DESIGN, SYNTHESIS AND EVALUATION OF NOVEL Δ^2- THIAZOLINO 2-PYRIDONE DERIVATIVES AS *MYCOBACTERIUM TUBERCULOSIS* TOLERANCE INHIBITORS

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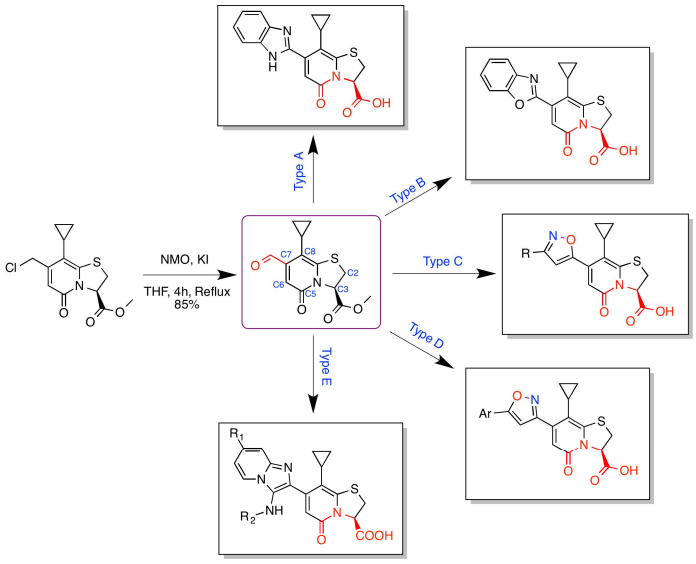
Antibiotic resistant infections are a dangerous, worldwide health problem. Chief among these pathogens is *Mycobacterium tuberculosis* (*Mtb*), which causes an estimated 1.5 million deaths a year. The emergence of drug-resistant *Mtb* strains, which constitute 20% of previously treated tuberculosis (TB) cases, has exacerbated this already alarming epidemic. The inadequacies of present TB therapies demand the discovery of new agents with unique mechanisms of action to treat *Mtb* infection. Towards this end, we have discovered and developed a new family of peptidomimetic ring-fused 2-pyridones (termed Mycobacterial Tolerance Inhibitors, MTIs) that invoke collateral sensitivity in *Mtb* by potently sensitizing *Mtb* to stresses encountered during infection and restoring activity to the frontline antibiotic isoniazid (INH) in otherwise INH-resistant katG mutant *Mtb* isolates. Based on our ability to functionalize the 2-pyridone central fragment, we have generated a robust structure activity relationship that has directed the design and synthesis of new more potent MTIs (Scheme 1). In this presentation we will describe our chemistry advancements and how we plan to generate a deeper understanding of the MTI's mode of action and their potential in synergistic interactions with INH.



Scheme 1. Development of new MTIs via C7 aldehyde of thiazolino 2-pyridone.