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Design, synthesis and biological evaluation of novel celastrol derivatives as potent and selective cytotoxic compounds

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Triterpenoids comprise a large and structurally diverse class of natural products. Among these, celastrol is one of the most active antitumour compounds. It has been reported to be highly active against a wide variety of tumours and to affect multiple cellular pathways. Therefore, celastrol is an ideal candidate for designing lead compounds for the development of new anticancer agents. In this communication we report the synthesis of novel celastrol derivatives as potent and selective cytotoxic compounds. Celastrol analogues, including carbamate derivatives, were designed and synthesised, and their anticancer activity was evaluated using different human cancer cell lines. Moreover, these new compounds were subjected to a preliminary structure–activity relationship study. The best derivatives were selected considering their best activity on malignant cell viability, combined with the highest selectivity between cancer cells and non-malignant fibroblasts. It was performed preliminary mechanistic studies with the best compound, which indicated a important cytotoxic effect on SKOV-3 human ovarian cancer cells (IC50 = 0.54 μM). Additionally, the results suggested that this compound presented an antiapoptotic activity, mediated mainly through activation of extrinsic apoptotic pathway. Furthermore, our results demonstrated the potential of this derivative as a new agent for combinatorial drug therapy for ovarian cancer.

Biography

Jorge A R Salvador has a degree in Pharmaceutical Sciences, a Master degree in Organic & Tecnological Chemistry, and a Ph.D. in Pharmaceutical Chemistry from the University of Coimbra in collaboration with the University of York, UK. He has a position as Full Professor at Faculty of Pharmacy of the University of Coimbra – Portugal. Author and co-author of over 90 publications in peer-review journals, 10 book chapters and 10 patents, two of them have been granted in US. Co-founder of the company CHEM4PHARMA, Lda, https://www.chem4pharma.com/.

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