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A facile Synthesis of Quinoxaline–Oxadiazole Hybrids with Bis (1,2,3-triazole) Scaffolds Through Click Chemistry

[1] Kuntla Krishnaveni, [2] Banda Padma, and [2] Panaganti Leelavathi*

[1] Research Scholar, Department of Chemistry, RBVRR women's college, Hyderabad, Telangana-500027.

[2] Department of Chemistry, University College of Science, Osmania University, Hyderabad, Telangana-500007.

*Corresponding author's email ID: leelaou@gmail.com

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ABSTRACT

In the present work, a modular synthetic approach based on click chemistry was employed to construct a novel series of bis(1,2,3-triazole)-linked quinoxaline–oxadiazole hybrids. The synthesis was accomplished via copper(I)-catalysed azide–alkyne cycloaddition (CuAAC), providing the target compounds in excellent yields with high regioselectivity. The structures of the synthesized hybrids were confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass spectrometry, and elemental analysis.

INTRODUCTION

1,2,3-Triazoles are a significant class of nitrogen-containing aromatic heterocycles, characterized by a five-membered ring comprising three contiguous nitrogen atoms (positions 1, 2, and 3) and two carbon atoms. Their notable features high dipole moments, strong hydrogen bonding, π-stacking interactions, and exceptional chemical and metabolic stability make them highly valuable in medicinal chemistry [1–3]. The development of Copper(I)-Catalysed Azide-Alkyne Cycloaddition (CuAAC), a landmark in "click chemistry" introduced by Sharpless and colleagues, has revolutionized the synthesis of 1,4-disubstituted triazoles, offering regioselective, high-yielding transformations under mild, often aqueous, conditions [4–6]. As a result, triazoles have been widely incorporated into pharmaceuticals, peptidomimetics, polymers, dendrimers, bioconjugates, and diagnostic agents [7,8].

Bis-1,2,3-triazoles, featuring two triazole rings bridged by flexible or rigid spacers, have gained attention for their ability to engage in multivalent interactions with biological targets. These molecules serve as hybrid pharmacophores and dual-action scaffolds, enhancing target affinity, selectivity, and pharmacokinetic behaviour [9–11]. They have also shown promise in molecular recognition, enzyme inhibition, and metal coordination chemistry [12,13].

Pharmacologically, 1,2,3-triazoles and their bis derivatives exhibit diverse biological profiles, including antibacterial, antifungal, antiviral, anticancer, antitubercular, anti-inflammatory, antimalarial, antioxidant, and enzyme inhibitory properties [14-17]. Their structural similarity to amide bonds allows them to function as bio isosteres in drug design, enhancing membrane permeability and metabolic stability [18]. Additionally, their ability to participate in key protein-ligand interactions makes them ideal scaffolds for enzyme inhibitors and receptor modulators [19].

Several clinically approved drugs incorporate triazole scaffolds (Figure 1). Notable examples include Fluconazole, itraconazole, voriconazole, and posaconazole are triazole-based antifungal agents that target fungal cytochrome P450 14α-demethylase, disrupting ergosterol biosynthesis [20]. Tazobactam, a ß-lactamase inhibitor, includes a triazole ring and is used alongside piperacillin to treat resistant bacterial infections [21]. TSAO (Tert-butyldimethylsilylspiro aminooxathiol-dioxide) is a triazole-based non-nucleoside reverse transcriptase inhibitor (NNRTI) developed for anti-HIV therapy [22]. Ravuconazole, a second-generation antifungal agent, and carboxyamidotriazole (CAI), a synthetic small molecule with anti-cancer, anti-inflammatory, and anti-angiogenic activity, also incorporate triazole rings [23,24]. Investigational compounds such as vorlabrutinib, a Bruton's tyrosine kinase (BTK) inhibitor, and various triazole-linked HDAC, PARP, and PDE inhibitors have shown promising nanomolar potencies in preclinical studies [25].

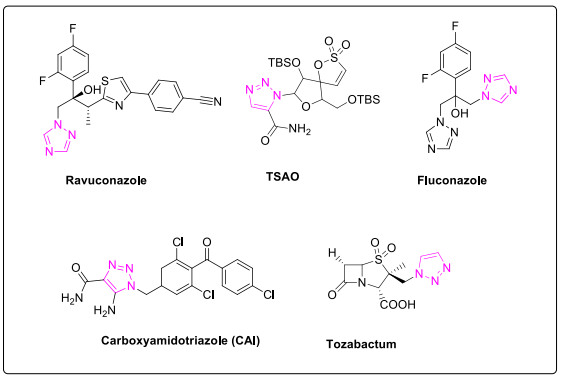


Figure 1. Representative examples of approved drugs featuring triazole scaffolds

1,2,4-Oxadiazoles are five-membered aromatic heterocycles composed of two nitrogen atoms and one oxygen atom. Their electron-deficient, planar structure, strong resonance stabilization, and π–π stacking interactions make them attractive scaffolds in pharmaceutical design [26]. Often used as bio isosteres for amide, ester, urea, and carboxylic acid functionalities, oxadiazoles enhance metabolic stability, membrane permeability, and oral bioavailability in lead optimization [27–30]. These replacements often lead to improved pharmacokinetic profiles, reduced off-target metabolism, and increased drug-likeness [31].

Biologically, 1,2,4-oxadiazole derivatives exhibit a wide range of activities including antibacterial, antifungal, anticancer, antiviral, antitubercular, anti-inflammatory, antioxidant, and CNS-related effects [32–35]. The oxadiazole moiety interacts with metalloenzymes and other biological targets via hydrogen bonding or metal coordination, making them relevant in the treatment of conditions like cancer, Alzheimer's disease, and diabetes [36–38]. Notable drugs (figure-2) include Raltegravir, the first FDA-approved HIV-1 integrase inhibitor, where the oxadiazole core contributes to strong target binding [39], and Zibotentan, a selective endothelin A receptor antagonist developed for prostate cancer [40].

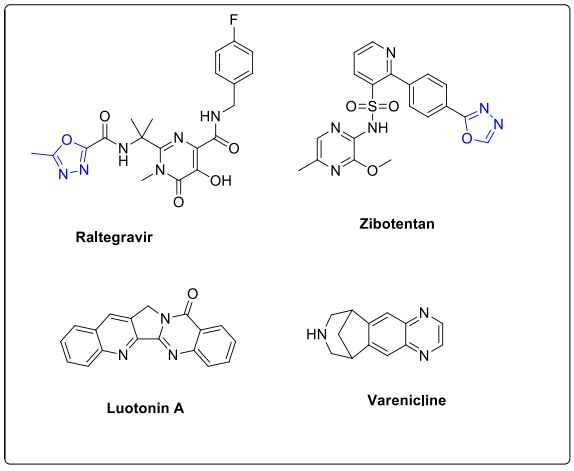


Figure 2. Representative examples of approved drugs featuring *Oxadiazoles* scaffolds

Quinoxalines (also called benzopyrazines) are fused bicyclic heterocycles combining a benzene ring with a pyrazine ring. Their planar, electron-rich conjugated systems support hydrogen bonding, π-stacking, and metal ion coordination features beneficial for biological interactions [41,42]. Quinoxaline derivatives have shown extensive pharmacological effects including anticancer, antibacterial, antifungal, antiviral, anti-inflammatory, antioxidant, antimalarial, antitubercular, analgesic, and neuroprotective activities [43–45]. Their π-system allows interaction with nucleic acids and enzyme active sites, improving their therapeutic relevance [46].

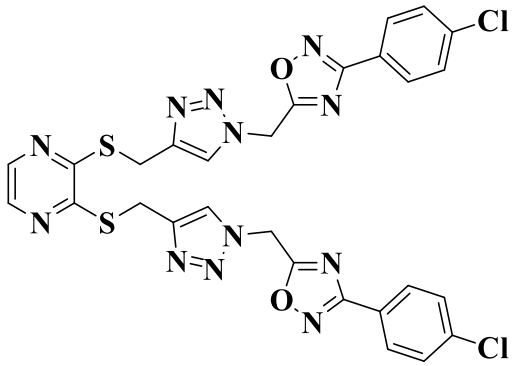
Several clinically important or investigational drugs contain quinoxaline cores. Echinomycin, a quinoxaline-based DNA bis-intercalator, displays potent anticancer and anti-HIV activity [47]. Luotonin A, (Figure-2) a natural alkaloid, is a promising topoisomerase I inhibitor [48]. Varenicline, an FDA-approved smoking cessation drug, contains a bridged quinoxaline-related ring and acts on nicotinic acetylcholine receptors [49]. Quinoxaline scaffolds also underpin novel kinase inhibitors, COX-2 inhibitors, and serotonin receptor antagonists [50].

The heterocyclic scaffolds 1,2,3-triazoles, 1,2,4-oxadiazoles, and quinoxalines play a vital role in drug discovery due to their structural uniqueness and broad biological activities. Their combination into hybrid pharmacophores offers a promising strategy to enhance therapeutic potential. The present study focuses on the design, synthesis such hybrids to develop potent and selective drug candidates for diverse biomedical applications.

MATERIALS AND METHODS

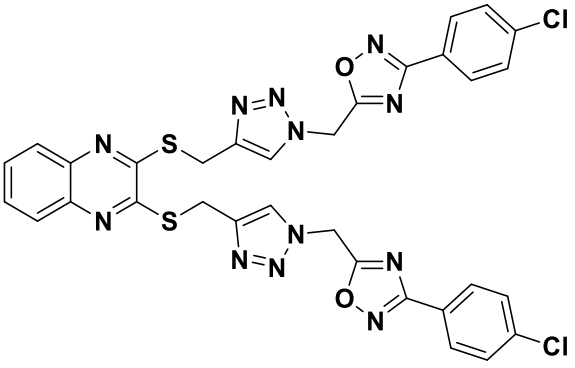
All chemicals and reagents used in the study were of laboratory grade and procured from Sigma-Aldrich. Melting points of the synthesized compounds were determined in open capillaries using Thiele's melting point apparatus and are reported uncorrected. The progress of reactions was monitored by thin layer chromatography (TLC) performed on silica gel G plates, pre-activated at 120 °C for 30 min. The developed spots were visualized by exposure to iodine vapours. ^{1}H NMR spectra were recorded on 400 MHz NMR spectrometer using $CDCl_3$ as solvent, with Tetramethyl silane (TMS) as the internal standard (δ = 0 ppm). The ^{13}C-NMR spectra were recorded on 101 MHz spectrometer in $CDCl_3$.

2,3-bis(((1-((3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)methyl)-1*H*-1,2,3-triazol-4-yl) methyl) thio)pyrazine (9a):



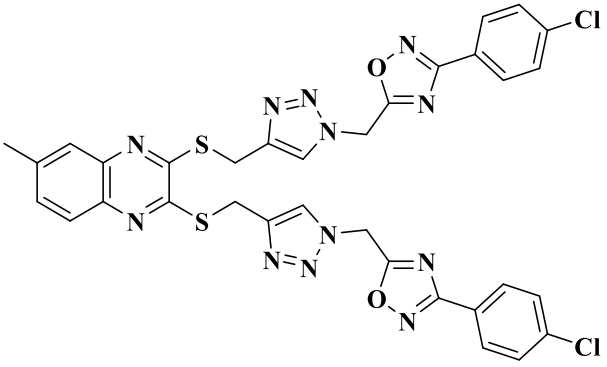
Pale white solid, m.p.205-207 ℃, Yield- 95 %; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.10 (s, 2H), 7.95 (d, *J* = 7.6 Hz, 4H), 7.79 (s, 2H), 7.45 (d, *J* = 7.6 Hz, 4H), 5.80 (s, 4H), 4.56 (s, 4H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 164.8 (2C), 145.0 (2C), 144.3 (2c), 138.7 (2C), 136 (2C), 131.5 (2C), 130.50 (2C), 130.0 (2C), 129.1 (2C), 127.8 (2C), 127.7 (2C), 121.46 (2C), 45.25 (2C), 30.1 (2C).

2,3-bis(((1-((3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)methyl)-1*H*-1,2,3-triazol-4-yl) methyl) thio)quinoxaline (9b):



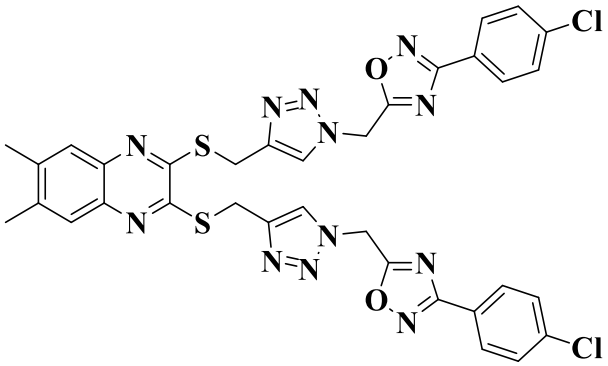
yellow solid, m.p.205-207 ℃, Yield- 85 %; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.90 (d, *J* = 7.6 Hz, 4H), 7.87 (s, 2H), 7.75 (d, *J* = 5.3 Hz, 2H), 7.56 (s, 2H), 7.43 (d, *J* = 8.0 Hz, 4H), 5.8 (s, 4H), 4.72 (s, 4H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 172.3 (2C), 169.4(2C), 153.2 (2C), 145.8 (2C), 142.7 (2C), 140.4 (2C), 130.1 (2C), 129.1 (4C), 128.2 (4C) 127.9 (2C), 124.23 (2C), 123.7 (2c), 45.8 (2C), 25.5 (2) .

5,5'-(((((6-methylquinoxaline-2,3-diyl)bis(sulfanediyl))bis(methylene))bis(1*H*-1,2,3-triazole-4,1-diyl))bis(methylene))bis(3-(4-chlorophenyl)-1,2,4-oxadiazole) (9C):



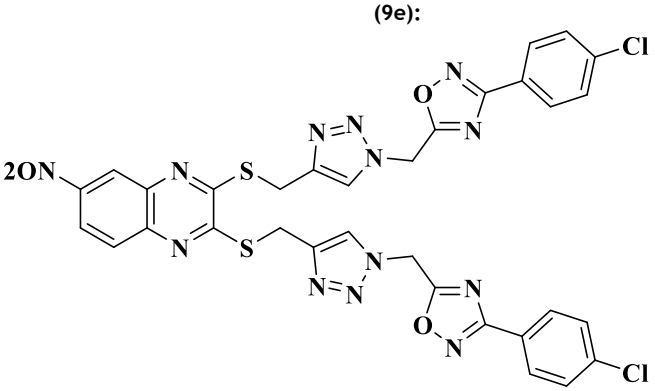
Pale white solid, m.p.205-207 ℃, Yield- 85 %; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.87 (d, *J* = 3.4 Hz, 2H), 7.85 (t, *J* = 2.1 Hz, 1H), 7.84 – 7.83 (m, 1H), 7.82 (dd, *J* = 4.1, 2.2 Hz, 2H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.64 (s, 1H), 7.40 – 7.35 (m, 4H), 7.35 – 7.30 (m, 1H), 5.78 (s, 4H), 4.65 (s, 4H), 2.46 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 172.4 (2C), 168.5 (2C), 153.7 (2C), 152.8 (2C), 151.8, 139.8, 139.1, 138.2 (3C), 137.9, 137.8, 130.6 (2C), 129.3 (4C), 128.7 (4C), 127, 126.6, 45.0 (2C), 24.8 (2C), 21.6 (2C).

5,5'-(((((6,7-dimethylquinoxaline-2,3-diyl)bis(sulfanediyl))bis(methylene))bis(1*H*-1,2,3-triazole-4,1-diyl))bis(methylene))bis(3-(4-chlorophenyl)-1,2,4-oxadiazole (9d):



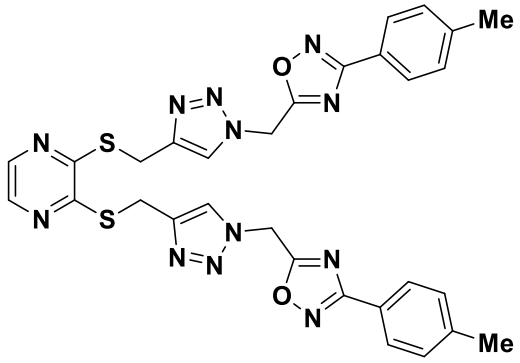
Yellow solid, m.p.205-207 ℃, Yield- 90 %; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.86 (d, *J* = 7.3 Hz, 6H), 7.64 (s, 2H), 7.39 (d, *J* = 8.1 Hz, 4H), 5.78 (s, 4H), 4.68 (s, 4H), 2.38 (s, 6H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 172.3 (2C), 169.4 (2C), 153.2 (2C), 152.8 (2C), 145.8 (2C), 142.7 (2C), 140.4 (2C), 139.1 (2C), 130.1 (2C), 129.1 (2C), 128.3 (4C), 127.9 (2C), 124.2 (2C), 45.8 (2C), 25.3 (C), 22.1 (2C).

5,5'-(((((6-nitroquinoxaline-2,3-diyl)bis(sulfanediyl))bis(methylene))bis(1*H*-1,2,3-triazole-4,1-diyl))bis(methylene))bis(3-(4-chlorophenyl)-1,2,4-oxadiazole (9e):



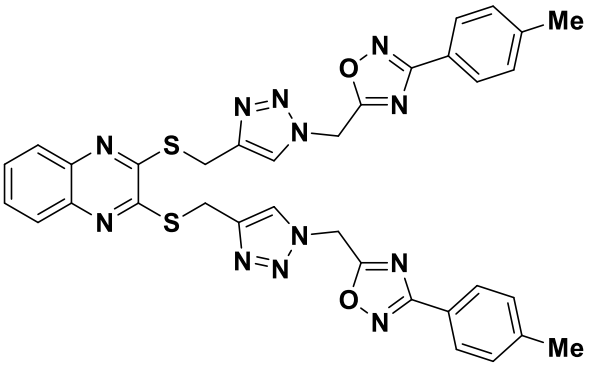
Yellow solid, m.p.205-207 ℃, Yield- 85 %; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.81 (s, 1H), 8.27 (d, *J* = 9.1 Hz, 1H), 7.95 (d, *J* = 9.1 Hz, 7H), 7.91 (d, *J* = 6.5 Hz, 4H), 5.82 (s, 4H), 4.72 (d, *J* = 4.0 Hz, 4H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 172.3 (2C), 169.4 (2C), 153.2 (2C), 148.8 (2C), 145.7 (2C), 140.4 (2C), 130.1 (2C), 129.1 (4C), 128.2 (4C) 127.9 (2C), 124.2 (2C), 123.7 (2c), 45.8 (2C), 25.5 (2C) .

5,6-bis(((1-((3-(p-tolyl)-1,2,4-oxadiazol-5-yl)methyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)-2,3-dihydropyrazine (9f):



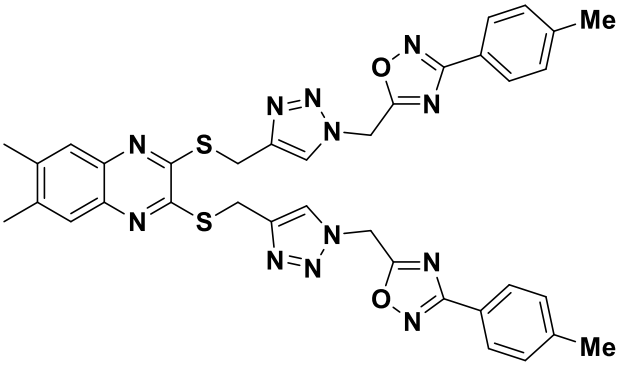
Brown solid, m.p.205-207 ℃, Yield- 70 %; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.65 (d, *J* = 5.3 Hz, 4H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.24 (t, *J* = 7.0 Hz, 4H), 5.44 (s, 4H), , 3.78 (s, 4H), 2.45 (s, 3H), 2.44 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 172.3 (2C), 169.2 (2C), 152.1 (2C), 142.5 (2C), 139.2 (2C), 139.1 (2C), 130.1 (2C), 127.8 (4C), 124.2 (4C), 123.4 (4C), 45.6 (2C), 25.2 (2C), 22.1 (2C).

3-(p-tolyl)-5-((4-(((3-(((1-((3-(p-tolyl)isoxazol-5-yl)methyl)-1*H*-1,2,3-triazol-4-yl) methyl) thio)quinoxalin-2-yl)thio)methyl)-1H-1,2,3-triazol-1-yl)methyl)-1,2,4-oxadiazole (9g):



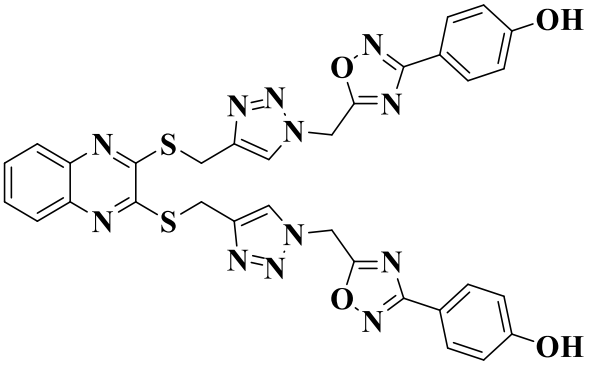
Pale white solid, m.p.205-207 ℃, Yield- 70 %; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.90 (s, 4H), 7.85 (d, *J* = 7.1 Hz, 4H), 7.56 (s, 2H), 7.26 (s, 2H), 5.78 (s, 4H), 4.72 (s, 4H), 4.12 (s, 4H), 2.41 (s, 6H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 172.3 (2C), 169.4 (2C), 145.8 (2C), 178.0 (2C), 142.6 (2C), 140.3 (4C), 130.1 (4C), 129.1 (4C), 128.2 (4C), 127.9 (4C), 45.8 (2C), 25.3 (2C), 22.1 (2C).

5,5'-((((((6,7-dimethylquinoxaline-2,3-diyl) bis(sulfanediyl)) bis(methylene)) bis (1*H*-1,2,3-triazole-4,1-diyl))bis(methylene))bis(3-(p-tolyl)-1,2,4-oxadiazole (9h):



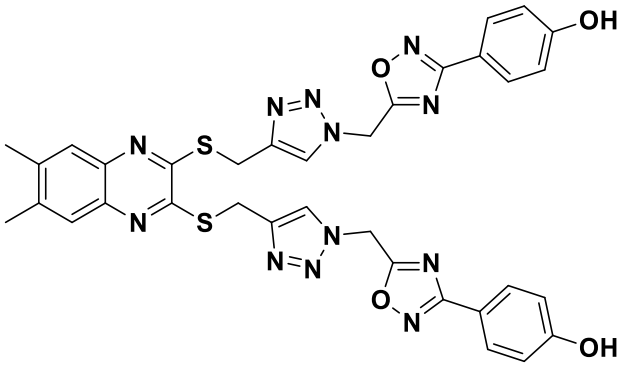
White solid, m.p.205-207 ℃, Yield- 75 %; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 10.19 (s, 2H), 8.32 (s, 2H), 7.74 (d, *J* = 22.0 Hz, 4H), 6.87 (s, 4H), 6.10 (s, 4H), 4.68 (s, 4H), 2.51 (s, 12H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 171.9 (2C), 168.8 (2c), 151.7 (2C), 142.1 (2C), 138.8 (2C), 138.7 (2C), 139.6 (2C), 129.6 (2C), 127.1 (2C), 126.9 (4C), 123.8 (2C), 123.0 (2C), 45.1 (2C), 29.7 (2C), 24.8 (2C), 21.6 (2C), 20.0 (2C).

4,4'-(((((quinoxaline-2,3-diylbis(sulfanediyl))bis(methylene))bis(1H-1,2,3-triazole-4,1-diyl))bis(methylene))bis(1,2,4-oxadiazole-5,3-diyl))diphenol (9i):



White solid, m.p.205-207 ℃, Yield- 85 %; **^{1}H NMR (400 MHz, DMSO):** δ 10.19 (s, 2H), 8.35 (s, 2H), 8.02 (s, 2H), 7.72 (d, *J* = 7.8 Hz, 4H), 6.89 (d, *J* = 7.8 Hz, 6H), 6.10 (s, 4H), 4.72 (s, 4H); **^{13}C NMR (101 MHz, DMSO):** δ 172.3 (2C), 169.4 (2C), 153.2 (2C), 148.8 (2C), 142.7 (2C), 140.4 (2C), 130.1 (2C), 129.1 (4C), 128.2 (4C) 127.9 (2C), 124.23 (2C), 123.71 (2C), 45.8 (2C), 25.5 (2C).

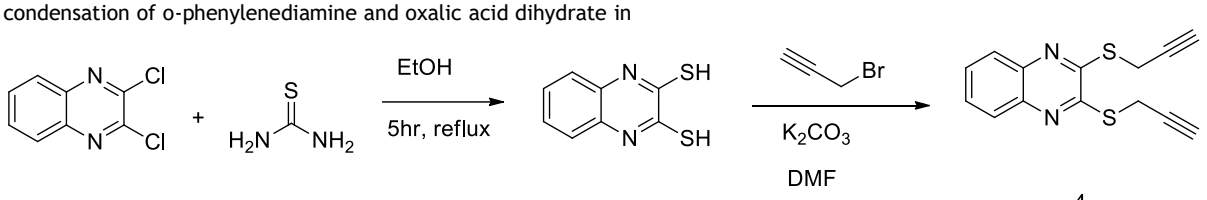
4,4'-((((((6,7-dimethylquinoxaline-2,3-diyl)bis(sulfanediyl))bis(methylene))bis(1H-1,2,3-triazole-4,1-diyl))bis(methylene))bis(1,2,4-oxadiazole-5,3-diyl))diphenol (9j):



White solid, m.p.207-209 ℃, Yield- 78 %; **^{1}H NMR (400 MHz, DMSO):** δ 10.19 (s, 2H), 8.32 (s, 2H), 7.76 (s, 2H), 7.74 (d, *J* = 21.0 Hz, 4H), 6.88 (d, *J* = 6.7 Hz, 4H), 6.10 (s, 4H), 4.68 (s, 4H), 2.51 (s, 6H). **^{13}C NMR (101 MHz, DMSO):** δ 171.9 (2C), 168.8 (2C), 158.7 (2C), 142.1 (2C), 138.8 (2C), 138.7 (2C), 139.6 (2C), 129.6 (2C), 127.1 (2C), 126.9 (4C), 123.8 (2C), 123.0 (2C), 45.1 (2C), 29.7 (2C), 24.8 (2C), 21.6 (2C), 20.0 (2C).

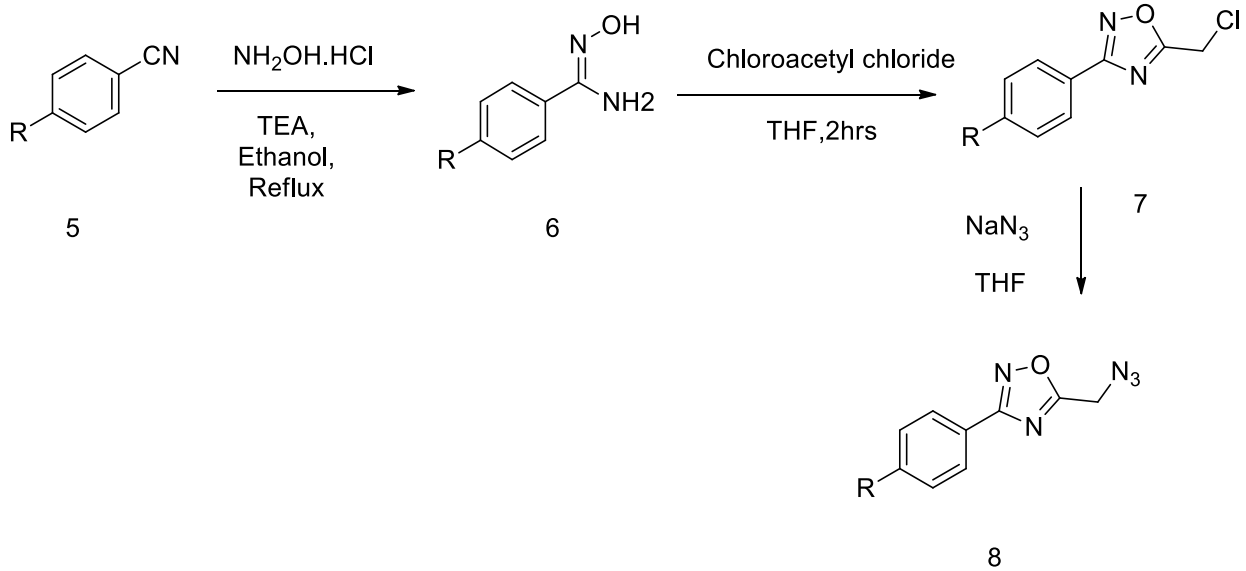
RESULT AND DISCUSSION

The synthesis of substituted 2,3-bis(((1-((3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)thio)quinoxaline derivatives employs a convergent multi-step strategy that integrates classical heterocyclic chemistry with modern Cu(I)-catalysed azide-alkyne cycloaddition (click chemistry). The synthetic route initiates with the condensation of o-phenylenediamine and oxalic acid dihydrate in hydrochloric acid under reflux conditions to produce quinoxaline-2,3-dione and then Chlorination of this product using phosphorus oxychloride ($POCl_3$) in the presence of catalytic DMF yields 2,3-dichloroquinoxaline (1), as reported previously [51]. This intermediate is then subjected to Thio nation using thiourea in ethanol under reflux, yielding quinoxaline-2,3-dithiol (3), which undergoes nucleophilic substitution with propargyl bromide in the presence of a base such as potassium carbonate (K_2CO_3) in an anhydrous solvent (DMF), yielding 2,3-bis(propargyl Thio)quinoxaline(4). This dialkyne derivative serves as a critical precursor for subsequent Cu(I)-catalysed 1,3-dipolar cycloaddition with azido-functionalized 1,2,4-oxadiazole intermediates to construct the final triazole-linked bis-substituted quinoxaline framework.



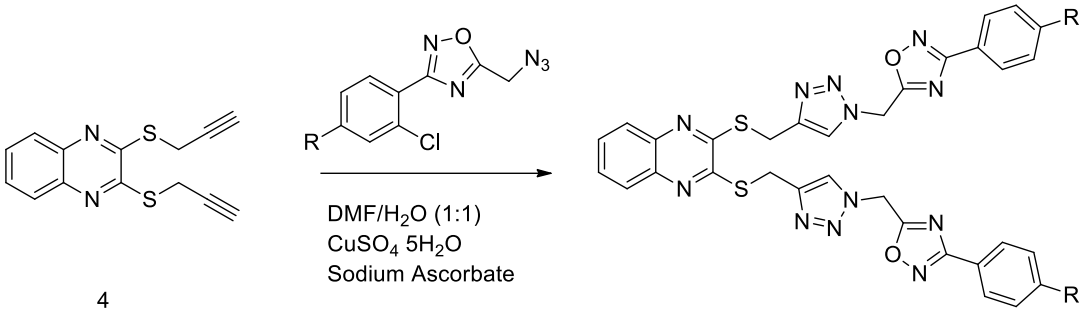
1 2 3 4

In a parallel sequence, 3-(4-chlorophenyl)-1,2,4-oxadiazole (7) is synthesized from benzonitrile (5) via an amidoxime intermediate. The amidoxime (6) is cyclized using Chloroacetyl chloride in tetrahydrofuran (THF), followed by treatment with sodium azide under reflux to yield the corresponding azido-oxadiazole (8).



5 6 7 8

The final step involves a copper(I)-catalysed azide alkyne cycloaddition (CuAAC) between 2,3-bis(propargylthio) quinoxaline (8) and two equivalents of the azido-oxadiazole in a suitable solvent system (DMF/H_2O), under mild conditions. This reaction forms two triazole rings, each linking the quinoxaline core to an oxadiazole moiety through a methylene bridge, giving the desired compound 9(a-j).



4 9(a-j)

To establish the optimal reaction conditions for the Cu(I)-catalysed azide–alkyne cycloaddition (CuAAC), a systematic solvent optimization study was conducted using 2,3-bis(propargylthio)quinoxaline and two equivalents of the azido-oxadiazole derivative (9a). Seven different solvent systems were screened DMF/H_2O (1:1), tert-butanol, DMSO, ethanol, methanol, acetonitrile, and THF under identical molar ratios and catalyst conditions ($CuSO_4 \cdot 5H_2O$/sodium ascorbate). Reactions were monitored by TLC and HPLC, and yields were calculated based on isolated pure products. the DMF/H_2O system, yielding 89% of the final bis-triazole product within 6h at 50 °C. This solvent mixture facilitated optimal miscibility of polar and nonpolar reactants while efficiently solubilizing the copper catalyst and reducing agent. The presence of water likely enhances the reactivity by stabilizing the Cu(I) species and assisting in the faster turnover of the catalytic cycle.

Table-1: Solvent optimization for CuAAC Reaction of compound (9a)

Entry	Solvent System	Temperature (°C)	Time (h)	Yield (%)
1	DMF /H_2O (1:1)	50	6	**89**
2	t-BuOH	60	8	76
3	DMSO	60	9	72
4	Ethanol	60	7	68
5	Methanol	60	8	65
6	Acetonitrile	60	10	54
7	THF	60	10	49

Moreover, the moderate polarity and amphiphilic nature of the DMF/H_2O system enabled effective dispersion of both hydrophilic azides and hydrophobic alkyne substrates, ensuring better collision frequency and regioselectivity. DMSO, both polar aprotic solvents, provided moderate yields of 76% and 72%, respectively, but required longer reaction times (8–9 h) and elevated temperatures (60 ^{0}C). These solvents offer good solubility for most organic compounds; however, they tend to coordinate with copper ions, which may inhibit the catalytic activity of Cu(I) by stabilizing off-cycle species with acceptable yields of 68% and 65%, respectively. Despite their eco-friendly profile, their protic nature may interfere with the coordination environment of the copper centre and lead to moderate deactivation of the catalyst. Furthermore, lower boiling points may limit their effectiveness under heating conditions. Acetonitrile and THF, being less polar and having lower hydrogen-bonding capacities, resulted in poor performance (54% and 49% yield, respectively) even after prolonged reaction times. The lower yields may be attributed to poor solubility of the substrates or catalyst, leading to incomplete conversion or precipitation of the reaction mixture. In conclusion, DMF/H_2O (1:1) proved to be the superior solvent system for this transformation, offering a balance of green chemistry compliance, high yield, operational simplicity, and compatibility with the CuAAC catalytic cycle. The solvent screening results are summarized in Table 1.

CONCLUSION

In this study, a modular synthetic approach based on click chemistry was successfully utilized to construct a series of bis (1,2,3-triazole)-linked quinoxaline–oxadiazole hybrids. The copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) strategy provided the target compounds in excellent yields with high regioselectivity, demonstrating the efficiency and versatility of this method. Structural confirmation was achieved through spectroscopic and analytical techniques.

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