SYNTHESIS AND ANTIMICROBIAL ACTIVITY STUDY OF 2,4-DIOXO-*N*-ARYL-3-(ARYLMETHYL)-1,3,7-TRIAZASPIRO[4.4]NONANE-7-CARBOXAMIDES

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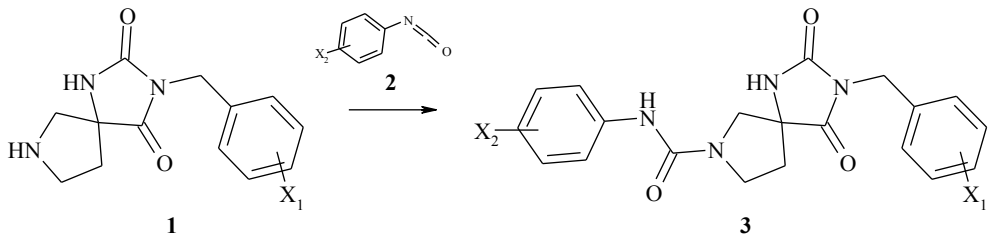
Introduction. The recent studies in the field of imidazoline-2,4-dione, which is also called hydantoin, confirm the high potential for antibacterial activity of the compounds with this fragment. Hydantoins were also reported as the compounds potentiating the antibiotic activity of oxacillin and cloxacillin, that is why the design of the promising antibacterials based on hydantoin moiety modification is a good way for modern antibacterial drugs discovery. It was earlier reported that 3-(arylmethyl)-1,3,7-triazaspiro[4.4]nonan-2,4-diones and the products of their secondary amine group acylation with arene carboxylic acids showed high antibacterial activity against the gram-positive and gram-negative bacteria and some strains of fungi.

Aim. The aim of our research was the development of synthetic method for 2,4-dioxo-*N*-aryl-3-(arylmethyl)-1,3,7-triazaspiro[4.4]nonane-7-carboxamide preparation and antimicrobial activity study thereof.

Materials and methods. All the reagents were obtained from the commercial sources. Synthesis was performed using the standard equipment for parallel liquid-phase procedures. The melting points (°C) were measured with a Kofler melting point apparatus and were not corrected. The structures of the obtained compounds were assigned using the ^{1}H, ^{13}C NMR and liquid-chromatography-MS methods. The antimicrobial activity study against the strains of gram-positive and gram-negative bacteria was performed using the agar "well" diffusion method.

Results and discussion. For the preparation of the target 2,4-dioxo-*N*-aryl-3-(arylmethyl)-1,3,7-triazaspiro[4.4]nonane-7-carboxamides **3** the reaction of the starting 3-(arylmethyl)-1,3,7-triazaspiro[4.4]nonan-2,4-diones with aromatic isocyanates was used according to the scheme 1.

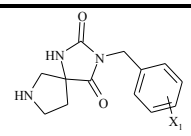
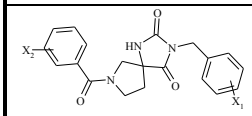
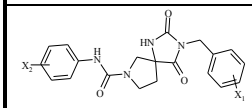
The series of the 2,4-dioxo-*N*-aryl-3-(arylmethyl)-1,3,7-triazaspiro[4.4]nonane-7-carboxamides **3** were tested for antimicrobial activity against the standard strains of bacteria and the strain of *Candida albicans* fungi. It was found that introduction of the aromatic urea fragment increases the antibacterial activity of the compounds **3**.



Scheme 1 *– Syntehsis of 2,4-dioxo-N-aryl-3-(arylmethyl)-1,3,7-triazaspiro[4.4]nonane-7-carboxamides*

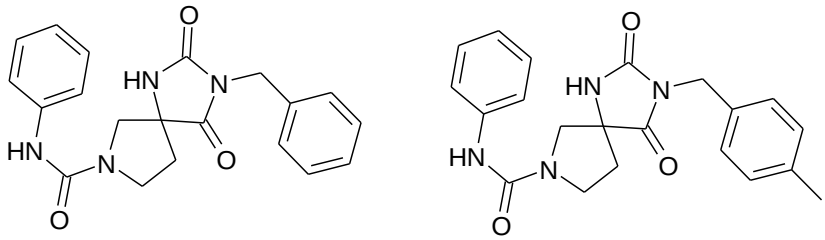
The obtained 2,4-dioxo-*N*-aryl-3-(arylmethyl)-1,3,7-triazaspiro[4.4]nonane-7-carboxamides **3** were found to be more active than the 3-(arylmethyl)-1,3,7-triazaspiro[4.4]nonan-2,4-diones **1** and also than the compounds modified with aroyl radicals (table 1).

Table 1

№	The average diameter of growth inhibition zones, mm					
	Gram-positive bacteria			**Gram-negative bacteria**		**Fungi**
	S. a.	***B. c.***	***E. c.***	***P. v.***	***P. a.***	***C. a.****
	16	16	15	14	14	14
	16	16	15	13	13	13
	17	17	17	16	16	20

**S. a.*– *Staphylococcus aureus* (ATCC 25923); *B. s.*– *Bacillus subtilis* (ATCC 6633); *E. c.*– *Escherichia coli* (ATCC 25922); *P. v.*– *Proteus vulgaris* (ATCC 4636); *P. a.*– *Pseudomonas aeruginosa* (ATCC 27853); *C. a.*– *Candida albicans* (ATCC 885/653).

Conclusions. The highest antifungal activity was determined for the compounds with unsubstituted phenyl radical in the urea fragment and the benzyl or 4-methylbenzyl radicals as the substituents at hydantoin cycle.



*The most active compounds **3** structures*

The similar compounds **3** with 3-methylbenzyl and 2,5-dimethylbenzyl substituents at hydantoin cycle effectively inhibited the growth of *Staphylococcus aureus* and *Bacillus subtilis.*