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SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF NEW DERIVATIVES OF 2-OXO-2,5-DIHYDROFURANS CONTAINING AN OXOTHIAZOLIDINYLIDENE RING

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New derivatives of 2-oxo-2,5-dihydrofurans containing an oxothiazolidinylidene ring were successfully synthesized based on thiosemicarbazones of 3-acetyl-2-oxo--2,5-dihydrofurans. The synthesized compounds exhibited moderate to defined antibacterial activities against Gram-positive (*Staphylococcus aureus* – 209p and 1) and Gram-negative (*Shigella Flexneri* 6858, *Esherichia coli* 0–55) bacteria compared to furazolidone.

***Keywords*:** 3-acetyl-2-oxo-2,5-dihydrofurans, thiosemicarbazones, oxothiazolidinylidene ring synthesis, antibacterial activity.

Introduction. Functionally substituted derivatives of unsaturated γ-lactones have a wide range of biological activity and exhibit various pharmacological actions [1–9]. The biological activity of unsaturated γ-lactones is due to the presence of an unsaturated C=C bond or an aromatic substituent [10, 11]. Unsaturated γ-lactones conjugated to a double bond are also plant growth stimulators [12, 13].

The antibacterial activity of unsaturated γ-lactones can be explained by their ability to interact with bacterial proteins, as well as with certain enzymes containing sulfhydryl groups and which are of great importance for the normal life of microorganisms, which are known in unsaturated γ-lactone series [14, 15]. It is assumed that the bactericidal action of 2-oxo-2,5-dihydrofuranes is associated with the ability of the lactone double bond to attach the SH groups present in bacterial proteins, inhibiting the development of bacteria.

Thiazolidine derivatives are of great biological importance due to their antidiabetic [16] and antibacterial [17] activity. One such compound, namely (*Z*)-*N*-(2--chloro-6-methylphenyl)-2-(3-methyl-4-oxo-1,3-thiazolidin-2-ylidene)acetamide (ralitoline), has been found to be effective in a preclinical anticonvulsant evaluation [18]. In view of the importance of 2-oxo-2,5-dihydrofuranes and 4-oxothiazolidin--2-ylidene ring, we described the synthesis and study of the antibacterial activity of the title compounds.

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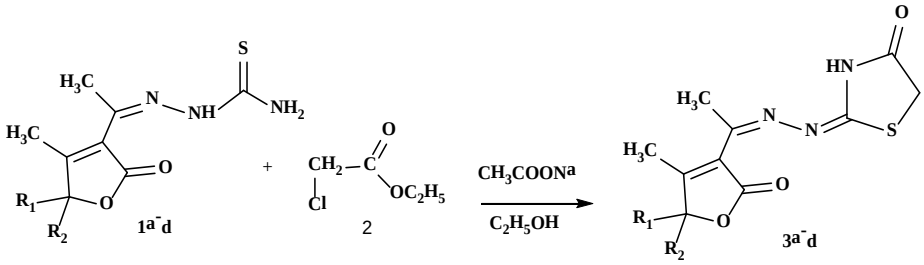
Results and Discussion. New derivatives of 2-oxo-2,5-dihydrofurans containing an oxothiazolidinylidene ring – 2-((1-(4-methyl-5,5-dialkyl-2-oxo-2,5-dihydrofuran-3-yl)ethylidene)hydrazono)thiazolidin-4-ones (**3 a–d**) were successfully synthesized by the condensation of thiosemicarbazones of 3-acetyl-2-oxo-2,5-dihydrofurans **1 a–d** [19] with chloroacetic acid ethyl ester **2** in the presence of sodium acetate, taken in a molar ratio of 1: 1.5: 3 in absolute ethanol.

The structures of the obtained compounds were determined from their spectroscopic data. Compounds **1 b** and **3 b** have an asymmetric carbon atom. The specific rotation was measured for these compounds. They are optically inactive compounds.



a. $R_1{=}R_2{=}CH_3$, **b.** $R_1{=}CH_3$, $R_2{=}C_2H_5$, **c.** $R_1,R_2{=}(CH_2)_4$, **d.** $R_1,R_2{=}(CH_2)_5$

Scheme.

The antibacterial activities of the starting **1 a–d** and obtained **3 a–d** compounds were evaluated against Gram-positive (*Staphylococcus aureus* – 209p and 1) and Gram-negative (*Shigella Flexneri* 6858, *Esherichia coli* 0–55) bacteria by the agar diffusion technique [20]. The antibacterial activities of compounds **1 a–d** and **3 a–d** were compared with the standard drug furazolidone [21].

*Antibacterial activities of **1 a–d** and **3 a–d** compounds in comparison to furazolidone*

Compounds	*Staphylococcus aureus*		*Shigell Flexneri* 6858	*Esherichia coli* 0–55
	209p	1		
	Zone of inhibition, *mm*			
1a	10.0±0.1	10.7±0.2	10.4±0.3	9.0±0.4
1b	11.0±0.6	10.0±0.7	10.4±0.5	9.9±0.1
1c	6.0±0.3	5.6±0.2	7.4±0.4	8.0±0.1
1d	11.0±0.4	6.7±0.4	11.4±0.1	11.0±0.6
3a	16.3±0.6	20.8±0.9	16.3±0.9	17.0±1.4
3b	10.0±0	10.0±0	13.0±1,0	13.3±0,6
3c	12.6±0,6	17.6±1,3	13.3±0,6	13.0±1,0
3d	17.3±0,9	10.0±1,0	16.0±1,0	20.3±0,9
Furazolidone	25±1.0	24±1.2	24±1.0	24±1.0

The antibacterial activities of compounds **1a–d** and **3a–d** are shown in Table. In comparison to furazolidone, compounds **1 a–d** exhibited weak activities towards the growth of both Gram-positive and Gram-negative bacteria. Replacing the carbothioamide group to oxothiazolidinylidene ring to compounds **3 a–d** enhanced the antibacterial activity. Compounds **3a–d** exhibited moderate to defined activities.

Experimental Part.

Chemical Part. The ^{1}H and ^{13}C NMR spectra were recorded at 300 *MHz* and 75 *MHz* on a Varian Mercury-300 *MHz* spectrometer in the mixture of solvents DMSO-d_6+CCl_4 (1 : 3) using tetramethylsilane as the internal standard and IR spectra on an Avatar 330FT-IR spectrometer using attenuated total reflectance (ATR) method. The reaction progress and the purity of the obtained substances were checked using TLC method on UV-254 plates with an acetone–benzene mixture (1 : 2) as an eluent, visualization with iodine vapors. All melting points were determined by measuring with an Electrothermal 9100 apparatus. Specific optical rotation was decided on a Polartronic H532 polarimeter.

Compound **1c** was synthesized by the known procedure [19].

*2-(1-(4-Methyl-2-oxo-1-oxaspiro[4.4]non-3-en-3-yl)ethylidene)hydrazine--carbothioamide (**1c**).* Yield 90%, R_f 0.57, m.p. 156–158°*C*. ^{1}H NMR spectrum, *δ*, *ppm*: 1.42 m (2H) and 1.58–1.85 m (6H, $(CH_2)_4$), 2.27 s (6H, $2CH_3$), 7.62 br.s (1H, NH), 7.90 br.s (2H, $C(S)NH_2$).

General Procedure for the Preparation of Compounds 3 a–d. To a well-stirred solution of compound **1 a**–**d** (4 *mmol*) and sodium acetate 0.74 *g* (12 *mmol*) in 10 *mL* absolute ethanol was added ethyl chloroacetate **2** 0.65 *mL* (6 *mmol*). The mixture was boiled for 10–12 *h*. The reaction mixture was cooled, water was added, stirred for 15 *min*, the precipitate was filtered off, washed with water.

*2-((1-(4,5,5-Trimethyl-2-oxo-2,5-dihydrofuran-3-yl)ethylidene)hydrazono)--thiazolidin-4-one (**3a**).* Yield 88%, R_f 0.56, m.p. 218–220°*C*. ^{1}H NMR spectrum, *δ*, *ppm*: 1.45 s (6H, $2CH_3$), 2.38 s (6H, $2C\underline{H}_3$), 3.75 s (2H, CH_2), 11.6 br.s (1H, NH). ^{13}C NMR spectrum, *δ*, *ppm*: 12.98 ($2CH_3$), 15.58 (CH_3), 24.16 ($S–CH_2$), 32.45 (CH_3), 84.47 (C_5), 122.65 (C_3), 155.88 (C_4), 164.33 (C=N), 168.97 (C=N), 169.84 (C=O),172.80 (C=O).

*2-((1-(5-Ethyl-4,5-dimethyl-2-oxo-2,5-dihydrofuran-3-yl)ethylidene)hydrazono)thiazolidin-4-one (**3b**).* Yield 87%, R_f 0.55, m.p. 230–232°*C*, $[\alpha]_D^{20}$ 0 c (0.5, DMSO). ^{1}H NMR spectrum, *δ*, *ppm*: 0.75 t (3H, *J* 7.3 *Hz*, $CH_2C\underline{H}_3$), 1.44 s (3H, CH_3), 1.78 d q (1H, $\underline{CH_2}CH_3$, *J* 14.6, 7.3 *Hz*), 1.94 d q (1H, $\underline{CH_2}CH_3$, *J* 14.6, 7.3 *Hz*), 2.38 s (6H, $2CH_3$), 3.74 c (2H, CH_2), 11.69 br.s (1H, NH). ^{13}C NMR spectrum, *δ*, *ppm*: 6.92 (CH_3), 11.99 (CH_3), 15.51 (CH_3), 23.27 (CH_2), 29.64 (CH_3), 32.49 ($S–CH_2$), 84.49 (C_5), 122.65 (C_3), 155.88 (C_4), 164.33 (C=N), 168.97 (C=*N*), 169.84 (C=O), 172.80 (C=O).

*2-((1-(4-Methyl-2-oxo-1-oxaspiro[4.4]non-3-en-3-yl)ethylidene)hydrazono)-thiazolidin-4-one (**3c**).* Yield 88%, R_f 0.54, m.p. 190–192°*C*. ^{1}H NMR spectrum, *δ*, *ppm*: 1.42 m (2H) and 1.58–1.85 m (6H, $(CH_2)_4$), 2.38 s (6H, $2C\underline{H}_3$), 3.75 s (2H, CH_2), 11.8 br.s (1H, NH). ^{13}C NMR spectrum, *δ*, *ppm*: 15.68 (CH_3), 22.10 (CH_2), 22.22 (CH_2), 25.09 (CH_2), 26.95 (CH_2), 27.13 ($S–CH_2$), 40.24 (CH_3), 83.64 (C_5), 120.68 (C_3), 155.64 (C_4), 169.13 (C=N), 168.97 (C=N), 172.23(C=O), 172.58 (C=O).

*2-((1-(4-Methyl-2-oxo-1-oxaspiro[4.5]dec-3-en-3-yl)ethylidene)hydrazono)-thiazolidin-4-one (**3d**).* Yield 85%, R_f 0.54, m.p. 210–212°*C* . ^{1}H NMR spectrum, *δ*, *ppm*: 1.42 m (2H) and 1.58–1.85 m (6H, $(CH_2)_4$), 2.38 s (6H, $2C\underline{H}_3$), 3.75 s (2H, CH_2), 11.8 br.s (1H, NH). ^{13}C NMR spectrum, *δ*, *ppm*: 15.68 (CH_3), 21.4 ($2CH_2$), 23.8 (CH_2), 32.3 ($2CH_2$), 24.30 ($S–CH_2$), 38.96 (CH_3), 84.47 (C_5), 122.65 (C_3), 155.88 (C_4), 164.33 (C=N), 168.97 (C=N), 170.84 (C=O),172.80 (C=O).

Biological Part. The data were analyzed statistically using Student's and Fisher's tests. The antibacterial activities of the starting compounds **1 a**–**d** and the obtained compounds **3 a**–**d** were evaluated against Gram-positive (*Staphylococcus aureus* – 209p and 1) and Gram-negative (*Shigella Flexneri* 6858, *Esherichia coli* 0–55) bacteria by the agar diffusion technique with microbial loading 20×10^6 microbes per *mL* of medium. Solutions of the tested compounds were prepared in DMSO at a 1 : 20 concentration and poured (0.1 *mL*) into cylinders placed on the surface of an agar medium inoculated with test strain in Petri dishes. The results were evaluated from the diameter (*d*, *mm*) of the microbe growth inhibition zone at the compound application site after growth for 20 *h* at 37°*C*. The tests were repeated three times. The zones of inhibition were measured in millimetre (*mm*) to estimate the potency of the test compound.

Conclusion. New derivatives of 2-oxo-2,5-dihydrofurans containing an oxo-thiazolidinylidene ring were successfully synthesized by the convenient and efficient method, based on the reaction of thiosemicarbazones of 3-acetyl-2-oxo--2,5-dihydrofurans with ethyl chloroacetate in the presence of sodium acetate. The synthesized compounds **3 a**–**d** exhibited moderate to defined antibacterial activities against Gram-positive (*Staphylococcus aureus* – 209p and 1) and Gram-negative (*Shigella Flexneri* 6858, *Esherichia coli* 0–55) bacteria compared to furazolidone.

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2-ՕՔՍՈ-2,5-ԴԻՀԻԴՐՈՖՈՒՐԱՆՆԵՐԻ ՕՔՍՈԹԻԱԶՈԼԻԴԻՆԻԼԻԴԵՆԱՅԻՆ ՕՂԱԿ ՊԱՐՈՒՆԱԿՈՂ ՆՈՐ ԱԾԱՆՑՅԱԼՆԵՐԻ ՍԻՆԹԵԶ ԵՎ ՀԱԿԱՄԱՆՐԷԱՅԻՆ ԱԿՏԻՎՈՒԹՅԱՆ ՈՒՍՈՒՄՆԱՍԻՐՈՒԹՅՈՒՆ

Ամփոփում

2-Օքսո-2,5-դիհիդրոֆուրանների օքսոթիազոլիդինիլիդենային օղակ պարունակող նոր ածանցյալները հաջողությամբ սինթեզվել են 3-ացետիլ-2--օքսո-2,5-դիհիդրոֆուրանների թիոսեմիկարբազոնների հիմքի վրա: Սինթեզված միացությունները ցուցաբերում են չափավոր կամ արտահայտված հակամանր է ային ակտիվություն գրամ-դրական (*Staphylococcus aureus* – 209p, 1) և գրամ-բացասական (*Shigella Flexneri* 6858, *Esherichia coli* 0–55) մանրէային շտամների նկատմամբ համեմատած որպես էտալոն ընտրված ֆուրազոլիդոնի հետ:

Г. Г. ТОКМАДЖЯН, Л. В. КАРАПЕТЯН, Р. В. ПАРОНИКЯН, Г. М. СТЕПАНЯН

СИНТЕЗ И ИЗУЧЕНИЕ АНТИБАКТЕРИАЛЬНОЙ АКТИВНОСТИ НОВЫХ ПРОИЗВОДНЫХ 2-ОКСО-2,5-ДИГИДРОФУРАНОВ, СОДЕРЖАЩИХ ОКСОТИАЗОЛИДИНИЛИДЕНОВОЕ КОЛЬЦО

Резюме

Новые производные 2-оксо-2,5-дигидрофуранов, содержащие оксотиазолидинилиденовое кольцо, синтезированы на основе тиосемикарбазонов 3-ацетил-2-оксо-2,5-дигидрофуранов. По сравнению с выбранным в качестве эталона фуразолидоном, синтезированные соединения проявляют умеренную или выраженную антибактериальную активность против грамположительных (*Staphylococcus aureus* – 209p и 1) и грамотрицательных (*Shigella Flexneri* 6858, *Esherichia coli* 0–55) бактерий.