

Mehdi Kalhor,^a Akbar Mobinikhaledi,^{b*} Akbar Dadras,^c
and Maryam Tohidpour^d

^aDepartment of Chemistry, Payame Noor University, Qom, Iran

^bDepartment of Chemistry, Arak University, Arak 38156-879, Iran

^cDepartment of Chemistry, Guilan University, Rasht 41335-1914, Iran

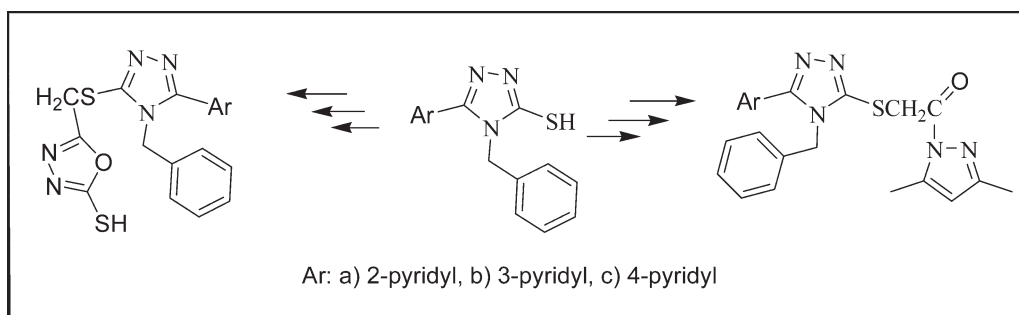
^dDepartment of Microbiology, Islamic Azad University, Shahre Ghods Branch, Tehran, Iran

*E-mail: akbar_mobini@yahoo.com

Received October 15, 2009

DOI 10.1002/jhet.718

Published online 30 June 2011 in Wiley Online Library (wileyonlinelibrary.com).



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 CS₂/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.

J. Heterocyclic Chem., **48**, 1366 (2011)

INTRODUCTION

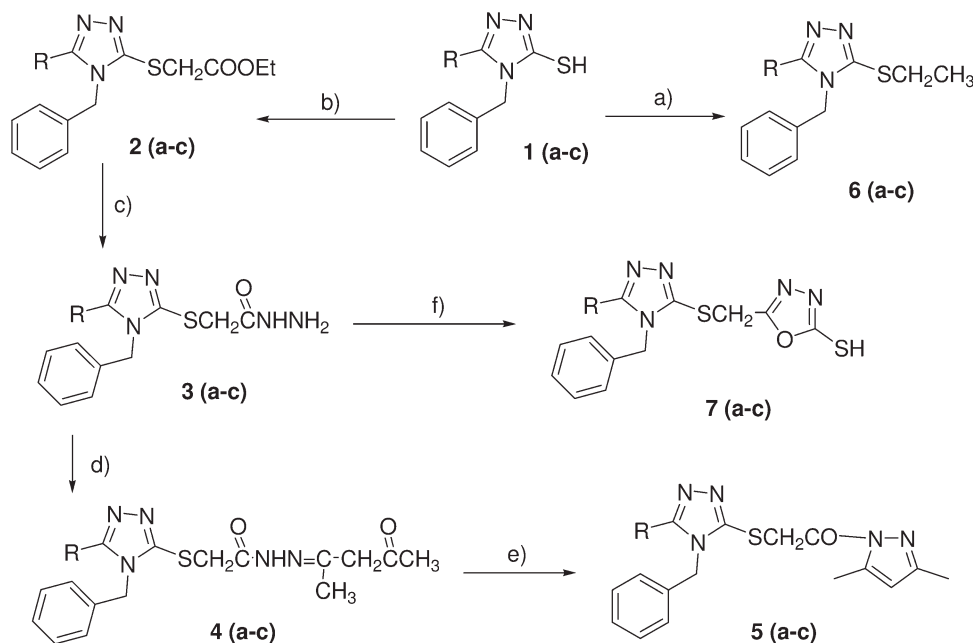
A variety of 1,2,4-triazole derivatives have been described for their biological activities including antidepressive, anti-inflammatory, antibacterial, antifungal, and insecticidal properties [1–4]. Oxadiazoles have been reported to show a broad spectrum of biological activities [5–7] such as anti-inflammatory, 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, ¹H NMR and Mass spectral data. In the ¹H NMR spectrum of **4b**, the

Scheme 1. Conditions: (a) Et-I, 96% EtOH, KOH, 12–15 h, reflux. (b) $\text{ClCH}_2\text{CO}_2\text{Et}$, NaOH, EtOH, 4–10 h, reflux. (c) 100% $\text{N}_2\text{H}_5\text{OH}$, 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. CS_2 , 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 $\text{O}=\text{CNHN}=\text{C}(\text{CH}_3)\text{CH}_2(\text{CH}_3)\text{C}=\text{O}$ 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 $1734\text{--}1743\text{ cm}^{-1}$. ^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 $\text{DMSO-}d_6$, 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 $2500\text{--}2658\text{ cm}^{-1}$ 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 ¹³C 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 Glaxys 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-oxobutylidene]] 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-oxobutylidene]] 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 (CDCl₃, 500 MHz): δ_H 1.92 (s, 3H, CH₃C=O), 2.03 (s, 3H, CH₃–C=N), 2.83 (s, 2H, N=C–CH₂), 4.20 (s, 2H, SCH₂), 5.35 (s, 2H, CH₂N), 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); ¹³C NMR (CDCl₃, 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 C₂₁H₂₂N₆O₂S: 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-oxobutylidene]] 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, CH₃C=O), 2.54 (s, 3H, CH₃–C=N), 4.04 (s, 2H, N=C–CH₂),

Table 2

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

Compound	<i>Escherichia coli</i>	<i>Staphylococcus aureus</i>	<i>Candida albicans</i>
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, SCH₂), 5.30 (s, 2H, CH₂N), 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 C₂₁H₂₂N₆O₂S: 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-oxobutylidene]] 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 (CDCl₃, 500 MHz): δ_H 1.85 (s, 3H, CH₃C=O), 2.03 (s, 3H, CH₃—C=N), 3.02 (s, 2H, N=C—CH₂), 4.46 (s, 2H, SCH₂), 5.35 (s, 2H, CH₂N), 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); ¹³C NMR (CDCl₃, 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 C₂₁H₂₂N₆O₂S: 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, 2CH₃ of pyrazole), 4.10 (s, 2H, SCH₂), 5.85 (s, 2H, CH₂N), 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 C₂₁H₂₀N₆O₃S: 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, 2CH₃ of pyrazole), 4.20 (s, 2H, SCH₂), 5.30 (s, 2H, CH₂N), 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. Calcd. for C₂₁H₂₀N₆O₃S: 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, 2CH₃ of pyrazole), 4.20 (s, 2H, SCH₂), 5.41 (s, 2H, CH₂N), 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); ¹³C 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 C₂₁H₂₀N₆O₃S: 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, CH₃), 3.10 (q, 2H, *J* = 7.3, CH₂), 5.80 (s, 2H, NCH₂), 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 C₁₆H₁₆N₄S: 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, CH₃), 3.20 (q, 2H, *J* = 7.3, CH₂), 5.30 (s, 2H, CH₂), 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 C₁₆H₁₆N₄S: 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 CH₃), 3.10 (q, 2H, *J* = 7.2, CH₂), 5.30 (s, 2H, CH₂), 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 C₁₆H₁₆N₄S: 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 / H₂O 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, SCH₂), 5.80

(s, 2H, CH₂N), 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 C₁₇H₁₄N₆OS₂: 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, SCH₂), 5.30 (s, 2H, CH₂N), 6.99–7.31 (m, 5H, phenyl), 7.52–8.77 (m, 4H, pyridyl), 13.00 (br., 1H, NH); ¹³C 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 C₁₇H₁₄N₆OS₂: 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, SCH₂), 5.30 (s, 2H, CH₂N), 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 C₁₇H₁₄N₆OS₂: 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.

Acknowledgments. We thank the Chemistry Department of Arak University for providing financial support and the Microbiology Department of Islamic Azad University, Shahre Ghods Branch of Tehran for the evaluation of the biological activities.

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.; Katakly, 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.; Katakly, 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 Pharmacol* 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.; Mirabolfa-thy 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.