Abstract

This bachelor thesis is part of a project focused on studying low-molecular mass compounds able to inhibit the interaction between DNA-binding domain of human forkhead transcription factor FOXO3 and the target DNA. FOXO3 is one of four members of FOXO class transcription factors which belong to forkhead family of transcription factors. Forkhead transcription factors are evolutionary conserved proteins playing important roles in numerous cellular processes. These include cell-cycle regulation, oxidative stress response, control of cellular metabolism and apoptosis. FOXO3 plays an important role in cancer cells where it acts not only as a tumor suppressor but also can enhance their resistance to chemotherapy. Considering its biological functions, the study of small-molecule inhibitors of FOXO3 transcription factor is of particular importance. This bachelor thesis was focused on compound S9 oxalate as a potential inhibitor of FOXO3-DNA interaction.

Main goals of this thesis were: (I) preparation of both unlabeled and ^{15}N labeled DNA-binding domain of FOXO3 transcription factor, (II) characterization of interactions between FOXO3 DBD and compound S9 oxalate using NMR and electrophoretic mobility shift analysis (EMSA), and (III) prediction of binding conformation and interactions between FOXO3 DBD and S9 oxalate using molecular docking.

Results revealed that S9 oxalate directly interacts with FOXO3 DBD residues responsible for DNA binding and therefore is able to inhibit FOXO3 binding to the target DNA. In addition, molecular docking simulations of S9 oxalate into the identified binding site suggested possible interactions between FOXO3 DBD and the compound.