EJ52-1999-53

Journal of the Chinese Chemical Society, **1999**, *46*, 53-62

The Syntheses of Triazinone and Pyrimidinone Biphenyltetrazoles as Angiotensin II Receptor Antagonists

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A series of biphenylyltetrazole substituted triazinones and structure-related pyrimidinones are systhesized, and their binding affinities for angiotensin II receptor are reported.

INTRODUCTION

Since the discovery of losartan (DuP 753, MK954, brand name: Cozaar),[1] the leading non-pepetide AT_1 (angiotensin II subtype 1) antagonist (Fig. 1), several highly potent AT_1 selective antagonists bearing heterocycles have been reported.[2] The tetrazole group is a common acidic function present in many of these antagonists. Recently, 1,2,4-oxadiazinone biphenyltetrazoles,[3] pyrimidinone biphenyltetrazoles,[4] 3*H*-dihydropyrimidinone biphenyltetrazoles,[5] and pyridone biphenyltetrazoles have been reported to be potent antagonists.[6] In our preliminary search for their structural analogs, we found that a series of 1,2,4-triazinone biphenyltetrazoles show high potencies in the *in vitro* binding assay. For comparative study, a series of structure-related pyrimidinone biphenyltetrazoles were also prepared and evaluated.[7]

RESULTS AND DISCUSSION

I. Synthesis

1) Triazinone Derivatives (Scheme I)

Treatment of an ice-cooled ethanolic free base **1** with formyl hydrazide gave formyl hydrazidine **2**. Compound **2** was heated with methyl pyruvate in isopropanol to give the intramolecular cyclization product **3** and the desired triazinone **4**. Similar treatment of **2** with 2-oxo-arylcarboxylic acids in DMF in the presence of *p*-TSA·H_2O gave **3** and the triazinones **5** (or **6**). The deformylation and triazinone ring formation were accomplished in an one-pot manner. The yield of **6** was greatly improved (11 to 45%) if *p*-TSA·H_2O was increased from 30 to 100 mole %. In the latter case, all of the basic NH moiety might be protonated by *p*-TSA, which is not suitable for the intramolecular ring formation. Alkylation of the triazinones **4**, **5** or **6** with *N*-(triphenylmethyl)-5-[4′-(bromomethyl)-biphenyl-2-yl]tetrazole **7** using Cs_2CO_3 as a base gave a mixture of *N*-alkylation products **8-13** and *O*-alkylation products (not shown). Separation of the *N*-alkylation products, followed by deprotection, gave triazinone biphenyltetrazoles **14-19**. The structures of the *N*(2)- and *N*(4)-alkylation products were determined by the HMBC spectra. As shown in Table 1, the correlation between the NCH_2 protons (H-7) and C(O) carbon (C-5) was observed in the *N*(4)-alkylation products (**14**, **16** and **18**) but not in the *N*(2)-alkylation products (**15**, **17**, or **19**).

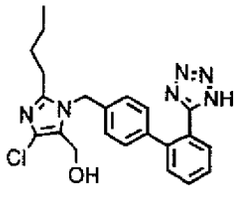


Fig. 1. Losartan, an angiotensin II antagonist.

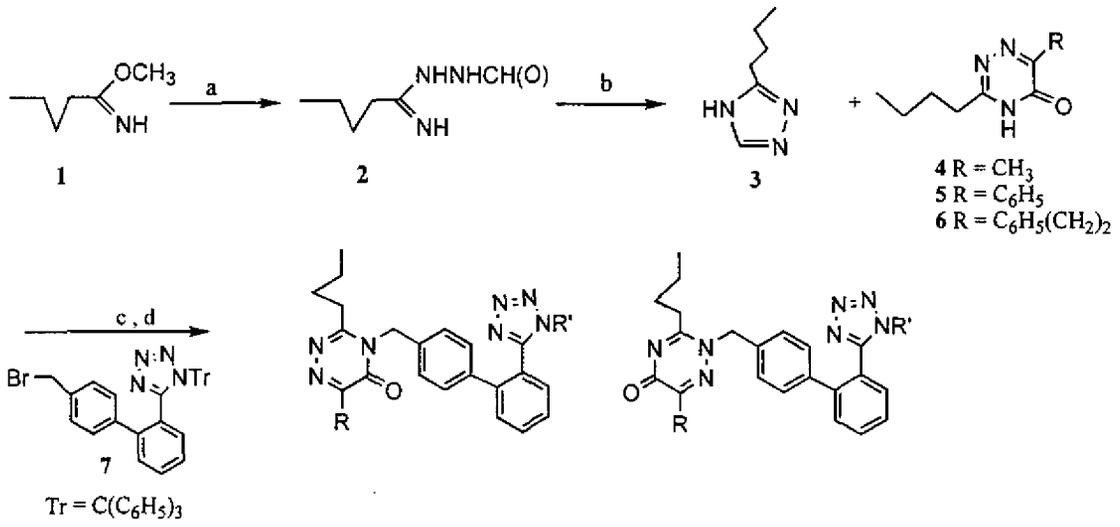
2) Pyrimidinone Derivatives (Scheme II)

Three types of pyrimidinones were prepared as follows:

(i) 2-Butyl-5-phenethyl-6-*O*-substituted Pyrimidinones: Condensation of the amidine hydrochloride **20** with dimethyl 2-phenethylmalonate **21** gave the pyrimidinone **22**, which was alkylated by Me_2SO_4 or Et_2SO_4 in DMF under basic condition to give pyrimidinones **23** and **24**. Treatment of **22** with NaH, followed by $MeSO_2Cl$ or $(EtO)_2P(O)Cl$, gave **25** and **26** respectively.

* Abstract Published in 5th Pacific Rim Biotechnology Conference & BioExpo' 96 Abstracts, November 13, 1996

Scheme I



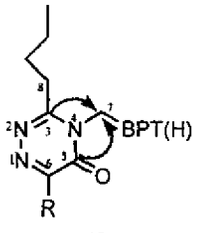
a. $NH_2NHCH(O)$ / EtOH b. $CH_3C(O)CO_2CH_3$ / *i*-PrOH , reflux or $RC(O)CO_2H$ / DMF, *p*-TSA (100 mole %), reflux (R= C_6H_5 or $C_6H_5(CH_2)_2$) c. Cs_2CO_3 / DMF, **7** d. 10 % HCl , THF

(ii) 2-Butyl-6-substituted-pyrimidinones: Condensation of **20** with β-ketoesters **31-34** using sodium ethoxide as the base gave the pyrimidinones **35-38**.[8]

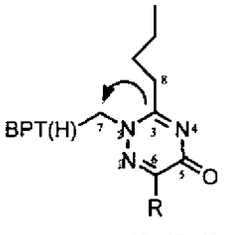
(iii) 2-Butyl-5-phenethyl-6-chloropyrimidinones and 2-butyl-5-phenethylpyrimidinones: Chlorination of **22** with phosphoryl chloride gave 2-butyl-5-phenethyl-4,6-dichloropyrimidine, which was partially hydrolyzed with sodium hydroxide in dioxane/water (2.5/1, v/v) to give **43**. Removal of the chlorine atom of **43** by hydrogenolysis gave **44**.

The biphenyltetrazole derivatives **27-30**, **39-42**, and **45-46** were prepared by alkylation with **7** according to the same method as that for triazinones.[9] It should be noted that **30** was prepared from the diphosphorylated pyrimidine **26** rather the monophosphorylated pyrimidinone. Thus the dephosphorylation and alkylation were accomplished in an one-pot manner.

Table 1. Selected Long Range ^1H-^{13}C Coupling Correlation of *N*-alkylation Products



14 , 16 , 18



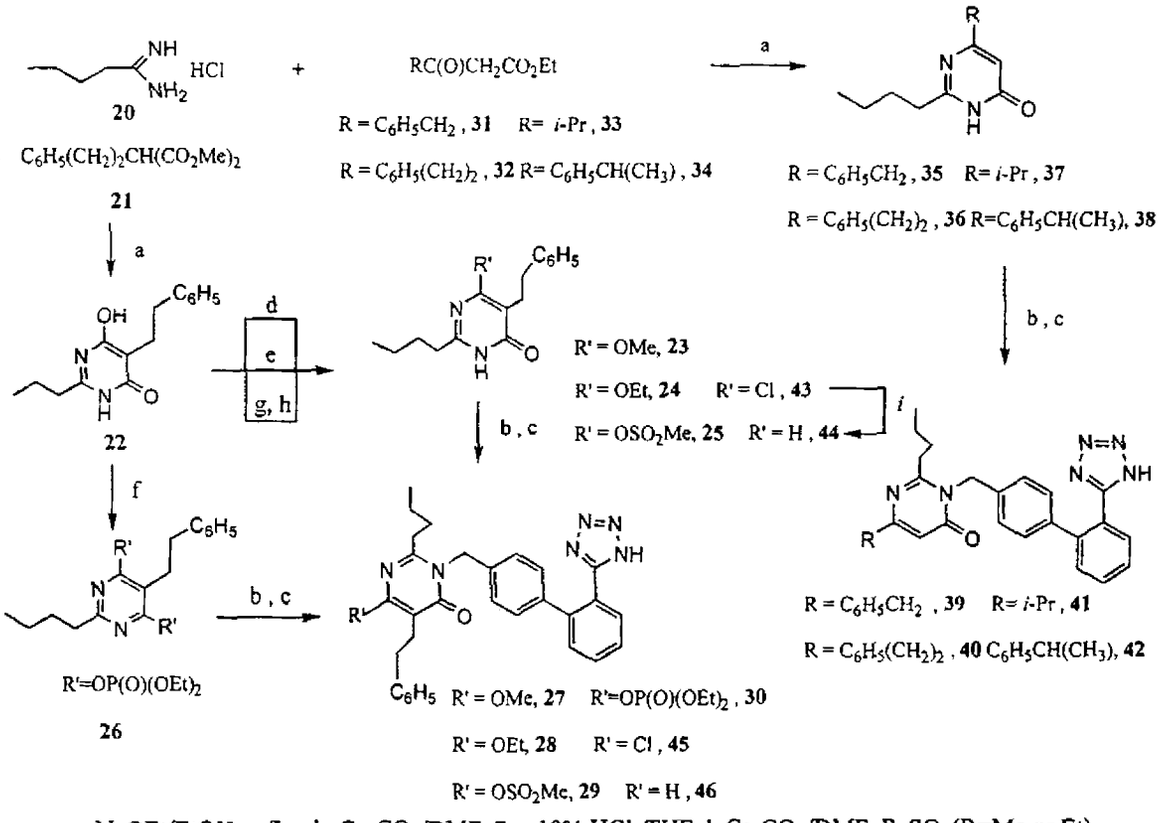
15 , 17 , 19

Compound	H*	δ/ppm	C*	δ/ppm	long rang correlation (H*)
14	H-7	5.18	C-5	153.7	$^3J_{C\text{-}H(H\text{-}7)}$
			C-3	157.2	$^3J_{C\text{-}H(H\text{-}7)}$
15	H-7	5.22	C-3	164.6	$^3J_{C\text{-}H(H\text{-}7)}$
16	H-7	5.20	C-5	152.6	$^3J_{C\text{-}H(H\text{-}7)}$
			C-3	157.2	$^3J_{C\text{-}H(H\text{-}7)}$
17	H-7	5.20	C-3	163.4	$^3J_{C\text{-}H(H\text{-}7)}$
18	H-7	5.18	C-5	153.2	$^3J_{C\text{-}H(H\text{-}7)}$
			C-3	157.2	$^3J_{C\text{-}H(H\text{-}7)}$
19	H-7	5.14	C-3	164.2	$^3J_{C\text{-}H(H\text{-}7)}$

II. Bioassays

The triazinone and pyrimidinone derivatives were evaluated by the conventional radioligand binding assay, based on displacement of monoiodinated angiotensin II from a membrane prepared from guinea pig adrenal glands and losartan employed as the positive standard compound.[12] The data of *in vitro* assays for these compounds are listed in Table 2.

Scheme II



a. NaOEt/EtOH, reflux b. Cs_2CO_3/DMF, 7 c. 10% HCl, THF d. Cs_2CO_3/DMF, R_2SO_4(R=Me or Et)
e. NaH/THF, $ClSO_2Me$ f. NaH/THF, $ClP(O)(OEt)_2$ g. $POCl_3$, reflux h. NaOH/dioxane/water, reflux
i. H_2/Pd on C, EtOH/NH_4OH

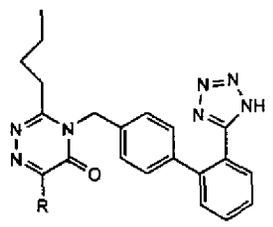
From entries 1-6, the phenethyl substituted triazinone **18** and **19** shows better potencies than other derivatives **14**, **15**, **16** or **17** with methyl or phenyl substituents. The potency appeared to be insensitive to the orientation of (2′-tetrazolebiphenyl-4-yl)methyl side chain (i.e. *N*(4) -or *N*(2)-isomers). Pyrimidinones **27-29** with 5-phenethyl-6-*O*-alkyl or 6-*O*-sulfonyl substituents showed low potencies (entries 7-9). However, 5-phenethyl-6-*O*-phosphorylpyrimidinone **30** exhibited a better potency (entry 10). The alkylpyrimidinone derivatives **39-41** showed good potencies (entries 11-13) except compound **42** (entry 14). By comparison of entries 11 and 14, a branching at the α-position of the phenyl group (compound **42**) adversely decreased the potency. As shown in entries 15 and 16, 5-phenethyl-6-chloro- and 5-phenethyl pyrimidinones **45** and **46** showed medium to excellent potencies. By comparison of entries 3 and 16, replacement of the carbon atom in pyrimidinone **46** by an N(1) atom in triazinone **18** seemed not to affect the *in vitro* potency.

In conclusion, the antagonists listed in Table 2 could be divided into two classes. The first class having a phenethyl group at the 5-position of pyrimidinone ring or at the 6-position of triazinone ring shows medium to excellent potency. The second class having an alkyl, benzyl or phenethyl substituent at the 6-position of pyrimidinone ring shows good to excellent except the one with an α-branched benzyl substituent. Among these compounds, pyrimidinone **46** shows the best potency (IC_{50} = 16.4 nM). A lipophilic pocket to accept the 6-substituents of triazinones or 5- and 6-substituents of the pyrimidinones seems to play an important role in receptor binding. The phenethyl group appers to be a substituent of choice for this binding.

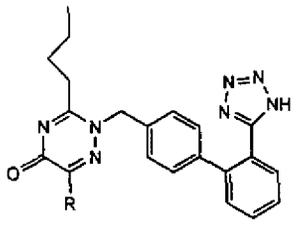
III. Molecular Modeling

The potent triazinone **18** and pyrimidinone **40** were selected for a comparative conformational study with that of losartan (Figs. 2 and 3). The conformational analyses were carried out by using geometry optimization, followed by "random search" of conformations within SYBYL.[10] The MOPAC program was used for geometry optimization.[11] Comparison of the calculated minimum energy conformations of these molecules, in terms of overlap of the

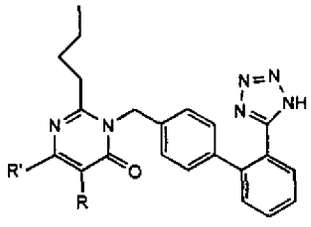
Table 2.



(Entries 1-3)



(Entries 4-6)



(Entries 7-16)

Entry	Compound	R	R′	*in vitro* (IC_{50} nM)
1	**14**	CH_3	–	309.5*
2	**16**	C_6H_5	–	62.6*
3	**18**	$C_6H_5(CH_2)_2$	–	55.1
4	**15**	CH_3	–	>400
5	**17**	C_6H_5	–	336.3
6	**19**	$C_6H_5(CH_2)_2$	–	67.5
7	**27**	$C_6H_5(CH_2)_2$	OMe	314.2*
8	**28**	$C_6H_5(CH_2)_2$	OEt	>400
9	**29**	$C_6H_5(CH_2)_2$	OSO_2Me	393.9
10	**30**	$C_6H_5(CH_2)_2$	$OP(O)(OEt)_2$	72.1*
11	**39**	H	$C_6H_5CH_2$	59.4
12	**40**	H	$C_6H_5(CH_2)_2$	33.2
13	**41**	H	*i*-Pr	44.6
14	**42**	H	$C_6H_5CH(CH_3)$	>400
15	**45**	$C_6H_5(CH_2)_2$	Cl	71.7*
16	**46**	$C_6H_5(CH_2)_2$	H	16.4
17	**losartan**	–	–	26.2

* Represents estimated IC_{50} value. Estimated IC_{50} was calculated from a mathematical equation which was derived from the relationship between experimemtal IC_{50} vs. binding affinity among the same series of analogs. Each compound was characterized by ^1H NMR, MS, HRMS, and/or HMBC spectrum.

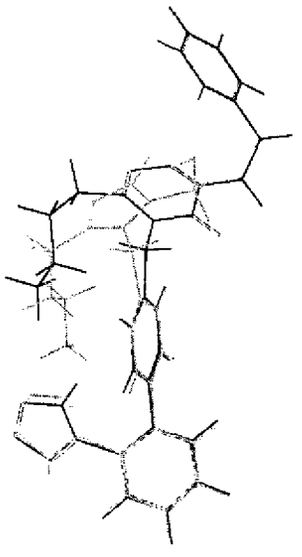


Fig. 2. Possible overlap of low energy structures for **18** (dark) and losartan.

biphenyltetrazoles, demonstrated that these molecules were able to mimic each other to a reasonable extent. It also indi-

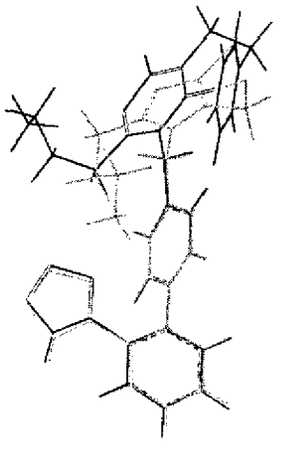


Fig. 3. Possible overlap of low energy structures for **40** (dark) and losartan.

cated that there is some room available for the surrounding of the C-5 position of the pyrimidinone ring or the C-6 position of the triazinone ring.

EXPERIMENTAL SECTION

Melting points are uncorrected. Infrared spectra were measured on a Perkin-Elmer 577 spectrometer. ^{1}H NMR spectra were recorded on AC-200 (200 MHz). ^{13}C NMR and HMBC spectra were recorded on DRX-500 (500 MHz). Mass spectra were collected on a JEOL-JMS-D100 instrument. Exact masses were measured by JEOL-JMSD-HX100 high resolution mass spectrometer.

Valeroyl-*N*-formyl Hydrazidine (2)

To an ice-cooled imidate free base **1** (1.15 g, 0.01 mol) in ethanol (10 mL) was added formyl hydrazide (0.60 g, 0.01 mol). The mixture was stirred for 3 h at room temperature and filtered to give **2** (0.69 g) as the first crop. The mother liquid was cooled in an ice-bath overnight and the precipitate was collected by filtration to give **2** (0.59 g) as the second crop. The overall yield of **2** is 1.28 g (88%). ^{1}H NMR (DMSO-d_6) δ 8.05 (s, 2H), 5.86 (br s, 1H), 2.20-2.03 (m, 2H), 1.65-1.57 (m, 2H), 1.54-1.24 (m, 2H), 0.91 (t, J = 7.2 Hz, 3H).

3-Butyl-1,2,4-triazole (3) and 3-Butyl-6-methyl-4*H*-[1,2,4]triazin-5-one (4)

To a solution of formyl hydrazidine (0.50 g, 3.50 mmol) in isopropanol (20 mL) was added a solution of methyl pyruvate (0.38 g, 4.35 mmol) in isopropanol (10 mL) dropwise. The mixture was stirred at room temperature for 4 h and refluxed for 12 h. The volatiles were evaporated under reduced pressure. The crude product was purified by silica gel column chromatography using ethyl acetate/hexane (1:2) as eluent to give **3** (0.25 g, 53%) and **4** (0.08 g, 13%). **3**: ^{1}H NMR ($CDCl_3$) δ 7.95 (s, 1H), 2.78 (t, J = 7.6 Hz, 2H), 1.77-1.62 (m, 2H), 1.41-1.20 (m, 2H), 0.85 (t, J = 7.2 Hz, 3H). **4**: ^{1}H NMR ($CDCl_3$) δ 2.74 (t, J = 7.6 Hz, 2H), 2.34 (s, 3H), 1.84-1.69 (m, 2H), 1.48-1.25 (m, 2H), 0.91 (t, J = 7.2 Hz, 3H).

3-Butyl-6-phenyl-4*H*-[1,2,4]triazin-5-one (5) and 3-Butyl-6-phenethyl-4*H*-[1,2,4]triazin-5-one (6)

To a solution of formyl hydrazidine (0.30 g, 2.10 mmol) and *p*-TSA·H_2O (0.13 g, 0.63 mol) in dry DMF (3.0 mL) was added by drops a solution of benzoyl formic acid (0.35 g, 2.31 mmol) in dry DMF (3.0 mL) dropwise. The mixture was stirred at room temperature for 4 h and refluxed for 12 h and then the solvent was evaporated. The residue was partitioned between dichloromethane and water. The organic layer was washed with water, dried ($MgSO_4$), and the solvent was evaporated. The crude product was purified by silica gel column chromatography using ethyl acetate/hexane (1:2) as eluent to give **5** (0.38 g, 80%). **5**: ^{1}H NMR (DMSO-d_6) δ 8.08-8.02 (m, 2H), 7.40-7.31 (m, 3H), 2.59 (t, J = 7.6 Hz, 2H), 1.79-1.68 (m, 2H), 1.43-1.25 (m, 2H), 0.87 (t, J = 7.2 Hz, 3H). Anal. Calcd for $C_{13}H_{15}N_3O$: C, 68.10; H, 6.59; N, 18.33; found C, 67.75; H, 6.35; N, 18.01. In a similar manner to the former procedure, **6** was synthesized in 45% yield from formyl hydrazidine (1.0 g, 7.00 mmol), *p*-TSA·H_2O (1.33 g, 7.00 mmol) and 2-oxo-4-phenyl-butyric acid (7.70 mmol). If the amount of *p*-TSA·H_2O was decreased to 30 mole %. The yield of **6** is only 11%. **6**: ^{1}H NMR ($CDCl_3$) δ 7.36-7.04 (m, 5H), 3.03 (br s, 4H), 2.71 (t, J = 7.5 Hz, 2H), 1.80-1.74 (m, 2H), 1.41-1.36 (m, 2H), 0.71 (t, J = 7.5 Hz, 3H). Anal. Calcd for $C_{15}H_{19}N_3O$: C, 70.01; H, 7.44; N, 16.33; found C, 70.32; H, 7.15; N, 16.21.

3-Butyl-6-methyl-4-[2′-(1-trityl-tetrazol-5-yl)-biphenyl-4-ylmethyl]-4*H*-[1,2,4]triazin-5-one (8) and 3-Butyl-6-methyl-2-[2′-(1-trityl-tetrazol-5-yl)-biphenyl-4-ylmethyl]-2*H*-[1,2,4]triazin-5-one (9)

To a stirred solution of **4** (0.35 g, 2.12 mmol) in dry DMF (4.5 mL) was added cesium carbonate (1.04 g, 3.19 mmol) followed by a solution of **7** (1.42 g, 2.55 mmol) in DMF (3.0 mL). After stirring at room temperature for 12 h, the volatiles was evaporated and the residue was partitioned between CH_2Cl_2 and water. The organic layer was washed with water, dried ($MgSO_4$) and the solvent was evaporated. The crude product was purified by silica gel column chromatography using ethyl acetate/hexane (1:2) as eluent to afford, in successive order *N*-alkylation products **8** (0.25 g, 18.5%) and **9** (0.61 g, 45%). **8**: ^{1}H NMR ($CDCl_3$) δ 7.97-7.92 (m, 1H), 7.70-7.50 (m, 14H), 7.00-6.88 (m, 8H), 5.10 (s, 2H), 2.62 (t, J = 7.6 Hz, 2H), 2.51 (s, 3H), 1.72-1.60 (m, 2H), 1.44-1.25 (m, 2H), 0.88 (t, J = 7.2 Hz, 3H). **9**: ^{1}H NMR ($CDCl_3$) δ 7.98-7.94 (m, 1H), 7.52-7.46 (m, 2H), 7.38-7.14 (m, 12H), 6.94-6.88 (m, 8H), 5.10 (s, 2H), 2.53 (t, J = 7.8 Hz, 2H), 2.31 (s, 3H), 1.75-1.60 (m, 2H), 1.36-1.22 (m, 2H),

0.86 (t, J = 7.2 Hz, 3H).

3-Butyl-6-phenyl-4-[2′-(1-trityl-tetrazol-5-yl)-biphenyl-4-ylmethyl]-4*H*-[1,2,4]triazin-5-one (10) and 3-Butyl-6-phenyl-2-[2′-(1-trityl-tetrazol-5-yl)-biphenyl-4-ylmethyl]-2*H*-[1,2,4]triazin-5-one (11)

Compounds **10** (0.36 g, 12.8%) and **11** (1.59 g, 56.6%) were prepared from **5** (0.92 g, 4.02 mmol), by similar procedures as those described for the preparation of **8** and **9** as colorless foams. **10**: ^{1}H NMR ($CDCl_3$) δ 8.33-8.28 (m, 1H), 7.97-7.93 (m, 1H), 7.53-7.11 (m, 18H), 7.00-6.87 (m, 8H), 5.20 (s, 2H), 2.71 (t, J = 7.6 Hz, 2H), 1.81-1.70 (m, 2H), 1.47-1.25 (m, 2H), 0.91 (t, J = 6.8 Hz, 3H). **11**: ^{1}H NMR ($CDCl_3$) δ 8.25-8.20 (m, 1H), 7.99-7.94 (m, 1H), 7.51-7.15 (m, 18H), 7.00-6.87 (m, 8H), 5.22 (s, 2H), 2.58 (t, J = 7.6 Hz, 2H), 1.80-1.64 (m, 2H), 1.43-1.25 (m, 2H), 0.88 (t, J = 7.2 Hz, 3H).

3-Butyl-6-phenethyl-4-[2′-(1-trityl-tetrazol-5-yl)-biphenyl-4-ylmethyl]-4*H*-[1,2,4]triazin-5-one (12) and 3-Butyl-6-phenethyl-2-[2′-(1-trityl-tetrazol-5-yl)-biphenyl-4-ylmethyl]-2*H*-[1,2,4]triazin-5-one (13)

Compounds **12** (0.57 g, 20%) and **13** (1.33 g, 47%) were prepared from **6** (0.95 g, 3.71 mmol), by a similar procedure as that described for the preparation of **8** and **9** as colorless foams. **12**: ^{1}H NMR ($CDCl_3$) δ 7.94-7.93 (m, 1H), 7.48-7.47 (m, 2H), 7.34-7.11 (m, 17H), 6.92-6.89 (m, 8H), 5.10 (s, 1H), 3.19-3.18 (m, 2H), 3.14-3.12 (m, 2H), 2.60 (t, J = 7.5 Hz, 2H), 1.69-1.68 (m, 2H), 1.35-1.31 (m, 2H), 0.87 (t, J = 7.5 Hz, 3H). **13**: 8.12-8.11 (m, 1H), 7.96-7.95 (m, 2H), 7.47-7.30 (m, 4H), 7.25-7.11 (m, 13H), 6.92-6.90 (m, 6H), 6.81-6.79 (m, 2H), 5.05 (s, 2H), 3.06 (br s, 4H), 2.47 (t, J = 8.0 Hz, 2H), 1.68-1.61 (m, 2H), 1.31-1.24 (m, 2H), 0.85 (t, J = 7.5 Hz, 3H).

3-Butyl-6-methyl-4-[2′-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-4*H*-[1,2,4]triazin-5-one (14) and 3-Butyl-6-methyl-2-[2′-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-2*H*-[1,2,4]triazin-5-one (15)

A solution of **8** (0.10 g, 0.16 mmol) in a mixture of THF (4.0 mL) and 10% HCl (2.0 mL) was stirred at room temperature for 2 h and the solvent was evaporated. The residue was partitioned between ethyl acetate and saturated sodium bicarbonate. The separated organic layer was washed with water, dried ($MgSO_4$) and the solvent was evaporated. The crude product was purified by silica gel column chromatography using ethyl acetate/hexane (1:1) as eluent to give **14** (0.03 g, 49%) as a colorless foam. ^{1}H NMR ($CDCl_3$) δ 7.86 (d, J = 7.6 Hz, 1H), 7.60-7.08 (m, 7H), 5.18 (s, 2H), 2.68 (t, J = 7.6 Hz, 2H), 2.38 (s, 3H), 1.70-1.58 (m, 2H), 1.41-1.25 (m, 2H), 0.85 (t, J = 7.2 Hz, 3H); MS (EI) *m/z* (rel intensity) 401 (M^+, 7), 359 (100), 235 (27), 178 (75). HRMS: Calcd for $C_{22}H_{23}N_7O$ (M^+) 401.1964, found 401.1965. Compound **15** (0.05 g, 74%) was prepared from **9** (0.11 g, 0.16 mmol), by a similar procedure as that described for the preparation of **14** as a colorless foam. ^{1}H NMR ($CDCl_3$) δ 7.83 (d, J = 7.2 Hz, 1H), 7.57-7.11 (m, 7H), 5.22 (s, 2H), 2.56 (t, J = 7.6 Hz, 2H), 2.23 (s, 3H), 1.60-1.57 (m, 2H), 1.35-1.25 (m, 2H), 0.83 (t, J = 7.2 Hz, 3H); HRMS: Calcd for $C_{22}H_{24}N_3O$ (M^++1) 402.2042, found 402.2038.

3-Butyl-6-phenyl-4-[2′-(1*H*-tetrazol-5-yl)biphenyl-4-ylmethyl]-4*H*-[1,2,4]triazin-5-one (16) and 3-Butyl-6-phenyl-2-[2′-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-2*H*-[1,2,4]triazin-5-one (17)

Compound **16** (0.05 g, 76%) was prepared from **10** (0.11 g, 0.15 mmol), by a similar procedure as that described for the preparation of **14** and **15** as colorless foams. **16**: ^{1}H NMR ($CDCl_3$) δ 8.09-8.05 (m, 2H), 8.04-7.08 (m, 11H), 5.20 (s, 2H), 2.70 (t, J = 7.6 Hz, 2H), 1.73-1.61 (m, 2H), 1.42-1.25 (m, 2H), 0.88 (t, J = 7.2 Hz, 3H); MS (EI) *m/z* (rel intensity) 463 (M^+, 35), 421 (100), 235 (23), 207 (59), 178 (91), HRMS: Calcd for $C_{27}H_{25}N_7O$ (M^+) 463.2121, found 463.2107. **17** (0.12 g, 95%) was prepared from **11** (0.20 g, 0.28 mmol), by a similar procedure as that described for the preparation of **16** as a colorless foam. ^{1}H NMR ($CDCl_3$) δ 8.12-8.07 (m, 2H), 7.80-7.09 (m, 11H), 5.25 (s, 2H), 2.55 (t, J = 7.6 Hz, 2H), 1.62-1.50 (m, 2H), 1.33-1.21 (m, 2H), 0.81 (t, J = 7.2 Hz, 3H).

3-Butyl-6-phenethyl-4-[2′-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl)-4*H*-[1,2,4]triazin-5-one (18) and 3-Butyl-6-phenethyl-2-[2′-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl)-2*H*-[1,2,4]triazin-5-one (19)

Compound **18** (0.43 g, 95%) was prepared from **12** (0.72 g, 0.92 mmol), by a similar procedure as that described for the preparation of **14** and **15** as a colorless foam. ^{1}H NMR ($CDCl_3$) δ 7.91-7.90 (m, 1H), 7.60-7.04 (m, 12H), 5.18 (s, 2H), 3.10-3.09 (m, 2H), 3.04-3.02 (m, 2H), 2.68 (t, J = 7.5 Hz, 2H), 1.71-1.68 (m, 2H), 1.40-1.36 (m, 2H), 0.90 (t, J = 7.5 Hz, 3H); MS (EI) *m/z* (rel intensity) 492 (M^++1, 43), 258 (32), 236 (26), 207 (100), HRMS: Calcd for $C_{29}H_{30}N_7O$ (M^++1) 492.2512, found 492.2522. **19** (0.31 g, 99%) was prepared from **13** (0.46 g, 0.60 mmol), by a similar procedure as that described for the preparation of **18** as a colorless foam. ^{1}H NMR ($CDCl_3$) δ 7.88-7.87 (m, 1H),

7.57-6.92 (m, 12H), 5.14 (s, 2H), 3.00 (br s, 4H), 2.49 (t, J = 7.5 Hz, 2H), 1.60-1.54 (m, 2H), 1.31-1.25 (m, 2H), 0.82 (t, J = 7.2 Hz, 3H); MS (EI) m/z (rel intensity) 492 (M^++1, 57), 258 (15), 235 (16), 207 (100), HRMS: Calcd for $C_{29}H_{30}N_7O$ (M^++1) 492.2512, found 492.2494.

2-Butyl-6-hydroxy-5-phenethyl-3*H*-pyrimidin-4-one (22)

A mixture of n-valeroylamidine hydrochloride **20** (15.5 g, 0.11 mol) and dimethyl 2-phenethyl malonate **21** (26.8 g, 0.11 mol) was refluxed in an ethanolic sodium ethoxide solution (prepared from sodium (7.84 g, 0.34 mol) and ethanol (320 mL)) for 4 h. The mixture was filtered and the solvent was evaporated. The residue was acidified with 10% HCl and filtered, the solid was dried successively by air and under vacuum to give **22** (29 g, 94%) as a white powder. mp 240-241 °C. ^{1}H NMR (DMSO-d_6) δ 7.40-7.20 (m, 5H), 2.80-2.70 (m, 2H), 2.68-2.50 (m, 4H), 1.70 (m, 2H), 1.38 (m, 2H), 0.96 (t, J = 7.2 Hz, 3H).

2-Butyl-6-methoxy-5-phenethyl-3*H*-pyrimidin-4-one (23) and 2-Butyl-6-ethoxy-5-phenethyl-3*H*-pyrimidin-4-one (24)

A mixture of **22** (2.30 g, 8.46 mmol), dimethyl sulfate (or diethyl sulfate) (4.44 mmol) and cesium carbonate (5.40 g, 16.60 mmol) in DMF (53 mL) was stirred at room temperature for 24 h. The mixture was filtered and evaporated under vacuum at 40 °C by a Kugelrohr apparatus. The residue was partitioned between dichloromethane and water. The organic layer was washed with water, dried ($MgSO_4$), and the solvent was evaporated. The crude product was purified by silica gel column chromatography using ethyl acetate/hexane (1:10) as eluent to afford **23** (1.65 g, 65%) (or **24** (1.86 g, 70%)) as colorless foams. **23**: ^{1}H NMR ($CDCl_3$) δ 7.30-7.15 (m, 5H), 3.85 (s, 3H), 2.77 (br s, 4H), 2.64 (t, J = 7.0 Hz, 2H), 1.76 (m, 2H), 1.40 (m, 2H), 0.96 (t, J = 7.0 Hz, 3H); MS (EI) m/z (rel intensity) 286.1 (M^+, 20), 244.1 (20), 195.1 (100). **24**: ^{1}H NMR ($CDCl_3$) δ 7.30-7.15 (m, 5H), 4.32 (q, J = 7.0 Hz, 2H), 2.68 (m, 4H), 2.62 (t, J = 7.4 Hz, 2H), 1.76 (m, 2H), 1.43 (m, 2H), 1.30 (t, J = 7.0 Hz, 3H), 0.96 (t, J = 7.4 Hz, 3H); MS (EI) m/z (rel intensity) 300.2 (M^+, 20), 258.1 (20), 209.2 (100).

Methanesulfonic Acid 2-Butyl-6-oxo-5-phenethyl-1,6-dihydro-pyrimidin-4-yl Ester (25) and 2-Butyl-4,6-(diethylphosphinyl)oxy-5-phenethyl-pyrimidine (26)

To an ice-cooled suspension of **22** (2.00 g, 7.35 mmol) in THF (30 mL) was added 60% NaH oil dispersion (0.33 g, 8.25 mmol). The mixture was allowed to stir at 0 °C for 0.5 h. Methanesulfonyl chloride (0.84 g, 7.35 mmol) (or diethylphosphoryl chloride (1.27 g, 7.35 mmol)) was added and the mixture was stirred at room temperature overnight. The resulting mixture was filtered and the solvent was evaporated. The residue was partitioned between dichloromethane and water. The organic layer was washed with water, dried ($MgSO_4$), and the solvent was evaporated. The crude product was purified by silica gel column chromatography using ethyl acetate/hexane (1:4) as eluent to give **25** (1.35 g, 45%) (or **26** (1.00 g, 25%)). **25**: yellow oil, ^{1}H NMR ($CDCl_3$) δ 7.33-7.16 (m, 5H), 3.52 (s, 3H), 2.83 (br s, 4H), 2.72 (t, J = 7.2 Hz, 2H), 1.79 (m, 2H), 1.46 (m, 2H), 0.97 (t, J = 7.2 Hz, 3H); FABMS: m/z 350 (M^+). **26**: yellow oil, ^{1}H NMR ($CDCl_3$) δ 7.30-7.10 (m, 5H), 4.35 (q, J = 7.2 Hz, 8H), 2.84 (br s, 4H), 2.80 (t, J = 7.2 Hz, 2H), 1.40 (t, J = 7.2 Hz, 12H), 1.35 (m, 2H), 0.93 (t, J = 7.2 Hz, 3H); MS (EI) m/z (rel intensity) 544.3 (M^+, 100), 499.2 (3), 389.2 (5), 348.1 (7), 317.1 (25), 181.1 (33).

2-Butyl-6-methoxy-5-phenethyl-3-[2′-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-3*H*-pyrimidin-4-one (27) and 2-Butyl-6-ethoxy-5-phenethyl-3-[2′-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-3*H*-pyrimidin-4-one (28)

Compound **27** (or **28**) was prepared from **23** (or **24**) (1.00 mmol) by alkylation with **7** (Cs_2CO_3/DMF) and deprotection of the resulting *N*-alkylation products as described in the preparation of triazinone biphenyltetrazols in 50% overall yields. **27**: ^{1}H NMR ($CDCl_3$) δ 7.90 (d, J = 7.0 Hz, 1H), 7.60-6.80 (m, 12H), 5.18 (s, 2H), 3.89 (s, 3H), 2.75 (m, 4H), 2.70 (t, J = 7.0 Hz, 1H), 1.73 (m, 2H), 1.39 (m, 2H), 0.91 (t, J = 7.0 Hz, 3H); MS (EI) m/z (rel intensity) 521 (20, M^++1), 479.3 (15), 386.2 (100), 192.1 (100); HRMS: Calcd for $C_{31}H_{33}N_6O_2$ (M^++1) 521.2665, found 521.2662. **28**: ^{1}H NMR ($CDCl_3$) δ 7.92 (d, J = 8.4 Hz, 1H), 7.60-6.80 (m, 12H), 5.18 (s, 2H), 4.32 (q, J = 7.0 Hz, 2H), 2.69 (m, 4H), 2.66 (t, J = 7.2 Hz, 2H), 1.70 (m, 2H), 1.35 (m, 2H), 1.28 (t, J = 7.0 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H); MS (EI) m/z (rel intensity) 534.4 (M^+, 20), 491.4 (5), 443.3 (80), 400.2 (50), 207.1 (70), 192.1 (100); HRMS: Calcd for $C_{32}H_{34}N_6O_2$ (M^+) 534.2743, found 534.2737.

Methanesulfonic Acid 2-Butyl-6-oxo-5-phenethyl-1-[2′-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1,6-dihydro-pyrimidin-4-yl Ester (29) and Diethylphosphonic Acid 2-Butyl-6-oxo-5-phenethyl-1-[2′-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1,6-dihydro-pyrimidin-4-yl Ester (30)

Compound **29** (or **30**) was prepared from **25** (or **26**)

(1.00 mmol) by alkylation with **7** (Cs_2CO_3/DMF) and deprotection of the resulting *N*-alkylation product as described in the preparation of triazinone biphenyltetrazoles in an 45% overall yield. **29**: ^{1}H NMR ($CDCl_3$) δ 8.00 (d, J = 8.4 Hz, 1H), 7.60-6.80 (m, 12H), 5.26 (s, 2H), 3.52 (s, 3H), 2.85 (m, 4H), 2.72 (t, J = 7.2 Hz, 2H), 1.70 (m, 2H), 1.40 (m, 2H), 0.91 (t, J = 7.2 Hz, 3H); MS (EI) *m/z* (rel intensity) 584.2 (M^+, 2), 541.4 (20), 450.2 (27), 372.2 (40), 192.1 (100); HRMS: Calcd for $C_{31}H_{32}N_6O_4S$ (M^+) 584.2206, found 584.2201. **30**: ^{1}H NMR ($CDCl_3$) δ 7.98 (d, J = 6.0 Hz, 1H), 7.60-6.80 (m, 12H), 5.18 (br s, 2H), 4.20 (q, J = 7.4 Hz, 4H), 2.84 (m, 4H), 2.56 (t, J = 8.0 Hz, 2H), 1.40 (t, J = 7.4 Hz, 6H), 1.35 (m, 2H), 0.87 (t, J = 8.0 Hz, 3H); MS (EI) *m/z* (rel intensity) 642 (5), 579 (10), 534 (10), 471 (30), 443 (40), 263 (100); HRMS: Calcd for $C_{34}H_{39}N_6O_5P$ (M^+) 642.2920, found 642.2918.

2-Butyl-6-alkyl-3*H*-pyrimidin-4-ones (35-38)

General procedure: A mixture of n-valeroylamidine hydrochloride **20** (2.40 g, 17.60 mmol) and β-ketoester (see **31-34**) (17.50 mmol) was refluxed in an ethanolic sodium ethoxide solution (prepared from sodium (0.80 g, 34.78 mmol) and ethanol (30 mL)) for 3 h. The mixture was filtered and the solvent was evaporated. The residue was acidified and taken into ethyl acetate and water, and the phases were separated. The organic layer was washed with water, dried ($MgSO_4$), and the solvent was evaporated. The crude product was purified by silica gel column chromatography using ethyl acetate/hexane (1:2) as eluent to give the pyrimidinone compound in 65-70% yield. **35**: ^{1}H NMR ($CDCl_3$) δ 7.10 (m, 5H), 5.76 (s, 1H), 4.01 (s, 1H), 2.91 (t, J = 7.2 Hz, 2H), 1.70 (m, 2H), 0.80 (t, J = 7.2 Hz, 3H); MS (EI) *m/z* (rel intensity) 242 (M^+, 100). **36**: ^{1}H NMR ($CDCl_3$) δ 7.30-7.10 (m, 5H), 6.11 (s, 1H), 3.00 (m, 2H), 2.80 (m, 2H), 2.67 (t, J = 7.2 Hz, 2H), 1.70 (m, 2H), 1.40 (m, 2H), 0.96 (t, J = 7.2 Hz, 3H); MS (EI) *m/z* (rel intensity) 256.1 (M^+, 100), 214.1 (60), 179.1 (30). **37**: ^{1}H NMR ($CDCl_3$) δ 6.19 (s, 1H), 2.80 (m, 1H), 2.69 (t, J = 7.2 Hz, 2H), 1.78 (m, 2H), 1.40 (m, 2H), 1.24 (d, J = 7.2 Hz, 6H), 0.95 (t, J = 7.2 Hz, 3H); MS (EI) *m/z* (rel intensity) 194.2 (M^+, 5), 179.2 (10), 165.1 (10), 152.1 (100). **38**: ^{1}H NMR ($CDCl_3$) δ 7.50-7.20 (m, 5H), 6.12 (s, 1H), 3.95 (q, J = 7.2 Hz, 3H), 2.65 (t, J = 7.2 Hz, 2H), 1.70 (m, 2H), 1.60 (d, J = 7.2 Hz, 3H), 0.95 (t, J = 7.2 Hz, 3H); MS (EI) *m/z* (rel intensity) 257.1 (M^++1, 80), 214.0 (100).

2-Butyl-6-alkyl-3-[2′-(1*H*-tetrazol-5-yl)-biphenyl-4-yl-methyl]-3*H*-pyrimidin-4-one (39-42)

Compounds **39-42** were prepared from the corresponding compounds **35-38** by alkylation with **7** in the presence of Cs_2CO_3 in DMF and deprotection of the resulting *N*-alkylation products as described in the preparation of triazinone biphenyltetrazoles in an 45-50% overall yield. **39**: ^{1}H NMR ($CDCl_3$) δ 8.00 (d, J = 8.0 Hz, 1H), 7.60-6.80 (m, 12H), 6.06 (s, 1H), 5.20 (s, 2H), 3.81 (s, 2H), 2.66 (t, J = 7.2 Hz, 2H), 1.60 (m, 2H), 1.35 (m, 2H), 0.89 (t, J = 7.2 Hz, 3H); MS (EI) *m/z* (rel intensity) 476.4 (M^+, 20), 165.1 (40), 149.1 (100); HRMS: Calcd for $C_{29}H_{28}N_6O$ (M^+) 476.2525, found 476.2325. **40**: ^{1}H NMR ($CDCl_3$) δ 7.85 (d, J = 8.0 Hz, 1H), 7.60-6.80 (m, 12H), 6.01 (s, 1H), 5.20 (s, 2H), 2.96 (t, J = 7.2 Hz, 2H), 2.76 (t, J = 7.6 Hz, 2H), 2.64 (t, J = 7.2 Hz, 2H), 1.67 (m, 2H), 1.36 (m, 2H), 0.90 (t, J = 7.2 Hz, 3H); MS (EI) *m/z* (rel intensity) 490.5 (M^+, 20), 447.4 (20), 255.3 (40), 192.2 (75), 178.2 (100); HRMS: Calcd for $C_{30}H_{30}N_6O$ (M^+) 490.2782, found 490.2484. **41**: ^{1}H NMR ($CDCl_3$) δ 7.90 (d, J = 6.5 Hz, 1H), 7.60-6.80 (m, 7H), 6.09 (s, 1H), 5.18 (br s, 2H), 2.65 (m, 3H), 1.64 (m, 2H), 1.34 (m, 2H), 1.17 (d, J = 7.2 Hz, 6H), 0.87 (t, J = 7.2 Hz, 3H); MS (EI) *m/z* (rel intensity) 428.5 (M^+, 100), 178.2 (50); HRMS: Calcd for $C_{25}H_{28}N_6O$ (M^+) 428.2325, found 428.2319. **42**: ^{1}H NMR ($CDCl_3$) δ 7.87 (d, J = 6.5 Hz, 1H), 7.60-6.80 (m, 12H), 6.13 (s, 1H), 5.13 (br s, 2H), 3.88 (q, J = 7.2 Hz, 1H), 2.63 (t, J = 7.2 Hz, 2H), 1.65 (m, 2H), 1.59 (d, J = 7.2 Hz, 3H), 0.92 (t, J = 7.2 Hz, 3H); MS (EI) *m/z* (rel intensity) 490.4 (M^+, 15), 447.6 (60), 405.3 (100); HRMS: Calcd for $C_{30}H_{30}N_6O$ (M^+) 490.2481, found 490.2484.

2-Butyl-6-chloro-5-phenethyl-1*H*-pyrimidine-4-one (43)

A mixture of **36** (4.30 g, 15.80 mmol) and phosphoryl chloride (10 mL, 0.11 mol) was refluxed in an oil bath for 50 min. The resulting mixture was poured onto 50 g of ice water and filtered. The obtained 4,6-dichloro pyrimidine was suspended in a mixture of 16% NaOH (12 mL) and dioxane (30 mL) and refluxed for 4 h. The solvent was evaporated and the residue was acidified with 10% HCl and filtered to give **43** (2.10 g, 46%) as a white powder. mp 168-169 °C. ^{1}H NMR ($CDCl_3$) δ 7.30-7.20 (m, 5H), 2.86 (m, 4H), 2.69 (t, J = 8.0 Hz, 2H), 1.80 (m, 2H), 1.46 (m, 2H), 0.97 (t, J = 8.0 Hz, 3H); MS (EI) *m/z* (rel intensity) 290.1 (M^+, 38), 199.1 (100).

2-Butyl-5-phenethyl-3*H*-pyrimidin-4-one (44)

A solution of **43** (0.30 g, 1.03 mmol) in a mixture of ethanol (30 mL) and ammonia water (1.0 mL) was hydrogenated under 40 psi in the presence of palladium on charcoal catalyst. The reaction was followed up by TLC. At the end of reaction, the mixture was filtered through Celite and the solvent was evaporated. The residue was recrystallized from 1:4 ethyl acetate/hexane to give **44** as a white powder. mp. 104-106 °C. ^{1}H NMR ($CDCl_3$) δ 7.30-7.20 (m, 5H), 2.90 (m, 4H), 2.69 (t, J = 7.4 Hz, 2H), 1.81 (m, 2H), 1.46 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H); MS (EI) *m/z* (rel intensity) 256.0 (M^+, 40), 214.1 (30), 165.1 (100); HRMS: Calcd for $C_{16}H_{20}N_2$ (M^+) 256.1576, found 256.1579.

2-Butyl-6-chloro-5-phenethyl-3-[2′-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-3*H*-pyrimidin-4-one (45) and 2-Butyl-5-phenethyl-3-[2′-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-3*H*-pyrimidin-4-one (46)

Compound **45** (or **46**) was prepared from **43** (or **53**) (2.0 mmol) by alkylation with **7** in the presence of Cs_2CO_3 in DMF and deprotection of the resulting *N*-alkylation products as described in the preparation of triazinone biphenyltetrazoles in an 50-55% overall yield. **45**: ^{1}H NMR ($CDCl_3$) δ 8.00 (d, J = 8.0 Hz, 1H), 7.60-7.00 (m, 12H), 5.26 (s, 2H), 2.88 (m, 4H), 2.66 (t, J = 7.2 Hz, 2H), 1.72 (m, 2H), 1.26 (m, 2H), 0.96 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) 13.69, 22.28, 28.86, 29.45, 33.10, 34.50, 47.02, 121.97, 122.57, 126.09, 126.85, 128.34, 128.48, 129.16, 129.70, 130.82, 131.38, 135.06, 139.07, 140.46, 141.00, 155.10, 159.97, 162.42; MS (EI) *m/z* (rel intensity) 524.4 (M^+, 20), 481.3 (10), 309.2 (20), 289.1 (40), 192.1 (100). HRMS: Calcd for $C_{30}H_{29}N_6OCl$ (M^+) 524.2091, found 524.2085. **46**: ^{1}H NMR ($CDCl_3$) δ 7.90 (m, 1H), 7.60 (s, 1H), 7.59 (m, 1H), 7.52 (m, 1H), 7.42 (m, 1H), 7.29-7.25 (m, 2H), 7.19 (m, 1H), 7.14-7.01 (m, 6H), 5.26 (s, 2H), 2.85 (t, J = 7.1 Hz, 2H), 2.73 (t, J = 7.1 Hz, 2H), 2.65 (t, J = 8.0 Hz, 2H), 1.64 (m, 2H), 1.34 (m, 2H), 0.89 (t, J = 8.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) 13.72, 22.27, 29.00, 29.72, 33.98, 34.52, 46.62, 122.88, 124.85, 126.11, 126.71,128.23, 128.39, 128.42, 129.68, 130.74, 130.89, 131.28, 135.28, 138.89, 140.63, 140.97, 160.87, 162.94; FABMS: *m/z* 490 (M^+); HRMS: Calcd for $C_{30}H_{30}N_6O$ (M^+) 490.2481, found 490.2478.

ACKNOWLEDGEMENT

We thank the Ministry of Economic Affairs, R.O.C. for financial support. We also thank Mr. Sheng-Wen Lin for his help to improve the yield of compound **6**. Analytical support by Dr. Yuh-Shan Chung's group of Development Center for Biotechnology is greatly appreciated.

Received May 18, 1998.

Key Words

Angiotensin II receptor antagonists; Triazinones; Pyrimidinones.

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