Abstract

Title: *In silico* screening of SIRT6 inhibitors

Author: Tomáš Kučera

Department: Department of Pharmaceutical Chemistry and Drug Control

Supervisor: prof. PharmDr. Martin Doležal, Ph.D.

Specialized supervisor: Maija Lahtela-Kakkonen, Ph.D.

Abstract: SIRT6 is called NAD-dependent protein deacetylase sirtuin-6 and it is a member of sirtuin protein family. It modulates acetylation of histone H3 (clinically important Lys9 and Lys56). The SIRT6 enzyme is an interesting drug target because of its role in DNA replication, glycolysis and inflammation – that is why the design of SIRT6 inhibitors is relevant in context of diabetes mellitus, arthritis and cancer.

The aim of the work was to identify small molecules to inhibit deacetylase activity of SIRT6 using methods of computational chemistry and molecular modeling. We tried to find new lead structures with possibility to be optimized in next phases of the drug discovery process.

The 9 known inhibitors and crystal structure of SIRT6 (PDB code 3K35) were used as input data during the modeling. Pharmacophoric and chemical similarity searches were selected from the group of ligand-based methods and molecular docking from the group of structure-based methods. The pharmacophore was defined after structural alignment of four known ligands and tested on set of ligands and non-ligands. As pattern molecules for chemical similarity search (BIT_MACCS fingerprint), known ligands and their fragments were used. Docking was done mainly using software MOE.

Together 44 molecules were selected and recommended for *in vitro* testing. 11 compounds have been tested so far and four of them show significant inhibition activity on SIRT6.

Keywords: SIRT6, sirtuins, inhibitor, virtual screening, histone