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Computational study of aromatic compounds inhibiting *Trypanosoma cruzi* glyceraldehyde 3-phosphate dehydrogenase

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Abstract: Chagas disease is caused by the protozoan *Trypanosoma cruzi* and is widely distributed throughout Latin America. Because it is a pathology neglected by the pharmaceutical industry and because existing drugs have low efficacy and several side effects, interest in new drugs has been increasing. Due to the necessity of the discovery of new structures, the objective of this work was to relate the biological activity of natural and semi-synthetic aromatic compounds, inhibitors of glyceraldehyde 3-phosphate dehydrogenase enzyme, with descriptors calculated by molecular modeling, such as HOMO-LUMO frontier orbitals, partition coefficient (LogP) and water solubility (LogS), in addition to performing a molecular docking study, in order to obtain a better molecular view of the interaction of the aromatic compounds with the active site of the enzyme. It was observed that the compounds involved in the study interacted attractively with the enzyme, in accordance with experimental studies, and had adequate solubility for good pharmacokinetics. It was also possible to relate the pharmacological activity of some compounds with the energy of the LUMO orbital. The study showed that the methodology used in this work can be used to understand the interaction of active compounds with their respective targets, saving time and resources.

Keywords: Chagas disease, molecular docking, molecular modeling, aromatic compounds

Graphical Abstract:
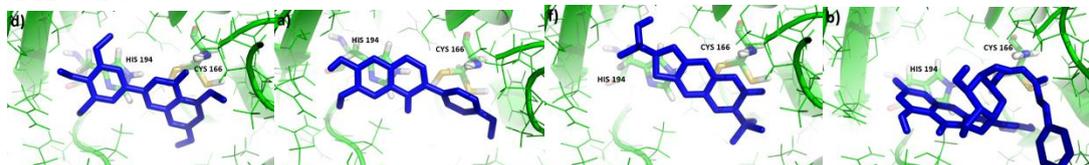
Introduction:

Chagas disease is an infectious process caused by the protozoan *Trypanosoma cruzi*, which in turn is transmitted to humans through triatomine insects commonly known as "barbers" [1-3].

A number of natural and synthetic compounds have been highlighted because they present high pharmacological activity against *T. cruzi*, through the inhibition of glyceraldehyde 3-phosphate dehydrogenase (GAPDH), a glycolytic enzyme responsible for the conversion of glyceraldehyde-3-phosphate to 1,3 - diphosphoglycerate and which has structural differences with respect to the human enzyme. The infective forms of *T. cruzi* are dependent on the glycolytic pathway, which makes the enzyme a promising target for the creation of antichagasic drugs, since the inhibition of GAPDH will cause the inhibition of the *T. cruzi* glycolytic pathway [4, 5].

Several studies have shown excellent results for inhibition of the GAPDH enzyme by aromatic compounds, such as the tiliroside flavonoids [6, 7], 7-hydroxy-4',6-dimethoxyisoflavone [8], 3',4',5',5,7-pentamethoxyflavone [9], quercetin and guajaverin [6], and chalepin, which is a synthetic coumarin derivative [10] (**Figure 1**).
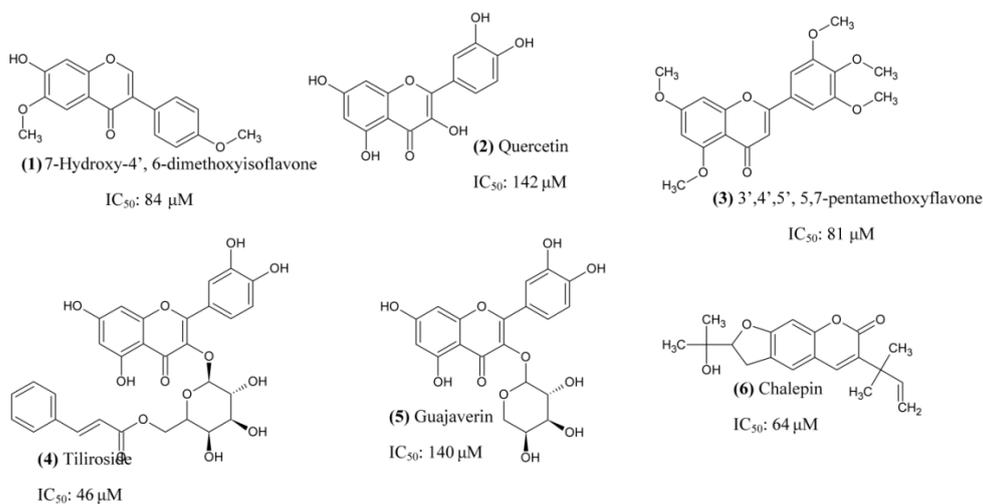
Figure 1. Glyceraldehyde 3-phosphate dehydrogenase inhibitors involved in the study

Flavonoids and coumarins are natural compounds found in several foods of plant origin and are characterized by two nuclei forming in some classes a heterocyclic [11]. These compounds have received much attention from the scientific community, including in the area of molecular modeling, not only for their anti-chagasic effect, but also due to several other pharmacological activities, such as antioxidant, antimicrobial, antithrombotic and anti-inflammatory, among others [12- 17].

Molecular modeling studies involving compounds with biological activity against the enzyme glyceraldehyde 3-phosphate dehydrogenase from *T. cruzi* contribute to a

mechanistic proposal of the interaction of these compounds with the enzyme.

Therefore, the objective of this work was to quantify the activity structure relationship of the aromatic compounds **1-6** inhibitors of the glyceraldehyde-3-phosphate dehydrogenase enzyme of *Trypanosoma cruzi* through calculations of frontier orbitals, logP and logS of the compounds, in addition To verify the interaction energy of the compounds in complex with the enzyme by molecular docking.

Materials and Methods:

2.1 Calculation of molecular descriptors

All structures of the ligands were drawn through *ChemSketch 11.0*. The molecular optimization and calculations of the frontier molecular orbitals of the compounds, were performed by quantum mechanics using the semi-empirical method PM7, with software *MOPAC7* [20].

The *ALOGPS 2.1* software was used for calculations of partition coefficient (log P) and water solubility (log S) of the compounds [21] *ALOGPS 2.1* predicts the partition coefficient (log P) and water solubility (log S) of the compounds [21-25].

2.2 Molecular Docking Study

The crystallographic structure of the enzymatic target GAPDH was obtained from the Protein Data Bank database [PDB ID: 1K3T].

AutoDock 4.0 software [26] was used as the choice to conduct the studies in the GAPDH target. The *AutoDock* Tools module was used to prepare and analyze the computational simulations. The *AutoGrid 4.0* software was used to generate the maps for the binders. The box was positioned in the catalytic region of the enzyme. The Lamarckian Genetic algorithm (GA-LS) was chosen to search for the best conformations [27-29]. 100 runs were performed for each binder (genetic algorithm with local search).

Results and Discussion:

3.1 Molecular Descriptors

In relation to the octanol / water partition coefficient (LogP) calculated by *ALOGPS 2.1*, the values found for compounds **1-6** can be visualized in **Table 1**. It can be observed that guajaverin and quercetin, compounds with higher experimental IC_{50} values (**Figure 1**), among the target compounds of the present study, were the compounds that presented the lowest logP value, which suggests that, even more soluble in organic solvents, the compounds have less efficiency in the permeability in hydrophobic biological barriers, when compared to Other target compounds of the present study.

Table 1. LogP and logS values of the compounds calculated by ALOPS 2.1

Compound	LogS (calc)	LogP (calc)	LogP (exp)
7-Hydroxy-4', 6-dimethoxyisoflavone	-3.85	2.71	-
3',4',5', 5,7-	-4.67	3.03	-

pentamethoxyflavone			
Quercetin	-3.06	1.81	1.82 [34]
Guajaverin	-2.50	0.70	-
Tiliroside	-3.52	2.97	2.71 [34]
Chalepin	-4.15	3.54	-

It was observed that 3',4',5',5,7-pentamethoxyflavone had the lowest value (less water soluble), while quercetin presented The highest value (higher solubility in water), in line with logP calculations.

The results show that all the compounds involved in this work have adequate solubility for a good bioavailability, because it can be said that compounds with logS values between -1 and -5 present hydrophilicity required for aqueous solubility and lipophilicity to interact with hydrophobic surfaces [31].

In order to predict the electronic characteristics of compounds **1-6**, the boundary molecular orbitals (HOMO and LUMO) were calculated by the semi-empirical quantum method PM7 (**Table 2**)

It can be observed that triliroside, the compound with the highest inhibitory activity of the enzyme GAPDH, showed the lowest energy of LUMO orbital, which indicates that its stability to the active site can occur by the interaction of the LUMO of the triliroside with HOMO orbital of the enzyme.

Table 2. Descriptors used in analysis

Compound	$IC_{50\,\mu M}$ (exp)	E_{HOMO} eV (calc)	E_{LUMO} eV (calc)	$\Delta E_{LUMO-HOMO}$
7-Hydroxy-4', 6-dimethoxyisoflavone	84	-8,604	-0,728	7,877
3',4',5', 5,7-pentamethoxyflavone	81	-8.808	-0,696	8,112
Quercetin	142	-9.089	-1,114	7,975
Guajaverin	140	-9.528	-1.087	8,441
Tiliroside	46	-9.150	-1.230	7,920
Chalepin	64	-8.949	-0.912	8,037

3.2 *Docking* Molecular

Table 3 shows the results obtained through the docking study between compounds **1-6** with the enzyme glyceraldehyde 3-phosphate dehydrogenase [33].

Table 3. Result of the docking study of the compounds with the enzyme glyceraldehyde 3-phosphate dehydrogenase.

Compound	Docking Free Energy (kcal/mol)

7-Hydroxy-4', 6-dimethoxyisoflavone	-6.69
3',4',5', 5,7-pentamethoxyflavone	-7.13
Quercetin	-5.62
Guajaverin	-6.17
Tiliroside	-7.29
Chalepin	-7.21

It can be seen that all compounds **1-6** interacted with the enzyme glyceraldehyde 3-phosphate dehydrogenase in an attractive way, and the compounds tiliroside, chalepin and 3', 4', 5',5,7-pentamethoxyflavone were those that obtained Lower interaction energy, showing to be more stable in complexes with the active site of the enzyme (GADPH).

Figure 2 shows the more stable conformation of compounds **1-6** at the site of action of the GADPH enzyme.
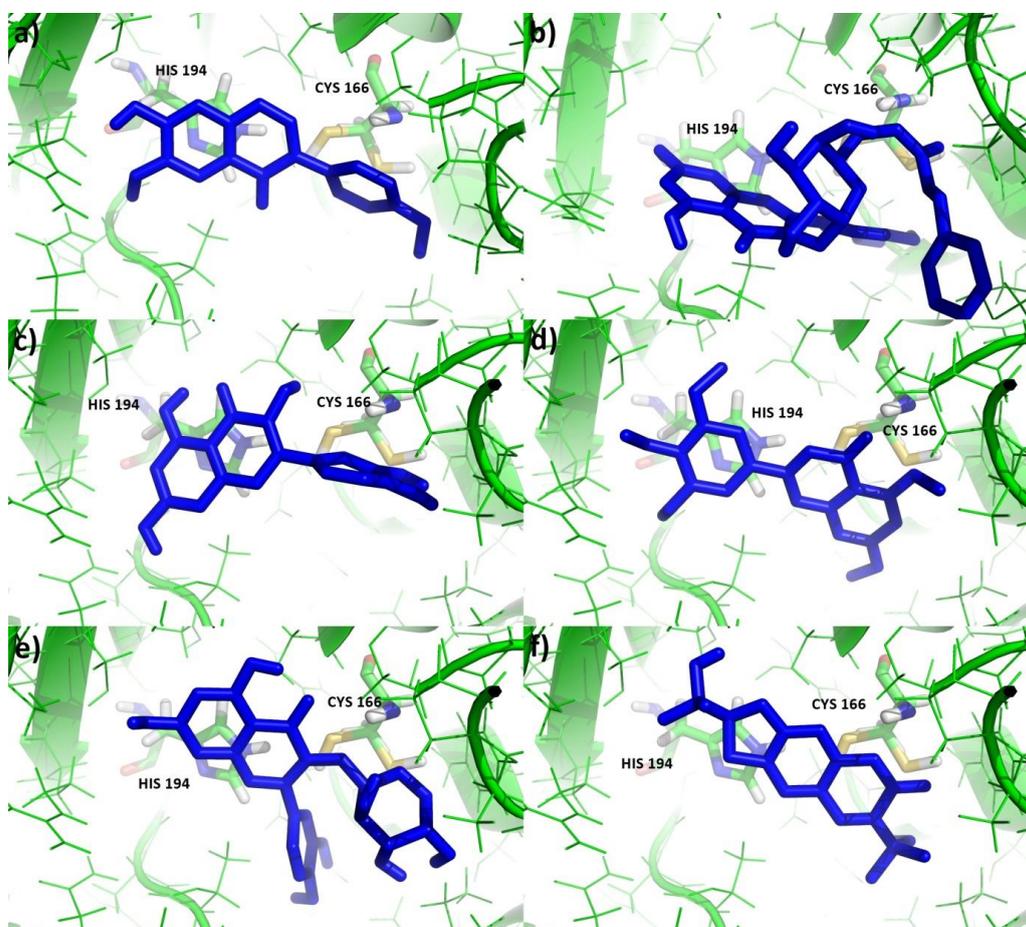
Figure 2. Compounds in the site of action of the enzyme GAPDH.a) quercetin; b) tiliroside; c) 7-Hydroxy-4', 6-dimethoxyisoflavone; d) 3',4',5', 5,7-pentamethoxyflavone; e) guajaverin; f) chalepin.

In **Figure 2** it can be seen that all the compounds have approached, through their ring systems, the amino acids HIS 194 and CYS 166, which are essential for catalytic activity of the

enzyme, since this activity involves the nucleophilic attack of catalytic cystine (CYS 166) on the substrate. This result suggests that all

ring structures of the compounds, besides the polar groups, are extremely important for the pharmacological activity of these compounds.

Conclusions:

The computational study carried out in this work allowed a better view, at a molecular level, regarding the interaction of compounds 1-6 with the enzyme, showing that the compounds

that have lower IC_{50} also have more stable energy of drug-receptor binding. This result suggests that there is a more selective mechanism of interaction in GAPDH.

Conflicts of Interest:
The authors declare no conflict of interest

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