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EXAMINATION OF 1,2,4-TRIAZOLE NUCLEUS. AN INTEGRATED APPROACH TO THE SEARCH FOR BIOLOGICALLY ACTIVE SUBSTANCES

Every day, the modern pharmaceutical industry enters new drugs and dosage forms into the world register. Among the many new drugs, a small number of basic molecules can be noted. Modification of such molecules leads to a change and increase in biological action as well as to a change in toxicity.

One such molecule is 1,2,4-triazole. The heterocycle attracts attention due to its excellent biological action on low toxicity. First of all, derivatives of this heterocycle are considered to be powerful antifungal and antimicrobial agents. However, other types of biological action are becoming more common. For example, in medical practice found drugs “Letrozole” and “Anastrozole” as effective antitumor drugs.

To achieve this purpose, ZSMU scientists¹ select a matrix based on the nucleus of 1,2,4-triazole at first. For this goal the literary base is worked out at the beginning. The

¹ Щербак, М. О. (2015). Дослідження синтетичних, фізико-хімічних і біологічних властивостей 4-аміно-5-(2-, 3-, 4-нітрофеніл)-1, 2, 4-триазол-3-тіонів та їх N-і S-заміщених (Doctoral dissertation, Запорізький державний медичний університет); Каплаушенко, А. Г., Книш, Є. Г., Панасенко, О. І., Самелюк, Ю. Г., Кучерявий, Ю. М., Щербак, М. О., ... & Гуліна, Ю. С. (2016). Практичне значення та застосування похідних 1, 2, 4-триазолу; Самелюк, Ю. Г. (2016). Синтез та дослідження біологічно активних похідних 1, 2, 4-триазол-3-тіону, що містять метоксибенільні замісники (Doctoral dissertation, Запорізький державний медичний університет); Рудь, А. М. (2018). «Пошук сполук гепатопротекторної дії серед (3-тіо-4-г-1, 2, 4-триазол-5-іл)(феніл) метанолів та їх похідних» 15.00. 02–фармацевтична хімія та фармакогнозія 22–Охорона здоров'я (Doctoral dissertation, Запорізький державний медичний університет); Shcherbyna, R. O., Panasenko, O. I., Knysh, Y. G., Fotina, H. A., Vashchuk, Y. V., & Fotina, T. I. (2016). The study of antimicrobial activity of 2-((4-R-3-(morpholinomethylene)-4H-1, 2, 4-triazole-5-yl) thio) acetic acid salts. Запорізький медичний журнал, (4), 97-100; Shcherbyna, R. O. (2016). The synthesis and prediction of biological activity in silico for new alkyl derivatives of 4-R-3-(MORFOLINOMETY-

viability of the molecule is then confirmed by computer screening using PASS-online programs and acute toxicity using GUSAR-online.

Thus, scientists have selected and synthesized more than 700 new, previously undescribed compounds derived from 1,2,4-triazole.

The synthesis of 1,2,4-triazole derivatives is carried out on basic matrices with aryl or heteroryl substituents in the 5 position. Examples of such compounds are shown in the Fig. 1

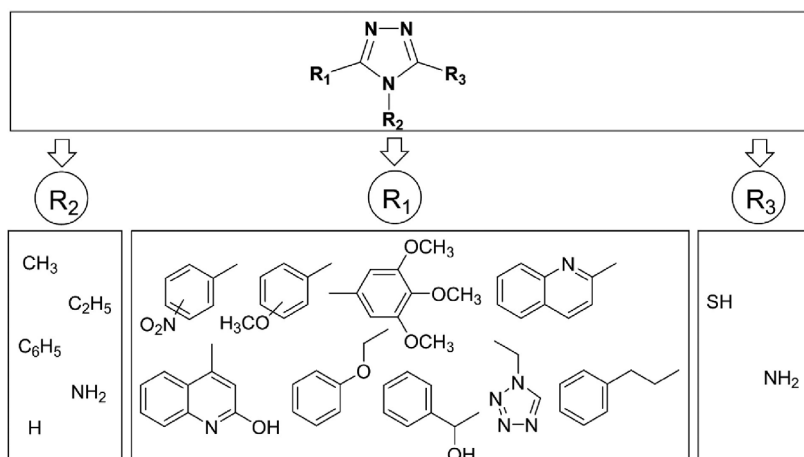


Fig. 1. Variants of basic matrices for searching for biologically active substances among 1,2,4-triazole derivatives

Investigation and detection of biologically active agents among 3-thio-4-amino-5-(nitrophenyl)-1,2,4-triazoles.

Thus, the authors² was used 3-thio-4-amino-5-(nitrophenyl)-1,2,4-triazoles. They synthesized a number of 3-alkyl(nitrophenyl)thio-4-amino-5-(2-, 3-, 4-nitrophenyl)-1,2,4-triazoles.

Subsequently, the Sulfur atom of 3-alkylthio-5-(2-, 3-, 4-nitrophenyl)-4-amino-1,2,4-triazoles was oxidized to the tetravalent and hexavalent states. A number of 2-(4-amino-5-(2-, 3-, 4-nitrophenyl)-1,2,4-triazole-3-ylthio)acetic acids and their salts were synthesized and the regularity of the effect of substituents on acid-base properties

LEN)-4H-1, 2, 4TRIAZOLE-5-THIOLES. Український біофармацевтичний журнал, (3), 34-38; 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; Shcherbyna, R., & Vashchuk, 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; Shcherbyna, R. (2020). An investigation of the pharmacokinetics and potential metabolites of potassium 2-((4-amino-5-(morfolinometyl)-4H-1, 2, 4-triazol-3-yl) thio) acetate on rats. Ankara Üniversitesi Eczacılık Fakültesi Dergisi, 44(2), 233-241.

- Щербак, М. О., & Каплаушенко, А. Г. (2013). Синтез, фізико-хімічні властивості та подальші перетворення 5-(3-, 4-нітрофеніл)-4-аміно-1, 2, 4-триазол-3-тіонів та їх ідентифікаційні похідних. Актуальні питання фармацевтичної і медичної науки та практики, (2), 129-132; Щербак, М. О., & Каплаушенко, А. Г. (2013). Методи синтезу, фізико-хімічні властивості та подальші перетворення в ряду 4-аміно-1, 2, 4-триазол-3-тіонів. Фармацевтичний журнал, (2), 10-19; Щербак, М. О., & Каплаушенко, А. Г. (2014). Вплив адсорбційних властивостей 3-алкілтіо-5-(2-, 3-, 4-нітрофеніл)-4-аміно-1, 2, 4-триазолів на їх токсичність та актопротекторну активність. Український біофармацевтичний журнал, (2), 68-72; Щербак, М. О., Беленічев, І. Ф., Абрамов, А. В., Бухтіярова, Н. В., Моргунцова, С. А., Павлов, С. В., & Каплаушенко, А. Г. (2014). Дослідження кардіопротекторної активності 3(4нітрофеніл) 5 (нонілсульфоніл) 1, 2, 4триазол4аміну. Фармакологія та лікарська токсикологія, (3), 64-69; Щербак, М. О., Каплаушенко, А. Г., Беленічев, І. Ф., Щербак, М. А., Каплаушенко, А. Г., & Беленічев, І. Ф. (2014). Гостра токсичність 4-аміно-5-(2-, 3-, 4-нітрофеніл)-1, 2, 4-триазол-3-тіонів та їх похідних.

for the selection of the optimal dosage form were established. A few of 1-R1-3-(3-thio-5-(2-, 3-, 4-nitrophenyl)-1,2,4-triazole-4-yl)thioureas were obtained. A preparative method for the selective reduction of the aliphatic C=N group was developed for 5-(2-, 3-, 4-nitrophenyl)-4-benzylideneamino-1,2,4-triazole-3-thiones.

The authors also developed 3-thio-5-(2-, 3-, 4-nitrophenyl)-1,2,4-triazole-4-diazonium chlorides. The optimal conditions for the diazotization reaction and subsequent azo coupling of these compounds were established.

It was found that their LD₅₀ is in the range of 512-1256 mg / kg in the study of acute toxicity of new 4-amino-5-(nitrophenyl)-1,2,4-triazole-3-thions and their derivatives. In the study of biological action 72 compounds with high indicators of antimicrobial (3), antioxidant (14), antihypoxic (2), diuretic (5), actoprotective (12), hypoglycemic (3) and antipyretic (4) effects were found.

It should be noted that the most toxic in majority cases were compounds containing 4-nitrophenyl substituent.

Alkylation of thions with halide alkanes led to a decrease in toxicity, increased diuretic and actoprotective effects. Increasing the length of the hydrocarbon chain increased the actoprotective effect. Oxidation of 3-alkylthio derivatives of 1,2,4-triazole (Fig. 2) led to a decrease in toxicity and diuretic activity, while increasing the antioxidant effect.

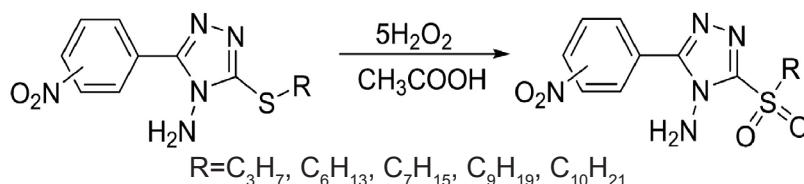


Fig. 2. Scheme of synthesis of 4-amino-5-(2-, 3-, 4-nitrophenyl)-3-alkylsulfonyl-1,2,4-triazoles

5-(2-, 3-, 4-methoxyphenyl, 3,4,5-trimethoxyphenyl)-1,2,4-triazole-3-thione. Synthesis and biological regularities among synthesized compounds

The authors³ were obtained several corresponding 3-alkylthio-substituted of 5-(methoxyphenyl)-1,2,4-triazole-3-thions. For compounds, 3-alkylthio-5-(2-, 3-, 4-methoxyphenyl, 3,4,5-trimethoxyphenyl)-1,2,4-triazoles were tested for surface activity. Studies have shown that with increasing length of the alkyl chain increases the ability of compounds to adsorb, which is characterized by an increase in acute toxicity and biological activity. The authors⁴ were investigated the oxidation conditions of the Sulfur atom of 3-alkylthio-5-(methoxyphenyl)-1,2,4-triazoles to the hexavalent state and 3-alkylcarboxymethylenethio-5-(methoxyphenyl)-1,2,4-triazoles to the tetravalent state by HPLC-MS. In⁵, the preparation of 2-(5-(methoxyphenyl)-1,2,4-triazole-3-ylthio)

3 Sameluk, Y. G., & Kaplaushenko, A. G. (2015). The synthesis and physicochemical properties of 2-(5-methoxyphenyl)-1H-1, 2, 4-triazole-3-ylthio) acetonitriles and their iminoethers. *Journal of Organic and Pharmaceutical Chemistry*, 13(3 (51)), 57-62.

4 Sameluk, Y. G., & Kaplaushenko, A. G. (2015). The synthesis and physicochemical properties of 2-(5-methoxyphenyl)-1H-1, 2, 4-triazole-3-ylthio) acetonitriles and their iminoethers. *Journal of Organic and Pharmaceutical Chemistry*, 13(3 (51)), 57-62.

5 Самелюк, Ю. Г., & Варинський, Б. О. (2015). Вивчення тіон-тіольної таутомерії 5-метоксифенільних похідних 3-тіо-1, 2, 4-тріазолу методом ВЕРХ-МС. *Повідомлення 1. Фармаком*, (3-4), 54-59.

acetymidate of hydrogen chlorides, amides, imidazolides, hydrazides and ylidene hydrazide 2-(5-(methoxyphenyl)-1,2,4-triazole-3-ylthio)ethanoic acid, 2-(2-(5-((methoxyphenyl)-1,2,4-triazole-3-ylthio)acetyl)hydrazino-1-carbothioamide, 2-(2-(5-(4-methoxyphenyl)-1,2,4-triazole-3-ylthio)acetyl)-N-(methyl, ethyl, phenyl)hydrazino-1-carbothioamides, and the conditions for further cyclization of the latter were studied.

Regarding biological action⁶. Acute toxicity studies have shown that by KK Sidorov's classification the obtained compounds belong to the class of non-toxic or low-toxic.

In the study of biological action, it was found that the replacement 2-, 3-, 4-methoxyphenyl substituents with 3,4,5-trimethoxyphenyl, as a rule, increases the indicators of acute toxicity, antipyretic, antioxidant and antihypoxic properties. Alkylation of thiols leads to increased antipyretic and actoprotective activities, while increasing the length of the alkyl residue increases the antipyretic effect; further introduction to the aliphatic fragment of the chlorine atom increases the hypoglycemic effect of the test substances; increase in diuretic properties was observed with the introduction of acetonitrile and amide groups. Salts of 2-(5-R-1,2,4-triazole-3-ylthio)ethanoic acids lead to themselves as the most active actoprotectors.

The authors⁷ pay attention to 2-(5-(3,4,5-trimethoxyphenyl)-1,2,4-triazole-3-ylthio)acetymidate hydrogen chloride (Fig. 3), which has high antioxidant and antihypoxic effects.

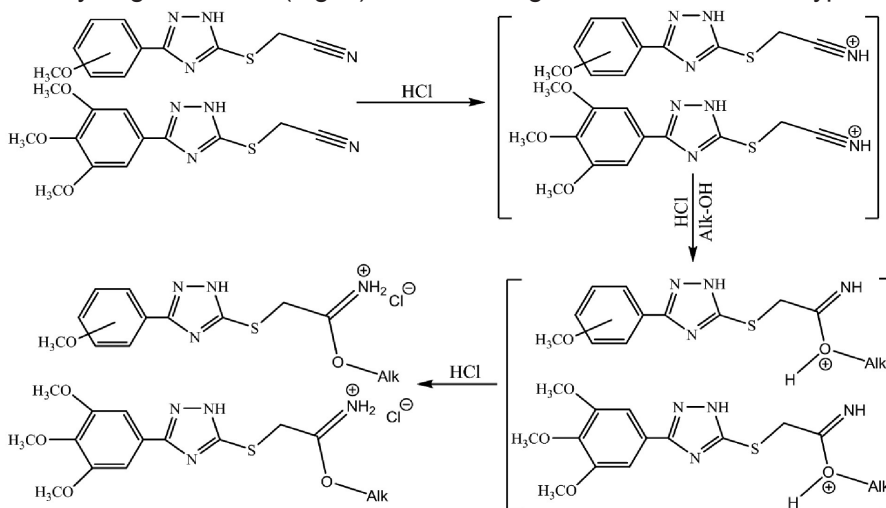


Fig. 3. Synthesis of alkyl 2-(5-(3-, 4-methoxyphenyl, 3,4,5-trimethoxyphenyl)-1,2,4-triazole-3-ylthio)acetimidate hydrogen chloride

- 6 Самелюк, Ю. Г., & Варинський, Б. О. (2015). Вивчення тіон-тіольної таутомерії 5-метоксифенільних похідних 3-тіо-1, 2, 4-триазолу методом ВЕРХ-МС. Повідомлення 1. Фармаком, (3-4), 54-59; Самелюк, Ю. Г., Каплаушенко, А. Г., Пругло, Є. С., Самелюк, Ю. Г., Каплаушенко, А. Г., & Пругло, Є. С. (2014). Синтез та актопротекторна активність солей 2-(5-(4-метоксифеніл-(3, 4, 5-триметоксифеніл)-)-1, 2, 4-триазол-3-ілтіо)ацетатних кислот; Самелюк, Ю. Г., Каплаушенко, А. Г., Камишний, О. М., Поліщук, Н. М., Самелюк, Ю. Г., Каплаушенко, А. Г., ... & Полищук, Н. Н. (2013). 4-метоксифенілден-2-(3-(4-метоксифеніл)-1Н-1, 2, 4-триазол-5-ілтіо)ацетогідрозид, що виявляє протимікробну та протигрибкову активність; Самелюк, Ю. Г., Беленічев, І. Ф., Абрамов, А. В., Бухтіярова, Н. В., Моргунцова, С. А., Павлов, С. В., & Каплаушенко, А. Г. (2015). Дослідження нейропротекторної активності пропіл 2-(5-(3-, 4, 5-триметоксифеніл)-1Н-1, 2, 4-триазол-3-ілтіо)ацетімідату гідрохлориду. Фармакологія та лікарська токсикологія, (6), 34-40.
- 7 Самелюк, Ю. Г. (2016). Синтез та дослідження біологічно активних похідних 1, 2, 4-триазол-3-тіону, що містять метоксифенільні замісники (Doctoral dissertation, Запорізький державний медичний університет); Самелюк, Ю. Г., & Варинський, Б. О. (2015). Вивчення тіон-тіольної таутомерії 5-метоксифенільних похідних 3-тіо-1, 2, 4-триазолу методом ВЕРХ-МС. Повідомлення 1. Фармаком, (3-4), 54-59.

Combination of 4-R-1,2,4-triazole-3-thiones with quinolinecarboxylic acids.**Biological action of compounds.**

The authors were developed methods for obtaining 5-(quinolin-2-yl-, 2-hydroxyquinolin-4-yl)-4-R₁-1,2,4-triazole-3-thions, for which further reactions involving electrophilic attack particles were studied; synthesized 3-alkyl- and 3-heterylthio-5-(quinolin-2-yl, 2-hydroxyquinolin-4-yl)-4-R-1,2,4-triazoles, 2-(5-(quinolin-2-yl-, 2-hydroxyquinolin-4-yl)-4-R₁-1,2,4-triazole-3-ylthio)acetonitrile and 2-(5-(quinolin-2-yl-, 2-hydroxyquinolin-4-yl)-4-R₁-1,2,4-triazole-3-ylthio)acetic acid.

Targeted synthesis⁸ of a number of iminoesters, hydrazides and ylidenehydrazides of 2-(5-(quinolin-2-yl, 2-hydroxyquinolin-4-yl)-4-R₁-1,2,4-triazole-3-thio)-acetate acids and a number of their salts.

The synthesized compounds were studied for 7 types of biological activity, such as acute toxicity, antimicrobial and antifungal, antiviral, antihypoxic, antioxidant and anti-edematous. The regularities of the influence of substituents in the position of the 5-nucleus of 1,2,4-triazole and on the Sulfur atom on the biological action were established. Introduction to position 5 of the nucleus of 1,2,4-triazole cycle of 2-hydroxyquinoline substituent increases the antimicrobial activity. Oxidation of the Sulfur atom of 3-alkylthio derivatives to the hexavalent state increases acute toxicity. Salts of 2-(5-(quinoline)-4-R₁-1,2,4-triazole-3-ylthio)acetic acids were showed a decrease in toxicity and a significant increase in antioxidant and antihypoxic activity. The most active antioxidant was 4-((2-((5-(5-(quinolin-2-yl)-1H-1,2,4-triazole-3-yl)thio)acetyl hydrazone) methyl)-benzoate (Fig. 4), which is low-toxic. Its authors²² were recommended as the most active compound.

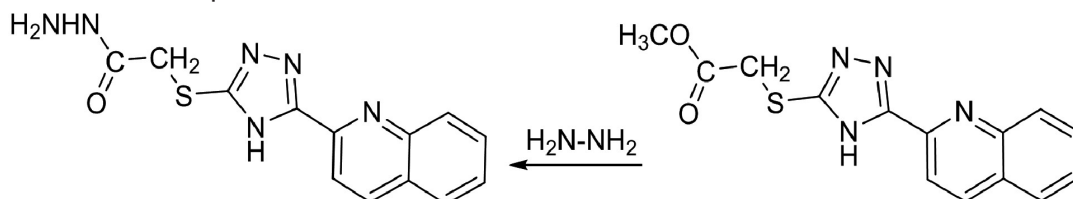


Fig. 4. Scheme of synthesis of hydrazide 2-(5-(quinolin-2-yl -4-1H-1,2,4-triazole-3-thio)-acetic acid

Synthesis of bioactive S-derivatives of 5-(phenoxyethylene)-4-R-1,2,4-triazole-3-thione.

The authors²³⁻²⁵ were synthesized 2-((5-(phenoxyethylene)-4-R-1,2,4-triazole-3-yl)thio)-ethan-1-ol and the corresponding ethyl chlorides. The alkylation of 2-((5-(phenoxyethylene)-4-R-1,2,4-triazole-3-yl)thio)ethyl chloride with the corresponding 5-R₁-4-R₂-1,2,4-triazole-3-thions were carried out. Methods for

8 Каплаушенко, Т. М., Панасенко, О. І., & Самелюк, Ю. Г. (2016). Синтез та встановлення фізикохімічних констант 2-(5-(хінолін-2-іл, 2-гідроксихінолін-4-іл)-4-гі-1, 2, 4-триазол-3-ілтіо) ацетатних кислот та їх естерів. Фармацевтичний журнал, (2), 53-59; Каплаушенко, Т. М., & Панасенко, О. І. (2016). Synthesis and physico-chemical properties of 3-alkylthio-5-(quinoline-2-yl, 2-hydroxyquinoline-4-yl)-4-R-2, 4-dihydro-3H-1, 2, 4-triazoles. Запорозький медичинський журнал, (3), 99-103; Каплаушенко, Т. М., Панасенко, О. І., & Кучерявий, Ю. М. (2016). Окиснення 2-(5-(хінолін-2-іл)-1, 2, 4-триазол-3-іл) тіо) етанової кислоти та її естерів до 3-ілсульфініл-та 3-ілсульфонілпохідних. Український біофармацевтичний журнал, (4), 56-60.

obtaining of 2-((5-(phenoxy)methylene)-4-R-1,2,4-triazole-3-yl)thio)aceto- and propanonitriles and 2-, 3-, 4-(((5-(phenoxy)methylene)-4-R-1,2,4-triazole-3-yl)thio) methyl)benzonitriles were established by HPLC-MS. The conditions of their further acid hydrolysis and counter-synthesis were obtained. As a result, the corresponding alkyl- and arylcarboxylic acids (Fig. 5), and salts and esters were synthesized to expand the range of studies of biological action⁹.

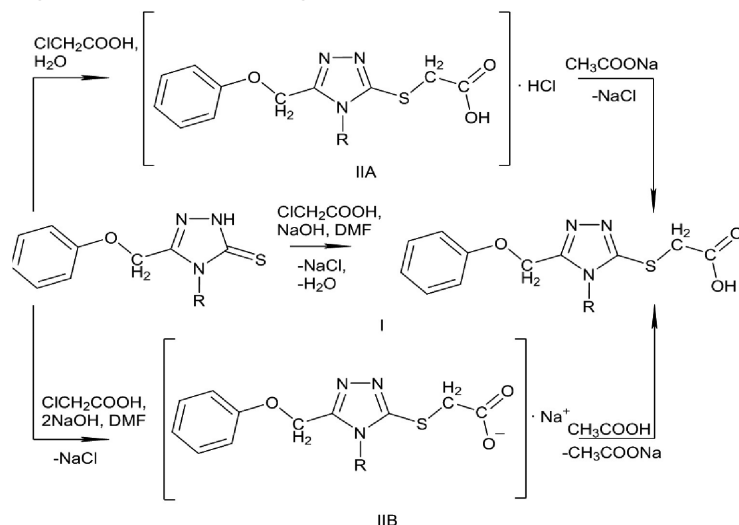


Fig. 5. Scheme of synthesis of 2-(5-(phenoxy)methylene)-4-R-1,2,4-triazole-3-ylthio)acetic acids

Hydrazides of 2-(5-(phenoxy)methylene)-4-R-1,2,4-triazole-3-yl)thio)acetic acids were used to obtain a number of suitable ylidenes. The presence of isomeric forms was determined by two-dimensional NOESY NMR spectrometry for it.

The authors were investigated antimicrobial and antifungal, antihypoxic, diuretic, antipyretic, actoprotective and hypoglycemic properties for derivatives of 5-(phenoxy)methylene)-4-R-1,2,4-triazole-3-thions.

As the most active hypoglycemic agent were proposed 2-(4-ethyl-5-(phenoxy)methylene) 1,2,4-triazole-3-ylthio)acetic acid hydrochloride.

Development of hepatoprotectors based on (3-thio-4-R-1,2,4-triazole-5-yl) (phenyl)methanols and their derivatives.

Scientists¹⁰ have synthesized a number of (3-alkyl, alkarylthio-4-R-4H-1,2,4-triazole-3-yl)(phenyl)methanols. The oxidation reactions of the Sulfur atom with potassium hy-

9 Кучерявий, Ю. М., Каплаушенко, А. Г., & Ал, З. Ф. (2015). Синтез 5-(феноксиметил)-4-R-3-алкілтіо 1, 2, 4-тріазолів та їх подальше окиснення до 3-алкілсульфонілпохідних. Актуальні питання фармацевтичної і медичної науки та практики, (3), 14-18; Кучерявий, Ю. М. (2016). Пошук потенційних протидіабетичних засобів серед деяких 3-тіопохідних 5-(феноксиметил)-4-R-1, 2, 4-тріазол-3-тіонів. Актуальні питання фармацевтичної і медичної науки та практики, (2), 15-19; Кучерявий, Ю. М. (2016). поиск потенциальных противодиабетических средств в ряду 3-тиопроизводных 5-(феноксиметил)-4-R-1, 2, 4-тріазол-3-тіонів. Актуальні питання фармацевтичної і медичної науки та практики, (2), 15-19.

10 Рудь, А. М., Каплаушенко, А. Г., Самелюк, Ю. Г., Рудь, А. М., Каплаушенко, А. Г., & Самелюк, Ю. Г. (2018). Синтез нових алкілсульфоніл (сульфініл) похідних 1, 2, 4-тріазолу на основі (3-(алкілтіо)-4-R-1, 2, 4-тріазол-5-іл)(феніл) метанолів; Рудь, А. М., & Кучерявий, Ю. М. (2015). Встановлення показників діуретичної активності ряду (4-аміно-5-(алкілтіо)-1, 2, 4-тріазол-3-іл)(феніл) метанолів.

drogen peroxosulfate and hydrogen peroxide of the starting (3-alkylthio-4-R-4H-1,2,4-triazole-3-yl)(phenyl)methanols were studied. A number of new 3-(5-(hydroxy(phenyl)methyl)-4-R-4H-1,2,4-triazole-3-yl)thio)aceto(propano-, methyl-2-, 3-, 4-benzo)nitriles, 2-((5-(hydroxy(phenyl)methyl)-4-R-4H-1,2,4-triazole-3-yl)thio)acetic and methylbenzoic acids, their esters, salts, alkyl 2-((5-(hydroxy(phenyl)methyl)-4-methyl-4H-1,2,4-triazole-3-yl)thio)acetimidate, 2-((5-(hydroxy(phenyl)methyl)-4-R-1,2,4-triazole-3-yl)thio)acetohydrazide, N'-R-(aryl)iden-2-((5-(hydroxy(phenyl)methyl)-4-R-1,2,4-triazole-3-yl)thio)acetohydrazides were synthesized.

The study of acute toxicity, antioxidant and actoprotective activity of (3-thio-4-R-1,2,4-triazole-5-yl)(phenyl)methanols and their derivatives were allowed to select a number of substances, among which promising highly active hepatoprotectors were identified.

According to the results of pharmacological screening²⁷ for in-depth study was recommended as a highly active potential hepatoprotector of antioxidant action, previously unknown 2-((5-(hydroxy(phenyl)methyl)-4-methyl-4H-1,2,4-triazole-3-yl)thio)acetoni- trile. The scheme of synthesis of 3-(5-(hydroxy(phenyl)methyl)-4-R-4H-1,2,4-triazole-3-ylthio)alkyl(alkylaromatic)acids was in Fig. 6.

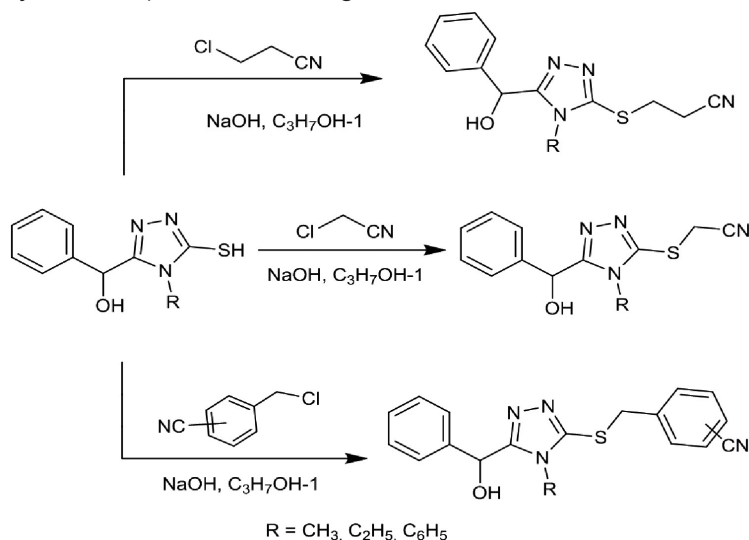


Fig. 6. Scheme for obtaining a number of nitriles of 3-(5-(hydroxy(phenyl)methyl)-4-R-4H-1,2,4-triazole-3-ylthio)alkyl(alkylaromatic)acids

The prospect of using 5-(1H-tetrazole-1-yl)-4-R-3-thio(amino)-1,2,4-triazole to create new biologically active substances.

The synthesis of alkyl-2-[[5-(1H-tetrazole-1-yl)methyl-4-R-(1,2,4-triazole-3-yl)thio]ethane (propane, benzyl)]imidates was had a hypoglycemic effect. The authors¹¹ were

11 Frolova, Y., Kaplaushenko, A., & Nagornaya, N. (2020). Design, synthesis, antimicrobial and antifungal activities of new 1, 2, 4-triazole derivatives containing 1h-tetrazole moiety; Hulina, Y. S., & Kaplaushenko, A. G. (2017). Synthesis and physical-chemical properties of 6-(5-(1H-tetrazole-1-ylmethyl)-4-R-1, 2, 4-triazole-3-ylthio) pyridin-3-amines and 6-((5-(1H-tetrazole-1-yl) methyl-4-R-1, 2, 4-triazole-3-ylthio) pyridin-3-yl)-(alk, ar, heter) yl-methanimines. Запорожский медицинский журнал, (19,№ 1), 100-104; Hulina, Y. S., & Kaplaushenko, A. G. (2018). Синтез, физико-химические свойства и дальнейшие превращения в ряду 5-((1H-тетразол-1-ил) ме-

received 2-[5-(1H-tetrazole-1-yl)methyl-4-R-(1,2,4-triazole-3-yl)thio]ethane(propane) and 2-, 4- [5-(1H-tetrazole-1-yl)methyl-4-phenyl-(1,2,4-triazole-3-yl)thiomethyl]benzoic acids, their salts.

Scientists have also obtained 6-(5-(1H-tetrazole-1-yl)methyl-4-R-(1,2,4-triazole-3-yl)thio)pyridin-3-amines, which were converted to 6-[(5-(1H-tetrazole-1-yl)methyl-4-R-(1,2,4-triazole-3-yl)thio)pyridin-3-yl)-(alkyl-, aryl)]methanimines (Fig. 7). Subsequently, the compounds were subjected to selective reduction of the double aliphatic C=N bond.

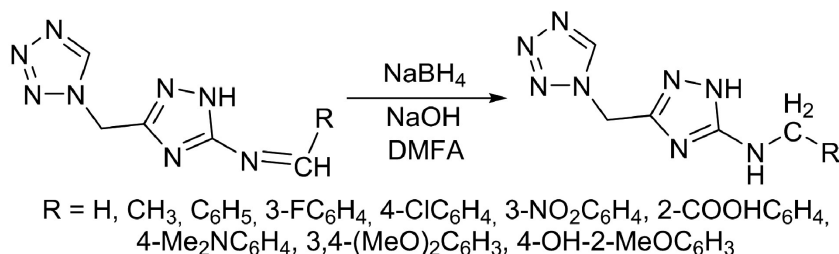


Fig. 7. Scheme of synthesis of 5-(1H-tetrazole-1-yl)methyl-4H-1,2,4-triazole-3-yl-1-(alkyl-, aryl-, heteryl)methanimines

Acute toxicity was investigated for the compounds. The LD₅₀ of 5-(1H-tetrazole-1-yl)methyl-4-R-3-thio(amino)-1,2,4-triazole derivatives was in the range of 357-1060 mg / kg. During the study of the biological activity of 1,2,4-triazole derivatives, substances were found that show high indicators of antimicrobial and fungal (6), diuretic (5), actoprotective (3), antihypoxic (6), antipyretic (2) and hypoglycemic (4) actions.

The authors¹² were recommended 5-(1H-tetrazole-1-yl)methyl-4H-1,2,4-triazole-3-yl-1-(5-nitrofuranyl)methanimine as antimicrobial and antifungal agent.

Also, scientists of Zaporizhzhia State Medical University are currently developing new unique compounds based on 4-R-5-phenethyl-2,4-dihydro-3H-1,2,4-triazole-3-thions, which has already given the first results¹³, among which, according to preliminary data, it is possible to select compounds with high rates of antihypoxic action.

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12 Hulina, Y. S., & Kaplaushenko, A. G. (2017). Synthesis and physical-chemical properties of 6-(5-(1H-tetrazole-1-yl)methyl)-4-R-1, 2, 4-triazole-3-ylthio) pyridin-3-amines and 6-((5-(1H-tetrazole-1-yl) methyl-4-R-1, 2, 4-triazole-3-ylthio) pyridin-3-yl)-(alk, ar, heter) ylmethanimines. Запорозький медичинський журнал, (19, № 1), 100-104.

13 Ihnatova, T. V., Kaplaushenko, A. G., & Frolova, Y. S. (2020). Синтез та дослідження фізико-хімічних властивостей похідних 1, 2, 4-триазолу, що містять фенетильний замісник у положенні 5. Журнал органічної та фармацевтичної хімії, 18(2 (70)), 48-53; 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; Ihnatova, T. V., Kaplaushenko, A. G., Фролова, Ю. С., Игнатова, Т. В., Каплаушенко, А. Г., & Фролова, Ю. С. (2019). Створення, дослідження фізичних і хімічних властивостей 2-((4-R-5-фенетил-4H-1, 2, 4-триазол-3-іл) тіо) етанових (пропанових, бензойних) кислот і солей 2-((4-R-5-фенетил-4H-1, 2, 4-триазол-3-іл) тіо) етанових кислот.