Efflux modulation activity of new pentacyclic diterpene polyesters isolated from *Euphorbia falcata* L.

Ana Martins[1], E. Sulyok[1], J. Molnár[2] and J. Hohmann[1]

[1]Institute of Pharmacognosy, Faculty of Pharmacy; [2]Department of Medical Microbiology and Immunobiology, Faculty of Medicine, University of Szeged, Szeged, Hungary

Many traditional uses of *Euphorbia* species have been claimed. In the literature, one can also find characterization of the components of different species of this family, as well as studies of their activity as anticancer agents or modulators of the activity of known anticancer agents. Because, multidrug resistance is a major health problem that affects the therapy of cancer, in this work four new pentacyclic euphohoppin-type diterpene polyesters isolated from *Euphorbia falcata* L. were tested for their activity as efflux modulators, in cancer cells. The isolated compounds were identified as di- (1), tetra- (2), penta- (3) and hexaester (4) derivatives of a polyfunctional euphoppin-related diterpene alcohol, acylated with acetic, propanoic, isobutanoic, n-hexanoic and benzoic acids. The 5-7-6-3 fused carbon skeleton refers that, biogenetically, the compounds may be formed from a lathyrane precursor. These types of diterpenes occur rarely and were previously isolated only from *E. aleppica* and *E. decipiens* species.

The new compounds were investigated for their antiproliferative activity against L5178 mouse T-cell lymphoma cells transfected with pHa MDR1/A retrovirus (MDR) and its parental cell line (non MDR).The activity as modulators of Rhodamine 123 efflux by MDR mouse lymphoma cells, that over express the human ABCB1 efflux pump, was also determined using flow cytometry. The compounds were also tested for their combination activity in the presence of doxorubicin, a known substrate of the ABCB1 pump.

The compounds presented very weak antiproliferative activity. However, when investigated for their capacity to modulate Rhodamine123 efflux by the MDR cell line, the compounds 2, 3 and 4 increased the retention of the dye in a concentration dependent manner. The obtained FAR values in the presence of 2 µM of compound were 29.81, 23.40 and 12.63, respectively for compounds 2, 3 and 4. These results were corroborated by those obtained by the checkerboard assay. Compounds 2, 3 and 4 decrease the IC50 of doxorubicin in a synergistic way, with FIX values of 0.4, 0.23 and 0.73, respectively.

No detailed structure activity analysis can be done at this time due to the number of compounds tested. However, compound 1, that was inactive in the studies previously described, structurally differs from the others by the absence of 7-OBz and 15-OAc groups, which therefore seem to be important for the activity of the compounds. The difference between the compounds 3 and 4 is an AcO group at position C-17 which seems to decrease the activity of the molecule.

The results of this work, mainly those observed in the combination assay with doxorubicin, are very promising for the finding of new effective compounds that can be used as adjuvants in therapy of multidrug resistant cancer. Therefore, further studies should be done with other related compounds in order to determine the relationship between their structures and the observed activity.

Acknowledgements

This work was supported by the Hungarian Research Fund (OTKA K72771) grant.