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

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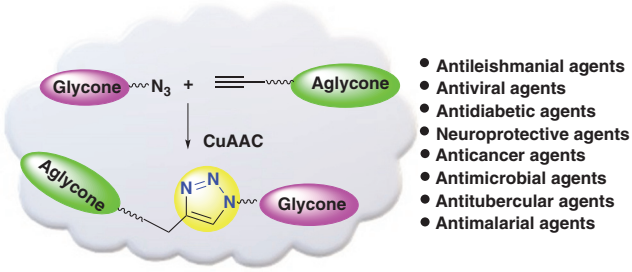
Click Chemistry and Drug Discovery



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Crowd-Reviewed

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 the 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

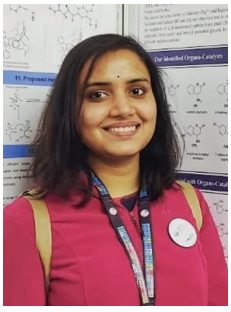
Keywords regioselective, stereodivergent, glycohybrids, cycloaddition, triazole, glycoconjugates, glucopyranoside, glycosidation

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'.[1] 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.[2] 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).[3] 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.[4] 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.[5] 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.[6] 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.[7] 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.



Kavita Singh completed her M.Sc. from Deen Dayal Upadhyaya University, Gorakhpur, UP, India in 2019. She qualified as CSIR-JRF then joined the Glycochemistry laboratory of the 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 focused on the development of new methods for the synthesis of carbohydrate fused heterocyclic molecules as bioactive glycohybrids. She is also interested in medicinal chemistry and the synthesis of natural product inspired bioactive scaffolds.

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

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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]

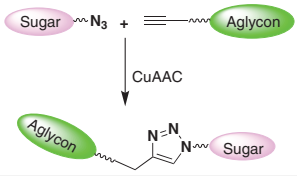
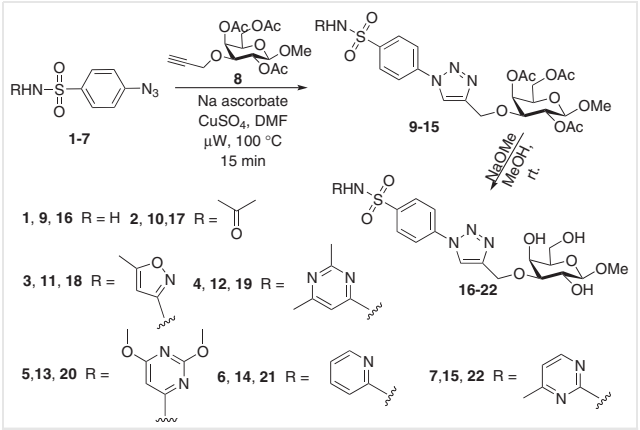


Figure 1 Typical chemical pathway resulting in 1,2,3-triazole linked molecules[11]

Glycohybrids or carbohybrids are a family of hybrid molecules that contain carbohydrate molecules merged, fused or linked with several natural product scaffolds. The bioactive natural product scaffolds attached with carbohydrate motif have extra benefits for ADME (absorption, distribution, metabolism, and excretion). Furthermore, the bioactivity of medicinal molecules can be increased when carbohydrate molecules are coupled to bioactive scaffolds.[12] Carbohydrates are one of the best structural moieties for diversity-oriented synthesis since they have several stereocentres 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 chemistry has 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-arylsulfonamides **1**–**7** with the alkyne-based sugar 3-*O*-propynyl-βGalOMe **8**,[17] followed by deacetylation of compounds **9**–**15** (Scheme 1).[18]

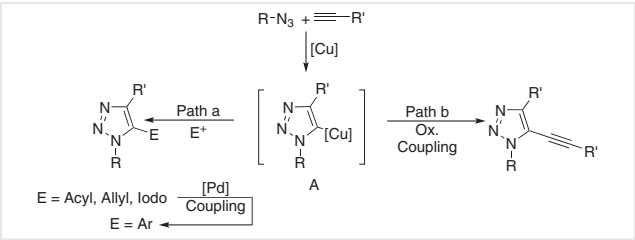


Scheme 1 Synthesis of triazole-linked galactosyl arylsulfonamides **16**–**22**

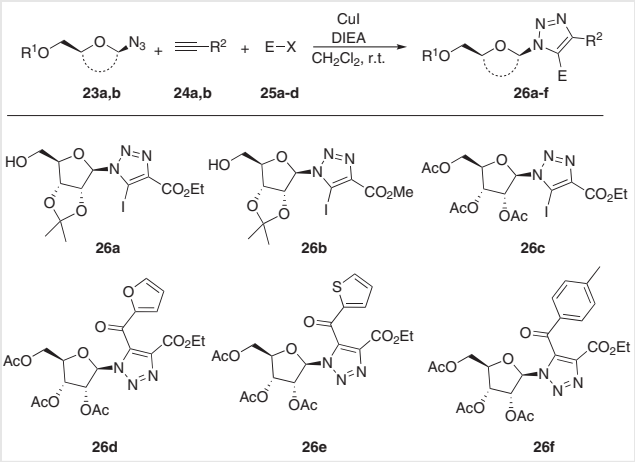
The *Trypanosoma cruzi* cell invasion inhibition experiments revealed that compounds **18** and **20**, with the corresponding 5-methylisoxazole and 2,4-dimethoxypyrimidine groups, displayed lower values of infection index (ca. 20) in *T. cruzi* cell invasion inhibition assays among the synthesized compounds **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

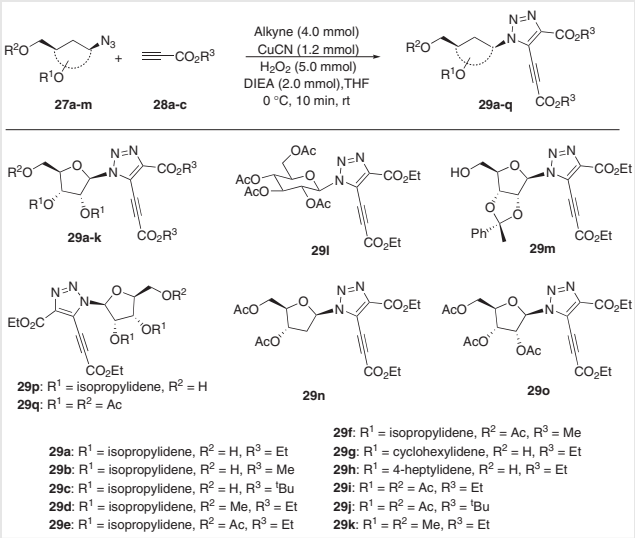
CuAAC/electrophilic trapping and second was CuAAC/oxidative coupling methods (Scheme 2, Scheme 3 and Scheme 4).[19]



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



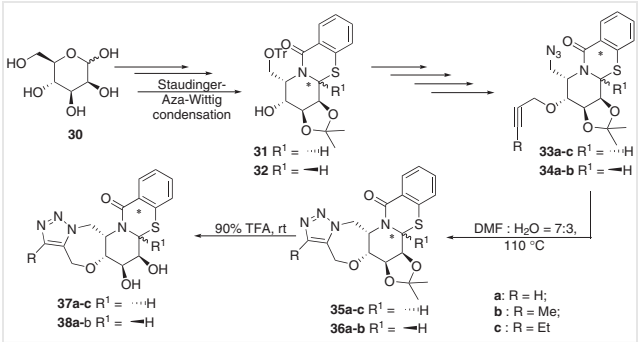
Scheme 3 Synthesis of triazoles **26a–f** through a CuAAC/electrophilic trapping sequence



Scheme 4 Synthesis of triazoles **29a–q** through a CuAAC/oxidative coupling reaction

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 tumour 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 triazolo[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 tandam 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% CF_3COOH, afforded the corresponding pentacyclic iminosugars **37a–c**, **38a**,**b** in good amount (Scheme 5).[25]

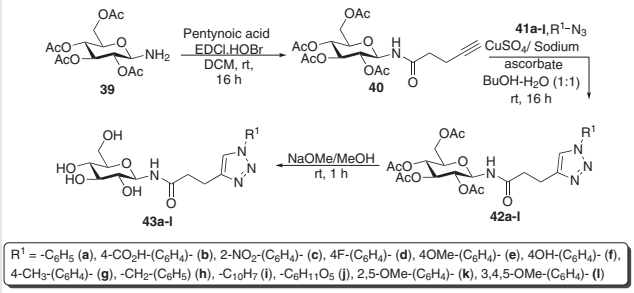


Scheme 5 Synthesis of pentacyclic iminosugars **37a–c** and **38a**,**b**

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 IC_{50} 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**

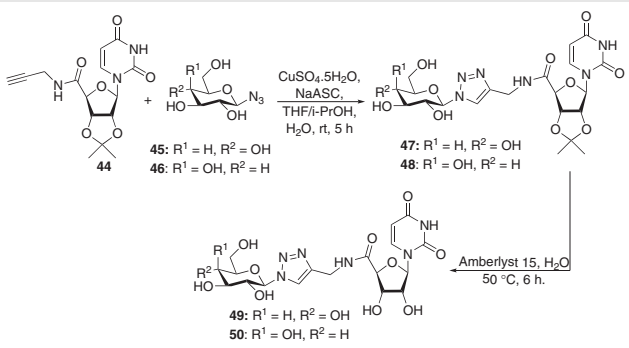
with 4-pentynoic acid in the presence of EDCI and glucopyranosylamine **39** was synthesized by reducing β-D-glucopyranosyl azide (Scheme 6).[26,27]



Scheme 6 Synthesis of **43a–l** glycohybrids

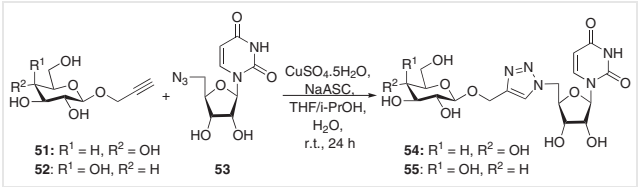
All the synthesized compounds **43a–l** were tested for their in vitro inhibitory activity against α-glucosidase (EC.3.2.1.20). In contrast to acarbose, which was utilised as the control and had an IC_{50} of 130.98 μM, the compounds **43e** (IC_{50} = 156.06 μM), **43f** (IC_{50} = 147.94 μM), **43k** (IC_{50} = 127.71 μM), and **43l** (IC_{50} = 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 uridin **44**,[28,29] 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**[30] using CuAAC cycloaddition reaction (Scheme 8).[31]



Scheme 7 Synthesis of compounds **49** and **50**

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. Additionally, the MTT assay was used to assess the anticancer efficacy of glycohybrids **49**, **50**, **54** and **55** (Table 1).



Scheme 8 Synthesis of compound **54** and **55**

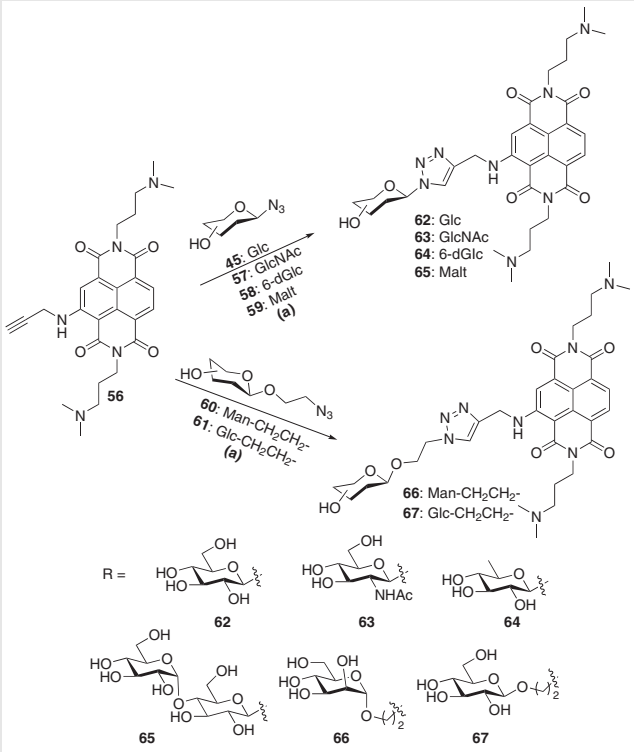
Table 1 Results of the Test for Bovine Milk β-1,4-Galactosyltransferase 1

Compound	% of inhibition at 0.8 mM	IC_{50} [mM]
49	15±1.1	–
50	3±0.5	–
54	48±2.4	0.72
55	14±2.6	–

Ruiz and co-workers synthesized six carbohydrate naphthalene diimide conjugates **62–67** by click cycloaddition reaction of azido glycosides **45**, **57–59**[32,33] and 2-azidoethyl glycoside **60–61**[34] with 2-*N*-propargyl naphthalene diimide **56** in the presence of sodium ascorbate, $CuSO_4$ and *t*-BuOH/H_2O (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 an excess of propargylamine and acetonitrile (Scheme 9).[35]

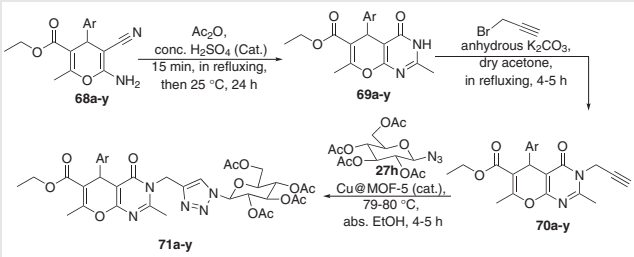
To test their potential selectivity in G4 binding and cell penetration, six carbohydrate naphthalene diimide conjugates (carb-NDIs) were synthesized as G4 ligands. Carb-NDIs have demonstrated some selectivity for G4 structures over DNA duplexes, although various sugar moieties have no impact on determining 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 1,2,3-1*H*-triazole derivatives of 4*H*-pyrano[2,3-*d*]pyrimidine **71a–y** (Scheme 10)[36] by applying click cycloaddition reaction of 3-propargyl-4*H*-pyrano[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-4*H*- pyrano[2,3-*d*]pyrimidine **70a–y** were synthesized by the propargylation of the N–H bond of 4*H*-pyrano[2,3-*d*]pyrimidines **69a–y** in the presence of propargylic bromide, K_2CO_3 in anhydrous acetone. 4*H*-Pyrano[2,3-*d*] pyrimidines



Scheme 9 Synthesis of compounds **62–67**

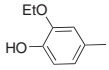
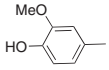
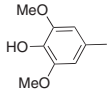
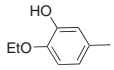
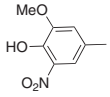
69a–y were also synthesized by ring-closing reaction of 4*H*-pyrano[2,3-*d*] pyrimidine **68a–y** in the presence of acetic anhydride and conc. sulfuric acid.[37–39]



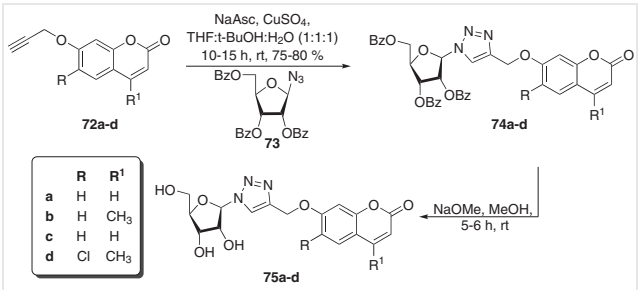
Scheme 10 Synthesis of compounds **71a–y**

All the synthesized compounds **71a–y** were tested in vitro for their ability to inhibit *Mycobacterium tuberculosis* protein tyrosine phosphatase B (MtbPtpB). Six compounds **71g**, **71t**, **71u**, **71v**, **71x** and **71y** were discovered to be active against *M. tuberculosis* PtpB, with an IC_{50} value ranging between 1.56 and 9.52 μM after all of the compounds were subjected to an in vitro inhibitory assessment on MtbPtpB (Table 2). 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. These compounds demonstrated more robust inhibitory action against MtbPtpB (with IC_{50} values <5 μM).

Table 2 IC_{50} Values of against *M. tuberculosis* PtpB

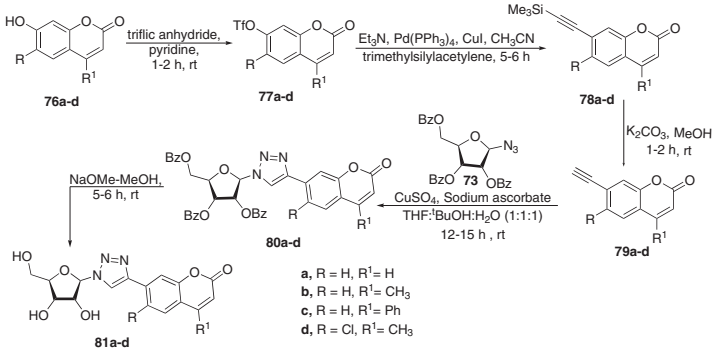
Compounds	Ph ring	IC_{50} (μM)
71g		9.52±1.13
71t		7.94±0.23
71u		7.51±0.33
71v		2.22±0.23
71x		3.53±0.19
71y		1.56±0.21

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-propargyloxycoumarins **72a–d**[41–43] followed by debenzoylation of the compounds **74a–d** (Scheme 11).[44]



Scheme 11 Synthesis of compounds **74a–d** and **75a–d**

Similarly, compounds **81a–d** were synthesized by the click reaction of azidosugar **73** and 7-acetynylcoumarins **79a–d**[45–49] accompanied by debenzoylation of compounds **80a–d** (Scheme 12).

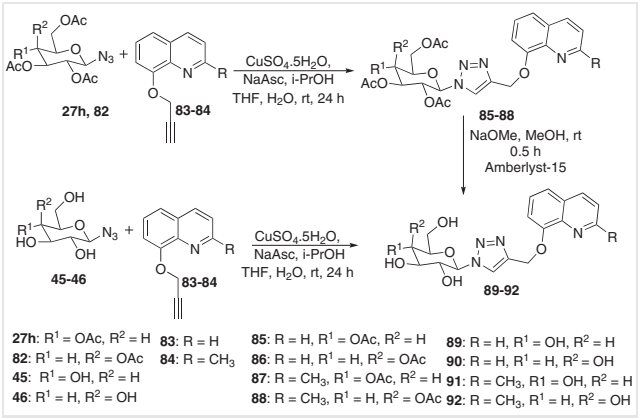


Scheme 12 Synthesis of compounds **80a–d** and **81a–d**

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 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 *M. tuberculosis* susceptible reference strain $H_{37}Rv$. 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 $H_{37}Rv$ 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**)[50] with quinoline derivatives **83** or **84**[51] in the presence of $CuSO_4{\cdot}5H_2O$, NaAsc in the solvent THF/^{i}PrOH (1:1) at room temperature for 24 h (Scheme 13).[52]



Scheme 13 Synthesis of compounds **85–92**

Table 3 MIC, MBC and MBC/MIC Ratio of Some Tested Compounds and First-Line Drugs against *M. tuberculosis* Sensitive Reference Strain $H_{37}Rv$ and Multidrug-Resistant Clinical Isolate 591

Compd	MIC against $H_{37}Rv$ strain (μM)	MIC against MDR clinical isolate 591 (μM)	MBC (μM)		MBC/MIC ratio	
			$H_{37}Rv$	591	$H_{37}Rv$	591
Isoniazid	0.2	2187.5	0.3	–	1.6	–
Rifampicin	0.02	151.9	–	–	–	–
Ethambutol	9.7	73.4	–	–	–	–
Streptomycin	0.43	69	–	–	–	–
74c	5.2	5.2	10.5	–	2	–
75b	5.1	10.3	6.4	11.5	1.25	1.13
75c	4.4	8.9	17.7	–	4	–
81b	16.6	22.2	16.7	22.2	1	1

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).

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

Compounds	% Inhibition at 0.8 mM
85	0
86	0
87	0
88	0
89	43±0.39
90	16±0.36
91	33±0.87
92	12±0.48

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-triazolyl-methyl-indoline-2,3- diones **96a–d** by the click cycloaddition reaction of N-propargylated isatin **93**[53] with different sugar azides (**27h**, **82**, **94**–**95**)[54,55] in the presence of $CuSO_4{\cdot}5H_2O$ (10 mol%), sodium ascorbate (20 mol%) and THF-H_2O (1:1) at room temperature. Furthermore, by the reaction of these 1,2,3-triazolyl-methyl-indoline-2,3-diones **96a–d** 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).[56]

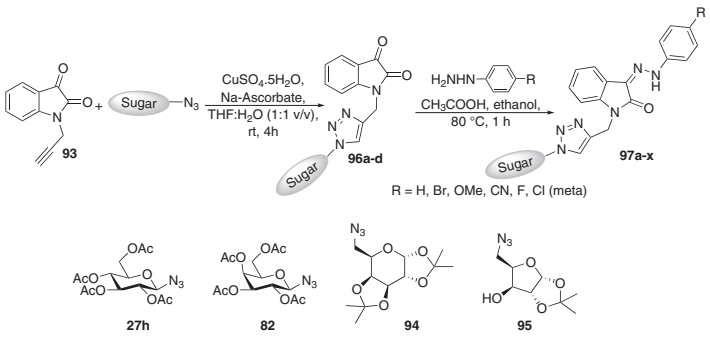
Table 5 Screening of Cytotoxicity of Glycoconjugate Derivatives of 8-Hydroxyquinoline[a]

Compounds	Activity IC_{50} (μM)			
	HeLa[b]	HCT 116[b]	MCF-7[c]	NHDF-Neo[b]
85	59.48±3.55	69.0±2.53	57.69±3.32	57.37±3.19
86	30.98±1.80	22.7±1.58	4.12±0.03	31.91±1.63
87	>800	750.9±28.93	>800	–
88	>800	457.7±15.3	>800	–
89	>800	212.0±7.71	185.34±2.21	247.24±11.64
90	339.35±6.96	265.5±5.02	254.94±8.81	703.45±17.30
91	>800	>800	>800	–
92	>800	>800	>800	–
Doxorubicin	1.2±0.03	5.59±0.14	0.67±0.01	>20

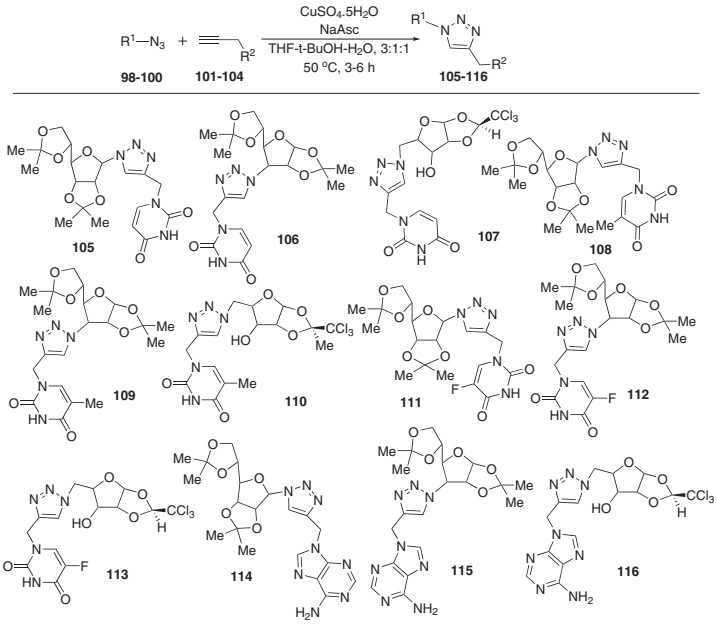
[a] Cytotoxicity was evaluated using MTT assay.
[b] Incubation time 24 h.
[c] Incubation time 72 h

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 *Pf*3D7 strain while some compounds of phenylhydrazono indolinones demonstrated excellent efficacy against the CQ-resistant *Pf*K1 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 $CuSO_4{\cdot}5H_2O$ and sodium ascorbate in the solvent THF/*t*-BuOH/H_2O (3:1:1) at 50 °C for 3–6 h (Scheme 15).[57] In this synthesis, azidofuranoses **98**–**100** were synthesized by three processes, firstly



Scheme 14 Synthesis of compounds **96a–d** and phenylhydrazono indolinones derivatives **97a–x**

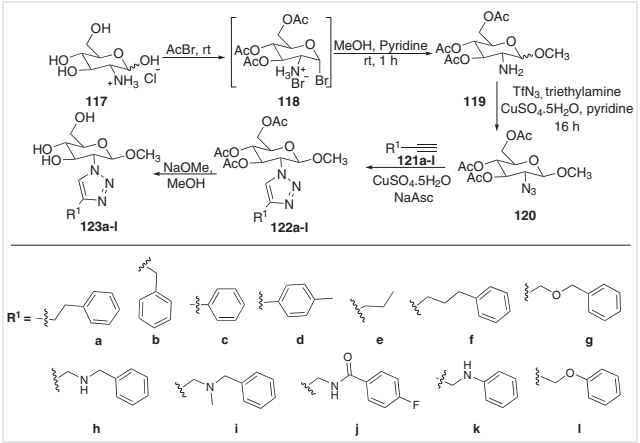


Scheme 15 Synthesis of compounds **105–116**

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[58–61] and propargylated nucleobases **101–104**[62] were synthesized by the propargylation of nucleobases (uracil, thymine, 5-fluorouracil, and adenine) with propargyl bromide in the presence of K_2CO_3 in DMF solvents at 50 °C for 8–12 h.

After the successful synthesis of the triazolylmethyl-linked nucleoside derivatives **105–116**, the cytotoxic potential of each synthesized substance was tested against five distinct human cancer cell lines. Among the tested compounds, nucleoside derivative **111** was shown to be the most effective cytotoxic agent, with promising potential against colon cancer HCT-116 cells (IC_{50} value of 35.6 μM). The nucleoside derivative **108** 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.

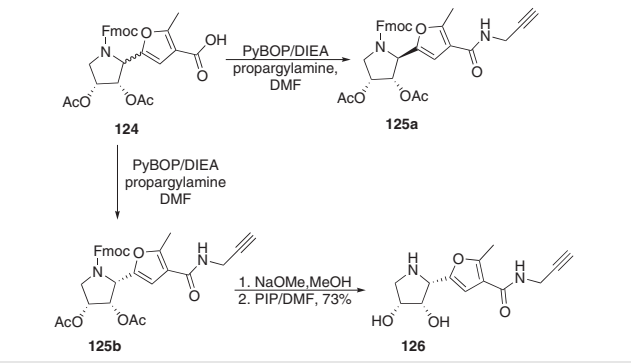
Igual and co-workers synthesized glucopyranoside triazole derivatives **123a–l** using 1,3-dipolar cycloaddition (CuAAC) reaction of the glucosyl azide **120** with terminal alkynes **121a–l** in the presence of $CuSO_4{\cdot}5H_2O$ and sodium ascorbate (Scheme 16).[63] In this synthesis, the first precursor, glucosyl azide, was synthesized by three processes. Firstly the very unstable glycosyl bromide was produced by treating glucosamine hydrochloride **117** with acetyl bromide, and it was then employed immediately in the subsequent glycosidation process to produced methyl 3,4,6-tri-*O*-acetyl-2-amine-2-deoxy-D-glucopyranoside (**119**) in the presence of MeOH and pyridine, which has the free amine group at the C-2 position. Glucosyl azide **120** was then synthesized by the reaction of **119** with triflyl azide solution in the presence of pyridine solvent.[64,65]



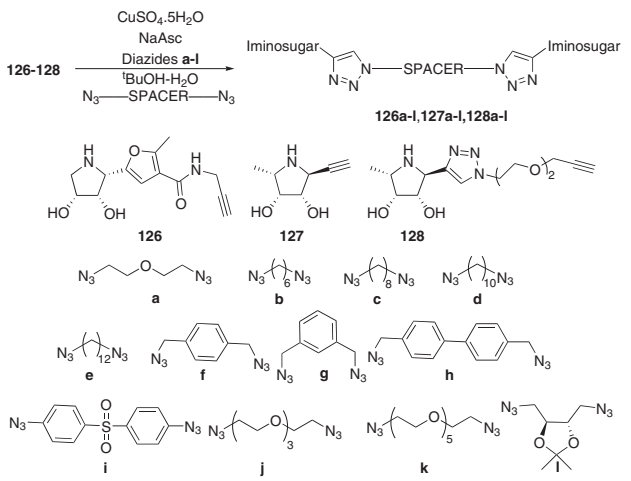
Scheme 16 Synthesis of glucopyranoside triazole derivatives **123a–l**

After the synthesis, compounds **123a–l** 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 **123a** (IC_{50} = 0.50±0.02 μM, OGA), **123k** (IC_{50} = 0.52±0.01 μM, OGA), and **123l** (IC_{50} = 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 $CuSO_4{\cdot}5H_2O$, sodium ascorbate and $^tBuOH/H_2O$ (Scheme 17 and Scheme 18).[66] In this synthesis, precursors alkynyl pyrrolidine **127** and **128** was synthesized from D-lyxose,[67] and (pyrrolidin-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 epimeric acids **124**[68] with propargyl amine.



Scheme 17 Synthesis of precursor **126**



Scheme 18 Synthesis of compounds **126a–l**, **127a–l** and **128a–l**

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 (K_i = 5.8 M), while dimer **127i** was found to be the best inhibitor of α-fucosidases from bovine kidney (K_i = 0.15 nM) and Homo sapiens (K_i = 60 nM) (Table 6).

Table 6 IC_{50} and K_i for Selected Dimers[a]

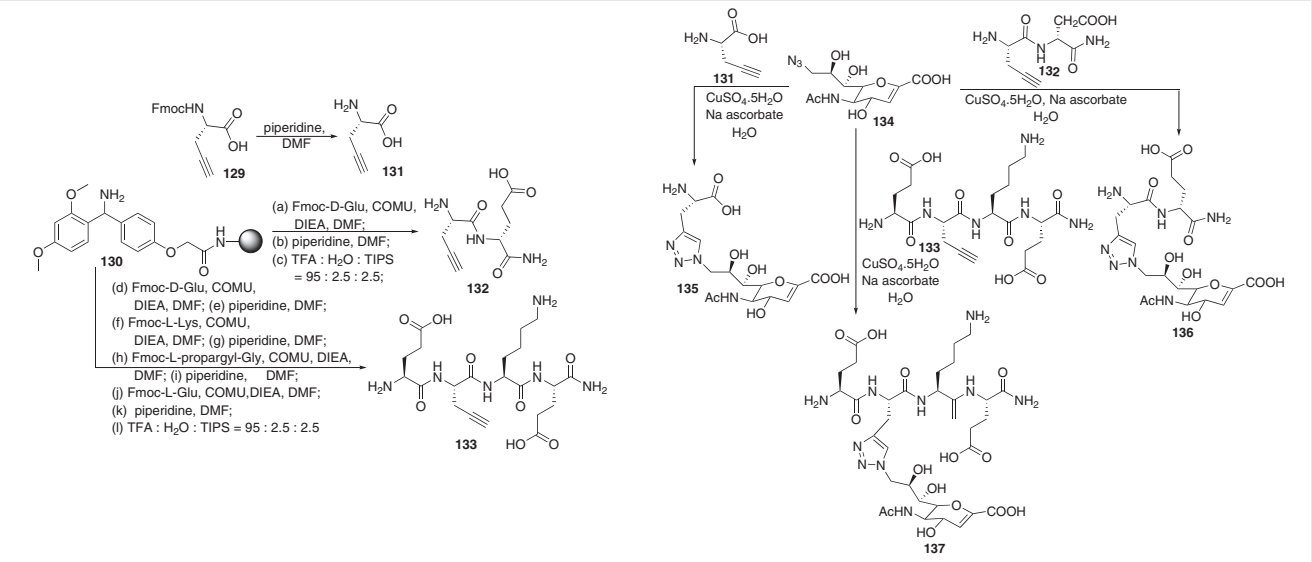
Compounds	α-Fucosidase (bovine kidney)	α-fucosidase (homo sapiens)	β-galactosidase (bovine liver)
Dimer **127i**	0.48×10^{-3} ($K_i = 0.15 \times 10^{-3}$, $K'_i = 0.15 \times 10^{-3}$)	0.21 (K_i = 0.060, K'_i = 0.15)	–[a]
Dimer **126e**	32	–[a]	9.6 (K_i = 5.8)[b]

[a] No inhibition detected at 0.1 mM of inhibitor.
[b] Competitive inhibition was observed for the inhibition of bovine liver β-galactosidase.

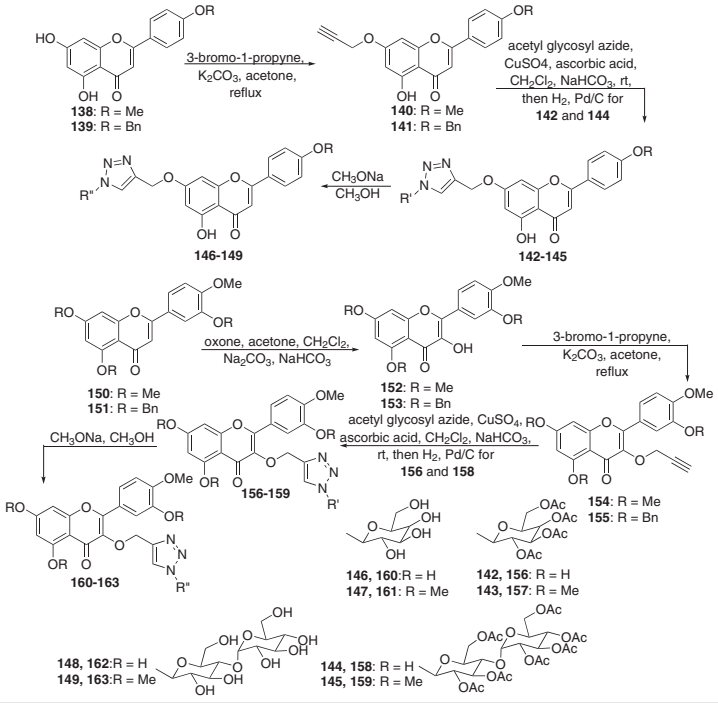
Slack and co-workers synthesized three derivatives **135**, **136** and **137** of 2-deoxy-2,3-didehydro-*N*-acetylneuraminic acid (Neu5Ac2en or DANA) by click cycloaddition reaction of Neu5Ac9N32en **134** with an amino acid L-alanine **131**, a dipeptide of L-alanine and D-glutamate **132**, or a tetrapeptide 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 fluorenylmethyloxycarbonyl (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).[69]

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 flavonoids derivatives **140**, **141** and **154**, **155** with acetylated sugar azides,[70,71] followed by deacetylation with sodium methoxide in anhydrous methanol (Scheme 20).[72] In this synthesis, alkylated flavonoid derivatives **140**, **141** and **154**, **155** were 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 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 IC_{50} values ranging from 14 to 54 μM.

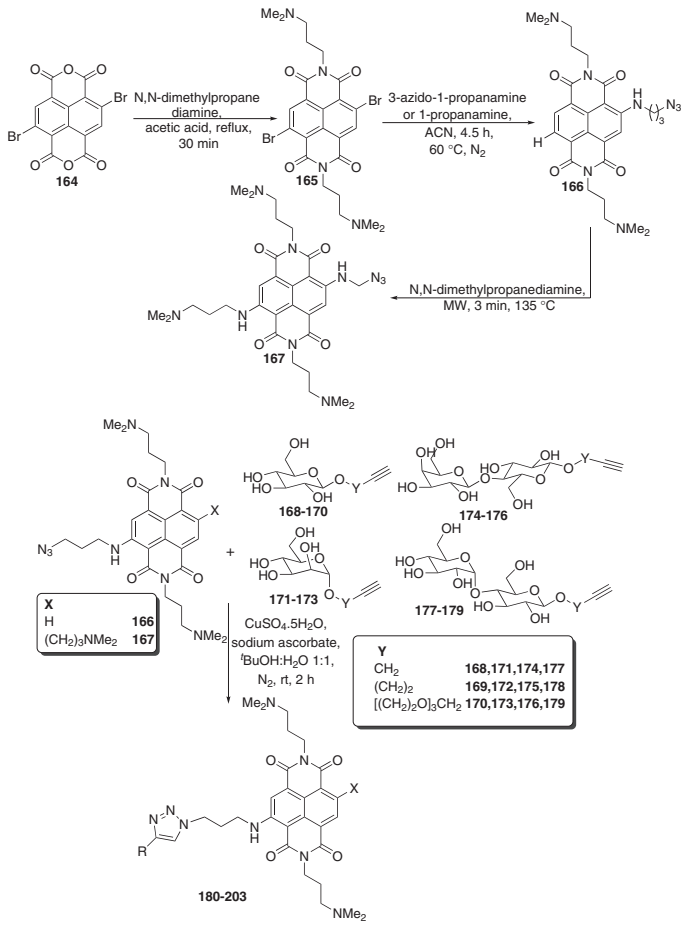


Scheme 19 Synthesis of compounds **135**, **136** and **137**



Scheme 20 Synthesis of 16 flavonoid triazolyl glycosides **142–149** and **156–163**

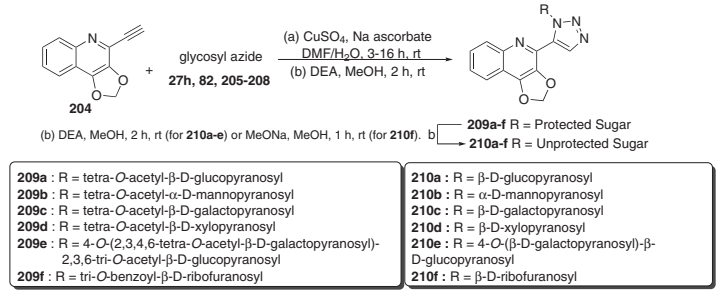
Zuffo and co-workers developed sugar-NDI conjugates (**180–203**) by the click cycloaddition reaction of azide-NDI (**166** and **167**) with alkynyl glycosides (**168–179**)[73–78] in the presence of $CuSO_4{\cdot}5H_2O$, sodium ascorbate and $^tBuOH/H_2O$ (1:1) at room temperature (Scheme 21).[79] 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**[80] from **164**, the 3-azido-1-propanamine 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-



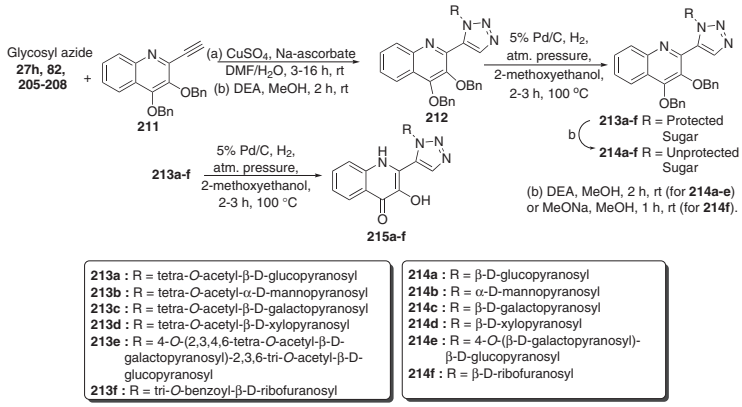
Scheme 21 Synthesis of sugar-NDI conjugates **180–203**

tivities against BSF *Trypanosoma brucei* and promastigote forms of *Leishmania major* of all the derived compounds **180-203**. It was found that β-glc-C2-diNDI (**181**), β-lac-TEG-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 IC_{50} values in the sub-mM range. Additionally, triamino-substituted carb-NDI, α-man-C-triNDI **195**, and diamino-substituted carb-NDI, β-glc-C2-diNDI, β-lac-TEG-diNDI, and β-malt-TEG-diNDI showed good IC_{50} 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-hydroxyquinoloneconjugates **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**[81] with sugar azides **27h**, **82** and **205–208**, respectively, in the presence of $CuSO_4$, Na ascorbate and DMF/H_2O 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/H_2 and 2-methoxyethanol at 100 °C (Scheme 22 and Scheme 23).[81]



Scheme 22 Synthesis of compounds **209a–f** and **210a–f**



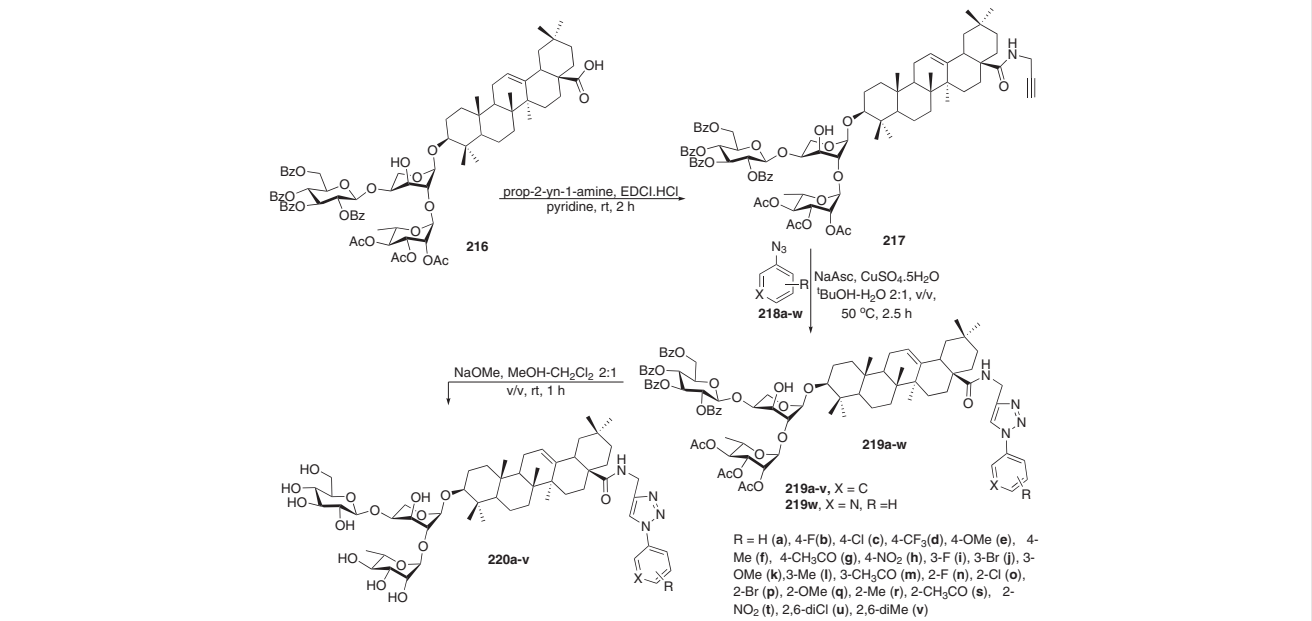
Scheme 23 Synthesis of compounds **213a–f** and **214a–f**

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 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_{100} 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_{100} 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.

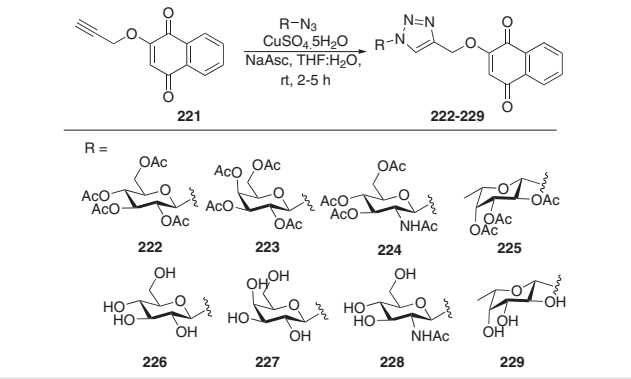
Li and co-workers synthesized 23 hederacolchiside A1 derivatives **220a–v** and **219a–w** by click cycloaddition reaction of compound **217** with differently substituted aromatic azides **218a–w**[82] in the presence of sodium ascrobate, $CuSO_4{\cdot}5H_2O$ and *t*-BuOH–H_2O (2:1, v/v) at 50 °C (Scheme 24).[83] 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_{50} = 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.

Ottoni and co-workers synthesized a series of glycosidic derivatives of lawsone **222–229** by click cycloaddition reaction of 2-*O*-propargyllawsone (**221**)[84,85] with different peracetylated glycosyl azides[86,87] in the presence of $CuSO_4{\cdot}5H_2O$, sodium ascorbate and THF/H_2O at room temperature (Scheme 25).[88]



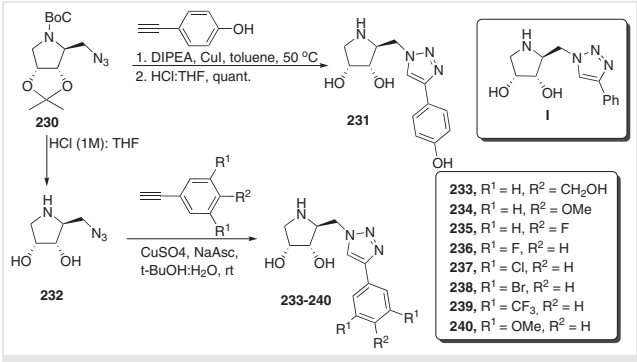
Scheme 24 Synthesis of compounds **220a–v**



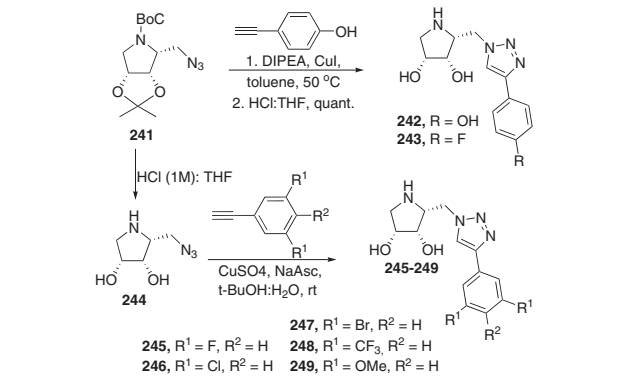
Scheme 25 Synthesis of compounds **222–229**

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 (IC_{50} = 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 (IC_{50}>50 μM) and cytotoxic to SKBR-3 (IC_{50} = 34.74 μM) and MCF-7 (IC_{50} = 38.85 μM).

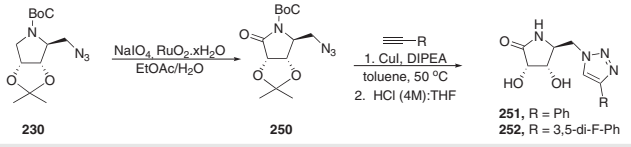
Bailéna and co-workers synthesized a series of pyrrolidine-aryltriazole hybrids **231**, **233–240**, **242–243**, **245–249**, **251–252** and **255**; pyrrolidine-aryltriazoles were synthesized by click cycloaddition reaction of pyrrolidine azides **230**,[89], **232**,[89] **241**,[89] **244**, **250** and **254** with substituted phenylacetylenes in the presence of $CuSO_4{\cdot}5H_2O$, NaAsc and $^tBuOH/H_2O$ at room temperature, respectively (Scheme 26, Scheme 27, Scheme 28 and Scheme 29).[90] Pyrrolidine azide **244** was synthesized by deprotection of **241**, pyrrolidine azide **250**[91] was synthesized by the oxidation of azide **230** in the presence $NaIO_4/RuO_2$ and $EtOAc/H_2O$, and pyrrolidine azide **254**[92] was synthesized by azido transfer reaction of aminomethyl pyrrolidine **253**.



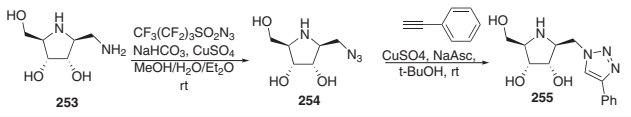
Scheme 26 Synthesis of compounds **233–240**



Scheme 27 Synthesis of compounds **242–243** and **245–249**



Scheme 28 Synthesis of compounds **251–252**



Scheme 29 Synthesis of compound **255**

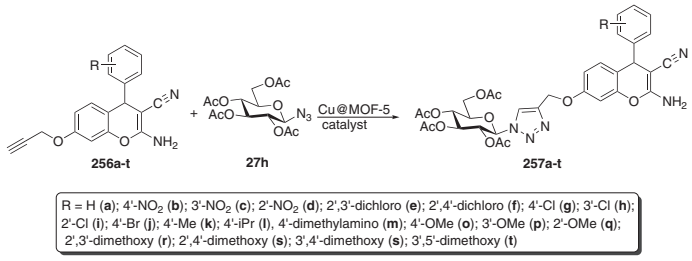
After the synthesis, a study of each triazole derivative's ability to inhibit two human glycosidases (GCase and galactosidase A) was conducted and it was found that β-glucosidase from almonds and GCase were moderately to favourably inhibited by derivatives **I**, **231** and **240** and *para*-substitution at the phenyl group lowered the inhibitory efficacy of the derivatives against GCase in comparison to the original non-substituted drug **I**. 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 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 (IC_{50} = 163 μM for **255** vs. IC_{50} = 8.0 μM for **I**).

Thanh and co-workers synthesized 1*H*-1,2,3-triazole-tethered 4*H*-chromene-D-glucose conjugates **257a–t** by click cycloaddition reaction of 2-amino-7-propargyloxy-4*H*-chromene-3-carbonitriles **256a–t** and tetra-*O*-acetyl-β-D-glucopyranosyl azide **27h**[26,93] in the presence of Cu@MOF-5 catalyst (Scheme 30).[94] The corresponding 2-amino-7-hydroxy-4*H*-chromene-3-carbonitriles and propargyl bromide were used to produce the series of propargyl ethers **256a–t** in the presence of anhydrous K_2CO_3 in dried acetone at 50 °C or NaH in dried DMF at 25 °C, and 2-amino-7-hydroxy-4*H*-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.

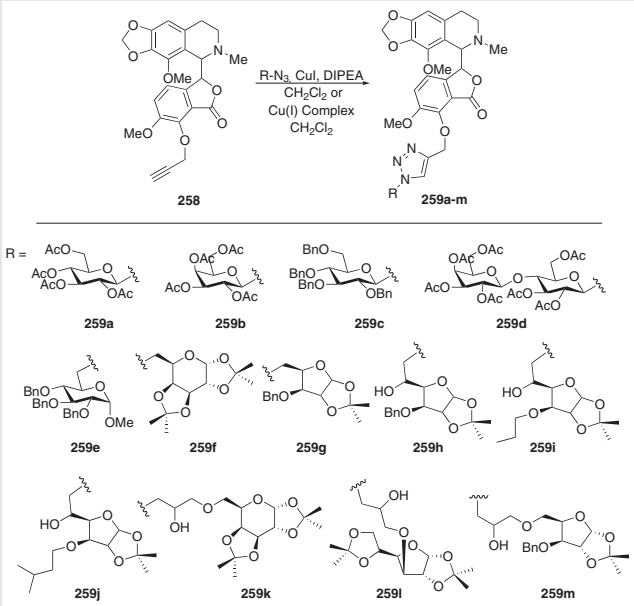
After the synthesis, triazoles **257a–t** were tested in vitro for anti-microorganism activities and it was found that a number of triazoles were active against four strains of Gram-negative, three strains of Gram-positive bacteria (MICs = 1.56–6.25 μM), with MICs ranging from 1.56 to 6.25 μM; several triazoles were active against four strains of fungi. 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.

Mishra and co-workers synthesized 7-O-glycosylated noscapine derivatives **259a–m** by the click cycloaddition reaction of propargylated noscapine derivative **258**[95,96] with different azido sugars in the presence of catalyst, dinuclear copper(I) thiodiacetate complex $[(PPh_3)_2Cu(\mu\text{-tda})Cu(PPh_3)_2]\cdot 6H_2O$ or CuI, DIPEA, CH_2Cl_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.



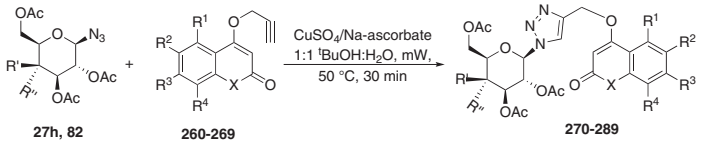
Scheme 30 Synthesis of compounds **257a–t**



Scheme 31 Synthesis of 7-O-glycosylated noscapine derivatives **259a–m**

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 **27h**[98] and 1-azido-2,3,4,6-tetra-*O*-acetyl β-D-galactose **82**[98] with various 4-*O*-propargyl coumarins **260–25** and 4-*O*-propargyl quinolones **266–269** in the presence of $CuSO_4{\cdot}5H_2O$, NaAsc and $^tBuOH/H_2O$ (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 K_2CO_3 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).

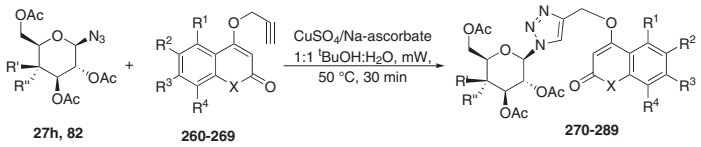
Table 7 Synthesis of Triazole Linked *N*-Glycopyranosides **270–289**



Entry	R′	R′′	R^1	R^2	R^3	R^4	X	Products
1	H/OAc	OAc/H	H	H	H	H	O	**270**/**280**
2	H/OAc	OAc/H	H	OCH_3	H	H	O	**271**/**281**
3	H/OAc	OAc/H	H	Cl	H	H	O	**272**/**282**
4	H/OAc	OAc/H	H	CH_3	H	H	O	**273**/**283**
5	H/OAc	OAc/H	H	Br	H	H	O	**274**/**284**
6	H/OAc	OAc/H	H	H	F	H	O	**275**/**285**
7	H/OAc	OAc/H	H	H	H	H	NH	**276**/**286**
8	H/OAc	OAc/H	H	H	H	F	NH	**277**/**287**
9	H/OAc	OAc/H	H	H	H	NO_2	NH	**278**/**288**
10	H/OAc	OAc/H	H	H	H	CF_3	NH	**279**/**289**

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 (IC_{50} 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).

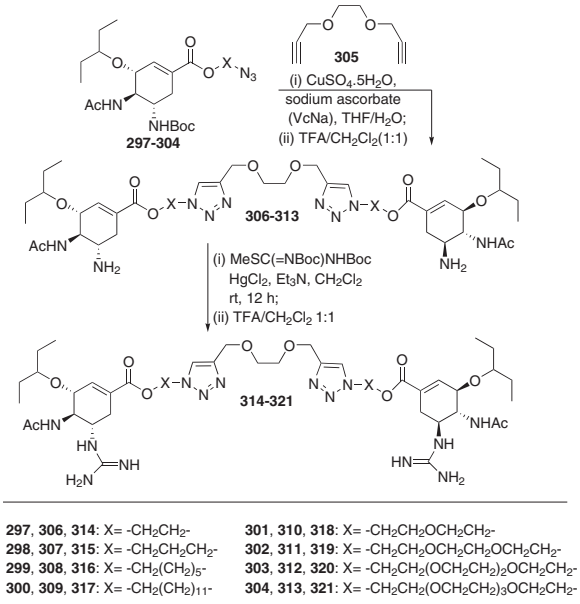
Table 8 Synthesis of Deacetylated Triazole-Linked *N*-Glycopyranosides **290–296**



Entry	R′	R′′	R^1	R^2	R^3	R^4	X	Product
1	OH	H	H	Cl	H	H	O	**290**
2	OH	H	H	CH_3	H	H	O	**291**
3	H	OH	H	H	H	H	O	**292**
4	H	OH	H	OCH_3	H	H	O	**293**
5	H	OH	H	CH_3	H	H	O	**294**
6	H	OH	H	Br	H	H	O	**295**
7	OH	H	H	H	H	NO_2	NH	**296**

Table 9 Anticancer Screening Results

Compounds	Cell viability (%) ± SD	
	HepG2	MCF-7
270	87.55±2.05	81.9±3.39
271	93.45±1.62	96.7±1.2
273	87.95±5.58	34.85±4.73
283	86.1±3.53	88.8±3.25
284	95.55±2.61	89.45±1.90
285	89.6±1.69	90.0±1.13
289	86.5±3.25	90.2±2.40
296	84.8±3.11	93.3±4.66
Doxorubicin	15.3±0.77	15.2±0.84

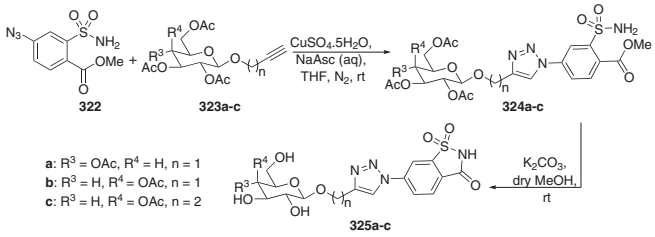


Scheme 32 Synthesis of oseltamivir triazole derivatives **306–321**

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**[102–106] with propargylated ethylene glycol **305** in the presence of $CuSO_4{\cdot}5H_2O$, sodium ascorbate, THF/H_2O, 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 $HgCl_2$, Et_3N, CH_2Cl_2 at room temperature (Scheme 32).[107,108]

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 IC_{50} values were found to be lower than those of the comparable animo divalent analogues **306–313**. This results from significant electrostatic interactions between the more basic gaunidino 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 $CuSO_4{\cdot}5H_2O$, sodium ascorbate and THF/H_2O, followed by deprotection of acetyl groups of sugars in the presence of potassium methoxide, generated in situ from K_2CO_3 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-

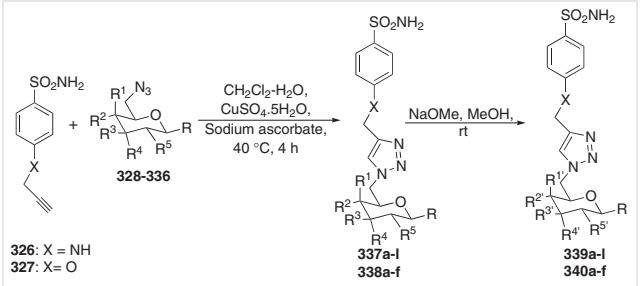


Scheme 33 Synthesis of saccharin-glycohybrids **324a–c** and **325a–c**

thesized by the reaction of β-D-galactose or β-D-glucose pentaacetates with propargylic alcohol in the presence of $BF_3{\cdot}Et_2O$ (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 **328–336**[110–112] with sulfonamide-derived alkyne derivatives[113] **326** or **327** in the presence of $CuSO_4{\cdot}5H_2O$, sodium ascorbate and DCM-H_2O at 40 °C, followed by deprotection of acetyl groups using sodium methoxide in methanol (Scheme 34, Table 10).[114]



Scheme 34 Synthesis of triazole-linked carbohydrate-based sulfonamides **339a–l** and **340a–f**

Table 10 Representation of Various Substituents for Scheme 34

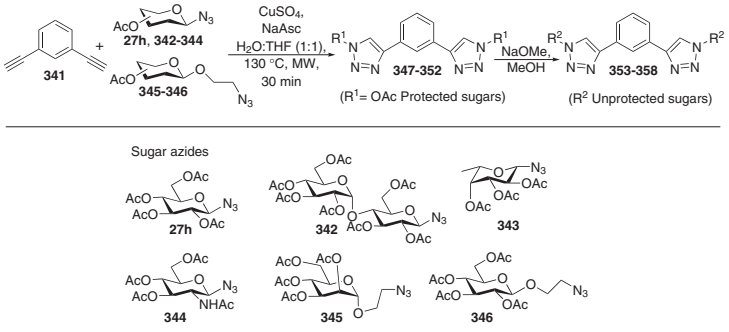
Entry	R	$R^1/R^{1'}$	$R^2/R^{2'}$	$R^3/R^{3'}$	$R^4/R^{4'}$	$R^5/R^{5'}$	X	Compounds
1	$-OCH_3$	H/H	OAc/OH	OAc/OH	H/H	OAc/OH	NH	**337a**/**339a**
2	$-OCH_2CH_3$	H/H	OAc/OH	OAc/OH	H/H	OAc/OH	NH	**337b**/**339b**
3	$-OCH_2CH_2CH_3$	H/H	OAc/OH	OAc/OH	H/H	OAc/OH	NH	**337c**/**339c**
4	$-OCH_3$	OAc/OH	H/H	OAc/OH	H/H	OAc/OH	NH	**337d**/**339d**
5	$-OCH_2CH_3$	OAc/OH	H/H	OAc/OH	H/H	OAc/OH	NH	**337e**/**339e**
6	$-OCH_2CH_2CH_3$	OAc/OH	H/H	OAc/OH	H/H	OAc/OH	NH	**337f**/**339f**
7	$-OCH_3$	H/H	OAc/OH	OAc/OH	H/H	OAc/OH	O	**337g**/**339g**
8	$-OCH_2CH_3$	H/H	OAc/OH	OAc/OH	H/H	OAc/OH	O	**337h**/**339h**
9	$-OCH_2CH_2CH_3$	H/H	OAc/OH	OAc/OH	H/H	OAc/OH	O	**337i**/**339i**
10	$-OCH_3$	OAc/OH	H/H	OAc/OH	H/H	OAc/OH	O	**337j**/**339j**
11	$-OCH_2CH_3$	OAc/OH	H/H	OAc/OH	H/H	OAc/OH	O	**337k**/**339k**
12	$-OCH_2CH_2CH_3$	OAc/OH	H/H	OAc/OH	H/H	OAc/OH	O	**337l**/**339l**
13	$-OCH_3$	H/H	OAc/OH	OAc/OH	H/H	NHTroc/NH_2	NH	**338a**/**340a**
14	$-OCH_2CH_3$	H/H	OAc/OH	OAc/OH	H/H	NHTroc/NH_2	NH	**338b**/**340b**
15	$-OCH_2CH_2CH_3$	H/H	OAc/OH	OAc/OH	H/H	NHTroc/NH_2	NH	**338c**/**340c**
16	$-OCH_3$	H/H	OAc/OH	OAc/OH	H/H	NHTroc/NH_2	O	**338d**/**340d**
17	$-OCH_2CH_3$	H/H	OAc/OH	OAc/OH	H/H	NHTroc/NH_2	O	**338e**/**340e**
18	$-OCH_2CH_2CH_3$	H/H	OAc/OH	OAc/OH	H/H	NHTroc/NH_2	O	**338f**/**340f**

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_{50}) value of 7 nM, being four times more potent than the clinically utilised drug acetazolamide (AAZ) (IC_{50} = 30 nM). Compound **339g** was also found to have 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 hypoxia and normoxic settings.

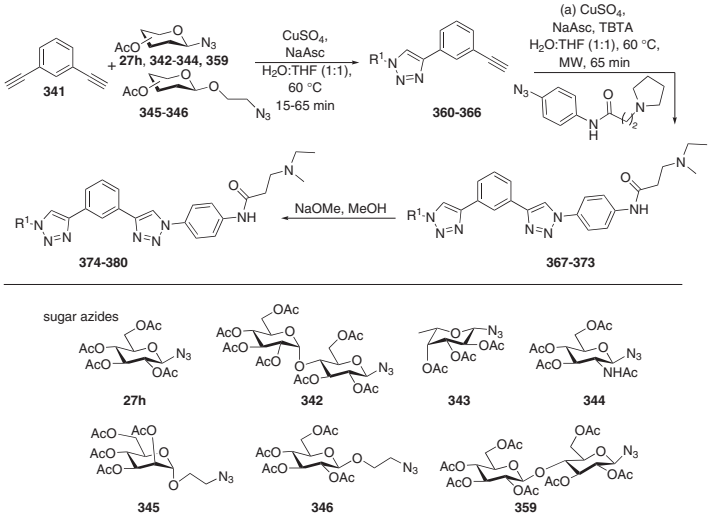
Ruiz and co-workers synthesized symmetric **353–358** and dissymmetric **374–380** carbohydrate-phenyl ditriazole (carb-PDTZ). In this synthesis, symmetric carb-PDTZ **353–358** were synthesized by click cycloaddition reaction of protected 1-azidosugars of glucose **27h**,[115] maltose **342**,[116] fucose **343**,[117] *N*-acetylglucosamine **344**,[118,119] 2-azidoethyl mannopyranoside **345**,[120,121] and 2-azidoethylglucopyranoside **346**[122,123] with diethynylbenzene in the presence of $CuSO_4$, Na-ascorbate, and H_2O/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 $CuSO_4$, Na-ascorbate, and H_2O/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).[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_{50} values than the control PDTZ; likely because certain derivatives lacked compound stability and had reduced cellular absorption.

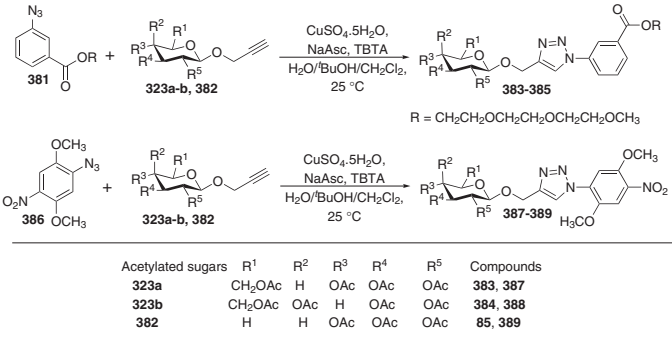
Malah and co-workers synthesized six novel carbohydrate-linked aryl-substituted 1,2,3-triazoles **383–385** and **387–389** by click cycloaddition reaction of 2-(2-(2-me-



Scheme 35 Synthesis of symmetric carbohydrate-phenyl ditriazole derivatives **353–358**



Scheme 36 Synthesis of *meta*-dissymmetric carbohydrate-phenyl ditriazole derivatives **374–380**



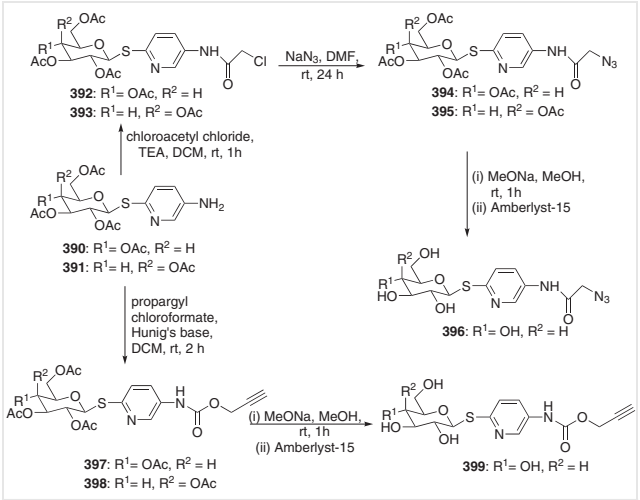
Acetylated sugars	R^1	R^2	R^3	R^4	R^5	Compounds
323a	CH_2OAc	H	OAc	OAc	OAc	**383**, **387**
323b	CH_2OAc	OAc	H	OAc	OAc	**384**, **388**
382	H	H	OAc	OAc	OAc	**85**, **389**

Scheme 37 Synthesis of compounds **383–385** and **387–389**

thoxyethoxy)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 $CuSO_4$, sodium ascorbate, TBTA and H_2O/ t-BuOH/CH_2Cl_2 at 25 °C (Scheme 37).[126]

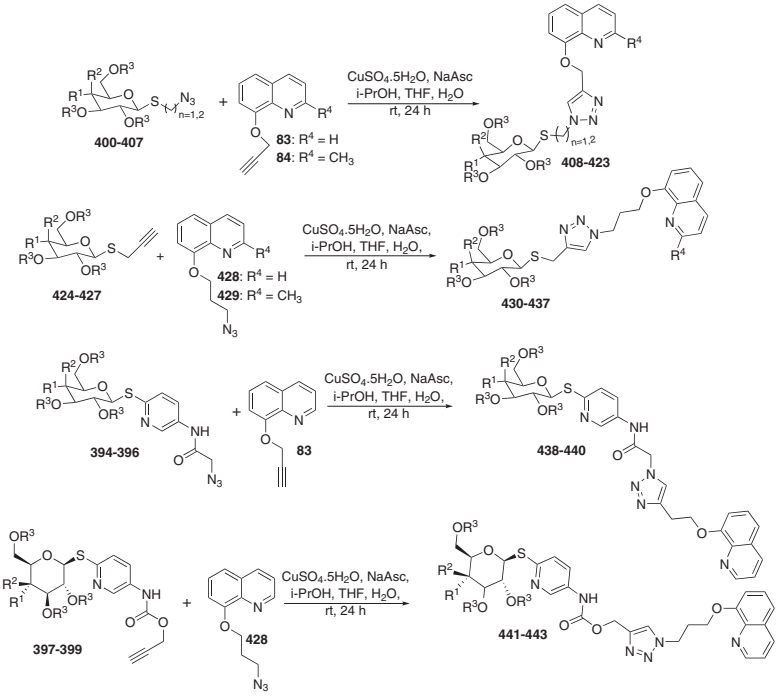
After the synthesis, the antibacterial activity of the synthesized molecules was analysed in comparison to Ampicillin against *S. aureus* and *P. aeruginosa*, while their antifungal activity was studied in comparison to Nystatin against *Candida albicans* and *Aspergillus niger*. Compound **384** was 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 $CuSO_4{\cdot}5H_2O$, NaAsc, *i*-PrOH, THF and H_2O 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 **400–407**[128] with propargyl derivatives of 8-hydroxyquinoline **83–84**,[129] glycohybrids **430–437** were synthesized by click cycloaddition reaction of propargyl derivatives of protected/deprotected-1-thio-β-D-glycopyranosides **424–427**[130] with azide derivatives of 8- hydroxyquinoline **428–429**,[51] 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 38 Synthesis of precursors **394–396** and **397–399**

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 Cu^{2+} ions then it was found that when copper was present, the activity of glycohybrids was greatly enhanced compared to when cells were treated with



Scheme 39 Synthesis of glycohybrids **408–423**, **430–437**, **438–440** and **441–443**

just glycohybrids in the absence of Cu^{2+}; the strongest levels of cytotoxicity of the compounds was observed against the MCF-7 cell line.

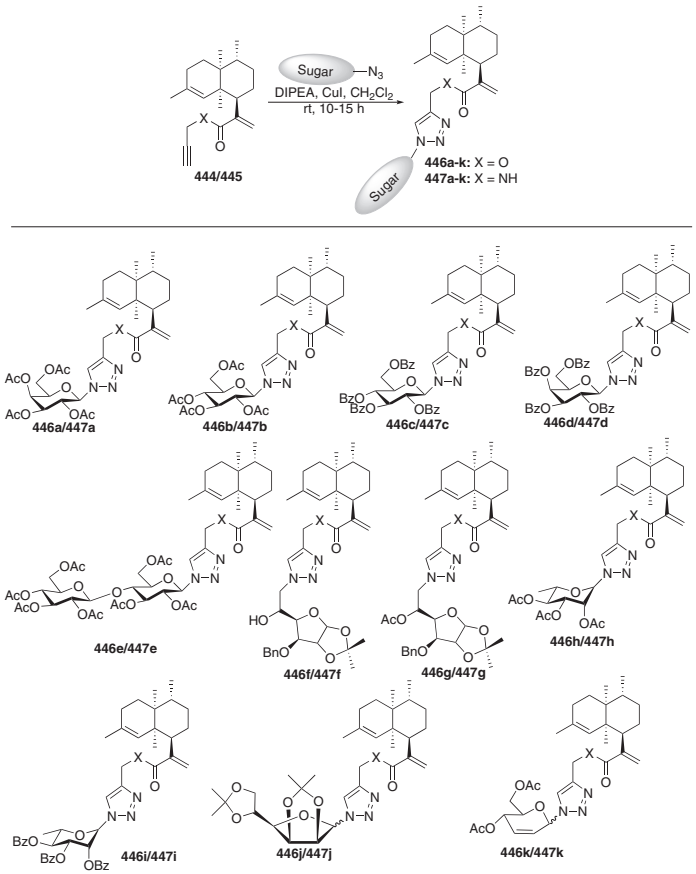
Kotammagari and co-workers synthesized 12-*O*-artemisinic acid-glycohybrids **(446a–k)** and 12-*N*-artemisinic acid-glycohybrids **(447a–k)** by click cycloaddition reaction of 12-*O*-propargylated artemisinic acid **444** and 12-*N*-propargylated artemisinic acid **445** with various sugar azides[70,131–139] in the presence of DIPEA, CuI and DCM at room temperature, respectively (Scheme 40).[140] 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.

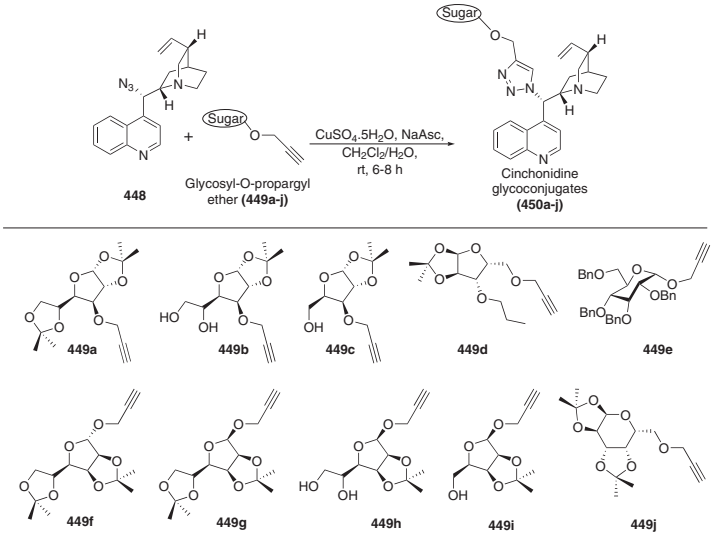
Mishra and co-workers synthesized cinchonidine-glycohybrids **450a–j** by click cycloaddition reaction of 9-epi-9-azido-9-deoxycinchonidine **448**[141] with glycosyl alkynes **449a–j**[142,143] in the presence of $CuSO_4{\cdot}5H_2O$, sodium ascorbate and DCM/H_2O (1:1) at room temperature (Scheme 41).[144] The effective interaction of synthesized compounds with the target proteins in molecular docking experiments for plasmepsin 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 $CuSO_4{\cdot}5H_2O$ and sodium ascorbate in THF at room temperature in good to excellent yields of 74–99% (Scheme 42).[145] Starting compound **451**, in turn, was prepared from the reaction of 1,6-dihydroxyl benzyl glucosides with propargyl bromide and sodium hydride in DMF.

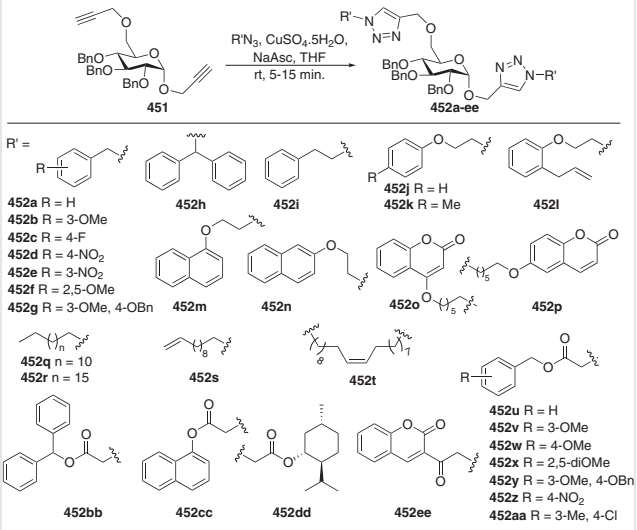
The synthesized 1,6-bis-triazole-benzyl-glucoside derivatives **452a–ee** were tested in vitro for their ability to inhibit α-glucosidase from *Saccharomyces cerevisiae* using acarbose as a control. The synthesized glucoside derivatives displayed moderate to good activity with IC_{50} values ranging from 3.73 to 53.34 μM, which were far better than that of acarbose, with an IC_{50} value of 146.25 μM. Compound **452dd**, with an IC_{50} 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 (IC_{50} 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 IC_{50} 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**

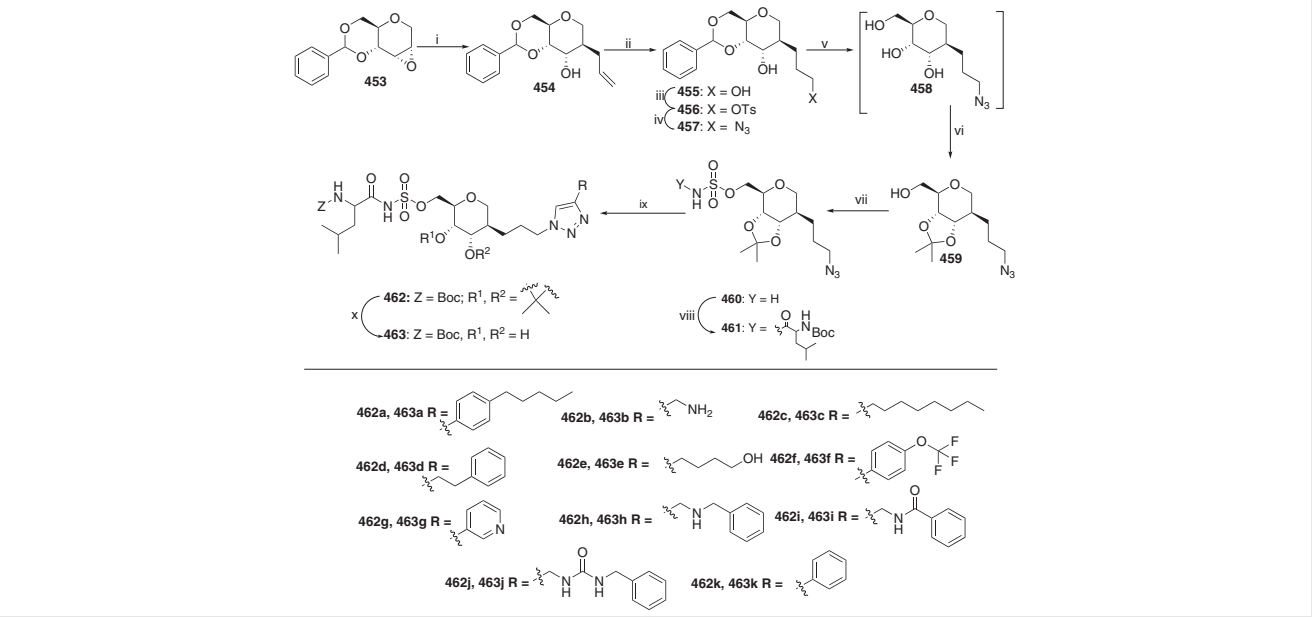


Scheme 42 Synthesis of 1,6-bis-triazole-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside derivatives **452a–ee**

same way, activity was found to decrease in the presence of electron-withdrawing groups like fluoro **452c** and nitro **452d–e** 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*-diaxial 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]

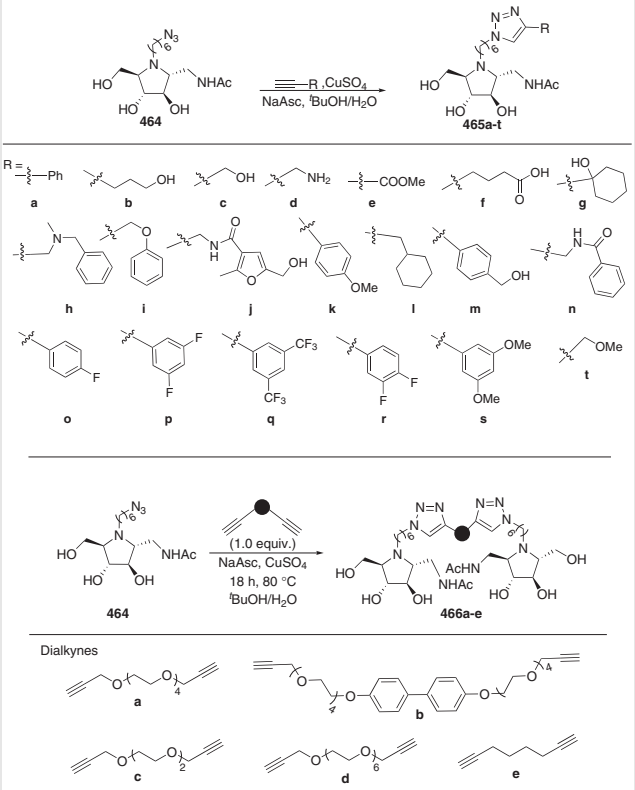
A previously established in-vitro aminoacylation assay was used to confirm that all new leucine linked compounds **463a–k** can inhibit LeuRS by observing the impact on the transfer of ^{14}C-radiolabeled leucine to tRNA^{Leu}. Despite the presence of similar chemical structures, the inhibitory potential of compounds **463a–k** was significantly affected by various triazole moiety replacements. With K_i^{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-



Scheme 43 Synthesis of compounds **463a–k**; (i) (1) CuI, allyl-MgCl, anhyd. THF. –30 °C, 15 min; (2) **1**, anhyd. THF, –30 °C, 1.5 h; (ii) (1) BH_3·THF, anhyd. THF, r.t., 1 h; (2) NaOH, H_2O_2, H_2O, 0 °C to r.t., overnight; (iii) (1) TEA, anhyd. DCM, 0 °C; (2) TsCl, anhyd. DCM, 0 °C to r.t., 2 d; (iv) NaN_3, anhyd. DMF, 55 °C, overnight; (v) PTSA·H_2O, THF/H_2O, 40 °C, 3 d; (vi) PTSA·H_2O, DMP, acetone, r.t., overnight; (vii) (1) chlorosulfonyl isocynate, HCOOH, 0 °C, 30 min; (2) anhyd. MeCN, r.t., 5 h; (3) **7**, DMA, r.t., overnight; (viii) Boc-Leu-OSu, Cs_2CO_3, anhyd. DMF, 0 °C to r.t., 3 d; (ix) CuI, TEA, respective alkyne, DMF, 50 °C, overnight; (x) TFA/H_2O, r.t., 5 h.

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**[147] with the corresponding alkynes in the presence of $CuSO_4{\cdot}5H_2O$, sodium ascorbate and t-BuOH/H_2O (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.



Scheme 44 Synthesis of mono- and dimeric pyrrolidine iminosugars **465a–t** and **466a–e**

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 acetylenes of tacrine (**467**) in the presence of CAN and CuI 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.

Table 11 Inhibitory Potency of Monovalent Triazole Derivatives

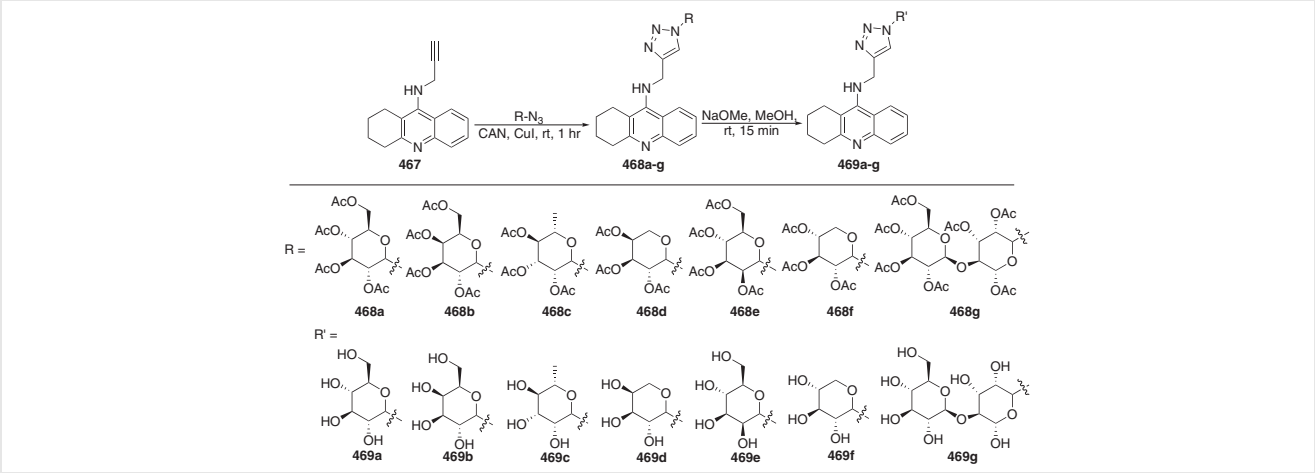
Compound	JbGlcNAcase	
	K_i [nM]	IC_{50} [nM]
465s	56±4	108±8
465t	127±10	246±20
464	327±44	632±85

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 IC_{50} 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.

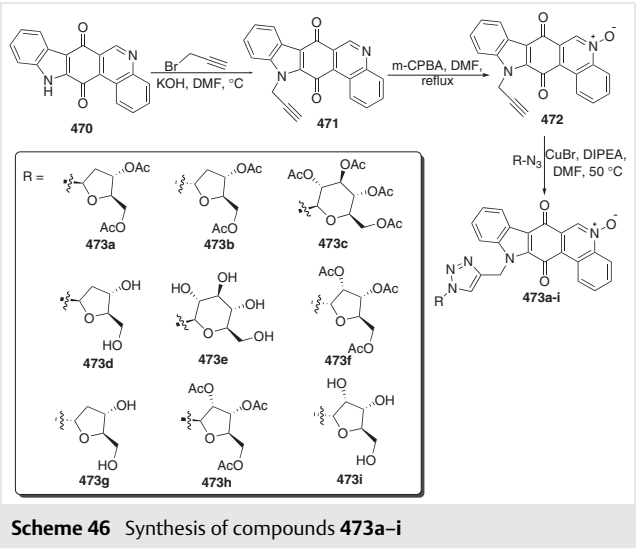
Yang and co-workers synthesized a series of novel Calothrixin A (CAA) derivatives **473a–i** by click cycloaddition reaction of compound **472** with different anomeric sugar azides in the presence of CuBr, *N*,*N*-diisopropylethylamine (DIPEA) and DMF at 50 °C (Scheme 46).[150] In this synthesis, compound **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-SY5Y 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 IC_{50} values of 20 and 50 nM, respectively, surpassing CAA, and showed no effect on human normal cells (IC_{50} > 800 nM, against 293T).

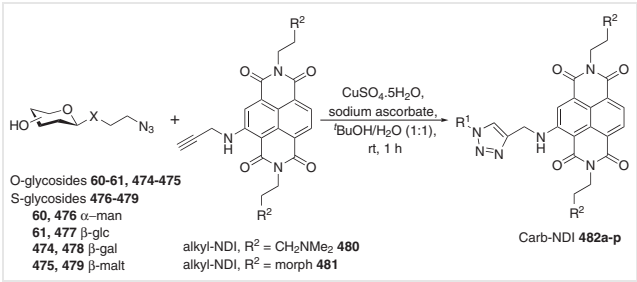
Reche and co-workers synthesized a series of carbohydrate-naphthalene diimide (carb-NDIs) conjugates **482a–p** by click cycloaddition reaction of N-propargylated NDI **480** and **481** with 2-azidoethyl O-glycoside derivatives **60–61**, **474–475**[35,152,153] and 2- azidoethyl S-glycoside derivatives **476–479**[154] in the presence of $CuSO_4{\cdot}5H_2O$, sodium ascorbate and t-BuOH/H_2O (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-



Scheme 45 Synthesis of compounds **468a** to **469g**



Scheme 46 Synthesis of compounds **473a–i**



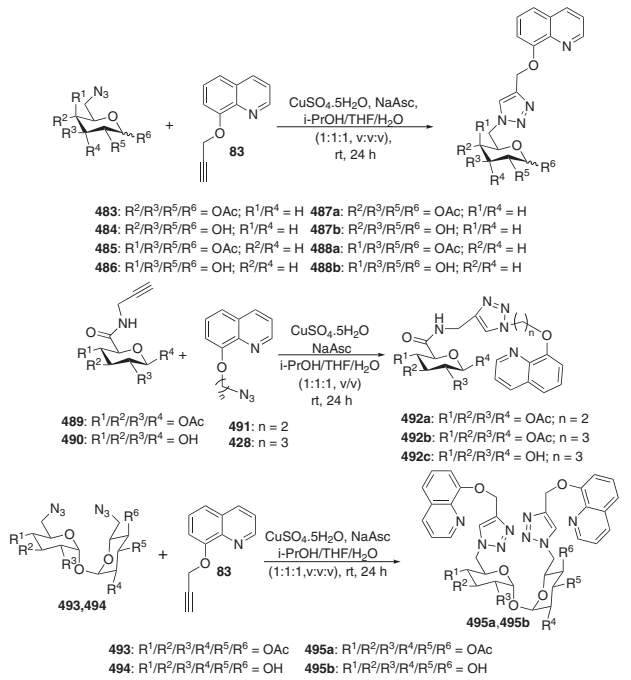
Scheme 47 Synthesis of carb-NDIs **482a–p**

naphthalentetracarboxylic 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-NMe_2 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 **282l** (β-malt-S-C2-NDI-NMe_2), 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**, **494**[160,161] with 8-(2-propyn-1-yloxy) quinoline **83**,[52,129] and sugar derivatives **489**, **490**[162] with 8-(2- azidoethoxy)quinoline **491**,[52,129] and 8-(3-azidopropoxy)quinoline **428**[52,129] in the presence of $CuSO_4{\cdot}5H_2O$, NaAsc, i-PrOH/THF/H_2O (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 utilising 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.

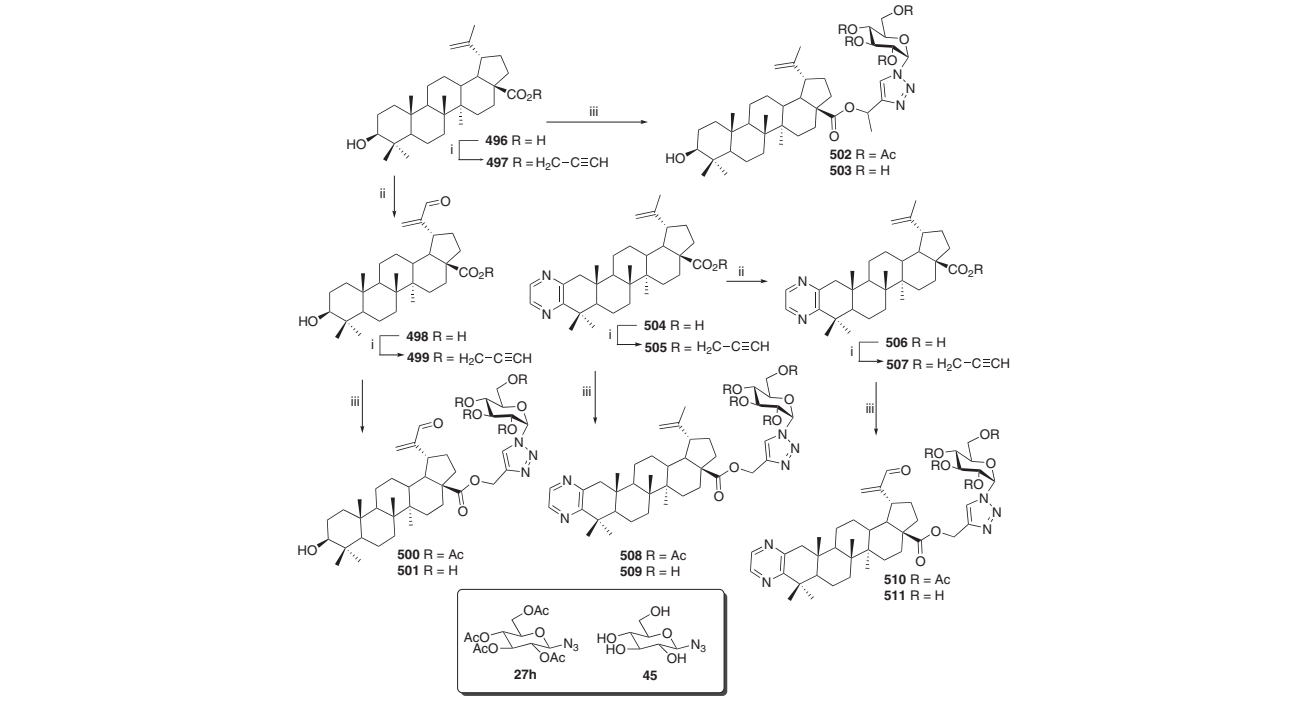


Scheme 48 Synthesis of type **487**, **488**, **492** and **495** glycohybrids

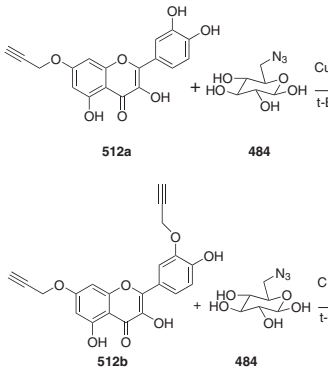
Hodon and co-workers synthesized a series of glucose conjugates **500–503**, **508–511** by click cycloaddition of the corresponding terpenic propargyl esters (**497**, **499**, **505** and **507**) with 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl azide **27h** or β-D-glucopyranosyl azide **45**[164] in 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 $CuSO_4{\cdot}5H_2O$, sodium ascorbate and t-BuOH/H_2O at 50 °C, respectively (Scheme 50).[166] 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 $Na_2B_4O_7{\cdot}10H_2O$ and $NaHCO_3$ at 50 °C.



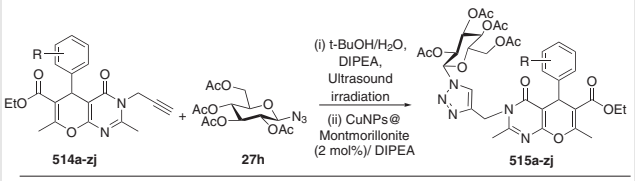
Scheme 49 Synthesis of triterpenoid conjugates with glucose **500–503** and **508–511**. (i) Propargyl bromide, K_2CO_3, DMF, r.t. (ii) SeO_2, 2-methoxyethanol, reflux; (iii) **27h** or **45**, CuI, DMF, 40 °C.



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

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 4*H*-pyrano[2,3-*d*]pyrimidine **515a–zj** by click cycloaddition reaction of polysubstituted 4*H*-pyrano[2,3-*d*]pyrimidines **514a–zj**[167] containing a propargyl group on the nitrogen atom, with peracetylated D-glucopyaranosyl azide **27** by using ultrasound, CuNPs@Montmorillonite as a catalyst, and DIPEA, in the presence of ^{t}BuOH/H_2O at 25 °C (Scheme 51).[168]

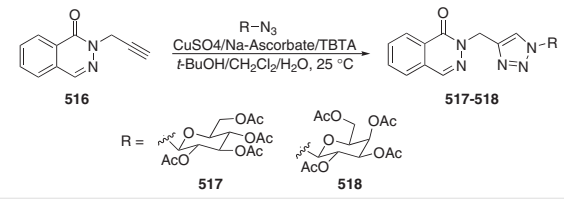


R = H (**a**); 3-NO_2 (**b**), 4-NO_2 (**c**); 3-Cl (**d**); 4-Cl (**e**); 2,3-diCl (**f**); 2,4-diCl (**g**); 4-Br (**h**); 2-Cl-5-NO_2 (**i**); 3-Cl-5-NO_2 (**j**); 4-Cl-3-NO_2 (**k**); 5-Cl-2-NO_2 (**l**); 2-Cl-4-Me (**m**); 3-Cl-4-Me (**n**); 2-Cl-4-OMe (**o**); 4-Cl-2-OMe (**p**); 5-Cl-2-OH-3-NO_2 (**q**); 4-OH-3-OMe-5-NO_2 (**r**); 3-OH (**s**); 4-OH (**t**); 2,3-diOH (**u**); 2,4-diOH (**v**); 3,4-diOH (**w**); 3-OMe (**x**); 4-OMe (**y**); 2,3-diOMe (**z**); 2,4-diOMe (**za**); 2,5-diOMe (**zb**); 2,6-diOMe (**zc**); 4-OH-3-OMe (**zd**); 3-OEt-4-OH (**ze**); 2-OH-3-OMe (**zf**); 2-OH-4-OMe (**zg**); 3-OH-4-OMe (**zh**); 4-OEt-3-OH (**zi**); 4-OH-3,5-diOMe (**zj**)

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

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 **515zg** against MCF-7, **515s**, **515t**, **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 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 azides[169–173] in the presence of $CuSO_4.5H_2O$, sodium ascorbate and tris(benzyltriazolylmethyl)amine in H_2O/tBuOH/CH_2Cl_2 (Scheme 52).[174] Compounds **517–518** were tested for their biological activity and compound **518** was found to have antiproliferative activity.



Scheme 52 Synthesis of compounds **517–518**

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 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 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, 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.

Conflict of Interest

The authors declare no conflict of interest.

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