SL03 Isolation of an elemanolide sesquiterpene from *Vernonia anthelmintica* (L.) Willd. seeds traditionally used for psoriasis

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The seeds of *Vernonia anthelmintica* (L.) Willd. (Asteraceae) (VA) have been used traditionally in Indian medicine to treat the skin disease psoriasis (1,2). Several extracts of the seeds of VA were assessed for anti-inflammatory activity using a radioimmunoassay to measure their inhibition on the generation of two pro-inflammatory mediators, thromboxane B_2 (TXB_2) and leukotriene B_4 (LTB_4). A methanol extract of the VA seeds (MET) was identified to display good inhibition of both LTB_4 and TXB_2. Fractionation of this extract was carried out by repeated silica gel column chromatography and preparative reversed phase HPLC. This led to the isolation of vernodalol, a sesquiterpene elemanolide lactone. It was identified from ^1H, ^{13}C and 2D NMR spectra recorded in $CDCl_3$ using tetramethylsilane (TMS) as the internal standard, as well as LCMS. Our studies have enabled for the first time the unambiguous assignment of the 3-carbonyl signals and the six olefinic carbon signals. A fraction of the MET extract composed predominantly of vernodalol as established from LCMS was found to inhibit the generation of both LTB_4 and TXB_2. This indicates the anti-inflammatory effect of vernodalol, a previously unreported effect. In addition, this compound was also found to display antiproliferative effects in an SVK-14 keratinocyte cell line. These anti-inflammatory and antiproliferative results clearly substantiate the traditional use of VA in psoriasis.

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SL04 Quantitative structure-activity relationships (QSAR) of cytotoxic and anti-inflammatory sesquiterpene lactones based on NMR spectral data and GA-PLS statistics

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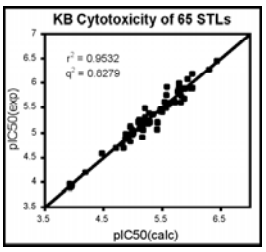
Sesquiterpene lactones (STLs) possess a wide variety of conspicuous biological activities. A major problem concerning their use as therapeutic agents is their high toxicity/low selectivity towards a particular target. A major goal of STL research must therefore be directed towards quantitative structure-activity relationships (QSAR), which might allow disctinction of structural features that render a compound more selective to a wanted biological effect.

In our continuing investigations on QSAR of natural products (1), we introduce here an approach based on the following assumption: if both, activity and molecular spectra, are functions of molecular structure, then it is very likely that activity can be expressed as a function of the molecular spectra (here ^{13}C-NMR spectra). The model-building process was carried out using established methods, i.e. genetic-algorithm-partial least squares regression (2).

NMR data (experimental and simulated) for 65 sesquiterpene lactones were used as spectral descriptors of biological activity with respect to cytotoxicity towards KB cells (see figure). Moreover, a data set of 41 STLs were analysed in the same way for their serotonin release inhibitory activity (3). Finally, semi-quantitative data for 28 STLs' inhibitory effect on NF-κB activity (4) were investigated. The resulting QSAR models are of very high statistical quality, yielding cross-validated correlation coefficients $q^2>0.75$ in all cases, as well as reasonable test set predicitions. It is especially noteworthy, that *calculated* NMR spectra lead to models at least as good as experimental spectra, so that predictions of compounds not available for testing become possible at low computational expense.



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