Summary of doctoral thesis

The aim of the dissertation was to obtain active furin inhibitors, the enzyme of the proprotein convertases family (PCs). This enzyme, together with other PCs is responsible for the proteolytic activation of the protein precursors which are essential for the proper cell functioning. However, many scientific studies have proved that they can also transform protoxins which are produced by viral and bacterial pathogens. It has been shown that PCs play an important role in the development of a variety of diseases, such as infections, inflammations or cancer diseases. Therefore, the inhibition of their unwanted activity seems to be a way of searching new therapeutic strategies. The primary obstacle during the development of effective inhibitors is the difficulty in designing selective and specific compounds that strongly inhibit the activity of the selected enzyme. It is caused by the high homology of the PCs structure and the way of their folding, as well as the compatibility of the catalytic domain sequence at the level of 57-70%.

The main goal of realized research was to receive active furin inhibitors by modifying the model compound Ac-RARRRKKRT-NH2, designed according to the structure of the immature influenza hemagglutinin virus H5N1. The proposed modifications consisted changes in the P5-P8 positions (the introduction of all of encoded (excluding cysteine) and selected non-coded amino acid residues in those positions).

Peptides were synthesized on the amide resin by standard solid phase synthesis (SPPS, Fmoc/tBu strategy) using the automatic synthesizer. The products were cleaved from the resin in the strong acidic conditions, purified (HPLC) and identified (MS, HPLC). Received pure compounds (>98%) were sent to collaborative research group (Pharmacology Institute, Medicine Department, University of Sherbrooke) to determine their activity toward furin. The inhibition constants were calculated according to data received from spectrophotometric analysis.

The realization of the research allows us to understand the structure-activity relationship (SAR) of furin and how the substitutions of different amino acid residues in the structure of the leading compound in P5-P8 positions influence the furin inhibition. The results show which modifications lead to increased inhibitory potency towards furin and which positions play the most significant role during binding the enzyme with the inhibitor.