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Development of Tdp1 inhibitors based on natural biologically active compounds as prototypes of antitumor drugs

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Motivation and Aim: Developing inhibitors for DNA repair enzymes is a promising approach to improve anticancer therapy, in particular for drug-resistant tumors. Tdp1 plays a key role in the repair of Top1-DNA covalent complexes formed by topoisomerase-1 (Top1) poisons such as drugs of the camptothecin group, which makes it a promising target in the treatment of cancer [1]. The development of new inhibitors of DNA repair enzymes based on natural compounds and their derivatives is particularly relevant, since such compounds often have complementarity to targets of biological origin and possess broad range of biological activities.
Methods and Algorithms: Screening of compounds – potential inhibitors is carried out using a real-time fluorescence measurement method, which makes it possible to determine the initial reaction rate with high accuracy [2]. The effect of the selected compounds on the proliferation of transplanted tumor cell lines and the evaluation of cell death are studied using the MTT test. We used derivatives of usnic acid, coumarin and adamantane for Tdp1 inhibitors screening.
Results: All studied classes of compounds have a pronounced inhibitory effect. The dependence of the inhibitory activity on the structure of the compounds was revealed. Among the inhibitors found, there are both moderately toxic and non-toxic compounds. Usnic acid, coumarin, and adamantan derivatives proved to be sensitizers of the tumor cell lines to Top1 poison topotecan, with twofold enhancement of cytotoxicity of topotecan [3–6].
Conclusion: The compounds studied can be used to develop on their basis effective sensitizers of malignant cells to Top1 poisons. The therapeutic effect of such substances can be a selective increase in the activity of Top1 poisons in tumors. Non-toxic inhibitors of Tdp1 are of particular interest, since will avoid additional side effects.
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