SYNTHESIS OF NOVEL ISOINDOLINE-1,3-DIONE N-DERIVATIVES AS PROMISING ANTICANCER AGENTS

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Introduction. Cyclic imides derivatives are widely used in modern medical practice as effective drugs. These compounds exhibit the versatile biological activities namely: anticonvulsant, anxiolytic, antidepressant, antineoplastic and more. It is important, that mentioned above compounds are promising objects for chemical modification. Thus, the new functional groups that modify the expression of pharmacological activity can be introduced in structure of cyclic imides.

Aim. Our research is devoted to the synthesis and anticancer activity evaluation of novel cyclic imides, that contain isoindoline-1,3-dione and 1,2,4-triazine moieties.

Materials and methods. The features of the reaction between initial 6-R-3-(2-aminophenyl)-1,2,4-triazin-5-ones (I) and phthalic anhydride in a glacial acetic acid were studied. The structure and purity of synthesized compounds were confirmed by the complex of physicochemical methods (^{1}H, ^{13}C NMR, IR, LC-MS, MS, X-ray study). Anticancer activity according to NCI DTP protocol were study for the four of synthesized compounds. Mentioned above activity was studied in vitro on 60 human cancer cell lines at 10.00 μM concentration.

Results and discussion. It was shown, that mentioned reaction led to the formation of 2-(2-(6-R-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)phenyl)isoindoline-1,3-diones with high yields. As we consider, reactions proceeded as multistep process wherein products of N-acylation played role of the intermediate. The direction of subsequent cyclisation caused by proximity of formed carboxylic group and amide fragment. The results of the biological activity screening showed that synthesized compounds exhibited moderate anticancer activity. Thus synthesized compounds inhibited the growth of kidney cancer (on 22%) and non-small lung cancer.

Conclusions. Interaction of 6-R-3-(2-aminophenyl)-1,2,4-triazin-5-ones with phthalic anhydride proceed as "classical" acylation followed by cyclization. The products of this reaction are the new derivatives, that contain isoindoline-1,3-dione and 1,2,4-triazine moieties. The structures of the synthesized compounds were confirmed by complex of instrumental methods. The obtained 2-(2-(6-R-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)phenyl)isoindoline-1,3-diones (II) reveal antitumor activity against kidney cancer, breast cancer, and non-small cell lung cancer.