Synthesis and properties of 2-(4-phenyl-5-(((5-phenylamino-1,3,4-thiadiazole-2-yl)thio)methyl)-1,2,4-triazole-3-yl)thio)ethanoic acid and its salts

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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

Analysis of the literature over the past decade has shown that the chemistry of 1,2,4-triazole and 1,3,4-thiadiazole attracts considerable interest from scientists around the world because of the many valuable properties of compounds of this class. Bibliosemantic analysis shows that the nuclei of 1,2,4-triazole and 1,3,4-thiadiazole are fragments of a number of known drugs and biologically active compounds. That is why the synthesis and study of physical-chemical, biological properties of salts and acids containing these heterocyclic fragments are quite relevant both from a theoretical and practical point of view.

The aim of the work was to targeted synthesis of 2-((4-phenyl-5-((5-phenylamino-1,3,4-thiadiazole-2-yl)thio)methyl)-1,2,4-triazole-3-yl) thio)ethanoic acid and its salts, as well as the establishment of physical-chemical properties of the synthesized compounds. Estimation of the biological potential of the obtained compounds by molecular modeling method.

Materials and methods. 4-Phenyl-5-(((5-phenylamino-1,3,4-thiadiazole-2-yl)thio)methyl)-1,2,4-triazole-3-thiol, which was synthesized by the classical method described in earlier works, was used as a key intermediate. The reaction of the corresponding thiol with sodium monochloroacetate in aqueous medium and subsequent acidification with ethanoic acid gave the target acid.

Inorganic salts of 2-((4-phenyl-5-(((5-phenylamino-1,3,4-thiadiazole-2-yl)thio)-methyl)-1,2,4-triazole-3-yl)thio)ethanoic acid was synthesized by the reaction of the acid with sodium hydroxide, potassium hydroxide, magnesium oxide, calcium carbonate or zinc sulfate in an aqueous medium. For analysis, the salts obtained were purified by crystallization from methanol. Organic salts of 2-((4-phenyl-5-(((5-phenylamino-1,3,4-thiadiazole-2-yl)thio)-methyl)-1,2,4-triazole-3-yl)thio)ethanoic acid was obtained by the interaction of the corresponding acid with organic bases (ammonia, diethylamine, diethylmonoethanolamine, morpholine, piperidine) in propan-2-ol followed by evaporation of the solvent. For analysis, the synthesized substances were purified by crystallization from a mixture of water – propan-2-ol (1:1).

Results. During the work, the method of obtaining 2-((4-phenyl-5-(((5-phenylamino-1,3,4-thiadiazole-2-yl)thio)methyl)-1,2,4-triazole-3-yl) thio)ethanoic acids was optimized. The role of the reaction medium at this stage was played by water. The conditions of the synthesis of organic and inorganic salts of the specified acid, their structure, and physical-chemical properties were established. The biological potential was preliminarily assessed with molecular docking.

Conclusions. As a result of synthetic studies, 11 new, previously undescribed compounds were obtained. The structure, composition and individuality of the synthesized substances was confirmed by a set of the latest physical-chemical methods of analysis.

Key words: thiadiazole, 1,2,4-triazole, physical-chemical properties, molecular docking.

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Синтез і властивості 2-((4-феніл-5-(((5-феніламіно-1,3,4-тіадіазол-2-іл)тіо)метил)-1,2,4-тріазол-3-іл)тіо)етанової кислоти та її солей

А. С. Гоцуля, С. О. Федотов

Аналіз фахової літератури за останнє десятиліття показав, що хімія 1,2,4-тріазолу та 1,3,4-тіадіазолу привертає увагу науковців світу через безліч цінних властивостей сполук цього класу. Бібліосемантичний аналіз свідчить, що ядра 1,2,4-тріазолу та 1,3,4-тіадіазолу є фрагментами низки відомих лікарських препаратів і біологічно активних сполук. Саме тому синтез і дослідження фізико-хімічних, біологічних властивостей солей і кислот, що містять названі гетероциклічні фрагменти, є доволі актуальними і з теоретичного, і практичного погляду.

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Key words: thiadiazole, 1,2,4-triazole, physical-chemical properties, molecular docking.

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Мета роботи – цілеспрямований синтез 2-((4-феніл-5-(((5-феніламіно-1,3,4-тіадіазол-2-іл)тіо)метил)-1,2,4-тріазол-3-іл)тіо)етанової кислоти та її солей, а також встановлення фізико-хімічних властивостей синтезованих сполук; оцінювання біологічного потенціалу сполук, що одержали, методом молекулярного моделювання.

Матеріали та методи. Як ключову проміжну сполуку використали 4-феніл-5-(((5-феніламіно-1,3,4-тіадіазол-2-іл)тіо)метил)-1,2,4-тріазол-3-тіол, який синтезували, використовуючи класичну методику. У результаті взаємодії названого тіолу з натрій монохлорацетатом у водному середовищі з наступним підкисленням кислотою етановою одержали цільову кислоту. Неорганічні солі 2-((4-феніл-5-(((5-феніламіно-1,3,4-тіадіазол-2-іл)тіо)метил)-1,2,4-тріазол-3-іл)тіо)етанової кислоти синтезували взаємодією цієї кислоти з натрій гідроксидом, калій гідроксидом, магній оксидом, кальцій карбонатом або цинк сульфатом у водному середовищі. Для аналізу одержані солі очистили кристалізацією з метанолу. Органічні солі 2-((4-феніл-5-(((5-феніламіно-1,3,4-тіадіазол-2-іл)тіо)метил)-1,2,4-тріазол-3-іл)тіо)етанової кислоти отримали взаємодією відповідної кислоти з органічними основами (амоніак, діетиламін, діетилмоноетаноламін, морфолін, піперидин) у середовищі пропан-2-олу з випарюванням розчинника. Для аналізу синтезовані речовини очистили кристалізацією з суміші вода – пропан-2-ол (1:1).

Результати. Протягом роботи оптимізували спосіб одержання 2-((4-феніл-5-(((5-феніламіно-1,3,4-тіадіазол-2-іл)тіо)метил)-1,2,4-тріазол-3-іл)тіо)етанової кислоти. Роль реакційного середовища на цьому етапі виконала вода. Встановили оптимальні умови синтезу органічних і неорганічних солей названої кислоти, їхню структуру та фізико-хімічні властивості. За допомогою методу молекулярного докінгу здійснили попереднє оцінювання біологічного потенціалу сполук, які синтезували.

Висновки. У результаті синтетичних досліджень одержали 11 нових, неописаних раніше сполук. Будову, склад та індивідуальність цих речовин підтвердили комплексом новітніх фізико-хімічних методів аналізу.

Ключові слова: тіадіазол, 1,2,4-тріазол, фізико-хімічні властивості, молекулярний докінг.

Актуальні питання фармацевтичної і медичної науки та практики. 2020. Т. 13, № 3(34). С. 330–336

Синтез и свойства 2-((4-фенил-5-(((5-фениламино-1,3,4-тиадиазол-2-ил)тио)метил)-1,2,4-триазол-3-ил)тио)этановой кислоты и ее солей

А. С. Гоцуля, С. О. Федотов

Анализ научной литературы за последнее десятилетие показал, что химия 1,2,4-триазола и 1,3,4-тиадиазола вызывает большой интерес учёных всего мира благодаря множеству ценных свойств соединений данного класса. Библиосемантический анализ свидетельствует, что ядра 1,2,4-триазола и 1,3,4-тиадиазола – фрагменты ряда известных лекарственных препаратов и биологически активных соединений. Именно поэтому синтез и исследование физико-химических, биологических свойств солей и кислот, содержащих указанные гетероциклические фрагменты, актуальны и с теоретической, и с практической точки зрения.

Цель работы – целенаправленный синтез 2-((4-фенил-5-(((5-фениламино-1,3,4-тиадиазол-2-ил)тио)метил)-1,2,4-триазол-3-ил)тио)этановой кислоты и ее солей, а также установление физико-химических свойств синтезированных соединений; оценка биологического потенциала полученных соединений методом молекулярного моделирования.

Материалы и методы. В качестве ключевого промежуточного соединения использован 4-фенил-5-((5-фениламино-1,3,4-тиадиазол-2-ил)тио)метил)-1,2,4-триазол-3-тиол, который синтезирован с использованием классической методики. В результате взаимодействия соответствующего тиола с натрий монохлорацетатом в водной среде и с последующим подкислением кислотой этановой получена целевая кислота.

Неорганические соли 2-((4-фенил-5-(((5-фениламино-1,3,4-тиадиазол-2-ил)тио)метил)-1,2,4-триазол-3-ил)тио)этановой кислоты синтезированы взаимодействием указанной кислоты с натрий гидроксидом, калий гидроксидом, магний оксидом, кальций карбонатом или цинк сульфатом в водной среде. Для анализа полученные соли очищены кристаллизацией из метанола. Органические соли 2-((4-фенил-5-(((5-фениламино-1,3,4-тиадиазол-2-ил)тио)метил)-1,2,4-триазол-3-ил)тио)этановой кислоты получены взаимодействием соответствующей кислоты с органическими основаниями (аммиак, диэтиламин, диэтилмоноэтаноламин, морфолин, пиперидин) в среде пропан-2-ола с последующим выпариванием растворителя. Для анализа синтезированные вещества очищены кристаллизацией из смеси вода – пропан-2-ол (1:1).

Результаты. В ходе работы оптимизирован способ получения 2-((4-фенил-5-(((5-фениламино-1,3,4-тиадиазол-2-ил)тио)метил)-1,2,4-триазол-3-ил)тио)-этановой кислоты. Роль реакционной среды на этом этапе выполнила вода. Установлены оптимальные условия синтеза органических и неорганических солей указанной кислоты, их структура и физико-химические свойства. С помощью метода молекулярного докинга осуществлена предварительная оценка биологического потенциала синтезированных веществ.

Выводы. В результате синтетических исследований получены 11 новых, неописанных ранее соединений. Строение, состав и индивидуальность синтезированных соединений подтверждены комплексом новейших физико-химических методов анализа.

Ключевые слова: тиадиазол, 1,2,4-триазол, физико-химические свойства, молекулярный докинг.

Актуальные вопросы фармацевтической и медицинской науки и практики. 2020. Т. 13, № 3(34). С. 330–336

An analysis of the literature sources over the last decade has shown that the chemistry of 1,2,4-triazole and 1,3,4-thiadiazole attracts significant interest from scientists around the world because of the many valuable properties of compounds of this class [1,2]. Bibliosemantic analysis shows that the nuclei of 1,2,4-triazole and 1,3,4-thiadiazole are fragments of a number of known drugs and biologically active compounds [3,4]. That is why the synthesis and study of physical-chemical, biological properties of salts and acids containing these heterocyclic fragments are quite relevant both from a theoretical and practical point of view [5,6].

Aim

The aim of this study is the directed synthesis of 2-((4-phenyl-5-(((5-phenylamino-1,3,4-thiadiazol-2-yl)thio)methyl)-1,2,4-triazole-3-yl)thio)ethanoic acid and its salts, as well as the establishment of physical-chemical properties of the synthesized compounds. Estimation of biological potential of the obtained compounds by molecular modeling method.

Materials and methods

4-Phenyl-5-(((5-phenylamino-1,3,4-thiadiazole-2-yl)thio) methyl)-1,2,4-triazole-3-thiol, which was synthesized by the classical method described in earlier works, was used as a key intermediate [7]. The reaction of the corresponding thiole with sodium monochloroacetate in aqueous medium and subsequent acidification with ethanoic acid gave the target acid. Inorganic salts of 2-((4-phenyl-5-(((5-phenylamino-1,3,4-thiadiazol-2-yl)thio)methyl)-1,2,4-triazole-3-yl)thio) ethanoic acid was synthesized by the interaction of this acid with sodium hydroxide, potassium hydroxide, magnesium oxide, calcium carbonate or zinc sulfate in an aqueous medium. For analysis, the salts obtained were purified by crystallization from methanol. Organic salts of 2-((4-phenyl-5-(((5-phenylamino-1,3,4-thiadiazol-2-yl)thio)methyl)-1,2,4-triazole-3-yl)thio)ethanoic acid is obtained by reacting the corresponding acid with organic bases (ammonia, diethylamine, diethylmonoethanolamine, morpholine, piperidine) in propan-2-ol followed by evaporation of the solvent. For analysis, the synthesized substances were purified by crystallization from a mixture of water – propan-2-ol (1 : 1).

The study of physical-chemical properties of the obtained compounds was carried out by methods listed in the State Pharmacopoeia of Ukraine. Melting points were determined by the open capillary method on an OptiMelt MPA 100 with a platinum RTD sensor. The elemental analysis was performed by the "Elementar vario EL cube" analyzer (Elementar Analysensysteme, Germany). IR spectra (4000–400 cm^{-1}) were taken off the module ALPHA-T of Bruker ALPHA FT-IR spectrometer (Bruker optics, Germany). ^1H NMR spectra (400 MHz) were recorded at "Varian-MR 400" spectrometer with $SiMe_4$ as internal standard in DMSO-d_6 solution. Chromatography-mass spectral studies were conducted on the instrument "Agilent 1260 Infinity HPLC" equipped with a mass spectrometer "Agilent 6120" (method of ionization – electrospray (ESI)).

2-((4-Phenyl-5-(((5-phenylamino-1,3,4-thiadiazole-2-yl) thio)methyl)-1,2,4-triazole-3-yl)thio)ethanoic acid (2) *(Fig. 1)*. It was heated 0.005 mol of 4-phenyl-5-(((5-phenylamino-1,3,4-thiadiazole-2-yl)thio)methyl)-1,2,4-triazole-3-thiol, 0.01 mol of NaOH, 50 H_2O and 0.005 mol of monochloroacetic acid in a round bottomed flask. The reaction mixture was boiled for 1 hour and cooled up to room temperature. The solution was neutralized with acetic acid. The obtained compound was filtered off, washed with H_2O and recrystallized from propan-1-ol. Yield–79 %. M. p.: 104–106 ºC.

2-((4-Phenyl-5-((5-phenylamino-1,3,4-thiadiazole-2-yl)thio) methyl)-1,2,4-triazole-3-yl)thio)ethanoic acid with organic bases. A mixture of 0.01 mol of the starting carboxylic acid, 15–20 ml of water and 0.012 mol of the corresponding organic base (diethylamine, diethylmonoethanolamine, morpholine, piperidine) was heated for 1 hour in a water bath, filtered, the solvent was evaporated to a total volume. The residue was added to acetone or propan-1-ol. The precipitated white crystalline substances were recrystallized from ethanol. The product was soluble in water, sparingly soluble in organic solvents.

Sodium, potassium salts of 2-((4-phenyl-5-((5-phenylamino-1,3,4-thiadiazole-2-yl)thio)methyl)-1,2,4-triazole-3-yl) thio)ethanoic acid *(Fig. 2)*. A mixture of 0.01 mol of the starting carboxylic acid and 0.01 mol of sodium or potassium hydroxide in 30 ml of water was heated in a water bath for 10–15 minutes, filtered and evaporated to its

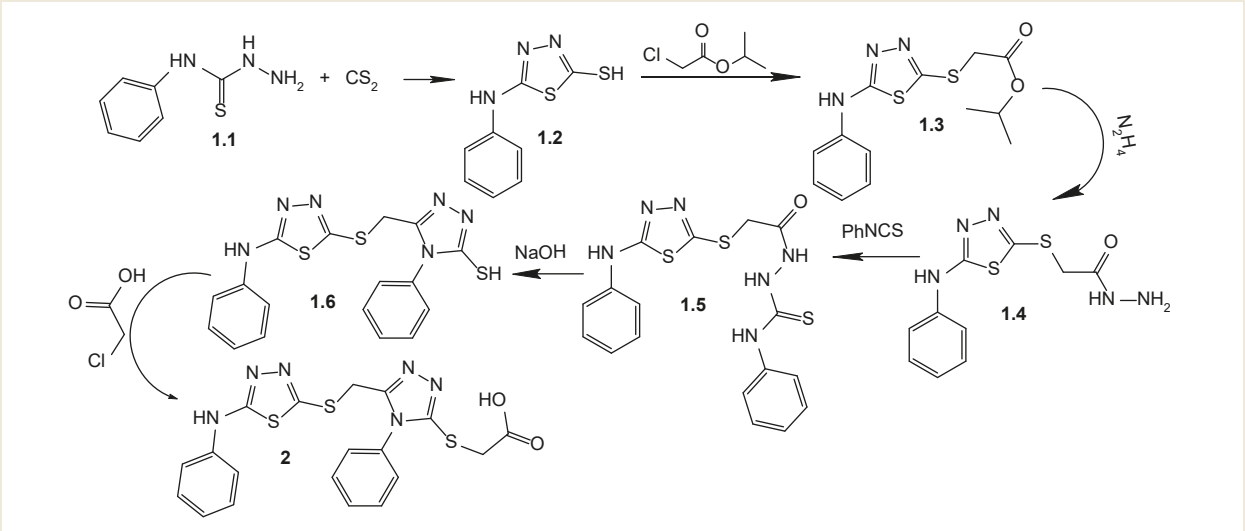

Fig. 1. Synthesis scheme of 2-((4-phenyl-5-(((5-phenylamino-1,3,4-thiadiazole-2-yl)thio)methyl)-1,2,4-triazole-3-yl)thio)ethanoic acid.

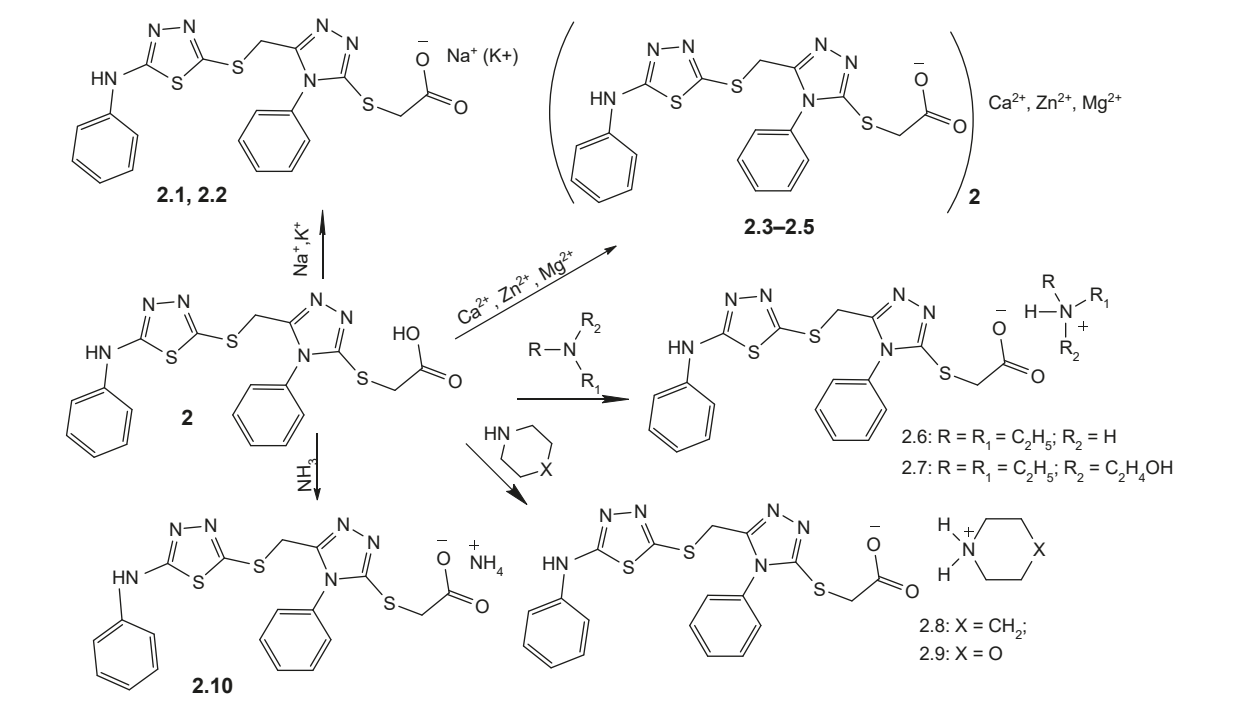

Fig. 2. Scheme for the synthesis of salts of 2-((4-phenyl-5-(((5-phenylamino-1,3,4-thiadiazole-2-yl)thio)methyl)-1,2,4-triazole-3-yl)thio)ethanoic acid.

original volume and precipitated by the addition of acetone. It was obtained white crystalline substances, sparingly soluble in organic solvents. The compound was recrystallized from ethanol for analysis.

Magnesium, calcium and zinc salts of 2-((4-phenyl-5-(((5-phenylamino-1,3,4-thiadiazole-2-yl)thio)methyl)-1,2,4-triazole-3-yl)thio)acetic acid *(Fig. 2)*. A mixture of 0.02 mol of the starting carboxylic acid, 25 ml of water and 0.01 mol of magnesium oxide or calcium carbonate or zinc sulphate, respectively, was heated to dissolve the precipitate, filtered and the filtrate was evaporated. The compounds were recrystallized from water. The resulting product was a white solid, sparingly soluble in water, sparingly soluble in organic solvents.

Ammonium 2-((4-phenyl-5-(((5-phenylamino-1,3,4-thiadiazole-2-yl)thio)methyl)-1,2,4-triazole-3-yl)thio)acetate. A solution of 0.01 mol of the original carboxylic acid in 30 ml of 25 % ammonia solution was evaporated. The product was recrystallized from 1,4-dioxane : water (3:1). The target compound was a white solid, slightly soluble in water, sparingly soluble in ethanol.

Results

The structure and individuality of the synthesized compounds were confirmed by a package of modern physical-chemical methods of analysis.

For example, in the IR spectra of all synthesized compounds there were absorption bands –C=N groups at 1607–1582 cm^{-1}, C–S groups – at 702–685 cm^{-1}, as well as symmetric and asymmetric absorption bands characteristic of carboxylic acid salts containing COO groups in the range of 1371–1342 cm^{-1} and 1597–1525 cm^{-1}, respectively. The IR spectra of salts also were contained absorption bands at 1508–1473 cm^{-1}, which indicates the presence of aromatic substituent's in their structure. For salts of organic bases there are wide absorption bands of primary and secondary amines in the range 3053–2907 cm^{-1} or 2712–2258 cm^{-1} and deformation oscillations in the range 1610–1563 cm^{-1}.

The IR spectrum of the ammonium salt were contained the absorption band of the valence vibrations of the ammonium group at 3435 cm^{-1}.

^{1}H NMR spectra of salts were confirmed by signals of the corresponding protonated amines. For example, in the spectrum of the diethylammonium salt, multiplets were observed in the intervals 3.12–3.01 and 1.40–1.33 ppm, respectively. In the spectrum of the diethylmonoethanolammonium salt there were two triplets at 4.03 ppm and 3.46 ppm, a singlet at 7.08 ppm, and an OH group signal in the form of a triplet at 4.16 ppm. The spectrum of the morpholine salt had a characteristic set of signals of the protonated cation of morpholine in the form of two multiplets at 3.96–3.83, 3.38–3.30 ppm and a singlet at 7.11 ppm. The piperidinium salt was characterized by proton signals of organic bases in the form of multiplets 3.15–3.11 ppm, 1.93–1.76 ppm, 1.55–1.42 ppm and 1.50 ppm and singlet 7.04 ppm.

2-((4-Phenyl-5-(((5-phenylamino-1,3,4-thiadiazole-2-yl)thio)methyl)-1,2,4-triazole-3-yl)thio)ethanoic acid. White crystalline substance in 77 % yield; m. p.: 204–206 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H, N*H*), 7.64–7.50 (m, 4H, NH-C$_6$*H*$_5$ H-3,5, C$_6$H$_5$ H-2,6), 7.46 (d, 2H, NH-C$_6$*H*$_5$ H-2,6), 7.37–7.26 (m, 3H, C$_6$*H*$_5$ H-3,5), NH-C$_6$*H*$_5$ H-4), 7.00

(t, J = 7.1 Hz, 1H, N-C$_6$$\underline{H}_5$ H-4), 4.36 (s, 2H, S-C$\underline{H}_2$), 3.86 (s, 2H, C$\underline{H}_2$COO).

Sodium 2-((4-phenyl-5-(((5-phenylamino-1,3,4-thiadiazole-2-yl)thio)methyl)-1,2,4-triazole-3-yl)thio)acetate. White crystalline substance in 83 % yield; m. p.: 228–230 °C. Analytical calculated (%) for $C_{19}H_{15}N_6NaO_2S_3$: C, 47.69; H, 3.16; N, 17.56; S, 20.10. Found: C, 47.80; H, 3.14; N, 17.52; S, 20.17.

Potassium 2-((4-phenyl-5-(((5-phenylamino-1,3,4-thiadiazole-2-yl)thio)methyl)-1,2,4-triazole-3-yl)thio)acetate. White crystalline substance in 79 % yield; m. p.: 247–249 °C. Analytical calculated (%) for $C_{19}H_{15}KN_6O_2S_3$: C, 46.13; H, 3.06; N, 16.99; S, 19.45. Found: C, 46.06; H, 3.07; N, 16.94; S, 19.48.

Magnesium 2-((4-phenyl-5-(((5-phenylamino-1,3,4-thiadiazole-2-yl)thio)methyl)-1,2,4-triazole-3-yl)thio)acetate. White crystalline substance in 74 % yield; m. p.: 194–196 °C.

Calcium 2-((4-phenyl-5-(((5-phenylamino-1,3,4-thiadiazole-2-yl)thio)methyl)-1,2,4-triazole-3-yl)thio)acetate. White crystalline substance in 69 % yield; m. p.: 222–224 °C.

Zinc 2-((4-phenyl-5-(((5-phenylamino-1,3,4-thiadiazole-2-yl)thio)methyl)-1,2,4-triazole-3-yl)thio)acetate. White crystalline substance in 81 % yield; m. p.: 213–215 °C.

Diethylammonium 2-((4-phenyl-5-(((5-phenylamino-1,3,4-thiadiazole-2-yl)thio)-methyl)-1,2,4-triazole-3-yl) thio)acetate. White crystalline substance in 78 % yield; m. p.: 179–181 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.48 (s, 1H, N$\underline{H}$), 9.24–9.19 (m, 3H, $^+$N$\underline{H}_2$-(C$_2$$\underline{H}_5$)$_2$,7.62–7.51 (m, 4H, NH-C$_6$$\underline{H}_5$ H-3,5, C$_6$H$_5$ H-2,6), 7.44 (d, 2H, NH-C$_6$$\underline{H}_5$ H-2,6), 7.35–7.25 (m, 3H, C$_6$$\underline{H}_5$ H-3,5), NH-C$_6$$\underline{H}_5$ H-4), 7.02 (t, J = 7.1 Hz, 1H, N-C$_6$$\underline{H}_5$ H-4), 4.36 (s, 2H, S-C$\underline{H}_2$), 3.86 (s,2H, C$\underline{H}_2$COO) 3.12–3.01 (m, 4H, $^+$NH$_2$-(C$\underline{H}_2$CH$_3$)$_2$), 1.40–1.33 (m, 6H, $^+$NH$_2$-(CH$_2$C$\underline{H}_3$)$_2$.Analytical calculated (%) for $C_{23}H_{27}N_7O_2S_3$: C, 52.15; H, 5.14; N, 18.51; S, 18.16. Found: C, 52.08; H, 5.16; N, 18.47; S, 18.19.

Piperidin-1-ium 2-((4-phenyl-5-(((5-(phenylamino)-1,3,4-thiadiazole-2-yl)thio)-methyl)-1,2,4-triazole-3-yl)thio)acetate. White crystalline substance in 80 % yield; m. p.: 197–199 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.48 (s, 1H, N$\underline{H}$), 7.61–7.50 (m, 4H, NH-C$_6$$\underline{H}_5$ H-3,5, C$_6$H$_5$ H-2,6), 7.41 (d, 2H, NH-C$_6$$\underline{H}_5$ H-2,6), 7.33–7.26 (m, 3H, C$_6$$\underline{H}_5$ H-3,5), NH-C$_6$$\underline{H}_5$ H-4), 7.04 (s, 2H, NH$_2$) 7.05 (t, J = 7.0 Hz, 1H, N-C$_6$$\underline{H}_5$ H-4), 4.35 (s, 2H, S-C$\underline{H}_2$), 3.83 (s,2H, C$\underline{H}_2$COO) 3.15-3.11 (m, 4H, piperidine H-2,6), 1.93–1.76 (m, 4H, piperidine *H-3,5*), 1.55–1.42 (m, 1H, piperidine H-4). Analytical calculated (%) for $C_{24}H_{27}N_7O_2S_3$: C, 53.21; H, 5.02; N, 18.10; S, 17.76. Found: C, 53.27; H, 5.00; N, 18.15; S, 17.76.

Morpholinium 2-((4-phenyl-5-(((5-phenylamino-1,3,4-thiadiazole-2-yl)thio)-methyl)-1,2,4-triazole-3-yl)thio) acetate. White crystalline substance in 84 % yield; m. p.: 189–191 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.45 (s, 1H, N$\underline{H}$), 7.59–7.48 (m, 4H, NH-C$_6$$\underline{H}_5$ H-3,5, C$_6$H$_5$ H-2,6), 7.38 (d, 2H, NH-C$_6$$\underline{H}_5$ H-2,6), 7.31–7.24 (m, 3H, C$_6$$\underline{H}_5$ H-3,5), NH-C$_6$$\underline{H}_5$ H-4), 7.11 (s, 2H, NH$_2$) 7.03 (t, J = 7.1 Hz, 1H, N-C$_6$$\underline{H}_5$ H-4), 4.33 (s, 2H, S-C$\underline{H}_2$), 3.80 (s,2H, C$\underline{H}_2$COO) 3.96–3.83 (m, 4H, morpholine H-*3,5*), 3.38–3.30 (m, 4H, morpholine H-2,6). Analytical calculated (%) for $C_{23}H_{25}N_7O_3S_3$: C, 50.81; H, 4.63; N, 18.03; S, 17.69. Found: C, 50.74; H, 4.62; N, 18.08; S, 17.72.

N,N-Diethyl-2-hydroxyethanaminium 2-((4-phenyl-5-(((5-phenylamino-1,3,4-thiadiazole-2-yl)thio)methyl)-1,2,4-triazole-3-yl)thio)acetate. White crystalline substance in 76 % yield; m. p.: 201–203 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.41 (s, 1H, N$\underline{H}$), 7.56–7.47 (m, 4H, NH-C$_6$$\underline{H}_5$ H-3,5, C$_6$H$_5$ H-2,6), 7.35 (d, 2H, NH-C$_6$$\underline{H}_5$ H-2,6), 7.30–7.25 (m, 3H, C$_6$$\underline{H}_5$ H-3,5), NH-C$_6$$\underline{H}_5$ H-4), 7,08 (s, 2H, NH$_2$) 6.98 (t, J = 7.1 Hz, 1H, N-C$_6$$\underline{H}_5$ H-4), 4.39 (s, 2H, S-C$\underline{H}_2$), 4.13 (s,2H, C$\underline{H}_2$COO) 4.16 (t, J = 6.8, Hz, 1H, O$\underline{H}$), 4.03 (t, J = 7.2 Hz, 2H, OH-C$\underline{H}_2$), 3.46 (t, 5.3 Hz, 2H, , OH-CH$_2$-C$\underline{H}_2$-), 3.30–3.24 (m, 4H, $^+$NH$_2$-(C$\underline{H}_2$-CH$_3$)$_2$), 1.35–1.28 (m, 6H, $^+$NH$_2$-(CH$_2$-C$\underline{H}_3$)$_2$). Analytical calculated (%) for $C_{25}H_{31}N_7O_3S_3$: C, 52.33; H, 5.45; N, 17.09; S, 16.77. Found: C, 52.28; H, 5.44; N, 17.13; S, 16.81.

Ammonium 2-((4-phenyl-5-(((5-phenylamino-1,3,4-thiadiazole-2-yl)thio)methyl)-1,2,4-triazole-3-yl)thio)acetate. White crystalline substance in 79 % yield; m. p.: 193–195 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.38 (s, 1H, N$\underline{H}$), 7.54–7.45 (m, 4H, NH-C$_6$$\underline{H}_5$ H-3,5, C$_6$H$_5$ H-2,6), 7.37 (d, 2H, NH-C$_6$$\underline{H}_5$ H-2,6), 7.31–7.24 (m, 3H, C$_6$$\underline{H}_5$ H-3,5, NH-C$_6$$\underline{H}_5$ H-4), 7,09 (s, 2H, NH$_2$) 6.95 (t, J = 7.1 Hz, 1H, N-C$_6$$\underline{H}_5$ H-4), 5.45 (s, 4H, $^+$N$\underline{H}_4$) 4.37 (s, 2H, S-C$\underline{H}_2$), 4.11 (s,2H, C$\underline{H}_2$COO). Analytical calculated (%) for $C_{11}H_{10}N_6S_3$: C, 40.98; H, 3.13; N, 26.06; S, 29.83. Found: C, 41.04; H, 3.12; N, 26.10; S, 29.80.

Today, the search for new effective drugs that would have anti-inflammatory and antimicrobial action remains an urgent problem. The fact remains that for many years the standard drugs Diclofenac sodium and Ketoconazole are used to treat inflammatory processes and fungal lesions [8–10].

Despite the pronounced anti-inflammatory and broad spectrum of antifungal action, these drugs are quite toxic to humans. In view of this, it is of some interest to obtain new substances with a similar mechanism of action, but with less toxicity.

Therefore, in the next stage of our work, we predicted the probability of anti-inflammatory activity among the synthesized substances using the *in silico* (molecular docking) method [11,12].

Molecular docking was performed using Autodock 4.2.6. Macromolecules from Protein Data Bank (PDB) were used as biological targets, namely COX-1 enzyme in complex with diclofenac and lanosterol-14α-demethylase in complex with ketoconazole *(Tables 1, 2)*. All programs used in the screening process are publicly available [13,14].

Discussions

As a result of the molecular docking for the synthesized salts of 2-((4-phenyl-5-(((5-phenylamino-1,3,4-thiadiazole-2-yl) thio)methyl)-1,2,4-triazole-3-yl)-thio)ethanoic acid established a promising level of anti-inflammatory effect. It should be noted that the conversion of the starting acid into a salt as a result of interaction with organic or inorganic bases leads to an increase in the likelihood of anti-inflammatory activity.

Table 1. Energy values of the intermolecular interactions of the studied compounds with COX-1 (4Z0L)

N	E_{min}, kJ × mol^{-1}	N	E_{min}, kJ × mol^{-1}	N	E_{min}, kJ × mol^{-1}
2	-33.47	2.4	-29.29	2.8	-32.66
2.1	-37.66	2.5	-25.10	2.9	-35.17
2.2	-25.1	2.6	-29.29	2.10	-33.91
2.3	-37.66	2.7	-29.29	Diclofenac	-35.17

*E_{min}: the minimum energy of complex formation, kJ × mol^{-1}.

Table 2. Energy values of the intermolecular interactions of the studied compounds with lanosterol-14α-demethylase (3LD6)

N	E_{min}, kJ × mol^{-1}	N	E_{min}, kJ × mol^{-1}	N	E_{min}, kJ × mol^{-1}
2	-41.03	2.4	-36.84	2.8	-40.61
2.1	-47.31	2.5	-39.77	2.9	-43.12
2.2	-45.22	2.6	-43.96	2.10	-43.96
2.3	-41.87	2.7	-37.68	Ketoconazole	-42.29

*E_{min}: the minimum energy of complex formation, kJ × mol^{-1}.

Regarding the results of the study of the affinity of the synthesized compounds to the active site of lanosterol-14α-demethylase, it should be noted that there is an increase in the energy of interaction with the enzyme as a result of the transition from acid to its salts.

Analysis of the results showed that the most promising compound for more in-depth study is sodium 2-((4-phenyl-5-(((5-phenylamino-1,3,4-thiadiazole-2-yl)thio)methyl)-1,2,4-triazole-3-yl)thio)acetate. This compound demonstrated the value of the energy of intermolecular interaction with the target enzymes, which to some extent exceeds the values for the reference compounds.

Conclusions

1. It was synthesized a number of salts of 2-((4-phenyl-5-(((5-phenylamino-1,3,4-thiadiazole-2-yl)thio)methyl)-1,2,4-triazole-3-yl)thio)ethanoic acid.

2. The optimal conditions for the synthesis of the target reaction products were established.

3. The structure and individuality were confirmed by means of spectral and chromatographic methods of the analysis.

4. The results of the molecular docking revealed promising compounds in a number of derivatives of 2-((4-phenyl-5-(((5-phenylamino-1,3,4-thiadiazole-2-yl)thio)methyl)-1,2,4-triazole-3-yl)thio)ethanoic acid for more in-depth study.

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