SynOpen

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

Kavita Singh, Rajdeep Tyagi, Vinay K Mishra, Ghanshyam Tiwari, Ram Sagar.

Affiliations below.

DOI: 10.1055/a-2130-7319

Please cite this article as: Singh K, Tyagi R, Mishra V K et al. Recent Advances in the Synthesis of Bioactive Glycohybrids via Click-Chemistry. SynOpen 2023. doi: 10.1055/a-2130-7319

Conflict of Interest: The authors declare that they have no conflict of interest.

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 carbohydrate 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 chemo- and regioselectivity, 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 using click reaction, 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.

1 Introduction
2 CuAAC click chemistry mediated synthesis of triazole based glycohybrids and their biological activities
3 Conclusions and perspective

Corresponding Author:
Prof. Ram Sagar, Jawaharlal Nehru University, School of Physical Sciences, Glycochemistry Laboratory, 110067 New Delhi, India, ramsagar.bhu@gmail.com, ram.sagar@jnu.ac.in

Affiliations:
Kavita Singh, Jawaharlal Nehru University, School of Physical Sciences, New Delhi, India
Rajdeep Tyagi, Jawaharlal Nehru University, School of Physical Sciences, New Delhi, India
Vinay K Mishra, Banaras Hindu University Faculty of Science, Chemistry, Varanasi, India
Ghanshyam Tiwari, Banaras Hindu University, Department of Chemistry, Varanasi, India
Ram Sagar, Jawaharlal Nehru University, School of Physical Sciences, New Delhi, India
Recent Advances in the Synthesis of Bioactive Glycohybrids via Click-Chemistry

Kavita Singh, Rajdeep Tyagi, Vinay Kumar Mishra, Ghanbhayam Tiwari, Ram Sagar

Glycochemistry Laboratory, School of Physical Sciences, Jawaharlal Nehru University, New Delhi 110067, India.
Department of Chemistry, Institute of Science, Banaras Hindu University, Varanasi, Uttar Pradesh, 221005, India.

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 chemo- and regioselectivity, 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 using click reaction, 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.

1 Introduction

The 1,3-dipolar cycloaddition reaction between terminal alkynes and azides was first discovered by Huisgen, brought back into focus by Sharpless and other 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 any unwanted 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 system. Linking small drug like molecules to carbohydrates via click chemistry appears a powerful, highly accurate and selective reactions that may produce diverse molecules in faster and consistently 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 medicinal scaffolds. When a triazole moiety got 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 is functioning passively. As an alternative, the triazole contributes when it is acting in an active capacity by interacting with the biological target directly.

Carbohydrates belong to a class of molecules, which are found inside or 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, posttranslational modifications of proteins, etc.
Glycohybrids or glyarylides are a family of hybrid molecules that contains carbohydrate molecules merged, fixed or linked with several natural product scaffolds. The bioactive natural product scaffolds attached with carbohydrate motifs have extra benefits for ADME (absorption, distribution, metabolism, and excretion). Further the bioactivity of medicinal molecules is increased when carbohydrate molecules are coupled to bioactive scaffolds. Carbohydrates are one of the best structural moieties for diversity-oriented synthesis since they have several stereocenters and may be used for carbohydrate based drugs and materials. The synthesis of glycosyl donors can be tedious and the process might be challenging to perform. In order to get over the difficulties in conventional glycosylation, a considerable amount of azidosugars (or glycosyl azides) can be synthesized and attached to aglycone by 1,3-cycloaddition. Thus click chemistry has been extensively used 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 done using this method.

2 CuAAC click chemistry mediated synthesis of triazole based glycohybrids and their biological activities

In this review the recent development on synthesis of glycohybrids via click chemistry and their biological activity have been summarized. Marchiori and co-workers have 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-β-GalOMe 8 followed by deacylation of compounds 9-15 (Scheme 1).

The *Trypanosoma cruzi* cell invasion inhibition experiments revealed that the compounds 18 and 20 with the corresponding 5-methylisoxazole and 2,4-dimethoxy pyrimidine groups displayed lower values of infection index (~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 have synthesized a 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, first one is CuAAC/electrophilic trapping and second one is CuAAC/oxidative coupling methods (Scheme 2 and 4).

---

**Figure 1** Typical chemical pathway resulting in 1,2,3-triazole linked molecules.

**Scheme 1** Synthesis of triazole-linked galactosyl arylsulfonamides 16-22

**Scheme 2** Synthesis of 1,2,3-trisubstituted triazolyl-nucleosides

---

*Accepted Manuscript*
Yan and co-workers developed a series of compounds in which the aromatic ring with electron-withdrawing substituents was accompanied by Amberlyst-15 deprotection 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 43a-l (Scheme 6).²⁷

Gupta and co-workers have 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-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 43a-l (Scheme 6).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 (43b-d) electron-withdrawing substituents 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 have synthesized glycohybrids 49 and 50 by the click cycloaddition (CuAAC) reaction of 1-azido sugars 45, 46 and propargylamine derivatives of uridine 44, accompanied by Amberlyst-15 deprotection (Scheme 7) they synthesized glycohybrids 54 and 55 from propargyl β-D-
glycosides 51, 52 and 5'-azido uridine derivative 53 using CuAAC cycloaddition reaction (Scheme 8).\textsuperscript{31}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Scheme_7_Synthesis_of_compounds_49_and_50}
\caption{Scheme 7 Synthesis of compounds 49 and 50}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Scheme_8_Synthesis_of_compounds_54_and_55}
\caption{Scheme 8 Synthesis of compounds 54 and 55}
\end{figure}

Evaluation of the inhibitory activity of compounds 49, 50, 54 and 55 against β-1,4-galactosyltransferase 1 (βGalT), a commercially available enzyme, revealed that compound 54 inhibited the enzyme in the μM range. Additionally, the MTT assay was used to assess the anticancer efficacy of glycohybrids 49, 50, 54 and 55 (Table 1).

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|}
\hline
Compounds & % of inhibition at 0.8 mM & IC\textsubscript{50} [mM] \\
\hline
49 & 15 ± 1.1 & - \\
50 & 3 ± 0.5 & - \\
54 & 48 ± 2.4 & 0.72 \\
55 & 14 ± 2.6 & - \\
\hline
\end{tabular}
\caption{Table 1 Results of the test for bovine milk β-1,4-galactosyltransferase 1}
\end{table}

Ruiz and co-workers synthesized six carbohydrate naphthalene diimide conjugates 62-67 by click cycloaddition reaction of azido glycosides 45, 57-59\textsuperscript{32,33} and 2-azidoethyl glycoside 60-61\textsuperscript{34} with 2-N-propargyl naphthalene diimide 56 in the presence of sodium ascorbate, CuSO\textsubscript{4} and t-BuOH/H\textsubscript{2}O (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 dianhydride in the presence of N,N'-dimethyl-1,3-propanediamine followed by nucleophilic aromatic substitution at 75 °C in the presence of excess of propargylamine and acetonitrile (Scheme 9).\textsuperscript{35}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Scheme_9_Synthesis_of_compounds_62-67}
\caption{Scheme 9 Synthesis of compounds 62-67}
\end{figure}

To test their potential selectivity in G4 binding and cell penetration, six carbohydrate naphthalene diimide conjugates (carb-NDIs) have been synthesized as G4 ligands. Carb-NDIs have demonstrated some selectivity for G4 structures over DNA duplexes, although various sugar moieties have no impact on if a 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 have synthesized 1,2,3-1H-triazoles derivatives of 4H-pyran[2,3-d]pyrimidine 71a-y (Scheme 10)\textsuperscript{36} 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 27b 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 N-H bond of 4H-pyran[2,3-d]pyrimidines 69a-y in the presence of propargylic bromide, K\textsubscript{2}CO\textsubscript{3} in dry acetone, also 4H-pyran[2,3-d]pyrimidines 69a-y were synthesized by ring closing reaction of 4H-pyran[2,3-d]pyrimidine 68a-y in the presence of acetic anhydride and conc. sulfuric acid\textsuperscript{37-39}.

All the synthesized compounds 71a-y were tested for their in vitro ability to inhibit Mycobacterium tuberculosis protein tyrosine phosphatase B (MtPtpB). Six compounds 71f, 71i, 71u, 71v, 71x and 71y were discovered to be active against M. tuberculosis PtpB with an IC\textsubscript{50} value ranging between 1.56 and 9.52 μM after all of the compounds were subjected to an in vitro inhibitory assessment on MtPtpB. Among the previously mentioned active compounds, 71v, 71x, and 71y had hydroxyl groups on the para-position and methoxy, ethyl groups on the meta-position of the benzene ring.
Srivastava and co-workers have synthesized a number of β-D-ribofuranosyl coumarin-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 have been synthesized by Cu(I) catalyzed click reaction of 1-azido-2,3,5-tri-O-benzoyl-β-D-ribofuranose (73) and 7-propargyloxy coumarins 72a-d [41-43], followed by debenzylation of the compounds 74a-d (Scheme 11) [44].

Similarly, compounds 81a-d have been synthesized by the click reaction of azidosugar 73 and 7-acyloxycoumarins 79a-d [45-49], accompanied by debenzylation of compounds 80a-d (Scheme 12).

Compared to 74a-d and 75a-d, coumarin derivatives are linked directly to the triazole 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 Mycobacterium tuberculosis susceptible reference strain H37Rv. According to the findings, the anticytobacterial activity of the conjugates with the oxyethylene linker namely 74a-d and 75a-d, were greater than that of the conjugates with direct linkage, namely 80a-d and 81a-d (Table 2) also 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 cell wall to exhibit its anticytobacterial activity.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>MIC against</th>
<th>MDR clinical</th>
<th>H37Rv isolate 591</th>
<th>MIC (µM)</th>
<th>MBC (µM)</th>
<th>MBC/MIC ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>74c</td>
<td>0.2</td>
<td>2187.5</td>
<td>0.3</td>
<td>0.43</td>
<td>0.52</td>
<td>1.6</td>
</tr>
<tr>
<td>75b</td>
<td>0.5</td>
<td>151.9</td>
<td>1.0</td>
<td>9.7</td>
<td>5.2</td>
<td>1.8</td>
</tr>
<tr>
<td>75c</td>
<td>4.4</td>
<td>8.9</td>
<td>6.4</td>
<td>0.43</td>
<td>0.52</td>
<td>2</td>
</tr>
<tr>
<td>81b</td>
<td>16.6</td>
<td>22.2</td>
<td>16.7</td>
<td>16.6</td>
<td>22.2</td>
<td>1</td>
</tr>
</tbody>
</table>

Also, the synthesized compounds weren’t 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 protected sugars (27b, 82, 45 and 46) [50] with quinoline derivatives 83 or 84 [51] in the presence of CuSO₄. 5H₂O, NaAsc in the solvent THF: PrOH (1:1) at room temperature for 24 h (Scheme 13). [52]
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, glycohybrids derivatives of D-glucose (89 and 91) are more active also derivatives with acetyl protection groups on the sugar unit do not exhibit enzyme inhibitory activity, only glycohybrids having an unprotected sugar portion do (Table 3).

### Table 3 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>

Seven cell lines HeLa, HCT 116, MCF-7, U-251 and Hs683, PANC-1 and AsPC-1 were used to test the cytotoxicity activity of quinoline derivatives 83 and 84, as well as the resulting glycohybrids 85-92. The cytotoxicity assay’s results showed that glycohybrids 85 and 86 demonstrated promising outcomes among all the tested compounds (Table 4). Also compound 86 was active only against PANC-1.

Thakur and co-workers have synthesized 1,2,3-triazolylmethyl-indole-2,3- diones 96a-d by the click cycloaddition reaction of N-propargylated isatin 93 in the presence of CuSO₄.5H₂O (10 mol%), sodium ascorbate (20 mol%) and THF:H₂O (1:1) at room temperature and by the reaction of these 1,2,3-triazolyl-methyl-indole-2,3-diones 96a-d with different substituted phenylhydrazine hydrochlorides, they have also synthesized glycohybrids of phenylhydrazino indolinones 97a-x in the presence of catalytic acetic acid at reflux temperature in the solvent ethanol (Scheme 14).³⁶

After the synthesis, in vitro testing of all the compounds was done to determine their antiplasmodial. Among all the synthesized compounds, some compounds of phenylhydrazino indolinones showed significant activity against CQ sensitive P/FD7 strain while some compounds of phenylhydrazino indolinones demonstrated excellent efficacy against the CQ-resistant P/K1 strain.

### Table 4 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>85</td>
<td>HeLa*: 59.48 ± 3.55, HCT 116*: 69.0 ± 2.53, MCF-7*: 57.69 ± 3.32, NHDF-Neo*: 57.37 ± 3.19</td>
</tr>
<tr>
<td>86</td>
<td>&gt;800</td>
</tr>
<tr>
<td>87</td>
<td>&gt;800</td>
</tr>
<tr>
<td>89</td>
<td>&gt;800</td>
</tr>
<tr>
<td>90</td>
<td>&gt;800</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, Doxorubicin: 5.59 ± 0.14, Doxorubicin: 0.67 ± 0.01, Doxorubicin: &gt;20</td>
</tr>
</tbody>
</table>

*Cytotoxicity was evaluated using MTT assay, ** Incubation time 24 h, *** Incubation time 72 h.

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-\(\text{-}\text{t-BuOH}\text{-}\text{H}_2\text{O}\ 3:1:1\) at 50 °C for 3-6 h (Scheme 15). In this synthesis azidonafuranoses \(98\text{-}100\) were synthesized by three processes, firstly protection of corresponding monosaccharides with either trichloroethylidene (for ribose) or isopropylidene (for mannose and glucose), after that the addition of a leaving group and its exchange with sodium azide\(\text{d}^6\text{d}^6\) and propargylated nucleobases \(101\text{-}104\) were synthesized by the propargylation of nucleobases (uracil, thymine, 5-fluouracil, and adenine) with propargyl bromide in the presence of \(\text{K}_2\text{CO}_3\) in DMF solvents at 50°C for 8-12 h.

After the successful synthesis all the triazolymethyl-linked nucleoside derivatives \(105\text{-}116\), the cytotoxic potential of each synthesized substance was tested against five distinct human cancer cell lines. Among all the tested compounds, the nucleoside derivative \(111\) was shown to be the most effective cytotoxic agent with promising potential against colon cancer HCT-116 cells and it has \(IC_{50}\) value of 35.6 μM. The nucleoside derivative \(108\) displayed respectable efficacy against the liver cancer Hep3B cell 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 \(123\text{-}a\text{-}l\) using 1,3-dipolar cycloaddition (CuAAC) reaction of the glucosyl azide \(120\) with terminal alkenes \(121\text{-}a\text{-}l\) in the presence of \(\text{CuSO}_4\text{-}5\text{H}_2\text{O}\) and Sodium ascorbate (Scheme 16). In this synthesis, the first precursor glucosyl azide has been synthesized by three processes. Firstly the very unstable glycosyl bromide was produced by treating glucosamine hydrochloride \(117\) with acetyl bromide, and it was then employed right away in the subsequent glycosidation process to produced methyl 3,4,6-tri-\(\text{-}O\text{-}\text{-acetyl-2-amine-2-deoxy-\text{-}D-glucopyranoside}\ 119\) in the presence of MeOH and pyridine, which has the free amine group at the C-2 position after that glucosyl azide \(120\) was synthesized by the reaction of 3,4,6-tri-\(\text{-}O\text{-}\text{-acetyl-2-amine-2-deoxy-\text{-}D-glucopyranoside}\ 119\) with triflyl azide solution in the presence of pyridine solvent.\(\text{d}^6\text{d}^6\)
After the synthesis, the resultant crude dimers were evaluated in situ against one β-galactosidase (126a-I) and two α-fucosidases (127a-I and 128a-I). This technique is advanced as trying to identify divalent glycosidase inhibitors. Dimer 126e was found to be the greatest 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>
<thead>
<tr>
<th>Compounds</th>
<th>α-fucosidase</th>
<th>α-fucosidase</th>
<th>β-galactosidase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Bovine kidney)</td>
<td>(Homo sapiens)</td>
<td>(Bovine liver)</td>
</tr>
<tr>
<td>Dimer 127i</td>
<td>0.48 × 10⁻³</td>
<td>0.21</td>
<td>Ni</td>
</tr>
<tr>
<td></td>
<td>(Kᵢ = 0.15 × 10⁻¹, Kᵢ’ = 0.060)</td>
<td>(Kᵢ’ = 0.15)</td>
<td></td>
</tr>
<tr>
<td>Dimer 126e</td>
<td>32</td>
<td>Ni</td>
<td>9.6</td>
</tr>
<tr>
<td></td>
<td>(Kᵢ = 5.8)²</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ni: No inhibition detected at 0.1 mM of inhibitor; *Competitive inhibition was observed for the inhibition of bovine liver β-galactosidase.

Slack and co-workers have synthesized three derivatives 135, 136 and 137 of 2-deoxy-2,3-didehydro-N-acetyleneuraminic acid (Neu5Ac2en or DANA) by click cycloaddition reaction of Neu5Ac9N3en 134 with an amino acid L-alanine 131, a dipetide of an L-alanine and a 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 fluorenylmethoxycarbonyl (Fmoc) group and the solid phase peptide synthesis (SPPS) procedure was used to synthesize the propargyl-modified peptides 132-133 utilising a Fmoc protected method (Scheme 19).

Wang and co-workers synthesized sixteen flavonoid triazolyl glycosides 142-149 and 156-163 in excellent yields by Cu(I)-catalyzed azide-alkyne cycloadditions of terminal alkylated flavonoids derivatives 140, 141 and 154, 155 with acetylated sugar azides, followed by deacetylation with sodium methoxide in anhydrous methanol (Scheme 20). In this synthesis, alkylated flavonoids derivatives 140, 141 and 154, 155 have been synthesized by refluxing flavonoids 138, 139 and 152, 153 with propargyl bromide in the presence of potassium carbonate and acetone respectively. After the synthesis, the antiproliferative activities 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) and then it was found that flavonoid triazolyl glycosides 145, 156, and 161 have significant antiproliferative properties with IC₅₀ values ranging from 14-54 μM.

 ![Scheme 18 Synthesis of compounds 126a-I, 127a-I and 128a-I](image)

![Scheme 19 Synthesis of compounds 135, 136 and 137](image)
Zuffo and co-workers have 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 tBuOH: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, 3-azido-1-propanamine moiety was added through a SnAr 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 by doing a second MW-assisted SNAr process on brominated NDI in the presence of N,N-dimethylpropanediamine as the solvent. They have evaluated the in vitro antiparasitic 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-lac-TEG-diNDI (188) and β-malt-TEG-diNDI (191) were found the most active compounds among all the synthesized compounds. Anti-leishmanial activity on L. major promastigotes was observed then it was found that several carb-NDIs had IC₅₀ values in the sub-mM range. Additionally, triaminosubstituted carb-NDI, a-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 triaminosubstituted 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. Whereas conjugates 210a-f were synthesized after the protection of acetyl/benzyl 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 the deprotection of acetyl group of sugar derivatives 213a-f in 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-methoxethanol at 100°C (Scheme 22 and 23).

Scheme 20 Synthesis of sixteen flavonoid triaryl glycosides 142-149 and 156-163

Scheme 21 Synthesis of Sugar-NDI conjugates 180-203

Scheme 22 Synthesis of compounds 209a-f and 210a-f
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 then 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 (MIC100=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 (MIC100=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 twenty three hederacolchiside A1 derivatives 220a-v and 219a-w by click cycloaddition reaction of compound 217 with differently substituted aromatic azides 218a-w in the presence of sodium ascorbate, CuSO4·5H2O and t-BuOH–H2O (2:1, v/v) at 50 °C (Scheme 24). In this synthesis, allyne 217 was synthesized by stirring the reaction mixture of compound 216 with prop-2-yn-1-amine and EDCl-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) then according to the preliminary SAR study, the majority of para- and meta-substituted compounds showed excellent broad spectrum cytoxic activity in vitro, particularly compound 220f (IC50=0.54±0.10, 0.93±0.08, 0.54±0.06, 2.66±0.09 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 respectively) and S-fluorouracil (8.45±0.56, 22.23±1.83, 59.12±5.02, 69.07±3.57 respectively) against all tested human cancer cell lines and also the findings of the cell cycle analysis and apoptosis assay 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.
EtOAc/H₂O and pyrrolidine azide 254 was synthesized by azido transfer reaction of aminomethyl pyrrolidine 253.

![Scheme 26 Synthesis of compounds 233-240](image)

After the synthesis, a study of each triazole derivative's ability to inhibit two human glycosidases (GCase and galactosidase A) was conducted then it was found that β-glucosidase from almonds and GCase were moderately to favourably inhibited by derivatives 1, 231 and 240 respectively and p-substitution at the phenyl group lowered the inhibitory efficacy of the derivatives against GCase in comparison to the original non-substituted drug I, also the presence of halogens (dICl, dBr, dIF₂ vs. dOMe-) in the 3,5-disubstitution pattern of the aromatic core certainly enhances the inhibition (10 vs 12, dBr- vs dOMe-). The corresponding C-2 epimers 242 and 249 were effective coffee bean α-galactosidase (IC₅₀ = 6.1–37 µM) but mild inhibitors of human α-galactosidase A. The effectiveness of the resultant lactams 251 and 252 (IC₅₀ = 1.8–2.0 µM) as inhibitors of almond β-glucosidase was enhanced by pyrrolidine core oxidation 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 (IC₅₀ = 163 µM for 255 vs IC₅₀ = 8.0 µM for I).

Thanh and co-workers synthesized 1H-1,2,3-Triazole-tethered 4H-chromene-D-glucose conjugates 257a-t by click cycloaddition reaction of 2-amino-7-propargylox-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). 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 K₂CO₃ in dried acetone 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 benzenedicarboxylic acids, malononitrile and resorcinol at room temperature for 24 h in the presence of sodium carbonate in water.

![Scheme 30 Synthesis of compounds 257a-t](image)

After the synthesis, all triazoles 257a-t were tested in vitro for anti-microbial activity then it was found that a number of triazoles were active against four strains of Gram (+), three strains of Gram (-), three strains of Gram (+) bacteria (MICs = 1.56–6.25 µM) and with MICs ranging from 1.56 to 6.25 µM, several triazoles were active against four strains of fungi. Triazoles 257c, 257d, 257f, 257h and 257t exerted anti-MRSA activities against all strains (MICs = 1.56–62.5 µM) and the cytotoxicity of triazoles 257c, 257d, 257f, 257h and 257t 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 [(PPh₃)₂Cu(m-thda)Cu(PPh₃)₂]·6H₂O or CuI, DIPEA, CH₂Cl₂ (Scheme 31).
After the synthesis, all the compounds 259a-m were tested against anticancer activity using HeLa cell line and anti-leishmanial activity against Leishmania donovani then it was found that five of the noscapine glycopyranosides that were synthesized—259a, 259b, 259c, 259e, and 259f—showed notable anti-proliferative action. However, four of these (numbers 259b, 259c, 259e, and 259f) had notable anti-leishmanial activity. Kumari and co-workers have synthesized two types of (total 27 molecules) 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 27b[98] and 1-azido-2,3,4,6-tetra-O-acetyl β-D-galactose 82[98] with various 4-O-propargyl coumarins 260-265 and 4-O-propargyl quinolines 266-269 in the presence of CuSO4·5H2O, NaAsc and BuOH:H2O (1:1) at 50 °C (Table 6). In this synthesis, 4-O-propargyl quinolones 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 they have also synthesized compounds 290-296 by deacetylation of compounds 272-273, 278, 280-284 in the presence of NaOMe and MeOH at room temperature. In this synthesis, 4-O-propargyl quinolones 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 respectively and they have also synthesized compounds 290-296 by deacetylation of compounds 272-273, 278, 280-284 in the presence of NaOMe and MeOH at room temperature. After the synthesis, 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 then it was found that the chosen library member was selectively hazardous to the MCF-7 cancer cell line, HepG2 (liver cancer cell line), HepG2 (liver cancer cell line), HepG2 (liver cancer cell line), and Huh 7.5 cell lines then it was found that the chosen library member was selectively hazardous to the MCF-7 cancer cell line, HepG2 (liver cancer cell line), HepG2 (liver cancer cell line), HepG2 (liver cancer cell line), and Huh 7.5 cell lines then it was found that the chosen library member was selectively hazardous to the MCF-7 cancer cell line, HepG2 (liver cancer cell line), HepG2 (liver cancer cell line), HepG2 (liver cancer cell line), and Huh 7.5 cell lines then it was found that the chosen library member was selectively hazardous to the MCF-7 breast cancer cell line at low micromolar concentrations (IC50 10.37 mM). Compound 273 (Table 8) has anticancer action that is unique to cell lines and mechanistic analyses revealed that the anticancer activity of 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 azide moiety 297-304[102,103] with propargylated ethylene glycol 305 in the presence of CuSO4·5H2O, sodium ascorbate, THF/H2O, followed by the deprotection of Boc group with trifluoroacetic acid (TFA) and, guanidino oseltamivir 314-321 were synthesized by the reaction of oseltamivir 306-313 with

<table>
<thead>
<tr>
<th>Table 6 Synthesis of triazole linked N-glycopyranosides 270-289</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>8</td>
</tr>
<tr>
<td>9</td>
</tr>
<tr>
<td>10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 7 Synthesis of deacetylated triazole linked N-glycopyranosides 290-296</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 8 Anticancer screening results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compounds</td>
</tr>
<tr>
<td>HepG2</td>
</tr>
<tr>
<td>270</td>
</tr>
<tr>
<td>271</td>
</tr>
<tr>
<td>272</td>
</tr>
<tr>
<td>273</td>
</tr>
<tr>
<td>283</td>
</tr>
<tr>
<td>284</td>
</tr>
<tr>
<td>285</td>
</tr>
<tr>
<td>286</td>
</tr>
<tr>
<td>Doxorubicin</td>
</tr>
</tbody>
</table>

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 azide moiety 297-304[102,103] with propargylated ethylene glycol 305 in the presence of CuSO4·5H2O, sodium ascorbate, THF/H2O, followed by the deprotection of Boc group with trifluoroacetic acid (TFA) and, guanidino oseltamivir 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,⁶⁰⁷ (Scheme 32).³⁰⁸

![Scheme 32 Synthesis of oseltamivir triazole derivatives 306-321](image)

After the synthesis, they evaluated Neuraminidase (NA) inhibition activity of all the oseltamivir and guanidino oseltamivir derivatives, then 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 were synthesized by the reaction of β-D-galactose or β-D-glucose pentacetates with propargyl alcohol in the presence of BF₃·Et₂O (Scheme 33).³⁰⁹

![Scheme 33 Synthesis of saccharin-glycohybrids 324a-c and 325a-c](image)

After the synthesis, the capability of compounds 325a-c to inhibit the soluble form of carbonyl anhydrase (CA) IX (0.1 mg/mL) and CA II (0.1 mg/mL) was used to determine their inhibitory activity. Then it was found that glucose and galactose molecules are comparable, and a longer linker has enabled better interaction of the sugar with the selectivity pocket and their CA IX selectivity is outstanding.

Hao and co-workers synthesized a number of novel carbohydrate-based sulfonamides 339a-c, 339g-i, 339d-12f, 339j-l and 340a-f, by click cycloaddition reaction of corresponding glycosyl azide 328-336 with sulfonamide-derived alkyne derivatives 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 in methanol (Scheme 34).³¹⁴

![Scheme 4 Synthesis of compounds triazole linked carbohydrate-based sulfonamides 339a-l and 340a-f](image)

**Table 9** Representation of various substituents for Scheme 36

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R₁/R₂</th>
<th>R₃/R⁴</th>
<th>R₅/R⁶</th>
<th>R₇/R₈</th>
<th>R₉/R₁₀</th>
<th>X</th>
<th>Compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-OCH₃</td>
<td>H/H</td>
<td>0Ac/0H</td>
<td>0Ac/0H</td>
<td>H/H</td>
<td>0Ac/0H</td>
<td>NH</td>
<td>337a/339a</td>
</tr>
<tr>
<td>2</td>
<td>-OCH₂CH₃</td>
<td>H/H</td>
<td>0Ac/0H</td>
<td>0Ac/0H</td>
<td>H/H</td>
<td>0Ac/0H</td>
<td>NH</td>
<td>337b/339b</td>
</tr>
<tr>
<td>3</td>
<td>-OCH₂CH₂CH₃</td>
<td>H/H</td>
<td>0Ac/0H</td>
<td>0Ac/0H</td>
<td>H/H</td>
<td>0Ac/0H</td>
<td>NH</td>
<td>337c/339c</td>
</tr>
<tr>
<td>4</td>
<td>-OCH₃</td>
<td>0Ac/0H</td>
<td>H/H</td>
<td>0Ac/0H</td>
<td>H/H</td>
<td>0Ac/0H</td>
<td>NH</td>
<td>337d/339d</td>
</tr>
<tr>
<td>5</td>
<td>-OCH₂CH₃</td>
<td>0Ac/0H</td>
<td>H/H</td>
<td>0Ac/0H</td>
<td>H/H</td>
<td>0Ac/0H</td>
<td>NH</td>
<td>337e/339e</td>
</tr>
<tr>
<td>6</td>
<td>-OCH₂CH₂CH₃</td>
<td>0Ac/0H</td>
<td>H/H</td>
<td>0Ac/0H</td>
<td>H/H</td>
<td>0Ac/0H</td>
<td>NH</td>
<td>337f/339f</td>
</tr>
<tr>
<td>7</td>
<td>-OCH₃</td>
<td>H/H</td>
<td>0Ac/0H</td>
<td>0Ac/0H</td>
<td>H/H</td>
<td>0Ac/0H</td>
<td>O</td>
<td>337g/339g</td>
</tr>
<tr>
<td>8</td>
<td>-OCH₂CH₃</td>
<td>H/H</td>
<td>0Ac/0H</td>
<td>0Ac/0H</td>
<td>H/H</td>
<td>0Ac/0H</td>
<td>O</td>
<td>337h/339h</td>
</tr>
<tr>
<td>9</td>
<td>-OCH₂CH₂CH₃</td>
<td>H/H</td>
<td>0Ac/0H</td>
<td>0Ac/0H</td>
<td>H/H</td>
<td>0Ac/0H</td>
<td>O</td>
<td>337i/339i</td>
</tr>
<tr>
<td>10</td>
<td>-OCH₃</td>
<td>0Ac/0H</td>
<td>H/H</td>
<td>0Ac/0H</td>
<td>H/H</td>
<td>0Ac/0H</td>
<td>O</td>
<td>337j/339j</td>
</tr>
<tr>
<td>11</td>
<td>-OCH₂CH₃</td>
<td>0Ac/0H</td>
<td>H/H</td>
<td>0Ac/0H</td>
<td>H/H</td>
<td>0Ac/0H</td>
<td>O</td>
<td>337k/339k</td>
</tr>
</tbody>
</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 tumor-related hCA IX then it was found that compound 339g was shown to be the most powerful and selective inhibitor of hCA IX with an inhibitory constant (IC₅₀) value of 7 nM, being four times more potent than the clinically utilized drug acetazolamide (AAZ) (IC₅₀ = 30 nM) and compound 339g also revealed the most notable anticancer activity and almost all compounds also shown modest antiproliferative effects against two cancer cell lines (HT29 and MDA-MB-231) in both hypoxic and normoxic settings.

Ruiz and co-workers synthesized symmetric 353-358 and disymmetric 374-380 carbohydrate-phenyl ditriazole (carb-PDTZ). In this study, 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-acetylgalactosamine 344,118,119, 2-azidoethyl mannosamine 345,120,121, 2-azidoethyl glucopyranoside 346,122,123 with diethynylbenzene in the presence of CuSO₄, Na-ascorbate, and H₂O-THF (1:1) at 130 °C in mw for 30 min followed by deprotection of acetyl groups in the presence of NaOMe, MeOH (Scheme 35) and; the two successive click reactions—first, a mono-substitution with the appropriate azido sugar in the presence of CuSO₄, Na-ascorbate, and H₂O-THF (1:1) at 60 °C in mw 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 disymmetric carb-PDTZ 8-14. (Scheme 36) 124

![Scheme 35 Synthesis of symmetric carbohydrate-phenyl ditriazole derivatives 353-358](image)

![Scheme 36 Synthesis of meta-disymmetric carbohydrate-phenyl ditriazole derivatives 374-380](image)

After the synthesis, the potential antitumoral activity of all the synthesized compounds was also measured by measuring their in vitro cytotoxicity on several cancer cell lines then it was found that all carb-PDTZ derivatives had greater IC₅₀ values than the control PDTZ most 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-methoxyethoxy)ethoxy)-ethyl 3-azidobenzoate 381 and substituted aryl azide 386 with terminal alkyne groups of acetylated sugars 323a-b and 382,125 in the presence of CuSO₄, sodium ascorbate, TBTA and H₂O/ t-BuOH/CH₂Cl₂ at 25 °C (Scheme 37). 126

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

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 a strong antibacterial activity among all the molecules which clearly demonstrated the beneficial effects of the triethylene glycol
sidearm and the acetylated sugar unit on 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). 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 400-407 with propargyl derivatives of 8-hydroxyquinoline 83-84. Glycohybrids 430-437 were synthesized by the click cycloaddition reaction of propargyl derivatives of protected/deprotected-1-thio-β-D-glycopyranosides 424-427 with azide derivatives of 8-hydroxyquinoline 428-429. Glycohybrids 438-440 were synthesized by the click cycloaddition reaction of azide derivatives of protected/deprotected-1-thio-β-D-glycopyranosides 394-396 with propargyl derivative of 8-hydroxyquinoline 83; and glycohybrids 441-443 were synthesized by click cycloaddition reaction of azide derivatives of protected/deprotected-1-thio-β-D-glycopyranosides 397-399 with azide derivative of 8-hydroxyquinoline 428. Also, 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; and 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 39 Synthesis of glycohybrids 408-423, 430-437, 438-440 and 441-443

Kotamagari 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 glycohybrids was evaluated against the MCF-7, HCT-116, and NHDF-Neo cell lines for their in vitro cytotoxic activities then it was found that only substances with acetyl protection of the hydroxyl groups in the sugar portion can stop 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-amino-2-pyridyl) moiety in the linker structure found to be the most active among the tested compounds. When for these compounds, additional antiproliferative activity studies were conducted in the presence of Cu2+ ions then it was found that when copper was present, it was shown that the activity of glycohybrids greatly enhanced compared to when cells were treated with just glycohybrids in the absence of Cu2+ and the strongest levels of cytotoxicity of the compounds was observed against the MCF-7 cell line.

Scheme 38 Synthesis of precursors 394-396 and 397-399
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·H₂O, sodium ascorbate and DCM/H₂O (1:1) at room temperature (Scheme 41). The effective interaction of synthesized compounds with the target protein 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·H₂O 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-dihydroxy benzyl glucosides with propargyl bromide and sodium hydride in DMF.

The synthesized 1,6-bis-triazole benzyl-glucohydride derivatives 452a-ee were tested in vitro for their ability to inhibit α-glucosidase from Saccharomyces cerevisiae using acarbose as a control. The synthesized 1,6-bis-triazole 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 having 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 revealed that the activity got increased to about 3 times with IC₅₀ of 3.86 μM after substituting methoxy group at ortho position of benzyl ring 452f as compared to the unsubstituted benzyl triazole compound 452a with IC₅₀ of 12.07 μM. In the same way activity was found to decrease in presence of electron withdrawing groups like fluoro 452c and nitro 452d at the benzyl ring.

Ruysscher and co-workers have 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-diaxial manner 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 5 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 eleven distinct alkynes using the standard azide alkyne click chemistry, they synthesized ten protected molecules. Finally, the required compounds 463a-k were produced by acidentally removing all protecting groups (Scheme 43).
A previously established in-vitro aminoclaylation assay was used to confirm that all new leucine linked compounds 463a-k can inhibit LeuRS by observing the impact on the transfer of the 14C-radiolabeled leucine to tRNA. Despite the presence of similar chemical structure, the inhibitory potential of compounds 463a-k was significantly affected by various triazole moiety replacements. With Ki 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 the decrease of inhibitory activity which suggested that phenyl substituent was key in defining the stronger LeuRS inhibition.

Pingitore and co-workers have synthesized two libraries of mono- and dimeric pyrrolidine iminosugars 465a-t and 466a-e by click cycloaddition reaction of azidohexylpyrrolidine 464 with corresponding alkynes in the presence of CuSO4·5H2O, sodium ascorbate and t-BuOH/H2O (Scheme 44).

After the synthesis, the crude reaction products were diluted in water and evaluated in-situ against JbGlnACase at a concentration of 0.25 μM then it was found that the inhibitory efficacy of the starting material 464 was greatly enhanced by the majority of triazoles (465a-t) also except for triazoles 465e and 465t, which obviously showed the lowest inhibitory potency, no discernible changes in inhibition were seen based on the aromatic/aliphatic nature of the moiety connected to the triazole.

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 anomic azides of sugars with terminal acetylenes of tacrine (467) in the presence of CAN and CuI at room temperature (Scheme 45). 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—\textbf{468a}, \textbf{468c}, \textbf{468d} and \textbf{468g}—were shown to have good enzyme inhibition among all the compounds and one of the most effective inhibitors \textbf{468a} has been found to have an \textit{IC}_{50} value of 0.448 \textmu M. According to biological findings, various sugars (both deacetylated and acetylated) 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 Calotrichin A (CA) derivatives \textbf{473a-1} by click cycladdition reaction of compound \textbf{472} with different anomic sugar azides in the presence of CuBr, N,N-dissopropylethylamine (DIPAE) and DMF at 50 °C (Scheme 46).\textsuperscript{138} In this synthesis, compound \textbf{472} was prepared by the reaction of Calotrichin B (\textbf{470})\textsuperscript{151} with propargyl bromide in the presence of KOH and DMF followed by oxidation with m-CPBA.

\begin{align*}
\text{Scheme 46 Synthesis of compounds 473a-1}
\end{align*}

All synthesized CA derivatives \textbf{473a-1} 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-SY5Y with low levels of Topo I and II expression, and human normal cell lines L02 and 293T then it was found that \textbf{473g} showed a significant antiproliferative activity against high Topo I and II expression cells A375 and HCT116, with \textit{IC}_{50} values of 20 and 50 nM, respectively surpassing CA and showed no effect on human normal cells (\textit{IC}_{50} > 800 nM, against 293T).

Reche and co-workers synthesized a series of carbohydrate-naphthalene diimide (carb-NDIs) conjugates \textbf{482a-p} by click cycladdition reaction of N-propargylated NDI \textbf{480} and \textbf{481} with 2-azidoethyl 0-glycoside derivatives \textbf{60-61}, \textbf{474-475}\textsuperscript{133,153} and 2-azidoethyl S-glycoside derivatives \textbf{476-479}\textsuperscript{154} in the presence of CuSO\textsubscript{4}·5H\textsubscript{2}O, sodium ascorbate and t-BuOH/H\textsubscript{2}O (1:1) at room temperature (Scheme 47).\textsuperscript{155} In this synthesis N-propargylated NDI \textbf{480} and \textbf{481} was synthesized by the imidation of the dibromo-1,4,5,8-naphthalenetetraacarbonyl dianhydride, in 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.

\begin{align*}
\text{Scheme 47 Synthesis of carb-NDIs 482a-p}
\end{align*}

All the synthesized compounds \textbf{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 then it was found that the sugar-NDI-NMe2 derivatives were more toxic than the sugar-NDI-morph molecules in mammalian cells and parasites and O-carb-NDIs and S-carb-NDIs exhibit very minor differences in cytotoxicity, with the exception of non-cancerous human fibroblasts MRC-5, where these sugar-NDIs frequently prove less hazardous. The best known chemical for carb-NDI derivatives is compound \textbf{2821} (b-malt-S-C2-NDI-NMe2), which exhibits strong growth inhibition efficacy against colon cancer cells at subM doses and exhibits remarkable selectivity over control human fibroblasts (9.8-fold).

Dominska and co-workers synthesized a series of 8-hydroxyquinoline derivatives \textbf{487a-b}, \textbf{488a-b}, \textbf{495a-b} and \textbf{492a-c} by the click cycladdition reaction of sugar derivatives \textbf{483}, \textbf{484}, \textbf{485}, \textbf{486}, \textbf{493}, \textbf{494}, \textbf{496}, \textbf{499}, \textbf{490}\textsuperscript{162} with 8-(2-propyn-1-xyloxy) quinoline \textbf{83}\textsuperscript{129} and sugar derivatives \textbf{489}, \textbf{490}\textsuperscript{162} with 8-(2-azidoethoxy)quinoline \textbf{491}\textsuperscript{129} and 8-(3-azidopropoxy)quinoline \textbf{428}\textsuperscript{129} in the presence of CuSO\textsubscript{4}·5H\textsubscript{2}O, NaAsc, i-PROH/THF/H\textsubscript{2}O (1:1:1, v:v:v) at rt. respectively (Scheme 48).\textsuperscript{163}

\begin{align*}
\text{Scheme 48 Synthesis of type 487, 488, 492 and 495 glycohids}
\end{align*}

After the synthesis, a number of in vitro biological studies were carried out on the synthesized compounds utilising the cancer cells HCT-116 and MCF-7 as well as the healthy cells NHDF-Neo.
then 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.

Hodan and co-workers synthesized a series of glucose conjugates 500-503, 508-511 by click cycloaddition of corresponding terpenic propargyl esters (497, 499, 505 and 507) with 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl azide 27h or β-D-glucopyranosyl azide 4S in the presence of CuI, and DMF at 40 °C (Scheme 49).565

After the synthesis, all compounds were evaluated for cytotoxicity in eight cancer cell lines and two non-cancer cell lines then 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 also compound 510 inhibits HCT116 and HeLa cell development and breaks down spheroid cultures, which is crucial for the treatment of solid tumors.

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 CuSO4·5H2O, sodium ascorbate and t-BuOH/H2O at 50 °C respectively (Scheme 50).566 In this synthesis, 7-propargyl-quercetin 512a and 7,3′'- dipropargyl-quercetin 512b were synthesized by the reaction of quercetin with propargyl bromide in the presence of Na2B4O7·10H2O and NaHCO3 at 50 °C.

After the synthesis of compounds 513a (Glu-Que) and 513b (2Glu-Que) the neuroprotective properties of these compounds were evaluated then 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-pyrrano[2,3-d]pyrimidine 515a-zj by click cycloaddition reaction of polysubstituted 4H-pyrrano[2,3-d]pyrimidines 514a-zj containing propargyl group on nitrogen atom with peracetylated D-glucopyranosyl azide 7 by using ultrasound, CuNPs@Montmorillonite as a catalyst and DIPEA in the presence of ‘BuOH/H2O at 25°C (Scheme 51).568

All 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 then it was found that Some compounds, such as 515v, 515x, 515z, 515zc, 515zf, and 515zg against MCF-7, 515x, 515s, 515w, 515zh and 515zi against HepG2, and 515h, 515j, 515zf and 515zh against HeLa cancer cell lines, demonstrated excellent activity against tested cancer cell lines with IC50 < 4 μM. In comparison to lapatinib, compounds 8v, 8x, 8zc, and 8zf significantly inhibited the activity of EGFR and HER2 tyrosine kinases.

Abdelgawad and co-workers synthesized a series of phthalozone tethered 1,2,3-triazole derivatives 517-518 by click cycloaddition reaction of alkyne-functionalized phthalozone 516 with different functionalized azides569-573 in the presence of CuSO4·5H2O, sodium ascorbate and tris (benzyltriazolymethyl)amine in H2O/tBuOH/CH2Cl2 (Scheme 52).574 The compounds 517-518 were tested for their biological activity and Compound 518 was found as an antiproliferative compound.
3 Conclusions and perspective

In summary, 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 glycochemistry, 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 pharmaceutical chemistry. The structure-activity relationship of these glycohybrids is 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 centered 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, antimarial, antitubercular, 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.

Funding Information
No funding information is available.

Acknowledgment

Authors are thankful to the Jawaharlal Nehru University (JNU) and Banaras Hindu University (BHU) for providing facilities to compile this review. Kavita, Rajdeep, and Vinay is thankful to UGC New Delhi for the Junior/Senior Research Fellowship. RS is grateful to Ulitz, Internation and Sanganer Foundation for supporting lab furniture to Glycochemistry laboratory at JNU.

Conflict of Interest
The authors declare no conflict of interest, financial or otherwise.

References

Biosketches

**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 post-doctoral 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 till Jan 2020. He subsequently got full professor at Jawaharlal Nehru University (JNU), New Delhi in January 2020 and 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.

**Kavita Singh** has been completed her M.Sc. from Deen Dayal Upadhyaya University, Gorakhpur, UP, India in 2019. She qualified CSIR-JRF then joined Glycochemistry laboratory of School of Physical Sciences, Jawaharlal Nehru University, New Delhi, as a junior research fellow in 2021. She is currently pursuing her PhD degree under the supervision of Prof. Ram Sagar. Her work is mainly focused on development of new methods for the synthesis of carbohydrate fused heterocyclic molecules as bioactive glycohybrids. She is also interested in medicinal chemistry and synthesis of natural product inspired bioactive scaffolds.

**Rajdeep Tyagi** has completed his M.Sc. in 2018 from Kirorimal college, University of Delhi, New Delhi, India. He joined Glycochemistry laboratory of School of Physical Sciences, Jawaharlal Nehru University, New Delhi, as a UGC junior research fellow in 2020. He is currently pursuing his Ph.D. degree under the supervision of Prof. Ram Sagar. His expertise lies in heterocyclic molecules, medicinal chemistry, organic synthesis, and the synthesis of indole based bioactive glycohybrids. He is also interested in developing new methods for glycoconjugate synthesis and their bioapplications.

**Vinay Kumar Mishra** has been completed his M.Sc. from Dr. Ram Manohar Lohia Avadh University UP, India. He joined Glycochemistry lab Department of Chemistry, Institute of Science, Banaras Hindu University in 2019 for pursuing his PhD degree under the supervision of Prof. Ram Sagar. His work is mainly focused on development of new methods for the synthesis of carbohydrate fused heterocyclic molecules as glycohybrids. He is also interested in synthesis of natural product inspired bioactive scaffolds.

**Ghanshyam Tiwari** completed his M.Sc. from Mahatma Gandhi Kashi Vidyapith, Varanasi, Uttar Pradesh, India. He joined Glycochemistry lab of the Department of Chemistry at the Institute of Science, Banaras Hindu University, as a research scholar in 2018. He completed his PhD in April 2023 under the supervision of Prof. Ram Sagar. His expertise lies in glycoscience, microwave assisted synthesis, organic synthesis, and the development of new methods for the natural product inspired glycohybrids.