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Medicinal and Biological Importance of 1,2,3-Triazoles in Click Chemistry

Jalal Hasan Mohammed

Department of Pharmaceutical Chemistry
University of Karbala,
Kerbala, Iraq

Abstract

In this study, 1,2,3-Triazole derivatives have acquired conspicuous significance due to their wide spectrum of biological activities. There is a growing demand for the preparation of new antimicrobial agents due to the developing resistance towards conventional antibiotics, 1,2,3-Triazoles are an important class of organic compounds due to their wide applications in the synthesis of pharmaceuticals, receptors, fluorinated hydrogels, antibiotics, ntitubercular agents, ligands, surfactants, nucleosides, and their applications in radiochemistry, Sharpless and coworkers defined click chemistry as a 'set of powerful, highly reliable, and selective reactions for the rapid synthesis of useful new compounds and combinatorial libraries **,**The example of a click reaction is the copper-catalyzed Huisgen's 1,3-dipolar cycloaddition of azides and terminal alkynes. This reaction is regioselective, forming only 1,4-substituted products, is insensitive to the solvent, and can be performed at room temperature, it proceeds with high yields and is about 107 times faster than the uncatalyzed reaction**.**

Keywords:*1,2,3-Triazoles, Antibacterial activity, Antivenom Effects, anti-inflammatory, Anti-cancer Activity.*

1. Introduction

In this study, 1,2,3-Triazole derivatives have acquired conspicuous significance due to their wide spectrum of biological activities. There is a growing demand for the preparation of new antimicrobial agents due to the developing resistance towards conventional antibiotics, 1,2,3-Triazoles are an important class of organic compounds due to their wide applications in the synthesis of pharmaceuticals, receptors, fluorinated hydrogels, antibiotics, ntitubercular agents, ligands, surfactants, nucleosides, and their applications in radiochemistry, Sharpless and coworkers defined click chemistry as a 'set of powerful, highly reliable, and selective reactions for the rapid synthesis of useful new compounds and combinatorial libraries **,**The example of a click reaction is the copper-catalyzed Huisgen's 1,3-dipolar cycloaddition of azides and terminal alkynes. This reaction is regioselective, forming only 1,4-substituted products, is insensitive to the solvent, and can be performed at room temperature, it proceeds with high yields and is about 107 times faster than the uncatalyzed reaction**.**gas phase[1]. They have been synthesized by Cu(I)-catalyzed 1,3-dipolar cycloadditions according to the procedures of Sharpless and Meldal. Also, they have been prepared using microwave irradiation and ultrasound. Introducing a Carbohydrates, a group of prominent biomolecules from renewable resources that have great structural diversity are crucial components at the interface of chemistry and biology due to the increase of its solubility in water and reduction in toxicity. Sugar based bis-1,2,3-triazoles have been prepared as nonionic surfactants starting from D-glucose and Dgalactose[2,3].

1,2,3-triazole links have emerged as a popular bridging units in carbohydrate chemistry because of the facile efficient method of their introduction, which referred to as "click chemistry". The later method is based on Cu(I)-catalyzed version of Huisgen's 1,3-dipolarcycloaddition of azido sugar to terminal alkynes and it has been successfully applied for the synthesis of various glycoconjugates including multivalent glycosides[4]The main obejctive of research work is Synthesis of new 1,2,3-triazoles by using copper (I) catalyzed 1,3-alkyne-azide cycloaddition "Click Chemistry".

2.BIOLOGICAL ACTIVITIES ON TRIAZOLE AND THEIR DERIVATIVES

2.1 Antibacterial activity

Synthesis of new 1,2,3-triazoles [4] were prepared by Jalal etal Four *n*-alkyl azides; *n*-heptyl azide, *n*-octyl azide, *n*-decyl azide and *n*-dodecyl azide (1a-d) were prepared via S_N2 reaction of alkyl halides and sodium azide. In different step, D-fructose was converted to 2,3:4,5-di-O-isopropylidene-D-fructopyranose (3) using acetone and sulfuric acid as catalyst. The reaction of compound (3) with propargyl bromide in DMF afforded the terminal acetylene (4) in very good yield. The derivative (4) was reacted with synthesized *n*-alkyl azides (1a-d) viacycloaddition reaction using Cu(I) as catalyst afforded D-fructose based 1,2,3-triazoles, All synthesized compound were identified by TLC, FTIR and most of them were characterized by 1H NMR, 13C NMR, COSY,

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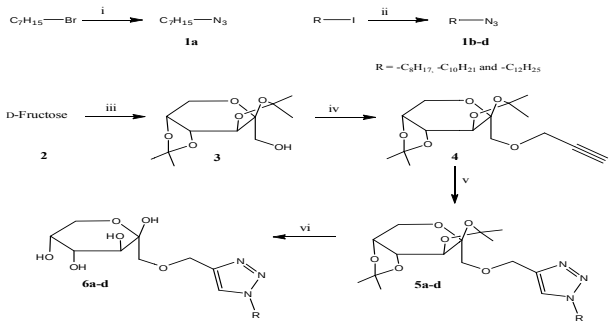
HSQC and HRMS. The synthesized compounds showed antibacterial activity *in vitro* against two kinds of bacteria: Escherichia coli (-) and Staphylococcus aurous (+).As shown in the Fig.1, 2, 3as below:



Reagents and coditions: i] NaN_3 , DMF, 70ºC, 24 h; ii] NaN_3 , DMF, 70ºC, 4 h; iii] Acetone, H_2SO_4, rt, 2 h; iv] propargyl bromide, NaOH, DMF, -20ºC - rt, 24 h; v] n-alkyl azide, Na ascorbate, $CuSO_4.5H_2O$, DMSO, 65ºC, 48h; vi] Amberlite IR 120 H^+, MeOH/H_2O, 60ºC, 48 h.

Fig. 1 Synthetic methods of 1,2,3-triazoles[4].

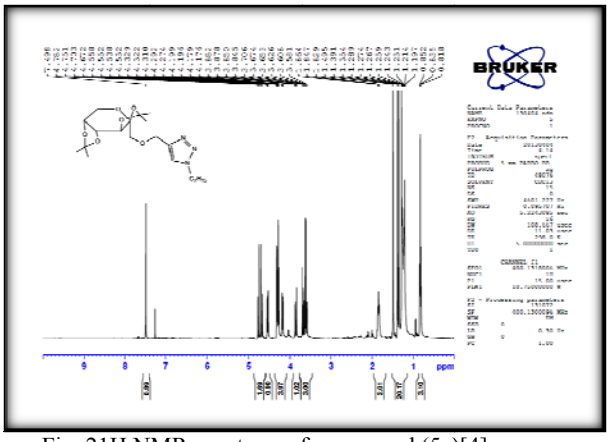


Fig. 21H NMR spectrum of compound (5a)[4].

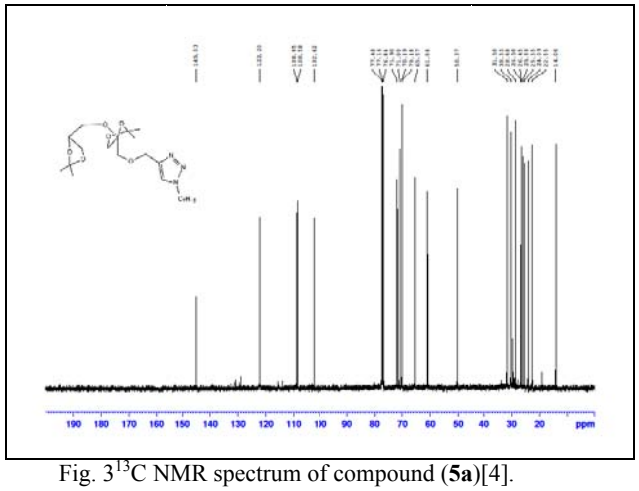


Fig. 3[13]C NMR spectrum of compound (**5a**)[4].

Table I Antibacterial activity of compounds 5a-d[4].

Compound	Zone of inhibition in (mm), concentration (µg/mL)					
	G^+*Staphylococcus*			G^-*Escherichia coli*		
	5	10	20	5	10	20
DMSO		-	-	-	-	-
Kanamycin	7	28	28	28	27	28
5a	-	02	04	-	02	05
5b	-	04	06	-	02	03
5c	-	04	07	-	03	05
5d	-	04	05	-	02	04
6a	-	03	05	-	03	03
6b	-	03	04	-	03	04
6c	-	04	06	-	05	10
6d	-	05	07	-	04	05

Adnan et.al [5] synthesis of D-iditol based tetrakis-1, 2, 3-triazoles has been reported. These heterocycles have displayed various biological activities against two types of bacteria. As shown in the Fig.4below

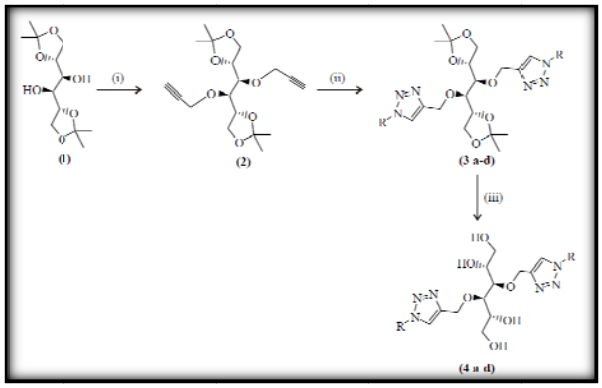


Fig.4 Synthesis of D-iditol based tetrakis-1, 2, 3-triazoles)[5]

Krim et. al [6]prepared A series of novel 1, 2, 3-triazole acyclo-nucleosides linked to nucleobases were prepared *via* copper (I) -catalyzed 1,3-dipolar cycloaddition . The pharmaceutical importance of triazoles has prompted the design and synthesis of various triazolonucleosides. As shown in theFig.5 below:

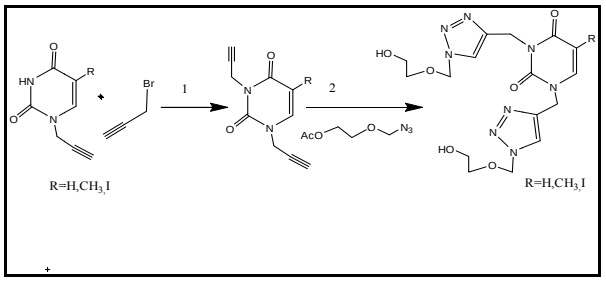


Fig. 5 Series of novel 1, 2, 3-triazole acyclo-nucleosides linked to nucleobases)[6]

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Sharba et al,[3] synthesized a new fructofuranosyl derivative comprising 1, 2, 3-triazole, 1, 2, 3-triazoline or tetrazole rings via 1,3-dipolar cycloaddition reaction. The biological activity of some prepared compounds was tested against one strain of Gram +ve bacteria (Staphylococcus aurous), Gram –ve bacteria (Eschericha coli), yeast (Candidas) and fungi (Aspergillus flavus) as Fig.6.

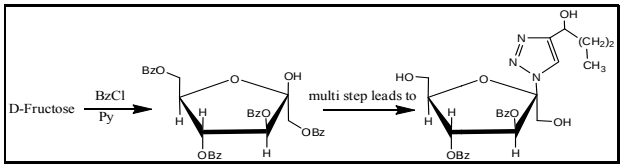

Fig 6. Synthesized a new fructofuranosyl derivative comprising 1, 2, 3-triazole)[3]

2.2Antivenom Effects

Domingos et.al. [7]synthesized six of a series of 1,2,3-triazole derivatives to inhibit some pharmacological effects caused by the venoms of Bothrops jararaca and Lachesis muta. In vitro assays showed that these compounds were impaired in a concentration-dependent manner, the fibrinogen or plasma clotting, hemolysis, and proteolysis produced by both venoms. Moreover, these compounds inhibited biological effects in vivo. . As shown in the Fig.7 below.

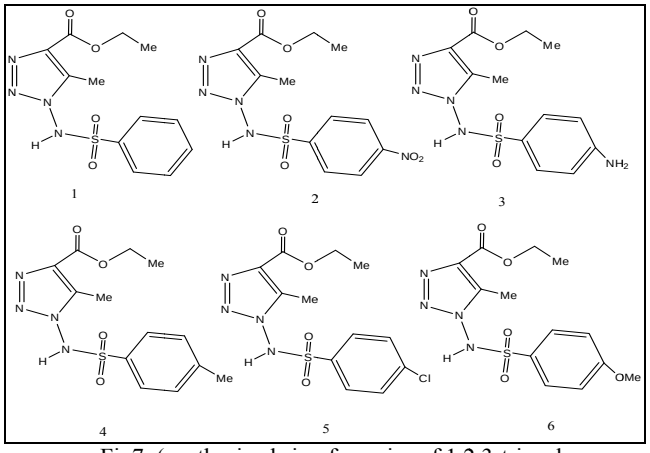

Fig7. (synthesized six of a series of 1,2,3-triazole derivatives)[7]

2.3**Anti-cancer Activity**

A series of 4-arylidenamino-4H-1, 2, 4-triazole derivatives were reported by Olcay et al. [8]. This series were synthesized from the treatment of 4-amino-4H-1, 2, 4-triazole with certain aldehydes. Compounds were characterized by elemental analyses and 1H NMR, 13C NMR, IR and UV spectral data. In recent years, various 1, 2, 4-triazoles and 4, 5-dihydro-1H-1, 2, 4-triazol-5-ones have been found to be associated with diverse pharmacological activities such as anticonvulsant, antifungal, anticancer, anti-inflammatory and antibacterial. As shown in the Fig.8 below

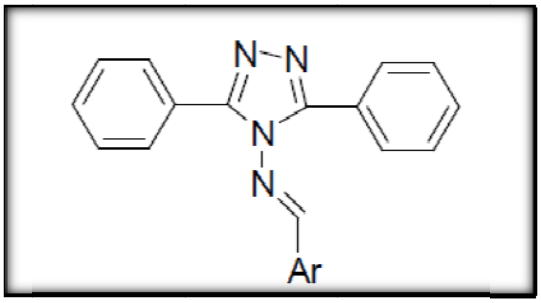

Fig.8 4-amino-4H-1, 2, 4-triazole[8]

2.4Anti-inflammation

Jun Hu [9] et.al synthesized a novel type of receptors based on 1,2,3-triazole glycyrrhetinic acid and derived from natural triterpenoid molecules has been synthesized via click chemistry and they showed high selectivity and affinity for Hg2+ ion by both the 1,2,3-triazole rings and aldehyde groups. Glycyrrhetinic acid is a facile pentacyclic triterpenoid presenting in the form of a glycone or glycosides from medicinal plants. It is mainly used for anti-inflammation, anti-virus and anti-tumor. As shown in the Fig.9 below:

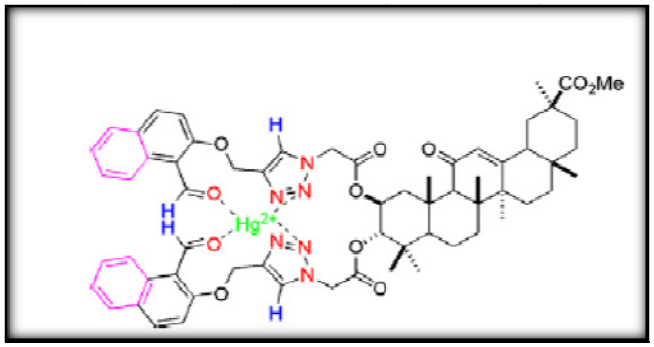

Fig.9 affinity for Hg^{2+} ion by both the 1,2,3-triazole rings)[9]

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2.5Glycosyl triazoles

Anand et al [2] synthesized glycohybrids were screened for them α-glycosidase, glycogen phosphorylase and glucose- 6-phosphatase inhibitory activities. A few of the glycohybrids showed promising inhibitory activities against these enzymes. As shown in the Fig.10below:

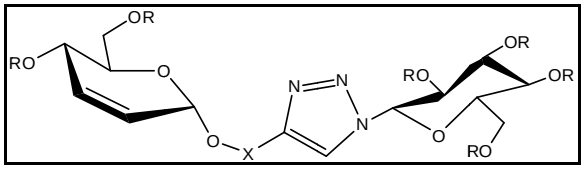

Fig.10 synthesized glycohybrids[2]

Gopi et.al [10]. investigated the structure–activity correlation of peptide conjugates that act as receptor site antagonists of HIV-1 gp120 The group synthesized derivatives of the original bioactive peptide on solid phases through the reaction of an immobilized azide-modified proline residue with alkynes containing different side chains. As shown in the Fig.11 below:

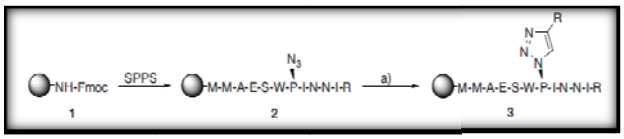

Fig.11 receptor site antagonists of HIV-1)[10]

3. Conclusions

Sugar based 1,2,3-triazoles were synthesized by using copper (I) catalyzed 1,3-alkyne-azide cycloaddition "Click Chemistry" from D-Fructose derivatives containing propargyl alkyne groups; these compounds containing 1,2,3-triazole segment were synthesized in good yields. In general, increasing the length of alkyl chain leads to increasing the melting temperature. The deprotection of di acetals from sugar moiety led to increase the polarity of target compounds. Adding to this, this work evaluates the biological activity of these glycoconjugates, the importance of 1,2,3-triazole derivatives, It is recommended to study in details other biological activities such as; antifungal activity, anticancer activity and antiviral activity.

Acknowledgments

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Jalal Hasan Mohammed was born in Karbala-Iraq on 11 November 1983 Graduated from the Karbala School and he received a BSc in Chemistry from Babylon University. He completed and received a master's degree in Organic Chemistry in Kerbala University. His contact is +9647810911159 email: jallal_hassan@yahoo.com.