Computational Analysis of Known HIV-1 Protease Inhibitors to Investigate Their Therapeutic Potential for Fatal Malaria Prevention

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Malaria is a devastating disease that kills over half a million people annually. Research shows the Plasmodium falciparum protozoan disrupts iron regulation by degrading ferroportin, allowing unregulated iron entry and creating a toxic intracellular environment. The parasite also breaks down hemoglobin via aspartic proteases called Plasmepsins, releasing insoluble iron protoporphyrin, contributing to iron-deficient anemia and worsening disease severity. This project aimed to develop a pan-isoform ligand inhibitor targeting Plasmepsin Isoforms I & II. Given the structural similarities between Plasmepsins and HIV-1 Protease, known HIV-1 inhibitors were docked using CHARMM-GUI. Of those tested, KNI-10006 and KNI-10283 showed promising binding across multiple platforms. Following energy-efficient binding site identification, High-Throughput Input Simulations generated NAMD/VMD topology files for Molecular Dynamics (MD) Simulations, which confirmed conformational changes upon allosteric binding. Protein-ligand interactions were analyzed using PyMol, revealing inconsistencies in predicted interactions and RMSD scores, suggesting potential binding site selection errors. Nevertheless, I proposed a novel ligand inhibitor model by preserving the carbon backbone of KNI-10006 and substituting its (-phenoxyl acetyl) group with the (N-[1S,2R]-2-Hydroxyindan-1-yl) group from KNI-10283. While preliminary results are promising, further validation is needed —currently, we are re-running simulations and modeling the inhibitor’s stability and effectiveness using open-source MD software. A pan-isoform inhibitor represents a compelling new approach to starving the parasite and combating growing drug resistance.

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