The research aims at application of approximate non-empirical quantum chemical (QM) model for the assessment of inhibitory activity of selected protein-inhibiotr systems.

Since standard methods used for the assessment of inhibitory activity are parametrized with non-physical constants (so called empirical or semi-empirical methods), they do not allow to investigate the physical basis of the receptor-ligand (e.g., enzyme-inhibitor) interaction. An alternative to such methods could be accurate QM computations, but they are time-and computational resources-consuming, and therefore inapplicable for high-throughput analysis of large molecular complexes like protein receptors.

In the presented reaserch, we propose a compromise between time-consuming QM methods and arbitrary empirical approaches, i.e., an approximate QM model based on long-range terms of interaction energy, which could be a useful prognostic tool for the assessment of relative interaction energy values. These interactions are, in general, less sensitive to the shortened contacts that are common in structures obtained from molecular docking, therefore they could serve as a tool for relative inhibitory activity assessment. Preliminary tests of such model on fatty acid amide hydrolase inhibitors (J. Phys. Chem. B. 2014, 118(51)) were encouraging, as allowed to score the inhbitory activity better or with comparably with the number of commercially available empirical methods. The aim of this project is to apply above described method for different inhibitor - receptor systems in order to validate proposed nonempirical approach and investigate its limitations.

The variational-perturbational partitioning of complete inhibitor-receptor interaction energy will serve as a reference model allowing analysis of the physical nature of binding energy. Both models will be tested on three systems: *(i)* ephrin type-A receptor 2 -- ephrin A1 and inhibitors of this interaction, which are litocholic acid-derivatives (J. Med. Chem. 2013, 56(7)), *(ii)* menin-MLL and selected inhibitors of their interaction, analogs of the tienopirymidine lead compound MI-136 (Cancer Cell, 2015, 27(4)), and *(iii)* phosphodiesterase type 5 and a series of inhibitors substituted with halogen atoms (J. Med. Chem. 2014, 57(8)). The studies on the first two systems are devoted to protein-protein interaction (PPI) inhibition, and the last system is a classical enzyme-inhibitor complex. The ephrin type-A receptor 2 -- ephrin A1 (EphA2-ephrin A1) interaction is linked to development of certain types of cancer, for instance, breast or prostate. Menin-MLL (Mixed Lineage Leukemia protein) interaction is connected with development of accute myeloid and lymphoblastic leukemias. Studies on hosphodiesterase type 5 inhibition are to establish the influence of the chosen halogen on the inhibitor binding.

The aim of this research is to perform extensive testing of the proposed method on various types of inhibitor-receptor systems, to evaluate its universality and to state its possible application limits. Universal model based on first principles of quantum mechanics without empirical parametrization can be applied for rapid assessment of relative inhibitory activity, which is still absent in the literature. Efficient analysis based on long-range terms of interaction energy could be used for high-throughput design of novel inhibitors, potential drug candidates. In each tested system such an approach allows to define the physical nature of inhbitor binding, and therefore rational design of novel inhibitors.