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Triazoles in the Carbohydrate World: Unlocking Multifunctional Glycohybrids

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Abstract

Triazoles have emerged as versatile linkers in carbohydrate chemistry, enabling the construction of stable and multifunctional glycohybrids. This review explores the use of triazoles in carbohydrate chemistry, focusing on how they can be used to create versatile compounds with applications in both medicine and materials science. A variety of glyco-triazole hybrids have been synthesized using efficient and sustainable click chemistry methods. These methods allow for the high-yield joining of sugars to other molecules under biocompatible conditions. This review highlights the diverse biological activities of these new compounds, including their use as antimicrobial, antifungal, and anticancer agents. A cationic chitosan derivative with triazole and quaternary ammonium groups showed strong antifungal and antioxidant properties. Other examples include carbohydrate-derived triazoles that inhibit glycogen phosphorylase, a feasible treatment for type 2 diabetes, and piperazine triazolyl sugar conjugates that show potent anticancer activity against HeLa cells. Beyond their medicinal uses, the review also covers the application of glyco-triazole hybrids in materials science and sensing. This review emphasises that while significant progress has been made, future work should focus on designing more complex structures, using greener synthesis methods, and addressing challenges like bioavailability and stability to move these promising compounds from the laboratory to real-world applications.

Keywords: carbohydrates, click chemistry, triazoles

1. Introduction

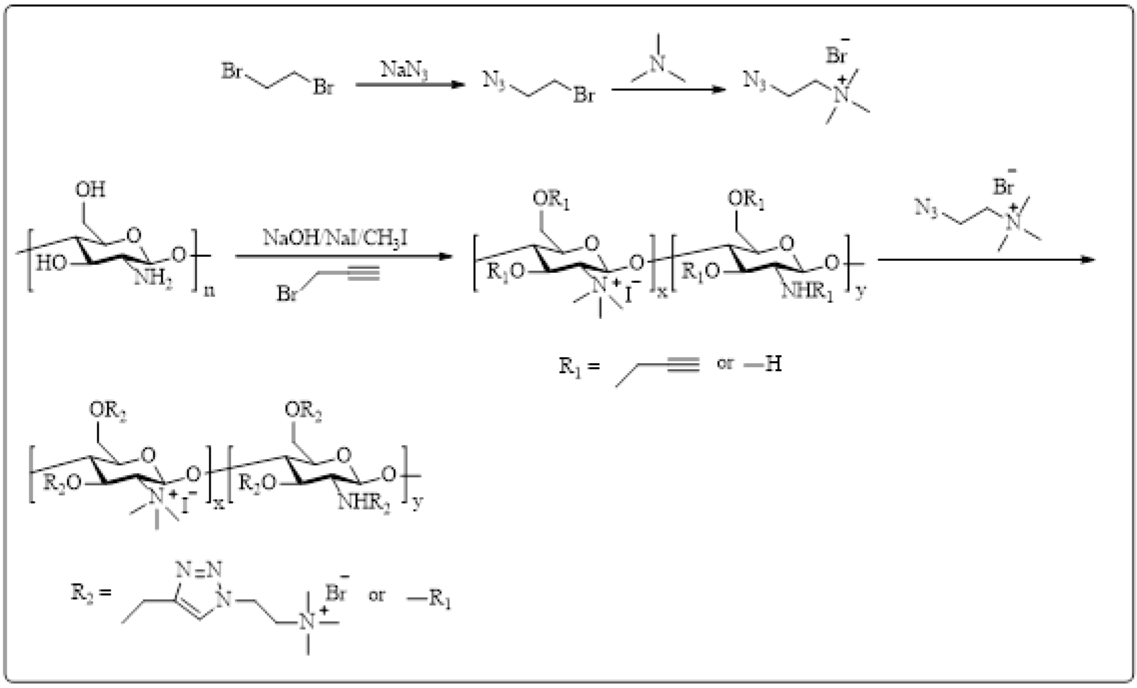
Carbohydrates are the most abundant and structurally varied biomolecules in nature, sustaining energy storage, cellular recognition, and systematically organized materials. Their stereochemistry and dense functionality make them unusually suitable scaffolds for molecular design in biology, materials science and, chemistry [1-4]. Over the past decade, click strategies, especially Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) and strain-promoted azide-alkyne cycloaddition (SPAAC), have transformed glycochemistry by enabling high-yield, selective coupling reactions of sugars to drug-like fragments and polymers under biocompatible conditions [5-8]. Recent studies have also emphasized the use of organobases to catalyze the synthesis of triazole-linked N-glycosides, providing metal-free, high-yielding substitutes for glycohybrid production [9]. These reactions make it possible to understand the combination of carbohydrate heterocycles as a versatile process. Triazoles offer hydrogen bonding linkers that are chemically stable and maintain glycan structure when pharmacophoric heterocycles are introduced, as demonstrated in early studies where mannose-triazole conjugates were synthesized as potent α-mannosidase inhibitors [10, 11]. Greener media (such as water and PEGs), solvent-free CuAAC, and flow-enabled azide-alkyne couplings have all improved sustainability at the same time by reducing waste and increasing the scalability of carbohydrate conjugates [12-14]. Glyco-triazole hybrids have progressed from basic concepts to promising drug-like compounds. Recent studies describe uridine glycoconjugates with anti-coronavirus activity [15], anti-diabetic agent [16], benzimidazole-triazole glycohybrids that inhibit cancer drivers [17], antibacterial [18] and antimalarial glycoconjugates showing how carbohydrate display can enhance efficacy, selectivity, absorption, distribution, metabolism, excretion, and toxicity (ADMET) [19]. In addition, efficient click chemistry strategies have been used to generate chromene-D-glucose triazole conjugates that display potent antibacterial activity against methicillin-resistant Staphylococcus aureus (MRSA), and antifungal effects [20]. In parallel, triazole-bridged sugar chromophores and polyaromatics have emerged as sturdy sensors (e.g., for nitroaromatic or metal ion detection), using electron-transfer and aggregation phenomena, while the glycan domain imparts solubility and recognition [21]. Fluorescent triazole–BODIPY conjugates bearing multiple sugar units further highlight the potential of such hybrids in imaging and diagnostic applications [22]. In addition to small molecules, self-assembling sugar phosphates and click-grafted glycans on polymers provide bioactive, viscoelastic materials and interfaces that resemble glycocalyx functionalities. Click chemistry has also become necessary to macrocyclization in peptides and pseudopeptides, clarifying how triazole geometry can pre-align pharmacophores, insights that interpret directly to glyco-macrocycles [23].

Glycosides have gained increasing significance due to their roles in energy provision, structural function, and intercellular communication in living organisms. This recognition has laid the foundation for advancements in glycobiology and pharmacology. The review traces the evolution of sugar modification methodologies to non-sugar moiety throughout the 20th century, resulting in the development of a novel coupling approach utilizing triazoles as molecular linkers. The triazole linkage can improve the stability and bioactivity of glycosides but also opens new platforms for the formation of drug candidates with enhanced efficacy and broader applications in medicinal chemistry. Glycotriazoles have emerged as an attractive class of compounds within medicinal chemistry, demonstrating significant potential for drug discovery and development by integrating the synthetic accessibility, stability and versatile biological interactions of triazole rings with the biologically relevant three-dimensional structures of carbohydrates. The diverse biological activities associated with triazoles, together with the functional versatility of carbohydrates, suggest that glycotriazoles are crucial in the advancement of therapeutic strategies in multiple fields [24-28]. For instance, triazole-bridged N-glycosides of pyrazolo[1,5-apyrimidinones have shown notable anticancer activity with strong docking-based support [29]. In combination, precise binding (enabled by CuAAC/SPAAC), greener and scalable processing, and richer heterocycle chemistry are opening up carbohydrate heterocycle conjugates with many different applications, from imaging and adaptive materials to oncology and antivirals. Meanwhile, continuous kinetic, mechanistic, and bio-orthogonal studies are helping to refine the best time and method for employing each click variant.

2. Synthetic Approaches to Carbohydrate Triazole Hybrids

2.1. Conventional methods

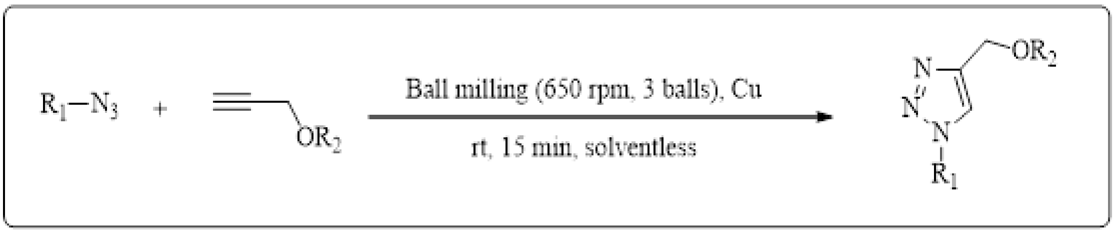
In 2018, Tan *et al*. [30] created a positively charged chitosan analogue consisting of 1,2,3-triazole and N,N,N-trimethyl structural units via a Cu(I)-catalyzed azide alkyne cycloaddition (CuAAC) reaction (Scheme 1). Over a broad pH range, this cationic chitosan analogue demonstrated high water solubility, excellent antifungal activity against several plant-threatening fungi, and enhanced antioxidant properties compared to pure chitosan. The addition of the triazole and quaternary ammonium groups into the chitosan support improved its water miscibility, antifungal activity, and antioxidant properties. At a concentration of 1.0 mg/mL, the cationic deacetylated chitin derivative exhibited more than 70% inhibition against the tested fungi, and at 1.6 mg/mL, it had full scavenging efficacy contrary to superoxide radicals. The improved biological properties of the cationic chitosan derivative are attributed to the synergistic effects of the quaternary ammonium and triazole moieties, which can disrupt fungal cell membranes and act as effective antioxidants. These findings suggest the cationic chitosan derivative has promising potential as an antifungal and antioxidant biomaterial. Additionally, using a traditional approach of CuAAC conversion of chitosan azides, Rathinam *et al*. (2024) reported the synthesis of water-soluble quaternary and protonable basic chitotriazolans and assessed their antibacterial efficacy [31].



Scheme 1. Synthetic route for cationic chitosan derivatives via Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC), showing enhanced solubility, antifungal, and antioxidant properties [30].

2.2 Modified methods

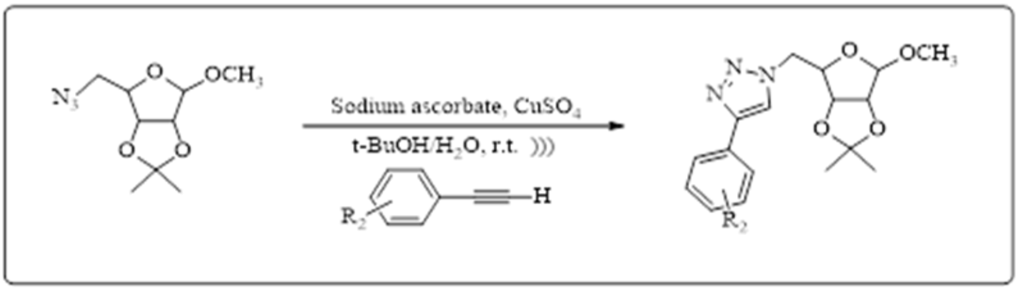
Hamadi *et al*. [32] presented an analysis of the synthesis of carbohydrate-derived triazoles and their potential as glycogen phosphorylase inhibitors. They designed a novel, quick, and practical technique for creating triazoles obtained from carbohydrates by utilizing a 1,3-dipolar cycloaddition reaction under ball milling (Scheme 2). Using a ball mill, the synthesis was conducted without the use of solvents, which is an environmentally benign method. They synthesized molecules similar to deprotected water-soluble compounds that are known to inhibit glycogen phosphorylase by using isopropylidene protecting groups.



Scheme 2. Mechanochemical synthesis of 1,2,3-triazole carbohydrate derivatives under solvent-free ball milling, developed as glycogen phosphorylase inhibitors [32].

Their work describes the successful synthesis of various triazole derivatives using different sugar azides and alkynes. Deprotection methods were explored, including the use of hydrochloric acid in methanol and a selective deprotection using CBr_4 in methanol under photoirradiation conditions. The produced compounds' ability to inhibit glycogen phosphorylase b (GPb) was evaluated. One of the synthesized compounds showed significant inhibition of rabbit muscle GPb with an IC_{50} value of 60 µM. According to the study, these triazoles formed from carbohydrates may be good candidates for the creation of novel glycogen phosphorylase inhibitors, which might be used to treat type 2 diabetes and other conditions that are linked to it. Overall, the study presents a novel synthetic approach for creating potential glycogen phosphorylase inhibitors and provides preliminary evidence of their effectiveness, suggesting a new platform for drug development in the treatment of diabetes and related condition.

Another study, carried out by Evangelista *et al*. in 2021, presented several main arguments and claims regarding the construction of methyl 2,3-O-isopropylidene-β-D-ribofuranoside and its utilization in preparing unusual 1,2,3-triazole glycoconjugates (Scheme 3).



Scheme 3. Triazole glycoconjugate synthesis using azido D-ribofuranoside [33].

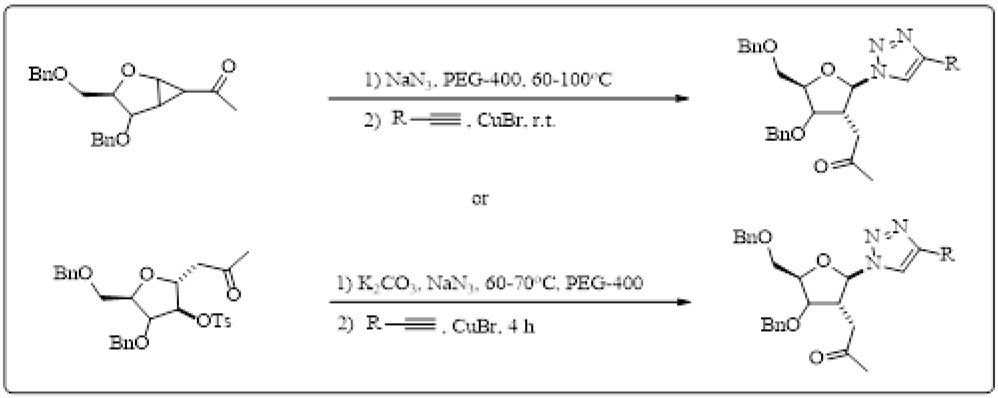
The work claimed to have created a modified process that uses sonication as a method to synthesize methyl 2,3-O-isopropylidene-β-D-ribofuranoside. This technique was reported to be more efficient, providing greater yields and faster reaction times.

After examining many reaction times, the study concluded that 25 minutes produced the best results, with a maximum yield of 85%. The yields were greatly impacted by shorter or longer reaction times. By effectively scaling up the reaction to 2.8g while retaining a high yield of 85%, the authors successfully demonstrated the scalability of their ultrasonic approach. The research outlines the profitable synthesis of new 1,2,3-triazole glycoconjugates utilizing the intermediate compound. The authors suggest that these glycoconjugates may possess several biological activities, citing previous research on similar compounds showing anti-tuberculosis, anti-inflammatory, anti-allergic, antimicrobial, and antiviral properties. This work presents a new, efficient method for synthesizing an important intermediate compound and demonstrates its use in creating novel 1,2,3-triazole glycoconjugates with potential biological activities. The research contributes to the sector of carbohydrate chemistry and opens up possibilities for further exploration in medicinal chemistry and drug discovery [33].

A two-step, one-pot method for synthesizing a range of 2-C-branched glycosyl triazoles, consisting glycopeptides and triazole-linked oligosaccharides, was developed by Shen *et al*. [34]. The scheme began with cyclopropanated sugars or 2'-acetonyl-2-O-Ts-C-furanosides (Scheme 4). The use of PEG-400 as the sole solvent for the reaction, which allows for the sequential azidation and CuAAC reactions to be carried out in a single pot, avoiding the need for intermediate isolation and purification steps. The protocol exhibits high stereoselectivity, mild reaction conditions, and good yields for the target glycosyl triazoles. The method provides a convenient and efficient approach to accessing diverse 2-C-acetonyl glycosyl triazoles, which have potential applications in glycoscience and the life science areas. The authors predicted that the developed protocol would find wide utility in glycoscience because the CuAAC reaction is so widely used, and they are currently investigating further applications of this strategy in their laboratory. The key advantages of this approach are the one-pot, two-step procedure, the use of PEG-400 as a green and sustainable solvent, and the ability to access a broad range of 2-C-branched glycosyl triazoles in an efficient and stereoselective manner.

2.3 Macrocyclic and polymer conjugates

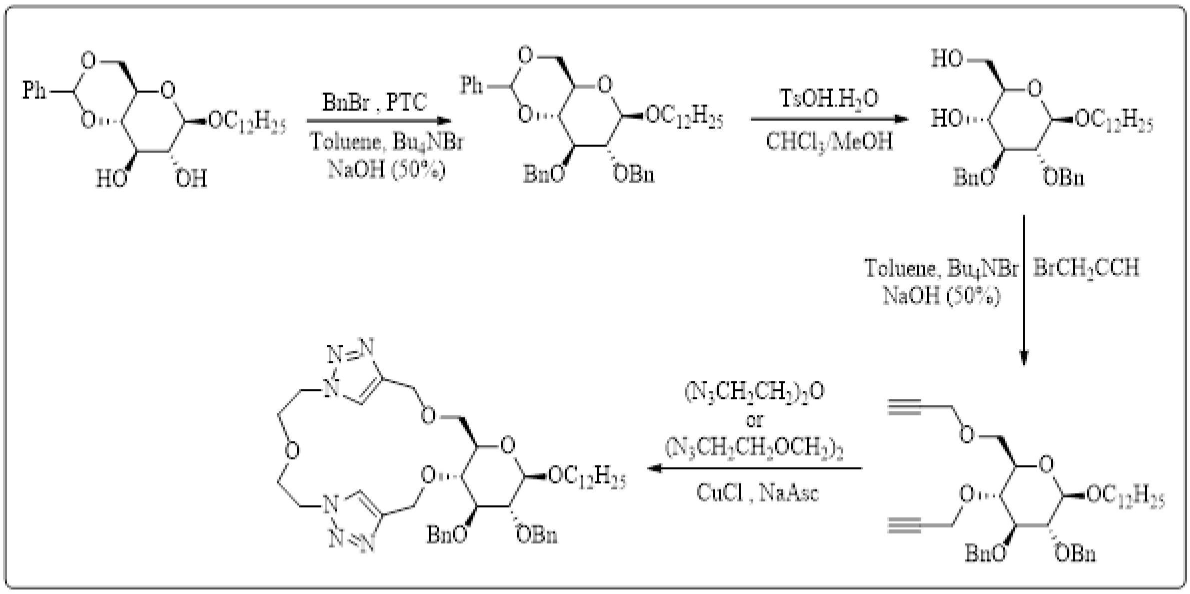
Kareem *et al*. [35] synthesized a series of novel macrocycles based on hydrocarbon glycosides obtained from D-Glucose (Scheme 5) and D-Galactose (Scheme 6). The dialkynyl derivatives and diazides reacted via a 1,3-cycloaddition process catalyzed by copper to produce these macrocycles. The vicinal dihydroxy derivatives were obtained via simple protecting group methods, while



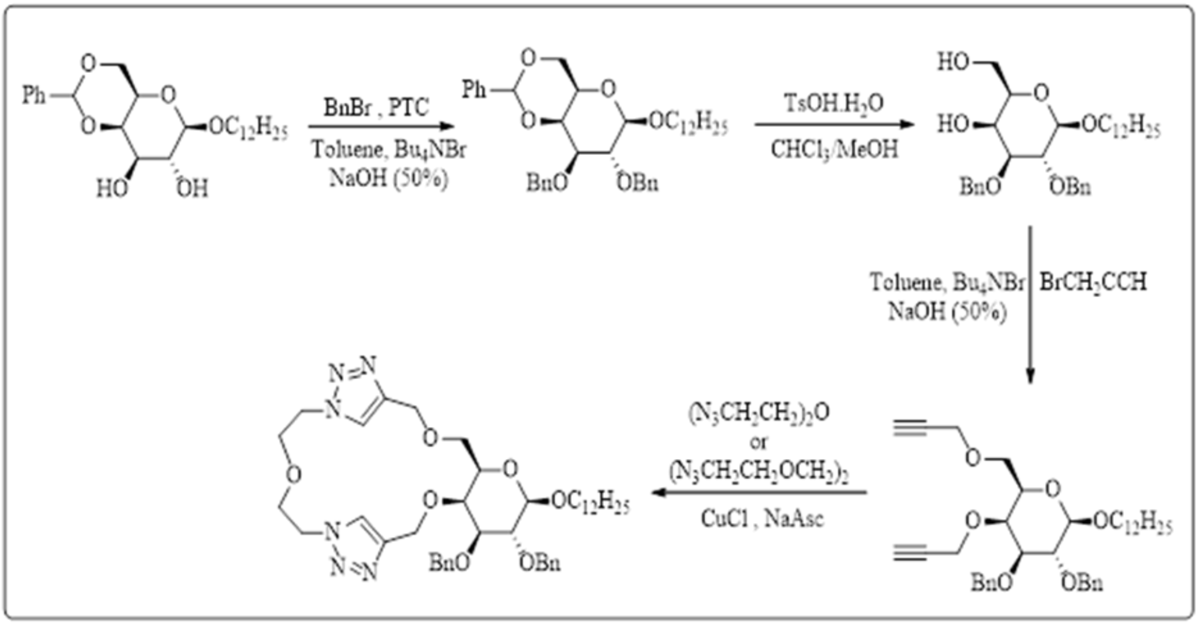
Scheme 4. One-pot synthesis of 2-C-branched glycosyl triazoles using PEG-400 as a green solvent for sequential azidation and CuAAC reactions [34].

dialkynyl derivatives were obtained by Williamson etherification with propargyl bromide. These macrocycles were constructed via a 1,3-Huisgen cycloaddition reaction, which was carefully studied for optimal macrocyclization in terms of reaction duration, catalysts, solvents, and temperature. The optimal reaction conditions for producing the macrocycles were determined to be 60°C, 2 mol% CuCl, 6 mol% sodium ascorbate, and aqueous ethanol. The highest yield was achieved at 60°C with C2H5OH:H2O (85:15) and 2 equivalents of CuCl and 6 equivalents of sodium ascorbate, after a variety of 1,3-Huisgen reaction conditions were investigated.

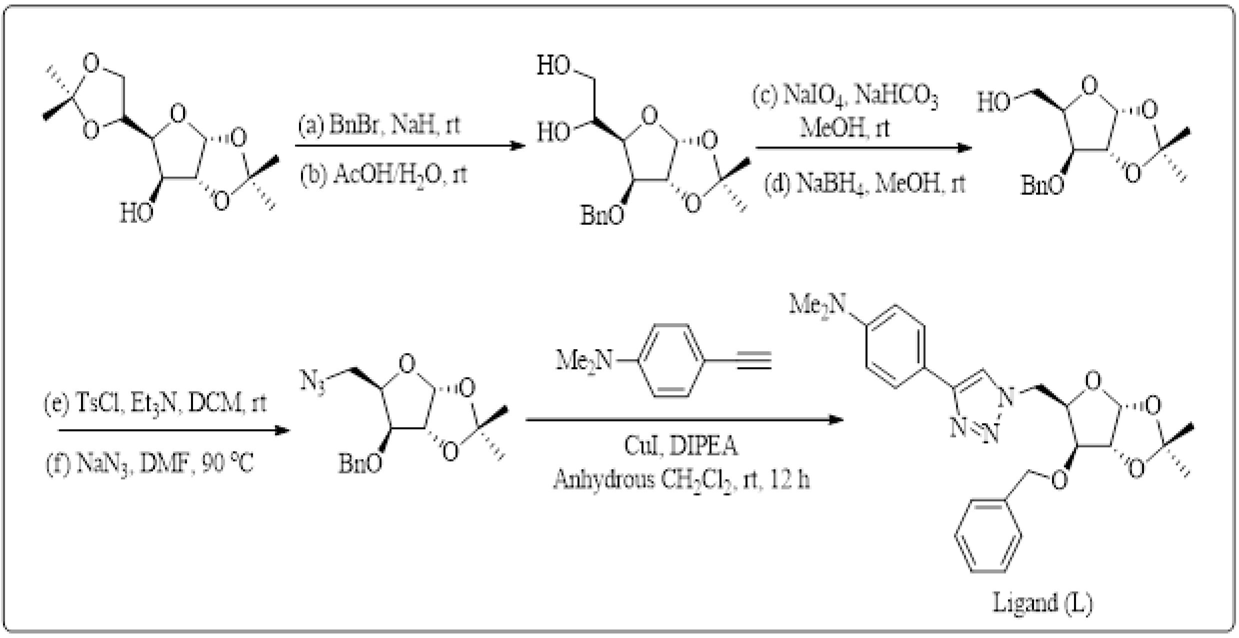
An efficient approach for the Sonogashira cross-coupling reaction between aryl halides and alkynyl sugars, which is catalyzed by Cu(I) employing 1,2,3-triazole attached glycohybrid ligands is described in the publication by Singh *et al*. [36]. When a glycosyl monotriazolyl ligand was present at 120 °C, the Sonogashira cross-coupling compounds were produced solely except the Glaser-Hay coupling reaction. However, when a bis-triazolyl-based macrocyclic glycohybrid ligand was present, the Glaser-Hay coupling compounds were produced at 60-70°C. The CuI/DIPEA-mediated regioselective CuAAC click reaction was used to create the glycosyl triazole ligands (Scheme 7).



Scheme 5. Macrocyclic triazole synthesis from glucose derivatives on 4,6-O-positions [35].

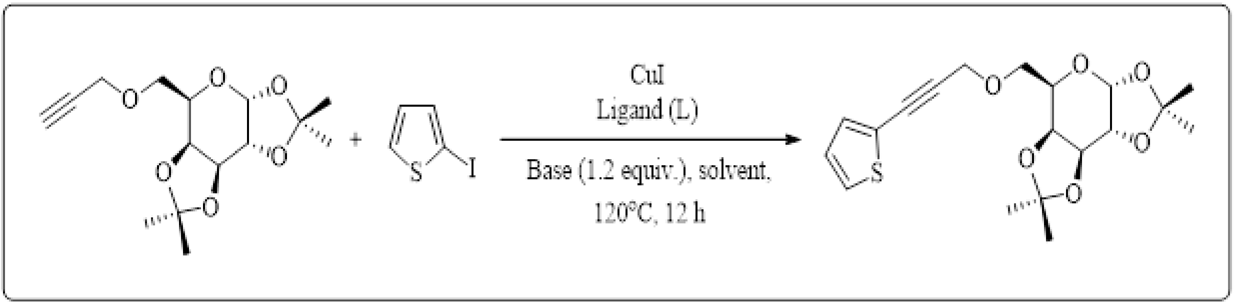


Scheme 6. Creation of macrocyclic triazoles from galactose derivatives at the 4,6-O-positions [35].



Scheme 7. Formation of ligand (L) starting from D-Glucose derived D-Glucose diacetonide [36].

A number of glycohybrids comprising galactose, mannose, and glucose alkynes, together with glycosyl rods, were produced in excellent yields (Scheme 8). Numerous spectroscopic methods, including nuclear magnetic resonance (NMR), high-resolution mass spectrometry (HRMS), and single-crystal X-ray diffraction, have given good characterizations of the produced glycohybrids. Heteroaryl and naphthyl halides respond well to the technique, and the mechanistic approach results in oxidative coupling aided by CuI and the ligand. Notable characteristics of the coupling process include its broad substrate range, low catalytic loading, affordability, and biocompatibility.



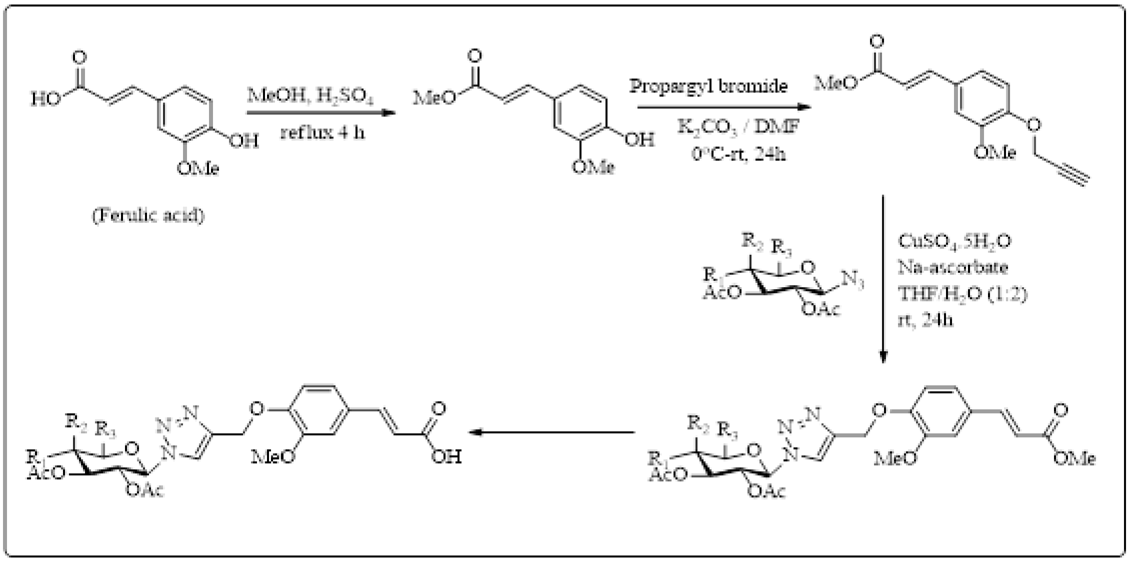
Scheme 8. Glycohybrid synthesis via glycosyl triazole ligand (L), enabling efficient C–C cross-coupling reactions with aryl and heteroaryl halides [36].

3. Biological Applications of Glyco-Triazole Hybrids

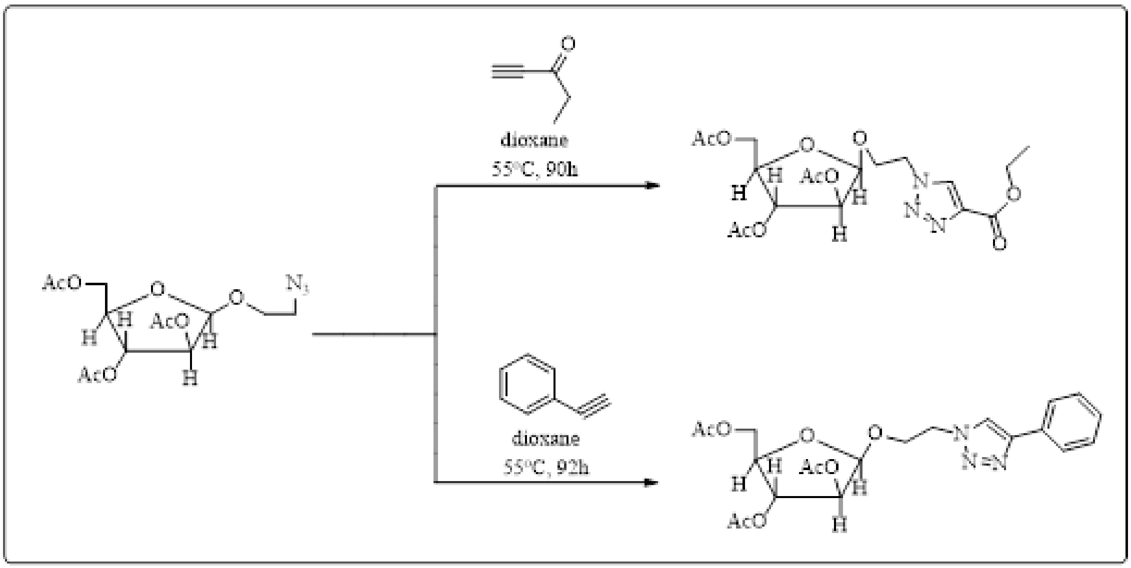
3.1 Antimicrobial and antifungal activity

The relevance of glyco-triazoles in anti-infective drug development is supported by the potential antimicrobial activities of a series of carbohydrate-linked 1,2,3-triazoles produced by El-Malah *et al*. [37]. The main focus of the study carried out by Tashkandi and group [38] is the design, synthesis, and assessment of distinct triazole-ferulic acid ester combined with sugar as potential antimicrobial agents. A variety of 1,2,3-triazole derivatives of ferulic acid with various sugar moieties were developed and synthesized using a Cu(I)-catalyzed click dipolar cycloaddition (Scheme 9). The synthesized compounds were evaluated for their antibacterial and antifungal properties. Compound 12 produced an inhibition zone of 18 mm against Bacillus cereus (comparable to tetracycline, 20 mm), while compound 14 reached 20 mm against Pseudomonas aeruginosa, exceeding that of tetracycline (18 mm). In antifungal assays, compounds 6 and 14 inhibited Candida albicans with zones of 18 mm and 20 mm, respectively, surpassing the reference cycloheximide (14 mm). These results highlight that the triazole–ferulic acid glycosides not only matched but also outperformed standard drugs in some cases. The binding relationships between the active chemicals and the microorganisms' target proteins were examined using molecular docking experiments. The majority of the compounds showed excellent binding affinity with the desired proteins, in line with earlier reports showing that triazole-linked glycoconjugates exhibit strong recognition toward galectin-3 [39]. Methicillin-resistant *Staphylococcus aureus* (MRSA) has also been demonstrated to become sensitive to β-lactam antibiotics when exposed to triazole-linked glycolipids, demonstrating the potential of these compounds to fight resistant bacterial strains [40].

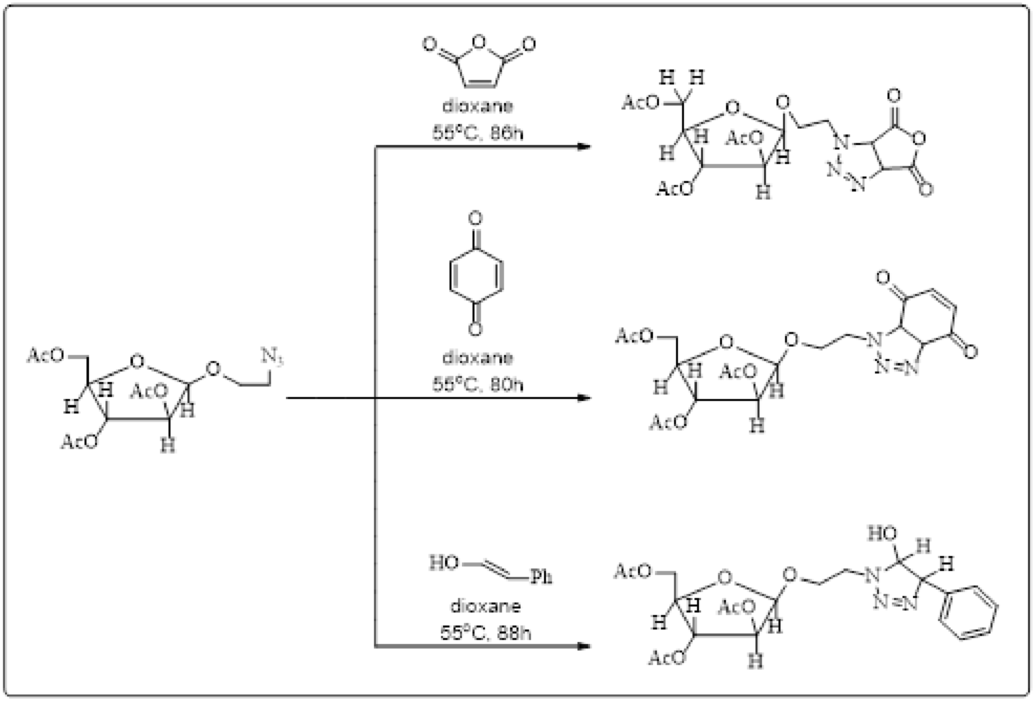
The paper by Alsaeedy *et al*. [41] describes the synthesis and identification of new 1,2,3-triazole and 1,2,3-triazoline glycosides derived from D-arabinose. These hybrid compounds were created by reacting azido ethyl-O-β-D-arabinofuranoside with various unsaturated hydrocarbons in a 1,3-dipolar cycloaddition process. Based on the antimicrobial screening's findings, the synthetic 1,2,3-triazole (Scheme 10) and 1,2,3-triazoline derivatives (Scheme 11) exhibited superior antibacterial qualities compared to the traditional medications utilized for comparison. At 0.60 mg/mL, this compound shows the highest broad-spectrum activity, showing inhibition zones of 29 mm (*E. coli*), 27 mm (*S. aureus*), and 28 mm (*C. albicans*), which were comparable to or better than standard drugs ampicillin (28 mm against *E. coli*, 25 mm against *S. aureus*) and cycloheximide (25 mm against *C. albicans*). Compound b also demonstrated strong antibacterial action (28 mm against *E. coli*), while compound c–e exhibited moderate but significant inhibitory activity. The study outlines how computational techniques were used to assess the synthesized compounds' physicochemical, pharmacokinetic (ADME), and drug-likeness characteristics.



Scheme 9. Ferulic acid system synthesis based on triazole glycosides [38].

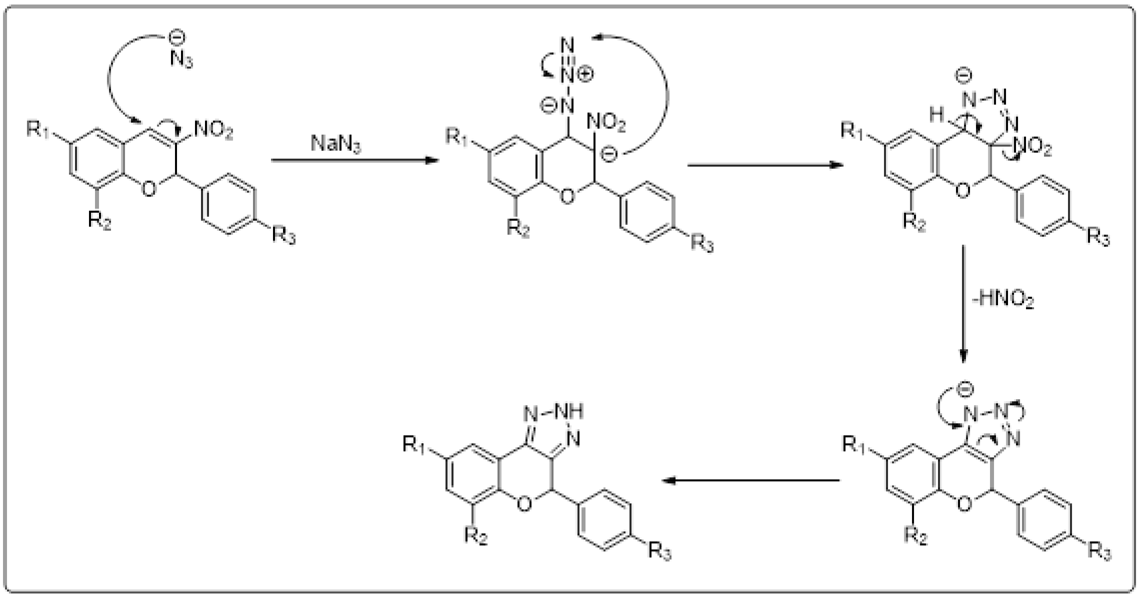


Scheme 10. Synthesis of 1,4-disubstituted-1,2,3-triazoles from arabinose derivatives through 1,3-dipolar cycloaddition [41]



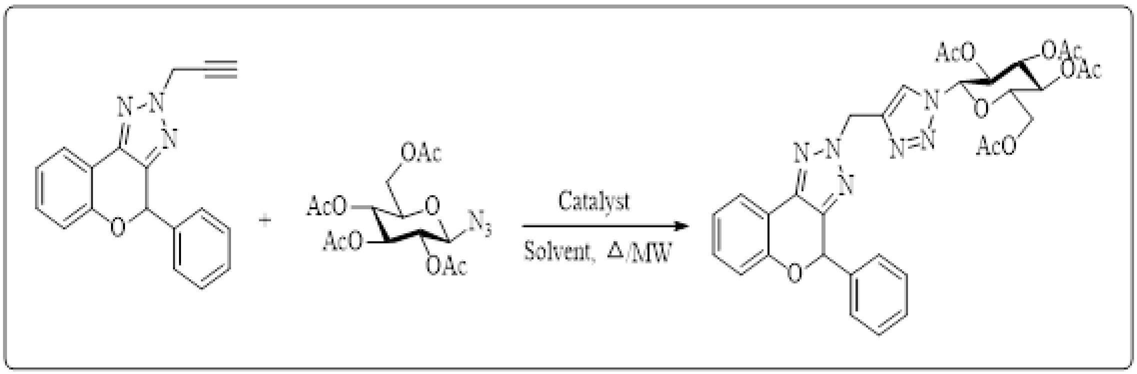
Scheme 11. Production of 1,4,5-trisubstituted-1,2,3-triazolines [41].

The compounds have high oral bioavailability, according to the data, and are attractive compounds for promoting drug discovery and progress as novel antimicrobials. The molecular geometry, frontier molecular orbitals, and reactivity of the produced compounds were examined operating density functional theory (DFT) calculations.



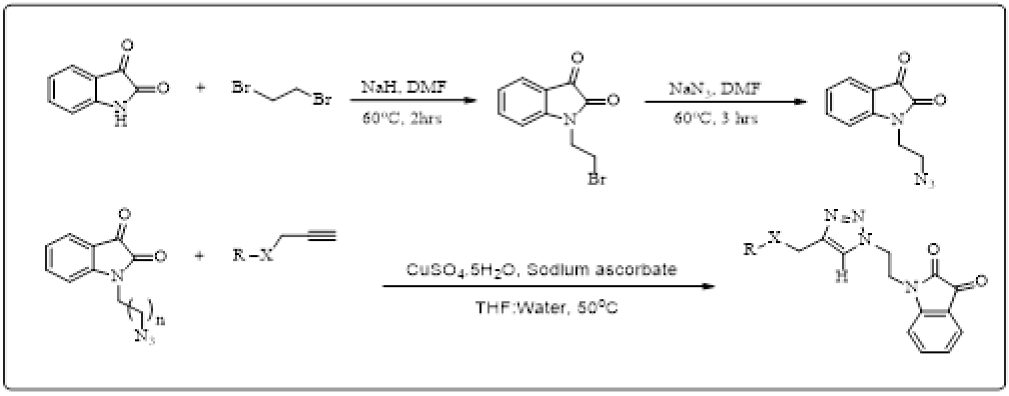
Scheme 12. Process by which nitrochrone is converted to chromene fused triazole [42].

The DFT analysis disclosed that one of the compounds has the lowest energy gap. Molecular docking was executed to assess the binding affinity of the generated compounds towards the bacterial target protein (*E. coli* MurB, PDB ID: 2Q85). The docking data, which had higher docking scores than the common medication ampicillin, were in good accordance with the experimental antibacterial activity. According to a study by Ahemad *et al*. 2024 [42], a CuAAC reaction was used to create a set of new 1,2,3-triazole hybrid benzopyran-derived glucose triazole conjugates from a benzopyran-incorporated 1,2,3-triazolyl extended alkyne and 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl azide (Scheme 12, 13). Significant antibacterial activity was demonstrated by the synthesized compounds against both Gram-negative *E. coli* and Gram-positive *S. aureus* bacteria.



Scheme 13. Formation of chromene fused triazole [42].

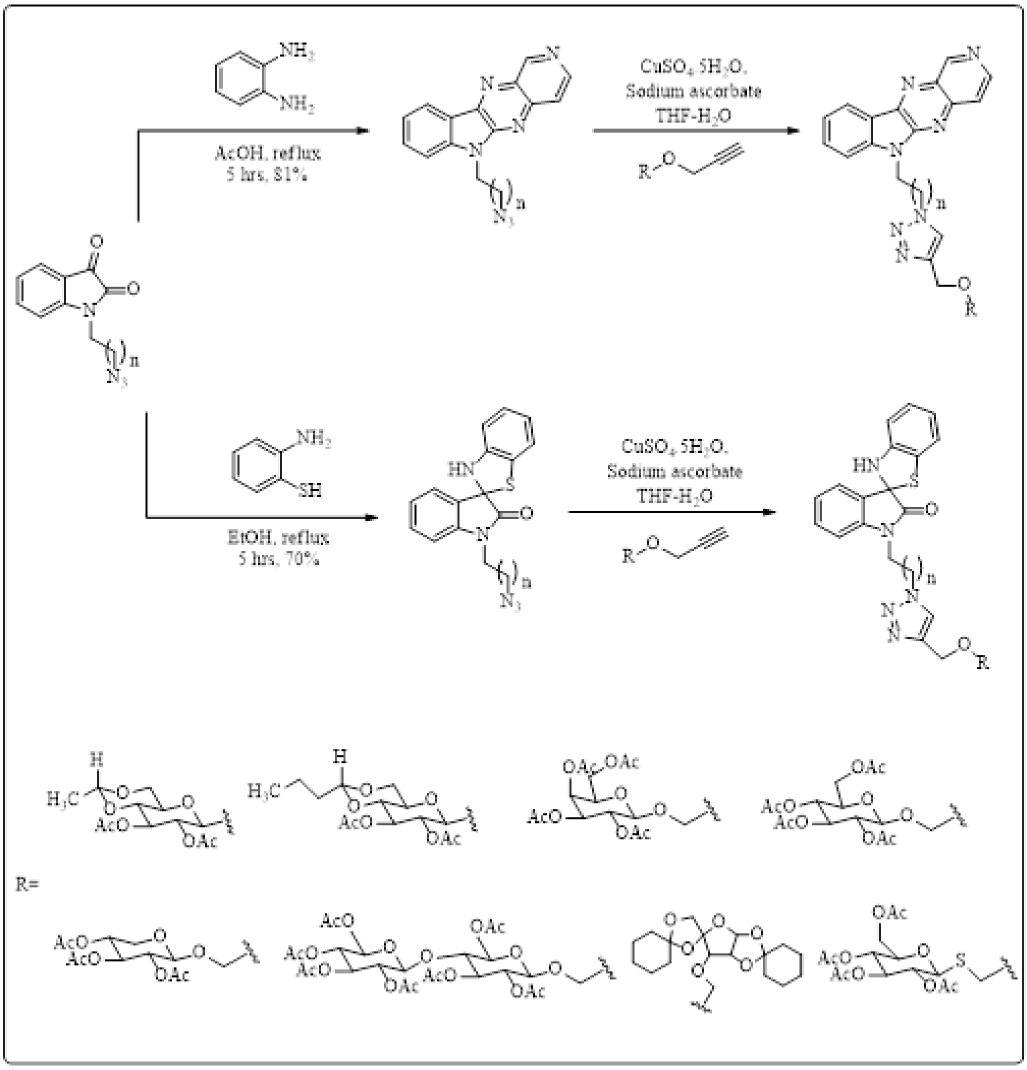
The most effective synthetic chemical was determined to have an inhibition zone (ZI) of 17 mm and a minimum inhibitory concentration (MIC) of 25 µg/mL in E. *coli* and a ZI of 16 mm and a MIC of 25 µg/mL in S. *aureus*. Certain compounds exhibited the highest level of DNA gyrase inhibitory activity, according to molecular docking studies; their binding affinities against E. *coli* DNA gyrase ranged from -9.7 kcal/mol to -9.0 kcal/mol. This novel class of glucose triazole conjugates based on 1,2,3-triazole-fused chromene may soon prove to be a powerful antibacterial medication.



Scheme 14. Synthesis of sugar based heterocyclic triazole derivative: isatin [43].

3.2 Anticancer agents

Jenifer and co-workers [43] discussed the synthesis and antioxidant characteristics of novel heterocyclic sugar-triazole derivatives. They synthesized three novel classes of heterocyclic sugar-triazole derivatives using 1,3-dipolar cycloaddition catalyzed by copper reactions. The synthesized compounds include isatin-sugar hybrids (Scheme 14), indoloquinoxaline-sugar hybrids, and spiro indolinones-benzothiazole-sugar hybrids (Scheme 15). Several spectroscopic methods, including NMR spectroscopy, were used to validate the structures of the produced compounds. The anomeric forms of the sugar moieties were found to be predominantly in the β-configuration. The 2,2-diphenyl-1-picrylhydrazy (DPPH) radical scavenging experiment was applied to estimate the antioxidant properties of the produced compounds. Among the synthesized compounds, the isatin-sugar hybrid with a thio-sugar moiety showed the highest antioxidant activity, with 89.2% hindrance at 18.29 µg/mL concentration. The antioxidant activity of the compounds was found to be impacted by factors such as the occurrence of protecting groups on the sugar moiety, the nature of the heterocyclic component, and the existence of hydrophobic alkyl chains. The study claims that this is the first report of isatin-based sugar-triazole compounds showing such high antioxidant activity contrast to remaining classes of sugar-heterocyclic compounds. The paper suggests that these novel heterocyclic sugar-triazole derivatives could potentially be developed as antioxidant agents, with implications for drug discovery and development. In addition, coumarin-based triazole glycosides and their analogs have been reported to induce apoptosis via the mitochondrial pathway and display significant anticancer effects, supported by docking simulations that elucidate their binding to key targets [44].

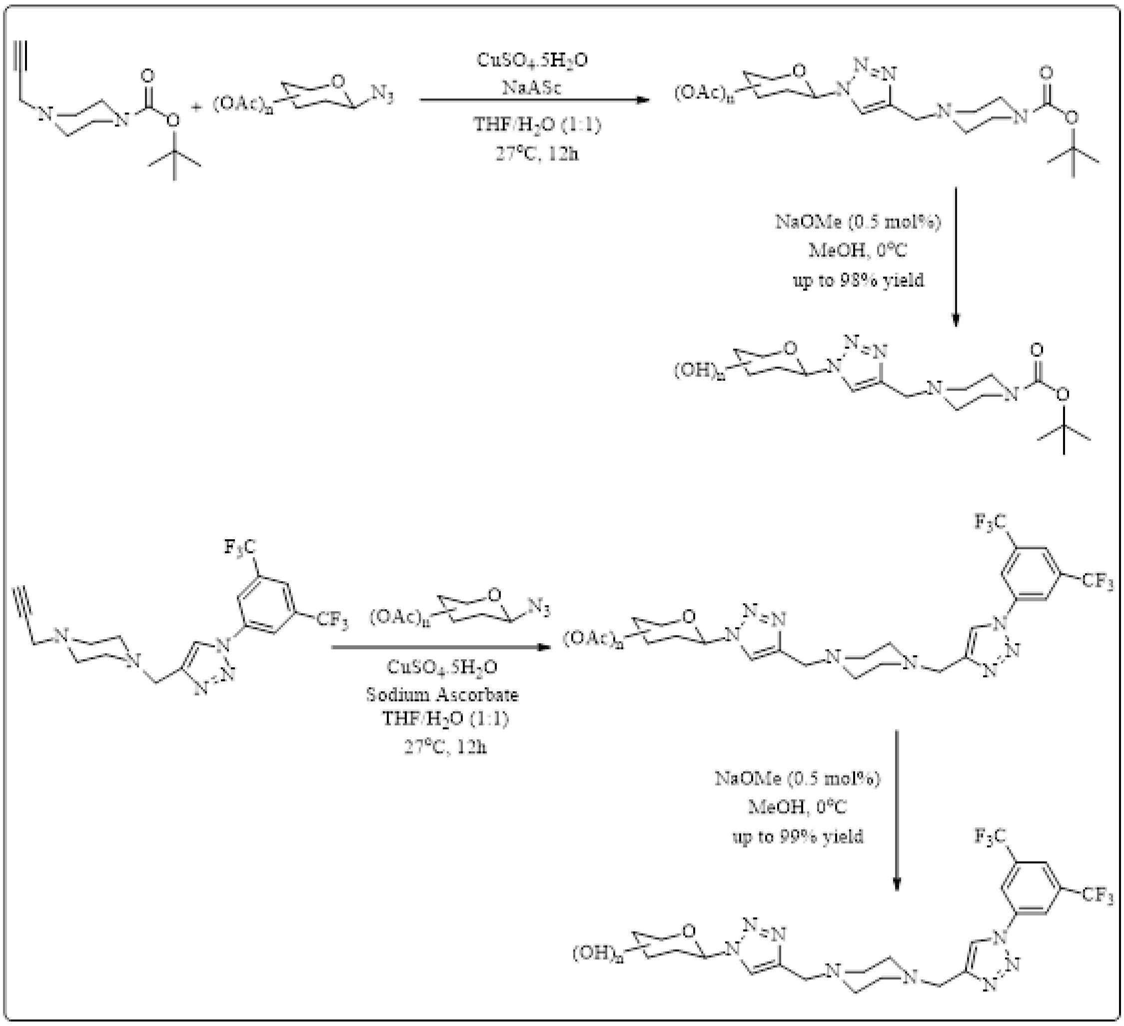


Scheme 15. Synthesis of sugar based heterocyclic triazole derivatives: indoloquinoxaline and spiro indolinones-benzothiazole [43].

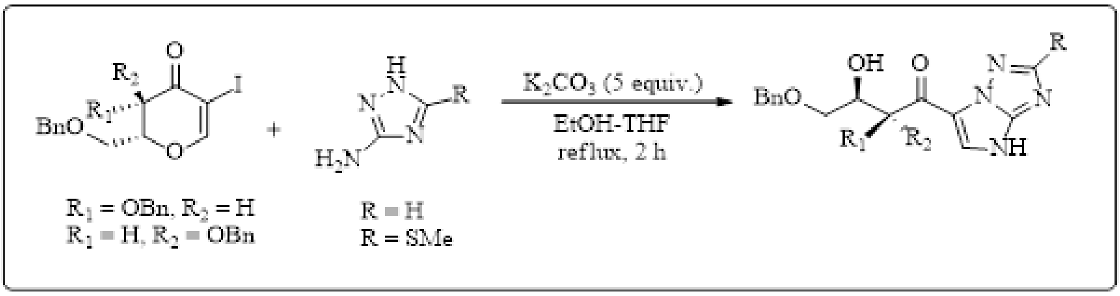
The paper by Bose *et al*. [45] depicted the synthesis of diverse piperazine-triazolyl sugar-conjugates through a click chemistry path with the focus of developing water-miscible and biocompatible motifs (Scheme 16). The study evaluates the potential of these glycoconjugates to inhibit cyclin-dependent kinases (CDKs) and exhibit anticancer activity against HeLa cancer cells using in vitro along with in silico routes. The most promising motifs, according to the study, were piperazine conjugates produced from galactose and mannose.

In particular, the greatest CDK interaction and notable anticancer activity were demonstrated by the galactosyl bis-triazolyl piperazine analogue. The paper describes the synthetic procedures for obtaining the piperazine alkynes, sugar azides, and the final piperazine-triazolyl glycoconjugates. The click chemistry approach was used to couple the sugar azides and piperazine alkynes to generate the target compounds. Docking studies were carried out to evaluate the binding interactions of the glycoconjugates with the CDK4 mimic CDK2 protein. The results showed that the mannose and galactose derivatives had the best binding interactions with the target protein. The anticarcinogenic potential of the synthesized compounds was evaluated using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) analysis on the HeLa cancer cell line. The results indicated that the galactosyl bis-triazolyl piperazine analogue had the highest potency with an IC_{50} of 3.31 µM.

Mishra and his group [46] demonstrated the efficient synthesis of discrete imidazo-triazole and imidazo-pyrazole based glycohybrid molecules (Scheme 17). The α-iodo-2,3-dihydro-4H-pyran-4-ones generated from carbohydrates were found to be appropriate precursors, and they were combined with different aminopyrazoles and aminotriazoles to create the intended glycohybrids. Imidazo-pyrazole and imidazo-triazole-based glycohybrids were produced in satisfactory yields in reduced reaction times using this straightforward and reliable established approach. The Michigan Cancer Foundation-7 (MCF-7) (hormone receptor) and M. D. Anderson Metastatic Breast-231 (MDA-MB-231) (human epidermal growth factor 2 receptor) breast cancer cell cultures were shown to be susceptible to submicromolar anticancer action from the novel glycohybrids.



Scheme 16. Production of 1-tert-butyl carboxyl 4-(1,2,3-triazol-4-yl)methyl)piperazine glyco-conjugates and 1,4-di-triazolyl -1-(3,5-bis(trifluoromethyl)phenyl)- piperazine glyco-conjugates [45].

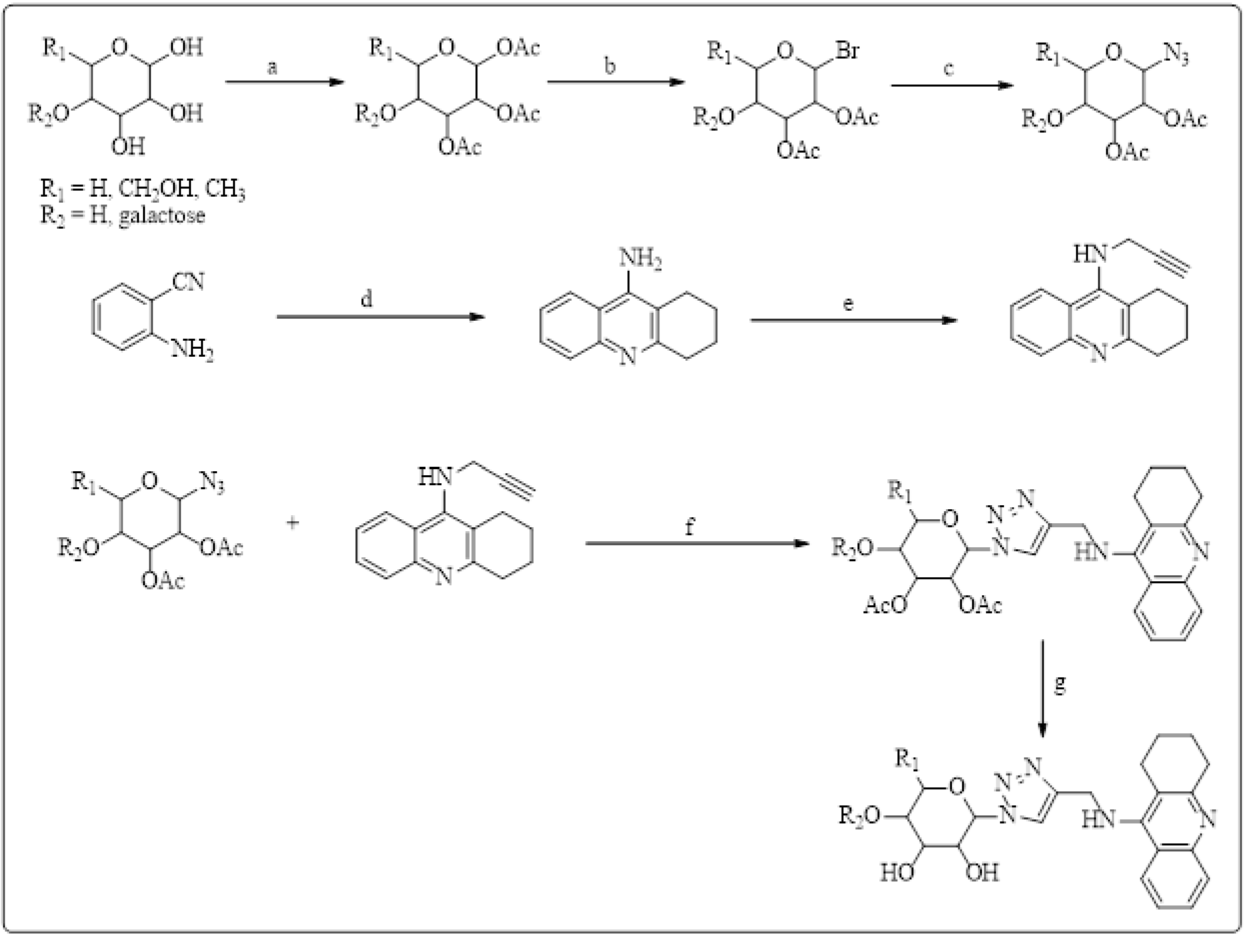


Scheme 17. Efficient synthesis of imidazo-pyrazole and imidazo-triazole glycohybrids from carbohydrate-derived iodoenones [46]. Reagents and conditions: iodoenone (0.22 mmol), 3-aminopyrazole (0.24 mmol), using potassium carbonate (1.11 mmol) as base in solvent system THF:Ethanol (14 mL, 1:1, v/v), 90°C, 2 hr.

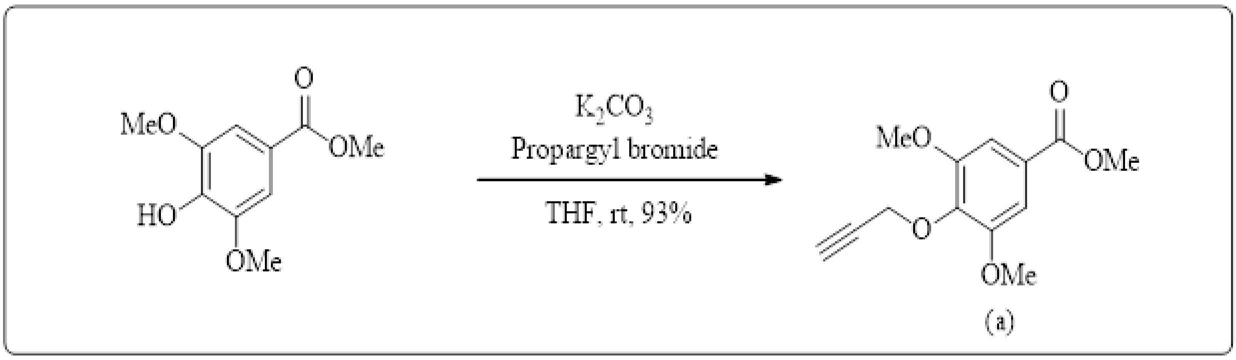
In silico docking studies suggest successful bonding of the imidazo-pyrazole or imidazo-triazole glycohybrids with the Hematopoietic Cell Kinase (HCK) protein's catalytic site, highlighting their potential as new chemical entities for pharmaceutical development.

The group reports the efficient synthesis of a series of imidazo-pyrazole and imidazo-triazole-based glycohybrid molecules. The glycohybrid structures were developed by combining several aminopyrazoles and aminotriazoles with carbohydrate obtained α-iodo-2,3-dihydro-4H-pyran-

4-ones, which they found to be appropriate key precursors. After optimizing the synthetic process, the researchers were able to produce the desired glycohybrids in short reaction times and with good to exceptional yields.



Scheme 18. Synthesis of tacrine-derived triazole glycoconjugates with reduced hepatotoxicity and acetylcholinesterase inhibition [52]. Conditions for reaction: a) (CH3CO)2O (1.2 equiv.), perchloric acid, CH2Cl2, stir at 0 oC, 1 h; b) HBr in CH3COOH, 0 oC, rt, 3 h ; c) Sodium azide (1.2 eq), DMF, 50 °C, 1hr; d) Cyclohexanone, $BF_3.OEt_2$, $C_6H_5CH_3$, aq NaOH, reflux 48 hrs; e) Propargyl bromide, sodium hydride (2 eq), DMF, 0 °C, rt; f) Ceric ammonium nitrate, CuI, r.t., 1 hr; g) Sodium methoxide, CH_3OH, rt, 15 min.

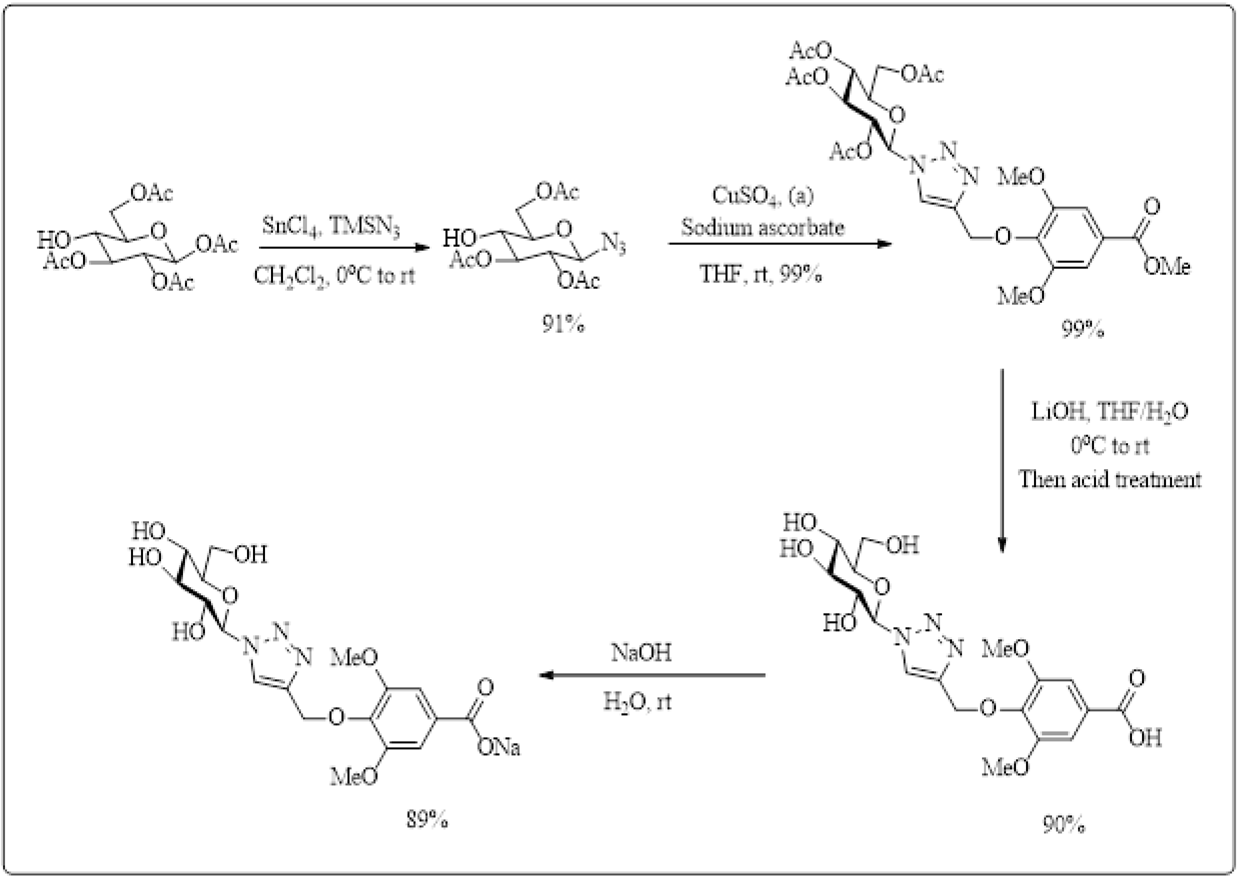


Scheme 19. Preparation of alkyne analogues for syringic acid–sugar conjugate [55].

Several compounds showed submicromolar potency, especially against MDA-MB-231 and MCF-7 cell lines, when the newly synthesized compounds were tested for their anticarcinogenic efficacy against several breast cancer cell cultures. In addition, in-silico docking studies were performed, which suggested that the imidazo-triazole and imidazo-pyrazole glycohybrids can effectively interact with the catalytic site of the HCK protein, a tyrosine kinase implicated in various cellular processes and cancer progression. This highlights the potential of these glycohybrid molecules as new chemical entities for further pharmaceutical development.

3.3 Antiviral, antimalarial and enzyme inhibitors

Triazole scaffolds have demonstrated promising antiviral properties through the inhibition of viral enzymes. Efavirenz-derived triazolyl phosphonates showed potent HIV-1 reverse transcriptase inhibition with IC_{50} values of 0.8-1.9 µM, comparable to the standard drug tenofovir disoproxil fumarate [47]. Similarly, triazole-nucleoside conjugates have been reported as influenza neuraminidase and SARS-CoV-2 main protease inhibitors, with low micromolar inhibitory concentrations [48]. These results support the strong potential of triazole-based glycoconjugates in antiviral drug discovery. In antimalarial studies, triazole-quinoline and triazole-chloroquine hybrids have shown high activity against *Plasmodium falciparum*. Quinoline-triazole hybrids inhibited the parasite cysteine protease falcipain-2 with IC_{50} values of 16.16 and 25.64 µM, and suppressed parasite development with EC_{50} values of 21.89–49.88 µM [49]. In addition, thiosemicarbazone-triazole hybrids demonstrated strong inhibition of cholinesterase enzymes, with acetylcholinesterase (AChE) inhibition ranging from 0.20 ± 0.05 µM to 12.20 ± 0.30 µM and butyrylcholinesterase (BuChE) inhibition between 0.40 ± 0.05 µM and 14.10 ± 0.40 µM, highlighting compounds 6q and 6o as the most potent analogues [50].

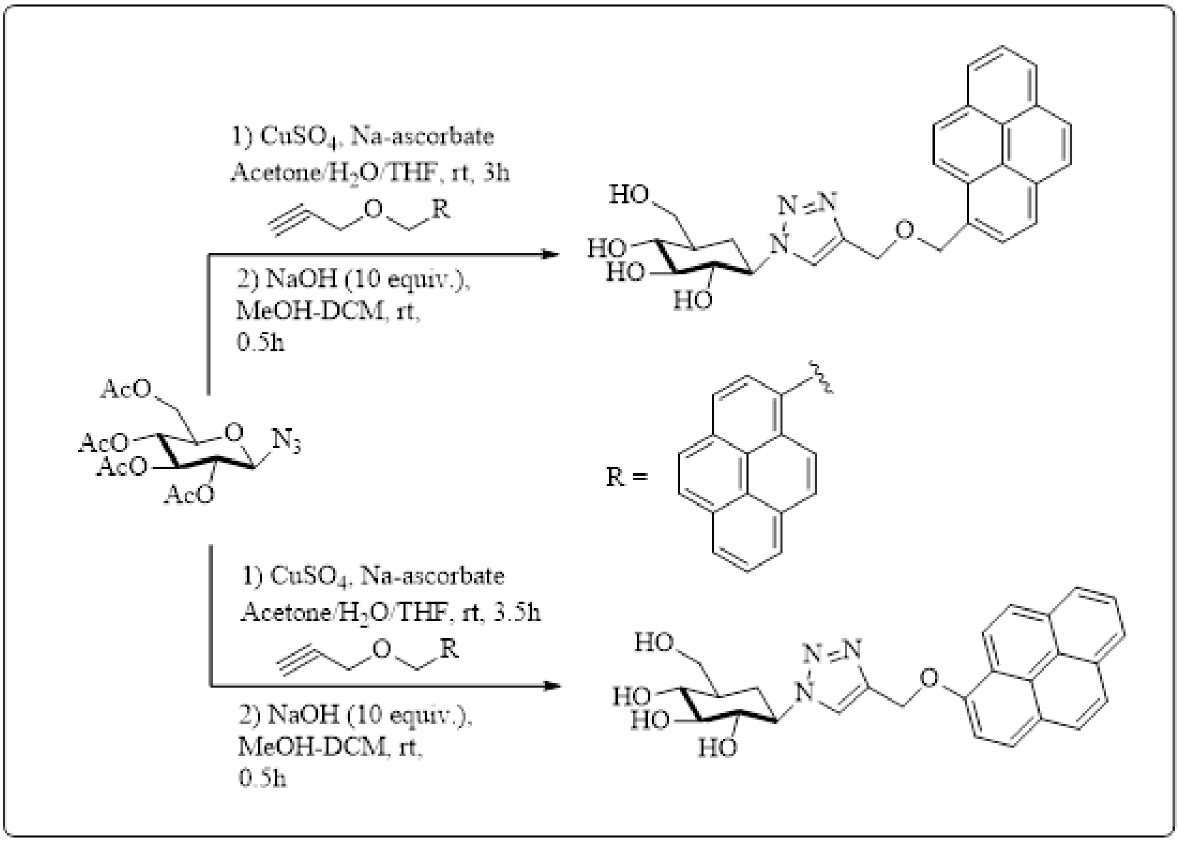


Scheme 20. Using click chemistry, the sugar-SA triazole conjugates are synthesized [55].

More recently, 1,2,3-triazole derivatives synthesized via click chemistry were shown to act as dual inhibitors of human carbonic anhydrase II and acetylcholinesterase, with nanomolar affinities (K_i = 144.3 nM for hCA II and 205.1 nM for AChE in compound 4f) [51]. New heteroannulated 1,2,3-triazole glycosides have also been demonstrated in recent studies to exhibit great antiviral potential by exhibiting strong in vitro and in vivo suppression of influenza A virus neuraminidase [52]. Even though tacrine is an established inhibitor of AChE, it has the drawback of being hepatotoxic.

A recent study synthesized tacrine-related triazole glycoconjugates in order to lessen the hepatotoxicity of tacrine. A range of triazole-based glycoconjugates with acetylated and free sugar hydroxyl groups at tacrine's amino site were synthesized and tested for hepatotoxicity and in vitro AChE inhibition (Scheme 18). At 200 µM (100% cell viability), all of the synthesized hybrids were non-toxic to the HepG2 cell line, in contrast to tacrine (35% cell viability) following a 24 h incubation time. One of the powerful hybrids, IC_{50} of 0.4 µM, was the subject of enzyme kinetic investigations, which demonstrated a mixed inhibition strategy. Molecular docking studies showed that the glyco-conjugates remain outside the constricted binding pocket of the CYP1A2 enzyme, thereby decreasing the possibility of devising hepatotoxic metabolites. Overall, the carbohydrate insertion into the tacrine framework is more favourable in advancing the hepatotoxicity of tacrine [53]. Glycosides with substituted pyridine cores linked via a triazole showed good anti-H5N1 activity and low cytotoxicity, highlighting the advantage of combining sugar and triazole scaffolds [54].

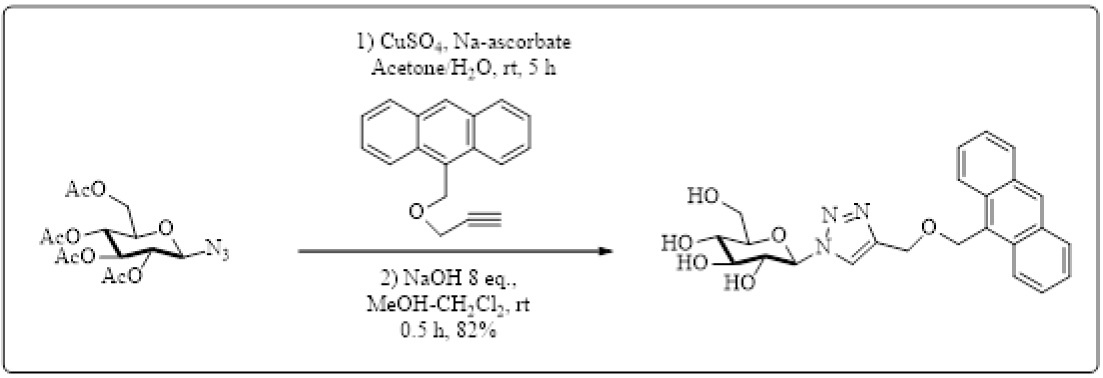
A series of sugar-syringic acid (SA) triazole conjugates are designed, synthesized, and characterized in the publication by Cao and colleagues [55] to enhance SA's low bioavailability and poor water solubility. SA is a potential regulator of lipid metabolism. In comparison to unmodified SA, they produced a set of sugar-SA triazole derivatives with improved water miscibility and stability by effectively conjugating polar sugar moieties to SA using a four-step click chemistry technique (Scheme 19-20). The most effective pancreatic lipase (PL) inhibition among the produced conjugates was demonstrated by the glucose conjugate (GS), which outperformed the FDA-approved drug orlistat. Bile salt and cholesterol binding were also markedly enhanced by GS. By acting through competitive inhibition, GS raised the Michaelis-Menten constant (K_m) without changing the maximum reaction rate (V_{max}) of PL, according to enzyme kinetic studies. The secondary and tertiary structures of PL were disrupted by GS binding, reducing its thermal stability, according to spectroscopic investigations using UV-visible, fourier-transform infrared (FT-IR), fluorescence, and differential scanning calorimetry (DSC). The enhanced effectiveness of GS over other sugar-SA triazole conjugates and unmodified SA was explained by molecular docking, which verified potent interactions between GS and important catalytic fragments of PL. The results show that GS may be used as a new lipid-lowering medication or as a functional food component to treat obesity and associated metabolic diseases.



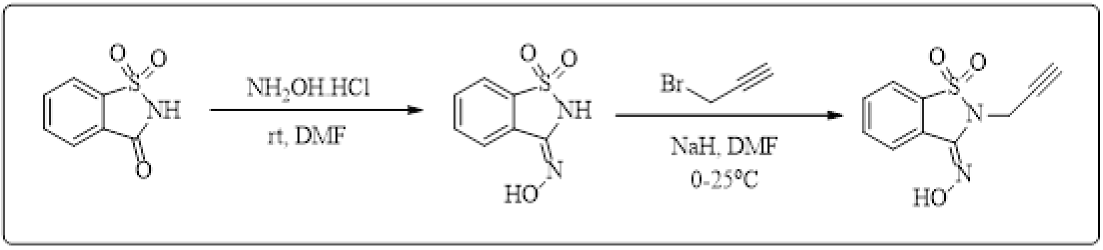
Scheme 21. Creation of triazole-based pyrene-N-glycosyl sensors [56].

4. Glyco-Triazole Hybrids in Material Science and Sensing

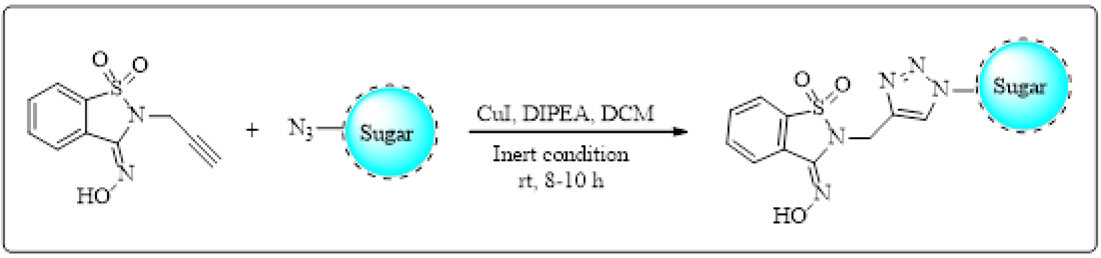
Affordable sensors for the instantaneous detection of picric acid were created using carbohydrates functionalized with triazole-linked pyrene, operating via a charge-transfer mechanism in semi-aqueous media (Scheme 21). Using the absorbance and fluorescence approaches, sensors demonstrated high sensitivity and selectivity towards picric acid over a broad range of nitroaromatics. With test strips, these sensors allowed for the rapid detection of picric acids. The sensor's pyrene and triazole/sugar residue have a tight intramolecular space, which explains why its sensitivity (Limit of Detection, LOD: 0.012 µM) is higher than that of another sensor (LOD: 0.093 µM). Spectroscopic investigations and DFT computations validated the complexes' structural characteristics and fluorescence quenching. Considerable intermolecular hydrogen bonds and other non-covalent interactions, for instance van der Waals contacts, stabilize the complexes, according to the DFT calculations [56].



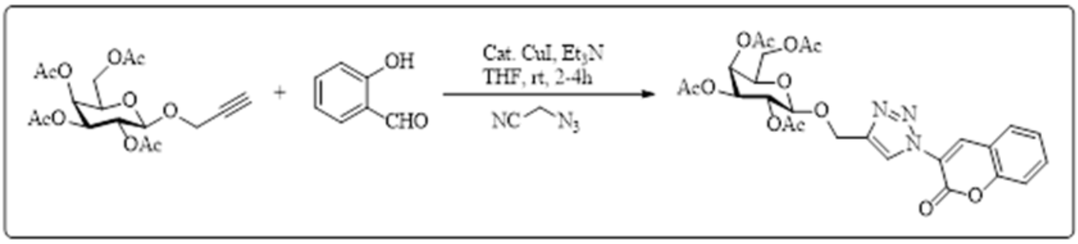
Scheme 22. Method of synthesis of a sugar anthracene derivative using a triazole bridge [57].



Scheme 23. Synthesis of hydroxyamino-saccharin alkyne [58].



Scheme 24. Synthesis of hydroxyamino-saccharin triazole [58].



Scheme 25. Production of 3-triazolyl-2 iminocoumarin derivatives under the influence of copper [59].

sensitivity towards picric acid with a detection limit of 0.09 µM and a Stern-Volmer quenching constant of 1.59×10^5 M^{-1} in an aqueous acetonitrile medium. The fluorescence quenching is attributed to the development of a non-emissive charge-transfer complex between receptor and picric acid. This receptor can also selectively detect Au (III) ions in 100% H_2O, having a detection limit of 0.094 µM and a Stern-Volmer constant of 1.8×10^5 M^{-1}. The quenching

Dey *et al.* [57] reported the synthesis and characterization of a triazole-bridged anthracene-sugar analogue and its ability to selectively detect Au (III) ions and picric acid (Scheme 22). The receptor showed excellent

mechanism is explained through a reverse photoinduced electron transfer (PET) process. The binding stoichiometry between the receptor and 2,4,6-trinitrophenol or Au (III) is determined to be 1:1. The study also demonstrates the practical application of the receptor in detecting picric acid in real water samples like running water, river, and pond with good recovery percentages. DFT calculations support the evolution of the non-emissive 1-picric acid complex and the interaction patterns between the receptor and the analytes.

Another study by Bose *et al*. [58] presented a series of novel saccharin glycoconjugates by means of a 1,2,3-triazole linker making use of click chemistry (Scheme 23, 24). These hybrid molecules were synthesized in good yield under moderate reaction conditions. The docking study depicted that the arising saccharin glycoconjugates exhibited selective and substantial interaction with the carbonic anhydrase 12 (CA12) macromolecule, with the milk sugar triazolyl saccharin analogue and the xylosyl 1,2,3-triazolyl benzosulfimide analogue showing the elevated binding energies of -8.5 kcal/mol and -8.2 kcal/mol respectively. The study states that the saccharin glycoconjugates can be recognized as selective CA12 interactive agents, as the docking study showed better fitting scores with CA12 compared to carbonic anhydrase 9 (CA9) and CDK4 mimic CDK2 protein. The validation of the docking method was executed using 2 established approaches - plotting scoring or rescoring values and superimposing the co-crystal structure, which confirmed the reliability and reproducibility of the docking result.

Furthermore, the synthesis of diverse of glycosylated iminocoumarins and glycosylated 3-triazolyl-2-iminocoumarin compounds through copper-catalyzed multicomponent reactions (Scheme 25) has been reported [59]. These compounds were synthesized in excellent yields through two different reaction pathways - a Cu-catalyzed tandem reaction of sulfonyl azides, salicylaldehydes, and sugar alkynes, and a cascade "CuAAC-aldol-cyclization-dehydration" sequence starting from 2-azidoacetonitrile, sugar alkynes, and salicylaldehydes. The resulting 3-triazolyl-2-iminocoumarins and glycosylated iminocoumarins were highlighted to have probable biological and medicinal purposes due to the privileged structural frameworks of coumarins and iminocoumarins

5. Future Directions and Challenges

Despite significant progress in the design and synthesis of glyco-triazole derivatives, several challenges remain before these compounds can achieve clinical translation. One of the most critical issues is low bioavailability, which can arise from poor solubility or limited membrane permeability. Future efforts should explore prodrug strategies, nanoparticle-based delivery systems, or lipid conjugation approaches to enhance pharmacokinetic performance. Another challenge is poor stability under physiological conditions, particularly hydrolytic or enzymatic degradation of glycosidic linkages. This could be addressed by incorporating non-hydrolyzable linkers, C-glycosides, or isosteric substitutions to improve metabolic stability without compromising biological activity. From a synthetic perspective, the scale-up of click chemistry processes remains a barrier to industrial application, often due to the need for expensive catalysts or harsh conditions. Research into green chemistry methods such as catalyst-free azide-alkyne cycloadditions, recyclable heterogeneous catalysts, or solvent-free microwave-assisted synthesis could make large-scale production more feasible and cost-effective.

Finally, while many studies demonstrate good activity in vitro, the lack of comprehensive in vivo validation and toxicological profiling is a major limitation. Future research should emphasize animal model testing, ADME/Toxicity studies, and structure-activity relationship (SAR) optimization to ensure that promising candidates can progress into preclinical and clinical pipelines. Overall, addressing these challenges with concrete experimental and translational strategies will accelerate the development of glyco-triazoles into viable therapeutic agents across antimicrobial, anticancer, antiviral, and enzyme-inhibition applications

6. Conclusion

The review gives a comprehensive outline of the emerging field of glyco-triazole hybrids, covering their synthetic approaches, biological applications, and future research directions. Click chemistry strategies, particularly CuAAC and SPAAC, have transformed glycochemistry by enabling efficient and biocompatible conjugation of carbohydrates to various fragments, polymers, and surfaces. Triazole linkers provide chemically robust and versatile connections that preserve glycan topology while incorporating pharmacologically relevant heterocycles. Glyco-triazole hybrids have demonstrated diverse biological activities, including antimicrobial, antifungal, anticancer, antiviral, and enzyme inhibitory properties. These compounds show promise as potential drug candidates, with several examples progressing towards further development. Beyond small molecules, glyco-triazole conjugates have also found applications in materials science, such as sensors, adaptive biomaterials, and imaging agents, highlighting their multifunctional potential. While significant progress has been made, the review identifies several future directions and challenges that need to be addressed to fully realize the potential of glyco-triazole hybrids. These include the development of more complex structures, the use of greener and scalable synthesis methods, and the need to better connect medicinal and material science applications. Overall, the review showcases the versatility and growing importance of glyco-triazole conjugates in various fields, while also outlining the ongoing efforts and future prospects for this rapidly evolving area of research

Author contributions

Jyoti Dahiya was responsible for conceptualization, methodology, literature review, data collection, and manuscript drafting. **Anudeep Kumar Narula** contributed to the investigation, critical analysis, data validation, and manuscript review. **Gulshan Kumar** provided supervision, project administration, manuscript editing, and gave final approval for publication. All authors have read and approved the final manuscript.

Conflicts of interest

There are no conflicts to declare.

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