Triazolinone Biphenylsulfonamides as Angiotensin II Receptor Antagonists with High Affinity for Both the AT_1 and AT_2 Subtypes

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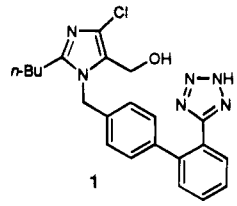
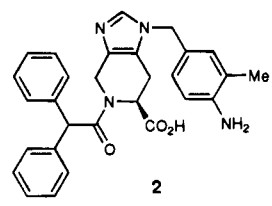
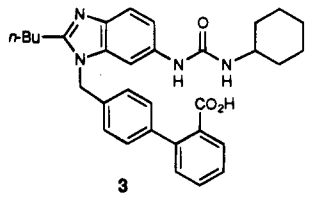
Angiotensin II (AII), the endogenous peptide ligand of the AII receptor, has equivalent high affinity for both the AT_1 and AT_2 receptor subtypes while most of the reported nonpeptide AII antagonists are AT_1-selective. In an effort to identify dual AT_1/AT_2 nonpeptide AII antagonists, we have pursued modifications of previously prepared trisubstituted 1,2,4-triazolinone biphenylsulfonamides which exhibited subnanomolar *in vitro* AT_1 (rabbit aorta) AII antagonism and AT_2 (rat midbrain) IC_{50} values of <40 nM. Present results show that a suitable amide (or reversed amide) side chain appropriately positioned on the N^2-aryl group of these compounds gave >15-fold enhancement in AT_2 binding affinity without sacrificing nanomolar AT_1 potency (IC_{50}). This added amide, combined with an appropriate choice of the N-substituent on the sulfonamide and the *ortho* substituent on the N^2-aryl group, led to an analogue (**46**, L-163,-007) which exhibited subnanomolar AT_1 binding affinity and an AT_2/AT_1 IC_{50} ratio of 3. This compound showed excellent iv activity at 1 mg/kg and oral efficacy at 3 mg/kg with >6 h duration in a conscious rat model. Available data suggest that the newly introduced amide side chain, mandatory for low nanomolar binding affinity at the AT_2 receptor, is well-tolerated by the AT_1 receptor and has minimal effect on the *in vivo* properties of these molecules.

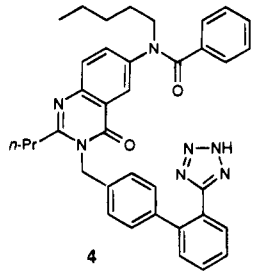
The renin–angiotensin system (RAS), which is of central importance in the regulation of blood pressure and electrolyte balance, has the octapeptide angiotensin II (AII, H-D R V Y I H P F-OH) as its principal active hormone.[2,3] Blockade of the RAS in antihypertensive therapy via angiotensin-converting enzyme (ACE) inhibitors, preventing the formation of AII from angiotensin I (AI), is well-documented.[4] However, ACE also has kininase activity, and this lack of specificity has been implicated in the occasional side effects of ACE inhibitors such as dry cough and angioedema.[5] Inhibition of the RAS at the interaction between AII and its cell surface receptor provides an approach to block the system which is independent of both the pathway and the site of formation of AII.[6]

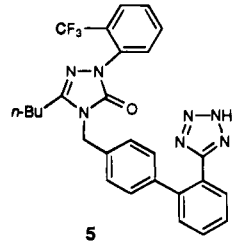
The two major subtypes of the AII receptor, designated as AT_1 and AT_2, have been identified in varying proportions in a number of mammalian tissues.[7] The AT_1 receptor is G-protein coupled[8] and mediates most of the known physiological effects of AII, including the maintenance of blood pressure.[7] In recent years, a number of highly active nonpeptide AT_1-selective AII antagonists have been described.[9] Structurally, the majority of these are patterned after the investigational antihypertensive drug losartan[10] (**1**, DuP 753, MK-954) in that they contain a [2′-(5-tetrazolyl)biphenyl-4-yl]-methyl side chain attached to a heterocyclic moiety. An array of heterocycles, ranging from fused rings containing the imidazole motif to a number of N- or C-linked nitrogen heterocycles, have been shown to be consistent with potent AT_1 binding affinity.[9] Losartan and several nonpeptide AT_2-selective ligands such as **2** (PD 123177)[11] have been important pharmacological tools in the identification of subtypes of the AII receptor.[12]

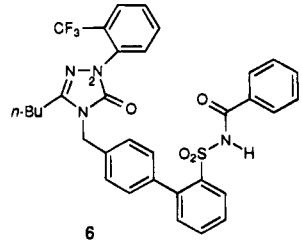












More recently, AT_2-selective ligands with affinity in the nanomolar range have been described.[13] The AT_2 receptor also has a 7-transmembrane domain and reportedly is linked to phosphotyrosine phosphatase

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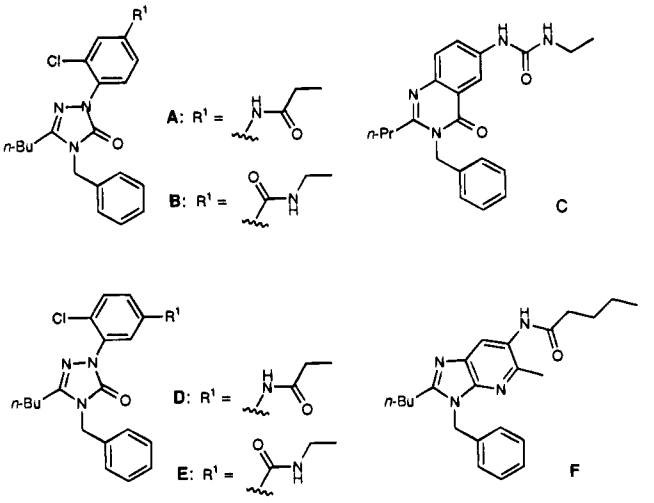
activity.[14] The physiological role of the AT_2 receptor has not yet been clearly defined. Recent reports suggest that this receptor may be involved in the regulation of renal function[15] and may play a role in restenosis following vascular injury,[16] in wound healing,[17] and in cardiac fibroblast collagen synthesis.[18] In addition, it has been implicated in various cell differentiation and cell proliferation processes.[7,19] Upon administration of an AT_1-selective antagonist, an increase in plasma levels of AII (presumably due to inhibition of AII-mediated renin formation and release) has been observed.[20] The physiological effect of prolonged stimulation of AT_2 receptors by elevated levels of circulating AII is not known. AII antagonists capable of equally blocking both receptor subtypes with high affinity (AT_1/AT_2-balanced AII antagonists) would be useful as pharmacological tools and could prove advantageous as therapeutic agents.[6d]

Most of the potent peptide ligands for the AII receptor, e.g., saralasin ([Sar^1, Ala^8]-AII), [Sar^1, Ile^8]-AII, and sarmesin ([Sar^1,(Me)Tyr^4]-AII), bind indiscriminately to both the AT_1 and the AT_2 receptors with high affinity.[7] However, partial agonism and poor pharmacokinetic properties have hampered their usefulness as pharmacological tools.[21] Several dual AT_1/AT_2 ligands with moderate selectivity and modest affinity have been reported [e.g., **3** (BIBS 39, $K_{iAT2}/K_{iAT1} = 17$, and AT_1 K_i = 29 nM)].[22] High-affinity nonpeptide AT_1/AT_2-balanced AII ligands were first realized by *N*-alkyl-*N*-acyl-6-quinazolinones such as **4** (L-159,689, $IC_{50AT2}/IC_{50AT1} = 0.41$, and AT_1 $IC_{50} = 1.7$ nM).[23]

We have described a series of 2,4-dihydro-3*H*-1,2,4-triazol-3-ones (triazolinones) bearing a (2′-tetrazolylbiphenyl-4-yl)methyl side chain at N^4, such as **5**, as potent AT_1-selective AII antagonists.[24] More recently, we demonstrated that compound **6** (L-159,913) in which the tetrazolyl functionality in **5** is replaced by a benzoylsulfamoyl group gave a 75-fold increase in AT_2 binding affinity over **5**.[25] Extensive structure–activity relationship (SAR) studies of **6** at the sulfonamide site uncovered a number of compounds with binding affinity of 40 nM or less for the AT_2 receptor (rat midbrain) while retaining subnanomolar binding affinity for the AT_1 receptor (rabbit aorta).[1] Stimulated by these findings, we sought to transform triazolinone sulfonamides into AT_1/AT_2-balanced AII antagonists. Initially, our goal was to identify compounds with subnanomolar or low nanomolar IC_{50} values for both the AT_1 and the AT_2 receptors and to achieve an AT_2/AT_1 IC_{50} ratio of ≤ 5. Ideally, for dual-action compounds, the AT_2/AT_1 IC_{50} ratio should be close to unity to ensure equivalent coverage of both receptors under physiological conditions.

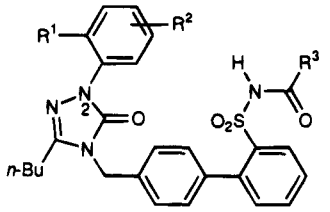
Two of the most interesting compounds to come out of the SAR studies of the sulfonamide moiety in **6** were compounds **7** and **8** (Table 1).[1] In the course of that study, it became clear that the sulfonamide groups in these compounds were nearly optimized for AT_2 binding. Any significant additional enhancement in AT_2 activity would need to be derived from changes made elsewhere in the molecule. Results from the aforementioned series of balanced quinazolinone tetrazoles[23] suggested that a suitably substituted amide, appropriately appended onto **7** or **8**, in the vicinity of N^2 of the triazolinone, could be instrumental in providing additional binding to the AT_2 receptor. To further investigate this hypothesis, we have prepared and evaluated several series of triazolinone sulfonamides (**9**–**46**) containing an N^2-aryl group substituted with an amide (or related structure) at the 4- or 5-position, with or without a substituent at the 2-position. As synthetic efforts got underway, partial triazolinone structures containing the added amide moiety were modeled[26] with equivalent portions from dual-action quinazolinone sulfonamides or imidazopyridine sulfonamides under investigation in these laboratories at the time (Figures 1, 2).[27,28] Figure 1a shows the overlay between a proposed 4-substituted triazolinone amide construct **A** (ArNHCOR arrangement) and a quinazolinone urea partial structure **C**.[27] For this pair, the carbonyl groups have divergent spatial orientations and the carbonylamino groups appear "mismatched". As shown in Figure 1b, a triazolinone "reversed amide" fragment **B** (ArCONHR arrangement) modeled well with **C**. In this case, the carbonyl groups are in close proximity and have similar orientations, and the nitrogen atoms are in good alignment. Both partial structures of the targeted 5-substituted triazolinone amides **D**, **E** overlapped well with a corresponding portion from an imidazopyridine amide **F**[28] as shown in Figure 2. In either of these pairs, although the amide groups lined up well, there was limited overlap between the pyrido moiety of **F** and the corresponding triazolinone phenyl group. The overlay between the triazolinone "reversed amide" **E** with **F** was particularly impressive with respect to the alignment of the carbonyl group (Figure 2b). Generally, these modeling results were supportive of our approach to improve AT_2 binding affinity.



Chemistry

Initial investigations were directed toward the synthesis of compounds with an amide [NHC(O)R] or a "reversed amide" [C(O)NHR] group linked to the 4-position of the aryl substituent at N^2 as in compounds **9-15**. In the triazolinone series, in contrast to several other heterocylic series,[27,28] it was quite feasible to prepare both the amides and the reversed amides at the 4- and 5-positions and to study their SAR. From our previous experience with AT_1-selective triazolinones,[24] retaining a substituent at the 2-position was deemed advantageous with respect to maintaining good AT_1 potency. This substituent was either chloro or trifluoromethyl,[24] selected according to the availability of starting materials. The synthesis of the amide series (compounds

Table 1. Physical Properties and in Vitro Binding Potencies for the AT_1 and AT_2 Receptor Subtypes of AII of Various N^2-Aryltriazolinone Biphenylsulfonamides



no.	R^1	R^2	R^3	method[a]	yield (%)	mp, °C	formula[b]	FAB-MS *m/e* (M + H)+[c]	IC_{50} (nM) AT_1 [rabbit aorta]	IC_{50} (nM) AT_2 [rat midbrain]	AT_2/AT_1 IC_{50} Ratio
5	CF_3	H	[tetrazole][d]						0.78	23,000	29,000
6[e]	CF_3	H	C_6H_5						0.43	300	700
7[f]	CF_3	H	(2-Cl)C_6H_4						0.11	36	360
8[f]	CF_3	H	O(*t*-Bu)						0.45	17	38
9	CF_3	4-NO_2	(2-Cl)C_6H_4	A	43	179–181	$C_{33}H_{27}ClF_3N_5O_6S$	714	1.6	190	120
10	CF_3	4-NH_2	(2-Cl)C_6H_4	B	88	134–136	$C_{33}H_{29}ClF_3N_5O_4S{\cdot}0.5H_2O$	684	0.56	58	100
11	CF_3	4-NHCOEt	(2-Cl)C_6H_4	C	41	204–206	$C_{36}H_{33}ClF_3N_5O_5S$[g]	740[g]	0.42	100	240
12	CF_3	4-$NHCH_2C_6H_5$	(2-Cl)C_6H_4	D	25	>107 (grad.)	$C_{40}H_{35}ClF_3N_5O_4S{\cdot}2CH_2Cl_2$	774	0.37	107	290
13	Cl	4-CONH(*n*-pentyl)	(2-Cl)C_6H_4	E	62	124–127	$C_{38}H_{39}Cl_2N_5O_5S{\cdot}H_2O$	748	2.4	185	77
14	Cl	4-CO_2Et	(2-Cl)C_6H_4	A	92	72–75	$C_{35}H_{32}Cl_2N_4O_6S{\cdot}0.5H_2O$	707	1.4	201	140
15	Cl	4-CO_2Et	O(*t*-Bu)	F	49	84–87	$C_{33}H_{37}ClN_4O_7S{\cdot}H_2O$	669	1.8	306	170
16	Cl	5-NO_2	(2-Cl)C_6H_4	A	48	>160 (grad.)	$C_{32}H_{27}Cl_2N_5O_6S{\cdot}0.75H_2O$	687[h]	0.41	230	560
17	Cl	5-NH_2	(2-Cl)C_6H_4	B	70	155–157	$C_{32}H_{29}Cl_2N_5O_4S$[i]	650[i]	0.56	390	700
18	Cl	5-NHCOMe	(2-Cl)C_6H_4	G	61	190–192	$C_{34}H_{31}Cl_2N_5O_5S{\cdot}0.6CH_2Cl_2$	731[j]	0.052	12	230
19	Cl	5-NHCOEt	(2-Cl)C_6H_4	C	40	160–162	$C_{35}H_{33}Cl_2N_5O_5S$[k]	706[k]	0.17	2.5	15
20	Cl	5-NH(*n*-Pr)	(2-Cl)C_6H_4	D	57	110–112	$C_{35}H_{35}Cl_2N_5O_4S{\cdot}0.33H_2O$	693	1.0	29	29
21	Cl	5-NHCO(*c*-Pr)	(2-Cl)C_6H_4	G	62	190–192	$C_{36}H_{33}Cl_2N_5O_5S{\cdot}0.6CH_2Cl_2$	718	0.08	4.4	55
22	Cl	5-NHCO(*i*-Pr)	(2-Cl)C_6H_4	G	75	158–160	$C_{36}H_{35}Cl_2N_5O_5S{\cdot}0.25CH_2Cl_2$	759[j]	0.18	4.4	24
23	Cl	5-NHCO(*n*-Pr)	(2-Cl)C_6H_4	G	65	>130 (grad.)	$C_{36}H_{35}Cl_2N_5O_5S$[l]	720[l]	0.11	2.3	21
24	Cl	5-NHCO(*n*-Bu)	(2-Cl)C_6H_4	C	48	>100 (grad.)	$C_{37}H_{37}Cl_2N_5O_5S$[m]	734[m]	0.16	1.6	10
25	Cl	5-NHCO(*i*-Bu)	(2-Cl)C_6H_4	G	76	163–165	$C_{37}H_{37}Cl_2N_5O_5S{\cdot}0.33CH_2Cl_2$	734	0.11	2.3	21
26	Cl	5-NHCO(*t*-Bu)	(2-Cl)C_6H_4	G	77	167–169	$C_{37}H_{37}Cl_2N_5O_5S{\cdot}0.33CH_2Cl_2$	734	0.16	13	81
27	Cl	5-$NHCOCH_2$(*t*-Bu)	(2-Cl)C_6H_4	G	74	173–175	$C_{38}H_{39}Cl_2N_5O_5S{\cdot}0.5CH_2Cl_2$	786[j]	0.21	5.6	27
28	Cl	5-$NHCH_2C_6H_5$	(2-Cl)C_6H_4	D	60	113–115	$C_{39}H_{35}Cl_2N_5O_4S{\cdot}0.33H_2O$	740	0.30	>10[n]	>30
29	Cl	5-$NHCOC_6H_5$	(2-Cl)C_6H_4	G	83	>147 (grad.)	$C_{39}H_{33}Cl_2N_5O_5S{\cdot}H_2O$	755	0.41	4.1	10
30	Cl	5-$NHCOCH_2C_6H_5$	(2-Cl)C_6H_4	G	32	157–160	$C_{40}H_{35}Cl_2N_5O_5S{\cdot}0.5CH_2Cl_2$	768	0.12	6.5	54
31	Cl	5-$NHCO(CH_2)_2C_6H_5$	(2-Cl)C_6H_4	G	72	159–161	$C_{41}H_{37}Cl_2N_5O_5S{\cdot}0.25CH_2Cl_2$	820[j]	0.25	2.9	12
32	Cl	5-$NHCO_2$(*n*-Pr)	(2-Cl)C_6H_4	H	74	>119 (grad.)	$C_{36}H_{35}Cl_2N_5O_6S{\cdot}0.5CH_2Cl_2$	737	0.26	6.6	25
33	Cl	5-NHCONH(*n*-Pr)	(2-Cl)C_6H_4	I	61	>208 (grad.)	$C_{36}H_{35}Cl_2N_6O_5S{\cdot}0.5CH_2Cl_2$	773[j]	0.14	4.8	34
34	Cl	5-CO_2Me	(2-Cl)C_6H_4	A	88	98–101	$C_{34}H_{30}Cl_2N_4O_6S{\cdot}0.5H_2O$	693	0.25	17	68
35	Cl	5-CONH(*n*-Bu)	(2-Cl)C_6H_4	E	91	>155 (grad.)	$C_{37}H_{37}Cl_2N_5O_5S{\cdot}0.33CH_2Cl_2$	735	0.14	2.4	17
36	Cl	5-CON(Me)(*n*-Bu)	(2-Cl)C_6H_4	J	36	>90 (grad.)	$C_{38}H_{39}Cl_2N_5O_5S{\cdot}0.6CH_2Cl_2$	748	0.63	58	92
37	Me	3-NHCO(*n*-Bu)	(2-Cl)C_6H_4	C	46	133–136	$C_{38}H_{40}ClN_5O_5S{\cdot}1.5H_2O$	752[j]	24	134	5.6
38	H	3-NO_2	(2-Cl)C_6H_4	A	95	92–95	$C_{32}H_{28}ClN_5O_6S{\cdot}0.4CH_2Cl_2$	646	31	173	5.6
39	H	3-NH_2	(2-Cl)C_6H_4	B	95	137–139	$C_{32}H_{30}ClN_5O_4S{\cdot}0.5H_2O{\cdot}0.25CH_2Cl_2$	616	5.8	142	24
40	H	3-NHCOEt	(2-Cl)C_6H_4	C	60	105–107	$C_{35}H_{34}ClN_5O_5S{\cdot}0.3CH_2Cl_2$	672	0.85	34	40
41	H	3-NHCO(*n*-Bu)	(2-Cl)C_6H_4	C	67	102–105	$C_{37}H_{38}ClN_5O_5S{\cdot}0.25CH_2Cl_2$	738	0.90	15	17
42	Cl	5-NHCOEt	(3,4-Cl_2)-2-furoyl	G	30	>223 dec	$C_{33}H_{30}Cl_3N_5O_6S$[o]	730[o]	0.043	3.4	79
43	Cl	5-NHCOEt	O(*t*-Bu)	F	51	133–135	$C_{33}H_{38}ClN_5O_6S{\cdot}0.5H_2O$	596[p]	0.21	1.6	7.6
44	Cl	5-NHCO(*n*-Bu)	O(*t*-Bu)	G	46	177–179	$C_{35}H_{42}ClN_5O_6S{\cdot}0.25H_2O$	568[p]	0.072	1.4	19
45	CF_3	5-NHCOEt	(2-Cl)C_6H_4	A	50	102–105	$C_{36}H_{33}ClF_3N_5O_5S$[q]	740[q]	0.21	2.1	10
46	CF_3	5-NHCOEt	O(*t*-Bu)	F	52	158–161	$C_{34}H_{38}F_3N_5O_6S{\cdot}H_2O$	702[r]	0.29	1.0	3.4

[a] Reaction used for the last step. (A) (2-Cl)$C_6H_4CO_2H$, Im_2CO, DBU; (B) $SnCl_2$/HCl; (C) NaH, BrCOR; (D) RCHO, piperidine, $NaBH_3CN$; (E) RNH_2; (F) NaH, $(BOC)_2O$; (G) RCOCl, DMAP, pyridine; (H) RCO_2Cl, DMAP, pyridine; (I) RNCO, DMAP, pyridine; (J) NHMe(*n*-Bu), BOP reagent. See the Experimental Section for detailed description of these methods. [b] Analyses for C, H, and N within ±0.4% of calculated values except where characterized by high resolution FAB-MS (FAB-HRMS). [c] *m/e* values reported are $(M + H)^+$ unless otherwise noted. [d] SO_2NHCOR^3 replaced by 5-tetrazolyl in **5**. This compound was characterized in ref 24, and the biological data shown were reported in ref 25. [e] This compound was characterized and the associated biological data were reported in ref 25. [f] This compound was characterized and the associated biological data were reported in ref 1. [g] FAB-HRMS *m/e* 740.1944 [calcd for $C_{36}H_{34}ClF_3N_5O_5S$ $(M + H)^+$ 740.1918]. [h] *m/e* reported for $(M + Li)^+$. [i] FAB-HRMS *m/e* 650.1374 [calcd for $C_{32}H_{30}Cl_2N_5O_4S$ $(M + H)^+$ 650.1393]. [j] *m/e* reported for $(M + K)^+$. [k] FAB-HRMS *m/e* 706.1636 [calcd for $C_{35}H_{34}Cl_2N_5O_5S$ $(M + H)^+$ 706.1655]. [l] FAB-HRMS *m/e* 720.1840 [calcd for $C_{36}H_{36}Cl_2N_5O_5S$ $(M + H)^+$ 720.1811]. [m] FAB-HRMS *m/e* 734.2044 [calcd for $C_{37}H_{38}Cl_2N_5O_5S$ $(M + H)^+$ 734.1968]. [n] This analogue showed 17% inhibition at 10 nM under the AT_2 assay protocol used. [o] FAB-HRMS *m/e* 730.1034 [calcd for $C_{33}H_{31}Cl_3N_5O_6S$ $(M + H)^+$ 730.1058]. [p] *m/e* reported for $[M + H - (t\text{-BOC})]^+$. The presence of the *tert*-butyl group was confirmed by NMR. [q] FAB-HRMS *m/e* 740.1934 [calcd for $C_{36}H_{34}ClF_3N_5O_5S$ $(M + H)^+$ 740.1918]. [r] FAB-HRMS *m/e* 702.2549 [calcd for $C_{34}H_{39}F_3N_5O_6S$ $(M + H)^+$ 702.2570].

9–12) is shown in Scheme 1. *N*-Carbethoxyvalerimidate **47**[24] was reacted with [4-nitro-2-(trifluoromethyl)-phenyl]hydrazine[29] and triethylamine to afford the triazolinone **48**, unsubstituted at N^4.[24,30] Alkylation of **48** with 4′-(bromomethyl)-*N*-*tert*-butyl-2-biphenylsulfonamide **49**[31] afforded the intermediate **50**. The *tert*-butyl group was removed by treatment with trifluoroacetic acid (TFA), and the free sulfonamide was acylated with (2-chlorobenzoyl)imidazolide to give compound **9**.[1,32] Acylation of the corresponding aniline **10**, obtained from **9** by tin(II) chloride reduction, afforded the amide **11**. The secondary amine **12** was prepared from **10** via reductive amination with benzaldehyde. For compounds in the corresponding reversed amide series

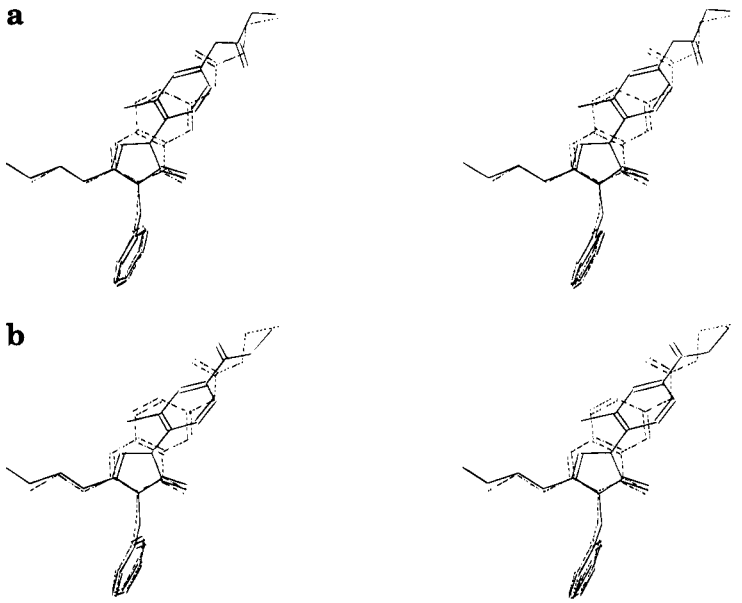


Figure 1. Stereoviews of computer-generated, energy-minimized conformations of partial structures (or proposed partial structures) of dual AT_1/AT_2 AII antagonists: (a) overlay of triazolinone **A** (solid) with quinazolinone **C** (dotted), (b) overlay of triazolinone **B** (solid) with **C** (dotted).

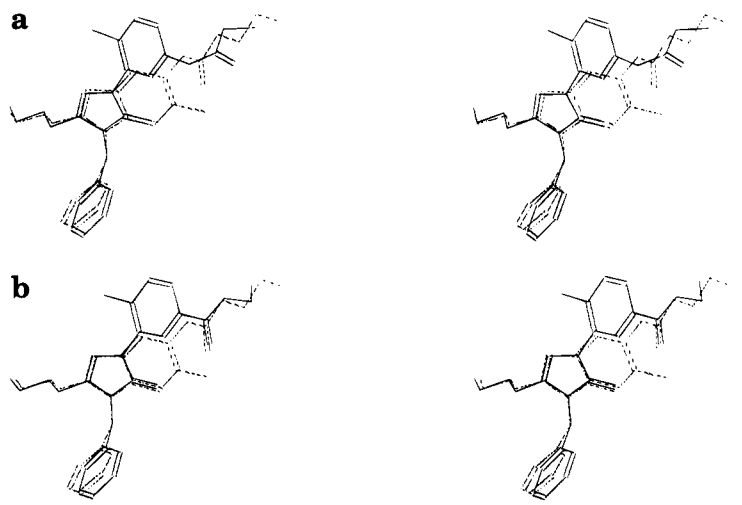
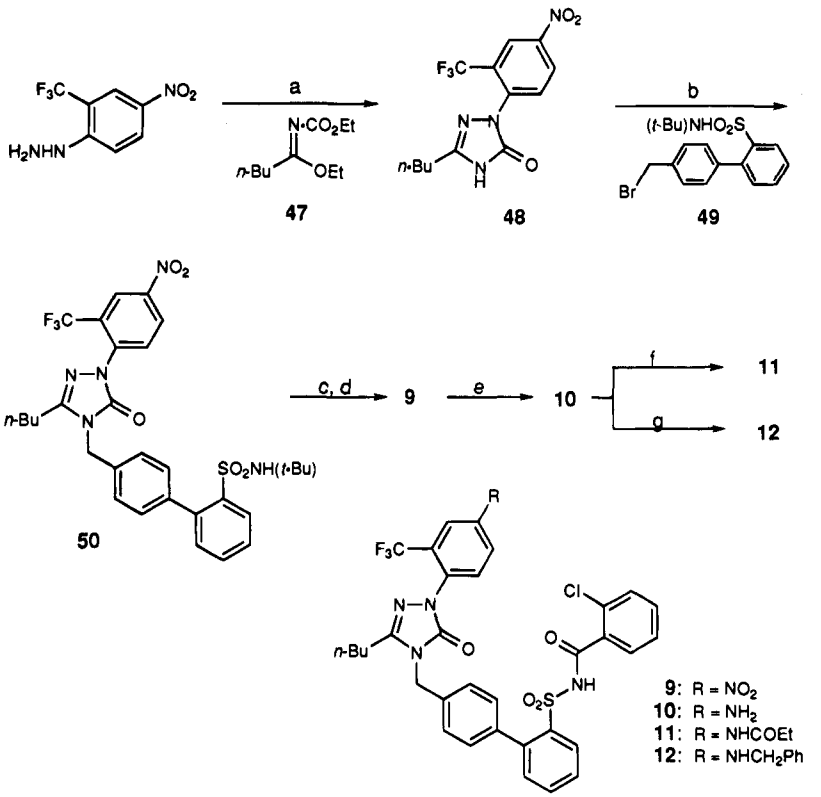


Figure 2. Stereoviews of computer-generated, energy-minimized conformations of partial structures (or proposed partial structures) of dual AT_1/AT_2 AII antagonists: (a) overlay of triazolinone **D** (solid) with imidazopyridine **F** (dotted); (b) overlay of triazolinone **E** (solid) with **F** (dotted).

(**13**–**15**), (4-carbethoxy-2-chlorophenyl)hydrazine (available from 2-chloro-4-methylaniline via *N*-acetyl-2-chloro-4-carbethoxyaniline) was reacted with imidate **47**. The product was then alkylated with the biarylmethylbromide **49**,[31] and the *tert*-butyl group was subsequently removed to provide the intermediate **51**. Acylation of this free sulfonamide afforded compound **14** as shown in Scheme 2. Treatment of **14** with *N*-pentylamine provided the reversed amide **13**. Deprotonation of the free sulfonamide intermediate **51**, followed by reaction with di-*tert*-butyl dicarbonate afforded the corresponding sulfonylcarbamate **15**.

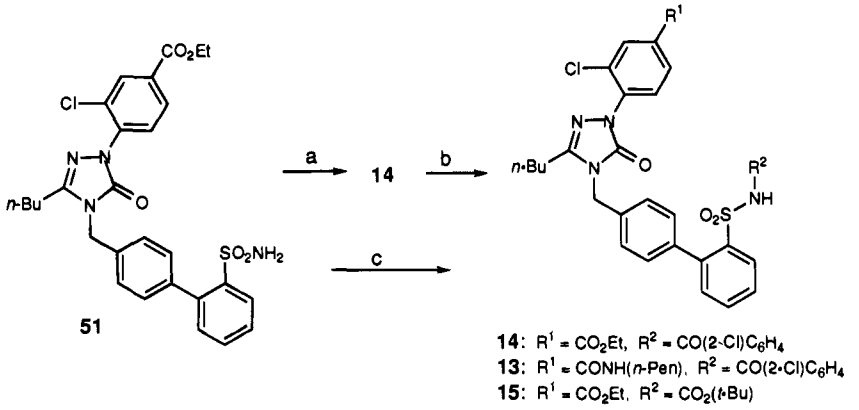
For the N^2-(2,5-disubstituted)phenyl series (compounds **16**–**36**), two key intermediates, **17** and **34**, were prepared from (2-chloro-5-nitrophenyl)hydrazine and (5-carbomethoxy-2-chlorophenyl)hydrazine, respectively, using synthetic sequences analogous to those discussed above. Further elaboration via one of the methods previously described, or acylation of the appropriate acyl chloride in pyridine with 1 equiv of 4-(dimethylamino)-pyridine (DMAP) at room temperature,[33] provided analogues **18**–**31** and **35**. The carbamate **32** and the urea **33** were prepared from **17** as shown in Scheme 3.[1] A tertiary amide on the 5-position of the N^2-aryl ring (**36**) was prepared by saponification of compound **34** followed by coupling of the resulting acid with *N*-methylbutylamine via (benzotriazol-1-yloxy)tris(dimethylamino)-phosphonium hexafluorophosphate (BOP reagent, Scheme 3).[34] An example of an N^2-(2,3-disubstituted phenyl) compound (**37**) and several analogues with an N^2-(3-substituted phenyl) group (**38**–**41**), unsubstituted at the 2-positon, were prepared from the appropriately substituted phenylhydrazines via a sequence parallel to that shown in Scheme 1. Compound **42**, bearing a heteroaroyl sulfonamide, was prepared by a sequence analogous to that shown in Scheme 1 also, using the appropriately substituted phenylhydrazine and acyl chloride. Because of incompatibility of the sulfonylcarbamate moiety with tin(II) chloride reduction, **43** was prepared by first elaborating the N^2-substituent as shown in Scheme 4. Thus, the intermediate **52** was reduced to the aniline (**53**) and acylated to give **54** before

Scheme 1[a]



[a] Key: (a) NEt_3, toluene, 90 °C; (b) NaH, DMF; (c) TFA, anisole; (d) method A: (2-Cl)$C_6H_4CO_2H$, Im_2CO, DBU, THF; (e) method B: $SnCl_2$/HCl; (f) method C: NaH, DMF, ClCOEt; (g) method D: C_6H_5CHO, piperidine, i-PrOH, $NaBH_3CN$, MeOH.

Scheme 2[a]



[a] Key: (a) (2-Cl)$C_6H_4CO_2H$, Im_2CO, DBU; (b) method E: $NH_2(CH_2)_4CH_3$; (c) method F: NaH, THF, $(BOC)_2O$.

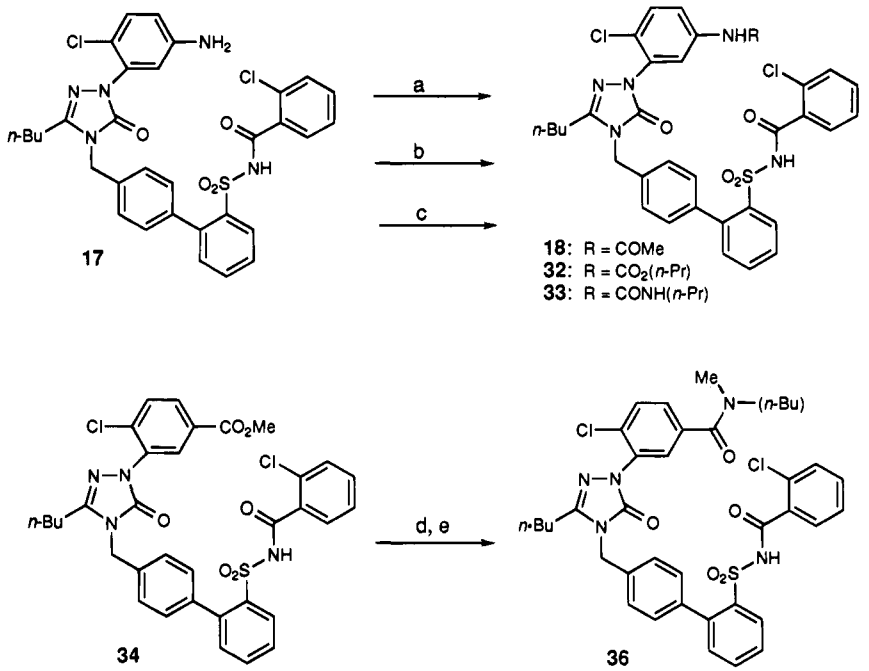
operating on the sulfonamide moiety to afford the desired analogue **43**. Alternatively, sulfonylcarbamates could be prepared by the route shown for compound **44**: hydrogenation of the intermediate **55** using PtO_2 as the catalyst followed by acylation (Scheme 4).

The synthesis of compounds **45** and **46** provided a challenge since the starting substituted phenylhydrazine was not easily accessible. We ultimately found a solution in a bromo-to-trifluoromethyl conversion,[35] as depicted in Scheme 5. Thus, the triazolinone **56** (obtained from (2-bromo-5-nitrophenyl)hydrazine using reactions analogous to Scheme 1, steps a,b) was heated with methyl 2-chloro-2,2-difluoroacetate, potassium fluoride, and copper(I) iodide in dimethylformamide (DMF). The resulting mixture of 2-trifluoromethyl and 2-chloro products, formed in a 54:46 ratio, was separated by flash chromatography to afford the desired intermediate **57**, containing the trifluoromethyl group. Further elaboration of **57** as indicated in Scheme 5 furnished analogues **45** and **46** in four more steps.

Biological Results and Discussion

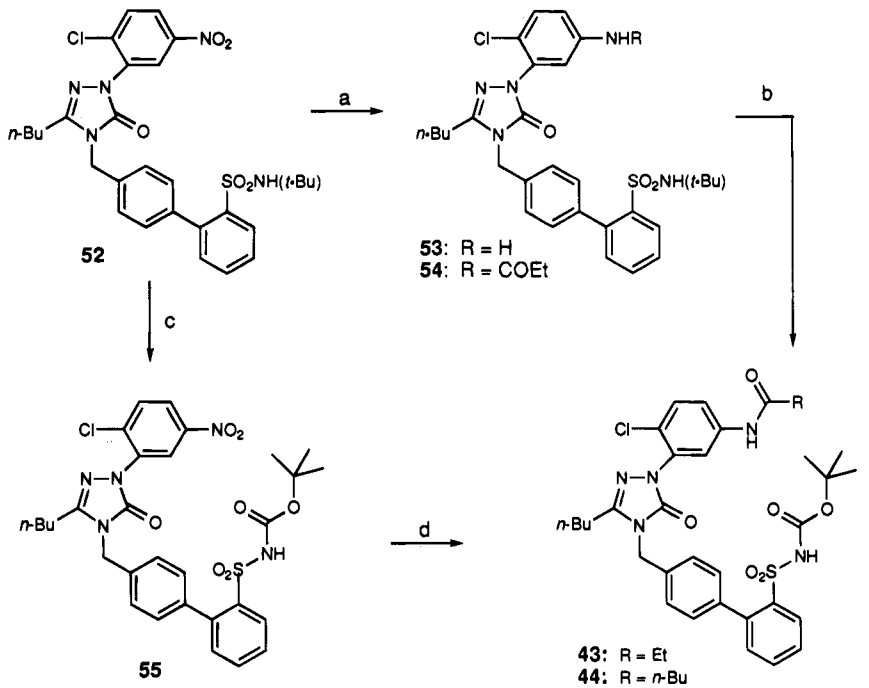
The *in vitro* binding affinities of triazolinones **9**–**46** for the AT_1 and the AT_2 receptors were evaluated by their ability to competitively block the specific binding of ^{125}I[Sar^1,Ile^8]AII to a rabbit aorta AT_1 receptor preparation and a rat midbrain AT_2 receptor preparation (see Table 1).[36] For each key compound, multiple runs of the assays were conducted to ensure consistency in the IC_{50} values obtained. Data from a series of compounds with an N^2-[4-substituted-2-(trifluoromethyl)phenyl] moiety (**9**–**12**) show that acylamino or alkylamino substituents at the 4-position are compatible with subnanomolar AT_1 binding affinity. However, these analogues all showed deleterious effects on AT_2 binding

Scheme 3[a]



[a] Key: (a) method G: CH_3COCl, DMAP, py; (b) method H: $ClCO_2(n\text{-Pr})$, DMAP, py; (c) method I: $OCN(n\text{-Pr})$, DMAP, py; (d) NaOH/MeOH, HCl; (e) method J: $NEt(i\text{-Pr})_2$, $NHMe(n\text{-Bu})$, BOP reagent.

Scheme 4[a]

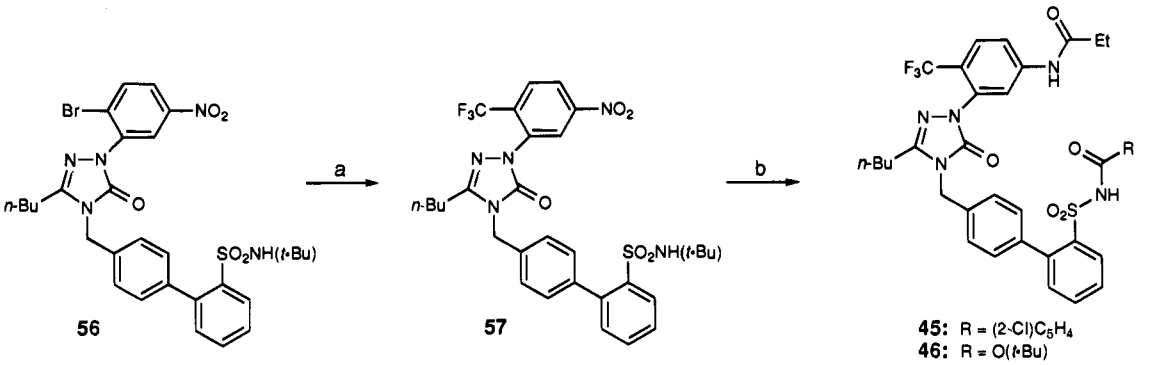


[a] Key: (a) (i) $SnCl_2$, HCl; (ii) NaH, DMF, BrCOEt; (b) (i) TFA, anisole, (ii) NaH, THF, $(BOC)_2O$; (c) (i) TFA, anisole, (ii) NaH, DMF, $(BOC)_2O$, (d) (i) H_2, 10% PtO_2, EtOAc, (ii) $ClCO(CH_2)_3CH_3$, DMAP, py.

affinity compared to compound **7**, unsubstituted at the 4-position. In a series of 4-substituted compounds bearing a carbonyl group directly attached to the N^2-aryl ring (**13**–**15**), substantial decreases in AT_1 activity and poorer AT_2 binding were observed. Analogues **14** and **15** compare acylsulfonamides vs sulfonylcarbamates in this series and demonstrate that there is no apparent advantage in the latter with respect to lowering the AT_2/AT_1 IC_{50} ratio. In contrast, the 4-unsubstituted sulfonylcarbamate derivative **8** displayed a superior AT_2/AT_1 IC_{50} ratio compared to the corresponding acylsulfonamide **7**. Therefore, although certain substituents at the 4-position of the N^2-aryl group are acceptable in their interaction with the AT_1 receptor, these substituents are incompatible with good AT_2 binding.

Concurrently, data from a series of compounds with an N^2-(5-substituted-2-chlorophenyl) group (**16**–**36**) became available. The 5-nitro and the 5-amino compounds (**16**–**17**) retained subnanomolar potency at the AT_1 receptor but lost considerable binding at the AT_2 receptor compared to the lead (**7**). However, initial

Scheme 5[a]



[a] Key: (a) $ClCF_2CO_2Me$, CuI, KF, DMF; (b) (i) H_2, PtO_2, EtOH/EtOAc, (ii) BrCOEt, DMAP, py, (iii) TFA, anisole, (iv) $(2\text{-Cl})C_6H_4CO_2H$, Im_2CO, DBU; or NaH, THF, $(BOC)_2O$.

results from a series of 5-acylamino derivatives provided renewed impetus. The propionamide **19**, the first compound prepared in this series, gave a 150-fold improvement in AT_2 binding affinity over that obtained for the 5-amino derivative **17** and a 14-fold gain relative to the 5-unsubstituted compound **7**. Data from compound **19** demonstrated that it is possible to bring the AT_2 binding affinity to the required low nanomolar range while maintaining subnanomolar AT_1 potency. Extensive derivatizations at the 5-acylamino moiety were undertaken, aimed at improving the AT_2/AT_1 IC_{50} ratio of 15 observed for compound **19**. This study brought out several points concerning the structure–activity relationships of the amide side chain. A comparison of the data for two pairs of compounds, **20** vs **19** and **28** vs **29**, clearly shows that the carbonyl function is required for nanomolar AT_2 binding affinity, although its absence had much less deleterious effect on AT_1 potency. Variations in the length and/or bulk of the amide side chain were carefully investigated (**18**, **19**, **21**–**27**, **29**–**31**). Among the straight chain derivatives (**18**–**19**, **23**–**24**), the valeramide (**24**) was the most active at the AT_2 receptor with an IC_{50} value of 1.6 nM. This compound retained excellent affinity for the AT_1 receptor resulting in a reduction of AT_2/AT_1 IC_{50} ratio to 10. The benzoylamino derivative (**20**) attained a comparable decrease in the AT_2/AT_1 IC_{50} ratio at the expense of intrinsic potency at both receptors. The acetylamino derivative **18** exhibited modest AT_2 binding. However, the propionyl homologue **19** was 5-fold more potent at this receptor. Therefore, a three-carbon (rather than 2-carbon) acyl chain length is apparently much more effective in making an important hydrophobic contact with the AT_2 receptor. Further extension of this amide side chain renders limited additional benefit on AT_2 binding affinity. This point is well-illustrated by a number of alkanoylamino derivatives (**18**, **19**, **23**–**25**). Branching on the carbon atom adjacent to the amide carbonyl contributed to loss in AT_2 potency as illustrated by analogues **19**, **22**, and **26**, which have varying degrees of substitution on the α-carbon. The pivaloylamino derivative **26** was 6-fold inferior to the propionylamino compound **19**. The added steric bulk in the former may interfere with the hydrogen-bonding ability of the amide carbonyl. In a series of five- or six-carbon acylamino derivatives, **24**–**27**, AT_2 activity decreased as the degree of branching increased, while AT_1 potency remained essentially unchanged. Several compounds with small amide substituents had very high AT_1 potency, demonstrated by the acetamide **18** and the cyclopropanecarboxamide **21**. In fact, analogues with 5-acylamino substituents ranging in size from acetylamino (**18**) to 3-(phenylpropionyl)amino (**31**) all retained subnanomolar AT_1 binding affinity. However, the AT_2 binding affinity seen for the propionamide **19** was exceeded only by the valeramide **24**. The carbamate and urea analogues of the amide **24** were prepared (**32**, **33**) to study the effects of isosteric substitution. While these all had comparable AT_1 potencies, the amide had the highest AT_2 binding affinity, followed by the urea and the carbamate.

An ester and several reversed amides at the 5-position were also evaluated (**34**–**36**). The results suggest that these have binding affinities similar to those of the corresponding amides at both the AT_1 and the AT_2 receptors (**35** vs **24**). The deleterious effect of a tertiary amide in this series is amply demonstrated by compound **36**, which suffered a 24-fold loss in AT_2 binding affinity and a 4-fold loss in AT_1 potency, compared to the corresponding secondary amide **35**. This substantial loss in AT_2 potency could be due either to steric (or conformational) factors or to a requirement for the NH as a hydrogen-bond donor. Compound **37** illustrates the importance of proper substitution pattern on the N^2-aryl moiety. This compound, which contains an N^2-(2-methyl-3-valeramidophenyl) group, suffered a >80-fold loss in binding affinity to both the AT_1 and AT_2 receptors compared to compound **24** where the substituents are *para* to each other on the phenyl ring. A series of compounds which bear only a 3-substituent on the N^2-aryl moiety were prepared to study the role of the *ortho*-substituent on this ring (**38**–**41**). As indicated in Table 1, loss in binding affinity for both receptors was observed, although proportionally there was a greater loss in AT_2 affinity (**40** vs **19** and **41** vs **24**). These data not only confirm our initial assumption concerning the need of a substituent at the *ortho* position of the N^2-aryl ring to optimize AT_1 potency but also suggest that this substituent may play a role in favorably biasing the orientation of the ligand for interaction with the AT_2 receptor. Alternatively, this *ortho* substituent could be involved in a direct interaction with the receptor to bring about the somewhat superior AT_2 binding affinity observed in analogues **19** and **24**. Interestingly, with an AT_2/AT_1 IC_{50} ratio close to 5, compounds **37** and **38** were the most balanced of the analogues studied thus

far. Unfortunately, their relatively poor intrinsic binding affinities at both receptors precluded further interest.

Several attempts were made to modify the sulfonamide site in an effort to increase binding affinity to the AT_2 receptor and improve the AT_2/AT_1 IC_{50} ratio. Drawing upon available SAR from a previous study,[1] compound **42**, bearing a (3,4-dichloro-2-furoyl)sulfonamide, was prepared. This compound, although highly active at the AT_1 receptor, had AT_2 affinity inferior to that of the (2-chlorobenzoyl)sulfonamide **19**. The (*tert*-butoxycarbonyl)sulfonamide analogues of several potent compounds were also prepared. Compounds **43** and **44** had binding affinity for the AT_2 receptor at least equivalent to that of the corresponding (2-chlorobenzoyl)sulfonamide analogues **19** and **24**. Both of these carbamates met the potency criteria, and **43**, analogous to **19**, emerged as the preferred derivative with an AT_2/AT_1 IC_{50} ratio of 8.

Compounds with an N^2-[2-(trifluoromethyl)-5-amidophenyl] moiety were of particular interest since, in previous studies, derivatives with an N^2-[2-(trifluoromethyl)phenyl] group exhibited superior *in vivo* properties relative to analogues containing an N^2-(2-chlorophenyl) group.[1,24] Compounds **45** and **46**, analogues of **19** and **43**, respectively, were evaluated. Data from the (2-chlorobenzoyl)sulfonamide pair, **45** and **19**, show that for the trifluoromethyl analogue, binding affinities altered somewhat at both the AT_1 and AT_2 receptors to give a compound with an AT_2/AT_1 IC_{50} ratio of 10. A more dramatic effect of the trifluoromethyl substitution was seen in compound **46**. With an AT_1 IC_{50} value of 0.29 nM and an AT_2 IC_{50} value of 1.0 nM, this derivative showed slightly decreased AT_1 potency but greater AT_2 binding affinity compared to the chloro analogue **43**, to attain an AT_2/AT_1 ratio of 3.

Models of the AT_1 receptor–ligand interactions for triazolinone-based AT_1-selective AII antagonists have been discussed.[1,24] The effects of substitutions on the aryl ring at N^2 and on the N-substituent of the sulfonamide have been examined at length.[1,24] Available data underlined the importance of an *ortho* substituent on the N^2-aryl moiety for achieving ligands with high affinity for the AT_1 receptor. Results from the present study not only corroborate this finding but also show that a wide range of 5-substituents on the N^2-aryl group are accommodated without much effect on AT_1 binding affinity, although small acylamino groups are most favorable. This remarkable tolerance to size, shape, and to some degree, different functional groups at the 5-position suggests that only a limited segment of this side chain makes contact with the AT_1 receptor. The noncontact region is rather spacious, able to accommodate groups as large as 3-(phenylpropionyl)amino.

The AT_2 receptor has been shown previously to be quite sensitive to changes in the N-substituent of the sulfonamide in triazolinone-based ligands.[1] The present study demonstrates a slight preference for *tert*-butyl sulfonylcarbamates over (2-chlorobenzoyl)sulfonamides for optimal AT_2 activity in a series of compounds incorporating a 5-carbamoyl or 5-acylamino substituent on the N^2-aryl moiety (**19** vs **43**, **24** vs **44**, and **45** vs **46**). More importantly, the substantial increase in AT_2 binding affinity attained by this 5-acylamino substituent (e.g., **7** vs **45**) strongly suggests that it is involved in a discrete interaction with the AT_2 receptor. The requirement of a carbonyl function in this substituent for nanomolar AT_2 binding affinity, whether in a carbamoyl or an acylamino arrangement, implies that the carbonyl group is directly involved in binding to the AT_2 receptor, perhaps serving as a hydrogen-bond acceptor. Our data suggest that the amide side chain extends into a spacious receptor cavity that contains a lipophilic region. The dimensions of this pocket may be inferred from the range of amide substituents evaluated here. High AT_2 affinity was achieved by medium-to-long alkyl or aralkyl groups, presumably capable of interacting with the hydrophobic site. In contrast, side chains too short to make substantial contact with this site, or too sterically congested near the carbonyl group, were much less favored.

Additionally, small conformational changes influencing the orientation of the amide side chain, and/or minor alterations of receptor contact by the 2-substituent on the N^2-aryl ring, may play a role in improving the AT_2/AT_1 IC_{50} ratios in this series. Thus, changing the 2-chloro substituent on the N^2-aryl ring to a 2-trifluoromethyl group, while maintaining all other structural features constant, gave more balanced compounds (**19** vs **45**; **43** vs **46**).

Table 2. Inhibition of AII Pressor Response by Triazolinone Derivatives in Conscious, Normotensive Rats

no.	dose (mg/kg)	route	peak inhibn (%)	duration,[a] (h)	N^b
7[c]	1.0	iv	91 ± 3	>24	4
	1.0	po	85 ± 5	>6, <24	4
8[c]	1.0	iv	83 ± 2	>6, <24	2
	1.0	po	87 ± 1	>6, <24	2
24	0.3	iv	91 ± 7	>6, <24	4
	1.0	po	41 ± 15	ND[d]	6
46	1.0	iv	90 ± 4	>6, <24	4
	1.0	po	74 ± 1	>5, <24	4
	3.0	po	95 ± 4	>6, <24	8

[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] Data taken from ref 1. [d] ND = not determined.

In Vivo Pharmacology

Several compounds were evaluated by their ability to inhibit the pressor response to AII challenge in conscious normotensive rats, as shown in Table 2.[37] By intravenous administration, the (2-chlorobenzoyl)sulfonamide **24** and the *tert*-butyl sulfonylcarbamate **46** were quite efficacious at 0.3 mg/kg and 1 mg/kg, respectively. Via this route, these compounds compared favorably with the corresponding N^2-(5-unsubstituted aryl) compounds[1] (**24** vs **7**, **46** vs **8**). Upon oral administration, compound **46** showed excellent efficacy and good duration of action at 3 mg/kg. At 1 mg/kg po, it was superior to the (2-chlorobenzoyl)sulfonamide **24**. Comparing the data for the *tert*-butyl sulfonylcarbamates **46** and **8**, it appears that the added 5-acylamino substituent in **46**, necessary for high AT_2 binding affinity, had minimal effects on the *in vivo* properties of this compound. The inhibition of the AII pressor response in rats by **46** (L-163,007) upon intravenous and oral administration is shown in Figure 3.

Conclusions

In order to identify dual-action ligands with high-affinity for both the AT_1 (rabbit aorta) and the AT_2 (rat midbrain) subtypes of the AII receptor, several series

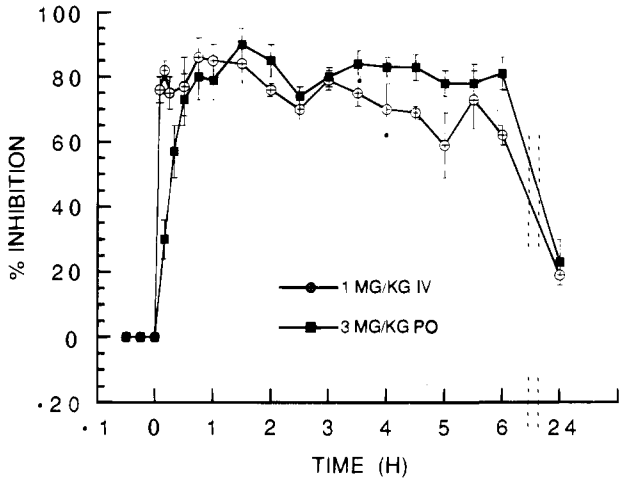


Figure 3. Percent inhibition of AII pressor response in conscious, normotensive rats by triazolinone **46** (L-163,007) at 1 mg/kg iv ($N = 4$) and 3 mg/kg po ($N = 8$). Results are expressed as mean ± SEM.

of trisubstituted triazolinones were made by a number of synthetic sequences. Starting with compounds **7** and **8**, which exhibited modest affinity for the AT_2 receptor (Table 1), several of the derivatives prepared showed nanomolar AT_2 IC_{50} values, subnanomolar AT_1 potency, and reduced AT_2/AT_1 IC_{50} ratios (**19**, **24**, **43**–**46**). These improvements in AT_2 binding affinity and AT_2/AT_1 IC_{50} ratio were achieved primarily by optimizing contacts with two putative binding sites on the AT_2 receptor: (a) a lipophilic pocket accessible to the acylsulfonamide or sulfonylcarbamate group and (b) a second site for the 5-acylamino or 5-carbamoyl substituent on the N^2-aryl moiety. These structural features apparently had minimal effects on the interactions between these ligands and the AT_1 receptor. While the amide moiety played an important role in improving AT_2 receptor binding, the orientation of the amide (NHCO vs CONH) was of little consequence. The interaction of this amide side chain with the AT_2 receptor appears to consist of both a hydrogen-bonding component and a hydrophobic component. In this study, **46** (L-163,007) evolved as the most balanced compound. It was somewhat more potent than **8** at the AT_1 receptor and had an AT_2 IC_{50} value of 1 nM, giving an AT_2/AT_1 IC_{50} ratio of 3 under the assay conditions. This compound demonstrated effective antihypertensive properties with good duration of action iv and orally at 1–3 mg/kg in a conscious rat model. The added 5-acylamino substituent, crucial for high AT_2 binding affinity, had limited impact on the *in vivo* properties of this compound. Further efforts toward achieving fully AT_1/AT_2-balanced AII antagonists in this series will be reported in the near future.

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), electrospray ionization (ESI), or electron impact (EI) mass spectra (MS) were obtained on Varian MAT 731, Finnigan MAT 90, JEOL HX110A, JEOL SX102, and Varian MAT 212 instruments. Flash column chromatography was carried out on EM Science silica gel 60 (230–400 mesh). Compounds showed satisfactory purity by TLC on Analtech silica gel GHLF plates (visualized by UV light at 254 nm and/or by 1% ceric sulfate in 10% aqueous H_2SO_4) in the indicated solvent systems. Elemental combustion analyses, where indicated only by the elements, were within ±0.4% of theoretical values and obtained from Robertson Microlit Laboratories, Inc. 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. Purities of final products characterized by high-resolution FAB-MS were checked by reversed-phase HPLC on a Beckman Ultrasphere ODS column [(octadecylsilyl) 4.6 mm x 15 cm 5 μm particle size], eluting with 45:55 ratio of 0.04 *M* phospate buffer:methanol at 37 °C at a flow rate of 1 mL/min, and detected by UV at 210 nm.

Anhydrous tetrahydrofuran (THF), methylene chloride, toluene, and dimethylformamide (DMF) were purchased from Aldrich Chemical Co. and kept under rubber septa. Reagent grade DMSO, MeOH, and EtOH were dried over 3 Å molecular sieves. Reactions were routinely conducted under N_2 (bubbler) unless otherwise indicated.

5-*n*-Butyl-2,4-dihydro-2-[4-nitro-2-(trifluoromethyl)-phenyl]-3*H*-1,2,4-triazol-3-one (48). To a solution of 2.00 g (9.05 mmol) of (4-nitro-2-(trifluoromethyl)phenyl)hydrazine[29] in 18 mL of toluene was added 2.00 g (9.95 mmol) of **47**,[24] and the solution was heated at 50 °C for 1.5 h. Subsequently, 1.40 mL (1.00 g, 9.95 mmol) of triethylamine was added, and the reaction mixture was stirred at 90 °C for 15 h. After the mixture was cooled to room temperature, volatiles were removed *in vacuo*. Flash chromatography of the residue (gradient elution with 0.5–5% MeOH in CH_2Cl_2) afforded 815 mg (27%) of the desired product as an orange solid, homogeneous by TLC (95:5 CH_2Cl_2/MeOH): mp 126–128 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.91 (t, $J = 7.3$ Hz, 3 H), 1.38 (m, 2 H), 1.66 (m, 2 H), 2.57 (t, $J = 7.6$ Hz, 2 H), 7.83 (d, $J = 8.8$ Hz, 1 H), 8.50 (dd, $J = 8.8$, 2.6 Hz, 1 H), 8.67 (d, $J = 2.6$ Hz, 1 H), 11.25 (br s, 1 H); high-resolution FAB-MS *m/e* 331.1025 [calcd for $C_{13}H_{14}F_3N_4O_3$ $(M + H)^+$ 331.1018]. Anal. ($C_{13}H_{13}F_3N_4O_3 \cdot 0.25H_2O$) C, H, N.

5-*n*-Butyl-4-[[2′-(*N*-*tert*-butylsulfamoyl)biphenyl-4-yl]-methyl]-2,4-dihydro-2-[4-nitro-2-(trifluoromethyl)phenyl]-3*H*-1,2,4-triazol-3-one (50). A mixture of 764 mg (2.32 mmol) of **48**, 66.8 mg (2.78 mmol) of sodium hydride (60% in oil), and 4.6 mL of dry DMF was stirred at 50 °C for 1 h. After the mixture was cooled to room temperature, a solution of 1.33 g (3.48 mmol) of **49**[31] dissolved in a minimal volume of DMF was added, and the resulting mixture was stirred at 50 °C for 1.5 h. The reaction was quenched at room temperature by addition of water and ethyl acetate (EtOAc). After separation of phases, the aqueous phase was re-extracted with EtOAc. The combined organic layers were washed with water and brine and dried over Na_2SO_4. After filtration and concentration of the filtrate *in vacuo*, the crude product was flash chromatographed (gradient elution with 0.5–5.0% MeOH/CH_2Cl_2) to yield 1.29 g (88%) of the product as an orange solid, homogeneous by TLC (98:2 CH_2Cl_2/MeOH): mp >78 °C (gradual); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.90 (t, $J = 7.4$ Hz, 3 H), 0.98 (s, 9 H), 1.40 (m, 2 H), 1.66 (m, 2 H), 2.50 (t, $J = 7.5$ Hz, 2 H), 3.47 (s, 1 H), 4.95 (s, 2 H), 7.25–7.60 (m, 7 H), 7.92 (d, $J = 9.1$ Hz, 1 H), 8.15 (dd, $J = 7.9$, 1.4 Hz, 1 H), 8.48 (dd, $J = 8.9$, 2.6 Hz, 1 H), 8.66 (d, $J = 2.5$ Hz, 1 H); high-resolution FAB-MS *m/e* 632.2162 [calcd for $C_{30}H_{33}F_3N_5O_5S$ $(M + H)^+$ 632.2154]. Anal. ($C_{30}H_{32}F_3N_5O_5S \cdot 0.25H_2O$) C, H, N.

5-*n*-Butyl-2,4-dihydro-2-[4-nitro-2-(trifluoromethyl)-phenyl]-4-[(2′-sulfamoylbiphenyl-4-yl)methyl]-3*H*-1,2,4-triazol-3-one (58). A solution of 660 mg (1.04 mmol) of **50** and 20 μL of anisole in 10 mL of trifluoroacetic acid (TFA) was stirred overnight at room temperature. The excess TFA and the volatiles were removed by a stream of nitrogen, and the residue was taken up in CH_2Cl_2, washed with 5% $NaHCO_3$, and dried over Na_2SO_4. The residue obtained after filtration and removal of solvents was flash chromatographed (gradient elution with 0.5–2% MeOH/CH_2Cl_2) to give 414 mg (69%) of a cream-colored solid, homogeneous by TLC (95:5 CH_2Cl_2/MeOH): mp 218–220 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, $J = 7.3$ Hz, 3 H), 1.38 (m, 2 H), 1.65 (m, 2 H), 2.52 (t, $J = 7.5$ Hz, 2 H), 4.20 (s, 2 H), 4.96 (s, 2 H), 7.25–7.61 (m, 7 H),

7.92 (d, J = 8.9 Hz, 1 H), 8.14 (dd, J = 7.7, 1.0 Hz, 1 H), 8.48 (dd, J = 8.8, 2.5 Hz, 1 H), 8.66 (d, J = 2.5 Hz, 1 H); high-resolution EI-MS m/e 575.1442 [calcd for $C_{26}H_{24}F_3N_5O_5S$ (M^+) 575.1451]. Anal. ($C_{26}H_{24}F_3N_5O_5S$) C, H, N.

Method A. 5-*n*-Butyl-4-[[2′-[*N*-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-2,4-dihydro-2-[4-nitro-2-(trifluoromethyl)phenyl]-3*H*-1,2,4-triazol-3-one (9). A solution of 213 mg (1.36 mmol) of 2-chlorobenzoic acid and 221 mg (1.36 mmol) of 1,1′-carbonyldiimidazole (Im_2CO) in 5 mL of THF was stirred at 50 °C for 3 h. Subsequently, a solution of 391 mg (0.68 mmol) of the free sulfonamide **58** and 203 μL (207 mg, 1.36 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in 10 mL of THF was added dropwise. After being stirred overnight at 50 °C, the reaction mixture was cooled to room temperature and quenched by addition of 5% aqueous citric acid and extracted with EtOAc twice. The combined organic layers were washed with 2 N HCl (aqueous), water, and brine and dried over Na_2SO_4. The crude product obtained after filtration and removal of solvents was flash chromatographed over SiO_2 (gradient elution using 0.5–5.0% MeOH/CH_2Cl_2) to afford 207 mg (43%) of the desired product as a cream-colored solid, homogeneous by TLC (95:5 CH_2Cl_2/MeOH): mp 179–181 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, J = 7.3 Hz, 3 H), 1.37 (m, 2 H), 1.64 (m, 2 H), 2.47 (t, J = 7.5 Hz, 2 H), 4.88 (s, 2 H), 7.17–7.70 (m, 10 H), 7.91 (d, J = 8.9 Hz, 1 H), 8.36 (dd, J = 7.9, 1.5 Hz, 1 H), 8.43 (s, 1 H), 8.49 (dd, J = 8.8, 2.6 Hz, 1 H), 8.67 (d, J = 2.6 Hz, 1 H); FAB-MS m/e 714 $(M + H)^+$. Anal. ($C_{33}H_{27}ClF_3N_5O_6S$) C, H, N.

Method B. 2-[4-Amino-2-(trifluoromethyl)phenyl]-5-*n*-butyl-4-[[2′-[*N*-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (10). At 0 °C, to a solution of 82 mg (0.115 mmol) of **9** dissolved in 1 mL of THF was added dropwise a solution of 182 mg (0.805 mmol) of stannous chloride dihydrate dissolved in 2.2 mL of concentrated HCl. After the mixture was stirred at 0 °C for 15 min the ice/water bath was removed, and stirring was continued until TLC indicated disappearance of all starting material (30 min). The reaction mixture was poured onto a mixture of 3 g of ice, 0.8 mL of 50% NaOH, and 1.6 mL of EtOAc. The phases were separated after stirring for 15 min at 0 °C, and the aqueous phase was re-extracted with EtOAc twice. The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and evaporated. Flash chromatography of the crude residue over silica gel (gradient elution using 0.5–2.0% MeOH/CH_2Cl_2) gave 53 mg (67%) of a cream-colored solid, homogeneous by TLC (90:10 CH_2Cl_2/MeOH): mp 134–136 °C; ^1H NMR (CD_3OD, 400 MHz) δ 0.87 (t, J = 7.4 Hz, 3 H), 1.35 (m, 2 H), 1.56 (m, 2 H), 2.52 (t, J = 7.5 Hz, 2 H), 4.99 (s, 2 H), 6.89–7.71 (m, 14 H), 8.29 (dd, J = 8.0, 1.3 Hz, 1 H); FAB-MS m/e 684 $(M + H)^+$. Anal. ($C_{33}H_{29}ClF_3N_5O_4S·0.5H_2O$) C, H, N.

Method C. 5-*n*-Butyl-4-[[2′-[*N*-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-2,4-dihydro-2-[4-(propionylamino)-2-(trifluoromethyl)phenyl]-3*H*-1,2,4-triazol-3-one (11). At room temperature, a solution of 45 mg (0.066 mmol) of **10** in DMF (0.5 mL) was stirred with 1.7 mg (0.072 mmol) of NaH for 3 h. Subsequently, 9.1 mg (0.099 mmol) of propionyl chloride was added, and the resulting mixture was stirred at 50 °C overnight. After the reaction was quenched with water, the organic material was extracted with EtOAc, washed with water and brine, and then dried over Na_2SO_4. The crude product obtained upon filtration and removal of volatiles was flash chromatographed over SiO_2 (gradient elution with 0.5–5% MeOH/CH_2Cl_2) to afford 26 mg (40%) of the desired material as a cream-colored solid, homogeneous by TLC (90:10 CH_2Cl_2/MeOH): mp 204–206 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.87 (t, J = 7.3 Hz, 3 H), 1.19 (t, J = 7.5 Hz, 3 H), 1.34 (m, 2 H), 1.61 (m, 2 H), 2.37 (q, J = 7.5 Hz, 2 H), 2.47 (t, J = 7.6 Hz, 2 H), 4.92 (s, 2 H), 6.37 (br s, 1 H), 7.14–7.75 (m, 12 H), 7.89 (s, 1 H), 8.19 (s, 1 H), 8.36 (d, J = 7.1 Hz, 1 H), 8.63 (br s, 1 H); HPLC retention time 42.25 min (98%); high-resolution FAB-MS m/e 740.1934 [calcd for $C_{36}H_{34}ClF_3N_5O_5S$ $(M + H)^+$ 740.1918].

Method D. 2-[4-(Benzylamino)-2-(trifluoromethyl)phenyl]-5-*n*-butyl-4-[[2′-[*N*-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (12). A solution of 70 mg (0.093 mmol) of **11**, 33 mg (0.31 mmol) of benzaldehyde, 2.1 μL of piperidine, and 2.5 mL of 2-propanol was stirred at 95 °C overnight. The crude material obtained after cooling and evaporation of volatiles was dissolved in 2.2 mL of MeOH, charged with 1.3 mL of a 1 M solution of sodium cyanoborohydride in THF (1.3 mmol), and stirred at room temperature for 2 h. Water (160 μL) was added at 0 °C, and resulting mixture stirred at 0 °C for 2 h. After evaporation of volatiles, the crude product was flash chromatographed over SiO_2 to afford 27 mg (38%) of the desired product as a cream-colored solid, homogeneous by TLC (90:10 CH_2Cl_2/MeOH): mp >107 °C (gradual); ^1H NMR (CD_3OD, 400 MHz) δ 0.87 (t, J = 7.3 Hz, 3 H), 1.33 (m, 2 H), 1.57 (m, 2 H), 2.51 (t, J = 7.5 Hz, 2 H), 4.41 (s, 2 H), 4.98 (s, 2 H), 6.82–7.73 (m, 19 H), 7.89 (s, 1 H), 8.29 (dd, J = 8.1, 1.4 Hz, 1 H); high-resolution FAB-MS m/e 774.2127 [calcd for $C_{40}H_{36}ClF_3N_5O_4S$ $(M + H)^+$ 774.2125]. Anal. ($C_{40}H_{35}ClF_3N_5O_4S·2CH_2Cl_2$) C, H, N.

5-*n*-Butyl-2-[4-carbethoxy-2-(trifluoromethyl)phenyl]-4-[[2′-[*N*-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (14). A solution of 220 mg (1.41 mmol) of 2-chlorobenzoic acid and 228 mg (1.41 mmol) of Im_2CO in 5 mL of THF was stirred at 65 °C for 4 h. Subsequently, a solution of 400 mg (0.704 mmol) of the free sulfonamide **51** [prepared from **47** and (4-carbethoxy-2-chlorophenyl)hydrazine via a sequence of reactions analogous to that used to prepare **58** (Scheme 1, steps a–c)], and 211 μL (214 mg, 1.41 mmol) of DBU in 10 mL of THF was added dropwise. After being stirred for 24 h at 50 °C, the reaction mixture was cooled to room temperature and quenched by addition of 5% aqueous citric acid and extracted with EtOAc twice. The combined organic layers were washed with 2 N HCl (aqueous), water, and brine and dried over Na_2SO_4. The crude product obtained after filtration and removal of solvents was flash chromatographed over SiO_2 (gradient elution using 0.5–5.0% MeOH/CH_2Cl_2) to afford 457 mg (92%) of the desired product as a cream-colored solid, homogeneous by TLC (95:5 CH_2Cl_2/MeOH): mp 72–75 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.90 (t, J = 7.3 Hz, 3 H), 1.37 (m, 2 H), 1.40 (t, J = 7.1 Hz, 3 H), 1.66 (m, 2 H), 2.49 (t, J = 7.4 Hz, 2 H), 4.39 (q, J = 7.1 Hz, 2 H), 4.89 (s, 2 H), 7.19–7.40 (m, 8 H), 7.55–7.66 (m, 4 H), 8.00 (dd, J = 1.9, 8.3 Hz, 1 H), 8.18 (d, J = 1.9 Hz, 1 H), 8.37 (dd, J = 7.9, 1.3 Hz, 1 H), 8.43 (br s, 1 H); high-resolution FAB-MS m/e 707.1500 [calcd for $C_{35}H_{33}Cl_2N_4O_6S$ $(M + H)^+$ 707.1502]. Anal. ($C_{35}H_{32}Cl_2N_4O_6S·0.5H_2O$) C, H, N.

Method E. 5-*n*-Butyl-4-[[2′-[*N*-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl-2,4-dihydro-2-[4-(*N*-*n*-pentylcarbamoyl)-2-(trifluoromethyl)phenyl]-3*H*-1,2,4-triazol-3-one (13). A solution of 80 mg (0.113 mmol) of **14** in 1 mL of *n*-amylamine was stirred at 95 °C for 48 h. After removal of excess amine, the crude product was flash chromatographed over SiO_2 (gradient elution with 0.8–2% MeOH/CH_2Cl_2) to give 55 mg (62%) of the desired product as a pale yellow solid, homogeneous by TLC (90:10 CH_2Cl_2/MeOH): mp 124–127 °C; ^1H NMR (CD_3OD, 400 MHz) δ 0.89 (t, J = 7.3 Hz, 3 H), 0.94 (t , J = 6.8 Hz, 3 H), 1.39 (m, 6 H), 1.64 (m, 4 H), 2.57 (t, J = 7.4 Hz, 2 H), 3.38 (t, J = 7.1 Hz, 2 H), 5.02 (s, 2 H), 7.13 (dd, J = 8.4, 1.4 Hz, 1 H), 7.26–7.40 (m, 6 H), 7.51–7.68 (m, 5 H), 7.88 (dd, J = 8.2, 1.9 Hz, 1 H), 8.04 (d, J = 1.9 Hz, 1 H), 8.28 (dd, J = 8.0, 1.2 Hz, 1 H); FAB-MS m/e 748 $(M + H)^+$. Anal. ($C_{38}H_{39}Cl_2N_5O_5S·H_2O$) C, H, N.

Method F. 4-[[2′-[*N*-(*tert*-Butoxycarbonyl)sulfamoyl]biphenyl-4-yl]methyl-5-*n*-butyl-2-[4-carbethoxy-2-(trifluoromethyl)phenyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (15). A solution of **51** [prepared from **47** and (4-carbethoxy-2-chlorophenyl)hydrazine via a sequence of reactions analogous to that used to prepare **58** (Scheme 1, steps a–c)] in 1 mL of THF was treated with 6.0 mg (0.25 mmol) of NaH in oil, and the mixture was stirred at 50 °C for 1 h. At room temperature, 48 mg (0.22 mmol) of di-*tert*-butyl dicarbonate, $(BOC)_2O$, was added and stirring continued for 24 h. After the mixture was cooled to room temperature, the volatiles were removed and the residue was flash chromatographed over SiO_2 (gradient elution using 1–10% MeOH/CH_2Cl_2) to give 35 mg (49%) of the desired material as a foam, homogeneous by TLC (95:5 CH_2Cl_2/MeOH): mp 84–87 °C; ^1H

NMR ($CDCl_3$, 400 MHz) δ 0.90 (t, J = 7.3 Hz, 3 H), 1.28 (s, 9 H), 1.37 (m, 2 H), 1.39 (t, J = 7.2 Hz, 3 H), 1.64 (m, 2 H), 2.53 (t, J = 7.6 Hz, 2 H), 4.38 (q, J = 7.2 Hz, 2 H), 4.96 (s, 2 H), 6.49 (s, 1 H), 7.29–7.42 (m, 5 H), 7.54–7.64 (m, 3 H), 8.00 (dd, J = 8.2, 1.8 Hz, 1 H), 8.17 (d, J = 1.8 Hz, 1 H), 8.23 (dd, J = 7.9, 1.2 Hz, 1 H); FAB-MS m/e 669 $(M + H)^+$. Anal. ($C_{33}H_{37}ClN_4O_7S \cdot H_2O$) C, H, N.

Method G. 2-[5-(Acetylamino)-2-chlorophenyl]-5-*n*-butyl-4-[[2′-[*N*-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]-methyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (18). At room temperature, a solution of 100 mg (0.154 mmol) of **17** [prepared from **47** and (2-chloro-5-nitrophenyl)hydrazine via a sequence of reactions analogous to that used to prepare **10** (Scheme 1, steps a–e)] in pyridine (1 mL) was stirred with 19 mg (0.154 mmol) of 4-(dimethylamino)pyridine (DMAP) and 55 μL (61 mg, 0.77 mmol) of acetyl chloride overnight. The reaction was quenched with water, and the organic material was extracted with EtOAc, washed with water and brine, and then dried over Na_2SO_4. After filtration and removal of volatiles, the crude product was flash chromatographed over SiO_2 (gradient elution with 1–5% MeOH/CH_2Cl_2) to afford 65 mg (61%) of the desired material as a cream-colored solid, homogeneous by TLC (90:10 CH_2Cl_2/MeOH): mp 190–192 °C; ^1H NMR (CD_3OD, 400 MHz) δ 0.89 (t, J = 7.3 Hz, 3 H), 1.37 (m, 2 H), 1.60 (m, 2 H), 2.13 (s, 3 H), 2.56 (m, 2 H), 5.01 (s, 2 H), 7.11 (dd, J = 7.0, 1.6 Hz, 1 H), 7.21 (m, 1 H), 7.27–7.34 (m, 5 H), 7.51–7.56 (m, 4 H), 7.59–7.65 (m, 2 H), 7.88 (d, J = 2.5 Hz, 1 H), 8.27 (dd, J = 8.0, 1.3 Hz, 1 H); FAB-MS m/e 731$(M + K)^+$. Anal. ($C_{34}H_{31}Cl_2N_5O_5S$) C, H, N.

Method H. 5-*n*-Butyl-4-[[2′-[*N*-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-2-[2-chloro-5-[(*n*-propoxycarbonyl)amino]phenyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (32). At room temperature, a solution of 20 mg (0.031 mmol) of **17** [prepared from **47** and 2-chloro-5-nitrophenylhydrazine via a sequence of reactions analogous to that used to prepare **10** (Scheme 1, steps a–e)], 3.8 mg (0.031 mmol) of DMAP, 18.9 mg (0.154 mmol) of *n*-propyl chloroformate, and 1 mL of pyridine was stirred overnight. After the reaction was quenched with methanol and water, the organic material was extracted with EtOAc, washed with water and brine, and dried over Na_2SO_4. The crude product obtained after filtration and removal of volatiles was flash chromatographed over SiO_2 (gradient elution with 0.5–5% MeOH/CH_2Cl_2) to give 15 mg (65%) of the desired compound as a white solid, homogeneous by TLC (90:10 CH_2Cl_2/MeOH): mp >119 °C (gradual); ^1H NMR (CD_3OD, 400 MHz) δ 0.89 (t, J = 7.3 Hz, 3 H), 0.99 (t, J = 7.4 Hz, 3 H), 1.37 (m, 2 H), 1.61 (m, 2 H), 1.69 (m, 2 H), 2.55 (t, J = 7.8 Hz, 2 H), 4.09 (t, J = 6.5 Hz, 2 H), 5.01 (s, 2 H), 7.13–7.75 (m, 14 H), 8.28 (d, J = 7.1 Hz, 1 H); FAB-MS m/e 737 $(M + H)^+$. Anal. ($C_{36}H_{35}Cl_2N_5O_6S \cdot 0.5CH_2Cl_2$) C, H, N.

Method I. 5-*n*-Butyl-4-[[2′-[*N*-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-2-[2-chloro-5-(*N*^{3}-propylureido)phenyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (33). At room temperature, a solution of 34 mg (0.052 mmol) of **17** [prepared from **47** and 2-chloro-5-nitrophenylhydrazine via a sequence of reactions analogous to that used to prepare **10** (Scheme 1, steps a–e)], 6.4 mg (0.052 mmol) of DMAP, 23 mg (0.26 mmol) of *n*-propyl isocyanate, and 1 mL of pyridine was stirred overnight. After the reaction was quenched with water, the organic material was extracted with EtOAc, washed with water and brine, and dried over Na_2SO_4. The crude product obtained after filtration and removal of volatiles was flash chromatographed over SiO_2 (gradient elution with 0.5–5% MeOH/CH_2Cl_2) to give 23 mg (61%) of the desired compound as a white solid, homogeneous by TLC (90:10 CH_2Cl_2/MeOH): mp >208 °C (gradual); ^1H NMR (CD_3OD, 400 MHz) δ 0.91 (m, 6 H), 1.38 (m, 2 H), 1.51 (m, 2 H), 1.61 (m, 2 H), 2.55 (t, J = 7.8 Hz, 2 H), 3.12 (m, 2H), 4.99 (s, 2 H), 7.12–7.70 (m, 14 H), 8.28 (dd, J = 7.9, 1.2 Hz, 1 H); FAB-MS m/e 773 $(M + K)^+$. Anal. ($C_{36}H_{36}Cl_2N_6O_5S \cdot 0.5CH_2Cl_2$) C, H, N.

5-*n*-Butyl-2-(5-carboxy-2-chlorophenyl)-4-[[2′-[*N*-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (59). A solution of 71 mg (0.102 mmol) of **34** [prepared from **47** and (5-carbomethoxy-2-chlorophenyl)-hydrazine via a sequence of reactions analogous to that used to prepare **9** (Scheme 1, steps a–d)] in 0.7 mL (0.7 mmol) of 1 N NaOH (methanolic) was stirred at 60 °C overnight and then concentrated to dryness. The residue was dissolved in 1 mL of methanol, acidified to approximately pH 1.5 by addition of 1 N HCl (methanolic), and again concentrated. The residue was dissolved in $CHCl_3$, dried over Na_2SO_4, and filtered through Celite. Evaporation of volatiles yielded 58 mg (84%) of the desired compound as a white solid, nearly homogeneous by TLC (90:10 CH_2Cl_2/MeOH): ^1H NMR ($CDCl_3$, 400 MHz) δ 0.90 (t, J = 7.3 Hz, 3 H), 1.39 (m, 2 H), 1.67 (m, 2 H), 2.50 (t, J = 7.7 Hz, 2 H), 4.91 (s, 2 H), 7.19–7.68 (m, 11 H), 8.00 (dd, J = 8.4, 1.9 Hz, 1 H), 8.13 (d, J = 2.0 Hz, 1 H), 8.37 (dd, J = 7.9, 1.5 Hz, 1 H), 8.77 (br s, 1 H); high-resolution FAB-MS m/e 679.1189 [calcd for $C_{33}H_{29}Cl_2N_4O_6S$ $(M + H)^+$ 679.1185]. Anal. ($C_{33}H_{28}Cl_2N_4O_6S \cdot H_2O$) C, H, N.

Method J. 5-*n*-Butyl-2-[5-(*N*-*n*-butyl-*N*-methylcarbamoyl)-2-chlorophenyl]-4-[[2′-[*N*-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (36). A solution of 40 mg (0.0589 mmol) of **59** and 51.3 μL (38.1 mg, 0.295 mmol) of *N*,*N*-diisopropylethylamine in 1 mL of CH_2Cl_2 and 0.3 mL of DMF was stirred at 0 °C under protection from moisture as 27.9 mL (20.5 mg, 0.236 mmol) of *N*-methylbutylamine was added, followed by 52.1 mg (0.118 mmol) of (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP reagent). The solution was stirred at 0 °C overnight and then concentrated. The residue was reconcentrated twice from toluene. It was then taken up in CH_2Cl_2 and washed twice with 5% citric acid (aqueous), twice with 5% $NaHCO_3$ (aqueous), and then with brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated. The residue was flash chromatographed on SiO_2 (gradient elution with 1–5% MeOH in CH_2Cl_2) and then further purified by HPLC on a semipreparative Zorbax C8 reversed-phase column (elution with 60:40 CH_3CN–H_2O) to give a 36% yield of the desired compound as a colorless, glassy solid, homogeneous by TLC (90:10 CH_2Cl_2/MeOH); by NMR, this material appeared to exist as a mixture of rotomers: mp >90 °C (gradual); ^1H NMR (CD_3OD, 400 MHz) δ 0.90 (t, J = 7.4 Hz, 6 H), 1.38 (m, 4 H), 1.62 (m, 4 H), 2.57 (t, J = 7.5 Hz, 2 H), 3.00 and 3.06 (s, total 3 H), 3.30 and 3.54 (t, J = 7.3 Hz, total 2 H), 5.02 (s, 2 H), 7.14 (dd, J = 7.0, 0.9 Hz, 1 H), 7.29–7.75 (m, 13 H), 8.30 (dd, J = 8.0, 1.3 Hz, 1 H); FAB-MS m/e 748 $(M + H)^+$, 770 $(M + Na)^+$. Anal. ($C_{38}H_{39}Cl_2N_5O_5S \cdot 0.6CH_2Cl_2$) C, H, N.

2-(5-Amino-2-chlorophenyl)-5-*n*-butyl-4-[[2′-(*N*-*tert*-butylsulfamoyl)biphenyl-4-yl]methyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (53). At 0 °C, to a solution of 250 mg (0.418 mmol) of 5-*n*-butyl-4-[[2′-(*N*-*tert*-butylsulfamoyl)biphenyl-4-yl]-methyl]-2-(2-chloro-5-nitrophenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (**52**) [prepared from **47** and 2-(chloro-5-nitrophenyl)-hydrazine via a sequence of reactions analogous to that used to prepare **50** (Scheme 1, steps a and b)] dissolved in 4 mL of THF was added dropwise a solution of 660 mg (2.93 mmol) of stannous chloride dihydrate, dissolved in 8 mL of concentrated HCl. After the mixture was stirred at 0 °C for 15 min, the ice/water bath was removed, and stirring was continued until TLC indicated disappearance of all starting material (1 h). The reaction mixture was poured onto a mixture of 10 g of ice, 9 mL of 50% NaOH, and 6 mL of EtOAc. The phases were separated after stirring for 1 h, and the aqueous phase was re-extracted with EtOAc twice. The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and evaporated. Flash chromatography of the crude residue over silica gel (gradient elution using 0.5–5.0% MeOH/CH_2Cl_2) gave 149 mg (63%) of a cream-colored solid, homogeneous by TLC (90:10 CH_2Cl_2/MeOH): mp 163–165 °C; ^1H NMR (CD_3OD, 400 MHz) δ 0.90 (t, J = 7.3 Hz, 3 H), 1.01 (s, 9H), 1.39 (m, 2 H), 1.62 (m, 2 H), 2.60 (m, 2 H), 5.04 (s, 2 H), 6.74–6.80 (m, 2 H), 7.22 (d, J = 8.6 Hz, 1 H), 7.31 (dd, J = 7.6, 1.4 Hz, 1 H), 7.33–7.40 (m, 2 H), 7.47–7.64 (m, 4 H), 8.10 (dd, J = 7.9, 1.2 Hz, 1 H); high-resolution FAB-MS m/e 568.2148 [calcd for $C_{29}H_{35}ClN_5O_3S$ $(M + H)^+$ 568.2149].

5-*n*-Butyl-4-[[2′-(*N*-*tert*-butylsulfamoyl)biphenyl-4-yl]-methyl]-2-[2-chloro-5-(propionylamino)phenyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (54). At room temperature, a solution of 81 mg (0.143 mmol) of **53** in DMF (1 mL) was stirred with 3.8 mg (0.157 mmol) of NaH for 3 h. Subse-

quently, 26 μL (29 mg, 0.286 mmol) of propionyl chloride was added, and the resulting mixture was stirred at 50 °C overnight. After the reaction was quenched with water, the organic material was extracted with EtOAc, washed with water and brine, and then dried over Na_2SO_4. After filtration and removal of volatiles, the crude product was flash chromatographed over SiO_2 (gradient elution with 0.5–5% MeOH/CH_2Cl_2) to afford 41 mg (46%) of the desired material as a cream-colored solid, homogeneous by TLC (90:10 CH_2Cl_2/MeOH): mp 105–107 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, J = 7.3 Hz, 3 H), 0.99 (s, 9 H), 1.16 (t, J = 7.5 Hz, 3 H), 1.36 (m, 2 H), 1.62 (m, 2 H), 2.32 (q, J = 7.5 Hz, 2 H), 2.48 (m, 2 H), 3.59 (br s, 1 H), 4.96 (s, 2 H), 7.26–7.40 (m, 5 H), 7.45–7.60 (m, 4 H), 7.77 (d, J = 2.5 Hz, 1 H), 8.15 (dd, J = 7.8, 1.5 Hz, 1 H), 8.23 (s, 1 H); high-resolution FAB-MS m/e 624.2391 [calcd for $C_{32}H_{39}ClN_5O_4S$ (M + H)$^+$ 624.2412].

5-*n*-Butyl-4-[(2′-sulfamoylbiphenyl-4-yl)methyl]-2-[2-chloro-5-(propionylamino)phenyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (60). A solution of 39 mg (0.063 mmol) of **54** and 5 μL of anisole in 0.6 mL of TFA was stirred overnight at room temperature. The excess TFA and other volatiles were removed by a stream of nitrogen, and the residue was coevaporated with toluene twice. The crude product was flash chromatographed (gradient elution with 0.5–5% MeOH/CH_2Cl_2) to give 30 mg (85%) of a cream-colored solid, homogeneous by TLC (95:5 CH_2Cl_2/MeOH): ^1H NMR ($CDCl_3$, 400 MHz) δ 0.87 (t, J = 7.2 Hz, 3 H), 1.13 (t, J = 7.5 Hz, 3 H), 1.36 (m, 2 H), 1.60 (m, 2 H), 2.29 (q, J = 7.5 Hz, 2 H), 2.52 (m, 2 H), 4.45 (br s, 2 H), 4.94 (s, 2 H), 7.27–7.34 (m, 4 H), 7.39 (dd, J = 8.6, 2.5 Hz, 1 H), 7.44–7.60 (m, 4 H), 7.75 (d, J = 2.5 Hz, 1 H), 8.11 (dd, J = 8.0, 1.4 Hz, 1 H), 8.27 (s, 1 H); high-resolution EI-MS m/e 567.1725 [calcd for $C_{28}H_{30}ClN_5O_4S$ (M^+) 567.1707].

5-*n*-Butyl-4-[[2′-[*N*-(*tert*-butoxycarbonyl)sulfamoyl]biphenyl-4-yl]methyl]-2-[2-chloro-5-(propionylamino)phenyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (43). A solution of 101 mg (0.18 mmol) of **60** in 1.5 mL of THF was treated with 5.1 mg (0.21 mmol) of NaH in oil, and the mixture was stirred at 50 °C for 3 h. At room temperature, 78 mg (0.36 mmol) of $(BOC)_2O$ was added, and stirring was continued for 48 h at 50 °C. After the mixture was cooled to room temperature, the reaction was quenched by addition of water and acidified to pH 3 using 2 N HCl (aqueous). The organic material was extracted with EtOAc twice. The combined organic layer was washed with water and brine, and dried over Na_2SO_4. The residue obtained after filtration and removal of solvents was flash chromatographed over SiO_2 (gradient elution using 0.5–5% MeOH/CH_2Cl_2) to give 61 mg (51%) of the desired material as a white solid, homogeneous by TLC (95:5 CH_2Cl_2/MeOH): mp 133–135 °C; ^1H NMR (CD_3OD, 400 MHz) δ 0.91 (t, J = 7.4 Hz, 3 H), 1.19 (t, J = 7.5 Hz, 3 H), 1.29 (s, 9 H), 1.40 (m, 2 H), 1.65 (m, 2 H), 2.39 (t, J = 7.5 Hz, 2 H), 2.63 (m, 2 H), 5.05 (s, 2 H), 7.30–7.40 (m, 5 H), 7.44–7.64 (m, 3 H), 7.69 (t, J = 7.5 Hz, 1 H), 7.93 (d, J = 2.3 Hz, 1 H), 8.15 (d, J = 8.0 Hz, 1 H); FAB-MS m/e 569 [M + H − (CO_2-*tert*-Bu)]$^+$. Anal. ($C_{33}H_{38}ClN_5O_6S$·0.5H_2O) C, H, N.

5-*n*-Butyl-2-(2-chloro-5-nitrophenyl)-2,4-dihydro-4-[(2′-sulfamoylbiphenyl-4-yl)-methyl]-3*H*-1,2,4-triazol-3-one (61). A solution of 1.18 g (1.98 mmol) of **52** [prepared from **47** and 2-chloro-5-nitrophenylhydrazine via a sequence of reactions analogous to that used to prepare **50** (Scheme 1, steps a and b)] and 0.1 mL of anisole in 20 mL of TFA was stirred at room temperature for 2 days. The excess TFA and the volatiles were removed by a stream of nitrogen, and the residue was dissolved in CH_2Cl_2, washed twice with 5% $NaHCO_3$, and dried over Na_2SO_4. The crude product obtained after filtration and removal of volatiles was flash chromatographed over SiO_2 (gradient elution with 0.5–5% MeOH/CH_2Cl_2) to give 791 mg (74%) of a cream-colored solid, homogeneous by TLC (95:5 CH_2Cl_2/MeOH): mp 159–161 °C (gradual); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.90 (t, J = 7.4 Hz, 3 H), 1.39 (m, 2 H), 1.67 (m, 2 H), 2.53 (t, J = 7.6 Hz, 2 H), 4.23 (s, 2 H), 4.96 (s, 2 H), 7.25–7.61 (m, 7 H), 7.69 (d, J = 8.8 Hz, 1 H), 8.14 (dd, J = 7.9, 1.2 Hz, 1 H), 8.20 (dd, J = 8.8, 2.6 Hz, 1 H), 8.39 (d, J = 2.6 Hz, 1 H); high-resolution EI-MS m/e 541.1194 [calcd for $C_{25}H_{24}ClN_5O_5S$ (M^+) 541.1186].

4-[[2′-[*N*-(*tert*-Butoxycarbonyl)sulfamoyl]biphenyl-4-yl]methyl]-5-*n*-butyl-2-(2-chloro-5-nitrophenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (55). A solution of 190 mg (0.35 mmol) of **61** in 3 mL of THF was treated with 10 mg (0.42 mmol) of NaH in oil, and the mixture was stirred at 50 °C for 4 h. At room temperature, 153 mg (0.70 mmol) of $(BOC)_2O$ was added, and stirring was continued for 48 h at 60 °C. After being cooled to room temperature, the reaction was quenched by addition of water and acidified to pH 3 using 2 N HCl (aqueous). The organic material was extracted with EtOAc twice. The combined organic layer was washed with water and brine and dried over Na_2SO_4. The crude product obtained after filtration and removal of solvents was flash chromatographed over SiO_2 (gradient elution using 0.5–1% MeOH/CH_2Cl_2) to give 128 mg (57%) of the desired material as a glassy solid, homogeneous by TLC (95:5 CH_2Cl_2/MeOH): mp 72–74 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.91 (t, J = 7.4 Hz, 3 H), 1.28 (s, 9 H), 1.39 (m, 2 H), 1.67 (m, 2 H), 2.53 (t, J = 7.5 Hz, 2 H), 4.97 (s, 2 H), 6.50 (s, 1 H), 7.29–7.38 (m, 5 H), 7.52–7.70 (m, 3 H), 8.19–8.24 (m, 2 H), 8.39 (d, J = 2.6 Hz, 1 H); high-resolution FAB-MS m/e 642.1766 [calcd for $C_{30}H_{33}ClN_5O_7S$ (M + H)$^+$ 642.1789].

2-(5-Amino-2-chlorophenyl)-4-[[2′-[*N*-(*tert*-butoxycarbonyl)sulfamoyl]biphenyl-4-yl]methyl]-5-*n*-butyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (62). A mixture of 128 mg (0.2 mmol) of **55**, 10 mg of 10% platinum oxide on carbon, and 2 mL of EtOAc was stirred under a balloon of hydrogen for 4 h. The mixture was then filtered through Celite, and the product was chromatographed over SiO_2 (gradient elution using 0.5–5% MeOH/CH_2Cl_2) to give 78 mg (64%) of the desired material as a white solid, homogeneous by TLC (90:10 CH_2Cl_2/MeOH): mp 185–188 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, J = 7.3 Hz, 3 H), 1.27 (s, 9 H), 1.37 (m, 2 H), 1.65 (m, 2 H), 2.51 (t, J = 7.6 Hz, 2 H), 4.95 (s, 2 H), 6.85 (br d, 1 H), 7.07 (br s, 1 H), 7.24–7.40 (m, 6 H), 7.50–7.65 (m, 2 H), 8.23 (d, J = 8 Hz, 1 H); high-resolution EI-MS m/e 510.1359 [calcd for $C_{30}H_{34}ClN_5O_5S$ [M − (CO_2-*tert*-Bu)]$^+$ 510.1364].

4-[[2′-[*N*-(*tert*-Butoxycarbonyl)sulfamoyl]biphenyl-4-yl]methyl]-5-*n*-butyl-2-[2-chloro-5-(valerylamino)phenyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (44). A solution of 78 mg (0.128 mmol) of **62**, 76 μL (77 mg, 0.64 mmol) of valeryl chloride, and 15.6 mg (0.128 mmol) of DMAP in 1 mL of dry pyridine was stirred overnight at room temperature. The mixture was quenched by addition of water and extracted twice with EtOAc. The combined organic fractions were washed twice with water and then with brine and dried over Na_2SO_4. The filtered solution was concentrated, and the residue was flash chromatographed twice on SiO_2 (gradient elution using 0.5–3% MeOH/CH_2Cl_2) to give 41 mg (46%) of the desired material as a white solid, homogeneous by TLC (90:10 CH_2Cl_2/MeOH): mp 177–179 °C; ^1H NMR (CD_3OD, 400 MHz) δ 0.91 (t, J = 7.4 Hz, 3 H), 0.95 (t, J = 7.4 Hz, 3 H), 1.29 (s, 9 H), 1.40 (m, 4 H), 1.66 (m, 4 H), 2.38 (t, J = 7.5 Hz, 2 H), 2.63 (t, J = 7.5 Hz, 2 H), 5.05 (s, 2 H), 7.33–7.70 (m, 9 H), 7.95 (d, J = 2.5 Hz, 1 H), 8.23 (d, J = 8.1 Hz, 1 H); FAB-MS m/e 597 [M + H − (CO_2-*tert*-Bu)]$^+$. Anal. ($C_{35}H_{42}ClN_5O_6S$·0.25H_2O) C, H, N.

5-*n*-Butyl-4-[[2′-(N-*tert*-butylsulfamoyl)biphenyl-4-yl]-methyl]-2,4-dihydro-2-[5-nitro-2-(trifluoromethyl)phenyl]-3*H*-1,2,4-triazol-3-one (57). To a solution of 600 mg (0.935 mmol) of 2-(2-bromo-5-nitrophenyl)-4-[[2′-(*N*-*tert*-butylsulfamoyl)biphenyl-4-yl]methyl]-5-*n*-butyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (**56**) [prepared from **47** and (2-bromo-5-nitrophenyl)hydrazine via a sequence of reactions analogous to that used to prepare **50** (Scheme 1, steps a and b)] in 1.87 mL of DMF were added 65 mg (1.12 mmol) of potassium fluoride, 179 mg (0.935 mmol) of cuprous iodide, and 197 μL (270 mg, 1.87 mmol) of methyl 2-chloro-2,2-difluoroacetate. The mixture was stirred in a sealed tube at 120 °C for 12 h. The cooled mixture was diluted with water and extracted with EtOAc three times. The combined organic extracts were washed with water and then brine and dried over Na_2SO_4. The residue obtained upon evaporation of the filtered solution was flash chromatographed on SiO_2 (gradient elution using 8.5:1 to 5:1 hexane/EtOAc) to give 216 mg (37%) of the desired material as an off-white solid, homogeneous by TLC (98:2 CH_2Cl_2/

MeOH): mp 135–137 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.90 (t, J = 7.3 Hz, 3 H), 0.98 (s, 9 H), 1.39 (m, 2 H), 1.66 (m, 2 H), 2.51 (t, J = 7.6 Hz, 2 H), 3.49 (s, 1 H), 4.96 (s, 2 H), 7.27 (dd, J = 7.3, 1.4 Hz, 1 H), 7.35 (d, J = 8.2 Hz, 2 H), 7.46–7.57 (m, 4 H), 7.99 (d, J = 8.7 Hz, 1 H), 8.15 (dd, J = 7.9, 1.4 Hz, 1 H), 8.36 (dd, J = 8.6, 1.4 Hz, 1 H), 8.47 (d, J = 2.2 Hz, 1 H); FAB-MS m/e 638 (M + Li)$^+$. Anal. ($C_{30}H_{32}F_3N_5O_5S$) C, H, N. Subsequently eluted was 187 mg (32%) of the corresponding 2-chloro-5-nitrophenyl analogue obtained as a byproduct, homogeneous by TLC (98:2 CH_2Cl_2/MeOH), with NMR and FAB-MS that were identical to those of **52**, an intermediate obtained by a different route: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91 (t, J = 7.3 Hz, 3 H), 0.98 (s, 9 H), 1.39 (m, 2 H), 1.66 (m, 2 H), 2.51 (t, J = 7.6 Hz, 2 H), 3.50 (s, 1 H), 4.96 (s, 2 H), 7.27 (dd, J = 7.5, 1.4 Hz, 1 H), 7.38 (d, J = 8.3 Hz, 2 H), 7.46–7.56 (m, 4H), 7.69 (d, J = 8.8 Hz, 1 H), 8.15 (dd, J = 7.9, 1.3 Hz, 1 H), 8.20 (dd, J = 8.9, 2.7 Hz, 1 H), 8.39 (d, J = 2.6 Hz, 1 H); FAB-MS m/e 598 (M + H)$^+$.

2-[5-Amino-2-(trifluoromethyl)phenyl]-5-*n*-butyl-4-[[2′-(*N*-*tert*-butylsulfamoyl)biphenyl-4-yl]methyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (63). A mixture of 200 mg (0.317 mmol) of **57**, 15 mg of PtO_2, 10 mL of EtOAc, and 2 mL of EtOH was shaken with hydrogen at approximately 4 atm for several hours until reduction was complete and then centrifuged. The supernatant was decanted off, and the catalyst pellet was extracted with EtOH three more times in the same manner. The combined supernatant fractions were concentrated to give 190 mg (100%) of the title compound as a brown glassy solid, which was suitable for use without further purification. This product was homogeneous by TLC (95:5 CH_2Cl_2/MeOH): mp 95–97 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ 0.89 (t, J = 7.4 Hz, 3 H), 0.99 (s, 9 H), 1.37 (m, 2 H), 1.59 (m, 2 H), 2.58 (t, J = 7.5 Hz, 2 H), 5.02 (s, 2 H), 6.71 (d, J = 2.3 Hz, 1 H), 6.79 (dd, J = 8.6, 1.9 Hz, 1 H), 7.29–7.62 (m, 8 H), 8.11 (d, J = 7.9 Hz, 1 H); high-resolution EI-MS m/e 601.2322 [calcd for $C_{30}H_{34}F_3N_5O_3S$ (M^+) 601.2335].

5-*n*-Butyl-4-[[2′-(*N*-*tert*-butylsulfamoyl)biphenyl-4-yl]methyl]-2,4-dihydro-2-[5-(propionylamino)-2-(trifluoromethyl)phenyl]-3*H*-1,2,4-triazol-3-one (64). A mixture of 90 mg (0.15 mmol) of **63**, 18 mg (0.15 mmol) of DMAP, 27 μL (41 mg, 0.30 mmol) of propionyl bromide, and 0.75 mL of pyridine was stirred at room temperature overnight. The reaction mixture was quenched with water, and the organic material was extracted with EtOAc, washed with water and brine, and then dried over Na_2SO_4. After filtration and removal of volatiles, the crude product was flash chromatographed over SiO_2 (gradient elution with 0.5–1.5% MeOH/CH_2Cl_2) to afford 89 mg (90%) of the desired material as a white foam, homogeneous by TLC (95:5 CH_2Cl_2/MeOH); mp 98–100 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.87 (t, J = 7.3 Hz, 3 H), 0.98 (s, 9 H), 1.16 (t, J = 7.4 Hz, 3 H), 1.35 (m, 2 H), 1.60 (m, 2 H), 2.32 (q, J = 7.4 Hz, 2 H), 2.47 (t, J = 7.5 Hz, 2 H), 3.57 (s, 1 H), 4.95 (s, 2 H), 7.26 (dd, J = 7.5, 1.3 Hz, 1 H), 7.33 (d, J = 8.1 Hz, 2 H), 7.45–7.57 (m, 6 H), 7.80 (br s, 1 H), 8.15 (dd, J = 7.9, 1.3 Hz, 1 H), 8.33 (br s, 1 H); ESI-MS m/e 658 (M + H)$^+$, 602 [M + H − (*tert*-Bu)]$^+$. Anal. ($C_{33}H_{38}F_3N_5O_4S$) C, H, N.

5-*n*-Butyl-2,4-dihydro-2-[5-(propionylamino)-2-(trifluoromethyl)phenyl]-4-[(2′-sulfamoylbiphenyl-4-yl)methyl]-3*H*-1,2,4-triazol-3-one (65). A solution of 70 mg (0.107 mmol) of **64** and 10 μL of anisole in 0.7 mL of TFA was stirred at room temperature overnight. The excess TFA and other volatiles were removed by a stream of nitrogen. The residue was coevaporated with toluene twice and then purified by flash chromatography (gradient elution with 0.5–2% MeOH/CH_2Cl_2) to give 58 mg (91%) of an off-white foam, homogeneous by TLC (95:5 CH_2Cl_2/MeOH): mp 125–127 °C (gradual); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.87 (t, J = 7.3 Hz, 3 H), 1.15 (t, J = 7.5 Hz, 3 H), 1.36 (m, 2 H), 1.60 (m, 2 H), 2.32 (q, J = 7.5 Hz, 2 H), 2.50 (t, J = 7.6 Hz, 2 H), 4.33 (s, 2 H), 4.95 (s, 2 H), 7.29–7.59 (m, 9 H), 7.80 (s, 1 H), 8.14 (dd, J = 7.9, 1.3 Hz, 1 H), 8.34 (s, 1 H); ESI-MS m/e 602 (M + H)$^+$. Anal. ($C_{29}H_{30}F_3N_5O_4S\cdot 1.5H_2O$) C, H, N.

5-*n*-Butyl-4-[[2′-[*N*-(2-chlorobenzoyl)sulfamoyl]biphenyl-4-yl]methyl]-2,4-dihydro-2-[5-(propionylamino)-2-(trifluoromethyl)phenyl]-3*H*-1,2,4-triazol-3-one (45). A solution of 31 mg (0.20 mmol) of 2-chlorobenzoic acid and 32 mg (0.20 mmol) of Im_2CO in 1 mL of THF was stirred at 65 °C for 3 h. Subsequently, a solution of 40 mg (0.067 mmol) of the free sulfonamide **65** and 30 μL (30 mg, 0.20 mmol) of DBU in 1 mL of THF was added dropwise. After being stirred at 50 °C for 24 h, the reaction mixture was cooled to room temperature, quenched by addition of 5% aqueous citric acid, and extracted with EtOAc three times. The combined organic layers were washed with water and then brine and dried over Na_2SO_4. The crude product obtained after filtration and removal of solvents was flash chromatographed over SiO_2 (gradient elution using 0.5–2.0% MeOH/CH_2Cl_2) to afford 25 mg (50%) of the desired product cleanly as a solid, homogeneous by TLC (90:10 CH_2Cl_2/MeOH): mp 102–105 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85 (t, J = 7.3 Hz, 3 H), 1.17 (t, J = 7.5 Hz, 3 H), 1.32 (m, 2 H), 1.57 (m, 2 H), 2.33–2.43 (m, 4 H), 4.79 (s, 2 H), 7.17 (d, J = 8.1 Hz, 2 H), 7.25–7.67 (m, 10 H), 7.78 (d, J = 8.7 Hz, 1 H), 7.95 (d, J = 8.5 Hz, 1 H), 8.39 (dd, J = 7.9, 1.4 Hz, 1 H), 9.58 (br s, 1 H); high-resolution FAB-MS m/e 740.1944 [calcd for $C_{36}H_{34}ClF_3N_5O_5S$ (M + H)$^+$ 740.1918].

4-[[2′-[*N*-(*tert*-Butoxycarbonyl)sulfamoyl]biphenyl-4-yl]methyl]-5-*n*-butyl-2,4-dihydro-2-[5-(propionylamino)-2-(trifluoromethyl)phenyl]-3*H*-1,2,4-triazol-3-one (46). A solution of 50 mg (0.083 mmol) of **65** in 1 mL of THF was treated with 2.4 mg (0.10 mmol) of NaH in oil, and the mixture was stirred at 50 °C for 2 h. At room temperature, 37 mg (0.17 mmol) of $(BOC)_2O$ was added and stirring continued for 20 h at 50 °C. After the reaction mixture was cooled to room temperature, the reaction was quenched by addition of water and 5% citric acid (aqueous). The organic material was extracted with EtOAc three times. The combined organic layer was washed with water and brine and dried over Na_2SO_4. The residue obtained after filtration and removal of solvents was flash chromatographed over SiO_2 (gradient elution using 1–2% MeOH/CH_2Cl_2) to give 43 mg (74%) of the desired material as an off-white solid, homogeneous by TLC (95:5 CH_2Cl_2/MeOH): mp 158–161 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ 0.90 (t, J = 7.4 Hz, 3 H), 1.19 (t, J = 7.6 Hz, 3 H), 1.30 (s, 9 H), 1.39 (m, 2 H), 1.63 (m, 2 H), 2.43 (q, J = 7.6 Hz, 2 H), 2.61 (t, J = 7.4 Hz, 2 H), 5.05 (s, 2 H), 7.30–7.40 (m, 5 H), 7.59 (dd, J = 7.5, 7.5 Hz, 1 H), 7.69 (dd, J = 7.5, 7.5 Hz, 1 H), 7.80 (m, 2 H), 7.96 (s, 1 H), 8.16 (d, J = 8.0 Hz, 1 H); high-resolution FAB-MS m/e 702.2549 [calcd for $C_{34}H_{39}F_3N_5O_6S$ (M + H)$^+$ 702.2570]. Anal. ($C_{34}H_{38}F_3N_5O_6S\cdot H_2O$) C, H, N.

Rabbit Aorta AT_1 Receptor Binding Assay. Rabbit aorta membrane pellets, prepared as previously described,[36] were suspended in binding buffer. No bovine serum albumin (BSA) was present in this version of the assay.[24,36] 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]AII 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 mM [Sar^1,Ile^8]AII (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 mixed and incubated in a water bath at 37 °C for 90 min. The mixture, after dilution with wash buffer, was filtered immediately under reduced pressure. The filters were washed with wash buffer, and the radioactivity associated with the membrane collected was measured. 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 mean) of the IC_{50} measurement in this assay is estimated to be less than 30%. For key compounds 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.[12a,36c] 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 for the AT_1 assay above. For key compounds the reported IC_{50} values represent an average of two or more determinations from separate assays.

Evaluation of AII Antagonists in Conscious, Normotensive Rats.[37] Male Sprague–Dawley rats were anesthetized with methohexital sodium and surgically instrumented with catheters for (a) measurements of arterial blood pressure and heart rate, (b) administration of AII, and (c) intravenous administration of test compound, as appropriate. The incisions were sutured, and the rats were allowed to recover overnight prior to testing. Angiotensin II (0.1 μg/kg iv) and methoxamine were each dissolved in saline solution and administered in injection volumes of 0.5 mL/kg iv in the appropriate vehicles as described previously. The responsiveness of the rat was verified by initial challenge with methoxamine followed by bolus injections of AII at 15 min intervals. Upon obtaining consistent AII responses, the test compound in its vehicle was administered intravenously or orally. AII was then given at fixed time points for as long as the test compound exhibited activity. At the conclusion of AII challenges, the catheter was flushed, and methoxamine 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, based on averaged results from two or more rats. A 30% inhibition of the AII pressor response is considered significant in this assay. The duration of action for a single bolus dose of the test compound is defined as the time from onset of activity until the inhibition of the AII-induced increase in MAP falls below 30% and remains at <30% for two subsequent AII challenges.

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