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 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 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.

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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, antiinflammatory, and antipruritic activity [2,6,13]. Special attention is paid to studying antimicrobial, anticonvulsant and antidepressant properties of these heterocycles. Nowadays, microbial infections are resistant to an antibiotic. That’s why it is one of the biggest problems, which threaten human health and the quality of life [10,12]. Infectious diseases are one of the main causes of a large number of deaths [4,11,15]. It is common knowledge that more efficient antimicrobial compounds can be synthesized by combining two or more biologically active heterocyclic systems in a single molecular framework [1,3,8].

Aim

The purpose of the 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 a key starting reagent. As a result of reaction with carbon disulfide in a dimethylforma
mide 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 (a frequency range 400 – 400 cm\(^{-1}\)) were obtained on the module ALPHA-T of Bruker ALPHA FT-IR spectrometer (Bruker optics, Germany). \(^1\)H NMR spectra (at 400 MHz) were recorded at “Varian-Mercury 400” spectrometer with SiMe\(_4\) as internal standard in DMSO-\(d_6\) 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-ylthio)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-ylthio)
methyl)-1,2,4-triazole-3-thione in 30 ml propan-2-ol was added an equivalent amount of alkylation reagent bromoalanes. 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 S-substituted 1,2,4-triazole has been carried out. The synthesis process for alkyldervatives 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)-4-phe-
nyl-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-H), 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_{15}H_{14}N_{3}S: C, 40.98; H, 3.12; 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-ylmethyl)-
1,3,4-thiadiazole-2-amine (2.2). Yield: 81 %; m. p.: 195-197 °C; 1H NMR (400 MHz), δ ppm: 7.52 (dd, J=7.7 Hz, 2H, C-H), 7.38 (t, 1H, C-H), 7.31 (t, 1H, C-H), 6.93 (t, 1H, C-H), 5.28 (s, 2H, H-N), 4.67 (s, 2H, S-CH), 2.70 (s, 3H, S-CH). Analytical calculated (%) for C_{15}H_{14}N_{3}S: C, 42.84; H, 3.59; N, 24.98; S, 28.59. Found: C, 42.75; H, 3.60; N, 25.03; S, 28.52.

5-((5-Ethylthio-4-phenyl-1,2,4-triazole-3-ylmethyl)
thio)-1,3,4-thiadiazole-2-amine (2.3). 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-CH-Ch), 1.40 (t, 3H, S-CH-Ch). Analytical calculated (%) for C_{16}H_{14}N_{3}S: C, 44.46; H, 4.02; N, 24.03; S, 27.39.

5-((5-Phenyl-5-propylthio-1,2,4-triazole-3-yl)methyl-
thio)-1,3,4-thiadiazole-2-amine (2.4). Yield: 77 %; m. p.: 185-187 °C; 1H NMR (400 MHz), δ ppm: 7.55 (dd, J=7.7 Hz, 2H, C-H), 7.37 (t, 1H, C-H), 7.30 (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-CH-Ch-Ch), 1.71-1.68 (m, 2H, S-CH-Ch-Ch), 1.05 (t, 3H, S-CH-Ch). Analytical calculated (%) for C_{17}H_{14}N_{3}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-ylmethyl)
thio)-1,3,4-thiadiazole-2-amine (2.5). Yield: 73 %; m. p.: 179-181 °C; 1H NMR (400 MHz), δ ppm: 7.53 (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-CH-Ch-Ch), 1.68-1.65 (m, 2H, S-CH-Ch-Ch), 1.41-1.37 (m, 2H, S(CH)-CH-Ch), 0.95 (t, 3H, S-CH-Ch). Analytical calculated (%) for C_{18}H_{16}N_{3}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-ylmethyl)
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-CH-Ch-Ch), 1.72-1.65 (m, 2H, S-CH-Ch-Ch), 1.38-1.34 (m, 4H, S-CH-Ch-Ch), 0.86 (t, 2H, S-CH-Ch). Analytical calculated (%) for C_{19}H_{18}N_{3}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.
5-((5-Hexylthio-4-phenyl-1,2,4-triazole-3-yl)methyl)thio)-1,3,4-thiadiazole-2-thione (2.7). Yield: 77%; m.p.: 180-187 °C; 1H NMR (400 MHz), δ, ppm: 7.56 (dd, J=7.7 Hz, 2H, СН), 7.38 (t, 1H, СН), 7.30 (t, 1H, СН), 6.90 (t, 1H, СН), 5.26 (s, 2H, НN), 4.69 (s, 2H, СНCH), 3.15 (t, 2H, S-CH₂-(CH₂)₂-CH₂), 1.67-1.63 (m, 2H, S-CH₂-(CH₂)₂-CH₂), 1.31-1.26 (m, 6H, S-CH₂-(CH₂)₂-CH₂), 0.92-0.86 (m, 2H, S-CH₂-(CH₂)₂-CH₂). Analytical calculated (%) for С₇H₇N₂S₂: 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-thione (2.8). Yield: 72%; m.p.: 171-169 °C; 1H NMR (400 MHz), δ, ppm: 7.52 (dd, J=7.7 Hz, 2H, СН), 7.36 (t, 1H, СН), 7.32 (t, 1H, СН), 6.88 (t, 1H, СН), 5.24 (s, 2H, НN), 4.67 (s, 2H, СНCH), 3.17 (t, 2H, S-CH₂-(CH₂)₂-CH₂), 1.72-1.68 (m, 2H, S-CH₂-(CH₂)₂-CH₂), 1.35-1.25 (m, 2H, S-CH₂-(CH₂)₂-CH₂), 0.91-0.88 (m, 2H, S-CH₂-(CH₂)₂-CH₂). Analytical calculated (%) for С₈H₈N₂S₂: 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-thione (2.9). Yield: 75%; m.p.: 163-161 °C; 1H NMR (400 MHz), δ, ppm: 7.50 (dd, J=7.7 Hz, 2H, СН), 7.39 (t, 1H, СН), 7.35 (t, 1H, СН), 6.91 (t, 1H, СН), 5.21 (s, 2H, НN), 4.70 (s, 2H, СНCH), 3.20 (t, 2H, S-CH₂-(CH₂)₂-CH₂), 1.71-1.64 (m, 2H, S-CH₂-(CH₂)₂-CH₂), 1.29-1.23 (m, 2H, S-CH₂-(CH₂)₂-CH₂), 0.96-0.91 (m, 2H, S-CH₂-(CH₂)₂-CH₂). Analytical calculated (%) for С₉H₉N₂S₂: 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-thione (2.10). Yield: 70%; m.p.: 167-165 °C; 1H NMR (400 MHz), δ, ppm: 7.54 (dd, J=7.7 Hz, 2H, СН), 7.44 (t, 1H, СН), 7.32 (t, 1H, СН), 6.88 (t, 1H, СН), 5.24 (s, 2H, НN), 4.67 (s, 2H, СНCH), 3.19 (t, 2H, S-CH₂-(CH₂)₂-CH₂), 1.73-1.67 (m, 2H, S-CH₂-(CH₂)₂-CH₂), 1.34-1.23 (m, 2H, S-CH₂-(CH₂)₂-CH₂), 0.87-0.81 (m, 2H, S-CH₂-(CH₂)₂-CH₂). Analytical calculated (%) for С₁₀H₁₀N₂S₂: 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-thione (2.11). Yield: 67%; m.p.: 161-159 °C; 1H NMR (400 MHz), δ, ppm: 7.51 (dd, J=7.7 Hz, 2H, СН), 7.37 (t, 1H, СН), 7.29 (t, 1H, СН), 6.91 (t, 1H, СН), 5.24 (s, 2H, НN), 4.69 (s, 2H, СНCH), 3.11 (t, 2H, S-CH₂-(CH₂)₂-CH₂), 1.73-1.70 (m, 2H, S-CH₂-(CH₂)₂-CH₂), 1.34-1.30 (m, 2H, S-CH₂-(CH₂)₂-CH₂), 1.27-1.22 (m, 12H, S-CH₂-(CH₂)₂-CH₂), 0.93-0.83 (m, 3H, S-CH₂-(CH₂)₂-CH₂). Analytical calculated (%) for С₁₁H₁₁N₂S₂: 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-thione 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 to 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 forms 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 this structure.

Conclusions

Using the appropriate bromalkanes as alkylating agents (bromopropane, bromobutane, bromopentane, bromhexane, bromoheptane, bromoctane, bromnan, 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 spectrumetry), 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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