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The antibacterial activity of substituted 4-(hydroxymethyl)-5,5-dimethyl-2,5-dihydro-2-oxofurans

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ABSTRACT

*The antibacterial activities of 4-(hydroxymethyl)-5,5-dimethyl-2,5-dihydro-2-oxofuran derivatives have been evaluated. They exhibited high antibacterial activities in vitro and in vivo. These compounds, especially compound **1**, definitely exceeded norsulfazole and furazolidone in case of study in vitro. They had analogous advantage in respect of norsulfazole during the study in vivo.*

Keywords: 4-(Hydroxymethyl)-2,5-dihydro-2-oxofurans, Antibacterial activity, Norsulfazole, Furazolidone.

INTRODUCTION

2,5-Dihydro-2-oxofuran derivatives are a large family of heterocycles that include synthetically useful compounds, several natural products [1-14], and a number of drugs with diverse biological activities such as antifungal, antibacterial, and anti-inflammatory properties [15-19]. Thus, there has been a continuous interest in the development of efficient and convenient methods for the preparation of these heterocycles and in their applications [10-14, 20-22].

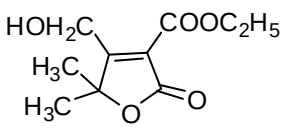
By considering the above facts and their increasing importance in pharmaceutical and biological field, it was considered of interest to synthesize some new compounds and to evaluate their biological activities.

Herein we described the *in-vitro and in-vivo* screenings and results of the antibacterial activities of the ethyl 4-(hydroxymethyl)-5,5-dimethyl-2-oxo-2,5-dihydrofuran-3-carboxylate (**1**) and 4-(hydroxymethyl)-5,5-dimethyl-2-oxo-2,5-dihydrofuran-3-carboxylic acid (**2**) [23].

MATERIALS AND METHODS

Source of chemicals

All chemicals used were of analytical grade. In view of the enormous biological potency associated with 2,5-dihydro-2-oxofuran derivatives, two synthesized ethyl 4-(hydroxymethyl)-5,5-dimethyl-2,5-dihydro-2-oxofuran-3-carboxylate (**1**) and 4-(hydroxymethyl)-5,5-dimethyl-2,5-dihydro-oxofuran-3-carboxylic acid (**2**) [23] were selected in the present work for the study of their antibacterial activity.



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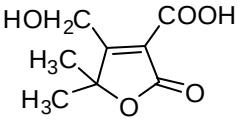

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Substituted 2,5-dihydro-2-oxofuran derivatives **1, 2** used in the present study;

Antibacterial activity

The antibacterial activities of compounds **1,2** were evaluated *in vitro* , viz., both by the agar diffusion technique and by the method of serial cultivation [24, 25] as well as *in vivo*, viz., by the generalized infection method of white mice [26]. The antibacterial activities of compounds **1, 2** were compared with standard drugs norsulfazole and furazolidone [27].

Antibacterial activity against Gram-positive (Staphylococcus aureus – 209p, 118, 1, 25923, 91, 93) and Gram-negative (Sh. Dysenteriae Flexneri 6858, E.typhi 79, Proteus vulgaris, E.coli 0–55) bacteria was tested by the method of "diffusion in agar".

In the method of serial cultivation Gram-positive (Staphylococcus aureus 209p, 25923) and Gram-negative (Sh. Dysenteriae Flexneri 6858, E.typhi 79) bacteria were used.

The antibacterial activities of compounds **1, 2** were studied by "diffusion in agar" and serial cultivation methods with microbial loading 20 x 10^6 microbes per mL of medium. Solutions of the tested compounds were prepared in DMSO at concentration of 1 : 20. Results were evaluated from the diameter (in mm) of the microbe growth inhibition zone at the compound application site after growth for 20 hours at 37^{o}C. The tests were repeated three times.

In the method of serial cultivation the experiments were performed in meat infusion broth (pH – 7.2 – 7.4). Serial dilutions were performed for each microbe using rows of 5 – 7 tubes containing growth medium with various concentrations of tested compounds. The tubes were inoculated with the same amount of bacterial suspension prepared from an 18 hours culture. The test results were evaluated from microbe growth after 20 – 24 hours of incubation at 37^{o}C.

The toxicities of compounds **1, 2** have been studied on 18 – 20 white mice. The researches were spent on mice at a time internal introduction. The compounds **1, 2** were poorly solubilize in water and was used with 0.5% carboxymethylcellulose solution.

The chemotherapeutic effects of compounds **1, 2** have been studied on 16–18 white mice during the Staphylococcus aureus 91, 93 and Sh. Dysenteriae Flexneri 6858 infections. The experimental animals were in usual laboratory conditions. The supervision over animals were spent for 10 days after introduction of drug. The infection has been obtained from the intraperitoneal introduction (by 1mL volume) of bacteria for 24 hours, after the suspension had been prepared with physiological liquid. It was used such dose, which afforded 90-100 % drop of untreated animals for 24–48 hours.

The compounds were introduced *peros*, at a time, with 200mg/kg dose (½ MED), with 0,5mL volume, with infection, simultaneously. The supervision over animals was spent for 10 days. The activity of compounds is appreciated by the total duration of experimental mice's life during the supervision, expressed by mice days and percentages in the mice group in respect of maximum possible duration of life. The significance of difference of the life duration of treated and untreated animals was established by calculation of X^2 criterion [28]. In the same conditions were tested norsulfazole and furazolidone (1500mg/kg and 500 mg/kg doses, respectively).

RESULTS AND DISCUSSION

Antibacterial activity

The results presented in Table 1 revealed that compounds **1, 2** exhibited obviously high antibacterial activities compared to the norsulfazole and furazolidone against both Gram-positive and Gram-negative bacteria.

The results presented in Table 2 revealed that the antibacterial activities of compounds **1, 2** and furazolidone were alike (Minimum Inhibitory Concentration (MIC) is 39–625 μg/mL), but the antibacterial activities of compounds **1, 2** exceeded the analogous activity of norsulfazole (MIC > 1250 μg/mL).

The experimental study has shown that compounds **1, 2** possessed considerably high toxicities and did not differ among themselves. Their absolutely lethal dose (LD_{100}) was 1250 mg/kg, and maximum endurable dose (MED) was 450 mg/kg. It was necessary to specify that the compounds **1, 2** were more toxic, than norsulfazole and furazolidone (MED = 3000mg/kg and 1000 mg/kg, respectively).

It has been established that compounds **1, 2** exhibited obviously medicinal effect during the Staphylococcus infections. They added the life duration of experimental mice 67-73% (Table 3). Analogous effect had furazolidone, but the advantage of compounds **1, 2** was obviously in respect of norsulfazole. These compounds and furazolidone exhibited analogous high activities during the Dysenteriae infection and significantly exceeded norsulfazole.

Thus, compounds **1, 2** exhibited high antibacterial activities during the studies *in vitro* and *in vivo*. These compounds, especially compound **1**, definitely exceeded norsulfazole and furazolidone in case of study *in vitro*. They have analogous advantage in respect of norsulfazole during the study *in vivo*.

Table 1: Zones of Inhibition of bacteria in mm

Compound Number	Gram-positive bacteria						Gram-negative bacteria			
	Staphylococcus aureus						Escherichia coli 0–55	Shigella dysenteriae Flexneri 6858,	E. typhi 79	Proteus vulgaris
	209p	1	118	25923	93	91				
1	26	28	27	28	28	27	19	28	28	18
2	24	27	26	26	27	26	20	27	27	18
Norsulfazole	20	18	20	20	15	20	12	14	16	10
Furazolidone	20	22	24	20	22	22	16	20	16	14

Table 2: Minimum Inhibitory Concentration (MIC)

Compound Number	MIC, µg/mL			
	Staphylococcus aureus 209p	Staphylococcus aureus 25923	Shigella dysenteriae Flexneri 6858	E.typhi 79
1	39	39	39	78
2	312	312	312	625
Norsulfazole	>1250	>1250	>1250	>1250
Furazolidone	39	39	39	78

Table 3: The chemotherapeutic effects of compounds 1 and 2

Bacteria	Compound number	Dose mg/kg	Quantity of animals	Quantity of living animals	The total duration of experimental mice's life		
					absolute *	%	P**
Staphylococcus aureus 91	1	200	15	11	110/150	73,3	<0,01
	2	200	15	10	100/150	66,6	<0,01
	Norsulfazole	1500	5	2	20/50	40	<0,01
	Furazolidone	500	10	7	70/100	70	<0,01
	Control	–	5	–	0/50	–	–
Staphylococcus aureus 93	1	200	10	7	70/100	70	<0,01
	2	200	10	7	70/100	70	<0,01
	Norsulfazole	1500	5	2	20/50	40	<0,01
	Furazolidone	500	10	7	70/100	70	<0,01
	Control	–	10	1	10/100	10	–
Sh. Dysenteriae Flexneri 6858	1	200	10	6	60/100	60	<0,01
	2	200	10	6	60/100	60	<0,01
	Norsulfazole	1500	5	2	20/50	40	<0,01
	Furazolidone	500	5	3	30/50	60	<0,01
	Control	–	5	–	0/50	–	–

** numerator – the quantity of mice days in the mice group*
denominator – the maximum possible quantity of mice days for 10 days supervision
*** the probable absence of difference between experimental and control groups*

CONCLUSION

The antibacterial activity of compounds **1, 2** was tested against Gram-positive (Staphylococcus aureus – 209p, 118, 1, 25923, 91, 93) and Gram-negative (Sh. Dysenteriae Flexneri 6858, E.typhi 79, Proteus vulgaris, E.coli 0–55) bacteria by the method of "diffusion in agar. Compounds **1, 2** exhibit obviously high antibacterial activities compared to the norsulfazole and furazolidone against both Gram-positive bacteria and Gram-negative bacteria. The antibacterial activity of synthesized compounds **1, 2** was tested against Gram-positive (Staphylococcus aureus 209p, 25923) and Gram-negative (Sh. Dysenteriae Flexneri 6858, E.typhi 79) bacteria by the method of serial

cultivation. The antibacterial activities of compounds **1, 2** and furazolidone were alike, but the antibacterial activities of compounds **1, 2** exceeded the analogous activity of norsulfazole.

Compounds **1, 2** possessed considerably high toxicity and did not differ among themselves. They were more toxic, than norsulfazole and furazolidone.

Compounds **1, 2** exhibited obviously chemotherapeutic effect during the Staphylococcus infections. They added the life duration of experimental mice 67–73%. Analogous effect had furazolidone, but their advantage was obvious in respect of norsulfazole. These compounds and furazolidone exhibited analogous high activity during the Dysenteriae infection and significantly exceeded norsulfazole.

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