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Click chemistry: a promising approach for 1,2,3-triazole synthesis

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Abstract: In this review we return to the click chemistry reaction and the importance of the compounds containing the 1,2,3-triazole cycle.

Keywords: Click chemistry, CuAAC, 1,2,3-triazole, regioisomer, azide-alkyne

1. 1,2,3-Triazoles compounds and their importance

The importance of heteroatoms indicates that they are a common part of a many types of active pharmaceutical installation and excipients [1,2]. It can also be used as raw materials in the preparation of organic compounds. In medicinal chemistry, mainly, heterocycles, cyclic compounds of five or six atoms, containing nitrogen, oxygen or sulfur atoms, have a major role in the discovery, identification, synthesis and design, of biologically active compounds. Statistics indicate that about 85% of the entities that owns biological activity have a heterogeneous cycle [3]. Therefore, heterogeneous cycles are of significant interest for chemists working in medicine to upgrade the drug chemical field and to work on greater efficient ways of drugs invention. In a study of heterocyclic systems with a fixed composition versus to organic compounds, triazoles rings were established as highly substantial

heterocyclic compounds for medication-related actions. It also named "pyrodiazole", has a five-atom unsaturated ring structure made up of three nitrogen atoms, and has two isomeric forms, 1H-1,2,3-triazole **1** and 1H-1,2,4-triazole **3**, **Fig. 1** [4].

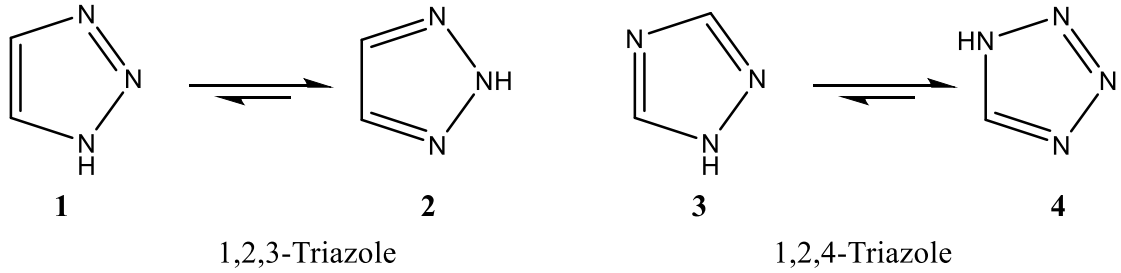


Fig. 1. 1,2,3-Triazole and 1,2,4-triazole.

1,2,3-Triazole is an unsaturated compound consisting of five atoms, aroma ring, that have л-excessive. It has two double-bonded carbon atoms and three nitrogen atoms. Whereas two nitrogen atoms are pyridine, and one is pyrrole. The 1,2,3-triazoles ring has the aromatic feature due the sp2 hybridization of the atoms and the 6л electrons surrounding the ring are separated.

1.1. 1,2,3-Triazole classification

Three families of 1,2,3-triazoles are acknowledged: 1,2,3-triazolium salts [5], 1,2,3-monocyclic 1,2,3-triazoles [6] and benzotriazoles [7] are listed in that order. The 1H- and 2H-1,2,3-triazole are in equilibrium in the gas and solution phases, so they are aromatic, contrary 4H-triazole which is non-aromatic. The hardships of obtaining triazoles via industrial processes and manufacturing these compounds establish that there is a substantial need for research and development in these areas [8].

1.2. The importance of 1,2,3-triazoles compounds

1,2,3-Triazoles are characterized as easily able to combine with biological objectives and stable to metabolic degradation, by dipole−dipole interactions and hydrogen bonding. Triazoles compounds are stable against both acidic and basic hydrolysis and have good aromatic stabilization. Triazoles have unique biological features that have been utilized for the creation of anti-cancer drugs. There are medicines that have a triazole ring in their composition and have anti-fungal, anti-microbial, anti-HIV, anti-allergic and anti-cancer properties **Fig. 2** [9].

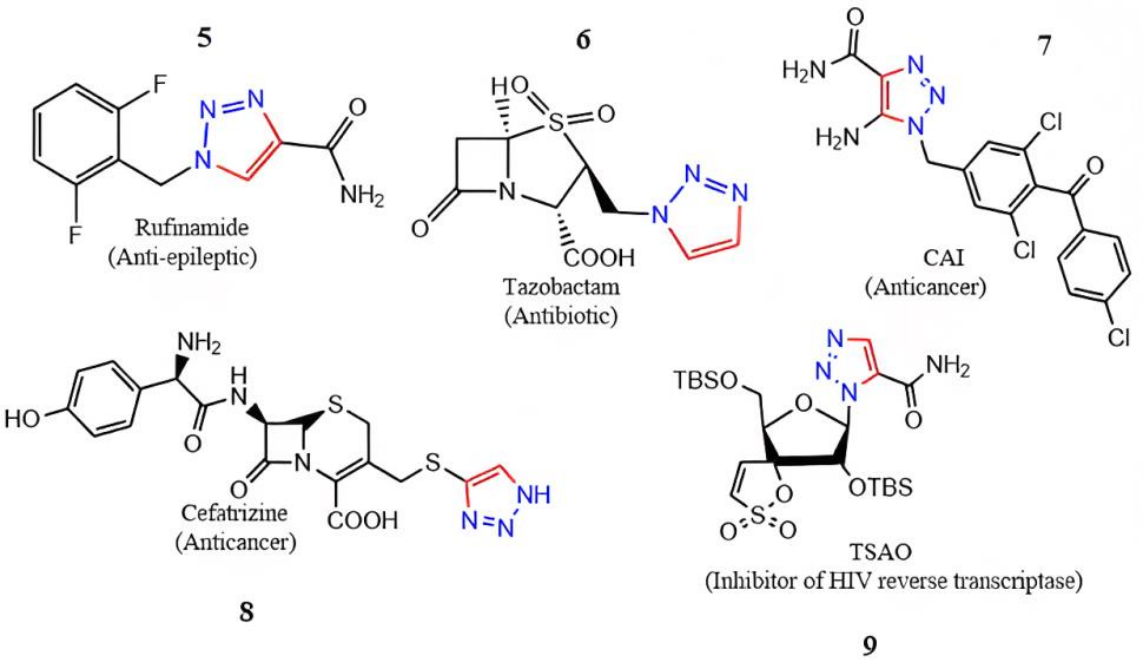
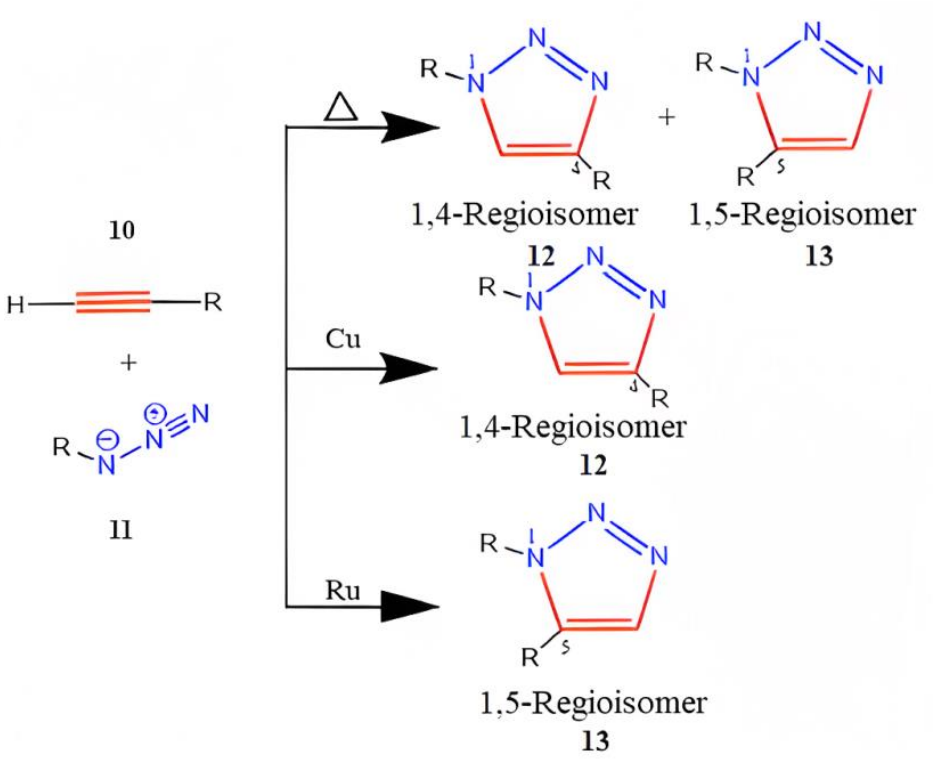


Fig. 2. 1,2,3-Triazole drugs.

2. Synthesis methods of 1,2,3-triazoles

Huisgen 1,3-dipolar cycloaddition, which is produced when azide and alkyne react to form 1,4 and 1,5-disubstituted-triazole regio-isomers, was the first thorough investigation into synthesizing triazole core. Number of transition metal-based approaches for controlling regio-selectivity have been developed. Azide alkyne cycloaddition reaction catalyzed by copper, developed by Sharpless [10] and Meldal [11] give rise to the 1,4-regioisomer through regioselective synthesis, whereas the 1,5-regioisomer was synthesized by the cycloaddition catalyzed by ruthenium [12] **Sch. 1**.



Sch. 1. Regio-selectivity of the 1,3-dipolar cycloaddition.

2.1. Generality

The typical process for creating 1,2,3-triazoles includes the presence of a transition metal as a catalyst. Because of its great selectivity and easily of application, the 1,3-dipolar cycloaddition reaction was catalyzed by copper, the primary click chemistry approach (CuAAC) is the reaction of an azido with terminal acetylenic substrate. Copper salts Cu(I) or Cu(II) are employed in the presence of reducing agents in an organic solvent or tert-butanol and water in a combination under standard circumstances. For obtaining efficient catalyst, actually, reducing Cu(II) salts is useful, cheaper, and environmentally friendly than reducing Cu(I) salts [13].

2.2. Click Chemistry: a promising approach for 1,2,3-triazole synthesis

2.2.1. Click chemistry

Click chemistry is one of the most major reactions in therapeutic chemistry and synthetic biology. It stands for an efficient and flexible instrument, which may be useful in the advantage to advance new anti-cancer drugs [14]. Click chemistry depicts reactions originally introduced and utilized in organic chemistry to synthesis compounds by joining small units together with heteroatom linkages (C-X-C). Over the last few decades, click chemistry has been widely used in bioscience fields, such as chemical biology, drug development and bionanoparticles, as a favourable appliance to modify biomolecules, such as (DNA), protein and virions.

Copper(I)-catalyzed alkyne-azide cycloaddition (CuAAC) is one of the most widely used click reactions, which reacts efficiently at room temperature and is stable to most functional groups to generate stable products. To label cells in situ using (CuAAC), an azide or alkyne is conjugated to a biomolecule in the cell, such as a nucleic acid, nucleoside, amino acid, monosaccharide or fatty acid, which is characterized the biosynthetic incorporating reaction. Thereafter, the complementary alkyne or azide labeled with the reporter group is linked with the biomolecules by click chemistry reaction using catalytic copper(I). Although, the (CuAAC) reaction is functional for bioconjugation, the reaction is restricted in live cells; because the copper, as a catalyst, is cytotoxic. So, some copper-free click chemistry ways have been sophisticated, such as Cu-free alkyne-azide cycloaddition, strain-promoted alkyne-azide cycloaddition (SPAAC), strain-promoted inverse electron-demand Diels-Alder cycloaddition (SPIEDAC), the thiol-ene reaction, etc. However, by using click reactions, fluorophores or other reporter molecules attach particular biomolecules, so the biomolecules can be identified, located and characterized [15]. Click chemistry is generally regarded as a potent and rapid chemical reaction with outstanding bioorthogonality. Copper(I)-catalyzed azide–alkyne 1,3-dipolar cycloaddition (CuAAC), pioneered independently by Fokin, Sharpless and Meldal in 2001 Fig. 3, is the most versatile, authorizing exclusive formation of 1,4-disubstituted-1,2,3-triazoles in good yields under mild reaction conditions; this reaction has opened up a new era in click chemistry [16]. A copper-catalyzed variant that follows a different mechanism can be conducted under aqueous conditions, even at room temperature. Additionally, whereas the classic Huisgen 1,3-dipolar cycloaddition overwhelmingly gives mixtures of regio-isomers Fig. 4, the copper-catalyzed reaction allows the synthesis of the 1,4-disubstituted regio-isomers specifically. By contrast, a later developed ruthenium-catalyzed reaction gives the opposite regioselectivity with the formation of 1,5-disubstituted triazoles Fig. 5. Thus, these catalyzed reactions comply fully with the definition of click chemistry and have put a focus on azide-alkyne cycloaddition as a prototype click reaction.

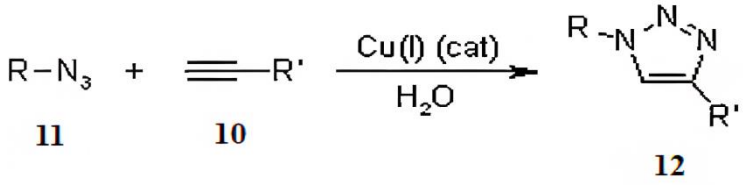


Fig. 3. Copper(I)-catalyzed azide–alkyne 1,3-dipolar cycloaddition (CuAAC) 'Click Chemistry'.

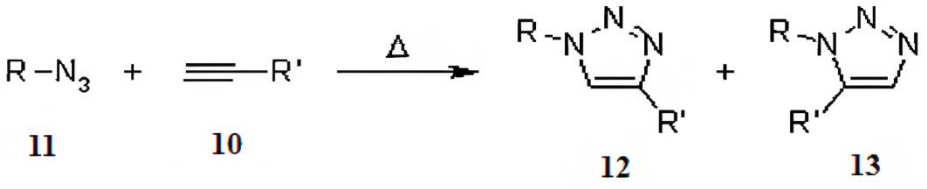


Fig. 4. Huisgen 1,3-dipolar cycloaddition.

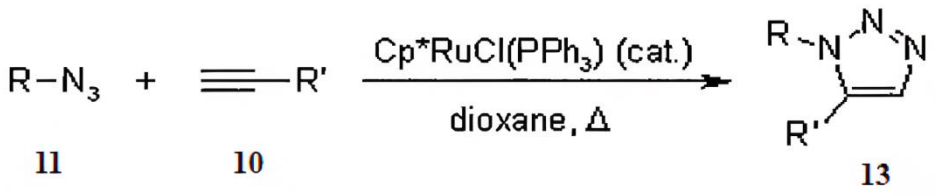


Fig. 5.

Sharpless and Meldal have reported the dramatic rate enhancement (up to 107 times) and improved regioselectivity of the Huisgen 1,3-dipolar cycloaddition reaction of an organic azide and terminal acetylene to afford, regio-specifically, the 1,4-disubstituted-1,2,3-triazole in the presence of Cu(I) catalyst. The thermal Huisgen's cycloaddition is less proper than click chemistry, calling for further severe conditions and offering weak stereospecificity (1,4- and 1,5- functionalized triazoles are created).

Click chemistry is a newer approach for the synthesis of drug like molecules that can accelerate the drug discovery process by utilizing a few practical and reliable reactions. The past two decades have seen exciting developments in the synthetic antiviral agents by the means of click chemistry approach, opening new possibilities for discovering and preparing novel antivirals. By combining specificity, spatial precision and flexibility with respect to the choice of the click ligand, the minimally-invasive modification of virion components via click chemistry allows virologists to fully profit from these technical advancements and to complement imaging studies by biochemical analyses. While the click labeling of viral nucleic acids has already yielded numerous insights into virus biology, the exploitation of click chemistry for labeling viral proteins has just begun, and the extension of the approach to the investigation of viral lipids still lies ahead.

2.2.2. Click chemistry reactions

Click chemistry is one of the most substantial reactions in therapeutic chemistry and synthetic biology. It's a powerful and flexible instrument, which may be helpful in the advantage of to advance new antitumor drugs [17]. The successfully established click chemistry reaction discovered by the Meldal and Sharpless research groups in 2002, gives only 1,4-disubstituted 1,2,3-triazoles circumstances, in contrast to the classic thermally induced Huisgen 1,3-dipolar cycloaddition reaction, which results in a mixture of compounds that are 1,4 and 1,5-disubstituted [18]. There are several types of click chemistry reactions, including the Huisgen reaction of the 1,3-dipole cyclic rotation of alkenes and azides, it has been widely used as synthetic and coupling tool. Excellent yields of the final products are synthesized by this reaction, and simple purification ways can be used to dispose the by-products with ease [19].

2.2.2.1. Types of click reactions

Click reactions have four different types: Cycloaddition reactions, Addition reactions, Carbonyl condensation and Nucleophilic ring-opening reactions [20].

2.2.2.1.1. Cycloaddition reactions

Azide-alkyne occurrences involving 1,3-dipolar cycloaddition and hetero-core is synthesized by combining Diels Alder cycloadditions **Fig. 6**. The most widely used reactions for producing pharmaceuticals are (CuAAC), which includes alkynes and azides owing to its biocompatibility, specificity, and the advantageous physicochemical features of triazoles [21]. There are many benefits for this type of reactions,

including high reaction yields, few adverse effects, and no additional catalysts are needed in the reaction media [22].

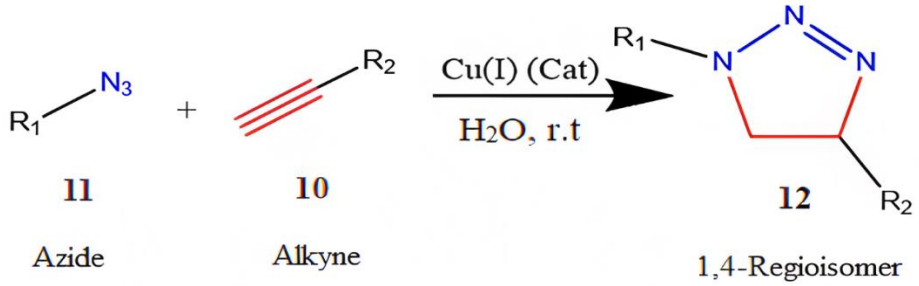


Fig. 6. Cu-catalyzed azido-alkyne cycloaddition.

2.2.2.1.2. Addition reactions

They are generally Michael additions to a various of carbon-carbon bonds, such as the addition of thiolyne, amine-ene and thiolyne **Fig. 7**.

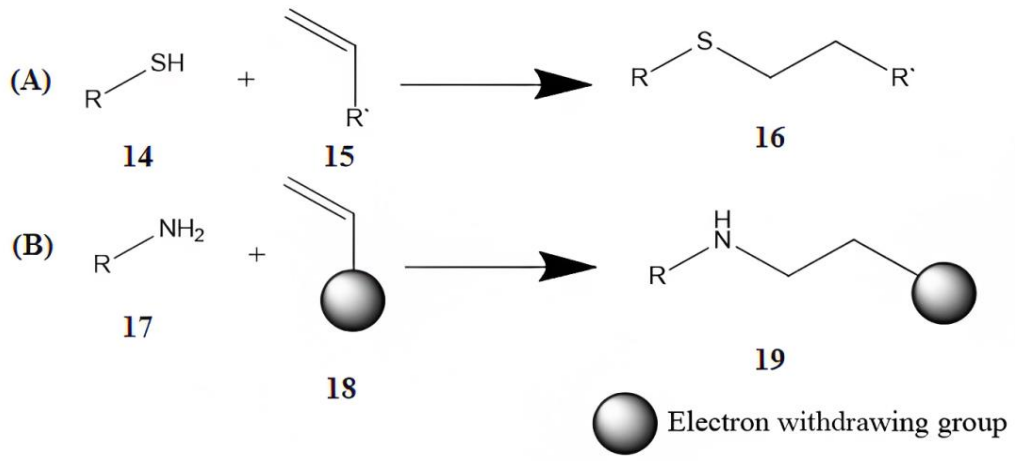


Fig. 7. (A) Thiolyl-ene addition reaction, (B) Michael addition.

2.2.2.1.3. Carbonyl condensation

Interactions of the non-aldol kind, as those resulting creation of oxime, hydrazones and hetero aromatic rings **Fig. 8**. Because they have longer reaction periods and smaller thermodynamic forces than non-aldol carbonyl-type interactions, aldol-type carbonyl interactions aren't thought of like click interactions [23].

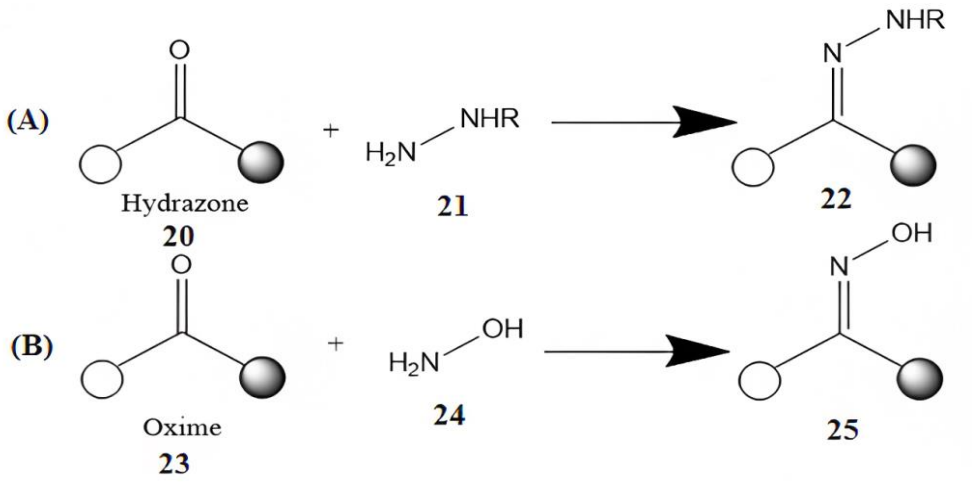


Fig. 8. Carbonyl condensation.

2.2.2.1.4. Nucleophilic ring-opening reactions

Aziridinium ions, epoxides, and aziridines are examples of heterocyclic molecules that fall under this category **Fig. 9**. Several bioactive chemicals were synthesized as a result of these interactions. Alcohol/water solvent combinations are used in these reactions to synthesized end products with high yields [24].

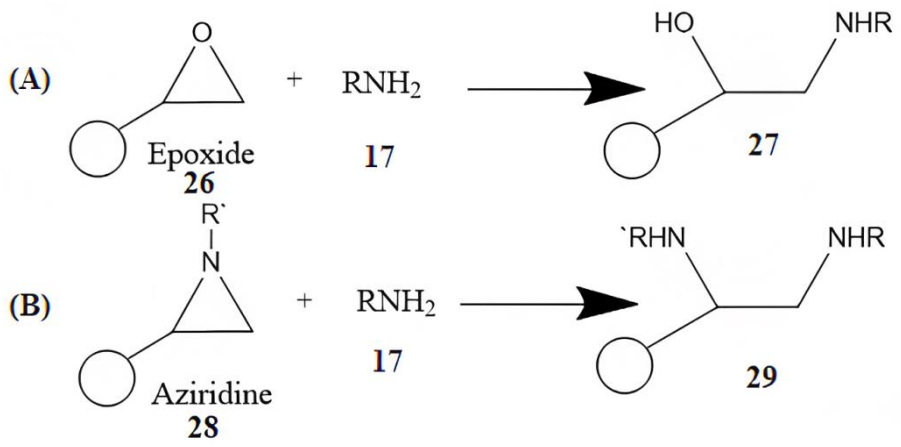


Fig. 9. Nucleophilic ring-cleavage for (A) epoxides, (B) aziridines.

2.2.3. Catalysts

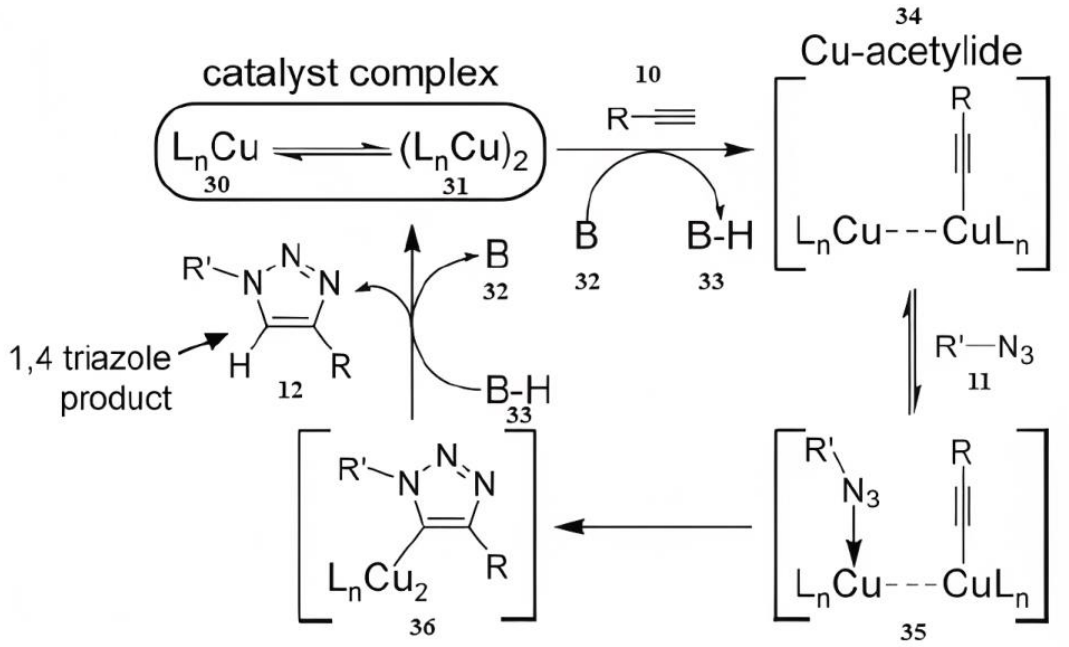
In (CuAAC) interactions, Cu(I) is the preferable catalyst. Copper sulfate is utilized with a reducing agent such as sodium ascorbate [25]. This technology is distinguished by quicker response times, lower costs, and tolerance for aqueous medium. The reducing agent helps to convert copper(II) to copper(I) while continuing to maintain its presence in the reaction media in very high quantities [26].

2.2.4 Solvents

One of the most crucial requirements for solvents in click chemistry is that they be inexpensive, readily available, biorenewable, and biodegradable, that they dissolve a wide variety of chemicals, and that they be chemically inert to the reactants or the reactions end products. The most frequently organic solvents employed in click chemistry most frequently are tetrahydrofuran [27], toluene [28], tert-butanol [29], dichloromethane [30], dimethylformamide [31], ethanol [32], dimethyl sulfoxide [33] and acetonitrile [34]. Green solvents can be utilized instead of organic solvents because they are biorenewable, environmentally friendly and nontoxic [35]. Green solvents like water [36], γ-valerolactone [37], glycerol [38], lactic acid [39] and 2-methyl-THF [40] can be used.

2.2.5. Click reaction mechanism

In 2006, Maarseveen et al. described the mechanistic specifics of the (CuAAC) response [20]. A stepwise process drives the cycloaddition interactions that are Cu-catalyzed, according to kinetic studies and density functional theory (DFT) simulations. There is a significant improvement of the overall interaction rate as a result of Cu(I)-addition. Compound Cu−alkyne π complex **34** is firstly formed through the stepwise catalytic cycle, then the alkyne proton is deprotonated, which causes a copper acetylide to form **34**, **Sch. 2**. Deprotonation in an aqueous mixture is straightforward as a result of the acetylenic protons increased acidity is triggered by the copper coordination. The Copper(I)-acetylide dimeric **34** coexist in equilibrium. By coordinating with the azide **35** and activating azide groups nitrogen present in terminal, the metallacycle is produced by one of the dimeric forms of copper-ions. The ring contraction due to the reaction of the double bond in the carbon with the pair of electrons present on nitrogen of azide. Compound **12** and the Cu(I)-catalyst are produced by protonation after a Cu-triazolide species **36** is generated [41].



Sch. 2. Cu(I)-catalyzed azide-alkyne cycloaddition mechanism.

2.2.6. Advantages and disadvantages of click reaction

It's noteworthy, (CuAAC) is the most potent, useful synthetic and reliable instrument for the synthesis of the triazole compounds and its derivatives [42]. Click chemical interactions provide medical and synthetic chemists an excessive number of benefits. Simple starting ingredients, reagents and eco-friendly solvents like water can all be utilized to perform a click interaction. Under ambient interaction circumstances, this interaction can be carried out with minimal product preparation. With relatively high yields, this click interaction technique makes with regio-specificity. The triazoles that are produced have advantageous physicochemical characteristics [43]. In addition, there is no doubt that using (NMR) spectroscopy makes it simple to monitor click interactions [44].

Among the less major flaws When one alkyne reacts with another, Cu(I)-saturation and undesired side interactions result in alkyne homocoupling [45]. As well as, some heavy metal azides have the potential to explode, which raises questions in click synthesis and medical research. Due to the aforementioned problems, other preparation strategies have also been explored, such as metal-free cycloadditions and Diels-Alder cycloaddition reactions [46].

2.2.7. Uses of click chemistry in pharmaceuticals

Latterly, click chemistry reactions have turned out to be one of the most commonly used chemical reactions in chemical biology and medicinal chemistry, and have been widely used in virus-related research. This research aims to provide synthetic anti-cancer agents from heterocyclic systems containing 1,2,3-triazole ring linked to glycosides using click chemistry approach.

Because of their dipole−dipole interactions and hydrogen bonding; 1,2,3-triazole compounds are characterized as easily able to combine with biological objectives and stable to metabolic degradation. Triazole compounds are stable against both acidic and basic hydrolysis and have good aromatic stabilization. Triazoles have unique biological features that have been employed for the creation of anti-cancer drugs [47].

2.3.. Huisgen 1,3-dipolar cycloadditions and (CuAAC) reactions

The Huisgen 1,3-dipolar cycloaddition is an approach synthesizing a 1,4-disubstituted 1,2,3-triazole ring with a strong regioselectivity [48]. Also, have been discovered to have beneficial biological effects. Without a catalyst, the interaction proceeds slowly and frequently requires high temperatures. This process produces a 1:1 mixture of 1,4- and 1,5-regioisomers, which makes it not non-selective and unsuitable to produce selective medical drugs **Fig. 10**.

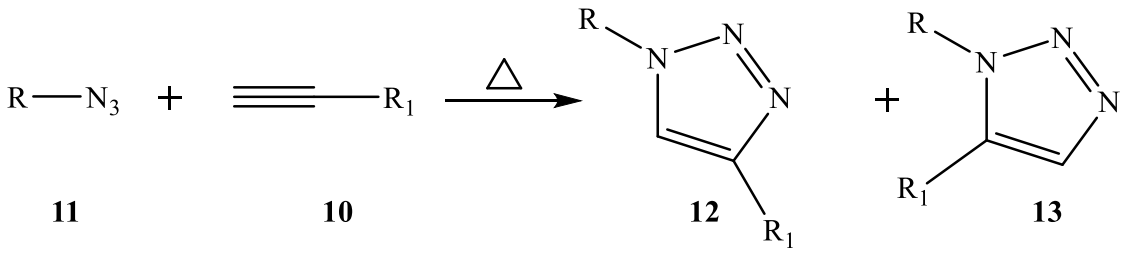


Fig. 10. Huisgen reaction.

This interaction modified by Rostovtsev et al. by conducting the reaction at ambient temperature and using Cu-catalysis. There is no requirement for high temperatures, because when Cu(I)-catalyst is used, the interaction rate increases and exclusively results in the synthesis of the 1,4-regioisomer [26] **Fig. 11**.

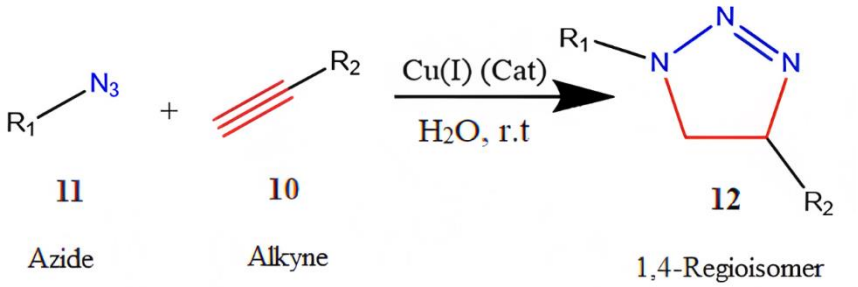


Fig. 11. Copper-catalyzed cycloaddition between alkynes and azides.

2.4. Metal free methods

There has been a lot of interest in regioselective 1,2,3-triazoles synthesis processes; due to the importance in most fields, especially in medical chemistry. Because they are limited to terminal alkynes and the heavy metals used in them are poisonous; these actions aren't the best for some biological applications [50]. Metal-catalyzed click interactions have recently been replaced by the more recent methods of organocatalytic triazoles preparations [51] **Fig. 12**.

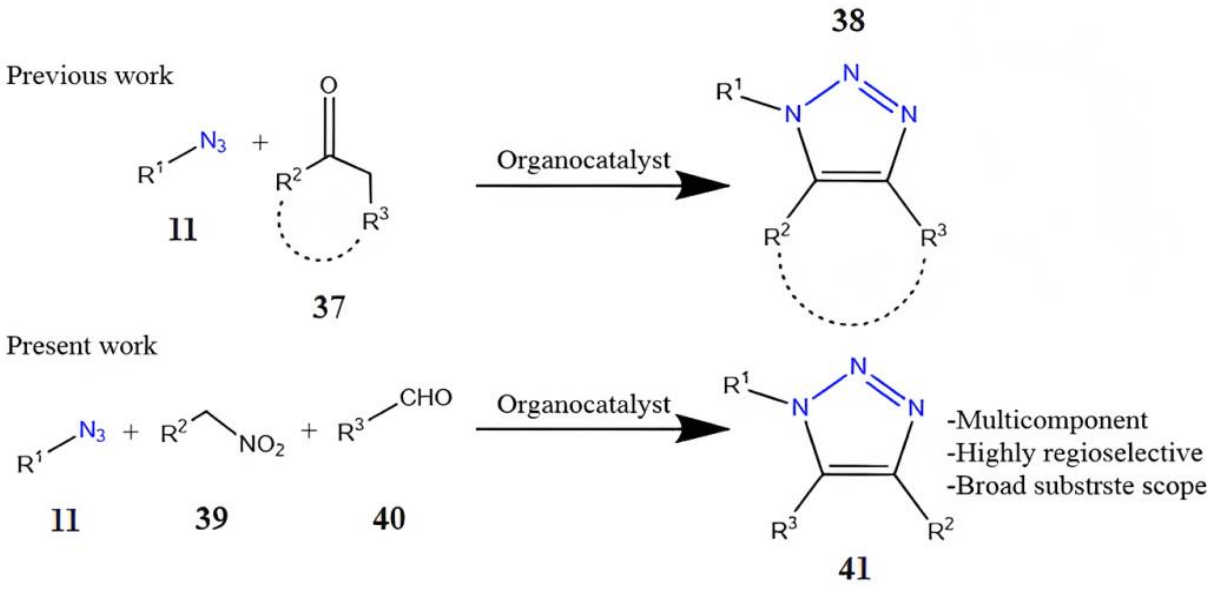


Fig. 12. Organo-catalytic routes to substituted 1,2,3-triazoles.

New 1,2,3-triazoles preparation without metals are available, where amine base organo-catalysts are employed. For the aim of specifically preparing 1,5-diaryl-1,2,3-triazoles, Fokin and colleagues described the first azide-alkyne cycloaddition without a transition metal [16]. The conditions utilized are simple and insensitive to oxygen; which gives the products excellent yields. Tetra alkyl ammonium hydroxide was employed as the catalyst. Using an enone and aryl-azido reagent at ambient temperature and utilizing a pyrrolidine catalyst, the regioselective synthesis of N-arylbenzotriazole compounds was actually finished [52]. Also, the utilizing of a piperidinium acetate in methanol; aldehydes containing indoles or aryls and phenylazide compounds or pyrazole compounds undergo a one-pot Knoevenagel/azide-alkyne cycloaddition process **Fig. 13** [53].

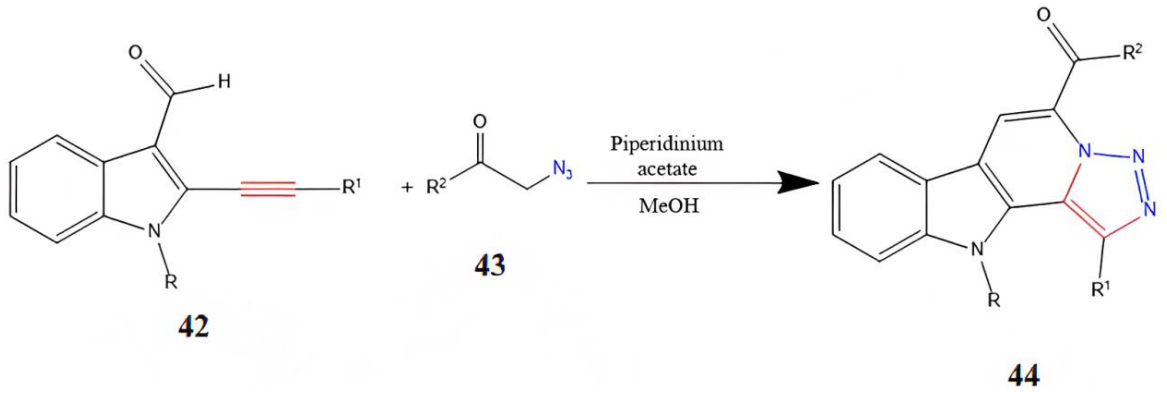


Fig. 13. Knoevenagel/N_3-alkyne cycloaddition utilizing an indolyl-aldehyde.

There have also been other successful metal-free triazole preparations. For example, the basic interaction of alkylidene malononitrile with aryl-azide which results in the 1,4-regioisomer **Fig. 14** [54].

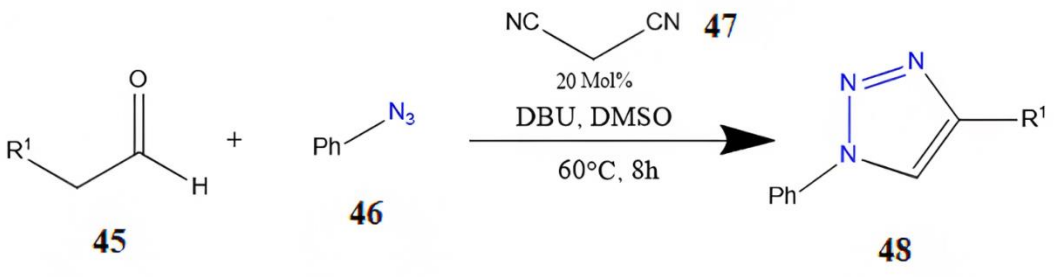


Fig. 14. Catalytic version of the metal free synthetic strategy.

2.5. Metal-catalyzed alkyne-azide cycloaddition processes

2.5.1. Cu-catalyzed azide-alkyne cycloadditions (CuAAC)

The 1,2,3-triazole can be bioavailable; due to its polar link and its amazing symmetrical shape in terms of both structural and electronic characteristics [55]. The (CuAAC) interaction is the most predominant type in organic reactions using a catalyst made of copper(I) and copper-sulfate with a Na-ascorbate in an aqueous mixture. The presence of iodide, bromide and chloride is also regarded as supportive anions since they propensity to function as inhibitors and have a negative impact on interaction rate and yield [56]. The efficient effect of halide ions has been established by (CuAAC) reactions using Cu(I) [57]. In 2007 a regioselective synthesized of N-sulfonyl-triazole compounds has been developed by Chang and Sharpless, and different terminal alkynes and sulfonyl azides were utilized as catalysts by Fokin. **Fig. 15**, condition **A**. Enhancements were made to the process of creating sulfonyl triazoles utilizing Cu(I)-acetylides and sulfonyl azides as catalysts **Fig. 15**, condition **B**. The rapid preparation of N-sulfonyl triazole compounds with high selectivity and yields was described by Hu-Wang and his colleagues in 2011 utilizing a various of copper(I)-catalytic techniques **Fig. 15**, condition **C** [58].

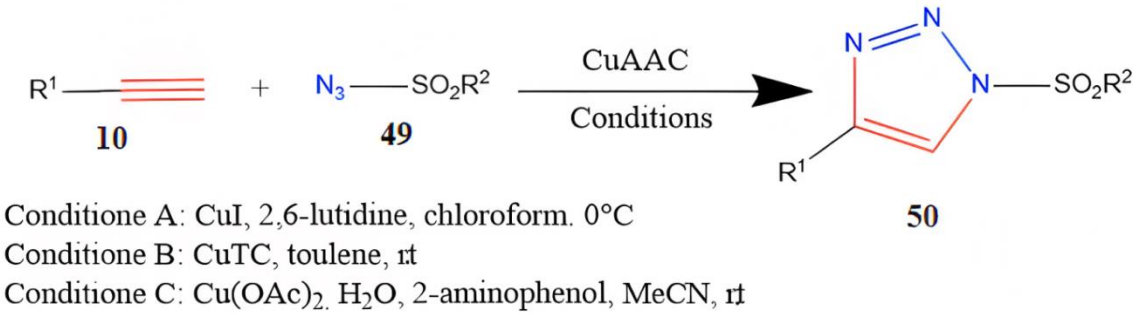
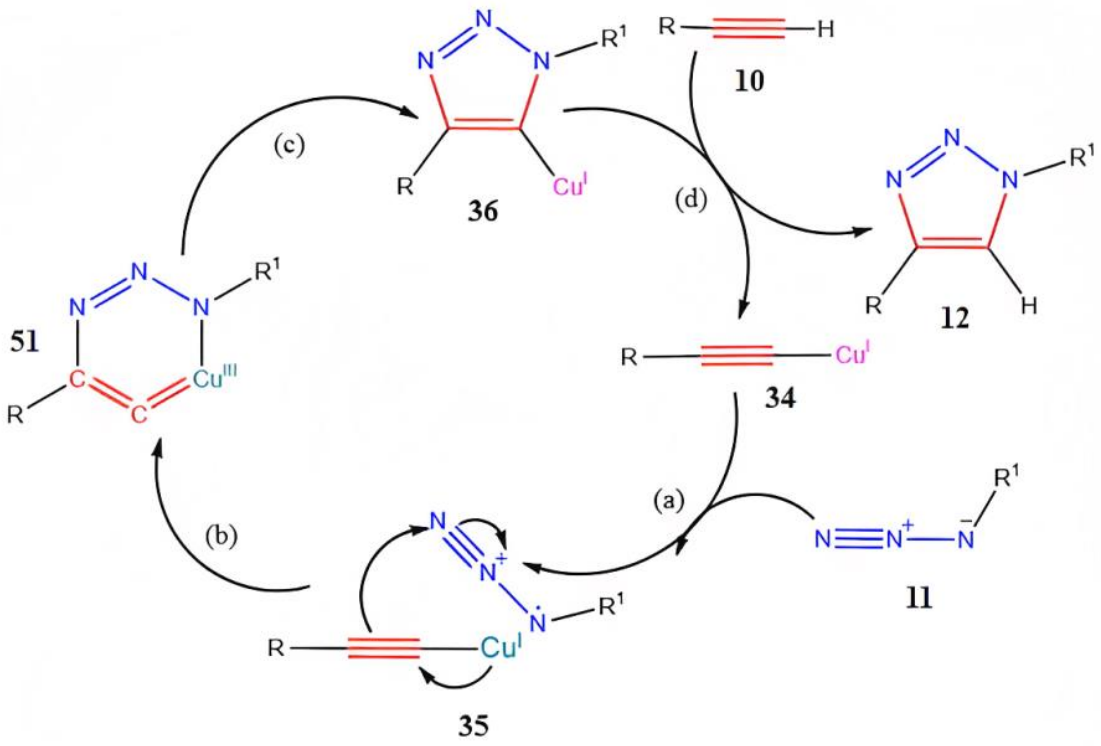


Fig. 15. N-sulfonyl-triazoles.

Initial mononuclear mechanism:

Fokin et al. proposed a technique that results in a complex of all three elements by alkylating one of the azide groups nitrogen atoms, which coordinates with Cu(I) **Sch. 3** [59].



Sch. 3. The mechanism of (CuAAC) proposed by Fokin and coworkers.

2.5.2. (RuAAC) reactions

Because of the successful application of Ru-catalyzed click reactions; 1,4 and 1,5-disubstituted monomers of triazolyl amino acids has spawned a lot of interest. The quantum chemistry analysis shows that the monomers have the characteristics special, indicating their capacity to generate number of weak energy conformers [60]. High temperatures are required for the thermal 1,3-dipolar cycloaddition reactions, which can also result in mixtures of the two potential regio-isomers when using asymmetric alkynes, making them ineligible for classification as true click interactions and traditional 1,3-dipolar cycloaddition reactions. The reaction of (CuAAC) gives 1,4-disubstituted regio-isomer **Fig. 16**, path **(A)**, unlike the reaction of (RuAAC) gives 1,5-disubstituted regio-isomer **Fig. 16**, path **(B)** [61].

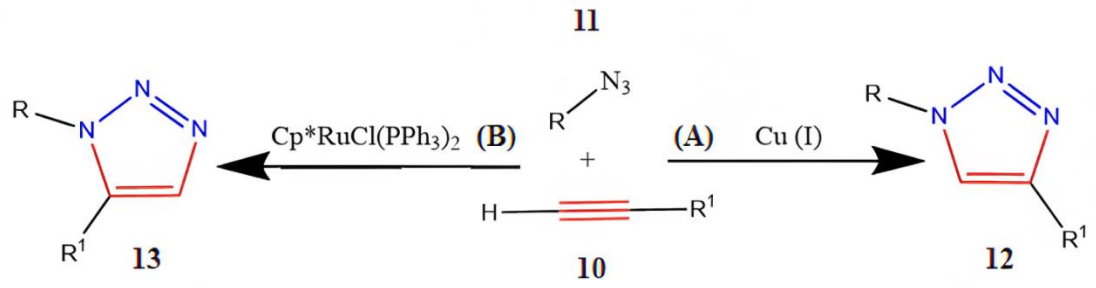


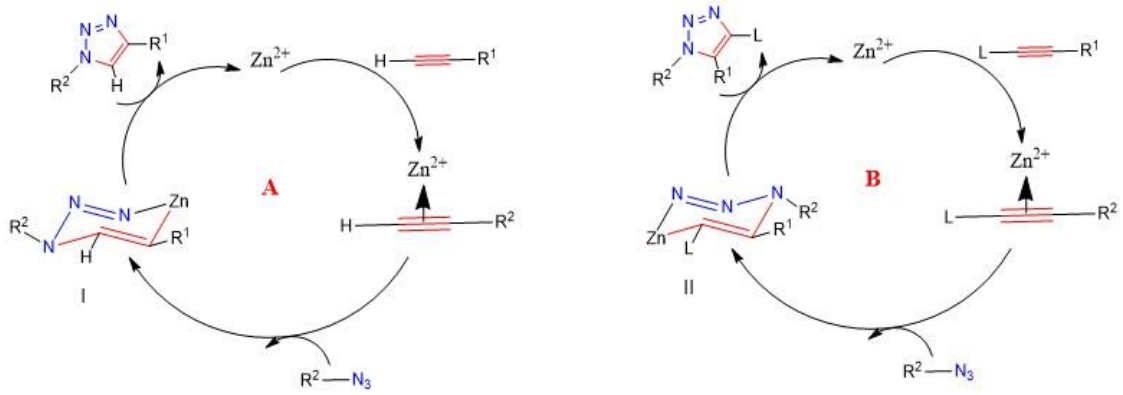
Fig. 16. Regio-selectivity of azide-alkyne cycloaddition.

2.5.3. (ZnAAC) reactions

In 2010 zinc was employed as a catalyst by Chen and coworkers, and it has showed excellent flexibility with regard to number of functional groups in azides and alkenes. Since water interferes with the catalytic system; (DMF) was utilized to achieve a good yield for 1,2,3-triazoles.

The mechanism of (ZnAAC):

The π-complex forms happens in the first phase, when acetylene and $Zn(OAc)_2$ interact. The resultant complex combines with the azide compound in the subsequent stage to produce the first metallacycle. The extrusion of Zn^{2+} from metallacycle(I) is the final stage in the regeneration process **Sch. 4** [62].



Sch. 4. Purposed mechanism of Zn-catalytic approach.

2.6. Ultrasound methods

A sodium azide and an alkyl halide are utilized to generate an alkyl azide in situ, which leads to the three-component reaction. A reported study discussed a 1,3-dipolar cycloaddition with Cu-acetate and Na-ascorbate which generating targeted triazole compounds **Fig. 17** [63].

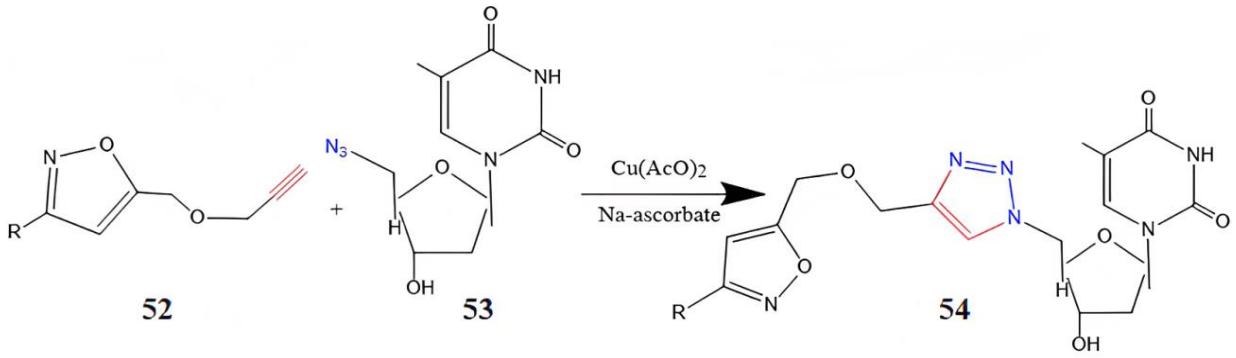


Fig. 17. Triazole compounds

By utilizing sono-chemically promoted interactions, it's possible to obtain oxo-amides or aryl-azides quickly and with good to outstanding yields when (DMSO) is used **Fig. 18** [64].

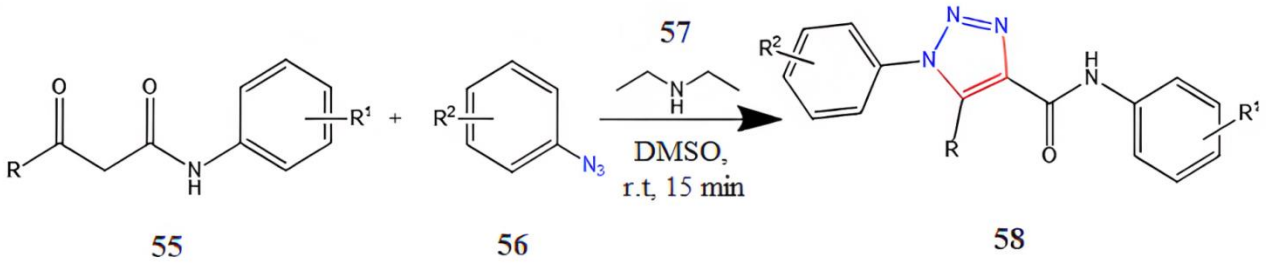


Fig. 18. Synthesis of 1,2,3-triazoles using (DMSO).

As a brand-new, recyclable, environmentally friendly and extremely efficient catalyst, a Cu-compound adsorbed on graphene oxide was generated. In order to get the required products in quick interaction times and good yields, Naeimi and Ansarian prepared hydroxyl-1,2,3-triazoles by using polymeric Cu-catalyst **Fig. 19** [65].

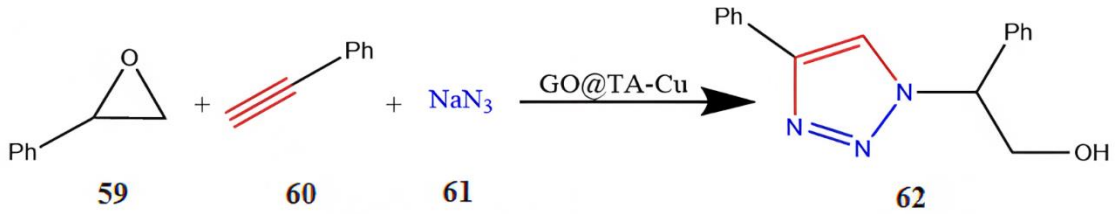


Fig. 19. hydroxyl-1,2,3-triazoles

2.7. Microwave assisted reactions methods

As a tool to enhance the rate of reactions, recently, unconventional energy sources such as microwave have been employed. Microwave coupling with click chemical techniques have been used. Lomas-Romero et al. utilized the catalyst sulfated-zirconia (SZ) in conjunction with sodium-azide, nitromethane and benzaldehyde while being exposed to microwave radiation in order to generate 4-aryl-NH-1,2,3-triazole compound **Fig. 20** [66].

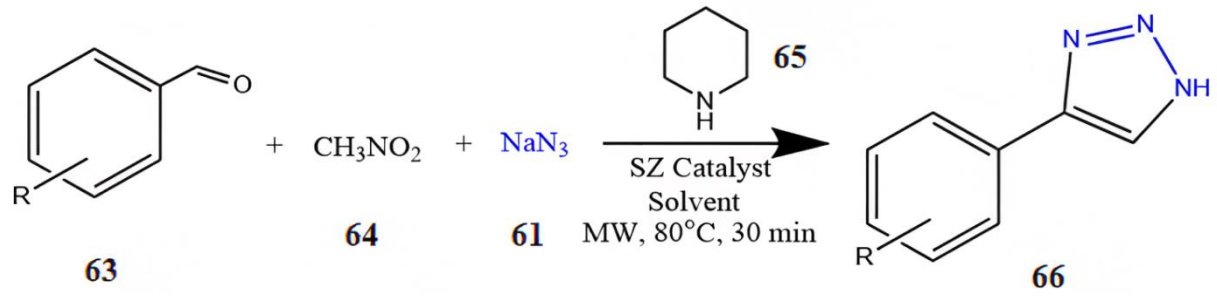


Fig. 20. Sulfated-zirconia (SZ) catalyzed synthesis of 1,2,3-triazole.

Haribabu and Biehl were able to generate benzotriazole compounds by using microwave [3+2]-cycloaddition on three components reactions. where an azide generated by reacting o-trimethylsilylaryl in the presence of cofactors is configured of aryne. Good benzotriazole compounds yields have been achieved by utilizing the microwave for 15 to 20 minutes at 125 ℃.

Thus, the interaction times are much less than the interaction under conventional heating **Fig. 21** [67].

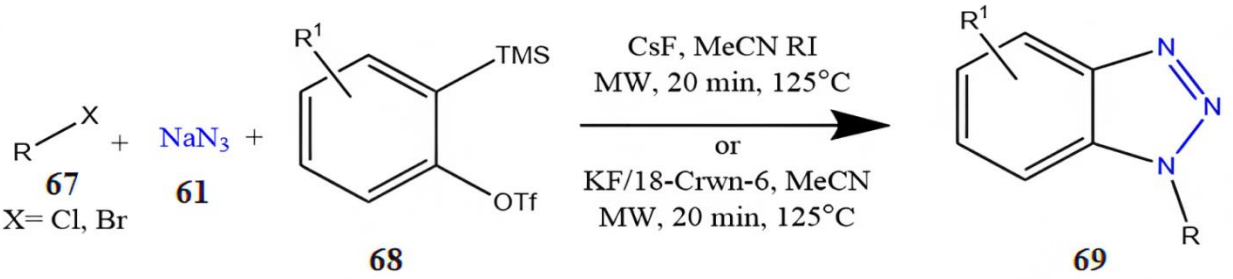


Fig. 21. Catalytic formation of 1,2,3-triazoles.

3. Compounds containing triazoles and sugar parts

The glycoconjugate action is remarkably dependent on the 1,2,3-triazole ring [68]. The distinctions between cancer cells and normal cells must be understood when developing pharmaceuticals. One of these differences is how glucose is specifically metabolized in cancer cells. Cancer cells require more glucose compared to healthy cells, which metabolize to get the energy they need to proliferate more. The Warburg effect is a phenomenon that results from alterations in mitochondrial metabolism. In other words, glycolysis provides energy to cancer cells [69]. Overexpression of (GLUT) transporters is linked to an increase in glycolysis in cancer cells. Therefore, sugars are a desirable vehicle for delivering pharmaceuticals directly to cancer cells. The (8-HQ) compounds can be conjugated with substitutes for sugar to generate compounds with enhanced bioavailability, solubility and selectivity [70]. The 1,2,3-triazole ring has been recently used in the synthesizing of a new glycoconjugate molecules [68] **Fig. 22**. The H-C(5) atom in triazoles acts as a H-bond donor, and the free e-pair on the N-(3) acts as an acceptor.

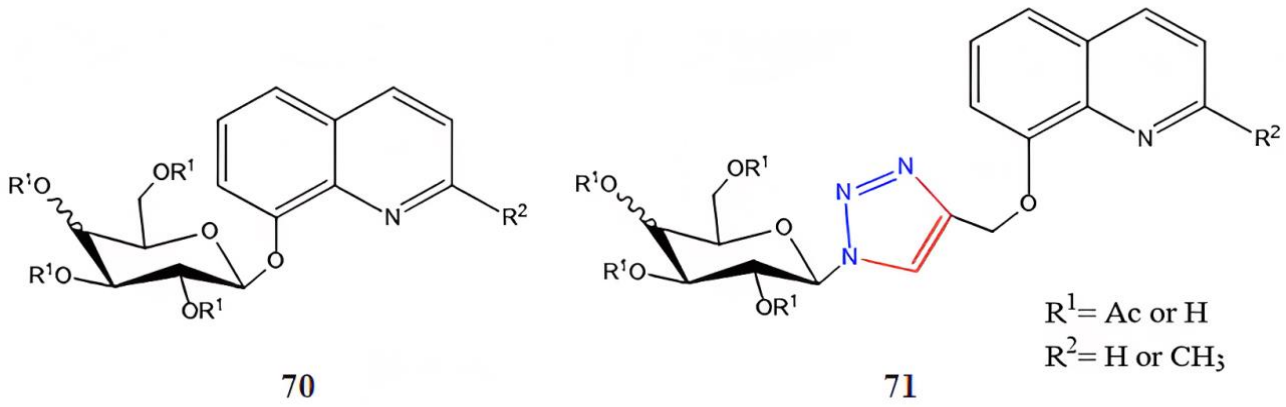


Fig. 22. Structures of previously obtained glycoconjugates.

Triazoles rings containing glycosides possess a vast array of biological properties, such as anti-microbial [71], anti-parasitic [72], anti-cancer [73] and anti-tuberculous [74]. Newly, it has been

found that 1,2,3-triazoles have a-glucosidase inhibitory activity [75]. Galectins 1 and 3 are crucial for the creation of anticancer drugs, and the glycosyl-triazoles function as inhibitors of these proteins [76]. Therefore, 1,2,3-triazole-glycosides are now helpful in the discover of new pharmaceuticals, and the creation of bioactive molecules based on carbohydrates is now a major search field [77].

3.1. Synthesis of sugar-based triazole derivatives

It's possible to generate sugar-triazole derivatives by combining stereo-defined 1-azido-sugar compound **72** and stereo-defined propargyl-glycopyranoside derivative **73** with CH_3CN as solvent and Cu(I) as catalyst at room temperature **Fig. 23** [78].

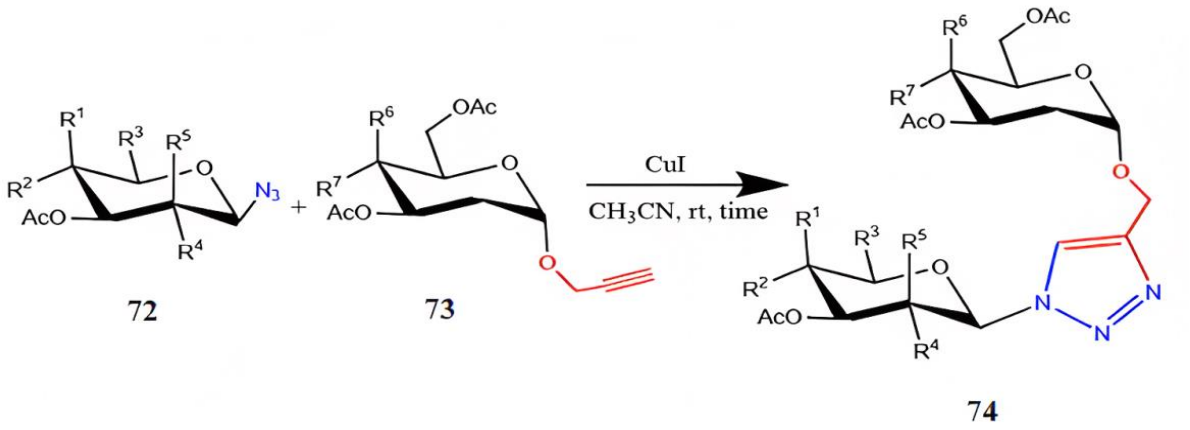


Fig. 23. Stereo-selective mimetic-glycolconjugates.

Several 1H-1,2,3-triazolyl glycohybrids containing at least two sugar units have been synthesized via altering glycosyl-azides alkynyl glycosyls or propargyl-oxy coumarins by the (CuAAC) reaction [79]. The ability of these hybrids to inhibit was tested. In comparison to Na_3VO_4 (Na-orthovandate) and $C_{25}H_{43}NO_{18}$ (acarbose), only a small portion of these triazolyl-glycohybrids **75** and **76** have revealed potential inhibitory effects **Fig. 24**.

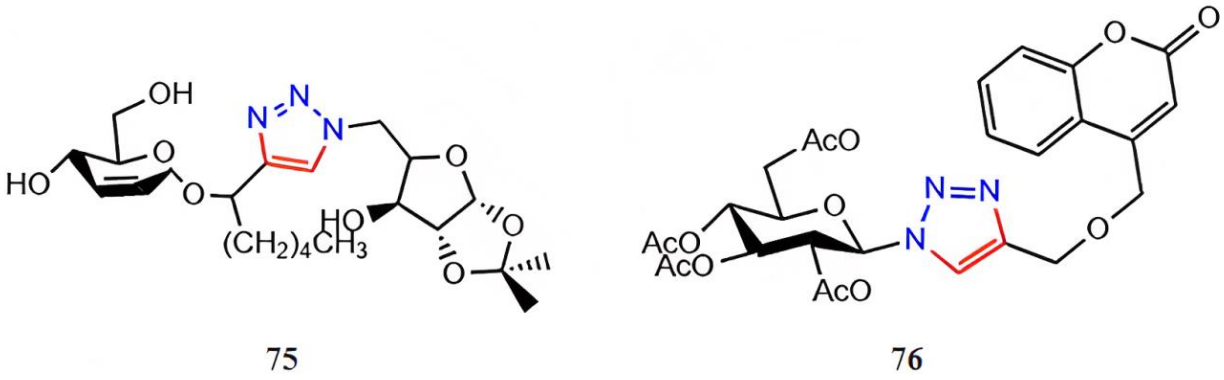
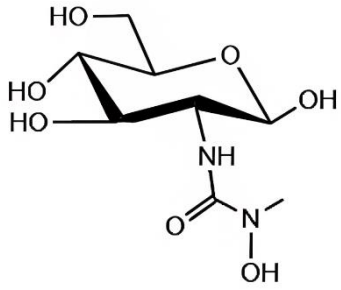


Fig. 24. Glycoconjugates with glucosidase inhibitory activities.

Streptozotocin **77** is used to treat pancreatic islet cell metastatic cancer **Fig. 25**. Also compound **77** rarely cures cancer; because a substantial risk of toxicity, thus, it can only be used by people whose cancer can't be surgically removed [80].



77

Fig. 25. Simple carbohydrate derivative used as drug.

Glycosyl-azides can be Synthesized in situ by glucal and trimethylsilyl-azide using Ferrier rearrangement, subject smooth coupling with alkynes under neutral conditions by using click chemistry reactions to provide 1,2,3-triazole-linked glycol-conjugates in good yields and with conservative stereoselectivity. The method gives a proper route to provide glycol-conjugates from glucals, trimethylsilyl-azide and alkynes by a three compounds reaction **Fig. 26**. 1,2,3-Triazoles are prospective targets for drug detection as they display a wide spectrum of biological properties such as anti-viral, anti-bacterial, anti-epileptic and anti-allergic behavior [81].

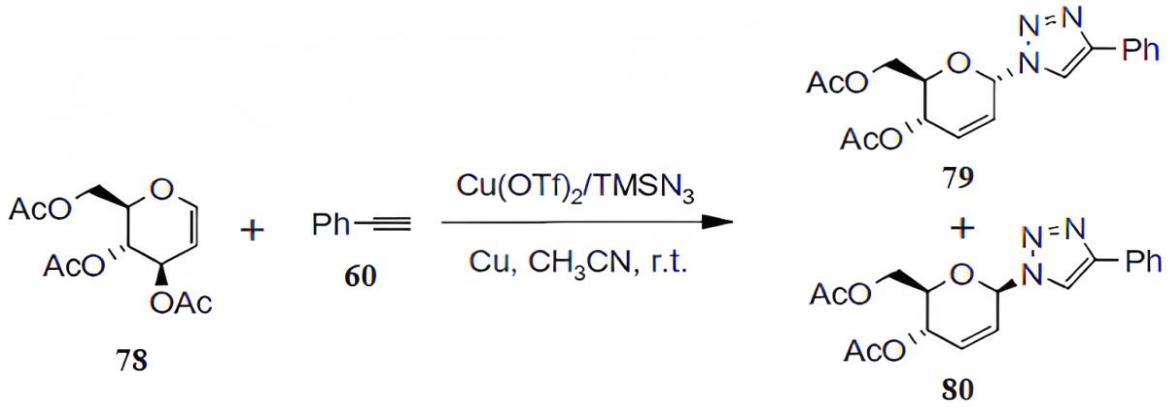


Fig. 26. Reaction of glucal, $TMSN_3$ and phenylacetylene.

3.1.1. Synthesis of mimic-glycoconjugates containing azido-monosaccharides and propargyl-monoglycosides

Eight mimic-glycoconjugates **74a-d**, **74`a-d** are synthesized by an interaction between two different forms of acetylenic mono-glycosides **73a-b** and different glycosyl-azides **72a-d**, **Fig. 27** [82].

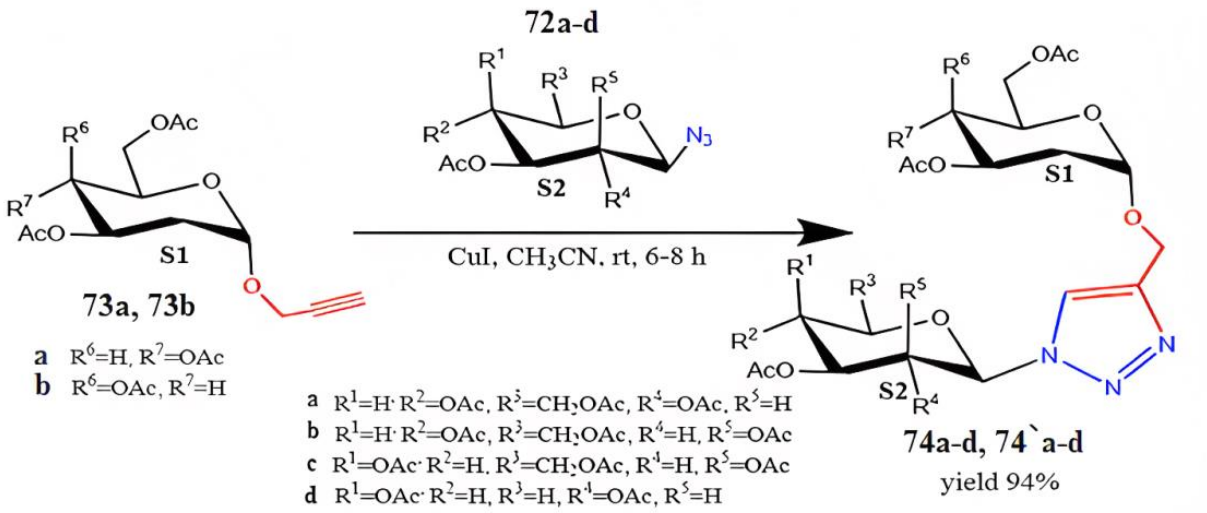


Fig. 27. Formation of compounds **74a-d** and **74`a-d**.

3.1.2. Synthesis of mimic-glycoconjugates containing azido-disaccharides and propargyl-monoglycosides

Mimic-glycol conjugates **82e-f**, **82`e-f** are synthesized in an interaction between two different forms of mono-glycosides with acetylene functionality **73a-b** and two azido-disaccharides **81e-f**, **Fig. 28** [82].

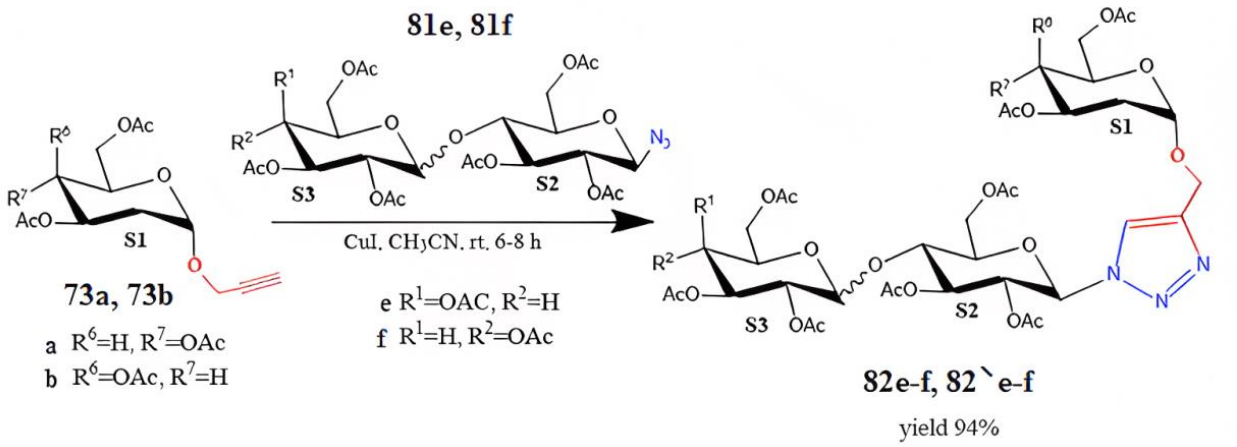


Fig. 28. Formation of compounds **82e-f** and **82`e-f**.

3.1.3. Synthesis of mimic-glycoconjugates containing azido-monosaccharides and propargyl-diglycosides

Mimic-glycoconjugates **84a-d**, **84`a-d** are synthesized in an interaction between four different azido-monosaccharides **72a-d**, and two different forms of propargyl-diglycosides **83c-d**, **Fig. 29** [82].

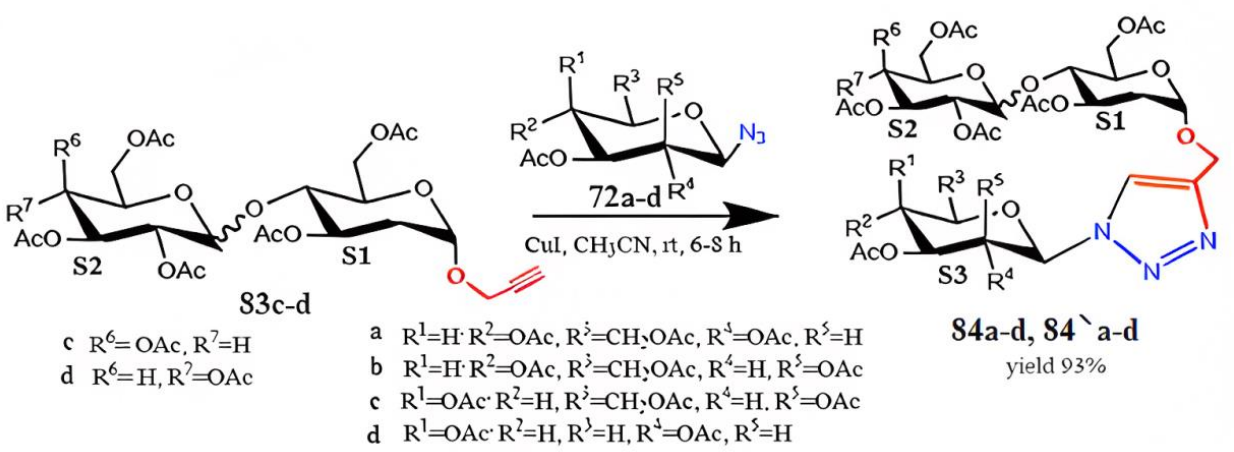


Fig. 29. Formation of compounds **84a-b** and **84`a-b**.

3.1.4. Synthesis of mimic-glycoconjugates containing azido-disaccharides and propargyl-diglycosides

Mimic-glycol conjugates **85e-f**, **85`e-f** are synthesized by an interaction between two different forms of diglycosides **83c-d** and different azido-disaccharides **81e-f**, **Fig. 30** [82].

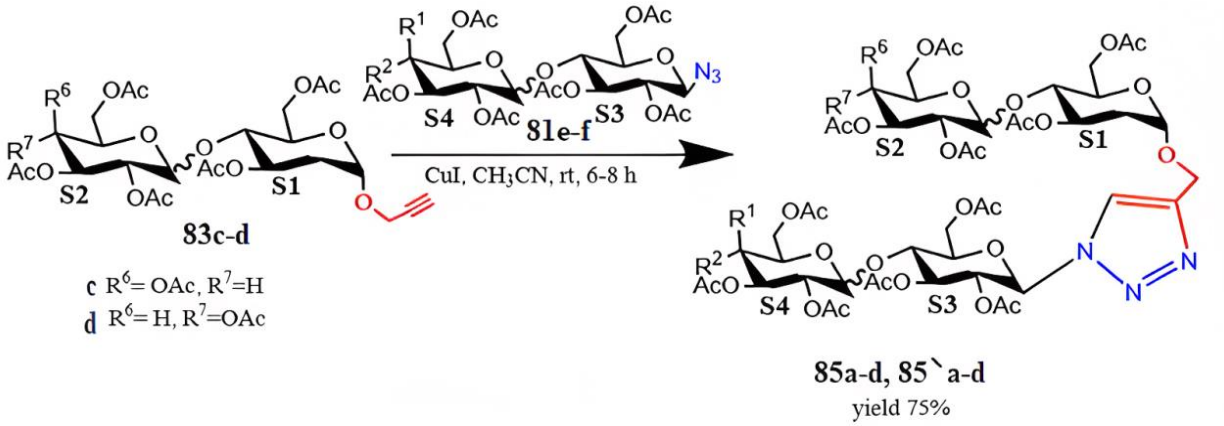
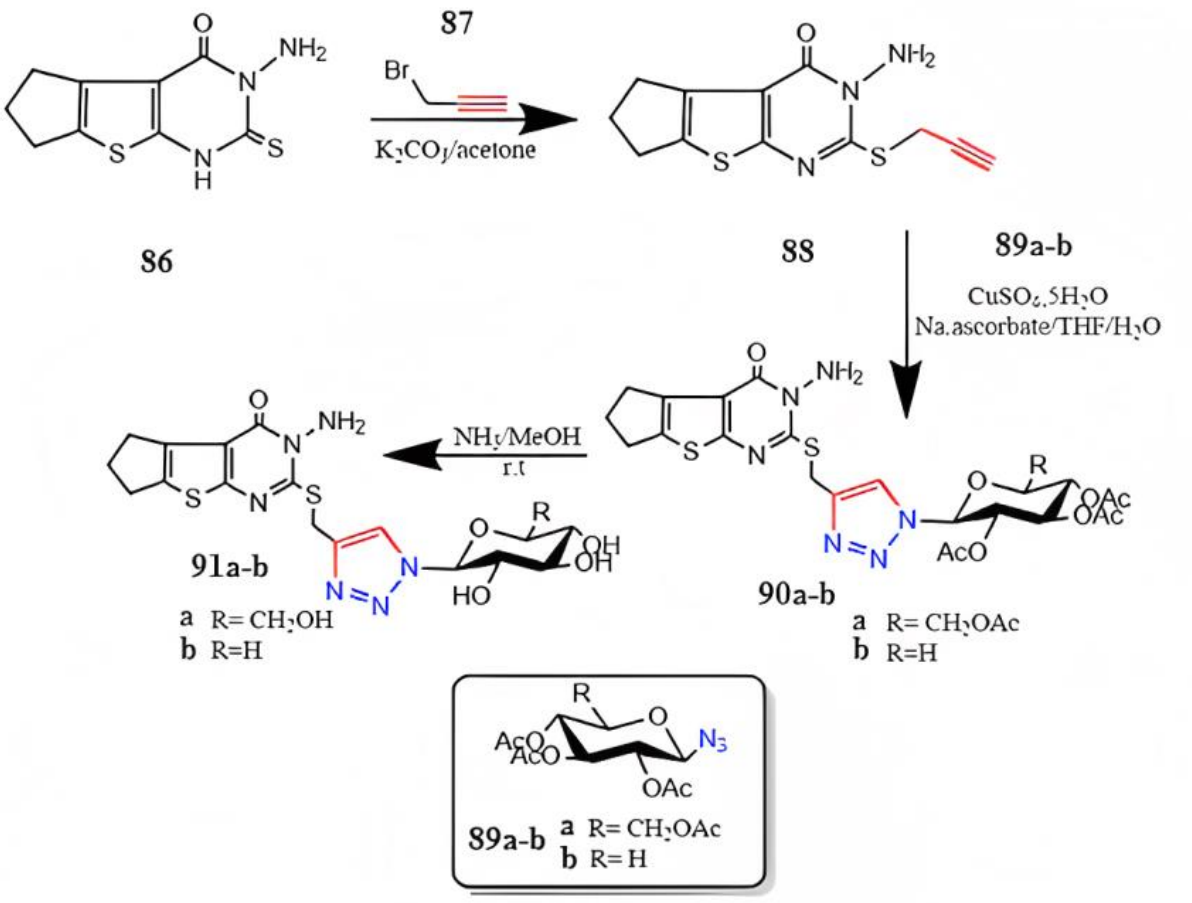


Fig. 30. formation of compounds **85e-f** and **85`e-f**.

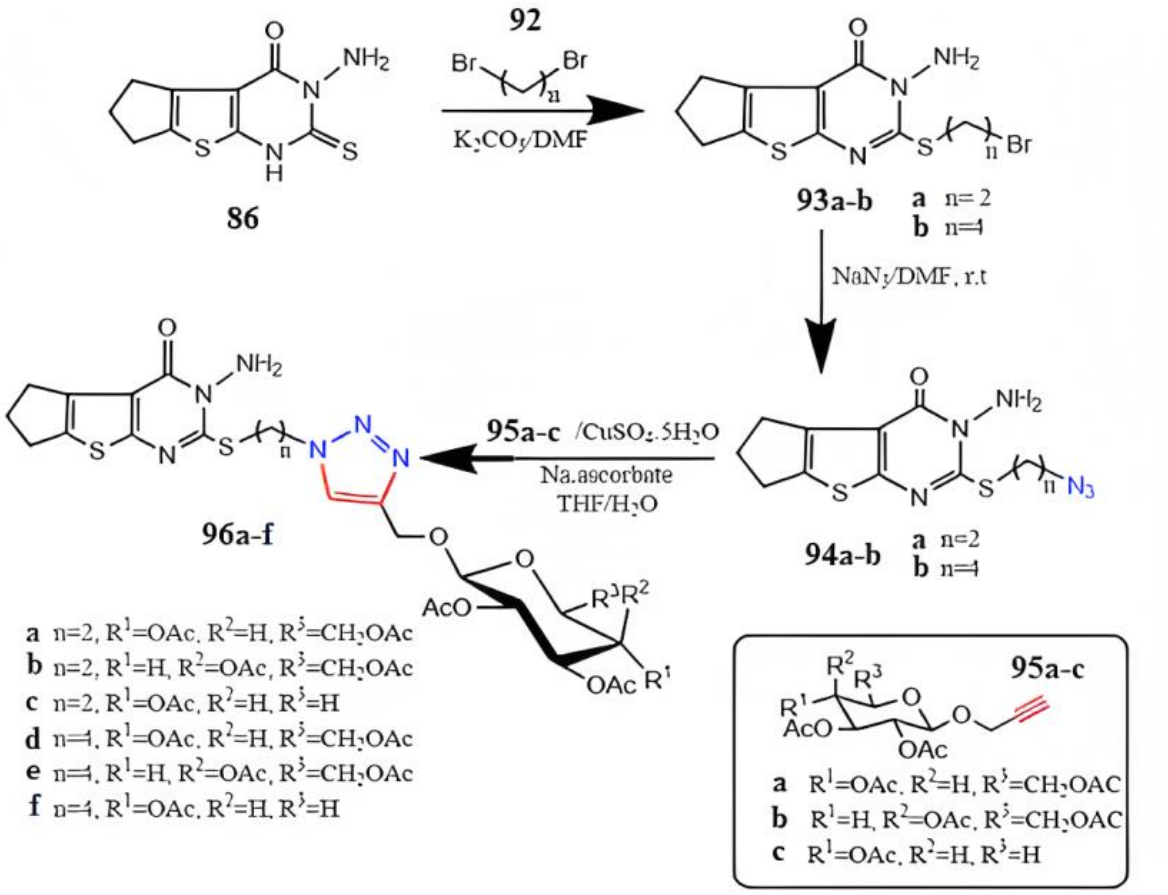
3.1.5. Thieno-pyrimidine system-based 1,2,3-triazole-glycosides synthesis

Two new derivatives possessing 1,2,3-triazole linked to thieno-pyrimidine-glycol conjugates were synthesized. A C-N1 connection between the carbohydrate moiety and the triazole immediately causes the first derivative, a 1,2,3-triazole-glycoside then is created **Sch. 5**.



Sch. 5. Triazole-glycosides-thienopyrimidine compounds.

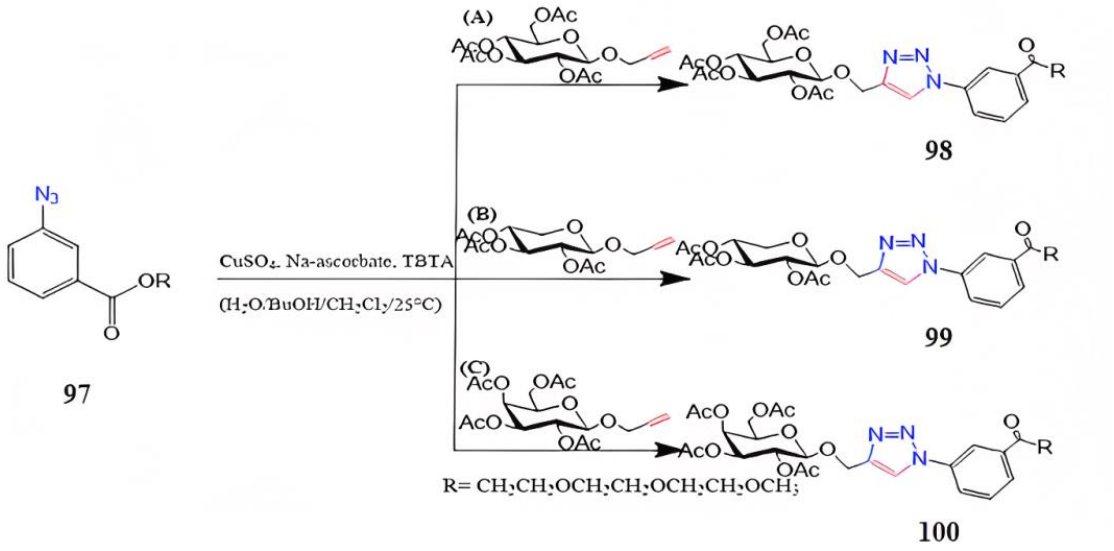
Thieno-pyrimidine bridging triazolyl-glycosides **Sch. 6**. The generated azides undergo a Cu-catalyzed dipolar cycloaddition reaction in a H_2O/THF (1:3) solvent with acetylenic glucose, galactose or xylose to create the required glycosyl-1,2,3-triazoles including thieno-pyrimidine system [83].



Sch. 6. Synthesis of C-linked glycosyl triazoles.

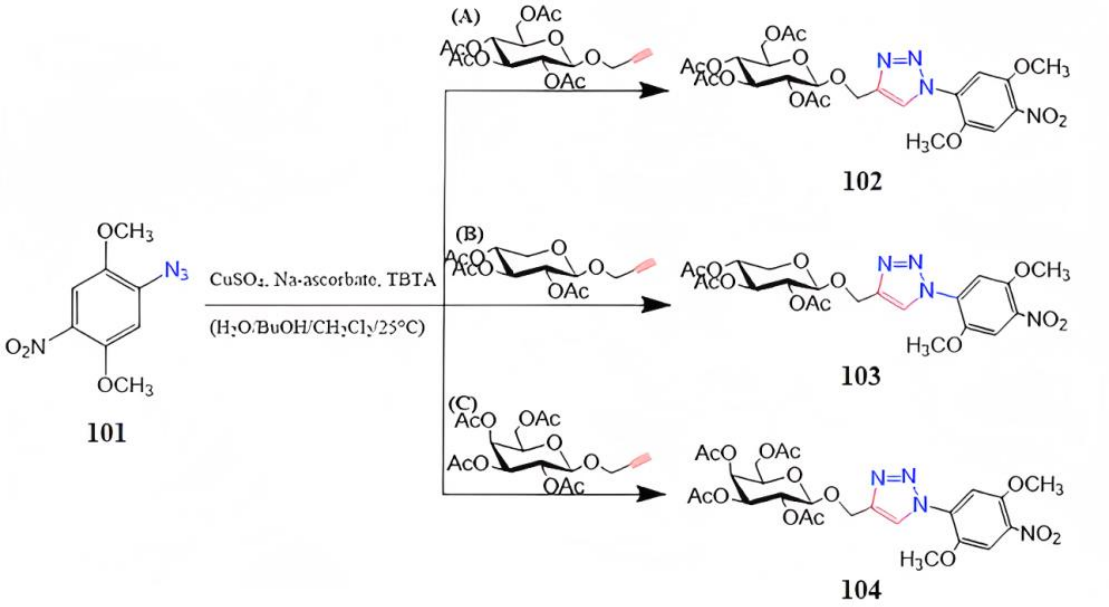
3.2. Click synthesis of 1,2,3-triazole glycosides

When the terminal alkyne groups of the acetylated forms of D-glucose **A**, D-xylose **B** and D-galactose **C** are combined with 3-azidobenzoate **97**, the corresponding 1,2,3-triazole based-glycosides **98-100** are created in excellent yields (75–81%). The aryl-substituted part and sugar units were connected through triazole core **Sch. 7** [84].



Sch. 7. Formation of compounds **98-100**.

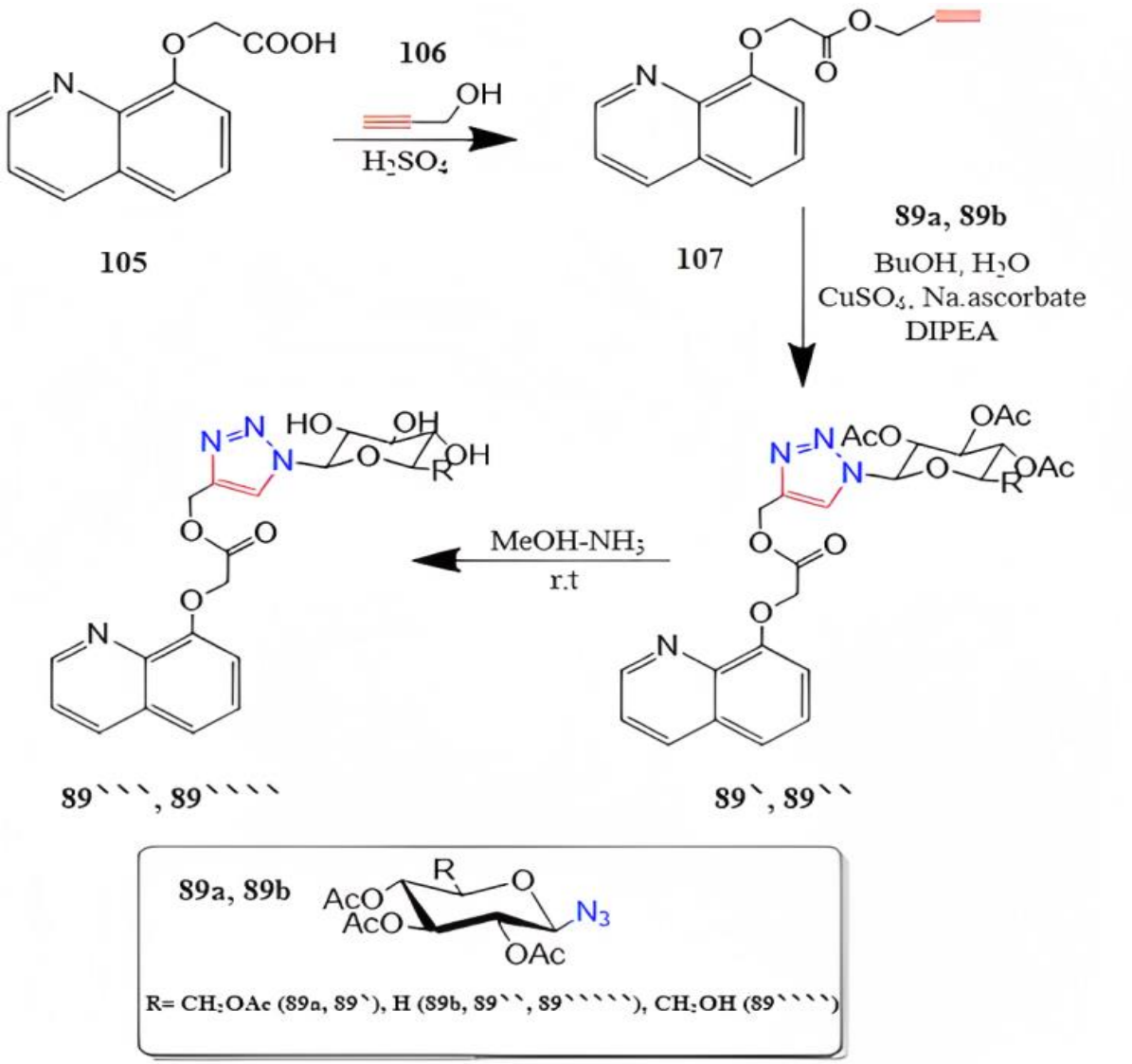
The aryl-azide compound **101**, undergo click with alkyne-sugars (pathway **A-C)** to create the require glucosides **102-104**, **Sch. 8** [84].



Sch. 8. Formation of compounds **102-104**.

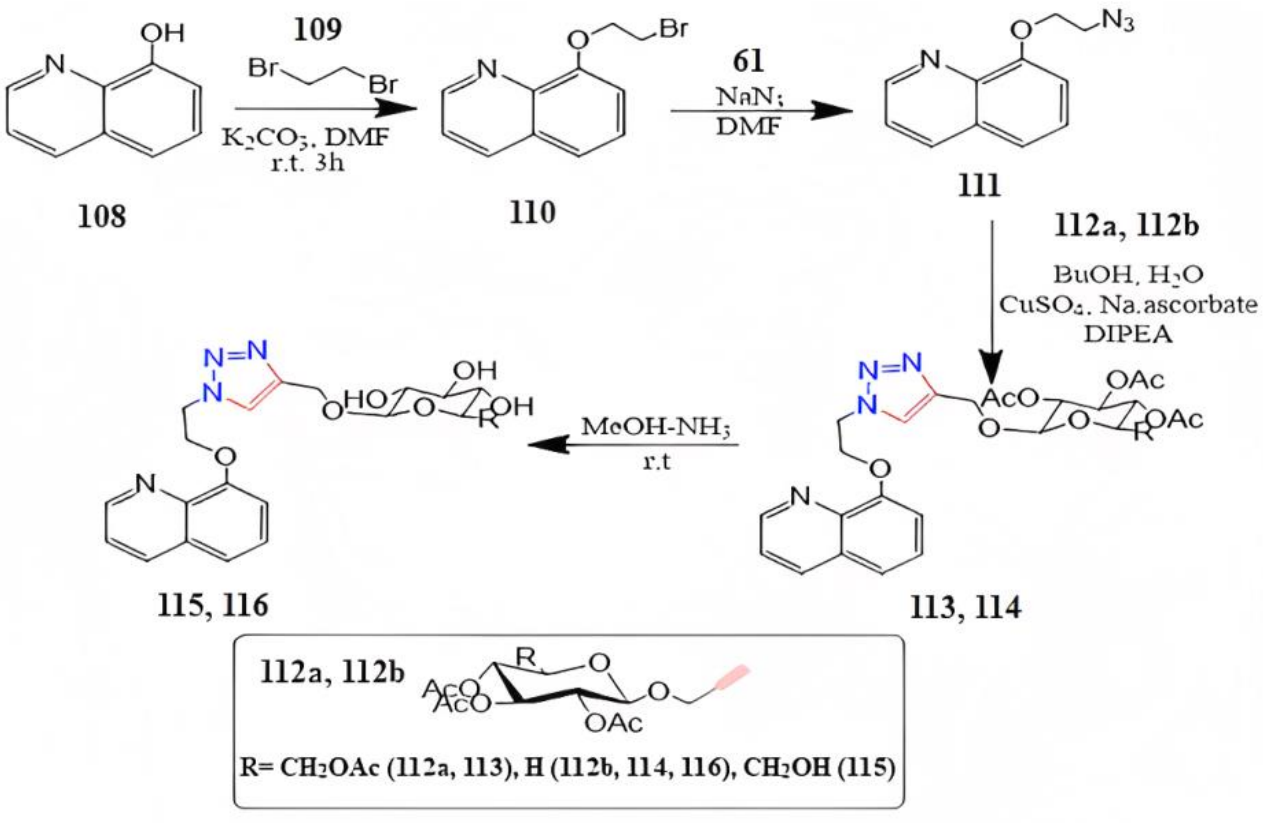
3.3. Synthesis of 1,2,3-triazole nucleosides and their analogs

Two molecules containing carbohydrates linked to quinolines were created by 1,2,3-triazole. The first quinoline **107**, which has an acetylene group, is generated via an esterification process between compound **105** and propargyl alcohol. The newly synthesized terminal acetylenic compound then engaged in a click dipolar cycloaddition interaction with azides **89a** and **89b**, resulting in the respective 1-glycosides **89`a** and **89`b**. The protected glycosides **89`** and **89``** were deacetylated to **89```** and **89`````**, **Sch. 9**.



Sch. 9. Synthesis of N1-1,2,3-triazole glycosides based quinoline system.

Glycosyl-1,2,3-triazole compounds were synthesized by introducing the created azide compound **111** with propargyl-sugars via a dipolar cycloaddition reaction, which was catalyzed by Cu **113** and **114** by utilizing a methanol-saturated ammonia solution, and the deacetylation of glycosides **113** and **114** was carried to give the corresponding final compounds **115** and **116**, **Sch. 10** [85].



Sch. 10. Synthesis of quiniline-O-alkyl-ilnked triazole glycosides.

4. Biological activity

Adding synthetic labels covalently to a biomolecular structure, such transformation of nucleic acids and proteins via the inclusion of chelates and fluorophores or when more than protein is combined together or when a complex carbohydrate is bonded to a peptide [86] is of interest for biocongigate achievement. 1,2,3-Triazole compounds, which are found in commercially available pharmaceuticals, have drawn great interest for synthesis, via click, of current medicines for conditions such as cancer, Alzheimer's disease, malaria, antiviral infections and tuberculosis [87-89]. It's possible to enhance pharmacodynamics, pharmacokinetics and physicochemical properties by combining a 1,2,3-triazole with various pharmacophores [90].

Sugar 1,2,3-triazoles were synthesized using click chemistry from galactose derivatives that contained either a C6 or C1 azide group (compound **117)**, **Fig. 31**. These derivatives proved to be moderate Trypanosoma cruzi trans-sialidase (TcTS) inhibitors in vitro (< 40% inhibition at 1 mm concentration), and acceptor substrates for TcTS-catalyzed trans-sialylation [91].

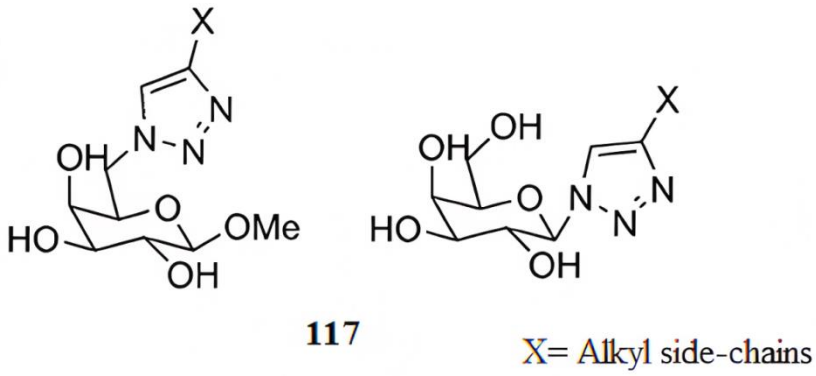


Fig. 31. Sugar 1,2,3-triazoles

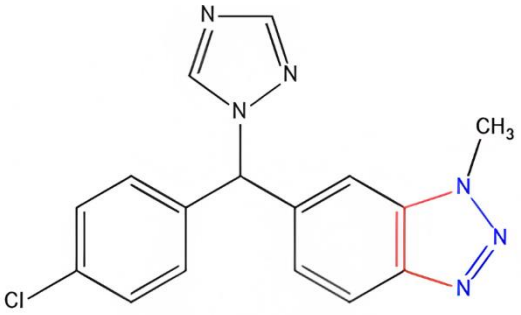
4.1. Triazoles as anticancer candidates

4.1.1. Triazoles as anticancer agents

According to the (WHO) fact sheet, published in September 2018, cancer is classified as the second leading cause of death worldwide, it accounted for 9.6 million deaths in 2018 [92]. Cancer is caused by gene mutations or interfering with normal cell differentiation which initiated by drugs, viruses, smoking or diet [93]. As one of the leading causes of death globally, cancer causes a great burden to both single human lives and the society as a whole. Although there have been progresses in the development of prevention and treatment of cancer, the successful treatment of cancer remains a challenge. Therefore, there is still an urgent need to search for some newer and safer anticancer agents that have broader spectrum of cytotoxicity to tumor cells.

The nitrogen containing class of compounds such as pyrimidine, triazole, peptide, and tetrazole that are found in many natural products are the important constituents of a number of modern drugs [94].

There are several anticancer drugs such as azole agents [95], alkylating agents [96], platinum agents [97], porphyrin drugs [98] etc. The majority of clinical pharmaceuticals have side effects such excessive toxicity, side curative effects and low selectivity. For this kind of disease, there are still no efficient chemotherapy therapies available. Therefore, pharmaceutical researchers are interested in developing new anticancer treatments with lower toxicity, better therapeutic effect and higher selectivity. Triazoles as Vorozole **118** are very important anticancer drugs **Fig. 32** [99].



Vorozole **118**

Fig. 32. Biologically potent compound containing triazole as an anti-cancer drug.

Numerous compounds with different biological functions containing triazole moiety are available **Fig. 33** [88].

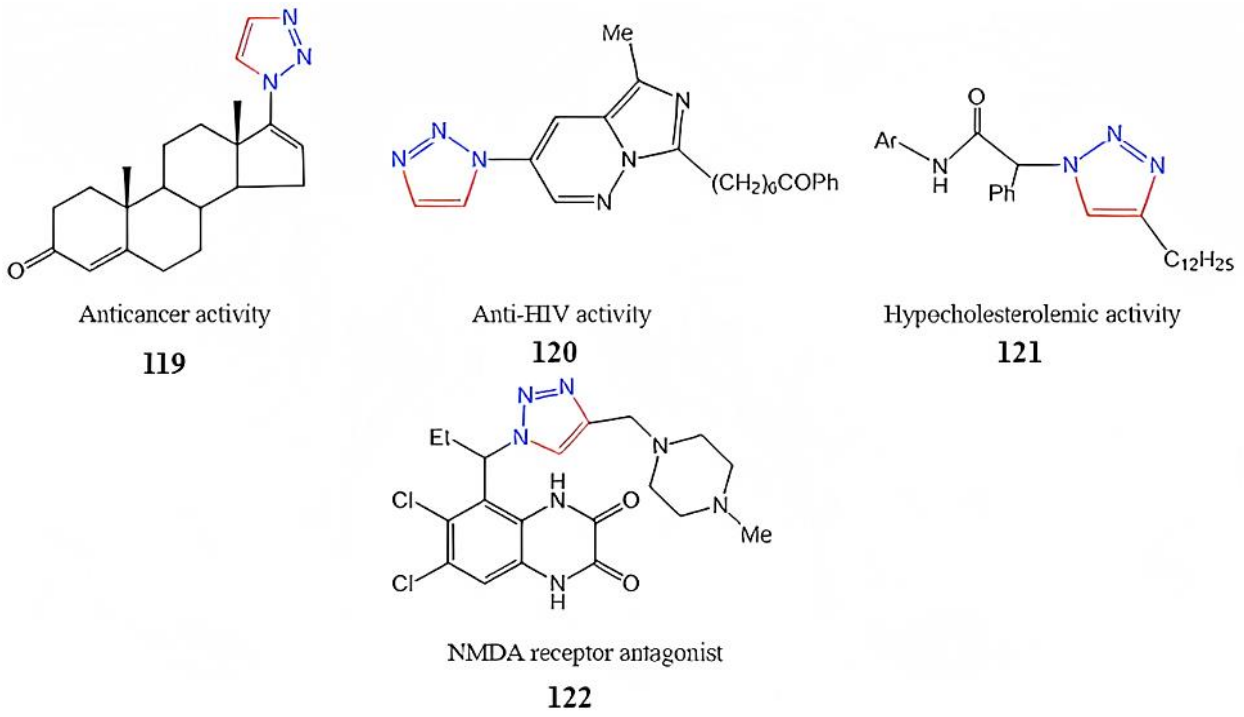
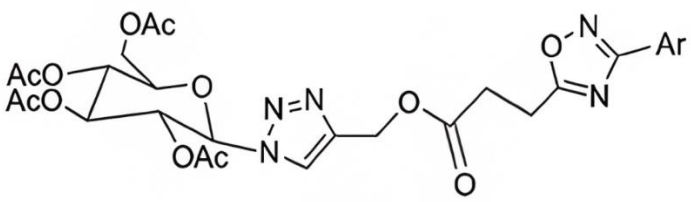


Fig. 33. Bioactive triazole-possessing molecules.

Analogs of triazolyl-functionalized oligo-nucleotide (ON) have considerable attentiveness as expectancy anticancer and antiviral agents [100].

Compound **123** showed weak cytotoxic activity (22–25% cell-growth inhibition against (NCl-H-292) lung carcinoma and (HEp-2) larynx carcinoma **Fig. 34** [111].



123

Fig. 34.

5. Compounds containing pyridine and triazole

Pyridine containing 1,2,3-triazole-carboline hybrid **126** (IC_{50}: 1.3 and 5.3 nM, MTS assay) and it's regio-isomer **127** (IC_{50}: 0.9 and 1.7 nM, MTS assay) could inhibit BET and elcade-resistant multiple myeloma cells JJN3R effectively with, respectively [102, 103]. In the patient-derived BR1077F triple-negative breast cancer xenografted mice model, compound **126** (oral administration) could inhibit 76% and 90% tumor growth at doses of 4.0 mg/kg and 6.0 mg/kg, respectively [102]. In the JJN3R xenografted mice model, compound **127** (1.0 mg/kg, oral administration) decreased 91% of tumor growth **Fig. 35** [103].

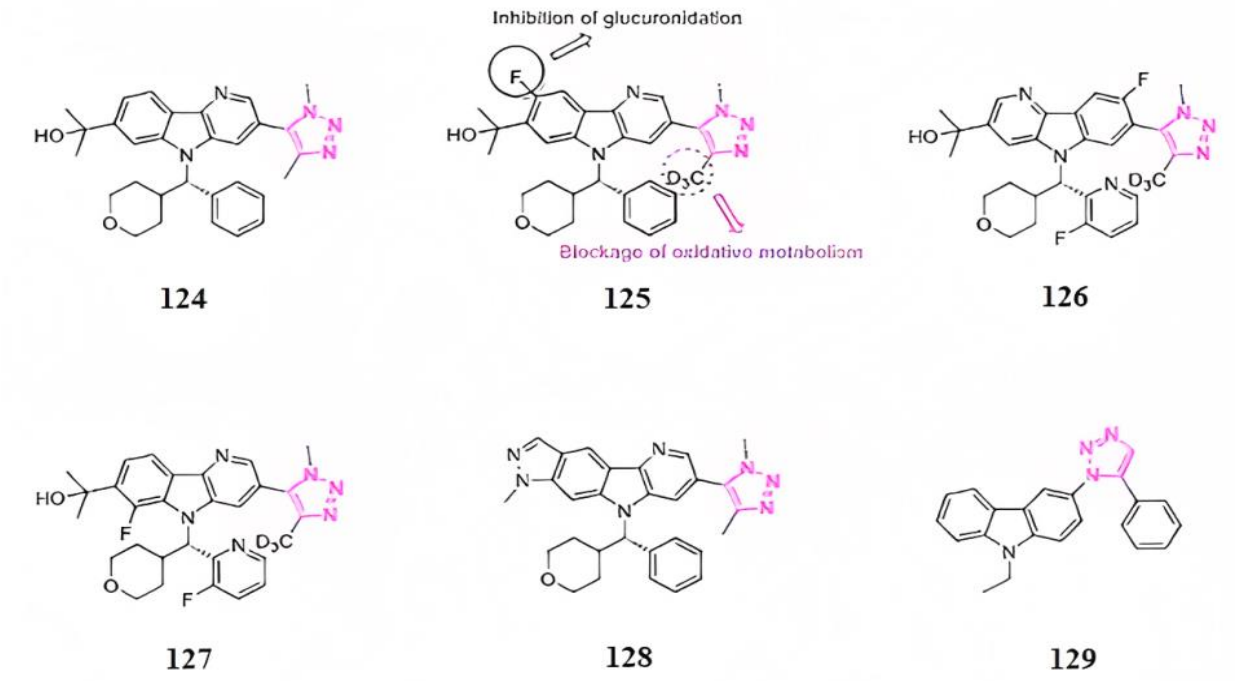


Fig. 35. Chemical structures of 1,2,3-triazole-carboline hybrids **124**–**129**.

The 1,2,3-triazole-pyridine hybrid **137** (IC_{50}: 5.2 nM, MTT assay) not only showed profound activity against (SH-SY5Y) cacner cells, but also displayed significant inhibitory effect against nicotinamide phosphoribosyltransferase (NAMPT, IC_{50}: 3.8 nM). The pharmacokinetic studies uncovered that compound **137** (10 mg/kg, intravenous administration) had acceptable pharmacokinetic profiles: t1/2 of 1.89 h and volume of distribution (Vd) of 31.8 L/kg. In the A2780

xenografted mice model, compound **137** (10 mg/kg, intraperitoneal injection) reduced ~50% tumor growth without significant affecting body weight **Fig. 36** [104].

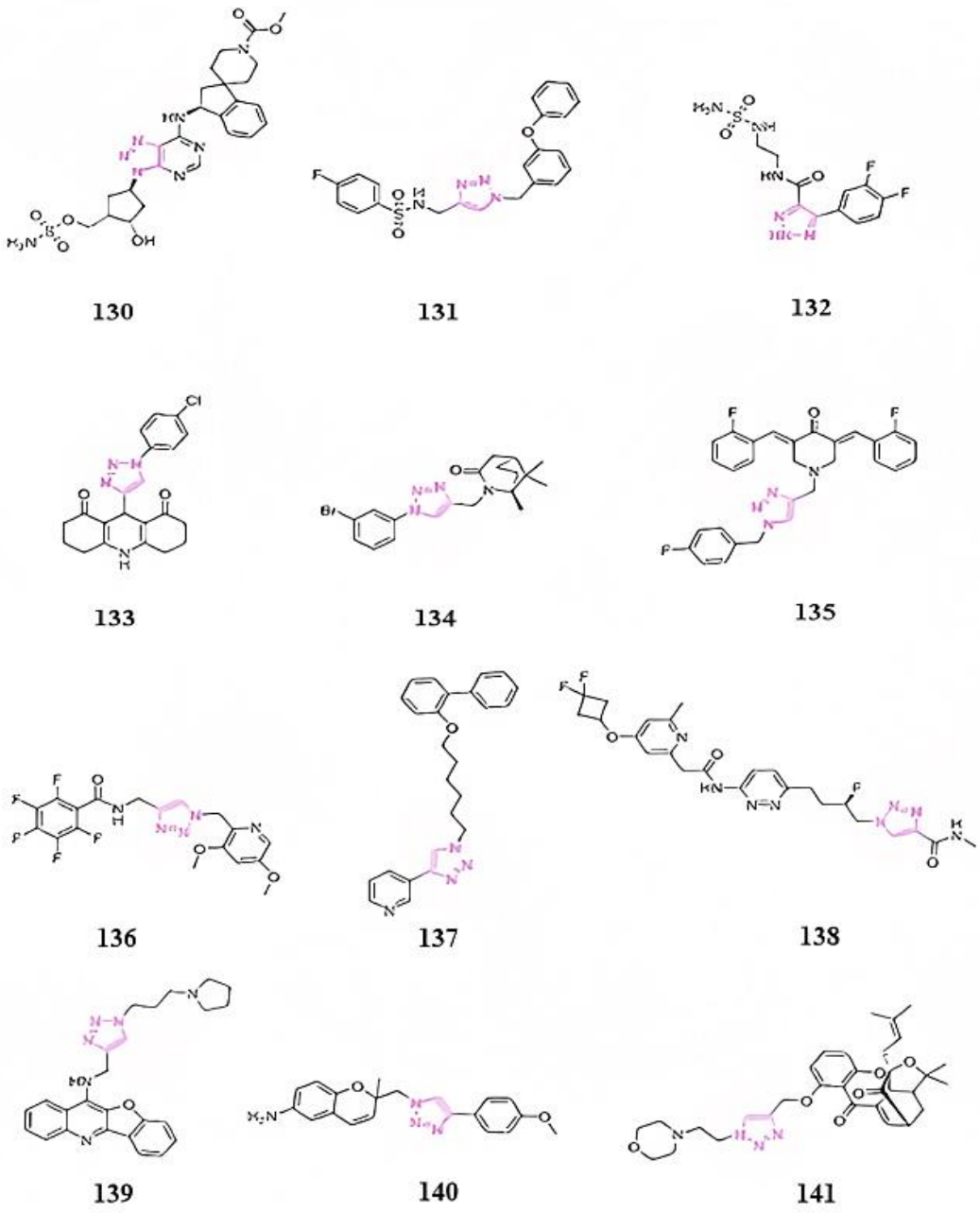


Fig. 36. Chemical structures of 1,2,3-triazole hybrids **130**–**141**.

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الملخص باللغة العربية
الكيمياء النقرية: نهج واعد لتخليق 1،2،3-تريازول

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في هذه المراجعة نعود إلى تفاعل الكيمياء النقرية وأهمية المركبات التي تحتوي على دورة 1،2،3-ترايازول.

الكلمات المفتاحية: الكيمياء النقرية، CuAAC، 1،2،3-ترايازول، ريجيوسومر، أزيد-ألكاين