ABSTRACT

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Title of diploma thesis: The potential role of inhibitor tipifarnib in the treatment of acute myeloid leukaemia

Anthracycline antibiotics, such as daunorubicin, are the gold standard in a treatment of acute myeloid leukaemia. However, they are not fully specific and besides cancer cells, they can damage also other structures, especially heart muscle cells. Moreover, the anthracycline resistance can develop. The daunorubicin is metabolized by carbonyl reducing enzymes to daunorubicinol, which has significantly worse therapeutic effect. This reaction can be prevented by using a specific inhibitor.

In the thesis, the inhibitor tipifarnib and its effect on reactions catalysed either by aldo-ketoreductases (AKR1A1, 1B1, 1B10 and 1C3) or short-chain dehydrogenases/reductases (CBR1) were tested.

The strongest inhibition was observed for AKR1C3. When using 10 μM tipifarnib in reaction, an inhibition of 88.0% was observed, and 50 μM inhibitor resulted in inhibition by 92.9%. That is why kinetic parameters were specified only for AKR1C3 in all other experiments. The IC50 value was experimentally determined to 0.51 ± 0.03 μM and the inhibition constant value to 0.26 ± 0.03 μM. The results suggested that it was a mixed type of inhibition tending to noncompetitive type and a reversibly binding inhibitor. The inhibitor tipifarnib was approved by the FDA in 2021 as a drug.