Preparation and Evaluation of Antibacterial Activity of Some New 1,2,4-Triazole Derivatives

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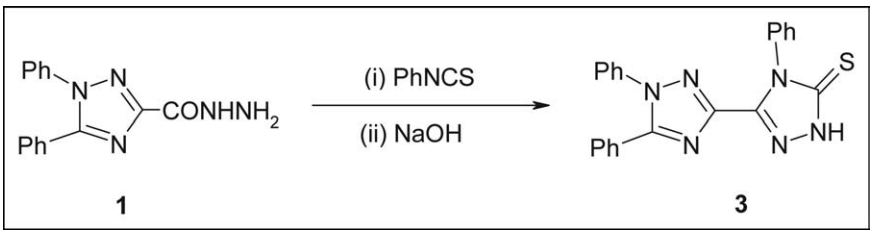

Cyclizations of 1,5-diphenyl[1,2,4]triazole-3-carbohydrazide **1** and the thiosemicarbazide **2** (derived from **1** by addition to phenylisothiocyanate) under various conditions afforded novel biheterocyclic systems. The newly prepared compounds were screened for their antibacterial activity. The results showed that several of these compounds exhibited significant antibacterial activity.

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INTRODUCTION

Many compounds consisting of five-membered heterocyclic rings such as triazoles, oxazdiazoles, and thiadiazoles were synthesized and evaluated for their biological activities [1–5]. During recent years, microorganisms have increased their resistance against commonly used antibiotics. Therefore, it was crucial to develop new antimicrobial and antiviral compounds [6]. Studies on 1,2,4-triazole compounds have a wide range in the area of pharmacology [7–14]. 4-Thiazolidinones are known to possess antibacterial [15–20], antifungal [21], antiviral [22,23], and antituberculosis [24] properties (Fig. 1).

4-Thiazolidinones have a novel mechanism for action that involves the inhibition of bacterial protein synthesis at a very early stage [25,26]. The traditional method for the preparation of thiazolidinones includes the reaction of an aromatic amine with substituted benzaldehyde in the presence of mercaptoacetic acid [26,27]. In addition, the method reported recently for the synthesis of thiazolidinones involved the reaction of thiosemicarbazides with chloroacetic acid [25]. During the recent years, there has been a broad investigation on different classes of thiadiazoles, many of which were found to possess an extensive spectrum of pharmacological activities [28–32]. Also, 1,2-pyrazole derivatives were found to possess various biological activities [33,34].

The cyclization of relatively small and linear molecules is one of the most common methods leading to the formation of heterocyclic compounds. For example, compounds that contain a thiosemicarbazide structure can be considered as suitable precursors for this purpose [34–37]. The NH_2 group of the hydrazide structure behaves as a good nucleophile in most reactions leading to formation of new heterocyclic rings such as 1,2,4-triazoles, 1,3,4-thiadiazoles [37–39].

In view of these facts, hereby we report the preparation of new 1,2,4-triazoles, connected to another heterocyclic ring such as 1,2,4-triazole, 1,3,4-thiadiazole, and 1,3-thiazolidin-4-one rings.

RESULTS AND DISCUSSION

The structure of the prepared compounds was elucidated using IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopic methods besides elemental analyses. The pathways leading to the products obtained have been depicted in Schemes 1 and 2. The key intermediate in this study is the 1,5-diphenyl-1*H*-[1,2,4]triazole-3-carboxylic acid hydrazide **1**, which was prepared according to a previously described procedure [40].

Acid hydrazide **1** and thiosemicarbazide **2** are of considerable interest as building blocks for nitrogen and/or sulfur containing heterocyclic systems, which might show biological activities. Therefore, our attempts are to prepare new five-membered heterocycles of expected biological activities utilizing compounds **1** and **2** as starting material.

When compound **1** was refluxed with phenylisothiocyanate, the expected thiosemicarbazide **2** was obtained in good yield. In the IR spectrum of compound **2**, the hydrazone NH stretching frequencies were observed at 3291, 3198, and 3146 cm^{-1}. The absorption band at

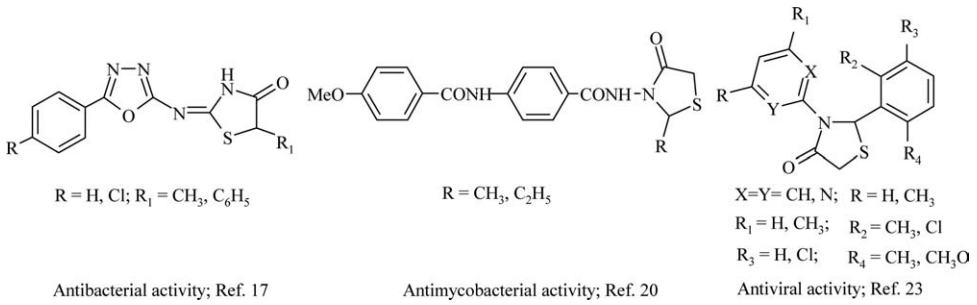
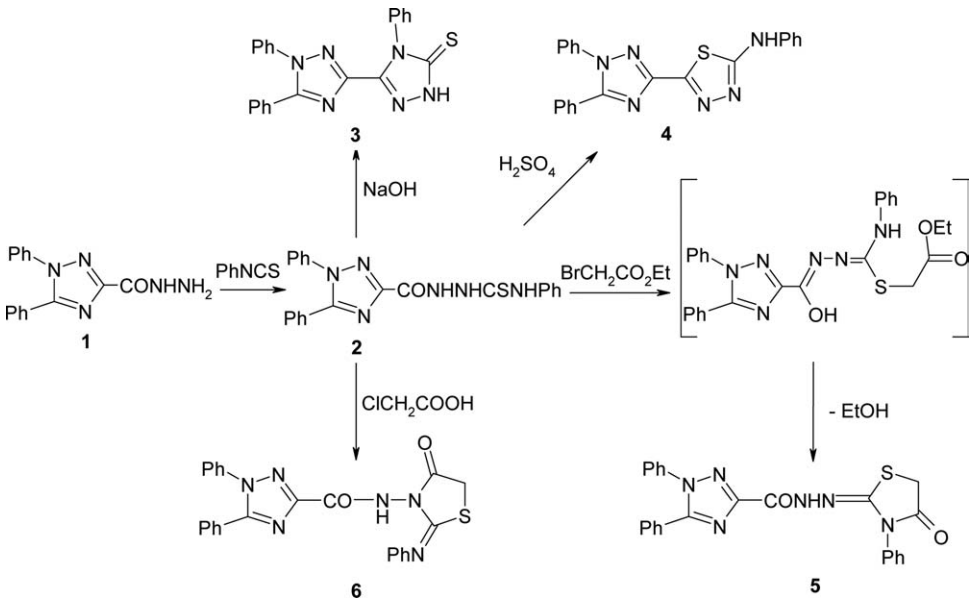


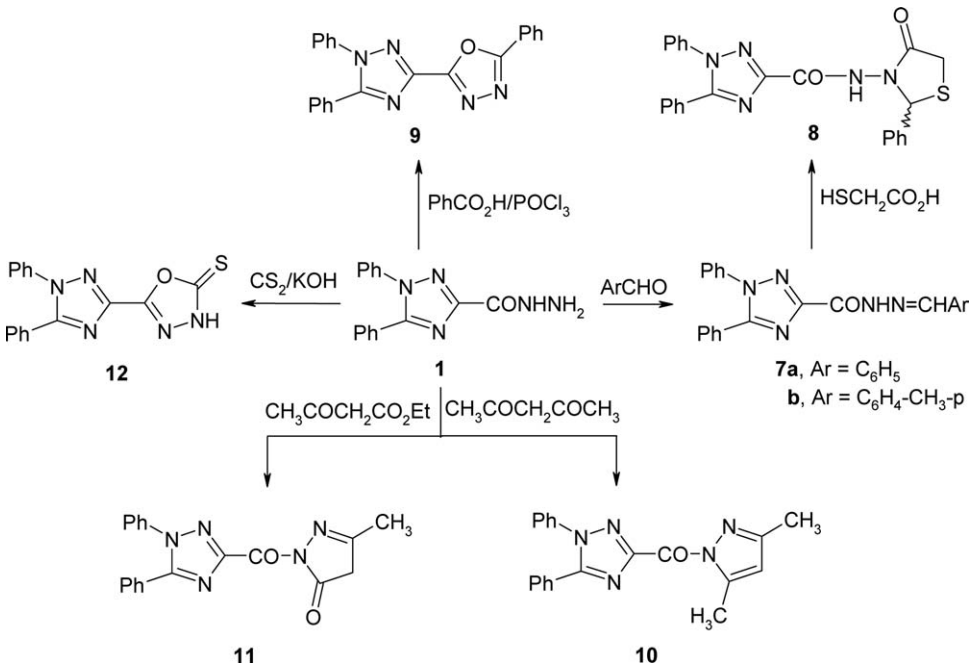
Figure 1

1666 cm^{-1} is due to the presence of C=O stretch. The C=S stretching frequency was observed at 1373 cm^{-1}. Further evidence for the formation of compound **2** was obtained by recording its mass spectrum. The mass spectrum of **2** showed the molecular ion at *m*/*z* 414 corresponding to $C_{22}H_{18}N_6OS$ and the base peak at *m*/*z* 220. Alkaline cyclization of the thiosemicarbazide **2** using 2*N* sodium hydroxide solution afforded the corresponding 4,1′,5′-triphenyl-1,4-dihydro-1′*H*-[3,3′]bi[1,2,4] triazolyl]-5-thione **3**. This reaction began with nucleophilic attack of thiosemicarbazide N-5 to carbonyl group in the side chain of compound **2**. The structure of compound **3** was confirmed on the basis of elemental analysis, IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopic methods. It is interesting to note that compound **3** is present in solid state in thionic form, C=S, as indicated by its IR spectrum, which showed the absence of absorption in the region of 2500–2660 cm^{-1} cited for SH group [41] and the presence of maximum at 1455 cm^{-1} characteristic for C=S group. Moreover, in the ^{1}H NMR spectrum of compound **3**, NH was observed as singlet at 9.32 ppm, therefore it was proved that compound **3** was found in thionic form also in DMSO. Furthermore, reacting thiosemicarbazide **2** with cold concentrated sulfuric acid resulted in the formation of the corresponding N-phenyl[5-(1,5-diphenyl-1*H*-[1,2,4]triazol-3-yl)-[1,3,4]thiadiazol-2-yl]-amine **4**. The reaction involved the nucleophilic attack of the C=S sulfur atom on the carbonyl C of compound **2**. In the ^{1}H NMR spectrum of compound **4** the presence of only one singlet for NH group integrated for one proton confirming the cyclization at the side chain of triazole ring in compound **2** to afford the thiadiazole **4**. Also, the mass spectrum of compound **4** gave molecular ion peak in agreement with its molecular formula. The thiazolidinone derivative **5** was obtained from the treatment of thiosemicarbazide **2** with ethyl bromoacetate in the presence of anhydrous sodium acetate in absolute ethanol. The first

Scheme 1



Scheme 2



step of this reaction is thought to be an S-alkylation of **2**. The second step is a release of ethanol to give thiazolidinone **5**, the IR spectrum of which showed the lactam C=O stretching band at 1708 cm^{-1}. The mass spectrum was also in agreement with the formation of thiazolidinone ring. In an extension of the above reaction to obtain another thiazolidinone derivative **6**, thiosemicarbazide **2** undergoes a ring closure reaction, on boiling in ethanol with monochloroacetic acid. The structure of compound **6** was elucidated on the basis of IR, ^1H NMR, and mass spectra as well as correct elemental analysis. The IR of **6** exhibited absorption bands at 3212 due to NH group and at 1719, 1665 cm^{-1} because of two carbonyl groups. ^1H NMR of **6** revealed a singlet at 3.62 because of CH_2 of thiazolidinone ring and singlet at 9.01 ppm for NH.

Additionally, the condensation of the acid hydrazide **1** with a variety of aromatic aldehydes in ethanol leading to the formation of compounds **7a**, **b**. Structure elucidation of the Schiff's bases **7a**, **b** was based on microanalysis and spectral data (Tables 1 and 2). 1,5-Diphenyl-1*H*-[1,2,4]triazole-3-carboxylic acid (4-oxo-2-phenyl-thiazolidin-3-yl)-amide **8** was obtained by refluxing the Schiff's base **7a** and thioglycolic acid in dry benzene for 10 h using a Dean-Stark water separator. The thiazolidinone **8** was characterized by IR absorption bands at

Table 1

Analytical data of the new compounds.

Comp. No.	Molecular formula	mp (°C)	Yield (%)	Elemental analyses found (calcd.)			
				%C	%H	%N	%S
2	$C_{22}H_{18}N_6OS$	215	80	63.64 (63.75)	4.57 (4.38)	20.11 (20.28)	7.80 (7.74)
3	$C_{22}H_{16}N_6S$	285	84	66.77 (66.65)	3.86 (4.07)	21.33 (21.20)	7.86 (8.09)
4	$C_{22}H_{16}N_6S$	179	85	66.42 (66.65)	4.24 (4.07)	21.00 (21.20)	8.21 (8.09)
5	$C_{24}H_{18}N_6O_2S$	210	82	63.61 (63.42)	4.24 (3.99)	18.35 (18.49)	7.22 (7.05)
6	$C_{24}H_{18}N_6O_2S$	202	78	63.57 (63.42)	3.78 (3.99)	18.32 (18.49)	7.15 (7.05)
7a	$C_{22}H_{17}N_5O$	175	81	72.12 (71.92)	4.51 (4.66)	19.13 (19.06)	–
7b	$C_{23}H_{19}N_5O$	187	88	72.22 (72.42)	5.00 (5.02)	18.57 (18.36)	–
8	$C_{24}H_{19}N_5O_2S$	220	80	65.55 (65.29)	4.24 (4.34)	15.59 (15.86)	7.33 (7.26)
9	$C_{22}H_{15}N_5O$	195	68	72.47 (72.32)	4.00 (4.14)	18.89 (19.17)	–
10	$C_{20}H_{17}N_5O$	240	75	70.06 (69.96)	4.82 (4.99)	20.11 (20.40)	–
11	$C_{19}H_{15}N_5O_2$	225	82	66.23 (66.08)	4.16 (4.38)	20.03 (20.28)	–
12	$C_{16}H_{11}N_5OS$	165	74	59.63 (59.80)	3.71 (3.45)	21.52 (21.79)	10.14 (9.98)

Table 2

Spectral data for the new compounds.

Comp. No.	Spectral data
2	IR (KBr, cm^{-1}): 3291, 3198, 3146 (NH), 1666 (C=O), 1604 (C=N) and 1373 (C=S). ms: *m/z* (%): 414 (M^+, 15.30).
3	IR (KBr, cm^{-1}): 3129, 1598 (C=N) and 1455 (C=S). ^{1}H NMR (DMSO-d_6, δ ppm): 7.01–7.48 (15H, m, aromatic protons) and 9.32 (1H, s, NH). ^{13}C NMR (DMSO-d_6, δ ppm): arom-C: [123.8 (2CH), 125.7 (4CH), 126.1 (2CH), 128.0 (1CH), 128.8 (6CH), 135.4 (1C), 137.5 (2C)], 154.0 (C5-triazole ring), 157.4 (C3 & C′3-triazole rings), 181.5 (C=S). ms: *m/z* (%): 396 (M^+, 42.10).
4	IR (KBr, cm^{-1}): 3187 (NH) and 1599 (C=N). ^{1}H NMR (DMSO-d_6, δ ppm): 5.10 (1H, s, NH) and 6.91–7.33 (15H, m, aromatic protons) ms: *m/z* (%): 396 (M^+, 13.80).
5	IR (KBr, cm^{-1}): 3330 (NH), 1708 (C=O), 1688 (C=O) and 1612 (C=N). ^{1}H NMR (DMSO-d_6, δ ppm): 3.67 (2H, s, CH_2 of thiazolidinone ring), 7.11–7.42 (15H, m, aromatic protons) and 9.23 (1H, s, NH). ms: *m/z* (%): 454 (M^+, 42.71)
6	IR (KBr, cm^{-1}): 3212 (NH), 1719 (C=O), 1665 (C=O) and 1605 (C=N). ^{1}H NMR (DMSO-d_6, δ ppm): 3.62 (2H, s, CH_2 of thiazolidinone ring), 7.05–7.38 (15H, m, aromatic protons) and 9.01 (1H, s, NH). ms: *m/z* (%): 454 (M^+, 12.80)
7a	IR (KBr, cm^{-1}): 3242 (NH), 1685 (C=O) and 1601 (C=N). ms: *m/z* (%): 367 (M^+, 26.37).
7b	IR (KBr, cm^{-1}): 3222 (NH), 1680 (C=O) and 1589 (C=N). ms: *m/z* (%): 381 (M^+, 37.14).
8	IR (KBr, cm^{-1}): 3251 (NH), 1722 (C=O) and 1704 (C=O). ^{1}H NMR (DMSO-d_6, δ ppm): 3.41 (1H, d, equatorial proton of thiazolidinone at C-5), 3.81 (1H, d, axial proton of thiazolidinone at C-5), 5.68 (1H, s, CH of thiazolidinone at C-2), 7.21–7.35 (15H, m, aromatic protons) and 9.51 (1H, s, NH). ^{13}C NMR (DMSO-d_6, δ ppm): 39.2 (C5-thiazolidinone ring), 55.9 (C2-thiazolidinone ring), arom-C: [124.5 (1CH), 125.0 (2 CH), 126.4 (3CH), 127.5 (3CH), 128.7 (6CH), 136.3 (1C), 137.4 (1C), 138.2 (1C)], 154.5 (C5-triazole ring), 158.4 (C-3 triazole ring), 165.7 (C=O), 167.6 (C4-thiazolidinone ring). ms: *m/z* (%): 441 (M^+, 27.08).
9	IR (KBr, cm^{-1}): 1599 (C=N). ms: *m/z* (%): 365 (M^+, 30.67).
10	IR (KBr, cm^{-1}): 1670 (C=O). ^{1}H NMR (DMSO-d_6, δ ppm):1.63, 1.81 (6H, 2s, $2CH_3$), 5.40 (1H, s, C4- pyrazole ring), 6.89–7.24 (10H, m, aromatic protons). ^{13}C NMR (DMSO-d_6, δ ppm): 8.2 ($2CH_3$), 109.6 (C4-pyrazole ring), arom-C: [124.3 (1CH), 125.1 (2 CH), 126.5 (2CH), 127.5 (1CH), 128.3 (4CH), 136.1 (1C), 137.7 (1C)], 149.9 (C3 & C5-pyrazole ring), 154.2 (C5-triazole ring), 159.5 (C-3 triazole ring), 169.6 (C=O). ms: *m/z* (%): 343 (M^+, 47.51).
11	IR (KBr, cm^{-1}): 1728 (C=O) and 1688 (C=O). ^{1}H NMR (DMSO-d_6, δ ppm): 2.01 (3H, s, CH_3), 3.26 (2H, s, CH_2 of pyrazolone ring) and 7.12–7.37 (10H, m, aromatic protons). ms: *m/z* (%):345 (M^+, 52.49).
12	IR (KBr, cm^{-1}): 3321 (NH). ^{1}H NMR (DMSO-d_6, δ ppm) 6.99–7.50 (10H, m, aromatic protons) and 10.85 (1H, s, NH). ms: *m/z* (%): 321 (M^+, 25.47).

3251, 1722, and 1704 cm^{-1} for NH and the two C=O groups, respectively. Its ^{1}H NMR exhibited two signals appearing as doublets at 3.41 ppm and 3.81 ppm because of the nonequivalent geminal CH_2 protons [42]. This splitting was not observed with derivatives **5**, **6**, and **11** which may be attributed to the lacking of the asymmetric carbon atom. A convenient method for the preparation of oxadiazole derivative **9** was deduced from refluxing the acid hydrazide **1** with an equimolar amount of benzoic acid in the presence of an excess of phosphorous oxychloride. The IR spectrum of compound **9** showed no absorption for NH groups, this indicating the cyclization of **1** into oxadiazole **9**. Also, the mass spectrum of **9** gave a molecular ion at *m/z* 365 corresponding to $C_{22}H_{15}N_5O$. The hydrazide **1** was allowed to react with acetyl acetone and ethyl acetoacetate to give dimethyl pyrazole derivative **10** and methyl pyrazolone derivative **11**, respectively. The IR of **11** showed absorption band at 1728 cm^{-1} characteristical for the pyrazole carbonyl group. ^{1}H NMR spectra of

compounds **10** and **11** showed singlets at 1.81 ppm and 2.01 ppm assigned for the methyl groups, respectively. The preparation of oxadiazole-2-thione **12** was achieved, according to a reported method of Young and Wood [43], by adopting a simple one-pot procedure that involves reacting **1** with carbon disulfide under strong basic conditions followed by acidification with diluted HCl. The oxadiazole derivative **12** was characterized by IR which showed band at 3321 cm^{-1} attributed to NH. The ^1H NMR spectrum of **12** displayed the NH resonance of the oxadiazole ring at 10.85 ppm.

ANTIBACTERIAL STUDIES

The newly prepared compounds were screened for their antibacterial activity against Gram positive (*Bacillus subtitis* and *Streptococci*) and Gram negative (*Klebsiella pneumoniae* and *Escherichia coli*) bacterial strains by the disc diffusion method [44], and the results are summarized in Table 3. The results obtained showed that Schiff's bases **7a** and **7b** were found to be the most active compounds against the employed microorganisms; this is probably due to their ability to increase the penetration in the bacterial cell [45]. In addition, the substituted thiazolidinones **5**, **6**, and **8** as well as the substituted pyrazole **11** exhibited promising activity against both Gram positive and negative bacteria. However, the pyrazole derivative **10** exhibited a low activity against Gram positive only. No satisfactory level of inhibition was observed with the other compounds.

CONCLUSIONS

This study reports a successful preparation and characterization of new 1,2,4-triazole derivatives. The antibacterial study revealed that, compounds **5**, **6**, **7a**, **7b**, **8**, and **11** showed low to moderate antibacterial activities. This result suggesting that Schiff's base, thiazolidinone, and pyrazole moieties play an important role in enhancing the antibacterial activities of this class of compounds.

Table 3

Screening for antibacterial activity of the new compounds (diameter zones of inhibitions in mm).

	Gram positive		Gram negative	
Comp. No.	*Bacillus subtitis*	*Streptococci*	*Klebsiella pneumoniae*	*Escherichia coli*
3	–	–	–	–
4	–	–	–	–
5	5	10	12	11
6	9	12	11	10
7a	20	23	18	19
7b	21	18	20	15
8	19	23	22	17
9	–	–	–	–
10	11	12	–	–
11	18	10	10	12
12	–	–	–	–
Control (DMSO)	–	–	–	–

EXPERIMENTAL

Chemistry. Melting points were determined in open-glass capillaries on a Stuart electric melting point apparatus and were uncorrected. Elemental analyses were performed by the Microanalysis center, Faculty of Science, Cairo University. Infrared spectra were recorded on Satellite 2000 spectrometer using KBr discs. Mass spectra were determined on GC-MS (QP/000 EX) Shimadzu spectrometer at an ionizing voltage of 70 eV. Nuclear magnetic resonance spectra were recorded on Varin Mercury 300 MHz spectrometer using TMS as an internal standard; chemical shifts are reported in δ units. Solvents were dried by standard procedures. Reaction progress and purity of the compounds were checked by TLC, making use of silica gel plates (Silica gel F254 on aluminum sheets).

Preparation of thiosemicarbazide 2. A solution of **1** (0.01 mol) and equimolar amount of phenylisothiocyanate in 50 mL of ethanol was heated under reflux for 5 h. The solid product obtained after concentration of the solution was collected by filtration and recrystallized from methanol to give yellow crystals.

Preparation of 4,1′,5′-triphenyl-1,4-dihydro-1′H-[3,3′]bi[[1,2,4]triazolyl]-5-thione 3. The thiosemicarbazide **2** (0.01 mol) in sodium hydroxide (2*N*, 15 mL) was refluxed for 8 h. The solution was cooled and neutralized using diluted hydrochloric acid. The formed solid was collected by filtration, washed with water, and recrystallized from methanol to give colorless crystals.

Preparation of N-phenyl[5-(1,5-diphenyl-1H-[1,2,4]triazol-3-yl)-[1,3,4]thiadiazol-2-yl]-amine 4. To an ice-cold stirred solution of thiosemicarbazide **2** (0.01 mol) in absolute ethanol (10 mL), concentrated sulfuric acid (10 mL) was added over a period of 30 min, the stirring was maintained at room temperature for an additional 5 h. Then, the reaction mixture was poured onto ice/water mixture. The solid was filtered off and recrystallized from dioxane to give colorless crystals.

Preparation of 1,5-diphenyl-1H-[1,2,4]triazole-3-carboxylic acid (4-oxo-3-phenyl-thiazolidin-2-ylidene)-hydrazide 5. A mixture of **2** (0.01 mol), ethyl bromoacetate (0.01 mole), and anhydrous sodium acetate (0.03 mol) in ethanol (30 mL) was refluxed for 5 h. The solid product obtained after concentration of the reaction mixture was collected by filtration and recrystallized from methanol to give pale yellow crystals.

Preparation of 1,5-diphenyl-1H-[1,2,4]triazole-3-carboxylic acid (4-oxo-2-phenylimino-thiazolidin-3-yl)-amide 6. A solution of **2** (0.01 mol) in ethanol (30 mL) was treated with monochloroacetic acid (0.01 mol), and the reaction mixture was refluxed for 5 h. The solid product obtained after concentration of the solution was collected by filtration and recrystallized from ethanol to give yellow crystals.

Preparation of 1,5-diphenyl-1H-[1,2,4]triazole-3-carboxylic acid benzylidene-hydrazide 7a, b. A solution of **1** (0.01 mol) and an appropriate aldehyde (0.01 mol) in ethanol (30 mL)

was refluxed for 5 h. The solid separated upon cooling was filtered and recrystallized from dioxane to give yellow crystals.

Preparation of 1,5-diphenyl-1H-[1,2,4]triazole-3-carboxylic acid (4-oxo-2-phenyl-thiazolidin-3-yl)-amide 8. A mixture of **7a** (0.01 mol) and thioglycolic acid (0.01 mol) was refluxed in dry benzene (75 mL) for 10 h, using a Dean-Stark water separator. The solvent was evaporated, and the reaction mixture was neutralized with cold dilute sodium bicarbonate solution. The formed solid was filtered off, dried, and recrystallized from ethanol to give yellow crystals.

Preparation of 2-(1,5-diphenyl-1H-[1,2,4]triazol-3-yl)-5-phenyl-[1,3,4]oxadiazole 9. A mixture of **1** (0.01 mol) and benzoic acid (0.01 mol) in $POCl_3$ (15 mL) was refluxed for 10 h. The reaction mixture was slowly poured onto ice/water mixture and then neutralized with sodium bicarbonate solution. The solid formed was filtered, washed with water, and recrystallized from ethanol to give pale yellow crystals.

Preparation of compounds 10 and 11. A mixture of **1** (0.01 mol) and acetyl acetone or ethyl acetoacetate (0.01 mol) in ethanol (50 mL) was refluxed for 5 h. The solid product obtained after concentration and cooling of the solution was collected by filtration and recrystallized from dioxane to give yellow crystals.

Preparation of 5-(1,5-diphenyl-1H-[1,2,4]triazol-3-yl)-3H-[1,3,4] oxadiazole-2-thione 12. To a mixture of **1** (0.01 mol) in ethanol (50 mL) was added a solution of potassium hydroxide (0.015 mol) in ethanol (50 mL), followed by carbon disulfide (30 mL). The reaction mixture was refluxed for 20 h. The solid product obtained after cooling and acidification with dilute HCl was collected by filtration and recrystallized from ethanol to give yellow crystals.

Antibacterial assay. Antibacterial screening of prepared compounds was done by the paper disc agar diffusion method [44] against Gram positive (*B. subtitis* and *Streptococci*) and Gram negative (*K. pneumoniae* and *E. coli*) strains. The compounds were dissolved in DMSO at a concentration of 1 mg mL^{-1}. Antibacterial activity of DMSO against the test microorganisms was investigated and was found to be nil. The nutrient agar medium was sterilized by autoclaving at 120°C for 15 min; the Petri dishes were sterilized in hot air oven at 160°C for an hour. Into each sterilized Petri plate, about 30 mL of molten agar medium inoculated with the respective strain of bacteria (6 mL inoculums to 300 mL of nutrient medium) was transferred. The plates were left at room temperature to allow solidification. Six-millimeter diameter holes were then punched carefully using a sterile cork borer and completely filled with the test solutions. The plates were incubated for 24 h at 37°C. The antibacterial activity was evaluated by measuring the diameter of the inhibition zone. All the experiments were carried out in doublet, and the average value was reported. The antibacterial activity results were summarized in Table 3.

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