



Synthesis and transformation in the series of 2-((5-(2,4- and 3,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-yl)thio)acetic acids

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

The aim of the work is to develop preparative methods for the synthesis of 2-((5-(2,4- and 3,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-yl)thio)acetic acids, to study the esterification reaction in this regard, to study physical and chemical properties of the obtained substances, and to predict their toxicity.

Materials and methods. Compounds were synthesized using reagents and solvents qualified as “ch.p.”. The IUPAC nomenclature as supplemented was used during the preparation. The melting temperature was determined with the capillary method according to HFC (2.2.14) on the device PTP (M). Elemental analysis was determined with the ELEMENTAR vario EL cube analyzer (manufactured in Germany) (standard – sulfonamide). IR spectra were recorded using spectrophotometer Specord M-80 (manufactured in Germany) within the range of 4000–500 cm⁻¹ (scanning was performed under the following conditions: slot program 3.0, time constant – τ = 3 s, scanning time 34 min, samples were analyzed in the form of tablets with potassium bromide). ¹H NMR spectra were recorded using Varian VXR-300 spectrophotometer (manufactured in the USA), dimethyl sulfoxide-D₆ solvent, and tetramethylsilane was used as an internal standard. The spectra were decoded using the computer program ADVASP 1.43. Thin layer chromatography was performed using Sorbfil plates (analytical, size 10 × 15 cm, base: polymer substrate, sorbent: silica gel STX-1A, grain: 5–17 μm, layer thickness: 110 m combination – silicazole).

Results. The synthesis of new 2-((5-(2,4- and 3,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-yl)thio)acetic acids was carried out. These products became a basis for synthesis of a number of relevant esters. Physical and chemical properties were investigated for the synthesized compounds. The structure of the obtained substances was confirmed by elemental analysis, IR-spectroscopy, ¹H NMR-spectrometry, and their individuality were established by thin-layer chromatography. Computer GUSAR-online prediction of acute toxicity of 2-((5-(2,4- and 3,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-yl)thio)acetic acids and their esters was performed.

Conclusions. Preparative methods for the synthesis of 2-((5-(2,4- and 3,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-yl)thio)acetic acids have been developed, for which esterification reactions have been studied. Thus, physical and chemical properties of the received substances were investigated, and indicators of their toxicity were predicted.

Key words: 2-((5-(2,4- and 3,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-yl)thio)acetic acids, esters, toxicity indicators.

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Синтез і перетворення в ряду 2-((5-(2,4- та 3,4-диметоксифеніл)-3H-1,2,4-тріазол-3-іл)тіо)ацетатних кислот

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Мета роботи – розробити препаративні методики синтезу 2-((5-(2,4- та 3,4-диметоксифеніл)-3H-1,2,4-тріазол-3-іл)тіо)ацетатних кислот, для яких вивчити реакцію естерифікації, дослідити фізико-хімічні властивості речовин, що отримали, та спрогнозувати параметри їхньої токсичності.

Матеріали та методи. Синтез сполук виконали з використанням реактивів і розчинників, що мають кваліфікацію «х.ч.». Під час підготовчої роботи використали номенклатуру IUPAC із доповненнями. Температуру плавлення визначали капілярним способом за ДФУ (2.2.14) на приладі ПТП (М). Елементний аналіз виконали на аналізаторі ELEMENTAR vario EL cube (ФРН) (стандарт – сульфаніламід). ІЧ-спектри записували, використовуючи спектрофотометр Specord M-80 (ФРН) в області 4000–500 см⁻¹ (сканування здійснювали в таких умовах: щільова програма 3.0, постійна часу – τ = 3 с, час сканування – 34 хв, проби аналізували у вигляді таблеток із калій бромідом). ¹H ЯМР-спектри реєстрували з використанням спектрофотометра Varian VXR-300 (США), розчинник – диметилсульфоксид-D₆, як внутрішній стандарт використали тетраметилсилан. Спектри розшифрували за допомогою комп'ютерної програми ADVASP 1.43. Тонкошарову хроматографію виконали, використовуючи пластинки Sorbfil (аналітичні, розмір 10 × 15 см, основа – полімерна підкладка, сорбент – силікагель СТХ-1А, зерно – 5–17 мкм, товщина шару – 110 мкм, речовина для сполучення – силіказоль).

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Key words: 2-((5-(2,4- and 3,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-yl)thio)acetic acids, esters, toxicity indicators.

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Результати. Здійснили синтез нових 2-((5-(2,4- та 3,4-диметоксифеніл)-3H-1,2,4-тріазол-3-іл)тіо)ацетатних кислот, що стали основою отримання ряду відповідних естерів. Дослідили фізико-хімічні властивості синтезованих сполук. Будову речовин підтверджено за допомогою елементного аналізу, ІЧ-спектроскопії та ¹H ЯМР-спектрометрії, а їхня індивідуальність встановлена методом тонкошарової хроматографії. Виконали комп'ютерне GUSAR-online прогнозування гострої токсичності 2-((5-(2,4- та 3,4-диметоксифеніл)-3H-1,2,4-тріазол-3-іл)тіо)ацетатних кислот та їхніх естерів.

Висновки. Розробили препаративні методики синтезу 2-((5-(2,4- та 3,4-диметоксифеніл)-3H-1,2,4-тріазол-3-іл)тіо)ацетатних кислот, для яких вивчили реакції естерифікації. Дослідили фізико-хімічні властивості речовин, що одержали, здійснили прогнозування показників їхньої токсичності.

Ключові слова: 2-((5-(2,4- та 3,4-диметоксифеніл)-3H-1,2,4-тріазол-3-іл)тіо)ацетатні кислоти, естери, показники токсичності.

Актуальні питання фармацевтичної і медичної науки та практики. 2021. Т. 14, № 1(35). С. 12–16

Синтез и превращения в ряду 2-((5-(2,4- и 3,4-диметоксифенил)-3H-1,2,4-триазол-3-ил)тио)ацетатных кислот

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Цель работы – разработать препаративные методики синтеза 2-((5-(2,4 и 3,4-диметоксифенил)-3H-1,2,4-триазол-3-ил)тио)ацетатных кислот, для которых изучить реакцию эстерификации, исследовать физико-химические свойства полученных веществ, спрогнозировать параметры их токсичности.

Материалы и методы. Синтез соединений проведен с использованием реактивов и растворителей, имеющих квалификацию «х.ч.». При подготовке работы использовали номенклатуру IUPAC с дополнениями. Температуру плавления определяли капиллярным способом по ГФУ (2.2.14) на приборе ПТП (М). Элементный анализ проведен на анализаторе ELEMENTAR vario EL cube (ФРГ) (стандарт – сульфаниламид). ИК-спектры записывали с использованием спектрофотометра Specord M-80 (ФРГ) в области 4000–500 см⁻¹ (сканирование осуществляли в таких условиях: щелевая программа 3.0, постоянная времени – τ = 3 с, время сканирования – 34 мин, пробы анализировали в виде таблеток с калий бромидом). ¹H ЯМР-спектры регистрировали с использованием спектрофотометра Varian VXR-300 (США), растворитель – диметилсульфоксид-D₆, в качестве внутреннего стандарта использован тетраметилсилан. Спектры расшифровали с помощью компьютерной программы ADVASP 1.43. Тонкослойная хроматография проведена с применением пластинок Sorbfil (аналитические, размер 10 × 15 см, основа – полимерная подложка, сорбент – силикагель СТХ-1А, зерно – 5–17 мкм, толщина слоя – 110 мкм, вещество для связывания – силиказоль).

Результаты. Проведен синтез новых 2-((5-(2,4 и 3,4-диметоксифенил)-3H-1,2,4-триазол-3-ил)тио)ацетатных кислот, ставших основой получения ряда соответствующих эфиров. Изучили физико-химические свойства синтезированных соединений. Строение веществ подтверждено с помощью элементного анализа, ИК-спектроскопии и ¹H ЯМР-спектроскопии, а их индивидуальность установлена методом тонкослойной хроматографии. Проведено компьютерное GUSAR-online прогнозирование острой токсичности 2-((5-(2,4 и 3,4-диметоксифенил)-3H-1,2,4-триазол-3-ил)тио)ацетатных кислот и их эфиров.

Выводы. Разработаны препаративные методики синтеза 2-((5-(2,4 и 3,4-диметоксифенил)-3H-1,2,4-триазол-3-ил)тио)ацетатных кислот, для которых изучены реакции эстерификации. Исследованы физико-химические свойства полученных веществ, проведено прогнозирование показателей их токсичности.

Ключевые слова: 2-((5-(2,4 и 3,4-диметоксифенил)-3H-1,2,4-триазол-3-ил)тио)ацетатные кислоты, сложные эфиры, показатели токсичности.

Актуальные вопросы фармацевтической и медицинской науки и практики. 2021. Т. 14, № 1(35). С. 12–16

Almost every year, unknown diseases, that require specific treatment, appear; unfortunately, existing drugs are not effective for some of them. Therefore, today the creation of affordable domestically manufactured drugs with a wide range of pharmacological activity remains an urgent task of pharmacy.

Analysis of the modern literature [1–5] indicates the prospects for the search for biologically active substances among 2-((5-(2,4- and 3,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-yl)thio)acetic acids and their esters. Analysis of the work of the scientific school of ZSMU, namely the dissertation [1] and articles [2–5], demonstrates that compounds containing 2-, 3-, 4-methoxy and 3,4,5-trimethoxyphenyl substituents are highly active antimicrobial, antifungal agents and can be the basis for the creation of promising drugs [2–4]. The pharmacological activity of 2-((5-(2,4- and 3,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-yl)thio)acetic acids and their esters has not been sufficiently studied. Therefore, the synthesis, study of physicochemical and biological properties

of 1,2,4-triazole-3-thioacetic acids containing 2,4- and 3,4-dimethoxyphenyl substituents, as well as acid esters, from our point of view have scientific novelty and theoretical and practical significance.

Aim

The purpose of the work is to develop preparative methods for the synthesis of 2-((5-(2,4- and 3,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-yl)thio)acetic acids, to study the esterification reaction in this regard, to study physical and chemical properties of the obtained substances, and to predict their toxicity.

Materials and methods

In the course of practical part of the research, 2-((5-(2,4- and 3,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-yl)thio)acetic acids were synthesized (compounds 2.5, 2.8, Fig. 1). This class of compounds was obtained in two ways. In the first case, the production of acids was carried out by the reaction

between 5-(2,4- and 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-thions (compounds 2.1, 2.2, Fig. 1) and monochloroacetic acid in the alkaline environment. As a solvent, a mixture of water and dimethylformamide in a ratio of 1 : 1 was used.

The second method was based on the interaction of ((5-(2,4- and 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-yl)thio)acetonitrile (compounds 2.3, 2.4, Fig. 1) with hydrochloric acid; water was used as a solvent.

Esters of 2-((5-(2,4- and 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-yl)thio)acetic acids were synthesized in order to reduce the acidic properties and prolong the biological action.

It is known that esters of 2-(1,2,4-triazole-3-ylthio)acetic acids demonstrate diuretic, neuroleptic, anti-inflammatory, moderate antimicrobial and other types of biological activity [3–5]. Moreover, the strength of these compounds action is influenced by both the substituents of 1,2,4-triazole nucleus, and the structure of a complex ester group.

Acid esters have high biological activity and can also be intermediates for the synthesis of amides, hydrazides, yliden hydrazides, and bicyclic structures – derivatives of 1,2,4-triazole.

Esters of 2-((5-(2,4- and 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-yl)thio)acetic acids (compounds 2.6, 2.7, 2.9, 2.10, Fig. 2) were obtained by a method involving the interaction of the corresponding 5-(2,4- and 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-thione (compounds 2.1, 2.2, Fig. 2) with methyl or ethyl chloroacetic acid ester in the presence of an equimolecular amount of alkali.

In order to achieve better yields of products and their higher purity, another method was used to obtain esters of 2-((5-(2,4- and 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-yl)thio)acetic acids (compounds 2.6, 2.7, 2.9, 2.10, Fig. 2), which involves the esterification of the above mentioned acids (compounds 2.5, 2.8) with methyl and ethyl alcohols in the presence of a catalytic amount of concentrated sulfuric acid. After the reaction, the excess alcohol was evaporated, the residue was first thoroughly washed with sodium bicarbonate solution (to pH 7–8), then with water (to pH 7), the precipitate was filtered off, further washed with water and dried.

Samples of esters of 2-((5-(2,4- and 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-yl)thio)acetic acids (compounds 2.6, 2.7, 2.9, 2.10, Fig. 2) were obtained by two methods that did not result in melting point depression.

After recrystallization, the individuation of 2-((5-(2,4- and 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-ylthio)acetic acids (compounds 2.5, 2.8) and their esters (compounds 2.6, 2.7, 2.9, 2.10) was confirmed by a complex use of elemental analysis, IR-spectrophotometry and their individuality was confirmed chromatographically. The results of the elemental analysis were confirmed with the data on the percentage of elements (C, H, N, S) in the samples of the obtained compounds. There were absorption bands $\text{—C}=\text{N}$ groups (in the cycle) at $1563\text{--}1603\text{ cm}^{-1}$, absorption bands of the aromatic ring at $1614\text{--}1598\text{ cm}^{-1}$ in the IR-spectra of all synthesized compounds. There were absorption bands of $\text{CH}_2\text{—COOH}$ groups at 1760 cm^{-1} in the IR-spectra of acids (compounds 2.5, 2.8) [6]. Moreover, the IR spectra of esters

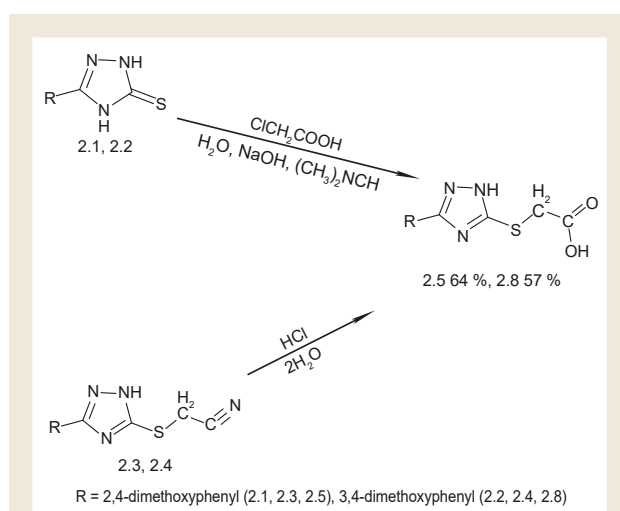


Fig. 1. Scheme of 2-((5-(2,4- and 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-yl)thio)acetic acids (compounds 2.5, 2.8) synthesis.

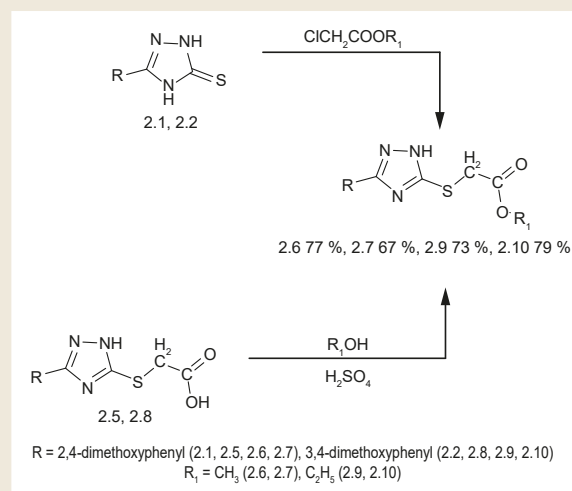


Fig. 2. Scheme of synthesis of 2-((5-(2,4- and 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-yl)thio)acetic acids (compounds 2.6, 2.7, 2.9, 2.10) esters.

(compounds 2.6, 2.7, 2.9, 2.10) were additionally characterized by the absorption bands of CO—C groups in the range of $1283\text{--}1227\text{ cm}^{-1}$ [6]. ^1H NMR-spectra of 2-((5-(2,4- and 3,4-dimethoxyphenyl)-3*H*-1,2,4-triazole-3-yl)thio)acetic acids (compounds 2.5, 2.8) and their esters (compounds 2.6, 2.7, 2.9, 2.10) were characterized by the presence of multiple signals of aromatic protons at 6.64–7.83 ppm, doublet signals of protons of methoxy groups at 3.65–3.90 ppm, singlet signals of the thiomethylene group have also been recorded at 3.32–3.43 ppm. In acetic acids, characteristic singlet signals of carboxyl groups were present at 12.32–12.34 ppm, and in esters of acetic acids there were signals of protons of the methyl group of the alcohol residue at 1.23–3.87 ppm.

The individuality of the synthesized compounds was proved by thin layer chromatography. The acetone : hexane : propanol 2 : 1 : 1 system was used as the mobile medium.

2-((5-(2,4- and 3,4-dimethoxyphenyl)-3H-1,2,4-triazol-3-yl)thio)acetic acid (compounds 2.5, 2.8)

Method A. In a glass of 250 ml 1 mole of the corresponding acetonitrile (2.3, 2.4) nitrile and 65 ml of hydrochloric acid were put, dissolved and left at room temperature for 5 days. Then 200 ml of water were added, precipitated, and the whole mixture was filtered off and dried.

Method B. 1 mole of the corresponding 5-(2,4- or 3,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-thione (compound 2.1), dissolved in 20 ml of dimethylformamide, was put into a 250 ml round bottom flask, equipped with a reflux condenser. 1 mole of NaOH (pre-dissolved in 20 ml of water) and 1 mole of monochloroacetic acid were added. It was heated to the pH of the solution in a slightly acidic medium, after which the resulting solution was evaporated.

As a result of the reactions, the following compounds were obtained: yellow (2.5) and orange (2.8) crystalline substances insoluble in water, soluble in solutions of alkalis and alkali metal carbonates, as well as in organic solvents and solutions of mineral acids. For analysis, substances were recrystallized from a mixture of dimethylformamide-water 2 : 1.

2-((5-(2,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-yl)thio)acetic acid (2.5). Yield 82 %, m.p. = 143–145 °C. Adsorption maxima in IR-spectra $V_{C=N \text{ cycle}} = 1598 \text{ cm}^{-1}$; $V_{CH_3}^{s/as} = 1388/1436 \text{ cm}^{-1}$; $V_{Ar} = 1609 \text{ cm}^{-1}$; $V_{C-S} = 701 \text{ cm}^{-1}$. $^1\text{H NMR}$ (400 MHz, DMSO-d₆) δ 3.32 (2H, s, S-CH₂); 3.84–3.90 (6H, d, O-CH₃); 4.2 (1H, s, CH); 6.67–7.83 (3H, m, C₆H₃); 12.34 (1H, s, COOH). Calcd for C₁₂H₁₃N₃O₄S %: C, 48.81; H, 4.44; N, 14.23; S, 10.86. Found %: C, 48.82; H, 4.45; N, 14.21; S, 10.86.

2-((5-(3,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-yl)thio)acetic acid (2.8). Yield 83 %, m.p. = 82–84 °C. Adsorption maxima in IR-spectra $V_{C=N \text{ cycle}} = 1602 \text{ cm}^{-1}$; $V_{CH_3}^{s/as} = 1370/1438 \text{ cm}^{-1}$; $V_{Ar} = 1601 \text{ cm}^{-1}$; $V_{C-S} = 694 \text{ cm}^{-1}$. $^1\text{H NMR}$ (400 MHz, DMSO-d₆) δ 3.38 (2H, s, S-CH₂); 3.65–3.83 (6H, d, O-CH₃); 4.22 (1H, s, CH); 6.98–7.49 (3H, m, C₆H₃); 12.32 (1H, s, COOH). Calcd for C₁₂H₁₃N₃O₄S %: C, 48.81; H, 4.44; N, 14.23; S, 10.86. Found %: C, 48.82; H, 4.45; N, 14.21; S, 10.86.

Esters of 2-((5-(2,4- and 3,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-yl)thio)acetic acids (compounds 2.6, 2.7, 2.9, 2.10).

Method A. To a solution of 0.01 mole of sodium hydroxide in 5 ml of water, 0.01 mole of the corresponding 5-R-1,2,4-triazole-3-thione (2.1, 2.2) in 50 ml of ethanol and 0.01 mole of monochloroacetic acid methyl ester were added. The mixture was boiled for 5 hours, the solvent was evaporated, the residue was washed with distilled water, and crystallized from a mixture of ethanol-water 3:1.

Method B. A mixture of 0.01 mole of the corresponding 2-((5-(2,4- or 3,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-yl)thio)acetic acid (compound 2.5, 2.8), 30 ml of alcohol (methanol, ethanol) and 0.5 ml of concentrated sulfuric acid was boiled for 10 hours, the solvent was evaporated, the residue was neutralized with sodium bicarbonate solution, which resulted in obtaining compounds 2.6, 2.7, 2.9, 2.10. White crystalline substances were insoluble in solutions of alkalis and alkali metal carbonates, sparingly soluble in water, and

soluble in organic solvents. For analysis, it was purified by recrystallization from ethanol-water 3 : 1.

Methyl 2-((5-(2,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-yl)thio)acetate (2.6). Yield 77 %, m.p. = 118–120 °C. Adsorption maxima in IR-spectra $V_{C=N \text{ cycle}} = 1603 \text{ cm}^{-1}$; $V_{CH_3}^{s/as} = 1367/1444 \text{ cm}^{-1}$; $V_{Ar} = 1598 \text{ cm}^{-1}$; $V_{CO} = 1663 \text{ cm}^{-1}$; $V_{C-O-C} = 1283 \text{ cm}^{-1}$; $V_{C-S} = 693 \text{ cm}^{-1}$. $^1\text{H NMR}$ (400 MHz, DMSO-d₆) δ 3.40 (2H, s, S-CH₂); 3.87 (3H, s, CH₃); 3.86–3.89 (6H, d, O-CH₃); 4.18 (1H, s, CH); 6.67–7.81 (3H, m, C₆H₃). Calcd for C₁₃H₁₅N₃O₄S %: C, 50.48; H, 4.89; N, 13.58; S, 10.36. Found %: C, 50.50; H, 4.90; N, 13.56; S, 10.35.

Ethyl 2-((5-(2,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-yl)thio)acetate (2.7). Yield 67 %, m.p. = 129–131 °C. Adsorption maxima in IR-spectra $V_{C=N \text{ cycle}} = 1598 \text{ cm}^{-1}$; $V_{CH_3}^{s/as} = 1383/1438 \text{ cm}^{-1}$; $V_{Ar} = 1603 \text{ cm}^{-1}$; $V_{CO} = 1723 \text{ cm}^{-1}$; $V_{C-O-C} = 1227 \text{ cm}^{-1}$; $V_{C-S} = 700 \text{ cm}^{-1}$. $^1\text{H NMR}$ (400 MHz, DMSO-d₆) δ 1.25 (3H, s, CH₃); 3.43 (2H, s, S-CH₂); 3.80–3.86 (6H, d, O-CH₃); 4.23 (1H, s, CH); 6.64–7.77 (3H, m, C₆H₃). Calcd for C₁₄H₁₇N₃O₄S %: C, 52.00; H, 5.30; N, 12.99; S, 9.91. Found %: C, 51.99; H, 5.28; N, 13.00; S, 9.90.

Methyl 2-((5-(3,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-yl)thio)acetate (2.9). Yield 73 %, m.p. = 120–122 °C. Adsorption maxima in IR-spectra $V_{C=N \text{ cycle}} = 1563 \text{ cm}^{-1}$; $V_{CH_3}^{s/as} = 1377/1470 \text{ cm}^{-1}$; $V_{Ar} = 1600 \text{ cm}^{-1}$; $V_{CO} = 1695 \text{ cm}^{-1}$; $V_{C-O-C} = 1230 \text{ cm}^{-1}$; $V_{C-S} = 704 \text{ cm}^{-1}$. $^1\text{H NMR}$ (400 MHz, DMSO-d₆) δ 3.37 (2H, s, S-CH₂); 3.84 (3H, s, CH₃); 3.69–3.89 (6H, d, O-CH₃); 4.17 (1H, s, CH); 6.97–7.50 (3H, m, C₆H₃). Calcd for C₁₃H₁₅N₃O₄S %: C, 50.48; H, 4.89; N, 13.58; S, 10.36. Found %: C, 50.50; H, 4.90; N, 13.56; S, 10.35.

Ethyl 2-((5-(3,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-yl)thio)acetate (2.10). Yield 79 %, m.p. = 115–117 °C. Adsorption maxima in IR-spectra $V_{C=N \text{ cycle}} = 1598 \text{ cm}^{-1}$; $V_{CH_3}^{s/as} = 1388/1433 \text{ cm}^{-1}$; $V_{Ar} = 1605 \text{ cm}^{-1}$; $V_{C-S} = 695 \text{ cm}^{-1}$. $^1\text{H NMR}$ (400 MHz, DMSO-d₆) δ 1.23 (3H, s, CH₃); 3.41 (2H, s, S-CH₂); 3.70–3.86 (6H, d, O-CH₃); 4.21 (1H, s, CH); 6.95–7.49 (3H, m, C₆H₃). Calcd for C₁₄H₁₇N₃O₄S %: C, 52.00; H, 5.30; N, 12.99; S, 9.91. Found %: C, 51.99; H, 5.28; N, 13.00; S, 9.93.

In order to exclude potentially toxic substances as unpromising objects of experimental pharmacological screening at the stage preceding the synthetic part, the prediction of acute toxicity of 2-((5-(2,4- and 3,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-yl)thio)acetic acids (compounds 2.5, 2.8) and their esters (compounds 2.6, 2.7, 2.9, 2.10) was performed using the GUSAR-online program. Computer prediction of acute toxicity of synthesized compounds was performed according to the structural formulas of the compounds in the online version of the program GUSAR-online [7].

Results

As predicted by GUSAR-online for tested 2-((5-(2,4- and 3,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-yl)thio)acetic acids (compounds 2.5, 2.8) and their esters (compounds 2.6, 2.7, 2.9, 2.10), the average lethal dose of LD₅₀ for the corresponding acetic acids was when administered: intraperitoneally – from 455.4 to 480.1 mg/kg, intravenously – from

315.1 to 340.5 mg/kg, orally – from 578.8 to 1235.0 mg/kg and subcutaneously – from 1043.0 to 1150.0 mg/kg. The average lethal dose of LD₅₀ for the corresponding esters of acetic acid was when administered: intraperitoneally – from 801.9 to 866.1 mg/kg, intravenously – from 246.6 to 351.0 mg/kg, orally – from 955.3 to 1457.0 mg/kg and subcutaneously – from 1121.0 to 2015.0 mg/kg.

According to the results of the prediction of the toxicity index, it should be noted that all compounds belong to low-toxic and practically non-toxic substances, which corresponds to the 4th and 5th toxicity class according to the classification of K. K. Sidorov and according to the OECD classification [8].

Discussion

New 2-((5-(2,4- and 3,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-yl)thio)acetic acids were synthesized, becoming the basis for the production of a number of suitable esters. The structure of the obtained substances was confirmed by elemental analysis, the obtained results confirm the data on the percentage of elements (C, H, N, S) in the samples of the obtained compounds, IR-spectroscopy, in the IR-spectra of acids (compounds 2.5, 2.8) CH₂ absorption bands -COOH groups at 1760 cm⁻¹ [6]. Besides, the IR spectra of esters (compounds 2.6, 2.7, 2.9, 2.10) were additionally characterized by absorption bands of CO-C groups in the range of 1283–1227 cm⁻¹ [6] and ¹H NMR-spectrometry. In acetic acids, characteristic singlet signals of carboxyl groups were present at 12.32–12.34 ppm, and in esters of acetic acids there were signals of protons of the methyl group of the alcohol residue at 1.23–3.87 ppm, and their individuality was established by thin layer chromatography. According to the results of computer GUSAR-online prediction of toxicity indicators, it should be noted that all compounds were low-toxic and virtually non-toxic substances, which corresponds to 4 and 5 toxicity class according to the classification of K. K. Sidorov and the OECD classification [8].

Conclusions

1. Preparative methods have been developed and the synthesis of 2-((5-(2,4- and 3,4-dimethoxyphenyl)-3H-1,2,4-triazole-3-yl)thio)acetic acids and their esters has been carried out.

2. The structure of the obtained compounds was confirmed by elemental analysis of IR-spectroscopy, ¹H NMR-spectra, and their individuality was justified by thin layer chromatography.

3. Computerized prediction of acute toxicity was performed for the synthesized compounds, which showed the possibility of searching for potential drugs based on them.

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