CHARACTERIZATION OF THE NATURAL PESTICIDE 6-DESOXYCLITORIACETAL: A QUANTUM STUDY

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Abstract— Currently Brazil occupies a prominent position in the world supply of cereals, fruits and other products of plant origin, so it is necessary to use insecticides to control pests. Billions of dollars are spent on trying to control insects and misuse and indiscriminate over several decades has caused several problems, contamination of water and soil are just a few examples. The search for new insecticides that meet the requirements of efficacy, and safety can be found in plant extracts. Rothenoids are organic pesticides of natural origin that have less environmental impact and greater safety in agricultural use. In this context, the present work aimed to characterize electronically and structurally the rotenoid 6-Desoxyclitoriacetal. In order to perform the structural optimization, semi-empirical quantum methods were used to obtain reactivity descriptors such as HOMO (-9.74499 eV), LUMO (-0.85641 eV), GAP (8.88858 eV), minimum potential energy (-112382.1204 kcalmol-1) , dipole moment (μ) in length (2.54469635 debye), formation heat (-182.0760 kcal mo-1l), Mulliken's atomic charges and also its structure with stable conformational geometry. The obtained data consist of an initial stage for a comparative analysis between its analogues and fundamental for future studies of relations between the three-dimensional rotenoid structure and its biological activities.

Keywords: LUMO. HOMO. Pesticide. Rotenoids. Theoretical chemistry.

1 INTRODUCTION

Brazil is a country that has a huge diversity of insects and plants due to its climatic and geographical plurality. Currently, this country occupies a prominent position in the world supply of cereals, fruits and other products of plant origin, so it is necessary to use insecticides to control pests. Insecticides are chemicals, organic or inorganic, used to kill, attract and repel insects. Billions of dollars are spent trying to control insects [1]. In addition, incorrect and indiscriminate use over several decades has caused several problems such as accumulation of toxic waste in food, contamination of water and soil, intoxication of rural producers, selection of resistant pests, among other problems [2].

The search for new insecticides that meet the requirements of efficacy, safety and selectivity can be found through the study of plant defense mechanisms. Some plant extracts have been used by man since the Old Age until today, but few of these plants, including those containing pyrethrins, rotenoids and alkaloids, have been used as a source of insecticides. The rotenoids are organic pesticides of natural origin and the rotenones, among them 6-Desoxyclitoriacetal, as a prime example [1], which present less environmental impact and greater safety in agricultural use [3].

Molecular modeling comprises a set of tools with the function of constructing, editing, visualizing, analyzing and storing complex molecular systems [4], providing the complete characterization of a structure [5], allowing the rational planning of organic compounds using certain parameters that relate activity and structure [6]. Thus, using in silico methods and theoretical calculations, computational chemistry characterizes the compounds [7], generating relevant indexes for the planning of organic compounds such as: HOMO, LUMO,

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GAP, potential minimum energy, dipole moment, heat formation and also structures with stable conformational geometry [8]. In this context, the objective of the present work was to characterize the descriptors of the reactivity of rotenone 6-Desoxyclitoriacetal, through semi-empirical calculations, so that it can be used in future studies to optimize the biological potential of this rotenone.

2 METHODOLOGY

The first step in this work was to obtain the following information: the two-dimensional molecular structure of rotenoide 6-Desoxyclitoriacetal, nomenclatures, physico-chemical properties, and its mechanisms of obtained through PubChem® virtual repositories [https://pubchem.ncbi.nlm.nih.gov/] and ChemSpider® [11]. The theoretical elementary analysis through the software MarvinSketch and MarvinView [12] [13]. For the geometric optimization of the molecule by means of semi-empirical quantum calculations, we used the freeware ArgusLab® [14] [15] [16] [17] [18] configured with Hamiltonian parameters (PM3) [19] [20]. In this way, it was possible to obtain the least potential energy conformation of the molecule, characterizing HOMO (Occupied Molecular Orbital of greater energy), LUMO (Molecular Orbital of less energy), GAP (Quantity of energy necessary for the electron to make a transition), heat formation, dipole moment, MEP (surface map of electrostatic potential) among other properties.

3 RESULTS AND DISCUSSIONS

Using the virtual repository, the initial two-dimensional structure (Cartesian coordinates) of rotenone 6-Desoxyclitoriacetal was obtained, and basic descriptors with: CID identification number (11740108), nomenclature according to the rules of the International Union of Pure and Applied Chemistry- IUPAC ((6aR, 12aR) -11,12a-dihydroxy-2,3,9-trimethoxy-6,6a-dihydrochromeno [3,4-b] chromen-12-one) and some solubility properties, which are fundamental for the study (1.15) for the lipophilicity of the compound from an octanol / water system and where the lower the most hydrophilic value is compound [21], LogS (-3.86), pKa (11.97) where the higher its value is lower its acidity and the solubility of the structure in water (0.05 mg mL-1) that allowed to define the solvent (polar or apolar) used in tests of molecular dynamics [Table 1].

Table 1: Solubility properties of compound 6-Desoxyclitoriacetal PubChem® and Marvin Sketch©

Property	Value	Property	Value
pKa	11.97	polarizability	37.02 Å^3
Solubility in water	0.05 mg/mL	Polar Surface Area	104 Å^2
LogP	1.15	Refractivity	92.51 m^3·mol^{-1}
LogS	-3.86		

Source*: Virtual Repository PubChem® [https://pubchem.ncbi.nlm.nih.gov/compound/11740108]. and Marvin Sketch©.*

The physico-chemical properties were obtained through another virtual repository, properties that are related to the structural composition of the molecule, and its density (1.4 ± 0.1 g cm-3), surface tension (61.3 ± 3.0 dyne cm-1) , molar volume (258.8 ± 3.0 cm3) and its ability to form hydrogen bonds by determining atoms with the potential to receive or donate electrons in hydrogen bonds among other properties [Table 2].

Table 2: Physical-chemical properties of the 6-Desoxyclitoriacetal ChemSpider®

Properties	Value	Properties	Value
Molecular Formula	$C_{19}H_{18}O_8$	Monoisotopic Mass	374.100159 Da
Density	1.4±0.1 g/cm^3	Refractive index	1.633
Boiling point	6 34.4±55.0 °C (760 mmHg)	Molar Refractivity	92.9±0.3 cm^3
Steam pressure	0.0±2.0 mmHg (25°C)	Superficial tension	61.9±3.0 dyne/cm
Enthalpy of	98.6±3.0	Molar	258.8±3.0

Vaporization	kJ/mol	Volume	cm^3
Receptors #H	8	Donors #H	2

Souce: Virtual Repository ChemSpider®
[http://www.chemspider.com/Chemical-Structure.9914815.html?rid=af94c0ec-f0cc-4baf-8cd7-389b09d93019].

The two-dimensional structure of 6-Desoxyclitoriacetal (Figure 1) was then in its ground state, presenting only the molecular formula (C19H18O8) and the connectivity of the atoms, with an initial easy-to-view conformation but with different potential energy from the molecule in its native form.

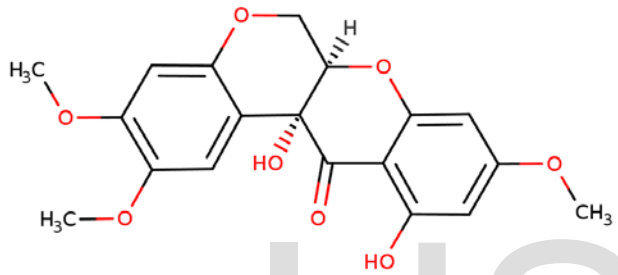

Fig.1 The two-dimensional structure 6-Desoxyclitoriacetal
Souce: Virtual Repository ChemSpider®
[http://www.chemspider.com/Chemical-Structure.9914815.html?rid=af94c0ec-f0cc-4baf-8cd7-389b09d93019]

The elementary analysis [Figure 2] is to determine which are the chemical elements of a compound (qualitative) and the proportion of each element (quantitative). The 6-Desoxyclitoriacetal had a molar mass of 374,345, an exact mass of 374.100167540, with a molecular formula C19 H18O8, being composed of 69.96% of Carbon, 34.19% of Oxygen and 4.85% of Hydrogen, with a total of 45 atoms. When subjected to mass spectral abundance m / z, it showed three peaks of 374, 375 and 376 [Figure 2].

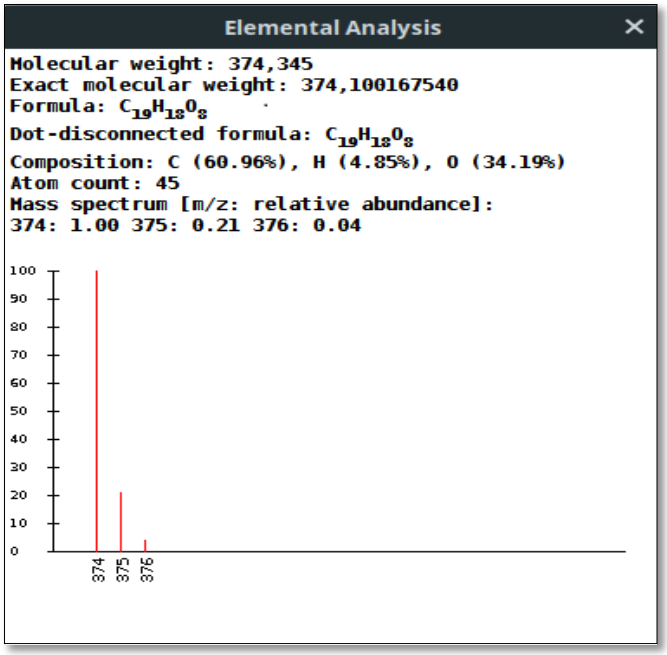

Fig.2. Elementary analysis of the basic descriptors of a structure.

When drawing a molecule two-dimensional or withdrawing it from an online repository, it is not in its most stable conformation. In order to obtain more precise calculations about the molecule and its final stable configuration, we need to perform a geometric optimization that uses the energy minimization process [22]. This geometric optimization was performed using the semi-empirical quantum method (method based on approximate solutions previously calculated from the Schöedinger equation that allows to eliminate the calculation of some integrals) with parameters QM_PM3 (Parametric Method 3) [19] [20] to perform uninterrupted cycles of 200 repeated interactions until the structure reaches a point of least possible potential minimum energy. In this way, each of the atoms that make up the structure occupied its lowest energy place in the system (TABLE 1) and the three-dimensional structure reached the most stable calculable point (Figure 3), presenting a spatial distribution that allows a smaller possible potential energy, making (-112382.1204 kcal mol-1), no longer varying, reaching a stationary point of the energy surface [4], the heat of formation (-182.0760 kcal mol-1) and dipole moment (μ) in length (2.54469635 debye). Some other properties of the structure are directly linked to the dipole moment (μ), as the melting and boiling points and their solubility in water [23].

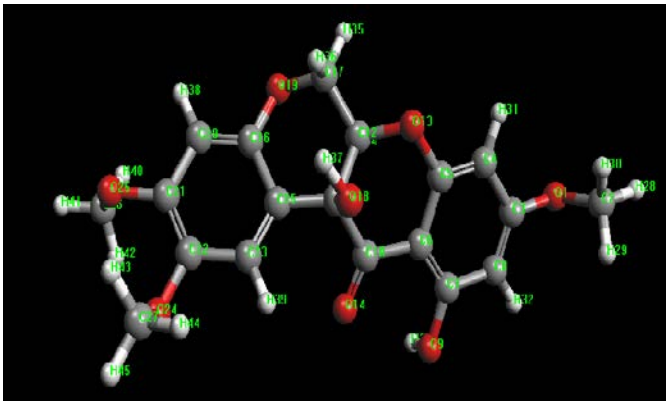

Fig. 3. Optimized structure of 6-Desoxyclitoriacetal

After geometric optimization, the molecule a theoretically more stable structure, it was possible to calculate the atomic charges using Mulliken Population Analysis as the method [24]. This method divides the charge density between two atoms uniformly. The atomic charges are useful in the correlational study between the structure of the molecule and its biological activity [25]. The calculations show that (TABLE 3) there was a large variation between the atomic charges of atoms of the same element, the oxygen with the highest charge was O13 with -0.1640 while the one with the lowest charge, O14 with -0.3078, varied 0.1438 of load; the carbons in the same way being the one of greater load the C10 with 0.3477 and the one of smaller load the C7 with -0.2924, varying 0.0553; As for the hydrogens the atomic charges varied from 0.0881 in hydrogen H44 to 0.2424 in hydrogen H39, presenting a variation of 0.1543.

Table 3: Cargas de Mulliken da rotenona 6-Desoxyclitoriacetal.

Átomo	Carga	Átomo	Carga
01 O	-0.2049	**24 O**	-0.1888
02 C	-0.1479	**25 O**	-0.1973
03 C	0.1236	**26 C**	-0.1488
04 C	-0.2675	**27 C**	-0.1508
05 C	0.1226	**28 H**	0.1150
06 C	-0.2493	**29 H**	0.0954
07 C	0.1858	**30H**	0.0949
08 C	-0.2924	**31 H**	0.2291
09 O	-0.2433	**32 H**	0.2297
10 C	0.3477	**33 H**	0.2349
11 C	0.1022	**34 H**	0.1598
12 C	-0.0960	**35 H**	0.1512
13 O	-0.1640	**36 H**	0.1191
14 O	-0.3078	**37 H**	0.2228
15 C	-0.1720	**38 H**	0.2274
16 C	0.0668	**39 H**	0.2424
17 C	-0.0919	**40 H**	0.0887
18 O	-0.2951	**41 H**	0.1113
19 O	-0.1808	**42 H**	0.1064
20 C	-0.2329	**43 H**	0.1012
21 C	0.0615	**44 H**	0.0881
22 C	0.0068	**45 H**	0.1126
23 C	-0.1153		

To identify the nucleophilic and electrophilic areas of the molecule the electrostatic potential map (MEP) was calculated; it is done by mapping the surface of electrostatic potential (Figures 4) on the surface of electronic density (Figures 5). In order to determine the

electrostatic potential map of the compound 6-Desoxyclitoriacetal (Figure 6), we can identify a greater concentration of electrons, nucleophilic region (in red), in the areas where the oxygen (O1, O9, O13, O14, O18, O24 and O25), but the rest of the structure is deficient in electrons, electrophilic region (blank), except in the regions where the rings and cycles formed by the carbons that remain in an area of neutrality (dark blue and light blue) [26].

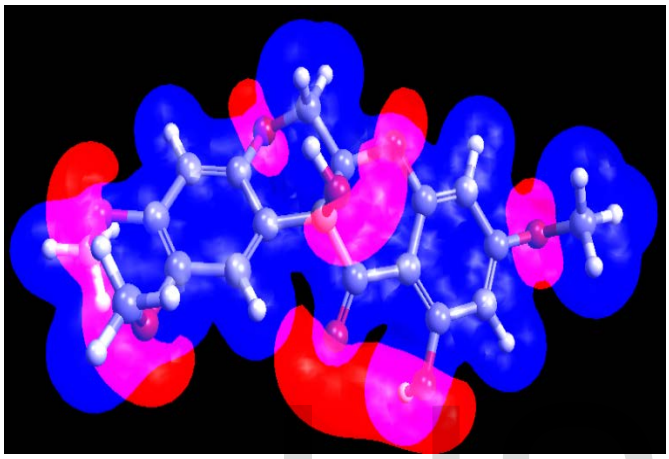

Fig. 4. *Electrostatic potential surface of rotenoid 6-Desoxyclitoriacetal*

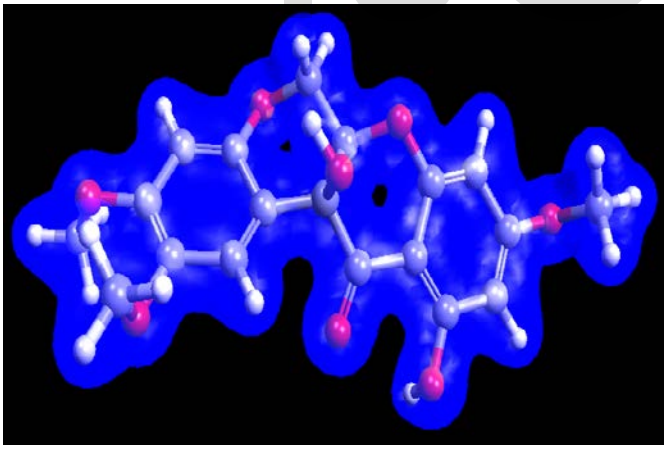

Fig. 5*. Routine Electronic Density Surface 6-Desoxyclitoriacetal*

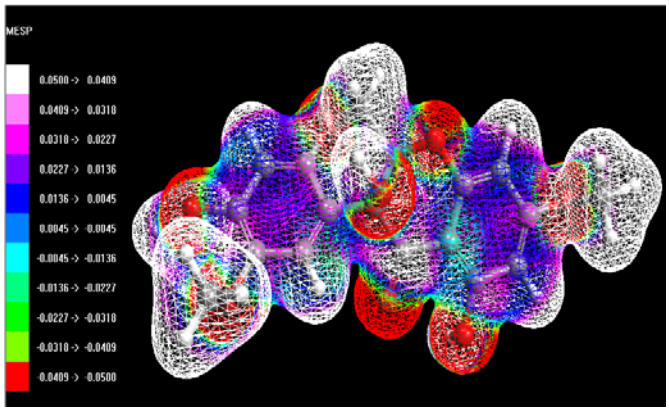

Fig. 6. *Map of electrostatic potential of rotenoide 6 - Desoxyclitoriacetal*

The global reactivity descriptors act as a bridge between structural stability and global chemical reactivity [27]. Also, these are information on fundamental characteristics of chemical reactivity, such as ionization potential, electron affinity, electronegativity, chemical potential, global hardness and overall softness. [28] (Table 4). A descriptor to determine these parameters is the energetic values of the border molecular orbitals (HOMO and LUMO). The difference between the HOMO-LUMO energy values is of extreme importance as a determinant of chemical stability. The molecules have the broadband gaps, which are generally stable and non-reactive, those with lower bandwidths are reactive because it facilitates interaction with the reagents [29]. In addition, the GAP (amount of energy required for the electron to make a transition) is calculated on the energy difference between HOMO (figure 7) and LUMO (figure 8).

Table 4 shows several parameters of the 6-Desoxyclitoriacetal compound, which were obtained by calculations using the HOMO (orbital 71) and LUMO (orbital 72) molecular orbitals, which showed symmetry between the negative and positive phases. The electron affinity (A) is described as the change in energy when an electron added to a neutral atom in the gas phase [27], the ionization potential (I) is the minimum energy required to remove an electron from an atom or molecule [27] [30], electronegativity (χ) and chemical hardness (η) help to predict on the formation of chemicals and the physical and chemical properties of the compound [27]. Further descriptors of overall reactivity are chemical softness (S) [31], electronic chemical potential (μ) as a

characteristic of the compound's electronegativity [32,33] and electrophilicity index (Ω) [34].

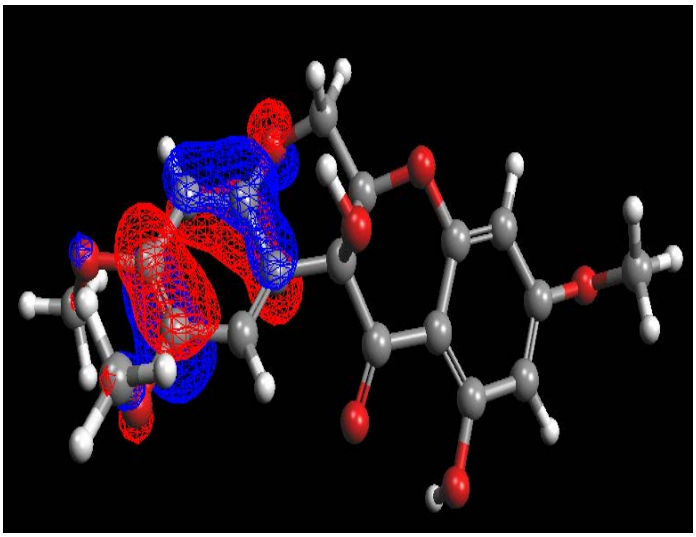

Fig. 7. *three-dimensional rendering of the HOMO orbit of rotenoid 6-Desoxyclitoriacetal*

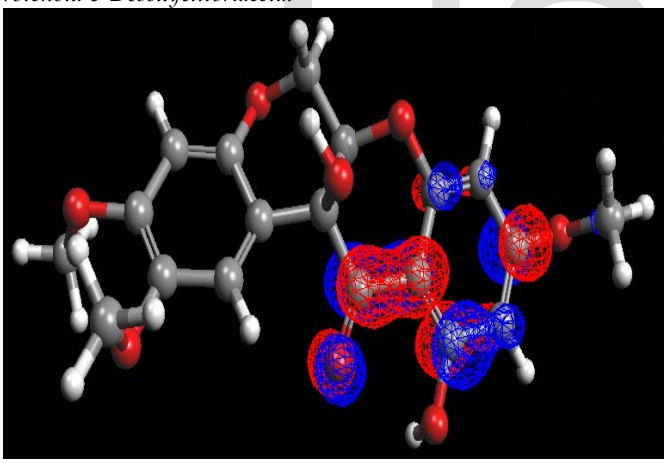

Fig. 8 *three-dimensional rendering of the LUMO orbit of rotenoid 6-Desoxyclitoriacetal*

Table 4: global reactivity properties 6-Desoxyclitoriacetal

Parâmetros	Valor
HOMO	-9.74499 eV
LUMO	-0.85641 eV
GAP	8.88858 eV
Eléctron affinity (A)	0.85641 eV
Eletronegativity (χ)	5.30070 eV
Vertical Ionization potential (I)	9.74499 eV
Chemical hardness (η)	4.44429 eV
Chemical softness (S)	0.11250 eV
Eletronic chemical potential (μ)	-5.30070 eV
Electrophilicity index (Ω)	3.16107 eV

4 CONCLUSIONS

The molecular structure of the rotenoid 6-Desoxyclitoriacetal was geometrically optimized by means of semi-empirical method calculations, obtaining at the end of this process the energy of (-112382.1204 kJ · mol-1), forming heat (-182.0760 kcal mol-1) and dipole moment (μ) in length (2.54469635 debye). By means of the map of electrostatic potential it was possible to verify the areas where the nucleophilic connections that comprise the whole area of the oxygen will occur. In addition, the atomic charges of Mulliken were obtained for the atoms of O, C, H, highlighting the variation of charges between atoms of the same species. In relation to HOMO and LUMO, one can obtain the GAP and some important rotenoid parameters. The obtained data consist of an initial stage for a comparative analysis between its analogues and fundamental for future studies of relations between the three-dimensional rotenoid structure and its biological activities.

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REFERENCES

[1] VIEGA JÚNIOR, C. Terpenes with insecticidal activity: an alternative for the chemical control of insects. Quim.Nova, v. 26, n.3, 2003.

[2] CORRÊA, J.C.R.; SALGADO, H.R.N. Insecticide activity of plants and applications: review. Rer.Bras.Med v.13, n.4, p. 500-506, 2011.

[3] MENEZES, E.L.A. Botanical insecticides: their active principles, mode of action and agricultural use. Seropédica, Rio de Janeiro: Embrapa Agrobiologia, p. 58, 2005.

[4] BARREIRO, E. J.; RODRIGUES, C. R..; ALBUQUERQUE, M. G.; De SANT'ANNA, C. M. R..; De ALENCASTRO, R. B. Molecular Modeling: A Tool for the Rational Planning of Drugs in Medicinal Chemistry. New Chemistry, v. 20, n.1, 1997.

[5] REGES, M.; MARINHO, M. M.; MARINHO, E. S. 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.

[6] COHEN, N. C.; BLANEY, J. M.; HUMBLET, C.; GUND, P.; BARRY, D. C. Molecular modeling software and methods for medicinal chemistry. Journal of medicinal chemistry, v. 33, n. 03, p. 883-894, 1990.

[7] REGES, M.; MARINHO, M. M.; MARINHO, E. S. 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.

[8] MARINHO, E. S.; MARINHO, M. M. A DFT study of synthetic drug topiroxostat: MEP, HOMO, LUMO. International Journal of Scientific & Engineering Research, v. 07, n. 08, p. 1264-1270, 2016.

[9] DEWAR, M. J.; ZOEBISCH, E. G.; HEALY, E. F.; STEWART, J. J. 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.

[10] KIM S, CHEN J, CHENG T, GINDULYTE A, HE J, HE S, LI Q, SHOEMAKER BA, THIESSEN PA, Yu B, ZASLAVSKY L, ZHANG J, Bolton E.E. PubChem 2019

[11] PENCE, H. E.; WILLIAMS, A. "ChemSpider: an online chemical information resource", 2010.

[12] CSIZMADIA, P. "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 1ą30 (p. 367ą369). 1999

[13] Using MarvinSketch', C. 5.5. 1.0, ChemAxon Kft, Hungary.

[14] THOMPSON, M. A. Planaria, Software LLC, Seattle, WA. http://www.arguslab.com

[15] THOMPSON, M. A.; ZEMER, M. C. J. Am. Chem. Soc., 113, 8210, 1991

[16] THOMPSON, M. A.; GLENDENING, E. D.; PHYS, D. F. J. Chem. 98, 10465-10476, 1994.

[17] THOMPSON, M. A.; PHYS, G. K. S. J. Chem. 99, 6374-6386, 1995.

[18] THOMPSON, M. A.; PHYS, G. K. S. J. Chem. 100, 14492-14507, 1996

[19] JAMES J. P. STEWART, J. Comp. Chem., 10, 209-220, 1989.

[20] JAMES J. P. STEWART, J. Chem., 10, 221-264, 1989.

[21] CHIANG, Po-Chang; HU, Yiding. Simultaneous determination of LogD, LogP, and pKa of drugs by using a reverse phase HPLC coupled with a 96-well plate auto injector. Combinatorial chemistry & high throughput screening, v. 12, n. 3, p. 250-257, 2009.

[22] CARVALHO, I.; PUPO, M. T.; BORGES, Á. D. L.; BERNARDES, L. S. C. "Introdução a modelagem molecular de fármacos no curso experimental de química farmacêutica" Química Nova, v. 26, n. 03, p. 428-438, 2003.

[23] ATKINS, P.W.; JONES, L. Principles of chemistry: questioning modern life and the environment. 3.ed. Porto Alegre: Bookman, 2006.

[24] ARROIO, A.; HONÓRIO, K. M.; DA SILVA, A. B. F.; Propriedades químicoquânticas empregadas em estudos das relações estrutura-atividade. Química Nova, v. 33, n. 3, p. 694-699, 2010.

[25] GUADAGNINI, P. H.; BRUNS, R. E.; SOUZA, A. A. Cargas atômicas em moléculas. Química Nova, v. 19, n. 2, p. 148-155, 1996.

[26] ARAÚJO, G. A.; SILVA, E. P.; SANABIO, E. P.; PINHEIRO, J. A.; CASTRO, R.R.; CASTRO, R.R.; MARINHO, M.M.; LIMA, F. K. S.; MARINHO, E.S. Characterization in Silico of the Structural Parameters of the Antifungal Agent Ketoconazole. Science Signpost Publishing, 2016

[27] VIJAVARAJ, R..; SUBRAMANIAN, V.; CHATTARAJ, P. K. "Comparison of global reactivity descriptors calculated using various density functionals: a QSAR perspective." Journal of chemical theory and computation 5.10: 2744-2753, 2009.

[28] PADMANABHAN, J.; PARTHASARATHI, R.; ELANGO, M.; SUBRAMANIAN, V.; KRISHNAMOORTHY, B.S.; GUTIERREZ-OLIVA, S. A. Toro-Labbe, D.R. Roy, P.K. Chattaraj, J. Phys. Chem. A 111, 9130 e 9138, 2007.

[29] ZHANG, G. & MUSGRAVE, C. B. Comparison of DFT methods for molecular orbital eigenvalue calculations. The Journal of Physical Chemistry A, 111(8), 1554-1561, 2007

[30] ERYMALZ, S.; GÜL, M.; INKAYA, E.; TAS, M. "Isoxazole derivatives of alpha-pinene isomers: Synthesis, crystal structure,

spectroscopic characterization (FT-IR/NMR/GC– MS) and DFT studies". Journal of Molecular Structure, 1108, 209-222. 2016.

[31] PEARSON, R.G. Pro. Nat. Acad. Scie 83 8440 e 8441, 1986.

[32] VEKTARIENE, A.; VEKTARIS, G.; & SVOBODA, J. Arkivoc, vii, 311, 2009.

[33] PARR, R. G.; & PEARSON, R. G. Absolute hardness: companion parameter to absolute electronegativity. Journal of the American Chemical Society, 105(26), 7512-7516, 1983.

[34] CHATTARAJ, P. K.; SARKAR, U.; & ROY, D. R. Electrophilicity index. Chemical reviews, 106(6), 2065-2091, 2006.