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Synthesis and biological activities of thio-triazole derivatives as novel potential antibacterial and antifungal agents

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A series of novel thio-triazole derivatives including thiols, thioethers and thiones as well as some corresponding triazolium compounds were conveniently and efficiently synthesized from commercially available halobenzyl halides and thiosemicarbazide. All the new compounds were characterized by ^{1}H NMR, ^{13}C NMR, FTIR, MS and HRMS spectra. Their antibacterial and antifungal activities *in vitro* were evaluated against four Gram-positive bacteria, four Gram-negative bacteria and two fungi by two-fold serial dilution technique. The preliminary bioassay indicated that some prepared triazoles exhibited effective antibacterial and antifungal activities. Especially, 3,4-dichlorobenzyl triazole-thione and its triazolium derivatives displayed the most potent activities against all the tested strains.

triazole, triazolium, antibacterial, antifungal, cyclization

1 Introduction

Triazole compounds have been attracting considerable attention due to their wide potential [1, 2] in the treatment of various diseases as antibacterial [3, 4], antifungal [5, 6], anti-tubercular [7, 8], anti-cancer [9, 10], anti-inflammatory [11], anti-convulsant [12] and other medicinal drugs. Numerous efforts have been directed toward the development of 1,2,4-triazole derivatives as antifungal agents due to their low toxicity, favorable safety profile and beneficial pharmacokinetic characteristics. A large amount of excellent triazole-based drugs, like Fluconazole and Itraconazole which were proved to target on P450-dependent sterol 14a-demethylase [13, 14], have been successfully marketed and widely used in clinics. In contrast to the well developed triazoles as antifungal agents, the exploration of triazoles as antibacterial agents was relatively rare. In recent years, some novel 1,2,4-triazoles have been reported to demonstrate remarkable antibacterial properties, especially against Methicillin-Resistant Staphylococcus aureus [13, 15–17]. It is well known that the increasing amount of multi-drug resistant microorganisms has become serious threatens to human health [18, 19], especially the very recent outbreaks of New Delhi metallo-β-lactamase 1 (NDM-1) superbugs [20] and enterohemorrhage *Escherichia coli* (EHEC) O104:H4 [21], which have resulted in weak efficacy for most of the first-line clinical antibiotics in the treatment of infectious diseases. Therefore, development of more effective triazole agents with broader antimicrobial spectrum in antibacterial and antifungal fields which are possibly helpful in overcoming drug-resistance has become an interesting topic for researchers [1, 22].

A large amount of literature has manifested that structural modification of the triazole ring with various substituents represents a practical strategy to explore new types of bio-

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active agents that could affect the interactions of triazoles with cells and tissues, thereby improving the biological effects [23–25]. In our previous work, halobenzyloxy and alkoxy groups were introduced into the 1,2,4-triazole ring to successfully improve bioactivities and broaden the antimicrobial spectrum [26]. As an extension of our study on novel potent bioactive compounds, it is of our great interest to incorporate thio-containing groups into the triazole ring replacing the oxyl moiety to investigate how these new 1,2,4-triazole derivatives affect the antimicrobial efficacy.

Many researches have revealed that introduction of the sulfur atom into the triazole ring could effectively enhance the bioactivities of target compounds [27, 28]. The presence of the sulfur moiety as an electron-rich center is able to improve lipophilicity and modulate electron density of the triazole ring, thereby influencing its transmembrane diffusion ability to the anticipant targets, as well as its interaction with hydrogen bond donors of the organism [29, 30]. As a result, investigation of 1,2,4-triazole-3-thiol and its derivatives as potential antimicrobial candidates [31, 32], which can be easily prepared by diverse methods, has become increasingly attractive. Furthermore, the mercapto group of triazoles as a nucleophilic center could conveniently react with electrophiles to produce corresponding triazole-thioethers [33, 34] and thione derivatives [35]. Moreover, modification of diverse triazole-thiols was demonstrated as a good treasure to increase antimicrobial activities and extend their biological spectrum [36, 37]. Recently, a great number of triazole-thioether and triazole-thione compounds have been reported to demonstrate efficient antibacterial and antifungal activities [38, 39].

Inspired by these observations and in continuation of our ongoing interests in the development of new antimicrobial agents [40, 41], herein a series of novel triazole-thiols, thioethers and thiones as well as some triazoliums were designed and synthesized. Their antibacterial and antifungal activities were evaluated, and some important effect factors on antimicrobial activities were also investigated. The target molecular structures were designed based on the following considerations:

(1) Halobenzyl and thiol moieties on the triazole ring were helpful in enhancing the bioactivities by improving lipid solubility which might result in the enhancement of the penetration of the agents into cells [42–44]. To this end, the 3,4-dichlorobenzyl, 2,4-difluorobenzyl, and thiol moieties were introduced into the triazole ring to yield halobenzyl triazole-thiol **2**.

(2) It was confirmed that thioethers and thiones could effectively increase the biological activities and broaden antimicrobial spectrum in a large number of reported literatures [45, 46]. In order to investigate the effects of the thiol substituent in the triazole ring on antibacterial and antifungal activities, some new thioethers and thiones were prepared.

(3) Our previous investigation evidenced that alteration of the aliphatic chain and aromatic substituents remarkably affected antimicrobial potency [26]. Therefore, a series of alkyl and halobenzyl triazoles were synthesized.

(4) Aromatic 1,2,4-triazole ring could exert multiple non-covalent interactions such as hydrogen bond, π-π stacking, ion-dipole, coordination bond, hydrophobic effect and van der Waals force with biological molecules and modulate physicochemical properties, thereby improving and broadening biological activities [47, 48]. Herein, a second triazole moiety was introduced into the target compounds through different linkers to prepare a series of bis-triazole compounds.

(5) Triazolium ring with a permanent positive charge on the triazole ring has been reported to affect the diffusion and interaction with biological tissues which could result in the enhancement of antimicrobial abilities [49]. Thereby, a series of triazolium derivatives were prepared to examine their effects on antimicrobial activities.

(6) Coumarin ring, with the benzopyrone skeleton structurally similar to the benzopyridone backbone of antibacterial drug quinolones, has received specific interests in medicinal chemistry as a new type of potential antibiotics. So far an increasing number of coumarin derivatives have been reported to exhibit good antimicrobial competence [50]. Therefore, the coumarin moiety was introduced into the triazoles to survey its contribution to antimicrobial activities.

All the structures of the synthesized triazole-thiol **2**, thioethers and thiones **3–8** and triazoliums **9–11** are shown in Scheme 1.

2 Experimental

2.1 Materials and measurements

Melting points were recorded on X-6 melting point apparatus and were uncorrected. TLC analysis was done using pre-coated silica gel plates. FT-IR spectra were carried out on a Bruker RFS100/S spectrophotometer (Bio-Rad, Cambridge, MA, USA) using KBr pellets in the 400–4000 cm^{-1} range. NMR spectra were recorded on a Bruker AV 300 spectrometer using TMS as an internal standard; Ph = phenyl ring and Ar = aromatic ring. The chemical shifts were reported in parts per million (ppm), the coupling constants (*J*) are expressed in hertz (Hz) and singlet (s), doublet (d) and triplet (t) as well as multiplet (m). The mass spectra (MS) were recorded on LCMS-2010A and the high-resolution mass spectra (HRMS) were recorded on an IonSpec FT-ICR mass spectrometer with ESI resource. All chemicals and solvents were commercially available, and used without further purification.

2.2 Synthesis

*1-(3,4-Dichlorobenzyl)-1H-1,2,4-triazole-3-thiol (**2a**)*

To a stirred mixture of thiosemicarbazide (11.01 g, 0.12

mol) in ethanol (30 mL), 3,4-dichlorobenzyl chloride (21.62 g, 0.11 mol) was added dropwise at 40 °C. Upon completion of the reaction (monitored by TLC, eluent, chloroform/methanol, 30/1, *v/v*), the solvent was evaporated under vacuum to give the crude 1-halobenzyl thiosemicarbazide as a white solid. Subsequently, this solid was dissolved in distilled water (30 mL) with stirring at 60 °C, followed by addition of formic acid (6.82 g, 0.15 mol) and concentrated sulfuric acid (0.5 mL). The reaction temperature was raised to 100 °C for 12 h until the reaction completed (monitored by TLC, eluent, chloroform/methanol, 30/1, *v/v*). The resulting solution was quenched with saturated sodium bicarbonate and extracted with chloroform (3 × 50 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated. The residue was purified via silica gel column chromatography (eluent, chloroform/methanol, 30/1, *v/v*) to give compound **2a** (23.01 g) as a white solid. Yield: 82.3%; mp 86–89 °C; IR (KBr) ν: 3114, 3061 (Ar–H), 2915, 2848 (CH_2), 2668 (SH), 1609, 1572, 1513, 1468 (aromatic frame), 1123, 1077, 1032, 1000, 907, 883, 820, 714 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.15 (s, 1H, S-triazole *H*), 7.46–7.31 (m, 2H, 3,4-Cl_2Ph 2,5-*H*), 6.20–6.17 (m, 1H, 3,4-Cl_2Ph 6-*H*), 4.30 (s, 2H, 3,4-Cl_2Ph-CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.6 (S-triazole S-*C*), 146.6 (S-triazole 5-*C*), 137.4 (3,4-Cl_2Ph 1-*C*), 132.4 (3,4-Cl_2Ph 3-*C*), 131.6 (3,4-Cl_2Ph 4-*C*), 130.7 (3,4-Cl_2Ph 2-*C*), 130.4 (3,4-Cl_2Ph 5-*C*), 128.2 (3,4-Cl_2Ph 6-*C*), 37.8 (*C*H_2) ppm; ESI-MS (*m/z*): 261 $[M+H]^+$; HRMS (ESI) calcd. for $C_9H_7Cl_2N_3S$ $[M+H]^+$, 259.9816; found, 259.9819.

*1-(2,4-Difluorobenzyl)-1H-1,2,4-triazole-3-thiol (**2b**)*

Compound **2b** was prepared employing a procedure similar to that used to synthesize compound **2a**, starting from thiosemicarbazide (10.10 g, 0.11 mol), 2,4-difluorobenzyl bromide (21.01 g, 0.10 mol) and formic acid (9.21 g, 0.21 mol). The pure product **2b** (17.82 g) was obtained as a white solid. Yield: 72.9%; mp 128–129 ºC; IR (KBr) ν: 3113, 3077 (Ar–H), 2998, 2775 (CH_2), 2709 (SH), 1602, 1584, 1503, 1458 (aromatic frame), 1381, 1139, 1065, 1027, 995, 865, 834, 777, 720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.16 (s, 1H, S-triazole *H*), 7.39–7.26 (m, 1H, 2,4-F_2Ph 6-*H*), 6.82–6.76 (m, 2H, 2,4-F_2Ph 3,5-*H*), 4.37 (s, 2H, 2,4-F_2Ph-CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.1, 163.9 (2,4-F_2Ph 2-*C*), 160.5, 160.1 (2,4-F_2Ph 4-*C*), 152.7 (S-triazole S-*C*), 145.6 (S-triazole 5-*C*), 130.5 (2,4-F_2Ph 6-*C*), 117.9, 117.7 (2,4-F_2Ph 1-*C*), 110.4, 110.2 (2,4-F_2Ph 5-*C*), 104.1, 103.7 (2,4-F_2Ph 3-*C*), 36.7 (*C*H_2) ppm; ESI-MS (*m/z*): 228 $[M+H]^+$; HRMS (ESI) calcd. for $C_9H_7F_2N_3S$ $[M+H]^+$, 228.0407; found, 228.0409.

*1-(3,4-Dichlorobenzyl)-3-(octylthio)-1H-1,2,4-triazole (**3a**)*

A mixture of compound **2a** (0.52 g, 2.0 mmol), potassium carbonate (0.33 g, 2.4 mmol), and tetrabutylammonium iodide (5 mg) in acetone (10 mL) was stirred at 40 °C for 20 min, and then 1-bromooctane (0.46 g, 2.4 mmol) was added. After the reaction completed in about 12 h (monitored by TLC, eluent, chloroform/petroleum ether, 3/1, *v/v*), the solvent was evaporated under vacuum and the residue was treated with water (50 mL) and extracted with chloroform (3 × 50 mL). The organic layers were combined, dried over anhydrous sodium sulfate, and concentrated. The crude product was purified via silica gel column chromatography (eluent, chloroform/petroleum ether, 1/1, *v/v*) to afford compound **3a** (0.35 g) as a helvolus oil. Yield: 47.1%; IR (KBr) ν: 3116 (Ar–H), 2927, 2858 (CH_2), 1601, 1502, 1468 (aromatic frame), 1358, 1181, 1134, 1029, 890, 722 (C–S–C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.89 (s, 1H, S-triazole *H*), 7.45 (s, 1H, 3,4–Cl_2Ph 2-*H*), 7.34–7.15 (m, 2H, 3,4-Cl_2Ph 5,6-*H*), 4.36 (s, 2H, 3,4-Cl_2Ph-CH_2), 3.97 (t, 2H, *J* = 7.5 Hz, $CH_3(CH_2)_6CH_2$), 1.73–1.71 (m, 2H, $CH_3(CH_2)_5CH_2$), 1.30–1.20 (m, 10H, $CH_3(CH_2)_5$), 0.88 (t, 3H, *J* = 6.0 Hz, CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 152.6 (S-triazole S-*C*), 144.5 (S-triazole 5-*C*), 137.1 (3,4-Cl_2Ph 1-*C*), 132.8 (3,4-Cl_2Ph 3-*C*), 131.6 (3,4-Cl_2Ph 4-*C*), 130.6 (3,4-Cl_2Ph 2-*C*), 130.4 (3,4-Cl_2Ph 5-*C*), 128.1 (3,4-Cl_2Ph 6-*C*), 46.1, 34.3, 30.2, 29.6, 29.3, 29.1, 26.5, 23.2 (*C*H_2), 14.4 (*C*H_3) ppm; ESI-MS (*m/z*): 373 $[M+H]^+$; HRMS (ESI) calcd. for $C_{17}H_{23}Cl_2N_3S$ $[M+H]^+$, 372.1068; found, 372.1072.

*1-(3,4-Dichlorobenzyl)-3-(3,4-dichlorobenzylthio)-1H-1,2,4-triazole (**3b**)*

Compound **3b** was synthesized employing a procedure similar to that used to synthesize compound **3a**, starting from compound **2a** (0.52 g, 2.0 mmol), 1,2-dichloro-4-(chloromethyl)benzene (0.47 g, 2.4 mmol) and potassium carbonate (0.33 g, 2.4 mmol). The crude product was obtained and purified via silica gel column chromatography (eluent, chloroform/petroleum ether, 1/1, *v/v*) to give pure compound **3b** (0.32 g) as a yellow oil. Yield: 38.3%; IR (KBr) ν: 3087, 3059 (Ar–H), 2933 (CH_2), 1612, 1491, 1446 (aromatic frame), 1356, 1134, 1061, 1030, 883, 819, 764, 710 (*C–S–C*) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.93 (s, 1H, S-triazole *H*), 7.41–7.32 (m, 4H, 3,4-Cl_2Ph 2,5-*H*), 7.15–6.94 (m, 2H, 3,4-Cl_2Ph 6-*H*), 5.13 (s, 2H, S-CH_2), 4.36 (s, 2H, 3,4-Cl_2Ph-CH_2-triazole) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 152.7 (S-triazole S-*C*), 146.1 (S-triazole 5-*C*), 137.8 (2C, 3,4-Cl_2Ph 1-*C*), 131.5 (2C, 3,4-Cl_2Ph 3-*C*), 130.9 (2C, 3,4-Cl_2Ph 4-*C*), 130.5 (2C, 3,4-Cl_2Ph 2-*C*), 130.2 (2C, 3,4-Cl_2Ph 5-*C*), 127.3 (2C, 3,4-Cl_2Ph 6-*C*), 45.6, 35.9 (*C*H_2) ppm; ESI-MS (*m/z*): 420 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{11}Cl_4N_3S$ $[M+H]^+$, 417.9506; found, 417.9520.

*1-(3,4-Dichlorobenzyl)-3-(2,4-difluorobenzylthio)-1H-1,2,4-triazole (**3c**)*

Compound **3c** was prepared employing a procedure similar to that used to synthesize compound **3a**, starting from

compound **2a** (0.52 g, 2.0 mmol), 1-(bromomethyl)-2,4-difluorobenzene (0.49 g, 2.4 mmol) and potassium carbonate (0.33 g, 2.4 mmol). The desired pure compound **3c** (0.15 g) was obtained as a yellow oil. Yield: 20.0%; IR (KBr) ν: 3078 (Ar–H), 2936, 2857 (CH_2), 1613, 1581, 1507, 1441 (aromatic frame), 1179, 1135, 1094, 969, 853, 780, 728 (C–S–C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.94 (s, 1H, S-triazole *H*), 7.40–7.33 (m, 3H, 3,4-Cl_2Ph 2,5-*H*, 2,4-F_2Ph 6-*H*), 7.21–6.97 (m, 3H, 3,4-Cl_2Ph 6-*H*, 2,4-F_2Ph 3,5-*H*), 5.18 (s, 2H, S-CH_2), 4.36 (s, 2H, 2,4-F_2Ph-CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.7, 164.5 (2,4-F_2Ph 2-*C*), 161.9, 158.6 (2,4-F_2Ph 4-*C*), 153.7 (S-triazole S-*C*), 151.9 (S-triazole 5-*C*), 137.0 (3,4-Cl_2Ph 1-*C*), 131.9 (3,4-Cl_2Ph 3-*C*), 131.5, 131.4 (2,4-F_2Ph 6-*C*), 130.9 (3,4-Cl_2Ph 4-*C*), 130.8 (3,4-Cl_2Ph 2-*C*), 130.5 (3,4-Cl_2Ph 5-*C*), 128.3 (3,4-Cl_2Ph 1-*C*), 118.1 (2,4-F_2Ph 1-*C*), 112.0, 111.7 (2,4-F_2Ph 5-*C*), 104.5, 104.1, 103.8 (2,4-F_2Ph 3-*C*), 45.3, 38.6 (*C*H_2) ppm; ESI-MS (*m/z*): 387 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{11}Cl_2F_2N_3S$ $[M+H]^+$, 386.0097; found, 386.0099.

*1-(2,4-Difluorobenzyl)-3-(octylthio)-1H-1,2,4-triazole (**3d**)*

Compound **3d** was prepared employing a procedure similar to that used to synthesize compound **3a**, starting from compound **2b** (0.45 g, 2.0 mmol), 1-bromooctane (0.46 g, 2.4 mmol) and potassium carbonate (0.33 g, 2.4 mmol). The pure product **3d** (0.26 g) was obtained as a yellow oil. Yield: 38.2%; IR (KBr) ν: 3121, 3078 (Ar–H), 2928, 2856 (CH_2), 1613, 1506, 1449 (aromatic frame), 1357, 1180, 1136, 968, 852, 731 (C–S–C), 665 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.88 (s, 1H, S-triazole *H*), 7.38–7.30 (m, 1H, 2,4-F_2Ph 6-*H*), 6.89–6.73 (m, 2H, 2,4-F_2Ph 3,5-*H*), 4.41 (s, 2H, 2,4-F_2Ph-CH_2), 3.95 (t, 2H, *J* = 7.5 Hz, $CH_3(CH_2)_6CH_2$), 1.74–1.72 (m, 2H, $CH_3(CH_2)_5CH_2$), 1.28–1.24 (m, 10H, $CH_3(CH_2)_5$), 0.88 (t, 3H, *J* = 6.0 Hz, CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.8, 162.2 (2,4-F_2Ph 2-*C*), 161.7, 160.9 (2,4-F_2Ph 4-*C*), 151.9 (S-triazole S-*C*), 145.3 (S-triazole 5-*C*), 128.7 (2,4-F_2Ph 6-*C*), 117.5 (2,4-F_2Ph 1-*C*), 111.6, 111.2 (2,4-F_2Ph 5-*C*), 104.5, 104.1 (2,4-F_2Ph 3-*C*), 45.7, 40.1, 32.6, 30.1, 29.3, 29.2, 26.7, 22.9 (*C*H_2), 14.5 (*C*H_3) ppm; ESI-MS (*m/z*): 339 $[M]^+$; HRMS (ESI) calcd. for $C_{17}H_{23}F_2N_3S$ $[M+H]^+$, 340.1659; found, 340.1661.

*3-(3,4-Dichlorobenzylthio)-1-(2,4-difluorobenzyl)-1H-1,2,4-triazole (**3e**)*

Compound **3e** was prepared employing a procedure similar to that used to synthesize compound **3a**, starting from compound **2b** (0.45 g, 2.0 mmol) and 3,4-dichloro-1-(chloromethyl) benzene (0.46 g, 2.4 mmol). The pure product **3e** (0.24 g) was obtained as a yellow syrup. Yield: 31.3%; IR (KBr) ν: 3107, 3074 (Ar–H), 2932, 2856 (CH_2), 1611, 1505, 1453 (aromatic frame), 1352, 1180, 1136, 1061, 967, 853, 763, 715 (C–S–C), 663 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.94 (s, 1H, S-triazole *H*), 7.38–7.36 (m, 1H, 2,4-F_2Ph 6-*H*), 7.32–7.23 (m, 2H, 3,4-Cl_2Ph 2,5-*H*), 7.00–6.98 (m, 1H, 3,4-Cl_2Ph 6-*H*), 6.83–6.74 (m, 2H, 2,4-F_2Ph 3,5-*H*), 5.12 (s, 2H, S-CH_2), 4.41 (s, 2H, 3,4-Cl_2Ph-CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.4, 163.7 (2,4-F_2Ph 2-*C*), 160.8, 160.2 (2,4-F_2Ph 4-*C*), 152.4 (S-triazole S-*C*), 148.2 (S-triazole 5-*C*), 137.1 (3,4-Cl_2Ph 1-*C*), 132.2 (3,4-Cl_2Ph 3-*C*), 131.3 (2,4-F_2Ph 6-*C*), 130.8 (3,4-Cl_2Ph 4-*C*), 130.7 (3,4-Cl_2Ph 2-*C*), 130.3 (3,4-Cl_2Ph 5-*C*), 128.2 (3,4-Cl_2Ph 6-*C*), 117.9 (2,4-F_2Ph 1-*C*), 111.5, 111.3 (2,4-F_2Ph 5-*C*), 104.4, 104.0 (2,4-F_2Ph 3-*C*), 48.3, 36.5 (*C*H_2) ppm; ESI-MS (*m/z*): 386 $[M]^+$; HRMS (ESI) calcd. for $C_{16}H_{11}Cl_2F_2N_3S$ $[M+H]^+$, 386.0097; found, 386.0092.

*1-(2,4-Difluorobenzyl)-3-(2,4-difluorobenzylthio)-1H-1,2,4-triazole (**3f**)*

Compound **3f** was prepared employing a procedure similar to that used to synthesize compound **3a**, starting from compound **2b** (0.45 g, 2.0 mmol), 1-(bromomethyl)-2,4-difluorobenzene (0.49 g, 2.4 mmol) and potassium carbonate (0.33 g, 2.4 mmol). The pure product **3f** (0.25 g) was obtained as a yellow oil. Yield: 35.1%; IR (KBr) ν: 3107, 3081 (Ar–H), 2933, 2857 (CH_2), 1613, 1504, 1430 (aromatic frame), 1361, 1183, 1138, 1093, 969, 852, 723 (C–S–C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.92 (s, 1H, S-triazole *H*), 7.32–7.30 (m, 2H, 2,4-F_2Ph 6-*H*), 6.90–6.72 (m, 4H, 2,4-F_2Ph 3,5-*H*), 5.19 (s, 2H, S-CH_2), 4.42 (s, 2H, 2,4-F_2Ph-CH_2-triazole) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.9, 161.8 (2C, 2,4-F_2Ph 2-*C*), 161.4, 160.5 (2C, 2,4-F_2Ph 4-*C*), 153.3 (S-triazole S-*C*), 147.7 (S-triazole 5-*C*), 132.1, 130.8 (2C, 2,4-F_2Ph 6-*C*), 118.2, 117.7 (2C, 2,4-F_2Ph 1-*C*), 111.6, 111.3 (2C, 2,4-F_2Ph 5-*C*), 104.7, 104.1 (2C, 2,4-F_2Ph 3-*C*), 46.9, 38.7 (*C*H_2) ppm; ESI-MS (*m/z*): 353 $[M]^+$; HRMS (ESI) calcd. for $C_{16}H_{11}F_4N_3S$ $[M+H]^+$, 354.0688; found, 354.0692.

*1-(3,4-Dichlorobenzyl)-2-octyl-1H-1,2,4-triazole-3(2H)-thione (**4a**)*

Pure compound **4a** (0.32 g) was prepared as a yellow oil according to the procedure described for compound **3a**. Yield: 43.2%; IR (KBr) ν: 3111, 3058 (Ar–H), 2923, 2853 (CH_2), 1564, 1496, 1460 (aromatic frame), 1354, 1264 (C=S), 1184, 1133, 1032, 989, 891, 820, 668 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.96 (s, 1H, S-triazole *H*), 7.49–7.35 (s, 2H, 3,4-Cl_2Ph 2,5-*H*), 7.26–7.22 (m, H, 3,4-Cl_2Ph 6-*H*), 4.26 (s, 2H, 3,4-Cl_2Ph-CH_2), 4.07 (t, 2H, *J* = 7.5 Hz, $CH_3(CH_2)_6CH_2$), 1.86–1.82 (m, 2H, $CH_3(CH_2)_5CH_2$), 1.29–1.25 (m, 10H, $CH_3(CH_2)_5$), 0.89 (t, 3H, *J* = 6.0 Hz, CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.7 (S=*C*), 144.9 (S-triazole 5-*C*), 138.1 (3,4-Cl_2Ph 1-*C*), 132.5 (3,4-Cl_2Ph 3-*C*), 131.2 (3,4-Cl_2Ph 4-*C*), 130.8 (3,4-Cl_2Ph 2-*C*), 130.5 (3,4-Cl_2Ph 5-*C*), 128.4 (3,4-Cl_2Ph 6-*C*), 48.7, 46.2, 31.4, 29.3, 29.0, 27.4, 26.7, 22.2 (*C*H_2), 14.7 (*C*H_3) ppm; ESI-MS (*m/z*): 372 $[M]^+$; HRMS (ESI) calcd. for $C_{17}H_{23}Cl_2N_3S$ $[M+H]^+$, 372.1068; found, 372.1066.

*1,2-Bis(3,4-dichlorobenzyl)-1H-1,2,4-triazole-3(2H)-thione (**4b**)*

Pure compound **4b** (0.41 g) was prepared as a yellow syrup according to the procedure described for compound **3b**. Yield: 31.0%; IR (KBr) ν: 3112 (Ar–H), 2930, 2853 (CH_2), 1601, 1575, 1461 (aromatic frame), 1358, 1267 (C=S), 1196, 1135, 1028, 886, 820, 761, 683 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.04 (s, 1H, S-triazole *H*), 7.47–7.31 (m, 4H, 3,4-Cl_2Ph 2,5-*H*), 7.22–7.03 (m, 2H, 3,4-Cl_2Ph 6-*H*), 5.21 (s, 2H, triazole-thione N^2-CH_2), 4.25 (s, 2H, triazole-thione N^1-CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.7 (S=*C*), 147.4 (S-triazole 5-*C*), 137.6 (2C, 3,4-Cl_2Ph 1-*C*), 131.2 (2C, 3,4-Cl_2Ph 3-*C*), 130.9 (2C, 3,4-Cl_2Ph 4-*C*), 130.8 (2C, 3,4-Cl_2Ph 2-*C*), 130.5 (2C, 3,4-Cl_2Ph 5-*C*), 128.1 (2C, 3,4-Cl_2Ph 6-*C*), 47.2, 44.3 (*C*H_2) ppm; ESI-MS (*m/z*): 419 $[M]^+$; HRMS (ESI) calcd. for $C_{16}H_{11}Cl_4N_3S$ $[M+H]^+$, 417.9506; found, 417.9509.

*1-(3,4-Dichlorobenzyl)-2-(2,4-difluorobenzyl)-1H-1,2,4-triazole-3(2H)-thione (**4c**)*

Pure compound **4c** (0.24 g) was prepared as a yellow syrup according to the procedure described for compound **3c**. Yield: 31.1%; IR (KBr) ν: 3111, 3083 (Ar–H), 2937, 2854 (CH_2), 1616, 1503, 1458 (aromatic frame), 1359, 1269 (C=S), 1182, 1137, 1093, 1026, 969, 853, 764, 674 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.04 (s, 1H, S-triazole *H*), 7.46–7.34 (m, 3H, 2,4-F_2Ph 6-*H*, 3,4-Cl_2Ph 2,5-*H*), 7.25–6.95 (m, 3H, 2,4-F_2Ph 3,5-*H*, 3,4-Cl_2Ph 6-*H*), 5.25 (s, 2H, triazole-thione N^2-CH_2), 4.24 (s, 2H, 3,4-Cl_2Ph-CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.7, 164.5 (2,4-F_2Ph 2-*C*), 161.5, 160.2 (2,4-F_2Ph 4-*C*), 158.9 (S=*C*), 151.8 (S-triazole 5-*C*), 138.2 (3,4-Cl_2Ph 1-*C*), 132.1 (3,4-Cl_2Ph 3-*C*), 131.6, 131.2 (2,4-F_2Ph 6-*C*), 131.1 (3,4-Cl_2Ph 4-*C*), 130.9 (3,4-Cl_2Ph 2-*C*), 130.5 (3,4-Cl_2Ph 5-*C*), 128.3 (3,4-Cl_2Ph 6-*C*), 117.7 (2,4-F_2Ph 1-*C*), 112.1, 111.9 (2,4-F_2Ph 5-*C*), 104.7, 104.3, 104.1 (2,4-F_2Ph 3-*C*), 46.8, 45.3 (*C*H_2) ppm; ESI-MS (*m/z*): 386 $[M]^+$; HRMS (ESI) calcd. for $C_{16}H_{11}Cl_2F_2N_3S$ $[M+H]^+$, 386.0097; found, 386.0094.

*1-(2,4-Difluorobenzyl)-2-octyl-1H-1,2,4-triazole-3(2H)-thione (**4d**)*

Pure compound **4d** (0.29 g) was prepared as a yellow syrup according to the procedure described for compound **3d**. Yield: 43.5%; IR (KBr) ν: 3112 (Ar–H), 2927, 2859 (CH_2), 1612, 1576, 1502, 1442 (aromatic frame), 1362, 1274 (C=S), 1186, 1025, 967, 852, 670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.98 (s, 1H, S-triazole *H*), 7.36–7.29 (m, 1H, 2,4-F_2Ph 6-*H*), 6.90–6.74 (m, 2H, 2,4-F_2Ph 3,5-*H*), 4.32 (s, 2H, 2,4-F_2Ph-CH_2), 4.06 (t, 2H, J = 7.5 Hz, $CH_3(CH_2)_6CH_2$), 1.88–1.82 (m, 2H, $CH_3(CH_2)_5CH_2$), 1.30–1.24 (m, 10H, $CH_3(CH_2)_5$), 0.89 (t, 3H, J = 6.0 Hz, CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.5, 161.7 (2,4-F_2Ph 2-*C*), 160.1, 159.7 (2,4-F_2Ph 4-*C*), 159.2 (S=*C*), 143.5 (S-triazole 5-*C*), 129.7 (2,4-F_2Ph 6-*C*), 123.0 (2,4-F_2Ph 1-*C*), 111.5, 111.2 (2,4-F_2Ph 5-*C*), 104.7, 104.5 (2,4-F_2Ph 3-*C*), 48.6, 34.2, 30.4, 29.8, 29.2, 27.2, 27.0, 22.1 (*C*H_2), 14.7 (*C*H_3) ppm; ESI-MS (*m/z*): 339 $[M]^+$; HRMS (ESI) calcd. for $C_{17}H_{23}F_2N_3S$ $[M+H]^+$, 340.1659; found, 340.1664.

*2-(3,4-Dichlorobenzyl)-1-(2,4-difluorobenzyl)-1H-1,2,4-triazole-3(2H)-thione (**4e**)*

Pure compound **4e** (0.23 g) was prepared as a yellow syrup according to the procedure described for compound **3e**. Yield: 34.1%; IR (KBr) ν: 3110 (Ar–H), 2938, 2857 (CH_2), 1611, 1500, 1451 (aromatic frame), 1358, 1272 (C=S), 1185, 1128, 967, 853, 763, 660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.05 (s, 1H, S-triazole *H*), 7.46–7.43 (m, 1H, 2,4-F_2Ph 6-*H*), 7.35–7.32 (m, 2H, 3,4-Cl_2Ph 2,5-*H*), 7.09–7.06 (m, 1H, 3,4-Cl_2Ph 6-*H*), 6.81–6.72 (m, 2H, 2,4-F_2Ph 3,5-*H*), 5.22 (s, 2H, triazole-thione N^2-CH_2), 4.32 (s, 2H, 2,4-F_2Ph-CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.8, 162.9 (2,4-F_2Ph 2-*C*), 161.1, 160.6 (2,4-F_2Ph 4-*C*), 158.6 (S=*C*), 148.5 (S-triazole 5-*C*), 137.2 (3,4-Cl_2Ph 1-*C*), 132.5 (3,4-Cl_2Ph 3-*C*), 131.7 (3,4-Cl_2Ph 4-*C*), 131.4 (2,4-F_2Ph 6-*C*), 130.5 (3,4-Cl_2Ph 2-*C*), 129.9 (3,4-Cl_2Ph 5-*C*), 128.1 (3,4-Cl_2Ph 6-*C*), 118.0 (2,4-F_2Ph 1-*C*), 111.7, 111.4 (2,4-F_2Ph 5-*C*), 104.1, 103.7 (2,4-F_2Ph 3-*C*), 47.7, 43.6 (*C*H_2) ppm; ESI-MS (*m/z*): 386 $[M]^+$; HRMS (ESI) calcd. for $C_{16}H_{11}Cl_2F_2N_3S$ $[M+H]^+$, 386.0097; found, 386.0096.

*1,2-Bis(2,4-difluorobenzyl)-1H-1,2,4-triazole-3(2H)-thione (**4f**)*

Compound **4f** (0.26 g) was prepared as a yellow syrup according to the procedure described for compound **3f**. Yield: 32.7%; IR (KBr) ν: 3111 (Ar–H), 2931, 2857 (CH_2), 1614, 1505, 1440 (aromatic frame), 1364, 1273 (C=S), 1184, 1138, 1092, 968, 851, 675 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.05 (s, 1H, S-triazole *H*), 7.35–7.33 (m, 2H, 2,4-F_2Ph 6-*H*), 6.90–6.73 (m, 4H, 2,4-F_2Ph 3,5-*H*), 5.27 (s, 2H, triazole-thione N^2-CH_2), 4.30 (s, 2H, triazole-thione N^1-CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.0, 162.4 (2C, 2,4-F_2Ph 2-*C*), 160.2, 159.1 (2C, 2,4-F_2Ph 4-*C*), 158.7 (S=*C*), 149.4 (S-triazole 5-*C*), 131.8, 131.6 (2C, 2,4-F_2Ph 6-*C*), 117.7, 117.3 (2C, 2,4-F_2Ph 1-*C*), 111.4, 110.7 (2C, 2,4-F_2Ph 5-*C*), 104.6, 104.2 (2C, 2,4-F_2Ph 3-*C*), 45.8, 41.5 (*C*H_2) ppm; ESI-MS (*m/z*): 353 $[M]^+$; HRMS (ESI) calcd. for $C_{16}H_{11}F_4N_3S$ $[M+H]^+$, 354.0688; found, 354.0691.

*3-(2-Bromoethylthio)-1-(3,4-dichlorobenzyl)-1H-1,2,4-triazole (**5a**)*

A mixture of 1-(3,4-dichlorobenzyl)-1*H*-1,2,4-triazole-3-thiol **2a** (2.00 g, 7.7 mmol) and potassium carbonate (1.21 g, 8.3 mmol) in acetone (10 mL) was stirred at 50 °C for 20 min, cooled to room temperature, and added 1,2-dibromoethane (1.73 g, 9.2 mmol). The resulting mixture was stirred

at 40 °C for 12 h. Upon completion of the reaction (monitored by TLC, eluent, chloroform/methanol, 30/1, *v/v*), the mixture was cooled to room temperature. The solvent was removed under vacuum and the residue was extracted with chloroform. The organic extracts were collected, dried over anhydrous sodium sulfate and concentrated. The crude product was purified by silica gel column chromatography (eluent, chloroform/methanol, 50/1, *v/v*) to afford pure compound **5a** (1.10 g) as a yellow oil. Yield: 40.5%; IR (KBr) ν: 3110, 3060 (Ar–H), 2967, 2930, 2853 (CH_2), 1562, 1499, 1473 (aromatic frame), 1356, 1176, 1133, 1060, 1032, 884, 823, 767, 724 (*C*–*S*–*C*) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.94 (s, 1H, S-triazole *H*), 7.45–7.35 (m, 2H, 3,4-Cl_2Ph 2,5-*H*), 7.19–7.16 (m, 1H, 3,4-Cl_2Ph 6-*H*), 4.39–4.36 (m, 4H, $BrCH_2CH_2$, 3,4-Cl_2Ph-CH_2), 3.63 (t, 2H, *J* = 6.0 Hz, $BrCH_2$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.8 (S-triazole S-*C*), 144.8 (S-triazole 5-*C*), 137.2 (3,4-Cl_2Ph 1-*C*), 132.3 (3,4-Cl_2Ph 3-*C*), 131.4 (3,4-Cl_2Ph 4-*C*), 130.8 (3,4-Cl_2Ph 2-*C*), 130.4 (3,4-Cl_2Ph 5-*C*), 128.1 (3,4-Cl_2Ph 6-*C*), 47.7, 36.5, 32.4 (CH_2) ppm; ESI-MS (*m/z*): 368 $[M+H]^+$; HRMS (ESI) calcd. for $C_{11}H_{10}BrCl_2N_3S$ $[M+H]^+$, 365.9234; found, 365.9238.

*3-(4-Bromobutylthio)-1-(3,4-dichlorobenzyl)-1H-1,2,4-triazole (**5b**)*

Compound **5b** was prepared employing a procedure similar to that used to synthesize compound **5a**, starting from 1-(3,4-dichlorobenzyl)-1*H*-1,2,4-triazole-3-thiol **2a** (2.01 g, 7.8 mmol), 1,4-dibromobutane (2.02 g, 9.4mmol) and potassium carbonate (1.21 g, 8.3 mmol). The pure product **5b** (1.22 g) was obtained as a yellow oil. Yield: 38.4%; IR (KBr) ν: 3113, 3062 (Ar–H), 2960, 2933, 2847 (CH_2), 1604, 1566, 1485, 1442 (aromatic frame), 1353, 1178, 1132, 1066, 1033, 884, 823, 759, 719 (C–S–C), 674 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.94 (s, 1H, S-triazole *H*), 7.46–7.30 (m, 2H, 3,4-Cl_2Ph 2,5-*H*), 7.21–7.16 (m, 1H, 3,4-Cl_2Ph 6-*H*), 4.36 (s, 2H, 3,4-Cl_2Ph-CH_2), 3.96 (t, 2H, *J* = 7.5 Hz, $Br(CH_2)_3CH_2$), 3.47 (t, 2H, *J* = 7.5 Hz, $BrCH_2$), 2.14–2.06 (m, 2H, $Br(CH_2)_2CH_2$), 1.99–1.92 (m, 2H, $BrCH_2CH_2$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 149.9 (S-triazole S-*C*), 143.6 (S-triazole 5-*C*), 137.0 (3,4-Cl_2Ph 1-*C*), 132.1 (3,4-Cl_2Ph 3-*C*), 131.5 (3,4-Cl_2Ph 4-*C*), 130.6 (3,4-Cl_2Ph 2-*C*), 130.5 (3,4-Cl_2Ph 5-*C*), 127.8 (3,4-Cl_2Ph 6-*C*), 46.6, 35.6, 31.7, 28.2, 27.6 (CH_2) ppm; ESI-MS (*m/z*): 396 $[M+H]^+$; HRMS (ESI) calcd. for $C_{13}H_{14}BrCl_2N_3S$ $[M+H]^+$, 393.9547; found, 393.9545.

*3-(6-Bromohexylthio)-1-(3,4-dichlorobenzyl)-1H-1,2,4-triazole (**5c**)*

Compound **5c** was prepared employing a procedure similar to that used to synthesize compound **5a**, starting from 1-(3,4-dichlorobenzyl)-1*H*-1,2,4-triazole-3-thiol **2a** (2.02 g, 7.8 mmol), 1,6-dibromohexane (2.43 g, 9.9mmol) and potassium carbonate (1.24 g, 8.3 mmol). The pure product **5c** (1.20 g) was obtained as a yellow oil. Yield: 37.6%; IR (KBr) ν: 3111, 3062 (Ar–H), 2965, 2934 (CH_2), 1560, 1495, 1472 (aromatic frame), 1362, 1182, 1130, 1032, 885, 730 (*C*–*S*–*C*), 681 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.95 (s, 1H, S-triazole *H*), 7.45–7.33 (m, 2H, 3,4-Cl_2Ph 2,5-*H*), 7.13–7.11 (m, 1H, 3,4-Cl_2Ph 6-*H*), 4.35 (s, 2H, 3,4-Cl_2Ph-CH_2), 3.97 (t, 2H, *J* = 6.0 Hz, $Br(CH_2)_5CH_2$), 3.44 (t, 2H, *J* = 6.0 Hz, $BrCH_2$), 1.97–1.91 (m, 2H, $Br(CH_2)_4CH_2$), 1.84–1.75 (m, 2H, $BrCH_2CH_2$), 1.34–1.21 (m, 4H, $Br(CH_2)_2CH_2CH_2$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.1 (S-triazole S-*C*), 142.8 (S-triazole 5-*C*), 137.2 (3,4-Cl_2Ph 1-*C*), 132.4 (3,4-Cl_2Ph 3-*C*), 131.8 (3,4-Cl_2Ph 4-*C*), 130.7 (3,4-Cl_2Ph 2-*C*), 130.5 (3,4-Cl_2Ph 5-*C*), 128.1 (3,4-Cl_2Ph 6-*C*), 47.2, 34.7, 34.5, 29.6, 28.9, 25.9, 25.8 (CH_2) ppm; ESI-MS (*m/z*): 424 $[M+H]^+$; HRMS (ESI) calcd. for $C_{15}H_{18}BrCl_2N_3S$ $[M+H]^+$, 421.9860; found, 421.9862.

*3-(2-Bromoethylthio)-1-(2,4-difluorobenzyl)-1H-1,2,4-triazole (**5d**)*

Compound **5d** was prepared employing a procedure similar to that used to synthesize compound **5a**, starting from 1-(2,4-difluorobenzyl)-1*H*-1,2,4-triazole-3-thiol **2b** (2.01 g, 8.9 mmol), 1,2-dibromoethane (2.04 g, 10.8 mmol) and potassium carbonate (1.24 g, 8.3 mmol). The pure product **5d** (0.73 g) was obtained as a yellow oil. Yield: 23.7%; IR (KBr) ν: 3111, 3076 (Ar–H), 2995 (CH_2), 1603, 1548, 1478 (aromatic frame), 1359, 1188, 1138, 1088, 967, 852, 724 (*C*–*S*–*C*) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.93 (s, 1H, S-triazole *H*), 7.38–7.29 (m, 1H, 2,4-F_2Ph 6-*H*), 6.81–6.75 (m, 2H, 2,4-F_2Ph 3,5-*H*), 4.57 (t, 2H, *J* = 6.0 Hz, $BrCH_2CH_2$), 4.29 (s, 2H, 2,4-F_2Ph-CH_2), 3.56 (t, 2H, *J* = 6.0 Hz, $BrCH_2$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.1, 162.8 (2,4-F_2Ph 2-*C*), 160.8, 160.1 (2,4-F_2Ph 4-*C*), 152.5 (S-triazole S-*C*), 142.2 (S-triazole 5-*C*), 131.5 (2,4-F_2Ph 6-*C*), 120.6, 120.3 (2,4-F_2Ph 1-*C*), 110.4, 110.2 (2,4-F_2Ph 5-*C*), 103.6, 103.2 (2,4-F_2Ph 3-*C*), 47.3, 33.4, 31.4 (CH_2) ppm; ESI-MS (*m/z*): 334 $[M]^+$; HRMS (ESI) calcd. for $C_{11}H_{10}BrF_2N_3S$ $[M+H]^+$, 333.9825; found, 333.9822.

*3-(4-Bromobutylthio)-1-(2,4-difluorobenzyl)-1H-1,2,4-triazole (**5e**)*

Compound **5e** was prepared employing a procedure similar to that used to synthesize compound **5a**, starting from 1-(2,4-difluorobenzyl)-1*H*-1,2,4-triazole-3-thiol **2b** (2.12 g, 9.2 mmol) and 1,4-dibromobutane (2.31 g, 10.7 mmol) and potassium carbonate (1.21 g, 8.3 mmol). The pure product **5e** (1.12 g) was obtained as a yellow oil. Yield: 33.2%; IR (KBr) ν: 3113 (Ar–H), 2998, 2987 (CH_2), 1607, 1501, 1481 (aromatic frame), 1361, 1192, 1139, 1079, 967, 852, 722 (*C*–*S*–*C*), 691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.92 (s, 1H, S-triazole *H*), 7.45–7.36 (m, 1H, 2,4-F_2Ph 6-*H*), 6.81–6.75 (m, 2H, 2,4-F_2Ph 3,5-*H*), 4.41 (s, 2H, 2,4-F_2Ph-CH_2), 3.97 (t, 2H, *J* = 6.0 Hz, $Br(CH_2)_3CH_2$), 3.36

(t, 2H, J = 7.5 Hz, BrCH_2), 2.04–1.96 (m, 2H, BrCH$_2$CH_2), 1.85–1.77 (m, 2H, Br(CH$_2$)$_2$CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.0, 163.4 (2,4-F_2Ph 2-*C*), 160.9, 160.7 (2,4-F_2Ph 4-*C*), 151.1 (S-triazole S-*C*), 145.5 (S-triazole 5-*C*), 130.7, 130.5 (2,4-F_2Ph 6-*C*), 118.8, 117.9 (2,4-F_2Ph 1-*C*), 110.3, 110.1 (2,4-F_2Ph 5-*C*), 103.2, 103.0 (2,4-F_2Ph 3-*C*), 46.6, 34.6, 31.5, 27.1, 26.8 (*C*H$_2$) ppm; ESI-MS (*m/z*): 362 $[M]^+$; HRMS (ESI) calcd. for $C_{13}H_{14}BrF_2N_3S$ $[M+H]^+$, 362.0138; found, 362.0138.

*3-(6-Bromohexylthio)-1-(2,4-difluorobenzyl)-1H-1,2,4-triazole (**5f**)*

Compound **5f** was prepared employing a procedure similar to that used to synthesize compound **5a**, starting from 1-(2,4-difluorobenzyl)-1*H*-1,2,4-triazole-3-thiol **2b** (2.01 g, 9.0 mmol), 1,2-dibromoethane (2.64 g, 10.7 mmol) and potassium carbonate (1.21 g, 8.3 mmol). The pure product **5f** (0.91 g) was obtained as a yellow oil. Yield: 25.5%; IR (KBr) ν: 3112 (Ar–H), 2988, 2834 (CH_2), 1610, 1508, 1471 (aromatic frame), 1351, 1166, 1114, 968, 853, 710 (*C*–*S*–*C*) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.93 (s, 1H, S-triazole *H*), 7.37–7.30 (m, 1H, 2,4-F_2Ph 6-*H*), 6.84–6.75 (m, 2H, 2,4-F_2Ph 3,5-*H*), 4.42 (s, 2H, 2,4-F_2Ph-CH_2), 3.98 (t, 2H, J = 7.5 Hz, Br(CH)$_5$CH_2), 3.41 (t, 2H, J = 6.0 Hz, BrCH_2), 1.96–1.88 (m, 2H, Br(CH$_2$)$_4$CH_2), 1.80–1.72 (m, 2H, BrCH$_2$CH_2), 1.28–1.17 (m, 4H, Br(CH$_2$)$_2$CH_2CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.1, 162.8 (2,4-F_2Ph 2-*C*), 160.7, 160.2 (2,4-F_2Ph 4-*C*), 152.4 (S-triazole S-*C*), 146.0 (S-triazole 5-*C*), 130.2, 130.0 (2,4-F_2Ph 6-*C*), 119.7, 119.5 (2,4-F_2Ph 1-*C*), 110.6, 110.4 (2,4-F_2Ph 5-*C*), 103.5, 103.2 (2,4-F_2Ph 3-*C*), 47.5, 33.2, 32.1, 29.8, 29.2, 25.6, 25.4 (*C*H$_2$) ppm; ESI-MS (*m/z*): 390 $[M]^+$; HRMS (ESI) calcd. for $C_{15}H_{18}BrF_2N_3S$ $[M+H]^+$, 390.0451; found, 390.0453.

*2-(2-Bromoethyl)-1-(3,4-dichlorobenzyl)-1H-1,2,4-triazole-3(2H)-thione (**6a**)*

Compound **6a** (1.00 g) was prepared as a yellow oil according to the procedure described for compound **5a**. Yield: 37.6%; IR (KBr) ν: 3110, 3059 (Ar–H), 2968, 2938 (CH_2), 1555, 1499, 1470 (aromatic frame), 1367, 1268 (C=S), 1185, 1133, 1031, 885, 823, 777 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.99 (s, 1H, S-triazole *H*), 7.49–7.33 (m, 2H, 3,4-Cl_2Ph 2,5-*H*), 7.23–7.21 (m, 1H, 3,4-Cl_2Ph 6-*H*), 4.47 (t, 2H, J = 6.0 Hz, BrCH$_2$CH_2), 4.26 (s, 2H, 3,4-Cl_2Ph-CH_2), 3.70 (t, 2H, J = 6.0 Hz, BrCH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.8 (S=*C*), 149.6 (S-triazole 5-*C*), 137.2 (3,4-Cl_2Ph 1-*C*), 132.3 (3,4-Cl_2Ph 3-*C*), 131.4 (3,4-Cl_2Ph 4-*C*), 130.8 (3,4-Cl_2Ph 2-*C*), 130.4 (3,4-Cl_2Ph 5-*C*), 128.1 (3,4-Cl_2Ph 6-*C*), 48.2, 34.5, 32.4 (*C*H$_2$) ppm; ESI-MS (*m/z*): 368 $[M+H]^+$; HRMS (ESI) calcd. for $C_{11}H_{10}BrCl_2N_3S$ $[M+H]^+$, 365.9234; found, 365.9230.

*2-(4-Bromobutyl)-1-(3,4-dichlorobenzyl)-1H-1,2,4-triazole-3(2H)-thione (**6b**)*

Compound **6b** (1.51 g) was prepared as a yellow oil according to the procedure described for compound **5b**. Yield: 34.9%; IR (KBr) ν: 3111, 3059 (Ar–H), 2961, 2933 (CH_2), 1602, 1558, 1496, 1447 (aromatic frame), 1360, 1272 (C=S), 1179, 1131, 1037, 885, 825, 771 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.98 (s, 1H, S-triazole *H*), 7.45–7.33 (m, 2H, 3,4-Cl_2Ph 2,5-*H*), 7.23–7.17 (m, 1H, 3,4-Cl_2Ph 6-*H*), 4.26 (s, 2H, 3,4-Cl_2Ph-CH_2), 4.08 (t, 2H, J = 6.0 Hz, Br(CH$_2$)$_3$CH_2), 3.39 (t, 2H, J = 6.0 Hz, BrCH_2), 2.13–2.06 (m, 2H, Br(CH$_2$)$_2$CH_2), 1.99–1.91 (m, 2H, BrCH$_2$CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.2 (S=*C*), 141.9 (S-triazole 5-*C*), 137.4 (3,4-Cl_2Ph 1-*C*), 132.5 (3,4-Cl_2Ph 3-*C*), 131.7 (3,4-Cl_2Ph 4-*C*), 130.9 (3,4-Cl_2Ph 2-*C*), 130.6 (3,4-Cl_2Ph 5-*C*), 127.7 (3,4-Cl_2Ph 6-*C*), 47.6, 36.5, 31.1, 27.7, 27.4 (*C*H$_2$) ppm; ESI-MS (*m/z*): 396 $[M+H]^+$; HRMS (ESI) calcd. for $C_{13}H_{14}BrCl_2N_3S$ $[M+H]^+$, 393.9547; found, 393.9550.

*2-(6-Bromohexyl)-1-(3,4-dichlorobenzyl)-1H-1,2,4-triazole-3(2H)-thione (**6c**)*

Compound **6c** (1.32 g) was prepared as a yellow oil according to the procedure described for compound **5c**. Yield: 46.5%; IR (KBr) ν: 3113, 3060 (Ar–H), 2962, 2931 (CH_2), 1561, 1491, 1452 (aromatic frame), 1361, 1267 (C=S), 1179, 1131, 1031, 887, 819, 765 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.97 (s, 1H, S-triazole *H*), 7.43–7.31 (m, 2H, 3,4-Cl_2Ph 2,5-*H*), 7.17–7.14 (m, 1H, 3,4-Cl_2Ph 6-*H*), 4.28 (s, 2H, 3,4-Cl_2Ph-CH_2), 4.07 (t, 2H, J = 7.5 Hz, Br(CH$_2$)$_5$CH_2), 3.46 (t, 2H, J = 7.5 Hz, BrCH_2), 2.01–1.92 (m, 2H, Br(CH$_2$)$_4$CH_2), 1.87–1.77 (m, 2H, BrCH$_2$CH_2), 1.28–1.19 (m, 4H, Br(CH$_2$)$_2$CH_2CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.1 (S=*C*), 142.5 (S-triazole 5-*C*), 137.3 (3,4-Cl_2Ph 1-*C*), 132.4 (3,4-Cl_2Ph 3-*C*), 131.4 (3,4-Cl_2Ph 4-*C*), 130.7 (3,4-Cl_2Ph 2-*C*), 130.5 (3,4-Cl_2Ph 5-*C*), 128.1 (3,4-Cl_2Ph 6-*C*), 46.6, 35.7, 30.9, 29.8, 29.2, 25.3, 25.2 (*C*H$_2$) ppm; ESI-MS (*m/z*): 424 $[M+H]^+$; HRMS (ESI) calcd. for $C_{15}H_{18}BrCl_2N_3S$ $[M+H]^+$, 421.9860; found, 421.9862.

*2-(2-Bromoethyl)-1-(2,4-difluorobenzyl)-1H-1,2,4-triazole-3(2H)-thione (**6d**)*

Compound **6d** (1.01 g) was prepared as a yellow oil according to the procedure described for compound **5d**. Yield: 35.1%; IR (KBr) ν: 3111 (Ar–H), 2996 (CH_2), 1604, 1503, 1459 (aromatic frame), 1369, 1266 (C=S), 1186, 1138, 1088, 967, 852, 731, 663 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.95 (s, 1H, S-triazole *H*), 7.41–7.33 (m, 1H, 2,4-F_2Ph 6-*H*), 6.83–6.76 (m, 2H, 2,4-F_2Ph 3,5-*H*), 4.51 (t, 2H, J = 6.0 Hz, BrCH$_2$CH_2), 4.32 (s, 2H, 2,4-F_2Ph-CH_2), 3.68 (t, 2H, J = 6.0 Hz, BrCH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.8, 162.7 (2,4-F_2Ph 2-*C*), 160.5, 160.3 (2,4-F_2Ph 4-*C*), 155.6 (S=*C*), 143.4 (S-triazole 5-*C*), 130.4 (2,4-F_2Ph 6-*C*), 118.2 (2,4-F_2Ph 1-*C*), 109.8, 109.6 (2,4-F_2Ph 5-*C*), 102.4, 102.1 (2,4-F_2Ph 3-*C*), 45.6, 43.5, 37.7 (*C*H$_2$) ppm; ESI-MS (*m/z*): 334 $[M]^+$; HRMS (ESI) calcd. for $C_{11}H_{10}BrF_2N_3S$ $[M+H]^+$, 333.9825; found, 333.9825.

*2-(4-Bromobutyl)-1-(2,4-difluorobenzyl)-1H-1,2,4-triazole-3(2H)-thione (**6e**)*

Compound **6e** (1.10 g) was prepared as a yellow oil according to the procedure described for compound **5e**. Yield: 34.9%; IR (KBr) ν: 3112, 3065 (Ar–H), 2993, 2789 (CH_2), 1603, 1581, 1506, 1453 (aromatic frame), 1367, 1259 (C=S), 1181, 1139, 1087, 1014, 967, 852, 762 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.99 (s, 1H, S-triazole *H*), 7.46–7.39 (m, 1H, 2,4-F_2Ph 6-*H*), 6.82–6.74 (m, 2H, 2,4-F_2Ph 3,5-*H*), 4.32 (s, 2H, 2,4-F_2Ph-CH_2), 4.09 (t, 2H, *J* = 7.5 Hz, Br$(CH_2)_3$CH_2), 4.04 (t, 2H, *J* = 7.5 Hz, BrCH_2), 2.15–2.10 (m, 2H, Br$(CH_2)_2$CH_2), 1.97–1.90 (m, 2H, BrCH_2CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.7, 164.2 (2,4-F_2Ph 2-*C*), 161.5, 160.8 (2,4-F_2Ph 4-*C*), 156.6 (S=*C*), 140.1 (S-triazole 5-*C*), 131.4, 131.1 (2,4-F_2Ph 6-*C*), 117.5 (2,4-F_2Ph 1-*C*), 111.1, 110.7 (2,4-F_2Ph 5-*C*), 104.1, 103.6 (2,4-F_2Ph 3-*C*), 47.8, 39.6, 34.5, 25.8, 25.6 (*C*H_2) ppm; ESI-MS (*m/z*): 362 $[M]^+$; HRMS (ESI) calcd. for $C_{13}H_{14}BrF_2N_3S$ $[M+H]^+$, 362.0138; found, 362.0141.

*2-(6-Bromohexyl)-1-(2,4-difluorobenzyl)-1H-1,2,4-triazole-3(2H)-thione (**6f**)*

Compound **6f** (1.31 g) was prepared as a yellow oil according to the procedure described for compound **5f**. Yield: 39.3%; IR (KBr) ν: 3117, 3068 (Ar–H), 2941, 2792 (CH_2), 1603, 1509, 1434 (aromatic frame), 1361, 1262 (C=S), 1185, 1144, 1093, 972, 848, 679 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.96 (s, 1H, S-triazole *H*), 7.39–7.29 (m, 1H, 2,4-F_2Ph 6-*H*), 6.80–6.74 (m, 2H, 2,4-F_2Ph 3,5-*H*), 4.31 (s, 2H, 2,4-F_2Ph-CH_2), 4.10 (t, 2H, *J* = 6.0 Hz, Br$(CH_2)_5$CH_2), 4.03 (t, 2H, *J* = 7.5 Hz, BrCH_2), 1.99–1.93 (m, 2H, Br$(CH_2)_4$CH_2), 1.84–1.76 (m, 2H, BrCH_2CH_2), 1.26–1.16 (m, 4H, Br$(CH_2)_2$CH_2CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.1, 162.8 (2,4-F_2Ph 2-*C*), 160.3, 159.7 (2,4-F_2Ph 4-*C*), 156.8 (S=*C*), 142.6 (S-triazole 5-*C*), 130.8, 130.6 (2,4-F_2Ph 6-*C*), 118.3 (2,4-F_2Ph 1-*C*), 110.5, 110.1 (2,4-F_2Ph 5-*C*), 104.5, 103.8 (2,4-F_2Ph 3-*C*), 46.1, 41.5, 35.3, 28.8, 28.6, 25.7, 25.6 (*C*H_2) ppm; ESI-MS (*m/z*): 390 $[M]^+$; HRMS (ESI) calcd. for $C_{15}H_{18}BrF_2N_3S$ $[M+H]^+$, 390.0451; found, 390.0456.

*3-(2-(1H-1,2,4-Triazol-1-yl)ethylthio)-1-(3,4-dichlorobenzyl)-1H-1,2,4-triazole (**7a**)*

To a stirred solution of 1*H*-1,2,4-triazole (0.07 g, 1.2 mmol) in acetonitrile (5 mL) was added potassium carbonate (0.17 g, 1.2 mmol). The mixture was heated at 60 ºC for 20 min, cooled to room temperature, and added compound **5a** (0.37 g, 1.0 mmol). The resulting mixture was stirred at 40 ºC until the reaction was completed (monitored by TLC, eluent, chloroform/methanol, 30/1, *v/v*). The solvent was evaporated under vacuum and the residue was treated with water (50 mL) and extracted with chloroform (3 × 50 mL). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated. The crude product was purified via silica gel column chromatography (eluent, chloroform/methanol, 40/1, *v/v*) to afford compound **7a** (0.32 g) as a yellow syrup. Yield: 90.9%; IR (KBr) ν: 3110, 3058 (Ar–H), 2956, 2851 (CH_2), 1557, 1504, 1471 (aromatic frame), 1360, 1178, 1136, 1012, 961, 882, 739 (*C*–*S*–*C*), 685 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.92 (s, 1H, triazole 3-*H*), 7.90 (s, 1H, S-triazole *H*), 7.74 (s, 1H, triazole 5-*H*), 7.40–7.34 (m, 2H, 3,4-Cl_2Ph 2,5-*H*), 7.12–7.10 (m, 1H, 3,4-Cl_2Ph 6-*H*), 4.60 (t, 2H, *J* = 6.0 Hz, SCH_2CH_2), 4.43 (t, 2H, *J* = 4.5 Hz, SCH_2), 4.24 (s, 2H, 3,4-Cl_2Ph-CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 152.1 (S-triazole S-*C*), 151.6 (triazole 3-*C*), 143.9 (S-triazole 5-*C*), 143.5 (triazole 5-*C*), 137.0 (3,4-Cl_2Ph 1-*C*), 132.3 (3,4-Cl_2Ph 3-*C*), 131.7 (3,4-Cl_2Ph 4-*C*), 130.7 (3,4-Cl_2Ph 2-*C*), 130.6 (3,4-Cl_2Ph 5-*C*), 128.4 (3,4-Cl_2Ph 6-*C*), 47.7, 46.8, 30.7 (*C*H_2) ppm; ESI-MS (*m/z*): 355 $[M]^+$; HRMS (ESI) calcd. for $C_{13}H_{12}Cl_2N_6S$ $[M+H]^+$, 355.0299; found, 355.0291.

*3-(4-(1H-1,2,4-Triazol-1-yl)butylthio)-1-(3,4-dichlorobenzyl)-1H-1,2,4-triazole (**7b**)*

Compound **7b** was prepared employing a procedure similar to that used to synthesize compound **7a**, starting from bromide **5b** (0.39 g, 1.0 mmol), 1*H*-1,2,4-triazole (0.07 g, 1.2 mmol) and potassium carbonate (0.17 g, 1.2 mmol). The pure product **7b** (0.33 g) was obtained as a yellow syrup. Yield: 85.1%; IR (KBr) ν: 3111, 3062 (Ar–H), 2941, 2856 (CH_2), 1612, 1505, 1475 (aromatic frame), 1355, 1176, 1137, 1011, 961, 882, 737 (C–S–C), 676 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.04 (s, 1H, triazole 3-*H*), 7.94 (s, 1H, triazole 5-*H*), 7.88 (s, 1H, S-triazole *H*), 7.44–7.34 (m, 2H, 3,4-Cl_2Ph 2,5-*H*), 7.17–7.14 (m, 1H, 3,4-Cl_2Ph 6-*H*), 4.35 (s, 2H, 3,4-Cl_2Ph-CH_2), 4.12 (t, 2H, *J* = 7.5 Hz, S$(CH_2)_3$CH_2), 3.96 (t, 2H, *J* = 6.0 Hz, SCH_2), 1.90–1.83 (m, 2H, S$(CH_2)_2$CH_2), 1.79–1.71 (m, 2H, SCH_2CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 152.0 (S-triazole S-*C*), 149.5 (triazole 3-*C*), 142.6 (S-triazole 5-*C*), 142.1 (triazole 5-*C*), 137.4 (3,4-Cl_2Ph 1-*C*), 132.8 (3,4-Cl_2Ph 3-*C*), 132.0 (3,4-Cl_2Ph 4-*C*), 130.9 (3,4-Cl_2Ph 2-*C*), 130.6 (3,4-Cl_2Ph 5-*C*), 127.6 (3,4-Cl_2Ph 6-*C*), 48.1, 47.8, 35.2, 27.7, 27.4 (*C*H_2), ppm; ESI-MS (*m/z*): 383 $[M]^+$; HRMS (ESI) calcd. for $C_{15}H_{16}Cl_2N_6S$ $[M+H]^+$, 383.0612; found, 383.0613.

*3-(6-(1H-1,2,4-Triazol-1-yl)hexylthio)-1-(3,4-dichlorobenzyl)-1H-1,2,4-triazole (**7c**)*

Compound **7c** was prepared employing a procedure similar to that used to synthesize compound **7a** starting from 3-(6-bromohexylthio)-1-(3,4-dichlorobenzyl)-1*H*-1,2,4-triazole **5c** (0.42 g, 1.0 mmol), 1*H*-1,2,4-triazole (0.07 g, 1.2 mmol) and potassium carbonate (0.17 g, 1.2 mmol). The pure product **7c** (0.34 g) was obtained as a yellow syrup. Yield: 83.4%; IR (KBr) ν: 3113, 3059 (Ar–H), 2936, 2859 (CH_2), 1562, 1506, 1471 (aromatic frame), 1356, 1179, 1139, 1014, 959, 879, 738 (C–S–C), 680 cm^{-1}; ^1H NMR

(300 MHz, $CDCl_3$) δ: 8.02 (s, 1H, triazole 3-*H*), 7.93 (s, 1H, triazole 5-*H*), 7.85 (s, 1H, S-triazole *H*), 7.43–7.34 (m, 2H, 3,4-Cl_2Ph 2,5-*H*), 7.19–7.15 (m, 1H, 3,4-Cl_2Ph 6-*H*), 4.33 (s, 2H, 3,4-Cl_2Ph-CH_2), 4.15 (t, 2H, *J* = 6.0 Hz, S$(CH_2)_5$CH_2), 3.95 (t, 2H, *J* = 7.5 Hz, SCH_2), 1.89–1.79 (m, 2H, S$(CH_2)_4$CH_2), 1.74–1.65 (m, 2H, SCH_2CH_2), 1.29–1.18 (m, 4H, S$(CH_2)_2$CH_2CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.8 (S-triazole S-*C*), 151.3 (triazole 3-*C*), 148.1 (S-triazole 5-*C*), 142.8 (triazole 5-*C*), 137.2 (3,4-Cl_2Ph 1-*C*), 132.6 (3,4-Cl_2Ph 3-*C*), 131.8 (3,4-Cl_2Ph 4-*C*), 130.7 (3,4-Cl_2Ph 2-*C*), 130.5 (3,4-Cl_2Ph 5-*C*), 128.2 (3,4-Cl_2Ph 6-*C*), 49.4, 48.3, 36.6, 29.5, 29.0, 25.8, 25.7 (*C*H_2) ppm; ESI-MS (*m/z*): 411 $[M]^+$; HRMS (ESI) calcd. for $C_{17}H_{20}Cl_2N_6S$ $[M+H]^+$, 411.0925; found, 411.0925.

*3-(2-(1H-1,2,4-Triazol-1-yl)ethylthio)-1-(2,4-difluorobenzyl)-1H-1,2,4-triazole (**7d**)*

Compound **7d** was prepared employing a procedure similar to that used to synthesize compound **7a** starting from bromide **5d** (0.33 g, 1.0 mmol), 1*H*-1,2,4-triazole (0.07 g, 1.2 mmol) and potassium carbonate (0.17 g, 1.2 mmol). The pure product **7d** (0.24 g) was obtained as a yellow syrup. Yield: 75.4%; IR (KBr) ν: 3115, 3078 (Ar–H), 2956 (CH_2), 1603, 1504, 1479 (aromatic frame), 1358, 1177, 1138, 1087, 1024, 967, 853, 719 (C–S–C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.95 (s, 1H, triazole 3-*H*), 7.93 (s, 1H, S-triazole *H*), 7.80 (s, 1H, triazole 5-*H*), 7.29–7.23 (m, 1H, 2,4-F_2Ph 6-*H*), 6.82–6.77 (m, 2H, 2,4-F_2Ph 3,5-*H*), 4.60 (t, 2H, *J* = 6.0 Hz, SCH_2CH_2), 4.42 (t, 2H, *J* = 6.0 Hz, SCH_2), 4.31 (s, 2H, 2,4-F_2Ph-CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.2, 161.1 (2,4-F_2Ph 2-*C*), 160.9, 159.2 (2,4-F_2Ph 4-*C*), 152.6 (S-triazole S-*C*), 152.2 (triazole 3-*C*), 143.8 (S-triazole 5-*C*), 143.6 (triazole 5-*C*), 131.8, 131.7 (2,4-F_2Ph 6-*C*), 119.9, 119.8 (2,4-F_2Ph 1-*C*), 111.5, 111.2 (2,4-F_2Ph 5-*C*), 104.4, 104.1, 103.7 (2,4-F_2Ph 3-*C*), 48.0, 47.4, 30.6 (*C*H_2) ppm; ESI-MS (*m/z*): 323 $[M+H]^+$; HRMS (ESI) calcd. for $C_{13}H_{12}F_2N_6S$ $[M+H]^+$, 323.0890; found, 323.0892.

*3-(4-(1H-1,2,4-Triazol-1-yl)butylthio)-1-(2,4-difluorobenzyl)-1H-1,2,4-triazole (**7e**)*

Compound **7e** was prepared employing a procedure similar to that used to synthesize compound **7a**, starting from bromide **5e** (0.36 g, 1.0 mmol), 1*H*-1,2,4-triazole (0.07 g, 1.2 mmol) and potassium carbonate (0.17 g, 1.2 mmol). The pure product **7e** (0.29 g) was obtained as a yellow syrup. Yield: 82.0%; IR (KBr) ν: 3113, 3077 (Ar–H), 2946, 2865 (CH_2), 1603, 1505, 1477 (aromatic frame), 1357, 1181, 1139, 1013, 967, 852, 735 (C–S–C), 681 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.03 (s, 1H, triazole 3-*H*), 7.94 (s, 1H, triazole 5-*H*), 7.89 (s, 1H, S-triazole *H*), 7.35–7.30 (m, 1H, 2,4-F_2Ph 6-*H*), 6.84–6.76 (m, 2H, 2,4-F_2Ph 3,5-*H*), 4.40 (s, 2H, 2,4-F_2Ph-CH_2), 4.13 (t, 2H, *J* = 6.0 Hz, S$(CH_2)_3$CH_2), 3.96 (t, 2H, *J* = 7.5 Hz, SCH_2), 1.94–1.76 (m, 4H, $SCH_2CH_2CH_2$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.7, 162.0 (2,4-F_2Ph 2-*C*), 160.9, 160.3 (2,4-F_2Ph 4-*C*), 152.2 (S-triazole S-*C*), 151.7 (triazole 3-*C*), 144.5 (S-triazole 5-*C*), 143.2 (triazole 5-*C*), 130.7, 130.4 (2,4-F_2Ph 6-*C*), 118.5, 118.1 (2,4-F_2Ph 1-*C*), 111.3, 111.0 (2,4-F_2Ph 5-*C*), 104.1, 103.6 (2,4-F_2Ph 3-*C*), 48.0, 45.3, 34.5, 27.3, 26.8 (*C*H_2) ppm; ESI-MS (*m/z*): 351 $[M+H]^+$; HRMS (ESI) calcd. for $C_{15}H_{16}F_2N_6S$ $[M+H]^+$, 351.1203; found, 351.1203.

*3-(6-(1H-1,2,4-Triazol-1-yl)hexylthio)-1-(2,4-difluorobenzyl)-1H-1,2,4-triazole (**7f**)*

Compound **7f** was prepared employing a procedure similar to that used to synthesize compound **7a**, starting from bromide **5f** (0.39 g, 1.0 mmol), 1*H*-1,2,4-triazole (0.07 g, 1.2 mmol) and potassium carbonate (0.17 g, 1.2 mmol). The pure product **7f** (0.30 g) was obtained as a yellow syrup. Yield: 78.7%; IR (KBr) ν: 3113, 3076 (Ar–H), 2942, 2860 (CH_2), 1603, 1505, 1476 (aromatic frame), 1359, 1178, 1139, 1014, 968, 853, 736 (C–S–C), 681 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.06 (s, 1H, triazole 3-*H*), 7.95 (s, 1H, triazole 5-*H*), 7.87 (s, 1H, S-triazole *H*), 7.35–7.30 (m, 1H, 2,4-F_2Ph 6-*H*), 6.86–6.77 (m, 2H, 2,4-F_2Ph 3,5-*H*), 4.37 (s, 2H, 2,4-F_2Ph-CH_2), 4.13 (t, 2H, *J* = 6.0 Hz, S$(CH_2)_5$CH_2), 3.97 (t, 2H, *J* = 7.5 Hz, SCH_2), 1.90–1.79 (m, 2H, S$(CH_2)_4$CH_2), 1.76–1.71 (m, 2H, SCH_2CH_2), 1.27–1.16 (m, 4H, S$(CH_2)_2$CH_2CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.5, 163.8 (2,4-F_2Ph 2-*C*), 160.4, 160.1 (2,4-F_2Ph 4-*C*), 151.6 (S-triazole S-*C*), 151.4 (triazole 3-*C*), 145.7 (S-triazole 5-*C*), 143.6 (triazole 5-*C*), 131.5, 131.3 (2,4-F_2Ph 6-*C*), 117.8 (2,4-F_2Ph 1-*C*), 111.0, 109.8 (2,4-F_2Ph 5-*C*), 104.5, 104.4 (2,4-F_2Ph 3-*C*), 48.6, 48.1, 36.2, 33.2, 29.8, 25.7, 25.5 (*C*H_2) ppm; ESI-MS (*m/z*): 479 $[M+H]^+$; HRMS (ESI) calcd. for $C_{17}H_{20}F_2N_6S$ $[M+H]^+$, 379.1516; found, 379.1512.

*2-(2-(1H-1,2,4-Triazol-1-yl)ethyl)-1-(3,4-dichlorobenzyl)-1H-1,2,4-triazole-3(2H)-thione (**8a**)*

Compound **8a** was prepared employing a procedure similar to that used to synthesize compound **7a**, starting from bromide **6a** (0.37 g, 1.0 mmol), 1*H*-1,2,4-triazole (0.07 g, 1.2 mmol) and potassium carbonate (0.17 g, 1.2 mmol). The pure product **8a** (0.24 g) was obtained as a yellow syrup. Yield: 71.8%; IR (KBr) ν: 3112 (Ar–H), 2964, 2857 (CH_2), 1558, 1506, 1472 (aromatic frame), 1354, 1263 (C=S), 1177, 1139, 1007, 972, 886, 681 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.97 (s, 1H, triazole 3-*H*), 7.66 (s, 2H, S-triazole *H*, triazole 5-*H*), 7.51–7.36 (m, 2H, 3,4-Cl_2Ph 2,5-*H*), 7.23–7.21 (m, 1H, 3,4-Cl_2Ph 6-*H*), 4.61–4.57 (m, 4H, S-triazole N^2-CH_2CH_2), 4.24 (s, 2H, 3,4-Cl_2Ph-CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 158.7 (S=*C*), 151.0 (triazole 3-*C*), 142.9 (S-triazole 5-*C*), 142.2 (triazole 5-*C*), 137.1 (3,4-Cl_2Ph 1-*C*), 132.7 (3,4-Cl_2Ph 3-*C*), 131.5 (3,4-Cl_2Ph 4-*C*), 130.7 (3,4-Cl_2Ph 2-*C*), 130.5 (3,4-Cl_2Ph 5-*C*), 128.1 (3,4-Cl_2Ph 6-*C*), 48.4, 46.4, 36.1 (*C*H_2) ppm; ESI-MS (*m/z*):

355 $[M]^+$; HRMS (ESI) calcd. for $C_{13}H_{12}Cl_2N_6S$ $[M+H]^+$, 355.0299; found, 355.0297.

*2-(4-(1H-1,2,4-Triazol-1-yl)butyl)-1-(3,4-dichlorobenzyl)-1H-1,2,4-triazole-3(2H)-thione (**8b**)*

Compound **8b** was prepared employing a procedure similar to that used to synthesize compound **7a** starting from bromide **6b** (0.39 g, 1.0 mmol), 1*H*-1,2,4-triazole (0.07 g, 1.2 mmol) and potassium carbonate (0.17 g, 1.2 mmol). The pure product **8b** (0.29 g) was obtained as a yellow syrup. Yield: 79.6%; IR (KBr) ν: 3110 (Ar–H), 2943, 2859 (CH_2), 1555, 1503, 1467 (aromatic frame), 1352, 1268 (C=S), 1180, 1142, 1013, 961, 880, 677 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.08 (s, 1H, triazole 3-*H*), 7.96 (s, 1H, S-triazole *H*), 7.95 (s, 1H, triazole 5-*H*), 7.49–7.33 (m, 2H, 3,4-Cl_2Ph 2,5-*H*), 7.24–7.22 (m, 1H, 3,4-Cl_2Ph 6-*H*), 4.24 (s, 2H, 3,4-Cl_2Ph-CH_2), 4.16 (t, 2H, *J* = 6.0 Hz, S-triazole N^2-$(CH_2)_3CH_2$), 4.08 (t, 2H, *J* = 6.0 Hz, S-triazole N^2-CH_2), 1.95–1.84 (m, 4H, S-triazole N^2-$CH_2CH_2CH_2$) ppm; ^1H NMR (300 MHz, DMSO-d_6) δ: 8.51 (s, 1H, triazole 3-*H*), 8.49 (s, 1H, S-triazole *H*), 7.95 (s, 1H, triazole 5-*H*), 7.62–7.51 (m, 2H, 3,4-Cl_2Ph 2,5-*H*), 7.36–7.32 (m, 1H, 3,4-Cl_2Ph 6-*H*), 4.28 (s, 2H, 3,4-Cl_2Ph-CH_2), 4.18–4.12 (m, 4H, S-triazole N^2-C$H_2(CH_2)_2CH_2$), 1.80–1.57 (m, 4H, S-triazole N^2-$CH_2CH_2CH_2$) ppm; ^{13}C NMR (75 MHz, DMSO) δ: 157.6 (S-triazole S=*C*), 151.3 (triazole 3-*C*), 143.4 (S-triazole 5-*C*), 142.6 (triazole 5-*C*), 138.6 (3,4-Cl_2Ph 1-*C*), 132.7 (3,4-Cl_2Ph 3-*C*), 132.3 (3,4-Cl_2Ph 4-*C*), 130.6 (3,4-Cl_2Ph 2-*C*), 130.3 (3,4-Cl_2Ph 5-*C*), 128.1 (3,4-Cl_2Ph 6-*C*), 49.3, 48.5, 35.3, 27.4, 27.3 (*C*H_2) ppm; ESI-MS (*m/z*): 383 $[M]^+$; HRMS (ESI) calcd. for $C_{15}H_{16}Cl_2N_6S$ $[M+H]^+$, 383.0612; found, 383.0603.

*2-(6-(1H-1,2,4-Triazol-1-yl)hexyl)-1-(3,4-dichlorobenzyl)-1H-1,2,4-triazole-3(2H)-thione (**8c**)*

Compound **8c** was prepared employing a procedure similar to that used to synthesize compound **7a** starting from bromide **6c** (0.42 g, 1.0 mmol), 1*H*-1,2,4-triazole (0.07 g, 1.2 mmol) and potassium carbonate (0.17 g, 1.2 mmol). The pure product **8c** (0.32 g) was obtained as a yellow syrup. Yield: 76.9%; IR (KBr) ν: 3112 (Ar–H), 2940, 2860 (CH_2), 1553, 1504, 1470 (aromatic frame), 1356, 1271 (C=S), 1179, 1138, 1014, 959, 879, 680 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.06 (s, 1H, triazole 3-*H*), 7.96 (s, 1H, S-triazole *H*), 7.94 (s, 1H, triazole 5-*H*), 7.48–7.32 (m, 2H, 3,4-Cl_2Ph 2,5-*H*), 7.25–7.22 (m, 1H, 3,4-Cl_2Ph 6-*H*), 4.21 (s, 2H, 3,4-Cl_2Ph-CH_2), 4.15 (t, 2H, *J* = 6.0 Hz, S-triazole N^2-$(CH_2)_5CH_2$), 4.05 (t, 2H, *J* = 7.5 Hz, S-triazole N^2-CH_2), 1.90–1.81 (m, 4H, S-triazole N^2-$CH_2CH_2(CH_2)_2CH_2$), 1.35–1.25 (m, 4H, S-triazole N^2-$(CH_2)_2CH_2CH_2$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.8 (S=*C*), 151.9 (triazole 3-*C*), 144.9 (S-triazole 5-*C*), 142.9 (triazole 5-*C*), 138.2 (3,4-Cl_2Ph 1-*C*), 132.1 (3,4-Cl_2Ph 3-*C*), 130.9 (3,4-Cl_2Ph 4-*C*), 130.2 (3,4-Cl_2Ph 2-*C*), 128.3 (3,4-Cl_2Ph 5-*C*), 126.9 (3,4-Cl_2Ph 6-*C*), 49.6, 49.4, 35.2, 29.5, 29.3, 25.8, 25.5 (*C*H_2) ppm; ESI-MS (*m/z*): 411 $[M]^+$; HRMS (ESI) calcd. for $C_{17}H_{20}Cl_2N_6S$ $[M+H]^+$, 411.0925; found, 411.0928.

*2-(2-(1H-1,2,4-Triazol-1-yl)ethyl)-1-(2,4-difluorobenz-yl)-1H-1,2,4-triazole-3(2H)-thione (**8d**)*

Compound **8d** was prepared employing a procedure similar to that used to synthesize compound **7a** starting from bromide **6d** (0.33 g, 1.0 mmol) and 1*H*-1,2,4-triazole (0.07 g, 1.2 mmol) and potassium carbonate (0.17 g, 1.2 mmol). The pure product **8d** (0.21 g) was obtained as a yellow syrup. Yield: 66.8%; IR (KBr) ν: 3114, 3078 (Ar–H), 2960 (CH_2), 1603, 1503, 1437 (aromatic frame), 1358, 1262 (C=S), 1189, 1137, 1087, 967, 853, 679 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.97 (s, 1H, triazole 3-*H*), 7.82 (s, 1H, S-triazole *H*), 7.79 (s, 1H, triazole 5-*H*), 7.40–7.34 (m, 1H, 2,4-F_2Ph 6-*H*), 6.83–6.78 (m, 2H, 2,4-F_2Ph 3,5-*H*), 4.62–4.59 (m, 4H, S-triazole N^2-CH_2CH_2), 4.31 (s, 2H, 2,4-F_2Ph-CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.5, 162.8 (3,4-F_2Ph 2-*C*), 160.8, 159.6 (3,4-F_2Ph 4-*C*), 159.1 (S=*C*), 151.9 (triazole 3-*C*), 146.9 (S-triazole 5-*C*), 143.0 (triazole 5-*C*), 130.7, 130.6, 130.5 (2,4-F_2Ph 6-*C*), 121.3 (2,4-F_2Ph 1-*C*), 110.4, 110.1 (3,4-F_2Ph 5-*C*), 103.3, 102.9, 102.8 (3,4-F_2Ph 3-*C*), 47.5, 47.2, 37.9 (*C*H_2) ppm; ESI-MS (*m/z*): 323 $[M+H]^+$; HRMS (ESI) calcd. for $C_{13}H_{12}F_2N_6S$ $[M+H]^+$, 323.0890; found, 323.0895.

*2-(4-(1H-1,2,4-Triazol-1-yl)butyl)-1-(2,4-difluorobenzyl)-1H-1,2,4-triazole-3(2H)-thione (**8e**)*

Compound **8e** was prepared employing a procedure similar to that used to synthesize compound **7a** starting from bromide **6e** (0.36 g, 1.0 mmol), 1*H*-1,2,4-triazole (0.07 g, 1.2 mmol) and potassium carbonate (0.17 g, 1.2 mmol). The pure product **8e** (0.26 g) was obtained as a yellow syrup. Yield: 74.6%; IR (KBr) ν: 3112 (Ar–H), 2946, 2866 (CH_2), 1603, 1564, 1503, 1446 (aromatic frame), 1358, 1265 (C=S), 1187, 1138, 1087, 1015, 967, 853, 681 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.06 (s, 1H, triazole 3-*H*), 7.98 (s, 1H, S-triazole *H*), 7.96 (s, 1H, triazole 5-*H*), 7.42–7.34 (m, 1H, 2,4-F_2Ph 6-*H*), 6.81–6.75 (m, 2H, 2,4-F_2Ph 3,5-*H*), 4.31 (s, 2H, 2,4-F_2Ph-CH_2), 4.18 (t, 2H, *J* = 6.0 Hz, S-triazole N^2-$(CH_2)_3CH_2$), 4.10 (t, 2H, *J* = 6.0 Hz, S-triazole N^2-CH_2), 2.05–1.94 (m, 4H, S-triazole N^2-$CH_2CH_2CH_2$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.1, 163.8 (2,4-F_2Ph 2-*C*), 161.1, 160.9 (2,4-F_2Ph 4-*C*), 159.9 (S=*C*), 151.1 (triazole 3-*C*), 143.6 (S-triazole 5-*C*), 142.2 (triazole 5-*C*), 130.1, 129.9 (2,4-F_2Ph 6-*C*), 119.1, 118.9 (2,4-F_2Ph 1-*C*), 111.5, 111.3 (2,4-F_2Ph 5-*C*), 104.7, 104.4 (2,4-F_2Ph 3-*C*), 48.0, 47.7, 33.4, 27.4, 27.2 (*C*H_2) ppm; ESI-MS (*m/z*): 351 $[M+H]^+$; HRMS (ESI) calcd. for $C_{15}H_{16}F_2N_6S$ $[M+H]^+$, 351.1203; found, 351.1203.

*2-(6-(1H-1,2,4-Triazol-1-yl)hexyl)-1-(2,4-difluorobenzyl)-1H-1,2,4-triazole-3(2H)-thione (**8f**)*

Compound **8f** was prepared employing a procedure sim-

ilar to that used to synthesize compound **7a** starting from bromide **6f** (0.39 g, 1.0 mmol), 1*H*-1,2,4-triazole (0.07 g, 1.2 mmol) and potassium carbonate (0.17 g, 1.2 mmol). The pure product **8f** (0.29 g) was obtained as a yellow syrup. Yield: 75.1%; IR (KBr) ν: 3111 (Ar–H), 2941, 2861 (CH_2), 1604, 1503, 1477 (aromatic frame), 1358, 1264 (C=S), 1187, 1139, 1088, 1019, 967, 853, 681 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.08 (s, 1H, triazole 3-*H*), 7.97 (s, 1H, S-triazole *H*), 7.94 (s, 1H, triazole 5-*H*), 7.44–7.36 (m, 1H, 2,4-F_2Ph 6-*H*), 6.81–6.75 (m, 2H, 2,4-F_2Ph 3,5-*H*), 4.32 (s, 2H, 2,4-F_2Ph-CH_2), 4.16 (t, 2H, *J* = 6.0 Hz, S-triazole N^2-$(CH_2)_5CH_2$), 4.07 (t, 2H, *J* = 7.5 Hz, S-triazole N^2-CH_2), 1.97–1.87 (m, 4H, S-triazole N^2-$CH_2CH_2(CH_2)_2CH_2$), 1.34–1.23 (m, 4H, S-triazole N^2-$(CH_2)_2CH_2CH_2$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.2, 164.0 (2,4-F_2Ph 2-*C*), 160.8, 160.5 (2,4-F_2Ph 4-*C*), 159.5 (S=*C*), 152.0 (triazole 3-*C*), 145.0 (S-triazole 5-*C*), 143.1 (triazole 5-*C*), 130.6, 130.4 (2,4-F_2Ph 6-*C*), 118.0, 117.9 (2,4-F_2Ph 1-*C*), 111.2, 110.9 (2,4-F_2Ph 5-*C*), 104.3, 104.1 (2,4-F_2Ph 3-*C*), 48.2, 47.8, 36.5, 30.3, 28.5, 25.8, 25.7 (*C*H_2) ppm; ESI-MS (*m/z*): 379 $[M+H]^+$; HRMS (ESI) calcd. for $C_{17}H_{20}F_2N_6S$ $[M+H]^+$, 379.1516; found, 379.1520.

*1-(4-(2-(3,4-Dichlorobenzyl)-4-hexyl-5-thioxo-2,5-dihydro-1H-1,2,4-triazol-4-ium-1-yl)butyl)-4-hexyl-1H-1,2,4-triazol-4-ium bromide (**9a**)*

A solution of thione **8b** (0.38 g, 1.0 mmol) and 1-bromooctane (0.40 g, 2.4 mmol) in anhydrous acetonitrile (5 mL) was stirred under reflux and monitored by TLC (eluent, chloroform/methanol, 30/1, *v/v*). Upon completion of the reaction, the solvent was evaporated under vacuum and the residue was washed three times with petroleum ether (30–60 ºC) and dried to afford pure compound **9a** (0.54 g) as a brown syrup. Yield: 76.2%; IR (KBr) ν: 3055 (Ar–H), 2928, 2858 (CH_2), 1605, 1561, 1500, 1473 (aromatic frame), 1271 (C=S), 1146, 1097, 1029, 972, 889, 851, 764, 684 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 10.39 (s, 1H, S-triazole *H*), 10.35 (s, 1H, triazole 3-*H*), 9.34 (s, 1H, triazole 5-*H*), 7.92–7.70 (m, 2H, 3,4-Cl_2Ph 2,5-*H*), 7.61–7.43 (m, 1H, 3,4-Cl_2Ph 6-*H*), 4.54–4.06 (m, 6H, S-triazole N^2-C$H_2$$(CH_2)_2CH_2$, S-triazole N^1-CH_2), 3.35–3.21 (m, 4H, S-triazole N^4-CH_2, triazole N^4-CH_2), 1.95–1.64 (m, 8H, S-triazole N^2-CH_2(CH_2)$_2$, S-triazole N^4-CH_2CH_2, triazole N^4-CH_2CH_2), 1.39–1.20 (m, 12H, S-triazole N^4-$(CH_2)_2$-(CH_2)$_3$, triazole N^4-$(CH_2)_2$(CH_2)$_3$), 0.87 (t, 6H, *J* = 6.0 Hz, S-triazole N^4-$(CH_2)_5CH_3$, triazole N^4-$(CH_2)_5CH_3$) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ: 159.2 (S=*C*), 154.7 (triazole 3-*C*), 147.1 (S-triazole 5-*C*), 142.8 (triazole 5-*C*), 137.0 (3,4-Cl_2Ph 1-*C*), 132.9 (3,4-Cl_2Ph 3-*C*), 131.5 (3,4-Cl_2Ph 4-*C*), 130.7 (3,4-Cl_2Ph 2-*C*), 130.3 (3,4-Cl_2Ph 5-*C*), 128.2 (3,4-Cl_2Ph 6-*C*), 51.4, 46.2, 45.6, 36.5, 32.4, 31.8, 28.7, 28.4, 27.5, 27.1, 25.7, 25.6, 22.6, 22.4 (*C*H_2), 14.3, 14.2 (*C*H_3) ppm; ESI-MS (*m/z*): 553 $[M–2Br]^+$; HRMS (ESI) calcd. for $C_{27}H_{42}Br_2Cl_2N_6S$ $[M–2Br+H]^+$, 554.6415; found, 554.6422.

*1-((2-(3,4-Dichlorobenzyl)-4-octyl-5-thioxo-2,5-dihydro-1H-1,2,4-triazol-4-ium-1-yl)methyl)-4-octyl-1H-1,2,4-triazol-4-ium bromide (**9b**)*

Compound **9b** was prepared employing a procedure similar to that used to synthesize compound **9a** starting from thione **8b** (0.38 g, 1.0 mmol) and 1-bromooctane (0.46 g, 2.4 mmol). The pure compound **9b** (0.51 g) was obtained as a brown syrup. Yield: 65.2%; IR (KBr) ν: 3115 (Ar–H), 2927, 2850 (CH_2), 1613, 1551, 1514, 1463 (aromatic frame), 1269 (C=S), 1142, 1091, 1023, 974, 848, 637 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 10.38 (s, 1H, S-triazole *H*), 10.36 (s, 1H, triazole 3-*H*), 9.35 (s, 1H, triazole 5-*H*), 7.79–7.50 (m, 2H, 3,4-Cl_2Ph 2,5-*H*), 7.42–7.27 (m, 1H, 3,4-Cl_2Ph 6-*H*), 4.71–4.19 (m, 6H, S-triazole N^2-C$H_2$$(CH_2)_2CH_2$, S-triazole N^1-CH_2), 3.34–4.19 (m, 4H, triazole N^4-CH_2, S-triazole N^4-CH_2), 2.33–1.75 (m, 8H, S-triazole N^2-CH_2(CH_2)$_2$, triazole N^4-CH_2CH_2, S-triazole N^4-CH_2CH_2), 1.35–1.27 (m, 20H, triazole N^4-CH_2CH_2 (CH_2)$_5$, S-triazole N^4-CH_2CH_2(CH_2)$_5$), 0.87 (t, 6H, *J* = 6.0 Hz, triazole N^4-$(CH_2)_7CH_3$, S-triazole N^4-$(CH_2)_7CH_3$) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ: 159.4 (S=*C*), 155.5 (triazole 3-*C*), 147.1 (S-triazole 5-*C*), 143.5 (triazole 5-*C*), 137.1 (3,4-Cl_2Ph 1-*C*), 132.6 (3,4-Cl_2Ph 3-*C*), 131.8 (3,4-Cl_2Ph 4-*C*), 131.0 (3,4-Cl_2Ph 2-*C*), 130.7 (3,4-Cl_2Ph 5-*C*), 128.5 (3,4-Cl_2Ph 6-*C*), 56.6, 50.7, 47.4, 47.3, 32.0, 31.7, 30.1, 29.7, 29.6, 29.5, 29.3, 29.0, 28.1, 27.6, 25.5, 25.3, 23.2, 22.9 (*C*H_2), 14.6, 14.3 (*C*H_3) ppm; ESI-MS (*m/z*): 690 $[M–Br]^+$, 609 $[M–2Br]^+$; HRMS (ESI) calcd. for $C_{31}H_{50}Br_2Cl_2N_6S$ $[M–2Br+H]^+$, 609.3273; found, 609.3275.

*1-((2,4-Bis(3,4-dichlorobenzyl)-5-thioxo-2,5-dihydro-1H-1,2,4-triazol-4-ium-1-yl)methyl)-4-(3,4-dichlorobenzyl)-1H-1,2,4-triazol-4-ium chloride (**10a**)*

Compound **10a** was prepared employing a procedure similar to that used to synthesize compound **9a**, starting from thione **8b** (0.38 g, 1.0 mmol) and 3,4-dichlorobenzyl chloride (0.47 g, 2.4 mmol). The pure product **10a** (0.55 g) was obtained as a brown syrup. Yield: 71.3%; IR (KBr) ν: 3123, 3084 (Ar–H), 2938 (CH_2), 1609, 1568, 1467 (aromatic frame), 1267 (C=S), 1140, 1032, 885, 625 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 10.64 (s, 1H, S-triazole *H*), 10.52 (s, 1H, triazole 3-*H*), 9.43 (s, 1H, triazole 5-*H*), 7.92–7.52 (m, 6H, 3,4-Cl_2Ph 2,5-*H*), 7.45–7.36 (m, 3H, 3,4-Cl_2Ph 6-*H*), 5.60 (s, 2H, S-triazole N^4-CH_2), 5.44 (s, 2H, triazole N^4-CH_2), 4.46–4.35 (m, 6H, S-triazole N^1-CH_2, triazole N^1-$CH_2(CH_2)_2CH_2$), 1.91–1.94 (m, 4H, triazole N^1-CH_2(CH_2)$_2$) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ: 161.5 (S=*C*), 155.7 (triazole 3-*C*), 146.6 (S-triazole 5-*C*), 144.7 (triazole 5-*C*), 138.9, 138.7 (3,4-Cl_2Ph 1-*C*), 133.7, 133.5, 132.9 (3,4-Cl_2Ph 3-*C*), 132.4, 132.1 (3,4-Cl_2Ph 4-*C*), 131.5, 131.3 (3,4-Cl_2Ph 2-*C*), 130.7, 130.5 (3,4-Cl_2Ph 5-*C*), 128.3, 128.0 (3,4-Cl_2Ph 6-*C*), 54.7, 51.5, 45.8, 45.1, 32.4, 26.3, 25.9

(CH_2) ppm; ESI-MS (*m/z*): 702 $[M-2Cl]^+$; HRMS (ESI) calcd. for $C_{29}H_{26}Cl_8N_6S$ $[M-2Cl+H]^+$, 701.0149; found, 701.0156.

*1-((2-(3,4-Dichlorobenzyl)-4-(2,4-difluorobenzyl)-5-thioxo-2,5-dihydro-1H-1,2,4-triazol-4-ium-1-yl)methyl)-4-(2,4-difluorobenzyl)-1H-1,2,4-triazol-4-ium bromide (**10b**)*

Compound **10b** was prepared employing a procedure similar to that used to synthesize compound **9a**, starting from thione **8b** (0.38 g, 1.0 mmol) and 2,4-difluorobenzyl bromide (0.49 g, 2.4 mmol). The pure product **10b** (0.57 g) was obtained as a white solid. Yield: 75.1%; mp 166−168 ºC; IR (KBr) ν: 3120, 3089 (Ar–H), 2997, 2931 (CH_2), 1612, 1559, 1506, (aromatic frame), 1278 (C=S), 1142, 1093, 970, 857, 814, 641 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 10.35 (s, 2H, triazole 3-*H,* S-triazole *H*), 9.37 (s, 1H, triazole 5-*H*), 7.74−7.63 (m, 2H, 3,4-Cl_2Ph 2,5-*H*), 7.54−7.48 (m, 2H, 2,4-F_2Ph 6-*H*), 7.43−7.35 (m, 1H, 3,4-Cl_2Ph 6-*H*), 7.24−7.05 (m, 4H, 2,4-F_2Ph 3,5-*H*), 5.61 (s, 2H, S-triazole N^4-CH_2), 5.43 (s, 2H, triazole N^4-CH_2), 4.48−4.45 (m, 6H, S-triazole N^1-CH_2, S-triazole N^2-CH_2(CH_2)CH_2), 1.91−1.88 (m, 4H, triazole-CH_2(CH_2)$_2$) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ: 164.2 (2,4-F_2Ph 2-*C*), 162.7, 160.8 (2,4-F_2Ph 4-*C*), 159.9 (S=*C*), 156.2 (triazole 3-*C*), 149.4 (S-triazole 5-*C*), 143.3 (triazole 5-*C*), 139.1 (3,4-Cl_2Ph 1-*C*), 133.6 (3,4-Cl_2Ph 3-*C*), 133.5 (3,4-Cl_2Ph 4-*C*), 133.3 (3,4-Cl_2Ph 2-*C*), 130.3 (3,4-Cl_2Ph 5-*C*), 127.5 (3,4-Cl_2Ph 6-*C*), 130.3, 130.0 (2,4-F_2Ph 6-*C*), 119.8, 119.6 (2,4-F_2Ph 1-*C*), 117.6, 117.4 (2,4-F_2Ph 5-*C*), 104.9, 104.7, 104.3 (2,4-F_2Ph 3-*C*), 51.7, 51.3, 44.8, 44.6, 30.7, 25.1, 25.0 (CH_2) ppm; ESI-MS (*m/z*): 637 $[M-2Br]^+$; HRMS (ESI) calcd. for $C_{29}H_{26}Br_2Cl_2F_4N_6S$ $[M-2Br+H]^+$, 637.1320; found, 637.1327.

*1-(4-(2-(3,4-Dichlorobenzyl)-4-(6-(4-methyl-2-oxo-2H-chromen-7-yloxy)hexyl)-5-thioxo-2,5-dihydro-1H-1,2,4-triazol-4-ium-1-yl)butyl)-4-(6-(4-methyl-2-oxo-2H-chromen-7-yloxy)hexyl)-1H-1,2,4- triazol-4-ium bromide (**11**)*

Compound **11** was prepared employing a procedure similar to that used to synthesize compound **9a** starting from thione **8b** (0.38 g, 1.0 mmol) and 7-(6-bromohexyloxy)-4-methyl-2*H*-chromen-2-one (0.81 g, 2.4 mmol). The pure product **11** (0.71 g) was obtained as a yellow syrup. Yield: 65.3%; IR (KBr) ν: 3127, 3067 (Ar–H), 2939, 2896 (CH_2), 1613, 1504, 1442 (aromatic frame), 1288 (C=S), 1203, 1146, 1072, 1021, 864, 638 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 10.28 (s, 1H, S-triazole *H*), 10.20 (s, 1H, triazole 3-*H*), 9.29 (s, 1H, triazole 5-*H*), 7.86−7.44 (m, 5H, 3,4-Cl_2Ph 2,5,6-*H*, coumarin 5-*H*), 6.92−6.96 (m, 4H, coumarin 6,8-*H*), 6.19 (s, 2H, coumarin 3-*H*), 5.55 (s, 2H, S-triazole N^4-CH_2), 5.41 (s, 2H, triazole N^4-CH_2), 4.51−4.46 (t, 2H, *J* = 7.5 Hz, S-triazole N^2-CH_2), 4.40 (s, 2H, S-triazole N^1-CH_2), 4.29−4.25 (t, 2H, *J* = 6.0 Hz, triazole N^1-CH_2), 4.09−4.03 (m, 4H, coumarin O-CH_2), 2.38 (s, 6H, coumarin-CH_3), 1.93−1.74 (m, 12H, coumarin O-CH_2CH_2(CH_2)$_2$-CH_2, triazole N^1-CH_2CH_2CH_2), 1.40−1.28 (m, 8H, coumarin O-(CH_2)$_2$CH_2CH_2) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ: 162.1 (2C, coumarin 2-*C*), 160.6 (2C, coumarin 7-*C*), 159.6 (S=*C*), 155.2 (2C, coumarin 9-*C*), 155.1 (triazole 3-*C*), 153.8 (2C, coumarin 4-*C*), 145.1 (S-triazole 5-*C*), 143.1 (triazole 5-*C*), 137.9 (3,4-Cl_2Ph 1-*C*), 132.0 (3,4-Cl_2Ph 3-*C*), 131.6 (3,4-Cl_2Ph 4-*C*), 130.9 (3,4-Cl_2Ph 2-*C*), 130.1 (3,4-Cl_2Ph 5-*C*), 129.6 (3,4-Cl_2Ph 6-*C*), 126.8 (2C, coumarin 5-*C*), 113.4 (2C, coumarin 3-*C*), 112.8 (2C, coumarin 10-*C*), 111.4 (2C, coumarin 6-*C*), 101.4 (2C, coumarin 8-*C*), 68.5, 61.0, 51.5, 51.2, 35.6, 33.1, 32.8, 32.6, 29.1, 28.7, 28.6, 28.3, 27.9, 27.7, 25.6, 25.2, 25.0 (CH_2), 18.6 (2C, CH_3) ppm; ESI-MS (*m/z*): 901 $[M-2Br]^+$; HRMS (ESI) calcd. for $C_{47}H_{54}Br_2Cl_2N_6O_6S$ $[M-2Br+H]^+$, 901.3281; found, 901.3290.

2.3 Biological assays

All the new 1,2,4-triazole derivatives **2–11** were evaluated for antimicrobial activities against MRSA (N315), *S. aureus* (ATCC25923), *B. subtilis* and *M. luteus* (ATCC4698) as Gram-positive bacteria, *E. coli* (DH52), *S. dysenteriae*, *P. aeruginosa* and *E. typhosa* as Gram-negative bacteria, as well as *C. albicans* (ATCC76615) and *C. mycoderma* as fungi according to the NCCLS [51, 52]. The tested microbial strains were provided by the School of Pharmaceutical Sciences, Southwest University and the College of Pharmacy, Third Military Medical University. Minimal inhibitory concentration (MIC, μg/mL) is defined as the lowest concentration of the tested compounds required to completely inhibit the growth of microbial strains, and determined by means of the standard two-fold serial dilution method in 96-well microtest plates taking Chloromycin, Norfloxacin and Fluconazole as reference drugs. To ensure that the solvent had no effect on bacterial growth, a control experiment was performed by testing the medium supplemented with DMSO at the same concentration used in the experiment. All the bacteria and fungi growth was monitored visually and spectrophotometrically. The antimicrobial active data are summarized in Table 3.

Antibacterial assays

The prepared compounds **2−11** were evaluated on their antibacterial activities against MRSA (N315), *S. aureus* (ATCC25923), *B. subtilis* and *M. luteus* (ATCC4698) as Gram-positive bacteria, *E. coli* (DH52), *S. dysenteriae*, *P. aeruginosa* and *E. typhosa* as Gram-negative bacteria. The bacterial suspension was adjusted with sterile saline to a concentration of 1×10^5 CFU. The tested compounds were dissolved in DMSO to prepare the stock solutions. The tested compounds and reference drugs were prepared in Mueller–Hinton broth (Guangdong Huaikai Microbial Sci.& Tech. Co., Ltd., Guangzhou, Guangdong, China) by

two-fold serial dilution to obtain the required concentrations of 512, 256, 128, 64, 32, 16, 8, 4, 2, 1, 0.5 μg/mL. These dilutions were inoculated and incubated at 37 ºC for 24 h.

Antifungal assays

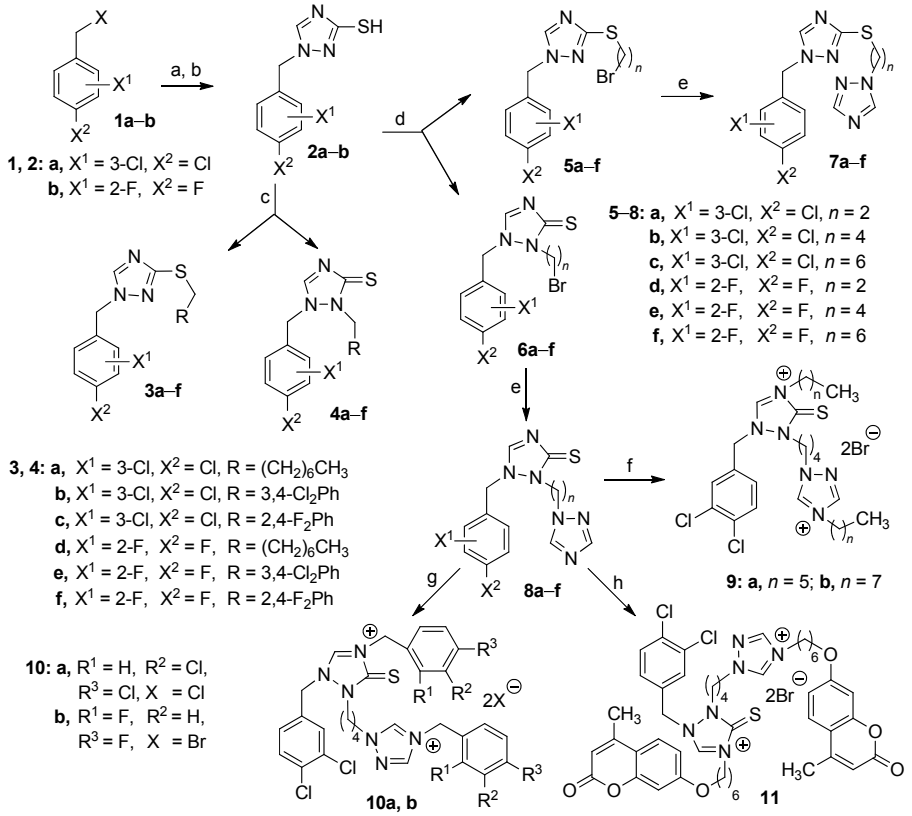
Compounds **2–11** were evaluated for their antifungal activities against *C. albicans* (ATCC76615) and *C. mycoderma*. A spore suspension in sterile distilled water was prepared from 1-day old culture of the fungi growing on Sabouraud agar (SA) media. The final spore concentration was 1–5 × 10^3 spore mL^{-1}. Using the stock solutions of the tested compounds and reference antifungal Fluconazole, dilutions in sterile RPMI 1640 medium (Neuronbc Laboraton Technology Co., Ltd, Beijing, China) were generated in eleven desired concentrations (0.5 to 512 μg/mL) for each tested compound. These dilutions were inoculated and incubated at 35 ºC for 24 h.

3 Results and discussion

3.1 Synthesis of triazole-thioethers and thiones

The synthetic route of the target thio-triazole compounds was outlined in Scheme 1. The 1-halobenzyl-1*H*-1,2,4-triazole-3-thiol **2** was prepared via a newly developed multi-component procedure without isolation of intermediates. This method provided an efficient procedure for the synthesis of triazole-thiols with easy and convenient operation, short reaction time and high yield etc. A possible mechanism is shown in Scheme 2. It could involve the generation of halobenzyl hydrazinecarbothioamide **A** which was generated by the substitution of halobenzyl halide **1** with thiosemicarbazide, and then further nucleophilic reaction of intermediate **A** with formic acid could afford the intermediate **B**. Subsequent cyclization of compound **A** under acid conditions could produce the desired triazole-thiol **2** whose structure was confirmed by spectral analysis.

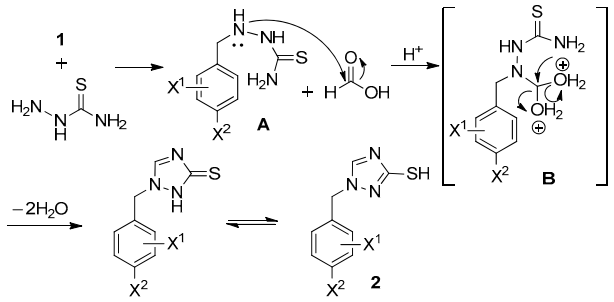
The experimental results manifested that the solvent and base significantly affected the formation of the products **2a** and **b** (Table 1). It was noticed that ethanol led to relatively high yields in contrast to acetonitrile because of the better solubility of thiosemicarbazide in ethanol. On the other hand, the presence of base resulted in lower yields of target compounds owing to the formation of by-products. Consequently, thiosemicarbazide and halobenzyl halides could react to produce compounds **2a** and **b** in satisfactory yields (72.9% and 82.3% respectively) when dissolved in ethanol in the absence of base.



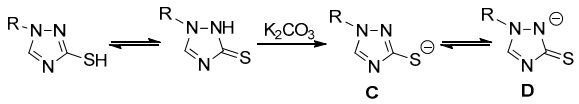
Scheme 1 Synthetic route of triazole-thiols and their derivatives. Conditions and reagents: (a) $NH_2NHCSNH_2$, CH_3CH_2OH, 40 °C; (b) HCOOH, H_2SO_4, H_2O, 100 °C; (c) alkyl or aryl halide, K_2CO_3, TBAI, CH_3COCH_3, 40 °C; (d) alkyl dibromide, K_2CO_3, TBAI, CH_3COCH_3, 40 °C; (e) 1,2,4-triazole, K_2CO_3, TBAI, CH_3CN, 40 °C; (f) alkyl bromide, CH_3CN, reflux; (g) aryl halide, CH_3CN, reflux; (h) 7-(6-bromohexyloxy)-4-methyl-2*H*-chromen-2-one, CH_3CN, reflux.

Table 1 The effects of solvent and base on yields of triazole-thiols **2a–b**

Solvent	EtOH			CH_3CN		
Base	NaOH	K_2CO_3	Absence	NaOH	K_2CO_3	Absence
Yield (%) **2a**	10.5	34.9	82.3	9.3	21.3	57.2
Yield (%) **2b**	12.7	40.1	72.9	10.8	18.5	63.4



Scheme 2 Possible mechanism for the synthesis of triazole-thiol **2**.



Scheme 3 Tautomerism of triazole-thiols in the presence of potassium carbonate.

Triazole-thioethers **3a–f** were prepared via the alkylation reaction of compounds **2a** and **b** with a series of halides in acetone using potassium carbonate as base and tetrabutylammonium iodide as phase-transfer catalyst, while triazole-thiones **4a–f** were synthesized employing a procedure similar to that used to synthesize compounds **3a–f**. This phenomenon was probably due to the existence of tautomeric forms **C** and **D** of triazole-thiols in the presence of potassium carbonate (Scheme 3). The experiments revealed that triazole-thione, the thermodynamic product [53], was obtained as the major product at higher temperature (80 ºC) via intermediate **D** and the thiol was generally converted into thioether at room temperature. The reaction took place at 40 ºC to give thioether **3** and thione **4** respectively in the yields of 20.0%–49.7%. The bromides **5** and **6** were simultaneously produced according to the general procedure described for the preparation of compounds **3** and **4** in the yields of 23.7%–46.5%, and their further reactions with 1,2,4-triazole in the presence of potassium carbonate and tetrabutylammonium iodide produced the bis-triazoles **7a–f** and **8a–f** in good yields (66.8%–91.7%).

3.2 Synthesis of triazoliums

The desired triazolium derivatives **9–11** were synthesized through the reactions of thione **8b** with excessive alkyl halides and aryl halides in acetonitrile under reflux. All the triazoliums were synthesized in satisfactory yields ranging from 65.2% to 75.1% after purification by washing with petroleum ether or dichloromethane. Notably, the formation of halobenzyl triazolium **10** (12 h) was faster than the alkyl triazolium **9** (24 h), while the preparation of the coumarin derived triazolium **11** required a longer reaction time (> 48 h), probably due to the steric hindrance of the coumarin moiety.

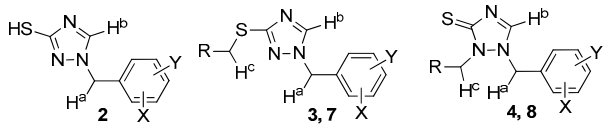
3.3 Spectral analysis

All the new compounds were characterized by ^{1}H NMR, ^{13}C NMR, FTIR, MS and HRMS spectra. The spectral data were in accordance with the assigned structures and were provided in the experimental protocol section. The mass spectra of all the target compounds were in agreement with their molecular formulas.

In the FTIR spectra of compounds **2a–b**, characteristic stretching frequencies of the thiol moiety at 2709–2668 cm^{-1} demonstrated the structure of the triazole-thiols, while their absence in compounds **3–11** suggested that the thiol group of triazole-thiols reacted with halides. Moreover, triazole-thione compounds **4a–f**, **6a–f** and **8a–f** gave strong absorption peaks at 1288–1259 cm^{-1} due to the stretching vibration of C=S in the triazole-thione moiety, while the bending vibration of *C–S–C* in thioethers **3a–f**, **5a–f** and **7a–f** gave absorption peaks at the region of 739–710 cm^{-1}. In addition, the moderate absorption bands at 3123–3055 cm^{-1} and 2998–2775 cm^{-1} were attributed to the stretching vibration of aromatic and aliphatic C–H, respectively, while the aromatic frame exhibited characteristic stretching frequencies in the region between 1616 and 1430 cm^{-1}. All the other absorption bands were also observed at expected regions.

As for ^{1}H NMR spectra, compounds **2–4**, **7** and **8** gave singlets at 4.42–4.24 ppm assigned to the methylene proton H^a (Table 2). Triazole-thiones **4** and **8** (4.32–4.21 ppm) displayed relatively upfield shifts for H^a when compared with triazole-thiol **2** and thioethers **3** and **7** (4.40–4.24 ppm) because of destruction of the conjugated system by the formation of triazole-thione, which resulted in the decreased electron-withdrawing ability of the triazole moiety. Furthermore, substitution of triazole-thiol **2** (8.16–8.15 ppm) to yield compounds **3**, **4**, **7** and **8** led to upfield shifts of H^b to 8.05–7.66 ppm. Moreover, in contrast to the thioethers **3** and **7**, the corresponding triazole-thiones **4** and **8** gave relatively downfield chemical shifts for H^b due to the electron-withdrawing character of C=S in the triazole-thione structure, except for compounds **7a**, **7d**, **8a** and **8d** (Figure 1). This phenomenon was probably ascribed to the remote interaction of the triazole ring with the triazole-thione moiety with a short $(CH_2)_2$ linker and thus caused a decrease of H^b in thiones **8a** and **8d**. Notably, proton H^b of halobenzyl derivatives **3b–c**, **3e–f**, **4b–c** and **4e–f** with the electron-withdrawing halobenzyl groups on the triazole ring gave higher chemical shifts than the corresponding alkyl-

Table 2 Some ^{1}H NMR data (δ/ppm) of compounds **2–4** and **7, 8**



Compds	H^a	H^b	H^c	Compds	H^a	H^b	H^c
2a	4.30	8.15	–	**2b**	4.37	8.16	–
3a	4.36	7.89	3.97	**4a**	4.26	7.96	4.07
3b	4.36	7.93	5.13	**4b**	4.25	8.04	5.21
3c	4.36	7.94	5.18	**4c**	4.24	8.04	5.25
3d	4.41	7.88	3.95	**4d**	4.32	7.98	4.06
3e	4.41	7.94	5.12	**4e**	4.32	8.05	5.22
3f	4.42	7.92	5.19	**4f**	4.30	8.05	5.27
7a	4.24	7.90	4.43	**8a**	4.24	7.66	4.59
7b	4.35	7.88	3.95	**8b**	4.24	7.96	4.08
7c	4.33	7.85	3.95	**8c**	4.21	7.96	4.05
7d	4.31	7.93	4.42	**8d**	4.31	7.82	4.60
7e	4.40	7.89	3.96	**8e**	4.31	7.98	4.18
7f	4.37	7.87	3.97	**8f**	4.32	7.97	4.16

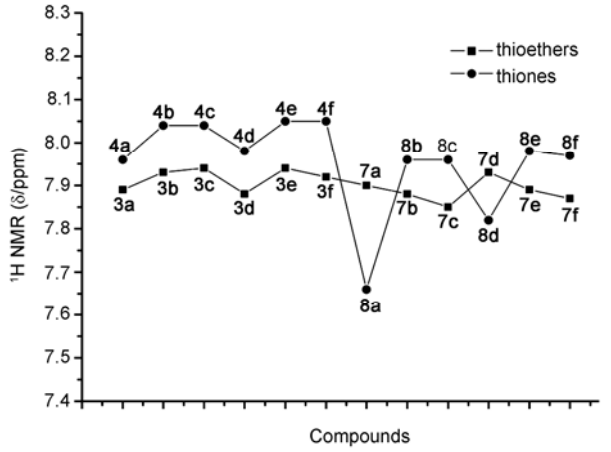


Figure 1 ^{1}H NMR shifts for H^b of thioethers **3** and **7** and thiones **4** and **8**.

compounds **3a**, **3d**, **4a** and **4d**. In addition, triazole-thioethers **3** and **7** displayed upfield shifts (5.19–3.97 ppm) for proton H^c when compared with the corresponding thiones **4** and **8** (5.27–4.05 ppm), which was probably related to the strong electron-donating ability of the thioether group.

Triazoliums **9–11** showed large downfield shifts for proton H^b in comparison with triazole-thione **8b**, due to the positive charge on the triazole-thione ring. Meanwhile, the formation of the second triazolium on the 1,2,4-triazole moiety also endowed protons H^d and H^e with larger δ values than compound **8b** (Figure 2). These evidences proved the structure of bis-triazolium, and the positive charges on nitrogen atoms resulted in obvious downfield shifts.

The ^{13}C NMR spectra of all the compounds were in accordance with the assigned structures. The conversions of triazole-thiols **2a** and **b** into thiones **4**, **6** and **8** resulted in

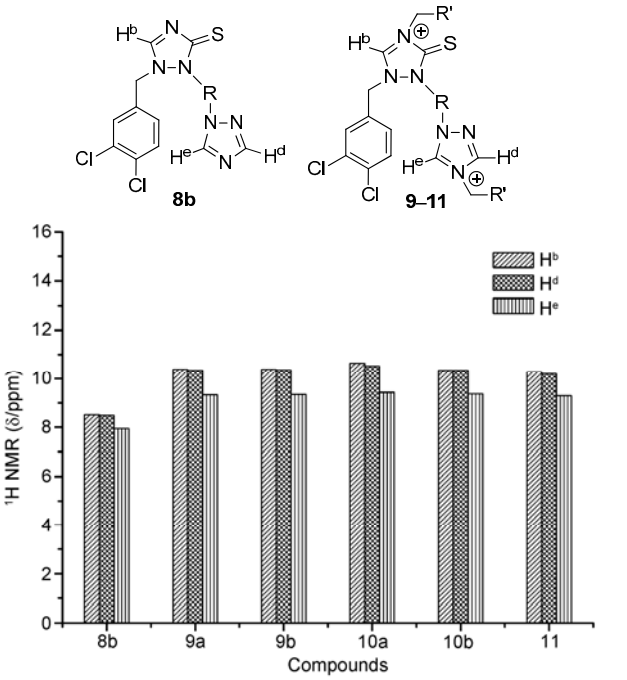


Figure 2 Some ^{1}H NMR data (δ/ppm) of compound **8b** and its triazoliums **9–11**.

downfield ^{13}C chemical shifts for C=S carbons of the S-triazole rings in contrast to the carbons (C–S) of the corresponding thioethers **3**, **5** and **7**. It was noticed that the 3-position carbons in the triazole and S-triazole rings gave larger δ values than the 5-position carbons for compounds **3–8**. In comparison with triazole thioethers **3**, **5** and **7** (153.7–151.6 ppm), the thiones **4**, **6** and **8** displayed relatively large ^{13}C signals at 160.1–155.6 ppm for the 3-position carbon of the S-triazole rings, which were ascribed to the electron-withdrawing characteristics of the thione moieties. However, all the carbons in the halobenzyl moieties linking with the N^1-position of S-triazoles exhibited no significant changes of chemical shifts for the thioethers and thiones. Moreover, the transformation of bis-triazole **8b** into its triazoliums **9–11** resulted in downfield ^{13}C shifts with 0.2–4.9 ppm for the carbons of triazole rings due to the formation of positive charges on both triazole and S-triazole groups, while all the other carbons gave ^{13}C peaks in the expected regions.

3.4 Antibacterial activity

The antibacterial activity results indicated that all the halobenzyl triazole-thiols as well as their derivatives could inhibit the growth of the tested bacteria *in vitro* to some extent. Particularly, bis-triazole thiones **8a–c** and the triazoliums **9–11** showed broader antimicrobial spectrum and potent antibacterial activities in comparison with other compounds. Furthermore, the results also showed that incorporation of the second triazolyl group, which formed compounds **7** and

8, gave superior antibacterial efficiency to those of the intermediates including triazole-thiol **2** and bromides **5** and **6**. However, most compounds exerted negative efficacy toward MRSA and *S. dysenteriae*.

Halobenzyl triazole-thiols **2a** and **b**, as shown in Table 3, exhibited poor activities against all the tested bacterial strains (MIC = 128–512 μg/mL). No significantly improved efficiency was obtained for thioethers **3a–f** and **5a–f** by introducing alkyl or aryl groups. Interestingly, introduction of the thione moiety to compounds **4a–f** and **6a–f** resulted in increased antibacterial potency to most tested strains in comparison with compounds **2a** and **b** and the corresponding thioethers **3** and **5**. Particularly, 3,4-dichlorobenzyl triazole-thiones **4b–c** with halobenzyl substituents exhibited moderate to good bioactivities (MIC = 32–128 μg/mL) in inhibiting the growth of all the tested bacteria, while triazole-thiones **6a–f** showed moderate activities against MRSA, *S. aureus, P. aeruginosa* and *E. typhosa* at the concentration below 128 μg/mL. The results manifested that thiones were more sensitive to bacteria than the corresponding thioethers, and introduction of different substituents specially the halobenzyl moieties could attribute to improved biological activities to some extent.

For the tested bis-triazole thioethers **7a–f**, all the compounds displayed good inhibitory efficiency toward bacterial strains when compared with their corresponding bromides **5a–f**. Notably, in contrast to 2,4-diflorobenzyl triazole-thioethers **7d–f**, the 3,4-dichlorobenzyl ones **7a–c** gave relatively lower MIC values to most tested strains especially *P. aeruginosa* (MIC = 16–64 μg/mL). Moreover, triazolylethyl 3,4-dichlorobenzyltriazole-thioether **7a** was sensitive to *E. typhosa* (MIC = 16 μg/mL) and *P. aeruginosa* (MIC = 16 μg/mL), which was comparable to the reference drug Chloromycin, while both compounds **7a** and **7f** could inhibit the growth of *S. aureus* at the moderate concentration of 32 μg/mL. Compared to mono-triazoles **6a–f** and bis-triazole thioethers **7a–f**, the bis-triazole thiones **8a–f** remarkably improved antibacterial properties. Additionally, the 3,4-dichlorobenzyl triazole-thiones **8a–c** displayed wide and good antibacterial activities particularly against *M. luteus* and *E. coli* at the concentrations ranging from 1 to 32 μg/mL, more effective than the 2,4-diflorobenzyl derivatives **8d–f**. It is worth noting that compound **8b** with the $(CH_2)_4$ linkage exhibited the best bioactivities among all the thiones to the bacteria (MIC = 1–64 μg/mL), particularly toward *M. luteus* with the MIC value of 1 μg/mL, which was equivalent to the reference drug Norfloxacin and 8-fold more active than Chloromycin. These results suggested that introduction of the second triazolyl moiety to the S-triazole compounds resulted in better antibacterial activities and broader spectrum. Furthermore, introduction of alkyl linkages with different lengths into triazolylalkyl triazole-thiones exhibited obvious effects on antibacterial activities.

Triazoliums **9–11** with various substituents including alkyl and aryl groups were designed and prepared to investigate the effect of the triazolium moiety on antimicrobial activities. The bioactive results manifested that all the triazoliums exhibited significantly enhanced antibacterial activities to all the tested strains (MIC = 1–128 μg/mL) than their precursor **8b**, particularly for *S. aureus*, *M. luteus* and *E. coli* with low inhibitory concentrations in the range of 1–16 μg/mL. It seemed that introduction of electropositive triazolium should be helpful in improving antibacterial efficacy. Moreover, alkyl triazolium **9** was more sensitive to the tested strains than other triazoliums **10–11** especially toward *S. aureus*, *B. subtilis*, *E. coli*, *P. aeruginosa* and *E. typhosa* with MIC values below 8 μg/mL, which was comparable to the reference drugs Chloromycin and Norfloxacin. Notably, the hexyl triazolium **9a** displayed comparable activities against all the tested strains to the reference drugs except for MRSA, particularly toward *E. coli* (MIC = 1 μg/mL), which was 2- and 4-fold more potent than Chloromycin and Norfloxacin, respectively. Furthermore, it showed more significant inhibition against *P. aeruginosa* than Chloromycin (MIC = 16 μg/mL) at the concentration of 4 μg/mL, while it was also highly active to *S. aureus* at the low concentration of 2 μg/mL. Moreover, the octyl triazolium **9b** gave lower anti-*P. aeruginosa* concentration (MIC = 8 μg/mL) than Chloromycin (MIC = 16 μg/mL). It was especially noteworthy that the 2,4-diflorobenzyl derived triazolium **10b** exhibited equipotent inhibitory activity to Norfloxacin (MIC = 4 μg/mL) against *E. coli*. Unexpectedly, incorporation of coumarin to yield the coumarin derived triazolium **11**, which was reported to be of great potential in antimicrobial abilities, did not lead to remarkable improvements of antibacterial efficacy in comparison with its corresponding precursor **8b**. These facts revealed that the alkyl triazoliums were specifically favorable for antibacterial efficacy.

Triazoliums, as quaternary ammonium salts with promising surface activities, have been proved to be favorable for external uses. Thereby, triazoliums **9a** and **b** with potent antibacterial efficiencies might be of much potential to be investigated as external antimicrobial agents.

Overall, the triazole-thione **8b** and triazoliums **9–11** showed the most potent activities among all the tested thio-triazole derivatives against most tested bacteria. Moreover, triazole-thione compounds were more favorable for antibacterial activities than triazole-thioethers as well as their precursory triazole-thiols. Meanwhile, the above discussion indicated that halobenzyl groups especially the 3,4-dichorobenzyl moiety exerted great effects on antibacterial activities of the target compounds. Additionally, the length of the alkyl chain also affected the bioactivities and the $(CH_2)_4$ spacer was found to be the most suitable substituent in this work to enhance antibacterial potency of triazole-thiol derivatives. Finally, incorporation of triazolium especially the alkyl-substituted ones significantly profited the antibacterial efficiency in contrast to their precursors.

Table 3 Antibacterial and antifungal activities for compounds **2–11** expressed as MIC (μg/mL) [a,b,c)]

Compds	Gram-positive bacteria				Gram-negative bacteria				Fungi	
	MRSA	*S. aureus*	*B. subtilis*	*M. luteus*	*E. coli*	*S. dysenteriae*	*P. aeruginosa*	*E. typhosa*	*C. albicans*	*C. mycoderma*
2a	128	512	128	128	128	256	128	128	256	128
2b	128	512	512	128	256	128	512	256	512	128
3a	>512	256	>512	>512	512	512	>512	512	>512	256
3b	>512	256	256	512	256	256	>512	256	>512	512
3c	512	256	256	256	128	128	512	256	256	512
3d	>512	256	512	>512	512	512	>512	512	256	256
3e	>512	128	256	512	512	256	>512	512	>512	512
3f	256	128	256	256	512	512	>512	512	256	256
4a	128	128	64	256	256	128	256	256	256	128
4b	128	64	32	64	128	64	128	128	64	128
4c	128	32	32	64	64	128	32	32	64	32
4d	512	128	256	256	256	256	512	512	512	256
4e	256	64	512	128	128	256	128	64	128	128
4f	128	128	128	64	64	128	256	128	128	256
5a	256	128	>512	64	128	512	256	512	64	256
5b	256	256	256	128	128	64	32	64	128	128
5c	512	512	512	256	128	256	256	256	512	256
5d	512	128	128	128	128	512	512	64	256	512
5e	512	512	512	256	128	256	512	512	256	256
5f	>512	>512	512	>512	>512	>512	>512	>512	>512	512
6a	128	64	256	128	128	128	128	128	64	64
6b	64	64	64	64	128	64	32	64	64	128
6c	128	64	256	128	512	64	64	64	64	64
6d	128	64	256	64	128	256	32	128	64	128
6e	128	128	128	128	128	64	64	64	128	64
6f	128	128	256	256	256	128	128	128	128	256
7a	128	32	256	256	128	512	16	16	128	4
7b	256	128	256	128	128	128	32	256	64	128
7c	128	128	128	64	128	64	64	64	2	128
7d	256	256	256	256	64	128	32	512	128	128
7e	256	256	256	128	128	256	128	512	256	256
7f	512	32	512	256	128	512	128	512	512	512
8a	64	64	64	32	32	128	64	64	16	64
8b	64	64	32	1	32	16	32	32	32	16
8c	64	64	64	16	32	64	32	64	32	128
8d	128	128	64	64	64	128	128	64	128	64
8e	128	128	64	64	128	128	128	128	64	64
8f	64	128	64	64	64	128	128	64	128	64
9a	32	2	8	16	1	16	4	8	2	16
9b	32	8	8	16	8	32	8	8	8	32
10a	64	8	64	8	16	128	32	64	8	32
10b	16	8	32	16	4	64	32	16	8	64
11	32	16	16	16	8	128	128	32	16	128
A	4	1	4	8	2	4	16	8	–	–
B	4	0.5	2	1	4	1	1	4	–	–
C	–	–	–	–	–	–	–	–	0.5	4

a) Minimal inhibitory concentrations were determined by micro broth dilution method for microdilution plates. b) **A** = chloromycin, **B** = norfloxacin, **C** = fluconazole. c) MRSA, Methicillin-Resistant *Staphylococcus aureus* (N315); *S. aureus*, *Staphylococcus aureus* (ATCC25923); *B. subtilis*, *Bacillus subtilis*; *M. luteus*, *Micrococcus luteus* (ATCC4698); *E. coli*, *Escherichia coli* (DH52); *S. dysenteriae*, *Shigella dysenteriae*; *P. aeruginosa*, *Pseudomonas aeruginosa*; *E. typhosa*, *Eberthella typhosa*; *C. albicans*, *Candida albicans* (ATCC76615); *C. mycoderma*, *Candida mycoderma*.

The thiones and triazoliums were promising compounds and worthy further investigation as potential antibacterial drugs.

3.5 Antifungal activity

The antifungal evaluation revealed that some synthesized triazole-thioether and triazole-thione derivatives displayed good activities against the tested fungi *C. albicans* and *C. mycoderma* to some extent. Similar to the antibacterial results, triazole-thiones **4a–c**, **6a–c** and **8a–c** bearing the 3,4-dichlorobenzyl moiety manifested better antifungal potential than 2,4-difluorobenzyl-substituted triazole-thiones **4d–f**, **6d–f** and **8d–f** and triazole-thioether compounds **3a–f**, **5a–f** and **7a–f**. Especially, the bis-triazole thiones **8a–c** and triazoliums **9–11** gave moderate antifungal abilities with MIC values below 32 μg/mL to the tested *C. albicans*. Noticeably, both 3,4-dichorobenzyl triazole-thioether **7c** and hexyl triazolium **9a** could effectively inhibit the growth of *C. albicans* at the concentration of 2 μg/mL. Furthermore, bis-triazole thioether **7a** gave satisfactory anti-*C. mycoderma* activity at the concentration of 4 μg/mL which was equivalent to the clinical drug Fluconazole. Moreover, it was noteworthy that all the triazoliums displayed remarkable bioactivities toward *C. albicans* with MIC values ranging from 2 to 16 μg/mL, making them potent for further investigation as potential antifungal agents.

4 Conclusions

In summary, a series of new triazole-thiols, thioethers and thiones as well as some corresponding triazolium derivatives have been successfully synthesized through convenient and efficient procedures in appreciable yields. All the new compounds were characterized by ^{1}H NMR, ^{13}C NMR, FTIR, MS and HRMS spectra. The *in vitro* antimicrobial tests revealed that most synthesized compounds showed moderate to good bioactivities against the selected pathogenic strains. The 3,4-dichlorobenzyl triazole-thiones exhibited superior antibacterial and antifungal efficacy to other thioether and thione compounds. Especially, compound **8b** with the $(CH_2)_4$ spacer gave 8-fold lower inhibitory concentration to *M. luteus* than Chloromycin with the MIC value of 1 μg/mL, which was equivalent to Norfloxacin. Moreover, triazoliums, especially the alkyl substituted ones, displayed the best antimicrobial activities among all the tested compounds against all the bacteria. Particularly, the hexyl triazolium **9a** showed comparable bioactivities against *S. aureus* (MIC = 2 μg/mL), *E. coli* (MIC = 1 μg/mL) and *P. aeruginosa* (MIC = 4 μg/mL) to the reference drugs Chloromycin and Norfloxacin. Equally important, the octyl triazolium **9b** exhibited equivalent or even better inhibitory potency toward *E. typhosa* and *P. aeruginosa* than the reference drug Chloromycin at the concentration of 8 μg/mL. In addition, the triazoliums were also sensitive to fungi, particularly to *C. albicans*. They could be of great potential as external antimicrobial agents for their satisfactory antibacterial and antifungal properties. These antimicrobial results demonstrated that some structural factors such as the alkyl and aryl substituents as well as alkyl spacers could significantly affect their antimicrobial competence. Furthermore, the prepared triazole-thiones were more suitable for bioactivities than thioethers. Especially, introduction of the triazolium moiety would lead to significant improvement of antimicrobial activities.

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