

DEVELOPMENT, SYNTHESIS, AND EVALUATION OF BIOACTIVE INDOLE DERIVATIVES FOR POTENTIAL APPLICATIONS IN BIOMEDICINE AND PHARMACOTHERAPY

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OBJECTIVE

To develop, synthesise, and evaluate indole compounds for potential applications in pharmacotherapy as antitumor agents and as modulators of drug-resistance.

RESULTS

A successful biomimetic partial synthesis of the new anti-tumor alkaloid, valparicine (low yield from natural source), has been carried out using the Potier-Polonovski method for C-ring contraction as the key step. This procedure has been used to prepare sufficient quantities of valparicine for an extended study of its cytotoxic effects. Valparicine was found to display pronounced cytotoxicity against several human cancer cell lines, including drug-sensitive and drug-resistant KB cells and Jurkat cells.

Various new tabersonine derivatives (jerantinines A-H) have been obtained from our ongoing studies in natural product and bioorganic chemistry. Preliminary studies have shown that these compounds are also cytotoxic (KB-cells). An extended study of the cytotoxic effects was carried out to establish structure-activity relationships. Towards this end, a series of semisynthetic derivatives were prepared for improved stability as well as for evaluation of relative potency.

The novel pentacyclic indole alkaloids, lirofolines A and B, were recently isolated from a Malayan *Tabernaemontana*. These alkaloids were found to reverse multidrug-resistance in drug-resistant KB cells and were postulated to have arisen from an *Iboga* precursor *via* fragmentation and rearrangement. Based on the proposed biogenesis, a partial synthesis of lirofoline A was successfully carried out.

Several novel bisindoles showing strong cytotoxic effects against human tumor cells *in vitro* have been obtained and their biological activity assessed. Possible pathways to these novel compounds will be presented.

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