Triazolinone Biphenylsulfonamide Derivatives as Orally Active Angiotensin II Antagonists with Potent AT_1 Receptor Affinity and Enhanced AT_2 Affinity[1,2]

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Several series of 2,4-dihydro-2,4,5-trisubstituted-3*H*-1,2,4-triazol-3-ones with acidic sulfonamide replacements of tetrazole at the 2′-position of the biphenyl-4-ylmethyl side chain at N^4 were prepared and tested as angiotensin II (AII) antagonists. Preferred substituents on the triazolinone ring were *n*-butyl at C^5 and 2-(trifluoromethyl)phenyl at N^2. Subnanomolar IC_{50} values at the AT_1 receptor subtype were observed for a variety of acylsulfonamides, including aroyl, heteroaroyl, and cycloalkylcarbonyl derivatives. Certain other acidic sulfonamides, such as sulfonylcarbamates and disulfimides also displayed high affinity for the AT_1 receptor. In addition, AT_2 binding for some of these compounds was increased by as much as 1000-fold over the corresponding tetrazole (e.g., AT_2 IC_{50} 17 nM for the *tert*-butyl sulfonylcarbamate **92**). When evaluated for inhibition of the AII pressor response, the benchmark benzoylsulfonamide **9** (L-159,913) was efficacious in several species and was superior to losartan (**1a**) in conscious rhesus monkeys. Several subsequent analogues, including the 2-chlorobenzoyl (**18**), (3-chlorothiophene-2-yl)carbonyl (**51**), ((*S*)-2,2-dimethylcyclopropyl)carbonyl (**80**), and *tert*-butoxycarbonyl (**92**) derivatives, were highly effective in rats, surpassing **9** and losartan in duration of action and/or potency. Compound **18** (L-162,223) displayed very prolonged AII antagonism in the rat model (>24 h at 1 mg/kg iv). At 1 mg/kg po in rats, **18** and **92** (L-162,234) produced 85–87% peak inhibition of the AII pressor response with duration exceeding 6 h. The identification of triazolinone-based sulfonamide derivatives combining high AT_1 affinity, considerably enhanced AT_2 potency, and favorable *in vivo* properties provides insights relevant to the design of dual AT_1/AT_2 receptor antagonists.

The renin–angiotensin system (RAS),[3] which is critically involved in homeostatic mechanisms for the regulation of blood pressure, electrolyte balance, and fluid volume, has been a prime target for cardiovascular disease therapy.[4] The primary effector hormone of the RAS is the octapeptide angiotensin II (AII), which is generated from an inactive precursor by angiotensin-converting enzyme (ACE). The value of ACE inhibitors in the treatment of hypertension and congestive heart failure is well established.[5] Because ACE also possesses kininase activity, inhibition of this enzyme may lead to elevated levels of bradykinin and substance P. Such secondary actions, extraneous to the RAS, are thought to be linked to the dry cough and angioneurotic edema experienced by some patients on ACE inhibitors.[6] Furthermore, under some circumstances, AII may be formed by one or more pathways not involving ACE.[7]

The most direct and potentially the most specific approach to blockade of the RAS is antagonism of AII at its receptor site.[8] Two major receptor subtypes, designated AT_1 and AT_2,[9] have been identified in a variety of human and animal tissues.[10] At the present time, the major physiological functions of AII appear to be associated with the G-protein-coupled AT_1 receptor subtype.[11] The significance of the AT_2 receptor remains largely speculative.[10,11] Although AII antagonists highly selective for the AT_2 subtype have been reported,[12] no therapeutic utility has yet emerged for them. In contrast, antagonism of AII at the AT_1 receptor offers real promise for the therapy of hypertension and heart failure.[10a,13] Paving the way for this new class of receptor antagonists, early imidazole-based leads from the Takeda group[14] served as the foundation for extensive structure-activity studies at the Du Pont laboratories, culminating in the clinical candidate losartan (DuP 753; MK-954; **1a**)[15] and its high-affinity carboxy metabolite, EXP3174 (**1b**).[16] Subsequently, novel nonpeptide AII antagonist structures have been reported by numerous laboratories.[17] To date, most of this published work has focused on variations of the losartan heterocyclic system, while retaining a [2′-(5-tetrazolyl)-biphenyl-4-yl]methyl (or closely related) side chain that is linked to the heterocycle directly or through a heteroatom. Indeed, the diversity of platforms compatible with effective AII antagonism is remarkable, encompassing numerous *N*- or *C*-linked 5- and 6-membered nitrogen heterocycles, as well as ring-fused congeners.[17] In most series, the tetrazole substituent on the biphenyl moiety has been found significantly superior to a carboxylic acid.[15b,18] Other acidic groups as tetrazole surrogates have received limited attention. AII antagonists incorporating squaric acid,[19] triflamide,[20] acylsulfonamide,[21] oxathiadiazole *S*-oxide,[22] or oxadiazolone[23] groups in place of tetrazole have recently been reported.

We have described potent AII antagonist activity in a series of appropriately substituted N^2-aryltriazolin-3-ones such as **2**.[24] The present study has explored the

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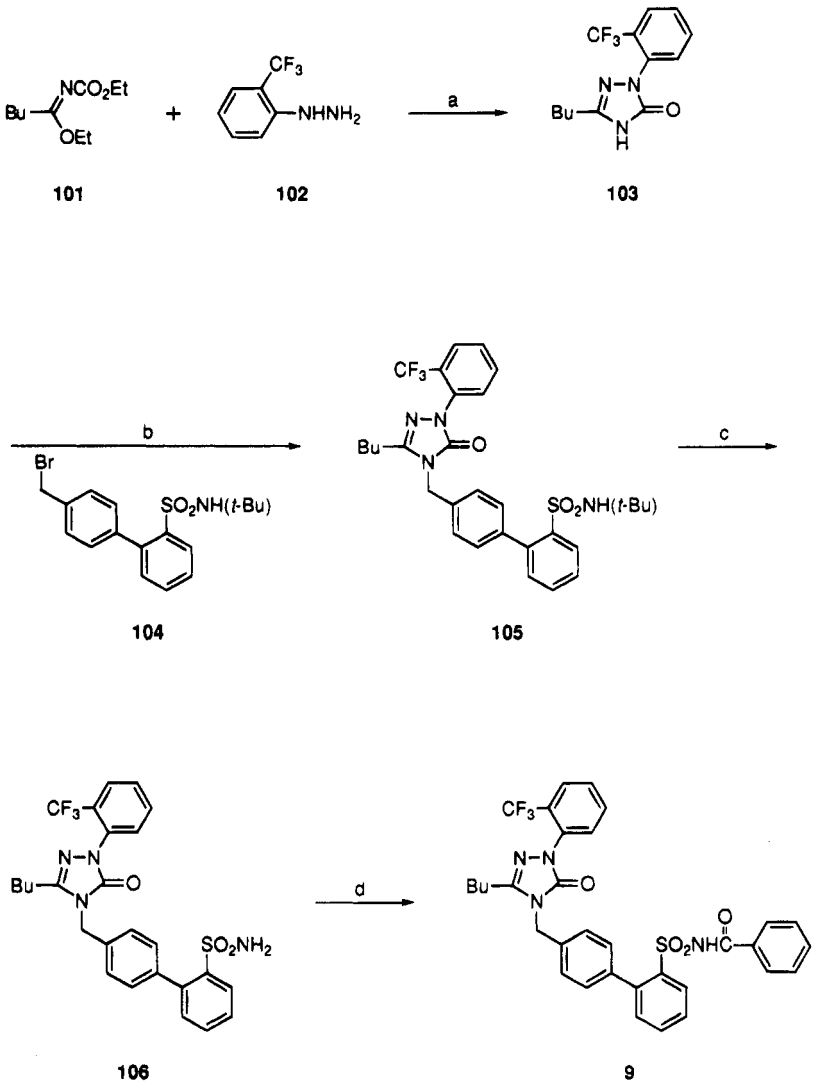
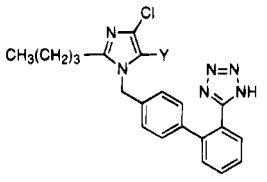
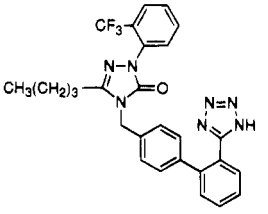
Scheme 1[a]



[a] (a) Et_3N, toluene, 50–90 °C; (b) NaH, DMF, 50 °C; (c) TFA, anisole; (d) $PhCOCl$, pyridine, 20 °C; or $PhCO_2H$, CDI, DBU, THF, 55 °C.



1a, Y = CH_2OH
1b, Y = CO_2H



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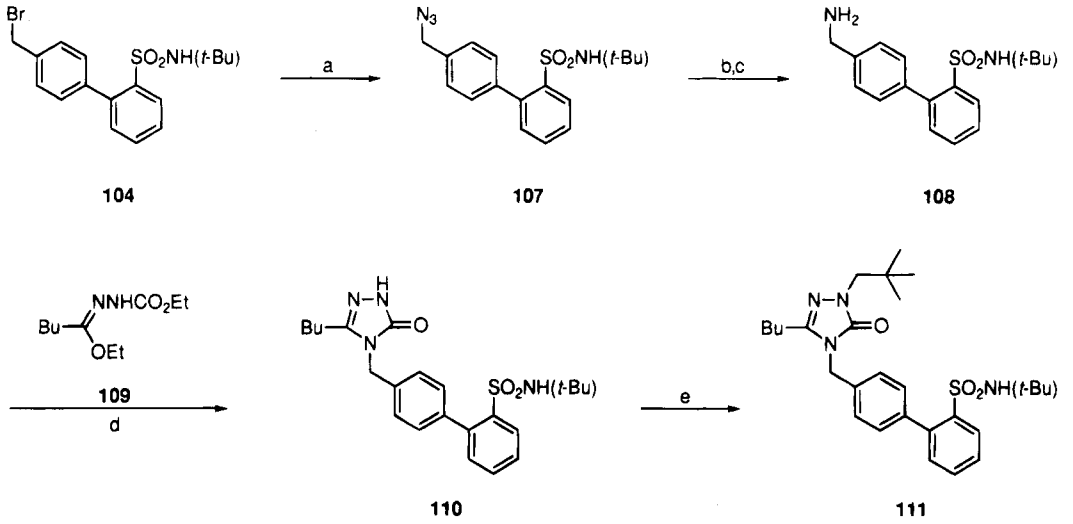
introduction of acylsulfonamides and other acidic sulfonamide derivatives as tetrazole replacements in analogues of **2**. One incentive for this study was the finding[25] that the tetrazole ring of losartan is subject to significant glucuronidation upon incubation with primate liver slices. Replacement of the tetrazole in AII antagonists by an acidic functional group metabolically resistant to glucuronidation might therefore lead to improved duration of action. In addition, the sulfonamides offered possibilities for a broad range of structural variations that could be of value for adjusting physicochemical properties or for accessing potential receptor binding sites unavailable to the tetrazole. In a preliminary communication,[1] we have documented the favorable biological properties of some of these sulfonamides compared to the corresponding tetrazoles. Full details of the synthesis and structure–activity relationships of these new compounds are described below.

Chemistry

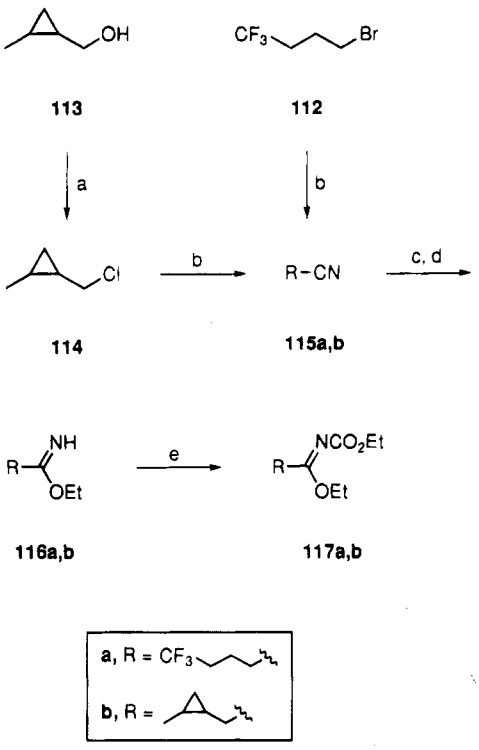
Tables 1–6 list the target triazolinones **3**–**100** prepared in this investigation. A representative synthesis of N^2-aryltriazolinones bearing an acylsulfonamide group at the 2′-position of the biphenyl system is illustrated in Scheme 1. By the method of Yabutani,[26] the *N*-carbethoxyvalerimidate **101**[24] was condensed with 2-(trifluoromethyl)phenylhydrazine (**102**) in the presence of triethylamine to yield the triazolinone **103**. We have previously reported the preparation of the 2-chlorophenyl analogue.[24] Alkylation of **103** with the (bromomethyl)biphenylsulfonamide intermediate **104**[21a,27] afforded **105**. Upon removal of the *tert*-butyl protecting group with trifluoroacetic acid, the resulting sulfonamide **106** was converted to **9** and its analogues by one of two methods. Acylation with the acid chloride[28] in the presence of pyridine was used in some cases. However, reaction with the *N*-acylimidazolide (formed *in situ* from the carboxylic acid and 1,1′-carbonyldiimi-

Scheme 2[a]



[a] (a) LiN_3, DMSO; (b) Ph_3P, THF, 40 °C; (c) H_2O, THF, 20 °C; (d) EtOH, Δ; (e) NaH, neopentyl iodide, DMF, 40–90 °C.

Scheme 3[a]



[a] (a) $SOCl_2$, pyridine, $CHCl_3$, 0–60 °C; (b) NaCN, DMSO, 110 °C; (c) HCl, EtOH, 0 °C; (d) 30% K_2CO_3(aq), Et_2O; (e) EtOCOCl, Et_3N, CH_2Cl_2, 0–20 °C.

dazole) in the presence of DBU[29] generally gave superior yields and greater ease of purification.

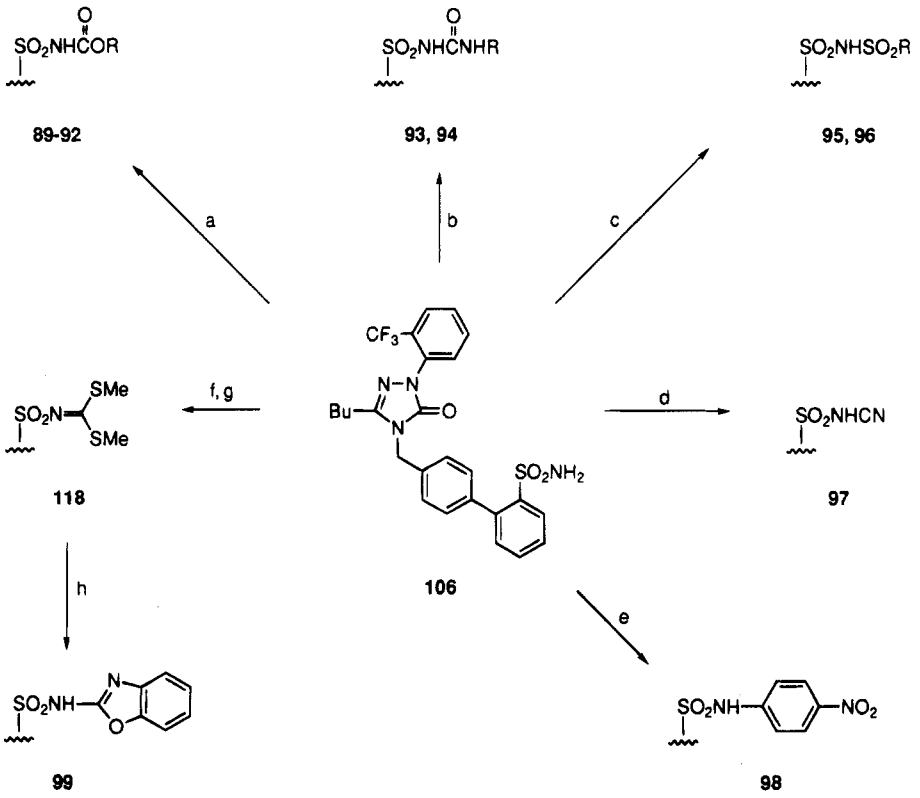
An alternative route (Scheme 2) was required for the preparation of the N^2-alkyltriazolinones **10, 11**. The benzylic bromide **104**[21a,27] was converted to the azide **107**, which was reduced to the amine **108** with triphenylphosphine.[30] Reaction of **108** with ethyl valerate carbethoxyhydrazone (**109**)[24] according to a literature method[31] yielded the triazolinone **110**. This underwent *N*-alkylation[24] to yield, for example, **111**, which was processed further, as in Scheme 1, to afford **11**.

Details for the introduction of some other groups at the 5-position of the triazolinone ring (for the synthesis of **14, 15, 19**) are shown in Scheme 3. Commercial 1-bromo-4,4,4-trifluorobutane (**112**) was heated with sodium cyanide in DMSO to give the nitrile **115a**. Similarly, 2-methylcyclopropanemethanol (**113**, a mixture of *cis*- and *trans*-isomers) was treated with thionyl chloride in the presence of pyridine to give **114**, which was further transformed, as above, to the nitrile **115b**. Reaction of **115** with anhydrous HCl and EtOH formed the imidate hydrochloride,[32] which was converted to the imidate free base **116**. By treatment with ethyl chloroformate in the presence of triethylamine, the *N*-carbethoxyimidate **117** was obtained, and this was carried forward as in Scheme 1.

Pathways to the formation of various other acidic sulfonamide derivatives (Table 6) from the intermediate **106** are presented in Scheme 4. Generation of the anion of **106** with sodium hydride, followed by treatment with an alkyl chloroformate or di-*tert*-butyl dicarbonate, afforded the sulfonylcarbamates **89–92**. Reaction of **106** with an isocyanate in the presence of triethylamine gave the sulfonylureas **93, 94**. The disulfimides **95, 96** were obtained from the sodium salt of **106** and a sulfonyl chloride. For the synthesis of the cyanosulfonamide **97**, the anion of **106** was formed with sodium bis(trimethylsilyl)amide and reacted with cyanogen bromide. A displacement reaction on 4-fluoronitrobenzene with the sodium salt of **106** gave **98**. By an anhydrous modification of the method of Meléndez and co-workers,[33] the sodium salt of **106** was reacted with carbon disulfide and then with iodomethane to yield the bis(methylthio)-methylene derivative **118**. Ring closure upon heating with *o*-aminophenol afforded the (benzoxazol-2-yl)sulfonamide **99**.

The trifluoromethanesulfonamide (triflamide) **100** was prepared as outlined in Scheme 5. Palladium-catalyzed cross-coupling of 2-bromonitrobenzene (**119**) with the stannane **120**[34] yielded the biphenyl derivative **121**. This was α-brominated to afford **122**, which alkylated the triazolinone **103** to give **123**. Following reduction of the nitro group with stannous chloride, the resulting amine **124** was reacted with trifluoromethanesulfonic anhydride in pyridine. The major product, the

Scheme 4[a]



[a] (a) NaH, ROCOCl or $(Boc)_2O$, THF, 20–55 °C; (b) RNCO, Et_3N, DMF, 75 °C; (c) NaH, RSO_2Cl, THF, 20–60 °C; (d) $NaN(TMS)_2$, BrCN, THF; (e) NaH, 4-fluoronitrobenzene, DMF, 60 °C; (f) NaH, CS_2, DMF; (g) MeI; (h) NaH, *o*-aminophenol, DMF, 110 °C.

bis((trifluoromethyl)sulfonyl) derivative **125** underwent hydrolysis to **100** upon treatment with sodium hydroxide.

In Vitro AII Antagonism

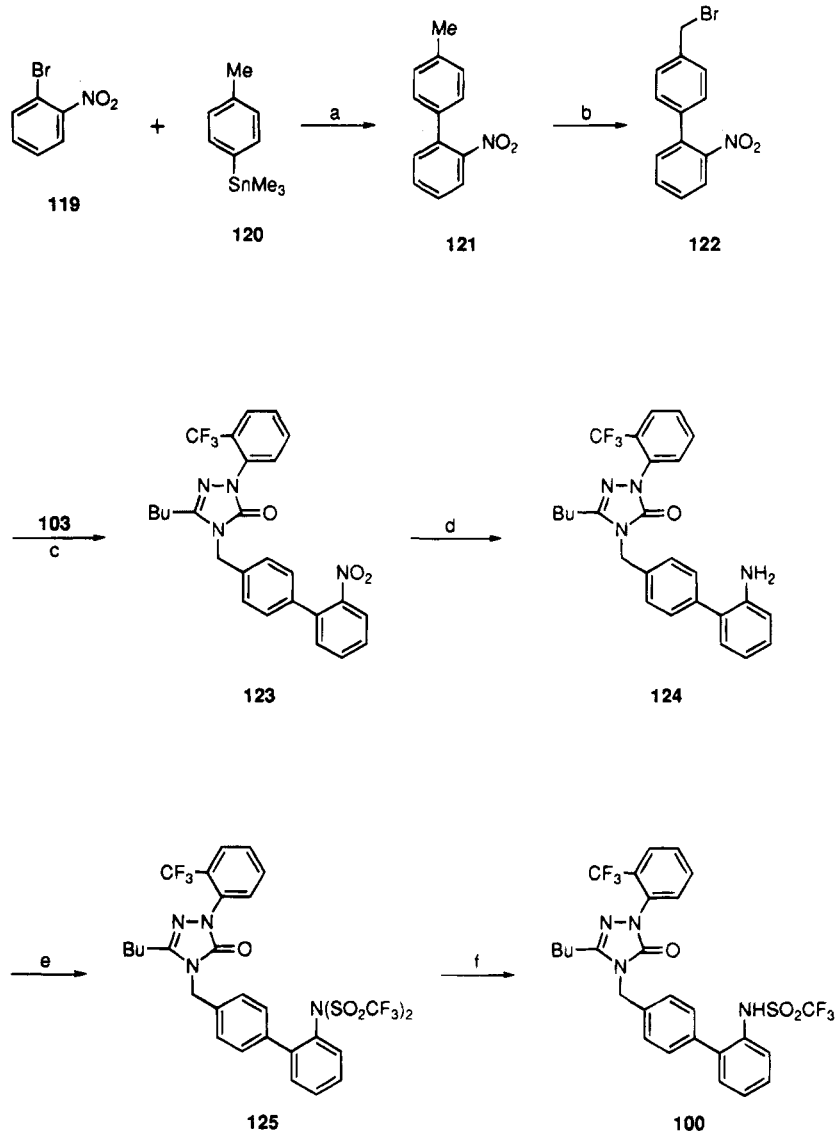
Compounds were evaluated as AII antagonists by competition with [^{125}I]Sar^{1}Ile^8-AII at the rabbit aorta AT_1 receptor and the rat midbrain AT_2 receptor.[35]

AT_1 Receptor. Initial rangefinding studies focused on key variations at N^2 and C^5 of the triazolinone, as well as the acylsulfonamide moiety (Table 1). With *n*-butyl at C^5 and 2-chlorophenyl at N^2, intermediates **3** and **4**, which would not be ionized under the assay conditions, had very weak receptor binding affinity. In contrast, the derivative rendered acidic by acylation on the sulfonamide with benzoyl (**5**) was a potent AT_1 antagonist with an IC_{50} value of approximately 1 nM, an improvement of roughly 3 orders of magnitude compared to **3** and **4**. The AT_1 binding affinity of **5** exceeded not only that of losartan (**1a**) but also that of its active metabolite EXP3174 (**1b**). Although the *N*-acetylsulfonamide **6** was 1 order of magnitude less potent than **5**, the trifluoroacetyl analogue **7** fully overcame this deficit. This may reflect either the increased lipophilicity or increased acidity of **7** compared to **6**. Replacement of 2-chlorophenyl by 2,6-dichlorophenyl at N^2 (**8**) had a somewhat detrimental effect on AT_1 affinity. Reduced potency upon incorporation of this bulkier, more sterically constrained group had also been observed in the biphenylyltetrazole series.[24] The 2-(trifluoromethyl)phenyl group, preferred at N^2 in the tetrazole series (cf. **2**), was again favored here. Indeed, the benzoylsulfonamide **9** had a subnanomolar IC_{50} value that surpassed the potency of the corresponding tetrazole **2**. As in the tetrazole series, triazolinones with alkyl groups at N^2 of the heterocycle (**10, 11**) were less effective than their counterparts with *ortho*-substituted phenyl at the 2-position.

Shortening the *n*-butyl side chain at C^5 of the triazolinone ring to *n*-propyl (**12**) decreased AT_1 potency by 30-fold. Another *n*-propyl derivative (**13**), with a (cyclopropylcarbonyl)sulfonamide acidic group, also suffered a loss in potency by 1 order of magnitude compared to its *n*-butyl homologue (**73**, Table 5). A similar trend for propyl vs butyl was observed in the tetrazole series.[24] Two additional butyl replacements (**14, 15**) were designed in part to diminish the potential for oxidative metabolism of the 5-alkyl side chain. Compared to **9**, substitution of 4,4,4-trifluorobutyl at C^5 in **14** was detrimental to binding affinity. A conformationally constrained side chain, (2-methylcyclopropyl)methyl in **15**, also proved to be an unsatisfactory replacement for *n*-butyl.

As the above study (combined with preliminary *in vivo* results) suggested that 2-(trifluoromethyl)phenyl at N^2 and *n*-butyl at C^5 were optimum substituents on the triazolinone ring, further investigations concentrated almost exclusively on variations of the sulfonamide moiety. The effects of substitution on the benzoylsulfonamide group are illustrated in Table 2. The unsubstituted benzoyl derivative **9** (L-159,913) displayed excellent AT_1 potency (IC_{50} 0.43 nM). Introduction of halogen at the *ortho*-position (**16, 18, 24**) resulted in equal or improved potency at the AT_1 receptor. Even with 4,4,4-trifluorobutyl replacing butyl at C^5, the (2-chlorobenzoyl)sulfonamide **19** maintained excellent AT_1 affinity. This is in contrast to the results described

Scheme 5[a]

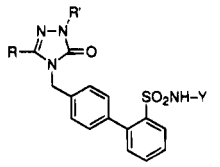


[a] (a) $(Ph_3P)_2PdCl_2$, DMF, 110 °C; (b) Br_2, CCl_4, *hν*, Δ; (c) NaH, DMF, 50 °C; (d) $SnCl_2$, concentrated HCl, THF; (e) $(CF_3SO_2)_2O$, pyridine; (f) NaOH, MeOH/H_2O.

above for the benzoylsulfonamide **14**. Chloro substitution at the *meta*- or *para*-positions (**20, 21**) gave less effective compounds. However, both the 2,3-dichloro (**22**) and 2,5-dichloro (**23**) derivatives had subnanomolar AT_1 potency. As in the case of the halogens, trifluoromethyl was very effective at the 2-position of the benzoyl (**25**) but was detrimental at the 3-position (**26**) and 4-position (**27**). Although a 2-methyl group (**28**) was well tolerated, 2,6-dimethyl (**29**) was quite unfavorable, suggesting sensitivity of the AT_1 receptor to steric crowding near the carbonyl group. Still, monosubstitution at the *ortho*-position with bulky groups such as phenyl (**30**) or benzyl (**31**) was consistent with good binding, although somewhat inferior to that of the parent compound **9**. Methoxy substitution at the 2-position (**32**) had a neutral effect compared to **9**, and a 4-methoxy group (**33**) was nearly as good. However, a 3,4,5-trimethoxy derivative (**34**) was the least potent of all the aroylsulfonamides tested. This may suggest further steric limitations of the acyl moiety. It is of interest that the 4-cyano derivative **35** was equivalent in potency to the 4-methoxy derivative **33**, despite the opposite electronic effects of these substituents. Both were significantly more effective than the 4-(trifluoromethyl) analogue **27**, implying that the lipophilicity of the CF_3 group rather than its electron withdrawal may be responsible for the deleterious influence of this substituent at the 4-position. Overall, improved AT_1 potency relative to **9** was obtained only by introduction of a small halogen (**16, 18**) or trifluoromethyl (**25**) at the 2-position of the benzoyl group.

Numerous heteroaroyl analogues of **9** were investigated (Table 3). The 2-furoyl (**36**–**41**) and benzofuran-2-ylcarbonyl (**42, 43**) derivatives, including those bearing additional substituents, were at least as potent as the benzoyl analogue **9** in the rabbit aorta AT_1 receptor assay. The 3-furoyl derivatives **44**–**47** were, in general, less active than the 2-furoyl analogues. Still, affinity could be enhanced by appropriate substitution on the furan ring of **44**, and the 5-methyl-2-(trifluoromethyl)-3-furoyl derivative **47** was among the most potent of the acylsulfonamides. If the polar oxygen atom of the 3-furoyl group interacts unfavorably with the receptor, the lipophilic and modestly bulky trifluoromethyl substituent may contribute to binding not only by direct interaction but also by shielding the oxygen.

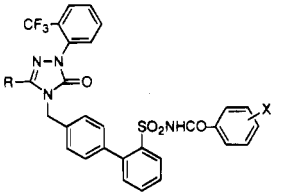
Table 1. Physical Properties and *in Vitro* AII Antagonist Potencies of Triazolinone Acylsulfonamides (and Precursors) Varied at N^2 and C^5



no.	R	R'	Y	method[a]	% yield	mp, °C	formula[b]	IC_{50}, nM: AT_1 (rabbit aorta)	IC_{50}, nM: AT_2 (rat midbrain)
1a	(losartan)							40[c]	74000
1b	(EXP3174)							2.8[c]	>50000
2	*n*-Bu	2-CF_3Ph	(tetrazole)[d]					0.78	23000
3	*n*-Bu	2-ClPh	*t*-Bu	A	76	glass	$C_{29}H_{33}ClN_4O_3S$	1300	11000
4	*n*-Bu	2-ClPh	H	B	89	83–85	$C_{25}H_{25}ClN_4O_3S$	820	24000
5	*n*-Bu	2-ClPh	COPh	C	60	108–109	$C_{32}H_{29}ClN_4O_4S{\cdot}1.3H_2O$	1.4	590
6	*n*-Bu	2-ClPh	$COCH_3$	D	84	105–107	$C_{27}H_{27}ClN_4O_4S{\cdot}0.33H_2O$	13	>1000
7	*n*-Bu	2-ClPh	$COCF_3$	C[e]	43	163–166	$C_{27}H_{24}ClF_3N_4O_4S$	1.1	450
8	*n*-Bu	2,6-Cl_2Ph	COPh	C	60	112–114	$C_{32}H_{28}Cl_2N_4O_4S$	2.6	500
9	*n*-Bu	2-CF_3Ph	COPh	C; D	75; 85	91–93	$C_{33}H_{29}F_3N_4O_4S{\cdot}0.33CH_2Cl_2$	0.43	300
10	*n*-Bu	$CHMe_2$	COPh	C	69	113–115	$C_{29}H_{32}N_4O_4S{\cdot}H_2O$	7.0	4600
11	*n*-Bu	CH_2CMe_3	COPh	D	92	93–95	$C_{31}H_{36}N_4O_4S{\cdot}0.25CH_2Cl_2$	3.3	2300
12	*n*-Pr	2-CF_3Ph	COPh	D	96	103–105	$C_{32}H_{27}F_3N_4O_4S$	13	520
13	*n*-Pr	2-CF_3Ph	CO(c-Pr)	D	94	210–212	$C_{29}H_{27}F_3N_4O_4S$	18	410
14	$CF_3(CH_2)_3$	2-CF_3Ph	COPh	D	47	197–199	$C_{33}H_{26}F_6N_4O_4S$	5.5	>300
15	(2-Me-c-Pr)CH_2	2-CF_3Ph	COPh	D	64	123–125	$C_{34}H_{29}F_3N_4O_4S{\cdot}1.25H_2O$	5.8	500

[a] A, **103**, NaH, **104**; B, TFA; C, RCOCl, pyridine; D, RCO_2H, CDI, DBU; E, **110**, NaH, RI. See the Experimental Section for detailed description of general methods. [b] Characterized by analyses for C, H, and N within ±0.4% or by high resolution FAB-MS within ±5 mmu. [c] Data from Ashton, W. T.; Hutchins, S. M.; Greenlee, W. J.; Doss, G. A.; Chang, R. S. L.; Lotti, V. J.; Faust, K. A.; Chen, T.-B.; Zingaro, G. J.; Kivlighn, S. D.; Siegl, P. K. S. Nonpeptide Angiotensin II Antagonists Derived from 1*H*-Pyrazole-5-carboxylates and 4-Aryl-1*H*-imidazole-5-carboxylates. *J. Med. Chem.* **1993**, *36*, 3595–3605. [d] SO_2NH-Y replaced by 1*H*-tetrazol-5-yl. [e] Acid anhydride used for acylation.

Table 2. Physical Properties and *in Vitro* AII Antagonist Potencies of Triazolinone Aroylsulfonamides

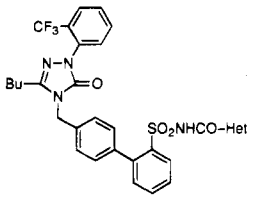


no.	R	X	method[a]	% yield	mp, °C	formula[b]	IC_{50}, nM: AT_1 (rabbit aorta)	IC_{50}, nM: AT_2 (rat midbrain)
9	*n*-Bu	H	(see Table I)				0.43	300
16	*n*-Bu	2-F	D	67	98–100	$C_{33}H_{28}F_4N_4O_4S{\cdot}0.25H_2O$	0.13	53
17	*n*-Bu	4-F	C	93	120–122	$C_{33}H_{28}F_4N_4O_4S{\cdot}H_2O$	0.68	500
18	*n*-Bu	2-Cl	D	60	168–170	$C_{33}H_{27}ClF_3KN_4O_4S$[c]	0.11	36
19	$CF_3(CH_2)_3$	2-Cl	D	24	93–96	$C_{33}H_{25}ClF_6N_4O_4S$	0.36	910
20	*n*-Bu	3-Cl	D	83	173–175	$C_{33}H_{28}ClF_3N_4O_4S$	2.4	150
21	*n*-Bu	4-Cl	D	48	166–168	$C_{33}H_{28}ClF_3N_4O_4S$	1.2	520
22	*n*-Bu	2,3-Cl_2	D	37	>120 (gradual)	$C_{33}H_{27}Cl_2F_3N_4O_4S{\cdot}H_2O$	0.72	780
23	*n*-Bu	2,5-Cl_2	D	83	142–145	$C_{33}H_{27}Cl_2F_3N_4O_4S$	0.48	26
24	*n*-Bu	2-Br	D	83	90–93	$C_{33}H_{28}BrF_3N_4O_4S{\cdot}0.25H_2O$	0.40	45
25	*n*-Bu	2-CF_3	D	35	197–199	$C_{34}H_{28}F_6N_4O_4S{\cdot}0.25H_2O$	0.27	220
26	*n*-Bu	3-CF_3	D	85	163–165	$C_{34}H_{28}F_6N_4O_4S$	3.3	580
27	*n*-Bu	4-CF_3	D	45	176–178	$C_{34}H_{28}F_6N_4O_4S$	3.8	1400
28	*n*-Bu	2-Me	D	87	93–95	$C_{34}H_{31}F_3N_4O_4S$	0.56	110
29	*n*-Bu	2,6-Me_2	D	19	113–115	$C_{35}H_{33}F_3N_4O_4S$	5.9	190
30	*n*-Bu	2-Ph	D	33	104–106	$C_{39}H_{33}F_3N_4O_4S$	0.60	330
31	*n*-Bu	2-CH_2Ph	D	91	216–218	$C_{40}H_{35}F_3N_4O_4S$	0.82	190
32	*n*-Bu	2-OMe	D	68	68–70	$C_{34}H_{31}F_3N_4O_5S$	0.41	72
33	*n*-Bu	4-OMe	D	30	130–132	$C_{34}H_{31}F_3N_4O_5S{\cdot}H_2O$	0.74	500
34	*n*-Bu	3,4,5-$(OMe)_3$	D	47	153–155	$C_{36}H_{35}F_3N_4O_7S$	21	6500
35	*n*-Bu	4-CN	D	64	193–195	$C_{34}H_{28}F_3N_5O_4S{\cdot}1.5H_2O$	0.76	400

[a] C, RCOCl, pyridine; D, RCO_2H, CDI, DBU. See the Experimental Section for detailed description of general methods. [b] Characterized by analyses for C, H, and N within ±0.4% or by high-resolution FAB-MS within ±5 mmu. [c] Potassium salt.

(Thiophene-2-ylcarbonyl)sulfonamides **48–54**, like their furan analogues, were highly potent AT_1 antagonists, particularly the 3-chlorothiophene (**51**) and benzothiophene (**54**) derivatives (IC_{50} ~0.3 nM). Also similar to the furans, thiophenes linked through the 3-position (**55–57**) tended to be less potent than their 2-linked isomers. Again, this could be remedied by appending suitable substituents, as in the case of the

Table 3. Physical Properties and *in Vitro* AII Antagonist Potencies of Triazolinone Heteroaroylsulfonamides



no.	Het	% yield[a]	mp, °C	formula[b]	IC_{50}, nM: AT_1 (rabbit aorta)	IC_{50}, nM: AT_2 (rat midbrain)
36	furan-2-yl	59	194–195	$C_{31}H_{27}F_3N_4O_5S$	0.26	120
37	3-Me-furan-2-yl	52	>95 (gradual)	$C_{32}H_{29}F_3N_4O_5S{\cdot}0.2H_2O{\cdot}0.3Et_2O$	0.21	46
38	5-Me-furan-2-yl[c]	74	210–211	$C_{32}H_{29}F_3N_4O_5S$	0.40	150
39	3,5-Me_2-furan-2-yl[c]	32	110–112	$C_{33}H_{31}F_3N_4O_5S{\cdot}0.6H_2O$	0.22	55
40	5-Br-furan-2-yl	78	>125 (gradual)	$C_{31}H_{26}BrF_3N_4O_5S{\cdot}H_2O$	0.40	170
41	3,4-Cl_2-furan-2-yl	66	>140 (gradual)	$C_{31}H_{25}Cl_2F_3N_4O_5S{\cdot}0.5CH_2Cl_2$	0.19	25
42	benzo[*b*]furan-2-yl	74	124–127	$C_{35}H_{29}F_3N_4O_5S{\cdot}H_2O{\cdot}0.2Et_2O$	0.17	160
43	3-Me-benzo[*b*]furan-2-yl	81	103–106	$C_{36}H_{31}F_3N_4O_5S$	0.43	130
44	furan-3-yl	45	125–127	$C_{31}H_{27}F_3N_4O_5S$	3.9	700
45	2-Me-furan-3-yl	87	154–157	$C_{32}H_{29}F_3N_4O_5S{\cdot}0.75H_2O$	3.0	110
46	2,5-Me_2-furan-3-yl	89	220–223	$C_{33}H_{31}F_3N_4O_5S{\cdot}0.75H_2O$	1.0	310
47	5-Me-2-CF_3-furan-3-yl	60	218–219	$C_{33}H_{28}F_6N_4O_5S$	0.17	60
48	thiophene–2–yl	74	>110 (gradual)	$C_{31}H_{27}F_3N_4O_4S_2$	0.94	540
49	3-Me-thiophene–2–yl	40	>145 (gradual)	$C_{32}H_{29}F_3N_4O_4S_2{\cdot}1.5H_2O{\cdot}0.5CH_2Cl_2$	0.81	80
50	5-Me-thiophene–2–yl	72	>125 (gradual)	$C_{32}H_{29}F_3N_4O_4S_2{\cdot}0.25CH_2Cl_2$	0.64	190
51	3-Cl-thiophene–2–yl	61	>200 (gradual)	$C_{31}H_{25}ClF_3KN_4O_4S_2{\cdot}0.3Et_2O$[d]	0.27	30
52	5-Cl-thiophene–2–yl	84	>125 (gradual)	$C_{31}H_{26}ClF_3N_4O_4S_2{\cdot}0.5H_2O$	1.3	260
53	3-Br-thiophene–2–yl	70	>200 (gradual)	$C_{31}H_{26}BrF_3N_4O_4S_2{\cdot}1.2H_2O$	0.72	43
54	benzo[*b*]thiophene–2–yl	50	177–179	$C_{35}H_{29}F_3N_4O_4S_2{\cdot}0.4CH_2Cl_2$	0.31	430
55	thiophene–3–yl	40	123–126	$C_{31}H_{27}F_3N_4O_4S_2$	5.0	300
56	2,5-Cl_2-thiophene–3–yl	58	>130 (gradual)	$C_{31}H_{25}Cl_2F_3N_4O_4S_2{\cdot}0.7CH_2Cl_2$	2.6	87
57	2,5-Br_2-thiophene–3–yl	59	>165 (gradual)	$C_{31}H_{25}Br_2F_3N_4O_4S_2{\cdot}H_2O$	0.67	84
58	1-Me-pyrrol-2-yl	67	>115 (gradual)	$C_{32}H_{30}F_3N_5O_4S$	1.6	500
59	4-Me-oxazol-5-yl	72	>155 (gradual)	$C_{31}H_{28}F_3N_5O_5S{\cdot}H_2O{\cdot}0.4CH_2Cl_2$	1.1	35
60	2-Cl-pyridin-3-yl	74	>130 (gradual)	$C_{32}H_{27}ClF_3N_5O_4S{\cdot}1.4H_2O$	1.0	520

[a] All compounds prepared by method D (RCO_2H, CDI, DBU). See the Experimental Section for detailed description. [b] Characterized by analyses for C, H, and N within ±0.4% or by high-resolution FAB-MS within ±5 mmu. [c] RCO_2H prepared according to Knight, D. W.; Nott, A. P. The Generation and Chemistry of Dianions Derived from Furancarboxylic Acids. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1125–1131. [d] Potassium salt.

2,5-dibromo derivative **57**. Investigated as isosteres of 3-methyl-2 furoyl (**37**), the pyrrole (**58**) and oxazole (**59**) derivatives were less potent at the AT_1 receptor. Similarly, **60**, a pyridine isostere of the 2-chlorobenzoyl compound **18**, had reduced binding affinity. Thus, among heteroaroyl analogues, only certain furan and thiophene derivatives compared favorably with the best of the aroylsulfonamides in the AT_1 receptor binding assay.

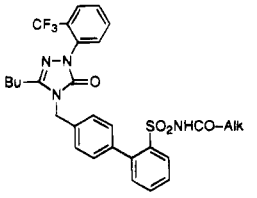
Alkanoylsulfonamides and their relatives were also evaluated (Table 4). Although no compounds prepared in this series matched the AT_1 potency of the benzoylsulfonamide **9**, several derivatives, such as trifluoroacetyl (**61**), isobutyryl (**62**), pivaloyl (**63**), *tert*-butylacetyl (**64**), and 3-cyclopentylpropionyl (**66**), had aorta IC_{50} values of approximately 1 nM. The alkanoyl moiety appeared to be relatively insensitive to size and substitution. Groups as large as octanoyl (**65**) and diphenylacetyl (**68**) or as small as trifluoroacetyl (**61**) spanned only a 4-fold range of AT_1 potency. No particularly striking effects could be attributed to the presence of a carboxylic acid (**69**), a basic amine (**70**), or an ether functional group (**71, 72**).

Many analogues of **9** bearing (cycloalkylcarbonyl)-sulfonamide groups (Table 5) had IC_{50} <1 nM against the rabbit aorta AT_1 receptor. Among unsubstituted cycloalkyl congeners (**73–77**), optimum ring size for AT_1 affinity was cyclohexyl (**76**). In fact, **76** was approximately 3-fold more potent than its aromatic counterpart **9**. Although cyclopropyl itself (**73**) was less potent on the AT_1 receptor than analogues with larger rings, introduction of one or more small, hydrophobic substituents, especially at the 2-position of the cyclopropane ring, led to AT_1 antagonists comparable in potency to **9**. Examples include 2-methyl (**79**), (*S*)-2,2-dimethyl (**80**), 2,2-difluoro (**82**), and 2,2-dichloro-1-methyl (**83**). However, simultaneous substitution with multiple groups at the 2- and 3-positions apparently creates an unfavorable steric environment, as evidenced by the weaker AT_1 affinity of the 2,2,3,3-tetramethyl compound **81**. The bicyclic 2-norbornanylcarbonyl derivative **84** was among the most potent of the cycloalkyl series.

A few saturated rings containing one or more heteroatoms were also examined (**85–88**). Compared to cyclopentylcarbonyl (**75**), the introduction of an oxygen atom into the ring (**85, 86**) clearly had a negative impact on AT_1 potency. In contrast, the dithiolanylcarbonyl derivatives **87, 88** had excellent affinity for the AT_1 receptor. Whether the superiority of the dithiolane ring system over that of the tetrahydrofuran reflects the greater lipophilicity of the former or steric/conformational effects is unknown.

In addition to the acylsulfonamide tetrazole replacements, several other types of sulfonamides bearing electron-withdrawing substituents to enhance acidity were investigated (Table 6). The first class consisted of the sulfonylcarbamates [(alkoxycarbonyl)sulfonamides] **89–92**. Several of these were comparable to **9**

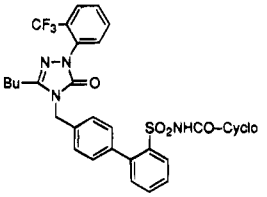
Table 4. Physical Properties and *in Vitro* AII Antagonist Potencies of Triazolinone Alkanoylsulfonamides and Related Derivatives



no.	Alk	method[a]	% yield	mp, °C	formula[b]	IC_{50}, nM: AT_1 (rabbit aorta)	IC_{50}, nM: AT_2 (rat midbrain)
61	CF_3	C[c]	29	125–127	$C_{28}H_{24}F_6N_4O_4S$	0.80	400
62	$CHMe_2$	D	61	93–95	$C_{30}H_{31}F_3N_4O_4S{\cdot}0.5H_2O$	0.80	150
63	CMe_3	D	86	176–178	$C_{31}H_{33}F_3N_4O_4S$	1.3	160
64	CH_2CMe_3	D	80	94–96	$C_{32}H_{35}F_3N_4O_4S$	1.1	46
65	$(CH_2)_6Me$	D	85	glass	$C_{34}H_{39}F_3N_4O_4S{\cdot}0.5H_2O$	2.9	450
66	$(CH_2)_2$-c-Pn	C	62	glass	$C_{34}H_{37}F_3N_4O_4S$	1.2	720
67	CH_2Ph	D	63	171–173	$C_{34}H_{31}F_3N_4O_4S$	1.6	240
68	$CHPh_2$	C	73	144–146	$C_{40}H_{35}F_3N_4O_4S$	2.8	320
69	$(CH_2)_3CO_2H$	D + E	22[d]	glass	$C_{31}H_{31}F_3N_4O_6S$	5.5	1500
70	$(CH_2)_5NH_2$	D + B	50[d]	138–140	$C_{32}H_{36}F_3N_5O_4S$	1.3	100
71	CH_2OEt	D	39	151–152	$C_{30}H_{31}F_3N_4O_5S{\cdot}0.1H_2O$	0.75	380
72	$(CH_2)_2OMe$	D	76	>65 (gradual)	$C_{30}H_{31}F_3N_4O_5S{\cdot}0.5H_2O$	2.0	270

[a] B, TFA; C, RCOCl, pyridine; D, RCO_2H, CDI, DBU; E, NaOH. See the Experimental Section for detailed description of general methods. [b] Characterized by analyses for C, H, and N within ±0.4% or by high-resolution FAB-MS within ±5 mmu. [c] Acid anhydride used for acylation. [d] Overall yield for two steps.

Table 5. Physical Properties and *in Vitro* AII Antagonist Potencies of Triazolinone (Cycloalkylcarbonyl)sulfonamides and Related Derivatives

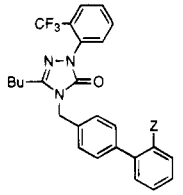


no.	Cyclo[a]	method[b]	% yield	mp, °C	formula[c]	IC_{50}, nM: AT_1 (rabbit aorta)	IC_{50}, nM: AT_2 (rat midbrain)
73	c-Pr	C	51	187–189	$C_{30}H_{29}F_3N_4O_4S{\cdot}0.25H_2O$	1.5	110
74	c-Bu	D	88	184–185	$C_{31}H_{31}F_3N_4O_4S{\cdot}0.05CHCl_3$	0.84	100
75	c-Pn	D	89	95–97	$C_{32}H_{33}F_3N_4O_4S{\cdot}0.2H_2O$	0.32	82
76	c-Hx	D	74	101–103	$C_{33}H_{35}F_3N_4O_4S$	0.15	160
77	c-Hp	D	69	246–249	$C_{34}H_{37}F_3N_4O_4S$	0.30	270
78	1-Me-c-Pr	D	89	193–195	$C_{31}H_{31}F_3N_4O_4S{\cdot}0.25H_2O$	0.80	76
79	2-Me-c-Pr (*cis/trans*, *RS*)	D	64	94–96	$C_{31}H_{31}F_3N_4O_4S$	0.56	120
80	2,2-Me_2-c-Pr (*S*)	D	74	93–95	$C_{32}H_{33}F_3N_4O_4S{\cdot}0.25H_2O$	0.36	220
81	2,2,3,3-Me_4-c-Pr	D	92	97–100	$C_{34}H_{37}F_3N_4O_4S$	3.3	130
82	2,2-F_2-c-Pr (*RS*)	D	42	178–180	$C_{30}H_{27}F_3N_4O_4S$	0.64	86
83	2,2-Cl_2-1-Me-c-Pr (*RS*)	D	40	189–191	$C_{31}H_{29}Cl_2F_3N_4O_4S$	0.37	120
84	2-norbornyl (*exo*, *RS*)	D	24	89–92	$C_{34}H_{35}F_3N_4O_4S$	0.39	100
85	tetrahydrofuran-2-yl (*RS*)	D	70	149–151	$C_{31}H_{31}F_3N_4O_6S{\cdot}0.5H_2O$	4.3	180
86	tetrahydrofuran-3-yl (*RS*)	D	56	154–155	$C_{31}H_{31}F_3N_4O_5S{\cdot}0.5H_2O$	2.8	280
87	1,3-dithiolan-2-yl	D	82	>75 (gradual)	$C_{30}H_{29}F_3N_4O_4S_3{\cdot}0.5H_2O$	0.35	35
88	2-Me-1,3-dithiolan-2-yl	D[d]	61	>75 (gradual)	$C_{31}H_{31}F_3N_4O_4S_3$	0.22	80

[a] c-Pr, cyclopropyl; c-Bu, cyclobutyl; c-Pn, cyclopentyl; c-Hx, cyclohexyl; c-Hp, cycloheptyl. [b] C, RCOCl, pyridine; D, RCO_2H, CDI, DBU. See the Experimental Section for detailed description. [c] Characterized by analytes for C, H, and N within ±0.4% or by high-resolution FAB-MS within ±5 mmu. [d] For preparation of RCO_2H, see: Minamida, I.; Ikeda, Y.; Uneyama, K.; Tagaki, W.; Oae, S. Acid Dissociation, UV spectra and Hydrolyses of Several α-Mercapto- and α-Alkoxyacetic Acids and their Ethyl Esters. *Tetrahedron* **1968**, *24*, 5293–5309.

in the AT_1 assay. The sulfonylureas (carbamoylsulfonamides) **93, 94** had reasonably good binding affinity. However, a comparison of the isosteric compounds **64**, **92**, and **94** suggests an intrinsic AT_1 potency order of sulfonylcarbamate > acylsulfonamide > sulfonylurea. Two disulfimides (sulfonylsulfonamides), **95, 96**, had exceptionally low AT_1 IC_{50} values (≤0.2 nM). The diminished potency of the cyanosulfonamide **97** may reflect the lack of a hydrophobic component in this functional group. It was hoped that attachment of the sulfonamide nitrogen to an electron-withdrawing heterocycle or aromatic ring might provide sufficient acidity to mimic the acylsulfonamides. Representative of a limited investigation along these lines, the benzoxazolylsulfonamide **99** was a moderately effective AT_1 antagonist. In contrast, the (*p*-nitrophenyl)sulfonamide **98** was particularly poor, suggesting that the pK_a of this derivative may be too high or that the positioning of the nitrophenyl group results in an unfavorable contact with the receptor. A compound with reversed sulfonamide orientation, the triflamide **100**, maintained relatively good potency against the AT_1 receptor. Other investiga-

Table 6. Physical Properties and *in Vitro* AII Antagonist Potencies of Miscellaneous Triazolinone Sulfonamide Derivatives



						IC_{50}, nM	
no.	Z	method[a]	% yield	mp, °C	formula[b]	AT_1 (rabbit aorta)	AT_2 (rat midbrain)
89	SO_2NHCO_2Et	F	43	79–81	$C_{29}H_{29}F_3N_4O_5S$	2.2	75
90	SO_2NHCO_2n-Bu	F	37	67–69	$C_{31}H_{33}F_3N_4O_5S$	0.59	190
91	SO_2NHCO_2i-Bu	F	31	171–173	$C_{31}H_{33}F_3N_4O_5S$	0.42	170
92	SO_2NHCO_2t-Bu	G	31	140–142	$C_{31}H_{33}F_3N_4O_5S$	0.45	17
93	$SO_2NHCONHi$-Pr	H	41	78–80	$C_{30}H_{32}F_3N_5O_4S$	1.1	300
94	$SO_2NHCONHt$-Bu	H	9	79–82	$C_{31}H_{34}F_3N_5O_4S$	2.6	130
95	SO_2NHSO_2i-Pr	I	15	glass	$C_{29}H_{31}F_3N_4O_5S_2$	0.16	3600
96	SO_2NHSO_2Ph	I	23	89–90	$C_{32}H_{29}F_3N_4O_5S_2$	0.20	2400
97	SO_2NHCN	J	9	187–190	$C_{27}H_{24}F_3N_5O_3S$	4.7	>1000
98	$SO_2NH(4\text{-}NO_2\text{-}Ph)$	K	43	186–187	$C_{32}H_{28}F_3N_5O_5S$	78	5200
99	SO_2NH(benzoxazol-2-yl)	L	57	109–111	$C_{33}H_{28}F_3N_5O_4S$	5.2	700
100	$NHSO_2CF_3$	M	63	168–170	$C_{27}H_{24}F_6N_4O_3S$	1.8	5500

[a] F, ROCOCl, NaH; G, $(Boc)_2O$, NaH; H, RNCO, Et_3N; I, RSO_2Cl, NaH; J, BrCN, $Na(TMS)_2$; K, ArF, NaH; L, *o*-aminophenol, NaH; M, Tf_2O, pyridine, then NaOH. See the Experimental Section for detailed description of general methods. [b] Characterized by analyses for C, H, and N within ±0.4% or by high-resolution FAB-MS within ±5 mmu.

tors have also reported the effectiveness of triflamide as a tetrazole replacement in AII antagonists.[20]

AT_2 Receptor. Many of the acylsulfonamides in the initial range-finding set (Table 1) bound to the rat midbrain AT_2 receptor with submicromolar IC_{50} values. The benzoylsulfonamide **9** displayed approximately an 80-fold increase in AT_2 affinity relative to the corresponding tetrazole **2**. Marked enhancement of AT_2 binding upon replacement of tetrazole by a lipophilic acylsulfonamide has also been observed in other heterocyclic series.[21] Further improvements in AT_2 potency were obtained upon introduction of a halogen at the 2-position of the benzoyl group (**16, 18, 24** in Table 2). Other small *ortho*-substituents led to somewhat lesser enhancements (**28, 32**). Although AT_2 structure–activity relationships sometimes paralleled those at AT_1, at other times there was considerable divergence between the two receptor subtypes. For example, the 2,3-dichlorobenzoyl (**22**) and 2,5-dichlorobenzoyl (**23**) derivatives had similar AT_1 affinity, but the 2,5-dichloro compound was 30-fold more effective as an AT_2 antagonist. In the case of **19**, the 4,4,4-trifluorobutyl modification at C^5 of the heterocycle was very detrimental to AT_2 potency (cf. **18**), in contrast to a modest AT_1 effect.

Several of the 5-membered heteroarylsulfonamides (Table 3) had AT_2 IC_{50} values <50 nM. All of these (**37, 41, 51, 53, 59**) possessed a small or medium-sized lipophilic substituent adjacent to the carbonyl group. This trend followed that of the aroylsulfonamides (Table 2). In view of the poor AT_2 results obtained with the 2,3-dichlorobenzoyl derivative **22**, as discussed above, it is somewhat surprising that the analogously substituted 3,4-dichloro-2-furoyl derivative **41** was especially effective in the midbrain assay.

Among the alkanoylsulfonamides (Table 4), only the *tert*-butylacetyl derivative **64** had an AT_2 IC_{50} <50 nM. In this series, AT_2 binding affinity varied over a wider range than that of AT_1, with the carboxy-subtituted derivative **69** having the poorest AT_2 activity. In the (cycloalkylcarbonyl)sulfonamide series (Table 5), AT_2 potency displayed a modest preference for the smaller carbocyclic ring sizes. No marked improvements were observed upon ring substitution. The 35 nM AT_2 IC_{50} for the dithiolanylcarbonyl derivative **87** was one of the lowest of all the acylsulfonamides.

The *tert*-butyl sulfonylcarbamate **92** (Table 6) had an exceptionally low IC_{50} (17 nM) against the AT_2 receptor. This represents a further 18-fold improvement in AT_2 potency relative to the benzoylsulfonamide **9**. Extending the alkyl group linearly beyond two carbon atoms, as in **90** and **91**, appeared to be unfavorable for AT_2 binding. The sulfonylurea **94** was 8-fold less potent on AT_2 than the isosteric sulfonylcarbamate **92**. Compounds in Table 6 bearing other classes of tetrazole replacements generally had weak affinity for the AT_2 receptor.

***In Vitro* Summary.** Compared to the corresponding tetrazole analogue **2**, the best of the sulfonamide derivatives were 4–7-fold more potent at the AT_1 receptor but 3 orders of magnitude more potent at the AT_2 receptor. For AT_1 binding affinity, the relatively subtle effects of the *N*-acyl (or analogous) group might be interpreted in terms of conformational effects influencing the presentation of the delocalized sulfonamide anion to the receptor surface. In the case of AT_2 binding, however, a discrete interaction of the lipophilic *N*-acyl (or similar) moiety with the receptor may be postulated. This kind of hydrophobic interaction would not be possible for the tetrazole analogue **2**.

In Vivo Pharmacology

Many of the triazolinone sulfonamides were evaluated as inhibitors of the pressor response to exogenous AII.[35b,36] A standard initial protocol consisted of administration of the test compound (in the form of the water-soluble potassium salt) intravenously at 1 mg/kg in conscious, normotensive rats. Compounds showing promise were subjected to more extensive *in vivo* testing, including oral dosage and, in some cases, the use of conscious rhesus monkey and/or dog models.

The benzoylsulfonamide **9** (L-159,913) was shown previously to have a longer duration of action than that

of the corresponding tetrazole **2** (3.5 h vs 1.5 h, respectively, at 1 mg/kg iv in the rat).[1] Thus, compound **9** became the benchmark compound for evaluation of other sulfonamide variations. Binding affinity in the radioligand assay did not necessarily predict efficacy in rats. Some triazolinones with subnanomolar AT_1 IC_{50} values (e.g., **17, 61, 71, 95**) had short duration (<1 h) at the 1 mg/kg iv dose (data not shown). The 2-chlorophenyl analogue **5** corresponding to **9** was inactive at this dose level, despite good potency *in vitro* (AT_1 IC_{50} 1.4 nM). Another 2-chlorophenyl derivative **7** displayed good duration (>4 h) at 1 mg/kg iv but was inactive orally at the same dose.

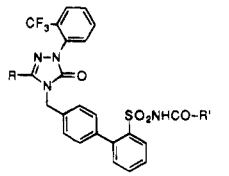
A number of new derivatives with 2-(trifluoromethyl)-phenyl at N^2 were very effective AII antagonists *in vivo*. Compounds demonstrating significant superiority over **9** and/or losartan in the rat model at one or more dose levels iv or po are shown in Table 7. In some cases (for example, **28** and **62**), the long duration of action (>6 h) at 1 mg/kg iv was lost upon oral administration. However, several compounds (**18, 51, 80, 82, 91, 92**) had outstanding activity by both routes. For certain analogues (**51, 64, 82, 91, 92**), good efficacy was demonstrated at 0.3 mg/kg po, a level at which **9** was inactive. The *tert*-butyl sulfonylcarbamate **92** retained activity even at 0.1 mg/kg po. Duration of at least 24 h was observed for the (2-chlorobenzoyl)sulfonamide **18** (at 1 mg/kg iv) and its trifluorobutyl analogue **19** (at 3 mg/kg po). Thus, in this experimental model, triazolinone derivatives superior to **9** emerged from several series: aroyl-, heteroaroyl-, alkanoyl-, and (cycloalkylcarbonyl)-sulfonamides, as well as alkyl sulfonylcarbamates. The antagonism of the AII pressor response in rats by intravenous and oral administration of **18** (L-162,223) is presented graphically in Figure 1.

In the rhesus monkey model, **9** surpassed losartan in efficacy when administered intravenously or orally (Table 8). The relatively short duration of losartan in this species may be attributable to extensive tetrazole glucuronidation and low levels of the active metabolite EXP3174.[25] Among a small number of other triazolinones tested in the monkey, none was markedly superior to **9**. Both **36** and **80**, however, demonstrated more consistent activity at 3 mg/kg po in this model. In conscious dogs (data not tabulated), **9** (1 mg/kg po) blocked the AII pressor response by a maximum of 73% and had a duration exceeding 4 h. Under the same conditions, **80** inhibited the pressor response by 100% and had a duration of >5.5 h. At 0.3 mg/kg po, the respective values for **80** were 66% and 4.5 h, whereas **9** was not active at this dose.

Conclusions

We have prepared and evaluated as angiotensin II antagonists an extensive series of 2,4,5-trisubstituted triazolin-3-ones bearing acidic sulfonamide tetrazole replacements on the biphenyl-4-ylmethyl moiety at N^4. In the triazolinone series, as in the case of imidazoles, quinazolinones, or imidazopyridines,[21] acylsulfonamides proved to be effective tetrazole surrogates. Structure–activity relationships of the substituents on the heterocycle paralleled those observed for our tetrazole-bearing triazolinones.[24] Again, 2-(trifluoromethyl)phenyl at N^2 and *n*-butyl at C^5 of the triazolinone ring appeared optimum for *in vitro* and *in vivo* activity. Subnanomolar

Table 7. Inhibition of AII Pressor Response by Selected Triazolinone Sulfonamide Derivatives in Conscious, Normotensive Rats



no.	R	R'	dose, mg/kg (route)	peak inhib, % (mean ± SEM)[a]	duration,[b] hr (mean ± SEM)[a]	N[c]
1a		(losartan)	1 (iv)	78 ± 6	>6	4
			0.3 (iv)	52 ± 10	5.5 ± 0.5	4
			3 (po)	94 ± 2	>6	4
			1 (po)	58 ± 8	ND	6
9	*n*-Bu		3 (iv)	87 ± 1	>6<24	2
			1 (iv)	73 ± 6	3.5 ± 1.5	2
			0.3 (iv)	31 ± 10	<0.5	2
			1 (po)	65 ± 2	>3.5<24	2
			0.3 (po)	NA	NA	2
18	*n*-Bu		1 (iv)	91 ± 3	>24	4
			1 (po)	85 ± 5	>6<24	4
19	$CF_3(CH_2)_3$		1 (iv)	67 ± 5	2.4 ± 1.2	2
			3 (po)[d]	76 ± 2	≥24	3
28	*n*-Bu		1 (iv)	89 ± 1	>6<24	2
			1 (po)	57 ± 2	≥2	3
36	*n*-Bu		1 (iv)	85 ± 5	>6<24	2
			1 (po)	70 ± 12	3.7 ± 0.7	3
37	*n*-Bu		1 (iv)	92 ± 4	>6<24	2
			1 (po)	71 ± 0	>3.5<24	2
48	*n*-Bu		1 (iv)	76 ± 8	>5.5<24	2
			1 (po)	61 ± 14	4.3 ± 1.8	2
51	*n*-Bu		1 (iv)	90 ± 6	>6<24	2
			0.3 (po)	64 ± 6	>5<24	2
62	*n*-Bu		1 (iv)	100 ± 0	>6<24	2
			1 (po)	45 ± 1	1.3 ± 0	2
64	*n*-Bu		0.3 (po)	69 ± 6	>5.5<24	2
80	*n*-Bu		0.3 (iv)	84 ± 9	>5.5<24	2
			1 (po)	76 ± 4	>6<24	2
82	*n*-Bu		1 (iv)	80 ± 1	>5<24	2
			0.3 (po)	59 ± 6	>4<24	2
91	*n*-Bu		1 (iv)	72 ± 2	>6<24	2
			0.3 (iv)	65 ± 6	>5<24	2
			1 (po)	63 ± 1	>5<24	2
			0.3 (po)	61 ± 7	>3.5<24	2
92	*n*-Bu		1 (iv)	83 ± 2	>6<24	2
			0.3 (iv)	78 ± 6	>4.5<24	3
			0.1 (iv)	76[e]	>4.5<24[e]	1[e]
			1 (po)	87 ± 1	>6<24	2
			0.3 (po)	81 ± 3	≥3.5<24	2
			0.1 (po)	77 ± 6	>3<24	2

[a] NA = not active; ND = not determined. [b] Time from onset of action until significant (i.e., ≥30%) inhibition of pressor response is no longer observed. [c] Number of animals treated. [d] No direct comparison with **9** at this dose, but cf. **9** at 3 mg/kg iv. [e] Results from one animal; inactive in a second animal.

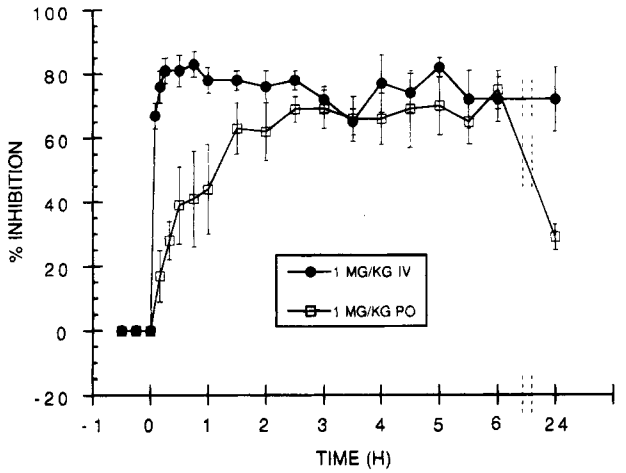


Figure 1. Percent inhibition of AII pressor response in conscious, normotensive rats by triazolinone **18** (L-162,223) at 1 mg/kg iv or po. Results are expressed as mean ± SEM (N = 4).

Table 8. Inhibition of AII Pressor Response by Selected Triazolinone Sulfonamide Derivatives in Conscious, Normotensive Rhesus Monkeys

no.	dose, mg/kg (route)	peak inhib, % (mean ± SEM)[a]	duration,[b] h (mean ± SEM)[a]	N[c]
1a	1 (iv)	78 ± 9	0.6 ± 0.2	3
(losartan)	0.3 (iv)	49 ± 5	0.1 ± 0	4
	10 (po)	50 ± 7	2.1 ± 0.9	3
	3 (po)	NA	NA	4
9	1 (iv)	88 ± 4	>6<24	2
	0.3 (iv)	80 ± 2	5 ± 1[d]	2
	10 (po)	76 ± 5	>4<24	2
	3 (po)	ND[e]	ND[e]	2
36	3 (po)	54 ± 0	4 ± 0.5	2
80	0.3 (iv)	54 ± 0	3.5 ± 1	2

[a] NA = not active; ND = not determined. [b] Time from onset of action until significant (i.e., ≥30%) inhibition of pressor response is no longer observed. [c] Number of animals treated. [d] Duration previously reported (ref 1) as 0.6 h in sodium-replete monkeys. [e] Variable results.

AT_1 IC_{50} values were achieved with a diversity of acylsulfonamides. In particular, N-acyl groups conferring an AT_1 potency advantage included benzoyl (**9**), o-halo- or o-(trifluoromethyl)benzoyl (**16, 18, 24, 25**), variously substituted furoyl (**36–43, 47**) or thiophene-2-ylcarbonyl (**51, 54**), medium-size cycloalkylcarbonyl (**75–77, 84**) or dithiolanylcarbonyl (**87, 88**), and cyclopropylcarbonyl suitably substituted with small, hydrophobic groups (**80, 83**). Some other acidic sulfonamides, such as sulfonylcarbamates (**90–92**) and disulfimides (**95, 96**), were also compatible with potent AT_1 affinity.

Unexpectedly, a number of the sulfonamides showed very significant binding in the AT_2 receptor assay (e.g., AT_2 IC_{50} 17 nM for **92**). Preferred sulfonamide substituents for AT_2 potency enhancement included o-halobenzoyl (**16, 18, 23, 24**), suitably substituted heteroaroyl (**37, 39, 41, 51, 53, 59**), and 1,3-dithiolan-2-ylcarbonyl (**87**), as well as certain compact, branched groups like *tert*-butylacetyl (**64**) and *tert*-butoxycarbonyl (**92**). In such compounds, the N-acyl or N-alkoxycarbonyl substituent on the sulfonamide may contribute substantial binding energy by direct interaction with a hydrophobic region of the AT_2 receptor.

Several of the triazolinone sulfonamides were highly effective inhibitors of the pressor response to exogenous AII in conscious animal models. Although generally inferior to losartan in rats, the benzoylsulfonamide L-159,913 (**9**) compares favorably with losartan in several species.[1] The present study has revealed a number of additional analogues with greatly improved activity in rats. For example, the 2-chlorobenzoyl (**18**), (3-chlorothiophene-2-yl)carbonyl (**51**), *tert*-butylacetyl (**64**), ((*S*)-2,2-dimethylcyclopropyl)carbonyl (**80**), (2,2-difluorocyclopropyl)carbonyl (**82**), isobutoxycarbonyl (**91**), and *tert*-butoxycarbonyl (**92**) sulfonamide derivatives were distinctly superior to **9** in this model. In particular, the efficacy and duration of the (2-chlorobenzoyl)-sulfonamide **18** (L-162,223) and the *tert*-butyl sulfonylcarbamate **92** (L-162,234) were noteworthy.

Although our understanding of the factors involved is far from complete, certain structural features of the acidic sulfonamide moiety in this series are shared by the analogues combining high *in vitro* and *in vivo* potency, good oral activity, and long duration of action. All contain an acylsulfonamide or sulfonylcarbamate that is lipophilic in character, moderate in size, and relatively compact rather than linear in shape. In addition to beneficial effects on AT_1 receptor affinity, these characteristics may be favorable for membrane transport, resistance to metabolism, or other pharmacologically important properties. In many cases, the same structural factors also led to a pronounced augmentation of AT_2 potency (for **92**, more than 1000-fold compared to the tetrazole **2**). We do not attribute any improvements in antihypertensive efficacy to the enhanced AT_2 affinity. For example, the close analogues **91** and **92**, similar in potency at AT_1 but differing by 10-fold at AT_2, were both highly effective in the rat model. Even for **92**, the AT_2/AT_1 IC_{50} ratio is approximately 40. Consequently, it cannot be assumed that AT_2 receptors are blocked to a physiologically significant extent at the dose levels required to inhibit the AII pressor response. Nevertheless, the fortuitous incorporation of considerable AT_2 potency into triazolinone biphenylsulfonamide derivatives with excellent *in vivo* activity has provided a foundation for the development of AT_1/AT_2-balanced AII antagonists. Simultaneous blockade of both receptor subtypes *in vivo* could be of pharmacological, and possibly therapeutic, interest.[8c,37] Our efforts toward this goal will be the subject of future publications.

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. Positive ion fast atom bombardment mass spectra (FAB-MS) were obtained on Varian MAT 731 and JEOL HX110 instruments, and electron-impact mass spectra (EI-MS) were obtained on a Varian MAT 212 instrument. Flash chromatography[38] was carried out on EM Science silica gel 60 (230–400 mesh). When required, final products were purified by semipreparative HPLC (Du Pont Zorbax C_8 reverse phase column, elution with acetonitrile–H_2O containing 0.1% trifluoroacetic acid). Compounds showed satisfactory purity by TLC on Analtech silica gel GF plates (visualized by UV light at 254 nm, I_2 staining, or ceric sulfate/sulfuric acid charring) 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 unavoidably were 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 Robertson Microlit Laboratories, Madison, NJ.

Dry solvents were purchased in anhydrous form, in septum-sealed bottles, from Aldrich Chemical Co. or Pierce Chemical Co. (THF, DMF, DMSO, pyridine, CH_2Cl_2); in some cases, reagent- or HPLC-grade solvents were dried over 4-Å or 3-Å molecular sieves (DMF, DMSO, pyridine, toluene, CH_2Cl_2, EtOH, MeOH). Glassware was oven- or flame-dried for moisture-sensitive reactions. Reactions were routinely conducted under N_2 (bubbler) unless otherwise indicated.

5-*n*-Butyl-2,4-dihydro-2-[2-(trifluoromethyl)phenyl]-3*H*-1,2,4-triazol-3-one (103). A solution of 970 mg (4.83 mmol) of ethyl *N*-carbethoxyvalerimidate (**101**)[24] and 772 mg (4.39 mmol) of 2-(trifluoromethyl)hydrazine (**102**) in 8.8 mL of toluene was stirred at 50 °C for 1.5 h. Next, 671 μL (487 mg, 4.83 mmol) of triethylamine was added, and the solution was stirred at 90 °C for 15 h. The cooled solution was concentrated *in vacuo*, and the residue was reconcentrated twice from toluene. Flash chromatography (gradient elution with 0.5–5% MeOH in CH_2Cl_2) afforded 1.05 g (84%) of a cream-colored solid: mp 123–125 °C; TLC in 95:5 CH_2Cl_2/MeOH; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, J = 7.3 Hz, 3 H), 1.34 (m, 2 H), 1.62 (m, 2 H), 2.52 (t, J = 7.8 Hz, 2 H), 7.5–7.6 (m, 2 H), 7.66 (dd, 1 H), 7.79 (d, 1 H), 11.75 (br s, 1 H); FAB-MS m/e 286 $(M + H)^+$.

Method A. 5-*n*-Butyl-4-[[2′-(*N*-*tert*-butylsulfamoyl)biphenyl-4-yl]methyl]-2,4-dihydro-2-[2-(trifluoromethyl)phenyl]-3*H*-1,2,4-triazol-3-one (105). A mixture of 227 mg (0.796 mmol) of **103**, 38.2 mg (0.955 mmol) of sodium hydride (60% in oil), and 1.6 mL of dry DMF was stirred at 50 °C for 1 h. Upon addition of 457 mg (1.20 mmol) of 4′-(bromomethyl)-*N*-*tert*-butyl-2-biphenylsulfonamide (**104**,[21a,27] dissolved in a small amount of DMF), the mixture was stirred at 50 °C for an additional 1.5 h. H_2O (15 mL) was added to the cooled mixture, which was then extracted with 3 × 10 mL of EtOAc. The combined organic fractions were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was reconcentrated twice from toluene. Flash chromatography (gradient elution with 0.3–10% MeOH in CH_2Cl_2) yielded 343 mg (74%) of a white solid: mp 173–175 °C; TLC in 98:2 CH_2Cl_2/MeOH; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, J = 7.4 Hz, 3 H), 0.97 (s, 9 H), 1.37 (m, 2 H), 1.64 (m, 2 H), 2.48 (t, J = 7.5 Hz, 2 H), 3.48 (s, 1 H), 4.95 (s, 2 H), 7.2–7.6 (m, 9 H), 7.66 (dd, J = 7, 7 Hz, 1 H), 7.78 (d, J = 7.8 Hz, 1 H), 8.15 (d, J = 6.6 Hz, 1 H); FAB-MS m/e 587 $(M + H)^+$.

Method B. 5-*n*-Butyl-2,4-dihydro-4-[(2′-sulfamoylbiphenyl-4-yl)methyl]-2-[2-(trifluoromethyl)phenyl]-3*H*-1,2,4-triazol-3-one (106). A solution of 200 mg (0.341 mmol) of **105** and 3 drops of anisole in 3.4 mL of anhydrous trifluoroacetic acid was stirred at room temperature overnight. The solvent was then evaporated under a gentle stream of N_2. The residue was taken up in CH_2Cl_2 and washed twice with 5% $NaHCO_3$ (aqueous). The organic phase was dried over Na_2SO_4, filtered, and concentrated. The residue was reconcentrated twice from toluene and flash chromatographed (gradient elution with 0.5–5% MeOH in CH_2Cl_2) to give 154 mg (85%) of a white solid: mp 74–76 °C; TLC in 95:5 CH_2Cl_2/MeOH; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, J = 7.2 Hz, 3 H), 1.36 (m, 2 H), 1.63 (m, 2 H), 2.50 (t, J = 7.6 Hz, 2 H), 4.23 (br s, 2 H), 4.95 (s, 2 H), 7.3–7.6 (m, 9 H), 7.65 (dd, J = 10 Hz, 2 Hz, 1 H), 7.78 (d, J = 10 Hz, 1 H), 8.14 (dd, J = 10 Hz, 1.5 Hz, 1 H); FAB-MS m/e 531 $(M + H)^+$.

Method C. 4-[[2′-(*N*-Benzoylsulfamoyl)biphenyl-4-yl]methyl]-5-*n*-butyl-2,4-dihydro-2-[2-(trifluoromethyl)phenyl]-3*H*-1,2,4-triazol-3-one (9). To a solution of 55.7 mg (0.105 mmol) of **106** in 1.0 mL of dry pyridine was added 122 μL (148 mg, 1.05 mmol) of benzoyl chloride. The flask was purged with N_2, stoppered, and stirred at room temperature for 12 h. The mixture was quenched by addition of 5 mL of saturated KH_2PO_4 (aqueous) and extracted with 3 × 10 mL of EtOAc. The combined organic fractions were washed with brine, dried (Na_2SO_4), filtered, and concentrated. Flash chromatography of the residue (gradient elution with 0.5–5% MeOH in CH_2Cl_2) afforded 52 mg (75%) of a white solid: mp 91–93 °C; TLC in 95:5 CH_2Cl_2/MeOH; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.87 (t, J = 7.4 Hz, 3 H), 1.36 (m, 2 H), 1.63 (m, 2 H), 2.47 (t, J = 7.5 Hz, 2 H), 4.86 (s, 2 H), 7.11 (d, J = 8.1 Hz, 2 H), 7.2–7.7 (m, 13 H), 7.75 (d, J = 7.5 Hz, 1 H), 8.25 (br s, 1 H), 8.39 (dd, J = 7.8 Hz, 2.2 Hz, 1 H); FAB-MS m/e 673 $(M + H)^+$. Anal. ($C_{33}H_{29}F_3N_4O_4S$·033CH_2Cl_2) C, H, N.

Method D. 4-[[2′-(*N*-Benzoylsulfamoyl)biphenyl-4-yl]methyl]-5-*n*-butyl-2,4-dihydro-2-[2-(trifluoromethyl)phenyl]-3*H*-1,2,4-triazol-3-one (9). A solution of 145 mg (1.18 mmol) of benzoic acid and 192 mg (1.18 mmol) of 1,1′-carbonyldiimidazole in 1 mL of THF was stirred under N_2 at 55 °C for 2 h. Then a solution of 157 mg (0.296 mmol) of **106** and 133 μL (135 mg, 0.888 mmol) of 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) in 1 mL of THF was added dropwise. After being stirred overnight at 55 °C, the mixture was partitioned between EtOAc and 5% citric acid (aqueous). The organic layer was washed with H_2O and then with saturated NaCl solution. The EtOAc phase was then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Flash chromatography of the residue as in the above method gave 159 mg (85%) of the product, identical in properties to the material prepared by method C.

4-[[2′-(*N*-Benzoylsulfamoyl)biphenyl-4-yl]methyl]-5-*n*-butyl-2,4-dihydro-2-[2-(trifluoromethyl)phenyl]-3*H*-1,2,4-triazol-3-one, Potassium Salt (9, K Salt). A 35-mg (0.055 mmol) sample of **9** (prepared according to method C or method D) was dissolved in 1.75 mL of MeOH and treated with 0.55 mL (0.055 mmol) of 0.1 N KOH in MeOH. The resulting solution was stirred for 1 h and then concentrated to dryness, giving a quantitative yield of the potassium salt as a glass: ^{1}H NMR (CD_3OD, 400 MHz) δ 0.90 (t, J = 7.3 Hz, 3 H), 1.40 (m, 2 H), 1.62 (m, 2 H), 2.56 (t, J = 7.5 Hz, 2 H), 4.97 (s, 2 H), 7.14–7.19 (m, 3 H), 7.24 (dd, J = 7.2, 7.3 Hz, 2 H), 7.34 (dd, J = 7, 7 Hz, 1 H), 7.41 (d, J = 8.2 Hz, 2 H), 7.49 (m, 2 H), 7.59–7.65 (m, 3 H), 7.71 (dd, J = 7.0, 7.0 Hz, 1 H), 7.81 (dd, J = 6.6, 6.7 Hz, 1 H), 7.88 (d, J = 6.7 Hz, 1 H), 8.26 (m, 1 H); FAB-MS m/e 711 $(M + K)^+$. In a larger run, the product was redissolved in THF and precipitated with hexane. The precipitate was collected on a filter and dried to give a 94% yield of an amorphous solid: high purity by HPLC (C_{18} reverse phase, elution with 40:60:0.1 H_2O/MeCN/TFA). Anal. ($C_{33}H_{28}F_3KN_4O_4S$) C, H, N, K.

4′-(Azidomethyl)-*N*-*tert*-butyl-2-biphenylsulfonamide (107). A solution of 700 mg (1.83 mmol) of 4′-(bromomethyl)-*N*-*tert*-butyl-2-biphenylsulfonamide (**104**)[21a,27] in 5.7 mL of dry DMSO was treated with 112 mg (2.29 mmol) of lithium azide, and the mixture was stirred at room temperature for 1.5 h. The solution was cooled in an ice bath, resulting in crystallization. The solid was collected on a filter, washed with H_2O, and dried to give 451 mg (72%) of a white powder: mp 122–124 °C; TLC in 9:1 hexane/EtOAc; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.98 (s, 9 H), 3.53 (s, 1 H), 4.41 (s, 2 H), 7.31 (d, J = 8 Hz, 1 H), 7.36–7.65 (m, 6 H), 8.19 (d, J = 8 Hz, 1 H); high-resolution FAB-MS m/e 345.1369 (calcd for $C_{17}H_{21}N_4O_2S$ $(M + H)^+$ 345.1386).

4′-(Aminomethyl)-*N*-*tert*-butyl-2-biphenylsulfonamide (108). To a solution of 431 mg (1.25 mmol) of **107** in 3.13 mL of dry THF was added portionwise 410 mg (1.57 mmol) of triphenylphosphine. The solution was stirred at 40 °C for 2 h. After being cooled to room temperature, 45.1 μL (45.1 mg, 2.51 mmol) of H_2O was added, and the solution was stirred overnight. Volatiles were removed by evaporation, and the residue was reconcentrated twice from CH_2Cl_2. Flash chromatography of the residue (gradient elution with 1–10% MeOH in CH_2Cl_2) provided 343 mg (86%) of a white solid: mp 156–158 °C; TLC in 95:5 CH_2Cl_2/MeOH; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.99 (s, 9 H), 1.68 (s, 2 H), 3.61 (s, 1 H), 3.92 (s, 2 H), 7.25–7.3 (m, 1 H), 7.35–7.59 (m, 6 H), 8.16 (dd, J = 7.9, 1.3 Hz, 1 H); high-resolution FAB-MS m/e 319.1475 (calcd for $C_{17}H_{23}N_2O_2S$ $(M + H)^+$ 319.1481).

5-*n*-Butyl-4-[[2′-(*N*-*tert*-butylsulfamoyl)biphenyl-4-yl]methyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (110). To a solution of 316 mg (0.994 mmol) of **108** in 3.2 mL of THF were added 226 mg (1.04 mmol) of ethyl valerate carbethoxyhydrazone (**109**)[24] and 2.5 mL of EtOH. The solution was stirred at 80 °C for 24 h and then concentrated *in vacuo*. The residue was reconcentrated twice from $CHCl_3$. The residue was flash chromatographed (gradient elution with 0.5–4% MeOH in CH_2Cl_2) to give 262 mg (47%) of a white solid: mp 179–181 °C; TLC in 9:1 CH_2Cl_2/MeOH; ^{1}H NMR ($CDCl_3$, 300 MHz) δ

0.89 (t, J = 7.3 Hz, 3 H), 0.97 (s, 9 H), 1.35 (m, 2 H), 1.60 (m, 2 H), 2.42 (t, J = 7.7 Hz, 2 H), 3.51 (s, 1 H), 4.87 (s, 2 H), 7.25 (partially obscured d, J = 7 Hz, 1 H), 7.32 (d, J = 8.3 Hz, 2 H), 7.44–7.56 (m, 4 H), 8.15 (dd, J = 7.9, 1.3 Hz, 1 H); high-resolution FAB-MS m/e 443.2117 (calcd for $C_{23}H_{31}N_4O_3S$ (M + H)$^+$ 443.2117).

5-*n*-Butyl-4-[[2′-(*N*-*tert*-butylsulfamoyl)biphenyl-4-yl]-methyl]-2,4-dihydro-2-(2,2-dimethyl-1-propyl)-3*H*-1,2,4-triazol-3-one (111). A mixture of 256 mg (0.579 mmol) of **110**, 46.4 mg (1.16 mmol) of sodium hydride (60% in oil), and 1.2 mL of dry DMF was stirred at room temperature for 3 h. Then 384 μL (574 mg, 2.90 mmol) of neopentyl iodide was added. The solution was stirred at 40 °C overnight and then at 90 °C for an additional day. The cooled reaction was quenched with H_2O and extracted with 3 portions of EtOAc. The combined organic fractions were washed twice with H_2O and then with brine. The organic phase was dried over Na_2SO_4, filtered, and evaporated *in vacuo*. Chromatographic purification (elution with 0.5% MeOH in CH_2Cl_2) yielded 125 mg (74%) of a flaky, white solid: mp 123–125 °C; TLC in 95:5 CH_2Cl_2/MeOH; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, J = 7.3 Hz, 3 H), 0.96 (s, 9 H), 0.98 (s, 9 H), 1.33 (m, 2 H), 1.57 (m, 2 H), 2.39 (t, J = 7.7 Hz, 2 H), 3.47 (s, 1 H), 3.57 (s, 2 H), 4.86 (s, 2 H), 7.24–7.30 (m, 3 H), 7.44–7.55 (m, 4 H), 8.14 (d, J = 7.9 Hz, 1 H); high-resolution FAB-MS m/e 513.2899 (calcd for $C_{28}H_{41}N_4O_3S$ (M + H)$^+$ 513.2899).

5,5,5-Trifluorovaleronitrile (115a). A suspension of 882 mg (18 mmol) of sodium cyanide in 9 mL of DMSO was heated in an oil bath at 80 °C for 10 min until most of the solid had dissolved. The mixture was then removed from the oil bath and treated with 2.87 g (15 mmol) of 4,4,4-trifluorobutyl bromide (**112**). After being heated to 110 °C for about 30 min, the mixture was cooled to room temperature and partitioned between H_2O and Et_2O. The aqueous layer was extracted with an additonal 2 portions of Et_2O. The combined organic fractions were washed successively with 2 N HCl (twice), H_2O (twice), and brine. The ethereal phase was dried over anhydrous Na_2SO_4, filtered, and concentrated to yield 1.99 g (97%) of the title compound as a colorless liquid, suitable for use without further purification: IR (neat) ν_{CO} 2260 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.94 (m, 2 H), 2.26 (m, 2 H), 2.46 (t, J = 7.1 Hz, 2 H).

Ethyl 5,5,5-Trifluorovalerimidate (116a). At 0 °C, HCl gas was bubbled into a stirred mixture of 1.64 g (12.0 mmol) of **115a** and 703 μL (551 mg, 12 mmol) of EtOH for 1 h. The resulting thick slurry was refrigerated overnight. Then the excess HCl was removed under a gentle stream of N_2 at 0 °C. The residue was treated at 0 °C with Et_2O, resulting in a precipitate, which was collected on a filter under N_2 to give 2.40 g of a fluffy, white solid. The major portion (2.19 g) of this imidate hydrochloride was treated with 10 mL of 30% K_2CO_3, and the mixture was immediately extracted with 3 × 20 mL of Et_2O. The combined ethereal fractions were washed (H_2O, brine), dried (Na_2SO_4), filtered, and concentrated (aspirator pump, room temperature) to yield 2.03 g of an oil, which, by NMR, had considerable Et_2O remaining but was estimated to contain approximately 1.45 g (72%) of the title compound: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.27 (t, J = 7.1 Hz, 3H), 1.82 (m, 2H), 1.95–2.2 (m, 2H), 2.31 (t, J = 7.4 Hz, 2H), 4.09 (br m, 2H), 6.92 (br s, 1H). Because of the volatility of the product, no attempt was made to remove the residual Et_2O, and the material was used directly in the next step.

Ethyl *N*-Carbethoxy-5,5,5-trifluorovalerimidate (117a). The crude product from the previous step, containing approximately 1.45 g (7.92 mmol) of **116a**, was dissolved in 20 mL of CH_2Cl_2 and cooled to 0 °C. To this was added 2.87 mL (2.09 g, 20.6 mmol) of triethylamine, followed by 1.89 mL (2.15 g, 19.8 mmol) of ethyl chloroformate. The thick mixture was diluted with an additional 10 mL of CH_2Cl_2 and stirred at room temperature for 1.5 h. Hexane was added, and the mixture was evaporated to dryness *in vacuo*. The residue was triturated with hexane and filtered to remove the insoluble triethylamine hydrochloride. Concentration of the filtrate gave an oil, which was flash chromatographed (elution with 1% MeOH in CH_2Cl_2) to afford 1.27 g (63%) of the desired material as an oil: TLC in 98:2 CH_2Cl_2/MeOH; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.22–1.35 (m, 6H), 1.89 (m, 2H), 2.10 (m, 2H), 2.48 (t, J = 7.3 Hz, 2H), 4.1–4.25 (m, 4H).

2-Methyl-1-(chloromethyl)cyclopropane (114). To a solution of 6.02 g (72.0 mmol) of 2-methylcyclopropanemethanol (**113**) and 5.6 mL (72.0 mmol) pyridine in 15 mL of $CHCl_3$ stirred at 0 °C was added dropwise a solution of 5.2 mL (72.0 mmol) of thionyl chloride in 30 mL of $CHCl_3$. The reaction mixture was allowed to warm slowly to room temperature and then heated at reflux for 1 h. After being cooled to room temperature, the mixture was evaporated under reduced pressure, and the residue was triturated with Et_2O. Insolubles were removed by filtration, and the filtrate was carefully concentrated to yield an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.41 (m, 1 H), 0.48 (m, 1 H), 0.73 (m, 1 H), 0.91 (m, 1 H), 1.05 (d, J = 6.0 Hz, 3 H), 3.41 (m, 2 H). Because of the volatility of the product, no attempt was made to remove the residual Et_2O, and the material was used directly in the next step.

2-Methylcyclopropaneacetonitrile (115b). By the procedure described for the preparation of **115a**, the crude **114** was reacted with sodium cyanide to give the title compound as a brown oil, which was used in the next step without further purification: IR (neat) ν_{CO} 2240 cm^{-1} (weak); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.37 (m, 1 H), 0.46 (m, 1 H), 0.70 (m, 2 H), 1.03 (d, J = 5.8 Hz, 3 H), 2.32 (d, J = 7.0 Hz, 2 H).

Ethyl (2-Methylcyclopropyl)acetimidate (116b). This compound was obtained from **115b** according to the procedure described for the preparation of **116a**, giving a 63% yield of a brown oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.26–0.32 (m, 2 H), 0.49–0.55 (m, 2 H), 1.03 (d, J = 5.5 Hz, 3 H) 1.24 (t, J = 7.0 Hz, 3 H), 2.09 (d, J = 6.6 Hz, 2 H), 4.09 (q, J = 7.0 Hz, 2 H). The material was used directly in the next step without further purification.

Ethyl *N*-Carbethoxy-(2-methylcyclopropyl)acetimidate (117b). By the procedure described for the synthesis of **117a**, the imidate **116b** was converted to the title compound, obtained in 44% yield as a colorless oil: TLC in 98:2 CH_2Cl_2/MeOH; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.20 (m, 1 H), 0.30 (m, 1 H), 0.55 (m, 1 H), 0.68 (m, 1 H), 0.97 (d, J = 6.0 Hz, 3 H), 1.20–1.35 (m, 6 H), 2.23 (dd, J = 7.1 Hz, 3.1 Hz, 2 H), 4.07–4.20 (m, 4 H).

Method E. 5-*n*-Butyl-4-[[2′-[*N*-(4-carboxybutyryl)sulfamoyl]biphenyl-4-yl]methyl]-2,4-dihydro-2-[2-(trifluoromethyl)phenyl]-3*H*-1,2,4-triazol-3-one (69). A solution of 37 mg (0.056 mmol) of 5-*n*-butyl-4-[[2′-[*N*-(4-carbomethoxybutyryl)sulfamoyl]biphenyl-4-yl]methyl]-2,4-dihydro-2-[2-(trifluoromethyl)phenyl]-3*H*-1,2,4-triazol-3-one (prepared in 59% yield according to method D) in 0.37 mL of THF was treated with 0.37 mL (0.37 mmol) of methanolic 1 N NaOH. The mixture was stirred overnight at room temperature and then concentrated to dryness. The residue was taken up in 1 mL of MeOH, brought to pH 1.5 with methanolic 1 N HCl, and reconcentrated. Next, the residue was extracted with $CHCl_3$, dried over Na_2SO_4, and filtered through Celite. The evaporation residue was flash chromatographed (gradient elution with 2–20% MeOH in $CHCl_2$) to give 13 mg (37%) of a glass: TLC in 9:1 CH_2Cl_2/MeOH; ^{1}H NMR (CD_3OD, 400 MHz) δ 0.89 (t, J = 7.4 Hz, 3 H), 1.38 (m, 2 H), 1.61 (m, 2 H), 1.71 (br m, 2 H), 1.97 (br t, J = 6.7 Hz, 2 H), 2.15 (br t, 2 H), 2.59 (t, J = 7.5 Hz, 2 H), 5.03 (s, 2 H), 7.25 (dd, J = 7.5, 1.4 Hz, 1 H), 7.30 (d, J = 8.2 Hz, 2 H), 7.44 (d, J = 8.2 Hz, 2 H), 7.47–7.63 (m, 3 H), 7.71 (m, 1 H), 7.81 (m, 1 H), 7.89 (d, J = 7.0 Hz, 1 H), 8.13 (dd, J = 7.9, 1.3 Hz, 1 H); high-resolution FAB-MS m/e 645.1983 (calcd for $C_{31}H_{31}F_3N_4O_6S$ (M + H)$^+$ 645.1995).

Method F. 5-*n*-Butyl-4-[[2′-(*N*-carbethoxysulfamoyl)-biphenyl-4-yl]methyl]-2,4-dihydro-2-[2-(trifluoromethyl)-phenyl]-3*H*-1,2,4-triazol-3-one (89). A mixture of 125 mg (0.236 mmol) of **106**, 11.3 mg (0.283 mmol) of sodium hydride (60% in oil), and 0.5 mL of dry THF was stirred at room temperature for 4 h. Then, 33.8 μL (38.4 mg, 0.354 mmol) of ethyl chloroformate was added, and the solution was stirred at ambient temperature overnight. The mixture was partitioned between EtOAc and H_2O, and the aqueous phase was extracted with an additional portion of EtOAc. The combined organic fractions were washed (H_2O, brine), dried (Na_2SO_4), filtered, and concentrated. The residue was flash chromatographed (gradient elution with 0.3–5% MeOH in CH_2Cl_2) to

yield 61 mg (43%) of a white solid: mp 79–81 °C; TLC in 95:5 CH_2Cl_2/MeOH; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, J = 7.3 Hz, 3 H), 1.12 (t, J = 7 Hz, 3 H), 1.38 (m, 2 H), 1.65 (m, 2 H), 2.51 (t, J = 7.7 Hz, 2 H), 4.04 (q, J = 7 Hz, 2 H), 4.96 (s, 2 H), 6.89 (s, 1 H), 7.29–7.36 (m, 5 H), 7.53–7.80 (m, 6 H), 8.26 (dd, J = 8.0, 1.2 Hz, 1 H); FAB-MS m/e 603 $(M + H)^+$. Anal. ($C_{29}H_{29}F_3N_4O_5S$) C, H, N.

Method G. 4-[[2′-[*N*-(*tert*-Butoxycarbonyl)sulfamoyl]-biphenyl-4-yl]methyl]-5-*n*-butyl-2,4-dihydro-2-[2-(trifluoromethyl)phenyl]-3*H*-1,2,4-triazol-3-one (92). A mixture of 150 mg (0.283 mmol) of **106**, 13.6 mg (0.340 mmol) of sodium hydride (60% in oil), and 0.6 mL of dry THF was stirred at room temperature for 4 h. Di-*tert*-butyl dicarbonate (97.6 μL, 92.8 mg, 0.425 mmol) was added, and the mixture was stirred at 55 °C for 2 days. Workup and chromatography as in method F (except that the EtOAc solution was also washed 5 times with 2 N HCl) afforded 56 mg (31%) of a glassy, white solid: mp 140–142 °C; TLC in 95:5 CH_2Cl_2/MeOH; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, J = 7.3 Hz, 3 H), 1.28 (s, 9 H), 1.36 (m, 2 H), 1.62 (m, 2 H), 2.50 (t, J = 7.6 Hz, 2 H), 4.96 (s, 2 H), 6.54 (br s, 1 H), 7.29–7.79 (m, 11 H), 8.23 (dd, J = 8.0, 1.3 Hz, 1 H); FAB-MS m/e 631 $(M + H)^+$. Anal. ($C_{31}H_{33}F_3N_4O_5S$) C, H, N.

Method H. 5-*n*-Butyl-2,4-dihydro-4-[[2′-[*N*-(*N*-isopropylcarbamoyl)sulfamoyl]biphenyl-4-yl]methyl]-2-[2-(trifluoromethyl)phenyl]-3*H*-1,2,4-triazol-3-one (93). A solution of 100 mg (0.19 mmol) of **106**, 350 μL (0.38 mmol) of triethylamine, and 186 μL (1.9 mmol) of isopropyl isocyanate in DMF (0.2 mL) was stirred at 74 °C overnight. The cooled reaction mixture was quenched by addition of water and extracted with EtOAc. The EtOAc layer was washed (2 N HCl, water, and brine) and dried over anhydrous Na_2SO_4. The crude material obtained after filtration and evaporation of volatiles was flash chromatographed (gradient elution with 0.5–5.0% MeOH/CH_2Cl_2). The residue from concentration of product fractions was triturated twice with ether to give 48 mg (41%) of a cream-colored solid: mp 78–80 °C; TLC in 95:5 CH_2Cl_2/MeOH; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, J = 7.3 Hz, 3 H), 0.96 (d, J = 6.6 Hz, 6 H), 1.34–1.43 (m, 2 H), 1.62–1.70 (m, 2 H), 2.54 (t, J = 7.6 Hz, 2 H), 3.70 (m, 1 H), 4.94 (s, 2 H), 5.82 (d, J = 7.7 Hz, 1 H), 6.53 (br s, 1 H), 7.28–7.42 (m, 5 H), 7.50–7.80 (m, 6 H), 8.13 (dd, J = 8.0, 1.2 Hz, 1 H); FAB-MS m/e 654 $(M + H)^+$.

Method I. 4-[[2′-[*N*-(Phenylsulfonyl)sulfamoyl]biphenyl-4-yl]methyl]-5-*n*-butyl-2,4-dihydro-2-[2-(trifluoromethyl)phenyl]-3*H*-1,2,4-triazol-3-one (96). A mixture of 50.6 mg (0.0955 mmol) of **106**, 4.6 mg (0.12 mmol) of sodium hydride (60% in oil), and 0.2 mL of dry THF was stirred at room temperature for 4.5 h. Next, 14.6 μL (20.2 mg, 0.115 mmol) of benzenesulfonyl chloride was added, and the mixture was stirred overnight at room temperature. Because a significant quantity of unreacted starting material remained, an additional 14.6 μL of benzenesulfonyl chloride was added, and the mixture was stirred at 60 °C for 4 h. The cooled reaction mixture was worked up and chromatographed as in method F. The residue from evaporation of the pooled product fractions was partitioned between CH_2Cl_2 and 2 N HCl. The organic layer was dried (Na_2SO_4), filtered, and concentrated to give 15 mg (23%) of a cream-colored solid: mp 89–90 °C; TLC in 9:1 CH_2Cl_2/MeOH; ^1H NMR (CD_3OD, 400 MHz) δ 0.88 (t, J = 7.3 Hz, 3 H), 1.37 (m, 2 H), 1.60 (m, 2 H), 2.56 (t, J = 7.5 Hz, 2 H), 5.00 (s, 2 H), 7.1–7.75 (m, 14 H), 7.81 (dd, J = 7.6, 7.6 Hz, 1 H), 7.89 (d, J = 7.0 Hz, 1 H), 8.04 (d, J = 8.0 Hz, 1 H); high-resolution FAB-MS m/e 671.1615 (calcd for $C_{32}H_{30}F_3N_4O_5S_2$ $(M + H)^+$ 671.1610).

Method J. 5-*n*-Butyl-4-[[2′-(*N*-cyanosulfamoyl)biphenyl-4-yl]methyl]-2,4-dihydro-2-[2-(trifluoromethyl)phenyl]-3*H*-1,2,4-triazol-3-one (97). To a solution of 135 mg (0.255 mmol) of **106** in 1.5 mL of dry THF stirred at 0 °C was added dropwise 0.255 mL (0.255 mmol) of 1 M sodium bis(trimethylsilyl)amide in THF. The mixture was stirred at room temperature for 1 h and then brought again to 0 °C. A solution of 28 mg (0.26 mmol) of cyanogen bromide in 0.2 mL of THF was added, and the mixture was stirred at room temperature overnight. The mixture was worked up as in method F. Flash chromatography (gradient elution with 1–5% MeOH in CH_2Cl_2) provided 13 mg (9%) of a glassy, white solid: mp 187–190 °C; TLC in 9:1 CH_2Cl_2/MeOH; ^1H NMR (CD_3OD, 400 MHz) δ 0.94 (t, J = 7.3 Hz, 3 H), 1.42 (m, 2 H), 1.63 (m, 2 H), 2.63 (t, J = 7.3 Hz, 2 H), 5.07 (s, 2 H), 7.32–7.95 (m, 11 H), 8.17 (d, J = 7.7 Hz, 1 H); high-resolution FAB-MS m/e 556.1633 (calcd for $C_{27}H_{25}F_3N_5O_3S$ $(M + H)^+$ 556.1635).

Method K. 5-*n*-Butyl-2,4-dihydro-4-[[2′-[*N*-(4-nitrophenyl)sulfamoyl]biphenyl-4-yl]methyl]-2-[2-(trifluoromethyl)phenyl]-3*H*-1,2,4-triazol-3-one (98). A mixture of 100 mg (0.19 mmol) of **106**, 7.6 mg (0.19 mmol) of sodium hydride (60% in oil), and 0.5 mL of dry DMF was stirred at room temperature for 2 h and then treated dropwise with a solution of 27 mg (0.19 mmol) of 4-fluoronitrobenzene in 0.3 mL of DMF. The resulting yellow mixture was stirred at 60 °C for 29 h. Workup and chromatography according to method F afforded 53 mg (43%) of an off-white solid: mp 186–187 °C; TLC in 95:5 CH_2Cl_2/MeOH; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.91 (t, J = 7.3 Hz, 3 H), 1.41 (m, 2 H), 1.70 (m, 2 H), 2.58 (t, J = 7.4 Hz, 2 H), 5.00 (s, 2 H), 6.50 (s, 1 H), 6.75 (dd, J = 7.1, 2.1 Hz, 2 H), 7.23–7.32 (m, 5 H), 7.54–7.82 (m, 6 H), 7.97 (dd, J = 7.0, 2.1 Hz, 2 H), 8.28 (dd, J = 7.8, 1.4 Hz, 1 H); high-resolution FAB-MS m/e 652.1869 (calcd for $C_{32}H_{28}F_3N_5O_5S$ $(M + H)^+$ 652.1896).

4-[[2′-[[[Bis(methylthio)methylene]amino]sulfonyl]-biphenyl-4-yl]methyl]-5-*n*-butyl-2,4-dihydro-2-[2-(trifluoromethyl)phenyl]-3*H*-1,2,4-triazol-3-one (118). A mixture of 265 mg (0.50 mmol) of **106**, 22 mg (0.55 mmol) of sodium hydride (60% in oil), and 1.2 mL of dry DMF was stirred at room temperature for 10 min. To the resulting mixture was added 16.5 μL (20.9 mg, 0.275 mmol) of carbon disulfide, and stirring was continued for 30 min. An additional 0.55 mmol of sodium hydride was added, followed after a few minutes by a further 0.275 mmol of carbon disulfide. Subsequently, the reaction mixture was cooled to 0 °C, and 93.4 μL (213 mg, 1.5 mmol) of iodomethane was added dropwise. The somewhat discolored reaction mixture was stirred overnight at room temperature and then quenched by addition of 8 g of ice/H_2O mixture and extracted with EtOAc (3 × 8 mL). The combined organic fractions were washed with H_2O (2 × 10 mL) and brine (1 × 10 mL). The organic phase was dried (Na_2SO_4), filtered, and concentrated. Flash chromatography of the residue (elution with 0.5% MeOH in CH_2Cl_2) gave 257 mg (81%) of a white foam: TLC in 95:5 CH_2Cl_2/MeOH; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, J = 7.3 Hz, 3 H), 1.34–1.38 (m, 2 H), 1.62–1.66 (m, 2 H), 2.24 (s, 6 H), 2.48 (t, J = 7.7 Hz, 2 H), 4.92 (s, 2 H), 7.25–7.30 (m, 3 H), 7.45–7.79 (m, 8 H), 8.25 (dd, J = 8.0, 1.3 Hz, 1 H); FAB-MS m/e 635 $(M + H)^+$.

Method L. 4-[[2′-[*N*-(Benzoxazol-2-yl)sulfamoyl]biphenyl-4-yl]methyl]-5-*n*-butyl-2,4-dihydro-2-[2-(trifluoromethyl)phenyl]-3*H*-1,2,4-triazol-3-one (99). A mixture of 14.2 mg (0.13 mmol) of *o*-aminophenol, 10.4 mg (0.26 mmol) of sodium hydride (60% in oil), and 1 mL of DMF was stirred at room temperature for 1.5 h. To this was added dropwise a solution of 75 mg (0.12 mmol) of **118** in DMF. This mixture was heated at 110 °C overnight. The cooled reaction mixture was treated with H_2O (3 mL), 1 N HCl (0.5 mL), and EtOAc (5 mL). The layers were separated, and the aqueous phase was further extracted with EtOAc (2 × 3 mL). The combined organic fractions were washed (H_2O, brine), dried (Na_2SO_4), filtered, and concentrated. The residue was flash chromatographed (elution with 0.5–1% MeOH in CH_2Cl_2) to give 43 mg (57%) of an off-white stiff foam: mp 109–111 °C; TLC in 95:5 CH_2Cl_2/MeOH; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.83 (t, J = 7.6 Hz, 3 H), 1.26–1.32 (m, 2 H), 1.48–1.55 (m, 2 H), 2.31 (t, J = 7.5 Hz, 2 H), 4.24 (s, 2 H), 6.91–6.93 (m, 2 H), 7.11–7.36 (m, 6 H), 7.50–7.79 (m, 7 H), 8.27 (dd, J = 7.3, 1.9 Hz, 1H), 9.53 (br s, 1 H); high-resolution FAB-MS m/e 648.1871 (calcd for $C_{33}H_{29}F_3N_5O_4S$ $(M + H)^+$ 648.1850).

4-Methyl-2′-nitrobiphenyl (121). A mixture of 4.04 g (20 mmol) of 2-bromonitrobenzene (**119**), 5.61 g (22 mmol) of trimethyl(4-methylphenyl)stannane (**120**),[34] 140 mmol (0.2 mmol) of bis(triphenylphosphine)palladium(II) dichloride, and 40 mL of dry DMF was stirred at 110 °C for 4 h. The nearly black reaction mixture was cooled and added to a mixture of 100 mL of 1 N KOH (aqueous) and 100 mL of saturated NaCl (aqueous). The product was extracted with 3 × 150 mL of EtOAc. The combined organic fractions were washed with an

additional portion of the 1:1 1 N KOH/saturated NaCl, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Flash chromatography of the residue (elution with 2.5% EtOAc in hexane) yielded 4.11 g (96%) of a light orange oil: TLC in 4:1 hexane/EtOAc; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.38 (s, 3 H), 7.21 (m, 4 H), 7.43 (m, 2 H), 7.58 (m, 1 H), 7.80 (dd, J = 8.1, 1.3 Hz, 1 H); EI-MS m/e 213 (M^+).

4-(Bromomethyl)-2′-nitrobiphenyl (122). A solution of 2.17 g (10.2 mmol) of **121** in 100 mL of CCl_4 was stirred at reflux. To this was added dropwise a bromine solution [prepared by diluting 11.2 mL (11.2 mmol) of commercial 1.0 M Br_2 in CCl_4 to a final volume of 40 mL with CCl_4], while the reaction mixture was irradiated with a 100-W tungsten lamp. After completion of the addition, the solution was cooled and concentrated. The residue was flash chromatographed (gradient elution with 1.5–10% EtOAc in hexane) to afford 2.68 g (77% yield, adjusted for purity) of **122** as an oil (85% pure by NMR, the remainder being the dibromomethyl derivative): TLC in 4:1 hexane/EtOAc; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.52 (s, 2 H), 7.29 (m, 2 H), 7.48 (m, 4 H), 7.61 (m, 1 H), 7.85 (dd, J = 8.1, 1.3 Hz, 1 H); FAB-MS m/e 292 $(M + H)^+$.

5-*n*-Butyl-2,4-dihydro-4-[(2′-nitrobiphenyl-4-yl)methyl]-2-[2-(trifluoromethyl)phenyl]-3*H*-1,2,4-triazol-3-one (123). By the procedure of method A, **103** was alkylated with **122**. Flash chromatography of the crude product (gradient elution with 0.5–5% MeOH in CH_2Cl_2) gave a 91% yield of **123** as a sticky foam: TLC in 98:2 CH_2Cl_2/MeOH; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, J = 7.3 Hz, 3 H), 1.36 (m, 2 H), 1.52 (m, 2 H), 2.48 (t, J = 7.7 Hz, 2 H), 4.95 (s, 2 H), 7.25–7.75 (m, 10 H), 7.80 (d, J = 8.0 Hz, 1 H), 7.87 (d, J = 8.0 Hz, 1 H); FAB-MS m/e 497 $(M + H)^+$.

4-[(2′-Aminobiphenyl-4-yl)methyl]-2-[2-(trifluoromethyl)phenyl]-5-*n*-butyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (124). To a solution of 217 mg (0.438 mmol) of **123** in 2.2 mL of THF stirred at 0 °C was added dropwise a solution of stannous chloride dihydrate in 1.2 mL of concentrated hydrochloric acid. After 15 min, the ice bath was removed, and the mixture was allowed to warm to room temperature. After an additional 2 h, it was added to a mixture of 10.6 g of ice, 3 mL of 50% NaOH, and 6 mL of Et_2O. The resulting mixture was sstirred at 0 °C for 1 h and then extracted with 2 × 10 mL of Et_2O and 1 × 10 mL of EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The residue was flash chromatographed twice (initial elution with a gradient of 0.5–5% MeOH in CH_2Cl_2, subsequent elution with 0.5% MeOH in CH_2Cl_2) to give 95 mg (47%) of a sticky foam, suitable for use in the next step: TLC in 98:2 CH_2Cl_2/MeOH; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.86 (t, J = 7.3 Hz, 3 H), 1.35 (m, 2 H), 1.62 (m, 2 H), 2.49 (t, J = 7.5 Hz, 2 H), 4.91 (s, 2 H), 6.86 (m, 2 H), 7.1–7.2 (m, 2 H), 7.32 (d, J = 8 Hz, 2 H), 7.46 (d, J = 8 Hz, 2 H), 7.5–7.6 (m, 2 H), 7.64 (dd, J = 7.5, 7.5 Hz, 1 H), 7.78 (d, J = 7.6 Hz, 1 H); FAB-MS m/e 467 $(M + H)^+$.

Method M. 5-*n*-Butyl-2,4-dihydro-4-[[2′-(trifluoromethanesulfonamido)biphenyl-4-yl]methyl]-2-[2-(trifluoromethyl)phenyl]-3*H*-1,2,4-triazol-3-one (100). A solution of 75 mg (0.161 mmol) of **124** in 1.0 mL of dry pyridine was treated with 135 μL (227 mg, 0.805 mmol) of trifluoromethanesulfonic anhydride. The resulting red solution was stirred at ambient temperature for 4 h. The reaction was quenched by addition of 7 mL of saturated KH_2PO_4 (aqueous), followed by extraction with 3 × 10 mL of EtOAc. The combined orgainic extracts were washed with 15 mL of brine, dried (Na_2SO_4), filtered, and concentrated. The residue was redissolved in a small volume of CH_2Cl_2 and shaken with 1 mL of 1 N HCl. The organic layer was separated, dried, and concentrated as above. The residue was flash chromatographed (gradient elution with 0.3–5% MeOH in CH_2Cl_2) to give as the major product (high R_f by TLC in 95:5 CH_2Cl_2/MeOH) 58 mg of the bis[(trifluoromethyl)sulfonyl]amino derivative **125** (FAB-MS m/e 730 $(M + H)^+$). This material was dissolved in 580 μL of MeOH and treated with 318 μL (0.795 mmol) of 2.5 N NaOH. The solution was stirred at 50 °C for 4 h and then concentrated. The residue was partitioned between 4 mL of CH_2Cl_2 and 1 mL of 1 N HCl. The organic phase was dried over Na_2SO_4, filtered, and evaporated *in vacuo*. Flash chromatography (elution with 0.3% and then 0.5% MeOH in CH_2Cl_2) afforded 30 mg (63%) of cream-colored crystals: TLC in 95:5 CH_2Cl_2/MeOH; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.87 (t, J = 7.3 Hz, 3 H), 1.36 (m, 2 H), 1.64 (m, 2 H), 2.49 (t, J = 7.6 Hz, 2 H), 4.95 (s, 2 H), 6.82 (br s, 1 H), 7.2–7.6 (m, 10 H), 7.65 (dd, J = 7.2, 7.2 Hz, 1 H), 7.78 (d, J = 8.1 Hz, 1 H); FAB-MS m/e 599 $(M + H)^+$. Anal. ($C_{27}H_{24}F_6N_4O_3S$) C, H, N.

Rabbit Aorta AT_1 Receptor Binding Assay. Methods for the rabbit aorta membrane preparation[35a] and binding assay[35a,b] have previously been described in detail. Bovine serum albumin (BSA) was omitted from this version of the assay.[24,35b] All binding assays were performed in duplicate tubes. 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.

Rat Midbrain AT_2 Receptor Binding Assay. Details for the rat midbrain membrane preparation and binding assay have been reported previously.[35a,c] Dithiothreitol (77 mg/mL) was included in the assay mixture to abolish residual AT_1 receptor binding. Calculations of the IC_{50} were performed as above.

Evaluation of AII Antagonists in Conscious, Normotensive Rats. Experimental procedures were as previously described,[35b] except that in some instances, PEG 400 was used to solubilize test compounds for oral administration. In brief, male Sprague–Dawley rats (300–400 g) were surgically instrumented with catheters for intravenous administration of compounds and for monitoring arterial blood pressure and heart rate. In the absence of test compound, challenge with a submaximal dose of AII (0.1 μg/kg iv) typically produced an increase in mean arterial pressure (MAP) of approximately 50 mmHg. The test compound was given intravenously or orally, followed by bolus doses of AII at specified intervals thereafter for as long as the test compound exhibited activity. 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 (based on averaged results from at least two rats, unless otherwise indicated). 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.

Evaluation of AII Antagonists in Conscious, Normotensive Dogs. The protocol has been described in detail.[36b] In brief, female mongrel dogs weighing 10–15 kg were surgically implanted with chronic arterial catheters with access ports (Access Technologies). Animals were maintained on a diet containing 60 mmol/day of sodium, with water available ad libitum. The dogs were denied food for 18 h prior to and during the experiment. On the morning of the experiment, the dogs were placed in slings. Aseptic procedures were employed throughout the experiment. AII and test compound were administered iv *via* catheters in the saphenous or brachial vein. Oral administration of test compound was by gavage. In other respects, the experimental protocol essentially followed that described for conscious rats.

Evaluation of AII Antagonists in Conscious, Normotensive Rhesus Monkeys. The protocol has been described in detail.[36b] Briefly, male and female rhesus monkeys (*Macaca mulatta*) weighing 3–7 kg were surgically implanted with chronic arterial catheters with access ports (Access Technologies). Animals were maintained on a low-sodium diet (<2 mmol/day of sodium) supplemented with fruit for 1 week. Furosemide (5 mg/kg iv) was administered the evening prior to the experiment. The monkeys were fasted for 18 h prior to and during the experiment, but water was available ad libitum. On the morning of the experiment, the monkeys were

placed in chairs with minimal restraint. Aseptic procedures were employed throughout the experiment. AII and test compound were administered iv via catheters in the saphenous or brachial vein. Oral administration of test compound was via nasogastric tube through the nostril. In other respects, the experimental protocol essentially followed that described for conscious rats.

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