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Abstract

First-in-Class, Thiosemicarbazide-Based, Dual Inhibitors of Human DNA Topoisomerase IIα and Indoleamine-2,3-Dioxygenase 1 (IDO-1) with Strong Anticancer Properties †

Barbara Kaproń [1,*] and Tomasz Plech [2,*]

[1] Department of Clinical Genetics, Medical University of Lublin, Radziwiłłowska 11, 20-080 Lublin, Poland
[2] Department of Pharmacology, Medical University of Lublin, Radziwiłłowska 11, 20-080 Lublin, Poland
* Correspondence: barbarakapron@umlub.pl (B.K.); tomasz.plech@umlub.pl (T.P.)
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Abstract: According to a WHO report from 2020, cancer constitutes one of the leading causes of death worldwide. The number of cancer deaths is estimated to be approximately 10 million per year. These epidemiological data confirm that cancer is an increasingly global healthcare problem that needs urgent action. From a biological point of view, the basic feature of cancer is the uncontrolled growth and spread of abnormal cells from the place of origin to another part of the body. Inhibition of uncontrolled proliferation is one of the main goals of anticancer therapy. During our preliminary studies, we identified a group of thiosemicarbazide-based human DNA topoisomerase II inhibitors that decreased the viability of cancer cells and inhibited intracellular biosynthesis of their DNA much stronger than etoposide, i.e., clinically relevant topoisomerase II inhibitor. What is also important isthat the investigated compounds were recognized as topoisomerase II poisons because of their ability to stabilize the DNA-topoII cleavable complex. The investigated thiosemicarbazide derivatives were examined as potential anticancer agents against a panel of ten cancer cell lines. Moreover, we have discovered and described the first-in-class dual inhibitors of human DNA topoisomerase II/indoleamine-2,3-dioxygenase 1 (IDO1) that can lead to the future use of thiosemicarbazide derivatives as relevant components of anticancer immunotherapy.

Keywords: thiosemicarbazides; human DNA topoisomerase II; indoleamine-2,3-dioxygenase 1; anticancer therapy

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