Abstract

Charles University in Prague
Faculty of Pharmacy in Hradec Králové
Department of Biochemical Sciences

Candidate: Mgr. Eliška Potůčková
Supervisor: Doc. PharmDr. Tomáš Šimůnek, Ph.D.

Title of Doctoral Thesis:
Study of antiproliferative effects of novel iron chelators

Recent studies demonstrate that iron chelators possess marked potential as anticancer agents and also as substances protecting sensitive tissues against oxidative stress. This thesis is dealing mainly with design and synthesis of new antiproliferative iron chelators based on the structure of salicylaldehyde isonicotinoyl hydrazone (SIH) and with a characterization of their pharmacological and toxicological properties. Antiproliferative effects of these substances were studied on human breast adenocarcinoma cell line and human leukemic cell line and the non-specific toxicity on neonatal rat cardiac tissue-derived cells. During these studies some novel structure-activity relationships have been found. Furthermore, the suitability of simultaneous administration of iron chelators with antineoplastic agents used in breast cancer treatment was studied. In this project the anthracycline antibiotic, doxorubicin, and, in particular, the estrogen receptor antagonist, tamoxifen, were identified as the most suitable agents for potential treatment combined with iron chelation therapy. The characterization of biological activities and structure-activity relationships of thiosemicarbazone chelators was also studied. One of the most potent thiosemicarbazone chelators identified in last years was characterized in terms of its biological activities. The chelation and antiproliferative activities of its recently identified phase I metabolites were also characterized and compared to the parent substance. The metabolic products were a few orders of magnitude less antiproliferatively active than its parent substance and non-toxic. Finally, we studied the ability of iron chelators to protect cardiac cells against oxidative stress-induced injury and anthracycline toxicity. Collectively, our results are important for further

development of this novel group of potential anticancer agents and substances able to protect cardiac tissue.