Aminothiazole Series Targeting *Mycobacterium Tuberculosis*

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Seattle Children's Summer Scholars Program

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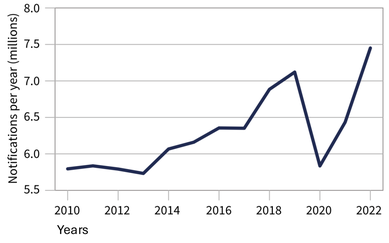
Rationales for Pursuing Novel Drug Discovery for Mycobacterium Tuberculosis (Mtb)

Global trend in case notifications of people newly diagnosed with TB, 2010–2022



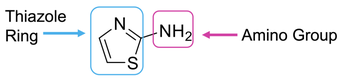
(World Health Organization Global Tuberculosis Report 2023)

- Mortality of approximately 1.3 million individuals worldwide in 2022
- Mtb attacks the pulmonary system
- Resistance to multiple drug and extensive drug resistance
- Prolonged therapeutic regimens: combination drug therapy
- Absence of medical intervention: a 50% survival rate

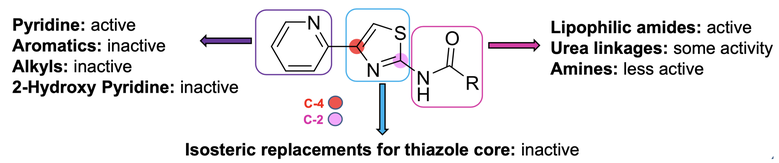
Background

- High- throughput screening libraries confirm that AmT series has proven to show anti-bacterial activity towards Mtb
- Aminothiazoles can accommodate many functional groups without significant activity loss

What is an Aminothiazole (AmT)?

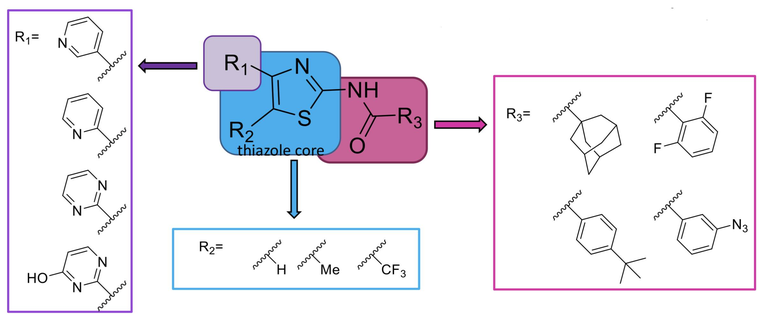


The Parish Lab previously conducted AmT SAR (Structure Activity Relationship) studies against Mtb by previously looking at the **C-2** and **C-4** position on the main aminothiazole core and replacement of the aminothiazole core. Summarization of findings are listed down below.



Project Aim: Differentiate Activity from Cytotoxicity

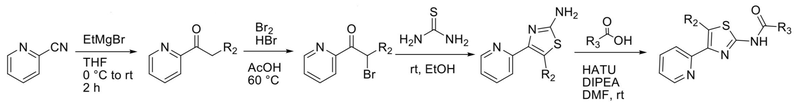
Substitution on thiazole and 1,3-pyrimidines previously no explored



Our overall goal was to synthesized novel AmT compounds and test *in vitro* assays against Mtb and HepG2 cells for activity and cytotoxicity.

Methods and Compound Synthesis Results

General Reaction Scheme



Reaction Procedure

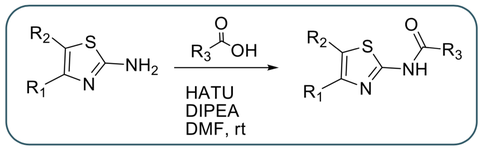
Step 1-Synthesis
- Variable temperature

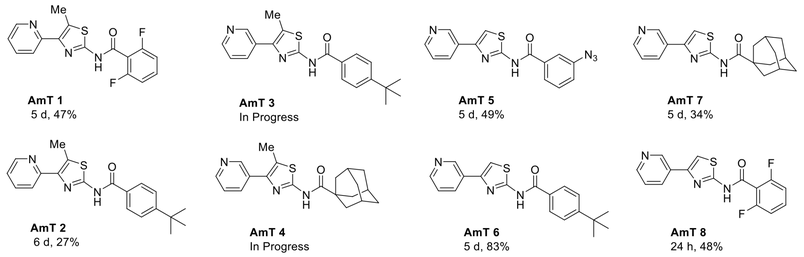
Step 2-Workup
- Rotavap
- Precipitation
- Aqueous workup

Step 3-Purification
- Trituration
- Chromatography

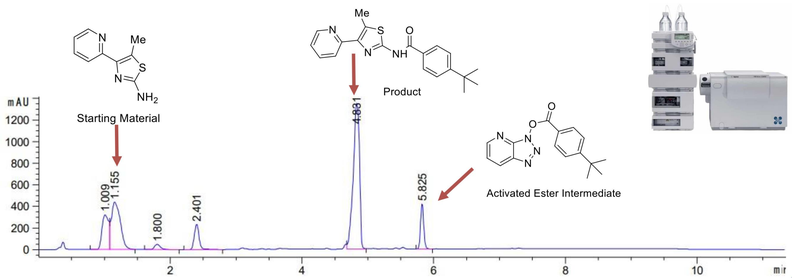
Step 4-Characterization
- Nuclear Magnetic Resonance (100 MHz)
- LC-MS (1100 Agilent)

Synthesis of Final Compounds Using HATU Coupling Reagent



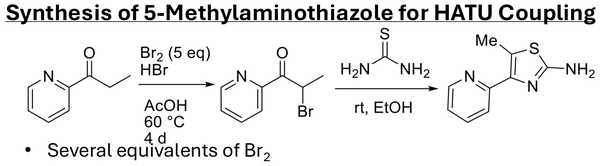


Compound Analysis of Liquid Chromatography Mass spectroscopy LC-MS



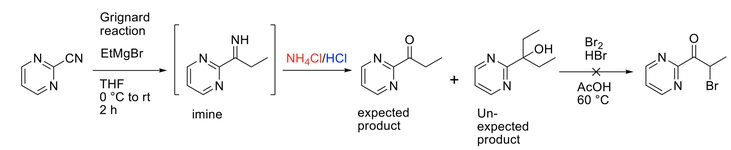
Challenges Faced

Synthesis of 5-Methylaminothiazole for HATU Coupling



- Several equivalents of Br_2
- Long duration
- Variable heat

Challenges Faced with Grignard Reaction

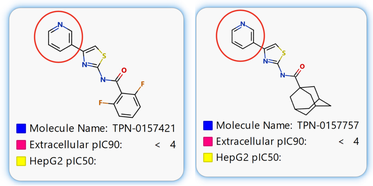


1st Grignard Reaction
- Addition of ammonium chloride
- Low isolation of imine
- LC-MS matched product's mass
- ^{1}H-NMR confirmed the imine intermediate

2nd Grignard Reaction
- Addition of 2mL HCL
- LC-MS showed product + byproduct
- Reaction pushed forward for bromination
- Bromination reaction failed

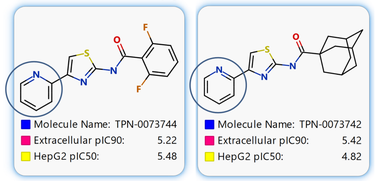
Biological Results

Current Biological Results
3-pyridine



Vs.

Previous Biological Results
2-pyridine



- IC90>100 micromolar

Conclusions and Future Directions

- Various AmT substitutions at the C-2 and C-4 position successfully synthesized as well as modifications on the thiazole core
- Potency data for the 3-pyridine compounds display that the compounds are inactive against Mtb
- 2-pyridine attached to the C-4 position of the thiazole core is preferred over the 3-pyridine
- In *vitro* assays results of 2 novel AmT compounds with substitution on the thiazole core that is attached to 2-pyridine ring shows excellent potency IC_{90} <10 μM and are cytotoxic against HepG2 cells

Our findings guide further exploration of alternative AmT scaffold regions with different substitutions for potential new drug discovery to reduce global mortality rates caused by Mtb.

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Abstract

References