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DNA REPAIR ENZYMES INHIBITION AS A PROMISING APPROACH TO NEW ANTI-CANCER DRUGS

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The cytotoxic effects of chemotherapy and radiation that are clinically used to treat malignances are directly related to their propensity to generate DNA damage. The capacity of cancer cells to recognize DNA damage and initiate DNA repair is a key mechanism for therapeutic resistance to chemotherapy. Therefore, the targeting of DNA repair enzymes can be used as a strategy to potentiate the cytotoxicity of the currently available DNA damaging agents towards cancer cells. PARP1 (poly ADP ribose polymerase 1, the enzyme involved in DNA repair) inhibitors such as Olaparib, Rucaparib and Niraparib are in clinical use already. New and very promising target for antitumor therapy is tyrosyl-DNA phosphodiesterase 1 (Tdp1). It plays a key role in the removal of DNA damage resulting from inhibition of topoisomerase 1 (Topo1) with camptothecin and its clinical derivatives irinotecan and topotecan. Furthermore, Tdp1 is known to be capable of removing the DNA damage induced by other anticancer drugs commonly used in clinical practice. To date, a number of Tdp1 inhibitors of various types including dual Tdp1/Topo1 inhibitors are known. A set of very potent Tdp1 inhibitors was found by us among natural products derivatives. We designed new inhibitors using targeted modifications of terpenoids, coumarins, usnic acid and other types of natural products. Moreover, we found that benzopentathiepine derivatives are very effective inhibitors of Tdp1. Important that the ability of the inhibitors used in non-toxic concentration to enhance the cytotoxicity of camptothecin and topotecan, the established topoisomerase 1 poison, was demonstrated. Thus, we discovered of new original Tdp1 inhibitors, effectively inhibiting DNA repair in tumor cells for use as the components of complex anticancer drugs.

Biography

Konstantin Volcho pursued his PhD in 1997 from Novosibirsk State University, Russia. Since then he has been working in the department of medicinal chemistry at Novosibirsk Institute of Organic Chemistry (Russia). He is a Professor of Russian Academy of Sciences. His research interests include development of novel treatments against nervous system disorders, antivirals and anticancer agents, usually based on natural products derivatization. He has published about 150 papers in reputed journals. He is an inventor in more than 35 issued patents. Three compounds found with his participation are currently in preclinical studies as anti-parkinsonian, analgesic and antidepressant agents.

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