Metabolism and Acute Toxicity of the Mesoionic Compound MI-D

Silvia Romão[a], Silvia M.S.C. Cadena[a], Juliana C. Amorim[a], Stelia C. Méndez-Sánchez[a], Aurea Echevarria[b], Edson F. Silva[b], Maria Eliane M. Rocha[a], Guilhermina R. Noleto[a], Eva G. S. Carnieri[a], Glaucia R. Martinez[a], Maria Benigna M. Oliveira[a]

[a]Departamento de Bioquímica e Biologia Molecular, UFPR; [b]Departamento de Química, UFRRJ.

The mesoionic compound 4-phenyl-5-[4-nitrocinnamoyl]-1,3,4-thiadiazolyl-2-phenylamine chloride (MI-D) has been shown antitumor activity and anti-inflammatory action *in vivo* in rats and mice. This study investigated aspects of metabolism and toxicological effects of MI-D. MI-D metabolism was investigated using microsomal fraction of mice hepatocytes induced with phenobarbital and detection of possible products of metabolism was performed by HPLC. It was shown a possible soluble product of MI-D metabolism (MET) in 7.7 min of chromatographic run, which increased along incubation time. MET spectrum was similar to MI-D when examined in the range between 200-750 nm. Analysis by ESI+/MS of the purified compound by HPLC indicated that the product has four additional hydroxyl groups (m/z = 465) compared to MI-D (m/z = 401). The kinetic parameters of reaction were determined by fluorescence detection of the product, with estimated values of Vmax = 1.5 ± 0.4 units fluorescence/s and Km = 19.5 ± 4.5 $\mu mol.L^{-1}$. MET was detected in blood and urine of mice after 1 and 3 h of treatment with MI-D (50 mg/kg). The estimated value of LD_{50} in mice for MI-D administered intraperitoneally was 181.2 mg/kg. Histological analysis of organs of the peritoneal cavity from survived animals, showed regions of serous membrane fusion of different organs and regions with accumulation of MI-D, and it was identified large leukocyte infiltration and granulomas. These results provide a breakthrough in the research of biological effects of this compound and also a methodological support for future pre-clinical studies. Supported by CNPq and CAPES.