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NEW S- AND N- SUBSTITUTED DERIVATIVES OF 5-ARYLOXYMETHYL-1,2,4-TRIAZOLES AND THEIR BIOLOGICAL ACTIVITY

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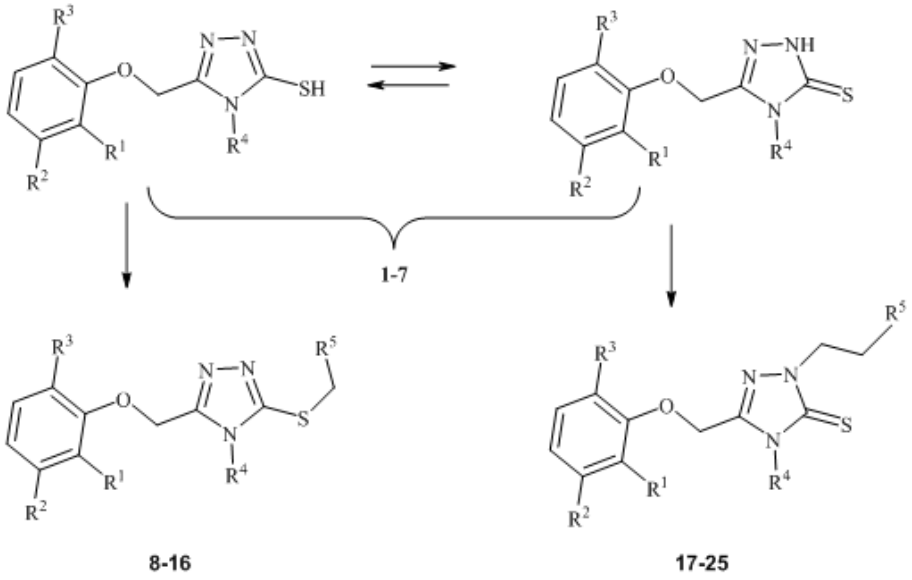
In order to find new biologically active compounds among 1,2,4-triazole derivatives, alkylation reactions of SH- and NH-tautomeric nucleophilic centers of the heterocycle with groups containing a polar substituent were carried out. The combination of hydrophobic groups in position 4 and polar groups in positions 3 and 5 of the triazole ring in the molecule will make it possible to trace the effect of increased polarity (hydrophilicity) of compounds on biological activity. It was shown that some derivatives of the synthesized 1,2,4-triazoles have moderate bacterial activity, some compounds have weak antimonoamineoxidase activity and are practically devoid of antiradical properties.

Библ. ссылок 14.

Studies on the synthesis of new functionalized derivatives of the five-membered 1,2,4-triazole heterocycle are still relevant due to the effectiveness of drugs based on them that have entered medical practice. Among them, of particular interest are antifungal agents - fluconazole, itraconazole, voriconazole, antiviral - ribavirin, antitumor agents - anastrozole, letrozole, vorozol [1,2], etc.

A pronounced antibacterial activity is exhibited by many polysubstituted 1,2,4-triazoles, which combine various pharmacologically active groups in their structure [3,4]. It has been established that the introduction of halogen-containing aryl- and aryloxymethyl substituents into various positions of the heterocycle ring significantly increases the activity or expands the spectrum of the biological action of the compound [5, 6].

Since hydrophobic aromatic groups reduce the solubility of the drug in an aqueous medium and thereby limit their applicability in clinical therapy [7], it seems appropriate to functionalize the 1,2,4-triazole ring with hydrophilic substituents, including hydroxyl, carboxyl, amine, and amide groups, which increase water solubility of compounds. We have previously reported on the antitumor and antibacterial properties of 1,2,4-triazole derivatives containing polar structural fragments [8], some of which inhibited the level of tumor DNA methylation [9]. Taking into consideration, the published data and based on our works, which testify to the prospects of research in this area, in this work we undertook the synthesis of new polyfunctional 1,2,4-triazoles according to the scheme:



1-7: R^1, R^2, R^3, R^4 = Me, H, H, Cy (**1**); Me, H, Me, Cy (**2**); All, H, H, Bn (**3**); All, H, H, Cy (**4**);

Me, H, H, Bn (**5**); H, H, Br, Bn (**6**); H, Br, H, Cy (**7**).

8-16: R^1 = Me, R^2 = R^3 = H, R^4 = Cy, R^5 = COOH (**8**); R^1=R^3=Me, R^2=H, R^4=Cy, R^5=COOEt (**9**),

COOH (**10**), $CONH_2$ (**11**); R^1 = All, R^2 = R^3 = H, R^4 = Bn, R^5 = COOH (**12**), $CONH_2$ (**13**);

R^4 = Cy, R^5 = COOH (**14**); R^1 = R^3 = H, R^2 = Br, R^4 = Cy, R^5 = COOEt (**15**), $CONH_2$ (**16**).

17-25. R^1 = Me, R^2 = R^3 = H, R^4 = Bn, R^5 = CN (**17**), COOH (**18**); R^4 = Cy, R^5 = CN (**19**),

R^1 = R^3 = Me, R^2 = H, R^4 = Cy, R^5 = CN (**20**), COOH (**21**) R^1 = All, R^2 = R^3 = H, R^4 = Bn,

R^5 = CN (**22**), COOH (**23**), R^1 = R^3 = H, R^2 = Br, R^4 = Bn,R^5 = CN (**24**), R^4 = Cy,R^5 = CN (**25**).

The starting 1,2,4-triazoles **1-7** were synthesized by intramolecular cyclization of the corresponding 1,4-disubstituted thiosemicarbazides in an alkaline medium [10]. Variation of substituents in the aromatic ring would make it possible to trace the change in biological properties and reveal a possible structure-activity relationship in the series of 3-aryloxymethyl-substituted 1,2,4-triazole-3-thiols **1-7**. For this purpose, the latter were alkylated with chloroacetic acid, chloroacetamide, chloroethylacetate under the conditions we developed earlier [11]. In the ^{1}H NMR spectra of the reaction products, singlet signals of the protons of SCH_2-groups appear in the region of 3.86-4.11 ppm, which, together with the data of the ^{13}C NMR spectra, confirm the alkylation reaction at the SH group of triazoles **1-7**. In the IR spectra of compounds **8-16** there are no absorption bands of NH, SH and C=S groups, which also indicates the reaction with the formation of S-alkylated 1,2,4-triazoles **8-16**. For comparative evaluation, N-substituted derivatives of 1,2,4-triazoles **17-25** were also obtained by cyanoethylation and carboxyethylation reactions. Cyanoethylation of triazoles **1-7** was carried out by heating them with freshly distilled acrylonitrile in the presence of the basic catalyst triethylamine; similarly, carboxyethylation was carried out by interaction with acrylic acid. In the ^{1}H NMR spectra of cyanoethylation products **17-25**, in contrast to sulfanyl-substituted 1,2,4-triazoles **8-16**, two-proton triplet signals of N^2-CH_2 groups are observed in the range of chemical shifts 4.32-5.37 ppm; in the IR spectra of compounds **22** and **24** there are absorptions bands in the region of 1128-1158 cm^{-1}, corresponding to vibrations of the C=S group in thioamides, confirming the reaction at the N^2 nucleophilic position of triazoles **1-7**. The purity and structure of all synthesized compounds were confirmed by TLC, elemental analysis, IR, ^{1}H NMR and ^{13}C spectroscopy.

Thus, the synthesis of new functionalized 1,2,4-triazoles with aryloxymethyl and electronegative substituents in the side chains, which are of interest as potential biologically active compounds, was carried out.

The antibacterial activity of compounds **8–25** was studied by the agar diffusion method [12] at a bacterial load of 20 million microbial bodies per 1 *ml* of medium. Gram-positive staphylococci (*Staphylococcus aureus 209 p,1*) and gram-negative rods (*Sh. dysenterial Flexneri 6858, E coli 0-55*) were used in the experiments. Solutions of the compounds were prepared in DMSO at dilutions of 1:20.

The well-known drug furazolidone was used as a positive control [13]. Studies have shown that in the series of synthesized compounds, only triazoles **8** and **11** with thioether substituents exhibit moderate activity, inhibiting the growth of all used microorganisms in a zone with a diameter of 15-16 *mm*, while the rest of the substances have a weak antibacterial effect (d = 10-11 *mm*). At the same time, compounds **8** and **11** are significantly inferior in activity to the control drug furazolidone (d=24-25 *mm*).

Most of the compounds do not have significant antimonoamineoxidase activity. Only S-substituted derivatives **12** and **13** inhibit deamination of 5-hydroxytryptamine by 60 and 31%, respectively ($p < 0.05$).The antiradical properties of only triazoles **8** and **12** were studied. The studies were carried out using their reaction with the free stable radical 2,2'-diphenyl-1-picrylhydrazyl in methanol at a temperature of 25 °C and a ratio of reagents of 1:1 [14]. It was found that compounds **8** and **12** were practically devoid of antiradical properties.

Experimental

Spectra ^{1}H and ^{13}C NMR were recorded on a Varian Mercury-300 VX instrument in DMSO-d_6-CCl_4 solution (1:3) at operating frequencies of 300 and 75 *MHz*, respectively, internal standard TMS. IR spectra were taken on a Nicolet Avatar 330-IR spectrometer in vaseline oil. The progress of the reactions and the individuality of the compounds obtained were monitored by TLC on Silikagel 60F254 plates (Germany) in the dioxane-benzene (1:2) system, visualization by UV irradiation.

Alkylation of 5-aryloxymethyl-substituted 4*H*-1,2,4-triazoles 1-7. A solution of 1.0 *mmol* of the corresponding triazole **1-7**, 0.056 *g* (1 *mmol*) KOH in 5 *ml* of ethanol is boiled for 20-30 *min*, then 1 *mmol* of the corresponding halide is added and heating is continued for another 3-4 *h*. The solvent is distilled off, 30 *ml* of water are added, the precipitate is filtered off and recrystallized from ethanol. In the case of chloroacetic acid, the reaction is carried out by boiling for 5-6 *h* in 15 *ml* of water in the presence of a 3-fold excess of KOH, followed by acidification and precipitation with acetic acid.

{[5-(2-Methylphenoxymethyl)-4-cyclohexyl-4*H*-1,2,4-triazol-3-yl]sulfanyl}acetic acid (8). Prepared by alkylation of triazole **1** with chloroacetic acid, yield 83%, m.p. 73-75 °C, R_f 0.61. IR spectrum, *ν*, cm^{-1}: 3410 (OH), 1709 (C = O), 1602 (arom.). ^{1}H NMR spectrum, *δ*, ppm, *Hz*: 1.28-1.49 m (3H, CH_2, C<u>H</u>H); 1.68-1.75 m (1H, CH_2, CH<u>H</u>); 1.87-1.96 m (4H, 2•CH_2); 2.04-2.16 m (2H, CH_2); 2.18 s (3H, 2-CH_3); 4.02 s (2H, SCH_2); 4.15-4.27 m (1H, NCH); 5.23 s (2H, OCH_2); 5.63 br.

(1H, OH); 6.83 td (1H_{arom}, J^1 = 7.1, J^2 = 1.4); 7.06-7.17 m (3H_{arom}.). ^{13}C NMR spectrum, *δ*, ppm: 15.7 (CH_3), 24.4 (CH_2), 25.5 (2CH_2), 30.05 (2CH_2), 35.1 (SCH_2), 56.0 (NCH), 60.01 (OCH_2), 111.0 (CH), 120.6 (CH), 125.3 (C), 126.5 (CH), 130.2 (CH), 149.2 (C), 155.3 (C), 168.7 (CO). Found, %: N 12.01; S 9.15. $C_{17}H_{21}N_3O_3S$. Calculated, %: N 12.09; S 9.23.

Ethyl {[5-(2,6-dimethylphenoxymethyl)-4-cyclohexyl-4*H*-1,2,4-triazol-3-yl]sulfanyl}acetate (9). Prepared by alkylation of triazole **2** with ethyl chloroacetate, yield 51.6%, m.p. 56-58 °C, R_f 0.74. IR spectrum, ν ,cm^{-1}: 3460 (OH), 1731 (C=O), 1589 (arom). ^{1}H NMR spectrum, δ, ppm, *Hz*: 1.29 t (3H, CH_3, J = 7.1); 1.34-1.53 m (3H, CH_2, C<u>H</u>H); 1.73-1.81 m (1H, CH_2, CH<u>H</u>); 1.91-2.04 m (4H, 2CH_2); 2.10-2.23 m (2H, CH_2); 2.25 s (6H, 2•CH_3); 4.11 s (2H, SCH_2), 4.17 c (2H, OCH_2, J = 7.1); 4.28-4.41 m (1H, NCH); 4.93 s (2H, OCH_2); 6.90 dd (1H_{arom}., J_1 = 8.4, J_2 = 6.3); 6.97-7.01 m (2 H_{arom}.). ^{13}C NMR spectrum, δ, ppm: 13.6 (CH_3), 16.1(2CH_3), 24.4 (CH_2), 25.4 (2CH_2), 30.6 (2CH_2,) 34.41(SCH_2), 56.0 (NCH), 60.71 (OCH_2), 63.7 (OCH_2), 123.8 (CH), 128.4 (2CH), 129.9 (CH), 148.1 (C), 151.6 (C), 155.0 (C), 166.9 (CO). Found, %: N 10.69; S 8.26. $C_{20}H_{27}N_3O_3S$. Calculated, %: N10.77; S 8.21.

{[5-(2,6-Dimethylphenoxymethyl)-4-cyclohexyl-4*H*-1,2,4-triazol-3-yl]sulfanyl}acetic acid (10). Prepared by alkylation of triazole **2** with chloroacetic acid, yield 98%, m.p. 216-218 °C, R_f 0.38. IR spectrum, *ν*, cm^{-1}: 3441 (OH), 1727 (C=O), 1593 (arom.). ^{1}H NMR spectrum, δ, ppm, *Hz*: 1.25-1.52 m (3H, CH_2, C<u>H</u>H); 1.73-1.82 m (1H, CH_2, CH<u>H</u>); 1.92-2.03 m (4H, 2CH_2); 2.12-2.25 m (2H, CH_2); 2.26 s (6H, 2CH_3); 4.04 s (2H, SCH_2); 4.29-4.41m (1H, NCH); 4.93 s (2H, OCH_2); 6.90 dd (1H_{arom}, J_1= 8.4, J_2= 6.2); 6.97-7.01m (2H_{arom}). ^{13}C NMR spectrum, δ, ppm: 16.1 (2CH_3), 24.4 (CH_2), 25.4 (2CH_2), 30.6 (2CH_2), 34.8 (SCH_2), 56.0 (NCH), 63.7 (OCH_2), 123.8 (CH), 128.4 (2CH), 129.9 (C), 148.7 (C), 151.5 (C), 155.0 (C), 168.5 (C). Found, %: N11.37; S 8.41. $C_{19}H_{25}N_3O_3S$. Calculated, %: N11.19; S 8.54.

{[5-(2,6-Dimethylphenoxymethyl)-4-cyclohexyl-4*H*-1,2,4-triazol-3-yl]sulfanyl}acetamide (11). Prepared by alkylation of triazole **2** with chloroacetamide, yield 91%, mp 85-86°C, R_f 0.43. IR spectrum, ν, *cm*$^{-1}$: 3303, 3191(NH_2), 1690 (C=O), 1645 (arom.). ^{1}H NMR spectrum, *δ*. ppm, *Hz*: 1.24-1.52 m (3H, CH_2, C<u>H</u>H); 1.72-1.81m (1H, CH_2, CH<u>H</u>); 1.92-2.02 m (4H, $2CH_2$); 2.14-2.15 m

(2H, CH_2); 2.26 s (6H, $2CH_3$); 3.96 s (2H, SCH_2); 4.30-4.42 m (1H, NCH), 4.93 s (2H, OCH_2); 6.87-7.01m ($3H_{arom}$); 6.95 and 7.54 br.s. (according to 1H, NH_2); ^{13}C NMR spectrum, δ, ppm: 16.2 ($2CH_3$), 24.4 (CH_2), 25.4 ($2CH_2$), 30.6 ($2CH_2$), 36.4 (SCH_2), 56.1(NCH), 63.8 (OCH_2), 123.8 (CH) , 128.4 (2CH), 130.0 (C), 149.51 (C), 15.6 (C), 155.1 (C), 168.2 (CO). Found, %: N 14.81; S 8.43. $C_{19}H_{26}N_4O_2S$. Calculated, %: N 14.96; S 8.56.

{[5-(2-Allylphenoxymethyl)-4-benzyl-4*H*-1,2,4-triazol-3-yl]sulfanyl}acetic acid (12). Prepared by alkylation of triazole **3** with chloroacetic acid, yield 83%, m.p. 114-115 °C, R_f 0.49. IR spectrum, ν, *cm*$^{-1}$: 3210 (OH), 1724 (C=O), 1600 (arom.). ^{1}H NMR spectrum, δ, ppm, Hz: 3.10 dt (2H, CH_2, J_1 =6.5, J_2 =1.5); 3.95 s (2H, SCH_2); 4.86-4.98 m (2H, $=CH_2$); 5.16 s (2H, OCH_2); 5.29 s (2H, NCH_2); 5.79 ddm (1H, =CH, J_1=16.9, J_2=10.3, J_3=6.5); 6.86 td ($1H_{arom}$., J_1 =7.3, J_2 =1.2); 7.01-7.18 m ($5H_{arom}$.); 7.23-7.32 m ($3H_{arom}$.); 12.58 br (1H, OH). ^{13}C NMR spectrum, *δ*, ppm: 33.1 (CH_2), 34.7 (CH_2), 46.8 (CH_2), 59.9 (OCH_2), 111.3 (CH), 115.0 (C), 120.7 (CH), 126.3 (2CH) , 126.3 (2CH), 126.8 (CH), 127.4 (CH), 127.7 (C), 128.2 (2CH), 129.2 (CH), 134.5 (C), 136.2 (C), 151.2 (C), 154.8 (C), 168.5 (C=O). Found, %: N 10.39; S 8.37. $C_{21}H_{21}N_3O_3S$. Calculated, %: N 10.62; S 8.11.

{[5-(2-Allylphenoxymethyl)-4-benzyl-4*H*-1,2,4-triazol-3-yl]sulfanyl}acetamide (13). Prepared by alkylation of triazole **3** with chloroacetamide , yield 56%, m.p. 121-122 °C, R_f 0.46. IR spectrum, ν, c*m*$^{-1}$: 3521, 3358, 3172 (NH_2), 1690 (C=O), 1601 (arom.). ^{1}H NMR spectrum, δ, ppm, *Hz*: 3.10 d (2H, CH_2, J = 6.5); 3.86 s (2H, SCH_2); 4.86-4.98 m (2H, $=CH_2$); 5.16 s (2H, NCH_2); 5.30 s (2H, OCH_2); 5.80 ddt (=CH , J_1 = 16.8, J_2 =10.2, J_3 = 6.5); 6.83-6.90 m ($1H_{arom}$.); 6.55–7.52 br.s. (1H, NH_2); 7.01-7.18 m ($5H_{arom}$.); 7.23-7.32 m ($3H_{arom}$.). ^{13}C NMR spectrum, δ, m,d: 33.1 (CH_2), 36.3 (CH_2), 46.8 (NCH_2), 59.8 (OCH_2), 111.3 (CH), 115.0 (CH_2), 120.7 (CH), 126.3 (2CH) , 126.8 (CH), 127.4 (CH), 127.7 (C), 128.3 (2CH), 129.2 (CH), 134.5 (C), 136.1 (CH), 151.2 (C), 151.3 (C), 154.8 (C), 168.0 (CO). Found, %: N 14.39; S 8.42. $C_{21}H_{22}N_4O_2S$. Calculated, %; N 14.20; S 8.13.

{[5-(2-Allylphenoxymethyl)-4-cyclohexyl-4*H*-1,2,4-triazol-3-yl]sulfanyl]} acetic acid (14). Prepared by alkylation of triazole **4** with chloroacetic acid, yield 73%, m.p. 101-103 °C, R_f 0.63. ^{1}H NMR spectrum, δ, ppm, *Hz*: 1.18-1.49 m (3H, CH_2,C<u>H</u>H); 1.67-1.76 m (1H, CH_2, CH<u>H</u>); 1.85-1.96 m (4H, $2CH_2$); 2.03-2.19 m (2H, CH_2); 3.32 d (2H, CH_2, J = 6.5); 4.03 s (2H, SCH_2); 4.14-4.26 m (1H, NCH); 4.93-5.02 m (2H, $=CH_2$); 5.24 s (2H, OCH_2); 5.90 ddt (1H, =CH, J_1 =16.7, J_2 = 10.3, J_3 = 6.6); 6.85-6.92 m ($1H_{arom}$.); 7.06-7.21 m ($3H_{arom}$.); 12.42 br (1H, OH). ^{13}C NMR spectrum, δ, ppm: 24.3 (CH_2), 25.2 ($2CH_2$), 30.5 (2 CH_2), 33.2 (CH_2), 34.7 (CH_2), 55.9 (NCH), 60.2 (OCH_2), 111.5

(CH), 115 ($=CH_2$), 120.7 (CH), 126.9 (CH), 127.4 (C), 129.3 (C), 136.0 (CH), 148.9 (C), 150.8 (C), 168.4 (CO). Found, %: N 10.62; S 8.13. $C_{20}C_{25}N_3O_3S$. Calculated, %: N 10.84; S 8.28.

Ethyl {[5-(3-bromophenoxymethyl)-4-cyclohexyl-4*H*-1,2,4-triazol-3-yl]sulfanyl]}acetate (15). Prepared by alkylation of triazole **4** with ethyl chloroacetat, yield 64%, oily, R_f 0.57. ^{1}H NMR spectrum, δ, ppm, *Hz*: 1.26 t (3H, CH_3, J = 7.1); 1.21-1.48 m (3H, CH_2, C<u>H</u>H); 1.68-1.77 m (1H, CH_2, CH<u>H</u>); 1.86-2.13 m (6H, $3CH_2$); 4.09 s (2H, SCH_2); 4.16 k (2H, OCH_2, J = 7.1); 4.04-4.11m

(2H, NCH); 5.27 s (2H, OCH_2); 7.02 ddd ($1H_{arom}$, J_1 = 8.2, J_2 = 2.4, J_3 = 1.0); 7.10 ddd ($1H_{arom}$, J_1 = 2.11, J_2 = 1.8 J_3 =1.0); 7.19 d ($1H_{arom}$., J = 8.2); 7.20-7.23 m ($1H_{arom}$.). ^{13}C NMR spectrum, δ, ppm: 13.6 (CH_2), 24.4 (CH_3), 25.2 ($2CH_2$), 30.6 ($2CH_2$) 34.3 (SCH_2), 56.1 (NCH_2), 60.4 (OCH_2), 113.4 (CH), 117.5 (CH), 122.1 (C), 123.9 (CH), 130.3 (CH), 148.6 (C), 150.4 (C), 158.0 (C), 166.9 (C). Found, %: N 9.12; S 7.31. $C_{19}H_{24}BrN_3O_3S$. Calculated, %: N 9.25; S 7.06.

{[5-(3-Bromophenoxymethyl)-4-cyclohexyl-4*H*-1,2,4-triazol-3-yl]sulfanyl}acetamide (16). Prepared by alkylation of triazole **4** with chloroacetamide, yield 85%, m.p. 92-93 °C, R_f 0.47. ^{1}H NMR spectrum, δ, ppm, *Hz*: 1.16-1.48 m (3H, CH_2, C<u>H</u>H); 1.66-1.76 m (1H, CH_2, CH<u>H</u>); 1.83-1.96 m (4H, $2CH_2$); 1.99-2.15 m (2H, CH_2); 3.93 s (2H, SCH_2); 4.10-4.21 m (1H, NCH.); 5.27 s (2H, OCH_2.); 6.95 br (1H) and 7.53 br (1H, NH_2.); 6.99-7.04 m ($1H_{arom}$.); 7.08-7.12 m ($1H_{arom}$,); 7.19d ($1H_{arom}$, J = 8.0); 7.21-7.23 m ($1H_{arom}$.). ^{13}C NMR spectrum, δ, ppm: 24.7 (CH_2), 25.3 ($2CH_2$), 30.06 ($2CH_2$), 36.3 (CH_2), 56.3 (NCH), 60.5 (OCH_2), 113.5 (CH), 117.6 (CH), 122.1 (C), 124.0 (CH), 130.4 (CH), 150.1 (C), 150.4 (C), 158.1 (C), 168.2 (C). Found, %: N 12.87; S 7.31, $C_{17}H_{21}BrN_4O_2S$. Calculated, %: N 13.17; S 7.54.

General procedure for the preparation of N-substituted 1,2,4-triazole-3-thiones 17-25. A mixture of 1 *mmol* of the corresponding triazole **1-7**, 30 *mmol* of freshly distilled acrylonitrile or acrylic acid in 4 *ml* of water and 3.02 (30 *mmol*), triethylamine was boiled for 8-10 *hours*. The solution was evaporated, the oily residue was treated with ice water, forming the crystals that were filtered off and recrystallized from ethanol.

3-[4-Benzyl-5-(3-methylphenoxymethyl)-3-thioxo-2*H*-1,2,4-triazol-2-yl]propanenitrile (17). Prepared by alkylation of triazole **5** with acrylonitrile, yield 91%, m.p. 84-86 °C, R_f 0.46. ^{1}H NMR spectrum, δ, ppm, *Hz*: 2.01s (3H, CH_3); 3.06 t (2H, CH_2CN, J = 6.6); 4.49 t (2H, NCH_2, J = 6.6); 5.00 s (2H, OCH_2); 5.40 s (2H, NCH_2); 6.81-6.92 m (2 $H_{arom.}$); 7.04-7.13 m (2$H_{arom.}$); 7.21-7.28 m (5 $H_{arom.}$). ^{13}C NMR spectrum, δ, ppm: 15.5 (CH_3), 15.7 (CH_2), 44.2 (CH_2), 47.2 (NCH_2), 59.6 (OCH_2), 110.8 (CH), 116.3 (C), 120.9 (CH), 125.7 (C), 126.4 (CH), 126.8 (2CH), 127.3 (CH), 128.1 (2CH), 130.2 (CH), 130.4 (C), 146.9 (C), 154.9 (C), 167.9 (CS). Found, %: N 15.09; S 8.53. $C_{20}H_{20}N_4OS$. Calculated, %: N 15.37, S 8.80.

3-[4-Benzyl-5-(3-methylphenoxymethyl)-3-thioxo-2*H*-1,2,4-triazol-2-yl]propanoic acid (18). Prepared by alkylation of triazole **5** with acrylic acid, yield 77%, mp: 91–92 °C, R_f 0.41. ^{1}H NMR spectrum, δ, ppm, *Hz*: 2.04 s (3H, CH_3); 2.79 t (2H, CH_2, J = 7.4); 4.41 t (2H, NCH_2, J = 7.4); 4.95 s (2H, NCH_2); 5.38 s (2H, OCH_2); 6.81-6.89 m (2 $H_{arom.}$), 7.03-7.12 m (2$H_{arom.}$), 7.20-7.28 m (5 $H_{arom.}$); 8.02 br (1H, COOH). Found, %: N 10.69; S 8.11. $C_{20}H_{21}N_3O_3S$. Calculated, %: N 10.96; S 8.36.

3-[5-(2-Methylphenoxymethyl)-3-thioxo-4-cyclohexyl-2*H*-1,2,4-triazol-2-yl]propanenitrile (19). Prepared by alkylation of triazole **1** with acrylonitrile, yield 67%, m.p. 84-86°C, R_f 0.67. ^{1}H NMR spectrum, δ, ppm, *Hz*: 1.16-1.50 m (3H, CH_2, C<u>H</u>H); 1.65-1.73 m (1H, CH_2, CH<u>H</u>); 1.84-1.95 m (4H, $2CH_2$); 2.22 s (3H, CH_3); 2.31-2.47 m (2H, CH_2); 3.01 t (2H, CH_2CN, J = 6.6); 4.41 t (2H, NCH_2, J = 6.6); 4.44-4.55 m (1H, NCH); 5.19 s (2H, OCH_2); 6.86 td (1H_{arom}, J_1 = 7.4; J_2 = 1.0); 7.02-7.18 m (3 $H_{arom.}$). ^{13}C NMR spectrum, δ, ppm: 15.5 (CH_2CN), 15.7 (CH_3), 24.4 ($2CH_2$), 25.2 ($2CH_2$), 28.5 (CH_2), 43.9 (NCH_2), 57.7 (NCH), 60.1 (OCH_2) , 110.1 (CH), 116.3 (C), 120.8 (CH), 125.3 (C), 126.5 (CH), 130.3 (CH), 146.5 (C), 154.9 (C), 166.5 (CS). Found, %: N 15.56; S 8.68. $C_{19}H_{24}N_4OS$. Calculated, %: N 15.72, S 8.99.

3-[5-(-2,6-Diphenylphenoxymethyl)-3-thioxo-4-cyclohexyl-2*H*-1,2,4-triazol-2-yl]propanenitrile (20). Prepared by alkylation of triazole **2** with acrylonitrile, yield 84%, oily, R_f 0.71. IR spectrum, *v*, cm^{-1}: 2253 (CN), 1185 (C=S). ^{1}H NMR spectrum, δ, ppm, *Hz*: 1.25-1.56 m (3H, $CH_2C\underline{H}H$); 1.71-1.81m (1H, $CH_2CH\underline{H}$); 1.88-2.01 m (4H, CH_2); 2.25 s (6H, $2CH_3$); 2.46-2.65 m (2H, CH_2); 2.99 t (2H, CH_2CN, J = 6.6); 4.40 t (2H, NCH_2, J = 6.6); 4.56-4.68 m (1H, NCH); 4.91 s (2H, OCH_2); 6.91 dd ($1H_{arom}$, J_1 = 8.4, J_2 = 5.9); 6.97-7.01 m ($2H_{arom}$.). ^{13}C NMR spectrum, δ, ppm: 15.5 (CH_2), 16.2 ($2CH_2$), 24.4 (CH_2), 25.4 ($2CH_3$), 28.8 (CH_2), 43.8 (NCH_2), 57.6 (NCH), 63.9 (OCH_2), 116.2 (C), 124.0 (CH), 122.5 (2CH), 129.8 (C), 147.1 (C)155. (C), 166.3(C). Found, %: N 14.87; S 8.41, $C_{20}H_{26}N_4OS$. Calculated, %: N 15.12; S 8.66.

3-[5-(2,6-Dimethylphenoxymethyl)-3-thioxo-4-cyclohexyl-2*H*-1,2,4-triazol-2-yl]propanoic acid (21). Prepared by alkylation of triazole **2** with acrylic acid, yield 76%, oily, R_f 0.67. ^{1}H NMR spectrum, δ, ppm, *Hz*: 1.24-1.55 m (3H, $CH_2C\underline{H}H$); 1.70-1.80 m (1H, $CH_2CH\underline{H}$); 1.85-2.01 m (4H, $2CH_2$); 2.24 s (6H, CH_3); 2.43-2.60 m (2H, CH_2); 2.71 t (2H, CH_2, J = 7.5); 4.32 t (2H, NCH_2, J = 7.5); 4.55-4.70 m (1H, NCH); 4.86 s (2H, OCH_2); 6.0 br (1H, OH); 6.88-7.01 m ($3H_{arom}$.). ^{13}C NMR spectrum, δ, ppm: 16.2 ($2CH_3$), 24.5 (CH_2), 25.5 ($2CH_2$), 25.0 (CH_2), 31.8 (CH_2), 44.1 (CH_2), 45.3 (CH_2), 57.4 (NCH), 64.2 (OCH_2), 124.0 (2C), 128.4 (2 CH), 129.9 (CH), 146.5 (C), 155.1 (C), 166.3 (CS), 171.2 (CO). Found, %: N 10.56; S 8.02. $C_{20}H_{27}N_3O_3S$. Calculated, %: N 10.79; S 8.23.

3-[5-(-2-Allylphenoxymethyl)-4-benzyl-3-thioxo-2*H*-1,2,4-triazol-2-yl]propanenitrile (22). Prepared by alkylation of triazole **3** with acrylonitrile, yield 71%, oily, R_f 0.65. IR spectrum, *v*, cm^{-1}: 2252 (CN), 1128 (C=S). ^{1}H NMR spectrum, δ, ppm. *Hz*: 3.06 t (2H, CH_2CN, J = 6.6,); 3.15 dt (2H, CH_2, J_1 = 6.4, J_2 = 1.5); 4.49 t (2H, NCH_2, J = 6.6); 4.94 dc (1H, $=CH_2$, J_1 = 16.7, J_2 = 1.5); 4.96-5.02 m (1H,$=CH_2$); 5.00 s (2H, OCH_2); 5.39 s (2H, NCH_2); 5.85 ddt (1H, =CH, J_1 = 16.7, J_2 = 10.1, J_3 = 6.4); 6.86-6.96 m (2 H_{arom}.); 7.04-7.12 m ($2H_{arom}$.); 7.20-7.31 m ($5H_{arom}$.). ^{13}C NMR spectrum, δ, ppm: 15.7 (CH_2), 33.1 (CH_2), 44.2 (NCH_2), 47.2 (NCH_2), 59.8 (OCH_2), 111.1 (=C), 115.2 (CH_2), 116.3 (C), 121.1 (CN), 126.8 (2CH), 126.9 (CH), 127.4 (CH), 127.7 (C), 128.1 (2CH), 129.3 (CH), 134.5 (C), 136.1 (C), 146.9 (C), 154.5 (C), 167.9(C). Found, %: N 14.31; S 8.24. $C_{22}H_{22}N_4OS$. Calculated, %: N 14.35; S 8.21.

3-[5-(-2-Allylphenoxymethyl)-4-benzyl-3-thioxo-2*H*-1,2,4-triazol-2-yl]propanic acid (23). Prepared by alkylation of triazole **3** with acrylic acid, yield 66%, m.p. 153-154 °C, R_f 0.59. ^{1}H NMR spectrum, δ, ppm, *Hz*: 2.80 t

(2H, CH_2, J = 7.5); 3.14 d (2H, CH_2, J = 7.5); 3.14 d (2H, CH_2, J = 6.5); 4.41t (2H, NCH_2, J = 7.5); 4.89-5.02 m (2H, $=CH_2$); 4.95 s (2H, OCH_2); 5.37 s (2H, NCH_2); 5.84 ddt (1H,=CH, J_1 = 16.8, J_2 = 10.3, J_3 = 6.5); 6.86-6.95 m ($2H_{arom.}$); 7.04-7.17 m ($2H_{arom.}$); 7.19-7.31 m ($5H_{arom.}$); 12.19 br (1H, OH). ^{13}C NMR spectrum, δ, ppm: 31.7 (CH_2), 33.1 (CH_2), 44.5 (NCH_2), 47.1 (NCH_2), 59.8 (OCH_2), 111.1 (CH), 115.2 (=CH2), 121.1 (CH), 126.9 (2CH), 127.3 (CH), 127.7 (C), 128.1 (2CH), 129.4 (CH), 134.7 (C), 136.1 (CH), 146.3 (C), 154.5 (C), 167.5 (C), 170.9 (C=O). Found, %: N10.01; S 7.54. $C_{22}H_{23}N_3O_3S$. Calculated, %: N 10.26; S 7.83.

3-[4-Benzyl-5-(3-bromophenoxymethyl)-3-thioxo-2*H*-1,2,4-triazol-2-yl]propanenitrile (24). Prepared by alkylation of triazole **6** with acrylonitrile, yield 67%, oily, R_f 0.63. IR spectrum, ν, cm^{-1}; 2253 (CN), 1158 (C=S). ^1H NMR spectrum, δ, ppm, *Hz*: 3.06 t (2H, CH_2CN, J = 6.6); 4.48 t (2H, NCH_2, J = 6.6); 5.02 s (2H, OCH_2); 5.37 s (2H, NCH_2); 6.75-6.80 m ($1H_{arom.}$); 6.85-6.92 m (1 $H_{arom.}$); 7.05-7.17 m ($2H_{arom.}$); 7.21-7.31 m ($5H_{arom.}$). ^{13}C NMR spectrum, δ, ppm: 15.8 (CH_2), 44.3 (NCH_2), 47.4 (NCH_2), 59.8 (OCH_2), 113.1 (CH), 116.4 (C), 117.7 (CH), 121.9 (C), 124.2 (CH), 127.3 (2CH), 128.0 (2CH), 130.2 (CH), 134.6 (C), 146.5 (C), 157.5 (C), 168.1 (C). Found, %: N 12.31; S 7.22. $C_{19}H_{17}BrN_4OS$. Calculated, %: N 13.05; S 7.47.

3-[5-(3-Bromophenoxymethyl)-3-thioxo-4-cyclohexyl-2*H*-1,2,4-triazol-2-yl]propanenitrile (25). Prepared by alkylation of triazole **7** with acrylonitrile, yield 79%, oily, R_f 0.69. ^1H NMR spectrum, δ, ppm, *Hz*: 1.18-1.49 m (3H, CH_2, C<u>H</u>H); 1.64-1.74 m (1H, CH_2, CH<u>H</u>); 1.83-1.95 m (4H, $2CH_2$); 2.18-2.36 m (2H, CH_2); 2.90 t (2H, CH_2CN, J = 6.6); 4.41 t (2H, NCH_2, J = 6.6); 5.20 s (2H, OCH_2); 6.99-7.04 m ($1H_{arom.}$); 7.11-7.25 m ($3H_{arom.}$). ^{13}C NMR spectrum, δ, ppm: 15.06 (CH_2), 24.5 (CH_2), 25.3 ($3CH_2$), 28.8 (CH_2), 44.0 (CH_2), 57.9 (NCH), 60.05 (OCH_2), 113.4 (CH), 116.4 (C), 117.6 (CH), 122.2 (C), 124.3 (CH), 130.5 (CH), 146.0 (C), 157.6 (C), 166.7 (C). Found %: N 13.36; S 7.39. $C_{18}H_{21}BrN_4OS$. Calculated, %: N13.30; S 7.61.

The article is dedicated to the blessed memory of Tagui Ruben Hovsepyan, a remarkable organic chemist, a scientist of high personal qualities, devoted to science and generously sharing her knowledge and experience with her colleagues.

5-ԱՐԻԼՕՔՍԻՄԵԹԻԼ-1,2,4-ՏՐԻԱԶՈԼՆԵՐԻ ՆՈՐ S- ԵՎ N-ՏԵՂԱԿԱԼՎԱԾ ԱԾԱՆՑՅԱԼՆԵՐԸ ԵՎ ՆՐԱՆՑ ԿԵՆՍԱԲԱՆԱԿԱՆ ԱԿՏԻՎՈՒԹՅԱՆ ՈՒՍՈՒՄՆԱՍԻՐՈՒԹՅՈՒՆԸ

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1,2,4-տրիազոլի ածանցյալների մեջ նոր կենսաբանորեն ակտիվ միացությունների հայտնաբերման նպատակով իրականացվել են հետերոցիկլի 3-SH- և 2-NH- տաուտոմեր նուկլեոֆիլ կենտրոնների ալկիլման ռեակցիաներ։

4-(բենզիլ, ցիկլոհեքսիլ)-5-արիլօքսիմեթիլ 4(H)-1,2,4-տրիազոլ-3-թիոլ ելանյութերը սինթեզվել են համապատասխան 1,4-դիտեղակալված թիոսեմիկարբազիդների ներմոլեկուլյար ցիկլիզացիայից հիմնային միջավայրում։ 4, 5 տեղակալված 1,2,4- տրիազոլ-3-թիոլների ալկիլացումից քլորքացախաթթվով, քլորացեդամիդով, քլորէթիլացետատով KOH-ի ներկայությամբ էթանոլի միջավայրում ստացվել են 2-((4-բենզիլ-, ցիկլոհեքսիլ-5-)(արիլօքսիմեթիլ)-4(H)-տրիազոլ-3-իլ թիո) քացախաթթու, վերջինիս ամիդը և էթիլ էսթերը։

Իրականացվել են ելային 1,2,4-տրիազոլ-3-թիոլների ցիանէթիլման և կարբօքսիէթիլման ռեակցիաներ տրիէթիլամինի առկայությամբ՝ ակրիլոնիտրիլի և ակրիլաթթվի հետ տաքացման պայմաններում։ Պարզվել է, որ այդ ռեագենտների հետ ռեակցիան ընթանում է տրիազոլի N2 նուկլեոֆիլ դիրքում, որի արդյունքում ստացվել են 4-(բենզիլ, ցիկլոհեքսիլ)-5-արիլօքսիմեթիլ-2,4-դիհիդրո 3(H)-1,2,4-տրիազոլ-3-թիոնի N^2 – ցիանոէթիլ և N^2 – կարբօքսիէթիլ ածանցյալներ։

Յույց է տրվել, որ սինթեզված 1,2,4-տրիազոլների որոշ ածանցյալներ ունեն չափավոր բակտերիալ ակտիվություն, որոշ միացություններ՝ թույլ հակամոնոամինօքսիդազային ակտիվությամբ և գործնականում զուրկ են հակառադիկալային ակտիվությունից։

НОВЫЕ S- и N-ЗАМЕЩЕННЫЕ ПРОИЗВОДНЫЕ 5-АРИЛОКСИМЕТИЛ-1, 2, 4- ТРИАЗОЛОВ И ИХ БИОЛОГИЧЕСКАЯ АКТИВНОСТЬ

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С целью изыскания новых биологически активных соединений среди производных 1,2,4-триазола осуществлены реакции алкилирования SH- и NH- таутомерных нуклеофильных центров гетероцикла группами, содержащими полярный заместитель. Комбинирование в молекуле гидрофобных групп в положении 4 и полярных групп в положениях 3 и 5 триазольного кольца позволит проследить влияние усиления полярности (гидрофильности) соединений на биологическую активность. Показано, что некоторые производные синтезированных 1,2,4-триазолов обладают умеренной бактериальной активностью, отдельные соединения – слабой антимоноаминооксидазной активностью и практически лишены антирадикальных свойств.

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