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STUDY OF THE BIOLOGICAL PROPERTIES OF SEMI- AND THIOSEMICARBAZONES OF CARBONYL DERIVATIVES OF 4-BUTANOLIDES

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Based on carbonyl derivatives of 4-substituted-4-butanolides, the appropriate semi- and thiosemicarbazones have been synthesized. It has been found that some representatives of thiosemicarbazones have pronounced algicidal activity against filamentous green alga *Cladophora* and blue-green alga (cyanobacterium) *Synechocystis* and some of the semi- and thiosemicarbazones exhibit moderate antitumor activity. The assessment of the antitumor activity of the compounds was carried out using strains of syngeneic and allogeneic tumor systems as test-objects: lymphocytic leukemia *P-388*, Lewis lung carcinoma, *B16* melanoma and Ehrlich's ascites tumor. It has also been established that some representatives of thiosemicarbazones exhibit antimutagenic properties. It has been reliably proven that with the formation of a thiazole ring, all properties disappear and a new property in the series of thiazololactones is revealed – antibacterial.

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***Keywords*:** 4-butanolides, cyclic esters, algicidal activity, antitumor activity, antibacterial activity.

Introduction. Of numerous natural organic compounds, cyclic esters of γ-hydroxy acids or γ-lactones stand out. Their biological activity is specific and depends on the structure, nature of substituents and position in the lactone ring. There are numerous natural substances containing a lactone fragment, small amounts of which in the body exhibit high physiological activity that cannot be achieved with other drugs. As an example, protoanemonin and vitamin C (ascorbic acid) can be presented (Scheme 1).

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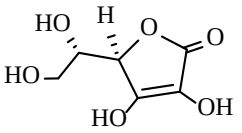
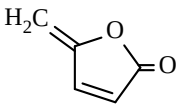


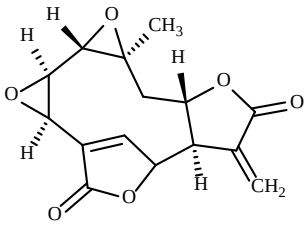
ascorbic acid



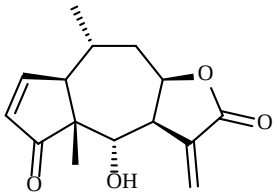
protoanemonin

Scheme 1.

It was established that the physiological activity of these compounds is due to the presence of a lactone cycle in the structure [1, 2]. It should be noted that various derivatives of natural, lactone-containing compounds also have valuable physiological properties, for example, mycanolide – antibacterial, helenalin – antifungal properties and others (see Scheme 2).



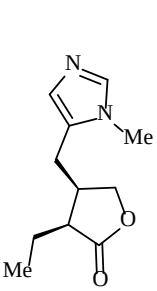
mycanolide



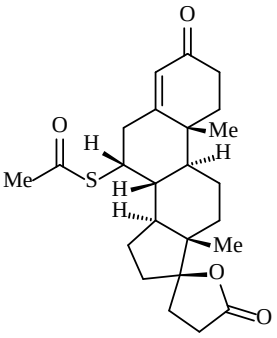
helenalin

Scheme 2.

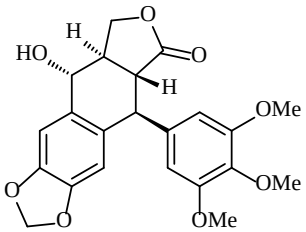
The area of γ-lactones application is vast. In the chemical industry, they are used as selective solvents in producing polymer compounds and polyester resins, in agriculture – as herbicides, pesticides and insecticides; they are the main components of cosmetics – creams, ointments, soaps and detergents [3, 4]. The most common representative of this class of compounds is γ-butyrolactone and some of its derivatives, which are widely used in pharmacology and medicine – they improve sleep, affect growth hormones [5]; a number of drugs based on γ-lactones such as pilocarpine [6], spironolactone [7], podofilox [8] and drospirenone [9] have been used in practical medicine for many years (see Scheme 3).



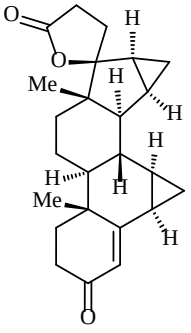
pilocarpine



spironolactone



podofilox



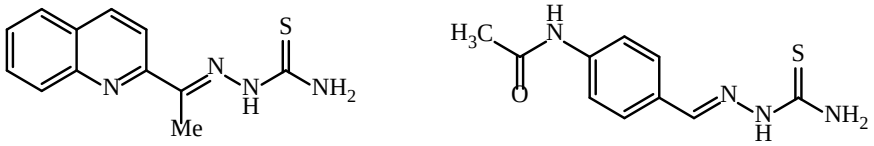
drospirenone

Scheme 3.

The expediency of the research in the field of the synthesis of new representatives of γ-lactones and identification of their useful properties is proved by the fact that despite more than age-old synthesis of the first representatives of this class

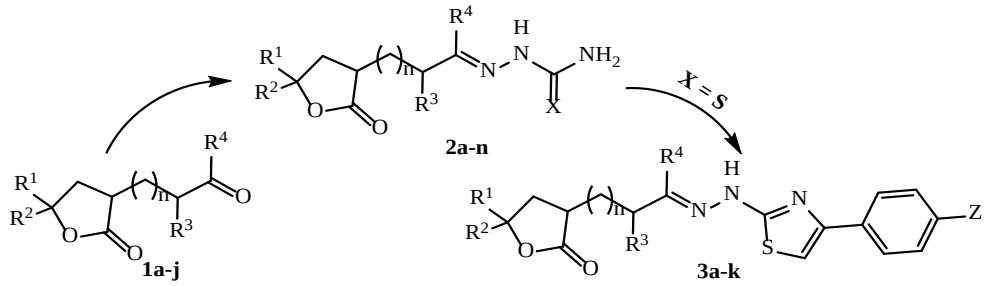
compounds, an intensive search for new routes for the synthesis, as well as for the isolation from natural raw materials and identification of their useful properties is being continued up to now; specifically, the search for drugs with anti-inflammatory [10], antiviral [11], cytotoxic properties [12] and inhibitors of NO production [13].

It is known that some pharmacophore groups, despite the general structure of the molecule, retain the type of biological activity. For example, thiosemicarbazones based on acetylquinoline [14] and p-acetaminobenzaldehyde [15] are known to be used as agents for treating fever and bacterial diseases:



Scheme 4.

Results and Discussion. Taking into account the above mentioned, as well as the numerous methods developed by us for the synthesis of lactone-containing carbonyl compounds, the corresponding semi- and thiosemicarbazones (**2**, **a**–**l**) were synthesized, according to the scheme below. Then, on the basis of thiosemicarbazones, thiazolo-γ-lactones (**3**, **a**–**k**) were obtained that are interesting in themselves as new heterocyclic systems.



Comp.	R^1	R^2	*n*	R^3	R^4	X
1a	H	$PrOCH_2$	0	H	Me	–
1b	H	$^{i}AmOCH_2$	0	H	Me	–
1c	H	$^{i}BuOCH_2$	0	H	Me	–
1d	H	$AmOCH_2$	0	H	Me	–
1e	H	Am	0	H	Me	–
1f	H	$AmOCH_2$	0	H	H	–
1g	H	Me	0	H	Me	–
1h	Me	Me	0	H	Me	–
1i	H	Me	1	Me	H	–
1j	Me	Me	1	Me	H	–
2a	H	$PrOCH_2$	0	H	Me	S
2b	H	$^{i}AmOCH_2$	0	H	Me	S
2c	H	$PrOCH_2$	0	H	Me	O
2d	H	$^{i}AmOCH_2$	0	H	Me	O
2e	H	$^{i}BuOCH_2$	0	H	Me	S
2f	H	$AmOCH_2$	0	H	Me	S
2g	H	Am	0	H	Me	S
2h	H	$AmOCH_2$	0	H	H	S

Comp.	R^1	R^2	*n*	R^3	R^4	X	Z
2i	H	Me	0	H	Me	S	–
2j	Me	Me	1	Me	H	S	–
2k	H	$AmOCH_2$	0	H	Me	S	–
2l	H	$^{i}BuOCH_2$	0	H	Me	S	–
2m	H	Me	1	H	Me	S	–
2n	Me	Me	1	H	Me	O	–
3a	Me	Me	1	H	Me	–	Cl
3b	H	Me	1	H	Me	–	Cl
3c	H	Me	1	H	Me	–	NO_2
3d	H	$^{i}BuOCH_2$	0	H	Me	–	Cl
3e	H	$^{i}BuOCH_2$	0	H	Me	–	NO_2
3f	H	$^{i}AmOCH_2$	0	H	Me	–	Cl
3g	H	$^{i}AmOCH_2$	0	H	Me	–	NO_2
3h	H	$AmOCH_2$	0	H	Me	–	Cl
3i	H	$AmOCH_2$	0	H	Me	–	NO_2
3j	H	Me	1	H	Me	–	H
3k	Me	Me	0	H	Me	–	H

Scheme 5.

2, **a–l** and **3**, **a–k** were published in articles [16, 17], however further biological studies of the newly synthesized compounds were carried out later. The results obtained are quite interesting and once again confirm that the research in the field of γ-lactones is very valuable and the likelihood of their application in practice is high.

It should be noted that a large number of γ-lactone derivatives have been studied; however, this article discusses the data that unambiguously confirm the value of the results obtained.

Table 1

*Influence of **2**, **a–d** on the growth of transplanted tumors in BDF_1 male mice* (* – $p < 0.05$)

Comp.	Strain tumors	Quantity of animals in the group	Dose, *mg/kg*	Cont. introduced day	Weight tumors, *g*	Inhibition of tumor growth, %	Increase prolong animal life, %
2a	lymphocytic leukemia *P-388*	9	control				
		5	75	8			15.4
		5	150	8			15.4
	lewis lung carcinoma	10	control		6.13±0.35		
		6	75	8	5.6±0.6	8.6	
		6	150	8	4.24±0.42	30.8	
	melanoma *B16*	9	control		2.3±0.34		
		5	75	8	0.9±0.44	60.9	
		5	150	8	2.5±0.6	–8.7	
2b	lymphocytic leukemia *P-388*	9	control				
		5	75	8			–5.1
		5	150	8			13.4
	lewis lung carcinoma	10	control		6.13±0.35	–39	
		6	75	8	8.57±1.4	36.4	
		6	150	8	3.9*		
	melanoma *B16*	11	control		1.16±0.12		
		5	75	8	1.02±0.23	12.1	
		5	150	8	0.73±0.29*	37.1	
2c	lymphocytic leukemia *P-388*	9	control				
		5	75	8		–9.3	
		5	150	8		–1.0	
	lewis lung carcinoma	10	control		6.13±0.35		
		5	75	8	5.75±0.45	6.0	
		5	150	8	4.68±0.29*	23.7	
	melanoma *B16*	11	control		1.16±0.12		
		5	75	8	0.53±0.09*		
		5	150	8	0.82±0.18		
2d	lymphocytic leukemia *P-388*	9	control				
		5	75	8			11.3
		5	150	8			11.0
	lewis lung carcinoma	10	control		6.13±0.35		
		6	75	8	4.0±0.7*	34.7	
		6	150	8	4.35	29.0	
	melanoma *B16*	11	control		1.58±0.3		
		6	75	9	1.3±0.19	17.7	
		6	150	9	0.9±0.24*	43.0	

Compounds **2**, **a**–**l** and **3**, **a**–**k** were tested in the following directions – antitumor, algicidal, antimutagenic and antibacterial activities.

***Antitumor Activity*.** Assessment of the antitumor activity of compounds **2**, **a**–**d** was carried out on strains of syngeneic and allogeneic tumor systems as test-objects: lymphocytic leukemia *P-388*, Lewis lung carcinoma, *B16* melanoma and Ehrlich's ascites tumor. The results are shown in Tab. 1.

All studied compounds inhibited the growth of melanoma B16, the inhibition index varied from 28.1% (compound **2b**) to 43% (**2d**). Lewis lung carcinoma turned out to be less sensitive to the studied compounds: 23.7% (**2c**) to 36.4% (**2b**). As for the strain of lymphocytic leukemia *P-388*, the compounds under study had absolutely no effect on this strain.

In addition to the above studies, acute toxicity of compounds **2**, **a**–**d** was also studied by the Litchfield and Wilcoxon method. It was found that with a single intraperitoneal injection, the LD_{50} of compounds **2**, **a**–**d** was more than 1000 *mg*/*kg*.

***Algicidal Activity*.** As the results of biological studies have shown, compounds **2**, **e**–**h** exhibit algicidal activity against filamentous green alga *Cladophora* and blue-green alga *Synechocystis*.

In solutions of all concentrations of the tested preparations, signs of their destructive action on algae are noted – filaments turn yellow, acquire a mushy consistency, turn white; the intermediate stages of the observed changes are the gradual blanching of algae, the cessation of the formation of gas bubbles, a noticeable decrease in the mass of algae lump and settling to the bottom. At the same time, algae contained in clean water retain their green color throughout the entire research period with active gas formation.

The breakdown of filamentous algae under the influence of compounds **2**, **e**–**h** is characterized by disruptions of the intracellular structure. The optimal application concentrations of **2**, **e**–**h** are 0.1–1.0 *mg*/*L* (Tabs. 2, 3). The highest algicidal effect was observed with interaction of preparation **2g**.

The process of cell destruction in solutions of **2g** proceeds more intensively; at the end of the experiment, which lasts 10 days, the number of completely destroyed cells is 42.9–60.1%. To compare the algicidal activity and toxicity, aquagon is used, which is a mixture containing cym-triazine derivatives, an emulsifier and auxiliary products. Aquagon is designed to kill weeds of aqueous vegetation; it is active against blue-green algae, filamentous green algae, etc. The LC_{50} value for fish is 3.5–21 *mg*/*L*. The applied concentrations of the drug usually do not exceed 0.2 *mg*/*L*.

Comparative tests of preparations **2**, **e**–**h** and aquagon were carried out in two directions: tests on the effect of the destruction of algae filaments and on the effect of the preparations on the oxygen productivity (photosynthesis) of algae.

The results of testing the destructive effect on the filaments of filamentous algae *Cladophora* showed that aquagon and **2**, **e**–**h** in this aspect were similar in action: with both preparations the destruction of filaments passed through the same phases, the quantitative ratios of destroyed cells almost did not differ.

The results of tests on the inhibition of algae photosynthesis by substances **2**, **e**–**h** and aquagon are presented in Tabs. 2 and 3.

From the data presented it can be seen that the violation of oxygen production occurs more intensively in **2**, **e**–**h** solutions of all tested concentrations than in aquagon solutions. The LC_{50} values for cyprinids at 96 *h* exposure to **2**, **e–h** are 15.3 *mg*/*kg* (**2 e**), 31.5 *mg*/*kg* (**2 f**), 34.7 *mg*/*kg* (**2 g**), 59.7 *mg*/*kg* (**2 h**).

Table 2

*Disruption of photosynthesis (P) of Cladophora in solutions **2**, **e**–**h** and aquagon after exposure for 1 h (t = 20°)*

Concentrations, *mg*/*L*	*P*, *mg* O_2/1 *h*				
	2 e	**2 f**	**2 g**	**2 h**	Aquagon
0.001	5.8	4.5	4.5	5.8	6.3
0.01	5.3	5.2	3.7	4.7	6.5
0.1	4.3	4.2	2.7	3.9	5.6
1.0	3.4	3.6	2.3	3.6	4.3
10.0	2.8	3.1	2.5	2.9	3.7

Table 3

*Disruption of photosynthesis (P) of Synechocystis in solutions **2**, **e**–**h** and aquagon after exposure for 1 h (t = 22°)*

Concentrations, *mg*/*L*	*P*, *mg* O_2/1 *h*				
	2 e	**2 f**	**2 g**	**2 h**	Aquagon
0.001	4.96	5.44	4.32	4.75	6.75
0.01	5.28	5.02	3.85	4.83	6.21
0.1	4.32	4.64	2.98	3.96	4.97
1.0	2.3	3.84	2.06	2.65	3.45
10.0	2.1	2.90	1.36	2.35	3.21

Thus, compounds **2**, **e**–**h** have increased algicidal activity compared to the aquagon used in practice.

***Antimutagenic Activity*.** Testing of thiosemicarbazones from a series of **2**, **a–h** has shown that some compounds have antimutagenic properties, of which the most promising **2**, **f**–**e** were selected for in-depth studies. N-methyl-N'-nitro-N-nitrozo-guanidine (NG), 2-aminofluorine (2-AF) and 2-acetylaminofluorene (2-AAF) were selected as reference mutagens. As a research method, the classical Ames test was applied using *Salmonella tiphimurium* A 100 bacteria. The culture of the specified strain was introduced into the nutrient medium containing a reference mutagen with a density of 100 $\mu g/mL$, and the compounds under study were administered in a ratio of 1:2 relative to the reference mutagen. Studies have shown that compounds **2**, **f**–**e** reduce the number of revertants by ≈50%. The antimutagenicity indices of the studied compounds with the use of mutagens NG, 2-AF, 2-AFF were calculated and it was shown that for compound **2 f** these indices are 1.3–1.4, 1.14–1.41, 1.26–1.29, and for **2 e** – 1.9–2.0, 2.55–3.34, 1.26–1.33, correspondingly. The data for **2 g** were somewhat inferior to those indicated. The data obtained make it possible to state that compounds **2 f** and **2 e** not only failed to have promutagenic properties, but also exhibited antimutagetic properties in the presence of known mutagens. Therefore, the investigated compounds can be used as antimutagenic agents to reduce the impact of potential mutagens and promutagens on the environment.

Antibacterial Activity. The antibacterial activity of 2-[2-(3-substituted phenylthiazol-2-yl)hydrazono]alkyl-2,4,4-trisubstituted butanolides (**3**, **a**–**f**) was also investigated. Antibacterial activity was studied by the plate method – the method of diffusion in agar with a microbial load of 2×10^6 microbial bodies per 1 *mL* of medium [18]. Gram-positive staphylococci (*209p, 93*) and gram-negative rods (*Sh.Flexneri 6858, E.Coli 0–55*) were used in the experiments.

Due to insolubility, the compounds were tested by dissolving in dimethyl sulfoxide (DMSO does not have antibacterial effect).

Compounds (0.1 *mL* from a dilution of 1:10) were applied to Petri dishes inoculated with microorganism strains. Active substances were also tested at dilutions of 1:20 and 1:40.

The results were recorded by the size of the diameter of the zones with the absence of microorganisms' growth at the site of the substance application (*d*, in *mm*) after daily cultivation in a thermostat at 37°. The known drug furazolidone in the same dilutions was used as a positive control.

Studies have shown that most of the compounds at a dilution of 1:10 exhibit moderate antibacterial activity against the strains used, inhibiting the growth of microorganisms in a zone with a diameter of 10–15 *mm* (Tab. 4). The table includes only those compounds that have shown reliable activity.

According to the data obtained, the compounds differ somewhat in terms of antibacterial effects. Thus, compound **3 d**, as distinct from others, affects only gram-positive staphylococci. It was also shown that the studied compounds at a dilution of 1:10 exhibited moderate antibacterial activity, being inferior in strength to furazolidone.

Table 4

*Antibacterial activity of compounds **3**, **d**–**i***

Compounds	*Stafilacoccus areus 209 p*			*Stafilacoccus areus 93*			*Sh.Flexneri 6858*			*E.Coli 0–55*		
	1:10	1:20	1:40	1:10	1:20	1:40	1:10	1:20	1:40	1:10	1:20	1:40
3 d	11	7	–	11	6	–	0	–	–	0	–	–
3 e	13	8	–	12	8	–	12	7	–	13	7	–
3 f	10	6	–	9	6	–	10	6	–	12	7	–
3 g	13	7	–	13	8	–	12	7	–	12	7	–
3 h	15	10	6	15	9	–	14	9	–	13	8	–
3 i	11	6	–	11	6	–	11	6	–	11	6	–
Furazolidone	24	22	15	17	20	14	20	16	12	22	12	10

Conclusion. Thus, our studies in the field of γ-butanolide derivatives allowed us to reveal new properties – algicidal and antimutagenic activity, previously not detected in representatives of γ-butanolides.

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4-ԲՈՒՏԱՆՈԼԻԴՆԵՐԻ ԿԱՐԲՈՆԻԼԱՅԻՆ ԱԾԱՆՑՅԱԼՆԵՐԻ ՍԵՄԻ- ԵՎ ԹԻՈՍԵՄԻԿԱՐԲԱԶՈՆՆԵՐԻ ԿԵՆՍԱԲԱՆԱԿԱՆ ՀԱՏԿՈՒԹՅՈՒՆՆԵՐԻ ՈՒՍՈՒՄՆԱՍԻՐՈՒԹՅՈՒՆ

4-Տեղակալված-4-բուտանոլիդների կարբոնիլային ածանցյալների հիման վրա սինթեզվել են սեմի- և թիոսեմիկարբազոններ: Հաստատվել է, որ սինթեզված թիոսեմիկարբազոններից որոշները ցուցաբերում են վառ արտահայտված ալգիցիդային ակտիվություն *Chladophora* թելանման կանաչ ջրիմուռների և *Synechocystis* կապտականաչ ջրիմուռների նկատմամբ, իսկ սեմի- և թիոսեմիկարբազոնների մի մասը ցուցաբերում է չափավոր հակաքաղցկեղային ակտիվություն: Հակաքաղցկեղային ակտիվության գնահատումը իրականացվել է, որպես թեստ թիրախներ օգտագործելով սինգենային և ալոգենային ուռուցքային համակարգերը՝ *P-388* լիմֆոցիտային լեյկոզ, Լյուիսի թոքերի կարցինոման, *B16* մելանոման և Էրլիխի ասցիտային ուռուցքը: Հաստատված է, որ թիոսեմիկարբազոններից որոշները ցուցաբերում են հակամուտագեն ակտիվություն: Ապացուցված է, որ թիազոլային օղակի առաջացումը բերում է վերոնշյալ հատկությունների կորստի և թիազոլոլակտոններում ի հայտ է գալիս նոր հատկություն՝ հակաբակտերիալ:

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ИССЛЕДОВАНИЕ БИОЛОГИЧЕСКИХ СВОЙСТВ СЕМИ- И ТИОСЕМИКАРБАЗОНОВ КАРБОНИЛЬНЫХ ПРОИЗВОДНЫХ 4-БУТАНОЛИДОВ

На основе карбонильных производных 4-замещенных-4-бутанолидов синтезированы соответствующие семи- и тиосемикарбазоны. Установлено, что некоторые представители тиосемикарбазонов проявляют ярко выраженную альгицидную активность по отношению к зеленой нитчатой водоросли *Chladophora* и сине-зеленой водоросли *Synechocystis*, а часть семи- и тиосемикарбазонов обладает умеренной противоопухолевой активностью. Оценку противоопухолевой активности соединений проводили с использованием в качестве тест-объектов штаммов сингенных и аллогенных опухолевых систем: лимфолейкоз *P-388*, карциному легкого Льюиса, меланому *B16* и асцитную опухоль Эрлиха. Установлено также, что некоторые представители тиосемикарбазонов проявляют антимутагенные свойства. Достоверно доказано, что при образовании тиазольного цикла все вышеуказанные свойства исчезают и выявляется новое свойство в ряду тиазололактонов – антибактериальное.