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Pharm logical Application of Click Chemistry: A review

Rana I. Faeq[1] Yusra J.Ahmed[1] Sarab M. Alazawi*[1]
[1]Department of chemistry, Collage of Science, Mustansiriyah University, Baghdad / Iraq
*Corresponding author: sarabmahdi@uomustansiriyah.edu.iq
ORCID ID https://orcid.org/0000-0002-0583-8203

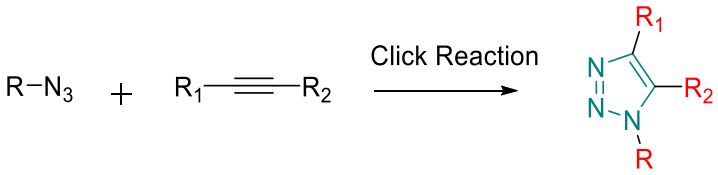
Abstract

The 1,2 ,3-triazole moiety is an important biomolecule produce by the click reaction. Copper, ruthenium catalyzedazide/alkyne cycloáddition pathway, click reaction is resulted of five membered rings. In order to be utilized as anticáncer, antimicrobial, antituberculosis, antiviral, anti-diabetic, antimalarial, anti-leishmanial and neuroprötective agents and also in fluorescent technology, biological targets required a method bearing the linker feature of 1,2,3 -triazles and a new type of 1,2,3-triazole including crosses with its conjugates. This review summarizes progresses over the last few years in application of 1, 2, 3-triazole derivatives and its utilities as a biomolecule. Researchers in organic fields, medicinal chemistry, photochemistry, and pharmacology will advantage from this study. This review offers important knowledge which attentive to readers.

Keywords: click chemistry, 1,2,3-triazole, antibacterial, delivery drugs, antiviral

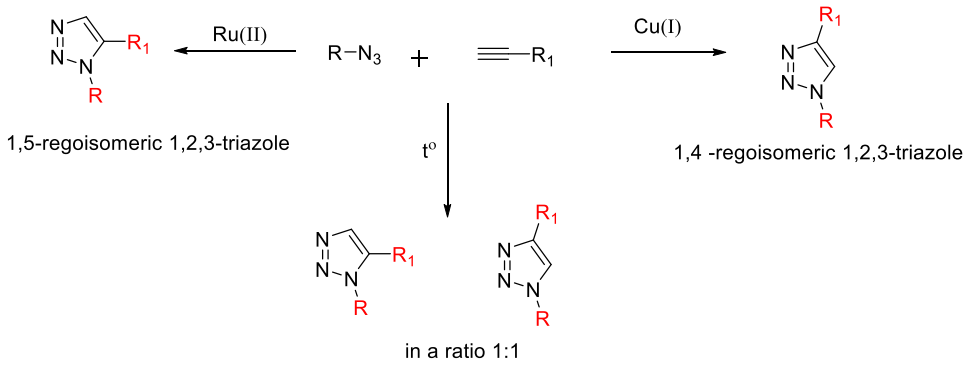
Introduction

The copper (I) catalysed Huisgen 1,3-dipolarcycloaddition,is a another term to "Click Chemistry" which was coined by Sharpless (Devaraj and Finn 2021). a 1,4-disubstituted triazole is a selective product form by alkyne and an azide moiety react together, as shown in Scheme 1. The merits of this reaction is very high yields, most by-products can be clean by common methods, and the product is regioselective. It can occur in most solvent and cheaper like aqueous solvents, resulting more environmentally - friendly than other reactions.



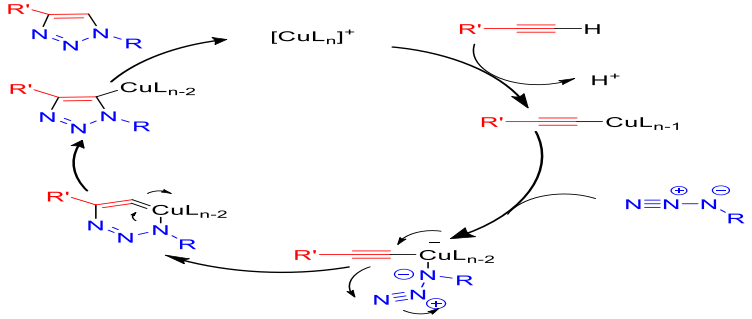
Scheme 1: Click reaction

The 1,3-dipolar cycloaddition, which holds Huisgen's name, developed in the 1960s after Huisgen's pioneering work on the 1,3-dipolar cyclization reaction, which was initially described by Michael in 1893[2,3]. Until Meldal and Tornoe discovered in 2002 that using copper(I) salts as catalysts for the reaction in organic solvents, the rate of reaction was increased, and only the 1,4-regioisomer was formed, the first reaction did not require the use of a catalyst and quite harsh conditions were required for click reaction (Tornøe, Christensen, and Meldal 2002). In the meantime, Sharpless developed a comparable reaction in a solution of water utilizing sodium ascorbate as a reducing agent to synthesize the active copper(I) species in situ(Rostovtsev et al. 2002). Also in 2005, same researcher declared to the formation of the 1,5-disubstituted triazole isomer by reaction between azides and terminal alkynes and using ruthenium cyclopentadienyl complexes as catalysis (RuAAC reaction)(Zhang et al. 2005)(Johansson et al. 2016). Other less efficient catalysts include Ni^{2+}(Golas et al. 2006), Pd^{2+},Pt^{2+}(Chowdhury, Mandal, and Achari 2005) and Au^{+1}(Powers et al. 2015)(Partyka et al. 2007). Copperçatalyzed azidealkyne cyçloaddition (CuAAC) considered as a type of Huisgen 1,3-dipolar cycloaddition and an important branch of click reaction, which is including different type of reaction such as thiolene, oxime, Diels-Alder, Michael addition and pyridyl sulphide reactions (Huisgen, Szeimies, and Möbius 1967).



Scheme 2: Copper -catalyzed azide-alkyne cycloaddition (CuAAC)(Liang and Astruc 2011)

1,4-disubstituted 1,2,3-triazoles is basic constriction for Cycloaddition (CuAAC) which including the interaction between an aliphatic azide and alkyne terminal part in the existence of copper. The click reaction has been improved to be a simple, selective and productive reaction via allow the two molecular building blocks in organic reactions to connection within moderate reaction circumstances with little or no impurities(Guo et al. 2006). The copper acetylide and the copper metallacycle are the next phases in the click reaction's process steps. However, a number of hypothesized processes exist. The copper is supposed to coordinate to the alkyne's -bond in the first proposed mechanism, which is illustrated in Scheme 3. Following the removal of the terminal proton, the copper acetylide is created. The copper then receives azide coordinates. The charge on the copper helped an intermolecular attack that caused the alkyne to link to the azide. In order to generate the triazole molecule and restore the copper catalyst, the six-membered copper metallacycle first experiences ring contraction(Worrell, Malik, and Fokin 2013).



Scheme 3: Mechanism proposed of CuAAC reaction(Rodionov, Fokin, and Finn 2005)

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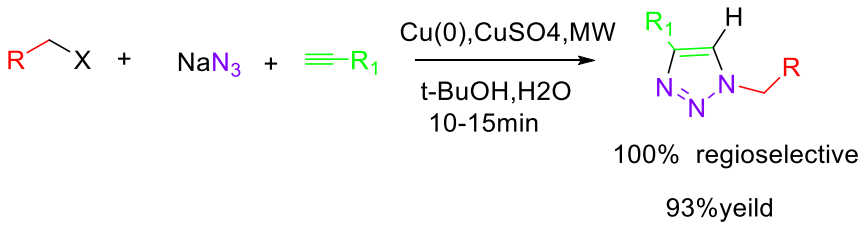
A several attempts have been reported over the last decade to developing the click approach, including non-traditional energy bases such as microwave radiation, ultrasound and photo-induced reactions rather than common chemical reactions(Rostovtsev et al. 2002). In term of an effective tool, this approach is improving the reaction speed of different chemical alterations. Recent literature have been described, a few microwave-Cu(I) coupled chemical click techniques. A Cu(I) catalysis was employed for microwave activation to increase the 1, 3-dipolar cyçloaddition of azide and alkynes terminal part under solvent-free circumstances resulting in synthesis 4-substituted 1 , 2, 3-triazol (Guezguez et al. 2006). The utilization of several alkyl halides and alkynes with different functionalities when irradiated with microwave radiation by Prasad Appukkuttan et al. allowed them to successfully shorten the associated reaction time from hours to minutes and enhance the product yield(Appukkuttan et al. 2004). The azide is produced in situ from belongs to halides, whereupon they are catch by copper (I) acetylides, which convert to 1, 4-disubstituted 1, 2, 3-triazoles Scheme 4. Performing both steps of this process under microwave heating lead to greatly decrease the reaction time. the products were obtained using normal filtering (Loupy 2004).



Scheme 4: 1, 4 -diasubstituted 1, 2 , 3-triazoles

It was found that this method effectively produced fully regioselective 1, 4 -disubstituted-1, 2, 3-triazoles, which frequently crystallize out of the reaction mixture and do not require challenging purification techniques. (Singh, Chowdhury, and Koley 2016). This technology offers a way to produce triazole compounds in their pure form while avoiding the isolation and handling of potentially unstable tiny organic like azide(Bräse et al. 2005)(Karimi 2017). The current study will emphasis mainly on the latest literature (up to 2013) of applications for click reaction in the medicinal chemistry field, in a specific utility of 1,2,3-triazole molecule as pharmacophore. Our study provides vital information to interested academics because this is a topic that is rapidly developing.

Synthesis of 1,2,3-triazoles

The CuAAC reactions

1, 2,3-triazoles is the basic characteristic of a click cycloaddition which is consisted CuI catályzed Huisgen1,3 -dipolarcyclóaddition of azides & terminal alkynes.1,4-substituted products that forms in this reaction making it regiospecific (Rostovtsev et al. 2002). The common preparation pathway of 1,2, 3-triazoles via click reaction is shown in scheme 1A. An interaction between organic azides and alkynes in presence of Cu(I)-catalysed is the basic route of Huisgen 1,3-dipolar cycloaddition, to form only the 1,4-regioisomeric 1,2,3-triazoles. Non-catalytic thermal pathway is known when ruthenium catalysts are used in place of Cú(I) and the major products is 1,5-regioisomeric 1,2,3-triazoles that produces from this process (Zhang et al. 2005). Numerous methods of preparation 1H-1, 2, 3-triazoles consisting of CuAAC have been successful and developed, using different copper source. $CuSO_4$ or $Cu(OAc)_2$ as the main source for copper by Sharpless and co-workers in Cu-AAC reaction. Copper compounds were used in conjunction with reducing agent like sodium ascorbate to form Cú(I) in situ in an aqueous environment (Hein and Fokin 2010). Since earlier publication, indicated that alternative sources of copper have been exploited due to the particular reaction conditions, for example when the CuAAC reaction was occurred in an organic solvents (CH_3CN, DMF, ĐMSO, THF), inthis cáse the suitable source of copper is CuI. This reaction effectively works in both aqueous and organic solvent to produce selectivity product which can be

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isolated with simple filtration. 1,2,3-triazole is tolerant of numerous functional group, triazole component is stáble and resistant to the oxidation, reduction and hydrolysis reaction.

The study by Yoo *et al*.(Yoo and Ahlquist 2007) have demonstrated that a catalytic quantity of CuI effect in the formation of the desired 1,4-disubstitued-1,2,3-triazole in organic conditions, however, it was found that using base is required in this reaction upon to promote the generation of an intermediate copper acetylide (Bock, Hiemstra, and Van Maarseveen 2006). Most CuAAC reaction usually produce triazole moiety with coordination to copper metals, this problem can overcome by extracting copper from the reaction media by washing with aqueous ammonia solution or ethylenediaminetetraacetic acid (EDTA) solution (Ornelas et al. 2007).

Biological application of Click chemistry

Click reaction as anticancer and antibacterial

Heterocyclic organic compound have been played an important role in pharmaceutical and medicinal chemistry particular, these compounds including five membrane nitrogen heterocyclic(Rejhová et al. 2018). Azole compound is one of promising compound, 1,2,3-triazole and 1,2,4-triazole are considered one of mainly heterocyclic compound present in the several agents of medicine(Abbood et al. 2022). Click reaction are represented by 1, 2,3, -triázole, a large number of studies have been performed on triazole and its derivatives, illustrating the pharmacological bearing of this heterocyclic nucleus due to their stability in hydrolysis in acid or base media, Furthermore, Both the acidic and basic properties of molecular triazoles are weak(Usachev 2018). The 2H-1,2,3-triazoles can be tautomerized but are rarely oxidized. Their susceptibility to reducing agents is greater. They are more susceptible to reducing agents. In addition, many other features such as great triazole system dipole moments, bioisosteric effects (Bozorov, Zhao, and Aisa 2019) and the triazole units are an important scaffold in medicinal chemistry and biological application due to the heteroatoms' collective structure(Bonandi et al. 2017).

Wu et al. presented BTTES1 , which included a ligand based on tris(triazolylmethyl)amine that interacted to Cu (I) throughout this reaction, resulting in a quick click reaction without obvious toxicity in organisms. The catalyst system allowed for non-intrusive visualization of fucosylated glycans throughout the early stages of zebra fish development.(Soriano del Amo et al. 2010) (Figure 1)

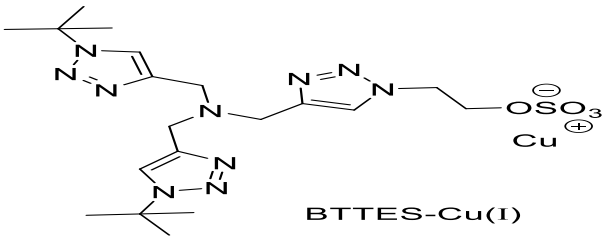

Figure 1: The structure of BTTES 1

Other report that examined the ability of bioothogonal reactions for bioconjugatin in four diverse in living systems. These molecules BTTAA, BTTES, TBTA and THPTA were developed as biocompatible. Unmatched bioconjugation efficiency was discovered in copper-catalyzed azide-alkyne cycloaddition, resulting in a very effective and adaptable approach for a greater variety of applications of biology(Besanceney-Webler et al. 2011).

On the other hands, click reaction has been use as anticancer, due to that 1,2,3-triazole units display various biological activities like anticancer or clinical agent. Numerous report has been reported about using various derivatives of 1,2,3-triazole as tumor inhibitor(Agalave, Maujan, and Pore 2011).

As a novel method for imaging cancer cells and/or radionuclide therapy, Yim et al. reported the preparation and biomedical evaluation a library of 4,7,10-tetraaza,cyclododecane-1,4,7, -tetraaceticacid (DOTA) connected monomeric, dimeric, and tetrameric [Tyr33] octreotide core

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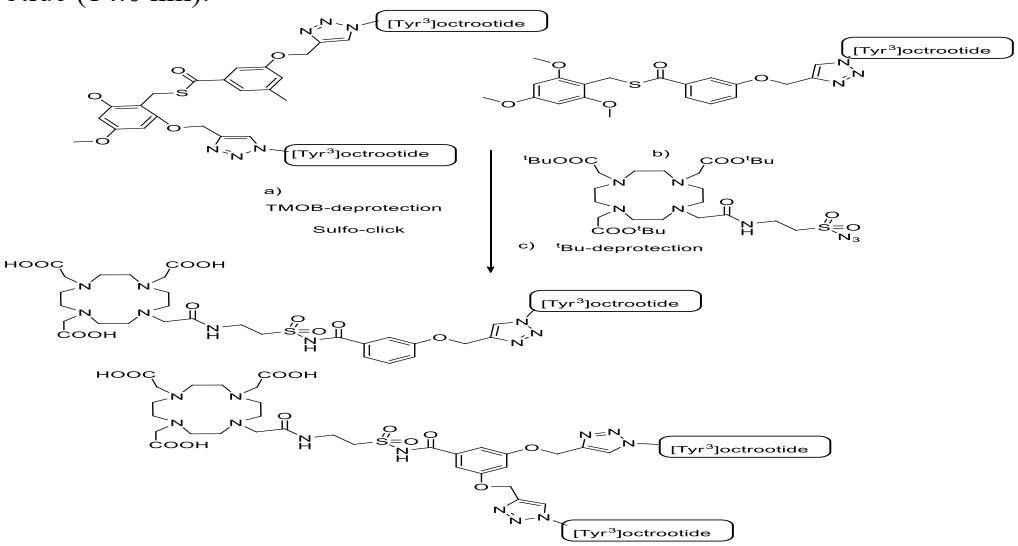
derivatives (Yim et al. 2010). Prepared derivatives of triazole were produced utilized CuI as catalyzed in 1,3 -dipolar cyçlo addition of peptidic azides and dendrimer produce alkynes and following presented free metal of DOTA by the thioacid part with sulfonylazide amidation (sulfo-click reaction). Rat pancreatic AR42J tumor cells is used to examine a competitive binding assay, The most powerful binding affinity ($IÇ_{50}$=1.32 nm) was demonstrated by the monomeric [yr3]octreotide conjugated tracked via dimeric [Tyr3]octreotide (2.45 nm), and tetrameric [Ťyr3]octreotide (14.0 nm).



Scheme 5: Sulfo-click reaction route

At the meantime, Carvalho *et al*. synthesized a series of sugar 1, 2, 3-triazoles derivatives via click reaction from galactose derivatives that consisted either a C6 or C1 azide group (compound) [66]. These compounds were found to have only moderate (40% inhibitory activity at 1 mm concentration) in *vitro* Trypanosoma cruzi trans-sialidase (TcTS) inhibitory action and to be acceptor substrates for TcTS-catalyzed trans-sialylation Figure 3. The derivatives of triazoles coupled sugar displayed low-hundreds of micromolar range of trypanocidal activity towards educated trypomastigote species of T. cruzi. The results suggested that these compounds show specific mode of antiparasite action against cultured mouse spleen cells instead of a generic cytotoxic effect(Hradilová et al. 2012).

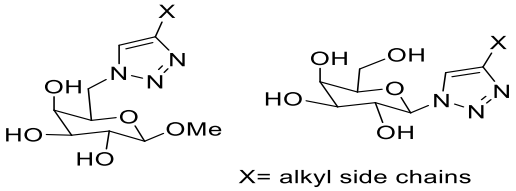


Figure 3: chemical structure of sugar triazole derivative

Yoon and *et al*. designed a new synthetic strategy for fast formation of 28-membered lavendustin-mimetic tiny compounds by click reaction. The synthesized molecules were assessment towards tumor cell lines. The molecules containing X=Ph$(CH_2)_3$ displayed harmful action against to the CCRF-CEM leukemia cell line with IC_{50} = 0.9 µm (Yoon and Ryu 2010) Figure 4.

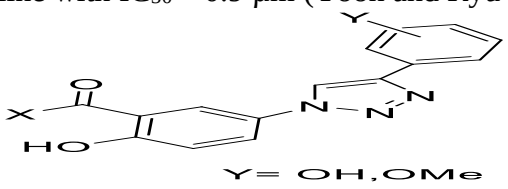


Figure 4: the structure of click reaction derivatives

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Moreover, Kumar *et al.* produced two kinds of 1, 4-disubstituted 1,2,3-triazoles in one-pót approach of á-tosyloxy ketones/a-haloketones, sodiumazide, in addition to alkyne terminal in existence of aqueous PÉG via a click reaction rout ; these derivatives were assessed for inhibitory activity of Srckinase. An analysis of structure activity relationship was illustrated that substituted with C_6H_5- and 4-$CH_3C_6H_4$- at the 4-substuted for both types with reduce the big size of aromatic group at the 1-loction in type 1 attributed typically to the moderated Src inhibition activity (IC_{50}=32–43 mm) of 1,4-disubstituted 1,2,3-triazole(Beckmann and Wittmann 2007) Figure 5.

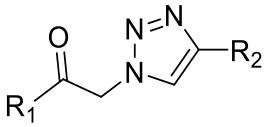
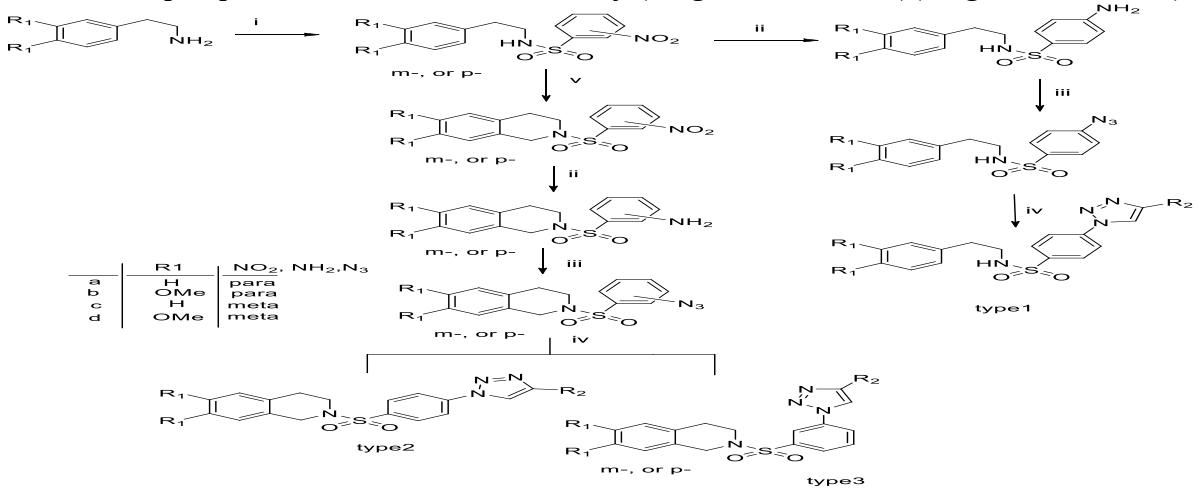


Figure 5: 1,4-disubstituted 1,2,3-triazole

On the other hands, Ratchanok P. *et al.* prepared novel series of 1,4-disubstituted-1,2,3-triazólesderivatives bearing sulfonamide core and assessed their aromatase inhibitory effects. The measurement revealed that analog of triazoles substitute with open chain sulfonamide a significant ability to inhibition the aromatase ($IÇ_{50}$ = 1.3 – 9.4 lM). Surprisingly, the *metá* derivative of triazöle, known asbenzene isulfonamide, which has 6, 7-dimethóxyl substituents on the isoquinolinoe ring, showed a strong aromatase inhibiting effect. (IC_{50} = 0.2 lM) without damaging healthy cells. Molecular docking was demonstrated that triazoles analogs toward aromatase could be specifically positioned in an active area of theenzyme byhydrophobic properties, π-π stacking, and bond of hydrogen relationships. The promising inhibition was found that the ability of meta compound to generate bonds of hydrogen with Met374 and Ser478 that were proposed could be the crucial remains(Bonfield et al. 2012). For further development the study provides that the meta derivative has a prospective for aromatase inhibitory (Pingaew et al. 2015)(Pingaew et al. 2014).



Scheme 6. Synthesis derivatives of 1,2, 3-triazole coupling sulfonamides 13–35 via the Click reaction. Reagents and conditions: (i) 3- or 4-benzenesulfonylchloride, Na_2CO_3, CH_2Cl_2, r.t.; (ii) $SnCl_2.2H_2O$, EtOH, reflux; (iii) $NaNO_2$, HCl/CH_3COOH, 0° C, NaN_3, rt; (iv) „–R2 , CuSO45H2O, sodium ascorbate, t-BuOH/H_2O, rt; (v) $(CH_2O)n$, HCOOH, reflux; pathway a = steps i–iv; route b = steps i–v (2015)

In 2016, the production of the original biodendrimer molecule, which contained ß-CD platforms on the primary and secondary sides by employing spacer arms, was described by Yousef T. *et al.* (Scheme7). Biological analysis of the per-ß-CD dendrimer performed in *vitro*, including the administration of medicines from complexes at various pHs, is additionally provided. On T47D cancer cells, the MTT test of the substance showed very little toxicity. It was found that the pH

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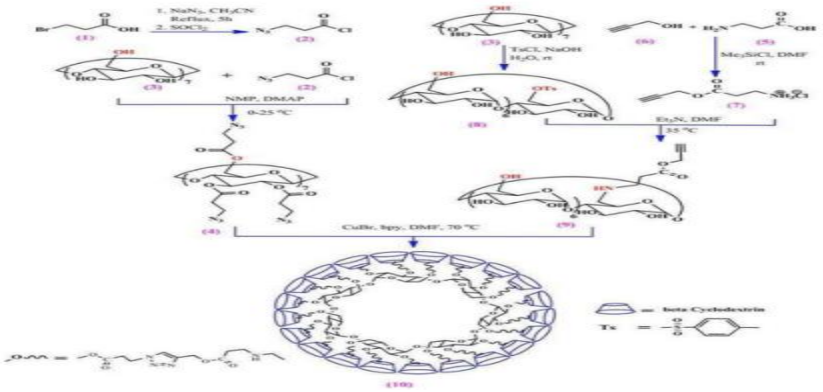
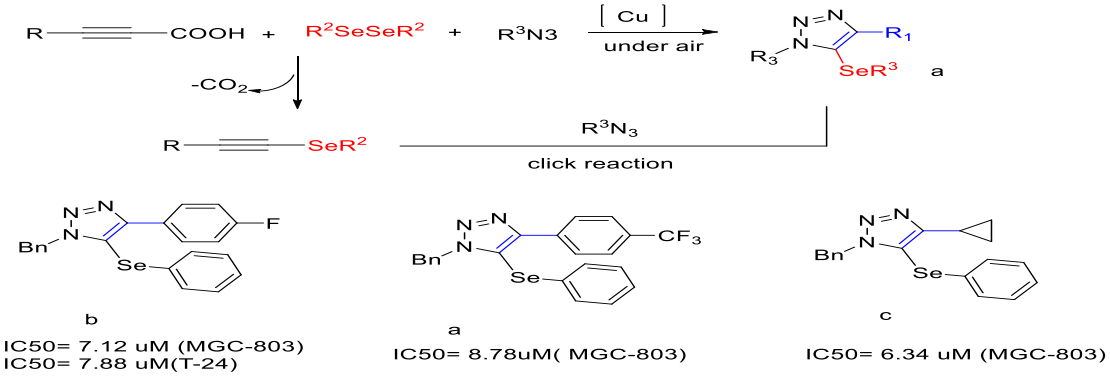
dependent when release manner in a vitro drug particular at pHs 7.4, 5, and 3(Toomari and Namazi 2016).



Scheme7: click reaction for the preparation of β-CD-(spacer-β-CD)

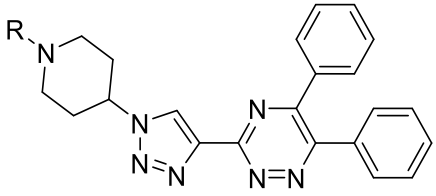
Currently, Fei-hucui *et al*. developed a easy and effective Cu-catalyzed decarboxylative / click process of the preparation of 1, 4-disuctile 5-arylselanyl-1,2, 3-triazoles between propolytic acids, diselenides, with azides. An alkynyl selenium intermediate is represented the intermolecular AAC reaction is occurred and confirmed by the mechanistic analysis. The derivatives of 5-seleno-1,2,3-triazoles tested against MTT assays the anticancer ability in vitro, The result showed that the derivates a, b and c have potent inhibition of tumor cell progress (Cui et al. 2018) scheme8.



Scheme 8: 1,4-disuctile 5-arylselanyl-1,2,3-triazoles

Click reaction as antibacterial

Another applications for 1, 2, 3- triazole are antibacterial abilities which play an essential role in biological activity, this application has been interested by researcher in the last decay and many papers has been published in this area, due to highly toxic, ineffective and resistant strain. A new, suitable, easy, and effective technique for preparation a new library of 3-[1-(1-substituted piperidin-4-yl)-1H-1,2,3 -triazole -yl]- 5,6 -diphenyl-1,2,4-triazines by Sangshetti and coworkers were developed via using $ZrOCl_2 \cdot 8H_2O$ as a catalyst [43,44].



R= H,Me,Et,Pr, Boc, Bn, etc

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Figure 6: 3-[1-(1-substituted piperidin- 4-yl)-1H-1, 2, 3-triazól-4 -yl]-5,6 -diphenyl-1,2 ,4-triazines

A quinalone core is commonly used to build many Synthetic substances with different medicinal properties. Antimicrobial activities of a novel 2-chloro-3-[(4-phenyl- 1H-1,2,3-triazol- 1-yl)-methyl]quinolone analogues s have been reported by Kategaonkar and co-workers towards a big number of fungal and bacterial strains(Kategaonkar et al. 2010)figure 7.

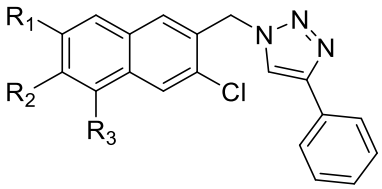
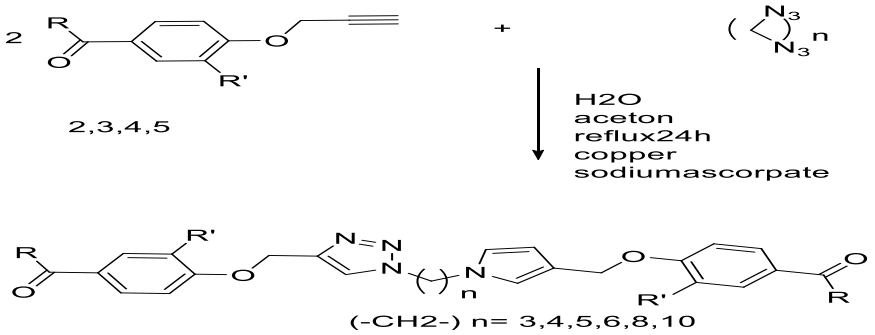


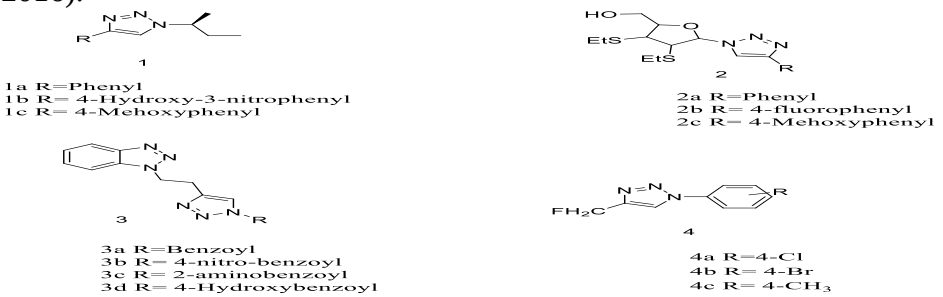
Figure 7: 2-chloro-3-[(4 -phenyl -1Ĥ- 1,2, 3-triazol -1 -yl)-methyl]quinólone derivatives

Other researcher, Esra D. and co-worker have produced an effective preparation for a new bis-1,2,3 -triazole derivatives 2-5(a-f) and connection with each other copper-catalyzed click chemistry via alkyl chain bridges. This method includes the phenoxy groups substituted with the main building blocks. The results showed that all compounds had moderate antibacterial activity against *E coli and Y. pseudotuberculosis* bacteria, and several molecules also had very weak antimycotic activities against *S. cerevisiae and C. albicans*[46,47].



Scheme 9: Preparation of bis-1,2, 3-triazole derivatives 2-5

At the same time, Julio M. *et al.* were used 1-benzyl-1, 2, 3-triazoles derivatives against DPPH and evaluated by using broth microdilution method. It was found that the compound 1-(1-Benzyl-1H1,2,3-triazol - 4-yl) cyçlopentánol (50 µg/mL to 200 µg/mL) showed modest level of inhibition to *Staphylococcüs aüreus* 3 growth while the similar impact of 3-(1-Benzyl-1H1,2, 3-triazol-4 -yl) propan-1-ol was noted towards *Escherichiacoli* AO11 , *E.coli* AO15 and *Salmonella entericá serovar Typhi*, also DPPH scavenging of 5g-i derivatives exhibited highest level. The inhibition of 1,2,3-triazole were considered from modesty toxic to non-toxic(Sarmiento-Sánchez et al. 2016).



Scheme 10: 1-benzyl-1,2,3-triazoles derivatives

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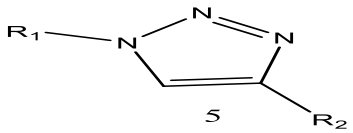

Table 1: antioxidant ability data of 1-benzyl-1,2,3-triazoles derivatives

				Toxicity	***Antioxidant effect*(%)**
Entry	**Product**	**R_1**	**R_2**	**LD_{50}**	Compounds assessed at 100 µg/mL)
				(µg/mL)a	
1	5a	Bn	formyl	490.69	-
2	5b	c-Pentyl	formyl	581.38	1.51
3	5c	Bn	2-ethanolyl	>1000	3.7
4	5d	Bn	3-propanolyl	>1000	3.38
5	5e	Bn	4-butanolyl	>1000	3.99
6	5f	Bn	1-ethanolyl	>1000	2.5
7	5g	Bn	2-aminophenyl	>1000	12.76
8	5h	Bn	3-aminophenyl	>1000	21.86
9	5i	Bn	4-aminophenyl	>1000	22.76
10	5j	Bn	1-naphthyl	491.24	-
11	5k	Bn	2-Propanyl-2-amine	>1000	-
12	5l	Bn	1-hydroxy-c-pentyl	513.73	-
13	5m	Bn	1-hydroxy-c-hexyl	>1000	-
14	5n	Bn1	$-CH_2-O-CH_2-$	>1000	-
15	5o	Bn	1,3-phenylen	>1000	-
16	5p	Bn	$-CH_2CH_2CH_2-$	485.26	-
17	Positive control		Trolox		80

Furthermore, W. Tan *et al* designed four new starch-coupled-1,2,3-triazole derivatives containing 6-hydroxymethyltriazole-6-deoxy starch (HMTST), 6-bromomethyltriazole-6-deoxy starch (BMTST), 6-chloromethyltriazole-6-deoxy starch (CMTST), and 6-carboxyltriazole-6-deoxy starch (CBTST). Escherichia coli (E. coli) were used in an in *vitro* investigation of their antibacterial activities and *Staphylococcus aureus* (*S. aureus*) respectively. The obtained of amphiprotic starch derivatives which have inhibitory properties showed significant improvement compared with starch. Inhibitory activity usually decreased in the following order: CBTST > CMTST > BMTST > HMTST > starch. The results revealed that the substitution groups with stronger electron withdrawing display more antibacterial effect than other derivatives[47].

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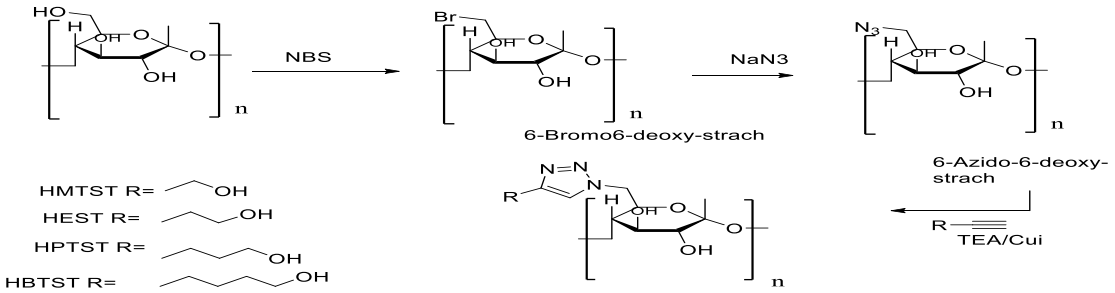
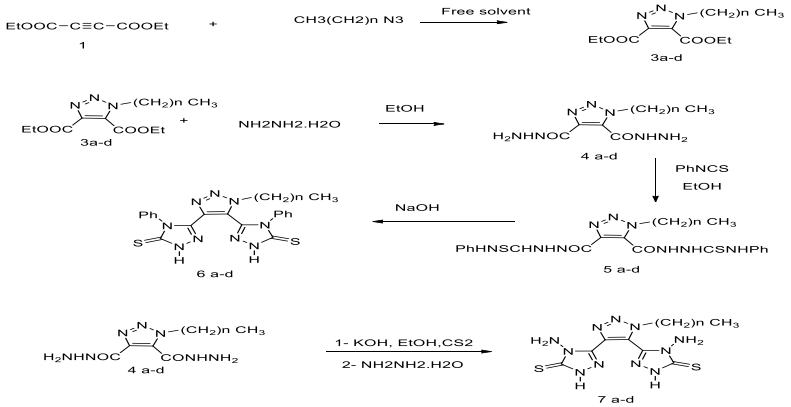


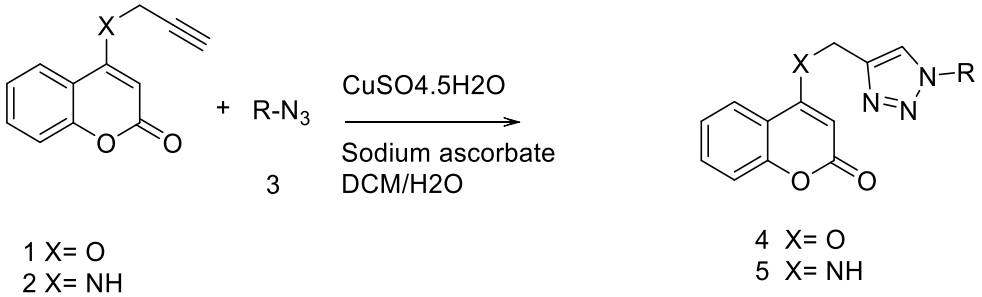
Scheme 10: Synthesis of starch derivatives

Aouad M. and co-worker synthesized a new library of 1,2 , 3-triazole bis-1,2 ,4-triazole -3-thiones 6á–đ and bịs-4-ámino-1 ,2, 4-triazole-3-thịones 7a–d by click reaction. All compounds were produced in higher yields and faster time of reaction. All compound were tested against Gram positive bacterial, Gram negative bacteria and compared these compound with Ciprofloxacin as standard, The findings of antibacterial activity have shown that, compared to Ciprofloxacin, All derivatives typically produce antibacterial activities that are comparable to or more effective against all bacterial species. also showed that the activity pattern of 1,2, 3-triazole-4,5-diyl)bis(4-phenyl-2,4-dihydro-1,2,4-triazole-3-thione derivatives 6a-d is same as to that of 1,2,3 -triazole bis-4-amino-1, 2, 4-triazole- 3-thione compounds 7a-d related to 1, 2, 3-triazole(Aouad et al. 2017).



Scheme 11: Synthesis 1, 2, 3-triazole bịs- 4-amino- 1,2, 4-triazole-3-thiones

After that, P. López-Rojas designed a novel libraries of coümarin-1, 2, 3-triazole subsequences with different alkyl, phenyland heterocyclic cores at C-4 ofthe triazole moieties were produced by a copper(I)-catalyzed Huisgèn 1,3- dipolar cyclo-addition approach including O-propargylated coümarin (1) or N-propargylated coumarin (2) with alkyl or aryl azides. Using minimal inhibitory concentrations (MICs) against specific pathogens, the majority of analogs shown notable anti-bacterial efficacy against Enterococcus faecal is (MIC = 12.5-50 g/mL). All of the synthetic triazoles were just mildly hazardous to human erythrocytes(López-Rojas et al. 2018) Scheme 12.



Scheme 12: Synthesis of 4- substituted 1,2, 3- triazole coumarian

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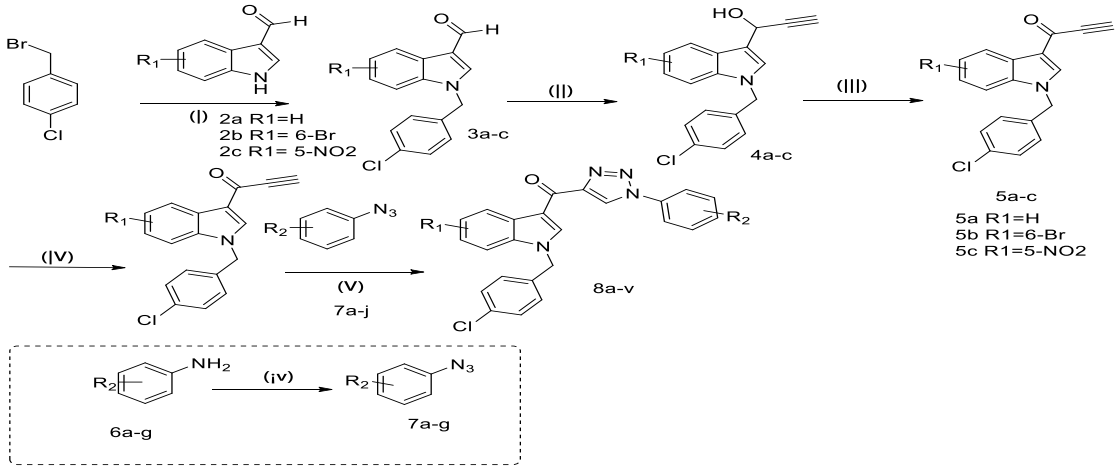
In 2019, Mohd A. S. *et al* designed a novel classes of 1-(4-chlorobenzyl- 1H-indol-3-yl)-1H-(1, 2, 3-triazole)methanones derivatives (8a-u), preparation & examined for its anti-microbial ability, with particular emphasized the potential on their anti-Candid and Candida biofilm inhibitory activity. The results was revealed that the crosses 8e, 8f, and 8o showed strong antifungal activity with MIC values range about 1.9 -7.8 µg / mL on most of the tested fungal strains(Shareef et al. 2019).



Scheme 13: synthesis of 1-(4-chlörobenzyl)-1H-indöl -3-yl) 1H-(1,2,3-triazol- 4-yl)methanones derivatives (8a-u)

	R1	R2		R1	R2
8a	H	3,4,5(OCH_3)$_3$	8I	6-Br	3,5(OCH_3)$_2$
8b	H	3,4(OCH_3)$_2$	8m	6-Br	4-Cl,2-F
8c	H	3,5(OCH_3)$_2$	8n	6-Br	2-Br, 4-F
8d	H	4-OCH_3	8o	6-Br	3,4-(F)$_2$
8e	H	3,4-(F)$_2$	8p	5-NO_2	3,4(OCH_3)$_2$
8f	H	4-CF3	8q	5-NO_2	3,5(OCH_3)$_2$
8g	H	4-Cl,2-F	8r	5-NO_2	4-CF_3
8h	H H	2-Br, 4-F	8s	5-NO_2	3,4-(F)$_2$
8i	6-Br	4-Br	8t	5-NO_2	4-Cl,2-F
8j	6-Br	3,4,5(OCH_3)$_3$			
8k		3,4(OCH_3)$_2$	8u	5-NO_2	2-Br,4-F

Table 2: Reagent and condition : (i) NaH,DMF,0C, rt, 3h, 70-79%;(ii) Ethynylmagnesum bromide, dry THF, 0C, rt, 4-5h, 68-74%: (iii) IBX,DMSO, 0C, rt, 2h, 71-76%; (iv) NaNO2 in HCl, NaN3,0C, 0,5-1h, (v) Sodium ascorbate (10mol%) ; CuSO4.5H2O(mol%) H2O/t-BuOH,(1:2)rt,5-8h,71-92%

Currently, the click reaction particular 1,2,3-triazole have been gained a significant important in biological activity. Y.Teng and coworkers synthesized a new library of 11-*o*-carbamoyl-3-*ö*-descladinosyl clarithrömycin analoges linking to the 1,2, 3 -triazöle core, and assessed their ability as antibacterial activity in vitro. The antibacterial study was showed that most objective compounds modest to highest activity towards resistant strains of bacteria, while some derivatives attributed their activity against responsive strains of bacteria compared to clarithromycin. It was found that 13d and 13g (Scheme 14) revealed the highest antibacterial ability towards resistant bacterial

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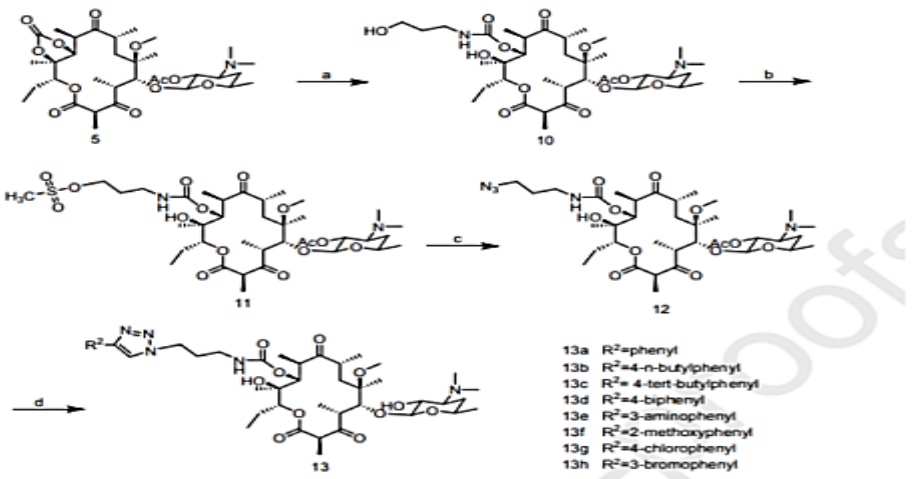
strains, consisting of *Staphylococcus aureus* ATCC25923 (4 µg/mL) and *Bacillus Subtilis* ATCC9372 (1 µg/mL). 13d had the best anti-bacterial activity about 16-times higher activity than that of CAM toward sensitive strains, containing *Streptococcus pneumoniae* B1 expressing the *erm*Bgene (16 µg/mL), *Streptococcus pneumoniae* AB11 expressing the *mef*A and *erm*Bgenes (16 µg/mL) and *Streptococcus pyogenes* R1 (16 µg/mL), respectively(Teng et al. 2020).



Scheme 14: Synthesis of 11-*O*-carbamoyl-3-*O*-descladinosyl clarithromycin compounds (13a–13h).

Click chemistry as antiviral and delivery drugs

Any compound including 1,2,3-triazole moiety is considered to be super candidate medicine to reduce the magnitude of any disease, according to the increase needed to increase the effectiveness of drugs. Drug- DNA is one of the important investigations which are allowed to study the molecular mechanism of drug activity, including a plan to create distinctive DNA that can be recognized as medicines and antiviral drugs. A.Hemamalini described and synthesized Sugar-[1,2,3-triazole] sugar-imine derivatives derived from uracil. Investigation of the sugar-triazole interaction with CT-DNA showed that all compounds could interact with CT-DNA mostly by groove binding, which was further verified by docking studies(Wen et al. 2016).

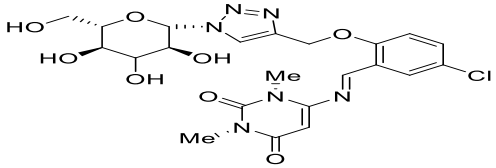


Figure 8: Sugar-[1,2, 3-triazole] sugar-imine derivatives

At 2016, in another important research, a new sequence of 1,2,3-triazolylbenzyl-aminophosphonate ribonucleosides was synthesized using CuAAC via the Kabachnik-Fields reaction by A. Quahrouch *et al*. It was discovered that compounds 1 and 2 showed modest amounts of respiratory syncytial virus (RSV) inhibitory action, whereas compound 3 showed modest amounts of Coxsackie virus B4 inhibitory effect in Figure 9 (Głowacka et al. 2014).

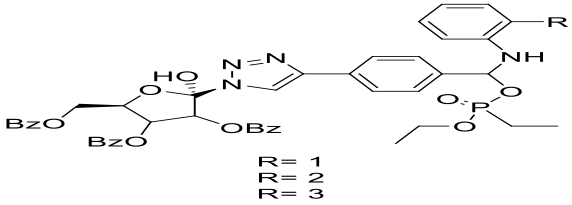


Figure 9: 1,2,3-triazolylbenzyl-aminophosphonate ribonucleosides

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W.A. El-Sayed synthesized new subsequences with substituted pyridine and carbohydrate cores that bearing 1,2,3-triazoles. O-propargylation of pyridone derivatives was introduced into propargyl group connected to the carbohydrate group in substituted pyridine core which was achieved by Cu-catalyzed cycloaddition of propargyl sugars with azidoethoxypyridine derivative or azidosugars with substituted (propargyl)oxypyridines which produce a high yields of 1,2,3-triazoles. Synthesized compounds were studied antiviral activity against H5N1 influenza virus, also the finding demonstrated that triazolyl glycoside 7 showed high activity with low cytotoxicity. It was studied that connected glycosyl triazole moieties to pyridinyl system, which has been revealed to enhance antiviral activity in SAR correlation(El-Sayed et al. 2017).

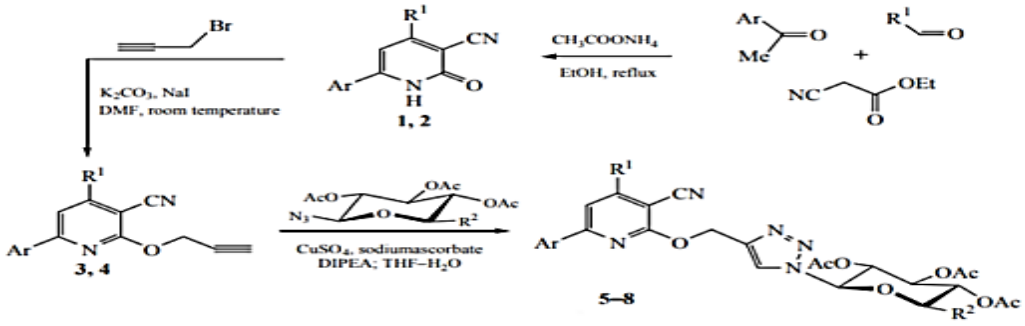
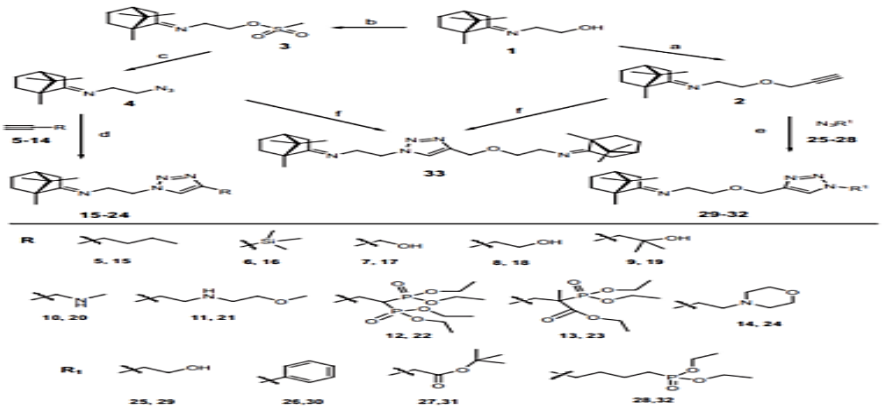


Figure10: Synthesis of 1,2,3-triazole glycosides from propargyloxypyridines and azidosugars

Other important study by Olieg I.Artyushin *et al.* who prepared a library of 1,7,7-trimethyl[2.2.1]bicycloheptane tetrazole derivatives via the click chemistry technique and identified by spectral technique .In vitro cytotoxicity and antiviral activity tests were recorded toward influenza disease A/PuertoRico/8/34 (H1N1) in cells of MDCK ofthe acquired derivative. An analysis the relationship between structure and activity reveals that compounds have virus-inhibiting activity when they have anoxygen atom with a short bonding (C2-C4), either as a hydroxylgroup (18,19,29), or a ketogroup (21) in their structure like a component of a heterocyclic characteristics(24), This investigation indicated that these substances have both potent antiviral activity and low toxicity (Artyushin et al. 2017).



Scheme 15: 1,7,7-trimethyl[2.2.1]bicycloheptane of tetrazole derivatives

A new hybrid with antiviral capabilities against the hepatitis B virus (HBV) was created by Liu Y. et al. utilizing 4- monosubstituted 2′-deoxy- 2′-fluoro- 4′-azido-D-arabinofuranosyl- 1,2,3-triazole scaffolds(Liu et al. 2018). The triazole drug (Fig. 12), which was also evaluated against HBV-infected duck models, was found to have impressive antiviral potential and effectiveness

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against the lamivudine-resistant HBV mutations. The results demonstrated that both the liver duck-HBV DNA levels (53.3%) and the serum levels (67.4%) significantly decreased with 94 following treatment(Bozorov et al. 2019).

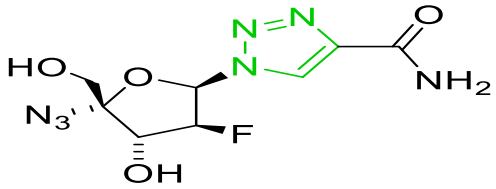

Figure 11: Triazole compound

Currently, HIV-1 CA is a type of protein which is a promising therapeutic goal for the improvement a novel antiviráls molecule. The most widely reported CA inhibitor , PF-3450074 (PF-74, explored by Pfizer), that determined an interprotomer concisely through the CA hexamer which have been described. Thus, Liu Sun *et al* designed, synthesized, and biological investigated a set of 4-phenyl-1H-1,2,3 -triazole phenyl álanine compounds as HİV-1 CA inhibitors depend on ƤF-74 scaffold. The finding showed mostof the derivatives confirmed the ability as antiviral agent, among all compounds, 6a-9 derivative is particularly prominent the anti-HIV-1 activity (EC50 = 3.13 μM). Direct and efficient interaction with recombinant CA proteins has been indicated by the SPR binding assay of certain derivatives (6a-9 , 6a-10 , 5b). The results also demonstrated that 6a-9 exhibit of HĨV-1 replication in both the early and late stages. MD simulation is used to analyze its linking to the activity position of HIV-1 CA monomer. As a result, these synthesized compounds have been found to be a key to developing a new classes of HIV-1 medication and efficacy of CA as a therapeutic agent (Sun et al. 2020).

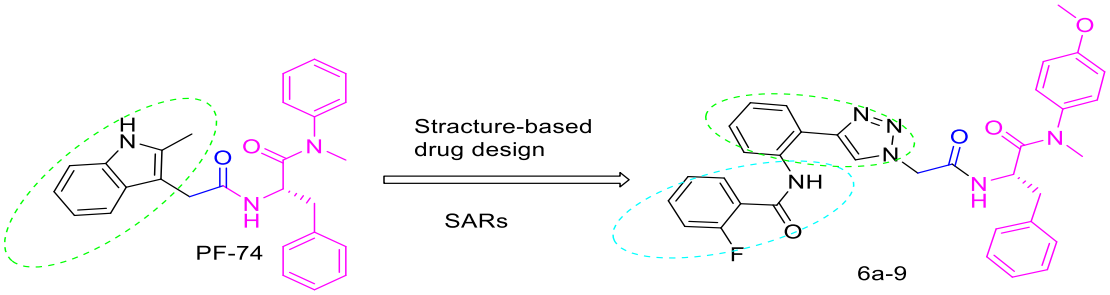

Figure 12: Design of 4-phenyl- 1H-1,2,3-triazole phenyl álanine compounds

Recently, Riyadh J. Nahi designed and combined new three pharmaphore including 1,2,3-triazole, furan and thiazolidin-4-one have identical framework in order to create a new scaffold. These new derivatives were characterized by using FT-IR, ^{1}HNMR, ^{13}CNMR spectroscopy. This study illustrated that the antioxidant ability of the target molecules 5a-d was demonstrated against DPPH radicals with five different concentrations of each one. DPPH assay practical results showed that compounds 5a-d have an antioxidant activity increased as increasing the concentration compared to the ascorbic acid. Also, the finding of the IC50 revealed that compounds 5a and 5d have a higher value compared to standard. These new compounds promising to develop new medicine(Nahi 2020).

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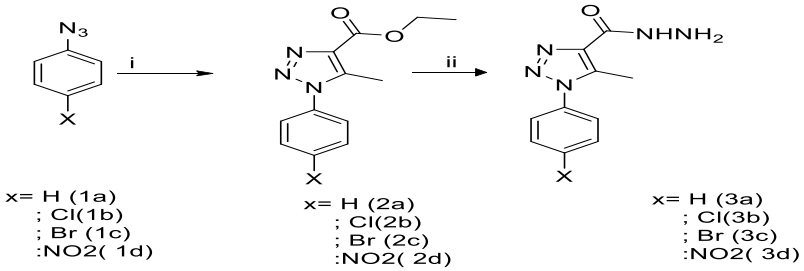

Scheme 16: Synthesis of compounds 3a-d: i) Ethyl acetoacetate, Eth3N; ii) Hydrazine hydrate, ethanol, reflux.

Conclusion

In conclusion, we have emphasized the significance of the key rules of click chemistry and how they apply to the design of novel pharmaceutically active molecules, with an emphasis on the efficient synthesis of diverse triazole compounds. Their applications in different areas such as organic synthesis, polymers, dendrimers, dendritic, and biomacromolecules are diverse, significant, and continually growing. In particular, the click reaction has been used to cross-link micelles, create novel dendrimers and polymeric delivery systems, and modify the surfaces of various nanoparticle methods of delivery. The reaction is perfect for bioconjugations due to the stiffness of 1,2,3-triazoles. According to this assessment, a click reaction is simple in some reactions with high yields and challenging in others with poor yields, depending on the catalyst that using in the reaction in order to get the desired product. Last but not least, click reaction serves as a delivery biomolecule that enables researchers to penetrate the cell and diagnose various tumor cells. In addressing these difficulties, click chemistry is essential for different science. Great strides have been made in a short period of time, as stated here

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Conflicts of Interest

The authors declare no conflict of interest.

References

Abbood, Sura M., Sura Mohammed Kadhim, Aziz Yasir Hasan Al-Ethari, Zyad H. AL-Qaisia, and Mustafa Taha Mohammed. (2022). “Review on Frankincense Essential Oils: Chemical Composition and Biological Activities.” Misan Journal of Academic Studies (Humanities and Social Sciences) 21(44). dol: 10.54633/2333-021-043-006

Agalave, Sandip G., Suleman R. Maujan, and Vandana S. Pore. (2011). “Click Chemistry: 1, 2, 3-triazoles as Pharmacophores.” Chemistry–An Asian Journal 6(10). https://doi.org/10.1002/asia.201100432

Aouad, Mohamed Reda, Mariem Mohammed Mayaba, Arshi Naqvi, Sanaa K. Bardaweel, Fawzia Faleh Al-blewi, Mouslim Messali, and Nadjet Rezki. (2017). “Design, Synthesis, in Silico and in Vitro Antimicrobial Screenings of Novel 1,2,4-Triazoles Carrying 1,2,3-Triazole Scaffold with Lipophilic Side Chain Tether.” Chemistry Central Journal 11(1). doi: 10.1186/s13065-017-0347-4.

Appukkuttan, Prasad, Wim Dehaen, Valery V Fokin, and Erik Van der Eycken. (2004). “A Microwave-Assisted Click Chemistry Synthesis of 1, 4-Disubstituted 1, 2, 3-Triazoles via a Copper (I)-Catalyzed Three-Component Reaction.” Organic Letters 6(23)

ISSN (Paper)-1994-697X (Online)-2706-722X

https://doi.org/10.1021/ol048341v

Artyushin, Oleg I., Elena V Sharova, Natalya M. Vinogradova, Galina K. Genkina, Aleksandra A. Moiseeva, Zinaida S. Klemenkova, Iana R. Orshanskaya, Anna A. Shtro, Renata A. Kadyrova, and Vladimir V Zarubaev (2017). "Synthesis of Camphecene Derivatives Using Click Chemistry Methodology and Study of Their Antiviral Activity." Bioorganic & Medicinal Chemistry Letters 27(10). https://doi.org/10.1016/j.bmcl.2017.03.051

Beckmann, Henning S. G., and Valentin Wittmann (2007). "One-Pot Procedure for Diazo Transfer and Azide-Alkyne Cycloaddition: Triazole Linkages from Amines." Organic Letters 9(1). doi: 10.1021/ol0621506.

Besanceney-Webler, Christen, Hao Jiang, Tianqing Zheng, Lei Feng, David Soriano del Amo, Wei Wang, Liana M. Klivansky, Florence L. Marlow, Yi Liu, and Peng Wu. (2011). "Increasing the Efficacy of Bioorthogonal Click Reactions for Bioconjugation: A Comparative Study." Angewandte Chemie International Edition 50(35). https://doi.org/10.1002/anie.201101817.

Bock, Victoria D., Henk Hiemstra, and Jan H. Van Maarseveen (2006). "CuI-catalyzed Alkyne–Azide 'Click' Cycloadditions from a Mechanistic and Synthetic Perspective." European Journal of Organic Chemistry 2006(1). https://doi.org/10.1002/ejoc.200500483

Bonandi, Elisa, Michael S. Christodoulou, Gaia Fumagalli, Dario Perdicchia, Giulio Rastelli, and Daniele Passarella (2017). "The 1, 2, 3-Triazole Ring as a Bioisostere in Medicinal Chemistry." Drug Discovery Today 22(10). https://doi.org/10.1016/j.drudis.2017.05.014

Bonfield, Kevin, Erica Amato, Tony Bankemper, Hannah Agard, Jeffrey Steller, James M. Keeler, David Roy, Adam McCallum, Stefan Paula, and Lili Ma (2012). "Development of a New Class of Aromatase Inhibitors: Design, Synthesis and Inhibitory Activity of 3-Phenylchroman-4-One (Isoflavanone) Derivatives." Bioorganic & Medicinal Chemistry 20(8). https://doi.org/10.1016/j.bmc.2012.02.042

Bozorov, Khurshed, Jiangyu Zhao, and Haji A. Aisa (2019). "1, 2, 3-Triazole-Containing Hybrids as Leads in Medicinal Chemistry: A Recent Overview." Bioorganic & Medicinal Chemistry 27(16). https://doi.org/10.1016/j.bmc.2019.07.005.

Bräse, Stefan, Carmen Gil, Kerstin Knepper, and Viktor Zimmermann (2005). "Organic Azides: An Exploding Diversity of a Unique Class of Compounds." Angewandte Chemie International Edition 44(33) https://doi.org/10.1002/anie.200400657

Chowdhury, Chinmay, Sukhendu B. Mandal, and Basudeb Achari (2005). "Palladium–Copper Catalysed Heteroannulation of Acetylenic Compounds: An Expeditious Synthesis of Isoindoline Fused with Triazoles." Tetrahedron Letters 46(49). https://doi.org/10.1016/j.tetlet.2005.10.006

Cui, Fei-hu, Jing Chen, Zu-yu Mo, Shi-xia Su, Yan-yan Chen, Xian-li Ma, Hai-tao Tang, Heng-shan Wang, Ying-ming Pan, and Yan-li Xu (2018). "Copper-Catalyzed Decarboxylative/Click Cascade Reaction: Regioselective Assembly of 5-Selenotriazole Anticancer Agents." Organic Letters 20(4) https://doi.org/10.1021/acs.orglett.7b03734

Devaraj, Neal K., and M. G. Finn (2021). "Introduction: Click Chemistry." Chem. Rev. 121(12), https://doi.org/10.1021/acs.chemrev.1c00469

Düğdü, Esra, Dilek Ünlüer, Fatih Çelik, Kemal Sancak, Şengül Alpay Karaoğlu, and Arzu Özel (2016). "Synthesis of Novel Symmetrical 1, 4-Disubstituted 1, 2, 3-Bistriazole Derivatives via 'Click Chemistry'and Their Biological Evaluation." Molecules 21(5) https://doi.org/10.3390/molecules21050659

El-Sayed, W. A., H. S. Khalaf, S. F. Mohamed, H. A. Hussien, O. M. Kutkat, and A. E. Amr. (2017).

ISSN (Paper)-1994-697X (Online)-2706-722X

"Synthesis and Antiviral Activity of 1, 2, 3-Triazole Glycosides Based Substituted Pyridine via Click Cycloaddition." Russian Journal of General Chemistry 87(10). https://link.springer.com/article/10.1134/S1070363217100279

Głowacka, Iwona E., Jan Balzarini, Graciela Andrei, Robert Snoeck, Dominique Schols, and Dorota G. Piotrowska (2014). "Design, Synthesis, Antiviral and Cytostatic Activity of ω-(1H-1, 2, 3-Triazol-1-Yl)(Polyhydroxy) Alkylphosphonates as Acyclic Nucleotide Analogues." Bioorganic & Medicinal Chemistry 22(14). https://doi.org/10.1016/j.bmc.2014.05.020

Golas, Patricia L., Nicolay V Tsarevsky, Brent S. Sumerlin, and Krzysztof Matyjaszewski. (2006). "Catalyst Performance in 'Click' Coupling Reactions of Polymers Prepared by ATRP: Ligand and Metal Effects." Macromolecules 39(19) https://doi.org/10.1021/ma061592u

Guezguez, Raja, Khalid Bougrin, Khalid El Akri, and Rachid Benhida (2006). "A Highly Efficient Microwave-Assisted Solvent-Free Synthesis of α-and β-2′-Deoxy-1, 2, 3-Triazolyl-Nucleosides." Tetrahedron Letters 47(28):4807–11. https://doi.org/10.1016/j.tetlet.2006.05.050

Guo, Zhimou, Aiwen Lei, Xinmiao Liang, and Qing Xu. (2006) "Click Chemistry: A New Facile and Efficient Strategy for Preparation of Functionalized HPLC Packings." Chemical Communications (43):4512–14. https://pubs.rsc.org/en/content/articlelanding/2006/cc/b610733h/unauth

Hein, Jason E., and Valery V Fokin (2010). "Copper-Catalyzed Azide–Alkyne Cycloaddition (CuAAC) and beyond: New Reactivity of Copper (I) Acetylides." Chemical Society Reviews 39(4):1302–15. https://pubs.rsc.org/en/content/articlelanding/2010/cs/b904091a/unauth

Hradilová, Ludmila, Monika Poláková, Barbora Dvořáková, Marián Hajdúch, and Ladislav Petruš (2012). "Synthesis and Cytotoxicity of Some D-Mannose Click Conjugates with Aminobenzoic Acid Derivatives." Carbohydrate Research 361:1–6. https://doi.org/10.1016/j.carres.2012.08.001

Huisgen, Rolf. (1963). "Kinetics and Mechanism of 1, 3-dipolar Cycloadditions." Angewandte Chemie International Edition in English 2(11) https://doi.org/10.1002/anie.196306331.

Huisgen, Rolf, Günter Szeimies, and Leander Möbius (1967). "1.3-Dipolare Cycloadditionen, XXXII. Kinetik Der Additionen Organischer Azide an CC-Mehrfachbindungen." Chemische Berichte 100(8):2494–2507. https://doi.org/10.1002/cber.19671000806

Johansson, Johan R., Tamas Beke-Somfai, Anna Said Stålsmeden, and Nina Kann (2016) "Ruthenium-Catalyzed Azide Alkyne Cycloaddition Reaction: Scope, Mechanism, and Applications." Chemical Reviews 116(23):14726–68. https://doi.org/10.1021/acs.chemrev.6b00466

Karimi, Hirbod (2017). "One-Pot Synthesis of 2-Amino-3-Cyanopyridine Derivatives Catalyzed by Zinc Zirconium Phosphate in Solvent-Free Conditions." Iranian Journal of Catalysis 7(2) https://ijc.shahreza.iau.ir/article_592883.html

Kategaonkar, Amol H, Pravin V Shinde, Atul H Kategaonkar, Sharad K. Pasale, Bapurao B. Shingate, and Murlidhar S. Shingare (2010). "Synthesis and Biological Evaluation of New 2-Chloro-3-((4-Phenyl-1H-1, 2, 3-Triazol-1-Yl) Methyl) Quinoline Derivatives via Click Chemistry Approach." European Journal of Medicinal Chemistry 45(7):3142–46. https://doi.org/10.1016/j.ejmech.2010.04.002

Liang, Liyuan, and Didier Astruc (2011). "The Copper (I)-Catalyzed Alkyne-Azide Cycloaddition (CuAAC)'Click' Reaction and Its Applications. An Overview." Coordination Chemistry Reviews 255(23–24):2933–45. https://doi.org/10.1016/j.ccr.2011.06.028

Liu, Yuan, Youmei Peng, Jingjing Lu, Jingwen Wang, Haoran Ma, Chuanjun Song, Bingjie Liu, Yan Qiao, Wenquan Yu, and Jie Wu. (2018). "Design, Synthesis, and Biological Evaluation of New 1, 2, 3-Triazolo-2′-Deoxy-2′-Fluoro-4′-Azido Nucleoside Derivatives as Potent Anti-HBV Agents." European Journal of Medicinal Chemistry 143(1). https://doi.org/10.1016/j.ejmech.2017.11.028

López-Rojas, Priscila, Monika Janeczko, Konrad Kubiński, Ángel Amesty, Maciej Masłyk, and Ana Estévez-Braun. (2018). "Synthesis and Antimicrobial Activity of 4-Substituted 1,2,3-Triazole-Coumarin Derivatives." Molecules 23(1) doi: 10.3390/molecules23010199.

Loupy, André (2004). "Solvent-Free Microwave Organic Synthesis as an Efficient Procedure for Green Chemistry." Comptes Rendus Chimie 7(2):103–12. https://doi.org/10.1016/j.crci.2003.10.015

Michael, Arthur, and Ueber Die Einwirkung Von Diazobenzolimid Auf. (1893). "Acetylendicarbonsäuremethylester." J. Prakt. Chem 48:94–95. https://ia800708.us.archive.org/view_archive.php?archive=/22/items/crossref-pre-1909-scholarly-works/10.1002%252Fprac.18900420129.zip&file=10.1002

Nahi, RIYADH J. (2020). "Combination of 1, 2, 3-Triazole, Furan and Thiazolidin-4-One Structures For Potential Pharmaceutical Applications." International Journal of Pharmaceutical Research 12(1). https://doi.org/10.31838/ijpr/2020.12.01.186

Naser, Huda Jaafar, and Faiza Mohammed Hussain Abdul-Ameer. (2023). "Plants Extract Oils and Their Antimicrobial Activity in Treatment of Denture Stomatitis: Lemongrass Essential Oil (A Review of Literature)." Misan Journal of Academic Studies (Humanities and Social Sciences) 22(45):360–71. https://www.iasj.net/iasj/download/c55815fce3bfde5c

Ornelas, Cátia, Jaime Ruiz Aranzaes, Eric Cloutet, Sandra Alves, and Didier Astruc (2007). "Click Assembly of 1, 2, 3-triazole-linked Dendrimers, Including Ferrocenyl Dendrimers, Which Sense Both Oxo Anions and Metal Cations." Angewandte Chemie 119(6):890–95 https://doi.org/10.1002/ange.200602858

Partyka, David V, James B. Updegraff, Matthias Zeller, Allen D. Hunter, and Thomas G. Gray. 2007. "Carbon− Gold Bond Formation through [3+ 2] Cycloaddition Reactions of Gold (I) Azides and Terminal Alkynes." Organometallics 26(1):183–86. https://doi.org/10.1021/om0607200

Pingaew, Ratchanok, Supaluk Prachayasittikul, Somsak Ruchirawat, and Virapong Prachayasittikul (2014). "Synthesis and Cytotoxicity of Novel 4-(4-(Substituted)-1 H-1, 2, 3-Triazol-1-Yl)-N-Phenethylbenzenesulfonamides." Medicinal Chemistry Research 23(4):1768–80. https://link.springer.com/article/10.1007/s00044-013-0777-z

Pingaew, Ratchanok, Veda Prachayasittikul, Prasit Mandi, Chanin Nantasenamat, Supaluk Prachayasittikul, Somsak Ruchirawat, and Virapong Prachayasittikul (2015). "Synthesis and Molecular Docking of 1, 2, 3-Triazole-Based Sulfonamides as Aromatase Inhibitors." Bioorganic & Medicinal Chemistry 23(13):3472–80. https://doi.org/10.1016/j.bmc.2015.04.036

Powers, Andrew R., Ion Ghiviriga, Khalil A. Abboud, and Adam S. Veige (2015). "Au-IClick Mirrors the Mechanism of Copper Catalyzed Azide–Alkyne Cycloaddition (CuAAC)." Dalton Transactions 44(33):14747–52. https://doi.org/10.1039/C5DT02405F

Rejhová, A., A. Opattová, A. Čumová, D. Slíva, and P. Vodička. (2018). "Natural Compounds and Combination Therapy in Colorectal Cancer Treatment." European Journal of Medicinal Chemistry 144:582–94. https://doi.org/10.1016/j.ejmech.2017.12.039

Rodionov, Valentin O., Valery V Fokin, and M. G. Finn. (2005). "Mechanism of the Ligand-free

CuI-catalyzed Azide–Alkyne Cycloaddition Reaction." Angewandte Chemie 117(15):2250–55. https://doi.org/10.1002/ange.200461496

Rostovtsev, Vsevolod V, Luke G. Green, Valery V Fokin, and K. Barry Sharpless (2002). "A Stepwise Huisgen Cycloaddition Process: Copper (I)-catalyzed Regioselective 'Ligation' of Azides and Terminal Alkynes." Angewandte Chemie 114(14):2708–11. https://doi.org/10.1002/1521-3757(20020715)114:14%3C2708::AID-ANGE2708%3E3.0.CO;2-0

Sangshetti, Jaiprakash N., and Devanand B. Shinde (2010). "One Pot Synthesis and SAR of Some Novel 3-Substituted 5, 6-Diphenyl-1, 2, 4-Triazines as Antifungal Agents." Bioorganic & Medicinal Chemistry Letters 20(2):742–45. https://doi.org/10.1016/j.bmcl.2009.11.048

Sarmiento-Sánchez, Juan I., Julio Montes-Ávila, Francisco Delgado-Vargas, Ignacio A. Rivero, Sylvia P. Díaz-Camacho, and Magdalena Uribe-Beltrán (2016). "Actividad Antioxidante y Evaluación Antibacterial de 1-Bencil-1,2,3-Triazol." Acta Universitaria 26(3):63–67. doi: 10.15174/au.2016.937.

Shareef, Mohd Adil, Hemshikha Rajpurohit, Kanugala Sirisha, and Ibrahim Bin Sayeed (2019)." Synthesis of new triazole fused imidazo[2,1-b]thiazole hybrids with emphasis on Staphylococcus aureus virulence factors' .Bioorganic & Medicinal Chemistry Letters 29(19) http://dx.doi.org/10.1016/j.bmcl.2019.08.025

Singh, Maya Shankar, Sushobhan Chowdhury, and Suvajit Koley. 2016. "Advances of Azide-Alkyne Cycloaddition-Click Chemistry over the Recent Decade." Tetrahedron 72(35):5257–83. doi: 10.1016/j.tet.2016.07.044.

Soriano del Amo, David, Wei Wang, Hao Jiang, Christen Besanceney, Amy C. Yan, Matthew Levy, Yi Liu, Florence L. Marlow, and Peng Wu (2010). "Biocompatible Copper (I) Catalysts for in Vivo Imaging of Glycans." Journal of the American Chemical Society 132(47):16893–99. https://doi.org/10.1021/ja106553e

Sun, Lin, Tianguang Huang, Alexej Dick, Megan E. Meuser, Waleed A. Zalloum, Chin-Ho Chen, Xiao Ding, Ping Gao, Simon Cocklin, and Kuo-Hsiung Lee (2020). "Design, Synthesis and Structure-Activity Relationships of 4-Phenyl-1H-1, 2, 3-Triazole Phenylalanine Derivatives as Novel HIV-1 Capsid Inhibitors with Promising Antiviral Activities." European Journal of Medicinal Chemistry 190:112085. https://doi.org/10.1016/j.ejmech.2020.112085

Tan, Wenqiang, Qing Li, Wancong Li, Fang Dong, and Zhanyong Guo. (2016). "Synthesis and Antioxidant Property of Novel 1,2,3-Triazole-Linked Starch Derivatives via 'Click Chemistry.'" International Journal of Biological Macromolecules 82:404–10. doi: 10.1016/j.ijbiomac.2015.10.007.

Teng, Yuetai, Yinhui Qin, Di Song, Xingbang Liu, Yingang Ma, Panpan Zhang, and Shutao Ma. (2020). "A Novel Series of 11-O-Carbamoyl-3-O-Descladinosyl Clarithromycin Derivatives Bearing 1, 2, 3-Triazole Group: Design, Synthesis and Antibacterial Evaluation." Bioorganic & Medicinal Chemistry Letters 30(2):126850. https://doi.org/10.1016/j.bmcl.2019.126850

Toomari, Yousef, and Hassan Namazi (2016). "Synthesis of Supramolecular Biodendrimeric β-CD-(Spacer-β-CD) 21 via Click Reaction and Evaluation of Its Application as Anticancer Drug Delivery Agent." International Journal of Polymeric Materials and Polymeric Biomaterials 65(10):487–96. https://doi.org/10.1080/00914037.2015.1129960

Tornøe, Christian W., Caspar Christensen, and Morten Meldal. (2002). "Peptidotriazoles on Solid Phase:[1, 2, 3]-Triazoles by Regiospecific Copper (I)-Catalyzed 1, 3-Dipolar Cycloadditions of

ISSN (Paper)-1994-697X (Online)-2706-722X

Terminal Alkynes to Azides." The Journal of Organic Chemistry 67(9):3057–64. https://doi.org/10.1021/jo011148j

Usachev, Boris I. (2018). "Chemistry of Fluoroalkyl-Substituted 1, 2, 3-Triazoles." Journal of Fluorine Chemistry 210:6–45. https://doi.org/10.1016/j.jfluchem.2018.02.012

Wen, Yi-ning, Zhi-feng Zhang, Ning-ning Liu, Yu-hong Xiang, Zhuo-yong Zhang, Graciela Andrei, Robert Snoeck, Dominique Schols, Qing-shan Zhang, and Qin-pei Wu. (2016). "Synthesis and Bioactivity of Novel Trisubstituted Triazole Nucleosides." Nucleosides, Nucleotides and Nucleic Acids 35(3):147–60. https://doi.org/10.1080/15257770.2015.1115523

Worrell, B. T., J. A. Malik, and Valery Valerievich Fokin. (2013). "Direct Evidence of a Dinuclear Copper Intermediate in Cu (I)-Catalyzed Azide-Alkyne Cycloadditions." Science 340(6131):457–60. https://doi.org/10.1126/science.1229506

Yim, Cheng-Bin, Ingrid Dijkgraaf, Remco Merkx, Cees Versluis, Annemarie Eek, Gwenn E. Mulder, Dirk T. S. Rijkers, Otto C. Boerman, and Rob M. J. Liskamp. (2010). "Synthesis of DOTA-Conjugated Multimeric [Tyr3] Octreotide Peptides via a Combination of Cu (I)-Catalyzed 'Click' Cycloaddition and Thio Acid/Sulfonyl Azide 'Sulfo-Click' Amidation and Their in Vivo Evaluation." Journal of Medicinal Chemistry 53(10):3944–53 https://doi.org/10.1021/jm100246m

Yoo, E. J., and M. Ahlquist. (2007). "Copper-Catalyzed Synthesis of N-Sulfonyl-1,2,3-triazoles: Controlling Selectivity." Angew. Chem 26:1760–63. https://doi.org/10.1002/anie.200604241

Yoon, Jieun, and Jae-Sang Ryu. (2010). "A Rapid Synthesis of Lavendustin-Mimetic Small Molecules by Click Fragment Assembly." Bioorganic & Medicinal Chemistry Letters 20(13):3930–35. https://doi.org/10.1016/j.bmcl.2010.05.014

Zaidan, Faez Sameer Salih-Raed Kadhim, and Khansa Abdul Razzaq Ali (2022). "Preparation of the Antioxidant Compounds from the Styrene and P-Benzoquinone Compounds to the Lubricant Oils." Misan Journal of Academic Studies (Humanities and Social Sciences) 21(44):299–318. dol: 10.54633/2333-021-043-006

Zhang, Li, Xinguo Chen, Peng Xue, Herman H. Y. Sun, Ian D. Williams, K. Barry Sharpless, Valery V Fokin, and Guochen Jia. (2005). "Ruthenium-Catalyzed Cycloaddition of Alkynes and Organic Azides." Journal of the American Chemical Society 127(46):15998–99. https://doi.org/10.1021/ja054114s

ISSN (Paper)-1994-697X (Online)-2706-722X