

## **Abstract**

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Title of diploma thesis: Study of ABC drug efflux transporter inhibition by selected tyrosine kinase inhibitors using accumulation methods with cytostatic substrates

ATP-binding cassette (ABC) drug efflux transporters are transmembrane proteins that utilize the energy from ATP hydrolysis to drive transport of endogenous and exogenous compounds out of the cell. The overexpression of ABC transporters plays a crucial role in the development of multidrug resistance (MDR), a phenomenon responsible for the failure of chemotherapy. Tyrosine kinase inhibitors (TKI) represent novel beneficial therapeutic approach in cancer treatment. TKI block tyrosine kinases which regulate important cellular processes. Deregulation of these enzymes can lead to various types of cancers. In the present work, we investigated interaction potential of selected TKI (alectinib, brivanib, osimertinib, selumetinib) in MDCKII parent cell line and those transduced with human efflux transporters ABCB1, ABCC1 and ABCG2. Using the accumulation studies, we determined the amount of accumulated model substrates (daunorubicin, mitoxantrone) and evaluated the inhibitory effect of individual TKI. Our results showed that brivanib and osimertinib significantly inhibited all of the above mentioned ABC transporters while alectinib inhibited only ABCG2 and ABCB1. Selumetinib was the only TKI that did not exhibit any remarkable inhibitory effects. In conclusion, we successfully characterized the potential of tested drug candidates to become perpetrators of pharmacokinetic drug-drug interactions and/or modulators of MDR mediated by examined ABC efflux transporters.