UDC 547.792.02-048.77:615.31.015.4
DOI: 10.15587/2519-4852.2026.356807

STRUCTURAL MODIFICATION OF THE 1,2,4-TRIAZOLE CORE AS A STRATEGY FOR THE DESIGN OF BIOLOGICALLY ACTIVE COMPOUNDS (LITERATURE REVIEW)

Dmytro Dovbnia, Andrii Kaplaushenko, Oleksandr Panasenko, Mariia Panasenko, Volodymyr Salionov, Tetiana Ihnatova, Kaloyan Georgiev, Iliya Slavov

The aim. *The aim of this review article is to systematize and summarize current literature data on methods of chemical modification of 1,2,4-triazole derivatives, as well as to analyze the impact of structural transformations on their biological activity and pharmacological potential.*

Materials and methods. *The analysis was based on scientific publications by domestic and international authors devoted to the synthesis, functionalization, and biological evaluation of 1,2,4-triazole derivatives. Data generalization was carried out using methods of systematic analysis, comparative assessment of synthetic approaches, and analysis of the results of in silico, in vitro, and in vivo studies (molecular docking, ADME analysis, SAR evaluation).*

Results. *It has been shown that 1,2,4-triazole derivatives are characterized by high chemical lability and the ability to undergo modification at the sulfur atom, amino group, and nitrogen atoms of the heterocyclic core. Alkylation and acylation reactions, salt formation, hybridization with other pharmacophoric fragments, as well as the application of microwave-assisted synthesis enable the development of compounds with a wide spectrum of biological activity. Among the studied derivatives, compounds exhibiting antioxidant, antimicrobial, antitumor, anti-inflammatory, neuroprotective, and hypoglycemic activities have been identified. A correlation between the chemical structure of the compounds, the nature of substituents, and their pharmacological properties has been established.*

Conclusions. *1,2,4-Triazole derivatives represent a promising pharmacophoric platform for the development of new biologically active compounds. Further targeted investigation of their chemical modification pathways and structure-activity relationships offer broad opportunities for the design of potential therapeutic agents*

Keywords: *1,2,4-triazole, chemical modification, biological activity, synthesis, pharmacophore, alkylation, hybrid compounds, molecular docking, ADME analysis, SAR*

How to cite:
Dovbnia, D., Kaplaushenko, A., Panasenko, O., Panasenko, M., Salionov, V., Ihnatova, T., Georgiev, K., Slavov, I. (2026). Structural modification of the 1,2,4-triazole core as a strategy for the design of biologically active compounds (Literature Review). ScienceRise: Pharmaceutical Science, 2 (60), 14–44. http://doi.org/10.15587/2519-4852.2026.356807

1. Introduction

Heterocyclic compounds based on the 1,2,4-triazole nucleus occupy a leading position in modern pharmaceutical chemistry due to the combination of high biological activity, chemical stability and the ability to undergo targeted structural modification [1–3]. 1,2,4-triazole derivatives are part of or are the structural basis of several drugs used as antifungal [4], antibacterial [5, 6], antiviral [7], antitumor [8, 9], antioxidant [10–13], anti-inflammatory [14, 15] and neurotropic [16, 17] agents. In the pharmaceutical systems of various countries of the world, particularly the USA, the European Union and Asia, 1,2,4-triazole fragments are widely used as pharmacophore platforms in the creation of new active pharmaceutical ingredients [18–20].

Over the past decade, the number of papers devoted to the synthesis and biological study of 1,2,4-triazole derivatives has significantly increased in international scientific periodicals [21–23]. The authors demonstrated the possibility of functionalizing the specified heterocycle at various reaction centers, in particular at the nitrogen atoms of the ring, the thiol fragment, amino groups and by condensation with other pharmacophore systems [24, 25]. At the same time, most of the published studies are focused either on individual types of reactions or on the study of a narrow spectrum of biological activity without a comprehensive analysis of the impact of structural changes on the pharmacological profile of the compounds.

A critical analysis of the modern literature shows that the predecessors have achieved significant success in developing synthetic approaches to obtain new 1,2,4-triazole derivatives and identifying promising biological effects. However, many works lack a systematic approach to summarizing data on the relationship "structure-biological activity", and the results of in silico, *in vitro* and *in vivo* studies are often considered fragmentary. In addition, the issues of combined chemical modification of various functional groups of the 1,2,4-triazole nucleus and its importance for optimizing pharmacological properties remain insufficiently generalized.

Thus, it is relevant to conduct a comprehensive review of modern scientific data aimed at systematizing

approaches to the chemical modification of 1,2,4-triazole derivatives and critically analyzing their biological activity. Such an approach allows us to identify unresolved aspects of the problem under study and outline promising directions for further research in the field of pharmaceutical chemistry.

The aim of the research. Generalization and critical analysis of modern literature data on methods of chemical modification of 1,2,4-triazole derivatives, as well as establishment of patterns of influence of structural transformations on their biological activity and pharmacological potential.

2. Research planning (methodology)

The planning of the review study was carried out taking into account the principles of the Quality by Design (QbD) concept and elements of risk analysis in order to ensure the completeness, reproducibility and scientific validity of the conclusions obtained. The key quality factors (Critical Quality Attributes) were the relevance of the sources, the representativeness of the sample of publications and the presence of experimental confirmation of the biological activity of the studied compounds.

The research methodology provided for a consistent selection of scientific publications according to clearly defined criteria: year of publication (no more than 10 years), affiliation to peer-reviewed international periodicals, the presence of a description of the synthesis methods and the results of biological studies. Attention was paid to works that used a comprehensive approach to assessing the activity of 1,2,4-triazole derivatives, including in silico prediction, experimental pharmacological models and analysis of toxicological indicators.

To minimize the risk of bias, a comparative analysis of data from different author groups was carried out, as well as an assessment of the reproducibility of the results. The material was structured according to types of chemical modification and directions of biological activity, which allowed us to logically substantiate the revealed patterns and form generalized conclusions.

3. Materials and methods

The materials for the review study were scientific articles published in international and national peer-reviewed journals in pharmaceutical and medicinal chemistry, available in open access electronic databases. The analysis included publications devoted to the synthesis, structural modification and biological study of 1,2,4-triazole derivatives.

The research methods included a systematic and comparative analysis of literature sources, a critical assessment of experimental data, as well as a generalization of the results of pharmacological, toxicological and in silico studies. When analyzing synthetic approaches, the reaction conditions, product yields, and the methods used for identification and confirmation of the structure (^{1}H- and ^{13}C-NMR spectroscopy, IR spectroscopy, mass spectrometry, X-ray structural analysis) were considered.

The assessment of biological activity was carried out based on published results of in vitro and in vivo studies performed in accordance with international ethical standards, the ARRIVE recommendations and the EU Directive 2010/63/EU. In silico analysis data (molecular docking, ADME and SAR assessment) were considered as an auxiliary tool for explaining the mechanisms of biological action and predicting pharmacokinetic properties.

The statistical processing of the results given in the sources was analyzed considering the methods and reliability criteria used by the authors. All terms, chemical nomenclature and symbols are given in accordance with generally accepted international standards [26–29].

4. Research results

The sulfur atom attached to the 1,2,4-triazole structure is a reactive center that plays a key role in directed chemical modification and the formation of new biologically active compounds [30–32]. Reactions occurring at the –SH group allow for the preparation of a wide range of derivatives, from simple S-alkyl- and S-acyl-substituted 1,2,4-triazoles to complex hybrid systems that include other pharmacophore moieties, such as thiadiazole, theophylline, piperidine, or acetamide [33, 34]. It is this structural variability that provides the possibility of fine-tuning the physicochemical and biological properties of the resulting substances.

The development of thiol moiety modification methods encompasses a variety of approaches, from classical alkylation and acylation to microwave synthesis, metal chelation, and the formation of hybrid conjugates with natural or synthetic bioactive nuclei [35–37]. The use of these strategies allows for the preparation of compounds with pronounced antioxidant, antimicrobial, anti-inflammatory, hypoglycemic, neuroprotective, and antitumor activity [38–40]. Many of them demonstrate high affinity for biological targets (COX-2 enzymes, α-glucosidase, tyrosine kinase, STAT3, EGFR, etc.) and favourable pharmacokinetic parameters, which confirms the promising potential of thiol derivatives of 1,2,4-triazole as starting compounds for the search for new drugs [41, 42].

Domestic scientists synthesized several alkyl derivatives of 5-(5-methyl-1H-pyrazol-3-yl)-4-phenyl-4H-1,2,4-triazole-3-thiol (Fig. 1), for which their antiradical activity was investigated by the *in vitro* method using the DPPH test [43]. The synthesis was carried out based on the cyclization of carboxylic acid hydrazides with subsequent alkylation of thiol groups (Fig. 1). Biological activity was assessed using the DPPH test, which showed that most of the obtained substances have moderate antioxidant activity. The highest results were demonstrated by compounds 8.7 and 8.5, which provided 84.10% and 78.12% neutralization of DPPH radicals, respectively, while standard ascorbic acid showed an activity of 92.42%. The authors attribute the decrease in activity in other alkyl derivatives to the alkylation of the thiol fragment, which reduces the reactivity of the –SH group, which is key to antiradical action.

Fedotov and co-authors [44] synthesized a series of S-alkyl 4-(4-chlorophenyl)-5-(pyrrol-2-yl)-1,2,4-triazole-3-thiol derivatives (Fig. 2). The synthesis of intermediates was carried out by standard methods, and con-

densation, alkylation, and cyclization reactions were implemented to obtain key scaffolds (Fig. 2). The construction of the heterocyclic fragment of 1,2,4-triazole was carried out by the interaction of hydrazides with isothiocyanates and subsequent cyclization, and further functionalization of the obtained derivatives was carried out using alkylation and acylation reactions, which allowed obtaining a series of new compounds (Fig. 2). The docking results showed that all synthesized compounds have a low probability of pronounced anti-inflammatory activity, since the minimum binding energy with the COX-2 enzyme was in the range of –0.4 to –8.5 kcal/mol, while for the standard drug celecoxib this figure was –13.4 kcal/mol. At the same time, when interacting with lanosterol-14α-demethylase (a target for antifungal agents), most compounds demonstrated a significantly better affinity, approaching that of the reference drug fluconazole. The complexation energy varied from –6.7 to –8.7 kcal/mol, while for fluconazole it was –10.9 kcal/mol. The most active was compound 15.7, which formed the largest number of contacts in the zone of the active center of the enzyme. ADME analysis showed that most of the substances (15.1–15.7) meet the criteria of Lipinski, Weber, Egen, Gose and Mügge, have high bioavailability (0.55) and good absorption from the gastrointestinal tract, which indicates their potential pharmacological suitability. The best set of pharmacokinetic parameters was noted in compounds 15.4 and 15.5, which are characterized by optimal lipophilicity and molecular weight and meet all the requirements of "drug-likeness".

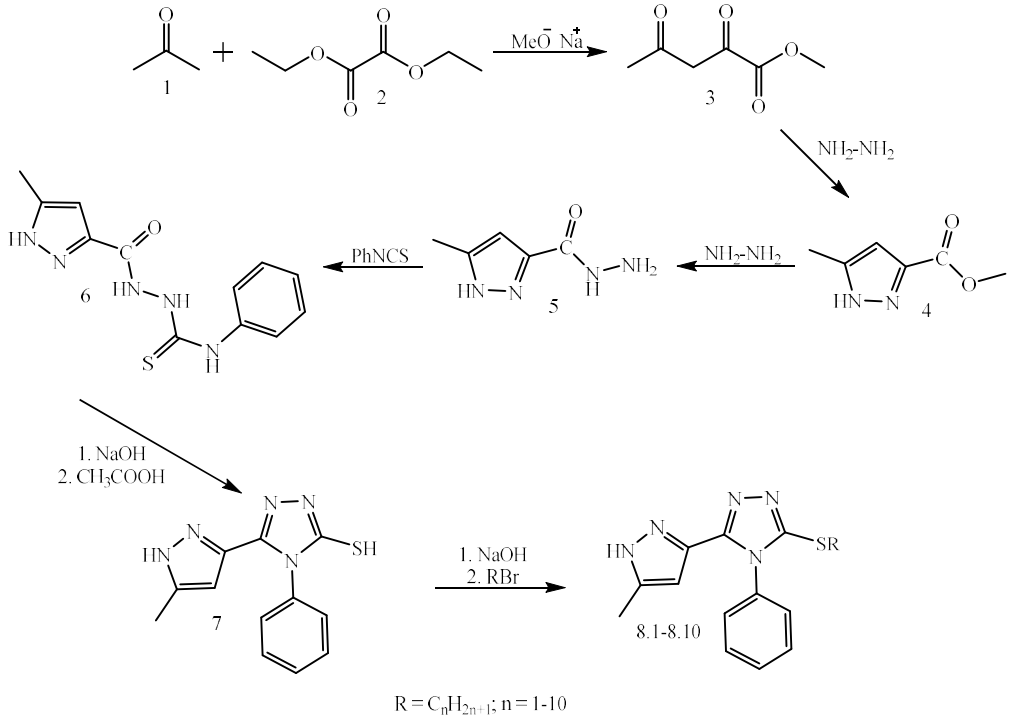

Fig. 1. Scheme of the alkylation reaction of 5-(5-methyl-1H-pyrazol-3-yl)-4-phenyl-4H-1,2,4-triazole-3-thiol derivatives

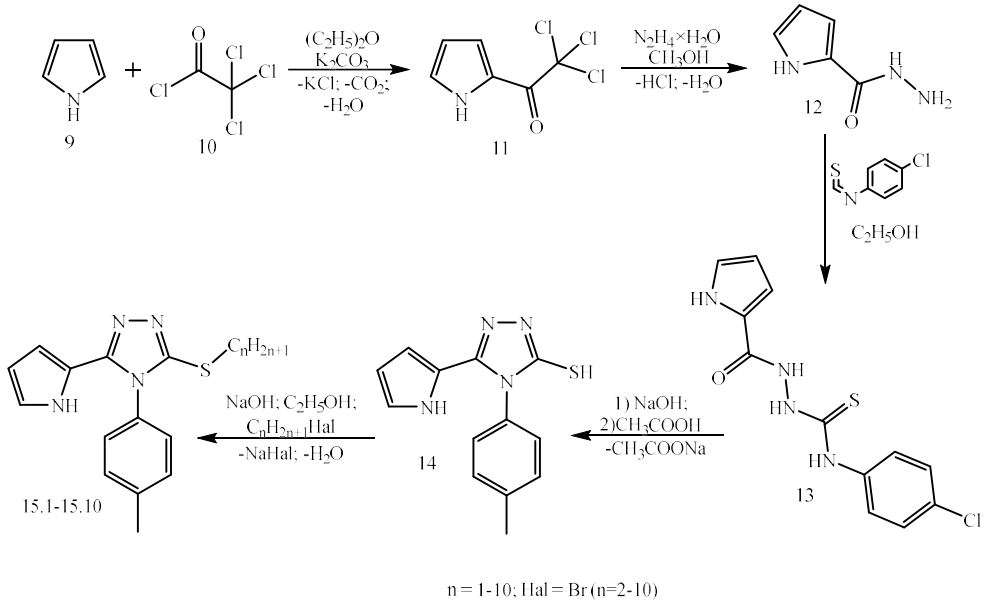

Fig. 2. Scheme of synthesis of S-alkyl derivatives of 4-(4-chlorophenyl)-5-(pyrrol-2-yl)-1,2,4-triazole-3-thiol

Syntheticists from ZSMPhU [16] created a number of 1,2,4-triazole derivatives containing theophylline and 1,3,4-thiadiazole fragments. To obtain the target compounds, the authors [45] obtained theophylline hydrazide, then carried out cyclization with the formation of a triazole nucleus, and at the final stage - condensation with 1,3,4-thiadiazole derivatives (Fig. 3). Biological activity was evaluated by the method of serial dilutions and diffusion in agar using test cultures *S. aureus ATCC* 25923*, E. coli ATCC* 25922*, E. faecalis ATCC* 29212*, C. albicans CCM* 885, as well as clinical isolates of *P. haemolytica, Enterobacter spp., Proteus spp., Staphylococcus spp., S. pyogenes*. Antimicrobial activity was demonstrated by two test compounds at a concentration of 3%, with 24.1 showing a zone of inhibition of up to 36 mm against *C. albicans* and 20–30 mm against Gram-positive bacteria (*S. pyogenes, S. spp., E. faecalis*). Compound 24.2 was effective against *Proteus spp.* (28 mm) and *S. pyogenes* (25 mm). The minimum inhibitory concentration (MIC) for most of the tested microorganisms was 750 μg/ml, indicating an average level of activity compared to typical reference antibacterial drugs such as ampicillin or fluconazole, which exhibit MICs in the range of 25–100 μg/ml. Thus, compounds 24.1 and 24.2 exhibited a broad spectrum of activity against bacteria and fungi, confirming the potential feasibility of combining 1,2,4-triazole, 1,3,4-thiadiazole, and theophylline moieties within a single structure. The highest activity among the tested samples was shown by 24.1, which significantly exceeded 24.2 in terms of antifungal activity against *Candida albicans*, while both compounds showed moderate antibacterial activity against Gram-positive and Gram-negative cultures.

Safonov and co-authors [46] synthesized a series of 3-R-4-substituted-5-((3-phenylpropyl)thio)-4H-1,2,4-triazole derivatives under the influence of microwave radiation in a closed system. 3-R-4-substituted-5-((3-phenylpropyl)thio)-4H-1,2,4-triazoles were obtained by adding (3-bromopropyl)benzene to the starting substances 4-amino-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazole-3-thiol and 5-(2-bromophenyl)-4-phenyl-4H-1,2,4-triazole-3-thiol (Fig. 4). The synthesis was carried out in an isopropanol medium with an equivalent amount of sodium hydroxide. The temperature of the reaction mixture was maintained at 165°C, the pressure was 12.2 bar, and the microwave radiation power was ≈ 540 W (Fig. 4). The microwave synthesis method allowed us to reduce the reaction time from 4–6 h (traditional conditions) to 10–15 min, the yield of products increased by 15–20%, and the compounds were characterized by high purity.

Subsequently, the authors [47] used the microwave synthesis method for new N-R-3-(alkylthio)-5-(thiophen-2-ylmethyl)-1,2,4-triazole-4-amines (Fig. 5). 4-R-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazole-3-thiols (29.1-29.5, 31) were used as starting materials, the reaction was carried out in an alcoholic (methanol, isopropanol) medium by adding a catalytic amount of HCl (Fig. 5). The mixture was heated for 45 minutes at a temperature of 150°C, a pressure of 14.4 bar, ΔMW = 200 W. The authors claim [47] that the microwave synthesis method allowed to reduce the reaction time, increase the yield of products and improve their purity compared to traditional synthesis conditions.

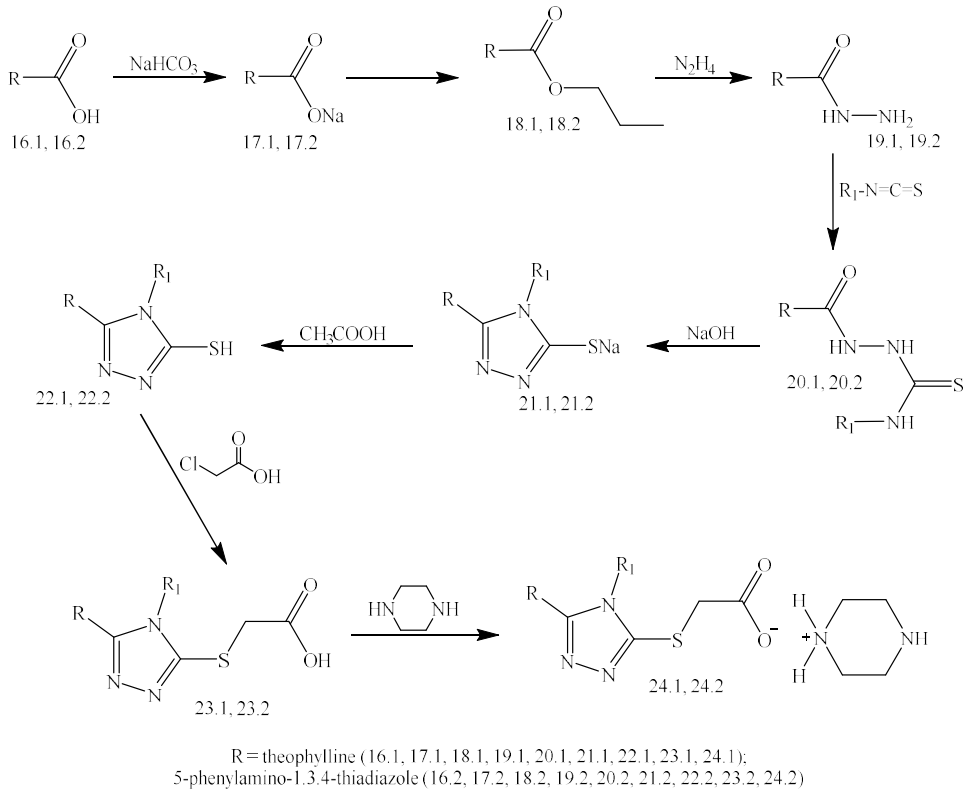

Fig. 3. Scheme of synthesis of 1,2,4-triazole derivatives containing theophylline and 1,3,4-thiadiazole fragments in their structure

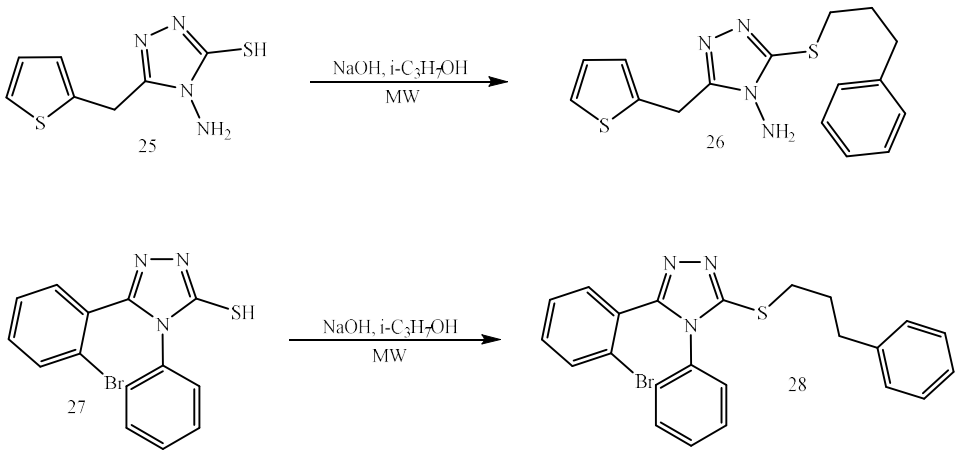

Fig. 4. Scheme of synthesis of 3-R-4-substituted-5-((3-phenylpropyl)thio)-4H-1,2,4-triazoles

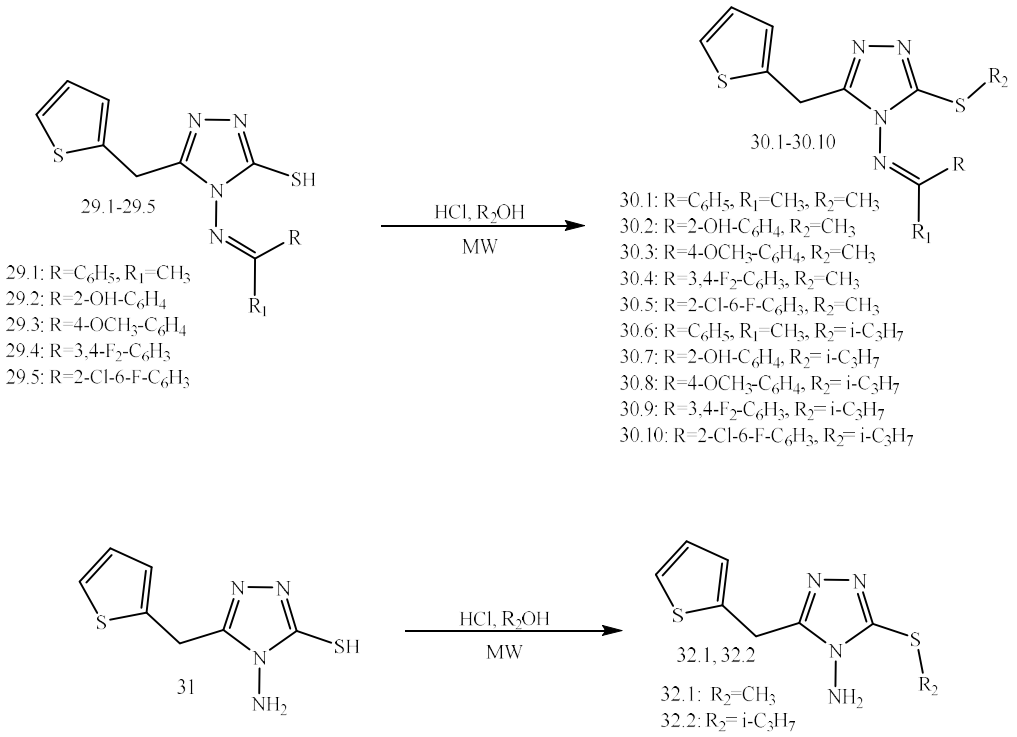

Fig. 5. Scheme of synthesis of 4-R-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazole-3-thiols

Also, Safonov and co-authors in their scientific works investigated histological changes in the liver of rats under conditions of acute immobilization stress [48], degradation under the influence of stress, determination of the stability of the substance and the injection solution [49], assessed the corrective effect, and investigated the effect of high doses on the brain tissue of white rats [50] of sodium 2-((4-amino-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-3-yl)thio)acetate. The target compound (Fig. 6) was synthesized by adding NaOH to an aqueous solution of the corresponding acetic acid and subsequent evaporation. According to the results of the study of the corrective effect of the administration of sodium 2-((4-amino-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-3-yl)thio)acetate in a therapeutic dose reduces the severity of pathological changes in the liver, contributes to the preservation of the structure of hepatocytes and the normalization of the state of blood vessels [19]. Administration of high doses of the test compound for 14 days causes moderate morphological changes in the brain tissue of rats, manifested by degeneration of some neurocytes, edema of perivascular spaces, and moderate microcirculation disorders, but gross damage to the brain tissue was not observed, which indicates the relative safety of the substance even when used in high doses [50].

Shcherbyna and his co-authors described the synthesis and antimicrobial activity [51] of a series of ylidene hydrazides of 2-((4-R-5-R1-4H-1,2,4-triazol-3-yl)thio)acetaldehydes (36.1–36.13), obtained by condensation of the corresponding aldehydes (34.1–34.3) with various hydrazides, including acetohydrazide, benzohydrazide, 3- and 4-nitrobenzohydrazides, nicotinohydrazide and isonicotinohydrazide (Fig. 7). The study of the antimicrobial activity of 13 compounds on 10 strains of microorganisms at concentrations of 0.1%, 0.2% and 0.5% revealed selective activity, in particular for compounds 36.1 and 36.9. The compound N'-(2-((5-methyl-1H-1,2,4-triazol-3-yl) thio)ethylidene)-4-nitrobenzohydrazide (36.9) showed

the highest activity against *Staphylococcus saprophyticus* and *Streptococcus pyogenes* with inhibition zones of 25 and 26 mm at a concentration of 0.5%.

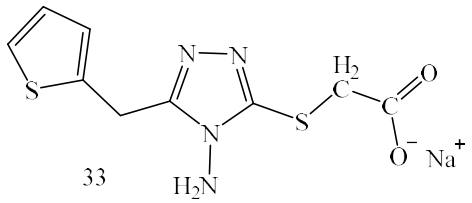

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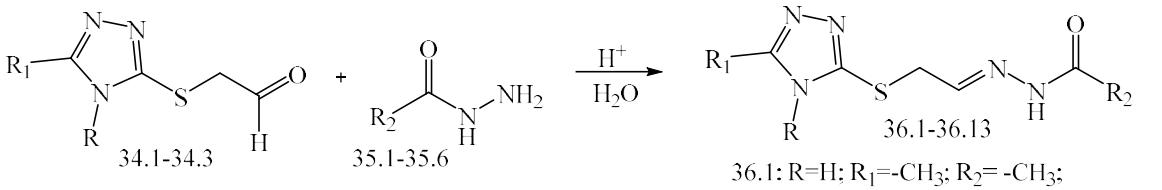
Fig. 6. Structural formula of sodium 2-((4-amino-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-3-yl)thio)acetate

Kalchenko and co-authors in their article [52] investigated the antioxidant potential of 5-(2-bromo-4-fluorophenyl)-4-ethyl-1,2,4-triazole-3-thiol derivatives (Fig. 8) by implementing molecular docking and a 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging test. As a result of in silico AOA studies of 5-(2-bromo-4-fluorophenyl)-4-ethyl-1,2,4-triazole-3-thiol derivatives, indicators were obtained indicating that 4 (37, 38.1, 38.4, 38.6) of the 8 studied compounds have a higher interaction energy with the active center of the protein compared to the reference drug ascorbic acid. By studying the antioxidant activity in vitro (DPPH free radical scavenging), the authors found that 6 (37, 38.1, 38.3-38.6) of the 8 studied substances exceed the AOA of the reference drug ascorbic acid (the most active compound is 3-(2-bromo-4-fluorophenyl)-4-ethyl-5-(heptylthio)-4H-1,2,4-triazole by 17.11%).

The search for potential APIs among 5-(2-bromo-4-fluorophenyl)-4-ethyl-1,2,4-triazole-3-thiol derivatives was continued by the researchers by studying their physicochemical properties by implementing ADME analysis and molecular docking to assess potential anti-inflammatory activity [53]. These studies demonstrated that alkyl derivatives of 5-(2-bromo-4-fluorophenyl)-4-ethyl-1,2,4-triazole-3-thiol (38.1-38.7) have favourable pharmacokinetic characteristics and high affinity for enzymes involved in inflammatory processes (COX-2, TNF-α).

Continuing their scientific activities, a team of Ukrainian authors in [54] described a study devoted to the study of the antioxidant activity of 4-R-3-(morpholinomethyl)-4H-1,2,4-triazole-5-thiols and their alkyl derivatives (Fig. 9) in vitro using the method of non-enzymatic initiation of lipid peroxidation. The study examined 45 compounds, of which 8 demonstrated varying degrees of AOA. The highest activity was shown by 4-amino-3-(morpholinomethyl)-4H-1,2,4-triazole-5-thiol (39.5), which reduced the level of active products reacting with 2-thiobarbituric acid (TBK-AP) by 42.50% ($p > 0.05$), as well as compound 40.5, which inhibited the formation of lipid peroxidation end products by 41.90% ($p < 0.001$), when compared with the reference drug ascorbic acid (30.7), they showed higher activity by 11.8% and 11.2%, respectively. The results showed that the introduction of a free amino group or a phenyl substituent to the N4 atom of the 1,2,4-triazole nucleus in alkyl derivatives contributes to an increase in AOA, while the presence of methyl or ethyl groups at this position often has the opposite effect, increasing the level of TBA-AP compared to the control groups. Increasing the length of the hydrocarbon chain in alkyl derivatives, especially when introducing an n-decyl fragment, reduced the AOA of the studied compounds.



34.1-34.3

34.1: R=H; R_1=-CH_3;
34.2: R=-CH_3; R_1=H;
34.3: R=-C_6H_5; R_1=H.

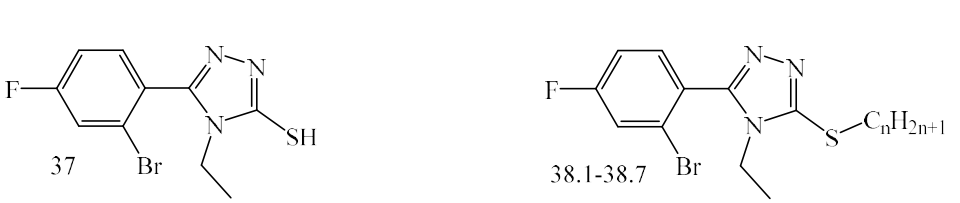
35.1-35.6

35.1: R_2= -CH_3;
35.2: R_2= -C_6H_5;
35.3: R_2= -3-NO_2-C_6H_4;
35.4: R_2= -4-NO_2-C_6H_4;
35.5: R_2= -3-C_5H_4N;
35.6: R_2= -4-C_5H_4N.

36.1-36.13

36.1: R=H; R_1=-CH_3; R_2= -CH_3;
36.2: R=-CH_3; R_1=H; R_2= -CH_3;
36.3: R=H; R_1=-C_6H_5; R_2= -CH_3;
36.4: R=H; R_1=-CH_3; R_2= -C_6H_5;
36.5: R=H; R_1=-C_6H_5; R_2= -C_6H_5;
36.6: R=H; R_1=-CH_3; R_2= -3-NO_2-C_6H_4;
36.7: R=-CH_3; R_1=H; R_2= -3-NO_2-C_6H_4;
36.8: R=H; R_1=-C_6H_5; R_2= -3-NO_2-C_6H_4;
36.9: R=H; R_1=-CH_3; R_2= -4-NO_2-C_6H_4;
36.10: R=-CH_3; R_1=H; R_2= -4-NO_2-C_6H_4;
36.11: R=H; R_1=-C_6H_5; R_2= -3-C_5H_4N;
36.12: R=-CH_3; R_1=H; R_2= -4-C_5H_4N;
36.13: R=H; R_1=-C_6H_5; R_2=-4-C_5H_4N.

Fig. 7. Scheme of synthesis of ylidene hydrazides of 2-((4-R-5-R1-4H-1,2,4-triazol-3-yl)thio)acetaldehydes

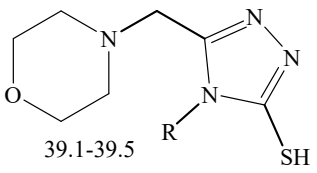


37

38.1-38.7

38.1: n=1;
38.2: n=3;
38.3: n=4;
38.4: n=5;
38.5: n=6;
38.6: n=7;
38.7: n=8.

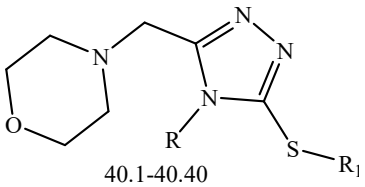
Fig. 8. Structural formulas of the studied derivatives of 5-(2-bromo-4-fluorophenyl)-4-ethyl-1,2,4-triazole-3-thiols



39.1-39.5

39.1: R=H;
39.2: R=-CH_3;
39.3: R=-C_2H_5;
39.4: R=-C_6H_5;
39.5: R=-NH_2.

40.1: R=H; R_1=-C_3H_7-n;
40.2: R=-CH_3; R_1=-C_3H_7-n;
40.3: R=-C_2H_5; R_1=-C_3H_7-n;
40.4: R=-C_6H_5; R_1=-C_3H_7-n;
40.5: R=-NH_2; R_1=-C_3H_7-n;
40.6: R=H; R_1=-C_4H_9-n;
40.7: R=-CH_3; R_1=-C_4H_9-n;
40.8: R=-C_2H_5; R_1=-C_4H_9-n;
40.9: R=-C_6H_5; R_1=-C_4H_9-n;
40.10: R=-NH_2; R_1=-C_4H_9-n;
40.11: R=H; R_1=-C_5H_{11}-n;
40.12: R=-CH_3; R_1=-C_5H_{11}-n;
40.13: R=-C_2H_5; R_1=-C_5H_{11}-n;
40.14: R=-C_6H_5; R_1=-C_5H_{11}-n;
40.15: R=-NH_2; R_1=-C_5H_{11}-n;
40.16: R=H; R_1=-C_6H_{13}-n;
40.17: R=-CH_3; R_1=-C_6H_{13}-n;
40.18: R=-C_2H_5; R_1=-C_6H_{13}-n;
40.19: R=-C_6H_5; R_1=-C_6H_{13}-n;
40.20: R=-NH_2; R_1=-C_6H_{13}-n;



40.1-40.40

40.21: R=H; R_1=-C_7H_{15}-n;
40.22: R=-CH_3; R_1=-C_7H_{15}-n;
40.23: R=-C_2H_5; R_1=-C_7H_{15}-n;
40.24: R=-C_6H_5; R_1=-C_7H_{15}-n;
40.25: R=-NH_2; R_1=-C_7H_{15}-n;
40.26: R=H; R_1=-C_8H_{17}-n;
40.27: R=-CH_3; R_1=-C_8H_{17}-n;
40.28: R=-C_2H_5; R_1=-C_8H_{17}-n;
40.29: R=-C_6H_5; R_1=-C_8H_{17}-n;
40.30: R=-NH_2; R_1=-C_8H_{17}-n;
40.31: R=H; R_1=-C_9H_{19}-n;
40.32: R=-CH_3; R_1=-C_9H_{19}-n;
40.33: R=-C_2H_5; R_1=-C_9H_{19}-n;
40.34: R=-C_6H_5; R_1=-C_9H_{19}-n;
40.35: R=-NH_2; R_1=-C_9H_{19}-n;
40.36: R=H; R_1=-$C_{10}H_{21}$-n;
40.37: R=-CH_3; R_1=-$C_{10}H_{21}$-n;
40.38: R=-C_2H_5; R_1=-$C_{10}H_{21}$-n;
40.39: R=-C_6H_5; R_1=-$C_{10}H_{21}$-n;
40.40: R=-NH_2; R_1=-$C_{10}H_{21}$-n.

Fig. 9. Structural formulas of the studied 4-R-3-(morpholinomethyl)-4H-1,2,4-triazole-5-thiols and their alkyl derivatives

Dovbnya and co-authors optimized the preparative method for the synthesis of salts of ((5-(2,4-, 3,4-dimethoxyphenyl)-3H-1,2,4-triazol-3-yl)thio)(acetic, benzoic) acids with inorganic bases for which the level of sugar-lowering action was investigated and acute toxicity indicators were predicted [55]. Ammonium, sodium and potassium salts of the corresponding acids (compounds 42.1–42.3, 42.11–42.13, 42.21, 42.22, Fig. 10) were synthesized by the interaction of the starting acids (41.1–41.3) with ammonia, sodium or potassium hydroxides in an aqueous medium with subsequent evaporation of the solvent. Zinc, copper (II) and iron (II) salts of acetic acids (compounds 42.4–42.6, 42.14–42.16, Fig. 10) were obtained by the interaction of sodium salts of 1,2,4-triazol-3-ylthio acetic acids (41.1, 41.2) with sulfates of the corresponding divalent metals. The study of the hypoglycemic effect of the synthesized salts of 2-((5-(2,4-, 3,4-dimethoxyphenyl)-3H-1,2,4-triazol-3-yl)thio)acetic and benzoic acids was evaluated by implementing an intraperitoneal glucose tolerance test (IGT) based on changes in glucose concentration in the blood of animals after its single intraperitoneal administration in the form of a 40% solution at a dose of 2 g/kg of rat body weight. According to the results of this study, the authors identified the leading compound – zinc (II) 2-((5-(3,4-dimethoxyphenyl)-3H-1,2,4-triazol-3-yl)thio)acetate (compound 42.16, Fig. 10), which showed higher efficiency in terms of the ability to reduce blood glucose levels, namely, by 27.3% (approximately 1.3 times) compared to a group of laboratory animals that received the reference drug metformin and according to *in silico* prediction of acute toxicity belongs to toxicity class 4 according to OECD classification standards.

Continuing the search for potential APIs among derivatives of 5-(2,4- and 3,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-thiones, the researchers synthesized a series of 2-((5-(2,4- and 3,4-dimethoxyphenyl)-3H-1,2,4-triazol-3-yl)thio)aceto(propane-, butane-, benzo)nitriles (compounds 44.1–44.11, Fig. 11) for which they studied antioxidant activity by the method of non-enzymatic initiation of free radical oxidation (FRO) [56]. The preparation of 2-((5-(2,4- and 3,4-dimethoxyphenyl)-3H-1,2,4-triazol-3-yl)thio)aceto(propane-, butane-, benzo)nitriles (compounds 44.1–44.11, Fig. 11) involved the interaction of the corresponding halogenonitriles (chloroacetonitrile, 3-chloropropanonitrile, 4-chlorobutanenitrile, 2-chlorobenzonitrile, 4-amino-2-chlorobenzonitrile, 3-(chloromethyl)benzonitrile) with the corresponding 1,2,4-triazole-3-thiones in an alkaline-alcoholic medium, under the influence of short-term heating at low temperature. The AOA study indicates that out of 11 tested compounds, 5 were able to inhibit free radical formation to varying degrees. Moderate AOA was exhibited by compounds 44.2, 44.10, which reduced the level of TBK-AP by 12.07–13.55% ($p < 0.001$). Compounds 44.1, 44.7 had high AOA, which reduced the content of TBK-AP by 16.55–16.71% ($p < 0.001$). The most pronounced AOA was 4-((5-(3,4-dimethoxyphenyl)-3H-1,2,4-triazol-3-yl) thio)butanonitrile (45.8), which reduced the content of TBA-AP by 29.03% ($p < 0.001$), but did not reach the level of ascorbic acid by 7.94%.

In the work [57], modern approaches for evaluating the antitumor activity of new 1,2,4-triazole derivatives synthesized by a stepwise reaction (Fig. 12). Chalcones 47.1–47.10 [1-(4-aminophenyl)-3-arylprop-2-en-1-one] were synthesized by a base-catalyzed Claisen–Schmidt

condensation reaction with various aldehydes 45.1–45.10 (Fig. 12). Treatment of chalcones 47.1–47.10 with bromoacetyl bromide in the presence of aqueous potassium carbonate as a base in dichloromethane (DCM) led to the synthesis of acylated chalcones 48.1–48.10. 1H-Indole-3-carbaldehyde (50) was synthesized by subjecting indole to Vilsmeier-Haak conditions with $POCl_3$ and DMF, after which it was oxidized with $KMnO_4$ in acetone, obtaining the corresponding acid (51) for which the esterification reaction was carried out (52), the resulting ethyl ester was subjected to hydrazinolysis (53), compound 53 was mixed with allyl or phenyl isothiocyanate in a minimum amount of ethanol under heating, evaporated, the residue was treated with 2 N KOH and boiled for 8 hours (Fig. 12). Intermediates 54.1, 54.2 were obtained after acidification to pH = 2. The authors obtained the target compounds by alkylation of thiols 54.1, 54.2 with acylated chalcone derivatives 48.1–48.10 in the presence of triethylamine (TEA) using acetonitrile as a solvent to obtain the target compounds 55.1-55.19 (Fig. 12).

The initial assessment of antiproliferative potential was carried out according to the NCI screening methodology [57]. To clarify the cytotoxic and antiproliferative effects, the MTT assay was used, which allowed us to determine the effect of the compounds on breast cells (MCF-10A line) and calculate the IC_{50} values. Further studies are aimed at studying molecular targets: an EGFR-TK inhibition test was performed for the most active derivatives, and inhibitory activity against c-MET was assessed. For a deeper understanding of the mechanisms of action, molecular docking was performed in the active centers of EGFR and c-MET.

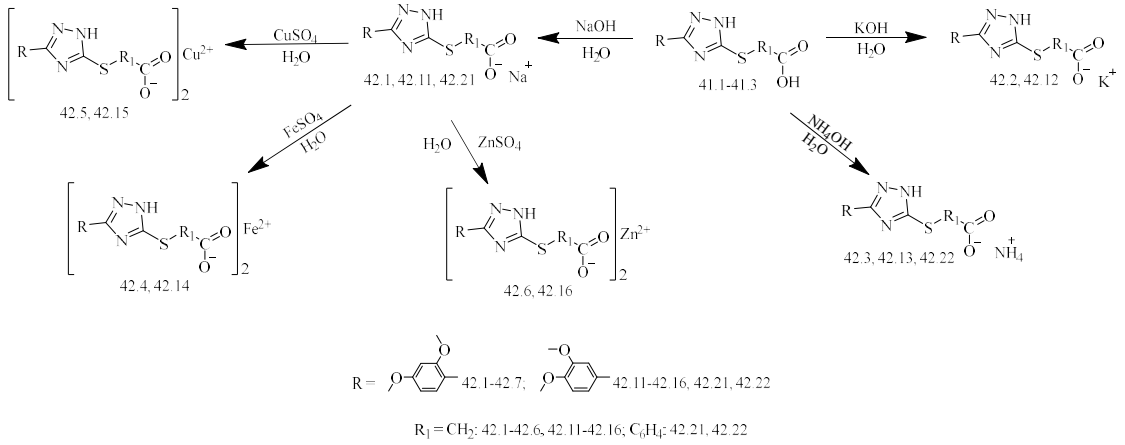


Fig. 10. Scheme of synthesis of salts of ((5-(2,4-, 3,4-dimethoxyphenyl)-3H-1,2,4-triazol-3-yl)thio)(acetic, benzoic) acids with inorganic bases

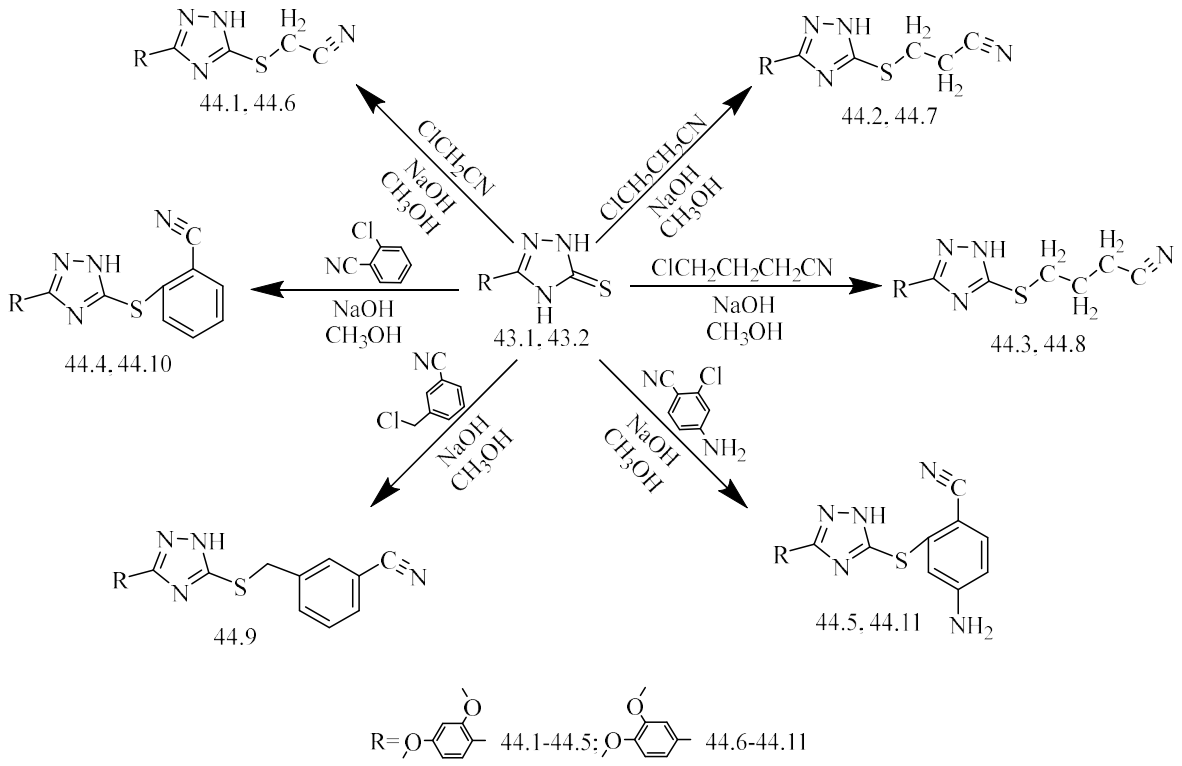


Fig. 11. Scheme of synthesis of ((5-(2,4- and 3,4-dimethoxyphenyl)-3H-1,2,4-triazol-3-yl)thio)aceto(propane-, butane-, benzo)nitriles

Among the series of synthesized derivatives (55.1–55.19), the most pronounced activity was demonstrated by the compounds: 55.1–55.5, 55.7, 55.9, 55.11, 55.14 and 55.15 – had a significant inhibitory effect on EGFR-TK (epidermal growth factor receptor. 55.2, 55.4, 55.5, 55.7 and 55.9 – showed high activity against c-MET (hepatocyte growth factor receptor tyrosine kinase). Scientists emphasize that these compounds, despite the pronounced antiproliferative effect, did not show toxicity towards normal breast cells MCF-10A, which was confirmed by the results of the MTT assay (cell viability over 84%). The most promising for further studies were compounds 55.2 and 55.4, which were analyzed in detail by the molecular docking method in in the active centers of EGFR and c-MET, which confirmed their ability to stably interact with key amino acid residues.

Irum Shahzadi and co-authors synthesized, according to the method already described in the previous work [57], a new series of ten hybrid compounds of acephylin and 1,2,4-triazole (56.1–56.10, Fig. 13), containing in their structure a fragment of N-phenyl/arylacetamide [58]. The study was focused on the assessment of the antitumor activity of these compounds, their mechanism of action and the analysis of the "structure-activity" relationship (SAR) using *in silico* and *in vitro* methods. According to the results of molecular docking against STAT3 (signal transducer and activator of transcription 3), compound 56.7 demonstrated the best binding energy (–6.2789 kcal/mol), which indicated its high affinity and stable interaction with the active site of the enzyme, compared to the standard drug acephylin (–4.6825 kcal/mol). Further SAR studies revealed that the highest cytotoxicity is provided by the presence of electron-donating substituents in the para position of the aryl ring. In particular, the methyl group at the para-position made compound 56.7 the most optimal candidate. Biological studies confirmed the high cytotoxicity of the synthesized compounds against breast cancer (MCF-7) and lung cancer (A549) cells. Compound 56.7 exhibited the strongest activity, especially against the lung cancer cell line A549, with the lowest IC_{50} value (1.25 ± 1.60 μM). In addition, hemolytic assay showed that most of the derivatives, including 56.7 (0.39% hemolysis), have low toxicity towards human erythrocytes, indicating their potential safety and selectivity towards cancer cells. Thus, the results confirm that compound 56.7 is a highly potent, selective STAT3 inhibitor based on the hybrid of acephylin and 1,2,4-triazole and is a promising candidate for further development of anticancer drugs.

[59] conducted a similar study, presenting the bio-oriented synthesis and investigation of new hybrid compounds based on 1,2,4-triazole and acetamide (Fig. 14) as potential anticancer agents. The starting compound for the synthesis was 2-(4-isobutylphenyl) propanoic acid (ibuprofen), which was transformed into the key intermediate 5-(1-(4-isobutylphenyl)ethyl)-1,2,4-triazole-2-thiol (Fig. 14) by multi-step synthesis. Further alkylation of this intermediate with N-substituted 2-bromoacetamides allowed obtaining the target library of compounds (57.1–57.6, Fig. 14). All synthesized derivatives were tested in vitro for antiproliferative activity against the human hepatocellular carcinoma cell line HepG2. The results showed that the compounds exhibit. SAR analysis (structure-activity relationship) revealed a clear relationship: the highest activity was demonstrated by compound 57.6, which contains two electron-donating methyl groups in the ortho-positions of the phenyl ring of the acetamide fragment, with an IC_{50} = 16.782 μg/ml; compound 57.4 with an electron-withdrawing chlorine atom in the ortho-position, on the contrary, was the least active (IC_{50} = 39.667 μg/ml). This suggests that the presence of electron-donating groups in the ortho-position of the benzene ring is a key factor for enhancing antitumor potential. In addition to high activity, the compounds also demonstrated low hemolytic activity, indicating their favourable cytotoxicity profile. To elucidate the possible mechanism of action, molecular docking was performed on five known cancer protein targets. The *in silico* results were fully consistent with the *in vitro* data and showed that the synthesized molecules have high affinity for kinase targets, in particular, protein kinase B (Akt) and c-kit tyrosine kinase. The lead compound 57.6 demonstrated the lowest binding energy (–176.749 kcal/mol with c-kit), forming stable hydrogen and hydrophobic bonds in the active site of the enzyme. Thus, the authors concluded that compound 57.6 is a promising candidate for further development of new anticancer drugs.

Hafiz Muhammad and co-authors in their work [60] presented the synthesis, already according to the method presented earlier in the article [57], and the biological study of a new series of ethanamide derivatives (58.1–58.15, Fig. 15), containing in their structure heterocyclic nuclei of 1,2,4-triazole and azinene (piperidine), assessed the potential of inhibition of enzymes by the obtained compounds, in particular acetylcholinesterase (AChE), α-glucosidase, urease, lipoxygenase (LOG) and butyrylcholinesterase (BHE). The results showed that the entire series of synthesized molecules exhibits high inhibitory activity against the AChE enzyme. Compounds 58.4 (with a 3-methylphenyl substituent) and 58.13 (with a 3,5-dimethylphenyl substituent) stood out in particular, which turned out to be more potent than the standard drug ezerin. Structure-activity relationship (SAR) analysis showed that the presence of methyl groups in the meta- and para-positions of the phenyl ring significantly enhances AChE inhibition. Even more impressive results were obtained for the enzyme α-glucosidase, where absolutely all synthesized derivatives demonstrated activity exceeding the activity of the reference standard acarbose. The most active compounds in this series were 58.4 and 58.14 (with a 2-ethyl-6-methylphenyl substituent). In general, the compounds demonstrated 1.4 times higher inhibitory capacity compared to acarbose, while the compounds showed significantly lower activity against the enzymes urease, LOG and BHE, which indicates their high selectivity of action.

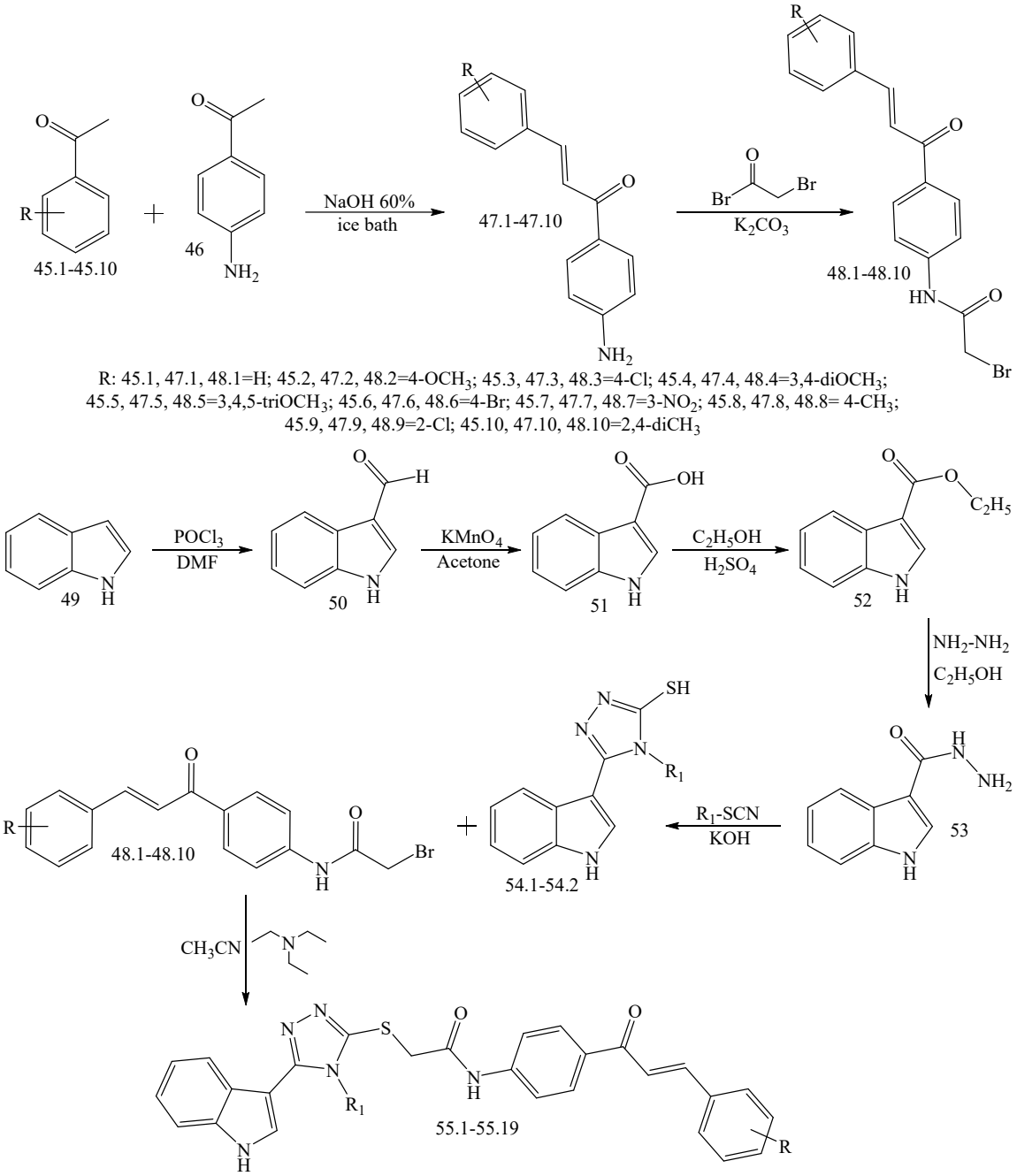
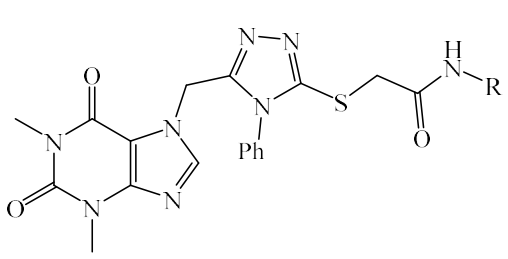


Fig. 12. Scheme of synthesis of 1,2,4-triazole derivatives with potential antitumor activity



56.1: R= C_6H_5;
56.2: R= 2,4-Cl_2-C_6H_3;
56.3: R= 2,4-Me_2-C_6H_3;
56.4: R= 3,4-Cl_2-C_6H_3;
56.5: R= 4-F-C_6H_4;
56.6: R= 2-Cl-C_6H_4;
56.7: R= 4-Me-C_6H_4;
56.8: R= 3,4-Me_2-C_6H_3;
56.9: R= 4-Cl-C_6H_4;
56.10: R= 2-F-C_6H_4.

Fig. 13. Structural features of the studied hybrid compounds of acephylline and 1,2,4-triazole, containing an N-phenyl/ arylacetamide fragment in their structure

[61] conducted a search for antimicrobial agents among compounds obtained by alkylation of theophylline-1,2,4-triazole derivatives with 2-bromo-N-phenylacetamide with various substituents. The studied compounds showed high activity against *S. aureus*, *E. coli* and *C. albicans*, with MICs of 1.8–3.0 mg/ml, which is not inferior to the activity of the comparator drugs penicillin and fluconazole. SAR analysis revealed that electron-withdrawing substituents, such as chlorine, increase hydrophobic interactions, while bulky groups reduce efficiency. Molecular docking confirmed strong binding to topoisomerase II and 14α-demethylase, which explains the mechanism of action through inhibition of key enzymes.

Numerous scientific works [62–64] prove that alkylation of 1,2,4-triazole derivatives leads to an increase in their pharmacological activity, for this reason, scientists from Italy carried out the reaction between 4-amino-5-(4-pyridinyl)-4H-1,2,4-triazole-3-thiol and alkyl halides in an alkaline medium (Fig. 16), and the synthesized compounds were studied for neuroprotective activity [65]. In vitro studies of the kinetics of α-syn aggregation using thioflavin-T and light scattering demonstrated that compounds 59–62 reduced aggregation (in particular, 61 and 62 were at the same level as reference inhibitors such as SynuClean-D), although 59 and 60 partially accelerated the reaction, probably due to the formation of β-sheets with higher affinity for Th-T. In vivo tests in mice with an MPTP-induced Parkinson's disease model showed that compound 62 (ethyl 2-((4-amino-5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)thio)acetate) at a dose of 10 mg/kg increased the levels of tyrosine hydroxylase and dopamine transporter, reduced the expression of α-syn in the midbrain, and improved motor functions. Immunohistochemical analysis confirmed the protective effect against neurodegeneration.

A recent study by [66] presents an innovative approach to the synthesis of novel 1,2,4-triazole-linked β-hydroxysulfides as inhibitors of bacterial tyrosinase (Fig. 17). The authors used fragment-oriented hybridization, integrating heterocyclic moieties (benzofuran, naphthofuran, acephylline) with substituted phenyl rings around the triazole core, modifying the thiol group with epoxides (e.g., 2-methyloxirane and 2-(phenoxymethyl)oxirane) via thiolysis (Fig. 17). *In vitro* evaluation showed that compounds 64.1, 64.3, 64.4 and 64.6 outperformed the reference inhibitors (ascorbic acid with IC_{50} = 11.5 mM and kojic acid with IC_{50} = 30.34 mM), with IC_{50} ranging from 4.52 to 7.67 mM. The most potent was compound 64.3 with a benzofuran moiety (IC_{50} = 4.52 mM), where structure-activity relationship (SAR) analysis highlighted the role of electron-donating and electron-withdrawing substituents, as well as hydrophobic interactions. Molecular docking confirmed the high affinity of 64.3 for the active site of tyrosinase (–7.08 kcal/mol), with hydrogen bonds, π-interactions, and coordination with copper ions exceeding standards. In addition, compounds 64.1 and 64.3 exhibited antibacterial activity against *S. aureus* and *E. coli* approaching penicillin (MIC 2.0–2.5 mg/mL against *Gram-positive bacteria*).

The study [67] focused on the synthesis and investigation of the potential antibacterial properties of Cu-MOFs based on 3,5-dimethyl-1,2,4-triazole. The authors optimized the synthesis using different copper valences (Cu(I)/Cu(II)), copper salt states (organic and inorganic), and organic ligands, synthesizing the MOFs at room temperature to maximize the Cu^{2+} ion content, which promotes sterilization. The most effective Cu-MOF synthesized with 3,5-dimethyl-1,2,4-triazole and tetrakis-(acetonitrile)copper(I) tetrafluoroborate was found to have a zone of inhibition of 40.17 mm against *S. aureus*, significantly exceeding standard antibiotics and other Cu-MOFs. A broad spectrum of activity was confirmed against *E. coli* and *A. baumannii*, with a mechanism involving electrostatic interactions, membrane disruption, and Cu^{2+} release. SAR analysis showed that the 1,2,4-triazole ligand enhances stability and antimicrobial activity compared to other heterocycles, while organic copper salts provide better dispersibility and bioavailability.

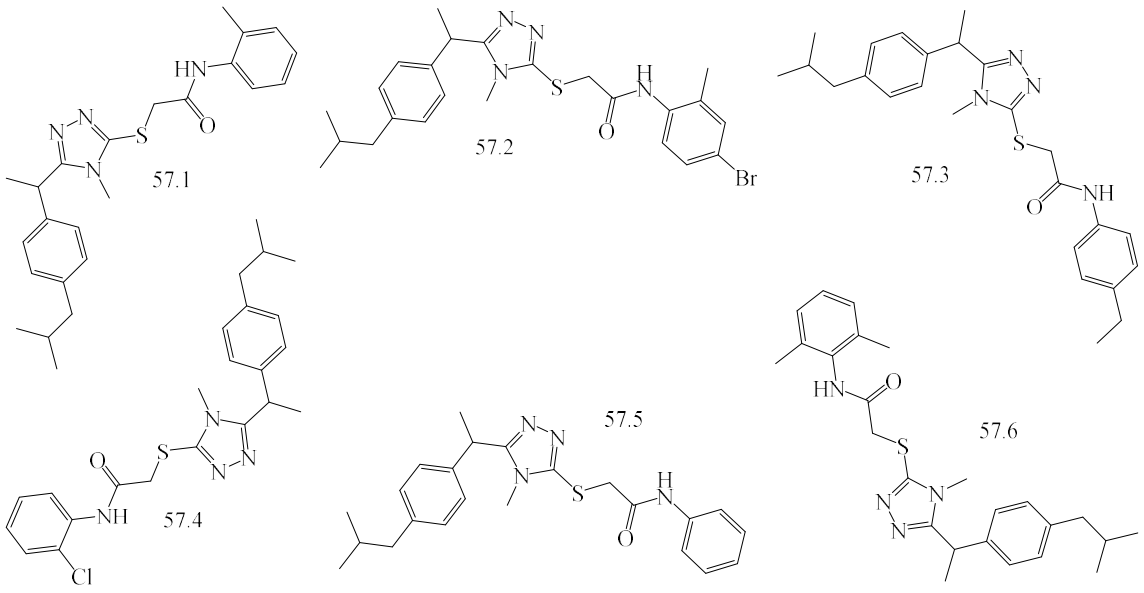


Fig. 14. Structural formula of 5-(1-(4-isobutylphenyl)ethyl)-1,2,4-triazole-2-thiol derivatives

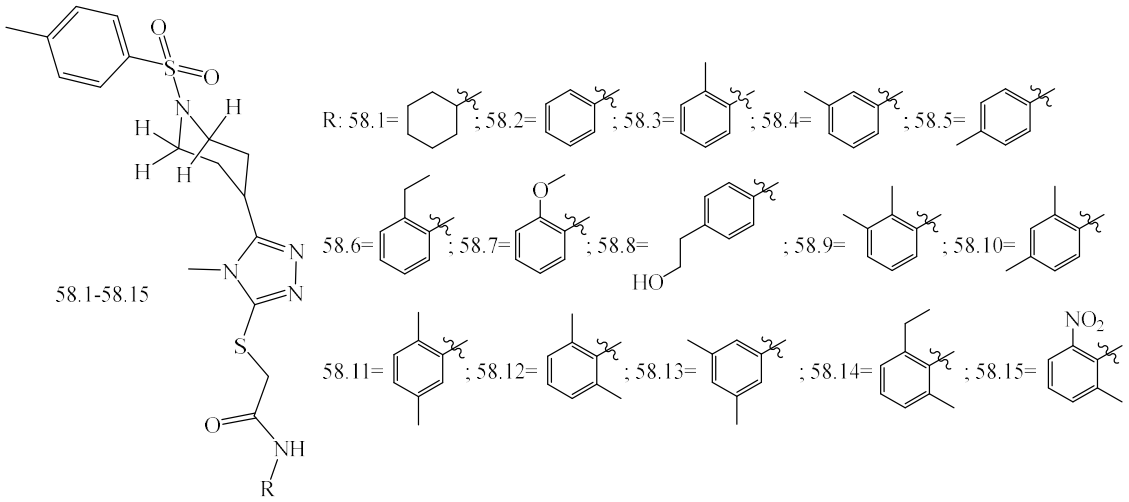


Fig. 15. Structural modelling of a series of ethanamide derivatives containing heterocyclic 1,2,4-triazole-azinan (piperidine) nuclei in their structure

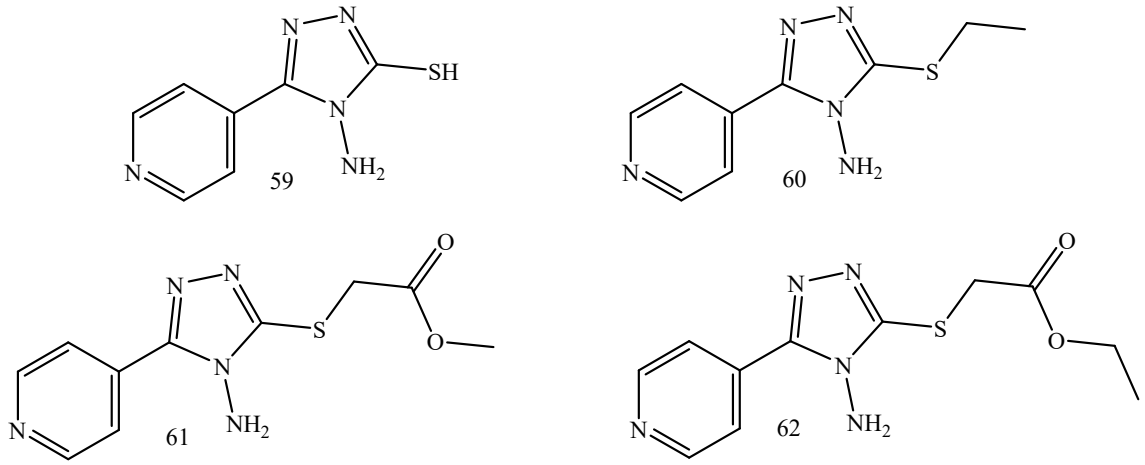


Fig. 16. Structural formulas of the studied 4-amino-5-(4-pyridyl)-4H-1,2,4-triazole-3-thiol and its derivatives

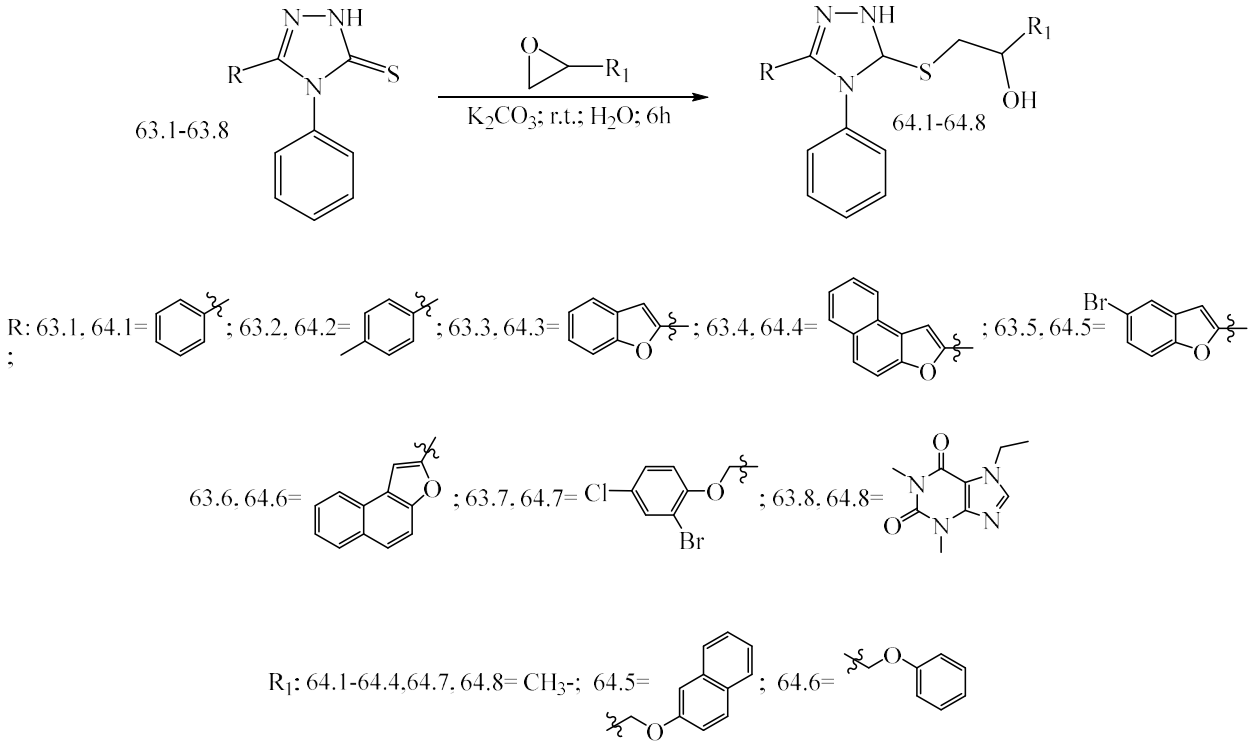


Fig. 17. Scheme of synthesis of 1,2,4-triazole derivatives linked to hydroxyl sulfides

Imran Khan and colleagues synthesized 19 1,2,4-triazole derivatives with bis-hydrazone moieties [68]. The main steps of the synthesis included the reaction of thiosemicarbazide with benzoyl chloride, cyclization to 3-mercapto-1,2,4-triazole, interaction with phenacyl bromides, and formation of the final bis-hydrazone derivatives by condensation with benzaldehyde (Fig. 18). All synthesized compounds demonstrated inhibitory activity against α-amylase and α-glucosidase enzymes in the IC_{50} range of 0.7–35.7 μM and 1.1–30.4 μM, respectively. Some compounds, in particular 70.15–70.17, showed activity significantly higher than the standard drug acabrose. Structure-activity relationships (SAR) showed that electron-withdrawing substituents, such as -Cl and -NO_2, increase the inhibitory potential. The position of the substituents is also significant: the ortho- and meta-orientations of the -Cl and -NO_2 groups affected the interaction with the active sites of the enzymes. Bulkier groups, such as dimethylamino, created steric hindrance and reduced the inhibitory activity. Computer modeling confirmed the interactions of the synthesized compounds with the active sites of α-amylase and α-glucosidase. The most active derivatives (70.15 and 70.17) formed hydrogen bonds, π-π interactions, and alkyl contacts with key amino acids of enzymes. Docking showed that the presence of dichloro and nitro groups promotes stable and strong interactions with enzymes, confirming the results of *in vitro* studies.

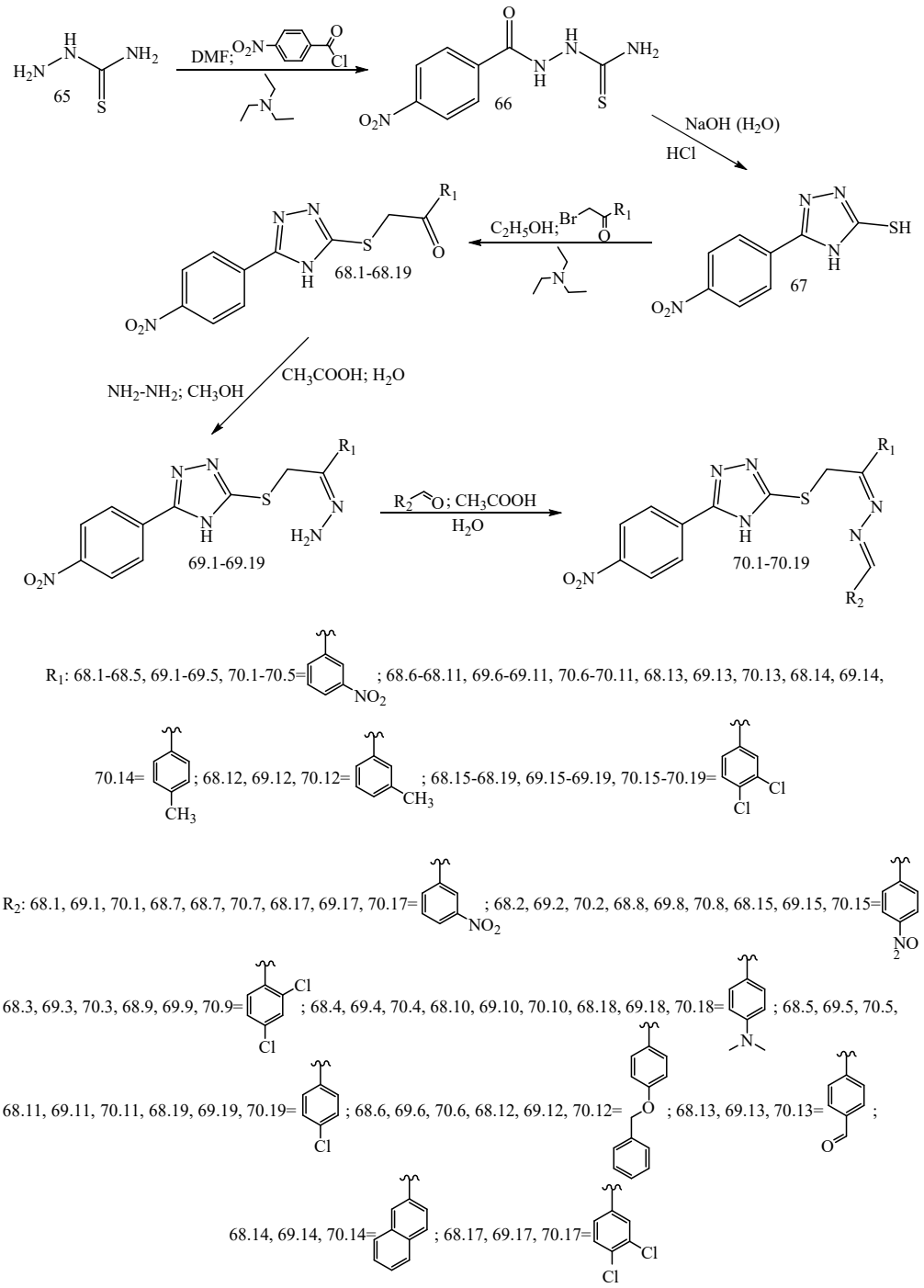


Fig. 18. Scheme of synthesis of 1,2,4-triazole derivatives with bis-hydrazone fragments

Scientists from Lithuania [69] synthesized and studied a series of new derivatives of 1,2,4-triazole-3-thiol (Fig. 19). The authors carried out the synthesis of the target compounds (74.1–74.5, 75.1–75.11) in several stages: the starting 1,2,4-triazole-5-thione (71) as a result of the reaction with ethyl chloroacetate formed ethyl ester (72), which upon further interaction with hydrazine hydrate was converted into the key intermediate synthon – 2-((4-phenyl-5-(2-(phenylamino)ethyl)-4H-1,2,4-triazol-3-yl)thio)acetohydrazide (73) (Fig. 19). Condensation of this hydrazide with various isatins or aromatic/heterocyclic aldehydes allowed to obtain the target hydrazones (Fig. 19). For the synthesized compounds, the scientists conducted an *in vitro* study of antitumor activity on three aggressive cancer cell lines: melanoma (IGR39), triple-negative breast cancer (MDA-MB-231) and pancreatic carcinoma (Panc-1). Cytotoxicity (MTT test), effect on cell migration (wound healing assay) and activity in 3D cultures (tumor spheroids) were evaluated. The results showed that compounds 74.1 75.6 and 75.10 are the most active in the tumor spheroid model, while compound 75.2 demonstrated significant inhibition of cancer cell migration, making it a promising candidate for the development of antimetastatic agents.

In the study [70], the main attention is paid to the synthesis and pharmacological evaluation of new hybrid compounds based on eugenol and 1,2,4-triazole as potential dual agents – anticancer and anti-inflammatory (COX-2 inhibitors). The synthesis of target derivatives 76–81 was carried out, according to the method demonstrated in the previous work [68], in several steps, the key to which was the condensation reaction of the intermediate acetohydrazide with various aromatic aldehydes, which led to the formation of the final products – Schiff bases (Fig. 20). Evaluation of antiproliferative activity *in vitro* on cancer cell lines of breast adenocarcinoma (MDA-MB 231), colon (HCT-116) and prostate (PC-3) revealed two leaders. Compounds containing a hydroxyl group in the aromatic substituent, in particular compound 79 (with a hydroxyphenyl moiety) and compound 80 (with a hydroxynaphthylene moiety), demonstrated the highest cytotoxicity. Of particular note is compound 80, which showed activity comparable to the reference drug doxorubicin against prostate cancer cells (IC_{50} = 5.69 μM) and breast cancer cells (IC_{50} = 1.42 μM). Other substituents, such as dimethylamino or methoxy groups, resulted in a significant decrease in activity. To elucidate the likely mechanism of anticancer activity, a COX-2 inhibition assay was performed. The results showed a direct correlation between cytotoxicity and COX-2 inhibition capacity. Compounds 79 and 80 were again the most potent, with IC_{50} values of 0.32 μM and 0.28 μM, respectively, which is comparable to the activity of the selective inhibitor celecoxib (IC_{50} = 0.25 μM). This suggests that the antiproliferative effect of these derivatives is likely to be mediated by inhibition of COX-2. In silico studies, including molecular docking and ADMET prediction, confirmed the experimental data. Docking showed that compounds 79 and 80 bind efficiently to the active site of the COX-2 protein, forming hydrogen bonds with key amino acid residues (Thr199, Asn67, His94), like celecoxib. Physicochemical property predictions showed that most of the compounds conformed to the Lipinski rule, and the toxicity profiles indicated their safety. Thus, the authors concluded that compound 80 is a promising candidate for further studies as an anticancer and anti-inflammatory agent, combining high efficacy with a good physicochemical profile.

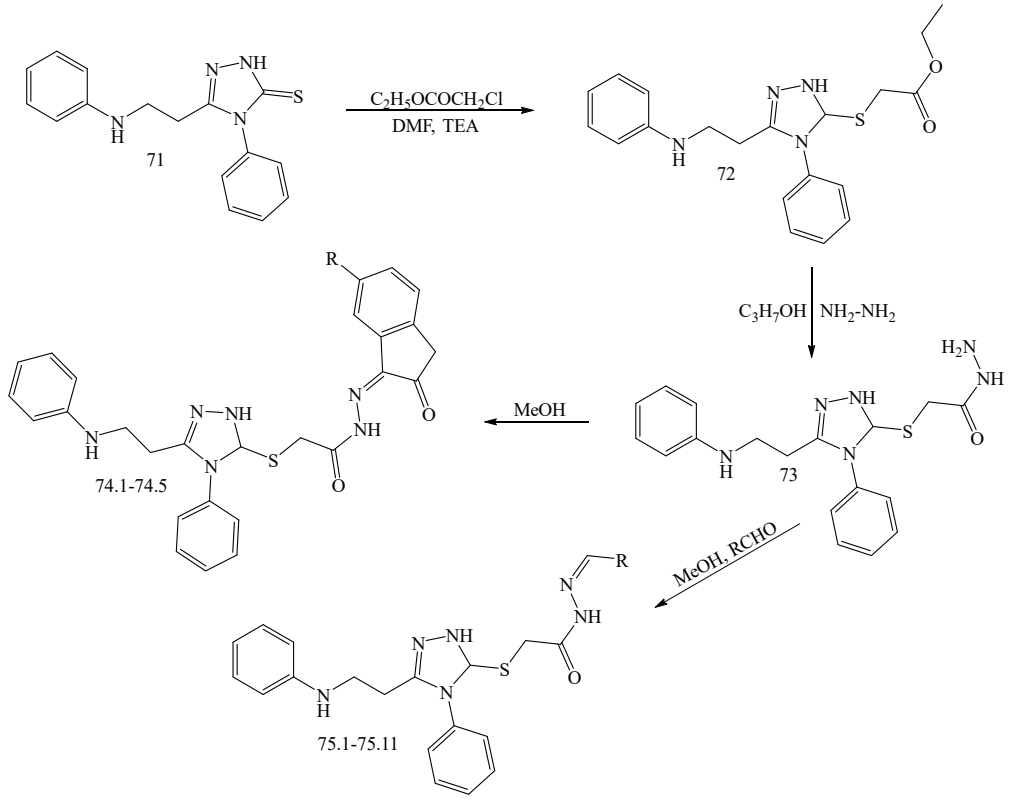
Analysis of modern literature data shows that modification of 1,2,4-triazole derivatives at the thiol sulfur atom is one of the most effective directions of targeted chemical transformation of this heterocycle. Reactions of alkylation, acylation, formation of salts and hybrid structures with bioactive fragments allow to significantly expand the boundaries of the chemical and pharmacological space of compounds of this class.

Among the obtained derivatives, samples with pronounced antioxidant (in particular, 5-(2,4- and 3,4-dimethoxyphenyl)-1,2,4-triazole-3-thiones and their nitriles), antimicrobial (hydrazones of 1,2,4-triazole-thioacetates, conjugates with thiadiazole and theophylline), antitumor (hybrids with acephylline, acetamide, eugenol) and metabolic (zinc, sodium, potassium salts) activity were found. It was proven that the presence of a thiol fragment provides key electron-donating properties that determine the affinity of compounds to the active centers of biological targets and affect their pharmacological selectivity.

Thus, the thiol functionality in 1,2,4-triazole derivatives serves as a universal platform for the creation of new compounds with a wide range of biological activity, and further study of the reactivity at the sulfur atom opens prospects for the development of new medicinal agents with desired properties.

The amino group at the nitrogen atom in the 1,2,4-triazole structure is one of the most reactive fragments of this heterocycle [71, 72]. Modification at the amino group opens the way to obtaining new polyfunctional structures with expanded pharmacophore potential, combining the properties of different biologically active nuclei [73, 74].

Among modern approaches, methods for constructing condensed systems, such as pyrazolo[1,5-*d*][1,2,4]triazolo[3,4-*f*][1,2,4]triazines [73], as well as the formation of Schiff bases [75] and hybrid structures with thiazolidin-4-one [76], mefenamic acid [77] or hydrazones [76] fragments, attract special attention. Due to the participation of the amino group in condensation and cyclization reactions, new triazole scaffolds with pronounced biological activity are obtained [73, 78]. Many of them demonstrate potent antibacterial [75, 79], antitumor [75, 77, 78], analgesic [78], antipyretic [78], and antioxidant [75] effects, which have been confirmed by both *in vitro* and *in vivo* experiments and *in silico* studies (docking, ADMET analysis, SAR evaluation). Thus, amino group modification reactions represent a promising direction in the creation of new medicinal compounds with multi-vector pharmacological activity.



R: 74.1= H; 74.2= OCH_3; 74.3= NO_2; 74.4= F; 74.5= OCF_3
R_1: 75.1= 4-CH_3C_6H4; 75.2= 4-$(CH_3)_2NC_6H_4$; 75.3= pyridin-4-yl; 75.4= pyridin-3-yl; 75.5= $HO_2CC_6H_4$; 75.6= pyrrol-2-yl; 75.7= 3-phenyl-1H-pyrazol-4-yl; 75.8= 1-methyl-1H-pyrazol-3-yl; 75.9= 2-OHC_6H_4; 75.10= 2-OH-5-$NO_2C_6H_3$; 75.11= $CH_3SC_6H_4$

Fig. 19. Scheme of synthesis of 2-((4-phenyl-5-(2-(phenylamino)ethyl)-4H-1,2,4-triazol-3-yl)thio)acetohydrazide derivatives

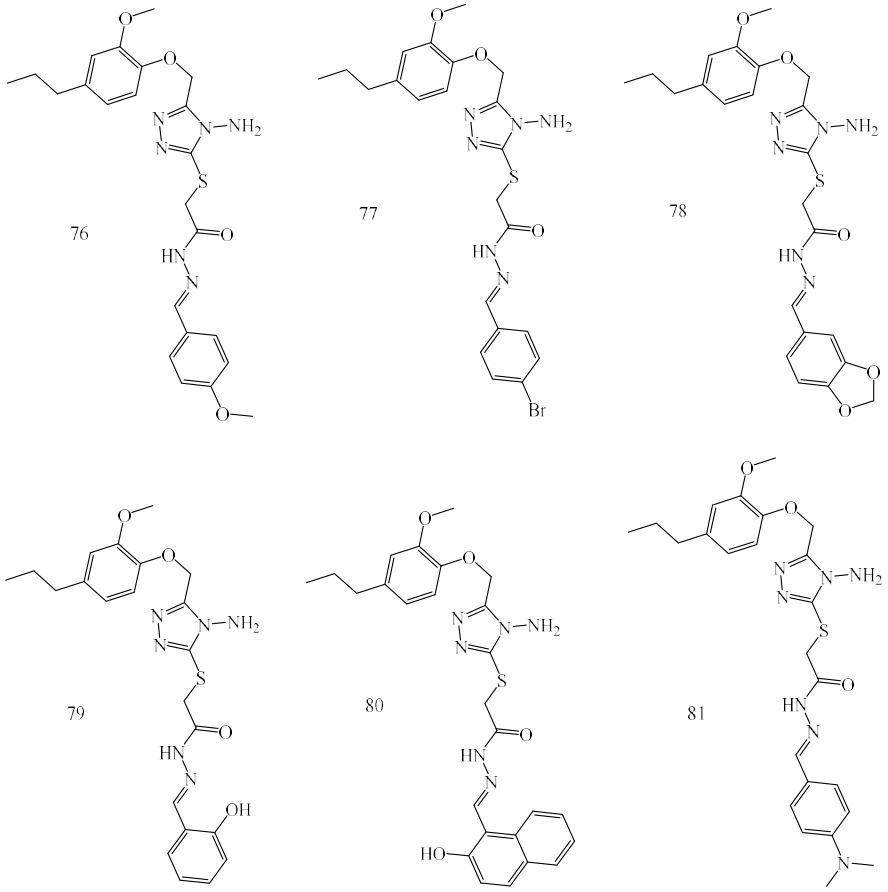


Fig. 20. Structural formulas of compounds based on 1,2,4-triazole and eugenol

Scientists from Zaporizhzhia [73] developed methods for the synthesis of pyrazolo[1,5-*d*][1,2,4]triazolo[3,4-*f*][1,2,4]triazines. The authors carried out the synthesis of the compounds in several stages. By interacting freshly prepared sodium methylate with a mixture of acetone and diethyl oxalate, they obtained ethyl 2,4-dioxopentanoate (83), which interacted with hydrazine hydrate to form 5-methylpyrazole-3-carbohydrazide (84), which, upon treatment with carbon disulfide, was converted into xanthate (84), which, upon interaction with hydrazine hydrate, formed 4-amino-5-(5-methylpyrazol-5-yl)-1,2,4-triazole-3-thiol (86), which was subjected to an alkylation reaction, and the resulting products (87.1–87.10) interacted with triethoxymethane, resulting in the target compounds (88.1–88.10, Fig. 21). For the synthesized compounds, scientists conducted an in silico study of anti-inflammatory and antifungal activity using molecular docking, it was found that the compounds exhibit moderate affinity for the enzyme cyclooxygenase-2 (COX-2), forming π–σ, π-alkyl and hydrogen interactions with amino acid residues of the active center, which indicates a potential anti-inflammatory effect. Compounds 88.4–88.6 were recognized as the most promising. The synthesized substances showed significantly higher affinity for lanosterol-14α-demethylase – a key enzyme in ergosterol biosynthesis. The system of hydrophobic, π-anionic and hydrogen bonds ensure stable binding, especially in the case of compounds 88.8-88.10, for which the minimum binding energy (–6.1 to –9.5 kcal/mol) was recorded. This indicates their strong potential as inhibitors of this enzyme and possible fungicidal agents. At the same time, the compounds of the series did not demonstrate a significant effect on receptor tyrosine kinase, indicating a low probability of antitumor activity.

Syntheticists from Iraq have created several new 1,2,4-triazole derivatives (Fig. 22) for which antibacterial and cytotoxic activity was studied [77]. Compound 90 was obtained by the interaction of the starting material 89 with 4-aminoacetophenone dissolved in ethanol with the addition of a few drops of acetic acid, the mixture was boiled for 8 hours, cooled to room temperature, filtered and purified from ethanol (Fig. 22). For the synthesis of 4-((E)-1-((4-((E)-1-((3,5-bis(4-methoxyphenyl)-4H-1,2,4-triazol-4-yl)imino)ethyl)phenyl)imino)ethyl)phenol (91), the authors boiled equimolar amounts of 4-hydroxyacetophenone and compound 90 for 8 hours in ethanol with acetic acid, filtered, and purified from ethanol. The synthesis of N-(3,5-bis(4-methoxyphenyl)-4H-1,2,4-triazol-4-yl)-N-(1-chloro-1-(4-(N-(1-chloro-1-(4-hydroxyphenyl)ethyl)acetamido) phenyl)ethyl)acetamide (92) was carried out by the interaction of compound 91 with dry benzene and acetyl chloride in an ice-water bath with constant stirring for an hour, then the reaction mixture was boiled for 2 hours, evaporated, the residue was washed with water, and purified with diethyl ether (Fig. 22). To obtain thiourea derivatives (93), the researchers heated a mixture of compound 92, thiourea, anhydrous sodium carbonate, and 20 mL of acetone for 6 hours, poured into ice water, filtered, and recrystallized from ethyl acetate (Fig. 22). The synthesis of the last target compound (94) was carried out by the reaction between 2-hydroxy-1,2-diphenylethan-1-one and compound 93 in dimethylformamide, boiled for 7 hours, cooled, a few drops of cold water were added, and stirred until a precipitate formed, filtered, and purified from ethyl acetate.

The antibacterial activity of the synthesized compounds (90–94) was investigated using the well diffusion method on three types of bacteria: *Staphylococcus aureus* (G+), *Klebsiella pneumoniae* (G–) and *Pseudomonas aeruginosa* (G–), ampicillin was used as a reference drug. According to the results of the study, compounds were found that showed higher antibacterial activity, compared to ampicillin, against some microorganisms, namely: compound 90 showed higher inhibition rates against *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, and substances 90–92, 94 against *Pseudomonas aeruginosa*.

Compounds 90 and 94 were tested for cytotoxic activity using three types of cancer cell lines: MCF-7 (human breast carcinoma cells), HepG-2 (human liver cancer cell line) and WRL-68 (human normal liver cell line). The viability of the test cells after the addition of different concentrations of compounds 90 and 94 was determined using an ELISA reader at a wavelength of 575 nm. Compound 90 showed a significant effect at a concentration of 400 µl/ml against the MCF-7 cell line, with cell viability of 37.81%, 24.19%, 12.27%, 5.71%, 4.05% and 5.13% at concentrations of 400, 200, 100, 50, 25, 12.5 µg/ml, respectively, with IC_{50} = 206.1. Compound 94 demonstrated a significant effect at a concentration of 400 µg/mL against the HepG-2 cell line, with cell viability being 61.23%, 54.47%, 38.39%, 20.87%, 4.28%, and 5.98% at concentrations of 400, 200, 100, 50, 25, 12.5 µg/mL, respectively, with IC_{50} = 82.60.

Hiba Alsaad et al. synthesized a new series of six 1,2,4-triazole derivatives (97.1–97.6) containing a 2-(2,3-dimethylaminobenzoic acid) moiety derived from mefenamic acid (Fig. 23) [77]. The study focused on evaluating the antitumor activity of these compounds, their mechanism of action, and structure-activity relationship (SAR) using in silico and in vitro methods. According to the results of molecular docking with epidermal growth factor receptor (EGFR) tyrosine kinase, compound 97.5 demonstrated the best binding energy (–8.32 kcal/mol), indicating its high affinity and stable interaction with the active site of the enzyme, compared to the standard drug erlotinib. Further SAR studies revealed that the highest cytotoxicity was provided by the presence of 4-nitrophenyl and 4-chlorophenyl substituents, making 97.5 the most optimal candidate. Biological studies confirmed the high cytotoxicity of all synthesized compounds against liver cancer (Hep G2) and lung cancer (A549) cells. Compound 97.5 showed the strongest activity against Hep G2, IC_{50} = 2.87, demonstrating high selectivity for cancer cells compared to normal fibroblasts. Compound 97.5 is a potent inhibitor of EGFR tyrosine kinase EC_{50} = 38.3. Treatment of Hep G2 cells with compound 97.5 resulted in cell cycle arrest in phases and induction of apoptosis, rather than necrosis. Molecular analysis confirmed this mechanism, showing an increase in the expression of proapoptotic genes and a decrease in the antiapoptotic gene. In addition, an in silico ADMET study showed that all compounds have a favorable profile, including the absence of predicted CNS side

effects and low carcinogenicity rates. Thus, the results confirm that compound 97.5 is a highly potent, selective 1,2,4-triazole-based EGFR inhibitor and a promising candidate for further anticancer development.

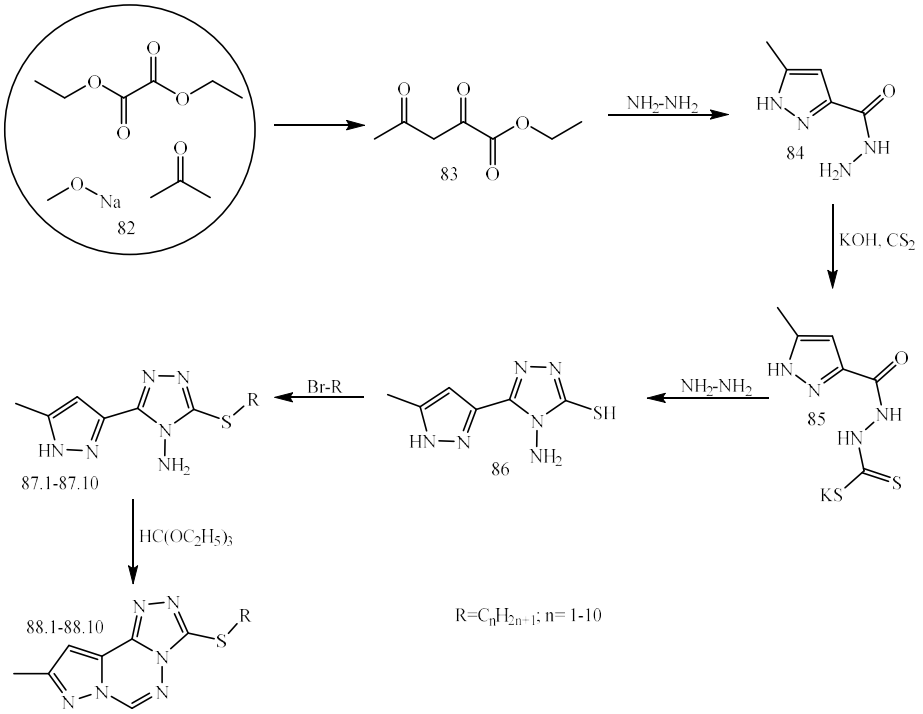


Fig. 21. Scheme of synthesis of 9-methylpyrazolo[1,5-*d*][1,2,4]triazolo[3,4-*f*][1,2,4]triazines

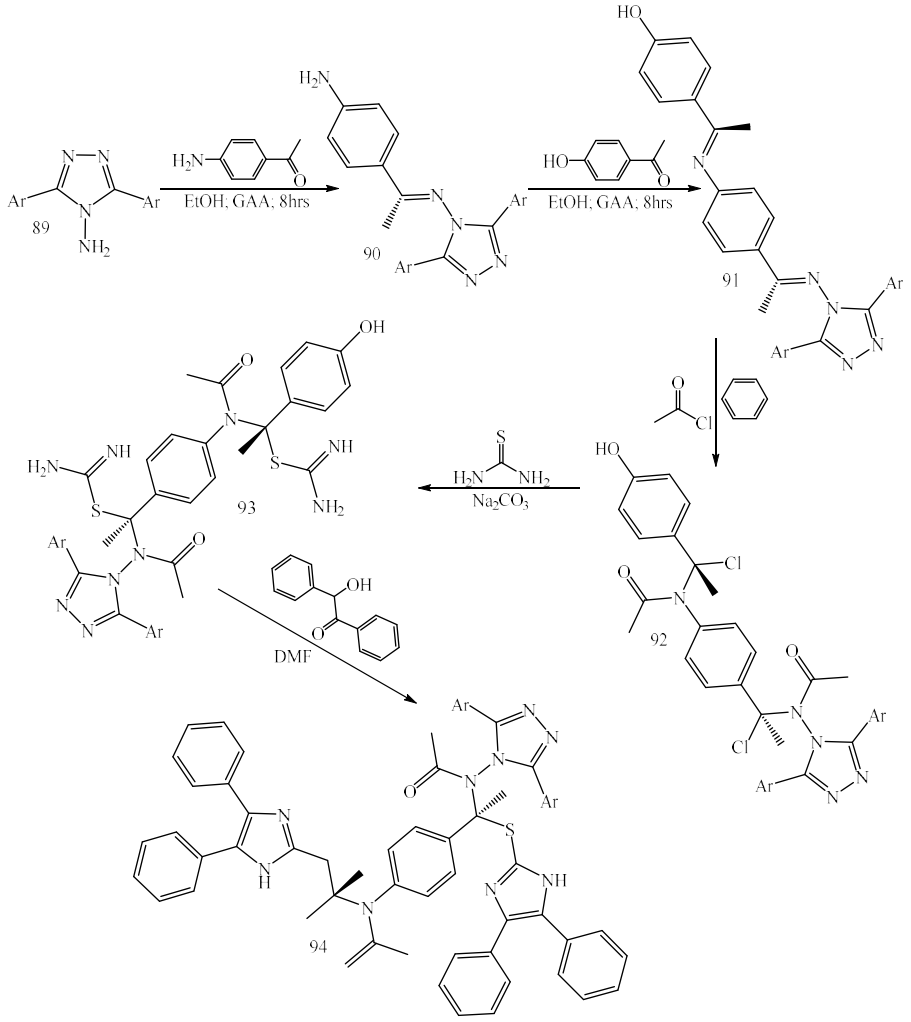


Fig. 22. Scheme of synthesis of 4*H*-1,2,4-triazol-4-amine derivatives

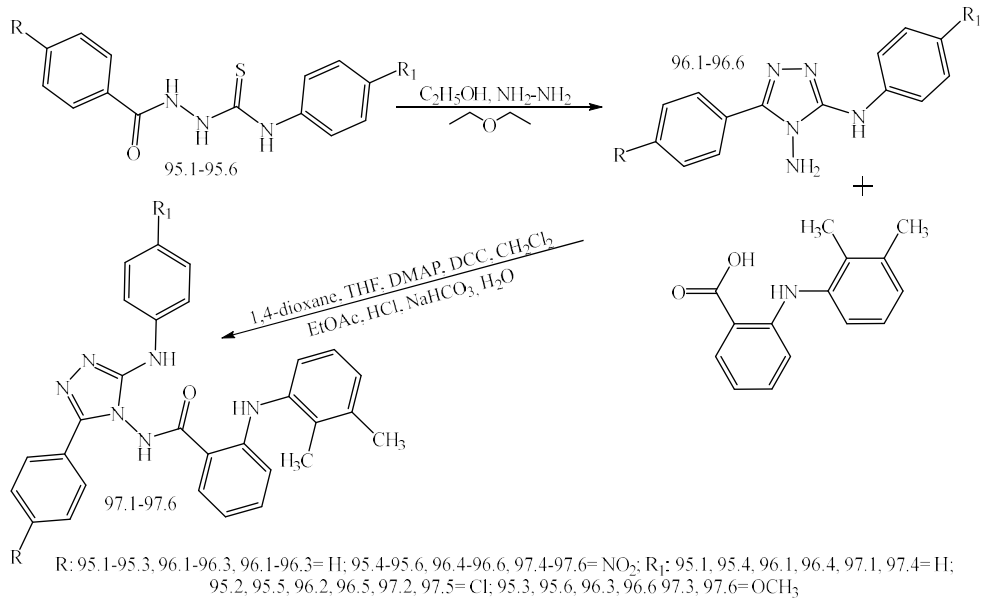


Fig. 23. Scheme of synthesis of 1,2,4-triazole derivatives containing a 2-(2,3-dimethylaminobenzoic acid) fragment

Tabinda Azim et al. evaluated the in vivo anti-inflammatory, analgesic and antipyretic activities of two optically active 1,2,4-triazole derivatives: compound 98 5-(1-hydroxyethyl)-4-amino-1,2,4-triazole-3-thiol and compound 99 1-(5-mercapto-4-[(pyridin-4-ylmethylene) amino]-4H-1,2,4-triazol-3-yl)ethanol (Fig. 24) [78]. The study aimed to determine their therapeutic potential compared to the standard drug ibuprofen. In anti-inflammatory activity studies in carrageenan- and egg albumin-induced paw edema models, both compounds demonstrated high efficacy. In particular, compound 98 (at a dose of 75 mg/kg) showed the highest inhibition of edema (91% in the carrageenan model), which exceeded that of ibuprofen (82%). This indicates a potent inhibition of inflammatory mediators in both the early (histamine, serotonin) and late (prostaglandins) phases. The analgesic effect was assessed using three models: in the acetic acid-induced twitch test (a visceral pain model), compound 98 (75 mg/kg) again outperformed ibuprofen, showing 83% inhibition versus 71%. In the formalin test, which assesses both neurogenic and inflammatory pain, the 1,2,4-triazole derivatives were particularly effective in the second (inflammatory) phase, where compound 98 (75 mg/kg) achieved 75% inhibition. The results of the tail-flick test (a central pain model) showed that both compounds significantly increased the pain threshold, indicating the presence of both central (opioid-like) and peripheral (NSAID-like) mechanisms of analgesia. In the antipyretic activity test, where fever was induced with brewer's yeast, both compounds showed a significant decrease in temperature. Compound 99 (100 mg/kg) was even more potent than ibuprofen, indicating its pronounced ability to inhibit prostaglandin E_2 synthesis in the hypothalamus. Thus, the results of the study prove that the investigated 1,2,4-triazole derivatives, especially compound 98, are promising candidates for further development of new anti-inflammatory and analgesic agents that can potentially outperform existing drugs, and compound 99 also showed itself as a highly effective antipyretic agent.

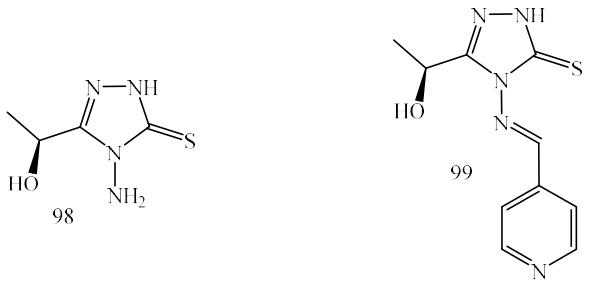
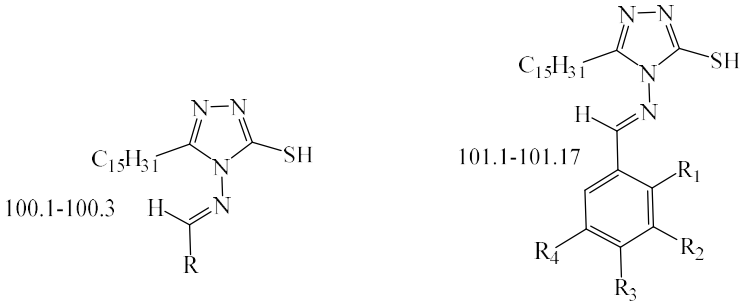


Fig. 24. Structural formulas of the studied compounds: 5-(1-hydroxyethyl)-4-amino-1,2,4-triazole-3-thiol and 1-(5-mercapto-4-[(pyridin-4-ylmethylene)amino]-4H-1,2,4-triazol-3-yl)ethanol

Mukesh Kumari et al. reported the synthesis, following the methodology presented in a previous work [68], and the pharmacological evaluation of a new series of twenty 1,2,4-triazole derivatives (100.1–100.3, 101.1–101.17), focusing on the study of antimicrobial, antioxidant, antiurea and antitumor activities to establish structure-activity relationships (SAR) [75] (Fig. 25). The study revealed that the biological activity of the synthesized compounds significantly depends on the nature and position of the substituents in the aromatic ring. In particular, the highest antibacterial activity was demonstrated by compound 101.5, which contains trimethoxy substituents, while the introduction of a nitro group in the para position (compound 101.17) significantly enhanced the antifungal activity. The introduction of electron-donating groups, such as aldehyde (compound 101.2) and methyl (compound 101.3), led to an increase in both antioxidant and antiurease activity. The most significant results were obtained during the screening of anticancer activity on a human colon cancer cell line (HCT116), where compounds 101.2 (with a para-aldehyde group) and 101.7 (with an ortho-hydroxyl group) showed outstanding cytotoxic activity with IC_{50} of 3.84 μM and 3.25 μM, respectively. These results are particularly promising, since the activity of the compounds signifi-

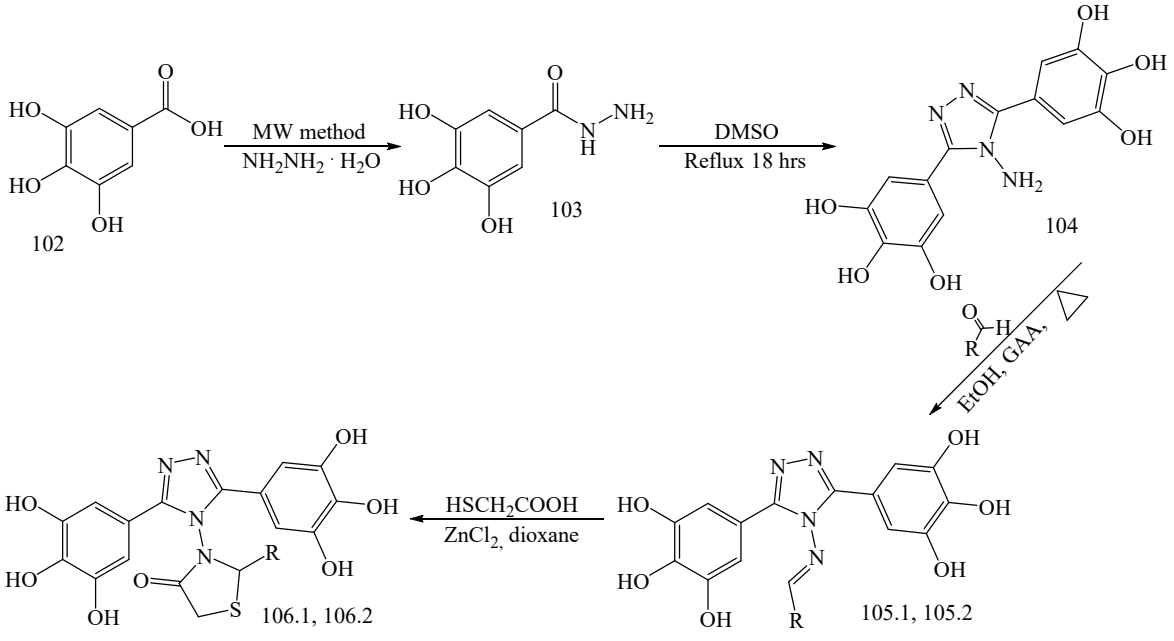
cantly exceeds that of the standard drug 5-fluorouracil, for which the IC_{50} is 25.36 μM. Thus, the study confirms that 1,2,4-triazole-based scaffolds are a promising platform for the development of new pharmacological agents, and compounds 101.2 and 101.7 are identified as potent antitumor agents that deserve further in-depth study.

In their work, foreign scientists [76] described the design, multi-step synthesis and biological evaluation of new thiazolidin-4-one derivatives containing a symmetrical 4-amino-1,2,4-triazole fragment in their structure (Fig. 26). The synthesis began with the preparation of haloylhydrazide (I) from gallic acid using an environmentally friendly method of microwave irradiation without a solvent (Fig. 26). At the next stage, haloylhydrazide (I) was subjected to a cyclization reaction to form the key intermediate product – symmetrical 5,5'-(4-amino-4H-1,2,4-triazole-3,5-diyl) *bis*(benzene-1,2,3-triol) (II) (Fig. 26). Further, by condensation of compound (II) with aromatic aldehydes, the corresponding Schiff bases (105.1, 105.2) were synthesized. The final target compounds – thiazolidin-4-one derivatives (106.1, 106.2) – were obtained because of the cyclocondensation reaction of Schiff bases with thioglycolic acid. *In vitro* biological studies showed that the synthesized compounds exhibit moderate to high antibacterial activity against strains of Gram-positive (*Staphylococcus aureus*) and Gram-negative (*Klebsiella pneumoniae*) bacteria, as well as antifungal activity against *Candida albicans*, compared to standard drugs ampicillin and fluconazole. According to the screening results, compounds 105.2 and 106.2 demonstrated the highest biological activity. Thus, the results of the study confirm that hybrid molecules that combine 1,2,4-triazole and thiazolidin-4-one pharmacophores are a promising class of compounds for further search and development of new antimicrobial agents.



R: 101.1= $C_{12}H_{10}O$; 101.2= $C_{10}H_{10}$; 101.3= C_6H_6O;
R_1: 101.1-101.6, 101.8-101.11, 101.13, 101.14, 101.16, 101.17= H; 101.7= OH; 101.12= Cl; 101.15= NO_2;
R_2: 101.1-101.3, 101.7-101.9, 101.11, 101.12, 101.14, 101.15, 101.17= H; 101.4, 101.5= OCH_3; 101.6= OH; 101.10= Cl; 101.13= Br; 101.16= NO_2;
R_3: 101.1, 101.6, 101.10, 101.13, 101.15, 101.16= H; 101.2= CHO; 101.3= CH_3; 101.4-101.6= OCH_3; 101.8= OH; 101.9= $N(CH_3)_2$; 101.11, 101.12= Cl; 101.14= Br; 101.17= NO_2;
R_4: 101.1-101.4, 101.6-101.17= H; 101.5= OCH_3.

Fig. 25. Structural formulas of the studied derivatives of 4-amino-5-pentadecyl-4*H*-1,2,4-triazole-3-thiol



R: 105.1. 106.1= C_6H_5; 105.2= 4-OH-; 106.2= 3,5-$OCH_3C_6H_2$

Fig. 26. Scheme of synthesis of thiazolidin-4-one derivatives containing a 4-amino-1,2,4-triazole fragment in their structure

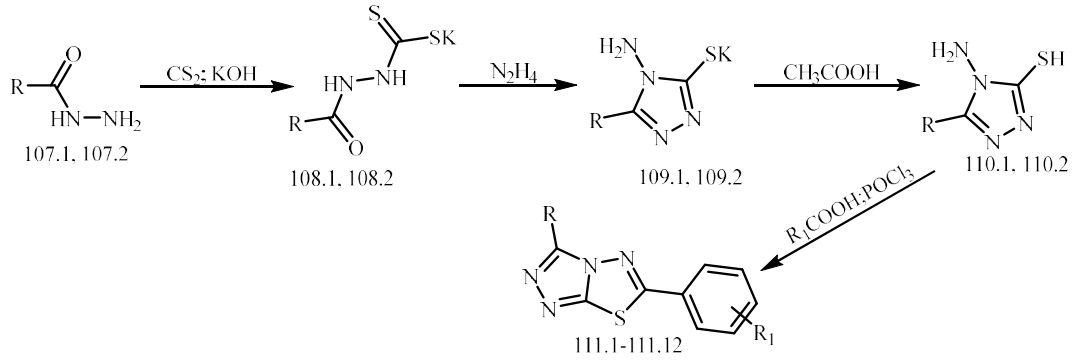
The analysis of literature sources shows that modification of 1,2,4-triazole derivatives at the amino group is one of the most effective methods of structural optimization of this heterocyclic platform. Alkylation, acylation, condensation reactions with aldehydes or acids, as well as the formation of hybrid systems based on amino derivatives of triazole allow obtaining compounds with high biological activity. Among the synthesized derivatives, substances that exhibit significant antitumor (in particular, EGFR and tyrosine kinase inhibitors), antimicrobial, antioxidant, anti-inflammatory and analgesic effects have been described.

It has been established that the presence of an amino group contributes to both the reactivity and biological efficacy of the compounds due to the formation of new hydrogen and π-interactions in the active site zone of enzymes. Hybridization of the 1,2,4-triazole fragment with other pharmacophores (pyrazole, thiazolidin-4-one, mefenamic acid, aryl substituents) significantly expands the spectrum of its biological action. Thus, amino derivatives of 1,2,4-triazole are a promising platform for the development of multifunctional pharmacological agents, and further improvement of their synthesis methods opens up new opportunities for the creation of drugs with high selectivity and efficacy.

The study [63] was devoted to the determination of the anti-inflammatory activity of a number of 4-amino-1,2,4-triazole-3-thiol derivatives. The target compounds were obtained as a result of stepwise chemical interactions, in the first stage the hydrazides of the corresponding carboxylic acids were treated with ammonium thiocyanate or isothiocyanates in the presence of acids or alkalis (Fig. 27). The obtained thiosemicarbazides were subjected to cyclization with the formation of condensed 1,2,4-triazole systems (Fig. 27). Which were subsequently subjected to reactions with aromatic and heterocyclic carboxylic acids in the presence of phosphoryl trichloride (Fig. 27). Molecular docking results showed that the compounds in the series exhibit varying degrees of affinity for three biological targets – cyclooxygenase-1 (COX-1), lanosterol-14α-demethylase, and anaplastic lymphoma kinase (ALK). For COX-1, the activity of the compounds was moderate: the binding energy ranged from –5.5 to –7.1 kcal/mol, which is lower than the reference drug diclofenac (–10.4 kcal/mol). For lanosterol-14α-demethylase, significantly better results were recorded: compounds 111.8–111.12 showed binding energy from –10.1 to –10.6 kcal/mol, which exceeds the activity of ketoconazole (–9.9 kcal/mol). The most active was compound 111.12, which formed numerous π-*S*, π-π and hydrogen interactions with amino acids of the active center (ALA A:311, CYS A:449, HIS A:314, MET A:487). In the case of anaplastic lymphoma kinase (ALK), an intermediate affinity was found: compounds 111.6 and 111.12 showed binding energies of –8.3 and –9.5 kcal/mol, respectively, which is only 0.7–1.9 kcal/mol lower than crizotinib (–10.2 kcal/mol).

[39] described a series of reactions for the synthesis of 1,2,4-triazole derivatives, namely, he carried out hydrazinolysis of [1,3,4]-oxadiazole-2-thione (112) at the oxygen atom to obtain 4-amino-5-[5-(1-methyl-1*H*-pyrrol-3-yl)-1-phenyl-1*H*-pyrazol-3-yl]-4*H*-[1,2,4]triazole-3-thiol (113), the author claims that hydrazinolysis does not occur at the thiol group (Fig. 28). For the synthesized compound 113, condensation with various aromatic aldehydes was carried out, resulting in Schiff bases 114.1–114.3, their subsequent interaction with morpholine and formaldehyde gave the corresponding Mannich bases 115.1–115.3 (Fig. 28). Methylation of oxadiazole-2-thione (112) with methyl iodide in an alcoholic solution of potassium hydroxide gave its methylthio derivative compound 116 (Fig. 28). For compounds 112, 113, 114.1–114.3, the author investigated the cytotoxic activity according to the methods described by Mossman, Gangadevi and Mutumara, to determine the antitumor activity against human colon cancer cell lines (HCT-116) using vinblastine as a reference drug. Among the tested compounds, the highest cytotoxic activity was shown by 4-amino-5-(5-(1-methyl-1*H*-pyrrol-3-yl)-1-phenyl-1*H*-pyrazol-3-yl)-4*H*-1,2,4-triazole-3-thiol (compound 113) IC_{50} = 4.16 μg, the efficacy of which is equivalent to the standard drug vinblastine (3.34 μg).

The study [40] aimed to investigate the promising anthelmintic and anti-inflammatory potential of a number of 1,2,4-triazole derivatives. Compounds 118.1–118.8 were obtained by the reaction of amidrazones 116.1–116.8 with itaconic anhydride. Isomerization of compounds 118.1–118.6 in alkaline solution led to the formation of derivatives 119.1–119.6 (Fig. 29). Higher yields were obtained for compounds 119.4 and 119.5, which may indicate that the 4-pyridine ring in the R1 position facilitates the reaction. On the contrary, isomerization products were not obtained for compounds 118.7 and 188.8, which may indicate that the presence of a 4-nitrophenyl substituent hinders the reaction. The authors investigated two groups of derivatives (118.1–118.8 and 119.1–119.6), which differ only in the position of the double bond in the methacrylic/propenoic acid side chain. Activity studies on the nematode *Rhabditis sp.* revealed two compounds with high nematocidal potential: compound 118.4 (with 4-pyridyl and phenyl substituents) showed the highest activity, surpassing the reference drug albendazole by approximately 8 times (LC_{50} = 2.475 ± 0.283 μg/μl vs. 19.24 μg/μl for albendazole). Compound 118.6 (with 2-pyridyl and 4-methylphenyl substituents) was also significantly more active, exceeding the efficacy of albendazole by 3 times. A critically important structural element for the anthelmintic action was the presence of a methylidene group (CH_2=) in the side chain (compounds 118.1–118.8), since derivatives obtained by isomerization (compounds 119.1–119.6) demonstrated significantly lower activity. It is noteworthy that the presence of a phenyl substituent at position R_2 in combination with a 2- or 4-pyridyl substituent at R_1 correlates with high activity. Evaluation of anti-inflammatory activity on LPS-induced peripheral blood mononuclear cells (PBMCs) showed that derivatives 119.1–119.6 (isomers with a methyl group) have a stronger anti-inflammatory profile. The compounds were generally non-toxic to PBMCs at concentrations up to 100 μg/ml. The most active anti-inflammatory compound is 119.5, which demonstrated multi-vector action, namely: strong inhibition of PBMC proliferation, a significant decrease in the production of pro-inflammatory cytokines TNF-α (up to ~84% inhibition) and IFN-γ, and no significant decrease in the production of the anti-inflammatory cytokine IL-10. Compound 118.4, in addition to high levels of anthelmintic activity, demonstrated anti-inflammatory activity (by inhibiting TNF-α).



R = 107.1, 108.1, 109.1, 110.1, 111.1-111.6=pyrrole-2-yl, 107.2, 108.2, 109.2, 110.2, 111.7-111.12=3-(indole-3-yl)methyl;
R_1 = C_6H_5, C_6H_4-2-OCH_3, C_6H_4-3-OCH_3, C_6H_3-2-Br-5-OCH_3, C_6H_3-2-Br-4-F, C_6H_3-2-Cl-5-NO_2

Fig. 27. Scheme of synthesis of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole derivatives

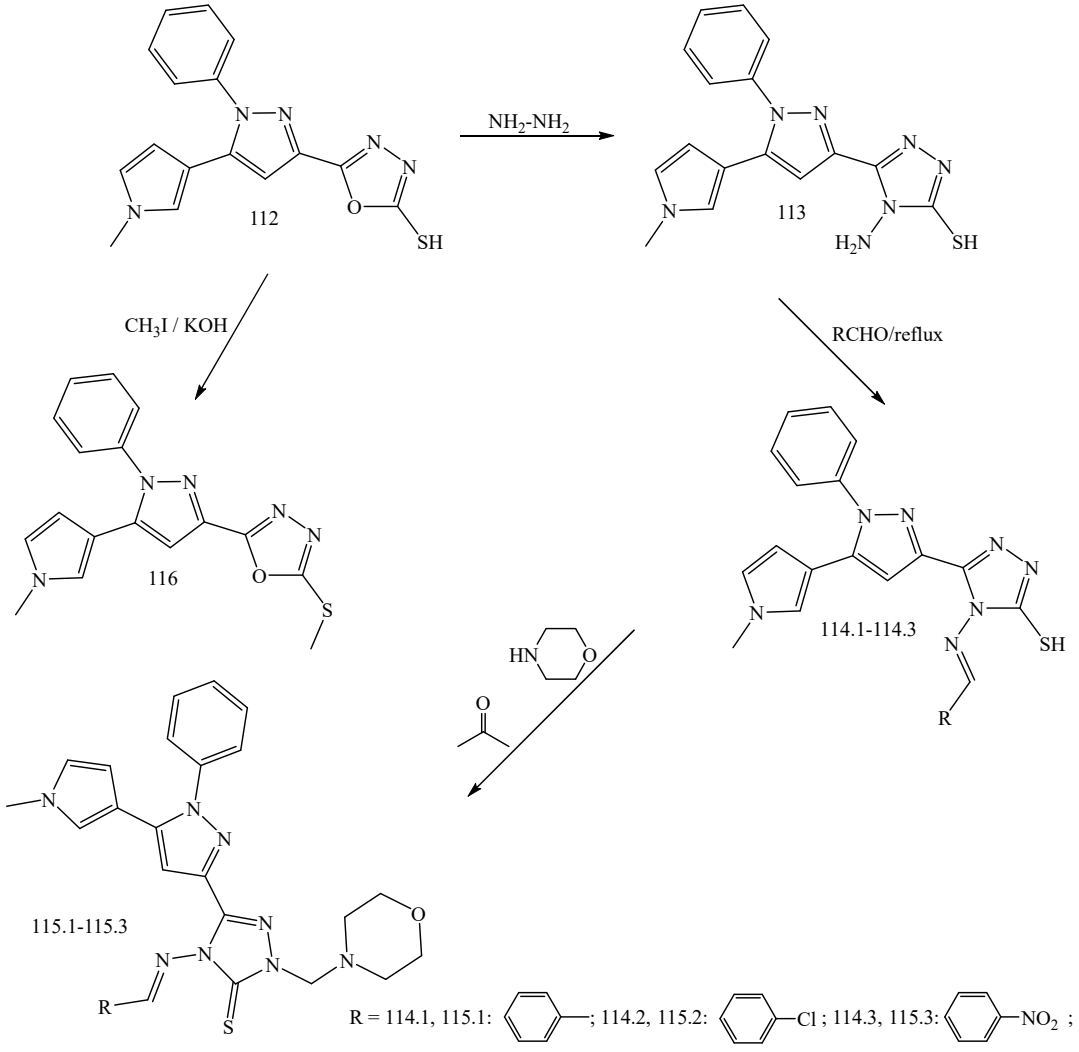
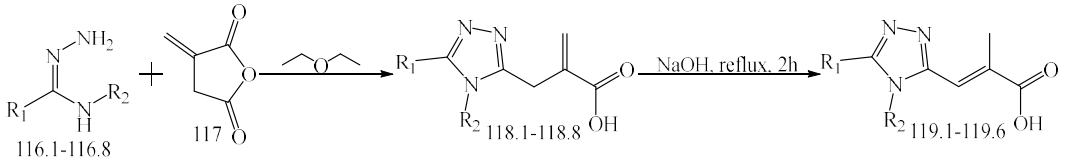


Fig. 28. Scheme of synthesis of 5-(5-(1-methyl-1*H*-pyrrol-3-yl)-1-phenyl-1*H*-pyrazol-3-yl)-1,3,4-oxadiazole-2-thiol derivatives



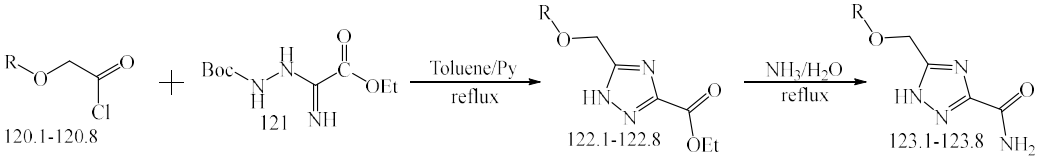
R_1: 116.1, 118.1, 119.1, 116.2, 118.2, 119.2, 116.6, 118.6, 119.6, 116.7, 118.7 = 2-Pyr; 116.3, 118.3, 119.3, 116.8, 118.8 = Ph; 116.4, 118.4, 119.4, 116.5, 118.5, 119.5 = 4-Pyr.
R_2:116.1, 118.1, 119.1 = 2-Pyr; 116.2-116.4, 118.2-118.4, 119.2-119.4 =Ph; 116.5, 118.5, 119.5, 116.6, 118.6, 119.6 = 4-Ph-CH_3; 116.7, 118.7, 116.8, 118.8 = 4-Ph-NO_2

Fig. 29. Scheme of synthesis of potential anthelmintic and anti-inflammatory agents based on 1,2,4-triazole heterocycle

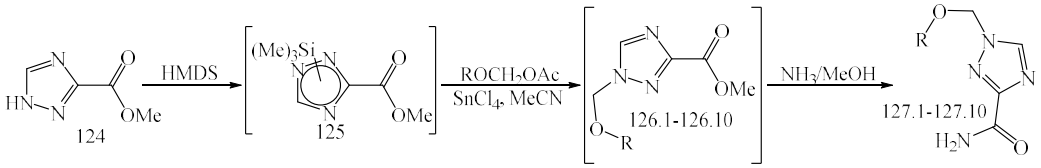
Mikhin and co-authors in their work [80] synthesized two series of deoxyacyclic ribavirin analogues: 5- and 1-alkyl/aryloxymethyl (123.1–123.8, 127.1–127.10) derivatives of 1,2,4-triazole-3-carboxamide, and investigated their ability to exhibit anticancer and antimicrobial activity (Fig. 30). Compounds 123.1–123.8 were obtained by cyclization of the 1,2,4-triazole fragment, derivatives 127.1–127.10 were synthesized by regioselective alkylation of methyl-1,2,4-triazole-3-carboxylate at the N_1 atom (Fig. 30). The results of the anticancer activity study demonstrate that compounds 123.6 and 127.7, which contain n-decyloxymethyl radicals, demonstrated the highest cytostatic and antiproliferative effects against leukemia cell lines (K562 and CCRF-SB). The C_{50} of compound 127.7 in K562 cells was approximately 20-fold lower than that of ribavirin and 4-fold lower than that of cytarabine (Cyt), indicating high efficacy. The new derivatives showed selective cytotoxicity against leukemia cells compared to normal peripheral blood mononuclear cells (PBMC). The results of the antimicrobial activity study demonstrate the absence of this effect in compounds 123.1–123.8, and derivatives 127.9, 127.10 showed bacteriostatic activity only against the gram-positive bacterium *Micrococcus luteus*.

A study by Chinese scientists [81] focused on the development of new anti-TB drugs against the backdrop of the growing global threat posed by multidrug-resistant and extensively drug-resistant strains of *Mycobacterium tuberculosis* (*Mtb*). The authors identified *Mtb* catalase-peroxidase (KatG), a key enzyme in the defense against reactive oxygen species (ROS), as a promising target for new agents. Inhibition of KatG can lead to the accumulation of ROS and bacterial death. Fifteen 1,2,4-triazole derivatives were synthesized by the condensation reaction between substituted aldehydes (aromatic or quinoline) and aminotriazoles (Fig. 31). The reactions were carried out in appropriate solvents (methanol, ethanol or dichloromethane) using catalytic amounts of glacial acetic acid (for compounds 130.1–130.5) or hydrochloric acid (for compounds 130.11–130.15) (Fig. 31). Compound 130.4 demonstrated the strongest anti-*Mtb* activity with an MIC of 2 μg/ml and exhibited a potent concentration- and time-dependent bactericidal effect, completely killing *Mtb* within 48 hours at an MIC of 4. Cytotoxicity studies confirmed the high selectivity of compound 130.4, as evidenced by a high Selectivity Index (SI > 10) against Vero cells. Mechanism of action analysis showed that compound 130.4 binds tightly to the active site of KatG (PDB ID: 1SJ2). In particular, π-π stacking interactions with the KatG heme and the formation of a hydrogen bond with Trp107 were noted, which probably disrupts the catalytic activity of the enzyme. This assumption was confirmed experimentally: compound 130.4 dose-dependently inhibits the KatG enzyme in vitro and causes significant intracellular accumulation of ROS in *Mtb* cells. The accumulation of ROS, in turn, leads to changes in bacterial morphology and damage to cell wall components. Thus, the main anti-*Mtb* effect of compound 130.4 is mediated by inhibition of the KatG enzyme, which provides a new strategy for the development of anti-TB drugs.

Studies by Chinese scientists [82] demonstrate that compound 131 (4-(3-(2-hydroxy-4-methoxyphenyl)-5-(2-hydroxyphenyl)-1*H*-1,2,4-triazol-1-yl) benzenesulfonamide) has significant potential as a neuroprotective and anti-inflammatory agent (Fig. 32). In mouse models with increased peritoneal capillary permeability, compound 131 reduced vascular permeability, indicating its anti-inflammatory effect. In rats and mice with acute ischemic stroke (MCAO model), the drug reduced neurological deficits, reduced brain edema, and normalized biochemical indicators of oxidative stress and inflammation, increasing superoxide dismutase activity and reducing levels of malondialdehyde, TNF-α, and IL-1β. Histological analysis showed that compound 131 reduced morphological damage to neurons and helped preserve cell structure. The drug also protected the integrity of the blood-brain barrier by reducing its permeability, inhibiting the degradation of the endothelial glycocalyx (increased syndecan-1 and decreased HS and HPSE), and regulating tight junctions between cells (increased claudin-5 and decreased MMP-9). Pharmacokinetic data indicate good bioavailability of compound 131, effective penetration across the blood-brain barrier, and a stable half-life. These results demonstrate that compound 131 is a promising neuroprotective agent, the action of which is associated with antioxidant and anti-inflammatory activities, as well as with maintaining the integrity of the blood-brain barrier, which allows it to effectively reduce brain edema and neurodegeneration in acute ischemic stroke. The studies of the Chinese authors make a significant contribution to understanding the potential of 1,2,4-triazole derivatives as therapeutic agents for the treatment of brain disorders.



R: 120.1, 122.1, 123.1= Me; 120.2, 122.2, 123.2= Et; 120.3, 122.3, 123.3= n-Pr; 120.4, 122.4, 123.4= i-Pr; 120.5, 122.5, 123.5= n-Bu; 120.6, 122.6, 123.6= n-$C_{10}H_{21}$; 120.7, 122.7, 123.7= Bn; 120.8, 122.8, 123.8= Ph



R: 126.1, 127.1= Me; 126.2, 127.2= Et; 126.3, 127.3= n-Pr; 126.4, 127.4= i-Pr; 126.5, 127.5= n-Bu; 126.6, 127.6= t-Bu; 126.7, 127.7= n-$C_{10}H_{21}$; 126.8, 127.8= Bn; 126.9, 127.9= cyclopentyl; 126.10, 127.10= cyclohexyl

Fig. 30. Scheme of synthesis of alkyl/aryloxymethyl derivatives of 1,2,4-triazole-3-carboxamides

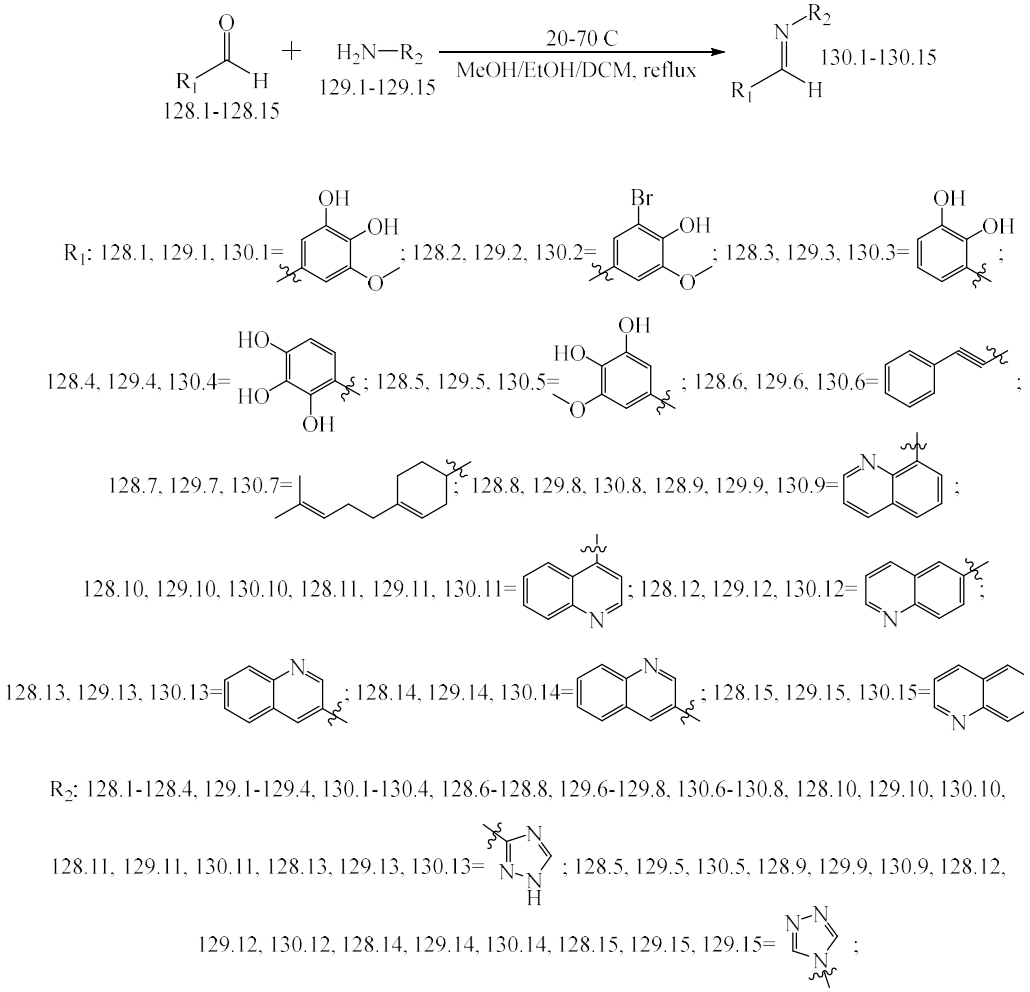


Fig. 31. Scheme of the synthesis of Schiff bases combined with a 1,2,4-triazole heterocycle

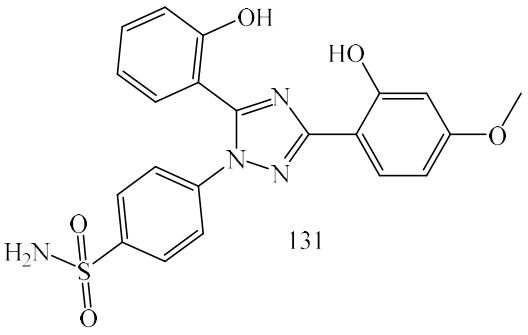


Fig. 32. Structural formula of (4-(3-(2-hydroxy-4-methoxyphenyl)-5-(2-hydroxyphenyl)-1*H*-1,2,4-triazol-1-yl)benzenesulfonamine)

Schiff bases, which feature an azomethine group (-C=N-), have gained considerable popularity among synthetic chemists due to their diverse pharmacological activities, including anticancer activity [83, 84]. For example, [85] reported novel alkylated indolyltriazole Schiff bases that are effective in the treatment of breast cancer. Compound 132 (Fig. 33) showed promising antiproliferative activity against a breast cancer cell line (MCF-7) with an IC_{50} value of 1.18 μM, compared to sorafenib (IC_{50} = 2.13 μM).

Baya and his team [86] investigated the anti-inflammatory effects of 1,2,4-triazole-isoaurone hybrids and found that compound 133 ((*E*)-4-(4-chlorophenyl)-2-(3-(4-((6-methoxy-2-oxobenzofuran-3(2*H*)-ylidene) methyl)phenoxy)propyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one) (Fig. 34) exhibited high inhibitory activity against COX-2 with a high selectivity coefficient (COX-1 IC_{50} = 18.59 μM and COX-2 IC_{50} = 2.6 μM), and also inhibited the release of pro-inflammatory factors, including NO and prostaglandin PGE_2. In addition, it was characterized by low toxicity when studied *in vivo* in a model of ear edema induced by xylene. The anti-inflammatory activity of derivative 133 (41.82%) was dose-dependent and higher than that of celecoxib (31.82%).

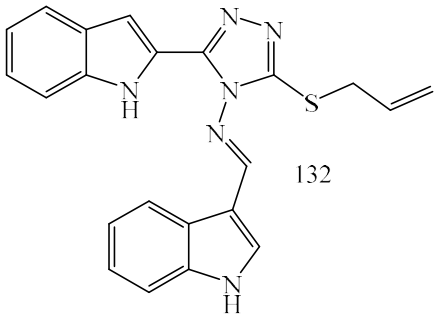
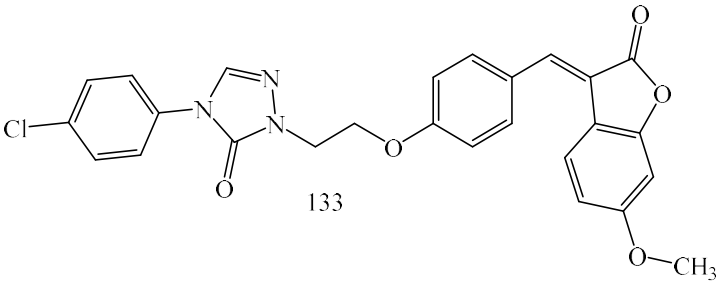


Fig. 33. Structural formula of (E)-N-(3-(allylthio)-5-(1*H*-indol-2-yl)-4*H*-1,2,4-triazol-4-yl)-1-(1*H*-indol-3-yl) methanimine, which exhibits antiproliferative activity



133

Fig. 34. (*E*)-4-(4-chlorophenyl)-2-(2-(4-((6-methoxy-2-oxobenzofuran-3(2*H*)-ylidene)methyl)phenoxy)ethyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one, which exhibits anti-inflammatory activity

[87] developed a series of 1,2,4-triazole-tetrahydroisoquinoline hybrids as potential COX-1/COX-2 inhibitors (Fig. 35). Compounds 134-136 (Fig. 34) showed high anti-inflammatory activity (COX-1 IC_{50} = 2.14–11.95 μM and COX-2 IC_{50} = 0.58–1.27 μM), showing activity comparable to the reference drug celecoxib (COX-1 IC_{50} = 15.18 μM, COX-2 IC_{50} = 0.82 μM), but with a reduced selectivity index. In an *in vivo* test of carrageenan-induced rat paw edema, these three compounds consistently demonstrated higher anti-inflammatory activity than celecoxib. Furthermore, they were highly effective in reducing the expression of pro-inflammatory mediators (PGE2, TNF-α, IL-6) and were much safer for gastric cells compared to indomethacin.

[88] studied the pharmacological activity of 1,2,4-triazole propanoic acids (Fig. 36). Derivatives 137.1 (with two 2-pyridyl substituents), 137.3 and 137.5 (4-pyridyl and phenyl) demonstrated the strongest anti-inflammatory effect, reducing the level of pro-inflammatory cytokines TNF-α and IFN-γ in stimulated MCPCs. The scientists paid special attention to compound 137.5, which, in addition to inhibiting pro-inflammatory factors, contributed to an increase in the level of the anti-inflammatory cytokine IL-10 at low concentrations, which is a favorable profile for combating chronic inflammation. The authors noted that the immunomodulatory effect of the compounds, unlike some NSAIDs, includes inhibition of IFN-γ, which indicates an effect on both innate and adaptive immunity. Compounds 137.1–137.7 had low antibacterial and low anthelmintic activity, while the researchers recorded antimycobacterial activity in five derivatives (137.1–137.3, 137.5, 137.6). The authors concluded that the decrease in the overall biological activity of compounds 137.1–137.7 compared to previously studied methacrylic acid analogues [40] is likely due to the absence of a double bond and branching in the propanoic acid side chain.

A study by a group of Croatian scientists in [89] is devoted to the study of biological activity and computer modelling of new hybrid compounds based on coumarin and 1,2,4-triazole (Fig. 37). The authors synthesized 27 hybrid coumarin-1,2,4-triazole compounds using an efficient one-reactor reaction in a eutectic solvent, which is an environmentally friendly approach. Further research was focused on the antifungal and antibacterial activity of the obtained substances. The results of antifungal screening showed that the synthesized compounds effectively inhibit the growth of mycelium of the phytopathogenic fungi *Sclerotinia sclerotiorum* and *Fusarium oxysporum*, while their activity against *Macrophomina phaseolina* and *Fusarium culmorum* was significantly lower. Structure-activity relationship analysis revealed that compounds in which the 1,2,4-triazole ring is attached to the coumarin nucleus at the C7 position and a methyl group is present at the C4 position demonstrate the highest efficacy. In particular, compound 139.10, which contains a p-tolyl substituent, showed the strongest inhibitory effect against three of the four fungi tested, reaching 76% inhibition of *S. sclerotiorum* growth. At the same time, none of the tested compounds showed antibacterial activity against pathogenic (*Pseudomonas syringae*, *Rhodococcus fascians*) or beneficial soil (*Bacillus mycoides*, *Bradhyrhizobium japonicum*) bacteria. Computational methods were applied to gain a deeper understanding of the mechanisms of action. QSAR modelling revealed key structural features that influence antifungal activity: the presence of a tertiary sp^2-hybridized carbon atom, the presence of an ether group, and the optimal distribution of electronegative atoms in the molecule. Molecular docking confirmed that the target enzyme for the studied compounds is lanosterol-14α-demethylase (LDM), which is key for ergosterol biosynthesis in fungi. The docking results showed that the compounds effectively bind to the active site of the enzyme, interacting with the iron ion in the heme cofactor, which is consistent with experimental data. The most active compounds, in particular 139.10, demonstrated binding energies similar to the commercial fungicide difenoconazole. Thus, the work of Croatian scientists makes a significant contribution to the field of agrochemistry, presenting the class of hybrid coumarin-1,2,4-triazole compounds as a promising basis for the development of new antifungal drugs. An integrated approach combining organic synthesis, biological screening and computer modelling allowed not only to identify highly active compounds, but also to establish important “structure-activity” relationships, which paves the way for further targeted structure optimization.

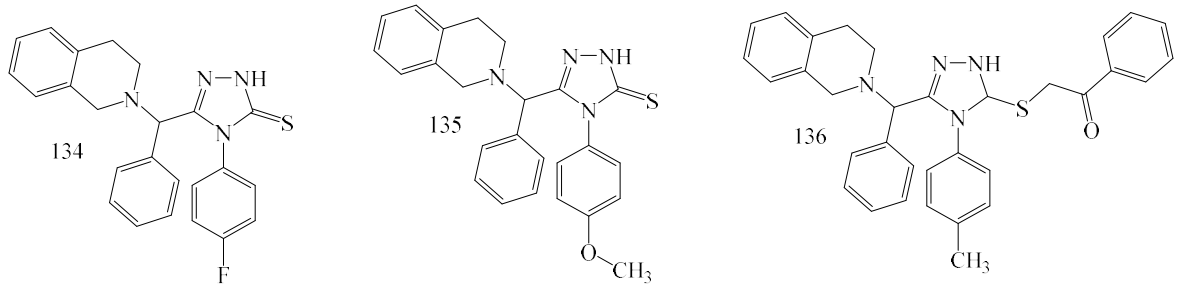
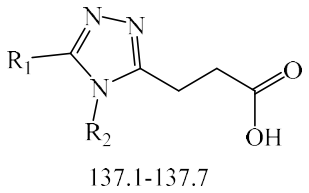


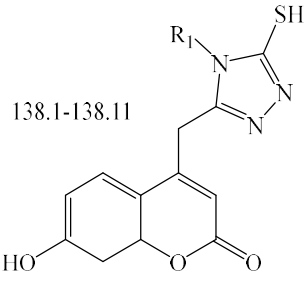
Fig. 35. Structural formulas of 1,2,4-triazole-tetrahydroisoquinoline derivatives



137.1-137.7

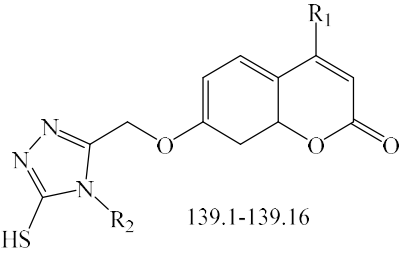
R_1: 137.1-137.4=2-Pyr; 137.5, 137.6=4-Pyr; 137.7=Ph
R_2: 137.1=2-Pyr; 137.2, 137.5, 137.7=Ph; 137.3, 137.6=4-Ph-CH_3; 137.4=4-Ph-NO_2

Fig. 36. Structural formula of the studied 1,2,4-triazole propanoic acids



138.1-138.11

R_1: 138.1= Me;
138.2= allyl;
138.3= Bn;
138.4= 3-OMePh;
138.5= 3-ClPh;
138.6= 4-ClPh;
138.7= 4-BrPh;
138.8= 4-OMePh;
138.9= *p*-tolyl;
138.10= Et;
138.11= Ph;



139.1-139.16

R_1: a-l= Me; m-p=h;
R_2: 139.1= Me;
139.2= allyl;
139.3, 139.13= Bn;
139.4= 3-OMePh;
139.5= 3-ClPh;
139.6= 3-BrPh;
139.7, 139.16= 4-FPh;
139.8= 1-naphthyl;
139.9, 139.14= 4-OMePh;
139.10= *p*-tolyl;
139.11= Et;
139.12= Ph;
139.15= 4-ClPh;

Fig. 37. Structural formulas of coumarin-1,2,4-triazole derivatives

5. Discussion of research results

The analysis of the literature indicates that the 1,2,4-triazole core is a stable and functionally flexible pharmacophore system [90–92], the modification of which allows for targeted influence on the biological properties of compounds [93–95]. The most significant result of the review is the establishment of a relationship between the type of structural modification and the spectrum of pharmacological activity, which is traced in the analyzed works [96–98].

A significant number of studies are devoted to transformations at the thiol fragment, in particular S-alkylation reactions [31, 32, 41]. The analyzed works of foreign authors [6, 9] show that the introduction of alkyl or functionalized substituents at the sulfur atom is accompanied by an increase in antimicrobial and antifungal activity, which is consistent with the data of domestic studies [31, 41, 44]. At the same time, some publications [47, 60] noted a decrease in the selectivity of action with an increase in the size of the substituent, which indicates the need to optimize the spatial parameters of the molecule.

Compared to the S-modification, substitution at the nitrogen atoms of the 1,2,4-triazole ring has been studied less systematically, but foreign publications have noted its positive effect on the pharmacokinetic characteristics of compounds [75–78], in particular solubility and bioavailability. The results of Ukrainian authors [72–74] generally confirm these trends, but the difference in the biological testing methods used complicates a direct comparison of the efficacy of the compounds.

A separate group is made up of studies devoted to the creation of hybrid pharmaceutical systems in which the 1,2,4-triazole fragment is combined with other biologically active heterocycles [1, 5, 19]. In the works of scientific groups from the EU, the USA and Asia [25, 39, 58] this approach is considered promising for obtaining compounds with polypharmacological action. Domestic studies [30, 63, 73] in this direction are fragmentary, which indicates the presence of an insufficiently filled scientific niche.

Analysis of the results of various studies [98–102] demonstrates that discrepancies in the pharmacological activity of structurally similar compounds are most often due to differences in synthesis methods, sample purity, biological models and activity assessment criteria. This confirms the feasibility of unifying approaches to the study of 1,2,4-triazole derivatives.

The obtained generalizations allow us to propose further research directions, in particular, the systematic study of structure–activity relationships with the involvement of computer modelling methods and the Quality by Design concept for predicting the properties of potential drug candidates.

The practical significance of the presented review lies in the possibility of using the results for rational planning of the synthesis of new 1,2,4-triazole derivatives and selecting the most promising areas of preclinical research.

The limitation of this study is its review nature, which implies dependence on the availability and quality of published literature data, as well as the lack of unified standardized methods for assessing biological activity in the analyzed works.

The prospects for further research are associated with the integration of synthetic, pharmacological and computer approaches to create structurally optimized 1,2,4-triazole derivatives with predicted pharmacological properties.

6. Conclusions

As a result of the review and critical analysis of modern literary sources, data on the chemical modification of 1,2,4-triazole derivatives and its effect on the pharmacological properties of the compounds were summarized, which fully corresponds to the goal of the study.

It has been established that the 1,2,4-triazole core is a universal pharmacophore platform, the structural flexibility of which allows for targeted modification of biological activity by functionalization of various reactive centers of the molecule. The most systematically studied direction is modification at the thiol fragment, in particular S-alkylation reactions, which in most of the analyzed works are associated with increased antimicrobial, antifungal and antitumor activity.

It has been shown that *N*-substitution and the formation of hybrid structures based on 1,2,4-triazole are promising approaches to optimizing pharmacokinetic characteristics and expanding the spectrum of biological action of compounds. However, a comparative analysis of domestic and foreign studies revealed the lack of unified approaches to assessing biological activity, which complicates direct comparison of results and indicates the need for standardization of methodologies.

The scientific novelty of the review consists in the systematization of modern directions of chemical modification of 1,2,4-triazole derivatives from the standpoint of their pharmacological feasibility, as well as in the identification of insufficiently researched aspects, in particular the creation of hybrid pharmaceutical systems and the application of rational drug design approaches.

The practical significance of the obtained generalizations lies in the possibility of their use to justify the choice of directions for the synthesis of new potentially biologically active compounds, as well as for planning preclinical studies in the field of pharmaceutical and medicinal chemistry.

Thus, the results of the review study create a theoretical basis for further targeted experimental work aimed at the development of new drug candidates based on 1,2,4-triazole derivatives with predicted pharmacological properties.

Conflict of interest

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this article.

Funding

The work was carried out within the framework of the research project «Creation of 1,2,4-triazole derivatives with polypharmacological activity for the needs of military medicine and combat victims» with registration number 0126U001480 and This study was funded by European Union-NextGenerationEU, through the National Recovery and Resilience Plan of the Republic of Bulgaria, project № BG-RRP-2.004-0009-C02.

Data availability

Manuscript has associated data in a data repository.

Use of artificial intelligence

The authors confirm that they used artificial intelligence technologies in the creation of the presented work, namely the ChatGPT model, version GPT-5.2 was used in the translation of the research publications from English to Ukrainian and formatting the list of used literature. The use of AI did not in any way affect the conclusions of the study.

Acknowledgments

The authors express their sincere gratitude to the Armed Forces of Ukraine, the staff of the Department of Physicocolloid and Analytical Chemistry of the Zaporizhia State Medical and Pharmaceutical University for fruitful cooperation, and to the university management for support and assistance in organizing scientific and research work.

Authors' contributions

Dmytro Dovbnia: Conceptualization, Methodology, Investigation, Writing – original draft, Visualization; **Andrii Kaplaushenko:** Conceptualization, Supervision, Project administration, Writing – review & editing; **Oleksandr Panasenko:** Validation, Resources, Supervision; **Mariia Panasenko:** Investigation, Data Curation; **Volodymyr Salionov:** Investigation, Formal analysis, Writing – review & editing; **Tetiana Ihnatova:** Investigation, Data Curation; **Kaloyan Georgiev:** Investigation, Formal analysis, Validation; **Iliya Slavov:** Investigation, Formal analysis, Validation.

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Received 11.02.2026
Received in revised form 05.03.2026
Accepted 08.04.2026
Published 30.04.2026

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