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Chapter 9: Glycoconjugated heterocyclic compounds: synthesis and applications

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Abstract: The conjugation of biologically active heterocycles with carbohydrates to form glycohybrids has gained attention as a valuable strategy for developing carbohydrate-based therapeutic agents that harness the distinctive properties of both components. This chapter presents extensive information of glycoconjugated heterocycles developed in the last decade and highlights the important synthetic strategies used for their construction. Furthermore, the chapter describes comprehensive analysis of biological activities associated with these class molecules; with a focus on structures that modulate pharmacological efficiency and therapeutic significance. The chapter encompasses the molecular hybridization of biologically privileged heterocycles—such as imidazole, oxadiazole, pyrazole, thiadiazole, pyridine, pyrimidine, indole, benzofuran, coumarin, and quinoline—with carbohydrate moieties, and investigates the resultant conjugates for their diverse biological activities.

Keywords: Biological activity, carbohydrate, glycohybrids, heterocycles, synthesis.

1 Introduction

Heterocyclic compounds are a widely studied class of compounds for their varied pharmacological activities, which makes them important motifs in drug discovery and development. Their

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structural flexibility and capability to interact with diverse biological targets has enhanced their importance in medicinal chemistry [Ogawa et al., 2020]. More than 90% of new drugs contain heterocyclic moieties, which fill the gap between chemistry and biology, where a great scientific research and applications takes place. The US Food and Drug Administration approved 33 % of small molecules with nitrogen heterocycles in 2023 [Torre et al.,2024]. In our chapter, we highlight a wide range of recently synthesized bioactive heterocycles that represent a promising new phase in the development of therapeutics with diverse biological activities, including antifungal, anti-inflammatory, antibacterial, antiviral, antioxidant, anticonvulsant, anthelmintic, antipyretic, anti-allergic, antihistamine, herbicidal, anticancer, antihypertensive, and anti-leprosy properties [Al-Mulla, 2024].

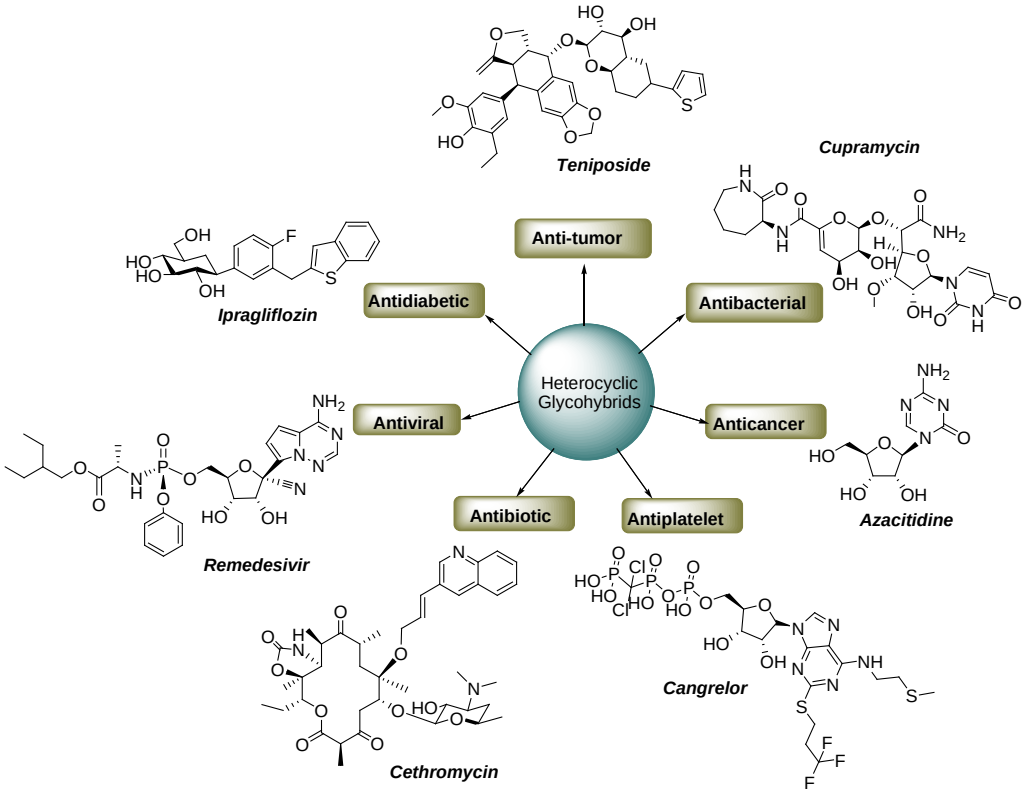


Fig. 1. Application of Heterocyclic glycohybrids

In the form of glycoconjugates, carbohydrates are a significant class of biomolecules found inside or on the surface of cells. These molecules have been found to be essential for many pathological and physiologically important biological processes, including cellular adhesion, migration, invasion, communication, bacterial/viral infection, tumour metastasis and posttranslational protein modifications [Varki, 2017]. Therefore, the

development of advanced antibacterial, antiviral, anticancer, and anti-inflammatory treatments, as well as vaccines and diagnostic tools, depends critically on the strategic design of glycoconjugates and carbohydrate mimetics that target these carbohydrate-mediated actions [Shailja and Singh, 2024]. The most noteworthy techniques in medicinal chemistry in the modern era of drug discovery has been molecular conjugation, which involves combining two active pharmacophoric units of either comparable or dissimilar bioactive units into a single molecular framework [Xu et al., 2019]. Comparing the resultant hybrid scaffolds to the parent pharmacophoric units, it was discovered that they generally showed better efficacy and less toxicity. Recent advances in synthetic chemistry have highlighted glycol-heterocyclic hybrid compounds as key targets, owing to their multifunctional architecture and promising bioactive profiles [Tiwari, 2020; Weymoth, 1997]. Consequently, glycol-heterocyclic hybrid compounds hold immense potential in the fields of new drug discovery and the development of innovative biomaterials, making the exploration and interest in searching for efficient synthetic methods essential for advancement in the field [Delopst et al., 2018].

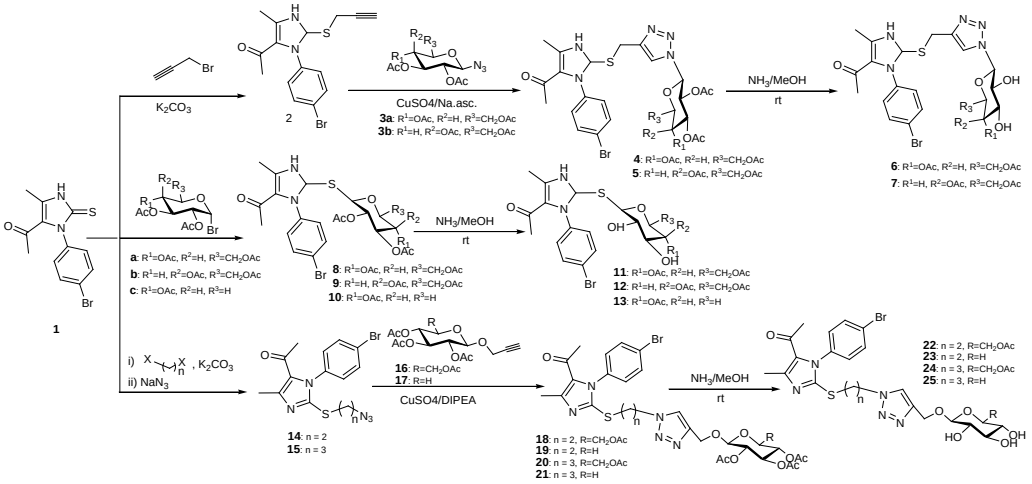
Several innovative drugs carbohydrate-based heterocycles are already in the market. Teniposide was the first carbohydrate-based heterocyclic molecule to be used as a drug with anticancer activity that had a carbohydrate moiety and a thiophene ring. In 1967, it was initially employed in clinical trials [Clark and Selvin, 1987; Cascinu et al., 1997]. In 2004, the FDA authorized azictidine having a ribose sugar attached to the pyrimidine ring *via* a glycosidic bond, for the treatment of myelodysplastic syndrome [Kaminskas et al., 2005]. The SGLT2 inhibitor Ipragliflozin was authorized in Japan in 2014 and has a fluorobenzene moiety connected to glucose and a benzothiophene unit [Poole and Dungo, 2014]. Capuramycins are uracil nucleosides having an unsaturated uronic acid moiety connected by means of an amide linkage to a caprolactame residue. It demonstrates rapid bacterial activity against several different mycobacterial species by inhibiting translocase I [Ready et al., 2008]. The quinoline-linked ketolide cethromycin shown exceptional antibacterial activity against *Francisella tularensis*, *Streptococci*, *B. anthracis*, *Y. pestis*, and *S. pneumoniae* [Rosenzweig et al., 2011; Frean et al., 2003; Hammerschlag et al., 2008]. Cethromycin was expedited for FDA clearance in 2009 as an orphan medication for the prevention of plague, tularemia, and anthrax inhalation. Cangrelor, an injectable antiplatelet medication that reversibly blocks the P2Y12 receptor to prevent blood clots in coronary arteries, was authorized by the FDA in 2015 [Marcano and Ferreiro, 2016; Vaduganathan et al., 2017]. One of the most effective anti-COVID-19 drugs remdesivir an adenosine analog with ribosyl moiety was developed by Gilead Sciences using ProTide technology. An Emergency Use Authorization has been granted by FDA the use of Remdesivir for the treatment of acute COVID-19 cases in hospitals [Ison et al., 2020] (Fig 1).

2. Synthetical study on five-membered heterocycles linked to carbohydrates

2.1 Imidazole glycohybrids

The imidazole ring is extremely polar, amphoteric, has several binding sites, and is easily able to donate or absorb protons. It can interact with a wide range of proteins present in living systems. Numerous pharmacologically relevant medications, such as metronidazole, pretomanid, ketoconazole, tipifarnib, megazole, nafimidone, losartan, and others, contain imidazole scaffold. Imidazole-based glycohybrids have been hailed as having one of the most promising biological profiles in the pharmaceutical industry. This profile includes antibacterial, antifungal, anti-Alzheimer's, antitubercular, antioxidant, antiulcer, antithyroid, antimalarial, anti-HCV, anti-HIV, and anticancer activities [Rulhania et al., 2021].

A new series of triazole-imidazole glycosyl hybrid analogues was recently synthesized by El-Sofany et al. using the click chemistry synthetic method. The compound 1-(3-(4-bromophenyl)-5-methyl-2-thioxo-2,3-dihydro-1*H*-imidazol-4-yl)ethan-1-one (compound **1**) was synthesized and subsequently reacted with propargyl bromide to form compound **2**. It was subjected to click reaction conditions with azido-functionalized *N*-acetyl glycosides to furnish the corresponding 1,2,3-triazole-linked *N*-acetylated glycosides (compounds **4** and **5**). These intermediates were further treated with methanolic ammonia, leading to the deacetylation and formation of free hydroxyl 1,2,3-triazole *N*-glycosides (compounds **6** and **7**, respectively). In another route, compound **1** was treated with two alkyl halides: 1,2-dibromoethane 1,3-dichloropropane and sodium azide to afford the corresponding azido derivatives **14** and **15** which underwent click reaction with terminal alkynyl glycosides to yield the 1,2,3-triazole-linked *C*-glycosides (compounds **18**–**21**). These triazole *C*-glycosides were then subjected to methanolic deacetylation, resulting in the formation of free hydroxyl thioglycosides (compounds **22–25**). In a parallel synthetic route, thioglycoside derivatives of compound **1** were prepared by glycosylation with acetylated glycosyl bromides, affording the *S*-glycoside analogs **8–10**, which, upon deacetylation, gave the corresponding free hydroxyl imidazolo-*S*-glycosides **11–13** (Scheme 1).

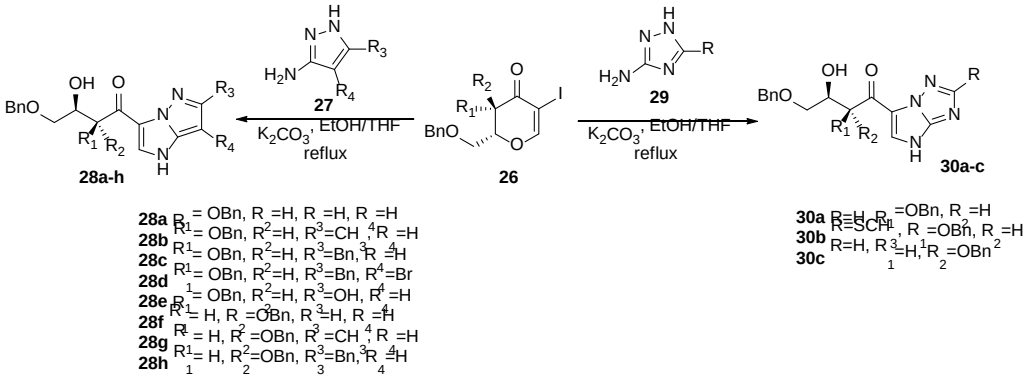


Scheme 1. Synthetic route for triazole-imidazole glycosyl hybrid

The synthesized compounds were evaluated for their anticancer activity against human breast cancer cell lines MCF-7 and MDA-MB-231 using the colorimetric MTT assay. Among the tested compounds, **6**, **12**, and **22** exhibited the most potent cytotoxicity, showing effects comparable to the reference drug doxorubicin [El-Sofany et al., 2022].

2.2 Pyrazole glycohybrids

Pyrazole and its derivatives have ability to modulate various biological targets through diverse substitution patterns. The incorporation of sugar moieties into pyrazole scaffolds not only improves their pharmacokinetic profiles but also facilitates targeted interactions with specific biological receptors or transporters [Ebenezer et al., 2022]. V. K. Mishra and their team reported an efficient synthetic protocol for the incorporation of bioactive scaffolds with carbohydrates, leading to a new class of imidazo-pyrazole (**28a-h**) and imidazo-triazole glycohybrid (**30a-c**) molecules (Scheme 2). The newly synthesized glycohybrids were evaluated for their anticancer potential, with select compounds exhibiting submicromolar activity against the MCF-7 breast cancer cell line [Mishra et al., 2024].

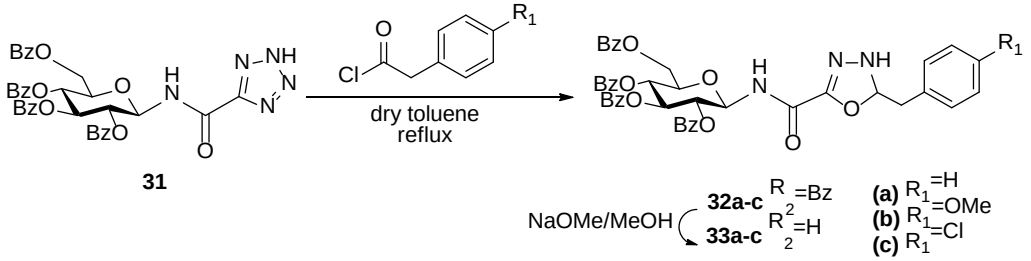


Scheme 2. Synthetic route for imidazo-pyrazole and imidazo-triazole glycohybrids

2.3 Oxadiazole glycohybrids

Over the last decade, approximately 686 patents have been filed on oxadiazole pharmacophore and its importance [Bostrom et al., 2020]. The 1,3,4-oxadiazole pharmacophore has gained greater attention over years due to exhibition of wide range of biological profiles owing to the existence of –N=C–O–toxophoric linkage [Rayam et al., 2020]. 2,5-Disubstituted oxadiazole subsidiaries have been encompassed with promising pharmacological profiles such as anticancer [Zhang et al., 2014], antimicrobial [Jha et al., 2010], antiepileptic [Rajak et al., 2013], analgesic [Ramaprasad et al., 2010], and sedative properties [Gollapalli et al., 2015]. Few compounds viz., zibotentan, ataluren, and raltegravir comprising oxadiazole as core nucleus are in the late stages of clinical trials substantiating the valuable privileges of the scaffold.

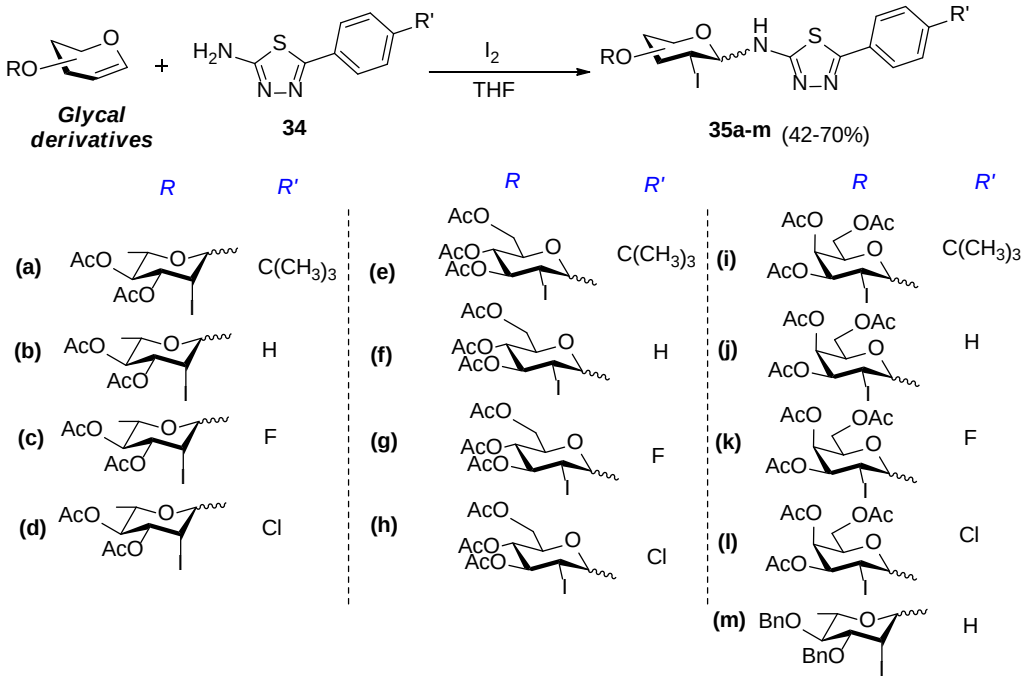
C-glucosyl(1,3,4-oxadiazolyl)arenes **33a-c** were reported by Sipos et al. by refluxing benzoyl-protected *N*-glucosyl tetrazole-5-carboxamide (**31**) with substituted phenylacetyl chlorides, followed by the removal of benzoyl groups (Scheme 3). These compounds along with *C*-glucosyl(heterocycle)arenes were tested for their ability to inhibit SGLT1/2 and GP. The most promising analogue among them was 5-benzyl-2-(β-D-glucopyranosyl)-1,3,4-oxadiazole (**33a**), which demonstrated no discernible inhibition of GP and an IC_{50} of 2.21 μM for SGLT2 and 23.72 μM for SGLT1 [Sipos et al., 2021].



Scheme 3. Synthetesis of *C*-glucosyl(1,3,4-oxadiazolyl)arenes as antidiabetic profile.

2.4 Thiadiazole glycohybrids

The thiazolidine ring system is a key structural component in numerous compounds with significant applications in medicinal and pharmaceutical chemistry. Several approved drugs and drug candidates, including Pioglitazone, Epalrestat, Letosteine, and Tidiacic, feature a thiazolidine nucleus as a core structural component. The presence of the N–C–S linkage in active compounds has been associated with their pronounced antimicrobial and anti-HIV properties [Mishra et al., 2012; Patela et al., 2012; Zurawska et al., 2021]. In a recent study, Zurawska et al. successfully synthesized *N*-glycosides of 2-amino-1,3,4-thiadiazole (**35a-m**) through glycosylation of with variously protected glycals using 2-amino thiadiazole using two equivalents of iodine catalyst under mild conditions (Scheme 4). MCF-7, HeLa, and HCT116 tumor cell lines were used in the cytotoxicity test. The results showed that the compounds **35a-m** were effective against HeLa and HCT116 but not against MCF-7 [Zurawska et al., 2021].

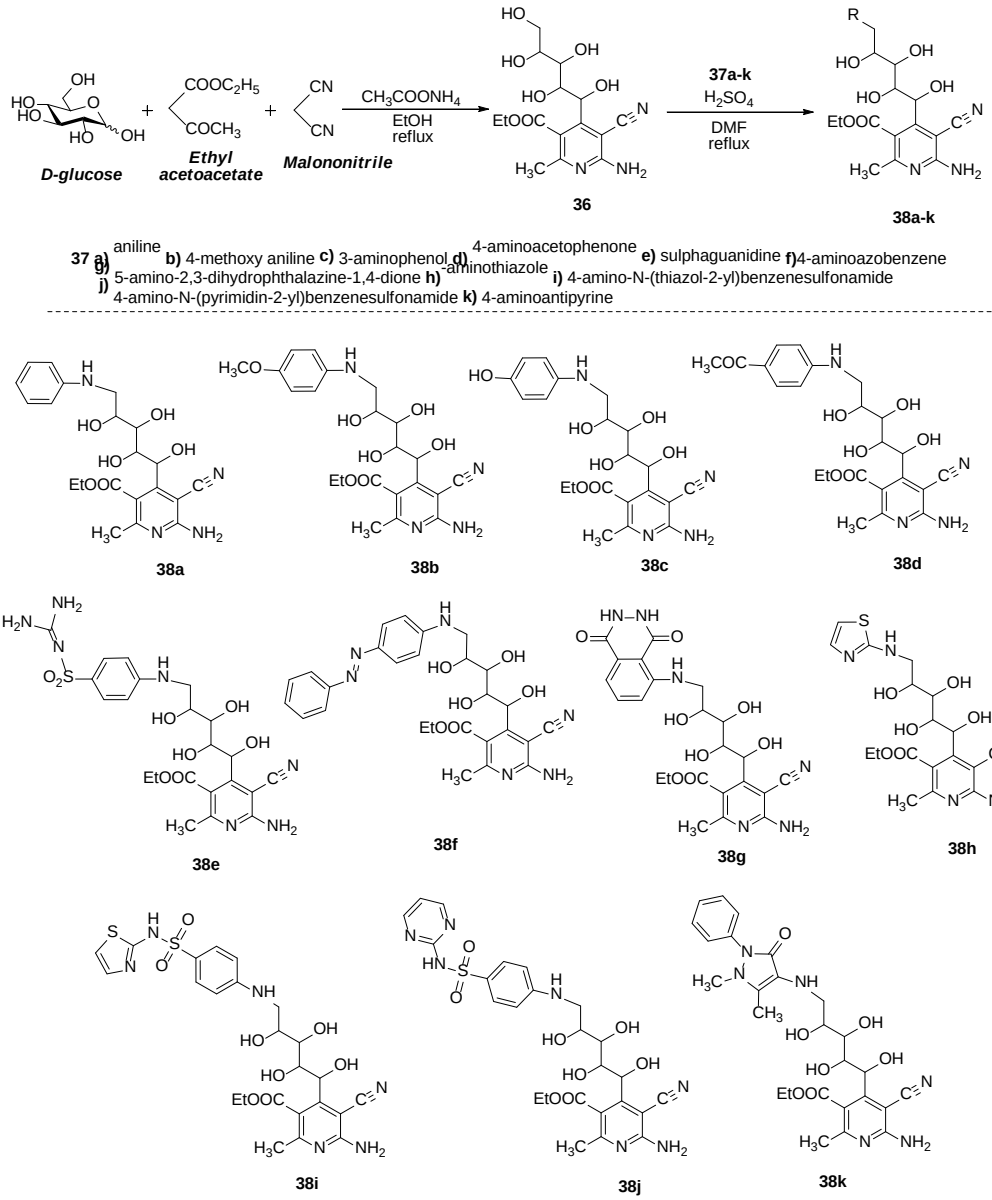


Scheme 4. Synthetesis of 1,2,4-thiadiazole glycoconjugates

3. Development of six-membered heterocycles linked to carbohydrates

3.1 Synthesis of pyridine glycohybrids

Pyridine derivatives have demonstrated a wide range of biological activities, including antiviral, anticancer, antimicrobial, antidiabetic, antitubercular, antileishmanial, antichagasic, antioxidant, anticoagulant, and antithrombin properties [De et al.,2022]. Mehany et al. reported the synthesis of thirteen molecularly designed nicotinate derivatives (**38a-k**) through the reaction of ethyl-6-amino-5-cyano-2-methyl-4-((1*S*,2*R*,3*R*,4*R*)-1,2,3,4,5-pentahydroxypentyl)nicotinate (**36**) with selected aromatic and heterocyclic amines (**37a-k**), which exhibited potential anticancer activity. Compound **36** was efficiently synthesized *via* a multicomponent reaction involving D-glucose, malononitrile, and ethyl acetoacetate in the presence of ammonium acetate (Scheme 5). All the newly synthesized compounds were prepared using both conventional methods and microwave-assisted techniques. The synthesized compounds have been assessed for their biological and anti-cancer properties. Because of their hydrophilic and lipophilic components, compounds **38c** and **38g** were also found to have greater cytotoxic effects than other compounds. Compound **38g** that has been radioiodinated is capable of effectively targeting the cancer site. Comprehensive studies suggest that the newly synthesized compounds could serve as promising novel theranostic agents for cancer treatment [Mehany et al., 2024].

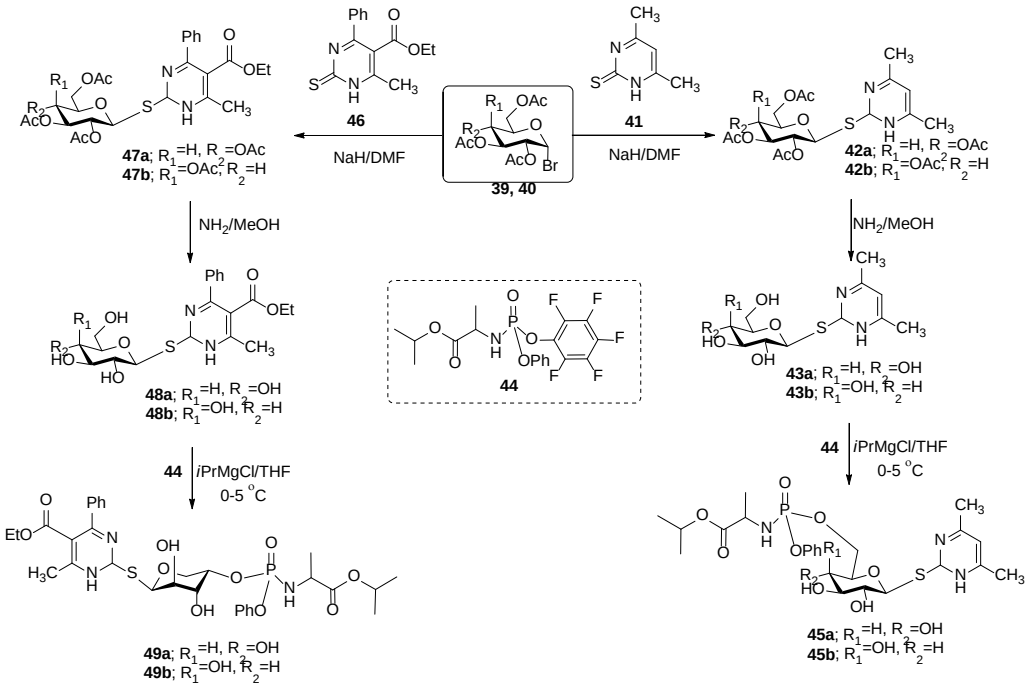


Scheme 5. Synthetic route for glycoconjugated nicotinate derivatives.

3.2 Synthesis of pyrimidine glycohybrids

Pyrimidines serve as fundamental building blocks in many naturally occurring bioactive compounds and are known for their diverse biological properties, such as anti-inflammatory, anti-allergic, antibacterial, antitumor, antipyretic, and antimalarial activities. They are essential for cellular growth and function, participating in the synthesis of critical biomolecules like DNA, RNA, glycoproteins, and membrane lipids [Singh and Kaur, 2016; Tyagi et al., 2023]. Two synthetic procedures were used to

synthesize the pyrimidine-based thioglycosidephosphoramidates **45a-b** and **49a-b**. The first step is to combine the proper mercapto-derivatized heterocyclic bases with peracetylatedbromoglycosides **39**, **40**. In the second, the acetate esters are hydrolyzed under basic conditions, and then they are conjugated with the phosphoramidating agent to produce the required thioglycosideprotides **45a-b** and **49a-b** (Schemes 6) [Tyagi et al., 2023].



Scheme 6. Synthesis of Pyrimidine Thioglycoside Phosphoramidate derivatives

4. Development of fused heterocycles linked to carbohydrates

4.1 Synthesis of coumarin

A thorough analysis of successful procedures for the synthesis of coumarin-functionalized glycosides was recently presented by A. Sau and colleagues. Five distinct coumarin glycohybrid structural types of coumarin *C*-glycosides, *O*-glycosides, *S*-glycosides, triazole-linked glycosides, and iminocoumarin glycosides are reviewed, arranged according to their manner of attachment. The employment of various catalysts and conditions is highlighted in the discussion of the synthesis of these glycohybrids. The study also provides an overview of a wide range of studies on coumarin glycosides and describes their biological actions, including their herbicidal, anti-inflammatory, antibacterial, antiallergic, antioxidant, anticonvulsant, antitumor, anti-HIV, and anticancer actions (Fig 2) [Sau et al., 2024].

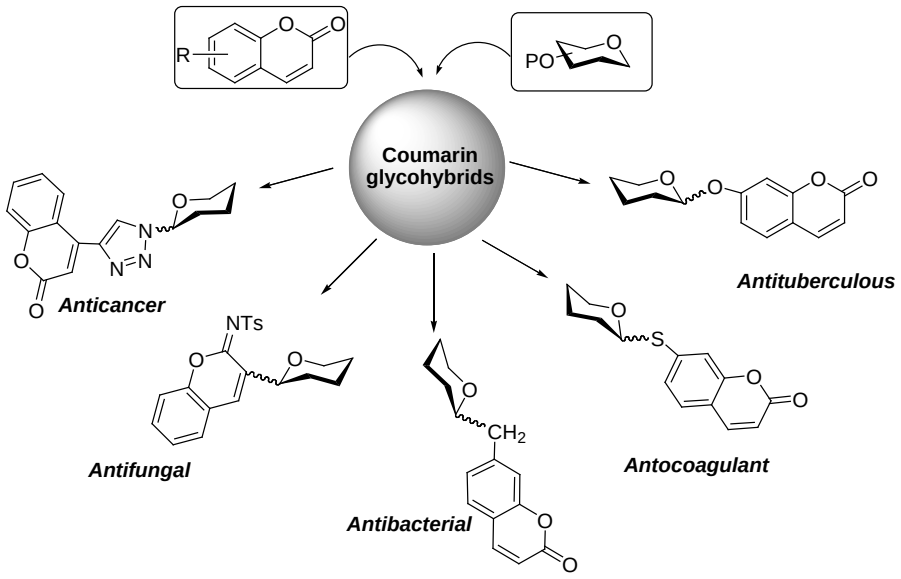
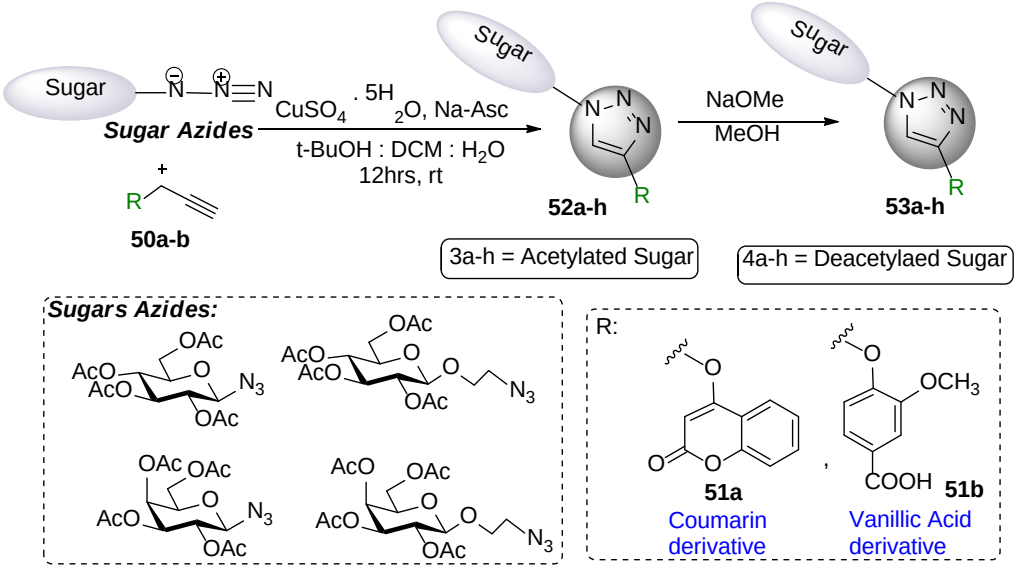


Fig. 2. Preparation of coumarin functionalized glycosides.

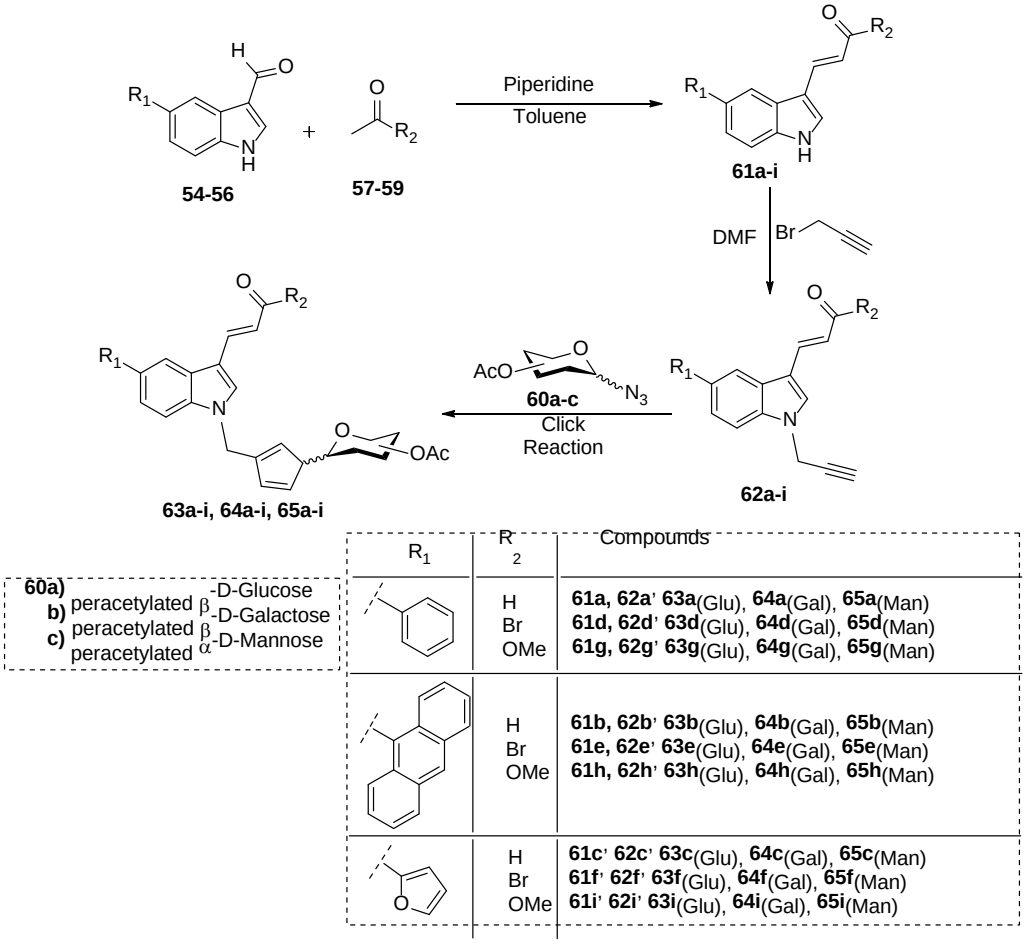
A library of triazole-linked glycoconjugates, such as carbohydrate-coumarin and carbohydrate-vanillic acid acetylated (**52a-h**) and deacetylated derivatives (**53a-h**), was created by Sharma et al. using copper catalysis to click-react glycosyl azide with aryl alkynes (**50a-b**). Both high yielding and regioselective reactions were observed (Schemes 7). The produced compounds demonstrated anti-parasitic activity against Leishmania donovani in *in vitro* with an IC_{50} range from 65 to 74 μM [Sharma et al., 2023].



Scheme 7. Synthesis of vanillic acid and coumarin glycohybrids.

4.2 Synthesis of indole

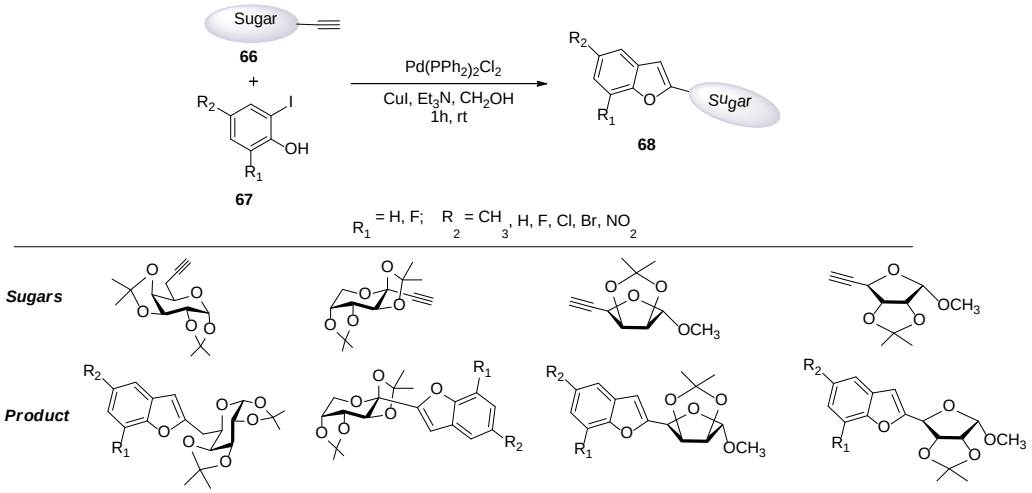
Indole attached with sugar which is used for the target-based design and development of anticancer, anti-inflammatory, antioxidant, antihypertensive, antidiabetic and antimicrobial agents [Halder et al., 2023]. A series of 1,2,3-triazole-linked indole-chalcone glycosides aimed at discovering new anticancer agents were developed by Tyagi et al. Indole-derived chalcones **61a–i** were first synthesized by performing Claisen–Schmidt condensation between 3-formyl indoles (**54–56**) and various ketones (**57–59**). Terminal alkylation of these chalcones was producing indole derivatives **62a–i**. The Click reaction of terminal acetylene armed compounds **62a-i** with per-acetylated β-D-gluco, β-D-galacto, and β-D-mannopyranosylazide **60a-c** then yielded the final products of three series of indole-chalcone based glycosides **63a-i**, **64a-i**, and **65a-i** (Scheme 8). Additionally, the resulting compounds *in vitro* anticancer activity was evaluated against the normal breast cells MCF-10A as well as the breast cancer cell lines MDA-MB231, MCF-7, and MDA-MB453. Compounds **63a**, **63c**, **63f**, **64a**, **64f**, and **64g** demonstrated strong and selective cytotoxicity against two cancer cell lines, MCF-7 (IC_{50} 1.05–9.37 μM) and MDA-MB-231 (IC_{50} 11.40–26.19 μM), without preventing normal cells (MCF-10A) from growing. Overall, compound **63c** exhibited the most inhibitory effect against the MDA-MB231 cell line (IC_{50} 11.40 μM and SI > 31), while compound **64f** demonstrated the strongest growth inhibitor of MCF-7 (IC_{50} 1.05 μM and SI > 161) [Tyagi et al., 2024].



Scheme 8. Synthesis of 1,2,3-triazole linked indole-chalcone glycoconjugates.

4.3 Synthesis of benzofuran

Benzofuran represents a significant class of heterocyclic compounds, found in a wide range of bioactive natural products, pharmaceuticals, and polymers. Numerous benzofuran derivatives have been identified as biologically and pharmacologically active molecules [Nevagi et al., 2015]. Through a one-pot cascade reaction coupling terminal sugar alkynes (**66**) with substituted 2-iodophenols (**67**), Z. Cao and co-workers have recently developed a novel procedure to acquire 2-benzofuranyl *C*-glycoside (**68**) with structurally dynamic sugar moieties. There were good yields (85%) of the intended goods (Scheme 9) [Cao et al., 2023].

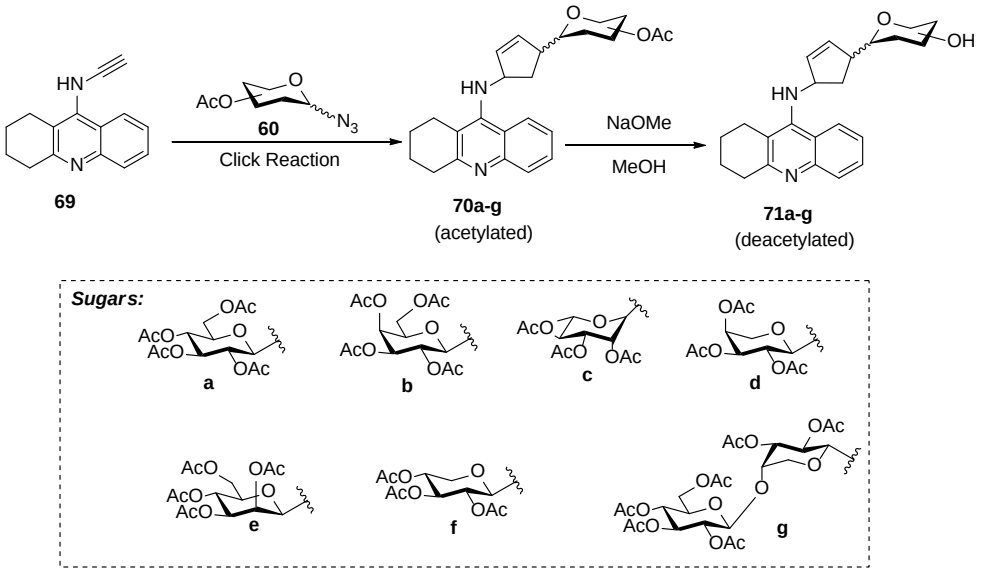


Scheme 9. One-pot synthesis of 2-benzofuranyl *C*-glycosides.

4.4 Synthesis of quinoline

Quinoline-based compounds play a crucial role in combating infectious diseases such as malaria, tuberculosis, HIV, and numerous bacterial, viral, and fungal infections. Several of these agents have received clinical approval, while many more are in various phases of clinical development [Matada et al., 2021]. Accordingly, researchers have investigated the glycoconjugation of quinoline derivatives to assess their pharmaceutical potential. In this context, researchers have also explored the glycoconjugation of quinoline derivatives investigating their pharmaceutical potential [Verma et al.,2023; Silvaet al., 2024; Simonetti et al., 2022; Kushwaha et al., 2025].

Several triazole-linked glycoconjugates containing acetyl groups (**70a-g**) and free sugar hydroxyl groups (**71a-g**) were reported by H. K. Gulati and colleagues. Triazole-linked glycoconjugates bearing acetyl groups (**70a–g**) were synthesized *via* a click cycloaddition reaction between anomeric sugar azides and terminal alkynes (**69**). Subsequently, the corresponding deacetylated glycoconjugates (**71a–g**) were obtained by removal of acetyl group using sodium methoxide in methanol of compounds **70a–g** (Scheme 10). All the synthesized compounds were evaluated for its inhibitory activity against the AChE enzyme. Among them, compounds **70a**, **70c**, **70d**, and **70g** showed the most significant inhibition, with **70a** exhibiting the strongest activity, having an IC_{50} value of 0.448 μM [Gulati et al., 2022].



Scheme 10. Synthetic protocol for triazole-linked glycoconjugates

Conclusions

The structural diversity and improved biological activity of carbohydrate-heterocycle glycoconjugates have received a lot of attention. These characteristics render them beneficial for drug research and therapeutic applications, including antiviral, antibacterial, anticancer, antidiabetic, and antimalarial properties. The incorporation of carbohydrates into heterocyclic compounds enhances their bioactivity and stability while reducing toxicity and adverse side effects. In this chapter, we have covered the recent developments on the synthesis of various glycohybrids molecules synthesized on the core structure of imidazole, oxadiazole, pyrazole, thiadiazole, pyridine, pyrimidine, indole, benzofuran, coumarin, and quinoline by using a variety of reaction conditions. The most selective and effective approach is cupper catalyzed azide-alkyne cycloaddition reaction providing 1,2,3-triazole rings for linking heterocycles to carbohydrates which enable to synthesize and modifying the complex bioactive molecules. The glycoconjugates of imidazole, pyrazole, thiadiazoles, indole and pyridine showed good to excellent anticancer activity against the MCF-7 (breast cancer) cell line whereas, 1,3,4-thiadiazole and coumarin glycoconjugatesinhibit the cancer associated carbonic anhydrase enzyme isoforms CA IX and CA XII. Pyrimidine thioglycosides proved to be effective antiviral agents against SARS-COV-2. Furthermore, quinoline shows binding affinity with gelatin 8N and inhibitory activity against the AChE enzyme. Coumarin glycoside showed antiparasitic against *Leishmania donovani*and thiadiazole demonstrated significant antifungal properoties.

As a result, diverse ranges of glycoconjugates were developed in large quantities for the efficient treatment of numerous major diseases. A holistic strategy that combines these elements offers significant promise for the development of next-generation therapeutics, harnessing the distinct advantages of carbohydrate and heterocyclic structures.

Conflict of Interest

Author(s) declares no conflict of interest, financial or otherwise.

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