

The research objective of my project is the optimization and expansion of a novel class of small-molecule inhibitors based on terphenyl core, that inhibit the interaction between human programmed death 1 protein and human programmed death ligand 1 (PD-1/PD-L1 interaction). The interaction plays an important role in intercellular communication of immune system's cells, causes inhibition of T-cell proliferation and recognition of the aberrant cells. The protein-protein interaction (PPI) is used to avoid immune response by microorganisms and mutated cells. PD-L1 protein is overexpressed in several types of cancers and connected with poor clinical prognosis. The studies have established, that the blockage of PD-1/PD-L1 interaction restores T-cells functions and normalizes immune response. The inhibition of immune checkpoints, including PD-1/PD-L1 interaction is a fundament of immunotherapy, being a novel approach in cancer treatment. The therapy allows restoration of immune system functions, proper recognition of cancer cells and their elimination. PD-1/PD-L1 interaction might be blocked by targeting both PD-1 or PD-L1 proteins, however, usage of monoclonal antibodies targeting PD-L1 has brought better results in clinical trials

The development of small-molecule inhibitors is expected to bring numerous profits on the field of PD-1/PD-L1 immune checkpoint blockage, e.g. lower production and treatment costs, higher stability, improved tumor penetration, amenability for oral administration and elimination of immunogenicity issues.

The aim of my project is the structural optimization of terphenyl moiety, which was discovered during my doctoral research, is capable of inhibiting hPD-1/hPD-L1 interaction and is the perfect starting point for further optimization, because of its high affinity to PD-L1 protein. The research goals will be achieved using linear synthesis as well as multicomponent reactions (MCR). The found core is a new proposition in the design of PD-L1 small molecule inhibitors, additionally, its structure could be easily modified. The binding affinity of obtained compounds towards PD-L1 will be tested due to *Homogeneous Time Resolved Fluorescence* (HTRF) assay.

Structure-Activity Relationship (SAR) analysis, that I would like to perform, might lead to obtaining the novel class of compounds useful in cancer treatment and, certainly, would lead to a novel class of chemical probes helpful in the understanding of PD-1/PD-L1 interaction.