S-Alkylated 1,2,4-Triazoles Derivatives
Synthesis, spectral analysis and cytotoxicity evaluation

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This paper presents synthesis, characterization and cytotoxicity assessment of six S-alkylated 1,2,4-triazoles derivatives that were obtained by treatment of some 1,2,4-triazole-3-thiones containing in the molecule phenylsulfonylphenyl and propyl or 4-bromophenylsulfonylphenyl and 4-methoxyphenyl fragments with different alkylation agents (ethyl bromide, ethyl chloroacetate or phenacyl bromide) in basic media. The synthesized compounds were physico-chemically characterized and the IR, ^{1}H-NMR, ^{13}C-NMR spectra were consistent with the assigned structures. The cytotoxicity of S-alkylated derivatives was evaluated on Daphnia magna crustacean.

Keywords: 1,2,4-triazole-3-thione, alkylation, cytotoxic effect, Daphnia magna

Nowadays it is well known that people are confronted with a very serious problem that is related to infectious diseases and cancer. Therefore, numerous research are currently geared towards discovery new molecules that to be active on bacteria and fungi resistant to the clinically authorized drugs used at the moment. Also, the discovery of new molecules as anticancer agents with direct cytotoxicity and apoptosis-inducing activity in tumor cell lines is a priority of global research.

Heterocyclic compounds from 1,2,4-triazole class have enjoy of special attention from researchers in the medicinal field, especially because of their biological properties. Moreover, some derivatives from this class have been extensively used in clinic, among Fluconazole, Itraconazole, Voriconazole (used for the fungal infection disease) or Letrozole and Anastrozole (anticancer agents, aromatase inhibitors) [1,2].

Also, 1,2,4-triazole-3-thione/thiole ring systems and their derivatives possess biological properties including antibacterial, antimycobacterial, antifungal, anticancer and antioxidant activity [2-12]. For instance, Hassan G.S. et al. investigated the antimicrobial and antitumoral activity of some 5-(2-aminothiazol-4-yl)-4-substituted-phenyl-4*H*-1,2,4-triazole-3-thiole derivatives, the results indicating that some of these derivatives have biological activity, comparatively with used drugs [3]. Zoumpoulakis P. et al. reported the antimicrobial activity evaluation of a series of 5-[2-(N-dimethylsulfamoyl)-4,5-dimethoxy-benzyl]-4-alkyl-s-triazole-3-thiones, most of them having antibacterial and antifungal activities, better than antibiotics used as standards, depending on the alkyl radical linked to the N-4 nitrogen atom from triazole ring [4]. Also, following the evaluation of antitumoral activity of some S-alkylated 1,2,4-triazoles, Hou I.P. et al. reported that the 3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-5-(2-fluorobenzylthio)-4-phenyl-4*H*-1,2,4-triazole was the most active against HEPG2 cancer cell line, comparable to the positive control [5].

Taking into account the importance of 1,2,4-triazole nucleus, many studies are dedicated to synthesis and biological testing of novel derivatives containing this heterocyclic ring with aim to discovery new biological agents with high bioactivity, with low toxicity and with good pharmacokinetic properties.

Our previously research focused on the synthesis, characterization and biological evaluation, including antibacterial, antifungal and antioxidant activity [13-16] of some new compounds from 1,2,4-triazole-3-thiones and S-alkylated-1,2,4-triazole derivatives in order to discover new biological agents.

The aim of the study from the present work was to extended the researcher in these class of S-alkylated-1,2,4-triazoles regarding to synthesis, characterization and cytotoxic evaluation of some derivatives.

The biological activity of the synthesized compounds was evaluated using *Daphnia magna* assay, an alternative method for prescreening of cytotoxicity activity [17,18]. Along with other bioassays, this method is widely used for toxicity risk assessment of new compounds, plant extracts, and pharmaceutical substances [19-21].

Experimental part

Materials and methods

The FT-IR spectra were recorded on a Vertex 70 Bruker spectrometer, using KBr pellets. The NMR spectra were recorded on a Varian Gemini 300BB spectrometer at 300

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MHz for ^{1}H-NMR and at 75 MHz for ^{13}C-NMR using $CDCl_3$ as solvent. The chemical shifts (ä) are reported in ppm relative to tetramethylsilane (TMS) as internal standard and coupling constants *J* are in Hz. The elemental analysis determined with a ECS-40-10-Costeh microdosimeter. The melting points were carried out on a Böetius apparatus and are uncorrected.

Synthesis of compounds

The alkylated derivatives presented in this paper, whose reaction scheme was presented in previous work [22], were prepared starting from 1,2,4-triazole-3-thiones **2a,b** known in literature [23,24] that have been synthesized by cyclization of the corresponding acylthiosemicarbazides **1a,b** in a 8% sodium hydroxide solution.

Thus, by treatment of 1,2,4-triazoles **2a** or **2b** with ethyl bromide, phenacyl bromide or ethyl chloroacetate, in sodium ethoxide media, the alkylated derivatives were obtained: 5-(4-(4-X-phenylsulfonyl)phenyl)-3-(ethylthio)-4-(propyl/4-methoxyphenyl)-4*H*-1,2,4-triazoles **3a,b**, *2-(5-(4-(4-X-phenylsulfonyl)phenyl)-4-*(propyl/4-methoxyphenyl)*-4H-1,2,4-triazol-3-ylthio)-1-phenyletha-none* **4a,b** and *ethyl 2-(5-(4-(4-X-phenylsulfonyl)phenyl)-4-*(propyl/4-methoxyphenyl)*-4H-1,2,4-triazol-3-ylthio)acetate* **5a,b** by the method described in the our previously papers [13,25] (scheme 1). The derivative **3a** was also obtained by treatment of the corresponding 1,2,4-triazole **2a** with a solution of NaOH 1N, or a mixture of sodium hydroxide and ethanol, followed of adding of ethyl bromide (see method B and C).

General procedure for the synthesis of S-alkylated 1,2,4-triazoles 3a,b - 5a,b (method A)

To a solution of sodium ethoxide (23 mg of sodium dissolved in 10 mL absolute ethanol) the 1,2,4-triazole-3-thione **2a**,**b** (1.0 mmol) was added with stirring for 30 min. To the obtained solution the alkylation agent (1.0 mmol) was added and the mixture was stirred for 12 h at room temperature. The mixture of the reaction was poured into ice water and the precipitate was filtered off, washed with water and the compound was purified by recristalization from ethanol.

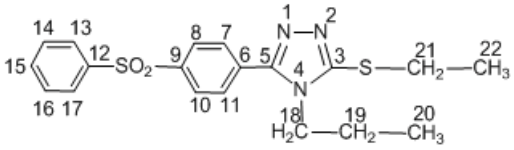
Method B (for derivative 3a)

An equimolar mixture formed by triazole **2a** (1.0 mmol) and a solution of NaOH 1N was stirred at room temperature till a solution was obtained. To the solution a stoechiometrical quantity of ethyl bromide (1.0 mmol) was added. The mixture was stirred at room temperature for 12 h and then was poured into ice water. The obtained precipitate was filtered off, washed with water until *p*H = 7 and recristalized from ethanol (yield = 47%).

Method C (for derivative 3a)

To a mixture formed by 1.0 mmol NaOH and 10 mL absolute ethanol was added 1.0 mmol of triazole **2a**. The mixture was stirred at the room temperature till a solution was obtained. The ethyl bromide (1.0 mmol) was added to the solution and the mixture was stirred for 12 h at room temperature. The mixture was poured into ice water and the obtained precipitate was filtered off, washed with water until *p*H = 7 and recristalized from ethanol (yield = 69%).

3-(Ethylthio)-5-(4-(phenylsulfonyl)phenyl)-4-propyl-4H-1,2,4-triazole ***3a***



m.p. = 131-133°C; yield = 74% (method A);

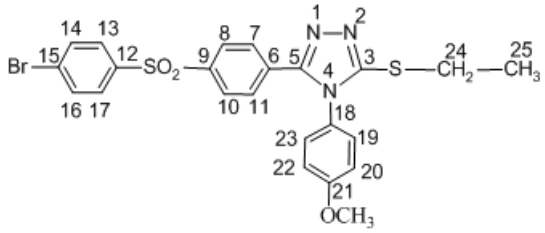
IR (KBr, ν, cm^{-1}): 3068w, 2970m, 2933w, 2875w, 1599w, 1570m, 1460s, 1320s, 1160vs, 1015m, 850m;

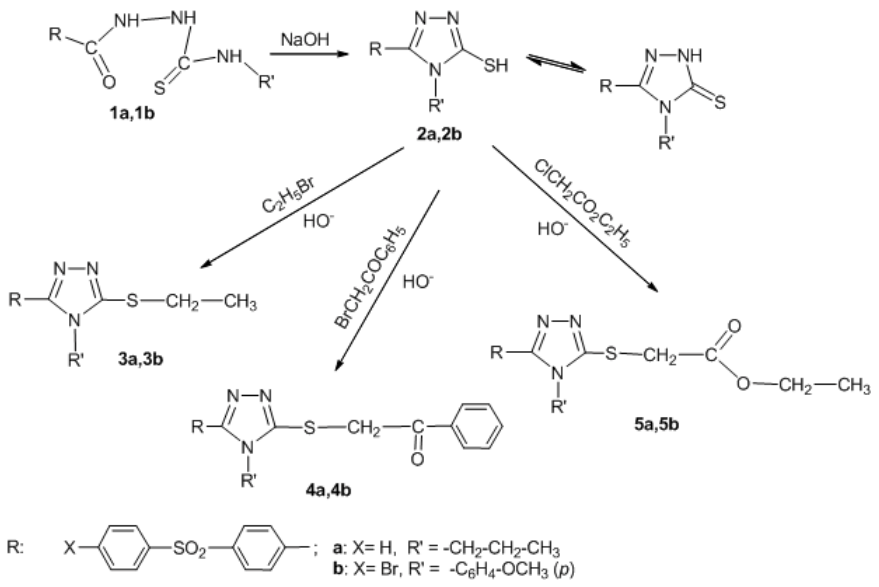
^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 8.07 (d, 2H, 8.4, H-8, H-10), 7.97 (dd, 2H, 7.5, 1.4, H-13, H-17), 7.76 (d, 2H, 8.4, H-7, H-11), 7.60 (tt, 1H, 7.5, 1.4, H-15), 7.56 (t, 2H, 7.5, H-14, H-16), 3.89 (t, 2H, 7.7, H-18), 3.33 (q, 2H, 7.3, H-21), 1.69 (sx, 2H, 7.7, H-19), 1.46 (t, 3H, 7.3, H-22), 0.84 (t, 7.7, 3H, H-20);

^{13}C-NMR ($CDCl_3$, δ ppm): 153.76 (C-3), 152.68 (C-5), 142.91 (C-9), 140.91 (C-12), 133.54 (C-15), 132.29 (C-6), 129.42 (C-14, C-16), 129.26 (C-7, C-11), 128.24 (C-8, C-10), 127.74 (C-13, C-17), 46.27 (C-18), 27.53 (C-21), 23.28 (C-19), 14.91 (C-22), 10.83 (C-20);

Elemental analysis: Anal. Calcd. for $C_{19}H_{21}N_3O_3S_2$ (387.52 g/mol): C: 58.89; H: 5.46; S: 16.55; N:10.84%. Found: C: 58.94; H: 5.39; S: 16.52; N: 10.78%;

5-(4-(4-Bromophenylsulfonyl)phenyl)-3-(ethylthio)-4-(4-methoxyphenyl)-4H-1,2,4-triazole ***3b***





Scheme 1. Synthesis of the compounds **3a,b - 5a,b**

m.p.=180-182 °C; yield = 68%;

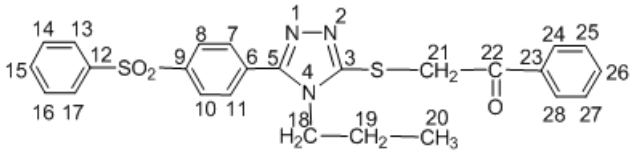
IR (KBr, ν, cm^{-1}): 3084w, 3014w, 2964w, 2933w, 2841w, 1604w, 1572w, 1513vs, 1326s, 1253s, 1160vs, 1069m, 1010m, 839m, 571m;

^{1}H-NMR ($CDCl_3$±DMSO-d_6 (10:1), δ ppm, *J* Hz): 7.83 (d, 2H, 8.5, H-8, H-10), 7.78 (d, 2H, 8.5, H-13, H-17), 7.67 (d, 2H, 8.5, H-14, H-16), 7.61 (d, 2H, 8.5, H-7, H-11), 7.16 (d, 2H, 8.9, H-19, H-23); 7.02 (d, 2H, 8.9, H-20, H-22), 3.88 (s, 3H, OCH_3), 3.25 (q, 2H, 7.4, H-24), 1.42 (t, 3H, 7.4, H-25);

^{13}C-NMR ($CDCl_3$±DMSO-d_6 (10:1), *d* ppm): 160.02 (C-21), 153.98 (C-3), 152.25 (C-5), 141.82 (C-9), 140.92 (C-12), 139.33 (C-18), 132.06 (C-14, C-16), 131.03 (C-6), 128.79 (C-13, C-17), 128.58 (C-19, C-23), 127.76 (C-7, C-11), 127.06 (C-8, C-10), 125.29 (C-15), 114.72 (C-20, C-22), 54.93 (OCH_3), 26.04 (C-24), 14.08 (C-25);

Elemental analysis: Anal. Calcd. for $C_{23}H_{20}BrN_3O_3S_2$ (530.46 g/mol): C:52.08; H:3.80; S:12.09%. Found: C:51.99; H:3.75; S:12.15%;

1-Phenyl-2-(5-(4-(phenylsulfonyl)phenyl)-4-propyl-4H-1,2,4-triazol-3-ylthio)ethanone ***4a***



m.p.=170-172°C; yield = 84%;

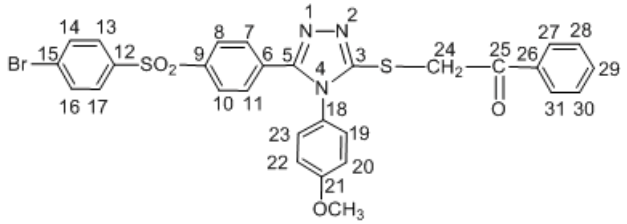
IR (KBr, *ν*, cm^{-1}): 3061w, 3030w, 2969w, 2933s, 2875w, 1692s, 1597w, 1470m, 1447m, 1316s, 1160vs, 1014m, 839w;

^{1}H-NMR ($CDCl_3$, *δ* ppm, *J* Hz): 8.07 (d, 2H, 8.4, H-8, H-10), 8.03 (bd, 2H, 7.3, H-24, H-28), 7.97 (bd, 2H, 7.0, H-13, H-17), 7.75 (d, 2H, 8.4, H-7, H-11), 7.40-7.60 (m, 6H, H-14, H-15, H-16, H-25, H-26, H-27), 5.00 (s, 2H, H-21), 3.95 (t, 2H, 7.8, H-18), 1.73 (sx, 2H, 7.8, H-19), 0.86 (t, 3H, 7.8, H-20);

^{13}C-NMR ($CDCl_3$, *d* ppm): 194.03 (C-22), 155.14 (C-3), 152.98 (C-5), 144.17 (C-9), 141.99 (C-12), 136.21 (C-23), 135.09 (C-26), 133.10 (C-15), 130.55 (C-6), 130.51 (C-24, C-28), 130.39 (C-25, C-27), 129.92 (C-14, C-16), 129.57 (C-7, C-11), 129.35 (C-8, C-10), 128.86 (C-13, C-17), 47.59 (C-18), 42.91 (C-21), 24.47 (C-19), 11.93 (C-20);

Elemental analysis: Anal. Calcd. for $C_{25}H_{23}N_3O_3S_2$ (477.60 g/mol): C:62.87; H:4.85; S:13.43; N:8.80%. Found: C:62.94; H:4.79; S:13.40; N:8.72%;

2-(5-(4-(4-Bromophenylsulfonyl)phenyl)-4-(4-methoxyphenyl)-4H-1,2,4-triazol-3-ylthio)-1-phenyl-ethanone ***4b***



m.p. = 210-211°C; yield = 76%;

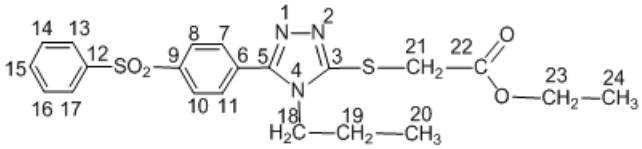
IR (KBr, ν, cm^{-1}): 3063w, 3014w, 2960w, 2918w, 2837w, 1680s, 1599m, 1573m, 1513vs, 1322s, 1255vs,1159vs, 1069s, 1008m, 840s, 575m;

^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 8.03 (dd, 2H, 7.7, 1.5, H-27, H-31), 7.82 (d, 2H, 8.6, H-8, H-10); 7.76 (d, 2H, 8.7, H-13, H-17), 7.63 (d, 2H, 8.7, H-14, H-16), 7.61 (bt, 1H, 7.7, H-29), 7.60 (d, 2H, 8.6, H-7, H-11), 7.49 (t, 2H, 7.7, H-28, H-30), 7.18 (d, 2H, 8.7, H-19, H-23), 7.01 (d, 2H, 8.7, H-20, H-22), 4.98 (s, 2H, H-24), 3.89 (s, 3H, OCH_3);

^{13}C-NMR ($CDCl_3$, δ ppm): 192.83 (C-25), 160.86 (C-21), 154.11 (C-3), 153.20 (C-5), 141.80 (C-9), 139.97 (C-12, C-18), 135.11 (C-26), 133.94 (C-29), 132.65 (C-14, C-16), 131.39 (C-6), 129.21 (C-13, C-17), 128.80 (C-28,C-30), 128.47 (C-27,C-31), 128.40 (C-7, C-11), 128.32 (C-19, C-23), 127.78 (C-8, C-10), 125.68 (C-15), 115.51 (C-20, C-22), 41.15 (C-24), 55.56 (OCH_3);

Elemental analysis: Anal. Calcd. for $C_{29}H_{22}BrN_3O_4S_2$ (620.54 g/mol): C:56.13; H:3.57; S:10.33%. Found: C:56.17; H:3.51; S:10.29%;

Ethyl 2-(5-(4-(phenylsulfonyl)phenyl)-4-propyl-4H-1,2,4-triazol-3-ylthio)acetate ***5a***



m.p.=88-90°C; yield = 72%;

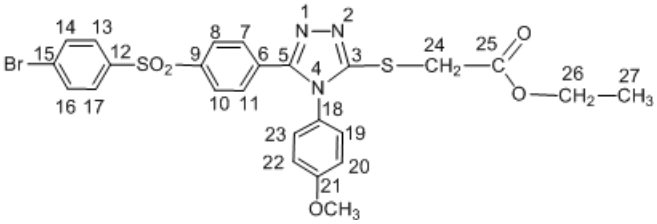
IR (KBr, ν, cm^{-1}): 3068w, 2971w, 2933w, 2875w, 1745vs, 1599w, 1470m, 1452s, 1306vs, 1157vs, 1028m, 849w;

^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 8.07 (d, 2H, 8.5, H-8, H-10), 7.96 (dd, 2H, 7.1, 1.6, H-13, H-17), 7.76 (d, 2H, 8.5, H-7, H-11), 7.61 (tt, 1H, 7.1, 1.6, H-15), 7.54 (t, 2H, 7.1, H-14, H-16), 4.21 (q, 2H, 7.2, H-23), 4.15 (s, 2H, H-21), 3.95 (t, 2H, 7.7, H-18), 1.71 (sx, 2H, 7.7, H-19), 1.27 (t, 3H, 7.2, H-24), 0.86 (t, 3H, 7.7, H-20);

^{13}C-NMR ($CDCl_3$, δ ppm): 168.15 (C-22), 154.08 (C-3), 151.29 (C-5), 143.05 (C-9), 140.86 (C-12), 133.56 (C-15), 132.02 (C-6), 129.42 (C-14, C-16), 129.28 (C-7, C-11), 128.25 (C-8, C-10), 127.74 (C-13, C-17), 62.10 (C-23), 46.47 (C-18), 35.22 (C-21), 23.43 (C-19), 14.04 (C-24), 10.83 (C-20);

Elemental analysis: Anal. Calcd. for $C_{21}H_{23}N_3O_4S_2$ (445.56 g/mol): C:56.61; H:5.20; S:14.39; N:9.43%. Found: C:56.69; H:5.14; S:14.35; N:9.52%;

Ethyl 2-(5-(4-(4-bromophenylsulfonyl)phenyl)-4-(4-methoxyphenyl)-4H-1,2,4-triazol-3-ylthio)aceta-te ***5b***



m.p. = 201-203 °C; yield = 77%;

IR (KBr, ν, cm^{-1}): 3082w, 2980w, 2933w, 2841w, 1734s, 1604w, 1573m, 1513vs, 1324s, 1255vs, 1160vs, 1070m, 1029m, 840m, 577m;

^{1}H-NMR ($CDCl_3$, δ ppm, *J* Hz): 7.83 (d, 2H, 8.7, H-8, H-10); 7.77 (d, 2H, 8.6, H-13, H-17), 7.64 (d, 2H, 8.6, H-14, H-16), 7.60 (d, 2H, 8.7, H-7, H-11), 7.18 (d, 2H, 9.1, H-19, H-23); 7.01 (d, 2H, 9.1, H-20, H-22); 4.22 (q, 2H, 7.1, H-26), 4.11 (s, 2H, H-24), 3.89 (s, 3H, OCH_3), 1.28 (t, 3H, 7.1, H-27);

^{13}C-NMR ($CDCl_3$, δ ppm): 167.98 (C-25), 161.14 (C-21), 153.93 (C-3), 153.39 (C-5), 142.18 (C-9), 140.43 (C-12, C-18), 132.84 (C-14, C-16), 131.68 (C-6), 129.30 (C-13, C-17), 128.95 (C-7, C-11), 127.86 (C-8, C-10), 127.75 (C-19, C-23), 126.06 (C-15), 115.63 (C-20, C-22), 62.01 (C-26), 55.67 (OCH_3), 34.57 (C-24), 14.06 (C-27);

Elemental analysis: Anal. Calcd. for $C_{25}H_{22}BrN_3O_5S_2$ (588.50 g/mol): C:51.02; H:3.77; S:10.90%. Found: C:51.10; H:3.71; S:10.86%.

Daphnia magna assay

The biological assay was performed in duplicate in PP tissue culture wells (Greiner Bio-One) with 10 organisms at a volume of 4 mL/sample [26]. The solvent, 1% DMSO was used as negative control. For each compound were tested 6 concentrations ranging from 0.5 to 50 ìg/mL. The observations were made at 24 and 48h, and lethality values (L%) were calculated. The lethality curves were plotted using the logarithm of concentrations and against L%. 50% lethal concentrations (LC50) and 95% confidence intervals (CI95%) were calculated by interpolation on lethality curves. The 48h LC50 was also predicted using Lazar and GUSAR software applications and compared with the value experimentally determined [27,28].

Results and discussions

In the IR spectra of alkylated compounds, the dissapearance of the stretching band of the NH group from 1,2,4-triazole-3-thiones (3439 cm^{-1} for **2a** and 3433 cm^{-1} for **2b**) is a proof that the alkylation of the triazoles with alkylation agents (ethyl bromide, phenacyl bromide or ethyl chloroacetate) took place. Also, the C=S stretching band from 1,2,4-triazole-3-thione **2a** (1256 $cm^{-1)}$ dissapeared in the IR spectra of compounds **3a-5a**, indicating the alkylation at sulfur atom. In the case of IR spectra of compounds **3b-5b** containing the methoxy group, the band of high intenstity from 1253-1255 cm^{-1} appeared due to antisimetric stretching vibration $\nu_{C\text{-}O\text{-}C}$.

In the IR spectra of compounds **4a** and **4b** obtained by reaction of triazoles **2a,b** with phenacyl bromide, the νC=O appeared in the region 1692 cm^{-1} (for **4a**) and 1680cm^{-1} (for **4b**).

The derivatives obtained by reaction of triazoles with ethyl chloroacetate contain in the IR spectra the absorption band due toνC=O from -COO group at 1745 cm^{-1} (for **5a**) and 1734 cm^{-1} (for **5b**).

În the ^{1}H-NMR spectra of S-ethyl triazoles **3a,b** the signals of ethyl protons appeared as quartet for methylene protons at 3.33 ppm for **3a** and 3.25 ppm for **3b** and as triplet for methyl protons at 1.46 ppm for **3a** and 1.42 ppm for **3b**.

The ethylacetate fragment from compounds **5a,b** recognized in the ^{1}H-NMR spectra by the signal of ethyl group: the protons from methyl group as singlet, at δ ~ 1.28 ppm and the protons from methylene group as quartet at ~4.21 ppm, with coupling constant *J*=7.2 Hz for **5a** and 7.1Hz for **5b**. The phenacylderivatives **4a,b** and esters **5a,b** contain a singlet signal corresponding to methlylene protons that appear at δ = 4.11-5.00 ppm.

The ^{13}C-NMR spectra of S-ethyl triazoles contain two new signals from ethyl group at 14.91 ppm for **3a** and 14.08 ppm for **3b** corresponding to carbon from methyl group and at 27.53 ppm **3a** and 26.04 ppm **3b** from methylene group. The characteristic signal from ^{13}C-NMR spectra of compounds **4a,b** is the signal of >C=O that appears at 194.03 ppm for **4a** and 192.83 ppm for **4b**. The presence of the ethyl esters derivatives is indicated in the ^{13}C-NMR by the signal corresponding to >C=O from ester group that appears at 168.15 ppm for **5a** and 167.98 ppm for **5b**. Also, in these compounds the new signals of ethyl group are presented at δ ~ 62 ppm for methylene and at ~ 14 ppm for methyl carbon. Moreover, the signal methylene carbon linked to sulfur atom appeared at 35,22 ppm for **5a** and at 34.57 ppm for **5b**. The same carbon signal appear in the ^{13}C-NMR spectra of phenacyderivatives at 42.91 ppm **4a** and 41.51 ppm **4b**.

The carbon signals from 1,2,4-triazole ring appear at 153.76-155.14 ppm for C-3 carbon and at 151.29-153.39 ppm for C-5 carbon. As has been shown in our other research [13,15,25], the carbon C-3 from these compounds is more shielded than the C=S carbon atom from the same position of the raw materials from triazoles class (167.50 ppm for **2a** and 169.28 ppm for **2b**), demonstrating that alkylation occurred at the sulfur atom.

Referring to the biological testing, the highest toxicity was induced by compound **3a**, followed by **3b** and **4a**. Compound **4b** showed cytotoxicity only at 48h, but lower toxicity than **3a**, **3b** and **4a**. Compounds **5a** and **5b** which contain an ethyl acetate group linked to the sulfur atom induced no significant toxic effects against *Daphnia magna* after 48h, the highest induced lethality being 30% (table 1; fig. 1).

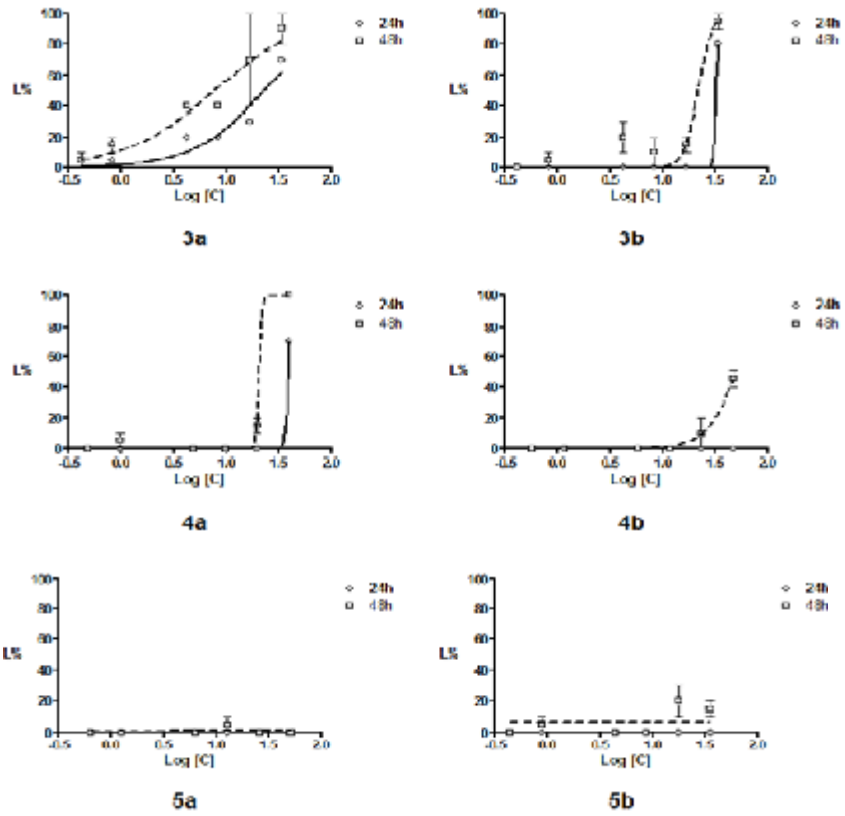


Fig. 1. Lethalithy curves on *Daphnia magna* at 24 and 48h for the tested compounds: **3a,b - 5a,b**

Compound	$LC50_{24h}$ (µg/mL)	95% CI of $LC50_{24h}$ (µg/mL)	$LC50_{48h}$ (µg/mL)	95% CI of $LC50_{48h}$ (µg/mL)	GUSAR (48h) (µg/mL)
3a	22.60	13.72 to 37.22	7.627	4.274 to 13.61	0.26
3b	32.04	NC	21.60	16.57 to 28.14	0.01
4a	~ 38.25	NC	~ 20.59	NC	0.05
4b	NC	NC	49.90	44.18 to 56.37	0.01
5a	NC	NC	NC	NC	0.14
5b	NC	NC	NC	NC	0.01

LC50 - 50% lethal concentration; 95% CI - 95% confidence interval; NC - not calculated due to the obtained results.

Table 1
RESULTS OF *Daphnia magna* BIOASSAY

The prediction using Lazar application failed to provide information regarding the toxicity of the synthesized compounds due to lack of similar structures. The Lazar software found only one structure related with our S-alkylated 1,2,4-triazoles derivatives, this compound being the dibenzothiophene 5,5-dioxide and having a very low similarity threshold of 0.25. The prediction with GUSAR showed lower values of 48h LC50 compared to the values obtained in our experiments (table 1).

Conclusions

The present work describes synthesis, characterization and cytoxicity evaluation of six S-alkylated 1,2,4-triazoles derivatives. The compounds were obtained by alkylation of some 1,2,4-triazole-3-thiones containing arylsulfonyl-phenyl and *n*-propyl/4-methoxyphenyl fragments with different alkylation agents. The chemical structure was confirmed by spectral analysis.

The compounds have been tested on *Daphnia magna* for their cytoxicity assessment. Of the synthesized compounds, **3a**, **4a**, **3b** and **4b** containing an ethyl or phenacyl group in the molecule showed high cytotoxicity to *Daphnia magna* (LC50<50 µg/mL), thereby a high biological activity.

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