DESIGN, SYNTHESIS AND OPTIMISATION WITHIN A LEAD CHEMICAL SERIES

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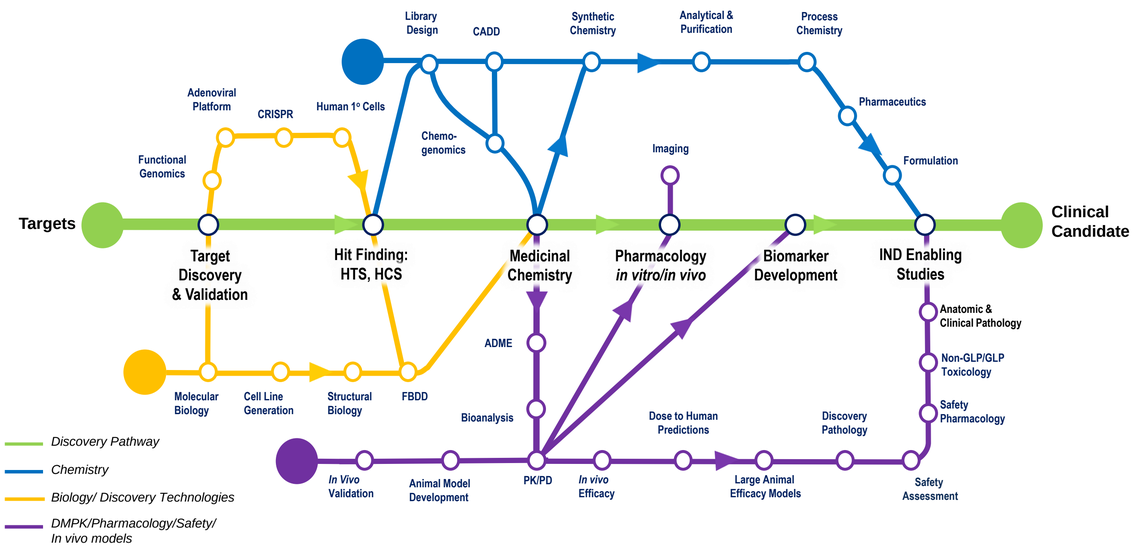
1 CHARLES RIVER LABORATORIES

Company Overview and Early Discovery

Charles River is a globally renowned pharmaceutical CRO (*Contract Research Organization*) with facilities across 16 countries. As a CRO Charles River offer end to end drug discovery services, from target discovery to candidate identification and safety assessment.

There are two main early discovery sites in the UK: Saffron Walden and Harlow. These sites offer expertise in biology, chemistry, CADD and scale-up synthesis within early-stage drug discovery.

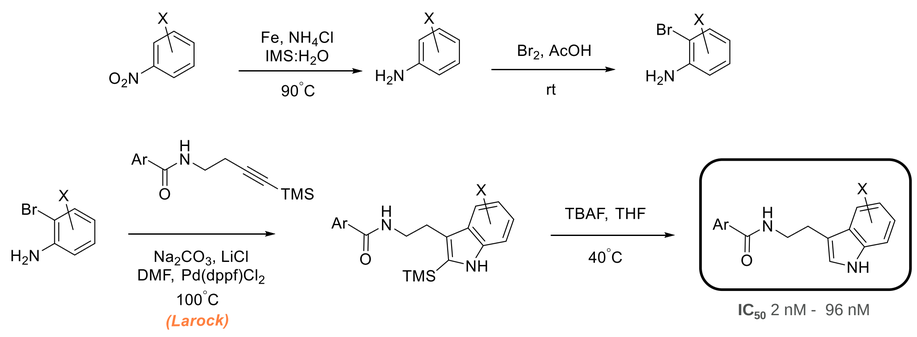


Project Overview

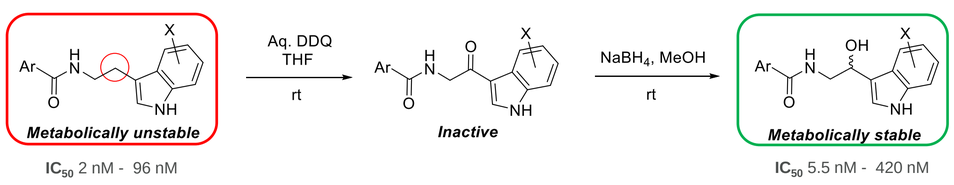
This project focuses on the development of a candidate drug for an anti-infective disease. The focus of this scientific poster is on the optimisation of the chemistry within a lead series based on a core heteroaromatic scaffold.

A phenotypic High-Throughput-Screen (HTS) was used to identify targets for synthesis and compounds synthesised were tested in the first instance through a phenotypic cellular assay.

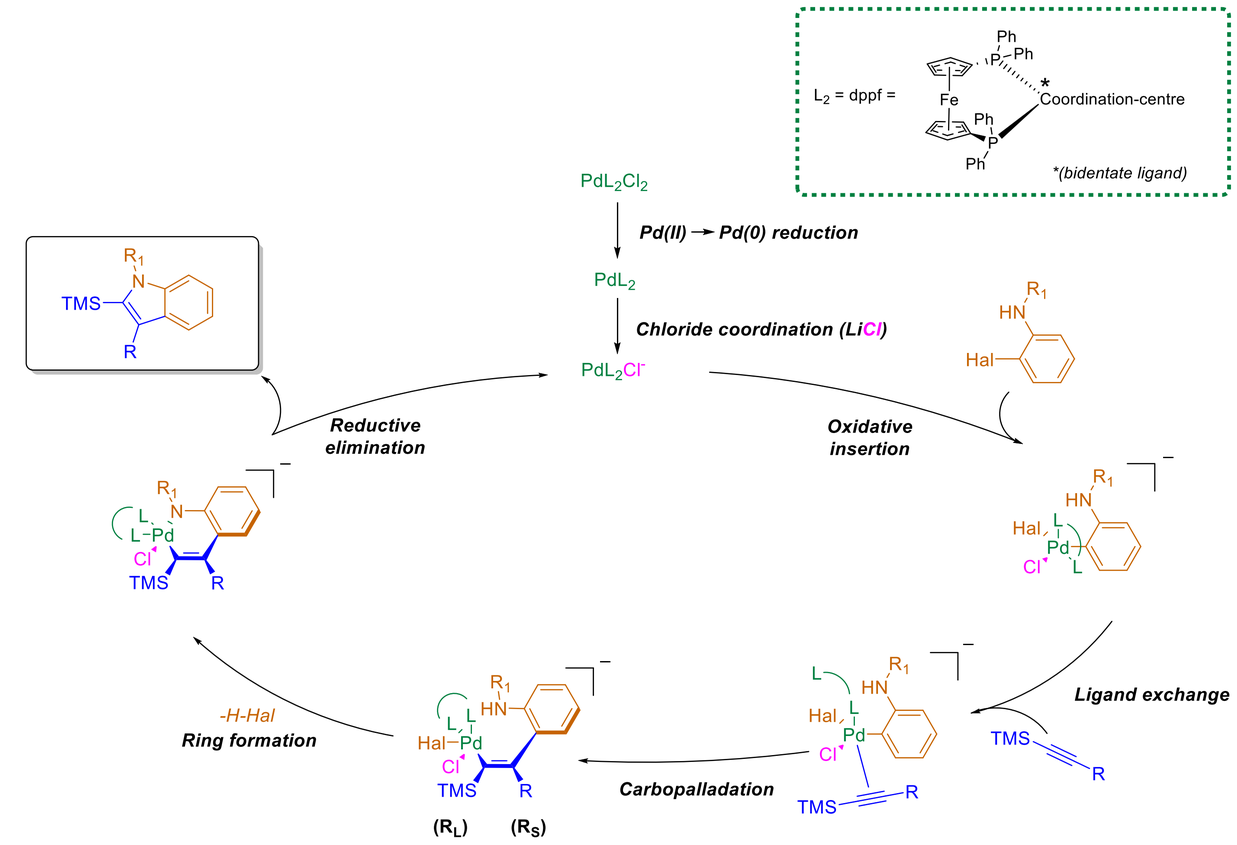
2 MEDICINAL AND SYNTHETIC CHEMISTRY



Indole analogues were formed stereoselectively by utilising Larock Indole palladium catalysed chemistry. Despite promising IC_{50} data for the initial targets within this series, the compounds were shown to be metabolically unstable. A number of chemical transformations were carried out about the metabolically unstable benzylic position to overcome this issue.



Chemical reduction of a biologically inactive ketone intermediate forms a biologically active, metabolically stable racemic mixture of compounds whereby enantiomers can be separated by SFC – (*R*) enantiomer 3-fold more potent than (*S*) enantiomer.



Larock Indole Catalytic Cycle – Stereoselectivity of large vs. small substituent on indole highlighted [1]

3 SUMMARY

- Chemistry within this project started at Charles River in January 2017.
  It is still in progress, currently at the hit-to-lead stage with the aim to deliver a candidate drug
- 363 compounds have been synthesised on this project for biological testing *in vitro.* Responsible for the synthesis of 72 final compounds during my year in industry

4 WHY CHARLES RIVER

- Opportunity to develop retrosynthetic, synthetic and purification skills to a high standard through supervision and guidance from a team of expert scientists
- Opportunity to attend lectures and training courses on all aspects of drug discovery and synthetic organic chemistry making this placement an excellent prospect for those considering a research based career within chemistry

[1] Larock, R. C., Yum, E. K., Refvik, M. D. Synthesis of 2,3-Disubstituted indoles via Palladium-Catalysed Annulation of Internal Alkynes. J. Org. Chem, ***1998,*** *63, 7652-7662*