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Review Article

Review on significant monosaccharides-based 1,2,3-triazoles; synthesis and their anticancer activity

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Abstract

1,2,3-Triazoles based on carbohydrates have become a promising class of compounds due to their miscellaneous chemical characteristics and their medical applications. A diverse range of carbohydrate scaffolds, such as ribose, glucose, mannose, and galactose, have been employed as precursors to produce a broad spectrum of 1,2,3-triazole derivatives that exhibit improved bioactivity and pharmacokinetic properties. Recent developments in the synthesis and anticancer activity of these derivatives are highlighted in this review. The copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction, which is commonly catalyzed by copper(I) to produce carbohydrate-based 1,2,3-triazoles, providing facile access to structurally diverse to derivatives with a variety of structural properties is also covered. The review also focused on the synthesis of some important sugar-derived azides and terminal alkynes.

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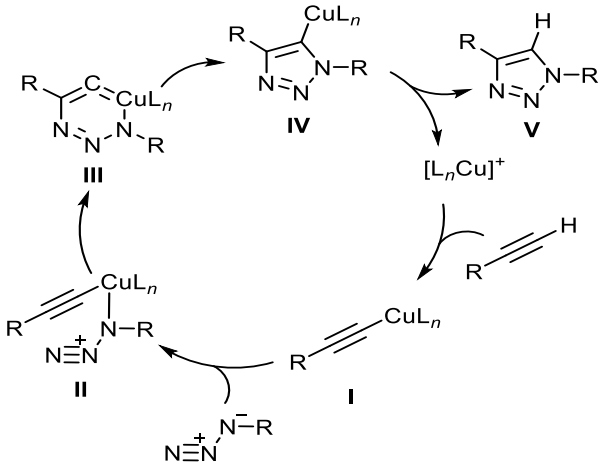
Introduction

The burden of cancer around the globe attracts scientists in different fields to find effective anticancer agents that have slight effect on normal cells [1−5]. One of the favorable approaches is incorporating carbohydrate moiety into therapeutic compounds [6−10]. On the other hand, many biochemical processes of abnormal cells are disrupted by 1,2,3-triazoles that also exhibit insignificant risk to the normal counterparts, which make them promising candidates in anticancer drug design [11−13]. Their mechanism of action on tumor cells can inhibit DNA repair, reducing the activity of the promoting enzymes, apoptosis triggering, and interruption of the essential cellular signaling of the malignant cells' survival [13−15]. However, the insolubility challenges of several triazoles lead to lack of achieving complete understanding of their biology [16,17]. For this purpose, the cell friendly molecules "carbohydrate" can be utilized to address the solubility issue and enhance the pharmacological properties of the drug [18]. These features such as cellular uptake, bioavailability, drug behavior, targeting specificity and pharmacokinetics are improved by inserting of sugars' hydrophilic moieties [19]. Also, to overcome the poor drug solubility that hiders the drug administration and formulation, sugar-functionalized anticancer drugs can be synthesized and developed for the mentioned target [20−21].

Synthetic Strategies

Synthesis of 1,2,3-triazoles via click chemistry

The copper(I)-catalyzed azide-alkyne cycloaddition reaction CuAAC, pioneered by Sharpless [22] and Meldal [23], has revolutionized the synthesis of 1,2,3-triazoles. It involves the reaction between an azide and an alkyne in the presence of a copper(I) catalyst to form the triazole ring. Carbohydrate-based azides and alkynes can be readily synthesized or derived from existing carbohydrate derivatives allowing for the efficient construction of triazole-containing carbohydrates. Basically, the mechanism of click reaction involves the *in situ* formation of Cu(I) through the reaction of Cu(II) salts such as copper sulfate with reducing agents like sodium ascorbate. The reaction is accelerated by the formation of copper acetylide **I** the regioselectively reacts with azide to produce the 1,4-disubstiuted-1,2,3 triazole **V** (Scheme XX)



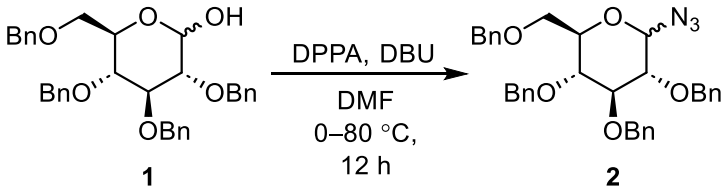
Scheme 1. Mechanism of copper(I)-catalyzed azide-alkyne cycloaddition reaction CuAAC

Sugar azide derivatives

There are many synthetic strategies to prepare sugar azide derivatives. However, the most popular are; direct azidation of sugars, Lewis acid catalyzed azidation and nucleophilic displacement of azide.

Direct azidation of sugars

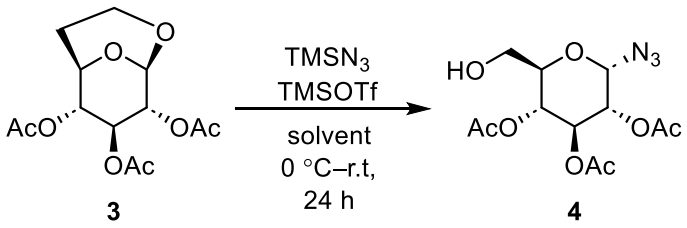
One of the most common methods involves directly introducing the azide group onto the sugar molecule. This can be achieved through nucleophilic substitution reactions using azidating agent in the presence of suitable activating agents or catalysts. For example, the reaction of a sugar alcohol with diphenylphosphoryl azide DPPA in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene DBU in DMF yields the corresponding sugar azide derivative (Scheme 2) [24].



Scheme 2. Synthesis of azide derivative **2**

Lewis acid catalyzed azidation

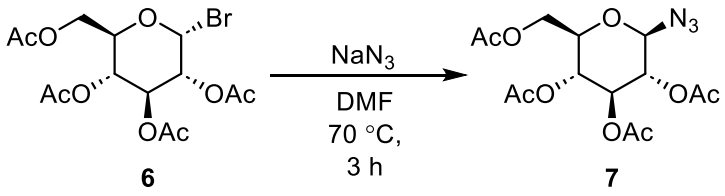
Lewis acids are frequently employed as catalysts to accelerate the nucleophilic substitution process between sugars and azide ions. For instance, A novel pathway to α-glycosyl azide **4** was achieved *via* the ring-opening of 1,6-anhydro sugar **3** with trimethylsilyl azide $TMSN_3$ in the presence of trimethylsilyl trifluoromethanesulfonate TMSOTf (Scheme 3) [25]



Scheme 3. Synthesis of sugar azide **4**

Nucleophilic displacement of azide

This is the well-known method to synthesize sugar derivatives as it requires to convert the hydroxyl group on sugar derivative to good leaving group such as tosyl OTs, mesyl OMs, iodo and bromo corresponding derivatives following by treatment with sodium azide NaN_3 or lithium azide LiN_3. For example, glycosyl azide **7** is easily produced in quantitative yield by the treatment of glycosyl bromide **6** with sodium azide in *N*,*N*-dimethylmethanamide DMF at 70 °C for 3 h (Scheme 4)[26]:



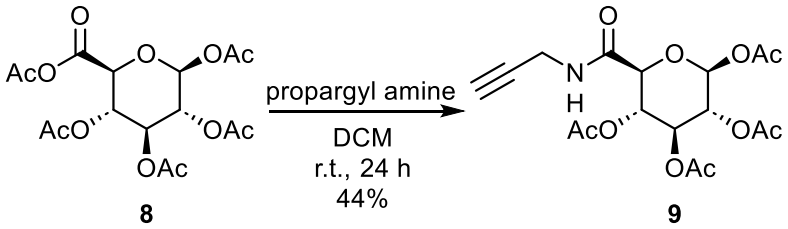
Scheme 4. Synthesis of glycosyl azide **7**

Sugar terminal alkynes

The synthesis of sugar terminal alkynes involves the introduction of an alkyne or propargyl functional group at selected position of a sugar molecule. Terminal alkynes are important building blocks in organic synthesis, particularly in the context of click chemistry reactions, where they can undergo efficient coupling with azides to form 1,2,3-triazoles. There are also various methods to access the sugar terminal alkynes. However, propargylations of monosaccharides with propargyl amine, propargyl bromide, or propargyl alcohol are the notable protocols in this field.

Propargyl amine protocol

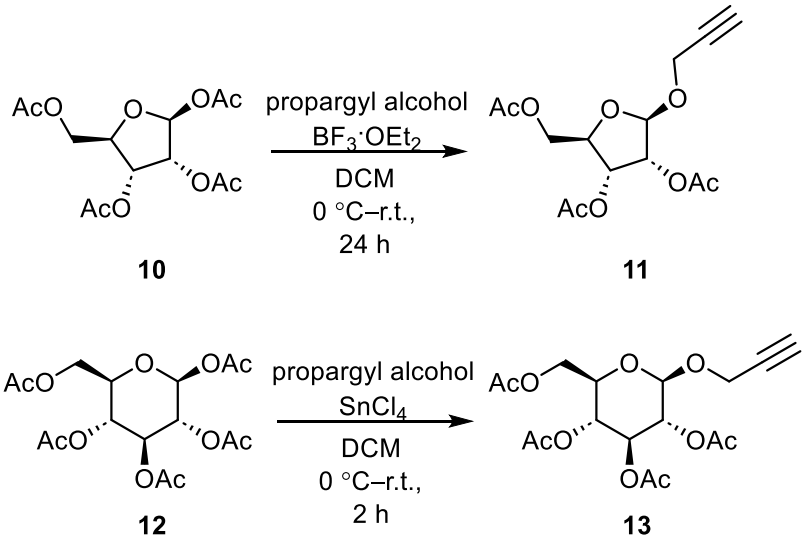
This method requires the presence of a carboxyl group or any of its derivatives i.e. acid chloride or ester on the sugar moiety in order to be coupled with propargyl amine to obtain propargyl amide. For example, the treatment of glucuronic acid eater **8** with propargyl amine in dichloromethane DCM at room temperature for 24 hours afforded the correspounding propargyl amide **9** in 44% yield (Scheme 5) [27]:



Scheme 5. Synthesis of propargyl derivative **9**

Glycosylation using propargyl alcohol

The anomeric site in reducing sugars such as ribose, xylose, glucose mannose and galactose can be exploited to insert propargyl moiety. In the peracetylated sugar derivatives **10** or **12**, the anomer acetate protecting group is prompted by the addition of Lewis acid i.e. boron trifluoride diethyl etherate $BF_3{\cdot}OEt_2$ or stannic chloride $SnCl_4$ allowing the anomeric acetate to leave followed by the attack of propargyl alcohol to give the propargyl glycoside derivatives **11** or **13** (Scheme 6) [27−29]:

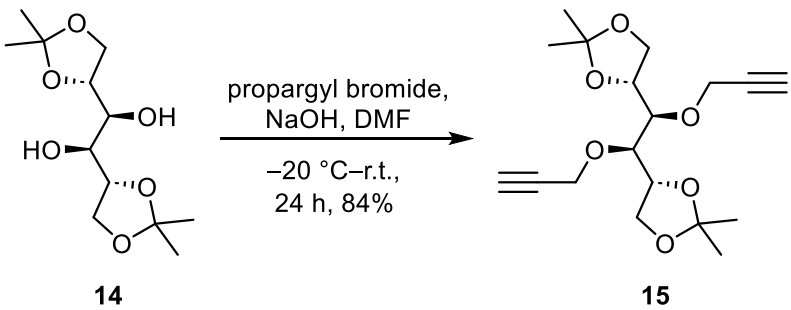


10 **11** **12** **13**

Scheme 6. Synthesis of propargyl derivatives **11** and **13**

Etherification of hydroxyl group with propargyl bromide

Propargyl bromide is a reactive alkyl halide and can react with 1° and 2° alcohol by the aid of various bases like alkali metals, alkali hydrides, alkali hydroxides and even alkali carbonates. It is reported that the treatment of protected mannitol derivative **14** with propargyl bromide in the presence of sodium hydroxide NaOH in DMF at −20 °C to room temperature for 24 hours affords the corresponding mannitol propargyl derivative **15** in very good yield (Scheme 7) [30,31]:



14 **15**

Scheme 7. Synthesis of dipropargyl mannitol **15**

Sugar-based 1,2,3-triazoles

Because carbohydrate moieties can be utilized to modify drug behavior in different pathways, including cellular uptake, bioavailability, pharmacokinetics, and targeting specificity, they are valuable additions to anticancer medicines. Anticancer drugs that have been carbohydrate-functionalized display improved stability and water solubility, which allows formulation and administration simpler while reducing common problems in therapeutic development like chemical instability and poor drug solubility [32].

Moreover, the addition of carbohydrate moieties can provide anticancer drugs better pharmacokinetic qualities, such as extended circulation times, less immunogenicity, and increased tissue penetration. Drug molecules conjugated with carbohydrates may be protected from the reticuloendothelial system's (RES) quick clearance, extending systemic exposure and improving therapeutic efficacy. Furthermore, carbohydrates can support receptor-mediated endocytosis, which enables anticancer drugs to be delivered intracellularly and gets past cellular barriers that prevent drugs from penetrating tumor tissues [33].

Epipodophyllotoxin-galactose hybrid 1,2,3-triazole derivatives have been synthesized through click protocol. They showed effective antiproliferative activity against A549 cells (IC_{50} = 4.07 µM, MTT assay) that is two times greater than that of cisplatin (**16**) (IC_{50} = 9.24 µM, MTT assay) and etoposide (**17**) (IC_{50} = 11.92 µM, MTT assay) (Figure 1).

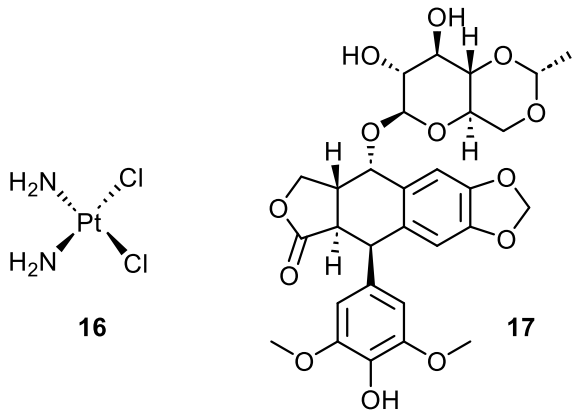
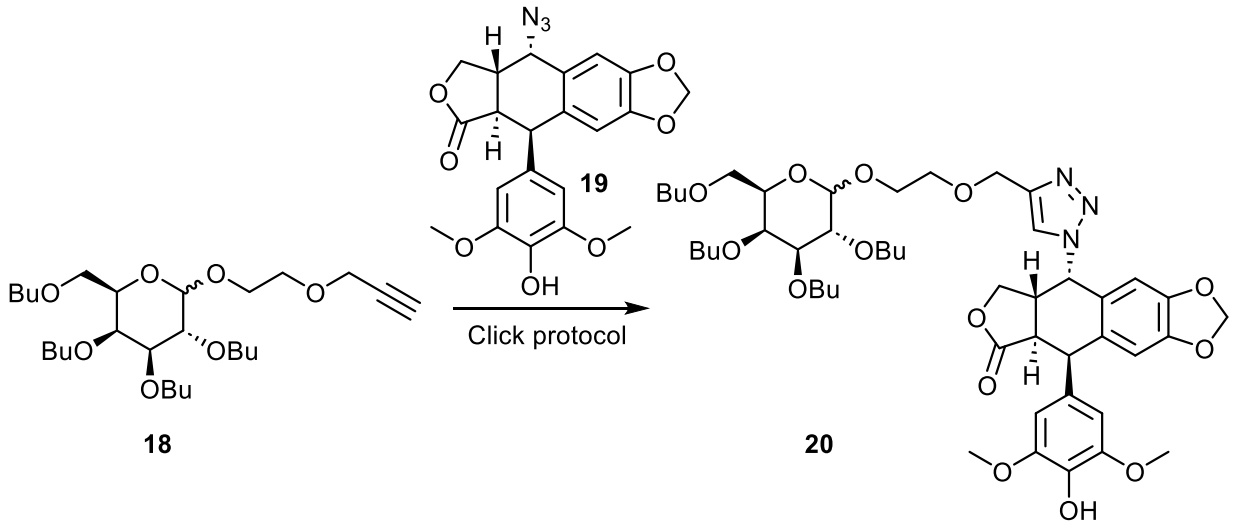


Figure 1. structures of cisplatin (**16**) and etoposide (**17**)

The structural activity relationship SAR study demonstrated that the esterification of hydroxyl groups of the galactose ring **20** increases the antiproliferative activity six-folds higher than cisplatin against A549 cells (Scheme 8) [34]:



Scheme 8. Synthesis of compound **20**

It is reported that the synthesized theophylline nucleoside based-1,2,3-triazole derivatives **21** and **22** (Figure exhibited powerful anticancer activity against A549 cells (IC50: 1.56 and 2.89 µm, MTT assay) respectively (Figure 2) [35]:

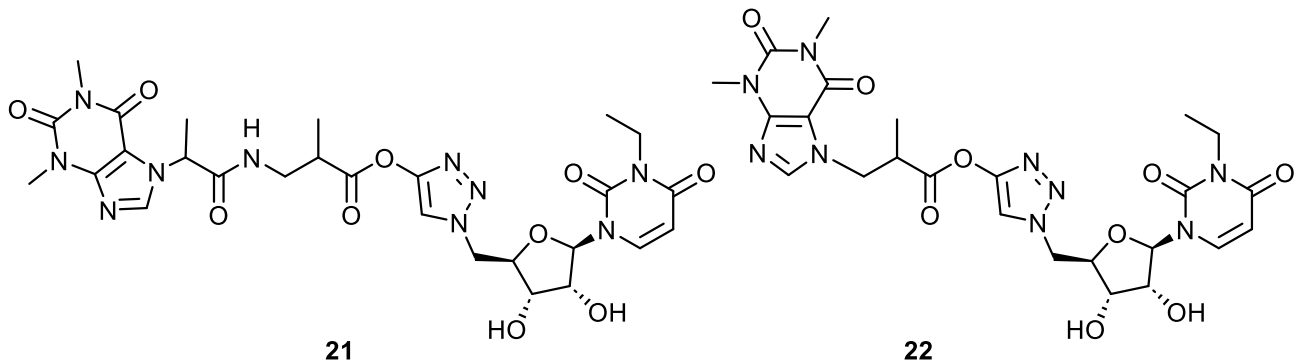
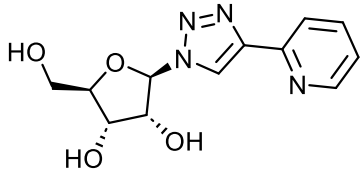


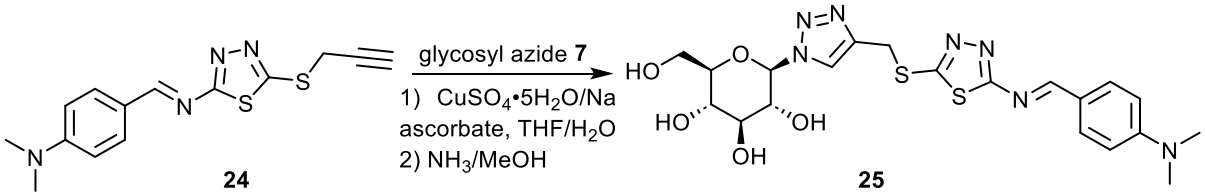
Figure 2. Structures of theophylline nucleoside based-1,2,3-triazole derivatives **21** and **22**

Jakukowski *et al.* [36] reported that ribofuranose-based1,2,3-triazole derivative containing pyridine moiety **23** also possesses antiproliferative activity against lung cancer about three and a half times more than cisplatin.



23

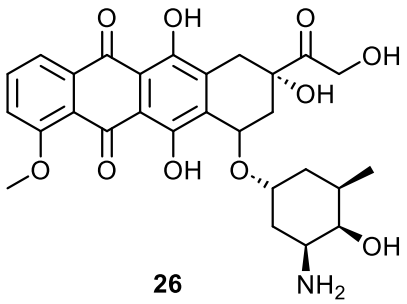
The triazole glycoside-tethered *p*-methoxyarylidine derivative **25** was synthesized by copper(I) catalyzed cycloaddition reaction between the glycosyl azide **7** and the propargyl derivative **24** followed by the hydrolysis of acetate protecting groups by the treatment with methanolic ammonia (Scheme 9) [37]:



24 **25**

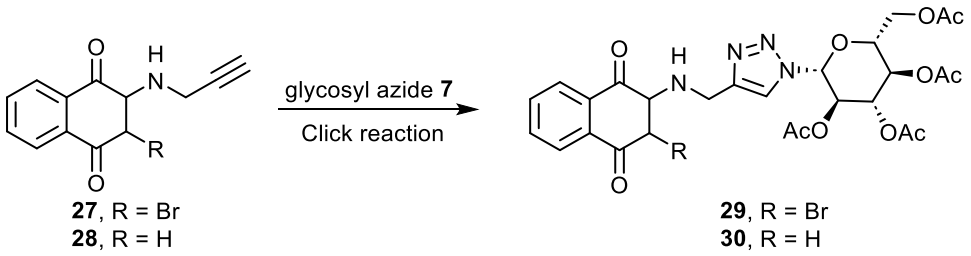
Scheme 9. Synthesis of triazole derivative **25**

This compound exhibited potent activity against MCF-7 human cancer cells comparable to the reference drug doxorubicin **26**. Derivative **25** also showed high activity against HCT-116 cell lines.



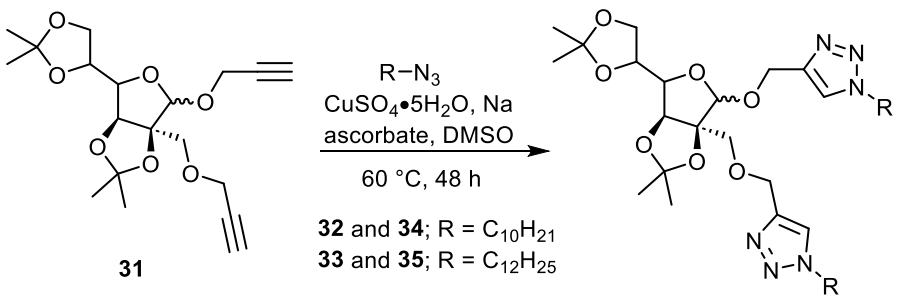
26

High anticancer activity was observed with IC_{50} values of 1.19 and 0.80 µM respectively for glucose-based 1,2,3-triazole derivatives **29** and **30** against HL-60. These compounds were synthesized by the click reaction of glycosyl azide **7** with corresponding propargyl derivatives **27** and **28** (Scheme 10) [38].



Scheme 10. Synthesis of compounds **29** and **30**

Mahdi *et al*. [39] synthesized mannosyl diacetonide-base 1,2,3-bistriazole derivatives **34** and **35** from mannosyl dipropargyl derivative **31** and the alkyl azides **32** and **33** respectively via copper(I) catalyzed cycloaddition reaction in dimethyl sulfoxide DMSO (Scheme 11). The bistriazole derivatives **34** and **35** were tested against breast cancer AMJ13 cells line and they demonstrated promising results IC_{50} of 167.64 µg/mL 171.61 µg/mL respectively.



Scheme 11. Synthesis of mannose bistriazoles **34** and **35**

Click chemistry was utilized to synthesize a series of 1H-1,2,3-triazole-4H-chromene-D-glucose hybrid compounds by employing 2-amino-7-propargyloxy-4H-chromene-3-carbonitrile derivatives and peracetylated D-glucopyranosyl azide **7**. All the 1H-1,2,3-triazoles that were synthesized had promising anticancer activity against the MCF-7, HepG2, and HeLa cancer cells. However, several compounds, such as **36**–**38** (Figure 3) exhibited significant activity against HepG2 cancer cell lines with an IC_{50} less than 5 µM [40].

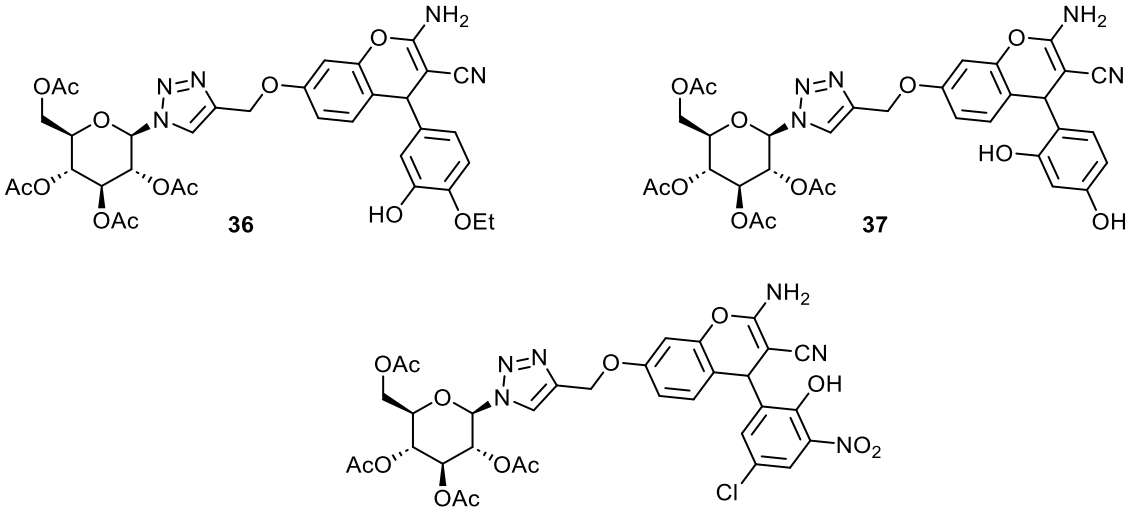


Figure 3. Structures of 1,2,3-triazole derivatives **36**–**38**

Conclusion

Using carbohydrates as building blocks for synthesis of 1,2,3-triazoles has become a common strategy in medicinal chemistry, providing a plethora of unique molecules with adaptable chemical properties and potential therapeutic uses. The significant advancements in using different carbohydrate scaffolds, such as ribose, glucose, mannose, and galactose, to produce a diverse range of 1,2,3-triazole derivatives have been highlighted in this review. These compounds are promising prospects for therapeutic development because they have better pharmacokinetic characteristics and increased bioactivity. In addition, the discovery of the copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction has given scientists an effective tool for successfully obtaining structurally varied carbohydrate-based 1,2,3-triazoles, broadening the range of possible uses for them. Examining current developments in synthesis techniques and emphasizing the anticancer properties for these compounds. This review advances the current investigation of 1,2,3-triazoles produced from carbohydrates as possible medicinal therapeutics. Furthermore, the synthesis of important sugar-derived azides and terminal alkynes has been clarified, providing important information about the synthetic methods that support the synthesis of these physiologically active compounds. In conclusion, this review highlights the importance of 1,2,3-triazoles based on carbohydrates in medicinal chemistry and offers a thorough analysis of their synthesis, pharmacological characteristics, and potential therapeutic uses.

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