ABSTRACT

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Title of diploma thesis: The effect of alisertib and brigatinib on the activity of selected human carbonyl reducing enzymes
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Protein kinases are enzymes, whose main function is based on a transfer of phosphate group from ATP to protein substrate. This common posttranslational modification is involved in the regulation of intracellular processes and cell signaling. Altered expression of protein kinases is often coupled with a development of cancer. Inhibition of protein kinases may prevent cancer cell proliferation and induce their cell death.

The main aim of the diploma thesis was to measure inhibition potential of protein kinase inhibitors, alisertib and brigatinib, against carbonyl-reducing enzymes. Overexpression of carbonyl-reducing enzymes in cancer cells may cause resistance to drugs followed by failure of chemotherapeutic therapy. In case of antracyclin chemotherapeutic daunorubicin, carbonyl-reducing enzymes reduce the carbonyl in C-13 giving rise a primary metabolite daunorubicinol, which has lower cytotoxic effect but higher cardiotoxicity. The effort to overcome resistance to daunorubicin and to decrease its cardiotoxic effects leads to search for inhibitors of carbonyl-reducing enzymes.

Based on a comparison of specific activity of carbonyl-reducing enzymes, which metabolize danorubicin to daunorubicinol, we found, that the highest activity was reached in enzyme CRB1, whereas specific activity of other enzymes decreased in following order AKR1C3, AKR1A1, AKR1B10, AKR7A2 and AKR1B1. Those active enzymes were treated with potential inhibitors – alisertinib and brigatinib. Alisertib in 50 μM concentration reduced activity of enzyme AKR1C3 to 14.24 % and AKR1B10 to 44.30 %. In case of alisertib, we determined the IC_{50} and K_i value for AKR1C3.