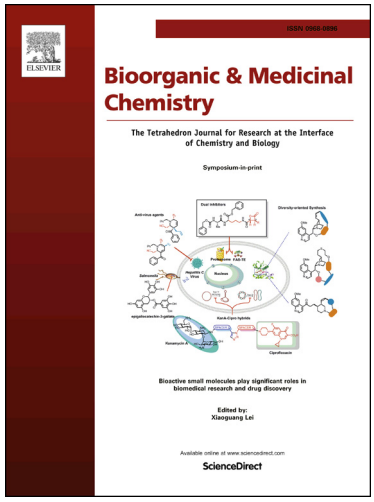

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THE SELECTIVE CYTOTOXICITY of NEW TRIAZENE COMPOUNDS TO HUMAN MELANOMA CELLS

Ana Sousa[a,1], Fábio Santos[a,1], Maria Manuela Gaspar[a], Susana Calado[a], João D. Pereira[a], Eduarda Mendes[a*], Ana Paula Francisco[a*], Maria Jesus Perry[a]

[a]*Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa. Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal.*

[1]AS and FS contributed equally to this work

*Corresponding authors

Abstract

Metastatic melanoma still remains one 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 ($t_{½} \geq 48h$), and most of them showed to be slowly hydrolysed in human plasma ($1.5 \leq t_{½}$ (h) ≤ 161). Compounds **3c**-**n** revealed to be excellent tyrosinase substrates ($0.74 \leq t_{½}$ (min) ≤ 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