ABSTRACT

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Title of Thesis: Synthesis of analogues of chelator SIH with increased stability towards hydrolysis

Excessive amounts of free iron ions in the body can catalyze the formation of hydroxyl radicals, which are involved in the development of various diseases. One of the ways how to protect the body is to chelate free iron ions with chelators, in order to prevent the development of iron-catalyzed oxidative stress.

Effective chelators are substances from the group of salicylaldehyde analogues of isonicotinoyl hydrazone. Salicylaldehyde isonicotinoyl hydrazone (SIH) is a chelator that forms complexes with Fe^{3+} ions. Due to its high lipophilicity can be administered orally. Its main disadvantage is the low stability in the aqueous environment caused by the rapid hydrolysis of the hydrazone bond.

The aim of this work was to synthesize a series of new aroylhydrazones derived from the SIH chelator, which supposed to have an improved ability to chelate iron ions and the associated ability to protect cells from oxidative stress and potentially increased stability to hydrolysis.

In the first series of SIH analogs - *N* '-(2-hydroxy-4,6-dimethoxybenzylidene)-hydrazide derivatives - two methoxy groups were introduced on the benzene nucleus, which on the one hand increase the electron density on the benzene nucleus and in addition the methoxy group in position 6 sterically protects the adjacent hydrazone bound. Eleven analogs of the SIH chelator were prepared. These substances were subsequently further studied at the Department of Biochemical Sciences, Faculty of Pharmacy, Charles University in Hradec Králové, where their cytoprotective activity was evaluated. From the studied substances, 4-chlorobenzohydrazide and cyclohexanecarbohydrazide derivatives showed the best results.

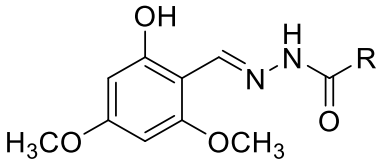

Figure 1. *N* '-(2-hydroxy-4,6-dimethoxybenzylidene)-hydrazide derivatives

A second series of cyclic SIH analogs - 3-(2-hydroxyphenyl)-4,5-dihydro-1H-pyrazole derivatives - have been designed to increase the stability of the hydrazine bond to hydrolysis, thereby extending the plasmatic half-life. Unfortunately, the final substances were not successfully synthesized. Only 1-acyl-3-(2-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole derivatives were prepared.

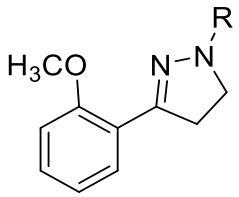

Figure 2. 1-acyl-3-(2-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole derivatives