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In silico design, synthesis and biological evaluation of inhibitors of hypoxia-inducible factor (HIF-1) as antitumor agents

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Solid tumors contain hypoxic regions, which confers resistance to radiation and chemotherapy, but in turn offers an attractive difference between normal and tumor cells that can be exploited to obtain selective drugs directed to specific targets on hypoxic cells. Hypoxia induces changes in gene expression profile through the induction of a transcriptional factor called hypoxia-inducible factor, HIF-1. This protein activates the transcription of genes related to cell survival. An interesting strategy for the development of antitumor agents is the use of pro-drugs, which after selective bio-reduction under hypoxic conditions, interact with DNA affecting the binding site of HIF-1. In this work, we have designed derivatives of amino-phenazine 5,10-dioxides as potential pro-drugs which bind selectively to the 5'-3'-ATACGTG and thereby prevent interaction with HIF-1. To determine the possible interaction mode, molecular docking calculations and molecular dynamics simulations were carried out. Some of the derivatives proposed interact with the region of interest and also intercalate into DNA with good affinity. The synthesis of compounds that show an adequate degree of affinity with the intended target has been performed, via nucleophilic substitution to formaldehyde followed by the addition of aliphatic alcohols that react with the imino intermediate, generating compounds with different degree of side branching, with yields moderate to good.

Biography

María Laura Lavaggi completed her PhD in Medicinal Chemistry in 2009 at the Facultad de Química, Udelar, Uruguay. She has been responsible of research grants involving anticancer pro-drug design and published several papers on the area. Also she has mentored Graduate students theses and Master's degree theses. Presently, she is involved in different research projects some of them based on the development novel anti-cancer and anti-neurodegenerative agents and ecotoxicology involving genotoxic damage of residual pesticides.

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