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Abstract

Royleanone Analogues from *Plectranthus* spp. Demonstrate P-gp Inhibition and PKC Modulation †

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Abstract: The number of multidrug resistant (MDR) cancer cases across the globe is continuing to rise, such that the search for novel anti-cancer therapeutics is paramount. For instance, the overexpression of membrane transport proteins, such as P-glycoprotein (P-gp), or the selective modulation of protein kinases C (PKC) isoforms continues to be a major impediment to effective therapy. Known for their medicinal properties, species from *Plectranthus* have been reported to have cytotoxicity against various cancer cell lines due to diterpenes, such as 7α-acetoxy-6β-hydroxyroyleanone (**Roy**) and 6,7-dehydroroyleanone (**DeRoy**). Based on molecular docking simulations, 10 semi-synthetic derivatives of **Roy** that displayed strong P-gp interactions in silico were prepared. The antitumoral activity was evaluated in resistant human cancer cell lines NCI-H460/R and DLD1-TxR, showing three derivatives having the most prominent selectivity towards cancer cells, compared to normal lung fibroblasts MRC5. Moreover, they showed a reduction in P-gp activity in Rho123 accumulation and indicated P-gp inhibition in the DOX accumulation assay using the same resistant cell lines. Overall, it was demonstrated that three abietane diterpenoids induced P-gp inhibition in MDR cancer cell lines. As regards the PKC activity, further analogues were tested as PKC (α, βI, δ, ε and ζ) modulators; one benzoylated derivative showed the ability to selectively activate PKC-δ, while the natural compound **DeRoy** displayed improved PKC activity, compared with the positive control, in all tested isoforms. Further investigations are ongoing to prepare analogues of other biologically active diterpenoids to obtain potential hits as P-gp and PKC modulators.

Keywords: royleanones; diterpenes; P-gp; PKC; analogues; cancer

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