PROCEEDINGS OF THE YEREVAN STATE UNIVERSITY

Chemistry and Biology 2020, **54**(1), p. 3–11

Chemistry

SYNTHESIS AND STUDY OF THE NEMATOCIDAL ACTIVITY OF 1,2,4-TRIAZOLO-1,2,4-TRIAZOLES

M. A. SAMVELYAN [1*], T. V. GHOCHIKYAN [1**], T. H. YEGANYAN [1***], M. SARFRAZ [2****], C. JAKOB [2*****],

[1] *Chair of Organic Chemistry, YSU, Armenia*
[2] *Chair of Pharmacy, Saarland University, Germany*

The method has been developed for the preparation of ethyl esters of triazolo-substituted thioglycolic acid, basis on which the corresponding hydrazides, thiosemicarbazides and 1,2,4-triazolo-1,2,4-triazoles were synthesized by successive transformations. By the data of ^{1}H and ^{13}C NMR spectroscopy and elemental analysis have been established the structures of obtained compounds. Biological studies have shown that triazolo-triazoles at concentrations of 50 and 100 *mkm/mL* reduce the viability of nematodes Steinernema Feltiae by 10–40%.

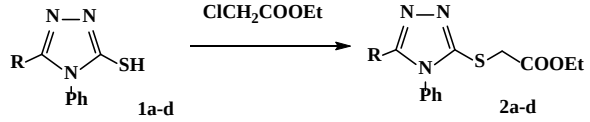
Keywords: 1,2,4-triazoles, hydrazides, 1,2,4-triazolo-1,2,4-triazoles, nematodes, nematocidal activity.

Introduction. It is known that one of the most common compounds in nature are heterocyclic compounds, which have an extensive spectrum of biological activity. It is not accidental that about 90% of drugs obtained by synthetic natural analogues are active aglycones. However, there are a number of heterocyclic compounds that are not found in animal and plant raw materials, have a purely synthetic origin, while possessing many useful properties, such as the derivatives of 1,2,4-triazoles and their structural isomers 1,2,3-triazoles. 1,2,3-Triazoles are relatively "young", but 1,2,4-triazoles have an old history, and many representtatives of this series are widely used in practical medicine as active ingredients of drugs such as Ribavirin, Rizatriptan, Anastrozole, Epoxiconazole, Tebuconazole, Myclobutanil, Propiconazole, etc. In recent years intensive research has continued in the area of developing new methods for synthesizing 1,2,4-triazoles and identifying new, biologically active representatives of this series. It has been established that some derivatives of this heterocyclic series exhibit antiviral [1], antimicrobial [2–4], antibacterial [5, 6], antitumor [7–9], anticonvulsant [10–12], antifungal [13, 14] activities. They are also antagonist receptors [15], tabulin and gestone deacetylases (HDACI) inhibitors [16] and are used in the treatment of Alzheimer's disease [17].

[*] E-mail: msamvelyan@ysu.am
[**] E-mail: ghochikyan@ysu.am
[***] E-mail: tigran.eganyan@ysumail.am
[****] E-mail: s8musarf@stud.uni-saarland.de
[*****] E-mail: c.jacob(at)mx.uni-saarland.de

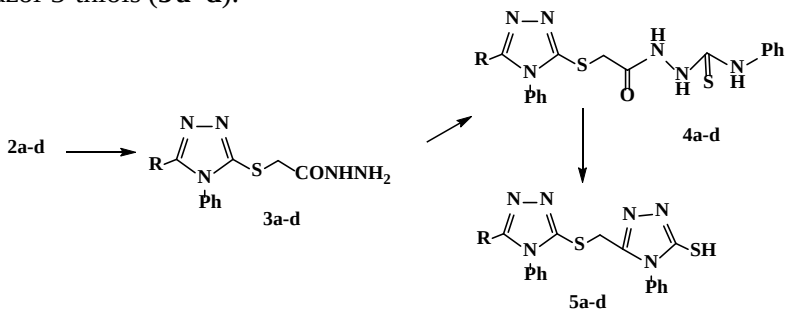
It is known, that derivatives of 1,2,4-triazoles exhibit nematocidal activity against the nematodes Bursaphelenchus xylophilus [18], and Meloidogyne incognita and Rotylenchulus reniformis [19]. As can be seen from the above literature data, the research in the field of triazoles are relevant.

Bearing in mind our previous studies in this field and the aim of expanding the range of 1,2,4-triazoles derivatives, as well as finding new, biologically active representatives of this series, we propose the following scheme for the synthesis of 1,2,4-triazol ethyl esters [18]:



1a,2a R=$HOCH_2CH_2CH_2$; **1b,2b** R= 3-pyridyl; **1c, 2c** R = 2-furyl; **1d,2d** R= 4-Br-C_6H_4

Further, on the basis of **2 a**–**d** the corresponding hydrazides and thiosemicarbazides were synthesized, which are under the alkaline medium turned up to intramolecular cyclization. As a result, new bioheterocyclic compounds are obtained 5-{(5-substituted-4-phenyl-4H-1,2,4-triazol-3-yl)methyl}-4-phenyl-4H-1,2,4-triazol-3-thiols (**5 a**–**d**).



3a,4a,5a R=$HOCH_2CH_2CH_2$; **3b,4b,5b** R= 3-pyridyl; **3c,4c,5c** R = 2-furyl; **3d,4d,5d** R= 4-Br-C_6H_4

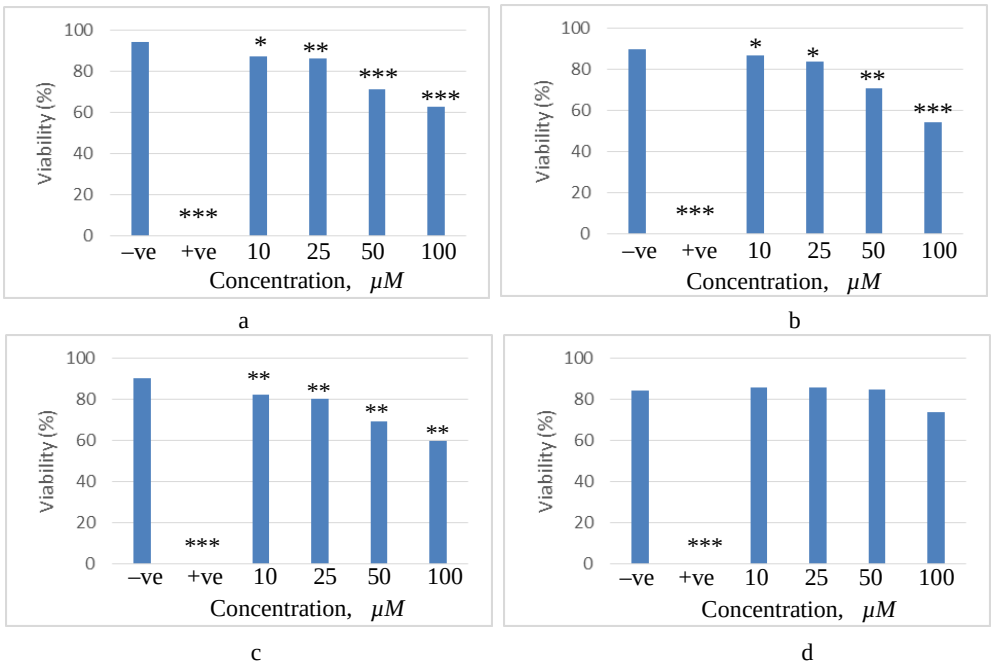
Biological Part. The synthesized compounds **5 a**–**d** were subjected to biological studies and were chosen as an object a positive nematodes *Steinernema feltiae*, which are important both plant growth regulators and in animal husbandry [20, 21].

As a result of processing the experimental data, the following graphs were obtained, which clearly illustrate the nematocidal activity of **5 a**–**c**. The experiments were performed using solutions of substances at concentrations of 10, 25, 50 and 100 μM.

It can be seen from Figure (a, b), that compounds **5 a** and **5 b** at a concentration of 100 μM show significant nematocidal activity, reducing the viability of nematodes by 40%, and at a concentration of 50 μM by 22% and 20%, respectively. At the indicated concentrations (100 and 50 μM), nematocidal activity of compound **5 c** is expressed in 30% and 20% (see Figure c), while compound **5 d** shows weak activity (10%) (see Figure d) only at a concentration of 100 μM. Compounds **5 a**–**c** at concentrations of 10 and 25 μM do not exhibit significant activity.

If we examine the structural formulas of compounds **5 a**–**d**, then it is obvious that these compounds differ only in the substituents at position **5** of the basic

triazole cycle (**1 a**–**d**), therefore, there is a direct connection between the nature of the indicated substituent and the biological activity of the examined series of chemical compounds. Based on the data obtained, it can be concluded that the degree of nematocidal activity of the proposed triazolo-triazoles can be controlled by controlling the nature of the substituent at position 5 of the triazole cycle.



Impact of compounds **5 a** (a), **5 b** (b), **5 c** (c) and **5 d** (d) on survival of *S. feltiae* after 24 *h*. Data expressed as mean ±SD; $n = 9$; * – significant difference against negative control ($p < 0.05$); ** – very significant difference against negative control ($p < 0.05$); *** – significant difference against negative control ($p < 0.001$). –ve – negative control (DMSO); +ve – positive control (EtOH).

Experimental Part.

Biology.

Analysis of Nematocidal Activity. The viability of fresh nematode suspensions was observed with a microscope pump (TR 200, VWRInter) at a fourfold magnification. For the experiment nematodes with a life of more than 90% were used. To analyze the nematocidal activity of 200 *mg*, nematode powder was suspended in 50 *mL* of phosphate-buffered saline (PBS, pH 7) or distilled water under moderate lighting stirred for 10 *min* at room temperature. 10 μL of suspension was added to a 96-well plate followed by the addition of the test sample at various concentrations. The final volume was made up to 100 μL with buffer. The number of live (N_0) and the total number of nematodes (N) were immediately determined. Then the plate was incubated in the dark for 24 *h* at room temperature, 50 μL of warm water (50°*C*) was added and the number of live nematodes was counted (N_{24}). Viability is determined by the following formulas

$$V_0 = \frac{N_0 \cdot 100}{N}, \qquad V_{24} = \frac{N_{24} \cdot 100}{N}.$$

The graphs are constructed on the basis of experimental data of the dependence of the viability of nematodes on the concentration of the investigated substances.

Preparation of PBS buffer

Reagent	Quantity added for 10×solution, *g*	Final concentration (×10), *mM*
NaCl	80	1370
KCl	2	27
Na_2PO_4	14.4	100
KH_2PO_4	2.4	18

If necessary, PBS can be supplemented by the following

$CaCl_2 \cdot 2H_2O$	1.33	10
$MgCl_2 \cdot 6H_2O$	1.0	5

Chemical Part. ^1H and ^{13}C NMR spectra were recorded on Varian Mercury-300 *MHz* in DMSO–CCl_4 mixture (1:3) or on Bruker AVANCE 400 *MHz* spectrometer in $CDCl_3$, DMSO-d_6. Chemical shifts were reported as quoted relative to the residual signals of chloroform-*d* (7.25 for ^1H NMR and 77.0 for ^{13}C NMR) or DMSO-d_6 (2.5 for ^1H NMR and 39.5 for ^{13}C NMR) as internal references. TLC analysis was performed on Silufol UV-254 plates. Starting compounds 1,2,4-triazoles **1a–d** were synthesized by a known method [17]. Melting points were determined on "Boetius" micro-heating stage.

General Method for Preparation of 2-{(5-substituted-4-phenyl-4H-1,2,4--triazol-3-yl)thio}ethylacetates (2a–d). A mixture of 8 *mmol* of the corresponding **1a–d** in 8 *mL* of acetone and 10 *mmol* of potash was stirred at room temperature for 15 *min*, then 8.8 *mmol* of ethyl chloroacetic acid was added. The mixture was heated for 7 *h* at 50–60°*C*. After removing the solvent, the mixture was cooled, water was added. The precipitated crystals were filtered, washed with 5% hydrochloric acid solution, then with water and dried.

*Ethyl 2-{[5-(3-hydroxypropyl)-4-phenyl-4H-1,2,4-triazol-3-yl]thio}acetate (**2a**).* Yield 65%, m.p. 71–72°*C* (ethanol:water=1:3), R_f 0.56 (ethanol:benzene:hexane= =1:1:3). ^1H NMR, δ, *ppm*: 1.26 t (3H, *J*=7.14 *Hz*, CH_3); 1.70–1.84 m (2H, CH_2); 2.58 t (2H, *J*=7.54 *Hz*, CH_2); 3.36–3.49 m (2H, CH_2); 3.93 s (2H, CH_2); 4.14 q (2H, *J*=7.14 *Hz*, CH_2); 4.18 br.s (1H, OH); 7.28–7.49 m (2H, arom.); 7.49–7.73 m (3H, arom.). ^{13}C NMR(126 *MHz*, $CDCl_3$), δ, *ppm*: 13.7; 21.2; 29.2; 33.7; 59.5; 60.7; 126.8; 129.3; 129.4; 132.8; 148.3; 155.2; 167.2.

Found, %: C 56.17; H 5.85; N 13.20; S 9.88. $C_{15}H_{19}N_3O_3S$. Calculated, %: C 56.06; H 5.96; N 13.07; S 9.98.

*Ethyl 2-{[4-phenyl-5-(pyridin-3-yl)-4H-1,2,4-triazol-3-yl]thio}acetate(**2b**).* Yield 88%, m.p. 138°*C* (ethanol:water=2:1), R_f 0.48 (ethanol:benzene=1:5). ^1H NMR, δ, *ppm*: 1.30 t (3H, *J*=7.1 *Hz*, CH_3); 4.06 s (2H, SCH_2): 4.18 k (2H, *J*=7.1 *Hz*, OCH_2); 7.27 dd (1H, J_1= 7.9 *Hz*, J_2= 4.8 *Hz*, C_5H_4N); 7.37–7.44 m (2H, $H_{arom.}$); 7.53–7.60 m (4H, $H_{arom.}$); 7.68 dt (1H, J_1=7.9 *Hz*, J_2=1.9 *Hz*, C_5H_4N); 8.49–8.54 m (2H, $H_{arom.}$). ^{13}C NMR(126 *MHz*, $CDCl_3$) δ, *ppm*: 13.66; 33.69; 60.81; 110.58; 110.78; 123.30; 127.05; 129.33; 129.75; 133.07; 140.98; 143.54; 146.85; 150.06; 166.93.

Found, %: C 60.10; H 4.85; N 16.55; S 9.49. $C_{17}H_{16}N_4O_2S$. Calculated, %: C 59.98; H 4.74; N 16.46; S 9.42.

Ethyl 2-{[5-(furan-2-yl)-4-phenyl-4H-1,2,4-triazol-3-yl]thio}acetate ***(2c)****.* Yield 85%, m.p. 124–125°*C* (ethanol : water = 3:2), R_f 0.56 (ethanol : benzene = 1:7). ^{1}H NMR, *δ*, *ppm*: 1.28 t (3H, *J*=6.75 *Hz*, CH_3); 4.02 s (2H, CH_2); 4.17 q (2H, *J*=7.14 *Hz*, CH_2)**;** 6.22 d (1H, *J*=3.97 *Hz*, CH_{furyl}); 6.37–6.41 m (1H, CH_{furyl}); 7.38–7.44 m (2H, $H_{arom.}$); 7.50–7.53 m (1H, CH_{furyl}); 7.57–7.63 m (3H, $H_{arom.}$). ^{13}C NMR (126 *MHz*, $CDCl_3$), *δ*, *ppm*: 13.66; 33.69; 60.81; 110.58; 110.78; 123.30; 127.05; 129.33; 129.75; 133.07; 140.98; 143.54; 146.85; 150.06; 166.93.

Found, %: C 58.42; H 4.70; N 12.85; S 9.70. $C_{16}H_{15}N_3O_3S$. Calculated, %: C 58.34; H 4.59; N 12.76; S 9.74.

Ethyl 2-{[5-(4-bromophenyl)-4-phenyl-4H-1,2,4-triazol-3-yl]thio}acetate ***(2d)****.* Yield 85%, m.p. 158°*C* (ethanol:water=2:1), R_f 0.58(ethanol:benzene =2:5). ^{1}H NMR, *δ*, *ppm*: 1.29 t (3H, *J*=7.1 *Hz*, CH_2CH_3); 4.03 s (2H, SCH_2); 4.17 k (2H, *J*=7.1 *Hz*, CH_2CH_3); 7.25–7.30 m (2H, $H_{arom.}$); 7.32–7.39 m (2H, $H_{arom.}$); 7.41–7.46 m (2H, H_{arom}); 7.53–7.58 m (3H, $H_{arom.}$). ^{13}C NMR (126 *MHz*, $CDCl_3$), *δ*, *ppm*: 13.7; 33.6; 39.5; 39.8; 60.8; 123.2; 125.4; 126.9; 129.1; 129.5; 131.0; 133.4; 150.8; 152.9; 166.9.

Found, %: C 51.75; H 3.77; Br 19.15; N 10.15; S 7.75. $C_{18}H_{16}BrN_3O_2S$. Calculated, %: C 51.68; H 3.86; Br 19.10; N 10.05; S 7.67.

General Method for Preparation of Hydrazides 2-{[5-substituted-4-phenyl--4H-1,2,4-triazol-3-yl]thio}acetates (3 a–d). To a mixture of 9.5 *mmol* of the corresponding ester **2 a**–**d** in 20 *mL* of ethanol was added 5.2 *mL* of an 85% solution of hydrazine hydrate, left for 2 *h* at room temperature and heated for 4 *h* at 75–80°*C*. After cooling, the mixture was diluted with water, the precipitate was filtered, washed with water, dried and recrystallized.

2-{[5-(3-Hydroxypropyl)-4-phenyl-4H-1,2,4-triazol-3-yl]thio}acetohydrazide (3a). Yield 70%, m.p. 149–150°*C* (ethanol:water = 2:3), R_f 0.50 (ethanol:benzene= =1:7). ^{1}H NMR, *δ*, *ppm*: 2.58 t (2H, *J*=7.54 *Hz*, CH_2); 3.36–3.49 m (2H, CH_2); 3.93 s (2H, CH_2); 4.14 q (2H, *J*=7.14 *Hz*, CH_2); 4.18 br.s (1H, OH); 6.10 d (1H, *J*=3.17 *Hz*, NH_2); 6.29 d (1H, *J*=5.55 *Hz*, NH_2); 7.28–7.49 m (2H, arom.); 7.49–7.73 m (3H, arom.); 9.28 br.s (1 H, NH).

Found, %: C 50.75; H 5.65; N 22.85; S10.53. $C_{13}H_{17}N_5O_2S$. Calculated, %: C 50.80; H 5.57; N 22.78; S 10.43.

2-{[4-Phenyl-5-(pyridin-3-yl)-4H-1,2,4-triazol-3-yl]thio}acetohydrazide(3b). Yield 90%, m.p. 225°*C* (ethanol : water = 5:1), R_f 0.50 (ethanol : benzene : hexane = =3:3:1). ^{1}H NMR, *δ*, *ppm*: 3.87 s (2H, SCH_2); 4.12 br (2H, NH_2); 7.27 dd (1H, J_1=7.8 *Hz*, J_2=4.8 *Hz*, C_5H_4N); 7.38–7.43 m (2H, $H_{arom.}$); 7.53–7.60 m (3H, $H_{arom.}$); 7.66 ddd (1H, J_1=7.8 *Hz*, J_2=2.1 *Hz*, J_3=1.8 *Hz*, C_5H_4N); 8.51 dt (1H, J_1=4.8 *Hz*, J_2=1.8 *Hz*, C_5H_4N); 8.53 d (1H, *J*=2.1 *Hz*, C_5H_4N); 9.29 br.s (1H, NH). ^{13}C NMR (126 *MHz*, $CDCl_3$), *δ*, *ppm*: 13.7; 33.7; 60.8; 122.5; 122.6; 127.0; 129.6; 129.7; 133.2; 134.4; 147.9; 179.7; 151.1; 151.8; 166.9.

Found, %: C 55.30; H 4.28; N 25.85; S 9.85. $C_{15}H_{14}N_6OS$. Calculated, %: C 55.20; H 4.32; N 25.75; S 9.82.

*2-{[5-(Furan-2-yl)-4-phenyl-4H-1,2,4-triazol-3-yl]thio}acetohydrazide(****3c****).* Yield 90%, m.p. 111–113°*C* (ethanol : water= 1:1), R_f0.50 (ethanol : benzene = 1:7). ^{1}H NMR, *δ*, *ppm*: 3.84 s (2H, CH_2); 4.08 br.s (2H, $2CH_{furyl}$); 6.13 d (1H, *J*=3.17 *Hz*, NH_2); 6.39 d (1H, *J*=5.55 *Hz*, NH_2); 7.39–7.45 m (2H, arom.); 7.52 s (1H, CH_{furyl});

7.55–7.62 m (3H, arom.) 9.28 br.s (1H, NH). ^{13}C NMR (126 *MHz*, $CDCl_3$), *δ*, *ppm*: 33.9; 110.5; 110.8; 127.2; 129.3; 129.7; 134.2; 141.0; 143.5; 150.9; 165.7.

Found, %: C 53.38; H 4.05; N 22.30; S 10.25. $C_{14}H_{13}N_5O_2S$. Calculated, %: C 53.32; H 4.16; N 22.21; S 10.17.

2-{[5-(4-Bromophenyl)-4-phenyl-4H-1,2,4-triazol-3-yl]thio}acetohydrazide ***(3d)***. Yield 91%, m.p. 230–232°*C* (ethanol), R_f 0.50 (ethanol : benzene=2 : 5). ^{1}H NMR, *δ*, *ppm*: 4.03 s (2H, SCH_2); 6.13 d (1H, *J*=3.17 *Hz*, NH_2); 7.25–7.30 m (2H, $H_{arom.}$); 7.32–7.39 m (2H, H_{arom}); 7.41–7.46 m (2H, $H_{arom.}$); 7.53–7.58 m (3H, $H_{arom.}$); 9.29 br.s (1H, NH). ^{13}C NMR (126 *MHz*, CDCl3), *δ*, *ppm*: 39.5; 39.8; 60.8; 123.2; 125.4; 126.9; 129.1; 129.5; 131.0; 133.4; 150.8; 152.9; 166.9.

Found, %: C 47.60; H 3.40; Br 19.70; N 17.40; S 8.05. $C_{16}H_{14}BrN_5OS$. Calculated, %: C 47.53; H 3.49; Br 19.76; N 17.32; S 7.93.

General Method for Preparation of 2-((5-substituted-4-phenyl-4H-1,2,4-triazol--3-yl)thio)acetyl)-N-phenylhydrazinecarbothioamide (4 a–d). 7.9 *mmol* of phenyl isothiocyanate was added to a solution of 7.9 *mmol* of hydrazide **3 a**–**d** in 10 *mL* of ethanol, stirred vigorously and left at room temperature for 2 *h*. It was heated for 1 *h* at 80–85°*C*, after cooling it was filtered, washed with ethanol, dried and recrystallized.

2-{2-[(5-(3-Hydroxypropyl)-4-phenyl-4H-1,2,4-triazol-3-yl)thio]acetyl}-N--phenylhydrazinecarbothioamide ***(4a)***. Yield 70%, m.p. 124°*C* (ethanol : water =1:1), R_f 0.51 (ethanol : benzene = 1 : 4). ^{1}H NMR, *δ*, *ppm*: 1.76 q (2H, *J*=6.8 *H*, CH_2); 2.58 s (2H, *J*=7.5 *Hz*, CH_2); 3.41 t (2H, *J*=5.9 *Hz*, CH_2); 3.60–3.90 br.s (1H, OH); 3.95 s (2H, SCH_2); 7.05–7.16 m (1H, arom.); 7.29 t (2H, *J*=7.9 *Hz*, $H_{arom.}$); 7.41–7.49 m (2H, $H_{arom.}$); 7.60–7.62 m (3H, $H_{arom.}$); 7.64–7.67 m (2H, $H_{arom.}$), 9.51 br.s (2H, NH–NH); 10.26 s (1H, NH). ^{13}C NMR (126 *MHz*, $CDCl_3$), *δ*, *ppm*: 33.2; 33.7; 59.5; 60.7; 126.8; 129.3; 129.4; 131.9; 132.8; 148.3; 148.7; 150.0; 153.8; 155.2; 155.6; 159.2; 160.1; 161.2; 165.5; 165.7; 167.2.

Found, %: C 54.35; H 5.05; N 20.05; S 14.55. $C_{20}H_{22}N_6O_2S_2$. Calculated, %: C 54.28; H 5.01; N 18.99; S 14.49.

N-Phenyl-2-{2-[(4-phenyl-5-(pyridin-3-yl)-4H-1,2,4-triazol-3-yl)thio]acetyl}--hydrazinecarbothioamide ***(4b)***. Yield 70%, m.p. 180°*C* (ethanol : water = 3:1), R_f 0.65 (ethanol : benzene : hexane = 4 : 1 : 1). ^{1}H NMR, *δ*, *ppm*: 3.95 s (2H, SCH_2); 7.08–7.14 m (1H, $H_{arom.}$); 7.24–7.32 m (3H, $H_{arom.}$); 7.41–7.46 m (2H, $H_{arom.}$); 7.54–7.68 m (6H, H_{arom}); 8.50–8.53 m (2H, $H_{arom.}$); 9.57 br.s (1H, NH); 9.59 br.s (1H, NH); 10.33 br.s (1H, NH). ^{13}C NMR (126 *MHz*, $CDCl_3$), *δ*, *ppm*: 60.8; 122.5; 122.6; 127.0; 129.6; 129.7; 133.2; 134.4; 147.9; 179.7; 151.1; 151.8; 166.9.

Found, %: C 57.35; H 4.05; N 21.30; S 13.55. $C_{22}H_{19}N_7OS_2$. Calculated, %: C 57.25; H 4.15; N 21.24; S 13.89.

2-{2-[(5-(Furan-2-yl)-4-phenyl-4H-1,2,4-triazol-3-yl)thio]acetyl}-N-phenyl--hydrazine-carbothioamide ***(4c)***. Yield 85%, m.p. 186°*C* (ethanol : water = 2 : 1), R_f 0.60 (ethanol : benzene = 1:5). ^{1}H NMR, *δ*, *ppm*: 3.90 s (2H, CH_2); 6.13 d (1H, *J*= 4.0 *Hz*, CH_{furyl}); 6.39 d (1H, *J* =4.0 *Hz*, CH_{furyl}); 7.39–7.45 m (2H, $H_{arom.}$); 7.52 s (1H, CH_{furyl}); 7.57–7.62 m (3H, $H_{arom.}$); 7.66–7.68 m (5H, $H_{arom.}$); 9.28 br.s (2H, NH–NH); 10.34 br.s (1H, NH). ^{13}C NMR (126 *MHz*, $CDCl_3$), *δ*, *ppm*: 33.9; 110.5; 110.8; 123.4; 127.2; 129.3; 129.7; 131.1; 134.2; 141.0; 143.5; 150.9; 166.7; 179.2; 180.0.

Found, %: C 55.90; H 4.10; N 18.75; S 14.35. $C_{21}H_{18}N_6O_2S_2$. Calculated, %: C 55.98; H 4.03; N 18.65; S 14.23.

*2-{2-[(5-(4-bromophenyl)-4-phenyl-4H-1,2,4-triazol-3-yl)thio]acetyl}-N--phenylhydrazine-1-carbothioamide (**4d**).* Yield 99%, m.p. 222°*C* (ethanol:water= 3:1), R_f 0.54 (ethanol : benzene =1.5 : 5). ^{1}H NMR, *δ*, *ppm*: 3.93 s (2H, SCH_2); 7.20–7.32 m (4H, $H_{arom.}$); 7.37–7.46 m (5H, $H_{arom.}$); 7.53–7.68 m (5H, $H_{arom.}$); 9.57 br.s (2H, NH–NH); 10.34 br.s (1H, NH). ^{13}C NMR (126 *MHz*, $CDCl_3$), *δ*, *ppm*: 33.9; 123.3; 124.2; 124.7; 125.4; 127.1; 127.3; 129.2; 129.6; 129.7; 131.1; 133.4; 138.8; 151.7; 152.9; 180.4.

Found, %: C 51.25; H 3.45; Br 14.70; N 15.50; S 11.95. $C_{23}H_{19}BrN_6OS_2$. Calculated, %: C 51.21; H 3.55; Br 14.81; N 15.58; S 11.89.

General Method for Preparation 4-phenyl-5-{[((5-substituted-4-phenyl)--4H-1,2,4-triazol-3-yl)thio]methyl}-4H-1,2,4-triazol-3-thioles (5 a–d). To an aqueous solution of 22.5 *mmol* NaOH (10 *mL* 10%) was added 7.5 *mmol* of corresponding thiosemicarbazide, stirred at room temperature for 1 *h* and refluxed for 7 *h*. After cooling, the mixture was diluted with water and acidified with hydrochloric acid (pH 2–3). The resulting crystals were washed with water and recrystallized.

*3-{5-[((5-Mercapto-4-phenyl-4H-1,2,4-triazol-3-yl)methyl)thio]-4-phenyl-4H--1,2,4-triazol-3-yl}propan-1-ol(**5a**).* Yield 65%, m.p. 108°*C* (ethanol:wather=1:1), R_f 0.70 (ethanol:hexane=2:1). ^{1}H NMR, *δ*, *ppm*: 1.76 q (2H, *J*=6.75 *Hz*, CH_2); 2.58 t (2H, *J*=7.54 *Hz*, CH_2); 3.41 t (2H, *J*=5.95 *Hz*, CH_2); 3.60–3.90 br.s (1H, OH); 4.04 s (2H, CH_2); 7.18–7.30 m (4H, $H_{arom.}$); 7.49–7.62 m (6H, $H_{arom.}$); 13.69 s (1H, SH).

Found, %: C 56.65; H 4.65; N 19.75; S 15.20. $C_{20}H_{20}N_6OS_2$. Calculated, %: C 56.58; H 4.75; N 19.80; S 15.11.

*4-Phenyl-5-{[(4-phenyl-5-(pyridin-3-yl)-4H-1,2,4-triazol-3-yl)thio]methyl}--4H-1,2,4-triazole-3-thiol (**5b**).* Yield 90%, m.p. 155–157°*C* (ethanol:wather=3:2), R_f 0.55 (ethanol:hexane=2:1). ^{1}H NMR, *δ*, *ppm*: 3.95 s (2H, SCH_2); 7.08–7.14 m (1H, H_{arom}); 7.24–7.32 m (3H, $H_{arom.}$); 7.41–7.46 m (2H, $H_{arom.}$); 7.54–7.68 m (6H, $H_{arom.}$); 7.66 ddd (1H, J_1=7.8 *Hz*, J_2=2.1 *Hz*, J_3=1.8 *Hz*, C_5H_4N); 8.50–8.53 m (2H, $H_{arom.}$); 8.51 dt (1H, J_1=4.8 *Hz*, J_2=1.8 *Hz*, C_5H_4N); 13.85 s (1H, SH).

Found, %: C 59.65; H 3.78; N 22.20; S 14.40. $C_{22}H_{17}N_7S_2$. Calculated, %: C 59.57; H 3.86; N 22.11; S 14.46.

*5-{[(5-(Furan-2-yl)-4-phenyl-4H-1,2,4-triazol-3-yl)thio]methyl}-4-phenyl-4H--1,2,4-triazole-3-thiol (**5c**).* Yield 90%, m.p. 159–160°*C* (ethanol:wather=3:2), R_f 0.59 (ethanol:hexane=2:1). ^{1}H NMR, *δ*, *ppm*: 4.13 s (2H, CH_2); 6.15–6.22 m (1H, CH_{furyl}); 6.35–6.43 m (1H, CH_{furyl}); 7.26 s (1H, CH_{furyl}); 7.42–7.65 m (10H, $H_{arom.}$); 13.72 s (1H, SH).

Found, %: C 58.35, H 3.80, N 19.50, S 14.90. $C_{21}H_{16}N_6OS_2$. Calculated, %: C 58.31, H 3.73, N 19.43, S 14.83.

*5-{[(5-(4-Bromophenyl)-4-phenyl-4H-1,2,4-triazol-3-yl)thio]methyl}-4-phenyl--4H-1,2,4-triazole-3-thiol (**5d**).* Yield 80%, m.p. 270°*C* (ethanol), R_f 0.41 (ethanol: benzene = 1:1). ^{1}H NMR, *δ*, *ppm*: 4.03 s (2H, SCH_2); 7.25–7.30 m (2H, $H_{arom.}$); 7.32–7.39 m (4H, $H_{arom.}$); 7.41–7.46 m (3H, $H_{arom.}$); 7.53–7.58 m (6H, $H_{arom.}$). ^{13}C NMR (126 *MHz*, $CDCl_3$), *δ*, *ppm*: 60.8; 123.2; 125.4; 126.9; 129.1; 129.5; 131.0; 133.4; 150.8; 152.9; 166.9.

Found, %: C 52.90; H 3.35; Br 15.40; N 16.40; S 12.40. $C_{23}H_{17}BrN_6S_2$. Calculated, %: C 52.98; H 3.29; Br 15.32; N 16.12; S 12.30.

Received 30.08.2019
Reviewed 02.03.2020
Accepted 10.04.2020

REFERENCES

1. Murlykina M.V., Sakhno Y.I., Desenko S.M., Shishkina S.V., Shishkin O.V., Sysoiev D.O., Kornet M.N., Schols D., Goeman J.L., Van der Eycken J., Van der Eycken E., Chebanov V.A. Study of the Chemoselectivity of Multicomponent Heterocyclizations Involving 3-amino-1,2,4-triazole and Pyruvic Acids as Key Reagents, and Biological Activity of the Reaction Products. *Eur. J. Org. Chem.*, **20** (2015), 4481 p. DOI:10.1002/ejoc.201500469
2. Bayrak H., Demirbas A., Demirbas N., Karaoglu S.-Al. Cyclization of Some Carbothioamide Derivatives Containing Antipyrine and Triazole Moieties and Investigation of Their Antimicrobial Activities. *Eur. J. Med. Chem.*, **45** : 11 (2010), 4726–4732. DOI:10.1016/j.ejmech.2010.07.018
3. Pandey S.K., Ahamd A., Pandey O.P., Nizamuddin Kh. Polyethylene Glycol Mediated, One-pot, Three-component Synthetic Protocol for Novel 3-[3-substituted-5-mercapto-1,2,4-triazol-4-yl]--spiro-(indan-1′,2-thiazolidin)-4-ones as New Class of Potential Antimicrobial and Anti-tubercular Agents. *J. Het. Chem.*, **51**:5 (2014), 1233 p. DOI:10.1002/jhet.1605
4. Gomha S.M, Mohamed A.M., Zaki Y.H., Ewies M.M., Elroby S.A. Structural Elucidation and Antimicrobial Evaluation of Novel [1,2,4]triazolo[4,3-a]pyrimidines and pyrido[2,3-d][1,2,4]triazolo[4,3-a]pyrimidinones. *J. Het. Chem.*, **55** : 5 (2018), 1147 p. DOI:10.1002/jhet.3146
5. Ünver Ya., Sancak K., Çelik F., Birinci Em., Küçük M., Soylu S., Burnaz N. New Thiophene-1,2,4-triazole-5(3)-ones: Highly Bioactive Thiosemicarbazides, Structures of Schiff Bases and Triazole-thiols. *Eur. J. Med. Chem.*, **84** (2014), 639–650. DOI:10.1016/j.ejmech.2014.01.014
6. Arafa W.A.A. Preparation and Evaluation of Antibacterial Activity of Some New 1,2,4-triazole Derivatives. *J. Het. Chem.*, **47** : 5 (2010), 1109–1115. DOI:10.1002/jhet.431
7. Vojtičková M., Dobiaš J., Hanquet G., Addová G., Cetin-Atalay R., Yildirim D.C., Boháč A. Ynamide Click Chemistry in Development of Triazole VEGFR2 TK Modulators. *Eur. J. Med. Chem.*, **103** (2015), 105–122. DOI:10.1016/j.ejmech.2015.08.012
8. Bakavoli M., Rahimizadeh M., Shiri A., Akbarzadeh M., Mousavi S.-H., Tayarani-Najaran Z., Mashhad H.A., Nikpour M. Synthesis of New Derivatives of 3-aryl-1,5-dimethyl-1H-[1,2,4]triazolo[4′,3′:1,2]pyrimido[4,5-e][1,3,4]oxadiazines as Potential Antiproliferative Agents. *J. Het. Chem.*, **48** : 1 (2011), 183–187. DOI:10.1002/jhet.509
9. Li Y.-H., Zhang B., Yang H.-K., Li Q., Diao P.-Ch., You W.-W., Zhao P.-L. Design, Synthesis and Biological Evaluation of Novel Alkylsulfanyl-1,2,4-triazoles as cis-Restricted Combretastatin A-4 Analogues. *Eur. J. Med. Chem.*, **125** (2017), 1098–1106. DOI:10.1016/j.ejmech.2016.10.051
10. Milen M., Földesi T., Dancsó A., Simig G., Volk B. Synthesis of Three New Tricyclic Ring Systems: Pyrrolotriazepines Condensed with an Imidazole, a Triazole or a Tetrazole Ring. *Synlett*, **26** : 17 (2015), 2418–2424. DOI:10.1055/s-0034-1380538.
11. Plech T., Kaprońa B., Łuszczki J., Paneth A., Siwek A., Kołaczkowski M., Żołnierek M., Nowaĸ G. Studies on the Anticonvulsant Activity of 4-alkyl-1,2,4-triazole-3-thiones and Their Effect on GABAergic System. *Eur. J. Med. Chem.*, **86** (2014), 690–699. DOI:10.1016/j.ejmech.2014.09.034
12. Ayati A., Emami S., Foroumadi A. The Importance of Triazole Scaffold in the Development of Anticonvulsant Agents. *Eur. J. Med. Chem.*, **109** (2016), 380–392. DOI:10.1016/j.ejmech.2016.01.009
13. Parmar K., Suthar Bh., Prajapati S., Suthar A. Synthesis and Biological Activity of Novel 1,3,5-trisubstituted 1,2,4-triazole Derivatives. *J. Het. Chem.*, **47** : 1 (2010), 156–161.
14. Hong-Xing S., De-Qing Sh. Synthesis and Fungicidal Activity of (e)-*α*-(methoxyimino)benzene-acetate Derivatives Containing 1,2,4-triazole Schiff Base Side Chain. *J. Het. Chem.*, **51** : 5 (2014), 1345–1348. DOI:10.1002/jhet.1795.
15. Federico S., Ciancetta A., Porta N., Redenti S., Pastorin G., Cacciari B., Klotz K., Moro S., Spalluto G. 5,7-Disubstituted-[1,2,4]triazolo[1,5-a][1,3,5]triazines as Pharmacological Tools to Explore the Antagonist Selectivity Profiles Toward Adenosine Receptors. *Eur. J. Med. Chem.*, **108** (2016), 529–541. DOI:10.1016/j.ejmech.2015.12.019
16. Aboeldahab Al., Beshr Em., Shoman M., Rabea S., Aly O. Spirohydantoins and 1,2,4-triazole-3-carboxamide Derivatives as Inhibitors of Histone Deacetylase: Design, Synthesis and Biological Evaluation. *Eur. J. Med. Chem.*, **146** (2018), 79–92. DOI:10.1016/j.ejmech.2018.01.021
17. Wang W., Wang We., Yao G., Ren Q., Di W., Wang Z., Liu P., Gao P., Zhang Y., Wang Sh., Song Sh. Novel Sarsasapogenin-triazolyl Hybrids as Potential anti-Alzheimer's Agents: Design, Synthesis and Biological Evaluation. *Eur. J. Med. Chem.*, **151** (2018), 351–362. DOI:10.1016/j.ejmech.2018.03.082

18. Samvelyan M.A., Ghochikyan T.V., Grigoryan S.V., Tamazyan R.A., Aivazyan A.G. Alkylation of 1,2,4-Triazole-3-thiols with Haloalkanoic Acid Esters. *Rus. J. Org. Chem*., **53** : 6 (2017), 935–940.
19. Irshaid F., Jacob J., Al-Soud Ya., Mohammed H. Nematocidal Effect of 1,2,4-triazole Derivatives Against Bursaphelenchus Xylophilus. *Asian J. Biochem*., **11** : 3 (2016), 156–161.
20. Mandala A., Duttab T., Gupta R. Microwave-induced Synthesis and Anti-nemic Activity of 4-amino-3--mercapto-5-pyridin-2-yl-4H-1,2,4-triazole Schiff Bases. *Indian J. Chem*., **54B** : 2 (2015), 228–239.
21. Blaxter M., Koutsovoulos G. The Evolution of Parasitism in Nematoda. *Parasitology*, **142** : S1 (2015), S26–S39.

Մ. Ա. ՍԱՄՎԵԼՅԱՆ, Տ. Վ. ՂՈՉԻԿՅԱՆ, Տ. Հ. ԵԳԱՆՅԱՆ, Մ. ՇԱՐՖՐԱԶ, Կ. ՋԵՅԿՈԲ

1,2,4-ՏՐԻԱԶՈԼՈ-1,2,4-ՏՐԻԱԶՈԼՆԵՐԻ ՍԻՆԹԵԶ ԵՎ ՆԵՄԱՏՈԴԱՅԻՆ ԱԿՏԻՎՈՒԹՅԱՆ ՈՒՍՈՒՄՆԱՍԻՐՈՒԹՅՈՒՆ

Ամփոփում

Մշակված է տրիազոտեղակալված թիոգլիկոլաթթվի էթիլէսթերի ստացման մեթոդ, որոնց հենքի վրա իրականացված փոխարկումների արդյունքում սինթեզված են համապատասխան՝ հիդրազիդները, թիոսեմիկարբազիդները և 1,2,4-տրիազոլո-1,2,4-տրիազոլները: ՄՄՌ սպեկտրոսկոպիայի ^{1}H և ^{13}C մեթոդներով և էլեմենտային անալիզի տվյալներով հաստատված են սինթեզված միացությունների կառուցվածքը: Կենսաբանական ակտիվության ուսումնասիրությունները ցույց են տվել, որ տրիազոլոտրիազոլները 50 և 100 *մկմ/մլ* չափաբաժինների դեպքում *Steinernema felatiae* նեմատոդի կենսունակությունը ընկճվում է 10–40%-ով:

М. А. САМВЕЛЯН, Т. В. КОЧИКЯН, Т. А. ЕГАНЯН, М. ШАРФРАЗ, К. ЯКОБ

СИНТЕЗ И ИССЛЕДОВАНИЕ НЕМАТОЦИДНОЙ АКТИВНОСТИ 1,2,4-ТРИАЗОЛО-1,2,4-ТРИАЗОЛОВ

Резюме

Разработан способ получения этиловых эфиров триазолозамещенной тиогликолевой кислоты, на основе которых последовательными превращениями синтезированы соответствующие гидразиды, тиосемикарбазиды и 1,2,4-триазоло-1,2,4-триазолы. Методами ЯМР ^{1}H- и ^{13}C-спектроскопии и элементного анализа установлены структуры полученных соединений. Биологическими исследованиями установлено, что триазоло-триазолы при концентрациях 50 и 100 *мкм/мл* снижают жизнеспособность нематод *Steinernema felatiae* на 10–40%.