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Design, Synthesis and Biochemical evaluation of novel serine protease inhibitors

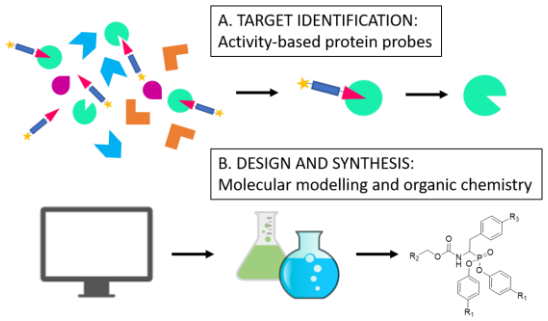
Alba Ramos Llorca – alba.ramosllorca@uantwerpen.be

Summary

The screening of a serine proteases inhibitors library in a Dry Eye Disease animal model showed a promising in-house compound, UAMC-00050, which has the potential to target different enzymes within the serine protease family. Firstly, the focus will be on understanding the mode of action of UAMC-00050 and the identification of the specific serine protease targeted by the inhibitor. This will be determined through activity-based protein profiling involving the synthesis and characterization of chemical probes. This study will also enable the design of new analogues of UAMC-00050 by molecular modelling. Hence, more specific and potent compounds will be synthesized and characterized.

State-of-the-art

Dry eye disease (DED) is a chronic, multifactorial disease of the ocular surface accompanied by ocular symptoms, such as ocular surface inflammation and tissue damage. DED has become a major and increasing healthcare problem due to its high prevalence and economic burden. Cyclosporine A is the only marketed drug for DED in Europe but has only demonstrated effectivity in severe keratitis DED patients. Recently, the US FDA has also approved Xiidra™ for the treatment of DED, however, experts in the field of DED have indicated that new and complementary therapies are needed. The laboratory of Medicinal Chemistry at the University of Antwerp (UAMC) has recently obtained promising results with a multi-target serine protease inhibitor. Topical application of this compound in the eye of a tear-deficient dry eye rat animal model gave a significant reduction of both tissue damage and a significant reduction of the inflammatory parameters. Several of the inhibited proteases are linked to extracellular matrix degradation and tissue damage as well as to inflammation.



Summary of the project: A. Target identification; B. Design and synthesis of new compounds

Techniques

Organic synthesis:

- Activity-based probes synthesis
- Click chemistry
- Phosphorus chemistry

Organic compound purification:

- Flash chromatography
- Recrystallization

Biochemistry:

- Protease screening

Compound characterization:

- Nuclear magnetic resonance
- Ultra-Performance Liquid Chromatography

Task description

- Design, synthesis and characterization of activity-based probes targeting serine protease
- Understand the interaction mechanism between UAMC-00050 and the target enzyme
- Design, synthesis and characterization of structural UAMC-00050 analogues
- Analytical and biochemical evaluation of the newly developed probes and serine-protease inhibitors
- Identify structure-activity relationships from the obtained data