ABSTRACT

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Title of diploma thesis: The influence of enasidenib, quizartinib and glasdegib inhibition on the activity of selected reductases from AKR and SDR superfamilies

Acute myeloid leukemia is the most common cancerous disease among the adult population. The treatment is dependent on many factors, where the effectiveness of anthracycline antibiotic cytostatic treatment plays a significant role. Therapy is often complicated by resistance to anthracyclines. This resistance can be caused by carbonyl reducing enzymes which also may aid in tumor growth.

Carbonyl reducing enzymes are NAD(P)H-dependent oxidoreductases, reducing anthracyclines to respective alcohols, which not only have lower toxicity towards the cancerous cells, but can also damage the cardiac tissue. These enzymes also aid in the differentiation and proliferation of cancerous cells and increase the tumor aggressiveness.

The topic of this thesis was to study the inhibitors of carbonyl-reducing enzymes from aldo-keto reductase and short chain dehydrogenase/reductase superfamilies, reducing daunorubicin to less effective metabolite daunorubicinol. The three selected inhibitors were: enasidenib, glasdegib and quizartinib. The most significant inhibitory potential was demonstrated by enasidenib against the AKR1C3 enzyme with an inhibition value of 97,0 % for a 50 μM concentration. The other 2 inhibitors showed significantly lower inhibitory potential, so only enasidenib was selected for further research.

The IC_{50} value and inhibition constant were set, and the type of inhibition was determined. IC_{50} was in range of 0,88–1,19 μM and K_i value was 0,44 ± 0,03 μM. Enasidenib acts as a competitive inhibitor against daunorubicin.

The results show that the use of enasidenib combinated with daunorubicin in acute myeloid leukemia therapy could increase the therapeutic efficacy of the treatment and reduce side effects.