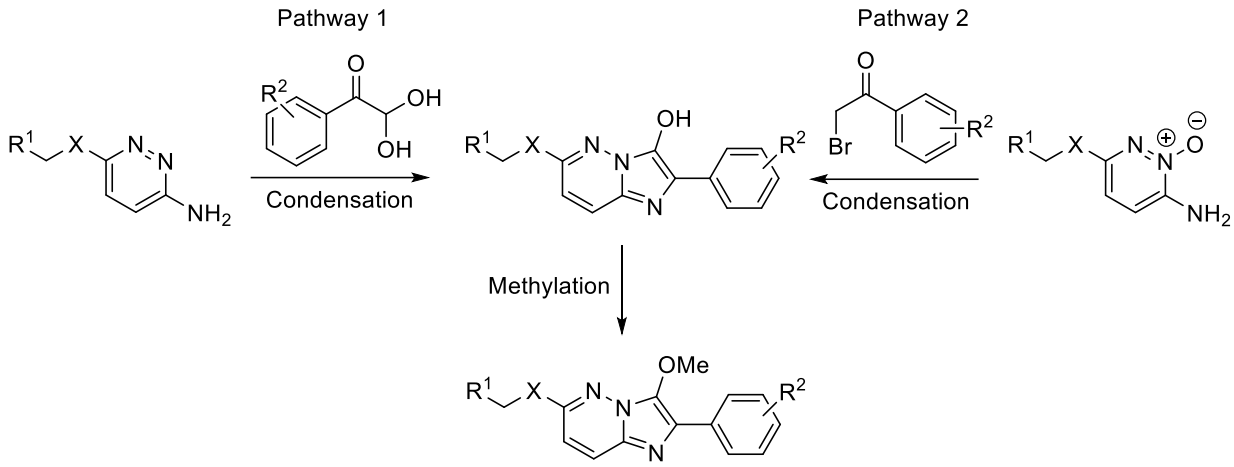
Thesis Summary

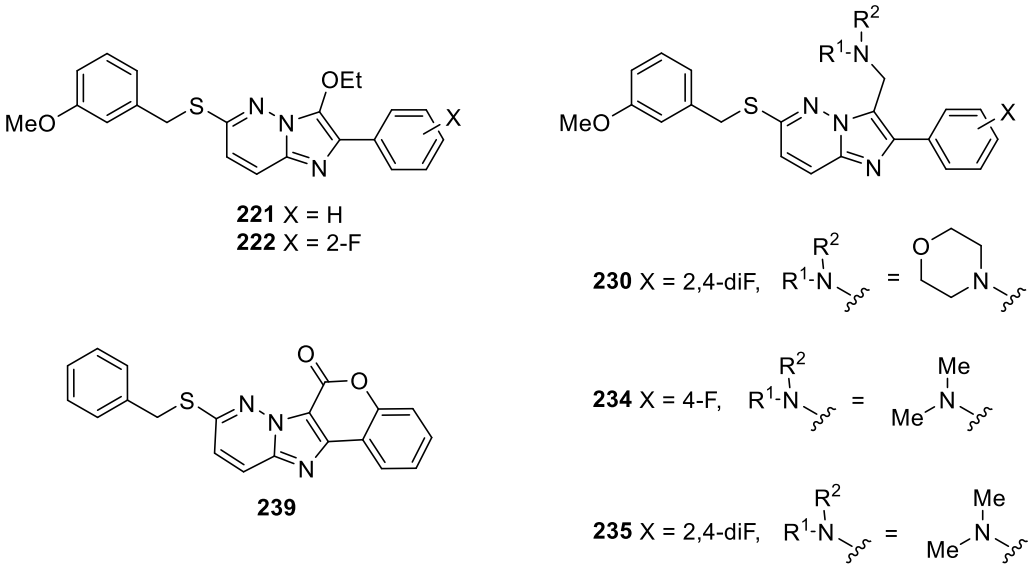
This thesis discusses the synthesis and biological evaluation of a library of imidazo[1,2-*b*]pyridazines as inhibitors of *Mycobacterium tubercuolosis (Mtb)*. Chapter 1 introduces the nature and impact of tuberculosis as well as the current methods used in treating the disease. Shortcomings of these methods, including a growing resistance to the drugs used in the current regimen, are highlighted. The drug discovery and development pipeline, a process which is used to find new antitubercular agents with the intention to alleviate these issues, is described. Compounds within the drug discovery and development pipeline, including Phase I clinical candidate Q203, are discussed. It is noted that Q203 possesses an imidazo[1,2-*a*]pyridine core structure which resembles the scaffold of interest, the imidazo[1,2-*b*]pyridazine. The antimycobacterial activity of these compounds became of interest after CSIRO (Commonwealth Science and Industrial Research Organisation) and GIBH (Guangzhou Institutes of Biomedicine and Health) screened 18,000 pre-existing CSIRO compounds against *Mtb* and discovered some to be highly active. High-throughput screening (HTS) results of a range of these imidazo[1,2-*b*]pyridazines from the CSIRO Compound Library are displayed and early structure-activity relationship (SAR) insights are discussed, providing the foundation for the design of the compounds synthesised in Chapter 2. Antitubercular imidazo[1,2-*b*]pyridazines were scarcely observed within the literature, which gave scope to claim intellectual property for these compounds and to move forward with this project.

Chapters 2 and 3 discuss the syntheses of a range of imidazo[1,2-*b*]pyridazines for screening against *Mtb.* Chapter 2 focuses on two synthetic pathways which converge at the condensation product, 2-phenylimidazo[1,2-*b*]pyridazin-3-ol, which can be methylated to form the desired 3-methoxy-2-phenylimidazo[1,2-*b*]pyridazine. Side-products discovered along these synthetic pathways are structurally elucidated and mechanisms for their production are proposed.



Overview of the synthetic pathways used to synthesise 3-methoxy-2-phenylimidazo[1,2-b]pyridazines

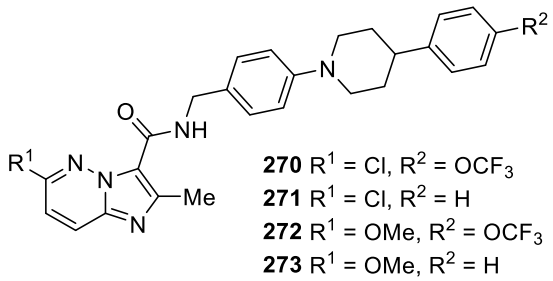
Chapter 3 discusses the syntheses of imidazo[1,2-*b*]pyridazines with other C3 substituents other than a methoxy moiety to probe this position for SARs. The compounds synthesised in this chapter include 3-ethoxy- (**221** and **222**), 3-dialkylaminomethyl- (**230**, **234** and **235**) and 3-carboxylate(lactone)- (**239**) substituted-imidazo[1,2-*b*]pyridazines shown below.



*The structures of 3-ethoxy- (**221** and **222**), 3-dialkylaminomethyl- (**230, 234** and **235**) and 3-carboxylate(lactone)-substituted (**239**) imidazo[1,2-b]pyridazines*

Chapter 4 discusses the attempts made to scaffold hop from an imidazo[1,2-*b*]pyridazine to an imidazo[2,1-*b*][1,3,4]thiadiazole core structure, in hope of finding a potent bioisostere to

inhibit *Mtb*. Furthermore, hybridisation of Q203 and TB47 (a GIBH compound structurally similar to Q203 with comparable potency against *Mtb* but contains a pyrazolo[1,5-*a*]pyridine core structure) and a scaffold hop to the imidazo[1,2-*b*]pyridazine led to the successful syntheses of "Q203/TB47 hybrid" imidazo[1,2-*b*]pyridazines **270** – **273**.



*The structures of "Q203/TB47 hybrid" imidazo[1,2-b]pyridazines **270** – **273***

SARs of the imidazo[1,2-*b*]pyridazines synthesised in Chapters 2, 3 and 4 are discussed in Chapter 5 on the basis of their *in vitro* antimycobacterial activities against *Mtb* and *Mm* (*Mycobacterium marinum*). The IC_{50} and MIC values of imidazo[1,2-*b*]pyridazines from the CSIRO library were also evaluated to gather further SAR data. Five compounds displaying highly potent *in vitro* activity were evaluated in a mouse *in vivo* study conducted at GIBH, discussed in Chapter 6. However, all five compounds exhibited no *in vivo* activity. Four of these compounds were evaluated for their physicochemical and metabolic properties at the CDCO at MIPS which provided reasons for their lack of *in vivo* activity.

In Chapter 7, conclusions from the work described in Chapters 2 - 6 are presented, followed by a discussion of future directions. Chapter 8 contains the experimental protocols for the compounds synthesised. The appendices are divided into two sections where Section 1 contains the NMR spectra, LC-MS and HRMS chromatograms/spectra for compounds tested against *Mtb* and Section 2 contains the NMR and HRMS spectra for miscellaneous compounds, mostly side-products, described throughout this thesis.