Articles

Potent and Orally Active Angiotensin II Receptor Antagonists with Equal Affinity for Human AT_1 and AT_2 Subtypes[1]

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In order to block the effects induced by the interactions between angiotensin II (AII) and both AT_1 and AT_2 receptors, we have pursued the discovery of orally active non-peptide AII antagonists that exhibit potent and equal affinity for human AT_1 and AT_2 receptor subtypes. A series of previously prepared nanomolar (IC_{50}) trisubstituted 1,2,4-triazolinone biphenylsulfonamide dual-acting AII antagonists has been modified at five different positions in order to increase AT_2 binding affinity, maintain AT_1 activity, and reduce the human adrenal AT_2/AT_1 potency ratio (IC_{50} ratio) from ≥10. The targeted human adrenal potency ratio of ≤1 was achieved with a number of compounds possessing an ethyl group at C^5 of the triazolinone and a 3-fluoro substituent at the N^4-biarylmethyl moiety. The most favored of these was compound **44** which exhibited subnanomolar potency at both the AT_1 (rabbit aorta) and AT_2 (rat midbrain) receptors, with a slight preference for the latter, and had a human adrenal AT_2/AT_1 IC_{50} ratio of 1. This *tert*-butyl sulfonylcarbamate with an N^2-[2-bromo-5-(valerylamino)phenyl] substituent had excellent iv activity at 1 mg/kg (100% peak inhibition, ≥4 h duration of action) and is orally active at 3 mg/kg with >6 h duration of action in a conscious rat model. The present study shows that the NH of the amide on the N^2-aryl moiety is not required for subnanomolar binding affinity to either receptor subtype, although a keto functionality at this position is essential for acceptable AT_2 binding. Receptor–ligand binding interactions derived from the structure–activity relationships are discussed with respect to both receptor subtypes.

Angiotensin II (AII) is the primary active hormone of the renin–angiotensin system (RAS), which plays a crucial role in blood pressure regulation as well as in fluid volume and electrolyte balance.[2] Blockade of the RAS to treat essential hypertension via the use of angiotensin-converting enzyme (ACE) inhibitors is well documented.[3] The rationale for the use of an AII receptor antagonist in lieu of ACE inhibitors has been discussed.[4] In brief, agents which block the binding of AII to its receptor would be inherently more specific as inhibitors of the RAS compared to ACE inhibitors. In addition, the action of AII generated by ACE-independent pathways will also be blocked by an AII receptor antagonist.

AII has equivalent affinity for both of the major subtypes of the AII receptor, AT_1 and AT_2.[5] The AT_1 receptor is G-protein coupled[6] and mediates most of the known physiological effects of AII, among the most prominent are those associated with the cardiovascular system and the kidney.[7] The physiological role of the AT_2 receptor has yet to be clearly defined.[7] Suggested roles for AT_2 receptors include regulation of renal function,[8] restenosis following vascular injury,[9] wound healing,[10] and cardiac fibroblast collagen synthesis.[11] In addition, it has been implicated in various cell differentiation and cell proliferation processes.[7,12] The antihypertensive drug losartan (DuP 753, MK-954, **1a**) is a non-peptide AT_1-selective agent.[13] High-affinity non-peptide AT_2-selective ligands have been described as well.[14] The administration of an AT_1-selective AII antagonist results in a renin-mediated increase in the plasma levels of AII.[15] The physiological effect of prolonged unopposed stimulation of AT_2 receptors with elevated levels of circulating AII is unknown. In contrast, the use of ACE inhibitors, which block the formation of AII from angiotensin I (AI), results in lowered plasma AII levels and limits stimulation of both the AT_1 and AT_2 receptors.[16] Therefore, AII antagonists capable of equivalent, simultaneous blockade of both receptor subtypes with high affinity (AT_1/AT_2-balanced AII antagonists) might more closely mimic the pharmacological actions of an ACE inhibitor with respect to its pharmacological effects on the RAS. Such balanced, dual-action AII antagonists with high affinity and good pharmacokinetic properties would facilitate pharmacological investigations of the possible merits of dual AT_1/AT_2 antagonism and might prove to be advantageous as therapeutic agents.[4d]

Besides the endogenous octapeptide AII, many potent peptide ligands for the AII receptor, e.g., saralasin ([Sar^1,Val^5,Ala^8]AII) and [Sar^1,Ile^8]AII, bind indiscriminantly to both the AT_1 and AT_2 receptors with high affinity.[7] However, partial agonism and poor pharma-

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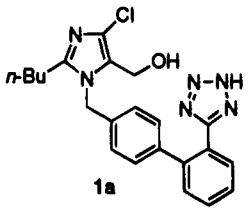
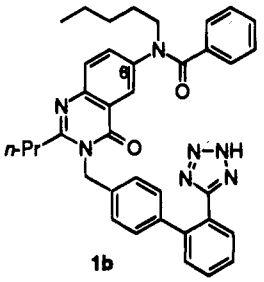
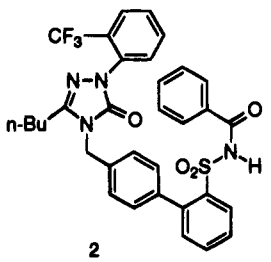
cokinetic properties have limited their usefulness as pharmacological tools.[17] The first high-affinity nonpeptide AT_1/AT_2-balanced AII antagonists were a series of 6-(*N*-alkyl-*N*-acyl)quinazolinone biphenyltetrazoles exemplified by **1b** [L-159,689; AT_1 IC_{50} = 1.7 nM (rabbit aorta), AT_2 IC_{50} = 0.7 nM (rat midbrain)].[18] Indeed, appropriately positioned *N*-acyl substituents on the heterocyclic moiety, paired with certain *N*-substituents on the acidic sulfonamide group, have transformed several series of AT_1-selective acidic sulfonamides into

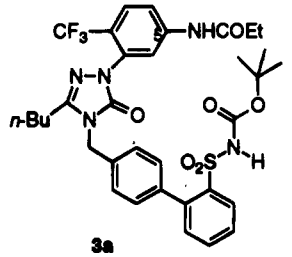


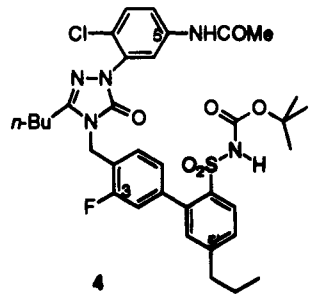


dual-acting AII antagonists.[19] Further improvements in AT_2 binding could be attained by the presence of a 3-fluoro group on the biarylmethyl moiety in several structural series.[1,20] This effect was first demonstrated on a series of imidazole-based AII antagonists by investigators at DuPont Merck.[20a] Additionally, the replacement of the terminal phenyl ring of the biaryl moiety by a 5-alkyl-substituted thienyl group has been shown to improve AT_2 activity in a series of imidazopyridine-based compounds.[21] The goal of our AT_1/AT_2-balanced AII antagonists program was to identify structurally diverse compounds with (1) subnanomolar or low nanomolar *in vitro* intrinsic potency for both receptor subtypes, (2) an AT_2/AT_1 IC_{50} value ratio of ≤ 1 in three pairs of tissue preparations (rat midbrain/rabbit aorta, rat adrenal, and human adrenal), and (3) good *in vivo* efficacy and oral activity. The requirement of an AT_2/AT_1 IC_{50} value ratio of ≤ 1 was designed to ensure equivalent coverage of both receptors under physiological conditions, owing to the lack of a direct pharmacological readout of an AT_2-mediated effect *in vivo*.

We have been pursuing the transformation of the potent, orally active AT_1-selective triazolinone-based AII antagonist **2** [L-159,913; AT_1 IC_{50} = 0.43 nM (rabbit aorta), AT_2 IC_{50} = 300 nM (rat midbrain)][22] into a nanomolar, balanced compound with oral activity in animal models. Initial investigations focused on the optimization of the *N*-substituent of the sulfonamide and the appropriate choice of amide at the 5-position of the N^2-aryl moiety.[19c,23] This led to a series of dual-acting AII antagonists exemplified by **3a** [L-163,007; AT_1 IC_{50} = 0.29 nM (rabbbit aorta), AT_2 IC_{50} = 1.0 nM (rat midbrain)].[19c] Further studies which incorporated the 3-fluoro and 5′-propyl groups on the N^4-biarylmethyl moiety yielded analogues such as **4**.[1a] This subnanomolar compound [AT_1 IC_{50} = 0.84 nM (rabbbit aorta), AT_2 IC_{50} = 0.24 nM (rat midbrain)] met the program requirement for *in vitro* balance by exhibiting AT_2/AT_1 IC_{50} ratios of <1 in all three pairs of assays. Unfortunately, these 3-fluoro-5′-propyl-substituted triazolinones were not orally active. Since the lack of oral activity was attributed partially to the presence of the 5′-propyl group,[1] we returned to the original series of dual-acting triazolinones (e.g., **3a**) as the starting point to obtain orally active, potent, and balanced AII antagonists. Toward this goal, we have prepared and evaluated (or further evaluated) a number of compounds (**3** and **5**–**49**, Table 1) in order to investigate the structure–activity relationships (SAR) of compounds based on the 2,4-dihydro-3*H*-2,4,5-trisubstituted-1,2,4-triazol-3-one (triazolinone) structure **I** (Table 1).





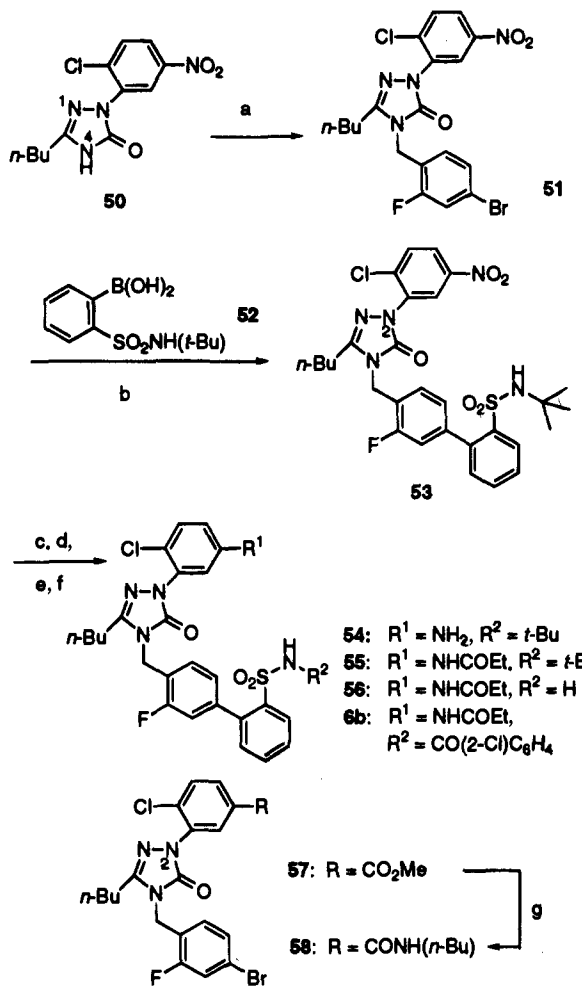


Chemistry

Several synthetic routes were used to prepare the new compounds shown in Table 1. The first compounds prepared for this study were obtained through the key intermediate **51**, also used in the synthesis of **4**, reported previously.[1a] Palladium(0)-mediated biaryl-coupling reaction between **51**[1a] and the boronic acid **52** would provide **53**, which has the N^4-biarylmethyl moiety in place (method A, Table 2). Compounds **5b**–**7b** and **8** were prepared using this route. The synthesis of **6b** shown in Scheme 1 is representative for compounds in the amide series (**I**, R^3 = NHCOR). The N^4-unsubstituted triazolinone **50**[19c] was alkylated with 4-bromo-2-fluorobenzyl bromide to provide **51**, which was coupled with [2-(*N*-*tert*-butylsulfamoyl)phenyl]boronic acid (**52**)[24] to afford the key intermediate **53**.[1a,21,25] The nitro substituent on the N^2-aryl ring was reduced to the aniline **54** via catalytic hydrogenation, and the aniline was acylated to yield the propionylamino derivative **55**. Removal of the *tert*-butyl group via trifluoroacetic acid (TFA) produced the free sulfonamide **56**, which was acylated via the acid imidazolide to provide the targeted (2-chlorobenzoyl)sulfonamide **6b**.[19c] For the preparation of the reversed amide **7b**, the required amide substituent on the 5-position of the N^2-aryl ring [**I**, R^3 = CONH-(*n*-Bu)] was best installed before the biaryl-coupling reaction, as shown for **57**→**58**.[19c] Under the Suzuki coupling conditions employed,[25] the amide **58** gave a much cleaner product mixture than the ester **57**. The fully elaborated (2-chlorobenzoyl)sulfonamide **7b** was obtained in another two steps via methods described previously for **55**→**6b**.

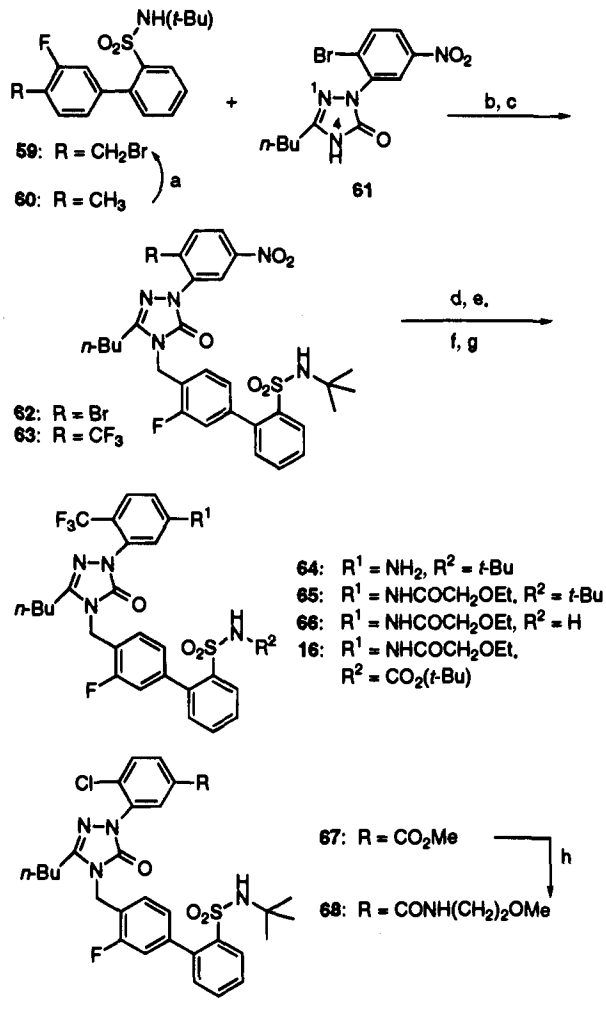
For the majority of the compounds listed in Table 1, the key intermediate corresponding to **53** was prepared by alkylation of the biarylmethyl bromide **59** with the appropriate N^4-unsubstituted triazolinone (methods B,

Scheme 1[a]



[a] Method A: (a) NaH/DMF, 4-bromo-2-fluorobenzyl bromide; (b) **52**, 5 mol % $Pd(PPh_3)_4$, NaOH, toluene/EtOH; (c) H_2, PtO_2, EtOH/EtOAc; (d) BrCOEt, DMAP, pyridine; (e) TFA, anisole; (f) 2-chlorobenzoic acid, CDI, DBU, THF; (g) n-$BuNH_2$, reflux.

Scheme 2[a]



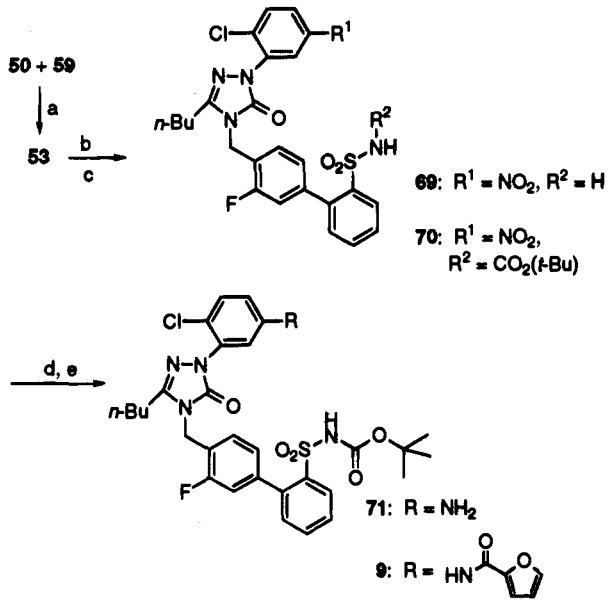
[a] Method B: (a) Br_2/CCl_4, $h\nu$; (b) NaH, DMF; (c) $ClCF_2CO_2Me$, KF, CuI, KBr, DMF; (d) PtO_2, EtOH/EtOAc; (e) BOP reagent, NEt_3, 3-ethoxyacetic acid, CH_2Cl_2; (f) TFA, anisole; (g) NaH/THF, $(BOC)_2O$; (h) 2-methoxyethylamine, 65 °C.

C, and E in Table 2).[19c] This general method is illustrated well by the preparation of compound **16** (Scheme 2). 3-Fluoro-4-methyl-2′-(*N*-*tert*-butylsulfamoyl)-biphenyl (**60**) was obtained from biaryl coupling between 4-bromo-2-fluorotoluene and the boronic acid **52**. Subsequent bromination provided the alkylating agent **59** which, when reacted with the anion of **61**, yielded the important intermediate **62**. [The requisite triazolinone **61** was prepared from (2-bromo-5-nitrophenyl)hydrazine[26] and *N*-carbethoxyvalerimidate as described previously.[19c]] Compound **62** was reacted with methyl chlorodifluoroacetate, potassium fluoride, and copper(I) iodide in dimethylformamide (DMF)[27] in the presence of 1 equiv of potassium bromide. This converted the bromo substituent to a trifluoromethyl group to provide the intermediate **63** in 62% yield. In the absence of potassium bromide, a complex product mixture was obtained wherein the chloro-substituted compound **53** was the major component. The aniline **64**, available from **63** via catalytic hydrogenation, was coupled with ethoxyacetic acid via (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP reagent) to provide **65**.[28] Treatment with trifluoroacetic acid gave the free sulfonamide, which was deprotonated and treated with di-*tert*-butyl dicarbonate to give the desired sulfonylcarbamate **16**.[23] For the preparation of the reversed amides (e.g., **12**), the methyl ester **67** [obtained by alkylation of 5-*n*-butyl-2-(2-chloro-5-carbomethoxyphenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one[19c] with **59**] was refluxed with methoxyethylamine as shown in Scheme 2 to provide compound **68** which was further transformed to the *tert*-butyl sulfonylcarbamate **12** as described for **56**→**16**.

The intermediate **53** has been prepared using method B as shown in Scheme 3 and then transformed in four steps to compound **71**. A number of analogues (e.g., **9**−**11**) were prepared from this aniline by coupling with the requisite acids. The conversion of **71** to **9** is typical (Scheme 3; method C, Table 2).

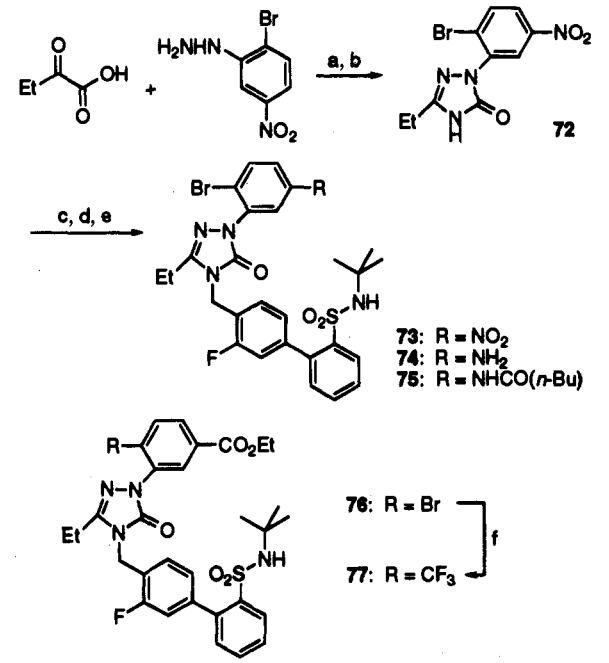
For compounds with a shortened alkyl group at R^1 of **I** (e.g., R^1 = Et, Me), the most expedient way to obtain the 2,5-disubstitutedtriazolinone (e.g., **72**) was via a β-keto acid arylhydrazone followed by treatment with diphenyl phosphorazidate (DPPA) (method E, Table 2).[29] A typical example is shown in Scheme 4, toward the synthesis of compound **44**.[1b] The arylhydrazone obtained from the reaction between β-ketobutyric acid and (2-bromo-5-nitrophenyl)hydrazine was heated with DPPA in triethylamine to provide **72** in good yields. Alkylation of this compound with **59** provided the intermediate **73** cleanly. The subsequent transformation to the corresponding aniline **74** was best effected via stannous chloride reduction. Catalytic hydrogenation produced

Scheme 3[a]



[a] Method C: (a) NaH, DMF; (b) TFA, anisole; (c) NaH/THF, $(BOC)_2O$; (d) H_2, PtO_2, EtOH; (e) 2-furoic acid, NEt_3, BOP, CH_2Cl_2.

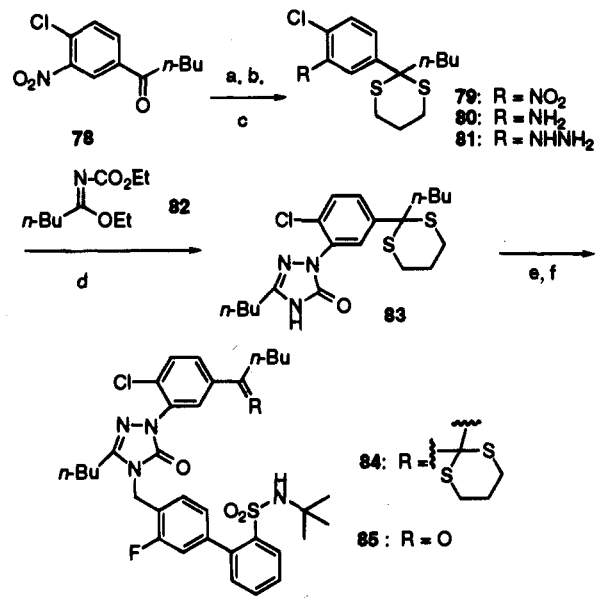
Scheme 4[a]



[a] Method E: (a) HCl; (b) DPPA, NEt_3, toluene; (c) NaH, DMF, **59**; (d) $SnCl_2$, HCl, THF; (e) *n*-BuCOCl, DMAP, pyridine; (f) $ClCF_2CO_2Me$, KF, CuI, KBr, DMF.

mainly the debrominated aniline. Acylation of **74** with valeryl chloride in pyridine in the presence of 4-(dimethylamino)pyridine (DMAP)[19c] afforded the intermediate **75**, which was transformed to **44** in two more steps using the sequence shown for **66**→**16** in Scheme 2. For the synthesis of compounds in the reversed amide series with a 2-trifluoromethyl group at the N^2-aryl moiety and a truncated alkyl group at R^1 of **I**, the methyl chlorodifluoroacetate-mediated bromo-to-trifluoromethyl conversion was attempted at several different stages of the synthetic sequence. The most expedient conversion was still from an intermediate such as **76**, as shown before in Scheme 2, even though the yields were only fair. Thus the bromo derivative **76** was transformed to the trifluoromethyl compound **77** in 37% yield as shown in Scheme 4. The (2-bromo-5-carbethoxyphenyl)hydrazine required for the preparation of **76** was obtained by nitration of ethyl 4-bromobenzoate followed by diazotization and stannous chloride reduction.

Scheme 5[a]



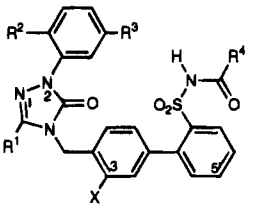
[a] Method D: (a) $HS(CH_2)_3SH$, $BF_3{\cdot}Et_2O$; (b) $SnCl_2$, HCl, THF; (c) $NaNO_2$, HCl, $SnCl_2$, Na_2CO_3; (d) **82**, NEt_3, toluene; (e) NaH, DMF, **59**; (f) NBS, CH_3CN/H_2O.

For the preparation of compound **14**, with a keto functionality at R^3 of **I**, alkylation of the *N*-methyl, *N*-methoxyl amide[30] derived from **67** was studied at length. However, in our hands, the reaction to form the ketone was not successful under a number of reaction conditions attempted. The synthesis was finally worked out as shown in Scheme 5 (method D, Table 2). Nitration of 4-chlorovalerophenone[31] provided the starting ketone **78** which was protected as the dithiane **79**.[32] Reduction of the nitro group followed by hydrazine formation afforded **81**. This intermediate was reacted with ethyl *N*-(carboxyethyl)valerate (**82**)[33] to provide **83**. Alkylation of the anion of **83** with the biarylmethyl bromide **59** gave **84**. Removal of the dithiane protection from the alkylated adduct **84** to provide the unmasked ketone **85** was best achieved by treatment with *N*-bromosuccinimide (NBS) in aqueous acetonitrile.[34] This intermediate was further transformed to the *tert*-butyl sulfonylcarbamate **14** using the same sequence as described for **65**→**16** in Scheme 2.

Biological Results and Discussion

The *in vitro* binding affinities of the compounds in Table 1 for the AT_1 and AT_2 receptors were evaluated for their ability to competitively block the specific binding of [^{125}I][Sar^1,Ile^8]AII to designated AT_1 and AT_2 receptor preparations.[35] The rabbit aorta (AT_1) and the rat midbrain (AT_2) assays results have been highly reliable in providing intrinsic binding affinities of the test compounds for the AII receptor subtypes. However, in view of the objectives of this study, ratios of AT_2/AT_1 IC_{50} values could conceivably be more meaningful if they were derived from assays using the same tissue from the same species. To this end, the AT_1 and AT_2 receptors in the rat adrenal and human adrenal tissues

Table 1. *In Vitro* Binding Potencies of Various N^2-Aryltriazolinone Biphenylsulfonamides for the AT_1 and AT_2 Receptor Subtypes of AII in Three Pairs of Tissue Preparations



I

						rabbit aorta/rat midbrain[a]			rat adrenal[a]			human adrenal[b]		
						IC_{50} (nM)		AT_2/AT_1 IC_{50}	IC_{50} (nM)		AT_2/AT_1 IC_{50}	IC_{50} (nM)		AT_2/AT_1 IC_{50}
no.	R^1	R^2	R^3	R^4	X	AT_1	AT_2	ratio	AT_1	AT_2	ratio	AT_1	AT_2	ratio
losartan						30	74000	*>2400*	NT[d]	NT[d]		88	NT[d]	
3a[c]	*n*-Bu	CF_3	NHCOEt	O(*t*-Bu)	H	0.29	1.0	*3.4*	0.30	1.1	*3.7*	1.8	18	*10*
3b	*n*-Bu	CF_3	NHCOEt	O(*t*-Bu)	F	0.28	0.29	*1.0*	0.24	0.27	*1.1*	0.74	2.9	*3.9*
5a[c]	*n*-Bu	Cl	NHCOEt	O(*t*-Bu)	H	0.21	1.6	*7.6*	0.13	0.89	*6.8*	0.28	5.8	*21*
5b	*n*-Bu	Cl	NHCOEt	O(*t*-Bu)	F	0.13	0.23	*1.8*	0.22	0.58	*2.6*	0.44	3.7	*8.4*
6a[c]	*n*-Bu	Cl	NHCOEt	(2-Cl)C_6H_4	H	0.17	2.5	*15*	0.11	3.7	*34*	NT[d]	NT[d]	
6b	*n*-Bu	Cl	NHCOEt	(2-Cl)C_6H_4	F	0.072	0.21	*2.9*	0.12	0.41	*3.4*	0.32	3.1	*9.7*
7a[c]	*n*-Bu	Cl	CONH(*n*-Bu)	(2-Cl)C_6H_4	H	0.14	2.4	*17*	0.071	1.1	*15*	NT[d]	NT[d]	
7b	*n*-Bu	Cl	CONH(*n*-Bu)	(2-Cl)C_6H_4	F	0.16	0.25	*1.6*	0.12	0.35	*2.9*	0.55	3.7	*6.7*
8	*n*-Bu	Cl	CONH(*n*-Bu)	O(*t*-Bu)	F	0.17	0.18	*1.1*	0.18	0.36	*2.0*	0.76	3.1	*4.1*
9	*n*-Bu	Cl	NHCO(2-furyl)	O(*t*-Bu)	F	0.37	0.89	*2.4*	0.11	0.62	*5.6*	1.5	20	*13*
10	*n*-Bu	Cl	$NHCOCH_2OEt$	O(*t*-Bu)	F	0.10	0.20	*2.0*	0.27	0.30	*1.1*	0.56	2.5	*4.4*
												0.38[e]	1.2[e]	*3.2*
11	*n*-Bu	Cl	$NHCO(CH_2)_2$ OMe	O(*t*-Bu)	F	0.14	0.39	*3.0*	0.18	0.70	*3.9*	0.14	1.8	*13*
12	*n*-Bu	Cl	$CONH(CH_2)_2$ OMe	O(*t*-Bu)	F	0.26	0.48	*1.8*	0.20	0.78	*3.9*	0.40	4.1	*10*
13	*n*-Bu	Cl	CONH(*n*-Pr)	O(*t*-Bu)	F	0.27	0.27	*1.0*	0.14	0.21	*1.5*	0.64	3.4	*5.3*
14	*n*-Bu	Cl	CO(*n*-Bu)	O(*t*-Bu)	F	0.91	0.80	*0.9*	0.17	0.26	*1.4*	2.2	7.5	*3.4*
15	*n*-Bu	CF_3	NHCO(*n*-Bu)	O(*t*-Bu)	F	0.42	0.22	*0.5*	0.22	0.16	*0.7*	0.90	3.8	*4.2*
												0.41[e]	0.88[e]	*2.1*
16	*n*-Bu	CF_3	$NHCOCH_2OEt$	O(*t*-Bu)	F	0.26	0.23	*0.9*	0.14	0.17	*1.2*	0.94	2.2	*2.3*
17	*n*-Bu	CF_3	NHCOEt	O(*i*-Pr)	F	0.24	0.29	*1.2*	0.18	0.56	*3.1*	0.45	2.7	*6.0*
18	*n*-Bu	CF_3	NHCOEt	OEt	F	0.13	0.58	*4.5*	0.55	0.83	*1.5*	<0.3	4.6	*>15*
19	*n*-Bu	CF_3	NHCOEt	CH_2(*t*-Bu)	F	0.20	0.21	*1.1*	0.24	0.84	*3.5*	1.0	4.3	*4.3*
20	*n*-Bu	CF_3	NHCOEt	C_6H_5	F	0.14	0.56	*4.0*	0.15	0.51	*3.4*	0.32	4.3	*13*
21	*n*-Bu	CF_3	NHCOEt	(2-F)C_6H_4	F	0.22	0.30	*1.4*	0.22	0.53	*2.4*	0.36	2.0	*5.6*
22	*n*-Bu	CF_3	NHCOEt	(2-Cl)C_6H_4	F	0.13	0.15	*1.1*	0.15	0.31	*2.1*	0.43	3.5	*8.1*
												0.25[e]	1.3[e]	*5.2*
23	*n*-Bu	CF_3	NHCOEt	(2,5-Cl_2)C_6H_3	F	0.36	0.37	*1.0*	0.16	0.33	*2.1*	0.96	5.1	*5.3*
24	*n*-Bu	CF_3	NHCOPh	O(*t*-Bu)	F	0.38	0.57	*1.5*	0.25	0.21	*0.8*	1.4	6.3	*4.5*
25	*n*-Bu	Br	NHCOEt	O(*t*-Bu)	F	0.12	0.39	*3.3*	0.15	0.28	*1.9*	0.50	2.3	*4.6*
26	*n*-Bu	Br	NHCOEt	O(*t*-Bu)	Cl	0.25	1.4	*5.6*	0.21	2.1	*10*	NT[d]	NT[d]	
27	*n*-Bu	Br	NHCOPh	O(*t*-Bu)	F	0.19	0.54	*2.8*	0.16	0.24	*1.5*	1.1	6.1	*5.5*
28	*n*-Pr	Br	NHCOPh	O(*t*-Bu)	F	0.24	0.22	*0.9*	0.089	0.21	*2.4*	2.0	3.6	*1.8*
29	*n*-Pr	Br	NHCOEt	O(*t*-Bu)	F	0.35	0.14	*0.4*	0.10	0.22	*2.2*	0.34	1.4	*4.1*
30	*n*-Pr	Br	NHCO(*n*-Bu)	O(*t*-Bu)	F	0.21	0.16	*0.8*	0.15	0.17	*1.1*	0.43	2.2	*5.1*
31	*n*-Pr	Br	CONH(*n*-Bu)	O(*t*-Bu)	F	0.28	0.32	*1.1*	0.21	0.29	*1.4*	0.84	2.5	*3.0*
32	*n*-Pr	Br	CONH(*n*-Bu)	(2,5-Cl_2)C_6H_3	F	0.44	0.36	*0.8*	0.12	0.092	*0.8*	1.6	2.0	*1.3*
33	*n*-Pr	CF_3	NHCOPh	O(*t*-Bu)	F	0.38	0.20	*0.5*	0.17	0.14	*0.8*	1.6	5.3	*3.3*
34	*n*-Pr	CF_3	$NHCOCH_2OEt$	O(*t*-Bu)	F	0.20	0.44	*2.2*	0.29	0.23	*0.8*	1.0	2.6	*2.6*
35	*n*-Pr	CF_3	CONH(*n*-Bu)	O(*t*-Bu)	F	0.44	0.29	*0.7*	0.25	0.19	*0.8*	0.88	2.6	*3.0*
36	*n*-Pr	CF_3	CONH(*n*-Pr)	(2,5-Cl_2)C_6H_3	F	0.19	0.19	*1.0*	0.072	0.053	*0.7*	1.0	1.7	*1.7*
37	Et	CF_3	CONH(*n*-Bu)	O(*t*-Bu)	F	0.53	0.30	*0.6*	0.88	1.3	*1.5*	8.8	8.2	*0.9*
38	Et	CF_3	NHCO(*n*-Bu)	O(*t*-Bu)	F	0.41	0.81	*2.0*	0.38	0.31	*0.8*	2.2	3.6	*1.6*
39	Et	Cl	NHCO(*n*-Bu)	O(*t*-Bu)	F	0.51	0.28	*0.5*	0.43	0.07	*0.2*	3.3	2.0	*0.6*
40	Et	Cl	$NHCOCH_2OEt$	O(*t*-Bu)	F	1.9	0.32	*0.2*	1.0	0.34	*0.3*	6.1	1.5	*0.2*
41	Et	Cl	NHCOPh	O(*t*-Bu)	F	3.7	0.29	*0.08*	1.2	0.73	*0.6*	28	10	*0.4*
42	Et	Br	NHCOPh	O(*t*-Bu)	F	1.5	0.93	*0.6*	0.48	0.18	*0.4*	24	4.1	*0.2*
43	Et	Br	NHCOEt	O(*t*-Bu)	F	0.56	0.48	*0.9*	0.88	1.1	*1.3*	3.4	1.7	*0.5*
44	Et	Br	NHCO(*n*-Bu)	O(*t*-Bu)	F	0.16	0.12	*0.8*	0.23	0.21	*0.9*	3.5	3.4	*1.0*
45	Et	Br	CONH(*n*-Bu)	O(*t*-Bu)	F	1.8	0.29	*0.2*	3.5	0.86	*0.2*	17	3.7	*0.2*
46	Et	Br	NHCO(*n*-Bu)	O(*i*-Pr)	F	0.82	0.10	*0.1*	0.69	0.18	*0.3*	4.3	1.1	*0.3*
47	Et	Br	NHCO(*n*-Bu)	(2,5-F_2)C_6H_3	F	0.23	0.21	*0.9*	0.22	0.15	*0.7*	1.9	1.5	*0.8*
48	Et	Br	NHCO(*n*-Bu)	(2-F)C_6H_4	F	0.22	0.25	*1.1*	0.18	0.16	*0.9*	0.72	0.64	*0.9*
49	Me	Br	NHCO(*n*-Bu)	O(*t*-Bu)	F	0.38	1.3	*3.4*	0.49	0.63	*1.3*	4.6	2.1	*0.5*

[a] For the rabbit aorta, rat midbrain, and rat adrenal binding assays, no BSA was added to the assay mixtures. [b] For the human adrenal assays, 0.2% BSA was present in the assay mixtures unless otherwise noted. [c] This compound was characterized, and the associated rabbit aorta and rat midbrain data are reported in ref 19c. [d] NT = not tested. [e] For this assay, only 0.02% BSA was present in the assay mixture.

were used. Compounds which showed an AT_2/AT_1 IC_{50} value ratio of <20 in the rat midbrain/rabbit aorta assays were further evaluated in the rat adrenal assays. Those with an IC_{50} value ratio of <10 from the rat adrenal assays were tested in the human adrenal AT_1 and AT_2 receptor tissue preparations. Multiple runs of the assays were conducted for the test compounds in the rabbit aorta/rat midbrain and the human adrenal assays to ensure consistency in the IC_{50} values obtained. Table 1 shows the *in vitro* IC_{50} values for both receptor

subtypes in all three sets of tissue preparations and the respective AT_2/AT_1 IC_{50} ratios for the test compounds, where data are available. For binding affinity determinations using rat adrenal tissue preparations, as was the case for the rabbit aorta and rat midbrain tissue preparations, no bovine serum albumin (BSA) was added to the assay mixtures. However, for the human adrenal assays, in order to achieve a satisfactory ratio of specific to nonspecific binding, it was necessary to add 0.2% BSA to the binding assay buffer.

Effect of a 3-F Substituent on the Biphenyl. Table 1 shows that in general, for these triazolinone-based ligands, the AT_1 binding potency remained consistently in the subnanomolar or low nanomolar level regardless of the substituents on R^1-R^4. We began our SAR studies by examining the effect of a 3-F substituent on the biphenyl moiety on three sets of compounds (**3a,b, 5a,b**, and **6a,b**). The 3-H compounds (**3a, 5a**, and **6a**) were reported previously.[19c] Table 1 shows that for these pairs of compounds, the addition of the fluoro substituent increased the AT_2 binding affinity by 3–12-fold in the rat midbrain and rat adrenal AT_2 assays (**3a** vs **3b**, **5a** vs **5b**, and **6a** vs **6b**). For the first time, compounds with subnanomolar binding affinity to the AT_2 receptor in both of these assays were obtained in this series. Thus, the 3-fluoro substituent again proved instrumental in increasing the AT_2 potency, although the degree of improvement depended on substituents R^1-R^4 in **I**. The much enhanced AT_2 potency coupled with the maintenance of subnanomolar AT_1 affinity resulted in a reduction in the AT_2/AT_1 IC_{50} ratio to 1–3 for **3b**, **5b**, and **6b**. In fact, in both pairs of assays, the mandated AT_2/AT_1 IC_{50} ratio of unity was achieved by **3b**, the fluorinated version of **3a**, an orally active compound.[19c]

The binding affinity data from the human adrenal assays were not as encouraging. For example, the human adrenal AT_2 IC_{50} value for **5b**, which contains the 3-F substituent, was only slightly better compared to that obtained for the corresponding 3-H compound **5a**. In addition, for **3b**, **5b**, and **6b**, the human adrenal AT_2 IC_{50} values were 6–13-fold higher than those obtained from the rat midbrain and rat adrenal AT_2 binding assays. There are several possible explanations for this discrepancy, which was observed in many of the triazolinone-based compounds studied. One possibility is that this could be a manifestation of the differences in primary structures between the human adrenal AT_2 receptor and the rat AT_2 receptor.[36] Another possible contributing factor could be the presence of bovine serum albumin in the assay mixtures (the "BSA effect").[33] For example, with these compounds, the BSA in the human adrenal binding assay mixture apparently affected the binding affinity to the AT_2 receptor to a much greater extent than that to the AT_1 receptor. This assertion is supported by data available for several compounds in Table 1 where the human adrenal assays were conducted in the presence of 0.02% BSA and 0.2% BSA (**10**, **15**, and **22**). In each case, the increase in AT_2 IC_{50} values in going from the 0.02% BSA assay to the 0.2% BSA assay was disproportionately greater compared to the corresponding increase in AT_1 IC_{50} values. For reasons not well understood, the AT_1 binding of these compounds is less affected by BSA concentrations than is AT_2 binding. This phenomenon could explain in part the larger AT_2/AT_1 IC_{50} ratios observed for the human adrenal assays compared to the other two pairs of assays. For instance, for **15** (the R^3 valeryl analogue of **3b**), the human adrenal AT_2/AT_1 IC_{50} ratios were 4.2 (0.2% BSA) and 2.1 (0.02% BSA) compared to 0.5 and 0.7 obtained from the aorta/midbrain and rat adrenal binding assays. It should be noted that the intrinsic potency of a given triazolinone-based ligand for the AT_1 receptor is essentially equivalent in all tissues tested. This equivalence has been shown previously by comparing AT_1 IC_{50} values obtained from a cloned human AT_1 receptor (no BSA required in the assay mixture), the rabbit aorta, and the rat adrenal AT_1 receptors for several compounds in this structural class.[1]

In the amide series (R^3 = NHCOR′ in **I**) the (2-chlorobenzoyl)sulfonamides tended to be somewhat more potent at the AT_1 receptor than the *tert*-butyl sulfonylcarbamates. Compounds **6b** and **5b** illustrate this point well. This trend was seen to a much lesser degree in the reversed amide (R^3 = CONHR′ in **I**) series (**7b** vs **8**). In this series, a 3–10-fold gain in AT_2 potency was also achieved by the added 3-F substituent, while the AT_1 affinity remained subnanomolar (**7a,b**).

SAR of I at R^2-R^4 When R^1 Is *n*-Butyl. Thus far, the most "balanced" compounds (**3b** and **8**) had human adrenal AT_2/AT_1 IC_{50} ratios of ca. 4, which needed to be brought to unity. In order to meet this target, we attempted structural modifications at R^1-R^4 of **I** (see Table 1). First, heteroatom incorporation into the amide side chain at R^3 was studied. Compared to the alkyl chain, it was hoped that the bond length and bond angle variations imparted by the heteroatom replacement would provide a better fit with the AT_2 receptor to yield more balanced compounds. The 2-furoylamino compound **9**, although possessing subnanomolar binding potency for both receptor subtypes, gave high human adrenal IC_{50} ratios. Similar results were obtained for each of the three (pyridinecarbonyl)amino derivatives (data not shown). Interruption of the valerylamino group with an oxygen atom provided **10** and **11**. The (3-methoxypropionyl)amino compound **11** was obviously inferior to **3b** regarding human adrenal IC_{50} ratios, and the (ethoxyacetyl)amino derivative **10** provided no apparent advantage over **8** or **3b** in this respect. In the reversed amide series, the analogue of **11** was prepared (**12**). The data for this compound were very similar to those obtained for **11**. When compared with the isosteric *N*-butylcarbamoyl derivative **8**, the deleterious effect of replacing the butyl group in **8** with a methoxyethyl group was evident with respect to AT_2 receptor binding affinity.

A few of these (alkoxyalkanoyl)amino derivatives were also prepared with a trifluoromethyl group at R^2. The best of these, **16**, was more potent at the AT_1 receptor than the valerylamino derivative **15**, and both were balanced in the aorta/midbrain and rat adrenal assays. In the human adrenal assays, **16** showed an IC_{50} ratio of 2.3, a 2-fold improvement over that obtained for **15**.

In a previous study, we had shown that the carbonyl of the amide or reversed amide at R^3 was essential for nanomolar AT_2 potency, but the requirement of the amide nitrogen for this purpose was equivocal.[19c] To see if an amide functionality in its entirety is essential to achieve good AT_2 binding, the ketone **14** isosteric to the reversed amide **13** was prepared. As shown in Table 1, the ketone retained subnanomolar intrinsic potency

Table 2. Preparation and Physical Properties of Various N^2-Aryltriazolinone Biphenylsulfonamides

no.	method[a]	yield (%)[b]	mp (°C)	formula[c]	FAB-MS	obsd species
3b	B	95	167–169	$C_{34}H_{37}F_4N_5O_6S$	726	M + Li
5b	A	91	137–140	$C_{33}H_{37}ClFN_5O_6S$	686	M + H
6b	A	65	>152 (grad)	$C_{35}H_{32}Cl_2FN_5O_5S{\cdot}0.5CH_3OH{\cdot}0.4CH_2Cl_2$	724.1576[d]	M + H
7b	A	42	218–220	$C_{37}H_{35}Cl_2FKN_5O_5S$	790.1420[e,f]	M + K
8	A	86	98–100	$C_{35}H_{40}ClFKN_5O_6S{\cdot}0.5CH_2Cl_2$[f]	714	M + H
9	C	51	145–147	$C_{35}H_{35}ClFN_5O_7S{\cdot}0.1CH_2Cl_2$	724	M + H
10	C	20	100–102	$C_{34}H_{39}ClFN_5O_7S{\cdot}CH_2Cl_2$	722	M + Li
11	C	53	122–124	$C_{34}H_{39}ClFN_5O_7S{\cdot}0.5CH_2Cl_2$	716	M + H
12	B	61	105–107	$C_{34}H_{39}ClFN_5O_7S{\cdot}0.15CH_2Cl_2$	716	M + H
13	B	61	133–135	$C_{34}H_{39}ClFN_5O_6S{\cdot}0.1CH_2Cl_2$	700	M + H
14	D	56	68–70	$C_{35}H_{40}ClFN_4O_6S{\cdot}0.05CH_2Cl_2$	699.2432[g]	M + H
15	B	91	179–182	$C_{36}H_{41}F_4N_5O_6S$	754	M + Li
16	B	72	118–120	$C_{35}H_{39}F_4N_5O_7S{\cdot}0.1CH_2Cl_2$	773	M + Na
17	B	38	205–208	$C_{33}H_{35}F_4N_5O_6S$	706	M + H
18	B	42	128–130	$C_{32}H_{33}F_4N_5O_6S{\cdot}0.5H_2O$	692	M + H
19	B	56	125–127	$C_{35}H_{39}F_4N_5O_5S{\cdot}0.15CH_2Cl_2$	718.2701[h]	M + H
20	B	76	109–111	$C_{36}H_{33}F_4N_5O_5S$	724.2235[i]	M + H
21	B	93	119–122	$C_{36}H_{32}F_5N_5O_5S$	741.2022[j]	M + H
22	B	60	181–183	$C_{36}H_{31}ClF_4KN_5O_5S$[f]	796	M + K
23	B	39	165–168	$C_{36}H_{31}Cl_2F_4KN_5O_5S{\cdot}0.5H_2O$[f]	830	M + K
24	B	95	117–120	$C_{38}H_{37}F_4N_5O_6S$	774	M + Li
25	B	58	123–126	$C_{33}H_{37}BrFN_5O_6S{\cdot}0.5H_2O$	736, 738	M + Li
26	B	60	143–146	$C_{33}H_{37}BrClN_5O_6S{\cdot}0.3H_2O$	646, 648	M − *t*-BOC
27	B	69	130–133	$C_{37}H_{38}BrFN_5O_6S{\cdot}0.5H_2O$	785, 787	M + Li
28	B	76	142–145	$C_{36}H_{36}BrFN_5O_6S{\cdot}0.75H_2O$	777, 779	M + 2Li
29	B	51	148–150	$C_{32}H_{35}BrFN_5O_6S$	716.1564[k]	M + H
30	B	56	146–148	$C_{34}H_{39}BrFN_5O_6S$	743,745	M + H
31	B	47	120–122	$C_{34}H_{39}BrFN_5O_6S{\cdot}0.5CH_2Cl_2$	756, 758	M + 2Li
32	B	51	190–193	$C_{36}H_{32}BrCl_2FKN_5O_5S{\cdot}0.8H_2O$[f]	855, 857	M + K
33	B	38	135–137	$C_{37}H_{35}F_4N_5O_6S{\cdot}0.25H_2O$	776	M + Na
34	B	40	128–130	$C_{34}H_{37}F_4N_5O_7S$	736.2465[l]	M + H
35	B	42	108–110	$C_{35}H_{38}F_4N_5O_6S{\cdot}0.5H_2O$	733	M + H
36	B	72	193–196	$C_{36}H_{30}Cl_2F_4KN_5O_5S$[f]	831	M + K
37	E	57	114–116	$C_{34}H_{37}F_4N_5O_6S{\cdot}0.5H_2O$	742	M + Na
38	E	39	121–123	$C_{34}H_{37}F_4N_5O_6S$	742	M + Na
39	E	78	143–145	$C_{33}H_{37}ClFN_5O_6S{\cdot}0.17CH_2Cl_2$	686	M + H
40	E	66	140–142	$C_{32}H_{35}ClFN_5O_7S{\cdot}0.25CH_2Cl_2$	688	M + H
41	E	34	79–81	$C_{35}H_{33}ClFN_5O_6S$[m]	706	M + H
42	E	49	154–156	$C_{35}H_{33}BrFN_5O_6S$	749.1317[n]	M
43	E	29	146–148	$C_{31}H_{33}BrFN_5O_6S{\cdot}0.5CH_2Cl_2$	701, 703	M + H
44	E	43	125–127	$C_{33}H_{37}BrFN_5O_6S{\cdot}0.15CH_2Cl_2$	730.1692[o]	M + H
45	E	49	115–117	$C_{33}H_{37}BrFN_5O_6S$	752, 754	M + Na
46	E	15	>120 (grad)	$C_{32}H_{35}BrFN_5O_6S{\cdot}0.75H_2O$	716, 718	M + H
47	E	67	>165 (grad)	$C_{35}H_{31}BrF_3N_5O_5S{\cdot}0.6CH_2Cl_2$	808, 810	M + K
48	E	68	>170 (grad)	$C_{33}H_{31}BrF_2KN_5O_5S{\cdot}0.75CH_2Cl_2$	790, 792	M + K
49	E	57	>125 (grad)	$C_{32}H_{35}BrFN_5O_6S$	715.1475[p]	M

[a] Synthetic methods are classified according to the methods by which the compounds are constructed as follows: (A) the distal ring of the biphenyl was appended onto an intermediate containing all of the other rings; (B) an appropriate biphenylmethyl bromide was used to alkylate the N^4 position of an N^2-substituted triazolinone; (C) R^3 in **I** was elaborated after the desired R^4 was installed; (D) this route was developed for this analogue specifically; (E) the triazolinone ring was derived from an arlhydrazine and an α-keto acid rather than from an imidate and an arylhydrazine. See the text and the Experimental Section for detailed descriptions. [b] Yield of final step. [c] Analyses for C, H, and N are within ±0.4% of calculated values except where noted and where charaterized by high-resolution FAB-MS and HPLC. [d] FAB-HRMS: calcd for $C_{35}H_{33}Cl_2FN_5O_5S$ $(M + H)^+$ 724.1563. [e] FAB-HRMS: calcd for $C_{37}H_{36}Cl_2FKN_5O_5S$ $(MH + K)^+$ 790.1435. [f] The potassium salt of this compound was analyzed. [g] FAB-HRMS: calcd for $C_{35}H_{41}ClFN_4O_6S$ $(M + H)^+$ 699.2419. [h] FAB-HRMS: calcd for $C_{35}H_{40}F_4N_5O_5S$ $(M + H)^+$ 718.2686. [i] FAB-HRMS: calcd for $C_{36}H_{34}F_4N_5O_5S$ $(M + H)^+$ 724.2217. [j] EI-HRMS: calcd for $C_{36}H_{33}F_5N_5O_5S$ (M^+) 741.2044. [k] FAB-HRMS: calcd for $C_{32}H_{36}{}^{79}BrFN_5O_6S$ $(M + H)^+$ 716.1654. [l] FAB-HRMS: calcd for $C_{34}H_{38}F_4N_5O_7S$ $(M + H)^+$ 736.2428. [m] N: calcd, 9.92; found, 9.44. [n] EI-HRMS: calcd for $C_{35}H_{33}{}^{79}BrFN_5O_6S$ $(M)^+$ 749.1319. [o] FAB-HRMS: calcd for $C_{33}H_{38}{}^{79}BrFN_5O_6S$ $(M + H)^+$ 730.1711. [p] EI-HRMS: calcd for $C_{32}H_{35}{}^{79}BrFN_5O_6S$ $(M)^+$ 715.1476.

at both receptors but was inferior to **13** in terms of intrinsic binding affinity. Nevertheless, some improvement in human adrenal IC_{50} ratio was achieved. Thus, the NH group of the amide is not required for subnanomolar intrinsic binding affinity at either receptor subtype.

A number of analogues were prepared to optimize the sulfonamide substituent (R^4 in **I**). In the sulfonylcarbamate series, groups less bulky than *tert*-butyl were studied (**17** and **18**). Compared to **3b**, increases in AT_2 IC_{50} values and the human adrenal IC_{50} ratios were observed. The (3,3-dimethylpropionyl)sulfonamide **19** retained subnanomolar potency at AT_1 and AT_2 but offered no advantage over the isosteric **3b** with respect to human adrenal IC_{50} ratios. In the benzoylsulfonamide series **20**–**23**, the parent compound **20** showed surprisingly high binding affinity for the AT_2 receptor, considering SAR data obtained from a related series of compounds.[23] All of these aroylsulfonamides had subnanomolar intrinsic potency, and the 2-fluorobenzoyl and 2,5-dichlorobenzoyl analogues appeared to be favored over the 2-chlorobenzoyl derivative in their human adrenal IC_{50} ratios. The best of the sulfonylcarbamates had somewhat better human adrenal IC_{50} ratios than the best of the aroylsulfonamides.

Several compounds with a 2-bromo substituent at the N^2-aryl of **I** (R^2 = Br) were prepared with a butyl group at R^1 (**25**–**27**). Analogues **25** and **26** differ in their 3-substituent on the biphenyl moiety. As shown in Table 1, compared to the 3-F substituent (**25**), a 3-Cl

group (**26**) was deleterious to AT_2 binding but had much less effect on AT_1 potency. Comparing **25** and **27** with the corresponding derivatives in the $R^2 = CF_3$ series (**3b** and **24**), these 2-bromo compounds were slightly more potent at the AT_1 receptor but had somewhat higher human adrenal IC_{50} ratios. Compounds **3b**, **5b**, and **25** differ only in the size of R^2. The chloro and bromo derivatives **5b** and **25** were more potent at the AT_1 receptor, but the chloro analogue **5b** showed a considerably worse human adrenal IC_{50} ratio than the bromo (**25**) or trifluoromethyl (**3b**) derivatives.

Optimization of R^1 and the Related SAR at R^2–R^4. After optimizing R^2–R^4 of **I**, the most balanced compound was **16**. This analogue still had a human adrenal IC_{50} ratio of 2.3. Finally, we resorted to shortening the alkyl chain length at R^1 of **I** as a means of achieving more balanced compounds. Our previous work with tetrazole[33] and sulfonamide analogues[23] of triazolinone-containing AT_1-selective ligands demonstrated that (1) subnanomolar AT_1 potency is required for acceptable *in vivo* activity in this series and (2) shortening of the *n*-butyl side chain at R^1 to *n*-propyl or cyclopropylmethyl resulted in a loss of at least 10-fold in AT_1 binding affinity. A shorter chain at R^1 met with further loss in AT_1 affinity. Extrapolating from these data, by shortening R^1 from *n*-butyl to *n*-propyl in the present series, we would not expect compounds with subnanomolar AT_1 IC_{50} values, and the effect of this change on AT_2 binding affinity was unknown. However, this approach was useful in the quinazolinone series in obtaining balanced compounds.[20c]

We prepared a number of compounds with R^1 = *n*-propyl and R^2 = Br. The first of these was compound **28**. We were gratified to see that, compared to the *n*-butyl derivative **27**, this analogue retained subnanomolar binding affinity for both the AT_1 and AT_2 receptors and reduced the human adrenal IC_{50} ratio to 1.8. Data from these compounds as well as from **25** and **29**, another butyl/propyl pair, showed that the rabbit aorta AT_1 potency for the propyl compounds **28** and **29** was slightly inferior to that of the corresponding butyl compounds **27** and **25**. However, the rat midbrain AT_2 binding affinity improved by ~2-fold for both of the propyl analogues. Overall, intrinsic subnanomolar potency was maintained at both receptors for these compounds. Analogues **30** and **31** are a pair of amide and reversed amide compounds in this series. Compound **31** was somewhat less potent at both receptors than **30** but was preferred over **30** based on its more favorable human adrenal IC_{50} ratio. Compound **32**, the (2,5-dichlorobenzoyl)sulfonamide analogue of **31**, reduced the human adrenal IC_{50} ratio by another 2-fold to 1.5.

Compounds with R^1 = *n*-propyl and $R^2 = CF_3$ were also evaluated. In this series, the maintenance of subnanomolar IC_{50} values was not accompained by as dramatic a reduction in the human adrenal IC_{50} ratios as that seen in the R^2 = bromo series (**33** vs **24** and **34** vs **16**). Results from **34** were particularly disappointing since, compared to **16** (the most balanced compound from the R^1 = *n*-butyl series), shortening R^1 to *n*-propyl did not provide a more balanced compound. Also in this series, **35** and **36** represent another pair in which the acylsulfonamide tended to provide greater AT_2/AT_1 balance than the sulfonylcarbamate in the human adrenal assays.

Pursuing the unexpected good results from the R^1 = *n*-propyl series, compounds with R^1 = ethyl were prepared (**37**–**48**). Data for a pair of compounds with $R^2 = CF_3$ (**37** and **38**) showed that, remarkably, nanomolar intrinsic potencies were retained even though the length of R^1 was further reduced. The reversed amide **37** gave a 3-fold improvement in human adrenal IC_{50} ratio without much loss in binding affinity in the aorta/midbrain assays compared to **38**. In fact, this compound, with a human adrenal IC_{50} ratio of 0.9, met our stringent target for *in vitro* balance. The amide **38** was not quite as well balanced. In the series with R^2 = Cl (**39**–**41**), the valerylamino compound **39** was 3-fold more potent at the AT_2 receptor than the corresponding compound in the $R^2 = CF_3$ series (**38**), even though it was a little less potent at the AT_1 receptor. However, isosteric replacement of a carbon in R^3 of **39** with an oxygen, as in compound **40**, resulted in a 2–4-fold loss in AT_1 potency.

A number of analogues with R^1 = Et and R^2 = Br were prepared. The benzoylamino compound **42** lost AT_1 potency by 6-fold compared to **28**, where R^1 = *n*-propyl, and gained no ground in terms of human adrenal IC_{50} ratio. Still, this compound, with a bromo substituent at R^2, was more potent at the AT_1 receptor than its analogue with a chloro substituent at that position (**41**). The propionylamino derivative **43** achieved balance in all three sets of *in vitro* assays but lost some AT_1 potency compared to its *n*-propyl analogue **29**. The valerylamino compound **44** not only retained the excellent *in vitro* potency shown by its higher homologue at R^1 (**30**) but also achieved a human adrenal IC_{50} ratio of unity. In contrast, **45**, the reversed amide of **44**, lost a good deal of AT_1 binding affinity compared to its homologue **31**, accompanied by a 5-fold preference for AT_2 receptor binding in all three sets of assays. A number of analogues of **44** with variations at R^4 were prepared in attempts to optimize the *in vitro* potency while maintaining balance in the human adrenal assays. Representative of these efforts are compounds **46**–**48**. The less bulky isopropyl sulfonylcarbamate **46** lost some AT_1 potency. The aroylsulfonamides **47** and **48** both improved the potency exhibited by **44**. Particularly impressive was compound **48**, the (2-fluorobenzoyl)-sulfonamide, which displayed excellent balance, and had subnanomolar IC_{50} values in *all* of the assays, including human adrenal. It is interesting to note that in a series of compounds differing at R^2 (**38**, **39**, and **44**), AT_1 binding affinity increased with the size of this substituent, the bromo analogue being the most potent. Finally, a derivative with R^1 = methyl (**49**) was prepared. Compared to its higher homologue **44**, this compound held quite well in AT_1 potency but lost considerable AT_2 potency in the midbrain assay.

Receptor–Ligand Binding Interactions. Receptor–ligand interactions for the triazolinone-based dual-acting AII antagonists have been discussed.[19c,23] Possible roles have been proposed for substituents on the N^2-aryl moiety and an appropriate acidic sulfonamide on the 2′-position of the biaryl. Briefly, for interactions with the AT_1 receptor: (1) the N^2-phenyl and the R^1 and R^2 groups on **I** are associated with hydrophobic pockets; (2) the 5-substituent on the N^2-aryl moiety makes

contact with another partially lipophilic area; (3) the keto group on the triazolinone is likely involved in a hydrogen-bonding interaction; and (4) the acidic sulfonamide is putatively involved in an ionic interaction. A wide range of *N*-substituents on the sulfonamide is tolerated. In contrast, binding with the AT_2 receptor is quite sensitive to changes in the size and shape of the *N*-subsiituent of the sulfonamide. The *tert*-butyl sulfonylcarbamates and the (2-chlorobenzoyl)sulfonamides did well in this regard. A carbonyl function at R^3 could be involved in hydrogen-bonding with the AT_2 receptor, and a lipophilic tail (at least two carbons in length) is needed to reach a hydrophobic pocket on the receptor. In addition, a 3-fluoro substituent on the biarylmethyl moiety improves the AT_2 binding. Data from the current study support these findings and reveal several additional points not previously appreciated. For simplicity and consistency with previous discussions,[19c,23] the ensuing discussion will only refer to data from the rabbit aorta (AT_1) and rat midbrain (AT_2) assays.

With respect to binding to the AT_1 receptor, in the R^1 = *n*-butyl series, AT_1 IC_{50} values were only slightly affected by changes in R^2 (e.g., **3b**, **5b**, and **25**), R^3 (e.g., **5b** and **8**–**13**), or R^4 (e.g., **3b** and **17**–**23**). This is also true for compounds studied in the R^1 = *n*-propyl series (**28**–**36**). However, in the R^1 = ethyl series (**37**–**48**), certain changes in R^2 or R^3 had significant effects on AT_1 IC_{50} values. For example, a comparison of **39** vs **41** shows that with R^2 = Cl, the compound with R^3 = benzoylamino lost ~7-fold AT_1 potency relative to that with R^3 = valerylamino. Similar results were observed between the benzoylamino (**42**) and valerylamino (**44**) derivatives in compounds with R^2 = Br. A comparison of analogues **42**–**44** with their respective higher homologues at R^1 (**28**–**30**) suggests that with the shortened length of R^1, differences in the length and shape of R^3 corresponded to a greater spread in the AT_1 IC_{50} values of the test compounds. Intuitively, this trend seems reasonable. The working hypothesis to explain the excellent retainment of AT_1 IC_{50} values from the R^1 = *n*-Bu to the R^1 = *n*-Pr series is as follows. Appropriate 2- and 5-substituents on the N^2-aryl ring (R^2 and R^3) can interact with the AT_1 receptor to compensate for the receptor–ligand binding with the R^1 group that may be diminished as R^1 is shortened. The degree of compensation depends on the exact combination of R^1–R^3. As R^1 is shortened to *n*-propyl and ethyl, the optimization of this realignment could become more and more dependent on both the size of R^2 and the orientation, length, and/or shape of R^3. Thus, for compounds with R^2 = Br, the IC_{50} values in the ethyl series **42**–**44** showed a greater dependence on R^3 than their analogues in the *n*-propyl series **28**–**30**. In keeping with this notion, it is not surprising that the AT_1 IC_{50} value of analogue **49** with R^1 = methyl was 2-fold worse than that of **44**, its ethyl analogue. Comparing AT_1 binding data of **30** and **31** with **44**–**45** shows that with R^2 = bromo, when R^1 is shortened, the amide linkage (NHCO) to the 5-position of the N^2-aryl is preferred over the reversed amide linkage (CONH). The compounds with shortened R^1 also showed more clearly the preference for bromo over chloro or trifluoromethyl at the R^2 position in this series (**44**, **40**, and **39** vs **25**, **5b**, and **3b**). This implies that a larger group at R^2 is better able to compensate for a shorter alkyl chain at R^1.

Table 3. Inhibition of AII Pressor Response by Triazolinone Derivatives in Conscious, Normotensive Rats

no.	dose (mg/kg)	route	peak inhibn (%)	duration[a] (h)	N^b
losartan[c]	1.0	iv	78 ± 6	>6	4
	3.0	po	94 ± 2	>4.5	4
3a[d]	1.0	iv	90 ± 4	>6 < 24	4
	1.0	po	74 ± 1	>5 < 24	4
	3.0	po	95 ± 4	>6 < 24	8
3b	1.0	iv	89 ± 4	>6 < 24	4
7b	1.0	iv	93 ± 3	>6 < 24	4
15	1.0	iv	71 ± 6	>6 < 24	3
	3.0	po	75 ± 8	>3.5 < 24	4
24	1.0	iv	92 ± 5	>6 < 24	3
	3.0	po	86 ± 3	>4 < 24	4
36	3.0	po	31 ± 11	>1 < 21	4
42	3.0	iv	100 ± 0	>6 < 24	4
	3.0	po	55 ± 9	ND[e,f]	8
	10.0	po	100 ± 0	>6 < 24	2
43	1.0	iv	100 ± 0	2.4 ± 0.6	4
44	0.3	iv	70 ± 8	>6 < 24	4
	1.0	iv	100 ± 0	≥4 < 24	3
	3.0	po	84 ± 9	>6 < 24	4
48	1.0	iv	85 ± 9	2.2 ± 1.0	4

[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 33. [d] Data taken from ref 19c. [e] ND = not determined. [f] Duration ranges from <1 to 6 h.

The binding affinity of compounds **13** and **14** suggests that although the amide NH is not essential for high potency at AT_2 receptors, its presence may be helpful in optimizing the intrinsic potency on both receptor subtypes. Available data suggest that the carbonyl group at R^3 most likely functions as a hydrogen bond acceptor through the carbonyl and not a donor through the NH.

Generally, a decrease in the length of R^1 had less effect on binding to AT_2 compared to AT_1. Optimal contact with the AT_2 receptor depended on the exact combination of R^1–R^4. For example, in the R^2 = Br series, among the three sulfonylcarbamates with R^3 = propionylamino (**25**, **29**, and **43**), the analogue with R^1 = *n*-Pr (**29**) was more potent than either its higher or lower homologues at R^1 (**25** and **43**). The same situation was found in a series of benzoylamino compounds (**27**, **28**, and **42**). However, when R^3 was lengthened to valerylamino as in **30** and **44**, the compound with R^1 = ethyl (**44**) was slightly better than its homologue with R^1 = *n*-propyl. Comparing **29** vs **30** and then **43** vs **44**, one sees that, as was in the case with the AT_1 binding, the spread in AT_2 binding potency among homologues in the ethyl series is greater than that seen in the *n*-propyl series. This may reflect the idea that as the length of R^1 decreases, the ligand reorients itself (relative to when R^1 = *n*-butyl) to optimize its contact with the AT_2 receptor. When R^1 becomes quite short, adequate length of the "alkyl tail" of the amide becomes important for achieving full interaction with the lipophilic pocket. Thus, when R^1 = Et, a valerylamino group at R^3 (**44**) fared better than a propionylamino group (**43**) in optimizing this hydrophobic interaction. Remarkably, compound **49**, where R^1 = methyl, maintained subnanomolar AT_1 binding affinity equivalent to that seen in compound **15**, a close analogue with a much longer alkyl group at R^1.

***In Vivo* Pharmacology.** The inhibition of the pressor response to exogenous AII challenges by a number of compounds from this study was studied in conscious normotensive rats, with results shown in Table 3.[37] Data

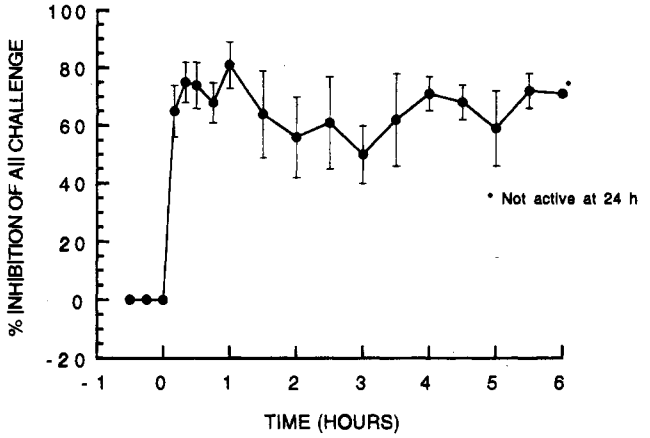


Figure 1. Percent inhibition of AII pressor response in conscious, normotensive rats by triazolinone **44** (L-163,958) at 3 mg/kg po ($N = 4$). Results are expressed as mean ± SEM.

for compound **3b** suggest that the added 3-F substituent on the biarylmethyl moiety has no effect on the efficacy or the duration of action of these compounds (cf. **3a** vs **3b** at 1.0 mg/kg iv). This is in agreement with data from other heterocyclic series.[20a] The data from compound **7b** indicate that reversed amides with a (2-chlorobenzoyl)sulfonamide are consistent with excellent efficacy and good duration of action following intravenous administration. However, data from compound **36** could imply that this structure type is not compatible with good oral activity. Limited data on a reversed amide from a previous study lend support to this notion.[19c] Returning to the amide series with $R^2 = CF_3$, data from analogues **15** and **24** show that the valerylamino and benzoylamino groups also gave compounds with good efficacy and duration of action. However, with a shortened group at R^1 and a bromo substituent at R^2, the benzoylamino derivative **42** was only marginally effective orally. In this series, the valerylamino *tert*-butyl sulfonylcarbamate **44** was the most effective following both iv and po administration, whereas the corresponding (2-fluorobenzoyl)sulfonamide **48** had much shorter duration of action at 1 mg/kg iv. Compound **44** compares well with both compound **3a** and losartan at both 1 mg/kg iv and 3 mg/kg po. The inhibition of the AII pressor response in rats by **44** (L-163,958) upon oral administration at 3 mg/kg is shown in Figure 1. Experiments are underway in these laboratories to evaluate possible pharmacological differences between AT_1/AT_2-balanced and AT_1-selective AII antogonists.

Conclusions

In pursuit of nanomolar, balanced AT_2/AT_1 AII antagonists with an AT_2/AT_1 IC_{50} ratio of ≤1 in human adrenal assays, and good efficacy and oral activity in animal models, we have studied the SAR on five positions of the trisubstituted triazolinone biarylsulfonamide structure **I** (Table 1). The data obtained support the previous finding that a 3-F substituent on the biarylmethyl group increases the AT_2 potency 5–10-fold in the rat midbrain assay while maintaining or improving slightly the AT_1 activity (rabbit aorta). Present data suggest that the NH group of the amide at the 5-position of the N^2-aryl moiety is not mandatory for acceptable AT_1 or AT_2 binding affinity. Heteroatom substitution in certain acyl substituents on the amide (or *N*-substituents of the reversed amide) can be tolerated. However, even in the best cases studied, these substitutions had little positive effect on the AT_2/AT_1 IC_{50} ratio from the human adrenal assays. Unexpectedly, shortening the alkyl group at the C^5-position of the triazolinone (R^1 in **I**) from *n*-butyl to *n*-propyl not only did not affect either the AT_1 or the AT_2 intrinsic potency but gave compounds with reduced human adrenal IC_{50} value ratios. With optimal combinations of R^2 and R^3, further truncation of R^1 to ethyl yielded additional potent compounds. One of these, derivative **44** (L-163,958), emerged as the most favored compound from this study based on its *in vitro* and *in vivo* profile. The combination of the added 3-F substituent on the biaryl moiety, the 2-bromo and 5-(valerylamino) substituents at N^2-aryl, and the ethyl group at the C^5-positon of the triazolinone ring, necessary to yield a truly balanced AT_2/AT_1 AII antagonist, had limited impact on the *in vivo* properties of these compounds (**44** vs **3a**). Compound **44** showed subnanomolar IC_{50} values from both the AT_1 (rabbit aorta) and AT_2 (rat midbrain) assays and exhibited an AT_2/AT_1 IC_{50} value ratio of unity in the human adrenal assays. This analogue also demonstrated effective antihypertensive properties with good duration of action intravenously at 0.3–1 mg/kg and orally at 3 mg/kg in a conscious rat model. Thus, starting from a subnanomolar, orally active AT_1-selective AII antagonist (**2**), via a series of systemic structural modifications, we have succeeded in improving the AT_2 binding affinity by 2500-fold and the AT_1 affinity by >2-fold, to obtain a potent, orally active AT_1/AT_2-balanced AII antagonist (**44**) with AT_2/AT_1 potency ratios of ≤1 in multiple assay systems.

Experimental Section

Melting points (uncorrected) were determined in open capillary tubes with a Thomas-Hoover apparatus. ^1H NMR spectra were recorded on a Varian XL-400, XL-300, or XL-200 spectrometer, 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, are within ±0.4% of theoretical values and were 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. Several compounds failed to give satisfactory elemental analysis even though they were homogeneous by analytical TLC. Due to meager supply, the purities of these compounds were characterized by high-resolution FAB-MS and checked by reversed-phase HPLC on a Beckman Ultrasphere ODS column (octadecylsilyl, 4.6 mm × 15 cm, 5 μm particle size) eluting with 45:55 ratio of 0.04 M phosphate 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.

Method A. 5-*n*-Butyl-2-(2-chloro-5-nitrophenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (50). To a solution of 1.86

g (9.92 mmol) of (2-chloro-5-nitrophenyl)hydrazine[26] in 20 mL of toluene was added 2.19 g (10.9 mmol) of ethyl *N*-carbethoxyvalerimidate,[33] and the solution was heated at 65 °C for 4 h. Subsequently, 1.52 mL (1.10 g, 10.9 mmol) of triethylamine was added, and the reaction mixture was stirred at 90 °C for 16 h. After the mixture was cooled to room temperature, volatiles were removed *in vacuo*. Flash chromatography of the residue (gradient elution with 0.5–4% MeOH in CH_2Cl_2) afforded 997 mg (34%) of the desired product as an orange solid, homogeneous by TLC (95:5 CH_2Cl_2/MeOH): mp 145–147 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91 (t, J = 7.3 Hz, 3 H), 1.39 (m, 2 H), 1.67 (m, 2 H), 2.58 (t, J = 7.7 Hz, 2 H), 7.70 (d, J = 8.9 Hz, 1 H), 8.22 (dd, J = 8.8, 2.6 Hz, 1 H), 8.38 (d, J = 2.6 Hz, 1 H), 11.62 (s, 1 H); FAB-MS m/e 297 $(M + H)^+$. Anal. ($C_{12}H_{13}ClN_4O_3$) C, H, N.

4-(4-Bromo-2-fluorobenzyl)-5-*n*-butyl-2-(2-chloro-5-nitrophenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (51). A mixture of 200 mg (0.714 mmol) of **50**, 21 mg (0.857 mmol) of sodium hydride (60% in oil), and 1.4 mL of dry DMF was stirred at 50 °C for 3 h. After the mixture was cooled to room temperature, a solution of 230 mg (0.857 mmol) of 4-bromo-2-fluorobenzyl bromide dissolved in a minimal volume of DMF was added, and the resulting mixture was stirred at 90 °C overnight. The reaction was quenched at room temperature by addition of 1 N HCl and extracted three times with ethyl acetate (EtOAc). The combined organic layers were washed with water and brine and dried over anhydrous Na_2SO_4. After filtration and concentration of the filtrate *in vacuo*, the crude product was flash chromatographed (gradient elution with 8:1–4:1 hexane/EtOAc) and afforded 261 mg (79%) of the alkylated product as an off-white foam, homogeneous by TLC (4:1 hexane/EtOAc): mp 104–106 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91 (t, J = 7.3 Hz, 3 H), 1.40 (m, 2 H), 1.65 (m, 2 H), 2.52 (t, J = 7.7 Hz, 2 H), 4.89 (s, 2 H), 7.24–7.32 (m, 3 H), 7.68 (d, J = 8.8 Hz, 1 H), 8.19 (dd, J = 8.8, 2.6 Hz, 1 H), 8.36 (d, J = 2.6 Hz, 1 H); FAB-MS m/e 483, 485 $(M + H)^+$. Anal. ($C_{19}H_{17}BrClFN_4O_3$) C, H, N.

[2-(*N*-*tert*-Butylsulfamoyl)phenyl]boronic Acid (52). At 0 °C, to a 0.5 M solution of benzenesulfonyl chloride in anhydrous CH_2Cl_2 was added *tert*-butylamine (2.2 equiv) slowly via a dropping funnel. After completion of addition, the reaction mixture was stirred at room temperature for 12 h. Subsequently, the solvent was removed under reduced pressure, and the residue was extracted into ether and washed with 2 N NaOH, water, and brine. The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford *N*-*tert*-butylbenzenesulfonamide (**52a**) which was used directly in the next reaction: mp 76–77 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.22 (s, 9 H), 4.77 (br s, 1 H), 7.45–7.57 (m, 3 H), 7.88–7.93 (m, 2 H); CI-MS m/e 214 $(M + H)^+$. Anal. ($C_{10}H_{15}NO_2S$) C, H, N.

At −40 °C, to a solution of 2.39 g (11.2 mmol) of *N*-*tert*-butylbenzenesulfonamide in anhydrous THF (20 mL) was added 22.3 mL of a 2.5 M *n*-BuLi solution (28 mmol) dropwise. The reaction mixture was warmed to room temperature and stirred for 2 h. At 0 °C, to this reaction mixture which contained the dianion was added 3.9 mL (3.18 g, 16.9 mmol) of triisopropyl borate, and the resulting mixture was stirred overnight at room temperature. The reaction was quenched by addition of 3 mL of 2 N HCl and stirring for 1 h. The solvent was removed under reduced pressure, and the residue obtained was extracted three times with EtOAc. The combined organic layers were washed with 2 N HCl, water, and brine and dried over anhydrous $MgSO_4$. Concentration of the filtrate *in vacuo* provided the crude [2-(*N*-*tert*-butylsulfamoyl)phenyl]-boronic acid which was used in the subsequent transformation without further purification: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.20 (s, 9 H), 5.03 (br s, 1 H), 6.05 (br s, 2 H), 7.46–7.62 (m, 2 H), 7.78–7.85 (m, 1 H), 7.95–8.15 (m, 1 H).

5-*n*-Butyl-4-[[2′-(*N*-*tert*-butylsulfamoyl)-3-fluorobiphenyl-4-yl]methyl]-2-(2-chloro-5-nitrophenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (53). A solution of 260 mg (0.538 mmol) of **51** in 7 mL of toluene was treated with 1.1 mL of a 250 mg/mL ethanolic solution (277 mg, 1.08 mmol) of **52**, 1.72 mL (2.15 mmol) of 1.25 N NaOH (aqueous), and 31 mg (0.0269 mmol, 5 mol %) of tetrakis(triphenylphosphine)palladium(0). The mixture was stirred at 90 °C for 4 h, cooled to room temperature, and concentrated. The residue was taken up in EtOAc and washed with water and brine. The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography (gradient elution with 6:1–4:1 hexane/EtOAc) and provided 172 mg (52%) of the coupled product as a stiff, pale yellow foam, homogeneous by TLC (4:1 hexane/EtOAc): mp 124–126 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.93 (t, J = 7.3 Hz, 3 H), 1.03 (s, 9 H), 1.43 (m, 2 H), 1.70 (m, 2 H), 2.59 (t, J = 7.7 Hz, 2 H), 3.62 (s, 1 H), 5.00 (s, 2 H), 7.2–7.6 (m, 6 H), 7.69 (d, J = 8.8 Hz, 1 H), 8.15 (dd, J = 7.8, 1.3 Hz, 1 H), 8.20 (dd, J = 8.8, 2.6 Hz, 1 H), 8.38 (d, J = 2.6 Hz, 1 H); FAB-MS m/e 616 $(M + H)^+$. Anal. ($C_{29}H_{31}ClFN_5O_5S\cdot0.8CH_3OH$) C, H, N.

2-(5-Amino-2-chlorophenyl)-5-*n*-butyl-4-[[2′-(*N*-*tert*-butylsulfamoyl)-3-fluorobiphenyl-4-yl]methyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (54). A mixture of 170 mg (0.276 mmol) of **53**, 15 mg of platinum oxide, and 3 mL of ethanol was stirred under a hydrogen atomosphere (balloon) for 3 h. The mixture was then centrifuged, the supernatent decanted, and the crude product chromatographed (gradient elution with 6:1–4:1 hexane/EtOAc) to yield 127 mg (78%) of the aniline as a stiff, off-white foam, homogeneous by TLC (1:1 hexane/EtOAc): mp 167–170 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.90 (t, J = 7.3 Hz, 3 H), 1.00 (s, 9 H), 1.39 (m, 2 H), 1.66 (m, 2 H), 2.53 (t, J = 7.7 Hz, 2 H), 3.74 (s, 1 H), 4.98 (s, 2 H), 6.68 (br m, 1 H), 6.85 (br m, 1 H), 7.19–7.30 (m, 4 H), 7.38–7.56 (m, 3 H), 8.14 (dd, J = 7.9, 1.4 Hz, 1 H); high-resolution EI-MS m/e 585.1965 [calcd for $C_{29}H_{33}ClFN_5O_3S$ (M^+) 585.1976].

5-*n*-Butyl-4-[[2′-(*N*-*tert*-butylsulfamoyl)-3-fluorobiphenyl-4-yl]methyl]-2-[2-chloro-5-(propionylamino)phenyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (55). A solution of 124 mg (0.218 mmol) of **54**, 98 μL (149 mg, 1.09 mmol) of propionyl bromide, and 27 mg (0.218 mmol) of 4-(dimethylamino)pyridine (DMAP) in 1 mL of dry pyridine was stirred overnight at room temperature. The reaction was quenched by addition of water and the mixture extracted twice with EtOAc. The combined organic layers were washed twice with water and then with brine and dried over anhydrous Na_2SO_4. The filtered solution was concentrated, and the residue was flash chromatographed (gradient elution with 3:1–1:1 hexane/EtOAc) to give 117 mg (84%) of the acylated compound as a white solid, homogeneous by TLC (1:1 hexane/EtOAc): mp 103–105 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91 (t, J = 7.3 Hz, 3 H), 1.02 (s, 9 H), 1.19 (t, J = 7.5 Hz, 3 H), 1.40 (m, 2 H), 1.65 (m, 2 H), 2.35 (q, J = 7.5 Hz, 2 H), 2.55 (t, J = 7.7 Hz, 2 H), 3.67 (s, 1 H), 5.00 (s, 2 H), 7.23–7.58 (m, 8 H), 7.71 (d, J = 2.5 Hz, 1 H), 8.15 (dd, J = 7.9, 1.3 Hz, 1 H); FAB-MS m/e 648 $(M + Li)^+$; high-resolution EI-MS m/e 641.2203 [calcd for $C_{32}H_{37}ClFN_5O_4S$ (M^+) 641.2239].

5-*n*-Butyl-2-[2-chloro-5-(propionylamino)phenyl]-2,4-dihydro-4-[(3-fluoro-2′-sulfamoylbiphenyl-4-yl)methyl]-3*H*-1,2,4-triazol-3-one (56). A solution of 117 mg (0.182 mmol) of **55** in 1.8 mL of trifluoroacetic acid (TFA) containing 2 drops of anisole was stirred overnight at room temperature. The excess TFA was removed by evaporation under a gentle stream of nitrogen. The residue was reconcentrated from toluene twice *in vacuo* and flash chromatographed (gradient elution with 0.5–5% MeOH in CH_2Cl_2) to give 96 mg (90%) of the free sulfonamide as a white solid, homogeneous by TLC (19:1 CH_2Cl_2/MeOH): mp 135–137 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91 (t, J = 7.4 Hz, 3 H), 1.17 (t, J = 7.5 Hz, 3 H), 1.40 (m, 2 H), 1.67 (m, 2 H), 2.33 (q, J = 7.5 Hz, 2 H), 2.57 (t, J = 7.7 Hz, 2 H), 4.48 (br s, 2 H), 4.99 (s, 2 H), 7.2–7.6 (m, 8 H), 7.71 (d, J = 2.3 Hz, 1 H), 7.75 (br s, 1 H), 8.14 (dd, J = 7.9, 1.3 Hz, 1 H); FAB-MS m/e 586 $(M + Li)^+$. Anal. ($C_{28}H_{29}ClFN_5O_4S\cdot0.1CH_2Cl_2$) C, H, N.

5-*n*-Butyl-4-[[2′-[*N*-(2-chlorobenzoyl)sulfamoyl]-3-fluorobiphenyl-4-yl]methyl]-2-[2-chloro-5-(propionylamino)phenyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (6b). A solution of 18 mg (0.113 mmol) of 2-chlorobenzoic acid and 18.3 mg (0.113 mmol) of 1,1-carbonyldiimidazole (Im_2CO) in 1 mL of dry THF was stirred at 60 °C for 3 h. Subsequently, a solution of 33 mg (0.564 mmol) of the free sulfonamide **56** and 17 μL (17.2 mg, 0.113 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 60 °C, the reaction mixture was cooled to room temperature, the reaction was quenched by addition of 5% aqueous citric acid, and the mixture was extracted twice with EtOAc. The combined organic layers were washed with 2 N HCl (aqueous), water, and brine and dried over anhydrous Na_2SO_4. The crude product obtained after filtration and removal of solvents was flash chromatographed (gradient elution with 1–5% MeOH in CH_2Cl_2) to give 26 mg (65%) of the target compound as a white solid, homogeneous by TLC (19:1 CH_2Cl_2/MeOH): mp >152 °C (gradual); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.91 (t, J = 7.4 Hz, 3 H), 1.18 (t, J = 7.6 Hz, 3 H), 1.40 (m, 2 H), 1.64 (m, 2 H), 2.39 (q, J = 7.6 Hz, 2 H), 2.59 (t, J = 7.5 Hz, 2 H), 5.05 (s, 2 H), 7.18–7.70 (m, 12 H), 7.90 (d, J = 2.5 Hz, 1 H), 8.29 (d, J = 7.9 Hz, 1 H); high-resolution FAB-MS m/e 724.1576 [calcd for $C_{35}H_{33}Cl_2FN_5O_4S$ $(M + H)^+$ 724.1563]. Anal. ($C_{35}H_{32}Cl_2FN_5O_4S$·0.5CH_3OH·0.4CH_2Cl_2) C, H, N.

4-(4-Bromo-2-fluorobenzyl)-5-*n*-butyl-2-[5-(*N*-*n*-butylcarbamoyl)-2-chlorophenyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (58). A solution of 50 mg (0.10 mmol) of **57** [obtained from alkylation of 5-*n*-butyl-2-(5-carbomethoxy-2-chlorophenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one[19c] and 4-bromo-2-fluorobenzyl bromide in the manner described for **51**] in 1 mL of *n*-butylamine was stirred overnight at 65 °C. After being cooled to room temperature, volatiles were evaporated *in vacuo*. The residue was flash chromatographed (gradient elution with 1–5% MeOH in CH_2Cl_2) to yield 41 mg (76%) of a colorless, glassy solid, homogeneous by TLC (19:1 CH_2Cl_2/MeOH): mp 114–116 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, J = 7.4 Hz, 3 H), 0.94 (t, J = 7.3 Hz, 3 H), 1.38 (m, 2 H), 1.58 (m, 4 H), 2.58 (t, J = 7.5 Hz, 2 H), 3.35 (t, J = 7.2 Hz, 2 H), 4.98 (s, 2 H), 7.25 (d, J = 8.0 Hz, 1 H), 7.35–7.45 (m, 2 H), 7.67(d, J = 8.4 Hz, 1 H), 7.89 (dd, J = 8.4, 2.2 Hz, 1 H), 7.96 (d, J = 2.2 Hz, 1 H); FAB-MS m/e 537, 539 $(M + H)^+$. Anal. ($C_{24}H_{27}BrClFN_4O_2$) C, H, N.

Method B. 3-Fluoro-4-methyl-2′-(*N*-*tert*-butylsulfamoyl)biphenyl (60). A solution of 1.27 mL (1.89 g, 10 mmol) of 4-bromo-2-fluorotoluene in 60 mL of toluene was treated with 4.27 g (16.6 mmol) of [2-(*N*-*tert*-butylsulfamoyl)phenyl]-boronic acid in 40 mL of ethanol, 26 mL (32 mmol) of 1.25 N NaOH (aqueous), and 289 mg (0.25 mmol, 2.5 mol %) of tetrakis(triphenylphosphine)palladium(0). The mixture was stirred at 90 °C for 4.5 h and then cooled and concentrated. The residue was taken up in EtOAc and washed with water and brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography (elution with 10:1–4:1 hexane/EtOAc) to give 2.96 g (92%) of the coupled product as an off-white foam, homogeneous by TLC (4:1 hexane/EtOAc): mp 123–124 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.01 (s, 9 H), 2.32 (s, 3 H), 3.59 (br s, 1 H), 7.13–7.28 (m, 4 H), 7.44–7.56 (m, 2 H), 8.14 (dd, J = 7.8, 1.4 Hz, 1 H); FAB-MS m/e 322 $(M + H)^+$. Anal. ($C_{17}H_{20}FNO_2S$·0.3H_2O) C, H, N.

[3-Fluoro-2′-(*N*-*tert*-butylsulfamoyl)biphenyl-4-yl]-methyl Bromide (59). A solution of 1.08 g (3.36 mmol) of **60** in 20 mL of CCl_4 was stirred at reflux under irradiation from a 100 W tungsten lamp as a solution of 3.5 mmol of bromine in ca. 13 mL of CCl_4 was added dropwise over 1.5 h. After being stirred at reflux overnight, the solution was cooled and concentrated. The residue was crystallized from EtOAc–hexane to give 1.10 g of the desired monobromide as an off-white solid, mp 138–140 °C [estimated purity (NMR) 87%, contains minor unbrominated and dibrominated compounds by TLC and NMR]: mp 139–141 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.01 (s, 9 H), 3.56 (br s, 1 H), 4.54 (s, 2 H), 7.2–7.6 (m, 6 H), 8.15 (dd, J = 8.0, 1.3 Hz, 1 H); FAB-MS m/e 400, 402 $(M + H)^+$.

2-(2-Bromo-5-nitrophenyl)-5-*n*-butyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (61). To a solution of 1.50 g (6.47 mmol) of (2-bromo-5-nitrophenyl)hydrazine[26] in 18 mL of toluene and 8 mL of THF was added 1.43 g (7.11 mmol) of ethyl *N*-carbethoxyvalerimidate,[33] and the solution was heated at 65 °C for 4 h. Subsequently, 0.911 mL (661 mg, 6.54 mmol) of triethylamine was added, and the reaction mixture was stirred at 90 °C for 20 h. After the mixture was cooled to room temperature, volatiles were removed *in vacuo*. Flash chromatography of the residue (gradient elution with 0.8–1.5% MeOH in CH_2Cl_2) afforded 1.92 g (87%) of the desired product as a brown solid, homogeneous by TLC (98:2 CH_2Cl_2/MeOH): mp 126–128 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.90 (t, J = 7.3 Hz, 3 H), 1.37 (m, 2 H), 1.66 (m, 2 H), 2.57 (t, J = 7.6 Hz, 2 H), 7.89 (d, J = 8.8 Hz, 1 H), 8.14 (dd, J = 8.8, 2.6 Hz, 1 H), 8.34 (d, J = 2.6 Hz, 1 H), 11.93 (br s, 1 H); high-resolution EI-MS m/e 340.0146 [calcd for $C_{12}H_{13}BrN_4O_3$ (M^+) 340.0171].

2-(2-Bromo-5-nitrophenyl)-5-*n*-butyl-4-[[2′-(*N*-*tert*-butylsulfamoyl)-3-fluorobiphenyl-4-yl]methyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (62). A mixture of 810 mg (2.38 mmol) of **61**, 57 mg (2.62 mmol) of sodium hydride (60% in oil), and 7.5 mL of dry DMF was stirred at room temperature for 3.5 h. Subsequently, a solution of 1.05 g (2.62 mmol) of **59** dissolved in 2.5 mL of DMF was added, and the resulting mixture was stirred at 35 °C for 24 h. The reaction was quenched at room temperature by addition of water and the mixture extracted three times with EtOAc. The combined organic layers were washed with water and brine and dried over anhydrous Na_2SO_4. After filtration and concentration of the filtrate *in vacuo*, the crude product was flash chromatographed (elution with 0.5% MeOH in CH_2Cl_2). Starting material (103 mg) was recovered along with 1.27 g (93% based on amount of **61** consumed) of the desired alkylated product as an off-white foam, homogeneous by TLC (98:2 CH_2Cl_2/MeOH): mp 137–139 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.93 (t, J = 7.4 Hz, 3 H), 1.03 (s, 9 H), 1.43 (m, 2 H), 1.70 (m, 2 H), 2.58 (t, J = 7.7 Hz, 2 H), 3.62 (s, 1 H), 5.00 (s, 2 H), 7.23–7.33 (m, 3 H), 7.42–7.58 (m, 3 H), 7.88 (d, J = 8.8 Hz, 1 H), 8.10–8.16 (m, 2 H), 8.33 (d, J = 2.6 Hz, 1 H); FAB-MS m/e 666, 668 $(M + Li)^+$. Anal. ($C_{29}H_{31}BrFN_5O_5S$) C, H, N.

5-*n*-Butyl-4-[[2′-(*N*-*tert*-butylsulfamoyl)-3-fluorobiphenyl-4-yl]methyl]-2,4-dihydro-2-[5-nitro-2-(trifluoromethyl)phenyl]-3*H*-1,2,4-triazol-3-one (63). A mixture of 400 mg (0.606 mmol) of **62**, 128 μL (175 mg, 1.21 mmol) of methyl chlorodifluoroacetate, 42 mg (0.73 mmol) of potassium fluoride, 116 mg (0.606 mmol) of cuprous iodide, 72 mg (0.606 mmol)) of potassium bromide, and 1.2 mL of DMF was stirred at 120 °C in a sealed tube for 15 h. After being cooled to room temperature, the mixture was diluted with water and extracted three times with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated, and the residue was flash chromatographed on silica gel (elution with 6:1 hexane/EtOAc) to give 243 mg (62%) of the desired compound along with 28 mg of the 2-chloro compound **53**. The desired 2-trifluoromethyl compound was a stiff, pale yellow foam, homogeneous by TLC (5:1 hexane/EtOAc): mp 145–146 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.92 (t, J = 7.3 Hz, 3 H), 1.02 (s, 9 H), 1.41 (m, 2 H), 1.68 (m, 2 H), 2.57 (t, J = 7.7 Hz, 2 H), 3.60 (s, 1 H), 5.00 (s, 2 H), 7.2–7.6 (m, 6 H), 7.99 (d, J = 8.8 Hz, 1 H), 8.15 (dd, J = 8.0, 1.3 Hz, 1 H), 8.35 (m, 1 H), 8.45 (d, J = 2.2 Hz, 1 H); FAB-MS m/e 656 $(M + Li)^+$. Anal. ($C_{30}H_{31}F_4N_5O_5S$) C, H, N.

2-[5-Amino-2-(trifluoromethyl)phenyl]-5-*n*-butyl-4-[[2′-(*N*-*tert*-butylsulfamoyl)-3-fluorobiphenyl-4-yl]methyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (64). A mixture of 150 mg (0.231 mmol) of **63**, 15 mg of platinum oxide, 2 mL of EtOAc, and 8 mL of ethanol was stirred under 2 atm of hydrogen (Parr shaker) for 2 h. The mixture was then centrifuged and the supernatant decanted, and the volatiles were evaporated to yield 130 mg (91%) of the aniline as a stiff, off-white foam, virtually homogeneous by TLC (95:5 MeOH/CH_2Cl_2): mp 103–104 °C; ^1H NMR (CD_3OD, 400 MHz) δ 0.91 (t, J = 7.4 Hz, 3 H), 1.03 (s, 9 H), 1.40 (m, 2 H), 1.62 (m, 2 H), 2.62 (t, J = 7.4 Hz, 2 H), 5.07 (s, 2 H), 6.68 (d, J = 2.3 Hz, 1 H), 6.79 (dd, J = 8.4, 1.8 Hz, 1 H), 7.24–7.34 (m, 4 H), 7.46 (d, J = 8.7 Hz, 1 H), 7.55 (dt, J = 7.5, 1.5 Hz, 1 H), 7.63 (dt, J = 7.5, 1.5 Hz, 1 H), 8.11 (dd, J = 7.9, 1.3 Hz, 1 H); high-resolution EI-MS m/e 619.2209 [calcd for $C_{30}H_{33}F_4N_5O_3S$ (M^+) 619.2240].

5-*n*-Butyl-4-[[2′-(*N*-*tert*-butylsulfamoyl)-3-fluorobiphenyl-4-yl]methyl]-2,4-dihydro-2-[5-[(ethoxyacetyl)amino]-2-(trifluoromethyl)phenyl]-3*H*-1,2,4-triazol-3-one (65). Ethoxyacetic acid (17.8 μL, 19.6 mg, 0.189 mmol) and BOP reagent (91.7 mg, 0.207 mmol) were taken up in 1.0 mL of

dry CH_2Cl_2 followed by addition of 29 μL (20.9 mg, 0.207 mmol) of triethylamine. The reaction mixture was stirred overnight at room temperature in a foil-covered flask. TLC (95:5 CH_2Cl_2/MeOH) showed disappearance of all starting material. Volatiles were evaporated, the residue was taken up in EtOAc and partitioned with 5% $NaHCO_3$, and the aqueous layer was reextracted with EtOAc. The organic layers were combined, washed with 5% $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4. The crude material obtained after filtration and removal of volatiles was flash chromatographed (gradient elution with 1–2% MeOH in CH_2Cl_2) to give 70 mg (88%) of the desired compound as a cream-colored solid, homogeneous by TLC (95:5 CH_2Cl_2/MeOH): mp 95–97 °C; ^1H NMR (CD_3OD, 400 MHz) δ 0.92 (t, J = 7.4 Hz, 3 H), 1.03 (s, 9 H), 1.28 (t, J = 7.0 Hz, 3 H), 1.41 (m, 2 H), 1.65 (m, 2 H), 2.63 (t, J = 7.4 Hz, 2 H), 3.65 (q, J = 7.0 Hz, 2 H), 4.11 (s, 2 H), 5.09 (s, 2 H), 7.27–7.35 (m, 4 H), 7.53–7.65 (m, 2 H), 7.81 (d, J = 8.7 Hz, 1 H), 7.93–8.00 (m, 2 H), 8.11 (dd, J = 8.0, 1.3 Hz, 1 H); FAB-MS m/e 706 $(M + H)^+$; high-resolution EI-MS m/e 705.2559 [calcd for $C_{34}H_{39}F_4N_5O_5S$ (M^+) 705.2608].

5-*n*-Butyl-2,4-dihydro-2-[5-[(ethoxyacetyl)amino]-2-(trifluoromethyl)phenyl]-4-[(3-fluoro-2′-sulfamoylbiphenyl-4-yl)methyl]-3*H*-1,2,4-triazol-3-one (66). The starting material (**65**; 65 mg, 0.0922 mmol) was dissolved in 1 mL of TFA, and 5 drops of anisole was added. The flask was purged with nitrogen and stoppered, and the reaction mixture was stirred at room temperature overnight. The excess TFA was removed by a stream of nitrogen, and the residue was coevaporated with toluene twice. The crude material was flash chromatographed over silica gel (gradient elution with 0.5–5% MeOH in CH_2Cl_2) to give 57 mg (95%) of the desired compound as a white solid, homogeneous by TLC (95:5 CH_2Cl_2/MeOH): mp 96–98 °C; ^1H NMR (CD_3OD, 400 MHz) δ 0.91 (t, J = 7.3 Hz, 3 H), 1.28 (t, J = 7.0 Hz, 3 H), 1.40 (m, 2 H), 1.64 (m, 2 H), 2.63 (t, J = 7.4 Hz, 2 H), 3.64 (q, J = 7.0 Hz, 2 H), 4.11 (s, 2 H), 5.09 (s, 2 H), 7.23–7.46 (m, 4 H), 7.53–7.65 (m, 2 H), 7.81 (d, J = 8.4 Hz, 1 H), 7.95–7.98 (m, 2 H), 8.11 (dd, J = 7.9, 1.3 Hz, 1 H); FAB-MS m/e 650 $(M + H)^+$; high-resolution EI-MS m/e 649.1995 [calcd for $C_{30}H_{31}F_4N_5O_5S$ (M^+) 649.1982].

4-[[2′-[*N*-(*tert*-Butoxycarbonyl)sulfamoyl]-3-fluorobiphenyl-4-yl]methyl]-5-*n*-butyl-2,4-dihydro-2-[5-[(ethoxyacetyl)amino]-2-(trifluoromethyl)phenyl]-3*H*-1,2,4-triazol-3-one (16). The starting material (**66**; 52 mg, 0.0801 mmol) dissolved in 1 mL of THF was treated with 2.31 mg (0.0961 mmol) of NaH (60% in oil), and the resulting reaction mixture was stirred at 50 °C for 4 h. Subsequently, 37 μL (35.0 mg, 0.160 mmol) of di-*tert*-butyl dicarbonate was added and the solution stirred overnight at 60 °C. The reaction was quenched by addition of water followed by two extractions with EtOAc. The organic layers were combined, washed twice with 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 0.5–2% MeOH in CH_2Cl_2) to give 43 mg (72%) of the target compound as a white solid, homogeneous by TLC (95:5 CH_2Cl_2/MeOH): mp 118–120 °C; ^1H NMR (CD_3OD, 400 MHz) δ 0.92 (t, J = 7.3 Hz, 3 H), 1.28 (t, J = 7.0 Hz, 3 H), 1.30 (s, 9 H), 1.42 (m, 2 H), 1.64 (m, 2 H), 2.65 (t, J = 7.4 Hz, 2 H), 3.64 (q, J = 7.0 Hz, 2 H), 4.11 (s, 2 H), 5.10 (s, 2 H), 7.17–7.20 (m, 2 H), 7.26 (t, J = 7.7 Hz, 1 H), 7.34 (dd, J = 7.6, 1.3 Hz, 1 H), 7.61 (dt, J = 7.6, 1.3 Hz, 1 H), 7.70 (dt, J = 7.6, 1.3 Hz, 1 H), 7.81 (d, J = 8.8 Hz, 1 H), 7.93–8.00 (m, 2 H), 8.16 (dd, J = 8.0, 1.2 Hz, 1 H); FAB-MS m/e 750 $(M + H)^+$. Anal. ($C_{35}H_{39}F_4N_5O_7S \cdot 0.1CH_2Cl_2$) C, H, N.

5-*n*-Butyl-4-[[2′-(*N*-*tert*-butylsulfamoyl)-3-fluorobiphenyl-4-yl]methyl]-2-[2-chloro-5-[*N*-(2-methoxyethyl)carbamoyl]phenyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (68). The starting material (**67**; 15 mg, 0.0239 mmol) was dissolved in 1 mL of 2-methoxyethylamine and stirred at 65 °C for 48 h. The excess amine was removed by a stream of nitrogen. The crude material was flash chromatographed over silica gel (gradient elution with 0.5–2% MeOH in CH_2Cl_2) to give 14 mg (88%) of the desired compound as a clear glass, homogeneous by TLC (95:5 CH_2Cl_2/MeOH): mp 85–87 °C; ^1H NMR (CD_3OD, 400 MHz) δ 0.93 (t, J = 7.4 Hz, 3 H), 1.04 (s, 9 H), 1.43 (m, 2 H), 1.66 (m, 2 H), 2.66 (t, J = 7.4 Hz, 2 H), 3.34 (s, 2 H), 3.36 (s, 2 H), 3.55 (s, 3 H), 5.10 (s, 2 H), 7.24–7.36 (m, 4 H), 7.55 (dt, J = 7.7, 1.4 Hz, 1 H), 7.62 (dt, J = 7.7, 1.4 Hz, 1 H), 7.70 (d, J = 8.4 Hz, 1 H), 7.93 (dd, J = 8.4, 2.3 Hz, 1 H), 7.99 (d, J = 2.1 Hz, 1 H), 8.11 (dd, J = 7.8, 1.2 Hz, 1 H); FAB-MS m/e 672 $(M + H)^+$; high-resolution EI-MS m/e 671.2350 [calcd for $C_{33}H_{39}ClFN_5O_5S$ (M^+) 671.2344].

Method C. 5-*n*-Butyl-4-[[2′-(*N*-*tert*-butylsulfamoyl)-3-fluorobiphenyl-4-yl]methyl]-2-(2-chloro-5-nitrophenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (53). A mixture of 456 mg (1.54 mmol) of **50**, 447 mg (1.85 mmol) of sodium hydride (60% in oil), and 2 mL of dry DMF was stirred at 50 °C for 4 h. Subsequently, a solution of 738 mg (1.85 mmol) of **59** dissolved in 1 mL of DMF was added, and the resulting mixture was stirred at 50 °C overnight. The reaction was quenched at room temperature by addition of water and the mixture extracted twice with EtOAc. The combined organic layers were washed with water and brine and dried over anhydrous Na_2SO_4. After filtration and concentration of the filtrate *in vacuo*, the crude product was flash chromatographed (elution with 0.5–1% MeOH in CH_2Cl_2) to give 711 mg (75%) of the desired alkylated product as an off-white foam, almost homogeneous by TLC (98:2 CH_2Cl_2/MeOH): mp 124–126 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.93 (t, J = 7.3 Hz, 3 H), 1.03 (s, 9 H), 1.43 (m, 2 H), 1.70 (m, 2 H), 2.59 (t, J = 7.7 Hz, 2 H), 3.62 (s, 1 H), 5.00 (s, 2 H), 7.2–7.6 (m, 6 H), 7.69 (d, J = 8.8 Hz, 1 H), 8.15 (dd, J = 7.8, 1.3 Hz, 1 H), 8.20 (dd, J = 8.8, 2.6 Hz, 1 H), 8.38 (d, J = 2.6 Hz, 1 H); FAB-MS m/e 616 $(M + H)^+$.

5-*n*-Butyl-2-(2-chloro-5-nitrophenyl)-2,4-dihydro-4-[(3-fluoro-2′-sulfamoylbiphenyl-4-yl)methyl]-3*H*-1,2,4-triazol-3-one (69). The starting material (**53**; 711 mg, 1.16 mmol) was dissolved in 11 mL of TFA, and 0.5 mL of anisole was added. The reaction mixture was stirred at room temperature overnight in a stoppered flask purged with nitrogen. The excess TFA was removed with a stream of nitrogen. After coevaporations with toluene, the residue was flash chromatographed over silica gel (gradient elution with 0.5–2% MeOH in CH_2Cl_2) to give 465 mg (72%) of the desired alkylated product, homogeneous by TLC (95:5 CH_2Cl_2/MeOH): mp 101–102 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.93 (t, J = 7.3 Hz, 3 H), 1.43 (m, 2 H), 1.70 (m, 2 H), 2.60 (t, J = 7.7 Hz, 2 H), 4.39 (s, 2 H), 5.00 (s, 2 H), 7.24–7.30 (m, 3 H), 7.43 (t, J = 7.6 Hz, 1 H), 7.52 (t, J = 7.6 Hz, 1 H), 7.59 (t, J = 7.3 Hz, 1 H), 7.68 (d, J = 8.8 Hz, 1 H), 8.13 (d, J = 7.8 Hz, 1 H), 8.19 (dd, J = 8.8, 2.6 Hz, 1 H), 8.38 (d, J = 2.8 Hz, 1 H); FAB-MS m/e 560 $(M + H)^+$; high-resolution EI-MS m/e 559.1093 [calcd for $C_{25}H_{23}ClFN_5O_5S$ (M^+) 559.1092].

4-[[2′-[*N*-(*tert*-Butoxycarbonyl)sulfamoyl]-3-fluorobiphenyl-4-yl]methyl]-5-*n*-butyl-2-(2-chloro-5-nitrophenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (70). The starting material (**69**; 300 mg, 0.536 mmol) was dissolved in 2 mL of THF, and 15.4 mg (0.643 mmol) of NaH (60% in oil) was added. The reaction mixture was stirred at 50 °C for 4 h before 246 μL (234 mg, 1.07 mmol) of di-*tert*-butyl dicarbonate was added. After being stirred at 55 °C overnight, the reaction mixture was cooled to room temperature, the reaction was quenched with water, and the organic material was extracted by EtOAc. The EtOAc layers were washed with water and brine and dried over anhydrous Na_2SO_4. The crude product obtained after filtration and removal of volatiles was flash chromatographed (gradient elution with 1–5% MeOH in CH_2Cl_2) to give 190 mg (54%) of the desired alkylated product, homogeneous by TLC (95:5 CH_2Cl_2/MeOH): mp 138–140 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.94 (t, J = 7.3 Hz, 3 H), 1.30 (s, 9 H), 1.44 (m, 2 H), 1.71 (m, 2 H), 2.61 (t, J = 7.4 Hz, 2 H), 5.01 (s, 2 H), 6.68 (br s, 1 H), 7.12–7.18 (m, 2 H), 7.29 (dd, J = 7.5, 1.3 Hz, 1 H), 7.39 (t, J = 7.8 Hz, 1 H), 7.55–7.73 (m, 3 H), 8.19 (dd, J = 8.8, 2.6 Hz, 1 H), 8.24 (dd, J = 7.9, 1.3 Hz, 1 H), 8.38 (d, J = 2.6 Hz, 1 H); FAB-MS m/e 566 [M + Li − (CO_2-*t*-Bu)]$^+$; high-resolution EI-MS m/e 559.1092 [calcd for $C_{25}H_{23}ClFN_5O_5S$ [M − (CO_2-*t*-Bu)]$^+$ 559.1092].

2-(5-Amino-2-chlorophenyl)-4-[[2′-[*N*-(*tert*-butoxycarbonyl)sulfamoyl]-3-fluorobiphenyl-4-yl]methyl]-5-*n*-butyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (71). The starting material (**70**; 190 mg, 0.288 mmol) was dissolved in 3 mL of EtOAc and 3 mL of EtOH, and 15 mg of PtO_2 was added. The

reaction mixture was hydrogenated using a Parr apparatus (~2 atm H_2) for 4 h. After filtration over a pad of Celite and evaporation of solvents, the crude material was flash chromatographed (gradient elution with 0.5–2% MeOH in CH_2Cl_2) to give 128 mg (82%) of the desired alkylated product as a white solid, homogeneous by TLC (95:5 CH_2Cl_2/MeOH): mp 207–209 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, J = 7.4 Hz, 3 H), 1.25 (s, 9 H), 1.40 (m, 2 H), 1.68 (m, 2 H), 2.57 (m, 2 H), 5.00 (s, 2 H), 7.05–7.20 (m, 2 H), 7.20–7.45 (m, 3 H), 7.50–7.70 (m, 3 H), 8.20–8.25 (m, 1 H); FAB-MS m/e 630 $(M + H)^+$; high-resolution EI-MS m/e 529.1330 [calcd for $C_{25}H_{25}ClFN_5O_5S$ $[M - (CO_2\text{-}t\text{-}Bu)]^+$ 529.1351].

4-[[2′-[*N*-(*tert*-Butoxycarbonyl)sulfamoyl]-3-fluorobiphenyl-4-yl]methyl]-5-*n*-butyl-2-[2-chloro-5-(2-furoylamino)phenyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (9). 2-Furoic acid (10.1 mg, 0.090 mmol) and BOP reagent (88 mg, 0.20 mmol) were taken up in 0.5 mL of dry CH_2Cl_2, and 14 μL (19 mg, 0.099 mmol) of triethylamine was added. The reaction mixture was stirred overnight at room temperature in a foil-covered flask. TLC (95:5 CH_2Cl_2/MeOH) showed disappearance of all starting material. Volatiles were evaporated, the residue was taken up in EtOAc and partitioned with 5% $NaHCO_3$, and the aqueous layer was reextracted with EtOAc. The organic layers were combined, washed with 5% $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4. The crude material obtained after filtration and removal of volatiles was flash chromatographed (gradient elution with 0.5–2% MeOH in CH_2Cl_2) to give 20 mg (51%) of the desired compound as a cream-colored solid, homogeneous by TLC (95:5 CH_2Cl_2/MeOH): mp 145–147 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.94 (t, J = 7.3 Hz, 3 H), 1.30 (s, 9 H), 1.44 (m, 2 H), 1.70 (m, 2 H), 2.68 (t, J = 7.4 Hz, 2 H), 5.11 (s, 2 H), 6.64 (dd, J = 3.4, 1.8 Hz, 1 H), 7.15–7.19 (m, 2 H), 7.26–7.37 (m, 3 H), 7.54–7.78 (m, 4 H), 7.82 (dd, J = 7.6, 2.6 Hz, 1 H), 8.04 (d, J = 2.6 Hz, 1 H), 8.16 (dd, J = 7.9, 1.3 Hz, 1 H); FAB-MS m/e 724 $(M + H)^+$. Anal. ($C_{35}H_{35}ClFN_5O_7S\cdot0.1CH_2Cl_2$) C, H, N.

Method E. 2-(2-Bromo-5-nitrophenyl)-2,4-dihydro-5-ethyl-3*H*-1,2,4-triazol-3-one (72). To a stirred mixture of 2.00 g (8.62 mmol) of (2-bromo-5-nitrophenyl)hydrazine[26] (obtained by diazotization of the corresponding amine) in 20 mL of water were added 2 mL of concentrated hydrochloric acid and 880 mg (8.62 mmol) of 2-ketobutyric acid (dissolved in 2 mL water). Ten milliliters of water was added to facilitate stirring, and the mixture was stirred at room temperature for 1 h when TLC (10% MeOH/CH_2Cl_2–0.1% HOAc) indicated disappearance of all starting hydrazine. Ethyl acetate was added, and the layers were separated. The organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. Filtration and removal of volatiles afforded 2.66 g (98%) of 2-ketobutyric acid (2-bromo-5-nitrophenyl)hydrazone as an orange solid (mp 263–265 °C) sufficiently pure to be used directly in the next reaction: ^1H NMR (DMSO-d_6, 400 MHz) δ 1.07 (t, J = 7.6 Hz, 3 H), 2.58 (m, 2 H), 7.62 (m, 1 H), 7.86 (m, 1 H), 8.15 (m, 1H); FAB-MS m/e 316, 318 $(M + H)^+$.

To a stirred solution of 2.66 g (8.42 mmol) of 2-ketobutyric acid (2-bromo-5-nitrophenyl)hydrazone and 1.2 mL (8.42 mmol, 850 mg) of triethylamine in 100 mL of toluene was added 1.81 mL (8.42 mmol, 2.32 g) of diphenyl phosphorazidate. The reaction mixture was heated gradually to 115 °C and stirred for 4 h when TLC (5% MeOH/CH_2Cl_2) indicated complete disappearance of starting material. Solvents were evaporated *in vacuo*, and the residue was taken up in EtOAc, washed twice with water and then with brine, and dried over anhydrous Na_2SO_4. The crude product obtained after filtration and removal of solvents was flash chromatographed (gradient elution using 0.5–2.0% MeOH in CH_2Cl_2) to afford 2.00 g (76%) of a cream-colored solid, homogeneous by TLC (95:5 CH_2Cl_2/MeOH): mp 191–193 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.29 (t, J = 7.6 Hz, 3 H), 2.63 (q, J = 7.6 Hz, 2 H), 7.89 (d, J = 8.9 Hz, 1 H), 8.13 (dd, J = 2.7, 8.9 Hz, 1 H), 8.34 (d, J = 2.7 Hz, 1 H), 11.5 (s, br, 1 H); FAB-MS m/e 312, 314 $(M + H)^+$. Anal. ($C_{10}H_9BrN_4O_3$) C, H, N.

2-(2-Bromo-5-nitrophenyl)-4-[[2′-(*N*-*tert*-butylsulfamoyl)-3-fluorobiphenyl-4-yl]methyl]-2,4-dihydro-5-ethyl-3*H*-1,2,4-triazol-3-one (73). A mixture of 2.00 g (6.39 mmol) of **72** and 184 mg (7.67 mmol) of NaH in 7 mL of DMF was stirred at 50 °C for 3 h. A solution of **59** dissolved in 6 mL of DMF was then added, and the resulting mixture was stirred at 50 °C for another 3 h. The reaction was quenched by addition of water followed by extractions with EtOAc, CH_2Cl_2, and MeOH. Water was removed, and the organic layers were washed with brine and dried over anhydrous Na_2SO_4. The entire crude product mixture thus obtained was flash chromatographed over silica gel (gradient elution using 0.5–2.0% MeOH in CH_2Cl_2) to afford 3.54 g (88%) of the desired product as a yellow solid, almost homogeneous by TLC (98:2 CH_2Cl_2/MeOH): mp 223–225 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.87 (s, 9 H), 1.15 (t, J = 7.4 Hz, 3 H), 2.49 (q, J = 7.4 Hz, 2 H), 4.86 (s, 2 H), 7.08–7.18 (m, 3 H), 7.19–7.26 (m, 1 H), 7.33–7.45 (m, 2 H), 7.77 (d, J = 8.8 Hz, 1 H), 7.92–8.05 (m, 2 H), 8.10 (d, J = 2.7 Hz, 1 H); FAB-MS m/e 631, 633 $(M + H)^+$. Anal. ($C_{27}H_{27}BrFN_5O_5S$) C, H, N.

2-(5-Amino-2-bromophenyl)-4-[[2′-(*N*-*tert*-butylsulfamoyl)-3-fluorobiphenyl-4-yl]methyl]-2,4-dihydro-5-ethyl-3*H*-1,2,4-triazol-3-one (74). At 0 °C, to a stirred solution of 1.00 g (1.58 mmol) of **73** in 5 mL of anhydrous THF was added dropwise a solution of 2.50 g (11.1 mmol) of stannous chloride dihydrate in 15 mL of concentrated HCl. After being stirred at room temperature for 6 h, the reaction mixture was treated with 50% aqueous NaOH and ice and extracted with EtOAc twice. The organic layers were combined, washed with water and brine, and dried over anhydrous Na_2SO_4. The crude product obtained after filtration and removal of volatiles was flash chromatographed (gradient elution using 0.5–3.0% MeOH in CH_2Cl_2) to afford (in addition to 481 mg of recovered starting material) 213 mg of the aniline, homogeneous by TLC (95:5 CH_2Cl_2/MeOH): mp 108–110 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.03 (s, 9 H), 1.28 (t, J = 7.4 Hz, 3 H), 2.57 (q, J = 7.4 Hz, 2 H), 3.61 (s, 1 H), 3.78 (s, 2 H), 5.28 (s, 2 H), 6.59 (dd, J = 2.8, 8.7 Hz, 1 H), 6.78 (d, J = 2.8 Hz, 1 H), 7.20–7.60 (m, 7 H), 8.14 (d, J = 7.6 Hz, 1 H); FAB-MS m/e 601, 603 $(M + H)^+$. Anal. ($C_{27}H_{29}BrFN_5O_3S\cdot0.6CH_3OH$) C, H, N.

2-[2-Bromo-5-(valerylamino)phenyl]-4-[[2′-(*N*-*tert*-butylsulfamoyl)-3-fluorobiphenyl-4-yl]methyl]-2,4-dihydro-5-ethyl-3*H*-1,2,4-triazol-3-one (75). To a mixture of 71 mg (0.12 mmol) of **74** and 14 mg (0.12 mmol) of DMAP in 1 mL of dry pyridine was added 71 mg (0.59 mmol) of valeryl chloride, and the resulting mixture was stirred overnight at room temperature. The reaction was quenched by addition of water, and the organic material was extracted by EtOAc twice. The combined organic layers were washed twice with water and brine and dried over anhydrous Na_2SO_4. The crude product obtained after filtration and evaporation of volatiles was flash chromatographed (gradient elution using 0.5–2.0% MeOH in CH_2Cl_2) to afford 36 mg (44%) of the desired compound, homogeneous by TLC (95:5 CH_2Cl_2/MeOH): mp 249–251 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.90 (t, J = 7.4 Hz, 3 H), 1.02 (s, 9 H), 1.27 (t, J = 7.4 Hz, 3 H), 1.35 (m, 2 H), 1.65 (m, 2 H), 2.32 (q, J = 7.7 Hz, 2 H), 2.57 (q, J = 7.4 Hz, 2 H), 3.68 (s, 1 H), 5.00 (s, 2 H), 7.20–7.35 (m, 3 H), 7.40–7.60 (m, 5 H), 7.70 (d, J = 2.3 Hz, 1 H), 8.15 (dd, J = 7.7, 1.0 Hz, 1 H); FAB-MS m/e 685, 687 $(M + H)^+$; high-resolution EI-MS m/e 685.1711 [calcd for $C_{32}H_{37}{}^{79}BrFN_5O_4S$ (M^+) 685.1734].

4-[[2′-(*N*-*tert*-Butylsulfamoyl)-3-fluorobiphenyl-4-yl]methyl]-2-[5-carbethoxy-2-(trifluoromethyl)phenyl]-2,4-dihydro-5-ethyl-3*H*-1,2,4-triazol-3-one (77). A mixture of 100 mg (0.152 mmol) of **76**, 32 μL (44 mg, 0.304 mmol) of methyl 2-chloro-2,2-difluoroacetate, 29 mg (0.152 mmol) of copper(I) iodide, 27 mg (0.228 mmol) of KBr, and 0.15 mL of dry DMF was placed in a sealed tube and stirred at 110 °C for 41 h. The reaction mixture was cooled to room temperature, diluted with EtOAc, and treated with water. The phases were separated, and the aqueous phase was further extracted with EtOAc twice. The organic layers were combined, washed with water and brine, and dried over anhydrous Na_2SO_4. After filtration and removal of volatiles, the crude product was flash chromatographed (gradient elution using 5:1 hexane/EtOAc) to afford 36 mg (37%) of the desired compound, homogeneous by TLC (95:5 CH_2Cl_2/MeOH): mp 168–170 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.01 (s, 9 H), 1.27 (t, J = 7.4 Hz, 3 H), 1.38 (t, J = 7.1 Hz, 3 H), 2.57 (q, J = 7.4 Hz, 2 H), 4.39 (q, J = 7.1 Hz, 2 H), 4.99 (s, 2 H), 7.23–7.45 (m, 3 H), 7.45–7.60

(m, 3 H), 7.85 (d, J = 8.4 Hz, 1 H), 8.13–8.20 (m, 3 H); FAB-MS m/e 649 $(M + H)^+$.

4-Chloro-3-nitrovalerophenone (78). 4-Chlorovalerophenone (10 g, 50.9 mmol) was added slowly to vigorously stirred 100 mL of nitric acid at 0 °C. Stirring was continued at 0 °C for 30 min after completion of addition. The contents of the flask were poured over 100 g of ice at 0 °C with stirring, and the resulting solution was extracted with EtOAc. The organic layer was washed with water, 5% $NaHCO_3$, and brine and dried over anhydrous Na_2SO_4. The crude material obtained after filtration and removal of volatiles was flash chromatographed (gradient elution using 8:1–2:1 hexane/EtOAc) to give the desired product as a yellow gum: ^1H NMR ($CDCl_3$, 400 MHz) δ 0.93 (t, J = 7.3 Hz, 3 H), 1.38 (m, 2 H), 1.70 (m, 2 H), 2.95 (t, J = 7.3 Hz, 2 H), 7.64 (d, J = 8.4 Hz, 1 H), 8.06 (dd, J = 8.4, 2.1 Hz, 1 H), 8.39 (d, J = 2.1 Hz, 1 H); EI-MS m/e 241 $(M)^+$.

2-*n*-Butyl-2-(4-chloro-2-nitrophenyl)-1,3-dithiane (79). The starting material (**78**; 2.07 g, 8.57 mmol) was dissolved in 20 mL of dry CH_2Cl_2; 1.39 g (12.9 mmol) of 1,3-propanedithiol was added followed by 1.83 g (12.9 mmol) of boron trifluoride etherate. The reaction mixture was stirred at room temperature overnight. TLC (10:1 hexane/EtOAc) indicated disappearance of all starting material. The reaction was quenched with 5% aqueous NaOH and the mixture extracted with EtOAc. The organic layers were combined and washed several times with 5% NaOH, water, and then brine. After drying over anhydrous Na_2SO_4, filtration, and evaporation of solvents, 3.13 g of the crude dithiane-protected ketone was obtained as a sticky yellow oil which was used in the next experiment without further purification: ^1H NMR ($CDCl_3$, 400 MHz) δ 0.80 (t, J = 7.1 Hz, 3 H), 1.20 (m, 4 H), 1.93 (m, 4 H), 2.62 (m, 4 H), 7.52 (d, J = 8.6 Hz, 1 H), 8.05 (dd, J = 8.6, 2.3 Hz, 1 H), 8.42 (d, J = 2.3 Hz, 1 H); FAB-MS m/e 332 $(M + H)^+$.

2-(2-Amino-4-chlorophenyl)-2-*n*-butyl-1,3-dithiane (80). The starting material (**79**; 1.73 g, 5.2 mmol) was mixed with 4 mL of THF. The solution was cooled to 0 °C before 8.2 g (36.5 mmol) of tin(II) chloride dihydrate (dissolved in 10 mL of concentrated HCl) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred vigorously overnight. TLC (10:1 hexane/EtOAc) indicated disappearance of all starting material. The contents of the flask were added to a stirred mixture of 12 mL of 50% NaOH (aqueous), ice, and EtOAc. The phases were separated, and the aqueous layer was further extracted with EtOAc twice. The combined organic layers were washed several times with water, 50% NaOH, and brine and dried over anhydrous Na_2SO_4. The crude product obtained after filtration and concentration was flash chromatographed (12:1 hexane/EtOAc) to give 1.26 g (80%) of a sticky yellow gum, homogeneous by TLC (10:1 hexane/EtOAc): ^1H NMR ($CDCl_3$, 400 MHz) δ 0.78 (t, J = 7.1 Hz, 3 H), 1.16 (m, 4 H), 1.89 (m, 4 H), 2.63 (m, 4 H), 4.05 (s, 2 H), 7.20 (m, 2 H), 7.33 (d, J = 2.4 Hz, 1 H); FAB-MS m/e 301 $(M + H)^+$.

2-*n*-Butyl-2-(2-hydrazino-4-chlorophenyl)-1,3-dithiane (81). The starting material (**80**; 650 mg, 2.16 mmol) was dissolved in 4 mL of concentrated HCl and 1 mL THF. At −5–0 °C, with vigorous stirring, 149 mg (2.16 mmol) of sodium nitrite (dissolved in 1 mL of water) was added dropwise. After being stirred at 0 °C for 1 h, the reaction mixture was cold-filtered, and the filtrate was added at 0 °C to a vigorously stirred solution of 975 mg (4.32 mmol) of tin(II) chloride dihydrate dissolved in 1.5 mL of concentrated HCl. The flask with the orange/yellow precipitate was kept overnight at 5 °C. The mixture was filtered, and the pasty solid was taken up in CH_2Cl_2 and treated with 1 N Na_2CO_3 (aqueous) twice. The organic material was washed with brine, dried over anhydrous Na_2SO_4, and filtered, and the solvents were evaporated. The material thus obtained (500 mg, 73% yield) was an orange gum, homogeneous by TLC (19:1 MeOH/CH_2Cl_2): ^1H NMR ($CDCl_3$, 400 MHz) δ 0.79 (t, J = 7.0 Hz, 3 H), 1.20 (m, 4 H), 1.92 (m, 4 H), 2.67 (m, 4 H), 7.25 (m, 2 H), 7.66 (d, J = 2.2 Hz, 1 H).

5-*n*-Butyl-2-[2-chloro-5-(2-*n*-butyl-1,3-dithian-2-yl)-phenyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (83). To a solution of 500 mg (1.58 mmol) of **81** in 5 mL of toluene was added 349 mg (1.74 mmol) of the imidate **82**, and the solution was heated at 50 °C for 2 h. Subsequently, 242 μL (176 mg, 1.74 mmol) of triethylamine was added, and the reaction mixture was stirred at 90 °C for 16 h. After the reaction mixture was cooled to room temperature, volatiles were removed *in vacuo*. Flash chromatography of the residue (gradient elution with 0.5–2% MeOH in CH_2Cl_2) afforded 186 mg (28%) of the desired product as a sticky yellow gum, homogeneous by TLC (95:5 CH_2Cl_2/MeOH): ^1H NMR ($CDCl_3$, 400 MHz) δ 0.81 (t, J = 7.1 Hz, 3 H), 0.91 (t, J = 7.4 Hz, 3 H), 1.23 (m, 4 H), 1.40 (m, 2 H), 1.77 (m, 2 H), 1.95 (m, 4 H), 2.57 (t, J = 7.4 Hz, 2 H), 2.65 (m, 4 H), 7.50 (d, J = 8.4 Hz, 1 H), 7.91 (dd, J = 8.4, 2.3 Hz, 1 H), 8.03 (d, J = 2.3 Hz, 1 H), 11.4 (br s, 1 H); FAB-MS m/e 425 $(M + H)^+$; high-resolution EI-MS m/e 425.1321 [calcd for $C_{20}H_{28}ClN_3OS_2$ (M^+) 425.1362].

5-*n*-Butyl-4-[[2′-(*N*-*tert*-butylsulfamoyl)-3-fluorobiphenyl-4-yl]methyl]-2-[2-chloro-5-(2-*n*-butyl-1,3-dithian-2-yl)phenyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (84). A mixture of 186 mg (0.437 mmol) of **83**, 13 mg (0.525 mmol) of sodium hydride (60% in oil), and 1 mL of dry DMF was stirred at 50 °C for 2 h. Subsequently, a solution of 210 mg (0.525 mmol) of **59** dissolved in 0.5 mL of DMF was added, and the resulting mixture was stirred at 50 °C for 3 h when TLC (4:1 hexane/EtOAc) indicated disappearance of all starting material. The reaction was quenched at room temperature by addition of water and the mixture extracted twice with EtOAc. The combined organic layers were washed with water and brine and dried over anhydrous Na_2SO_4. After filtration and concentration of the filtrate *in vacuo*, the crude product was flash chromatographed (gradient elution with 10:1–2:1 hexane/EtOAc) to give 257 mg (79%) of the desired alkylated product as a cream-colored foam, homogeneous by TLC (4:1 hexane/EtOAc): mp 95–97 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.80 (t, J = 7.2 Hz, 3 H), 0.92 (t, J = 7.4 Hz, 3 H), 1.02 (s, 9 H), 1.23 (m, 4 H), 1.42 (m, 2 H), 1.57 (m, 2 H), 1.91 (m, 4 H), 2.56 (t, J = 7.8 Hz, 2 H), 2.66 (m, 4 H), 3.60 (s, 1 H), 5.01 (s, 2 H), 7.21–7.35 (m, 3 H), 7.40–7.60 (m, 4 H), 7.90 (dd, J = 8.4, 2.4 Hz, 1 H), 8.06 (d, J = 2.4 Hz, 1 H), 8.15 (dd, J = 7.7, 1.4 Hz, 1 H); FAB-MS m/e 745 $(M + H)^+$; high-resolution EI-MS m/e 744.2448 [calcd for $C_{37}H_{46}ClFN_4O_3S_3$ (M^+) 744.2404].

5-*n*-Butyl-4-[[2′-(*N*-*tert*-butylsulfamoyl)-3-fluorobiphenyl-4-yl]methyl]-2-(2-chloro-5-valerylphenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (85). The starting material (**84**; 257 mg, 0.345 mmol) dissolved in 1.6 mL of anhydrous acetonitrile was added to a stirred solution of 269 mg (2.07 mmol) of *N*-bromosuccinimide dissolved in 2.7 mL of acetonitrile and 0.73 mL of water at 0 °C. The reaction mixture turned yellow upon addition of **84**. After being stirred at room temperature for 3 h, the reaction mixture was treated with EtOAc. The mixture was shaken successively with saturated $NaHSO_3$ solution (aqueous), saturated $NaHCO_3$, water, and brine. The organic layer was dried over anhydrous Na_2SO_4 and filtered, and the solvents were evaporated. TLC (19:1 CH_2Cl_2/MeOH) indicated some residual starting material (80:20 mixture in favor of the desired compound by ^1H NMR analysis). Flash chromatography (gradient elution using 0.5% MeOH in CH_2Cl_2) would not separate product from residual starting material. Repeated treatment with a large excess of NBS failed to push the reaction to completion. Finally, flash chromatography using a 200:1 loading ratio and gradient elution with 0.1–0.2% MeOH in CH_2Cl_2 provided 82 mg (36%) of the desired product as a white solid, almost homogeneous by TLC (5% MeOH in CH_2Cl_2): mp 78–80 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.85 (t, J = 7.4 Hz, 6 H), 0.95 (s, 9 H), 1.41 (m, 2 H), 1.62 (m, 2 H), 2.52 (t, J = 7.2 Hz, 2 H), 2.88 (t, J = 7.3 Hz, 2 H), 3.31 (s, 1 H), 4.94 (s, 2 H), 7.15–7.35 (m, 3 H), 7.35–7.60 (m, 4 H), 7.90 (m, 1 H), 7.97 (d, J = 2.1 Hz, 1 H), 8.05 (dd, J = 7.9, 1.2 Hz, 1 H); FAB-MS m/e 599 [$(M + H - (t\text{-}Bu)]^+$; high-resolution EI-MS m/e 654.2416 [calcd for $C_{34}H_{40}ClFN_4O_4S$ (M^+) 654.2443].

Rabbit Aorta AT_1 Receptor Binding Assay. Rabbit aorta membrane pellets, prepared as previously described,[35] were suspended in binding buffer. No bovine serum albumin (BSA) was present in this version of the assay.[33,35] 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 were 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 [Sar^1,Ile^8]AII (1 μM final concentration 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, onto Whatman GF-B filters, to collect [^{125}I]-[Sar^1,Ile^8]AII bound to receptor membrane. The filters were washed with wash buffer. The radioactivity trapped on the filters was counted using a γ-counter. 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%. In all 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.[5a,35c] 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. In all cases, the reported IC_{50} values represent an average of two or more determinations from separate assays.

Rat and Human Adrenal AT_1 and AT_2 Receptor Binding Assays. The preparation of membranes from various tissues and specific [^{125}I][Sar^1,Ile^8]AII binding assays followed a previously described procedure[35a] with the exception that BSA was omitted in the binding assay buffers for the rat adrenal assay. BSA (2 mg/mL) was added to the binding buffer for the human adrenal assay. All binding assays were performed in duplicate tubes. Specific [^{125}I][Sar^1,Ile^8]AII binding was defined as the difference between total and nonspecific binding. IC_{50} values were determined by regression analysis of displacement curves. Since both AT_1 and AT_2 receptor subtypes were present in these tissues, the IC_{50} values on AT_1 and AT_2 were determined in the presence of 1 μM PD121981 (WL-19) or losartan to prevent binding of the radioligand to AT_2 and AT_1, respectively. 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 the rat adrenal assays, the majority of the reported IC_{50} values was derived from single runs of the assays. For the human adrenal assays, in all cases, the reported IC_{50} values represent an average of two or more determinations from separate assays.

Evaluation of AII Antagonists in Conscious, Normotensive Rats.[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, on the basis of averaged results from two or more rats. Thirty percent and greater inhibition of the AII pressor response was 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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References

(1) (a) For the preceding paper in this series, see: Chang, L. L.; Ashton, W. T.; Flanagan, K. L.; Rivero, R. A.; Chen, T.-B.; O'Malley, S. S.; Zingaro, G. J.; Kivlighn, S. D.; Siegl, P. K. S.; Lotti, V. J.; Chang, R. S. L.; Greenlee, W. J. Potent Triazolinone-Based Angiotensin II Receptor Antagonists With Equivalent Affinity for Both the AT_1 and AT_2 Subtypes. *BioMed. Chem. Lett.* **1994**, *4*, 2787–2792. (b) Some of this work has been described briefly, see: Ashton, W. T.; Chang, L. L.; Flanagan, K. L.; Mantlo, N. B.; Ondeyka, D. L.; Kim, D.; de Laszlo, S. E.; Glinka, T. W.; Rivero, R. A.; Kevin, N. J.; Chang, R. S. L.; Siegl, P. K. S.; Kivlighn, S. D.; Greenlee, W. J. AT_1/AT_2-Balanced Angiotensin II Antagonists. In *Proc. XIII Int. Symp. Med. Chem.*, Paris, 1994; Muller, J.-C.; Ed.; Elsevier: Paris, France, 1995; pp 255s–266s. *Ibid. Eur. J. Med. Chem.* **1995**, *30* (Suppl.), 255s–266s.

(2) (a) Vallotton, M. B. The Renin-Angiotensin System. *Trends Pharmacol. Sci.* **1987**, *8*, 69–74. (b) Johnston, C. I. Biochemistry and Pharmacology of the Renin–Angiotensin System. *Drugs* **1990**, *39* (Suppl. 1), 21–31.

(3) (a) Ondetti, M. A.; Cushman, D. W. Inhibition of the Renin-Angiotensin System. A New Approach to the Therapy of Hypertension. *J. Med. Chem.* **1981**, *24*, 355–361. (b) Waeber, B.; Nussberger, J.; Brunner, H. R. Angiotensin-Converting-Enzyme Inhibitors in Hypertension. In *Hypertension: Pathophysiology, Diagnosis and Management*; Laragh, J. H., Brenner, B. M., Ed.; Raven Press: New York, 1990; pp 2209–2232.

(4) (a) Timmermans, P. B. M. W. M.; Carini, D. J.; Chiu, A. T.; Duncia, J. V.; Price, W. A., Jr.; Wells, G. J.; Wong, P. C.; Wexler, R. R.; Johnson, A. L. Nonpeptide Angiotensin II Receptor Antagonists. *Am. J. Hypertens.* **1990**, *3*, 599–604. (b) Timmermans, P. B. M. W. M.; Wong, P. C.; Chiu, A. T.; Herblin, W. F. Nonpeptide Angiotensin II Receptor Antagonists. *Trends Pharmacol. Sci.* **1991**, *12*, 55–62. (c) Dzau, V. J.; Sasamura, H.; Hein, L. Heterogeneity of Angiotensin Synthetic Pathways and Receptor Subtypes: Physiological and Pharmacological Implications. *J. Hypertens.* **1993**, *11* (Suppl. 3), S13–S18. (d) Levens, N. R.; de Gasparo, M.; Wood, J. M.; Bottari, S. P. Could the Pharmacological Differences Observed Between Angiotensin II Antagonists and Inhibitors of Angiotensin Converting Enzyme be Clinically Beneficial? *Pharmacol. Toxicol.* **1992**, *71*, 241–249.

(5) (a) Chang, R. S. L.; Lotti, V. J. Two Distinct Angiotensin II Receptor Binding Sites in Rat Adrenal Revealed by New Selective Nonpeptide Ligands. *Mol. Pharmacol.* **1990**, *37*, 347–351. (b) Chiu, A. T.; Herblin, W. F.; McCall, D. E.; Ardecky, R. J.; Carini, D. J.; Duncia, J. V.; Pease, L. J.; Wong, P. D.; Wexler, R. R.; Johnson, A. L.; Timmermans, P. B. M. W. M. Identification of Angiotensin II Receptor Subtypes. *Biochem. Biophys. Res. Commun.* **1989**, *165*, 196–203.

(6) (a) Sasaki, K.; Yamano, Y.; Bardhan, S.; Iwai, N.; Murray, J. J.; Hasegawa, M.; Matsuda, Y.; Inagami, T. Cloning and Expression of a Complementary DNA Encoding a Bovine Adrenal Angiotensin II Type-1 Receptor. *Nature* **1991**, *351*, 230–233. (b) Murphy, T. J.; Alexander, R. W.; Griendling, K. K.; Runge, M. S.; Bernstein, K. E. Isolation of a cDNA Encoding the Vascular Type-1 Angiotensin II Receptor. *Nature* **1991**, *351*, 233–236.

(7) (a) Timmermans, P. B. M. W. M.; Wong, P. C.; Chiu, A. T.; Herblin, W. F.; Benfield, P.; Carini, D. J.; Lee, R. J.; Wexler, R. R.; Saye, J. A. M.; Smith, R. D. Angiotensin II Receptors and Angiotensin II Receptor Antagonists. *Pharmacol. Rev.* **1993**, *45*,

205–251. (b) Bottari, S. P.; de Gasparo, M.; Steckelings, U. M.; Levens, N. R. Angiotensin II Receptor Subtypes: Characterization, Signalling Mechanisms, and Possible Physiological Implications. *Front. Neuroendocrinol.* **1993**, *14*, 123–171.

(8) (a) Lo, M.; Liu, K.-L.; Lanteime, P.; Sassard, J. Subtype 2 of Angiotensin II Receptors Controls Pressure-Natriuresis in Rats. *J. Clin. Invest.* **1995**, *95*, 1394–1397. (b) Keiser, J. A.; Bjork, F. A.; Hodges, J. C.; Taylor, D. G., Jr. Renal Hemodynamic and Excretory Responses to PD 123319 and Losartan, Nonpeptide AT_1 and AT_2 Subtype-Specific Angiotensin II Ligands. *J. Pharmacol. Exp. Ther.* **1992**, *262*, 1154–1160. (c) Cogan, M. G.; Liu, F. Y.; Wong, P. C.; Timmermans, P. B. M. W. M. Comparison of Inhibitory Potency by Nonpeptide Angiotensin II Receptor Antagonists PD 123177 and DuP 753 in Proximal Nephron and Renal Transport. *J. Pharmacol. Exp. Ther.* **1991**, *259*, 687–691.

(9) (a) Janiak, P.; Pillon, A.; Prost, J.-F.; Vilaine, J.-P. Role of Angiotensin Subtype 2 Receptor in Neointima Formation After Vascular Injury. *Hypertension* **1992**, *20*, 737–745. (b) Pratt, R. E.; Wang, D.; Hein, L.; Dzau, V. J. The AT_2 Isoform of the Angiotensin Receptor Mediates Myointimal Hyperplasia Following Vascular Injury. *Hypertension* **1992**, *20*, 432.

(10) Viswanathan, M.; Saavedra, J. Expression of Angiotensin II AT_2 Receptors in the Rat Skin During Experimental Wound Healing. *Peptides* **1992**, *13*, 783–786.

(11) Brilla, C. G.; Zhou, G.; Matsubara, L.; Weber, K. T. Collagen Metabolism in Cultured Adult Rat Cardiac Fibroblasts – Response to Angiotensin-II and Aldosterone. *J. Mol. Cell. Cardiol.* **1994**, *26*, 809–820.

(12) (a) de Gasparo, M.; Whitebread, S.; Levens, N.; Ramjoué, H.-P.; Criscione, L.; Rogg, J.; Baum, H.-P.; Brechler, V.; Buehlmayer, P.; Wood, J. M.; Bottari, S. P. Pharmacology of Angiotensin-II-Receptor Subtypes. In *Cellular and Molecular Biology of the Adrenal Cortex*; Saez, J. M., Brownie, A. C., Capponi, A., Chambaz, E. M., Mantero, F., Eds.; J. Libbey Eurotext: Paris, France, 1992; pp 3–17. *Ibid. Colloq. INSERM* **1992**, *222*. (b) Wong, P. C.; Hajj-ali, A. F. Functional Correlates of Angiotensin Receptor Stimulation. In *Medicinal Chemistry of the Renin Angiotensin System*; Timmermans, P. B. M. W. M., Wexler, R. R., Eds.; Elsevier: New York, 1995; in press.

(13) (a) Duncia, J. V.; Carini, D. J.; Chiu, A. T.; Johnson, A. L.; Price, W. A.; Wong, P. C.; Wexler, R. R.; Timmermans, P. B. M. W. M. The Discovery of DuP 753, a Potent, Orally Active Nonpeptide Angiotensin II Receptor Antagonist. *Med. Res. Rev.* **1992**, *12*, 149–191. (b) Carini, D. J.; Duncia, J. V.; Aldrich, P. E.; Chiu, A. T.; Johnson, A. L.; Pierce, M. E.; Price, W. A.; Santella, J. B., III; Wells, G. J.; Wexler, R. R.; Wong, P. C.; Yoo, S.-E.; Timmermans, P. B. M. W. M. Nonpeptide Angiotensin II Receptor Antagonists: The Discovery of a Series of *N*-(Biphenylylmethyl)imidazoles as Potent, Orally Active Antihypertensives. *J. Med. Chem.* **1991**, *34*, 2525–2547. (c) Wong, P. C.; Barnes, T. B.; Chiu, A. T.; Christ, D. D.; Duncia, J. V.; Herblin, W. F.; Timmermans, P. B. M. W. M. Losartan (DuP 753), An Orally Active Nonpeptide Angiotensin II Receptor Antagonist. *Cardiovasc. Drug Rev.* **1991**, *9*, 317–339. (d) For recent reviews on AT_1-selective AII antagonists, see: Ashton, W. T. Nonpeptide Angiotensin II Receptor Antagonists. *Exp. Opin. Invest. Drugs* **1994**, *3*, 1105–1142. (e) Murray, W. V. Angiotensin II Receptor Antagonists: The Next Step in the Evolution of Antihypertensive Therapy. *Chemtracts: Org. Chem.* **1993**, *6*, 263–284. (f) Bühlmeyer, P. Angiotensin II Receptor Antagonists: Patent Activity since the Discovery of DuP 753. *Curr. Opin. Ther. Pat.* **1992**, 1693–1718. (g) Hodges, J. C.; Hamby, J. M.; Blankley, C. J. Angiotensin II Receptor Binding Inhibitors. *Drugs Future* **1992**, *17*, 575–593. (h) Greenlee, W. J.; Siegl, P. K. S. Angiotensin/Renin Modulators. *Annu. Rep. Med. Chem.* **1992**, *27*, 59–68.

(14) (a) Wu, M. T.; Ikeler, T. J.; Ashton, W. T.; Chang, R. S. L.; Lotti, V. J.; Greenlee, W. J. Synthesis and Structure-Activity Relationships of a Novel Series of Non-Peptide AT_2-Selective Angiotensin II Receptor Antagonists. *BioMed. Chem. Lett.* **1993**, *3*, 2023–2028. (b) Klutchko, S.; Hamby, J. M.; Hodges, J. C. Tetrahydroisoquinoline Derivatives With AT_2-Specific Angiotensin II Receptor Binding Inhibitory Activity. *BioMed. Chem. Lett.* **1994**, *4*, 57–62. (c) Glinka, T. W.; De Laszlo, S. E.; Tran, J.; Chang, R. S.; Chen, T.-B.; Lotti, V. J.; Greenlee, W. J. L-161,638: A Potent AT_2 Selective Quinazolinone Angiotensin II Binding Inhibitor. *BioMed. Chem. Lett.* **1994**, *4*, 1479–1484.

(15) (a) Christen, Y.; Waeber, B.; Nussberger, J.; Porchet, M.; Borland, R. M.; Lee, R. J.; Maggon, K.; Shum, L.; Timmermans, P. B. M. W. M.; Brunner, H. R. Oral Administration of DuP 753, a Specific Angiotensin II Receptor Antagonist, to Normal Male Volunteers: Inhibition of Pressor Response to Exogenous Angiotensin I and II. *Circulation* **1991**, *83*, 1333–1342. (b) Goldberg, M. R.; Tanaka, W.; Barchowsky, A.; Bradstreet, T. E.; McCrea, J.; Lo, M.-W.; McWilliams, E. J.; Bjornsson, T. D. Effects of Losartan on Blood Pressure, Plasma Renin Activity, and Angiotensin II in Volunteers. *Hypertension* **1993**, *21*, 704–713.

(16) (a) Abdelrahman, A. M.; Burrell, L. M.; Johnston, C. I. Blockade of the Renin-Angiotensin System at Different Sites: Effect on Renin, Angiotensin and Aldosterone. *J. Hypertens.* **1993**, *11* (Suppl. 3), S23–S26. (b) Brunner, H. R.; Nussberger, J.; Waeber, B. Angiotensin II Blockade Compared With Other Pharmacological Methods of Inhibiting the Renin-Angiotensin System. *J. Hypertens.* **1993**, *11* (Suppl. 3), S53–S58. (c) Rush, J. E.; Rajfer, S. I. Theoretical Basis for the Use of Angiotensin II Antagonists in the Treatment of Heart Failure. *J. Hypertens.* **1993**, *11* (Suppl. 3), S69–S71.

(17) Streeten, D. H. P.; Anderson, G. H., Jr. Angiotensin-Receptor Blocking Drugs. In *Clinical Pharmacology of Antihypertensive Drugs (Handbook of Hypertension, Vol. 5)*; Doyle, A. I., Ed.; Elsevier: Amsterdam, The Netherlands, 1984; pp 264–271.

(18) de Laszlo, S. E.; Quagliato, C. S.; Greenlee, W. J.; Patchett, A. A.; Chang, R. S. L.; Lotti, V. J.; Chen, T.-B.; Scheck, S. A.; Faust, K. A.; Kivlighn, S. S.; Schorn, T. S.; Zingaro, G. J.; Siegl, P. K. S. A Potent, Orally Active, Balanced Affinity Angiotensin II AT_1 Antagonist and AT_2 Binding Inhibitor. *J. Med. Chem.* **1993**, *36*, 3207–3210.

(19) (a) Mantlo, N. B.; Kim, D.; Ondeyka, D.; Chang, R. S. L.; Kivlighn, S. D.; Siegl, P. K. S.; Greenlee, W. J. Imidazo[4,5-*b*]-Pyridine-Based AT_1/AT_2 Angiotensin II Receptor Antagonists. *BioMed. Chem. Lett.* **1994**, *4*, 17–22. (b) Glinka, T. W.; de Laszlo, S. E.; Siegl, P. K. S.; Chang, R. S.; Kivlighn, S. D.; Schorn, T. S.; Faust, K. A.; Chen, T.-B.; Zingaro, G. J.; Lotti, V. J.; Greenlee, W. J. A New Class of Balanced AT_1/AT_2 Angiotensin II Antagonists: Quinazolinone AII Antagonists With Acylsulfonamide and Sulfonylcarbamate Acidic Functionalities. *BioMed. Chem. Lett.* **1994**, *4*, 81–86. (c) Chang, L. L.; Ashton, W. T.; Flanagan, K. L.; Chen, T.-B.; O'Malley, S. S.; Zingaro, G. J.; Siegl, P. K. S.; Kivlighn, S. D.; Lotti, V. J.; Chang, R. S. L.; Greenlee, W. J. Triazolinone Biphenylsulfonamides as Angiotensin II Receptor Antagonists with High Affinity for Both the AT_1 and AT_2 Subtypes. *J. Med. Chem.* **1994**, *37*, 4464–4478. (d) Ondeyka, D. L.; Mantlo, N. B.; Kim, D.; Chang, R. S. L.; Kivlighn, S. D.; Siegl, P. K. S.; Greenlee, W. J. Discovery of L-163,017: A Potent Angiotensin II Antagonist With Equal Affinity For Human AT_1 and AT_2 Receptor Subtypes. 24th National Med. Chem. Symp., Salt Lake City, UT, 1994; Poster Abstr. 8.

(20) (a) Quan, M. L.; Olson, R. E.; Carini, D. J.; Ellis, C. D.; Hillyer, G. L.; Lalka, G. K.; Liu, J.; VanAtten, M. K.; Chiu, A. T.; Wong, P. C.; Wexler, R. R.; Timmermans, P. B. M. W. M. Balanced Angiotensin II Receptor Antagonists. I. The Effects of Biphenyl "Ortho"-Substitution on AT_1/AT_2 Affinities. *BioMed. Chem. Lett.* **1994**, *4*, 2011–2016. (b) Santella, J. B., III; Duncia, J. V.; Ensinger, C. L.; VanAtten, M. K.; Carini, D. J.; Wexler, R. R.; Chiu, A. T.; Wong, P. C.; Timmermans, B. M. W. M. Balanced Angiotensin II Receptor Antagonists. III. The Effects of Substitution at the Imidazole 5-Position. *BioMed. Chem. Lett.* **1994**, *4*, 2235–2240. (c) Glinka, T. W.; De Laszlo, S. E.; Siegl, P. K. S.; Chang, R. S.; Kivlighn, S. D.; Schorn, T. S.; Faust, K. A.; Chen, T.-B.; Zingaro, G. J.; Lotti, V. J.; Greenlee, W. J. Development of Angiotensin II Antagonists with Equipotent Affinity for Human AT_1 and AT_2 Receptor Subtypes. *BioMed. Chem. Lett.* **1994**, *4*, 2337–2342.

(21) Kevin, N. J.; Rivero, R. A.; Greenlee, W. J.; Chang, R. S. L.; Chen, T. B. Substituted Phenylthiophene Benzoylsulfonamides With Potent Binding Affinity to Angiotensin II AT_1 and AT_2 Receptors. *BioMed. Chem. Lett.* **1994**, *4*, 189–194.

(22) Chang, L. L.; Ashton, W. T.; Flanagan, K. L.; Naylor, E. M.; Chakravarty, P. K.; Patchett, A. A.; Greenlee, W. J.; Bendesky, R. J.; Chen, T.-B.; Faust, K. A.; Kling, P. J.; Schaffer, L. W.; Schorn, T. W.; Zingaro, G. J.; Chang, R. S. L.; Lotti, V. J.; Kivlighn, S. D.; Siegl, P. K. S. Triazolinones as Nonpeptide Angiotensin II Antagonists. 2. Discovery of a Potent and Orally Active Triazolinone Acylsulfonamide. *BioMed. Chem. Lett.* **1994**, *4*, 115–120.

(23) Ashton, W. T.; Chang, L. L.; Flanagan, K. L.; Hutchins, S. M.; Naylor, E. M.; Chakravarty, P. K.; Patchett, A. A.; Greenlee, W. J.; Chen, T.-B.; Faust, K. A.; Chang, R. S. L.; Lotti, V. J.; Zingaro, G. J.; Schorn, T. W.; Siegl, P. K. S.; Kivlighn, S. D. Triazolinone Biphenylsulfonamide Derivatives as Orally Active Angiotensin II Antagonists with Potent AT_1 Receptor Affinity and Enhanced AT_2 Affinity. *J. Med. Chem.* **1994**, *37*, 2808–2824.

(24) (a) Lombardino, J. G. Preparation of Substituted 1,2-Benzoisothiazolin-3-one 1,1-Dioxides (o-Benzoic Sulfimides). *J. Org. Chem.* **1971**, *36*, 1843–1845. (b) Sharp, M. J.; Cheng, W.; Snieckus, V. Synthetic Connections to the Aromatic Directed Metalation Reaction. Functionalized Aryl Boronic Acids by Ipso Borodesilylation. General Syntheses of Unsymmetrical Biphenyls and *m*-Terphenyls. *Tetrahedron Lett.* **1987**, *28*, 5093–5096.

(25) Miyamura, N.; Yanagi, T.; Suzuki, A. The Palladium-Catalyzed Cross-Coupling Reaction of Phenylboronic Acid with Haloarenes in the Presence of Bases. *Synth. Commun.* **1981**, *11*, 513–519.

(26) Substituted phenylhydrazines that were not commercially available were prepared from the corresponding anilines according to Stroh, H. H.; Westphal, G. Condensation of Carbonyl Compounds With Hydrazines. VI. The Basicity Constants of Nucleus-Substituted Phenylhydrazines. *Chem. Ber.* **1963**, *96*, 184–187.

(27) Su, D.-B.; Duan, J.-X.; Chen, Q.-Y. Methyl Chlorodifluoroacetate: A Convenient Trifluoromethylating Agent. *Tetrahedron Lett.* **1991**, *31*, 7689–7690.

(28) Castro, B.; Dormoy, J. R.; Evin, G.; Selve, C. Peptide Couplings IV (1)-Benzotriazol-1-yloxy-tris(dimethylamino)phosphonium Hexafluorophosphate (BOP Reagent). *Tetrahedron Lett.* **1975**, 1219–1222.

(29) (a) Maravetz, L. U. S. Patent 4,705,557, 1987. (b) Theodoridis, G. International Patent Application WO87/03782, 1987. (c) Lyga, J. W. A Convenient Synthesis of 1-Aryl-Δ^2-1,2,4-Triazolin-5-ones From Arylhydrazines. *Synth. Commun.* **1986**, *16*, 163–167.

(30) Nahm, S.; Weinreb, S. M. N-Methoxy-N-Methylamides As Effective Acylating Agents. *Tetrahedron Lett.* **1981**, *22*, 3815–3818.

(31) Le Fèvre, C. G.; Le Fèvre, R. J. W. Comparison of the Directive Powers of Elements Having Consecutive Atomic Numbers. Part III. Nitration of Halogeno-2-phenylbenzopyrylium Salts. *J. Chem. Soc.* **1932**, 1988–1992.

(32) Marshall, J. A.; Belletire, J. L. Heterolytic Fragmentation of 1,3-Dithianyl Tosylates. *Tetrahedron Lett.* **1971**, 871–874.

(33) Chang, L. L.; Ashton, W. T.; Flanagan, K. L.; Strelitz, R. A.; MacCoss, M.; Greenlee, W. J.; Chang, R. S. L.; Lotti, V. J.; Faust, K. A.; Chen, T.-B.; Bunting, P.; Zingaro, G. J.; Kivlighn, S. D.; Siegl, P. K. S. Triazolinones as Nonpeptide Angiotensin II Antagonists. 1. Synthesis and Evaluation of Potent 2,4,5-Trisubstituted Triazolinones. *J. Med. Chem.* **1993**, *36*, 2558–2568.

(34) Corey, E. J.; Erickson, B. W. Oxidative Hydrolysis of 1,3-Dithiane Derivatives to Carbonyl Compounds Using N-Halosuccinimide Reagents. *J. Org. Chem.* **1971**, *36*, 3553–3560.

(35) (a) Chang, R. S. L.; Siegl, P. K. S.; Clineschmidt, B. V.; Mantlo, N. B.; Chakravarty, P. K.; Greenlee, W. J.; Patchett, A. A.; Lotti, V. J. *In Vitro* Pharmacology of L-158,809, a Highly Potent and Selective Angiotensin II Receptor Antagonist. *J. Pharmacol. Exp. Ther.* **1992**, *262*, 133–138. (b) Ashton, W. T.; Cantone, C. L.; Chang, L. L.; Hutchins, S. M.; Strelitz, R. A.; MacCoss, M.; Chang, R. S. L.; Lotti, V. J.; Faust, K. A.; Chen, T.-B.; Bunting, P.; Schorn, T. W.; Kivlighn, S. D.; Siegl, P. K. S. Nonpeptide Angiotensin II Antagonists Derived from 4*H*-1,2,4-Triazoles and 3*H*-Imidazo[1,2-*b*][1,2,4]triazoles. *J. Med. Chem.* **1993**, *36*, 591–609. (c) Chang, R. S. L.; Lotti, V. J.; Chen, T. B.; Faust, K. A. Two Angiotensin II Binding Sites In Rat Brain Revealed Using [^{125}I]Sar^1,Ile^8-Angiotensin II and Selective Nonpeptide Antagonists. *Biochem. Biophys. Res. Commun.* **1990**, *171*, 813–817.

(36) Tsuzuki, S.; Ichiki, T.; Nakakabo, H.; Kitami, Y.; Gui, D.-F.; Shirai, H.; Inagami, T. Molecular Cloning and Expression of the Gene Encoding Human Angiotensin II Type 2 Receptor. *Biochem. Biophys. Res. Commun.* **1994**, *200*, 1449–1454.

(37) Siegl, P. K. S.; Chang, R. S. L.; Mantlo, N. B.; Chakravarty, P. K.; Ondeyka, D. L.; Greenlee, W. J.; Patchett, A. A.; Sweet, C. S.; Lotti, V. J. *In Vivo* Pharmacology of L-158,809, a New Highly Potent and Selective Nonpeptide Angiotensin II Receptor Antagonist. *J. Pharmacol. Exp. Ther.* **1992**, *262*, 139–144.

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