Abstract

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Title of diploma thesis: Synthesis of novel inhibitors of human Topoisomerase based on highly substituted phenyl scaffold.

Despite progress in anticancer therapy, cancer is still one of the leading causes of death in the world. Patients treated with current anticancer therapy suffer from many side effects. This is caused by the low selectivity of the current drugs. The development of chemotherapeutics aims to prepare more selective and therefore better tolerated anticancer drugs.

Topoisomerases are nuclear enzymes occurring in every cell. They have an essential role – to preserve DNA and repair it. Topoisomerase isoform IIα is an isoform that controls and edits the conformation of DNA during cell replication. Its expression is highly elevated in proliferating cells. That makes it a good target for anticancer drugs.

The design of synthesized molecules is based on previously reported ATP-competitive inhibitors of human topoisomerase IIα. Alterations of 3,4-dichloro-5-methyl-*N*-phenyl-1*H*-pyrrole-2-carboxamide have been synthesized based on Computational-Aided Drug Design. The *in silico* study is based on the previous discovery of the ATP cavity biding pattern. It was found that halogen-substituted pyrrole-2-carboxamide moiety is crucial for the inhibition of the target.

This project aimed to synthesize novel inhibitors of topoisomerase IIα. Synthesized compounds were tested for inhibitory activity and the IC_{50} on hTopoII is 25 μM. Further details of synthesis and biological evaluations will be discussed in the thesis.