## Abstract

The aspartic protease cathepsin D (CatD) is associated with numerous pathologies, and therefore the molecular mechanisms of its activation are studied for their potential uses in biomedicine. This dissertation thesis is focused on new, natural endogenous inhibitors of CatD, the analysis of their interaction, and the development of synthetic inhibitory biomimetics.

Two groups of inhibitors of CatD, which are the first specific endogenous regulators of this enzyme, have been identified. (1) Sphingolipids are complex modulators of human CatD, depending on their structure. While sphingosines and ceramides are inhibitors of CatD, their phosphorylated derivates act as activators of CatD. A correlation was found between the action of these sphingolipids on CatD and their modulatory effect on cancer cells. (2) Using the analysis of a CatD of parasitic origin, a new mechanism of inhibition was identified, which is conserved in aspartic proteases of the pepsin family. A peptide fragment is released autocatalytically from the zymogen of CatD, which then acts as an allosteric inhibitor, binding to an exosite on the surface of the catalytically active enzyme. Furthermore, synthetic macrocyclic inhibitors of CatD were prepared, which mimic the binding conformation of the bacterial inhibitor pepstatin in the active site of aspartic proteases. Based on these results of the structure-function analysis, it is possible to purposefully modify the properties of these biomimetic inhibitors.

This thesis contains important new information about three new types of inhibitors of CatD and regulation mechanisms, which can be used for an intelligent design of inhibitory drugs for pathologies associated with CatD-like aspartic proteases.