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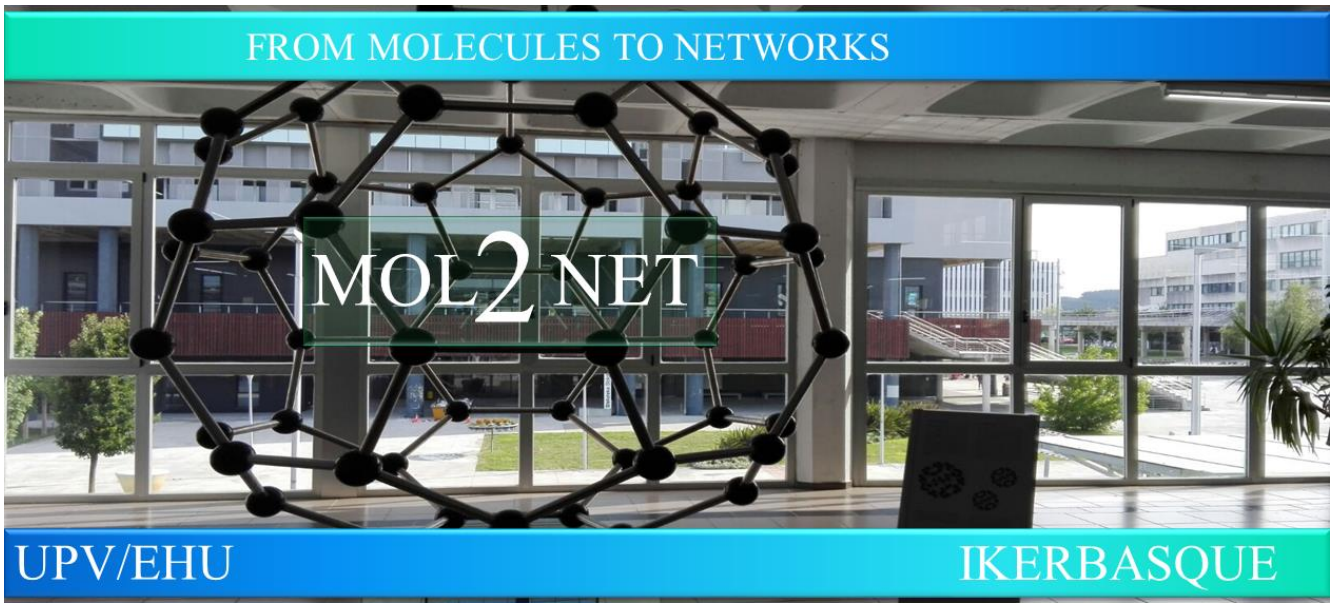

Molecular docking study on silica of chemical constituents of *Paubrasilia echinata* Lam., against chagas disease

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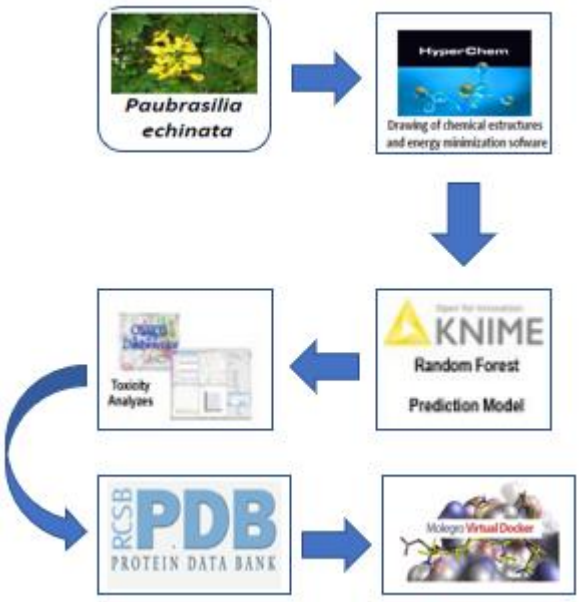
Graphical Abstract	**Abstract.**
	Neglected diseases are caused due to a set of ecological, evolutionary and biological factors, there is a higher incidence in the number of cases in countries with tropical climate. Chagas disease is one of the most important neglected diseases that affects several countries. The



etiologic agent that causes this disease is the flagellate protozoan Trypanosoma cruzi. The disease presents in two clinical phases: acute and chronic. This disease pose a significant burden to people's health in general. The drugs available to treat it are not able to meet your clinical needs. Aiming at the analysis of a chemical constituent of pau brasil (Paubrasilia echinata Lam.*), the present study aimed to evaluate the action of antichagasic constituents through an in silico study.*

Introduction

The incidence of neglected diseases, arise due to the combination of ecological, evolutionary and biological factors, there is a higher incidence in the number of cases in countries with tropical and subtropical climate. The drugs currently registered for the treatment of tropical diseases are not able to meet the clinical needs of patients. In this sense, in recent decades there has been an expansion in efforts to elucidate new therapeutic systems [1].

Chagas disease (CD) is one of the most relevant neglected diseases that affects several countries. The etiologic agent that affects this disease is *Trypanosoma cruzi*, a flagellated protozoan. The disease presents itself in two clinical phases: the one that can be identified or not (acute) and its evolution that can become (chronic). With the predominance of cases of Chagas disease in the resulting chronic phase, Brazil in recent years has reached approximately three million infected, and the occurrence of CD in an acute form has arrived in several states of the federation, with a greater number of cases. cases in the region that corresponds to the legal Amazon, an area that corresponds to 59% of the Brazilian territory [2].

The flagellate protozoan that causes Chagas disease is *Trypanosoma cruzi*. In vertebrates, it lives in peripheral blood and muscle fibers, especially cardiac and digestive fibers, in the form of trypomastigote, which is extremely mobile, and, in tissues, as amastigotes present in the digestive tract of the insect vector, where an evolutionary cycle takes place. of this parasite, originating in the infective form, found in the feces and urine of the insect vector [3].

The present study aimed at a computational study, aiming at the analysis of a chemical constituent of pau brasil (*Paubrasilia echinata* Lam.), aiming to evaluate the action of antichagasic constituents against Chagas disease.

Materials and Methods

In this study, robust cheminformatics tools were used, in order to reduce the loss of information, initially geometric optimizations of the chemical structures of ten molecules were carried out in the MarvinSketh software, it was used to design the molecule, add hydrogen and place the chemical structure in 3D (keeping the respective stereochemistry) [4] and HyperChem, semi-empirical optimization was performed, using the semi-empirical method AM1 and molecular mechanics [5]. Standardizer was the method used to gather the structures with their retention time information [6]. We used the KNIME Analytics Platform, a free and open source software to create data science [7], in this study RandomForest was used as a classifier and Weka as a predictor. After this procedure, it was possible to eliminate molecules with undesirable properties (inactive), already classified as active, it was directed to the software called OSIRIS DataWarrior 5.0, the compounds the molecule under study were selected and their cytotoxic parameters evaluated using this property explorer to predict the molecular mutagenic, tumorigenic, irritant and reproductive properties of compounds [7]. In the next step, molecular docking was performed, with crystallographic protein structures recovered from the RCSB, choosing a docking protocol from RMSD values below 3Å, Protein Data Bank (PDB), (PDB ID: 3KKU) and (PDB ID : 3DMT) [8]. The ligands were optimized and then saved as pdb files, the program used in the simulations was Molegro Virtual Docker , where the three-dimensional structure of the protein-ligand complex was computationally simulated against Chagas disease [9]; [10].

Results and Discussion

The structures of 10 molecules studied had their structures optimized using the HyperChem software , based on semi-empirical methods , (AM1) and molecular mechanics (MM+), then RandomForest was used as a classifier and Weka as a predictor, where it was possible to detect active and inactive molecules, of the tested compounds, only one was active (Figure 1).

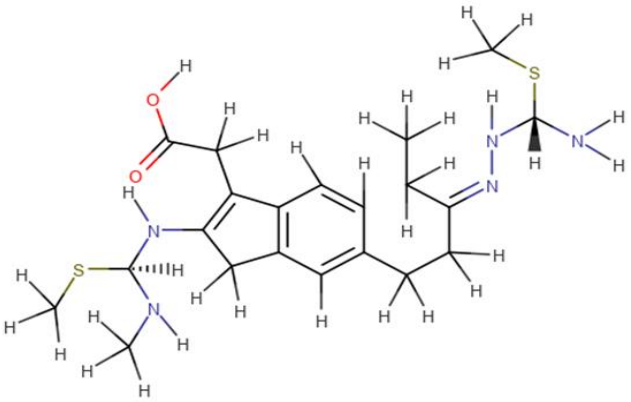


Figure 1. Structure of the 2D studied molecule.

For the toxicity parameters, following the mentioned methodology, it was possible to observe that the studied molecule did not present any serious risk in any of the analyzed parameters: mutagenic, tumorigenic, irritant and reproductive molecular values, effective properties of the compounds. After this analysis, the compound was conducted with the help of the Molegro Virtual docking software, for the study of molecular docking.

Table 1. Molecular Docking

PDB ID protein	Name	Moldesk score	rerank score	Bond
3KKU	studied molecule	-112,751	-9,839	-2,776
	Control: Benznidazole	-82,932	-63,232	-2,478
3DMT	studied molecule	-142,339	-78,357	-7,063
	Control: Benznidazole	-98,493	-89,057	-7,320

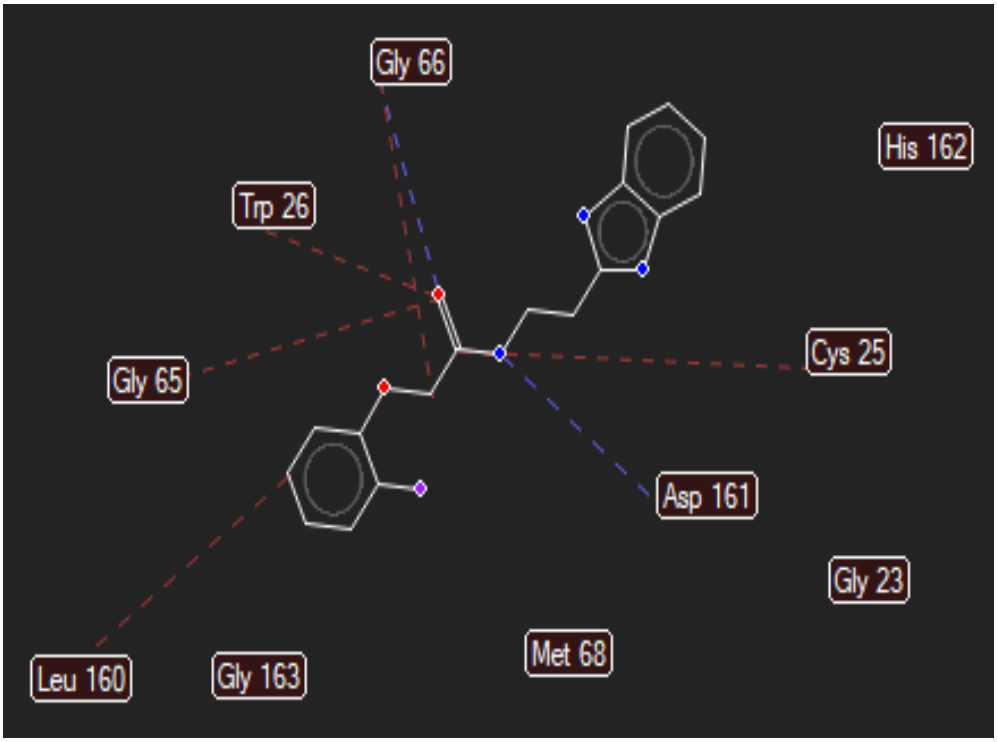


Figure 1. Steric interactions with Benznidazole, PDB ID: SKKU

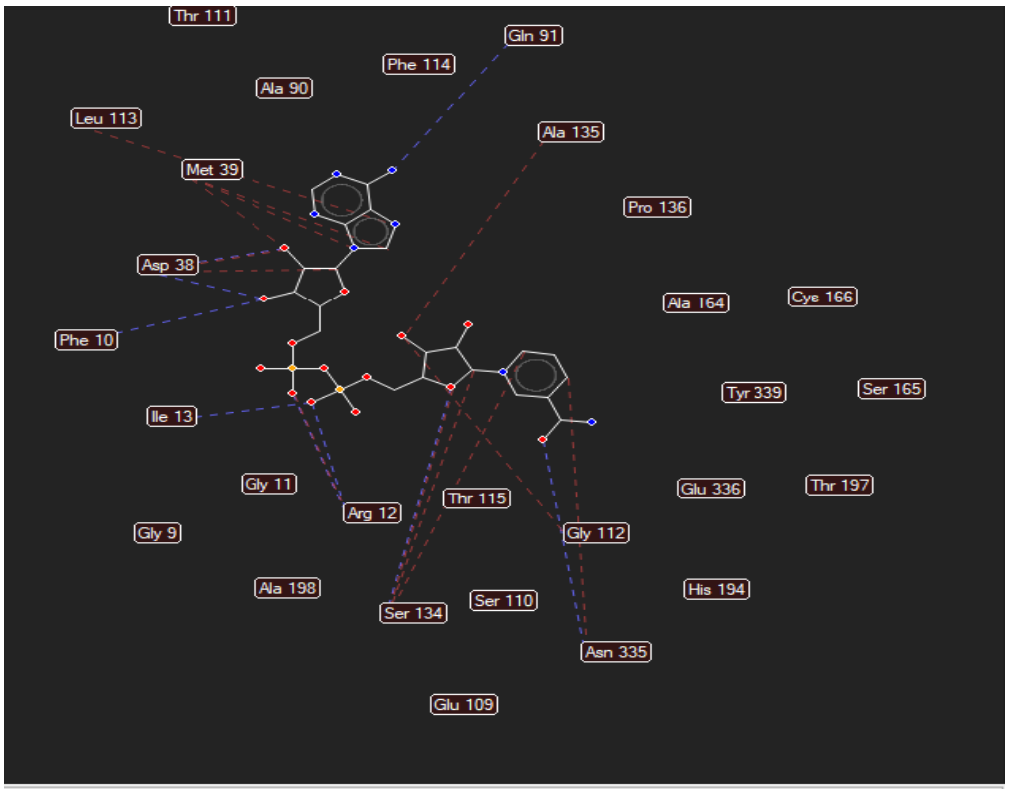


Figure 2. Steric interactions with Benznidazole , PDB ID: 3DMT

Table 2. Steric and hydrogen interactions

PDB ID protein	Molecule	interactions waste	Hydrogen interactions	steric interactions
SKKU	Benznidazole	Asp 162	1	0
		Trp 26	0	1
		Leu 160	0	1
		Cys 25	0	1
		Gly 65	0	1
		Gly 66	1	1
		Gln 91	1	0
3DMT		Leu 113	0	1
		Met 39	0	3
		Asp 38	3	3
		Ph 10	1	0
		Le 13	1	0
		Arg 12	1	1
		be 134	1	3
		Gly 112	0	1
		Asn 335	1	1
		Ala 135	0	1
		Gln 91	1	0

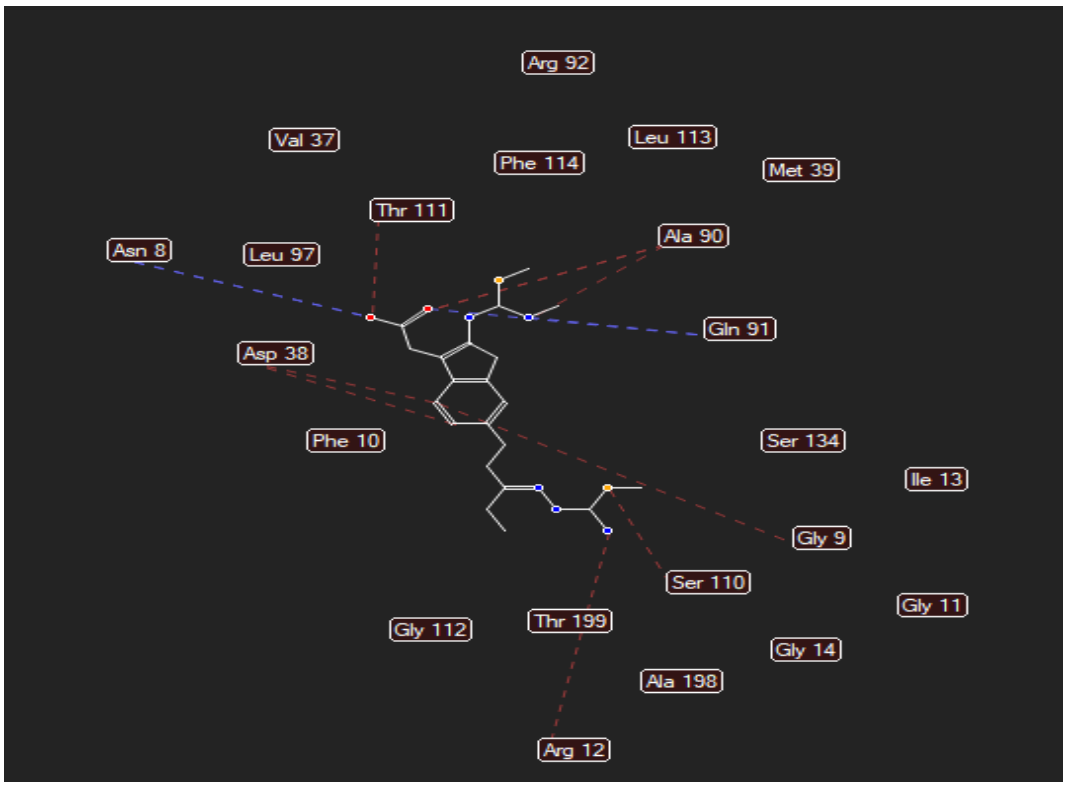


Figure 3. Interactions with the molecule under study 3DMT

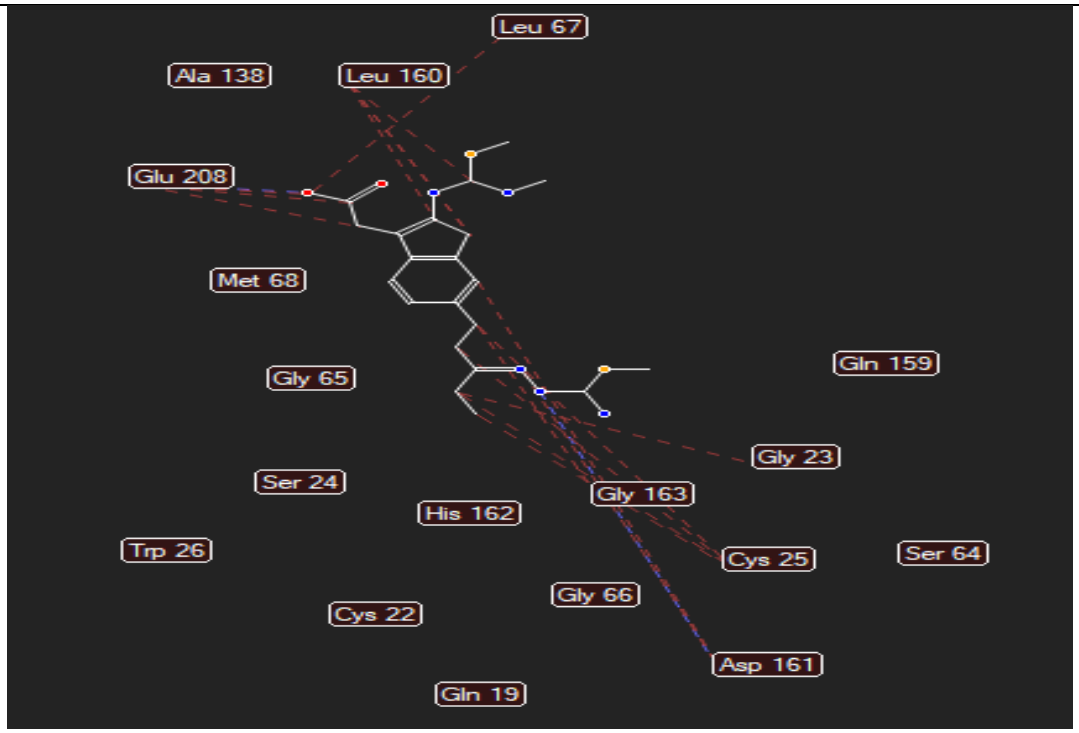


Figure 4. Interactions with the molecule under study 3KKU

Table 2. Interactions of the studied molecule

PDB ID protein	Molecule	interactions waste	Hydrogen interactions	steric interactions
		Thr 11	0	1
		asn 8	1	0
		Asp 38	0	3
3DMT		Arg 12	0	1
		be 110	0	1
		Gly 9	0	1
		Gln 91	1	0
	studied molecule	Ala 90	0	3
		Leu 160	0	3
		Leu 67	0	1
		Glu 208	1	3
SKKU		Asp 161	1	1
		Cys 25	0	4
		Gly 23	0	1

Based on what was explained above in table 1, in this study molecular docking techniques were used to have a more precise notion of the types of receptor-ligand interaction, presenting good results for the molecule under study. The study of steric interactions, presented in figures 1 and 2 for Benznidazole and 3 and 4 for the molecule studied, in this way it is possible to affirm that they demonstrate good interactions with residues presented in the figures, respectively.

Conclusions

The chemical constituents obtained through extracts of leaves, bark of pau brasil (*Paubrasilia echinata* Lam.) , are widely studied by several researchers, among the most diverse constituents, phenolic compounds are the most representative class of secondary metabolites in several studies, and these constituents, associated with other studies, may be promising against Chagas disease. Molecular docking allowed the analysis of the ligands under study, showing a better affinity for the receptor, showing which of them has a greater efficiency, in addition to the study of the main interactions carried out in the receptor-ligand complex formed. Thus, it is important to emphasize the importance of studies like this one, in order to possibly elucidate the risks of toxicity, opening the possibility of studying this compound for several biological analyses. Of the ten molecules studied, only the one shown in figure 1 was found to have activity and no toxicity.

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