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ABSTRACT BOOK

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Coimbra evening landscape by José Luís Ribeiro

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New Diagnostic and Therapeutic Tools against Multidrug Resistant Tumours

UNIVERSITÀ DEGLI STUDI DI TORINO

Cytotoxic Activity of diterpenes from *Plectranthus* spp. for MDR cancer therapy

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Abstract:

Plectranthus genus (Lamiaceae family) is widely used in traditional medicine, and the presence of pharmacologically active compounds, specifically diterpenes, is well reported. The cytotoxic diterpene royleanones 7α-acetoxy-6β-hydroxyroyleanone (**Roy**) and 6,7-dehydroroyleanone (**DeRoy**) are the major compounds of *P. grandidentatus* Gürke (acetonic extract) and *P. madagascariensis* (Pers.) Benth. (essential oil), respectively. In this work, **Roy** and **DeRoy** were investigated as potential antitumor agents through the activation of protein kinase C (PKC) isoforms (α, βI, δ, ε and ζ) and inhibition of the efflux pump, P-glycoprotein (P-gp). Additionally, the reactivity of **Roy** and **DeRoy** was explored to synthesize a library of new derivatives to be also evaluated as cytotoxic agents. PKC-α, βI, δ, ε, and ζ activation was tested on a yeast-based screening assay. Interestingly, one benzoylated derivative showed selective PKC-δ activation, while **DeRoy** exhibited enhanced PKC activity in all tested isoforms, compared to the positive control. Moreover, inhibition of P-gp activity was evaluated in human non-small cell lung carcinoma NCI-H460 and its MDR counterpart NCI-H460/R. It was possible to identify an analogue with P-gp inhibitory activity higher than the natural diterpenes **Roy** and **DeRoy**, and comparable to Dexverapamil (positive control). Several other semi-synthetic products are currently under investigation as potential chemotherapeutic agents.

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