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Research Article

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Synthesis, physical and chemical properties of new esters of 2-((4-R-3-R_1-1,2,4-triazole-5-yl)thio)acetic acids

R. O. Shcherbyna[a*], E. S. Pruglo[b], O. I. Panasenko[a] and Ye. H. Knysh[c]

[a]Department of Toxicology and Inorganic Chemistry, Zaporozhye State Medical University, Zaporozhye, Zaporozhye State, Ukraine
[b]Department of Clinical Pharmacy, Pharmacotherapy and MFE of FPE, Zaporozhye State Medical University, Zaporozhye, Zaporozhye State, Ukraine
[c]Department of Management and Pharmacy Economics, Medical and Pharmaceutical Commodity Research, Zaporozhye State Medical University, Zaporozhye, Zaporozhye State, Ukraine

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ABSTRACT

In order to create new biologically active compounds among 4-R-3-R_1-1,2,4-triazole-5-thioles preparative synthesis methods of esters of 2-((4-R-3-R_1-1,2,4-triazole-5yl)thio)acetic acids were offered, the structure of which is confirmed with ^{1}H NMR-spectroscopy, chromatography-mass spectrometry and elemental analysis

Key words: 1,2,4-triazoles, synthesis, physical and chemical properties.

INTRODUCTION

Now days medicine and pharmacy require new and effective drugs. Derivative of 1,2,4-triazoles occupy a special place among the wide variety of active organic compounds. This interest is caused with quite high biological activity data derived [3, 5, 6], low toxicity [10] and accessibility in synthesis. Thus, derivative of 1,2,4-triazoles [1, 4] are known and active used in medicine. It is important to say, that a large number of scientists synthetics paid more attention to this heterocyclic system [5, 6, 10]. However, there are a lot information in literature dedicated to derivative of 1,2,4-tiazoles just esters of 2-((4-R-3-R_1-1,2,4-triazole-5yl)thio) acetic acids are not investigated. However, esters of acids have high biological activity [5, 6] and in addition can be intermediate product for the synthesis of amides, hydrazides, benzylidenhydrazides of acids.

Therefore, the main aim of this work is the synthesis of new esters of 2-((4-R-3-R_1-1,2,4-Triazole-5yl)thio) acetic acids and establishing their physical and chemical parameters for subsequent biological research.

EXPERIMENTAL SECTION

Materials and methods.. The melting point is defined the open capillary method on the OptiMelt MPA100 device (US production). The elemental composition of synthesized compounds was established in the universal analyzer Elementar Vario L cube (CHNS) (standard - sulfonamides). The ^{1}H NMR spectra were obtained on a Varian Mercury VX-200 (1H, 200 MHz) in dimethyl-d6 sulfoxide with tetramethylsilane as the internal standard and analyzed with ADVASP(tm) Analyzer program (Umatek International Inc.) [2]. Chromatography-mass spectral studies were carried out on the gas-liquid chromatograph Agilent 1260 Infinity HPLC with mass spectrometer Agilent 6120 (ionization in electro-sprey (ESI) [9].

RESULTS AND DISCUSSION

We have obtained esters of 2-((4-R-3-R_1-1,2,4-triazole-5yl)thio)acetic acids in two ways. The first method involves the interaction of previously synthesized 4-R-3-R_1-1,2,4-triazole-5-thioles (1.1-1.12) [7, 8] with the corresponding esters of 2-chloroacetic acid in the presence of equivalent amount of sodium hydroxide. The second method involves the etherification of 2-((4-R-3-R_1-1,2,4-triazole-5yl)thio)acetic acids (2.1-2.12) [7] with methyl, ethyl, i-propyl, n-propyl and n-butyl alcohol in the presence of a catalytic amount of concentrated sulfuric acid (fig. 1). 3.1-3.29 compounds obtained with different methods do not give melting point depression. It should be noted that the practical yield of the reaction of the method B is higher in comparison with the meyhod A (fig. 1).

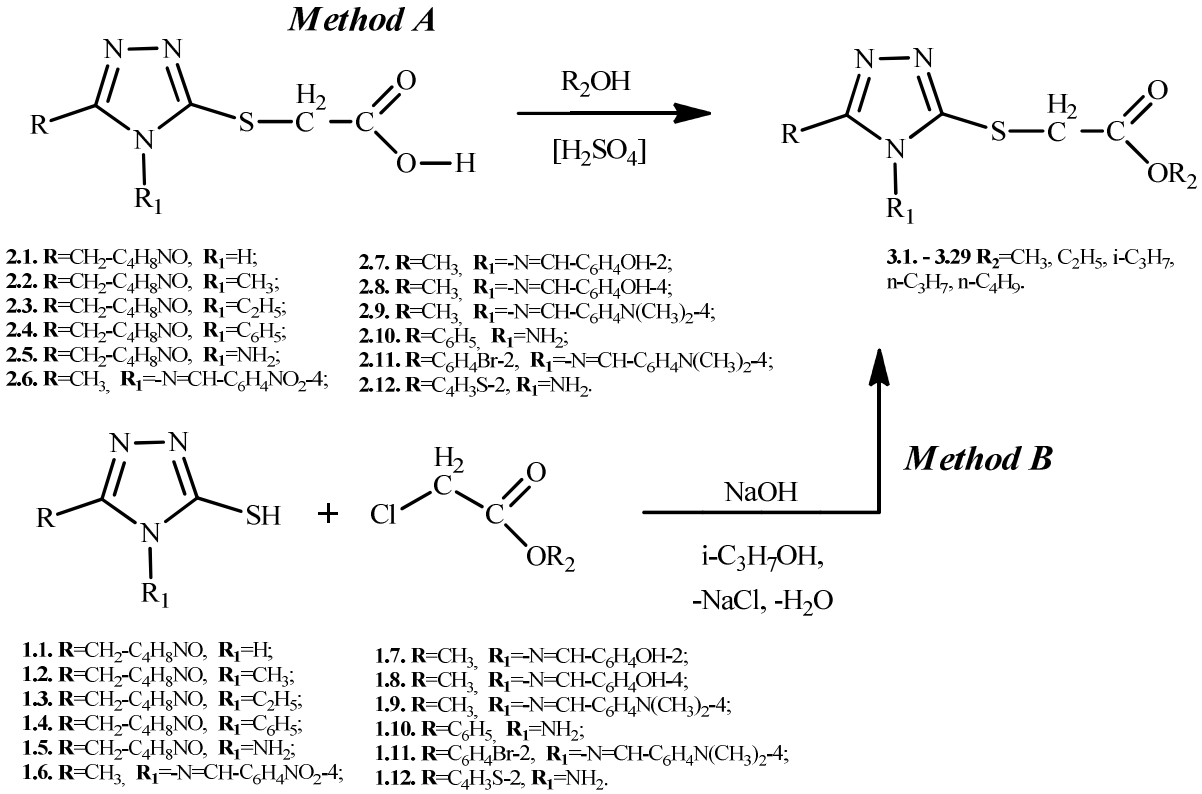


Figure1 Scheme of synthesis of 2-((4-R-3-R_1-1,2,4-triazole-5yl)thio)acetic acids

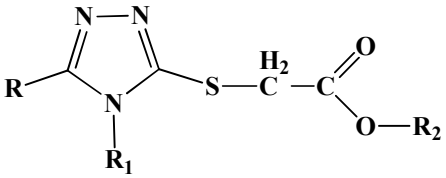
General procedure for the preparations esters of 2-((4-R-3-R_1-1,2,4-triazole-5yl)thio)acetic acids (3.1-3.29)

Method A. A mixture of 0,01 mol of 2-((4-R-3-R_1-1,2,4-triazole-5yl)thio)acetic acid (2.1-2.12) in 30 ml of the appropriate alcohol (methyl, ethyl, i-propyl, n-propyl and n-butyl) and 0,5 ml of concentrated sulfuric acid is boiled for 10 hours, the solvent was evaporated, the residue was neutralised with sodium bicarbonate, filtered and dried.

Method B. To a solution of 0,01 mol of NaOH in 5 ml of water and 50 ml i-propanol was added 0,01 mole of 4-R-3-R_1-1,2,4-triazole-5-thiole (1.1-1.12) and 0,01 mole of corresponding ester 2-chloroacetic acid (methyl, ethyl, i-propyl, n-propyl and n-butyl), boiled to a neutral environment for 3 hr., filtered, the solvent was evaporated.

In connection with difficulties in the selection of compounds 3.2, 3.6, 3.7, 3.10-3.12, 3.15, 3.16, they were obtained as hydrochloride. Esters of 2-((4-R-3-R_1-1,2,4-triazole-5yl)thio)acetic acids are crystalline (3.1-3.18, 3.20, 3.22-3.25, 3.27-3.29) or amorphous (3.19, 3.21, 3.26) soluble substances (3.2, 3.6, 3.7, 3.10-3.12, 3.15, 3.16), or sparingly soluble (3.1, 3.3-3.5, 3.8, 3.9, 3.13, 3.14, 3.17-3.29) in water, у воді, carbonates solutions of alkali metal and alkali, soluble in organic solvents. To analyze the esters of 2-((4-R-3-R_1-1,2,4-triazole-5yl)thio)acetic acids (3.1-3.3, 3.6, 3.28, 3.29), purified by recrystallization from methanol, compounds (3.4, 3.5, 3.7-3.9, 3.14, 3.15, 3.17-3.20, 3.22, 3.26, 3.27) recrystallized from i-propanol, substance (3.10-3.12, 3.16, 3.21, 3.23, 3.24) from n-butanol. The synthesized compound 3.13 recrystallized from diethyl ester, and the substance 3.25 from mixture i-propanol:water 1:1.

Table 1 Esters of 2-((4-R-3-R_1-1,2,4-triazole-5yl)thio)acetic acids



Compound	R	R_1	R_2	M.p. (°C)	Molecular formula	Yield (%)
3.1	$-CH_2-C_4H_8NO$	$-CH_3$	$-CH_3$	76-78	$C_{11}H_{18}N_4O_3S$	81
3.2	$-CH_2-C_4H_8NO$	$-C_2H_5$	$-CH_3$	151-153	$C_{12}H_{21}ClN_4O_3S$*	84
3.3	$-CH_2-C_4H_8NO$	$-C_6H_5$	$-CH_3$	77-79	$C_{16}H_{20}N_4O_3S$	88
3.4	$-CH_2-C_4H_8NO$	$-NH_2$	$-CH_3$	191-193	$C_{10}H_{17}N_5O_3S$	81
3.5	$-CH_2-C_4H_8NO$	$-CH_3$	$-C_2H_5$	102-104	$C_{12}H_{20}N_4O_3S$	79
3.6	$-CH_2-C_4H_8NO$	$-C_2H_5$	$-C_2H_5$	152-154	$C_{13}H_{23}ClN_4O_3S$*	85
3.7	$-CH_2-C_4H_8NO$	$-C_6H_5$	$-C_2H_5$	156-158	$C_{17}H_{23}ClN_4O_3S$*	92
3.8	$-CH_2-C_4H_8NO$	$-NH_2$	$-C_2H_5$	150-152	$C_{11}H_{19}N_5O_3S$	94
3.9	$-CH_2-C_4H_8NO$	$-CH_3$	$-C_3H_7$-n	98-100	$C_{13}H_{22}N_4O_3S$	90
3.10	$-CH_2-C_4H_8NO$	$-C_2H_5$	$-C_3H_7$-n	134-136	$C_{14}H_{25}ClN_4O_3S$*	87
3.11	$-CH_2-C_4H_8NO$	$-C_6H_5$	$-C_3H_7$-n	139-141	$C_{18}H_{25}ClN_4O_3S$*	83
3.12	$-CH_2-C_4H_8NO$	$-NH_2$	$-C_3H_7$-n	173-175	$C_{12}H_{22}ClN_5O_3S$*	83
3.13	$-CH_2-C_4H_8NO$	H	$-C_3H_7$-i	93-95	$C_{12}H_{20}N_4O_3S$	88
3.14	$-CH_2-C_4H_8NO$	$-CH_3$	$-C_3H_7$-i	125-127	$C_{13}H_{22}N_4O_3S$	91
3.15	$-CH_2-C_4H_8NO$	$-C_2H_5$	$-C_3H_7$-i	230-232	$C_{14}H_{25}ClN_4O_3S$*	87
3.16	$-CH_2-C_4H_8NO$	$-C_6H_5$	$-C_3H_7$-i	246-248	$C_{18}H_{25}ClN_4O_3S$*	88
3.17	$-CH_2-C_4H_8NO$	$-NH_2$	$-C_3H_7$-i	185-187	$C_{12}H_{21}N_5O_3S$	93
3.18	$-CH_3$	$-N=CH-C_6H_4NO_2$-4	$-C_3H_7$-i	202-204	$C_{15}H_{17}N_5O_4S$	88
3.19	$-CH_3$	$-N=CH-C_6H_4OH$-2	$-C_2H_5$	217-219	$C_{15}H_{18}N_4O_3S$	91
3.20	$-CH_3$	$-N=CH-C_6H_4OH$-4	$-C_2H_5$	181-183	$C_{15}H_{18}N_4O_3S$	83
3.21	$-CH_3$	$-N=CH-C_6H_4N(CH_3)_2$-4	$-C_2H_5$	223-225	$C_{17}H_{23}N_5O_2S$	89
3.22	$-C_6H_5$	$-NH_2$	$-CH_3$	174-176	$C_{11}H_{12}N_4O_2S$	92
3.23	$-C_6H_5$	$-NH_2$	$-C_3H_7$-i	156-158	$C_{13}H_{16}N_4O_2S$	85
3.24	$-C_6H_5$	$-NH_2$	$-C_3H_7$-n	172-174	$C_{13}H_{16}N_4O_2S$	79
3.25	$-C_6H_4Br$-2	$-N=CH-C_6H_4N(CH_3)_2$-4	$-C_2H_5$	156-158	$C_{21}H_{22}BrN_5O_2S$	90
3.26	C_4H_3S-2	$-NH_2$	$-CH_3$	133-135	$C_9H_{10}N_4O_2S_2$	90
3.27	C_4H_3S-2	$-NH_2$	$-C_3H_7$-i	135-137	$C_{11}H_{14}N_4O_2S_2$	92
3.28	C_4H_3S-2	$-NH_2$	$-C_3H_7$-n	123-125	$C_{11}H_{14}N_4O_2S_2$	86
3.29	C_4H_3S-2	$-NH_2$	$-C_4H_9$-n	113-115	$C_{12}H_{16}N_4O_2S_2$	82

** - compounds which were obtained as hydrochloride.*

The structure of synthesized compounds in all cases confirmed with modern instrumental methods of analysis (^{1}H NMR-spectroscopy, chromatography-mass spectrometry and elemental analysis).

Individual peaks of synthesized substance have established in conducting chromato-mass-spectrometric studies. Theoretical calculations of atomic masses correspond to collected data [9].

^{1}H NMR-spectra of obtained substance show compliance synthesized compounds to specified formulas (table. 2). Thus, the spectrum of the compound of methyl esters 2-((4-methyl-3-(morpholinomethyl)-4H-1,2,4-triazol-5-yl)thio)acetate (3.1) is characterized with proton chemical shifts of two methylen groups as two protons singlets at 4,45 та 4,16 ppm. The protons of methyl group in the ester residue appear as three protons singlet at 3,68 ppm., protons of – CH_3 group of 1,2,4-triazole nucleus resonate in more strong field at 3.20 ppm. Protons of morpholine residue available in the form of common multiplet at 3.41 ppm. It is important, that there are no signals in the spectrum at 12-10 ppm which may indicate the presence of proton of carboxyl groups in the studied compound.

Table 2 Data of chemical shifts of protons in the ^{1}H NMR spectra of esters of 2-((4-R-3-R$_1$-1,2,4-triazole-5yl)thio)acetic acids and their elemental composition (3.1-3.29)

Compound	^{1}H NMR DMSO-d$_6$, δ ppm	Elemental analysis calculated % [found %]			
		C	H	N	S
3.1	4.45 (s, 2H, -CH$_2$-), 4.16 (s, 2H, -CH$_2$-), 3.68 (s, 3H, -CH$_3$) 3.41 (m, 4H, morpholine), 3.20 (s, 3H, -CH$_3$)	46,14 [46,25]	6,34 [6,32]	19,57 [19,61]	11,20 [11,18]
3.2	4.43 (s, 2H, -CH$_2$-), 4.13 (m, 4H, -CH$_2$-), 3.32 (m, 4H, morpholine), 3.17 (s, 3H, -CH$_3$), 1.24 (m, 3H, -CH$_3$)	42,79 [42,89]	6,28 [6,26]	16,63 [16,66]	9,52 [9,50]
3.3	7.46 (m, 5H, -C$_6$H$_5$), 4.32 (s, 2H, -CH$_2$-), 3.78 (s, 3H, -CH$_3$), 3.44 (m, 4H, morpholine), 3.21 (s, 3H, -CH$_3$)	55,16 [55,24]	5,79 [5,83]	16,08 [16,05]	9,20 [9,17]
3.4	5.83 (s, 2H, -NH$_2$), 4.25 (s, 2H, -CH$_2$-), 3.84 (s, 3H, -CH$_3$), 3.31 (m, 4H, morpholine), 3.11 (s, 3H, -CH$_3$)	41,80 [41,94]	5,96 [5,94]	24,37 [24,31]	11,16 [11,17]
3.5	4.43 (s, 2H, -CH$_2$-), 4.29 (s, 2H, -CH$_2$-), 4.12 (m, 2H, -CH$_2$-), 3.71 (s, 3H, -CH$_3$), 3.21 (m, 4H, morpholine), 1.31 (s, 3H, -CH$_3$)	47,98 [48,09]	6,71 [6,70]	18,65 [18,63]	10,67 [10,69]
3.6	4.45 (s, 2H, -CH$_2$-), 4.21 (s, 2H, -CH$_2$-), 4.10 (m, 4H, -CH$_2$-), 3.24 (m, 4H, morpholine), 1.29 (m, 6H, -CH$_3$)	44,50 [44,59]	6,61 [6,63]	15,97 [15,99]	9,14 [9,12]
3.7	7.31 (m, 5H, -C$_6$H$_5$), 4.47 (s, 2H, -CH$_2$-), 4.14 (m, 4H, -CH$_2$-), 3.43 (m, 4H, morpholine), 1.25 (t, 3H, -CH$_3$)	51,19 [51,27]	5,81 [5,82]	14,05 [14,06]	8,04 [8,06]
3.8	5.94 (s, 2H, -NH$_2$), 4.47 (s, 2H, -CH$_2$-), 4.24 (m, 4H, -CH$_2$-), 3.48 (m, 4H, morpholine), 1.31 (t, 3H, -CH$_3$)	43,84 [43,94]	6,35 [6,34]	23,24 [23,23]	10,64 [10,67]
3.9	4.43 (s, 2H, -CH$_2$-),4.15 (m, 4H, -CH$_2$-), 3.54 (m, 4H, morpholine), 3.38 (s, 3H, -CH$_3$), 1.19 (m, 2H, -CH$_2$-), 0.99 (t, 3H, -CH$_3$)	49,66 [49,84]	7,05 [7,03]	17,82 [18,84]	10,20 [10,22]
3.10	4.48 (s, 2H, -CH$_2$-), 4.20 (m, 4H, -CH$_2$-), 3.58 (m, 4H, morpholine), 1.74 (m, 2H, -CH$_2$-), 1.24 (t, 3H, -CH$_3$), 0.97 (t, 3H, -CH$_3$)	51,20 [51,29]	7,37 [7,38]	17,06 [17,03]	9,76 [9,74]
3.11	7.41 (m, 5H, -C$_6$H$_5$), 4.44 (s, 2H, -CH$_2$-), 4.19 (m, 4H, -CH$_2$-), 3.72 (m, 4H, morpholine), 1.42 (t, 3H, -CH$_3$), 1,01 (t, 3H, -CH$_3$)	52,36 [52,43]	6,10 [6,12]	13,57 [13,60]	7,77 [7,75]
3.12	5.76 (s, 2H, -NH$_2$), 4.51 (s, 2H, -CH$_2$-), 4.13 (m, 4H, -CH$_2$-), 3.82 (m, 4H, morpholine), 1.54 (m, 2H, -CH$_2$-), 1,07 (t, 3H, -CH$_3$)	40,96 [41,05]	6,30 [6,31]	19,90 [19,93]	9,11 [9,09]
3.13	12.93 (s, 1H, NH-triazole), 4.93 (m, 1H, -CH-), 4.41 (s, 2H, -CH$_2$-), 4.25 (s, 2H, -CH$_2$-), 3.70 (m, 4H, morpholine), 1,32 (d, 6H, -CH$_3$)	47,98 [48,07]	6,71 [6,72]	18,65 [18,67]	10,67 [10,69]
3.14	4.87 (m, 1H, -CH-), 4.36 (s, 2H, -CH$_2$-), 4.19 (s, 2H, -CH$_2$-), 4,03 (s, 3H, -CH$_3$), 3.72 (m, 4H, morpholine), 1,29 (d, 6H, -CH$_3$)	49,66 [49,74]	7,05 [7,04]	17,82 [17,86]	10,20 [10,17]
3.15	4.83 (m, 1H, -CH-), 4.34 (s, 2H, -CH$_2$-), 4.12 (m, 4H, -CH$_2$-), 3.69 (m, 4H, morpholine), 1,33 (d, 6H, -CH$_3$), 1,28 (t, 3H, -CH$_3$)	46,08 [46,13]	6,91 [6,92]	15,35 [15,37]	8,79 [8,81]
3.16	7.58 (m, 5H, -C$_6$H$_5$), 4.88 (m, 1H, -CH-), 4.32 (s, 2H, -CH$_2$-), 4.24 (s, 2H, -CH$_2$-), 4.09 (s, 2H, -CH$_2$-), 3.65 (m, 4H, morpholine), 1,39 (d, 6H, -CH$_3$)	52,36 [52,43]	6,10 [6,11]	13,57 [13,59]	7,77 7,79
3.17	5.73 (s, 2H, -NH$_2$), 4.92 (m, 1H, -CH-), 4.35 (s, 2H, -CH$_2$-), 4.21 (s, 2H, -CH$_2$-), 3.74 (m, 4H, morpholine), 1,39 (d, 6H, -CH$_3$)	45,70 [45,82]	6,71 [6,69]	22,21 [22,18]	10,17 [10,15]
3.18	9.95 (s, 1H, -N=CH-), 8.24 (m, 4H, -C$_6$H$_4$), 4.95(m, 1H, -CH-), 4.45 (s, 2H, -CH$_2$-), 2,41 (s, 3H, -CH$_3$), 1,33 (d, 6H, -CH$_3$)	49,58 [49,63]	4,72 [4,70]	19,27 [19,25]	8,82 [8,84]
3.19	9.89 (s, 1H, -N=CH-), 8.33 (m, 4H, -C$_6$H$_4$), 5.31 (s, 1H, -OH), 4.84(m, 1H, -CH-), 4.16 (s, 2H, -CH$_2$-), 2,45 (s, 3H, -CH$_3$), 1,42 (d, 6H, -CH$_3$)	53,88 [53,95]	5,43 [5,44]	16,75 [16,78]	9,59 [9,62]
3.20	9.85 (s, 1H, -N=CH-), 8.35 (m, 4H, -C$_6$H$_4$), 5.35 (s, 1H, -OH), 4.83(m, 1H, -CH-), 4.19 (s, 2H, -CH$_2$-), 2,40 (s, 3H, -CH$_3$), 1,49 (d, 6H, -CH$_3$)	53,88 [53,96]	5,43 [5,44]	16,75 [16,79]	9,59 [9,61]
3.21	9.92 (s, 1H, -N=CH-), 8.29 (m, 4H, -C$_6$H$_4$), 4.91(m, 1H, -CH-), 4.22 (s, 2H, -CH$_2$-), 3,02 (s, 6H, N-(CH$_3$)$_2$), 2,49 (s, 3H, -CH$_3$), 1,39 (d, 6H, -CH$_3$)	56,49 [56,55]	6,41 [6,42]	19,38 [19,40]	8,87 [8,89]
3.22	8.15 (m, 5H, -C$_6$H$_5$), 5.79 (s, 2H, -NH$_2$), 4.24 (s, 2H, -CH$_2$-), 3,49 (s, 3H, -CH$_3$)	49,99 [50,06]	4,58 [4,57]	21,20 [21,18]	12,13 [12,15]
3.23	7.98 (m, 5H, -C$_6$H$_5$), 6.21 (s, 2H, -NH$_2$), 4.99(m, 1H, -CH-), 4.05 (s, 2H, -CH$_2$-), 1,13 (d, 6H, -CH$_3$)	53,41 [53,49]	5,52 [5,51]	19,16 [19,14]	10,97 [10,99]
3.24	7.93 (m, 5H, -C$_6$H$_5$), 6.05 (s, 2H, -NH$_2$), 4,13 (m, 4H, -CH$_2$-), 1.79 (s, 2H, -CH$_2$-), 1,09 (t, 3H, -CH$_3$)	53,41 [53,49]	5,52 [5,51]	19,16 [19,15]	10,97 [10,95]
3.25	9.97 (s, 1H, -N=CH-), 8.39 (m, 4H, -C$_6$H$_4$), 8.15 (m, 4H, -C$_6$H$_4$),), 4,19 (m, 4H, -CH$_2$-), 3,06 (s, 6H, N-(CH$_3$)$_2$), 1,49 (t, 3H, -CH$_3$)	51,64 [51,72]	4,54 [4,53]	14,34 [14,32]	6,57 [6,55]
3.26	7,69 (m, 3H, thiophene), 5.89 (s, 2H, -NH$_2$), 4.16 (s, 2H, -CH$_2$-), 3,57 (t, 3H, -CH$_3$)	39,99 [40,10]	3,73 [3,74]	20,73 [20,76]	23,72 [23,78]
3.27	7,75 (m, 3H, thiophene), 5.81 (s, 2H, -NH$_2$), 4.97(m, 1H, -CH-), 4,18 (s, 2H, -CH$_2$-), 1,45 (d, 6H, -CH$_3$)	44,28 [44,31]	4,73 [4,76]	18,78 [18,81]	21,49 [21,45]
3.28	7,71 (m, 3H, thiophene), 5.78 (s, 2H, -NH$_2$), 4.19 (m, 4H, -CH$_2$-), 2.20 (m, 2H, -CH$_2$-), 0,98 (t, 3H, -CH$_3$)	44,28 [44,36]	4,73 [4,74]	18,78 [18,84]	21,49 [21,51]
3.29	7,79 (m, 3H, thiophene), 5.81 (s, 2H, -NH$_2$), 4.21 (m, 4H, -CH$_2$-), 1.69 (m, 2H, -CH$_2$-), 1.51 (m, 2H, -CH$_2$-), 0,95 (t, 3H, -CH$_3$)	46,13 [46,19]	5,16 [5,18]	17,93 [17,90]	20,53 [20,56]

CONCLUSION

1. 29 new compounds, esters of 2-((4-R-3-R$_1$-1,2,4-triazole-5yl)thio)acetic acids have been synthesized as a result of studying.
2. The structure of synthesized compounds is confirmed with modern instrumental methods of analysis in all cases (^{1}H NMR-spectroscopy, chromato-mass-spectrometry and elemental analysis).
3. The synthesized compounds can be used in further biological studies.

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