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SYNTHESIS OF NOVEL S-ALKYL DERIVATIVES OF 4-ETHYL-5-(((3-(PYRIDIN-4-YL)-1*H*-1,2,4-TRIAZOL-5-YL)THIO)METHYL)-4*H*-1,2,4-TRIAZOLE-3-THIOLS

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Abstract

1,2,4-triazole belongs to one of the most promising heterocyclic systems in the world. This paper reports on the synthesis and structure of new alkyl derivatives of 4-ethyl-5-(((3-(pyridin-4-yl)-1*H*-1,2,4-triazol-5-yl)thio)methyl)-4*H*-1,2,4-triazole-3-thiol (**1**) and study some of their physicochemical properties. The chemical structure was evaluated through NMR spectroscopic analysis, Elemental analysis (CHNS), Gas-Chromatographic mass spectral analysis. Nucleophilic substitution reaction of 4-ethyl-5-(((3-(pyridin-4-yl)-1*H*-1,2,4-triazol-5-yl)thio)methyl)-4*H*-1,2,4-triazole-3-thiol (**1**) was studied using a set of bromoalkanes as alkylation agents, which yielded new 4-(5-((((5-(alkylthio)-4-ethyl-4*H*-1,2,4-triazol-3-yl)methyl)thio)-1*H*-1,2,4-triazol-3-s)pyridines (**2-11**).

Keywords: 1,2,4-triazole, 1H NMR, synthesis, heterocyclic compounds**.**

INTRODUCTION

Nowadays 1,2,4-triazole belongs to one of the most promising heterocyclic systems [1-5]. Modeling of 1,2,4-triazole cycle containing various substituents paves the way for further search of new biologically active compounds. A combination of different reactivity sites in this heterocyclic system confers possibilities for creation of new molecules with various biological properties.

Many of 1,2,4-triazole derivatives may potentially find applications as effective medicines and active pharmaceutical ingredients since they exhibit antimicrobial, antiviral, antifungal, and antioxidant activities [6, 7]. In this way, development of new low-toxic drugs based on 1,2,4-triazole derivatives with wide array of biological activities is a promising direction in research [8, 9].

The analysis of current literature rendered us to focus on bis-1,2,4-triazoles, which can encompass several active pharmacophore parts. The combination of two 1,2,4-triazole cycles increases the entire reactivity of the molecule due to active site doubling, as well as it positively affects the variability in substance modeling, which may contain diverse substituents. The purpose of our work was to synthesize new alkyl derivatives of 4-ethyl-5-(((3-(pyridin-4-yl)-1*H*-1,2,4-triazol-5-yl)thio)methyl)-4*H*-1,2,4-triazole-3-thiol (**1**) and study some of their physicochemical properties.

EXPERIMENTAL

Reagents

The starting compound 4-ethyl-5-(((3-(pyridin-4-yl)-1*H*-1,2,4-triazol-5-yl)thio)methyl)-4*H*-1,2,4-triazole-3-thiol (**1**) (Fig. 1) was synthesized at the Department of Natural Sciences for Foreign Students and Toxicological Chemistry of Zaporizhzhia State Medical University. Bromomethane (98%), bromoethane (98%), 1-bromopropane (98%), 1-bromobutane (98%), 1-bromopentane (98%), 1-bromohexane (98%), 1-bromoheptane (98%), 1-bromooctane (98%), 1-bromononane (98%) and 1-bromodecane (98%) were obtained from Sigma-Aldrich (Germany). All chemicals and solvents used in the synthesis were of analytical grade.

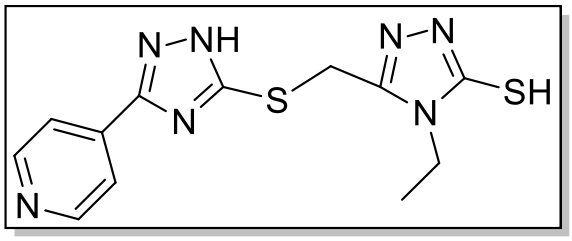

*Fig. 1. Structure of 4-ethyl-5-(((3-(pyridin-4-yl)-1H-1,2,4-triazol-5-yl)thio)methyl)-4H-1,2,4-triazole-3-thiol (**1**)*

Equipment

The identity of 4-(5-((((5-(alkylthio)-4-ethyl-4*H*-1,2,4-triazol-3-yl)methyl)thio)-1*H*-1,2,4-triazol-3-yl)pyridines (**2-11**) has been confirmed by gas chromatography via Agilent 7890B GC system connected with Agilent 5977B mass spectrometry detector (USA). The column used for separation was DB-5ms with the following dimensions: 30 m x 250 μm x 0.25 μm. Carrier gas (helium) flow rate was 2.0 mL/min. Injection volume: 0.5 μL. Flow split was 1:20. Temperature of the injection system was programmed as follows: 300 °C → 10 °C/s → 310 °C. Oven temperature: programmable, with initial temperature of 130 °C (1 minute delay) → 20 °C/min → 250 °C. (delay 5 min). Total time of chromatographic run was 12 min. GS-MS interface was thermostatted at 280 °C; ion source temperature was 230 °C; temperature of quadrupole mass analyzer was 150 °C. Type of ionization: electron impact (EI) with electron energy of 70 eV. Range of scanned mass ratios: 50-500 m/z.

Melting points were determined according to open capillary method using OptiMelt MPA100 apparatus (USA) equipped with platinum RTD sensor and temperature measurement possibility of up to 400 °C and 0.1 °C resolution.

Elemental analysis of the synthesized compounds was afforded using Elementar Vario L cube multipurpose elemental analyzer (CHNS) produced by Analysensysteme GmbH (Germany) using sulfanilamide as the standard.

^{1}H NMR spectra were recorded at 400 MHz and 100 MHz using Varian MR-400 spectrometer with DMSO-d_6 as the solvent. Spectra were processed via ADVASP™ Analyzer software (Umatek International Inc.). Chemical shifts are reported in ppm (δ scale) down field with residual protons of the solvent (DMSO-d_6) present at δ = 2.49 ppm and using a common internal standard.

Chemical synthesis

The derivatives of 4-ethyl-5-(((3-(pyridin-4-yl)-1*H*-1,2,4-triazol-5-yl)thio)methyl)-4*H*-1,2,4-triazole-3-thiol (**1**) were synthesized applying widely known and accepted method described in works [10].

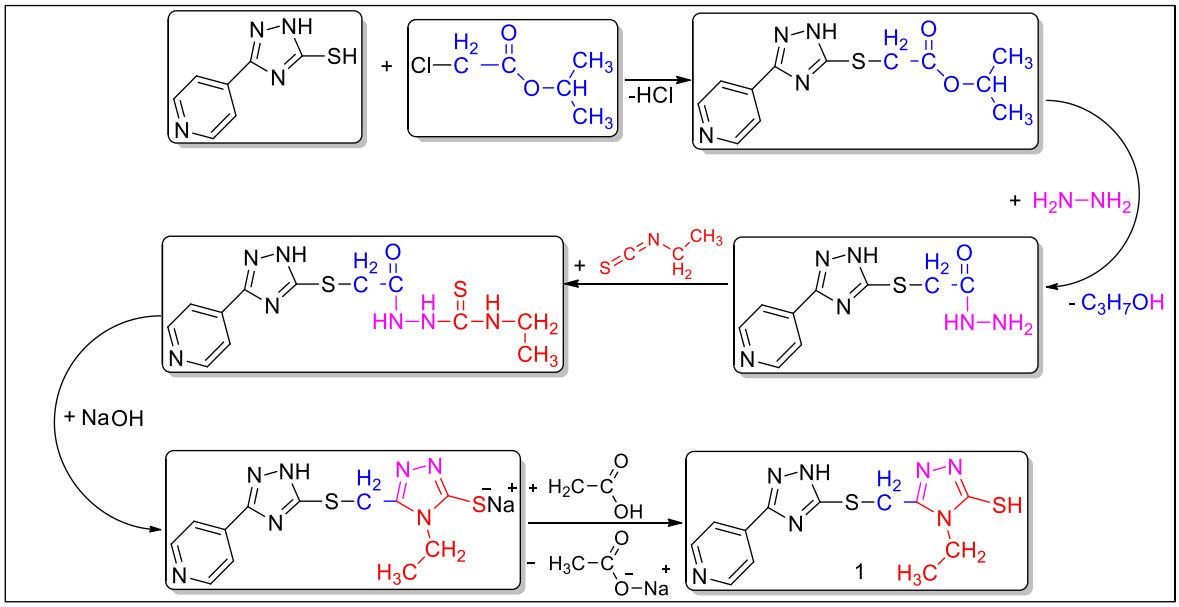

*Fig. 2. Synthesis of 4-ethyl-5-(((3-(pyridin-4-yl)-1H-1,2,4-triazol-5-yl)thio)methyl)-4H-1,2,4-triazole-3-thiols (**1**)*

Physical and chemical characteristics of the starting thiol **1** (Table 1) have been previously described by other authors and, thus, are known [11]. The alkylation of 4-ethyl-5-(((3-(pyridin-4-yl)-1*H*-1,2,4-triazol-5-yl)thio)methyl)-4*H*-1,2,4-triazole-3-thiol (**1**) was conducted using the corresponding bromoalkanes in isopropanol medium with an addition of equivalent amount of KOH. This afforded a series of new derivatives (Fig. 3).

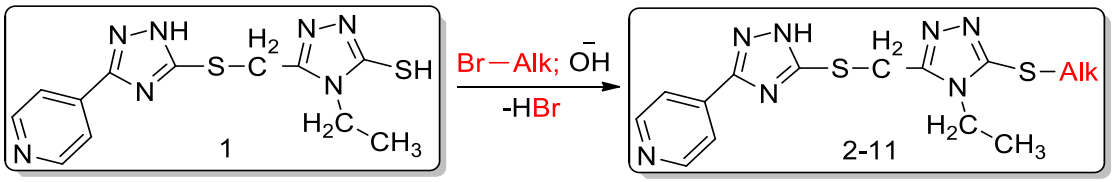

*Fig. 3. Synthesis of 4-(5-((((5-(alkylthio)-4-ethyl-4H-1,2,4-triazol-3-yl)methyl)thio)-1H-1,2,4-triazol-3-s)pyridines (**2-11**).*

The synthesized compounds appear as light red crystalline substances, which are soluble in water (**2-6**) and organic solvents (**2-11**). For analytical purposes, the obtained compounds were purified via recrystallization from methanol.

General procedure for the synthesis of compounds 2-11

The next step in our work was to obtain the series of 4-(5-(((5-(alkylthio)-4-methyl-4H-1,2,4-triazol-3-yl)methyl)thio)-1H-1,2,4triazol-3-yl)pyridine derivatives. A number of the corresponding bromoalkanes were used as alkylating agents (Scheme 2). The reaction was carried out according to the widely known method described in the previous works [11]. A mixture of sodium hydroxide (0.01 mol, 0.40 g) and 4-methyl-5-(((3-(pyridin-4-yl)-1H-1,2,4-triazol-5-yl)thio)methyl)-4H-1,2,4-triazole-3-thiol (0.01 mol, 3,05 g) in methanol was heated until the solid was dissolved and after this add bromomethane (0.01 mol, 0.95 g). After cooling the residue was filtered, dried and recrystallized from water-methanol (1:1).

RESULTS AND DISCUSSION

Structures of the synthesized compounds were confirmed using a set of appropriate physical and instrumental methods of analysis. Identity and fragmentation of the compounds were studied by GC-MS. Physicochemical parameters of the obtained compounds **2-11** are given in Table 1.

Table 1.

Physicochemical properties of the synthesized compounds

Compd.	Alk	Molecular formula	M.W.	mp (°C)	Yield (%)	Elemental analysis: calc. (found)			
						C	H	N	S
1	-	$C_{12}H_{13}N_7S_2$	319.41	199–201	80	45.12 (45.23)	4.10 (4.06)	30.70 (30.72)	20.08 (19.96)
2	CH_3	$C_{13}H_{15}N_7S_2$	333.43	189–191	82	46.83 (46.75)	4.53 (4.56)	29.41 (29.20)	19.23 (19.19)
3	C_2H_5	$C_{14}H_{17}N_7S_2$	347.46	186-188	78	48.39 (48.61)	4.93 (4.79)	28.22 (28.39)	18.46 (18.30)
4	C_3H_7	$C_{15}H_{19}N_7S_2$	361.49	205-207	76	49.84 (49.90)	5.30 (5.19)	27.12 (27.07)	17.74 (17.54)
5	C_4H_9	$C_{16}H_{21}N_7S_2$	375.51	197-199	89	51.18 (51.31)	5.64 (5.92)	26.11 (25.79)	17.08 (16.81)
6	C_5H_{11}	$C_{17}H_{23}N_7S_2$	389.54	111-113	81	52.42 (52.39)	5.95 (5.85)	25.17 (25.22)	16.46 (16.59)
7	C_6H_{13}	$C_{18}H_{25}N_7S_2$	403.57	205-207	86	53.57 (53.47)	6.24 (6.29)	24.30 (24.41)	15.89 (15.88)
8	C_7H_{15}	$C_{19}H_{27}N_7S_2$	417.59	176-178	72	54.65 (54.50)	6.52 (6.57)	23.48 (23.31)	15.36 (15.60)
9	C_8H_{17}	$C_{20}H_{29}N_7S_2$	431.19	208-210	79	55.65 (55.49)	6.77 (6.88)	22.72 (22.78)	14.86 (14.74)
10	C_9H_{19}	$C_{21}H_{31}N_7S_2$	445.65	169-171	86	56.60 (56.36)	7.01 (7.12)	22.00 (22.22)	14.39 (14.25)
11	$C_{10}H_{21}$	$C_{22}H_{33}N_7S_2$	459.68	192–194	73	57.48 (57.46)	7.24 (7.32)	21.33 (21.12)	13.95 (14.98)

After establishing the melting points and elemental composition, the next step was GC-MS analysis of the synthesized compounds. Main chromatographic parameters were obtained, including retention times, peak areas, and mass-to-charge ratios. Hard ionization conditions produced pseudo-molecular peaks of the corresponding compounds with mass-to-charge ratios lower by one point. The most suitable explanation for this is that molecules lost one hydrogen atom during the ionization. Mass spectrum of 4-ethyl-5-(((3-(pyridin-4-yl)-1*H*-1,2,4-triazol-5-yl)thio)methyl)-4*H*-1,2,4-triazole-3-thiol (**1**) is characterized by the presence of a very weak molecular peak at 318 m/z (fig. 4).

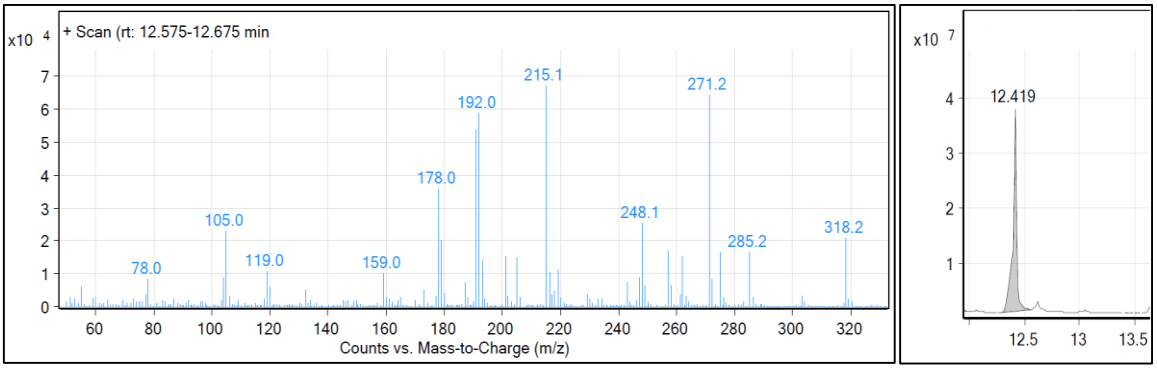

*Fig 4. Chromatographic and mass spectrometric parameters of 4-ethyl-5-(((3-(pyridin-4-yl)-1H-1,2,4-triazol-5-yl)thio)methyl)-4H-1,2,4-triazole-3-thiol (**1**)*

Application of EI yields spectra rich in fragment ions, which allowed for unambiguous identification of the starting thiol compound (**1**). Main ionization pathways for 4-ethyl-5-(((3-(pyridin-4-yl)-1*H*-1,2,4-triazol-5-yl)thio)methyl)-4*H*-1,2,4-triazole-3-thiols (**1**) include loss of thiol group, breakage of S-methyl bond bridging two 1,2,4-triazole cycles together, detachment of ethyl (-CH_2-CH_3) substituent, loss of pyridine ring, and opening of the two 1,2,4-triazole rings (Fig. 5). A similar fragmentation path was introduced by scientists from Iran [12].

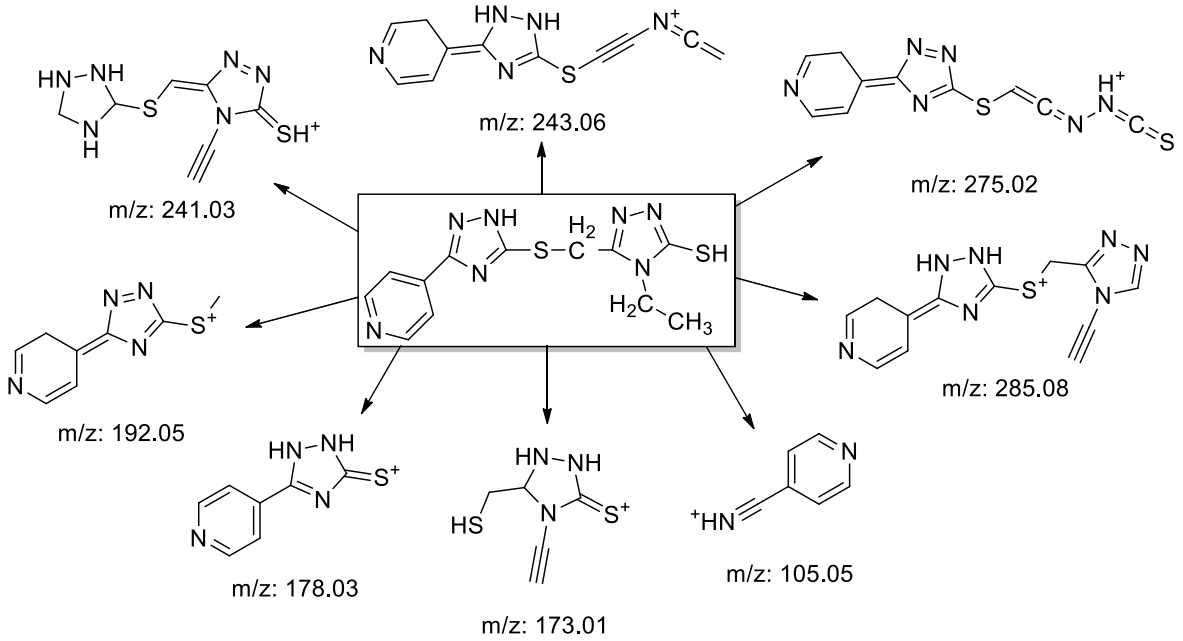

*Fig 5. Mass spectrometric fragmentation pattern of 4-ethyl-5-(((3-(pyridin-4-yl)-1H-1,2,4-triazol-5-yl)thio)methyl)-4H-1,2,4-triazole-3-thiol (**1**)*

According to the observed mass-spectrometric behavior of the compound investigated under hard ionization conditions, it is safe to say that this compound is congruent with 4-ethyl-5-(((3-(pyridin-4-yl)-1*H*-1,2,4-triazol-5-yl)thio)methyl)-4*H*-1,2,4-triazole-3-thiol (**1**) structural characteristics.

The studied behavior of the S-substituted alkyls under GC-MS conditions is very similar with respect to each other, and hence only compound 4-(5-((((5-(butylthio)-4-ethyl-4*H*-1,2,4-triazol-3-yl)methyl)thio)-1*H*-1,2,4-triazol-3-s)pyridine (**5**) was selected to illustrate the properties of the entire set (Fig. 6).

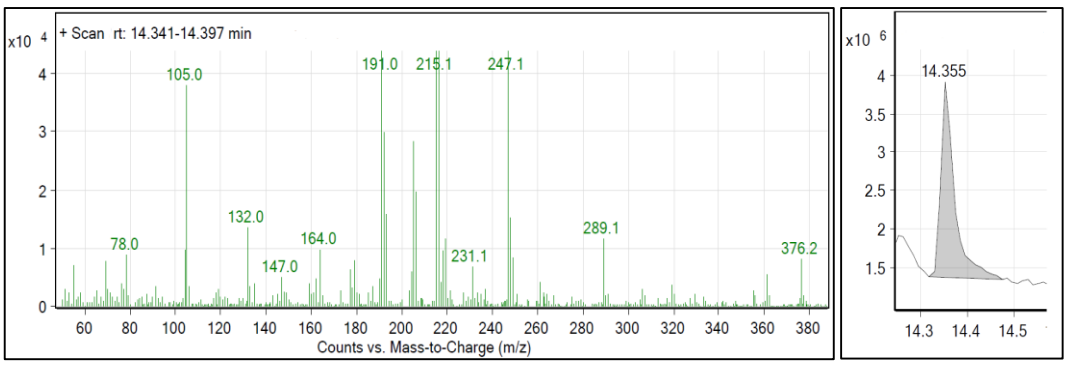

*Fig. 6. Chromatographic and mass spectrometric parameters of 4-(5-(((4-ethyl-5-butyllthio)-4H-1,2,4-triazol-3-yl)methyl)thio)-1H-1,2,4-triazol-3-yl)pyridine (**5**).*

Elongation of the alkyl chain leads to decrease in polarity of the molecules, but, in spite of this fact, retention times of compounds of higher molecular weight, using nonpolar stationary phase, are growing. It leads to the conclusion that the main effect that causes increase in retention time is gain in molecular weight despite the slight decrease in polarity. The fragmentation of the 4-(5-(((4-ethyl-5-butyllthio)-4*H*-1,2,4-triazol-3-yl)methyl)thio)-1*H*-1,2,4-triazol-3-yl)pyridine (**5**) is similar to the fragmentation of 4-ethyl-5-(((3-(pyridin-4-yl)-1*H*-1,2,4-triazol-5-yl)thio)methyl)-4*H*-1,2,4-triazole-3-thiol (**1**) (Fig. 7).

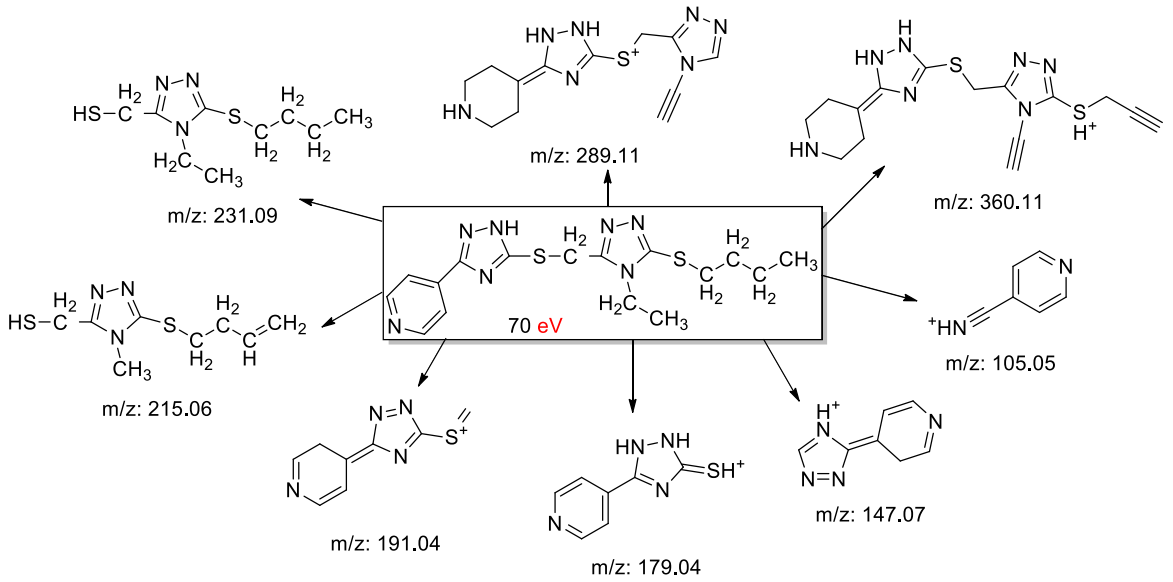

*Fig. 7. Mass spectrometric fragmentation pattern of 4-(5-(((4-ethyl-5-butyllthio)-4H-1,2,4-triazol-3-yl)methyl)thio)-1H-1,2,4-triazol-3-yl)pyridine (**5**).*

Mass spectrometric fragmentation of 4-(5-(((4-ethyl-5-(pentylthio)-4*H*-1,2,4-triazol-3-yl)methyl)thio)-1*H*-1,2,4-triazol-3-yl)pyridine (**6**) is rather similar to the fragmentation pathway demonstrated for 4-(5-(((4-ethyl-5-butyllthio)-4*H*-1,2,4-triazol-3-yl)methyl)thio)-1*H*-1,2,4-triazol-3-yl)pyridine (**5**) (Fig. 7). The only difference between **6** and **5** in the fragmentation is the shortening of the alkyl substituent by one methylene (-CH_2-) group. This applies to all synthesized compounds that are homologous having in mind the alkyl chain.

The ^{1}H NMR spectra of the compounds are characterized by the presence of a singlet in high field in the region of 4.47-4.55 ppm (Fig. 8, the ^{1}H NMR spectrum of compound **8** is geven), which corresponds to the ethylene linker. Particular note is the spin-spin interaction constant for carbon atoms – 10 - 11 in the pyridine ring, so it is significantly reduced, which indicates the acceptor effect of 1,2,4-triazole ring. The protons of the methylene groups in the alkyl moiety resonate as a two-proton triplet at 3.10 ppm and a multiplet at 0.78-1.22 ppm. The ethyl substituent at the second 1,2,4-triazole ring is registered at 4.49 ppm, in a stronger field than the S-methyl radical due to the manifestation of the acceptor effect of 1,2,4-triazole.

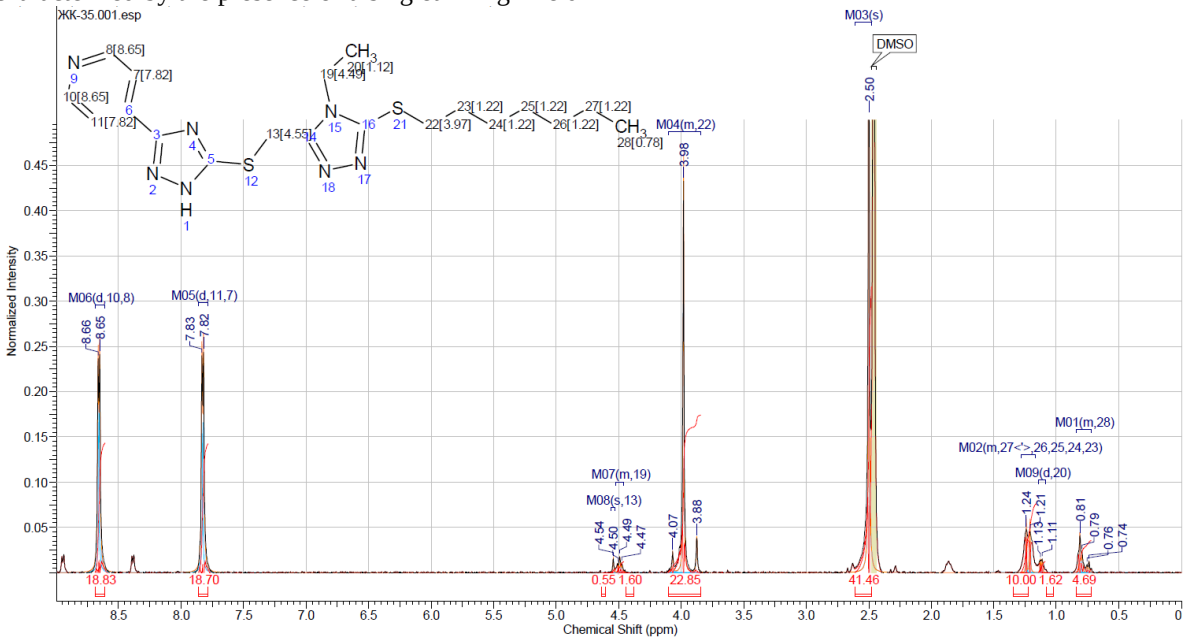

*Fig. 8. ^{1}H NMR spectra of 4-(5-(((4-ethyl-5-(heptylthio)-4H-1,2,4-triazol-3-yl)methyl)thio)-1H-1,2,4-triazol-3-yl)pyridine (**8**)*

4-ethyl-5-(((3-(pyridin-4-yl)-1H-1,2,4-triazol-5-yl)thio)methyl)-4H-1,2,4-triazole-3-thiol (1)

White powder, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.24 (t, J=7.03 Hz, 3 H) 3.32 (br. s., 2 H) 4.20 (q, J=7.03 Hz, 2 H) 7.27 (t, J=4.27 Hz, 1 H) 7.68 (d, J=3.51 Hz, 1 H) 7.86 (d, J=5.02 Hz, 1 H) 13.96 (br. s., 2 H)

4-(5-(((4-ethyl-5-(methylthio)-4H-1,2,4-triazol-3-yl)methyl)thio)-1H-1,2,4-triazol-3-yl)pyridine

Red powder, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.18 - 1.20 (m, 3 H) 2.53 (br. s., 3 H) 3.69 (s, 2 H) 4.16 - 4.32 (m, 2 H) 7.82 (d, J=5.02 Hz, 2 H) 8.60 (d, J=5.02 Hz, 2 H)

4-(5-(((4-ethyl-5-(ethylthio)-4H-1,2,4-triazol-3-yl)methyl)thio)-1H-1,2,4-triazol-3-yl)pyridine

Red powder, ^{1}H NMR: (400 MHz, DMSO-d_6) δ 1.09 (t, J = 7.1 Hz, 3H,), 1.36 (t, J = 7.1 Hz, 3H), 3.17 (q, J = 7.1 Hz, 2H), 3.90 (q, J = 7.1 Hz, 2H), 4.46 (s 2H), 7.66 (ddd, J = 5.2, 2.7, 0.4 Hz, 2H), 8.62 (ddd, J = 5.2, 1.8, 0.4 Hz, 2H).

4-(5-(((4-methyl-5-(propylthio)-4H-1,2,4-triazol-3-yl)methyl)thio)-1H-1,2,4-triazol-3-yl)pyridine

Red powder, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.77 - 0.89 (m, 3 H) 1.10 - 1.22 (m, 3 H) 1.87 (q, J=7.03 Hz, 2 H) 3.71 (s, 2 H) 3.95 - 4.05 (m, 2 H) 4.40 (t, J=7.03 Hz, 2 H) 7.83 (d, J=5.02 Hz, 2 H) 8.59 (d, J=5.00 Hz, 2 H)

4-(5-(((4-ethyl-5-(butylthio)-4H-1,2,4-triazol-3-yl)methyl)thio)-1H-1,2,4-triazol-3-yl)pyridine

Red powder, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.88 (t, J=6.50 Hz, 3 H) 1.26 (t, J=7.50 Hz, 3 H) 1.81 - 1.88 (m, 2 H) 2.63 (br. s., 2 H) 3.78 (s, 2 H) 3.92 (s, 2 H) 4.45 - 4.50 (m, 2 H) 7.83 (d, J=4.50 Hz, 2 H) 8.65 (d, J=4.50 Hz, 2 H)

4-(5-(((4-ethyl-5-(pentylthio)-4H-1,2,4-triazol-3-yl)methyl)thio)-1H-1,2,4-triazol-3-yl)pyridine

Red powder, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.72 - 0.85 (m, 3 H) 1.10 - 1.32 (m, 8 H) 1.81 - 1.89 (m, 3 H) 3.69 (s, 2 H) 4.38 - 4.45 (m, 2 H) 7.82 (d, J=4.52 Hz, 2 H) 8.59 (d, J=4.52 Hz, 2 H)

4-(5-(((4-ethyl-5-(hexylthio)-4H-1,2,4-triazol-3-yl)methyl)thio)-1H-1,2,4-triazol-3-yl)pyridine

Red powder, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.73 - 0.87 (m, 3 H) 1.09 - 1.33 (m, 10 H) 1.83 - 1.95 (m, 3 H) 4.49 (t, J=7.03 Hz, 2 H) 4.56 (s, 2 H) 7.87 (d, J=5.52 Hz, 2 H) 8.65 (d, J=5.52 Hz, 2 H)

4-(5-(((4-ethyl-5-(heptylthio)-4H-1,2,4-triazol-3-yl)methyl)thio)-1H-1,2,4-triazol-3-yl)pyridine

Red powder, ^{1}H 1H NMR (400 MHz, DMSO-d_6) δ ppm 0.72 - 0.84 (m, 3 H) 1.12 (d, J=5.02 Hz, 3 H) 1.16 - 1.28 (m, 10 H) 3.84 - 4.10 (m, 2 H) 4.46 - 4.52 (m, 2 H) 4.54 (s, 2 H) 7.83 (d, J=5.52 Hz, 2 H) 8.66 (d, J=5.02 Hz, 2 H) (The deleted signal at 2.50 belongs to DMSO-d_6)

4-(5-(((4-ethyl-5-(octylthio)-4H-1,2,4-triazol-3-yl)methyl)thio)-1H-1,2,4-triazol-3-yl)pyridine

Red powder, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.76 - 0.83 (m, 3 H) 0.98 - 1.05 (m, 3 H) 1.13 - 1.27 (m, 12 H) 1.85 (d, J=8.53 Hz, 2 H) 3.70 (s, 2 H) 4.43 (t, J=7.03 Hz, 2 H) 7.82 (d, J=5.02 Hz, 2 H) 8.59 (d, J=5.02 Hz, 2 H)

4-(5-(((4-ethyl-5-(nonylthio)-4H-1,2,4-triazol-3-yl)methyl)thio)-1H-1,2,4-triazol-3-yl)pyridine

Red powder, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.79 (t, J=7.00 Hz, 3 H) 1.16 - 1.25 (m, 14 H) 1.82 - 1.88 (m, 2 H) 3.71 - 3.85 (m, 2 H) 4.42 - 4.49 (m, 2 H) 4.53 (s, 3 H) 7.83 (d, J=5.02 Hz, 2 H) 8.62 (d, J=5.02 Hz, 2 H)

4-(5-(((4-ethyl-5-(decylthio)-4H-1,2,4-triazol-3-yl)methyl)thio)-1H-1,2,4-triazol-3-yl)pyridine

Red powder, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.77 - 0.83 (m, 3 H) 1.10 - 1.30 (m, 17 H) 1.83 - 1.90 (m, 2 H) 3.16 - 3.21 (m, 2 H) 3.70 (s, 2 H) 4.44 (t, J=7.03 Hz, 2 H) 7.82 (d, J=5.02 Hz, 2 H) 8.60 (d, J=5.02 Hz, 2 H)

Conclusions

Nucleophilic substitution reaction of 4-ethyl-5-(((3-(pyridin-4-yl)-1*H*-1,2,4-triazol-5-yl)thio)methyl)-4*H*-1,2,4-triazole-3-thiol (**1**) was studied using a set of bromoalkanes as alkylation agents, which yielded new 4-(5-((((5-(alkylthio)-4-ethyl-4*H*-1,2,4-triazol-3-yl)methyl)thio)-1*H*-1,2,4-triazol-3-yl)pyridines (**2-11**). Structures of the synthesized compounds were confirmed using appropriate instrumental methods of analysis, while the identity of compounds was scrutinized using GC-MS.

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