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Development and *in silico* and *in vitro* evaluation of promising *N*-Acylhydrazone derivatives for the treatment of malaria

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BACKGROUND

Malaria is a tropical and subtropical disease caused by protozoa of the genus *Plasmodium sp.* and transmitted by the bite of infected female *Anopheles* mosquitoes. In an attempt to combat this disease, the World Health Organization has implemented different types of chemotherapy treatments, to which resistance associated with severe toxicity has been reported. Thus, *N*-acylhydrazonic derivatives, such as JR-09, JR-18, JR-19 and JR-30, represent potential antiparasitic compounds with reported antimalarial activity.

OBJECTIVES

This study aims to develop and evaluate the *in silico* and *in vitro* activity of the most promising *N*-acylhydrazone derivatives for the treatment of malaria.

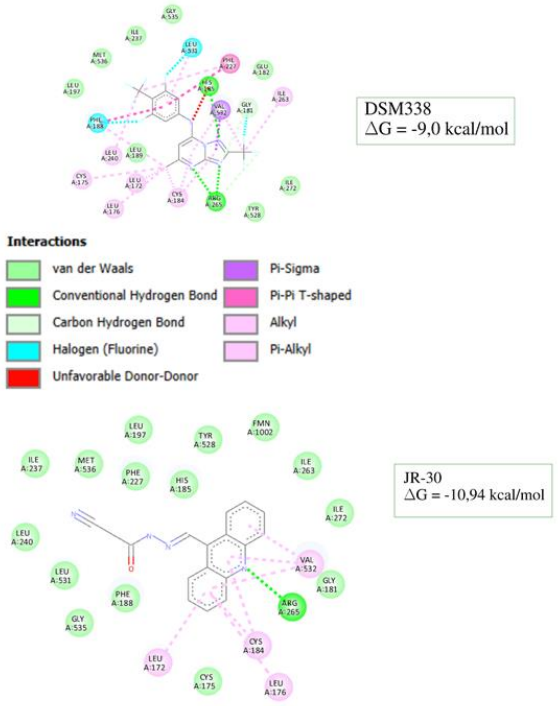
METHODS

For the *in silico* study, the JRs were subjected to molecular docking in the enzyme dihydroorotate dehydrogenase DHODH from *P. falciparum* (PDB ID: 4ORM) using the *AutoDock Tools* software. From this, the compound with the best result was selected for the *in vitro* assay. The antimalarial activity tests were performed at the Laboratory of Tissue Engineering and Immunopharmacology of the Gonçalo Moniz Research Center (CPqGM), Fiocruz-BA. The W2 strain of *P. falciparum* was maintained in continuous culture of human erythrocytes (O+). Mefloquine (Mfq) was used as the standard drug.

RESULTS AND DISCUSSION

In molecular docking, it was observed that JR-30 showed greater affinity with the malaria target compared to DSM338 and other compounds, since more negative ΔG values indicate greater stability of the ligand-macromolecule complex. This can be explained by the interaction with essential residues that are part of the enzyme's active site, such as Val^{532}, Arg^{265} and Cys^{184}. The malarial activity of JR-30 was verified in human erythrocytes infected with the W2 strain of *P. falciparum*. Thus, it was noted that this compound has antimalarial potential with an IC_{50} in the parasite of 1.2 ± 0.82 µM compared to (mefloquine) 0.04 ± 0.01 µM demonstrating antimalarial potential (figure 1).

Figure 1 – 2D diagrams of molecular docking



CONCLUSION

In the *in silico* study, JR-30 stood out in relation to the others and in the *in vitro* study, it presented good results. Therefore, it is concluded that JR-30 has potential antimalarial activity but more clinical studies are needed in order to analyze the therapeutic efficacy.