Phenylethyl maleimide derivatives as novel apoptosis inducers on L5178-Y murine leukemia cells

(\textit{in silico}, \textit{in vitro} and \textit{in vivo} study)

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Conventional cancer therapies have been shown to have many side effects, the main challenge is to find molecules with higher selectivity to tumor cells rather than normal cells. A main differences between cancer and normal cells, are the levels of thiol-containing compounds, a scavenging mechanism of Reactive Oxygen Species. Cancer cells seem to have higher levels of glutathione than normal cells, and this allow them to survive in adverse conditions, even in chemotherapy. Therefore, glutathione has become a target for the new anticancer therapy. The aim of this contribution was to develop a series of \( \alpha,\beta \)-unsaturated compounds derivate of endogenous amines that may deplete the levels of glutathione, as well as, induce cancer cells to death by apoptosis. Pharmacokinetic evaluation (\textit{in silico}) showed a good score on the the parameters such as human intestinal absorption, plasma protein binding, biotransformation evaluated by cytochrome CYP2C9 affinity and CYP2D6 affinity, P-glycoprotein substrate, LopP, etc. The \textit{in vitro} assays showed a EC50 of 5\( \mu \)M for molecule MF01 and a EC50 of 30 \( \mu \)M for molecule MF02 evaluated by MTT method at 24 and 48h, \textit{in vivo} experiments include LD50 and survival experiment. It was estimated a LD50 for MF01 of 8mg/kg and 80mg/kg for molecule MF02, which means that molecule MF02 is 10 times less toxic that molecule MF01. There wasn’t significant difference on the survival experiment at the dose used, but there was a delay on the tumor’s development on the treated group. These results allow us to try others candidates which might possess the same properties.

Biography

Erik Andrade-Jorge is a Doctorate student in the Department of Biochemistry at Instituto Politecnico Nacional. He is a chemist-pharmaceutical-biologist and has a Master degree in Pharmacology and is currently in the seventh semester of the Doctorate in research in medicine. Currently, he has two different lines research one of these is cancer cell proliferation and another one is in Parkinson’s disease. He has been focused on the rational drug design based on the molecular mechanisms of different pathologies and in the physicochemical properties of the ligands.

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