Abstract

The thesis specializes in the computational description of pharmaceutically important compounds.

A substantial number of pharmaceutical drugs are small molecules that are bound to an active site of an enzyme by the “lock (binding site) and key (drug)" model through non-covalent interactions. The association of enzymes with drugs cause an increase or decrease in the activity of enzymes. The main topic is focused on the computational elucidation of the structural basis for the interactions of the purine-like compounds with the enzyme cyclin-dependent kinase 2 that belongs to the protein-kinase enzyme family. These enzymes play an important role in the cell cycle regulation; their increased activity significantly contributes to the loss of control over cell proliferation, which is one of the primary causes of cancer cell formation. The study describes the binding motifs of roscovitine, which shows an inhibitory effect on the function of cyclin-dependent kinases, and its analogues containing bioisosteric central heterocycles in the complex with cyclin-dependent kinase 2. The binding affinity between the cyclin-dependent kinase 2 enzyme and the inhibitors was quantified as calculated binding scores and evaluated in relation to the conformation of the optimized structures. The hybrid model combining the quantum mechanics – QM (DFT-D) and semiempirical quantum mechanics – SQM (PM6-D3H4X) method was used. The solvent effect was described by the continuum solvation model COSMO at the SQM level for the whole system.

The second topic is aimed at the computational estimate physicochemical properties of several groups of neuroactive compounds that modulate the activity of the *N*-methyl-$_{D}$-aspartate receptor. This receptor belongs to the family of glutamate receptors that are present in nerve cells. It is thought that it is connected with a variety of neurological disorders such as epilepsy, Parkinson's and Alzheimer's diseases. The computational studies investigate the lipophilic qualities and solvation free energy of neuroactive compounds as these properties are inherent characteristics of the substances and influence their interactions with the *N*-methyl-$_{D}$-aspartate receptor. The solvation free energy was calculated in the SMD continuum solvation model at the HF/6-31G* level. The calculated logP was estimated on the basis of the change in the molecular conformation related to the transfer between *n*-octanol and water. The studied compounds were optimized by the RI-DFT-D3/B-LYP/TZVPP//COSMO method and their SP energy was calculated at the same level of accuracy.

This thesis is based on five of the ten publications that have been published on these topics.

Keywords: non-covalent interactions, *in silico* drug design, CDK2, purine analogues, NMDA receptor, neuroactive compounds