In search of specific inhibitors of myeloperoxidase, from mechanistic studies to application in enzymatic and cellular systems

Myeloperoxidase (MPO) is an important member of the haem peroxidases and plays an essential role in the antimicrobial and antiviral defense system in mammals. MPO utilizes hydrogen peroxide (H_2O_2) and halide ions to produce hypohalous acids (e.g. HOCl). These powerful MPO-derived oxidants are capable of killing various pathogens during infections but also those species generated in excess are thought to be a key factor in pathogenicity of many diseases. Therefore, there is an appreciable interest in the development of MPO inhibitors.

In this project an emphasis will be put on searching, synthesis and validation of selective and highly specific inhibitors of myeloperoxidase among hydroxamic acids analogs and nitroxides. Hydroxamic acids, including derivatives of salicylhydroxamic acid (SHA), are reported to be promising inhibitors of MPO, whereas nitroxides can inhibit the chlorinating and nitrating activity of myeloperoxidase and interacting with compounds I and II of this haem peroxidase. Studied MPO inhibitors will also be validated in cellular systems.

Due to limitations of a currently used assays for monitoring of a MPO-derived hypochlorous acid (HOCl), it is essential to develop a new method that can be utilized in high-throughput screening of MPO inhibitors. Therefore, this project is also dedicated to the development of a novel and reliable screening method of myeloperoxidase inhibitors. The optimal methodology will be established in the course of research.

The realization of this project will help to find more specific inhibitors of myeloperoxidase and validate them in cellular systems, while finding optimal methodology of high-throughput screening of MPO inhibitors will accelerate the search of the most effective one. From a wider point of view, the research proposed in the project is extremely important for the reduction of MPO-derived disease pathogenesis and further studies in the field.