ARTICLE

A CuAAC Based Click Chemistry Approach for Synthesis of Quinoxaline-1,2,3-Triazole Hybrid Molecular Library and Its Antimicrobial Evaluation

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ABSTRACT

Copper(I)-catalyzed azide alkyne cycloaddition (CuAAC) methodology to develop a library of 3-methyl quinoxaline-1,2,3-triazole hybrid molecules. The designed molecules were synthesized *via* efficient and purification free method. The structures of the achieved compounds were recognized based on their spectral data. The antimicrobial activity for the synthesized compounds was evaluated against four bacterial species and two fungal strains. Six compounds are broad spectrum molecule, which can inhibit the growth of both Gram-positive and Gram-negative bacteria. Two molecules show mainly antifungal activity. Compound **6e** shows highest antibacterial as well as antifungal activity.

KEYWORDS

3-Methyl quinoxaline, 1,2,3-Triazole, [3+2] Cycloaddition, Click chemistry, Antimicrobial activity.

INTRODUCTION

In last decades of research and development in the pharma sector, there has been most-increasing necessity for very quick and useful reactions that come across the three main basic principles of chemical synthesis: applications, flexibility and selectivity for the target drug molecules. These types of reactions would give access to the researchers to modify the synthetic practices that allows them to speedy and reliable development of molecules and libraries of compounds [1]. Click chemistry is an innovative way to the synthesis of drug-like molecules which able to fast-track the drug discovery process by employing a practical and reliable reactions [2].

The main aim to synthesize the triazole ring skeleton is due to its biological activity. Triazole is a useful and most effective five-membered heterocycle core skeleton for the developing of new bioactive molecules. The electron-rich triazole heterocycle excellently binds to various types of enzymes and receptors through wide-ranging linkage. Thus, triazole compounds exhibit a dynamic part in biological activities [3]. Wonderfully, after the discovery of click chemistry, it turns out to be an efficient and quick tool for the regioselective synthesis of 1,2,3-triazole. A large number of triazole compounds used as clinical drugs or highly potent candidates have been employed daily to deal with various types of diseases.

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Compounds containing 1,2,3-triazoles exhibit a wide range of biological activity, including anticancer [4-7], anti-inflammatory [8,9], antitubercular [10-12], antibacterial activity [13] and antimicrobial activity [14].

Hein *et al.* [15] reviewed on the importance of triazole and described the synthesis and different biological activities of triazoles. The quinoxaline moiety has a wide range of pharmacological properties and received a great attention in the medicinal chemistry research. As a result, in present work, the fusion of triazole and quinoxaline for the development of some novel molecules is carried out, which would be useful for the library synthesis. To the best of our knowledge, the statistics of the biological activities of quinoxaline derivatives containing 1,2,3-triazole moiety have been rarely reported. Quinoxaline-triazole hybrid products are less explored. So, ongoing interest to construct a 1,2,3-triazole and quinoxaline as a core skeleton by click transformation.

EXPERIMENTAL

Chemicals and solvents were purchased from the Sigma-Aldrich Chemical Co., Merck Chemicals and Spectrochem Ltd. were of the highest purity grade and the entire chemicals used without further purification. Precoated plates of silica gel G60 F_{254} (0.2 mm, Merck) were used for thin-layer chromatography. Visualization was made under UV light (254 and 365 nm). Spectral analysis was done with the help of FTIR-8400 (Shimadzu), AVANCE-II (400 MHz) NMR spectrophotometer and GC-MS QP-2010 mass spectrophotometer. NMR (^{1}H & ^{13}C) has been done using DMSO-d_6 as a solvent and TMS as an internal standard. Mass analysis was performed by the direct probe method. Melting points were measured in digital melting point apparatus and are uncorrected.

Synthesis of 3-methylquinoxalin-2-ol (1): To a stirred solution of *o*-phenylene diamine (10.0 mmol) in ethanol was added ethyl pyruvate (12.0 mmol) at room temperature and the resulting mixture was refluxed for 3 h. The reaction was monitored by TLC (20% EtOAc:hexane). After completion of the reaction, the mixture was poured into ice-cold water with vigorous stirring. Filtered the mixture, washed with hexane and dried it to obtain pure 3-methylquinoxalin-2-ol (yield: 99%, m.p.: 156-158 ºC).

Synthesis of 2-chloro-3-methylquinoxaline (2): In 3 necked round bottom flask, 3-methylquinoxalin-2-ol (10.0 mmol) was charged with $POCl_3$ (110.0 mmol) at room temperature. Then reaction mixture was stirred for 3 h at reflux temperature. The reaction was monitored by TLC (20% EtOAc: hexane). After completion of the reaction, the mixture was poured into ice-cold water with vigorous stirring and neutralized by $NaHCO_3$ and solid product was obtained, filtered the solid mass, washed with cold water and dried it to obtain pure product 2-chloro-3-methylquinoxaline (yield: 85%, m.p.: 170-172 ºC).

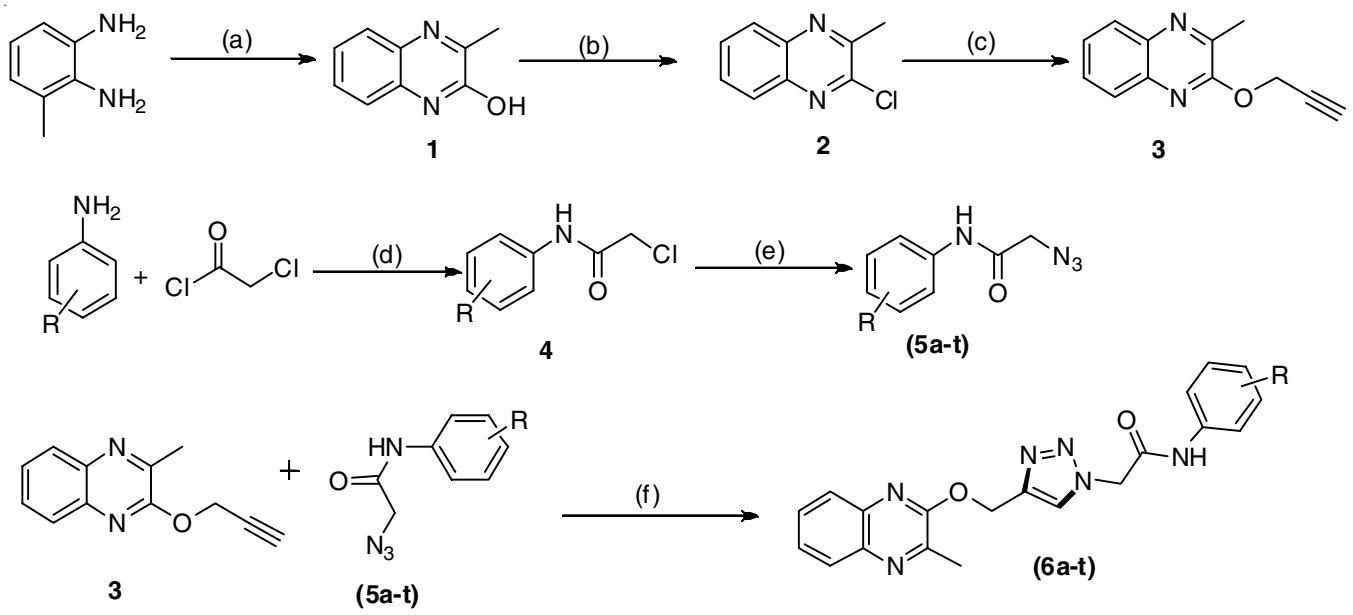
Synthesis of 2-methyl-3-(prop-2-yn-1-yloxy)quinoxaline (3): In a single-necked flat-bottomed flask equipped with Teflon-coated magnetic stir bar, 2-chloro-3-methylquinoxaline (10 mmol) in THF was added dry potassium *tert*-butoxide (30 mmol) and propargyl alcohol (12 mmol) by drop wise manner and stirred the resulting mixture for 3 h at reflux temperature. The reaction was monitored by TLC (50% EtOAc:hexane). After completion of the reaction, the mixture was poured into ice-cold water with vigorous stirring. Filtered the mixture, washed with petroleum ether and dried to obtain pure product 2-methyl-3-(prop-2-yn-1-yloxy)quinoxaline (**3**) (yield: 92%, m.p.: 188-190 ºC).

Synthesis of 2-azido-*N*-substituted phenylacetamide (5a-t): To a solution of substituted aniline (5.0 mmol) in acetone and chloroacetyl chloride (5.0 mmol) was added by drop wise manner, the resulting mixture was stirred for 15 min at room temperature. The reaction mixture was then poured onto the crushed ice and intermediate product was precipitated out. The solid product was isolated by simple vacuum filtration, washed with *n*-hexane. The product was used without further purification. Intermediate products (5.0 mmol) and NaN_3 (15.0 mmol) in DMF were stirred for 24 h at room temperature. After the completion of the reaction-mass was poured onto crushed ice and the desired product (**5a-t**) was precipitated out. Filtered, washed with *n*-hexane to get the desired product (**5a-t**) (yield: 80-90%).

General procedure for derivatives 2-(4-(((3-methylquinoxalin-2-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-phenylacetamide (6a-t): Intermediate (**1a**) (1.0 mmol) and compound **2a-t** (1.0 mmol) was dissolved in 5 mL, a mixture of DMF:H_2O:*t*-BuOH (1:1:1). Sodium ascorbate (1.0 mol%) was added, followed by copper(II)sulphate pentahydrate (5.0 mol%) in water. The reaction mass was stirred continuously for 3-4 h at room temperature. The reaction was a monitor on TLC (1:9, MeOH:DCM). After all the starting material was consumed on TLC, the reaction mass was quenched in a saturated NH_4Cl solution, cooled on ice and the precipitate was collected by filtration, washed with methanol (2 × 10 mL), dried to afford the pure product as a solid powder (yield: 85-98%) (**Scheme-I**).

***N*-(4-Chlorophenyl)-2-(4-(((3-methylquinoxalin-2-yl)-oxy)methyl)-1*H*-1,2,3-triazol-1-yl)acetamide (6a):** Off white amorphous powder, yield: 90%, m.p. 170-172 ºC, IR (KBr, ν_{max}, cm^{-1}): 3263, 3124, 3070,1682, 1597, 1550, 1496, 1427, 1319, 1249, 1219, 1188, 1141, 1095, 1018, 972, 825, 763, 709, 678, 609, 509, 432; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.37 (3H, s, Me), 5.12 (3H, s, -CH_2O), 5.31 (3H, s, -CH_2), 7.28-7.35 (2H, m, aryl), 7.51 (1H, td, *J* = 7.5, 1.5 Hz, aryl), 7.61-7.67 (2H, m, aryl), 7.67-7.78 (2H, m, aryl), 7.91 (1H, dd, *J* = 7.5, 1.5 Hz, aryl), 8.14 (1H, s, aryl), 10.31 (1H, s, -NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.06 (Me), 52.19 (-CH_2O), 59.46 (-CH_2), 120.77, 126.62, 126.75, 127.34, 127.79, 128.81, 129.19, 137.32, 138.14, 138.94, 141.98, 147.80, 155.28 (aryl C), 164.36 (CO). MS (ESI): 408 [M^+].

2-(4-(((3-Methylquinoxalin-2-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-nitrophenyl)acetamide (6b): Off white solid, yield: 85%, m.p. 184-186 ºC, IR (KBr, ν_{max}, cm^{-1}): 3217, 3155, 3055, 1705, 1573, 1504, 1419, 1342, 1257, 1180, 1111, 1057,972, 856, 756, 686, 609, 493; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.38 (3H, s, Me), 5.13 (3H, s, -CH_2O), 5.30 (3H, s, -CH_2), 7.67-7.79 (2H, m, aryl), 7.87-7.97 (3H, m, aryl), 8.14 (1H, s, aryl), 8.15- 8.22 (2H, m, aryl), 10.51 (1H, s, -NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.06 (Me), 52.33 (-CH_2O), 59.46 (-CH_2), 119.05, 125.05, 126.63, 126.75, 126.81, 127.78,



6a: R= 4-Cl	**6b**: R= 4-NO_2	**6c**: R= 3-Cl, 4-F	**6d**: R= 2-Cl	**6e**: R= 3,4-diCH_3
6f: R= 3- Cl	**6g**: R= 1,5-di-Cl	**6h**: R= 2,4-di-Cl	**6i**: R= -H	**6j**: R= 2,4-di-F
6k: R= -pyrimidine	**6l**: R= 4-Br	**6m**: R= 2-pyridine	**6n**: R= 3-pyridine	**6o**: R=Napthalene
6p: R= benzothiazole	**6q**: R= thiazole	**6r**: R= 2,4-di-F	**6s**: R= 5-Br-pyridine	**6t**: R= 5-Me pyridine

Reaction condition: (a) ethyl pyruvate, EtOH, Reflux (b) $POCl_3$, reflux (c) Propargyl alcohol, KtOBu, THF, RT, (d) Acetone,0 °C to RT, (e) NaN_3, DMF, RT, (f) $CuSO_4{\cdot}5H_2O$, Sodium Ascorbate, DMF:H_2O: *t*-BuOH

Scheme-I: Synthesis of target compounds (**6a-t**)

129.20, 138.14, 138.94, 142.02, 142.56, 144.55, 147.80, 155.27 (aryl C), 164.34 (CO). MS (ESI): 420 $[M+H]^+$.

***N*-(3-Chloro-4-fluorophenyl)-2-(4-(((3-methylquinoxalin-2-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)acetamide (6c):** Pale yellow solid, yield: 92%, m.p. 180-182 ºC, IR (KBr, ν_{max}, cm^{-1}): 3255, 3140, 3063, 1681, 1604, 1550, 1504, 1419, 1319, 1226, 1049, 972, 887, 825, 763, 709, 609, 563, 501, 439; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.55 (3H, s, Me), 5.38 (3H, s, -CH_2O), 5.63 (3H, s, -CH_2), 7.17 (1H, s, Aryl), 7.38-7.42 (1H, t, *J* = 8.0 Hz, aryl), 7.47-7.50 (1H, m, aryl), 7.60-7.63 (1H, t, *J* = 6.8 Hz, aryl), 7.68-7.72 (1H, t, *J* = 8.0 Hz, aryl), 7.88-89 (1H, d, *J* = 7.2 Hz, aryl), 7.93-7.95 (1H, d, *J* = 8.4 Hz, aryl), 8.34 (1H, s, aryl), 10.96 (1H, s, -NH). ^{13}C NMR (100 MHz, DMSO): δ 20.05 (Me), 52.15 (-CH_2O), 59.45 (-CH_2), 116.93, 117.15, 119.10, 119.29, 119.50, 119.57, 120.63, 120.63, 126.61, 126.71, 126.77, 127.76, 129.15, 135.76, 138.15, 138.93, 141.96, 147.76, 152.08, 154.50, 155.25 (aryl C), 164.55 (CO). MS (ESI): 426 $[M^+]$.

***N*-(2-Chlorophenyl)-2-(4-(((3-methylquinoxalin-2-yl)-oxy)methyl)-1*H*-1,2,3-triazol-1-yl)acetamide (6d):** Off white solid, yield: 89%, m.p. 172.174 ºC, IR (KBr, ν_{max}, cm^{-1}): 3255, 3063, 1681, 1589, 1453, 1424, 1365, 1327, 1296, 1219, 1188, 1141, 1049, 972, 864, 810, 756, 686, 439; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.55 (3H, s, Me), 5.46 (3H, s, -CH_2O), 5.63 (3H, s, -CH_2), 7.20-7.23 (1H, t, *J* = 7.2 Hz, aryl), 7.32-7.35 (1H, t, *J* = 7.6Hz, aryl), 7.51-7.53 (1H, d, *J* = 7.6 Hz, aryl), 7.60-7.63 (1H, t, *J* = 6.8 Hz, aryl), 7.68-7.74 (2H, m, aryl), 7.87-89 (1H, d, *J* = 7.2 Hz, aryl), 7.93-7.95 (1H, d, *J* = 8.4 Hz, aryl), 8.34 (1H, s, aryl), 10.07 (1H, s, -NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.20 (Me), 52.45 (-CH_2O), 59.62 (-CH_2), 120.82, 122.76, 125.44, 126.12, 127.76, 128.18, 129.32, 136.14, 139.54, 143.89, 145.89, 154.28 (aryl C), 169.02 (CO); MS (ESI): 408 $[M^+]$.

***N*-(3,4-Dimethylphenyl)-2-(4-(((3-methylquinoxalin-2-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)acetamide (6e):** Pale yellow solid, yield: 96%, m.p. 182-184 ºC, IR (KBr, ν_{max}, cm^{-1}): 3279, 3140, 2939, 1681, 1597, 1543, 1427, 1327, 1280, 1226, 1188, 1049, 1018, 972, 825, 763, 717, 609, 555, 439; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.15 (3H, s, Me), 2.17 (3H, s, Me), 2.55 (3H, s, Me), 5.37 (3H, s, -CH_2O), 5.62 (3H, s, -CH_2), 7.04-7.06 (1H, d, *J* = 8.4 Hz, aryl), 7.31-7.32 (2H, m, aryl), 7.32-7.35 (1H, t, *J* = 7.6Hz, aryl), 7.51-7.53 (1H, d, *J* = 7.6 Hz, aryl), 7.59-7.63 (1H, t, *J* = 6.8 Hz, aryl), 7.68-7.71 (2H, m, aryl), 7.87-89 (1H, d, *J* = 7.2 Hz, aryl), 7.92-7.94 (1H, d, *J* = 8.4 Hz, aryl), 8.34 (1H, s, aryl), 10.65 (1H, s, -NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.20 (Me), 19.35 (Me), 20.11 (Me), 52.64 (-CH_2O), 59.62 (-CH_2), 117.91, 120.41, 120.96, 124.77, 125.92, 126.27, 127.89, 129.23, 134.19, 136.84, 138.04, 139.47, 139.81, 143.92, 145.66, 154.28 (aryl C), 168.76 (CO); MS (ESI): 402 $[M^+]$.

***N*-(3-Chlorophenyl)-2-(4-(((3-methylquinoxalin-2-yl)-oxy)methyl)-1*H*-1,2,3-triazol-1-yl)acetamide (6f):** Off white solid, yield: 88%, m.p. 176-178 ºC, IR (KBr, ν_{max}, cm^{-1}): 3286, 3140, 3063, 1681, 1597, 1543, 1481, 1427, 1365, 1327, 12226, 1188, 1049, 956, 864, 810, 763, 709, 678, 609, 555, 439; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.57 (3H, s, Me), 5.13 (2H, s, -CH_2O), 5.31 (2H, s, -CH_2), 7.04-7.08 (1H, d, *J* = 8.4 Hz, aryl), 7.26-7.30 (1H, m, aryl), 7.45-7.47 (1H, t, *J* = 7.6Hz, aryl), 7.51-7.53 (1H, d, *J* = 7.6 Hz, aryl), 7.59-7.63 (1H, t, *J* = 6.8 Hz, aryl), 7.67 -7.78 (2H, m, aryl), 7.89-7.91 (1H, d, *J* = 7.2 Hz,

aryl), 8.14 (1H, s, aryl), 10.34 (1H, s, -NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.11 (Me), 52.64 (-CH_2O), 59.62 (-CH_2), (119.73, 120.57, 120.82, 124.00, 125.37, 125.98, 126.31, 127.76, 129.92, 133.36, 139.28, 143.92, 145.89, 154.28 (aryl C), 168.88 (CO); MS (ESI): 408 [M$^+$].

***N*-(3,5-Dichlorophenyl)-2-(4-(((3-methylquinoxalin-2-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)acetamide (6g):** Off white solid, yield: 91%, m.p. 190-192 ºC, IR (KBr, ν_{max}, cm^{-1}): 3255, 3055, 1681, 1581, 1535, 1465, 1427, 1327, 1280, 1219, 1188, 1134, 1095, 1049, 972, 902, 810, 756, 678, 547, 439; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.55 (3H, s, Me), 5.58 (2H, s, -CH_2O), 5.72 (2H, s, -CH_2), 7.05-7.08 (1H, d, *J* = 8.4 Hz, aryl), 7.27-7.32 (1H, m, aryl), 7.46-7.49 (1H, t, *J* = 7.6 Hz, aryl), 7.50-7.53 (1H, d, *J* = 7.6 Hz, aryl), 7.60-7.63 (1H, t, *J* = 6.8 Hz, aryl), 7.67-7.78 (2H, m, aryl), 7.90-7.92 (1H, d, *J* = 7.2 Hz, aryl), 8.17 (1H, s, aryl), 10.37 (1H, s, -NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.18 (Me), 52.59 (-CH_2O), 59.59 (-CH_2), 119.73, 120.82, 124.13, 125.44, 125.98, 126.62, 127.76, 128.30, 128.70, 129.59, 130.98, 134.83, 139.86, 143.93, 146.00, 154.28 (aryl C), 168.42 (CO), MS (ESI): 442 [M$^+$].

***N*-(2,4-Dichlorophenyl)-2-(4-(((3-methylquinoxalin-2-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)acetamide (6h):** Off white solid, yield: 89%, m.p. 194-196 °C, IR (KBr, ν_{max}, cm^{-1}): 3595, 3471, 3255, 3055, 1674, 1589, 1550, 1427, 1327, 1280, 1226, 1188, 1141, 1033, 972, 817, 763, 717, 609, 547, 493, 439; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.57 (3H, s, Me), 5.56 (2H, s, -CH_2O), 5.67 (2H, s, -CH_2), 7.04-7.06 (1H, d, *J* = 8.4 Hz, aryl), 7.26-7.30 (1H, m, aryl), 7.47-7.49 (1H, t, *J* = 7.6Hz, aryl), 7.50-7.52 (1H, d, *J* = 7.6 Hz, aryl), 7.60-7.64 (1H, t, *J* = 7.6 Hz, aryl), 7.68-7.72 (2H, m, aryl), 7.88-7.90 (1H, d, *J* = 7.2 Hz, aryl), 8.21 (1H, s, aryl), 10.35 (1H, s, -NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.20 (Me), 52.60 (-CH_2O), 59.62 (-CH_2), 118.99, 120.80, 122.52, 125.45, 125.99, 126.62, 127.69, 134.54, 139.86, 143.93, 146.00, 154.28, 168.43 (aryl C), 168.43 (CO) MS (ESI): 442 [M$^+$].

2-(4-(((3-Methylquinoxalin-2-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-phenylacetamide (6i): Off white solid, yield: 97%, m.p. 170-172 ºC, IR (KBr, ν_{max}, cm^{-1}): 3263, 3140, 3063, 1681, 1597, 1550, 1496, 1427, 1357, 327, 1219, 1188, 1049, 1010, 964, 825, 756, 694, 609, 555, 493, 439; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.55 (3H, s, Me), 5.46 (2H, s, -CH_2O), 5.73 (2H, s, -CH_2), 7.10-7.12 (1H, d, *J* = 7.6 Hz, aryl), 7.14-7.18 (2H, m, aryl), 7.27-7.29 (1H, t, *J* = 7.6Hz, aryl), 7.30-7.32 (1H, d, *J* = 7.6 Hz, aryl), 7.40-7.44 (1H, t, *J* = 7.6 Hz, aryl), 7.48-7.52 (3H, m, aryl), 7.68-7.70 (1H, d, *J* = 7.2 Hz, aryl), 8.12 (1H, s, aryl), 10.37 (1H, s, -NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.28 (Me), 52.50 (-CH_2O), 59.25 (-CH_2), 121.34, 124329, 124.77, 125.80, 126.88, 127.66, 129.13, 139.78, 144.10, 145.89, 154.16 (aryl C), 168.94 (CO); MS (ESI): 373 [M$^+$].

***N*-(2,4-Difluorophenyl)-2-(4-(((3-methylquinoxalin-2-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)acetamide (6j):** Off white crystalline powder, yield: 85%, m.p. 196-198 ºC, IR (KBr, ν_{max}, cm^{-1}): 3263, 3070, 1681, 1612, 1550, 1504, 1427, 1373, 1319, 1265, 1226, 1188, 1141, 1103, 1049, 1018, 956, 848, 817, 763, 694, 609, 486, 439; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.58 (3H, s, Me), 5.51 (2H, s, -CH_2O), 5.71 (2H, s, -CH_2), 7.14-7.17 (2H, d, *J* = 7.6 Hz, aryl), 7.42-7.51 (2H, t, *J* = 7.6Hz, aryl), 7.72-7.78 (3H, m, aryl), 7.89-7.95 (3H, m, aryl), 8.14 (1H, s, aryl), 10.42 (1H, s, -NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.28 (Me), 52.52 (-CH_2O), 59.59 (-CH_2), 105.49, 112.16, 120.80, 122.26, 125.15, 125.35, 125.84, 126.29, 127.83, 139.61, 143.92, 146.00, 153.58, 154.28, 156.20, 158.69 (aryl C), 168.38 (CO); MS (ESI): 410 [M$^+$].

2-(4-(((3-Methylquinoxalin-2-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(pyrimidin-2-yl)acetamide (6k): Off white solid, yield: 88%, m.p.198-200 ºC, IR (KBr, ν_{max}, cm^{-1}): 3140, 3070, 3009, 2962, 2916, 1689, 1581, 1519, 1419, 1388, 1311, 1273, 1234, 1180, 1134, 1057, 1010 979, 864, 825, 763, 694, 601, 547, 439; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.55 (3H, s, Me), 5.63 (4H, s, -CH_2O and -CH_2), 7.21-7.23 (2H, t, *J* = 4.4 Hz, aryl), 7.61-7.71 (2H, m, aryl), 7.87-7.89 (2H, t, *J* = 8.0 Hz, aryl), 7.92-7.94 (2H, t, *J* = 8.0 Hz, aryl), 8.31 (1H, s, aryl), 8.68-8.69 (2H, t, *J* = 4.8 Hz, aryl), 11.10 (1H, s, -NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.20 (Me), 52.32 (-CH_2O), 59.21 (-CH_2), 115.11, 120.96, 124.69, 125.85, 139.67, 144.14, 145.89, 154.16, 156.51, 157.73 (aryl C), 168.08 (CO) MS (ESI): 377 [M$^+$].

***N*-(4-Bromophenyl)-2-(4-(((3-methylquinoxalin-2-yl)-oxy)methyl)-1*H*-1,2,3-triazol-1-yl)acetamide (6l):** Off white solid, yield: 98%, m.p. 178-180 ºC, IR (KBr, ν_{max}, cm^{-1}): 3348, 3140, 3055, 2955, 1681, 1597, 1550, 1489, 1435, 1373, 1327, 1226, 1180, 1049, 987, 825, 763, 609, 563, 501;^{1}H NMR (400 MHz, DMSO-d_6) δ 2.55 (3H, s, Me), 5.35 (2H, s, -CH_2O), 5.63 (2H, s, -CH_2), 7.50-7.56 (4H, m, aryl), 7.61-7.72 (2H, m, aryl), 7.87-7.89 (2H, t, *J* = 8.0 Hz, aryl), 7.92-7.94 (2H, t, *J* = 8.0 Hz, aryl), 8.33 (1H, s, aryl), 10.61 (1H, s, -NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.28 (Me), 52.64 (-CH_2O), 59.62 (-CH_2), 117.91, 120.80, 122.18, 126.01, 126.65, 127.83, 131.63, 139.61, 143.61, 146.01, 154.28 (aryl C), 168.80 (CO); MS (ESI): 454 [M$^+$].

***N*-(6-Aminopyridin-2-yl)-2-(4-(((3-methylquinoxalin-2-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)acetamide (6m):** Off white solid, yield: 95%, m.p. 94.196 ºC, IR (KBr, ν_{max}, cm^{-1}): 3225, 3047, 2955, 2924, 1697, 1581, 1435, 1319, 1219, 1180, 1141, 1057, 964, 871, 810, 756, 609, 578, 509;^{1}H NMR (400 MHz, DMSO-d_6) δ 2.55 (3H, s, Me), 5.43 (2H, s, -CH_2O), 5.62 (2H, s, -CH_2), 7.12-7.15 (2H, t, *J* = 6.0 Hz, aryl), 7.61-7.63 (1H, t, *J* = 6.8 Hz, aryl), 7.68-7.72 (1H, t, *J* = 8.0 Hz, aryl), 7.77-7.81 (1H, t, *J* = 8.0 Hz, aryl), 7.87-7.89 (1H, t, *J* = 8.0 Hz, aryl) 7.92-7.95 (1H, t, *J* = 8.0 Hz, aryl), 7.97-7.99 (1H, t, *J* = 8.0 Hz, aryl), 8.34 (1H, s, aryl), 11.01 (1H, s, -NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.21 (Me), 52.53 (-CH_2O), 59.59 (-CH_2), 105.99, 120.91, 124.75, 125.42, 126.64, 127.81, 140.01, 144.10, 145.89, 150.08, 154.16, 156.87 (aryl C), 168.58 (CO); MS (ESI): 390 [M$^+$].

***N*-(5-Aminopyridin-2-yl)-2-(4-(((3-methylquinoxalin-2-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)acetamide (6n):** Off white solid, yield: 90%, m.p. 190-192 ºC, IR (KBr, ν_{max}, cm^{-1}): 3394, 3132, 3055, 3009, 1705, 162, 1558, 1481, 1419, 1365, 1319, 1219, 1180, 1141, 1064, 1033, 972, 810, 763, 709, 609, 563, 447;^{1}H NMR (400 MHz, DMSO-d_6): δ 2.57 (3H, s, Me), 5.41 (2H, s, -CH_2O), 5.63 (2H, s, -CH_2), 7.41 (1H, s, aryl), 7.61-7.63 (1H, t, *J* = 8.0 Hz, aryl), 7.68-7.72 (1H, t, *J* = 8.0 Hz, aryl), 7.87-7.92 (2H, m, aryl) 8.00-8.02 (1H, d, *J* = 8.4 Hz, aryl), 8.35 (1H, s, aryl), 10.74 (1H, s, -NH). ^{13}C NMR (100

MHz, DMSO-d_6): δ 20.11 (Me), 52.40 (-CH_2O), 59.55 (-CH_2), 115.03, 120.93, 120.96, 124.75, 125.49, 126.63, 127.80, 137.57, 139.09, 139.81, 144.14, 145.89, 149.55, 154.17 (aryl C), 169.64 (CO); MS (ESI): 390 [M^+].

***N*-(4-Bromophenyl)-2-(4-(((3-methylquinoxalin-2-yl)-oxy)methyl)-1*H*-1,2,3-triazol-1-yl)acetamide (6o)**: Off white solid, yield: 92%, m.p. 180-182 ºC, IR (KBr, ν_{max}, cm^{-1}):3248, 3055, 2947, 1666, 1550, 1504, 1427, 1327, 1273, 1219, 1180, 1049, 972, 763, 717, 609, 586, 439;^{1}H NMR (400 MHz, DMSO-d_6): δ 2.55 (3H, s, Me), 5.56 (2H, s, -CH_2O), 5.63 (2H, s, -CH_2), 7.48-7.52 (1H, m, aryl), 7.54-7.63 (3H, m, aryl), 7.68-7.72 (2H, m, aryl), 7.78-7.82 (1H, d, *J* = 8.0 Hz, aryl), 7.88-7.90 (1H, d, *J* = 8.4 Hz, aryl), 7.93-7.97 (2Hm, aryl), 8.14-8.16 (1H, d, *J* = 7.6 Hz, aryl), 8.39 (1H, s, aryl), 10.45 (1H, s, -NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.18 (Me), 52.50 (-CH_2O), 59.92 (-CH_2), 114.77, 118.51, 120.18, 126.10, 126.17, 126.75, 126.82, 126.90, 127.18, 127.71, 127.85, 131.16, 134.33, 138.22, 139.85, 143.77, 146.00, 154.56 (aryl C), 168.64 (CO); MS (ESI): 424 [M^+].

***N*-(Benzo[*d*]thiazol-2-yl)-2-(4-(((3-methylquinoxalin-2-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)acetamide (6p):** Off white solid, yield: 86%, m.p. 198-200 ºC, IR (KBr, ν_{max}, cm^{-1}): 3441, 3186, 2916, 1689, 1581, 1419, 1365, 1319, 1288, 1219, 1180, 1064, 964, 817, 763, 717, 617, 516, 439;^{1}H NMR (400 MHz, DMSO-d_6) δ 2.56 (3H, s, Me), 5.50 (2H, s, -CH_2O), 5.63 (2H, s, -CH_2), 7.27-7.28 (1H, d, *J* = 3.2 Hz, aryl), 7.50-7.51 (1H, d, *J* = 3.6 Hz, aryl), 7.60-7.63 (1H, t, *J* = 8.0 Hz, aryl), 7.68-7.72 (1H, t, *J* = 8.0 Hz, aryl), 7.87-7.89 (1H, d, *J* = 8.4 Hz, aryl), 7.93-7.95 (1H, d, *J* = 8.4 Hz, aryl), 8.36 (1H, s, aryl), 12.60 (1H, s, -NH). ^{13}C NMR (100 MHz, DMSO) δ 20.12 (Me), 52.05 (-CH_2O), 59.51 (-CH_2), 120.18, 124.47, 124.90, 126.15, 126.65, 127.19, 127.89, 131.34, 139.49, 143.81, 146.00, 151.35, 154.28, 159.57 (aryl C), 168.13 (CO); MS (ESI): 431 [M^+].

2-(4-(((3-Methylquinoxalin-2-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(thiazol-2-yl)acetamide (6q): Off white solid powder, yield: 88%, m.p. 188-190 °C, IR (KBr, ν_{max}, cm^{-1}): 3549, 3186, 3063, 2893, 762, 1689, 1581, 1427, 1365, 1319, 1288, 1226, 1180, 1057, 964, 825, 763, 617, 516, 439;^{1}H NMR (400 MHz, DMSO-d_6): δ 2.56 (3H, s, Me), 5.50 (2H, s, -CH_2O), 5.63 (2H, s, -CH_2), 7.27-7.28 (1H, d, *J* = 3.2 Hz, aryl), 7.50-7.51 (1H, d, *J* = 3.2 Hz, aryl), 7.60-7.63 (1H, t, *J* = 7.2 Hz, aryl), 7.68-7.72 (1H, t, *J* = 7.6Hz, aryl), 7.87-7.89 (1H, d, *J* = 8.4 Hz, aryl), 7.93-7.95 (1H, d, *J* = 8.4 Hz, aryl), 8.37 (1H, s, aryl), 12.65 (1H, s, -NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.48 (Me), 52.39 (-CH_2O), 59.28 (-CH_2), 111.54, 120.93, 120.96, 124.51, 125.85, 129.94, 128.18, 137.28, 139.47, 143.57, 145.89, 154.20, 160.59 (aryl C), 168.41 (CO) MS (ESI): 381 [M^+].

***N*-(3,5-Difluorophenyl)-2-(4-(((3-methylquinoxalin-2-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)acetamide (6r):** Off white solid, yield: 94%, m.p. 174-176 ºC, IR (KBr, ν_{max}, cm^{-1}): 3263, 3070, 1674, 1612, 1558, 1504, 1427, 1373, 1327, 1265, 1226, 1188, 1141, 1103, 1049, 964, 848, 763, 694, 609, 486, 439;^{1}H NMR (400 MHz, DMSO-d_6): δ 2.55 (3H, s, Me), 5.43 (2H, s, -CH_2O), 5.62 (2H, s, -CH_2), 7.06-7.10 (1H, t, *J* = 6.8 Hz, aryl), 7.34-7.39 (1H, t, *J* = 9.2 Hz, aryl),7.60-7.63 (1H, t, *J* = 7.2 Hz, aryl), 7.68-7.72 (1H, t, *J* = 7.6 Hz, aryl), 7.81-7.89 (2H, m, aryl), 7.93-7.95 (1H, d, *J* = 8.4 Hz, aryl), 8.33 (1H, s, aryl), 10.33 (1H, s, -NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.16 (Me), 52.64 (-CH_2O), 59.55 (-CH_2), 104.16, 120.85, 125.42, 126.29, 127.76, 139.80, 143.89, 146.00, 154.28, 161.55, 164.17 (aryl C), 168.37 (CO) MS (ESI): 410 [M^+].

***N*-(5-Bromopyridin-2-yl)-2-(4-(((3-methylquinoxalin-2-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)acetamide (6s):** Off white solid, yield: 87%, m.p. 196-198 ºC, IR (KBr, ν_{max}, cm^{-1}): 3209, 3155, 3016, 1697, 1573, 1543, 1458, 1427, 1373, 1319, 1219, 1180, 1134, 1095, 1064, 1003, 972, 871, 817, 756, 709, 609, 501, 439;^{1}H NMR (400 MHz, DMSO-d_6): δ 2.55 (3H, s, Me), 5.44 (2H, s, -CH_2O), 5.62 (2H, s, -CH_2), 7.60-7.63 (1H, t, *J* = 7.2 Hz, aryl), 7.68-7.72 (1H, t, *J* = 7.6 Hz, aryl), 7.87-7.89 (1H, d, *J* = 7.6 Hz, aryl), 7.92-7.98 (2H, m, aryl), 8.02-8.04 (1H, t, *J* = 7.6 Hz, aryl), 8.34 (1H, s, aryl), 8.48 (1H, s, aryl), 11.20 (1H, s, -NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.26 (Me), 52.53 (-CH_2O), 59.62 (-CH_2), 112.78, 115.25, 120.82, 126.01, 126.65, 127.83, 139.67, 143.61, 146.01, 148.75, 150.92, 154.28 (aryl C), 169.34 (CO); MS (ESI): 454 [M^+].

***N*-(5-Methylpyridin-2-yl)-2-(4-(((3-methylquinoxalin-2-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)acetamide (6t):** Off white solid, yield: 93%, m.p. 182-184 ºC, IR (KBr, ν_{max}, cm^{-1}): 3178, 3039, 2962, 1689, 1597, 1558, 1473, 1427, 1388, 1319, 1219, 1180, 1141, 1064, 972, 871, 817, 756, 609, 509, 439^{1}H NMR (400 MHz, DMSO-d_6): δ 2.25 (3H, s, Me), 2.55 (3H, s, Me), 5.41 (2H, s, -CH_2O), 5.62 (2H, s, -CH_2), 7.60-7.62 (2H, t, *J* = 7.6 Hz, aryl), 7.68-7.72 (1H, t, *J* = 7.6Hz, aryl), 7.87-7.89 (1H, d, *J* = 7.6 Hz, aryl), 7.92-7.95 (1H, d, *J* = 8.0 Hz, aryl), 8.18 (1H, s, aryl), 8.34 (1H, s, aryl), 10.92 (1H, s, -NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.01 (Me), 20.23 (Me), 52.40 (-CH_2O), 59.51 (-CH_2), 112.84, 120.91, 120.93, 124.77, 125.49, 126.63, 127.97, 137.47, 139.55, 144.14, 145.89, 14736, 150.80, 154.17 (aryl C), 169.53 (CO); MS (ESI): 389 [M^+].

Biological evaluation: *in vitro* antimicrobial activity of the synthesized compounds **6a**, **6b**, **6c**, **6e**, **6i**, **6j**, **6k**, **6l**, **6p** and **6t** were screened against four bacterial species, namely *Bacillus subtilis, Staphylococcus aureus* as a Gram-positive bacteria, *Pseudomonas aeruginosa* and *Escherichia coli* as a Gram-negative bacteria and two fungal strains, namely *Aspergillus paraciticus* and *Aspergillus niger*. Streptomycin, ampicillin and nystatin were used as antibacterial and antifungal reference drugs, respectively. Dimethyl sulfoxide (DMSO) was used as solvent as well as negative reference.

The minimum inhibitory concentration (MIC) was further applied for the selected compounds having good antimicrobial activity. The MIC was determined *via* the double dilution technique. Five concentrations were prepared for each selected compound (1000, 500, 250, 125 and 62.5 µg/mL). The bacteria were inoculated and incubated at 37 ºC for 24 h in nutrient broth medium; however, the fungal strains were inoculated in malt extract broth and incubated for 48 h.

RESULTS AND DISCUSSION

In order to explore the catalytic activity and to optimize the reaction conditions for the [3+2] cycloaddition, the reaction between 2-azido-*N*- phenylacetamide and 2-methyl-3-(prop-2-yn-1-yloxy)quinoxaline was chosen as a model [3+2] cyclo-

addition reaction. As starting point, different reaction conditions such as copper sources, reductant and amount of catalyst were investigated and the present results show that among the studied Cu(I)-catalysts, $CuSO_4·5H_2O$ is the most efficient one for the 1,2,3-triazole click reactions performed under strict click chemistry conditions, specifically by using water as a tertiary solvent along with DMF and *t*-butanol, working at room temperature. Having identified $CuSO_4·5H_2O$ as efficient catalytic systems for the reactions; the effect of the catalyst amount on the conversion yields and the catalyst loading being enhanced from 1 to 4 mol% were explored. As a result, the conversion yields were decreased from 93 to 70% by increasing of catalyst amount.

The reaction conditions were optimized and concluded that $CuSO_4$ has been best catalyst along with sodium ascorbate. Sodium ascorbate play a dual role, it acts as a ligand and reducing agent. It was observed that without the use of reducing agent reaction was not progressed (Table-1). For further investigation, the reaction methodology against various amine substrate scopes was checked. The reaction was successfully carried out without the any problem. All substrates are sufficient pure and having a moderate yield. Proposed reaction mechanism is shown in **Scheme-II**, and it showed that copper(II) convert into copper(I) reduction by sodium ascorbate, it also works as a ligand and made adduct with b convert into c, intermediate c spontaneous react with intermediate d to form intermediate e, intermolecular [3+2] cycloaddition take place and convert into h *via* g and f; lastly ligand and Cu(I) eliminated and went to next cycles.

TABLE-1
OPTIMIZATION OF REACTION CONDITIONS BY SELECTING PROPER Cu SOURCE AND APPROPRIATE REACTION TIME FOR THE COMPLETION OF THE REACTION

Cu source (mol %)	Reductants (mol %)	Time (h)	Yield[a] (%)
–	Sodium ascorbate (5)	12	–
–	Sodium ascorbate (20)	20	–
CuBr(5)	Sodium ascorbate (10)	12	70
CuI(5)	Sodium ascorbate (10)	12	75
Cu_2O(5)	Sodium ascorbate (5)	12	60
$CuSO_4·5H_2O$ (1)	Sodium ascorbate (5)	4	97
$CuSO_4·5H_2O$ (2)	Sodium ascorbate (5)	10	85
$CuSO_4·5H_2O$ (3)	Sodium ascorbate (5)	10	70
$CuSO_4·5H_2O$ (4)	Sodium ascorbate (5)	10	60
$CuSO_4·5H_2O$ (4)	Sodium ascorbate (-)	10	–

Reaction conditions: 2-Azido-*N*-phenylacetamide (1.0 eq), 2-methyl-3-(prop-2-yn-1-yloxy)quinoxaline (1.0 eq.), DMF + *t*-BuOH + Water (1:1:1).

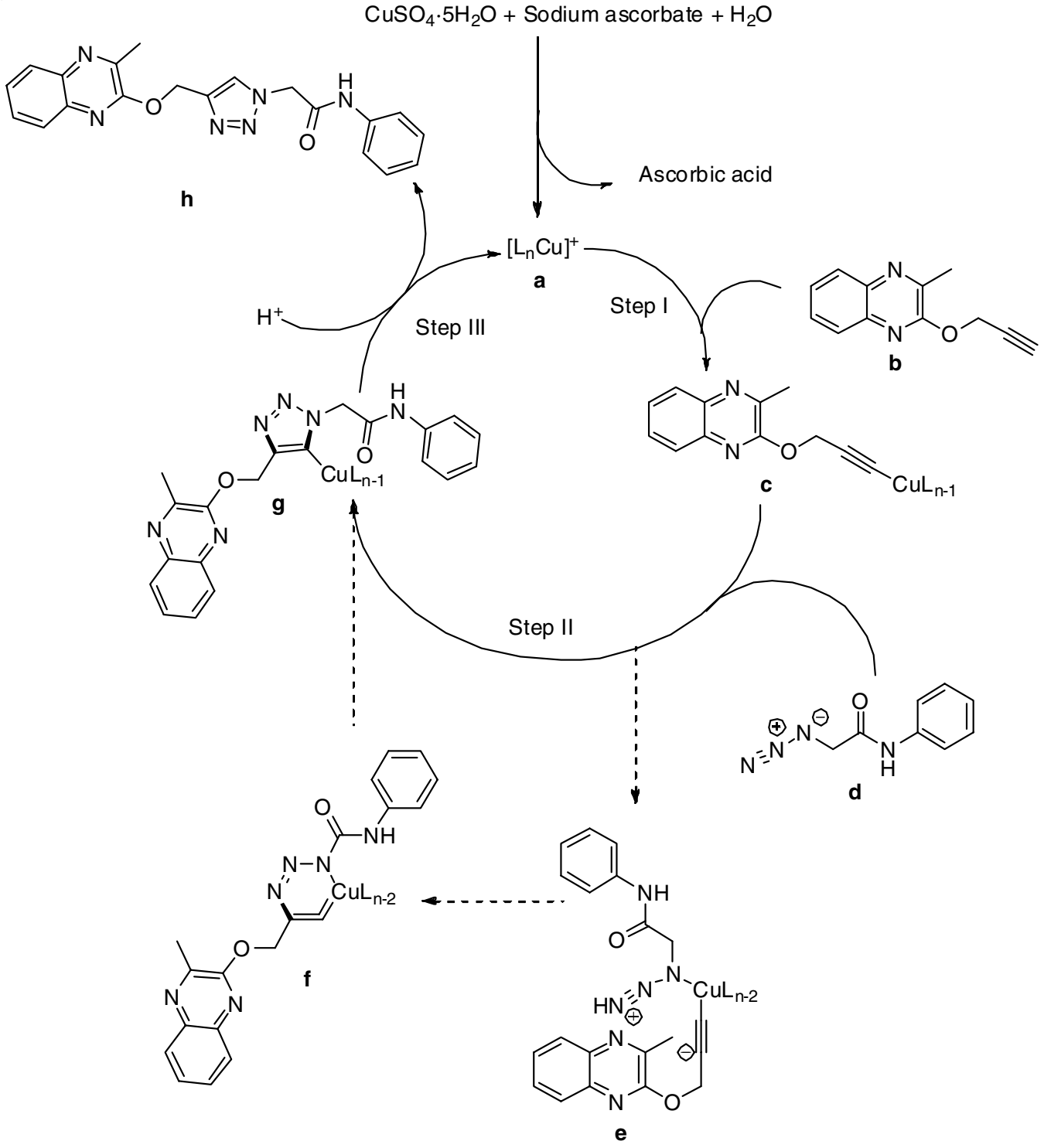
Biological activity: MIC values of the tested compounds for different microorganisms are given in Table-2. Compounds **6c**, **6e** and **6j** presented the highest antibacterial activity against the Gram-positive bacterium *Staphylococcus aureus* and *Bacillus subtilis* with MIC 62.5 µg/mL. The tested compounds **6e** showed the highest antibacterial activity against the Gram-negative bacterium *Pseudomonas aeruginosa* and *Escherichia coli* with MIC 62.5 µg/mL. Compound **6t** exhibited the highest antifungal activity against both *Staphylococcus aureus* and *Aspergillus niger* with MIC 62.5 µg/mL. On the other hand, compounds **6l** and **6e** showed the highest antifungal activity against the *Staphylococcus aureus*. Moreover, several tested compounds presented a good antibacterial activity (compounds **6i**, **6p** and **6t** against *Staphylococcus aureus* and *Bacillus subtilis*; compounds **6c** against *Pseudomonas aeruginosa* and *Escherichia coli*; compounds **6t** against *Escherichia coli*).

Conclusion

In summary, a simple and efficient synthetic method for 20 new quinoxalines-triazole hybrids was developed and also evaluated of their antimicrobial activity. The synthesized compounds were fully characterized using spectral analysis. The tested compounds showed reasonable antibacterial and antifungal activity against the strains. Furthermore, among all the synthesized compounds, only **6e**, **6l** and the **6t** have considerable antifungal activity. Compound **6t** exhibited the highest antifungal activity against both *Aspergillus paraciticus* and *Aspergillus niger* having a MIC value of 62.5 µg/mL. On the other hand, compound **6e** showed the highest antibacterial activity against the Gram-negative bacterium and Gram-positive bacterium having MIC value of 62.5 µg/mL. The results indicated that the methyl functionality on azide may enhance its antifungal activity, while functionalization of quinoxaline with aromatic amines enhances its antibacterial activity.

TABLE-2
THE MINIMAL INHIBITORY CONCENTRATION (MIC: µg/mL) OF THE TESTED COMPOUNDS

Compounds	*Staphylococcus aureus*	*Bacillus subtilis*	*Pseudomonas aeruginosa*	*Escherichia coli*	*Aspergillus paraciticus*	*Aspergillus niger*
Streptomycin	–	–	50	50	–	–
Ampicillin	100	100	–	–	–	–
Nystatin	–	–	–	–	100	100
6a	1000	1000	1000	1000	1000	1000
6b	1000	1000	1000	1000	500	500
6c	125	125	125	125	1000	1000
6e	62.5	62.5	62.5	62.5	62.5	1000
6i	250	250	250	500	1000	1000
6j	62.5	62.5	500	125	1000	1000
6k	1000	1000	1000	1000	1000	1000
6l	1000	1000	1000	1000	62.5	1000
6p	250	250	250	250	250	500
6t	250	250	1000	125	62.5	62.5



Scheme-II: Plausible reaction mechanism for synthesis of 1,2,3-triazole derivatives

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