



**University of Venda**

**Design and synthesis of potential malaria cysteinyl  
protease inhibitors**

By

**Sedzani A Nethavhani**

**Student Number: 11573877**

Submitted in fulfilment of the requirements for the Degree of

Master of Science (Chemistry)

in the Department of Chemistry

School of Mathematical and Natural Sciences

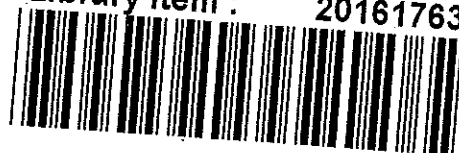
at the University of Venda

Supervisor: Prof. T. van Ree

Co-supervisor: Prof. I.D.I. Ramaite

Date submitted: August 2015

**UNIVEN LIBRARY**  
Library Item : 20161763



## Abstract

The overall objective of this project was to design and synthesize cysteinyl protease inhibitors that are envisaged to have antimalarial activity. Several synthesis routes leading to the rigid heterocyclic 2-pyridone scaffold were explored. The syntheses of the 2-pyridones involved constructing and investigating derivatives with hydrophilic and hydrophobic moieties, using a methodology that seems to have a wide scope. Intermediates as well as the target pyridones were docked into the falcipain-2 active site and tested against chloroquine-sensitive and resistant *Plasmodium falciparum* strains; three 3-cyano-2-pyridones showed promising results. Using this collection of synthesis methodologies, a wide variety of di- and tripeptides based on a substituted 2-pyridone scaffold in the P2 position, have become accessible.

**Keywords:** *Plasmodium; protease; cysteinase; 2-pyridone; antimalarial.*