Analysis of biological properties of 1,2,4-triazole-containing compounds (literature review)

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

In the latest conditions of development and formation of the pharmaceutical industry, the introduction of new synthetic medicines requires continuous monitoring of the quality and safety of their use. For many years, synthetic drugs have remained an essential tool in the prevention and control of diseases of various etiologies. Among the synthetic class of substances, first of all, those that are low-toxic, safe, and effective deserve attention. In recent decades scientific publications prove the prospects of searching for new biologically active compounds among derivatives of 1,2,4-triazoles with fragments of various heterocyclic systems. Scientists claim that the combination of several structural fragments of heterocycles in one molecule leads to the emergence of new types of biological action, and sometimes to an increase in known pharmacological effects. At the same time, the synthesized compounds belong to the class of low-toxic or practically non-toxic substances.

The aim of our work is to analyze foreign and native sources on the biological activity of 1,2,4-triazole derivatives.

Conclusions. Among these derivatives, molecules that exhibit broad antifungal and antimicrobial activity, antitubercular, antiviral, actoprotective, antihypoxic, analgesic effects, etc. were found. After analyzing the known data, a number of «structure-action» regularities were established. The obtained results will be useful for further research work of scientists.

Key words: 1,2,4-triazole, biological properties, activity.

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Аналіз біологічних властивостей 1,2,4-тріазолвмісних сполук (огляд літератури)

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У сучасних умовах розвитку і становлення фармацевтичної промисловості впровадження нових синтетичних лікарських засобів потребує постійного контролю якості та безпеки їх використання. Протягом багатьох років синтетичні ліки залишаються суттєвим інструментом щодо профілактики та боротьби з хворобами різної етіології. Серед синтетичного класу речовин передусім заслуговують на увагу ті, що є малотоксичними, безпечними й ефективними. Наукові публікації в останні десятиліття показують перспективність пошуку нових біологічно активних сполук серед похідних 1,2,4-тріазолів із фрагментами різних гетероциклічних систем. Учені стверджують, що поєднання декількох структурних фрагментів гетероциклів в одній молекулі призводить до появи нових видів біологічної дії, інколи і до посилення відомих фармакологічних ефектів. До того ж синтезовані сполуки належать до класу малотоксичних чи практично нетоксичних речовин.

Мета роботи – аналіз закордонних і вітчизняних джерел щодо біологічної активності 1,2,4-тріазолпохідних.

Висновки. Серед зазначених похідних виявлено молекули, які проявляють широку протигрибкову та протимікробну активність, протитуберкульозну, противірусну, актопротекторну, антигіпоксичну, анальгетичну дію тощо. Проаналізувавши відомі дані, встановлено низку закономірностей «будова – дія». Результати будуть корисними для подальшої науково-дослідної роботи вчених.

Ключові слова: 1,2,4-тріазол, біологічні властивості, активність.

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Анализ биологических свойств 1,2,4-триазолсодержащих соединений (обзор литературы)

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В новейших условиях развития и становления фармацевтической промышленности внедрение новых синтетических лекарственных средств требует постоянного контроля качества и безопасности их использования. В течение многих лет синтетические лекарства

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Key words: 1,2,4-triazole, biological properties, activity.

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остаются существенным инструментом в профилактике и борьбе с болезнями разной этиологии. Среди синтетического класса веществ прежде всего заслуживают внимания малотоксичные, безопасные и эффективные. Научные публикации за последние десятилетия доказывают перспективность поиска новых биологически активных соединений среди производных 1,2,4-триазолов с фрагментами различных гетероциклических систем. Учёные утверждают, что сочетание нескольких структурных фрагментов гетероциклов в одной молекуле приводит к появлению новых видов биологического действия, а иногда и к усилению известных фармакологических эффектов. При этом синтезированные соединения относятся к классу малотоксичных или практически нетоксичных веществ.

Цель работы – анализ зарубежных и отечественных источников, касающихся биологической активности 1,2,4-триазолпроизводных.

Выводы. Среди указанных производных найдены молекулы, которые проявляют широкую противогрибковую и противомикробную активность, противотуберкулезное, противовирусное, актопротекторное, антигипоксическое, анальгетическое действие и т. д. Проанализировав известные данные, установили ряд закономерностей «строение – действие». Результаты будут полезны для дальнейшей научно-исследовательской работы учёных.

Ключевые слова: 1,2,4-триазол, биологические свойства, активность.

Актуальные вопросы фармацевтической и медицинской науки и практики. 2022. Т. 15, № 1(38). С. 102–106

According to the World Health Organization, people's average life expectancy has increased over the past fifty years. Achievements in the field of Medicine and pharmacy played not the least role in this. A qualitative leap occurred with the rapid development of chemistry, it became possible to install the active components of many drugs and introduce the first purely synthetic drugs. Later on, synthetic chemists began to practice various chemical modifications of already existing active molecules. But despite all the scientific achievements, the problem of finding new highly effective biologically active substances still does not lose its relevance. The reason for this is the low effectiveness or lack of it in well-known drugs used for the prevention and treatment of a few pathological conditions, as well as the presence of side effects.

Aim

The aim of our work was to summarize scientific data in recent years concerning the biological properties of 1,2,4-triazole derivatives. This work will be useful for synthetic chemists who are engaged in the design and development of new compounds consisting of a 1,2,4-triazole core, in order to obtain new and better tools in terms of efficiency and safety.

Scientists have proven that chemical structures containing fragments of 1,2,4-triazole and quinoline have a wide range of chemotherapeutic properties [1], they have demonstrated high antibacterial activity against both drug-sensitive and drug-resistant bacteria. Establishing a structure-activity relationship (SAR) is necessary for further rational development of 1,2,4-triazole-containing synthetic systems against sensitive and Drug-Resistant Pathogens. It has been experimentally proven that a small number of metal ions included in the structure of 1,2,4-triazole increases the activity of molecules [2]. In particular, the Schiff bases having-nucleophilic substituent's OH, –SH, and –NH2 in the ortho-position azomethine group have the corresponding structures to coordinate with metal ions, forming more stable metalal-chelates. The unique properties of chelates, which act as an intermediate bond between conventional organic and inorganic compounds, provide innovative opportunities in the field of pharmaceutical chemistry. Bio-organic compounds play an important role in the development of a new strategy for creating effective drugs, in particular phenylenediamine derived mono- and bis-Schiff bases, 2-{[(4-aminophenyl)imino]methyl}-6-methoxyphenol and 2,2'-{benzene-1,2-diylbis[nitrilomethylylidene]} bis(6-methoxyphenol) [2]. The authors identified a few biological activities in such molecules: antifungal, antibacterial, antioxidant.

Bacterial infections are mainly caused by Gram-positive and Gram-negative microorganisms due to the intensive reproduction of harmful strains. Antibiotics can disrupt the processes necessary for the growth and proliferation of bacterial cells, and they are an effective weapon for fighting bacterial infections. However, excessive and improper use of antibiotics leads to an increase in antibiotic resistance among microorganisms, which creates an urgent need to develop new effective drugs.

Molecules containing the triazole fragment have a broad spectrum of action against a group of clinically important bacteria, including drug-resistant pathogens [3], so the rational design of these derivatives can open the door to the possibility of developing new effective agents against resistant strains. A team of scientists has developed methods for obtaining new complexes based on 4-[(5-amino-1*H*-1,2,4-triazole-3-YL)imino]methylbenzene-1,3-diol and 2-[(5-amino-1*H*-1,2,4-triazole-3-YL)imino]methyl}-6-methoxyphenol with a number of transition metals [4]. The compounds were also thoroughly tested for antibacterial activity against five bacterial strains (*Halomonas halophila, Chromohalobacter israelensis, Escherichia coli, Chromohalobacter salexigens,* and *Halomonas salina*) and bioanalysis of enzyme inhibition. The efficiency of synthesized derivatives is proved [4]. Another team synthesized effective derivatives of a number of 1,2,4-triazole-3-yltioacetamide and 5-pyrazine-2-YL-3h – [1,3,4] oxadiazole antitrypanosomal activity [5]. The compounds showed moderate cytotoxicity with selectivity indexes from 12 to 102 and effective activity (IC_{50} = 6,10 micromoles and IC_{90} 8.66 micromoles) eight times higher than the reference drug, standard water-soluble tetrazolium-8 (WST-8) (IC_{50} 0,79 micromoles and IC_{90} 1.35 micromoles), respectively.

Tuberculosis (TB) is an infectious disease caused primarily by Mycobacterium tuberculosis and is responsible for 4.000

deaths per day in 2019 worldwide [6]. The authors proved the possibility of effective control of this bacterial infection with the help of new derivatives of thiazole, thiotriazole, and semicarbazones [6]. Scientists have also developed a series of new hybrids 1,2,4-triazole-norfloxacin. The compounds showed a higher antibacterial effect than norfloxacin against gram-positive and gram-negative bacteria [7]. In addition, hemolysis was not observed at a concentration of 64 micrograms/ml, which indicates the good biocompatibility of molecules. Molecular docking showed the lowest binding energy from -9.4 to -9.7 kcal/mol. It was also predicted that all compounds exhibit excellent affinity for bacterial topoisomerase IV [7]. Original and interesting research will be offered by scientists developing coumarin-containing heterocyclic compounds [8]. The possibility of combining coumarin and 1,2,4-triazole fragments to solve the problem of creating innovative antibacterial derivatives has been proven by a team of scientists [8]. Other authors have developed a series of 4-amine-3-hydrazino-5-mercapto-1,2,4-triazole Schiff bases – effective antifungal agents [9].

A group of scientists conducted interesting studies on the antiviral activity of 1,2,4-triazole-containing compounds [19]. The activity was studied against viruses, hepatitis C, influenza A, and influenza B, herpes of the first and second types, etc. As a base agent, the already well-known drug Ribavirin was chosen, in the structure of which there is a 1,2,4-triazole fragment. Ribavirin analogs were obtained that have a vinylaryl substituent in the fifth position of the triazole ring (E and Z isomers). After studying this activity, it became known that only E-isomers are highly active, while Z-isomers are inactive. After analyzing the structure-action, it became known that the high activity of E-isomers is associated with a rigid bond between triazole and the aryl ring, as well as due to the presence of a lipophilic substituent in the para-position of the aryl ring [18].

Another group of scientists obtained a few acetamide-substituted analogs of Doravirin, which is a nucleoside reverse transcriptase inhibitor and is used to treat HIV infections [20]. Most of the obtained compounds showed inhibitory properties against HIV, but the compound that had a 1,2,4-triazole substituent in the amide fragment showed a result exceeding the comparison agent Doravirin.

Condensed derivatives of 1,2,4-triazole, namely stable σ-aducts of 1,2,4-triazolo[5,1-c]triazines and 1,2,4-triazolo-[1,5-a] pyrimidines with various polyphenols, were also studied for antiviral activity [21]. The resulting triazoloazines modified with fluoroglycin showed high activity against the influenza A virus, after molecular modeling, it was found that their action is directed against viral hemagglutinin, a protein that ensures the ability of the virus to attach to the host cell.

The search for new promising compounds among 1,2,4-triazole derivatives is carried out not only by foreign scientists but also by domestic ones, in particular, scientists of Zaporizhzhia State Medical University have been obtaining and investigating new molecules based on 1,2,4-triazoles for many years. Over the years, a considerable number of interesting compounds have been obtained, which today have practical value and are used in various industries.

In the modern world, the majority of society lives at a fast pace, constant physical and emotional stress, is influenced by technological progress, as well as global urbanization, all this together leads to stress, anxiety and general fatigue of people. As a result, there is constant fatigue, a sharp decrease in the protective and adaptive mechanisms of the body, immunity, which in turn contributes to the emergence of a number of other negative processes in the body. That is why, recently, the general interest in actoprotective agents has been increasing, because these are drugs that help preserve and increase the body's resistance to physical exertion, increase efficiency.

Native scientists have obtained a number of thiophene derivatives, among which high actoprotective activity was detected, and it was found that the introduction of aromatic pharmacophores with a bromine or fluorine atom into the corresponding 1- R_2-2-((4-R1-5-(thiophene-3-ylmethyl)-1,2,4-triazole-3-yl)thio)ethanones increases actoprotective activity [10]. High results on actoprotective action were demonstrated by some salts of 3-(thiophene-2-ylmethyl)-1*H*-1,2,4-triazole-5-thiol, namely potassium 2-((3-(thiophene-2-ylmethyl)-1*H*-1,2,4-triazole-5-yl)thio)acetate, it is interesting that when replacing the potassium cation with a sodium cation, the actoprotective activity decreases [11].

Among the obtained fluorophenyl-containing 1,2,4-triazoles found compounds that are sensitive to strains of Staphylococcus aureus – 5-(2-fluorophenyl)-4-((5-nitrofuran-2-yl)methylene)amino-4*H*-1, 2,4-triazole-3-thiol and Candida albicans – 5-(2-fluorophenyl)-4-((4-bromophenyl) ylidene)amino-1,2,4-triazole-3-thiol, it should be noted that the highest indicators obtained by replacing aromatic substituents of 1,2,4-triazole with a fragment of nitrofuran [12]. As evidence that most derivatives of 1,2,4-triazoles exhibit antifungal and antimicrobial activity a number of S-alkyl-substituted 4-R-5-(3-(3-(pyridin-4-yl)-1*H*-1,2,4-triazole-5-yl) thio)methyl)-4*H*-1,2,4-triazole-3-thiols were obtained and studied which demonstrated a sufficiently high level of this activity [13]. Compounds 4-(5-((5-(alkylthio)-4-methyl-4*H*-1,2,4-triazole-3-yl)thio)-1*H*-1,2,4-triazole-3-yl)pyridine and 4-(5-((5-(alkylthio)-4-ethyl-4*H*-1,2,4-triazole-3-yl)thio)-1*H*-1,2,4-triazole-3-yl)pyridine had moderate antimicrobial activity against test-strain Staphylococcus aureus. After studying the obtained results, conclusions were made regarding the relationship between the length of the carbon chain of the obtained S-alkyl-substituted thiols and the increase in the corresponding activity.

The obtained results are undoubtedly significant for pharmaceutical science, as fungal infections are widespread and have the ability to develop resistance to drugs that are presented in the pharmaceutical market.

Among all diseases, heart disease ranks first in mortality. It has recently become known that a significant role in myocardial damage is played by the inability of the cardiomyocyte energy system to utilize oxygen. As a result, the formation of free radical, active forms of oxygen increases, which contributes to damage to functionally important proteins, nucleic acids, and other structures of cardiomyocytes, which inevitably leads to the development and progression of ischemic

myocardial damage. In this regard, pharmacological drugs for antiischemic protection of the myocardium – antihypoxants – are currently being actively developed and implemented in clinical practice.

For this purpose, the antihypoxic activity of compounds of a number of S-substituted 1,2,4-bis-1,2,4-triazoles was studied, and a certain pattern was established during the study, namely, the introduction of an acetyl radical into the molecule causes an increase in the antihypoxic effect, and the introduction of a phenocyl group by the sulfur atom led to a decrease in this effect [14]. The highest activity is set for 1-((4-ethyl-5-(((3-(pyridin-4-il)-1*H*-1,2,4-triazol-5-il)tio)methyl)-4*H*-1,2,4-triazol-3-il)tio)propane-2-on.

However, it should not be forgotten that the most common cause of cardiovascular diseases is atherosclerosis. Atherosclerosis is a disease that affects arterial vessels due to the proliferation of connective tissue and the formation of arterial plaques. This pathology leads to heart attacks and strokes.

Until recently, this disease was considered a disease of old age, but every year this disease "gets younger". That is why it is very important to look for new compounds that will show hypolipidemic activity. Among the morpholinium salts of 2-(4-R-5-R_1-4*H*-1,2,4-triazole-3-ylthio)acetic acids, compounds were found that showed quite high results [15]. The formation of atherosclerosis was determined by the level of several indicators: total cholesterol, β-lipoproteins, triglycerides, and cholesterol levels in aortic tissues. According to the results of the research, interesting regularities of structure-action dependence have been established. Thus, in the transition from 2-methylphenyl to 4-bromophenyl and 2-methoxyphenyl radicals at the position of the N4 atom of the nucleus of 1,2,4-triazole in the morpholine molecule 2-(5-(4-pyridyl)-4-R-1,2,4-triazole-3-ylthio)acetate a gradual loss of hypocholesterolemic activity was observed in. When replacing a methyl radical with phenyl and 2-methylphenyl radical at the position of the atom of the 1,2,4-triazole nucleus in the morpholine molecule 2-(5-(4-pyridyl)-4-R-1,2,4-triazole-3-ylthio)acetate showed a gradual loss of hypotriglyceridemic activity. A total of twelve compounds were analyzed, of which morpholine 2-(5-(2-pyridin-1-yl)-4*H*-1,2,4-triazol-3-ylthio)acetate showed the highest activity against all indicators.

The search for substances that have analgesic effects has long been a priority in pharmacology because pain is a key symptom of most diseases. Analgesics are a group of drugs used to relieve pain caused by inflammation or damage to tissues and organs. There are many members of this pharmacological group, both synthetic and herbal, but they all have a few contraindications and side effects. It is known that condensed 1,2,4-triazole derivatives have a high analgesic effect [16]. Given the fact that most 1,2,4-triazole derivatives are low-toxic compounds, the search for derivatives of this series of new analgesics is promising. Native scientists have combined the pyrimidine and triazole cycles to obtain new compounds [17]. As a result, a few 5-methyl-3-aryl-[1,2,4]triazolo[4,3-a]pyrimidin-7-ol derivatives were obtained, the effectiveness of which outperformed that of the reference drug (ketorolac). The hot plate test was used to determine the latent reaction period. The highest activity was determined for a compound containing a methyl group in the fourth position of the aryl substituent, and when halogens are introduced into the aryl moiety, a decrease in this effect is observed.

Conclusions

In the course of our work, scientific works of native and foreign scientists were processed in order to analyze and generalize known data on the biological activity of a number of derivatives of 1,2,4-triazole. The already obtained results indicate the prospects of these derivatives because they demonstrate a fairly wide range of biological activities and low toxicity.

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