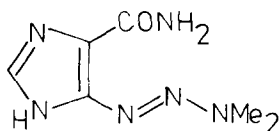


SEARCH FOR DRUG INTERACTIONS BETWEEN THE ANTITUMOUR AGENT DTIC AND OTHER CYTOTOXIC AGENTS

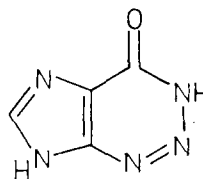
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DTIC (1) used in the treatment of malignant melanoma is a 'masked' diazonium compound (Stevens 1976). Interpretation of the molecular basis of its anti-tumour activity is complicated by two unusual features: the drug is sensitive to light and is photo-transformed to other biologically-active species (Peatey & Stevens 1978): metabolic degradation of the drug leads to a chemically reactive monomethyl metabolite which can methylate nucleic acids (Mizuno & Decker 1976). The optimum dosage schedule for DTIC in the treatment of malignant melanoma involves repeated small daily doses. The drug is therefore exposed to possible chemical interactions with other cytotoxic agents when used in combination regimens.

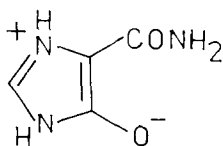
The stability of DTIC solutions in the presence of a range of cytotoxic agents has been monitored by uv/visible spectrometry both in the dark and in ambient laboratory light. No detectable interaction occurred with the antimetabolites methotrexate, 5-fluorouracil and cytosine arabinoside; with the alkylating agents cyclophosphamide, BCNU and CCNU; and with the natural products vinblastine, bleomycin, adriamycin and actinomycin D. The only notable chemical change was the photo-decomposition of DTIC itself which afforded 2-azahypoxanthine (2) when experiments were conducted at pH > 7, or 4-carboxamidoimidazolium-5-olate (3) at pH < 7.



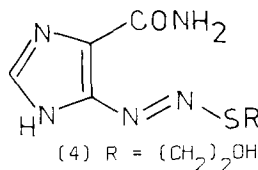
(1)



(2)



(3)

(4) R = (CH₂)₂OH(5) R = CH₂CH(NH₂)CO₂H

DTIC couples with the thiol groups of 2-mercaptoethanol or L-cysteine in the presence of light to yield unstable azothioethers (4) and (5) respectively. In contrast there is no reaction between DTIC and the thiol group of 6-mercaptopurine in the dark or light.

Stevens, M.F.G. (1976) *Progr. Medicin. Chem.* 13: 205-269

Peatey, L., Stevens, M.F.G. (1978) *J. Pharm. Pharmacol.* 30S: 47P

Mizuno, N.S., Decker, R.W. (1976) *Biochem. Pharmacol.* 25: 2643-2647