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Electronic and Structural Characterization of γ-Alkylidenobutenolides Nostoclides I And II: A Semi-Empirical Quantum Study

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***Abstract*— The use of substances with antimicrobial action has made great advances in relation to the prevention and treatment of infectious diseases. However, the widespread use of these substances has led to several problems, especially the development of resistance of microorganisms to antibiotics. Thus, the need arose to study compounds at the molecular level with more effective and less toxic actions. Nostoclides I and II are secondary metabolites, which belong to a family of natural compounds known as γ-alkylidenobutenolides. Since their discovery, these γ-alkylidenobutenolides have been the target of study of synthetic organic chemicals, resulting in different approaches to achieve the total synthesis of these secondary metabolites. The present study aimed to electronically characterize the structures of nostoclid I and II. The structures were optimized using the semi-empirical quantum formalism of the Austin Model 1 (AM1) method. With data from energy minimization and geometry optimization, it was possible to perform the conformational analysis of structures, Mulliken's population loads and plot the electrostatic potential (MEP) surface map and characterize and plot the boundary orbitals. The results presented in this study represent an initial for future studies of molecular docking and drug desing.**

***Keywords*— Austin Model 1. γ-alkylidenobutenolides. Semi-Empirical. Theoretical Chemistry.**

I. INTRODUCTION

The use of substances with antimicrobial action provided a great advance in relation to the prevention and treatment of infectious diseases, making it necessary to study new antimicrobial agents due to the emergence of resistant microorganisms. However, the continuous use of these substances has caused several problems, especially the development of resistance of microorganisms to antibiotics[1-2].

According to Balunas[3]a point to highlight is the use of the study as the first screening in the discovery of the pharmacological activity of new therapeutic compounds. Thus, such research can contribute considerably to the development of the health field in the search for bioactive molecules as therapeutic alternatives [4], identifying substances with a more effective and less toxic action in the race against resistance and the emergence of pathogenic microorganisms [5-6].

The therapeutic action of a substance results from its behavior with biological systems, the interactions present in the system are related to its chemical structure. Thus, two structurally similar compounds can be distinguished only 'by an atom or in terms of its location in the molecule, capable of showing differences, according to their physical-chemical and biological properties, or can be described quantitatively by means of electronic parameters. physical-chemical or appropriate structural descriptors [7].

The structures of nostoclide I and II (Figure 1) are secondary metabolites, belong to a family of natural compounds known as γ-alkylidenobutenolides [4]. These compounds were isolated from a green-blue alga, Nostoc sp. which is found in a lichen called Peltigera canina[8]. Since their discovery, these γ-alkylidenobutenolides have been the subject of study by researchers, mainly synthetic

organic chemists, resulting in different approaches to achieve the total synthesis of these secondary metabolites. Nostoclide I and II have cytotoxic action, and in addition they exhibit a wide range of biological activity, such as antibiotic activity exhibited by protoanemonine [4]. The biological activity of these compounds is still under investigation in research programs and allelopathic activity has been observed since the 1990s [8].

In this perspective, through the molecular modeling methodology, the present study aims to electronically characterize the structures of nostoclide I and II. The results presented in this study represent an initial step for drug desing and molecular docking studies.

II. METHODOLOGY

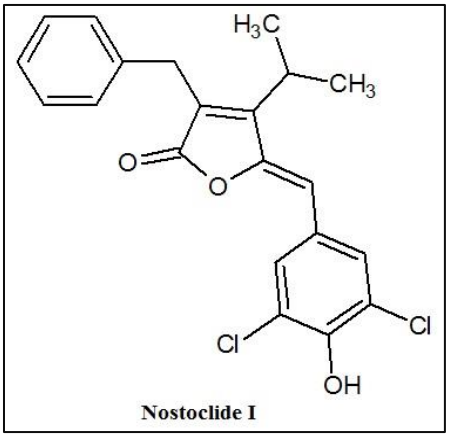
The research had as methodological scope the use of computational tools for the molecular modeling of pharmacological compounds, based on chemical-quantum calculations from a set of descriptors selected to obtain the empirical parameters of nostoclide compounds I and II.

At first, there was the study of the structures of nostoclide in the PubChem repository[9]then the rendering of the structures in the ACD / chemSketch® [10] software (freeware), where it was possible to obtain some physical-chemical and molecular properties of the structures. The Avogadro[11] program was also used to determine the properties of atoms and properties of bonds.

According to this context, calculations were obtained by virtual simulations at the quantum level through the semi-empirical method (Austin Model 1 - AM1) [12-13], using the Hartree-Fock SFC (HF-SCF) approach, open shell (UHF) -Unrestricted Hartree-Fock), with a maximum number of 300 interactions, (1000 cycles), with a convergence value of 10-10 kcal mol-1 [14-15]. Using the output files and considering the molecule in the ground state, energy minimization and geometry optimization were obtained, conformational analysis of the structures exploring the spatial arrangements / energetically favorable forms of a molecule, Mulliken population analysis and the surface map electrostatic potential (MEP) [16-17]. All simulation calculations were performed using the algorithms available in the ArgusLab [18-19] code.

III. RESULTS AND DISCUSSION

Through resources available in the free access repositories for the study of drugs already approved, the structures of nostoclide I and II were obtained in the database of molecules operated and maintained by the National Center for Biotechnology Information, which is part of the National Library of Medicine , PubChem (https://www.ncbi.nlm.nih.gov/), with the purpose of obtaining accurate information about these molecules and the study literature [20]in the current database available on the network . According to Estacio [21], the first step involved in molecular modeling studies is to draw the structure of the molecule. The graphic representation of a chemical substance shows how its atoms are arranged and connected to each other, allowing the researcher to understand and analyze the molecule in different three-dimensional visualizations [22]. Since the physical, chemical and biological properties of a molecule are directly linked to its three-dimensional and conformational structure, nucleotide structures I and II have been designed (figure 1)



Nostoclide I

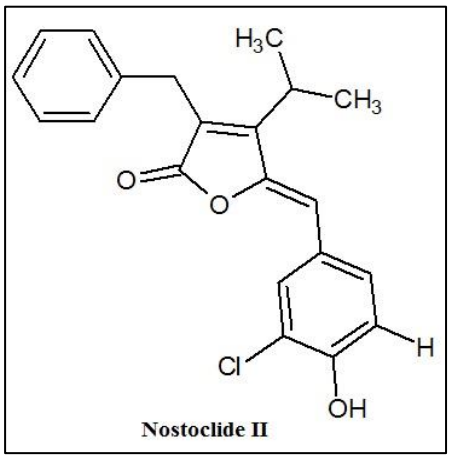


Fig.1. Two-dimensional structures of γ-alkylidenobutenolides, nostoclide I and II.

When rendering the two-dimensional structure, it was possible to obtain the basic molecular properties for the structures under study. The nostoclide compound I, has molecular formula C21H18Cl2O3, formula weight 354.82676, molar refractivity 105.12 ± 0.3 cm3, molar volume 286.0 ± 3.0 cm3, density 1.360 ± 0.06 g / cm3, polarizability 41, 67 ± 0.5 10-24 cm3. While the nostoclide II molecule, it presents molecular formula C21H19ClO3, formula weight 389.27182, molar refractivity 100.22 ± 0.3 cm3, molar volume 274.1 ± 3.0 cm3, density 1.294 ± 0.06 g / cm3, polarizability 39 , 73 ± 0.5 10-24 cm3.

The work sought to investigate the physical-chemical and electronic properties of these molecules through quantum mechanics. The quantum mechanics evaluation methods aim to obtain the energy of the system by solving the Erwin Schrodinger equation (eq.1) that describes the electronic system structure and molecular interactions, basically comprising the study in ab initio, semi-empirical methods , functional density, among others (MORGON, 2000; SANTANA, 2009). In a simple way, the use of quantum methods is more precise in the results obtained, providing more detailed data on the electronic structure and chemical bonds (BARREIRO; RODRIGUES, 1996). The calculations are based on different methods that solve Schrodinger's equation a associated with a molecular Hamiltonian that leads to the evaluation of a large number of integrals [23]. In this context, based on mathematical methods in quantum mechanics, following the energy minimization process through AM1 calculations (Austim Model 1), the structures were subjected to semi-empirical calculations. Based on the studies carried out by Dewar and collaborators (1985) [12],[24], using the empirical methodology proposed by them, it was possible to perform a conformational analysis of the structures of nostoclide I and II (figures 2 and 3), Then using the files From the outset, a better visualization of structures was sought in the Avogadro software, exploring the spatial arrangements / energetically favorable forms of a molecule [25].

$$(H\Psi = E\ \Psi) \quad (1)$$

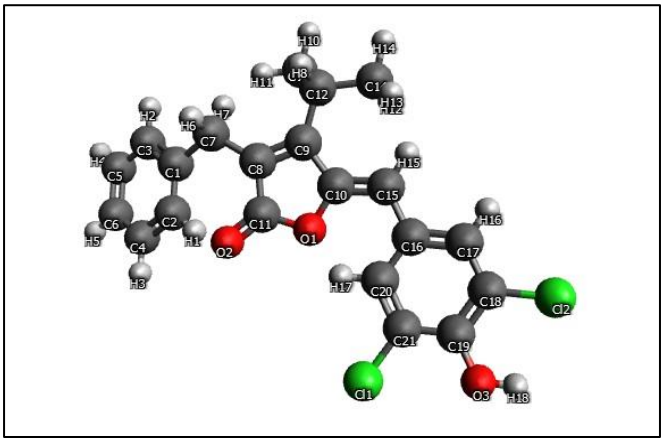


Fig. 2.Structural conformation of the nostoclide I.

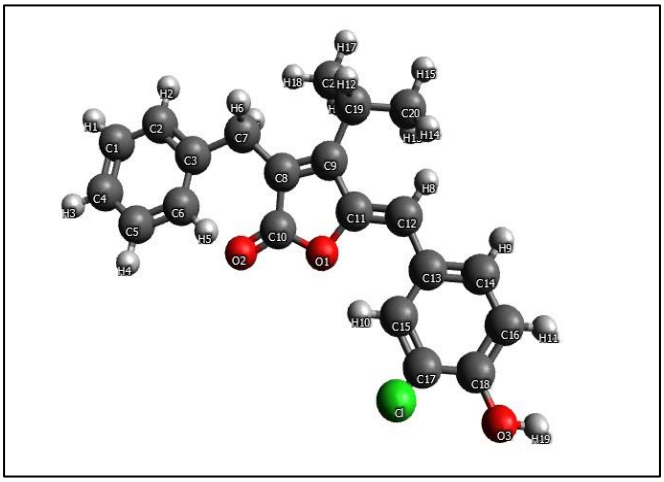


Fig. 3.Structural conformation of the nostoclide II.

Following the energy minimization process, calculations using the empirical method AM1 revealed that, for nostoclide I, energy is more stable (-170.49708 kcal mol-1) than nostoclide II (-158, 31564 kcal mol-1), presenting a variation of energy ΔE equal to -12.18144 kcal mol-1.

Therefore, it was also possible to calculate the formal charges of each atom and its valence of the nostoclide compounds I and II. The nostoclide structures presented carbon atoms with a valence variation between 3 and 4, oxygen valence 2, chlorine and hydrogen with valence equal to 1. It is important to highlight the variation in charges between the nostoclide I atoms (table I) , the carbon atom (C4) presented a minimum value of (-0.062) while in carbon (C10) it presented a maximum value of (0.342), oxygen atoms, as expected, presented negative values among them (O24) was more electronegative of all with a very high value (-0.505). Therefore, for the structure of Nostoclide II (table II) the charge variation was minimal between the two compounds, highlighting the carbon atom (C6) presented a minimum value of (-0.062) while the carbon (C10) presented the maximum value of (0.341), oxygen atoms, as expected, presented negative values among them (O26) was more electronegative of all with a very high value (-0.504).

Table I

Atomic properties of nostoclide I

Atom	**Element /type**		**Valence**	**Partial charge**
1	C	Car	3	-0.043
2	C	Car	3	-0.058
3	C	Car	3	-0.058
4	C	Car	3	-0.061
5	C	Car	3	-0.061
6	C	Car	3	-0.062
7	C	C3	4	0.005
8	C	C2	3	0.048
9	C	C2	3	0.008
10	C	C2	3	0.341
11	C	C2	3	0.136
12	O	O3	2	-0.422
13	O	O2	2	-0.245
14	C	C3	4	-0.018
15	C	C3	4	-0.059
16	C	C3	4	-0.059
17	C	C2	3	-0.012
18	C	Car	3	-0.019
19	C	Car	3	-0.032
20	C	Car	3	0.084
21	C	Car	3	0.153
22	C	Car	3	-0.032
23	C	Car	3	0.084
24	Cl	Cl	1	-0.080
25	Cl	Cl	1	-0.080
26	O	O3	2	-0.504

Table II

Atomic properties of nostoclide II

Atom	**Element /type**		**Valence**	**Partial charge**
1	C	Car	3	-0.061
2	C	Car	3	-0.058
3	C	Car	3	-0.043
4	C	Car	3	-0.062
5	C	Car	3	-0.061
6	C	Car	3	-0.058
7	C	C3	4	0.005
8	C	C2	3	0.048
9	C	C2	3	0.008
10	C	C2	3	0.341
11	C	C2	3	0.136
12	O	O3	2	-0.422
13	C	C2	3	-0.012
14	C	Car	3	-0.020
15	C	Car	3	-0.051
16	C	Car	3	-0.033
17	C	Car	3	-0.018
18	C	Car	3	-0.083
19	C	Car	3	0.135
20	O	O2	1	-0.245
21	C	C3	4	-0.018
22	C	C3	4	-0.059
23	C	C3	4	-0.059
24	O	O3	2	-0.505
25	Cl	Cl	1	-0.080

One way to evaluate the charge distribution of a molecule is through the population analysis of Mulliken [26], it is a very precise and expanded calculation method among chemists, obtained directly by a self-

consistent field calculation (SFC, Self-Consistent-Field) [27]. Following the same empirical calculation parameters, the preliminary study of Mulliken's atomic charges was sought [28][29]. Table 3 shows the values for each charge, which made it possible to highlight some values in the atoms present in the nostoclide molecules I and II. According to these data, it highlights the possible probable sites in the drug / receptor interaction for nostoclide I, the carbonyl group (O13 = C11), as expected, the oxygen and chlorine atoms showed a higher electronic density, mainly in hydroxyl (O26– H44) and Cl25, which highlights these regions, as being nucleophilic sites. As for nostoclide II, hydroxyl (O24 – H44) showed a higher electronic density and chlorine compared to structure I showed a lower electronic density, called nucleophilic regions.

Also according to the studies carried out it was possible to analyze some descriptors (chemical bonds) of the compounds, such as bond type, bond order, rotation and length in Angstrom (Å)[30]. Considering tables (IV and V), the nostoclide compounds did not show rotation, the binding order varies between 1 and 2 in all carbon-carbon, carbon-oxygen, carbon-chlorine bonds. As for the carbon-hydrogen and oxygen-hydrogen bonds, they present a connection order of 1. The nostoclide I structure highlights the carbon-carbon (CC) bonds, with a minimum value of 1.3857 (Å) while the maximum value (CC) of 1.53248 (Å). The carbon-oxygen (C-O) bonds show the values of length (Å) very close with small variations between 1.20932 (Å) to 1.35894 (Å). Carbon-hydrogen (C-H) bonds, on the other hand, showed values between 1,032 (Å) and 1.07 (Å), and hydroxyl showed a value of 0.937 (Å).

Table III

Mulliken atomic charges from Nostoclide

Nostoclide I		**Nostoclide I**	
Atom	**Charge**	**Atoms**	**Charge**
1 C	-0.1272	1 C	-0.1205
2 C	-0.0998	2 C	-0.1071
3 C	-0.1814	3 C	-0.1870
4 C	-0.2108	4 C	-0.2098
5 C	-0.2011	5 C	-0.1976
6 C	-0.1906	6 C	-0.1960
7 C	-0.1413	7 C	-0.1377
8 C	-0.1906	8 C	-0.1937
9 C	-0.0597	9 C	-0.1205
10 C	0.0204	10 C	-0.0027
11 C	0.3704	11 C	0.3849
12 O	-0.1980	12 O	-0.2664
13 O	-0.2890	13 O	-0.3072
14 C	-0.1124	14 C	-0.1218
15 C	-0.3501	15 C	-0.3462
16 C	-0.3543	16 C	-0.3487
17 C	-0.1486	17 C	-0.2136
18 C	-0.0890	18 C	-0.1360
19 C	-0.1123	19 C	-0.1375
20 C	-0.1739	20 C	-0.2816
21 C	0.1339	21 C	0.1033
22 C	-0.1172	22 C	-0.0990
23 C	-0.1090	23 C	-0.1088
24 Cl	0.0066	24 O	-0.2913
25 Cl	-0.0261	25 Cl	-0.0035
26 O	-0.2892		

Table IV

Structural descriptors (chemical binding) nostoclide I

Start storm	**End storm**	**Bond order**	**Rotable**	**Length(Å)**
C1	C2	1	No	1.38845
C1	C3	2	No	1.38587
C1	C7	1	No	1.53146
C2	C4	2	No	1.38483
C3	C5	1	No	1.38685
C4	C6	1	No	1.38411
C5	C6	2	No	1.3857
C7	C8	1	No	1.52506
C8	C9	2	No	1.33481
C8	C11	1	No	1.45891
C9	C10	1	No	1.48197
C9	C12	2	No	1.33959
C10	C15	1	No	1.34227
C11	O1	2	No	1.35894
C11	O2	2	No	1.20932
O1	C10	1	No	1.36704
C12	C13	1	No	1.53248
C12	C14	1	No	1.53236
C15	C16	1	No	1.48227
C16	C20	1	No	1.38905
C17	C18	1	No	1.38843
C17	C16	2	No	1.38711
C18	C19	2	No	1.38723
C18	Cl2	1	No	1.72341
C19	C21	1	No	1.38483

C19	O3	1	No	1.35897
C20	C21	2	No	1.38245
C21	Cl1	1	No	1.72284
C2	H1	1	No	1.032
C3	H2	1	No	1.032
C4	H3	1	No	1.032
C5	H4	1	No	1.032
C6	H5	1	No	1.032
C7	H6	1	No	1.07
C7	H7	1	No	1.07
C12	H8	1	No	1.07
C15	H9	1	No	1.07
C16	H10	1	No	1.07
C19	H11	1	No	1.07
C20	H12	1	No	1.07
C20	H13	1	No	1.07
C20	H14	1	No	1.07
C21	H15	1	No	1.032
C21	H16	1	No	1.032
C21	H18	1	No	1.032
O3	H19	1	No	0.937

Table V
Structural descriptors (chemical binding) nostoclide II

Start storm	**End storm**	**Bond order**	**Rotable**	**Length(Å)**
C1	C2	1	No	1.38589
C2	C3	2	No	1.38638
C3	C4	2	No	1.38525
C4	C5	1	No	1.38476
C5	C6	2	No	1.38478
C6	C3	1	No	1.3866
C3	C7	1	No	1.52271
C7	C8	1	No	1.52859
C8	C9	2	No	1.33201
C8	C10	1	No	1.46564
C9	C11	1	No	1.47267
C10	O1	1	No	1.3728
O1	C11	1	No	1.34227
C11	C12	2	No	1.34227
C12	C13	1	No	1.47451
C13	C14	2	No	1.3862
C13	C15	1	No	1.38682
C14	C16	1	No	1.3856
C15	C17	2	No	1.38596
C16	C18	2	No	1.38519
C18	C17	1	No	1.38615
C10	O2	2	No	1.21048
C9	C19	1	No	1.53123
C19	C20	1	No	1.53139
C19	C21	1	No	1,52893
C18	O3	1	No	1.35984
C17	Cl	1	No	1.04919
C1	H1	1	No	1.03200
C2	H2	1	No	1.03200
C4	H3	1	No	1.03200
C5	H4	1	No	1.03200
C6	H5	1	No	1.03200
C7	H6	1	No	1.0700
C7	H7	1	No	1.0700
C12	H8	1	No	1.03200
C14	H9	1	No	1.03200
C15	H10	1	No	1.03200
C16	H11	1	No	1.03200
C19	H12	1	No	1.07000
C20	H13	1	No	1.07000
C20	H14	1	No	1.07000
C20	H15	1	No	1.07000
C21	H16	1	No	1.07000
C21	H17	1	No	1.07000
C21	H18	1	No	1.07000
O3	H19	1	No	0.93700

Another way to evaluate the electronic properties of a molecule is through the electrostatic potential (MEP, from the English Electrostatic Potential Maps), used to interpret electrophilic and nucleophilic reactions [31]. The molecular electrostatic potential (MEP), is calculated through a grid of points located in different layers around the molecule, built from the Van Der Waals spheres in each atom, resulting in the three-dimensional surfaces revealing possible regions of attraction and repulsion of the structure through color variation [32][33]. However, it is possible to identify regions that have the presence of a greater electronic density, the warm tones that tend to red, indicate regions of attraction, which are located a partial negative charge (δ-) and the cooler tones (with a tendency in blue) represent the repulsion regions, where a positive partial charge (δ +) is located[34][35][36]. The electrostatic potential map (figures 4 and 5) shows

the electronic densities of the nostoclide compounds I and II. Analysis of the MEP of the nostoclide compounds I and II shows that the oxygen atoms attached to the lactonic ring (O13 = C11) and the hydroxyl group attached to the aromatic ring substituent (O26 = H44) attract the electronic density of the negative formal charge, which due to its electronegative character it pulls the electrons towards you leaving the carbon atoms, with its hydrogen carrying the positive formal charge.

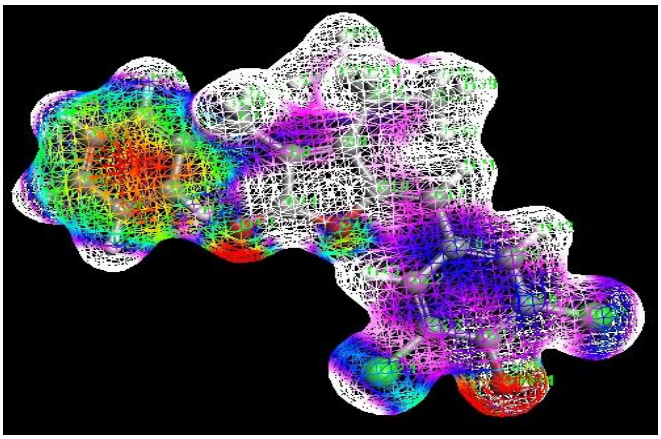


Fig. 4.Potential surface map of nostoclide I

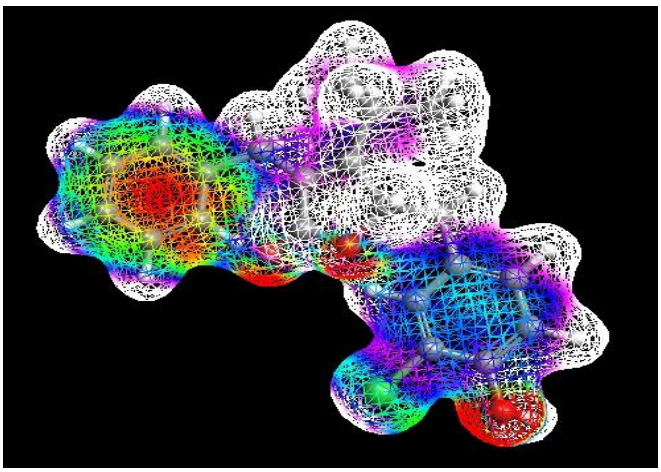


Fig. 5.Potential surface map of nostoclide II

By performing Hamiltonian mechanical-quantum calculations[24][22], the energies of the HOMO and LUMO orbitals of the nostoclide compounds I and II were also obtained. Figure 6 shows, the highest occupied molecular orbital (HOMO, in English highest occupied molecular orbital), is shown by the red and blue continuous lobes, with energy equal to 0.312995 eV. Most of the volume represented by the HOMO corresponds to the empty p orbital in the sp2 hybridized state present in the aromatic ring through the interactions between the π ligand orbital. The lowest energy unoccupied molecular orbital (LUMO, in English lowest unoccupied molecular orbital, shown by the red and blue lobes energy equal to -0.042910 eV, the LUMO orbital is located on the protoanemonine atoms, exercised by the π C8, C9, C11 and O13.

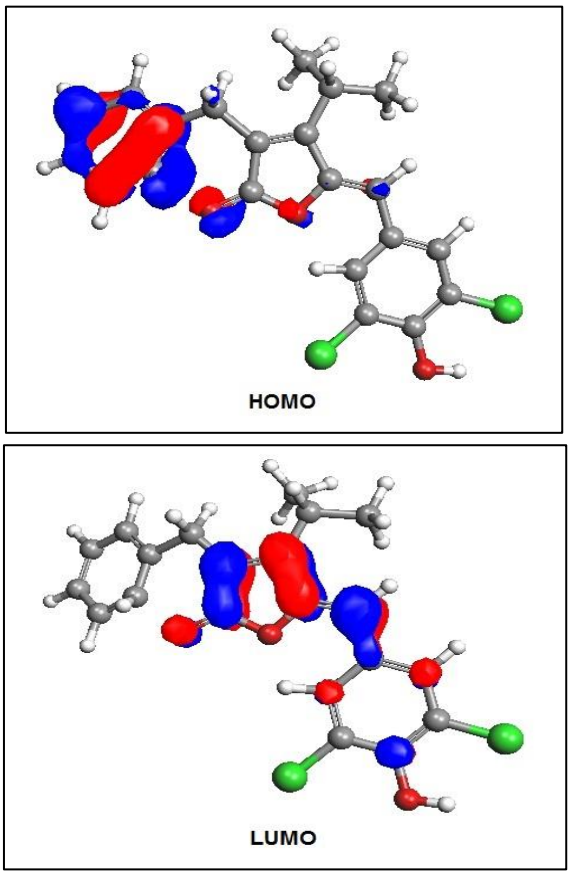


Fig. 6. Three-dimensional rendering of the Frontier orbitals of Nostoclide I.

Figure 7 shows the molecular orbits of the nostoclide compound II, since most of the volume represented by the HOMO with energy equal to -0.315115eV, corresponds to the hybridized state sp2 present in the carbon atoms C11, C14, C15, C16 and C18 , the chlorine atom and the hydroxyl oxygen atom. In the LUMO orbital of nostoclide II it presented an energy equal to -0.027009eV, there were no changes in its formation in relation to the atoms of the LUMO orbital of nostoclide I, being located on the atoms of the protoanemonine, exercised by the π bonds of carbon.

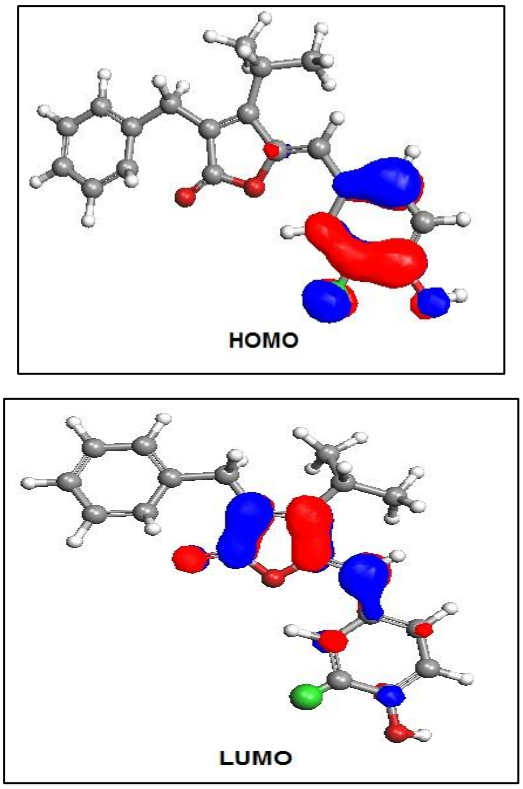


Fig. 7. Three-dimensional rendering of the Frontier orbitals of Nostoclide II.

From the energies of the HOMO-LUMO orbitals it was possible to obtain GAP (ΔEHOMO – LUMO) an important indicator of molecular stability. This molecular descriptor is related to the reactivity of the molecule, indicating that a high GAP value indicates high stability of the molecule (low reactivity) in chemical reactions, while molecules with a low GAP value are generally reactive (DA SILVA et al., 2017). For the nostoclide I compound, the GAP was equivalent to -0.270085eV, while the nostoclide II GAP was -0.288106eV, the energy required for the first quantum leap (MARINHO et al., 2019).

IV. CONCLUSIONS

Using the semi-empirical quantum formalism, it was possible to electronically and structurally characterize nostoclide I and II, obtaining their thermodynamically more stable conformational structures, characterize the distribution of charges both in atomic terms and on the surface of the molecule, and through the frontier orbitals to obtain the reactivity descriptors, the results of this work being a fundamental step in the process of developing new therapeutic agents..

V. ACKNOWLEDGMENT

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