ABSTRACT

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Title of diploma thesis: The impact of synthetic chelators from the group of 4-acylpyrazole-5-ones on alcohol dehydrogenase

Inhibitors of alcohol dehydrogenase play a key role in the treatment of poisoning caused by methanol, ethanol, ethylene glycol, and their toxic metabolites. Such treatment can therefore be considered as life-saving. In clinical practice, a single substance, fomepizole, is used. This thesis is aimed at investigation of the effect of eleven experimental chelators from the 4-acylpyrazol-5-ones group on equine and yeast alcohol dehydrogenases, and the possible definition of structural features that would be the most suitable for interaction with this enzyme. Due to the ability of these substances to chelate zinc ions, it is believed that they could inhibit an enzyme that has a zinc molecule in the structure. The measurement itself is based on principle of increase in absorbance during the enzymatic reaction, which is caused by the formation of NADH. This measurement is relatively simple, efficient and, due to used kinetic method, also less susceptible to be affected by absorbance of the tested substances. Measurement showed that six tested substances (HQ^{ph}, HQ^{phptBu}, HQ^{phpNO2}, HQ^{thi}, HQ^{etCP} and HQ^{naph}) inhibited the yeast enzyme at a concentration of 200 μM more effectively than fomepizole. Equine enzyme was inhibited at 500 μM by HQ^{phptBu}, HQ^{phpNO2}, HQ^{thi}, and HQ^{naph}, but none of them was more effective than fomepizole. The results of the subsequent correlation analysis showed that inhibition rate of ADH and chelation rate of Zn^{2+} ions are not related. Thus, the tested substances do not appear to be appropriate inhibitors of ADH due to high concentrations required for their effect, but it cannot be ruled out that more active inhibitors could be prepared by modifying these molecules.