University of Venda

Design and synthesis of potential malaria cysteinyl protease inhibitors

By

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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.*