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Review on the Synthesis and Biological Importance of Triazole Ring-containing Structures

Watandost Hamimullah [1*], Atif Abdul wali [2] , Kochai Khudaidad [3], Ahmadzai Ziaullah[4] and Ulfat Waliimam [5]

[1]Department of Chemistry, Faculty of Education, Paktia University, Gardez 2201, Afghanistan.

[2]Department of Chemistry, Faculty of Education, Paktia University, Gardez 2201, Afghanistan.

[3]Department of Chemistry, Faculty of Education, Nangarhar University, Jalalabad 2601, Afghanistan

[4]Department of Biology, Faculty of Education, Paktia University, Gardez 2201, Afghanistan.

[5]Department of Chemistry, Faculty of Science, Nangarhar University, Jalalabad 2601, Afghanistan

*Corresponding author email hamimullah92@gmail.com

ABSTRACT

Currently, many organic compounds have been synthesized and identified by chemists in chemical laboratories, numbering in the millions. The triazole ring is categorized as a subset of organic heterocyclic compounds. It constitutes a significant and extensive subject matter, and an in-depth examination of triazoles and their derivatives can lead to the development of specialized medical and biological chemical agents aimed at preventing a range of diseases. This article generally has two parts, the first part of the article is dedicated to triazole syntheses, in which the research of different authors is reviewed from 2005 to 2021, and the second part of this article is the biological importance of the triazole ring. Based on the special importance of medicine, we can mention antimicrobial and antifungal drugs that have a high level of medicinal activity. Unfortunately, we don't have standard chemical labs, to perform experiments. Nowadays, lab researches are replacing one group by another or one atom by another to obtain compound with deferent properties.

Keywords: 1,2,4-Triazole derivatives, Biological activity of triazole, Medicinal importance

Introduction

Heterocyclic compounds have a vital role in shaping the structure and categorization of compounds used in the field of medicine (Keri, et al., 2015). Nitrogen-containing heterocycles like triazoles and their modified versions have garnered significant interest in various domains, including pharmaceutical research and agricultural chemistry. They have also become a focal point in material science because of their distinctive structure and properties (Santiago, et al., 2019). Triazoles have interesting biological functions such as anti-cancer, anti-immune-deficiency virus, and anti-fungal properties, and they also have the role of antibiotics (Deng, et al., 2012). Figure 1 shows biological agents. Established pioneering examples show that a multicomponent reaction (MCR) is a simple and powerful tool for the synthesis of various heterocycle molecules, especially Triazoles (Chen et al., 2014). Additionally, the only purpose of writing this article is that teachers and students of chemistry and biology departments can get familiar with such heterocyclic compounds and use such compounds for addressing a range of medical conditions.

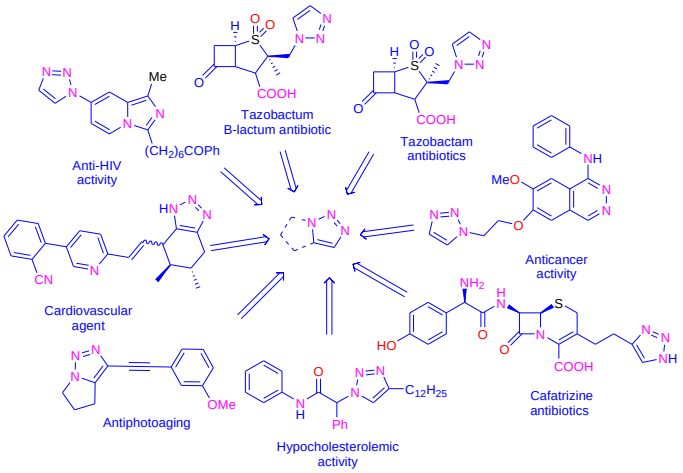
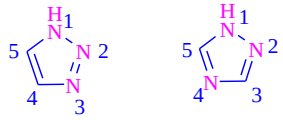


Figure 1: An active biological agent used as an antibiotic.

There are many rings. In this article, two possible Triazoles isomers (structures 1 and 2) are presented according to the nitrogen atom's location in Figure 2 (Holla et al 2005).



1 1,2,3-triazole **2** 1,2,4-triazole

Figure 2: Structures 1 and 2 vary with the nitrogen atom's placement.

Triazoles, commonly referred to as azoles, belong to a class of organic heterocyclic compounds. They feature an unsaturated five-membered ring structure comprising three nitrogen atoms and two carbon atoms that are not adjacent. Each of these structures exists in three distinct tautomeric forms (a, b, and c), with variation based on which nitrogen atom is involved in hydrogen bonding (Keri et al., 2015).

Synthesis of Triazoles structures using 3-amino-1,2,4-triazole

One of the important methods for Triazoles synthesis involves the reactions of aminoazoles in the form of multi-component, or single and di nuclear or polynuclear reactions with different electrophiles.The presence of multiple reaction centers in the group of amino azoles makes them valuable reagents, offering the potential for producing a variety of chemical substances (Figure 3) (Dai Hong et al., 2011).

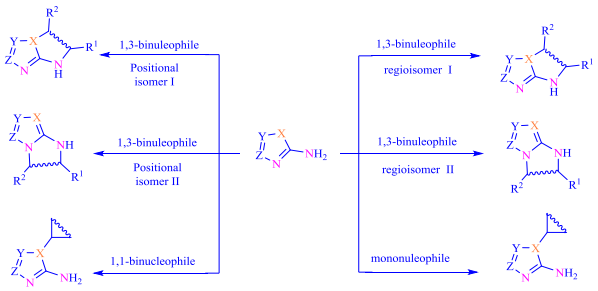


Figure 3: Variation related to cyclization of heterocycles using amino azoles.

In a study, Chebanov et al., (2005) reported a three-component condensation method involving pyruvic acid (3), aromatic aldehydes, and 3-amino-1,2,4-triazole (2) for synthesizing 5-aryl-5,8-dihydroazole (1,5-a)

pyrimidine-7-carboxylic acid (4). They conducted this reaction in a mixture of acetic acid and DMF. Interestingly, when they reacted 3-amino-1,2,4-triazole with pyruvic acid and aldehydes in DMF under reflux conditions, two isomers (4 and 5) were formed. Figure 4 in their study illustrates the influence of the solvent type on the resulting product's structure.

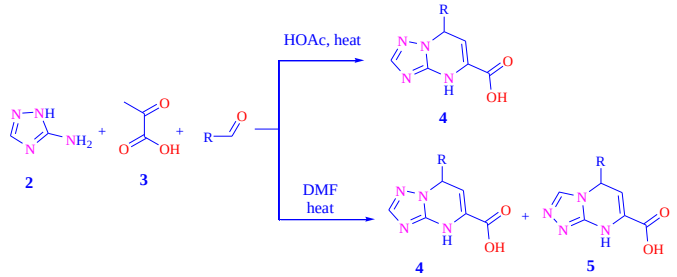


Figure 4: Synthesis of two isomers of 5-aryl-5,8-dihydroazole(1,5-a)pyrimidine-7-carboxylic acid.

Similarly, Parchinsky et al., (2006), successfully generated appropriate products of imidazole-[1,2-b] [1,2,4]-triazole (7) through a multicomponent reaction involving 3-amino-1,2,4-triazole (2), various aldehydes, and isonitrile (6). This is depicted in Figure 5. Additionally, it was observed that the desired heterocyclic structures could be efficiently produced with medium to good yields when employing benzyl isonitriles. Oxidation primarily occurred at the benzylic positions, resulting in the formation of N-alkylidene-4H-imidazo[1,2-b] [1,2,4] triazol-6-amine 8.

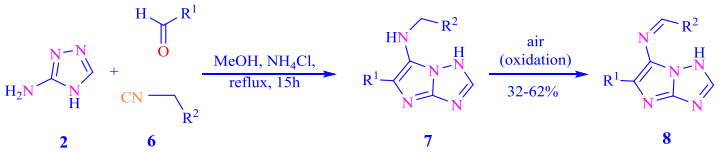


Figure 5: Condensation of 3-amino-1,2,4-triazole, aldehyde and isonitrile.

Sakhno et al, (2008) conducted a study focusing on the multicomponent reaction involving 3-amino-1,2,4-triazole (5-aminotetrazole 2), phenylpyruvic acid 9, and aromatic aldehydes. They carried out this reaction using conventional heating, ultrasound, and microwave dielectric methods. Notably, the study revealed the existence of two distinct pathways, influenced by either kinetic or thermodynamic control, depending on temperature and reaction conditions. These pathways led to the formation of different structures. As a result, by adjusting the reaction temperature, one could easily modify the chemical products obtained. When the starting materials were subjected to sonication for 30 minutes at room temperature or heated in acetic acid for 2 minutes at 140°C, they produced triazolopyrimidine products 10, while employing higher temperatures (acetic acid, microwave) resulted in the formation of thermodynamic products 11, as illustrated in Figure 6.

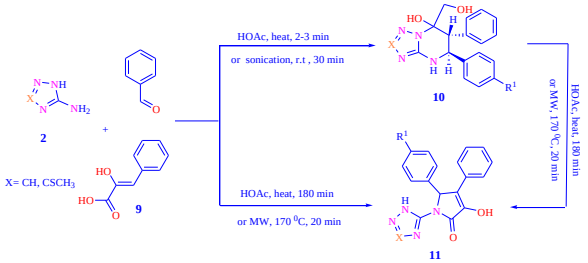


Figure 6: Various methods for the synthesis of triazolopyrimidine and pyrroles.

In addition, Schiff base 12 with phenyl pyruvic acid 9 in acetic acid with heating leads to the synthesis of triazolopyrimidine 10.

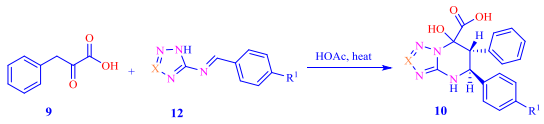


Figure 7:Synthesis of triazolopyrimidine via Schiff base with phenylpyruvic acid.

Lipson et al., (2009) conducted a study on a three-component condensation process involving 3-amino-5-alkylthio-1,2,4-triazole 2, aromatic aldehydes, and β-acetoester 13 to establish a quasi-Biginelli reaction aimed at generating compounds 14 and 15. The researchers observed that the choice of reaction solvent and the properties of the beta-ketoester significantly influenced the reaction outcome. Notably, this study represents the initial report on the directional aspects of the pseudo-Biginelli reaction.

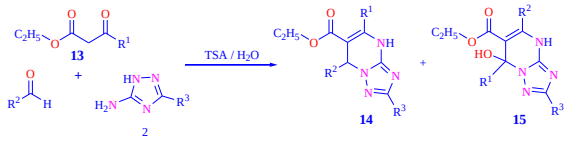


Figure 8: The result of pseudo Biginelli reaction in ethanol

Gorobets et al. (2010) found that a quasi-biginely three-component condensation, involving use of 3-amino-1,2,4-triazole, leads to an unexpected alternative pathway of formation of the hydroxylases tetra hydro pyrimidine ring 19 and the oxygen-bridged tetra hydro pyrimidine ring 20. It was concluded that 3-amino-1,2,4-triazole behaves differently from di amino azole. Moreover, the aldehyde component reacts with the amino group outside the 3-amino-1,2,4-triazole ring instead of the nitrogen inside the ring, resulting in the production of product 19. The reaction under normal heating and microwave conditions and using salicylic aldehyde is an efficient method to produce compounds related to the tetra hydro pyrimidine ring with an oxygen bridge of 20 is presented in Figure 8.

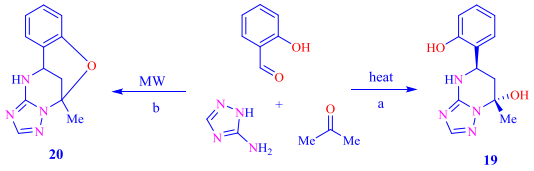


Figure 9: Synthesis of the tetrahydropyrimidine ring depending on the reaction conditions

Study conducted by Saitoet al., (2011) easily replaced the stearic esters with malonic ester or sodium nitro malon aldehyde monohydrate. They used malonic esters 27 as effective initial substances for creating azolazines 28 with a substituent at position 5 which is presented in Figure 9.

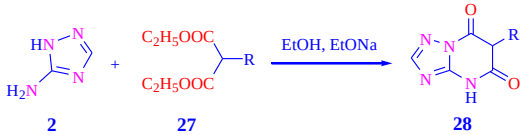


Figure 10: Malonic ester is used for the synthesis of azoloazine

Moreover, Gladkov et al., (2012) investigated two types of heterocyclic reactions involving 4-amino-5-carboxy amide 1,2,3-triazole 24 and cyclic ketones 25 under conventional heating, microwave and ultrasonic waves. The multi-component reaction of the system with chemical differentiation between cyclopentanone and cyclohexanone molecules leads to products 26 under different reaction conditions. The best results in this synthesis were observed in microwave conditions with the help of methanol at a temperature of 120.Figure 10 presents their process.

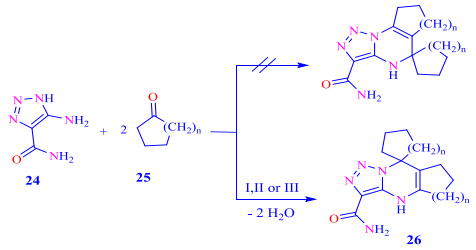


Figure 11: Multicomponent and sequential reaction of 4-amino-5-carboxamide-1,2,3-triazole with cyclic ketones.

Petrova, et al., (2013) synthesized indole- [1,2, c]-azolo [1,5, a]-quinazoline-8- and 10-diones as shown in Figure 12 as a result of multicomponent reactions that 1,3-diketones and 3-aminotriazoles were used.Certain additional aspects of the interaction may reveal distinct behaviors. Therefore, Peter and his co-workers synthesized multi-ring heterocyclic compounds, exemplified by the structures illustrated in Figure 11.

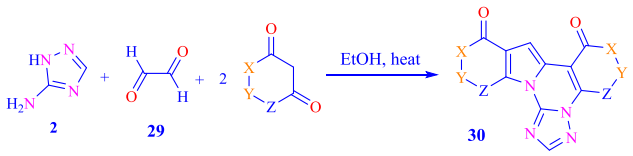


Figure 12: Multicomponent reaction between amino-azole, 1,3-diketone and glyoxal derivatives.

Moreover, Niu et al., (2014) proposed a sequential process without using transition metals for the synthesis of 1,2,4-triazoloquinoxaline 32. The synthesis of this three-ring compound employs aromatic nucleophilic substitution reactions. This approach is particularly suitable for compounds containing aromatic aldehydes with halogens or nitrogen substituents, as demonstrated in Figure 12. Various derivatives of 1,2,4-triazoloquinoxaline 32 are synthesized by condensation and aromatic nucleophilic substitution in a one-pot process without intermediate metal. Notably, this synthesis method is applicable not only to aromatic aldehydes but also to aromatic ketones, effectively yielding three-ring compoundsshown in Figure 12.

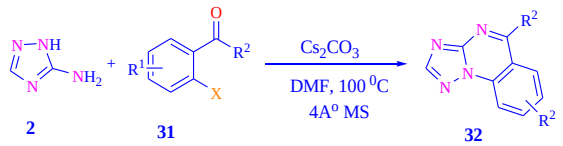


Figure 13: Synthesis of 1,4-triazoloquinoxaline in a process without intermediate metal.

Karami et al., (2015) and Weiet al., (2016) conducted studies involving 1-ethyl-4-pyridinone 33 attached to the C-H acidic group of aromatic aldehydes. In the presence of 3-amino-1,2,4-triazole, heating the mixture in

acetonitrile solvent at 100 °C yielded the product prided- [3,4, d]-triazolo- [3,4, a]-pyrimidine 34. Following this, oxidation was initiated as seen in Figure 13.

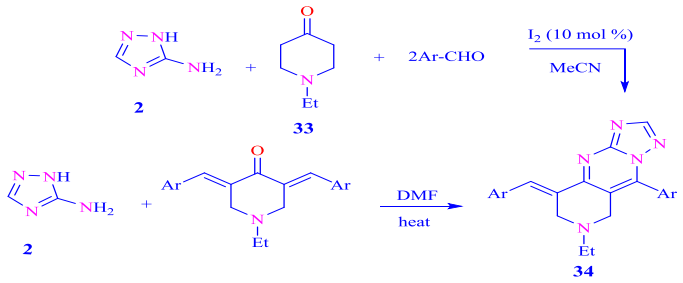


Figure 14: Synthesis of pyrido[4,3-d]triazolo[1,5-a]pyrimidine by condensation of 1-ethyl-4-pyridineone in CH-acid

Moreover, Komykhovet al., (2017) investigated an examination of three-component reactions involving (5S,7R)-aryl-7-methyl-4,5,6,7-tetrahydro [1,2,4]-pyrimidin-7-yl 47. This investigation resulted in the generation of two products, one from the interaction between 1H-1,2,4-triazole and 3-amine, and the other from the reaction of aromatic aldehydes and acetone, with TSOH serving as the solvent. These products displayed antifungal properties and were subjected to comprehensive laboratory analysis, as depicted in Figure 14.

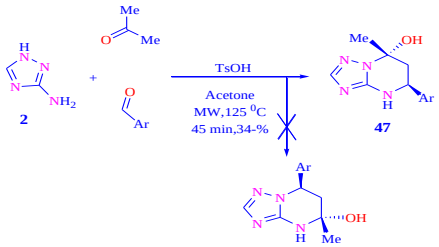


Figure 15: A four-component strategy for the synthesis of [1,2,4]- triazole-[1,5-a] pyrimidine-6-carboxamide derivatives.

Gladkov et al., (2018) synthesized novel spiro dihydro-1,2,4-triazolo[1,5-a]-pyrimidine derivatives (48) through a three-component reaction. This reaction involved 3-amino-1,2,4-triazole (2), amines, malonitrile, and cyclohexanone. The reaction was conducted under both microwave and conventional heating conditions, yielding the desired heterocyclic product, as depicted in Figure 15. Similarly, a one-pot synthesis of highly efficient compounds was achieved using 5-amino imidazo-[2,1-c] [1,2,4]-triazole derivatives (50) through straightforward reactions. These compounds were produced from readily available starting materials, including aromatic aldehydes, benzoylcyanide (49), and 3-amino-1,2,4-triazole (2), all in the presence of pyridine under controlled microwave heating. This method is environmentally friendly, operationally simple, time-efficient, and demonstrates high reaction efficiency, as reported by Sadek K., (2019) and illustrated in Figure 16.

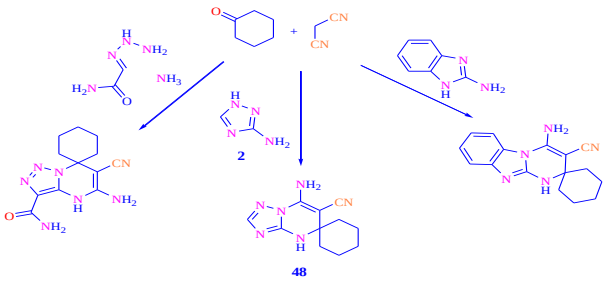


Figure 16: Three-component reaction of amines with cyclohexanone and malonitrile

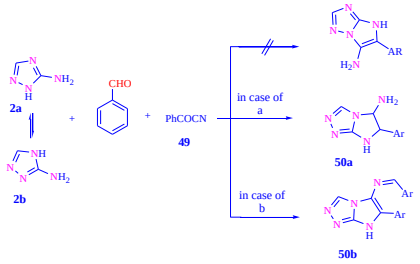


Figure 17: Synthesis of –amino imidazo-[2,1-c] [1,2,4] triazole derivatives 50.

Ashok et al., (2020) employed a nitrogen-containing triazole ring along with an acid catalyst and mineral clay. They successfully synthesized a range of novel compounds, specifically 3-(5-methyl-1-aryl-1H-1,2,3-triazol-4-yl)-1-phenyl-1H-pyrazole-4-carbaldehydes (4(a–g)) and their corresponding Benz imidazole derivatives (6(a–g)). These compounds were obtained using both conventional and microwave irradiation techniques, as shown in Figure 17.

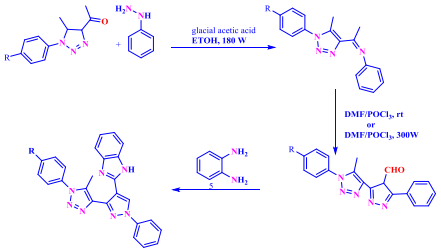


Figure 18: synthesis of 3-(5-methyl-1-aryl-1H-1,2,3-triazol-4-yl)-1-phenyl-1H-pyrazole-4-carbaldehydes.

And finally, Pacifico, et al., (2021) identified and synthesized an important drug that is of great importance in medicinal chemistry today. In this reaction, an environmental catalyst was used; therefore, they can be used as the leading biological compound (Figure 18).

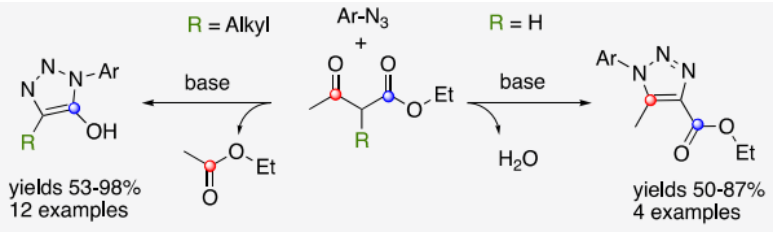


Figure 19: Synthesis of triazole derivatives that have medicinal properties.

The medicinal and biological importance of Triazoles

In recent decades, triazole rings have attracted unique interest from both chemists and biologists has been piqued because of their value in chemotherapy Holla et al, (2005).They exhibit a diverse array of medicinal activities such as antimicrobial activity (Sheremet et al., 2004), anti-inflammatory (Holla et al., 2005)analgesic(Hafez et al., 2007), antineoplastic (Guan et al., 2007), anticonvulsant(Passannanti et al.,1998), anti-proliferative (Manfredini et al., 2000),In addition, they have anti-cancer (Duran et al., 2002), antimalarial (Gujjar et al., 2009),and antiviral activities (Johns et al., 2009). They also exhibit inhibitory activity against phosphor diesterases (Beasley et al.,1998), hepatitis C (De Clercq et al. 1997), beta-lactamase inhibitors (Weide et al., 2010), insecticides (Chai et al., 2003), and other cases.

Triazoles as antifungal agents

Triazoles are a major component of antifungal drugs, which are used medicinally. Such compounds have minimal adverse effects and are toxic at low levels. A lot of research has been done in this regard and a lot of research is still going on in this field. To conclude, it should be noted that this type of anti-fungal drug is less toxic, and in recent years, the research on anti-fungal drugs is as follows (Zhou et al., 2012):

(1) Optimizing the structure of anti-fungal products, improving their chemical and physical properties in the process, and their compatibility, which results in increased biological activity. And it does this for the purpose of reducing the problems and increasing the benefits of antifungal drugs.

(2) To extract new antifungal agents, new derivatives can be obtained from triazole. In this process, the triazole ring combines with other drugs, from which a new compound or triazole derivative is obtained, the quality of the synthesized product is better than the original compound. And this drug can open the way as a new anti-fungal drug.

Modifying the Structure of Clinical Azole Antifungal Drugs

Figure 19 shows the uses of triazole in clinical fields: terconazole, itraconazole, fluconazole, bittertanol, cyproconazole as a fungicide, trazodone as an antidepressant, and triazolam as a sedative and hypnotic. is used (Keri et al., 2015).

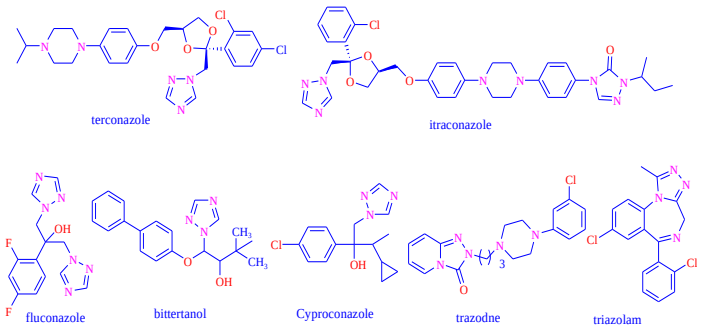


Figure 20: Clinical azole anti-fungal drugs

Pairing the Triazole Ring with Different Pharmacophores

The triazole ring has been found to engage in reactions with other drugs, leading to the creation of novel antifungal compounds. Recent years have seen increased research in this area, yielding a substantial number of new compounds with potent antifungal properties. It is widely recognized that chitin serves as the principal structural component in the cell walls of fungi. Given its absence in mammals, a promising eco-friendly approach for combating pathogenic fungi involves targeting the enzyme chitin synthase responsible for chitin synthesis. Nikkomycin, a naturally occurring chitin synthase inhibitor, has been pivotal in this regard. By substituting the peptide bond in nikkomycin with a triazole moiety, which shares similar atom placement and electronic properties, new derivatives (21a-c) were developed, resulting in a significant enhancement of antifungal activity, as demonstrated by (Chaudhary et al., 2009).

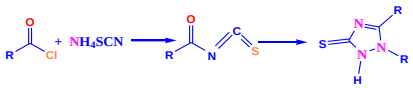
MATERIALS AND METHODS

In this article, a qualitative bibliographic method has been used, in which various scientific research articles have been used and it should also be said that most of the sources used in this article are new and have been published after 2010.

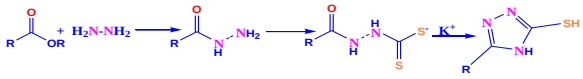
Introduction of Synthesis Triazoles

Following are five methods for triazole synthesis:

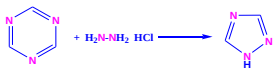
1. From thiocyanates:



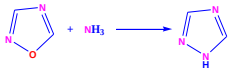
2. From esters:



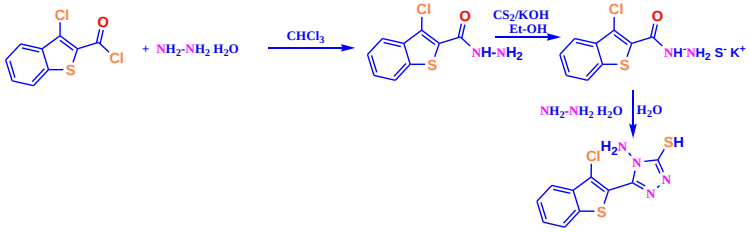
3. From 1,3,5 thiazines':



4. From 1,2,4 Oxdiazole.



5. From acid chlorides:



Physical properties

There are usually solid state tri azoles. Substituted triazole derivatives melt with respect to 1, 2, 4-triazole during high-temperature exothermic (when the temperature is 316 °C) continuously heated for 30 min (Holla et al., 2005). This compound exhibits limited solubility in solvents that lack polarity. Nevertheless, introducing substitutions on the nitrogen atom can enhance the solubility of these substances in non-polar solvents (Sheremet et al., 2004).

Introduction of MTT colorimetric method in investigating the cytotoxic effect of pharmaceutical compounds

Measuring the survival, growth and proliferation of cells has various applications in research. In the enzymatic method of investigating the effect of cytotoxicity, soluble tetrazolium salts are used as the starting material of the reaction, the most important of which is MTT. This test allows for the assessment of how various cells react to external influences like growth factors, cytotoxic drugs, and other chemical substances. This allows for the assessment of whether the level of activity and speed of cell proliferation may increase or remain unchanged under the influence of hormones, growth factors, cytokines, and mitogens. Additionally, under the influence of certain drugs and cytotoxic agents, such as anti-cancer drugs, cells may undergo necrosis or apoptosis, leading to a decrease in the speed of their reproduction or growth. Therefore, the MTT colorimetric method is used to investigate the effect of cytotoxicity of pharmaceutical compounds on the growth and proliferation of cancer cells, as well as to determine the IC 50 value for these compounds (Asif et al., 2014).

RESULTS

Triazoles are widely used in medicine, biology and agricultural research chemistry as drugs. Triazoles and their derivatives are active compounds. Today, numerous research studies are conducted, leading to the emergence of new medicinal compounds with strong biological activity that is widely employed. Today, imidazole has replaced the Triazoles as an important drug. Triazoles are considered azo esters and imidazole's in which the imidazole carbon atom is substituted on nitrogen in the form of azo esters. Currently, Triazoles find extensive application as drugs for conditions such as depression, neoplastic, malaria, viral, reproductive, cancer, pain, wound healing, CNS stimulants, sedatives, anxiety, anti-microbial, anti-fungal activities. This phrase seems incomplete and unclear. Please provide more context or rephrase. Triazole derivatives are significant due to their enhanced biological activity and their crucial role in heterocyclic chemistry (Tendon. V. K., 2004). Therefore, triazole has proved to be useful as a good pharmaceutical agent among the researchers working in this field, Due to its lower toxicity. Consequently, modifying different positions of triazole is suggested as a means to enhance the biological activity of these compounds and to facilitate synthesize of novel compounds in the future.

DISCUSSION

Triazoles are an integral part of a person, responsible for various biological functions. This article consolidates the collaborative research endeavors of multiple investigators, centering on the medicinal prospects of compounds derived from the triazole ring, resulting in the creation of innovative derivatives. These partial compounds are incorporated into Triazoles as a whole. This article is written in the light of specific biological activities and specific methods. It is evident from the presented information that 1,2,4-triazole derivatives offer the capacity for ring-opening reactions and the subsequent introduction of novel functional groups. Currently, extensive research and efforts are dedicated to improving the properties of 1,2,4-triazoles. Notably, heterocyclic compounds, including triazoles, are being increasingly recognized for their profound medicinal potential. As we navigate this research landscape, it is conceivable that novel 1,2,4-triazole derivatives with enhanced attributes will be uncovered. Such derivatives may eventually serve as therapeutic agents against many prevailing medical conditions. Furthermore, the reaction involving the combination of activated methylene, halogen derivatives in astatine, and beta-nitrothiazolidine as a bifunctional molecule in ethanol offers an accessible method (Asif., 2014).

CONCLUSION

Considering the remarkable activity exhibited by 1,2,4-triazole derivatives, they offer a versatile platform for synthesizing a range of heterocyclic compounds through methods like ring opening and group transfer. The heightened significance of these novel, Triazoles in the realm of disease treatment underscores their growing prominence. These heterocyclic compound derivatives have solidified their reputation as potent pharmaceutical agents. It remains optimistic that ongoing research in this area will yield further insights, potentially uncovering novel triazole compounds poised to address a spectrum of global medical challenges.

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REFERENCES

Ashok, D., Ram Reddy, M., Nagaraju, N., Dharavath, R., Ramakrishna, K., Gundu, S., ... & Sarasija, M. (2020). Microwave-assisted synthesis and in vitro antiproliferative activity of some novel 1, 2, 3-triazole-based pyrazole aldehydes and their benzimidazole derivatives. *Medicinal Chemistry Research*, *29*, 699-706.

Asif, M. (2014). A mini review on antimalarial activities of biologically active substituted triazoles derivatives. *Int J Adv Res Chem Sci*, *1*, 22-28.

Beasley, S. C., Cooper, N., Gowers, L., Gregory, J. P., Haughan, A. F., Hellewell, P. G., ... & Warneck, J. B. (1998). Synthesis and evaluation of a novel series of phosphodiesterase IV inhibitors. A potential treatment for asthma. *Bioorganic & medicinal chemistry letters*, *8*(19), 2629-2634.

Chai, B., Qian, X., Cao, S., Liu, H., & Song, G. (2003). Synthesis and insecticidal activity of 1, 2, 4-triazole derivatives. *Arkivoc*, *2*, 141-145.

Chaudhary, P. M., Chavan, S. R., Shirazi, F., Razdan, M., Nimkar, P., Maybhate, S. P., ... & Deshpande, S. R. (2009). Exploration of click reaction for the synthesis of modified nucleosides as chitin synthase inhibitors. *Bioorganic & medicinal chemistry*, *17*(6), 2433-2440.

Chebanov, V. A. (2005). Sakhno Ya. I., Desenko SM, Shishkina SV, Musatov VI, Shishkin OV, Knyazeva IV. *Synthesis*, *2597*.

Chen, X. B., Liu, Z. C., Yang, L. F., Yan, S. J., & Lin, J. (2014). A Three-component catalyst-free approach to regioselective synthesis of dual highly functionalized fused pyrrole derivatives in water–ethanol media: Thermodynamics versus kinetics. *ACS Sustainable Chemistry & Engineering*, *2*(5), 1155-1163.

DAI Hong, L. I. U., MIAO, W. K., WU, S. S., ZHANG, X., WANG, T. T., & FANG, J. X. (2011). Synthesis and bioactivities of novel thiazole amide derivatives containing a 2-substituted-1, 3-thiazolidine ring. *Chinese Journal of Organic Chemistry*, *31*(11), 1943.

De Clercq, E. R. I. K. (1997). In search of a selective antiviral chemotherapy. *Clinical Microbiology Reviews*, *10*(4), 674-693.

Deng, Q., Shi, H. W., Ding, N. N., Chen, B. Q., He, X. P., Liu, G., ... & Chen, G. R. (2012). Novel triazolyl bis-amino acid derivatives readily synthesized via click chemistry as potential corrosion inhibitors for mild steel in HCl. *Corrosion Science*, *57*, 220-227.

Duran, A., Dogan, H. N., & Rollas, S. (2002). Synthesis and preliminary anticancer activity of new 1, 4-dihydro-3-(3-hydroxy-2-naphthyl)-4-substituted-5H-1, 2, 4-triazoline-5-thiones. *Il Farmaco*, *57*(7), 559-564.

Gladkov, E. S., Gura, K. A., Sirko, S. M., Desenko, S. M., Groth, U., & Chebanov, V. A. (2012). Features of the behavior of 4-amino-5-carboxamido-1, 2, 3-triazole in multicomponent heterocyclizations with carbonyl compounds. *Beilstein Journal of Organic Chemistry*, *8*(1), 2100-2105.

Gladkov, E. S., Sirko, S. M., Musatov, V. I., Shishkina, S. V., Tkachenko, I. G., Komykhov, S. A., & Desenko, S. M. (2018). New spiro derivative of dihydro-1, 2, 3-triazolo [1, 5-a] pyrimidine as a product of the multicomponent reaction. *Chemistry of Heterocyclic Compounds*, *54*, 1139-1144.

Gorobets, N. Y., Sedash, Y. V., Ostras, K. S., Zaremba, O. V., Shishkina, S. V., Baumer, V. N., ... & Van der Eycken, E. V. (2010). The unexpected alternative direction of a Biginelli-like multicomponent reaction with 3-amino-1, 2, and 4-triazole as the urea component. *Tetrahedron Letters*, *51*(16), 2095-2098.

Guan, L. P., Jin, Q. H., Tian, G. R., Chai, K. Y., & Quan, Z. S. (2007). Synthesis of some quinoline-2 (1H)-one and 1, 2, 4-triazolo [4, 3-a] quinoline derivatives as potent anticonvulsants. *J Pharm Pharm Sci*, *10*(3), 254-62.

Gujjar, R., Marwaha, A., El Mazouni, F., White, J., White, K. L., Creason, S., ... & Phillips, M. A. (2009). Identification of a metabolically stable triazolopyrimidine-based dihydroorotate dehydrogenase inhibitor with antimalarial activity in mice. *Journal of medicinal chemistry*, *52*(7), 1864-1872.

H Zhou, C., & Wang, Y. (2012). Recent research in triazole compounds as medicinal drugs. *Current medicinal chemistry*, *19*(2), 239-280.

Hafez, H., Abbas, H. A., & El-Gazzar, A. R. (2008). Synthesis and evaluation of analgesic, anti-inflammatory and ulcerogenic activities of some triazolo-and 2-pyrazolyl-pyrido [2, 3-]-pyrimidines. *Acta Pharmaceutica*, *58*(4), 359-378.

Holla, B. S., Mahalinga, M., Karthikeyan, M. S., Poojary, B., Akberali, P. M., & Kumari, N. S. (2005). Synthesis, characterization, and antimicrobial activity of some substituted 1, 2, and 3-triazoles. *European journal of medicinal chemistry*, *40*(11), 1173-1178.

Johns, B. A., Weatherhead, J. G., Allen, S. H., Thompson, J. B., Garvey, E. P., Foster, S. A., ... & Miller, W. H. (2009). The use of oxadiazole and triazole substituted naphthyridines as HIV-1 integrase inhibitors. Part 1: Establishing the pharmacophore. *Bioorganic & medicinal chemistry letters*, *19*(6), 1802-1806.

Karami, B., Farahi, M., & Banaki, Z. (2015). A novel one-pot method for the highly regioselective synthesis of triazoloapyrimidinedicarboxylates using silica sodium carbonate. *Synlett*, 1804-1807.

Keri, R. S., Patil, S. A., Budagumpi, S., & Nagaraja, B. M. (2015). Triazole: a promising antitubercular agent. *Chemical biology & drug design*, *86*(4), 410-423.

Komykhov, S. A., Bondarenko, A. A., Musatov, V. I., Diachkov, M. V., Gorobets, N. Y., & Desenko, S. M. (2017). (5 S, 7 R)-5-Aryl-7-methyl-4, 5, 6, 7-tetrahydro-[1, 2, 4] triazolo [1, 5-a] pyrimidin-7-ols as products of three-component condensation. *Chemistry of Heterocyclic Compounds*, *53*, 378-380.

Lipson, V. V., Karnozhitskaya, T. M., Shishkina, S. V., Shishkin, O. V., & Turov, A. V. (2009). Reactions of 3-amino-1, 2, 4-triazoles with cinnamic aldehydes. *Russian Chemical Bulletin*, *58*, 1441-1444.

Manfredini, S., Vicentini, C. B., Manfrini, M., Bianchi, N., Rutigliano, C., Mischiati, C., & Gambari, R. (2000). Pyrazolo-triazoles as light activable dna cleaving agents. *Bioorganic & medicinal chemistry*, *8*(9), 2343-2346.

Niu, X., Yang, B., Fang, S., Li, Y., Zhang, Z., Jia, J., & Ma, C. (2014). An efficient one-pot synthesis of 1, 2, 4-triazoloquinoxalines. *Tetrahedron*, *70*(31), 4657-4660.

Pacifico, R., Destro, D., Gillick-Healy, M. W., Kelly, B. G., & Adamo, M. F. (2021). Preparation of Acidic 5-Hydroxy-1, 2, 3-triazoles via the Cycloaddition of Aryl Azides with β-Ketoesters. *The Journal of Organic Chemistry*, *86*(17), 11354-11360.

Parchinsky, V. Z. (2006). Schuvalova O. Ushalova O. Krachenko DV. Krasavin M. *Tetrahedron Lett*, *47*, 947.

Passannanti, A., Diana, P., Barraja, P., Mingoia, F., Lauria, A., & Cirrincione, G. (1998). Pyrrolo [2, 3-d] [1, 2, 3] triazoles as potential antineoplastic agents. *Heterocycles*, *6*(48), 1229-1235.

Petrova, O. N., Zamigajlo, L. L., Shishkina, S. V., Shishkin, O. V., Musatov, V. I., Borisov, A. V., & Lipson, V. V. (2013). A facile one-pot highly chemo-and regioselective synthesis of the novel heterocyclic system indolo [1, 2-c] azolo [1, 5-a] quinazoline-8, 10-dione. *Tetrahedron*, *69*(52), 11185-11190.

Sadek, K. U., Abdel-Hameed, A. M., Abdelnabi, H. A., & Meleigy, Y. (2019). An efficient green synthesis of novel 1 H-imidazo [1, 2-a] imidazole-3-amine and imidazo [2, 1-c] [1, 2, 4] triazole-5-amine derivatives via Strecker reaction under controlled microwave heating. *Green Processing and Synthesis*, *8*(1), 297-301.

Saito, T., Obitsu, T., Minamoto, C., Sugiura, T., Matsumura, N., Ueno, S., ... & Toda, M. (2011). Pyrazolo [1, 5-a] pyrimidines, triazolo [1, 5-a] pyrimidines, and their tricyclic derivatives as corticotropin-releasing factor 1 (CRF1) receptor antagonists. *Bioorganic & medicinal chemistry*, *19*(20), 5955-5966.

Sakhno, Y. I., Desenko, S. M., Shishkina, S. V., Shishkin, O. V., Sysoyev, D. O., Groth, U., ... & Chebanov, V. A. (2008). Multicomponent cyclocondensation reactions of aminoazoles, arylpyruvic acids, and aldehydes with controlled chemoselectivity. *Tetrahedron*, *64*(49), 11041-11049.

Santiago, J. V., & Burtoloso, A. C. (2019). Synthesis of Fused Bicyclic [1, 2, 3]-Triazoles from γ-Amino Diazoketones. *ACS omega*, *4*(1), 159-168.

Sheremet, E. A., Tomanov, R. I., Trukhin, E. V., & Berestovitskaya, V. M. (2004). Synthesis of 4-Aryl-5-nitro-1, 2, 3-triazoles. *Russian Journal of Organic Chemistry*, *40*(4), 594-595.

Wei, F., Wang, W., Ma, Y., Tung, C. H., & Xu, Z. (2016). Regioselective synthesis of multi substituted 1, 2, 3-triazoles: moving beyond the copper-catalyzed azide–alkyne cycloaddition. *Chemical Communications*, *52*(99), 14188-14199.

Weide, T., Saldanha, S. A., Minond, D., Spicer, T. P., Fotsing, J. R., Spaargaren, M., ... & Fokin, V. V. (2010). NH-1, 2, 3-triazole inhibitors of the VIM-2 metallo-β-lactamase. *ACS Medicinal Chemistry Letters*, *1*(4), 150-154.