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Design, synthesis and cytotoxic evaluation of novel a-ring cleaved ursolic acid derivatives in human non-small cell lung cancer cells

Vanessa I S Mendes[1,2], Geoffrey A Bartholomeusz[3], Mary Ayres[3], Varsha Gandhi[3], Andreia F O Gonçalves[4] and **Jorge A R Salvador[2,4]**
[1]Chem4Pharma, Portugal
[2]Center for Neurosciences and Cell Biology, Portugal
[3]The University of Texas MD Anderson Cancer Center, USA
[4]University of Coimbra, Portugal

Lung cancer is a leading cause of cancer-related deaths worldwide, with non-small cell lung cancer (NSCLC) accounting for 80 to 85% off all lung cancer diagnosis. Despite advances in diagnostics and therapeutics, the outcome for patients with lung cancer remains poor. Therefore, novel anti-lung cancer agents are greatly needed. Ursolic acid (UA) is a pentacyclic triterpenoid with recognized anticancer properties, and could be used as a starting-point for the development of more potent anticancer drugs. Hence, in this study we designed and synthetized a series of new A-ring cleaved UA derivatives and evaluated their cytotoxic activity in NSCLC cell lines using 2D and 3D culture models. Compound 1, bearing a cleaved A-ring with a secondary amide at C3, was found to be the most active compound, with potency in 2D and 3D culture models systems. The preliminary study on the molecular mechanism showed that compound 1 induced apoptosis via activation of caspases-8 and -7 and via decrease of Bcl-2. Futhermore, induction of autophagy was also detected with increased levels of Beclin-1 and LC3A/B-II, and decreased levels of mTOR and p62. Given its activity and mechanism of action, compound 1 might be potential lead candidate for further development for NSCLC treatment.

vane7sm@gmail.com