Synthesis and characterisation of novel 1,3-bis{(6-aryl-1,2,4-triazolo [3,4-*b*][1,3,4]thiadiazol-3-yl)-methoxy}benzenes under microwave irradiation

Qinggang Mei, Jie Yang, Yongle Peng and Zhigang Zhao*

College of Chemistry and Environmental Protection Engineering, Southwest University for Nationalities, Chengdu 610041, P. R. China

Eleven novel 1,3-bis{(6-aryl-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)-methoxy}benzenes have been synthesised in high yields by the condensation of 5,5′-[1,3-phenylene-bis(oxymethylene)]bis(4-amino-3-mercapto-1,2,4-triazole) with substituted benzoic acids in the presence of phosphorus oxychloride under microwave irradiation. Compared with the conventional heating method, this method is facile, rapid and efficient. The structures of all new compounds were characterised by ^{1}H NMR, IR, MS and elemental analysis.

Keywords: bis-1,2,4-triazole, bis-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole, microwave irradiation

Derivatives of 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole are a group of highly important heterocyclic compounds. Thousands of compounds containing triazolo[3,4-*b*][1,3,4]thiadiazole fragment have been synthesised and studied, and many of them have been used in research and development of agrochemicals and pharmaceutical chemistry due to their diverse biological activities such as antimicrobial,[1–3] anti-inflammatory,[4] antifungal,[5] antiviral,[6] antitumor,[7] vascular relaxing,[8] analgesic,[9] herbicidal[10] and plant growth regulatory[11] effects. However, most of the compounds contain only one 1,2,4-triazolo [3,4-*b*][1,3,4]thiadiazole unit in one molecule. Published data on the synthesis of bis-triazolothiadiazoles substituted in the 3 and 6 positions by aryl or heterocyclic moieties are very scarce.[12] Until recently, Holla *et al*.[13] reported the synthesis of bis-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles *via* the reaction of bis-4-amino-5-mercapto-1,2,4-triazoles with various aromatic carboxylic acids, and most of these compounds were found to be active against dozens of cancer cell lines. Wang *et al*.[14] reported that pyridine derivatives containing bis-triazolo [3,4-*b*][1,3,4]thiadiazole units, synthesised by cyclisation of pyridine-2,6-dicarboxylic acid with various 1,2,4-triazoles, possess good antibacterial activities, but their preparation requires a prolonged reaction time of 13 h or so.

Moreover, it is observed that incorporation of aryloxymethyl substituents into heterocyclic ring systems augments their biological activities considerably.[15] Some of the substituted phenoxyacetic acid derivatives are reported to have excellent inhibitory activities against roots and stalks of dicotyledon plants.[16] In view of these findings and the principle of active superposition, we designed and synthesised a series of functionalised bis-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives possessing the 1,3-phenylenebis(oxy-methylene) moiety derived from hydrazide **3**. We anticipated that these new bis-triazolothiadiazoles might have a useful biological activity.

Green chemistry is an important part of modern organic chemistry. Microwave-assisted chemistry has blossomed into a useful technique in green chemistry for a variety of applications in organic synthesis and transformations.[17–19] In continuation of our investigations into the synthesis of organic compounds using microwave activation,[20–22] we report here a new access to novel bis-triazolothiadiazoles linked to a 1,3-phenylenebis(oxymethylene) moiety under microwave irradiation. The synthetic route is depicted in Scheme 1.

Results and discussion

The structures of compounds **6a–k** were established by different spectroscopic techniques (IR, NMR, and MS) and by elemental analysis. The IR spectrum of **5** exhibited characteristic absorption bands in the region 3269–3186 cm^{-1} due to the NH_2 stretching frequency, which were absent in the IR spectra of **6a–k**. The strong absorption bands at about 1596, 1278, and 684 cm^{-1} were assigned to the C=N, C=N–N, and C–S–C functions of the thiadiazole ring, respectively. The ^{1}H NMR spectrum of **5** displayed two singlets at 13.79 and 5.10 ppm corresponding to the SH and NH_2 groups respectively, which were not present in the spectra of compounds **6a–k**. The three multiplet signals in the range of 7.30–6.79 ppm resulted from the four aromatic protons of the central benzene ring; a sharp singlet at about 5.6 ppm corresponded to the OCH_2 unit. Their ESI-MS spectra showed the expected molecular ion peaks with high intensity.

Comparison of microwave irradiation and conventional heating

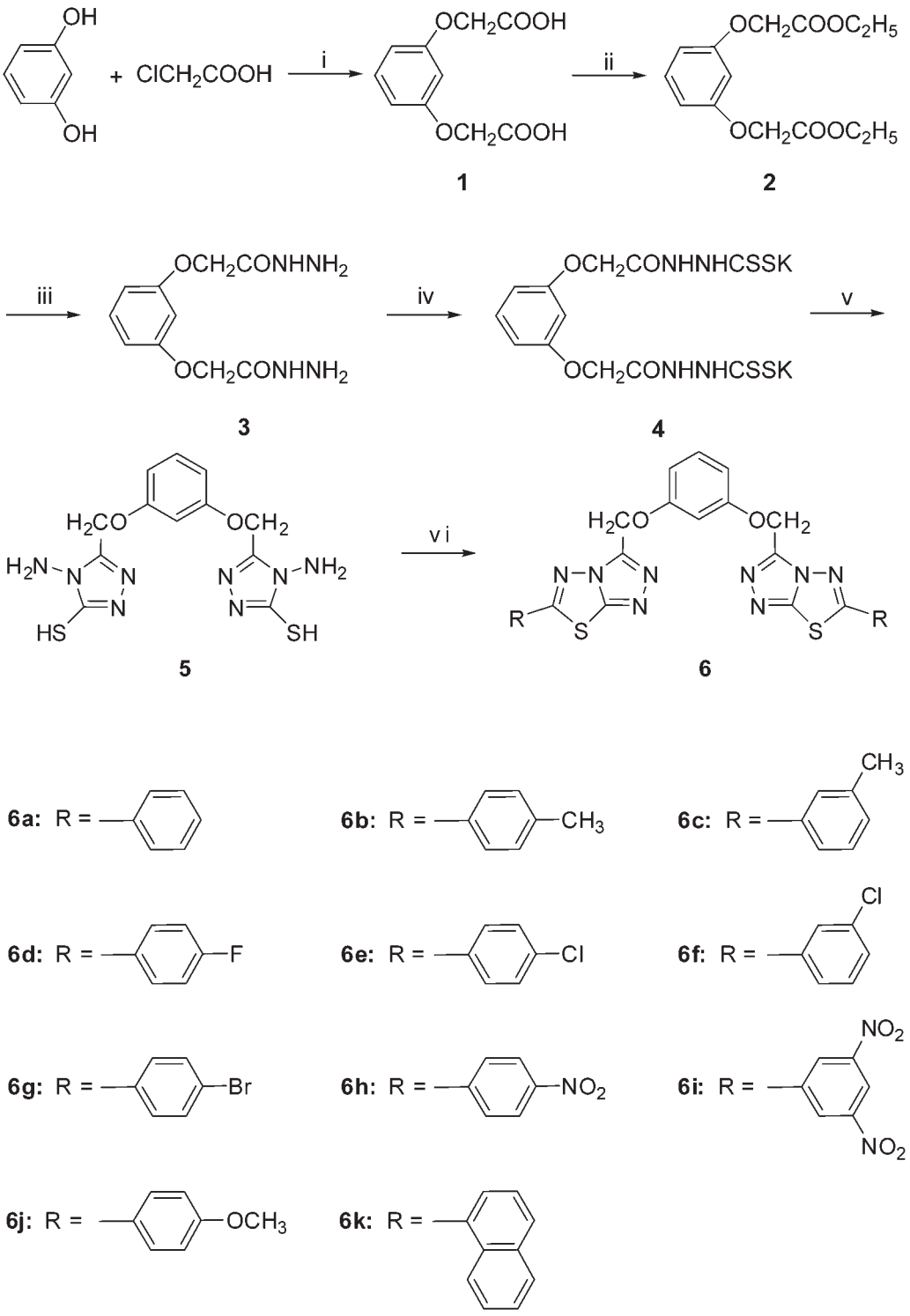
As illustrated in Table 1, the preparation of target compounds required much longer reaction times (480–600 min) at 105 °C under conventional heating. However, under microwave irradiation just 7–12 min were required. The ratios of the T_C/T_{MW} were 49–75, and hence the reaction rate was enhanced greatly. At the same time, the yields were increased from 43–65% to 80–90%. From these data, we conclude that the microwave-enhanced procedure is a facile, rapid and efficient synthetic method to access triazolothiadiazoles. The details of biological activities of the obtained products **6a–k** are currently under further study.

Experimental

Melting points were determined on a micro-melting point apparatus and the thermometer was uncorrected. IR spectra were obtained on 1700 Perkin-Elmer FTIR using KBr disks. ^{1}H NMR spectra were recorded on a Varian INOVA 400 MHz spectrometer using DMSO-d_6 as solvent and TMS as internal standard. Mass spectra were measured on Finnigan LCQ^{DECA} instrument. Elemental analysis was performed on a Carlo-Erba-1106 autoanalyzer. All reactions were performed in open containers with a commercial microwave reactor (XH-100A, 100–1000 W, Beijing Xianghu Science and Technology Development Co. Ltd, Beijing, P.R. China). All the solvents were purified before use. Intermediate **1** was synthesised according to the literature proecdure.[23]

2,2′-[1,3-Phenylenebis(oxy)]bis-acetic hydrazide (**3**): A mixture of 2,2′-[1,3-phenylenebis(oxy)]bis-acetic acid **1** (5 mmol), ethanol (15 mL) and thionyl chloride (0.2 mL) contained in a dried round-bottom flask was placed in the microwave oven and irradiated (75 W) for 4 min. After cooling, the excess thionyl chloride was distilled off under reduced pressure. Then the reaction mixture was added to 85% hydrazine hydrate (2 mL) and subjected to microwave irradiation (75 W) for 3 min. The mixture was evaporated to give the crude product. The crude product was recrystallised from water to afford the desired compound **3** as a white solid, yield 93%, m.p. 223–224 °C (lit.[24] 220 °C), IR (cm^{-1}): 3315, 3260, 2913, 1684, 1631, 1597, 1500, 1437, 1197. ESI-MS *m/z* (%): 255 [(M+1)$^+$, 100].

* Correspondent. E-mail: zzg63129@yahoo.com.cn



Scheme I Reagents and conditions: (i) NaOH; (ii) $SOCl_2$, C_2H_5OH, MWI; (iii) $NH_2NH_2{\cdot}H_2O$, MWI; (iv) CS_2, KOH, C_2H_5OH; (v) $NH_2NH_2{\cdot}H_2O$, MWI; (vi) RCOOH, $POCl_3$, MWI.

5,5'-[1,3-Phenylenebis(oxymethylene)]bis(4-amino-3-mercapto-1,2,4-triazole) (**5**): A solution of carbon disulfide (0.8 mL) in 10 mL of absolute ethanol was added dropwise during 120 min to a mixture of compound **3** (4 mmol) and potassium hydroxide (16 mmol) dissolved in absolute ethanol (50 mL) at 0–5 °C. After complete addition, the reaction mixture was stirred for further 12 h at room temperature. The precipitated solid was collected by suction filtration, washed with ethanol (2 × 15 mL), and vacuum dried to afford **4** as a white solid, which was used directly in the next procedure without further purification. The potassium salt **4** (2 mmol) and hydrazine hydrate (4 mL) were added to a round-bottomed flask (50 mL). The mixture was irradiated (300 W) for 5 min, left to cool, then poured into crushed ice. The resulted reaction mixture was acidified with dilute hydrochloric acid until pH = 5. The resulting solid was collected by filtration, washed with ethanol (2 × 10 mL), and crystallised from methanol to obtain a pure **5** as a silvery white solid, yield 78%, m.p. 172–174 °C (lit.[25] 110–112 °C). IR (cm^{-1}): 3269, 3186, 3033, 2927, 1597, 1455, 1299, 1257, 1026, 686; ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.79 (s, 2H, SH), 7.23 (t, J = 8.4 Hz, 1H, ArH), 6.76 (s, 1H, ArH), 6.69 (dd, J = 8.4, 8.4 Hz, 2H, ArH), 5.65 (s, 4H, OCH_2), 5.10 (s, 4H, NH_2). ESI-MS *m/z* (%): 367 [$(M+1)^+$, 100]. Anal. Calcd for $C_{12}H_{14}N_8O_2S_2$: C, 39.33; H, 3.85; N, 30.58. Found: C, 39.21; H, 3.87; N, 30.69%.

Table 1 Comparison of the synthesis of compounds **6a–k** between microwave irradiation and conventional heating

Compounds		Conventional method		Microwave method		T_C/T_{MW}
		Time/min	Yield/%	Time/min	Yield/%	
6a	R = C_6H_5	540	63	10	88	54
6b	R = 4-$CH_3C_6H_4$	600	59	9	85	67
6c	R = 3-$CH_3C_6H_4$	600	65	8	87	75
6d	R = 4-FC_6H_4	540	52	9	80	60
6e	R = 4-ClC_6H_4	540	64	11	90	49
6f	R = 3-ClC_6H_4	600	47	12	81	50
6g	R = 4-BrC_6H_4	540	56	10	83	54
6h	R = 4-$NO_2C_6H_4$	540	51	9	84	60
6i	R = 3,5-$(NO_2)_2C_6H_3$	480	53	7	82	69
6j	R = 4-$CH_3OC_6H_4$	600	43	12	83	50
6k	R = 1-naphthyl	540	58	11	80	49

T_C, conventional method time; T_{MW}, microwave method time.

Microwave method for the preparation of **6a–k**

Compound **5** (1 mmol), a substituted benzoic acid (2.2 mmol) and phosphorus oxychloride (10 mL) were mixed thoroughly in a 50 mL flask. The flask with a reflux condenser was placed in the microwave oven and irradiated at 450 W for 7–12 min. After completion of the reaction, the mixture was cooled to ambient temperature. Excess phosphorus oxychloride was removed under reduced pressure and an ice–water mixture was poured onto the residue with vigorous stirring. The reaction mixture was neutralised with concentrated sodium hydroxide solution and allowed to stand overnight. The solid precipitate formed was filtered and washed with cold water, dilute $NaHCO_3$ solution and dried in air. The crude product was purified by column chromatography on silica gel H using methanol-ethyl acetate as eluent. The physical and spectra data of title compounds **6a–k** are as follows.

*1,3-Bis{(6-phenyl-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)-methoxy}benzene* (**6a**): Pale yellow solid, yield 88%, m.p. 199–201 °C. IR (KBr) (ν_{max}/cm^{-1}): 3075, 2930, 1596, 1462, 1278, 1038, 684; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.96 (d, *J* = 7.2 Hz, 4H, ArH), 7.67 (t, *J* = 7.2 Hz, 2H, ArH), 7.60 (t, *J* = 8.0 Hz, 4H, ArH), 7.29 (t, *J* = 8.4 Hz, 1H, ArH), 6.99 (s, 1H, ArH), 6.80 (dd, *J* = 8.0, 8.0 Hz, 2H, ArH), 5.57 (s, 4H, OCH_2). HRMS (ESI) *m/z* Calcd for $C_{26}H_{18}N_8O_2S_2$: 538.0994. Found: 539.1074[M+H]$^+$.

*1,3-Bis{(6-(4-methylphenyl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)-methoxy}benzene* (**6b**): Pale yellow solid, yield 85%, m.p. 214–216 °C. IR (KBr) (ν_{max}/cm^{-1}): 3033, 2921, 1600, 1458, 1253, 1007, 680; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.84 (d, *J* = 8.4 Hz, 4H, ArH), 7.39 (d, *J* = 8.4 Hz, 4H, ArH), 7.28 (t, *J* = 8.4 Hz, 1H, ArH), 7.00 (s, 1H, ArH), 6.79 (dd, *J* = 8.4, 8.0 Hz, 2H, ArH), 5.56 (s, 4H, OCH_2), 2.39 (s, 6H, CH_3). ESI-MS *m/z* (%): 567 [(M+1)$^+$, 100]. Anal. Calcd for $C_{28}H_{22}N_8O_2S_2$: C, 59.35; H, 3.91; N, 19.77. Found: C, 59.22; H, 3.89; N, 19.84%.

*1,3-Bis{(6-(3-methylphenyl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)-methoxy}benzene* (**6c**): Pale yellow solid, yield 87%, m.p. 202–204 °C. IR (KBr) (ν_{max}/cm^{-1}): 3046, 2923, 1596, 1461, 1276, 1028, 686; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.74 (t, *J* = 4.4 Hz, 4H, ArH), 7.47 (d, *J* = 5.2 Hz, 4H, ArH), 7.28 (t, *J* = 8.4 Hz, 1H, ArH), 7.01 (s, 1H, ArH), 6.79 (dd, *J* = 8.4, 8.4 Hz, 2H, ArH), 5.57 (s, 4H, OCH_2), 2.39 (s, 6H, CH_3). ESI-MS *m/z* (%): 589 [(M+23)$^+$, 100]. Anal. Calcd for $C_{28}H_{22}N_8O_2S_2$: C, 59.35; H, 3.91; N, 19.77. Found: C, 59.52; H, 3.90; N, 19.71%.

*1,3-Bis{(6-(4-fluorophenyl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)-methoxy}benzene* (**6d**): White solid, yield 80%, m.p. 203–205 °C. IR (KBr) (ν_{max}/cm^{-1}): 3037, 2971, 1594, 1462, 1236, 1003, 687; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04 (dd, *J* = 8.8, 8.8 Hz, 4H, ArH), 7.46 (t, *J* = 8.8 Hz, 4H, ArH), 7.28 (t, *J* = 8.4 Hz, 1H, ArH), 6.98 (s, 1H, ArH), 6.79 (dd, *J* = 8.4, 8.0 Hz, 2H, ArH), 5.57 (s, 4H, OCH_2). ESI-MS *m/z* (%): 575 [(M+1)$^+$, 100]. Anal. Calcd for $C_{26}H_{16}F_2N_8O_2S_2$: C, 54.35; H, 2.81; N, 19.50. Found: C, 54.46; H, 2.82; N, 19.45%.

*1,3-Bis{(6-(4-chlorphenyl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)-methoxy}benzene* (**6e**): Yellow solid, yield 90%, m.p. 214–216 °C. IR (KBr) (ν_{max}/cm^{-1}): 3051, 2926, 1594, 1462, 1254, 1011, 678; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.00–7.96 (m, 4H, ArH), 7.69–7.66 (m, 4H, ArH), 7.28 (t, *J* = 8.4 Hz, 1H, ArH), 6.99 (s, 1H, ArH), 6.79 (dd, *J* = 8.4, 8.4 Hz, 2H, ArH), 5.57 (s, 4H, OCH_2). ESI-MS *m/z* (%): 607 [(M+1)$^+$, 100]. Anal. Calcd for $C_{26}H_{16}Cl_2N_8O_2S_2$: C, 51.40; H, 2.65; N, 18.45. Found: C, 51.59; H, 2.63; N, 18.41%.

*1,3-Bis{(6-(3-chlorophenyl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)-methoxy}benzene* (**6f**): Pale yellow solid, yield 81%, m.p. 165–167 °C. IR (KBr) (ν_{max}/cm^{-1}): 3062, 2959, 1597, 1461, 1283, 1029, 678; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.92 (d, *J* = 7.6 Hz, 2H, ArH), 7.75–7.71 (m, 2H, ArH), 7.68–7.60 (m, 4H, ArH), 7.28 (t, *J* = 8.4 Hz, 1H, ArH), 7.01 (s, 1H, ArH), 6.80 (d, *J* = 8.0 Hz, 2H, ArH), 5.59 (s, 4H, OCH_2). ESI-MS *m/z* (%): 629 [(M+23)$^+$, 100]. Anal. Calcd for $C_{26}H_{16}Cl_2N_8O_2S_2$: C, 51.40; H, 2.65; N, 18.45. Found: C, 51.52; H, 2.63; N, 18.39%.

*1,3-Bis{(6-(4-bromophenyl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)-methoxy}ben-zene* (**6g**): Yellow solid, yield 83%, m.p. 222–224 °C. IR (KBr) (ν_{max}/cm^{-1}): 3082, 2929, 1589, 1461, 1246, 1005, 689; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.90 (d, *J* = 8.4 Hz, 4H, ArH), 7.80 (d, *J* = 8.4 Hz, 4H, ArH), 7.28 (t, *J* = 8.4 Hz, 1H, ArH), 6.99 (s, 1H, ArH), 6.79 (dd, *J* = 8.0, 8.4 Hz, 2H, ArH), 5.57 (s, 4H, OCH_2). ESI-MS *m/z* (%): 697 [(M+1)$^+$, 100]. Anal. Calcd for $C_{26}H_{16}Br_2N_8O_2S_2$: C, 44.84; H, 2.32; N, 16.09. Found: C, 44.71; H, 2.33; N, 16.04%.

*1,3-Bis{(6-(4-nitrophenyl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)-methoxy}benzene* (**6h**): Yellow solid, yield 84%, m.p. 144–146 °C. IR (KBr) (ν_{max}/cm^{-1}): 3061, 2957, 1598, 1462, 1348, 1283, 1025, 684; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.40 (d, *J* = 8.8 Hz, 4H, ArH), 8.23 (d, *J* = 8.8 Hz, 4H, ArH), 7.29 (t, *J* = 8.4 Hz, 1H, ArH), 6.99 (s, 1H, ArH), 6.81 (d, *J* = 8.0 Hz, 2H, ArH), 5.60 (s, 4H, OCH_2). ESI-MS *m/z* (%): 629 [(M+1)$^+$, 100]. Anal. Calcd for $C_{26}H_{16}N_{10}O_6S_2$: C, 49.68; H, 2.57; N, 22.28. Found: C, 49.56; H, 2.59; N, 22.23%.

*1,3-Bis{(6-(3,5-dinitrophenyl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)-methoxy}ben-zene* (**6i**): Yellow solid, yield 82%, m.p. 153–155 °C. IR (KBr) (ν_{max}/cm^{-1}): 3087, 2930, 1595, 1473, 1345, 1283, 1009, 732; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.02 (t, *J* = 2.0 Hz, 2H, ArH), 8.99 (d, *J* = 2.0 Hz, 4H, ArH), 7.30 (t, *J* = 8.4 Hz, 1H, ArH), 7.00 (s, 1H, ArH), 6.82 (dd, *J* = 8.4, 8.4 Hz, 2H, ArH), 5.65 (s, 4H, OCH_2). ESI-MS *m/z* (%): 719 [(M+1)$^+$, 100]. Anal. Calcd for $C_{26}H_{14}N_{12}O_{10}S_2$: C, 43.46; H, 1.96; N, 23.39. Found: C, 43.40; H, 1.97; N, 23.47%.

*1,3-Bis{(6-(4-methoxyphenyl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)-methoxy}ben-zene* (**6j**): Pale yellow solid, yield 83%, m.p. 183–185 °C. IR (KBr) (ν_{max}/cm^{-1}): 3041, 2932, 1601, 1461, 1259, 1033, 683; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.89 (d, *J* = 8.8 Hz, 4H, ArH), 7.28 (t, *J* = 8.4 Hz, 1H, ArH), 7.12 (d, *J* = 8.4 Hz, 4H, ArH), 7.01 (s, 1H, ArH), 6.79 (d, *J* = 8.0 Hz, 2H, ArH), 5.55 (s, 4H, OCH_2), 3.86 (s, 6H, OCH_3). ESI-MS *m/z* (%): 1219 [(2M+23)$^+$, 100]. Anal. Calcd for $C_{28}H_{22}N_8O_4S_2$: C, 56.18; H, 3.70; N, 18.72. Found: C, 56.32; H, 3.72; N, 18.67%.

*1,3-Bis{(6-(1-naphthyl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)-methoxy}benzene* (**6k**): Pale yellow solid, yield 80%, m.p. 195–197 °C. IR (KBr) (ν_{max}/cm^{-1}): 3049, 2953, 1596, 1465, 1283, 1021, 679; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.62 (t, *J* = 5.6 Hz, 2H, ArH), 8.24 (d, *J* = 8.0 Hz, 2H, ArH), 8.08 (t, *J* = 5.2 Hz, 2H, ArH), 7.97 (d, *J* = 7.2 Hz, 2H, ArH), 7.69 (t, *J* = 8.0 Hz, 2H, ArH), 7.64-7.59 (m, 4H, ArH), 7.29 (t, *J* = 8.4 Hz, 1H, ArH), 6.99 (s, 1H, ArH), 6.82 (dd, *J* = 8.0, 8.0 Hz, 2H, ArH), 5.63 (s, 4H, OCH_2). ESI-MS *m/z* (%): 639 [(M+1)$^+$, 100]. Anal. Calcd for $C_{34}H_{22}N_8O_2S_2$: C, 63.93; H, 3.47; N, 17.54. Found: C, 63.79; H, 3.48; N, 17.60%.

Conventional method for the preparation of **6a–k**

Compound **5** (1 mmol), a substituted benzoic acid (2.2 mmol) and phosphorus oxychloride (10 mL) were mixed thoroughly in a 50 mL

flask and the contents were heated under reflux in an oil bath for 8–10 h at 105 °C. On completion of the reaction, the mixture was cooled to ambient temperature. Excess phosphorus oxychloride was removed under reduced pressure and an ice-water mixture was added to the residue with vigorous stirring. The reaction mixture was neutralised with concentrated sodium hydroxide solution and allowed to stand overnight. The resulting solid was washed with cold water, dilute $NaHCO_3$ solution and dried in air. The crude product was purified by column chromatography on silica gel H using metanol-ethyl acetate as eluent.

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