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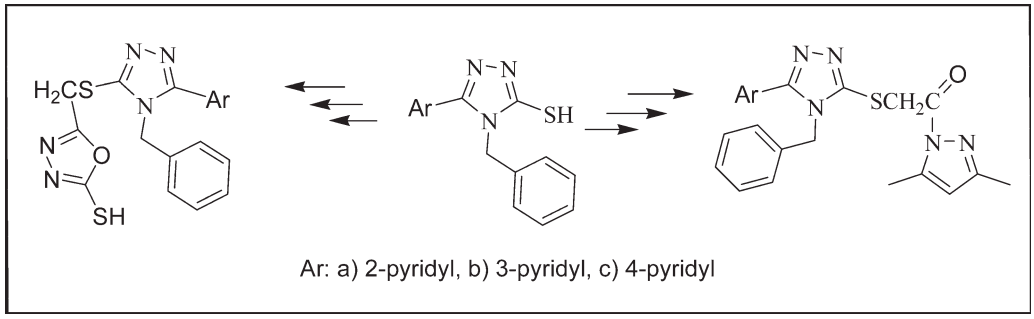

Several derivatives of substituted 1,2,4-triazole bearing the pyrazole (or oxadiazole) ring were synthesized *via* the reaction of 2,4-dihydro-4-benzyl-5-(isomeric pyridyl)-3H-1,2,4-triazole-3-thione **1a–c** with ethyl chloroacetate, hydrazine hydrate, and acetyl acetone (or CS_2/KOH) in absolute ethanol. The intermediate then undergoes an intramolecular cyclization in acidic medium. The newly synthesized compounds **4a–c** to **7a–c** were characterized using IR, NMR, and MS Spectroscopy. Some of the synthesized compounds **4,5,7a–c** were evaluated for their antibacterial and antifungal activities. Most of these compounds indicated activity comparable to Gentamycine. Also some of them are more active than Tolnaftate, a known antifungal drug.

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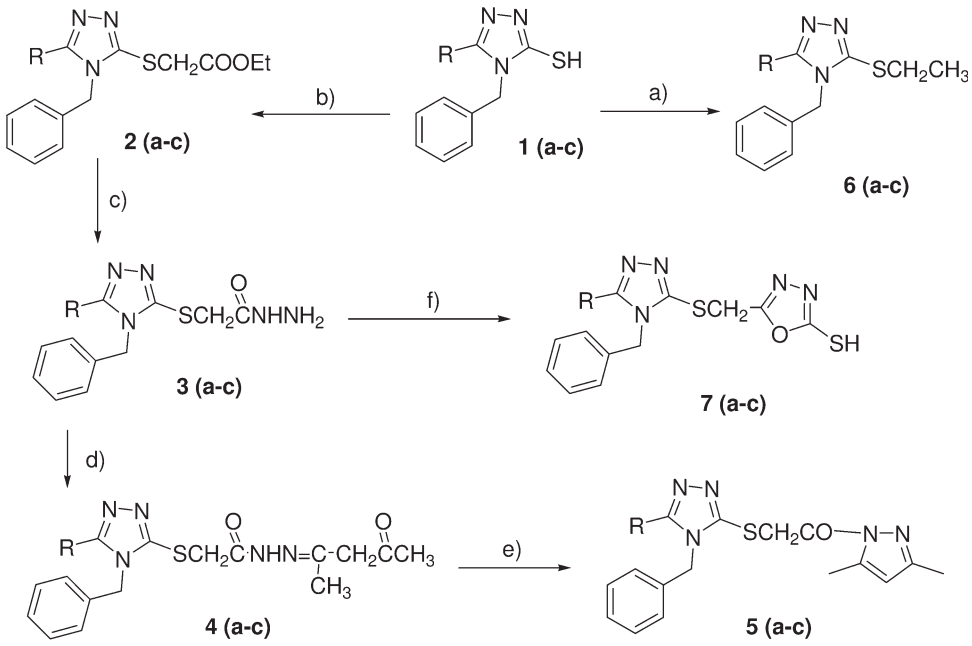
INTRODUCTION

A variety of 1,2,4-triazole derivatives have been described for their biological activities including antidepressive, anti-inflammatory, antibacterial, antifungal, and insecticidal properties [1–4]. Oxadiazoles have been reported to show a broad spectrum of biological activities [5–7] such as anti-inflammatory, fungicidal, and herbicidal activities [8–12]. Pyrazole derivatives are also used as important reagents in organic synthesis and have found applications as pharmaceutical, multidrug resistance (MDR) modulators, herbicide, herbicide fungicide, insecticide, and dyestuffs [13–17]. Some of the reported compounds bearing a pyrazole ring are used as analgesic, anti-inflammatory [18], and anticancer agents [19], which are selective as *in vitro* inhibitors of human T and B leukemias [20]. Likewise, the 1,2,4-triazole ring is associated with a broad spectrum of biological activities e.g., fungicidal [21] and hypoglycemic activity [22]. It is also known that if an active nucleus is linked to another nucleus, the resulting molecule may possess greater potential for biological activity. A triazole-pyrazole or triazole-oxadiazole system may be viewed as a cyclic analogue of two very important components. In view of this report and also as a continuation of our work on the synthesis of heterocyclic compounds with biological interest [23,24], the synthesis of new 1,2,4-triazole ring bearing 1,3,4-oxadiazoles or pyrazoles in a single molecular framework is reported.

RESULTS AND DISCUSSION

The synthetic routes for the preparation of the target compounds are outlined in Scheme 1. 2,4-Dihydro-4-benzyl-5-(isomeric pyridyl)-3H-1,2,4-triazole-3-thiones **1a–c** were synthesized according to the previously reported procedure [25]. The esters **2a–c** and acid hydrazides **3a–c** were also prepared from triazole thiones **1a–c** as previously reported [26]. The hydrazones **4a–c** were synthesized by reaction of mercaptoacetic acid hydrazides **3a–c** with acetylacetone in absolute ethanol. One of the substituted hydrazones **4b**, which was synthesized as an intermediate for preparation of substituted pyrazoles, was characterized using FTIR, ^{1}H NMR and Mass spectral data. In the ^{1}H NMR spectrum of **4b**, the

Scheme 1. Conditions: (a) Et-I, 96% EtOH, KOH, 12–15 h, reflux. (b) $ClCH_2CO_2Et$, NaOH, EtOH, 4–10 h, reflux. (c) 100% N_2H_5OH, EtOH, 4.5–7 h, reflux. (d) acetyl acetone, EtOH, 1.5–5 h, reflux. (e) EtOH, 0.1 mL 37% HCl, 22.5–30 h, reflux. (f) 1. CS2, KOH, EtOH, 6–14 h, reflux, 2. HCl.



R: **a**) 2-pyridyl, **b**) 3-pyridyl, **c**) 4-pyridyl

two singlets were observed due to the resonance of the two methyl groups which were observed at 2.51 and 2.54 ppm. ^{13}C NMR spectra of compounds **4a** and **4c**, showed 19 and 17 peaks, respectively, for aliphatic and aromatic carbons in the expected region, which are consistent with their structures. The resonance of all other protons appeared in the expected region of spectrum. The mass spectra of this compound exhibited a low molecular radical cation peak at *m/z* 422 (18%). Elimination of the $O{=}CNHN{=}C(CH_3)CH_2(CH_3)C{=}O$ radical gave a cation as a base peak at *m/z* 281 (100%).

The intramolecular dehydrative cyclization of hydrazone derivatives of 1,2,4-triazoles **4a–c** in absolute ethanol and acidic medium as catalyst afforded **5a–c**. In the IR spectra of these compounds, a prominent peak was observed for the carbonyl absorption at 1734–1743 cm^{-1}. ^1H NMR spectra of **5a–c** exhibited two singlets at 2.3–3.6 ppm related to the resonance of two methyl groups substituted on the pyrazole ring. All other required peaks appeared in the exhibited region of the spectrum.

However, the proton on position 4 of the pyrazole ring was not observed in the spectrum of all synthesized pyrazoles, probably due to the effect of exchange of this acidic proton of the pyrazole ring with deuterium of small amounts of D_2O, which is present in DMSO-d_6, which was used as a solvent [27].

In the mass spectra of **5a–c**, the molecular radical cation was observed at *m/z* 404 in low intensities (5–8%). Although, the molecular radical cation of compounds was observed in low intensities, the mass spectral fragmentation patterns are in support of the novel synthesized compounds. Further evidence for the formation of the pyrazole ring was obtained from the ^{13}C NMR spectra of compound **5c**. ^{13}C NMR of compound **5c** exhibited 15 peaks for aliphatic and aromatic carbons in the expected region of the spectrum and the carbonyl carbon of this compound was observed at 169 ppm.

Ethyl sulfide derivatives of triazoles **6a–c** were obtained by reaction of respective triazole with ethyl iodides in alkaline ethanol. The IR spectra of the synthesized compounds showed the elimination of bands in the region 2500–2658 cm^{-1} due to the thiol group. 1,3,4-oxadiazole derivatives of the triazoles **7a–c** were obtained by reaction of an alkaline solution of **3a–c** in ethanol with carbon disulfide. In the IR spectra of the synthesized compounds, the absence of a carbonyl group is in support of the expected reaction. The reflux time, melting point, yield and solvent for recrystallization of all synthesized compounds are tabulated in Table 1.

Antimicrobial activities. Applying the agar plate diffusion technique [6], some of newly synthesized compounds were screened *in vitro* for antimicrobial activities against *Staphylococcus aureus* PTCC-1337 (Gram-positive), *Escherichia coli* PTCC-1338 (Gram-negative)

Table 1

Physicochemical data of the novel compounds (**4-7 a–c**).

No.	R	Compound	M.p./°C	Time/h	Yield/%
1	2-pyridyl	**4a**	192–193	1.5	67
2	3-pyridyl	**4b**	201.5–203	5	66.5
3	4-pyridyl	**4c**[a]	221	–	63
4	2-pyridyl	**5a**	97	22.5	68
5	3-pyridyl	**5b**	121–122	30	89
6	4-pyridyl	**5c**	171.5–172	23	76
7	2-pyridyl	**6a**	103–104	12	75
8	3-pyridyl	**6b**	81–82	15	65
9	4-pyridyl	**6c**	70–71	14	70
10	2-pyridyl	**7a**	193–194	6	66
11	3-pyridyl	**7b**	191–191.5	8	58
12	4-pyridyl	**7c**	221–222	14	67

[a] In this case, after 40 s stirring the product was formed.

bacteria. The compounds were also tested against *Candida albicans* PTCC-5027 fungi (Table 2). The compounds were diluted in DMSO for bioassay. The solvent control was included, although no antibacterial and antifungal activity has been noted. Gentamycine and Tolnaftate as drug references were included for comparison with compounds (**4, 5, 7a–c**). All samples were tested in triplicate, and the average results were recorded. In this method, a standard 8-mm diameter sterile filter paper disk impregnated with the test compound (500 μg) was placed on an agar plate seeded with the microorganism (1.5×10^8 CFU mL^{-1}). The plates were incubated at 5°C for 11 h to permit good diffusion and then incubated at 37°C for 24 h. Fungi were incubated at 25–28°C for 48 h. The zone of inhibition of bacteria and fungi growth around the disk was observed and recorded in mm. The screening results are given in Table 2.

The screening results indicate that all compounds (except for **5a**) are active against *E. Coli* and *S. aureus*. Compound **7c** shows the highest inhibitory effect against all organism tests. Oxadiazole **7c** also shows the highest inhibition zone diameter against *C. albicans* (16 mm) compared with Tolnaftate (10 mm), which was used as a standard in the same procedure (500 μg $disk^{-1}$). Compounds **4a, 4b, 5b, 7a,** and **7c** were found to be more active against *C. albicans* than Tolnaftate, which is a known antifungal drug. We can also compare the inhibitory effects of compounds **4a–c** with their products, pyrazoles **5a–c**, after cyclization. For instance, after cyclization of **4b** and **4c**, the inhibitory effect of the resulting pyrazoles **5b** and **5c** is essentially the same as before. Interestingly, the inhibitory effect of **4a** completely disappears upon ring formation to **5a**.

In conclusion, we have synthesized some new 1,2,4-triazole rings bearing 1,3,4-oxadiazole or pyrazole in a single molecular framework and also were evaluated the antimicrobial activities of these synthesized bicycles.

EXPERIMENTAL

Melting points were measured in open capillaries tubes and are uncorrected. ^1H and ^{13}C NMR spectral data were obtained using a Bruker 500-MHz FTNMR spectrometer in DMSO-d_6 as a solvent. The IR spectral data were obtained using a Glaxy FTIR 5000 spectrometer with KBr sample disk. The Mass spectra were recorded on a Varian model Mat MS-311 spectrometer at 70 eV. Elemental analyses were performed on a Vario EL III elemental analyzer. The purity of all compounds was confirmed on silica gel coated aluminum plates (Merck). Benzyl isothiocyanate, 4-Benzyl-1-(isomeric pyridoyl) thiosemicarbazides were synthesized as previously reported method [25].

General procedure for the synthesis of 2-{[-4-benzyl-5-(isomeric pyridyl)-4H-1,2,4-triazole-3-ylthio]-N (2) [1-methyl-3-oxobutilidin]} acetohydrazide (4a–c). Compounds **3a–c** (0.4 g, 1 mmol) was dissolved in absolute ethanol (15 mL) and mixed with acetylacetone (0.18 mL, 1.7 mmol). The mixture was refluxed for 1.5–5 h. After cooling, the precipitate was filtered and recrystallized from ethanol to give pure (**4a–c**).

2-{[-4-Benzyl-5-(2-pyridyl)-4H-1,2,4-triazole-3-ylthio]-N(2) [1-methyl-3-oxobutilidin]} acetohydrazine, (4a) IR (KBr): 3331 (N—H), 2953 (C—$H_{aliphatic}$), 1734 (C=O), 1475, 1423, 1389, 1290 (C=N, C=C), 719 (C—S—C) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ_H 1.92 (s, 3H, CH_3C=O), 2.03 (s, 3H, CH_3-C=N), 2.83 (s, 2H, N=C—CH_2), 4.20 (s, 2H, SCH_2), 5.35 (s, 2H, CH_2N), 6.98 (d, J = 7.6 Hz, 2H, phenyl), 7.22–7.33 (m, 3H, phenyl), 7.38 (t, 1H, J = 6.0 Hz, pyridyl), 7.83–8.01 (m, 2H, pyridyl), 8.33 (d, 1H, J = 5.2 Hz, pyridyl), 12.97 (br., 1H, NH); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C 16.3, 27.8, 38.1, 49.0, 51.6, 91.9, 121.2, 124.2, 127.0, 128.5, 128.3, 134.9, 136.9, 148.5, 149.0, 153.1, 155.3, 158.2, 169.3; Anal. Calcd for $C_{21}H_{22}N_6O_2S$: C, 59.70; H, 5.25; N, 19.89; S, 7.59. Found: C, 59.58; H, 5.27; N, 19.86; S, 7.61.

2-{[-4-Benzyl-5-(3-pyridyl)-4H-1,2,4-triazole-3-ylthio]-N(2) [1-methyl-3-oxobutilidin]} acetohydrazine (4b) IR (KBr): 3360 (N—H), 3037 (C—$H_{aromatic}$), 2991 (C—$H_{aliphatic}$), 1709 (C=O), 1611, 1488, 1415, 1294 (C=N, C=C), 723 (C—S—C) cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz): δ_H 2.51 (s, 3H, CH_3C=O), 2.54 (s, 3H, CH_3-C=N), 4.04 (s, 2H, N=C—CH_2),

Table 2

Results of antimicrobial activity using the agar plate diffusion technique[a] (inhibition zone diameter in mm).

Compound	*Escherichia coli*	*Staphylococcus aureus*	*Candida albicans*
4a	11	10	15
4b	11	11	11
4c	12	12	–[b]
5a	–[b]	–[b]	–[b]
5b	10	10	14
5c	10	10	–[b]
7a	10	10	14
7b	11	11	13
7c	18	11	16
Gentamycine[c]	28	33	–[b]
Tolnaftate[c]	–[b]	–[b]	10

[a] The concentration of the tested compounds was 500 μg $disk^{-1}$.
[b] Activity was not observed.
[c] Reference compound.

4.10 (s, 2H, SCH_2), 5.30 (s, 2H, CH_2N), 6.91–7.30 (m, 5H, phenyl), 7.50–8.70 (m, 4H, pyridyl), 12.95 (br., 1H, NH); Ms (*m/z*, %): 422 (M^+, 18), 368 (63), 299 (20), 281 (100), 267 (50), 234 (63), 91 (42). Anal. Calcd. for $C_{21}H_{22}N_6O_2S$: C, 59.70; H, 5.25; N, 19.89; S, 7.59. Found: C, 59.77; H, 5.26; N, 19.85; S, 7.56.

2-{[-4-Benzyl-5-(4-pyridyl)-4H-1,2,4-triazole-3-ylthio]-N(2)[1-methyl-3-oxobutilidin]} acetohydrazin, (4c). IR (KBr): 3317 (NH), 3009 (C—$H_{aromatic}$), 2995 (C—$H_{aliphatic}$), 1718 (C=O), 1618, 1464, 1402, (C=C, C=N), 725 (C—S—C) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ_H 1.85 (s, 3H, CH_3C=O), 2.03 (s, 3H, CH_3-C=N), 3.02 (s, 2H, N=C—CH_2), 4.46 (s, 2H, SCH_2), 5.35 (s, 2H, CH_2N), 7.05 (d, J = 7.0 Hz, 2H, pyridyl), 7.32–7.39 (m, 3H, phenyl), 7.49 (d, J = 5.7 Hz, 2H, pyridyl), 8.68 (d, J = 4.9 Hz, 2H, pyridyl), 12.94 (br., 1H, NH); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C 16.5, 27.2, 37.8, 48.8, 51.9, 92.2, 122.7, 126.4, 128.9, 129.7, 134.9, 135.3, 150.6, 153.5, 154.1, 156.2, 166.4; Anal. Calcd. for $C_{21}H_{22}N_6O_2S$: C, 59.70; H, 5.25; N, 19.89; S, 7.59. Found: C, 59.83; H, 5.24; N, 19.91; S, 7.58.

General procedure for synthesis of 1-[(4-benzyl)-5-(isomeric pyridyl)-4H-1,2,4-triazol-3-ylthiomethyl carboxyl]-3,5-dimethyl-1H-pyrazole, (5a–c). Compounds **4a–c** (0.2 g, 0.47 mmol) was dissolved in absolute ethanol or methanol (25 mL), then treated with HCl (37%, 0.2 mL) and refluxed for 22.5–30 h. The reaction mixture was then cooled and poured in to cold water. The solid product was filtered, washed with water, and recrystallized from ethyl acetate to give pure **5a–c.** The reaction progress was monitored by TLC (ethyl acetate/methanol, 5:6, R_f: 0.8).

1-[(4-Benzyl)-5-(2-pyridyl)-4H-1,2,4-triazol-3-ylthiomethyl-carboxyl]-3,5-dimethyl-1H-pyrazole (5a). IR (KBr): 3047 (C—$H_{aromatic}$), 2999 (C—$H_{aliphatic}$), 1740 (C=O), 1589, 1469, 1387, 1303 (C=N, C=C), 711 (C—S—C) cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz): δ_H 2.38 (s, 6H, $2CH_3$ of pyrazole), 4.10 (s, 2H, SCH_2), 5.85 (s, 2H, CH_2N), 7.12 (d, 2H, J = 7.7 Hz, phenyl), 7.26 (m, 3H, phenyl), 7.49 (t, 1H, J = 6.1 Hz, pyridyl), 7.96 (t, 1H, J = 7.8 Hz, pyridyl), 8.13 (d, 1H, J = 8.0 Hz, pyridyl), 8.65 (d, 1H, J = 4.3 Hz, pyridyl); Ms (*m/z*, %): 404 (M^+, 6), 353 (20), 340 (22), 325 (100), 282 (21), 267 (27), 235 (42). Anal. Calcd. for $C_{21}H_{20}N_6OS$: C, 62.36; H, 4.98; N, 20.78; S, 7.93. Found: C, 62.19; H, 4.96; N, 20.82; S, 7.91.

1-[(4-Benzyl)-5-(3-pyridyl)-4H-1,2,4-triazol-3-ylthiomethyl-carboxyl]-3,5-dimethyl-1H-pyrazole (5b). IR (KBr): 3025 (C—$H_{aromatic}$), 2892 (C—$H_{aliphatic}$), 1734 (C=O), 1604, 1450,1303, 1164 (C=N, C=C), 709 (C—S—C) cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz): δ_H 2.30 (s, 6H, $2CH_3$ of pyrazole), 4.20 (s, 2H, SCH_2), 5.30 (s, 2H, CH_2N), 6.30 (s, 1H, CH of pyrazole), 7.00 (d, 2H, J = 5.1 Hz, phenyl), 7.30 (m, 3H, phenyl), 7.67 (t, 1H, J = 5.2 Hz, pyridyl), 8.18 (d, 1H, J = 7.9 Hz, pyridyl), 8.77 (d, 1H, J = 5.0 Hz, pyridyl) and 8.85 (s, 1H, pyridyl); Ms (*m/z*, %): 404 (M^+, 5), 340 (64), 309 (14), 281 (22), 267 (13), 94 (100), 95 (85), 91 (84). Anal. Cald. for $C_{21}H_{20}N_6OS$: C, 62.36; H, 4.98; N, 20.78; S, 7.93. Found: C, 62.23; H, 4.94; N, 20.69; S, 7.96.

1-[(4-Benzyl)-5-(4-pyridyl)-4H-1,2,4-triazol-3-ylthiomethyl-carboxyl]-3,5-dimethyl-1H-pyrazole (5c). IR (KBr): 3084 (C—$H_{aromatic}$), 2964 (C—$H_{aliphatic}$), 1743 (C=O), 1635, 1496, 1379, 1165 (C=N, C=C), 740 (C—S—C) cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz): δ_H 2.33 (s, 6H, $2CH_3$ of pyrazole), 4.20 (s, 2H, SCH_2), 5.41 (s, 2H, CH_2N), 7.05 (d, 2H, J = 7.5 Hz, phenyl), 7.34 (m, 3H, phenyl), 7.91 (d, 2H, J = 5.0 Hz, pyridyl), 8.83 (d, 2H, J = 6.1 Hz, pyridyl); ^{13}C NMR (DMSO-d_6, 125 MHz): δ_C 34.9, 48.4, 53.4 ($C_{aliphatic}$), 103.8, 120.2, 124.9, 127.2, 129.0, 129.8, 135.4, 136.1, 140.5, 145.7, 152.9, 154.5 ($C_{aromatic}$), 169.0 (—C=O); Ms (*m/z*, %): 404 (M^+, 8), 353 (21), 340 (100), 325 (8), 281 (56), 267 (50), 235 (15). Anal. Calcd. for $C_{21}H_{20}N_6OS$: C, 62.36; H, 4.98; N, 20.78; S, 7.93. Found: C, 62.41; H, 5.01; N, 20.72; S, 7.90.

General procedure for synthesis of 4-Benzyl-5-(isomeric pyridyl)-4H-1,2,4-triazol-3- ylethyl sulfides (6a–c). A solution of **1a–c** (0.2 g, 70 mmol) in alkaline ethanol (0.04 g, 70 mmol KOH in 25 mL ethanol 95%) was mixed with ethyl iodide (0.057 mL, 70 mmol) refluxed for 12–15 h. After cooling the reaction mixture was poured in crushed ice**.** The precipitate was separated by filtration, which then recrystallized from ethanol and water to give the pure product. The reaction progress was monitored by TLC (ethyl acetate/n-hexane, 8:5, R_f: 0.5).

4-Benzyl-5-(2-pyridyl)-4H-1,2,4-triazol-3-ylethyl sulfides (6a). IR (KBr): 3080 (C—$H_{aromatic}$), 2972 (C—$H_{aliphatic}$), 1585, 1457, 1400 (C=N, C=C), 725 (C—S—C) cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz): δ_H 1.30 (t, 3H, J = 7.3, CH_3), 3.10 (q, 2H, J = 7.3, CH_2), 5.80 (s, 2H, NCH_2), 7.12–7.31(m, 5H, phenyl), 7.49–8.66 (m, 4H, pyridyl); Ms (*m/z*, %): 296 (M^+, 8), 297 (65), 235 (43), 213 (100), 184 (43), 91 (15). Anal. Calcd. for $C_{16}H_{16}N_4S$: C, 64.84; H, 5.44; N, 18.90; S, 10.82. Found: C, 64.61; H, 5.51; N, 18.83; S, 10.79.

4-Benzyl-5-(3-pyridyl)-4H-1,2,4-triazol-3-ylethyl sulfides (6b). IR (KBr): 3020 (C—$H_{aromatic}$), 2982 (C—$H_{aliphatic}$), 1588, 1389, 1346 (C=N, C=C), 705 (C—S—C) cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz): δ_H 1.30 (t, 3H, J = 7.3, CH_3), 3.20 (q, 2H, J = 7.3, CH_2), 5.30 (s, 2H, CH_2), 6.94–7.31 (m, 5H, phenyl), 7.52–8.75 (m, 4H, pyridyl); Ms (*m/z*, %): 296 (M^+, 12), 297 (52), 235 (37), 213 (100), 184 (48), 91 (32). Anal. Calcd. for $C_{16}H_{16}N_4S$: C, 64.84; H, 5.44; N, 18.90; S, 10.82. Found: C, 65.05; H, 5.47; N, 18.82; S, 10.75.

4-Benzyl-5-(4-pyridyl)-4H-1,2,4-triazol-3-ylethyl sulfides (6c). IR (KBr): 3040 (C—$H_{aromatic}$), 2990 (C—$H_{aliphatic}$), 1606, 1429, 1369, 1209 (C=N, C=C), 736 (C—S—C) cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz): δ_H 1.30 (t, 3H, J = 7.2 CH_3), 3.10 (q, 2H, J = 7.2, CH_2), 5.30 (s, 2H, CH_2), 6.96–7.34 (m, 5H, phenyl), 7.60–8.69 (m, 4H, pyridyl); Ms (*m/z*, %): 296 (M^+, 17), 297 (62), 235 (48), 213 (100), 184 (31), 9 (24). Anal. Calcd. for $C_{16}H_{16}N_4S$: C, 64.84; H, 5.44; N, 18.90; S, 10.82. Found: C, 64.81; H, 5.45; N, 18.93; S, 10.79.

General procedure for synthesis of 5-[4-benzyl-5-(isomeric pyridyl)-1,2,4-triazole-3-ylthiomethyl] oxadiazole-2(3H)-thione (7a–c). Compounds, **3a–c** (0.2 g, 0.58 mmol) were dissolved in a solution of KOH in ethanol (1.6 mmol in 5 mL absolute ethanol). The solution of carbon disulfide (1.16 mL, 19 mmol) in absolute ethanol (15 mL) was added, and the reaction mixture refluxed for 6–14 h. The reaction progress was monitored by TLC (ethyl acetate/methanol, 1:1, R_f: 0.5). The mixture was cooled to room temperature and diluted with water (5 mL). Acidification with dilute hydrochloric acid gave a white solid, which then filtered washed with water and recrystallized from AcOH / H_2O to give **pure 7a**, **7b** and methanol to give **7c**.

5-[4-Benzyl-5-(2-pyridyl)-1,2,4-triazole-3-ylthiomethyl]oxadiazole-2(3H)-thione (7a). IR (KBr): 3311 (NH), 2935 (C—$H_{aliphatic}$), 2520–2610 (SH), 1734 (C=N) of oxadiazole, 1479, 1432, 1377, 1352 (C=N, C=C), 727 (C—S—C) cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz): δ_H 4.00 (s, 2H, SCH_2), 5.80

(s, 2H, CH_2N), 7.12–7.31 (m, 5H, phenyl), 7.48–8.66 (m, 4H, pyridyl), 13.00 (br., 1H, NH); Ms (*m*/*z*, %): 382 (M^+, 13), 325 (60), 281 (22), 267 (9), 235 (43), 91 (100). Anal. Calcd. for $C_{17}H_{14}N_6OS_2$: C, 53.39; H, 3.69; N, 21.97; S, 16.77. Found: C, 53.25; H, 3.70; N, 22.04; S, 16.74.

5-[4-Benzyl-5-(3-pyridyl)-1,2,4-triazole-3-ylthiomethyl][oxadiazole-2(3H)-thione (7b). IR (KBr): 3020 (C—$H_{aromatic}$), 2982 (C—$H_{aliphatic}$), 1707 (C=N) of oxadiazole ring, 1604, 1473, 1415 (C=N, C=C), 1294 (C=S), 721 (C—S—C) cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz): δ_H 4.10 (s, 2H, SCH_2), 5.30 (s, 2H, CH_2N), 6.99–7.31 (m, 5H, phenyl), 7.52–8.77 (m, 4H, pyridyl), 13.00 (br., H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz): δ_C 35.6, 48.3 ($C_{aliphatic}$), 124.1, 124.6, 127.1, 128.8, 129.7, 135.0 136.0, 149.3, 151.2, 151.8, 152.4, 153.9, ($C_{aromatic}$), 170.2 (C=S); Ms (*m*/*z*, %): 382 (M^+, 25), 325 (15), 281 (88), 280 (100), 267 (44), 235 (21), 91 (50). Anal. Calcd. for $C_{17}H_{14}N_6OS_2$: C, 53.39; H, 3.69; N, 21.97; S, 16.77. Found: C, 53.51; H, 3.70; N, 21.89; S, 16.75.

5-[4-Benzyl-5-(4-pyridyl)-1,2,4-triazole-3-ylthiomethyl]oxadiazole-2(3H)-thione (7c). IR (KBr): 3294 (NH), 3037 (C—$H_{aromatic}$), 2982 (C—$H_{aliphatic}$), 1722 (C=N) of oxadiazole, 1618, 1464, 1394 (C=N, C=C), 1215 (C=S), 725 (C—S—C) cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz): δ_H 4.10 (s, 2H, SCH_2), 5.30 (s, 2H, CH_2N), 7.01–7.34 (m, 5H, phenyl), 7.54–7.69 (m, 4H, pyridyl), 13.10 (br., 1H, NH); Ms (*m*/*z*, %): 382 (M^+, 4), 325 (7), 281 (100), 267 (18), 91 (32). Anal. Calcd. for $C_{17}H_{14}N_6OS_2$: C, 53.39; H, 3.69; N, 21.97; S, 16.77. Found: C, 53.55; H, 3.68; N, 21.96; S, 16.81.

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REFERENCES AND NOTES

[1] Misra, U.; Hitkari, A.; Saxena, A., Gurtu, S.; Shanker, K. Eur J Med Chem 1996, 31, 629.

[2] Goswami, B. N.; Kataky, C. J. S.; Baruah, J. N. J Heterocyclic Chem 1984, 21, 1225.

[3] Luo, Y. P.; Lin, L. L.; Yang, G. F. J Heterocyclic Chem 2007, 44, 937.

[4] Chen, Q.; Jiang, L. L.; Chen, C. N.; Yang, G. F. J Heterocyclic Chem 2009, 46, 139.

[5] Gogoi, P. C.; Kataky, J. Indian J Chem 1990, 29B, 1159.

[6] El-masry, A. H.; Fahmy, H. H.; Abdelwahed, S. H. A. Molecules 2000, 5, 1429.

[7] Maslat, A. O.; Abussaud, M.; Tashtoush, H.; Al-Talib, M. Pol J Phrmacol 2002, 54, 55.

[8] Omar, F. A.; Mahfouz, N. M.; Rahman, M. A. Eur J Med Chem 1996, 31, 819.

[9] Li, Y.; Liu, J.; Zhang, H.; Yanga, X.; Liub, Z. Bioorg Med Chem Lett 2006, 16, 2278.

[10] Chen, Q.; Zhu, X. L.; Jiang, L. L.; Liu, Z. M.; Yang, G. F. Eur J Med Chem 2008, 43, 595.

[11] Chen, Q.; Liu, Z. M.; Chen, C. N.; Jiang, L. L.; Yang, G. F. Chem Biodivers 2009, 6, 1254.

[12] Liu, Z.; Yang, G.; Qin, X. J Chem Technol Biotechnol 2001, 76, 1154.

[13] Singh, P.; Paula, K.; Holzer, W. Bioorg Med Chem 2006, 14, 5061.

[14] Suzuki, H.; Hanaue, M.; Nishikubo, M. Jpn. Kokai Tokkyo Koho JP03,236,368,1993; Suzuki, H.; Hanaue, M.; Nishikubo, M. Chem Abstr 116, 106285.

[15] Ahmad, R.; Zia-Ul-Haq, M.; Jabeen, R.; Duddeck, H. Turk J Chem 1996, 20, 186.

[16] Zhao, P. L.; Wang, L; Xiao-Lei Zhu, X. L.; Huang, X.; Zhan, C. G.; Wu, J. W.; Yang, G. F. J Am Chem Soc 2010, 132, 185.

[17] Zhao, P. L.; Wang, F.; Zhang, M. Z.; Liu, Z. M.; Huang, W.; Yang, G. F. J Agric Food Chem 2008, 56, 10767.

[18] Zaki, M. E. A. Molecules 1998, 3, 71.

[19] Wheate, N. J., Broomhead, J. A.; Collins, J. G.; Day, A. I. Aust J Chem 2001, 54, 141.

[20] Almerico, A. M.; Lauria, A.; Diana, P.; Barraja, P.; Cirrincione, G.; Dattolo, G. Arkivoc 2000, 1, 486.

[21] Yoo, B. R.; Suk, M. Y.; Yu, Y.; Hong, S.; Jung, N. Bull Korean Chem Soc 1998, 19, 358.

[22] Colanceska-Ragenovic, K.; Dimova, V.; Kakurinov, V.; Molnar, D. G.; Buzarovskal, A. Molecules 2001, 6, 815.

[23] Mobinikhaledi, A.; Foroughifar, N.; Alipour Safari, J.; Amini, E. J Heterocycl Chem 2007, 44, 697.

[24] Mobinikhaledi, A.; Foroughifar, N.; Kalhor, M.; Mirabolfathy M. J Heterocycl Chem 2010, 47, 77.

[25] Iqbal, R.; Zamani, K.; Rama, N. H. Turk J Chem 1996, 20, 295.

[26] Zamani, K.; Iqbal, R., Faghihi, K. Orient J Chem 2001, 17, 31.

[27] Wu, E. C.; Vaughan, J. D. J Org Chem 1970, 35, 1146.