SUSTAINABLE DRUG DISCOVERY USING VIRTUAL SCREENING TECHNIQUES

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Introduction

Nine to ten percent of Africa's entire disease burden is caused by *P. falciparum.* A (W.H.O., 2014) study suggests that if malaria had been eliminated 35 years ago, Sub-Saharan Africa's GDP could be $100 billion greater.

Background

Malaria burden can be reduced by discovering novel drugs with new mechanisms of action that overcome the current problem of drug resistance while reducing the cost of production.

Objective

To develop a database of natural products of Kenya, identify suitable scaffolds with desirable binding properties against (P*f*DHODH) enzyme, and synthesize promising molecules for *in vitro* assay against *P. falciparum*.

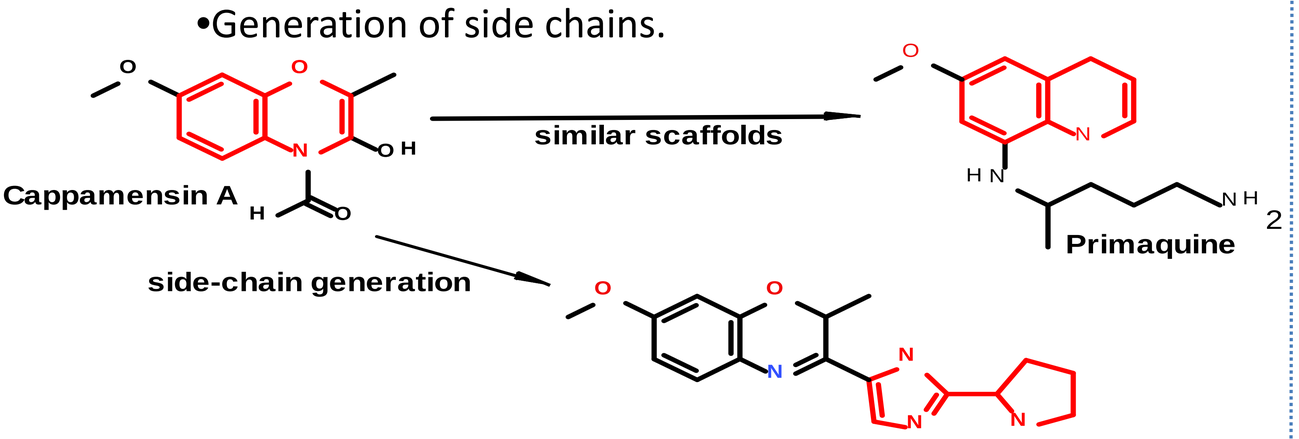
Methodology

A cost effective *in-silico* approach is used to screen a database of natural products of Kenya for antiplasmodial agents. This approach reduces the cost of reagents used in the initial trial stages frequently applied in the process of drug discovery.

The strategy comprised of :

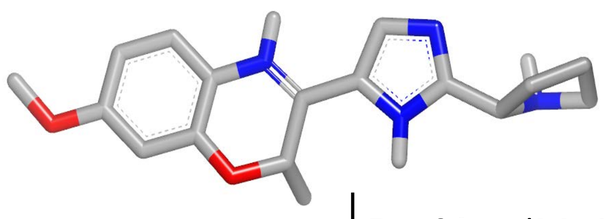
a) Generating a database of 1200 compounds which were used in two ways.

- Identification of scaffolds.
- Generation of side chains.

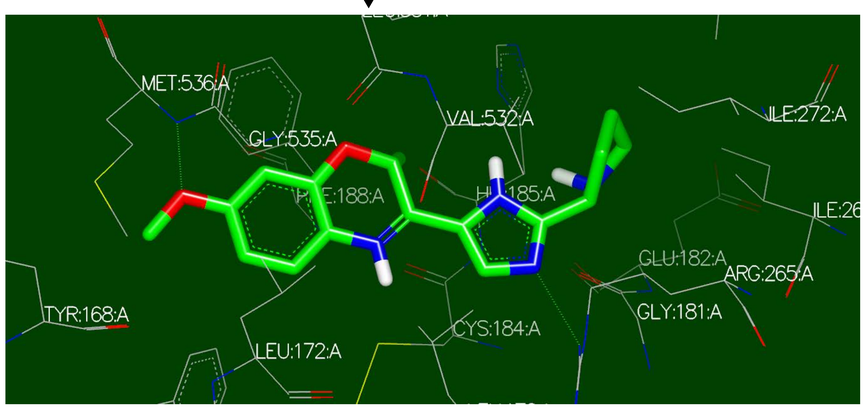


b) Binding the molecules to P*f*DHODH enzyme

3D-Virtual Screening



Docking (McGann, 2012)



Generation of probability of activity

The molecules were virtually screened, given a score and ranked. A probabilistic approach is applied to choose a number of compounds to pursue in the next level. Docking scores are converted to Z-Scores using the formula:

$$z = \frac{(x-\mu)}{\sigma}$$

Where z=z-score, x=docking score,
μ=mean, σ=standard deviation of scores

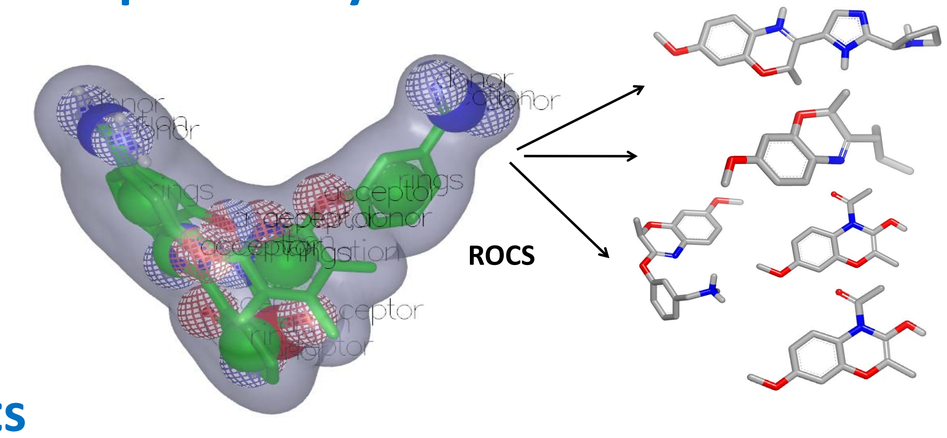
A z score of 3 or greater and 4 or greater equates to 1% and 5% chances of observing activity respectively.

Assigning Probability (Binning)

A dataset of known inhibitors for *pfDHODH* from BindingDB.org were also docked to the same target and their z scores generated. Together with the database molecules, the z scores were binned in integer increments of z=1,2,3,4 e.t.c and the probability of finding an active assigned by calculating the fraction of active molecules and dividing the number of active molecules by the total number of compounds in the bin. (Swann et al., 2011)

c) 3-D shape comparison

Rapid Shape overlay Characteristics

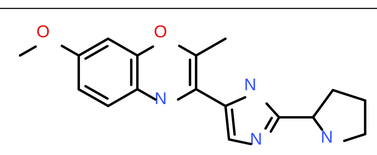
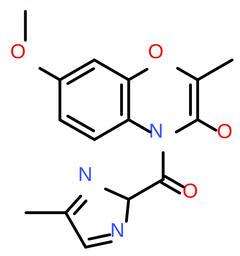
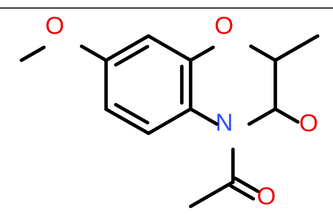


Results

Based on computational calculations and modeling, the promising molecules that can then be synthesized are shown in Table 1.

	z=1	z=2	z=3	z=4
Actives	75	30	10	1
Decoys	206	85	20	3
Probability	0.001296	0.003069	0.016667	0.083333

Table 1: Probability of obtaining an active cpd in a docked dataset

	Prob= 8%
	Prob= 8%
	Prob= 0.31%

References

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Swann, S. L., Brown, S. P., Muchmore, S. W., Patel, H., Merta, P., Locklear, J., & Hajduk, P. J. (2011). A Unified, Probabilistic Framework for Structure- and Ligand-Based Virtual Screening. *Journal of Medicinal Chemistry*, *54*(5), 1223–1232

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