/2 \times 3$  H), 2.38 (s,  $1/2 \times 3$  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  $\times$  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*<sub>6</sub>)  $\delta$  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,  $1/2 \times 1$  H), 7.00 (s,  $1/2 \times 1$  H), 2.40 (s, 3 H). Anal. (C<sub>21</sub>H<sub>17</sub>FO<sub>2</sub>S) 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  $\times$  200 mL). The organic layer was dried over anhydrous magnesium sulfate, and the solvent was removed under vacuum to provide 0.58 g (15%) of 133 as a yellow oil: NMR (CDCl<sub>3</sub>)  $\delta$  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<sub>15</sub>H<sub>12</sub>N<sub>3</sub>F) 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<sub>3</sub>)  $\delta$  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<sub>23</sub>H<sub>21</sub>ClFN<sub>3</sub>O-0.8H<sub>2</sub>O-0.1C<sub>4</sub>H<sub>8</sub>O<sub>2</sub>) 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<sup>40</sup> (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<sub>3</sub>)  $\delta$  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<sub>15</sub>H<sub>18</sub>O<sub>3</sub>) C, H.

**3-Carboethoxy-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  $\times$  500 mL) and brine (1  $\times$  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<sub>3</sub>)  $\delta$  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<sub>14</sub>H<sub>16</sub>O<sub>4</sub>) C, H.

**3-Carboethoxy-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  $\times$  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<sub>3</sub>)  $\delta$  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<sup>19</sup> by the procedures described for the preparations of 79, 84, and 2: mp 158.5–160.0 °C; NMR (DMSO-*d*<sub>6</sub>)  $\delta$  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<sub>20</sub>H<sub>21</sub>ClN<sub>2</sub>O<sub>4</sub>) C, H, N.

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**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-iodo-

benzoate, 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

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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  $\mu$ M. This value is as good as those of the best GABA-uptake inhibitors known today.

$\gamma$ -Aminobutyric acid (GABA, 1) is a major neurotransmitter in mammals.<sup>1-9</sup> Dysfunctioning of GABA-ergic synapses has been invoked for diseases such as Parkinson's disease,<sup>10-13</sup> Huntington's chorea,<sup>14</sup> epilepsy,<sup>15,16</sup> and some forms of schizophrenia.<sup>17-19</sup> One of the possible ways to palliate GABA deficiency lies in the inhibition of uptake mechanisms of this neurotransmitter.<sup>20-24</sup> Taking in account the results of various studies devoted to this GABA-ergic regulation approach<sup>25-27</sup> 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)<sup>28</sup> (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,<sup>29</sup> cyclobutyl,<sup>29</sup> cyclopentyl,<sup>30</sup> cyclopentenyl,<sup>30</sup> cyclohexyl,<sup>29,31</sup> cyclohexenyl,<sup>29</sup> and cyclohexadienyl<sup>29</sup> 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<sup>30</sup> 3 and 4, respectively (Figure 1). Some

heterocyclic amino acids were also described as GABA-uptake inhibitors, especially in the pyrrolidine<sup>29</sup> and pi-

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