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Design, Synthesis and Biochemical evaluation of novel RIPK1 inhibitors

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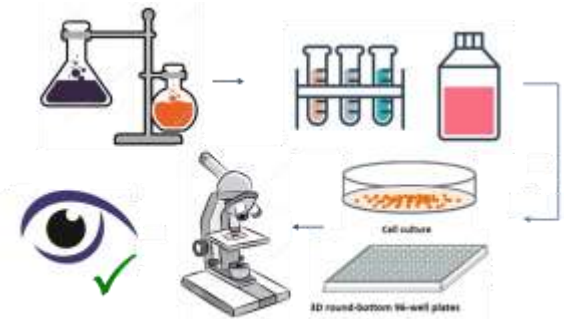
Summary

Starting from the evidence of cell death in Dry Eye Disease (DED), the project targets a specific type of cell death: necroptosis. The design and chemical synthesis is focused on inhibition of Receptor Interacting Serine/Threonine Kinase 1 (RIPK1) for preventing necroptosis. Thus, starting from an already synthesized library of molecules in the UAMC group, the aim of the project is to synthesize novel small molecules targeting necroptosis for DED treatment.



Synthesis, analysis and biological screening of new dry eye inhibitors

State-of-the-art

Dry Eye Disease is a chronic, multifactorial disease of the ocular surface and is a major and increasing healthcare problem. However, the development of new therapies for patients suffering from DED is still a major challenge. Recently, inflammation is recognized to be one of the major causes of dry eyes. Connected with these inflammatory pathways are the accumulation of radical oxidative species (ROS). There are indications of cell death in DED models stressing the relevance of this cell death mechanism. Specifically, there is evidence of necroptosis in cornea and conjunctival cells proving its role in the pathogenesis of DED. The Medicinal Chemistry group at the University of Antwerp (UAMC) developed a new series of necroptosis inhibitors as type I kinases inhibitor of RIPK1.

Techniques

Organic chemistry:

- Different synthetic procedures;
- Sample charachterization with High Performance Liquid Chromatography (HPLC), Nuclear Magnetic Resonance (NMR); Mass Spectrometry (MS);
- Sample purification by chromatography;

Biochemistry:

- Cell cultures;
- Confocal microscopy and Flow Cytometry.

Task description

Building further on the experience of the UAMC group with enzyme inhibitors, the project focusses on design, synthesis and characterization of novel RIPK1 inhibitors, an emerging kinase target in the field of regulated necrosis

At the University of Antwerp we perform the design, synthesis and characterization of the novel molecules.

At the University of Valladolid, in collaboration with IOBA institute, the analytical and biochemical evaluation of the compounds are carried out in cornea and conjunctival cell lines.

At the industrial partner Mercachem the synthesis of the novel necroptosis inhibitors will be scaled up.