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The Syntheses of Triazole, Sulfur-Containing Diazole And *N*-Phenylthiatriazole Biphenyltetrazoles as Potential Angiotensin II Receptor Antagonists

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The syntheses of triazole, sulfur-containing diazole and *N*-phenylthiatriazole analogs of imidazole angiotensin II antagonist, DuP 753, are reported. 5-Butyl-3-[(2-trifluoromethyl)phenyl]-2,1,3,4-1*H*-thiatriazole-2-one biphenyltetrazole (**63**) is found to have good *in vitro* activity.

INTRODUCTION

Angiotensin II in the renin angiotensin system plays an important role in regulating the blood pressure.[1] The recent introduction and approval of non-peptidic angiotensin II antagonist losartan (DuP 753, MK954, brand name: Cozaar),[2] prompted us to synthesize its analogs.[3] The imidazole ring of losartan could be replaced by a fused imidazole or other heterocycles such as benzimidazoles,[4] quinazolinones,[5] triazolones,[6] pyridinones,[7] spiroimidazolines,[8] and triazoles[9] without decreasing its potency. A few sulfur-containing analogs which include benzothiadiazine dioxides,[10] triazolinethiones,[6] thiazoles[11] and thiadiazoles[11] were also studied. Based on our suspicion that sulfur atom might act as a ligand for the metal of the A II receptor, we are interested in the properties of these compounds. We report herein the synthesis and receptor affinity of several DuP 753 analogs, including 1,2,4,-triazole, oxadiazole, oxathiadiazole-2-oxide, thioxadiazole and *N*-phenylthiatriazoles bearing a (2′-tetrazolebiphenyl-4-yl)methyl side chain attaching to the nitrogen atom, as potential angiotensin II antagonists. (Fig. 1).

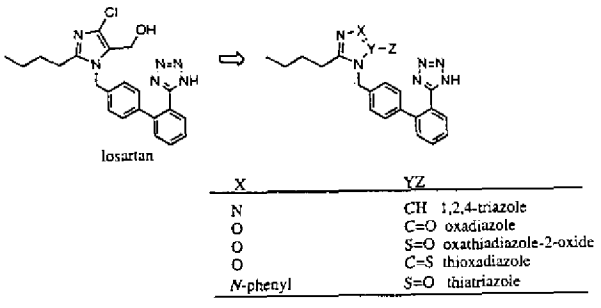


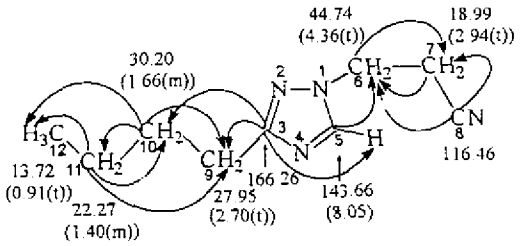
Fig. 1.

RESULTS AND DISCUSSION

Chemistry Part

1) 1,2,4-Triazole Derivative (Scheme I)

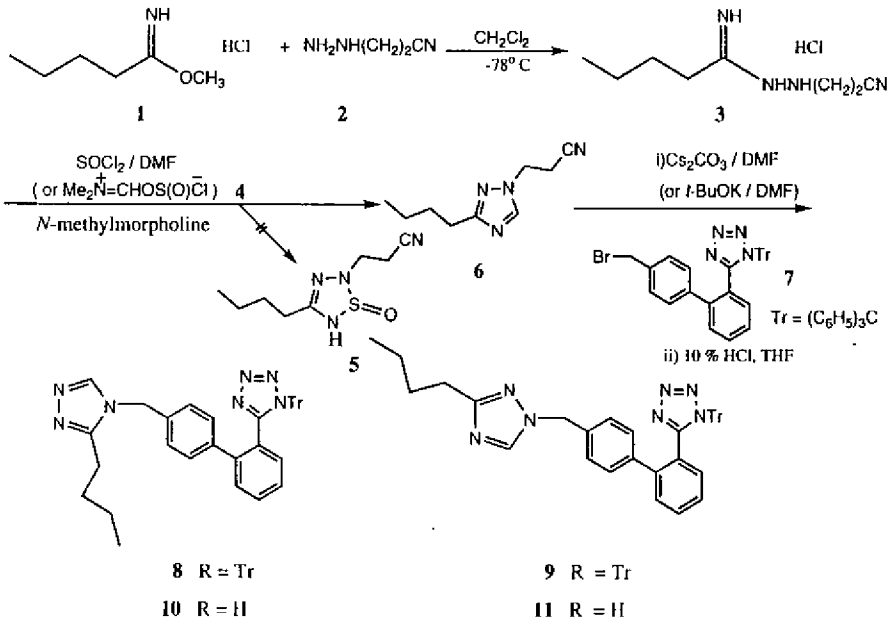
This derivative was obtained quite unexpectedly. Thus reaction of methyl valerimidate hydrochloride **1**[12] with β-cyanoethylhydrazine **2**[13] in CH_2Cl_2 at -78 °C gave the corresponding hydrazidine hydrochloride **3**. But treatment of the cooled DMF solution of **3** with *N*-methylmorpholine and thionyl chloride gave triazole **6** instead of the expected thiatrizloe **5**. The regiochemistry of **6** was confirmed by a HMBC spectrum (Fig. 2). Alkylation of **6** with 5-(4′-bro-



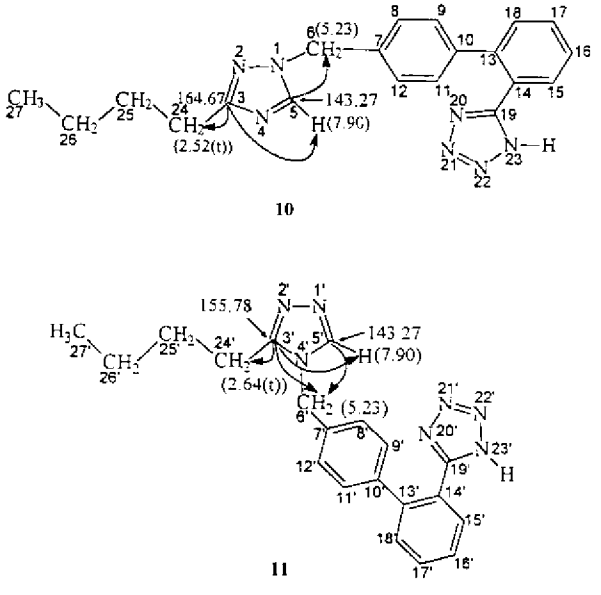
HMBC correlation of 6 (arrow)

Fig. 2.

Scheme I



momethy)biphenyl-1-trityltetrazole **7**[2e] using Cs_2CO_3 as base in DMF and deprotection of the resulting alkylated products **8** and **9** gave 1,2,4-triazole biphenyltetrazole derivatives **10** and **11** as a mixture of regioisomers. The structures of **10** and **11** followed from their HMBC spectra (Fig. 3). In these transformations, we found: (1) thionyl chloride and DMF are versatile agents for the cyclodehydration of hydrazidine; the actual cyclodehydration species might be



HMBC correlation of (**10**, **11**), arrows show some important HMBC correlation

Fig. 3.

chlorosulfonylmethylene(dimethyl)ammonium chloride **4**, formed by reaction of $SOCl_2$ and DMF,[14] (2) cyanoethylprotected 1,2,4-triazole could be deprotected in organic solvent under mild conditions (Cs_2CO_3/DMF, room temperature). Note that the corresponding tetrazoles and thiatriazoles were deprotected in aqueous protic solvent ($NaOH/H_2O$, MeOH),[15] and (3) a facile method for the regioselective introduction of a base-removable cyanoethyl group into a 1,2,4-triazole ring.

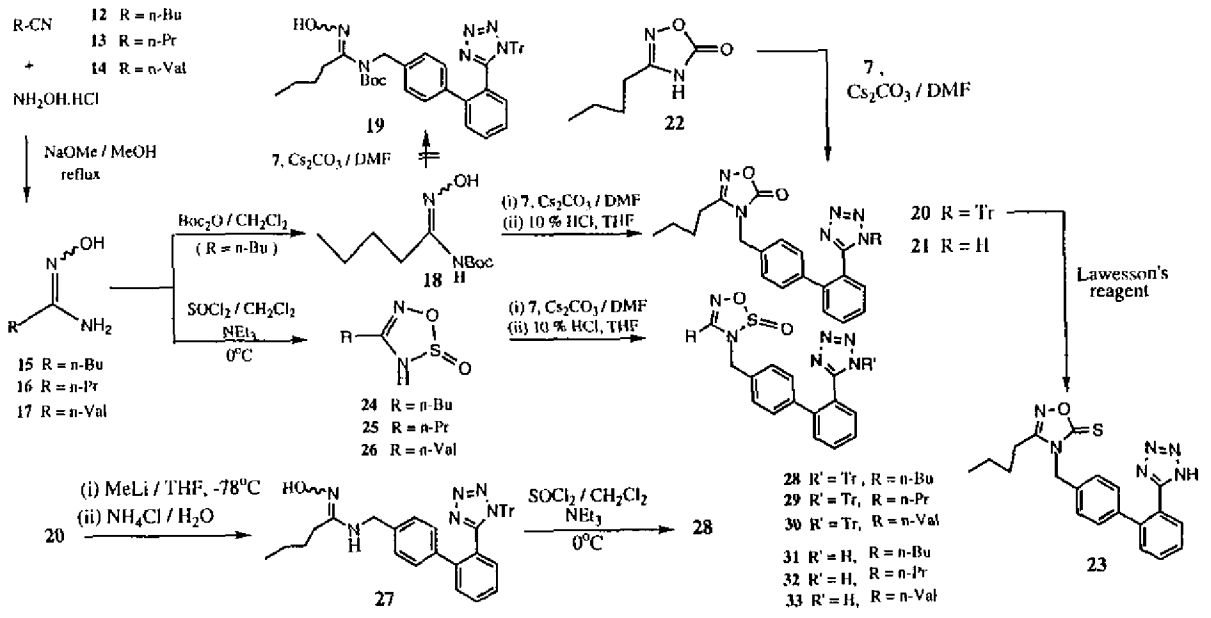
2) Oxadiazole Derivative (Scheme II)

This derivative was also prepared in an unexpected manner. Refluxing of H_2NOH·HCl with valeronitrile (**12**) under basic condition (NaOMe/MeOH) gave the corresponding amidoxime **15**. Reaction of **15** with Boc_2O afforded **18**, which was subsequently alkylated with **7** in the presence of Cs_2CO_3 in DMF to afford oxadiazole deriative **20** instead of the expected **19**. The structure of compound **20** was confirmed by alkylation of oxadiazole **22** using a known procedure.[16] Deprotection of **20** gave **21**.

3) Oxathiadiazole-2-Oxide Derivatives (Scheme II)

Method A: Treatment of **15** with thionyl chloride under basic condition gave oxathiadiazole 2-oxide **24**, which was alkylated with **7**. Deprotection of the alkylated product **28** gave 2-oxo-oxathiadiazole biphenyltetrazole **31**. Two other homologs **32** and **33** were also prepared. In view of related studies on other heterocycles,[10,16,17] the regiochemistry of **31** remains ambiguous, although the ^1H NMR signal of *N*-benzylic protons appeared as a AB quartet. Clarification was carried out by following unambiguous synthesis.

Scheme II

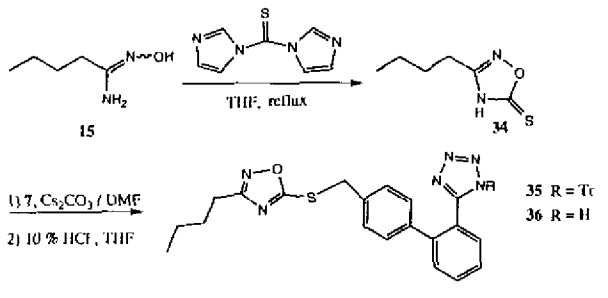


Method B: Ring-opening of oxadiazole biphenyl derivative **20** with methyllithium (3-5 equiv) followed by neutralization gave the amidoxime biphenyl derivative **27**, which was treated with thionyl chloride under basic conditions to afford a cyclized product identical to compound **28** prepared by Method A. Attempts to open the oxadiazole ring in **20** with sodium hydroxide in aqueous methanol at either room temperature or by heating failed.

4) Oxadiazolethione Derivatives (Schemes II and III)

Refluxing of the oxadiazole biphenyl derivative **20** with Lawesson's reagent in dioxane afforded oxadiazolethione derivative **23** directly. (Scheme II). In this transformation, thionation and deprotection were accomplished simultaneously. From compound **15** we obtained **34**, and alkylation of the latter with **7** resulted in the formation of *S*-alkylated product **35**. Deprotection of **35** by treatment with acid gave **36** (Scheme III). The structure of **36** was determined by comparing the chemical shifts of the *N*-benzylic protons at δ 4.89 with those of **23** at δ 5.08

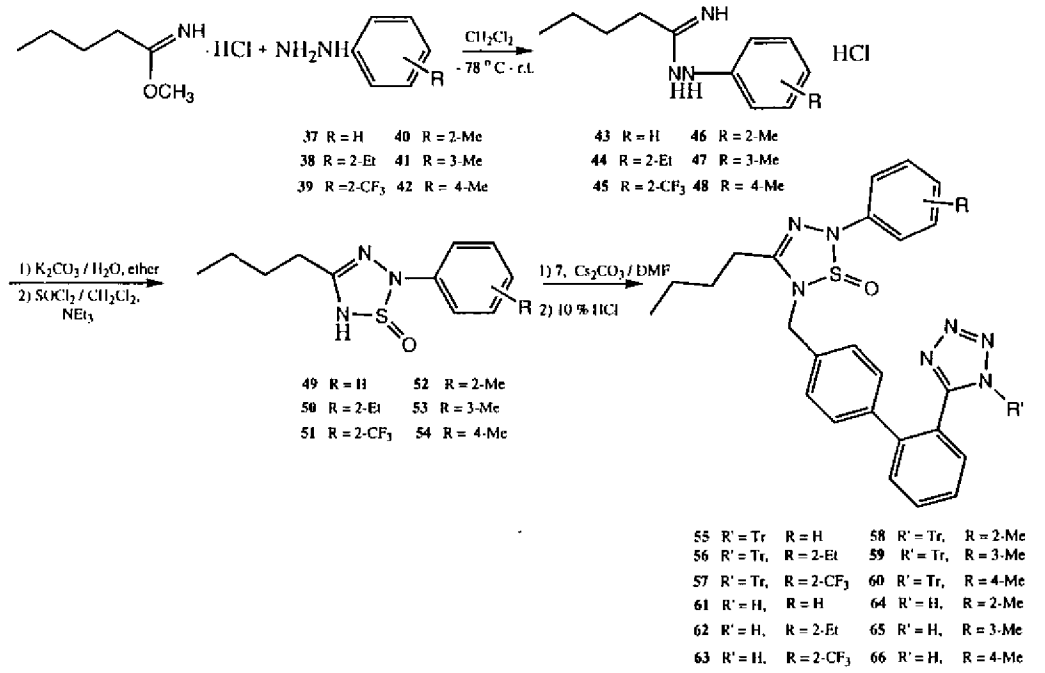
Scheme III



5) Thiatriazole Derivatives (Schemes IV, V and VI)

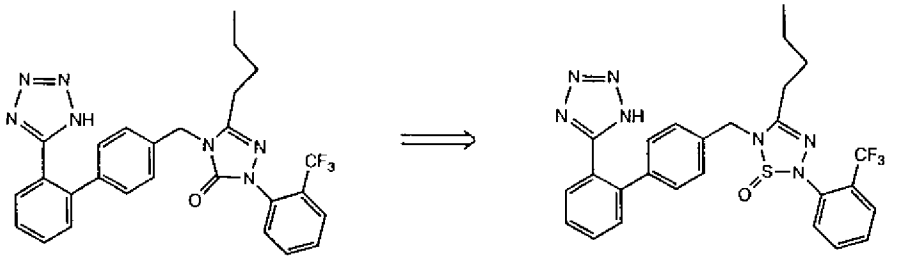
Among *N*-(substituted)triazolinone biphenyltetrazoles, which have been reported to be excellent angiotensin II receptor antagonists,[12] *N*-(trifluoromethyl)phenyltriazolinone biphenyltetrazole is one of the most potent. The preparation of its thia-analogs was studied (Fig. 4). Triazolinone are obtainable by reaction of ethyl *N*-carbethoxyvalerimidate with arylhydrazines,[12] the difficult access ofthe corresponding *N*-sulfinylethoxyvalerimidate and the uncertainty of its role in the subsequent cyclization prompted us to develop an alternative method (Scheme IV). Accordingly, reaction of methyl valerimidate with arylhydrazines **37-42** in dichloromethane at -78 °C gave the corresponding 1-(phenylhydrazono)-pentylamine hydrochlorides **43-48**. The free 1-(phenylhydrazono)-pentylamines were liberated from their HCl salts with aqueous potassium carbonate and extracted into ether. Treatment of ice-cooled dichloromethane solutions of 1-(phenyl-hydrazono)-pentylamines with triethylamine and thionyl chloride successively gave thiatriazoles **49-51**. Alkylation of thiatriazoles with **7** and deprotection of the resulting alkylated products **55-60** afforded thiatriazole biphenylterazole derivatives **61-66**. The structures of the products were determinated by comparing the NMR chemical shifts of the *N*-benzylic protons in **55** (δ 4.86, 4.65, ABq), **56** (δ 4.92, 4, 70, ABq), **57** (δ 4.92 4.70, ABq) and **68** (δ 3.95, 3.83, ABq). Compound **68** was prepared by alkylation of **3** with **7** and followed by cyclization

Scheme IV



($SOCl_2/CH_2Cl_2$, NEt_3) of the resulting alkylated product **67** (Scheme V). For biological activity comparison, a biphenyl-2-carboxylic acid derivative **71** was also prepared by alkylation of **51** with **69**[2e] followed by deprotection of the alkylated product **70** with trifluoroacetic acid (Scheme VI).

The compounds described in Table I were evaluated in a conventional radioligand binding assay, based on displacement of monoiodinated angiotensin II from a membrane prepared from guinea pig adrenal glands. The assay procedures have been described in detail.[18,19] All the oxathiadiazole derivative and its analogs described in Table I have only micromolar potency in *in vitro* binding assay and these compounds are less potent than triazole and *N*-phenylthiatriazoles. It seems that an additional lengthening from the "x" position would increase the receptor binding affinity (see Table 1, general structure). However, in the case of oxathiadiazole derivative and its analogs, such modification is impossible. *N*-(2-Substituted)phenylthiatriazoles **62** and **63** show no significant differences from their parent *N*-phenylthiatriazole **61**, and *N*-(*o*, *m* or *p*-CH_3)phenylthiatriazoles **64-66** show poor potency. The difference between **63** and **62** might be explained in terms of hydrogen bonding ability or electronegativity. Additionally, the obvious difference between **63** and **71** indicates that tetrazole ring is es-

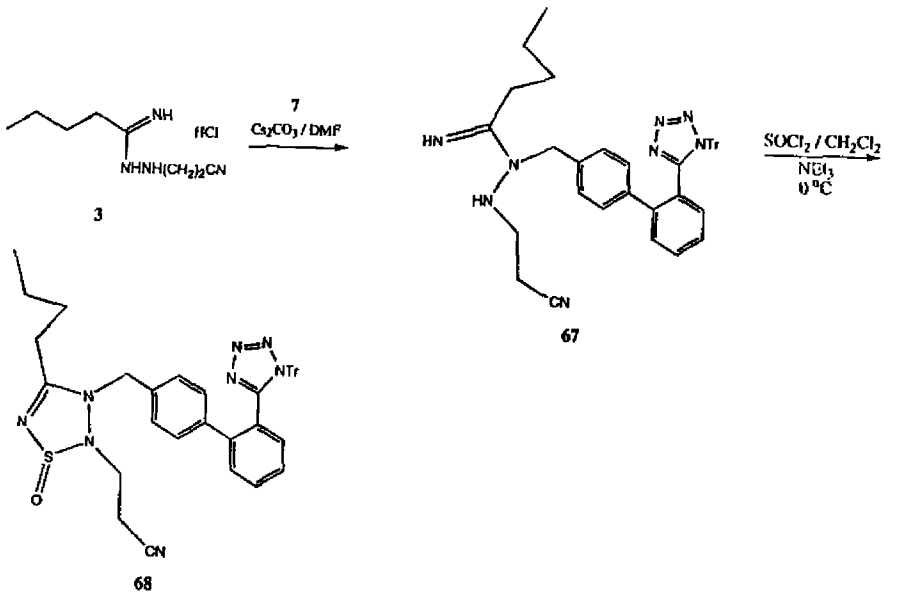


^{2}N-(trifluoromethyl)phenyl triazolinone biphenyltetrazole

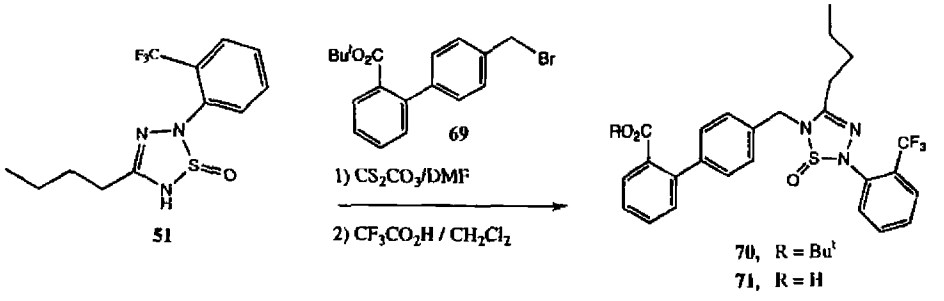
^{2}N-(2-substituted)phenyl thiatrizolinone biphenyltetrazole

Fig. 4.

Scheme V



Scheme VI



sential in thiatriazole series. Finally, the comparison of **63** (IC_{50} = 137.2 nM) with **72** (IC_{50} = 1.2 nM) shows an adverse effect of substitution at the 3-position of triazolinone ring with a sulfur atom because considerable loss of potency was observed.

In summary, we have replaced the imidazole of DuP 753 with a series of novel sulfur containing heterocycles and proved the structures by HMBC spectra, unambiguous synthesis and correlation method.

EXPERUMENTAL SECTION

Melting points are uncorrected Infrared spectra were measured on a Perkin-Elmer 577 spectrometer. ^{1}H NMR spectra were recorded on Bruker-200 (200 MHz). ^{13}C NMR and HMBC spectra were recorded on Bruker-500 (500 MHz). Mass spectra were collected on a JEOL-JMS-DI00 instrument. Exact masses were measured by a JEOL-JMSD-HXI00 high resolution mass spectrometer.

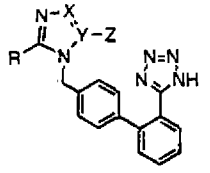
3-[*N'*-(1-Aminopentylidene)hydrazino]propionitrile Hydrochloride 3

A mixture of methyl valerimidate **1** (9 g, 59 mmol) and β-cyanoethylhydrazine (5 g, 59 mmol) in dichloromethane (90 mL) was stirred at -78 °C for 0.5 h and allowed to reach room temperature overnight. The solvent was removed and recooled to 0 °C. The solidified product was collected and triturated with ether or acetone. It was then filtered and dried in vacuo to give **3** (10.4 g, 86%) as a yellowish hygroscopic powder, mp 103-104 °C, ^{1}H NMR (D_2O) δ 2.99 (t, *J*= 6.3 Hz, 2H), 2.49 (t, *J* = 6.3 Hz, 2H), 2.27 (t, *J* = 7.6 Hz, 2H), 1.44 (m, 2H), 1.18 (m, 2H), 0.70 (t, *J* = 76 Hz, 3H); MS (EI) *m/z* (rel. int) 169 (M^+-Cl, 100).

1-β-Cyanoethyl-3-butyl-1,2,4-triazole 6

To a mixture of **3** (6.5 g, 31.8 mmol) and *N*-methylmorpholine (9.63 g, 95.3 mmol) was cooled at -78 °C, an

Table 1.



Compound	R	X	YZ	*in vitro* (IC_{50} nM)
(**10**,**11**)[a]	n-Bu	N	CH	370.1
21	n-Bu	O	C=O	>500
31	n-Bu	O	S=O	>500
32	n-Pr	O	S=O	>500
33	n-Val	O	S=O	>500
36[b]				>500
61	n-Bu	N-C_6H_5	S=O	320
62	n-Bu	N-(2-EtC_6H_4)	S=O	430
63	n-Bu	N-(2-$CF_3C_6H_4$)	S=O	137.6
64	n-Bu	N-(2-$CH_3C_6H_4$)	S=O	>500
65	n-Bu	N-(3-$CH_3C_6H_4$)	S=O	>500
66	n-Bu	N-(4-$CH_3C_6H_4$)	S=O	>500
71[c]				>500
DuP 753	n-Bu	C-Cl	C-CH_2OH	26
72	n-Bu	N-(2-$CF_3C_6H_4$)	C=O	1.2[12]

[a] (**10**,**11**) was submitted as a mixture, the ratio of **10** to **11** is 2:3 determined by ^{1}H NMR.
[b] see Scheme *III*.
[c] see Scheme VI.

ice-cooled solution of thionyl chloride (4.0 g, 33.6 mmol) in DMF (50 mL) was added. It was stirred at -78 °C for 1 h, the cooling bath was removed and the reaction was allowed to rise to room temperature during 2 h period. After being stirred at room temperature for 18 h, the reaction mixture was distilled under vacuum in Kügelrohr to remove the solvent. The residue was partitioned between brine and ethyl acetate, and the ethyl acetate solution was dried and evaporated to give crude product, which was purified on silica gel column chromatography using ethyl acetate/hexane (1 : 2) as eluent to give **6** (5.1 g, 89.6%) as a brown oil. IR ($CHCl_3$) 2320 (s), 1200 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.05 (s, 1H), 4.36 (t, J = 7.0 Hz, 2H), 2.94 (t, J = 7.0 Hz, 2H), 2.70 (t, J = 7.0 Hz, 2H), 1.66 (m, 2H), 1.40 (m, 2H), 0.91 (t, J = 7.0 Hz, 3H); MS (EI) *m/z* (rel intensity) 179 (M$^+$+1, 100), 136 (30); HRMS calcd for $C_9H_{15}N_4$ (M$^+$+1) 179. 1297, found 179. 1284; ^{13}C NMR ($CDCl_3$) δ 166.26 (C-3), 143.66 (C-5), 116.46, 44.74, 30.20, 27.95, 22.27, 18.99, 13.72; HMBC (see Fig. 2) δ_C/δ_H 116.46 to 4.36, 2.94, 18.99 to 4.36, 143.66 to 4.36, 44.74 to 2.94, 166.6 to 8.05, 2.70, 1.66, 27.95 to 1.66, 1.40, 30.20 to 2.70, 1.40, 0.91. 22.27 to 2.70, 166, 0.91, 13.72 to 1.66, 1.40.

4′-[(3-Butyl-4*H*-1,2,4-triazol-4-yl)methyl]biphenyl-2-(1-trityl)tetrazole 8 and 4′-[(3-Butyl-1*H*-1,2,4-triazol-1-yl)methyl]biphenyl-2-(1-trityl)tetrazole 9

Method A: A mixture of **6** (0.18 g, 1 mmol), **7** (0.56 g, 1 mmol) and cesium carbonate (0.72 g, 2.2 mmol) in DMF (7 mL) was stirred at room temperature for 24 h. The resulting mixture was filtered and evaporated under vaccum at 40 °C in a Kügelrohr apparatus. The residue was partitioned between CH_2Cl_2 and brine. The CH_2Cl_2 layer was washed with water, dried and evaporated. The residue was purified by silica gel column chromatography using ethyl acetate/hexane (1 : 10) as eluent to give **8** and **9** (0.54 g, 83%) as an isomeric mixture. ^{1}H NMR shows that the ratio of **8** and **9** is 2 to 3. The alkylation was also accomplished as follows.

Method B: The THF solution of **6** (5.4 g, 30 mmol) was stirred with t-BuOK (3.4 g, 30 mmol) at 0 °C for 0.5 h. The solvent was removed and the residue was added DMF (210 mL) and followed by **7** (16.8 g, 30 mmol). The mixture was stirred at room temperature for 24 h. The reaction gave **8** and **9** (colorless foam) in 90% yield, ^{1}H NMR ($CDCl_3$) δ 8.00 (d, J = 7.2 Hz, 1H), 7.81, 7.86 (each s, 1H), 6.80-7.60 (m, 22H), 5.15, 5.19 (each s, 2H), 2.62, 2.68 (each t, J = 7.6 Hz, 2H), 1.67 (m, 2H), 1.40 (m, 2H), 0.92 (t, J = 7.6 Hz, 2H).

4′-[(3-Butyl-4*H*-1,2,4-triazol-4-yl)methyl]biphenyl-2-tetrazole 10 and 4′-[(3-Butyl-1*H*-1,2,4-triazol-1-yl)methyl]biphenyl-2-tetrazole 11

A solution of **8** and **9** (2.50 g, 4.1 mmol) in a mixture of THF (60 mL) and 10% HCl (30 mL) was stirred at room temperature for 2 h. The solution was evaporated and the residue was partitioned between ethyl acetate and brine. The ethyl acetate solution was dried and evaporated under vacuum and the product was purified by silica gel column chromatography using ethyl acetate as eluent to give **10** and **11** (0.96 g, 65%) as a colorless foam. ^{1}H NMR ($CDCl_3$) δ 7.90 (s, 1H), 7.76 (d, J = 7.2 Hz, 1H), 7.00-7.60 (m, 7H), 5.23 (s, 2H), 2.52, 2.64 (each t, J = 7.0 Hz, 2H), 1.53 (m, 2H), 1.24 (m, 2H), 0.86 (t, J = 7.0 Hz, 3H); MS (EI) *m/z* (rel intensity) 359 (M$^+$, 100), 178 (75); HRMS calcd for $C_{22}H_{21}N_7$ (M$^+$) 359.1859, found 359.1860; ^{13}C NMR ($CDCl_3$) δ 164.67 (C-3), 155.78 (C-3′), 143.27 (C-5, C-5′), 140.72 (C-13, C-13′), 139.68 (C-10), 139.49 (C-10′), 134.48 (C-8, C-8′), 134.24 (C-12,C-12′), 131.14 (C-19, C-17, C-19′, C-17′), 130.86 (C-15, C-15′), 130.70 (C-18. C-18′), 129.61 (C-11, C-9, C-11′, C-9′), 128.14 (C-16, C-16′), 127.68 (C-7), 127.16 (C-7′), 123.43 (C-14, C-14′), 52.76 (C-6), 51.40 (C-6′), 30.19 (C-25′), 29.35 (C-25), 27.52 (C-24), 25.23 (C-24′), 22.20, 22.12 (C-26, C-26′), 13.60, 13.49 (C-27, C-27′); HMBC (partial, see Fig. 3) δ_C/δ_H 164.67 to

7.90, 2.52; 155.78 to 7.90, 5.23, 2.64; 143.27 to 5.23.

General Procedure for Preparation of Amidoxime 15, 16 and 17

Alkanenitrile (**12**, **13** or **14**) (0.1 mol) was added to the refluxing solution of hydroxylamine, prepared from 0.1 mol each of H_2NOH·HCl and NaOMe in 70 mL of MeOH, and refluxed overnight. The mixture was filtered and evaporated to give a residue, which was diluted with dichloromethane and washed with water. The organic layer was dried and evaporated to give amidoxime (90-95% yield) as a pale blue oil. **15**, ^{1}H NMR ($CDCl_3$) δ 7.70 (br s, 1H), 4.70 (br s, 2H), 2.14 (t, J = 7.3 Hz, 2H), 1.20-1.60 (m, 4H), 0.94 (t, J = 7.3 Hz, 3H); MS (EI) *m/z* (rel intensity) 117 (M^++1, 100). **16**, ^{1}H NMR ($CDCl_3$) δ 7.40 (br s, 1H), 4.60 (br s, 2H), 2.11 (t, J = 7.3 Hz, 2H), 1.60 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H); MS (EI) *m/z* (rel intensity) 103 (M^++1, 100); **17**, ^{1}H NMR ($CDCl_3$) δ 8.60 (br s, 1H), 4.57 (br s, 2H), 2.15 (t, J = 8.0 Hz, 2H), 1.60 (m, 2H), 1.35 (m, 4H), 0.95 (t, J = 8.0 Hz, 3H); MS(EI) *m/z* (rel intensity) 131 (M^++1, 100).

***N*-Boc Pentanamidoxime 18**

To a stirred solution of **15** (4.6 g, 0.04 mmol) in dichloromethane (60 mL) was added Boc_2O (8.7 g, 0.04 mmol). The mixture was stirred at room temperature and kept overnight. The solvent was evaporated to give **18** (8.7 g, 96%) as a white powder, mp 64-66 °C, IR ($CHCl_3$) 3300 (s), 3040 (s), 1600 (m), 1200 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.65 (br s, 2H), 2.21 (t, J = 7.5 Hz, 2H), 1.60 (m, 2H), 1.49 (s, 9H), 0.89 (t, J = 7.5 Hz, 3H); MS (EI) *m/z* (rel intensity) 217 (M^++1, 20), 161 (60), 74 (100).

4′-[(3-Butyl-5-oxo-1,2,4-5*H*-oxadiazol-4-yl)methyl] biphenyl-2-(1-trityl)tetrazole 20 and 4′-[(3-Butyl-5-oxo-1,2,4-5*H*-oxadiazol-4-yl)methyl]biphenyl-2-tetrazole 21

Compound **20** (3.7 g, 6.0 mmol) was prepared as a colorless foam in 60% yield from **18** (2.2 g, 10 mmol) by the similar procedure as described for the preparation of **8** and **9** ^{1}H NMR ($CDCl_3$) δ 7.90 (d, J = 8.0 Hz, 3H), 6.80-7.50 (m, 22H), 4.63 (s, 2H), 2.27 (t, J = 8.0 Hz, 2H), 1.20-1.60 (m, 4H), 0.85 (t, J = 7.2 Hz, 3H). Compound **20** (3.7 g, 6.0 mmol) was deprotected, by the similar procedure as that described for the preparation of **10** and **11**, to give **21** (1.7 g, 4.5 mmol) in 75% yield as a colorless foam. IR ($CHCl_3$) 3360 (s), 1600 (m), 1200 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.02 (d, J = 7.2 Hz, 1H), 7.60-7.20 (m, 7H), 4.76 (s, 2H), 2.49 (t, J = 8.0 Hz, 2H), 1.60 (m, 2H), 1.40 (m, 2H), 0.91 (t, J = 7.2 Hz, 3H); MS (EI) *m/z* (rel intensity) 377 (M^++1, 100), 235 (75), HRMS calcd for $C_{20}H_{21}O_2N_6$ (M^++1) 377.1727, found 377.1735.

4′-[(3-Butyl-5-thioxo-1,2,4-5*H*-oxadiazo-4-yl)methyl]biphenyl-2-tetrazole 23

A mixture of **20** (0.97 g, 1.57 mmol) and Lawesson's reagent (0.86 mmol) was refluxed in dioxane (15 mL) for 12 h, evaporated, and the residue was purified by silica gel column chromatography using ethyl acetate as eluent to give **23** (0.3 g, 57%) as a colorless foam. IR ($CHCl_3$) 3400 (s), 1600 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.82 (d, J = 7.6 Hz, 1H), 7.00-7.60 (m, 7H), 5.08 (s, 2H), 2.51 (t, J = 7.2 Hz, 2H), 1.60 (m, 2H), 1.38 (m, 2H), 0.85 (t, J = 7.2 Hz, 3H); MS (FAB) *m/z* (rel intensity) 393 (M^++1, 100), 235 (92), HRMS calcd for $C_{20}H_{21}ON_6S$ (M^++1) 393.1498, found 393.1481.

General Procedure for Preparation of 4-Alkyl-3*H*-1,2,3,5-oxathiadiazole 2-oxides (24, 25 and 26)

To an ice-cooled solution of amidoxime (**15**, **16** or **17**) (0.05 mol) in dichloromethane (50 mL) and pyridine (0.104 mol) was added dropwise a solution of thionyl chloride (0.052 mol) in dichloromethane (15 mL). The reaction mixture was allowed to stir 0.5 h. It was washed with 2% HCl and water, dried and evaporated under vacuum. The crude product was purified by silica gel column chromatography using ethyl acetate/hexane (1 : 10) as eluent to give **24**, **25** or **26** in 55-60% yield as yellow oil. **24**, IR (neat) 1200 (s), 1130 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.10 (br s, 1H), 2.60 (t, J = 7.2 Hz, 2H), 1.66 (m, 2H), 1.40 (m, 2H), 0.94 (t, J = 7.2 Hz, 3H); MS (EI) *m/z* (rel intensity) 163 (M^++1, 20), 120 (46), 84 (100); HRMS calcd for $C_5H_{11}N_2O_2S$ (M^++1) 163.0542, found 163.0537. **25**, IR (neat) 1180 (s), 1130 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.59 (t, J = 7.2 Hz, 2H), 1.72 (m, 2H), 1.01 (t, J = 7.2 Hz, 3H); MS (EI) *m/z* (rel intensity) 149 (M^++1, 15), 120 (100). HRMS calcd for $C_4H_9N_2O_2S$ (M^++1) 149.0385, found 149.0695. **26**, IR (neat) 1200 (s), 1125 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.58 (t, J = 7.2 Hz, 2H), 1.62 (m, 2H), 1.35 (m, 4H), 0.88 (t, J = 7.2 Hz, 3H); MS (EI) *m/z* (rel intensity) 177 (M^++1, 10), 120 (100); HRMS calcd for $C_6H_{13}N_2O_2S$ (M^++1) 177.0698, found 177.0695.

4-Alkyl-3-[2′-(1-trityl-tetrazol-3-yl)biphenyl]methyl-1,2,3,5-3*H*-oxathiazole 2-oxides (28, 29 and 30) and 4-Alkyl-3-[2′-(tetrazole-3-yl)biphenyl]methyl-1,2,3,5-3*H*-oxathiadiazole (31, 32 and 33)

Method A: Compound **28**, **29** and **30** was prepared from **24**, **25** and **26**, respectively, by the similar procedure as that described for the preparation of **8** and **9** in 55-60% yields as colorless foam. **28**, ^{1}H NMR ($CDCl_3$) δ 7.96 (d, J = 8.0 Hz, 1H), 6.80-7.50 (m, 22H), 4.72, 4.53 (ABq, J = 16.7 Hz, 2H), 2.30 (m, 2H), 1.60 (m, 2H), 1.40 (m, 2H), 0.90 (t, J= 7.0 Hz, 3H). **29**, ^{1}H NMR ($CDCl_3$) δ 7.93 (d, J = 8.0 Hz, 1H), 6.80-7.50 (m, 22H), 4.67, 4.48 (ABq, J = 16.5 Hz, 2H),

2.34 (t, J = 7.3 Hz, 2H), 1.62 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H). **30**, ^{1}H NMR ($CDCl_3$) δ 7.93 (d, J = 8.0 Hz, 1H), 6.80-7.50 (m, 22H), 4.67, 4.48 (ABq, J = 16.6 Hz, 2H), 2.31 (m, 2H), 1.60 (m, 2H), 1.25 (m, 4H), 0.85 (t, J = 7.2 Hz, 3H). Compounds **28**, **29** and **30** (2 mmol) were deprotected, by the similar procedure as that described for **10** and **11**, to give **31**, **32** and **33** in 60-65% yields as colorless foam. **31**, IR ($CHCl_3$) 1200 (s), 1160 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.92 (d, J = 7.2 Hz, 3H), 7.60-6.80 (m, 7H), 4.79 (s, 2H), 2.50 (m, 2H), 1.66 (m, 2H), 1.38 (m, 2H), 0.92 (t, J = 7.2 Hz, 3H); MS (FAB) *m/z* (rel intensity) 399 (M^++1, 40), 235 (100); HRMS calcd for $C_{19}H_{21}O_2N_6S$ (M^++1) 397.1448, found 397.1462. **32**, IR (neat) 1200 (s), 1170 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.95 (d, J = 7.2 Hz, 1H), 6.80-7.60 (m, 7H), 4.80 (d, J = 3.4 Hz, 2H), 2.46 (m, 2H), 1.65 (m, 2H), 1.00 (t, J = 7.2 Hz, 3H); MS (FAB) *m/z* (rel intensity) 383 (M^++1, 30), 235 (100); HRMS calcd for $C_{18}H_{19}O_2N_6S$ (M^++1) 383.1290, found 383.1280. **33**, IR (neat) 1200 (s), 1165 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.90 (d, J = 7.2 Hz, 3H), 7.60-7.00 (m, 7H), 4.76 (s, 2H), 2.45 (m, 2H), 1.66 (m, 2H), 1.28 (m, 4H), 0.85 (t, J = 7.2 Hz, 3H); MS (FAB) *m/z* (rel intensity) 411 (M^++1, 25), 235 (100); HRMS calcd for $C_{20}H_{23}O_2N_6S$ (M^++1) 411.603, found 411.1601.

Method B: Compound **20** (1.2 g, 2 mmol) in THF (30 mL) was added a 5% methyllithium ether solution (3.8-6.3 mL, 6-10 mmol). The mixture was stirred while temperature rose from -78 °C to room temperature during 1 h period. The resulting solution was neutralized with saturated NH_4Cl aqueous solution (1.0 mL) and evaporated under vacuum. The residue was partitioned between ethyl acetate and brine. The ethyl acetate solution was dried and evaporated to give ring-opening product **27** as a yellow foam. The crude **27** was cyclized on treating with $SOCl_2$, by the similar procedure as that described for the preparation of **24**, to give **28** in 37-45% overall yield.

3-Butyl-5*H*-1,2,4-oxadiazol-5-thione 34

A mixture of **15** (2.3 g, 0.02 mol) and thiocarbonyldiimidazole (4.6 g, 0.026 mol) in THF (40 mL) was refluxed for 3 h. The mixture was evaporated and the residue was partitioned between chloroform and 3 N HCl. The organic layer was washed with water, dried and evaporated to give the crude product, which was purified by silica gel column chromatography using ethyl acetate/hexane (1 : 1) as eluent to give **34** (2.0 g, 63%) as a yellow oil, IR (neat) 3480 (s), 1630 (m) cm^{-1}; ^{1}H NMR showed that **34** exists as tautomers. ^{1}H NMR ($CDCl_3$) δ 8.30 (br s, 0.4H), 5.20 (br s, 0.6H), 2.77 (t, J = 7.8 Hz, 1/3H), 2.61 (t, J = 7.8 Hz, 1/3H), 2.24 (t, J = 7.8 Hz, 1/3H), 1.60 (m, 2H), 1.40 (m, 2H), 0.93 (t, J = 7.6 Hz, 3H); MS (EI) *m/z* (rel intensity) 158 (M^+, 11), 116 (100); HRMS calcd for $C_6H_{10}N_2OS$ 158.0515, found 158.0528

4′-[(3-Butyl-1,2,4-oxadiazole-5-sulfanyl)methyl]biphenyl-2-(1-trityl)-tetrazole 35 and 4′-[(3-Butyl-1,2,4-oxadiazole-5-sulfanyl)methyl]biphenyl-2-tetrazole 36

Compound **35** (1.9 g, 3 mmol) was prepared from **34** (0.86 g, 5.45 mmol), by the similar procedures as that described for the preparation of **8** and **9**, in 55% yield as a colorless foam, ^{1}H NMR ($CDCl_3$) δ 7.98 (d, J = 8.0 Hz, 1H), 6.80-7.60 (m, 22H), 4.85 (s, 2H), 2.41 (t, J = 8.0 Hz, 1H), 1.60 (m, 2H), 1.30 (m, 2H), 0.90 (t, J = 7.5 Hz, 3H). Compound **35** was deprotected, by the similar procedure as that described for **10** and **11**, to give **36** in 60-65% yield as a colorless foam. IR ($CHCl_3$) 3000 (s), 1740 (s), 1200 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.90 (d, J = 7.5 Hz 1H), 7.00-7.60 (m, 7H), 4.89 (s, 2H), 2.50 (t, J = 7.8 Hz, 2H), 1.60 (m, 2H), 1.30 (m, 2H), 0.88 (t, J = 7.5 Hz, 3H); MS (FAB) *m/z* (rel intensity) 393 (M^++1, 5), 235 (35), 224 (100); HRMS calcd for $C_{20}H_{21}ON_6S$ (M^++1) 393.1498 found 393.1472.

General Procedure for Preparation of 1-(Phenylhydrazono)pentylamine Hydrochloride 43-48

The title compounds (~20 mmol each) were prepared from the corresponding phenylhydrazines **37-42** and imidate **1**, by the similar procedure as that described for the preparation of **3**, to give **43-48** in 85-90% yields as white hygroscopic powders. **43**, ^{1}H NMR (D_2O) δ 7.00-7.23 (m, 2H), 6.80-7.00 (m, 3H), 2.60 (t, J = 7.2 Hz, 2H), 1.70 (m, 2H), 1.40 (m, 2H), 0.90 (t, J = 7.2 Hz, 2H); MS (EI) *m/z* (rel intensity) 191 (M^+-HCl, 60), 174 (30), 149 (20), 104 (100). **44**, ^{1}H NMR (d_6-DMSO) δ 7.00 (m, 2H), 6.70 (m, 2H), 2.60 (m, 4H), 1.75 (m, 2H), 1.35 (m, 2H), 1.20 (t, J = 7.2 Hz, 3H); MS (EI) *m/z* (rel intensity) 219 (M^+-HCl, 100). **45**, ^{1}H NMR (D_2O) δ 7.40-7.60 (m, 2H), 6.80-7.20 (m, 3H), 2.60 (t, J = 7.2 Hz, 2H), 1.70 (m, 2H), 1.38 (m, 2H), 0.87 (t, J = 7.2 Hz, 2H); MS (EI) *m/z* (rel intensity) 259 (M^+-HCl, 100), 159 (50). **46**, ^{1}H NMR (d_6-DMSO) δ 7.00 (m, 2H), 6.70 (m, 2H), 2.50 (t, J = 7.2 Hz, 2H), 2.15 (s, 3H), 1.60 (m, 2H), 1.35 (m, 2H), 0.86 (t, J = 7.2 Hz, 3H); MS (EI) *m/z* (rel intensity) 205 (M^+-HCl, 90), 188 (15), 104 (100). **47**, ^{1}H NMR (d_6-DMSO) δ 6.80-7.10 (m, 4H), 2.42 (t, J = 7.2 Hz, 2H), 2.21 (s, 3H), 1.60 (m, 2H), 1.30 (m, 2H), 0.90 (t, J = 7.2 Hz, 3H); MS (EI) *m/z* (rel intensity) 205 (M^+-HCl, 60), 188 (10), 105 (100). **48**, ^{1}H NMR (d_6-DMSO) δ 7.00 (d, J = 8.2 Hz, 2H), 6.73 (d, J = 8.2 Hz, 2H), 2.40 (t, J = 7.2 Hz, 2H), 2.20 (s, 3H), 1.60 (m, 2H), 1.40 (m, 2H), 0.94 (t, J = 7.2 Hz, 3H); MS(EI) *m/z* (rel intensity) 205 (M^+-HCl, 30), 188 (10), 105

(100).

General Procedure for Preparation of 5-Butyl-3-phenyl-2,1,3,4-1*H*-thiatriazole-2-ones 49-54

1-(Phenylhydrazono)pentylamine hydrochlorides **43-48** (~10 mmol each) were dissloved in 33% K_2CO_3 (30 mL), and extracted three times with ether. The combined ether extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the 1-(phenylhydrazono)pentylamine free bases as clear oils. Compounds **49-54** were prepared from the corresponding 1-(phenylhydrazono)pentylamine free bases and thionyl chloride, by the similar procedure as that described for the preparation of **24**, in 60-65% yields as yellow oils. They were also prepared by treating an ice-cooled suspension of 1-(phenylhydrazono)pentylamine hydrochlorides in dichloromethane with 3 equiv of NEt_3 and lequiv of $SOCl_2$. **49**, ^{1}H NMR ($CDCl_3$) δ 8.48 (s, 1H), 7.10-7.60 (m, 2H), 2.60 (t, *J* = 7.2 Hz, 2H), 1.65 (m, 2H), 1.30 (m, 2H), 0.93 (t, *J* = 7.2 Hz, 3H), MS (EI) *m/z* (rel intensity) 237 (M^+, 100), 197(20). **50**, ^{1}H NMR ($CDCl_3$) δ 7.50 (d, *J* = 8.0 Hz, 1H), 7.00-7.40 (m, 3H), 3.08 (t, *J* = 7.2 Hz, 2H), 2.60 (t, *J* = 7.2 Hz, 2H), 1.36 (m, 2H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.20 (m, 2H), 1.00 (t, *J* = 7.2 Hz, 3H); MS (EI) *m/z* (rel intensity) 265 (M^+, 60), 222(100). **51**, ^{1}H NMR ($CDCl_3$) δ 8.00 (br s, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.30-7.60 (m, 3H), 2.58 (t, *J* = 7.2 Hz, 2H), 1.65 (m, 2H), 1.40 (m, 2H), 0.94 (t, *J* = 7.2 Hz, 3H); MS (EI) *m/z* (rel intensity) 205 (M^+, 100). **52**, ^{1}H NMR ($CDCl_3$) δ 7.20-7.80 (m, 4H), 2.60 (t, *J* = 7.2 Hz, 2H), 2.40 (s, 3H), 1.65 (m, 2H), 1.40 (m, 2H), 0.94 (t, *J* = 7.2 Hz, 3H); MS (EI) *m/z* (rel intensity) 251 (M^+, 15), 215 (20), 173 (100), 91 (90). **53**, ^{1}H NMR ($CDCl_3$) δ 7.88 (s, 1H), 7.20-7.40 (m, 3H), 6.90-7.00 (m, 1H), 2.60 (t, *J* = 7.2 Hz, 2H), 2.36 (s, 3H), 1.60 (m, 2H), 1.40 (m, 2H), 0.90 (t, *J* = 7.2 Hz, 3H); MS (EI) *m/z* (rel intensity) 251 (M^+, 100), 208 (15). **54**, ^{1}H NMR ($CDCl_3$) δ 7.94 (br s, 1H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 2.60 (t, *J* = 7.2 Hz, 2H), 2.35 (s, 3H), 1.68 (m, 2H), 1.42 (m, 2H), 0.96 (t, *J* = 7.2 Hz, 3H); MS (EI) *m/z* (rel intensity) 251 (M^+, 100), 208 (20).

4′-{[5-(2-Butyl-3-phenyl)-2,1,3,4-1*H*-thiatriazol-2-on-1-yl]methyl}biphenyl-2-(1-trityl)tetrazole (55-60) and 4′-{[5-(2-Butyl-3-phenyl)-2,1,3,4-1*H*-thiatriazol-2-on-1-yl]methyl}biphenyl-2-tetrazole (61-66)

Compounds **55-60** (~3 mmol) were prepared from the corresponding **49-54** (~5 mmol) by the similar method (Cs_2CO_3/DMF) as described for **8** and **9** to give **55-60** in 55-60% yields, as colorless foam. **55**, ^{1}H NMR ($CDCl_3$) δ 7.98 (d, *J* = 8.0 Hz, 1H), 6.80-7.60 (m, 27H), 4.86, 4.65 (ABq, *J* = 16.1 Hz, 2H), 2.44 (m, 2H), 1.66 (m, 2H), 1.40 (m, 2H), 0.91 (t, *J* = 7.2 Hz, 3H). **56**, ^{1}H NMR ($CDCl_3$) δ 7.95 (d, *J* = 8.0 Hz, 1H), 6.80-7.60 (m, 26H), 4.92, 4.70 (ABq, *J* = 16.4 Hz, 2H), 2.77 (t, *J* = 7.2 Hz, 2H), 2.40 (m, 2H), 1.60 (m, 2H), 1.40 (m, 2H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.90 (t, *J* = 7.2 Hz, 3H). **57**, ^{1}H NMR ($CDCl_3$) δ 7.98 (d, *J* = 8.0 Hz, 1H), 6.80-7.60 (m, 25H), 4.92, 4.70 (ABq, *J* = 16.6 Hz, 2H), 2.37 (m, 2H), 1.60 (m, 2H), 1.30 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H). Compounds **58-60** were deprotected without purification in acidic solution (10% HCl, THF) to give **61-66** in 60-65% yields as colorless foam. **61**, IR ($CHCl_3$) 1200 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.82 (d, *J* = 8.0 Hz, 1H), 7.00-7.60 (m, 12H), 4.83 (d, *J* = 3.3 Hz, 2H), 2.47 (m, 2H), 1.69 (m, 2H), 1.38 (m, 2H), 0.91 (t, *J* = 7.2 Hz, 3H); MS (EI) *m/z* (rel intensity) 471 (M^+, 10), 235 (100), HRMS, calcd for $C_{25}H_{25}ON_7S$ 471.1841, found 471.1860. **62**, IR ($CHCl_3$) 1200 (s) cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 7.80 (d, *J* = 7.5 Hz, 1H), 7.00-7.60 (m, 11H), 4.80 (m, 2H), 2.60 (m, 2H), 2.40 (m, 2H), 1.60 (m, 2H), 1.30 (m, 2H), 1.20 (m, 2H), 0.84 (t, *J* = 7.4 Hz, 3H); MS (EI) *m/z* (rel intensity) 499 (M^+, 5), 469 (20), 336 (90), 235 (100); HRMS, calcd for $C_{27}H_{29}ON_7S$ 499.2154, found 499.2152. **63**, IR ($CHCl_3$) 1200 (s) cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 8.10 (d, *J* = 7.5 Hz, 1H), 7.62 (d, *J* = 7.5 Hz, 1H), 7.20-7.60 (m, 10H), 4.99 (d, *J* = 7.0 Hz, 2H), 2.49 (m, 2H), 1.60 (m, 2H), 1.40 (m, 2H), 0.93 (t, *J* = 7.2 Hz, 3H); MS (EI) *m/z* (rel intensity) 539 (M^+, 50), 496 (20), 235 (100); HRMS, calcd for $C_{26}H_{24}ON_7SF_3$ 539.1715, found 539.1743. **64**, IR ($CHCl_3$) 1180 (s) cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 8.00 (d, *J* = 8.0 Hz, 1H), 7.00-7.62 (m, 11H), 4.92 (m, 2H), 2.50 (m, 2H), 1.67 (m, 2H), 1.35 (m, 2H), 0.91 (t, *J* = 7.2 Hz, 3H); MS (EI) *m/z* (rel intensity) 485 (M^+, 10), 235(100); HRMS, calcd for $C_{26}H_{27}ON_7S$ 485.1998, found 485.1993. **65**, IR ($CHCl_3$) 1190 (s) cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 7.88 (d, *J* = 8.0 Hz, 1H), 7.00-7.60 (m, 11H), 4.85 (m, 2H), 2.50 (m, 2H), 2.34 (s, 3H), 1.70 (m, 2H), 1.35 (m, 2H), 0.94 (t, *J* = 7.2 Hz, 3H); MS (EI) *m/z* (rel intensity) 485 (M^+, 100), 442 (30), 235 (30); HRMS, calcd for $C_{26}H_{27}ON_7S$ 485.1998, found 485.2003. **66**, IR ($CHCl_3$) 1200 (s) cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 8.06 (d, *J* = 8.0 Hz, 1H), 7.00-7.62 (m, 11H), 4.93 (m, 2H), 2.54 (m, 2H), 1.76 (m, 2H), 1.40 (m, 2H), 0.97 (t, *J* = 7.2 Hz, 3H); MS (EI) *m/z* (rel intensity) 485 (M^+, 100), 235 (40); HRMS, calcd for $C_{26}H_{27}ON_7S$ 485.1998, found 485.2004.

3-[*N*′-[2-[(1-Trityltetrazole)biphenyl-4-yl]methyl]-*N*′-(1-iminopentyl)hydrazino]propionitrile Hydrochloride (67) and 4′-[(5-Butyl-3-cyanoethyl-2,1,3,4-4*H*-thiatriazol-2-on-4-yl)methyl]biphenyl-2-(1-trityl)tetrazole (68)

A mixture of **3** (1.8 g, 8.8 mmol) and cesium carbonate (7.2 g, 22.1 mmol) was stirred at 50 °C for 13 h. The resulting mixture was filtered, and placed in a Kügelrohr apparatus and evaporated under vaccum at 40 °C. The residue was

partitioned between ethyl acetate and brine. The ethyl acetate solution was washed with water, dried and evaporated and the crude product was purified by chromatography, eluted with 5% methanol in ethyl acetate to give **67** (45%) as a yellow foam. ^{1}H NMR ($CDCl_3$) δ 7.88 (d, J = 8.0 Hz, 1H), 6.80-7.50 (m, 22H), 3.78 (s, 2H), 3.05 (t, J = 7.0 Hz, 2H), 2.43 (m, 2H), 2.18 (t, J = 7.3 Hz, 2H), 1.30 (m, 2H), 1.20 (m, 2H), 0.80 (t, J = 7.2 Hz, 2H). Compound **68** was prepared from **67**, by the similar procedure as that described for the preparation of **28**, in 80% yield as a white powder, mp 139-140 °C from ether-hexane. IR ($CHCl_3$) 2320 (s), 1200 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.00 (d, J = 7.5 Hz, 1H), 6.80-7.60 (m, 22H), 3.95, 3.83 (ABq, J = 13.2 Hz, 2H), 3.11 (m, 2H), 2.80 (m, 2H), 2.40 (m, 2H), 1.60 (m, 2H), 1.40 (m, 2H), 0.94 (t, J = 7.2 Hz, 3H); Anal. Calcd for $C_{41}H_{38}ON_8S$: C, 71.28; H, 5.54; N, 16.22; found C, 70.90; H, 5.58; N, 15.95.

4′-{[5-Butyl-3-(2-trifluoromethyl)phenyl-2,1,3,4-1*H*-thiatriazol-2-on-1-yl]methyl}biphenyl-2-*t*-butylcarboxylate 70 and 4′-{[5-Butyl-3-(2-trifluoromethyl)phenyl-2,1,3,4-1*H*-thiatriazol-2-on-1-yl]methyl}biphenyl-2-carboxylic acid 71

Compound **70** (1.2 g, 2.10 mmol) was prepared from **51** and **69**[2e], by the similar procedure (Cs_2CO_3/DMF) as that described for **8** and **9**, in 50% yield as a yellow oil. IR ($CHCl_3$) 1710 (s) cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 7.80 (d, J = 8.0 Hz, 1H), 7.00-7.60 (m, 11H), 5.03, 4.89 (ABq, J = 16.3 Hz, 2H), 2.33 (t, J = 7.2 Hz, 2H), 1.60 (m, 2H), 1.35 (m, 3H), 1.27 (s, 9H), 0.87 (t, J = 7.2 Hz, 3H). Compound **70** was deprotected via a known methodology[16] (CF_3COOH/ CH_2Cl_2) to give **71** in 60% yield as a colorless foam. IR ($CHCl_3$) 1710 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.95 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 4.60 (dd, J = 21.9, 16.0 Hz), 2.60 (m, 2H), 2.40 (m, 2H), 1.75 (m, 2H), 1.40 (m, 2H), 0.96 (t, J = 7.2 Hz, 3H). MS (EI) m/z (rel intensity) 515 (M^+, 20), 367 (30), 258 (25), 211 (100); HRMS, calcd for $C_{26}H_{24}O_3N_3SF_3$ 515.1491, found 515.1489.

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