Synthesis of mannoside probes for the study of PIMs biosynthesis

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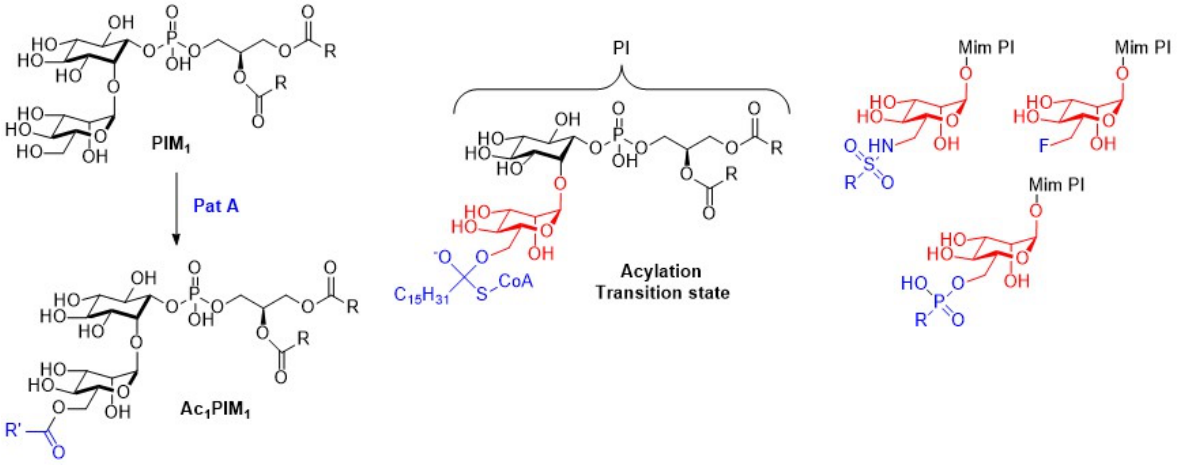
Mycobacterium tuberculosis is the second most deadly infectious agent in the world after COVID-19. Drug treatment require daily dosage of two to four drugs over six months, and compliance is poor. Most recently, there has been an alarming rise of multi-drug resistant and extensively drug resistant tuberculose (TB), making discovery of new drugs crucial. Current anti-TB drugs are targeting diverse biological processes[1] but no molecules are designed to target PIMs biosynthesis. PIMs (Phosphatidyl-*myo*-Inositol Mannosides) are the precursors of two major lipoglycans implicated in host-mycobacteria interactions. According to the currently accepted model, the biosynthesis starts with the transfer by essential mannosyltransferases PimA and PimB of a mannopyranosyl residue to the 2 and 6-position of the inositol ring of PI leading to PIM_1 and then PIM_2. The acyltransferase PatA catalyzes the transfer of a palmitoyl moiety to the 6-position of the mannose ring linked to the 2-position of inositol in PIM_1 or PIM_2, to obtain Ac_1PIM_1 or Ac_1PIM_2.[2] Docking studies of PatA gave useful information for inhibitors design.[3]

We are therefore focused on the synthesis of a panel of molecules with mannopyranosyl scaffold with the aim to develop new PatA inhibitors. Structures present different aglycones to mimic the PI part and different groups at the 6-position of mannose mimicking the acylation tetrahedral transition state. The following step will be to study the molecule/enzyme interactions, to determine the inhibitory activities and to test the best molecules on *Mycobacterium tuberculosis.*



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