Synthesis and Structure-Activity Relationships of Nonpeptide, Potent Triazolone-Based Angiotensin II Receptor Antagonists

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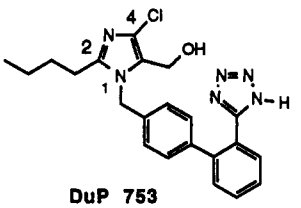
2,5-Dibutyl-2,4-dihydro-4-[[2-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4'-yl]methyl]-3*H*-1,2,4-triazol-3-one, SC-51316, was synthesized as a potent and orally active angiotensin II (AII) receptor antagonist with a long duration of action. To explore the lipophilic pocket in the AII receptor interacting with the substituent at the 2-position of triazolone-based antagonists, a series of compounds were prepared and evaluated for receptor binding affinity and antagonism of AII-contracted rabbit aortic rings. It has been found that the pocket is very spacious and can accommodate different sizes of lipophilic groups and various functionalities. Acidic groups generally result in a slight decrease in binding affinity. Branched chains are unfavorable. The freedom of rotation around C2-C3 in the flexible side chain is crucial for good binding. The 2-phenylethyl-substituted triazolone analogue exhibits the highest *in vitro* potency among all compounds that have been synthesized.

The renin-angiotensin system plays a fundamental role in blood pressure and fluid and electrolyte homeostasis. Angiotensin II receptor antagonists, ACE (angiotensin converting enzyme) inhibitors and renin inhibitors have all been used to investigate the involvement of the renin-angiotensin system in essential hypertension. ACE inhibitors, such as captopril and enalapril, have been shown to be effective in the treatment of hypertension and congestive heart failure.[1] Nevertheless, ACE inhibitors also inhibit the metabolism of other peptides (bradykinin, substance P), and some of the side effects associated with ACE inhibitor therapy, including persistent cough and angioedema, may be related to the accumulation of bradykinin or substance P.[2] Selective AII receptor antagonists may block only the actions of AII and therefore would have fewer undesirable side effects. Although potent peptide AII receptor antagonists are available, they possess partial agonist activity, have a short half-life, and lack oral bioavailability.[3] In 1982, the Takeda group reported the discovery of weakly active but selective nonpeptidic AII receptor antagonists.[4] More recently the Du Pont group reported a series of biphenylylimidazoles as nonpeptidic, potent, selective, and orally active AII receptor antagonists.[5] Since then, numerous novel AII receptor antagonists have been discovered.[6,7]

We believe that besides the well-explored lipophilic pocket which accommodates substituents at the 2-position of the imidazole ring in the DuP 753 series,[5] there is a secondary lipophilic pocket which accepts substituents at the 4-position.[8] Also, a hydrogen-bond accepting group at the 5-position may enhance the binding affinity to the AII receptor. Triazolone is one of the heterocycles that can accommodate these structural features.[7] Herein we report the discovery of a triazolone-based AII antagonist 1 (Scheme I) which is potent and orally active and has a long duration of action (SC-51316, R = butyl, A = tetrazole).[9] A structure-activity relationship study (SAR)



DuP 753

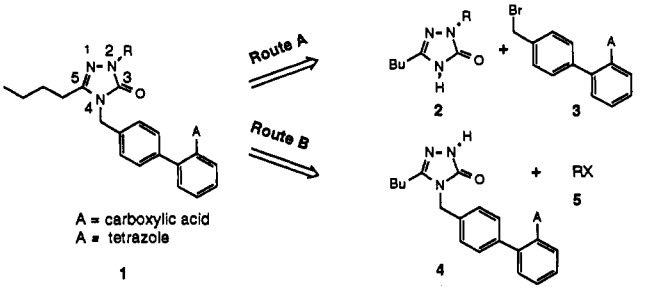
of the 2-position of triazolones (corresponding to the 4-position of imidazoles) will also be described.

Chemistry

As shown in Scheme I, N,N'-disubstituted triazolones 1 were prepared by coupling of N(2)-substituted triazolone 2 with biphenylylmethyl bromide 3 (route A) or by alkylation of *N*(4)-(biphenylylmethyl)triazolone 4 with various electrophiles 5 (route B). Compounds with a side chain at the 2-position which cannot be attached by the alkylation method (route B) were prepared via route A.

Syntheses of various biphenylylmethyl intermediates used for the preparation of compounds in this paper are described in Scheme II.[10] Hydrolysis of ester 6 and treatment of the resulting acid 7 with 2-methylpropene and sulfuric acid followed by bromination of the resulting *tert*-butyl ester 8 with NBS yielded bromide 9. Displacement of bromide with sodium azide and hydrogenation of the resulting azide on Pd/C afforded amino ester 10. Conversion of acid 7 to an amide via the corresponding acid chloride followed by dehydration of the amide

Scheme I



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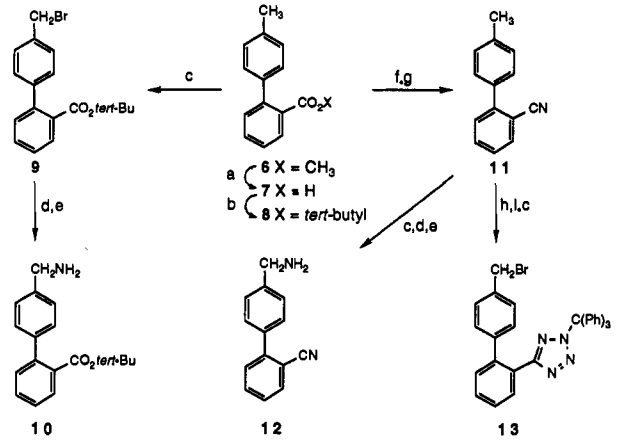
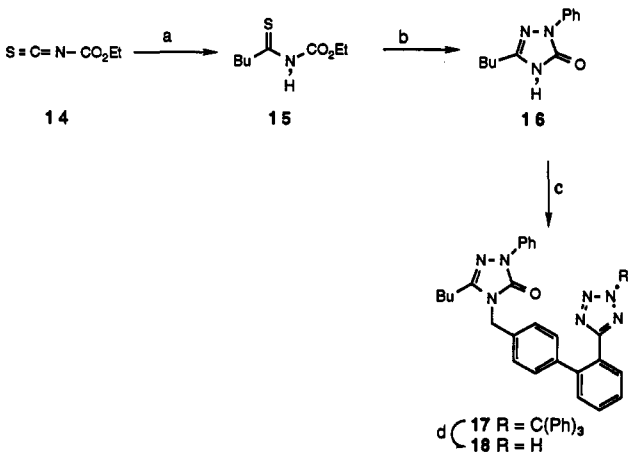
Scheme II[a]



[a](a) NaOH, H_2O–MeOH, reflux (99%); (b) 2-methylpropene, sulfuric acid, ether, 25 °C (94%); (c) NBS, AIBN, CCl_4, reflux; (d) NaN_3, DMF, 25 °C; (e) H_2, 45 psi, Pd/C; (f) $(COCl)_2$, THF; then NH_3; (g) $SOCl_2$, reflux; (h) trimethyltin azide, toluene, reflux; then anhydrous HCl, THF-toluene; (i) triphenylmethyl chloride, Et_3N, CH_3Cl.

Scheme III[a]



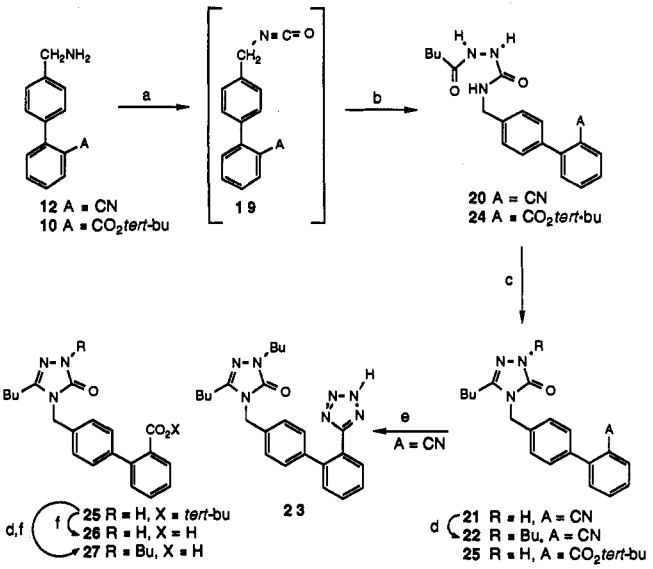
[a](a) Butylmagnesium chloride, ether, −78 °C; (b) phenylhydrazine, EtOH, reflux; (c) **13**, K_2CO_3, DMF, 25 °C; (d) 10% H_2O in acetic acid.

afforded nitrile **11**. Bromination of nitrile **11**, displacement of bromide with sodium azide, and hydrogenation of the resulting azide on Pd/C gave amino nitrile **12**. Conversion of nitrile **11** to a tetrazole with trimethyltin azide and protection of the resulting tetrazole with trityl chloride followed by bromination with NBS provided bromide **13**. With these key intermediates in hand, we turned our attention to the construction of the triazolone ring and their subsequent coupling.

The general procedure for the preparation of compounds via route A (Scheme I) is exemplified in Scheme III for the preparation of 5-butyl-2-phenyltriazolone **18**. Ethoxycarbonyl isothiocyanate **14** was reacted with butylmagnesium chloride to give *N*-ethoxycarbonyl thioamide **15**. The thioamide **15** was converted to 1,2,4-triazolone **16** with phenylhydrazine.[11] Coupling of triazolone **16** with bromide **13** and deprotection of the resulting trityltetrazole **17** with aqueous acetic acid yielded tetrazole **18**.

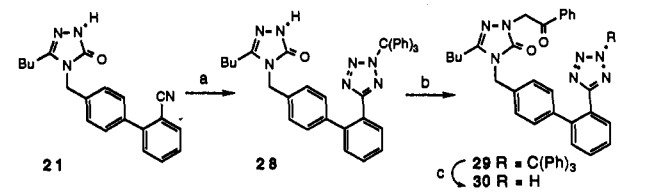
The general procedure used to prepare compounds via route B (Scheme I) is illustrated in Scheme IV for the preparation of dibutyltriazolone **23**, SC-51316. Amino nitrile **12** was reacted with phosgene to give isocyanate **19** which without isolation was treated with valeric hydrazide to give semicarbazide **20**. Semicarbazide **20** was cyclized with sodium methoxide in MeOH at reflux to give

Scheme IV[a]



[a](a) $COCl_2$, toluene; (b) $BuC(O)NHNH_2$, CH_2Cl_2 (73%); (c) NaOMe, MeOH, reflux (93%); (d) potassium *tert*-butoxide, DMF; then iodobutane, 25 °C (85%); (e) Me_3SnN_3, DMF, reflux (77%); (f) trifluoroacetic acid, chloroform, 25 °C.

Scheme V[a]



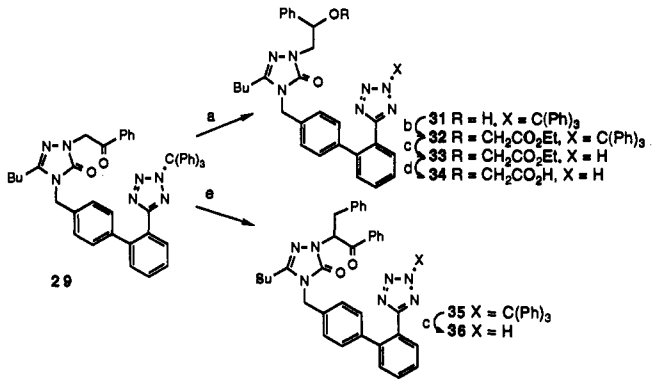
[a](a) Me_3SnN_3, DMF, reflux; then triphenylmethyl chloride, Et_3N, CH_3Cl, 25 °C (94%); (b) potassium *tert*-butoxide, DMF; then 2-bromoacetophenone, 25 °C (quantitative); (c) 10% H_2O in acetic acid, 25 °C (86%).

triazolone **21**.[12] Triazolone **21** was alkylated with iodobutane, and the resulting nitrile **22** was converted to tetrazole **23**. Preparation of carboxylic acid analogues were carried out with amino *tert*-butyl ester **10** via intermediate semicarbazide **24** and ester **25** to give **26** and **27**.

As mentioned earlier in the introduction, we believe that there is a lipophilic pocket interacting with the substituent at the 2-position of the triazolone. To explore that pocket, a more efficient synthetic route was needed to generate various 2-substituted triazolone analogues without having to go through the long synthesis for each compound. For that purpose, a modified synthetic sequence was established and demonstrated in Scheme V for the preparation of *N*-acetophenone-substituted triazolone **30**. Nitrile **21** was converted to a tetrazole with trimethyltin azide and protected with trityl chloride to give triazolone **28**. Most of the compounds in this paper were prepared very efficiently by alkylating this precursor with various electrophiles. For example, precursor **28** was alkylated with 2-bromoacetophenone, and the resulting product **29** was detritylated with aqueous acetic acid to give tetrazole **30**. Alkylated products that have ester groups in the side chains were also hydrolyzed with LiOH in aqueous THF to the corresponding carboxylic acids.

To study the effect of branching in the sidechain on the binding affinity, *N*-acetophenone **29** was used to prepare derivatives that have a substituent at either 1- or 2-position of the phenylethyl backbone. A general procedure is demonstrated in Scheme VI. Acetophenone **29** was reduced to alcohol **31** and alkylated to give various

Scheme VI[a]



[a](a) $NaBH_4$, MeOH–THF, 0 °C (95%); (b) NaH, THF; then ethyl bromoacetate (83%); (c) 10% H_2O in acetic acid; (d) LiOH, H_2O–THF (94%); (e) LDA, THF, −20 °C; then benzyl bromide (90%).

2-alkoxyphenylethyl analogues. For example, alcohol **31** was treated with NaH in THF, quenched with ethyl bromoacetate, and detritylated to give ester **33**. Ester **33** was hydrolyzed to acid **34**. Alkylation of the enolate generated from *N*-acetophenone **29** with different electrophiles gave the 1-substituted phenyl ketone analogues, such as **35**.

Biological Results

Of all the compounds synthesized, the dibutyltriazolone **23**, SC-51316, was selected for further pharmacological evaluation. SC-51316 inhibited ^{125}I-labeled AII binding to the AT_1 receptor in rat uterine membranes with an IC_{50} of 5.1 nM (Table I). The compound was a competitive and reversible antagonist of AII-mediated contraction of rabbit aortic rings with a pA_2 of 8.86 (Table I). Thus, SC-51316 has high receptor binding affinity and is a potent AII receptor antagonist. To determine whether SC-51316 was active *in vivo*, rats were given an intravenous infusion of AII, and SC-051316 was administered at 1, 3, 10 mg/kg ig. Figure 1 shows that SC-51316 inhibited the pressor response to AII; the extent and duration of the response to SC-51316 were dose-dependent. The ID_{50} for SC-51316 was 2.1 mg/kg ig. We conclude that SC-51316 antagonizes the action of AII *in vivo* and is orally active.

Discussion

The SAR of the triazolone 2-position is summarized in Tables I–III. The discussion on the SAR of these compoounds is mainly based on the receptor binding affinity data (IC_{50}).

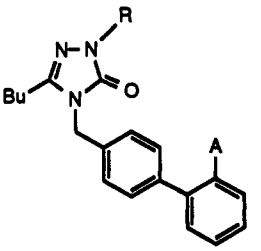
Compounds **26**, **27**, **37**, and **23** were prepared to study the effect of the 2-substituent in compounds with different acidic groups in the biphenyl ring system (Table I). Replacing a carboxylic acid group in the biphenyl moiety with a tetrazole caused a dramatic increase in binding affinity (35-fold for 2-unsubstituted analogues **26** and **37** and 20-fold for 2-butyl analogues **27** and **23**).

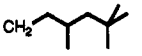
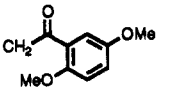
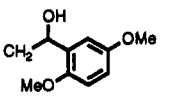
The optimal alkyl chain length at the 2-position is four atoms, and the binding affinity showed a dramatic decrease for the *n*-octyl derivative (**23**, **38**–**42** in Table I). A branched alkyl group seems to slightly lower the binding affinity (**43**, **44**), but the pocket is much more spacious than originally perceived. The pocket can accommodate bulky groups, such as *tert*-butyl, cyclohexyl, and even adamantyl with some decrease in the binding affinity (**45**, **47**, and **48**). Interestingly, while the binding affinity of carboxylic acid **26** (where R is a hydrogen) showed a 15-fold increase by replacing the 2-hydrogen with a butyl group (**27**), that of tetrazole **37** showed only an 8-fold increase after the same replacement to give **23**, SC-51316.

Various functional groups, such as alcohol, ketone, acid, or ester **48**–**51**, **30**, and **60** (Table I), when compared to pentyl (**40**) or phenylethyl analogues (**57**), do not have significant adverse effects on receptor binding affinity, although the acids, especially the short-chain acid (**50**), have lower binding affinity than their corresponding esters (**49**–**55**). Quite surprisingly, the long-chain esters (**52** and **54**), which have overall seven and nine atoms along their chains, when compared with the eight-atom alkyl analogue **42**, showed very impressive binding affinity.

Compounds **18**, **30**, and **56**–**64** all have aryl groups at the

Table I. Triazolone Angiotensin II Antagonists: SAR at the 2-Position



no.[a]	R	A	IC_{50}, nM[b]	pA_2[c]
26	H	CO_2H	1,500	5.5
27	*n*-butyl	CO_2H	101	7.0
37	H	tetrazole	42	7.1
38	ethyl	tetrazole	22	7.6
39	propyl	tetrazole	15	8.2
23	*n*-butyl	tetrazole	5.1	8.9
40	*n*-pentyl	tetrazole	5.6	9.0
41	*n*-hexyl	tetrazole	8.7	8.9
42	*n*-octyl	tetrazole	170	8.5
43	isopropyl	tetrazole	20	8.5
44	2-butyl	tetrazole	10	8.7
45		tetrazole	35	7.9
46	cyclopropylmethyl	tetrazole	15	8.0
47	cyclohexylethyl	tetrazole	18	7.9
48	$CH_2C(=O)$-1-adamantyl	tetrazole	25	8.1
49	CH_2CO_2Et	tetrazole	9.0	7.8
50	CH_2CO_2H	tetrazole	91	7.8
51	$CH_2CO_2CH(CH_3)_3$	tetrazole	16	7.1
52	$CH_2(CH_2)_3CO_2CH_3$	tetrazole	4.4	9.4
53	$CH_2(CH_2)_3CO_2H$	tetrazole	12	8.0
54	$CH_2(CH_2)_4CO_2Et$	tetrazole	9.8	7.6
55	$CH_2(CH_2)_4CO_2H$	tetrazole	17	8.7
18	phenyl	tetrazole	59	7.2
56	benzyl	tetrazole	16	8.1
57	CH_2CH_2Ph	tetrazole	3.1	9.8
58	$CH_2CH_2CH_2Ph$	tetrazole	18	8.0
59	*trans*-$CH_2CH=CHPh$	tetrazole	290	6.6
30	$CH_2C(=O)Ph$	tetrazole	7.9	8.5
60	$CH_2CH(OH)Ph$	tetrazole	3.6	8.3
61	1-naphthylmethyl	tetrazole	50	7.7
62	2-naphthylmethyl	tetrazole	280	6.5
63		tetrazole	21	8.0
64		tetrazole	22	8.1

[a] New compounds were identified by spectroscopic data and confirmed by either elemental analysis or high-resolution mass spectroscopy. Purity was checked by reverse phase HPLC. [b] Inhibition of ^{125}I-AII binding to rat uterine membranes (IC_{50}) had standard errors of 10% or less. For more details, see the Experimental Section. [c] Antagonism of AII-induced contraction of rabbit aortic rings (pA_2) were the average of two rabbit aortas. In our assays, DuP 753 had an IC_{50} of 36 nM and a pA_2 of 8.1 See the Experimental Section for further details.

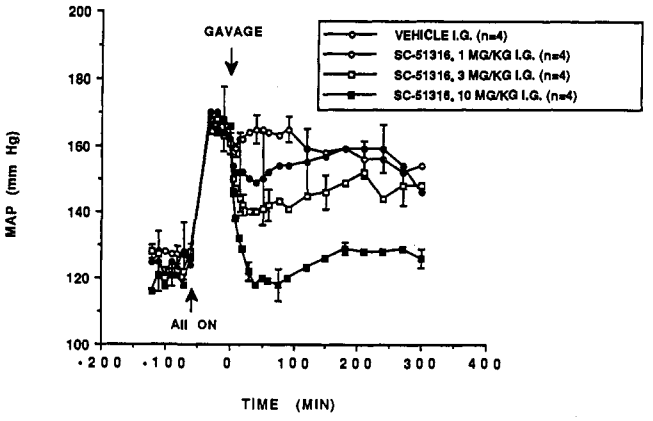
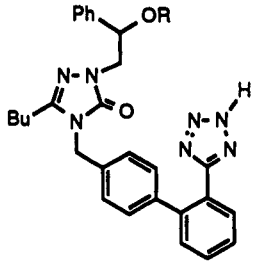


Figure 1. Inhibition of presser response to angiotensin by SC-51316 in anesthetized, ganglion-blocked rats. The rats were given an intravenous infusion of AII and SC-51316 was administered at 1, 3, 10 mg/kg ig.

Table II. SAR of Triazolone AII Antagonist with 2-Alkoxy-2-phenylethyl at the 2-Position



no.[a]	R	IC_{50}, nM[b]	pA_2[c]
65	CH_3	12	7.8
66	CH_2CH_3	15	8.5
67	$CH_2CH_2CH_3$	45	8.1
68	CH_2Ph	280	7.7
33	CH_2CO_2Et	180	8.3
34	CH_2CO_2H	30	8.6

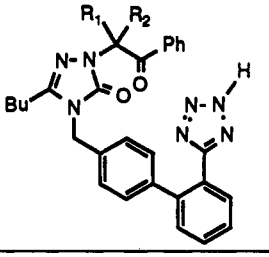
[a-c] See Table I for an explanation of the tabulated data.

end of the chains (Table I). Phenylethyl analogue **57** with an IC_{50} of 3.1 nM and a pA_2 of 9.8 is the most potent compound in this triazolone series. A shorter or longer alkyl chain decreases the binding affinity (**18**, **56**, and **58**). Comparing **58** and **59**, the introduction of a *trans* C2–C3 double bond results in a 16-fold decrease in binding affinity. 2-Naphthylmethyl **62**, which is quite similar to the cinnamyl analogue **59**, suffers the same degree of loss in the binding affinity. 1-Naphthylmethyl **61** resembling a phenylethyl analogue **18**, which has its phenyl ring locked into a position coplanar with the C1–C2 bond, also suffers a 16-fold decrease in binding affinity due to the lack of freedom to rotate around the C2–C3 bond.

Ketone **30** and alcohol **60** show no significant difference from their parent phenylethyl analogue **57** (Table I). Ketone **63** and alcohol **64**, 2,5-disubstituted phenyl analogues, have similar binding affinities, but have lower binding affinities than their unsubstituted analogues (**30** and **60**).

Compared with phenylethyl **57** (IC_{50} = 3.1 nM) or 2-hydroxy-2-phenylethyl **60** (IC_{50} = 3.6), substitution at the 2-position of the 2-phenylethyl side chain causes a decrease in binding affinity (Table II), especially with bigger groups such as ethyl acetate or benzyl (**68** and **33**). Substitution with a bulky group at the 1-position of the acetophenone analogue also results in decreased binding affinity (**36**, Table III).

Table III. SAR of Triazolone AII Antagonist with 1-Substituted Acetophenone at the 2-Position



no.[a]	R_1	R_2	IC_{50}, nM[b]	pA_2[c]
69	CH_3	CH_3	43	7.7
36	CH_2Ph	H	5,800	
70	CH_2CO_2Et	H	36	7.8

[a-c] See Table I for an explanation of the tabulated data.

Conclusion

In contrast to the lipophilic pocket which accommodates the substituent at the 5-position of the triazolones which has been well established to be very narrow and short-ranged by the Du Pont group in the imidazole series,[5] the pocket in the receptor interacting with the 2-substituent of the triazolone antagonist is quite spacious. The SAR on the 2-position of the triazolone which explored the secondary lipophilic pocket suggests that generally the optimal length of the side chain is around four to five carbons. Long-chain esters, however, have good binding affinity. Branching in the side chain generally lowers the binding affinity slightly. Bulky groups, such as *tert*-butyl, cyclohexyl, and adamantyl, attached to the end of the chain also cause a loss in the binding affinity, but to a lesser degree than expected. Functional groups, such as alcohols and ketones, have no significant effect on the receptor binding affinity, although acids have lower binding affinity than the corresponding esters or alkyls. The phenylethyl side chain yielded the most potent compound in this series. For flexible side chains the rotation around the C2–C3 bond is crucial for good binding.

The development of a synthetic route which provides a quick entry into compounds with various substituents at the 2-position of the triazolone has facilitated the completion of the SAR of triazolone-based AII antagonists in a very short period of time and with minimal resources. The information gathered from this study has also provided new insights into the understanding of the interacting sites in the receptor and may be applicable to other monocyclic heterocycles.

Experimental Section

Preparation of compounds **7**, **8**, **9**, **11**, and **13** has been published earlier with similar procedures.[5c] The starting material, biphenylcarboxylic acid methyl ester **6**, was purchased from Chemo Dynamics. Ethoxycarbonyl isothiocyanate **14** was purchased from Aldrich. New compounds were confirmed either by elemental analyses or by high-resolution mass spectra (HRMS). Melting points were determined without correction on a Thomas-Hoover Unimelt apparatus. NMR spectra were obtained on a Varian VXR-300 300 MHz. High-resolution mass spectra were obtained on a Finnigan MAT 90 or a VG Model 250T spectrometer with FAB ionization. Purities of final products were checked by reverse-phase HPLC on a C18 column (Vydac Cat. no. 218TP54), eluting with water and CH_3CN containing 0.05% trifluoroacetic acid, and detected by UV at 254 nm. Retention time, purity, and HPLC conditions for new compounds are included in each individual experimental procedure. Elemental analyses for C, H, N were obtained from Galbraith Laboratories, Inc.

Biology. Angiotensin II was purchased from Peninsula Labs. ^{125}I-AII (specific activity of 2200 Ci/mmol) was purchased from

Du Pont-New England Nuclear. All other chemicals were obtained from Sigma Chemical.

AII Receptor Binding (IC_{50}). Compounds were tested for binding to the AII receptor in rat uterine membrane preparations as described previously.[9] IC_{50} values are reported for binding to the AT_1 receptor.

Antagonism of AII-Induced Contraction of Vascular Smooth Muscle. Compounds were tested for their ability to antagonize the AII-mediated contraction of rabbit aortic rings *in vitro* as described previously.[9]

Inhibition of AII Pressor Response in Conscious AII-Infused Rats. Male Sprague–Dawley rats were anesthetized with Brevital, 30 mg/kg ip, (methohexital sodium, Eli Lilly & Co., Indianapolis, IN). Catheters were implanted in the femoral artery and vein to measure arterial pressure and administer compound, respectively. Animals were placed in a restrainer and allowed to recover from surgery and anesthesia for 3 h. Blood pressure was measured continuously from the arterial catheter with a pressure transducer and recorded on a polygraph. Arterial pressure was recorded for 1 h for baseline values before initiating an infusion of AII (50 ng/kg/min iv). The change in mean arterial pressure in response to AII was compared at various time points prior to and following the administration of the compounds intragastrically at doses of 1–10 mg/kg. Potency (ID_{50}) was estimated from the dose of compound required to produce 50% inhibition of the control pressor response to AII.

Chemistry. *tert*-Butyl 4′-(Aminomethyl)biphenylcarboxylate (10). The mixture of bromide **9** (11.0 g, 0.032 mol) and 4.6 g (0.071 mol) of sodium azide in 42 mL of DMF and 4.2 mL of water was stirred at room temperature for 24 h and concentrated. The residue was extracted with EtOAc, and the combined extracts were washed with water, dried ($MgSO_4$), and concentrated to give 10 g (quantitative) of 4-(azidomethyl)-2′-(*tert*-butoxycarbonyl)biphenyl as a yellow oil: ^1H NMR ($CDCl_3$) δ 1.26 (s, 9H), 4.38 (s, 2H), 7.2–7.9 (m, 8H).

A suspension of 10 g (32 mmol) of the (azidomethyl)biphenyl from above and 0.6 g of 10% palladium on carbon in 30 mL of absolute EtOH was agitated on a Parr apparatus under a hydrogen atmosphere at 40 psi for 20 h. The mixture was filtered through a pad of Celite and concentrated to give 9.2 g (quantitative) of **10** as a yellow oil: ^1H NMR ($CDCl_3$) δ 1.28 (s, 9H), 1.71 (broad s, 2H), 3.92 (s, 2H), 7.2–7.9 (m, 8H).

2-Cyano-4′-(aminomethyl)biphenyl (12). The title compound was prepared from **11** according to the procedure described in the preparation of **10**. Intermediate 2-cyano-4′-(bromomethyl)biphenyl: ^1H NMR ($CDCl_3$) δ 4.55 (s, 2H), 7.40–7.60 [m (with d at 7.53, J = 1.8 Hz), 6H], 7.60–7.72 (m, 1H), 7.78 (d, J = 7.5 Hz, 1H).

Intermediate 2-cyano-4′-(azidomethyl)biphenyl: ^1H NMR ($CDCl_3$) δ 4.43 (s, 2H), 7.38–7.54 [m (with d at 7.45, J = 8.1 Hz), 4H], 7.59 (d, J = 8.1 Hz, 2H), 7.62–7.70 (m, 1H), 7.77 (d, J = 8.4 Hz, 1H).

The title compound **12**: ^1H NMR ($CDCl_3$) δ 1.65 (br s, 2H), 3.95 (s, 2H), 7.35 (m, 8H); mass spectrum (FAB), *m/e* (relative intensity) 209 (32), 192 (12), 121 (100), 102 (50).

N-(Ethoxycarbonyl)thiovaleramide (15). To 95 mL of 2 M (0.190 mol) butylmagnesium chloride in ether and 55 mL of anhydrous ether at −60 °C (chloroform–dry ice) was added dropwise 24.4 g (0.162 mol) of ethoxycarbonyl isothiocyanate **14** in 205 mL of anhydrous ether over a period of 2 h. The resulting mixture was stirred cold for 3 h and allowed to slowly warm to room temperature. The solvent was decanted and the solid was washed with four 50-mL portions of ether. The solid was partitioned between 200 mL of ether and 200 mL of saturated ammonium chloride. The aqueous layer was extracted with two 50-mL portions of ether, and the combined extracts were dried ($MgSO_4$) and concentrated. The red oily residue was distilled under reduced pressure to give 18 g (58%) of **15** as an yellow oil: bp 86 °C (1.5 Torr); ^1H NMR ($CDCl_3$) δ 0.90 (t, J = 7.5 Hz, 3H), 1.20–1.5 (m, 5H), 1.65–1.8 (m, 2H), 3.20 (t, J = 7.5 Hz, 2H), 4.2 (q, J = 7.2 Hz, 2H), 9.2 (broad s, 1H).

5-Butyl-2-phenyltriazol-3-one (16). To 1.5 g (7.94 mmol) of **15** in 15 mL of absolute EtOH at room temperature was added 1.5 mL (15 mmol) of 97% phenylhydrazine in 4 mL of EtOH. The resulting solution was stirred at reflux for 12 h and concentrated. The resulting solid was dissolved in ether/hexane, recrystallized at −20 °C, and collected by filtration to give 0.9 g (52%) of triazolone **16** as a white solid: ^1H NMR ($CDCl_3$) δ 0.97 (t, J = 7.3 Hz, 3H), 1.45 (septet, J = 7.5 Hz, 2H), 1.75 (quintet, J = 7.7 Hz, 2H), 2.64 (t, J = 7.4 Hz, 2H), 7.22 (t, J = 7.5 Hz, 1H), 7.43 (t, J = 8.4 Hz, 2H), 7.94 (d, J = 8.7 Hz, 2H); mass spectrum (FAB), *m/e* (relative intensity) 218(100), 175(20).

5-Butyl-2-phenyl-4-[[2-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4′-yl]methyl]-1*H*-1,2,4-triazol-3-one (18). To 150 mg (0.692 mmol) of triazolone **16** in 8 mL of DMF and 94 mg (0.68 mmol) of K_2CO_3 was added 0.46 g (0.826 mmol) of **13**. The resulting solution was stirred at room temperature for 18 h and concentrated. The residue was chromatographed to give 290 mg (60%) of trityl-protected compound as a solid: ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 7.2 Hz, 3H), 1.2–1.4 (m, 2H), 1.53–1.70 (m, 2H), 2.38 (t, J = 7.3 Hz, 2H), 4.78 (s, 2H), 6.92 (d, J = 7.2 Hz, 6H), 7.0–7.15 (m, 4H), 7.2–7.6 (m, 20H), 7.9–7.98 (m, 1H), 8.02 (d, J = 7.8 Hz, 2H).

The trityl-protected compound from above was dissolved in 11 mL of glacial acetic acid and 1.1 mL of water. The resulting solution was stirred at room temperature for 18 h and concentrated. The solid residue was stirred with 5 mL of saturated $NaHCO_3$ and 10 mL of ether for 10 min. The ethereal solution was removed, and the aqueous layer was washed twice with fresh ether. The resulting aqueous layer was acidified with 3 N HCl to pH 3 and extracted with three 10-mL portions of chloroform. The combined extracts were dried ($MgSO_4$) and concentrated to give 160 mg (85%) of tetrazole **18** as a white solid: mp 191.8–192.4 °C; ^1H NMR ($CDCl_3$) δ 0.92 (t, J = 7.5 Hz, 3H), 1.42 (septet, J = 7.2 Hz, 2H), 1.69 (quintet, J = 7.5 Hz, 2H), 2.53 (t, J = 7.5 Hz, 2H), 4.88 (s, 2H), 7.22 (AB q, J = 8.1 Hz, 4H), 7.35–7.45 (m, 3H), 7.50–7.53 (m, 2H), 7.92 (dd, J = 8.7, 0.9 Hz, 2H), 8.05 (dd, J = 7.5, 1.5 Hz, 1H); HPLC retention time 11.71 min (99.8%), eluting with 45% CH_3CN in water, 1.5 mL/min; HRMS calcd for M + H 452.2198, found 452.2236.

2-Cyano-4′-[[[[2-(1-oxopentyl)hydrazino]carbonyl]amino]methyl]-1,1′-biphenyl (20). To 160 mL of 1 M (160 mmol) phosgene in toluene at 0 °C was added dropwise a solution of 10.3 g (49.5 mmol) of amino nitrile **12** and 13 mL (160 mmol) of pyridine in 180 mL of methylene chloride over a 40-min period. The resulting mixture was stirred at 0 °C for 1 h, and the excess of phosgene was removed at 25 °C under a low vacuum. To the mixture were added 8 g (69 mmol) of valeric acid hydrazide (Lancaster Synthesis) and 13 mL (160 mmol) of pyridine, and the resulting mixture was stirred at room temperature for 20 h. The reaction mixture was concentrated, and the residue was chromatographed over silica gel (eluted with 2-PrOH/hexane, 1:5) to give 12.8 g (73%) of **20** as a solid: mp 167.0–168 °C; ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7.2 Hz, 3H), 1.32 (septet, J = 7.8 Hz, 2H), 1.50–1.67 (m, 2H), 2.20 (t, J = 7.5 Hz, 2H), 4.43 (d, J = 5.7 Hz, 2H), 5.95 (br t, 1H), 7.3–7.55 (m, 6H), 7.58–7.68 (m, 1H), 7.74 (d, J = 7.4 Hz, 1H), 7.9–8.03 (br s, 1H); HRMS calcd for M + H 351.1821, found 351.1819.

5-Butyl-2,4-dihydro-4-[(2-cyano-1,1′-biphenyl-4′-yl)methyl]-3*H*-1,2,4-triazol-3-one (21). To 12.8 g (36.6 mmol) of the above semicarbazide **20** in 345 mL of MeOH was added 4 g (74 mmol) of sodium methoxide, and the resulting mixture was stirred under vigorous reflux for 30 h with a moisture trap (molecular sieve, 3A) attached between a condenser and the reaction vessel. The base was neutralized with acetic acid, and the reaction mixture was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2, filtered, and concentrated to give 11.3 g (93%) of compound **21** as a solid: mp 133.5–135.0 °C; ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 7.25 Hz, 3H), 1.35 (septet, J = 7.7 Hz, 2H), 1.60 (quintet, J = 7.7 Hz, 2H), 2.43 (t, J = 7.25 Hz, 2H), 4.89 (s, 2H), 7.36 (d, J = 8.1 Hz, 2H), 7.40–7.50 (m, 2H), 7.54 (d, J = 8.1 Hz, 2H), 7.64 (dt, J = 1.2, 7.7 Hz, 1H), 7.76 (dd, J = 0.8, 7.7 Hz, 1H); HRMS calcd for M + H 333.1715, found 333.1745.

2,5-Dibutyl-2,4-dihydro-4-[(2-cyano-1,1′-biphenyl-4′-yl)methyl]-3*H*-1,2,4-triazol-3-one (22). To a solution of 15 g (45 mmol) of **21** in 230 mL of DMF at 0 °C was added dropwise 55 mmol of potassium *tert*-butoxide (1 M solution in THF), and the resulting red solution was stirred cold for 10 min. To the mixture was added 17.5 mL (153 mmol) of iodobutane, and the mixture was stirred at 25 °C for 17 h. The reaction mixture was quenched with 2 mL of acetic acid, concentrated, and chromatographed (eluting with EtOAc/hexane, 1:5) to give 15 g (85%) of **22** as a solid: ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7.3 Hz, 3H), 0.94 (t, J = 7.3 Hz, 3H), 1.20–1.47 (m, 4H), 1.57 (quintet, J = 7.6 Hz,

2H), 1.74 (quintet, J = 7.3 Hz, 2H), 2.41 (t, J = 7.5 Hz, 2H), 3.80 (t, J = 7.3 Hz, 2H), 4.87 (s, 2H), 7.34 (d, J = 8.2 Hz, 2H), 7.38–7.58 [m (with d at 7.52, J = 8.2 Hz), 4H], 7.62 (td, J = 7.7, 1.3 Hz, 1H), 7.74 (d, J = 7.4 Hz, 1H).

2,5-Dibutyl-2,4-dihydro-4-[[2-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4′-yl]methyl]-3*H*-1,2,4-triazol-3-one (23). The mixture of 12 g (31 mmol) of **22** and 30 g (146 mmol) of trimethyltin azide in 17 mL of DMF was stirred at reflux for 60 h and concentrated *in vacuo*. The mixture was slowly poured into a saturated $NaHCO_3$ solution and washed with three 200-mL portions of ether/hexane. The aqueous layer was carefully acidified with 3 N HCl to pH 3, extracted with four 400-mL portions of $CHCl_3$/EtOAc, dried ($MgSO_4$), and concentrated *in vacuo*. The solid residue was recrystallized from EtOAc/hexane to give 13.4 g (quantitative) of **23** as a white solid: mp 128–129 °C; ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 7.1 Hz, 6H), 1.15–1.42 (m, 4H), 1.42–1.70 [m (with two quintet at 1.50 and 1.61, J = 7.4 and 7.3 Hz), 4H], 2.34 (t, J = 7.5 Hz, 2H), 3.64 (t, J = 7.2 Hz, 2H), 4.69 (s, 2H), 7.06 (q, J = 8.1 Hz, 4H), 7.27 (broad s, 1H), 7.41 (d, J = 7.5 Hz, 1H), 7.45–7.65 (m, 2H), 7.82 (d, J = 7.2 Hz, 1H); HPLC retention time 10.36 min (99.1%), eluting with 45% CH_3CN in water, 1.0 mL/min; mass spectrum (FAB), *m/e* (relative intensity) 432 (40), 207 (100), 178 (25); HRMS calcd for M + H 432.2512, found 432.2510. Anal. ($C_{24}H_{29}N_7O$) C, H, N.

***tert*-Butyl 4′-[[[[2-(1-Oxopentyl)hydrazino]carbonyl]amino]methyl][1,1′-biphenyl]-2-carboxylate (24).** The title compound was prepared from amino ester **10** and valeric hydrazide following the procedure for the preparation of **20**: ^{1}H NMR ($CDCl_3$) δ 0.86 (t, J = 7.2 Hz, 3H), 1.28 (s, 9H), 1.20–1.40 (m, 2H), 1.56 (quintet, J = 7.2 Hz, 2H), 2.20 (t, J = 7.5 Hz, 2H), 4.38 (d, J = 6 Hz, 2H), 6.27 (broad t, 1H), 7.2–7.5 (m, 7H), 7.76 (dd, J = 7.5, 1.0 Hz, 1H), 7.95–8.05 (m, 1H), 8.85 (broad s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.7, 22.3, 27.4, 27.7, 33.6, 43.7, 127.0, 128.8, 129.7, 130.7, 132.7, 127.7, 140.7, 141.7, 158.3, 167.9, 173.0.

***tert*-Butyl 4′-[(3-Butyl-4,5-dihydro-5-oxo-1,2,4-triazol-4-yl)methyl][1,1′-biphenyl]-2-carboxylate (25).** The title compound was prepared from semicarbazide **24** according to the procedure described in the preparation of **21**: ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7.2 Hz, 3H), 1.24 (s, 9H), 1.30–1.45 (m, 2H), 1.62 (quintet, J = 7.8 Hz, 2H), 2.43 (t, J = 7.5 Hz, 2H), 4.87 (s, 2H), 7.2–7.55 (m, 7H), 7.78 (dd, J = 7.5, 1.2 Hz, 1H).

4′-[(3-Butyl-4,5-dihydro-5-oxo-1,2,4-triazol-4-yl)methyl][1,1′-biphenyl]-2-carboxylic Acid (26). To 80 mg (0.197 mmol) of ester **25** in 2 mL of chloroform was added 2 mL (26 mmol) of trifluoroacetic acid (TFA). The resulting solution was stirred at room temperature for 20 h and concentrated. The residue was treated with Na_2CO_3 solution and washed with ether. The aqueous layer was acidified to pH 3 with 3 N HCl, extracted with $CHCl_3$, dried ($MgSO_4$), and concentrated. The residue was chromatographed over silica gel (EtOAc–MeOH–acetic acid, 9:1:0.5) to give 60 mg (87%) of **26** as a solid: ^{1}H NMR ($CDCl_3$) δ 0.84 (t, J = 7.3 Hz, 3H), 1.31 (septet, J = 7.5 Hz, 2H), 1.54 (quintet, J = 7.6 Hz, 2H), 2.41 (t, J = 7.5 Hz, 2H), 3.2–4.0 (br, 1H), 4.87 (s, 2H), 7.19 (d, J = 8.1 Hz, 2H), 7.3–7.39 [m (with d at 7.34, J = 8.0 Hz), 3H], 7.43 (t, J = 7.1 Hz, 1H), 7.54 (td, J = 7.5, 1.1 Hz, 1H), 7.92 (dd, J = 7.2, 1.1 Hz, 1H); HRMS calcd for M + H 352.1661, found 352.1683.

4′-[(1,3-Dibutyl-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-4-yl)methyl][1,1′-biphenyl]-2-carboxylic Acid (27). The *tert*-butyl-protected title compound was prepared from ester **25** and iodobutane according to the procedure described for the preparation of **22**: ^{1}H NMR ($CDCl_3$) δ 0.8–1.0 (m, 6H), 1.24 (s, 9H), 1.24–1.45 (m, 4H), 1.50–1.68 (m, 2H), 1.68–1.80 (m, 2H), 2.41 (t, J = 7.5 Hz, 2H), 3.80 (t, J = 7.2 Hz, 2H), 4.86 (s, 2H), 7.20–7.34 [m (with s at 7.28), 5H], 7.35–7.55 (m, 2H), 7.78 (dd, J = 7.5, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.2, 20.3, 22.8, 26.3, 28.1, 28.5, 31.4, 45.0, 45.6, 127.4, 127.8, 129.7, 130.2, 131.0, 131.2, 133.4, 135.5, 141.8, 142.2, 146.7, 154.6, 168.3; mass spectrum (FAB), *m/e* (relative intensity) 470 (40), 414 (100).

To 165 mg (0.356 mmol) of the above *tert*-butyl ester in 2 mL of chloroform was added 1 mL (13 mmol) of trifluoroacetic acid (TFA). The resulting solution was stirred at room temperature for 15 h and concentrated. The residue was chromatographed over silica gel (EtOAc–MeOH–acetic acid, 85:10:5) to give 152 mg (quantitative) of acid **27** as a solid: ^{1}H NMR ($CDCl_3$) δ 0.75–1.0 (m, 6H), 1.2–1.4 (m, 4H), 1.52 (quintet, J = 7.8 Hz, 2H), 1.69 (quintet, J = 7.5 Hz, 2H), 2.37 (t, J = 7.5 Hz, 2H), 3.78 (t, J = 6.9 Hz, 2H), 4.85 (s, 2H), 7.12 (d, J = 7.8 Hz, 2H), 7.2–7.32 (m, 4H), 7.37 (t, J = 7.2 Hz, 1H), 7.50 (t, J = 7.5 Hz, 1H), 7.88 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.11, 14.13, 20.2, 22.6, 26.1, 28.4, 31.2, 45.0, 45.7, 127.1, 127.8, 129.6, 130.7, 131.0, 131.4, 132.2, 135.0, 141.5, 142.9, 147.4, 154.5, 172.5; mass spectrum (FAB), *m/e* (relative intensity) 408 (33), 390 (20), 211 (100).

5-Butyl-2,4-dihydro-4-[[2-[1-(triphenylmethyl)-1*H*-tetrazol-5-yl][1,1′-biphenyl]-4′-yl]methyl]-3*H*-1,2,4-triazol-3-one (28). A mixture of 6 g (18.1 mmol) of nitrile **21** and 12 g (58.3 mmol) of trimethyltin azide in 25 mL of DMF was stirred at reflux for 3 days. The resulting mixture was concentrated *in vacuo*. The residue was partially dissolved in CH_2Cl_2–MeOH and filtered through a pad of Celite. The filtrate was concentrated *in vacuo* to give 7 g of crude tetrazole. To the oily residue in 75 mL of $CHCl_3$ was added 6.7 g (24.0 mmol) of triphenylmethyl chloride and 5 mL (36.0 mmol) of triethylamine dropwise. The resulting solution was stirred at room temperature for 48 h and washed with water. The aqueous layer was extracted with $CHCl_3$. The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was recrystallized from a mixture of EtOAc, ether, and hexane to give 10.5 g (94%) of **28** as an off-white solid: mp 147.0–P149.0 °C; ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 7.3 Hz, 3H), 1.28 (septet, J = 7.5 Hz, 2H), 1.53 (quintet, J = 7.7 Hz, 2H), 2.29 (t, J = 7.3 Hz, 2H), 4.71 (s, 2H), 6.90 (d, J = 7.2 Hz, 6H), 7.01 (d, J = 8.3 Hz, 2H), 7.12 (d, J = 8.2 Hz, 2H), 7.2–7.4 (m, 10H), 7.4–7.55 (m, 2H), 7.9–8.0 (m, 1H), 9.0 (s, 1H); mass spectrum (FAB), *m/e* (relative intensity) 624 (22), 568 (4), 388 (30), 382 (18), 339 (100); HRMS calcd for M + H 624.3063, found 624.3089.

5-Butyl-2,4-dihydro-2-(2-oxo-2-phenylethyl)-4-[[2-[1-(triphenylmethyl)-1*H*-tetrazol-5-yl][1,1′-biphenyl]-4′-yl]methyl]-3*H*-1,2,4-triazol-3-one (29). A solution of 550 mg (0.972 mmol) of triazolone **28** in 9 mL of DMF was added dropwise 1.14 mmol of of potassium *tert*-butoxide (1.0 M in THF), and the resulting yellow solution was stirred at room temperature for 10 min. To the mixture was added in portions 215 mg (1.08 mmol) of 2-bromoacetophenone. The resulting solution was stirred at room temperature for 1 h and concentrated. The crude product was purified by silica gel chromatography, eluting with EtOAc/hexane, to give 712 mg (99%) of trityltetrazole **29** as a solid: ^{1}H NMR ($CDCl_3$) δ 0.76 (t, J = 7.3 Hz, 3H), 1.1–1.30 (m, 2H), 1.46 (quintet, J = 7.8 Hz, 2H), 2.25 (t, J = 8.0 Hz, 2H), 4.72 (s, 2H), 5.22 (s,2H), 6.88 (dd, J = 7.1, 5.6 Hz, 6H), 7.00 (d, J = 8.4 Hz, 2H), 7.08 (d, J = 8.2 Hz, 2H), 7.15–7.33 (m, 12H), 7.34–7.50 (m, 4H), 7.50–7.60 (m, 1H), 7.83–7.9 (m, 1H)

5-Butyl-2,4-dihydro-2-(2-oxo-2-phenylethyl)-4-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-3*H*-1,2,4-triazol-3-one (30). A solution of **29** (220 mg, 0.299 mmol) in 12 mL of glacial acetic acid and 1.2 mL of water was stirred at room temperature for 20 h and concentrated. The solid residue was stirred with 5 mL of saturated $NaHCO_3$ and 10 mL of ether for 10 min. The ethereal solution was separated, and the aqueous layer was washed twice with fresh ether. The resulting aqueous layer was acidified with 3 N HCl to pH 3 and extracted with three 10-mL portions of chloroform. The combined extracts were dried ($MgSO_4$) and concentrated to give 127 mg (86%) of tetrazole **30** as a white solid: ^{1}H NMR ($CDCl_3$) δ 0.80 (t, J = 7.25 Hz, 3H), 1.27 (septet, J = 7.7 Hz, 2H), 1.51 (quintet, J = 7.26 Hz, 2H), 2.36 (t, J = 7.66 Hz, 2H), 4.74 (br s, 2H), 5.17 (br s, 2H), 7.02 (br s, 4H), 7.30–7.65 (m, 6H), 7.79 (d, J = 7.25 Hz, 1H), 7.86 (d, J = 7.25 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.43, 21.87, 25.36, 27.34, 44.30, 51.62, 73.80, 126.81, 127.83, 127.87, 128.69, 129.47, 129.52, 130.46, 130.64, 130.73, 133.83, 134.15, 134.91, 138.97, 138.99, 140.50, 147.55, 154.92, 191.96; MS (FAB) m/e (relative intensity) 494 (17), 451 (3), 376 (8), 207 (100); HRMS calcd for M + H 494.2304, found 494.2300.

5-Butyl-2,4-dihydro-4-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-3*H*-1,2,4-triazol-3-one (37). The title compound was prepared by deprotection of **28** according to the procedure described in the preparation of **30**: mp 216–218 °C dec; ^{1}H NMR ($CDCl_3$) δ 0.75 (t, J = 7.3 Hz, 3H), 1.22 (septet, J = 7.7 Hz, 2H), 1.45 (quintet, J = 7.9 Hz, 2H), 2.25 (t, J = 7.8 Hz, 2H), 2.42 (br s, 1H), 4.66 (s, 2H), 6.95–7.10 (m, 4H), 7.28–7.52 (m, 3H), 7.57 (m, 1H), 10.68 (br s, 1H); HPLC retention time 4.14 min (98.6%), eluting with 35% CH_3CN in water, 1.5 mL/min; HRMS calcd for M + H 376.1886, found 376.1928.

5-Butyl-2,4-dihydro-2-ethyl-4-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-3*H*-1,2,4-triazol-3-one (38). The title compound was prepared from **28** and ethyl iodide according to the procedures described in the preparation of **29** and **30**: mp 193–195 °C dec; ^{1}H NMR (CD_3OD) δ 0.87 (t, $J \approx 7.25$ Hz, 3H), 1.20–1.42 (m, 5H), 1.52 (quintet, $J = 7.25$ Hz, 2H), 2.43 (t, $J = 7.66$ Hz, 2H), 3.82 (q, $J = 7.25$ Hz, 2H), 7.12 (d, $J = 8.05$ Hz, 2H), 7.19 (d, $J = 8.05$ Hz, 2H), 7.56 (t, $J = 7.65$ Hz, 2H), 7.68 (d, $J = 7.25$ Hz, 2H); HPLC retention time 7.92 min (94.4%), eluting with 35% CH_3CN in water, 1.5 mL/min; HRMS calcd for M + H 404.2199, found 404.2206.

5-Butyl-2,4-dihydro-4-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-2-propyl-3*H*-1,2,4-triazol-3-one (39). The title compound was prepared from **28** and propyl iodide according to the procedures described in the preparation of **29** and **30**: mp 154–155 °C; ^{1}H NMR (CD_3OD) δ 0.8–1.0 (m with two t at 0.87 and 0.91, $J = 7.25$ Hz, 6H), 1.32 (septet, $J = 7.65$ Hz, 2H), 1.49 (quintet, $J = 7.66$ Hz, 2H), 1.75 (septet, $J = 7.25$ Hz, 2H), 2.44 (t, $J = 7.25$ Hz, 2H), 3.74 (t, $J = 7.25$ Hz, 2H), 7.12 (d, $J = 8.06$ Hz, 2H), 7.18 (d, $J = 8.06$ Hz, 2H), 7.56 (t, $J = 6.85$ Hz, 2H), 7.66 (d, $J = 7.25$ Hz, 2H); HPLC retention time 11.84 min (100%), eluting with 35% CH_3CN in water, 1.5 mL/min; HRMS calcd for M + H 418.2355, found 418.2365.

5-Butyl-2,4-dihydro-2-pentyl-4-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-3*H*-1,2,4-triazol-3-one (40). The title compound was prepared from **28** and 1-iodopentane according to the procedures described in the preparation of **29** and **30**: mp 107.3–109.0 °C; ^{1}H NMR (DMSO-d_6) δ 0.7–0.9 (m, 6H), 1.13–1.32 (m, 6H), 1.41 (quintet, $J = 7.2$ Hz, 2H), 1.61 (quintet, $J = 6.9$ Hz, 2H), 2.37 (t, $J = 7.7$ Hz, 2H), 3.64 (t, $J = 6.8$ Hz, 2H), 4.79 (s, 2H), 7.05 (d, $J = 8.46$ Hz, 2H), 7.11 (d, $J = 8.46$ Hz, 2H), 7.45–7.6 (m, 2H), 7.60–7.7 (m, 2H); MS (FAB) *m/e* (relative intensity) 446 (68), 235 (10), 207 (100), 192 (20), 178 (20); HPLC retention time 7.93 min (95.5%), eluting with 45% CH_3CN in water, 2.0 mL/min; HRMS calcd for M + H 446.2668, found 446.2705.

5-Butyl-2,4-dihydro-2-hexyl-4-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-3*H*-1,2,4-triazol-3-one (41). The title compound was prepared from **28** and iodohexane according to the procedures described in the preparation of **29** and **30**: mp 125.5–126.2 °C; ^{1}H NMR (DMSO-d_6) δ 0.7–0.9 (m, 6H), 1.15–1.32 (m, 8H), 1.41 (q, $J = 7.25$ Hz, 2H), 1.5–1.7 (m, 2H), 2.37 (t, $J = 7.26$ Hz, 2H), 3.64 (t, $J = 6.85$ Hz, 2H), 4.79 (s, 2H), 7.05 (d, $J = 8.06$ Hz, 2H), 7.10 (d, $J = 8.06$ Hz, 2H), 7.45–7.60 (m, 2H), 7.60–7.70 (m, 2H); HPLC retention time 7.94 min (98.4%), eluting with 45% CH_3CN in water, 2.0 mL/min; HRMS calcd for M + H 460.2825, found 460.2820. Anal. ($C_{26}H_{33}N_7O$) C, H, N.

5-Butyl-2,4-dihydro-4-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-2-octyl-3*H*-1,2,4-triazol-3-one (42). The title compound was prepared from **28** and octyl iodide according to the procedures described in the preparation of **29** and **30**: mp 115–117 °C; ^{1}H NMR (CD_3OD) δ 0.8–0.95 (m, 6H), 1.20–1.40 (m, 12H), 1.52 (quintet, $J = 7.26$ Hz, 2H), 1.73 (quintet, $J = 6.85$ Hz, 2H), 2.44 (t, $J = 7.66$ Hz, 2H), 3.77 (t, $J = 6.85$ Hz, 2H), 7.12 (d, $J = 8.05$ Hz, 2H), 7.18 (d, $J = 8.06$ Hz, 2H), 7.55 (t, $J = 9.0$ Hz, 2H), 7.62–7.72 (m, 2H); HPLC retention time 10.48 min (100%), eluting with 55% CH_3CN in water, 1.5 mL/min; HRMS calcd for M + H 488.3138, found 488.3125.

5-Butyl-2,4-dihydro-2-(1-methylethyl)-4-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-3*H*-1,2,4-triazol-3-one (43). The title compound was prepared from **28** and 2-iodopropane according to the procedures described in the preparation of **29** and **30**: mp 185.8–187.7 °C; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, $J = 7.2$ Hz, 3H), 1.22–1.42 [m (with d at 1.29, $J = 6.6$ Hz), 8H], 1.56 (quintet, $J = 7.8$ Hz, 2H), 2.41 (t, $J = 7.8$ Hz, 2H), 4.34 (quintet, $J = 6.6$ Hz, 1H), 4.73 (s, 2H), 7.14 (AB q, $J = 8.4$ Hz, 4H), 7.42 (dd, $J = 7.8$, 1.5 Hz, 1H), 7.48–7.55 (m, 2H), 7.97 (dd, $J = 7.5$, 1.5 Hz, 1H); HPLC retention time 3.28 min (81.9%), eluting with 55% CH_3CN in water, 1.5 mL/min; HRMS calcd for M + H 418.2355, found 418.2379.

5-Butyl-2,4-dihydro-2-(1-methylpropyl)-4-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-3*H*-1,2,4-triazol-3-one (44). The title compound was prepared from **28** and 2-iodobutane according to the procedures described in the preparation of **29** and **30**: mp 192.0–193.2 °C; ^{1}H NMR ($CDCl_3$) δ 0.76 (t, $J = 7.5$ Hz, 3H), 0.87 [m (with d at 1.28, $J = 6.9$ Hz,), 5H], 1.50–1.68 (m, 3H), 1.68–1.85 (m, 1H), 2.42 (t, $J = 7.5$ Hz, 2H), 4.0–4.17 (m, 1H), 4.76 (s, 2H), 7.14 (AB q, $J = 8.4$ Hz, 4H), 7.42 (dd, $J = 7.5$, 1.5 Hz, 1H), 7.49–7.65 (m, 2H), 7.98 (dd, $J = 7.5$, 1.5 Hz, 1H); HPLC retention time 3.67 min (100%), eluting with 55% CH_3CN in water, 1.5 mL/min; HRMS calcd for M + H 432.2512, found 432.2533.

5-Butyl-2,4-dihydro-4-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-2-(3,5,5-trimethylhexyl)-3*H*-1,2,4-triazol-3-one (45). The title compound was prepared from **28** and 1-bromo-3,5,5-trimethylhexane according to the procedures described in the preparation of **29** and **30**: ^{1}H NMR ($CDCl_3$) δ 0.70–0.95 (m, 15H), 1.02 (dd, $J = 13.2$, 5.7 Hz, 1H), 1.16 (dd, $J = 13.2$, 2.8 Hz, 1H), 1.29 (septet, $J = 7.25$ Hz, 2H), 1.35–1.6 (m, 4H), 1.60–1.77 (m, 1H), 2.36 (t, $J = 8.06$ Hz, 2H), 3.55–3.75 (m, 2H), 4.68 (br s, 2H), 7.07 (AB quartet, $J = 7.7$ Hz, 4H), 7.40 (d, $J = 7.7$ Hz, 1H), 7.49 (t, $J = 7.25$ Hz, 1H), 7.57 (t, $J = 7.26$ Hz, 1H), 7.86 (d, $J = 7.25$ Hz, 1H); HPLC retention time 10.72 min (100%), eluting with 55% CH_3CN in water, 1.5 mL/min; MS (FAB) *m/e* (relative intensity) 502 (28), 444 (5), 403 (3), 235 (5), 207 (100), 192 (20), 178 (20); HRMS calcd for M + H 502.3294, found 502.3295.

5-Butyl-2-(cyclopropylmethyl)-2,4-dihydro-4-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-3*H*-1,2,4-triazol-3-one (46). The title compound was prepared from **28** and (bromomethyl)cyclopropane according to the procedures described in the preparation of **29** and **30**: mp 169.0–170.5 °C; ^{1}H NMR (DMSO-d_6) δ 0.28 (q, $J = 4.8$ Hz, 2H), 0.44 (q, $J = 5.6$ Hz, 2H), 0.79 (t, $J = 7.25$ Hz, 3H), 1.00–1.08 (m, 1H), 1.24 (septet, $J = 7.65$ Hz, 2H), 1.42 (quintet, $J = 7.25$ Hz, 2H), 2.39 (t, $J = 7.25$ Hz, 2H), 3.54 (d, $J = 6.9$ Hz, 2H), 4.79 (s, 2H), 7.06 (d, $J = 8.05$ Hz, 2H), 7.12 (d, $J = 8.06$ Hz, 2H), 7.45–7.75 (m, 4H); HPLC retention time 7.92 min (97.6%), eluting with 45% CH_3CN in water, 1.0 mL/min; HRMS calcd for M + H 430.2355, found 430.2395.

5-Butyl-2-(2-cyclohexylethyl)-2,4-dihydro-4-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-3*H*-1,2,4-triazol-3-one (47). The title compound was prepared from **28** and 2-cyclohexylethyl bromide according to the procedures described in the preparation of **29** and **30**: mp 154.0–155.5 °C; ^{1}H NMR (DMSO-d_6) δ 0.77 (t, $J = 7.25$ Hz, 3H), 0.8–0.95 (m, 2H), 1.0–1.3 (m, 6H), 1.3–1.8 (m, 9H), 2.37 (t, $J = 7.65$ Hz, 2H), 3.67 (t, $J = 7.26$ Hz, 2H), 4.79 (s, 2H), 7.07 (d, $J = 8.46$ Hz, 2H), 7.10 (d, $J = 8.46$ Hz, 2H), 7.45–7.60 (m, 2H), 7.60–7.70 (m, 2H); HPLC retention time 17.73 min (96.5%), eluting with 45% CH_3CN in water, 2.0 mL/min; HRMS calcd for M + H 486.2981, found 486.3012.

5-Butyl-2,4-dihydro-2-[2-oxo-2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)ethyl]-4-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4′-yl]methyl]-3*H*-1,2,4-triazol-3-one (48). The title compound was prepared from **28** and 1-adamantyl bromomethyl ketone according to the procedure for the preparation of **30**: mp 128.0–129.0 °C; ^{1}H NMR (DMSO-d_6) δ 0.77 (t, $J = 7.25$ Hz, 3H), 1.22 (m, 2H), 1.38 (quintet, $J = 7.26$ Hz, 2H), 1.67 (br s, 6H), 1.80 (br s, 6H), 1.98 (br s, 3H), 2.37 (t, $J = 7.25$ Hz, 2H), 4.76 (br s, 2H), 4.81 (br s, 2H), 6.87 (d, $J = 8.05$ Hz, 2H), 7.14 (d, $J = 8.06$ Hz, 2H), 7.48–7.60 (m, 2H), 7.60–7.72 (m, 2H); HPLC retention time 6.74 min (100%), eluting with 55% CH_3CN in water, 1.5 mL/min; MS (FAB) *m/e* (relative intensity) 552 (35), 207 (100), 178 (40); HRMS calcd for M + H 552.3087, found 552.3108. Anal. ($C_{32}H_{37}N_7O$) C, H, N.

Ethyl 3-Butyl-4,5-dihydro-5-oxo-4-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1*H*-1,2,4-triazole-1-acetate (49). The title compound was prepared from **28** and ethyl bromoacetate according to the procedures described in the preparation of **29** and **30**: mp 150.0–151.0 °C; ^{1}H NMR (DMSO-d_6) δ 0.77 (t, $J = 7.65$ Hz, 3H), 1.10–1.30 [m (with t at 1.17, $J = 6.85$ Hz), 5H], 1.41 (quintet, $J = 7.25$ Hz, 2H), 2.39 (t, $J = 7.65$ Hz, 2H), 4.12 (q, $J = 6.9$ Hz, 2H), 4.55 (s, 2H), 4.83 (s, 2H), 7.06 (d, $J = 8.06$ Hz, 2H), 7.12 (d, $J = 8.46$ Hz, 2H), 7.45–7.75 (m, 4H); HPLC retention time 3.66 min (95.5%), eluting with 45% CH_3CN in water, 2.0 mL/min; MS (FAB) *m/e* (relative intensity) 462 (85), 446 (10), 235 (15), 207 (100), 192 (18); HRMS calcd for M + H 462.2254, found 462.2277.

3-Butyl-4,5-dihydro-5-oxo-4-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1*H*-1,2,4-triazole-1-acetic Acid (50). A mixture of 170 mg (0.368 mmol) of ethyl ester **49** in 3.4 mL of THF and 3.4 mL of 2 N aqueous lithium hydroxide was stirred at room temperature for 2 h. Volatiles were removed. The aqueous layer was washed with three 4-mL portions of ether and

acidified with 3 N hydrochloric acid to pH 3. The mixture was filtered, and the solid was washed with water. The solid was dried *in vacuo* to give 100 mg of the title compound. The filtrate was extracted with chloroform, dried ($MgSO_4$), concentrated, and triturated with ether to give an additional 50 mg of the title compound as a white solid, with a total yield of 94%: mp 252–254 °C dec; ^1H NMR (DMSO-d_6) δ 0.78 (t, J = 7.25 Hz, 3H), 1.17–1.32 (m, 2H), 1.32–1.50 (m, 2H), 2.39 (t, J = 7.26 Hz, 2H), 4.43 (s, 2H), 4.82 (s, 2H), 7.06 (d, J = 8.06 Hz, 2H), 7.13 (d, J = 8.06 Hz, 2H), 7.45–7.60 (m, 2H), 7.58–7.7 (m, 2H); HPLC retention time 4.15 min (100%), eluting with 35% CH_3CN in water, 1.5 mL/min; MS (FAB) *m/e* (relative intensity) 440 (25), 429 (12); HRMS calcd for M + H 434.1941, found 434.1977.

1,1-Dimethylethyl 3-Butyl-4,5-dihydro-5-oxo-4-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1*H*-1,2,4-triazole-1-acetate (51). The title compound was prepared from **28** and *tert*-butyl bromoacetate according to the procedures described in the preparation of **29** and **30**: mp 185.5–187.5 °C; ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 7.25 Hz, 3H), 1.35 (m, 2H), 1.59 (quintet, J = 7.25 Hz, 2H), 2.43 (t, J = 7.25 Hz, 2H), 4.43 (s, 2H), 4.78 (s, 2H), 7.18 (AB quartet, J = 8.5 Hz, 4H), 7.41 (d, J = 7.7 Hz, 1H), 7.48–7.65 (m, 2H), 8.02 (dd, J = 7.7, 1.2 Hz, 1H); HPLC retention time 18.58 min (92.8%), eluting with 35% CH_3CN in water, 1.0 mL/min; MS (FAB) *m/e* (relative intensity) 496 (39), 440 (60), 412 (45), 397 (25), 235 (22), 207 (100), 192 (40), 178 (60); HRMS calcd for M + H 490.2567, found 490.2598.

Methyl 3-Butyl-4,5-dihydro-5-oxo-4-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1*H*-1,2,4-triazole-1-pentanoate (52). The title compound was prepared from **28** and methyl 5-bromovalerate according to the procedures described in the preparation of **29** and **30**: ^1H NMR ($CDCl_3$) δ 0.89 (t, J = 7.3 Hz, 3H), 1.35 (septet, J = 7.5 Hz, 2H), 1.50–1.68 (m, 4H), 1.75 (quintet, J = 8.04 Hz, 2H), 2.32 (t, J = 7.5 Hz, 2H), 2.42 (t, J = 8.0 Hz, 2H), 3.62 (s, 3H), 3.76 (t, J = 6.8 Hz, 2H), 4.78 (s, 2H), 7.17 (d, J = 7.96 Hz, 2H), 7.22 (d, J = 8.5 Hz, 2H), 7.42 (dd, J = 7.4, 1.5 Hz, 1H), 7.50–7.68 (m, 2H), 8.02 (dd, J = 7.7, 1.2 Hz, 1H); HPLC retention time 4.53 min (90.4%), eluting with 45% CH_3CN in water, 1.5 mL/min; MS (FAB) *m/e* (relative intensity) 490 (20), 430 (8), 235 (8), 207 (100), 192 (30), 178 (50); HRMS calcd for M + H 490.2567, found 490.2570.

3-Butyl-4,5-dihydro-5-oxo-4-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1*H*-1,2,4-triazole-1-pentanoic Acid (53). Via the hydrolysis procedure for the preparation of acid **50**, 80 mg (0.163 mmol) of ester **52** was converted to 74 mg (94%) of the title compound as a white solid: mp 149.5–151 °C; ^1H NMR (DMSO-d_6) δ 0.78 (t, J = 7.25 Hz, 3H), 1.10–1.53 (m, 6H), 1.63 (quintet, J = 8.06 Hz, 2H), 2.22 (t, J = 7.25 Hz, 2H), 2.37 (t, J = 7.66 Hz, 2H), 3.65 (t, J = 6.85 Hz, 2H), 4.79 (s, 2H), 7.06 (d, J = 8.46 Hz, 2H), 7.12 (d, J = 8.06 Hz, 2H), 7.45–7.72 (m, 4H), 11.7–12.3 (br s, 1H); HPLC retention time 3.25 min (90.2%), eluting with 55% CH_3CN in water, 1.5 mL/min; HRMS calcd for M + H 476.2410, found 476.2411.

Ethyl 3-Butyl-4,5-dihydro-5-oxo-4-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1*H*-1,2,4-triazole-1-hexanoate (54). The title compound was prepared from **28** and ethyl 6-bromohexanoate according to the procedures described in the preparation of **29** and **30**: mp 107.3–108.5 °C; ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7.2 Hz, 3H), 1.18–1.37 [m (with t at 1.23, J = 7.2 Hz), 7H], 1.51–1.72 (m, 6H), 2.25 (t, J = 7.5 Hz, 2H), 2.39 (t, J = 7.5 Hz, 2H), 3.69 (t, J = 6.9 Hz, 2H), 4.08 (q, J = 7.2 Hz, 2H), 4.72 (s, 2H), 7.13 (s, 4H), 7.43 (dd, J = 7.5, 1.2 Hz, 1H), 7.49–7.64 (m, 2H), 7.91 (d, J = 6.3 Hz, 1H); HPLC retention time 4.88 min (96.7%), eluting with 50% CH_3CN in water, 1.5 mL/min; MS (FAB) *m/e* (relative intensity) 519 (48), 445 (27), 284 (4), 236 (10), 208 (100); HRMS calcd for M + H 518.2880, found 518.2945.

3-Butyl-4,5-dihydro-5-oxo-4-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1*H*-1,2,4-triazole-1-hexanoic Acid (55). Via the hydrolysis procedure for the preparation of acid **50**, title compound **55** was prepared from ester **54** as a white solid: mp 86.0–88.0 °C; ^1H NMR (CD_3OD) δ 0.73 (t, J = 7.35 Hz, 3H), 1.14–1.29 (m, 4H), 1.32–1.42 (m, 2H), 1.42–1.58 (m, 2H), 1.59–1.71 (m, 2H), 2.14 (t, J = 7.35 Hz, 2H), 2.30 (t, J = 7.65 Hz, 2H), 3.65 (t, J = 6.9 Hz, 2H), 4.75 (s, 2H), 6.96–7.12 (m, 4H), 7.41 (t, J = 7.65 Hz, 2H), 7.48–7.58 (m, 2H), 7.74 (s, 1H); HPLC retention time 3.38 min (94.8%), eluting with 45% CH_3CN in water, 1.5 mL/min; MS (FAB) *m/e* (relative intensity) 490 (15), 444 (30), 235 (11), 207 (100), 178 (36); HRMS calcd for M + H 490.2567, found 490.2602.

2-Benzyl-2,4-dihydro-5-butyl-4-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-3*H*-1,2,4-triazol-3-one (56). The title compound was prepared from **28** and benzyl bromide according to the procedures described in the preparation of **29** and **30**: mp 110.2–113.0 °C; ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7.25 Hz, 3H), 1.34 (septet, J = 7.5 Hz, 2H), 1.58 (quintet, J = 7.6 Hz, 2H), 2.44 (t, J = 7.25 Hz, 2H), 4.81 (s, 2H), 4.91 (s, 2H), 7.19 (s, 4H), 7.22–7.35 (m, 4H), 7.42 (dd, J = 7.7, 1.6 Hz, 1H), 7.48–7.65 (m, 2H), 8.05 (dd, J = 7.7, 1.2 Hz, 1H); HPLC retention time 5.21 min (97.5%), eluting with 45% CH_3CN in water, 2.0 mL/min; HRMS calcd for M + H 466.2355, found 466.2395.

5-Butyl-2,4-dihydro-2-(2-phenylethyl)-4-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-3*H*-1,2,4-triazol-3-one (57). The title compound was prepared from **28** and 2-bromo-1-phenylethane according to the procedures described in the preparation of **29** and **30**: ^1H NMR ($CDCl_3$) δ 0.81 (t, J = 7.34 Hz, 3H), 1.25 (septet, J = 7.66 Hz, 2H), 1.48 (quintet, J = 7.7 Hz, 2H), 2.31 (t, J = 7.25 Hz, 2H), 2.98 (t, J = 7.25 Hz, 2H), 3.95 (t, J = 7.66 Hz, 2H), 4.66 (s, 2H), 6.90 (d, J = 7.7 Hz, 2H), 7.03 (d, J = 8.1 Hz, 2H), 7.08–7.30 (m, 5H), 7.30–7.60 (m, 3H), 7.70 (d, J = 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.44, 21.87, 25.34, 27.68, 34.58, 43.93, 46.03, 126.29, 126.53, 128.23, 128.64, 129.45, 130.46, 130.59, 130.66, 134.92, 137.72, 139.09, 140.84, 146.32, 153.65; HPLC retention time 6.93 min (96.4%), eluting with 45% CH_3CN in water, 1.5 mL/min; HRMS calcd for M + H 480.2512, found 480.2559.

5-Butyl-2,4-dihydro-2-(3-phenylpropyl)-4-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-3*H*-1,2,4-triazol-3-one (58). The title compound was prepared from **28** and 1-bromo-3-phenylpropane according to the procedures described in the preparation of **29** and **30**: mp 153.5–157.0 °C; ^1H NMR ($CDCl_3$) δ 0.82 (t, J = 7.25 Hz, 3H), 1.27 (septet, J = 7.25 Hz, 2H), 1.50 (quintet, J = 7.25 Hz, 2H), 2.01 (quintet, J = 7.25 Hz, 2H), 2.31 (t, J = 7.66 Hz, 2H), 2.59 (t, J = 7.65 Hz, 2H), 3.75 (t, J = 6.85 Hz, 2H), 4.71 (br s, 2H), 6.95–7.30 (m, 9H), 7.30–7.60 (m, 3H), 7.68 (d, J = 7.25 Hz, 1H); HPLC retention time 7.10 min (98.8%), eluting with 50% CH_3CN in water, 1.5 mL/min; MS (FAB) *m/e* (relative intensity) 494 (32), 207 (100), 178 (45); HRMS calcd for M + H 494.2268, found 494.2678.

5-Butyl-2,4-dihydro-2-(3-phenyl-2(*E*)-propenyl)-4-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-3*H*-1,2,4-triazol-3-one (59). The title compound was prepared from **28** and cinnamyl bromide according to the procedures described in the preparation of **29** and **30**: mp 100.0–102.0 °C; ^1H NMR (DMSO-d_6) δ 0.78 (t, J = 7.25 Hz, 3H), 1.24 (septet, J = 7.66 Hz, 2H), 1.42 (quintet, J = 7.65 Hz, 2H), 2.40 (t, J = 7.65 Hz, 2H), 4.46 (d, J = 5.24 Hz, 2H), 4.82 (s, 2H), 6.31 (dt, J = 16.1, 5.6 Hz, 1H), 6.49 (d, J = 16.1 Hz, 1H), 7.07 (d, J = 8.06 Hz, 2H), 7.15 (d, J = 8.06 Hz, 2H), 7.20–7.75 (m, 9H); HPLC retention time 10.03 min (94.7%), eluting with 45% CH_3CN in water, 1.5 mL/min; MS (FAB) *m/e* (relative intensity) 492 (38), 464 (3), 376 (3), 243 (12), 207 (87), 178 (20), 117 (100); HRMS calcd for M + H 492.2512, found 492.2542.

5-Butyl-2,4-dihydro-2-(2-hydroxy-2-phenylethyl)-4-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-3*H*-1,2,4-triazol-3-one (60). To a solution of 400 mg (0.544 mmol) of crude ketone **29** obtained from the preparation of **30** in 4 mL of MeOH and 2 mL of THF at 0 °C was added 25 mg (0.661 mmol) of sodium borohydride in portions. The resulting solution was stirred at 0 °C for 2 h and quenched with saturated ammonium chloride. Volatiles were removed. The aqueous layer was extracted with chloroform, dried ($MgSO_4$), and concentrated to give 380 mg (95%) of the desired alcohol **31**. Via the deprotection procedure described in the preparation of **30**, 200 mg (0.271 mmol) of the alcohol obtained was detritylated, and the resulting solid was recrystallized to give 102 mg (76%) of the title compound as a white solid: mp 89.5–92.5 °C; ^1H NMR (DMSO-d_6) δ 0.77 (t, J = 7.25 Hz, 3H), 1.10–1.28 (m, 2H), 1.28–1.45 (m, 2H), 2.34 (t, J = 7.65 Hz, 2H), 3.73 (dd, J = 13.7, 6.0 Hz, 1H), 3.85 (dd, J = 13.7, 7.7 Hz, 1H), 4.74 (br s, 2H), 4.88 (q, J = 6 Hz, 1H), 5.54 (d, J = 4.8 Hz, 1H), 6.97 (d, J = 8.1 Hz, 2H), 7.04 (d, J = 8.4 Hz, 2H), 7.10–7.40 (m, 5H), 7.45–7.60 (m, 2H), 7.60–7.70 (m, 2H); HPLC retention time 7.66 min (84.1%), eluting with 35% CH_3CN in water, 1.0 mL/min; MS (FAB) *m/e* (relative intensity) 496 (5),

478 (12), 435 (3), 207 (100); HRMS calcd for M + H 496.2461, found 496.2501. Anal. ($C_{28}H_{29}N_7O_2$) C, H, N.

5-Butyl-2,4-dihydro-2-(1-naphthalenylmethyl)-4-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-3*H*-1,2,4-triazol-3-one (61). The title compound was prepared from **28** and 1-(bromomethyl)naphthalene according to the procedures described in the preparation of **29** and **30**: mp 144.0–146.0 °C; ^{1}H NMR (DMSO-d_6) δ 0.73 (t, J = 7.25 Hz, 3H), 1.1–1.25 (m, 2H), 1.25–1.4 (m, 2H), 2.34 (t, J = 7.66 Hz, 2H), 4.84 (s, 2H), 5.31 (s, 2H), 7.05 (d, J = 8.46 Hz, 2H), 7.12 (d, J = 7.06 Hz, 2H), 7.36 (d, J = 6.45 Hz, 1H), 7.40–7.65 (m, 7H), 7.80–8.0 (m, 2H), 8.18–8.3 (m, 1H); HPLC retention time 9.66 min (94.6%), eluting with 45% CH_3CN in water, 1.5 mL/min; HRMS calcd for M + H 516.2512, found 516.2534.

5-Butyl-2,4-dihydro-2-(2-naphthalenylmethyl)-4-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-3*H*-1,2,4-triazol-3-one (62). The title compound was prepared from **28** and 2-(bromomethyl)naphthalene according to the procedures described in the preparation of **29** and **30**: ^{1}H NMR ($CDCl_3$) δ 0.81 (t, J = 7.25 Hz, 3H), 1.27 (septet, J = 7.25 Hz, 2H), 1.50 (quintet, J = 8.06 Hz, 2H), 2.34 (t, J = 7.25 Hz, 2H), 4.69 (s, 2H), 5.04 (s, 2H), 6.95–7.10 (m, 4H), 7.30–7.60 (m, 7H), 7.55–7.8 (m, 5H); HPLC retention time 12.72 min (94.8%), eluting with 45% CH_3CN in water, 1.5 mL/min; MS (FAB) *m/e* (relative intensity) 516 (25), 326 (30), 242 (25), 207 (100), 192 (30), 178 (35), 141 (100); HRMS calcd for M + H 516.2512, found 516.2455.

5-Butyl-2,4-dihydro-2-[2-(2,5-dimethoxyphenyl)-2-oxoethyl]-4-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-3*H*-1,2,4-triazol-3-one (63). The title compound was prepared from **28** and 2,5-dimethoxyphenacyl bromide according to the procedures described in the preparation of **29** and **30**: ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 7.65 Hz, 3H), 1.32 (septet, J = 7.65 Hz, 2H), 1.58 (quintet, J = 7.65 Hz, 2H), 2.41 (t, J = 8.06 Hz, 2H), 3.75 (s, 3H), 3.90 (s, 3H), 4.82 (s, 2H), 5.15 (s, 2H), 6.92 (d, J = 9.27 Hz, 1H), 7.09 (dd, J = 8.87, 3.2 Hz, 1H), 7.15 (d, J = 8.06 Hz, 2H), 7.21 (d, J = 8.06 Hz, 2H), 7.33–7.6 (m, 4H), 7.92 (dd, J = 8.06, 1.2 Hz, 1H); HPLC retention time 7.15 min (98.8%), eluting with 45% CH_3CN in water, 1.5 mL/min; MS (FAB) *m/e* (relative intensity) 576 (13), 554 (38), 207 (100), 165 (63); HRMS calcd for M + H 554.2516, found 554.2567.

5-Butyl-2,4-dihydro-2-[2-(2,5-dimethoxyphenyl)-2-hydroxyethyl]-4-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-3*H*-1,2,4-triazol-3-one (64). The title compound was prepared from ketone **63** according to the procedure described for the preparation of **60**: ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7.4 Hz, 3H), 1.25–1.42 (m, 2H), 1.50–1.63 (m, 2H), 2.42 (t, J = 7.4 Hz, 2H), 3.67 (s, 3H), 3.81 (s, 3H), 4.0–4.25 (m, 2H), 4.76 (s, 2H), 5.13–5.25 (m, 1H), 6.70–6.83 (m, 2H), 6.92–7.00 (m, 1H), 7.05–7.20 (m, 4H), 7.35–7.43 (m, 1H), 7.45–7.65 (m, 2H), 7.96–8.08 (m, 1H); MS (FAB) *m/e* (relative intensity) 578 (35), 538 (90), 510 (3), 495 (6), 235 (12), 207 (100), 192 (30), 178 (30); HRMS calcd for M + H 556.2672, found 556.2691.

Ethyl [2-[3-Butyl-4,5-dihydro-5-oxo-4-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1*H*-1,2,4-triazol-1-yl]-1-phenylethoxy]acetate (33). To a solution of 160 mg (0.217 mmol) of alcohol **31** obtained from the preparation of **60** in 4 mL of dry THF was added 18 mg (0.45 mmol) of sodium hydride (60% in oil) in one portion, and the resulting suspension was stirred at room temperature for 10 min. After gas evolution has ceased, 76 μL (0.866 mmol) of ethyl bromoacetate was added. The resulting solution was stirred at room temperature for 4 h and quenched with saturated ammonium chloride. The mixture was concentrated, dissolved in chloroform, and washed with water. The aqueous layer was extracted with three 10-mL portions of chloroform, and the combined extracts were dried ($MgSO_4$) and concentrated. Via the deprotection procedure described in the preparation of **30**, the trityl group was removed to give 105 mg (83%) of the title compound as a white solid: ^{1}H NMR (DMSO-d_6) δ 0.75 (t, J = 7.66 Hz, 3H), 1.06–1.46 [m (with t at 1.12, J = 7.25 Hz), 7H], 2.31 (t, J = 7.65 Hz, 2H), 3.70–4.20 (m, 5H), 4.73 (s, 2H), 4.82 (d, J = 6.9 Hz, 1H), 6.91 (d, J = 8.05 Hz, 2H), 6.95–7.20 [m (with d at 7.01, J = 8.06 Hz), 3H], 7.20–7.40 (m, 5H), 7.45–7.75 (m, 4H); HPLC retention time 4.19 min (88%), eluting with 55% CH_3CN in water, 1.5 mL/min; MS (FAB) *m/e* (relative intensity) 582 (10), 478 (18), 235 (15), 207 (100), 192 (48), 178 (28); HRMS calcd for M + H 582.2829, found 582.2832.

[2-[3-Butyl-4,5-dihydro-5-oxo-4-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1*H*-1,2,4-triazol-1-yl]-1-phenylethoxy]acetic Acid (34). Via the hydrolysis procedure described for the preparation of **50**, 80 mg (0.138 mmol) of ester **33** was converted to 72 mg (94%) of the title compound as a white solid: mp 83–89 °C dec; ^{1}H NMR (DMSO-d_6) δ 0.75 (t, J = 7.26 Hz, 3H), 1.08–1.48 (m, 4H), 2.30 (t, J = 8.05 Hz, 2H), 3.70–4.15 (m, 4H), 4.65–4.90 [m (with s at 4.71), 3H], 6.88 (d, J = 8.06 Hz, 2H), 6.95–7.18 [m (with d at 7.01, J = 8.46 Hz), 3H], 7.20–7.40 (m, 5H), 7.45–7.75 (m, 4H); MS (FAB) *m/e* (relative intensity) 554 (8), 478 (12), 450 (5), 235 (10), 207 (100), 192 (30), 178 (25); HRMS calcd for M + H 554.2516, found 554.2536.

5-Butyl-2,4-dihydro-2-[2-phenyl-2-methoxyethyl]-4-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-3*H*-1,2,4-triazol-3-one (65). The title compound was prepared from **31** and iodomethane according to the procedure described in the preparation of **33**: mp 99.0–103.0 °C; ^{1}H NMR ($CDCl_3$) δ 0.9 (t, J = 7.5 Hz, 3H), 1.20–1.40 (m, 2H), 1.42–1.64 (m, 2H), 2.40 (t, J = 7.5 Hz, 2H), 3.16 (s, 3H), 3.76–3.85 (dd, J = 3.1, 14.7 Hz, 1H), 4.03–4.17 (dd, J = 9.2, 13.5 Hz, 1H), 4.56 (m, 1H), 4.79 (s, 2H), 7.05–7.40 (m, 10H), 7.40–7.48 (d, J = 6.1 Hz, 1H), 7.50–7.68 (m, 2H), 8.07 (d, J = 7.5 Hz, 1H); HPLC retention time 6.92 min (91.0%), eluting with 50% CH_3CN in water, 2.0 mL/min; MS (FAB) *m/e* (relative intensity) 532 (84), 510 (45), 478 (28), 207 (78), 121 (100); HRMS calcd for M + H 510.2617, found 510.2629.

5-Butyl-2,4-dihydro-2-(2-phenyl-2-ethexyethyl)-4-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-3*H*-1,2,4-triazol-3-one (66). The title compound was prepared from **31** and iodoethane according to the procedure described in the preparation of **33**: mp 77.0–81.0 °C; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 7.8 Hz, 3H), 1.05 (t, J = 7.8 Hz, 3H), 1.34 (septet, J = 8.3 Hz, 2H), 1.56 (quintet, J = 8.3 Hz, 2H), 2.42 (t, J = 7.8 Hz, 2H), 3.2–3.3 (m, 1H), 3.33–3.45 (m, 1H), 3.82 (dd, J = 13.5, 4.8 Hz, 1H), 4.06 (dd, J = 13.6, 8.3 Hz, 1H), 4.69 (dd, J = 9.4, 5.8 Hz, 1H), 4.75 (s, 2H), 7.07 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 7.28 (s, 5H), 7.42 (d, J = 7.9 Hz, 1H), 7.5–7.64 (m, 2H), 8.06 (d, J = 7.9 Hz, 1H); HPLC retention time 8.47 min (99.2%), eluting with 50% CH_3CN in water, 2.0 mL/min; MS (FAB) *m/e* (relative intensity) 546 (15), 524 (100), 478 (42), 207 (88), 135 (91); HRMS calcd for M + H 524.2774, found 524.2783.

5-Butyl-2,4-dihydro-2-(2-phenyl-2-propoxyethyl)-4-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-3*H*-1,2,4-triazol-3-one (67). The title compound was prepared from **31** and iodopropane according to the procedure described in the preparation of **33**: ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 7.6 Hz, 3H), 0.89 (t, J = 7.6 Hz, 3H), 1.25–1.60 (m, 6H), 2.39 (t, J = 7.5 Hz, 2H), 3.06–3.18 (m, 1H), 3.24–3.32 (m, 1H), 3.77 (dd, J = 15, 5.4 Hz, 1H), 4.03 (dd, J = 15, 9.6 Hz, 1H), 4.65 (dd, J = 9.7, 5.1 Hz, 1H), 4.74 (d, J = 4.1 Hz, 2H), 7.06 (d, J = 9.2 Hz, 2H), 7.15 (d, J = 9.2 Hz, 2H), 7.28 (s, 5H), 7.42 (d, J = 7.7 Hz, 1H), 7.5–7.64 (m, 2H), 8.01 (d, J = 7.7 Hz, 1H); MS (FAB) *m/e* (relative intensity) 538 (11), 478 (18), 235 (13), 207 (100), 192 (26); HRMS calcd for M + H 538.2930, found 538.2951.

5-Butyl-2,4-dihydro-2-[2-phenyl-2-(phenylmethoxy)ethyl]-4-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-3*H*-1,2,4-triazol-3-one (68). The title compound was prepared according to the procedure described for the preparation of **33**: mp 211–213 °C dec; ^{1}H NMR (DMSO-d_6) δ 0.75 (t, J = 7.25 Hz, 3H), 1.10–1.38 (m, 2H), 1.35 (quintet, J = 7.66 Hz, 2H), 2.34 (t, J = 7.65 Hz, 2H), 3.77 (dd, J = 14.1, 5.44 Hz, 1H), 4.03 (dd, J = 13.7, 8.46 Hz, 1H), 4.21 (d, J = 12.1 Hz, 1H), 4.39 (d, J = 12.1 Hz, 1H), 4.70–4.82 [m (with s at 4.76), 4H], 6.99 (br s, 4H), 7.10–7.43 (m, 10H), 7.43–7.72 (m, 4H); HPLC retention time 7.14 min (100%), eluting with 55% CH_3CN in water, 1.5 mL/min; MS (FAB) *m/e* (relative intensity) 586, 478 (18), 243 (100), 207 (88); HRMS calcd for M + H 586.2930, found 586.2979.

2-(1-Benzoyl-1-methylethyl)-5-butyl-2,4-dihydro-4-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-3*H*-1,2,4-triazol-3-one (69). Via the procedure for the preparation of **30**, 100 mg (0.162 mmol) of triazolone **28** in 2 mL of DMF was reacted with 0.2 mmol of potassium *tert*-butoxide in THF and 41 μL (0.24 mmol) of 2-bromo isobutyrophenone. TLC analysis indicated that the reaction was not complete. To the reaction mixture was added 15 mg (0.38 mmol) of sodium hydride (60% in oil), and the resulting mixture was stirred at 25 °C for 2 h. The mixture was concentrated and chromatographed over silica gel (eluting with EtOAc/hexane) to give 30 mg (24%) of the trityl protected

product: ^{1}H NMR ($CDCl_3$) δ 0.84 (t, J = 7.31 Hz, 3H), 1.18–1.32 (m, 2H), 1.47 (quintet, J = 7.46 Hz, 2H), 1.90 (s, 6H), 2.29 (t, J = 7.7 Hz, 2H), 4.55 (s, 2H), 6.59 (d, J = 8.2 Hz, 2H), 6.89 (d, J = 7.7 Hz, 6H), 6.97 (d, J = 8.08 Hz, 2H), 7.15–7.48 (m, 12H), 7.48–7.55 (m, 3H), 7.78 (d, J = 7.2 Hz, 2H), 7.90–7.98 (m, 1H).

The alkylated product was deprotected by following the deprotection procedure described in the preparation of **30**, and the crude product was recrystallized to give 16 mg (80%) of the title compound as a white solid: mp 94.5–95.8 °C; ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 7.25 Hz, 3H), 1.30 (septet, J = 7.6 Hz, 2H), 1.62 (quintet, J = 7.25 Hz, 2H), 1.78 (s, 6H), 2.39 (t, J = 8.05 Hz, 2H), 4.50 (s, 2H), 6.55 (d, J = 8.06 Hz, 2H), 6.87 (d, J = 8.06 Hz, 2H), 7.15–7.30 (m, 2H), 7.30–7.42 (m, 2H), 7.45–7.70 (m, 4H), 7.85–7.95 (m, 1H); HPLC retention time 10.58 min (98.4%), eluting with 45% CH_3CN in water, 1.5 mL/min; MS (FAB) *m/e* (relative intensity) 544 (20), 522 (20), 416 (5), 235 (5), 207 (100), 192 (45), 178 (30); HRMS calcd for M + H 522.2617, found 522.2658.

2-(1-Benzoyl-2-phenylethyl)-5-butyl-2,4-dihydro-4-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-3*H*-1,2,4-triazol-3-one (36). To a solution of 0.24 mL (0.36 mmol) of lithium diisopropylamide (1.5 M in THF, Aldrich) at −20 °C was added a solution of 105 mg (0.143 mmol) of ketone **29** (obtained from the preparation of **30**) in 2.5 mL of dry THF via cannula. The resulting solution was stirred cold for 10 min. To the solution was added 25 μL (0.21 mmol) of benzyl bromide, and the resulting solution was stirred at room temperature for 2 h. The reaction was quenched with ammonium chloride, evaporated, and worked up with water and methylene chloride. The crude was chromatographed over silica gel, eluting with EtOAc/hexane, to give 106 mg (90%) of the trityl-protected desired product. Via the deprotection procedure described in the preparation of **30**, the alkylated product was deprotected to give 60 mg (80%) of the title compound as a white solid: ^{1}H NMR ($CDCl_3$) δ 0.75 (t, J = 7.05 Hz, 3H), 1.00–1.51 (m, 4H), 1.83–2.00 (m, 1H), 2.00–2.20 (m, 1H), 3.36 (dd, J = 13.3, 4.4 Hz, 1H), 3.85 (t, J = 12.9 Hz, 1H), 4.99 (dd, J = 10.9, 3.6 Hz, 1H), 5.11 (AB quartet, J = 17.7 Hz, 2H), 7.0–7.7 (m, 14H), 7.90 (d, J = 7.26 Hz, 4H); HPLC retention time 6.71 min (100%), eluting with 55% CH_3CN in water, 1.5 mL/min; MS (FAB) *m/e* (relative intensity) 584 (15), 325 (60), 260 (100), 207 (10); HRMS calcd for M + H 584.2774, found 584.2794.

Ethyl 3-Benzoyl-3-[3-butyl-4,5-dihydro-5-oxo-4-[[2′-(1*H*-tetrazol-5-yl)-1,1′-biphenyl]-4-yl]methyl]-1*H*-1,2,4-triazolyl]-1-propanoate (70). The title compound was prepared according to the procedure described for the preparation of **36**: ^{1}H NMR (DMSO-d_6) δ 0.66 (t, J = 7.3 Hz, 3H), 0.86 (quintet, J = 7.0 Hz, 2H), 1.05 (septet, J = 7.2 Hz, 2H), 1.15 (t, J = 6.73 Hz, 3H), 2.27 (t, J = 7.2 Hz, 2H), 2.95 (dd, J = 16.3, 6.9 Hz, 1H), 3.14 (dd, J = 16.3, 7.2 Hz, 1H), 4.05 (q, J = 6.8 Hz, 2H), 4.79 (s, 2H), 6.00 (t, J = 7.3 Hz, 1H), 6.84 (d, J = 8.2 Hz, 2H), 6.99 (d, J = 8.0 Hz, 2H), 7.15–7.40 (m, 3H), 7.40–7.80 (m, 4H), 7.88 (d, J = 8.0 Hz, 2H); HPLC retention time 4.56 min (96.3%), eluting with 55% CH_3CN in water, 1.5 mL/min; HRMS calcd for M + H 580.2672, found 580.2714

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