https://www.sworldjournal.com/index.php/swj/article/view/swj11-03-053
DOI: 10.30888/2663-5712.2022-11-03-053

УДК 547.792.04

SYNTHETIC FEATURES OF NEW 1,2,4-TRIAZOLE DERIVATIVES

Khilkovets A.,
ORCID: 0000-0001-7401-9458
PhD-student of the Department of Natural Sciences for Foreign Students and Toxicological Chemistry, Zaporizhzhia State Medical University, Ukraine.
Parchenko V.,
ORCID: 0000-0002-2283-1695
Professor, Doctor of Pharmaceutical Science of the Department of Natural Sciences for Foreign Students and Toxicological Chemistry, Zaporizhzhia State Medical University, Ukraine.

Abstract. *The relevance of our study is due to the constant need to obtain new promising molecules that can have high pharmacological activity and low toxicity. That is why synthetic chemists around the world are actively searching for new methods for the synthesis of biologically active compounds and modifying already known molecules. Among heterocyclic systems, 1,2,4-triazole attracts our attention. It has been repeatedly proven that among the derivatives of 1,2,4-triazole, many interesting compounds have been found that have practical applications in medicine, pharmacy, veterinary medicine and in industry. So, in order to systematize and generalize the known data on new methods for obtaining derivatives of 1,2,4-triazole, we have analyzed many domestic and foreign literature sources.*

Key words: *synthesis, physical and chemical properties, derivatives of 1,2,4-triazole.*

Introduction.

The creation of new promising molecules of synthetic origin is a priority task of modern pharmaceutical science [1]. A special place among the huge number of synthetic compounds is occupied by 1,2,4-triazoles, which have remained under the close attention of scientists for many decades [2, 3]. This attractiveness of this heterocyclic system has a reasoned explanation: 1,2,4-triazoles are quite reactive, most derivatives of 1,2,4-triazole are biologically active compounds, have little toxicity [4]. Scientists almost all over the world are engaged in the synthesis of new original molecules among 1,2,4-triazole derivatives [5, 6]. Among them, a number of effective antibacterial, antiviral compounds, substances with antitumor, fungicidal, and antioxidant activity were identified [7, 8]. Other derivatives are used as Anticorrosive agents, plasticizers of plastics, etc. [9].

Thus, the expansion of the arsenal of new derivatives of 1,2,4-triazole is a necessary condition for further effective targeted introduction of new promising substances in various spheres of human life.

The aim of our work was to systematize known methods for the synthesis of new derivatives of 1,2,4-triazole and draw certain conclusions about the priority and prospects of their use for further organic syntheses.

1,2,4-Triazole derivatives are known to be a powerful class of heterocyclic compounds that are the basic base for creating active pharmaceutical ingredients (APIs) of various drugs. Today, there is a well-known series of effective medicines that are actively used in medical practice, the active substances of which belong to the derivatives of 1,2,4-triazole (fig. 1).

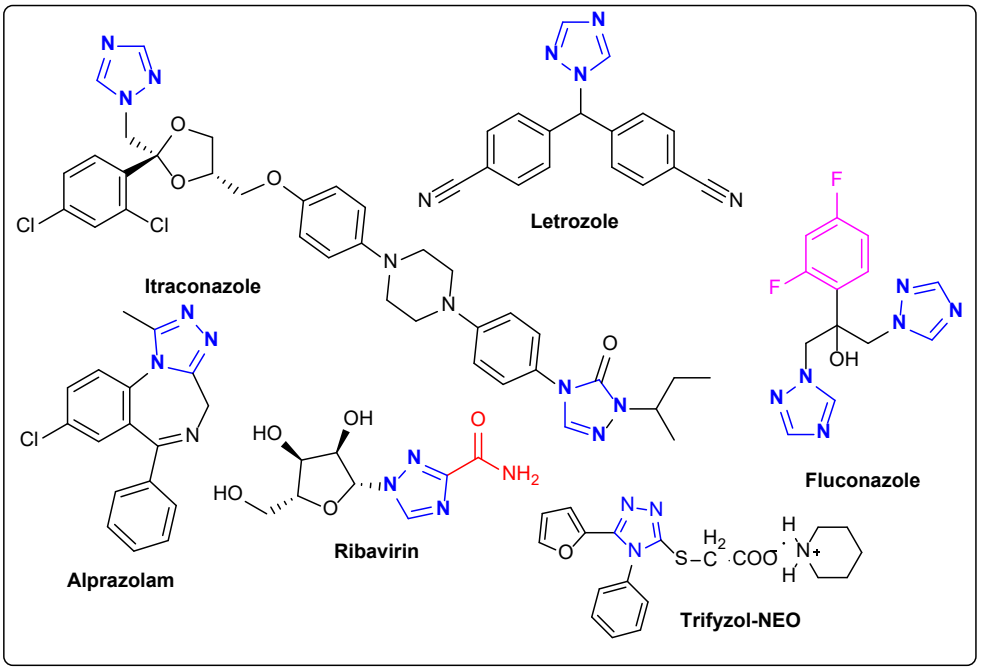

Fig. 1. Some medicinal products whose pharmaceutical ingredients belong to 1,2,4-triazole derivatives.

Over the past two decades, interest in 1,2,4-triazole derivatives has been constantly growing due to their diverse biological activity. A large number of compounds of antibacterial, fungicidal, anti-inflammatory, antihypertensive, antiviral, antitumor effects, etc.were found [10]. It has also been reported that high rates of biological activity of 1,2,4-triazole derivatives are associated with its dipole nature and rather high resistance to metabolic degradation [11]. It is proved that among the typical pharmacophores responsible for antimicrobial activity is 1,2,4-triazole [12]. Promising antimicrobial and antitumor compounds are obtained by the Mannich reaction [13-15].

A rather original method for the synthesis of 1,2,4-triazoles was proposed by a team of scientists who used hydrazine and formamide under microwave irradiation as starting materials [6]. The reaction occurs in the absence of a catalyst and with sufficiently high yields of terminal compounds (fig. 2).

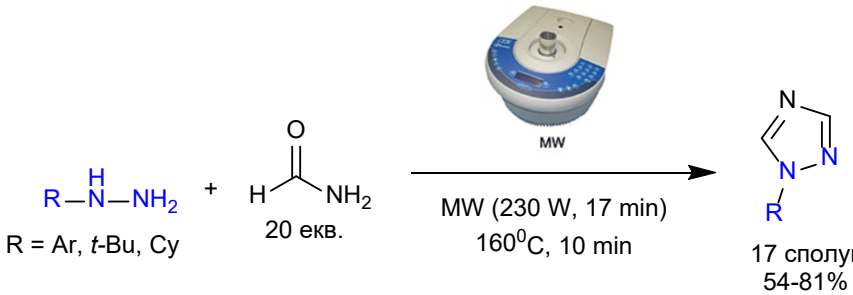

Fig. 2-synthesis of 1,2,4-triazole derivatives by microwave synthesis

A modern scientifically based method for obtaining new 1,2,4-triazoles is proposed by scientists using a multicomponent electrochemical reaction of arylhydrazines, paraformaldehyde, ammonium acetate and alcohols [9]. Alcohols are used as solvents, and ammonium acetate is a source of nitrogen atoms (fig. 3).

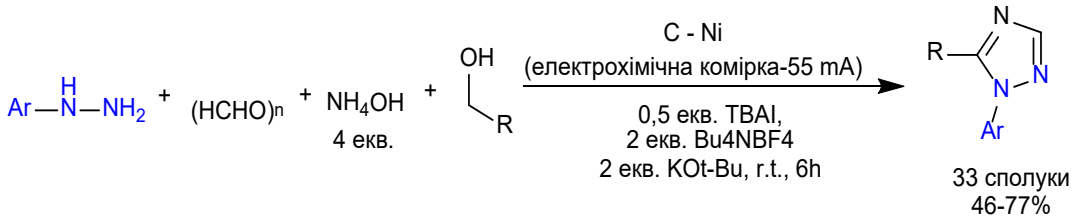

Fig. 3 Production of 1,2,4-triazoles by microwave synthesis

Chinese scientists were able to synthesize derivatives of 1,2,4-triazole by Cascade-addition-oxidative cyclization of nitriles with 2-aminopyridines or amidines [11]. The chemical reaction was performed in the presence of a 1,10-phenanthroline functionalized Cuprum (I) Complex, a specific catalyst, and air as an oxidizer. This original approach provides a wide range of high-yield 1,2,4-triazole derivatives (Figure 4).

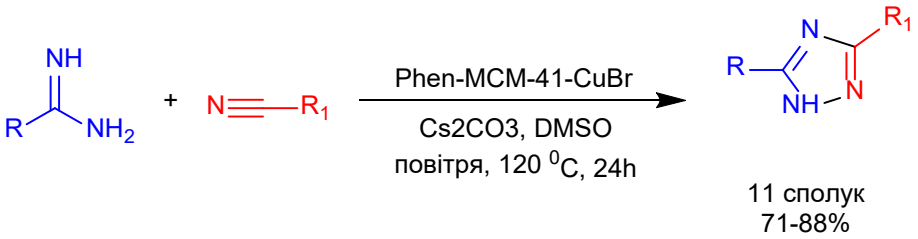

Fig. 4 Cyclization of nitriles to form 1,2,4-triazoles.

Another method for the synthesis of 2,4,6-triazines and 2,6-disaminated 1,3,5-triazines and 1,3-disaminated 1,2,4 triazoles was proposed by a team of scientists [12]. The process is simple and includes a universal catalytic system, a green oxidizer, significant tolerance to functional groups, and high regioselectivity (fig. 5).

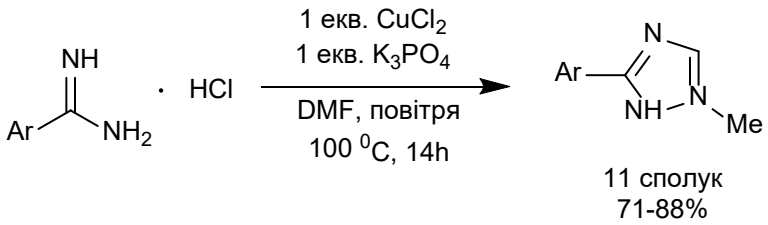

Fig. 5 Method for obtaining 2,4,6-triazines and 2,6 - disaminated 1,3,5-triazines and 1,3-disaminated 1,2,4 triazoles.

A very promising method for the synthesis of 1,3,5 tri-substituted 1,2,4-triazoles from hydrazones and aliphatic amines is proposed by Chinese scientists [13]. They proved the metal-free nature of synthesis by functionalizing the CH cascade, forming C=N double bonds, and the oxidative sequence (fig. 6).

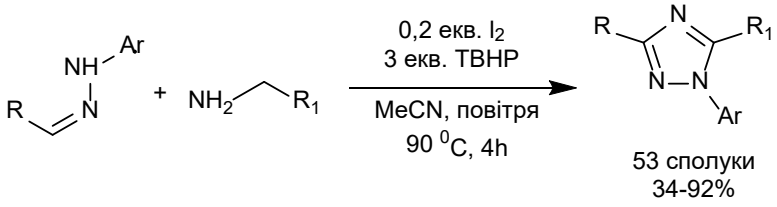

Fig. 6 Synthesis of 2,4,6-triazines and 2,6 - disembodied 1,3,5-triazines and 1,3-disembodied 1,2,4 triazoles.

A team of Indian scientists [14] proposed a metal-free, environmentally friendly and convenient strategy for the synthesis of 4,5-disubstituted N-condensed 3-amino-1,2,4-triazoles from isothiocyanates (fig. 7).

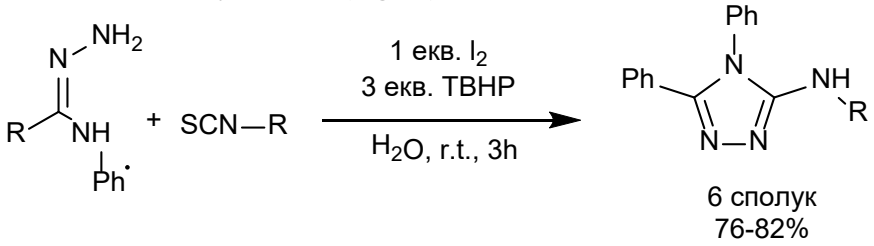

Fig. 7 Synthesis of 4,5-substituted N-condensed 3 amino-1,2,4-triazoles

A simple and fairly efficient method for the synthesis of 1,5-substituted 1,2,4 triazoles was initiated by Liu J.-Q. and his colleagues [15] proved the possibility of this synthesis in the presence of a CU (II) Catalyst (fig.8). A number of new 1,5-substituted 1,2,4-triazoles were obtained with a high yield under the action of the AG (I) catalyst (fig. 8).

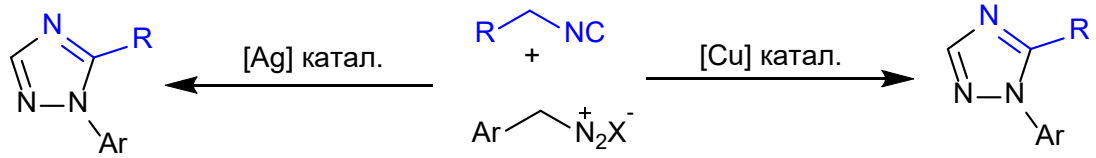

Fig. 8 Cycloaddition of isocyanides with aryldiazonium salts in the synthesis of 1,2,4-triazole derivatives.

Another team of scientists has developed a convenient synthetic approach for the production of 3-aryl-1,2,4-triazoles [16, 17]. The authors developed a method that consists in the reaction of benzamides and chloral hydrate to form chloramides, which then react with a mixture of phosphorus pentachloride / phosphorus oxychloride to form an intermediate of N-(1,2,2,2-tetrachloroethyl)benzimidoyl chloride, which, after adding hydrazinehydrate, turns into 3-aryl-1,2,4-triazoles (fig. 9).

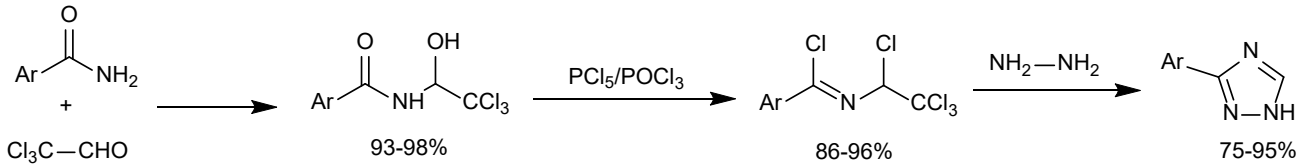

Fig. 9 Synthesis of 3-aryl-1,2,4-triazoles.

Using modern physico-chemical methods of analysis, a team of scientists proved the formation of new 4-ethyl-5-(((3-(pyridine-4-YL)-1H-1,2,4-triazole-5-YL)Thio)methyl)-4h-1,2,4-triazole-3 – thiols-promising antimicrobial agents [18].

Another team of Russian authors proposed an original method for the synthesis of 3-(3-fluorophenyl)-6-(aryl-, heteryl)-[1,2,4]triazole[3,4-B][1,3,4]thiadiazoles (fig. 10). The reaction was performed in the presence of an excess of POCl3 during three-hour boiling of the reaction mixture. The final product was obtained by adding an ammonia solution to a neutral medium after pouring the mixture on ice [19].

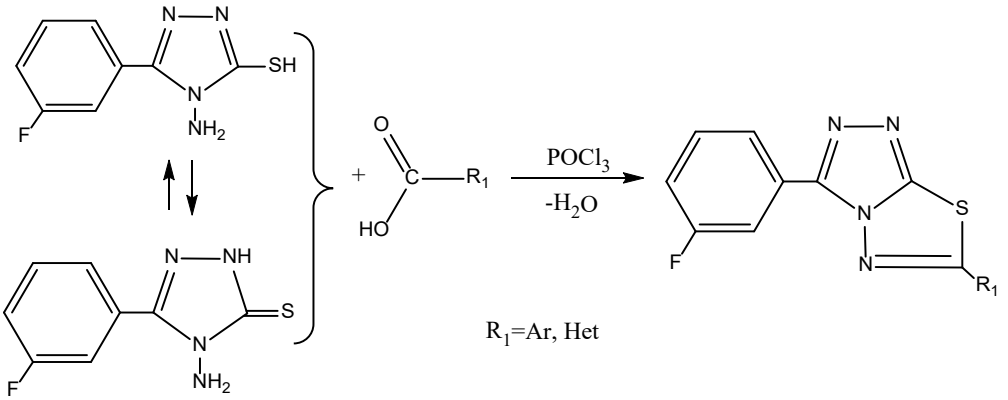

Fig. 10 Synthesis of 3-(3-fluorophenyl)-6-(aryl-, heteryl)-[1,2,4]triazole[3,4-B][1,3,4]thiadiazole.

Continuing, according to the authors, the search for promising compounds of a number of 1,2,4-triazoles and in order to expand the arsenal of biologically active substances based on fluorophenyl derivatives of 1,2,4-triazole-3-thiols, scientists conducted a reaction of 5-(2-fluorophenyl)-4-amino-1,2,4-triazole-3-thiol in the presence of aromatic and heterocyclic carboxylic acids in the POCl3 medium (fig. 11). At the same time, a number of new individual compounds were obtained, the structure of which is confirmed by modern physico-chemical methods of analysis [20].

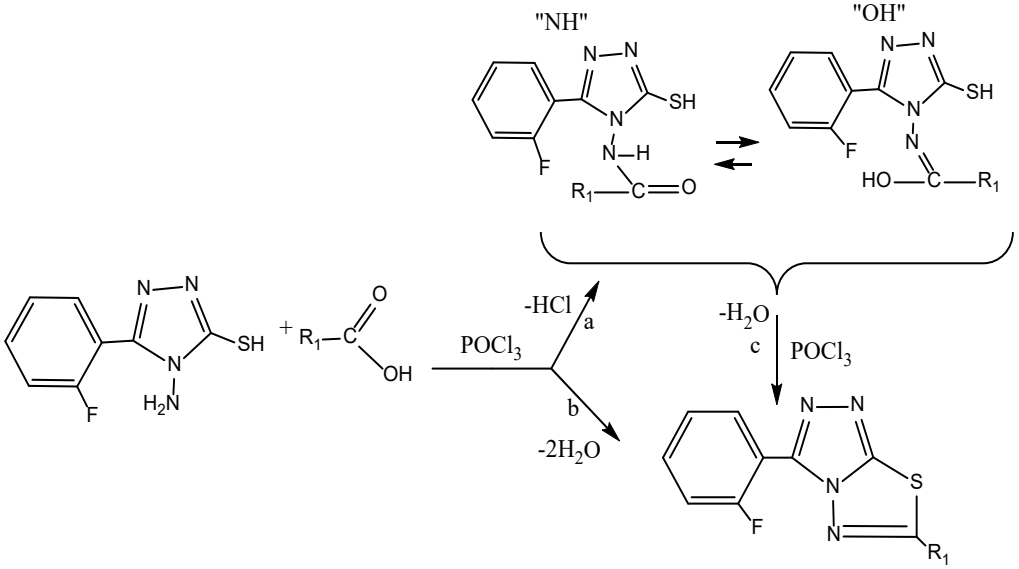

Fig. 11. Synthesis of 3-(2-fluorophenyl)-6-R1-[1,2,4]triazole[3,4-B][1,3,4]thiadiazole.

A simple and promising method for the synthesis of new bicyclic derivatives of 1,2,4-triazole is proposed by domestic scientists [21, 22] they studied the reaction of 5-(2-fluorophenyl)-4-amino-1,2,4-triazole-3-thiol and 5-(3-fluorophenyl)-4-amino-1,2,4-triazole-3-thiol with an equivalent amount of 2-Bromo-1-aryletanone and 1-brompropane-2-one in an isopropanol medium (fig. 12). A series of new 3-(2-fluorophenyl, 3-fluorophenyl)-6-R3-7h[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines were obtained with high yields.

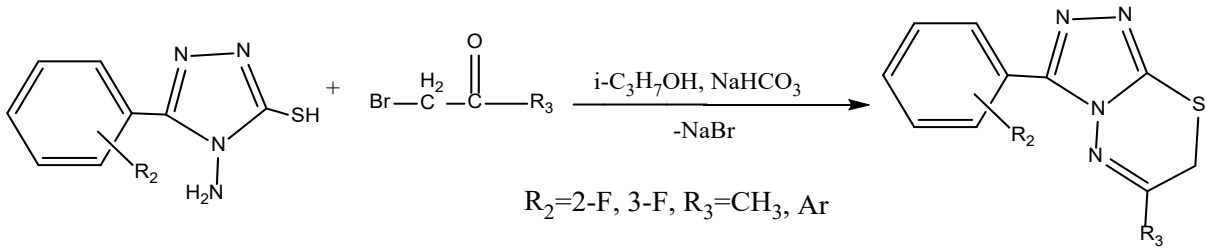

Fig. 12 synthesis of 3-(2-fluorophenyl, 3-fluorophenyl)-6-R3-7H[1,2,4]triazolo[3,4-B][1,3,4]thiadiazines.

Conclusions. The known methods of synthesis of new derivatives of 1,2,4-triazole are generalized in order to identify the most optimal and promising ones for further synthetic tests.

References

1. The investigation of antimicrobial activity of some s-substituted bis-1,2,4-triazole-3-thiones / Yevhen Karpun , Volodymyr Parchenko, Volodymyr Nahornyi, Natalia Nahorna // Pharmacia 2021 68(4): 797–804.

2. Antimicrobial Activity of Some Furans Containing 1,2,4-Triazoles / Volodymyr Zazharskyi, Oleksii Bigdan, Volodymyr Parchenko, Maryna Parchenko // Archives of Pharmacy Practice Volume 12 ¦ Issue 2 ¦ Apr-Jun 2021, p. 60-65.

3. Синтез, фізико-хімічні властивості та антигіпоксична активність деяких S-похідних 4-R-5-(((3-(піридин-4-іл)-1H-1,2,4- триазол-5-іл)тіо)метил)-4H-1,2,4-триазол-3-тіолів / Карпун Є.О., Парченко В.В. // Фармацевтичний журнал, 2020, Т. 75, № 6 С. 56-64.

4. Physicochemical properties of new S-derivatives of 5-(5-bromofuran-2-yl)-4-methyl-1,2,4-triazol-3-thiols / V. Zazharskyi, M. Parchenko, V. Parchenko // Voprosy khimii i khimicheskoi tekhnologii, 2020, No. 6, pp. 50-58.

5. H. Nagai, Y.H. Kim, Cancer prevention from the perspective of global cancer burden patterns, J. Thorac. Dis. 9 (2017) 448e451, https://doi.org/10.21037/jtd.2017.02.75.

6. Shelke, G. M., Rao, V. K., Jha, M., та ін. Microwave-assisted catalyst-free synthesis of substituted 1,2,4-triazoles. Synlett. 2015. Vol. 26, No. 3. C. 404–407. doi. 10.1055/s-0034-1379734.

7. Tozkoparan B., Peli E., Ilada E. Y., and Ertan M.; Preparation of 5-aryl-3-alkiltio-1,2,4-triazoles and corresponding sulfones with anti-inflammatory-analgesic activity; Bioorganic & Medicinal Chemistry 15 (2007) 1808-1814.

8. Bhat K.S., Poojary B., Prasad D.J., Naik P., Holla B.S; Synthesis and antitumor activity studies of some new fused 1,2,4-triazole derivatives carrying 2,4-dichloro-5-fluorophenyl moiety; European Journal of Medicinal Chemistry 44 (2009) 5066-5070.

9. Shelke, G. M., Rao, V. K., Jha, M., та ін. Microwave-assisted catalyst-free synthesis of substituted 1,2,4-triazoles. Synlett. 2015. Vol. 26, No. 3. C. 404–407. doi. 10.1055/s-0034-1379734.

10. Yang, N., Yuan, G. A Multicomponent Electrosynthesis of 1,5-Disubstituted and 1-Aryl 1,2,4-Triazoles. Journal of Organic Chemistry. 2018. Vol. 83, No. 19. C. 11963–11969. doi. 10.1021/acs.joc.8b01808.

11. Xia, J., Huang, X., Cai, M. Heterogeneous Copper(I)-Catalyzed Cascade Addition-Oxidative Cyclization of Nitriles with 2-Aminopyridines or Amidines: Efficient and Practical Synthesis of 1,2,4-Triazoles. Synthesis (Germany). 2019. Vol. 51, No. 9. C. 2014–2022. doi. 10.1055/s-0037-1611712.

12. Huang, H., Guo, W., Wu, W., та ін. Copper-Catalyzed Oxidative C(sp3)-H Functionalization for Facile Synthesis of 1,2,4-Triazoles and 1,3,5-Triazines from Amidines. Organic Letters. 2015. Vol. 17, No. 12. C. 2894–2897. doi. 10.1021/acs.orglett.5b00995.

13. Chen, Z., Li, H., Dong, W., та ін. I2-Catalyzed Oxidative Coupling Reactions of Hydrazones and Amines and the Application in the Synthesis of 1,3,5-Trisubstituted 1,2,4-Triazoles. Organic Letters. 2016. Vol. 18, No. 6. C. 1334–1337. doi. 10.1021/acs.orglett.6b00277.

14. Jatangi, N., Tumula, N., Palakodety, R. K., та ін. I2-Mediated Oxidative C-N and N-S Bond Formation in Water: A Metal-Free Synthesis of 4,5-Disubstituted/N-Fused 3-Amino-1,2,4-triazoles and 3-Substituted 5-Amino-1,2,4-thiadiazoles. Journal of Organic Chemistry. 2018. Vol. 83, No. 10. C. 5715–5723. doi. 10.1021/acs.joc.8b00753.

15. Liu, J. Q., Shen, X., Wang, Y., та ін. Cycloaddition of Isocyanides with Aryl Diazonium Salts: Catalyst-Dependent Regioselective Synthesis of 1,3- and 1,5-Disubstituted 1,2,4-Triazoles. Organic Letters. 2018. Vol. 20, No. 21. C. 6930–6933. doi. 10.1021/acs.orglett.8b03069.

16. Guirado, A., López-Caracena, L., López-Sánchez, J. I., та ін. A new, high-yield synthesis of 3-aryl-1,2,4-triazoles. Tetrahedron. 2016. Vol. 72, No. 49. C. 8055–8060. doi. 10.1016/j.tet.2016.10.045.

17. Chavez, D.E.; Parrish, D.A. New Heterocycles from tetrazines and oxadiazoles. J. Heterocycl. Chem. 2009, 46, 88–90.

18. Karpun Ye. O. (2020) Synthesis of novel S-alkyl derivatives of 4-ethyl-5-(((3-(pyridin-4-yl)-1H-1,2,4-triazol-5-yl)thio)methyl)-4H-1,2,4-triazole-3-thiols Slovak international scientific journal. № 43, Vol. 1. –p. 6 – 12.

19. Бігдан О. А. Синтез та фізико-хімічні властивості деяких похідних 5-(3-фторфеніл)-4-метил-1,2,4-триазол-3-тіолу / Бігдан О. А., Парченко В. В. // Фармацевтичний журнал. – 2017, №2. С. 38-47.

20. Бігдан О. А. Фізико-хімічні властивості S-похідних 5-(3-фторфеніл)-4-аміно-1,2,4-тріазол-3-тіолу / Бігдан О. А., Парченко В. В. // Актуальні питання фармацевтичної і медичної науки та практики. – 2017. – Том 10, № 2(24) – С. 135 – 140.

21. Some aspects of synthesis 3-(2-florphenyl)-6-R1-[1,2,4]triazol[3,4-b][1,3,4]thiadiazole and 3-(2-, 3-ftorphenyl)-6-R2-7H[1,2,4]triazolo[1,3,4]tiadiazines / Bihdan O. A., Parchenko V. V. // Research Journal of Pharmaceutical, Biological and Chemical Sciences. – 2018. № 9(3). P. 463—470.

22. Studying of physico-chemical properties of 5-(2-,3-fluorophenyl)-4-((aryl-,geteryl)yliden)amino-1,2,4-triazole-3-thiols and any of their retrieval products / Bihdan O.A., Parchenko V.V. Zazharskyi, V.V., Fotina T., Davydenko P. // Researh journal of pharmaceutical, biological and chemical sciences2018. – 10(1)., P. 464-474.