Abstract

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Title of diploma thesis: Study of the antipoliferative properties of the series of novel aroylhydrazone iron chelators

Aroylhydrazones are tridental lipophilic iron chelators with good cell-membrane permeability. In the last decades some compounds of this chemical group have been demonstrated to have a significant antiproliferative activity. Salicylaldehyde isonicotinoyl hydrazone (SIH), an aroylhydrazone with an oral availability, showed a significant antiproliferative activity in previous experiments in our laboratory as well as the ability to protect cells from the oxidative stress-induced damage. The main disadvantage of SIH is low stability caused by rapid hydrolysis of the hydrazone bond in aqueous environment. To deal with this issue, the Department of Organic and Inorganic Chemistry of the Faculty of Pharmacy (Charles University) designed and synthesized analogues of SIH, derived from aromatic ketones, which showed significantly improved stability in rabbit plasma in comparison with the parent SIH.

The aim of this study is to expand the previous experiments and it is focused on further structure modifications of the parent compound of SIH and their influence on the antiproliferative activity. This study was conducted on breast carcinoma cell line MCF-7. The proliferation of the cells was evaluated after 72 hours of exposure to the tested compounds and was determined by the method of neutral red uptake assay.

The results of this experiment showed a statistically significant and dose-dependent decrease of cellular proliferation for all of the tested aroylhydrazone derivatives, although in some of the compounds only in very high concentrations. Five of nine compounds showed a significant increase of antiproliferative activity in comparison to the parent SIH. Reduction of the hydrazone bond led to the significant loss of activity, whereas the bromination of the aromatic ring in the ketone part of the molecule had no significant influence. The branching on the hydrazone carbon led to increased activity in one case but to decreased activity in another.

Obtained IC_{50} values were further compared to the toxicity data for neonatal rat cardiomyocyte cell line H9c2. Five of nine compounds exerted improved selectivity for carcinoma cells vs. non-carcinoma cells in comparison with the parent chelator SIH.