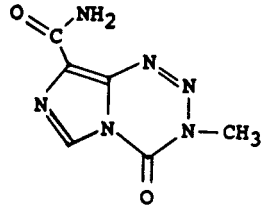
THE ANALYSIS AND MURINE PHARMACOKINETICS OF A NEW ANTITUMOUR AGENT: CCRG81045

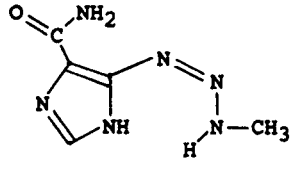
J.A. Slack, C. Goddard, M.F.G. Stevens, G.U. Baig and M.J. Griffin. CRC Experimental Chemotherapy Group, Pharmaceutical Sciences Institute, Aston University Birmingham B4 7ET.

CCRG 81045 (8-carbamoyl-3-methylimidazo[5,1-d]-1,2,3,5-tetrazin-4(3H)-one; NSC 362856, M&B 39831) is currently under preclinical investigation prior to Phase I clinical evaluation in the UK. CCRG 81045 has the ability to spontaneously generate the ring-opened triazene 5-(3-methyltriazen-1-yl)-imidazo-4-carboxamide (MTIC) which is the proposed active metabolite of DTIC (Dacarbazine).



CCRG 81045

A HPLC method has been developed for the quantitative analysis of CCRG 81045 in biological fluids. The method involves the addition of the internal standard (8-carbamoyl-3-ethylimidazo[5,1-d]-1,2,3,5-tetrazin-4(3H)-one) to acidified plasma, or urine and subsequent extraction with ethyl acetate. Following removal and evaporation of the organic layer the residue was redissolved in mobile phase prior to analysis by HPLC.



MTIC

CCRG 81045 and the internal standard were separated on a C_{18}, 10u, 5 mm ID, Waters radial compression cartridge with a mobile phase of methanol/5% acetic acid (10/90) and UV detection at 325 nm was utilised. The detection limits of the method were less than 10 ng/ml of CCRG 81045 in plasma with a coefficient of variation on replicate extractions (n=6) of 2%.

Stability studies undertaken on CCRG 81045 indicated that the drug decomposed in phosphate buffer (0.2 M, pH7.4) at 37° with a half life of 89.3 minutes. In human plasma and human plasma ultrafiltrate at pH 7.4 and 37° the decomposition half lives were 32.2 and 34.8 minutes respectively. Solutions of CCRG 81045 (30 $mg.ml^{-1}$) formulated in dimethylsulphoxide show no detectable decomposition when stored in the dark over a 14 week period.

In order to evaluate the essential pharmacokinetic parameters of CCRG 81045 in mice, male Balb C mice were dosed at 20 $mg.kg^{-1}$ by both the intraperitoneal and oral routes of administration. Peak plasma levels were attained within 10 minutes of drug administration and were 25.84 and 19.64 $mg.L^{-1}$ for the IP and PO routes respectively. Elimination half lives were 1.13 and 1.29 h for the IP and PO routes with no evidence for 2-compartment pharmacokinetics. AUCs were determined trapezoidally over the period 0-8 h with 36.71 $mg.h.L^{-1}$ obtained for the IP dosed animals and 36.56 $mg.h.L^{-1}$ for the orally dosed animals.

CCRG 81045 had previously been shown (Langdon et al 1985) to be more active than DTIC against model tumours, and has the potential advantage of being active following oral administration.

Langdon, S.P. et al (1985) Proc. Amer. Assoc. Cancer Res. 26: 1006.