Cytotoxicity of 1,3,4-thiadiazolium Mesoionic Derivatives on Human Hepatocellular Carcinoma Cells (HepG2) compared to Primary Rat Hepatocytes

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INTRODUCTION: The lack of selectivity against tumor cells is a limiting factor for the use of antitumor drugs. Mesoionic compounds with a 1,3,4-thiadiazole ring have shown an important antitumor activity against murine melanoma. With the aim to investigate a possible selectivity for these compounds, we evaluated the cytotoxicity of 4-phenyl-5-[2-Y, 4-X-cinnamoyl] derivatives, namely MI-J (Y=H and X=OH), MI-F (Y=H and X=F) and MI-2,4diF (X=Y =F) on tumor cells (Human Hepatocellular Carcinoma - HepG2) and primary culture of rat hepatocytes.

MATERIALS AND METHODS: The cytotoxicity was determined using 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method and lactate dehydrogenase (LDH) leakage assay. Cell death process was evaluated by staining with FITC-annexin V and propidium iodide by flow cytometry in HepG2 or fluorescence microscopy in rat hepatocytes.

DISCUSSION AND RESULTS: All mesoionic derivatives, MI-J, MI-F and MI-2,4diF (25 µM - 24 h) reduced HepG2 cells viability around 50% when analyzed by MTT, and 55%, 24% and 16%, respectively, by LDH leakage assay. The compounds (25 µM - 24 h) increased FITC - annexin V and PI staining at 35% (MI-J), 11% (MI-F) and 16% (MI-2,4diF), suggesting that cells were in later-stage apoptosis. On the other hand, no changes were observed in MTT or LDH assays after treatment of hepatocytes with MI-J and MI-F derivatives (25 µM - 18 h). However, MI-2,4diF decreased the viability of hepatocytes at 36% (25 µM - 18 h) only in MTT assay. These results were confirmed by FITC - annexin V and PI staining, where no staining was observed for all derivatives treatments (25 µM - 18 h). CONCLUSION: Taken together, these results indicate that MI-J, MI-F and MI-2,4diF are more cytotoxic to HepG2 cells in comparison to primary rat hepatocytes, encouraging further studies with these compounds.

Keywords: 1,3,4-thiadiazolium mesoionic derivatives, cytotoxicity, HepG2 cells, rat hepatocytes.

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