ABSTRACT

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Title of diploma thesis: Effect of selected tyrosine kinase inhibitors on the activity of human carbonyl reducing enzymes
Key words: tyrosin kinases, screening, carbonyl, daunorubicin, inhibition

Tyrosine kinases are a subclass of protein kinases, catalysing the transfer of ATP phosphate residue to a protein, thereby playing an important role in cellular signaling. Abnormal tyrosine kinase activity is present in various malignancies. In certain cases, inhibition of their function can prevent tumor cell proliferation and eventually induce apoptosis. At the same time, some tyrosine kinase inhibitors have demonstrated the ability to inhibit efflux transporters, which are often involved in the development of resistance to anticancer treatment.

In this diploma thesis, the inhibitory effect of imatinib, nilotinib, dasatinib and acalabrutinib (tyrosine kinase inhibitors) has been studied on carbonyl reducing enzymes, whose overexpression by tumor cells may lead to resistance to chemotherapy. In particular, in the case of anthracyclines, the reduction of carbonyl group on C-13 results in not only lower cytotoxic activity, but also increased cardiotoxicity of metabolites.

By comparing the specific activity of selected carbonyl reducing enzymes with anthracycline substrate, we found that CBR1, AKR1C3, AKR1A1, AKR7A2, AKR1B10 and to a lesser extent AKR1B1 have the ability to metabolize daunorubicin to daunorubicinol. Subsequently, the interactions between active enzymes and potential inhibitors were investigated. Dasatinib at 50 μM effectively reduced AKR1B10 activity to 9.3 % and AKR1C3 to 39.1 %. At the same concentration, acalabrutinib reduced AKR1C3 activity up to 3.7 %. Finally, the IC_{50} of dasatinib and the IC_{50} and K_i of acalabrutinib were determined with AKR1C3.