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Abstract Title	Novel Potential Antimalarials through Drug Repurposing and Multitargeting: A Computational Approach
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Abstract

1. Abstract Title	Novel Potential Antimalarials through Drug Repurposing and Multitargeting: A Computational Approach

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3. Abstract

Objectives
This study aims to identify potential antimalarials from Food and Drug Administration (FDA) approved drugs.

Methods

796 drugs from DrugBank were docked against 36 *Plasmodium falciparum* protein structures from screening

Protein Data Bank (sc-PDB) using QuickVina-W. In order to improve the mean ranking error (MRE) and to account for molecular properties, ligand efficiency indices (lipophilic efficiency (LipE), surface efficiency index (SEI) and binding efficiency index (BEI)) and GRaph Interaction Matching (GRIM) were combined. This later was also used with binding site similarity information to identify potential multitarget inhibitors. Scores standardization was done to reduce interprotein scoring noise and complex ranking to reveal highly selective protein-ligand systems. Selected complexes stabilities were assessed in molecular dynamics simulations through their Root Mean Square Deviations (RMSD) and hydrogen bonding.

Results

In docking validation, 77% of the most energetically favourable poses had RMSD <= 2 Å when compared to related co-crystalized ligands. Score standardization and complex ranking improved the MRE. Out of 28656 (36x796) docking experiments, 26 protein-ligand complexes were selected having moderate (-6 kcal/mol) to low binding affinity (-11 kcal/mol). Their minimum LipE, SEI and BEI were 4, 23 and 7 respectively while their GRIM scores (0.58 to 0.78) indicated interaction similarity to co-crystalized ligands. During simulations, complexes were stable: the maximum RMSD for proteins was 5 Å while that for ligands was 3.7 Å with a good hydrogen bonding (average number of 1.4). Six potential multitarget ligands were identified, having a high Grscore (>0.7) on two proteins having similar binding sites and showing stability in MD simulation. Six hits had antimalarial activity in literature and selected drugs presented new scaffolds. As approved drugs, good toxicity profile is expected. Targets diversity offers potential for new modes of action and parasite liver stage agents.

Conclusions

Using a combined computational workflow, 32 drugs are proposed for repositioning as antimalarials.

4. Non Technical or Lay Abstract

Objectives
This study aims to identify potential antimalarials from Food and Drug Administration (FDA) approved drugs.

Methods

796 drugs from DrugBank binding modes and strengths were predicted on 36 Plasmodium falciparum targets from screening Protein Data Bank (sc-PDB). Lipophilic efficiency (LipE), surface efficiency index (SEI) and binding efficiency index (BEI) and GRaph Interaction Matching (GRIM) were used to account for drugs molecular properties (for safe and effective drugs) and to prioritize high-quality drugs. Selected drug-targets stabilities were further assessed in simulations in an vivo-like environment.

Results

First validating the computational experiment using targets original inhibitors/substrate as controls, 77% of the predictions were in agreement with the controls. Out of 28656 (36x796) experiments, 26 drug-targets were selected having moderate (-6 kcal/mol) to good binding strength (-11 kcal/mol). Their minimum LipE, SEI, BEI and Grscore were 4, 23, 7 0.58 respectively (all in at least acceptable thresholds). During simulations, drugs were stable maintaining their initial binding pose and strong binding with their targets (average hydrogen bonding=1.4). Six hits had antimalarial activity in literature. As approved drugs, good toxicity profile is expected. Targets diversity offers potential for new modes of action and parasite liver stage agents.

Conclusions

Using a combined computational workflow, 32 drugs are proposed for repurposing as antimalarials.

5. Abstract's Thematic Area	Bioinformatics