NOVEL PROMISING INHIBITORS OF TYROSYL-DNA PHOSPHODIESTERASE I (TDP 1) COMBINING 4-ARYLCOUMARIN AND MONOTERPENOID MOIETIES

T. Khomenko¹, A. Zakharenko², A. Chepanova², E. Ilina², O. Zakharova², V. Kaledin³, V. Nikolin³, N. Popova³, D. Korchagina¹, K. Volcho¹, N. Salakhutdinov¹ and O. Lavrik²

¹N.N. Vorozhtsov Novosibirsk Institute of Organic Chemistry,
Siberian Branch of the Russian Academy of Sciences,
630090, Russia, Novosibirsk, pr. Lavrentieva, 9.

²Novosibirsk Institute of Chemical Biology and Fundamental Medicine,
Siberian Branch of the Russian Academy of Sciences,
630090, Russia, Novosibirsk, pr. Lavrentieva, 8.

³Institute of Cytology and Genetics, 10, acad. Lavrentjev Ave., 630090 Novosibirsk, Russia.

DOI: 10.19163/MedChemRussia2021-2021-293

E-mail: chomenko@nioch.nsc.ru

Tyrosyl-DNA phosphodiesterase 1 (Tdp1) is a promising inhibition target for the development of new chemosensitizing agents due to its ability to remove DNA damage caused by topoisomerase 1 (Top1) poisons, such as topotecan. We have synthesized new arylcoumarin (neoflavonoid) derivatives with monoterpene substituents for testing their inhibitory activity against Tdp1, and studying the synergistic effect with topotecan, a clinically-important Top1 inhibitor, in *in vivo* experiments. Substituted coumarins were prepared by the reaction of monoterpene bromides with coumarins synthesized by the Pechmann condensation of resorcinol with β -ketoesters.

Our results showed that arylcoumarin-monoterpene hybrids are potent Tdp1 inhibitors with IC₅₀ values in the submicromolar range [1]. *In vivo* experiments with mice were revealed that the derivative of geraniol and 4-arylcoumarin (R₁=F) (IC₅₀ 0.62 μ M) induced a significant increase in the antitumor effect of topotecan on the Krebs-2 ascites tumor model. In addition, these compounds presented the good physicochemical properties required for oral bioavailability. Thus, this type of arylcoumarin-monoterpene hybrids represents an excellent starting point for the further development of adjuvant therapy against cancer in combination with Top 1 poisons.

This work was supported by the Russian Science Foundation (grant 19-13-00040).

References

[1] T. M. Khomenko, A. Zakharenko, A. Chepanova et al. Int. J. Mol. Sci. 2020, 21, 126.