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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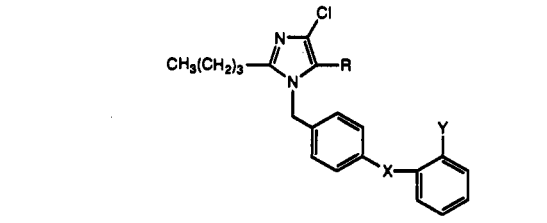
Received October 26, 1992

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 C^3 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 N^4. Among numerous variations at C^5, 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**, IC_{50} 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**, IC_{50} 7.8 nM). The effects of hydrophobic, hydrogen-bonding, and ionic interactions with the AT_1 receptor are considered.

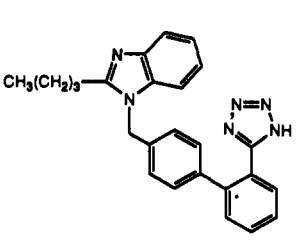
The importance of the renin–angiotensin system[1,2] as a target for cardiovascular disease therapy is well-established.[3-6] Angiotensin-converting enzyme (ACE) inhibitors, which block the conversion of angiotensin I (AI) to the potent vasoconstrictor angiotensin II (AII), are widely used for the treatment 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 group[12] 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 C^4–C^5 bond of the imidazole has produced interesting bicyclic AII antagonists such as the benzimidazole **2**[18] 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 AT_1 receptor subtype, the site of the major physiological functions of AII known to date.[21] A series of nonpeptide AT_2-selective antagonists has also been reported.[22]

Chart I



	R	X	Y
1a	CH_2CO_2Me	NHCO	CO_2H
1b	CH_2OH	—	CO_2H
1c	CH_2OH	—	CN_4H
1d	CO_2H	—	CN_4H



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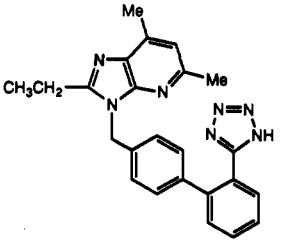

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While some studies have explored further variations of the side chains at N^1 and/or C^5 of the imidazole,[23-27] we were interested in replacement of the imidazole ring by another heterocycle. The 1,2,4-triazole system seemed to be a reasonable candidate, 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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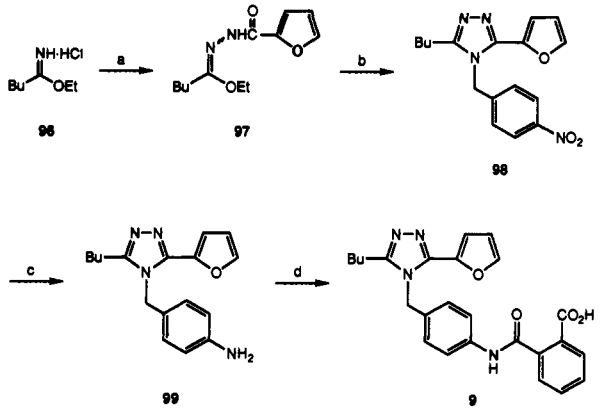
Scheme I[a]



[a] (a) 2-Furoic acid hydrazide, EtOH, −10 to 5 °C; (b) 4-nitrobenzylamine, EtOH, 45–70 °C; (c) $SnCl_2 \cdot 2H_2O$, 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]

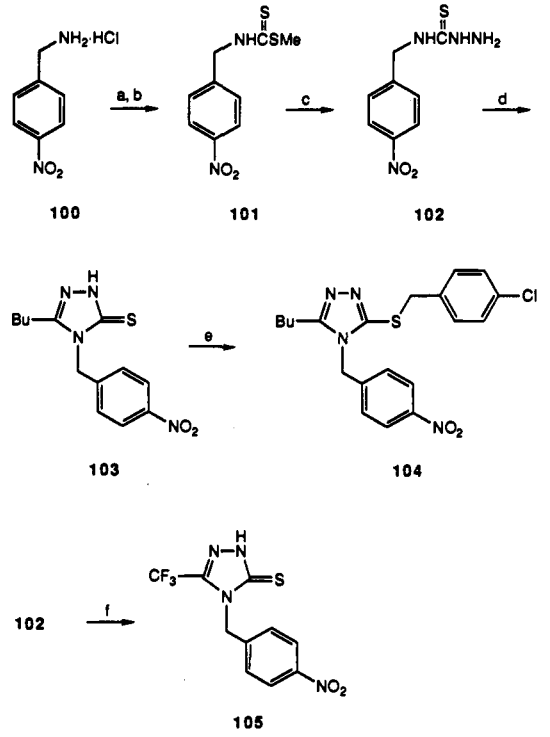
Chemistry

Initially, synthetic efforts focused on triazoles (**4–45**) bearing the 4-[(2-carboxybenzoyl)amino]benzyl side chain at N^4, as in the imidazole EXP6803 (**1a**). Following a literature route,[30,31] 3-alkyl-5-aryl(or heteroaryl)-4-(arylmethyl)-4*H*-1,2,4-triazoles were prepared as in Scheme I. In the example shown, imidate hydrochloride **96**[32] 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 orthovalerate. Selective alkylation on sulfur[33] 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 temperature[34] 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**.

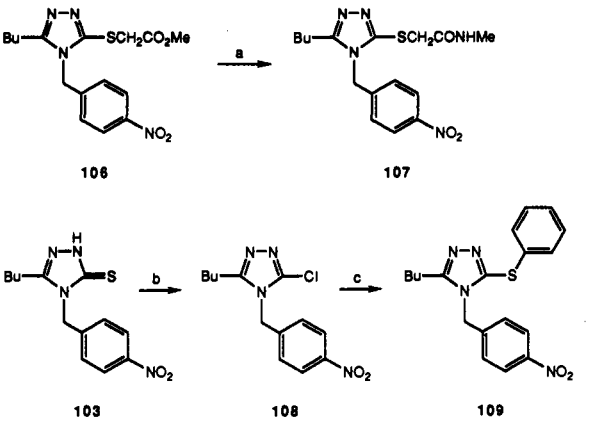
In triazoles **46–49**, the carboxy substituent of the amide-bridged side chain at N^4 was replaced by a tetrazole group. As illustrated in Scheme IV, the 4-aminobenzyl derivative **110** was reacted with 2-cyanobenzoyl chloride (**111**). Heating the resulting product **112** with trimethyltin azide[15,36,37]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

Scheme II[a]



[a] (a) CS_2, Et_3N, MeOH; (b) MeI; (c) $H_2NNH_2 \cdot H_2O$, EtOH, Δ; (d) $BuC(OMe)_3$, $MeO(CH_2)_2OH$, Δ; (e) 4-chlorobenzyl chloride, *i*-Pr_2NEt, $MeO(CH_2)_2OH$; (f) TFA, Δ.

Scheme III[a]

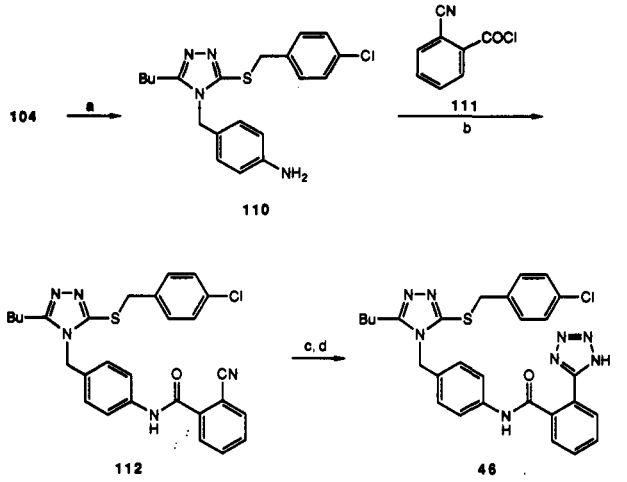


[a] (a) 40% $MeNH_2$ (aqueous), MeOH; (b) Cl_2, CH_2Cl_2; (c) thiophenol, *i*-Pr_2NEt, DMF, Δ.

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/HBF_4,[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.

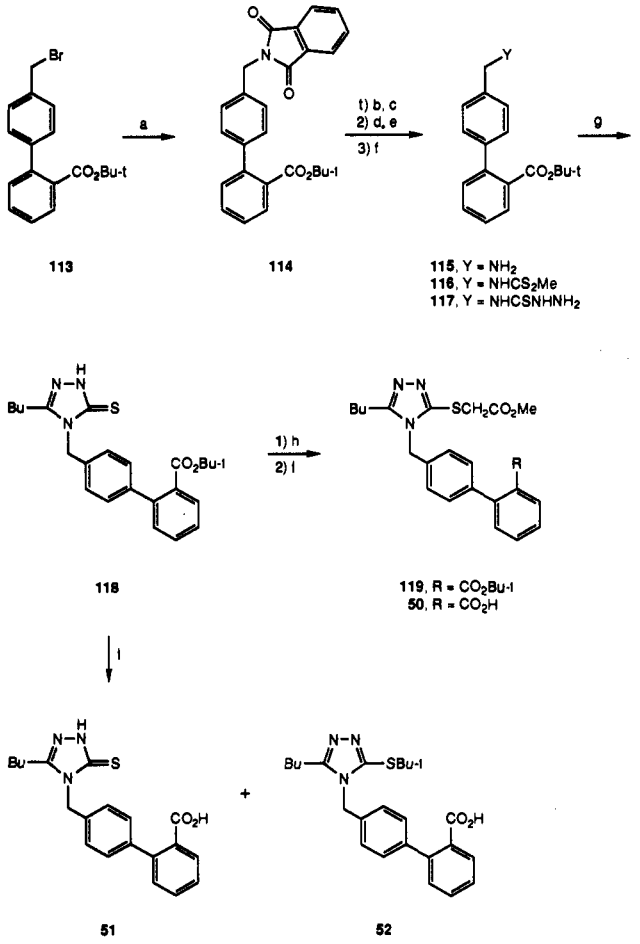
Triazoles **50–53**, containing a biphenylcarboxylic acid side chain analogous to that of the imidazole **1b**, were prepared as shown in Scheme V. The amine **115** was obtained in a Gabriel synthesis from the bromo derivative **113**.[15] By methods paralleling Scheme II, the (alkylthio)-triazole **119** 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) $SnCl_2 \cdot 2H_2O$, concentrated HCl, THF; (b) *i*-Pr_2NEt, THF; (c) Me_3SnN_3, toluene, Δ; (d) silica gel, MeOH.

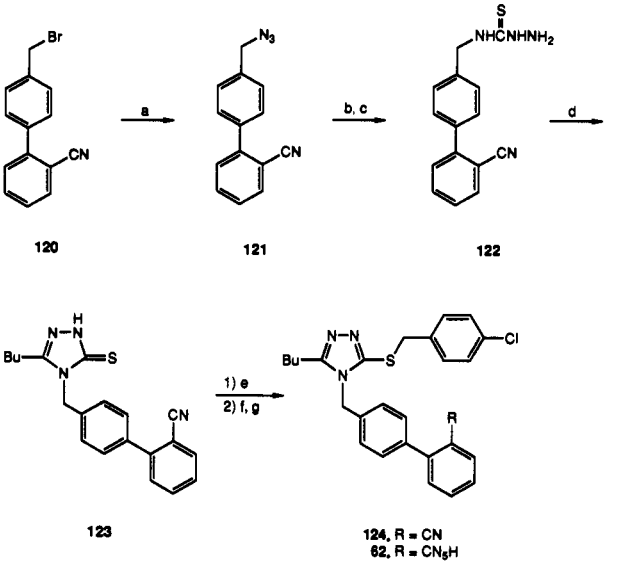
Scheme V[a]



[a] (a) Potassium phthalimide, DMF; (b) H_2NNH_2, EtOH; (c) AcOH; (d) CS_2, Et_3N, MeOH; (e) MeI; (f) $H_2NNH_2 \cdot H_2O$, EtOH, Δ; (g) $BuC(OMe)_3$, $MeO(CH_2)_2OH$, Δ; (h) methyl chloroacetate, *i*-Pr_2NEt, CH_2Cl_2; (i) TFA.

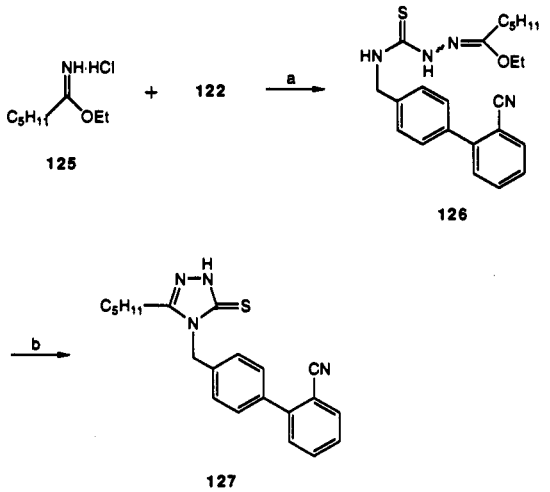
The remaining target AII antagonists **53–95** incorporated the biphenylyltetrazole side chain present in the reference compounds **1c,d**, **2**, and **3**. A typical sequence is shown in Scheme VI. A convenient route to the thiosemicarbazide intermediate **122** was developed. The bromo nitrile **120**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

Scheme VI[a]



[a] (a) LiN_3, DMSO; (b) Ph_3P, CS_2; (c) $H_2NNH_2 \cdot H_2O$, THF; (d) $BuC(OMe)_3$, $MeO(CH_2)_2OH$, Δ; (e) 4-chlorobenzyl chloride, *i*-Pr_2NEt, $MeO(CH_2)_2OH$; (f) Me_3SnN_3, toluene, Δ; (g) silica gel, MeOH.

Scheme VII[a]

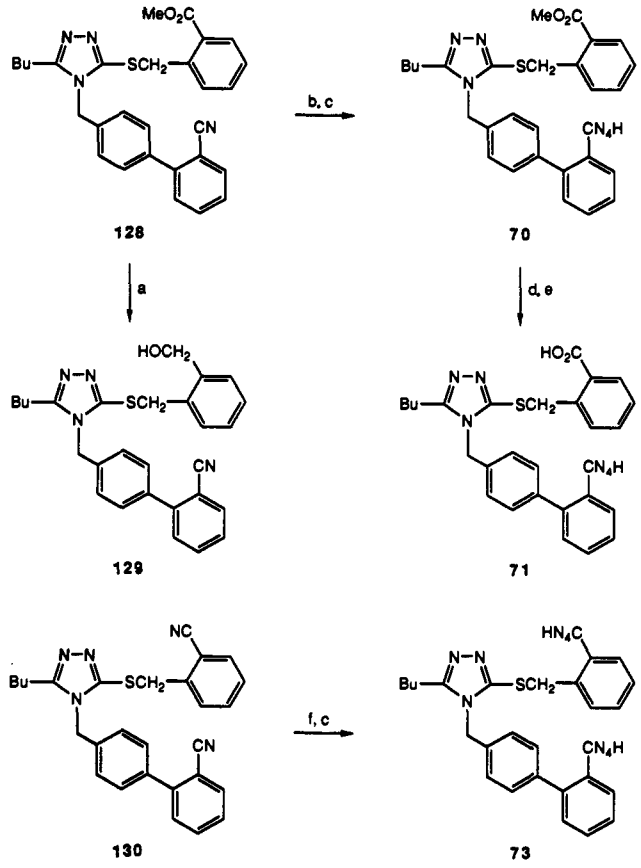


[a] (a) DMF; (b) DBU, THF, Δ.

Because trimethyl orthohexanoate was not commercially available, we investigated an alternative route to the pentyl analogue **63** (Scheme VII). The work of Milcent[40] 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.

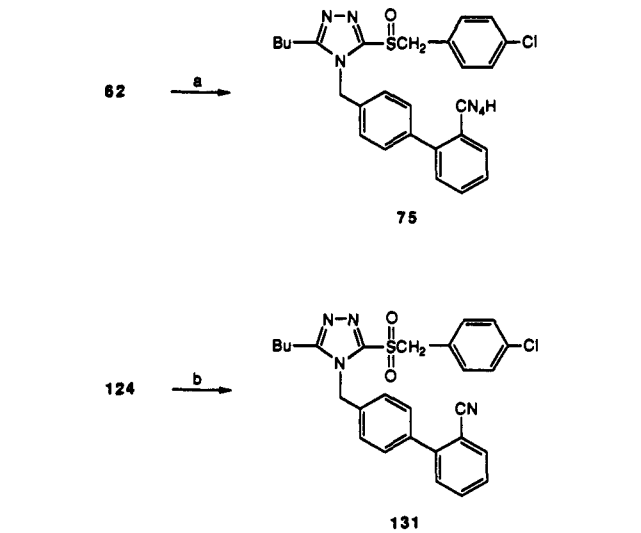
For the synthesis of **72**, the ester intermediate **128** was reduced to the corresponding hydroxymethyl derivative **129** (Scheme VIII). Reaction of **128** with trimethyltin azide yielded **70**, and subsequent saponification provided **71**.

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**.

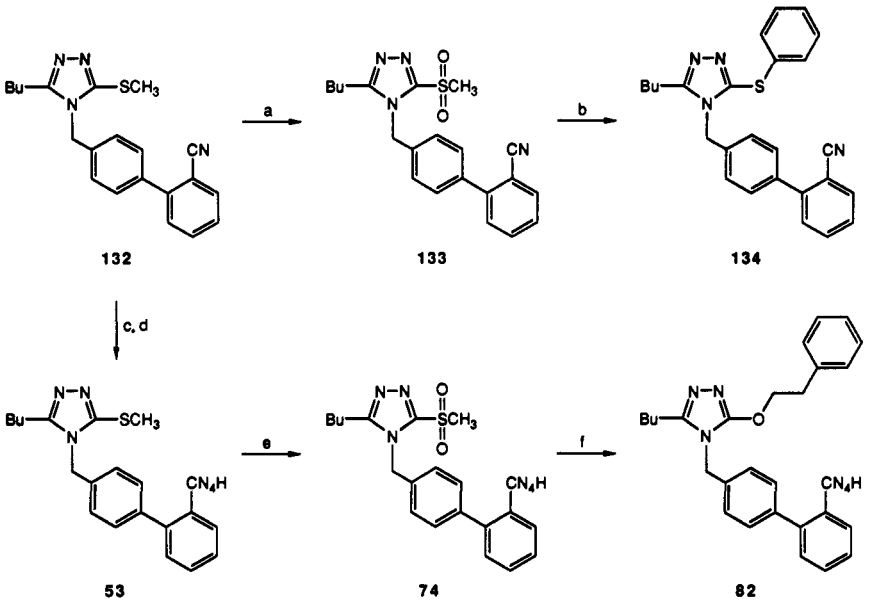
The sulfoxide **75** was readily prepared from **62** by treatment with 30% hydrogen peroxide in acetic acid (Scheme IX). Although the corresponding sulfone **76** could also be prepared directly from **62**, in this case there was a purification advantage in performing the MCPBA oxidation at the nitrile 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-aminotriazoles[43] 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 (triazolinethiones). 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 (benzylamino)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 Sellstedt[50] (Scheme XII). Treatment of **144** with hydrazine hydrate[51] afforded the semioxamazide 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.

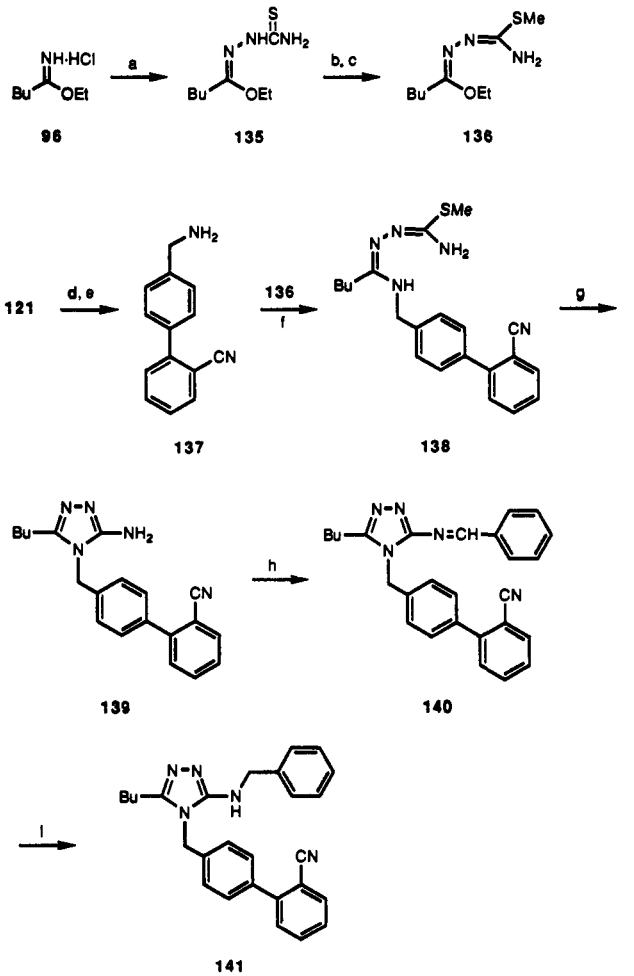
The availability of the aminotriazole intermediate **139** offered an entry into a series of 3*H*-imidazo[1,2-*b*][1,2,4]-triazoles **89–95** using modifications of the methods of Babichev and co-workers.[52] For example, reaction of **139** with the α-bromo ketone **148** yielded the triazolium salt **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, CH_2Cl_2; (b) thiophenol, *i*-Pr_2NEt, DMF, Δ; (c) Me_3SnN_3, toluene, Δ; (d) silica gel, MeOH; (e) 10% AcOOH, AcOH; (f) phenethyl alcohol sodium salt, 65 °C.

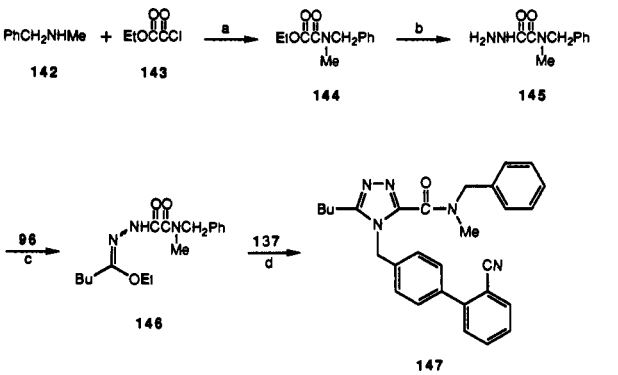
Scheme XI[a]



[a] (a) Thiosemicarbazide, DMF; (b) MeI, CH_2Cl_2; (c) aqueous Na_2CO_3; (d) Ph_3P, THF; (e) H_2O; (f) EtOH; (g) MCPBA, CH_2Cl_2; (h) benzaldehyde, catalytic piperidine, *i*-PrOH, Δ; (i) $NaBH_4$, 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, CH_2Cl_2; (b) $H_2NNH_2 \cdot H_2O$, EtOH; (c) EtOH, −10 to −5 °C; (d) EtOH, 45–70 °C.

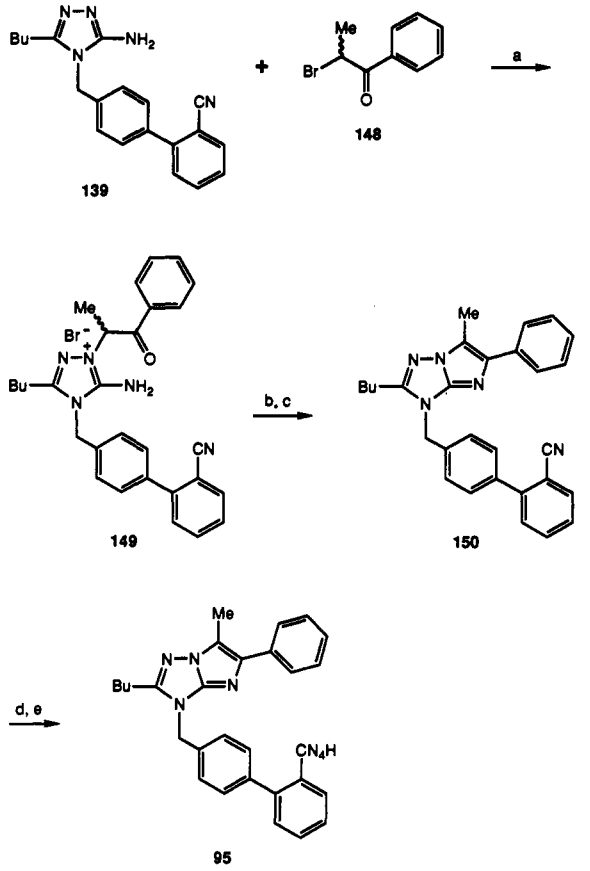
amine.[54] Subsequent conversion of the nitrile to tetrazole was achieved with trimethyltin azide as described above.

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 dehydration[57] 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

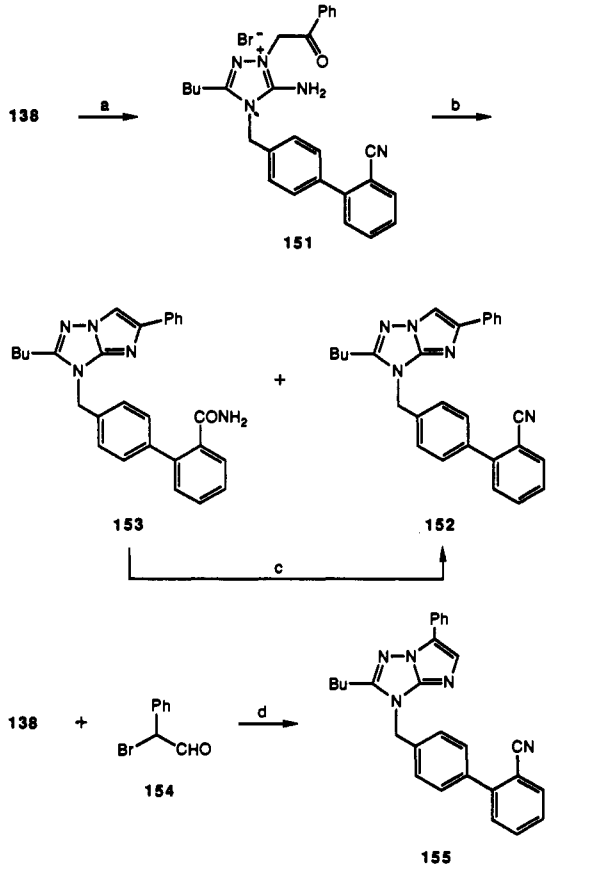
In Vitro AII Antagonism. The new triazole and imidazotriazole compounds **4–95** were evaluated as AII antagonists by displacement of [^{125}I]Sar^{1}Ile^8-AII at the rabbit aorta AT_1 receptor. Triazoles **4–49**, bearing an amide-bridged acidic side chain at N^4, are presented in Table I. The 3-butyl-5-phenyl derivative **4** was a modest antagonist, having an IC_{50} (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.

Scheme XIV[a]



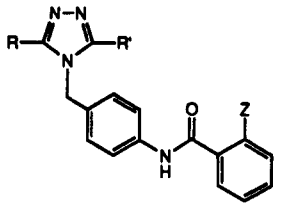
[a] (a) Phenacyl bromide, EtOH, Δ; (b) PPA, 85 °C; (c) PPE, $CDCl_3$, Δ; (d) EtOH, Δ.

(**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 C^5. 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 C^5 (**15–17**) were quite poor.

Numerous triazoles with butyl at C^3 and substituted mercapto groups at C^5 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 at N^4, 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 N^4 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 biphenylyltetrazole 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 C^3. 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, 1*H*-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



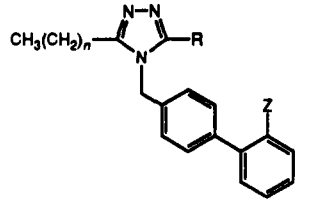
no.	R	R′	Z	method[a]	% yield	mp, °C	formula[b]	FAB-MS *m/e* $(M+H)^+$	rabbit aorta AT_1 IC_{50},[c] nM
1a	(imidazole, EXP6803)								420[d]
4	Bu	Ph	CO_2H	A[e,f]	64	187–188	$C_{27}H_{26}N_4O_3 \cdot 1.25H_2O$	455	930
5	EtS	Ph	CO_2H	A[e]	60	177.5–178	$C_{25}H_{22}N_4O_3S \cdot 0.2H_2O$	459	1900
6	PrS	Ph	CO_2H	A[e,f]	72	166.5–167	$C_{26}H_{24}N_4O_3S \cdot 0.6H_2O \cdot 0.7Et_2O$	473	1600
7	Bu	4-pyridyl	CO_2H	A[e,f]	63	152–153	$C_{26}H_{25}N_5O_3 \cdot H_2O \cdot 0.25Et_2O$	456	1400
8	Bu	3-pyridyl	CO_2H	A[e,f]	54	108–109	$C_{26}H_{25}N_5O_3$	456.2059[g]	1700
9	Bu	2-furyl	CO_2H	A	85	169.5–171	$C_{25}H_{24}N_4O_4 \cdot 0.4H_2O$	445	1000
10	EtS	CH_2Ph	CO_2H	A	67	179–180	$C_{26}H_{24}N_4O_3S \cdot 0.25H_2O$	473	1000
11	PrS	CH_2Ph	CO_2H	A[e,f]	85	>95 (gradual)	$C_{27}H_{26}N_4O_3S \cdot 1.5H_2O \cdot 0.5THF$	487	380
12	PrS	$(CH_2)_2Ph$	CO_2H	A[e,f,h]	65	147–147.5	$C_{28}H_{28}N_4O_3S$	501	75
13	PrS	$(CH_2)_3Ph$	CO_2H	A[e,f]	91	152–153	$C_{29}H_{30}N_4O_3S$	515	320
14	PrS	CH_2SPh	CO_2H	A[e,f,i]	44	159–160	$C_{27}H_{26}N_4O_3S_2 \cdot 0.4H_2O$	519	1200
15	EtS	CH_2OMe	CO_2H	A	90	192–193	$C_{21}H_{23}N_4O_4S$	428	5200
16	EtS	CF_3	CO_2H	A[e,f]	59	154–156	$C_{20}H_{17}F_3N_4O_3S \cdot 0.4Et_2O$	451	4800
17	PrS	CF_3	CO_2H	A[e,j]	9	167–169	$C_{21}H_{19}F_3N_4O_3S \cdot H_2O \cdot 0.9AcOH$	487[k]	2100
18	Bu	SCH_2CO_2Me	CO_2H	A[e,j]	77	161–162	$C_{24}H_{26}N_4O_5S$	483	330
19	Bu	$SCH_2CONHMe$	CO_2H	A[e,f]	73	137–139	$C_{24}H_{27}N_5O_4S \cdot 0.25H_2O$	482	720
20	Bu	SCH_2CO_2H	CO_2H	D[l]	60	135–137	$C_{23}H_{24}N_4O_5S \cdot 1.5H_2O$	*m*	770
21	Bu	$S(CH_2)_2OH$	CO_2H	A[e,f,n]	69	157–159	$C_{23}H_{26}N_4O_4S \cdot 0.3H_2O$	455	480
22	Bu	$SCH(Et)CO_2Me$	CO_2H	A[e,f]	82	129–130	$C_{26}H_{30}N_4O_5S$	511	300
23	Bu	SCH_2COPh	CO_2H	A[e,f]	52	92–93	$C_{29}H_{28}N_4O_4S \cdot 0.75H_2O \cdot 0.4Et_2O$	529	190
24	Bu	SPh	CO_2H	A[e,f]	42	144–146	$C_{27}H_{26}N_4O_3S \cdot H_2O$	487	60
25	Bu	SCH_2Ph	CO_2H	A[e,f]	85	158–160	$C_{28}H_{28}N_4O_3S \cdot 0.5H_2O \cdot 0.1Et_2O$	501	15
26	Bu	$S(CH_2)_2Ph$	CO_2H	A[e,f]	71	112–114	$C_{29}H_{30}N_4O_3S \cdot H_2O$	515	70
27	Pr	SCH_2Ph	CO_2H	A	92	196–197	$C_{27}H_{26}N_4O_3S \cdot 0.4H_2O$	487	120
28	Bu	$SCH_2Ph(2\text{-}Me)$	CO_2H	A	66	166–168	$C_{29}H_{30}N_4O_3S \cdot 0.25H_2O$	515	14
29	Bu	$SCH_2Ph(3\text{-}Me)$	CO_2H	A[e,n]	78	164–165	$C_{29}H_{30}N_4O_3S$	515	32
30	Bu	$SCH_2Ph(4\text{-}Me)$	CO_2H	A	75	135–137	$C_{29}H_{30}N_4O_3S \cdot 0.4H_2O$	515	7.6
31	Bu	$SCH_2Ph(2\text{-}Cl)$	CO_2H	A	85	165–166	$C_{28}H_{27}ClN_4O_3S$	535	30
32	Bu	$SCH_2Ph(3\text{-}Cl)$	CO_2H	A	85	169–170	$C_{28}H_{27}ClN_4O_3S$	535	26
33	Bu	$SCH_2Ph(4\text{-}Cl)$	CO_2H	A[e,f]	77	115–116	$C_{28}H_{27}ClN_4O_3S \cdot 0.25H_2O$	535	6.8
34	Bu	$SCH_2Ph(3\text{-}OMe)$	CO_2H	A[e,f]	79	94–95	$C_{29}H_{30}N_4O_4S \cdot 0.25H_2O$	531	21
35	Bu	$SCH_2Ph(4\text{-}OMe)$	CO_2H	A[e,f,n]	29	180–182	$C_{29}H_{30}N_4O_4S \cdot 1.1H_2O$	531	3.0
36	Bu	$SOCH_2Ph(4\text{-}OMe)$	CO_2H	E[o]	11	109–110 dec	$C_{29}H_{30}N_4O_5S$	547.2033[p]	7.4
37	Bu	$SCH_2Ph(2\text{-}CN)$	CO_2H	A[e,f]	74	140–142	$C_{29}H_{27}N_5O_3S \cdot 0.85H_2O \cdot 0.2Et_2O$	526	60
38	Bu	$SCH_2Ph(4\text{-}CF_3)$	CO_2H	A[e,f]	59	118–120	$C_{29}H_{27}F_3N_4O_3S \cdot 0.3H_2O \cdot 0.1Et_2O$	569	42
39	Bu	$SCH_2(2\text{-naphthyl})$	CO_2H	A[e,f]	80	>95 (gradual)	$C_{32}H_{30}N_4O_3S \cdot 0.5H_2O \cdot 0.2Et_2O$	551	49
40	Bu	$SCH(CO_2Me)Ph$	CO_2H	A[e,f]	71	118–119 dec	$C_{30}H_{30}N_4O_5S \cdot 0.6H_2O \cdot 0.25Et_2O$	559	6.1
41	Bu	$SCH(CO_2H)Ph$	CO_2H	D[l]	77	143–145 dec	$C_{29}H_{28}N_4O_5S \cdot 2H_2O$	545	20
42	Bu	$SCH_2Ph(2\text{-}CO_2Me)$	CO_2H	A[e,f]	86	106–108	$C_{30}H_{30}N_4O_5S$	559	14
43	Bu	$SCH_2Ph(2\text{-}CO_2H)$	CO_2H	D[l]	76	134–136	$C_{29}H_{28}N_4O_5S \cdot 0.1H_2O \cdot 0.5CH_2Cl_2$	545	3.3
44	Bu	$SCH_2Ph(3\text{-}CO_2Me)$	CO_2H	A[e,f]	77	115–116 dec	$C_{30}H_{30}N_4O_5S \cdot 0.75H_2O \cdot 0.25Et_2O$	559	30
45	Bu	$SCH_2Ph(3\text{-}CO_2H)$	CO_2H	D[l]	84	130–132 dec	$C_{29}H_{28}N_4O_5S \cdot 2.5H_2O \cdot 0.1Et_2O$	545	15
46	Bu	$SCH_2Ph(4\text{-}Cl)$	CN_4H	B-1	10	175–176 dec	$C_{28}H_{27}ClN_8OS \cdot 0.5H_2O$	559	6.8
47	Bu	$SCH_2Ph(4\text{-}OMe)$	CN_4H	B-5	6	130–132 dec	$C_{29}H_{30}N_8O_2S \cdot 0.5H_2O$	555	4.1
48	Bu	$SOCH_2Ph(4\text{-}Cl)$	CN_4H	E	42	150–152	$C_{28}H_{27}ClN_8O_2S \cdot 0.3H_2O$	575	33
49	Bu	$SOCH_2Ph(4\text{-}OMe)$	CN_4H	E	72	135–137	$C_{29}H_{30}N_8O_3S \cdot 0.25H_2O \cdot 0.15EtOAc$	571	28

[a] A: phthalic anhydride; B: trimethyltin azide: D: NaOH; E: 30% H_2O_2. 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 Et_2O. [g] Calcd for $C_{28}H_{28}N_5O_3$ $(M+H)^+$ 456.2036. [h] Recrystallized from *i*-PrOH. [i] Recrystallized from *i*-PrOH/EtOH/Et_2O. [j] Chromatographed (95:5:0.05 and 95:5:0.1 CH_2Cl_2/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 CH_2Cl_2/MeOH/AcOH). [p] Calcd for $C_{29}H_{31}N_4O_5S$ $(M+H)^+$ 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 IC_{50} values for **84** and **85**. The *N*-benzylcarbamoyl analogue **86** was only moderately potent (IC_{50} 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



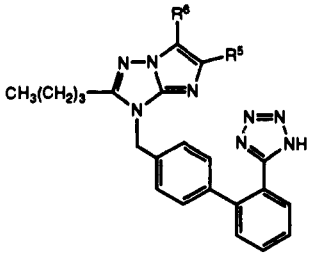
no.	*n*	R	Z	method[a]	% yield	mp, °C	formula[b]	FAB-MS *m/e* $(M + H)^+$	rabbit aorta AT_1 IC_{50},[c] nM
1b		(imidazole)							230[d]
1c		(imidazole, DuP 753)							19,[d] 50[e]
1d		(imidazole, EXP3174)							37,[f] 6[e]
50	3	SCH_2CO_2Me	CO_2H	C-1	97	157.5–159	$C_{23}H_{25}N_3O_4S$	440	540
51	3	SH	CO_2H	C-2	21	218–219	$C_{20}H_{21}N_3O_2S \cdot 0.5H_2O$	368	860
52	3	$SCMe_3$	CO_2H	C-2	43	166.5–168 dec	$C_{24}H_{29}N_3O_2S \cdot 0.2H_2O$	424	890
53	3	SMe	CN_4H	B-5	56	100–102	$C_{21}H_{23}N_7S \cdot 0.5H_2O \cdot 0.3CH_2Cl_2$	406	310
54	3	SCH_2CHMe_2	CN_4H	B-1	49	90–91	$C_{24}H_{28}N_7S \cdot 0.15CH_2Cl_2$	448	72
55	3	SCH_2-cyclohexyl	CN_4H	B-5	60	89–91	$C_{27}H_{33}N_7S \cdot 0.2H_2O \cdot 0.1CH_2Cl_2$	488	36
56	3	SPh	CN_4H	B-2	51	84–85 dec	$C_{28}H_{25}N_7S \cdot 0.75H_2O \cdot 0.15CH_2Cl_2$	468	100
57	3	SCH_2Ph	CN_4H	B-2	82	107 dec	$C_{27}H_{27}N_7S \cdot 0.5H_2O \cdot 0.05CH_2Cl_2$	482	7.1
58	3	$S(CH_2)_2Ph$	CN_4H	B-2	67	79–80	$C_{28}H_{29}N_7S \cdot 0.75H_2O$	496	35
59	3	SCH_2Ph(2-Me)	CN_4H	B-5	71	79–80	$C_{28}H_{29}N_7S \cdot 0.5H_2O$	496	17
60	3	SCH_2Ph(2-Cl)	CN_4H	B-2	47	79–80	$C_{27}H_{26}ClN_7S \cdot 0.1CH_2Cl_2$	516	110
61	2	SCH_2Ph(4-Cl)	CN_4H	B-2	58	90–92	$C_{26}H_{24}ClN_7S \cdot 0.2H_2O \cdot 0.8MeOH$	502	98
62	3	SCH_2Ph(4-Cl)	CN_4H	B-2	37	92–93	$C_{27}H_{26}ClN_7S \cdot 0.6H_2O$	516	24
63	4	SCH_2Ph(4-Cl)	CN_4H	B-2	80	97–99	$C_{28}H_{28}ClN_7S \cdot 0.75H_2O$	530	94
64	3	SCH_2Ph(2-NO_2)	CN_4H	B-2	69	>115 dec	$C_{27}H_{26}N_8O_2S \cdot 0.75H_2O$	527	130
65	3	SCH_2Ph(4-NO_2)	CN_4H	B-2	84	88–90	$C_{27}H_{26}N_8O_2S \cdot 0.2CH_2Cl_2$	527	6.6
66	3	SCH_2Ph(3-OMe)	CN_4H	B-2	59	78–80	$C_{28}H_{29}N_7OS$	512.2210[g]	94
67	3	SCH_2Ph(4-OMe)	CN_4H	B-2	52	95–97	$C_{28}H_{29}N_7OS \cdot 1.05H_2O$[h]	512.2200[g]	31
68	3	SCH_2Ph(4-CO_2Me)	CN_4H	B-1	39	97–98	$C_{28}H_{29}N_7O_2S \cdot 0.15CH_2Cl_2$	540	120
69	3	SCH_2Ph(4-CO_2H)	CN_4H	D[i]	81	139–141 dec	$C_{28}H_{27}N_7O_2S \cdot 2H_2O \cdot 0.2Et_2O$	526	24
70	3	SCH_2Ph(2-CO_2Me)	CN_4H	B-3	54	foam	$C_{29}H_{29}N_7O_2S \cdot 1.5H_2O \cdot 0.2CH_2Cl_2$	540	90
71	3	SCH_2Ph(2-CO_2H)	CN_4H	D	75	>50 dec (gradual)	$C_{28}H_{27}N_7O_2S \cdot 0.75H_2O \cdot 0.125Et_2O$	526	1.5
72	3	SCH_2Ph(2-CH_2OH)	CN_4H	B-2	40	93–95	$C_{28}H_{28}N_7OS \cdot 0.3H_2O \cdot 0.25CH_2Cl_2$	512	36
73	3	SCH_2Ph(2-CN_4H)	CN_4H	B-4	27	>140 (gradual)	$C_{28}H_{27}N_{11}S$	550.2236[j]	1.4
74	3	SO_2Me	CN_4H	F	70	98–100	$C_{21}H_{23}N_7O_2S \cdot 0.33H_2O \cdot 0.25Et_2O$	438	400
75	3	$SOCH_2Ph$(4-Cl)	CN_4H	E	65	208–209 dec	$C_{27}H_{26}ClN_7OS \cdot 0.25H_2O$	532	11
76	3	SO_2CH_2Ph(4-Cl)	CN_4H	B-5	16	180–182 dec	$C_{27}H_{26}ClN_7O_2S \cdot 0.5H_2O \cdot 0.3CH_2Cl_2$	548	48
77	3	$SOCH_2Ph$(4-NO_2)	CN_4H	E[k]	50	222–223	$C_{27}H_{26}N_8O_3S \cdot 0.5H_2O$	543	8.9
78	3	$SOCH_2Ph$(4-OMe)	CN_4H	E	20	125–126	$C_{28}H_{29}N_7O_2S$	528.2175[l]	50
79	3	$SOCH_2Ph$(2-CO_2Me)	CN_4H	E	69	>65 dec (gradual)	$C_{28}H_{28}N_7O_3S \cdot 0.4H_2O \cdot 0.1Et_2O$	556	40
80	3	$SOCH_2Ph$(2-CO_2H)	CN_4H	D	80	>65 dec (gradual)	$C_{28}H_{27}N_7O_3S \cdot 0.4H_2O \cdot 0.4EtOAc$	542	10
81	3	OCH_2Ph	CN_4H	G	12	glass	$C_{27}H_{27}N_7O$	466.2205[m]	370
82	3	$O(CH_2)_2Ph$	CN_4H	G	50	76–77	$C_{28}H_{29}N_7O$	480.2513[n]	63
83	3	$NHCH_2Ph$	CN_4H	B-3	51	>70 (gradual)	$C_{27}H_{28}N_8 \cdot 0.9H_2O \cdot 0.45AcOH$	465	28
84	3	$NHCH_2Ph$(4-Cl)	CN_4H	B-3	69	>130 (gradual)	$C_{27}H_{27}ClN_8 \cdot 0.8H_2O$	499	140
85	3	$NHCH_2Ph$(4-OMe)	CN_4H	B-3	75	>120 (gradual)	$C_{28}H_{30}N_8O \cdot H_2O$	495	780
86	3	$CONHCH_2Ph$	CN_4H	B-3	67	>90 (gradual)	$C_{28}H_{28}N_8O$	493.2457[o]	57
87	3	$CON(Me)CH_2Ph$	CN_4H	B-3	59	>95 (gradual)	$C_{28}H_{30}N_8O \cdot 0.75H_2O$	507	89
88	3	CON(Me)Ph	CN_4H	B-3	37	>100 (gradual)	$C_{28}H_{28}N_8O \cdot 0.15CH_2Cl_2$	493	350

[a] B: trimethyltin azide; C: TFA; D: NaOH; E: 30% H_2O_2; 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 $C_{28}H_{30}N_7OS$ $(M + H)^+$ 512.2232. [h] Characterized by elemental analysis as well as high-resolution FAB-MS. [i] Obtained as a precipitate upon acidification. [j] Calcd for $C_{28}H_{28}N_{11}S$ $(M + H)^+$ 550.2250. [k] Precipitated from reaction mixture; recrystallized from 2-methoxyethanol. [l] Calcd for $C_{28}H_{30}N_7O_2S$ $(M + H)^+$ 528.2182. [m] Calcd for $C_{27}H_{28}N_7O$ $(M + H)^+$ 466.2357. [n] Calcd for $C_{28}H_{30}N_7O$ $(M + H)^+$ 480.2512. [o] Calcd for $C_{28}H_{29}N_8O$ $(M + H)^+$ 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 C^5 and C^6 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 C^5, and this compound, having phenyl at C^6, was a weak antagonist. The 5,6-dimethyl derivative **93** (IC_{50} 7.8 nM) was 7-fold more potent than the 5-methyl analogue **89**, indicating a positive contribution for the methyl group at C^6. A phenyl group in place of methyl at C^6 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 proposed[14] 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 *m/e* $(M + H)^+$	rabbit aorta AT_1 IC_{50},[c] nM
2	(benzimidazole)							96[d]
3	(imidazopyridine, L-158,809)							0.3[e]
89	Me	H	B-6	31	124–125	$C_{23}H_{24}N_8 \cdot 1.5H_2O \cdot 0.75Et_2O$	413	55
90	Et	H	B-6	24	>100 (gradual)	$C_{24}H_{26}N_8 \cdot 1.2H_2O \cdot 0.1Et_2O$	427	55
91	Ph	H	B-6	44	>160 (gradual)	$C_{28}H_{26}N_8 \cdot 0.25H_2O \cdot 0.25Et_2O$	475	30
92	H	Ph	B-6	46	>70 (gradual)	$C_{28}H_{26}N_8 \cdot 0.4CH_2Cl_2 \cdot Et_2O$	475	220
93	Me	Me	B-6	40	138–141	$C_{24}H_{26}N_8 \cdot 0.3H_2O \cdot 0.25CH_2Cl_2$	427	7.8
94	Me	Ph	B-6	32	>108 (gradual)	$C_{29}H_{28}N_8 \cdot 0.7H_2O \cdot 0.9Et_2O$	489	170
95	Ph	Me	B-6	25	207–208	$C_{29}H_{28}N_8 \cdot 0.5H_2O \cdot 0.25Et_2O$	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 ±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 C^2, the chloro substituent at C^4, and at least a portion of the biphenyl or amide-bridged side chain at N^1; and (c) a hydrogen bond linking the C^5-substituent to a proton donor on the receptor. A similar hydrogen-bonding interaction has been proposed[19] 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-workers[15] 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 models[59] (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 carboxamide[60] 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 assay[19]) and the recently reported DuP 532.[61] Lin and co-workers[27] 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 N^3 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 AT_1 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-

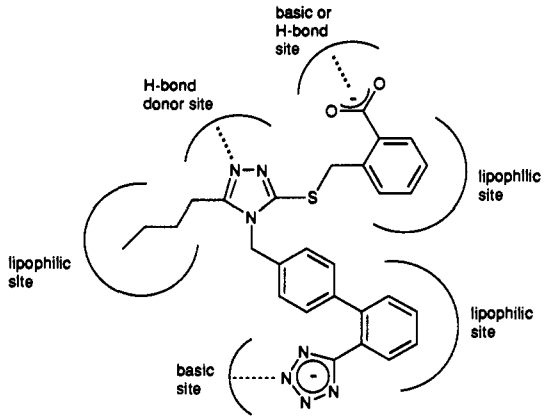


Figure 1. Proposed binding of triazole **71** to the AT_1 receptor through hydrophobic, ionic, and hydrogen-bonding interactions at multiple sites.

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 N^4 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 biphenylyltetrazole 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 4*H*-1,2,4-triazoles and a related series of 3*H*-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 C^3, a benzylthio moiety at C^5, and a [(2-carboxybenzoyl)amino]-benzyl, [[2-(1*H*-tetrazol-5-yl)benzoyl]amino]benzyl, or [2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl side chain at N^4. 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 biphenylyltetrazole 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 (IC_{50} 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 3*H*-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 I_2) 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 N_2. 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 CH_2Cl_2, MeOH, and EtOH were dried

over 3-Å molecular sieves. Reactions were routinely conducted under N_2 (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 CH_2Cl_2) to give 2.18 g (58%) of an oil, which was sufficiently pure by TLC (97:3 CH_2Cl_2/MeOH) for use in the next step. NMR indicated that the material exists as a mixture of syn and anti isomers: ^{1}H NMR ($CDCl_3$, 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 Et_2O and saturated aqueous Na_2CO_3) 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 CH_2Cl_2) 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 CH_2Cl_2/MeOH; ^{1}H NMR ($CDCl_3$, 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 Et_2O and then with 2 × 20 mL of EtOAc. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography of the residue (elution with 97:3 CH_2Cl_2/MeOH) yielded 123 mg (83%) of pale yellow powder: mp 111–111.5 °C; TLC in 95:5 CH_2Cl_2/MeOH; ^{1}H NMR ($CDCl_3$, 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 Et_2O. 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 CH_2Cl_2/MeOH/AcOH; ^{1}H NMR (CD_3OD, 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 ^{1}H 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 (176 g, 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 Et_2O and 2 L of 0.2 N HCl. The ethereal phase was washed with 2 L of saturated aqueous NaCl, dried over $MgSO_4$, 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; ^{1}H NMR ($CDCl_3$, 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. ($C_9H_{10}N_2O_2S_2$) 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 CH_2Cl_2/MeOH/concentrated NH_4OH; ^{1}H 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. ($C_8H_{10}N_4O_2S$) 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 orthovalerate, 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 Et_2O. The resulting solid was collected on a filter, washed with Et_2O, and dried to yield 45.2 g (62%) of white crystals: mp 159–160 °C; TLC in 95:5 CH_2Cl_2/MeOH; ^{1}H 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. ($C_{13}H_{16}N_4O_2S$) 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 $MgSO_4$, the EtOAc solution was filtered and concentrated in vacuo. The residue was chromatographed on a silica gel column (elution with 0.75% MeOH in CH_2Cl_2) to provide 326 mg (77%) of an oil: TLC in 95:5 CH_2Cl_2/MeOH; ^{1}H NMR ($CDCl_3$, 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. ($C_{20}H_{21}ClN_4O_2S \cdot 0.05CH_2Cl_2$) 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 $NaHCO_3$ (about 10 mL total), and the mixture was stirred thoroughly until CO_2 evolution had ceased. The solid was collected on a filter, washed thoroughly with H_2O, and then dried in vacuo over P_2O_5 to give 1.07 g (80%) of a pale yellow solid: mp 155–157 °C; TLC in 95:5 CH_2Cl_2/MeOH; ^{1}H 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. ($C_{10}H_7F_3N_4O_2S$) 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 CH_2Cl_2/MeOH; ^{1}H NMR ($CDCl_3$, 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. ($C_{16}H_{20}N_4O_4S$) C, H, N.

3-n-Butyl-5-[[(N-methylcarbamoyl)methyl]thio]-4-(4-nitrobenzyl)-4H-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 H_2O, the solid was collected on a filter, washed with H_2O, air-dried, and washed further with Et_2O to give 413 mg (83%) of a white solid: mp 132–133 °C; TLC in 95:5 CH_2Cl_2/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. ($C_{16}H_{21}N_5O_3S$) C, H, N.

3-n-Butyl-5-chloro-4-(4-nitrobenzyl)-4H-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 CH_2Cl_2 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 $NaHCO_3$, 400 mL of H_2O, and finally 400 mL of saturated aqueous NaCl. The EtOAc phase was dried over $MgSO_4$, filtered, and concentrated. Column chromatography of the residue (elution with a gradient of 0–1% MeOH in CH_2Cl_2) yielded 1.90 g (37%) of a yellow oil: TLC in 95:5 CH_2Cl_2/MeOH; ^1H NMR ($CDCl_3$, 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. ($C_{13}H_{15}ClN_4O_2$·0.33H_2O) C, H, N, Cl.

3-n-Butyl-4-(4-nitrobenzyl)-5-(phenylthio)-4H-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 Et_2O and 50 mL of 0.2 N HCl. The ethereal phase was washed with saturated aqueous Na_2CO_3, then dried, filtered, and concentrated. The residue was chromatographed on a silica gel column (gradient elution with 0–2% *i*-PrOH in $CHCl_3$) to give 28 mg (22%) of an oil: TLC in 97:3 $CHCl_3$/*i*-PrOH; ^1H NMR ($CDCl_3$, 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]-4H-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 $CHCl_3$/MeOH; ^1H NMR ($CDCl_3$, 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. ($C_{20}H_{23}ClN_4S$·0.25H_2O) C, H, N.

3-n-Butyl-5-[(4-chlorobenzyl)thio]-4-[4-[(2-cyanobenzoyl)amino]benzyl]-4H-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 $NaHCO_3$ followed by 50 mL of saturated aqueous NaCl. The organic phase was dried ($MgSO_4$), 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 ($CDCl_3$, 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. ($C_{28}H_{26}ClN_5OS$·0.4EtOAc) C, H, N.

Method B-1. 3-n-Butyl-5-[(4-chlorobenzyl)thio]-4-[4-[[2-(1H-tetrazol-5-yl)benzoyl]amino]benzyl]-4H-1,2,4-triazole (46). A mixture of 159 mg (0.31 mmol) of **112** and 222 mg (1.08 mmol) of trimethyltin azide[36] 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 Et_2O. 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 P_2O_5 and then added as a slurry in CH_2Cl_2 to a column of silica gel, which was eluted with 1% MeOH, then 10% MeOH, and finally 18% MeOH in CH_2Cl_2. 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 CH_2Cl_2/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. ($C_{28}H_{27}ClN_8OS$·H_2O·0.33CH_2Cl_2) 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 Et_2O and 250 mL of H_2O. After being washed with 4 × 250 mL of H_2O, the organic phase was dried ($MgSO_4$), filtered, and concentrated. The residue was leached twice with hot Et_2O (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 ($CDCl_3$, 300 MHz) δ 1.17 (s, 9 H), 4.90 (s, 2 H), 7.2–7.9 (m, 12 H). Anal. ($C_{28}H_{23}NO_4$) 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 Et_2O and washed twice with saturated aqueous Na_2CO_3. 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 Na_2CO_3 solution (**CAUTION**: gas evolution). The oil which separated was extracted with 100 mL of Et_2O. The organic phase was dried (Na_2SO_4), 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 CH_2Cl_2/MeOH/concentrated NH_4OH; ^1H NMR ($CDCl_3$, 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. ($C_{18}H_{21}NO_2$·0.25H_2O) 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 ($CDCl_3$, 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. ($C_{20}H_{23}NO_2S_2$) C, H, N.

4-[[2′-(*tert*-Butoxycarbonyl)biphenyl-4-yl]methyl]-3-thiosemicarbazide (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 CH_2Cl_2/MeOH), affording 1.15 g (79%) of a stiff, white foam: mp >45 °C (gradual); TLC in 95:5 CH_2Cl_2/MeOH; ^1H NMR ($CDCl_3$, 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. ($C_{19}H_{23}N_3O_2S$·0.1H_2O) C, H, N.

4-[[2′-(*tert*-Butoxycarbonyl)biphenyl-4-yl]methyl]-5-n-butyl-2,4-dihydro-3H-1,2,4-triazole-3-thione (118). Using the procedure for **103**, **117** was reacted with trimethyl orthovalerate. The crude product was chromatographed (gradient elution with 0–1% MeOH in CH_2Cl_2), 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 CH_2Cl_2/MeOH; ^1H NMR ($CDCl_3$, 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. ($C_{24}H_{29}N_3O_2S$) 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 CH_2Cl_2 was added 435 μL (322 mg, 2.5 mmol) of *N,N*-diisopropylethylamine followed by 219 μL (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 Et_2O and 25 mL of saturated aqueous NH_4Cl. The organic layer was washed with another portion of the NH_4Cl solution and then dried over $MgSO_4$. The filtered solution was concentrated, and the residual oil was chromatographed (elution with a gradient of 0–5% *i*-PrOH in CH_2Cl_2) to give 639 mg (86%) of a colorless gum: TLC in 97:3 CH_2Cl_2/*i*-PrOH; ^{1}H NMR ($CDCl_3$, 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. ($C_{27}H_{33}N_3O_4S$) 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 N_2. The clear residual gum was treated with approximately 25 mL of Et_2O and stirred vigorously in a stoppered flask, resulting in crystallization. After about 20 min, the solid was collected on a filter, washed with Et_2O, and dried in vacuo to give 426 mg (97%) of white crystals: mp 157.5–159 °C; TLC in 95:5:0.1 CH_2Cl_2/MeOH/AcOH; ^{1}H 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. ($C_{23}H_{25}N_3O_4S$) 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 N_2. Column chromatography of the residue (gradient elution with 1–5% MeOH in CH_2Cl_2 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 Et_2O, yielding 9.5 mg (21%) of **51** as a white powder: mp 218–219 °C; TLC in 95:5:0.1 CH_2Cl_2/MeOH/AcOH; ^{1}H 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. ($C_{20}H_{21}N_3O_2S\cdot 0.5H_2O$) 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 CH_2Cl_2/MeOH/AcOH; ^{1}H 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. ($C_{24}H_{29}N_3O_2S\cdot 0.2H_2O$) C, H, N.

4′-(Azidomethyl)-2-biphenylcarbonitrile (121). A mixture of 1.97 g (7.25 mmol) of 4′-(bromomethyl)-2-biphenylcarbonitrile (**120**),[15] 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 Et_2O and 100 mL of H_2O. The organic phase was washed (3 × 100 mL of H_2O), dried ($MgSO_4$), 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; ^{1}H NMR ($CDCl_3$, 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 Et_2O, 25 mL of CH_2Cl_2, and 75 mL of H_2O. 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 CH_2Cl_2/MeOH; ^{1}H 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. ($C_{15}H_{14}N_4S$) 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 orthovalerate 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 N_2 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 CH_2Cl_2/MeOH; ^{1}H NMR ($CDCl_3$, 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. ($C_{20}H_{20}N_4S$) 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 CH_2Cl_2) to give a 71% yield of **124** as a slightly cloudy gum: TLC in 98:2 CH_2Cl_2/MeOH; ^{1}H NMR ($CDCl_3$, 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. ($C_{27}H_{25}ClN_4S\cdot 0.25H_2O$) 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 CH_2Cl_2/MeOH) afforded a 37% yield of **62** as an off-white solid: mp 92–93 °C; TLC in 80:20 CH_2Cl_2/MeOH; ^{1}H 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. ($C_{27}H_{26}ClN_7S\cdot 0.6H_2O$) 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 H_2O. The organic phase was washed with 100 mL of H_2O and then 100 mL of saturated aqueous NaCl. Next it was dried over $MgSO_4$, filtered, and concentrated. Column chromatography of the residue (elution with CH_2Cl_2) gave 860 mg (50%) of a foam, which by NMR appeared to consist of a mixture of syn and anti isomers: TLC in CH_2Cl_2; ^{1}H NMR ($CDCl_3$, 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. ($C_{23}H_{28}N_4OS\cdot 0.2H_2O$) 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 μL (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 Et_2O and filtered. The material on the filter was purified by column chromatography (gradient elution with 0.5–2% MeOH in CH_2Cl_2) to yield 468 mg (67%) of a solid: mp 209–209.5 °C; TLC in 95:5 CH_2Cl_2/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. ($C_{21}H_{22}N_4S \cdot 0.05CH_2Cl_2$) C, H, N.

3-n-Butyl-4-[(2′-cyanobiphenyl-4-yl)methyl]-5-[[2-(methoxycarbonyl)benzyl]thio]-4H-1,2,4-triazole (128). Alkylation of **123** with methyl 2-(bromomethyl)benzoate[62] was accomplished according to the procedure used for **104**. Column chromatography of the crude product (gradient elution with 0.5–5% MeOH in CH_2Cl_2) yielded 567 mg (76%) of a colorless gum: TLC in 95:5 CH_2Cl_2/MeOH; ^1H NMR ($CDCl_3$, 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. ($C_{29}H_{28}N_4O_2S \cdot 0.2CH_2Cl_2$) C, H, N.

3-n-Butyl-4-[(2′-cyanobiphenyl-4-yl)methyl]-5-[[2-(hydroxymethyl)benzyl]thio]-4H-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 CH_2Cl_2 (20 mL) and H_2O (20 mL). The organic phase was washed again with H_2O, dried ($MgSO_4$), filtered, and concentrated. The crude product was chromatographed (gradient elution with 0–3% MeOH in CH_2Cl_2) to yield 75 mg (32%) of a foam: TLC in 95:5 CH_2Cl_2/MeOH; ^1H NMR ($CDCl_3$, 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, 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′-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4H-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 ($MgSO_4$), 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 CH_2Cl_2 to the top of a silica gel column. Gradient elution with 1–10% MeOH in CH_2Cl_2 afforded 54% yield of a stiff, cream-colored foam: TLC in 80:20 CH_2Cl_2/MeOH; ^1H NMR ($CDCl_3$, 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. ($C_{29}H_{29}N_7O_2S \cdot 1.5H_2O \cdot 0.2CH_2Cl_2$) C, H, N.

Method D. 3-n-Butyl-5-[(2-carboxybenzyl)thio]-4-[[2′-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4H-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 $MgSO_4$, filtered, and concentrated. Trituration of the residue with Et_2O gave 71 mg (75%) of an amorphous, white solid: TLC in 80:20 CH_2Cl_2/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. ($C_{28}H_{27}N_7O_2S \cdot 0.75H_2O \cdot 0.125Et_2O$) C, H, N.

3-n-Butyl-5-[(2-cyanobenzyl)thio]-4-[(2′-cyanobiphenyl-4-yl)methyl]-4H-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 CH_2Cl_2) gave 58% yield of a nearly colorless, stiff gum: TLC in 95:5 CH_2Cl_2/MeOH; ^1H NMR ($CDCl_3$, 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. ($C_{28}H_{25}N_5S \cdot 0.4H_2O$) C, H, N.

Method B-4. 3-n-Butyl-5-[[2-(1H-tetrazol-5-yl)benzyl]thio]-4-[[2′-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4H-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 CH_2Cl_2/MeOH, dried over $MgSO_4$, 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 CH_2Cl_2 to a column of silica gel (eluted successively with 98:2:0.2, 95:5:0.5, and 90:10:1 CH_2Cl_2/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 Et_2O gave 29.2 mg (27%) of a light beige powder: TLC in 90:10:1 CH_2Cl_2/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 $C_{28}H_{28}N_{11}S$ $(M + H)^+$ 550.2250), 572.2082 (calcd for $C_{28}H_{27}N_{11}NaS$ $(M + Na)^+$ 572.2069).

Method E. 3-n-Butyl-5-[(4-chlorobenzyl)sulfinyl]-4-[[2′-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-4H-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 ($MgSO_4$), filtered, and concentrated in vacuo. Trituration of the residue with Et_2O yielded 77 mg (65%) of a white solid: mp 208–209 °C dec (preliminary discoloration); TLC in 80:20 CH_2Cl_2/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. ($C_{27}H_{26}ClN_7OS \cdot 0.25H_2O$) C, H, N.

3-n-Butyl-5-[(4-chlorobenzyl)sulfonyl]-4-[(2′-cyanobiphenyl-4-yl)methyl]-4H-1,2,4-triazole (131). A stirred solution of 47 mg (0.1 mmol) of **124** in 0.3 mL of dry CH_2Cl_2 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 Na_2CO_3. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo to give 48 mg (95%) of a gum: TLC in 95:5 CH_2Cl_2/MeOH; ^1H NMR ($CDCl_3$, 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)-4H-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 CH_2Cl_2), an 85% yield of the product was obtained as an oil: TLC in 95:5 CH_2Cl_2/MeOH; ^1H NMR ($CDCl_3$, 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. ($C_{21}H_{22}N_4S \cdot 0.5H_2O$) C, H, N.

3-n-Butyl-4-[(2′-cyanobiphenyl-4-yl)methyl]-5-(methylsulfonyl)-4H-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 CH_2Cl_2/MeOH; ^1H NMR ($CDCl_3$, 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 CH_2Cl_2) provided a 50% yield of a stiff gum: TLC in 95:5 CH_2Cl_2/MeOH; ^1H NMR ($CDCl_3$, 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. ($C_{28}H_{24}N_4S$) 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 CH_2Cl_2/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. ($C_{21}H_{23}N_7S \cdot 0.5H_2O \cdot 0.3CH_2Cl_2$) 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 ($MgSO_4$), filtered, and concentrated in vacuo. Trituration of the residue with Et_2O yielded 117 mg (70%) of a white solid: mp 98–100 °C (preliminary softening); TLC in 90:10:1 CH_2Cl_2/MeOH/concentrated NH_4OH; ^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. ($C_{21}H_{23}N_7O_2S \cdot 0.33H_2O \cdot 0.25Et_2O$) 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 H_2 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 ($MgSO_4$), filtered, and concentrated. Column chromatography of the residue (elution with 1% and then 5% MeOH in CH_2Cl_2) afforded 29 mg (50%) of a white solid: mp 76–77 °C; TLC in 90:10:1 CH_2Cl_2/MeOH/concentrated NH_4OH; ^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 $C_{28}H_{30}N_7O$ $(M + H)^+$ 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 H_2O. The organic layer was dried over $MgSO_4$, 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 CH_2Cl_2/MeOH: ^1H NMR ($CDCl_3$, 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. ($C_8H_{17}N_3OS$) 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 CH_2Cl_2 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 Et_2O (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 Et_2O. Next it was partitioned between 100 mL of saturated aqueous Na_2CO_3 and a mixture of 200 mL of Et_2O and 50 mL of CH_2Cl_2. The organic phase was dried over Na_2SO_4, 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 CH_2Cl_2/MeOH; ^1H NMR ($CDCl_3$, 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. ($C_8H_{19}N_3OS$) 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 H_2O 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 CH_2Cl_2). The residue from evaporation of the pooled product fractions was partitioned between Et_2O/CH_2Cl_2 and saturated aqueous Na_2CO_3. The organic phase was dried (Na_2SO_4), filtered, and concentrated to yield 4.64 g (89%) of nearly white crystals (air-sensitive): mp 54–55 °C; TLC in 9:1 CH_2Cl_2/MeOH; ^1H NMR ($CDCl_3$, 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. ($C_{14}H_{12}N_2$) 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 CH_2Cl_2) 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 CH_2Cl_2/MeOH; ^1H NMR ($CDCl_3$, 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 95:5:0.5 CH_2Cl_2/MeOH/concentrated NH_4OH, 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 CH_2Cl_2 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 Et_2O. The solid which precipitated upon agitation was collected on a filter and washed thoroughly with H_2O and then with some Et_2O. After vacuum-drying at 100 °C, 3.56 g of a cream-colored solid was obtained: mp 206–207 °C; TLC in 90:10:1 CH_2Cl_2/MeOH/AcOH; ^1H NMR ($CDCl_3$, 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. ($C_{20}H_{21}N_5$) C, H, N. From partial evaporation of the Et_2O 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 Et_2O to provide 227 mg (90%) of a pale yellow powder: mp 140.5–141.5 °C; TLC in 95:5 CH_2Cl_2/

MeOH; ^{1}H 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. ($C_{27}H_{25}N_5$) 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_2O. Recrystallization from EtOAc gave 101 mg (68%) of white crystals: mp 138–140 °C; TLC in 95:5 CH_2Cl_2/MeOH; ^{1}H 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. ($C_{27}H_{27}N_5 \cdot 0.33H_2O$) 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_2O 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; ^{1}H 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 °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 CH_2Cl_2/MeOH: ^{1}H 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. ($C_{10}H_{13}N_3O_2 \cdot 0.2H_2O$) 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 °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 CH_2Cl_2/MeOH; ^{1}H 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. ($C_{17}H_{25}N_3O_3 \cdot 0.1$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 °C (gradual); TLC in 95:5 CH_2Cl_2/MeOH; ^{1}H 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. ($C_{29}H_{29}N_5O \cdot 0.6H_2O$) C, H, N.

5-Amino-1-(1-benzoylethyl)-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 CH_2Cl_2/MeOH/AcOH; ^{1}H NMR (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_2O. The filtered Et_2O 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 CH_2Cl_2/MeOH; ^{1}H NMR (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-[[2′-(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_2O to give a 25% yield of a tan solid: mp 207–208 °C; TLC in 90:10:1 CH_2Cl_2/MeOH/AcOH; ^{1}H NMR (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. ($C_{29}H_{28}N_8 \cdot 0.5H_2O \cdot 0.25Et_2O$) 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 CH_2Cl_2/MeOH/AcOH; ^{1}H 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 CH_2Cl_2/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 $(M + H)^+$.

Subsequently eluted was 211 mg of the amide **153** as a yellow solid of indefinite melting point: TLC in 95:5 CH_2Cl_2/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 $(M + H)^+$.

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 °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 CH_2Cl_2/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 $(M + H)^+$.

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 °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 × 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 nonspecific 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 antiotensin II), and, as appropriate, the left femoral vien (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 μL/mL) was added to enhance solubility.

The responsiveness of the rat was verified by an initial challenge with methoxamine (50 μg/kg iv) via the AII catheter. When the animal was stable, bolus injections of AII (0.1 μg/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.

Acknowledgment. We thank Dr. Lawrence F. Colwell, Jr., Ms. Amy Bernick, and Dr. Jack L. Smith for mass spectral determinations. We are grateful to Dr. P. Eskola and co-workers for the preparation of certain intermediates and to Drs. W. J. Greenlee, R. L. Tolman, and A. A. Patchett for encouragement and support.

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