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BOOK OF ABSTRACTS

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ST3: Antimelanoma Potential of New Telmisartan Analogues Without AT1 Receptor Activity

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Melanoma is one of the most aggressive malignancies, where the prognosis for metastatic patients remains extremely poor. Our group has shown that the antihypertensive drug telmisartan has antimelanoma potential[1]. Given that the antihypertensive effect is not favorable in cancer patients, the aim of this study was to design and test novel telmisartan derivatives without the angiotensin receptor 1 (AT1R) binding activity. New derivatives were designed by modification of the carboxylic group, in order to alter telmisartan geometry and its AT1R binding properties. Eight derivatives, from which the lack of AT1R antagonistic activity could be expected based on molecular docking, were synthetized and selected for *in vitro* testing. After the cytotoxicity test on human melanoma cell lines A375 and 518a2, three derivatives that were twice more potent than telmisartan itself were selected for further analysis. The new derivatives induced mitochondrial fragmentation, generation of the mitochondrial reactive oxygen species, and decrease of mitochondrial membrane potential in melanoma cells, the mechanism we previously shown for induction of apoptosis by telmisartan in melanoma cells. As the new derivatives showed more potent effect on melanoma cells than telmisartan these results lay a ground for further preclinical testing in melanoma.

[1]Grahovac *et al*. (2019) Cancer Biol Med, 16(2):247-263.