UNIVERSITY OF NAIROBI

MODELING AND SYNTHESIS OF ANTIPLASMODIAL BENZOXAZINES FROM NATURAL PRODUCTS OF KENYA

BY

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DECLARATION

I declare that this thesis is my original work and has not been submitted elsewhere for examination, award of a degree or publication. Where other people's work or my own work has been used, this has been acknowledged and referenced in accordance with the University of Nairobi's requirements.

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DEDICATION

I dedicate this work to Opata and family

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ABSTRACT

Natural products research has taken place in Kenya for decades. This has led to the explosion of data about natural products which largely remains scattered in theses, published articles and books of abstracts and proceedings. As a result, natural products of Kenya are not accessible for drug design studies. Therefore the objective of this study was to create a web-based database of natural products of Kenya and use it in molecular modeling studies for the design of antiplasmodial compounds.

Currently the database contains 1112 compounds. It has been named *Mitishamba*, a Kiswahili word referring to herbal medicine and is hosted online at (http://mitishamba.uonbi.ac.ke). The compounds in the database were utilized in the generation of suitable fragments for molecular modeling studies using the *OpenyEye* scientific software suite. Benzoxazine scaffold was identified as a suitable molecular framework, due to its similarity to Primaquine (an existing antimalarial drug). Analogs of the scaffold were generated and subjected to docking against the target, 3D shape comparison and electrostatics studies with promising molecules synthesized and assayed.

A validated *Plasmodium falciparum* enzyme target, *Plasmodium falciparum* dihydroorotate dehydrogenase *(Pf*DHODH*),* was used in the docking studies. Three benzoxazines, 7-Methoxy-4H-1, 4-benzoxazin-3-one (**25**), (7-methoxy-3-oxo-1,4-benzoxazine-4-carbaldehyde (**54**) and 4-acetyl-7-methoxy-1,4-benzoxazin-3-one (**56**) were synthesized and then subjected to *in vitro* antiplasmodial assay against chloroquine resistant K1 and chloroquine sensitive 3D7 strains of *P. falciparum*. The results showed 7-methoxy-3-oxo-1,4-benzoxazine-4-carbaldehyde had an activity of 11.05 µg/mL against chloroquine resistant K1 isolate while 4-acetyl-7-methoxy-1,4-benzoxazin-3-one had an activity of 8.32µg/mL. The latter has activity classified by the WHO as active and should be pursued further through optimization to investigate its antimalarial potency.

The results above demonstrate the potential use of the database in the identification of lead antiplasmodial compounds. Therefore more benzoxazine derivatives should be identified through virtual screening and synthesized to optimize their antiplasmodial activity.

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