ABSTRACT

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Title of diploma thesis: The use of selected inhibitors to overcome anthracycline resistance in cancer therapy (in vitro study)

Resistance to chemotherapy is a severe problem in treating cancer patients, significantly reducing their chances of recovery. The increased expression of carbonyl reductases in tumour cells is one of the leading causes of the resistance. These enzymes can reduce anthracycline-based chemotherapy drugs to their less effective derivatives and thus significantly reduce their efficiency. Therefore, the inhibitors of carbonyl reductases could increase the effectiveness of anthracycline-based chemotherapy. The goal is to find an inhibitor with high inhibitory activity and low side effects.

This thesis tested inhibitors asciminib, tucatinib, sotorasib, and umbralisib hydrochloride against carbonyl reductases from the aldo-keto reductase superfamily (AKR1C3, 1A1, 1B1, 1B10) and short-chain dehydrogenases/reductases superfamily (CBR1), using chemotherapy drug daunorubicin.

The most significant inhibitory potential was observed between asciminib and the enzyme AKR1C3, therefore only this inhibitor was used to obtain other kinetic parameters. The 10μM inhibitor showed inhibition of 38.9 %, and the 50 μM inhibitor reached inhibition of 70.7 %. The IC50 value was 17.4 ± 2.0 μM, and the Ki value was 16.3 ± 0.7 μM. The inhibitor asciminib acts as a non-competitive inhibitor. FDA approved this inhibitor for the treatment of chronic myeloid leukaemia in 2021.