ABSTRACT

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Title of diploma thesis: The influence of bosutinib, neratinib and ibrutinib inhibition on the activity of selected reductases from AKR and SDR superfamilies

Anthracycline antibiotics (ANTs) are antineoplastic drugs. Daunorubicin (DAUN) is used in the treatment of acute leukaemia. Enzymes from aldo-keto reductase (AKR) and short-chain dehydrogenase/reductase (SDR) superfamilies mediate the reduction of DAUN to its C-13 alcohol metabolite daunorubicinol (DAUNOL), which is more cardiotoxic, less antineoplastic and is causing anthracycline resistance.

In my diploma thesis, I examined the inhibitory effect of bosutnib, neratinib and imatinib on the activity of enzymes from the SDR and AKR superfamilies.

The specific enzyme activity and inhibitory effect were estimated on the base of *in* vitro enzymatic production of DAUNOL by the ultra-high-performance liquid chromatography (UHPLC) system. MTT assay was used to measure DAUN and ibrutinib cytotoxicity effect on HCT116 cell culture.

In vitro enzymatic activities for recombinant enzymes were decreased in order CBR1 > AKR1C3 > AKR1B1 > AKR1A1 > AKR7A2 > AKR1B10 > AKR1C1 > AKR1C2 > AKR1C4 > CBR3. The most effective inhibitor was ibrutinib. It inhibited the most enzyme AKR1C3 (non-competitive mode of inhibition, Ki = 2,1 μM; IC_{50} = 1,5 μM). Furthermore, experiments on HCT116 demonstrated that the combination of DAUN with ibrutinib decreased viability in AKR1C3 overexpressing cells.

Based on these findings, it is possible to presume that combination of DAUN and ibrutinib may have the potential to enhance the therapeutic effectiveness and safety of ANT via inhibition of AKR1C3.