

Title: Employing Hexahydroquinolines as *Pf*CDPK4 Inhibitors to Combat Malaria Transmission: An Advanced Computational Approach

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Abstract: Background: Existing antimalarial drugs primarily target blood-stage parasites, but there is a need for transmission-blocking drugs to combat malaria effectively. *Plasmodium falciparum* Calcium-dependent Protein Kinase 4 (CDPK4) is a promising target for such drugs. This study employed advanced in silico analyses of hexahydroquinolines (HHQ) derivatives to identify *Pf*CDPK4 inhibitors capable of disrupting malaria transmission. Structure-based virtual screening (SBVS) was employed to discover HHQ derivatives with the highest binding affinities against the 3D structure of *Pf*CDPK4 (PDB 1D: 4QOX). **Methods:** Interaction analysis of protein-ligand complexes utilized Discovery Studio Client, while druglikeness and ADMET properties were assessed using SwissADME and pkCSM web servers, respectively. Quantum mechanical calculations of the top hits were conducted using density functional theory (DFT), and GROMACS was employed to perform the molecular dynamics (MD) simulations. Binding free energy was predicted using the MMPBSA.py tool from the AMBER package. **Results:** SBVS identified ten best hits possessing docking scores within the range of – 11.2 kcal/mol and – 10.6 kcal/mol, surpassing the known inhibitor, BKI-1294 (– 9.9 kcal/mol). Among these, 4-[4-(Furan-2-carbonyl)piperazin-1-yl]-1-(naphthalen-2-ylmethyl)-2-oxo-4a,5,6,7,8,8a-hexahydroquinoline-3-carbonitrile (PubChem ID: 145784778) exhibited the highest binding affinity (– 11.2 kcal/mol) against *Pf*CDPK4.

Conclusion: Comparative analysis of this compound with BKI-1294 using advanced computational approaches demonstrated competitive potential. These findings suggest the potential of 4-[4-(Furan-2-carbonyl)piperazin-1-yl]-1-(naphthalen-2-ylmethyl)-2-oxo-4a,5,6,7,8,8a-hexahydroquinoline-3-carbonitrile as a promising *Pf*CDPK4 inhibitor for disrupting malaria transmission. However, further experimental studies are warranted to validate its efficacy and safety profile.

Key words: antimalarial drugs, drug design, gametocidal activity, malaria, molecular dynamics

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