

# **In Silico Characterization of the Amburoside D Compound Using MMFF94 Classic Force Field**

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**Abstract—** The worldwide interest in medicines obtained from medicinal plants has grown significantly. This is due to the significant contribution of the plant kingdom in the supply of substances useful for the treatment of diseases that affect mankind and the difficulty of obtaining some substances with complex molecular structures through synthetic processes. Found in the Semiarid region, *Amburanacearensis* A.C. Smith (Leguminosae - Papilionoideae), better known as cumaru, has chemical features that contain pharmacological characteristics of extreme importance for the therapy of some diseases. Thus, the present work aimed to characterize Amburoside D, derived from *Amburanacearensis*, in silico, as an initial step for the creation of new drugs. The molecular structure characterized using the classic force field MMFF94, obtaining the potential energy (508,735 kJ · mol<sup>-1</sup>), the dipolar moment (2,491), the ligant angles, the torsion, the ligant lengths and the representation of Van der Waals surface. The present work is an initial step for future studies of semi-empirical molecular modeling and molecular docking, seeking to optimize the biological potential of this compound.

**Keywords—** Amburoside D. MMFF94. Molecular modeling. Theoretical chemistry.

## I. INTRODUCTION

Currently there has been a significant increase in worldwide interest in medicines obtained from medicinal plants [1]. This is due to the growing use of herbal products [2]. Another reason for this growth is the significant contribution of the plant kingdom in the supply of substances useful for the treatment of diseases that affect humanity [3]. In addition, it is difficult to obtain some substances with complex

molecular structures by synthetic processes [3]. For the development of these new drugs, it has been using drug design techniques, which seeks to develop more efficient drugs with less side effects. Often a molecular skeleton (pharmacophorus) is used as a starting point for modifications, which are generally taken from naturally occurring bioactive substances [4]. Found in the Semiarid region, *Amburanacearensis* AC Smith (Leguminosae - Papilionoideae), better known as cumaru, has chemical aspects that contain extremely important pharmacological characteristics for the therapy of some diseases, such as asthma, rheumatism, bronchitis, among others [5]. Due to the wide use of *A. cearensis* for therapeutic purposes, it has become indispensable for scientific studies to justify its use as a herbal medicine [6].

Molecular modeling comprises a set of tools with the function of building, editing, visualizing, analyzing and storing complex molecular systems [7] providing the complete characterization of a structure [8], allowing the rational planning of drugs using certain parameters that relate structure and activity [9]. Thus, using in silico methods and theoretical calculations, computational chemistry characterizes the compounds [10], generating relevant indices for drug planning such as: minimum potential energy, heat formation, dipole moment and also structures with high fidelity rate. to native structures with stable conformational geometry [11].

Molecular Mechanics or force-field methods use classical type models to predict the energy of a molecule as a function of its conformation. This

allows predictions of Equilibrium geometries, transition states and Relative energies between conformers or between different Molecules. In molecular mechanics, molecules are described as a set of "atoms connected," rather than nuclei and electrons, as in quantum methods. The model of molecular mechanics is justifiable because the parameters associated with sets of atoms remain fairly constant between different structures, provided that the type and hybridization of the involved atoms are the same. What is done in the molecular mechanics is to develop the so-called force field, a set of energy functions that determine energetic penalties for moving away from the structure of these "normal" values [12-13], seeking to minimize energy, ie, uses a mathematical algorithm seeking to achieve a minimum state of energy, where the attractive forces are maximized and the value of the repulsive forces is reduced (Equation 1) (Fig.1).

$$E = \sum k_b (r - r_0)^2 \quad (1)$$

Express energy due to stretching bonds as a Taylor series about the equilibrium position  $r_e$  (EQUATION 2):  $E(R) = k_2(R - r_e)^2 + k_3(R - r_e)^3 + \dots$  (2), Where  $R$  is a ligant length. The first term should dominate,  $k_2$ ,  $k_3$  are parameters of adjustments, obtained experimentally or by quantum mechanics, Having as main idea the use of constants for other molecules, since Most C – H bond lengths are 1.06 to 1.10 ° A in, with stretching frequencies between 2900 and 3300  $\text{cm}^{-1}$ . This strategy is refined using different "atom types [14] field of force MMFF94 (Merck Molecular Force Field 94), which is a " classical force field ", where the atoms and their chemical bonds are treated as spring-mass type systems, reproducing very well the computational data used in their parameterization. In addition, MMFF94 reproduces experimental bond lengths (0.014 Å mean square root [rms]), bonding angles (1.2° rms), vibrational frequencies (61  $\text{cm}^{-1}$  rms), conformational energies (0.38 kcal / mol / rms) and rotating barriers (0.39 kcal / mol rms) almost as well as MM3 for comparable systems [15]. Being banant used particularly well with organic compounds. The MMFF94 was

specifically parameterized for organic compounds [16].

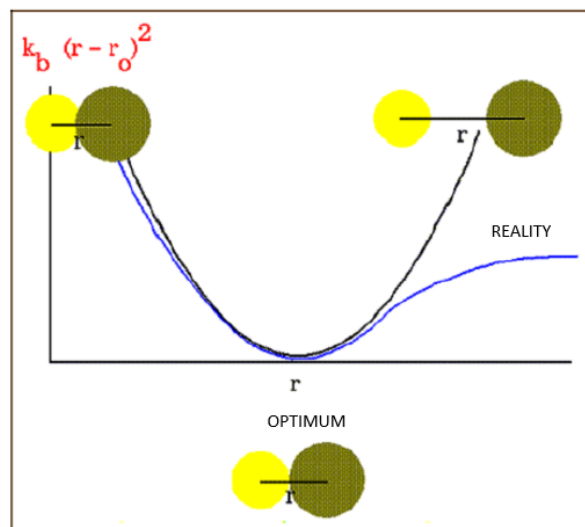


Fig. 1 Energy depending on the connection distance described by the model of molecular mechanics in Source: Sant'Anna (2000).

In this context the present work aimed to use the force field MMFF94 to characterize in silico amburoside D as an initial step for the development of new drugs.

## II. METHODOLOGY

Using the methodology proposed by Dewar and collaborators [17], the first step of the work was to obtain essential information of the compound, such as the two-dimensional molecular structure of the Amburoside D compound and its physicochemical properties. These data were obtained through the molecular modeling programs MarvinSketch [18] [19] and ChemSketch [20]. Then, for the geometric optimization of the molecule through classical force field calculations (MMFF94), the freeware Avogadro® [16] [21-22] configured for cycles of 100 interactions of the descending steepest algorithm was used. In this way it was possible to obtain the lowest potential energy conformation of the compound, characterizing the torsion angles, the bonds and the dihedral angles, besides rendering the surface map of Van der Waals and visualizing the dipole moment. All mechanical force field (MMFF94) calculations were performed using Avogadro® open license software [17], [21], [22] (version 1.2.0).

### III. RESULTS AND DISCUSSIONS

As for the structure in question, Amburoside D, the MarvinSketch [18-19] program was used to obtain the initial structure and some other physical chemical properties (Table I) necessary to study the structure in molecular modeling, highlighting the coefficient. LogP (0.96), the solubility of the structure in water (0.06 mg / mL) that allowed to define the solvent (polar or nonpolar) used in docking tests or molecular dynamics and also its ability to form hydrogen bonds when determining atoms with potential to receive or donate electrons in hydrogen ligands.

TABLE I  
Physico-chemical properties of compound  
Amburosideo D

Property	Value	Property	Value
Solubility in water	0.06 mg/mL	Polar Surface	172.21
LogP	0.96	Refractivity	109.93
Receptors #H	9	Donors #H	5

Other physical and chemical properties (Table II) could be obtained through the ChemSketch program [20], properties linked to the structural composition of the molecule, of which we can highlight its density ( $1.493 \pm 0.06$  g cm<sup>3</sup>) and its surface tension (67, 6  $\pm$  3.0 dyne cm).

TABLE II  
Physical-chemical properties of the compound  
Amburosideo D

Properties	Value	Properties	Value
Molecular Formula	C <sub>22</sub> H <sub>24</sub> O <sub>11</sub>	Monoisotopic Mass	464.131862 Da
Density	1.493 $\pm$ 0.06 g/cm <sup>3</sup>	Refractive index	1.636 $\pm$ 0.02
Superficial tension	67.6 $\pm$ 3.0 dyne/cm	Molar Refractivity	111.48 $\pm$ 0.3 cm <sup>3</sup>
Molar Volume	310.9 $\pm$ 3.0 cm <sup>3</sup>	Polarizability	44.19 $\pm$ 0.510 <sup>-24</sup> cm <sup>3</sup>

The two-dimensional structure of the Amburoside D compound [Fig. 2], obtained through MarvinSketch [18-19], was then in its ground state, presenting only the molecular formula (C<sub>22</sub>H<sub>24</sub>O<sub>11</sub>) and the connectivity of atoms, with an initial conformation of easy to visualize but with potential energy different from the molecule in its native form.

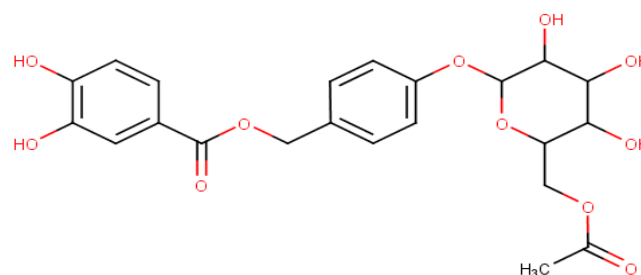


Fig. 2 The two-dimensional structure of Amburosideo D

By drawing a molecule two-dimensionally or drawing it from an online repository, it is not in its most stable conformation. Thus, to obtain more accurate calculations about the molecule and its more stable final conformation, we need to perform a geometric optimization that uses the energy minimization process [23]. This geometric optimization can be performed using the Avogadro® open license software [17] [21] [22], configuring it to perform uninterrupted interaction cycles calculated using the force field MMFF94, parameterized with the Steepest Descent algorithm. The goal of using molecular mechanics is because it represents molecules as a set of connected atoms, thus developing energetic functions that maximize attraction forces and reduce repulsion forces [12] [13]. Therefore, the obtained structure [Fig. 3], considered theoretically more stable, has a spatial distribution that allows the lowest possible potential energy, causing the integral potential energy of the molecule to assume a value of (508,735 kJ · mol<sup>-1</sup>), no longer varying, reaching a stationary point of the energy surface [7].

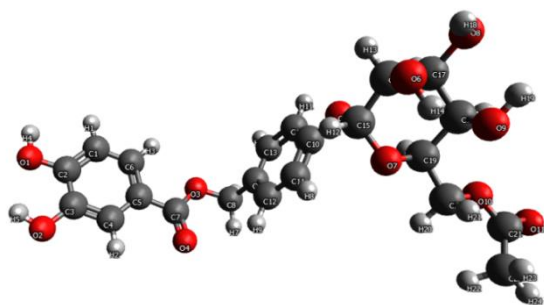


Fig. 3 Optimized structure of the compound Amburoside D using the force field MMFF94

After geometric optimization, the molecule a theoretically more stable structure, it was possible to calculate the formal and partial charges of all atoms as well as their valence. All atoms showed zero formal charge and significant variations in their partial charges were found, such as Hydrogen from 0.034 to 0.292, Carbon from -0.052 to 0.340 and Oxygen from -0.503 to -0.245. These data [Table III], especially valence, correspond to the literature, which serves to validate the results obtained.

Despite the neutrality through optimization, it is possible to observe in the results obtained [Table III] the largest and smallest (residual) partial loads. Atoms 9 (C) and 7 (O) were found to have a larger and smaller partial charge respectively, charges from the electrons being closer or farther from one of the ligant atoms, carrying charge [24].

TABLE III

Atomic properties of the Amburoside compound D obtained after optimization using the field of force classic MMFF94 (Except Hydrogens)

Atom	Elementtype		Valence	Partialchange
1	C	Car	3	-0.016
2	C	Car	3	0.158
3	C	Car	3	0.159
4	C	Car	3	-0.003
5	C	Car	3	0.063
6	C	Car	3	-0.044
7	O	O3	2	-0.503
8	O	O3	2	-0.503
9	C	C2	3	0.340
10	O	O3	2	0.456
11	O	O2	1	-0.245
12	C	C3	4	0.118
13	C	Car	3	-0.010

14	C	Car	3	0.124
15	C	Car	3	-0.019
16	C	Car	3	-0.052
17	C	Car	3	-0.052
18	C	Car	3	-0.019
19	O	O3	2	-0.461
20	C	C3	4	0.231
21	C	C3	4	0.145
22	O	O3	2	-0.383
23	C	C3	4	0.115
24	C	C3	4	0.113
25	C	C3	4	0.125
26	O	O3	2	-3.330
27	O	O3	2	-0.386
28	O	O3	2	-0.386
29	C	C3	4	0.121
30	O	O3	2	-0.462
31	C	C2	3	0.304
32	C	C3	4	0.033
33	O	O2	1	-0.251

In the final geometry of Amburoside D after optimization, all the bonds analyzed were characterized by the predominance of covalence, where we can highlight the bonds between oxygen-carbon ((O11 - C21) and (O4 - C7)) as second order bonds, and carbon bonds ((C15 - C16), (C19 - C18), (C17 - C16), (C18 - C17) and (C20 - C19) are rotatable [Table IV].

TABLE IV

Properties of Amburoside D After Optimization Using Classical Forcefield MMFF94

InitialAtom	FinalAtom	Order of Bond	Rotability	Length(Å)
O11	C21	2	NO	1.227050
H24	C22	1	NO	1.094430
C21	C22	1	NO	1.500560
C21	O10	1	NO	1.354600
C22	H22	1	NO	1.092200
C22	H23	1	NO	1.092140
O10	C20	1	NO	1.438780
H16	C18	1	NO	1.095770
H20	C20	1	NO	1.096310
C20	H21	1	NO	1.095480
C20	C19	1	YES	1.532800
H17	C19	1	NO	1.097650

C19	C18	1	YES	1.537940
C19	O7	1	YES	1.437710
C18	O9	1	NO	1.441380
C18	C17	1	YES	1.534470
H15	C17	1	NO	1.095810
H19	O9	1	NO	0.979358
H6	C8	1	NO	1.096210
H10	C13	1	NO	1.087620
H11	C14	1	NO	1.087380
C17	O8	1	NO	1.438900
C17	C16	1	YES	1.536760
C13	C14	2	NO	1.397090
C13	C9	1	NO	1.399030
O8	H18	1	NO	0.980209
H7	C8	1	NO	1.096920
C14	C10	1	NO	1.397010
O7	C15	1	YES	1.436370
C8	C9	1	NO	1.506580
C8	O3	1	NO	1.432610
C9	C12	2	NO	1.400730
O5	C10	1	NO	1.366850
O5	C15	1	NO	1.430540
C10	C11	2	NO	1.393820
C12	C11	1	NO	1.399180
C12	H9	1	NO	1.089670
C11	H8	1	NO	1.085530
C15	C16	1	YES	1.541820
C15	H12	1	NO	1.097460
C16	H13	1	NO	1.095750
C16	O6	1	NO	1.442200
H14	O6	1	NO	0.983287
O3	C7	1	NO	1.354650
O4	C7	2	NO	1.220440
C7	C5	1	NO	1.488390
H3	C6	1	NO	1.087820
C5	C6	2	NO	1.407200
C5	C4	1	NO	1.400720
C6	C1	1	NO	1.399800
H2	C4	1	NO	1.087100
C4	C3	2	NO	1.387780
C1	H1	1	NO	1.085460
C1	C2	2	NO	1.389040
C3	C2	1	NO	1.393090
C3	O2	1	NO	1.365500
C2	O1	1	NO	1.366840
O2	H5	1	NO	0.978068
O1	H4	1	NO	0.972846

About the conformational characterization, all angles between the bonds and the torsion angles could be calculated. Taking as examples of greater and smaller angles between joints, the angles (C11 - C10 - O5) and (C18 - O9 - H19) with  $126.2229^\circ$  and  $104.6334^\circ$  respectively; also, for example, the largest and smallest torsion angles, the systems (C6 - C1 - C2 - O1) and (H11 - C14 - C10 - C11) with  $179.9974^\circ$  and  $-179.9754^\circ$  respectively.

Regarding the properties calculated using the Avogadro® software, it is possible to calculate the dipolar moment ( $\mu$ ) of the structure which, motivated by the electronegativity difference between atoms, is related to the way the electric charges are distributed by the molecule and the polarization, separation between positive and negative charges [24]. Some other properties of the structure are directly linked to the dipolar moment ( $\mu$ ), such as melting and boiling points and their solubility in water [25]. Brivaracetam had a dipolar moment ( $\mu$ ) estimated at 2,491 D, characterizing the molecule as polar.

Finally, the software also allows rendering and visualization of the surface of Van der Waals [figure 4]

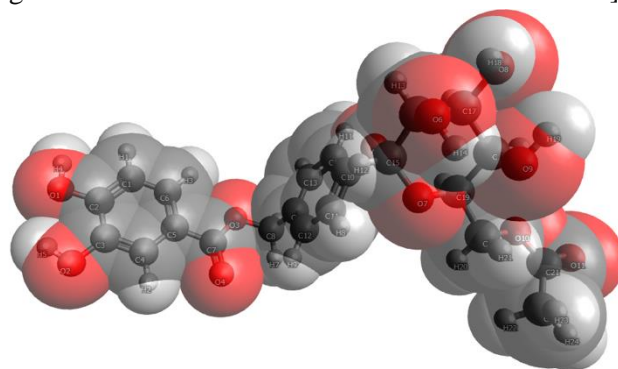


Fig. 4 Van der Waals surface of the Amburoside D.

#### IV. CONCLUSIONS

The molecular structure of the Amburoside D compound was geometrically optimized by classical force field calculations using Avogadro® freeware configured in MMFF94 steepest descent to the point of lowest potential energy, achieving theoretically more stable and more stable conformation. Close to its native form, obtaining at the end of this process the energy of  $[508,735 \text{ kJ} \cdot \text{mol}^{-1}]$  and dipolar momentum

(2,491 D). It was possible to realize that all atoms had zero formal charge and significant variations in their partial charges were found, such as hydrogen from 0.034 to 0.292, carbon from -0.052 to 0.340 and oxygen from -0.503 to -0.245. In addition, atoms 9 (C) and 7 (O) presented higher and lower partial charge respectively. After optimizing the structure it was possible to calculate the covalence-predominant bond lengths, where we can highlight the bonds between oxygen-carbon ((O11 - C21) and (O4 - C7)) as second order bonds, and the bonds between carbons ((C15 - C16), (C19 - C18), (C17 - C16), (C18 - C17) and (C20 - C19)) for their rotability. In relation to the conformational characterization, a greater and smaller angulation between bonds was obtained, highlighting (C11 - C10 - O5) and (C18 - O9 - H19) with 126.2229 ° and 104.6334 ° respectively; it was also possible to perceive the largest [179.9974 °] and smallest [-179.9754 °] torsion angles. In addition, the van der Waals surface of the structure was rendered. The data obtained constitute an initial step for future studies of semi-empirical molecular modeling and molecular docking, seeking to optimize this compound and its possible biological potential analogues.

## V. ACKNOWLEDGMENT

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## VI. REFERENCES

- [1] A. C. B. Carvalho, D. S. G. Nunes, T. G. Baratelli, N. S. M. S. A. Q. Shuqair, E. M. Neto, Aspectos da legislação no controle dos medicamentos fitoterápicos. T&C Amazônia, v. 5, n. 11, 2007.
- [2] A. R. A. Lopes, M. L. S. Vargas, A. S. S. Cavalcanti, A. G. Silva, Plantas e seus extratos -administração e biodisponibilidade de fitoterápicos aplicados na pele. Natureza online v.4, n.2, p.62-66, 2006.
- [3] C. A. Montanari, V. da S. Bolzani, Planejamento racional de fármacos baseado em produtos naturais. Quim. Nova, Vol. 24, No. 1, 105-111, 2001.
- [4] Awale, Suresh et al. Design and synthesis of functionalized coumarins as potential anti-austerity agents that eliminates cancer cells' tolerance to nutrition starvation. Bioorganic & medicinal chemistry letters, v. 29, n. 14, p. 1779-1784, 2019.
- [5] M.F. Agra, J. M. Barbosa Filho, Ethnomedicinal and phytochemical investigation of the Solanum species in the Northeast of Brazil. In: Nee, M., Symon, D.E., Lester, R.N., Jessop, J.P. (editors) Solanaceae IV. Kew: Royal Botanic Gardens, p.341-343. 1990.
- [6] K. M. Canuto, E. R. Silveira, A. M. E. Bezerra, L. K. A. M. Leal, G. S. B. Viana, Uso de Plantas Jovens de Amburana cearensis A. C. Smith: Alternativa para Preservação e Exploração Econômica da Espécie. Embrapa Semi-Árido, Petrolina, 2008.
- [7] E. J. Barreiro, C. R. Rodrigues, M. G. Albuquerque, C. M. R. de Sant'anna, R. B. de Alencastro, Molecular Modeling: A Tool for the Rational Planning of Drugs in Medicinal Chemistry. New Chemistry, v. 20, n.1, 1997.
- [8] M. Reges, M. M. Marinho, E. S. Marinho, In Silico Characterization of Hypoglycemic Agent Phenformin Using Classical Force Field MMFF94. International Journal of Recent Research and Review, v. 11, n. 2, p. 36-43, 2018.
- [9] N. C. Cohen, J. M. Blaney, C. Humblet, P. Gund, D. C. Barry, Molecular modeling software and methods for medicinal chemistry. Journal of medicinal chemistry, v. 33, n. 03, p. 883-894, 1990.
- [10] M. Reges, M. M. Marinho, E. S. Marinho, Semi-Empirical Study of the Drug Riociguat, an Important Drug for Oral Treatment against Chronic Thromboembolic Pulmonary Hypertension. International Journal of Scientific Engineering and Science, v. 01, n. 01, p. 13-17, 2017.
- [11] E. S. Marinho, M. M. Marinho, A DFT study of synthetic drug topiroxostat: MEP, HOMO, LUMO. International Journal of Scientific & Engineering Research, v. 07, n. 08, p. 1264-1270, 2016.
- [12] U. Oburkert and N. L. Allinger, Molecular Mechanics. ACS Monograph no 177, American Chemical Society, Washington, 1982
- [13] Carlos Mauricio R. Sant'Anna, "Molecular modeling methods for the study and planning of bioactive compounds: An introduction." Virtual Journal of Chemistry 1.1: 49-5, 2009
- [14] Y. Shao, et al. Advances in methods and algorithms in a modern quantum chemistry program package. Physical Chemistry Chemical Physics, v. 8, n. 27, p. 3172-3191, 2006.
- [15] T. A. Halgren, J. Comput. Chem. 17, 490. DOI: [http://dx.doi.org/10.1002/\(SICI\)1096-](http://dx.doi.org/10.1002/(SICI)1096-)

[987X\(199604\)17:6<490::AID-JCC1>3.3.CO;2-V](#),  
1996.

- [16] M. D. Hanwell, D. E. Curtis, D. C. Lonie, T. Vandermeersch, E. Zurek, G. R. Hutchison, «Avogadro: An advanced semantic chemical editor, visualization, and analysis platform». *J. Cheminform.* 4 (1). 17 páginas. PMC 3542060 PMID 22889332. doi:10.1186/1758-2946-4-17,2012.
- [17] M. J. Dewar, E. G. Zoebisch, E. F. Healy, J. J. Stewart, Development and use of quantum mechanical molecular models. 76. AM1: a new general purpose quantum mechanical molecular model. *Journal of the American Chemical Society*, 107(13), 3902-3909, 1985.
- [18] P. Csizmadia, “MarvinSketch and MarvinView: molecule applets for the World Wide Web. In Proceedings of ECSOC-3, the third international electronic conference on synthetic organic chemistry, September 1-30(p. 367-369). 1999.
- [19] Using MarvinSketch’, C. 5.5. 1.0, ChemAxonKft, Hungary.
- [20] ACD/ACD/Chemsketch®. Advanced Chemistry Development, Inc. ACD/Labs Release:12.00, version 12.01, Build 30815, 10 Feb. 2009.
- [21] R. Mera-Adasme, F. Mendizbal, C. Olea-Azar, S. Miranda-Rojas, P. Fuentealba, «A Computationally Efficient and Reliable Bond Order Measure». *J. Phys. Chem. A.* 115 (17): 4397-4405. PMID 21469689. doi:10.1021/jp107498h, 2011.
- [22] M. Saliccioli, W. Yu, M. A. Barteau, J. G. Chen, D. G. Vlachos, «Differentiation of O-H and C-H Bond Scission Mechanisms of Ethylene Glycol on Pt and Ni/Pt Using Theory and Isotopic Labeling Experiments». *J. Am. Chem. Soc.* 133 (20): 7996-8004. PMID 21526776. doi:10.1021/ja201801t, 2011.
- [23] I. Carvalho, M. T. Pupo, Á. D. L. Borges, L. S. C. Bernardes, Introduction to molecular modeling of drugs in the experimental course of pharmaceutical chemistry. *New Chemistry*, v. 26, n. 03, p. 428-438, 2003.
- [24] J. C. Kotz, P. Treichel, J. R. Townsend, Bonding and Molecular Structure. *Chemistry and chemical reactivity*, v. 07, 2009.
- [25] P. W. Atkins, L. Jones, Principles of chemistry: questioning modern life and the environment. 3.ed. Porto Alegre: Bookman, 2006.