# Scaffold-Hopping Strategy and Bespoke Syntheses Towards a Clinical Candidate For Visceral Leishmaniasis

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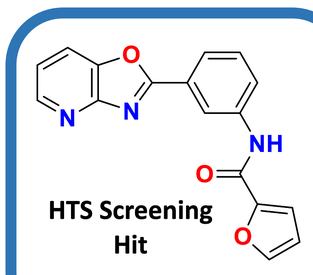
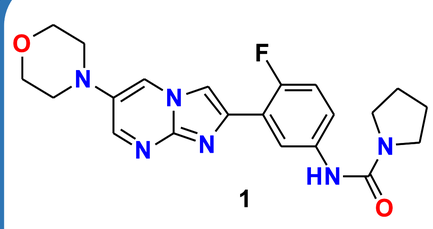
## Introduction

Visceral Leishmaniasis is a parasitic infection responsible for approx. 50,000 deaths a year. It mainly affects parts of Asia and East Africa.
There is an urgent need for new treatments.



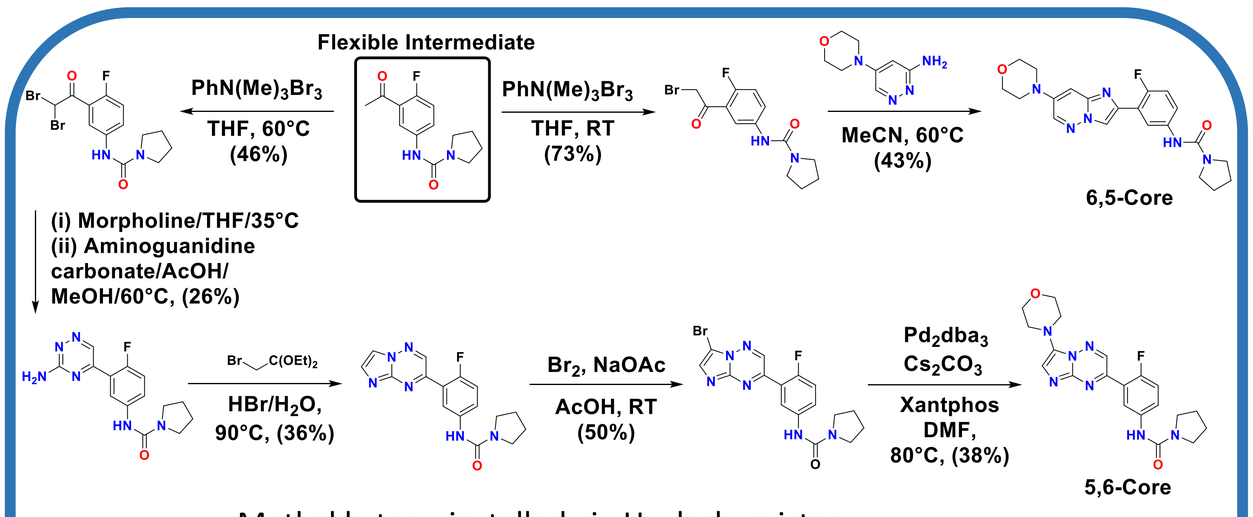

Phenotypic screening




**Early Lead**
- Orally efficacious
- Poorly soluble (Biorelevant media)
- Genotoxic

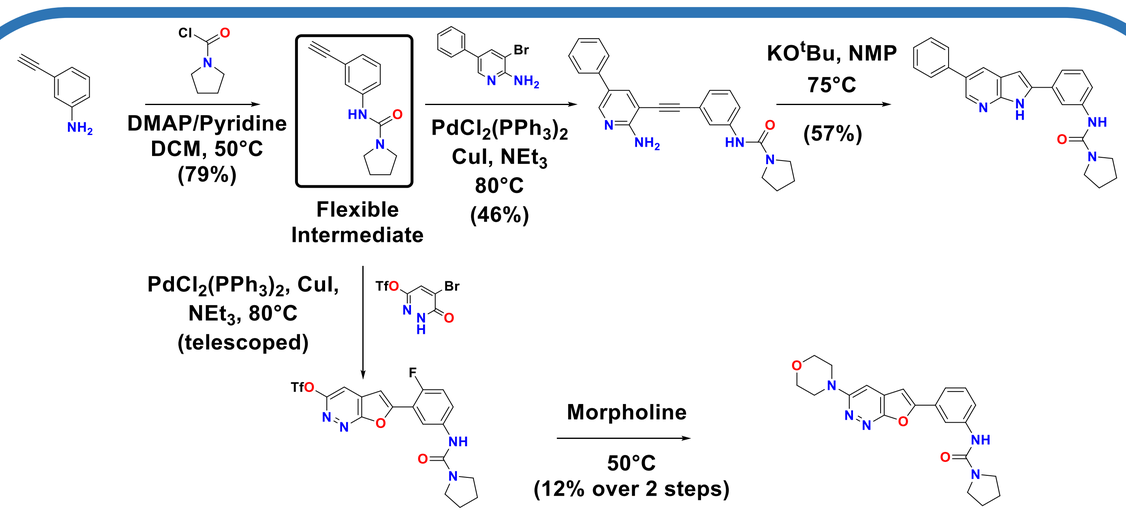
Scaffold-Hopping strategy employed to find new soluble and efficacious scaffolds, due to tight SAR of pendant groups

## Bromination/Condensation



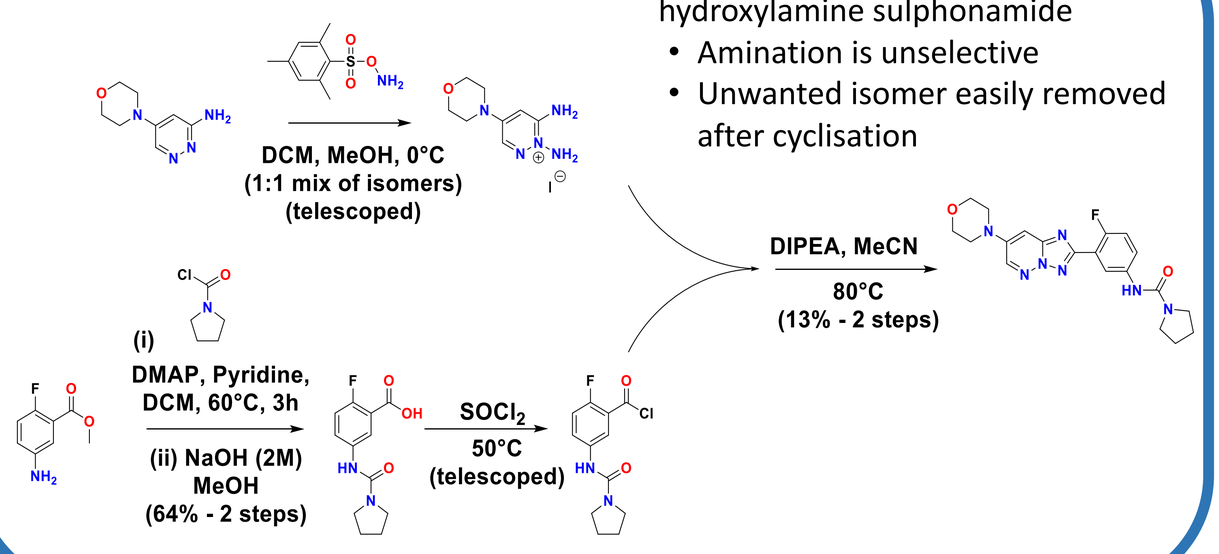

- Methyl ketone installed via Heck chemistry
- Mono/di-bromination strategies to access divergent intermediates
- Allowed access to first 'reversed' 5,6-core
  - Key change for medicinal chemistry program

## Sonogashira/Condensation



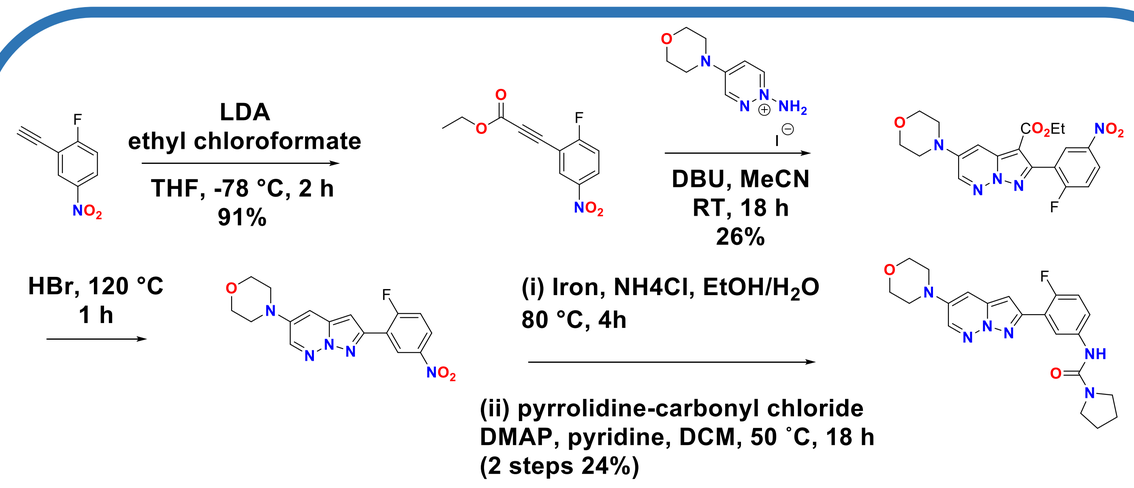

- Sonogashira installs alkyne
  - Cyclisation occurs as 2 steps, or concerted
- Pyrazine triflate motif allows $S_NAr$ access to amino functions
- Route allowed rapid access to 5-phenyl pyrrolopyridine analogue
  - Alternative route needed for N-linked aliphatic functions

## Heterocycle N-Amination/Condensation



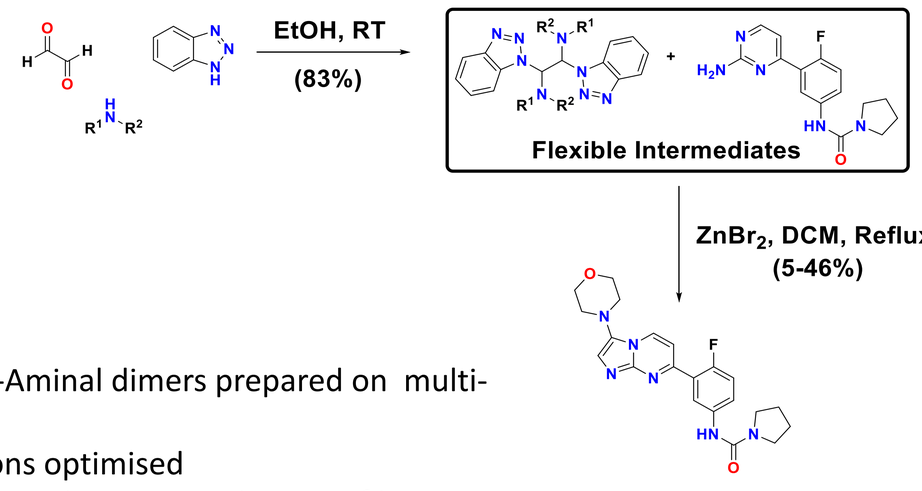

- Core amination via mesitylene hydroxylamine sulphonamide
  - Amination is unselective
  - Unwanted isomer easily removed after cyclisation

## Alternate Core Via Cycloaddition




- Acetylene carboxylate cyclisation (1,3 dipolar cycloaddition [4+2])
- Followed by hydrolysis/decarboxylation
- Access to alternative heterocycle core with deleted nitrogen

## Aminal Dimer – CH Amination




- Benzotriazole-Aminal dimers prepared on multi-gram scale
- $ZnBr_2$ conditions optimised
- Cyclisations sometimes gave mixtures of isomers
  - Diamino adducts, regioisomers (5/6 mixtures)
  - separated by chromatography
- Key scaffold: maintained potency, enhanced solubility, removed genotoxicity

https://drugdiscovery.dundee.ac.uk/about/careers

## Summary

- Early lead compound with poor solubility and toxicity issues
- Scaffold-Hopping strategy applied
  - Allows access to multiple heterocyclic cores: 24 scaffolds synthesised
  - Flexible intermediates allowed rapid access to diverse structures
- Led to candidate with improved solubility and toxicity profile
- Compound **2** nominated as pre-clinical candidate for Visceral Leishmaniasis
- Dosed FTIH September 2020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