Recent Advances in the Synthesis of Bioactive Glycohybrids via Click-Chemistry

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Abstract Carbohydrates, traditionally known for their energy-providing role, have gained significant attention in drug discovery due to their diverse bioactivities and stereodiversity. However, pure carbohydrate molecules often exhibit limited bioactivity and suboptimal chemical and physical characteristics. To address these challenges, functional groups with bioactive scaffolds have been incorporated into carbohydrates to enhance their bioactivity and improve their overall properties. Among the various synthetic methods available, click chemistry has emerged as a powerful tool for the synthesis of carbohydrate-containing bioactive scaffolds, known as glycohybrids. Click chemistry offers several advantages, including high chemoselectivity, mild reaction conditions, easy purification, and compatibility with multiple functional groups. In the present review, we have emphasized the recent advances and most pertinent research on the development of 1,2,3-triazole-containing glycohybrids via click chemistry, their biological evaluations and the structure-activity relationship during 2017–2023. These newly synthesised glycohybrids could potentially be developed as new chemical entities (NCE) in pharmaceutical chemistry and may encourage the use of carbohydrates in drug discovery processes.

Keywords regioselective, stereodivergent, glycohybrids, cycloaddition, triazole, glycoconjugates, glucopyranoside, glycosidation

1 Introduction

The 1,3-dipolar cycloaddition reaction between terminal alkynes and azides was first discovered by Huisgen, and brought back into focus by Sharpless and others when they introduced the idea of ‘click chemistry’. Chemical transformations that are energetically favoured, precise, adaptable and result in a single reaction product with high yield are referred by the snappy name ‘click’. In other words, simplicity and effectiveness are the fundamental components of ‘click’ chemistry. The Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC) to regioselectively form 1,2,3-triazoles reaction has emerged as the most successful click chemistry reaction for the development of new molecules with useful chemical properties, delivering an impressive volume of diverse molecules in a short amount of time (Figure 1). The initial process, called the Huisgen cyclization, required heat treatment of both reagents and produced the respective triazoles (1,4- vs. 1,5-substituted) as a 1:1 mixture with no regioselectivity at all. The idea of ‘click chemistry’ has been put out as a potent instrument for joining two molecules together quickly and frequently without the production of side products. Because of their powerful dipole moments and exceptional stability to hydrolysis and oxidative/reductive conditions, these kinds of compounds can actively engage in hydrogen bonds and dipole–dipole interactions in biological systems. Linking small drug-like molecules to carbohydrates via click chemistry appears to be a powerful, highly accurate and selective reaction that may produce diverse molecules in rapid and consistent manner. Due to its high degree of dependability, full specificity, and the biocompatibility of the reactants, the 1,2,3-triazole production from azides and terminal acetylenes has become an effective tool for the development of new
Biographical Sketches

Prof. Ram Sagar received his Ph.D. in Organic Chemistry from Central Drug Research Institute (CDRI) Lucknow and University of Agra in 2006. After his Ph.D., he pursued his Research Associate with Prof. Y.D. Vankar at IIT Kanpur during 2006–2007. He pursued his first postdoctoral research at Seoul National University South Korea with Prof. Seung Bum Park during 2007–2008. He moved to University of Oxford and worked with Prof. Benjamin G. Davis as BBSRC postdoctoral fellow until August 2012. He returned to India in August 2012 and held a faculty position at Shiv Nadar University (SNU). He moved to Department of Chemistry, Banaras Hindu University (BHU) as Associate Professor in February 2018 and worked there until Jan 2020. He subsequently became a Full Professor at Jawaharlal Nehru University (JNU), New Delhi in January 2020 and is presently working there as Professor of Chemistry in School of Physical Sciences. His current research interests include devising newer ways for efficient chemical synthesis of natural product inspired small molecules, glycohybrids and glycopeptides implicated in various diseases including tuberculosis and cancer.

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medicinal scaffolds. When a triazole moiety is incorporated in a pharmacophore, it can either perform a passive or active function. A non-labile covalent spacer between discrete N-1 and C-4 or C-5 substituents is provided by the triazole when it functions passively. As an alternative, the triazole contributes when it acts in an active capacity by interacting with the biological target directly.8

Carbohydrates belong to a class of molecules that are found both inside and on the surface of cells as glycoconjugates, have been found to be essential for a number of pathological and physiologically important biological processes, including cellular recognition, adhesion, migration, invasion, communication, bacterial/viral infection, tumour metastasis, and posttranslational modifications of proteins.9,10

Carbohydrates are one of the best structural moieties for diversity-oriented synthesis since they have several stereo-centres and may be used for carbohydrate-based drugs and materials.13,14 Carbohydrate diversity is frequently preceded by glycosylation utilising glycosyl donors. The synthesis of glycosyl donors can be tedious and the process might be challenging to perform. In order to overcome the difficulties in conventional glycosylation, a considerable number of azidosugars (or glycosyl azides) can be synthesized and attached to aglycone by 1,3-cycloaddition.15 Thus, click chemistries have been used extensively for the synthesis of glycohybrids, glycoconjugates and carbohydrate macrocycles in the area of carbohydrate chemistry, in which a sugar with an azido function is grafted onto a saccharide, peptide, or polymeric chain and the production of glycosidase inhibitors has also been achieved using this method.16

2 CuAAC Click Chemistry Mediated Synthesis of Triazole-Based Glycohybrids and their Biological Activities

In this review, recent developments on synthesis of glycohybrids via click chemistry and their biological activity have been summarized. Marchiori and co-workers synthesized a series of triazole-linked galactosyl arylsulfonamides 16–22 by the click cycloaddition reaction of the azide-aryl-sulfonamides 1–7 with the alkyne-based sugar 3-O-propynyl-βGalOMe 8,17 followed by deacetylation of compounds 9–15 (Scheme 1).18

The Trypanosoma cruzi cell invasion inhibition experiments revealed that compounds 18 and 20, with the corresponding 5-methylisoxazole and 2,4-dimethoxy pyrimidine groups, displayed lower values of infection index (ca. 20) in T. cruzi cell invasion inhibition assays among the synthesized compounds 16–22; these compounds also displayed higher binding affinities to galectin-3 (EC_{50} 17–18 μM) in Corning Epic label-free assays. So, the discovery of compounds 3 and 5 as possible galectin-3 binding-related T. cruzi cell invasion blockers reveal galectin-3 as a crucial host target for the development of new antitrypanosomal medicines.

Amdouni and co-workers synthesized nucleoside analogues 26a–f and 29a–q, with 1,4,5-trisubstituted 1,2,3-triazole aglycones, by utilising simple tandem click/electrophilic addition and tandem click/oxidative coupling methods, respectively. In this synthesis they used modified CuAAC approaches that enable the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles and thereby enhance structural modularity, as opposed to conventional CuAAC, which only generates 1,4-disubstituted 1,2,3-triazoles and narrows the accessible structural diversity. They used two methods to produce fully decorated 1,2,3-triazoles; the first was
CuAAC/electrophilic trapping and second was CuAAC/oxidative coupling methods (Scheme 2, Scheme 3 and Scheme 4).19

![Scheme 2 Synthesis of 1,2,3-trisubstituted triazolyl-nucleosides](image)

![Scheme 3 Synthesis of triazoles 26a-f through a CuAAC/electrophilic trapping sequence](image)

![Scheme 4 Synthesis of triazoles 29a-q through a CuAAC/oxidative coupling reaction](image)

The authors have conducted cell culture tests as well as SAR analysis of synthesized compounds and found that these unique substances have powerful antileukemic effects on a number of hematopoietic cell lines. They demonstrated substantial activity (>5000-fold stronger than acadesine) and were very effective against imatinib- and azacitidine-resistant myeloid cell lines, also without significantly increasing toxicity, and compound 29a caused tumor regression in mice that were xenotransplanted with azacitidine-resistant MDS cells.

Yan and co-workers developed a series of compounds in which tricyclic iminosugars fused benzo[e][1,3]thiazin-4-ones 31 and 32 were employed to produce novel pentacyclic iminosugars 37 and 38, which had restricted butterfly-like conformation. By joining the scaffolds of triazole[5,1-c][1,4]oxazepine and benzo[e][1,3]thiazin-4-one, the pentacyclic iminosugar was produced. The desired pentacyclic iminosugars were synthesized in six steps by using the tricyclic iminosugars fused benzo[e][1,3]thiazin-4-one 31 and 32. These starting materials 31 and 32 were synthesized by the tandem Staudinger–Aza-Wittig condensation starting from D-glucose 30.20–24 After the intramolecular click reaction, compound 35a–c, 36a–b were synthesized, which, on further deprotection of the isopropylidene group using 90% CF3COOH, afforded the corresponding pentacyclic iminosugars 37a–c, 38a,b in good amount (Scheme 5).25

The HIV reverse transcriptase (RT) inhibiting properties of the pentacyclic iminosugars 37a–c, 38a,b, and their corresponding protected precursors 35a–c, and 36a,b, were investigated. It was showed that all substances may successfully block RT activity. The one with the highest RT inhibitory action, compound 35c, had an IC50 value of 0.69 µM. The structural activity relationship (SAR) study suggested that the multicyclic inhibitors’ antiHIV-RT inhibitory efficacy could gain from an increase in hydrophilicity.

Gupta and co-workers synthesized a group of N-substituted amide linked triazolyl-D-glucopyranoside derivatives 43a–l using click cycloaddition reaction of terminal alkyne 40 with different organic azides 41a–l,26 in the presence of copper sulfate/sodium ascorbate catalyst, followed by deacetylation of the compounds 42a–l with sodium methoxide in methanol. In this synthesis, terminal alkyne 40 was synthesized by the reaction of glucopyranosylamine 39.
with 4-pentynoic acid in the presence of EDCI and glucopyranosylamine 39 was synthesized by reducing β-D-glucopyranosyl azide (Scheme 6).26,27

All the synthesized compounds 43a–l were tested for their in vitro inhibitory activity against α-glucosidase (EC 3.2.1.20). In contrast to acarbose, which was utilised as the control and had an IC₅₀ of 130.98 µM, the compounds 43e (IC₅₀ = 156.06 µM), 43f (IC₅₀ = 147.94 µM), 43k (IC₅₀ = 127.71 µM), and 43l (IC₅₀ = 121.33 µM) showed substantial inhibitory action. It was observed that the aromatic ring with electron-withdrawing substituents (43b–d) significantly reduced their ability to block α-glucosidase; however, the capacity of the compounds to inhibit α-glucosidase was improved by the addition of electron-donating groups to the phenyl ring (43e–g, 43k, and 43l).

Gawolek and co-workers synthesized glycohybrids 49 and 50 by the click cycloaddition (CuAAC) reaction of 1-azido sugars 45, 46 and propargylamide derivatives of uridine 44 accompanied by Amberlyst-15 deprotection (Scheme 7). They also synthesized glycohybrids 54 and 55 from propargyl β-O-glycosides 51, 52 and 5'-azido uridine derivative 53 using CuAAC cycloaddition reaction (Scheme 8).31

Evaluation of the inhibitory activity of compounds 49, 50, 54 and 55 against β-1,4-galactosyltransferase 1 (b4GalT), a commercially available enzyme, revealed that compound 54 inhibited the enzyme in the mM range. Addi-

<table>
<thead>
<tr>
<th>Compound</th>
<th>% of inhibition at 0.8 mM</th>
<th>IC₅₀ [mM]</th>
</tr>
</thead>
<tbody>
<tr>
<td>49</td>
<td>15±1.1</td>
<td>–</td>
</tr>
<tr>
<td>50</td>
<td>3±0.5</td>
<td>–</td>
</tr>
<tr>
<td>54</td>
<td>48±2.4</td>
<td>0.72</td>
</tr>
<tr>
<td>55</td>
<td>14±2.6</td>
<td>–</td>
</tr>
</tbody>
</table>

Ruiz and co-workers synthesized six carbohydrate naphthalene diimide conjugates 62–67 by click cycloaddition reaction of azido glycosides 45, 57–59 and 2-azidoethyl glycoside 60–61 with 2-N-propargyl naphthalene diimide 56 in the presence of sodium ascorbate, CuSO₄ and t-BuOH/H₂O (1:1, v/v) at room temperature. In this synthesis, 2-N-propargyl naphthalene diimide, 56 was synthesized by the imidation of 2,6-dibromo-1,4,5,8-naphthalenetetracarboxylic dihydride in the presence of N,N′-dimethyl-1,3-propanediamine followed by nucleophilic aromatic substitution at 75 °C in the presence of an excess of propargylamine and acetonitrile (Scheme 9).35

To test their potential selectivity in G4 binding and cell penetration, six carbohydrate naphthalene diimide conjugates (carb-NDIs) were synthesized as G4 ligands. Carb-NDIs have demonstrated some selectivity for G4 structures over DNA duplexes, although various sugar moieties have no impact on determining whether one G4 topolog is preferred over another. Interestingly, the cellular absorption of monosaccharides that were connected to the NDI scaffold through a short ethylene linker was two to three times more effective than when the sugar was directly attached through its anomeric position.

Thanh and co-workers synthesized 1,2,3,1H-triazole derivatives of 4H-pyran[2,3-d]pyrimidine 71a–y (Scheme 10) by applying click cycloaddition reaction of 3-propargyl-4H-pyran[2,3-d]pyrimidine 70a–y with 2,3,4,6-tetra-O-acetyl-D-glucopyranosyl azide 27h and Cu@MOF-5 was used to catalyse the reaction. In this synthesis, 3-propargyl-4H-pyran[2,3-d]pyrimidine 70a–y were synthesized by the propargylation of the N–H bond of 4H-pyran[2,3-d]pyrimidines 69a–y in the presence of propargyl bromide, K₂CO₃ in anhydrous acetone. 4H-Pyran[2,3-d] pyrimidines
Srivastava and co-workers synthesized a number of β-D-ribofuranosyl coumarinyl-1,2,3-triazoles using a cycloaddition procedure involving azidosugar 73 and 7-O/-7-alkynylated coumarins (72a-d/79a-d). In this synthesis compounds 75a-d were synthesized by Cu(I) catalyzed click reaction of 1-azido-2,3,5-tri-O-benzoyl-β-D-ribofuranose (73)40 and 7-propargylocoumarins 72a-d41-43 followed by debenzoylation of the compounds 74a-d (Scheme 11).44

Similarly, compounds 81a-d were synthesized by the click reaction of azidosugar 73 and 7-acetylcoumarins 79a-d45-48 accompanied by debenzoylation of compounds 80a-d (Scheme 12).
Compounds 74a–d and 75a–d possess coumarin derivatives linked to the trizole ring attached to a sugar moiety through oxymethylene (Scheme 11), whereas in the case of compounds 80a–d and 81a–d, coumarin derivatives are linked directly to the trizole ring containing sugar moiety (Scheme 12). All the synthesized compounds mentioned above were tested for their efficacy against the multidrug resistant clinical isolate 591 and the M. tuberculosis susceptible reference strain H₃⁷Rᵥ. According to the findings, the antimycobacterial activity of the conjugates with the oxymethylene linker, namely 74a–d and 75a–d, were greater than that of the conjugates with direct linkage, namely 80a–d and 81a–d (Table 3); the most effective compounds were compounds 74c, 75b, and 75c, with MICs ≤5.2 μM against the sensitive reference strain H₃⁷Rᵥ and MICs ≤10.3 μM against the multidrug-resistant clinical isolate 591. The most bactericidal compound 75b and its directly linked conjugate 81b shows inhibition against bacterial enzymes InhA and DNA gyrase B and interferes with the constitution of the cell wall to exhibit its antimycobacterial activity.

Furthermore, the synthesized compounds were not harmful, according to a cytotoxicity investigation employing the MTT test on compounds 74c, 75a, 75b, 75c, 81b, and 81c on THP-1 macrophage cell line.

Krawczyk and co-workers synthesized a number of 8-HQ glycoconjugate derivatives 85–92 by the click cycloaddition reaction of 1-glycosyl azide of protected or deprotected sugars (27h, 82, 45 and 46) with quinoline derivatives 83 or 84 in the presence of CuSO₄·5H₂O, NaAsc in the solvent THF/iPrOH (1:1) at room temperature for 24 h (Scheme 13).

Table 3 MIC, MBC and MBC/MIC Ratio of Some Tested Compounds and First-Line Drugs against M. tuberculosis Sensitive Reference Strain H₃⁷Rᵥ and Multidrug-Resistant Clinical Isolate 591

<table>
<thead>
<tr>
<th>Compd</th>
<th>MIC against H₃⁷Rᵥ strain (μM)</th>
<th>MIC against MDR clinical isolate 591 (μM)</th>
<th>MBC (μM)</th>
<th>MBC/MIC ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>H₃⁷Rᵥ</td>
<td>591</td>
<td>H₃⁷Rᵥ</td>
<td>591</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>0.2</td>
<td>2187.5</td>
<td>0.3</td>
<td>1.6</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>0.02</td>
<td>151.9</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>9.7</td>
<td>73.4</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>0.43</td>
<td>69</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>74c</td>
<td>5.2</td>
<td>5.2</td>
<td>10.5</td>
<td>2</td>
</tr>
<tr>
<td>75b</td>
<td>5.1</td>
<td>10.3</td>
<td>6.4</td>
<td>11.5</td>
</tr>
<tr>
<td>75c</td>
<td>4.4</td>
<td>8.9</td>
<td>17.7</td>
<td>4</td>
</tr>
<tr>
<td>81b</td>
<td>16.6</td>
<td>22.2</td>
<td>16.7</td>
<td>22.2</td>
</tr>
</tbody>
</table>
All synthesized compounds were tested for their inhibitory efficacy against β-1,4-GalT, which is commercially available. The findings show that the kind of connected sugar and the presence of the protective groups in the sugar moiety are both important for action against β-1,4-GalT. Compared to analogues containing a D-galactose unit, glycohybrid derivatives of D-glucose (89 and 91) are more active. Furthermore, derivatives with acetyl protection groups on the sugar unit do not exhibit enzyme inhibitory activity; only glycohybrids having an unprotected sugar portion do (Table 4).

Seven cell lines HeLa, HCT 116, MCF-7, U-251 and Hs683, PANC-1 and AsPC-1 were used to test the cytotoxic activity of quinoline derivatives 83 and 84, as well as the resulting glycohybrids 85–92. The results of the cytotoxicity assay showed that glycohybrids 85 and 86 demonstrated promising outcomes among all the tested compounds (Table 5). Compound 86 appeared most active among glycohybrids that were tested against all additional cell lines, while 85 was active only against PANC-1.

Thakur and co-workers synthesized 1,2,3-triazolylmethyl-indoline-2,3-diones 96a–d by the click cycloaddition reaction of N-propargylated isatin 93 with different sugar azides (27h, 82, 94–95) in the presence of CuSO4·5H2O (10 mol%), sodium ascorbate (20 mol%) and THF:H2O (1:1) at room temperature. Furthermore, by the reaction of these 1,2,3-triazolylmethyl-indoline-2,3-diones with different substituted phenyl hydrazine hydrochlorides they also synthesized glycohybrids of phenylhydrazono indolinones 97a–x in the presence of catalyst acetic acid at reflux temperature in the solvent ethanol (Scheme 14).

Table 4 Bovine Milk β-1,4-Galactosyltransferase I Assay Results

<table>
<thead>
<tr>
<th>Compounds</th>
<th>% Inhibition at 0.8 mM</th>
</tr>
</thead>
<tbody>
<tr>
<td>85</td>
<td>0</td>
</tr>
<tr>
<td>86</td>
<td>0</td>
</tr>
<tr>
<td>87</td>
<td>0</td>
</tr>
<tr>
<td>88</td>
<td>0</td>
</tr>
<tr>
<td>89</td>
<td>43±0.39</td>
</tr>
<tr>
<td>90</td>
<td>16±0.36</td>
</tr>
<tr>
<td>91</td>
<td>33±0.87</td>
</tr>
<tr>
<td>92</td>
<td>12±0.48</td>
</tr>
</tbody>
</table>

Table 5 Screening of Cytotoxicity of Glycoconjugate Derivatives of 8-Hydroxyquinoline

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Activity IC50 (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HeLa&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>85</td>
<td>59.48±3.55</td>
</tr>
<tr>
<td>86</td>
<td>30.98±1.80</td>
</tr>
<tr>
<td>87</td>
<td>&gt;800</td>
</tr>
<tr>
<td>88</td>
<td>&gt;800</td>
</tr>
<tr>
<td>89</td>
<td>&gt;800</td>
</tr>
<tr>
<td>90</td>
<td>339.35±6.96</td>
</tr>
<tr>
<td>91</td>
<td>&gt;800</td>
</tr>
<tr>
<td>92</td>
<td>&gt;800</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>1.2±0.03</td>
</tr>
</tbody>
</table>

<sup>a</sup> Cytotoxicity was evaluated using MTT assay.  
<sup>b</sup> Incubation time 24 h.  
<sup>c</sup> Incubation time 72 h

After the synthesis, in vitro testing of all the compounds was done to determine their antiplasmodial activity. Among the synthesized compounds, some compounds of phenylhydrazono indolinones showed significant activity against CQ sensitive Pf3D7 strain while some compounds of phenylhydrazono indolinones demonstrated excellent efficacy against the CQ-resistant PfK1 strain.

Halay and co-workers synthesized triazolylmethyl-linked nucleoside derivatives 105–116 by click cycloaddition reaction of azidofuranoses 98–100 with propargylated nucleobases 101–104 in the presence of CuSO4·5H2O and sodium ascorbate in the solvent THF/t-BuOH/H2O (3:1:1) at 50 °C for 3–6 h (Scheme 15). In this synthesis, azidofuranoses 98–100 were synthesized by three processes, firstly...
protection of corresponding monosaccharides with either trichloroethyliene (for ribose) or isopropylidene (for mannose and glucose), after that the addition of a leaving group and its exchange with sodium azide and propargylated nucleobases were synthesized by the propargylation of nucleobases (uracil, thymine, 5-fluorouracil, and adenine) with propargyl bromide in the presence of K2CO3 in DMF solvents at 50 °C for 8–12 h.

After the successful synthesis of the triazolymethyl-linked nucleoside derivatives, the cytotoxic potential of each synthesized substance was tested against five distinct human cancer cell lines. Among the tested compounds, nucleoside derivative was shown to be the most effective cytotoxic agent, with promising potential against colon cancer HCT-116 cells (IC50 value of 35.6 μM). The nucleoside derivative displayed respectable efficacy against liver cancer Hep3B cells in comparison to most substances, and it was shown that all nucleoside derivatives were effective in inhibiting the Hep3B cell line and had good efficacy against the other evaluated cell lines.

Igual and co-workers synthesized glucopyranoside triazole derivatives using 1,3-dipolar cycloaddition (CuAAC) reaction of the glucosyl azide with terminal alkynes in the presence of CuSO4·5H2O and sodium ascorbate (Scheme 16). In this synthesis, the first precursor, glucosyl azide, was synthesized by three processes. Firstly the very unstable glycosyl bromide was produced by treating glucosamine hydrochloride with acetyl bromide, and it was then employed immediately in the subsequent glycosidation process to produced methyl 3,4,6-tri-O-acetyl-2-amino-2-deoxy-D-glucopyranoside in the presence of MeOH and pyridine, which has the free amine group at the C-2 position. Glucosyl azide was then synthesized by the reaction of with triflyl azide solution in the presence of pyridine solvent.

After the synthesis, compounds were tested for their cytotoxicity and inhibitory activity. According to the MTT experiments, none of the compounds were cytotoxic. Western Blot analysis and subsequent inhibitory experiments showed that the most effective and selective compounds in the series were (IC50 = 0.50±0.02 μM, OGA), 123k (IC50 = 0.52±0.01 μM, OGA), and 123l (IC50 = 0.72±0.02 μM, OGA).
Carmona and co-workers developed a series of dimeric iminosugars (126a–l, 127a–l, and 128a–l) by the click cycloadDITION reaction of three distinct alkynyl pyrrolidines (126, 127, and 128) with a group of diazides (a–l) in the presence of CuSO4·5H2O, sodium ascorbate and tBuOH/H2O (Scheme 17 and Scheme 18). In this synthesis, precursors alkynyl pyrrolidine 127 and 128 was synthesized from D-lyxose and (pyrroloidin-2-yl)furan 126 was synthesized by the deprotection of 125b, which was obtained by the chromatographic separation of reaction mixture of 125a and 125b, produced via the conventional amide coupling of epi-meric acids 124 with propargyl amine.

Scheme 17  Synthesis of precursor 126

![Scheme 17](image)

After the synthesis, the resultant crude dimers were evaluated in situ against one β-galactosidase (126a–l) and two α-fucosidases (127a–l and 128a–l). This technique is advanced as trying to identify divalent glycosidase inhibitors. Dimer 126e was found to be the best inhibitor of β-galactosidase from bovine liver (Ki = 5.8 M), while dimer 127i was found to be the best inhibitor of α-fucosidases from bovine kidney (Ki = 0.15 nM) and Homo sapiens (Ki = 60 nM) (Table 6).

Table 6  IC50 and Ki for Selected Dimers

<table>
<thead>
<tr>
<th>Compounds</th>
<th>α-Fucosidase (bovine kidney)</th>
<th>α-fucosidase (homo sapiens)</th>
<th>β-galactosidase (bovine liver)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimer 127i</td>
<td>0.48 × 10^-3 (Ki = 0.15 × 10^-1; K′i = 0.15 × 10^-3)</td>
<td>0.21 (Ki = 0.060, K′i = 0.15)</td>
<td>-19</td>
</tr>
<tr>
<td>Dimer 126e</td>
<td>32 (Ki = 9.6)</td>
<td>-19</td>
<td>22</td>
</tr>
</tbody>
</table>

a No inhibition detected at 0.1 mM of inhibitor.

b Competitive inhibition was observed for the inhibition of bovine liver β-galactosidase.

Slack and co-workers synthesized three derivatives 135, 136 and 137 of 2-deoxy-2,3-didehydro-N-acetylneuraminic acid (Neu5Ac2en or DANA) by click cycloaddition reaction of Neu5Ac9N32en 134 with an amino acid L-alanine 131, a dipeptide of L-alanine and D-glutamate 132, or a tetrapeptide of L-glutamate-L-alanine-L-lysine-L-glutamate 133 with a propargyl group, which can be produced by substituting the side chain of the L-alanine, respectively. In this synthesis, compound 131 was synthesized from commercially available Fmoc-protected propargyl glycine by removing the fluorenylmethyloxy carbonyl (Fmoc) group and the solid-phase peptide synthesis (SPPS) procedure was used to synthesize the propargyl-modified peptides 132–133 utilising a Fmoc protection method (Scheme 19).

After the synthesis of compounds 135, 136 and 137, their inhibitory actions were evaluated and it was found that glycopeptide E-(TriazoleNeu5Ac2en)-AKE (137) and compound (TriazoleNeu5Ac2en)-A (135) were selective inhibitors of Vibrio cholerae sialidase, whereas glycopeptide analogue (TriazoleNeu5Ac2en)-AdE (136) inhibited both Vibrio cholerae and A. ureafaciens sialidases.

Wang and co-workers synthesized 16 flavonoid triazolyl glycosides 142–149 and 156–163 in excellent yields by Cu(I)-catalyzed azide–alkyne cycloadditions of terminal alkylated flavonoid derivatives 140, 141 and 154, 155 with acetylated sugar azides70,71 followed by deacetylation with sodium methoxide in anhydrous methanol (Scheme 20). In this synthesis, alkylated flavonoid derivatives 140, 141 and 154, 155 were synthesized by refining flavonoids 138, 139 and 152, 153 with propargyl bromide in the presence of potassium carbonate and acetone, respectively. After the synthesis, the antiproliferative effects of all the compounds 142–149 and 156–163 were evaluated against three human cancer cell lines (Hela, HCC1954 and SK-OV-3) in vitro then it was found that flavonoid triazolyl glycosides 145, 156, and 161 had significant antiproliferative properties with IC50 values ranging from 14 to 54 μM.
Zuffo and co-workers developed sugar-NDI conjugates (180–203) by the click cycloaddition reaction of azide-NDI (166 and 167) with alkynyl glycosides (168–179) in the presence of CuSO₄·5H₂O, sodium ascorbate and BuOH/H₂O (1:1) at room temperature (Scheme 21). In this synthesis the first precursor, azide-NDI (166 and 167) derivatives were synthesized in three steps i.e., after the initial imidation, which produced 165 from 164, the 3-azido-1-propyamine moiety was added through an S_NAr reaction and in the presence of excess diamine, the precursor and product undergo competitive dehalogenation, producing the desired dehalogenated product 166 as well as the brominated NDI and, after that, compound 167 was synthesized through a second MW-assisted SNAr process on brominated NDI in the presence of N,N-dimethylpropanediamine as the solvent. The authors evaluated the in vitro antiparasitic ac-
activities against BSF Trypanosoma brucei and promastigote forms of Leishmania major of all the derived compounds 180–203. It was found that β-gluc-C2-diNDI (181), β-lactEG-diNDI (188) and β-malt-TEG-diNDI (191) were the most active among the synthesized compounds. Anti-leishmanial activity on L. major promastigotes were observed then it was found that several carb-NDIs had IC₅₀ values in the sub-mM range. Additionally, triamino-substituted carb-NDI, α-man-C-triNDI 195, and diamino-substituted carb-NDI, β-gluc-C2-diNDI, β-lac-TEG-diNDI, and β-malt-TEG-diNDI showed good IC₅₀ values and all of the triamino-substituted carb-NDI conjugates 192–203 showed higher selectivity (13.5–34.0, with the exception of compounds 192 and 200 with 5.7 and 8.5, respectively) than the diamino-substituted carb-NDIs in general (1.2–7.5, with the exception of compounds 189 and 191 with 16.1 and 82.5, respectively).

Šamšulová and co-workers synthesized a series of 2-((1-glycosyl)-1,2,3-triazol-4-yl)-3-hydroxyquinolone conjugates 209a–f, 210a–f, 213a–f, 214a–f and 215a–f. In this synthesis, conjugates 209a–f and 213a–f were synthesized by click cycloaddition of alkyne 204 and 211 with sugar azides 27h, 82 and 205–208, respectively, in the presence of CuSO₄, Na ascorbate and DMF/H₂O solvent at room temperature. Conjugates 210a–f were synthesized after the deprotection of acetyl/benzoyl protective groups at saccharide unit 209a–f in the presence of diethylamine/MeOH (for 210a–e) or MeONa/MeOH (for 210f). Compounds 214a–f were prepared by deprotection of the acetyl group of sugar derivatives 213a–f in the presence of diethylamine/MeOH (for 214a–e) or MeONa/MeOH (for 214f); and 215a–f were synthesized by the removal of benzyl groups from 213a–f by catalytic hydrogenolysis in the presence of 5% Pd/C/H₂ and 2-methoxyethanol at 100 °C (Scheme 22 and Scheme 23).
After the synthesis, all the compounds were tested for antimicrobial activity against Gram-positive (Micrococcus luteus CCM 331, Bacillus subtilis CCM 2216, Paenibacillus larvae CCM 4483 and P. larvae CCM 4486) and Gram-negative (Escherichia coli CCM 3954, Serratia marcescens CCM 8587) bacterial strains and it was found that four out of six 214a–f were active against G(+) strains and 214e was active against P. larvae CCM 4483 only, with moderate bactericidal activity (MIC<sub>100</sub> 200 μM) and all G(+) strains were sensitive to conjugates 214a, 214c and 214d. All four of the tested G(+) strains were equally active against the conjugates made from glucose 214a and galactose 214c (MIC<sub>100</sub> 200 μM). Xylose conjugate 214d was found to be strongest inhibitor of all G+ strains and when the protecting benzyl groups from the quinoline unit of compounds 214a–f were removed, the activity of conjugates 215a–f was completely lost.

Li and co-workers synthesized 23 hederacolchiside A1 derivatives 220a–v and 219a–w by click cycloaddition reaction of compound 217 with differently substituted aromatic azides 218a–w<sup>82</sup> in the presence of sodium ascorbate, CuSO<sub>4</sub>·5H<sub>2</sub>O and t-BuOH·H<sub>2</sub>O (2:1, v/v) at 50 °C (Scheme 24).<sup>83</sup> In this synthesis, alkyne 217 was synthesized by stirring the reaction mixture of compound 216 with prop-2-yn-1-amine and EDCI·HCl in the presence of pyridine at room temperature for 2 h.

The synthetic compounds were tested for their in vitro inhibitory activities against two suspension leukaemia cell lines (HL60 cells and U937 cells) as well as four adherent human cancer cell lines (prostate cancer PC3 cells, colon carcinoma HT29 cells, hepatocellular carcinoma HepG2 cells, and lung cancer A549 cells) and, according to the preliminary SAR study, the majority of para- and meta-substituted compounds showed excellent broad-spectrum cytotoxic activity in vitro, particularly compound 220f (IC<sub>50</sub> = 0.54±0.10, 0.93±0.08, 0.54±0.06, 2.66±0.09 μM, respectively), which was more potent than the positive controls hederacolchiside A1 (0.85±0.08, 4.77±0.55, 4.21±0.30, 5.41±0.09 μM, respectively) and 5-fluorouracil (8.45±0.56, 22.23±1.83, 59.12±5.02, 69.07±3.57 μM, respectively) against all tested human cancer cell lines. The findings of the cell cycle analysis and apoptosis assay also showed that 220f could clearly stop the growth of HepG2 cancer cells by causing apoptosis and inhibiting the cell cycle at the G1 and S phases.

Otoni and co-workers synthesized a series of glycosidic derivatives of lawson<sup>222–229</sup> by click cycloaddition reaction of 2-O-propargyllawson<sup>221</sup> with different per-acetylated glycosyl azides<sup>86,87</sup> in the presence of CuSO<sub>4</sub>·5H<sub>2</sub>O, sodium ascorbate and THF/H<sub>2</sub>O at room temperature (Scheme 25).<sup>88</sup>
Bailéna and co-workers synthesized a series of pyrrolidine-aryltriazole hybrids 231, 233–240, 242–243, 245–249, 251–252 and 255; pyrrolidine-aryltriazoles were synthesized by click cycloaddition reaction of pyrrolidine azides 230, 232, 241, 244, 250 and 254 with substituted phenylacetylenes in the presence of CuSO4·5H2O, NaAsc and t-BuOH/H2O at room temperature, respectively (Scheme 26, Scheme 27, Scheme 28 and Scheme 29). Pyrrolidine azide 244 was synthesized by deprotection of 241, pyrrolidine azide 250 was synthesized by the oxidation of azide 230 in the presence NaO3/RuO2 and EtOAc/H2O, and pyrrolidine azide 254 was synthesized by azido transfer reaction of aminomethyl pyrrolidine 253.

All synthesized glycosides were tested against one primary gingival tissue culture-derived non-tumour human fibroblasts (HGF) and three human breast cancer cell lines (SKBR-3, MDA-MB-231, and MCF-7), and it was found that the glycosyl triazoles 222 and 223 had the highest levels of cytotoxicity (IC50 = 0.78 M and 1.27 M, respectively) against SKBR-3 and exhibited a similar level of selectivity (SI22), and among all deacetylated glycosyl triazoles, only compound 226 exhibited cytotoxicity against tumour cells, was non-cytotoxic to non-tumour cells HGF (IC50 > 50 μM) and cytotoxic to SKBR-3 (IC50 = 34.74 μM) and MCF-7 (IC50 = 38.85 μM).
galactosidase A) was conducted and it was found that derivatives (diCl-, diBr-, diCF$_3$- vs. diOMe-) in the 3,5-disubstituted pattern of the aromatic core also clearly enhanced the inhibition of the resultant compounds 251–252 (IC$_{50}$ = 1.8–2.0 µM) as inhibitors of al- 
}

and their cytotoxicity against RAW 264.7 cells were quite low.

Mishra and co-workers synthesized 7-O-glycosylated noscapine derivatives 259a–m by the click cycloaddition reaction of propargylated noscapine derivative 258 with different azido sugars in the presence of catalyst, dinuclear copper(I) thiodiacetate complex $[(PPh_3)_2Cu(\mu$-tda)-Cu(PPh$_3$)$_2]$-H$_2$O or Cul, DIPEA, CH$_2$Cl$_2$ (Scheme 31).$^{97}$

After the synthesis, compounds 259a–m were tested for anticancer activity using HeLa cell line and anti-leishmanial activity against Leishmania donovani, and it was found that five of the noscapine glycohybrids (259a, 259b, 259c, 259e, and 259l) showed notable anti-proliferative action. Four of them (259b, 259c, 259e, and 259l) had notable anti-leishmanial activity.

$$\text{Scheme 27 Synthesis of compounds 242–243 and 245–249}$$

$$\text{Scheme 28 Synthesis of compounds 251–252}$$

$$\text{Scheme 29 Synthesis of compound 255}$$

$$\text{Scheme 30 Synthesis of compounds 257a–t}$$

After the synthesis, a study of each triazole derivative’s ability to inhibit two human glycosidases (GCase and galactosidase A) was conducted and it was found that β-glycosidase from almonds and GCase were moderately to favourably inhibited by derivatives 1, 231 and 240 and para-substitution at the phenyl group lowered the inhibitory efficacy of the derivatives against GCase in comparison to the original non-substituted drug 1. The presence of halogens (diCl-, diBr-, diCF$_3$- vs. diOMe-) in the 3,5-disubstitution pattern of the aromatic core also clearly enhanced the inhibition (238 vs. 240, diBr- vs. diOMe-). The corresponding C-2 epimers 242 and 249 were effective coffee bean α-galactosidase (IC$_{50}$ = 6.1–37 µM) but mild inhibitors of human α-galactosidase A. The effectiveness of the resultant lactams 251 and 252 (IC$_{50}$ = 1.8–2.0 µM) as inhibitors of al- 

$$\text{Scheme 27 Synthesis of compounds 242–243 and 245–249}$$

$$\text{Scheme 28 Synthesis of compounds 251–252}$$

$$\text{Scheme 29 Synthesis of compound 255}$$

$$\text{Scheme 30 Synthesis of compounds 257a–t}$$

dation at C-5 but this change reduced the inhibition of 

human β-glucosidase. The inhibition of the human enzyme was similarly affected by the addition of a hydroxymethyl substituent at C-5 (compound 255), although in this case, the inhibition of the plant enzyme was not enhanced (IC$_{50}$ = 163 µM for 255 vs. IC$_{50}$ = 8.0 µM for I).

Thành and co-workers synthesized 1H-1,2,3-triazole-tethered 4H-chromene-6-glucose conjugates 257a–t by click cycloaddition reaction of 2-amino-7-propargyloxy-4H-chromene-3-carbonitriles 256a–t and tetra-O-acetyl-β-D-glucopyranosyl azide 27h in the presence of Cu@MOF-5 catalyst (Scheme 30).$^{94}$ The corresponding 2-amino-7-hydroxy-4H-chromene-3-carbonitriles and propargyl bromide were used to produce the series of propargyl ethers 256a–t in the presence of anhydrous K$_2$CO$_3$ in dried acetonite at 50 °C or NaH in dried DMF at 25 °C, and 2-amino-7-hydroxy-4H-chromene-3-carbonitriles were synthesized by the reaction of (un)substituted benzaldehydes, malononitrile and resorcinol at room temperature for 24 h in the presence of sodium carbonate in water.

After the synthesis, triazoles 257a–t were tested in vitro for anti-microorganism activities and it was found that a number of triazoles were active against four strains of Gram-negative, three strains of Gram-positive bacteria (MICs = 1.56–6.25 µM), with MICs ranging from 1.56 to 6.25 µM; several triazoles were active against four strains of fun- 
gi. Triazoles 257c, 257d, 257f, 257h and 257r exerted anti-MRSA activities against all strains (MICs = 1.56–6.25 µM) and their cytotoxicity against RAW 264.7 cells were quite low.

After the synthesis, triazoles 257a–t were tested in vitro for anti-microorganism activities and it was found that a number of triazoles were active against four strains of Gram-negative, three strains of Gram-positive bacteria (MICs = 1.56–6.25 µM), with MICs ranging from 1.56 to 6.25 µM; several triazoles were active against four strains of fun- 
gi. Triazoles 257c, 257d, 257f, 257h and 257r exerted anti-MRSA activities against all strains (MICs = 1.56–6.25 µM) and their cytotoxicity against RAW 264.7 cells were quite low.
Kumari and co-workers synthesized two types (total 27 molecules) of triazole linked N-glycosides of coumarins 270–279 and quinolones 280–289 using click cycloaddition reaction of 1-azido-2,3,4,6-tetra-O-acetyl β-D-glucose 27h88 and 1-azido-2,3,4,6-tetra-O-acetyl β-D-galactose 8218 with various 4-O-propargyl coumarins 260–25 and 4-O-propargyl quinolones 266–269 in the presence of CuSO₄·5H₂O, NaAsc and tBuOH/H₂O (1:1) at 50 °C (Table 7).99 In this synthesis, 4-O-propargyl coumarins 260–265 and 4-O-propargyl quinolones 266–269 were synthesized by the reaction of 4-hydroxycoumarins and 4-hydroxyquinolones with propargyl bromide in the presence of K₂CO₃ and DMF,100,101 respectively, and the authors also synthesized compounds 290–296 by deacetylation of compounds 272–273, 278, 280–284 in the presence of NaOMe and MeOH at room temperature (Table 8).

After the synthesis, the anticancer activity of these newly synthesized triazole-linked N-glycosides of coumarins and quinolones was thoroughly evaluated against MCF-7 (breast cancer cell line), HepG2 (liver cancer cell line), HCT-116 (colon cancer cell line) and Huh-7.5 cell lines, and it was found that the chosen library member was selectively hazardous to the MCF-7 breast cancer cell line at low-micromolar concentrations (IC₅₀ 10.97 mM). Compound 273 (Table 9) has anticancer action that is unique to cell lines, and mechanistic analyses revealed that the anticancer activity of the active compound was caused by the production of reactive oxygen species (ROS).
Yan and co-workers synthesized a series of divalent oseltamivir 306–313 and guanidino oseltamivir 314–321 derivatives with esterification on the carboxyl acid group as powerful inhibitors of influenza virus neuraminidase. In this synthesis, oseltamivir 306–313 were synthesized by click cycloaddition reaction of the azide moiety 297–304 with propargylated ethylene glycol 305 in the presence of CuSO4·5H2O, sodium ascorbate, THF/H2O, followed by the deprotection of the Boc group with trifluoroacetic acid (TFA); guanidino oseltamivir derivatives 314–321 were synthesized by the reaction of oseltamivir 306–313 with MeSC(=NBoc)NHBoc in the presence of HgCl2, Et3N, CH2Cl2 at room temperature (Scheme 32).

After the synthesis, the authors evaluated Neuraminidase (NA) inhibition activity of the oseltamivir and guanidino oseltamivir derivatives, and it was found that the inhibitory activities of 314–321 were increased by the guanidino group, and submicromolar IC50 values were found to be lower than those of the comparable amino divalent analogues 306–313. This results from significant electrostatic interactions between the more basic guanidino group and the acidic peptide residues in the active site of NA.

Murray and co-workers synthesized saccharin-glycohybrids 325a–c by click cycloaddition of 6-azido saccharin derivative 322 with propargyl glucoside 323a–c in the presence of CuSO4·5H2O, sodium ascorbate and THF/H2O, followed by deprotection of acetyl groups of sugars in the presence of potassium methoxide, generated in situ from K2CO3 and methanol. In this synthesis, 6-azido saccharin derivative 322 was synthesized in three steps starting from nitro-saccharin, and propargyl glucoside 323a–c were syn-
thesized by the reaction of β-D-galactose or β-D-glucose pentaacetates with propargylic alcohol in the presence of BF₃·Et₂O (Scheme 33).109

After the synthesis, the capability of compounds 325a–c to inhibit the soluble form of carbonic anhydrase (CA) IX (0.1 mg/mL) and CA II (0.1 mg/mL) was used to determine their inhibitory activity, and it was found that gluco and galacto molecules are comparable and that a longer linker enabled better interaction of the sugar with the selectivity pocket, resulting in outstanding CA IX selectivity.

Hao and co-workers synthesized a number of novel carbohydrate-based sulfonamides 339a–c, 339g–i, 339d–f, 339j–l and 340a–f by click cycloaddition reaction of corresponding glycosyl azide 328–336110–112 with sulfonamide-derived alkyne derivatives 326 or 327 in the presence of CuSO₄·5H₂O, sodium ascorbate and DCM·H₂O at 40 °C, followed by deprotection of acetyl groups using sodium methoxide in methanol (Scheme 34, Table 10).114

Table 10 Representation of Various Substituents for Scheme 34

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R'</th>
<th>R''</th>
<th>R'''</th>
<th>X</th>
<th>Compounds</th>
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<td>1</td>
<td>-OCH₃</td>
<td>H</td>
<td>H</td>
<td>OAc</td>
<td>OAc/NOH</td>
<td>NH 337a/339a</td>
</tr>
<tr>
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<td>H</td>
<td>OAc</td>
<td>OAc/NOH</td>
<td>NH 337b/339b</td>
</tr>
<tr>
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<td>H</td>
<td>H</td>
<td>OAc</td>
<td>OAc/NOH</td>
<td>NH 337c/339c</td>
</tr>
<tr>
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<td>H</td>
<td>OAc</td>
<td>OAc/NOH</td>
<td>NH 337d/339d</td>
</tr>
<tr>
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<td>OAc</td>
<td>H</td>
<td>OAc</td>
<td>OAc/NOH</td>
<td>NH 337e/339e</td>
</tr>
<tr>
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<td>H</td>
<td>OAc</td>
<td>OAc/NOH</td>
<td>NH 337f/339f</td>
</tr>
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<td>H</td>
<td>OAc</td>
<td>OAc/NOH</td>
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<td>OAc/NOH</td>
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<td>H</td>
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<td>H</td>
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<td>H</td>
<td>H</td>
<td>OAc</td>
<td>OAc/NOH</td>
<td>O  338f/340f</td>
</tr>
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</table>
All newly synthesized compounds were tested in vitro for their inhibitory action against the three carbonic anhydrase (CA, EC 4.2.1.1) isozymes (hCA I, hCA II, and hCA IX), and effective inhibition against all three CA isoforms was seen; particularly, the tumour-related hCA IX for which it was found that compound 339g was the most powerful and selective inhibitor, with an inhibitory constant (IC\textsubscript{50}) value of 7 nM, being four times more potent than the clinically utilised drug acetazolamide (AAZ) (IC\textsubscript{50} = 30 nM). Compound 339g was also found to have the most notable antitumoral activity, and almost all compounds also shown modest antiproliferative effects against two cancer cell lines (HT29 and MDA-MB-231) in both hypoxia and normoxic settings.

Ruiz and co-workers synthesized symmetric 353–358 and dissymmetric 374–380 carbohydrate-phenyl ditriazole (carb-PDTZ). In this synthesis, symmetric carb-PDTZ 353–358 were synthesized by click cycloaddition reaction of protected 1-azidosugars of glucose 27h,115 maltose 342,116 fucose 343,117 N-acetylglucosamine 344,118,119 2-azidoethylmannopyranoside 345,120,121 and 2-azidoethylglucopyranoside 346\textsuperscript{122,123} with diethynylbenzene in the presence of CuSO\textsubscript{4}, Na-ascorbate, and H\textsubscript{2}O/THF (1:1) at 130 °C in a microwave for 30 min followed by deprotection of acetyl groups in the presence of NaOMe, MeOH (Scheme 35); the two successive click reactions—first, a mono-substitution with the appropriate azido sugar in the presence of CuSO\textsubscript{4}, Na-ascorbate, and H\textsubscript{2}O/THF (1:1) at 60 °C in microwave for 15–65 min, and then a second click reaction with the azidobenzene pyrrolidinyl moiety followed by deprotection of acetyl groups—were used to synthesize the dissymmetric carb-PDTZ 8–14 (Scheme 36).\textsuperscript{124}

After the synthesis, the potential antitumoral activity of all the synthesized compounds was also looked at by measuring their in vitro cytotoxicity on several cancer cell lines, and it was found that all carb-PDTZ derivatives had greater IC\textsubscript{50} values than the control PDTZ; likely because certain derivatives lacked compound stability and had reduced cellular absorption.

Malah and co-workers synthesized six novel carbohydrate-linked aryl-substituted 1,2,3-triazoles 383–385 and 387–389 by click cycloaddition reaction of 2-(2-(2-methyl-...
the presence of CuSO₄·5H₂O, NaAsc, TBTA and azide derivatives of 8-hydroxyquinoline in the reaction of two types of azide and propargyl derivatives of protected/deprotected sugars with substituents aryl azide,323b,382 with terminal alkyne groups of acetylated sugars 323a–b and 382,125 in the presence of CuSO₄·5H₂O, sodium ascorbate, TBTA and H₂O/ t-BuOH/CH₂Cl₂ at 25 °C (Scheme 37).126

After the synthesis, the antibacterial activity of the synthesized molecules was analysed in comparison to Ampicillin against S. aureus and P. aeruginosa, while their antifungal activity was studied in comparison to Nystatin against Candida albicans and Aspergillus niger. Compound 384 was shown to have the strongest antibacterial activity among all the molecules, which clearly demonstrated the beneficial effects of the triethylene glycol sidearm and the acetylated sugar unit for the increased biological activity.

Krawczyk and co-workers synthesized glycohybrids 408–423, 430–437, 438–440 and 441–443 by click cycloaddition reaction of two types of azide and propargyl derivatives of protected/deprotected sugars with two types of propargyl and azide derivatives of 8-hydroxyquinoline in the presence of CuSO₄·5H₂O, NaAsc, i-PrOH, THF and H₂O at room temperature (Scheme 38).127 In this synthesis, glycohybrids 408–423 were synthesized by the click cycloaddition reaction of azidomethyl and 2-azidoethyl derivatives of protected/deprotected-1-thio-β-D-glycopyranosides 400–407128 with propargyl derivatives of 8-hydroxyquinoline 83–84,129 glycohybrids 430–437 were synthesized by click cycloaddition reaction of propargyl derivaties of protected-deprotected-1-thio-β-D-glycopyranosides 424–427130 with azide derivatives of 8-hydroxyquinoline 428–429,131 glycohybrids 438–440 were synthesized by the click cycloaddition reaction of azide derivatives of protected/deprotected-1-thio-β-D-glycopyranosides 394–396 with the propargyl derivative of 8-hydroxyquinoline 83, and glycohybrids 441–443 were synthesized by click cycloaddition reaction of propargyl derivatives of protected/deprotected-1-thio-β-D-glycopyranosides 397–399 with the azide derivative of 8-hydroxyquinoline 428. Azide derivatives of protected/deprotected-1-thio-β-D-glycopyranosides 394–396 were synthesized by the reaction of compounds 390 or 391 with chloroacetyl chloride then sodium azide in DMF followed by deacetylation in the presence of MeONa and MeOH. Propargyl derivatives of protected/deprotected-1-thio-β-D-glycopyranosides 397–399 were synthesized by the reaction of compounds 390 or 391 with propargyl chloroformate in anhydrous DCM at room temperature (Scheme 39).

![Scheme 37 Synthesis of compounds 383–385 and 387–389](image)

![Scheme 38 Synthesis of precursors 394–396 and 397–399](image)

After the synthesis, the novel quinoline glycohybrids were evaluated against the MCF-7, HCT-116 and NHDF-Neo cell lines for their in vitro cytotoxic activities, and it was found that only substances with acetyl protection of the hydroxyl groups in the sugar portion stopped the growth of tumour cells, and low activity was seen in derivatives with an unprotected sugar fragment. The glycohybrids 438–442, which have an extra heteroaromatic (5-amine-2-pyridyl) moiety in the linker structure, were found to be the most active among the tested compounds. When additional antiproliferative activity studies were conducted for these compounds in the presence of Cu²⁺ ions then it was found that when copper was present, the activity of glycohybrids was greatly enhanced compared to when cells were treated with...
just glycohybrids in the absence of Cu²⁺; the strongest levels of cytotoxicity of the compounds was observed against the MCF-7 cell line.

Kotammagari and co-workers synthesized 12-O-artemisinic acid-glycohybrids (446a–k) and 12-N-artemisinic acid-glycohybrids (447a–k) by click cycloaddition reaction of 12-O-propargylated artemisinic acid 444 and 12-N-propargylated artemisinic acid 445 with various sugar azides in the presence of DIPEA, CuI and DCM at room temperature, respectively (Scheme 40). In this synthesis, 12-O-propargylated artemisinic acid 444 was synthesized by the reaction of artemisinic acid with propargyl alcohol in the presence of EDC·HCl, and 12-N-propargylated artemisinic acid 445 was synthesized by the reaction of artemisinic acid with propargyl amine in the presence of HATU and DIPEA.

After the synthesis, the inhibitory effect of each synthesized glycohybrid was evaluated against the MCF7 cell line and research on their anticancer showed that, with the exception of compounds 444 and 446d, all synthesized compounds reduced the development of MCF7 cells in a dose-dependent way. However, these substances had a mild cytotoxic effect.

Mishra and co-workers synthesized cinchonidine-glycohybrids 450a–j by click cycloaddition reaction of 9-epi-9-azido-9-deoxycinchonidine 448 with glycosyl alkynes 449a–j in the presence of CuSO₄·5H₂O, sodium ascorbate and DCM/H₂O (1:1) at room temperature (Scheme 41). The effective interaction of synthesized compounds with the target proteins in molecular docking experiments for plasmpesin inhibition showed positive results.

Chaidam and co-workers synthesized bis-triazole compounds 452a–ee from the reaction between various azide compounds and 1,6-di-propargyl benzyl glucoside 451 through the 1,3-dipolar cycloaddition reaction using CuSO₄·5H₂O and sodium ascorbate in THF at room temperature in good to excellent yields of 74–99% (Scheme 42). Starting compound 451, in turn, was prepared from the reaction of 1,6-dihydroxyl benzyl glucosides with propargyl bromide and sodium hydride in DMF.

The synthesized 1,6-bis-triazole-benzyl glucoside derivatives 452a–ee were tested in vitro for their ability to inhibit a-glucosidase from Saccharomyces cerevisiae using acarbose as a control. The synthesized glucoside derivatives displayed moderate to good activity with IC₅₀ values ranging from 3.73 to 53.34 μM, which were far better than that of acarbose, with an IC₅₀ value of 146.25 μM. Compound 452dd, with an IC₅₀ value of 3.73 μM, was discovered to be the best inhibitor among the synthesized glucosides. Structure–activity relationship studies revealed that the activity increased to about three times (IC₅₀ of 3.86 μM) after substituting a methoxy group at the ortho- and meta-position of benzyl ring 452f, as compared to the unsubstituted benzyl triazole compound 452a, with IC₅₀ of 12.07 μM. In the
Scheme 40 Synthesis of 12-O-artemisinic acid-glycohybrids (446a–k) and 12-N-artemisinic acid-glycohybrids (447a–k)

Scheme 41 Synthesis of cinchonidine glycosides 450a–j
same way, activity was found to decrease in the presence of electron-withdrawing groups like fluoro 452c and nitro 452e at the benzyl ring.

Ruysscher and co-workers synthesized LeuRS (clinically validated target for the development of antimicrobials) inhibitors containing different substituted triazoles. The first

step in the synthetic process involved the commercially available allitol epoxide 453. The epoxide was made to open regio- and stereoselectively at the C2-position in a trans-di-axial manner by using the allylmagnesium chloride-based Gilman reagent. After the obtained alkene 454 underwent a hydroboration-oxidation reaction and selective tosylation of the ensuing primary alcohol, compound 457 was produced. This molecule next underwent in-situ azide substitution, enabling the coupling of a number of alkynes. Up to this point, the azide 458 was transformed into the isopropylidene protected alcohol 459. The acquired sulfamate functional group was then coupled to leucine to produce compound 461 through further sulfamoylation. By connecting 11 distinct alkynes using the standard azide alkyne click chemistry, the authors synthesized 10 protected molecules. Finally, the required compounds 463a–k were produced by acidic removal of all protecting groups (Scheme 43).146

A previously established in-vitro aminoacylation assay was used to confirm that all new leucine linked compounds 463a–k can inhibit LeuRS by observing the impact on the transfer of 14C-radioabeled leucine to tRNALeu. Despite the presence of similar chemical structures, the inhibitory potential of compounds 463a–k was significantly affected by various triazole moiety replacements. With \( K_{\text{app}} \) values of 5.51 and 2.48 nM, the best compounds, 463a and 463k, carried a phenyl substituent at C13 on the triazole ring. Substituting the phenyl ring with electron-releasing or electron-
withdrawing moieties resulted in a decrease of inhibitory activity, which suggested that the phenyl substituent was key to defining the stronger LeuRS inhibition.

Pingitore and co-workers synthesized two libraries of mono- and dimeric pyrrolidine iminosugars 465a–t and 466a–e by click cycloaddition reaction of azidohexylpyrrolidine 464 with the corresponding alkynes in the presence of CuSO4·5H2O, sodium ascorbate and t-BuOH/H2O (Scheme 44).148 After the synthesis, the crude reaction products were diluted in water and evaluated in situ against JbGlcNAcase at a concentration of 0.25 μM, and it was found that the inhibitory efficacy of the starting material 464 was greatly enhanced by the majority of triazoles (465a–t), except for triazoles 465e and 465t, which clearly showed the lowest inhibitory potency (Table 11). No discernible changes in inhibition were seen based on the aromatic/aliphatic nature of the moiety connected to the triazole.

<table>
<thead>
<tr>
<th>Compound</th>
<th>JbGlcNAcase IC50 [nM]</th>
</tr>
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<tbody>
<tr>
<td>465s</td>
<td>56±4</td>
</tr>
<tr>
<td>465t</td>
<td>127±10</td>
</tr>
<tr>
<td>464</td>
<td>327±44</td>
</tr>
</tbody>
</table>

Table 11 Inhibitory Potency of Monovalent Triazole Derivatives

Gulati and co-workers synthesized a series of triazole-based glycohybrids with both acetyl groups (468a–g) and free sugar hydroxyl groups (469a–g) by click cycloaddition reaction of anomeric azides of sugars with terminal acetyl-"eles of tacrine (467) in the presence of CAN and Cul at room temperature (Scheme 45).149 In this synthesis, terminal acetylenes of tacrine was synthesized by the reaction of tacrine with propargyl bromide in the presence of sodium hydride.

After the synthesis, all the compounds were tested against AChE enzyme, and it was found that compounds 468a, 468c, 468d and 468g had good enzyme inhibition, with the most effective inhibitor being 468a, which was found to have an IC50 value of 0.448 μM. According to biological findings, various sugars (both acetylated and deacetylated) and their stereochemistry affect AChE inhibitory action in different ways and also deacetylated substances were less effective in inhibiting enzymes than acetylated substances.

Yang and co-workers synthesized a series of novel Calothrixin A (CAA) derivatives 473a–i by click cycloaddition reaction of compound 472 with different anomeric sugar azides in the presence of CuBr, N,N-diisopropylethylamine (DIEPA) and DMF at 50 °C (Scheme 46).150 In this synthesis, compound 472 was prepared by the reaction of Calothrixin B (470)151 with propargyl bromide in the presence of KOH and DMF followed by oxidation with m-CPBA.

The synthesized CAA derivatives 473a–i were tested for their antiproliferative effects on cancer cell lines A549, MCF-7, A375, HCT116, and MDA-MB-231 with high levels of Topo I or II expression, the cancer cell line SH-SYSY with low levels of Topo I and II expression, and human normal cell lines L02 and 293T, and it was found that 473g showed a significant antiproliferative activity against high Topo I and II expression cells A375 and HCT116, with IC50 values of 20 and 50 nM, respectively, surpassing CAA, and showed no effect on human normal cells (IC50 > 800 nM, against 293T).

Reche and co-workers synthesized a series of carbohy-"drate-naphthalene diimide (carb-NDIs) conjugates 482a–p by click cycloaddition reaction of N-propargylated NDI 480 and 481 with 2-azidoethyl O-glycoside derivatives 60–61, 474–475152,153 and 2-azidoethyl S-glycoside derivatives 476–479154 in the presence of CuSO4·5H2O, sodium ascorbate and t-BuOH/H2O (1:1) at room temperature (Scheme 47).155 In this synthesis, N-propargylated NDI 480 and 481 was synthesized by the imidation of the dibromo-1,4,5,8-
naphthalentetra carboxylic dianhydride, in the presence of 3-(dimethylamino)-1-propylamine or 4-(2-aminoethyl)morpholine followed by nucleophilic aromatic substitution on the NDI in the presence of an excess of propargylamine in acetonitrile.

The synthesized compounds 482a-p were tested for their antiproliferative effects on colon cancer cells as well as their antiparasitic effects on the parasites T. brucei and L. major, and it was found that the sugar-NDI-NMe₂ derivatives were more toxic than the sugar-NDI-morph molecules in mammalian cells and parasites, and that O-carb-NDIs and S-carb-NDIs exhibit very minor differences in cytotoxicity, with the exception of non-cancerous human fibroblasts MRC-5, where thiosugar-NDIs frequently prove less hazardous. The best known chemical for carb-NDI derivatives is compound 2821 (β-malt-S-C2-NDI-NMe₂), which exhibits strong growth inhibition efficacy against colon cancer cells at sub-mM doses and exhibits remarkable selectivity over control human fibroblasts (9.8-fold).

Dominska and co-workers synthesized a series of 8-hydroxyquinoline derivatives 487a-b, 488a-b, 495a-b and 492a-c by the click cycloaddition reaction of sugar derivatives 483, 484, 156,157 485, 486,158,159 and 493, 494160,161 with 8-(2-propyn-1-yloxy)quinoline 83,52,129 and sugar derivatives 489, 490162 with 8-(2-azidoethoxy)quinoline 491,52,129 and 8-(3-azidopropoxy)quinoline 42852,129 in the presence of CuSO₄·5H₂O, NaAsc, i-PrOH/THF/H₂O (1:1:1, v:v:v) at room temperature (Scheme 48).163

After the synthesis, a number of in vitro biological studies were carried out on the synthesized compounds utilizing the cancer cells HCT-116 and MCF-7 as well as the healthy cells NHDF-Neo, and it was found that the glycohybrids with the triazole-quinoline connected through the triazole nitrogen atom to the D-glucose unit directly to the carbon at the C-6 position, showed the maximum cytotoxicity of both cancer cell lines in the MTT test.
Hodon and co-workers synthesized a series of glucose conjugates 500–503, 508–511 by click cycloaddition of the corresponding terpenic propargyl esters (497, 499, 505 and 507) with 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl azide \( \text{27h} \) or β-D-glucopyranosyl azide \( \text{45} \) in the presence of CuI, and DMF at 40 °C (Scheme 49).\(^{165}\)

After the synthesis, the compounds were evaluated for cytotoxicity in eight cancer cell lines and two non-cancer cell lines, and it was found that they lost their selectivity against resistant cells, despite having enhanced cell penetration and substantial cytotoxicity in the CCRF-CEM cell line, and numerous studies revealed that most of them trigger apoptosis via the mitochondrial route. Compound 510 inhibits HCT116 and HeLa cell development and breaks down spheroid cultures, which is crucial for the treatment of solid tumours.

Wang and co-workers synthesized two types of glycosylated quercetins, Glu-Que 513a and 2Glu-Que 513b, by click cycloaddition reaction of 7-propargyl-quercetin 512a and 7,3′-dipropargyl-quercetin 512b with azido sugar 484 in the presence of \( \text{CuSO}_4 \cdot 5\text{H}_2\text{O} \), sodium ascorbate and t-BuOH/H\(_2\)O at 50 °C, respectively (Scheme 50).\(^{166}\) In this synthesis, 7-propargyl-quercetin 512a and 7,3′-dipropargylquercetin 512b were synthesized by the reaction of quercetin with propargyl bromide in the presence of \( \text{Na}_2\text{B}_4\text{O}_7 \cdot 10\text{H}_2\text{O} \) and NaHCO\(_3\) at 50 °C.

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\( \text{Scheme 48} \) Synthesis of type 487, 488, 492 and 495 glycohybrids

\( \text{Scheme 49} \) Synthesis of triterpenoid conjugates with glucose 500–503 and 508–511. (i) Propargyl bromide, \( \text{K}_2\text{CO}_3 \), DMF, r.t. (ii) \( \text{SeO}_2 \), 2-methoxyethanol, reflux; (iii) \text{27h} \) or 45, CuI, DMF, 40 °C.
After the synthesis of compounds 513a (Glu-Que) and 513b (2Glu-Que), the neuroprotective properties of these compounds were evaluated, and it was found that 2Glu-Que 513b showed higher neuroprotective potential than Glu-Que 513a and this brought SOD, MDA, and GSH close to normal levels and reduced the ischemic area to 5.06%.

Thanh and co-workers synthesized a series of 36 derivatives of 4H-pyrazolo[2,3-d]pyrimidine 515a–zj by click cycloaddition reaction of polysubstituted 4H-pyrazolo[2,3-d]pyrimidines 514a–zj containing a propargyl group on the nitrogen atom, with peracetylated D-glucopyranosyl azide 27 by using ultrasound, CuNPs@Montmorillonite as a catalyst, and DIPEA, in the presence of tBuOH/H$_2$O at 25 °C (Scheme 51).168

The synthesized compounds 515a–zj were tested against five typical human cancer cell lines, including breast adenocarcinoma cells MCF-7, hepatocellular carcinoma cells HepG2, and cervical cancer cells HeLa, by using three reference drugs: Doxorubicin (DOX), Lapatinib, and Erlotinib. It was found that some compounds, such as 515v, 515x, 515z, 515zc, 515zf, and 515zf against MCF-7, 515s, 515t, 515w, 515zh and 515zl against HepG2, and 515h, 515j, 515zf, and 515zh against HeLa cancer cell lines, demonstrated excellent activity against tested cancer cell lines with IC$_{50}$ <4 μM. In comparison to lapatinib, compounds 8v, 8z, 8zc, and 8zf significantly inhibited the activity of EGFR and HER2 tyrosine kinases.

Abdelgawad and co-workers synthesized a series of phthalazone-tethered 1,2,3-triazole derivatives 517–518 by click cycloaddition reaction of alkyne-functionalized phthalazone 516 with different functionalized azides169–173 in the presence of CuSO$_4$5H$_2$O, sodium ascorbate and tris(benzyltriazolymethyl)amine in H$_2$O/tBuOH/CH$_2$Cl$_2$ (Scheme 52).174 Compounds 517–518 were tested for their biological activity and compound 518 was found to have antiproliferative activity.

### Scheme 50 Synthesis of glycosylated quercetins Glu-Que 513a and 2Glu-Que 513b

![Scheme 50](image)

### Scheme 51 Synthesis of compounds 515a–zj

![Scheme 51](image)

### Scheme 52 Synthesis of compounds 517–518

![Scheme 52](image)

### 3 Conclusions and Perspective

This paper has explored the recent advances in the synthesis of bioactive glycohybrids through the utilization of click chemistry. By investigating the potential of click chemistry in glycoscience, we have witnessed the emergence of a powerful tool for the development of diverse and complex glycohybrids as glycoconjugates with enhanced biological activities. Through click chemistry methodologies, researchers have successfully bridged the gap between synthetic chemistry and glycobiology, enabling the efficient construction of glycohybrids with precise control over their structures. The bioorthogonality and selectivity of click reactions have facilitated the conjugation of carbohydrates with various bioactive molecules, such as peptides, proteins, drugs and nanoparticles.
Herein, this review focuses on recent advancements and significant research in the development of glycohybrids containing 1,2,3-triazole moieties. These glycohybrids exhibit promising biological activities and have shown potential as new chemical entities in the pharmaceutical chemistry. The structure-activity relationships of these glycohybrids are explored, highlighting the influence of the 1,2,3-triazole-containing bioactive scaffolds on their pharmacological properties. The integration of these glycohybrids in drug-discovery processes can open up new avenues for the utilization of carbohydrates in pharmaceutical chemistry. This review article has centred on the synthesis of triazole-linked glycohybrids through the well-established copper(I)-catalyzed click chemistry method. These glycohybrids encompass a diverse range of molecules that exhibit significant biological activities, including anticancer, antiviral, antifungal, antimalarial, antibacterial, and carbonic anhydrase inhibition. These bioactive glycohybrids consist primarily of biologically relevant molecules, such as heterocyclic rings and hydrocarbon chains, connected to sugar moieties via triazole linkers using Cu(I)-catalyzed reactions.

The integration of click chemistry into glycoscience has revolutionized the synthesis of bioactive glycohybrids, enabling researchers to explore new frontiers in the development of biologically relevant molecules. The continued advancements in this field will undoubtedly contribute to the understanding of glycan functions and pave the way for innovative solutions in healthcare and biotechnology. The advancement of these glycohybrids as novel chemical entities holds great potential for the development of improved drugs and may pave the way for a renewed exploration of carbohydrates in the field of drug discovery.

Conflict of Interest
The authors declare no conflict of interest.

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