DR-44. SYNTHESIS AND CYTOTOXIC EFFECT OF 1-ARYL-SUBSTITUTED-6-IMINO-2,7-DIOXABICYCLO[3.2.1]OCTANE-4,4,5-TRICARBONITRILES

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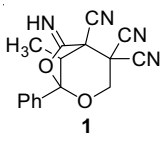
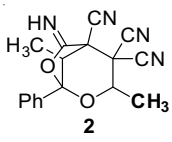
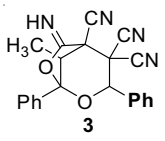
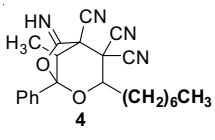
Directed synthesis of compounds with antitumor activity is one of the most important tasks of modern organic, pharmaceutical and medical chemistry. It is the first step to the creation of novel available and low cost medicals, which are so necessary nowadays.

Compounds of heterobicyclo[3.2.1]octane series are unique objects for studying their biological activity. This rigid skeleton determines an unambiguous arrangement of functional groups in three-dimensional space, which is the most important condition for an effective interaction of a molecule with a specified biotarget, that allows the substance to be selective in various physiological processes.

The cytotoxic effect of 6-imino-2,7-dioxabicyclo[3.2.1]octane-4,4,5-tricarbonitriles on various cancer cell lines has been previously reported [1]. Moreover, we also reported that 1-aryl-substituted derivatives are among the best of studied agents of the 2,7-dioxabicyclo[3.2.1]octane series. In this work have synthesized several 1-phenyl-substituted 6-imino-2,7-dioxabicyclo[3.2.1]octane-4,4,5-tricarbonitriles **1–4** according to the our described procedure [2] and studied their cytotoxicity to find an influence of substituent in the third position of bridge system (see Table).

The cytotoxicity of the compounds was studied *in vitro* using the MTT-test [3] on a human cervical adenocarcinoma cell line (*HeLa*). The exposure duration of the cell line with the test agent ranged from 24 to 72 h.

Half maximal (50 %) inhibitory concentration (IC) of compounds 1–4 at different duration of exposure on *HeLa* cell line

Parameter	Compound								
	 **1**			 **2**		 **3**	 **4**		
IC_{50}, μM	> 100	67	57	25	25	40	68	34	26
Exposure duration, h	24	48	72	48	72	48	24	48	72

Studies of the cytotoxic effect of the synthesized compounds **1–4** showed that compounds **2** and **4** with an alkyl moiety in the third position have a good cytotoxic effect after 48 and 72 h of exposure on the cell line. For compound **3** with phenyl ring in the third position of bridge system moderate cytotoxicity was noted. Good results of alkyl-substituted compounds **2** and especially **4** can be explained by an increased lipophilicity of the molecules, that shows us the prospective for further investigations.

References

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