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Electronic/Structural Characterization of Antiparkinsonian Drug Istradefylline: A Semi-Empirical Study

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Abstract **- Parkinson's disease is a neurological disease that affects all ethnic groups and socioeconomic classes worldwide, affecting about 1% of the world population over 65 (WHO) with an estimated prevalence of 100-200 cases per 200,000 inhabitants. Nerve cells in the brain, which produce dopamine, end up being destroyed slowly, causing the deficiency of this substance, thus, nerve cells in the brain do not communicate properly, leading to loss of muscle function. The substance Istradefylline, commercially available under the name Nouriast®, is a drug belonging to the caffeine family, being an antagonist of A2A receptors. The aim of the present work was to use the semi-empirical quantum mechanical method Parametric Method 3 to characterize the drug Istradefylline, obtaining the optimized structure (SFC - 105624.5724 kcal mol-1), the Mulliken charges, the orbitals (HOMO and LUMO) and the map of electrostatic potential, where we identified the possible sites of nucleophilic and electrophilic connection with the data obtained, with a view to the development of more efficient analogues, aiming the optimization of the drug.**

Keywords **- Istradefylline, Parametric Method 3,Parkinson's disease,Chemical Theory, Self Consistent Field.**

I.INTRODUCTION

Parkinson's disease (PD) is defined as a progressive neurological disorder, characterized by the degeneration of cells (neurons) located in the ventral layer of the compact part of the substantia *nigra*, which is responsible for the production of dopamine in the brain, which degeneration causes deficiency in the production of dopamine, generating a set of symptoms determined by motor disorders. The main signs of the disease are motor symptoms which, by their intensity, often obscure non-motor symptoms. Bradykinesia, presence of tremors, muscular rigidity, difficulty of muscular movements and postural stability due to loss of postural reflexes are symptoms and signs that manifest themselves in the most varied combinations [1]. According to Van Den Eedenand collaborators [2], the main cause of risk associated with PD is age, known as the second most common neurodegenerative disease in the elderly, usually occurring in patients close to 60 years of age, affecting people in all ranges age groups. Patients who have onset of the disease before 40 years, are denominated as parkinsonism of early onset [3]. In addition, up to 80% of PD patients may suffer dementia concomitantly [4], a factor associated with an increased risk of mortality in these patients [5]. Its origins are of unknown causes and the diagnosis is essentially clinical, so PD has no cure, but with the available forms of treatment, it is possible to control the symptoms presented by it. There is evidence that caffeine is a non-selective adenosine antagonist, it exhibits antiparkinsonian action with improvement of motor functions [6] strengthening the potential of these receptors in the treatment of PD symptoms [7] [8]. To date, the most successful drug with satisfactory results at this target was Istradefylline (Fig. 1). In May 2013, Kyowa Hakko Kirin Co Ltd of Japan launched Nouriast® 20 mg tablets, commonly known as Istradefylline (caffeine analogue), the first antiparkinsonian drug with a specific receptor antagonistic action of Adenosine A2A [9].

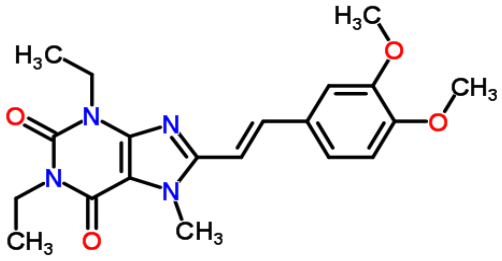

Fig. 1. Istradefylline chemical structure available from the ChemSpider® Repository.

However, studies in the USA in Parkinson's patients have shown that the drug Istradefylline associated with L-DOPA (levodopa), is a compound capable of blocking these A2A receptors, its administration resulted in an improvement in patients with motor fluctuations [10] [11] presenting a pharmacological profile with significant results, however, it is still necessary to carry out some studies, although the drug has already been used in the USA and Japan for the treatment of Parkinson's disease [12].In the face of technological advances, in the most diverse areas of research in the scientific field, especially in the planning and discovery of new drugs, molecular modeling emerged, providing the search for better results in the process of characterization of molecules in their pharmacological action. Among the various applications of chemistry, we have the computational chemistry that has been playing a relevant role in molecular modeling, providing the development of high performance software in the use of two-dimensional and three-dimensional images, allowing a better visualization of the models, employed by the scientific community to represent the atomic arrangements and the processes involved in physicochemical phenomena [13].

The aim of the present work was to use the semi-empirical quantum mechanical method Parametric Method 3 to characterize the drug Istradefylline, thus creating a database for the future development of more efficient analogues.

II.METHODOLOGY

The present work was carried out with a computational support, using the software compatible with the Microsoft Windows Seven® operating system. The software used has a free license for academic purposes.

Initially, a search of the Istradefylline structure was performed in the ChemSpider® repository (http://www.chemspider.com/.) [14], where it was possible to obtain the pharmacological structure, the visualization of the two-dimensional structure (2D) (Fig. 1) and some of its pharmacological properties.

Using the methodology proposed by Dewar and collaborators [15], he used the software Arguslab® [16] to perform the calculations based on the semi-empirical method (Parametric Method 3), (HF-SCF) open shell (UHF-Unrestricted Hartree-Fock), configured for 300 interactions (1000 cycles), with a convergence value of 10 -10 kcal mol-1 with STO-6G base function sets [17], obtaining the optimization of geometry, Mulliken's charges, the frontier orbitals (HOMO, LUMO), the Electrostatic Potential Mapping (MEP) and the Van der Waals surface map in Avogadro® software (https://avogadro.cc/).

III. RESULTS AND DISCUSSIONS

The ChemSpider® repository is a database of chemical substances, it is a bioinformatics resource for free access to research, it also provides technical data on the molecule for guidance in laboratory research as well as data (C20H24N4O4), storage (Store at + 4 ° C), degree of purity (≥ 99% (HPLC)), identification code (5311037) (≥ 99% (HPLC)), solubility data [(7.69 mg / mL) (20mM)], CAS identification number (155270-99-8), name according to IUPAC (8 - [(1E) - 2- (2- (3,4-Dimethoxyphenyl) ethenyl] -1,3-diethyl-3,7-dihydro-7-methyl-1H-purine-2,6-dione) and physicochemical properties for the molecular modeling study.The present study was carried out based on the quantum mechanics calculations, using the quantum physics equations to calculate the properties of a molecule from the interactions between its electrons and nuclei, considering that, since the electrons spin in

around the core it is possible to determine the electron energy separately from nuclear energy [18]. The calculations of quantum mechanics follow some approximations based on empirical data, subdivided into two methods, ab initio applied to small molecules, does not need stored data, but requires a large capacity of memory and calculation time of the computer and semi-empirical, can be used in energy minimization and optimization of molecules ranging from 10 to 120 atoms, the energy obtained is calculated through the Schroedinger equation from stored parameters, in a short time interval [18] [19].The ArgusLab® software works with a semi-empirical method, which in turn is frequently used on the Hamiltonian operator and subdivided with methods AM1, PM3 and MNDO. The molecules designed in a two-dimensional and three-dimensional way are not always in their most stable formation, thus there are some distortions in the molecular structure, that is, presenting an unfavorable formation of lengths and angles of connection, in which the process of optimization and energy minimization are used to correct these distortions [19]. In this context, the calculations were performed based on quantum mechanics using the semi-empirical method Parametric Method 3 (PM3), (NDDO), using the Hartree-Fock (HF-SCF) open shell approach (UHF-Unrestricted Hartree-Fock) to the maximum of 300 interactions [20] [21]. With these parameters, the optimization of geometry was determined by the interaction method SFC -105624.5724 Kcal mol-1 (Fig. 2), which can visualize the molecule on another aspect.

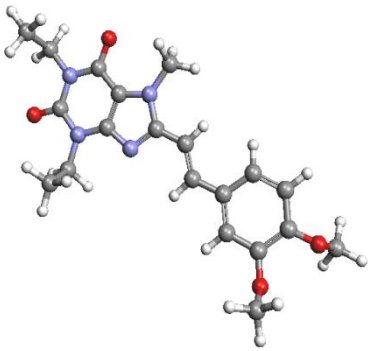

Fig. 2.Optimized structure of the drug Istradefylline.

As for the electron densities of the HOMO orbital, with higher occupied energy and the LUMO orbital, with lower vacant energy, these are characterized by the fact that they provide information about the electron-donor and / or electron-acceptor character of a compound, however, for HOMO energy greater than its electron-donor capacity, and the smaller the LUMO energy the lower the resistance to accepting electrons [21]. However, we can visualize these orbitals of the Istradefylline structure from Figure 3 (A) and 3 (B), which identified the following atoms present in the HOMO formation: (C1), (C2), (C4), (C8), (C8), (C10), (C11), (N3), (N6), (N9) and (O19), and in the formation of the LUMO orbital atoms: (C2), (C8), (C10), (C11), (C13), (C16), (C17), (C24), (N7) and (N9) which will contribute to the formation of these orbitals.

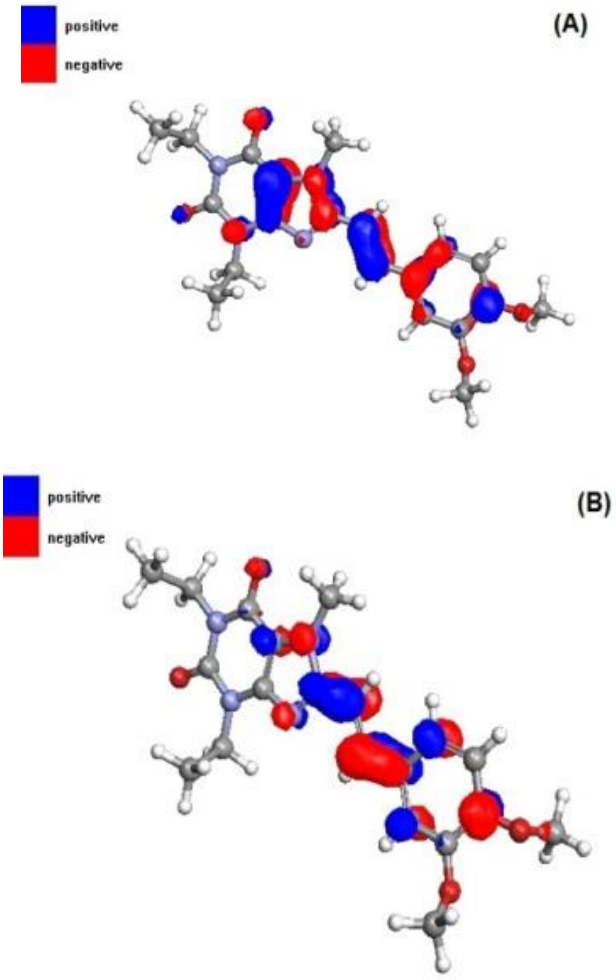

Fig. 3**.** Frontier molecular orbitals for Istradefylline: (A) Orbital HOMO; (B) LUMO Orbital.

Based on the molecular orbitals theory, Mulliken population analysis is one of the most widely used methods among chemists in which a set of molecular orbitals is determined by the linear combination of K of base functions, with definition in the coefficients by the method of Hartree-Fock [22]. Due to a methodology built from basic functions, it is expected results with a high dependence on the values presented according to the choice of the base function, these loads are obtained through standard energy calculations without any computational cost in obtaining it [23]. However, with Mulliken's population analysis of the Istradefylline molecule, regions with a higher electronegativity were identified in carbon atoms (C4), nitrogen (N7), oxygen (O18) and higher positivity in carbon atoms (C13, C14) and nitrogen (N3, N6, N9) [24].

TABLE II
Population analysis of Mulliken for the C, N and O atoms of the molecule Istradefylline

1 C	**-0.2225**
2 C	-0.1752
3 N	0.2826
4 C	-0.5316
5 C	-0.2525
6 N	0.7678
7 N	-0.0470
8 C	-0.2969
9 N	0.4949
10 C	-0.1560
11 C	-0.1973
12 C	-0.0247
13 C	0.0777
14 C	0.0802
15 C	-0.2831
16 C	-0.2692
17 C	-0.1904
18 O	-0.2347
19 C	-0.1859
20 C	-0.3483
21 C	-0.3841
22 C	-0.2561
23 C	-0.3512
24 C	-0.1581
25 C	-0.1648
26 C	-0.1342
27 C	-0.1345
28 C	-0.4370

To understand the main factors that manage the drug-receptor interactions, addressing the possible nucleophilic and electrolytic binding sites of a molecule, we have as one of the electronic parameters, the electrostatic potential map (MEP), this being one of the descriptors most used by the scientific community in locating the electrostatic potentials in the structure [13]. The three-dimensional maps define the distribution of the electrostatic potential on the molecular surface, that is, they present a grid of points around the molecule, located at a considerable distance, being generated after the overlap of a positive point load under the van der contact surface Waals (Fig. 4) in each atom, identifying regions of repulsion and attraction of the molecule, from the differentiation of colors, common features in computational software [25]. It is soon understood that the regions of lighter color (which tends to blue), represent the zones of positive potential, i.e. electrophilic regions poor in electrons, while regions of stronger coloration (which tend to red), have electronegative potential, that is, nucleophilic regions with higher electron densities having a high concentration in electrons [13].

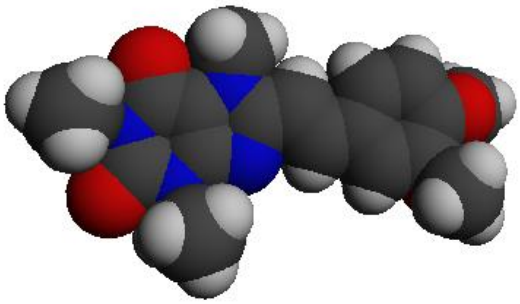

Fig.4. Istradefylline Van der Waals Balls

According to what has been described, the ArgusLab® software [16] allows us to perform these types of calculations that generates the visualization of the electrostatic potential map (Fig. 5). However, by means of theoretical calculations (PM3), the possible nucleophilic bond sites in the nitrogen and oxygen atoms were identified, with a high

concentration of electrons and carbon and hydrogen atoms (mainly carbon) being a more nucleophilic point [13].

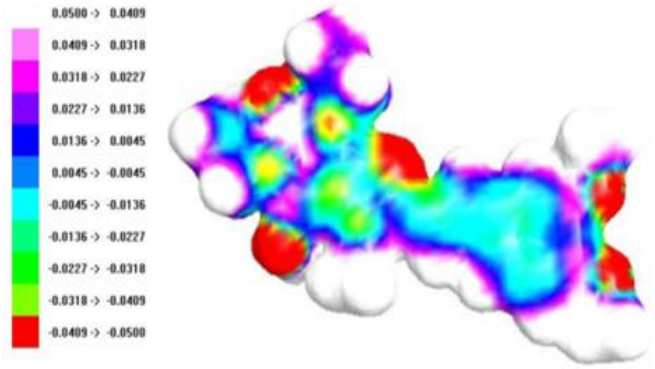

Fig. 5.Istradefylline drug MEP

IV. CONCLUSIONS

The in silico study of the drug Istradefylline, using Parametric Method 3, allowed the realization of energy minimization and optimization calculations, obtaining a stable energy conformation through the interactions of the Self Consistent Field method (-105624.5724 kcal mol-1) . With the calculations of the HOMO and LUMO frontier orbitals, it was possible to identify the atoms involved in the formation of these orbitals. In the population analysis of Mulliken, it was obtained a difference in the load variations, presenting the minimum and maximum values in the atoms: carbon, varying from -0.5316 to 0.0777; oxygen, ranging from -0.0470 to 0.7678; nitrogen, ranging from -0.2347 to -0.1581. Finally, the three-dimensional map of the study drug was generated, presenting regions of attraction (nucleophilic) in the oxygen and nitrogen atoms (N7), in which regions of repulsion in carbon atoms (C13) and nitrogen were identified (N3) (N6) (N9), electrophilic region. The data obtained in this study may serve as a basis for future Drug design studies.

V. ACKNOWLEDGMENT

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