

4th World Congress on Cancer Science & Therapy

October 20-22, 2014 DoubleTree by Hilton Hotel Chicago-North Shore Conference Center, USA

Aryl maleimides as apoptosis inducers on L5178-Y murine leukemia cells (*in silico*, *in vitro* and *ex vivo* study)

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Mitochondria is one of the most important organelles and alterations in the function of their membranes, like those caused by high levels of free radical, are pivotal in the initiation of cell death by apoptosis. Thiol oxidation or cross-linking reactions are associated with a higher probability of an open transmembrane pore leading to the release of pro-apoptotic molecules and cell death via apoptosis. Therefore, the aim of the present study was to design a series of aryl maleimides that are α,β -unsaturated compounds to test their selectivity for thiols in different experiments. NMR spectra confirmed the structures of eight aryl maleimides synthesized (1a-1h). Two aryl maleimides (1f and 1h) were tested with an *in vitro* and *ex vivo* model to evaluate their reactivity with thiols and their activity in L5178-Y murine leukemia cells, the *in vitro* reactions clearly showed a chemoselective Michael type 1,4-addition reaction between thiols and the aryl maleimides as predicted in theoretical calculations. In cell cultures, the compounds induced a decreasing cellular viability and an apoptotic effect of up to 59.8% at 48 h. This was confirmed by cytofluorometry, DNA fragmentation and morphological changes in the cells. The *ex vivo* experiment showed an important reduction of thiol levels in cells treated with 1h. Results strongly suggest that aryl maleimides can make cancer cells more susceptible to die by apoptosis due to decreasing the levels of glutathione; therefore, aryl maleimides could be used to make cancer cells more sensitive to a less aggressive treatment than the currently used chemotherapy.

Biography

Erik Andrade-Jorge is a Doctorate student in the Department of Biochemistry at Politecnico Nacional. He is a chemist pharmaceutical biologist and has a Master degree in Pharmacology Science and is currently in the second semester of the Doctorate in medicinal investigation. Currently, he has three different research lines one of these is cancer cell proliferation, another one is in Parkinson's disease and the third one is in obesity. He has focused on the rational drug design based on the molecular mechanisms of different pathologies.

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