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Structural and Electronic Characterization of the Vasopressin Drug Treprostinil, an in Silico Study with Semi-Empirical Quantum Approach

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Abstract - ***Pulmonary hypertension (HP) is a disease characterized by high blood pressure levels in the pulmonary arteries, thus causing overload and failure of the right side of the heart. The treatment can only be established after the diagnosis by the definition of the clinical groups, although there is no cure for this disease the treatment is given through medicines of adequate use. The drug treprostinil is a synthetic analogue of prostacyclin, indicated in the treatment of pulmonary hypertension, a vasodilator, used to decrease the symptoms associated with HP, however this medicine presents serious risks, including serious infections of blood flow. The present work aimed to characterize the structure and electronically the drug treprostinil, using the semi-empirical quantum method. In the first moment, the two-dimensional visualization and download of the molecule occurred in the DrugBank repository, followed by the drawing of the Treprostinil molecule in the Marvin Sketch® software, which obtained some of its specific properties. In the second moment, the process of optimization of molecular geometry with the aid of the ArgusLab® software configured to use the semi-empirical method PM3, based on the quantum mechanics, using Hartree-Fock SFC approximation, was carried out. A more stable energy conformation and heat of formation equal to - 57,388 Kcal mol-1, the population analysis of Mulliken, showed a small variation in the load difference, which was possible to identify the minimum and maximum values in the Atoms: carbon and oxygen. In the last step, the three-dimensional electrostatic potential map of the drug demonstrated to be rather nucleophilic in the oxygen and carbon atoms of the aromatic ring, whereas the carbon and hydrogen atoms had an electrophilic region. The data obtained in this work may be used in the future, proposing possible modifications of structures for more efficient analogues.***

Keywords - Computational simulation. Pulmonary hypertension. Treprostinil.

I. INTRODUCTION

Pulmonary hypertension (HP) is a rare disease, characterized by the increase of blood pressure levels in the pulmonary vascular territory, that is, the increase of blood pressure occurs due to the narrowing of pulmonary arterial hypertension (PAH) causing possible more serious complications the health. In addition, this problem usually overwhelms the right side of the heart, impairing blood circulation throughout the body and possibly bankruptcy on the right side of the heart.

According to the Ministry of Health [1], the French presented data on the occurrence of the disease among women (1.7 women: 1 man) with approximately 6 cases per million inhabitants per year, mostly reaching the elderly.Clinical studies show a survival of two and a half to three years because the symptoms presented are very similar to other types of diseases, the patient with pulmonary hypertension is usually diagnosed at an advanced stage, thus limiting the same to a healthy life [2].

Over the last few decades, HP has undergone transformations in its clinical studies, attending to the need to revise concepts and existing classifications, resulting in the regrouping of several HP diseases, which share the same physiopathological similarities in the therapeutic approaches related to the same subgroup [2]. However, the treatment can only be established after performing the diagnosis because of the definition of the clinical groups [3].Although there

is no cure for this disease the treatment is given through specific use medications.

In 1995, the use of intravenous prostacyclin (fig 1A) in patients with PH was approved in order to improve hemodynamic changes and quality of life of these individuals [4]. With the measures adopted in the last decades, later the prostacyclin analogs of which example Treprostinil (fig.1B) [3] appeared. Treprostinil (generic name) is a synthetic analog that binds to the prostacyclin receptor, indicated in the treatment of pulmonary hypertension, commercially known as Remodulin®, a vasodilator, used to decrease symptoms [5]. Remodeling may be administered as a continuous subcutaneous infusion or continuous intravenous infusion. However, this drug presents risks associated with permanent central venous catheters, including serious blood flow infections [6].

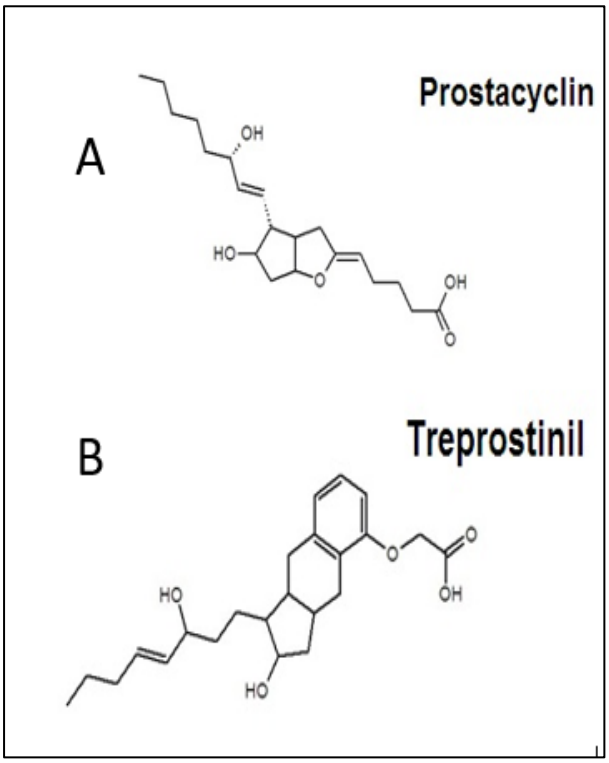

Fig. 1. Structures prostacyclin (A) and its analogue treprostinil (B). Source:Drugbank®

Currently, advances in computational chemistry have been significant in relation to the pharmaceutical market in the area of drug development. Recent advances in the computational field have demonstrated efficient quantum-chemistry algorithms providing molecular parameters of the ab-initio and semi-empirical methods, expressing geometric and electronic properties of the molecules and their interactions in a short time interval [7].The molecular modeling is based on a set of tools that aims to study molecular properties from structural design to virtual characterization, which involves visualization, analysis and storage of molecular systems [8].

In this perspective, through molecular modeling methodology the present work aimed to perform the structural and electronic characterization of the drug treprostinil, using the semi-empirical quantum method Parametric Method 3 (PM3).

II. METHODOLOGY

For the accomplishment of this work, we used Computer simulation softwares with free license for academic and research purposes.All simulations were performed on a personal computer, based on the Microsoft Windows Seven® Operating System.

In the first moment, the two-dimensional visualization and downloading of the molecule in the DrugBank® version 5.0 [10] was performed, followed by the drawing of the molecule Treprostinil in the Marvin Sketch © software which obtained elementary analysis of some basic descriptors, that is, some of its specific properties.

Following the methodology proposed by Dewar and colleagues [11], the molecular geometry of the treprostinil drug was optimized using the ArgusLab® software [12]. According to Silva et al. [13], molecular descriptors are currently considered a very important tool in the prediction of molecular properties, by providing information about the physicochemical nature of the activity or properties under study in a mathematically quantified and computerized way. Following this context, the virtual simulation calculations were obtained through the semi-empirical method PM3 (Parametric Method 3), based on quantum mechanics, using a Hartree-Fock SFC approximation, with a maximum number of 500 interactions (MOL), the Mulliken population analysis, the frontier orbitals (HOMO and LUMO), the electrostatic potential map (MEP), and the Van Der Waals surface map in the Avogadro software ®

version: 1.2.0, library version: 1.2.0, Open Babel Version: 2.3.90, Qt version: 4.8.6).

III. RESULTS AND DISCUSSIONS

Action and the effect of drugs on the human body are usually rigid by the molecular structure of drugs. The optimization of physicochemical properties plays a fundamental role in the early stages of the discovery and design of molecules, there is, taking into account that the physicochemical and biological properties of a molecule is directly linked to its three-dimensional and conformational structure, structure Treprostinil was submitted to the Elemental Analysis Plugin in the program Marvin Sketch © (freeware), which obtained some of its specific properties as molecular formula C23H32O5, molar mass 388,504, percentage composition C (71.11%), H (8.30 %), O (20.59%) and the mass spectrum result (Figure 2) [m / z: (388: 1.00) (389: 0.25) (390: 0.04) 391: 0.01)], the mass distribution of the input molecule is calculated by considering the relative abundance of the isotopes [m / z].

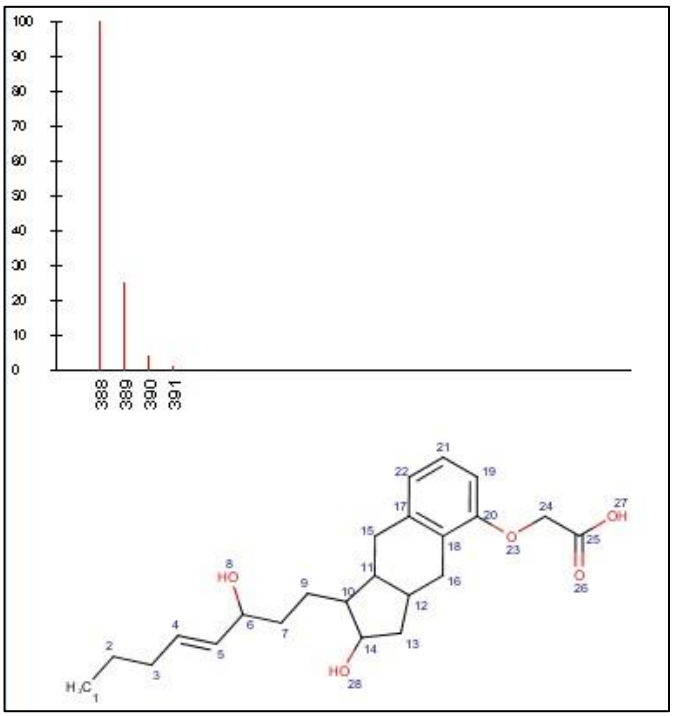

Fig. 2. Elementary analysis of the basic descriptors of a structure.

During the design of a defined molecule, the irregular formation of its conformation (angles and length) in its structural can occur. These distortions are corrected from mathematical methods, which experimentally explore characteristics of a structure through its conformational analysis, used interactively in the process of energy minimization and geometry optimization, in order to determine a stable energy conformation, providing a molecule under new perspective [14]. In this context, based on mathematical methods in quantum mechanics, the process of energy minimization and geometry optimization was used with the help of Arguslab® software. The calculations were performed using the Hamiltonian semi-empirical method (PM3-Parametric Method 3) using the Hartree-Fock (HF-SCF) open shell approach (UHF-Unrestricted Hartree-Fock), configured for 500 interactions), with a convergence value of 10-10 kcal mol-1 [15]. According to these parameters a stable energy formation was determined through the interactions SFC -1081.3789 kcal.mol-1, formation -57.388 Kcal.mol-1, being possible to plot three-dimensional the conformational structure (Figure 3).

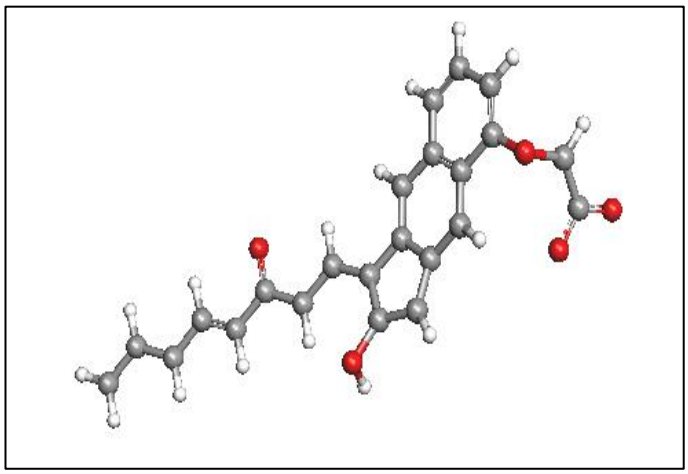

Fig. 3.Structure of the treprostinil drug optimized by the semi-empirical method PM3

According to Leal and collaborators [16], the electric dipole moment, is measured in debyes (D), through the relevance of the partial loads and the distances between the ends of a dipole. However, through the quantum mechanics calculations, it was

possible to determine the value of the dipole moment of the Remodulin® structure of agreements with the Cartesian coordinates, obtaining the moment value in the X-axis (-2.1202 D), Y (0.0046 D) and Z (-0.6788) with resulting vector in the length of 2.2263 Å.

Molecular orbitals contribute significantly to the advancement of all research frontiers in the field of chemistry, especially the HOMO orbitals and the LUMO orbitals. These orbitals have arisen in analysis of the electron density in each atom of the border orbitals, by a group of Japanese who investigated the reactivity of aromatic compounds [17]. The definition of these orbitals is related to two important characteristics, the HOMO energy having an electron-donor character and energy LUMO measures the electron-acceptor character [7-8] The data obtained in the geometric optimization, allowed to plot the frontier orbitals, where HOMO (Figure 4) shows asymmetry between the positive (blue) and negative (red) (C5, C6, C7, C10, C13, C15, C16) and oxygen (O8). It was possible to observe that it was formed from the carbon atoms (C1, C3, C5, C9, C10, C13) and also showed asymmetry between the positive and negative phases.

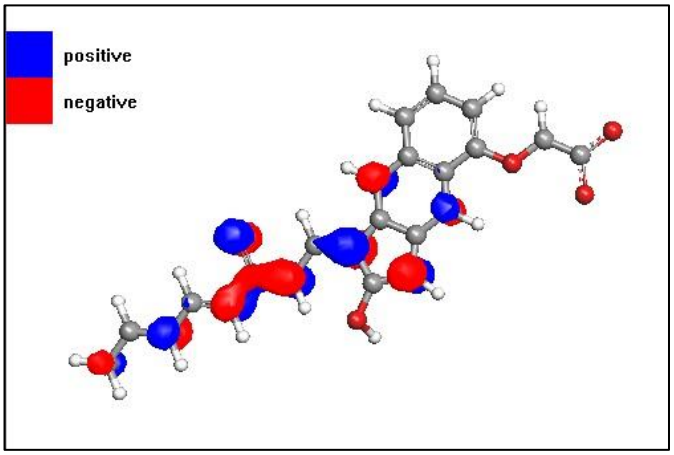

Fig. 4. Frontier molecular orbitals (HOMO) for the molecule of Treprostinil by semi-empirical method PM3.

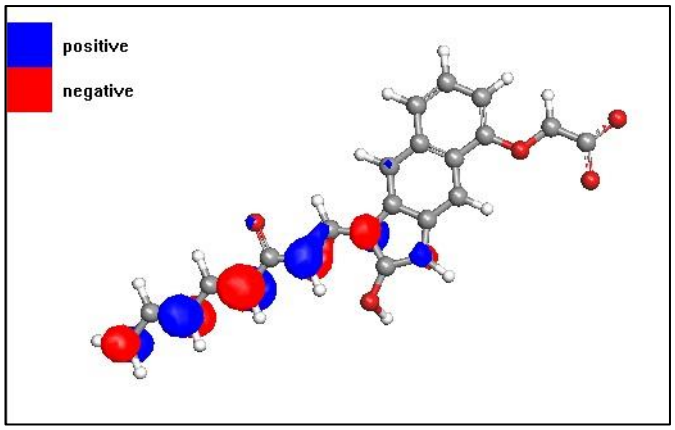

Fig. 5. Frontier molecular orbitals (LUMO) for the molecule Treprostinil by semi-empirical method PM3.

According to Guadagnini and Bruns [18], the electronic parameters used for the calculation of atomic charges are due to the implementation and interpretation of the atomic charges. In this context, numerous methods describe the molecular electronic distribution, among which is the population analysis of Mulliken. The current Mulliken load calculation method, such as Mulliken's population analysis, is a base set used in a partition scheme in the use of matrix density to distribute electrons in a molecular entity among its various pairs: atoms, bonds, and orbital [19]. Its popularity is due to the intensive applications that are used in the theory of molecular orbitals that can be easily calculated by directly obtaining all the variables necessary to carry out the population analysis, and no computational cost is necessary [18]. From the analysis of the SCF wave function the calculation performed with the Mulliken charge property (Table I) for the treprostinil molecule, a very nucleophilic end was identified at the carbon (C4) and oxygen (O9) atoms, which has been identified as an electrophilic region on the carbon atoms (C6), (C18) and (C21).

TABLE I

Population analysis of Mulliken for the C and O atoms of the molecule *treprostinil*

1 C	-0,3069
2 C	-0,2459
3 C	-0,0657
4 C	-0,4155
5 C	-0,2661
6 C	0,3374
7 C	-0,3303
8 C	-0,2288
9 O	-0,4107
10 C	-0,1295
11 C	-0, 1074
12 C	-0,1065
13 C	-0,0053
14 C	-0,1836
15 C	-0,1793
16 C	-0,1708
17 C	-0,2214
18 C	0,0618
19 C	-0,3361
20 C	-0,1339
21 C	0,1325
22 C	-0,2302
23 O	-0,1183
24 C	-0,1528
25 C	-0,3678
26 O	-0,3650
27 O	-0,2396

According to Sant'Anna [20], electrostatic potential is established as the work to transport a positive unit charge from infinity to a certain point in space, to which these electrostatic potentials are represented by three-dimensional maps used to understand the electrostatic contribution on the molecular surface through color differences, through computational resources from molecular modeling. Following the Sant'Anna context, the map of molecular electrostatic potential (MEP) is calculated through a grid of points detected in different layers, constructed as an overlap of Van Der Waals spheres (Figure 5) on each atom around the molecule.

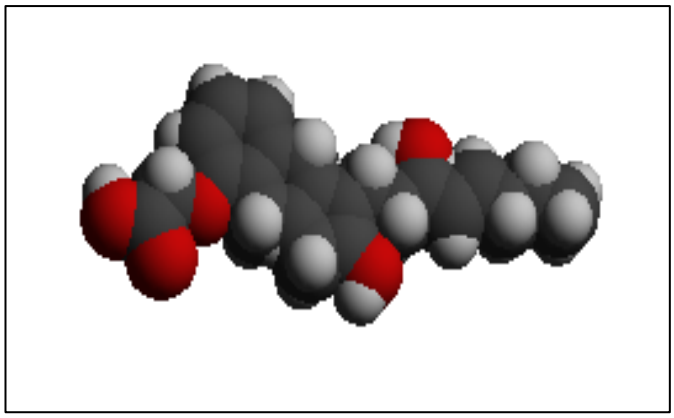

Fig. 6. Treprostinil Van der Waals Balls

The three-dimensional electrostatic maps allow us to predict the possible sites of nucleophilic and electrophilic bonds between biological molecules and their respective receptors [21], which confirms the theoretical concepts of the formation of bonds between atoms, involving forces of an electrostatic nature between signal charging poles in reverse [22]. In this way, by means of semi-empirical theoretical calculations, it was possible to obtain the map of electrostatic potential (Figure 4) of the molecule Treprostinil, which could be noticed in the colors that tend to red a nucleophilic electronic density very concentrated in the atoms of oxygen and carbon of the aromatic ring and this region is conducive to possible nucleophilic binding sites. Therefore, the lighter colors that tend to blue, have identified an electrophilic region, establishing this area as electropositive, deficient in electrons in the atoms of carbon and hydrogen, mainly in the carbon atoms [23].

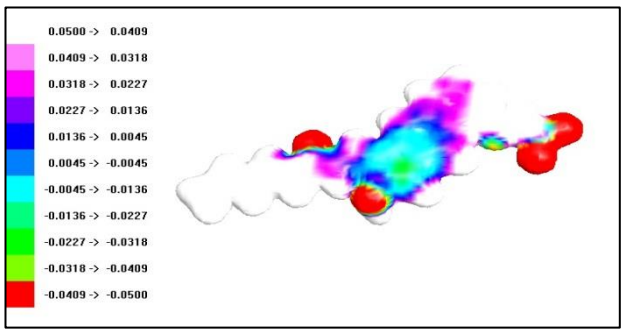

Fig. 7. Treprostinil drug MEP

IV. CONCLUSIONS

According to the cited literature and results obtained using the Marvin Sketch ©, Arguslab® and Avogrado® computational freeware software, the calculations performed allowed to obtain basic properties of the treprostinil molecule, and the electronic and structural characterization of this drug, which identified a stable energy conformation, potential energy of -1081.3789 kcal.mol^{-1} and formation heat -57.388 Kcal.mol^{-1} through the semi-empirical method (PM3). The calculations also allowed observing the contributions in terms of HOMO-LUMO molecular orbitals, in which the present atoms were obtained in the formation of these orbitals. Based on the literature on the Mulliken atomic charges, it was possible to obtain the results through the SCF wave function, showing a small variation in the charge difference, indicating the minimum and maximum values in the carbon atoms, varying from (-0.4155 to 0.0618) and oxygen ranged from -0.4107 to -0.1183. The three-dimensional maps of the study drug, calculated using the van der Waals spheres overlapping methodology on each atom around the molecule, was generated by the ArgusLab® software by means of semi-empirical theoretical calculations showing a rather nucleophilic end in the atoms of oxygen (O9); (O23); (O26); (O27); (028) and aromatic ring carbon (C12); (C19); (C20), already the atoms of carbon and hydrogen presenting an electrophilic region. This paper presents the structural and electronic results that can be used in the near future in the development of new compounds. Thus, with this data we can propose and evaluate the development of more efficient drugs in the molecule of treprostinil, that is, proposing possible modifications of structures for analogues more effective, attempts to seek better therapeutic effects in the optimization of drugs.

V. ACKNOWLEDGMENT

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