Lead Optimisation of Pan-Trypanosomatid Inhibitors Inspired by Nature

Victoria Schroeder-Finckh (versf1@st-andrews.ac.uk)
Supervised by Dr. Gordon Florence, Department of Chemistry

University of St Andrews

Introduction

Neglected Tropical Diseases (NTDs) are a group of twenty diverse conditions, mainly found in tropical areas[1]. According to the World Health Organization (WHO), these affect more than one billion people[1], mostly in impoverished communities[2]. **Human African trypanosomiasis** (HAT) is an example of a NTD that is caused by two parasites: *T. brucei gambiense* and *T. brucei rhodesiense*[3]. Symptoms include headaches, fever, behavioural changes, neurological decline, daytime somnolence and nocturnal insomnia, and if left untreated HAT is fatal[2,4]. Although some treatments are available, these have severe side effects, are difficult to administer (mostly by injection), are expensive and resistances are emerging[5]. Thus, novel, safer medicines are a necessity.

Project Aim

The aim of this project is to **investigate the effect of introducing a modification into the lead compound 1** (Figure 1), which previously showed a wide range of activity against Trypanosoma parasites. Several compounds will be synthesized with a **variation of the "R-group"** (Figure 2), with the aim of optimizing the activity and selectivity of the lead compound against *T. brucei*. This will allow a deeper understanding into the structure-activity relationship of the compounds.

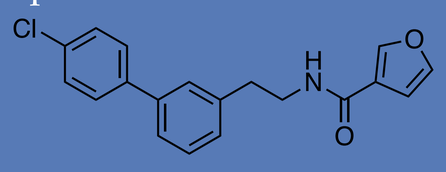


Figure 1 | Lead Compound 1

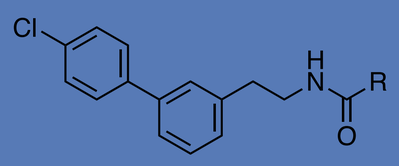


Figure 2 | General compound with "R-group" that will be chemically varied

Synthesis

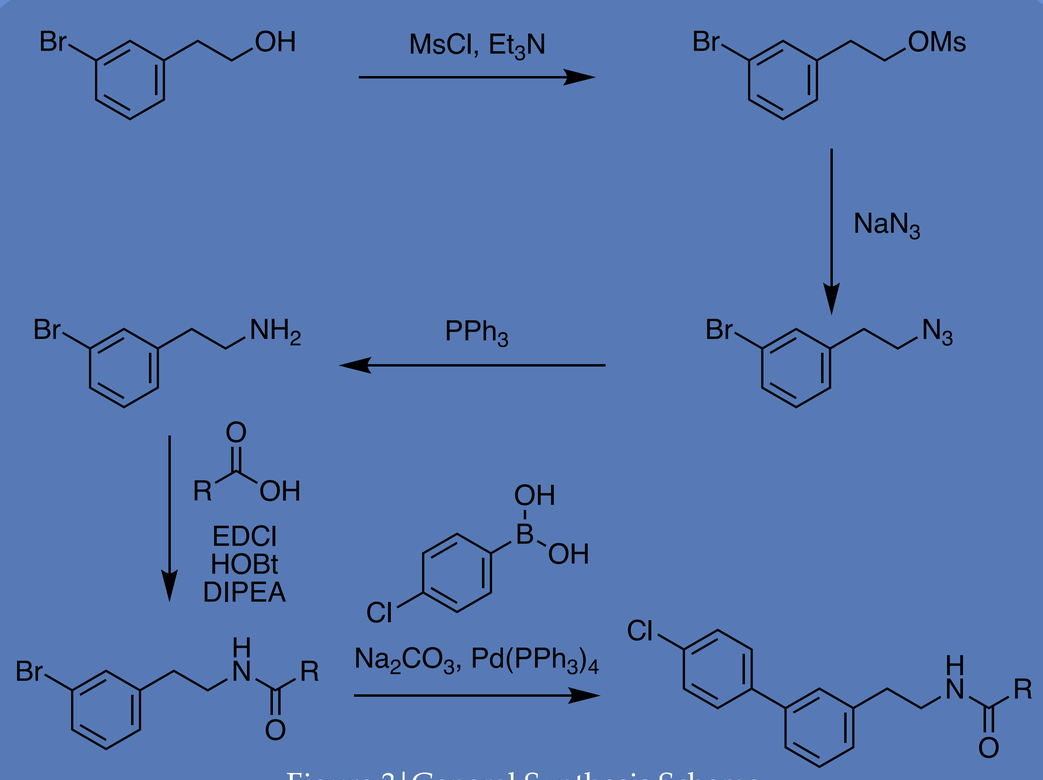
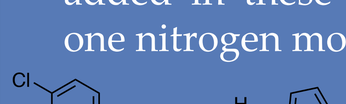


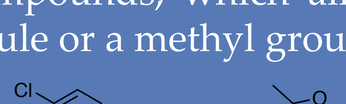
Figure 3 | General Synthesis Scheme

Results

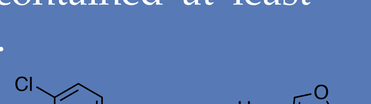
Overall, 5 new synthetic compounds were synthesised (compounds **2-6**). Due to time constraints, these were not biologically tested for their trypanocidal activity. Analysis of the compounds by ^{1}H NMR, showed that only compound **2** was synthesised with sufficient purity to allow for biological testing, indicating that the synthetic route chosen was suitable. However, compounds **3-6** showed impurities, including a debromination product visible as a triplet at ~2.90 ppm in compound **3**. Additionally, compound **3** was lacking a hydrogen, which was expected for correct product formation. The final step Suzuki-Miyaura coupling reaction, resulted in a by-product seen as a multiplet at ~6.79 ppm, for compounds **3, 4, 5**, and **6.** This indicates that the synthetic route chosen (as seen in figure **3**) was unsuitable for the heterocycles added in these compounds, which all contained at least one nitrogen molecule or a methyl group.



Compound **2**



Compound **3**



Compound **4**

Compound **5**

Compound **6**

Future Work

Future work includes experimenting with different synthetic routes, to obtain the desired products with high purity, allowing for biological testing. Alternative synthetic routes include conducting the amide coupling prior to the Suzuki-Miyaura coupling or starting the synthesis with a Suzuki-Miyaura coupling between the primary alcohol (2-(3-bromophenyl)-1-ethanol) and 4-chlorophenylboronic acid.
Once the desired compounds are synthesised with sufficient purity, these must be biologically tested to evaluate their trypanocidal activity, as well as their toxicity through tests with Hela cells. The results regarding the compounds activity and selectivity can then be further analysed to understand the structure-activity relationship, allowing for optimisation of the lead compound.

References

1 Neglected tropical diseases, https://www.who.int/health-topics/neglected-tropical-diseases#tab=tab_1, (accessed 19 July 2023).
2 N. Feasey, M. Wansbrough-Jones, D. C. W. Mabey and A. W. Solomon, *Br. Med. Bull.*, 2010, **93**, 179–200.
3 D. Gambino and L. Otero, *Front. Chem.*, 2021, **9**, DOI:10.3389/fchem.2021.816266.
4 Trypanosomiasis, human African (sleeping sickness), https://www.who.int/news-room/fact-sheets/detail/trypanosomiasis-human-african-(sleeping-sickness), (accessed 17 August 2023).
5 P. E. Cockram and T. K. Smith, *J. Nat. Prod.*, 2018, **81**, 2138–2154.

LAIDLAW SCHOLARS

This project was completed as part of the Laidlaw Scholarship Programme for Leadership and Research, at the University of St. Andrews. I would like to sincerely thank my supervisor Dr Gordon Florence for his continued support and guidance. Many thanks also to Siyao Chen and Yahan Zhang for their advice and support. I would also like to express my gratitude to Lord Laidlaw and the Laidlaw Foundation for the opportunity and funding to conduct this important and interesting work.