Note

Synthesis of Novel Biphenyltetrazole Derivatives Containing 5-Methylisoxazole Substituted 1,2,4-Triazole

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An efficient route to synthesize the target compounds was developed. Fifteen new 5-[4′-(5-isoxazol-4-aryl-1,2,4-triazol-3-yl-sulfanylmethyl)-biphenyl-2-yl]-tetrazoles derivatives were synthesized. The structures of the new compounds synthesized were confirmed by elemental analyses and spectral data.

Keywords: Biphenyltetrazole; 1,2,4-Triazole; 5-Methylisoxazole.

INTRODUCTION

The discovery of losartan as a potent and effective oral angiotensin AT_1 selective A II antagonist has generated significant interest in the search for other nonpeptide A II antagonists.[1] Up till now, several highly potent AT_1 selective antagonists containing heterocycles have been reported. The great majority of them contain a biphenyltetrazole moiety appended to a five-membered or a six-membered heterocycle. The biphenyltetrazole moiety is considered to be an essential acidic functional group for antagonism.

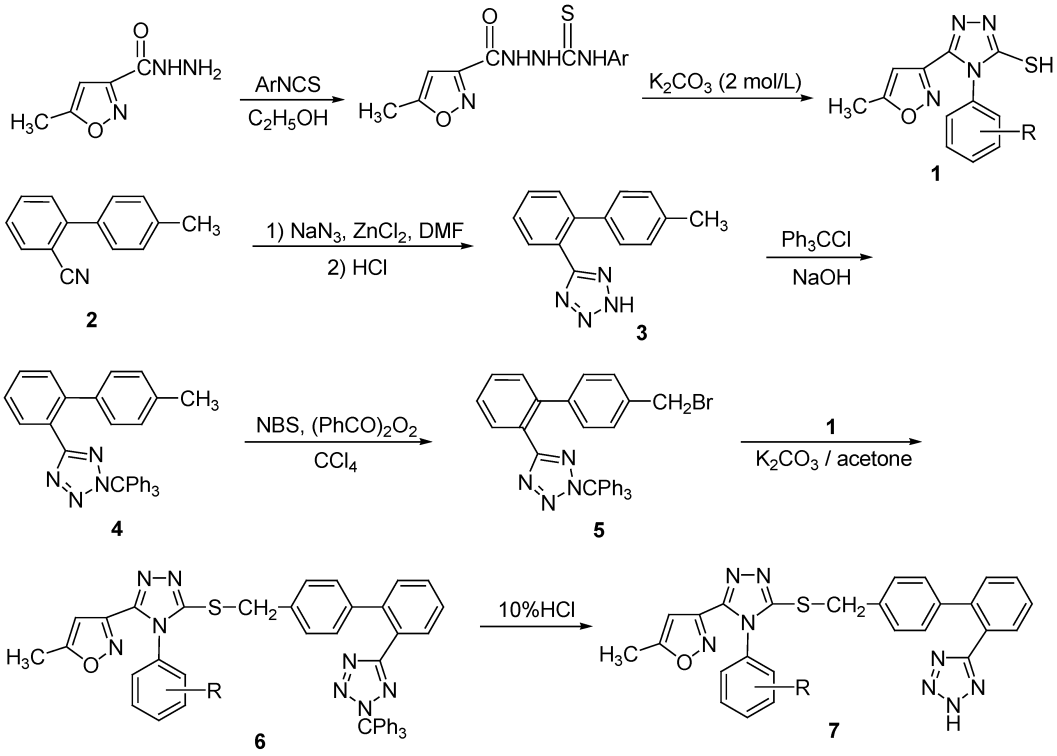
Substituted 1,2,4-triazole derivatives have shown broad-spectrum biological activities such as antibacterial,[2] pesticide,[3] herbicide,[4] phytohormone[5] and antihypertensive[6] activities. 5-Methylisoxazole derivatives have also shown biological effects such as antibacterial[7,8] and phytohormone[9] effects. So far, biphenyltetrazole compounds containing 5-methylisoxazole substituted 1,2,4-triazole moiety have not been reported. Combining biphenyltetrazole with isoxazole substituted 1,2,4-triazole by -SCH_2- is expected to give novel heterocyclic compounds with better antibacterial activities. In this paper, we describe the synthesis of novel compounds which bear both biphenyltetrazole and 5-methylisoxazole substituted 1,2,4-triazole moieties.

RESULTS AND DISCUSSION

5-Methylisoxazole-3-carbohydrazide, which is required as a starting material, was prepared according to the literature.[10a] As shown in Scheme I, 4-aryl-5-(5-methylisoxazol-3-yl)-1,2,4-triazol-3-thiols (**1a-1o**) were prepared by the reaction of 5-methylisoxazole-3-carbohydrazide with arylisothiocyanates and then cyclization in the presence of 2 mol/L aqueous potassium carbonate solution.[10b] An important class of compounds in this paper is the biphenyltetrazoles. The classical method of synthesizing tetrazoles from nitriles employing ammonium chloride/sodium azide is not suitable for sterically hindered nitriles.[11] The method of Duncia[12] using trimethyltin or tributyltin azide is not convenient; moreover, organic tin reagents are usually highly toxic. In this paper, 5-(4′-methyl-biphenyl-2-yl)tetrazole (**3**) was synthesized from **2** using sodium azide/zinc chloride by a modified method described by Rocco.[13] Treatment of **3** with triphenylmethyl chloride in NaOH aqueous solution gave trityl protected tetrazole **4**. The yield of the two steps was obviously improved by optimizing the experimental conditions (previous yield 68%, optimal yield 87%). Bromination of **4** with *N*-bromosuccinimide provided **5**. Alkylation of **1** with **5** in the presence of potassium carbonate at the refluxing temperature of acetone afforded *S*-alkylated products **6a-6o** in moderate to good yields. The trityl group was successfully removed by treatment with 10% aqueous hydrochloric acid in THF/CH_3OH to yield the desired compounds **7a-7o**. All steps only need simple recrystallization for purification, if necessary. So it is an efficient route to synthesize the target compounds.

The structures of **7a-7o** were confirmed by elemental analyses and spectral data. The ^{1}H NMR spectra of **6a-6o** and **7a-7o** exhibited two doublets for SCH_2 at 4.34-4.56

Scheme I



R = H (**a**), *o*-CH_3 (**b**), *m*-CH_3 (**c**), *p*-CH_3 (**d**), *o*-Cl (**e**), *m*-Cl (**f**), *p*-Cl (**g**), *o*-Br (**h**), *m*-Br (**i**), *p*-Br (**j**), *o*-CH_3O (**k**), *p*-CH_3O (**l**), *o*-EtO (**m**), *p*-EtO (**n**), 3,4-diCH_3 (**o**)

ppm, no matter whether the *ortho*-group R is an electron-withdrawing group or an electron-donating group. The reason is likely that the *ortho*-group R is much closer to SCH_2, which makes the groups crowded and blocks free rotation of the *sigma*-bond in SCH_2 and results in a different chemical environment for two protons. When R is a *meta*-group or a *para*-group, SCH_2 normally exhibited a singlet. The IR spectra displayed an absorption band in the region of 1413-1497 cm^{-1} due to C-S-C, whereas the characteristic absorption bands for C=N and N-N=C functions appeared in the range of 1604-1607 cm^{-1} and 1235-1254 cm^{-1}, respectively. The molecular ions of **7a-7o** could be detected by FAB-MS.

Compounds **7a-7o** were screened for their antibacterial activity against *Escherichia coli* and *Staphylococcus aureu*. The antibacterial activity showed that most of the

Table 1. Physical properties and elemental analyses of compounds **6a-6o** and **7a-7o**

No.	Yield (%)	Mp (°C)	Formula	Elemental anal. Found (Calcd.) (%)		
				C	H	N
6a	83	174-175	$C_{45}H_{34}N_8OS$	73.28 (73.55)	4.54 (4.66)	14.98 (15.25)
6b	72	167-168	$C_{46}H_{36}N_8OS$	73.41 (73.77)	4.78 (4.85)	14.58 (14.96)
6c	77	118-119	$C_{46}H_{36}N_8OS$	73.62 (73.77)	4.95 (4.85)	14.33 (14.96)
6d	69	135-136	$C_{46}H_{36}N_8OS$	73.44 (73.77)	4.58 (4.85)	14.68 (14.96)
6e	67	123-125	$C_{45}H_{33}ClN_8OS$	69.88 (70.25)	4.05 (4.32)	14.23 (14.57)
6f	69	153-154	$C_{45}H_{33}ClN_8OS$	69.94 (70.25)	4.16 (4.32)	14.24 (14.57)
6g	57	135-137	$C_{45}H_{33}ClN_8OS$	69.91 (70.25)	4.01 (4.32)	14.31 (14.57)
6h	64	116-118	$C_{45}H_{33}BrN_8OS$	66.12 (66.42)	3.98 (4.09)	13.89 (13.77)
6i	66	169-170	$C_{45}H_{33}BrN_8OS$	66.09 (66.42)	3.84 (4.09)	13.58 (13.77)
6j	72	127-128	$C_{45}H_{33}BrN_8OS$	66.10 (66.42)	3.80 (4.09)	13.42 (13.77)
6k	40	171-172	$C_{46}H_{36}N_8O_2S$	72.41 (72.23)	4.78 (4.74)	14.30 (14.65)

6l	81	102-104	$C_{46}H_{36}N_8O_2S$	72.02 (72.23)	4.89 (4.74)	14.36 (14.65)
6m	77	150-153	$C_{47}H_{38}N_8O_2S$	72.22 (72.47)	4.83 (4.92)	14.06 (14.39)
6n	61	156-157	$C_{47}H_{38}N_8O_2S$	72.16 (72.47)	4.71 (4.92)	14.08 (14.39)
6o	78	130-131	$C_{47}H_{38}N_8OS$	73.68 (73.99)	4.85 (5.02)	14.32 (14.69)
7a	51	129-130	$C_{26}H_{20}N_8OS$	63.12 (63.40)	3.86 (4.09)	22.36 (22.75)
7b	81	120-121	$C_{27}H_{22}N_8OS$	63.79 (64.02)	4.28 (4.38)	21.78 (22.12)
7c	81	119-121	$C_{27}H_{22}N_8OS$	63.84 (64.02)	4.30 (4.38)	21.99 (22.12)
7d	96	122-123	$C_{27}H_{22}N_8OS$	63.76 (64.02)	4.46 (4.38)	21.75 (22.12)
7e	75	149-150	$C_{26}H_{19}ClN_8OS$	59.54 (59.26)	3.78 (3.63)	21.02 (21.26)
7f	65	178-179	$C_{26}H_{19}ClN_8OS$	59.38 (59.26)	3.76 (3.63)	20.94 (21.26)
7g	81	128-129	$C_{26}H_{19}ClN_8OS$	59.06 (59.26)	3.71 (3.63)	20.96 (21.26)
7h	94	185-186	$C_{26}H_{19}BrN_8OS$	54.83 (54.65)	3.66 (3.35)	19.42 (19.61)
7i	78	179-180	$C_{26}H_{19}BrN_8OS$	54.83 (54.65)	3.59 (3.35)	19.29 (19.61)
7j	90	133-134	$C_{26}H_{19}BrN_8OS$	54.36 (54.65)	3.42 (3.35)	19.88 (19.61)
7k	70	124-125	$C_{27}H_{22}N_8O_2S$	61.78 (62.06)	4.36 (4.24)	21.11 (21.44)
7l	56	158-160	$C_{27}H_{22}N_8O_2S$	61.75 (62.06)	4.35 (4.24)	21.15 (21.44)
7m	80	109-110	$C_{28}H_{24}N_8O_2S$	62.95 (62.67)	4.78 (4.51)	20.54 (20.88)
7n	51	136-137	$C_{28}H_{24}N_8O_2S$	62.48 (62.67)	4.32 (4.51)	20.62 (20.88)
7o	67	136-138	$C_{28}H_{24}N_8OS$	64.41 (64.60)	4.75 (4.65)	21.25 (21.52)

Table 2. ^{1}H NMR data of compounds **6a-6o**

No.	^{1}H NMR ($CDCl_3$, δ, ppm)
6a	8.00-7.97 (m, 1H, ArH), 7.51-6.85 (m, 27H, ArH), 6.55 (s, 1H, hetH), 4.45 (s, 2H, CH_2S), 2.42 (s, 3H, CH_3)
6b	7.97 (d, *J* = 6.9 Hz, 1H, ArH), 7.46-6.99 (m, 25H, ArH), 6.87 (d, *J* = 7.5 Hz, 1H, ArH), 6.56 (s, 1H, hetH), 4.49 (d, *J* = 12.3 Hz, 1H, SCH_2), 4.43 (d, *J* = 12.3 Hz, 1H, SCH_2), 2.41 (s, 3H, CH_3), 1.96 (s, 3H, $ArCH_3$)
6c	7.99 (d, *J* = 6.3 Hz, 1H, ArH), 7.47-6.94 (m, 25H, ArH), 6.86 (d, *J* = 7.8 Hz, 1H, ArH), 6.54 (s, 1H, hetH), 4.45 (s, 2H, CH_2S), 2.42 (s, 3H, CH_3), 2.31 (s, 3H, $ArCH_3$)
6d	8.00-7.96 (m, 1H, ArH), 7.46-7.02 (m, 25H, ArH), 6.87 (d, *J* = 6.9 Hz, 1H, ArH), 6.55 (s, 1H, hetH), 4.45 (s, 2H, CH_2S), 2.42 (s, 3H, CH_3), 2.39 (s, 3H, $ArCH_3$)
6e	7.99-7.97 (m, 1H, ArH), 7.54-6.86 (m, 26H, ArH), 6.64 (s, 1H, hetH), 4.54 (d, *J* = 9.3 Hz, 1H, SCH_2), 4.39 (d, *J* = 9.3 Hz, 1H, SCH_2), 2.42 (s, 3H, $ArCH_3$)
6f	8.01-7.98 (m, 1H, ArH), 7.63-7.05 (m, 25H, ArH), 6.86 (d, *J* = 8.1 Hz, 1H, ArH), 6.61 (s, 1H, hetH), 4.44 (s, 2H, CH_2S), 2.43 (s, 3H, CH_3)
6g	7.98 (d, *J* = 5.1 Hz, 1H, ArH), 7.46-7.05 (m, 25H, ArH), 6.88 (d, *J* = 7.5 Hz, 1H, ArH), 6.60 (s, 1H, hetH), 4.45 (s, 2H, CH_2S), 2.43 (s, 3H, CH_3)
6h	7.99-7.96 (m, 1H, ArH), 7.71-7.68 (m, 1H, ArH), 7.47-6.87 (m, 25H, ArH), 6.63 (s, 1H, hetH), 4.54 (d, *J* = 12.3 Hz, 1H, SCH_2), 4.40 (d, *J* = 12.3 Hz, 1H, SCH_2), 2.41 (s, 3H, CH_3)
6i	8.00-7.96 (m, 1H, ArH), 7.51-6.84 (m, 26H, ArH), 6.60 (s, 1H, hetH), 4.44 (s, 2H, CH_2S), 2.44 (s, 3H, CH_3)
6j	7.99-7.96 (m, 1H, ArH), 7.60-6.86 (m, 26H, ArH), 6.58 (s, 1H, hetH), 4.43 (s, 2H, CH_2S), 2.42 (s, 3H, CH_3)
6k	7.98-7.96 (m, 1H, ArH), 7.49-6.96 (m, 25H, ArH), 6.87 (d, *J* = 6.9 Hz, 1H, ArH), 6.56 (s, 1H, hetH), 4.49 (d, *J* = 12.3 Hz, 1H, SCH_2), 4.36 (d, *J* = 12.3 Hz, 1H, SCH_2), 3.65 (s, 3H, CH_3O), 2.41 (s, 3H, $ArCH_3$)
6l	8.00-7.97 (m, 1H, ArH), 7.47-6.86 (m, 26H, ArH), 6.55 (s, 1H, hetH), 4.45 (s, 2H, CH_2S), 3.80 (s, 3H, CH_3O), 2.42 (s, 3H, $ArCH_3$)
6m	7.97 (d, *J* = 6.9 Hz, 1H, ArH), 7.50-6.86 (m, 26H, ArH), 6.56 (s, 1H, hetH), 4.50 (d, *J* = 12.9 Hz, 1H, SCH_2), 4.36 (d, *J* = 12.9 Hz, 1H, SCH_2), 3.97 (q, *J* = 2.4, Hz, 1H, CH_3CH_2O), 3.97 (q, *J* = 2.4, Hz, 1H, CH_3CH_2O), 2.41 (s, 3H, CH_3), 1.11 (t, *J* = 6.9 Hz, 3H, CH_3CH_2O)
6n	7.99-7.96 (m, 1H, ArH), 7.48-6.84 (m, 26H, ArH), 6.53 (s, 1H, hetH), 4.43 (s, 2H, CH_2S), 4.01 (q, *J* = 6.9 Hz, 2H, CH_3CH_2O), 2.42 (s, 3H, CH_3), 1.41 (t, *J* = 6.9 Hz, 3H, CH_3CH_2O)
6o	8.00-7.97 (m, 1H, ArH), 7.49-6.85 (m, 26H, ArH), 6.54 (s, 1H, hetH), 4.45 (s, 2H, CH_2S), 2.41 (s, 3H, CH_3), 2.28 (s, 3H, $ArCH_3$), 2.24 (s, 3H, $ArCH_3$)

Table 3. ^{1}H NMR data of compounds **7a-7o**

No.	^{1}H NMR ($CDCl_3$, δ, ppm)
7a	7.84 (d, *J* = 7.8 Hz, 1H, ArH), 7.53-6.99 (m, 12H, ArH), 6.33 (s, 1H, HetH), 4.26 (s, 2H, SCH_2), 2.36 (s, 3H, CH_3)
7b	7.87 (d, *J* = 6.6 Hz, 1H, ArH), 7.57-7.22 (m, 8H, ArH), 7.20-7.00 (m, 3H, ArH), 6.34 (s, 1H, HetH), 4.30 (s, 2H, SCH_2), 2.36 (s, 3H, CH_3), 1.92 (s, 3H, CH_3)
7c	7.83 (d, *J* = 7.8 Hz, 1H, ArH), 7.56-6.96 (m, 11H, ArH), 6.31 (s, 1H, HetH), 4.27 (s, 2H, SCH_2), 2.36 (s, 6H, CH_3, $ArCH_3$)
7d	7.83 (d, *J* = 7.8 Hz, 1H, ArH), 7.56-6.98 (m, 11H, ArH), 6.32 (s, 1H, HetH), 4.26 (s, 2H, SCH_2), 2.40 (s, 3H, CH_3), 2.36 (s, 3H, CH_3)
7e	7.63-6.95 (m, 12H, ArH), 6.43 (s, 1H, HetH), 4.39 (d, *J* = 12.9 Hz, 1H, SCH_2), 4.15 (d, *J* = 12.9 Hz, 1H, SCH_2), 2.33 (s, 3H, CH_3)
7f	7.54 (d, *J* = 6.9 Hz, 1H, ArH), 7.44-7.02 (m, 11H, ArH), 6.42 (s, 1H, HetH), 4.34 (s, 2H, SCH_2), 2.35 (s, 3H, CH_3)
7g	7.84 (d, *J* = 6.6 Hz, 1H, ArH), 7.56-6.99 (m, 11H, ArH), 6.41 (s, 1H, HetH), 4.28 (s, 2H, SCH_2), 2.38 (s, 3H, CH_3)
7h	7.83 (d, *J* = 6.6 Hz, 1H, ArH), 7.71-6.99 (m, 11H, ArH), 6.42 (s, 1H, HetH), 4.32 (d, *J* = 13.5 Hz, 1H, SCH_2), 4.25 (d, *J* = 13.5 Hz, 1H, SCH_2), 2.36 (s, 3H, CH_3)
7i	7.56 (d, *J* = 6.9 Hz, 1H, ArH), 7.38-7.03 (m, 11H, ArH), 6.42 (s, 1H, HetH), 4.34 (s, 2H, SCH_2), 2.35 (s, 3H, CH_3)
7j	7.87 (d, *J* = 6.9 Hz, 1H, ArH), 7.62-7.00 (m, 11H, ArH), 6.41 (s, 1H, HetH), 4.29 (s, 2H, SCH_2), 2.39 (s, 3H, CH_3)
7k	7.82 (d, *J* = 6.9 Hz, 1H, ArH), 7.54-6.96 (m, 11H, ArH), 6.34 (s, 1H, HetH), 4.22 (d, *J* = 13.5 Hz, 1H, SCH_2), 4.15 (d, *J* = 13.5 Hz, 1H, SCH_2), 3.68 (s, 3H, CH_3O), 2.34 (s, 3H, CH_3)
7l	7.54 (d, *J* = 10.5 Hz, 1H, ArH), 7.35-6.93 (m, 11H, ArH), 6.30 (s, 1H, HetH), 4.34 (s, 2H, SCH_2), 3.78 (s, 3H, CH_3O), 2.34 (s, 3H, CH_3)
7m	7.81 (d, *J* = 7.5 Hz, 1H, ArH), 7.52-6.96 (m, 11H, ArH), 6.34 (s, 1H, HetH), 4.21 (d, *J* = 12.9 Hz, 1H, SCH_2), 4.12 (d, *J* = 12.9 Hz, 1H, SCH_2), 3.94 (q, *J* = 6.6 Hz, 2H, CH_3CH_2O), 2.35 (s, 3H, CH_3), 1.08 (t, *J* = 6.6 Hz, 3H, CH_3CH_2O)
7n	7.81 (d, *J* = 7.5 Hz, 1H, ArH), 7.52-6.91 (m, 11H, ArH), 6.30 (s, 1H, HetH), 4.25 (s, 2H, SCH_2), 4.04 (q, *J* = 7.2 Hz, 2H, CH_3CH_2O), 2.34 (s, 3H, CH_3), 1.41 (t, *J* = 7.2 Hz, 3H, CH_3CH_2O)
7o	7.83 (d, *J* = 7.2 Hz, 1H, ArH), 7.53-6.89 (m, 10H, ArH), 6.31 (s, 1H, HetH), 4.26 (s, 2H, SCH_2), 2.36 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.24 (s, 3H, CH_3)

compounds were inactive against these microorganisms. Further investigation on biological activities of these compounds is in progress.

EXPERIMENTAL

The melting points were taken on an X-4 microscopic melting point apparatus and are uncorrected. IR spectra were recorded on a Nicloet NEXUS 670 FT-IR spectrometer in KBr disc. ^{1}H NMR and ^{13}C NMR spectra were recorded at room temperature on a Varian Mercury-300 MHz spectrometer with TMS as internal standard. Mass spectra were performed on a VG ZAB-HS (FAB) instrument. Elemental analysis was performed on an Elementar Vario EL apparatus.

4′-Methylbiphenyl-2-carbonitrile (**2**) is a commercial reagent. 4-Aryl-5-(5-methylisoxazol-3-yl)-1,2,4-triazol-3-thiols (**1a-1o**) were synthesized according to the literature.[10b]

Preparation of 5-(4′-methylbiphenyl-2-yl)-1H-tetrazole (3)

A mixture of **2** (0.1 mol), zinc chloride (0.3 mmol), sodium azide (0.9 mmol), and 150 mL of dry DMF was refluxed for 36 h. The reaction mixture was allowed to cool to room temperature and acidified with 10% aqueous hydrochloric acid (pH = 1). The resulting solution was added with stirring to ice-water (1320 mL), and the mixture was stirred for 1 h. The precipitate was collected, washed with water, dried and recrystallized from ethyl acetate to provide **3** as a white solid in 96% yield. mp 158-160 °C (lit.[13] 144-148 °C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 11.52 (s, 1H, NH), 8.12 (d, *J* = 7.0 Hz, 1H, ArH), 7.55-7.03 (m, 7H,

Table 4. ^{13}C NMR data of compounds **7a-7o**

No.	^{13}C NMR ($CDCl_3$, δ, ppm)
7a	170.09, 155.33, 153.90, 151.91, 146.82, 140.85, 138.79, 135.76, 133.00, 131.03, 130.80, 130.61, 130.45, 129.67, 129.26, 129.13, 127.95, 127.23, 122.96, 101.36, 36.51, 12.01
7b	170.12, 153.83, 151.89, 146.77, 140.85, 138.82, 135.83, 135.70, 132.22, 131.42, 131.07, 130.80, 130.63, 129.25, 128.00, 127.50, 127.30, 122.93, 100.98, 36.09, 17.34, 12.07
7c	170.03, 153.94, 151.90, 146.75, 140.85, 139.90, 138.77, 135.72, 132.85, 131.26, 130.99, 130.79, 130.59, 129.38, 129.25, 129.11, 127.90, 127.57, 124.16, 123.00, 101.35, 36.48, 21.23, 11.99
7d	170.03, 155.33, 154.07, 151.94, 146.85, 140.86, 140.74, 138.77, 135.72, 130.99, 130.80, 130.59, 130.32, 129.23, 129.11, 128.61, 127.90, 126.87, 122.99, 101.36, 36.45, 21.30, 11.99
7e	170.08, 155.29, 153.48, 151.84, 146.65, 140.88, 138.77, 135.70, 133.66, 132.71, 132.04, 131.05, 130.77, 130.60, 129.49, 129.23, 128.76, 128.61, 127.93, 127.66, 126.80, 122.91, 122.18, 100.98, 36.41, 11.97
7f	170.27, 155.37, 153.65, 151.81, 146.65, 140.88, 138.77, 135.70, 133.66, 132.71, 132.04, 131.05, 130.77, 130.60, 129.49, 129.23, 128.76, 128.61, 127.93, 127.66, 126.80, 122.91, 122.18, 101.28, 36.61, 11.97
7g	170.26, 155.35, 153.85, 151.87, 146.75, 140.80, 138.85, 136.57, 135.76, 131.49, 131.08, 130.80, 130.64, 129.95, 129.29, 129.14, 128.68, 128.01, 122.90, 101.39, 36.55, 12.01
7h	170.08, 155.29, 153.49, 151.84, 146.65, 140.88, 138.77, 135.70, 133.66, 132.71, 132.04, 131.05, 130.77, 130.60, 129.49, 129.23, 128.76, 128.61, 127.93, 127.66, 126.81, 122.91, 122.18, 100.98, 36.66, 11.99
7i	170.01, 155.40, 153.50, 151.80, 146.65, 140.88, 138.77, 135.70, 133.66, 132.71, 132.04, 131.05, 130.77, 130.60, 129.49, 129.23, 128.76, 128.61, 127.93, 127.66, 126.80, 122.91, 122.18, 100.68, 36.69, 12.02
7j	170.26, 153.79, 151.90, 146.71, 140.82, 138.89, 135.83, 132.96, 132.04, 131.09, 130.80, 130.65, 129.31, 129.20, 128.94, 128.04, 127.86, 124.76, 122.91, 101.42, 36.60, 12.04
7k	169.85, 155.24, 154.48, 153.84, 151.96, 147.32, 140.88, 138.66, 135.73, 132.07, 130.97, 130.85, 130.54, 129.22, 129.05, 128.58, 127.87, 123.04, 121.80, 120.91, 112.34, 101.06, 55.77, 36.57, 11.98
7l	168.59, 160.06, 159.29, 153.17, 151.13, 145.72, 140.28, 139.29, 132.88, 129.72, 128.87, 128.35, 127.45, 127.11, 126.65, 125.82, 125.64, 113.54, 100.25, 54.36, 35.54, 10.84
7m	169.79, 155.30, 153.73, 152.07, 147.38, 140.88, 138.68, 135.76, 131.90, 130.96, 130.85, 130.54, 129.22, 129.05, 128.51, 127.86, 123.07, 121.95, 120.72, 113.13, 101.03, 64.26, 36.63, 14.34, 11.99
7n	170.02, 160.19, 155.65, 154.46, 151.97, 147.03, 140.83, 138.85, 135.63, 130.79, 130.56, 129.22, 129.03, 128.38, 127.84, 125.13, 123.37, 115.14, 101.36, 63.77, 36.34, 14.63, 11.99
7o	169.98, 155.36, 154.11, 151.94, 146.80, 140.85, 139.41, 138.76, 138.39, 135.72, 130.97, 130.80, 130.67, 130.47, 129.25, 129.11, 127.89, 127.74, 124.27, 123.02, 101.38, 36.44, 19.79, 19.67, 12.01

ArH), 2.33 (s, 3H, CH_3).

Preparation of 5-(4′-methylbiphenyl-2-yl)-2-trityltetrazole (4)

To a suspension of **3** (5 mmol) in toluene (20 mL) at room temperature were added 10 mol/L sodium hydroxide solution (0.50 mL) and triphenylmethyl chloride (5 mmol), and the resulting mixture was stirred at room temperature for 3 h. To the reaction mixture was added distilled water (3 mL) and petroleum ether (7 mL), and the resulting slurry was stirred at 0 °C for 3 h. The slurry was filtered and the solids were washed with water. The solution was extracted with methylene dichloride. The organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to afford **4** as a white solid. The solid was recrystallizd from ethyl acetate/methylene dichloride to furnish 2.17 g of **4** (91%). mp 166-169 °C (lit.[14] 163-165 °C); ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.92 (d, J = 7.0 Hz, 1H, ArH), 7.50-6.92 (m, 22H, ArH), 2.29 (s, 3H, CH_3).

Preparation of 5-(4′-bromomethylbiphenyl-2-yl)-2-trityltetrazole (5)

A solution of **4** (10 mmol), *N*-bromosuccinimide (10 mmol) and dibenzoyl peroxide (1 mmol) in 60 mL of dry carbon tetrachloride was refluxed for 8 h, cooled to room temperature, and then filtered. The filtrate was concentrated under reduced pressure to afford the product. Trituration of the product with diethyl ether furnished **5** as a white

Table 5. FAB-MS and IR data of compounds **7a-7o**

No.	MS (*m/z*)	IR ν_{max}/cm^{-1}				
		$\nu_{C=N}$	$\nu_{N-N=C}$	ν_{C-O}	ν_{C-S-C}	
7a	492.6 (M+1)	1605	1243	1158	1497	1414
7b	506.6 (M+1)	1606	1243	1158	1474	1414
7c	506.6 (M+1)	1607	1239	1159	1474	1413
7d	506.6 (M+1), 528.5 (M+22)	1606	1242	1156	1474	1414
7e	525.6 (M), 547.4 (M+21), 569.3 (M+43)	1606	1243	1157	1490	1414
7f	527.6 (M+2), 548.4 (M+22), 570.2 (M+44)	1605	1235	1188	1483	1415
7g	526.6 (M+1)	1606	1242	1157	1494	1414
7h	569.9 (M)	1606	1245	1158	1485	1414
7i	594.0 (M+24), 615.6 (M+46)	1604	1236	1153	1485	1413
7j	571.9 (M+2)	1606	1242	1157	1490	1415
7k	522.6 (M+1)	1605	1246	1161	1473	1414
7l	522.6 (M+1), 544.5 (M+22), 566.3 (M+44)	1606	1253	1163	1511	1413
7m	536.6 (M+1), 559.5 (M+23)	1605	1243	1161	1476	1415
7n	536.6 (M+1)	1605	1254	1169	1476	1413
7o	520.5 (M+1)	1607	1240	1157	1475	1416

solid in 92% yield. mp 135-137 °C (lit.[13] 135-138 °C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.98-7.94 (m, 1H, ArH), 7.51-6.87 (m, 22H, ArH), 4.38 (s, 2H, CH_2).

General procedure for preparation of 5-[4′-(5-methyl-isoxazol-4-aryl-1,2,4-triazol-3-yl-sulfanylmethyl)-biphenyl-2-yl]-2-trityltetrazoles (6a-6o)

To a solution of **1a-1o** (1 mmol) in acetone (30 mL) was added K_2CO_3 (5 mmol). The mixture was stirred for 2 h at the refluxing temperature. Compound **5** (1.5 mmol) was then added to the solution, which was refluxed for 10-12 h. The reaction mixture was cooled to room temperature and filtered. Then the solvent was evaporated under vacuum; the analytical pure product was obtained directly by recrystallization from acetone or petroleum ether-acetone.

General procedure for preparation of 5-[4′-(5-methyl-isoxazol-4-aryl-1,2,4-triazol-3-yl-sulfanylmethyl)-biphenyl-2-yl]-tetrazoles (7a-7o)

A solution of compounds **6a-6o** (0.2 mmol), 10% hydrochloric acid (1.73 mL), tetrahydrofuran (8 mL), and methanol (8 mL) was stirred at room temperature for 8 h. To the solution was added 2 mol/L aqueous sodium hydroxide until pH = 12, and the solvents were removed under vacuum. The resulting residue was dissolved in water, and the mixture was filtered to remove the triphenylmethanol. The filtrate was adjusted to pH = 3 employing 10% aqueous hydrochloric acid. The resulting precipitate was collected by filtration and further purified by recrystallization from acetone.

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