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# Antimalarial acridine N-acylidrazonic derivatives: ADME in silico studies and molecular docking

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Malaria is one of the neglected diseases, and according to WHO it affects approximately 214 million people around the world. In addition to being an aggressive disease, the drugs used are scarce, have severe adverse effects and are often ineffective due to the development of parasite resistance mechanisms. In addition to these factors, difficulties in P&D of new drugs, due to pharmacokinetic and bioavailability limitations of antimalarial candidates, are difficult for the development of therapeutically useful new drugs. In this context, this work was aimed at using in silico studies of ADMET and molecular docking to predict pharmacokinetic parameters, and the interaction of acridine derivatives with the enzyme Dihydrofolate reductase (DHFR-TS) of *P.falciparum*. For the ADMET study was using the SwissADME free software. For the docking, the enzyme PfDHFR-TS (PDB code id: 4DPD) was chosen, and the acridine derivatives published in the paper by PEREIRA (2016) were used as binders. Molecular docking was performed by the Moqueiro Virtual Docking 6.0 program, in which the protein was optimized and the compounds were submitted to molecular coupling after optimization of the geometry. The results indicate that all derivatives have desirable molecular properties for a new drug, as well as indicate good gastrointestinal absorption (TPSA ≤ 140 Å2) and bioavailability. The molecules studied have the potential to inhibit the CYP2C19, CYP2C9 and CYP3A4 isoforms, however, none of them possibly interact with the P-gp protein. Molecular docking results indicate that all compounds showed negative binding energy, with AC-10 being the best result, indicating the possibility of stable interactions with the enzyme PfDHFR-TS, which is responsible for the resistance of *P. falciparum* to many antiamalarials agents

**Keywords:** malaria, acridine derivatives, ADMET, molecular docking,in silico studies

## 1. Introduction

Despite being an old disease, malaria is one of the neglected diseases that affects approximately 214 million people around the world[1]. In addition to the toxicity and resistivity of Plasmodium to

antimalarials, the P&D process of new drugs is also a problem for the creation of new antimalarials due to the problems of pharmacokinetics and detection of toxic effects (CALIXTO; SIQUEIRA, 2008).

Among the recent strategies to repair these problems are *in silico* studies, such as the *docking molecule* and the ADMET, which have as main advantages the reduction of time expenditures and investments in biological assays of derivatives with high probability of pharmacokinetic and toxic problems in the future[3].

Due to its reputation as a privileged sturgeon, as well as its wide biological action, mainly for neglected diseases such as malaria[4], acridine derivatives are excellent candidates for *in silico* studies.

Thus, the main purpose of the present work is to predict by means of in silico studies parameters of ADME, and to evaluate the best ligands of the enzyme PfDHFR-TS, of new acridine derivatives.

### 2.1 ADME *in silico* studies

According to table 1, all compounds have desirable molecular properties for drugs, since they follow the Lipinski's 5 rule (nALH ≤ 10; nDLH≤5; PM≤ 500 g / mol; miLogP≤5; TPSA≤ 140 Å2)[5]. In addition, all compounds had Log S values between -6.293 and -8.107, indicating that all are poorly soluble in water[5] and values of TPSA <140 ° indicating that these may have a good absorption in the intestine[6].

**Table 1**: lipinsk parameters PM the acridína derivatives

| Comp. | Parameters of Lipinski | | | | | Log S |
|---|---|---|---|---|---|---|
| | PM | ALD | DLH | cLogP | TPSA $(A^o)^2$ | |
| AC-01 | 426,91 | 3 | 1 | 5.607 | 69,97 | -6,634 |
| AC-04 | 444,89 | 4 | 2 | 5.7078 | 69,97 | -6,655 |
| AC-05 | 461, 34 | 3 | 1 | 6,213 | 69,97 | -7,077 |
| AC-06 | 442,90 | 4 | 2 | 6,173 | 87,04 | -6,414 |
| AC-10 | 443,89 | 4 | 3 | 4,9297 | 113,06 | -6,417 |
| AC-12 | 420,89 | 4 | 2 | 6,0991 | 87,04 | -6,293 |

**Table 2**: Interaction of acrylic derivatives with P-glycoprotein (Pgp) and cytochrome P-450 isoforms

| Subst. | P-gp | CYP1A4 | CYP2C19 | CYP2C9 | CYP2D6 | CYP3A4 |
|---|---|---|---|---|---|---|
| AC-01 | No | No | Yes | Yes | No | Yes |
| AC-04 | No | No | Yes | Yes | No | Yes |
| AC-05 | No | No | Yes | Yes | No | Yes |
| AC-10 | No | Yes | Yes | Yes | Yes | Yes |
| AC-12 | No | Yes | Yes | Yes | No | Yes |

## 2. Results and Discussion

Furthermore, as shown in Table 2 the acridine derivatives studied inhibited CYP2C19, CYP2C9 and CYP3A4 isoforms. Among them, CAs 01, 04 and 05 should be highlighted, since they do not interact with all isoforms, and consequently can present better efficiency and lower toxicity[7]. The possible lack of interaction with P-gp (glycoprotein-P) is also satisfactory, since interactions with this glycoprotein may decrease the therapeutic efficacy or potentiate toxic side effects[8].

When analyzing the graphs of Bioavaliality Radar it is observed that the compost AC-12 can present a better bioavailability profile of the evaluated compost, once all the parameters are in the pink area (figure 1). On the other hand, compost AC-05 is the one that can present less satisfactory results for this item (Figure 1).

### 2.2 Docking molecular with PfDHFR-TS enzyme

Knowing the importance of the enzyme PfDHFR-TS in the process of antimalarial resistance by P. falciparum[9], the molecular docking of this enzyme with the proposed molecules was carried out. Therefore, it is possible to observe (table 3) that all the compounds presented negative values of binding energy ranging from -154.457 to -174.109 Kcal / mol, this being an indication that all molecules have good stability when bound to this enzyme.

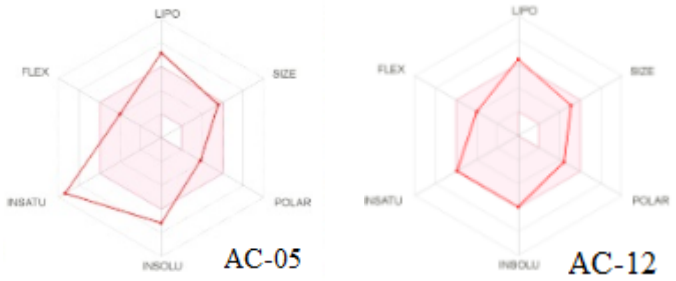


**Figura**: Bioavaliality Radar of the acridines derivatives

**Table 3**: Binding energy of the acridinium derivatives and PfDHFR-TS

| Ligantes | Energia de ligação |
|---|---|
| AC-01 | -163,901 |
| AC-04 | -167,7 |
| AC-05 | -159.093 |
| AC-06 | -170.631 |
| AC-10 | -174.109 |
| AC-12 | -154.457 |

## 3. Materials and Methods

The acridine derivatives used were previously published in the work of Pereira (2016)[10], all of them with their physicochemical characteristics obtained and structural elucidation proved.

For the predictive evaluation of ADME parameters, as Lipinsk rule, topological polar surface area (TPSA), interactions with CYP450 isoforms and interaction with P-glycoprotein (P-gp); were evaluated using SwissADME free software (http://www.swissadme.ch/). In addition, SwissADMe was also used to form the Bioavaliality Radar.

The protein used was the crystalline structure of the enzyme dihydrofolate reductase-thymididate synthase (PfDHFR-TS) obtained by the PDB (Protein Database) code id: 4DPD

The compounds were designed and the optimized geometries, using the program Hiperchem 8.0, using force field of molecular mechanics (MMFF). A second optimization of the geometry was done, adopting the semi-empirical method AM1 (Austin Model 1).

Molecular docking 6.0 was used for molecular docking, where the compounds were submitted to molecular coupling. The 4DPD protein was optimized with the removal of water and cofactors. Anchorage was performed as the same standard parameters of the software using a 15Å GRID in the radius and 0.30Å resolution at the enzyme binding site with the structures. After that, the Moldock score algorithm was evaluated to predict the best interaction between ligand and receptor; evidencing the map of the 2D ligand.

## 4. Conclusions

All acridine derivatives had desirable molecule properties for Lipinsk parameters, moderate solubility in aqueous medium (LogS) and TPSA <140 ° indicating good permeability in biological membranes as well as gastrointestinal absorption

Most compounds may inhibit CYP2C19, CYP2C9 and CYP3A4 isoforms, however, none of them have interacted with P-gp, indicating that they may exhibit good therapeutic efficacy.

Regarding the Bioavaliality Radar graphs all the compounds showed good bioavailability, being the AC-12 compost highlighted for this parameter.

As for the molecular docking, all the acridine derivatives, especially the AC-10 derivative (-174, 0 Kcal / mol) q, presented negative binding energy indicating the possibility of interaction with the enzyme PfDHFR-TS, responsible for the resistivity of *P . falciparum* to antimalarial drugs.

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