# Structural modifications on the phenazine N,N?-dioxide-scaffold looking for new selective hypoxic cytotoxins

Lavaggi, María Laura

Nieves, Marcos

Cabrera, Mauricio

Olea-Azar, Claudio

López De Ceráin, Adela

Monge, Antonio

Cerecetto, Hugo

González, Mercedes

We have identified phenazine 5,10-dioxides as prodrugs for antitumour therapy that undergo hypoxic-selective bioreduction to form cytotoxic species. Here, we investigated some structural modifications in order to find new selective hypoxic cytotoxins and to establish the structural requirements for adequate activity. Three different chemical-series were prepared and the clonogenic survival of V79 cells on aerobic and anaerobic conditions was determined. Electrochemical- and DNA-interaction studies were done for the most relevant derivatives. The new fluoro-derivative 7-fluoro-2-aminophenazine 5,10-dioxide displayed selective toxicity towards hypoxic V79 cells having adequate hypoxic cytotoxicity ratio (HCR = 6.8) and being the most potent hypoxic cytotoxins (P = 2.5 ?M) described for this family of bioreductive agents. The reduction potential of the N-oxide moiety in this new fluoro-derivative was in the range for adequate bioreduction property. According to the fluorescence studies, t