Study of benzo[a]phenazine 7,12-dioxide as selective hypoxic cytotoxin-scaffold. Identification of aerobic-antitumoral activity through DNA fragmentation

Lavaggi, María Laura

Cabrera, Mauricio

Aravena, María de los Ángeles

Olea-Azar, Claudio

López de Ceráin, Adela

Monge, Antonio

Pachón, Gisela

Cascante, Marta

Bruno, Ana María

Pietrasanta, Lía I.

González, Mercedes

Cerecetto, Hugo

Phenazine 5,10-dioxides are prodrugs for antitumor therapy that undergo hypoxic-selective bioreduction to form cytotoxic species. Here we investigate the expanded system benzo[a]phenazine 7,12-dioxides as selective hypoxic cytotoxin-scaffold. The clonogenic survival of V79 cells on aerobic and anaerobic conditions, conduct us to study antiproliferative activity on Caco-2 tumoral cells in normoxia. Electrochemical, DNA-interaction and DNA-damage studies were performed to establish the mode of action. The results demonstrated the potential biological properties of the studied scaffold being derivatives 6-10 structural hits for further chemical-modifications to become into therapeutics for solid tumors. Compounds 6 and 8 with cytotoxicity against V79 cells in both conditions (aerobia and anaerobia) were also cytotoxic against Caco-2 tumoral cells in aerobiosis.