

## SYNTHESIS AND EVALUATION OF TRIAZENE PRODRUGS AS CANDIDATES FOR MELANOCYTE-DIRECTED ENZYME PRODRUG THERAPY (MDEPT)

Eduarda Mendes<sup>a</sup>, Jim Iley<sup>b</sup>, and Rui Moreira<sup>a</sup>, M. Jesus Perry<sup>a</sup>

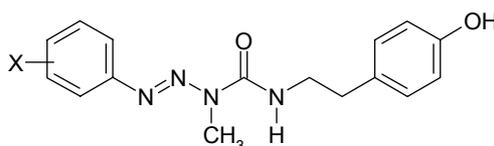
<sup>a</sup>CECF, Faculdade de Farmácia da Universidade de Lisboa,  
1699 Lisboa Codex, Portugal

<sup>b</sup>Chemistry Department, The Open University, Walton Hall,  
Milton Keynes MK7 6AA, UK

The approach which has been developed for triazene prodrugs is based on melanocyte-directed enzyme prodrug therapy (MDEPT). Triazenes have significant activity against malignant melanoma but show intolerable side effects. The mechanism sustaining their ability to act in cancer chemotherapy is the alkylation of DNA, through *in vivo* generation of methyldiazonium cations. Based on the unique occurrence of tyrosinase expression in melanocytes, the attachment of a drug to tyrosine would deliver the free drug only at the tumour site. To avoid systemic toxicity, the drug linker must be stable until drug release is required, and enzyme activity in blood and normal tissues must be very low.

To evaluate the feasibility of this approach, we have synthesised a range of triazene derivatives **1**. The stability of compounds **1** in phosphate buffer pH 7.4 and human plasma at 37°C has been determined. Compounds **1** are stable in pH 7.4 buffer for prolonged times (10 days) and in human plasma half-lives are > 70 h. The ability of prodrugs to liberate toxic agents upon exposure to tyrosinase is under study.

The authors thank Fundação para a Ciência e Tecnologia (Portugal) and FEDER for financial support.



**1**