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Identification of flavonoid with potential for inhibitor Enoyl-ACP Reductase in *Plasmodium falciparum* by hierarquical virtual screening

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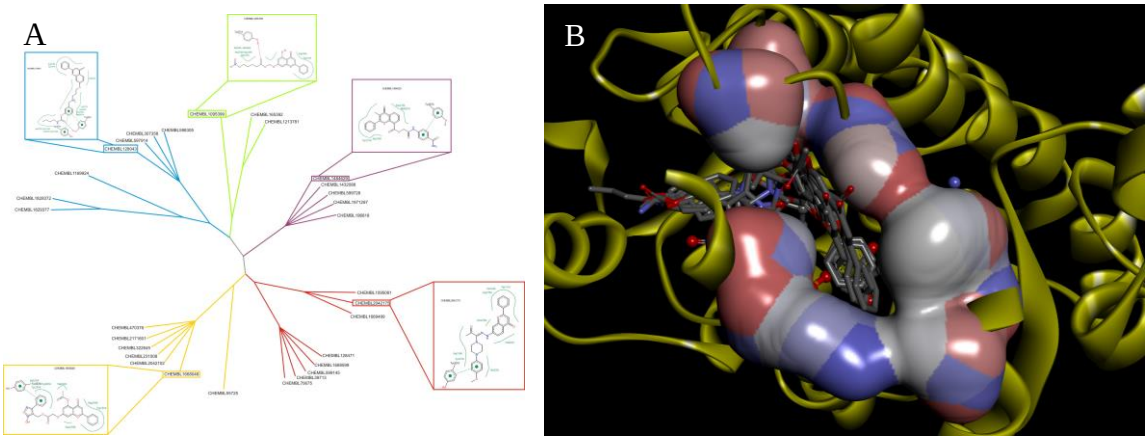
Abstract: Malaria is a parasitic infection and is considered a serious global public health problem [1]. *Plasmodium falciparum* provides easy adaptability by mutation, causing resistance to antimalarials [2]. This study aimed to search antimalarial potential showed by some flavonoids to inhibit promising target, enoyl-ACP reductase (PfENR), present in limiting step in the biosynthesis of fatty acids type II (FAS II) of *P. falciparum* [2-3]. A flavonoid library obtained in CHEMBL (n = 4008) was filtered through physic-chemical similarity using the Euclidean distance. Inhibitors described in the literature were used as reference molecules. The 3057 selected molecules were submitted to molecular docking using DOCK 6.5. The analysis of the docking parameters was performed by analysis of RMSD value and ROC analysis. The results showed RMSD = 0.54 Å and AUC = 0.86, indicating good performance of the docking method. The top 30 ranked molecules of docking were selected for analysis by self-organizing maps using AuPosSOM program with the objective of cluster molecules according to intermolecular interactions. The 5 higher leafs were selected based on the proximity of the branches of Newick's tree. Thus, a representative molecule of each leaf was selected, in order to illustrate the interaction pattern within these leafs (Figure 1A). The intermolecular interactions analyzed corroborate with that described in the literature. This is because studies show hydrogen interactions, electrostatic and hydrophobic between the catalytic site inhibitor and the PfENR [4-5]. The detailed analysis of intermolecular interactions of the five molecules representing each leaf and PfENR enzyme showed that there are an essential interactions pattern favoring the ligand - receptor complex stability, and consequently result in better binding energy values. It was possible to identify the hydrophobic pocket that performs flavonoid moiety interactions with the core (Figure 1B). This analysis shows the importance of flavonoid moiety for inhibiting PfENR, confirming the choice of this metabolite class to study and development of new antimalarial candidates. Furthermore, it is possible to infer the importance of a candidate molecule inhibitor of the enzyme aromatic PfENR, that have regions that allow electrostatic interactions with the NAD501and Tyr277 or Tyr267 or regions that allow the hydrogen interaction with these residues, especially Tyr277. Thus, it can be proposed that a successful PfENR inhibitor needs to interact with the Tyr277, and thus occupy the space of interaction with the natural substrate in order to block its role in catalysis. This approach allowed the selection of flavonoids

with potential affinity against PfENR. In addition, it was possible to recognize which intermolecular interactions contribute to the molecular recognition process.

Figure 1. A- The 5 leaves selected of the Newick tree and the representative molecule of each leaf. **B-** Region of hydrophobic interactions of PfENR with the flavonoid nucleus of the top five molecules.



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