Review Article

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Prospects For the Search For New Biologically Active Compounds Among the Derivatives of the Heterocyclic System of 1,2,4-Triazole

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ABSTRACT

The purpose of this literature review was to systematize data from studies of the biological activity of 1,2,4-triazole derivatives with substituents in positions 4 and 5. The authors set the task of forming an idea of current directions in the selection of substitutions for 1,2,4-triazole based on research.

As a result of the study, 75 literature sources were analyzed. This made it possible to form a further vector in terms of searching for biologically active structures among 1,2,4-triazole derivatives. The review develops a modern approach to the search for biologically active substances among 1,2,4-triazole derivatives. Systematized data on the nature of substituents in the core of 1,2,4-triazole, which affect a specific type of activity.

The search material was selected over the past decade with the highest number of citations at the time of literature analysis.

Keywords: Biological activity, bibliosemantic method, organic synthesis, 1,2,4-triazole

1. Introduction

Modern medical and pharmaceutical practice is based on the active use of drugs of synthetic origin. The arsenal of biologically active structures includes derivatives of heterocyclic systems, namely furan, pyrrole, pyrazole, pyridine, pyrimidine, purine and many others. Particular attention is drawn to such structures with low rate toxicity and high rate pharmacological effect. Undoubtedly, the starting heterocyclic substance must have several reactive centers for the construction of the most effective pharmacophores.

Studies by scientists from around the world point to the prospect of using derivatives of the heterocyclic system 1,2,4-triazole as models for new biologically active substances (further BAS)

Researchers from Ukraine are also looking for promising pharmacophores among 1,2,4-triazole derivatives. This is confirmed by articles [1-10]. Scientists are engaged in the synthesis [1-6], study of biological [1, 2, 5] action and analysis [7-10] of synthesized compounds based on 1,2,4-triazole nucleus.

The purpose of this review was to summarize data on the biological activity of 1,2,4-triazole derivatives and to form a general idea of the effect of substituents on the biological activity of the above heterocyclic system.

2. Antifungal activity of 1,2,4-triazole derivatives.

Derivatives of the heterocyclic system of 1,2,4-triazole have excellent antifungal action. This is evidenced by the use of drugs Itraconazole, Fluconazole in the world medical practice. The works of scientists [11-20] confirm this. Systematizing the literature, we can conclude that the substituents adamantane, 5-amino-2-hydroxybenzoate, 4-fluoro-2-phenoxyphenyl, 2-bromophenyl and hydroxybenzylidene fragment in the 5 position of the heterocyclic system of 1,2,4-triazole lead to an increase in antifungal action. It should be noted that the best antifungal action is observed in hydrazides of 2-((5-substituted)-1,2,4-triazol-3-ylthio)-alkyl(aryl, hetaryl) carboxylic acids (fig. 1). The results considered in [11-19] indicate inhibition *P. cubensis, A. niger, S. fuligenea, F. oxysporum, X. Axonopodis, C. cassiicola* and other strains of pathogenic fungi.

Among the analyzed literature sources, the authors note high rates of antifungal activity of 99 molecules. Of these, 12 are recommended for further in-depth study (fig. 2)

3.Antimicrobial activity of 1,2,4-triazole derivatives.

Medicine today is increasingly faced with the problem of antimicrobial drugs resistance. This emphasizes the need for the introduction of new BAS molecules with antimicrobial properties.

The most important aspect in the creation of such drugs is the question of selectivity of the action of the molecule on the pathogenic flora. Wherein it is necessary that the BAS has low toxicity. 1,2,4-triazoles have this set of properties. The antimicrobial action of triazoles is described in [15, 21-30]. Analysis of the literature indicates that the molecules have

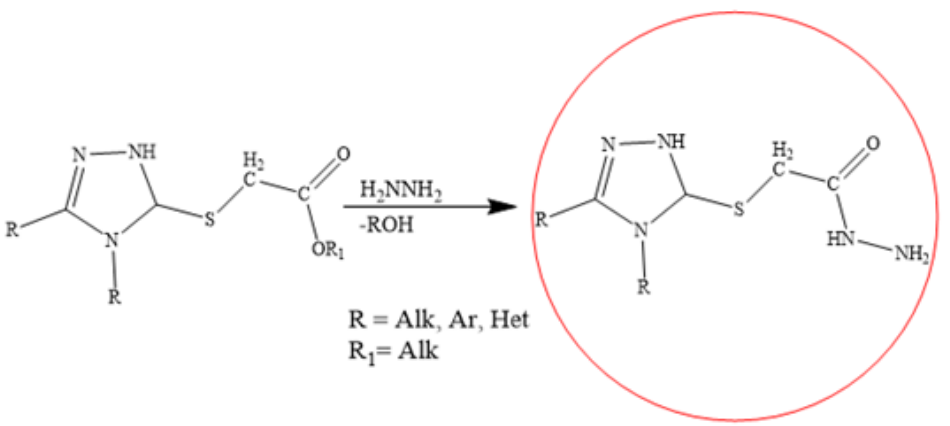

Figure 1. Structures based on 1,2,4-triazoles with the best antifungal effect.

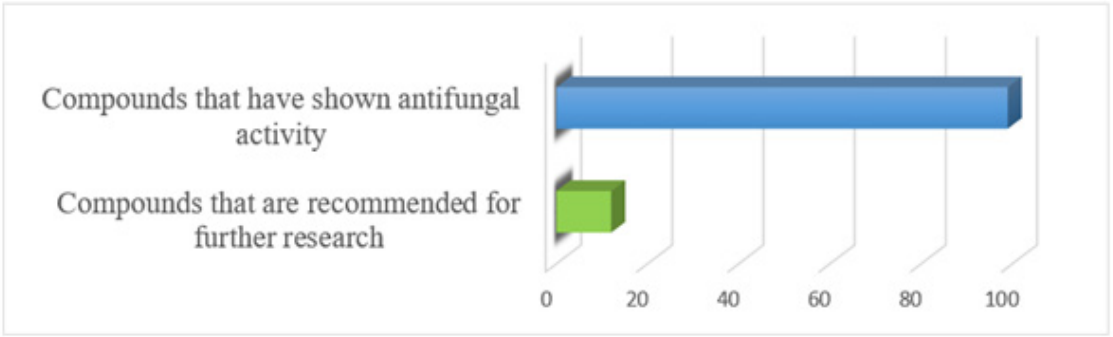

Figure 2. The ratio of active molecules that have shown antifungal activity and are recommended for further studies.

a broad spectrum of antimicrobial activity and low toxicity. Herewith it can be concluded that the best indicators of biological action are inherent in molecules with an unsubstituted amino group in the 4th position of the nucleus of 1,2,4-triazole cycle (fig. 3). Also as highly effective antimicrobial BAS have acted Schiff bases based on 1,2,4-triazole matrix (fig. 3). The vast majority of compounds published in scientific papers [21-30] had low rates of acute toxicity. Also 1,2,4-triazoles with methoxyphenyl moiety had a pronounced antimicrobial effect.

Data from literature sources [21-30] allowed us to assess the prospect of searching for antimicrobial agents among 1,2,4-triazole derivatives, namely: 74 new compounds were synthesized and studied (fig. 4), recommended for in-depth studies of 9 compounds (fig. 4).

4. Anti-cancer and anti-tumor activity of 1,2,4-triazole derivatives.

One of the most important pharmacological effects of 1,2,4-triazoles is anti-tumor and anti-cancer action. Based on these types of activity, the drugs Letrazole and Anastrazole were created, which are successfully used in modern medicine.

On the example of researchers [31-34] we can conclude that much attention is paid to research by molecular docking. This makes it possible to narrow the range of target compounds and to predict the desired biological effect with great accuracy. But the relevance of creating compounds with anti-cancer activity encourages us to move on to the practical part as soon as possible. Therefore in studies [32, 35-40] described the anti-cancer and anti-tumor activities of already synthesized compounds.

Analysis of literature data [31-40] shows that scientists can recommend about 10% of active molecules for further research.

Preferable the pronuntsed activity is inherent in the combined forms of 1,2,4-triazoles wit and nitrile radical. In our opinion, one of the simplest ways to combine 1,2,4-triazole derivatives with a nitrile radical is the chloroacetonitrile alkylation reaction. The scheme of receipt is shown in fig. 5.

According to the results of molecular docking, 67 biologically active molecules were identified, among which 10 compounds require special attention. Studies on live cultures indicate the prospects of 127 compounds, with 9 biologically active compounds isolated as leading compounds (fig. 6).

5. Cytoprotective activity of 1,2,4-triazoles.

Separately to the ability to proliferate, 1,2,4-triazole derivatives are able to have a cytoprotective effect. Cytoprotection is manifested in antioxidant [41-45], antihypoxic [46-50], hepatoprotective [51-55], neuroprotective [56-60] action. In particular, scientists [60] conducted an extensive review of 64 compounds that can find their application in the treatment of Alzheimer's disease.

In terms of the fundamental work of the authors, it can be concluded that the most pronounced compounds with electron-donor fragments possess cytoprotection. Water-soluble compounds were in most cases more active than water-insoluble analogues. In our opinion the best cytoprotectors are salts of 2-(5-R-4-R-1,2,4-triazol-3-ylthio)acetic acids with organic(inorganic) cations containing Nitrogen heteroatom (fig. 7).

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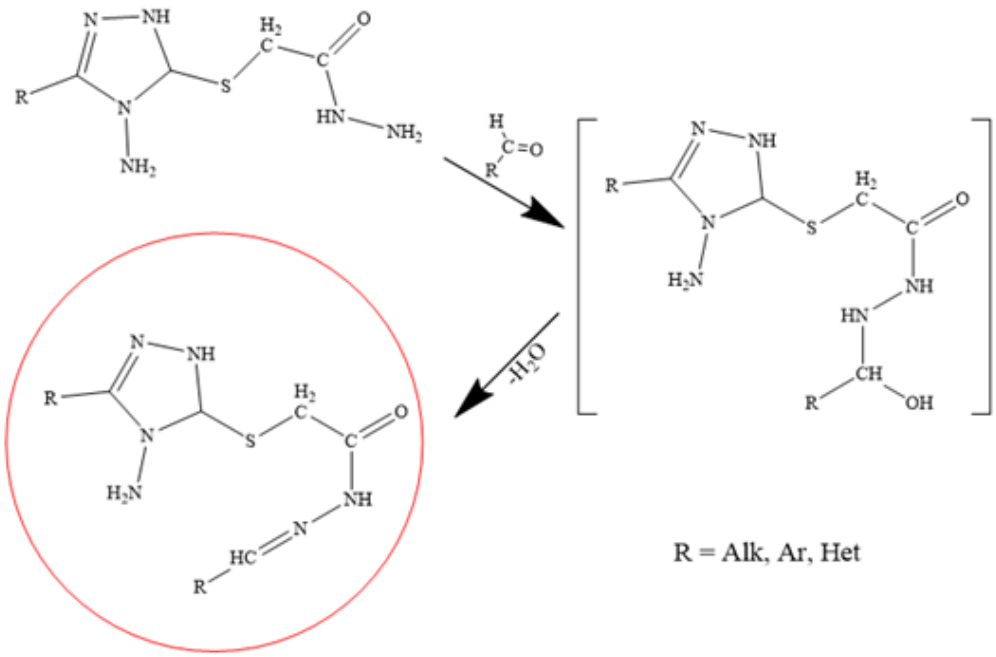

Figure 3. Structures based on 1,2,4-triazoles with the best antimicrobial effect.

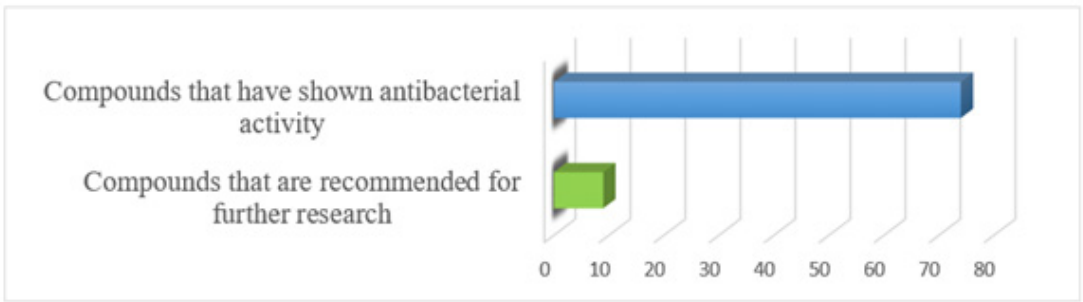

Figure 4. The ratio of active molecules of 1,2,4-triazole that have shown antimicrobial activity and are recommended for further studies.

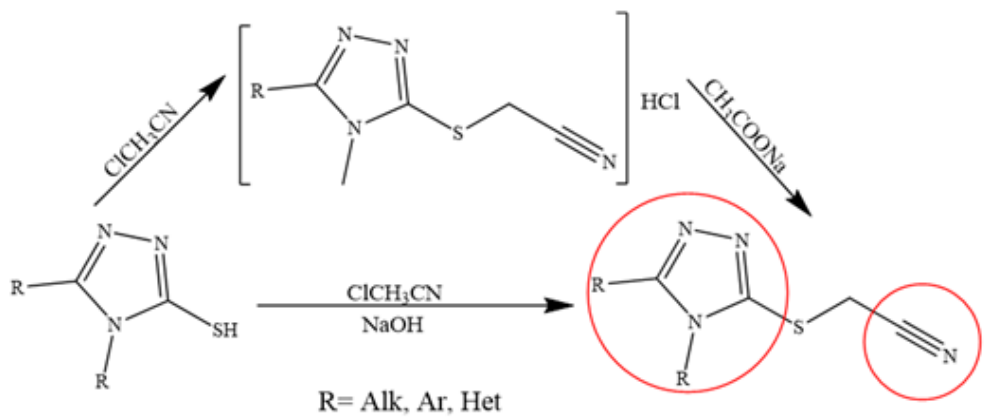

Figure 5. The simplest combination of 1,2,4-triazole derivatives with a nitrile radical to search for new anticancer and antitumor agents.

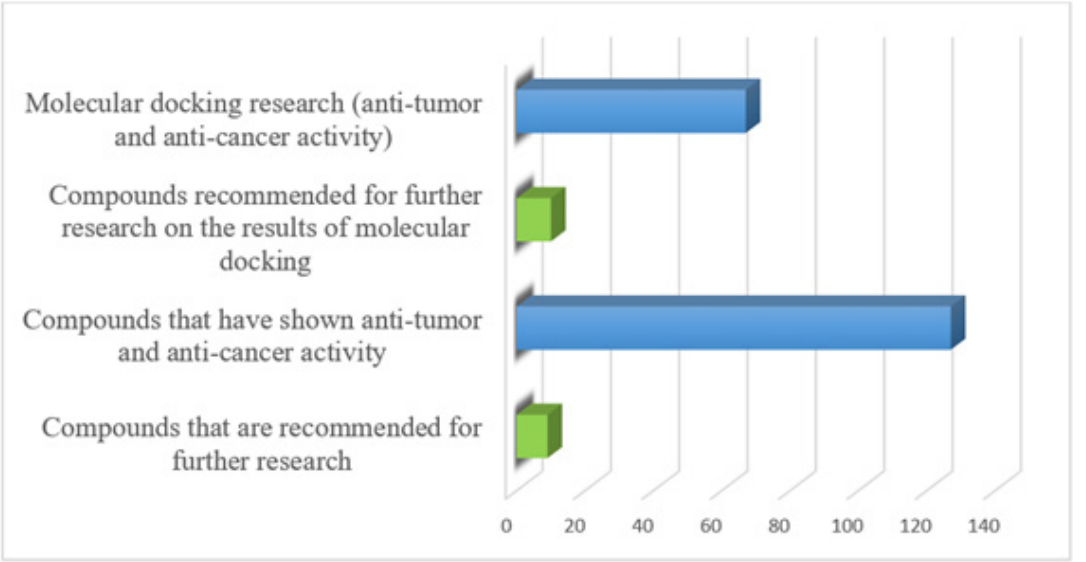

Figure 6. The ratio of active molecules that have shown anti-inflammatory and anti-cancer activity and are recommended for further studies.

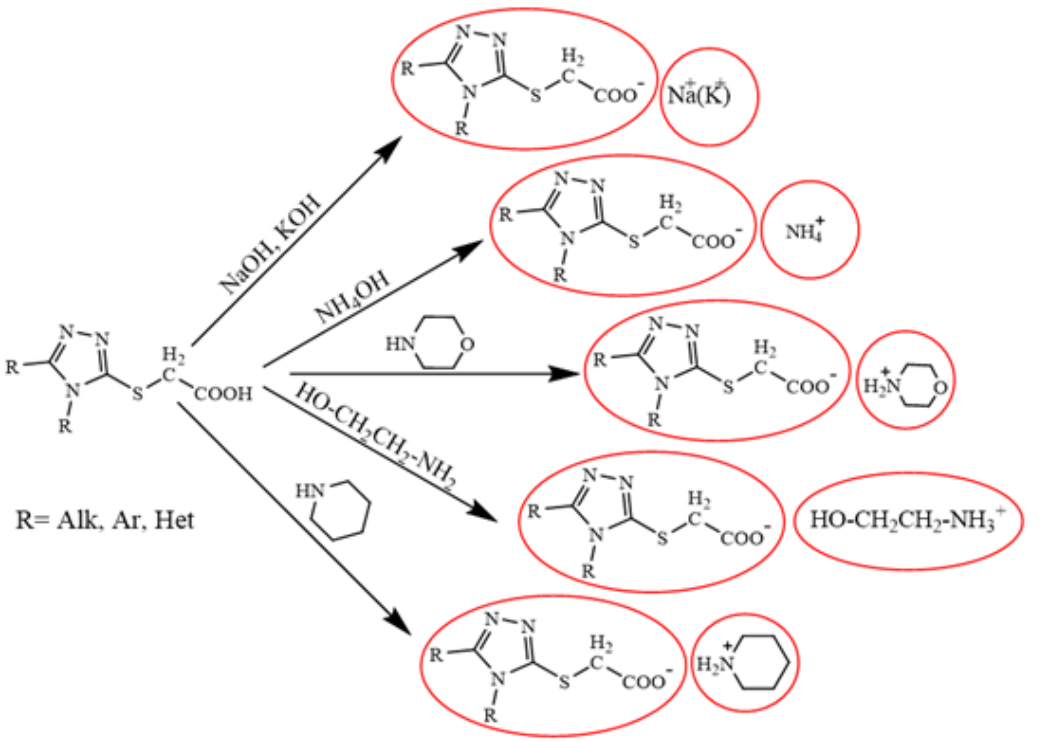

Figure 7. Examples of structures based on 1,2,4-triazoles with the best cytoprotective effect

In the analyzed works [41-60], 40 potential antioxidants were identified, among which the authors separately Note 4 molecules; 44 compounds with antihypoxic activity were identified, of which 5 are recommended for further study. 106 potential neuroprotectors were identified, of which 7 attract special attention of scientists. 54 hepatoprotectors were found, of which 7 were the most active. Comparative results are shown in Fig.8.

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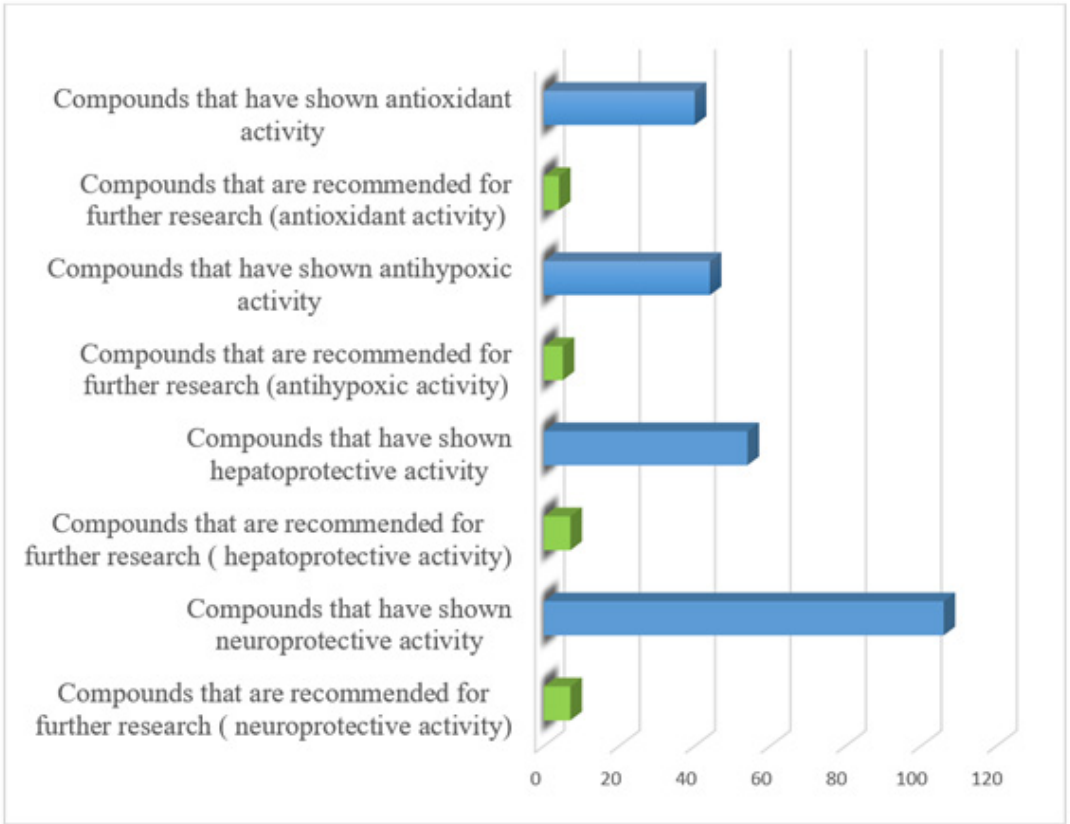

Figure 8. Ehe ratio of active molecules of 1,2,4-triazole, which have a cytoprotective effect (antioxidant, antihypoxic, neuroprotective, hepatoprotective effect) and are recommended for further studies.

6. Other types of biological activity.

According to the studied literature sources [61, 62] derivatives of 1,2,4-triazole are able to show actoprotective effect (today, this is an actual issue, because due to the COVID-19 pandemic, one of the consequences of the disease is excessive fatigue).

1,2,4-Triazole derivatives can be used as effective diuretics. The works [63-65] evidence this. The molecules recommended by the authors can be considered by the authors as remedy that increases the excretory function of the kidneys.

Modified 1,2,4-triazole molecules can be used in diabetic conditions because they are able to show hypolipidemic action [66-70] and hypoglycemic action.

It is also possible to intensify the effect on a specific receptor (epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR), γ-Aminobutyric acid type A ($GABA_A$) receptors, CB1 Cannabinoid Receptor, Liver X Receptor (LXR)) with the help of modern methods of computer modeling of BAS molecules. An example is the work of scientists [70-75].

Based on the results of the analysis, it was found that two literature sources describe the actoprotective activity of 22 compounds, 5 of which the authors proposed to study in more detail. Diuretic activity was found in 50 compounds, 3 of which were the most active. 44 compounds have hypolipidemic activity and 8 are recommended.the ability to influence EGFR, VEGFR, GABAA, CB1, and LXR receptors is inherent in 85 compounds, and 3 compounds attracted special attention of the authors. The ratio of the number of active compounds recommended by the authors is shown in Fig. 9.

7.Conclusions.

Among the analyzed literature sources, 806 active molecules were identified that have antifungal, antimicrobial, antitumor and anti-cancer, antioxidant, antihypoxic, neuroprotective, hepatoprotective, diuretic, actoprotective, hypolipidemic effects and

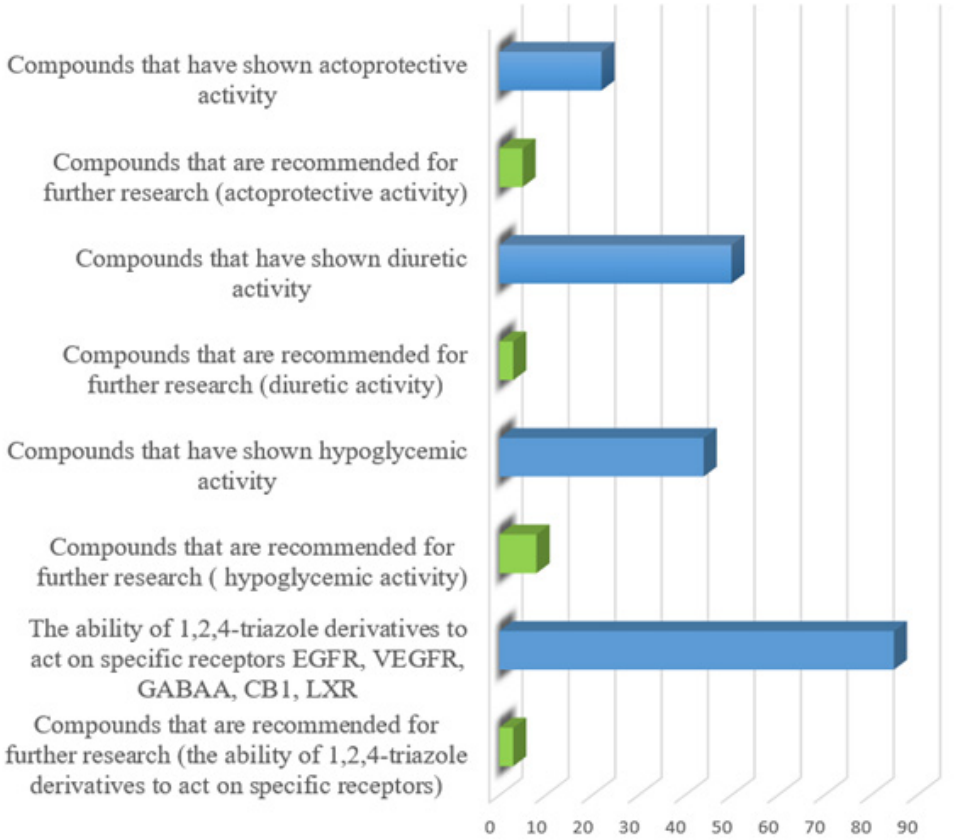

Figure 9. The ratio of active molecules of 1,2,4-triazole, which have actoprotective, diuretic, lipid-lowering effects, have a receptor effect and are recommended for further studies.

the ability to influence EGFR, VEGFR, GABAA, CB1, LXR receptors. Among biologically active molecules, the authors especially note 82. the ratio of the number of literature sources to the biologically active 1,2,4-triazoles found is shown in the comparative graph in Fig. 10

The 1,2,4-triazole nucleus is a multifunctional matrix for the creation of new BAS, which may differ low rates of acute toxicity. Due to the high reactivity of thio- and aminotriazoles, it is possible to create molecules for targeted exposure to a target receptor group or a specific receptor.

Widely studied molecules of 3-thio-1,2,4-triazoles having substituents at the ^{4}N and ^{5}N positions. However, in our opinion, it is expedient to emphasize the combination of two heterocyclic triazole systems in one BAS molecule and to continue the search for biologically active agents on the di-triazole matrix.

In this literature review the main directions of biological researches among 1,2,4-triazole derivatives are collected. From the carried out review we can draw the following conclusion:

At the first stage of research, it is expedient to carry out molecular docking and to establish theoretical influence on oxidative processes of cells, tumors and cancers diseases. Make computer calculations of hepatoprotective, diuretic, actoprotective, hypolipidemic and hypoglycemic action

In vitro to make research the antioxidant effect, antimicrobial and antifungal action.

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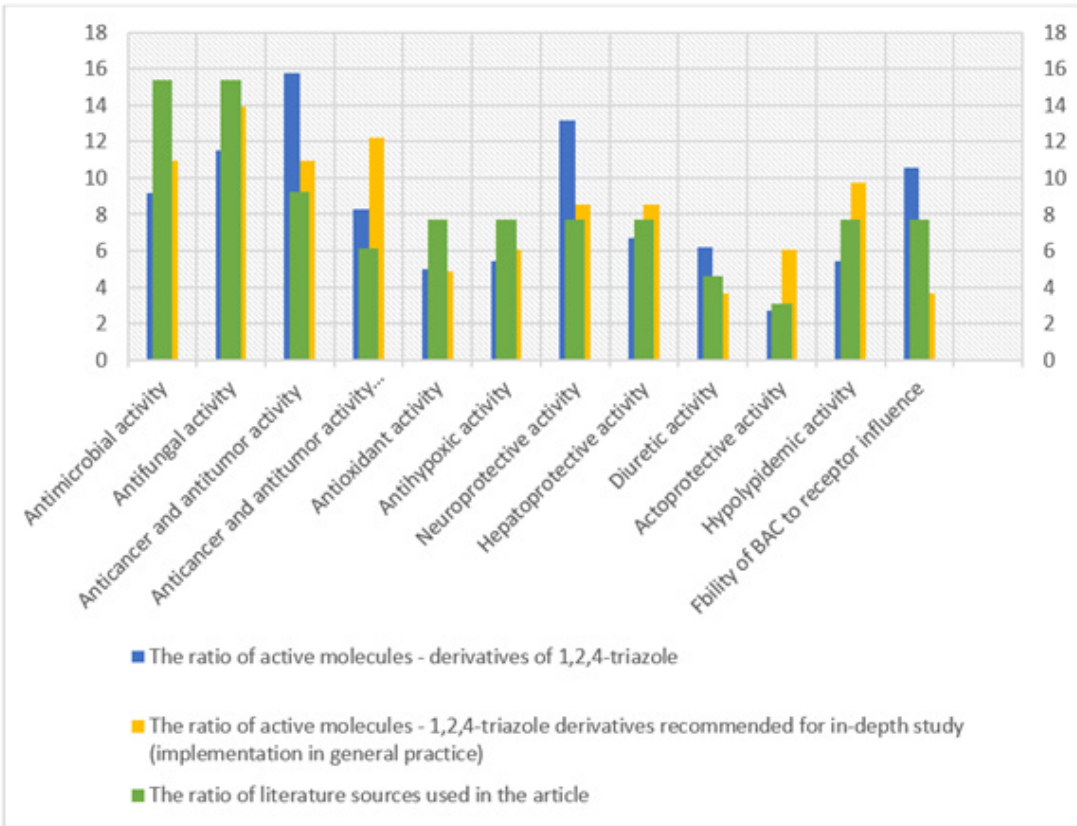

Figure 10. Percentage of analyzed literature sources to found and recommended biologically active molecules

Conflict of interest

The authors declare no conflict of interest.

Author contributions

Conception: Yu. S.; Design: A. K., N. N.; Supervision: Yu. S; Resources: L. O; Analysis and/or interpretation: Yu. S, F. D., B. G.; Literature search: Yu. S., A. K., N. N., L. O., F. D., B. G.; Writing manuscript: Yu. S.; Critical review: Yu. S., A. K.

References

1. Dovbnya, D., Kaplaushenko, A., Frolova, Y., & Pruglo, E. (2022). Synthesis and antioxidant properties of new (2,4- and 3,4-dimethoxyphenyl)-1,2,4-triazoles. *Pharmacia*, *69*(1), 135-142. doi: 10.3897/pharmacia.69.e74107
2. Frolova, Y., Kaplaushenko, A., & Nagornaya, N. (2020). Design, synthesis, antimicrobial and antifungal activities of new 1,2,4-triazole derivatives containing 1*H*-tetrazole moiety. *Journal of Faculty of Pharmacy of Ankara University*, *44*(1), 70-88.
3. Safonov, A. method of synthesis novel n'-substituted-2-((5-(thiophen-2-ylmethyl)-4h-1, 2, 4-triazol-3-yl) thio) acetohydrazides. *ankara* üniversitesi *eczacılık fakültesi dergisi, 44*(2), 242-252.
4. Safonov, A. A. Microwave synthesis of new 3-(alkylthio)-5-(thiophen2-ylmethyl)-1, 2, 4-triazol-4-amines. *Ankara Üniversitesi Eczacılık Fakültesi Dergisi*, *44*(1), 89-98.
5. Samelyuk, Y. G., & Kaplaushenko, A. G. (2014). Synthesis of 3-alkylthio (sulfo)-1, 2, 4-triazoles, Containing methoxyphenyl substituents at C5atoms, Their antipyretic activity, Propensity to adsorption and acute toxicity. *Journal of Chemical and Pharmaceutical Research*, *6*(5), 1117-1121.
6. Safonov, A., Panasenko, O., & Knysh, Y. (2017). Synthesis, physical and chemical properties of 2-((4-(R-amino)-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-3-yl)thio)acetic acids salts. *Current Issues In Pharmacy And Medicine: Science And Practice, 0*(3). doi: 10.14739/2409-2932.2017.3.112751
7. Shcherbyna, R., Parchenko, V., Varynskyi, B., & Kaplaushenko, A. (2019). The development of HPLC-DAD method for determination of active pharmaceutical ingredient in the potassium 2-((4-amino-5-(morpholinomethyl)-4H-1, 2, 4-triazol-3-yl) thio) acetate substance. *Current Issues In Pharmacy And Medical Sciences*, *32*(1), 5-9.

8. Varynskyi, B., & Kaplaushenko, A. (2019). The Force Degradation Study of The Morpholinium 2-((4-(2-Methoxyphenyl)-5-(Pyridin-4-YL)-4H-1,2,4-Triazol-3-YL)Thio) Acetate. *Indonesian Journal of Pharmacy*, *30*(1), 25.
9. Varynskyi, B., & Kaplaushenko, A. (2020). Metabolism study of morpholinium 2-((4-(2-methoxyphenyl)-5-(pyridin-4-yl)-4-1,2,4-triazole-3-yl)thio) acetate. *Current Issues in Pharmacy and Medical Sciences*, *33*(2), 72-75.
10. Varynsky, B. O., Parchenko, V. V., Knysh, E. H., Panasenko, O. Y., & Kaplaushenko, A. H. (2017). Development and validation method for determination of the active ingredient of the drug" a vesstym" in the poultry eggs. *Azerbaijan Pharmaceutical and Pharmacotherapy Journal*, *17*(2), 10-17.
11. Joshi, R., Kumari, A., Singh, K., Mishra, H., & Pokharia, S. (2020). Triorganotin (IV) complexes of Schiff base derived from 1, 2, 4-triazole moiety: Synthesis, spectroscopic investigation, DFT studies, antifungal activity and molecular docking studies. *Journal of Molecular Structure*, *1206*, 127639.
12. Zoidis, G., Kritsi, E., Lecinska, P., Ivanov, M., Zoumpoulakis, P., Sokovic, M., & Catto, M. (2021). The triazole ring as a privileged scaffold for putative antifungals: Synthesis and evaluation of a series of new analogues. *ChemMedChem*, *16*(1), 134-144.
13. Pagniez, F., Lebouvier, N., Na, Y. M., Ourliac-Garnier, I., Picot, C., Le Borgne, M., & Le Pape, P. (2020). Biological exploration of a novel 1, 2, 4-triazole-indole hybrid molecule as antifungal agent. *Journal of enzyme inhibition and medicinal chemistry*, *35*(1), 398-403.
14. Dhanavath, R., Dharavath, R., Kothula, D., Bitla, S., Yaku, G., Birdaraju, S., ... & Atcha, K. R. (2022). Synthesis and Biological Evaluation of Novel 2-Arylquinoline-3-Fused Thiazolo [2, 3-c] 1, 2, 4-Triazole Heterocycles as Potential Antiproliferative and Antimicrobial Agents. *Journal of Heterocyclic Chemistry*.
15. Ardón-Muñoz, L. G., & Bolliger, J. L. (2022). Synthesis of Benzo [4, 5] thiazolo [2, 3-c][1, 2, 4] triazole Derivatives via CH Bond Functionalization of Disulfide Intermediates. *Molecules*, *27*(5), 1464.
16. Ahuja, R., Sidhu, A., Bala, A., Arora, D., & Sharma, P. (2020). Structure based approach for twin-enzyme targeted benzimidazolyl-1, 2, 4-triazole molecular hybrids as antifungal agents. *Arabian Journal of Chemistry*, *13*(6), 5832-5848.
17. Safonov, A. A., & Nevmyvaka, A. V. (2020). A study of antimicrobial and antifungal activity of 2-((5-(2-bromophenyl)-4-substituted-4H-1, 2, 4-triazol-3-yl) thio) acetates.
18. Goyal, R., Sidhu, A., & Sharma, A. B. (2022). 1, 2, 4-Triazolyl functionalized allyl sulfide with antifungal potential for the control of Fusarium fujikuroi causing foot rot of rice. *European Journal of Plant Pathology*, 1-9.
19. Ayyash, A. N. (2020, December). A new [1, 2, 4] triazolo [3, 4-B][1, 3, 4] thiadiazepine derivatives: Synthesis and antimicrobial studies. In *AIP Conference Proceedings* (Vol. 2290, No. 1, p. 030040). AIP Publishing LLC.
20. Tratrat, C. (2020). 1, 2, 4-Triazole: A privileged scaffold for the development of potent antifungal agents-a brief review. *Current Topics in Medicinal Chemistry*, *20*(24), 2235-2258.
21. Chehrouri, M., Othman, A. A., Moreno-Cabrerizo, C., Gholinejad, M., & Sansano, J. M. (2020). Synthesis of 5-heptadecyl-and 5-heptadec-8-enyl substituted 4-amino-1, 2, 4-triazole-3-thiol and 1, 3, 4-oxadiazole-2-thione from (Z)-octadec-9-enoic acid: preparation of Palladium (II) complexes and evaluation of their antimicrobial activity. *Monatshefte für Chemie-Chemical Monthly*, *151*(2), 173-180.
22. Elkanzi, N. A. A., & Hrichi, H. (2020). Design and Evaluation of Antimicrobial Activity of New Pyrazole, 1, 2, 4-Triazole, and 1, 3, 4-Thiadiazol Derivatives Bearing 1, 4-Dihydroquinoxaline Moiety. *Russian Journal of Bioorganic Chemistry*, *46*(5), 715-725.
23. Guzeldemirci, N. U., Satana, D., & Kucukbasmaci, O. (2020). Synthesis and antimicrobial activity evaluation of new hydrazide-hydrazones derived from 1, 2, 4-triazole. *Journal of the Faculty of Pharmacy of Istanbul University*, *50*(1), 49-54.
24. Venugopala, K. N., Kandeel, M., Pillay, M., Deb, P. K., Abdallah, H. H., Mahomoodally, M. F., & Chopra, D. (2020). Anti-Tubercular Properties of 4-Amino-5-(4-Fluoro-3-Phenoxyphenyl)-4H-1, 2, 4-Triazole-3-Thiol and Its Schiff Bases: Computational Input and Molecular Dynamics. *Antibiotics*, *9*(9), 559.
25. Beyzaei, H., Kudeyani, M. G., Delarami, H. S., & Aryan, R. (2020). Synthesis, antimicrobial and antioxidant evaluation, and molecular docking study of 4, 5-disubstituted 1, 2, 4-triazole-3-thiones. *Journal of Molecular Structure*, *1215*, 128273.
26. Verma, D., Sharma, S., Sahni, T., & Arora, G. (2020). Green Tamarind Extract Catalyzed Synthesis of 4-Amino-1, 2, 4-Triazole Derivatives and Their In-vitro Antimicrobial Activity. *International Research Journal of Pure and Applied Chemistry*, 44-56.
27. Wu, S., Qi, L., Ren, Y., & Ma, H. (2020). 1, 2, 4-triazole-3-thione Schiff bases compounds: Crystal structure, hirshfeld surface analysis, DFT studies and biological evaluation. *Journal of Molecular Structure*, *1219*, 128591.
28. Dincel, E. D., Ulusoy-Güzeldemirci, N., Şatana, D., & Küçükbasmacı, Ö. (2021). Design, synthesis, characterization and antimicrobial evaluation of some novel hydrazinecarbothioamide, 4-thiazolidinone and 1, 2, 4-triazole-3-thione derivatives. *Journal of Heterocyclic Chemistry*, *58*(1), 195-205.

ISSN: 2458 - 8806

29. Brahimi, F. T., Belkhadem, F., Trari, B., & Othman, A. A. (2020). Diazole and triazole derivatives of castor oil extract: synthesis, hypoglycemic effect, antioxidant potential and antimicrobial activity. *Grasas y Aceites*, *71*(4), 378.

30. Yildirim, N. (2020). Synthesis of Novel 3-(4-tert-Butylphenyl)-5-Cylopropyl-4H-1, 2, 4-Triazole Derivatives with Antioxidative and Antimicrobial Activities. *Letters in Drug Design & Discovery*, *17*(8), 954-964.

31. Ghanaat, J., Khalilzadeh, M. A., Zareyee, D., Shokouhimehr, M., & Varma, R. S. (2020). Cell cycle inhibition, apoptosis, and molecular docking studies of the novel anticancer bioactive 1, 2, 4-triazole derivatives. *Structural Chemistry*, *31*(2), 691-699.

32. Turky, A., Sherbiny, F. F., Bayoumi, A. H., Ahmed, H. E., & Abulkhair, H. S. (2020). Novel 1, 2, 4-triazole derivatives: Design, synthesis, anticancer evaluation, molecular docking, and pharmacokinetic profiling studies. *Archiv der Pharmazie*, *353*(12), 2000170.

33. Kumar, V. (2021). In silico characterization, molecular docking, and in vitro evaluation of triazole derivatives as potential anticancer agents. *Asian Journal of Pharmaceutical and Clinical Research*, 22-28.

34. Gomha, S. M., Muhammad, Z. A., Ezz El-Arab, E., Elmetwally, A. M., El-Sayed, A. A., & Matar, I. K. (2020). Design, Synthesis, Molecular Docking Study and Anti-Hepatocellular Carcinoma Evaluation of New Bis-Triazolothiadiazines. *Mini reviews in medicinal chemistry*, *20*(9), 788-800.

35. Al-Hussain, S. A., Farghaly, T. A., Zaki, M. E., Abdulwahab, H. G., Al-Qurashi, N. T., & Muhammad, Z. A. (2020). Discovery of novel indolyl-1, 2, 4-triazole hybrids as potent vascular endothelial growth factor receptor-2 (VEGFR-2) inhibitors with potential anti-renal cancer activity. *Bioorganic Chemistry*, *105*, 104330.

36. Turky, A., Bayoumi, A. H., Sherbiny, F. F., El-Adl, K., & Abulkhair, H. S. (2021). Unravelling the anticancer potency of 1, 2, 4-triazole-N-arylamide hybrids through inhibition of STAT3: synthesis and in silico mechanistic studies. *Molecular Diversity*, *25*(1), 403-420.

37. Aouad, M. R., Al-Mohammadi, H. M., Al-Blewi, F. F., Ihmaid, S., Elbadawy, H. M., Althagfan, S. S., & Rezki, N. (2020). Introducing of acyclonucleoside analogues tethered 1, 2, 4-triazole as anticancer agents with dual epidermal growth factor receptor kinase and microtubule inhibitors. *Bioorganic chemistry*, *94*, 103446.

38. Patel, K. R., Brahmbhatt, J. G., Pandya, P. A., Daraji, D. G., Patel, H. D., Rawal, R. M., & Baran, S. K. (2021). Design, synthesis and biological evaluation of novel 5-(4-chlorophenyl)-4-phenyl-4H-1, 2, 4-triazole-3-thiols as an anticancer agent. *Journal of Molecular Structure*, *1231*, 130000.

39. Gomaa, H. A., El-Sherief, H. A., Hussein, S., Gouda, A. M., Salem, O. I., Alharbi, K. S., ... & Youssif, B. G. (2020). Novel 1, 2, 4-triazole derivatives as apoptotic inducers targeting p53: Synthesis and antiproliferative activity. *Bioorganic Chemistry*, *105*, 104369.

40. Khan, B., Naiyer, A., Athar, F., Ali, S., & Thakur, S. C. (2021). Synthesis, characterization and anti-inflammatory activity evaluation of 1, 2, 4-triazole and its derivatives as a potential scaffold for the synthesis of drugs against prostaglandin-endoperoxide synthase. *Journal of Biomolecular Structure and Dynamics*, *39*(2), 457-475.

41. Beyzaei, H., Kudeyani, M. G., Delarami, H. S., & Aryan, R. (2020). Synthesis, antimicrobial and antioxidant evaluation, and molecular docking study of 4, 5-disubstituted 1, 2, 4-triazole-3-thiones. *Journal of Molecular Structure*, *1215*, 128273.

42. Khokhar, D., Jadoun, S., Arif, R., Jabin, S., & Budhiraja, V. (2021). Copolymerization of o-phenylenediamine and 3-Amino-5-methylthio-1H-1, 2, 4-triazole for tuned optoelectronic properties and its antioxidant studies. *Journal of Molecular Structure*, *1228*, 129738.

43. Geetha, B. M., Brinda, K. N., Achar, G., Małecki, J. G., Alwarsamy, M., Betageri, V. S., & Budagumpi, S. (2020). Coumarin incorporated 1, 2, 4–triazole derived silver (I) N–heterocyclic carbene complexes as efficient antioxidant and antihaemolytic agents. *Journal of Molecular Liquids*, *301*, 112352.

44. Brahimi, F. T., Belkhadem, F., Trari, B., & Othman, A. A. (2020). Diazole and triazole derivatives of castor oil extract: synthesis, hypoglycemic effect, antioxidant potential and antimicrobial activity. *Grasas y Aceites*, *71*(4), 378.

45. Ihnatova, T., Kaplaushenko, A., Frolova, Y., & Pryhlo, E. (2021). Synthesis and antioxidant properties of some new 5-phenethyl-3-thio-1, 2, 4-triazoles. *Pharmacia*, *68*, 129-133.

46. Zykova, S. S., Talismanov, V. S., Tsaplin, G. V., Bulatov, I. P., Popkov, S. V., Karmanova, O. G., & Savinkov, A. V. (2019). Study of acute toxicity and antihypoxic activity of N4-substituted 5-(1, 2, 4-triazole-1-ylmethyl)-1, 2, 4-triazole-3-thiones. *International Journal of Pharmaceutical Research*, *11*(3), 1189-1192.

47. Kravchenko, T. V., Panasenko, O. I., & Knysh, E. G. (2016). Biological activity of the derivatives of 1, 2, 4-triazole. *Farmatsevtychnyi zhurnal*, (5), 25-30.

48. Odyntsova V. M., Knysh Ye. G., & Panasenko O. I. (2018). Syntesis, physical and chemical properties, antihypoxic activity of some 5-[((5-(adamantane-1-yl)- 4-R-4*H*-1,2,4-triazole-3-yl)thio)methyl]-N-R1-1,3,4-thiadiazole-2-amines and 5-[((5-(adamantane-1-yl)- 4-R-4*H*-1,2,4-triazole-3-yl) thio)methyl]-4-R1-4*H*-1,2,4-triazole-3-thiols. *Current issues in pharmacy and medicine: science and practice*, *11*(1), 17-22.

49. Kucheryavyi, Y. M., Kaplaushenko, A. G., & Korzhova, A. S. (2014). Synthesis of 5-R-4-R1-3-alkylthio-1, 2, 4-triazoles and study influence of their adsorption ability on the results of toxicity and anti-hypoxic activity. *The Pharma Innovation*, *3*(1, Part A), 69.

50. Odyntsova, V., & Pruglo, Y. (2015). Synthesis, physical-chemical properties and the study of anti-hypoxemic activity of 5-(adamantane-1-yl)-4-R-1,2,4-triazole-3-thion alkylderivatives. *Zaporozhye Medical Journal*, *0*(2). doi: 10.14739/2310-1210.2015.2.42123.

51. Shcherbyna, R., & Vashchyk, Y. (2019). The research of 1, 2, 4-triazole derivatives hepatoprotective activity under tetracycline and infectious hepatitis. *Ankara Üniversitesi Eczacılık Fakültesi Dergisi*, *43*(2), 135-146.

52. Shcherbyna, R. O., Samura, T. O., Kyrychko, B. P., Zvenihorodska, T. V., & Hyrenko, I. V. (2017). The research of ammonium 2-((4-amino-5-(morpholinomethyl)-4H-1, 2, 4-triazole-3-yl) thio) acetate (PKR-177) influence on biochemical indices in rats blood under hepatitis initiated by tetrachloride methane. *Запорожский медицинский журнал*, (19, № 6), 819-822.

53. Rud, A. M., Kaplaushenko, A. G., Pruglo, Y. S., Sameliuk, Y. G., & Frolova, Y. S. (2018). Hepatoprotective activity of 1,2,4-triazole-3-thione derivatives, which contains on C5 atomic carbon hydroxy(phenyl)methyl dependent. *Ukrainian biopharmaceutical journal*, (3 (56)), 10-15.

54. Shi, Y., Wang, Q., Rong, J., Ren, J., Song, X., Fan, X., ... & Yu, L. (2019). Synthesis and biological evaluation of (1, 2, 4) triazole [4, 3-a] pyridine derivatives as potential therapeutic agents for concanavalin A-induced hepatitis. *European journal of medicinal chemistry*, *179*, 182-195.

55. Goher, S. S., Griffett, K., Hegazy, L., Elagawany, M., Arief, M. M., Avdagic, A., ... & Elgendy, B. (2019). Development of novel liver X receptor modulators based on a 1, 2, 4-triazole scaffold. *Bioorganic & medicinal chemistry letters*, *29*(3), 449-453.

56. Liao, L., Jiang, C., Chen, J., Shi, J., Li, X., Wang, Y., ... & Zhang, J. (2020). Synthesis and biological evaluation of 1, 2, 4-triazole derivatives as potential neuroprotectant against ischemic brain injury. *European journal of medicinal chemistry*, *190*, 112114.

57. Koparir, P., Sarac, K., & Omar, R. A. (2022). Synthesis, molecular characterization, biological and computational studies of new molecule contain 1, 2, 4-triazole, and Coumarin bearing 6, 8-dimethyl. *Biointerface Research in Applied Chemistry*, *12*(1), 809-823.

58. Sayed, Y. S., Gaber, M., Fahmy, R. M., & Fathallah, S. Characterization, theoretical computation, DNA-binding, molecular docking, antibacterial and antioxidant activities of new metal complexes of (E)-1-((1H-1,2,4-triazol-3-yl) diazenyl) naphthalen-2-ol. *Applied Organometallic Chemistry*, e6628.

59. Sarojini, B. K., Manjulaa, P. S., & Rajc, C. G. D. (2015). In vivo neuroprotection study of two 1, 2, 4-triazole derivatives in Drosophila melanogaster Oregon K flies. *Journal of Pharmacy Research*, *9*(6), 351-358.

60. Xu, M., Peng, Y., Zhu, L., Wang, S., Ji, J., & Rakesh, K. P. (2019). Triazole derivatives as inhibitors of Alzheimer's disease: Current developments and structure-activity relationships. *European journal of medicinal chemistry*, *180*, 656-672.

61. Safonov, A. and Nevmyvaka, A., 2020. Actoprotective activity research of 2-((5-(2-bromophenyl)-4-substituted-4H-1,2,4-triazole-3-yl)thio)acetates. *Current issues in pharmacy and medicine: science and practice*, 13(2(33), pp.260-264.

62. Bihdan, O. A. (2020). Actoprotective activity of some 5-(thiophen-3-ylmethyl)-4-R1-1, 2, 4-triazole-3-thiols derivatives. *Farmatsevtychnyi zhurnal*, (3), 80-85.

63. Danilchenko, D. M., & Safonov, A. A. (2017). Diuretic activity of 2-((4-amino-5-R-4H-1, 2, 4-triazole-3-yl) thio) acetohydrazides. *Запорожский медицинский журнал*, (19,№ 4), 517-519.

64. Kucheryavyi, Y. N., Kaplaushenko, A. G., & Pruhlo, E. S. (2014). Synthesis and diuretic activity of 2-(5-(phenoxymethyl)-4-r1-1, 2, 4-triazole-3-ylthio) acetic acids and their salts. *Запорожский медицинский журнал*, (6), 101-104.

65. Kravchenko, T., 2018. The search for new 4-amino-5-methyl-4H-1,2,4-triasole-3-thion derivatives with diuretic activity. *Zaporozhye Medical Journal*, 20(3), pp.421-424.

66. El Sayed, H., Farahat, M. M., Awad, L. F., Balbaa, M., Yusef, H., Badawy, M. E., & Abd Al Moaty, M. N. (2022). New 4-(arylidene) amino-1, 2, 4-traizole-5-thiol derivatives and their acyclo thioglycosides as α-glucosidase and α-amylase inhibitors: Design, synthesis, and molecular modelling studies. *Journal of Molecular Structure*, 132733.

67. Nawaz, S., Shareef, M., Shahid, H., Mushtaq, M., & Sarfraz, M. (2017). A review of antihyperlipidemic effect of synthetic phenolic compounds. *Matrix Science Medica*, *1*(1), 22-26.

68. Kholodnyak, S. V., Schabelnyk, K. P., Shernova, G. A., Sergeieva, T. Y., Ivchuk, V. V., Voskoboynik, O. Y., ... & Shishkina, S. V. (2015). Hydrolytic cleavage of the pyrimidine ring in 2-aryl-[1, 2, 4] triazole [1, 5-c] quinazolines: physico-chemical properties and the hypoglycemic activity of the compounds synthesized. *News of Pharmacy*, (3 (83)), 9-17.

69. Brahimi, F. T., Belkhadem, F., Trari, B., & Othman, A. A. (2020). Diazole and triazole derivatives of castor oil extract: synthesis, hypoglycemic effect, antioxidant potential and antimicrobial activity. *Grasas y Aceites*, *71*(4), 378.

ISSN: 2458 - 8806

70. Menteşe, E., Baltaş, N., & Bekircan, O. (2019). Synthesis and kinetics studies of N′-(2-(3, 5-disubstituted-4H-1, 2, 4-triazol-4-yl) acetyl)-6/7/8-substituted-2-oxo-2H-chromen-3-carbohydrazide derivatives as potent antidiabetic agents. *Archiv der Pharmazie*, *352*(12), 1900227.

71. Goher, S. S., Griffett, K., Hegazy, L., Elagawany, M., Arief, M. M., Avdagic, A., ... & Elgendy, B. (2019). Development of novel liver X receptor modulators based on a 1, 2, 4-triazole scaffold. *Bioorganic & medicinal chemistry letters*, *29*(3), 449-453.

72. Kaproń, B., Łuszczki, J., Paneth, A., Wujec, M., Siwek, A., Karcz, T., ... & Plech, T. (2017). Molecular mechanism of action and safety of 5-(3-chlorophenyl)-4-hexyl-2, 4-dihydro-3H-1, 2, 4-triazole-3-thione-a novel anticonvulsant drug candidate. *International journal of medical sciences*, *14*(8), 741.

73. Ghaleb, A., Aouidate, A., Ghamali, M., Sbai, A., Bouachrine, M., & Lakhlifi, T. (2017). 3D-QSAR Modeling and Molecular Docking Studies on a Series of 1, 2, 4 Triazole Containing Diarylpyrazolyl Carboxamide as CB1 Cannabinoid Receptor Ligand. *International Research Journal of Pure and Applied Chemistry*, 1-13.

74. Kaproń, B., Łuszczki, J. J., Płazińska, A., Siwek, A., Karcz, T., Gryboś, A., ... & Plech, T. (2019). Development of the 1, 2, 4-triazole-based anticonvulsant drug candidates acting on the voltage-gated sodium channels. Insights from in-vivo, in-vitro, and in-silico studies. *European Journal of Pharmaceutical Sciences*, *129*, 42-57.

75. Mioc, M., Avram, S., Tomescu, A. B., Chiriac, D. V., Heghes, A., Voicu, M., ... & Kurunczi, L. (2017). Docking Study of 3-mercapto-1, 2, 4-triazole derivatives as inhibitors for VEGFR and EGFR. *Rev. Chim*, 4-7.