Terpenoids for overcoming multidrug resistance

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Cancer is one of the major public health problems worldwide. In the future, the burden of cancer is expected to increase, as the world´s population continues to grow and age. Chemotherapy is the most effective treatment for metastatic tumors. However, multidrug resistance (MDR), the ability of cancer cells to become simultaneously resistant to many functionally and structurally unrelated anticancer drugs, is the major obstacle for successful cancer treatment. MDR is a multifactorial phenomenon that can result from several mechanisms, including an increased drug efflux, due to overexpression of P-glycoprotein (P-gp) that transports anticancer drugs out of the cells. Thus, the role of this transporter has made it a therapeutic target and the development of P-gp modulators considered among the most realistic approaches for overcoming P-gp-mediated MDR [1].

In our search for effective plant-derived P-gp modulators, we have isolated two scaffold types from which several compounds displayed strong Pgp inhibitory properties on cancer cells overexpressing this ABC transporter. They include macrocyclic diterpenes from *Euphorbia* species and cucurbitane-type triterpenes obtained from the African medicinal plant *Momordica balsamina*. Based on literature data and structural features of macrocyclic diterpenes, we have proposed a 4-point pharmacophore. Some of these MDR reversers were assayed, *in vitro*, for their antiproliferative effects in combination with antitumour drugs. Most of them synergistically enhanced the effect of the antitumour drug providing evidence that they may be valuable as lead compounds for the development of P-gp modulators in multidrug-resistant cancer cells.

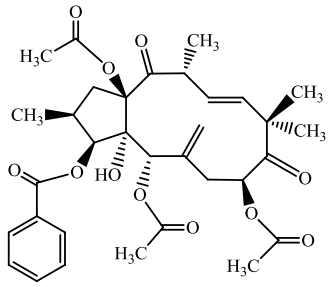

Figure 1. Macrocyclic diterpene with strong Pgp inhibitory properties

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References

[1] Szakács G., Paterson J., Ludwig J., Genthe C. and Gottesman M. (2006). Targeting multidrug resistance in cancer. *Nat. Rev. Drug Discov.* 5: 219 – 234.