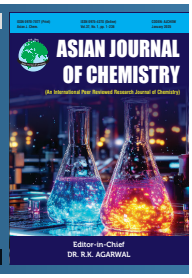
Asian Journal of Chemistry; Vol. 37, No. 4 (2025), 745-757

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2025.33012



REVIEW

Exploring the Impact of Click Chemistry on Carbohydrate Derivatives and their Biological Properties

DIPALI G. PISAL[1,2], SUSHENRAO R. PATIL[3], CHANDRASHEKHAR P. MANE[2] and DNYANDEO N. ZAMBARE[1,*]

[1]Department of Chemistry, Kisan Veer Mahavidyalaya, Wai-412803, India
[2]Department of Chemistry, L.B.S. College, Satara-415002, India
[3]Department of Chemistry, College of Pharmacy, Shriram Shikshan Sanstha, Paniv-413113, India

*Corresponding author: E-mail: dipalipisalwai@gmail.com

Received: 9 November 2024; *Accepted*: 15 February 2025; *Published online*: 29 March 2025; AJC-21933

The application of click chemistry in the synthesis of intricate carbohydrate derivatives has revolutionized the domains of chemical biology and synthetic chemistry. This review examines the function of click chemistry, namely the copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC), in effectively altering carbohydrate structures and producing practical glycoconjugates. Carbohydrates are essential in several biological functions, such as cellular recognition and immunological responses, however, their complicated structure makes production difficult. Click chemistry provides an optimal answer to these issues due of its simplicity, high yields and bioorthogonality. This methodology has been extensively used in the advancement of glycoproteins, glycodendrimers and glycopeptides, which play a crucial role in the fields of drug discovery, vaccine development and diagnostics. In addition, click chemistry has facilitated the development of biodegradable polymers and glycomacromolecules that have the potential to be used in materials science, namely for sustainable materials and smart technology. The flexibility and accuracy of CuAAC in producing carbohydrate-based structures provides new opportunities for investigation, stimulating advancements in both biomedicine and industrial applications. This evaluation also emphasizes the capacity of click chemistry to expedite the advancement of multifunctional therapeutic drugs that target intricate ailments like cancer.

Keywords: Azide-alkyne cycloaddition, Carbohydrate derivatives, Glycoconjugates, Glycodendrimers, Glycomacromolecules.

INTRODUCTION

The synthesis of intricate organic compounds has been a key obstacle in the field of synthetic chemistry, where accuracy, effectiveness and adaptability are of utmost importance. Click chemistry is a very influential methodology that has significantly transformed the field of molecular assembly. The approach, popularized by Barry Sharpless, has offered chemists a collection of reactions that are not only extremely efficient but also surprisingly straightforward, dependable and widely applicable [1].

Carbohydrates, being vital biomolecules, play a crucial role in a diverse range of biological processes. Sugar-based molecules play a vital role in important activities such as cellular recognition, immunological responses and the control of different metabolic pathways [2]. Glycoconjugates are often seen as intricate structures in which carbohydrate units are connected to proteins, lipids or other macromolecules. Comprehending and controlling these formations is crucial for progressing sectors such as biomedicine, where glycoconjugates contribute to drug discovery, vaccine design and illness diagnostics [3].

An extremely helpful method in click chemistry for the synthesis and modification of carbohydrates is the copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) [4]. Since its inception in the early 2000s by the Meldal & Sharpless research groups [5], CuAAC has gained recognition for its remarkable capacity to selectively react at specific sites, produce a large amount of desired product and operate under gentle conditions. This reaction has played a crucial role in the formation of 1,4-disubstituted 1,2,3-triazoles, which function as stable and bior-thogonal connectors in the synthesis of glycoconjugates [6]. The versatility of CuAAC in accommodating different functional groups and its ability to withstand a wide range of reaction conditions, including aquatic environments, make it highly suitable

for the intricate process of building carbohydrate-based structures [7]. Both click chemistry and enzymatic labeling, with their site-specificity and fast reaction rates, have been suggested as effective methods for functionalizing therapeutic compounds to address biological issues. The amalgamation of the two ideas has resulted in a robust and versatile instrument, reminiscent of a "Swiss Army knife". The click reactions that are often utilized in conjunction with lipid-modifying enzymes are shown Fig. 1.

The application of click chemistry in carbohydrate research has significantly expanded the toolkit available to chemists and biologists [9]. It allows for the rapid and selective synthesis of a wide range of glycoconjugates, including glycoproteins, glycolipids and glycopeptides. These compounds are essential in exploring the biological roles of carbohydrates and in developing new therapeutic agents [10]. The use of click chemistry in the discovery of new bioactive molecules provides a means for the fast exploration of chemical space, facilitating lead optimization by structure-activity relationship (SAR) through the generation of analogue libraries. The application of click chemistry has also been extended to materials science and chemical biology including, respectively, the construction of polymeric structures and biological probes for selective labeling of biomolecules either in cells or within living organisms [11,12]. The ease with which click chemistry can be integrated into carbohydrate synthesis has led to its widespread adoption, enabling researchers to overcome many of the challenges traditionally associated with carbohydrate chemistry [13].

This review seeks to provide a comprehensive overview of the role of click chemistry in the synthesis of carbohydrates and their conjugates. The foundational aspects of click chemistry, with a focus on CuAAC and explore its application in the efficient construction of various glycoconjugates will be discussed. The review will highlights recent advancements, methodological innovations and practical applications, emphasizing the significance of click chemistry in the continued exploration and exploitation of carbohydrates in biological and medicinal chemistry.

Click chemistry: Click chemistry, a term coined by K.B. Sharpless in 1999, encompasses a set of very efficient chemical reactions which are simple, adaptable and deliver significant amounts of desired products while generating few unwanted byproducts. These reactions are distinguished by their dependability and capacity to be carried out in harmless solvents under gentle conditions, making them appropriate for a broad range of scientific applications [14,15]. Out of all these, the Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) is the most well-known and commonly used [16]. The basis of this reaction is the 1,3-dipolar cycloaddition between organic azides and alkynes, which was first investigated by Rolf Huisgen in 1960s. Nevertheless, the first thermal cycloaddition lacked selectivity, resulting in a combination of 1,4- and 1,5-disub-stituted triazoles [17]. In 2001, Sharpless & Meldal [5] found that copper(I) catalysis could be used to guide the reaction toward producing just 1,4-regioisomer. This discovery greatly enhanced the speed and efficiency of the synthesis. This advancement was a notable leap, converting the formerly slow process into one that operates at a speed more than 100 times quicker, solidifying the CuAAC reaction as a fundamental element of click chemistry [18].

Click responses may be categorized into four distinct groups. Various types of chemical reactions, which includes the cycloaddition of unsaturated species, such as 1,3-dipolar cycloaddition reactions and Diels-Alder transformations. It also mentions nucleophilic substitution chemistry, which involves ring-opening reactions of strained heterocyclic electrophiles like epoxides, aziridines and aziridinium and episulfonium ions [19]. It also encompasses reactions involving carbonyl groups, which are not aldol, including those producing oxime ethers, hydrazones, thioureas, ureas, *etc*. Finally, it discusses the addition reactions to C-C multiple bonds, which have proven useful for mild polymer synthesis. These reactions include epoxidation, dihydroxylation, aziridination, sulfenyl halide addition and Michael additions of Nu-H reactants such as thiolene reactions (nucleophile- or radical-mediated) [19,20]. Reactions using click chemistry are readily executed, rapid, very specific, unaffected by oxygen and water and may result in significant structural variety with high yields [21]. Furthermore, the analysis of these reactions is straightforward and does not need extensive chromatographic purifications. Out of all these reactions, the cycloadditions, namely the Huisgen 1,3-dipolar cycloaddition catalyzed by Cu(I) that involve the formation of bonds between carbon and heteroatoms, are the most often used [22].

The Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) is a prominent example of click reactions, which have several kinds of reactions. The CuAAC reaction proceeds along a distinct route compared to the uncatalyzed thermal reaction. It exhibits exceptional regioselectivity, resulting in the exclusive formation of 1,4-disubstituted 1,2,3-triazoles [23]. Furthermore, the CuAAC reaction occurs at a much quicker pace, about 107 times faster than the thermal reaction. The increased efficiency is a result of the sequential mechanism of CuAAC, which is different from other cycloaddition processes that occur simultaneously [24]. The process begins with the coordination of Cu(I) to a terminal alkyne, resulting in the formation of a copper acetylide complex [25]. The organic azide reacts with this complex by nucleophilic attack, resulting in the formation of a six-membered metallacycle that contains copper. The catalytic efficiency of copper not only speeds up the reaction but also guarantees a high level of regioselectivity, resulting in the exclusive synthesis of the 1,4-disubstituted 1,2,3-triazole product. In addition, the reaction has a high tolerance for a broad range of solvents, including aqueous systems and is compatible with a multitude of functional groups [26]. The favourable reaction conditions, along with its straightforward operation, make CuAAC a compelling approach for altering intricate molecular structures. Although the copper-catalyzed method is widely used, a different approach called ruthenium-catalyzed azide-alkyne cycloaddition (RuAAC) was introduced in 2005 [27]. This alternate method allows for the selective production of 1,5-disubstituted triazoles. While RuAAC offers increased tolerance for certain functional groups, its use is restricted since the catalytic system is sensitive to the reaction media [28].

Carbohydrates, essential biomolecules involved in several biological processes, have seen extensive exploration using

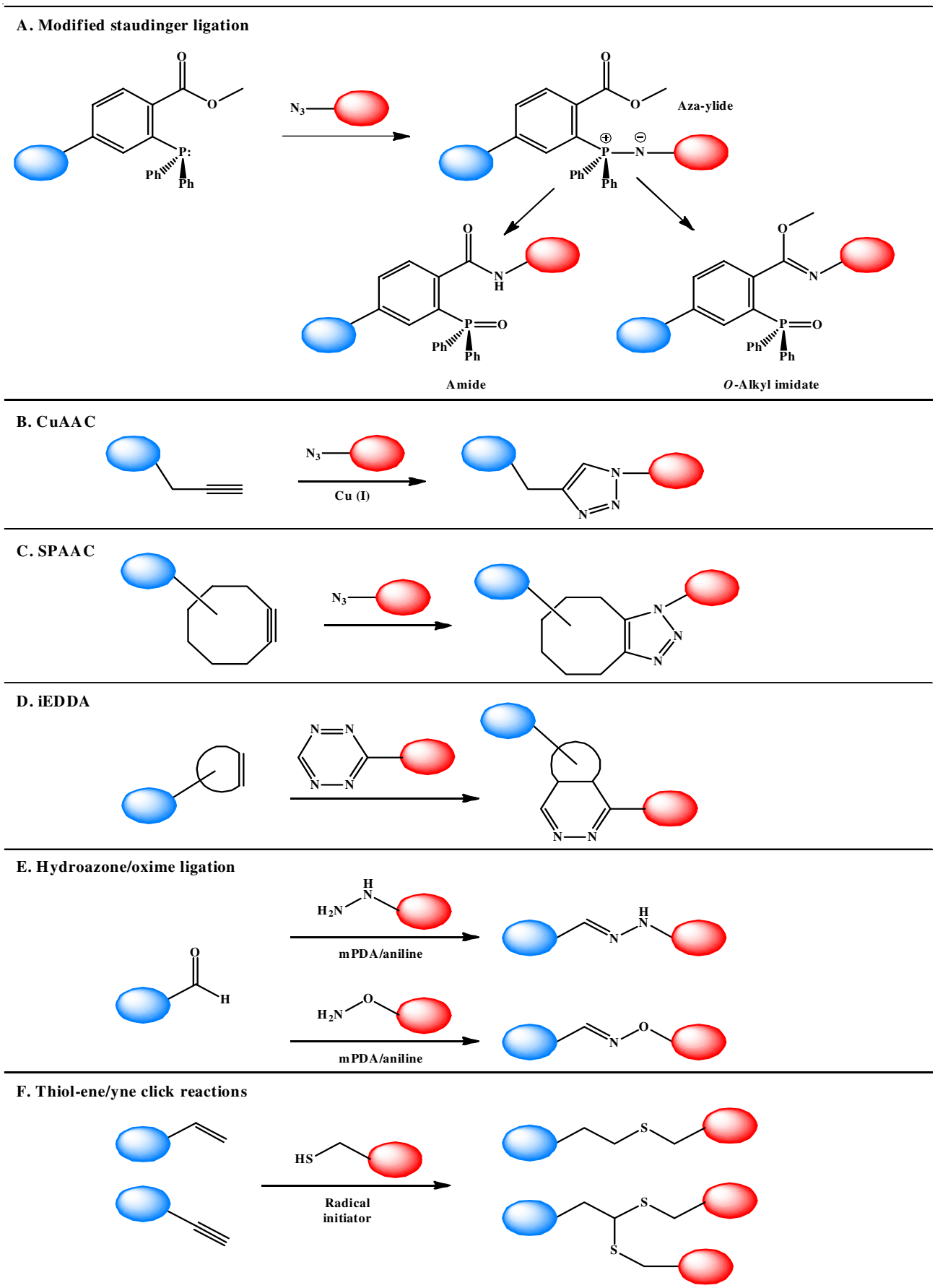


Fig. 1. Reaction scheme of bio-orthogonal click reactions for modifying proteins of interest [Ref. 8]

click chemistry [29]. Their structural complexity and diverse functional roles in cellular recognition, adhesion and immune responses make them important targets in drug development and bioconjugation studies. However, the synthesis of carbohydrate derivatives is often hindered by stereochemical complexity and the necessity for protection/deprotection strategies [30]. CuAAC has proven particularly valuable in this context, enabling the efficient coupling of azide- or alkyne-functionalized carbohydrate moieties to generate a wide range of glycoconjugates. This method has been applied to the synthesis of biologically relevant molecules such as glycopeptides, glycodendrimers and glycopolymers. These glycoconjugates are invaluable in various scientific fields, including drug discovery and diagnostics, where they are used to develop glyco-arrays for high-throughput screening or to explore carbohydrate-protein interactions [31].

Incorporating azide and alkyne functionalities into carbohydrate scaffolds allows for the straightforward synthesis of complex molecules, bypassing several difficulties traditionally associated with carbohydrate chemistry [32]. The ability of CuAAC to proceed under aqueous conditions is particularly advantageous, as several biological processes occur in such environments. Furthermore, the triazoles formed through click chemistry are highly stable and biocompatible, making them ideal for applications in medicinal chemistry and chemical biology [33]. Click chemistry has significantly contributed to the synthesis of neoglycopolymers and glycomacromolecules, which hold potential uses in vaccine development and treatments. The use of click chemistry in carbohydrate synthesis not only simplifies the process of glycan derivatization but also opens new avenues for the design of functional biomolecules with enhanced pharmacological properties. This powerful and versatile approach continues to expand its utility in the synthesis of carbohydrate-based structures, offering new possibilities for future research in glycobiology and related fields [34].

Carbohydrate derivatives synthesized *via* click chemistry: The CuAAC reaction is also widely used to prepare carbohydrate derivatives. Numerous examples can be found in recent literature [35], including the synthesis of N-glycosyl triazoles from acetylenes or derivatives containing the acetylenic function connected to sugars or amino acids. Fig. 2 shows carbohydrate based triazoles 1, 2, 3, 4, 5, 6 and 7 as examples. Click reactions have been used for the synthesis of oligosaccharides, glycopolycycles and macrocycles, glycopeptides, glycoclusters and carbohydrates immobilized on plastic microtitre plates [36], in addition to glycosides. In addition, the Huisgen cyclization reactions can be used to form multi-cyclic structures from monosaccharides or disaccharides that contain azide/alkyne functions through intermolecular coupling. This process is demonstrated in the synthesis of cyclic dimer **8** from building block **9** and the creation of novel cyclodextrinmimics **11a** and **11b** using compound **10** [37]. This reaction has also been used in the binding of antibodies, conjugation with DNA and modification with sugars to create biological probes [38]. Thus, it can be concluded that CuAAC reactions do not replace current synthetic techniques, but instead provide new opportunities for synthesizing innovative building blocks and polymeric polymers that may imitate or represent pharmacophores [39].

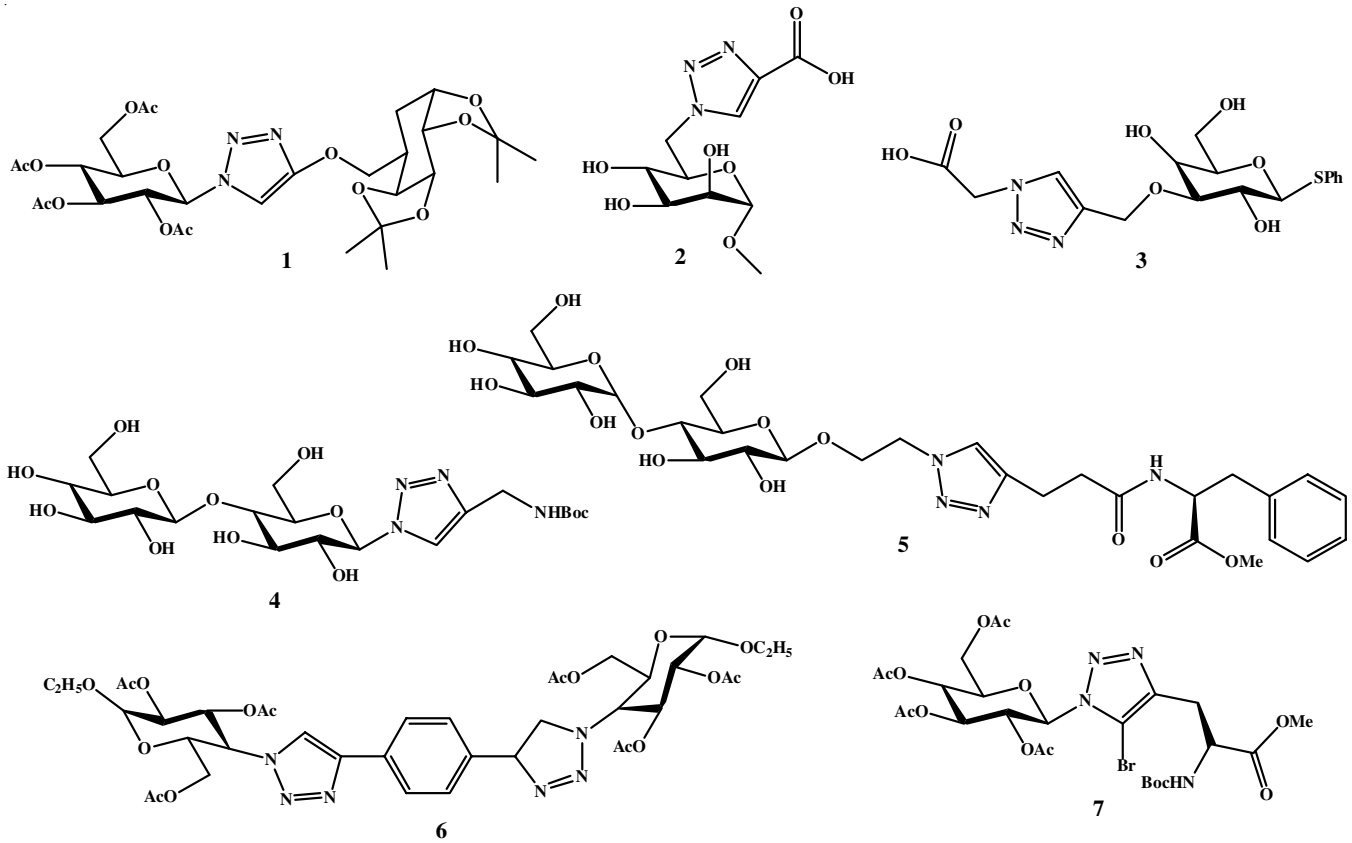


Fig. 2. Mimetic glycosides obtained by cycloaddition reaction between azide and alkyne derivatives

Carbohydrate derivatives in medicinal chemistry: The addition of an azide and/or an alkyne group to a carbohydrate structure allows for the exploration of a wider range of structural variations in the molecules *via* click reactions (Fig. 3). In recent times, the Cu(I) catalyzed click reaction has become a significant approach for the identification and improvement of lead compounds as well as for investigating its potential as a promising medication candidate against different treatment strains [40]. Carbohydrates play a crucial role in important metabolic processes, including cell-cell contact, cell motility and pathogen defense. This makes carbohydrates a very interesting option for drug development [41]. Nevertheless, the intricate nature linked to its production, particularly regarding the anomeric stereochemistry, subpar pharmacological qualities and moderate affinity for several receptors, hinders its progress as a potential medicine. However, the suitability of Cu(I)-catalyzed coupling between azides derived from carbohydrates and alkynes [42].

Click chemistry is also extensively used in the identification and enhancement of primary compounds as well as in the development of novel drugs targeting different therapeutic objectives. Click chemical processes have been used to develop novel neuraminidase inhibitors to develop more potent drugs for treating avian influenza virus (AIV) infection [43]. Neuraminidase facilitates the separation of glycoproteins and glycolipids by breaking the glycosidic link, resulting in the liberation of terminal Neu5Ac (sialic acid) residues. This process enables the release of new viral particles and enhances the virus's ability to move throughout the respiratory tract. Shen *et al.* [44] conducted the synthesis of a range of zanamivir analogues including various substituted triazoles. Beginning with a crucial intermediate that includes an azide group, a collection of neuraminidase inhibitors was successfully generated. Compound **13** exhibited the most potent antiviral activity, with an IC_{50} value of 6.4 μm, which is close to zanamivir's IC_{50} value of 2.8 μm.

Synthetic pathways for carbohydrate derivatives: The synthesis of carbohydrates has been significantly enhanced using click chemistry, thanks to its high efficiency, modularity and compatibility with the biological systems [45]. The predominant reaction used in this domain is the Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC), which enables the bonding of carbohydrate derivatives to diverse functional groups. This

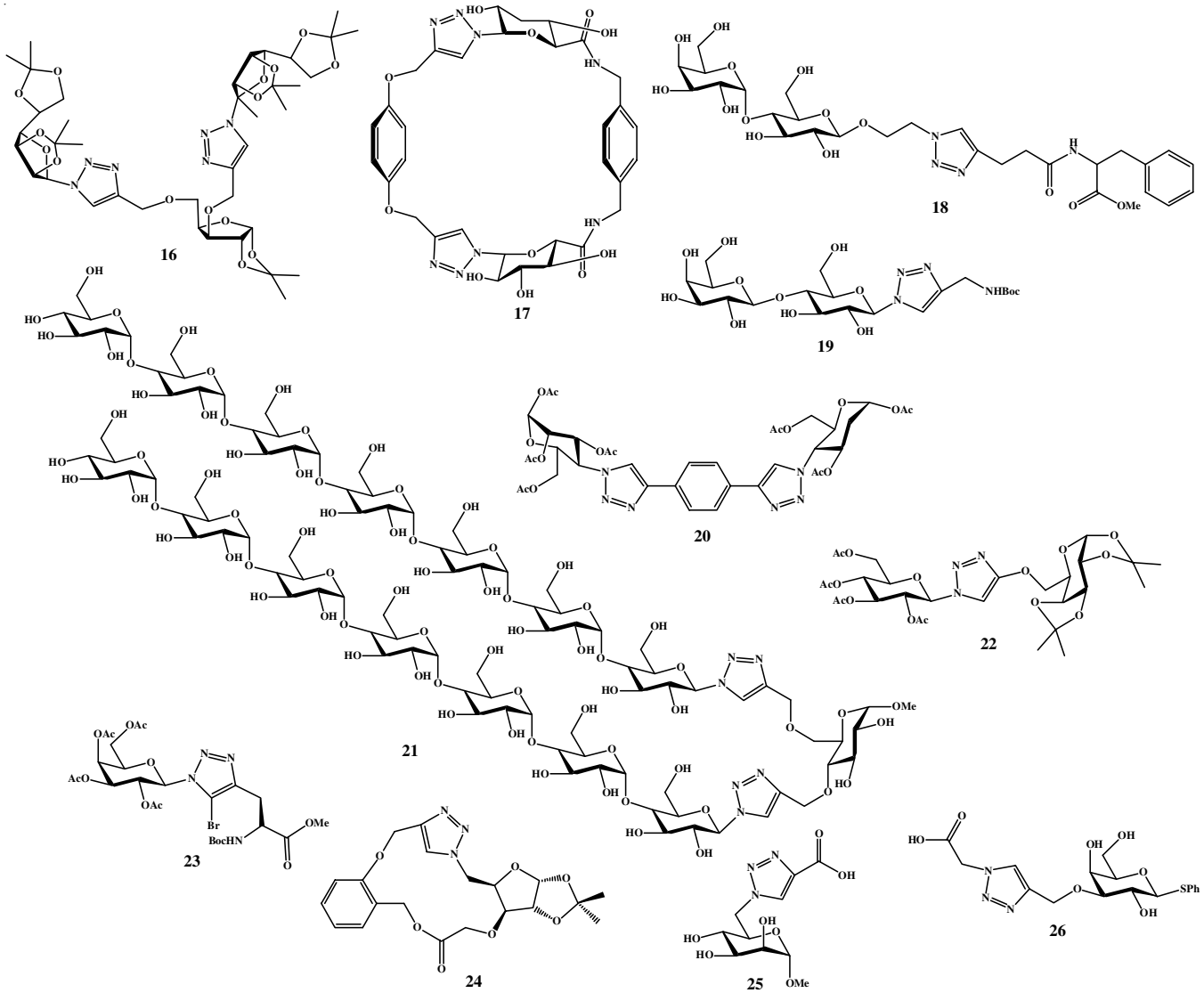


Fig. 3. Carbohydrate-based triazole scaffolds obtained from CuAAC reaction

reaction is highly beneficial for producing intricate glycoconjugates, glycopolymers and other structures based on carbohydrates. It provides efficient solutions to common challenges in carbohydrate chemistry, such as controlling stereochemistry and carrying out protection or deprotection steps [46].

The synthesis route starts by incorporating azide or alkyne functionalities into carbohydrate molecules. Azide groups are often introduced by nucleophilic substitution, in which halides or tosylated carbohydrate derivatives react with sodium azide [47]. Alternatively, propargyl derivatives may be used to add alkyne groups by esterification or etherification processes. After the synthesis of azide- or alkyne-functionalized carbohydrates, the CuAAC reaction may be used to connect these components. The reaction occurs in moderate circumstances, using either water or a mixture of solvents. Copper(I) acts as catalyst, which may be obtained in the reaction mixture by reducing copper(II) sulfate with sodium ascorbate [48]. The reaction has a high degree of regioselectivity, producing only 1,4-disubstituted 1,2,3-triazoles. It occurs with exceptional efficiency, even under normal environmental conditions, making it well-suited for changing intricate molecular structures [49].

Click chemistry, specifically CuAAC, is extensively used in the production of glycoconjugates, which have crucial functions in the biological processes [50]. This encompasses the fabrication of glycopeptides, glycodendrimers and glycopolymers. The CuAAC method has shown significant use in the synthesis of glycopeptides, facilitating the attachment of sugars to peptides or proteins. This process is essential for the development of drugs and the design of vaccines [51]. Glycodendrimers and glycopolymers, however, derive advantages from the multivalency provided by these structures, hence augmenting their biological interactions. The utilization of CuAAC in connecting carbohydrate units to functional molecules such as biotin or fluorophores has additionally propelled research in glycoarrays, which are used for high-throughput screening of carbohydrate-protein interactions [52].

Although CuAAC continues to be the most widely used approach, other cycloaddition reactions such as strain-promoted azide-alkyne cycloaddition (SPAAC) and ruthenium-catalyzed azide-alkyne cycloaddition (RuAAC) provide alternate routes [53]. SPAAC, which obviates the need for copper, is especially advantageous *in vivo*, where copper has the potential to be cytotoxic. RuAAC, while less often used, enables the synthesis of 1,5-disubstituted triazoles, hence enhancing the range of structural variations in glycoconjugate synthesis [54]. Although click chemistry offers several benefits, the stereochemical complexity of carbohydrate molecules poses significant obstacles. Acetyl or benzyl protecting groups are often used to safeguard hydroxyl groups during functionalization, hence guaranteeing certain reactions. Once the click chemical processes are finished, the protective groups may be readily eliminated, resulting in the desired carbohydrate structures [55].

Recent studies on carbohydrate derivatives: Jiang *et al.* [56] used click chemistry to synthesize derivatives of zanamivir, a potent drug used to treat avian influenza (H5N1) due to its ability to block the enzyme neuraminidase. This enzyme promotes the removal of sialic acid from the glycoproteins and glycolipids of the host cells [57]. This process is crucial for the replication of the influenza virus. Neuraminidase inhibitors directly treat influenza by inhibiting the manufacture of neuraminidase enzyme [58]. A series of 16 zanamivir analogues, each containing a C-4 triazole substitution, was synthesized using a shared starting material and then subjected to screening. The molecule exhibited significant anti-AIV action, with an IC_{50} value of 6.4 μm, which is like the IC_{50} value of 2.8 μm seen for zanamivir [59]. Carvalho *et al.* [60] investigated the use of Cu(I)-catalyzed azide-alkyne 1,3-dipolar cycloaddition to prepare a library of 1,4-disubstituted 1,2,3-triazole galactose derivatives. They found that these derivatives are effective inhibitors of *Trypanosoma cruzi trans*-sialidase (TcTS) enzyme, which is crucial in the process of identifying and infiltrating host cells, as well as facilitating the parasite's evasion of the human immune system. Wong *et al.* [61] also used Cu(I) catalyzed 1,3-dipolar cycloaddition on a microtiter plate to develop a collection of 85 GDP-triazoles. They maintained GDP as the shared framework while modifying the hydrophobic group and the linker chain tied to it. Among all the substances that were tested, it has been identified as the most effective inhibitor for the R-1,3-fucosyltransferase VI.

Field *et al.* [62] catalyzed CuAAC processes to construct a collection of 21 α-D- and β-D-glucopyranosyl triazoles. The reaction between β-D-glucopyranosyl azide and the corresponding isomer with specific alkynes, using triazoles as reaction conditions produced *via* CuAAC of glycosyl-azides and phenylacetylene, was evaluated against sweet almond glucosidase (SAG). Subsequently, the compounds underwent deacetylation and the resulting products were evaluated for their activity against β-glycosidases, namely *Escherichia coli* galactosidase (ECG) and bovine liver galactosidase (BLG). The findings were compared with the established glycosidase inhibitors, deoxygalactonojirimycin (DNJGal) and deoxynojirimycin (DNJGluco), although only a little inhibition was seen for some compounds against ECG and BLG glycosidases.

Biological properties of click chemistry carbohydrate derivatives: Carbohydrate derivatives made utilizing click chemistry are a powerful drug development framework due to their wide range of structures and ability to precisely target biological systems. The carbohydrate glycosylation patterns, often present as glycoproteins and glycolipids on the surfaces of cells, have crucial functions in processes such as cellular identification, signal transduction and immunological responses. Scientists may use the modular nature of click chemistry to produce carbohydrate derivatives that have strong antiviral, antibacterial and anticancer properties [62].

Due to their capacity to suppress glycosyltransferases and viral polymerase, they exhibit strong efficacy as therapeutic agents against drug-resistant bacterial strains and viral infections [63]. Carbohydrate derivatives in the field of oncology have shown the ability to disrupt the metabolic processes of cancer cells, namely by hindering glycolysis. As a result, these derivatives prompt the programmed cell death of cancer cells, known as apoptosis. These qualities provide a structure for developing targeted anticancer medications that have little impact on healthy cells [64].

Furthermore, the use of click chemistry to modify carbohydrate scaffolds results in improved immunomodulatory effects. The significance of sialic acids in immune regulation is apparent and their modification using click chemistry has facilitated the development of medications that specifically target autoimmune illnesses, including multiple sclerosis and inflammatory ailments. Sialic acids are also involved in the process of viral attachment to host cells and their alteration provides opportunities for the development of antiviral treatments, specifically targeting viruses such as influenza and adenoviruses [64]. Table-1 provides an overview of various carbohydrate derivatives synthesized through click chemistry, detailing their therapeutic applications, mechanisms of action and potential uses in combating a range of medical conditions.

Carbohydrate-based potential glycosidase inhibitors: Glycoside hydrolase, also referred to as glycosidase, is a group of enzymes that are essential for catalyzing the hydrolysis of the glycosidic bond. The use of glycosidase inhibitors for the treatment of viral infections, cancer, diabetes and genetic diseases is promoted due to their ability to alter the production, maturation and transport of glycoproteins by inhibiting glycosidase enzymes [79]. Iminosugars have shown their promise as medicinal agents and have also emerged as a promising moiety for inhibiting glycosidases. D'Alonzo *et al.* [80] conducted a study on the biochemistry of L-iminosugar and discovered that it exhibits interactions and inhibitory effects on enzymes.

Carbohydrate-mimetics as potential sialyltransferase inhibitors: The sialylation of glycoconjugates at their non-reducing end is a crucial factor in several biological processes, including cellular recognition, tumor metastasis and immunological response. The regulation of this process is controlled by sialyl transferase (ST) enzymes; hence, the suppression of these enzymes has important biochemical and physiological implications. Inhibition of ST has been identified as a possible therapeutic approach for treating conditions such as different types of cancer, viral infections, inflammation, immunological response and neurological problems [70]. Sialyl transferases facilitate the transfer of a sialyl residue from a certain sugar nucleotide donor to a glycoconjugate acceptor with a specified terminal structure of the sugar residue. Therefore, it is possible to selectively synthesize sugar-acceptor analogs that might potentially act as inhibitors of sialyl transferase [81-84].

Carbohydrate-based antibacterial and antiviral agents: Multiple research projects have investigated the antibacterial properties of click chemistry carbohydrate derivatives, showing their efficacy against a wide range of bacterial species [85]. These compounds have shown the ability to specifically target vital bacterial enzymes, namely glycosyltransferases, which play a critical role in the creation of bacterial cell walls. In research conducted by Cao *et al.* [86], it was shown that carbohydrate derivatives coupled with triazole had strong inhibitory effects against *Escherichia coli* and *Staphylococcus aureus*. This finding suggests a potential approach to combat antibiotic resistance in both Gram-positive and Gram-negative bacteria.

Click chemistry carbohydrate derivatives have been studied for their antiviral properties, namely in their ability to hinder viral reproduction, in addition to their antibacterial effects. An influential work conducted by Ding *et al.* [67] showcased the efficacy of carbohydrate-based triazole derivatives in inhibiting the entrance of influenza virus into host

TABLE-1
THERAPEUTIC APPLICATIONS OF CARBOHYDRATE DERIVATIVES SYNTHESIZED VIA CLICK CHEMISTRY

Therapeutic area	Carbohydrate derivative	Mechanism of action	Potential application	Ref.
Antibacterial agents	Triazole-carbohydrate derivatives	Inhibits glycosyltransferases involved in bacterial cell wall formation	Effective against *Escherichia coli*, *Staphylococcus aureus*	[66]
Antiviral agents	Carbohydrate-based triazole derivatives	Binds hemagglutinin glycoproteins, impeding viral fusion	Influenza virus prevention	[67]
	Azide-alkyne click compounds	Inhibits HIV-1 reverse transcriptase	HIV treatment	[68]
Glycosidase inhibitors	L-Iminosugar	Inhibits glycosidase enzymes, affecting glycoprotein processing	Treatment of viral infections, cancer, diabetes	[69]
Sialyltransferase inhibitors	N-Acetyl-β-lacosamide derivatives	Inhibits α-(2-6)-sialyltransferase, blocking sialylation	Cancer treatment, antiviral, and immune regulation	[70]
Anticancer agents	Streptozotocin	Alkylating agent that destroys pancreatic β-cells	Treats islets of langerhans cancer, potential antidiabetic application	[71]
	Prumycin	Antineoplastic properties	Cancer treatment	[72]
Immunomodulatory agents	Glycopeptides modified by click chemistry	Enhances T-cell and macrophage activation, improving immune response	Autoimmune diseases, cancer immunotherapy	[73]
Antioxidant agents	Click chemistry-derived carbohydrate scaffolds	Neutralizes reactive oxygen species (ROS), reduces oxidative stress	Neurological, cardiovascular diseases, Alzheimer's, atherosclerosis	[74]
Miscellaneous therapeutics	Auranofin	Sugar-based gold complex with anti-HIV capabilities	Reduces HIV viral reservoir, anti-rheumatic	[75]
	Topiramate	Sulfamate-substituted monosaccharide modulates neurotransmitter release	Epilepsy treatment, migraine prevention, Lennox-gastaut syndrome management	[76]
	Vidarabine	Arabinosyl nucleoside that inhibits viral DNA polymerase	Treats varicella-zoster, herpes simplex	[77]
	Lactulose	Osmotic laxative, composed of fructose and galactose	Treats constipation, hepatic encephalopathy	[78]

cells. This was achieved by binding these derivatives to hemagglutinin glycoproteins, thereby impeding viral fusion. Furthermore, Mudgal *et al.* [68] synthesized a group of azide-alkyne click compounds that could hinder the activity of HIV-1 reverse transcriptase. This finding highlights their potential in the development of antiviral medications.

Carbohydrate-based molecules with miscellaneous activities: Various carbohydrate derivatives and glycoconjugates exhibit remarkable bioactivity and possess substantial therapeutic applications (Fig. 4). Auranofin is an orally taken anti-rheumatic medication that consists of a sugar-based gold complex. Cunha *et al*. [87] reported the anti-HIV capabilities of carbohydrate derivatives and glycoconjugates since it has been shown to reduce the HIV viral reservoir. Topiramate is an FDA-approved medication that belongs to the sulfamate-substituted monosaccharide class and is used to treat epilepsy and is effective in preventing migraines and managing Linnox-Gastaut Syndrome [88]. Arabinosyl nucleoside vidarabine was first developed to treat cancer, however, additional research revealed its antiviral properties. This medicine treats varicella zoster and herpes simplex infections [89]. Streptozotocin is an FDA-approved medication often used to treat Islets of Langerhans cancer and a naturally occurring substance that may damage the β-cells in the pancreas responsible for producing insulin [90]. This compound is an alkylating antineoplastic drug that is used to treat cancer and can be harmful to these cells. Lactu-

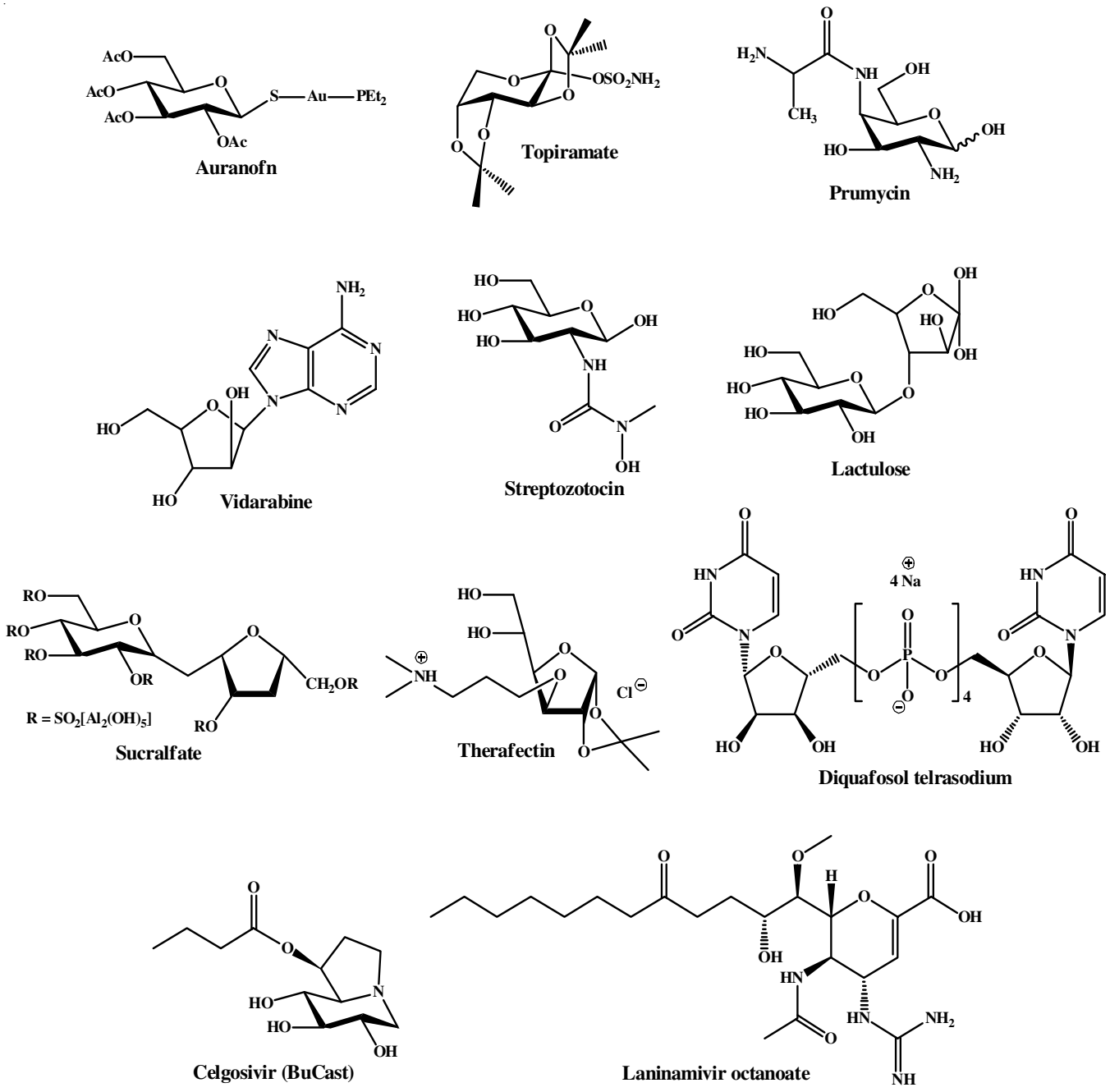


Fig. 4. Structure of some carbohydrate-based drugs of miscellaneous profiles

lose is a carbohydrate-based drug, which is used for the treatment of persistent constipation and hepatic encephalopathy. The compound consisting of fructose and galactose is classified as an osmotic laxative according to the standards set by the World Health Organization (WHO) [91].

Carbohydrate-based immunomodulatory and antioxidant agents: Click chemistry carbohydrate derivatives have also garnered considerable scientific attention for their immunomodulatory characteristics, which enable them to regulate immunological responses. These compounds have shown the ability to engage with receptors on immune cells, hence impacting the production of cytokines and the activation of immune cells. Barchi *et al.* [92] conducted research showing that glycopeptides changed *via* click chemistry and increased the activation of T-cells and macrophages, resulting in a stronger immunological response. This creates opportunities for their use in the treatment of autoimmune illnesses, where the regulation of immune activation is crucial [92]. Moreover, these derivatives have been investigated in the field of cancer immunotherapy, where they facilitate the immune system in efficiently identifying and attacking tumor cells by improving the detection of cancer antigens.

Another important field of study is investigating the antioxidant characteristics of carbohydrate derivatives synthesized *via* click chemistry. Reactive oxygen species (ROS) and oxidative stress have a role in several illnesses, such as neurological and cardiovascular disorders. Research conducted by Xiao *et al.* [93] showed that carbohydrate scaffolds produced from clicks can eliminate free radicals and mitigate cellular oxidative damage. These compounds exhibited significant antioxidant properties by counteracting reactive oxygen species (ROS), hence reducing the advancement of illnesses associated with oxidative stress [93]. The advancement of these antioxidants derived from carbohydrates showcases its prospective use in age-related illnesses and situations characterized by excessive oxidative harm such as Alzheimer's disease and atherosclerosis.

The immunomodulatory and antioxidant capabilities of click chemistry carbohydrate derivatives greatly expand their potential for therapy, making them interesting candidates for treating complex illnesses characterized by immunological dysregulation and oxidative damage. The immunomodulatory properties of these compounds, namely their capacity to regulate the activity of immune cells and the generation of cytokines, have prospective uses in the treatment of autoimmune illnesses, cancer immunotherapy and chronic inflammatory conditions. For instance, these compounds enhance the ability of immune cells to identify cancer antigens, hence enhancing the immune system's capacity to attack tumors [73].

Carbohydrate derivatives produced through click chemistry possess both immunomodulatory and antioxidant effects and display multiple biological activities. This makes them potentially useful for treating various diseases, such as autoimmune conditions, cancer, neurodegeneration and cardiovascular diseases. The progress made in studying carbohydrate derivatives creates opportunities for the creation of focused and multifaceted treatments that may effectively tackle intricate disease systems. This positions them as a crucial asset in the future of drug exploration and advancement [94].

Comparison with traditional methods

Comparative efficiency, precision and yield: The 1,3-dipolar cycloaddition of azides and alkynes, often known as click chemistry, is well recognized for its exceptional efficiency and straightforward implementation. Conventional techniques, such as glycosylation utilizing glycosyl halides or acetates, often need more rigorous reaction conditions and extended reaction periods, resulting in decreased yields and difficulties in achieving regioselectivity [95]. Table-2 compares the traditional glycosylation methods with click chemistry, highlighting key differences in terms of efficiency, selectivity and yield. On the other hand, reactions based on click chemistry are very efficient, often reaching completion within a few minutes and yielding a large amount of product with exceptional selectivity for certain regions. This method is very beneficial for creating intricate carbohydrates and glycomimetics, where the ability to choose specific stereoisomers is of utmost importance [96].

In addition, click chemistry exhibits advantages over standard carbohydrate synthesis techniques in terms of selectivity.

TABLE-2
COMPARISON OF TRADITIONAL AND CLICK CHEMISTRY METHODS FOR CARBOHYDRATE DERIVATIVES SYNTHESIS

Aspects	Traditional methods	Click chemistry (modern methods)
Reaction efficiency	Often requires more rigorous conditions and extended reaction times, leading to decreased yields.	Highly efficient, often reaching completion within minutes with exceptional selectivity
Regioselectivity	Difficult to achieve precise regioselectivity due to variable reactivity and protection groups.	Provides exceptional regioselectivity, preferentially producing 1,4-disubstituted triazoles.
Stereoselectivity	Challenges in achieving stereoselectivity due to effects of protecting groups and donor reactivity.	Highly selective, producing specific stereoisomers with ease.
Reaction conditions	Often requires harsh conditions and external activating agents.	Typically occurs under milder conditions without the need for external activators.
Yield	It can be poor due to steric hindrance and stringent activation conditions.	Achieves high yields, often approaching quantitative values, under mild conditions
Rate of reaction	Generally slower, with reactions sometimes requiring several hours.	Rapid reactions, often completed within minutes.
Selectivity control	Requires multiple stages to achieve comparable selectivity, often leading to lower overall efficiency.	Provides inherent selectivity, reducing the need for additional stages.
Example research	Sonication in traditional synthesis improves speed but not selectivity	High yields of triazole-linked derivatives, surpassing traditional methods

Conventional glycosylation reactions often face challenges in achieving stereoselectivity due to the impact of protecting groups and the varying reactivity of different glycosyl donors. In contrast, click chemistry offers highly selective reactions that preferentially produce 1,4-disubstituted triazoles over other potential regioisomers [37]. Attaining this degree of control is challenging using conventional approaches since they often need many stages to obtain comparable selectivity. For instance, Obadele *et al.* [97] observed that using sonication in conventional carbohydrate synthesis resulted in significant improvements in reaction speeds, although it failed to achieve the intrinsic selectivity provided by click chemical reactions.

Click chemistry-based carbohydrate synthesis regularly achieves higher yields compared to previous approaches. Conventional glycosylation processes, particularly those that use "disarmed" glycosyl donors such as phenyl thioglycosides, sometimes encounter poor yields because of steric hindrance or the need for strict activation conditions. Nevertheless, click chemistry processes, which occur under less severe conditions and do not need external activating agents, attain superior yields. Carbohydrate-based click reactions have shown high yields, approaching quantitative values, as shown in research conducted by Misra *et al.* [98]. In these investigations, triazole-linked carbohydrate derivatives were synthesized with yields that much surpassed those produced by traditional glycosylation techniques.

Possible drawbacks of click chemistry: Although click chemistry provides significant benefits in terms of effectiveness, specificity and productivity, it is not exempt from difficulties and restrictions. A major obstacle is the need for precise reaction conditions, especially when using copper-catalyzed azide-alkyne cycloaddition (CuAAC), which is the most often used click reaction [99]. Copper ions, although advantageous in facilitating the reaction, may be harmful to biological systems, which restricts their use in bioconjugation and drug development applications where preserving biocompatibility is essential. Despite attempts to create copper-free click chemistry alternatives, such as strain-promoted azide-alkyne cycloaddition (SPAAC), these methods frequently have slower reaction rates and poorer yields, which may reduce their overall effectiveness [100].

Click chemistry has a constraint when it comes to the range of substrates it can work with and its ability to tolerate different functional groups. Although click chemistry exhibits great selectivity towards azide and alkyne groups, incorporating these functional groups onto complicated compounds like polysaccharides might provide synthetic challenges [101]. The incorporation of azides or alkynes into starting materials may need supplementary procedures, complicating the synthetic process and perhaps diminishing the total yield. This issue is especially troublesome when it comes to creating big, intricate compounds. In such cases, the several stages involved in adding functional groups might lead to unwanted side reactions or decrease the purity of the product [102].

In addition, click chemistry reactions may encounter challenges in achieving regioselectivity, particularly when used with substrates that have many reactive sites. Although the production of 1,4-disubstituted triazoles is generally preferred, some substrates may still produce unwanted byproducts, especially when numerous alkyne or azide groups are present [103]. When faced with such situations, attaining absolute selectivity might be challenging, therefore requiring the implementation of further purification procedures. Furthermore, click reactions may not be universally suitable for all types of compounds and alternate approaches may be necessary when dealing with extremely hindered substrates or when precise control over stereochemistry is essential. The significance of choosing suitable reaction conditions and substrates to get the best results in click chemistry is emphasized by these limitations [101].

Recent advancements and future directions: Click chemistry has gained popularity in medicinal chemistry for the synthesis of glycohybrid compounds. These molecules are formed by combining carbohydrates with various bioactive scaffolds, resulting in the creation of very effective therapeutic medicines. Research has shown that these glycohybrid molecules have improved biological functions such as being effective against cancer, germs and viruses [104]. An important progress involves the utilization of Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) to produce carbohydrate derivatives that exhibit specific inhibition of enzymes like glycosyltransferases and neuraminidase, rendering them valuable for the development of drugs targeting diseases such as influenza and cancer [15]. Furthermore, click chemistry has expedited the efficient production of a wide range of glycoconjugates with different structures. This has greatly facilitated the investigation of interactions between carbohydrates and proteins, which play a vital role in important biological processes including cell-cell communication and immunological recognition [105].

Click chemistry has significantly transformed the process of modifying carbohydrate-based polymers in the field of materials research. This development has expanded the potential for creating biocompatible materials that can be used in tissue engineering, medication delivery and nanotechnology. Click chemistry enables precise and selective changes of carbohydrate backbones, facilitating the creation of customized polymers that may imitate natural glycopolymers or add new functions for targeted medicinal uses [106].

Speculation on future research directions and potential applications: Applying click chemistry to carbohydrates offers many prospects for future study and development in several sectors. Medical research in the future will likely prioritize the development of multi-functional glycohybrid compounds capable of targeting numerous disease pathways concurrently [107]. This method has great potential for treating intricate illnesses like cancer since it allows for the targeting of various molecular pathways, leading to enhanced effectiveness of therapy and decreased development of drug resistance. In addition, click chemistry may be used to develop personalized drugs, in which carbohydrate-based pharmaceuticals are customized to match individual glycan profiles. This approach provides more efficient therapies with fewer adverse effects [108].

Click chemistry in agriculture has also immense potential to develop insecticides and fertilizers made from carbohydrates

that are more effective and eco-friendly [109]. Researchers may use click chemistry to create carbohydrate-derived compounds that selectively target insect enzymes or interfere with plant pathogen glycosylation processes. This approach minimizes the reliance on toxic chemical substances. Moreover, the use of click chemistry to produce carbohydrate-based materials has the potential to optimize the transportation of essential nutrients to crops, resulting in enhanced growth and production, while simultaneously reducing the negative effects on the environment [110].

The future of click chemistry, from an industrial standpoint, is focused on the development of sustainable materials derived from carbohydrates. Click reactions may be used to produce biodegradable polymers and nanomaterials with high accuracy and effectiveness. These materials can be used for many applications such as packaging, coatings and more [111]. These materials have the potential to substitute petrochemical-based plastics, therefore promoting more sustainable industrial processes and decreasing the environmental impact of the manufacturing sector. The adaptability of click chemistry products formed from carbohydrates also shows potential in the creation of intelligent materials that can react to environmental factors such as temperature, pH or light. This makes them well-suited for advanced applications like sensors and wearable technology [112].

Conclusion

The chemistry of carbohydrate chemistry has been greatly influenced by click chemistry, specifically the copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC). This method has provided a revolutionary way to synthesize and modify carbohydrate derivatives. The capacity of CuAAC reaction to enable the efficient, specific and dependable synthesis of glycoconjugates, including glycoproteins, glycolipids and glycopeptides, has established it as an essential tool in both fundamental research and practical applications. The reaction's ability to work well in many conditions, including in water and its strong preference for certain positions in a molecule, have increased its usefulness in producing stable, biocompatible molecules that are essential for biological and medical purposes. By incorporating click chemistry into carbohydrate research, the synthesis of complicated glycoconjugates has been made more efficient and streamlined. Moreover, it has facilitated the fast exploration of chemical space by generating various libraries of glycoanalogues. This has sped up the discovery and refining of drugs, creating fresh possibilities for the development of innovative medicinal substances. In addition to its use in drug development, click chemistry has been used in materials science to facilitate the production of biodegradable polymers and smart materials. These materials play a crucial role in promoting sustainable industrial practices and environmental conservation. In future, click chemistry is poised to have a significant impact in several domains, including customized medicine and agriculture. Future research might prioritize the development of multifunctional glycohybrid molecules for precise disease treatments and carbohydrate-based solutions for agricultural issues. This may result in more efficient medicines and ecologically sustainable practices. The ongoing advancements in the click chemistry present opportunities to drive innovation across various scientific domains, reinforcing its significance as a core method in synthetic processes and bioconjugation.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

REFERENCES

1. H.C. Kolb, M.G. Finn and K.B. Sharpless, *Angew. Chem. Int. Ed.*, **40**, 2004 (2001); https://doi.org/10.1002/1521-3773(20010601)40:11<2004::AID-ANIE2004>3.0.CO;2-5
2. A. Varki, *Glycobiology*, **3**, 97 (1993); https://doi.org/10.1093/glycob/3.2.97
3. C.R. Bertozzi and L.L. Kiessling, *Science*, **291**, 2357 (2001); https://doi.org/10.1126/science.1059820
4. S.V. Giofrè, M. Tiecco, A. Ferlazzo, R. Romeo, G. Ciancaleoni, R. Germani and D. Iannazzo, *Eur. J. Org. Chem.*, **2021**, 4777 (2021); https://doi.org/10.1002/ejoc.202100698
5. V.V. Rostovtsev, L.G. Green, V.V. Fokin and K.B. Sharpless, *Angew. Chem. Int. Ed.*, **41**, 2596 (2002); https://doi.org/10.1002/1521-3773(20020715)41:14<2596::AID-ANIE2596>3.0.CO;2-4
6. J.E. Hein and V.V. Fokin, *Chem. Soc. Rev.*, **39**, 1302 (2010); https://doi.org/10.1039/b904091a
7. F. Amblard, J.H. Cho and R.F. Schinazi, *Chem. Rev.*, **109**, 4207 (2009); https://doi.org/10.1021/cr9001462
8. R.E. Bird, S.A. Lemmel, X. Yu and Q.A. Zhou, *Bioconjug. Chem.*, **32**, 2457 (2021); https://doi.org/10.1021/acs.bioconjchem.1c00461
9. R. Zhao, J. Zhu, X. Jiang and R. Bai, *Eur. J. Med. Chem.*, **264**, 116037 (2024); https://doi.org/10.1016/j.ejmech.2023.116037
10. S.S. Shivatare, V.S. Shivatare and C.-H. Wong, *Chem. Rev.*, **122**, 15603 (2022); https://doi.org/10.1021/acs.chemrev.1c01032
11. P.N. Jadhav, Y.P. Patil and S.K. Pasale, *Afr. J. Biomed. Res.*, **27(1S)**, 328 (2024).
12. K. Nwe and M.W. Brechbiel, *Cancer Biother. Radiopharm.*, **24**, 289 (2009); https://doi.org/10.1089/cbr.2008.0626
13. N.Z. Fantoni, A.H. El-Sagheer and T. Brown, *Chem. Rev.*, **121**, 7122 (2021); https://doi.org/10.1021/acs.chemrev.0c00928
14. Z.F. Saeed, *Samarra J. Pure Appl. Sci.*, **5**, 1 (2023); https://doi.org/10.54153/sjpas.2023.v5i4.451
15. V.K. Tiwari, B.B. Mishra, K.B. Mishra, N. Mishra, A.S. Singh and X. Chen, *Chem. Rev.*, **116**, 3086 (2016); https://doi.org/10.1021/acs.chemrev.5b00408
16. M. Bonnard, S. Pinet, L. Chabaud and M. Pucheault, *Eur. J. Org. Chem.*, **27**, e202400580 (2024); https://doi.org/10.1002/ejoc.202400580
17. R. Huisgen, *Angew. Chem.*, **75**, 604 (1963); https://doi.org/10.1002/ange.19630751304
18. S.I. Presolski, V.P. Hong and M. Finn, *Curr. Protoc. Chem. Biol.*, **3**, 153 (2011); https://doi.org/10.1002/9780470559277.ch110148
19. N.K. Devaraj and M.G. Finn, *Chem. Rev.*, **121**, 6697 (2021); https://doi.org/10.1021/acs.chemrev.1c00469
20. C.E. Hoyle and C.N. Bowman, *Angew. Chem. Int. Ed.*, **49**, 1540 (2010); https://doi.org/10.1002/anie.200903924
21. W.H. Binder and R. Sachsenhofer, *Macromol. Rapid Commun.*, **28**, 15 (2007); https://doi.org/10.1002/marc.200600625
22. V.D. Bock, H. Hiemstra and J.H. van Maarseveen, *Eur. J. Org. Chem.*, **2006**, 51 (2006); https://doi.org/10.1002/ejoc.200500483

23. N.V. Sokolova and V.G. Nenajdenko, *RSC Adv.*, **3**, 16212 (2013); https://doi.org/10.1039/c3ra42482k
24. S.I. Presolski, V. Hong, S.-H. Cho and M.G. Finn, *J. Am. Chem. Soc.*, **132**, 14570 (2010); https://doi.org/10.1021/ja105743g
25. L. Zhu, C.J. Brassard, X. Zhang, P.M. Guha and R.J. Clark, *Chem. Rec.*, **16**, 1501 (2016); https://doi.org/10.1002/tcr.201600002
26. Q. Wang, T.R. Chan, R. Hilgraf, V.V. Fokin, K.B. Sharpless and M.G. Finn, *J. Am. Chem. Soc.*, **125**, 3192 (2003); https://doi.org/10.1021/ja021381e
27. L. Zhang, X. Chen, P. Xue, H.H.Y. Sun, I.D. Williams, K.B. Sharpless, V.V. Fokin and G. Jia, *J. Am. Chem. Soc.*, **127**, 15998 (2005); https://doi.org/10.1021/ja054114s
28. B.C. Boren, S. Narayan, L.K. Rasmussen, L. Zhang, H. Zhao, Z. Lin, G. Jia and V.V. Fokin, *J. Am. Chem. Soc.*, **130**, 8923 (2008); https://doi.org/10.1021/ja0749993
29. A. Dondoni and A. Marra, *Chem. Soc. Rev.*, **41**, 573 (2012); https://doi.org/10.1039/C1CS15157F
30. P.H. Seeberger and D.B. Werz, *Nature*, **446**, 1046 (2007); https://doi.org/10.1038/nature05819
31. J.M. de la Fuente and S. Penadés, *Glycoconj. J.*, **21**, 149 (2004); https://doi.org/10.1023/B:GLYC.0000044846.80014.cb
32. V. Aragão-Leoneti, V.L. Campo, A.S. Gomes, R.A. Field and I. Carvalho, *Tetrahedron*, **66**, 9475 (2010); https://doi.org/10.1016/j.tet.2010.10.001
33. N.J. Agard, J.A. Prescher and C.R. Bertozzi, *J. Am. Chem. Soc.*, **126**, 15046 (2004); https://doi.org/10.1021/ja044996f
34. K. Godula and C.R. Bertozzi, *J. Am. Chem. Soc.*, **132**, 9963 (2010); https://doi.org/10.1021/ja103009d
35. A.H. El-Sagheer and T. Brown, *Chem. Soc. Rev.*, **39**, 1388 (2010); https://doi.org/10.1039/b901971p
36. V. Wittmann and R.J. Pieters, *Chem. Soc. Rev.*, **42**, 4492 (2013); https://doi.org/10.1039/c3cs60089k
37. S. Slavin, J. Burns, D.M. Haddleton and C.R. Becer, *Eur. Polym. J.*, **47**, 435 (2011); https://doi.org/10.1016/j.eurpolymj.2010.09.019
38. M.F. Debets, S.S. van Berkel, S. Schoffelen, F.P.J.T. Rutjes, J.C.M. van Hest and F.L. van Delft, *Chem. Commun.*, **46**, 97 (2010); https://doi.org/10.1039/B917797C
39. J.E. Moses and A.D. Moorhouse, *Chem. Soc. Rev.*, **36**, 1249 (2007); https://doi.org/10.1039/B613014N
40. A. Manoharan, J. Jayan, T.M. Rangarajan, K. Bose, F. Benny, R.S. Ipe, S. Kumar, N. Kukreti, M.A. Abdelgawad, M.M. Ghoneim, H. Kim and B. Mathew, *ACS Omega*, **8**, 44437 (2023); https://doi.org/10.1021/acsomega.3c04960
41. Z. Wang, Z.S. Chinoy, S.G. Ambre, W. Peng, R. McBride, R.P. de Vries, J. Glushka, J.C. Paulson and G.-J. Boons, *Science*, **341**, 379 (2013); https://doi.org/10.1126/science.1236231
42. M. Meldal and C.W. Tornøe, *Chem. Rev.*, **108**, 2952 (2008); https://doi.org/10.1021/cr0783479
43. H. Ju, S. Xiu, X. Ding, M. Shang, R. Jia, B. Huang, P. Zhan and X. Liu, *Eur. J. Med. Chem.*, **187**, 111940 (2020); https://doi.org/10.1016/j.ejmech.2019.111940
44. R.S. Xiong, Q.J. Zhao, H.H. Zhu, Z. Liu,Y.B. Wei and J.S. Shen, *Chinese Chem. Lett.*, **21**, 1338 (2010); https://doi.org/10.1016/j.cclet.2010.06.021
45. E.M. Sletten, C.R. Bertozzi, *Angew. Chem. Int. Ed. Engl.*, **48**, 6974 (2009); https://doi.org/10.1002/anie.200900942
46. C.S. McKay and M.G. Finn, *Chem. Biol.*, 21, 1075 (2014); https://doi.org/10.1016/j.chembiol.2014.09.002
47. R. Zhang and K.J. Edgar, *Carbohydr. Polym.*, **122**, 84 (2015); https://doi.org/10.1016/j.carbpol.2014.12.020
48. K. Kowalski, *Coord. Chem. Rev.*, **479**, 214996 (2023); https://doi.org/10.1016/j.ccr.2022.214996
49. T.-C. Chi, P.-C. Yang, S.-K. Hung, H.-W. Wu, H.-C. Wang, H.-K. Liu, L.-W. Liu and H.-H. Chou, *J. Org. Chem.*, **89**, 5401 (2024); https://doi.org/10.1021/acs.joc.3c02836
50. A.K. Agrahari, P. Bose, M.K. Jaiswal, S. Rajkhowa, A.S. Singh, S. Hotha, N. Mishra and V.K. Tiwari, *Chem. Rev.*, **121**, 7638 (2021); https://doi.org/10.1021/acs.chemrev.0c00920
51. D.P. Gamblin, E.M. Scanlan and B.G. Davis, *Chem. Rev.*, **109**, 131 (2009); https://doi.org/10.1021/cr078291i
52. S. Zhang, K.Y. Chen and X. Zou, *Commun. Inf. Syst.*, **21**, 147 (2021); https://doi.org/10.4310/CIS.2021.v21.n1.a7
53. D.P. Vala, R.M. Vala and H.M. Patel, *ACS Omega*, **7**, 36945 (2022); https://doi.org/10.1021/acsomega.2c04883
54. D. Janreddy, V. Kavala, C.-W. Kuo, W.-C. Chen, C. Ramesh, T. Kotipalli, T.-S. Kuo, M.-L. Chen, C.-H. He, C.-F. Yao, *Adv. Synth. Catal.*, **355**, 2918 (2013); https://doi.org/10.1002/adsc.201300344
55. T.J. Boltje, T. Buskas and G.-J. Boons, *Nat. Chem.*, **1**, 611 (2009); https://doi.org/10.1038/nchem.399
56. J. Li, M. Zheng, W. Tang, P.L. He, W. Zhu, T. Li, J.P. Zuo, H. Liu and H. Jiang, *Bioorg. Med. Chem. Lett.*, **16**, 5009 (2006); https://doi.org/10.1016/j.bmcl.2006.07.047
57. A.N. Iseli, M.O. Pohl, I. Glas, E. Gaggioli, P. Martínez-Barragán, S.C. David, A. Schaub, B. Luo, L.K. Klein, N. Bluvshtein, K. Violaki, G. Motos, W. Hugentobler, A. Nenes, U.K. Krieger, T. Peter, T. Kohn and S. Stertz, *J. Virol.*, **97**, e01271 (2023); https://doi.org/10.1128/jvi.01271-23
58. J. Yang, S. Liu, L. Du and S. Jiang, *Rev. Med. Virol.*, **26**, 242 (2016); https://doi.org/10.1002/rmv.1879
59. J. Li, M. Zheng, W. Tang, P.-L. He, W. Zhu, T. Li, J.-P. Zuo, H. Liu and H. Jiang, *Bioorg. Med. Chem. Lett.*, **16**, 5009 (2006); https://doi.org/10.1016/j.bmcl.2006.07.047
60. I. Carvalho, P. Andrade, V.L. Campo, P.M.M. Guedes, R. Sesti-Costa, J.S. Silva, S. Schenkman, S. Dedola, L. Hill, M. Rejzek, S.A. Nepogodiev and R.A. Field, *Bioorg. Med. Chem.*, **18**, 2412 (2010); https://doi.org/10.1016/j.bmc.2010.02.053
61. L.V. Lee, M.L. Mitchell, S.J. Huang, V.V. Fokin, K.B. Sharpless, C.H. Wong, *J. Am. Chem. Soc.*, **125**, 9588 (2003); https://doi.org/10.1021/ja0302836
62. S. Dedola, D.L. Hughes, S.A. Nepogodiev, M. Rejzek and R.A. Field, *Carbohydr. Res.*, **345**, 1123 (2010); https://doi.org/10.1016/j.carres.2010.03.041
63. S.I. Maffioli, Y. Zhang, D. Degen, T. Carzaniga, G. Del Gatto, S. Serina, P. Monciardini, C. Mazzetti, P. Guglierame, G. Candiani, A.I. Chiriac, G. Facchetti, P. Kaltofen, H.-G. Sahl, G. Dehò, S. Donadio and R.H. Ebright, *Cell*, **169**, 1240 (2017); https://doi.org/10.1016/j.cell.2017.05.042
64. X. Zhang and Y. Zhang, *Molecules*, **18**, 7145 (2013); https://doi.org/10.3390/molecules18067145
65. M. von Itzstein, *Nat. Rev. Drug Discov.*, **6**, 967 (2007); https://doi.org/10.1038/nrd2400
66. B.S. Panda, M.A. Ahemad, S. Mohapatra, E. Naik, S. Nayak, S. Mohapatra, P.K. Naik, D. Bhattacharya, C.R. Sahoo and M.K. Sahoo, *J. Mol. Struct.*, **1318**, 139323 (2024); https://doi.org/10.1016/j.molstruc.2024.139323
67. H. Cheng, J. Wan, M.-I. Lin, Y. Liu, X. Lu, J. Liu, Y. Xu, J. Chen, Z. Tu, Y.-S.E. Cheng and K. Ding, *J. Med. Chem.*, **55**, 2144 (2012); https://doi.org/10.1021/jm2013503
68. M.M. Mudgal, N. Birudukota and M.A. Doke, *Int. J. Med. Chem.*, **2018**, 2946730 (2018); https://doi.org/10.1155/2018/2946730
69. D.A. Kuntz, C.A. Tarling, S.G. Withers and D.R. Rose, *Biochemistry*, **47**, 10058 (2008); https://doi.org/10.1021/bi8010785
70. R. Al-Saoud, A. Hamrouni, A. Idris, W.K. Mousa and T.A. Izneid, *Biomed. Pharmacother.*, **165**, 115091 (2023); https://doi.org/10.1016/j.biopha.2023.115091
71. Z. Wang and H. Gleichmann, *Diabetes*, **47**, 50 (1998); https://doi.org/10.2337/diab.47.1.50
72. M.C. Korrapati, Puromycin, Encyclopedia of Toxicology, Reference Module in Biomedical Sciences, Elsevier, edn. 3, pp. 1141-1142 (2014).
73. M. Shi, Z.-W. Liu and F.-S. Wang, *Clin. Exp. Immunol.*, **164**, 1 (2011); https://doi.org/10.1111/j.1365-2249.2011.04327.x

74. M.T. Sayed and M.F. Mady, *Eur. J. Med. Chem.*, **286**, 117270 (2025); https://doi.org/10.1016/j.ejmech.2025.117270
75. T.D. Epstein, B. Wu, K.D. Moulton, M. Yan and D.H. Dube, *ACS Infect. Dis.*, **5**, 1682 (2019); https://doi.org/10.1021/acsinfecdis.9b00251
76. B.E. Maryanoff, M.J. Costanzo, S.O. Nortey, M.N. Greco, R.P. Shank, J.J. Schupsky, M.P. Ortegon and J.L. Vaught, *J. Med. Chem.*, **41**, 1315 (1998); https://doi.org/10.1021/jm970790w
77. W. Shen, J.-S. Kim, P.E. Kish, J. Zhang, S. Mitchell, B.G. Gentry, J.M. Breitenbach, J.C. Drach and J. Hilfinger, *Bioorg. Med. Chem. Lett.*, **19**, 792 (2008); https://doi.org/10.1016/j.bmcl.2008.12.031
78. M.R. Clausen and P.B. Mortensen, *Drugs*, **53**, 930 (1997); https://doi.org/10.2165/00003495-199753060-00003
79. V.H. Lillelund, H.H. Jensen, X. Liang and M. Bols, *Chem. Rev*., **102**, 515 (2002); https://doi.org/10.1021/cr000433k
80. D. D'Alonzo, A. Guaragna and G. Palumbo, *Curr. Med. Chem.*, **16**, 473 (2009); https://doi.org/10.2174/092986709787315540
81. K.-Y. Lee, H.G. Kim, M.R. Hwang, J.I. Chae, J.M. Yang, Y.C. Lee, Y.K. Choo, Y.I. Lee, S.-S. Lee and S.-I. Do, *J. Biol. Chem.*, **277**, 49341 (2002); https://doi.org/10.1074/jbc.M209618200
82. J. Guo, W. Li, W. Xue and X.-S. Ye, *J. Med. Chem*., **60**, 2135 (2017); https://doi.org/10.1021/acs.jmedchem.6b01644
83. F. Amann, C. Schaub, B. Müller and R.R. Schmidt, *Angew. Chem*., **4**, 1106 (1998); https://doi.org/10.1002/(SICI)1521-3765(19980615)4:6<1106::AID-CHEM1106>3.0.CO;2-7
84. M. Izumi, K. Wada, H. Yuasa and H. Hashimoto, *J. Org. Chem.*, **70**, 8817 (2005); https://doi.org/10.1021/jo0512608
85. X.-P. He, Y.-L. Zeng, Y. Zang, J. Li, R.A. Field and G.-R. Chen, *Carbohydr. Res*., **429**, 1 (2016); https://doi.org/10.1016/j.carres.2016.03.022
86. X. Cao, X. Du, H. Jiao, Q. An, R. Chen, P. Fang, J. Wang and B. Yu, *Acta Pharm. Sin. B*, **12**, 3783 (2022); https://doi.org/10.1016/j.apsb.2022.05.020
87. B.M. Cunha, L.M.H. Mota, G.S. Pileggi, I.P. Safe and M.V.G. Lacerda, *Autoimmun. Rev*., **14**, 396 (2015); https://doi.org/10.1016/j.autrev.2015.01.001
88. G.C. Minton, A.D. Miller, P.B. Bookstaver and B.L. Love, *J. Cent. Nerv. Syst. Dis.*, **3**, JCNSD.S4365 (2011); https://doi.org/10.4137/JCNSD.S4365
89. S. Holzer, N.J. Rzechorzek, I.R. Short, M. Jenkyn-Bedford, L. Pellegrini and M.L. Kilkenny, A*CS Chem. Biol*., **14**, 1904 (2019); https://doi.org/10.1021/acschembio.9b00367
90. V. Descamps, F. Helle, C. Louandre, E. Martin, E. Brochot, L. Izquierdo, C. Fournier, T.W. Hoffmann, S. Castelain, G. Duverlie, A. Galmiche and C. François, *Antiviral Res*., **118**, 93 (2015); https://doi.org/10.1016/j.antiviral.2015.03.012
91. J. Capdevila, M. Ducreux, R. García Carbonero, T. Halfdanarson, M. Pavel, E. Grande, S. Tafuto, S. Welin, V. Valentí and R. Salazar, *Neuroendocrinology*, **112**, 1155 (2022); https://doi.org/10.1159/000524988
92. J.J. Barchi Jr., *Front. Immunol*., **13**, 852147 (2022); https://doi.org/10.3389/fimmu.2022.852147
93. Z. Xiao, Y. Gu, H. Dong, B. Liu, W. Jin, J. Li, P. Ma, H. Xu and W. Hou, *Eur. J. Med. Chem. Rep.*, **9**, 100113 (2023); https://doi.org/10.1016/j.ejmcr.2023.100113
94. A. Manoharan, J. Jayan, T.M. Rangarajan, K. Bose, F. Benny, R.S. Ipe, S. Kumar, N. Kukreti, M.A. Abdelgawad, M.M. Ghoneim, H. Kim and B. Mathew, *ACS Omega*, **8**, 44437 (2023); https://doi.org/10.1021/acsomega.3c04960
95. A. Sharma, M.K. Jaiswal, M.S. Yadav, D. Ansari, R.P. Tripathi and V.K. Tiwari, *Carbohydr. Res.*, **552**, 109415 (2025); https://doi.org/10.1016/j.carres.2025.109415
96. C.D. Hein, X.-M. Liu and D. Wang, *Pharm. Res*., **25**, 2216 (2008); https://doi.org/10.1007/s11095-008-9616-1
97. C.P. Mungwari, C.K. King'ondu, P. Sigauke and B.A. Obadele, *Sci. Afr.*, **27**, e02509 (2025); https://doi.org/10.1016/j.sciaf.2024.e02509
98. P.K. Parida, A. Sau, T. Ghosh, K. Jana, K. Biswas, S. Raha and A.K. Misra, *Bioorg. Med. Chem. Lett*., **24**, 3865 (2014); https://doi.org/10.1016/j.bmcl.2014.06.054
99. C.J. Pickens, S.N. Johnson, M.M. Pressnall, M.A. Leon and C.J. Berkland, *Bioconjug. Chem*., **29**, 686 (2018); https://doi.org/10.1021/acs.bioconjchem.7b00633
100. M. González-Lainez, M. Gallegos, J. Munarriz, R. Azpiroz, V. Passarelli, M.V. Jiménez and J.J. Pérez-Torrente, *Organometallics*, **41**, 2154 (2022); https://doi.org/10.1021/acs.organomet.2c00246
101. T. Luu, K. Gristwood, J.C. Knight and M. Jörg, *Bioconjug. Chem.*, **35**, 715 (2024); https://doi.org/10.1021/acs.bioconjchem.4c00084
102. X. Meng and K.J. Edgar, *Prog. Polym. Sci.*, **53**, 52 (2016); https://doi.org/10.1016/j.progpolymsci.2015.07.006
103. P. Gogoi, M. Rahman, R. Hazarika, B. Das, K. Deori and D. Sarma, *New J. Chem.*, **48**, 16609 (2024); https://doi.org/10.1039/D4NJ03273J
104. J. Sheng, N. Ma, Y. Wang, W.-C. Ye and B.-X. Zhao, *Drug Des. Devel. Ther*., **9**, 1585 (2015); https://doi.org/10.2147/DDDT.S56038
105. Y. Zhang, S. Luo, Y. Tang, L. Yu, K.-Y. Hou, J.-P. Cheng, X. Zeng and P.G. Wang, *Anal. Chem*., **78**, 2001 (2006); https://doi.org/10.1021/ac051919+
106. A. Solberg, I.V. Mo, L. Omtvedt, B.L. Strand, F.L. Aachmann, C. Schatz and B.E. Christensen, *Carbohydr. Polym*., **278**, 118840 (2022); https://doi.org/10.1016/j.carbpol.2021.118840
107. R.R. Ramsay, M.R. Popovic-Nikolic, K. Nikolic, E. Uliassi and M.L. Bolognesi, *Clin. Transl. Med*., **7**, 3 (2018); https://doi.org/10.1186/s40169-017-0181-2
108. P. Valverde, A. Ardá, N.-C. Reichardt, J. Jiménez-Barbero and A. Gimeno, *MedChemComm*, **10**, 1678 (2019); https://doi.org/10.1039/C9MD00292H
109. M.-M. Chen, P.M. Kopittke, F.-J. Zhao and P. Wang, *Trends Plant Sci*., **29**, 167 (2024); https://doi.org/10.1016/j.tplants.2023.07.003
110. J. Baranwal, B. Barse, A. Fais, G.L. Delogu and A. Kumar, *Polymers*, **14**, 983 (2022); https://doi.org/10.3390/polym14050983
111. X. Li and Y. Xiong, *ACS Omega*, **7**, 36918 (2022); https://doi.org/10.1021/acsomega.2c03931
112. A.B. Lowe, C.E. Hoyle and C.N. Bowman, *J. Mater. Chem*., **20**, 4745 (2010); https://doi.org/10.1039/b917102a