Synthesis methods of 1,2,4-triazole-3-thiones: review

Yu. S. Frolova*[1,A,B,D], A. H. Kaplaushenko[1,B,E], T. V. Ihnatova[2,B,F], T. M. Kaplaushenko[3,C,F]

[1]Zaporizhzhia State Medical and Pharmaceutical University, Ukraine, [2]Private Higher Educational Institution "Pylyp Orlyk International Classical University", Mykolaiv, Ukraine, [3]Medical College of Zaporizhzhia State Medical and Pharmaceutical University, Ukraine

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

1,2,4-Triazole-containing compounds are unique heterocyclic compounds present in an array of pharmaceuticals and biologically important compounds used in drug-discovery studies against cancer cells, microbes, and various types of diseases in the human body.

The aim of the study was to analyze in detail and combine the available literature materials to study the reactions associated with the formation of different classes of derivatives of 1,2,4-triazole-3-thione and to study their physical-chemical properties.

Various innovative methods have been proposed and explored for synthesizing different classes of 1,2,4-triazole compounds, each with distinct applications and potential medicinal benefits. When analyzing the outcomes of studies aimed at obtaining new 1,2,4-triazole-3-thiones, it's crucial to recognize the multiple stages involved in their synthesis. These stages typically include the esterification of carboxylic acids, hydrazinolysis, the formation of carbothioamides, and thiones through alkaline cyclization. Subsequently, reactions involving the S-function are conducted, leading to the formation of various classes of derivatives of 1,2,4-triazole.

The study by a team of scientists introduced a novel method for synthesizing imidazolyl- and imidazole-1,2,4-triazoles, targeting the design of safer analgesic and anti-inflammatory agents.

Moreover, researchers have successfully synthesized derivatives of 3-[2-(5-thio-4-aryl-4*H*-1,2,4-triazole-3-yl)ethyl]quinoxalin-2(1*H*)-one, *N*-(3-thio-5-aryl-[1,2,4]triazole-4-yl)acylamides, 5-alkylthio-4-amino-3-(5,7-dimethyl-1,2,4-triazolo[1,5-a]pyrimidine-2-thiomethyl)-1,2,4-triazole and 3-(5,7-dimethyl-1,2,4-triazolo[1,5-a]pyrimidine-2-thiomethyl)-6-aryl-5,6-dihydrogen-1,2,4-triazole-[3,4-b]-1,3,4-thiadiazole, 5,5'-(alkyldiyl-bis(sulfandiyl))bis(*N*-(arylidene)-3-thiophen-2-ylmethyl)-4*H*-1,2,4-triazole-4-amines, 3-(arylsulfonyl)-4-phenyl-5-(3,4,5-trimethoxyphenyl)-4*H*-1,2,4-triazole, expanding the scope of 1,2,4-triazole-based, compounds with potential pharmacological activities. Furthermore, the synthesis of molecules containing two 1,2,4-triazole and two benzole rings has gained traction, offering new avenues for drug development.

Mannich bases were synthesized from the corresponding thiones through a reaction with *N*-methylpiperazine or *N*-phenylpiperazine in dimethylformamide in the presence of formaldehyde.

Additionally, the synthesis of salts derived from 1,2,4-triazole highlights its importance in pharmaceutical formulations, with studies focusing on both organic and inorganic salts for potential therapeutic applications.

Conclusions. The analysis of the above-mentioned publications indicates that the search for new biologically active compounds among derivatives of 1,2,4-triazole-3-thiones is promising. Many 1,2,4-triazole-3-thiones exhibit a wide spectrum of biological activity with little toxicity.

Keywords: 1,2,4-triazole, physical-chemical properties, transformation.

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Методи синтезу 1,2,4-тріазол-3-тіонів: огляд

Ю. С. Фролова, А. Г. Каплаушенко, Т. В. Ігнатова, Т. М. Каплаушенко

Сполуки, що містять 1,2,4-тріазол, є унікальними гетероциклічними сполуками, містяться в низці фармацевтичних препаратів і біологічно важливих сполук. Похідні 1,2,4-тріазолу використовують у лікарських засобах, зокрема вони містяться в препаратах проти ракових клітин, мікробів і різних типів захворювань в організмі людини.

Мета роботи – детально проаналізувати й об'єднати відомості наукової літератури щодо вивчення реакцій, пов'язаних з утворенням різних класів похідних 1,2,4-тріазол-3-тіону, а також вивчити їхні фізико-хімічні властивості.

Запропоновано та досліджено інноваційні методи синтезу різних класів сполук 1,2,4-тріазолу; кожен із них застосовують, і кожен має потенційну медичну користь.Під час аналізу результатів досліджень, спрямованих на отримання нових 1,2,4-тріазол-3-тіонів, важливо розрізняти етапи їх синтезу. Ці стадії зазвичай включають етерифікацію карбонових кислот, гідразиноліз, утворення кар-

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***E-mail:** yuliia_hulina@ukr.net

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ботіоамідів і тіонів шляхом лужної циклізації. Згодом проводять реакції за участю S-функції, що призводять до утворення різних класів похідних 1,2,4-тріазолу.

Розроблено новий метод синтезу імідазоліл- та імідазол-1,2,4-тріазолів, спрямований на розробку безпечніших анальгетиків і протизапальних засобів.

Синтезовано похідні 3-[2-(5-тіо-4-арил-4Н-1,2,4-тріазол-3-іл)етил]хіноксалін-2(1*H*)-ону, *N*-(3-тіо-5-арил-[1,2,4]тріазол-4-іл)ациламіди, 5-алкілтіо-4-аміно-3-(5,7-диметил-1,2,4-тріазоло[1,5-а]піримідин-2-тіометил)-1,2,4-тріазол і 3-(5,7-диметил-1,2,4-тріазоло[1,5-а] піримідин-2-тіометил)-6-арил-5,6-дигідроген-1,2,4-тріазол-[3,4-b]-1,3,4-тіадіазол, 5,5'-(алкілдііл-біс(сульфандііл))біс(*N*-(арилі-ден)-3-тіофен-2-ілметил)-4*H*-1,2,4-тріазол-4-аміни, 3-(арилсульфоніл)-4-феніл-5-(3,4,5-триметоксифеніл)-4*H*-1,2,4-тріазол, що розширює сферу застосування сполук на основі 1,2,4-тріазолу з потенційною фармакологічною активністю. Перспективним для розроблення ліків є синтез молекул, що містять два 1,2,4-тріазолових і два бензольних кільця.

Основи Манніха синтезували з відповідних тіонів реакцією з *N*-метилпіперазином або *N*-фенілпіперазином у диметилформаміді за наявності формальдегіду.

Синтез солей, отриманих із 1,2,4-тріазолу, підкреслює його важливість у фармацевтичних композиціях. Актуальними є дослідження органічних і неорганічних солей для потенційного терапевтичного застосування.

Висновки. Аналіз фахової літератури свідчить про перспективність пошуку нових біологічно активних сполук з-поміж похідних 1,2,4-тріазол-3-тіонів. Чимало 1,2,4-тріазол-3-тіонів характеризуються широким спектром біологічної активності з незначними показниками гострої токсичності.

Ключові слова: 1,2,4-тріазол, фізико-хімічні властивості, перетворення.

Актуальні питання фармацевтичної і медичної науки та практики. 2024. Т. 17, № 2(45). С. 187-196

Compounds containing 1,2,4-triazole are an exceptional class of heterocyclic compounds found in a diverse range of pharmaceuticals and biologically significant substances utilized in studies for discovering drugs targeting cancer cells, microbes, and various diseases in humans.

Prior to integrating a novel bioactive compound into medical or veterinary practices, it is customary that meticulous selection of research subjects is a prerequisite for a favorable outcome in developing original, effective, and low-toxicity medications. It is noteworthy that presently, scientists worldwide are actively involved in simulating the 1,2,4-triazole system, exploring various properties of the heterocycle and the formation of its fundamental "structures", which could pave the way for the discovery of new molecules possessing unique properties akin to 1,2,4-triazole derivatives.

Before embarking on the creation of a new molecule, it is imperative to thoroughly review recent literature and explore the amalgamation of different atomic and molecular fragments within a molecule containing 1,2,4-triazole. This investigation holds significant interest for medical professionals, pharmaceutical experts, and synthetic chemists alike.

A comprehensive examination of recent literature underscores the importance of studying the properties of derivatives of 1,2,4-triazole in contemporary research. Among these derivatives, particular attention is warranted for derivatives of 1,2,4-triazole-3-thione, which serve as focal points in various research endeavors. Notably, there exists a lack of systematic organization of information regarding the research findings concerning derivatives of 1,2,4-triazole-3-thione.

Aim

The purpose of the study was to analyze in detail and combine the available literature materials to study the reactions associated with the formation of different classes of derivatives of 1,2,4-triazole-3-thione and to study their physical-chemical properties.

This research review used systems and content analysis to process the literature over the past ten years.

The synthesis of 1,2,4-triazole holds significant importance in both domestic [1,2,3,4,5,6,7,8,9] and international synthetic chemistry [10,11,12,13,14,15,16] today. When analyzing the outcomes of studies aimed at obtaining new 1,2,4-triazole-3-thiones, it's crucial to recognize the multiple stages involved in their synthesis. These stages typically include the esterification of carboxylic acids, hydrazinolysis, the formation of carbothioamides, and thiones through alkaline cyclization [17]. Subsequently, reactions involving the S-function are conducted, leading to the formation of various classes of derivatives of 1,2,4-triazole.

A team of scientists [18] has proposed an innovative method for the synthesis of imidazolyl-1,2,4-triazoles, with the aim of designing and synthesizing new, safer analgesic and anti-inflammatory agents. The desired structures were synthesized by first obtaining the ethyl ester of 5-methyl-1*H*-imidazole-4-carboxylic acid. Subsequent reaction of hydrazine hydrate with this ether yielded 5-methyl-1*H*-imidazole-4-carboxylic acid hydrazide, which was then converted into 4-R-5-(5-methyl-1*H*-imidazole-4-yl)-4*H*-1,2,4-triazole-3-thione through the addition of potassium thiocyanate or isothiocyanate *(Fig. 1)*.

The authors [18] conducted a study to assess the analgesic and anti-inflammatory activities of the synthesized structures as potential medicinal products. Upon analyzing the compounds, it was found that 4-methyl-5-(5-methyl-1*H*-imidazole-4-yl)-4*H*-1,2,4-triazole-3-thione, 4-phenyl-5-(5-methyl-1*H*-imidazole-4-yl)-4*H*-1,2,4-triazole-3-thione, and 5-(5-methyl-1*H*-imidazole-4-yl)-4-(4-methylphenyl)-4*H*-1,2,4-triazole-3-thione exhibited significant analgesic properties and demonstrated high levels of anti-inflammatory action compared to the control, indomethacin.

Continuing our literature analysis, we came across a publication by Indian scientists [19] outlining the synthesis of novel

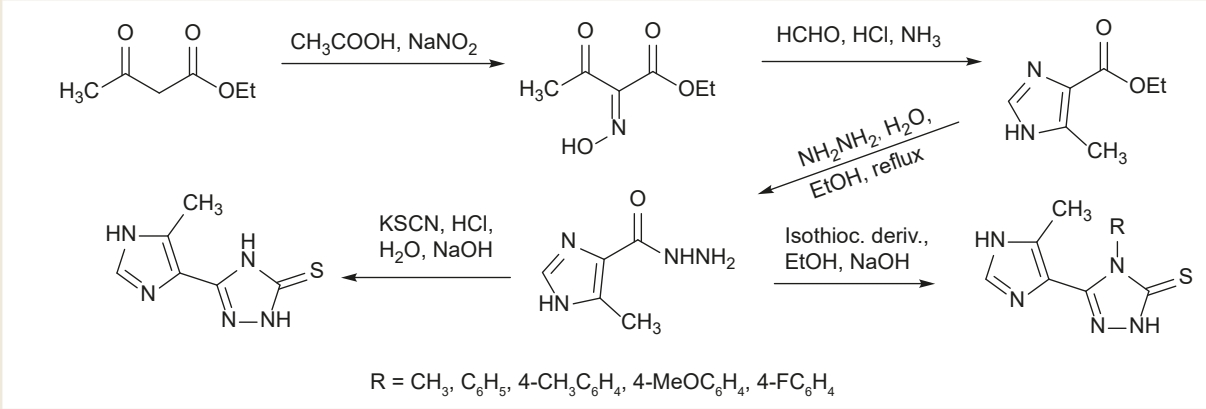

Fig. 1. Scheme of synthesis of 4-R-5-(5-methyl-1*H*-imidazol-4-yl)-4*H*-1,2,4-triazole-3-thione.

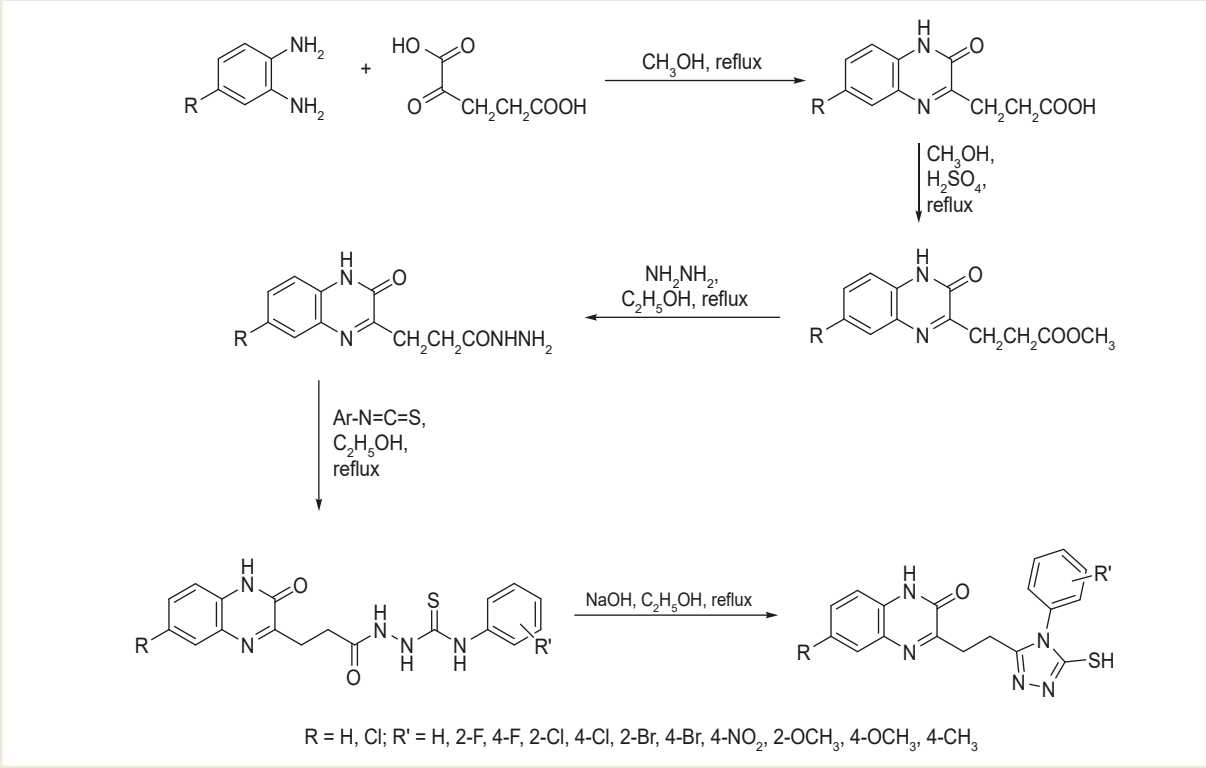

Fig. 2. Stages of synthesis of 3-[2-(5-thio-4-aryl-4*H*-1,2,4-triazole-3-yl)ethyl]quinoxalin-2(1*H*)-one derivatives.

derivatives of 3-[2-(5-thio-4-aryl-4*H*-1,2,4-triazole-3-yl) ethyl]quinoxalin-2(1*H*)-one. The starting materials employed were 4-R-benzene-1,2-diamine and 4-chlorobenzene-1,2-diamine, along with α-ketoglutaric acid. Through successive stages of synthesis, in *Fig. 2*, the researchers successfully obtained 3-[2-(5-thio-4-aryl-4*H*-1,2,4-triazole-3-yl)ethyl] quinoxalin-2(1*H*)-one and 7-chloro-substituted quinoxaline derivatives.

In recent times, the synthesis of molecules containing two 1,2,4-triazole rings has gained widespread use [20]. An original synthesis method involves the creation of a molecule consisting of 4-R_1-2-[(4-R2-piperazin-1-yl)methyl]-5-{[3-(4-chlorophenyl)-5-(4-methoxy-benzyl)-4*H*-1,2,4-triazole-4-yl]methyl}-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones, incorporating two 1,2,4-triazole heterocycles [21]. The synthesis reactions of the target compounds are illustrated in *Fig. 3*. Specifically, the reaction of 2-[3-(4-chlorophenyl)-5-(4-methoxybenzyl)-4*H*-1,2,4-triazole-4-yl]acetohydrazide with various isothiocyanates resulted in the formation of 2-{[3-(4-chlorophenyl)-5-(4-methoxybenzyl)-4*H*-1,2,4-triazole-4-yl]acetyl}-4-alkyl/aryl-thiosemicarbazides. Subsequent alkaline cyclization of these compounds with NaOH yielded the corresponding 5-{[3-(4-chlorophenyl)-5-(4-methoxybenzyl)-4*H*-1,2,4-triazole-4-yl]methyl}-4-alkyl/aryl-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones.

The intramolecular cyclization of 2-[3-(4-chlorophenyl)-5-(4-methoxybenzyl)-4*H*-1,2,4-triazole-4-yl]acetohydrazide with carbon disulfide in the presence of potassium

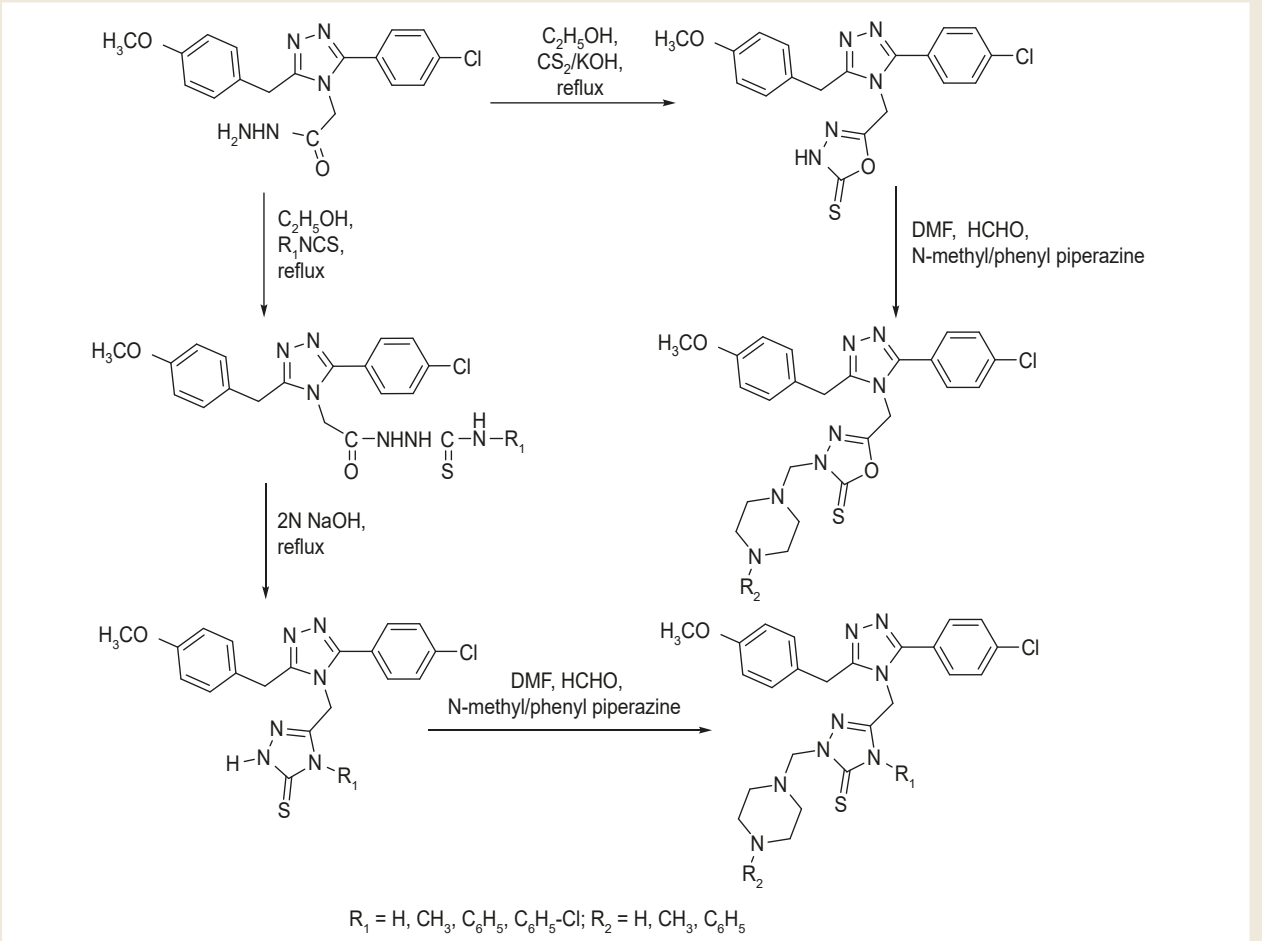

Fig. 3. Scheme of obtaining of 4-R_1-2-[(4-R2-piperazin-1-yl)methyl]-5-{[3-(4-chlorophenyl)-5-(4-methoxybenzyl)-4*H*-1,2,4-triazole-4-yl]methyl}-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones.

hydrazide in an alcoholic medium yielded 5-{[3-(4-chlorophenyl)-5-(4-methoxybenzyl)-4*H*-1,2,4-triazole-4-yl]methyl}-1,3,4-oxydiazole-2(3*H*)-thione.

Mannich bases were synthesized from the corresponding thiones through a reaction with *N*-methylpiperazine or *N*-phenylpiperazine in dimethylformamide in the presence of formaldehyde *(Fig. 3)*.

Continuing our analysis of substances containing the 1,2,4-triazole core and exhibiting pharmacological activity, it's noteworthy to highlight the synthesis of 2-((5-(4-(1*H*-benzimidazol-2-yl)phenyl)-4-methyl-4*H*-1,2,4-triazole-3-yl)thio)-1-R-1-ones, which demonstrate antifungal effects [22]. The synthesis of these target compounds was carried out as depicted in *Fig. 4*.

In the initial stage, methyl-4-(5(6)-R-1*H*-benzimidazol-2-yl)benzoates were synthesized through the reaction of methyl-4-formylbenzoate with the respective o-phenylenediamine in the presence of $Na_2S_2O_5$. Subsequently, the synthesized compounds underwent treatment with excess hydrazine hydrate to yield hydrazides of 4-(5(6)-R-1*H*-benzimidazol-2-yl)benzoic acid. In the third stage, these hydrazides of benzoic acid were reacted with alkyl isothiocyanates. Following this, cyclization in an alkaline medium facilitated the formation of the corresponding 1,2,4-triazole-3-thiones. Finally, a substitution reaction occurred between 2-bromoacetophenones and the synthesized thiones, resulting in the desired target compounds *(Fig. 4)* [22].

A team of scientists from Switzerland [23] introduced an innovative synthesis method for 4-(1*H*-1,2,4-triazole-5-ylthio)-1,2-dihydropyrazole-3-one. This compound was synthesized through the hydrazinolysis of 5-ethoxymethylenethiazolo[3,2-b][1,2,4]triazole-6-one in an ethanol environment. The modification of 1*H*-1,2,4-triazole-3-thione involved a two-step reaction: S-alkylation with chloroethanoic acid following the conditions of the Williamson reaction, succeeded by a one-step cyclization through condensation with triethylorthoformate in the medium of ethanoic anhydride *(Fig. 5)*. The structural elucidation of the compounds was confirmed through LC-MS, NMR spectra, and independently validated via X-ray structural analysis.

Another intriguing synthesis is the production of 6-R-3-(1,4-benzodioxan-2-yl)thiazolo[2,3-c][1,2,4]triazole-5(6*H*)-ones, known for their antimicrobial properties. Initially, 2-[5-(1,4-benzodioxan-2-yl)-4*H*-1,2,4-triazole-3-ylthio]ethanoic acid was synthesized through the reaction of

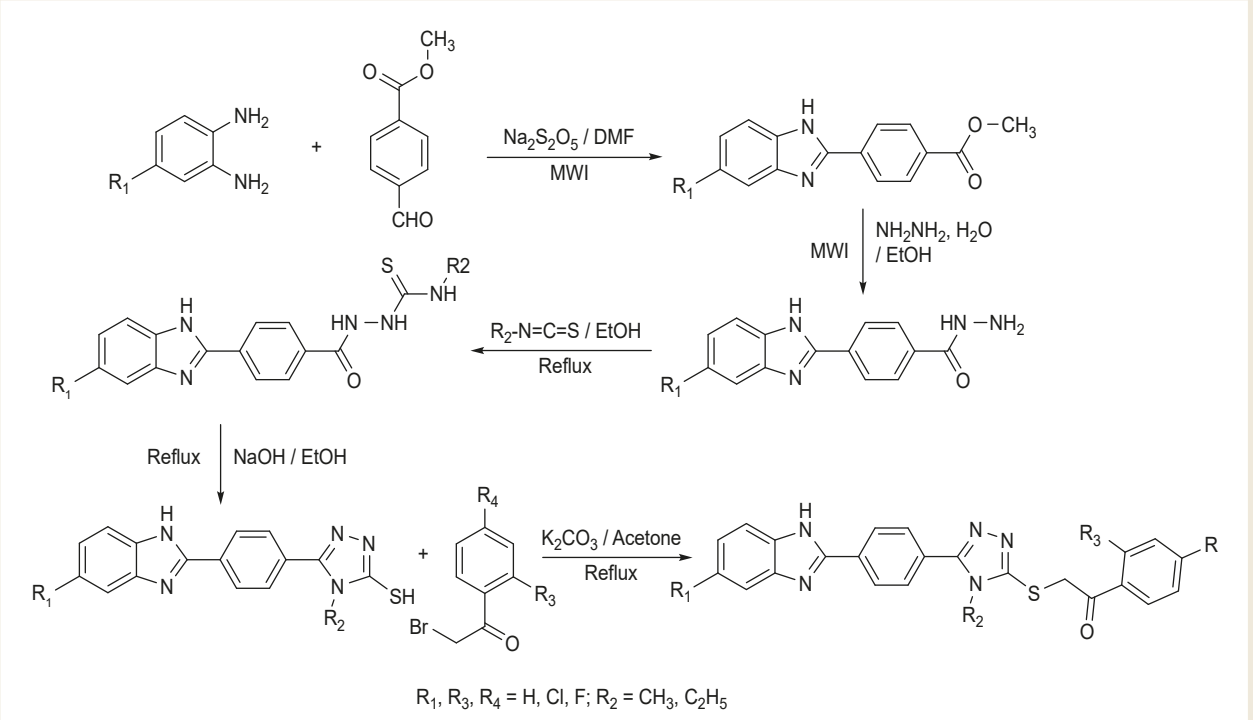

Fig. 4. Synthesis of target compounds of 2-((5-(4-(1*H*-benzimidazol-2-yl)phenyl)-4-methyl-4*H*-1,2,4-triazole-3-yl)thio)-1-R-1-ones.

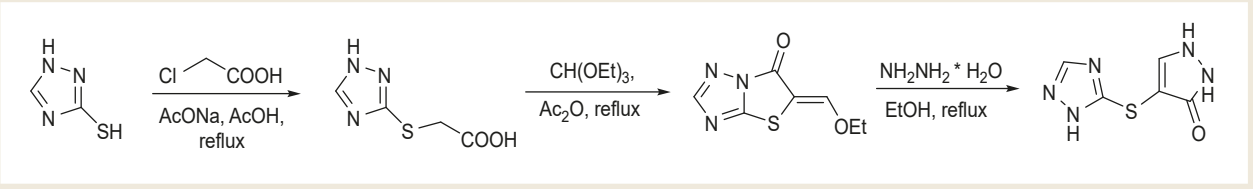

Fig. 5. Synthesis scheme of 5-ethoxymethylenediazolo[3,2-b][1,2,4]triazole-6-one and 4-(1*H*-[1,2,4]triazole-5-ylthio)-1,2-dihydropyrazole-3-one.

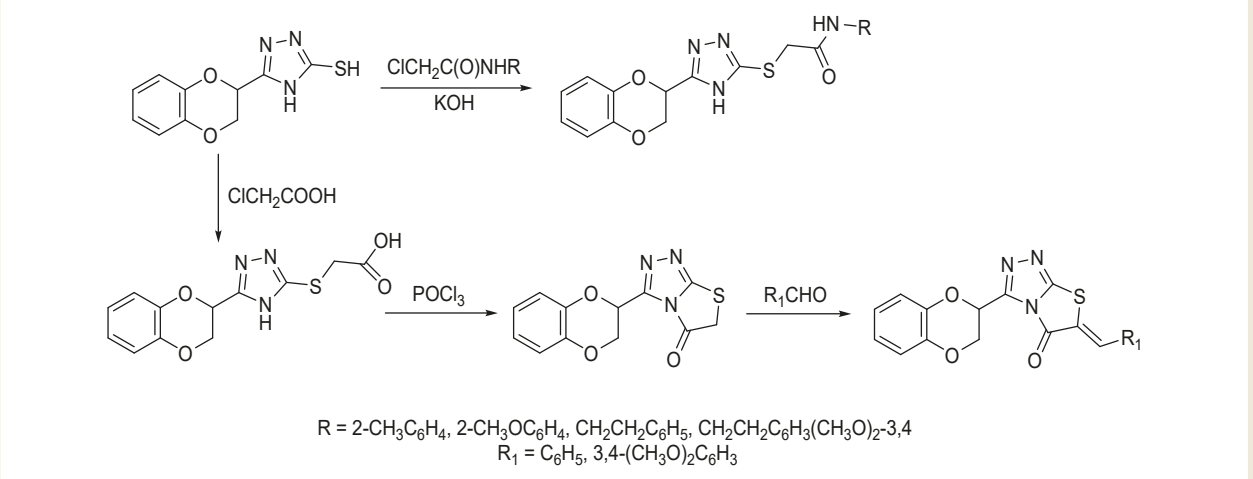

Fig. 6. Synthesis of 6-R-3-(1,4-benzodioxan-2-yl)thiazolo[2,3-c][1,2,4]triazole-5(6*H*)-ones.

5-(1,4-benzodioxan-2-yl)-4*H*-1,2,4-triazole-3-thione with chloroethanoic acid *(Fig. 6)*. Subsequently, the synthesized compound underwent cyclization under the influence of phosphorus oxychloride, yielding 3-(1,4-benzodioxan-2-yl) thiazolo[2,3-c][1,2,4]triazole-5(6*H*)-one.

Due to an active methylene fragment, 3-(1,4-benzodioxan-2-yl)thiazolo[2,3-c][1,2,4]triazole-5(6*H*)-one underwent reaction with aromatic aldehydes, leading to the formation of new thiazolotriazolones. The synthetic potential of 5-(1,4-benzodioxan-2-yl)-4*H*-1,2,4-triazole-3-thione can

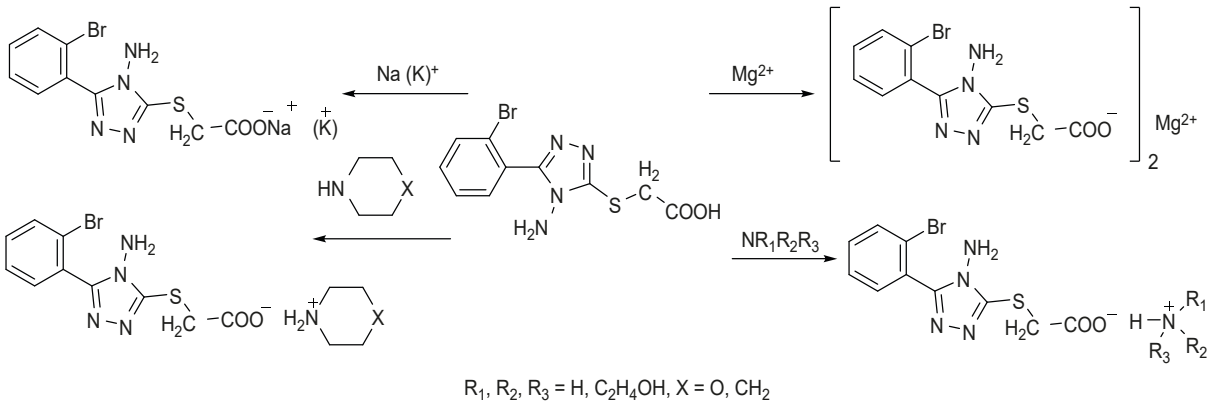

Fig. 7. Synthesis scheme of salts of 2-(5-(2-bromophenyl)-4-amino-4*H*-1,2,4-triazole-3-ylthio)ethanoic acid.

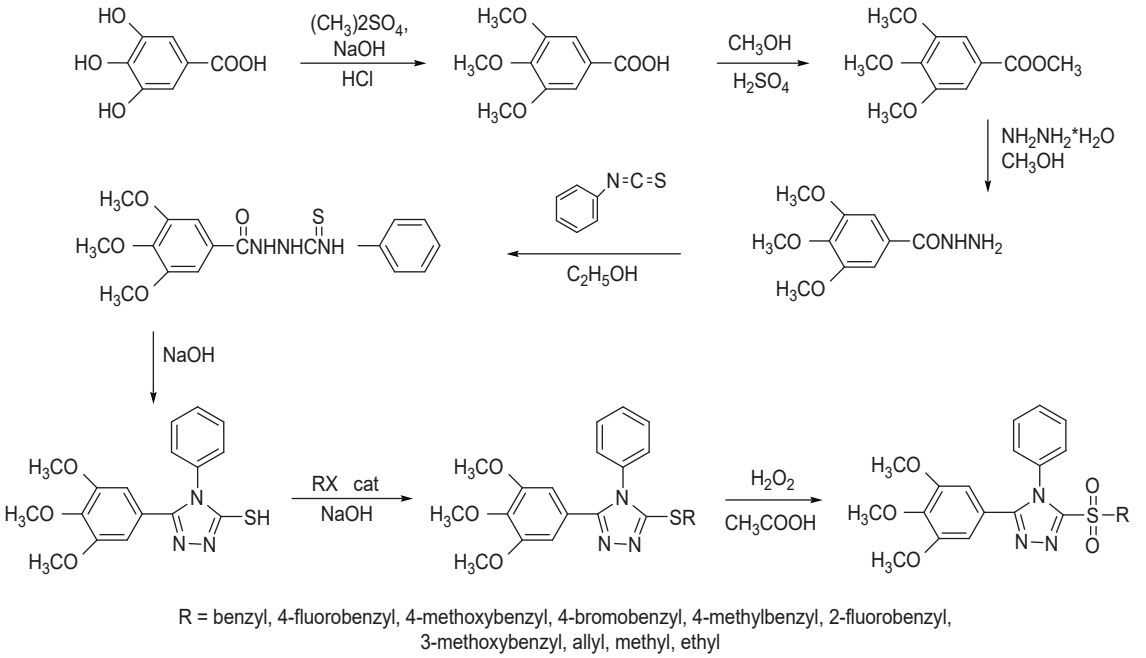

Fig. 8. Synthesis scheme of 3-(arylsulfonyl)-4-phenyl-5-(3,4,5-trimethoxyphenyl)-4*H*-1,2,4-triazole.

be further expanded through reaction with amides of chloroethanoic acid, as suggested by the authors, which undergo electrophilic substitution at the sulfur atom.

Having conducted an analysis of the pharmaceutical market, it can be inferred that approximately 50 % of all molecules constituting the foundation of pharmaceutical preparations used in drug therapy are introduced in the form of salts. This observation underscores the significance of developing new salts based on 1,2,4-triazole, making it an integral aspect of the pharmaceutical industry. Consequently, the synthesis of both organic and inorganic salts derived from the aforementioned heterocycle remains relevant [24,25,26,27,28,29].

One notable study involves the synthesis and investigation of physical-chemical and biologically active salts derived from 2-(5-(2-bromophenyl)-4-amino-4*H*-1,2,4-triazole-3-ylthio)ethanoic acid [30]. In this research, 2-(5-(2-bromophenyl)-4-amino-4*H*-1,2,4-triazole-3-thio)ethanoic acid was selected as the starting material to synthesize salts with both organic and inorganic bases *(Fig. 7)*.

The structural characterization of the compounds was confirmed through elemental analysis, ^{1}H NMR spectroscopy, and individuality was established via chromato-mass-spectral studies. Interestingly, the highest yields of salt products were observed when water was utilized as a solvent.

Another group of Chinese scientists [31] delved into the synthesis methods of 3-R-4-phenyl-5-(3,4,5-trimethoxyphenyl)-4*H*-1,2,4-triazoles. They utilized 4-phenyl-5-(3,4,5-trimethoxyphenyl)-4*H*-1,2,4-triazole-3-thione as the starting material for synthesizing the aforementioned compounds. The synthesized compound underwent conversion into

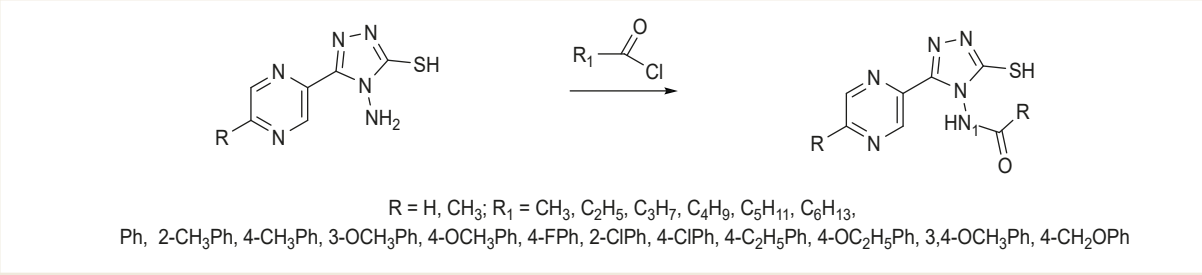

Fig. 9. Synthesis scheme of *N*-(3-thio-5-aryl-[1,2,4]triazole-4-yl)amides.

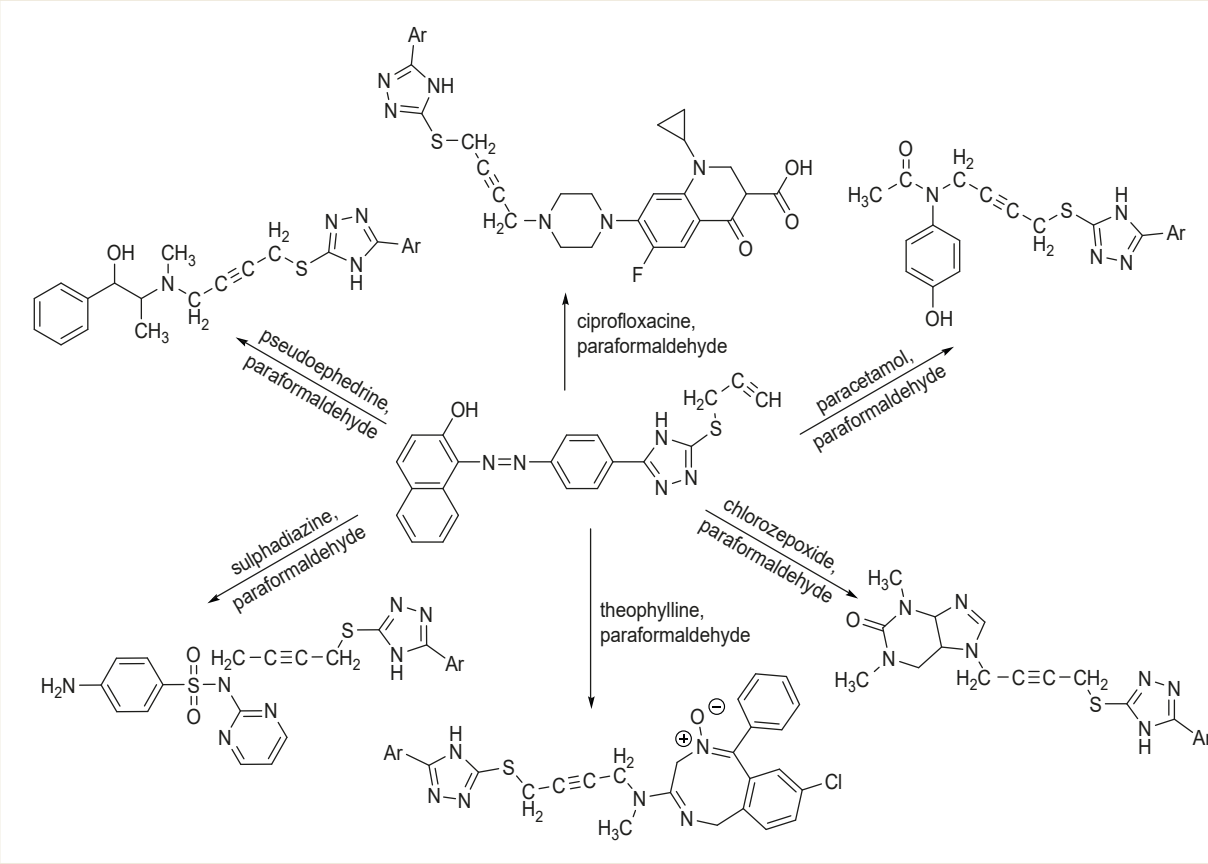

Fig. 10. Synthesis scheme of derivatives of 1-((4-(5-(prop-2-yn-1-ylthio)-4*H*-1,2,4-triazole-3-yl)phenyl)diazenyl)naphthalen-2-ol.

thioether through thioesterification reaction with halogenides (RX). In the final stage, a mixture of ethanoic acid and 30 % H_2O_2 solution was added to 3-(R-methylthio)-4-phenyl-5-(3,4,5-trimethoxyphenyl)-4*H*-1,2,4-triazole, resulting in the formation of 3-(arylsulfonyl)-4-phenyl-5-(3,4,5-trimethoxyphenyl)-4*H*-1,2,4-triazole *(Fig. 8)*.

The structures of all compounds were confirmed through IR spectrometry, ^{1}H NMR spectroscopy, and elemental analysis. Additionally, 3-(3-methoxybenzylsulfonyl)-4-phenyl-5-(3,4,5-trimethoxyphenyl)-4*H*-1,2,4-triazole underwent detailed investigation through X-ray crystallography [31].

A similar synthesis of (3-(alkylsulfonyl)-4-R-1,2,4-triazole-5-yl)(phenyl)methanol was conducted by scientists at Zaporizhzhia State Medical and Pharmaceutical University [32].

To broaden the scope of the search for pharmacologically active substances, Indian scientists [33] synthesized *N*-(3-thio-5-aryl-[1,2,4]triazole-4-yl)acylamides. According to the authors, the reaction was conducted in dry 1,4-dioxane, with the gradual addition of carboxylic acid chloride to 4-amino-5-aryl-4*H*-[1,2,4]triazole-3-thione under stirring, followed by heating the reaction mixture for 10 hours. The progress of the reaction was monitored using thin-layer chromatography *(Fig. 9)*.

Muhannad Musa Kareem introduced an original method for the Mannich reaction, as detailed in their publication [34], demonstrating the synthesis of new derivatives of 1,2,4-triazole. Mannich bases were obtained through the interaction of 1-((4-(5-(prop-2-yn-1-ylthio)-4*H*-1,2,4-triazole-3-yl)phenyl)diazenyl)naphthalen-2-ol with paraformaldehyde and second-

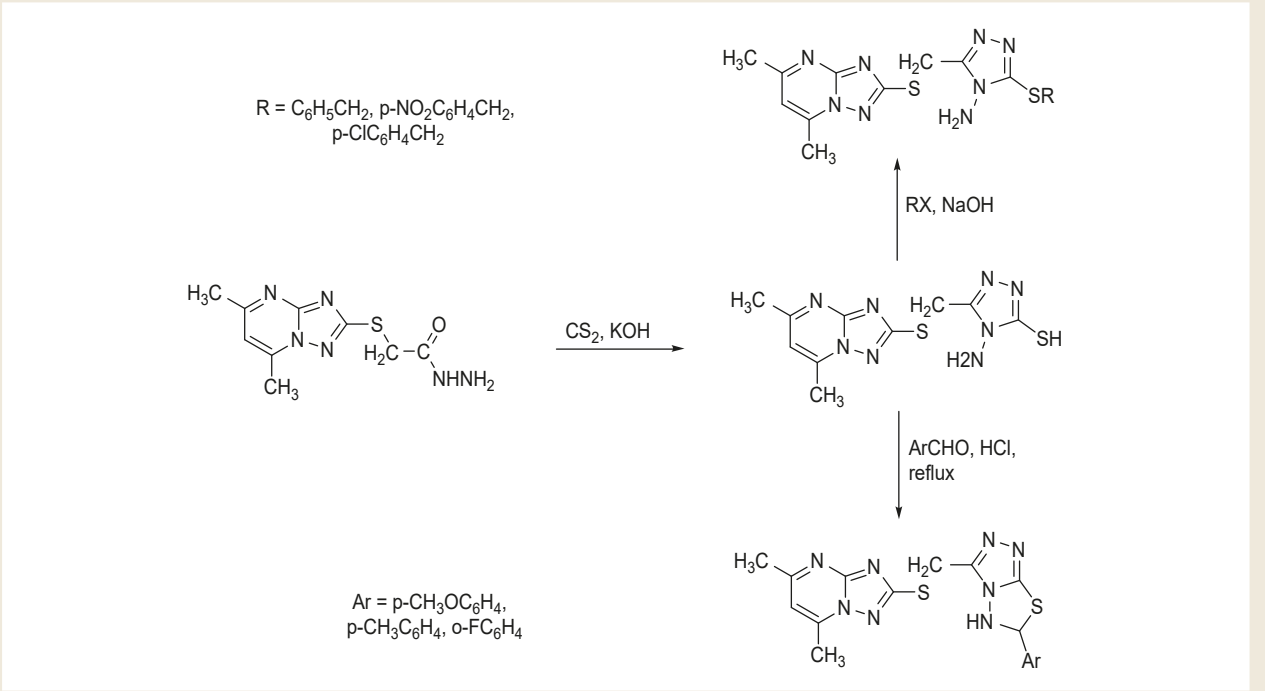

Fig. 11. Synthesis scheme of 5-alkylthio-4-amino-3-(5,7-dimethyl-1,2,4-triazolo[1,5-a]pyrimidine-2-thiomethyl)-1,2,4-triazole and 3-(5,7-dimethyl-1,2,4-triazolo[1,5-a]pyrimidine-2-thiomethyl)-6-aryl-5,6-dihydrogen-1,2,4-triazole-[3,4-b]-1,3,4-thiadiazole.

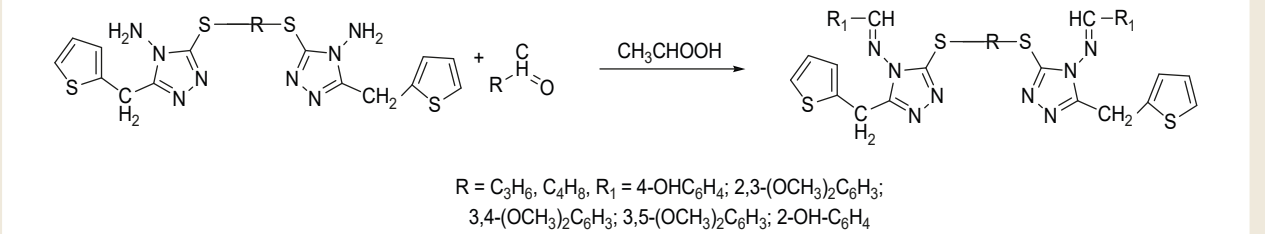

Fig. 12. Synthesis scheme of 5,5'-(alkyldiyl-*bis*(sulfandiyl))*bis*(*N*-(arylidene)-3-thiophen-2-ylmethyl)-4*H*-1,2,4-triazole-4-amines.

ary amines of ciprofloxacin, paracetamol, pseudoephedrine, theophylline, chlorodisepoxide, and sulfadiazine *(Fig. 10)*.

The synthesized substances underwent characterization using UV- and IR-spectroscopy, as well as ^{1}H NMR and ^{13}C NMR spectroscopy, to confirm their structural properties.

Chinese scientists [35] synthesized two compounds: 5-alkylthio-4-amino-3-(5,7-dimethyl-1,2,4-triazolo[1,5-a] pyrimidine-2-thiomethyl)-1,2,4-triazole and 3-(5,7-dimethyl-1,2,4-triazolo[1,5-a]pyrimidine-2-thiomethyl)-6-aryl-5,6-dihydrogen-1,2,4-triazole-[3,4-b]-1,3,4-thiadiazole, as shown in *Fig. 11*.

In the initial stage, 4-amino-3-(5,7-dimethyl-1,2,4-triazolo[1,5-a]pyrimidine-2-thiomethyl)-1,2,4-triazole-5-thiol was obtained by the interaction of potassium hydroxide and 2-thioacetohydrazide-5,7-dimethyl-1,2,4-triazolo[1,5-a] pyrimidine in ethanol. Then, carbon disulfide was added dropwise to the synthesized mixture for half an hour at room temperature, resulting in the formation of 4-amino-3-(5,7-dimethyl-1,2,4-triazolo[1,5-a]pyrimidine-2-thiomethyl)-1,2,4-triazole-5-thiol.

5-Alkylthio-4-amino-3-(5,7-dimethyl-1,2,4-triazolo[1,5-a] pyrimidine-2-thiomethyl)-1,2,4-triazole was obtained by reacting 4-amino-3-(5,7-dimethyl-1,2,4-triazolo[1,5-a] pyrimidine-2-thiomethyl)-1,2,4-triazole-5-thiol with benzylhalogen derivatives in methanol and hydroxide in water. On the other hand, 3-(5,7-dimethyl-1,2,4-triazolo[1,5-a] pyrimidine-2-thiomethyl)-6-aryl-5,6-dihydrogen-1,2,4-triazolo-[3,4-b]-1,3,4-thiadiazole was obtained by reacting the corresponding aromatic aldehyde with ethanol *(Fig. 11)*. The target products were synthesized in high yields.

Continuing the discussion on methods for synthesizing 3-thio-1,2,4-triazole derivatives, let's delve into the synthesis of 5,5'-(alkyldiyl-*bis*(sulfandiyl))*bis*(*N*-(arylidene)-3-thiophen-2-ylmethyl)-4*H*-1,2,4-triazole-4-amines. In this process, 5,5'-(alkyldiyl-*bis*(sulfandiyl))*bis*-3-(thiophen-2-ylmethyl)-4*H*-1,2,4-triazole-4-amine served as the starting material. Subsequently, the authors heated the mixture in ethanoic acid, with the addition of aromatic aldehyde variants such as 2-hydroxybenzaldehyde, 4-hydroxybenzaldehyde, 2,3-dimethoxybenzaldehyde, 3,4-dimethoxybenzaldehyde,

and 3,5-dimethoxybenzaldehyde, to synthesize 5,5'-(alkyldiyl-*bis*(sulfandiyl))*bis*(*N*-(arylidene)-3-thiophen-2-ylmethyl)-4*H*-1,2,4-triazole-4-amines (*Fig. 12*) [36].

Conclusions

1. The analysis of the aforementioned publications highlights the promising search for new biologically active compounds among derivatives of 1,2,4-triazole-3-thiones.

2. The chemistry of 1,2,4-triazole and its heterocyclic derivatives has garnered significant attention in recent years owing to their synthetic and biological relevance.

3. Many 1,2,4-triazole-3-thiones demonstrate a wide spectrum of biological activity with minimal toxicity. In a subsequent review, we will delve into a more detailed exploration of the various biological properties exhibited by these compounds.

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Information about the authors:
Frolova Yu. S., PhD, Assistant of the Department of Physical and Colloidal Chemistry, Zaporizhzhia State Medical and Pharmaceutical University, Ukraine.
ORCID ID: 0000-0002-3995-5088
Kaplaushenko A. H., PhD, DSc, Professor of the Department of Physical and Colloidal Chemistry, Zaporizhzhia State Medical and Pharmaceutical University, Ukraine.
ORCID ID: 0000-0003-3704-5539
Ihnatova T. V., PhD, Associate Professor, Dean of the Faculty of Health Care, Private Higher Educational Institution "Pylyp Orlyk International Classical University", Mykolaiv, Ukraine.
ORCID ID: 0000-0002-7229-6715
Kaplaushenko T. M., PhD, Lecturer, Medical College of Zaporizhzhia State Medical and Pharmaceutical University, Ukraine.
ORCID ID: 0000-0001-5092-3370

Відомості про авторів:
Фролова Ю. С., PhD, асистентка каф. фізколоїдної хімії, Запорізький державний медико-фармацевтичний університет, Україна.
Каплаушенко А. Г., д-р фарм. наук, професор, зав. каф. фізколоїдної хімії, Запорізький державний медико-фармацевтичний університет, Україна.
Ігнатова Т. В., PhD, доцент, декан факультету охорони здоров'я, Приватний заклад вищої освіти «Міжнародний класичний університет імені Пилипа Орлика», м. Миколаїв, Україна.
Каплаушенко Т. М., канд. мед. наук, викладач, Медичний фаховий коледж, Запорізький державний медико-фармацевтичний університет, Україна.

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