

SYNTHESIS OF NEW DERIVATIVES OF 1,2,4-TRIAZOLES

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On the basis of 3,5-disubstituted dihydrofuran-2(3*H*)-ones, hydrazides of substituted γ -hydroxybutyric acids were synthesized, which were further converted into the corresponding thiosemicarbazides and 1,2,4-triazoles. The synthesized compounds have not been previously described in the literature, and they cannot be obtained by any other way.

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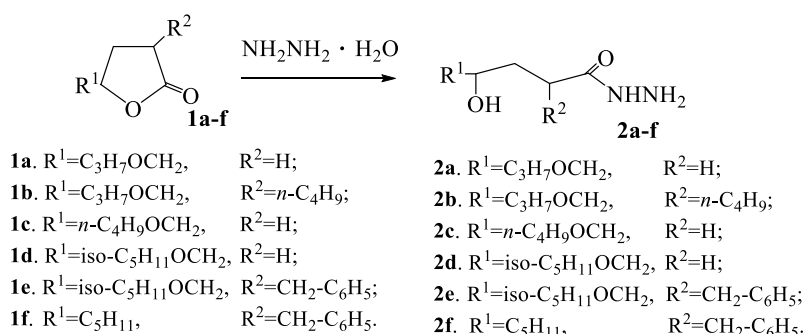
Keywords: 3,5-disubstituted dihydrofuran-2(3*H*)ones, γ -hydroxybutyric acid, hydrazides, thiosemicarbazides, 1,2,4-triazoles, biological activity.

Introduction. It is known that the majority of medicinal drugs contain fragments of heterocyclic compounds as active fragments, which can be of natural or synthetic origin. However, among numerous heterocyclic compounds, there are compounds that have not been revealed in plant and animal raw materials. They are triazoles that are obtained only synthetically. Literature data confirm the expediency of the research in the field of 1,2,4-triazoles, since these compounds are distinguished by low toxicity, wide spectrum of biological action with high effectiveness. The literature review precisely indicates that the compatibility of various functional groups in triazole-containing compounds leads to a quantitative or qualitative change in the beneficial properties of particular representatives of 1,2,4-triazoles. This is confirmed by the data on the biological activity of triazole-containing compounds described in the literature. Over the past decade, new derivatives have been revealed that show antifungal [1, 2], antibacterial [3], antitumor [4] activity. A number of compounds have been identified that can be used as enzyme inhibitors [5, 6], tubulin modulators [7], antiviral [8, 9], antiparasitic [10, 11], antileishmanial agents [12, 13] and so on. Along with the latest data presented, there are numerous drugs based on 1,2,4-triazoles, used in medical practice. As examples of such drugs that are highly efficient and at the same time low-toxic can be mentioned antifungals – Fluconazole, Itraconazole, Posaconazole, Voriconazole, Revuconazole; anticonvulsants – Estazolam, Loreclezole; anti-depressant – Trazodone; headache drugs – Antimigren, Rizatriptan; antiviral – Ribavirin; antitumor – Anastrozole; aromatase inhibitor – Letrozole, etc. These facts once again confirm the expediency of research in the field of 1,2,4-triazoles.

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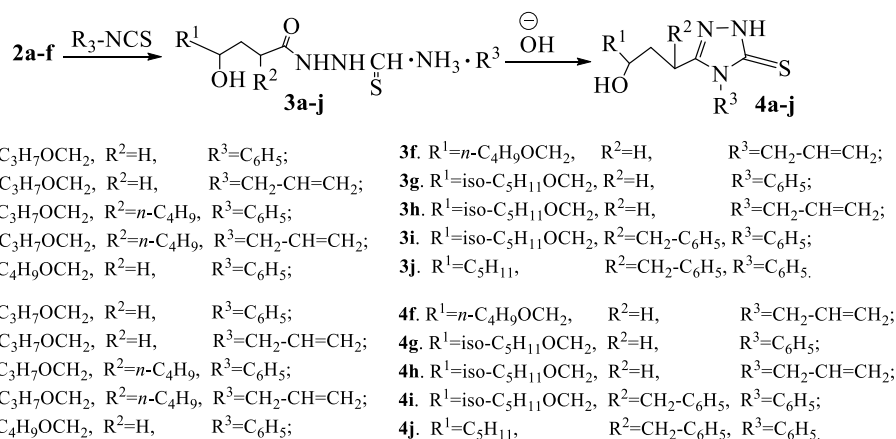
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Results and Discussion. As is known, one of the generally accepted methods for the synthesis of 1,2,4-triazoles is the method based on hydrazides of the corresponding acids. However, not all hydrazides can be synthesized by the ordinary method, in particular, γ -hydroxybutyric acid hydrazides that are unstable and upon heating undergo intramolecular cyclization with the formation of cyclic esters (Scheme 1). Based on the foregoing and aimed at introducing a hydroxypropyl radical into the structure of the expected triazoles, we have described a method for producing α -hydroxypropylbutyric acid hydrazides [14].



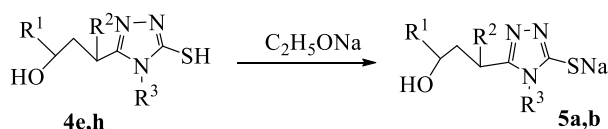
Scheme 1.

To achieve this goal, by the interaction of **2a–f** with isothiocyanates in a 96% ethanol medium, the corresponding disubstituted thiosemicarbazides (**3a–j**) were obtained, which by intramolecular cyclization with 10% solution of sodium (potassium) hydroxide afforded the target trisubstituted 1,2,4-triazoles (**4a–j**) (Scheme 2).



Scheme 2.

To obtain comparative data on various derivatives, sodium salts of compounds **4e** and **4h** were synthesized (Scheme 3).



Scheme 3.

The structures of compounds **3a–j** and **4a–j** were established by the data of elemental analysis, IR and ^1H NMR spectroscopy. In the IR spectra of compounds **3a–j**, characteristic absorption bands were detected, ν , cm^{-1} : C=O (amide) 1680; C–O–C 1180, 1250; OH 3380; NH 3200; C=C (ar.) 1600; C=C 1610; =CH (ar.) 3080. For compounds **4a–j**, the absorption bands characteristic of C=O (amide) were completely absent and C=N 1580 characteristic of the triazole cycle was detected. ^1H and ^{13}C NMR analysis data are given in the experimental section.

Experimental Part. ^1H and ^{13}C NMR spectra were recorded on Varian Mercury-300 MHz in DMSO:CCl₄ mixture (1 : 3). Chemical shifts (δ) in ppm are reported as quoted relative to the residual signals of DMSO-*d*₆ (2.5 for ^1H NMR and 39.5 for ^{13}C NMR) as internal references. The coupling constants (*J*) are given in hertz. IR spectra were recorded on a Nicolet 205 (FTIR) spectrophotometer. TLC analysis was performed on Silufol UV-254 plates. All reagents were of reagent grade and used as such or distilled prior to use. Melting points were determined on a “Boetius” micro-heating stage.

General Method for Obtaining Thiosemicarbazides of 4-Hydroxy-2,4-disubstituted Butyric Acids (3a–j). 0.02 mol of the corresponding acid hydrazide (**2a–f**), 10 mL of ethyl alcohol and 0.02 mol of the corresponding isothiocyanate are placed in a flask. The whole is vigorously stirred until homogenization and left for 3 h. The precipitated crystals are filtered off, washed with ether and dried. Recrystallized from aqueous alcohol (1:1).

2-(4-Hydroxy-5-propoxypentanoyl)-N-phenylhydrazinecarbothioamide (3a). Yield 91%, m.p. 143–144°C. *R*_f 0.44 (ethanol : benzene : hexane = 1 : 3 : 5). Found, %: C 55.40; H 7.15; N 12.85; S 9.90. C₁₅H₂₃N₃O₃S. Calculated, %: C 55.36; H 7.12; N 12.91; S 9.85.

^1H NMR, (300 MHz, DMSO/CCl₄, 1/3), δ , ppm: 10.42–9.76 m (1H, NH), 9.68–9.19 m (2H, NH), 7.49–7.41 m (2H_{arom}), 7.40–7.32 m (2H_{arom}); 7.12 ddt (*J* = 8.1, 6.5, 1.3 Hz, 1H_{arom}); 4.72 br.s (1H, OH); 3.52–3.41 m (1H, CHOH); 3.38 dd (*J* = 11.6, 5.2 Hz, 1H_a, OCH₂CHOH); 3.14 dt (*J* = 11.1, 5.1 Hz, 1H_a, CH₃CH₂CH₂); 3.06 dd (*J* = 11.6, 5.2 Hz, 1H_b, OCH₂CHOH); 2.88 dt (*J* = 11.1, 5.1 Hz, 1H_b, CH₃CH₂CH₂); 2.32–2.13 m (1H_a, CH₂CH₂CO); 2.12–1.88 m (2H, CH₂CH₂CO, 1H_b, CH₂CH₂CO); 1.57 qt (*J* = 7.9, 5.1 Hz, 2H, CH₃CH₂); 0.80 t (*J* = 8.0 Hz, 3H, CH₃).

^{13}C NMR (75 MHz, DMSO/CCl₄, 1/3), δ , ppm: 180.6; 174.0; 141.4; 128.8; 127.3; 123.5; 73.8; 73.6; 70.7; 33.7; 31.6; 23.8; 11.8.

N-Allyl-2-(4-hydroxy-5-propoxypentanoyl)hydrazinecarbothioamide (3b). Yield 77%, m.p. 125–126°C. *R*_f 0.40 (ethanol : benzene : hexane=1: 3: 5). Found, %: C 49.85; H 8.05; N 14.48; S 11.00. C₁₂H₂₃N₃O₃S. Calculated, %: C 49.80; H 8.01; N 14.52; S 11.08.

^1H NMR (300 MHz, DMSO/CCl₄, 1/3), δ , ppm: 9.88–9.80 m (1H, NHNHCS); 9.17–9.09 m (1H, NHCO); 7.68 t (*J* = 4.7 Hz, 1H, NHCH₂); 5.83 ddt (*J* = 16.2, 10.8, 5.3 Hz, 1H, CHCH₂NH); 5.11 ddq (*J* = 13.6, 2.9, 0.9 Hz, 2H, CH₂CHCH₂NH); 4.72 br.s (1H, OH); 4.13 ddt (*J* = 5.6, 4.7, 1.0 Hz, 2H, NHCH₂); 3.54–3.38 m (1H, CHOH); 3.22 d (*J* = 5.2 Hz, 2H, OCH₂CHOH); 3.01 t (*J* = 5.0 Hz, 2H, CH₃CH₂CH₂); 2.16–2.05 m (2H, CH₂CH₂CO); 2.04–1.94 m (2H, CH₂CO); 1.57 qt (*J* = 7.9, 5.0 Hz, 2H, CH₃CH₂); 0.80 t (*J* = 8.0 Hz, 3H, CH₃).

^{13}C NMR (75 MHz, DMSO/ CCl_4 , 1/3), δ , ppm: 182.7; 174.0; 134.8; 115.4; 73.8; 73.6; 70.7; 45.6; 33.7; 31.6; 23.8; 11.8.

2-(2-(2-Hydroxy-3-propoxypropyl)hexanoyl)-*N*-phenylhydrazinecarbothioamide (**3c**). Yield 93%, m.p. 153–154°C. R_f 0.43 (ethanol : benzene : hexane = 1 : 3 : 5). Found, %: C 59.85; H 8.15; N 14.55; S 8.35. $\text{C}_{19}\text{H}_{31}\text{N}_3\text{O}_3\text{S}$. Calculated, %: C 59.81; H 8.19; N 11.01; S 8.40.

^1H NMR (300 MHz, DMSO/ CCl_4 , 1/3), δ , ppm: 10.42–9.76 m (1H, NH); 9.68–9.19 m (2H, NH); 7.48–7.41 m (2H_{arom}); 7.40–7.33 m (2H_{arom}); 7.12 ddt ($J = 8.1, 6.5, 1.3$ Hz, 1H_{arom}); 4.72 br.s (1H, OH); 3.54–3.42 m (1H, CHOH); 3.38 dd ($J = 11.6, 5.5$ Hz, 1H_a, OCH_2CHOH); 3.14 dt ($J = 11.1, 5.1$ Hz, 1H_a, $\text{CH}_3\text{CH}_2\text{CH}_2\text{O}$); 3.06 dd ($J = 11.5, 5.5$ Hz, 1H_b, OCH_2CHOH); 2.88 dt ($J = 11.1, 5.1$ Hz, 1H_b, $\text{CH}_3\text{CH}_2\text{CH}_2\text{O}$); 2.30 tt ($J = 8.3, 6.6$ Hz, 1H, CHCO); 1.88 dt ($J = 14.7, 8.3$ Hz, 1H_a, CHCH_2CHOH); 1.70–1.19 m (1H_b, CHCH_2CHOH , 2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$, 2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{O}$, 2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$, 2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$); 0.91–0.74 m (6H, CH_3).

^{13}C NMR (75 MHz, DMSO/ CCl_4 , 1/3), δ , ppm: 180.0; 177.8; 141.4; 128.8; 127.3; 123.5; 74.1; 73.8; 69.9; 40.5; 36.5; 33.1; 30.3; 23.8; 23.1; 13.8; 11.8.

N-Allyl-2-(2-(2-hydroxy-3-propoxypropyl)hexanoyl)hydrazinecarbothioamide (**3d**). Yield 89%, m.p. 165–166°C. R_f 0.45 (ethanol : benzene : hexane = 1 : 3 : 5). Found, %: C 55.70; H 9.10; N 12.20; S 9.35. $\text{C}_{16}\text{H}_{31}\text{N}_3\text{O}_3\text{S}$. Calculated, %: C 55.62; H 9.04; N 12.16; S 9.28.

^1H NMR (300 MHz, DMSO/ CCl_4 , 1/3), δ , ppm: 10.31–9.65 m (1H, NH); 9.61–9.12 m (2H, NH); 5.78 ddt ($J = 16.5, 10.5, 6.3$ Hz, 1H, =CH); 5.19–5.12 m (1H_a, =CH₂); 5.11 m (1H_b, =CH₂); 4.75 br.s (1H, OH); 4.40 dd ($J = 30.4, 6.2$ Hz, 2H, NCH₂); 3.56 m (1H, OCH); 3.42 dd ($J = 12.3, 5.6$ Hz, 1H_a, OCH₂); 3.31 t ($J = 7.6$ Hz, 2H, OCH₂); 3.24 dd ($J = 12.3, 5.7$ Hz, 1H_b, OCH₂); 2.32 m (1H, CHC=O); 1.63–1.47 m (5H, CH₂); 1.45–1.27 m (5H, CH₂); 1.02–0.93 m (6H, CH₃).

^{13}C NMR (75 MHz, DMSO/ CCl_4 , 1/3), δ , ppm: 181.9; 175.1; 134.8; 114.8; 74.9; 72.2; 67.4; 45.6; 40.3; 36.7; 31.5; 29.0; 22.4; 22.1; 13.6; 10.3.

2-(5-Butoxy-4-hydroxypentanoyl)-*N*-phenylhydrazinecarbothioamide (**3e**). Yield 87%, m.p. 158–159°C. R_f 0.53 (ethanol : benzene : hexane = 1 : 3 : 5). Found, %: C 56.65; H 7.45; N 12.45; S 9.50. $\text{C}_{16}\text{H}_{25}\text{N}_3\text{O}_3\text{S}$. Calculated, %: C 56.61; H 7.42; N 12.38; S 9.45.

^1H NMR (300 MHz, DMSO/ CCl_4 , 1/3), δ , ppm: 10.42–9.76 m (1H, NH); 9.68–9.19 m (2H, NH); 7.47–7.41 m (2H_{arom}); 7.40–7.32 m (2H_{arom}); 7.12 ddt ($J = 8.1, 6.5, 1.3$ Hz, 1H_{arom}); 4.72 br.s (1H, OH); 3.53–3.41 m (1H, CHOH); 3.22 ddd ($J = 96.5, 11.6, 5.3$ Hz, 2H, OCH_2CHOH); 2.95 td ($J = 6.7, 0.9$ Hz, 2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$); 2.22 m (1H_a, $\text{CH}_2\text{CH}_2\text{CO}$); 2.01 m (2H, CH_2CO , 1H_b, $\text{CH}_2\text{CH}_2\text{CO}$); 1.57 pd ($J = 6.7, 0.6$ Hz, 2H, $\text{CH}_3\text{CH}_2\text{CH}_2$); 1.36 m (2H, CH_3CH_2); 0.87 t ($J = 6.9$ Hz, 3H, CH_3).

^{13}C NMR (75 MHz, DMSO/ CCl_4 , 1/3), δ , ppm: 180.6; 174.0; 141.4; 128.8; 127.3; 123.5; 73.6; 71.2; 70.7; 33.7; 31.6; 31.4; 17.7; 13.4.

N-Allyl-2-(5-butoxy-4-hydroxypentanoyl)hydrazinecarbothioamide (**3f**). Yield 92%, m.p. 124–125°C. R_f 0.46 (ethanol : benzene : hexane = 1 : 3 : 5). Found, %: C 51.50; H 8.25; N 13.90; S 10.60. $\text{C}_{13}\text{H}_{25}\text{N}_3\text{O}_3\text{S}$. Calculated, %: C 51.46; H 8.30; N 13.85; S 10.57.

^1H NMR (300 MHz, DMSO/ CCl_4 , 1/3), δ , ppm: 9.88–9.80 m (1H, NHNHCS); 9.17–9.09 m (1H, NHCO); 7.68 t ($J = 4.7$ Hz, 1H, CH_2NH); 5.83 ddt ($J = 16.2, 10.8, 5.3$ Hz, 1H, CHCH_2NH); 5.11 ddq ($J = 13.6, 2.9, 0.9$ Hz, 2H, $\text{CH}_2\text{CHCH}_2\text{NH}$); 4.72 br.s (1H, OH); 4.13 ddt ($J = 5.6, 4.7, 1.0$ Hz, 2H, CH_2NH); 3.54–3.38 m (1H, CHOH); 3.22 d ($J = 5.2$ Hz, 2H, OCH_2CHOH); 2.95 t ($J = 6.7$ Hz, 2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$); 2.17–2.05 m (2H, $\text{CH}_2\text{CH}_2\text{CO}$); 2.04–1.95 m (2H, CH_2CO); 1.57 pd ($J = 6.7, 0.6$ Hz, 2H, $\text{CH}_3\text{CH}_2\text{CH}_2$); 1.45–1.27 m (2H, CH_3CH_2); 0.87 t ($J = 6.9$ Hz, 3H, CH_3).

^{13}C NMR (75 MHz, DMSO/ CCl_4 , 1/3), δ , ppm: 182.7; 174.0; 134.8; 115.4; 73.6; 71.2; 70.7; 45.6; 33.7; 31.6; 31.4; 17.7; 13.4.

2-(4-Hydroxy-4-(isopentyloxy)butanoyl)-*N*-phenylhydrazinecarbothioamide (**3g**). Yield 93%, m.p. 131–132°C. R_f 0.43 (ethanol : benzene : hexane = 1 : 3 : 5). Found, %: C 56.55; H 7.45; N 12.45; S 9.50. $\text{C}_{16}\text{H}_{25}\text{N}_3\text{O}_3\text{S}$. Calculated, %: C 56.61; H 7.42; N 12.38; S 9.45.

^1H NMR (300 MHz, DMSO/ CCl_4 , 1/3), δ , ppm: 10.42–9.76 m (1H, NH); 9.68–9.19 m (2H, NH); 7.48–7.41 m (2H_{arom}); 7.40–7.32 m (2H_{arom}); 7.18–7.06 m (1H_{arom}); 4.78 br.s (1H, OH); 4.15 dtd ($J = 5.3, 4.3, 1.2$ Hz, 1H, CHOH); 3.01 ddt ($J = 78.8, 11.1, 7.0$ Hz, 2H, $\text{CH}_3\text{CHCH}_2\text{CH}_2$); 2.14–1.90 m (2H, CH_2CO , 1H_a, $\text{CH}_2\text{CH}_2\text{CO}$); 1.89–1.67 m (1H, CH_3CH , 1H_b, $\text{CH}_2\text{CH}_2\text{CO}$); 1.48 qd ($J = 6.9, 4.5$ Hz, 2H, CH_3CHCH_2); 0.97 d ($J = 6.6$ Hz, 6H, CH_3).

^{13}C NMR (75 MHz, DMSO/ CCl_4 , 1/3), δ , ppm: 180.6; 174.0; 141.4; 128.8; 127.3; 123.5; 99.7; 67.0; 39.0; 30.1; 29.9; 25.8; 22.9.

N-Allyl-2-(4-hydroxy-4-(isopentyloxy)butanoyl)hydrazinecarbothioamide (**3h**). Yield 84%, m.p. 102–103°C. R_f 0.54 (ethanol : benzene : hexane = 1 : 3 : 5). Found, %: C 51.50; H 8.35; N 13.90; S 10.50. $\text{C}_{13}\text{H}_{25}\text{N}_3\text{O}_3\text{S}$. Calculated, %: C 51.46; H 8.30; N 13.85; S 10.57.

^1H NMR (300 MHz, DMSO/ CCl_4 , 1/3), δ , ppm: 9.88–9.80 m (1H, NHNHCS); 9.17–9.09 d, m (1H, NHCO); 7.68 t ($J = 4.7$ Hz, 1H, CH_2NH); 5.83 ddt ($J = 16.2, 10.7, 5.3$ Hz, 1H, CHCH_2NH); 5.11 ddq ($J = 13.5, 2.9, 0.9$ Hz, 2H, $\text{CH}_2\text{CHCH}_2\text{NH}$); 4.78 br.s (1H, OH); 4.15 td ($J = 5.3, 4.3$ Hz, 1H, CHOH); 3.63 ddt ($J = 5.6, 4.7, 1.0$ Hz, 2H, CH_2NH); 3.01 t ($J = 6.9$ Hz, 2H, $\text{CH}_3\text{CHCH}_2\text{CH}_2$); 2.08–1.95 m (2H, CH_2CO); 1.94–1.71 m (2H, $\text{CH}_2\text{CH}_2\text{CO}$, 1H, CH_3CH); 1.48 q ($J = 6.9$ Hz, 2H, CH_3CHCH_2); 0.97 d ($J = 6.6$ Hz, 6H, CH_3).

^{13}C NMR (75 MHz, DMSO/ CCl_4 , 1/3), δ , ppm: 182.7; 174.0; 134.8; 115.4; 99.7; 67.0; 45.6; 39.0; 30.1; 29.9; 25.8; 22.9.

2-(2-Benzyl-4-hydroxy-4-(isopentyloxy)butanoyl)-*N*-phenylhydrazinecarbothioamide (**3i**). Yield 92%, m.p. 153–154°C. R_f 0.54 (ethanol : benzene : hexane = 1 : 3 : 8). Found, %: C 64.35; H 7.35; N 9.75; S 7.50. $\text{C}_{23}\text{H}_{31}\text{N}_3\text{O}_3\text{S}$. Calculated, %: C 64.31; H 7.27; N 9.78; S 7.46.

^1H NMR (300 MHz, DMSO/ CCl_4 , 1/3), δ , ppm: 10.42–9.76 m (1H, NH); 9.68–9.19 m (2H, NH); 7.47–7.41 m (2H_{arom}); 7.40–7.33 m (2H_{arom}); 7.33–7.24 m (4H_{arom}); 7.22–7.06 m (2H_{arom}); 4.78 br.s (1H, OH); 4.15 td ($J = 6.4, 4.5$ Hz, 1H, CHOH); 3.51 ddt ($J = 78.8, 11.1, 7.0$ Hz, 2H, $\text{CH}_3\text{CHCH}_2\text{CH}_2$); 3.06 ddt ($J = 14.2, 7.2, 1.1$ Hz, 1H_a, $\text{C}_6\text{H}_5\text{CH}_2$); 2.72 tt ($J = 8.5, 7.2$ Hz, 1H, CHCO); 2.56 ddt ($J = 14.2, 7.3, 1.1$ Hz, 1H_b, $\text{C}_6\text{H}_5\text{CH}_2$); 2.08 dddd ($J = 85.4, 15.2, 8.6, 6.5$ Hz, 2H, CHCH_2CHOH); 1.88–1.71 m (1H, CH_3CH); 1.48 qd ($J = 6.8, 4.5$ Hz, 2H, CH_3CHCH_2); 0.97 d ($J = 6.6$ Hz, 6H, CH_3).

^{13}C NMR (75 MHz, DMSO/ CCl_4 , 1/3), δ , ppm: 180.0; 172.9; 141.4; 139.2; 129.1; 128.8; 128.4; 127.3; 127.0; 123.5; 100.7; 67.0; 40.9; 39.0; 38.2; 36.2; 25.8; 22.9.

2-(2-Benzyl-4-hydroxynonanoyl)-N-phenylhydrazinecarbothioamide (3j). Yield 81%, m.p. 158–159°C. R_f 0.45 (ethanol : benzene : hexane = 1 : 3 : 8). Found, %: C 66.85; H 7.50; N 10.20; S 7.70. $\text{C}_{23}\text{H}_{31}\text{N}_3\text{O}_2\text{S}$. Calculated, %: C 66.79; H 7.56; N 10.16; S 7.75.

^1H NMR (300 MHz, DMSO/ CCl_4 , 1/3), δ , ppm: 10.42–9.76 m (1H, NH); 9.68–9.19 m (2H, NH); 7.48–7.41 m (2H_{arom}); 7.40–7.34 m (2H_{arom}); 7.33–7.24 m (4H_{arom}); 7.23–7.07 m (2H_{arom}); 3.88 br.s (1H, OH); 3.11 ttd ($J = 7.7, 6.7, 5.8$ Hz, 1H, CHOH); 2.56 ddt ($J = 14.1, 7.3, 1.0$ Hz, 1H_a, $\text{C}_6\text{H}_5\text{CH}_2$); 2.22 tt ($J = 8.3, 7.3$ Hz, 1H, CHCO); 2.06 ddt ($J = 14.1, 7.3, 1.0$ Hz, 1H_b, $\text{C}_6\text{H}_5\text{CH}_2$); 1.75 dddd ($J = 79.4, 14.7, 8.4, 7.6$ Hz, 2H, CHCH_2CHOH); 1.56–1.41 m (1H_a, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$); 1.40–1.15 m (2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$, 2H, $\text{CH}_3\text{CH}_2\text{CH}_2$, 1H_b, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$, 2H, CH_3CH_2); 0.91–0.78 m (3H, CH_3).

^{13}C NMR (75 MHz, DMSO/ CCl_4 , 1/3), δ , ppm: 180.0; 172.9; 141.4; 139.2; 129.1; 128.8; 128.4; 127.3; 127.0; 123.5; 67.6; 43.4; 39.3; 38.0; 36.2; 31.8; 25.5; 22.8; 14.1.

General Method for Obtaining 3,4-Disubstituted-5-mercapto-4H-1,2,4-triazoles (4a–j). 3 g (0.075 mol) of sodium hydroxide in the form of a 10% aqueous solution, 0.05 mol of the corresponding **2a–j** are placed in a flask and stirred. The mixture is heated in a boiling water bath for 4 h, cooled, acidified with a dilute solution of hydrochloric acid to pH 6. The precipitated crystals are filtered off, washed with water and dried. Recrystallized from aqueous alcohol (1 : 1).

3-(3-Hydroxy-4-propoxybutyl)-4-phenyl-1H-1,2,4-triazole-5(4H)-thione (4a). Yield 90%, m.p. 100–101°C. R_f 0.65 (ethanol : benzene : hexane = 1 : 3 : 5). Found, %: C 58.65; H 6.85; N 13.70; S 10.50. $\text{C}_{15}\text{H}_{21}\text{N}_3\text{O}_2\text{S}$. Calculated, %: C 58.61; H 6.89; N 13.67; S 10.43.

^1H NMR (300 MHz, DMSO/ CCl_4 , 1/3), δ , ppm: 13.26 br.s (1H, NH); 7.61 ddt ($J = 7.7, 6.5, 1.3$ Hz, 1H_{arom}); 7.54–7.42 m (2H_{arom}); 7.41–7.31 m (2H_{arom}); 4.72 br.s (1H, OH); 3.52–3.42 m (1H, CHOH); 3.38 dd ($J = 11.6, 5.1$ Hz, 1H_a, OCH_2CHOH); 3.14 dt ($J = 11.1, 5.1$ Hz, 1H_a, $\text{CH}_3\text{CH}_2\text{CH}_2$); 3.06 dd ($J = 11.6, 5.1$ Hz, 1H_b, OCH_2CHOH); 2.88 dt ($J = 11.1, 5.1$ Hz, 1H_b, $\text{CH}_3\text{CH}_2\text{CH}_2$); 2.16–1.98 m (2H, $\text{CH}_2\text{CH}_2\text{CHOH}$); 1.79–1.45 m (2H, $\text{CH}_2\text{CH}_2\text{CHOH}$, 2H, CH_3CH_2); 0.80 t ($J = 8.0$ Hz, 3H, CH_3).

^{13}C NMR (75 MHz, DMSO/ CCl_4 , 1/3), δ , ppm: 175.8; 151.7; 140.1; 128.9; 128.1; 127.4; 73.8; 73.6; 70.7; 34.9; 25.1; 23.8; 11.8.

4-Allyl-3-(3-hydroxy-4-propoxybutyl)-1H-1,2,4-triazole-5(4H)-thione (4b). Yield 92%, m.p. 102–103°C. R_f 0.71 (ethanol : benzene : hexane = 1 : 3 : 5). Found, %: C 53.15; H 7.85; N 15.55; S 11.75. $\text{C}_{12}\text{H}_{21}\text{N}_3\text{O}_2\text{S}$. Calculated, %: C 53.11; H 7.80; N 15.48; S 11.82.

^1H NMR (300 MHz, DMSO/ CCl_4 , 1/3), δ , ppm: 13.48 br.s (1H, NH); 5.66–5.46 m (1H, $\text{CH}_2\text{CHCH}_2\text{N}$); 4.72 br.s (1H, OH); 4.67–4.58 m (2H, $\text{CH}_2\text{CHCH}_2\text{N}$); 4.50 dt ($J = 6.8, 1.0$ Hz, 2H, $\text{CH}_2\text{CHCH}_2\text{N}$); 3.46 tdt ($J = 7.1, 5.9, 4.9$ Hz, 1H, CHOH); 3.22 d ($J = 5.1$ Hz, 2H, OCH_2CHOH); 3.01 d ($J = 10.1$ Hz, 2H, $\text{CH}_3\text{CH}_2\text{CH}_2$); 2.03 t ($J = 9.1$ Hz, 2H, $\text{CH}_2\text{CH}_2\text{CHOH}$); 1.69–1.48 m (2H, $\text{CH}_2\text{CH}_2\text{CHOH}$, 2H, CH_3CH_2); 0.80 t ($J = 8.0$ Hz, 3H, CH_3).

^{13}C NMR (75 MHz, DMSO/ CCl_4 , 1/3), δ 165.4; 147.5; 133.1; 117.6; 73.8; 73.6; 70.7; 45.1; 34.9; 24.1; 23.8; 11.8.

3-(2-Hydroxy-1-propoxyoctan-4-yl)-4-phenyl-1H-1,2,4-triazole-5(4H)-thione (**4c**). Yield 91%, m.p. 103–105°C. R_f 0.69 (ethanol : benzene : hexane = 1 : 3 : 5). Found, %: C 62.78; H 8.04; N 11.56; S 8.82. $\text{C}_{19}\text{H}_{29}\text{N}_3\text{O}_2\text{S}$. Calculated, %: C 62.78; H 8.04; N 11.56; S 8.82.

^1H NMR (300 MHz, DMSO/ CCl_4 , 1/3), δ , ppm: 13.01 br.s (1H, NH); 7.61 ddt ($J = 7.7, 6.5, 1.3$ Hz, 1H_{arom}); 7.54–7.42 m (2H_{arom}); 7.41–7.31 m (2H_{arom}); 4.72 br.s (1H, OH); 3.53–3.42 m (1H, CHOH); 3.38 dd ($J = 11.5, 5.3$ Hz, 1H_a , OCH_2CH); 3.14 dt ($J = 11.1, 5.1$ Hz, 1H_a , $\text{CH}_3\text{CH}_2\text{CH}_2\text{O}$); 3.06 dd ($J = 11.6, 5.3$ Hz, 1H_b , OCH_2CH); 2.88 dt ($J = 11.1, 5.1$ Hz, 1H_b , $\text{CH}_3\text{CH}_2\text{CH}_2\text{O}$); 2.08 tt ($J = 8.7, 7.0$ Hz, 1H, CHCH_2CHOH); 1.90–1.71 m (1H_a , CHCH_2CHOH , 1H_a , $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$); 1.65–1.51 m (1H_b , CHCH_2CHOH , 2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{O}$); 1.50–1.38 m (1H_b , $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$); 1.37–1.18 m (2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$); 1.17–0.95 m (2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$); 0.86–0.74 m (3H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{O}$, 3H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$).

^{13}C NMR (75 MHz, DMSO/ CCl_4 , 1/3), δ , ppm: 173.7; 152.8; 135.0; 129.3; 128.1; 127.9; 74.1; 73.8; 69.9; 38.9; 36.2; 33.8; 30.3; 23.8; 23.1; 13.8; 11.8.

4-Allyl-3-(2-hydroxy-1-propoxyoctan-4-yl)-1H-1,2,4-triazole-5(4H)-thione (**4d**). Yield 86%, m.p. 84–85°C. R_f 0.68 (ethanol : benzene : hexane = 1 : 3 : 5). Found, %: C 58.65; H 9.00; N 12.85; S 9.85. $\text{C}_{16}\text{H}_{29}\text{N}_3\text{O}_2\text{S}$. Calculated, %: C 58.68; H 8.93; N 12.83; S 9.79.

^1H NMR (300 MHz, DMSO/ CCl_4 , 1/3), δ , ppm: 13.49 br.s (1H, NH); 5.66–5.46 m (1H, $\text{CH}_2\text{CHCH}_2\text{N}$); 4.72 br.s (1H, OH); 4.67–4.54 m (2H, $\text{CH}_2\text{CHCH}_2\text{N}$); 3.95 dt ($J = 7.1, 1.0$ Hz, 2H, $\text{CH}_2\text{CHCH}_2\text{N}$); 3.46 tdt ($J = 8.2, 6.1, 5.2$ Hz, 1H, CHOH); 3.52 d ($J = 5.3$ Hz, 2H, OCH_2CH); 3.01 d ($J = 10.1$ Hz, 2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{O}$); 2.08 tt ($J = 8.9, 7.1$ Hz, 1H, CHCH_2CHOH); 1.75–1.48 m (2H, CHCH_2CHOH , 2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$, 2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{O}$); 1.36–1.83 m (2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$); 1.16–0.99 m (2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$); 0.86–0.74 m (3H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{O}$, 3H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$).

^{13}C NMR (75 MHz, DMSO/ CCl_4 , 1/3), δ , ppm: 133.1; 117.6; 74.1; 73.8; 69.9; 45.3; 37.1; 36.2; 33.8; 30.3; 23.8; 23.1; 13.8; 11.8.

3-(4-Butoxy-3-hydroxybutyl)-4-phenyl-1H-1,2,4-triazole-5(4H)-thione (**4e**). Yield 89%, m.p. 109–110°C. R_f 0.67 (ethanol : benzene : hexane = 1 : 3 : 5). Found, %: C 59.75; H 7.25; N 13.15; S 9.95. $\text{C}_{16}\text{H}_{23}\text{N}_3\text{O}_2\text{S}$. Calculated, %: C 59.78; H 7.21; N 13.07; S 9.98.

^1H NMR (300 MHz, DMSO/ CCl_4 , 1/3), δ , ppm: 13.78 br.s (1H, NH); 7.61 ddt ($J = 7.7, 6.5, 1.3$ Hz, 1H_{arom}); 7.54–7.42 m (2H_{arom}); 7.41–7.31 m (2H_{arom}); 4.72 br.s (1H, OH); 3.53–3.42 m (H, CHOH); 3.22 ddd ($J = 96.5, 11.6, 5.1$ Hz, 2H, OCH_2CH); 2.95 td ($J = 6.7, 0.9$ Hz, 2H, $\text{CH}_2\text{OCH}_2\text{CH}$); 2.16–1.90 m (2H, CH_2C); 1.79–1.45 m (4H, $\text{CH}_3\text{CH}_2\text{CH}_2$, $\text{CH}_2\text{CH}_2\text{C}$); 1.45–1.27 m (2H, CH_3CH_2); 0.87 t ($J = 6.9$ Hz, 3H, CH_3).

^{13}C NMR (75 MHz, DMSO/ CCl_4 , 1/3), δ , ppm: 175.8; 151.7; 140.0; 128.9; 128.1; 127.4; 73.6; 71.2; 70.7; 34.9; 31.4; 25.1; 17.7; 13.4.

4-Allyl-3-(4-butoxy-3-hydroxybutyl)-1H-1,2,4-triazole-5(4H)-thione (**4f**). Yield 87%, m.p. 116–117°C. R_f 0.70 (ethanol : benzene : hexane = 1 : 3 : 5).

Found, %: C 54.75; H 8.05; N 14.75; S 11.20. C₁₃H₂₃N₃O₂S. Calculated, %: C 54.71; H 8.12; N 14.72; S 11.23.

¹H NMR (300 MHz, DMSO/CCl₄, 1/3), δ , ppm: 12.81 br.s (1H, NH); 5.66–5.46 m (1H, CH₂CHCH₂N); 4.72 br.s (1H, OH); 4.67–4.56 m (2H, CH₂CHCH₂N); 4.51 dt ($J = 6.8, 1.0$ Hz, 2H, CH₂CHCH₂N); 3.46 tdt ($J = 7.1, 5.9, 5.0$ Hz, 1H, CHOH); 3.22 d ($J = 5.1$ Hz, 2H, OCH₂CHOH); 2.95 d ($J = 13.5$ Hz, 2H, CH₃CH₂CH₂CH₂); 2.03 t ($J = 9.1$ Hz, 2H, CH₂CH₂CHOH); 1.60 m (2H, CH₂CH₂CHOH, 2H, CH₃CH₂CH₂); 1.36 m (2H, CH₃CH₂); 0.87 t ($J = 6.9$ Hz, 3H, CH₃).

¹³C NMR (75 MHz, DMSO/CCl₄, 1/3), δ , ppm: 165.4; 147.5; 133.1; 117.6; 73.6; 71.2; 70.7; 45.1; 34.9; 31.4; 24.1; 17.7; 13.4.

3-(3-Hydroxy-4-(isopentyloxy)butyl)-4-phenyl-1H-1,2,4-triazole-5(4H)-thione (4g). Yield 91%, m.p. 121–122°C. R_f 0.57 (ethanol : benzene : hexane = 1 : 3 : 5). Found, %: C 60.90; H 7.55; N 12.50; S 9.60. C₁₇H₂₅N₃O₂S. Calculated, %: C 60.87; H 7.51; N 12.53; S 9.56.

¹H NMR (300 MHz, DMSO/CCl₄, 1/3), δ , ppm: 13.00 br.s (1H, NH); 7.61 ddt ($J = 7.8, 6.5, 1.4$ Hz, 1H_{arom}); 7.54–7.42 m (2H_{arom}); 7.41–7.31 m (2H_{arom}); 4.72 br.s (1H, OH); 3.52–3.42 m (1H, CHOH); 3.22 ddd ($J = 96.5, 11.6, 5.1$ Hz, 2H, OCH₂CHOH); 2.90 td ($J = 6.9, 0.9$ Hz, 2H, CH₃CHCH₂CH₂); 2.16–1.90 m (2H, CH₂CH₂CHOH); 1.89–1.76 m (1H, CH₃CH); 1.75–1.47 m (2H, CH₂CH₂CHOH); 1.41 q ($J = 6.8$ Hz, 2H, CH₃CHCH₂); 0.97 d ($J = 6.6$ Hz, 6H, CH₃).

¹³C NMR (75 MHz, DMSO/CCl₄, 1/3), δ , ppm: 175.8; 151.7; 140.1; 128.9; 128.1; 127.4; 73.6; 70.7; 69.9; 38.6; 34.9; 25.1; 25.0; 22.6.

4-Allyl-3-(3-hydroxy-4-(isopentyloxy)butyl)-1H-1,2,4-triazole-5(4H)-thione (4h). Yield 89%, m.p. 97–98°C. R_f 0.76 (ethanol : benzene : hexane = 1 : 3 : 5). Found, %: C 56.20; H 8.45; N 14.00; S 10.75. C₁₄H₂₅N₃O₂S. Calculated, %: C 56.16; H 8.42; N 14.03; S 10.71.

¹H NMR (300 MHz, DMSO/CCl₄, 1/3), δ , ppm: 14.00 br.s (1H, NH); 5.66–5.46 m (1H, CH₂CHCH₂N); 4.72 br.s (1H, OH); 4.63–4.51 m (2H, CH₂CHCH₂N); 4.45 dt ($J = 6.8, 1.0$ Hz, 2H, CH₂CHCH₂N); 3.46 tdt ($J = 7.1, 5.9, 4.9$ Hz, 1H, CHOH); 3.22 d ($J = 5.1$ Hz, 2H, OCH₂CHOH); 2.90 d ($J = 13.7$ Hz, 2H, CH₃CHCH₂CH₂); 2.03 t ($J = 9.1$ Hz, 2H, CH₂CH₂CHOH); 1.81 dp ($J = 13.2, 6.6$ Hz, 1H, CH₃CH); 1.62 td ($J = 9.1, 7.1$ Hz, 2H, CH₂CH₂CHOH); 1.41 q ($J = 6.8$ Hz, 2H, CH₃CHCH₂); 0.97 d ($J = 6.6$ Hz, 6H, CH₃).

¹³C NMR (75 MHz, DMSO/CCl₄, 1/3), δ , ppm: 165.4; 147.5; 133.1; 117.6; 73.6; 70.7; 69.9; 45.1; 38.6; 34.9; 25.0; 24.1; 22.6.

3-(4-Hydroxy-5-(isopentyloxy)-1-phenylpentan-2-yl)-4-phenyl-1H-1,2,4-triazole-5(4H)-thione (4i). Yield 84%, m.p. 95–96°C. R_f 0.61 (ethanol : benzene : hexane = 1 : 3 : 8). Found, %: C 67.70; H 7.30; N 9.90; S 7.55. C₂₄H₃₁N₃O₂S. Calculated, %: C 67.73; H 7.34; N 9.87; S 7.53.

¹H NMR (300 MHz, DMSO/CCl₄, 1/3), δ , ppm: 13.66 br.s (1H, NH); 7.61 ddt ($J = 7.7, 6.5, 1.3$ Hz, 1H_{arom}); 7.54–7.42 m (2H_{arom}); 7.41–7.31 m (2H_{arom}); 7.29–7.10 m (5H_{arom}); 4.72 br.s (H, OH), 4.02–3.92 m (1H, CHOH); 3.52 ddd ($J = 96.5, 11.5, 5.3$ Hz, 2H, OCH₂CHOH); 2.90 td ($J = 6.9, 0.9$ Hz, 2H, CH₃CHCH₂CH₂); 2.75–2.42 m (2H, C₆H₅CH₂, 1H, C₆H₅CH₂CH); 1.91–1.69 m (1H_a, CHCH₂CHOH, 1H, CH₃CH); 1.57 ddd ($J = 14.8, 8.7, 8.0$ Hz, 1H_b, CHCH₂CHOH); 1.41 q ($J = 6.8$ Hz, 2H, CH₃CHCH₂); 0.97 d ($J = 6.6$ Hz, 6H, CH₃).

^{13}C NMR (75 MHz, DMSO/ CCl_4 , 1/3), δ , ppm: 173.7; 148.0; 139.2; 135.0; 129.3; 129.1; 128.4; 128.1; 127.9; 127.0; 74.1; 69.9; 43.7; 38.6; 36.6; 34.4; 25.0; 22.6.

3-(4-Hydroxy-1-phenylnonan-2-yl)-4-phenyl-1H-1,2,4-triazole-5(4H)-thione (4j). Yield 81%, m.p. 161–162°C. R_f 0.60 (ethanol : benzene : hexane = 1 : 3 : 3). Found, %: C 69.84; H 7.39; N 10.62; S 8.11. $\text{C}_{23}\text{H}_{29}\text{N}_3\text{OS}$. Calculated, %: C 69.84; H 7.39; N 10.62; S 8.11.

^1H NMR (300 MHz, DMSO/ CCl_4 , 1/3), δ , ppm: 13.81 br.s (1H, NH); 7.61 ddt ($J = 7.7, 6.5, 1.3$ Hz, 1H_{arom}); 7.54–7.42 m (2H_{arom}); 7.41–7.31 m (2H_{arom}); 7.30–7.12 m (5H_{arom}); 3.88 br.s (1H, OH), 3.11 ttd ($J = 7.6, 6.5, 5.6$ Hz, 1H, CHOH); 2.73–2.47 m (2H, $\text{C}_6\text{H}_5\text{CH}_2$, 1H, $\text{C}_6\text{H}_5\text{CH}_2\text{CH}$); 1.81 ddd ($J = 14.8, 8.8, 7.6$ Hz, 1H_a , CHCH_2CHOH); 1.64–1.42 m (1H_b , CHCH_2CHOH , 1H_a , $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$); 1.41–1.16 m (2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$, 2H, $\text{CH}_3\text{CH}_2\text{CH}_2$, 1H_b , $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$, 2H, CH_3CH_2); 0.91–0.78 m (3H, CH_3).

^{13}C NMR (75 MHz, DMSO/ CCl_4 , 1/3), δ , ppm: 173.7; 148.0; 139.2; 135.0; 129.3; 129.1; 128.4; 128.1; 127.9; 127.0; 67.6; 43.7; 38.1; 38.0; 36.6; 31.8; 25.5; 22.7; 14.1.

General Method for Obtaining Sodium 5-(4,4'-Disubstituted-3-hydroxybutyl)-4H-1,2,4-triazole-3-thiolate (5a, 5b). 0.02 mol of the corresponding disubstituted 5-mercapto-1,2,4-triazole in 30 mL of abs. ethanol is placed in a flask. An alcoholic solution of sodium ethylate is added dropwise until a pink color appears (according to phenolphthalein indicator). In a vacuum of 15–20 mm Hg, ethyl alcohol is removed and the crystalline residue is dried in a vacuum desiccator. The yields of the final products are quantitative.

Sodium 5-(4-Butoxy-3-hydroxybutyl)-4-phenyl-4H-1,2,4-triazole-3-thiolate (5a). Yield 95%, m.p. 191–193°C. Found, %: C 56.00; H 6.40; N 12.30; Na 6.65; S 9.30. $\text{C}_{16}\text{H}_{22}\text{N}_3\text{NaO}_2\text{S}$. Calculated, %: C 55.96; H 6.46; N 12.24; Na 6.69; S 9.34.

Sodium 4-Allyl-5-(3-hydroxy-4-(isopentyloxy)butyl)-4H-1,2,4-triazole-3-thiolate (5b). Yield 98%, m.p. 197–198°C. Found, %: C 52.35; H 7.50; N 13.10; Na 7.20; S 10.05. $\text{C}_{14}\text{H}_{24}\text{N}_3\text{NaO}_2\text{S}$. Calculated, %: C 52.32; H 7.53; N 13.07; Na 7.15; S 9.98.

Screening studies have established that compounds **3a–j** and **4a–j** have neurotropic, antitumor activity and stimulate the growth of phytoplankton.

Thus, on the basis of 3,5-disubstituted dihydrofuran-2-ones, a method was developed for obtaining hydrazides of a new structure, which makes it possible to synthesize new derivatives of 1,2,4-triazoles. The value of this method lies in the fact that only this method allows introducing an aliphatic alcohol group into the 3 position of 1,2,4-triazole.

It has also been established that both intermediate thiosemicarbazides (**3a–j**) and horseradish 1,2,4-triazoles (**4a–j**) have valuable properties, and their further studies are expedient.

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1,2,4-ՏՐԻԱԶՈԼՆԵՐԻ ՆՈՐ ԱԾԱՆՑՅԱԼՆԵՐԻ ՍԻՆԹԵԶ

3,5-Դիհիդրոֆուրան-2(3*H*)-ոնների հիման վրա սինթեզվել են տեղակալված γ -հիդրօքսիկարագաթթվի հիդրագիդրներ, որոնք հետագայում փոխարկվել են համապատասխան թիոսեմիկարբազիդների և 1,2,4-տրիազոլների: Սինթեզված միացությունները գրականության մեջ նկարագրված չեն և դրանք հնարավոր չէ ստանալ այլ ճանապարհով:

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СИНТЕЗ НОВЫХ ПРОИЗВОДНЫХ 1,2,4-ТРИАЗОЛОВ

На основе 3,5-дизамещенных дигидрофуран-2(3*H*)-онон синтезированы гидразиды замещенных γ -гидроксимасляных кислот, которые в дальнейшем превращены в соответствующие тиосемикарбазиды и 1,2,4-триазолы. Синтезированные соединения ранее не были описаны в литературе, и их невозможно получить другим способом.