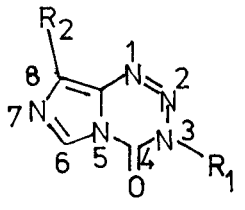
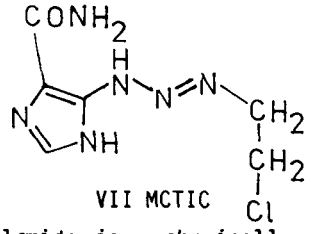
ANTITUMOUR IMIDAZOTETRAZINONES: THE CRYSTAL AND MOLECULAR STRUCTURE OF MITOZOLOMIDE AND FIVE OF ITS ANALOGUES

P. R. Lowe, C. H. Schwalbe, C. D. Whiston and M. F. G. Stevens, Pharmaceutical Sciences Institute, Aston University, Aston Triangle, Birmingham B4 7ET.

The novel antitumour compound mitozolomide (I) is a derivative of a new bicyclic ring system and entered Phase 1 clinical trial in 1983. A large number of analogues have since been synthesised with varying substituents at the N(3) and C(8) ring positions; the crystal structure of the title compound has been reported (Lowe et al, 1985) and this communication correlates structural studies on more analogues.



	R_1	R_2
I	CH_2CH_2Cl	$CONH_2$
II	Me	$CONH_2$
III	CH_2CH_2OMe	$CONH_2$
IV	CH_2CH_2Cl	SO_2NHMe
V	CH_2CH_2Cl	SO_2NMe_2
VI	CH_2CH_2Cl	SO_2Me



VII MCTIC

It has been proposed (Stevens et al, 1984) that mitozolomide is a chemically-activated prodrug: after achieving access to the tumour cells nucleophilic attack at C(4) initiates cleavage of the C(4)-N(5) bond leading to the formation of the cytotoxic triazene MCTIC (VII) which alkylates DNA. Experimentally determined bond lengths and interatomic angles for the six structures show the planar imidazotetrazinone moiety to be quite resistant to change on modifying the substituents at N(3) and C(8). An average of these bond lengths together with the average charge distribution for mitozolomide computed using an STO-3G *ab initio* molecular orbital calculation is shown in the Figure.

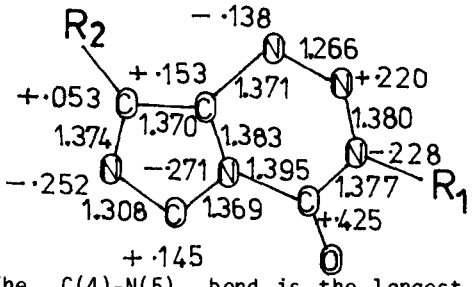


Figure. Average bond lengths (Å) and charge distribution.

The C(4)-N(5) bond is the longest and presumably weakest in the ring system (Av = 1.395 Å) and C(4) (residual charge +0.425) is electron deficient and thus open to nucleophilic attack. The results of this study suggest that ring-opening is possible for all the reported structures. However, this is not sufficient *per se* for antitumour activity. Whereas mitozolomide (I) and its 3-methyl analogue (II) display potent activity against a broad spectrum of mouse tumours *in vivo* (e.g. L1210 and P388 leukaemias, TLX5 lymphoma, B16 melanoma, M5076 sarcoma) the 3-(2-methoxyethyl)-analogue (III) is inactive against the L1210 and TLX5 tumours. The 3-(2-chloroethyl)-derivatives with sulphonamide (IV and V) and sulphone substituents (VI) at C(8) are equi-active with mitozolomide in L1210 and TLX5 tests.

Lowe, P.R., Schwalbe, C.H. and Stevens, M.F.G. (1985) J. Chem. Soc. Perkin II, 357-361.

Stevens, M.F.G., Hickman, J.A., Stone, R., Gibson, N.W., Baig, G.U., Lunt, E. and Newton, C.G. (1984) J. Med. Chem. 27, 196-201.