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Development of catalytic inhibitors of topoisomerase IIα as chemotherapeutic agents

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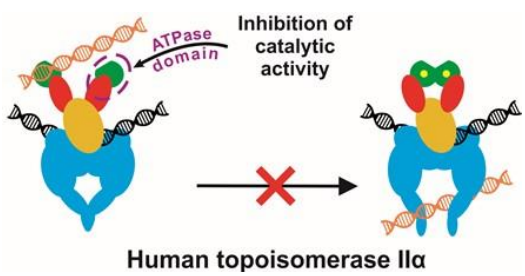
Human DNA topoisomerase IIα (htIIα) is a well-established anticancer target because it enables topological changes in the DNA molecule which are essential for transcription and translation [1]. There are several ways to inhibit htIIα, and agents targeting it are divided into two groups. In the established group of topoisomerase poisons, several molecules are used in clinical practice, such as doxorubicin and etoposide. Due to the frequent occurrence of serious side effects, predominantly cardiotoxicity and induction of secondary tumours, further drug development efforts have been made to take advantage of other inhibition paradigms available in the topo IIα catalytic cycle. This has led to the development of catalytic inhibitors that inhibit htIIα via alternative mechanisms. Such molecules could, in principle, possess an improved safety profile with comparable anticancer efficacy [2].
In our research, we develop catalytic inhibitors of htIIα that target the ATP binding site. In the first study based on a structural comparison of ATPase domains of human and bacterial type II topoisomerases, we discovered a series of substituted 4,5'-bithiazoles that act as catalytic ATP-competitive inhibitors. These compounds showed promising cytotoxicity against selected cancer cell lines, did not induce DNA double-strand breaks, and arrested the cell cycle mainly in G1 phase. This confirmed the mechanism of action, different from that of topoisomerase poisons also at the cellular level. [3]. In the second study, we utilized htIIα as a model target to outline a dynophore-based approach to catalytic inhibitor design. Based on molecular simulations of a known catalytic inhibitor [4] and the native ATP ligand analogue, AMP-PNP, we derived a joint dynophore model that supplements the static structure-based-pharmacophore information with a dynamic component. Subsequently, derived pharmacophore models were employed in a virtual screening campaign of a library of natural compounds. Experimental evaluation identified flavonoid compounds with htIIα catalytic inhibition and confirmed binding to its ATPase domain. [5].



References

[1] K. Bergant, et al., *Curr. Med. Chem.*, **2018**, 25, 3284-3316.
[2] B. Pogorelčnik, et al., *Curr. Med. Chem.*, **2013**, 20, 694-709.
[3] K. Bergant Loboda, et al., *J. Chem. Inf. Model.*, **2020,** 60, 3662-3678.
[4] B. Pogorelčnik, et al, *Bioorg. Med. Chem.*, **2015**, 23, 4218-4229.
[5] M. Janežič, et al., *Int. J. Mol. Sci.*, **2021**, 22, 1347