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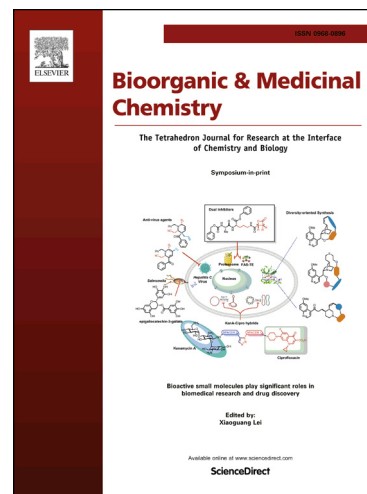
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THE SELECTIVE CYTOTOXICITY of NEW TRIAZENE COMPOUNDS TO HUMAN

MELANOMA CELLS

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Abstract

Metastatic melanoma still remains one of the most difficult cancers to overcome. The aim of our research was the design of anti-tumour triazene compounds **3** for application to a melanoma-specific therapy. The strategy exploits the unique enzyme pathway of melanin biosynthesis for conversion of non-toxic prodrugs into toxic drugs in the melanoma cell. The compounds **3** were designed by coupling two active moieties, the alkylating triazenes and different tyrosinase substrates. All compounds **3** revealed to be chemically stable in isotonic phosphate buffer (PBS) at physiologic pH ($t_{1/2} \geq 48\text{h}$), and most of them showed to be slowly hydrolysed in human plasma ($1.5 \leq t_{1/2} (\text{h}) \leq 161$). Compounds **3c-n** revealed to be excellent tyrosinase substrates ($0.74 \leq t_{1/2} (\text{min}) \leq 6$) with the best tyrosinase substrate **3l** releasing **MMT** 45 seconds after tyrosinase activation. Structure-activity relationship studies allowed the identification of the better structural features for enzyme affinity. Furthermore, the derivatives **3l** and **3m** showed cell selectivity with significant cytotoxic effects (IC_{50} values of 46-65 μM) against melanoma cell lines with tyrosinase overexpression MNT-1 and B16F10.

Key words: Triazenes, Melanoma cell lines, tyrosinase, target approach, enzyme activation

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