SYNTHESIS OF MANNOSIDES AS INHIBITORS OF PIMs BIOSYNTHESIS

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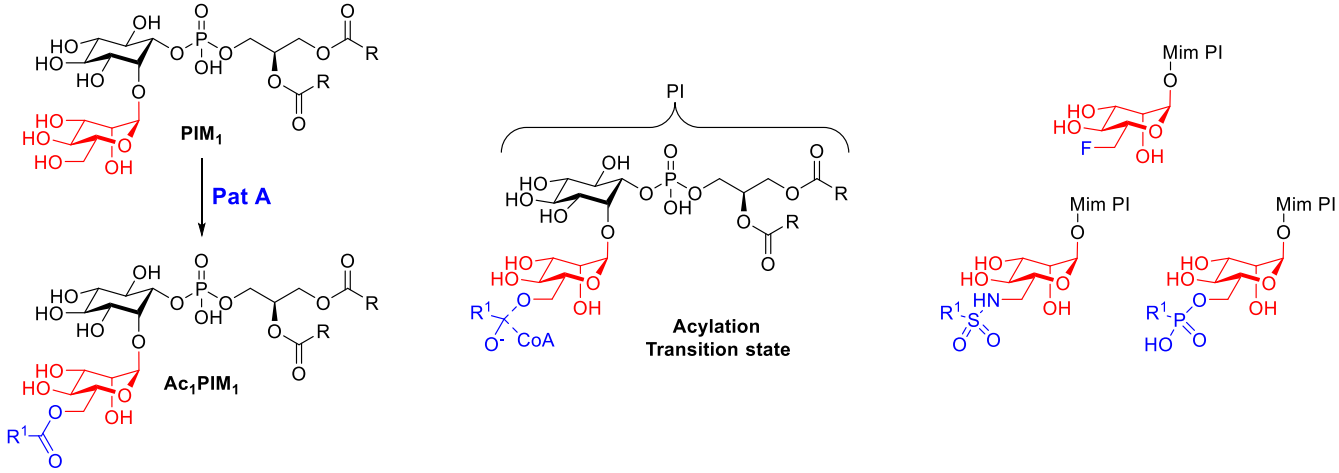
Mycobacterium tuberculosis, the causative pathogen of tuberculosis (TB), is the second most deadly infectious agent in the world, affecting several million people and causing around one million deaths every year. In addition, the World Health Organization is warning of the emergence and proliferation of multidrug-resistant strains, on which current treatments have little or no effect. It is therefore crucial to find new therapeutic targets and develop new treatments. 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 essential components of mycobacterial cell wall and the precursors of two major lipoglycans implicated in host-pathogen interactions. According to the currently accepted model, the biosynthesis starts with the transfer of mannopyranosyl residues to the inositol ring of PI leading to PIM_1 and PIM_2 [2]. Then, the membrane-associated acyltransferase PatA catalyzes the transfer of a palmitoyl moiety from palmitoyl coenzyme A to the 6-position of the first transferred mannose in PIM_1/PIM_2 to give Ac_1PIM_1/Ac_1PIM_2.This enzyme was recently found to be essential for mycobacteria growth *in vitro* and *in vivo* making it a novel therapeutic target for drug discovery [3].



Therefore, we currently focus on the synthesis of a panel of molecules with mannopyranosyl scaffold with the aim to develop PatA inhibitors. Structures present different aglycones to mimic the PI part and different groups at the 6-position of mannose as a fluorine or a group mimicking the acylation tetrahedral transition state. The synthesized molecules will be tested on PatA as well as on *Mycobacterium tuberculosis*.

References:

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