Synthesis and Evaluation of Antimicrobial Activity of Some New Hetaryl-Azoles Derivatives Obtained from 2-Aryl-4-methylthiazol-5-carbohydrazides and Isonicotinic Acid Hydrazide

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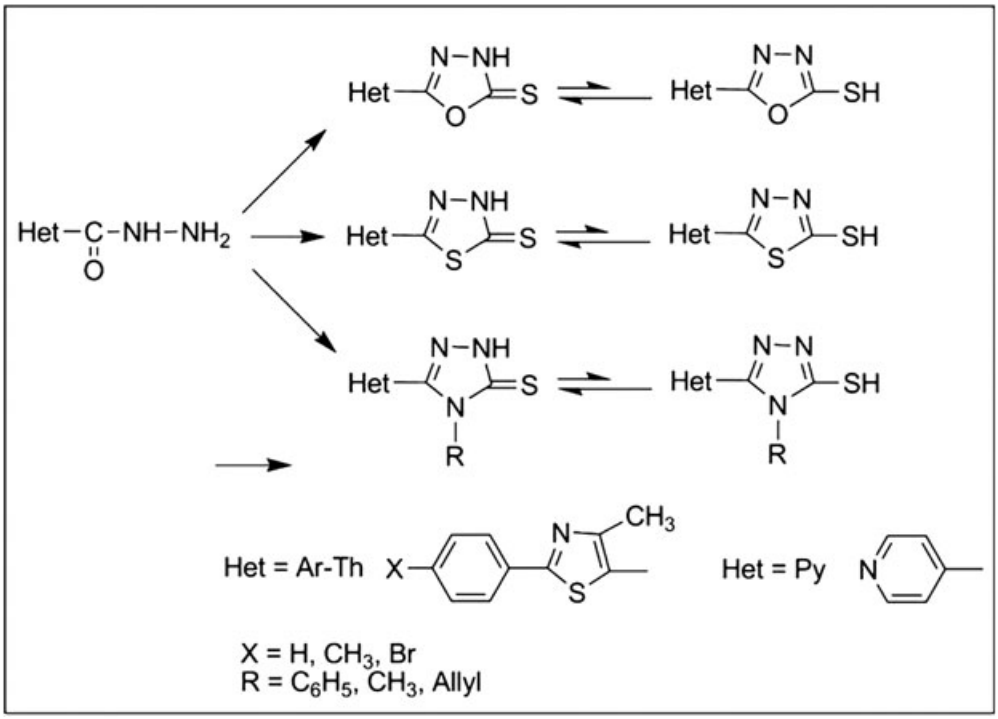

A series of new 1,3,4-oxadiazole/thiadiazole and 1,2,4-triazole derivatives have been synthesized starting from 2-aryl-4-methylthiazol-5-carbohydrazides and isonicotinic acid hydrazide. All the newly synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry. The synthesized compounds were screened for their antibacterial and antifungal activity, assessed as growth inhibition diameter. Some of them showed good antibacterial activity against gram positive *Staphylococcus aureus*, while the antibacterial activity against *Listeria monocytogenes*, *Escherichia coli*, and *Salmonella typhymurium* and antifungal activity against *Candida albicans* was modest. None of the tested compounds showed inhibitory activity against gram positive bacteria *Enterococcus faecalis* and *Bacillus cereus* and against gram negative bacteria *Pseudomonas aeruginosa*.

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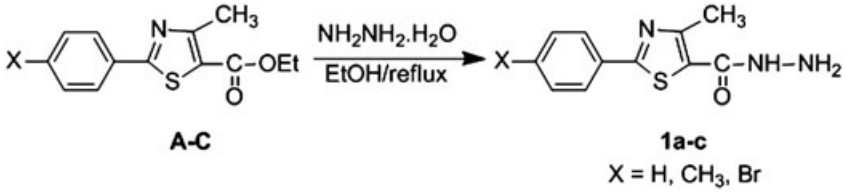
INTRODUCTION

The problem of multidrug resistant microorganisms has reached an alarming level around the world in the past decades, and represents a challenge for the development of new antimicrobial agents, with novel mechanisms and a broadened spectrum of activity. In the past years, some azole derivatives were developed as new antimicrobial agents, for instance, Linezolid and Eperezolid are currently used for the treatment of multidrug-resistant gram positive

Scheme 1



A-C **1a-c**

X = H, CH_3, Br

infections [1–3]. There is some important antifungal drugs containing thiazole or 1,2,4-triazole ring in their structures, such as Ravuconazole, Fluconazole, Voriconazole, and Itraconazole, [4]. Also, thiazole derivatives are found to be associated with various biological activities such as antibacterial [5], antifungal [6], antiinflammatory [7], antihypertensive [8], anti-HIV [9], antitumor [10–13], antifilarial [12, 13], anticonvulsant [14], herbicidal, insecticidal, schistosomicidal, and anthelmintic [15]. Heterocyclic compounds containing 1,3,4-oxadiazole, 1,3,4-thiadiazole or 1,2,4-triazole moiety present a wide spectrum of biological activities such as antimicrobial, antiviral, anti-inflammatory, and antitumoral [16–21]. Acid hydrazides were documented as important compounds, due to their high reactivity in heterocycles synthesis, as key starting materials for 1,2,4-triazole, 1,3,4-oxadiazole or 1,3,4-thiadiazole synthesis [22, 23].

In view of the wide interest in the biological activity of these compounds and as a continuation of our research in this area [24–26], our aim was to synthesize new isolated heterocyclic systems, as antimicrobial agents, that comprise both the thiazole/pyridine and the 1,2,4-triazole, 1,3,4-oxadiazole or 1,3,4-thiadiazole rings, using 2-aryl-4-methylthiazol-5-carbohydrazides and isonicotinic acid hydrazide as starting materials. The compounds were designed to investigate the effect of such structural variation on the anticipated antimicrobial activities.

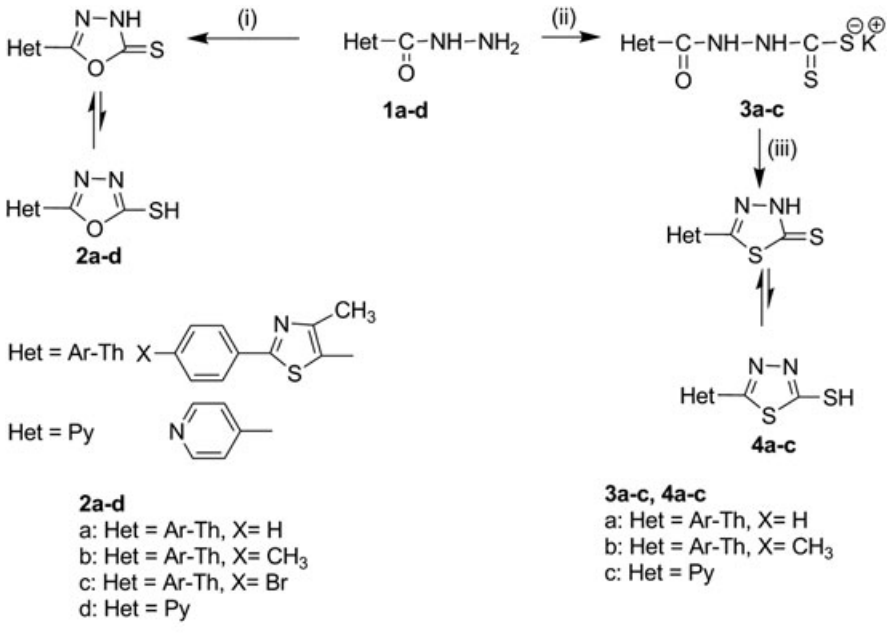
RESULTS AND DISCUSSION

Chemistry. The reaction sequences used for the synthesis of target compounds are shown in Schemes 1–3. The structures of the newly synthesized compounds were confirmed by analytical and spectral data (IR, ^{1}H NMR, ^{13}C NMR, and MS).

The key intermediates 2-aryl-4-methylthiazol-5-carbohydrazides **1a–c** (X H, CH_3, and Br) were prepared by the reaction of ethyl-2-aryl-4-methylthiazol-5-carboxylates (**A–C**) with hydrazine hydrate in absolute ethanol, according to the literature [27] (Scheme 1).

The 1,3,4-oxadiazole derivatives **2a–d** were obtained in good yield, by the reaction of the carbohydrazides **1a–c** and isonicotinic acid hydrazide **1d** with CS_2 and KOH in

Scheme 2

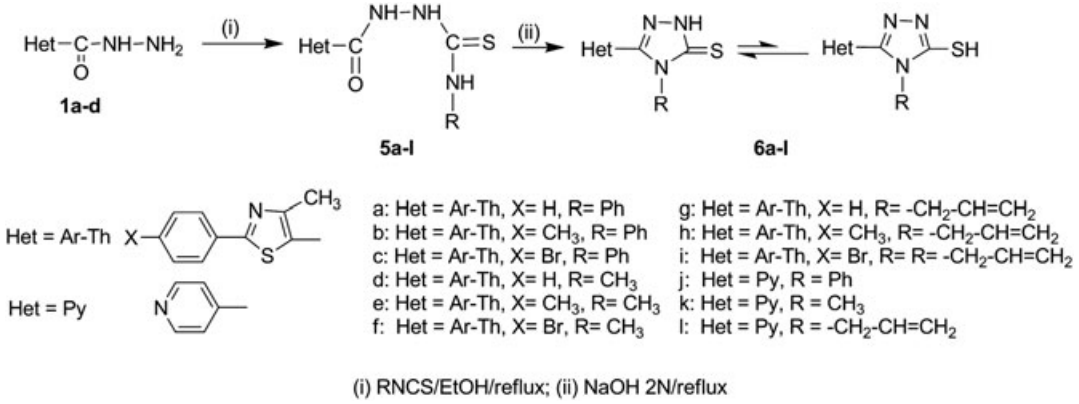


2a-d
a: Het = Ar-Th, X= H
b: Het = Ar-Th, X= CH_3
c: Het = Ar-Th, X= Br
d: Het = Py

3a-c, 4a-c
a: Het = Ar-Th, X= H
b: Het = Ar-Th, X= CH_3
c: Het = Py

(i) CS_2/KOH/EtOH/reflux; (ii) CS_2/KOH/EtOH/10^{0}C; (iii) H_2SO_4/rt;

Scheme 3



(i) RNCS/EtOH/reflux; (ii) NaOH 2N/reflux

refluxing ethanol, followed by hydrochloric acid work up. Reaction of **1a–b**, respectively, **1d** with CS_2 and KOH in absolute ethanol below 10°C resulted in the formation of potassium dithiocarbazates **3a–c**. Dehydrative cyclization of compounds **3a–c** using sulfuric acid at room temperature yielded the 1,3,4-thiadiazoles **4a–c** (Scheme 2).

4-Alkyl/aryl-1-(2-aryl-4-methylthiazol-5-carbonyl)-thiosemicarbazides **5a–i** and 4-alkyl/aryl-1-(pyridin-4-carbonyl)-thiosemicarbazide **5j–l** were obtained from hydrazides **1a–d** and the corresponding alkyl/arylisothiocyanates. The thiosemicarbazides **5a–l**, on heating with NaOH 2 *N* in ethanol, underwent cyclization through dehydration to afford 4-alkyl/aryl-3-(2-aryl-4-methylthiazol-5-yl)-1H-1,2,4-triazol-5(4H)-thiones **6a–i** and 4-alkyl/aryl-3-(pyridin-4-yl)-1H-1,2,4-triazol-5(4H)-thiones **6j–l** (Scheme 3), respectively.

IR spectra of thiosemicarbazides **5a–l** displayed absorption peaks at 3115–3308 cm^{-1} for NH, 1650–1682 cm^{-1} for C O, and 1214–1265 cm^{-1} corresponding to C S stretching vibrations. ^{1}H NMR spectra showed the three signals for the CONH, CSNH, and NH protons, as singlets at 10–10.3, 9.3–9.85, and 8.1–8.8 ppm, respectively, confirming the formation of thiosemicarbazide.

IR spectra of **2a–d**, **4a–c**, and **6a–l** exhibited NH bands in 3448–3463, 3438–3400, and 3070–3187 cm^{-1}, respectively. The absorption bands at 1597–1616, 1541–1599, and 1538–1614 cm^{-1} are due to the presence of C N stretch of the oxadiazole, thiadiazole, and triazole ring system, respectively. The absence of the C O absorption in **2a–d**, **4a–c**, and **6a–l** provided strong evidences for the formation of the new products. Also, the presence of bands for the C S group in the 1232–1275, 1242–1258, and 1214–1286 cm^{-1} proved that the compounds were in thione form in the solid state. In the ^{1}H NMR spectra of **1a–c**, the NH proton appeared in the 9.56–9.72 ppm region, whereas in compounds **2a–d**, **3a–c**, and **6a–l**, the NH signal was shifted to 14.1–14.4 ppm, indicating the thiol–thione tautomerism in solution. In the ^{13}C NMR spectra of **2a–d**, **3a–c**, and **6a–l**, the C S gave a peak at 169.9–172.9, 182.9–183.6, 168.6–171.4 ppm, respectively, indicating that the crystal structures of the compounds correspond to the thione form. The mass spectra of the prepared compounds showed the correct molecular ions (M^+ or M + 1) as suggested by their molecular formulas.

Antibacterial and antifungal activity. The newly synthesized compounds were tested for their antimicrobial activity, at a concentration of 10 mg/mL, against four gram positive bacterial strains: *Staphylococcus aureus* (ATCC 49444), *Enterococcus faecalis* (ATCC 29211), *Bacillus cereus* (ATCC 11778), *Listeria monocytogenes* (ATCC 13076); three gram negative bacterial strains: *Escherichia coli* (ATCC 25922), *Salmonella typhymurium* (ATCC 14028), *Pseudomonas aeruginosa* (ATCC 27853); and one fungal strain: *Candida albicans* (ATCC 10231), by the cup-plate agar diffusion method [28]. Each microorganism was suspended in Mueller Hinton (MH) broth and diluted approximately to 10^6 colony forming unit (cfu)/mL. They were "flood inoculated" onto the surface of MH agar and MH dextroxe agar (MDA) and then dried. For *C. albicans*, MDA was used. Six millimeter diameter wells were cut from the agar using a sterile cork-borer, and 10 μL of each compound solution were delivered into the wells. The plates were incubated at 37°C, and the diameters of the growth inhibition zones were measured after 24 h in case of bacteria and after 48 h in case of *C. albicans*. Stock solution of each compound (10 mg/mL) was prepared in dimethyl sulfoxide (DMSO; Merck, Germany). Gentamicin (10 μg per well) and Fluconazole (25 μg per well) were used as standard drugs. The controls were performed with only sterile broth and with only overnight culture and 10 μL of DMSO. Results were obtained in duplicate. The results of the antimicrobial screening are summarized in Table 1.

All the tested compounds were inactives against *E. faecalis*, *B. cereus,* and *P. aeruginosa*. Some of the compounds are active and showed moderate-to-good activity against *S. aureus*: thiazolyl-1,3,4-oxadiazoles **2a–c**, potassium dithiocarbazates **3a–c**, thiazolyl-1,3,4-tiadiazoles **4a–b**, and thiazolyl-thiosemicarbazides **5a–d** and **5g–h**. As it can be seen in Table 1,

Table 1

Antimicrobial activity of the synthesized compounds.[a]

Compound	Gram positive bacteria		Gram negative bacteria		Fungi
	S. aureus	*L. monocytogenes*	*E. coli*	*S. typhymurium*	*C. albicans*
1a	-	5	4	5	10
1b	-	4	4	4	12
1c	-	4	4	4	-
2a	16	3	4	-	-
2b	20	3	3	-	-
2c	22	4	4	-	-
3a	15	3	4	-	6
3b	15	3	4	-	-
3c	20	-	-	-	9
4a	7	-	3	-	-
4b	15	3	4	-	-
5a	7	3	4	-	-
5b	10	3	4	-	-
5c	9	3	3	-	-
5d	6	3	4	-	-
5e	-	3	4	-	15
5f	-	3	4	-	10
5g	6	3	4	-	-
5h	6	-	4	-	-
5i	4	-	4	-	-
6a	4	-	4	-	-
6b	-	-	4	-	-
6c	-	-	4	-	-
6d	-	-	4	-	-
6e	-	-	4	-	-
6f	-	-	4	-	-
6g	-	-	4	-	-
6h	-	-	4	-	-
6i	4	-	4	-	-
Gentamicin	19	18	22	18	-
Fluconazole	-	-	-	-	25

Gentamycin (10 μg per well) and Fluconazole (25 μg per well) were used as standard drugs.
- Indicates the compound has no activity.
[a]Zones of inhibition in millimeter.

oxadiazole derivatives **2a–c** were more active than the thiadiazole derivatives **4a–b**. The most active compound was **2c** with a 4-bromophenyl group in position 2 of the thiazole ring, the inhibitory activity being more powerful than that of Gentamicin (10 μg per well), used as standard drug. All the synthesized compounds were slightly sensitive against gram positive *B. cereus* and *L. monocytogenes* and gram negative bacteria *E. coli*. The antifungal screening data reveal that most of the new compounds are inactive, only six compounds displayed weak inhibitory activity against *C. albicans*: acid hydrazides **1a**, **1b**, potassium dithiocarbazates **3a**, **3c**, and thiazolyl-thiosemicarbazides **5e**, **5f**.

In conclusion, a series of new thiazolo/pyridin-1,3,4-oxadiazole, thiazolo/pyridin-1,3,4-thiadiazole, and thiazolo/pyridin-1,2,4-triazole derivatives have been synthesized starting from 2-aryl-4-methylthiazol-5-carbohydrazides and isonicotinic acid hydrazide and evaluated for their antibacterial and antifungal activity against various gram positive, gram negative bacteria, and *C. albicans*.

EXPERIMENTAL

Reagents were commercial grade and were used as supplied. Thin layer chromatography was used to analyze the reaction progress and purity of the synthesized compounds and was carried out on precoated Silica Gel 60F254 sheets using heptan–ethyl acetate 1:1 system and ultraviolet light for visualization. Melting points were determined in open glass capillary method with an electrothermal melting point meter and were uncorrected. IR spectra were obtained in KBr disks on a Nicolet 210 FT-IR spectrometer. The ^{1}H NMR spectra were recorded at room temperature on a Bruker Avance NMR spectrometer (500 MHz) using TMS as internal standard. The samples were prepared by dissolving the compounds in DMSO-d_6 (δH = 2.51ppm) as solvent and the spectra were recorded using a single excitation pulse of 12 μs. ^{13}C NMR spectra were recorded on Bruker spectrometer (125 MHz) in DMSO-d_6. Mass spectra were recorded by Agilent 1100, type SL spectrometer (positive ionization) and with a Varian MAT CH-5 spectrometer (70 eV). Elemental analysis was registered with a Vario El CHNS instrument, results were found to be in good agreement (±0.4%) with the calculated

values. The hydrazides **1a–c** were already published [27], but they were characterized only by elemental analysis and melting points.

2-Aryl-4-methylthiazol-5-carbohydrazides (1a–c) [27]. To a solution of ethyl 2-aryl-2-methylthiazol-5-carboxylates **A–C** (58.7 mmol) in absolute ethanol (100 mL), hydrazine hydrate (5.87 g, 117.4 mmol) was added and the resulting mixture was heated to 100°C for 4 h. The mixture was concentrated under reduced pressure. Water was added to the residue and the resulting solid was filtered, washed with water, and recrystallized from ethanol to give compounds **1a–c**, as white crystals.

4-Methyl-2-phenylthiazol-5-carbohydrazide (1a). Yield 13 g, 55.8 mmol, (95%), mp 168–169°C [27]; IR (KBr): v 1620 (C N), 1670 (C O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.77 (s, 3H, CH_3), 4.21 (s, 2H, NH_2), 7.46–7.96 (m, 5H, Ar H), 9.72 (s, 1H, NH) ppm; MS: *m/z* (%) 233 (M^+, 100). Anal. Calcd. for $C_{11}H_{11}N_3OS$: C, 56.63; H, 4.75; N, 18.01; S, 13.74. Found: C, 56.59; H, 4.77; N, 17.94; S, 13.67.

4-Methyl-2-p-tolylthiazol-5-carbohydrazide (1b). Yield 13.63g, 55.18 mmol, (94%), mp 186–187°C (Ref. [27] 182–183°C); IR (KBr): v 1625 (C N), 1675 (C O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.36 (s, 3H, CH_3), 2.59 (s, 3H, CH_3), 4.64 (s, 2H, NH_2), 7.32–7.83 (m, 4H, Ar H), 9.56 (s, 1H, NH) ppm; MS: *m/z* (%) 247 (M^+, 100). Anal. Calcd. for $C_{12}H_{13}N_3OS$: C, 58.28; H, 5.30; N, 16.99; S, 12.97. Found: C, 58.21; H, 5.33; N, 16.92; S, 12.95.

2-(4-Bromophenyl)-4-methylthiazol-5-carbohydrazide (1c). Yield 16.85g, 54 mmol, (92%), mp 218–219°C (Ref. [27] 215–216° C; IR (KBr): v 1615 (C N), 1677 (C O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.7 (s, 3H, CH_3), 4.13 (s, 2H, NH_2), 7.68–7.73 (m, 4H, Ar H), 9.67 (s, 1H, NH) ppm; MS: *m/z* (%) 312 (M^+, 100). Anal. Calcd. for $C_{11}H_{10}BrN_3OS$: C, 42.32; H, 3.23; N, 13.46; S, 10.27. Found: C, 42.35; H, 3.28; N, 13.41; S, 10.22.

5-(2-Aryl-4-methylthiazol-5-yl)-1,3,4-oxadiazol-2(3H)-thione (2a–c); 5-(pyridin-4-yl)-1,3,4-oxadiazol-2(3H)-thione (2d). To a solution of **1a–d** (10 mmol) in absolute ethanol (100 mL), carbon disulfide (20 mmol) and potassium hydroxide (12.5 mmol) were added and the resulting solution was heated to reflux for 24 h. The reaction mixture was concentrated and the residue was dissolved in water and acidified with diluted hydrochloric acid. The resulting solid was filtered, dried, and recrystallized from ethanol to afford compounds **2a–d** as yellow solids.

5-(4-Methyl-2-phenylthiazol-5-yl)-1,3,4-oxadiazol-2(3H)-thione (2a). Yield 2.13 g, 7.73 mmol, (77.3%), mp 243–244°C; IR (KBr): v 1155 (C O C), 1271 (C S), 1612 (C N), 3448 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.48 (s, 3H, CH_3), 7.54–8.0 (m, 5H, Ar H), 14.17 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ 17.01 (CH_3), 115.8 (CH), 126.17 (CH), 129.71 (CH), 132.3 (C), 134.7 (C), 144.5 (C), 156.9 (C), 167.5 (C), 169.9 (C S) ppm; MS: *m/z* (%) 276 (M + 1, 100). Anal. Calcd. for $C_{12}H_9N_3OS_2$: C, 52.34; H, 3.29; N, 15.26; S, 23.29. Found: C, 52.32; H, 3.26; N, 15.24; S, 23.26.

5-(4-Methyl-2-p-tolylthiazol-5-yl)-1,3,4-oxadiazol-2(3H)-thione (2b). Yield 2.46 g, 8.52 mmol, (85.2%), mp 247–248°C; IR (KBr): v 1158 (C O C), 1267 (C S), 1596 (C N), 3463 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.37 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 7.3–7.8 (m, 4H, Ar H), 14.26 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ 16.9 (Th CH_3), 21.38 (Ar CH_3), 117.4 (CH), 126.5 (CH), 129.7 (C), 131.6 (C), 141.5 (C), 144.3 (C), 156.9 (C), 167.5 (C), 172.9 (C S) ppm; MS: *m/z* (%) 290 (M + 1, 100). Anal. Calcd. for $C_{13}H_{11}N_3OS_2$: C, 53.96; H, 3.83; N, 14.52; S, 22.16. Found: C, 53.93; H, 3.81; N, 14.49; S, 22.15.

5-(2-(4-Bromophenyl)-4-methylthiazol-5-yl)-1,3,4-oxadiazol-2 (3H)-thione (2c). Yield 2.99 g, 8.45 mmol, (84.5%), mp 255–257°C; IR (KBr): v 1156 (C O C), 1275 (C S), 1608 (C N), 3452 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.68 (s, 3H, CH_3), 7.73–7.96 (m, 4H, Ar H), 14.93 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ 17.63 (CH_3), 114.3 (C), 125.45 (CH), 128.89 (CH), 131.42 (C), 132.9 (C), 156.2 (C), 156.9 (C), 167.2.5 (C), 183.9 (C S) ppm; MS: *m/z* (%) 354 (M + 1, 100). Anal. Calcd. for $C_{12}H_8BrN_3OS_2$: C, 40.69; H, 2.28; N, 11.86; S, 18.1. Found: C, 40.68; H, 2.27; N, 11.83; S, 18.02.

5-(Pyridin-4-yl)-1,3,4-oxadiazol-2(3H)-thione (2d) [29]. Yield 1.46 g, 7.49 mmol, (75%); mp 264–265°C; IR (KBr): v 1232 (C S), 1352 (C O C), 1616 (C N), 3450 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.63 (dd, 2H, J = 5, 3-Py), 8.76 (dd, 2H, J = 5, 2–Py), 14.73 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ 121.9 (2CH), 139.8 (C), 149.1 (C), 150.1 (2CH), 182.7 (C S) ppm; MS: *m/z* (%) 179 (M^+, 20). Anal. Calcd. for $C_7H_5N_3OS$: C, 46.92; H, 2.81; N, 23.45; S, 17.89. Found: C, 46.78; H, 2.70; N, 23.25; S, 17.76.

Potassium 2-(2-aryl-4-methylthiazol-5-carbonyl)-hydrazinecarbodithioate (3a–c). To a solution of **1a–b** and **1d** (20 mmol) in 40 mL ethanol refrigerated below 10°C, a solution of 1.68 g potassium hydroxide (30 mmol) in 60 mL ethanol and 3.04 g carbon disulfide (30 mmol) were added and the reaction mixture was refrigerated 3 h. The resulting solid was filtered, washed with ether, and dried to afford compounds **3a–c** as yellow–orange solids.

Potassium 2-(4-methyl-2-phenylthiazol-5-carbonyl)-hydrazinecarbodithioate (3a). Yield 4.6 g, 13.3 mmol, (66.5%); IR (KBr): v 3444, 3228 (2NH), 1647 (C O) cm^{-1}.

Potassium 2-(4-methyl-2-p-tolylthiazol-5-carbonyl)-hydrazinecarbodithioate (3b). Yield 6.6 g, 18.28 mmol, (91.4%); IR (KBr): v 3443, 3223 (2NH), 1652 (C O) cm^{-1}.

Potassium pyridin-4-carbonyl-hydrazinecarbodithioate (3c). Yield 3.91 g, 15.57 mmol, (78%); IR (KBr): v 3370, 3309 (2NH), 1675 (C O) cm^{-1}.

5-(2-Aryl-4-methylthiazol-5-yl)-1,3,4-tiadiazol-2(3H)-thione (4a–b); 5-(pyridin-4-yl)-1,3,4-thiadiazol-2(3H)-thione (4c). Potassium hydrazinecarbodithioates **3a–c** (10 mmol) were added portion wise to 98% sulfuric acid (25 mL) and the resulted clear solution was stirred at room temperature for 24 h. The mixture was cautiously added to crushed ice, stirred for 1h, refrigerated for 4 h, and the separated precipitate was filtered, washed with water, and dried and crystallized from ethanol to afford compounds **4a–c**, as yellow solids.

5-(4-Methyl-2-phenylthiazol-5-yl)-1,3,4-tiadiazol-2(3H)-thione (4a). Yield 1.98 g, 6.8 mmol, (68.1%), mp 204–205°C; IR (KBr): v 1242 (C S), 1541 (C N), 3438 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.6 (s, 3H, CH_3), 7.5–8.1 (m, 5H, Ar H), 14.2 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ 17.2 (CH_3), 120.1 (CH), 126.2 (CH), 128.9 (CH), 133.3 (C), 143.7 (C), 153.6 (C), 156.7 (C), 161.2 (C), 182.9 (C S) ppm; MS: *m/z* (%) 292 (M + 1, 100). Anal. Calcd. for $C_{12}H_9N_3S_3$: C, 49.46; H, 3.11; N, 14.42; S, 33.01. Found: C, 49.42; H, 3.10; N, 14.41; S, 33.04.

5-(4-Methyl-2-p-tolylthiazol-5-yl)-1,3,4-tiadiazol-2(3H)-thione (4b). Yield 2.9 g, 5.28 mmol, (52.8%), mp 250–251°C; IR (KBr): v 1243 (C S), 1558 (C N), 3410 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.44 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 7.32–7.92 (m, 4H, Ar H), 14.92 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ 17.67 (Th CH_3), 21.55 (Ar CH_3), 120.8 (CH), 126.7 (CH), 126.9 (C), 129.8 (C), 130.3 (C), 141.9 (C), 154.8 (C), 167.8 (C), 183.6 (C S) ppm; MS: *m/z* (%) 306 (M + 1, 100). Anal. Calcd. for $C_{13}H_{11}N_3S_3$: C, 51.12; H, 3.63; N, 13.76; S, 31.49. Found: C, 51.13; H, 3.61; N, 13.76; S, 31.50.

5-(Pyridin-4-yl)-1,3,4-thiadiazol-2(3H)-thione (4c). Yield 1.10g, 5.63 mmol (56.5%); mp 280–282°C; IR (KBr): v 1258 (C S), 1599 (C N), 3400 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.66 (dd, 2H, J = 5, 3-Py), 8.78 (dd, 2H, J = 5, 2-Py), 14.68 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ122.1 (2CH), 139.7 (C), 148.8 (C), 150.5 (2CH), 183.1 (C S) ppm; MS: *m/z* (%) 195 (M^+, 36). Anal. Calcd. for $C_7H_5N_3S_2$: C, 43.06; H, 2.58; N, 21.52; S, 32.84. Found: C, 43.19; H, 2.54; N, 21.44; S, 32.64.

4-Alkyl/aryl-1-(2-aryl-4-methylthiazol-5-carbonyl)-thiosemicarbazides (5a–i); 4-alkyl/aryl-1-(pyridin-4-yl-carbonyl)-thiosemicarbazides (5j–). To a solution of 4 mmol **1a–d** in 30 mL ethanol, 4 mmol of the appropriate isothiocyanate were added. The resulting mixture was heated under reflux for 3 h. After cooling the precipitate was separated and recrystallized from methanol/acetone to afford thiosemicarbazides **5a–l**.

1-(4-Methyl-2-phenylthiazol-5-carbonyl)-4-phenyl-thiosemicarbazide (5a). This was obtained as yellow crystal; Yield 1.35 g, 3.68 mmol, (92%), mp 184–185°C; IR (KBr): v 1231 (C S), 1532 (C N), 1672 (C O), 3115 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.67 (s, 3H, CH_3), 7.16–7.32 (m, 5H, Ar H), 7.95–7.97 (m, 5H, Ar H), 8.3 (s,1H, NH C S), 9.6 (s, 1H, NH C S), 10.13 (s, 1H, NH C O) ppm; ^{13}C NMR (DMSO-d_6): δ 17.9 (CH_3), 123.1 (2CH), 126.2 (4CH), 129.6 (4CH), 130.3 (C), 131.5 (C), 132.7 (C), 157.8 (C O), 160.7 (C), 167.1 (C), 182.9 (C S) ppm; MS: *m/z* (%) 369 (M + 1, 100). Anal. Calcd. for $C_{18}H_{16}N_4OS_2$: C, 58.67; H, 4.38; N, 15.21; S, 17.4. Found: C, 58.65; H, 4.36; N, 15.18; S, 17.38.

1-(4-Methyl-2-p-tolylthiazol-5-carbonyl)- 4-phenyl-thiosemicarbazide (5b). This was obtained as yellow solid; Yield 1.4 g, 3.66 mmol, (91%), mp 179–180°C; IR (KBr): v 1234 (C S), 1534 (C N), 1615 (C O), 3317 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.37 (s, 3H, CH_3), 2.69 (s, 3H, CH_3), 7.24–7.52 (m, 5H, Ar H), 7.35 (d, 2H, J = 8.5 Hz, Ar), 7.85 (d, 2H, J = 8.5 Hz, Ar), 8.7 (s,1H, NH C S), 9.8 (s, 1H, NH C S), 10.3 (s, 1H, NH C O) ppm; ^{13}C NMR (DMSO-d_6): δ 17.95 (Th CH_3), 21.5 (Ar CH_3), 126.7 (4CH), 127.2 (CH), 128.5 (4CH), 130.2 (C), 130.4 (C), 139.7 (C), 141.6 (C), 160.4 (C O), 167.1 (C), 182.1 (C S) ppm; MS: *m/z* (%) 383 (M + 1, 100). Anal. Calcd. for $C_{19}H_{18}N_4OS_2$: C, 59.66; H, 4.74; N, 14.65; S, 16.77. Found: C, 59.63; H, 4.71; N, 14.63; S, 16.78.

1-(2-(4-bromophenyl)-4-methylthiazol-5-carbonyl)-4-phenyl-thiosemicarbazides (5c). This was obtained as yellow crystal; Yield 1.7 g, 3.8 mmol, (95%), mp 254–256°C; IR (KBr): v 1214 (C S), 1567 (C N), 1670 (C O), 3300 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.5 (s, 3H, CH_3), 7.17–7.36 (m, 5H, Ar H), 7.74 (d, 2H, J = 9 Hz, ar), 7.90 (d, 2H, J = 8.5 Hz, ar), 8.3 (s,1H, NH C S), 9.5 (s, 1H, NH C S), 10.1 (s, 1H, NH C O) ppm; ^{13}C NMR (DMSO-d_6): δ 17.4 (Th CH_3), 124.7 (C), 128.2 (2CH), 129.4 (C), 129.9 (3CH), 130.5 (2CH), 131.2 (2CH), 132.6 (C), 134.3 (C), 156.1 (C), 159.9 (C O), 164 (C),180.8 (C S) ppm; MS: *m/z* (%) 448 (M + 1, 100). Anal. Calcd. for $C_{18}H_{15}BrN_4OS_2$: C, 48.33; H, 3.38; N, 12.52; S, 14.33. Found: C, 48.32; H, 3.36; N, 12.49; S, 14.34.

1-(4-Methyl-2-phenylthiazol-5-carbonyl)- 4-methyl-thiosemicarbazide (5d). This was obtained as white solid; Yield 0.95 g, 2.58 mmol, (64.5%), mp 205–207°C; IR (KBr): v 1265 (C S), 1527 (C N), 1660 (C O), 3113 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.6 (s, 3H, CH_3), 2.8 (d, 3H, J = 4.5 Hz, NCH_3), 7.11–7.28 (m, 5H, Ar H), 8.1 (s,1H, NH C S), 9.7 (s, 1H, NH C S), 10.11 (s, 1H, NH C O) ppm; ^{13}C NMR (DMSO-d_6): δ 17.9 (CH_3), 31.48 (NCH_3), 125.2 (CH), 126.8 (2CH), 129.9 (2CH), 130.7 (C), 131.6 (C), 132.8 (C), 157.9 (C O), 161.6 (C), 167.2 (C), 183.4 (C S) ppm; MS: *m/z* (%) 307 (M + 1, 100). Anal. Calcd. for $C_{13}H_{14}N_4OS_2$: C, 50.96; H, 4.61; N, 18.29; S, 20.93. Found: C, 50.92; H, 4.59; N, 18.24; S, 20.90.

1-(4-Methyl-2-p-tolylthiazol-5-carbonyl)- 4-methyl-thiosemicarbazide (5e). This was obtained as white solid; Yield 1.2 g, 3.75 mmol, (64.5%), mp 208–209°C; IR (KBr): v 1233 (C S), 1540 (C N), 1650 (C O), 3315 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.43 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 2.9 (d, 3H, J = 4.5 Hz, NCH_3), 7.54 (d, 2H, J = 8.5 Hz, Ar), 7.97 (d, 2H, J = 8.5 Hz, Ar), 8.81 (s,1H, NH C S), 9.85 (s, 1H, NH C S), 10.31 (s, 1H, NH C O) ppm; ^{13}C NMR (DMSO-d_6): δ17.7 (Th CH_3), 21.4 (Ar CH_3), 31.24 (NCH_3), 124.5 (2CH), 127.3 (2CH), 131.5 (C), 136.6 (C), 138.8 (C), 159.9 (C O), 161.2 (C), 166.7 (C), 182.1 (C S) ppm; MS: *m/z* (%) 321 (M + 1, 100). Anal. Calcd. for $C_{14}H_{16}N_4OS_2$: C, 52.48; H, 5.03; N, 17.48; S, 20.01. Found: C, 52.47; H, 5.04; N, 17.45; S, 20.05.

1-(2-(4-Bromophenyl)-4-methylthiazol-5-carbonyl)-4-methyl-thiosemicarbazides (5f). This was obtained as yellow solid; Yield 1.25 g, 3.25 mmol, (81.2%), mp 220–221°C; IR (KBr): v 1232 (C S), 1567 (C N), 1658 (C O), 3307 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.43 (s, 3H, CH_3), 2.88 (d, 3H, J = 4.5 Hz, NCH_3), 7.48 (d, 2H, J = 8.5 Hz, Ar), 7.90 (d, 2H, J = 8.5 Hz, Ar), 8.4 (s,1H, NH C S), 9.5 (s, 1H, NH C S), 10.2 (s, 1H, NH C O) ppm; ^{13}C NMR (DMSO-d_6): δ 17.61 (CH_3), 31.14 (NCH_3), 126.2 (2CH), 129.1 (2CH), 133.4 (C), 138.2 (C), 139.8 (C), 160.1 (C O), 163.4 (C), 168.2 (C), 181.9 (C S) ppm; MS: *m/z* (%) 386 (M + 1, 100). Anal. Calcd. for $C_{13}H_{13}BrN_4OS_2$: C, 40.52; H, 3.40; N, 14.54; S, 16.64. Found: C, 40.49; H, 3.41; N, 14.52; S, 16.6.

4-Allyl-1-(4-methyl-2-phenylthiazol-5-carbonyl)-thiosemicarbazide (5g). This was obtained as white solid; Yield 1.22 g, 3.68 mmol, (92%), mp 185–188°C; IR (KBr): v 1235 (C S), 1530 (C N), 1660 (C O), 3302 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.7 (s, 3H, CH_3), 4.11 (m, 2H, CH_2), 5.06 (d, 2H, CH_2), 5.8 (m, 1H, CH), 7.17–7.36 (m, 5H, Ar H), 8.3 (s,1H, NH C S), 9.4 (s, 1H, NH C S), 10.1 (s, 1H, NH C O) ppm; ^{13}C NMR (DMSO-d_6): δ 17.9 (CH_3), 46.3 (CH_2), 114.9 (CH_2), 125.7 (CH), 126.6 (2CH), 128.4 (CH), 129.4 (2CH), 130.1 (C), 131.9 (C), 132.6 (C), 157.4 (C O), 161.2 (C), 166.9 (C), 181.8 (C S) ppm; MS: *m/z* (%) 333 (M + 1, 100). Anal. Calcd. for $C_{15}H_{16}N_4OS_2$: C, 54.19; H, 4.85; N, 16.85; S, 19.29. Found: C, 54.16; H, 4.84; N, 16.81; S, 19.27.

4-Allyl-1-(4-methyl-2-p-tolylthiazol-5-carbonyl)-thiosemicarbazide (5h). This was obtained as white solid; Yield 1.06 g, 3.07 mmol, (76.7%), mp 199–200°C; IR (KBr): v 1226 (C S), 1545 (C N), 1662 (C O), 3125 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.38 (s, 3H, CH_3), 2.69 (s, 3H, CH_3), 4.1 (m, 2H, CH_2), 5.05 (d, 2H, CH_2), 5.82 (m, 1H, CH), 7.41 (d, 2H, J = 8 Hz, Ar), 7.89 (d, 2H, J = 8 Hz, Ar), 8.4 (s,1H, NH C S), 9.3 (s, 1H, NH C S), 10.06 (s, 1H, NH C O) ppm; ^{13}C NMR (DMSO-d_6): δ 17.4 (Th CH_3), 21.25 (Ar CH_3), 46.1 (CH_2), 115.2 (CH_2), 124.6 (C), 124.4 (2CH), 128.9 (2CH), 128.7 (CH), 131.2 (C), 132.2 (C), 136.7 (C O), 161.9 (C), 165.9 (C), 181.7 (C S) ppm; MS: *m/z* (%) 347 (M + 1, 100). Anal. Calcd. for $C_{16}H_{18}N_4OS_2$: C, 55.47; H, 5.24; N, 16.17; S, 18.51. Found: C, 55.44; H, 5.22; N, 16.14; S, 18.46.

4-Allyl-1-(2-(4-bromophenyl)-4-methylthiazol-5-carbonyl)-thiosemicarbazides (5i). This was obtained as yellow solid; Yield 1.35 g, 3.28 mmol, (82%), mp 224–225°C; IR (KBr): v 1264 (C S), 1558 (C N), 1668 (C O), 3173 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.67 (s, 3H, CH_3), 4.12 (m, 2H, CH_2), 5.12 (d, 2H, CH_2), 5.8 (m, 1H, CH), 7.74 (d, 2H, J = 9 Hz, Ar), 7.9 (d, 2H, J = 9 Hz, Ar), 8.36 (s,1H, NH C S), 9.48 (s, 1H, NH C S), 10.19 (s, 1H, NH C O) ppm; ^{13}C NMR (DMSO-d_6): δ 17.89 (CH_3), 46.4 (CH_2), 115.7 (CH_2), 124.2 (C), 124.9 (2CH), 128.3 (2CH), 128.6 (CH), 131.9 (C), 132.9 (C), 135.9

(C O), 161.4 (C), 165.8 (C), 183.9 (C S) ppm; MS: *m/z* (%) 412 (M + 1, 100). Anal. Calcd. for $C_{15}H_{15}BrN_4OS_2$: C, 43.80; H, 3.68; N, 13.62; S, 15.59. Found: C, 43.81; H, 3.66; N, 13.59; S, 15.55.

4-Phenyl-1-(pyridin-4-yl-carbonyl)-thiosemicarbazide (5j). This was obtained as white solid; Yield 0.84 g, 3.10 mmol (81%); mp 187–189°C (Ref. [30] 120°C); MS: *m/z* (%) 272 (M^+, 18). Anal. Calcd. for $C_{13}H_{12}N_4OS$: C, 57.33; H, 4.44; N, 20.57; S, 11.77. Found: C, 57.44; H, 4.28; N, 20.65; S, 11.35.

4-Methyl-1-(pyridine-4-yl-carbonyl)-thiosemicarbazide (5k). This was obtained as white solid; Yield 0.68 g, 3.22 mmol (80.5%); mp 265–267°C; IR (KBr): v 1252(C S), 1553(C N), 1673(C O), 2971, 2975, 3114, 3263(3NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.8 (d, 3H, J = 5 Hz, NCH_3), 7.78 (dd, 2H, J = 5, 3-Py), 8.79 (dd, 2H, J = 5, 2-Py), 8.40 (s, 1H, NH C S), 9.48 (s, 1H, NH C S), 10.57 (s, 1H, NH C O) ppm; ^{13}C NMR (DMSO-d6): δ 32.2 (NCH_3), 121.8 (2CH), 138.6 (C), 148.9 (2CH), 164.7 (C O), 180.9 (C S) ppm; MS: *m/z* (%) 210 (M^+, 40). Anal. Calcd. for $C_8H_{10}N_4OS$: C, 45.70; H, 4.79; N, 26.65; S, 15.25. Found: C, 45.94; H, 4.53; N, 26.32; S, 15.10.

4-Allyl-1-(pyridine-4-yl-carbonyl)-thiosemicarbazide (5l). This was obtained as white solid; Yield 0.80 g, 3.4 mmol (85.8%); mp 210–211°C; IR (cm^{-1}): v 1229 (C S), 1526 (C N), 1676 (C O), 3219, 3268, 3308 (3NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 4.11 (d, 2H, CH_2), 5.14 (dd, 2H, CH_2), 5.82 (m, 1H, CH), 7.83 (dd, 2H, J = 5, 3-Py), 8.77 (dd, 2H, J = 5, 2-Py), 8.42 (s, 1H, NH C S), 9.51 (s, 1H, NH C S), 10.69 (s, 1H, NH C O) ppm; ^{13}C NMR (DMSO-d6): δ 46.4 (CH_2), 115.7 (CH_2), 122.1 (2CH), 135.4 (CH), 140.0 (C), 150.6 (2CH), 164.9 (C O), 182.0 (C S) ppm; MS: *m/z* (%) 237 (M + 1, 100). Anal. Calcd. for $C_{10}H_{12}N_4OS$: C, 50.83; H, 5.12; N, 23.71; S, 13.57. Found: C, 50.99; H, 5.4.87; N, 23.40; S, 13.31.

4-Alkyl/aryl-3-(2-aryl-4-methylthiazol-5-yl)-1H-1,2,4-triazol-5(4H)-thione (6a–i); 4-alkyl/aryl-3-(pyridin-4-yl)-1H-1,2,4-triazol-5(4H)-thione (6j–l). A solution of corresponding thiosemicarbazide **5a–l** (3.5 mmol) in 20 mL NaOH 2N was refluxed for 2 h. The resulting solution was cooled to room temperature, diluted with water, and acidified to pH 5–6. The precipitate was filtered, washed with water, and recrystallized from ethanol to afford the triazolyl–thiones **6a–l** as white solids.

3-(4-Methyl-2-phenylthiazol-5-yl)-4-phenyl-1H-1,2,4-triazol-5(4H)-thione (6a). Yield 1.18 g, 3.4 mmol, (97%), mp 272–274°C; IR (KBr): v 1265 (C S), 1531 (C N), 1570 (C N), 3110 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.48 (s, 3H, CH_3), 7.44–7.56 (m, 5H, Ar H), 7.6–7.99 (m, 5H, Ar H), 14.1 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ 17.04 (CH_3), 115.1 (C), 126.1 (CH), 126.3 (3CH), 129.9 (4CH), 131.2 (2CH), 132.3 (C), 142.5 (C), 144.5 (C), 156.8 (C), 160.7 (C), 165.1 (C), 168.9 (C S) ppm; MS: *m/z* (%) 350 (M^+, 100). Anal. Calcd. for $C_{18}H_{14}N_4S_2$: C, 61.69; H, 4.03; N, 15.99; S, 18.30. Found: C, 61.65; H, 4.01; N, 15.94; S, 18.27.

3-(4-Methyl-2-p-tolylthiazol-5-yl)-4-phenyl-1H-1,2,4-triazol-5(4H)-thione (6b). Yield 0.92 g, 2.62 mmol, (75%), mp 267–269°C; IR (KBr): v 1257 (C S), 1520 (C N), 1538 (C N), 3102 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.38 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 7.45–7.55 (m, 5H, Ar H), 7.34 (d, 2H, J = 8 Hz, Ar), 7.86 (d, 2H, J = 9 Hz, Ar), 14.2 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ 16.9 (Th CH_3), 21.5 (Ar CH_3), 117.2 (C), 124.8 (C), 126.2 (2CH), 127.8 (3CH), 128.8 (2CH), 132.1 (2CH), 130.4 (C), 140.1 (C), 142.6 (C), 144.4 (C), 157.1 (C), 170.2 (C S) ppm; MS: *m/z* (%) 364 (M^+, 100). Anal. Calcd. for $C_{19}H_{16}N_4S_2$: C, 62.61; H, 4.42; N, 15.37; S, 17.59. Found: C, 62.58; H, 4.41; N, 15.32; S, 17.53.

3-(2-(4-Bromophenyl)-4-methylthiazol-5-yl)-4-phenyl-1H-1,2,4-triazol-5(4H)-thione (6c). Yield 1.39 g, 3.24 mmol, (92.5%), mp 295–296°C; IR (KBr): v 1268 (C S), 1515 (C N), 1557 (C N), 3172 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.45 (s, 3H, CH_3), 7.44–7.56 (m, 5H, Ar H), 7.67 (d, 2H, J = 9 Hz, Ar), 7.7 (d, 2H, J = 9 Hz, Ar), 14.37 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ 17.42 (CH_3), 115.9 (C), 124.7 (C), 128.4 (2CH), 129.5 (3CH), 129.9 (2CH), 130.5 (2CH), 131.5 (C), 132.8 (C), 134.0 (C), 144.85 (C), 156.5 (C), 168.72 (C S) ppm; MS: *m/z* (%) 429 (M^+, 100). Anal. Calcd. for $C_{18}H_{13}BrN_4S_2$: C, 50.33; H, 3.02; N, 13.01; S, 14.89. Found: C, 50.35; H, 3.05; N, 13.05; S, 14.94.

4-Methyl-3-(4-methyl-2-phenylthiazol-5-yl)-1H-1,2,4-triazol-5(4H)-thione (6d). Yield 0.92 g, 3.19 mmol, (91%), mp 228–229°C; IR (KBr): v 1280 (C S), 1488 (C N), 1541 (C N), 3070 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.48 (s, 3H, CH_3), 3.48 (s, 3H, NCH_3), 7.54–7.99 (m, 5H, Ar H), 14.17 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ 17.04 (CH_3), 31.8 (NCH_3), 115.1 (C), 126.8 (CH), 129.9 (2CH), 131.6 (2CH), 132.6 (C), 144.8 (C), 156.3 (C), 167.9 (C), 168.8 (C S) ppm; MS: *m/z* (%) 289 (M + 1, 100). Anal. Calcd. for $C_{13}H_{12}N_4S_2$: C, 54.14; H, 4.19; N, 19.43; S, 22.24. Found: C, 54.13; H, 4.18; N, 19.39; S, 22.19.

4-Methyl-3-(4-Methyl-2-p-tolylthiazol-5-yl)-1H-1,2,4-triazol-5(4H)-thione (6e). Yield 0.84 g, 2.77 mmol, (79%), mp 278–279°C; IR (KBr): v 1279 (C S), 1522 (C N), 1540 (C N), 3092 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.37 (s, 3H, CH_3), 2.69 (s, 3H, CH_3), 3.42 (s, 3H, NCH_3), 7.35 (d, 2H, J = 8 Hz, Ar), 7.86 (d, 2H, J = 9 Hz, Ar), 14.31 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ 17.2 (Th CH_3), 21.38 (Ar CH_3), 31.6 (NCH_3), 116.2 (C), 124.7 (C), 126.6 (2CH), 129.7 (2CH), 131.9 (C), 138.6 (C), 144.8 (C), 154.9 (C), 169.7 (C S) ppm; MS: *m/z* (%) = 303 (M + 1, 100). Anal. Calcd. for $C_{14}H_{14}N_4S_2$: C, 55.6; H, 4.67; N, 18.53; S, 21.21. Found: C, 55.58; H, 4.65; N, 18.49; S, 21.18.

3-(2-(4-Bromophenyl)-4-methylthiazol-5-yl)-4-methyl-1H-1,2,4-triazol-5(4H)-thione (6f). Yield 1.24 g, 3.4 mmol, (97%), mp 283–285°C; IR (KBr): v 1280 (C S), 1521 (C N), 1541 (C N), 3095 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.46 (s, 3H, CH_3), 3.5 (s, 3H, NCH_3), 7.6 (d, 2H, J = 9 Hz, Ar), 7.7 (d, 2H, J = 9 Hz, Ar), 14.37 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ 17.4 (Th CH_3), 31.9 (NCH_3), 115.6 (C), 124.9 (C), 128.2 (2CH), 129.4 (2CH), 131.2 (C), 132.9 (C), 144.5 (C), 156.5 (C), 171.4 (C S) ppm; MS: *m/z* (%) 367 (M^+, 100). Anal. Calcd. for $C_{13}H_{11}BrN_4S_2$: C, 42.51; H, 3.02; N, 15.25; S, 17.46. Found: C, 42.52; H, 3.02; N, 15.21; S, 17.42.

4-Allyl-3-(4-methyl-2-phenylthiazol-5-yl)-1H-1,2,4-triazol-5(4H)-thione (6g). Yield 1.03 g, 3.3 mmol, (94%), mp 214–216°C; IR (KBr): v 1267 (C S), 1533 (C N), 1573 (C N), 3099 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.48 (s, 3H, CH_3), 4.65 (m, 2H, CH_2), 4.85–5.16 (dd, 2H, CH_2), 5.82 (m, 1H, CH), 7.55–7.99 (m, 5H, Ar H), 14.21 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ 17.7 (CH_3), 46.2 (CH_2), 113.7 (CH_2), 115.9 (C), 126.6 (CH), 129.8 (2CH), 130.3 (2CH), 131.7 (CH), 140.2 (C), 144.4 (C), 156.2 (C), 162.9 (C), 170.8 (C S) ppm; MS: *m/z* (%) 314 (M + 1, 100). Anal. Calcd. for $C_{15}H_{14}N_4S_2$: C, 57.30; H, 4.49; N, 17.82; S, 20.40. Found: C, 57.27; H, 4.47; N, 17.78; S, 20.36.

4-Allyl-3-(4-Methyl-2-p-tolylthiazol-5-yl)-1H-1,2,4-triazol-5(4H)-thione (6h). Yield 1.1 g, 3.3 mmol, (94%), mp 185–186°C; IR (KBr): v 1279 (C S), 1522 (C N), 1540 (C N), 3187 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.37 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 4.66 (m, 2H, CH_2), 4.86–5.17 (dd, 2H, CH_2), 5.87 (m, 1H, CH), 7.34 (d, 2H, J = 8 Hz, Ar), 7.86 (d, 2H, J = 9 Hz, Ar), 14.26 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ 16.97 (Th CH_3), 21.48 (Ar CH_3),

46.27 (CH_2), 113.9 (CH_2), 117.7 (C), 126.7 (2CH), 129.9 (2CH), 130.4 (C), 131.89 (CH), 141.6 (C), 144.5 (C), 156.6 (C), 167.9 (C), 168.67 (C S) ppm; MS: *m/z* (%) 329 (M + 1, 100). Anal. Calcd. for $C_{16}H_{16}N_4S_2$: C, 58.51; H, 4.91; N, 17.06; S, 19.52. Found: C, 58.49; H, 4.90; N, 17.01; S, 19.49.

4-Allyl-3-(2-(4-bromophenyl)-4-methylthiazol-5-yl)-1H-1,2,4-triazol-5(4H)-thione (6i). Yield 1.34 g, 3.4 mmol, (98%), mp 259–260°C; IR (KBr): v 1286 (C S), 1533 (C N), 1558 (C N), 3108 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.7 (s, 3H, CH_3), 4.13 (m, 2H, CH_2), 5.05–5.17 (dd, 2H, CH_2), 5.86 (m, 1H, CH), 7.66 (d, 2H, J = 9 Hz, Ar), 7.71 (d, 2H, J = 9 Hz, Ar), 14.4 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ 17.4 (Th CH_3), 46.7 (CH_2), 114 (CH_2), 116.7 (C), 128.9 (2CH), 131.2 (2CH), 131.9 (CH), 133.2 (C), 143.9 (C), 144.9 (C), 156.8 (C), 164.7 (C), 168.7 (C S) ppm; MS: *m/z* (%) 393 (M^+, 100). Anal. Calcd. for $C_{15}H_{13}BrN_4S_2$: C, 45.80; H, 3.33; N, 14.24; S, 16.30. Found: C, 45.77; H, 3.32; N, 14.22; S, 16.27.

4-Phenyl-3-(pyridin-4-yl)-1H-1,2,4-triazol-5(4H)-thione (6j). Yield 0.66 g, 2.6 mmol (74.6%); mp 279–280°C (Ref. [30] 122° C); MS: *m/z* (%) = 254 (M^+, 100). Anal. Calcd. for $C_{13}H_{10}N_4S$: C, 61.39; H, 3.96; N, 22.03; S, 12.61. Found: C, 61.30; H, 3.65; N, 21.86; S, 12.51.

4-Methyl-3-(pyridin-4-yl)-1H-1,2,4-triazol-5(4H)-thione (6k). Yield 0.50 g, 2.62 mmol, (75%); mp 283–284°C; IR (KBr): v 1226 (C S), 1571 (C N), 1609 (C N), 3271 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.45 (s, 3H, NCH_3), 7.46 (dd, 2H, J = 5 Hz, 3-Py), 8.64 (dd, 2H, J = 5 Hz, 2-Py), 14.16 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ 31.64 (NCH_3), 123.1 (2CH), 133.6 (C), 149.5 (C N), 151.2 (2CH), 168.8 (C S) ppm; MS: *m/z* (%) 192 (M^+, 100). Anal. Calcd. for $C_8H_8N_4S$: C, 49.98; H, 4.09; N, 29.14; S, 16.68. Found: C, 50.11; H, 3.93; N, 29.48; S, 16.41.

4-Allyl-3-(pyridin-4-yl)-1H-1,2,4-triazol-5(4H)-thione (6l). Yield 0.595 g, 2.73 mmol (78%); mp 210–212°C; IR (KBr): v 1262 (C S), 1571 (C N), 1614 (C N), 3337 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 4.8 (d, 2H, CH_2), 5.01 (dd, 2H, CH_2), 5.86 (m, 2H, CH), 7.66 (dd, 2H, J = 5 Hz, 3-Py), 8.77 (dd, 2H, J = 5 Hz, 2-Py), 14.26 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ 46.7 (CH_2), 117.7 (CH_2), 122.6 (2CH), 130.4 (CH), 133.8 (C), 149.7 (C N), 150.8 (2CH), 168.6 (C S) ppm; MS: *m/z* (%) 218 (M^+, 25). Anal. Calcd. for $C_{10}H_{10}N_4S$: C, 55.02; H, 4.62; N, 25.67; S, 14.69. Found: C, 55.05; H, 4.34; N, 25.94; S, 14.47.

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