INVESTIGATION OF CYTOTOXIC ACTIVITY OF NATURALLY OCCURING ACRIDONE ALKALOIDS

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Acridone alkaloids constitute a small group of natural products found exclusively in the family Rutaceae. They are known to exhibit a wide range of pharmacological activities including cytotoxic effect, which are presumed to be exerted by the inhibition of an intracellular enzyme, topoisomerase-II [1].

The aim of the present study was the investigation of cytotoxic effect of 7 furanoacridones (rutacridone, isogravacridone chlorine, gravacridondiol, gravacridontriol, gravacridondiol monomethyl ether and the mixture of gravacridontriol monoglycoside and gravakridondiol monoglycoside) and 2 further akridones (arborinine and evoxanthine) isolated from *Ruta graveolens* L.

Cytotoxic effects were measured *in vitro* on three human cell lines: MCF-7 (breast adenocarcinoma), HeLa (cervix adenocarcinoma), and A431 (skin epidermoid carcinoma).The cytotoxicity of the compounds was measured by the MTT ([3-(4,5-dimethylthiazol-2-yl)2,5-diphenyltetrazolium bromide]) assay [2]. Doxorubicin and cisplatin were used as positive controls. Oil/water partition constants (expressed as log P) were calculated for the furanoacridones with the computer program MOE 2004.03.

Arborinine proved to be an outstandingly potent cytotoxic agent, especially on HeLa cells. Its calculated IC_{50} values are comparable with those of cisplatin. The tested furanoacridones exhibited a wide range of activity (IC_{50} values ranging from 3.02 to over 90 μM). The antiproliferative potency of these compounds and lipid solubility displayed a clear parallelism. Evoxanthine was not effective on any cell line.

In summary, our results indicate that naturally occurring acridone alkaloids, including furanoacridones, may be used as starting structures for the development of novel anticancer agents.

[1] Bastow KF, Itoigawa M, Furukawa H, Kashiwada Y, Bori ID, Ballas LM et al. Antiproliferative actions of 7-substituted 1,3-dihydroxyacridones; possible involvement of DNA topoisomerase II and protein kinase C as biochemical targets. Bioorg Med Chem 1994; 2: 1403-11

[2] Mosmann T. Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays. J Immunol Methods 1983; 65: 55-63