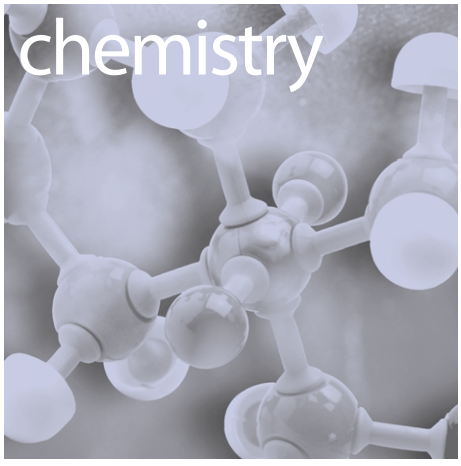
Monitor Editor: Matthew Thorne
m.thorne@elsevier.com

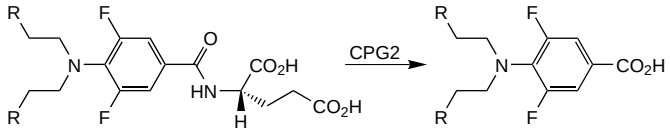
monitor



MOLECULES

Novel fluorinated prodrugs for gene-directed enzyme prodrug therapy

Gene-directed enzyme prodrug therapy (GDEPT) represents an attractive two-step approach towards the targeted activation of cancer chemotherapeutic agent prodrugs directly in tumors [1]. Selective introduction of a foreign gene for a prodrug-activating enzyme allows selective expression of the enzyme at the tumor site. Administration of a nontoxic prodrug would then lead to conversion by the enzyme to a cytotoxic agent at the site of the tumor, reducing the normal tissue toxicity associated with the cytotoxic therapy through localized activation.



(i): R=Br
(ii): R=I

(iii): R=Br
(iv): R=I

Davies and co-workers [2] (Institute of Cancer Research, Sutton, UK) have recently reported very promising *in vivo* antitumor activity through application of the GDEPT concept. Eight novel polyfluorinated alkylating agent prodrugs (plus their corresponding drugs) were prepared and evaluated as substrates for the bacterial enzyme carboxypeptidase G2 (CPG2). All di- and tri-fluorinated prodrugs were efficiently cleaved and were found to be differentially cytotoxic by more than two orders of magnitude towards a human breast tumor cell line (MDA MB 361) expressing CPG2, compared with control cells that did not express the enzyme. Most notably difluorinated prodrugs **(i)** and **(ii)** were found to have excellent therapeutic activity in an MDA MB 361 xenograft model. Both compounds were excellent substrates for CPG2, yielding drugs **(iii)** and **(iv),** respectively, with short half-lives (<5 mins) and producing a sustained delay and curative activity in the growth of tumors *in vivo*.

1 Niculescu-Duvaz, I. *et al.* (1999) Prodrugs for antibody- and gene-directed enzyme prodrug therapies (ADEPT and GDEPT). *Anticancer Drug Des.* 14, 517–538.
2 Davies, L. C. *et al.* (2005) Novel fluorinated prodrugs for activation by carboxypeptidase G2 showing good *in vivo* antitumor activity in gene-directed enzyme prodrug therapy. *J. Med. Chem.* 48, 5321–5328.

Andrew D. Westwell
andrew.westwell@nottingham.ac.uk

1359-6446/05/$ – see front matter PII: S1359-6446(05)03648-2