ISSN 1070-3632, Russian Journal of General Chemistry, 2020, Vol. 90, No. 1, pp. 142–147. © Pleiades Publishing, Ltd., 2020.

Cu(I) Catalyzed 1,3-Dipolar Click Synthesis of S-Heterocyclic 1,2,3-Triazole Derivatives, Their Antibacterial Activity

V. Turukarabettu[a], B. Kalluraya[a,*], K. Hemanth[b], and B. C. Revanasiddappa[b]

[a] *Department of Chemistry, Mangalore University, Mangalore, Karnataka, 574199 India*
[b] *Department of Pharmaceutical Chemistry, NGSM Institute of Pharmaceutical Sciences, Nitte (Deemed to be University), Mangalore, Karnataka, 575018 India*
**e-mail: bkalluraya@gmail.com*

Received August 1, 2019; revised Ocrober 15, 2019; accepted January 11, 2020

Abstract—A novel series of 1,2,3-triazoles is synthesized by 1,3-dipolar cycloaddition of aromatic azides and terminal alkynes containing 1,2,4-triazole/1,3,4-oxadiazole in presence of Cu(I) catalyst in aqueous medium. The compounds are characterized by spectral and analytical data. The novel triazoles demonstrate moderate to excellent antibacterial activity and good docking score.

Keywords: 1,3-dipolar cycloaddition, 1,2,3-triazole, oxadiazoles, Cu(I) catalyst, antibacterial

DOI: 10.1134/S1070363220010223

INTRODUCTION

The 1,3-dipolar Click reaction of acetylenes with azides is one of the most efficient synthetic approaches to 1,2,3-triazoles [1]. The Cu(I) catalyzed cycloaddition reactions are characterized by several advantages over conventional method of synthesis of a single isomer of 1,4-disubstituted-1,2,3-triazole derivatives [2]. Several other catalytic reactions for 1,2,3-triazole synthesis were developed [3]. Close interest in developing new approaches to this class of heterocycles is initiated by a wide range of their biological activities including antifungal [4], antibacterial [5], anti-inflammatory [6], antiviral [7], anticancer [8], and many more. 1,3,4-Oxadiazoles are also reported as antibacterial [9], analgesic [10], antifungal [11] and antioxidant [12] agents. By combining two or more pharmacophores in a single compound may promote their biological activity [13].

Encouraged by the above information and in continuation of our study on dipolar addition reaction [14, 15] and synthesis of bioactive 1,2,3-triazole derivatives [16, 17] we have singled out Cu(I) catalyst for the Huisgen [3+2] cycloaddition reaction. The study was devoted to cycloaddition of heterocyclic terminal alkynes containing 1,2,4-triazole/1,3,4-oxadiazole moieties with aryl azides in THF–water (1 : 1) medium that led to synthesis of novel series of 1,4-disubstituted-1,2,3-triazoles (Scheme 1). For the mentioned above reasons, the novel compounds were tested for their antibacterial and anti-radical activities *in vitro*. Docking study of the binding ability of the synthesized compounds with target protein was carried out.

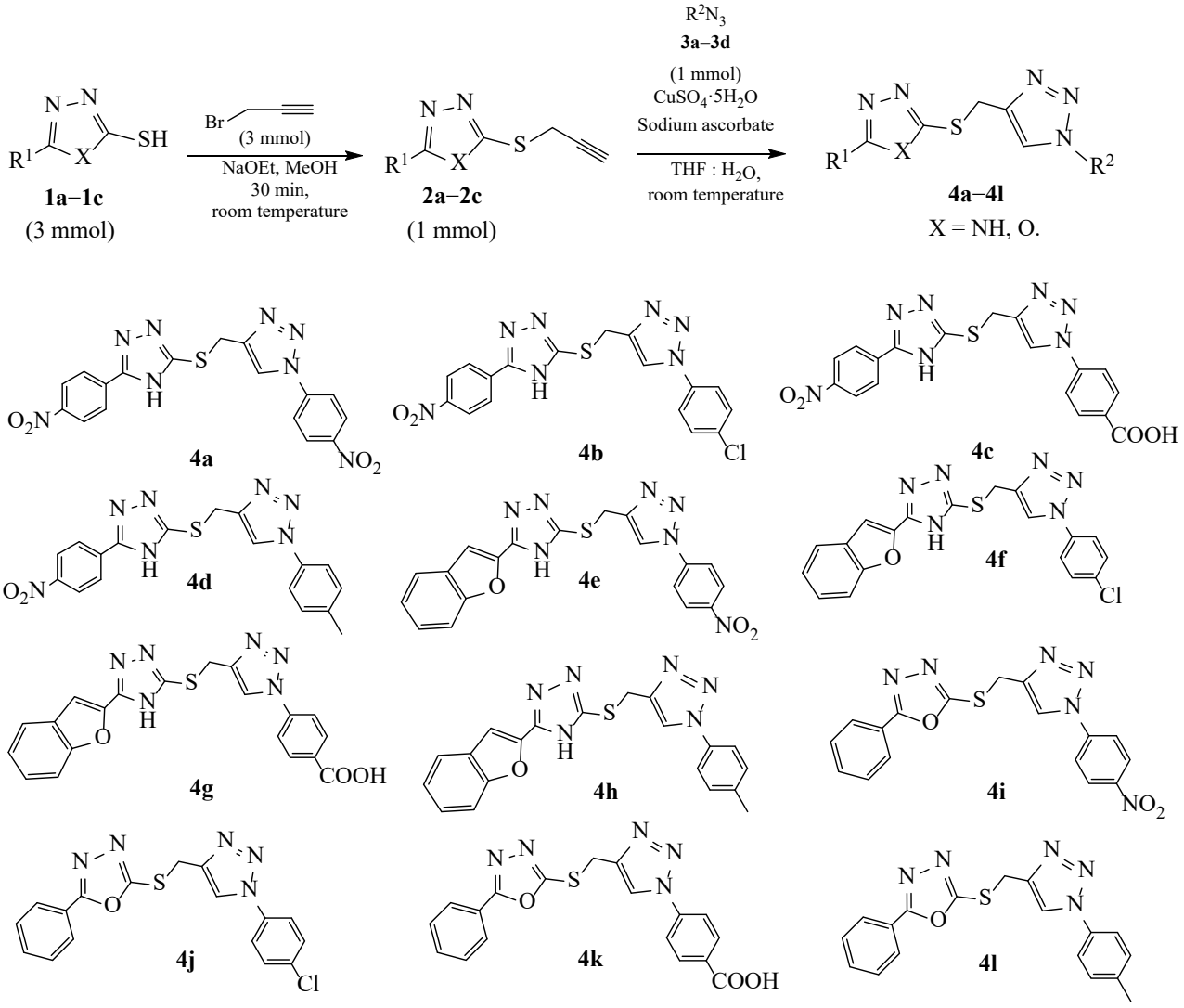
RESULTS AND DISCUSSION

Upon treating 5-aryl-1,2,4-triazol-5-thione (**1a**, **1b**)/5-aryl-1,3,4-oxadiazol-2-thione (**1c**) with propargyl bromide in presence of sodium methoxide, terminal alkynes **2a**–**2c** were obtained (Scheme 1). The latter compounds underwent 1,3-dipolar cyclo-addition reaction with aryl azides **3a**–**3d** in presence of Cu(I) catalyst in THF:water (1 : 1) leading to novel 1,2,3-triazole derivatives **4a**–**4l**. All synthesized compounds were characterized by spectral and analytical methods.

Antibacterial activity. The *in vitro* antibacterial activity [18] of the products was studied against two gram-positive (*Staphylococcus aureus*, *Bacillus subtilis*) and two gram-negative (*Escherichia coli*, *Pseudomonas aeruginosa*) bacterial strains (see Table 1). All newly synthesized compounds exhibited excellent activity against gram negative bacteria *E. coli* and *P. auroginosa*. Benzofuranyl 1,2,3-triazole derivatives **4e**–**4h** were determined to be more potent as antibacterial agents against all the bacterial strains than the other compounds involved in the study. The compounds **4a** and **4g** demonstrated the highest antibacterial activity against all the bacterial strains (see Table 1).

Molecular docking. Docking study was performed for distinguishing interactions of the synthesized compounds

Scheme 1. Synthesis of the cycloaddition products **4a**–**4l.**



with the target protein 2VF5 (Glucosamine-6-phosphate syntheses) that contains the active residues: Lys 603, Gln 345, Ser 604, Gly 301, Ser 303, and Thr 302. According to the simulation, the synthesized compounds could form hydrogen bonds with Gly 301, Lys 603, Gln 348, and Ser 349 (Fig. 1). Compounds **4c**, **4f**, and **4g** fit into binding cleft of 2VF5 receptor with G-score –5.44, –4.40, and 4.40 kcal/mol, respectively.

Anti-radical activity. DPPH free radical scavenging assay was performed using Brand–Williams method [19]. Except the compounds **4a** and **4c**, the rest demonstrated lower than 50% free radical scavenging ability at 10 mg/mL concentration (see Table 1).

EXPERIMENTAL

Commercially available analytical grade chemicals were purchased and used without additional purification. Silica gel of 5–20 μm (Merck, 60–120 mesh) was used for column chromatography. Melting points were determined using a DSC-SDT Q600 instrument. FTIR spectra were recorded on a Shimadzu FTIR 157 spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured on an Agilent VNMRS-400MHz NMR spectrometer using TMS as an internal standard and $CDCl_3$ as a solvent (unless stated otherwisw). Mass spectra were measured on a Shimadzu 8030 mass spectrometer. Elemental analysis was carried out on a Vario-EI Elementar III elemental analyzer.

Table 1. Antibacterial and anti-radical activity of novel compounds (**4a**–**4l**)

Comp. no.	Antibacterial activity (zone of inhibition, mm)				Antiradical activity (% DPPH assay)
	S. aureus	*B. subtilis*	*E. coli*	*P. auroginosa*	
4a	13.00±0.57	13.33±1.45	15.66±1.45	14.33±0.88	53±0.8
4b	10.53±0.68	9.00±0.65	12.66±1.20	10.00±0.09	30±1.03
4c	12.00±1.00	11.00±0.57	13.00±0.57	11.66±0.33	54±1.2
4d	9.26±0.49	10.00±1.58	10.61±0.20	10.00±0.07	31±0.5
4e	13.66±1.45	16.00±0.00	11.66±0.88	13.33±1.45	37±0.4
4f	11.66±0.88	17.00±0.57	12.33±1.20	14.66±1.20	20±0.9
4g	12.33±1.20	16.66±1.20	17.33±0.88	19.66±0.88	43±1.0
4h	13.66±0.88	14.00±1.00	11.00±1.00	8.33±0.88	23±0.2
4i	14.00±1.00	8.00±1.00	13.00±1.00	13.66±0.88	34±0.8
4j	9.33±1.20	10.00±1.00	13.33±0.88	13.00±1.00	23±0.8
4k	9.01±1.02	10.00±0.62	11.29±0.20	12.00±0.33	39±1.3
4l	9.00±0.57	9.00±1.73	12.33±0.88	12.00±0.00	21±1.1
Neomycin	17.00±0.88	17.00±1.2	14.55±0.88	15.54±1.73	BHT 96±1.02

Synthesis of 3-aryl substituted-5-(prop-2-ynylthio)-4*H*-1,2,4-triazoles (2a, 2b) and 2-phenyl-5-(prop-2-ynylthio)-1,3,4-oxadiazole (2c). To a solution of a 3-aryl-1*H*-1,2,4-triazole-5(4*H*)-thione **1a**, **1b** (3 mmol) or 5-phenyl-1,3,4-oxadiazole-2(3*H*)-thione **1c** (3 mmol) and NaOEt (0.27 g, 4 mmol) in methanol (15 mL) was added propargyl bromide (3 mmol) dropwise upon external cooling by ice. Then the mixture was warmed up to room temperature and stirred upon TLC monitoring. Then the reaction mixture was poured into crushed ice, the solid precipitated was filtered off and recrystallized from ethanol.

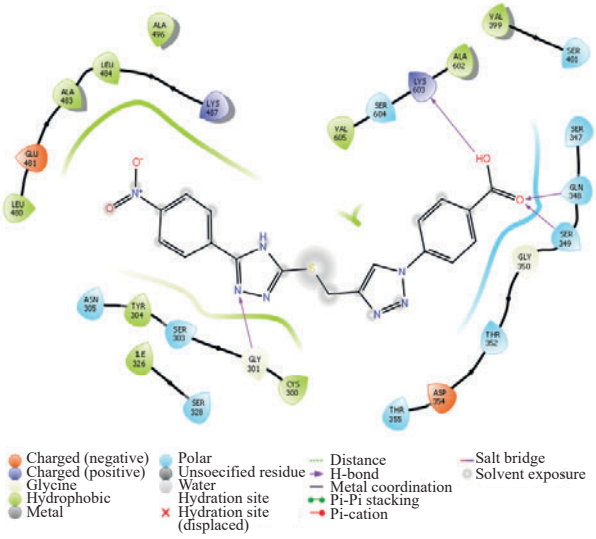


Fig. 1. Ligand interactions of **4c** with 2VF5.

3-(4-Nitrophenyl)-5-(prop-2-ynylthio)-4*H*-1,2,4-triazole (2a). Yield 69%, mp 114–116°C. IR spectrum, ν, cm^{-1}: 3550 (N–H), 2127 (C≡C), 1514 (NO_2 asym.), 1340 (NO_2 sym.), 665 (≡C–H). ^{1}H NMR spectrum, δ, ppm: 2.35 t, (1H, ≡CH), 3.94 d (2H, SCH_2), 8.24 d (2H, ArH), 8.29 d (2H, ArH). ^{13}C NMR ($CDCl_3$) δ_C, ppm: 25.3, 72.6, 77.9, 122.4, 128.6, 137.2, 148.4, 157.9, 159.5. MS: m/z: 259.35 [*M* + H]$^+$. Found, %: C 50.67; H 3.05; N 21.48. $C_{11}H_8N_4O_2S$. Calculated, %: C 50.76; H 3.10; N 21.53.

3-(Benzofuran-2-yl)-5-(prop-2-ynylthio)-4*H*-1,2,4-triazole (2b). Yield 61%, mp 154–155°C. IR spectrum, ν, cm^{-1}: 3280 (N–H), 2152 (C≡C), 634 (≡C–H). ^{1}H NMR spectrum, δ, ppm: 2.29 t (1H, ≡CH), 3.95 d (2H, SCH_2), 7.26 t (1H, ArH), 7.35 t (1H, ArH), 7.43 s (1H, furan-H), 7.53 d (1H, ArH), 7.64 d (1H, ArH). ^{13}C NMR spectrum, δ_C, ppm: 24.9, 71.4, 77.2, 105.4, 111.8, 122.2, 125.3, 126.2, 154.4, 158.6, 158.9. MS: *m/z*: 255.65 [*M* + H]$^+$. Found, %: C 61.01; H 3.51; N 16.48. $C_{13}H_9N_3OS$. Calculated, %: C 61.16; H 3.55; N 16.46.

2-Phenyl-5-(prop-2-ynylthio)-1.3.4-oxadiazole (2c). Yield 65%, mp 83–85°C. IR spectrum, ν, cm^{-1}: 3209 (N–H), 2193 (C≡C), 696 (≡C–H). ^{1}H NMR spectrum, δ,

ppm: 2.32 t (1H, ≡CH), 4.05 d (2H, SCH_2), 7.46–7.55 m (3H, ArH), 7.99 d (2H, triazole-H). ^{13}C NMR spectrum, δ_C, ppm: 25.2, 70.8, 77.8, 126.5, 128.4, 128.8, 130.7, 165.4, 168.8. MS: *m/z*: 216.55 [*M* + H]$^+$. Found, %: C 59.81; H 3.67; N 12.75. $C_{11}H_8N_2OS$. Calculated, %: C 61.09; H 3.73; N 12.95.

Synthesis of 1,2,3-triazoles (4a–4l). To a solution of an aryl azide **3a**–**3c** (1 mmol) in THF (0.5 mL), the corresponding terminal alkyne **2a**–**2c** (1 mmol), sodium ascorbate (0.016 g) and $CuSO_4 \cdot 5H_2O$ (0.008 g) solution in distilled water (0.5 mL) were added. Sonication of the reaction mixture at 45°C lasted for 40 min, followed by stirring at room temperature (TLC). Brine solution (3.5%, 3 mL) was added, and the mixture was extracted with dichloromethane (3×5 mL). The combined organic layers were washed with brine solution and dried with $MgSO_4$. The organic solvent was roto evaporated and the corresponding product was purified by column chromatography using hexane–ethylacetate (9 : 1) mixture as an eluent.

3-(4-Nitrophenyl)-5-[1-(4-nitrophenyl-1*H*-1,2,3-triazol-4-yl)methylthio]-4*H*-1,2,4-triazole (4a). Yield 54%, mp 190–192°C. IR spectrum, ν, cm^{-1}, 3113 (N–H), 1600 (C=N), 1517 (C=N). ^1H NMR spectrum, δ, ppm: 4.57 s (2H, SCH_2), 7.26–8.27 m (8H, ArH), 8.73 s (1H, triazole-H), 14.5 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 34.7, 119.8, 122.1, 128.5, 131.2, 135.2, 136.8, 145.6, 148.3. MS: *m/z*: 423.40 [*M* + H]$^+$. Found, %: C 48.02; H 2.75; N 26.29. $C_{17}H_{12}N_8O_4S$. Calculated, %: C 48.11; H 2.85; N 26.40.

3-{[1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl]-methylthio}-5-(4-nitrophenyl)-4*H*-1,2,4-triazole (4b). Yield 63%, mp 163°C. IR spectrum, ν, cm^{-1}: 2984 (N–H), 1606 (C=C), 1510 (C=N). ^1H NMR (DMSO-d_6) spectrum, δ, ppm: 4.60 s (2H, SCH_2), 7.60 d (2H, ArH), 7.87 d (2H, ArH), 8.22- 8.31 m (4H, ArH), 8.75 s (1H, triazole-H), 14.6 s (1H, NH). ^{13}C NMR (DMSO-d_6) spectrum, δ_C, ppm: 34.9, 122.1, 122.2, 124.6, 127.4, 130.1, 133.4, 134.9, 135.7, 148.2. MS: *m/z*: 413.30 [*M* + H]. Found, %: C 49.16; H 2.81; N 23.55. $C_{17}H_{12}N_7O_2SCl$. Calculated, %: C 49.34; H 2.92; N 23.69.

4-(4-{[5-(4-Nitrophenyl)-4*H*-1,2,4-triazol-3-ylthio]-methyl}-1*H*-1,2,3-triazol-1-yl)benzoic acid (4c). Yield 50%, mp 254°C. IR spectrum, ν, cm^{-1}: 3104 (N–H), 1684 (C=O), 1510 (C=N). ^1H NMR spectrum, δ, ppm: 4.56 s (2H, SCH_2), 7.64–8.07 m (4H, ArH) 8.32 m (4H, ArH), 8.71 s (1H, triazole-H), 13.06 s (1H, OH), 14.51 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 34.8, 119.7, 121.9, 128.4, 129.8, 131.0, 135.1, 136.6, 145.3, 148.3, 157.5, 171.6. MS: *m/z*: 421.90 [*M* – 1]$^+$. Found, %: C 50.92; H 2.95; N 23.02. $C_{18}H_{13}N_7O_4S$. Calculated, %: C 51.06; H 3.09; N 23.16.

3-(4-Nitrophenyl)-5-[(1-*p*-tolyl-1*H*-1,2,3-triazol-4-yl)methylthio]-4*H*-1,2,4-triazole (4d). Yield 61%, mp 176°C. IR spectrum, ν, cm^{-1}: 1596 (C=C), 1517 (C=N). ^1H NMR spectrum, δ, ppm: 2.33 s (3H, CH_3), 4.60 s (2H, SCH_2), 7.15–7.37 m (4H, ArH), 7.74 d (2H, ArH), 8.20–8.28 d (4H, ArH), 8.75 s (1H, triazole-H), 14.56 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 24.2, 34.8, 119.2, 122.8, 126.8, 129.7, 131.5, 136.7, 138.4, 145.5, 148.2. MS: *m/z*: 393.40 [*M* + H]$^+$. Found, %: C 54.79; H 3.76; N 24.79. $C_{18}H_{15}N_7O_2S$. Calculated, %: C 54.95; H 3.84; N 24.92.

3-(Benzofuran-2-yl)-5-{[1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl]methylthio}-4*H*-1,2,4-triazole (4e). Yield 55%, mp 265°C. IR spectrum, ν, cm^{-1}: 3070 (N–H), 1597 (C=C), 1523 (C=N). ^1H NMR spectrum, δ, ppm: 4.62 s (2H, SCH_2), 7.44 s (1H, furan-H), 7.23–8.17 m (8H, ArH), 8.74 s (1H, triazole-H), 14.62 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 35.1, 103.4, 111.6, 119.5, 121.3, 125.1, 126.3, 130.2, 135.7, 145.4, 148.6, 155.2, 158.7. Found, %: C 54.31; H 3.02; N 23.26. $C_{19}H_{13}N_7O_3S$. Calculated, %: C 54.41; H 3.12; N 23.38.

3-(Benzofuran-2-yl)-5-{[1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl]methylthio}-4*H*-1,2,4-triazole (4f). Yield 62%, mp 250°C. IR spectrum, ν, cm^{-1}: 3074 (N–H), 1598 (C=C). ^1H NMR spectrum, δ, ppm: 4.62 s (2H, SCH_2), 7.43 s (1H, furan-H), 7.18–8.06 m (8H, ArH), 8.70 s (1H, triazole-H), 14.61 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 34.6, 102.9, 111.6, 119.2, 120.9, 123.7, 125.4, 128.6, 132.1, 135.5, 145.3, 155.0, 158.5. MS: *m/z*: 408.55 [*M* + H]$^+$. Found, %: C 55.41; H 3.12; N 20.36. $C_{19}H_{13}N_6OSCl$. Calculated, %: C 55.81; H 3.20; N 20.55.

4-(4-{[5-(Benzofuran-2-yl)-4*H*-1,2,4-triazol-3-ylthio]methyl}-1*H*-1,2,3-triazol-1-yl)benzoic acid (4g). Yield 51%, mp 170°C. IR spectrum, ν, cm^{-1}: 3113 (N–H), 1666 (C=O), 1612 (C=C), 1500 (C=N). ^1H NMR spectrum, δ, ppm: 4.61 s (2H, SCH_2), 7.22–8.06 m (8H, ArH), 7.44 s (1H, furan-H), 8.84 s (1H, triazole-H), 13.22 s (1H, OH), 14.65 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 35.2, 102.9, 111.6, 120.3, 122.3, 124.7, 131.2, 133.9, 146.1, 155.2, 158.8, 169.7. MS: *m/z*: 418.75 [*M* + H]$^+$. Found, %: C 57.30, H 3.22; N 19.88. $C_{20}H_{14}N_6O_3S$. Calculated, %: C 57.41; H 3.37; N 20.08.

3-(Benzofuran-2-yl)-5-[(1-*p*-tolyl-1*H*-1,2,3-triazol-4-yl)methylthio]-4*H*-1,2,4-triazole (4h). Yield 57%, mp

172°C. IR spectrum, ν, cm^{-1}: 3098 (N–H), 1592 (C=C), 1617 (C=C). ^{1}H NMR (DMSO-d_6) spectrum, δ, ppm: 2.33 s (1H, CH_3), 4.60 s (2H, SCH_2), 7.43 s (1H, furan H), 7.18–7.81 m (9H, ArH), 8.66 s (1H, triazole-H), 14.46 s (1H, NH). ^{13}C NMR (DMSO-d_6) spectrum, δ_C, ppm: 24.3, 35.2, 103.5, 111.6, 119.6, 121.2, 125.0, 126.5, 131.6, 135.7, 138.3, 148.8, 155.6, 158.7. MS: *m/z*: 388.75 [*M* + H]$^+$. Found, %: C 61.72; H 4.11; N 21.50. $C_{20}H_{16}N_6OS$. Calculated, %: C 61.84; H 4.15; N 21.63.

1-(4-Nitrophenyl)-4-[(5-phenyl-1,3,4-oxadiazol-2-ylthio)methyl]-1*H*-1,2,3-triazole (4i). Yield 59%, mp 237°C. IR spectrum, ν, cm^{-1}: 2981 (C–H), 1595 (C=C), 1517 (NO_2), 1465 (C=N), 1336 (NO_2). ^{1}H NMR spectrum, δ, ppm: 4.68 s (2H, SCH_2), 7.47–7.53 m (3H, ArH), 7.94–7.98 m (4H, ArH) 8.38 s (1H, triazole-H), 8.406 m (2H, ArH). ^{13}C NMR spectrum, δ_C, ppm: 26.5, 121.4, 122.4, 125.5, 130.8, 132.7, 139.3, 144.5, 148.6, 163.6. MS: *m/z*: 380.40 [*M* + H]. Found, %: C 53.51; H 3.06; N 22.10. $C_{17}H_{12}N_6O_3S$. Calculated, %: C 53.68; H 3.18; N 22.09.

1-(4-Chlorophenyl)-4-[(5-phenyl-1,3,4-oxadiazol-2-ylthio)methyl]-1*H*-1,2,3-triazole (4j). Yield 62%, mp 187–189°C. IR spectrum, ν, cm^{-1}: 2991 (C–H), 1590 (C=C), 1460 (C=N). ^{1}H NMR spectrum, δ, ppm: 4.67 s (2H, SCH_2), 7.37–7.43 m (3H, ArH), 7.74–7.82 m (4H, ArH), 8.09 m (2H, ArH), 8.25 s (1H, triazole-H). ^{13}C NMR spectrum, δ_C, ppm: 26.9, 120.3, 121.4, 126.2, 128.9, 134.2, 138.4, 145.2, 163.7. MS: *m/z*: 369.50 [*M* + H]$^+$. Found, %: C 55.10; H 3.24; N 18.79. $C_{17}H_{12}N_5OSCl$. Calculated, %: C 55.21; H 3.27; N 18.94.

4-{4-[(5-Phenyl-1,3,4-oxadiazol-2-ylthio)methyl]-1*H*-1,2,3-triazol-1-yl}benzoic acid (4k). Yield 55%, mp 263°C. IR spectrum, ν, cm^{-1}: 3134 (N–H), 1681 (C=O), 1600 (C=C), 1558 (C=N). ^{1}H NMR (DMSO-d_6) specrum, δ, ppm: 4.73 s (2H, SCH_2), 7.53–7.61 m (3H, ArH), 7.93–7.96 m (2H, ArH) 8.90 s (1H, triazole-H), 7.99–8.0 m (2H, ArH), 8.08–8.12 d (2H, ArH), 13.20 s (1H, OH). ^{13}C NMR (DMSO-d_6) spectrum, δ_C, ppm: 27.2, 120.2, 122.6, 123.5, 126.8, 129.8, 131.1, 132.4, 139.8, 144.3, 163.3, 166.7. MS: m/z: 379.60 [*M* + H]$^+$. Found, %: C 56.77; H 3.36; N 22.50. $C_{18}H_{13}N_5O_3S$. Calculated, %: C 56.98; H 3.45; N 18.46.

4-[(5-Phenyl-1,3,4-oxadiazol-2-ylthio)methyl]-1-*p*-tolyl-1*H*-1,2,3-triazole (4l). Yield 60%, mp 156–158°C. IR spectrum, ν, cm^{-1}: 2980 (C–H), 1596 (C=C), 1467 (C=N). ^{1}H NMR spectrum, δ, ppm: 3.30 s (3H, CH_3), 4.67 s (2H, SCH_2), 7.262 d (2H, ArH), 7.45–7.51 m (3H, ArH), 7.55 d (2H, ArH) 7.96 d (2H, ArH), 8.18 s (1H, triazole-H). ^{13}C NMR spectrum, δ_C, ppm: 21.03, 26.9, 120.5, 121.5, 123.4, 126.6, 129.0, 130.18, 131.7, 134.5, 138.9, 143.5, 163.8. MS: *m/z*: 349.60 [*M* + H]$^+$. Found, %: C 61.58; H 4.26; N 20.10. $C_{18}H_{15}N_5OS$. Calculated, %: C 61.87; H 4.33; N 20.04.

Docking study. All computational analysis was carried out on a Schrodinger suite device Maestro 11.7.012 [20]. The protein (PDB code: 2VF5, resolution 2.5 Å) was downloaded from protein data bank and refined using protein preparation wizard [21].

CONCLUSIONS

Ascorbic acid stabilized Cu(I) successfully catalyzes the 1,3-dipolar cycloadditon reaction of heteroaryl- containing terminal alkyne with aromatic azide in aqueous medium to give moderate yield of 1,4-disubstituted-1,2,3-triazole derivatives. The compounds are determined to be active antibacterial agents and products **4a** and **4g** demonstrate good activity against all the bacteria under study.

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

REFERENCES

1. Sambasiva, R.P., Chinnu, A.K., Jitender, D.G., Ravi, K.N., Srinivas, P.V.S.S., Thomas, B.V., and Narasaiah, B., *Synth. Commun.*, 2017, vol. 47, no. 5, p. 457. https://doi.org/10.1080/00397911.2016.1271133
2. Katritzky, A.R., Zhang, Y., and Singh, S.K., *Heterocycles*, 2003, vol. 60, no. 5, p. 1225. https://doi.org/10.3987/REV-02-562
3. Singh, M.S., Chowdhury, S., and Koley, S., *Tetrahedron*, 2016, vol. 72, no. 35, p. 5257. https://doi.org/10.1016/j.tet.2016.07.044
4. Wang, Z., Gao, Y., Hou, Y., Zhang, C., Yu, S., Bian, Q., Li, Z., and Zao, W., *Eur. J. Med. Chem*., 2014, vol. 86, p. 87. https://doi.org/10.1016/j.ejmech.2014.08.029
5. Kiran, K., Ashok, D., Rao, B.A., Sarasija, M., and Rao, A.S., *Russ. J. Gen. Chem.*, 2017, vol. 87(6), p. 1288. https://doi.org/10.1134/S1070363217060251
6. Rollas, S. and Kucukguzel, S.G., *Molecules*, 2007, vol. 12, no. 8, p. 1910. https://doi.org/10.3390/12081910
7. El-Sayed, W.A., Khalaf, H.S., Mohamed, S.F., Hussien, H.A., Kutkat, O.M., and Amr, A.E., *Russ. J. Gen. Chem.*, 2017, vol. 87, no. 10, p. 2444. https://doi.org/10.1134/S1070363217100279
8. Lakkakula, R., Roy, A., Mukkanti, K., and Sridhar, G.,

Russ. J. Gen. Chem., 2019, vol. 89, p. 831. https://doi.org/10.1134/S1070363219040315

9. Keshari, K.J., Abdul, S., Kumar, Y., Shaharyar, M., Khosa, R.L., Jain, J., Kumar, V., and Singh, P., *Eur. J. Med. Chem.*, 2010, vol. 45, p. 4963. https://doi.org/10.1016/j.ejmech.2010.08.003
10. Hassert, G.L., Poutsiava, J.W., Papadrianos, D., Barke, J.C., and Graver, B.N., *Taxicol. Appl. Pharm*., 1961, vol. 3, p. 726. https://doi.org/10.1016/0041-008X (61)90036-9
11. Ming-Zhi, Z., Nick, M., David, B., Dianne, I., Yu-Cheng, G., Qiong, C., Guang-Fu, Y., and John, C., *Eur. J. Med. Chem*., 2013, vol. 63, p. 22. https://doi.org/10.1016/j.ejmech.2013.01.038
12. Kotaiah, Y., Harikrishna, N., Nagaraju, K. and Venkata, C.R., *Eur. J. Med. Chem*., 2012, vol. 58, p. 340. https://doi.org/10.1016/j.ejmech.2012.10.007
13. Thotla, K., Giri, N.V., Kedika, B., and Reddy, K., *Russ. J. Gen. Chem.*, 2019, vol. 89, p. 789. https://doi.org/10.1134/S1070363219040248
14. Kalluraya, B., *Int. J. Curr. Adv. Res.*, 2015, vol. 4, p. 98.
15. Mallya, S., Kalluraya, B., and Girisha, K.S., *J. Heterocyclic Chem.*, 2015, vol. 52, p. 527. https://doi.org/10.1002/jhet.2092
16. Shetty, S., Asma, and Kalluraya, B., *Indian J. Chem. B*, 2016, vol. 55, p. 501.
17. Shyma, P.C., Kalluraya, B., Peethambar, S.K., and Vijesh, A.M., *Med. Chem. Res*., 2016, vol. 25, p. 2680. https://doi.org/10.1007/s00044-016-1629-4
18. Ansari, F.L., Nazir, S., Noureen H., and Miraza, B., *Chem. Biodivers.*, 2005, vol. 2, p. 1656. https://doi.org/10.1002/cbdv.200590135
19. Brand-Williams, W., Cuvelier, M.E., and Berset, C., *LWT-Food Sci. Technol.*, 1995, vol. 28, p. 25. https://doi.org/10.1016/S0023-6438(95)80008-5
20. Schrodinger Release 2019-2: Maestro, Schrödinger, LLC, New York, 2019
21. Mouilleron, S., Badet-Denisot, M.A., and Golinelli-Pimpaneau, B., *J. Mol. Biol.*, 2008, vol. 377, no. 4, p. 1174. https://doi.org/10.1016/j.jmb.2008.01.077