Semi-Empirical Study Drug antiparkinsonian bromocriptine Using the Parametric Method 7: MESP, HOMO, LUMO and Analysis Population of Mulliken

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Abstract— Parkinson's disease (PD) is a progressive neurodegenerative disorder caused by the degeneration of dopaminergic neurons, which ends up causing the loss of control of many motor functions. This is consisting of an idiopathic and still incurable disease, however there are few therapeutic procedures that are used in order to alleviate and control the symptoms cause the same, as is the case of drug treatment, and, among antiparkinsonian drugs used in this treatment against bromocriptine, marketed under the name Parlodel®. This drug acts in the body by stimulating dopamine receptors, collaborating in the production of dopamine and restore the neurochemical balance, making it effective in all stages of the disease. However, despite its efficacy, it causes some aversive effects in its users, there is therefore a need to review and refine this drug. In this perspective, this study aimed to characterize the antiparkisonian drug Bromocriptine through molecular modeling, using the semi-empirical method Parametric Method 7 (PM7). Aiming, view and identify the nucleophilic and electrophilic sites of this molecule, seeking likewise optimize their geometry in order to obtain the most stable conformation for this drug, targeting an improvement of its effectiveness as well, its mechanism of action. Initially, we used the ChemSpider repository, where it was possible to obtain the molecular structure and some important properties of the Bromocriptine; It was then used MOPAC2016 program configured to operate in accordance with the semi-empirical method PM7 (Parametric Method 7) through it gave the most stable conformation to Bromocriptine molecule with a total energy eV and equal to -6554.36967 heat of formation equal to 1 kcal mol 775.06413; the Mulliken atomic charges which highlighted the values of the charges of atoms: (O2) (O3) (O 4) (O 5) (C 11) (C16) (C17) (C 22) (C 27) (C 28) (C 32) (C 37) (C 38) (C 39) (C 40); and potential surface map electrostatic (MESP) the highlighting atoms (O2) (O3) (O 4) (O 5) (C 11) (C16) (C17) (C 22) (C 27) (C 28) (C 32) (C 37) (C 38) (C 39) (C 40), these being the nucleophilic sites in this molecule, places where biological attacks are more favorable; It was obtained even energies of the HOMO and LUMO frontier orbitals, which are equal (-8700 eV) and (-2437 eV), respectively. Thus, in silico analysis in which the molecule has undergone Bromocriptine was conducted satisfactorily, and these data are used for future virtual screening studies.

Keywords: Calculations semiempirical. HOMO. LUMO. MESP. Parkinson's disease. Parametric Method 7.

1 Introduction

Currently, it has been noticed that Brazil has undergone a process of population aging. Since with the individual elderly increase in population also increases the number of diseases and / or associated with aging, such as chronic diseases, being among these, Parkinson's disease (PD) [1] , since it is customary to appear in individuals aged over 50 years [2], reaching 2 in 100 people over 65 years, predominantly in males (3 male / 2 female) [3] being important to note that most of the chronic diseases that afflict the elderly have, in their own age, as a major risk factor [4]. Parkinson's disease (PD) is a neurological disease that has most affected the contemporary man and can affect all ethnic groups and all socioeconomic classes. This is to be a chronic change, progressive and idiopathic central nervous system. Having been first reported in 1817 by James Parkinson English physician, being initially called paralysis agitans or PK (Paralysis agitans) [4]. This disorder is defined as a progressive neurodegenerative disorder caused by degeneration and / or selective death of dopaminergic neurons [5] cells located and synthesized in a region of the brain known as the substantia nigra [6]. Accordingly, dopamine deficiency caused by neurodegeneration, or the progressive loss of structure or function of neurons [4] eventually causes several functional changes in structures in the brain, which are associated with the control of many movements,

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causing as a consequence the appearance of signs and symptoms of the disease [7].

And among the symptoms presented by the same, they are: muscle stiffness, immobility, bradykinesia, tremor and postural instability, decreased muscle strength and physical fitness, and also non-motor symptoms such as cognitive changes, trend isolation and depression. These symptoms can cause major complications in the patient's quality of life [8]. Among the treatments used against Parkinson's disease are: the therapeutic treatment, physical therapy and surgery, and this must first compulsory indication, having as main objective the control of symptoms of the same, being mainly in the replacement of dopamine [1]. Among the antiparkinsonian drugs used in this process is the Bromocriptine marketed by the name of Parlodel®.Synthesized from Novartis Biosciences S.A. the Parlodel® Bromocriptine part of drugs classified as dopamine agonists (AD) of the ergot class, these drugs act directly stimulate dopamine receptors without being metabolized by the presynaptic neuron [9]. Thus its dopaminergic activity can restore the neurochemical balance in the striatum, improving parkinsonian symptoms experienced by patients in all stages of the disease, showing thus, its effectiveness in this treatment. However, it is worth noting also that although this drug is effective account the DP, it causes some aversive effects in its users as: headache, problems with your vision, stomach pain and difficulty breathing, and therefore there is a need to analyze and refine this drug.

The computational chemistry is an interdisciplinary field of chemistry, which is the use of software designed to resolve problems of chemical, biochemical, and industrial technology. His great extent leads to identify some lines, such as the Molecular Modeling (Molecular Simulation), chemometrics, cheminformatics and Bioinformatics [10]. Since one of the major purposes of this area if it consists in finding new drugs [11]. Thus, the use of computational methods in studies and planning of bioactive compounds have been increasingly frequent nowadays, as these computational processes can be used as instruments in the rational design of compounds, in order to facilitate and optimize this process, bringing itself hypotheses about the mechanisms of action of these bioactives [12].

Therefore, molecular modeling, are employed quantum methods, derived from resolution of the Schrödinger equation, used for performing the calculation of energies, and these can be performed ab beginning or semiempiricamente through a simplified Hamiltonian operator and properly adjusted parameters supported by experimental data [13].Dewar et al [14] in order to increase the accessibility of modeling software, developed a series of programs for semi-empirical calculations of molecular orbitals that also provide chemically precise structural information such as AM1 (Austin Model 1) and PM3 (Parametric Method 3) [15] and has recently been developed PM7 (Parametric Method 7) [16]. All these methods have many similarities but differ in their parameters.

In this perspective, this study aimed to characterize the antiparkisoniano drug Parlodel (Bromocriptine) through molecular modeling, using the semi-empirical method Parametric Method 7 (PM7). Aiming, view and identify the nucleophilic and electrophilic sites of this molecule, seeking likewise optimize their geometry in order to obtain the most stable conformation for this drug, targeting an improvement of its effectiveness as well, its mechanism of action.

2 METHODOLOGY

For the development of this work were used free software, based on Microsoft Windows operating system, using a PC with Core 2 Duo processor (2 GHz), with 4.00 GB of RAM.To this research was initially used ChemSpider repository, it is possible, through this, to obtain the basic properties of this molecule (molecular formula, density, boiling point, vapor pressure, recovery of enthalpy, inflation point refractivity Molar, polarizability, surface tension and the molar volume), and also other necessary information about it.

This study was conducted according to the following steps: (1) obtaining the structure of Parlodel (Bromocriptine) from ChemSpider repository (http://www.chemspider.com/); (2) Following the methodology proposed by Dewar et al [14] to optimize the structure and get energy parameters (total energy, nuclear power, power electronics, energy of molecular orbitals of ε_{HOMO} borders (HOMO-Highest Occupied Molecular Orbital and ε_{LUMO} (LUMO Lowest Unoccupied Molecular Orbital), heat of formation) was used Molecular Orbital Package program (MOPAC2016) 16.111W Version [16] configured to perform method semi-empirical Parametric method 7 (PM7), using the approach Hartree Fock (HF-SCF) to the wavefunction (RHF-Restricted Hartree-Fock), with water as solvent and being a molecule in its ground state. semi-empirical calculation realization using Molecular Orbital Package software - MOPAC2016, 16.111W Version [16], which is configured to act according to the semi-empirical method PM7 (Parametric method 7).

Using the output file generated by the optimization of the structure, the parameters were obtained by getting energy parameters (total energy, electronic energy, core-core repulsion, potential ionization, energy of border molecular orbital (HOMO and LUMO) and the heat of formation) and the frontier orbitals were generated HOMO and LUMO, and the potential of the electrostatic surface map (MESP) that can be expressed according to equation (1).

$$V(r) = \sum_{A} \frac{Z_A}{|\vec{R}_A - \vec{r}|} - \int \frac{\rho(\vec{r})}{|\vec{r}' - \vec{r}|} dr' \quad (1)$$

Where ZA is the charge of the nucleus A, located in RA, ϱ (R) is the electron density function for the molecule, V (r) is the resulting electrostatic net effect produced at the point r by both the electrons and the nuclei of molecule, where the

first term represents the contributions due to the potential for electrons and the second term on the basis of core [17].

To correlate structure and reactivity of molecules was used the values of the frontier orbitals to calculate the GAP (Eq 2) [18].

$$GAP = (\varepsilon_{HOMO} - \varepsilon_{LUMO}) \quad (2)$$

3 RESULTS AND DISCUSSIONS

The ChemSpider repository is consists of an online database, which offers free more than 57 million chemical structures form, providing the molecular properties, 2D and 3D viewing and downloading these chemical compounds, providing further information on chemical structures, such as addresses and sources for research, these sources can be: academic and commercial sites, papers, chemical suppliers, links and references. Thus, using this repository is possible to obtain important information about Bromocriptine molecule, such as bi-demensional structure (Figure 1), the molecular properties (Table 1) as well as the name according to the International Union of Pure and Applied Chemistryoficial ((5'a) -2-bromo-12'-H ydroxy-2 '- (- 1-methyl lethyl) -5' - (2-methyl lpropyl) ergotaman-3 ', 6', 18 trione).

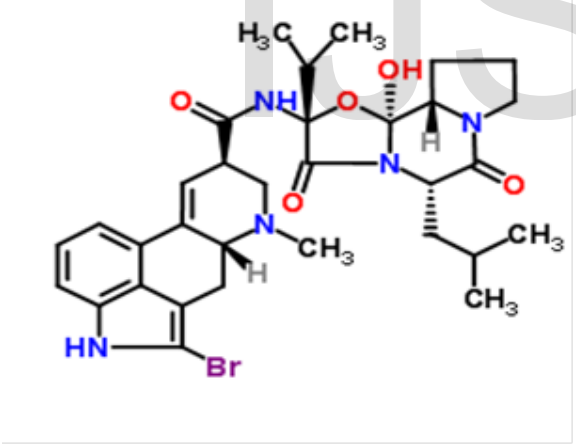

Fig.1 drug chemical structure Parlodel (Bromocriptine). Source: ChemSpider repository, 2016. http://www.chemspider.com/)

TABLE 1
Molecular properties of Parlodel (Bromocriptine) obtained by ChemSpider

PROPERTIES	*VALUES*
Molecular formula	$C_{32}H_{40}BrN_5O_5$
Density	1,6 ± 0,1 g cm $^{-3}$
Boiling point	865,1 ± 75,0 ° C a 760 mmHg
Steam pressure	0,0 ± 0,3 mmHg a 25 ° C
Vaporization enthalpy	131,7 ± 3,0 kJ mol^{-1}
Refractive index	1.740
Refractivity molar	162,7 ± 0,5 centímetros^3
Polarizability	64,5 ± 0,5 10 -24 cm^3
Superficial tension	60,6 ± 7,0 dine cm^{-1}
Molar volume	403,4 ± 7,0 cm^3

Advances in computational methods are arising from new technologies developed to accelerate the processing speed of the hardware, which are necessary for studies involving conformational energies to be extensive and costly theoretical calculations. Therefore, this computer development enabled the software developments able to sketch chemical structures, perform calculations optimizations and conformational energies in pursuit of more stable compounds, thus enabling simulate interactions between receptor and active sites. As the computer, a primary tool in achieving the conformational energy calculations involving, using the methods already proposed [19].

The energy minimization principle it consists of a mathematical procedure that aims to achieve the most stable conformations (mímimos power) for a given molecule by molecular mechanics calculations or mechanical-quantum [20], and the methods of quantum mechanics (quantum mechanical) or (quantum Chemistry), compute the properties of a given system, based on approximate solutions to Schroedinger equation [21].

Therefore, to calculate the lowest potential energy structure uses a series of equations called equations Hartree-Fock (HF), which assumes that each electron moves in the average field produced by other electrons and the nuclei [20], and the Hartree-Fock uses a technique of optimization by means of the approximation of self-consistent field (SCF Self-Consistent field) method, showing bearing, satisfactory results for geometric properties of light atoms calculating low barrier power with precision [21].

In an attempt to expand the range of applicability of semi-empirical methods, we developed a new method named PM7 (Parametric Method 7), this is based on other semi-empirical methods, such as RM1 and PM3, based on expressions of Fock matrix like those used in the MNDO method, and this new method (PM7) the most accurate among the semi-empirical methods type NDDO [15]. Therefore, using the semi-empirical method PM7 with the Hartree-Fock approximation (HF-SCF), gave the full optimization of all Bromocriptine geometries through internal coordinates of geometrical parameters, where by means of these coordinates are obtained a more stable conformation with a total energy equal to -6554.36967 eV, can these convergências, be displayed step by step through chart (Figure 2), being possible to observe a certain energy range near optimizations 646 and 967, reaching some stability through the optimizations 968 and 1613.

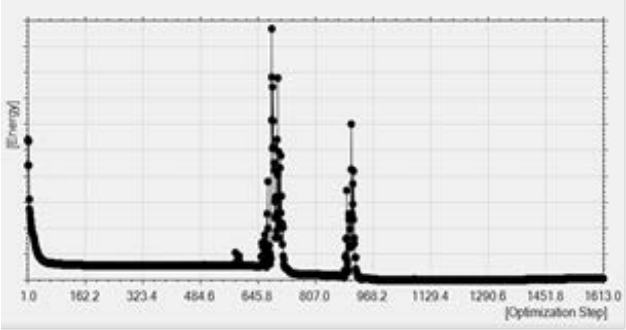

Fig.2. Bromocriptine convergence geometry of the drug obtained by the method PM7

For this molecule was found still an electronic energy equal to -11132.79934 EV, core-core repulsion of 4578.42968 EV, potential ionization equal 8.699640 EV and heat of formation equal to 775.06413 KCAL mol-1, which obtained the most stable conformation to this molecule (Fig. 3).

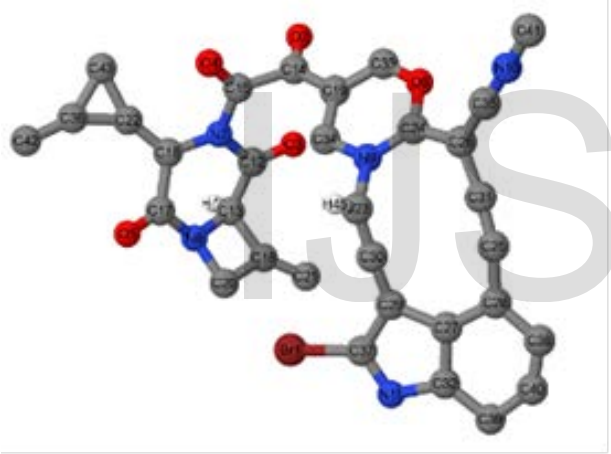

Fig. 3: Structure optimized drug Bromocriptine PM7 obtained by the method

The dipole moment of a given molecule is determined by the difference between the charge times the distance between the different loads. Since the distance between the loads vary with the vibration of the atoms of the molecule [22]. Thus, for the dipole moment of this structure antiparkinsonian therapy it was found the value of 38.57681 debye.

For the area cosmos and the cosmos volume values were found: 491.82 629.91 A2 and A3, respectively. And you can also plot the surface of Van de Walls of Bromocriptine drug (Fig. 4).

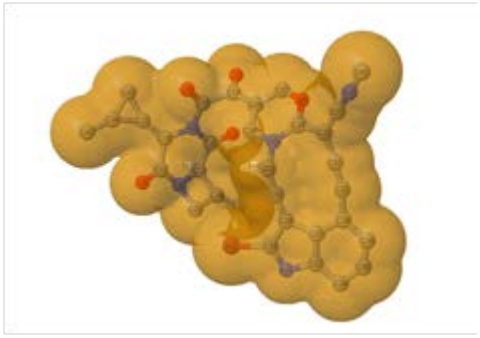

Fig. 4: Surface of Van der Waals drug Bromocriptine obtained by the method PM7

Population analysis of Mulliken [23] is a classic method widely used among the chemical, which is based on molecular orbital theory [24], which distributes electrons, almost perfectly between the various atomic orbitals of different atoms a [23], equally divided the electron densities between two atoms, even if they have different electronegativities [25] molecule. Therefore, the Mulliken population analysis is a quantitative method that divides the electrons in atoms in order to generate generate partial atomic charges, based on the use of matrix density and coverage for the distribution of electrons in a molecular compound so between fractional parts (atoms, bonds, orbitals), which is useful procedure for the quantitative description of intramolecular interactions of chemical reactivity [20].With this, analyzing Bromocriptine molecular entity using the semi-empirical method PM7, gave the Mulliken atomic charges for the C-atoms N, O and BR (Table 2). In which it was possible to highlight some atomic charge to the C atoms and these values located in the atom: (16C -4.57232124), (17C -4.15766776), (22C -5.67315853), (36C -6.74816531), (42C -7.39973588) and (-6.67928244 43C); for the charges of the atoms included: (2O -3.03451783) (3O -2.32732671) (4O -4.13139029) and (5O -4.42761242); as the loads of N atoms obtained a more prominent atoms: (7N -3.72147541) and (8N -3.41263963), since the Br atom this gave a load equal to 0.36053416. So by population analysis of loads of Mulliken [23] it was possible to highlight the respective values of loads the C, O and N, as ends favorable to the biological interactions, which are nucleophilic sites.

Table 2
Mulliken population analysis for C-atoms N, O and Br drug Bromocriptine

CHARGES MULLIKEN			
1 Br	0.36053416	2 O	-3.03451783
3 O	-2.32732671	4 O	-4.13139029
5 O	-4.42761242	6 O	0.84760150
7 N	-3.72147541	8 N	-3.41263963
9 N	0.53901004	10 N	3.32245013
11 N	3.10937145	12 C	-3.00034156
13 C	-3.17368236	14 C	-2.56990444
15 C	-3.54581852	16 C	-4.57232124
17 C	-4.15766776	18 C	-1.92339626
19 C	-1.21606217	20 C	-2.27114672
21 C	-0.87600175	22 C	-5.67315853
23 C	0.98361120	24 C	1.32029289
25 C	4.26302799	26 C	2.66034844
27 C	3.86355688	28 C	4.77426117
29 C	2.39862283	30 C	1.63321206
31 C	3.57301725	32 C	4.27183473
33 C	-0.35121834	34 C	-0.78033136
35 C	3.00157504	36 C	-6.74816531
37 C	2.06937664	38 C	6.05739047
39 C	5.59395869	40 C	6.30108389
41 C	3.63126587	42 C	-7.39973588
43 C	-6.67928244		

The electrostatic potentials Molecular, or MEP (Molecular Electrostatic Potential) it consists of electrostatic properties of a compound, based on the calculated charge density directly molecular wave function [20], this is then calculated by setting the distribution energy with each grid point associated with the molecular surface [12]. Thus, the distribution of electrostatic potential on this surface can be observed through the MESP (potential surface map electrostatic), these maps enable us to visualize and predict the possible nucleophilic and electrophilic sites, sites where there were interactions between biological molecules and their respective receptors [26].Thus, by this characterization in silica using the PM7 method gave the potential surface map Electrostatic for the molecule Bromocriptine (Fig. 5), which by means of this, it could be noted that the nucleophilic sites of this molecule are located in the atoms (O 2) (O 3) (O 4) (O 5) (C 11) (C16) (C17) (C22) (C 27) (C 28) (C 32) (C 37) (C 38) (C 39) (C 40) the latter being the places where biological attacks are more favorable to occur.

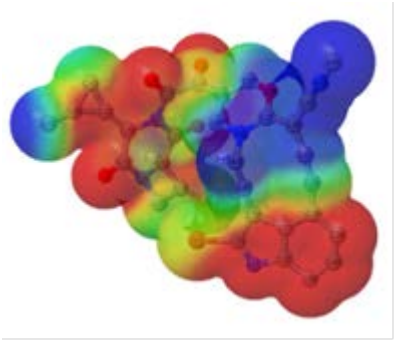

Fig. 5: Potential Map Electrostatic Parlodel (Bromocriptine), obtained by the method PM7

According with the molecular orbital theory (TOM), the frontier orbitals are usually the first to be involved in reactive processes. Therefore, the proximity TOM provides satisfactory results for the analyzes behavior of many molecules [27]. With this, they are used the energies of the busiest molecular orbital HOMO (Highest Occupied Molecular Orbital) and unoccupied molecular orbital low energy LUMO (Lowest Unoccupied Molecular Orbital), where the energy of the HOMO defines the electron-donor character of a compound and the energy of the LUMO set the electron-acceptor character. Since the higher the energy of the HOMO greater electron-donating ability, and the lower the energy of the LUMO is less resistance to accept electrons [18].

Therefore, through this modeling molecular orbitals were obtained (HOMO and LUMO), known as [28] frontier orbitals to Bromocriptine molecule, it being possible calculate 16 occupied orbitals and 16 orbital idle identifying the orbital 9 as the HOMO (Figure 6) as the orbital LUMO 10 (Figure 7). Where analyzing Fig. 6 it can be observed that the orbital of the C atoms (27, 32; 38; 39; 40) contributed symmetrically between the negative phase (red) and positive (blue) to form the HOMO orbital, collaborating so for the electron affinity of Bromocriptine. Similarly, analyzing Figure 7 it could be seen that the orbitals of the C atoms (24, 31, 35, 41) and N (10), also of symmetrical shape between phases, contributed to the formation of the orbital (LUMO) thus contributing in ionization potential of this therapeutic molecule.

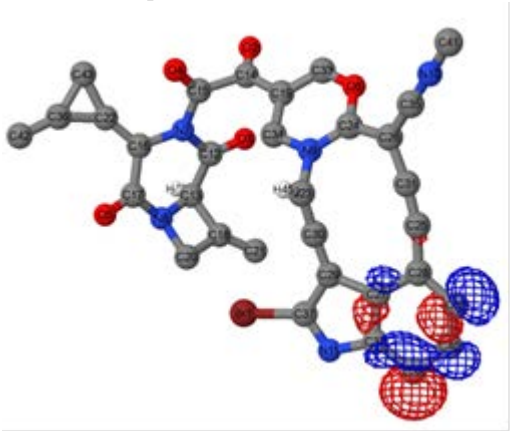

Fig. 6: Molecular Orbital boundary for the drug bro-

mocriptine, using the method (PM7), Orbital HOMO

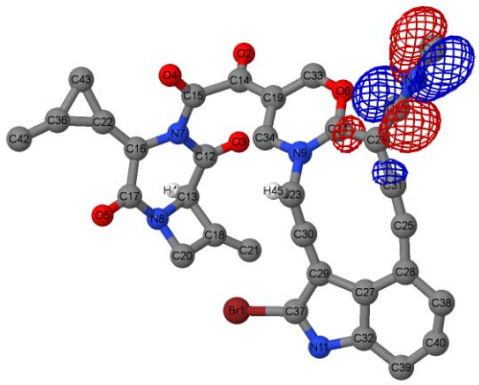

Fig7: frontier molecular orbitals for the drug bromocriptine, using the method PM7, the LUMO

The definition of GAP gives the difference or "gap" between the energies of the frontier orbitals (HOMO and LUMO), that is, a value obtained by difference: HOMO - LUMO. This becomes important and decisive to describe and identify the molecular stability of a compound [19], since the higher the value GAP more stable and non-reactive is the molecule hence the lower the more reactive GAP value is the [29] molecule. Therefore, a great difference or gap between the HOMO and LUMO indicates that the molecule has high stability, and low reactivity in chemical reactions [30].

Thus, through this modeling in silico using the semi-empirical Hamiltonian PM7 configuration could be seen that the HOMO frontier orbital energies obtained -8700 (eV) and lumo energies -2437 (eV), thus being the difference between the GAP the energies of HOMO and LUMO, we obtained a difference value of - 6.263, showing what would be theoretically the first energetic barrier to the transition of the electron, stop first excited energy state, represented in the energy levels diagram (fig. 8).

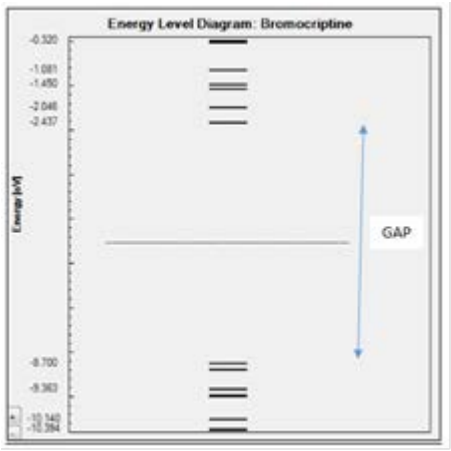

Fig. 8: Diagram of energy levels for the molecule Bromocriptine

4 CONCLUSION

The Computational Chemistry is one of the areas that have contributed and favored for the improvement and rational new bioactive compounds, as this has provided increasingly modern equipment and software, which enables the handling of compounds (are these great or small) accurately and minimizing time and costs by generating and providing further information on the same, this information can be used in various fields, such as pharmacology.

Thus, by using resources and methods provided by computational chemistry, it was possible to characterize the drug antiparkinsonian Parlodel® Bromocriptine, through which ChemSpider repository was possible to obtain the molecular structure and some important properties of Bromocriptine. By using the program Molecular Orbital Package (MOPAC2016) configured to operate according to the method semi-empirical method PM7 (Parametric Method 7) (NDDO), there was obtained a more stable conformation with a total energy equal to -6554.36967 eV; in population analysis of Mulliken atomic charges, where it was possible to understand and highlight the values of the loads of the following atoms: (16C), (17C), (22C), (36C), (42C), (43C), (2O) (3O), (4o), (5O) (7N) and (8N) as being favorable to nucleophilic ends interactions of this molecule; By means of the potential surface map electrostatic (MESP) it was also possible to display the possible nucleophilic sites of this molecule, which are located in the atoms (O 2) (O 3) (O 4) (O 5) (C 11) (C16) (C17) (C22) (C 27) (C 28) (C 32) (C 37) (C 38) (C 39) (C 40), and therefore the places where biological attacks are more favorable; It was obtained even energies of the HOMO and LUMO frontier orbitals, which are equal (-8700 eV) and (-2437 eV), respectively. Thus, in silico analysis in which the molecule has undergone Bromocriptine was conducted satisfactorily, and these data are used for future virtual screening studies.

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5 REFERENCES

[1] T. C. SAITO, A Doença de Parkinson e Seus Tratamentos: uma revisão bibliográfica. Paper Specialization Londrina: Centro Universitário Filadélfia, 2011. Disponível em: <

http://web.unifil.br/pergamum/vinculos/000004/00000414.pdf> Acesso em: 04 set. 2016

[2] A. C. R. CAMARGOS, F. C. Q CÓPIO, T. R. R. SOUSA, F. GOULART, O impacto da doença de Parkinson na qualidade de vida: uma revisão de literatura. Revista Brasileira de Fisioterapia, v. 8, n.3, p. 267-272, 2004. Disponível em: <http://www.rbf-bjpt.org.br/files/v8n3/v8n3a13.pdf> Acesso em: 02 set. 2016.

[3] C. S. MOREIRA, K. F. C. MARTINS, V. C. CARVALHO-NERI, P. G. ARAÚJO, Doença de Parkinson: como diagnosticar e tratar. Revista Científica da Faculdade de Medicina de Campos. v. 2, n. 2, p. 19-29, 2007. Disponível em: <http://www.fmc.br/revista/V2N2P19-29.pdf > Acesso em : 02 set. 2016.

[4] L. A. LEANDRO Fatores associados ao desempenho funcional de idosos portadores da doença de Parkinson. Curitiba: Universidade Federal do Paraná. 2011. Disponível em: < http://acervodigital.ufpr.br/bitstream/handle/1884/26323/DISSERTACAO%20DE%20MESTRADO%20%28UFPR%29.pdf?sequence=1&isAllowed=y> Acesso em: 03 set. 2016

[5] F. D. FERREIRA, F. M. D. FERREIRA, R. B. HELENO, S. E. MELLA JÚNIOR Doença de Parkinson: aspectos fisiopatológicos e terapêuticos. Revista Saúde e Pesquisa, v. 3, n. 2, p. 221-228, maio/ago. 2010. Disponível em:<http://periodicos.unicesumar.edu.br/index.php/saudpesq/article/view/1353> Acesso em: 02 set. 2016.

[6] C.F.M. SOUZA, H.C.P. ALMEIDA, J.B. SOUZA, P.H. COSTA, Y.S.S. SILVEIRA, J.C.L. BEZERRA, Doença de Parkinson e o Processo de Envelhecimento Motor: Uma Revisão de Literatura. Revista Neurociência. v.19, n.4, p. 718-723, 2011. Disponível em :< http://revistaneurociencias.com.br/edicoes/2011/RN1904/revisao%2019%2004/570%20revisao.pdf > Acesso em: 03 set. 2016.

[7] L. C. S. CRISÓSTOMO, C. L. MORAIS FILHO, M. M. MARINHO, R. R. CASTRO, E. S. MARINHO Estudo in silico da molécula ácido (S)-2-amino-3-(3,4-dihidroxiphenil) propanoico (Levodopa) e seus análogos. In: XXI Encontro de Iniciação à Pesquisa Universidade de Fortaleza, 21., 2015, Fortaleza. Anais eletrônicos dos Encontros Científicos. Fortaleza: UNIFOR, 2015. Disponível em: < http://uol.unifor.br/oul/conteudosite/?cdConteudo=6105204> Acesso em: 03 set. 2016.

[8] C. R SANT, S. G. OLIVEIRA, E. L. ROSA, J. S. DURANTE, S. R. POSSER Abordagem fisioterapêutica na doença de Parkinson. Revista Brasileira de Ciências do Envelhecimento Humano, Passo Fundo, v. 5, n. 1, p. 80-89, jan./jun. 2008. Disponível em: < http://seer.upf.br/index.php/rbceh/article/view/259 > Acesso em: 02 set. 2016.

[9] H. B. FERRAZ, Agonistas Dopaminérgicos no tratamento da Doença de Parkinson. Revista Neurociências, v. 12, n. 4, out/dez, 2004. available in: <http://www.revistaneurociencias.com.br/edicoes/2004/RN%2012%2004/Pages%20from%20RN%2012%2004-4.pdf> Acesso em: 02 set. 2016

[10] F. M. S. S. FERNANDES, Perspectivas da química computacional. Faculdade de Ciências Universidade de Lisboa, 2011 available in: http://www.spq.pt/magazines/BSPQ/653/article/30001695/pdf

[11] D. H. S. LEAL, Macrolactamas derivadas de carboidratos: síntese e análise conformacional por métodos quanto-mecânicos. Doctoral thesis Belo Horizonte. Faculdade de Farmácia da UFMG. 2009. available in: <http://www.bibliotecadigital.ufmg.br/dspace/handle/1843/FARD-82SFJC > Acesso em: 06 set. 2016.

[12] C. M. R. Sant'anna " Métodos de modelagem molecular para estudo e planejamento de compostos bioativos: Uma introdução". Revista Virtual de Química. n. 1, v. 1, p. 49-57, 2009

[13] G. A ARAUJO, E. P. SILVA, R. G. SANABIO, J. A. PINHEIRO, M. B. ALBUQUERQUE, R. R. CASTRO, M. M. MARINHO, F. K. S. LIMA, E. S. MARINHO, Characterization in Silico of the Structural Parameters of the Antifungal Agent Ketoconazole. Rev Science Signpost Publishing, v. 3, p. 133-142, maio 2016. Disponível em: < http://www.ss-pub.org/article/characterization-in-silico-of-the-structural-parameters-of-the-antifungal-agent-ketoconazole/> Acess in: 05 set 2016.

[14] M.J.S. DEWAR, E.G. ZOEBISCH E.F, HEALY, J.J.P. STEWART, AM1: A new general purpose quantum mechanical molecular model. J. Am. Chem. Soc., v. 107, p. 3902-3909, 1985.

[15] J. J. P. STEWART,. Optimization of parameters for semiempirical methods VI: more modifications to the NDDO approximations and re-optimization of parameters. Journal of Molecular Modeling, v. 19, n.1, p. 1-32, 2013.

[16] J.J. P. STEWART MOPAC2016, Version: 16.111W, , 2016.

[17] N. PRABAVATHI, A. NILUFER, V. KRISHNAKUMAR " Vibrational spectroscopic (FT-IR and FT-Raman) studies, natural bond orbital analysis and molecular electrostatic potential surface of Isoxanthopterin". Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, v. 114, p. 101–113, 2013.

[18] A. ARROIO, M. K. HONÓRIO, ,A. B. F. DA SILVA, "Propriedades Químico Quânticas Empregadas em estudos das relações estrutura−atividade".Química Nova, Vol. 33, No. 3, 694-699, 2010.

[19] W. R. LIMA JÚNIOR Estudo da relação estrutura atividade de Chalconas com ação antitumoral. Masters dissertation. Universidade Estadual de Goiás, março, 2014.

[20] C. M. R. SANT'ANNA Glossário de termos usados no planejamento de fármacos (recomendações da IUPAC para 1997). Revista Química Nova. São Paulo, v. 25, n. 3, p. 505-512, 2002. Disponível em: <http://dx.doi.org/10.1590/S0100-40422002000300027> Acesso em: 07 set. 2016.

[21] SILVA, L. S. Estudos Computacionais de Esfingomielinases D: Docking, Dinâmica Molecular e Métodos Híbridos QM/MM. doctoral thesis. Universidade Estadual Paulista. São José do Rio Preto. 2015.

[22] MARIN, E. P. Espectroscopia de Infravermelho e Suas Aplicações. Completion of course work Universidade Estadual Paulista Julio de Mesquita Filho. São Paulo, 2013.

[23] R.S. MULLIKEN Electronic Population Analysis on LCAO–MO Molecular Wave Functions.I. J. Chem. Phys, v. 23, p. 1833, 1955.

[24] GUADAGNINI, P. H.; BRUNS, R. E.; SOUZA, A. A. Cargas atômicas em moléculas. Revista Química Nova, v. 19, n. 2, p. 138-155 .1996.

[25] F. SEGALIN, Parâmetros de Carga para o campo de força e Análise Estrutural do Aminoesteróide Esqualamina. Masters dissertation.Porto Alegre. Universidade Federal do Rio Grande do Sul, 2008.

[26] F.K.S. LIMA. G.C. BATISTA, M.M. MARINHO, R.R. CASTRO, E.S. MARINHO, Estudos Preliminares de Modelagem Molecular do Ácido Gama-Aminobutírico (GABA). In: XX Encontro de Iniciação à Pesquisa Universidade de Fortaleza, 20., 2014, Fortaleza. Anais eletrônicos dos Encontros Científicos. Fortaleza: UNIFOR, 2014. Available in: < http://uol.unifor.br/oul/conteudosite/?cdConteudo=4998524> Acess in: 03 set. 2016.

[27] V. F. TRAVEN, Frontier orbitals and proprerties of organic molecules. Ellis Horwood, p. 401. New York. 1992.

[28] S. S. CARNEIRO, A. R. LIMA, M. M. MARINHO, E. S. MARINHO, In silico Study Of The Therapeutic Agent In The Treatment Of Non-Hodgkin's Lymphomas, Peripheral TCell Belinostat, A Semi-Empirical Approach". Imperial Journal of Interdisciplinary Research (IJIR) Vol-2, Issue-8, 1645- 1648, 2016

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

[30] C. A ALBUQUERQUE. Modelagem Molecular aplicada ao desenvolvimento de sistemas Nanoscópicos Bioativos. Masters dissertation. Universidade Federal de Itajubá. Minas Gerais. 2008