ABSTRACT

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Title of diploma thesis: Study of the effect of cyclin-dependent kinase inhibitors on the expression of selected AKR and CBR enzymes in human cell lines

Cyclin-dependent kinase inhibitors (CDKi) are considered as a suitable treatment especially in patients with wrong prognosis or advanced stage of cancer. It has only recently been discovered that CDKi are able to influence the activity of some enzymes from aldo-keto reductase (AKR) and short-chain dehydrogenase/reductase (SDR) superfamilies.

AKR and SDR enzymes belong to a group of carbonyl reducing enzymes that are involved in the metabolism of endobiotics and xenobiotics. An important group of drugs that are metabolized by these enzymes to less efficient compounds are anthracyclines.

The aim of this diploma thesis was to find out whether purvalanol A, roscovitin, dinaciclib, AZD5438 and R547 can affect the expression of the most important anthracycline reductases (AKR1A1, AKR1B10, AKR1C3, AKR7A2 and CBR1) in human HepG2 and HL-60 cell lines.

Expression of anthracycline reductases in cells exposed to CDKi was evaluated at mRNA level by RT-qPCR and at protein level by Western blotting. The most significant changes in mRNA expression were observed for roscovitin and purvalanol A. Roscovitin caused a statistically significant reduction in mRNA expression of the AKR1A1, AKR1B10, AKR7A2 and CBR1 enzymes. Decreased expression of AKR1A1 and AKR7A2 enzymes at mRNA level was detected also in the case of purvalanol A. Expression at protein level was evaluated only for AKR1C3. However, no statistically significant changes were observed.