SYNTHESIS OF NEW 1,2,4-TRIAZOLE DERIVATIVES AND STUDY OF THEIR ANTINEMATODE ACTIVITY

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A method for obtaining methyl esters of β-1,2,4-triazole-substituted alanines by condensation of methyl acrylate with 3,4-disubstituted 5-mercapto-1,2,4-triazoles has been developed. Based on the products obtained, a number of new biheterocyclic systems, previously not described in the literature, have been synthesized. By testing the obtained compounds it was established that individual representatives of the latter exhibited antinematode activity for agricultural nematodes Steinernema feltiae, increasing the viability of the latter by 3–5%.

Keywords: 1,2,4-triazoles, β-heterocyclic alanines, triazolo-triazoles, antinematode activity.

Introduction. It is known that most of the drugs contain derivatives of heterocyclic compounds as active ingredients. Among the latter, a special place is occupied by nitrogen-containing five-membered heterocyclic compounds, in particular, 1,2,4-triazoles. The interest in this class of compounds is explained by a wide range of biological activities; a large number of them are already used in practical medicine as drugs, for example, voriconazole, triazolam, fluconazole, itraconazole, furacilin, alprazolam, estazolam, etc. On the other hand, intensive research on elaborating synthesis of new representatives of the aforementioned series of compounds and studying their biological properties is in progress. In recent years, numerous methods have been developed for the synthesis of new 1,2,4-triazole derivatives combined with various heterocycles [1–9], condensed systems [10–12], and in some cases with application of microwave radiation [13, 14]. Biological studies have shown that the new 1,2,4-triazole derivatives exhibit antioxidant [15], insecticidal [16, 17], antimicrobial [18, 19], antibacterial [20, 21], anticonvulsant [22, 23], antineoplastic [24, 25], anti fungal [26, 27] properties, they are inhibitors of p38 mitogen-activated protein (MAP) kinases [28], etc. The data presented unequivocally show that studies of 1,2,4-triazoles are relevant and appropriate.

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Results and Discussion. In order to expand the assortment of 1,2,4-triazole derivatives and to search for new useful features in their series, new representatives of methyl esters of β-triazole-substituted alanines were synthesized according to the method developed by us earlier [29]. Based on compounds 2, a–d, according to the Scheme below, a number of transformations leading to the new derivatives of functionally substituted 1,2,4-triazoles were carried out.

Hydrolysis and hydrazinolysis of compounds 2, a–d have been studied and it has been established that alkaline hydrolysis with a 40% aqueous alkali solution resulted in the appropriate acids that are analogs of β-alanine (3, a–d), and the hydrazinolysis products are hydrazides of acids 4, a–d that have a unique structure and could be employed in fine organic synthesis for the construction of various biheterocyclic systems. In particular, based on 4, a–d a method for the synthesis of triazole-triazoles of a new structure (6, a–d) has been developed. It should be noted that the substituents in position 3 of the triazole ring do not influence the course of the reactions, all processes proceed chemoselectively, under mild conditions and provide high yields of the target products.

The structures of all synthesized compounds were established by modern physicochemical methods. The purity and individuality were checked by TLC.

Biological Part. Some of the synthesized compounds were subjected to biological studies and positive nematodes Steinernema feltiae, which are of great importance both in plant growth (as regulators) and in animal husbandry, were chosen as an object [30].

The use of nematodes in biological studies is due to the fact that they are easily obtained, cultivated, processed and can be used as a reliable organism for preliminary toxicological research. Nematodes are an ideal model of a multicellular living organism to be studied under a microscope as well as in studying the absorption and distribution of a biologically active compound in a small and primitive multicellular organism [31].

As a result of processing the experimental data, the following graphs were obtained that clearly illustrate the nematode activity of some compounds. In particular, Fig. 1 shows that compounds 3a and 3c increase the viability of nematodes by 5 and 4%, respectively, and compound 3b does not display significant activity.
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A similar picture is observed in studying compounds 4, a–c. While compounds 4b and 4c increase the viability of nematodes by 3 and 4%, respectively, compound 4a is inactive.

Studies of compounds 6a and 6b have shown that these compounds do not exhibit significant activity.

As follows from the formulas given, the sulfur atom can be in different states – thiol or thionic. Thiol or unblocked sulfur is easily oxidized and the produced forms rapidly affect and inhibit thiol-proteins and enzymes. In consequence of this, they are considered to be an independent class of oxidative stressors [32]. The thionic form has an antioxidant property, which is clearly established by studies on ergothioneine [33].

The thionic form is a fixed state of sulfur, does not have a higher oxidative state, and consequently acts as an antioxidant providing the growth of nematodes. All that has been said is clearly observed in the case of compounds 3 and 4. As for
compounds 6, a–d, the molecules of these compounds contain both closed and unblocked sulfur, hence the inactivity of 6, a–d can be interpreted as the antagonistic interaction between the two forms. The thiol form acts as an oxidative stressor, and the thionic form acts as an antioxidant.

Thus, based on 1,2,4-triazoles, methods for the preparation of new functional derivatives and biheterocyclic compounds have been developed, a nematode property in the series of 1,2,4-triazoles has been revealed. An attempt has been made to establish a relationship between the structure and biological activity of the compounds proposed.

**Experimental Part.**

**Biology Part: Analysis of Antinematode Activity.** The viability of fresh nematode suspensions was observed with a microscope (TR 200, VWR Inter.) at a fourfold magnification. For the experiment, nematodes with a viability greater than 90% were used. For the analysis of antinematode activity, 200 mg of nematode powder was suspended in 50 mL of phosphate buffered saline solution (PBS) (pH 7) or distilled water. Under moderate illumination, the mixture was stirred for 10 min at room temperature. 10 μL of the suspension was added to each well of a 96-well plate, followed by the addition of the test substance at different concentrations. The final volume was adjusted to 100 μL with buffer. The number of live (N₀) and total number of nematodes (N) were immediately determined. The plate was then incubated in the dark for 24 h at room temperature, 50 μL of warm water (50ºC) was added and the number of live nematodes (N₂₄) was counted. Viability is determined by the following formula:

$$Viability_0 = \frac{N_0}{N} \times 100\%,$$

$$Viability_{24} = \frac{N_{24}}{N} \times 100\%.$$

Based on experimental data, graphs of the dependence of the viability of nematodes on the concentration of the substances under study are constructed.

**Preparation of PBS buffer**

<table>
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<th>Quantity added for 10 × solution, g</th>
<th>Final concentration (×10), mM</th>
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<td>27</td>
</tr>
<tr>
<td>Na₂HPO₄</td>
<td>14.4</td>
<td>100</td>
</tr>
<tr>
<td>KH₂PO₄</td>
<td>2.4</td>
<td>18</td>
</tr>
</tbody>
</table>

*If necessary, PBS was supplemented with the following:*

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Quantity added for 10 × solution, g</th>
</tr>
</thead>
<tbody>
<tr>
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<td>1.33</td>
</tr>
<tr>
<td>MgCl₂·6H₂O</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**Chemical Part.** ¹H and ¹³C NMR spectra were recorded on Varian Mercury-300 MHz in DMSO–CCl₄ mixture (1:3) or on Bruker AVANCE 400 MHz spectrometer in CDCl₃, DMSO-d₆. Chemical shifts (δ, ppm) are reported as quoted relative to the residual signals of chloroform-d (7.25 for ¹H NMR and 77.0 for ¹³C NMR) or DMSO-d₆ (2.5 for ¹H NMR and 39.5 for ¹³C NMR) as internal references. ESI–MS spectra were measured with a MicroTof Bruker Daltonics instrument. TLC analysis was performed on Silufol UV-254 plates. All reagents were of reagent grade and were used as such or distilled prior to use. Starting 1,2,4-triazoles 1, a–d were prepared as previously reported [34]. Melting points were determined on Boetius micro-heating stage.
**General Procedure for the Preparation of Esters (2, a–d).** To a mixture of 8 mmol of the corresponding triazole in 40 mL of acetonitrile was added 0.8 mL of 1 M solution of sodium methyleate in methanol, 9.7 mmol of methyl acrylate and the whole was stirred for 4 h at room temperature and 5 h at 50–60°C. The mixture was cooled, and the solvent was removed in vacuum. The crystals formed were recrystallized.

Methyl 3-[3-(methylphenyl)-4-phenyl-5-sulfanylidene-4,5-dihydro-1H-1,2,4-triazol-1-yl]propanoate (2a). Yield 86%, m.p. 125–126°C (H₂O : MeOH = 1: 10).

³¹H NMR (400 MHz, CDCl₃), δ, ppm: 7.53–7.42 m (3H_arom.), 7.35–7.26 m (2H_arom.), 7.21–7.15 m (2H_arom.), 7.15–7.07 m (1H_arom.), 7.02–6.91 m (1H_arom.), 4.64 t (J = 7.4 Hz, 2H, NCH₂-CH₃), 3.74 s (3H, OCH₃), 3.03 t (J = 7.4 Hz, 2H, NCH₂-CH₃), 2.25 s (3H, CH₃Ar).¹³C NMR (101 MHz, CDCl₃), δ, ppm: 171.2, 168.4, 149.8, 138.7, 135.2, 131.5, 129.8, 129.7, 129.0, 128.5, 128.4, 125.3, 125.2, 52.1, 45.2, 32.5, 21.4. HRMS (ESI) m/z: [M+H]⁺ calculated for C₁₆H₁₇NO₃S: 354.1276. Found: 354.1284.

Methyl 3-[3-(4-methylphenyl)-4-phenyl-5-sulfanylidene-4,5-dihydro-1H-1,2,4-triazol-1-yl]propanoate (2b). Yield 88%, m.p. 137–139°C (H₂O : EtOH = 1: 10).

³¹H NMR (400 MHz, CDCl₃), δ, ppm: 7.54–7.42 m (3H_arom.), 7.33–7.24 m (2H_arom.), 7.20–7.10 m (2H_arom.), 7.10–7.02 m (2H_arom.), 4.63 t (J = 7.4 Hz, 2H, NCH₂-CH₃), 3.73 s (3H, OCH₃), 3.02 t (J = 7.4 Hz, 2H, NCH₂-CH₃), 2.30 s (3H, CH₃Ar).¹³C NMR (101 MHz, CDCl₃), δ, ppm: 171.2, 168.3, 149.8, 141.1, 135.2, 129.8, 129.7, 129.4, 128.4, 128.1, 122.4, 52.1, 45.2, 32.5, 21.5. HRMS (ESI) m/z: [M+H]⁺ calculated for C₁₆H₁₇NO₃S: 354.1276. Found: 354.1284.

Methyl 3-[3-(phenoxymethyl)-4-phenyl-5-sulfanylidene-4,5-dihydro-1H-1,2,4-triazol-1-yl]propanoate (2c). Yield 78%, colorless oil [35, 36].

Methyl 3-[3-benzyl-4-phenyl-5-sulfanylidene-4,5-dihydro-1H-1,2,4-triazol-1-yl]propanoate (2d). Yield 82%, m.p. 54–55°C [29].

**General Procedure for the Preparation of Acids (3, a–d).** A mixture of 0.015 mol of the corresponding 2, a–d, 3 mL of ethanol and 1.2 g of sodium hydroxide as a 40% solution was heated at 80–90°C for 5 h. After cooling, the mixture was diluted with water and acidified with hydrochloric acid to pH 2–3. The precipitated crystals were filtered off, washed with water, dried and recrystallized.

3-[3-(Methylphenyl)-4-phenyl-5-sulfanylidene-4,5-dihydro-1H-1,2,4-triazol-1-yl]propanoic acid (3a). Yield 92%, m.p. 183–184°C (EtOH : H₂O = 1: 1.125).

³¹H NMR (400 MHz, CDCl₃), δ, ppm: 7.54–7.43 m (3H_arom.), 7.35–7.27 m (2H_arom.), 7.23–7.16 m (2H_arom.), 7.13 t (J = 7.6 Hz, 1H_arom.), 6.98 d (J = 7.6 Hz, 1H_arom.), 4.65 t (J = 7.3 Hz, 2H, CH₂N), 3.11 t (J = 7.3 Hz, 2H, CH₂C=O), 2.26 s (3H, CH₃Ar).¹³C NMR (101 MHz, CDCl₃), δ, ppm: 176.0, 167.9, 149.4, 138.2, 134.6, 131.0, 129.4, 129.2, 128.5, 128.0, 127.9, 124.8, 124.6, 44.3, 31.8, 20.9. Found, %: C 63.57; H 5.16; N 12.50; S 9.31. C₁₆H₁₇NO₃S. Calculated, %: C 63.70; H 5.05; N 12.38; S 9.45.

3-[3-(4-Methylphenyl)-4-phenyl-5-sulfanylidene-4,5-dihydro-1H-1,2,4-triazol-1-yl]propanoic acid (3b). Yield 94%, m.p. 185–187°C.³¹H NMR (400 MHz, CDCl₃), δ, ppm: 7.55–7.39 m (3H_arom.), 7.36–7.22 m (2H_arom.), 7.17 d (J = 8.2 Hz, 2H_arom.), 7.08 d (J = 8.1 Hz, 2H_arom.), 4.64 t (J = 7.3 Hz, 2H, CH₂N), 3.09 t (J = 7.3 Hz, 2H, CH₂C=O), 2.31 s (3H, CH₃Ar).¹³C NMR (101 MHz, CDCl₃), δ, ppm: 175.8, 167.9, 149.4, 140.6, 134.7, 129.3, 129.0, 127.9, 127.7, 121.9, 44.3, 31.8, 21.0. Found, %: C 63.55; H 4.89; N 12.55; S 9.56. C₁₈H₁₉NO₃S. Calculated, %: C 63.70; H 5.05; N 12.38; S 9.45.
3-[3-(Phenoxymethyl)-4-phenyl-5-sulfanylidene-4,5-dihydro-1H-1,2,4-triazol-1-yl]propanoic acid (3e). Yield 95%, m.p. 109–110°C [33].

3-[3-(Benzyl-4-phenyl-5-sulfanylidene-4,5-dihydro-1H-1,2,4-triazol-1-yl]-propanoic acid (3d). Yield 93%, m.p. 164–165°C (H₂O). ¹H NMR (300 MHz, DMSO:CCI₃ = 1:3), δ, ppm: 12.22 br.s (1H, OH), 7.52–7.37 m (3H arom.), 7.28–7.01 m (5H arom.), 6.96–6.81 m (2H arom.), 4.49–4.30 m (2H, CH₂N), 3.86 s (2H, CH₂Ph), 2.87–2.79 m (2H, CH₂C=O). ¹³C NMR (75 MHz, DMSO : CCl₄ = 1: 3), δ, ppm: 171.2, 167.0, 149.2, 133.9, 133.7, 129.0, 128.8, 128.1, 128.0, 126.5, 44.3, 31.9, 31.2. Found, %: C 63.56; H 5.18; N 12.49; S 9.30. C₁₉H₁₇N₃O₂S. Calculated, %: C 63.70; H 5.05; N 12.38; S 9.45.

**General Procedure for the Synthesis of Hydrazides (4, a–d).** To a mixture of 6 mmol of compounds 2, a–d in 20 mL of ethanol was added 0.34 mL of 85% solution of hydrazine, stirred for 5 h at room temperature and 2 h at 50–60°C. After removal of the solvent, the residue was recrystallized.

3-[3-(Methylphenyl)-4-phenyl-5-sulfanylidene-4,5-dihydro-1H-1,2,4-triazol-1-yl]propanehydrazide (4a). Yield 93%, m.p. 199–201°C. ¹H NMR (400 MHz, DMSO), δ, ppm: 9.19 s (1H, NH), 7.58–7.41 m (3H arom.), 7.41–7.28 m (2H arom.), 7.28–7.08 m (3H arom.), 7.06–6.88 m (1H arom.), 4.43 t (J = 7.6 Hz, 2H, CH₂N), 4.25 br.s (2H, NH₂), 2.68 t (J = 7.6 Hz, 2H, CH₂C=O), 2.20 s (3H, CH₃Ar). ¹³C NMR (101 MHz, DMSO), δ, ppm: 168.6, 167.4, 149.3, 138.0, 135.0, 131.2, 129.6, 129.4, 128.9, 128.7, 128.4, 125.4, 125.3, 45.3, 31.8, 20.8. HRMS (ESI) m/z: [M + H]⁺ calculated for C₁₉H₁₇N₃O₂S: 354.1389. Found: 354.1394.

3-[3-(Methylphenyl)-4-phenyl-5-sulfanylidene-4,5-dihydro-1H-1,2,4-triazol-1-yl]propanehydrazide (4b). Yield 89%, m.p. 194–197°C (H₂O : EtOH = 1: 1). ¹H NMR (400 MHz, CDCl₃), δ, ppm: 9.20 s (1H, NH), 7.53–7.42 m (3H arom.), 7.38–7.28 m (2H arom.), 7.23–7.15 m (2H arom.), 7.15–7.06 m (2H arom.), 4.43 t (J = 7.5 Hz, 2H, CH₂N), 4.28 br.s (2H, NH₂), 2.68 t (J = 7.5 Hz, 2H, CH₂C=O), 2.25 s (3H, CH₃Ar). ¹³C NMR (101 MHz, CDCl₃), δ, ppm: 168.6, 167.4, 149.3, 140.5, 135.0, 129.6, 129.4, 129.2, 128.7, 128.3, 122.5, 45.3, 31.9, 20.9. HRMS (ESI) m/z: [M + H]⁺ calculated for C₁₉H₁₉N₃O₂S²⁺: 354.1389. Found: 354.1376.

3-[3-(Phenoxymethyl)-4-phenyl-5-sulfanylidene-4,5-dihydro-1H-1,2,4-triazol-1-yl]propanehydrazide (4c). Yield 94%, m.p. 149°C (H₂O : EtOH = 4 : 1) [34].

3-[Benzyl-4-phenyl-5-thi oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl]propane hydrazide (4d). Yield 86%, m.p. 113°C (H₂O : EtOH = 40 : 1) [29].

**General Procedure for the Synthesis of Hydrazinecarbothioamides (5, a–d).** 4.95 mmol of the appropriate isothiocyanate was added to a mixture of 4.5 mmol of the corresponding hydrazide 4, a–d in 10 mL of ethanol, stirred for 1 h at room temperature and 4 h at 75–80°C. The mixture was cooled the precipitate was filtered off, washed with ethanol, dried and recrystallized.

2-[3-[3-(Methylphenyl)-4-phenyl-5-sulfanylidene-4,5-dihydro-1H-1,2,4-triazol-1-yl]propanoyl]-N-(prop-2-en-1-yl)hydrazine-1-carbothioamide (5a). Yield 92%, m.p. 166–168°C. ¹H NMR (300 MHz, DMSO : CCl₃ = 1: 3), δ, ppm: 10.02–9.28 m (1H, NH), 9.26–9.00 m (1H, NH), 7.82 t (J = 5.7 Hz, 1H, NH), 7.58–7.39 m (3H arom.), 7.39–7.24 m (2H arom.), 7.22–7.07 m (4H arom.), 5.81 ddt (J = 17.0, 10.3, 5.2 Hz, 1H, CH=CH₂), 5.24–5.08 m (1H, CH₂CH₂), 5.08–4.96 m (1H, CH₂), 4.53 t (J = 7.4 Hz, 2H, NCH=CH₂=CH₂), 4.07 t (J = 5.4 Hz, 2H, CH₂CH₂=CH₂), 2.84 t
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$J = 7.4 \ Hz$, 2H, CH$_2$(C=O), 2.33 s (3H, CH$_2$Ar). Found: % C 58.21; H 5.51; N 18.77; S 14.02. C$_2$H$_2$N$_2$O$_2$S$_2$. Calculated: % C 58.38; H 5.34; N 18.57; S 14.17.

N-Phenyl-2-[3-(4-methylphenyl)-4-phenyl-5-sulfonylidene-4,5-dihydro-1H-1,2,4-triazol-1-yl]propanoyl]hydrazine-1-carbothioamide (5b). Yield 97%, m.p. 194–196°C. $^1$H NMR (300 MHz, DMSO : CCl$_4$ = 1: 3), $\delta$, ppm: 10.20–9.75 m (1H, NH), 9.70–9.03 m (2H, NH), 7.61–7.40 m (5H$_{arom}$), 7.34–7.22 m (4H$_{arom}$), 7.19–7.01 m (5H$_{arom}$), 6.62–6.42 m (2H, NCH$_2$CH$_2$CO), 3.03–2.83 m (2H, NCH$_2$CH$_2$CO), 2.32 s (3H, CH$_2$Ar). Found: % C 61.63; H 4.78; N 17.38; S 13.21. C$_2$H$_2$N$_2$O$_2$S$_2$. Calculated: % C 61.45; H 4.95; N 17.20; S 13.12.

N-Phenyl-2-[3-(phenoxymethyl)-4-phenyl-5-sulfonylidene-4,5-dihydro-1H-1,2,4-triazol-1-yl]propanoyl]hydrazine-1-carbothioamide (5c). Yield 81%, m.p. 80–82°C (H$_2$O : EtOH = 1: 1.5). $^1$H NMR (300 MHz, DMSO : CCl$_4$ = 1: 3), $\delta$, ppm: 10.24–9.75 m (1H, NH), 9.72–9.11 m (2H, NH), 7.57–7.44 m (6H$_{arom}$), 7.32–7.14 m (6H$_{arom}$), 7.06–6.84 m (8H$_{arom}$), 0.81–0.67 m (2H$_{arom}$), 0.85 s (2H, CH$_2$O), 0.41 t ($J = 7.13\ Hz$, 2H, CH$_2$N), 2.85 t ($J = 7.3\ Hz$, 2H, CH$_2$C=O). Found: % C 59.32; H 4.60; N 16.86; S 12.90. C$_2$H$_2$N$_2$O$_2$S$_2$. Calculated: % C 59.50; H 4.79; N 16.65; S 12.71.

N-Phenyl-2-[3-Benzyl-4-phenyl-5-sulfonylidene-4,5-dihydro-1H-1,2,4-triazol-1-yl]propanoyl]hydrazine-1-carbothioamide (5d). Yield 89%, m.p. 137–139°C (H$_2$O : EtOH = 2 : 1) [29].

General Procedure for the Synthesis of bis-1,2,4-triazoles (6, a–d). To a solution of 4 mL of 10% KOH was added 3.5 mmol of the corresponding thiosemicarbamide, stirred for 2 h at room temperature and 4 h at 85–90°C. After cooling, the mixture was diluted with water and acidified with hydrochloric acid to pH 2–3. The precipitated crystals were filtered off, washed with water, dried and recrystallized.

4-Phenyl-5-(3-methylphenyl)-2-[2-[4-(prop-2-en-1-yl)-5-sulfonylidene-4,5-dihydro-1H-1,2,4-triazol-3-yl]ethoxy]-2,4-dihydro-3H-1,2,4-triazole-3-thione (6a). Yield 88%, m.p. 79–81°C. $^1$H NMR (400 MHz, CDCl$_3$), $\delta$, ppm: 12.01–11.38 m (1H, NH), 7.54–7.43 m (3H$_{arom}$), 7.34–7.27 m (2H$_{arom}$), 7.22–7.16 m (2H$_{arom}$), 7.16–7.09 m (1H$_{arom}$), 7.00–6.93 m (1H$_{arom}$), 5.92 ddt ($J = 15.7, 10.5, 5.3\ Hz$, 1H, CH$_2$CH), 5.29 br.d ($J = 10.3\ Hz$, 1H, CH$_2$CH), 5.22 br.d ($J = 17.2\ Hz$, 1H, CH$_2$CH), 4.77 br.d ($J = 5.3\ Hz$, 2H, CH$_2$CH=CH$_2$), 4.37–4.30 m (2H, NCH$_2$CH$_2$), 2.26 s (3H, ArCH$_3$). $^{13}$C NMR (101 MHz, CDCl$_3$), $\delta$, ppm: 168.1, 149.1, 138.3, 134.5, 131.2, 129.9, 129.4, 129.3, 128.5, 128.1, 127.8, 124.9, 124.4, 118.5, 45.7, 45.6, 23.6, 20.9. HRMS (ESI) m/z: [M + H]$^+$ calculated for C$_2$H$_2$N$_2$S$_2$: 435.1426. Found: 435.1410.

4-Phenyl-5-(4-methylphenyl)-2-[2-[4-phenyl-5-sulfonylidene-4,5-dihydro-1H-1,2,4-triazol-3-yl]ethoxy]-2,4-dihydro-3H-1,2,4-triazole-3-thione (6b). Yield 97%, m.p. 132–135°C. $^1$H NMR (400 MHz, CDCl$_3$), $\delta$, ppm: 12.47–11.93 m (1H, NH), 7.62–7.50 m (3H$_{arom}$), 7.50–7.37 m (5H$_{arom}$), 7.34–7.21 m (2H$_{arom}$), 7.16–7.02 m (4H$_{arom}$), 4.61 t ($J = 7.1\ Hz$, 2H, CH$_2$N), 3.16 t ($J = 7.1\ Hz$, 2H, NCH$_2$CH$_3$), 2.30 s (3H, ArCH$_3$). $^{13}$C NMR (101 MHz, CDCl$_3$), $\delta$, ppm: 168.8, 168.6, 150.1, 149.6, 141.2, 135.0, 133.2, 130.3, 130.1, 129.8, 129.8, 129.5, 128.3, 128.2, 128.1, 122.2, 45.7, 24.6, 21.5. HRMS (ESI) m/z: [M+H]$^+$ calculated for C$_2$H$_2$N$_2$S$_2$: 471.1426. Found: 471.1433.

5-Phenoxymethyl-4-phenyl-2-[2-[4-phenyl-5-sulfonylidene-4,5-dihydro-1H-1,2,4-triazol-3-yl]ethoxy]-2,4-dihydro-3H-1,2,4-triazole-3-thione (6c). Yield 82%, m.p. 85–90°C. $^1$H NMR (300 MHz, DMSO : CCl$_4$ = 1: 3), $\delta$, ppm: 13.67 br.s (1H, NH), 7.61–7.39 m (10H$_{arom}$), 7.21–7.14 m (2H$_{arom}$), 6.94–6.85 m (1H$_{arom}$), 6.80–6.71 m...
(2H$_{\text{nen}}$), 4.88 s (2H, CH$_3$O), 4.46 t ($J = 7.2$ Hz, 2H, NCH$_2$CH$_3$), 3.03 t ($J = 7.2$ Hz, 2H, NCH$_2$CH$_3$). Found, %: C 61.52; H 4.68; N 17.45; S 13.05. Calculated, %: C 61.71; H 4.56; N 17.27; S 13.18.

5-Benzyl-4-phenyl-2-f(4-phenyl-5-sulfanylidene-4,5-dihydro-1H-1,2,4-triazol-3-yl)-ethyl]2,4-dihydro-3H-1,2,4-triazole-3-thione (6d). Yield 93%, m.p. 113–114°C (H$_2$O : EtOH = 2 : 1) [29].

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