Synthesis and properties of 5-((5-amino-1,3,4-thiadiazole-2-yl)thio)methyl)-4-phenyl-1,2,4-triazole-3-thione and its some S-derivatives

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Increased attention to thiadiazole and 1,2,4-triazole derivatives is determined by the extensive structural modification capabilities of heterocyclic system derivatives and their high pharmacological potential. Synthesis of new molecules containing, along with the 1,2,4-triazole moiety, thiadiazole is a promising trend in the field of biologically active substances.

The aim of this work was to study the reaction of nucleophilic substitution of 5-((5-amino-1,3,4-thiadiazole-2-ylthio)methyl)-1,2,4-triazole-3-thione with haloalkanes and to establish the structure of the obtained compounds.

Materials and methods. Thiosemicarbazide was used as the key starting reagent. As a result of the reaction of the starting material with carbon disulfide in dimethylformamide, a thione was obtained which was further reacted with the iso-propyl ester of the chloroethane acid. The resulting ester was used for further transformations using hydrazinolysis reaction, nucleophilic addition, and intramolecular alkaline heterocyclization. The alkyl derivatives of the obtained 5-((5-amino-1,3,4-thiadiazole-2-ylthio)methyl)-1,2,4-triazole-3-thione were synthesized by reaction with bromoalkanes, in an alcohol medium with an equimolecular amount of alkali. The structure of the synthesized compounds was confirmed by modern physical-chemical methods of analysis: \textsuperscript{1}H NMR spectroscopy, IR spectrophotometry, and elemental analysis data. The individuality of substances was established by means of high-performance liquid chromatography.

Results. The method of obtaining 5-((5-amino-1,3,4-thiadiazole-2-ylthio)methyl)-1,2,4-triazole-3-thione has been optimized. The optimal conditions for the synthesis \textsuperscript{S}-alkyl derivatives of 5-((5-amino-1,3,4-thiadiazole-2-ylthio)methyl)-1,2,4-triazole-3-thione were determined. The structure of the synthesized compounds was established and their physical properties were investigated.

Conclusions. A number of \textsuperscript{S}-alkyl derivatives of 5-((5-amino-1,3,4-thiadiazole-2-ylthio)methyl)-1,2,4-triazole-3-thione were obtained and their structure was confirmed by modern physical-chemical methods of analysis.

Синтез і властивості 5-((5-аміно-1,3,4-тіадіазол-2-ілтіо)метил)-4-феніл-1,2,4-тріазол-3-тіону та його деяких \textsuperscript{S}-похідних

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Увага до похідних тіадіазолу та 1,2,4-тріазолу зумовлена широкими можливостями структурної модифікації похідних цих гетероциклічних систем та їхнім високим фармакологічним потенціалом. Синтез нових молекул, що містять тіадіазол поряд із фрагментом 1,2,4-тріазолу, – перспективний напрям у галузі створення біологічно активних субстанцій.

Мета роботи – вивчення реакції нуклеофільного заміщення 5-((5-аміно-1,3,4-тіадіазол-2-ілтіо)метил)-1,2,4-тріазол-3-тіону за участю галогенахлоридів у спиртовому середовищі.

Матеріали та методи. Як ключовий реактив використали тіосемікарбазид. У результаті реакції взаємодії вихідної речовини з карбон дисульфідом у середовищі диметилформаміду отримали тіон, який наступно піддали взаємодії з ізо-пропіловим естером кислоти хлоретанової. Естер, що одержали, застосували для наступних перетворень, використовуючи реакцію гідразинолізу, нуклеофільного приєднання та внутрішньомолекулярної лужної гетероциклізації. Алькілпохідні 5-((5-аміно-1,3,4-тіадіазол-2-ілтіо)метил)-1,2,4-тріазол-3-тіону синтезовані взаємодією з бромоалканами в спиртовому середовищі.

Результати. Оптимізували методику одержання 5-((5-аміно-1,3,4-тіадіазол-2-ілтіо)метил)-1,2,4-тріазол-3-тіону. Встановили оптимальні умови синтезу \textsuperscript{S}-алкілпохідних 5-((5-аміно-1,3,4-тіадіазол-2-ілтіо)метил)-1,2,4-тріазол-3-тіону.

Ключові слова: 5-амінотіадіазол, 1,2,4-тріазол, фізико-хімічні властивості.

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Синтез и свойства 5-((5-амино-1,3,4-тиадиазол-2-ил)тио)(метил)-4-фенил-1,2,4-триазол-3-тиона и его некоторых S-производных

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Повышенное внимание к производным тиадиазола и 1,2,4-триазола определяется широкими возможностями структурной модификации производных этих гетероциклических систем и их высоким фармакологическим потенциалом. Синтез новых молекул, содержащих тиадиазол наряду с фрагментом 1,2,4-триазола, – перспективное направление в области создания биологически активных субстанций.

Цель работы – изучение реакции нуклеофильного замещения 5-((5-амино-1,3,4-тиадиазол-2-ил)тио)(метил)-1,2,4-триазол-3-тиона при участии галогеналканов, а также установление структуры полученных соединений.

Материалы и методы. В качестве ключевого исходного реагента использован тиосемикарбазид. В результате реакции взаимодействия исходного вещества с карбон дисульфидом в среде диметилформамида получен тион, который подвергли взаимодействию с изо-пропиловым эфиром хлорэтиловой. Полученный эфир использован для дальнейших преобразований с использованием реакций гидразинолиза, нуклеофильного присоединения и внутримолекулярной щелочной гетероциклизации. Аликилпроизводные полученного 5-((5-амино-1,3,4-тиадиазол-2-илтиметил)(метил)-1,2,4-триазол-3-тиона синтезированы взаимодействием с бромалканами в присутствии эквимолекулярного количества щелочи в спиртовой среде. Структура синтезированных соединений подтверждена с помощью современных физико-химических методов анализа: "H ЯМР спектроскопии, ИК-спектрофотометрии и данными элементного анализа. Индивидуальность веществ установлена с помощью высокоэффективной жидкостной хроматографии.

Результаты. Оптимизирована методика получения 5-((5-амино-1,3,4-тиадиазол-2-илтиметил)(метил)-1,2,4-триазол-3-тиона. Определены оптимальные условия синтеза 5-алкилпроизводных 5-((5-амино-1,3,4-тиадиазол-2-илтиметил)(метил)-1,2,4-триазол-3-тиона, установлена строение синтезированных соединений и исследованы их физические свойства.

Выводы. Получен ряд 5-алкилпроизводных 5-((5-амино-1,3,4-тиадиазол-2-илтиметил)(метил)-1,2,4-триазол-3-тиона, структура которых подтверждена с помощью современных физико-химических методов анализа.

Ключевые слова: 5-аминотиадиазол, 1,2,4-триазол, физико-химические свойства.

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It is known that derivatives of 1,3,4-thiadiazole and 1,2,4-triazole have a broad spectrum of pharmacological activities such as analgesic, antimicrobial, anti-inflammatory, antiviral, anticonvulsant, and antidepressant activity [2,6,13]. Special attention is paid to studying antimicrobials and antidepressant properties of these heterocyclic systems and their high pharmacological potential. Synthesis of new molecules containing 1,2,4-triazole together with a fragment of 1,3,4-thiadiazol is a promising direction in the field of creating biologically active compounds.

Aim

The purpose of the work was to study the reaction of nucleophilic substitution of 5-((5-amino-1,3,4-thiadiazole-2-ythio)methyl)-1,2,4-triazole-3-thione with haloalkanes and to establish the structure of the obtained compounds.

Materials and methods

Thiosemicarbazide was used as a key starting reagent. As a result of reaction with carbon disulfide in a dimethylformamide medium, 1,2,4-triazole-3-thion was obtained. It was subsequently reacted with isopropyl ether of chlorehanoic acid. The resulting ester was used in reactions of hydrazinolysis, nucleophilic addition of phenylisothiocyanate and intramolecular alkaline heterocyclization with acidification of the medium to neutral [5,7].

The modern analysis methods were used to establish the structure and confirm the purity of the obtained compounds. Melting points were established in open capillary tubes using “Stanford Research Systems Melting Point Apparatus 100” (SRS, USA). The elemental analysis (C, H, N, S) was realized by the “Elementar vario EL cube” analyzer (Elementar Analysensysteme, Germany). IR spectra (in the frequency range 400 – 400 cm⁻¹) were obtained on the module ALPHA-T of Bruker ALPHA FT-IR spectrometer (Bruker optics, Germany). 1H NMR spectra (at 400 MHz) were recorded at “Varian-Mercury 400” spectrometer with SiMe₃ as internal standard in DMSO-d₄ solution. Chromatography-mass spectral studies were conducted on the “Agilent 1260 Infinity HPLC” fitted with a mass spectrometer “Agilent 6120” (method of ionization – electrospray (ESI)) [9,14].

S-alkylderivatives of 5-((5-amino-1,3,4-thiadiazole-2-ythio)methyl)-1,2,4-triazole-3-thione (table 1). To a previously obtained solution of 0.005 mol sodium hydroxide and 0.005 mol of 5-((5-amino-1,3,4-thiadiazole-2-ythio)
methyl)-1,2,4-triazole-3-thione in 30 ml propan-2-ol was added an equivalent amount of alkylation reagent bromoalkanes. The mixture was boiled for two hours and cooled. Than white crystalline substances were crystallized from methanol (Fig. 1) [16].

**Results**

The synthesis of the number of substituted 1,2,4-triazole has been carried out. The synthesis process for alkylderivatives of 5-((5-amino-1,3,4-thiadiazole-2-ylthio)methyl)-1,2,4-triazole-3-thiol is presented in Fig. 1. The establishment of optimal reaction conditions was carried out in carbinol with NaOH, at various temperatures of the reaction mass and chemical process time. The purity of the new compounds was confirmed in acceptable mistakes interval by elemental analyses, and their identities were confirmed by 1H NMR and IR spectra.

5-((5-Amino-1,3,4-thiadiazole-2-ylthio)methyl)-1,2,4-triazole-3-thiol (2.1). Yield: 73 %; m. p.: 216-218 °C; 1H NMR (400 MHz), δ ppm: 12.71 (s, 1H, SH) 7.54 (dd, J=7.7 Hz, 2H, C_H2), 7.40 (t, 1H, C_H), 7.32 (t, 1H, C_H), 6.90 (t, 1H, C_H), 5.26 (s, 2H, H_N), 4.14 (s, 2H, S-CH). Analytical calculated (%) for C_{12}H_{12}N_S: C; 40.98; H; 3.13; N; 26.06; S; 29.83. Found: C; 41.06; H; 3.12; N; 26.00; S; 29.89.

5-((5-Methylthio-4-phenyl-1,2,4-triazole-3-yl)methyl)-1,3,4-thiadiazole-2-amine (2.2). Yield: 83 %; m. p.: 192-194 °C; 1H NMR (400 MHz), δ ppm: 7.50 (dd, J=7.7 Hz, 2H, C_H), 7.40 (t, 1H, C_H), 7.32 (t, 1H, C_H), 6.87 (t, 1H, C_H), 5.24 (s, 2H, H_N) 4.69 (s, 2H, S-CH), 3.25 (t, 2H, S-CH2-CH), 1.40 (t, 3H, S-CH2-CH). Analytical calculated (%) for C_{11}H_{12}N_S: C; 44.46; H; 4.02; N; 22.16; S; 25.45. Found: C; 44.46; H; 4.02; N; 22.30; S; 25.39.

5-((4-Phenyl-5-propylthio-1,2,4-triazole-3-yl)methyl)thio)-1,3,4-thiadiazole-2-amine (2.4). Yield: 77 %; m. p.: 179-181 °C; 1H NMR (400 MHz), δ ppm: 7.55 (dd, J=7.7 Hz, 2H, C_H), 7.37 (t, 1H, C_H), 7.35 (t, 1H, C_H), 6.90 (t, 1H, C_H), 5.21 (s, 2H, H_N), 4.66 (s, 2H, S-CH), 3.16 (t, 2H, S-CH2-CH2-CH), 1.71-1.68 (m, 2H, S-CH2-CH2-CH), 1.05 (t, 3H, S-CH3). Analytical calculated (%) for C_{15}H_{18}N_S: C; 46.13; H; 4.42; N; 23.06; S; 26.39. Found: C; 46.22; H; 4.43; N; 23.01; S; 26.34.

5-((5-Butylthio-4-phenyl-1,2,4-triazole-3-yl)methyl)thio)-1,3,4-thiadiazole-2-amine (2.5). Yield: 73 %; m. p.: 215-217 °C; 1H NMR (400 MHz), δ ppm: 7.52 (dd, J=7.7 Hz, 2H, C_H), 7.35 (t, 1H, C_H), 7.31 (t, 1H, C_H), 6.88 (t, 1H, C_H), 5.25 (s, 2H, H_N) 4.69 (s, 2H, S-CH), 3.13 (t, 2H, S-CH2-CH2-CH), 1.68-1.65 (m, 2H, S-CH2-CH2-CH), 1.41-1.37 (m, 2H, S-CH2-CH2-CH), 0.95 (t, 3H, S-CH3). Analytical calculated (%) for C_{16}H_{20}N_S: C; 47.59; H; 4.79; N; 22.20; S; 25.41. Found: C; 47.50; H; 4.78; N; 22.16; S; 25.45.

5-((5-Pentythio-4-phenyl-1,2,4-triazole-3-yl)methyl)thio)-1,3,4-thiadiazole-2-amine (2.6). Yield: 75 %; m. p.: 175-173 °C; 1H NMR (400 MHz), δ ppm: 7.51 (dd, J=7.7 Hz, 2H, C_H), 7.41 (t, 1H, C_H), 7.29 (t, 1H, C_H), 6.92 (t, 1H, C_H), 5.23 (s, 2H, H_N) 4.67 (s, 2H, S-CH), 3.09 (t, 2H, S-CH2-CH2-CH), 1.72-1.65 (m, 2H, S-CH2-CH2-CH), 1.38-1.34 (m, 4H, S-CH2-CH2-CH), 0.86 (t, 2H, S-CH2-CH). Analytical calculated (%) for C_{17}H_{22}N_S: C; 48.95; H; 5.14; N; 21.41; S; 24.50. Found: C; 49.01; H; 5.13; N; 21.38; S; 24.54.

**Fig. 1.** The synthesis of alkylderivatives of 5-((5-amino-1,3,4-thiadiazole-2-ylthio)methyl)-1,2,4-triazole-3-thiol.
5-((5-Hexylthio-4-phenyl-1,2,4-triazole-3-yl)methyl)thio)-1,3,4-thiadiazole-2-amine (2.7). Yield: 77%; m. p.: 180-187 °C; 1H NMR (400 MHz), δ, ppm: 7.56 (dd, J=7.7 Hz, 2H, СΗ), 7.38 (t, 1H, СΗ), 7.30 (t, 1H, СΗ), 6.90 (t, 1H, СΗ), 5.26 (2H, J=3.16 Hz, 2H, СΗ), 4.69 (s, 2H, СΗ), 3.15 (t, 2H, С=CH-(CH=CH₂)-СΗ), 1.67-1.63 (m, 2H, С=CH-(CH=CH₂)-СΗ), 1.31-1.26 (m, 6H, С=CH-(CH=CH₂)-СΗ), 0.92-0.86 (m, 3H, С-(CH₃)-СΗ). Analytical calculated (%) for С₇₆Н₉₈S₂: C, 50.22; H, 5.45; N, 20.67; S, 23.66. Found: C, 50.31; H, 5.46; N, 20.63; S, 23.61.

5-((5-Heptylthio-4-phenyl-1,2,4-triazole-3-yl)methyl)thio)-1,3,4-thiadiazole-2-amine (2.8). Yield: 72%; m. p.: 171-169 °C; 1H NMR (400 MHz), δ, ppm: 7.52 (dd, J=7.7 Hz, 2H, СΗ), 7.36 (t, 1H, СΗ), 7.32 (t, 1H, СΗ), 6.88 (t, 1H, СΗ), 5.24 (2H, J=3.16 Hz, 2H, СΗ), 4.67 (s, 2H, СΗ), 3.17 (t, 2H, С=CH-(CH=CH₂)-СΗ), 1.72-1.68 (m, 2H, С=CH-(CH=CH₂)-СΗ), 1.35-1.25 (m, 8H, С=CH-(CH=CH₂)-СΗ), 0.91-0.88 (m, 3H, С-(CH₃)-СΗ). Analytical calculated (%) for С₇₆Н₉₈S₂: C, 51.40; H, 5.75; N, 19.98; S, 22.87. Found: C, 51.30; H, 5.76; N, 19.94; S, 22.82.

5-((5-Octylthio-4-phenyl-1,2,4-triazole-3-yl)methyl)thio)-1,3,4-thiadiazole-2-amine (2.9). Yield: 75%; m. p.: 163-161 °C; 1H NMR (400 MHz), δ, ppm: 7.50 (dd, J=7.7 Hz, 2H, СΗ), 7.39 (t, 1H, СΗ), 7.35 (t, 1H, СΗ), 6.91 (t, 1H, СΗ), 5.21 (2H, J=3.16 Hz, 2H, СΗ), 4.70 (s, 2H, СΗ), 3.20 (t, 2H, С=CH-(CH=CH₂)-СΗ), 1.72-1.64 (m, 2H, С=CH-(CH=CH₂)-СΗ), 1.29-1.23 (m, 10H, С=CH-(CH=CH₂)-СΗ), 0.91-0.86 (m, 3H, С-(CH₃)-СΗ). Analytical calculated (%) for С₇₆Н₉₈S₂: C, 52.50; H, 6.03; N, 19.34; S, 22.13. Found: C, 52.41; H, 6.04; N, 19.30; S, 22.17.

5-((5-Nonylthio-4-phenyl-1,2,4-triazole-3-yl)methyl)thio)-1,3,4-thiadiazole-2-amine (2.10). Yield: 70%; m. p.: 167-165 °C; 1H NMR (400 MHz), δ, ppm: 7.54 (dd, J=7.7 Hz, 2H, СΗ), 7.42 (t, 1H, СΗ), 7.32 (t, 1H, СΗ), 6.88 (t, 1H, СΗ), 5.24 (2H, J=3.16 Hz, 2H, СΗ), 4.67 (s, 2H, СΗ), 3.19 (t, 2H, С=CH-(CH=CH₂)-СΗ), 1.73-1.66 (m, 2H, С=CH-(CH=CH₂)-СΗ), 1.34-1.23 (m, 12H, С=CH-(CH=CH₂)-СΗ), 0.87-0.81 (m, 3H, С-(CH₃)-СΗ). Analytical calculated (%) for С₇₆Н₉₈S₂: C, 53.54; H, 6.29; N, 18.73; S, 21.44. Found: C, 53.64; H, 6.27; N, 18.77; S, 21.39.

5-((5-Decylthio-4-phenyl-1,2,4-triazole-3-yl)methyl)thio)-1,3,4-thiadiazole-2-amine (2.11). Yield: 67%; m. p.: 161-159 °C; 1H NMR (400 MHz), δ, ppm: 7.51 (dd, J=7.7 Hz, 2H, СΗ), 7.37 (t, 1H, СΗ), 7.29 (t, 1H, СΗ), 6.91 (t, 1H, СΗ), 5.24 (2H, J=3.16 Hz, 2H, СΗ), 4.69 (s, 2H, СΗ), 3.11 (t, 2H, С=CH-(CH=CH₂)-СΗ), 1.73-1.70 (m, 2H, С=CH-(CH=CH₂)-СΗ), 1.34-1.30 (m, 2H, С-(CH₃)-СΗ), 1.27-1.22 (m, 12H, С-(CH₃)-СΗ), 0.93-0.83 (m, 3H, С-(CH₃)-СΗ). Analytical calculated (%) for С₇₆Н₉₈S₂: C, 54.51; H, 6.54; N, 18.16; S, 20.79. Found: C, 54.40; H, 6.53; N, 18.20; S, 20.83.

Discussion
Analyzing the results of spectral studies, it should be noted that the 1H NMR spectra of the substances obtained correspond to the above formulas. Thus, the spectrum of 5-((5-amino-1,3,4-thiadiazole-2-yl)thio)methyl)-4-phenyl-1,2,4-triazole-3-thiol is characterized by characteristic chemical shifts of protons. The protons of the free amino group (-NH₂) appear as a two-proton singlet at 5.26 ppm. The presence of a singlet at δ 12.71 may be due to the proton SH, indicating that compound 2.1 existed as a thiol tautomeric form in solution. The protons of the S-alkyl moiety are fixed in the expected magnetic field, and their parameters correspond to the literature.

For example, the proton signals of a methyl group are expressed in 2.70 as a singlet (2.2). Increasing the length of the alkyl chain causes the proton signals to shift in the direction of a stronger field. Thus, the proton signals of the methyl moiety (2.2–2.11) gradually changed to 0.83 ppm; the proton signals of the methylene moiety were observed in the strong field in the form of triplets (3.25–3.11) or multiplets (1.42–1.21 ppm, 1.75–1.65 ppm). In the field of absorption of aromatic protons, there are signals in the form of multiplets (7.87–7.54 ppm).

The IR spectra of the synthesized compounds (2.1–2.11) show characteristic absorption bands that reflect the valence or deformation vibrations of the structural elements of the molecule: 3473–3419 cm⁻¹ (amino groups), 3346–3293 cm⁻¹ (amino groups), 1612–1578 cm⁻¹ (amino groups). In the IR-spectrum of synthesized alkyl derivatives (2.2–2.11) observe deformation vibrations of alkyl groups in ranges from 645 cm⁻¹ to 1390 cm⁻¹ and H–C–H fragment in a narrow area of frequency 1485–1360 cm⁻¹.

In the mass spectrum, there are molecular ion peaks and fragment ion peaks that confirm the structure.

Conclusions
Using the appropriate bromalkanes as alkylating agents (bromopropane, bromobutane, bromopentane, bromhexane, bromoheptane, bromoctane, bromonan, bromodecane), the reaction of nucleophilic substitution of 5-((5-amino-1,3,4-thiadiazole-2-yl)methyl)-4-phenyl-1,2,4-triazole-3-thiol was investigated. 11 new compounds were obtained. The structure was confirmed by complex modern physical-chemical methods of analysis (elemental analysis, 1H NMR spectroscopy, IR spectrometry), and their individuality was proved with chromatographic mass spectrometry.

Prospects for further research
According to the research results it is planned to expand the line and identify among them promising biologically active compounds.

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Conflicts of interest: authors have no conflict of interest to declare.
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