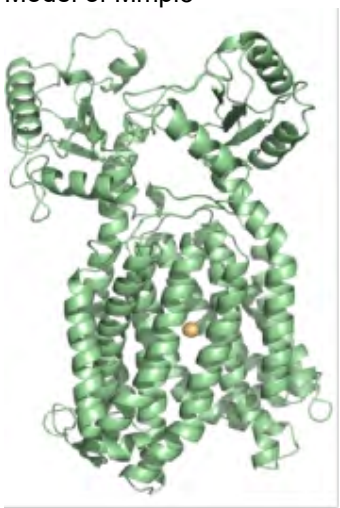
**MS02-2-3 Structure-based design and synthesis of piperidinol-containing molecules as new Mycobacterium abscessus inhibitors**
**#MS02-2-3**

**J. De Ruyck [1]**
**[1]University of Lille - Villeneuve Ascq (France)**

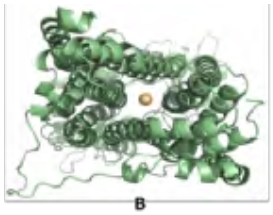
**Abstract**
Non-tuberculous mycobacterium (NTM) infections, such as those triggered by *Mycobacterium abscessus*, are increasing globally. *M. abscessus* pulmonary diseases in particular are of health concern as they are often recalcitrant to standard chemotherapy due to the intrinsic drug resistance mechanisms developed by this mycobacterium. We previously demonstrated that a piperidinol derivative, named PIPD1, is an efficient molecule both against *M. abscessus* and *Mycobacterium tuberculosis*, the agent of tuberculosis that targets the mycolic acid transporter MmpL3. In order to refine the properties of PIPD1 we determined the pharmacokinetics properties of PIPD1 and showed, that intraperitoneal administration of PIPD1 led to serum concentration of 600 ng/ml, to the distribution in different organs and an elimination half-life of 3.2 hours. We also designed, synthesized and determined the biological activity of a series of piperidinol derivatives against *M. abscessus*. Structure–activity relationship (SAR) studies pointed to the sites on the scaffold that can tolerate slight modifications. Interestingly, the Van der Waals radius of substituents present on the ortho position of the aromatic ring B seems to have a great importance for the biological activity. These results allow identifying FMD-88 with a similar antimycobacterial activity as PIPD1.

**References**
Structure-Based Design and Synthesis of Piperidinol-Containing Molecules as New Mycobacterium abscessus Inhibitors de Ruyck *et al*, ChemistryOpen, 2020, 9, 351-365

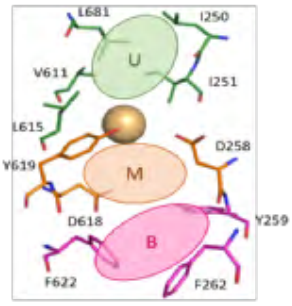
Model of Mmpl3



A



B




C

Putative binding site of FMD-88