Structure-based Repurposing of Anti-malaria Drugs to Inhibit RNA-dependent RNA Polymerase Domain of Dengue Virus

[1,2]Adeniyi Ayinde Abdulwahab
[1]Chemoinformatics Academy, Nigeria.
[2]Faculty of Pharmaceutical Sciences, Bayero University, Kano, Nigeria.

Background

- Dengue virus (DENV) is one of the most rapidly spreading mosquito-borne diseases worldwide, causing 100–400 million infections annually, with 96 million of those infections showing signs of severe illness.
- The RNA-dependent RNA polymerase (RdRp) catalytic domain resides within the NS5 protein from dengue virus and plays a vital role in the production of new viral particles.
- Inhibition of RdRp offers a novel approach for combating the DENV infection.
- The aim of this study is to employ a structure-based approach for repurposing anti-malaria drugs to inhibit the RdRp domain of DENV.

Methods

- Approved anti-malaria drugs (n=31) were downloaded from PubChem.
- The crystal structure of the target receptor (2J7W) was obtained from the Protein Data Bank.
- Docking validation was done, followed by molecular docking and Molecular Mechanics/Generalized Born Surface Area (MM/GBSA) study.
- Assessment of physicochemical properties and ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) parameters for the top-ranking drugs was conducted (**Fig. 1**).

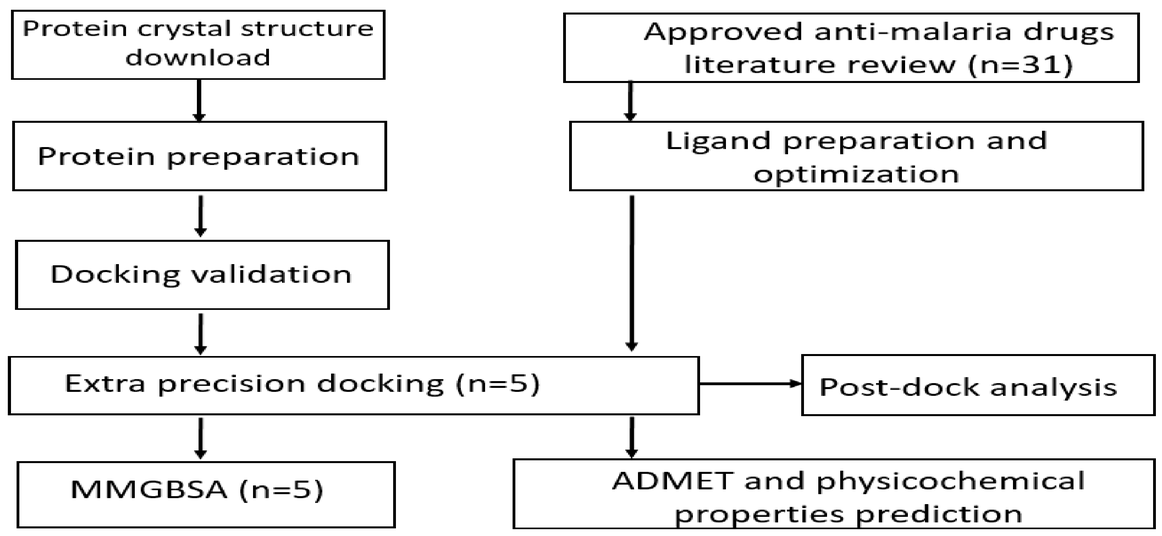

Fig. 1. Study outline.

Results

- The RMSD superposition value of 1.4 Å was obtained for the minimized and redocked ligand.
- The binding affinity and MMGBSA scores of the top 5 drugs and co-ligand are displayed in **Fig. 2.**
- The ADMET and physicochemical properties of the drugs were found to be relatively good.

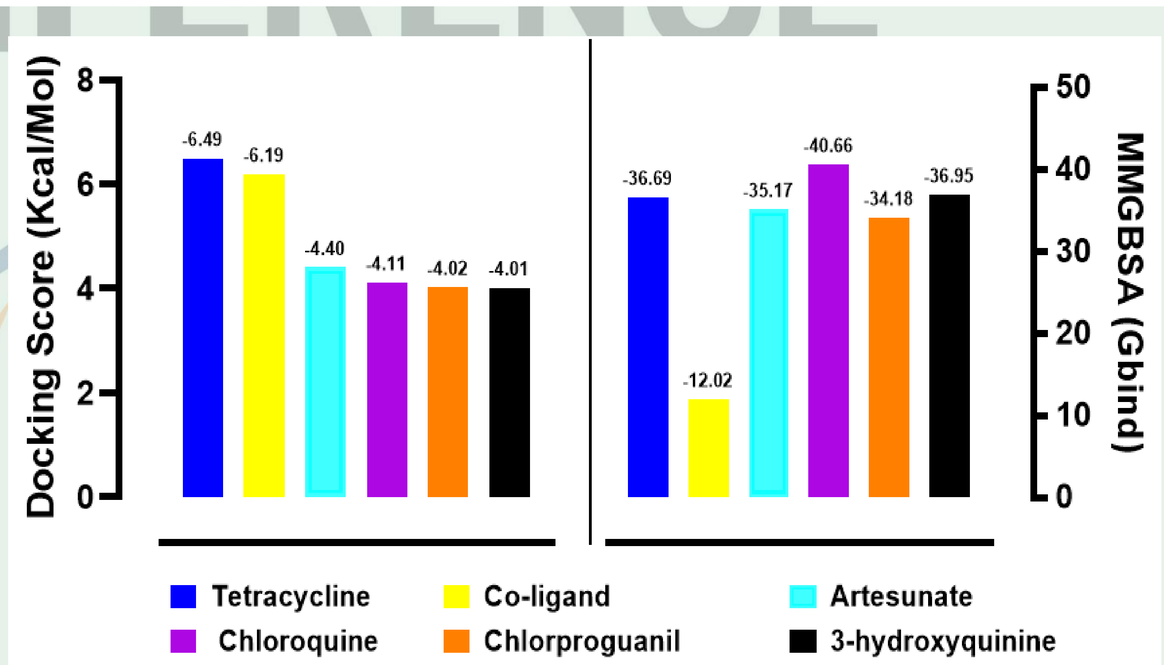

Fig. 2. Docking and MMGBSA scores of the top 5 drugs and co-ligand.

Conclusions and Recommendations

- Using a structure-based computational approach, potent inhibitors of dengue virus RdRp were identified from the approved and currently available antimalarial drugs.
- In vitro and in vivo studies should be performed to provide more concrete information on the efficacy of these top 5 antimalarial drugs as potent inhibitors of DENV RdRp.

Contact: Adeniyi Ayinde Abdulwahab. **Email**: adeniyiabdulwahab3@gmail.com **Phone:** +2348187881931