J. Pharm. Pharmacol. 1998, 50 (Supplement): 260

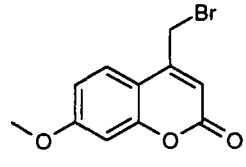
Toxicity and biotransformation of the anti-cancer agent 7-methoxy-4-bromomethylcoumarin

J. SIMPSON, M. D. COLEMAN, D. L. RATHBONE AND D. C. BILLINGTON

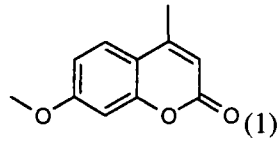
Pharmaceutical Sciences Institute, Aston University, Aston Triangle, Birmingham B4 7ET

4-Bromomethylcoumarins are known anti-proliferative agents with high activity against leukaemia and melanoma cells *in vitro*. As part of a cancer screening programme 7-methoxy-4-bromomethylcoumarin (MBMC) (1) was tested against two murine adenocarcinoma cell lines, MAC13 and MAC16, which are both generally refractive to standard cytotoxic agents. For both the MAC13 and the cachexia inducing MAC16 cell lines, MBMC had a profound anti-proliferative effect with IC_{50} values of below 1.5μM for the two cell lines.

The mode of action of MBMC has not been determined, however, the lack of any anti-tumour activity shown by the related compound 7-methoxy-4-methylcoumarin (MMC) (2) indicates that its activity is likely to be due to the alkylating ability of the 4-bromomethyl group.



MBMC



(1)

(2) MMC

Comparative direct toxicity of MBMC and MMC was determined using trypan blue exclusion in human mononuclear leukocytes (MNL) isolated from healthy volunteers and incubated with both compounds at concentrations of 50, 100 and 250μM. Toxicity was found to be significant with MBMC, compared with control (3.1±1.2%), at 250μM (14.1 ± 3.3%) and 100μM (8.0 ± 4.0%), but not at 50μM (5.3 ± 2.0%).

In the presence of a metabolizing system (2mg rat microsomes, 1mM NADPH) the toxicity of MBMC was significantly reduced (4.5 ± 2.2%) compared with control (18.5% ± 5.5%), suggesting that it underwent biotransformation to a less toxic compound. MMC showed no significant toxicity to MNLs in the presence of a metabolizing system. As MMC has the same basic structure as MBMC, the bromomethyl moiety may be responsible for both its toxicity and efficacy.

MBMC may be useful as a lead structure in the development of anti-proliferative compounds for use in the treatment of resistant cancers. Due to its biotranformationally mediated detoxification it is conceivable, that if delivered directly to the site of the tumour, systemic toxicity may be minimized when compared to other cytotoxic drugs.

Goto. J (1993) Anticancer agents containing coumarins Patent JP 0500,945 [9300,945]