Asian Journal of Chemistry; Vol. 29, No. 10 (2017), 2171-2176

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2017.20671

Click Synthesis of Some mono/*bis* 1,2,3-Triazoles with Ester Linkage and their Microbicidal Activity

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Received: 25 March 2017; *Accepted*: 31 May 2017; *Published online*: 31 August 2017; AJC-18514

Synthesis of some new 1,4-disubstituted 1,2,3-triazoles with ester functionality is reported employing Cu(I) catalyzed Huisgen [3+2] cycloaddition reaction of prop-2-yn-1-yl benzoates with 1,4-phenylenebis(methylene) bis(2-azidoacetate) and benzyl 2-azidoacetates. The synthesized compounds were well characterized through FTIR, ^{1}H NMR, ^{13}C NMR and HRMS. Further, the synthesized triazole derivatives were accessed for *in vitro* antimicrobial activity against one Gram-positive bacterial strain *Staphylococcus aureus*, three Gram-negative bacterial strains *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter aerogenes* and two fungi *Candida albicans* and *Aspergillus niger*. Few of the synthesized disubstituted 1,2,3-triazoles displayed moderate to good inhibitory activity against tested microbial strains.

Keywords: Click synthesis, Huisgen [3+2] dipolar cycloaddition, Disubstituted 1,2,3-triazoles, Antibacterial activity, Antifungal activity.

INTRODUCTION

Now days, effective treatment for microbial infections has become major concern to medicinal researchers due to increase in number of drug resistant pathogens. The emerging microbial resistance stimulated interest of organic researchers into triazole derivatives to explore as significant antimicrobial agent [1,2]. 1,2,3-Triazoles, an active class of heterocycles has been reported to exhibit broad spectrum of biological applications as antiviral [3], antitubercular [4,5], antimalarial [6], antimicrobial [7-10], antibiotic [11], antioxidant [12], antibiofilm [13], anticancer [14], anti-HIV [15,16], anticonvulsant [17], antithrombotic [18], antitumour [19] *etc*. Despite of this undeniable importance in medicinal field, triazoles also displayed paramount applications in the fields like polymer chemistry [20], material sciences [21] and drug discovery [22]. Strong dipole moment, stability to acidic/basic hydrolysis assists triazole moieties for active participation in hydrogen bonding and dipole-dipole interactions with biological targets.

Earlier, Huisgen 1,3-dipolar cycloaddition [23] between terminal alkynes and organic azides at thermal conditions were extensively used for the synthesis of disubstituted 1,2,3-triazole. This method leads to generation of both 1,4 and 1,5 regioisomers at elevated temperature. Thereafter, in 2002, Sharpless *et al.* [24] and Meldal *et al.* [25] discovered a new synthetic tool for the exclusive construction of 1,4-regioisomer by catalyzing the reaction with Cu(I) salts. This Cu(I) assisted azide-alkyne cycloaddition reaction has become one of the powerful click reaction owing to its regioselectivity, efficiency, wide scope, versatility and functional group compatibility.

Therefore, in continuation of our quest of synthesis of biologically potent 1,2,3-triazoles [26], we planned to synthesize ester linked mono and *bis* 1,4-disubstituted 1,2,3-triazoles from prop-2-yn-1-yl benzoates and benzyl 2-azidooacetates/ 1,4-phenylenebis(methylene) *bis*(2-azidoacetate) *via* Cu(I) catalyzed click reaction. All the synthesized triazole derivatives were characterized by FTIR, ^{1}H NMR, ^{13}C NMR, HRMS and screened against four bacterial strains *i.e. Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae, Enterobacter aerogenes* and two fungal strains *i.e. Candida albicans* and *Aspergillus niger*.

EXPERIMENTAL

All the reagents used in present work were procured in commercially available grade and used without further purification.Melting points of target compounds were determined by open capillary tubes on Electrothermal Melting Point apparatus, LABCO, India and are uncorrected. IR absorption spectral data were measured on SHIMAZDUIR AFFINITY-I FT-IR using potassium bromide powder and wave numbers (ν) were expressed in cm^{-1}. The progress of reaction was monitored by readymade silica gel plates (SIL G/UV254, ALUGRAM) and visualization was carried out with ultraviolet lamp. The ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on BRUKER AVANCE II 400 MHz spectrometer at 400 MHz

and 100 MHz respectively in $CDCl_3$/DMSO-d_6. Values of coupling constant (*J*) were given in Hz. High resolution mass spectra (HRMS) were acquired on Waters Micromass Q-T of Micro (ESI) spectrometer.

General procedure for synthesis of prop-2-yn-1-yl benzoates (4a-4e): Synthesis of prop-2-yn-1-yl benzoates (**4a-4e**) was carried out drop-wise addition of benzoyl chlorides (1.0 mmol) in the stirred solution of prapargyl alcohol (1.0 mmol) in dichloromethane using N,N-dimethylaminopyridine (1.2 mmol) as base and resultant mixture was continuously stirred at 0-10 °C for 2-4 h [27]. On completion of reaction, dilute solution of hydrochloric acid was added in reaction mixture and organic product was isolated by extraction with dichloromethane (3 × 30 mL). Thereafter, solvent was distilled under vacuum to yield desired terminal alkynes (**4a-4e**).

General procedure for synthesis of benzyl 2-bromoacetates/1,4-phenylene *bis*(methylene) *bis*(2-bromoacetate) (2a-2e)/(5): For synthesis of benzyl 2-bromooacetates/1,4-phenylene *bis*(methylene) *bis*(2-bromoacetate) **(2a-2e)/(5)**,1,4-phenylenedimethanol/benzyl alcohols (1.0 mmol) were taken in acetonitrile in round bottom flask. To this, sodium bicarbonate (1.5 mmol/3.0 mmol) was added as base followed by slow addition of bromoacetylbromide (1.2 mmol/2.4 mmol). The mixture was stirred with aid of magnetic stirrer at 0-4 °C for 45 min. Upon completion of reaction, product extracted with dichloromethane (3 × 30 mL) and evaporation of solvent in vacuum furnished product in good yield.

General procedure for synthesis of 1,4-disubstituted 1,2,3-triazoles (3a-3e)/(6a-6e): For synthesis of target compounds, to stirred solution of benzyl 2-bromo acetates/1,4-phenylene *bis*(methylene) *bis*(2-bromoacetate) (1.0 mmol) **(2a-2e)/(5)** in dimethylsulfoxide, aqueous sodium azide (3.0 mmol/6.0 mmol) was added at 25-40 °C and continue stirring for 1 h. Thereafter, prop-2-yn-1-yl benzoates (1.0 mmol/2.0 mmol) **(4a-4e)**, aqueous copper sulphate pentahydrate (0.1 mmol/0.2 mmol) and sodium ascorbate (0.4 mmol/0.8 mmol) were added to above resultant mixture and stirring was continued for 5-10 h at same temperature. When reaction was completed, ice cold water was added and precipitated solid residue was filtered and washed with ammonia solution. Crude product thus obtained purified by washing with ethyl acetate and dried under vaccum to afford target product **(3a-3e)/(6a-6e)** in good yield.

Characterization of synthesized compounds

1-[2-(Benzyloxy)-2-oxoethyl]-1*H*-1,2,3-triazol-4-yl)methyl-4-fluorobenzoate (3a): White solid; Yield: 85 %; m.p.: 86-90 °C; FT-IR (KBr, ν_{max}, cm^{-1}): 3152 (C-H str., triazole ring), 3076 (C-H str., aromatic ring), 2958 (C-H str., aliphatic), 1752, 1720 (C=O str., ester), 1603, 1508 (C=C str., aromatic ring), 1274 (C-O asym. str., ester), 1054 (C-O sym. str., ester); ^{1}H NMR (400 MHz, $CDCl_3$): 5.23(s, 2H, NCH_2), 5.25 (s, 2H, OCH_2), 5.46 (s, 2H, OCH_2), 7.06-7.11 (m, 2H, Ar-H), 7.31-7.34 (m, 5H, Ar-H), 7.89 (s, 1H, C-H triazole), 8.02-8.05 (m, 2H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 50.7, 58.0, 67.9, 115.45 (d, 2C, Ar-C, *J* = 20.0 Hz), 125.5 (C_5 triazole), 125.95 (d, 1C, Ar-C, *J* = 3.0 Hz), 128.4, 128.6, 128.7, 132.25 (d, 2C, Ar-C, *J* = 10.0 Hz), 134.4, 143.0 (C_4 triazole), 165.2 (C=O ester), 165.75 (d, 1C, Ar-C, *J* = 250.0 Hz), 166.0 (C=O ester) ppm; HRMS (*m/z*) calculated for $C_{19}H_{16}N_3O_4F$ $[M+H]^+$: 370.1158. Found: 370.1128.

1-(2-((4-Methoxybenzyl)oxy)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)methyl 4-fluorobenzoate (3b): White solid; Yield: 88 %; m.p.: 88-92 °C; FT-IR (KBr, ν_{max}, cm^{-1}): 3148 (C-H str., triazole ring), 3076 (C-H str., aromatic ring), 2986 (C-H str., aliphatic), 1752, 1720 (C=O str., ester), 1604, 1510 (C=C str., aromatic ring), 1282 (C-O asym. str., ester), 1057 (C-O sym. str., ester); ^{1}H NMR (400 MHz, DMSO-d_6): 3.80 (s, 3H, OCH_3), 5.23 (s, 2H, NCH_2), 5.33 (s, 2H, OCH_2), 5.57 (s, 2H, OCH_2), 6.88 (d, 2H, Ar-H, *J* = 8.0 Hz), 7.28 (d, 2H, Ar-H, *J* = 8.0 Hz), 7.32-7.36 (m, 2H, Ar-H), 8.00-8.04 (m, 2H, Ar-H), 8.31 (s, 1H, C-H triazole) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 50.7, 55.3, 58.3, 67.9, 114.1, 116.45 (d, 2C, Ar-C, *J* = 20.0 Hz), 125.4 (C_5 triazole), 125.85 (d, 1C, Ar-C, *J* = 3.0 Hz), 126.5, 130.5, 132.25 (d, 2C, Ar-C, *J* = 10.0 Hz), 143.1 (C_4 triazole), 160.1, 165.2 (C=O ester), 165.75 (d, 1C, Ar-C, *J* = 250.0 Hz), 166.1 (C=O ester) ppm; HRMS (*m/z*) calculated for $C_{20}H_{18}N_3O_5F$ $[M+H]^+$: 400.1264. Found: 400.1236.

1-(2-((4-Nitrobenzyl)oxy)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)methyl 4-fluorobenzoate (3c): White solid; Yield: 87 %; m.p.: 90-94 °C; FT-IR (KBr, ν_{max}, cm^{-1}): 3137 (C-H str., triazole ring), 3081 (C-H str., aromatic ring), 2958 (C-H str., aliphatic), 1748, 1720 (C=O str., ester), 1604, 1459 (C=C str., aromatic ring),1529 (N-O asym. str., NO_2), 1349 (N-O sym. str., NO_2), 1275 (C-O asym. str., ester), 1057 (C-O sym. str., ester); ^{1}H NMR (400 MHz,DMSO-d_6): 5.36(s, 2H, NCH_2), 5.43 (s, 2H, OCH_2), 5.57 (s, 2H, OCH_2), 7.33-7.37 (m, 2H, Ar-H), 8.00-8.04 (m, 2H, Ar-H), 7.65 (d, 2H, Ar-H, *J* = 8.4 Hz), 8.23 (d, 2H, Ar-H, *J* = 8.4 Hz), 8.31 (s, 1H, C-H triazole) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 50.9, 58.5, 66.0, 116.40 (d, 2C, Ar-C, *J* = 20.0 Hz), 124.0, 126.45 (d, 1C, Ar-C, *J* = 3.0 Hz), 126.9 (C_5 triazole), 129.0, 132.25 (d, 2C, Ar-C, *J* = 10.0 Hz), 142.4, 143.5 (C_4 triazole), 147.7, 165.0 (C=O ester), 165.75 (d, 1C, Ar-C, *J* = 250.0 Hz), 167.5 (C=O ester) ppm HRMS (*m/z*) calculated for $C_{19}H_{15}N_4O_6F$ $[M+H]^+$: 415.1009. Found: 415.0965.

1-(2-((4-Chlorobenzyl)oxy)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)methyl 4-fluorobenzoate (3d): White solid; Yield: 92 %; m.p.: 89-93 °C; FT-IR (KBr, ν_{max}, cm^{-1}): 3143 (C-H str., triazole ring), 3081 (C-H str., aromatic ring), 2935 (C-H str., aliphatic), 1719, 1706 (C=O str., ester), 1603, 1462 (C=C str., aromatic ring), 1283 (C-O asym. str., ester), 1057 (C-O sym. str., ester); ^{1}H NMR (400 MHz,DMSO-d_6): 5.35 (s, 2H, NCH_2), 5.43 (s, 2H, OCH_2), 5.57 (s, 2H, OCH_2), 7.32-7.36 (m, 2H, Ar-H), 7.41-7.45 (m, 4H, Ar-H), 8.00-8.03 (m, 2H, Ar-H),8.58 (s, 1H, C-H triazole) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 50.7, 58.3, 67.9, 116.40 (d, 2C, Ar-C, *J* = 20.0 Hz), 125.4 (C_5 triazole), 126.2 (d, 1C, Ar-C, *J* = 3.0 Hz), 129.0, 129.9, 132.65 (d, 2C, Ar-C, *J* = 10.0 Hz), 132.9, 134.8, 143.1 (C_4 triazole), 165.0 (C=O ester), 165.65 (d, 1C, Ar-C, *J* = 250.0 Hz), 166.0 (C=O ester) ppm; HRMS (*m/z*) calculated for $C_{19}H_{15}N_3O_4ClF$ $[M+H]^+$: 404.0813 (^{35}Cl), 406.0784 (^{37}Cl). Found: 404.0735 (^{35}Cl), 406.0706 (^{37}Cl).

1-(2-((4-Methylbenzyl)oxy)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)methyl 4-fluorobenzoate (3e): White solid; Yield: 85 %; m.p.: 84-88 °C; FT-IR (KBr, ν_{max}, cm^{-1}): 3148 (C-H

str., triazole ring), 3076 (C-H str., aromatic ring), 2935 (C-H str., aliphatic), 1742, 1720 (C=O str., ester), 1603, 1440 (C=C str., aromatic ring), 1291 (C-O asym. str., ester), 1053 (C-O sym. str., ester); ^{1}H NMR (400 MHz, $CDCl_3$): 2.23 (s, 3H, CH_3), 5.10(s, 2H, NCH_2), 5.15 (s, 2H, OCH_2), 5.38 (s, 2H, OCH_2), 6.96-7.12 (m, 6H, Ar-H), 7.81 (s, 1H, C-H triazole), 7.92-7.95 (m, 2H, Ar-H)ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1, 50.8, 58.0, 67.9, 115.50 (d, 2C, Ar-C, *J* = 20.0 Hz), 125.6 (C_5 triazole), 125.9 (d, 1C, Ar-C, *J* = 3.0 Hz), 128.6, 129.3, 131.5, 132.25 (d, 2C, Ar-C, *J* = 10.0 Hz), 138.6, 142.9 (C_4 triazole), 165.2 (C=O ester), 165.75 (d, 1C, Ar-C, *J* = 250.0 Hz), 166.1 (C=O ester) ppm; HRMS (*m/z*) calculated for $C_{20}H_{18}N_3O_4F$ $[M+H]^+$: 384.1315. Found: 384.1290.

(1,1'-(((1,4-Phenylene*bis*(methylene))*bis*(oxy))*bis*(2-oxoethane-2,1-diyl))*bis*(1*H*-1,2,3-triazole-4,1-diyl))*bis*-(methylene) dibenzoate (6a): White solid; Yield: 85 %; m.p.: 148-152 °C; FT-IR (KBr, ν_{max}, cm^{-1}): 3148 (C-H str., triazole ring), 3085 (C-H str., aromatic ring), 2958 (C-H str., aliphatic), 1729, 1702 (C=O str., ester), 1611, 1460 (C=C str., aromatic ring), 1270 (C-O asym. str., ester), 1054 (C-O sym. str., ester); ^{1}H NMR (400 MHz,DMSO-d_6): 5.22 (s, 4H, NCH_2), 5.42 (s, 4H, OCH_2), 5.52 (s, 4H, OCH_2), 7.32-7.36 (m, 4H, Ar-H), 7.57 (t, 2H, Ar-H, *J* = 8.0 Hz), 8.05 (d, 4H, Ar-H, *J* = 8.0 Hz), 8.30 (s, 1H, C-H triazole) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 50.8, 59.1, 66.6, 126.9 (C_5 triazole), 128.3, 128.6, 129.6, 129.8, 133.2, 135.9, 142.5 (C_4 triazole), 164.5 (C=O ester), 167.5 (C=O ester) ppm; HRMS (*m/z*) calculated for $C_{32}H_{28}N_6O_8$[M+H]$^+$: 625.2002. Found: 625.1913.

(1,1'-(((1,4-Phenylene*bis*(methylene))*bis*(oxy))*bis*(2-oxoethane-2,1-diyl))*bis*(1H-1,2,3-triazole-4,1-diyl))*bis*-(methylene) *bis*(4-methoxybenzoate)(6b): White solid; Yield: 85 %; m.p.: 166-170 °C; FT-IR (KBr, ν_{max}, cm^{-1}): 3137 (C-H str., triazole ring), 3084 (C-H str., aromatic ring), 2958 (C-H str., aliphatic), 1758, 1712 (C=O str., ester), 1606, 1509, 1460 (C=C str., aromatic ring), 1257 (C-O asym. str., ester), 1054 (C-O sym. str., ester); ^{1}H NMR (400 MHz,DMSO-d_6): 3.83 (s, 6H, OCH_3), 5.21(s, 4H, NCH_2), 5.39 (s, 4H, OCH_2), 5.51 (s, 4H, OCH_2), 7.05 (d, 4H, Ar-H, *J* = 8.8 Hz), 7.37 (s, 4H, Ar-H), 7.92 (d, 4H, Ar-H, *J* = 8.8 Hz), 8.27 (s, 2H, C-H triazole) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 50.9, 55.9, 57.8, 67.0, 114.6, 122.0, 126.8 (C_5 triazole), 128.6, 131.8, 135.9, 142.6 (C_4 triazole), 163.8, 165.6 (C=O ester), 167.5 (C=O ester) ppm; HRMS (*m/z*) calculated for $C_{34}H_{32}N_6O_{10}$ $[M+H]^+$: 685.2213. Found: 685.2112.

(1,1'-(((1,4-Phenylene*bis*(methylene))*bis*(oxy))*bis*(2-oxoethane-2,1-diyl))*bis*(1H-1,2,3-triazole-4,1-diyl))*bis*-(methylene) *bis*(4-nitrobenzoate) (6c): White solid; Yield: 85 %; m.p.: 142-146 °C; FT-IR (KBr, ν_{max}, cm^{-1}): 3154 (C-H str., triazole ring), 3081 (C-H str., aromatic ring), 2958 (C-H str., aliphatic), 1749, 1718 (C=O str., ester), 1609, 1449 (C=C str., aromatic ring),1544 (N-O asym. str., NO_2), 1352 (N-O sym. str., NO_2), 1268 (C-O asym. str., ester), 1051 (C-O sym. str., ester); ^{1}H NMR (400 MHz,DMSO-d_6): 5.22(s, 4H, NCH_2), 5.50 (s, 4H, OCH_2), 5.52 (s, 4H, OCH_2), 7.39 (s, 4H, Ar-H), 8.19 (d, 4H, Ar-H, *J* = 8.8 Hz), 8.33 (d, 4H, Ar-H, *J* = 8.8 Hz), 8.36 (s, 2H, C-H triazole) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 50.8, 59.1, 66.9, 124.4, 127.0 (C_5triazole), 128.7, 131.2, 135.9, 141.9, 142.5 (C_4triazole), 150.8, 164.5 (C=O ester), 167.6 (C=O ester) ppm; HRMS (*m/z*) calculated for $C_{32}H_{26}N_8O_{12}$ $[M+H]^+$: 715.1704. Found: 715.1611.

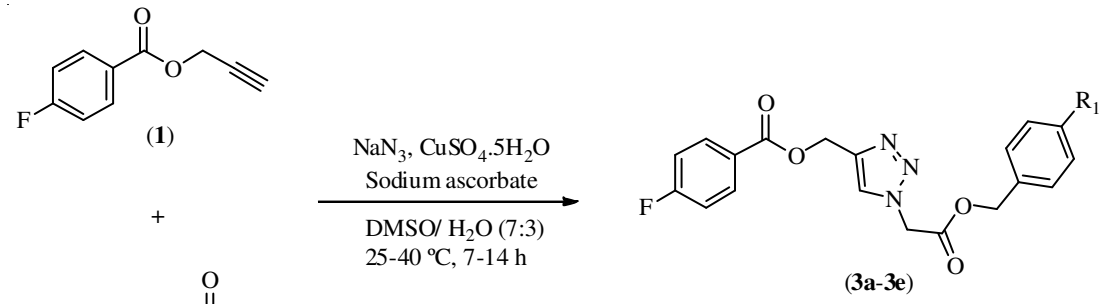
(1,1'-(((1,4-Phenylene*bis*(methylene))*bis*(oxy))*bis*(2-oxoethane-2,1-diyl))*bis*(1H-1,2,3-triazole-4,1-diyl))*bis*-(methylene) *bis*(4-fluorobenzoate) (6d): White solid; Yield: 85 %; m.p.: 136-140 °C; FT-IR (KBr, ν_{max}, cm^{-1}): 3137 (C-H str., triazole ring), 3087 (C-H str., aromatic ring), 2958 (C-H str., aliphatic), 1740, 1721 (C=O str., ester), 1606, 1509 (C=C str., aromatic ring), 1275 (C-O asym. str., ester), 1054 (C-O sym. str., ester); ^{1}H NMR (400 MHz,DMSO-d_6): 5.21(s, 4H, NCH_2), 5.43 (s, 4H, OCH_2), 5.51 (s, 4H, OCH_2), 7.35 (d, 4H, Ar-H, *J* = 8.8 Hz), 7.38 (s, 4H, Ar-H), 8.01-8.05 (m, 4H, Ar-H), 8.29 (s, 2H, C-H triazole) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 50.9, 58.5, 66.6, 116.46 (d, 2C, Ar-C, *J* = 20.0 Hz), 126.9 (C_5 triazole), 126.41 (d, 1C, Ar-C, *J* = 3.0 Hz), 128.7, 132.65 (d, 2C, Ar-C, *J* = 10.0 Hz), 135.9, 142.3 (C_4 triazole), 165.0 (C=O ester), 165.65 (d, 1C, Ar-C, *J* = 250.0 Hz), 167.6 (C=O ester) ppm; HRMS (*m/z*) calculated for $C_{32}H_{26}N_6O_8F_2$ $[M+H]^+$: 661.1814. Found: 661.1730.

(1,1'-(((1,4-Phenylene*bis*(methylene))*bis*(oxy))*bis*(2-oxoethane-2,1-diyl))*bis*(1H-1,2,3-triazole-4,1-diyl))*bis*-(methylene) *bis*(4-methylbenzoate) (6e): White solid; Yield: 85 %; m.p.: 162-166 °C; FT-IR (KBr, ν_{max}, cm^{-1}): 3154 (C-H str., triazole ring), 3031 (C-H str., aromatic ring), 2963 (C-H str., aliphatic), 1750, 1721 (C=O str., ester), 1611, 1446 (C=C str., aromatic ring), 1270 (C-O asym. str., ester), 1049 (C-O sym. str., ester); ^{1}H NMR (400 MHz,DMSO-d_6): 2.38(s, 6H, CH_3), 5.20 (s, 4H, NCH_2), 5.41 (s, 4H, OCH_2), 5.51 (s, 4H, OCH_2), 7.34 (d, 4H, Ar-H, *J* = 8.0 Hz), 7.37 (s, 4H, Ar-H), 7.86 (d, 4H, Ar-H, *J* = 8.0 Hz), 8.29 (s, 2H, C-H triazole) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.6, 50.8, 57.8, 66.6, 126.9 (C_5 triazole), 127.1, 128.6, 129.7, 129.9, 135.8, 142.5 (C_4 triazole), 144.3, 165.9 (C=O ester), 167.6 (C=O ester) ppm; HRMS (*m/z*) calculated for $C_{34}H_{32}N_6O_8$ $[M+H]^+$: 653.2315. Found: 653.2232.

General procedure for *in vitro* antimicrobial evaluation: All the newly synthesized mono and *bis* ester linked 1,4-disubstituted 1,2,3-triazoles**(3a-3e)/(6a-6e)** were accessed for *in vitro* antimicrobial activity against one Gram-positive bacterial strain *viz. Staphylococcus aureus* (MTCC 3160), three Gram-negative bacterial strains *viz. Escherichia coli* (MTCC 443), *Klebsiella pneumonia* (NCDC 138) and *Enterobacter aerogenes* (NCDC 106) and two fungi *viz. Candida albicans* (MTCC 227) and *Aspergillus niger* (MTCC 282)] using standard serial dilution technique.

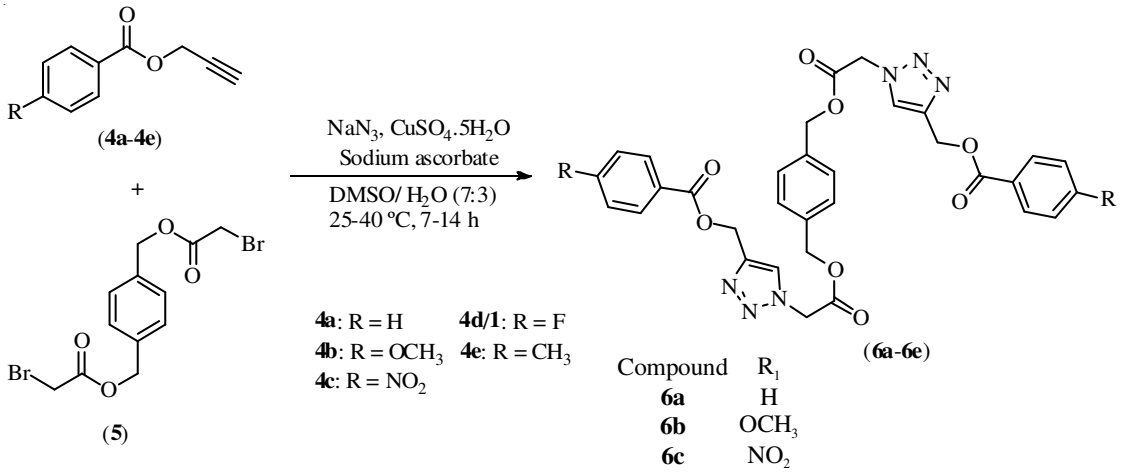
RESULTS AND DISCUSSION

Synthetic route of desired target compounds **(3a-3e)/(6a-6e)** with ester functionality were outlined in **Scheme-I** and **II**. Prop-2-yn-1-yl benzoates **(4a-4e)** were synthesized by dropwise addition of benzoyl chlorides in stirred solution of propargyl alcohol in dry dichloromethane taking N,N-dimethylamino-pyridine as base. Synthesis of benzyl 2-bromooacetates/1,4-phenylene*bis*(methylene) *bis*(2-bromoacetate) **(2a-2e)/(5)** were carried out by taking 1,4-phenylenedimethanol/benzyl alcohols, sodium bicarbonate in acetonitrile and adding slowly bromoacetyl bromide in it. Finally, the ester linked desired 1,4-disubstituted 1,2,3-triazoles



Compound	R_1
3a	H
3b	OCH_3
3c	NO_2
3d	Cl
3e	CH_3

Scheme-I



Compound	R_1
6a	H
6b	OCH_3
6c	NO_2
6d	F
6e	CH_3

Scheme-II

(3a-3e)/(6a-6e) were synthesized *via* click reaction between prop-2-yn-1-yl benzoates **(4a-4e)** and 2-azidoacetates/1,4-phenylene*bis*(methylene) *bis*(2-azido-acetate)which were prepared by *in situ* reaction of respective bromides **(2a-2e)/(5)** with sodium azide.

Afterwards, synthesized target compounds were characterized by various spectral techniques like FTIR, ^{1}H NMR, ^{13}C NMR spectroscopy and HRMS. In FTIR spectra, C-H stretching of triazole ring absorbed in the region at 3154-3137 cm^{-1}. Absorption bands in the region at 1758-1719 cm^{-1} and 1721-1702 cm^{-1} owing to >C=O stretching of esters confirm the formation of triazole derivatives. Absorption bands due to C-H stretching of aromatic rings were observed in the range at 3087-3031 cm^{-1}. Likewise, in ^{1}H NMR spectra, characteristic singlet due to triazolyl proton exhibited in the region at δ 7.81-8.58. Signals due to other aromatic protons were exhibited in their expected range. Moreover, appearance of two signals in region at δ 125.4-127.0 and 142.3-143.5 due to C_5 and C_4 of triazole moiety respectively is significant feature of ^{13}C NMR spectra of ester linked triazole derivatives. Signals in ^{13}C NMR at δ 164.5-165.9 and δ 166.0-167.6 assigned to carbonyl carbon. Values obtained from high resolution mass spectra were in accordance with calculated values.

***in vitro* Microbicidal activity:** Synthesized 1,4-disubstituted 1,2,3-triazole derivatives with ester functionality **(3a-3e)/(6a-6e)**were accessed for *in vitro* microbicidal activity against one Gram-positive bacterial strain *i.e*. *Staphylococcus aureus* (MTCC 3160), three Gram-negative bacterial strains *i.e*. *Escherichia coli* (MTCC 443), *Klebsiella pneumonia* (NCDC 138) and *Enterobacter aerogenes* (NCDC 106) and two fungi *i.e. Candida albicans* (MTCC 227) and *Aspergillus niger* (MTCC 282)] by standard serial dilution technique [28]. Results were represented in minimum inhibitory concentrations (MIC) in terms of μmol/mL. Norfloxacin and fluconazole were used as standard drug for antibacterial and antifungal strains respectively.

It can be analyzed from Table-1 that the synthesized compounds exhibited average to good antibacterial activity against tested bacterial strains. Some of the synthesized triazoles **3d** (MIC, 0.0310), **6c** (MIC, 0.0350), **6d** (MIC, 0.0378) against *S. aureus*; **3c** (MIC, 0.0302), **6c** (MIC, 0.0350), **6d** (MIC, 0.0378) against *E. coli*; **3b** (MIC, 0.0313), **3c** (MIC, 0.0302), **6c** (MIC, 0.0350), **6d** (MIC, 0.0378), against *Klebsiella pneumoniae*; **3c** (MIC, 0.0603), **3d** (MIC, 0.0619), **6c** (MIC, 0.0700), **6d** (MIC, 0.0757) against *Enterobacter aerogenes* revealed apppreciable bactericidal efficacy. Compound **6c** and

TABLE-1
in vitro ANTIBACTERIAL AND ANTIFUNGAL ACTIVITIES OF 1,4-DISUBSTITUTED 1,2,3-TRIAZOLES

Compound	Minimum inhibitory concentration (MIC, μmol/mL)					
	Antibacterial activity				Antifungal activity	
	Gram-positive bacteria		Gram-negative bacteria		*C. albicans*	*A. niger*
	S. aureus	*E. coli*	*K. pneumoniae*	*E. aerogenes*		
3a	0.1354	0.1354	0.1354	0.1354	0.0677	0.1354
3b	0.0626	0.0626	0.0313	0.1252	0.0626	0.0626
3c	0.0603	0.0302	0.0302	0.0603	0.0302	0.0151
3d	0.0310	0.0619	0.1238	0.0619	0.0310	0.0155
3e	0.1304	0.0652	0.0652	0.1304	0.1304	0.0652
6a	0.0400	0.0400	0.0801	0.0801	0.0801	0.0400
6b	0.0730	0.0730	0.0730	0.1461	0.0730	0.0365
6c	0.0350	0.0350	0.0350	0.0700	0.0350	0.0175
6d	0.0378	0.0378	0.0378	0.0757	0.0189	0.0189
6e	0.0766	0.0766	0.0766	0.1532	0.0766	0.0766
Norfloxacin	0.0391	0.0391	0.0391	0.0783	–	–
Fluconazole	–	–	–	–	0.0408	0.0102

6d found to possess broad spectrum antibacterial efficiency against all tested bacterial strains in comparison to standard.

Antibacterial screening data revealed that in case of compounds **3a**-**3e**, triazoles having 4-substituted benzyl moiety displayed better antibacterial activity in comparison to unsubstituted benzyl moiety. Compounds possessing electron withdrawing nitro group on benzyl moiety/benzoate moiety are more prolific than compounds substituted with electron releasing groups.

As listed in Table-1, compound **3c** (MIC, 0.0302), **3d** (MIC, 0.0310), **6c** (MIC, 0.0350), showed comparable antifungal activity to standard drug against *C. albicans*. Compound **6d** (MIC, 0.0189) showed two fold antifungal efficacy to standard drug against *C. albicans*. Compound **3c** (MIC, 0.0151), **3d** (MIC, 0.0155), **6c** (MIC, 0.0175), **6d** (MIC, 0.0189) found to possess better antifungal efficacy against *A. niger*.

Conclusion

In summary, a convenient and straightforward click synthesis of some mono and *bis* 1,4-disubstituted 1,2,3-triazoles was carried out *via* Cu(I) catalyzed reaction of prop-2-yn-1-yl benzoates with 1,4-phenylene*bis*(methylene) *bis*(2-azidoacetate) and benzyl 2-azidoacetates. All synthesized triazole derivatives were characterized by IR, NMR and mass spectrometry and also evaluated for *in vitro* microbicidal activity. Compound **6c** and **6d** were found to display good antibacterial efficiency while, compound **6d** was found to possess excellent efficiency against fungus *C. albicans*.

ACKNOWLEDGEMENTS

The authors are highly grateful to University Grants Commission, New Delhi, India for financial assistance.

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