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Synthesis of New Substituted 1,2,4-Triazoles and 1,3,4-Thiadiazoles and Their Effects on DNA Methylation Level

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Abstract—Continuing the search for biologically active compounds among functionally substituted azoles, new 1,2,4-triazole-3-thiols and 1,3,4-thiadiazoles derivatives bearing pharmacologically active carboxamide, hydroxyl or carboxyalkyl moieties, as well as *N*-acyclonucleoside, *N*-cyano- or carboxyethyl fragments were synthesized. Ability of some compounds obtained to inhibit the methylation of tumor DNA in vitro was revealed. The compound with the highest activity was selected for further in vivo studies.

Keywords: 1,2,4-triazole, 1,3,4-thiadiazole, cyanoethylation, alkylation, acyclonucleoside, DNA methylation

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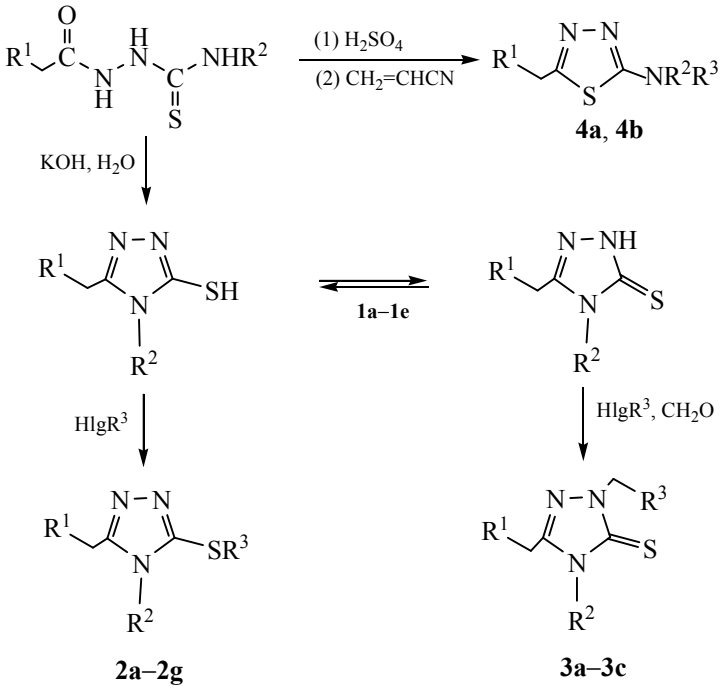
In recent years, 1,2,4-triazole and 1,3,4-thiadiazole derivatives are of great interest due to the fact that many of them exhibit a wide spectrum of biological activity [1, 2], have been used as drugs or are on the way to introduction into medical practice as antineoplastic [3–5], antibacterial [6, 7], antifungal [8, 9], antiviral [10, 11], anticonvulsant [12, 13] and other drugs.

Among some previously synthesized compounds with 4-bromophenyl [14], 4-bromo(chloro)phenoxymethylene [15], 4-alkoxybenzyl [16, 17] substituents, substances possessing a moderate antitumor effect on tumor DNA methylation, mutagenic and antimutagenic effects have been revealed [18]. Most of these compounds are of little or no toxicity. Diversity of the biological properties of 1,2,4-triazole and 1,3,4-thiadiazole derivatives indicates a peculiar influence of pharmacologically active substituents in certain positions of heterocycles on biological activity. In this regard, it seems promising to expand the range of this class of compounds by developing new ways of their functionalization and continuing to study their pharmacological activity.

Herein we reported the synthesis of new 1,2,4-triazole-3-thiol and 1,3,4-thiadiazole derivatives bearing 3-bromophenoxymethylene and benzyl substituents at the 5-position of heterocycles and some their transformations (Scheme 1). The valuable biological properties of 1,2,4-triazole-3-thiols [1] served as the basis for the introduction of new functionalities into the heteroring by the previously known methods [19]. The starting 4*H*-1,2,4-Triazole-3-thiols **1a**–**1e** were obtained by intramolecular cyclization of 1,4-disubstituted thio-semicarbazides by the method reported in [14]. Aliphatic acids halides, 2-chloroacetamide, as well as ethylene chlorohydrin (2-chloroethanol) were chosen as alkylating agents. Structure of triazoles **2a**–**2g** was confirmed by the IR and ^{1}H NMR spectroscopy data. The singlet signals of the SCH_2 group in the range of 3.80–4.10 ppm in the ^{1}H NMR spectra of compounds **2a**–**2g** indicate that the alkylation proceeds at the SH nucleophilic site of compounds **1a**–**1e**.

The Mannich reaction of triazole **1b** with morpholine at room temperature resulted in the N^2-aminomethyl derivative **3a**. The carboxy- or cyanoethylation reactions with freshly distilled acrylonitrile and acrylic

Scheme 1.



R^1 = Ph, R^2 = Ph (**1a**), C_6H_{11} (**1b**); R^1 = 3-BrC_6H_4O, R^2 = Bn (**1c**), All (**1d**), C_6H_{11} (**1e**); R^1 = Ph, R^2 = C_6H_{11}, R^3 = CH_2CH_2OH (**2a**); R^1 = 3-BrC_2H_4O, R^2 = Bn, R^3 = CH_2CH_2OH (**2b**), CH_2CONH_2 (**2c**), CH_2COOH (**2d**), $CH(CH_3)COOH$ (**2e**); R^1 = 3-BrC_2H_4O, R^2 = C_6H_{11}, R^3 = CH_2COOH (**2f**); R^1 = 3-BrC_2H_4O, R^2 = All, R^3 = CH_2CONH_2 (**2g**); R^1 = Ph, R^2 = C_6H_{11}, R^3 = morpholin-4-yl (**3a**); R^1 = R^2 = Ph, R^3 = CH_2CN (**3b**), CH_2COOH (**3c**); R^1 = Ph, R^2 = H, R^3 = COPh (**4a**); R^1 = Ph, R^2 = CH_2CH_2CN, R^3 = COPh (**4b**).

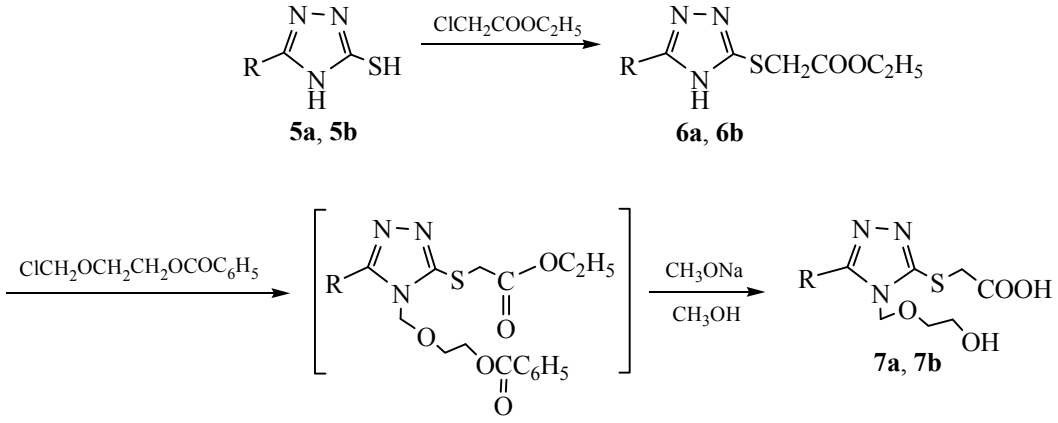
acid in the presence of triethylamine as a catalyst furnished N^2-substituted 1,2,4-triazoles **3b** and **3c**. In the ^{1}H NMR spectrum of compound **3a**, in contrast to the spectra of *S*-alkylated derivatives **2a**–**2g**, a relatively weak-field singlet signal of the NCH_2N group is observed in the 5.02 ppm region. In the spectra of compounds **3b** and **3c**, there are triplet signals of the NCH_2CH_2 group in the corresponding regions, which confirm the structure of compounds obtained.

4-Benzoyl substituted thiosemicarbazide underwent readily cyclization to the corresponding 1,3,4-thiadiazole **4a** when dehydrated in the presence of concentrated sulfuric acid. Taking into account binucleophilic reactivity of 1,3,4-thiadiazole-2-amines, the obtained *N*-(5-benzyl-1,3,4-thiadiazole-2-yl)benzamide **4a** was subjected to cyanoethylation in order to clarify to which reaction site—endocyclic N^3 atom or amine nitrogen atom in the side chain—a cyanoethyl group is attached. In a similar reaction with 5-substituted 1,3,4-thiadiazole-2-thiols, not the SH group, but the endocyclic nitrogen atom N^3 is subjected to cyanoethylation [20]. In this case, the analysis of ^{1}H and ^{13}C NMR spectra confirmed the formation of *N*-(5-benzyl-1,3,4-thiadiazol-2-yl)-*N*-(2-cyanoethyl)benzamide **4b**.

In order to functionalize the 1,2,4-triazole ring, using compounds **5a** and **5b** as examples, an attempt was made to introduce 2-(hydroxyethoxy)methyl fragment into position 4, which has structural similarity to the carbohydrate part of the structure of natural nucleosides and is a component of the antiviral drug acyclovir [21, 22] (Scheme 2).

The starting triazoles **6a**, **6b** were obtained by alkylation of 1,2,4-triazole-3-thiols **5a**, **5b** [1, 18]; 2-(chloromethoxy)ethyl benzoate was synthesized by chloromethylation of 2-hydroxyethyl benzoate according to the procedure [22, 23]. From the known methods for the synthesis of acyclonucleosides [21–23], we chosen the simplest and most accessible—fusion of the starting materials at 110–120°C. Intermediate benzoates were isolated by column chromatography and, without further purification, were debenzylated by reacting with sodium methoxide in absolute methanol [24]. After appropriate purification by column cromatography, compounds **7a** and **7b** were

Scheme 2.



R = Bn, 4-Br-C_6H_4.

isolated as pale yellow crystalline compounds. Structure of compounds obtained was proved by analytical and spectral data, indicating that ethoxycarbonyl groups are subjected to saponification in the reaction medium with the formation of the corresponding sulfanylacetic acids. In the ^{1}H NMR spectra, a broad singlet signal of the OH group is characteristic in the range of 4.46–4.47 ppm.

The IR spectra of compounds **7a** and **7b** contain the bands of stretching and bending vibrations of the CH_2OCH_2, CH_2OH, C=O, and COOH groups.

We studied the effect of functionalized 1,2,4-triazoles **2**, **3**, **7**, and 1,3,4-thiadiazoles **4a**, **4b** on the level of tumor DNA methylation in vitro on the sarcoma 180 (C-180) model according to the method described in [25].

A clear difference between DNA samples from tumor tissue after exposure to the studied compounds was found only in relation to the content of 5-methylcytosine (5-MC). Compounds **2f**, **2a**, **2g**, which suppress the methylation level of tumor DNA by 63.5, 43.2, and 40.5%, respectively, have the most activity (see the table). Compounds **2c** (32.4%), **2d** (35.1%), and **3a** (35.1%) have weak demethylation activity. Compounds **2b**, **2e**, and **7a** cause an increase in the amount of 5-methylcytosine. From the data obtained, it can be seen that half of the compounds with tumor DNA activity that inhibit methylation (**2a**, **2f**, **3a**) contain the cyclohexyl group in the position 4 of the heterocycle. Compounds **2f** was chosen for further in vivo screening.

In summary, a new series of functionally substituted 1,2,4-triazoles and 1,3,4-thiadiazoles were synthesized. Some of the compounds obtained inhibit the methylation of tumor DNA, indicating the promise of searching for anticancer drugs among the studied class of compounds.

EXPERIMENTAL

IR spectra were registered on a Nicolet Avatar 330 FT-IR spectrometer in petroleum oil. NMR spectra were recorded on a Varian Mercury-300VX instrument in DMSO-d_6 relative to internal TMS. Melting points were determined on a Boetius 72/2064 instrument. The reaction progress and individuality of the obtained compounds were monitored by TLC on Silica gel $60F_{254}$ plates (Germany), eluting with a benzene–dioxane, 2 : 1 (**1a**–**1e**, **2a**–**2g**, **3a**–**3c**), benzene–dioxane, 1 : 1 (**4a**, **4b**), or benzene–ethyl acetate, 1 : 1 (**6**, **7a**, **7b**), detecting with UV irradiation.

4,5-Disubstituted 4*H*-1,2,4-triazole-3-thiols **1a**–**1e** were synthesized according to the method reported in [16]; physico-chemical constants of triazoles **1a**, **1b** correspond to literature data [2].

4-Benzyl-5-(3-bromophenoxymethyl)-4*H*-1,2,4-triazole-3-thiol (1c). Yield 88%, mp 159–160°C. IR spectrum, ν, cm^{-1}: 3062, 2766, 1589, 1577, 1494, 1470, 1284, 1226, 1044, 941, 860. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.97 s (2H, OCH_2), 5.32 s (2H, NCH_2), 6.76 d. d. d ($1H_{Ar}$, *J* = 8.0, 2.5, 1.2), 6.92 d. d ($1H_{Ar}$, *J* = 2.5, 1.7), 7.07 d. d. d ($1H_{Ar}$, *J* = 7.9, 1.7, 1.2), 7.14 d. d ($1H_{Ar}$, *J* = 8.0, 7.9), 7.22–7.29 m ($5H_{Ar}$). ^{13}C NMR spectrum, δ_C, ppm: 46.0 (NCH_2), 59.9 (OCH_2), 113.1 (CH), 117.5 (CH), 121.8 (C), 124.1 (CH), 126.9 (2CH), 127.1 (CH), 127.9 (2CH), 130.1 (CH), 135.1 (C), 146.8 (C), 157.6 (C), 168.51 (C). Found, %: N 11.29; S 8.67. $C_{16}H_{14}BrN_3OS$. Calculated, % : N 11.17; S 8.52.

The effect of compounds **1–7** on the level of tumor DNA methylation

Compound	Base content in DNA, mol%		Change in methylation level, %
	5-MC	G+C+5-MC	
DNA source, (C-180)-control	0.74±0.02	42.66	
2a	0.42±0.02	43.34	43.2[a]
2b	1.03±0.02	42.08	_
2c	0.05±0.01	43.72	32.4[a]
2d	0.48±0.02	42.06	35.1[a]
2e	1.53±0.01	42.00	_
2f	0.27±0.02	42.48	63.5[a]
2g	0.44±0.02	42.02	40.5a
3a	0.48±0.02	44.72	35.1[a]
3b	0.68±0.01	42.02	_
3c	0.53±0.01	42.78	28.4
4a	0.61±0.02	44.76	17.6
4b	0.72±0.02	42.12	_
7a	1.05±0.01	43.00	_
7b	0.61±0.01	42.68	17.6

[a] $p < 0.05$.

4-Allyl-5-(3-bromophenoxymethyl)-4*H*-1,2,4-triazole-3-thiol (1d). Yield 89%, mp 108–109°C. IR spectrum, ν, cm^{-1}: 3311, 3209, 3051, 2678, 1630, 1596, 1549, 1535, 1511, 1477, 1455, 1424, 1413, 1358, 1334, 1300, 1280, 1239, 1205, 1160, 1072, 1029, 939, 879, 866. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.71 d. t (2H, NCH_2, *J* = 5.7, 1.5), 5.11 s (2H, OCH_2), 5.10–5.25 m (2H, $=CH_2$), 5.85–5.98 m (1H, =CH), 6.98 d. d. d ($1H_{Ar}$, *J* = 8.2, 2.5, 1.0), 7.06 m ($2H_{Ar}$), 13.75 br. s (1H, SH). Found, %: N 12.61; S 9.59. $C_{12}H_{12}BrN_3OS$. Calculated, %: N 12.88; S 9.83.

5-(3-Bromphenoxymethyl)-4-cyclohexyl-4*H*-1,2,4-triazole-3-thiol (1e). Yield 91%, mp 123–124°C. IR spectrum, ν, cm^{-1}: 3091, 3041, 2749, 1590, 1577, 1495, 1471, 1456, 1424, 1370, 1352, 1342, 1297, 1279, 1244, 1222, 1031, 854, 771. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.14–1.29 m (1H), 1.35–1.52 m (2H), 1.66–1.74 m (1H), 1.83–1.94 m (4H) and 2.09–2.28 m (2H, C_6H_{11}), 4.44–4.58 m (1H, NCH), 5.15 s (2H, OCH_2), 6.99 d. d. d ($1H_{Ar}$, *J* = 8.2, 2.5, 1.1), 7.12 d. d. d ($1H_{Ar}$, *J* = 7.7, 1.8, 1.1), 7.18–7.24 m ($2H_{Ar}$), 13.68 s (1H, SH). Found, %: N 11.26; S 8.52. $C_{15}H_{18}BrN_3OS$. Calculated, %: N 11.41; S 8.71.

Alkylation of 4,5-disubstituted 4*H*-1,2,4-triazole-3-thiols **1a**–**1e** was performed as described in [16].

2-[(5-Benzyl-4-cyclohexyl-4*H*-1,2,4-triazol-3-yl)-sulfanyl]ethanol (2a). Yield 88%, mp 94–95°C. IR spectrum, ν, cm^{-1}: 3164, 1691, 1519, 1494, 1456, 1440, 1412, 1377, 1367, 1332.6, 1282, 1199, 1073. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.05–1.45 m (5H), 1.54–1.78 m (3H) and 1.86–2.02 m (2H, C_6H_{11}), 3.28 t (2H, SCH_2, *J* = 6.5), 3.71 q (2H, $C\underline{H}_2OH$, *J* = 6.5), 3.82–3.93 m (1H, NCH), 4.16 s (2H, CCH_2C), 4.77 t (1H, OH, *J* = 5.6), 7.17–7.31 m ($5H_{Ar}$). Found, %: N 13.41; S 10.31. $C_{17}H_{23}N_3OS$. Calculated, %: N 13.23; S 10.10.

2-{[4-Benzyl-5-(3-bromophenoxymethyl)-4*H*-1,2,4-triazol-3-yl]sulfanyl}ethanol (2b). Yield 83%, mp 84–85°C. IR spectrum, ν, cm^{-1}: 3311, 1592, 1577, 1527, 1466, 1398, 1377, 1282, 1222, 1068, 1014. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.28 t (2H, SCH_2, *J* = 6.4), 3.70 q (2H, $C\underline{H}_2OH$, *J* 6.5), 4.75 t (1H, OH, *J* = 5.7), 4.95 s (2H, OCH_2), 5.21 s (2H, NCH_2), 6.74 d. d. d ($1H_{Ar}$, *J* = 8.0, 2.5, 1.2), 6.89 d. d ($1H_{Ar}$, *J* = 2.5, 1.2), 7.04 d. d. d ($1H_{Ar}$, *J* = 7.9, 1.7, 1.2), 7.12 d. d ($1H_{Ar}$, *J* = 8.0, 7.9), 7.19–7.27 m ($5H_{Ar}$). Found, %: N 9.48; S 7.31. $C_{18}H_{18}BrN_3O_2S$. Calculated, %: N 9.99; S 7.63.

2-{[4-Benzyl-5-(3-bromophenoxymethyl)-4*H*-1,2,4-triazol-3-yl]sulfanyl}acetamide (2c). Yield 98%, mp 186–188°C. IR spectrum, ν, cm^{-1}: 3388, 3106, 1698, 1638, 1593, 1578, 1473, 1457, 1440, 1395, 1378, 1282, 1220, 1025. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.87 s (2H, SCH_2), 5.18 s (2H, OCH_2), 5.27 s (2H, NCH_2), 6.85 d. d. d ($1H_{Ar}$, *J* = 8.2, 2.5, 1.0), 6.95 br. s (1H), 7.52 br. s (1H, NH_2), 7.00–7.08 m ($3H_{Ar}$), 7.10–7.15 m ($2H_{Ar}$), 7.26–7.34 m ($3H_{Ar}$). Found, %: N 12.81; S 7.28. $C_{18}H_{17}BrN_4O_2S$. Calculated, %: N 12.93; S 7.40.

2-{[4-Benzyl-5-(3-bromophenoxymethyl)-4*H*-1,2,4-triazol-3-yl]sulfanyl}acetic acid (2d). Yield 93%, mp 155–156°C. IR spectrum, ν, cm^{-1}: 1948, 1706.1, 1592, 1579, 1472, 1443, 1400, 1341, 1282, 1219, 1202, 1190, 1018. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.94 s (2H, SCH_2), 3.01 br. s (1H, COOH), 5.17 s (2H, OCH_2), 5.28 s (2H, NCH_2), 6.86 d. d. d ($1H_{Ar}$, *J* = 8.2, 2.5, 1.0), 6.99–7.02 m ($2H_{Ar}$), 7.03–7.07 m ($1H_{Ar}$), 7.11–7.15 m (2H) and 7.25–7.31 m ($3H_{Ar}$). Found, %: N 9.46; S 7.21. $C_{18}H_{16}BrN_3O_3S$. Calculated, %: N 9.67; S 7.38.

2-{[4-Benzyl-5-(3-bromophenoxymethyl)-4*H*-1,2,4-triazol-3-yl]sulfanyl}propanoic acid (2e). Yield 91%, mp 145–146°C. IR spectrum, ν, cm^{-1}: 1721, 1587, 1578, 1464, 1451, 1377, 1360, 1284, 1225, 1194. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.57 d (3H, $CH\underline{CH_3}$, *J* = 7.1), 3.90 br. s (1H, COOH), 4.20 q (1H, CH, *J* = 7.1), 5.17 s (2H, OCH_2), 5.28 s (2H, NCH_2), 6.85 d. d. d ($1H_{Ar}$, *J* = 8.2, 2.4, 1.1), 7.00 d. d ($1H_{Ar}$, *J* = 2.4, 1.7), 7.04–7.10 m ($3H_{Ar}$), 7.14 d. d ($1H_{Ar}$, *J* = 8.2, 7.8), 7.25–7.33 m ($3H_{Ar}$). Found, %: N 9.12; S 7.01. $C_{19}H_{18}BrN_3O_3S$. Calculated, %: N 9.37; S 7.15.

2-{[5-(3-Bromphenoxymethyl)-4-cyclohexyl-4*H*-1,2,4-triazol-3-yl]sulfanyl}acetic acid (2f). Yield 81%, mp 79–80°C. IR spectrum, ν, cm^{-1}: 1723, 1589, 1577, 1465, 1376, 1280, 1221, 1183, 1027. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.18–1.48 m (3H), 1.67–1.77 m (1H), 1.85–1.97 m (4H) and 2.00–2.15 m (2H, C_6H_{11}), 3.65 br. s (1H, COOH), 4.00 s (2H, SCH_2), 4.08–4.21 m (1H, NCH), 5.26 s (2H, OCH_2), 7.01 d. d. d ($1H_{Ar}$, *J* = 8.2, 2.4, 1.0), 7.08–7.12 m ($1H_{Ar}$), 7.19 d ($1H_{Ar}$, *J* = 8.2), 7.21–7.23 m ($1H_{Ar}$). Found, %: N 9.67; S 7.38. $C_{17}H_{20}BrN_3O_3S$. Calculated, %: N 9.86; S 7.52.

2-{[4-Allyl-5-(3-bromophenoxymethyl)-4*H*-1,2,4-triazol-3-yl]sulfanyl}acetamide (2g). Yield 79%, mp 147–148°C. IR spectrum, ν, cm^{-1}: 3394, 3105, 1698, 1637, 1592, 1579, 1533, 1467, 1378, 1282, 1219, 1022, 762. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.86 s (2H, CH_2), 4.68 d. t (2H, NCH_2, *J* = 5.4, 1.6), 5.08 d. q (1H, $=CH_2$, *J* = 17.0, 1.6), 5.23 s (2H, OCH_2), 5.24 d. q (1H, $=CH_2$, *J* = 10.5, 1.6), 5.94 d. d. t (1H, =CH, *J* = 17.0, 10.5, 1.6), 6.92 br. s (1H), 7.50 br. s (1H, NH_2), 7.01 d. d. d (1H, *J* = 8.2, 2.5, 1.0), 7.09 d. d. d (1H, C_6H_4, *J* = 7.8, 1.8, 1.0) and 7.18 d. d (1H$_{Ar}$, *J* = 8.2, 7.8), 7.21 d. d ($1H_{Ar}$, *J* = 2.5, 1.8). Found, %: N 14.43; S 8.11. $C_{14}H_{15}BrN_4O_2S$. Calculated, %: N 14.62; S 8.37.

5-Benzyl-2-[(morpholin-4-yl)methyl]-4-cyclohexyl-2*H*-1,2,4-triazole-3-thione (3a). To a solution of triazole **1c** (0.27 g, 1 mmol) in 8–10 mL of methanol were added 0.12 g (1.3 mmol) of morpholine and 0.14 g (1.6 mmol) of formalin. The obtained mixture was stirred at room temperature for 8–10 h. The precipitate was filtered off, washed with 5–10 mL of water and recrystallized from ethanol. Yield 67%, mp 94–96°C. ^{1}H NMR spectrum, δ, ppm: 1.09–1.34 m (3H), 1.40–1.67 m (3H), 1.71–1.83 m (2H) and 2.08–2.36 br. s (2H, C_6H_{11}), 2.70–2.74 m [4H, $O(CH_2)_2$], 3.56–3.63 m [4H, $O(CH_2)_2$], 4.14 s (2H, CH_2), 4.25–4.37 m (1H, NCH), 5.00 m (2H, NCH_2N), 7.18–7.36 m ($5H_{Ar}$). ^{13}C NMR spectrum, δ_C, ppm: 24.2 (CH_2), 25.3 ($2CH_2$), 28.3 ($2CH_2$), 31.5 (CH_2), 50.2 ($2CH_2$), 56.9 (NCH_2), 65.8 ($2CH_2$), 68.0 (NCH), 126.8 (CH), 127.8 (CH), 128.1 (CH), 134.7 (C), 148.6 (C), 167.6 (CS). Found, %: N 14.87; S 8.41. $C_{20}H_{28}N_4OS$. Calculated, %: N 15.04; S 8.60.

3-(5-Benzyl-3-thioxo-4-phenyl-2*H*-1,2,4-triazol-2-yl)propanenitrile (3b). A mixture of 0.26 g (1 mmol) of triazole **1a**, 1.62 g (30 mmol) of freshly distilled acrylonitrile, 4 mL of water and 3.0 g (30 mmol) of triethylamine was refluxed for 8–10 h. The solution was evaporated; the crystalline residue was recrystallized from ethanol. Yield 62%, mp 74–75°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.08 t (2H, CH_2CN, *J* = 6.6), 3.90 s (2H, CH_2), 4.47 t (2H, NCH_2, *J* = 6.6), 6.88–6.96 m ($2H_{Ar}$), 7.11–7.21 m ($5H_{Ar}$), 7.41–7.51 m ($3H_{Ar}$). ^{13}C NMR spectrum, δ_C, ppm: 15.7 (CH_2), 31.6 (CH_2), 43.9 (NCH_2), 116.4 (C≡N), 126.4 (CH), 127.8 (2CH), 127.9 (2CH), 128.10 (2CH), 128.7 (2CH), 129.0 (CH), 133.3 (C), 133.6 (C), 149.6 (C), 167.5 (C). Found, %: N 17.23; S 9.73. $C_{18}H_{16}N_4S$. Calculated, %: N 17.48; S 10.00.

3-(5-Benzyl-3-thioxo-4-phenyl-2*H*-1,2,4-triazol-2-yl)propanoic acid (3c) was obtained similarly from 0.26 g (1 mmol) of triazole **1a** and 0.22 g (3 mmol) of acrylic acid. Yield 82%, mp 157–158°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.83 t (2H, CH_2CO, *J* = 7.5), 3.86 s (2H, CH_2), 4.39 t (2H, NCH_2, *J* = 7.5), 6.86–6.92 m ($2H_{Ar}$), 7.11–7.19 m ($5H_{Ar}$), 7.39–7.48 m

($3H_{Ar}$). ^{13}C NMR spectrum, δ_C, ppm: 31.2 (CH_2), 31.8 (CH_2), 44.2 (NCH_2), 126.4 (CH), 127.9 (4CH), 128.1 (2CH), 128.7 (2CH), 128.9 (CH), 133.6 (C), 133.8 (C), 149.1 (C), 167.1 (C), 171.1 (C). Found, %: N 12.21; S 9.78. $C_{18}H_{17}N_3O_2S$. Calculated, %: N 12.38; S 9.44.

***N*-(5-Benzyl-1,3,4-thiadiazol-2-yl)benzamide (4a)** was synthesized according to the procedure [20]. Yield 88%, mp 226–227°C. IR spectrum, ν, cm^{-1}: 1662, 1600, 1578, 1530, 1486, 1463, 1377, 1321, 1302, 1255, 694. ^1H NMR spectrum, δ, ppm (*J*, Hz): 4.32 s (2H, CH_2), 7.17–7.32 m ($2H_{Ar}$), 7.40–7.55 m (3H) and 8.07–8.13 m ($2H_{Ar}$), 12.59 m (1H, NH). Found, %: N 14.57; S 10.61. $C_{16}H_{13}N_3OS$. Calculated, %: N 14.23; S 10.86.

***N*-(5-Benzyl-1,3,4-thiadiazol-2-yl)-*N*-(2-cyanoethyl)benzamide (4b)** was prepared similarly to compound **3b**. Yield 93%, mp 109–110°C. IR spectrum, ν, cm^{-1}: 1608, 1572, 1547, 1497, 1483, 1416, 1389, 1366, 1320, 1298. ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.14 t (2H, CH_2CN, J = 6.5), 4.24 s (2H, CH_2), 4.72 t (2H, NCH_2, J = 6.5), 7.24–7.35 m ($5H_{Ar}$), 7.39–7.52 m (3H), 8.19–8.23 m ($2H_{Ar}$). ^{13}C NMR spectrum, δ_C, ppm: 16.1 (CH_2), 35.9 (CH_2), 45.3 (CH_2), 116.4 (CN), 126.8 (CH), 127.4 (2CH), 128.3 (2CH), 128.4 (2CH), 128.9 (2CH), 131.3 (CH), 135.4 (C), 157.9 (C), 165.2 (C), 172.5 (C). Found, %: N 15.79; S 9.37. $C_{19}H_{16}N_4OS$. Calculated, %: N 16.08; S 9.20.

Triazoles **5** and **6** were synthesized by known methods [2, 18], their physico-chemical constants correspond to literature data.

Compounds 7a, 7b. A mixture of 1 mmol of finely ground triazole **6a** or **6b** and 1 mmol of freshly distilled 2-(chloromethoxy)ethyl benzoate was heated in an oil bath until complete melting of compounds **6**, then heated for 1–1.5 h at the same temperature (110–120°C). The resulting glassy mass was dissolved in 3–4 mL of benzene and chromatographed on a column of silica gel. The reaction product was eluted first with benzene, then with a mixture benzene–ethyl acetate, 1 : 1. The glassy substances isolated after distillation of the solvents without further purification were debenzylated according to the procedure described in [24].

2-{5-Benzyl-4-[(2-hydroxyethoxy)methyl]-4*H*-1,2,4-triazol-3-yl-sulfanyl}acetic acid (7a). Yield 53%, mp >260°C. IR spectrum, ν, cm^{-1}: 3445, 3155, 1705, 1640, 1564, 1462, 1378, 1275, 1226, 1120, 1061, 931. ^1H NMR spectrum, δ, ppm: 3.45–3.58 m (4H, $O\underline{CH_2}\underline{CH_2}OH$), 3.67 s (1H) and 3.77 s (1H, CH_2Ph), 3.90 s (1H) and 4.14 s (1H, CH_2S), 4.63 br. s (1H, OH), 5.38 s (1H) and 5.39 s (1H, NCH_2), 7.13–7.29 m ($5H_{Ar}$). Found, %: C 51.67; H 5.18; N 12.71; S 9.69. $C_{14}H_{17}N_3O_4S$. Calculated, %: C 51.99; H 5.30; N 12.99; S 9.91.

2-{5-(4-Bromophenyl)-4-[(2-hydroxyethoxy)methyl]-4*H*-1,2,4-triazol-3-yl-sulfanyl}acetic acid (7b). Yield 67%, mp 131–132°C. IR spectrum, ν, cm^{-1}: 3406, 3161, 1727, 1599, 1466, 1398, 1360, 1199, 1117, 1069, 1011. ^1H NMR spectrum, δ, ppm: 3.52–3.57 m (2H, CH_2), 3.58–3.64 m (2H, CH_2), 4.0 m ($2H_{Ar}$), 12.51 br. s (1H, COOH). Found, %: C 40.03; H 3.27; N 10.68; S 16.17. $C_{13}H_{14}N_3O_4S$. Calculated, %: C 40.22; H 3.64; N 10.82; S 8.26.

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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