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Upscaling of lead compounds from WP1 and enantioselective synthesis of the serine protease inhibitor UAMC-00050

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Summary

In the past years the group of medicinal chemistry of the University of Antwerp developed a series of small molecules for treatment of Dry Eye Disease: the most promising molecule (UAMC-00050) has recently demonstrated an *in vivo* proof of concept as multi-target serine protease inhibitor (inhibits uPA, tryptase, matriptase, cathepsin G, KLK4 and KLK8). UAMC-00050 actually is synthetized as a racemic mixture, to improve the activity we need to know which one of the two enantiomers is more active.

Synthesis of the two enantiomers using a kilo laboratory reactor

State-of-the-art

Dry Eye Disease (DED) is a multifactorial disease of the ocular surface, characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles. Serine protease and RIPK1 are involve in the inflammation process and the death of the eye cells. α-Amino-phoshonates, a class of compound known since 1890, have shown a high biological activity as inhibitors of proteases and catalytic antibodies. In addition, they have been used as antibacterial and anti-HIV agents. In our case a α-amino-carbobenzyl aryl-phoshonates showed an inhibitory activity on serine protease. Synthesis of α-amino aryl-phoshonates is quite challenging and very few research has been done for the stereoselective synthesis of these compounds.

Techniques

- Perform a synthesis of α-amino phoshonates on a 10 g scale, starting from a process optimization on a 100 mg scale
- Design of the process model and screening of the key reaction parameters (catalyst, solvent, etc.)
- Monitoring the reaction in real time with UPLC-MS or NMR analysis
- Up-scaling the reaction in our kilo facility at LIOS
- Screening of the chiral compounds with *in vitro* tests

Task description

Development of synthetic routes suitable for 10-20 g scale synthesis of lead compounds resulting from serine protease and/or RIPK1 inhibitor discovery programs (WP1). This includes route scouting, and optimization of problematic steps to meet the requirements of safe, cost effective and environmentally benign manufacturing process.

During the secondment in the university of Antwerp I will be able to compare biological activity of enantiomers using *in vitro* tests. During the secondment in the research centre of Merchachem in the Netherlands I will learn the GMP guidelines and the green chemistry approach for upscaling of a synthetic process.