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In Silico Study of Antiparkinson Drug Levodopa and Drug Design of Four Theoretical Analogues

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Abstract **- Levodopa or (S) -2-amino-3- (3,4-dihydroxyphenyl) propanoic acid is an antiparkinsonian drug, precursor of Dopamine and used in the treatment of Parkinson's disease. Its use in massive quantities can lead to secondary problems for the patient. Using a semi-empirical quantum approach, the electronic and structural characterization of the drug Levodopa and its theoretical analogues were performed. We concluded that the possible replacement of the acid hydroxyl by SH, NH2 and F, respectively, can generate drugs with distinctive characteristics of the original molecule, being the beginning for the development of new drugs more efficient against Parkinson's disease, thus seeking more structures stable.**

Keywords **- molecular modeling, Parametric Method 3, Parkinson's disease, Semi-empirical, Theoretical chemistry.**

I. INTRODUCTION

Parkinson's disease is a chronic and progressive neurological disease resulting from the degeneration of the substantia nigra cells of the midbrain. This disease presents a prevalence of 700 / 100,000 in people aged 60 years and 69 years, and 1500 / 100,000 in people with age range ranging from 70 to 79 years, can also occur in younger people[1]. The degeneration of neurons in the black brain region results in decreased dopamine production with nigrostriatal pathway dysfunction and subsequent loss of striatal dopamine [2]. A dopamine is a neurotransmitter that, other functions, controls the movements [1], thus, when its own deficiency, causes the employee in structures located deep in the brain, which are involved without movement control, causing the appearance of the main signals symptoms of the disease, which are bradykinesia (slow movement), rest tremor, stiffness and postural instability [2]. Among the drugs used to treat this disease is (S) -2-amino-3- (3,4-dihydroxyphenyl) propanoic acid (Levodopa), a drug of the antiparkinsonian family. This drug crosses the blood-brain barrier and the central nervous system is converted into dopamine by the enzymatic action of dopa-decarboxylase3. However, much of it undergoes decarboxylation before reaching the central nervous system [4], which leads to side effects. For this reason, it is administered together with carbidopa, a peripheral dopa-decarboxylase inhibitor, to increase therapeutic potency and avoid gastrointestinal adverse effects [5]. It inhibits extra-cerebral decarboxylation, ensuring more levodopa in the brain, and consequently more dopamine production [5].

Due to the side effects caused by this medicine and the need to guarantee a quality treatment for patients, it becomes relevant the development of new drugs with the same beneficial characteristics and less damage to the human biological system. In this way, medical chemistry uses chemical computational programs and databases as tools for the planning of new drugs or derivatives, in the investigation of chemical linker-receptor interactions and in the exploration of structural factors related to the biological effect, such as elucidation of the pharmacologist, which is the structural part responsible for biological action.

Molecular modeling allows the study and planning of new drugs and the understanding of the structure-activity relationship (REA) to elucidate mechanisms of action, using three-dimensional computational graphics and numerical values [6]. In this sense, interest in this study was based on the application of semi-empirical quantum methods (Parametric Method 3) to understand the physicochemical and reactivity properties of new analogous derivatives of (S) -2-amino-3- (3,4-dihydroxyphenyl) propanoic acid, which may be of interest for the antiparkinsonian mechanism of action, the present study being a fundamental step for the rational planning of new derivatives and new drug candidates with higher antiparkinsonian activity and reduced toxicity.

II. METHODOLOGY

The great development of theoretical chemistry in recent years is due in large part to the advance of computational resources in terms of hardware and software [7]. For the elaboration of this work, softwares of the area of computational chemistry with free license for academic purposes were used. The research started with the search in the ChemSpider repository (http://www.chemspider.com/) where the molecular structure of levodopa (.mol format) was obtained, as well as its nomenclature according to IUPAC, molecular formula , molar mass. Using ACDLabs Advanced Chemistry Development software, ChemSketch®, to modify structure (theoretical analogues) and perform an analysis of the basic molecular properties, visualization of the two-dimensional structure and the map of electronic density [8][9]. Using the Arguslab® software [10], configured to use the quantum method (QM) and the semi-empirical method Parametric Method 3 (PM3) (NDDO), using the Hartree-Fock (HF-SCF) open shell (UHF-Unrestricted Hartree-Fock), configured for 200 interactions (1000 cycles), with a convergence value of 10 -10 kcal mol-1 using STO- 6G, with the purpose of minimizing energy, aiming at the identification of the electronic and structural properties, determination of the map of electrostatic potential (MEP).

III. RESULTS AND DISCUSSIONS

ChemSketch® is a design package that allows you to design chemical structures, including organic, organometallic compounds and polymers [11]. It also includes features such as calculation of molecular properties (molecular weight, molar density), visualization of 2D and 3D structures. Using the ChemsSketch® program, we visualized the structures of Levodopa and its analogs in 2D (Fig. 1) and 3D (Fig. 2), performed all the essential calculations, and thus, due to these calculations favored by the program, the molecular properties were obtained of the Levodopa molecule and its analogs (Table I), where it was possible to observe that the theoretical Analog A, which differs by the substitution of the acid hydroxyl by a sulfhydryl group, caused a great increase in molar refraction, molar volume and polarizability.

TABLE I

Properties of the molecule Levodopa and its analogs, obtained in silico, by the ChemSketch®

Propriedade	levodopa	AnalogousA	AnalogousB	AnalogousC	analogous D
molar refraction	49.25 ± 0.3 cm^3	55,61 +- 0,3 cm^3	51.25 ± 0.3 cm^3	47.88 ± 0.3 cm^3	-
molar volume	134.2 ± 3.0 cm^3	150,8 +- 3,0 cm^3	140.4 ± 3.0 cm^3	142.2 ± 3.0 cm^3	-
Refractive index	1.654 ± 0.02	1.659 +- 0.02	1.650 ± 0.02	1.588 ± 0.02	-
Superficial tension	80.2 ± 3.0 dynec m^{-3}	70.4 +- 3.0 dynec m^{-3}	75.5 ± 3.0 dyne cm^{-3}	59.2 ± 3.0 dyne cm^{-3}	-
Density	1.468 ± 0.06 gcm^{-3}	1.413 +- 0.06 g cm^{-3}	1.396 ± 0.06 g cm^{-3}	1.400 ± 0.06 g cm^{-3}	-
polarizability	19.52 ± 0.5 $10^{-24}cm^3$	22.04 +- 0.5 10^{-24} cm^3	20.31 ± 0.5 $10^{-24}cm^3$	18.98 ± 0.5 $10^{-24}cm^3$	-

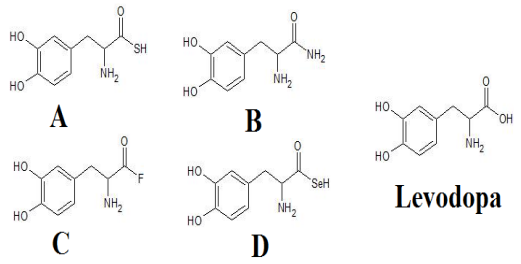

Fig. 1. Levodopa® molecule and 4 theoretical analogs using ChemSketch® software.

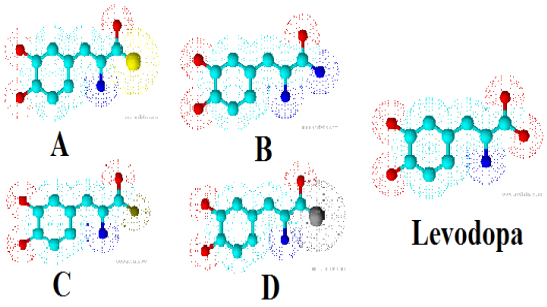

Fig. 2. Three-dimensional (3D) images of the molecule Levodopa and its analogues (A, B, C and D), provided by ChemSketch® software

he Arguslab® [10] is a software that allows generating and observing the map of electrostatic potential (MEP), calculating the energies of orbitals among other information relevant to the study of a given molecule. In this way, the molecule of Levodopa had its optimized geometry (Figure 3), obtaining in this way a molecular structure with the final energy equal to (-59339.0566 kcal mol^{-1}) and heat of formation equal to (-152.2349 kcal mol^{-1}). The theoretical analogues were submitted to the same procedure performed with the original structure obtaining their respective values of heat of formation and final energy (Table II).

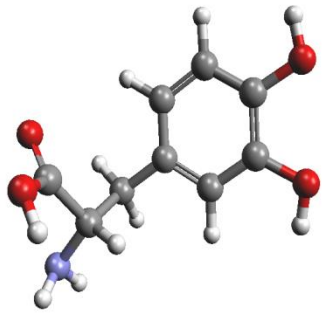

Fig.3.Optimized geometry of the Levodopa® molecule

With the Arguslab® software [10 -11] it was possible to generate the electrostatic potential map (MEP) of the original Levodopa molecule and its analogs (Figure 04). The MEP allowed us to identify which atoms have the highest and lowest electrostatic potential, being an indication of reactivity, that is, where the active sites of the substance are located [12].

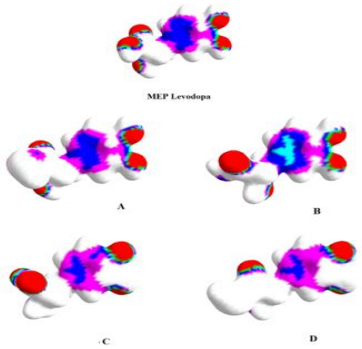

Fig. 4. Levodopa® Electrostatic Potential Map and its analogues

In the map of electrostatic potential (MEP) the regions with high concentrations of electrons are shown in the coloring tending to red, whereas the less concentrated regions tend to white in the following order: RED <GREEN <BLUE <VIOLET <WHITE, this helps in the identification of nucleophilic and electrophilic sites [12], besides allowing to predict the places where the interaction between the molecule and the receptor could occur.It can be observed according to the map of electrostatic potential of the molecule Levodopa® that the most electronegative points are in the atoms of O1, O2, O3, O4 and N5. In the analogues after the replacement of an oxygen atom with another element, a change in the structure and in the electronegative regions can be observed. In the D analogue, a greater change was observed, since it was visibly the one that showed the greatest decrease in the electronegative area, where as the analogues A, B and C showed a smaller decrease in the electronegative areas.

In analogue A we observed the regions of O1, O2, O3 and S25 as being the most electronegative; in analog B the regions O1, O2, O3, N4 and N24 were observed; in the C analog the regions O1, O2, O3,

N11 and F24 were observed and in the analog D the O1, O2, O3, N4 and Se25 regions were observed. In fact, as can be observed in Figure 4, there was no major change in the electronegative characteristic of each analogue. However, among the four theoretical analogs created, the analogues A, B and C showed smaller decreases in electronegativity. Since it is possible to observe in figure 4 that both have larger regions in the coloring tending to red and blue, which in the order of electronegativity are the strongest (more electronegative).With the substitution of an oxygen of the carboxyl group of the molecule of Levodopa® by other elements, it is possible to observe variation in the energy of formation and final energy of each analog created (Table II). It was observed that by replacing oxygen with a sulfur atom (analogue A) the formation energy was -87.0345 kcal mol -1 and the final energy of -56838.9040 kcal mol -1, when replacing with a nitrogen atom (analog B) the formation energy was -101.7176 kcal $mol^{-1}$and the final energy -62100.2927 kcal mol^{-1}, when substituting a fluid atom (analogue C) the formation energy was -150.0363 kcal / mol and the final energy of -62359.5374 kcal / mol and when replacing with a selenium atom (analog D) the formation energy was -94.4282 kcal / mol and the final energy of -57049.1421 kcal / mol. These differences generated in each analogue, however small, are of great relevance for the selection of candidates for the development of new drugs.

TABLE II

Formation and final energies calculated on the Arguslab® of levodopa and its theoretical analogues

Molecule	Formation Energy	Final Energy
Levodopa	-152.2349 kcal mol -1	-59339.0566 kcal mol -1
A	-87.0345 kcal mol -1	-56838.9040 kcal mol -1
B	-101.7176 kcal mol -1	-62100.2927 kcal mol -1
C	-150.0363 kcal mol -1	-62359.5374 kcal mol -1
D	-94.4282 kcal mol -1	-57049.1421 kcal mol -1

IV. CONCLUSIONS

Molecular modeling provides essential information for the drug discovery process. It allows the achievement of specific properties of a molecule that can influence the interaction with the receptor. The substitution of acid hydroxyl, a sulfhydryl group, caused a great increase in the molar refraction, the molar volume and the polarizability, with respect to potential energy. The same procedure indicated that the substitution by Nitrogen and Fluoride, respectively, indicated to be more stable analogs. We conclude that the possible replacement of the acid hydroxyl by SH, NH2 and F, respectively, can generate drugs with more stable characteristics of the original molecule, being the beginning for the development of new drugs more efficient against Parkinson's disease.

V. ACKNOWLEDGMENT

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