OXAZOLOPYRIDINES TOWARDS THE TREATMENT OF HUMAN AFRICAN SLEEPING SICKNESS

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“The first thing you have to know is yourself. Someone who knows himself can step outside himself and watch his own reactions like an observer.”
— Adam Smith

DECLARATION

This Thesis entitled “Oxazolopyridine towards the treatment of Human African sleeping sickness” is a piece of original work and contains no material that has, to the best of my knowledge, been previously submitted for a degree or diploma in any university, nor does contain material published or written by another person, except where due reference is made. I certify that every effort has been made to acknowledge previously published material. Diagrams from electronic resources have been referenced.

Basmah Mohammed Khelewi

November 2014

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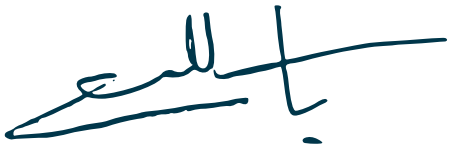

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Abstract

This thesis describes the synthesis and structure activity relationship (SAR) of oxazolopyridine and related analogues against *Trypanosoma brucei*, the causative agent of Human African Trypanosomiasis, a neglected, fatal parasitic disease that is a major cause of death and disability affecting many sub-Saharan African countries.

Collaborators at Monash Institute of Pharmaceutical Science (MIPs), and ESKITIS institute found eight compounds as potential candidates *via* high throughput screening (HTS) of a large library of compounds against the disease. Amongst the compounds screened, an oxazolo[4,5-*b*]pyridine compound was of particular interest. In collaboration with MIPS, this work aimed to modify certain regions of the lead compounds and to develop a SAR against *T. brucei*, aiming for the synthesis of better analogues of the lead compound, as discussed in Chapter 2 and Chapter 3. A number of compounds have been made through modification around the central phenyl ring and the heterocyclic oxazolopyridine core. Modification at the central phenyl ring revealed the intolerance of that position for substitution, while the best compounds remained either the lead compound itself or its analogues, with the chlorine being replaced by either a hydrogen or substituting the 2-furyl amide for its 3-furyl counterpart. Modification of the heterocyclic core has resulted in a number of active compounds. We suggested that the modification and substitutions on oxazolopyridine core is more favourable for better activity.

In addition to the anti-trypanosomal activities, these compounds are similar to heterocyclic amine derivatives found in cooked meat and fish, which has the potential to cause cancer. This has prompted us to investigate the potential for DNA damage activity of these compounds and the amine precursors, as discussed in Chapter 4.

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Abbreviation

DMF Dimethyl formamide

DMAP Dimethylaminopyridine

DNDi Drugs for Neglected Diseases initiative

HTS High throughput screening

MS Mass spectrometry

NMR Nuclear Magnetic resonance

PPA Polyphosphoric acid

SAR Structure activity relationship

EDCI 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide

T. Brucei *Trypanosoma brucei*

TLC Thin layer chromatography

Author's Contribution

As part of this thesis, the author contributed to the synthesis and structural characterisation to library of compounds. These compounds were synthesised by the author and were sent to collaborators in Professor Jonathan Baell's group (Monash University) to add to a larger library where the screening against *T. brucei* were conducted at the ESKITIS institute at Griffith University. These compounds and their hetrocyclic-amine precursors were also assessed for DNA damage activity, by Associate Professor Nuri Guven (Pharmacy School at UTAS).

Publication (Co-author)

Ferrins, L.; Rahmani, R.; Sykes, M. L.; Jones, A.; Avery, V. M.; Teston, E.; Almohaywi, B.; Yin, J.; Smith, J.; Hyland, C.; White, K. L.; Ryan, E.; AU - Campbell, M.; Charman, S. A.; Kaiser, M.; Baell, J. B., 3-(Oxazolo[4,5-*b*]pyridin-2-yl)anilides as a novel class of potent inhibitors for the kinetoplastid Trypanosoma brucei, the causative agent for human African trypanosomiasis. *European Journal of Medicinal Chemistry* **2013**, (http://dx.doi.org/10.1016/j.ejmech.2013.05.007) [1].

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