

Nonpeptide Angiotensin II Antagonists Derived from 4*H*-1,2,4-Triazoles and 3*H*-Imidazo[1,2-*b*][1,2,4]triazoles

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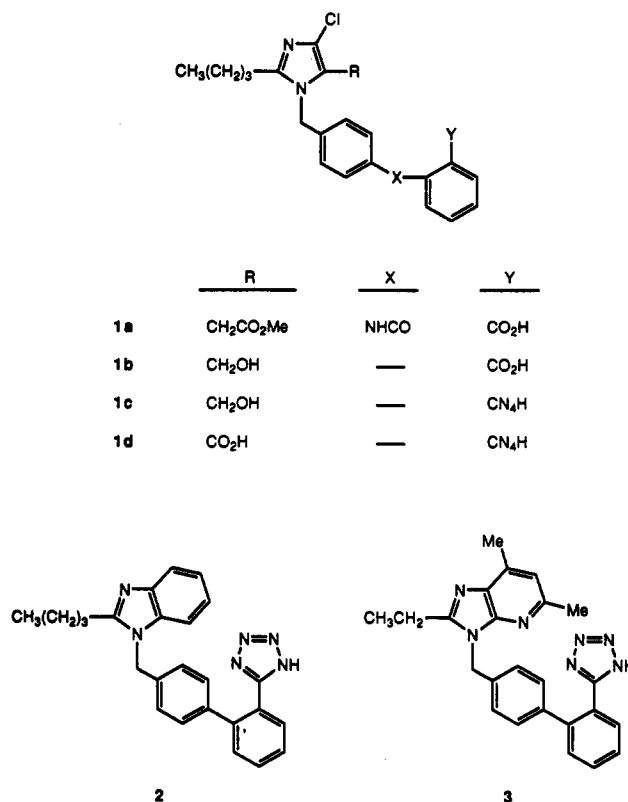
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By a variety of synthetic routes, we have synthesized a series of 3,4,5-trisubstituted 4*H*-1,2,4-triazoles and a related series of 3*H*-imidazo[1,2-*b*][1,2,4]triazoles and evaluated them in vitro and in vivo as angiotensin II (AII) antagonists. Principal efforts focused on triazoles bearing an *n*-alkyl substituent at C³ and a 4-[(2-carboxybenzoyl)amino]benzyl, (2'-carboxybiphenyl-4-yl)methyl, or [2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl side chain at N⁴. Among numerous variations at C⁵, benzylthio groups gave the best potency. Particularly noteworthy was 3-*n*-butyl-5-[(2-carboxybenzyl)thio]-4-[[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-4*H*-1,2,4-triazole (71, IC₅₀ 1.4 nM), which blocked the AII pressor response in conscious rats at 0.3 mg/kg iv with a duration of action of approximately 6 h, similar to that of DuP 753. Although 71 was active orally only at a 10-fold higher dose level, good oral bioavailability was demonstrated for a monoacidic analogue 62. Most potent among the bicyclic derivatives was 2-*n*-butyl-5,6-dimethyl-3-[[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-3*H*-imidazo[1,2-*b*][1,2,4]triazole (93, IC₅₀ 7.8 nM). The effects of hydrophobic, hydrogen-bonding, and ionic interactions with the AT₁ receptor are considered.

The importance of the renin-angiotensin system^{1,2} as a target for cardiovascular disease therapy is well-established.³⁻⁶ Angiotensin-converting enzyme (ACE) inhibitors, which block the conversion of angiotensin I (AI) to the potent vasoconstrictor angiotensin II (AII), are widely used for the treatment of hypertension and congestive heart failure.⁴ However, some side effects of ACE inhibitors have been attributed to elevated levels of bradykinin, which is also a substrate for this enzyme.⁷ Inhibitors of renin, the highly specific enzyme responsible for the transformation of angiotensinogen to AI, have been shown experimentally to exert potent antihypertensive effects, but efforts to develop renin inhibitors as drugs have been hampered by poor oral bioavailability and limited duration of action.⁵

Specific inhibition of the terminal step in the renin-angiotensin cascade, the action of AII at its receptor site, offers the potential for antihypertensive therapy with minimal side effects.^{5,8} Peptide AII antagonists such as saralasin have been known for several years, but these have typically suffered from lack of oral absorption, rapid metabolism and/or clearance, and partial agonist activity.⁹ The prototype imidazole-based nonpeptide AII antagonists reported from the Takeda laboratories^{10,11} a decade ago have recently spawned a new generation of potent and specific AII antagonists (Chart I). The pioneering efforts of the Du Pont group¹² have generated such promising lead structures as EXP6803 (1a)^{13,14} and 1b.¹⁵ These investigations have culminated in the discovery of DuP 753 (1c),^{15,16} now in advanced clinical evaluation, and its active metabolite EXP3174 (1d).^{15,17} Fusion of a 6-membered ring at the C⁴-C⁵ bond of the imidazole has produced interesting bicyclic AII antagonists such as the benzimidazole 2¹⁸ and the exceptionally potent imidazo[4,5-*b*]pyrimidine L-158,809 (3).^{19,20} All of these compounds are believed to be selective for the AT₁ receptor subtype, the site of the major physiological functions of AII known

Chart I

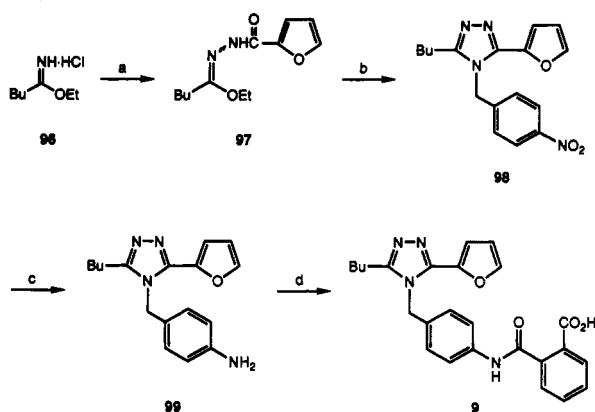


to date.²¹ A series of nonpeptide AT₂-selective antagonists has also been reported.²²

While some studies have explored further variations of the side chains at N¹ and/or C⁵ of the imidazole,²³⁻²⁷ we were interested in replacement of the imidazole ring by another heterocycle. The 1,2,4-triazole system seemed to be a reasonable candidate, being very similar in geometry to the imidazole moiety. Furthermore, the additional nitrogen atom in the ring was expected to exert an electron-withdrawing effect similar to the 4-chloro substituent in

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Scheme I^a

^a (a) 2-Furoic acid hydrazide, EtOH, -10 to 5 °C; (b) 4-nitrobenzylamine, EtOH, 45–70 °C; (c) SnCl₂·2H₂O, concentrated HCl, THF; (d) phthalic anhydride, THF.

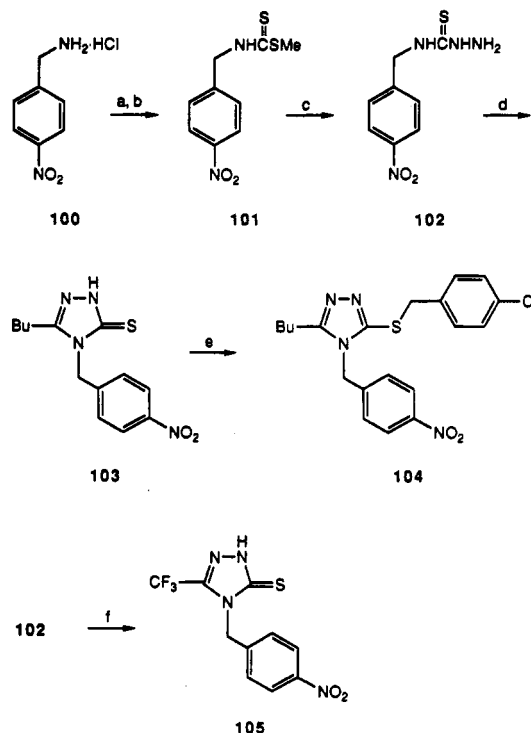
1. Therefore, we prepared and evaluated a series of 3,4,5-trisubstituted 4*H*-1,2,4-triazoles (4–88, Tables I and II) related to 1. In addition, we have extended the triazole-based AII antagonists to a series of 3*H*-imidazo[1,2-*b*]-[1,2,4]triazoles (89–95, Table III) related to the bicyclic compounds 2 and 3. A few examples of 4*H*-1,2,4-triazoles prepared as AII antagonists have been reported recently by the Du Pont group.^{28,29}

Chemistry

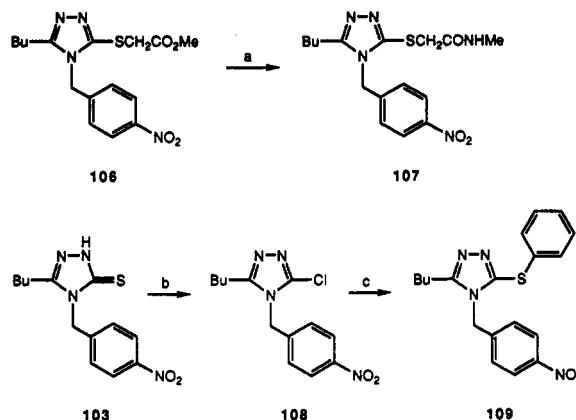
Initially, synthetic efforts focused on triazoles (4–45) bearing the 4-[(2-carboxybenzoyl)amino]benzyl side chain at N⁴, as in the imidazole EXP6803 (1a). Following a literature route,^{30,31} 3-alkyl-5-aryl(or heteroaryl)-4-(aryl-methyl)-4*H*-1,2,4-triazoles were prepared as in Scheme I. In the example shown, imidate hydrochloride 96³² was reacted with 2-furoic acid hydrazide to give 97, which was converted to the triazole 98 upon heating with 4-nitrobenzylamine. Stannous chloride reduction of the nitro group and treatment of the resulting amine 98 with phthalic anhydride afforded the target compound 9.

Considerable attention was directed to triazoles having substituted mercapto groups at the 5-position.³³ As shown in Scheme II, the thiosemicarbazide derivative 102, obtained from the dithiocarbamate 101, was cyclized to the triazolinethione 103 by heating with trimethyl ortho-valerate. Selective alkylation on sulfur³³ yielded 104, which was further elaborated to 33 as in Scheme I. For triazoles 10–15, the requisite ortho esters were prepared via the imidates according to a literature method.³² Cyclization of 102 with trifluoroacetic acid at elevated temperature³⁴ provided the trifluoromethyl analogue 105, a precursor of 16 and 17. For the synthesis of 19, the amide side chain was generated by direct treatment of ester intermediate 106 with aqueous methylamine (Scheme III). In order to prepare the phenylthio-substituted triazole 24, the chlorotriazole 108 was made by treatment of 103 with chlorine.³⁵ Displacement of the chloro group with thiophenol in the presence of *N,N*-diisopropylethylamine gave 109.

In triazoles 46–49, the carboxy substituent of the amide-bridged side chain at N⁴ was replaced by a tetrazole group. As illustrated in Scheme IV, the 4-aminobenzyl derivative 110 was reacted with 2-cyanobenzoyl chloride (111). Heating the resulting product 112 with trimethyltin azide^{15,36,37} furnished 46. Yields were low for this reaction because of the thermal instability of 112, probably

Scheme II^a

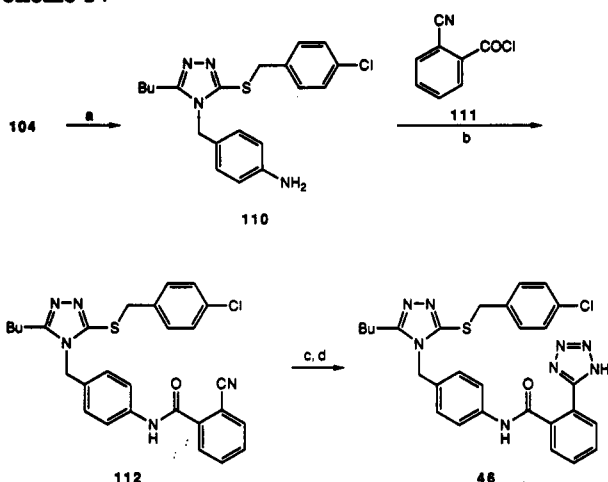
^a (a) CS₂, Et₃N, MeOH; (b) MeI; (c) H₂NNH₂·H₂O, EtOH, Δ; (d) BuC(OMe)₃, MeO(CH₂)₂OH, Δ; (e) 4-chlorobenzyl chloride, *i*-Pr₂NEt, MeO(CH₂)₂OH; (f) TFA, Δ.

Scheme III^a

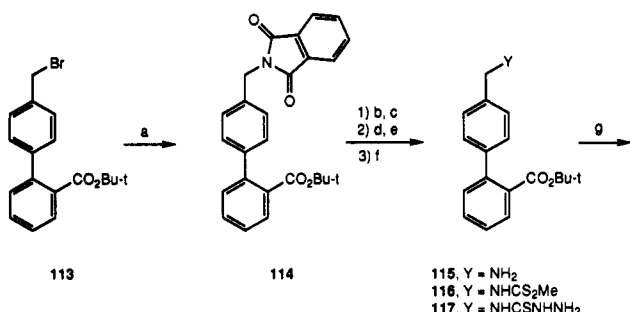
^a (a) 40% MeNH₂ (aqueous), MeOH; (b) Cl₂, CH₂Cl₂; (c) thiophenol, *i*-Pr₂NEt, DMF, Δ.

reflecting a susceptibility of the nitrile to attack by the adjacent amide carbonyl. Various methods have been reported for the deprotection of intermediate (trialkylstannyl)tetrazoles, including anhydrous HCl,³⁷ KF/HBF₄,³⁸ and aqueous sodium hydroxide.¹⁵ We have found, in the course of this work, that treatment with silica gel is normally quite effective for destannylation of the tetrazole. The absence of trimethyltin contamination in the final products was readily confirmed by NMR.

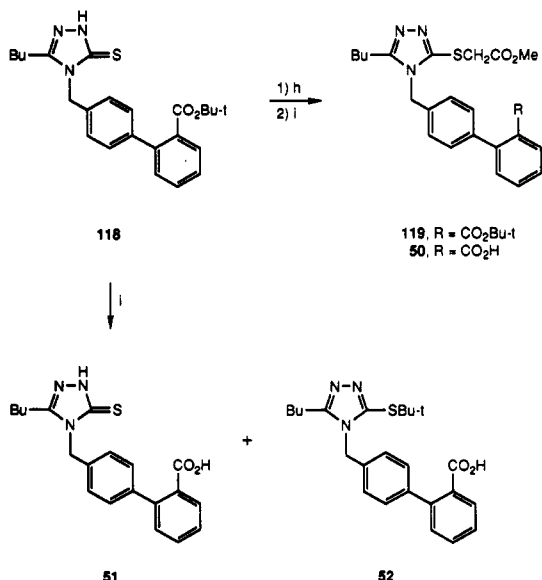
Triazoles 50–53, containing a biphenylcarboxylic acid side chain analogous to that of the imidazole 1b, were prepared as shown in Scheme V. The amine 115 was obtained in a Gabriel synthesis from the bromo derivative 113.¹⁵ By methods paralleling Scheme II, the (alkylthio)triazole 119 was synthesized, and the *tert*-butyl ester was deprotected with TFA to give 50. Similar deprotection of 118 gave a readily separable mixture of 51 and 52, the latter arising from *tert*-butyl migration.

Scheme IV^a

^a (a) $\text{SnCl}_4 \cdot 2\text{H}_2\text{O}$, concentrated HCl, THF; (b) $i\text{-Pr}_2\text{NEt}$, THF; (c) Me_3SnN_3 , toluene, Δ ; (d) silica gel, MeOH.

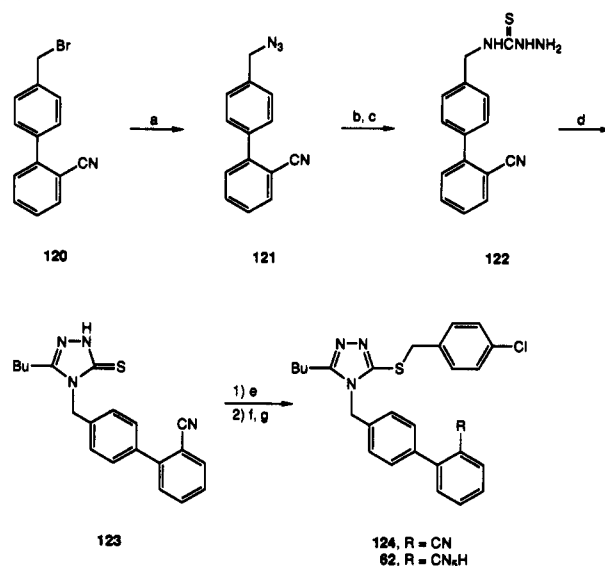
Scheme V^a

115, Y = NH_2
116, Y = NHCS_2Me
117, Y = NHCSNHNH_2

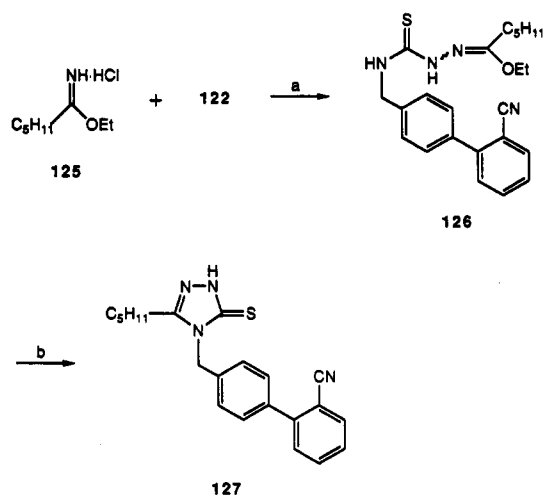


^a (a) Potassium phthalimide, DMF; (b) H_2NNH_2 , EtOH; (c) AcOH; (d) CS_2 , Et_3N , MeOH; (e) MeI; (f) $\text{H}_2\text{NNH}_2 \cdot \text{H}_2\text{O}$, EtOH, Δ ; (g) $\text{BuC}(\text{OMe})_3$, $\text{MeO}(\text{CH}_2)_2\text{OH}$, Δ ; (h) methyl chloroacetate, $i\text{-Pr}_2\text{NEt}$, CH_2Cl_2 ; (i) TFA.

The remaining target AII antagonists 53–95 incorporated the biphenyltriazole side chain present in the reference compounds 1c,d, 2, and 3. A typical sequence is shown in Scheme VI. A convenient route to the thiosemicarbazide intermediate 122 was developed. The bromo nitrile 120 was converted to the azido derivative 121. Using the method of Tsuge,³⁹ the azide was transformed to the corresponding isothiocyanate with tri-

Scheme VI^a

^a (a) LiN_3 , DMSO; (b) Ph_3P , CS_2 ; (c) $\text{H}_2\text{NNH}_2 \cdot \text{H}_2\text{O}$, THF; (d) $\text{BuC}(\text{OMe})_3$, $\text{MeO}(\text{CH}_2)_2\text{OH}$, Δ ; (e) 4-chlorobenzyl chloride, $i\text{-Pr}_2\text{NEt}$, $\text{MeO}(\text{CH}_2)_2\text{OH}$; (f) Me_3SnN_3 , toluene, Δ ; (g) silica gel, MeOH.

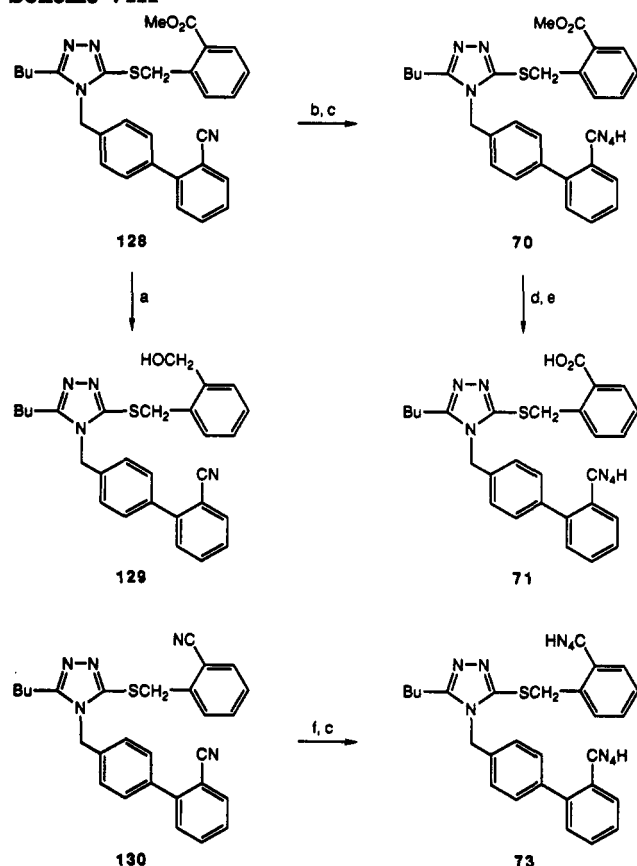
Scheme VII^a

^a (a) DMF; (b) DBU, THF, Δ .

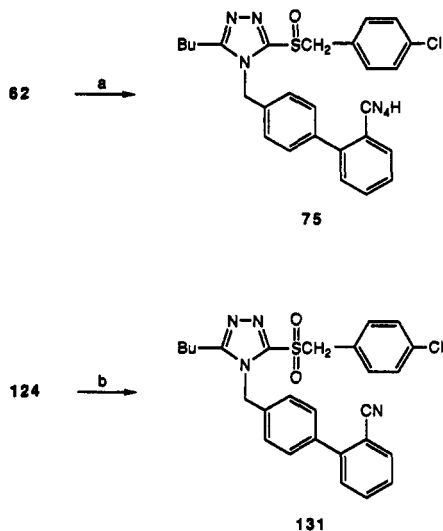
phenylphosphine and carbon disulfide. Without isolation, this was treated with hydrazine hydrate to give 122. By methods described in the previous schemes, 62 and related analogues were thus prepared.

Because trimethyl orthoheptanoate was not commercially available, we investigated an alternative route to the pentyl analogue 63 (Scheme VII). The work of Milcent⁴⁰ had demonstrated the synthesis of mercaptotriazoles by addition of thiosemicarbazide to an imidate hydrochloride and reaction of the intermediate ester thiosemicarbazone with a substituted amine. Since we had in hand the 4-substituted thiosemicarbazide derivative 122, this was added to ethyl hexanimidate hydrochloride (125),⁴¹ and the resulting adduct 126 was effectively cyclized to the desired triazole 127 by heating it in the presence of DBU. This approach differs from the Milcent synthesis in that the incipient N^4 -substituent is already in place on the thiosemicarbazide.

For the synthesis of 72, the ester intermediate 128 was reduced to the corresponding hydroxymethyl derivative 129 (Scheme VIII). Reaction of 128 with trimethyltin azide yielded 70, and subsequent saponification provided 71.

Scheme VIII^a

^a (a) LiBH_4 , THF; (b) Me_3SnN_3 , toluene, Δ ; (c) silica gel, MeOH; (d) 2.5 N NaOH, MeOH; (e) 2 N HCl; (f) Me_3SnN_3 , dioxane, Δ .

Scheme IX^a

^a (a) 30% H_2O_2 , AcOH; (b) MCPBA, CH_2Cl_2 .

As an analogue of 71, the dinitrile intermediate 130 was converted to the ditetrazole derivative 73.

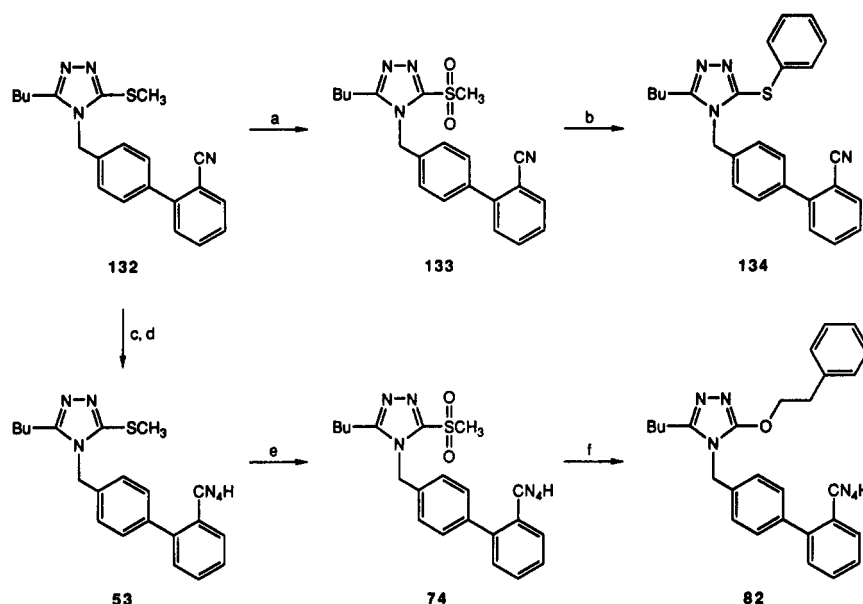
The sulfoxide 75 was readily prepared from 62 by treatment with 30% hydrogen peroxide in acetic acid (Scheme IX). Although the corresponding sulfone 76 could also be prepared directly from 62, in this case there was a purification advantage in performing the MCPBA oxidation at the nitrile stage, transforming 124 to 131. Certain triazoles were most conveniently obtained by displacement of a methanesulfonyl substituent (Scheme X). Oxidation of the methylthio derivative 132 with excess

MCPBA provided the sulfone 133. Reaction of this with thiophenol in DMF at reflux in the presence of *N,N*-diisopropylethylamine yielded the (phenylthio)triazole 134, a precursor of 56. Also, 132 was converted to the tetrazole 53, which was oxidized to the sulfone 74 with 10% peracetic acid. In accord with the work of Åkerblom and Campbell,⁴² reaction of 74 with the sodium salt of phenethyl alcohol gave the ether-linked triazole 82.

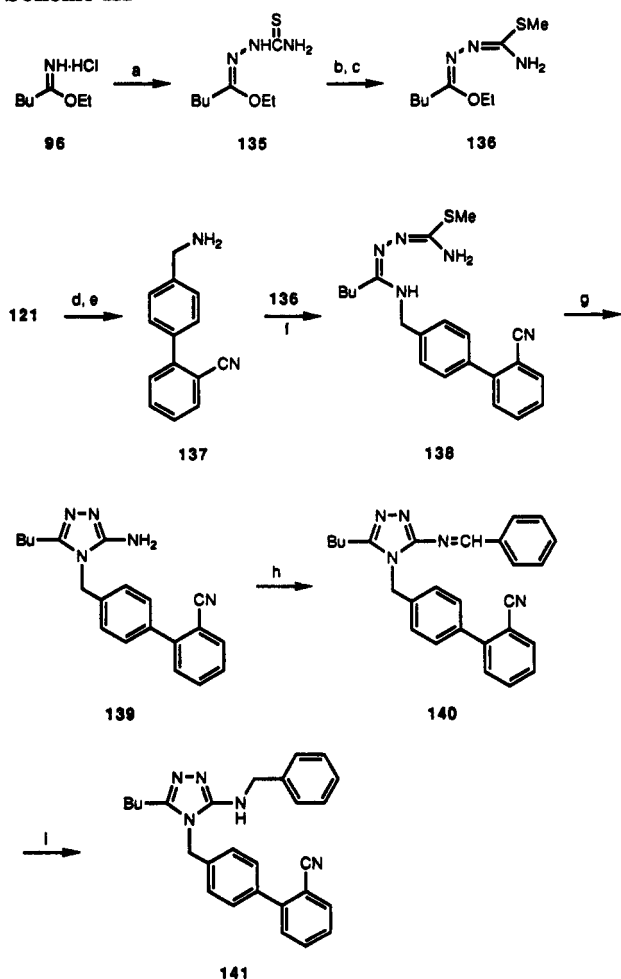
We were unable to synthesize triazoles with a substituted amino group at the 3(5)-position (i.e., 83-85) by displacement of a methanesulfonyl group from 133 or 74. 4,5-Disubstituted 3-aminotriazoles⁴³ have generally been prepared by cyclization of (acylamino)guanidines and related methods, but these procedures tend to give mixtures of isomers.^{44,45} We sought a pathway which would be regiospecific and unequivocal. Following the work of Milcent,⁴⁰ imidate hydrochloride 96 was converted to the ester thiosemicarbazone 135. These investigators had shown that compounds analogous to 135 reacted with primary amines to give mercaptotriazoles (triazoline-thiones). We reasoned that, if the sulfur moiety could be converted to a better leaving group, the reaction could lead to aminotriazoles in preference to mercaptotriazoles. First, 135 was treated with iodomethane to give the *S*-methylisothiosemicarbazone 136 (Scheme XI). At the same time, amine 137 was prepared from the azide 122 by triphenylphosphine reduction.⁴⁶ Reaction of 136 with 137 at room temperature yielded the amide isothiosemicarbazone 138. Although a modest yield of the desired aminotriazole 139 could be achieved by thermal cyclization of 138, a much cleaner and more efficient method was to treat 138 at room temperature with MCPBA. This resulted in spontaneous cyclization to 139, presumably via oxidation of the methylthio group to a readily displaceable methylsulfinyl or methylsulfonyl moiety. Analogous to the work of Reiter,^{47,48} 139 was condensed with benzaldehyde, and the resulting Schiff base 140 was reduced to the (benzyl-amino)triazole 141.

Carbamoyltriazoles 86-88 were prepared according to the route of Pesson and Antoine,⁴⁹ which represents a variation on Scheme I. The substituted oxamic ester 144 was made by the method of Sellstedt⁵⁰ (Scheme XII). Treatment of 144 with hydrazine hydrate⁵¹ afforded the semioxamamide derivative 145, which reacted with the imidate 96 to give the adduct 146. Upon heating 146 with the amine 137, the carbamoyltriazole intermediate 147 was readily obtained.

The availability of the aminotriazole intermediate 139 offered an entry into a series of 3*H*-imidazo[1,2-*b*][1,2,4]-triazoles 89-95 using modifications of the methods of Babichev and co-workers.⁵² For example, reaction of 139 with the α -bromo ketone 148 yielded the triazolium salt 149 (Scheme XIII). NMR and mass spectral data were fully consistent with the structural assignment of 149. Whereas Babichev et al.⁵² had used vigorous, strongly acidic conditions for the cyclization of aminotriazolium salts analogous to 149, we found that such conditions were inefficient and destructive to the molecule in this case. Among several reagents investigated for promoting the cyclization, only poly(phosphoric acid) (PPA) at about 80 °C led to complete and relatively clean reaction. However, a complication stemmed from the ability of PPA to convert nitriles to primary amides.⁵³ In general, mixtures of nitrile and amide were obtained in the PPA cyclization. In some cases these were separated chromatographically, and only

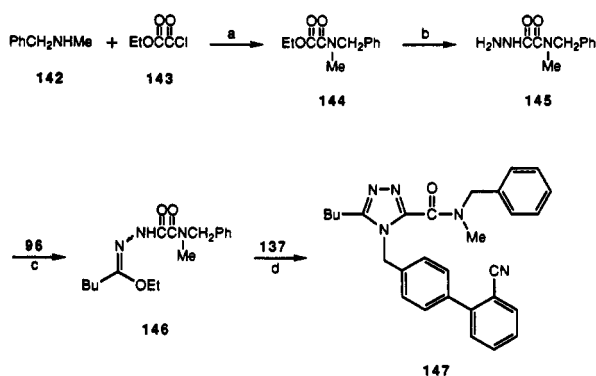
Scheme X^a

^a (a) MCPBA, CH₂Cl₂; (b) thiophenol, *i*-Pr₂NEt, DMF, Δ; (c) Me₃SnN₃, toluene, Δ; (d) silica gel, MeOH; (e) 10% AcOOH, AcOH; (f) phenethyl alcohol sodium salt, 65 °C.

Scheme XI^a

^a (a) Thiosemicarbazide, DMF; (b) MeI, CH₂Cl₂; (c) aqueous Na₂CO₃; (d) Ph₃P, THF; (e) H₂O; (f) EtOH; (g) MCPBA, CH₂Cl₂; (h) benzaldehyde, catalytic piperidine, *i*-PrOH, Δ; (i) NaBH₄, EtOH.

the isolated nitrile was carried forward. For the synthesis of 150, the nitrile was regenerated in situ by treatment with trichloroacetyl chloride in the presence of triethyl-

Scheme XII^a

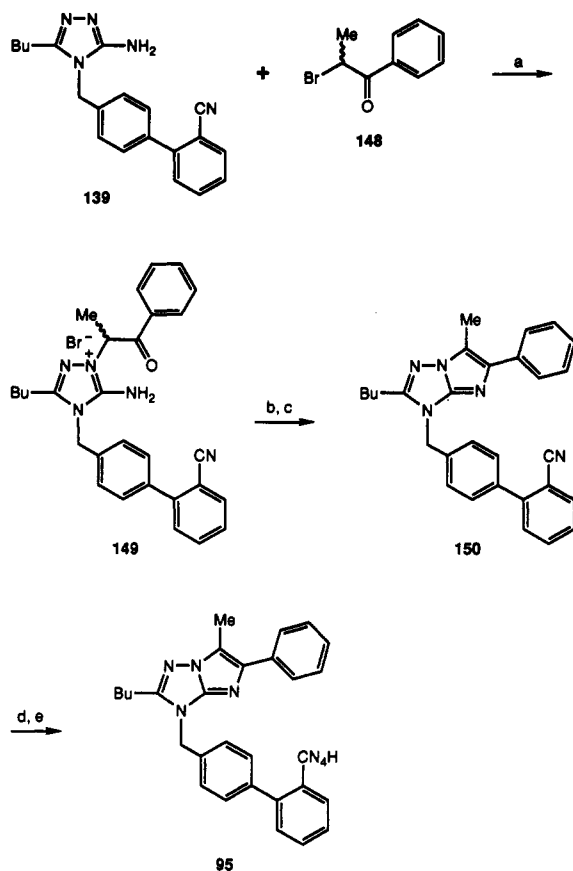
^a (a) Pyridine, CH₂Cl₂; (b) H₂NNH₂·H₂O, EtOH; (c) EtOH, -10 to -5 °C; (d) EtOH, 45-70 °C.

amine.⁵⁴ Subsequent conversion of the nitrile to tetrazole was achieved with trimethyltin azide as described above.

We found that the use of trichloroacetyl chloride for the amide dehydration was unsuitable for imidazotriazoles having a hydrogen at position 6, as trichloroacetylation of the ring also occurred. The susceptibility of the 6-position in imidazo[1,2-*b*][1,2,4]triazoles to electrophilic attack has been documented.⁵⁵ The use of poly(phosphate ester)⁵⁶ for the nitrile dehydration⁵⁷ avoided this problem, as shown in Scheme XIV for the synthesis of 152, the precursor of 91. In the pathway to the 6-phenylimidazo[1,2-*b*][1,2,4]triazole 92, it was found that simply heating aminotriazole 138 with 2-bromo-2-phenylacetaldehyde (154)⁵⁸ led directly to the bicyclic product 155.

Biological Results and Discussion

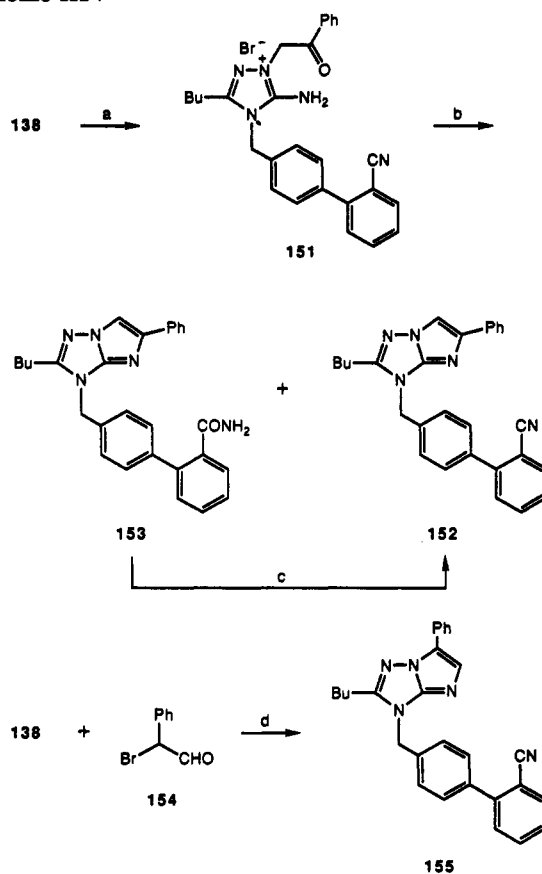
In Vitro AII Antagonism. The new triazole and imidazotriazole compounds 4-95 were evaluated as AII antagonists by displacement of [¹²⁵I]Sar¹Ile⁸-AII at the rabbit aorta AT₁ receptor. Triazoles 4-49, bearing an amide-bridged acidic side chain at N⁴, are presented in Table I. The 3-butyl-5-phenyl derivative 4 was a modest antagonist, having an IC₅₀ (930 nM) about twice as high as that of the structurally related imidazole, EXP6803

Scheme XIII^a

^a (a) EtOH, Δ ; (b) PPA, 80 °C; (c) Cl_3CCOCl , Et_3N , CH_2Cl_2 ; (d) Me_3SnN_3 , toluene, Δ ; (e) silica gel, MeOH.

(1a). Replacement of the butyl side chain in 4 by either ethylthio (5) or propylthio (6) led to approximately a 2-fold decrease in potency. Replacement of the phenyl substituent in 4 by heterocycles (7–9) also led to somewhat lesser potency. Several additional analogues with ethylthio or propylthio at the 3-position (10–17) were examined to evaluate the effects of various other carbon-linked substituents at C⁵. A comparison of 11–13 with 6 indicated that, in this homologous series, the optimum chain length at the 5-position was phenethyl (12; IC_{50} 75 nM). The (phenylthio)methyl analogue 14 was surprisingly ineffective, possibly reflecting an unfavorable orientation of the phenyl group. Small methoxymethyl and trifluoromethyl substituents at C⁵ (15–17) were quite poor.

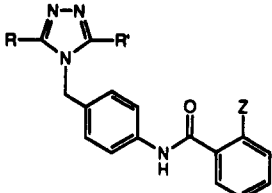
Numerous triazoles with butyl at C³ and substituted mercapto groups at C⁵ were investigated. A breakthrough in activity was observed for benzylthio (25; IC_{50} 15 nM), which was significantly more potent than either phenylthio (24) or phenethylthio (26). Replacement of the 3-butyl substituent in 25 by propyl (27) decreased potency 8-fold. Among the various analogues of 25 having simple substituents on the benzyl ring, improved affinity was observed for 4-methyl (30), 4-chloro (33), and especially 4-methoxy (35; IC_{50} 3.0 nM). Meta and ortho substituents tended to be ineffective. A sulfoxide analogue (36) of 35 had reduced potency. Carboxylic acid and ester substituents on the benzyl moiety of 25 displayed a distinct structure–activity pattern (40–45). The α -(methoxycarbonyl) derivative 40 showed enhanced potency (IC_{50} 6.1 nM). The 2-carboxy analogue 43 (IC_{50} 3.3 nM) was uniquely active among ortho-substituted derivatives of 25. Compounds 46 and 47, having a tetrazole as the acidic moiety on the side chain

Scheme XIV^a

^a (a) Phenacyl bromide, EtOH, Δ ; (b) PPA, 85 °C; (c) PPE, CDCl_3 , Δ ; (d) EtOH, Δ .

at N⁴, were similar in activity to their carboxy counterparts 33 and 35, respectively. The corresponding sulfoxides 48 and 49 were considerably less potent.

Triazoles containing a biphenylcarboxylic acid variant of the N⁴ side chain were briefly explored (50–52, Table II). These were relatively weak antagonists, about 2–4-fold less potent than the reference imidazole 1b with this side chain. In one direct comparison, 50 was somewhat less potent than the identically substituted analogue 18 in the amide-bridged series. The remainder of the compounds in the triazole series (53–88, Table II) contained the biphenyltetrazole side chain present in the imidazole leads DuP 753 (1c) and EXP3174 (1d). Many of the structure–activity relationships paralleled those in the amide-bridged series. For example, an outstanding antagonist was the 3-butyl-4-(benzylthio) compound 57. Analogous to the earlier series, 57 was superior to the phenylthio (56) and phenethylthio (58) homologues and also superior to the saturated cyclohexylmethyl analogue 55. From a comparison of 61–63, butyl was again the preferred chain length at C³. However, in contrast to the amide-bridged series, para substitution on the benzyl moiety did not lead to enhanced potency. In fact, substitution on the benzyl group was almost uniformly detrimental. A striking exception was the 2-carboxybenzyl derivative 71 (IC_{50} 1.5 nM), which was 4-fold more potent than the diacidic imidazole EXP3174 (1d) in this assay. As in the case of 43, a carboxy substituent at the ortho position of the benzyl seems to be involved in a significant binding interaction. Replacement of the carboxyl in 71 by another acidic group, 1H-tetrazol-5-yl, gave a compound (73) with similar potency.

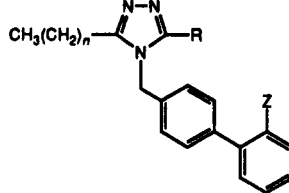
Table I. Physical Properties and in Vitro AII Antagonist Potencies of 4*H*-1,2,4-Triazoles with Amide-Bridged Side Chains


no.	R	R'	Z	method ^a	% yield	mp, °C	formula ^b	FAB-MS <i>m/e</i> (M + H) ⁺	rabbit aorta AT ₁ IC ₅₀ , ^c nM
1a	(imidazole, EXP6803)								420 ^d
4	Bu	Ph	CO ₂ H	A ^{e,f}	64	187–188	C ₂₇ H ₂₆ N ₄ O ₃ ·1.25H ₂ O	455	930
5	EtS	Ph	CO ₂ H	A ^e	60	177.5–178	C ₂₅ H ₂₂ N ₄ O ₃ S·0.2H ₂ O	459	1900
6	PrS	Ph	CO ₂ H	A ^{e,f}	72	166.5–167	C ₂₆ H ₂₄ N ₄ O ₃ S·0.6H ₂ O·0.7Et ₂ O	473	1600
7	Bu	4-pyridyl	CO ₂ H	A ^{e,f}	63	152–153	C ₂₆ H ₂₅ N ₅ O ₃ ·H ₂ O·0.25Et ₂ O	456	1400
8	Bu	3-pyridyl	CO ₂ H	A ^{e,f}	54	108–109	C ₂₆ H ₂₅ N ₅ O ₃	456.2059 ^g	1700
9	Bu	2-furyl	CO ₂ H	A	85	169.5–171	C ₂₅ H ₂₄ N ₄ O ₄ ·0.4H ₂ O	445	1000
10	EtS	CH ₂ Ph	CO ₂ H	A	67	179–180	C ₂₆ H ₂₄ N ₄ O ₃ S·0.25H ₂ O	473	1000
11	PrS	CH ₂ Ph	CO ₂ H	A ^{e,f}	85	>95 (gradual)	C ₂₇ H ₂₆ N ₄ O ₃ S·1.5H ₂ O·0.5THF	487	380
12	PrS	(CH ₂) ₂ Ph	CO ₂ H	A ^{e,f,h}	65	147–147.5	C ₂₈ H ₂₈ N ₄ O ₃ S	501	75
13	PrS	(CH ₂) ₃ Ph	CO ₂ H	A ^{e,f}	91	152–153	C ₂₉ H ₃₀ N ₄ O ₃ S	515	320
14	PrS	CH ₂ SPh	CO ₂ H	A ^{e,f,i}	44	159–160	C ₂₇ H ₂₆ N ₄ O ₃ S ₂ ·0.4H ₂ O	519	1200
15	EtS	CH ₂ OMe	CO ₂ H	A	90	192–193	C ₂₁ H ₂₃ N ₄ O ₄ S	428	5200
16	EtS	CF ₃	CO ₂ H	A ^{e,f}	59	154–156	C ₂₀ H ₁₇ F ₃ N ₄ O ₃ S·0.4Et ₂ O	451	4800
17	PrS	CF ₃	CO ₂ H	A ^{e,j}	9	167–169	C ₂₁ H ₁₈ F ₃ N ₄ O ₃ S·H ₂ O·0.9AcOH	487 ^k	2100
18	Bu	SCH ₂ CO ₂ Me	CO ₂ H	A ^{e,j}	77	161–162	C ₂₄ H ₂₆ N ₄ O ₅ S	483	330
19	Bu	SCH ₂ CONHMe	CO ₂ H	A ^{e,f}	73	137–139	C ₂₄ H ₂₇ N ₅ O ₄ S·0.25H ₂ O	482	720
20	Bu	SCH ₂ CO ₂ H	CO ₂ H	D ^l	60	135–137	C ₂₃ H ₂₄ N ₄ O ₅ S·1.5H ₂ O	<i>m</i>	770
21	Bu	S(CH ₂) ₂ OH	CO ₂ H	A ^{e,f,n}	69	157–159	C ₂₃ H ₂₆ N ₄ O ₄ S·0.3H ₂ O	455	480
22	Bu	SCH(Et)CO ₂ Me	CO ₂ H	A ^{e,f}	82	129–130	C ₂₆ H ₃₀ N ₄ O ₅ S	511	300
23	Bu	SCH ₂ COPh	CO ₂ H	A ^{e,f}	52	92–93	C ₂₉ H ₂₈ N ₄ O ₄ S·0.75H ₂ O·0.4Et ₂ O	529	190
24	Bu	SPh	CO ₂ H	A ^{e,f}	42	144–146	C ₂₇ H ₂₆ N ₄ O ₃ S·H ₂ O	487	60
25	Bu	SCH ₂ Ph	CO ₂ H	A ^{e,f}	85	158–160	C ₂₈ H ₂₈ N ₄ O ₃ S·0.5H ₂ O·0.1Et ₂ O	501	15
26	Bu	S(CH ₂) ₂ Ph	CO ₂ H	A ^{e,f}	71	112–114	C ₂₈ H ₃₀ N ₄ O ₃ S·H ₂ O	515	70
27	Pr	SCH ₂ Ph	CO ₂ H	A	92	196–197	C ₂₇ H ₂₆ N ₄ O ₃ S·0.4H ₂ O	487	120
28	Bu	SCH ₂ Ph(2-Me)	CO ₂ H	A	66	166–168	C ₂₉ H ₃₀ N ₄ O ₃ S·0.25H ₂ O	515	14
29	Bu	SCH ₂ Ph(3-Me)	CO ₂ H	A ^{e,n}	78	164–165	C ₂₉ H ₃₀ N ₄ O ₃ S	515	32
30	Bu	SCH ₂ Ph(4-Me)	CO ₂ H	A	75	135–137	C ₂₉ H ₃₀ N ₄ O ₃ S·0.4H ₂ O	515	7.6
31	Bu	SCH ₂ Ph(2-Cl)	CO ₂ H	A	85	165–166	C ₂₈ H ₂₇ ClN ₄ O ₃ S	535	30
32	Bu	SCH ₂ Ph(3-Cl)	CO ₂ H	A	85	169–170	C ₂₈ H ₂₇ ClN ₄ O ₃ S	535	26
33	Bu	SCH ₂ Ph(4-Cl)	CO ₂ H	A ^{e,f}	77	115–116	C ₂₈ H ₂₇ ClN ₄ O ₃ S·0.25H ₂ O	535	6.8
34	Bu	SCH ₂ Ph(3-OMe)	CO ₂ H	A ^{e,f}	79	94–95	C ₂₉ H ₃₀ N ₄ O ₄ S·0.25H ₂ O	531	21
35	Bu	SCH ₂ Ph(4-OMe)	CO ₂ H	A ^{e,f,n}	29	180–182	C ₂₉ H ₃₀ N ₄ O ₄ S·1.1H ₂ O	531	3.0
36	Bu	SOCH ₂ Ph(4-OMe)	CO ₂ H	E ^o	11	109–110 dec	C ₂₉ H ₃₀ N ₄ O ₅ S	547.2033 ^p	7.4
37	Bu	SCH ₂ Ph(2-CN)	CO ₂ H	A ^{e,f}	74	140–142	C ₂₉ H ₂₇ N ₅ O ₃ S·0.85H ₂ O·0.2Et ₂ O	526	60
38	Bu	SCH ₂ Ph(4-CF ₃)	CO ₂ H	A ^{e,f}	59	118–120	C ₂₉ H ₂₇ F ₃ N ₄ O ₃ S·0.3H ₂ O·0.1Et ₂ O	569	42
39	Bu	SCH ₂ (2-naphthyl)	CO ₂ H	A ^{e,f}	80	>95 (gradual)	C ₃₂ H ₃₀ N ₄ O ₃ S·0.5H ₂ O·0.2Et ₂ O	551	49
40	Bu	SCH(CO ₂ Me)Ph	CO ₂ H	A ^{e,f}	71	118–119 dec	C ₃₀ H ₃₀ N ₄ O ₅ S·0.6H ₂ O·0.25Et ₂ O	559	6.1
41	Bu	SCH(CO ₂ H)Ph	CO ₂ H	D ^l	77	143–145 dec	C ₂₉ H ₂₈ N ₄ O ₅ S·2H ₂ O	545	20
42	Bu	SCH ₂ Ph(2-CO ₂ Me)	CO ₂ H	A ^{e,f}	86	106–108	C ₃₀ H ₃₀ N ₄ O ₆ S	559	14
43	Bu	SCH ₂ Ph(2-CO ₂ H)	CO ₂ H	D ^l	76	134–136	C ₂₉ H ₂₈ N ₄ O ₆ S·0.1H ₂ O·0.5CH ₂ Cl ₂	545	3.3
44	Bu	SCH ₂ Ph(3-CO ₂ Me)	CO ₂ H	A ^{e,f}	77	115–116 dec	C ₃₀ H ₃₀ N ₄ O ₆ S·0.75H ₂ O·0.25Et ₂ O	559	30
45	Bu	SCH ₂ Ph(3-CO ₂ H)	CO ₂ H	D ^l	84	130–132 dec	C ₂₉ H ₂₈ N ₄ O ₆ S·2.5H ₂ O·0.1Et ₂ O	545	15
46	Bu	SCH ₂ Ph(4-Cl)	CN ₄ H	B-1	10	175–176 dec	C ₂₈ H ₂₇ ClN ₅ O ₃ S·0.5H ₂ O	559	6.8
47	Bu	SCH ₂ Ph(4-OMe)	CN ₄ H	B-5	6	130–132 dec	C ₂₉ H ₃₀ N ₅ O ₃ S·0.5H ₂ O	555	4.1
48	Bu	SOCH ₂ Ph(4-Cl)	CN ₄ H	E	42	150–152	C ₂₈ H ₂₇ ClN ₅ O ₂ S·0.3H ₂ O	575	33
49	Bu	SOCH ₂ Ph(4-OMe)	CN ₄ H	E	72	135–137	C ₂₉ H ₃₀ N ₅ O ₃ S·0.25H ₂ O·0.15EtOAc	571	28

^a A: phthalic anhydride; B: trimethyltin azide; D: NaOH; E: 30% H₂O₂. See Experimental Section for a detailed description of the general methods. ^b Analyses for C, H, and N were within ±0.4% except where characterized by high-resolution FAB-MS. ^c BSA (0.2%) included in the assay mixture. ^d Data for rat adrenal cortical receptor assay from ref 14. ^e Entire reaction mixture concentrated to dryness. ^f Triturated with Et₂O. ^g Calcd for C₂₆H₂₅N₅O₃ (M + H)⁺ 456.2036. ^h Recrystallized from *i*-PrOH. ⁱ Recrystallized from *i*-PrOH/EtOH/Et₂O. ^j Chromatographed (95:5:0.05 and 95:5:0.1 CH₂Cl₂/MeOH/AcOH). ^k (M + Na)⁺. ^l Obtained as a precipitate upon acidification. ^m Molecular ion not observed. ⁿ Triturated with acetone. ^o Purified by preparative TLC (95:5:0.5 CH₂Cl₂/MeOH/AcOH). ^p Calcd for C₂₉H₃₁N₄O₅S (M + H)⁺ 547.2015.

In this series, oxidation of the thioether to sulfoxide did not confer any clear trend in activity. Whereas 75 and 79 were somewhat more potent than 62 and 70, respectively, 77 was about equivalent to 65, and 78 was somewhat less effective than 67. Sulfoxide 80 was less than one-sixth as potent as the corresponding thioether 71, suggesting that the 2-carboxy substituent may be forced into a less favorable orientation in 80. Two sulfones, 74 and 76, appeared modestly less active than their thioether counterparts 53 and 62, respectively.

Replacement of the benzylthio group of 57 by benzyloxy in 81 led to a dramatic decrease in binding affinity. The phenethyloxy homologue 82 was 6-fold more potent than 81 but still nearly an order of magnitude less potent than 57. The benzylamino analogue 83 was only 4-fold less effective than 57, but para substitution on the benzyl moiety led to much higher IC₅₀ values for 84 and 85. The *N*-benzylcarbamoyl analogue 86 was only moderately potent (IC₅₀ 57 nM), and further modifications of this side chain (87 and 88) failed to improve the activity.

Table II. Physical Properties and in Vitro AII Antagonist Potencies of 4*H*-1,2,4-Triazoles with Biphenyl Side Chains


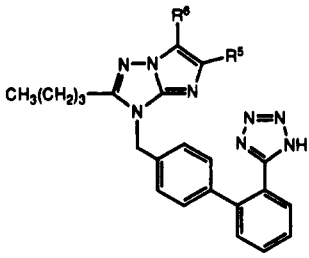
no.	n	R	Z	method ^a	% yield	mp, °C	formula ^b	FAB-MS <i>m/e</i> (M + H) ⁺	rabbit aorta AT ₁ IC ₅₀ , ^c nM
1b		(imidazole)							230 ^d
1c		(imidazole, DuP 753)							19, ^d 50 ^e
1d		(imidazole, EXP3174)							37/ ^e 6 ^e
50	3	SCH ₂ CO ₂ Me	CO ₂ H	C-1	97	157.5–159	C ₂₃ H ₂₅ N ₃ O ₄ S	440	540
51	3	SH	CO ₂ H	C-2	21	218–219	C ₂₀ H ₂₁ N ₃ O ₂ S·0.5H ₂ O	368	860
52	3	SCMe ₃	CO ₂ H	C-2	43	166.5–168 dec	C ₂₄ H ₂₆ N ₃ O ₂ S·0.2H ₂ O	424	890
53	3	SMe	CN ₄ H	B-5	56	100–102	C ₂₁ H ₂₃ N ₇ S·0.5H ₂ O·0.3CH ₂ Cl ₂	406	310
54	3	SCH ₂ CHMe ₂	CN ₄ H	B-1	49	90–91	C ₂₄ H ₂₆ N ₇ S·0.15CH ₂ Cl ₂	448	72
55	3	SCH ₂ -cyclohexyl	CN ₄ H	B-5	60	89–91	C ₂₇ H ₃₃ N ₇ S·0.2H ₂ O·0.1CH ₂ Cl ₂	488	36
56	3	SPh	CN ₄ H	B-2	51	84–85 dec	C ₂₆ H ₂₆ N ₇ S·0.75H ₂ O·0.15CH ₂ Cl ₂	468	100
57	3	SCH ₂ Ph	CN ₄ H	B-2	82	107 dec	C ₂₇ H ₂₇ N ₇ S·0.5H ₂ O·0.05CH ₂ Cl ₂	482	7.1
58	3	S(CH ₂) ₂ Ph	CN ₄ H	B-2	67	79–80	C ₂₈ H ₂₉ N ₇ S·0.75H ₂ O	496	35
59	3	SCH ₂ Ph(2-Me)	CN ₄ H	B-5	71	79–80	C ₂₈ H ₂₉ N ₇ S·0.5H ₂ O	496	17
60	3	SCH ₂ Ph(2-Cl)	CN ₄ H	B-2	47	79–80	C ₂₇ H ₂₆ ClN ₇ S·0.1CH ₂ Cl ₂	516	110
61	2	SCH ₂ Ph(4-Cl)	CN ₄ H	B-2	58	90–92	C ₂₆ H ₂₄ ClN ₇ S·0.2H ₂ O·0.8MeOH	502	98
62	3	SCH ₂ Ph(4-Cl)	CN ₄ H	B-2	37	92–93	C ₂₇ H ₂₆ ClN ₇ S·0.6H ₂ O	516	24
63	4	SCH ₂ Ph(4-Cl)	CN ₄ H	B-2	80	97–99	C ₂₈ H ₂₈ ClN ₇ S·0.75H ₂ O	530	94
64	3	SCH ₂ Ph(2-NO ₂)	CN ₄ H	B-2	69	>115 dec	C ₂₇ H ₂₆ N ₈ O ₂ S·0.75H ₂ O	527	130
65	3	SCH ₂ Ph(4-NO ₂)	CN ₄ H	B-2	84	88–90	C ₂₇ H ₂₆ N ₈ O ₂ S·0.2CH ₂ Cl ₂	527	6.6
66	3	SCH ₂ Ph(3-OMe)	CN ₄ H	B-2	59	78–80	C ₂₈ H ₂₉ N ₇ OS	512.2210 ^g	94
67	3	SCH ₂ Ph(4-OMe)	CN ₄ H	B-2	52	95–97	C ₂₈ H ₂₉ N ₇ OS·1.05H ₂ O ^h	512.2200 ^g	31
68	3	SCH ₂ Ph(4-CO ₂ Me)	CN ₄ H	B-1	39	97–98	C ₂₉ H ₂₉ N ₇ O ₂ S·0.15CH ₂ Cl ₂	540	120
69	3	SCH ₂ Ph(4-CO ₂ H)	CN ₄ H	D ⁱ	81	139–141 dec	C ₂₈ H ₂₇ N ₇ O ₂ S·2H ₂ O·0.2Et ₂ O	526	24
70	3	SCH ₂ Ph(2-CO ₂ Me)	CN ₄ H	B-3	54	foam	C ₂₉ H ₂₉ N ₇ O ₂ S·1.5H ₂ O·0.2CH ₂ Cl ₂	540	90
71	3	SCH ₂ Ph(2-CO ₂ H)	CN ₄ H	D	75	>50 dec (gradual)	C ₂₈ H ₂₇ N ₇ O ₂ S·0.75H ₂ O·0.125Et ₂ O	526	1.5
72	3	SCH ₂ Ph(2-CH ₂ OH)	CN ₄ H	B-2	40	93–95	C ₂₈ H ₂₉ N ₇ OS·0.3H ₂ O·0.25CH ₂ Cl ₂	512	36
73	3	SCH ₂ Ph(2-CN ₄ H)	CN ₄ H	B-4	27	>140 (gradual)	C ₂₈ H ₂₇ N ₁₁ S	550.2236 ^j	1.4
74	3	SO ₂ Me	CN ₄ H	F	70	98–100	C ₂₁ H ₂₃ N ₇ O ₂ S·0.33H ₂ O·0.25Et ₂ O	438	400
75	3	SOCH ₂ Ph(4-Cl)	CN ₄ H	E	65	208–209 dec	C ₂₇ H ₂₆ ClN ₇ OS·0.25H ₂ O	532	11
76	3	SO ₂ CH ₂ Ph(4-Cl)	CN ₄ H	B-5	16	180–182 dec	C ₂₇ H ₂₆ ClN ₇ O ₂ S·0.5H ₂ O·0.3CH ₂ Cl ₂	548	48
77	3	SOCH ₂ Ph(4-NO ₂)	CN ₄ H	E ^k	50	222–223	C ₂₇ H ₂₆ N ₈ O ₂ S·0.5H ₂ O	543	8.9
78	3	SOCH ₂ Ph(4-OMe)	CN ₄ H	E	20	125–126	C ₂₈ H ₂₉ N ₇ O ₂ S	528.2175 ^l	50
79	3	SOCH ₂ Ph(2-CO ₂ Me)	CN ₄ H	E	69	>65 dec (gradual)	C ₂₉ H ₂₉ N ₇ O ₂ S·0.4H ₂ O·0.1Et ₂ O	556	40
80	3	SOCH ₂ Ph(2-CO ₂ H)	CN ₄ H	D	80	>65 dec (gradual)	C ₂₈ H ₂₇ N ₇ O ₂ S·0.4H ₂ O·0.4EtOAc	542	10
81	3	OCH ₂ Ph	CN ₄ H	G	12	glass	C ₂₇ H ₂₇ N ₇ O	466.2205 ^m	370
82	3	O(CH ₂) ₂ Ph	CN ₄ H	G	50	76–77	C ₂₈ H ₂₉ N ₇ O	480.2513 ⁿ	63
83	3	NHCH ₂ Ph	CN ₄ H	B-3	51	>70 (gradual)	C ₂₇ H ₂₈ N ₈ ·0.9H ₂ O·0.45AcOH	465	28
84	3	NHCH ₂ Ph(4-Cl)	CN ₄ H	B-3	69	>130 (gradual)	C ₂₇ H ₂₇ ClN ₈ ·0.8H ₂ O	499	140
85	3	NHCH ₂ Ph(4-OMe)	CN ₄ H	B-3	75	>120 (gradual)	C ₂₈ H ₃₀ N ₈ O·H ₂ O	495	780
86	3	CONHCH ₂ Ph	CN ₄ H	B-3	67	>90 (gradual)	C ₂₈ H ₂₈ N ₈ O	493.2457 ^o	57
87	3	CON(Me)CH ₂ Ph	CN ₄ H	B-3	59	>95 (gradual)	C ₂₉ H ₃₀ N ₈ O·0.75H ₂ O	507	89
88	3	CON(Me)Ph	CN ₄ H	B-3	37	>100 (gradual)	C ₂₈ H ₂₈ N ₈ O·0.15CH ₂ Cl ₂	493	350

^a B: trimethyltin azide; C: TFA; D: NaOH; E: 30% H₂O₂; F: peracetic acid; G: sodium alkoxide. See the Experimental Section for a detailed description of the general methods. ^b Analyses for C, H, and N were within ±0.4% except where characterized by high-resolution FAB-MS. ^c BSA (0.2%) included in assay mixture for 50–52 only. ^d Data for rat adrenal cortical receptor assay from ref 15. ^e Data for rabbit aorta receptor assay from ref 19. ^f Data for rat adrenal cortical receptor assay from ref 17. ^g Calcd for C₂₈H₃₀N₇OS (M + H)⁺ 512.2232. ^h Characterized by elemental analysis as well as high-resolution FAB-MS. ⁱ Obtained as a precipitate upon acidification. ^j Calcd for C₂₈H₂₈N₁₁S (M + H)⁺ 550.2250. ^k Precipitated from reaction mixture; recrystallized from 2-methoxyethanol. ^l Calcd for C₂₈H₃₀N₇O₂S (M + H)⁺ 528.2182. ^m Calcd for C₂₇H₂₈N₇O (M + H)⁺ 466.2357. ⁿ Calcd for C₂₈H₃₀N₇O (M + H)⁺ 480.2512. ^o Calcd for C₂₈H₂₈N₈O (M + H)⁺ 493.2466.

Several of the 3*H*-imidazo[1,2-*b*][1,2,4]triazoles (Table III) were moderately potent AII antagonists. Although we were unable to prepare the analogue unsubstituted at both C⁵ and C⁶ by our method, some effects of ring substitution were evident. Among 5-substituents, phenyl (91) was twice as potent as methyl (89) or ethyl (90), the latter two being equivalent. Only one example (92) was unsubstituted at C⁵, and this compound, having phenyl at C⁶, was a weak antagonist. The 5,6-dimethyl derivative 93 (IC₅₀ 7.8 nM) was 7-fold more potent than the 5-methyl analogue 89, indicating a positive contribution for the methyl group at C⁶. A phenyl group in place of methyl at C⁶ led to a large decrease in activity for 94 compared to 93. However, replacement of the 5-methyl in 93 by

phenyl in 95 was tolerated with only a modest loss of binding affinity. Although 93 and 95 fell far short of the potency of the imidazopyridine L-158,809 (3), they appeared substantially more effective than the benzimidazole reference compound 2.

Conclusions about Receptor Interactions. According to the Du Pont model as originally proposed¹⁴ and as subsequently refined,¹⁵ the binding of imidazoles 1a–d to the AII receptor can be interpreted in terms of multiple interactions: (a) an ionic attraction between a cationic group on the receptor and an acidic substituent on the ortho position of the distal ring of the biphenyl or amide-bridged side chain; (b) hydrophobic associations between lipophilic pockets on the receptor and the linear alkyl chain

Table III. Physical Properties and in Vitro AII Antagonist Potencies of 3*H*-Imidazo[1,2-*b*][1,2,4]triazoles


no.	R ⁵	R ⁶	method ^a	% yield	mp, °C	formula ^b	FAB-MS <i>m/e</i> (M + H) ⁺	rabbit aorta AT ₁ IC ₅₀ , nM
2		(benzimidazole)						96 ^d
3		(imidazopyridine, L-158,809)						0.3 ^c
89	Me	H	B-6	31	124–125	C ₂₃ H ₂₄ N ₈ •1.5H ₂ O•0.75Et ₂ O	413	55
90	Et	H	B-6	24	>100 (gradual)	C ₂₄ H ₂₆ N ₈ •1.2H ₂ O•0.1Et ₂ O	427	55
91	Ph	H	B-6	44	>160 (gradual)	C ₂₈ H ₂₈ N ₈ •0.25H ₂ O•0.25Et ₂ O	475	30
92	H	Ph	B-6	46	>70 (gradual)	C ₂₈ H ₂₈ N ₈ •0.4CH ₂ Cl ₂ •Et ₂ O	475	220
93	Me	Me	B-6	40	138–141	C ₂₄ H ₂₆ N ₈ •0.3H ₂ O•0.25CH ₂ Cl ₂	427	7.8
94	Me	Ph	B-6	32	>108 (gradual)	C ₂₉ H ₂₈ N ₈ •0.7H ₂ O•0.9Et ₂ O	489	170
95	Ph	Me	B-6	25	207–208	C ₂₉ H ₂₈ N ₈ •0.5H ₂ O•0.25Et ₂ O	489	13

^a B: trimethyltin azide. See the Experimental Section for a detailed description of the general methods. ^b Analyses for C, H, and N within $\pm 0.4\%$. ^c Assay run in absence of BSA. ^d Data for guinea pig adrenal receptor assay from ref 18. ^e Data for rabbit aorta receptor assay from ref 19.

at C², the chloro substituent at C⁴, and at least a portion of the biphenyl or amide-bridged side chain at N¹; and (c) a hydrogen bond linking the C⁵-substituent to a proton donor on the receptor. A similar hydrogen-bonding interaction has been proposed¹⁹ to explain the marked enhancement of binding affinity induced by the pyrido nitrogen atom in the imidazo[4,5-*b*]pyridines such as 3 compared to structurally similar benzimidazoles.

The present results suggest that some modification of this view of the receptor surface may be in order, at least for triazole-based AII antagonists. Carini and co-workers¹⁵ noted that, in their imidazole series, small hydrogen-bonding substituents were preferred at the 5-position, although a wide range of groups could be tolerated. In the equivalent 5-position in the 3,4,5-trisubstituted 4*H*-1,2,4-triazoles, we have observed superior activity for bulky lipophilic groups such as benzylthio. This implies access to a major hydrophobic area of the receptor more distant from the heterocycle binding site than previously suspected. Molecular models⁵⁹ (not shown) indicate that the benzylthio moiety cannot occupy the same space as the 4-chloro substituent in 1 without a major displacement of the triazole relative to the imidazole ring. Of course, the presumed hydrophobic pocket which binds the benzyl group may be an extension of that which binds the imidazole 4-chloro substituent. Molecular models also suggest that the 5-phenyl substituent on 95, one of the most potent of the 3*H*-imidazo[1,2-*b*][1,2,4]triazoles, may occupy roughly the same region of space as the phenyl ring of the (benzylthio)triazoles. The potency enhancement by this substituent in 95 and, to a lesser extent, in 91 is thus not surprising.

Does the sulfur atom in the benzylthio side chain of triazoles such as 25 and 57 fulfill the role of a hydrogen bond acceptor as proposed for the imidazole 5-substituent? Thioethers are poor proton acceptors, and the observed superiority of the benzylthio group relative to benzylamino and benzyloxy (or phenethyloxy) substituents is not in agreement with the reported acceptor order of N > O > S.⁶⁰ It is true that the difference in bond angle and bond lengths for the sulfur linkage may position the benzyl moiety more favorably for hydrophobic interactions,

canceling out any diminished hydrogen-bonding capability for the sulfur atom. Still, the mixed or disappointing results upon incorporation of such powerful proton acceptors as sulfoxide or substituted carboxamide⁶⁰ at the 5-position provide little support for any well-defined function of hydrogen bonding here.

The unique and important contribution of acidic substituents at the ortho position of the benzylthio side chain in 43, 71, and 73 suggests a discrete interaction with the receptor, involving either ionic forces or hydrogen bonding. It is interesting to speculate whether this putative binding site on the receptor is also involved in the strong affinity observed (under certain assay conditions) for imidazole-5-carboxylic acids such as EXP3174 (1d; nearly an order of magnitude more potent than DuP 753 in our assay¹⁹) and the recently reported DuP 532.⁶¹ Lin and co-workers²⁷ have proposed an interaction between the imidazole-5-carboxylic acid and a basic region on the receptor. Molecular modeling studies (not shown) were inconclusive but did not rule out the possibility that the carboxy substituent on the benzyl group and that on the imidazole could approach the same receptor site from different directions. With respect to binding mode, one may also consider a possible relationship of our (2-carboxybenzyl)thio substituent on the triazole to the (Z)-2-carboxy-3-(2-thienyl)-1-propenyl side chain preferred at the imidazole 5-position in the recently described SmithKline Beecham AII antagonists.²⁴

Although not explicitly part of the Du Pont model, it is reasonable to suppose that the 5-membered heterocycle, in addition to directing the array of substituents in a favorable orientation, may itself be involved in a significant interaction with the receptor. The importance of N³ as a binding point in benzimidazoles related to 2 has been demonstrated.¹⁸ Both 1-alkyl-1*H*-imidazole and 4-alkyl-4*H*-1,2,4-triazole are extremely effective hydrogen bond acceptors.⁶⁰ A 2-dimensional representation summarizing the postulated interactions of 71 with the AT₁ receptor is shown in Figure 1.

In Vivo Pharmacology. Several of the 4*H*-1,2,4-triazole derivatives were evaluated as inhibitors of the pressor response to exogenous AII in conscious, normo-

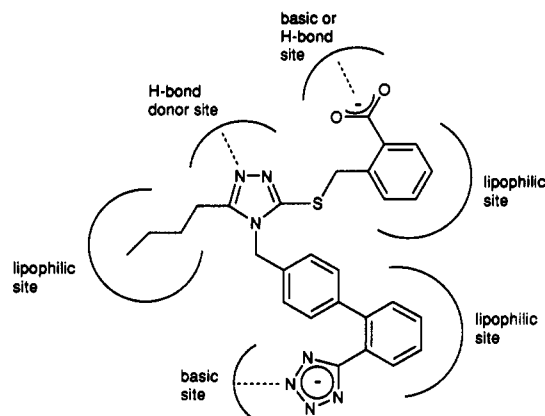


Figure 1. Proposed binding of triazole 71 to the AT₁ receptor through hydrophobic, ionic, and hydrogen-bonding interactions at multiple sites.

Table IV. Inhibition of AII Pressor Response by Triazole Derivatives in Conscious, Normotensive Rats

no.	dose, mg/kg (route)	peak inhibn, % (mean ± SEM)	duration, ^a h (mean ± SEM)	N ^b
1c (DuP 753)	0.3 (iv)	52 ± 6	5.5 ± 0.5	4
	3 (po)	94 ± 2	>4.5	4
	0.3 (po)	36 ± 8	>3.5	2
1d (EXP3174)	0.3 (iv)	100 ± 0	>29	2
	1 (po)	72 ± 10	>7	2
	0.3 (po)	63 ± 10	2.8 ± 2.6	2
25	30 (po)	33 ± 14	0.4 ± 0.1	4
28	3 (iv)	56 ± 2	0.5 ± 0	2
30	3 (iv)	50 ± 4	0.1 ± 0	2
43	1 (iv)	100 ± 0	1.4 ± 0.6	2
	0.3 (iv)	74 ± 4	0.9 ± 0.5	4
	0.3 (po)	NA ^c	NA	2
47	1 (iv)	70 ± 1	0.2 ± 0	2
50	10 (iv)	93 ± 7	0.9 ± 0.1	3
62	3 (iv)	62 ± 4	1.0 ± 1	2
	3 (po)	50 ± 10	1.5 ± 0.9	3
65	3 (iv)	65 ± 10	1.4 ± 0.9	4
71	0.3 (iv)	100 ± 0	5.5 ± 0.5	2
	3 (po)	54 ± 6 ^d	>6 ^d	3 ^d
	0.3 (po)	0 ± 0	NA	2
73	1 (iv)	62 ± 4	0.6 ± 0.1	2
75	1 (iv)	42 ± 6	0.1 ± 0	2

^a Time from onset of action until significant (i.e., ≥30%) inhibition of pressor response is no longer observed. ^b Number of animals treated. ^c NA = not active. ^d Results shown for 3 out of 4 animals. The compound was inactive in one additional animal.

tensive rats, and representative data are shown in Table IV. Compounds containing an amide-bridged side chain at N⁴ were characterized by a short duration of action and little, if any, oral activity. However, the (2-carboxybenzyl)thio analogue 43, reflecting its excellent in vitro potency, was active at an intravenous dose as low as 0.3 mg/kg, and its peak inhibition was greater than that observed for DuP 753 (1c) at the same dose. In the biphenyltetrazole series, significant oral bioavailability was obtained for the (4-chlorobenzyl)thio compound 62, which displayed comparable activity orally and intravenously at 3 mg/kg. Again, the (2-carboxybenzyl)thio analogue 71 had remarkable activity. At 0.3 mg/kg iv its peak inhibition (100%) was equivalent to that of EXP3174 (1d) and superior to that of DuP 753 (1c). At this intravenous dose level, 71 had a relatively long duration of action (5.5 h), which was comparable to that of DuP 753 but inferior to that of EXP3174. Not unexpectedly, in view of its diacidic character, 71 was inactive orally at 0.3 mg/kg, although EXP3174 did have oral activity at this level. At 3 mg/kg po 71 was active in 3 out of 4 rats with good duration (>6

h). The failure in one animal may reflect variability in absorption. Surprisingly, the ditetrazole analogue 73, which had potency similar to that of 71 in vitro, was much less effective than 71 in vivo by intravenous administration.

General Conclusions

An extensive series of 3,4,5-trisubstituted 4H-1,2,4-triazoles and a related series of 3H-imidazo[1,2-b][1,2,4]-triazoles have been synthesized by a variety of routes and evaluated as AII antagonists in vitro and in vivo. The most active triazoles had an *n*-butyl substituent at C³, a benzylthio moiety at C⁵, and a [(2-carboxybenzoyl)amino]benzyl, [[2-(1H-tetrazol-5-yl)benzoyl]amino]benzyl, or [2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl side chain at N⁴. For in vitro and in vivo activity (especially by the intravenous route), the optimum appendage at the 5-position was (2-carboxybenzyl)thio, as in 43 and 71. It is likely that this substituent is able to participate effectively in both hydrophobic and ionic interactions with the receptor. In agreement with the Du Pont imidazole investigations,¹⁵ the biphenyltetrazole grouping was superior in vivo to the amide-bridged side chains at the 4-position. The diacidic derivative 71 was characterized by high potency in vitro (IC₅₀ 1.4 nM) and compared favorably to DuP 753 (1c) in a rat model at 0.3 mg/kg iv with respect to peak antagonism of the AII pressor response and duration of action. Upon oral administration at 3 mg/kg, 71 displayed modest activity and a duration of >6 h.

A limited exploration of bicyclic compounds derived from the 1,2,4-triazole nucleus produced some reasonably potent antagonists. The best of the 3H-imidazo[1,2-b][1,2,4]triazoles, 93 and 95, were superior to DuP 753 (1c) but substantially inferior to the bicyclic AII antagonist L-159,809 (3) in vitro. The relatively good activity of the 5-phenyl derivatives 95 and 91 demonstrates an area of bulk tolerance at this position which might be exploited by further substitution.

Experimental Section

Melting points (uncorrected) were determined in open capillary tubes with a Thomas-Hoover apparatus. ¹H NMR spectra were recorded on Varian XL-400, XL-300, or XL-200 spectrometers, using tetramethylsilane as internal standard. Positive ion fast atom bombardment (FAB) or electron impact (EI) mass spectra (MS) were obtained on Varian MAT 731, Finnigan MAT 90, JEOL HX110, and Varian MAT 212 instruments. Optical rotations at the sodium D line were measured on a Perkin-Elmer 241 polarimeter using water-jacketed cells at 20 °C. Column chromatography was carried out on EM Science silica gel 60 (70–230 mesh) or grade 62 (60–200 mesh) for gravity columns and silica gel 60 (230–400 mesh) for flash columns. Compounds showed satisfactory purity by TLC on Analtech silica gel GF plates (visualized by UV light at 254 nm and/or I₂) in the indicated solvent systems. Elemental combustion analyses, where indicated only by the elements, were within ±0.4% of theoretical values. Many of the compounds were unavoidably analyzed as solvates, owing to their tendency to retain solvent under nondestructive drying conditions. Where solvation is indicated, the presence of solvent in the analytical sample was verified by NMR. Microanalyses were performed by the laboratory of Mrs. Jane T. Wu at Merck or by Robertson Microlit Laboratories, Madison, NJ.

Dry tetrahydrofuran (THF) was obtained by distillation from sodium/benzophenone ketyl under N₂. Dry dimethyl sulfoxide (DMSO) was withdrawn directly from Pierce silylation grade Hypo-vials, or HPLC grade DMSO was dried over 4-Å molecular sieves. Reagent grade CH₂Cl₂, MeOH, and EtOH were dried

over 3-Å molecular sieves. Reactions were routinely conducted under N₂ (bubbler) unless otherwise indicated.

Ethyl Valerate-2-Furoylhydrazone (97). A solution of 2.40 g (15.2 mmol) of ethyl valerimidate hydrochloride (96)³² in 25 mL of dry EtOH was stirred at -10 °C (ice/NaCl bath) under protection from moisture as a solution of 1.97 g (15.6 mmol) of 2-furoic acid hydrazide in 60 mL of dry EtOH was added dropwise over 15 min. Upon completion of the addition, the flask was stoppered and kept at 5 °C for 3 days. The filtered solution was concentrated, and the residue was flash chromatographed (elution with 1.5% MeOH in CH₂Cl₂) to give 2.18 g (58%) of an oil, which was sufficiently pure by TLC (97:3 CH₂Cl₂/MeOH) for use in the next step. NMR indicated that the material exists as a mixture of syn and anti isomers: ¹H NMR (CDCl₃, 200 MHz) δ 0.8–0.95 (m, 2 H), 1.2–1.4 (m, 5 H), 2.3–2.5 (m, 2 H), 4.1–4.25 (m, 2 H), 6.46 (m, 1 H), 7.13 (m, 1 H), 7.42 (s, 1 H), 8.38, 9.53 (br s, total 1 H); FAB-MS *m/e* 239 (M + H)⁺.

3-*n*-Butyl-5-(2-furyl)-4-(4-nitrobenzyl)-4*H*-1,2,4-triazole (98). To 678 mg (2.85 mmol) of 97 dissolved in 3 mL of EtOH was added a solution of 514 mg (2.16 mmol) of 4-nitrobenzylamine (generated from the hydrochloride by partitioning between Et₂O and saturated aqueous Na₂CO₃) in 3 mL of EtOH. The resulting solution was heated at 45–50 °C for 2 h and then at 70 °C overnight. The solution was cooled and concentrated. Column chromatography of the residue (gradient elution with 0.5–2.5% MeOH in CH₂Cl₂) afforded 432 mg (61%) of a yellow oil, which upon standing at 5 °C crystallized to give a solid: mp 91–92.5 °C; TLC in 97:3 CH₂Cl₂/MeOH; ¹H NMR (CDCl₃, 300 MHz) δ 0.87 (t, *J* = 7 Hz, 3 H), 1.37 (m, 2 H), 1.71 (m, 2 H), 2.65 (t, *J* = 7.5 Hz, 2 H), 5.46 (s, 2 H), 6.49 (dd, *J* = 3.5, 1 Hz, 1 H), 7.01 (d, *J* = 3.5 Hz, 1 H), 7.18 (d, *J* = 8 Hz, 2 H), 7.42 (d, *J* = 1 Hz, 1 H), 8.18 (d, *J* = 8 Hz, 2 H); FAB-MS *m/e* 327 (M + H)⁺.

4-(4-Aminobenzyl)-3-*n*-butyl-5-(2-furyl)-4*H*-1,2,4-triazole (99). To a solution of 161 mg (0.493 mmol) of 98 in 4 mL of dry THF stirred in an ice bath was added dropwise a solution of 1.11 g (4.93 mmol) of stannous chloride dihydrate in 1.5 mL of concentrated HCl. The ice bath was removed, and the mixture was stirred at room temperature for 2.5 h. It was then poured into a vigorously stirred mixture of 7 mL of 50% NaOH (aqueous) and 25 g of ice. After 30 min, the mixture was extracted with 3 × 18 mL of Et₂O and then with 2 × 20 mL of EtOAc. The combined organic extracts were dried (Na₂SO₄), filtered, and concentrated in vacuo. Flash chromatography of the residue (elution with 97:3 CH₂Cl₂/MeOH) yielded 123 mg (83%) of pale yellow powder: mp 111–111.5 °C; TLC in 95:5 CH₂Cl₂/MeOH; ¹H NMR (CDCl₃, 200 MHz) δ 0.86 (t, *J* = 7.5 Hz, 3 H), 1.37 (m, 2 H), 1.69 (m, 2 H), 2.68 (t, *J* = 7.5 Hz, 2 H), 3.70 (br s, 2 H), 5.23 (s, 2 H), 6.49 (dd, *J* = 3.5, 1 Hz, 1 H), 6.60 (d, *J* = 8 Hz, 2 H), 6.81 (d, *J* = 8 Hz, 2 H), 6.91 (d, *J* = 3.5 Hz, 1 H), 7.51 (d, *J* = 1 Hz, 1 H); FAB-MS *m/e* 297 (M + H)⁺.

Method A. 3-*n*-Butyl-4-[4-[(2-carboxybenzoyl)amino]benzyl]-5-(2-furyl)-4*H*-1,2,4-triazole (9). A solution of 80.5 mg (0.272 mmol) of 99 in 2 mL of dry THF was treated with 40.2 mg (0.272 mmol) of phthalic anhydride. The resulting solution was stirred at room temperature for 4 h in a stoppered flask. The precipitate was collected on a filter and washed with Et₂O. The material was evaporated three times from MeOH and dried to give 104 mg (85%) of a white powder: mp 169.5–171 °C; TLC in 90:10:1 CH₂Cl₂/MeOH/AcOH; ¹H NMR (CD₃OD, 300 MHz) δ 0.95 (t, *J* = 7.5 Hz, 3 H), 1.43 (m, 2 H), 1.71 (m, 2 H), 2.83 (t, *J* = 7.5 Hz, 2 H), 5.53 (s, 2 H), 6.67 (dd, *J* = 3.5, 1 Hz, 1 H), 7.03 (d, *J* = 3.5 Hz, 1 H), 7.08 (d, *J* = 8 Hz, 2 H), 7.5–7.7 (m, 5 H), 7.77 (d, *J* = 1 Hz, 1 H), 8.03 (d, *J* = 8 Hz, 1 H); partial ¹H NMR (DMSO-*d*₆, 300 MHz) δ 10.38 (s, 1 H), 12.95 (v br s, 1 H); FAB-MS *m/e* 445 (M + H)⁺.

Methyl *N*-(4-Nitrobenzyl)dithiocarbamate (101). To a stirred solution of 150 g (795 mmol) of 4-nitrobenzylamine hydrochloride (100) and 243 mL (1.75 mol) of triethylamine in 780 mL of MeOH was added gradually a solution of 54 mL (68.9 g, 906 mmol) of carbon disulfide in 300 mL of MeOH. The internal temperature was maintained below 30 °C during the addition, which took 75 min. After an additional hour at room temperature, the reaction mixture was cooled to -10 °C in an ice/MeOH bath as a solution of 50 mL (113 g, 795 mmol) of iodomethane in 125 mL of MeOH was added gradually over about

20 min. The cooling bath was removed, and the mixture was allowed to stir at room temperature for 2 h. It was then concentrated in vacuo to a volume of approximately 500 mL and partitioned between 2 L of Et₂O and 2 L of 0.2 N HCl. The ethereal phase was washed with 2 L of saturated aqueous NaCl, dried over MgSO₄, filtered, and concentrated to give a yellow solid. Trituration with petroleum ether and vacuum-drying afforded 187 g (97%) of solid: mp 106–107 °C; TLC in 2:1 hexane/EtOAc; ¹H NMR (CDCl₃, 300 MHz) δ 2.66 (s, 3 H), 5.06 (d, *J* = 6 Hz, 2 H), 7.23 (br m, 1 H), 7.46 (d, *J* = 8 Hz, 2 H), 8.19 (d, *J* = 8 Hz, 2 H); FAB-MS *m/e* 243 (M + H)⁺. Anal. (C₉H₁₀N₂O₂S₂) C, H, N.

4-(4-Nitrobenzyl)-3-thiosemicarbazide (102). A solution of 187 g (772 mmol) of 101 and 450 mL of hydrazine hydrate in 1400 mL of absolute EtOH was stirred mechanically and heated to reflux. Precipitation began by the time the internal temperature reached about 40 °C. After 2 h at reflux, the mixture was cooled and allowed to stand at room temperature. The solid was collected on a filter, washed with EtOH, and dried to give 105 g (60%) of light yellow crystals: mp 196–198 °C; TLC in 95:5:0.5 CH₂Cl₂/MeOH/concentrated NH₄OH; ¹H NMR (DMSO-*d*₆, 300 MHz) δ 4.56 (br s, 2 H), 4.83 (d, *J* = 6 Hz, 2 H), 7.54 (d, *J* = 9 Hz, 2 H), 8.18 (d, *J* = 9 Hz, 2 H), 8.56 (v br s, 1 H), 8.88 (br s, 1 H); FAB-MS *m/e* 227 (M + H)⁺. Anal. (C₈H₁₀N₄O₂S) C, H, N.

5-*n*-Butyl-2,4-dihydro-4-(4-nitrobenzyl)-3*H*-1,2,4-triazole-3-thione (103). A mixture of 56.6 g (250 mmol) of 102, 63.1 mL (59.4 g 370 mmol) of trimethyl orthoacetate, and 500 mL of 2-methoxyethanol was stirred at reflux for approximately 24 h. The cooled red-orange solution was concentrated, and the residue was triturated with Et₂O. The resulting solid was collected on a filter, washed with Et₂O, and dried to yield 45.2 g (62%) of white crystals: mp 159–160 °C; TLC in 95:5 CH₂Cl₂/MeOH; ¹H NMR (DMSO-*d*₆, 300 MHz) δ 0.76 (t, *J* = 7 Hz, 3 H), 1.22 (m, 2 H), 1.44 (m, 2 H), 2.49 (t, *J* = 8 Hz, 2 H), 5.38 (s, 2 H), 7.48 (d, *J* = 8 Hz, 2 H), 8.24 (d, *J* = 8 Hz, 2 H); FAB-MS *m/e* 293 (M + H)⁺. Anal. (C₁₃H₁₆N₄O₂S) C, H, N.

3-*n*-Butyl-5-[(4-chlorobenzyl)thio]-4-(4-nitrobenzyl)-4*H*-1,2,4-triazole (104). A solution of 292 mg (1 mmol) of 103 and 322 mg (2 mmol) of 4-chlorobenzyl chloride in 3 mL of 2-methoxyethanol was treated with 348 μL (259 mg, 2 mmol) of *N,N*-diisopropylethylamine. The solution was stirred at room temperature for 3.5 h and then concentrated in vacuo. The residue was partitioned between 50 mL of EtOAc and 50 mL of 0.2 N HCl. The organic layer was washed with 50 mL of 0.2 N HCl and 50 mL of saturated aqueous NaCl. After drying over MgSO₄, the EtOAc solution was filtered and concentrated in vacuo. The residue was chromatographed on a silica gel column (elution with 0.75% MeOH in CH₂Cl₂) to provide 326 mg (77%) of an oil: TLC in 95:5 CH₂Cl₂/MeOH; ¹H NMR (CDCl₃, 300 MHz) δ 0.86 (t, *J* = 7.5 Hz, 3 H), 1.32 (m, 2 H), 1.63 (m, 2 H), 2.52 (t, *J* = 7.5 Hz, 2 H), 4.33 (s, 2 H), 4.92 (s, 2 H), 6.97 (d, *J* = 9 Hz, 2 H), 7.20 (m, 4 H), 8.13 (d, *J* = 9 Hz, 2 H); FAB-MS *m/e* 417 (M + H)⁺. Anal. (C₂₀H₂₁ClN₄O₂S·0.05CH₂Cl₂) C, H, N.

2,4-Dihydro-4-(4-nitrobenzyl)-5-(trifluoromethyl)-3*H*-1,2,4-triazole-3-thione (105). A suspension of 1.00 g (4.42 mmol) of 102 in 1.1 mL of anhydrous trifluoroacetic acid was heated in an oil bath at 75 °C for 1 h and then at 125 °C for 24 h. The solid obtained upon cooling was treated portionwise with saturated aqueous NaHCO₃ (about 10 mL total), and the mixture was stirred thoroughly until CO₂ evolution had ceased. The solid was collected on a filter, washed thoroughly with H₂O, and then dried in vacuo over P₂O₅ to give 1.07 g (80%) of a pale yellow solid: mp 155–157 °C; TLC in 95:5 CH₂Cl₂/MeOH; ¹H NMR (DMSO-*d*₆, 300 MHz) δ 5.49 (s, 2 H), 7.50 (d, *J* = 8 Hz, 2 H), 8.22 (d, *J* = 8 Hz, 2 H); FAB-MS *m/e* 305 (M + H)⁺. Anal. (C₁₀H₇F₃N₄O₂S) C, H, N.

3-*n*-Butyl-5-[(methoxycarbonyl)methyl]thio]-4-(4-nitrobenzyl)-4*H*-1,2,4-triazole (106). By the procedure used to prepare 104, 103 was reacted with methyl chloroacetate to give a quantitative yield of 106 as an oil: TLC in 95:5 CH₂Cl₂/MeOH; ¹H NMR (CDCl₃, 300 MHz) δ 0.86 (t, *J* = 7 Hz, 3 H), 1.36 (m, 2 H), 1.69 (m, 2 H), 2.61 (t, *J* = 7 Hz, 2 H), 3.73 (s, 3 H), 4.03 (s, 2 H), 5.25 (s, 2 H), 7.21 (d, *J* = 8 Hz, 2 H), 8.24 (d, *J* = 8 Hz, 2 H); FAB-MS *m/e* 365 (M + H)⁺. Anal. (C₁₆H₂₀N₄O₄S) C, H, N.

3-*n*-Butyl-5-[(*N*-methylcarbamoyl)methyl]thio]-4-(4-nitrobenzyl)-4*H*-1,2,4-triazole (107). To a stirred solution of 502 mg (1.37 mmol) of 106 in 2.2 mL of MeOH was added 2.2 mL of 40% methylamine (aqueous). Within 15 min a heavy precipitate had formed. After dilution with H₂O, the solid was collected on a filter, washed with H₂O, air-dried, and washed further with Et₂O to give 413 mg (83%) of a white solid: mp 132–133 °C; TLC in 95:5 CH₂Cl₂/MeOH; ¹H NMR (DMSO-*d*₆, 300 MHz) δ 0.81 (t, *J* = 7 Hz, 3 H), 1.28 (m, 2 H), 1.53 (m, 2 H), 2.56 (d, *J* = 4 Hz, 3 H), 2.62 (t, *J* = 8 Hz, 2 H), 3.82 (s, 2 H), 5.38 (s, 2 H), 7.32 (d, *J* = 8 Hz, 2 H), 8.13 (br m, 1 H), 8.24 (d, *J* = 8 Hz, 2 H); FAB-MS *m/e* 364 (M + H)⁺. Anal. (C₁₆H₂₁N₅O₃S) C, H, N.

3-*n*-Butyl-5-chloro-4-(4-nitrobenzyl)-4*H*-1,2,4-triazole (108). Chlorine gas was bubbled through a stirred solution of 5.00 g (17.1 mmol) of 103 in 260 mL of dry CH₂Cl₂ at room temperature for 1.5 h, during which time a precipitate (not the desired product) formed. The reaction mixture was poured into 400 mL of EtOAc and washed with 3 × 500 mL of saturated aqueous NaHCO₃, 400 mL of H₂O, and finally 400 mL of saturated aqueous NaCl. The EtOAc phase was dried over MgSO₄, filtered, and concentrated. Column chromatography of the residue (elution with a gradient of 0–1% MeOH in CH₂Cl₂) yielded 1.90 g (37%) of a yellow oil: TLC in 95:5 CH₂Cl₂/MeOH; ¹H NMR (CDCl₃, 300 MHz) δ 0.89 (t, *J* = 7 Hz, 3 H), 1.38 (m, 2 H), 1.71 (m, 2 H), 2.64 (t, *J* = 7.5 Hz, 2 H), 5.21 (s, 2 H), 7.22 (d, *J* = 8 Hz, 2 H), 8.26 (d, *J* = 8 Hz, 2 H); EI-MS *m/e* 294 (M⁺). Anal. (C₁₃H₁₅ClN₄O₂·0.33H₂O) C, H, N, Cl.

3-*n*-Butyl-4-(4-nitrobenzyl)-5-(phenylthio)-4*H*-1,2,4-triazole (109). A solution of 100 mg (0.34 mmol) of 108, 140 μL (150 mg, 1.36 mmol) of thiophenol, and 237 μL (176 mg, 1.36 mmol) of *N,N*-diisopropylethylamine in 1 mL of dry DMF was stirred at reflux for 2 h. The cooled, dark solution was concentrated in vacuo, and the residue was partitioned between 50 mL of Et₂O and 50 mL of 0.2 N HCl. The ethereal phase was washed with saturated aqueous Na₂CO₃, then dried, filtered, and concentrated. The residue was chromatographed on a silica gel column (gradient elution with 0–2% *i*-PrOH in CHCl₃) to give 28 mg (22%) of an oil: TLC in 97:3 CHCl₃/*i*-PrOH; ¹H NMR (CDCl₃, 300 MHz) δ 0.86 (t, *J* = 7 Hz, 3 H), 1.34 (m, 2 H), 1.70 (m, 2 H), 2.58 (t, *J* = 7.5 Hz, 2 H), 5.22 (s, 2 H), 6.91 (d, *J* = 8 Hz, 2 H), 7.1–7.3 (m, 5 H), 8.04 (d, *J* = 8 Hz, 2 H); FAB-MS *m/e* 369 (M + H)⁺.

4-(4-Aminobenzyl)-3-*n*-butyl-5-[(4-chlorobenzyl)thio]-4*H*-1,2,4-triazole (110). By the procedure used to prepare 99, 104 was reduced with stannous chloride to give a 92% yield of 110 as an oil: TLC in 9:1 CHCl₃/MeOH; ¹H NMR (CDCl₃, 300 MHz) δ 0.86 (t, *J* = 7.5 Hz, 3 H), 1.32 (m, 2 H), 1.62 (m, 2 H), 2.56 (t, *J* = 8 Hz, 2 H), 3.68 (br s, 2 H), 4.72 (s, 2 H), 6.54 (d, *J* = 9 Hz, 2 H), 6.66 (d, *J* = 9 Hz, 2 H), 7.20 (m, 4 H); FAB-MS *m/e* 387 (M + H)⁺. Anal. (C₂₀H₂₃ClN₄S·0.25H₂O) C, H, N.

3-*n*-Butyl-5-[(4-chlorobenzyl)thio]-4-[4-[(2-cyanobenzoyl)amino]benzyl]-4*H*-1,2,4-triazole (112). A solution of 450 mg (1.16 mmol) of 110, 418 mg (2.53 mmol) of 2-cyanobenzoyl chloride (111), and 438 μL (325 mg, 2.52 mmol) of *N,N*-diisopropylethylamine in 10 mL of dry THF was stirred overnight at room temperature. The mixture was filtered, and the filtrate was concentrated in vacuo. The residue was dissolved in 50 mL of EtOAc and washed with 2 × 60 mL of saturated aqueous NaHCO₃ followed by 50 mL of saturated aqueous NaCl. The organic phase was dried (MgSO₄), filtered, and concentrated. The residue was chromatographed on a silica gel column, which was eluted briefly with hexane and then with a stepwise gradient from 1:1 hexane/EtOAc to 100% EtOAc. Two major products were eluted, the second of which corresponded to the desired product. Fractions containing this material were combined and concentrated to yield 229 mg (36%) of a solid: mp 75–77 °C; TLC in 1:3 hexane/EtOAc; ¹H NMR (CDCl₃, 300 MHz) δ 0.88 (t, *J* = 7.5 Hz, 3 H), 1.35 (m, 2 H), 1.67 (m, 2 H), 2.59 (t, *J* = 7.5 Hz, 2 H), 4.32 (m, 2 H), 4.90 (s, 2 H), 6.9–8.1 (m, 12 H), 8.73 (s, 1 H); FAB-MS *m/e* 516 (M + H)⁺. Anal. (C₂₈H₂₆ClN₅OS·0.4EtOAc) C, H, N.

Method B-1. 3-*n*-Butyl-5-[(4-chlorobenzyl)thio]-4-[4-[[2-(1*H*-tetrazol-5-yl)benzoyl]amino]benzyl]-4*H*-1,2,4-triazole (46). A mixture of 159 mg (0.31 mmol) of 112 and 222 mg (1.08 mmol) of trimethyltin azide³⁶ in 3 mL of dry toluene was

stirred at reflux for 1 day. The precipitate was isolated on a filter and washed with a small volume of toluene followed by Et₂O. The dried solid was dissolved as completely as possible in hot MeOH and concentrated onto 1 g of silica gel to give a powder. This was vacuum-dried over P₂O₅ and then added as a slurry in CH₂Cl₂ to a column of silica gel, which was eluted with 1% MeOH, then 10% MeOH, and finally 18% MeOH in CH₂Cl₂. The product fractions were combined and concentrated to yield 18 mg (10%) of a pale yellow solid: mp 175–176 °C dec (preliminary shrinking); TLC in 80:20 CH₂Cl₂/MeOH; ¹H NMR (DMSO-*d*₆, 300 MHz) δ 0.84 (t, *J* = 7.5 Hz, 3 H), 1.29 (m, 2 H), 1.54 (m, 2 H), 2.61 (t, *J* = 7.5 Hz, 2 H), 4.31 (s, 2 H), 4.99 (s, 2 H), 6.92 (d, *J* = 9 Hz, 2 H), 7.3–7.7 (m, 9 H), 7.86 (d, *J* = 8 Hz, 1 H), 10.82 (s, 1 H); FAB-MS *m/e* 559 (M + H)⁺. Anal. (C₂₈H₂₇ClN₅O·0.33CH₂Cl₂) C, H, N.

***N*-[[2'-(*tert*-Butoxycarbonyl)biphenyl-4-yl]methyl]phthalimide (114).** A mixture of 2.99 g (8 mmol, based on 93% purity) of *tert*-butyl 4'-(bromomethyl)biphenyl-2-carboxylate (113),¹⁵ 1.63 g (8.8 mmol) of potassium phthalimide, and 24 mL of dry DMF was stirred at room temperature for 7 h and then partitioned between 200 mL of Et₂O and 250 mL of H₂O. After being washed with 4 × 250 mL of H₂O, the organic phase was dried (MgSO₄), filtered, and concentrated. The residue was leached twice with hot Et₂O (15–20 mL), which was decanted off after cooling. The remaining solid was collected on a filter, washed with petroleum ether, and dried to yield 2.08 g of colorless crystals: mp 108.5–109 °C; TLC in 4:1 hexane/EtOAc; ¹H NMR (CDCl₃, 300 MHz) δ 1.17 (s, 9 H), 4.90 (s, 2 H), 7.2–7.9 (m, 12 H). Anal. (C₂₆H₂₃NO₄) C, H, N. A satisfactory second crop of crystals (0.58 g) was isolated from the mother liquor for a total yield of 2.66 g (82%).

***tert*-Butyl 4'-(Aminomethyl)biphenyl-2-carboxylate (115).** A mixture of 2.62 g (6.35 mmol) of 114, 1.21 mL (1.25 g, 25 mmol) of 100% hydrazine hydrate, and 35 mL of absolute EtOH was stirred at room temperature for 7.5 h. During this time the solid gradually dissolved, followed by precipitation. Glacial acetic acid (3.7 mL) was added, and stirring was continued overnight. The white solid was then removed by filtration, and the filtrate was concentrated at room temperature. The residual oil was taken up in Et₂O and washed twice with saturated aqueous Na₂CO₃. Next the product was extracted from the ethereal solution with 50 mL of 0.5 N HCl. The aqueous layer was separated and basified by addition of excess saturated Na₂CO₃ solution (CAUTION: gas evolution). The oil which separated was extracted with 100 mL of Et₂O. The organic phase was dried (Na₂SO₄), filtered, and concentrated at 30 °C to give 1.58 g (88%) of a very pale yellow, viscous oil: TLC in 95:5:0.5 CH₂Cl₂/MeOH/concentrated NH₄OH; ¹H NMR (CDCl₃, 300 MHz) δ 1.27 (s, 9 H), 1.50 (br s, 2 H), 3.92 (s, 2 H), 7.2–7.8 (m, 8 H). Anal. (C₁₅H₂₁NO₂·0.25H₂O) C, H, N.

Methyl *N*-[[2'-(*tert*-Butoxycarbonyl)biphenyl-4-yl]methyl]dithiocarbamate (116). By the procedure used to prepare 101, 115 was reacted with carbon disulfide/triethylamine followed by iodomethane to give 1.57 g (84%) of nearly colorless crystals: mp 127.5–128.5 °C; TLC in 4:1 hexane/EtOAc; ¹H NMR (CDCl₃, 300 MHz) δ 1.28 (s, 9 H), 2.66 (s, 3 H), 4.97 (d, *J* = 5 Hz, 2 H), 7.13 (br m, 1 H), 7.2–7.8 (m, 8 H); FAB-MS *m/e* 374 (M + H)⁺. Anal. (C₂₀H₂₃NO₂S₂) C, H, N.

4-[[2'-(*tert*-Butoxycarbonyl)biphenyl-4-yl]methyl]-3-thiosemicarbazine (117). A mixture of 1.53 g (4.1 mmol) of 116, 796 μL (820 mg, 16.4 mmol) of hydrazine hydrate, and 10 mL of absolute EtOH was stirred at reflux for 2 h. The cooled solution was concentrated, and the residue was chromatographed on a silica gel column (elution with 99:1 and then 98:2 CH₂Cl₂/MeOH), affording 1.15 g (79%) of a stiff, white foam: mp >45 °C (gradual); TLC in 95:5 CH₂Cl₂/MeOH; ¹H NMR (CDCl₃, 300 MHz) δ 1.28 (s, 9 H), 3.76 (br s, 2 H), 4.90 (d, *J* = 5 Hz, 2 H), 7.2–7.8 (m, 9 H); FAB-MS *m/e* 358 (M + H)⁺. Anal. (C₁₉H₂₃N₃O₂S·0.1H₂O) C, H, N.

4-[[2'-(*tert*-Butoxycarbonyl)biphenyl-4-yl]methyl]-5-*n*-butyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (118). Using the procedure for 103, 117 was reacted with trimethyl orthoformate. The crude product was chromatographed (gradient elution with 0–1% MeOH in CH₂Cl₂), and trituration of the resulting gum with petroleum ether yielded 828 mg (63%) of a crystalline solid: mp 135–137 °C; TLC in 95:5 CH₂Cl₂/MeOH; ¹H NMR (CDCl₃, 300 MHz) δ 0.87 (t, *J* = 7 Hz, 3 H), 1.22 (s, 9 H), 1.32 (m, 2 H),

1.62 (m, 2 H), 2.48 (t, $J = 7$ Hz, 2 H), 5.27 (s, 2 H), 7.2–7.5 (m, 7 H), 7.74 (d, $J = 8$ Hz, 1 H); FAB-MS m/e 424 (M + H)⁺. Anal. (C₂₄H₂₃N₃O₂S) C, H, N.

4-[[2'-(*tert*-Butoxycarbonyl)biphenyl-4-yl]methyl]-3-*n*-butyl-5-[[[(methoxycarbonyl)methyl]thio]-4*H*-1,2,4-triazole (119). To a stirred solution of 636 mg (1.5 mmol) of 118 in 4 mL of dry CH₂Cl₂ was added 435 μ L (322 mg, 2.5 mmol) of *N,N*-diisopropylethylamine followed by 219 μ L (271 mg, 2.5 mmol) of methyl chloroacetate. The resulting solution was stirred at room temperature for 7.5 h and then partitioned between 50 mL of Et₂O and 25 mL of saturated aqueous NH₄Cl. The organic layer was washed with another portion of the NH₄Cl solution and then dried over MgSO₄. The filtered solution was concentrated, and the residual oil was chromatographed (elution with a gradient of 0–5% *i*-PrOH in CH₂Cl₂) to give 639 mg (86%) of a colorless gum: TLC in 97:3 CH₂Cl₂/*i*-PrOH; ¹H NMR (CDCl₃, 300 MHz) δ 0.90 (t, $J = 7$ Hz, 3 H), 1.24 (s, 9 H), 1.40 (m, 2 H), 1.72 (m, 2 H), 2.67 (t, $J = 7.5$ Hz, 2 H), 3.74 (s, 3 H), 4.03 (s, 2 H), 5.19 (s, 2 H), 7.09 (d, $J = 8$ Hz, 2 H), 7.2–7.5 (m, 5 H), 7.79 (d, $J = 8$ Hz, 1 H); FAB-MS m/e 496 (M + H)⁺. Anal. (C₂₇H₃₃N₃O₄S) C, H, N.

Method C-1. 3-*n*-Butyl-4-[(2'-carboxybiphenyl-4-yl)methyl]-5-[[[(methoxycarbonyl)methyl]thio]-4*H*-1,2,4-triazole (50). To 496 mg (1 mmol) of 119 was added 3 mL of anhydrous trifluoroacetic acid. The resulting solution was stirred at room temperature for 24 h and then evaporated under a stream of N₂. The clear residual gum was treated with approximately 25 mL of Et₂O and stirred vigorously in a stoppered flask, resulting in crystallization. After about 20 min, the solid was collected on a filter, washed with Et₂O, and dried in vacuo to give 426 mg (97%) of white crystals: mp 157.5–159 °C; TLC in 95:5:0.1 CH₂Cl₂/MeOH/AcOH; ¹H NMR (DMSO-*d*₆, 300 MHz) δ 0.82 (t, $J = 7$ Hz, 3 H), 1.29 (m, 2 H), 1.54 (m, 2 H), 2.64 (t, $J = 7$ Hz, 2 H), 3.64 (s, 3 H), 4.05 (s, 2 H), 5.23 (s, 2 H), 7.14 (d, $J = 8$ Hz, 2 H), 7.3–7.6 (m, 5 H), 7.73 (d, $J = 8$ Hz, 1 H), 12.76 (br s, 1 H); FAB-MS m/e 440 (M + H)⁺. Anal. (C₂₃H₂₅N₃O₄S) C, H, N.

Method C-2. 5-*n*-Butyl-4-[(2'-carboxybiphenyl-4-yl)methyl]-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (51) and 3-*n*-Butyl-5-(*tert*-butylthio)-4-[(2'-carboxybiphenyl-4-yl)methyl]-4*H*-1,2,4-triazole (52). A solution of 51 mg (0.12 mmol) of 118 in 0.5 mL of anhydrous trifluoroacetic acid was stirred at room temperature for 2 h and then evaporated to dryness under a stream of N₂. Column chromatography of the residue (gradient elution with 1–5% MeOH in CH₂Cl₂ containing 0.1% AcOH) afforded two major products. Concentration of fractions containing the first (higher *R_f*) product gave a residue which solidified upon trituration with Et₂O, yielding 9.5 mg (21%) of 51 as a white powder: mp 218–219 °C; TLC in 95:5:0.1 CH₂Cl₂/MeOH/AcOH; ¹H NMR (DMSO-*d*₆, 300 MHz) δ 0.79 (t, $J = 7.5$ Hz, 3 H), 1.25 (m, 2 H), 1.46 (m, 2 H), 2.53 (partially obscured t, $J = 8$ Hz, 2 H), 5.29 (s, 2 H), 7.25–7.4 (m, 5 H), 7.45 (dd, $J = 8, 8$ Hz, 1 H), 7.57 (dd, $J = 8, 8$ Hz, 1 H), 7.72 (d, $J = 8$ Hz, 1 H), 12.7 (v br s, 1 H); FAB-MS m/e 368 (M + H)⁺. Anal. (C₂₀H₂₁N₃O₂S·0.5H₂O) C, H, N.

Similar concentration and workup of fractions containing the second (lower *R_f*) product provided 21.9 mg (43%) of 52 as a white powder: mp 166.5–168 °C dec; TLC in 95:5:0.1 CH₂Cl₂/MeOH/AcOH; ¹H NMR (DMSO-*d*₆, 300 MHz) δ 0.82 (t, $J = 7$ Hz, 3 H), 1.28 (m, 2 H), 1.36 (s, 9 H), 1.55 (m, 2 H), 2.65 (t, $J = 7.5$ Hz, 2 H), 5.33 (s, 2 H), 7.03 (d, $J = 8$ Hz, 2 H), 7.25–7.35 (m, 3 H), 7.44 (dd, $J = 7.5, 7.5$ Hz, 1 H), 7.55 (dd, $J = 7.5, 7.5$ Hz, 1 H), 7.71 (d, $J = 8$ Hz, 1 H), 12.75 (v br s, 1 H); FAB-MS m/e 424 (M + H)⁺. Anal. (C₂₄H₂₃N₃O₂S·0.2H₂O) C, H, N.

4'-(Azidomethyl)-2-biphenylcarbonitrile (121). A mixture of 1.97 g (7.25 mmol) of 4'-(bromomethyl)-2-biphenylcarbonitrile (120),¹⁶ 445 mg (9.1 mmol) of lithium azide, and 5 mL of dry DMSO was stirred at room temperature for 1 h and then partitioned between 100 mL of Et₂O and 100 mL of H₂O. The organic phase was washed (3 \times 100 mL of H₂O), dried (MgSO₄), filtered, and concentrated in vacuo. The residue, which solidified on standing, was triturated with petroleum ether, collected on a filter, washed with petroleum ether, and dried to yield 1.15 g (68%) of white crystals: mp 69–70 °C; TLC in 4:1 hexane/EtOAc; ¹H NMR (CDCl₃, 300 MHz) δ 4.41 (s, 2 H), 7.4–7.7 (m, 7 H), 7.75 (d, $J = 8$ Hz, 1 H); EI-MS m/e 234 (M⁺).

4-[(2'-Cyanobiphenyl-4-yl)methyl]-3-thiosemicarbazide (122). A mixture of 1.12 g (4.8 mmol) of 121, 1.57 g (6.0 mmol) of triphenylphosphine, and 8 mL of carbon disulfide was stirred at room temperature for 5.5 h and then evaporated to dryness. The residue was dissolved in 12 mL of THF and stirred vigorously at room temperature as 0.699 mL (720 mg, 14.4 mmol) of hydrazine hydrate was added all at once. The mixture immediately turned milky but soon clarified with the separation of a small, second liquid phase. After 10 min the mixture was partitioned between 40 mL of Et₂O, 25 mL of CH₂Cl₂, and 75 mL of H₂O. The solid which separated was collected on a filter, dried, and recrystallized from EtOAc to give 661 mg of white crystals: mp 163–163.5 °C; TLC in 95:5 CH₂Cl₂/MeOH; ¹H NMR (DMSO-*d*₆, 300 MHz) δ 4.55 (s, 2 H), 4.80 (d, $J = 6$ Hz, 2 H), 7.4–7.8 (m, 7 H), 7.94 (d, $J = 8$ Hz, 1 H), 8.45 (br m, 1 H), 8.80 (s, 1 H); FAB-MS m/e 283 (M + H)⁺. Anal. (C₁₅H₁₄N₄S) C, H, N, S. By reworking the mother liquor and the organic layer of the filtrate, additional product of satisfactory purity was isolated for a total yield of 1.01 g (75%).

5-*n*-Butyl-4-[(2'-cyanobiphenyl-4-yl)methyl]-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (123). The reaction of 122 with trimethyl orthoacetate was carried out according to the procedure used for 103, except that after a reaction time of 4 h the solvent was evaporated under a stream of N₂ while the bath temperature was maintained at 125 °C. The residue was recrystallized from nitromethane to give a 64% yield of white crystals: mp 168–168.5 °C; TLC in 98:2 CH₂Cl₂/MeOH; ¹H NMR (CDCl₃, 300 MHz) δ 0.88 (t, $J = 7$ Hz, 3 H), 1.35 (m, 2 H), 1.62 (m, 2 H), 2.54 (t, $J = 7$ Hz, 2 H), 5.33 (s, 2 H), 7.35–7.7 (m, 7 H), 7.77 (d, $J = 8$ Hz, 1 H), 11.06 (br s, 1 H); FAB-MS m/e 349 (M + H)⁺. Anal. (C₂₀H₂₀N₄S) C, H, N.

3-*n*-Butyl-5-[(4-chlorobenzyl)thio]-4-[(2'-cyanobiphenyl-4-yl)methyl]-4*H*-1,2,4-triazole (124). This material was prepared by reaction of 123 with 4-chlorobenzyl chloride according to the procedure used for 104, except that the reaction was run overnight. The crude product was chromatographed (gradient elution with 0–1% MeOH in CH₂Cl₂) to give a 71% yield of 124 as a slightly cloudy gum: TLC in 98:2 CH₂Cl₂/MeOH; ¹H NMR (CDCl₃, 300 MHz) δ 0.89 (t, $J = 7$ Hz, 3 H), 1.35 (m, 2 H), 1.67 (m, 2 H), 2.60 (t, $J = 8$ Hz, 2 H), 4.33 (s, 2 H), 4.92 (s, 2 H), 6.97 (d, $J = 9$ Hz, 2 H), 7.24 (d, $J = 9$ Hz, 2 H), 7.4–7.7 (m, 7 H), 7.77 (d, $J = 8$ Hz, 1 H); FAB-MS m/e 473 (M + H)⁺. Anal. (C₂₇H₂₅ClN₄S·0.25H₂O) C, H, N.

Method B-2. 3-*n*-Butyl-5-[(4-chlorobenzyl)thio]-4-[(2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl)methyl]-4*H*-1,2,4-triazole (62). The cyano intermediate 124 was reacted with trimethyltin azide and worked up according to the procedure used for 46, except that the reaction was allowed to proceed for 2 days. Chromatography on silica gel (elution with 9:1 CH₂Cl₂/MeOH) afforded a 37% yield of 62 as an off-white solid: mp 92–93 °C; TLC in 80:20 CH₂Cl₂/MeOH; ¹H NMR (DMSO-*d*₆, 300 MHz) δ 0.80 (t, $J = 7.5$ Hz, 3 H), 1.24 (m, 2 H), 1.48 (m, 2 H), 2.55 (t, $J = 7.5$ Hz, 2 H), 4.29 (s, 2 H), 5.02 (s, 2 H), 6.84 (d, $J = 8$ Hz, 2 H), 7.03 (d, $J = 8$ Hz, 2 H), 7.3–7.7 (m, 8 H); FAB-MS m/e 516 (M + H)⁺. Anal. (C₂₇H₂₆ClN₇S·0.6H₂O) C, H, N.

Ethyl Hexanoate 4-[(2'-Cyanobiphenyl-4-yl)methyl]thiosemicarbazone (126). A solution of 750 mg (4.17 mmol) of ethyl hexamimidate hydrochloride (125)⁴¹ in 5 mL of dry DMF was treated with 1.17 g (4.17 mmol) of 122, and the solution was stirred at room temperature for about 1.5 h. The turbid mixture was concentrated in vacuo at 45 °C to small volume and then partitioned between 100 mL of EtOAc and 100 mL of H₂O. The organic phase was washed with 100 mL of H₂O and then 100 mL of saturated aqueous NaCl. Next it was dried over MgSO₄, filtered, and concentrated. Column chromatography of the residue (elution with CH₂Cl₂) gave 860 mg (50%) of a foam, which by NMR appeared to consist of a mixture of syn and anti isomers: TLC in CH₂Cl₂; ¹H NMR (CDCl₃, 300 MHz) δ 0.8–0.95 (m, 3 H), 1.2–1.4 (m, 7 H), 1.5–1.65 (m, 2 H), 2.30 (m, 2 H), 4.01, 4.09 (minor and major q, $J = 7$ Hz, total 2 H), 5.00 (m, 2 H), 7.35–7.8 (m, 8 H), 8.00, 8.98 (minor and major br s, total 1 H); FAB-MS m/e 409 (M + H)⁺. Anal. (C₂₃H₂₈N₄OS·0.2H₂O) C, H, N.

4-[(2'-Cyanobiphenyl-4-yl)methyl]-2,4-dihydro-5-*n*-pentyl-3*H*-1,2,4-triazole-3-thione (127). A solution of 776 mg (1.9 mmol) of 126 and 284 μ L (290 mg, 1.9 mmol) of DBU in 8 mL

of dry THF was stirred at reflux for approximately 30 h and then cooled, resulting in precipitation. The mixture was diluted with Et₂O and filtered. The material on the filter was purified by column chromatography (gradient elution with 0.5–2% MeOH in CH₂Cl₂) to yield 468 mg (67%) of a solid: mp 209–209.5 °C; TLC in 95:5 CH₂Cl₂/MeOH; ¹H NMR (DMSO-*d*₆, 300 MHz) δ 0.76 (t, *J* = 7 Hz, 3 H), 1.1–1.25 (m, 4 H), 1.46 (m, 2 H), 2.56 (t, *J* = 7.5 Hz, 2 H), 5.34 (s, 2 H), 7.40 (d, *J* = 8 Hz, 2 H), 7.55–7.65 (m, 4 H), 7.79 (dd, *J* = 8, 8 Hz, 1 H), 7.95 (d, *J* = 8 Hz, 1 H); FAB-MS *m/e* 363 (M + H)⁺. Anal. (C₂₁H₂₂N₄S·0.05CH₂Cl₂) C, H, N.

3-*n*-Butyl-4-[(2'-cyanobiphenyl-4-yl)methyl]-5-[[2-(methoxycarbonyl)benzyl]thio]-4*H*-1,2,4-triazole (128). Alkylation of 123 with methyl 2-(bromomethyl)benzoate⁶² was accomplished according to the procedure used for 104. Column chromatography of the crude product (gradient elution with 0.5–5% MeOH in CH₂Cl₂) yielded 567 mg (76%) of a colorless gum: TLC in 95:5 CH₂Cl₂/MeOH; ¹H NMR (CDCl₃, 300 MHz) δ 0.84 (t, *J* = 7.5 Hz, 3 H), 1.32 (m, 2 H), 1.63 (m, 2 H), 2.55 (t, *J* = 7.5 Hz, 2 H), 3.88 (s, 3 H), 4.78 (s, 2 H), 4.84 (s, 2 H), 6.97 (d, *J* = 8 Hz, 2 H), 7.3–7.5 (m, 7 H), 7.62 (dd, *J* = 8, 8 Hz, 1 H), 7.74 (d, *J* = 8 Hz, 1 H), 7.96 (d, *J* = 8 Hz, 1 H); FAB-MS *m/e* 497 (M + H)⁺. Anal. (C₂₉H₂₈N₄O₂S·0.2CH₂Cl₂) C, H, N.

3-*n*-Butyl-4-[(2'-cyanobiphenyl-4-yl)methyl]-5-[[2-(hydroxymethyl)benzyl]thio]-4*H*-1,2,4-triazole (129). To 250 mg (0.5 mmol) of 128 at 0 °C was added 1.5 mL (3 mmol) of 2 M lithium borohydride in THF. The mixture was stirred at room temperature for 1 day and then quenched with MeOH and neutralized with AcOH. The residue obtained upon concentration was partitioned between CH₂Cl₂ (20 mL) and H₂O (20 mL). The organic phase was washed again with H₂O, dried (MgSO₄), filtered, and concentrated. The crude product was chromatographed (gradient elution with 0–3% MeOH in CH₂Cl₂) to yield 75 mg (32%) of a foam: TLC in 95:5 CH₂Cl₂/MeOH; ¹H NMR (CDCl₃, 300 MHz) δ 0.85 (t, *J* = 7 Hz, 3 H), 1.33 (m, 2 H), 1.64 (m, 2 H), 2.58 (t, *J* = 7.5 Hz, 2 H), 4.52 (s, 2 H), 4.77 (s, 2 H), 4.94 (s, 2 H), 7.01 (d, *J* = 8 Hz, 2 H), 7.15–7.5 (m, 8 H), 7.64 (dd, *J* = 8 Hz, 1 H), 7.76 (d, *J* = 8 Hz, 1 H); FAB-MS *m/e* 469 (M + H)⁺.

Method B-3. 3-*n*-Butyl-5-[[2-(methoxycarbonyl)benzyl]thio]-4-[[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-4*H*-1,2,4-triazole (70). The nitrile intermediate 128 was reacted with trimethyltin azide as described for 46. However, after completion of the reaction, the entire mixture was cooled and concentrated in vacuo. The residual foam was dissolved in EtOAc, washed several times with 0.5 N HCl, dried (MgSO₄), filtered, and concentrated. The residue was treated with silica gel and MeOH, stirred overnight, and evaporated in vacuo to give a dry powder. This was added as a slurry in CH₂Cl₂ to the top of a silica gel column. Gradient elution with 1–10% MeOH in CH₂Cl₂ afforded 54% yield of a stiff, cream-colored foam: TLC in 80:20 CH₂Cl₂/MeOH; ¹H NMR (CDCl₃, 300 MHz) δ 0.83 (t, *J* = 7.5 Hz, 3 H), 1.25 (m, 2 H), 1.53 (m, 2 H), 2.39 (t, *J* = 8 Hz, 2 H), 3.85 (s, 3 H), 4.59 (s, 2 H), 4.77 (s, 2 H), 6.59 (d, *J* = 8 Hz, 2 H), 7.01 (d, *J* = 8 Hz, 2 H), 7.2–7.6 (m, 6 H), 7.90 (m, 2 H); FAB-MS *m/e* 540 (M + H)⁺. Anal. (C₂₉H₂₉N₇O₂S·1.5H₂O·0.2CH₂Cl₂) C, H, N.

Method D. 3-*n*-Butyl-5-[[2-(2-carboxybenzyl)thio]-4-[[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-4*H*-1,2,4-triazole (71). A suspension of 97 mg (0.18 mmol) of 70 in 0.72 mL (1.8 mmol) of 2.5 N NaOH was stirred at room temperature as MeOH (0.36 mL) was added gradually to give a clear solution. After 1.5 h excess 2 N HCl was added, resulting in the separation of a gummy precipitate which was isolated and extracted with several small portions of EtOAc. The combined EtOAc fractions were dried over MgSO₄, filtered, and concentrated. Trituration of the residue with Et₂O gave 71 mg (75%) of an amorphous, white solid: TLC in 80:20 CH₂Cl₂/MeOH; ¹H NMR (DMSO-*d*₆, 300 MHz) δ 0.81 (t, *J* = 7.5 Hz, 3 H), 1.25 (m, 2 H), 1.48 (m, 2 H), 2.56 (t, *J* = 7.5 Hz, 2 H), 4.67 (s, 2 H), 5.00 (s, 2 H), 6.87 (d, *J* = 8 Hz, 2 H), 7.03 (d, *J* = 8 Hz, 2 H), 7.3–7.7 (m, 7 H), 7.91 (d, *J* = 8 Hz, 1 H); FAB-MS *m/e* 526 (M + H)⁺. Anal. (C₂₈H₂₇N₇O₂S·0.75H₂O·0.125Et₂O) C, H, N.

3-*n*-Butyl-5-[[2-(2-cyanobenzyl)thio]-4-[(2'-cyanobiphenyl-4-yl)methyl]-4*H*-1,2,4-triazole (130). By the procedure used for 104, 123 was alkylated with α-bromo-*o*-tolunitrile. Column chromatography of the crude product (gradient elution with 0–2%

MeOH in CH₂Cl₂) gave 58% yield of a nearly colorless, stiff gum: TLC in 95:5 CH₂Cl₂/MeOH; ¹H NMR (CDCl₃, 300 MHz) δ 0.87 (t, *J* = 7 Hz, 3 H), 1.34 (m, 2 H), 1.67 (m, 2 H), 2.60 (t, *J* = 8 Hz, 2 H), 4.53 (s, 2 H), 5.01 (s, 2 H), 7.01 (d, *J* = 8 Hz, 2 H), 7.3–7.7 (m, 9 H), 7.75 (d, *J* = 8 Hz, 1 H); FAB-MS *m/e* 464 (M + H)⁺. Anal. (C₂₈H₂₆N₆S·0.4H₂O) C, H, N.

Method B-4. 3-*n*-Butyl-5-[[2-(1*H*-tetrazol-5-yl)benzyl]thio]-4-[[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-4*H*-1,2,4-triazole (73). A mixture of 95 mg (0.2 mmol) of 130, 412 mg (2 mmol) of trimethyltin azide,³⁶ and 2 mL of dioxane was stirred at reflux for 40 h. The cooled mixture was concentrated in vacuo, and the residue was partitioned between EtOAc (5 mL) and 2 N HCl (3 mL). The aqueous phase was further extracted with 3 × 4 mL of EtOAc. The combined EtOAc extracts were diluted with CH₂Cl₂/MeOH, dried over MgSO₄, filtered, and concentrated in vacuo. The residue (340 mg) was dissolved in 10 mL of dry MeOH and stirred overnight with 3.5 g of silica gel in a stoppered flask. The mixture was concentrated under vacuum and dried to give a powder, which was added as a slurry in CH₂Cl₂ to a column of silica gel (eluted successively with 98:2:0.2, 95:5:0.5, and 90:10:1 CH₂Cl₂/MeOH/AcOH). The product so obtained was chromatographed twice more under similar conditions to remove a trimethyltin-containing contaminant. Trituration of the crude product with Et₂O gave 29.2 mg (27%) of a light beige powder: TLC in 90:10:1 CH₂Cl₂/MeOH/AcOH; ¹H NMR (DMSO-*d*₆, 300 MHz) δ 0.82 (t, *J* = 7 Hz, 3 H), 1.27 (m, 2 H), 1.50 (m, 2 H), 2.53 (partially obscured t, *J* = 7.5 Hz, 2 H), 4.89, 4.91 (overlapping s, each 2 H), 6.78 (d, *J* = 8 Hz, 2 H), 6.98 (d, *J* = 8 Hz, 2 H), 7.2–7.7 (m, 7 H), 8.03 (d, *J* = 8 Hz, 1 H); high-resolution FAB-MS *m/e* 550.2236 (calcd for C₂₈H₂₈N₁₁S (M + H)⁺ 550.2250), 572.2082 (calcd for C₂₈H₂₇N₁₁NaS (M + Na)⁺ 572.2069).

Method E. 3-*n*-Butyl-5-[(4-chlorobenzyl)sulfinyl]-4-[[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-4*H*-1,2,4-triazole (75). To a stirred solution of 113 mg (0.22 mmol) of 62 in 1.2 mL of glacial AcOH was added dropwise 1.2 mL of 30% hydrogen peroxide (aqueous). A small amount of additional acetic acid was added to give a clear solution, which was stirred at room temperature for 17.5 h. The solution was then partitioned between 15 mL of EtOAc and 15 mL of dilute HCl (pH 1.5–2). The aqueous phase was extracted twice more with EtOAc. The combined organic fractions were washed with dilute HCl, dried (MgSO₄), filtered, and concentrated in vacuo. Trituration of the residue with Et₂O yielded 77 mg (65%) of a white solid: mp 208–209 °C dec (preliminary discoloration); TLC in 80:20 CH₂Cl₂/MeOH (indistinguishable from starting material by TLC); ¹H NMR (DMSO-*d*₆, 300 MHz) δ 0.79 (t, *J* = 7.5 Hz, 3 H), 1.25 (m, 2 H), 1.46 (m, 2 H), 2.59 (m, 2 H), 4.75 (AB q, *J* = 12.5 Hz, 2 H), 5.33 (AB q, *J* = 16 Hz, 2 H), 6.89 (d, *J* = 7 Hz, 2 H), 7.03 (d, *J* = 7 Hz, 2 H), 7.29 (d, *J* = 8 Hz, 2 H), 7.40 (d, *J* = 8 Hz, 2 H), 7.4–7.75 (m, 4 H); FAB-MS *m/e* 532 (M + H)⁺. Anal. (C₂₇H₂₆ClN₅OS·0.25H₂O) C, H, N.

3-*n*-Butyl-5-[(4-chlorobenzyl)sulfonyl]-4-[(2'-cyanobiphenyl-4-yl)methyl]-4*H*-1,2,4-triazole (131). A stirred solution of 47 mg (0.1 mmol) of 124 in 0.3 mL of dry CH₂Cl₂ was treated with 63 mg (0.3 mmol) of 80–85% *m*-chloroperbenzoic acid. Precipitation began within a few minutes. After 2.5 h the mixture was taken up in 25 mL of EtOAc and washed with 3 × 25 mL of saturated aqueous Na₂CO₃. The organic phase was dried over MgSO₄, filtered, and concentrated in vacuo to give 48 mg (95%) of a gum: TLC in 95:5 CH₂Cl₂/MeOH; ¹H NMR (CDCl₃, 300 MHz) δ 0.87 (t, *J* = 7 Hz, 3 H), 1.32 (m, 2 H), 1.66 (m, 2 H), 2.60 (t, *J* = 8 Hz, 2 H), 4.78 (s, 2 H), 5.25 (s, 2 H), 6.94 (d, *J* = 7 Hz, 2 H), 7.2–7.5 (m, 8 H), 7.63 (m, 1 H), 7.74 (d, *J* = 8 Hz, 1 H); FAB-MS *m/e* 505 (M + H)⁺.

3-*n*-Butyl-4-[(2'-cyanobiphenyl-4-yl)methyl]-5-(methylthio)-4*H*-1,2,4-triazole (132). The alkylation of 123 with iodomethane followed the procedure described for 104. After column chromatography (gradient elution with 0–2% MeOH in CH₂Cl₂), an 85% yield of the product was obtained as an oil: TLC in 95:5 CH₂Cl₂/MeOH; ¹H NMR (CDCl₃, 300 MHz) δ 0.87 (t, *J* = 7.5 Hz, 3 H), 1.36 (m, 2 H), 1.68 (m, 2 H), 2.65 (t, *J* = 8 Hz, 2 H) overlapping 2.67 (s, 3 H), 5.08 (s, 2 H), 7.16 (d, *J* = 8.5 Hz, 2 H), 7.4–7.7 (m, 5 H), 7.75 (d, *J* = 8 Hz, 1 H); FAB-MS *m/e* 363 (M + H)⁺. Anal. (C₂₁H₂₂N₄S·0.5H₂O) C, H, N.

3-*n*-Butyl-4-[(2'-cyanobiphenyl-4-yl)methyl]-5-(methylsulfonyl)-4*H*-1,2,4-triazole (133). Oxidation of 132 with 3 equiv

of *m*-chloroperbenzoic acid proceeded as described for 131 to give a 58% yield of a gum: TLC in 95:5 CH₂Cl₂/MeOH; ¹H NMR (CDCl₃, 300 MHz) δ 0.87 (t, *J* = 7 Hz, 3 H), 1.36 (m, 2 H), 1.69 (m, 2 H), 2.67 (t, *J* = 8 Hz, 2 H), 3.44 (s, 3 H), 5.51 (s, 2 H), 7.26 (d, *J* = 8 Hz, 2 H), 7.4–7.7 (m, 5 H), 7.76 (d, *J* = 8 Hz, 1 H); FAB-MS *m/e* 395 (M + H)⁺.

3-*n*-Butyl-4-[(2'-cyanobiphenyl-4-yl)methyl]-5-(phenylthio)-4*H*-1,2,4-triazole (134). Reaction of 133 with thiophenol was accomplished as described for the synthesis of 109. Column chromatography (elution with 0.8% MeOH in CH₂Cl₂) provided a 50% yield of a stiff gum: TLC in 95:5 CH₂Cl₂/MeOH; ¹H NMR (CDCl₃, 300 MHz) δ 0.86 (t, *J* = 7.5 Hz, 3 H), 1.34 (m, 2 H), 1.69 (m, 2 H), 2.63 (t, *J* = 7.5 Hz, 2 H), 5.19 (s, 2 H), 6.92 (d, *J* = 8 Hz, 2 H), 7.15–7.7 (m, 10 H), 7.75 (d, *J* = 8 Hz, 1 H); FAB-MS *m/e* 425 (M + H)⁺. Anal. (C₂₆H₂₄N₄S) C, H, N.

Method B-5. 3-*n*-Butyl-5-(methylthio)-4-[[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-4*H*-1,2,4-triazole (53). This material was prepared from 132 according to the procedure used for 70, except that the partitioning step was omitted, yielding 56% of the product as a stiff foam: mp 100–102 °C (preliminary softening); TLC in 9:1 CH₂Cl₂/MeOH; ¹H NMR (DMSO-*d*₆, 300 MHz) δ 0.83 (t, *J* = 7 Hz, 3 H), 1.28 (m, 2 H), 1.52 (m, 2 H), 2.55 (s, 3 H), 2.61 (t, *J* = 7.5 Hz, 2 H), 5.14 (s, 2 H), 7.01 (d, *J* = 8 Hz, 2 H), 7.10 (d, *J* = 8 Hz, 2 H), 7.5–7.7 (m, 4 H); FAB-MS *m/e* 406 (M + H)⁺. Anal. (C₂₁H₂₃N₇S·0.5H₂O·0.3CH₂Cl₂) C, H, N.

Method F. 3-*n*-Butyl-5-(methylsulfonyl)-4-[[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-4*H*-1,2,4-triazole (74). A solution of 145 mg (0.36 mmol) of 53 in 0.5 mL of 10% peracetic acid in acetic acid was stirred at room temperature in a stoppered flask for 3 days and then partitioned between 15 mL of EtOAc and 15 mL of dilute HCl (pH 2.5). The aqueous phase was further extracted with 2 × 15 mL of EtOAc. The combined organic fractions were dried (MgSO₄), filtered, and concentrated in vacuo. Trituration of the residue with Et₂O yielded 117 mg (70%) of a white solid: mp 98–100 °C (preliminary softening); TLC in 90:10 CH₂Cl₂/MeOH/concentrated NH₄OH; ¹H NMR (DMSO-*d*₆, 300 MHz) δ 0.81 (t, *J* = 7 Hz, 3 H), 1.28 (m, 2 H), 1.52 (m, 2 H), 2.63 (t, *J* = 8 Hz, 2 H), 3.48 (s, 3 H), 5.53 (s, 2 H), 7.11 (apparent s, 4 H), 7.5–7.75 (m, 4 H), 11.93 (br s, 1 H); FAB-MS *m/e* 438 (M + H)⁺. Anal. (C₂₁H₂₃N₇O₂S·0.33H₂O·0.25Et₂O) C, H, N.

Method G. 3-*n*-Butyl-5-(2-phenylethoxy)-4-[[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-4*H*-1,2,4-triazole (82). A 1.3 M solution of sodium 2-phenylethoxide was prepared by adding a 150-mg pellet of sodium to 5 mL of phenethyl alcohol and heating at 75 °C until dissolution occurred and H₂ evolution ceased. To 51 mg (0.12 mmol) of 74 was added 400 μL (0.5 mmol) of the freshly prepared alkoxide solution, and the mixture was stirred overnight at 65 °C. The mixture was diluted with 25 mL of EtOAc and washed with 2 × 20 mL of 0.2 N HCl. The organic phase was dried (MgSO₄), filtered, and concentrated. Column chromatography of the residue (elution with 1% and then 5% MeOH in CH₂Cl₂) afforded 29 mg (50%) of a white solid: mp 76–77 °C; TLC in 90:10 CH₂Cl₂/MeOH/concentrated NH₄OH; ¹H NMR (DMSO-*d*₆, 300 MHz) δ 0.82 (t, *J* = 7 Hz, 3 H), 1.27 (m, 2 H), 1.46 (m, 2 H), 2.49 (partially obscured t, *J* = 7.5 Hz, 2 H), 3.06 (t, *J* = 7 Hz, 2 H), 4.55 (t, *J* = 7 Hz, 2 H), 4.85 (s, 2 H), 6.99 (m, 4 H), 7.2–7.7 (m, 9 H); high-resolution FAB-MS *m/e* 480.2513 (calcd for C₂₈H₃₀N₇O (M + H)⁺ 480.2512).

Ethyl Valerate Thiosemicarbazone (135). A solution of 10.79 g (65 mmol) of ethyl valerimidate hydrochloride (96)³² in 130 mL of dry DMF was stirred at room temperature as 5.91 g (65 mmol) of thiosemicarbazide was added. The mixture was stirred at room temperature for 2.5 h and then partitioned between 1 L of EtOAc and 800 mL of H₂O. The organic layer was dried over MgSO₄, filtered, and concentrated in vacuo. The residual oil solidified upon standing to yield 11.05 g (84%) of a nearly white solid, which by NMR appeared to exist as a mixture of syn and anti isomers: mp 73–74.5 °C; TLC in 97:3 CH₂Cl₂/MeOH; ¹H NMR (CDCl₃, 300 MHz) δ 0.91 (t, *J* = 7 Hz, 3 H), 1.25–1.4 (m, 5 H), 1.55 (m, 2 H), 2.31 (m, 2 H), 4.03, 4.07 (overlapping minor and major q, *J* = 7 Hz, total 2 H), 6.03 (distorted br s, 1 H), 6.80, 6.95 (minor and major br s, total 1 H), 8.05, 8.97 (minor and major br s, total 1 H); FAB-MS *m/e* 204 (M + H)⁺. Anal. (C₈H₁₇N₃OS) C, H, N.

Ethyl Valerate *S*-Methylisothiosemicarbazone (136). To a stirred solution of 11.02 g (54.2 mmol) of 135 in 50 mL of CH₂Cl₂ was added 6.75 mL (15.39 g, 108.4 mmol) of iodomethane. A mild exotherm was observed. After 2.5 h at ambient temperature, the solution was agitated as Et₂O (150–175 mL) was added gradually until crystallization began. After aging for at least 1 h, the solid was collected on a filter and washed with Et₂O. Next it was partitioned between 100 mL of saturated aqueous Na₂CO₃ and a mixture of 200 mL of Et₂O and 50 mL of CH₂Cl₂. The organic phase was dried over Na₂SO₄, filtered, and concentrated in vacuo at ≤30 °C to give 4.85 g (41%) of a white solid: mp 80–82 °C; TLC in 95:5 CH₂Cl₂/MeOH; ¹H NMR (CDCl₃, 300 MHz) δ 0.90 (t, *J* = 7.5 Hz, 3 H), 1.29 (t, *J* = 7 Hz, 3 H), 1.36 (m, 2 H), 1.58 (m, 2 H), 2.27 (t, *J* = 8 Hz, 2 H), 2.40 (s, 3 H), 4.31 (br q, *J* = 7 Hz, 2 H), 5.07 (br s, 2 H); FAB-MS *m/e* 218 (M + H)⁺. Anal. (C₉H₁₉N₃OS) C, H, N.

4'-(Aminomethyl)-2-biphenylcarbonitrile (137). A solution of 5.85 g (25 mmol) of 121 in 50 mL of dry THF was treated portionwise with 6.55 g (25 mmol) of triphenylphosphine over 3–4 min. The solution was stirred at ambient temperature, and gas evolution proceeded at a moderate rate. A mild exotherm occurred, and the solution was cooled in a water bath as necessary. After 2 h, 675 μL (37.5 mmol) of H₂O was added, and stirring was continued at room temperature. The solution was concentrated in vacuo after 22 h, and the residual oil was chromatographed (gradient elution with 2–10% MeOH in CH₂Cl₂). The residue from evaporation of the pooled product fractions was partitioned between Et₂O/CH₂Cl₂ and saturated aqueous Na₂CO₃. The organic phase was dried (Na₂SO₄), filtered, and concentrated to yield 4.64 g (89%) of nearly white crystals (air-sensitive): mp 54–55 °C; TLC in 9:1 CH₂Cl₂/MeOH; ¹H NMR (CDCl₃, 300 MHz) δ 1.50 (br s, 2 H), 3.92 (s, 2 H), 7.35–7.65 (m, 7 H), 7.75 (d, *J* = 8 Hz, 1 H); FAB-MS *m/e* 209 (M + H)⁺. Anal. (C₁₄H₁₂N₂) C, H, N.

4-[(2'-Cyanobiphenyl-4-yl)methyl]valeramide *S*-Methylisothiosemicarbazide (138). A mixture of 5.50 g (25.3 mmol) of 136, 6.55 g (31.5 mmol) of 137, and 57 mL of dry EtOH was stirred at room temperature for 6 days and then concentrated in vacuo at ≤30 °C. The residue was chromatographed (gradient elution with 0.5–2% MeOH in CH₂Cl₂) to give 6.86 g (71%) of a yellow gum, which by NMR appeared to exist as a mixture of syn and anti isomers: TLC in 95:5 CH₂Cl₂/MeOH; ¹H NMR (CDCl₃, 300 MHz) δ 0.91 (m, 3 H), 1.37 (m, 2 H), 1.55–1.75 (m, 2 H), 2.28, 2.73 (major and minor t, *J* = 8 Hz, total 2 H), 2.40, 2.58 (major and minor s, total 3 H), 4.45 (d, *J* = 7 Hz, 2 H), 4.82, 5.18 (minor and major br s, total 2 H), 6.51 (br t, *J* = 7 Hz, 1 H), 7.35–7.55 (m, 6 H), 7.63 (dd, *J* = 8, 8 Hz, 1 H), 7.75 (d, *J* = 8 Hz, 1 H); FAB-MS *m/e* 380 (M + H)⁺. Upon further elution of the column with 95:5 CH₂Cl₂/MeOH/concentrated NH₄OH, 1.59 g of unreacted 137 was recovered.

3-Amino-5-*n*-butyl-4-[(2'-cyanobiphenyl-4-yl)methyl]-4*H*-1,2,4-triazole (139). A solution of 6.86 g (18.1 mmol) of 138 in 55 mL of CH₂Cl₂ was stirred at room temperature as 6.09 g (28.2 mmol, based on 80% purity) of *m*-chloroperbenzoic acid was added gradually in small portions over approximately 1.5 h. A mild exotherm and some gas evolution were observed during the addition. After 5 h, the mixture was added to 50 mL of 2.5 N NaOH and 150 mL of Et₂O. The solid which precipitated upon agitation was collected on a filter and washed thoroughly with H₂O and then with some Et₂O. After vacuum-drying at 100 °C, 3.56 g of a cream-colored solid was obtained: mp 206–207 °C; TLC in 90:10 CH₂Cl₂/MeOH/AcOH; ¹H NMR (CDCl₃, 300 MHz) δ 0.90 (t, *J* = 7.5 Hz, 3 H), 1.38 (m, 2 H), 1.72 (m, 2 H), 2.63 (t, *J* = 8 Hz, 2 H), 4.06 (br s, 2 H), 4.99 (s, 2 H), 7.20 (d, *J* = 8 Hz, 2 H), 7.4–7.5 (m, 2 H), 7.55 (d, *J* = 8 Hz, 2 H), 7.65 (dd, *J* = 8, 8 Hz, 1 H), 7.75 (d, *J* = 8 Hz, 1 H); FAB-MS *m/e* 332 (M + H)⁺. Anal. (C₂₀H₂₁N₅) C, H, N. From partial evaporation of the Et₂O phase of the filtrate, a satisfactory second crop (0.28 g) was isolated. The total yield was 3.84 g (64%).

3-(Benzylideneamino)-5-*n*-butyl-4-[(2'-cyanobiphenyl-4-yl)methyl]-4*H*-1,2,4-triazole (140). A mixture of 199 mg (0.6 mmol) of 139, 183 μL (191 mg, 1.8 mmol) of benzaldehyde, 10 μL of piperidine, and 1 mL of *i*-PrOH was stirred at reflux. After 14.5 h the solution was cooled and concentrated in vacuo. The residue was triturated with Et₂O to provide 227 mg (90%) of a pale yellow powder: mp 140.5–141.5 °C; TLC in 95:5 CH₂Cl₂/

MeOH; ^1H NMR (CDCl_3 , 300 MHz) δ 0.88 (t, J = 7 Hz, 3 H), 1.37 (m, 2 H), 1.70 (m, 2 H), 2.67 (t, J = 8 Hz, 2 H), 5.33 (s, 2 H), 7.28 (d, J = 8 Hz, 2 H), 7.4–7.55 (m, 7 H), 7.62 (dd, J = 8, 8 Hz, 1 H), 7.74 (d, J = 8 Hz, 1 H), 7.96 (d, J = 8 Hz, 2 H), 9.43 (s, 1 H); FAB-MS m/e 420 ($M + H$) $^+$. Anal. ($\text{C}_{27}\text{H}_{25}\text{N}_5$) C, H, N.

3-(Benzylamino)-5-*n*-butyl-4-[(2'-cyanobiphenyl-4-yl)methyl]-4*H*-1,2,4-triazole (141). A stirred suspension of 147 mg (0.35 mmol) of 140 in 1 mL of dry EtOH was treated with 26.5 mg (0.7 mmol) of sodium borohydride, resulting rapidly in a clear, colorless solution. After 25 min the mixture was quenched by cautious, dropwise addition of glacial AcOH until no more gas was evolved. The mixture was concentrated in vacuo at room temperature. Trituration of the residue with H_2O gave a solid, which was collected on a filter and washed with H_2O and then with Et $_2\text{O}$. Recrystallization from EtOAc gave 101 mg (68%) of white crystals: mp 138–140 $^\circ\text{C}$; TLC in 95:5 $\text{CH}_2\text{Cl}_2/\text{MeOH}$; ^1H NMR (CDCl_3 , 300 MHz) δ 0.89 (t, J = 7.5 Hz, 3 H), 1.39 (m, 2 H), 1.68 (m, 2 H), 2.64 (t, J = 8 Hz, 2 H), 3.61 (br t, J = 6 Hz, 1 H), 4.53 (d, J = 6 Hz, 2 H), 4.94 (s, 2 H), 7.15 (d, J = 8 Hz, 2 H), 7.26 (m, 5 H), 7.46 (m, 2 H), 7.53 (d, J = 8 Hz, 2 H), 7.65 (dd, J = 8, 8 Hz, 1 H), 7.77 (d, J = 8 Hz, 1 H); FAB-MS m/e 422 ($M + H$) $^+$. Anal. ($\text{C}_{27}\text{H}_{27}\text{N}_5 \cdot 0.33\text{H}_2\text{O}$) C, H, N.

Ethyl *N*-Benzyl-*N*-methyloxamate (144). To a solution of 3.22 mL (3.03 g, 25 mmol) of *N*-benzylmethylamine and 4.04 mL (3.96 g, 50 mmol) of dry pyridine in 95 mL of dry CH_2Cl_2 stirred in an ice bath was added gradually over 10 min 2.94 mL (3.58 g, 26.3 mmol) of ethyloxalyl chloride. After completion of the addition, the mixture was allowed to stir at room temperature for 5 h. The solution was diluted with 300 mL of Et $_2\text{O}$ and washed with 3×250 mL of 0.2 N HCl followed by 250 mL of saturated aqueous NaHCO_3 . The organic phase was dried (MgSO_4), filtered, and concentrated to provide 5.36 g (97%) of a pale yellow oil. NMR indicated a nearly 1:1 mixture of rotamers: TLC in 4:1 hexane/EtOAc; ^1H NMR (CDCl_3 , 300 MHz) δ 1.31, 1.36 (t, J = 7 Hz, total 3 H), 2.85, 2.88 (s, total 3 H), 4.32, 4.34 (q, J = 7 Hz, total 2 H), 4.42, 4.58 (s, total 2 H), 7.2–7.4 (m, 5 H); FAB-MS m/e 222 ($M + H$) $^+$.

5-Benzyl-5-methylsemioxamazide (145). A solution of 3.32 g (15 mmol) of 144 and 1.46 mL (1.50 g, 30 mmol) of hydrazine hydrate in 30 mL of EtOH was stirred overnight at room temperature. The filtered solution was then evaporated in vacuo at $<40^\circ\text{C}$. The residue was taken up in 50 mL of CH_2Cl_2 , filtered, and washed with 50 mL of 0.1 N HCl followed by 50 mL of saturated aqueous NaHCO_3 . The CH_2Cl_2 phase was dried over MgSO_4 , filtered, and concentrated to give 1.92 g (61%) of a nearly colorless gum, which appeared by NMR to exist as a mixture of rotamers in approximately a 1:1 ratio: TLC in 95:5 $\text{CH}_2\text{Cl}_2/\text{MeOH}$; ^1H NMR (CDCl_3 , 300 MHz) δ 2.90, 3.28 (s, total 3 H), 3.92 (br s, 2 H), 4.60, 5.03 (s, total 2 H), 7.2–7.4 (m, 5 H), 8.34 (br s, 1 H); FAB-MS m/e 208 ($M + H$) $^+$. Anal. ($\text{C}_{10}\text{H}_{13}\text{N}_3\text{O}_2 \cdot 0.2\text{H}_2\text{O}$) C, H, N.

Ethyl Valerate 5-Benzyl-5-methylsemioxamazone (146). To a stirred solution of 1.06 g (6.38 mmol) of ethyl valerimidate hydrochloride (96) 32 in 10 mL of dry EtOH at -10°C (ice/MeOH bath) was added dropwise over 15–20 min a solution of 1.32 g (6.38 mmol) of 145 in 20 mL of EtOH. After being stirred at -10 to -5°C for an additional 30 min, the cloudy solution was allowed to stand at approximately 5°C for 42 h, during which time a precipitate formed. The mixture was evaporated in vacuo at $<35^\circ\text{C}$, and the residue was partitioned between 30 mL of EtOAc and 30 mL of H_2O . The EtOAc phase was dried (MgSO_4), filtered, and concentrated to yield 2.09 g (100%) of a colorless, viscous oil. The complexity of the NMR spectrum suggested the presence of syn and anti isomers as well as amide rotamers: TLC in 95:5 $\text{CH}_2\text{Cl}_2/\text{MeOH}$; ^1H NMR (CDCl_3 , 300 MHz) δ 0.90 (m, 3 H), 1.2–1.4 (m, 5 H), 1.5–1.7 (m, 2 H), 2.2–2.45 (m, 2 H), 2.92, 3.39 (s with small satellite peaks, total 3 H), 4.0–4.25 (m, 2 H), 4.62, 5.16 (s, with small satellite peaks, total 2 H), 7.2–7.4 (m, 5 H), 9.46, 10.20 (apparent br d, total 1 H); FAB-MS m/e 320 ($M + H$) $^+$. Anal. ($\text{C}_{17}\text{H}_{25}\text{N}_3\text{O}_3 \cdot 0.1\text{EtOAc}$) C, H, N.

3-(*N*-Benzyl-*N*-methylcarbamoyl)-5-*n*-butyl-4-[(2'-cyanobiphenyl-4-yl)methyl]-4*H*-1,2,4-triazole (147). Following the procedure for 98, 146 was reacted with 1.5 equiv of 137. Column chromatography of the crude product (gradient elution with 0.25–5% *i*-PrOH in CH_2Cl_2) gave a 74% yield of 147 as a hard glass, which by NMR appeared to exist as a nearly 1:1 mixture of amide

rotamers: mp $>40^\circ\text{C}$ (gradual); TLC in 95:5 $\text{CH}_2\text{Cl}_2/\text{MeOH}$; ^1H NMR (CDCl_3 , 300 MHz) δ 0.90 (m, 3 H), 1.40 (m, 2 H), 1.76 (m, 2 H), 2.73 (m, 2 H), 2.94, 3.18 (s, total 3 H), 4.64, 4.95 (s, total 2 H), 5.45, 5.47 (s, total 2 H), 7.1–7.25 (m, 7 H), 7.4–7.5 (m, 4 H), 7.64 (m, 1 H), 7.75 (m, 1 H); FAB-MS m/e 464 ($M + H$) $^+$. Anal. ($\text{C}_{29}\text{H}_{29}\text{N}_5\text{O} \cdot 0.6\text{H}_2\text{O}$) C, H, N.

5-Amino-1-(1-benzoyl-4-yl)-3-*n*-butyl-4-[(2'-cyanobiphenyl-4-yl)methyl]-4*H*-1,2,4-triazolium Bromide (149). A mixture of 211 mg (0.636 mmol) of 139, 101 μL (141 mg, 0.664 mmol) of 2-bromopropiophenone, and 4.5 mL of absolute EtOH was stirred in an oil bath at 80°C for 8 h. The cooled solution was concentrated and dried in vacuo to give 315 mg (91%) of a stiff, yellow foam, suitable for use in the next step without further purification: TLC in 90:10:0.1 $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{AcOH}$; ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 0.69 (t, J = 7.3 Hz, 3 H), 1.10 (m, 2 H), 1.36 (m, 2 H), 1.72 (d, J = 7.0 Hz, 3 H), 2.58 (t, J = 7.7 Hz, 2 H), 5.38 (s, 2 H), 6.28 (q, J = 7.1 Hz, 1 H), 7.22 (d, J = 8.3 Hz, 2 H), 7.55–7.85 (m, 8 H), 7.92 (d, J = 7.5 Hz, 2 H), 7.96 (d, J = 7 Hz, 1 H); FAB-MS m/e 484 (M^+ for cation).

2-*n*-Butyl-3-[(2'-cyanobiphenyl-4-yl)methyl]-6-methyl-5-phenyl-3*H*-imidazo[1,2-*b*][1,2,4]triazole (150). A mixture of 303 mg (0.556 mmol) of 149 and 6 g of poly(phosphoric acid) was stirred at 80°C for 5 h. The cooled mixture was treated with an excess of ice. After the ice had melted, the H_2O was decanted off, and the residue was partitioned between EtOAc and saturated aqueous NaHCO_3 (CAUTION: gas evolution). The organic phase was dried over Na_2SO_4 , filtered, and concentrated in vacuo. The residual oil was dissolved in a minimum volume of CH_2Cl_2 and treated with 200 μL (145 mg, 1.43 mmol) of triethylamine. The resulting solution was stirred at 0°C as 137 μL (223 mg, 1.23 mmol) of trichloroacetyl chloride was added. The solution was warmed to room temperature, stirred for 1 h, and then concentrated. The residue was leached with 25 mL of Et $_2\text{O}$. The filtered Et $_2\text{O}$ extract was washed with 25 mL of 0.2 N HCl and then with 25 mL of 0.2 N NaOH. The organic phase was dried (Na_2SO_4), filtered, and evaporated to dryness. Column chromatography of the residue (elution with 1% and then 2% MeOH in CH_2Cl_2) gave 95 mg (39%) of 150 as a brown solid of indefinite melting point, suitable for use in the next step: TLC in 95:5 $\text{CH}_2\text{Cl}_2/\text{MeOH}$; ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 0.85 (t, J = 7.4 Hz, 3 H), 1.35 (m, 2 H), 1.63 (m, 2 H), 2.54 (s, 3 H), 2.83 (t, J = 7.7 Hz, 2 H), 5.38 (s, 2 H), 7.21 (dd, J = 7, 7 Hz, 1 H), 7.37 (dd, J = 7.7, 7.7 Hz, 2 H), 7.48 (d, J = 8.3 Hz, 2 H), 7.55–7.6 (m, 4 H), 7.67 (d, J = 7.7 Hz, 2 H), 7.76 (dd, J = 8, 8 Hz, 1 H), 7.93 (d, J = 7.7 Hz, 1 H); FAB-MS m/e 446 ($M + H$) $^+$.

Method B-6. 2-*n*-Butyl-6-methyl-5-phenyl-3-[(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl-3*H*-imidazo[1,2-*b*][1,2,4]triazole (95). The reaction of 150 with trimethyltin azide was carried out essentially according to the procedure for 53. Column chromatography (gradient elution with 1–5% MeOH in CH_2Cl_2) afforded a yellow gum, which was triturated with Et $_2\text{O}$ to give a 25% yield of a tan solid: mp 207–208 $^\circ\text{C}$; TLC in 90:10:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{AcOH}$; ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 0.86 (t, J = 7.3 Hz, 3 H), 1.34 (m, 2 H), 1.60 (m, 2 H), 2.53 (s, 3 H), 2.77 (t, J = 7.5 Hz, 2 H), 5.27 (s, 2 H), 7.09 (d, J = 8.1 Hz, 2 H), 7.21 (dd, J = 7, 7 Hz, 1 H), 7.27 (d, J = 8.1 Hz, 2 H), 7.38 (dd, J = 7.7, 7.7 Hz, 2 H), 7.45–7.7 (m, 6 H); FAB-MS m/e 489 ($M + H$) $^+$. Anal. ($\text{C}_{29}\text{H}_{28}\text{N}_8\text{O} \cdot 0.5\text{H}_2\text{O} \cdot 0.25\text{Et}_2\text{O}$) C, H, N.

5-Amino-3-*n*-butyl-4-[(2'-cyanobiphenyl-4-yl)methyl]-1-phenacyl-4*H*-1,2,4-triazolium Bromide (151). Acylation of 139 with phenacyl bromide under the conditions described for 149 gave an 86% yield of 151 as a stiff, yellow foam, suitable for use in the next step without further purification: TLC in 90:10:0.1 $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{AcOH}$; ^1H NMR (CDCl_3 , 400 MHz) δ 0.83 (t, J = 7.3 Hz, 3 H), 1.31 (m, 2 H), 1.59 (m, 2 H), 2.51 (t, J = 7.5 Hz, 2 H), 5.63 (s, 2 H), 6.12 (s, 2 H), 7.36 (d, J = 8.3 Hz, 2 H), 7.4–7.65 (m, 8 H), 7.72 (d, J = 7.7 Hz, 1 H), 7.97 (d, J = 8.4 Hz, 2 H), 8.82 (s, 2 H); FAB-MS m/e 450 (M^+ for cation).

2-*n*-Butyl-3-[(2'-cyanobiphenyl-4-yl)methyl]-5-phenyl-3*H*-imidazo[1,2-*b*][1,2,4]triazole (152) and 2-*n*-Butyl-3-[(2'-carbamoylbiphenyl-4-yl)methyl]-5-phenyl-3*H*-imidazo[1,2-*b*][1,2,4]triazole (153). The entire quantity of 151 prepared as above from 0.637 mmol of 139 was treated with 5 g of poly(phosphoric acid) and stirred at 85°C for 6 h. The cooled reaction mixture was treated with ice and allowed to stand for 2 h. The resulting mixture was added to 75 mL of EtOAc and shaken with

100 mL of saturated aqueous NaHCO_3 (CAUTION: gas evolution). The EtOAc phase was washed with an additional portion of NaHCO_3 solution, dried over Na_2SO_4 , filtered, and concentrated in vacuo. Upon column chromatography of the residual oil (gradient elution with 1–5% MeOH in CH_2Cl_2), two products were isolated. First eluted was 36.3 mg (13% overall) of 152 as a yellow oil: TLC in 95:5 $\text{CH}_2\text{Cl}_2/\text{MeOH}$; ^1H NMR (CDCl_3 , 400 MHz) δ 0.89 (t, $J = 7.3$ Hz, 3 H), 1.39 (m, 2 H), 1.70 (m, 2 H), 2.67 (t, $J = 7.7$ Hz, 2 H), 5.31 (s, 2 H), 7.2–7.65 (m, 11 H), 7.73 (d, $J = 7.8$ Hz, 1 H), 7.80 (d, $J = 8.3$ Hz, 2 H); FAB-MS m/e 432 ($M + \text{H}$) $^+$.

Subsequently eluted was 211 mg of the amide 153 as a yellow solid of indefinite melting point: TLC in 95:5 $\text{CH}_2\text{Cl}_2/\text{MeOH}$; ^1H NMR (CDCl_3 , 400 MHz) δ 0.91 (t, $J = 7.3$ Hz, 3 H), 1.40 (m, 2 H), 1.72 (m, 2 H), 2.69 (t, $J = 7.7$ Hz, 2 H), 5.24 (partially obscured br s, 1 H), 5.28 (s, 2 H), 5.40 (br s, 1 H), 7.2–7.5 (m, 10 H), 7.71 (d, $J = 7.0$ Hz, 1 H), 7.78 (d, $J = 7.7$ Hz, 2 H); FAB-MS m/e 450 ($M + \text{H}$) $^+$.

2-*n*-Butyl-3-[(2'-cyanobiphenyl-4-yl)methyl]-5-phenyl-3*H*-imidazo[1,2-*b*][1,2,4]triazole (152) from 153. To 211 mg (0.468 mmol) of 153 was added 6 mL of a solution consisting of poly(phosphate ester) 56 and CDCl_3 (used as a surrogate for alcohol-free CHCl_3) in a ratio of approximately 2:1. The mixture was stirred at reflux for 3 h and then evaporated in vacuo. The residue was cooled in an ice bath and treated with an excess of saturated aqueous Na_2CO_3 . The mixture was stirred for about 1 h and then extracted with EtOAc. The organic fraction was dried (Na_2SO_4), filtered, and concentrated. The residual crude product was chromatographed (elution with 1% and then 2% MeOH in CH_2Cl_2) to give 188 mg of a yellow oil, which solidified upon standing: mp 88–90 $^\circ\text{C}$; identical to 152 prepared above from 139 by TLC, FAB-MS, and NMR, except for the presence of phosphate ester contaminant peaks observed in the NMR [δ 1.35 (t, $J = 7.1$ Hz), 4.23 (m)]. The material was suitable for use in the preparation of 91.

2-*n*-Butyl-3-[(2'-cyanobiphenyl-4-yl)methyl]-6-phenyl-3*H*-imidazo[1,2-*b*][1,2,4]triazole (155). A mixture of 212 mg (0.640 mmol) of 139, 151 mg (0.757 mmol) of α -bromophenylacetaldehyde, 58 and 2 mL of absolute EtOH was stirred at reflux for 6 h. The mixture was cooled and concentrated under vacuum. Column chromatography of the residue (elution with 1% and then 4% MeOH in CH_2Cl_2) afforded 65.3 mg (24%) of 155 as a yellow oil: TLC in 95:5 $\text{CH}_2\text{Cl}_2/\text{MeOH}$; ^1H NMR (CDCl_3 , 400 MHz) δ 0.93 (t, $J = 7.3$ Hz, 3 H), 1.44 (m, 2 H), 1.76 (m, 2 H), 2.77 (t, $J = 7.7$ Hz, 2 H), 5.29 (s, 2 H), 7.2–7.5 (m, 8 H), 7.53 (d, $J = 8.0$ Hz, 2 H), 7.62 (dd, $J = 8, 8$ Hz, 1 H), 7.74 (d, $J = 7.0$ Hz, 1 H), 7.91 (d, $J = 7.3$ Hz, 2 H); FAB-MS m/e 450 ($M + \text{H}$) $^+$.

Rabbit Aorta AT $_1$ Receptor Binding Assay. Rabbit aorta membrane pellets, prepared as previously described, 20 were suspended in 30 volumes of binding buffer, containing 50 mM Tris-HCl, pH 7.4, 5 mM MgCl_2 , and 0.2 mg/mL bacitracin. The original version of the assay (used for compounds 4–52) also included 0.2% bovine serum albumin (BSA; heat-denatured and essentially globulin-free).

Test compounds were dissolved at 2.7 mM in 1:1 DMSO/MeOH and serially diluted to five concentrations bracketing the IC_{50} . All binding assays were performed in duplicate tubes. To each incubation tube was added 10 μL of [^{125}I]Sar 1 Ile 8 -angiotensin II (New England Nuclear) at a final concentration of 20–40 pM and 10 μL of one of the following: (a) buffer vehicle (for total binding); (b) unlabeled 1 μM Sar 1 Ile 8 -angiotensin II (for nonspecific binding); or (c) the test compound solution (for displacement of specific binding). Finally 250 μL of the above membrane preparation was added to each tube. The tubes were vortex-mixed and incubated in a shaking water bath at 37 $^\circ\text{C}$ for 90 min. The incubation mixtures were diluted with 4 mL of ice-cold wash buffer (containing 0.15 M NaCl and 10 mM Tris-HCl, pH 7.4) and immediately filtered through glass fiber filters (GF/B Whatman, presoaked with 0.1% BSA in wash buffer) under reduced pressure with a Brandel cell harvester. The filters were rapidly washed with 3 \times 4 mL of cold wash buffer, and radioactivity associated with the membrane collected on the filters was measured by a Packard Autogamma counter. In typical experiments, the total binding of [^{125}I]Sar 1 Ile 8 -AII in the absence of antagonist (control) was about 1500–2000 cpm, while non-specific binding amounted to about 150–200 cpm in the presence

of BSA or 300–350 cpm in the absence of BSA. After correction for nonspecific binding, the bound radioactivity in the presence of a given concentration of test compound was compared to specific binding in the control to determine the percent inhibition. The concentration required to inhibit specific binding of [^{125}I]Sar 1 Ile 8 -AII to the receptor by 50% (IC_{50}) was calculated using nonlinear regression analysis of the displacement curves. On the basis of the results of several standard compounds having three or more determinations, the standard error (expressed as percent of means) of the IC_{50} measurement in this assay is estimated to be less than 30%. In some cases the reported IC_{50} values represent an average of two or more determinations from separate assays.

Evaluation of AII Antagonists in Conscious, Normotensive Rats. Male Sprague-Dawley rats (300–400 g) were anesthetized with methohexital sodium (50 mg/kg ip) and surgically instrumented with catheters in the right femoral artery (for arterial blood pressure and heart rate measurements via a pressure transducer), the right femoral vein (for administration of antihypertensive II), and, as appropriate, the left femoral vein (for intravenous administration of test compound). Catheters were filled with heparinized saline solution to maintain patency. The incisions were sutured, and the rats were allowed to recover overnight prior to testing. Drinking water was freely available, but food was withheld if the test compound was to be administered orally.

Angiotensin II (Peninsula Laboratories) and methoxamine were each dissolved in saline solution and administered in injection volumes of 0.5 mL/kg iv as described below. The test compound was prepared in a mortar with pestle. For intravenous administration (total volume 1 mL/kg), the compound was dissolved, if possible, in saline. If this was precluded by limited solubility, the vehicle consisted of a 15:35:50 mixture of saturated aqueous NaHCO_3 , saline, and H_2O . For oral administration (total volume 2 mL/kg), the compound was dissolved or suspended in 0.5% methylcellulose. If necessary, 1 N NaOH (100 $\mu\text{L}/\text{mL}$) was added to enhance solubility.

The responsiveness of the rat was verified by an initial challenge with methoxamine (50 $\mu\text{g}/\text{kg}$ iv) via the AII catheter. When the animal was stable, bolus injections of AII (0.1 $\mu\text{g}/\text{kg}$ iv) were given at –45, –30, and –15 min. Provided that AII responses were consistent, the test compound or its vehicle was administered intravenously or orally at 0 min. AII was then given at 5, 10, 15, 30, 45, and 60 min and every 30 min thereafter for as long as the test compound exhibited activity. At the conclusion of AII challenges, the catheter was flushed with saline, and methoxamine (see above) was administered as a control.

From measurement of the change in mean arterial pressure (ΔMAP) upon AII challenge, the percent inhibition of the AII pressor response in the presence of test compound was calculated at each time point. For each compound at a given dose, the peak percent inhibition and duration of action were determined, on the basis of averaged results from at least two rats. A 30% inhibition of the AII pressor response is considered significant in this assay. The duration of action for a single bolus dose of the test compound is defined as the time from onset of activity until the inhibition of the AII-induced increase in MAP falls below 30% and remains at <30% for two subsequent AII challenges.

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