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GREEN SYNTHESIS OF 1,4- DISUBSTITUTED 1,2,3-TRIAZOLE ACETAMIDE DERIVATIVES BY UTILIZING THE CLICK CHEMISTRY APPROACH

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ABSTRACT

A library of 1,4-disubstituted 1,2,3-triazole acetamide derivatives has been designed and synthesized via a click chemistry approach by using thiazole acetamide azide and acetylene derivative of quinoxaline is described. All the final compounds obtained in an excellent yield (>90%) and were well characterized by analytical spectroscopic methods like ^{1}H NMR, ^{13}C NMR, and Mass spectroscopy. The work reported herewith demonstrates the importance of green chemical synthesis using alternative solvents (water & n-butanol) in experiments to reduce the environmental impact of chemical processes.

Keywords: 1,2,3- triazole, Green Chemistry, Thiazole, Quinoxaline, Click Chemistry, Triazole Acetamide
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INTRODUCTION

Nitrogenous heterocyclic analogs are a significant source of therapeutic drugs in medicinal chemistry.[1] 1,2,3-triazoles are essential nitrogen-containing heterocyclic aromatic molecules with good chemical stability.[2] The broad range of biological activities exhibited by 1,2,3-triazoles has made them a valuable resource for pharmaceutical research and other applications.[3-7] They have exhibited bioactivity against various ailments such as cancer, fungi, diabetes, bacteria, Alzheimer's disease, depression, and influenza. 1,2,3-triazole core moiety is present in various drugs that have been approved by Food and Drug Administration (FDA), including Tazobactam, cefatrizine, rufinamide, TSAO, ribavirin analogs, and the CAI (carbonic anhydrase inhibitors)(Fig.-1).[8-15] Click chemistry has made it possible to synthesize 1,2,3-triazoles rapidly and effectively in the cycloaddition reaction between azides and alkynes, catalyzed by copper. The term "Click Chemistry" was introduced by Sharpless *et al.*[16] The wide range of its applications has had a beneficial effect on many science fields.[17,18] At room temperature, the click reaction that works best is the Huisgen [3+2] cycloaddition of terminal alkynes and organic azides. However, few pieces of literature report that the reaction requires homogenous catalysts and organic solvents that can be dangerous, have low yields, have longer reaction times, have difficult reaction mechanisms, have side products that are bad for the environment, and time-consuming reaction work-up.[19,20]

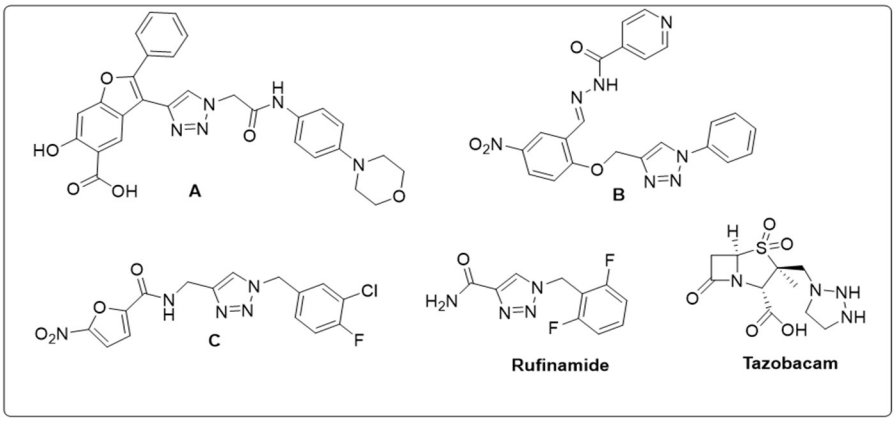

Fig.-1: Drugs and Biologically Active Compounds with the 1,2,3-triazole Unit

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Green chemistry principles are required in click chemistry to promote sustainability and reduce the environmental impact of chemical reactions. By using green chemistry principles, click chemistry can be designed to be more efficient, safer, and less wasteful. This includes using non-toxic reagents, minimizing the use of toxic solvents, and reducing energy consumption. Incorporating the green chemistry concept can make click chemistry more feasible. Research for effective, eco-friendly processes is one of the key objectives in the field of organic synthesis, which focuses on biologically active compounds.[21-25]

Many studies have reported the biological importance of thiazole and quinoxaline as a heterocyclic scaffold ensuring a bright future in medicinal chemistry.[26] Whereas the 1,2,3-triazole acetamide linkage has also been proven to be significantly more effective for a number of biological activities.[27, 28]

In addition to this, we also have previously reported the novel 1,2,3-triazole scaffold coupled to dihydropyridines/dihydropyridines and found to be potent anticancer agents.[29, 30] These findings along with our earlier studies encouraged to create a library of 1,2,3-triazole acetamide derivatives linking the thiazole and the quinoxaline moieties.

EXPERIMENTAL

Material and Methods

All the substances and solvents were from Merck, Loba, and BLD Pharma and had not been further purified before usage. The open capillary technique was used to calculate melting points. Thin layer chromatography (TLC) was used with silica-coated aluminum TLC plates (TLC silica gel 60 f254, Merck) and several eluent systems to track the reaction's progress and the purity of the chemicals. By exposing the dried plates to UV light, KMnO4 stain, and iodine vapor, the spots could be seen. On a Bruker 400 MHz NMR spectrometer, ^{1}H and ^{13}C NMR spectra in DMSO-d_6 were noted. Chemical shift values (δ) relative to tetramethylsilane (TMS), the internal standard reagent, are reported in parts per million (ppm).

A Common Procedure for Formation of 1,2,3-triazole Acetamide Linked with Thiazole and Quinoxaline Derivatives (11a-h, 12a-i)

A stirred solution of various thiazole acetamide azide (7a-e) and (10a-e) (1.0 eq) in water: n-butanol (1:1), and acetylene derivative of quinoxaline (1.0 eq), $CuSO_4.5H_2O$ (40 mol%), and L-sodium ascorbate (0.1 eq), was added at room temperature. For 4 to 5 hours, the reaction mixture was stirred at ambient temperature while the progress of the reaction was monitored using thin-layer chromatography. When the reaction was complete, the mixture was added to chilled water, and the resulting solid was filtered and dried under a vacuum.

N-(4-phenylthiazol-2-yl)-2-(4-((quinoxalin-2-yloxy)methyl)-*1H*-1,2,3-triazol-1-yl)acetamide (11a)

Compound 11a was synthesized from 2-azido-N-(4-phenylthiazol-2-yl)acetamide (0.1 g, 0.39 mmol), 2-(ethynyloxy)quinoxaline (0.066 g, 0.39 mmol), L-sodium ascorbate (0.0076 g, 0.039 mmol) and $CuSO_4.5H_2O$ (40 mol %). Yield 0.162 g (95%); ^{1}H NMR (DMSO-d_6) δ 5.43 (2H, s, CH_2)., 5.55 (2H, s, CH_2), 7.23 (1H, s, ArH), 7.35 (1H, d, J = 6.4, ArH), 7.41 (3H, t, J = 7.6 Hz, ArH), 7.68 (1H, t, J = 7.6 Hz, ArH), 7.86(3H, m, ArH), 8.16 (1H, s, ArH), 8.34 (1H, s, ArH), 12.7 (1H, s, NH). ^{13}C NMR (DMSO-d_6) δ 60.29, 108.9, 121.05, 123.2, 126.1, 127.9, 128.3, 129.2, 130.9, 134.6, 139.4, 141.6, 141.7, 144.2, 148.3, 158.06. MS m/z: 444.4 (MH^+, 100%)

N-(4-(4-nitrophenyl)thiazol-2-yl)-2-(4-((quinoxalin-2-yloxy)methyl)-*1H*-1,2,3-triazol-1-yl)acetamide (11b)

Compound 11b was synthesized from 2-azido-N-(4-(4-nitrophenyl)thiazol-2-yl)acetamide (0.1 g, 0.32 mmol), 2-(ethynyloxy)quinoxaline (0.056 g, 0.32 mmol), L-sodium ascorbate (0.0064 g, 0.032 mmol) and $CuSO_4.5H_2O$ (40 mol %). Yield 0.15 g (93%);^{1}H NMR (DMSO-d_6) δ 5.29 (2H, s, CH_2)., 5.54 (2H, s, CH_2), 7.39 (2H, t, J = 7.6 ArH), 7.77 (2H, d, J = 12.1, ArH), 7.82 (1H, dd, J = 7.2, 8.0 Hz, ArH), 7.97 (1H, s, ArH), 8.25(4H, m, ArH), 8.32 (1H, s, ArH), 12.5 (1H, s, NH). ^{13}C NMR (DMSO-d_6) δ 55.0, 60.2, 113.3, 121.05, 123.2, 124.7, 127.0, 127.9, 130.9, 139.4, 140.6, 141.6, 141.7, 144.2, 146.9, 148.3, 158.0. MS m/z: 488 (MH^+, 100%).

2-(4-((quinoxalin-2-yloxy)methyl)-*1H*-1,2,3-triazol-1-yl)-N-(4-(p-tolyl)thiazol-2-yl)acetamide (11c)

Compound 11c was synthesized from 2-azido-N-(4-(p-tolyl)thiazol-2-yl)acetamide (0.1 g, 0.36 mmol), 2-(ethynyloxy)quinoxaline (0.062 g, 0.36 mmol), L-sodium ascorbate (0.0072 g, 0.036 mmol) and

$CuSO_4.5H_2O$ (40 mol %). Yield 0.155 g (93%); ^{1}H NMR (DMSO-d_6) δ 2.33 (3H, s, CH_2)., 5.43 (2H, s, CH_2), 5.55 (2H, s, CH_2), 7.24 (2H, d, *J* = 7.7 ArH), 7.35 (1H, d, *J* = 6.4, ArH), 7.43 (1H, dt, *J* = 14.8, 7.6 Hz, ArH), 7.60 (1H, d, *J* = 8.5 Hz, ArH), 7.68 (2H, t, *J* = 7.7 ArH), 7.79 (1H, d, *J* = 7.2 ArH), 7.89 (1H, dd, J = 13.2, 7.8, ArH), 8.16 (1H, s, ArH), 8.34 (1H, s, ArH), 12.6 (1H, s, NH). ^{13}C NMR (DMSO-d_6) δ 21.2, 59.3, 72.3, 108.03, 115.7, 124.1, 125.9, 126.08, 129.8, 130.2, 131.6, 131.9, 133.3, 137.6, 179.4, 150.6. MS m/z: 458.5 (MH^+, 100%).

N-(4-(4-fluorophenyl)thiazol-2-yl)-2-(4-((quinoxalin-2-yloxy)methyl)-*1H*-1,2,3-triazol-1-yl)acetamide (11d)

Compound 11d was synthesized from 2-azido-N-(4-(4-fluorophenyl)thiazol-2-yl)acetamide (0.1 g, 0.36 mmol), 2-(ethynyloxy)quinoxaline (0.061 g, 0.36 mmol), L-sodium ascorbate (0.0071 g, 0.036 mmol) and $CuSO_4.5H_2O$ (40 mol %). Yield 0.15 g (90%); ^{1}H NMR (DMSO-d_6) δ 5.43 (2H, s, CH_2)., 5.55 (2H, s, CH_2), 7.27 (2H, t, *J* = 8.5Hz, ArH), 7.41 (1H, t, *J* = 7.6 Hz, ArH), 7.67 (2H, dd, *J* = 15.5, 7.5 Hz, ArH), 7.80 (1H, d, *J* = 8.4 Hz, ArH), 7.87 (1H, d, *J* = 7.9 Hz, ArH), 7.98-7.90 (2H, m, ArH), 8.2 (1H, s, ArH), 8.3 (1H, s, ArH), 12.8 (1H, s, NH). ^{13}C NMR (DMSO-d_6) δ 60.2, 78.4, 113.3, 121.1, 123.1, 124.6, 126.9, 127.9, 130.9, 139.3, 140.6, 141.7, 144.5, 146.9, 148.3, 157.2. MS m/z: 462.4 (MH^+, 100%).

N-(4-(4-chlorophenyl)thiazol-2-yl)-2-(4-((quinoxalin-2-yloxy)methyl)-*1H*-1,2,3-triazol-1-yl)acetamide (11e)

Compound 11e was synthesized from 2-azido-N-(4-(4-chlorophenyl)thiaol-2-yl)acetamide (0.1 g, 0.34 mmol), 2-(ethynyloxy)quinoxaline (0.058 g, 0.34 mmol), L-sodium ascorbate (0.0067 g, 0.034 mmol) and $CuSO_4.5H_2O$ (40 mol %). Yield 0.148 g (91%); ^{1}H NMR (DMSO-d_6) δ 5.43 (2H, s, CH_2), 5.55 (2H, s, CH_2), 7.41 (1H, t, *J* = 7.7 Hz, ArH), 7.51 (2H, d, *J* = 8.2 Hz, ArH), 7.68 (3H, t, *J* = 7.7 Hz, ArH), 7.73 (3H, m, ArH), 8.2 (1H, s, ArH), 8.3 (1H, s, ArH), 12.8 (1H, s, NH). ^{13}C NMR (DMSO-d_6) δ 60.1, 73.2, 115.7, 115.9, 116.2, 124.1, 125.9, 128.1, 130.2, 131.3, 131.6, 132.6, 133.3, 142.01, 150.6, 154.5, 161.03, 163.4. MS m/z: 478.9 (MH^+, 100%).

2-(4-(((6-nitroquinoxalin-2-yl)oxy)methyl)-*1H*-1,2,3-triazol-1-yl)-N-(4-phenylthiazol-2-yl)acetamide (11f)

Compound **11f** was synthesized from 2-azido-N-(4-phenylthiazol-2-yl)acetamide (0.1 g, 0.38 mmol), 2-(ethynyloxy)-6-nitroquinoxaline (0.082 g, 0.38 mmol), L-sodium ascorbate (0.0076 g, 0.038 mmol) and $CuSO_4.5H_2O$ (40 mol %). Yield 0.175 g (93%); ^{1}H NMR (DMSO-d_6) δ 5.52 (2H, s, CH_2)., 5.68 (2H, s, CH_2), 7.32 (1H, s, ArH), 7.42 (2H, s, ArH), 7.64 (1H, s, ArH), 7.84 (1H, d, *J* = 6.4 Hz, ArH), 8.26 (1H, d, *J* = 9.2 Hz, ArH), 8.39 (1H, t, *J* = 7.2 Hz, ArH), 8.46 (1H, s, ArH), 8.72 (1H, s, ArH), 8.85 (1H, s, ArH), 12.8 (1H, s, NH). ^{13}C NMR (DMSO-d_6) δ 60.2, 108.9, 121.05, 123.2, 126.1, 127.9, 128.3, 129.2, 130.9, 134.6, 139.4, 141.6, 141.7, 144.2, 148.3, 158.06. MS m/z: 489.3 (MH^+, 100%).

N-(4-(4-nitrophenyl)thiazol-2-yl)-2-(4-(((6-nitroquinoxalin-2-yl)oxy)methyl)-*1H*-1,2,3-triazol-1-yl)acetamide (11g)

Compound 11g was synthesized from 2-azido-N-(4-(4-nitrophenyl)thiazol-2-yl)acetamide (0.1 g, 0.32 mmol), 2-(ethynyloxy)-6-nitroquinoxaline (0.071 g, 0.32 mmol), L-sodium ascorbate (0.0064 g, 0.032 mmol) and $CuSO_4.5H_2O$ (40 mol %). Yield 0.16 g (91%); ^{1}H NMR (DMSO-d_6) δ 5.54 (2H, s, CH_2)., 5.69 (2H, s, CH_2), 8.02 (1H, s, ArH), 8.16 (2H, d, *J* = 8.1 Hz, ArH), 8.29 (3H, dd, *J* = 18.2, 8.7 Hz, ArH), 8.39 (1H, dd, *J* = 9.0, 2.6, Hz, ArH), 8.72 (1H, s, ArH), 8.88 (1H, s, ArH), 13.07 (1H, s, NH). ^{13}C NMR (DMSO-d_6) δ 55.0, 60.2, 113.3, 121.05, 123.5, 124.7, 127.0, 127.9, 130.9, 139.4, 140.6, 141.6, 141.7, 144.2, 146.9, 148.3, 158.05. MSS m/z: 534.5 (MH^+, 100%).

2-(4-(((6-nitroquinoxalin-2-yl)oxy)methyl)-*1H*-1,2,3-triazol-1-yl)-N-(4-(p-tolyl)thiazol-2-yl)acetamide (11h)

Compound 11h was synthesized from 2-azido-N-(4-(p-tolyl)thiazol-2-yl)acetamide (0.1 g, 0.36 mmol), 2-(ethynyloxy)-6-nitroquinoxaline (0.078 g, 0.36 mmol), L-sodium ascorbate (0.0072 g, 0.036 mmol) and $CuSO_4.5H_2O$ (40 mol %). Yield 0.17 g (92%); ^{1}H NMR (DMSO-d_6) δ 5.53 (2H, s, CH_2)., 5.69 (2H, s, CH_2), 7.25 (2H, d, *J* = 7.8 Hz, ArH), 7.60 (1H, s, ArH), 7.79 (3H, d, *J* = 7.7 Hz, ArH), 8.26 (1H, d, *J* = 9.0 Hz, ArH), 8.39 (1H, dd, *J* = 9.0, 2.5 Hz, ArH), 8.48 (1H, s, ArH), 8.71 (1H, d, *J* = 2.5 Hz, ArH), 8.85 (1H, s,

ArH), 12.82 (1H, s, NH). ^{13}C NMR (DMSO-d_6) δ 51.5, 60.2, 108.1, 121.03, 123.2, 126.08, 128.0, 129.8, 130.9, 137.7, 139.9, 141.6, 148.3, 149.5, 157.9, 165.3. MS m/z: 503.5 (MH^+, 100%).

N-phenyl-2-(4-((quinoxalin-2-yloxy)methyl)-*1H*-1,2,3-triazol-1-yl)acetamide (12a)
Compound 12a was synthesized from 2-azido-N-phenylacetamide (0.1 g, 0.57 mmol), 2-(ethynyloxy)quinoxaline (0.069 g, 0.57 mmol), L-sodium ascorbate (0.011 g, 0.057 mmol) and $CuSO_4.5H_2O$ (40 mol %). Yield 0.15 g (98%); ^{1}H NMR (DMSO-d_6) δ 5.28 (2H, s, CH_2)., 5.54 (2H, s, CH_2), 7.08 (1H, t, *J* = 7.4 Hz ArH), 7.32 (2H, t, *J* = 7.8 Hz, ArH), 7.41 (1H, t, *J* = 7.7 Hz, ArH), 7.55 (2H, d, *J* = 8.0 Hz, ArH), 7.72 - 7.63(1H, m, ArH), 7.79 (1H, d, J = 8.7 Hz, ArH), 7.87 (1H, DD, *J* = 8.0, 1.5 Hz, ArH), 8.12 (1H, s, ArH), 8.33 (1H, s, ArH), 10.45 (1H, s, NH). ^{13}C NMR (DMSO-d_6) δ 52.64, 115.74, 119.63, 124.1, 124.2, 125.9, 129.3, 130.2, 131.5, 132.6, 133.3, 138.8, 141.8, 150.6, 154.4, 164.5. MS m/z: 361.3 (MH^+, 100%).

N-(4-bromophenyl)-2-(4-((quinoxalin-2-yloxy)methyl)-*1H*-1,2,3-triazol-1-yl)acetamide (12b)
Compound 12b was synthesized from 2-azido-N-(4-bromophenyl)acetamide (0.1 g, 0.39 mmol), 2-(ethynyloxy)quinoxaline (0.067 g, 0.39 mmol), L-sodium ascorbate (0.008 g, 0.039 mmol) and $CuSO_4.5H_2O$ (40 mol %). Yield 0.16 g (93%); ^{1}H NMR (DMSO-d_6) δ 5.28 (2H, s, CH_2)., 5.54 (2H, s, CH_2), 7.4 (1H, t, *J* = 7.6 Hz ArH), 7.51 (4H, q, *J* = 9.2 Hz, ArH), 7.68 (1H, q, *J* = 7.6 Hz, ArH), 7.78 (1H, d, *J* = 8.4 Hz, ArH), 7.86 (1H, d, *J* = 7.2 Hz, ArH), 8.12 (1H, s, ArH), 8.33 (1H, s, ArH), 10.58 (1H, s, NH). ^{13}C NMR (DMSO-d_6) δ 52.6, 115.7, 115.8, 121.5, 124.1, 125.9, 130.2, 131.5, 132.2, 132.6, 133.3, 138.2, 141.9, 150.6, 154.4, 164.7. MS m/z: 441.3 (MH^+, 100%).

N-(4-nitrophenyl)-2-(4-((quinoxalin-2-yloxy)methyl)-*1H*-1,2,3-triazol-1-yl)acetamide (12c)
Compound 12c was synthesized from 2-azido-N-(4-nitrophenyl)acetamide (0.1 g, 0.45 mmol), 2-(ethynyloxy)quinoxaline (0.077 g, 0.45 mmol), L-sodium ascorbate (0.0089 g, 0.039 mmol) and $CuSO_4.5H_2O$ (40 mol %). Yield 0.175 g (95%); ^{1}H NMR (DMSO-d_6) δ 5.37 (2H, s, CH_2)., 5.55 (2H, s, CH_2), 7.4 (1H, t, *J* = 8.0 Hz, ArH), 7.68 (1H, q, *J* = 7.2 Hz, ArH), 7.85 – 7.76 (3H, m, ArH), 7.87 (1H, dd, *J* = 8.0, 1.5, Hz, ArH), 8.14 (1H, s, ArH), 8.29 – 8.20 (3H, m, ArH), 8.33 (1H, s, ArH), 10.05 (1H, s, NH). ^{13}C NMR (DMSO-d_6) δ 52.7, 115.7, 119.4, 124.1, 125.5, 125.9, 130.2, 131.6, 132.6, 133.3, 141.9, 143.03, 144.9, 150.6, 154.9, 165.7, MS m/z: 406.3 (MH^+, 100%).

N-(4-chlorophenyl)-2-(4-((quinoxalin-2-yloxy)methyl)-*1H*-1,2,3-triazol-1-yl)acetamide (12d)
Compound 12d was synthesized from 2-azido-N-(4-chlorophenyl)acetamide (0.1 g, 0.47 mmol), 2-(ethynyloxy)quinoxaline (0.081 g, 0.47 mmol), L-sodium ascorbate (0.0093 g, 0.047 mmol) and $CuSO_4.5H_2O$ (40 mol %). Yield 0.173 g (92%); ^{1}H NMR (DMSO-d_6) δ 5.28 (2H, s, CH_2)., 5.54 (2H, s, CH_2), 7.45 – 7.34 (3H, m, ArH), 7.63 – 7.54 (2H, m, ArH), 7.67 (1H, ddd, J = 8.6, 7.3, 1.6 Hz, ArH), 7.79 (1H, dd, *J* = 8.5, 1.2, Hz, ArH), 7.86 (1H, dd, *J* = 8.0, 1.5 Hz, ArH), 8.12 (1H, s, ArH), 8.33 (1H, s, ArH), 10.59 (1H, s, NH). ^{13}C NMR (DMSO-d_6) δ 52.6, 115.7, 121.2, 124.1, 125.9, 127.8, 129.3, 130.2, 131.5, 132.6, 133.3, 137.7, 141.9, 150.5, 154.4, 164.7. MS m/z: 395.4 (MH^+, 100%).

N-(3,4-dichlorophenyl)-2-(4-((quinoxalin-2-yloxy)methyl)-*1H*-1,2,3-triazol-1-yl)acetamide (12e)
Compound 12e was synthesized from 2-azido-N-(3,4-dichlorophenyl)acetamide (0.1 g, 0.41 mmol), 2-(ethynyloxy)quinoxaline (0.069 g, 0.41 mmol), L-sodium ascorbate (0.0080 g, 0.041 mmol) and $CuSO_4.5H_2O$ (40 mol %). Yield 0.168 g (96%); ^{1}H NMR (DMSO-d_6) δ 5.29 (2H, s, CH_2)., 5.53 (2H, s, CH_2), 7.45 – 7.38 (2H, m, ArH), 7.58 (1H, d, *J* = 8.8 Hz, ArH), 7.66 (1H, t, *J* = 8.4 Hz, ArH), 7.78 (1H, d, *J* = 8.4, Hz, ArH), 7.85 (1H, d, *J* = 8.0, Hz, ArH), 7.9 (1H, d, *J* = 7.4, Hz, ArH), 8.1 (1H, s, ArH), 8.32 (1H, s, ArH), 10.74 (1H, s, NH). ^{13}C NMR (DMSO-d_6) δ 52.6, 115.7, 119.7, 120.9, 124.1, 125.7, 125.9, 130.2, 131.3, 131.5, 132.6, 133.3, 138.8, 141.9, 150.6, 154.4, 165.2. MS m/z: 429.3 (MH^+, 100%).

2-(4-(((6-nitroquinoxalin-2-yl)oxy)methyl)-*1H*-1,2,3-triazol-1-yl)-n-phenylacetamide (12f)
Compound 12f was synthesized from 2-azido-N-phenylacetamide (0.1 g, 0.56 mmol), 2-(ethynyloxy)-6-nitroquinoxaline (0.122 g, 0.56 mmol), L-sodium ascorbate (0.011 g, 0.056 mmol) and $CuSO_4.5H_2O$ (40 mol %). Yield 0.21 g (91%); ^{1}H NMR (DMSO-d_6) δ 5.37 (2H, s, CH_2)., 5.76 (2H, s, CH_2), 7.07 (1H, t, *J* = 7.2 Hz, ArH), 7.31 (3H, t, *J* = 7.6 Hz, ArH), 7.55 (2H, d, *J* = 8.0 Hz, ArH), 7.82 (1H, d, *J* = 9.2, Hz, ArH),

8.25 – 8.13 (1H, m, ArH), 8.48 (1H, s, ArH), 8.49 (1H, s, ArH), 10.45 (1H, s, NH). ^{13}C NMR (DMSO-d_6) δ 52.7, 76.9, 111.3, 116.8, 119.7, 124.2, 126.9, 129.3, 131.9, 138.8, 143.2, 153.3, 164.4. MS m/z: 405.3 (MH^+, 100%).

N-(4-nitrophenyl)-2-(4-(((6-nitroquinoxalin-2-yl)oxy)methyl)-*1H*-1,2,3-triazol-1-yl)acetamide (12g)
Compound 12g was synthesized from 2-azido-N-(4-nitrophenyl)acetamide (0.1 g, 0.45 mmol), 2-(ethynyloxy)-6-nitroquinoxaline (0.097 g, 0.45 mmol), L-sodium ascorbate (0.0089 g, 0.045 mmol) and $CuSO_4.5H_2O$ (40 mol %). Yield 0.19 g (93%); ^{1}H NMR (DMSO-d_6) δ 5.37 (2H, s, CH_2)., 5.55 (2H, s, CH_2), 7.4 (1H, t, J = 8.0 Hz, ArH), 7.68 (1H, q, J = 7.2 Hz, ArH), 7.85 – 7.76 (2H, m, ArH), 7.87 (1H, dd, J = 8.0, 1.5, Hz, ArH), 8.14 (1H, s, ArH), 8.29 – 8.20 (3H, m, ArH), 8.33 (1H, s, ArH), 10.05 (1H, s, NH). ^{13}C NMR (DMSO-d_6) δ 52.7, 115.7, 119.4, 124.1, 125.5, 125.9, 130.2, 131.6, 132.6, 133.3, 141.9, 143.03, 144.9, 150.6, 154.9, 165.7. MS m/z: 450. (MH^+, 100%).

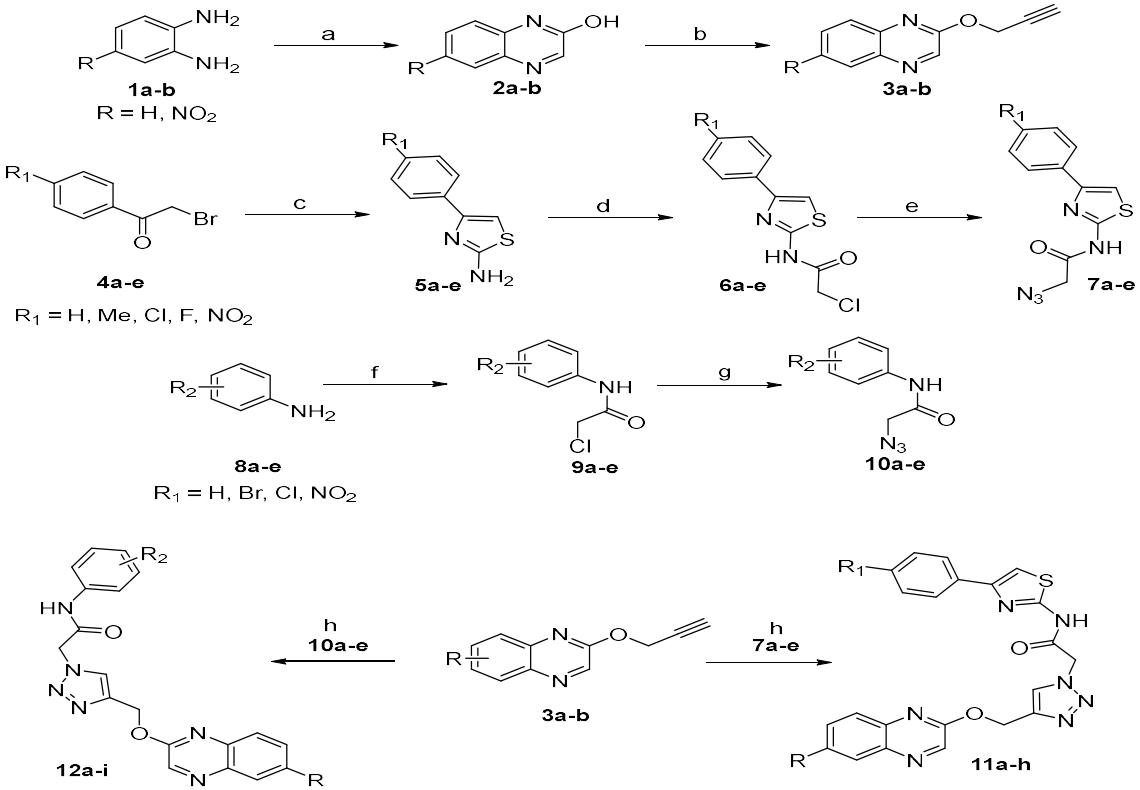
N-(4-bromophenyl)-2-(4-(((6-nitroquinoxalin-2-yl)oxy)methyl)-*1H*-1,2,3-triazol-1-yl)acetamide (12h)
Compound 12h was synthesized from 2-azido-N-(4-bromophenyl)acetamide (0.1 g, 0.39 mmol), 2-(ethynyloxy)-6-nitroquinoxaline (0.084 g, 0.39 mmol), L-sodium ascorbate (0.0077 g, 0.039 mmol) and $CuSO_4.5H_2O$ (40 mol %). Yield 0.174 g (92%); ^{1}H NMR (DMSO-d_6) δ 5.28 (2H, s, CH_2)., 5.54 (2H, s, CH_2), 7.4 (1H, t, J = 7.6 Hz ArH), 7.51 (2H, t, J = 10.1 Hz, ArH), 7.81 (1H, d, J = 9.6 Hz, ArH), 8.16 (2H, t, J = 6.4 Hz, ArH), 8.3 – 8.23 (1H, m, ArH), 8.42 (1H, s, ArH), 8.48 (1H, s, ArH), 10.59 (1H, s, NH). ^{13}C NMR (DMSO-d_6) δ 58.7, 77.3, 111.3, 116.8, 119.7, 121.5, 124.1, 126.9, 131.5, 132.0, 133.3, 138.2, 143.2, 150.6, 153.2, 164.5. MS m/z: 490.7 (MH^+, 100%).

N-(4-chlorophenyl)-2-(4-(((6-nitroquinoxalin-2-yl)oxy)methyl)-*1H*-1,2,3-triazol-1-yl)acetamide (12i)
Compound 12i was synthesized from 2-azido-N-(4-chlorophenyl)acetamide (0.1 g, 0.47 mmol), 2-(ethynyloxy)-6-nitroquinoxaline (0.102 g, 0.47 mmol), L-sodium ascorbate (0.01 g, 0.047 mmol) and $CuSO_4.5H_2O$ (40 mol %). Yield 0.2 g (96%); ^{1}H NMR (DMSO-d_6) δ 5.28 (2H, s, CH_2)., 5.54 (2H, s, CH_2), 7.4 (1H, t, J = 7.6 Hz ArH), 7.51 (2H, t, J = 10.1 Hz, ArH), 7.81 (1H, d, J = 9.6 Hz, ArH), 8.16 (2H, t, J = 6.4 Hz, ArH), 8.3 – 8.23 (1H, m, ArH), 8.42 (1H, s, ArH), 8.48 (1H, s, ArH), 10.59 (1H, s, NH). ^{13}C NMR (DMSO-d_6) δ 58.7, 77.3, 111.3, 116.8, 119.7, 121.5, 124.1, 126.9, 131.5, 132.0, 133.3, 138.2, 143.2, 150.6, 153.2, 164.5. MS m/z: 490.7 (MH^+, 100%).

RESULTS AND DISCUSSION

As shown in Scheme 1, initially benzene-1,2-diamine and 4-nitrobenzene-1,2-diamine was used as the starting material to synthesize compounds 2a-b by reacting them with glyoxylic acid in methanol. Propargyl bromide was reacted with compounds 2a – b to yield desired quinoxaline acetylene derivatives compounds 3a – b. Simultaneously, substituted phenacyl bromide derivatives 4a-e were reacted with thiourea to give 2-amino thiazole derivatives, 5a-e. These were then reacted with chloroacetyl chloride in methanol followed by sodium azide in DMF to yield the compounds 6a-e and 7a-e respectively. Additionally substituted azido phenyl acetamide compounds 10a–e was also synthesized by using the methods mentioned above. The final compounds 11a-h and 12a-i were synthesized by using a click reaction between compounds 3a-b and 7a-e and 10a-e respectively under suitable solvent and reaction conditions.

The reaction conditions for forming 1,2,3-triazoles acetamide were optimized as shown in Table-1. As per the literature reported, this reaction makes use of the commonly accessible $CuSO_4$ $5H_2O$ as a catalyst, as well as water and n-butanol as solvents. The reaction conditions were optimized by using different solvents and catalysts. Optimized reaction conditions of compound 11a are shown in Table-1. Initially, the starting materials 3a and 7a were processed in a mixture of water, DMF, and n-butanol (1: 1: 1), together with $CuSO_4 5H_2O$ and sodium ascorbate, for 16 hours at room temperature, yielding 62% of the intended product. Various solvent systems having different polarity were used in the reaction, however, it was found that in combination with water, a more polar solvent gives a better yield (Table-1, entry 6). In addition to this, after confirmation of the reaction solvents system, a few different Cu sources were also used (Table-1, entries 6-10). The best reaction condition was found to be the use of $CuSO_4 5H_2O$ as a copper source and an equal ratio of water and n-butanol giving compound 11a an excellent yield.



Reagents and Conditions: (a) Glyoxylic acid, methanol, 2.0 h, 80-85%; (b) Propargyl bromide, K_2CO_3, acetone, 30 min, 75-78%; (c) $SC(NH_2)_2$, IPA, 10 min, 60−80%; (d) $ClCH_2COCl$, methanol, 1 h, 90-95%; (e) NaN_3, DMF, 10 min, 91-93% ; (f) $ClCH_2COCl$, methanol, 1 h, 91-95%; (g) NaN_3, DMF, 10 min, 90% ; (h) $CuSO_4.5H_2O$, Sodium ascorbate, H_2O:n-Butanol = 1:1, 4-5 h, 90-98%

Scheme-1: Synthetic Method 1,2,3-triazole Acetamide Derivatives

Table-1: Optimization of Cu Source Catalysts in CuAAC Reaction[a].

Entry	Catalyst	Solvent	Time	Yield[b] (%)
1	$CuSO_4.5H_2O$	H_2O: DMF: n-butanol (1:1:1)	16h	62
2	$CuSO_4.5H_2O$	H_2O: THF: t-butanol (1:1:1)	18h	60
3	$CuSO_4.5H_2O$	H_2O: THF: n-butanol (1:1:1)	13h	76
4	$CuSO_4.5H_2O$	H_2O: DCM (1:1)	24h	30
5	$CuSO_4.5H_2O$	H_2O: DMF (1:1)	24h	15
6	$CuSO_4.5H_2O$	H_2O: n-butanol (1:1)	4h	95
7	$Cu(OAc)_2$	H_2O: n-butanol (1:1)	24h	15
8	Cu Powder	H_2O: n-butanol (1:1)	24h	48
9	$CuSO_4$, $NH_2NH_2.H_2O$	H_2O: n-butanol (1:1)	18h	54
10	CuI	H_2O: n-butanol (1: 1)	24h	10

Reaction methodology: [a]Compound 7a (0.39 mmol), compound 3a (0.39 mmol), 40 mole% of Cu reagents, and 0.03 mmol reductants were stirred in 1 mL each of water and n-butanol for a specific time as stated in the table. [b]Isolated yields.

Various diversified compounds containing triazole acetamide linked with quinoxaline derivatives were synthesized by utilizing the above best reaction conditions. The substrate scope with the yield of the final products is shown in Table-2. The final compounds (11a-h and 12a-i) were obtained with various substitutions at the aromatic ring or at the quinoxaline ring in high yield.

Table-2: Substrate Diversity for CuAAC Reaction

Compd	R	R_1	R_2	Yield (%)
11a	-H	-H	-	95
11b	-H	$-NO_2$	-	93
11c	-H	$-CH_3$	-	93
11d	-H	-F	-	90

11e	-H	-Cl	-	91
11f	$-NO_2$	-H	-	93
11g	$-NO_2$	$-NO_2$	-	91
11h	$-NO_2$	$-CH_3$	-	92
12a	-H	-	-H	98
12b	-H	-	-Br	93
12c	-H	-	$-NO_2$	95
12d	-H	-	-Cl	92
12e	-H	-	3,4 di-Cl	96
12f	$-NO_2$	-	-H	91
12g	$-NO_2$	-	$-NO_2$	93
12h	$-NO_2$	-	-Br	92
12i	$-NO_2$	-	-Cl	96

^{1}H NMR

The ^{1}H NMR spectrum of molecule 12f (Fig.-2) confirms the linking of quinoxaline and thiazole scaffold by confirmation of $-CH_2$ group (C-13 and C-19) observed as singlet on 5.43 and 5.69 δ ppm respectively. The protons in quinoxaline, C-6, C-3, C-1, and C-8, in the aromatic region with multiple centers, give a singlet and doublet on 7.91 δ ppm, 8.64 δ ppm, 8.86 δ ppm, and 8.26 δ ppm, respectively. The protons in the phenyl thiazole ring at 7.33 δ ppm, 7.43 δ ppm, and 7.97 δ ppm correspond to the protons of C-30, 32, and C-26. The protons present in the triazole at C-14 are observed at 7.66 δ ppm. The proton of the –NH appeared on 12.82 δ ppm.

^{13}C NMR

The ^{13}C NMR analysis of molecule 12f confirms the carbons of heterocyclic molecules: thiazole, quinoxaline, and triazole. The carbon nuclei in the final product have a range of chemical shifts from δ = 158.06 to 60.29 ppm. The C-20 carbonyl, which is located in a highly electronegative environment and is an amide group, appears at δ = 148.36 ppm. The C-9 and C-8 carbons linked to the nitrogen atom are observed at δ = 158.06 and δ = 139.46 ppm, respectively. The presence of the nitro group shifts the aromatic ring carbon (C1 to C6) peaks in a range from 121.50 to 148.36 δ. The carbons of the phenyl thiazole ring, which are attached to the phenyl ring C-23 to C-33, have chemical shifts in the range of δ = 108.91-141.79 ppm. The C-14 and C-15 peaks of the triazole ring were observed more deshielded at δ = 121.06 and 128.33 ppm, respectively due to the presence of the N atom. The alkane carbon at C-13 and C-19 is directly attached to a nitrogen atom and a carbonyl group separately, which results in chemical shifts of δ = 52.59 and 60.29 ppm, respectively.

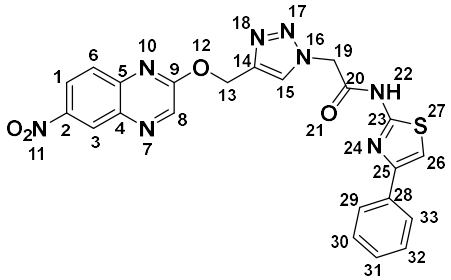


Fig.-2: Chemical Structure of Compound 12f

Mass

The molecular ion (m/z) value in the mass spectrum is 489.3 when considering the (M+H) region.

CONCLUSION

In conclusion, we have successfully synthesized a total of 17 compounds that consist of triazole acetamide linked with thiazole and quinoxaline using the green approach of click chemistry. The characterization of the compounds was carried out through the use of ^{1}H NMR, ^{13}C NMR, and mass spectrometry techniques. We were able to access 1,4-disubstituted 1,2,3-triazole acetamide easily, affordably, and with excellent

yield. The reaction displayed excellent functional group tolerance, and gentle reaction conditions, and used green solvents such as water and n-butanol. The synthesized compounds have great potential for future studies and applications, which are currently being explored.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing, and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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