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QUANTUM STUDY OF GEOMETRIC PROPERTIES OF THE ANTI-HIVCOUMARIN HERACLENOL: A STUDY OF DENSITY FUNCTIONAL THEORY (DFT)

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ABSTRACT
Coumarins are a class of secondary metabolites derived from cinnamic acid, widely distributed in the plant kingdom, which present important biological activities (antioxidant, anti-inflammatory, anticoagulant, antiviral and anticancer). Heraclenol is a coumarin that exhibits HIV replication inhibitory activity in vitro. Molecular modeling consists of a set of features and software for visualization, construction, editing and analysis of molecules that serve as the basis for pharmacological planning. The purpose of this study was to characterize electronically and structurally, coumarin Heraclenol, using the theory of functional density (DFT), as a stage of rational development of new drugs (Drug Design). The methodology of the present study was developed in the following steps: the Heraclenol molecule (obtained from the chewspider® repository) was constructed and visualized and pre-optimized using Avogadro® software. Afterwards, the heraclenol structure was optimized through the principle of energy minimization, using the DFT (functional density theory), calculations performed with the GAMESS software by the Hartree-Fock method with hybrid functions B3LYP and the base function 6 - 311G **, obtaining the molecular structure with potential energy of - 2136.01968455 Eh. The optimization of the structure generated some results as: Components (Nuclear repulsion: 1808.5375955740 Eh; Electronic energy: -1070.3301436839 Eh; An electric energy: -5053.8978063137 Eh, Electric energy two: 2175.0300670558 Eh), Components Virial (kinetic energy: 1065.6895408749 Eh; Virial: 2,0043545541); Dipole Moment (4.88971 Debye). With the data obtained from the optimization, it was possible to plot the surface map of electrostatic potential (MESP), making it possible to identify the regions of higher nucleophilicity in the oxygen atoms (O1, O2, O3, O5, O6) and the more electrophilic region in the hydrogen atoms (H23, H24, H34, H35, H36, H37, H38), justified by the difference in electronegativity between the oxygen and hydrogen atoms. It was also possible to plot the HOMO frontier orbitals (-6.121262 eV) and LUMO (-1.893912 eV). Using the Homo and Lumo values, it was possible to calculate several molecular descriptors such as: Calculated Ionization Potential (I = -6, 122562 eV), electronic affinity (A = -1.893912 eV), chemical motility (S = -0.23648 eV), chemical potential (η = -2,11432 eV), electrophilicity index (ω = -3.79931 eV), electronic chemical potential (μ = 4.00824 eV), Electronegativity (χ = -4.008237 eV) which help to predict the formation of chemical bonds and the physical and chemical properties of the compound. The present work is a fundamental step for future studies of drug design, aiming at understanding and promoting the antiviral potential of coumarin Heraclenol.

Keywords:
MESP. Quantum methods. Frontier orbital.

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INTRODUCTION

Brazil is a rich country in its biodiversity, being a source for the discovery of natural products with diverse biological activities, which allows the bioprospection for the development of antiviral therapies. Among the disease-causing retroviruses is the human immunodeficiency virus (HIV) that produces the pathological basis of the acquired immunodeficiency syndrome (AIDS), which is a worldwide health problem of unprecedented dimensions [1] which has the selective depletion of CD4 lymphocytes, as its main feature [2]. The treatment of diseases caused by retroviruses consists, and one uses drugs (usually in associations, called "cocktails ") That prevent RNA synthesis. In this context, the search for natural products that have antiretroviral activity is a hope for the cure of several diseases [3][4][5], have been shown to have an anti-inflammatory, anti-inflammatory, anti-inflammatory and anti-inflammatory activity [6]. Coumarin Heraclenol, has in vitro inhibitory activity on HIV replication [7].

Molecular modeling consists of a set of features and software for visualization, construction, editing and analysis of molecules that serve as a basis for drug planning [8]. In this study, use of molecular modeling calculations is focused on the theory of functional density (DFT) [9]. This method emerged as an alternative to traditional ab initio and semi-empirical methods in the study of the fundamental state properties of molecular systems. The great advantage of DFT over other ab initio and semi-empirical methods (methods based on Hartree-Fock HF) lies in the gain of computational speed and memory space, besides maintaining a quite satisfactory calculation precision [9]. In this context, the objective of this study was to characterize electronically and structurally, coumarin Heraclenol, using the theory of functional density (DFT), as a stage of rational development of new drugs (Drug Design).

Materials and Methods

In this work, we used the free softwares with licenses registered in their official Web sites, based on the Windows 10 operating system. All DFT calculations were performed using the General Atomic and Molecular Electronic Structure System (GAMESS) (ab initio, DFT and semiempirical SCF-MO) [10].

The chewspider® repositories were used to obtain the molecule and its chemical physical properties. Following the methodology proposed by [11] was used for a preparatory phase (initial geometric optimization) Avogrado® freeware software (version: 1.2.0, library version: 1.2.0, Open Babel Version: 2.3 .90, Qt version: 4.8.6) configured to perform classic MMFF94 force field calculations with 500 steepest descent optimization cycles with 10e-7 convergence. In the next step, the GAMESS (The General Atomic and Molecular Structure Electronic System) software [10] was used to perform molecular modeling calculations using quantum methods, based on Functional Density Theory (DFT), for optimization geometric expression of coumarin Heraclenol. Noting that the software was configured to use the B3LYP functional, with the base function 6-311G ** (VTZP Valence Triple Zeta + Polarization on All Atoms). With the data obtained through the geometric optimization calculations, it was possible to obtain the potential energy of the molecule, the atomic charges of mulliken, the coordinates of the drug, and plot the boundary orbitals (HOMO and LUMO) and the surface map of the electrostatic potential (MESP).

Results and Discussions

The Open Chemistry database [12] was designed to provide and encourage access to the chemical structures of small organic molecules and their biological activities containing structural information, names and identifiers, chemical and physical properties, biological test results. When we performed a search in this molecular database, it was possible to obtain important data for the Heraclenol molecule, such as its classification (heterocyclic compound, furanosidic), CAS identification number (31575-93-6), name according to IUPAC (304.095 g mol-1), monoisotope mass (304.095 g / mol), sodium bicarbonate solution (304.095 g / mol) mol), polar topological surface area (89.1 Å2), XLogP3 (1,2), formal charge (0,0), identifies stereocenter number (1), rotational possibility links (2), atoms donors (2) and hydrogen bonding acceptors (6), thus indicating the possibility of forming eight intermolecular Hydrogen bonds. With regard to atomic connectivity, it was possible to obtain the two-dimensional structures (figure 1A) and the 3D conformer (Figure 1B).

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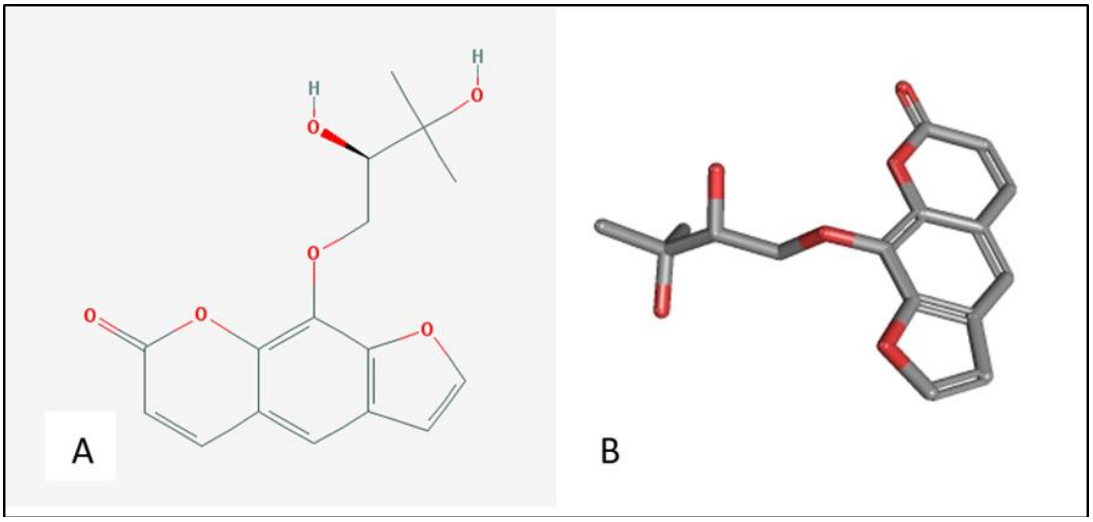

Figure 1: Molecular structure of the drug Heraclenol (A) two-dimensional and (B) 3D conformers.
Source: PubChem ® Repository

In the repositories, the molecule, although presenting the atomic coordinates, these represent with fidelity only the connectivity of the atoms, being necessary to perform calculations of molecular optimization, in order to reach a conformation with less potential energy, that is, perform calculations of energy minimization [13]. Using the Avogadro® software we can perform a pre-optimization using the MMFF94 force field, obtaining a theoretically more stable structure (Figure 2), which assumed a value of 434,577 kJ mol-1, where each atom of the molecule occupied a smaller energy ratio by making its 3D structure stable with the molecular structure in a more stable conformation than that available in the repository, having a calculated molar mass of 304,295 g mol -1 with a difference of 0.003 g mol -1 of the mass available from the repository. Regarding connectivity, 38 atoms were characterized by a total of 40 chemical bonds (Figure 2).

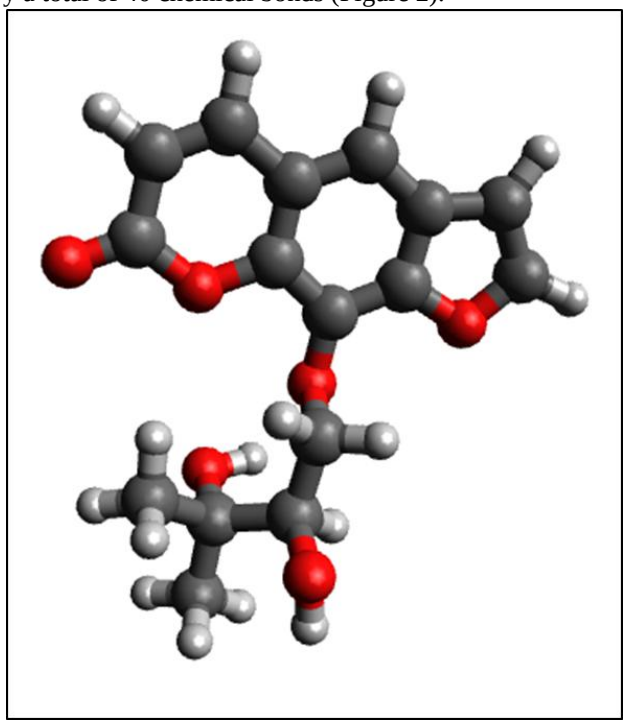

Figure 2: Pre-optimized conformational structure of the drug heraclenol

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One of the parameters analyzed in the pre-geometric optimization was the formal charge, which can be defined as the load closest to the real charges of the atoms in molecules and ions, where their calculation is based on the structure of Lewis, it is assumed that the pair of electrons shared in a bond is equally divided between the atoms that form the covalent bond [14]. In the molecule of Heraclenol, it was possible to observe that, all atoms remained in a conformation and load distribution, close to neutrality. In relation to the partial loads, the molecule of Heraclenol, presented variations variation in Oxygen atoms, (-0.482 to 0.245), Carbon (-0.016 to 0.337) and Hydrogen (-0.026 to 0.103), this variation is explained by the fact that in polar covalent bonds, the electron pair will be closer to one of the atoms, thus causing the two atoms to acquire residual charges or (7.003 D), which is shown in Figure 3, where we can observe the vector with direction of the positive charge for the negative charge [15]. , the intensity being proportional to the accumulation of positive and negative charges. Another factor represented by the vector was the force field representation of the molecule (figure 4). Both properties, force field and dipole moment are important because they influence other properties, such as melting point, boiling and solubility [14].

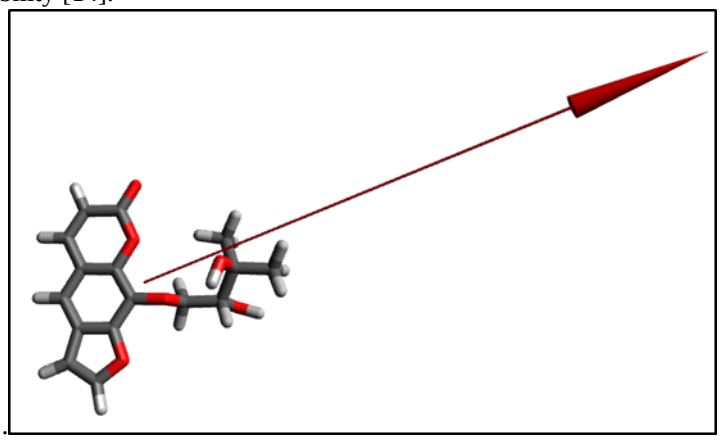

Figure 3: Representation of the dipole moment vector of coumarin Heraclenol.

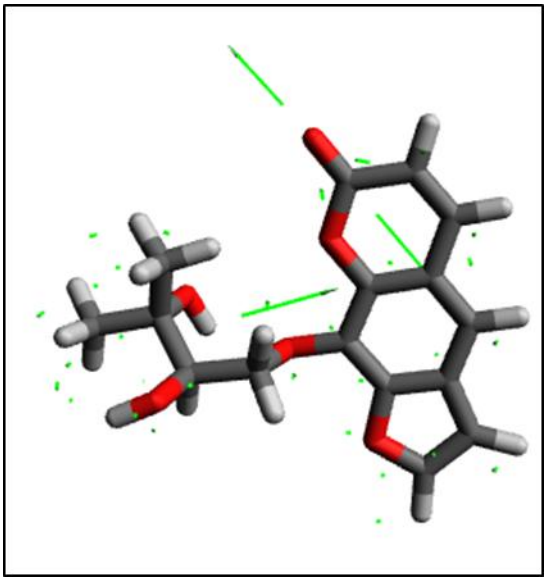

Figure 4: Representation of the force field vector of coumarin Heraclenol.

The theory of functional density (DFT), it is considered that the energy of a set of electrons (under the influence of an external field) can be treated with a unique function of electronic density [16], this relation can be observed in two terms, called functional exchange and functional correlation.One of the advantages of DFT in

relation to the other methods lies in its relation to how it considers energy, as we can see, according to the conclusions of [16]:

> *"Since energy is expressed as a function of a single" variable ", the electron density (which is a function of the 3 Cartesian coordinates), the equations that result from the application of this model are simpler than those resulting from the Hartree-Fock theory, where "variables" are the set of wave functions of an electron (which are functions of 3N variables, where N is the number of atoms in the system).*

To work with organic molecules, currently the Becke 3-parameter hybrid exchange functional model and the Lee-Yang-Parr correlation functional (B3LYP), has been widely used, due to the quality of its results [16]. Using the DFT quantum method with B3LYP functional, it was possible to optimize the structure of the drug Heraclenol (Figure 5), and in this conformation, a total energy stationary value was obtained -1070.3301436839 Eh, with potential energy of -2136 , 0196845587 Eh, kinetic energy on the order of 1065.6895408749 Eh, as well as calculate all the thermodynamic values required to configure the system energetically (Table 1), observing a gradual value in the potential energy of the molecule, when compared to the energy obtained in the pre- optimization.

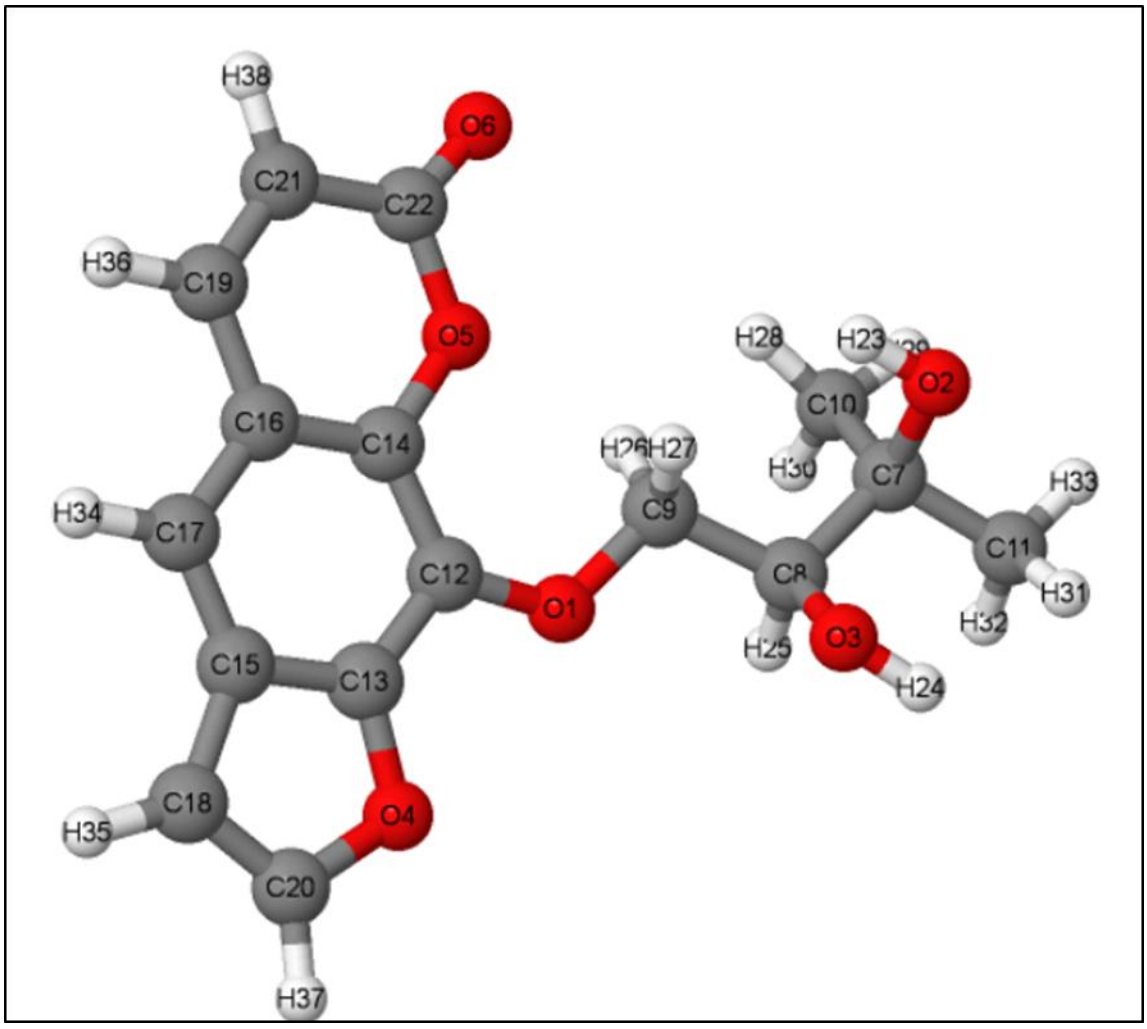

Figure 5:Optimum conformational structure (DFT) of coumarin Heraclenol

Table 1:Energy components, thermodynamic parameters and properties calculated by the DFT method of cumarinhHeraclenol

Source: search data

Nuclear repulsionenergy	1808.5375955740 Eh
Electron-electronpotentialenergy	2175.0300670558 Eh
Core-electronpotentialenergy	-6119.5873471885 Eh
Core-corepotentialenergy	1808.5375955740 Eh
Energy ofaneletron	-5053.8978063137 Eh
Potentialenergy	-2136.0196845587 Eh
Kineticenergy	1065.6895408749 Eh
Virial coefficient (V / T)	2.0043545541 Eh
Total number of BASIS SET SHELLS	174
Number of Cartesian Gaussians (Base Functions)	514
Numberofelectrons	160
Multiplicityof spin	1

With respect to the distribution of charges in the molecule (partial loads), we used the population analysis of Mulliken, which is based on the theory of molecular orbitals, where a set of molecular orbitals is defined by a linear combination of atomic K orbitals, also called of basic functions, whose coefficients are determined by the method of HartreeFock[17]. With respect to coumarin Heraclenol, it was possible to calculate the variation in the charges of the Carbon atoms (-0.008008 to -0.446712), Hydrogen (0.080659 to 0.234730) and Oxygen (-0.265165 to -0.398234) (Table 2), making it possible to calculate the average charge for the atoms of Carbon (0,011976), Hydrogen (0.123936) and Oxygen (-0.36243). With respect to the dipole moment vector, it was calculated in the value of 4,88971 DEBYE.

Table 2: Population analysis of Mulliken's drug Heraclenol

ATOM	CHARGE	ATOM	CHARGE
O1	-0,3667	C20	0,083335
O2	-0,3958	C21	-0,252283
O3	-0,3982	C22	0,446712
O4	-0,2652	H23	0,23473
O5	-0,3931	H24	0,236035
O6	-0,3556	H25	0,113298
C7	-0,008008	H26	0,137585
C8	0,062357	H27	0,109265
C9	0,022166	H28	0,108947
C10	-0,245482	H29	0,114449
C11	-0,260632	H30	0,097562
C12	0,179968	H31	0,099507
C13	0,194502	H32	0,105241
C14	0,231785	H33	0,122759
C15	-0,061967	H34	0,080659
C16	-0,137266	H35	0,09281
C17	-0,004275	H36	0,09978

C18	-0,143176	H37	0,112011
C19	0,083876	H38	0,118345

Using as a basis the van de Waals spherical representation, one can plot in a grid of points located in different layers around the molecule, which we call the surface map of electrostatic potential (MESP). The MESP is generated after the overlap in the molecule of a positively charged particle running through the van der Waals contact surface and revealing a repulsion region, represents the blue-positive positive potential, and a region of attraction represents the negative potential of red staining [18] The surface map of Van de Waals, from Heraclenol (Figure 6), was used for the construction of the electrostatic potential surface map (Figure 7), where it was possible the regions of higher nucleophilicity at the oxygen atoms (O1 (H23, H24, H34, H35, H36, H37, H38), justified by the difference of electrons (H 2, O 2, O 3, O 5, O 6) and the most electrophilic region between the oxygen and hydrogen atoms.

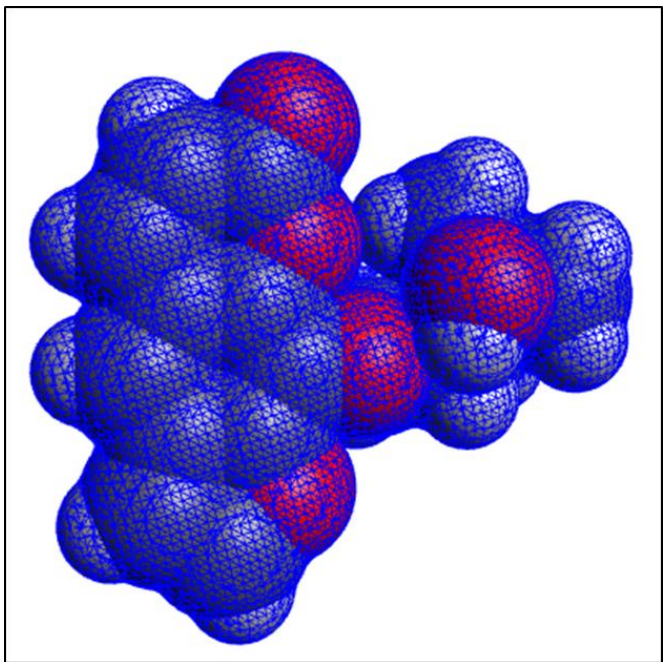

Figure 6: Van de Waals's representation of the drug Heraclenol.

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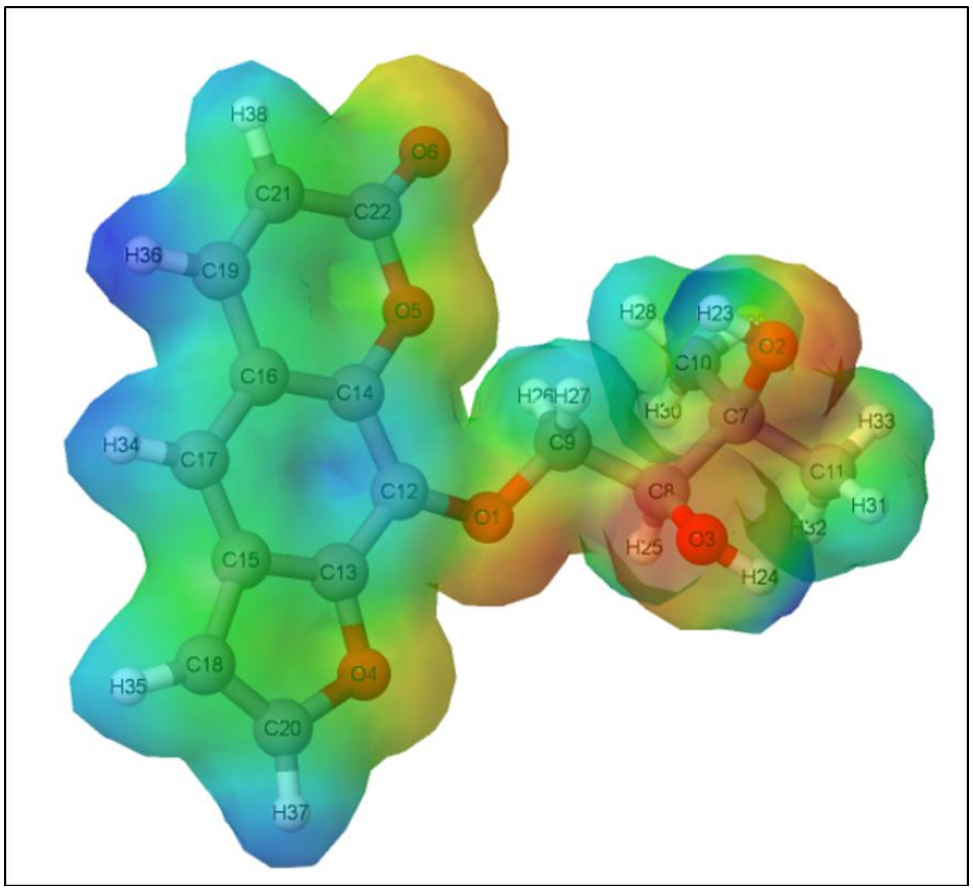

Figure 7: Electrostatic potential map of coumarin Heraclenol, obtained by DFT.

Molecular orbitals are constructed through linear combinations of atomic orbitals, where in these combinations, high coefficients present in the mathematical expression, used for the calculation, indicate a high probability of finding electrons. The molecular orbital diagrams can be assembled according to experimental results where the energy of these orbitals is found by photoelectric (UV) or by computational methods (theoretical calculations) [19]. The theory of border orbitals is based on the reaction principle between the molecular orbitals of two reactants that begin to interact and overlap, leading to the formation of two new molecular orbitals, one of higher energy and one of lower energy [11][16]. The boundary orbital energy, which involves the highest Occupied Molecular Orbital (HOMO) and the low-power unoccupied molecular orbital (LOMO) are widely used chemical-quantum descriptors that play a important role in the chemical reactions and in the formation of several charge transfer complexes [20]. For the coumarin Heraclenol, the Homo orbital (figure 8), has a symmetrical distribution between the positive phases (Blue) and the negative phases (red), with an energy value equal to -0.20017 Eh. With respect to LUMO (figure 9), we can also observe a symmetrical distribution between the phases, however it presents an energy value equal to -0.02549 Eh. Using the values of the orbitals, it was possible to obtain the energy diagram (figure 10), where we can observe the formation of a Gap (HOMO Energy - LUMO Energy) equal to 20,016.9745 Eh, which can be assigned with the necessary energy for the first quantum leap, which is an important molecular descriptor for future thermodynamic studies related to molecular reactivity. The HOMO and LUMO energies are used as chemical descriptors of reactivity and are generally associated with other indices such as electron affinity and ionization potential. The global reactivity descriptors act as a bridge between structural stability and global chemical reactivity [21][22][23][24]. Using the HOMO and LUMO energy values, it was possible to calculate the gap (4.2286 eV) (figure 10) Ionization Potential (I = -6, 122562 eV), which is the minimum energy required to remove an electron from an atom or molecule, the electronic affinity (A = -1.893912 eV), which is described as the change of energy when an electron added to a

neutral atom in the gas phase, chemical motility (S = -0.23648 eV), electronic chemical potential (ω = -4.008237 eV), and chemical hardness (η = -2,11432 eV), electrophilicity index (ω = -3.79931 eV), which help to predict formation of chemical bonds and the physical and chemical properties of the compound.

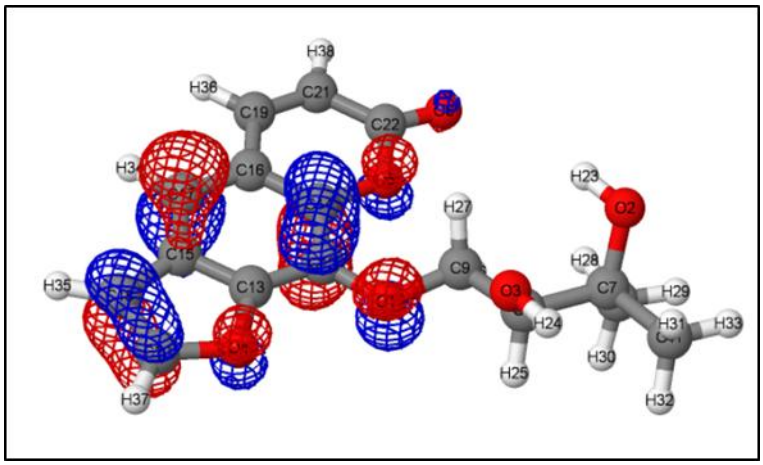

Figure 8: Orbital HOMO of coumarin Heraclenol obtained by DFT.

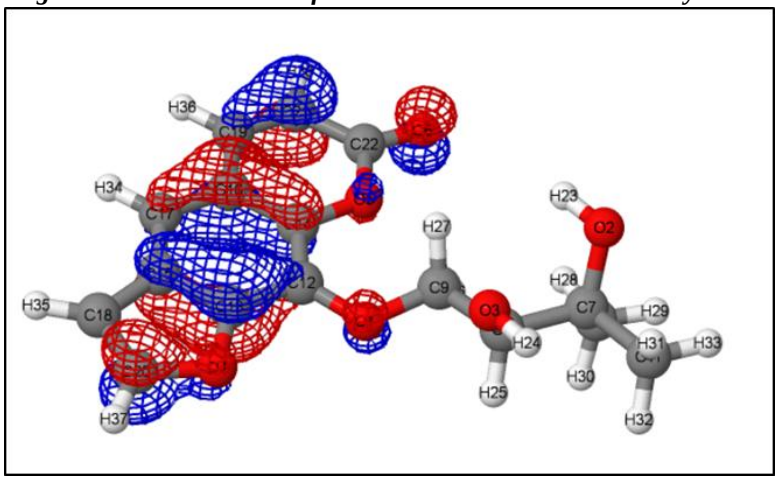

Figure 9: Orbital LUMO of the coumarin Heraclenol obtained by DFT.

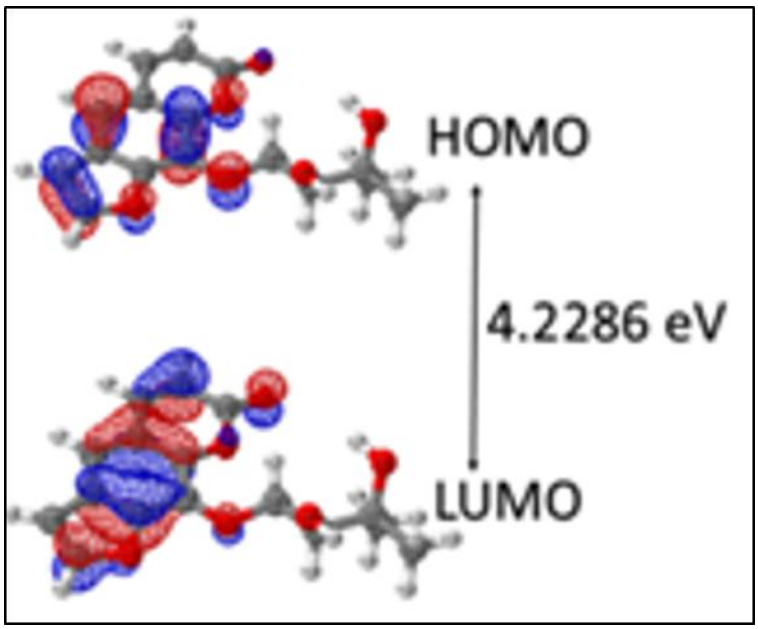

Figure 10: Gaf of coumarin Heraclenol obtained by DFT

CONCLUSION

The use of the Density Theory of functional, brings huge advantages and benefits to molecular modeling. With these features it was possible to optimize the structure of the coumarin Heraclenol, to characterize its three-dimensional structure in the more stable conformation, to plot the surface map of electrostatic potential, the border orbitals, and to calculate molecular descriptors that help to predict the formation of chemical bonds and the physical and chemical properties of the compound. The present work is a fundamental step for future studies of drug design, in order to understand the antiviral potential of coumarin Heraclenol.

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The State University of Ceará (UECE), especially Pro-Rector of Post-Graduation and Research (Propgpq) for the support of this work. FundaçãoCearense de Amparo à Pesquisa (FUNCAP) and the Coordination for the Improvement of Higher Education Personnel (Capes), foundation of the Ministry of Education (MEC) for granting a scholarship as financial support for scientific development.

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