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Research Article

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Synthesis of 3-alkylthio(sulfo)-1,2,4-triazoles, containing methoxyphenyl substituents at C^5 atoms, their antipyretic activity, propensity to adsorption and acute toxicity

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ABSTRACT

To find new low-toxic, biologically active compounds, we have synthesized a series of alkylthio(sulfo)derivatives of 1,2,4-triazoles, which contain 2-, 3-, 4-methoxyphenyl or 3,4,5- trimethoxyphenyl substitutes at the C^5 atom of 1,2,4-triazole nucleus. The structure of the obtained compounds has been confirmed by complex of modern physical and chemical methods of analysis. Acute toxicity and antipyretic effects has been investigated, the data of surface activity and propensity to adsorption have been set for the synthesized compounds. Based on these data, the correlations of results of the biological activity towards data of adsorption properties of new compounds have been conducted.

Keywords: 1,2,4-triazoles, physical and chemical properties, antipyretic activity, propensity to adsorption, toxicity.

INTRODUCTION

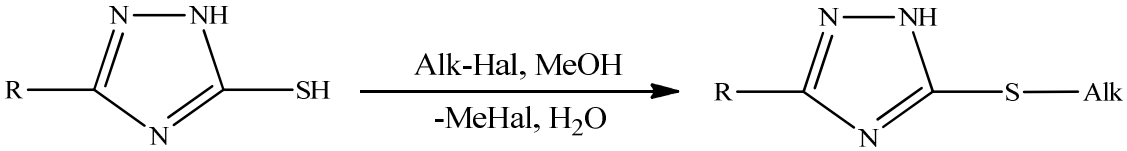
Fever is the most common and one of the major symptoms of diseases both for children and adults. Modern medicine arsenal includes a large amount of drugs with antipyretic effects. But it should be noticed that the application of many drugs can lead to unwanted side effects.

At present time, there is evidence [5,1] that anti-inflammatory and analgesic properties which are inherent to nonsteroidal anti-inflammatory drugs with distinct antipyretic effects are also inherent to 1,2,4-triazoles. Their advantage consists in the fact that they have low acute toxicity and almost never lead to side effects.

Purpose of the work: the main purpose of our work was the synthesis of new highly efficient and low-toxic compounds, which are derivatives of 1,2,4-triazoles-3-thione, which contain methoxyphenyl substituents at the C^5 atom of triazole cycle nucleus and alkyl remains in sulfur (II) and (VI) atom; the establishment of relationships between chemical structure and biological effects, studies of antipyretic activity, acute toxicity and dependence of the obtained results on surface activity and adsorption.

EXPERIMENTAL SECTION

Materials and methods: Alkylation of obtained earlier [6] 5-(2-,3-,4-methoxyphenyl, (3-,4-,5-trimethoxy- phenyl)-)-1,2,4-triazoles-3-thiones halogen alkanes (propyl bromide, amil bromide, hexyl bromide, heptyl bromide, oktyl bromide, nonil bromide, decyl bromide) was carried out [93] in ethanol medium at the presence of equimolecular amount of alkali (Fig. 1).



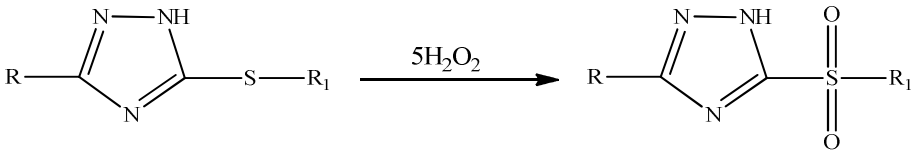
R= $C_6H_4OCH_3$-2, $C_6H_4OCH_3$-3, $C_6H_4OCH_3$-4, $C_6H_2(OCH_3)_3$-3,4,5

Fig. 1. Scheme of synthesis of 3-alkylthio-5-R-1 ,2,4-triazoles

Thus obtained 3-alkylthio-5-R-1,2,4-triazoles (1-11 Table 1) are white (4, 8) or yellow (1-3, 5-7, 9-11) substances poorly soluble in water, soluble in organic solvents. For the analysis 3-alkylthio-1,2,4-triazoles (1-11) have been purified by recrystallization from mixture ethanol : water (4:1).

Continuing the search of biologically active compounds among S-alkyl thioderivatives 5-(methoxyphenyl)-1,2,4-triazoles-3-thiones, the oxidation of corresponding 3-alkylthio-5-R-1,2,4-triazoles with the solution of hydrogen peroxide in the medium of concentrated acetic acid has been conducted (Fig. 2). The oxidation of sulfur has been carried out at room temperature or while heating the reaction mixture. The results obtained using the two temperature modes are identical.

Thus obtained 3-alkylsulfonyl-5-R-1,2,4-triazoles (12-17 Fig. 1 Table 1) are yellow crystalline substances, slightly soluble in water, soluble in organic solvents. For the analysis all synthesized substances have been purified by recrystallization from a mixture of acetic acid : water 1:1.



(1-3, 5-7) (12-17), 74-92%

R= $C_6H_4OCH_3$-2, $C_6H_4OCH_3$-3, $C_6H_4OCH_3$-4; R_1=C_3H_7, C_6H_{13}, C_8H_{17}, C_9H_{19}, $C_{10}H_{21}$

Fig. 2. Scheme of the synthesis of 3-alkylsulfonyl-5-R-1,2,4-triazoles

The structure of the obtained 3-alkyl (sulfonyl)-5-R-1,2,4-triazoles (1-17 Fig. 2) has been set using the methods of PMR spectroscopy (Table 1), chromato-mass spectrometry, elemental analysis (Table 2) and by spectrophotometry in the infrared region of the spectrum [3] (Table 3).

The research of acute toxicity and antipyretic activity (Table 4) has been carried out at the Department of Clinical Pharmacy, Pharmacotherapy and Economical Management of Pharmacy, Faculty of Postgraduate Education of Zaporozhye State Medical University (responsible executor – candidate of pharmaceutical sciences, Pruhlo E.S.).
The acute toxicity has been determined by express – method of V.B. Prozorovskiy [4] on nonlinear white rats, the results are shown in Table 4.

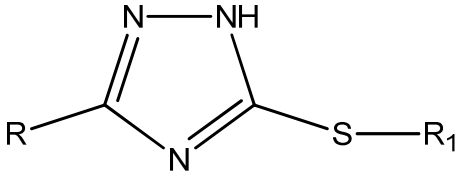
The research of antipyretic activity of compounds has been conducted on a group of white nonlinear rats [5] weighting 200-260g. The experimental fever has been reproduced by administering 2,4-dinitrophenol (disconnector of oxidative phosphorylation) at a dose of 20 mg / kg.

The investigated substance has been introduced in 0.5 hours (T0,5) after the introducing of 2,4-DNP, the rectal temperature of body during 1 hour (T1) has been fixed. The initial rectal temperature (T0) has been registered before intraperitoneal injection of 2,4-DNP.

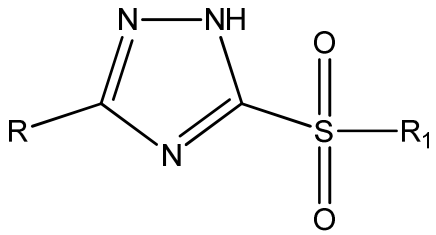
The acetylsalicylic acid in the dose of 100 mg/ kg has been used as a standard of comparison.

The experimental data of the surface tension of the solutions of substances at the border interface of liquid – gas has been used for the research of adsorption properties and subsequent conduction of the result's correlation of pharmacological indicators. The surface tension has been determined by the Rebinder's method [2]. Adsorption has been calculated according to the equation of Gibbs [2]. The research has been conducted at the Department of Physical and Colloid Chemistry of ZSMU. The results are presented in Table 4.

Table 1 Physicochemical constants of 3-alkyl (sulfonyl) -5 - (methoxyphenyl) -1,2,4-triazoles



№ of compounds	R	R_1	T. melt., °C	Gross formula	Output, %	PMR (δ, m.p., TMS)
1	$C_6H_4OCH_3$-2	C_3H_7	145-146	$C_{12}H_{15}N_3O_3S$	93	0.92 (3H, m, CH_2-**CH_3**); 1.43 (2H, m, **CH_2**-CH_3); 3.10 (2H, m, S-**CH_2**); 3.82(3H, s O-CH_3); 7.10-7.65(4H, m C_6H_4);
2	$C_6H_4OCH_3$-3	C_8H_{17}	75-76	$C_{17}H_{25}N_3O_3S$	95	0.88 (3H, m, CH_2-**CH_3**); 1.34 (2H, m, **CH_2**-CH_3); 3.15 (2H, m, S-**CH_2**); 3.84(3H, s O-CH_3); 6.93-7.84(4H, m C_6H_4);
3	$C_6H_4OCH_3$-4	C_3H_7	123-124	$C_{12}H_{15}N_3OS$	72	0.91 (3H, m, CH_2-**CH_3**); 1.45 (2H, m, **CH_2**-CH_3); 3.11 (2H, m, S-**CH_2**); 3.85 (3H, s O-CH_3); 7.08-8.0 (4H, m C_6H_4);
4	$C_6H_4OCH_3$-4	C_5H_{11}	82-83	$C_{14}H_{10}N_3OS$	85	0.93 (3H, m, CH_2-**CH_3**); 1.34 (2H, m, **CH_2**-CH_3); 3.13 (2H, m, S-**CH_2**); 3.87 (3H, s O-CH_3); 7.03-7.98 (4H, m C_6H_4);
5	$C_6H_4OCH_3$-4	C_6H_{13}	101-103	$C_{15}H_{21}N_3OS$	76	0.87 (3H, m, CH_2-**CH_3**); 1.35 (2H, m, **CH_2**-CH_3); 3.08 (2H, m, S-**CH_2**); 3.87 (3H, s O-CH_3); 7.08-7.87 (4H, m C_6H_4);
6	$C_6H_4OCH_3$-4	C_9H_{19}	73-74	$C_{18}H_{27}N_3OS$	92	0.89 (3H, m, CH_2-**CH_3**); 1.34 (2H, m, **CH_2**-CH_3); 3.15 (2H, m, S-**CH_2**); 3.83 (3H, s, O-CH_3); 7.10-7.89 (4H, m, C_6H_4);
7	$C_6H_4OCH_3$-4	$C_{10}H_{21}$	76-78	$C_{19}H_{29}N_3OS$	73	0.88 (3H, m, CH_2-**CH_3**); 1.32 (2H, m, **CH_2**-CH_3); 3.10 (2H, m, S-**CH_2**); 3.84 (3H, s, O-CH_3); 7.12-7.90 (4H, m, C_6H_4);
8	$C_6H_2(OCH_3)_3$-3,4,5	C_3H_7	151-152	$C_{14}H_{19}N_3O_3S$	77	0.91 (3H, m, CH_2-**CH_3**); 1.42 (2H, m, **CH_2**-CH_3); 3.12 (2H, m, S-**CH_2**); 3,90 (9H, t,-O-CH3); 6,81 (2H, d, C_6H_2)
9	$C_6H_2(OCH_3)_3$-3,4,5	C_6H_{13}	147-148	$C_{17}H_{25}N_2O_3S$	96	0.94 (3H, m, CH_2-**CH_3**); 1.45 (2H, m, **CH_2**-CH_3); 3.15 (2H, m, S-**CH_2**); 3,85(9H, t,-O-CH3); 6,83 (2H, d, C_6H_2)
10	$C_6H_2(OCH_3)_3$-3,4,5	C_7H_{15}	171-172	$C_{18}H_{27}N_3O_3S$	63	0.88 (3H, m, CH_2-**CH_3**); 1.45 (2H, m, **CH_2**-CH_3); 3.09 (2H, m, S-**CH_2**); 3,92(9H, t,-O-CH3); 6,78 (2H, d, C_6H_2)
11	$C_6H_2(OCH_3)_3$-3,4,5	$C_{10}H_{21}$	155-156	$C_{21}H_{33}N_3O_3S$	92	0.91 (3H, m, CH_2-**CH_3**); 1.44 (2H, m, **CH_2**-CH_3); 3.08 (2H, m, S-**CH_2**); 3,92(9H, t,-O-CH3); 6,83 (2H, d, C_6H_2)



№ of compounds	R	R_1	T. melt., °C	Gross formula	Output , %	PMR (δ, m.p., TMS)
12	$C_6H_4OCH_3$-2	C_3H_7	103-104	$C_{12}H_{15}N_3O_3S$	89	0.95 (3H, m, CH_2-**CH_3**); 1.44 (2H, m, **CH_2**-CH_3); 3.16 (2H, m, S-**CH_2**); 3.84(3H, s O-CH_3);7.14-7.67(4H, m C_6H_4);
13	$C_6H_4OCH_3$-3	C_8H_{17}	82-84	$C_{17}H_{25}N_3O_3S$	81	0.86 (3H, m, CH_2-**CH_3**); 1.31 (2H, m, **CH_2**-CH_3); 3.18 (2H, m, S-**CH_2**); 3.81(3H, s O-CH_3);6.90-7.87(4H, m C_6H_4);
14	$C_6H_4OCH_3$-4	C_3H_7	115-116	$C_{12}H_{15}N_3O_3S$	74	0.94 (3H, m, CH_2-**CH_3**); 1.46 (2H, m, **CH_2**-CH_3); 3.10 (2H, m, S-**CH_2**); 3.81 (3H, s O-CH_3);7.12-8.04 (4H, m C_6H_4);
15	$C_6H_4OCH_3$-4	C_6H_{13}	71-72	$C_{15}H_{21}N_3O_3S$	85	0.82 (3H, m, CH_2-**CH_3**); 1.36 (2H, m, **CH_2**-CH_3); 3.12 (2H, m, S-**CH_2**); 3.84 (3H, s O-CH_3);7.09-7.91 (4H, m C_6H_4);
16	$C_6H_4OCH_3$-4	C_9H_{19}	86-87	$C_{18}H_{27}N_3O_3S$	77	0.91 (3H, m, CH_2-**CH_3**); 1.37 (2H, m, **CH_2**-CH_3); 3.17 (2H, m, S-**CH_2**); 3.79 (3H, s, O-CH_3);7.12-7.91 (4H, m, C_6H_4);
17	$C_6H_4OCH_3$-4	$C_{10}H_{21}$	95-97	$C_{19}H_{29}N_3O_3S$	92	0.94 (3H, m, CH_2-**CH_3**); 1.29 (2H, m, **CH_2**-CH_3); 3.12 (2H, m, S-**CH_2**); 3.87 (3H, s, O-CH_3);7.09-7.92 (4H, m, C_6H_4);

R= $C_6H_4OCH_3$-2, $C_6H_4OCH_3$-3, $C_6H_4OCH_3$-4, $C_6H_2(OCH_3)_3$-3,4,5

Conditions for synthesis:

5-R-3-alkylthio-1,2,4-triazoles (1-11).

The 0.02 mole of the 5-R-1,2,4-triazoles-3-thione and 0.02 mole of distilled halogen alkanes (propyl bromide, amil bromide, hexylbromide, heptyl bromide, oktyl bromide, nonil bromide, decyl bromide) are added to the solution of 0.02 mole of potassium or sodium hydroxide in 30 ml of ethanol. The mixture is boiled for 3h to (pH = 7), filtered, the solvent is evaporated.

White (4, 8) or yellow (1-3, 5-7, 9-11) substances are slightly soluble in water, soluble in organic solvents. For the analysis 3-alkylthio-1,2,4-triazoles (1-11) are crystallized from the mixture of ethanol: water (4:1).

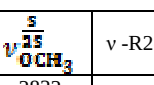
5-R-3-alkylsulfonyl-1,2,4-triazoles (12-17).
10 ml of 33% solution of hydrogen peroxide is added to the solution of 0.02 mole of 5-(2-,3-,4-methoxyphenyl)-3-alkylthio-1,2,4-triazoles in 30 ml of concentrated acetic acid during one hour. The mixture is heated for five hours in a water bath at the temperature of 75°C, the solvent is evaporated. The residue is crystallized from the mixture of acetic acid : water (1:1).

Yellow (12-17) substances are slightly soluble in water, soluble in organic solvents.

Table 2. The elemental composition of 3-alkyl (sulfonyl) -5 - (methoxyphenyl) -1,2,4-triazoles

№ of compounds	Found, %				Computed, %			
	C	H	N	S	C	H	N	S
1	58.01	6.16	16.91	12.69	57.81	6.06	16.85	12.86
2	63.72	7.95	13.27	10.33	63.91	7.89	13.15	10.04
3	58.03	6.08	16.93	12.59	57.81	6.06	16.85	12.86
4	60.48	6.95	15.35	11.73	60.62	6.90	15.15	11.56
5	61.77	6.98	14.38	11.24	61.82	7.06	14.42	11.00
6	64.59	8.47	12.71	9.68	64.83	8.16	12.6	9.61
7	66.95	8.63	12.2	9.36	66.67	8.41	12.09	9.29
8	54.62	6.21	13.52	10.38	54.35	6.19	13.58	10.36
9	58.12	7.28	12.18	9.18	58.09	7.17	11.96	9.12
10	59.22	7.48	11.63	9.02	59.15	7.45	11.5	8.77
11	61.95	8.12	1.01	7.62	61.88	8.16	10.31	7.87
12	51.06	5.39	14.98	11.81	51.23	5.37	14.94	11.4
13	58.28	6.95	12.12	9.18	58.09	7.17	11.96	9.12
14	51.29	5.42	15.12	14.09	51.23	5.37	14.94	11.4
15	55.85	6.37	13.21	9.58	55.71	6.54	12.99	9.91
16	59.24	7.38	11.27	8.98	59.15	7.45	11.5	8.77
17	60.27	7.37	10.93	58.34	60.13	7.70	11.07	58.45

Table 3 IR spectra of absorption of 3-alkyl (sulfonyl) -5 - (methoxyphenyl) -1,2,4-triazoles

№ of compounds	ν C=N in the cycle	ν Ar	ν C-S	ν s/ as -CH2-	ν s / as -CH3		ν -R2-SO2-
1	1520	1605	631	2850/2922	2826/2970	2832	-
2	1487	1609	648	2849/2921	2829-2965	2839	-
3	1484	1610	666	2851/2913	2827/2979	2845	-
4	1499	1606	658	2852/2912	2830/2949	2841	-
5	1495	1602	636	2882/2943	2826/2975	2829	-
6	1514	1608	671	2863/2945	2828/2971	2832	-
7	1498	1612	645	2849/2921	2832/2963	2856	-
8	1482	1608	628	2864/2906	2830/2970	2787	-
9	1476	1612	637	2838/2933	2831/2961	2769	-
10	1487	1604	675	2878/2929	2831/2958	2830	-
11	1489	1607	662	2849/2915	2828/2979	2853	-
12	1480	1612	638	2853/2918	2827/2951	2793	1125
13	1495	1605	648	2858/2937	2830/2969	2814	1134
14	1514	1610	645	2851/2914	2832/2959	2802	1112
15	1513	1608	635	2876/2938	2831/2968	2843	1150
16	1498	1614	657	2866/2931	2832/2973	2831	1127
17	1478	1609	661	2860/2909	2829/2967	2799	1138

RESULTS AND DISCUSSION

As a result of conducting synthetic studies, we have synthesized 17 new, not previously described compounds, derivatives of 1,2,4-triazoles, which contain methoxyphenyl substitutes at C^5 atom of triazole cycle nucleus. With the help of modern physical and chemical analysis methods such as PMR (Table 1), mass spectrometry, IR – spectroscopy [3] (Table 3), elemental analysis (Table 2), the structure of the synthesized compounds has been confirmed and their identity has been established.

The antipyretic activity has been studied for all synthesized compounds. The data of primary analysis has showed that all the substances have demonstrated the antipyretic activity in the range of -1.08% to -7.07%, indicating that all the synthesized compounds inherent antipyretic activity. Compounds 3-5, 7, 9, 10, 12-15 have exceeded the standard of comparison - acetylsalicylic acid, which has lowered the temperature by -3.03%. The most pronounced antipyretic effects has been showed by compound 9 (3- (hexyltio) -5-(3-,4-,5-trimethoxyphenyl)-1H-1 ,2,4-

triazoles), lowering the temperature for -7.07%. The application has been completed on compound 9 for the patent of Ukraine for the useful model.

The study of acute toxicity has been found (Table 4), LD50 of chemical compounds of this class is in the range of 367 to 512 mg / kg and on the classification K.K. Sidorov [4] they belong to the class IV toxicity (low toxic substances).

The study of the adsorption properties [2] of the synthesized compounds (Table 4) made it possible to follow the next dependance: in a number of synthesized compounds with increasing of hydrocarbon radical on several CH_2-group, with the introduction of 3,4,5-trimethoxyphenyl radical and with increasing of concentration the adsorption capacity of substance increases too. Thus the increase of the ability of compounds to adsorption leads to the increase of toxicity and the biological activity.

Table 4. Toxicity, ability to adsorb, antipyretic activity of 3-alkyl (sulfonyl) -5 - (methoxyphenyl) -1,2,4-triazoles

№ of compounds	LD_{50}	Decrease in rectal temperature of rats relative to the control group, %	$G \cdot 10^{-6}$, mole/m^2
1	469	-5.03	4.3
2	398	-2.15	4.32
3	465	-3.21	4.48
4	435	-3.17	4.34
5	424	-6.28	4.76
6	407	-2.11	4.51
7	402	-4.17	4.61
8	469	-2.35	4.37
9	431	-7.07	4.76
10	449	-4.07	4.8
11	425	-2.12	4.69
12	512	-3.32	4.28
13	434	-5.02	4.83
14	475	-4.04	4.30
15	408	-5.12	4.69
16	367	-2.19	4.74
17	501	-1.08	4.83

Prospects for further research: the data of computer prediction of the biological activity for the aforementioned compounds showed that this class is very promising for the study of antihypoxic and antioxidant activity. In further studies expansion of the biologically active range of compounds as well as more in-depth conducting of biological activities is planned.

CONCLUSION

1. Were synthesized 17 new compounds, the derivatives of 5-(2-,3-,4-methoxyphenyl (3-,4-,5-trimetoxyphenyl))-1,2,4-triazoles-3-thiones containing alkyl radical over sulfur atom.
2. The structure of all synthesized compounds has been confirmed by complex of modern physical-chemical methods of analysis.
3. The research of acute toxicity and antipyretic activity has been conducted, the results of the research showed that this class of compounds is promising for potential drugs.
4. The dependence of the ability of compounds to adsorption on the length of alkyl radical has been set.
5. The dependence of the structure, the ability to adsorb and toxicity has been studied.

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