HEALTH, ENVIRONMENT, DEVELOPMENT

SYNTHETIC AND BIOLOGICAL ASPECTS OF STUDYING THE PROPERTIES OF 1,2,4-TRIAZOLE DERIVATIVES

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Summary

1,2,4-triazoles belong to a well-known class of heterocyclic compounds that are of both theoretical and practical interest. This class has been known for about 100 years, and in recent decades 1,2,4-triazoles have become one of the most attractive objects of research in the chemistry of heterocyclic compounds due to their unique properties. Recently, a considerable number of innovative synthesis methods have been developed and interesting modification of chemical variations has been proposed, for example, a three-component reaction of aryldiazonium salts with fluorinated diazoreagents and nitriles, or a combination of a fragment of 1,2,4-triazole with coumarins or naphthalene-substituted compounds in one combined molecule, and so on. As a result, scientists have obtained new derivatives of 1,2,4-triazoles with a certain number of structural features that contribute to the production of promising substances with antimicrobial, antifungal, antitubercular, antioxidant, antitumor effects, etc.

These derivatives are used not only in the medical and veterinary sphere, but also in the agricultural and industrial sectors. They have found their application as dyes, corrosion inhibitors, photosensitizers, fungicides, plant growth regulators, etc.

The aim of our work was to analyze and summarize the known literature data on new synthetic approaches to the production of new derivatives of 1,2,4-triazole and systematize information related to the biological properties of these compounds.

Keywords: 1,2,4-triazole, medical chemistry, biological activity, heterocycle, organic chemistry.

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1. Introduction

Triazoles are part of a five-membered heterocycle family, scientific interest is constantly growing to it *(Parchenko V.V., 2014)*. This is primarily due to the wide range of applications of derivatives of this system in the pharmaceutical, agricultural and technical industries *(Bigdan O. A., 2017: 135-140)*. 1,2,4-Triazole is a system with a symmetric arrangement of three nitrogen atoms and two carbon atoms, which give unique properties to these derivatives *(Parchenko V. V., 2011: 49-53)*. In addition, 1,2,4-triazoles are a key building block of a large number of molecular structures with antibacterial, antifungal, anti-tuberculosis, antioxidant, antitumor, analgesic, anti-inflammatory activity, etc. *(Borisenko N.N., 2019: 1-5)*. The possibility of additional introduction of various substituents into the "framework" of 1,2,4-triazole is crucial in modeling new "libraries" of promising compounds *(Bigdan O.A., 2016: 90-97)*. Therefore, the strategy of "building" new substituted 1,2,4-triazole is popular among scientists due to the additional introduction of various pharamcoforic residues. The wide range of biological and pharmacological properties of 1,2,4-triazole encourages scientists in many countries of the world to develop new synthetic approaches for the targeted production of new derivatives of 1,2,4-triazole.

The aim of our work was to analyze and summarize the known literature data on new synthetic approaches to the production of 1,2,4-triazole derivatives and systematize information related to the biological properties of these compounds.

2. Review of potential prospects for 1,2,4-triazoles

An original method for the synthesis of both symmetric and unbalanced 3,4,5-triaryl-1,2,4-triazoles using B(C6F5)3 as a catalyst is proposed by a team of scientists *(Guru M. M., 2019: 7964–7974)*. The authors proved that B(C6F5)3 performs a dual role, firstly, it activates the corresponding hydrazone for nucleophilic attack, and secondly, it initiates the formation of a frustrated Lewis pair for dehydrogenation. This method is economical, and without the presence of oxidizing agents, it can become a potential platform for chemical conversion catalyzed by the main group without the use of a transitive metal.

Isocyanoacetates are universal substrates for the synthesis of heterocyclic compounds. The authors investigated the reaction of decarboxylative cancellation of 2-aryl-2-isocyanoacetates with aryldiazonium salts *(Tian Y. T., 2021: 227-233)*. This method makes it possible to produce a large number of new molecules in a number of 1,3-diaryl-1,2,4-triazoles, including binaphthalene, potential drug compounds, and synthetic intermediates of drug-like molecules. The three-component reaction of aryldiazonium salts with fluorinated diazoreagents and nitriles deserves attention. *(Peng X., 2020: 4432–4437)*. The method makes it possible

to expand the spectrum of difluoromethylated N1-aryl-1,2,4-triazoles, most of which show similarity to drug molecules.

The development of powerful urease inhibitors can be considered as a promising area of scientific research. A team of scientists has developed structurally diverse compounds containing coumarin and thiazolo-1,2,4-triazole in one combined molecule *(Khan, I., 2020: 345–354)*. The combination of fragments of 1,2,4-triazole and naphthalene-substituted compounds in one molecule leads to the formation of substances with high antitumor activity *(Luo L., 2021: 113039)*. Some compounds have cytotoxicity in vitro, stopping the cell cycle and inducing apoptosis in MDA-MB-231 cells. in addition, the compounds have been found to inhibit the growth of 4T1 breast tumors. Another team of scientists described in detail the production of new spirocyclic and chiral triazolopiperazines *(Lorthioir O., 2020: 152600)*. The authors have developed a practical, fast and reliable synthetic pathway for the synthesis of these derivatives, which allows you to control Regio - and stereochemistry. The reaction conditions are quite mild. Available amino acids and amidins can be used as starting components. The resulting 5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazines are attractive molecules for finding potential drugs among them. Heterocyclic nitrogen compounds are important structural subunits that are widely found in bioactive natural products, pharmaceuticals, agrochemicals, and the like. Recently, attention has been paid to arendiazonium salts, which are a source of nitrogen – the main component in the synthesis of nitrogen-containing heterocyclic compounds *(Liu J., 2020: 4876–489)*. According to the authors, the direction of combining 1,2,4-triazole and the Quinoline "core" in one molecule due to condensation of 5-(4-chlorphenoxymethyl)-2,4-dihydro-1,2,4-triazole-3-thiones and 5-(pyridine-3-yl)-4H-1,2,4-triazole-3-thiols with substituted 2-chlorquinoline-3-carbaldehydes is promising *(D'Souza V. T., 2021: 129503)*.

The strategy of donor-acceptor diazoactivation is a promising area of synthetic testing. The authors convincingly proved the possibility of constructing molecules by condensation using diazonium salts, and also found that the intermediate product undergoes cyclization to form indazoles *(Li X., 2020: 4151–4155)*. Various new 1,2,4-triazolo[4,3-b][1,2,4,5]tetrazines and 1,2,4-triazolo[4,3-B][1,2,4]triazines can be obtained by heterocyclicizing 3-substituted 4-amino-1,2,4-triazoles with (α and β) bifunctional compounds *(El-Reedy A. A. M., 2020: 1-18)*. Their effectiveness against various pathogenic strains of microbes and fungi has been proven. Some of them show high anti-inflammatory activity. An original approach to the production of 1,2,4-triazole derivatives by cyclization of nitriles with 2-aminopyridines is proposed by a team of scientists *(Xia J., 2019: 2014–2022)*. Another team proposed an original synthesis method 1-(morpholine-4-yl-methyl)-3-alkyl(aryl)-4-[4-(dimethylamino)-benzylidenamino]-4,5-dihydro-1H-1,2,4-triazole-5-one *(Gürsoy Kol Ö., 2016: 105-120)*. The compounds showed high antioxidant activity in various models. A number of new 2-pyridyl substituted[1,2,4] triazolo[1,5-α]azines were synthesized by the reaction of cyanopyridines with mesitilensulfonates *(Shubin, V. G., 2020: 10-13)*. New spiro[fluorene-9,3'-[1,2,4]triazoles were obtained with high yields by the reaction of N3-substituted benzamidrazones and (2,4,7-trinitro-9H-fluorene-9-ylidene) propandinitriles in ethyl acetate solution *(Gomaa M. A. M., 2018: 138-140)*. Another paper describes and characterizes the production of heterocyclic carbene ligands from the core of 1,2,4–triazole *(Geetha B. M., 2020: 1-9)*. A number of compounds with high antioxidant and antihemolytic properties have been identified among them. The original method for the synthesis of 4-aryl-3-(o-carboxyphenyl)-5-phenyl-1,2,4-triazoles is proposed by a team of scientists *(Aly A. A., 2017: 2375–2379)*. The reaction takes place in the presence of equimolar amounts of phthaloyl chloride and N-arylbenzamidrazone in the presence of two triethylamine (Et3N) equivalents. The high reactivity of amidins makes them valuable intermediates in the

synthesis of heterocyclic compounds, organocatalysts, and metal complexes. The authors studied in detail the reactivity of amidins in the synthesis of 1,2,4-triazole-containing compounds *(Aly A. A., 2018: 85-138)*. Another team of scientists has developed a lightweight and versatile catalytic system that includes a copper catalyst, K3PO4, and an oxidizer to ensure efficient synthesis of 2,4,6-triazines, 2,6-dizaminated 1,3,5-triazines, and 1,3-dizaminated 1,2,4-triazines *(Huang H., 2015: 2894–2897)*.

Aldose reductase (AR) is a key enzyme that causes excessive accumulation of sorbitol in tissues, leading to severe microvascular complications caused by diabetes. It is scientifically proven that inhibiting this enzyme is a well-developed strategy to mitigate these complications. Scientists have proven that new 2-[(4-amino-5-aryl-4H-1,2,4-triazole-3-yl)thio]-N-(thiazolbenzothiazole-2-yl)acetamides are potent aldose reductase inhibitors *(Sever B., 2021)*.

Various studies on the study of 1,2,4-triazoles are available. The literature has shown that a compound containing 1,2,4-triazole has a variety of biological activities. Some 1,2,4-triazole condensed acyclic and macrocyclic compounds with potential antimicrobial activity *(Manicrao A.M., 2009: 1268-1272)*. Derivatives of 1,2,4 triazoles with antibacterial activity against Staphylococcus aureus, Klebsiella pneumonia, Escherichia coli and Pseudomonas aeurogenosa were studied by seeding on a Petri dish and revealed high antibacterial activity *(Somani R.R., 2009: 168-173)*. Some 1,2,4-triazole analogues are being investigated to assess their antifungal activity against C. albicans, A. Niger *(Bayrak H, 2009: 1057-66)*. Some new 1,2,4 triazoles and their Mannich and Schiff bases exhibit high antimicrobial activity against E. coli, Y. pseudotuberculosis, P. aeriginosa, Enterococcus faecalis, S. aureus, B. cereus, C. tropicalis and C. albicans. Some derivatives of 1,2,4-triazole have been shown to be active against E. Coli, Klebsiella pneumonia, Yersinia pseudotuberculosis, Enterobacter aerogenes, P. aeurogenosa, Staphylococcus aureus, E. faecalis, Bacillus ceretropical, Canansis, Can. Glabrata *(Bektaş H., 2010: 2427-2438)*. Condescension products of 1-acylthiosemicarbazides, 1,3,4-oxadiazoles, 1,3,4-thiadiazoles, and 1,2,4-triazole-3-thiones describe anti-inflammatory activity using the carrageenan paw edema test (CPE) *(Hacer B., 2009: 4362-4366)*. 5-aryl-3-alkyltio-1,2,4-triazoles and sulfones have anti-inflammatory and analgesic activity *(Umut S., 2007: 5738-5751)*. 1-Acylthiosemicarbazides, 1,2,4-triazole-5(4H)-thiones, 1,3,4-thiadiazoles, and hydrazones containing 5-methyl-2-benzoxazolinones showed analgesic, anti-inflammatory, and antimicrobial activity against Candida krusei, Candida albicans, and Candida parapsilosis. Derivatives of 4H-1,2,4-triazole exhibit analgesic activity *(Goyal P.K., 2010: 1992-1997)*.

In previous years, the synthesis of heterocyclic systems with a high nitrogen content has been involved in many areas of the pharmaceutical and agrochemical industries. Triazole, which is a five-membered heterocyclic nucleus, has attracted widespread attention from chemists in the search for new therapeutic molecules. The triazole core is one of the most important heterocycles, which is a property of natural products and medicines. The triazole core uses its importance as a center of activity. Nitrogen-containing heterocyclic substances are found in large quantities in most medicinal compounds *(Shiradkar M., 2006: 807-816)*. Triazoles are called imidazole isosters, in which the carbon atom of imidazole is isosterically replaced by nitrogen. Triazole and its derivatives have a wide range of applications and play a vital role in biological fields *(Kartritzky A.R., 1985)*. These skeletons have different potential against multiple activities. In the last few decades, much attention has been paid to the chemistry of triazoles and their condensed heterocyclic derivatives due to their synthetic and effective biological activity (fig. 1.1). Drugs containing the triazole group are also known on the market, for example. fluconazole, intraconazole, voriconazole, triazolam, alprazolam, etizolam and furacilin. This review includes the microwave synthesis of triazoles and its derivatives.

Derivatization of the triazole ring is based on the phenomenon of bioisosterism, in which the oxygen of the oxadiazole core is replaced by a nitrogen analog of triazole. This review provides a brief overview of the medical chemistry of the triazole system and highlights some examples of recent drugs containing this part in the current literature. Triazole is a unique component that is responsible for a variety of biological activities. This article highlights the research work of many researchers, which is described in the literature on various pharmacological activities for synthesized triazole compounds. This review provides comprehensive information about triazole analogues, powerful compounds that have been reported for certain pharmacological activity, as well as the method involved in the evaluation process *(Kumar R, 2013: 1844-1869)*. So far, it has been observed that modifications of the triazole part lead to the formation of compounds with valuable biological activity. It will be interesting to note that these modifications can be used as powerful therapeutic agents in the future.

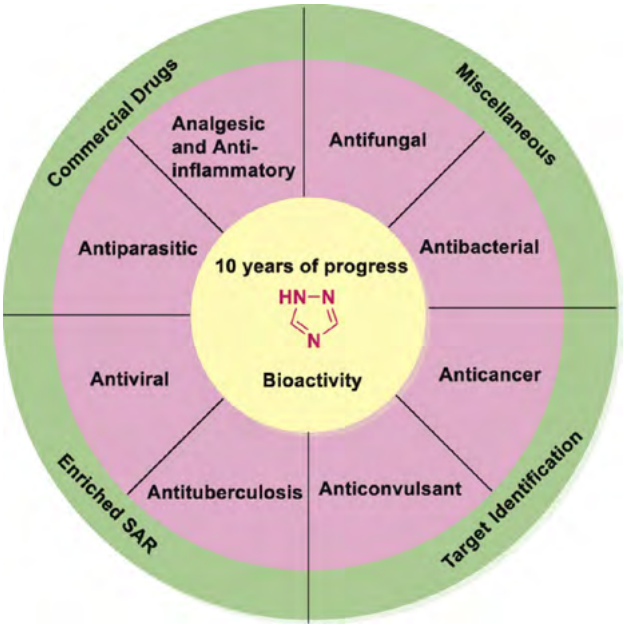

Fig. 1. Progress in studying of the biological activity of the 1,2,4-triazole nucleus

3. Conclusions

1,2,4-Triazoles have attracted considerable attention in the field of Medicine and agrochemical research, as well as in materials science due to their unique structure and properties. 1,2,4-triazole and its derivatives belong to the class of exclusively active compounds with many pharmacological properties. Some triazole derivatives are also known to exhibit antitumor activity. 1,2,4-riazoles are of great importance, as they have also been studied for their depressive, pesticide, antimycobacterial, hypoglycemic, diuretic, insecticidal and herbicidal effects on the central nervous system. Sulfonamide preparations (sulfonamide preparations) were the first antimicrobials to pave the way for the antibiotic revolution in medicine. From a structural point of view, sulfonamides are interesting because of their tendency to form different hydrogen bond systems in the solid state by introducing various hydrogen bond donors and acceptors

as substituents into simple sulfonamide molecules. In addition, sulfur-containing heterocycles represent an important group of sulfur compounds that are promising for practical applications. Among these heterocycles, mercapto - and Thion-substituted 1,2,4-triazole ring systems have been well studied, and so far the diverse biological activity of a large number of their derivatives has been reported. It has been reliably established that various triazole derivatives have a wide range of pharmacological properties. 1,2,4 is a triazole fragment present in various natural products and compound synthesis. This part has attracted the attention of both chemists and biologists. Compounds containing different heterocyclic fragments will be tested for antimicrobial activity against different strains of pathogens. Similarly, some of the compounds will also be tested for anti-inflammatory and analgesic effects. Many therapeutically important medications available, such as ketoconazole, itraconazole, voriconazole, and fluconazole, contain this heterocyclic nucleus. Taking into account the above facts and continuing interest in heterocycles containing the 1,2,4-triazole fragment, identify as a new molecule that may be important in the development of new, powerful, selective and less toxic antimicrobial agents. This combination is seen as an attempt to investigate the effect of structure variation on predicted biological activity, hoping to add some synergistic biological significance to the target molecules.

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