ABSTRACT

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Title of diploma thesis: The influence of belinostat inhibition on the activity of selected reductases from AKR and SDR superfamilies

Anthracycline antibiotics (ANTs) are important antineoplastic agents. One of them, daunorubicin (DAUN), is used for the treatment of acute leukaemia and other malignancies in children and adults. Factors limiting its clinical use include mainly resistance and cardiotoxicity. Enzymes from aldo-keto reductase (AKR) and short-chain dehydrogenase/reductase (SDR) superfamilies mediated the reduction of DAUN to its C-13 alcohol metabolite daunorubicinol (DAUNOL). The metabolite is more cardiotoxic, less antineoplastic, and is causing anthracycline resistance. This diploma thesis aimed to examine the inhibitory effect of belinostat on the activity of AKR1A1, 1B1, 1B10, 1C3, and CBR1. The specific enzyme activity and inhibitory potential were estimated *in vitro* using recombinant enzymes, and the enzymatic production of DAUNOL was evaluated by the liquid chromatography (UHPLC) system. The inhibition was decreased in order AKR1C3 > AKR1B10 > AKR1A1 > AKR1B1 > CBR1. The most inhibited enzyme, AKR1C3, expressed 50,7% inhibition by 10μM belinostat and 89,2% inhibition by 50μM belinostat. In comparison with other similar publications, we can conclude that belinostat is relatively strong inhibitor against AKR1C3 (IC_{50} = 9,5 ± 0,6 μM, K_i = 8,9 ± 0,4 and acts as a non-competitive one). Based on these findings, we can presume that the combination of DAUN and belinostat may potentially enhance the therapeutic effectiveness and safety of ANT via inhibition of AKR1C3. It can also be designed like a chemotherapeutic agent for many diseases associated with upregulation of AKR1C3.