УДК: 615.31.015.4 : 547.792.057

SYNTHESIS AND STUDY OF THE ACTOPROTECTIVE ACTIVITY OF 4-R-5-ADAMANTANE-1-YL-3(ALKYLTHIO)-4-H-1,2,4-TRIAZOLES,2-(4-R-5-ADAMANTANE-1-YL-4H-1,2,4-TRIAZOLE-3-YLTHIO)ACETIC ACIDS AND THEIR SALTS.

V.M. Odintsova[a], A.A Safonov[b], Ye.S Pruhlo[d], O.I. Panasenko[b], Ye.G. Knysh[c], T.V. Panasenko

[a]Department of Pharmacognosy, pharmacology and botany, Zaporizhzhia State Medical University, 26 Mayakovskiy Ave., Zaporizhzhia, Ukraine;
[b]Department of Toxicology and Inorganic Chemistry, Zaporizhzhia State Medical University, 26 Mayakovskiy Ave., Zaporizhzhia, Ukraine;
[c]Department of Management and Pharmacy Economics, Medical and Pharmaceutical Commodity Research, Zaporizhzhia State Medical University, 26 Mayakovskiy Ave., Zaporizhzhia, Ukraine;
[d]Department of Clinical Pharmacy, Pharmacotherapy and MFE of FPE, Zaporizhzhia State Medical University, 38 Stalevariv st., Zaporizhzhia, Ukraine;
[e]Department of Chemistry, Zaporizhzhia National University, 66 Zhukovskiy st., Zaporizhzhia, Ukraine;

Keywords: derivatives of 1,2,4-triazoles, physico-chemical properties, actoprotective activity

ABSTRACT

Synthesized new S-derivatives of 5-(adamantane-1-yl)-4-R-4H-1,2,4-triazoles-3-thiols: 3-alkyl-5-(adamantane-1-yl)-4-R -4H-1,2,4-triazoles, 2-(5-(adamantane-1-yl)-4-R-4H-1,2,4-triazoles-3-iltio)acetate acids and their salts, where R-methyl, phenyl. It studied the structure and physico-chemical properties of the synthesized compounds, investigated their actoprotective activity.

The problem of physical and mental fatigue is a scourge in today's society. The last decade there has been a tendency to increase working hours and workload of workers and managers. So people suffer from fatigue, which leads to stress and various

diseases. When the rest can not solve this problem, doctors use actoprotectors. Namely drugs that enhance mental and physical activity. But they have a number of side effects.

Derivatives of 1,2,4-triazoles show different types of activities: antioxidant, hypolipidemic, hypocholesterolemic, hepatoprotective, antimicrobial and others [1, 3, 4, 5, 7, 8].

The target of our work was the synthesis of s-derivatives of 5-(adamantane-1-yl)-4-R-4H-1,2,4-triazoles-3-thiols: 3-alkyl-5-(adamantane-1-yl)-4-R-4H-1,2,4-triazoles, 2-(5-(adamantane-1-yl)-4-R-4H-1,2,4-triazoles-3-ylthio)acetic acids and its salts, where R-methyl, phenyl and study of their actoprotective activity.

Materials and methods

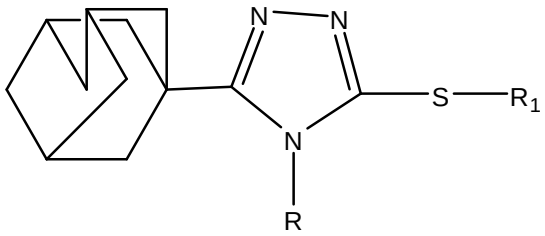
The objects of study are 4-R-5-adamantane-1-yl-3-(alkylthio)-4H-1,2,4-triazoles, 2-(4-R-5-adamantane-1-yl-4H-1,2,4-triazoles-3-ylthio)acetic acids and their salts.

As starting materials we have used 2-(adamantane-1-yl)-N-phenylhydrazinecarbothioamide and 2-(adamantane-1-yl)-N-metylhydrazinecarbothioamide which were synthesized by reaction of adamantane-1-carboxylic acid, hydrazide with phenylisothiocyanate and methylisothiocyanate accordingly in the base of methyl alcohol. Synthesis of 5-(adamantane-1-yl)-4-R-4H-1,2,4-triazoles-3-thiols was carried out by cyclization of 2-(adamantane-1-yl)-N-phenylhydrazinecarbothioamide and 2-(adamantane-1-yl)-N-metylhydrazinecarbothioamide in an alkaline base. Getting 3-alkylthio-5-(adamantane-1-yl)-4-R-4H-1,2,4-triazoles by the addition of α-halogenalkanes to the corresponding 5-(adamantane-1-yl)-4-R-4H-1,2,4-triazolo-3-thiols in n-butanol base. For 2-(5-(adamantane-1-yl)-4-R-4H-1,2,4- triazoles-3-ylthio) of acetic acids in isopropanol base to 5-(adamantane-1-yl)-4-R-4H-1,2,4-triazoles-3-thiol was added an equivalent amount of sodium hydroxide, the precipitate was dissolved by heating and added monochloracetic acid in aqueous solution. The salts of the corresponding acids were obtained by interaction of corresponding acids (compounds I, II, Table 1.) With organic (morpholine, piperidine, diethanolamine, diethylamine, monoethanolamine), inorganic bases (aqueous ammonia, potassium hydroxide) and salts (zinc sulfate, iron (III) chloride) in alcoholic or aqueous media.

Therefore, got compounds are white crystalline substances (compound I, Ia, Ib, Ic, Id, Ie, If, Ig, II, IIa, IIb, IIc, IId, IIe, IIf, IIg Table 1.; III, IIIb, IV, IVa, IVc, IVd, IVe Table 2.), light yellow (compound IIId, IIIg, IVf, IVh, IVi Table 2.), yellow (compound IVg Table 2.) light brown (compounds IIIa, IIIc, IIIe, IIIf, Table IVb. 2). For analysis the obtained compounds were recrystallized from methanol or i-propanol or n-butanol. Physico-chemical constants of the obtained compounds are given in Table. 1 and 2.

Table 1

Physico-chemical constants of 3-R_1thio 5-(adamantane-1-yl)-4-R-4H-1,2,4-triazoles



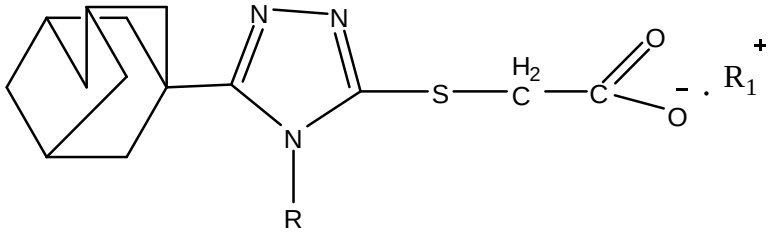
№ compounds	R	R_1	T. of melt., ^oC	Formula	result, %
I	CH_3	H	235-237	$C_{13}H_{19}N_3S$	73,40
II	C_6H_5	H	132-133	$C_{18}H_{21}N_3S$	78,67
Ia	CH_3	н-C_4H_9	>230	$C_{17}H_{27}N_3S$	73,77
Ib	CH_3	н-C_5H_{11}	>230	$C_{18}H_{29}N_3S$	74,50
Ic	CH_3	н-C_6H_{13}	>230	$C_{19}H_{31}N_3S$	80,52
Id	CH_3	н-C_7H_{15}	>230	$C_{20}H_{33}N_3S$	75,54
Ie	CH_3	н-C_8H_{17}	178-180	$C_{21}H_{35}N_3S$	76,12
If	CH_3	н-C_9H_{19}	>230	$C_{22}H_{37}N_3S$	73,33
Ig	CH_3	н-$C_{10}H_{21}$	>230	$C_{23}H_{39}N_3S$	77,17
IIa	C_6H_5	н-C_4H_9	>230	$C_{22}H_{29}N_3S$	69,72
IIb	C_6H_5	н-C_5H_{11}	105-108	$C_{23}H_{31}N_3S$	65,57
IIc	C_6H_5	н-C_6H_{13}	>230	$C_{24}H_{33}N_3S$	66,45
IId	C_6H_5	н-C_7H_{15}	>230	$C_{25}H_{35}N_3S$	72,51
IIe	C_6H_5	н-C_8H_{17}	150-152	$C_{26}H_{37}N_3S$	70,11
IIf	C_6H_5	н-C_9H_{19}	>230	$C_{27}H_{39}N_3S$	71,42
IIg	C_6H_5	н-$C_{10}H21$	>230	$C_{28}H_{41}N_3S$	65,74

№ compounds	found, %				calculated, %			
	C	H	N	S	C	H	N	S
I	62,45	7,70	16,82	12,83	62,61	7,68	16,85	12,86
II	69,21	6,82	13,53	10,31	69,42	6,80	13,49	10,30
Ia	67,01	8,93	13,72	10,48	66,84	8,91	13,76	10,50
Ib	67,82	9,12	13,17	10,07	67,66	9,15	13,15	10,04
Ic	68,21	9,39	12,62	9,58	68,42	9,37	12,60	9,61
Id	69,30	9,54	12,13	9,26	69,11	9,57	12,09	9,23
Ie	69,54	9,78	11,63	8,90	69,75	9,76	11,62	8,87
If	70,17	9,90	11,21	8,55	70,35	9,93	11,19	8,54
Ig	70,72	10,07	10,81	8,24	70,90	10,09	10,78	8,23

IIa	72,06	7,92	11,40	8,69	71,89	7,95	11,43	8,72
IIb	72,25	8,17	11,04	8,43	72,40	8,19	11,01	8,40
IIc	73,05	8,39	10,59	8,13	72,87	8,41	10,62	8,11
IId	73,08	8,60	10,28	7,81	73,30	8,61	10,26	7,83
IIe	73,93	8,78	9,95	7,54	73,71	8,80	9,92	7,57
IIf	73,91	8,97	9,63	7,34	74,09	8,98	9,60	7,33
IIg	74,59	9,12	9,33	7,11	74,45	9,15	9,30	7,10

Table 2

Physico-chemical constants of 2-(5-(adamantane-1-yl)-4-R-4H-1,2,4-triazoles-3-ylthio)acetic acids and their salts



№ compounds	R	R_1	T. of melt., °C	Formula	result, %
III	CH_3	H	140-142	$C_{15}H_{21}N_3O_2S$	67,65
IV	C_6H_5	H	156-158	$C_{20}H_{23}N_3O_2S$	65,24
IIIa	CH_3	1/3Fe	184-185	$C_{45}H_{60}FeN_9O_6S_3$	84,11
IIIb	CH_3	½ Zn	>230	$C_{30}H_{40}N_6O_4S_2Zn$	85,54
IIIc	CH_3	morpholinum	60-62	$C_{19}H_{30}N_4O_3S$	66,40
IIId	CH_3	piperidinum	96-98	$C_{20}H_{32}N_4O_3S$	64,96
IIIe	CH_3	diethylaminum	98-100	$C_{19}H_{32}N_4O_2S$	68,82
IIIf	CH_3	diethanolaminum	58-60	$C_{19}H_{32}N_4O_4S$	67,41
IIIg	CH_3	monoethanolaminum	134-136	$C_{17}H_{28}N_4O_3S$	51,63
IVa	C_6H_5	K	76-77	$C_{20}H_{22}KN_3O_2S$	69,59
IVb	C_6H_5	1/3Fe	>230	$C_{60}H_{66}FeN_9O_6S_3$	88,77
IVc	C_6H_5	½ Zn	>230	$C_{40}H_{44}N_6O_4S_2Zn$	89,77
IVd	C_6H_5	NH_4	167-169	$C_{20}H_{26}N_4O_2S$	65,89
IVe	C_6H_5	morpholinum	184-186	$C_{24}H_{32}N_4O_3S$	68,62
IVf	C_6H_5	piperidinum	160-162	$C_{25}H_{34}N_4O_2S$	69,07
IVg	C_6H_5	monoethanolaminum	50-52	$C_{22}H_{30}N_4O_3S$	52,08
IVh	C_6H_5	diethanolaminum	71-73	$C_{24}H_{34}N_4O_4S$	69,40
IVi	C_6H_5	diethylaminum	175-177	$C_{24}H_{34}N_4O_2S$	70,94

№	found, %	calculated, %

compounds	C	H	N	S	C	H	N	S
III	58,43	6,87	13,66	10,46	58,61	6,89	13,67	10,43
IV	64,85	6,28	11,40	8,67	65,01	6,27	11,37	8,68
IIIa	55,59	6,18	12,96	9,88	55,43	6,20	12,93	9,87
IIIb	52,97	5,96	12,36	9,48	53,13	5,94	12,39	9,46
IIIc	57,99	7,68	14,17	8,14	57,84	7,66	14,20	8,13
IIId	61,01	8,20	14,24	8,19	61,19	8,22	14,27	8,17
IIIe	59,79	-	14,76	8,40	59,97	-	14,72	8,43
IIIf	55,48	7,84	13,60	7,75	55,32	7,82	13,58	7,77
IIIg	55,54	7,67	15,16	8,72	55,41	7,66	15,20	8,70
IVa	58,26	-	10,34	7,85	58,44	-	10,31	7,87
IVb	61,87	5,75	10,84	8,29	62,06	5,73	10,86	8,28
IVc	59,73	5,54	10,49	7,96	59,88	5,53	10,47	7,99
IVd	61,96	6,77	14,47	8,32	62,15	6,78	14,50	8,30
IVe	63,29	7,04	12,30	7,04	63,13	7,06	12,27	7,02
IVf	65,85	7,52	12,35	7,07	66,05	7,54	12,32	7,05
IVg	61,55	7,03	13,04	7,44	61,37	7,02	13,01	7,45
IVh	60,59	7,21	11,82	6,77	60,73	7,22	11,80	6,76
IVi	64,92	7,77	12,64	7,24	65,13	7,74	12,66	7,24

5-(adamantane-1-yl)-4-methyl-4H-1,2,4-triazoles-3-thiol and 5-(adamantane-1-yl)-4-phenyl-4H-1,2,4-triazolo-3-thiol (6, 7, table1.)

A. 0.15 mol of KOH is added to an aqueous solution of 0.1 mol of 2-(adamantane-1-yl)-N-methylhydrazinecarbothioamide or 2-(adamantane-1-yl)-N-phenylhydrazinecarbotioamide and boiled for 1 hr. It is neutralized by acetic acid. It is formed a white precipitate, which was filtered and recrystallized (dioxane:water, 20:1)

3-alkylthio-5-(adamantane-1-yl)-4-R-4H-1,2,4-triazoles

0.01 mol of NaOH is added to 0.01 mol of 5-(adamantane-1-yl)-4-R-4H-1,2,4-triazoles-3-thiol, where R – phenyl or methyl, in butanol base. It is heated to the dissolving of the precipitate. It is added 0.01 mol of halogenalkanes (1-brombutane or 1-brompentane or 1-bromhexane or 1-bromheptane or 1-bromoktane or 1-bromnonane or 1-bromdekane). It is boiled to the neutral pH base. It is evaporated. It is recrystallized from n-butanol. It is received such substances (Ia – Ig, IIa – IIg, table1.).

2-(5-(adamantane-1-yl)-4-methyl-4H-1,2,4-triazoles-3-ylthio)acetic acids and 2-(5-(adamantane-1-yl)-4-phenyl-4H-1,2,4-triazoles-3-ylthio)acetic acids (9, 17, tabl. 2).

A. 0.01 mol of NaOH is added to 0.01 mol of 5-(adamantane-1-yl)-4-R-4H-1,2,4-triazoles-3-thiol, where R – phenyl or methyl, in 40 ml of i-propanol. The mixture was heated to the dissolving of the precipitate pre-dissolved in a minimum amount of water 0.01 mol of monochloracetic acid is gradually added. The reactive mixture is boiled for 5 hours, cooled. It is added 40 ml of water. It is formed a white precipitate. For further analysis the substances (I, II, table 2.) are recrystallized from i-propanol.

Salts of 2-(5-(adamantane-1-yl)-4-R-4H-1,2,4-triazoles-3-ylthio)acetic acids (compounds Ia – Ib, IIa – IIg, table2).

A. 0.01 mole of monoethanolamine and morpholine or piperidine or diethanolamine or diethylamine is added to a solution of 0.01 mol of 2-(5-(adamantane-1-yl)-4-R-4H-1,2,4-triazoles-3-ylthio)acetic acids in 30 ml of i-propanol, correspondenly, is heated in a water bath to the dissolving of the precipitate. It is evaporated. It is washed by the diethyl ester, dried, recrystallized from methanol (13, 20, 21, 48, table 2.), i-propanol (12, 14, 15, 16, table 2.), n-butanol (18, 19, table 2).

B. 0.01 mol of KOH is added to a solution of 0.01 mol of 2-(5-(adamantane-1-yl)-4-R-4H-1,2,4-triazoles-3-ylthio)acetic acids in 30 ml of water. It is dissolved by heating and adding 0.005 mol of $ZnSO_4$. The precipitate that formed was filtered and washed by water, dried, and get substances (89, 90, table 2).

C. 0.01 mol of KOH is added to a solution of 0.01 mol of 2-(5-(adamantane-1-yl)-4-R-4H-1,2,4-triazoles-3-ylthio)acetic acids in 30 ml of water. It is dissolved by heating and adding 0.0033 mol of $FeCl_3$. The precipitate that formed was filtered and washed by water, dried, and get substances (91, 92, table 2).

D. 0.01 mol of NH_4OH or KOH are added to a solution of 0.01 mol of 2-(5-(adamantane-1-yl)-4-R-4H-1,2,4-triazoles-3-ylthio)acetic acids in 30 ml of water. The solution was heated on a water bath to the total dissolving of the precipitate. It is evaporated and recrystallized from methanol, and get substances (10, 11, table 2).

RESULTS OF THE RESEARCH AND DISCUSSIONS

The structure of all synthesized compounds by us, is confirmed by the complex using of modern physico-chemical methods of analysis: elemental, IR-, UV-spectroscopy, PMR-spectrometry, and its individuality is made by the method of thin layer chromatography [6].

In IR-spectra of compounds I, II band fluctuations groups are present characteristic for the nucleus of 1,2,4-triazoles: NH– in the range of 3400-3100 cm^{-1}, –C=N – 1690-1620 cm^{-1}. There are also band fluctuations of –C–S groups at 705-570 cm^{-1}. There are bands fluctuations within the 2600-2550 cm^{-1}, which may indicate to the presence in the molecule of –SH groups.

There are band fluctuations groups characteristic for the nucleus of 1,2,4-triazoles: NH– in the range of 3400-3100 cm^{-1}, –C=N – 1690-1620 cm^{-1} studying in IR-spectra of compounds Ia – Ig, IIa – IIg. There are also present band fluctuations groups –C–S – at 705-570 cm^{-1}. There are band fluctuations characteristic for $–CH_3$ group within 2975-2950 cm^{-1} and group $–CH_2$ – 2940-2915 cm^{-1}.

In IR-spectra of compounds III, IV (Fig. 1) there are bands fluctuations groups characteristic for the nucleus of 1,2,4-triazoles: NH– in the range of 3400-3550 cm^{-1}, –C=N – 1690-1620 cm^{-1}. There are also present band fluctuations of –C–S – groups at 705-570 cm^{-1} and there are no fluctuations bands within the 2600-2550 cm^{-1}, which may indicate to the presence in the molecule of –SH groups. There are band fluctuations characteristic for group –COOH within 1725-1700 cm^{-1}.

In the study of IR-spectra of compounds IIIa – IIIg, IVa – IVi we found the bands of valent fluctuations of NH– groups within 3400-3550 cm^{-1}, group –C=N – at 1690-1620 cm^{-1}. It is found characteristic fluctuations of $–COO^-$ groups within the 1420-1300 cm^{-1} and 1610-1550 cm^{-1}. There are characteristic fluctuations of $–NH_2^+$ groups within the 1620-1560 cm^{-1}, $–NH_3^+$ groups within 1620-1560 cm^{-1} and –OH within 1000-1075 cm^{-1}.

The study was conducted on a group of white non-linear rats weighing 200-260 g. In the study of actoprotective activity we used the method of forced swimming with a load of 10 % of the rat's weight [2]. The load was fixed at the base of the animal's tail. Swimming was performed to exhaustion, which was fixed after 10-seconds immersion of laboratory animals under water. Rats were individually immersed in a container of a large size of the layer of water that exceeds 60 cm. Water temperature was $24\text{-}26^0$ C. The researched compounds and standard of comparison – riboxinum was injected intraperitoneally 20 minutes prior the animals'diving at a dose of 100 mg/kg. The time

of swimming is recorded in seconds. A control group of animals that received saline intraperitoneally 20 minutes before the diving was also used in comparison.

Table 3

Actoprotective activity of s-derivatives 5-(adamantane-1-yl)-4-R-4H-1,2,4-triazoles-3-thiols in comparison with riboxinum

№ з/п	code compounds/group	Average duration of forced rats' swimming, M±m	P	Correlation in comparison with control group , Δ%
1	control	227,71±8,692		0
2	IVg	194,14±13,984	>0,05	-14,74
3	IIc	257,29±16,475	>0,05	12,99
4	IVa	293,00±12,877	<0,05	28,67
5	IIf	274,71±21,198	>0,05	20,64
6	IIIe	301,29±10,877	<0,05	32,31
7	IIIc	223,86±14,395	>0,05	-1,69
8	IIe	96,00±10,335	<0,05	-57,84
9	III	75,43±7,467	<0,05	-66,88
10	Riboxinum	278,00±23,639	>0,05	22,08

The study of actoprotective activity (table 3) of s-derivatives of 5-(adamantane-1-yl)-4-R-4H-1,2,4-triazoles-3-thiols indicates that given compound show actoprotective activity in the range of 66,88 – 32,31 %. Diethylammonium 2-(5-(adamantane-1-yl)-4-methyl-4H-1,2,4-triazoles-3-ylthio) acetate (compound IIIe), which contains C_5 carbon atom of 1,2,4-triazole cycle adamantane-1-yl substituent methyl radical to C_4 carbon atoms, a carboxyl group and the cation of diethylammonium has the most expressed actoprotective activity of 32,31 % ($P < 0.05$).

IIc, IIf, IVa compounds have showed moderate actoprotective activity increasing action with the interval of 12,99 – 28,67 %. It is identified a compound, which is in 6,59 % higher than the standard in comparison with riboxinum. It is potassium 2-(5-(adamantane-1-yl)-4-phenyl-4H-1,2,4-triazoles-3-ylthio) acetate (compound IVa),

containing phenyl radical cation and potassium the replacement of which is on cation monoethanolamonium (IVg) was accompanied by a reduction of up to 14,74 % ($P > 0,05$).

The replacement of diethylammonium cation on the cation of morpholine in diethylammonium 2-(5-(adamantane-1-yl)-4-methyl-4H-1,2,4-triazoles-3-ylthio) acetate reduces the actoprotective activity (compound IIIe, IIIc).

Introduction of potassium cation leads to increased activity, whereas methyl substitution on phenyl radical in the molecule of potassium 2-(5-(adamantane-1-yl)-4-phenyl-4H-1,2,4-triazoles-3-ylthio) acetate reduces the actoprotective activity (compound IVa).

Reducing of the carbon chain in the molecule of 3-(adamantane-1-yl)-5-(oktylthio)-4-phenyl-4H-1,2,4-triazoles to 3-(adamantane-1-yl)-5-(hexylthio)-4-phenyl-4H-1,2,4-triazoles leads to a slight increase of activity, to the enlargement of the number of carbon atoms to 3-(adamantane-1-yl)-5-(nonylthio)-4-phenyl-4H-1,2,4-triazoles contributes to actoprotective action of (compound IIc, IIe, IIf).

Conclusions

1. It is synthesized a series of new compounds of 5-(adamantane-1-yl)-4-R-4H-1,2,4-triazoles-3-thiols, the structure of which was confirmed by the complex using of modern physico-chemical methods of analysis.
2. The researched compounds are derivatives of 5-(adamantane-1-yl)-4-R-4H-1,2,4-triazoles-3-thiols which show actoprotective activity.
3. Diethylammonium 2-(5-(adamantane-1-yl)-4-methyl-4H-1,2,4-triazoles-3-ylthio) acetate has the most expressed actoprotective activity of 32,31 % ($P < 0,05$) the activity of which is greater than the known standard drug riboxinum on 10,23 %.

LITERATURE

1. Антиоксидантна активність деяких похідних 1,2,4-траізолу при експериментальній гіперліпідемії / Є. С. Пругло, І. М. Білай, А. Г. Каплаушенко [та ін.] // Фармац. часопис. – Тернопіль, 2010. – Вип 1 (10), – С. 61-65.
2. Бобков Ю. Г. Фармакологическая коррекция утомления / Ю. Г. Бобков, В. И. Виноградов, В. Ф. Катков [и др.]. – М. : Медицина, 1984. – 208 с.

3. Вивчення гіпохолестеринемічної дії заміщених 2-(4-R-5-R_1-4H-1,2,4-тріазол-3-ілтіо) оцтових кислот та їх солей / Пругло Є. С., Білай І. М., Щербина Р. О. [та ін.] // Фармація України. Погляд у майбутнє. Матеріали VII Нац. з'їзду фармацевтів України. Харків., 2010, Том 2. – С. 114.
4. Гіпо-β-ліпопротеїдемічні властивості нових заміщених 1,2,4-тріазолу/ Є. С. Пругло, І. М. Білай, В. В. Парченко [та ін.] // Український науково-медичний молодіжний журнал. – Київ, 2009. – № 3, С. 19–21.
5. Експериментальне вивчення гіпохолестеринемічної дії деяких заміщених 1,2,4 – тріазолу / Є. С. Пругло, І. М. Білай, А. Г. Каплаушенко [та ін.] // Запор. мед. журнал. – 2009. – Том 11, № 2. – С. 103 – 106.
6. Казицына Л. А., Куплетская Н. Б. Применение УФ-, ИК-, и ЯМР-спектроскопии в органической химии. – М. : Высш. шк., 1971. – 264 с.
7. Пат. 16835 Україна, C07D 248/08 A61K 31/41. 2-[5-(Фуран-2-іл)-4-феніл-4H-1,2,4-тріазол-3-ілтіо]-1-(4-хлорфенілетанон), який проявляє протисудомну активність / Книш Є. Г., Парченко В. В., Панасенко Т. О., Самура І. Б., Літовченко А. Л., Самура Б. А. // Заявл. 27.03.2006; Опубл. 155.08.2006, Бюл. №8.
8. Пат. 18863 Україна, C07D 249/08 A61K 31/41. Піперидиній 2-[5-(фуран-2-іл)-2H-1,2,4-тріазол-3-ілтіо]ацетат, який проявляє противірусну активність / Книш Є. Г., Парченко В. В., Панасенко Т. О., Дзюблик І. В., Трохименко О. П. // Заявл. 13.06.2006; Опубл. 15.11.2006, Бюл. № 11.