Molecular electrostatic potential surface, HOMO–LUMO, and computational analysis of synthetic drug Rilpivirine

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Abstract—The Acquired Immune Deficiency Syndrome (AIDS) is a disease caused by the HIV virus, which attacks the cells responsible for defending the body, leaving the person vulnerable to opportunistic diseases, currently 781,000 people living infected with the virus in Brazil and there are only 22 types of drugs designed to control the disease, highlighting the need for further studies and research that seek to enhance drugs already used in the control of AIDS, but also to develop new drugs. The computational chemistry and molecular modeling software represent important tools in the development of pharmaceuticals and several pathologies. O treatment strategies present study sought through the semi-empirical approach to characterize the structural and electronic properties of the drug sintetic rilpivirine using the approach semi-empirical where it can be concluded that modeling and optimization showed that the molecule has stable conformation, has potential energy -99219.0042 kcal mol-1and heat of formation 184.4424 kcal mol-1. The Mulliken population analysis is noted that the carbon atom has a higher energy variation, with a value of 0.6338 KJ Mol-1 and the Hydrogen atoms has the smallest variation, which is 0.1843 KJ Mol-1 identifying the nucleophilic sites located in nitrogen atoms.

Keywords: AIDS. drug synthetic. rilpivirine. semi-empirical. HOMO. LUMO. MEP.

1 INTRODUCTION

The Human Immunodeficiency Virus (HIV) belongs to a group of viruses known as retroviruses. This infectious agent acts within the lymphocytes, the main defense cells of the immune system, to get into that cell, HIV integrates its genetic code. When HIV infects a human cell, it converts its RNA into DNA, in order to use the machinery of the human cell to create new virus. The virus has a core consisting of a coat proteins terminating the RNA and the enzymes necessary for viral replication, the center is surrounded by an outer membrane, from which projects the strips originating proteins (envelope protein)[1]. Among the lymphocytes, the type most affected by the virus is called CD4 T lymphocyte, used by HIV to generate copies of itself, infected by the virus, these cells start to function less efficiently until they are destroyed. Thus, over time, the ability of the organism to combat common diseases decreases, allowing then the appearance of opportunistic infections [2].

According to the latest epidemiological bulletin published in 2015 by UNAIDS (Programme Joint United Nations on HIV / AIDS) since the beginning of the epidemic in Brazil were registered in the country 798,366 AIDS cases, the study found that only in 2005 to June 2015, 410,101 new cases were reported, attesting that the emergence of AIDS and the increasing incidence of HIV infection continue as one of the major global challenges for the twenty-first century [3]. In response to epidemic various mechanisms have been developed to retard the progression of disease in infected, then they suggest many reverse transcriptase inhibitors drugs responsible for delaying the infection of human immunodeficiency virus - HIV. The European Medicines Agency defines Rilpivirine as a non-nucleoside reverse transcriptase inhibitor (NNRTI) that blocks the activity of reverse transcriptase, an enzyme produced by HIV-1, and allows to produce more virus in infected cells. By blocking this enzyme, Edurant© (medicine containing as the active substance Rilpivirine, taken in combination with other antiviral medications reduces the amount of HIV in the blood and keep the virus at low levels. The use of this drug does not cure HIV infection or AIDS, but may delay the damage to the immune system and the development of infections and diseases associated with AIDS [4].

The Rilpivirine diarylpyrimidine is a class of molecules resemble que pyrimidine nucleotides found in DNA. Officially known as 4 - {[4 - ({4 - [(1E) -2-

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Aminoethyl-1-en-1-yl] -2,6-dimethylphenyl} amino) pyrimidin-2-yl] amino} benzonitrile with molecular formula $C_{22}H_{18}O_6$, in Edurant© presents itself in the form of tablets for oral use 25 mg each. The taxonomic classification, this product belongs to the class of organic compounds known the benzonitriles, these are organic compounds containing a benzene ring having a nitrile substituent. The FDA (Food and Drug Administration - Food and Drug Administration) approved the drug on May 20, 2011 [5]. Through study and characterization of Rilpivirine, this study aimed by molecular modeling has structural and electronic parameters of the synthetic synthetic drug that can be used for future studies of the synthetic drug and thus make possible the realization structure of enhancements to improve the pharmacological action of this drug.

The computational chemistry followed a long path to become the main option for representation of molecules and operation of its characteristics in three-dimensional perspective, this chemistry branch has stood out for its effectiveness and efficiency in the statement of calculations and properties and the exploration of how these molecules will behave in a reaction, making it the most comprehensive and complete research. The development of computational chemistry brought a breakthrough in the area of drugs, the modeling of molecules allowed to obtain specific properties that can influence the interaction with the receptor, other important information can also be obtained from the structural comparison between different molecules, which can enable the generation of a similarity index may be correlated with pharmacological activity. Molecular modeling also enables three-dimensional visualization (3D) the essential drug-receptor complex and provides information on the structural requirements that allow a proper interaction of the drug at its receptor site. This tool also has the potential to plan theoretically new molecules which meet the electronic and structural properties for a perfect fit on the receiving site [6].

Thus, this study has a central role aimed at modeling rilpivirine molecule to obtain its pharmacodynamic and pharmacokinetic properties optimized using modern biotechnological tools - computational chemistry applied to molecular modeling, which provides fundamental importance information for the discovery and development of new drugs, besides improving the biological activity of drugs that are already on the market, such as the rilpivirine [7].

2 METHODOLOGY

For this work were used software developed in computational chemistry, and ChemSketch® ArgusLab 4.0® programs worked in Microsoft Windows 7® platform to display the Rilpivina molecule in three dimensions and provide essential data for this study [8].

After obtaining the rilpivirine structure modeling was held in ChemSketch® software for visualization of the molecule and 3D representation of your map of electron density. The modeling using ArgusLab 4.0® program was developed more weighted manner because this application is more complex and larger amount performs calculations, first the molecule is designed and optimized according to the methodology proposed by Dewar et al (1985) [9], wherein the software was set to optimize the structure by semi-empirical calculations (Austin Model 1 -QM-AM1) following the Hartree-Fock approximation to the maximum of 200 interactions. Using the output files, realized the potential Mapping Electrostatic (MEP) and the frontier orbitals (HOMO-Highest Occupied Molecular Orbital), (LUMO-Lowest Unoccupied Molecular Orbital).

3 RESULTS AND DISCUSSIONS

Molecular modeling of rilpivirine had its beginning from the design of its chemical structure and molecule optimization so that it remained the most stable conformation as possible (Fig. 1) using the ACD software / freeware ChemSketch (www.acdlabs.com), which it is a basic computational chemistry package that allows you to draw chemical structures (organic compounds, organometallic, polymers and Markush structures), includes features such as calculation of molecular properties, allows the structural visualization in 2D and 3D, and also has the functionality to name structures (with less than 50 ring atoms, and 3) predicting log P.

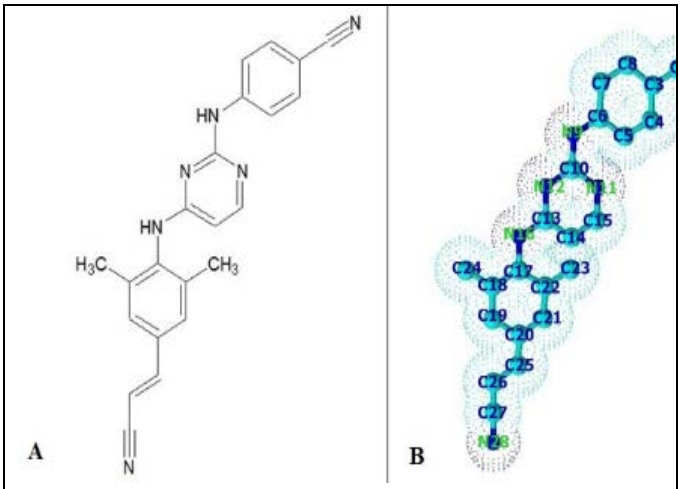

Fig.1. [A] Chemical Structure of rilpivirine; [B] Electron density map of rilpivirine

The quantum methods (based on molecular orbital theory), considered as one of the greatest intellectual achievements of the twentieth century, are based on a set of laws called quantum mechanics, which provides a mathematical description of the molecular structure in terms of atomic nuclei and electronic distribution around them.

To describe the state of a system in quantum mechanics, it was postulated the existence of a coordinate function called molecular wave function or state function), which is the solution of the Schrödinger equation (1); where H is the Hamiltonian, a mathematical expression of the energy terms of the molecule comprising the potential to kinetic energy of the electron system is particles and Ψ molecular wave function described in terms of spatial coordinates of the particles constituting the system in a certain state [10].

$$H\Psi = E\Psi \quad (1)$$

In 1985, Dewar and colleagues inserted the Gaussian functions in MNDO [9] method, this change led AM1 mainly enabling parameterization for hydrogen bonding and formation of heat with better performance than the old method [10]. The AM1 is parameterized for the elements C, H, O, N, B, F, Al, Si, P, S, Cl, Zn, Ge, Br, I, and Hg [11]. Getting loads of Mulliken, the potential map Electrostatic (MEP) and the HOMO and LUMO of Orbital Border derived software ArgusLab © 4.0, the molecule has been optimized using the Hamiltonian parameter QM - AM1 (Austin Model 1), calculation Hartree Fock with maximum 200 peak interactions and steps taken 500, the optimization converges after two rounds with the above parameters. The optimization showed that the molecule has stable conformation, has potential energy -99219.0042 kcal mol-1and heat of formation 184.4424 kcal mol-1. Population analysis Mulliken (TABLE 1) is based on the molecular orbital theory, where a set of molecular orbitals is defined by a linear combination of K atomic orbitals also called base functions, the coefficients of which are determined by the method Hartree -Fock. The atomic charges are applied in the study of the correlation between structure and biological activity of drugs [12].

TABLE 1

Population analysis de Muliken

Carbon (C)		Nitrogen (N)		Hydrogen (H)	
C 2	-0.0560	N 1	-0.0876	H 29	0.2114
C 3	-0.0455	N 9	-0.3697	H 30	0.2270
C 4	-0.1346	N 11	-0.3130	H 31	0.2039
C 5	-0.1782	N 12	-0.2850	H 32	0.2123
C 6	0.0996	N 16	-0.3697	H 33	0.2326
C 7	-0.2363	N 28	-0.0807	H 34	0.2995
C 8	-0.1256			H 35	0.2050
C 10	0.2470			H 36	0.2019
C 13	-0.0209			H 37	0.1355
C 14	-0.3868			H 38	0.1392
C 15	0.2211			H 39	0.1435
C 17	0.0473			H 40	0.1516
C 18	-0.0620			H 41	0.1467
C 19	-0.1641			H 42	0.1281
C 20	-0.0728			H 43	0.2053
C 21	-0.1572			H 44	0.2196
C 22	-0.0991			H 45	0.2366
C 23	-0.3207			H 46	0.3124
C 24	-0.3126				
C 25	-0.1185				
C 26	-0.1520				
C 27	-0.0782				

The table 1 shows great variation between the charges of atoms, with lower carbon value is -0.3868 and the highest load is 0.2470, the values of minimum and maximum loads of nitrogen are -0.3697 and -0.0807, respectively . Since the hydrogen values ranging from 0.1281 to 0.3124. The minimum energy relationship to maintain more stable conformation for the molecule. The values of the loads quantitatively describe intramolecular interactions, chemical reactivity and structural regularities [13].

Electronic parameters are one of the main factors that govern the drug-receptor interaction, in this sense, the molecular electrostatic potential map (MEP) may be an alternative approach in order to understand the electrostatic contribution of these derivatives for the activity. The MEP is one of the descriptors used in most studies and intends to disclose the total molecular size

and location of electrostatic potentials in the molecule. The three-dimensional surfaces of potential molecular electrostatic maps (MEPs) are generated after the overlap in the molecule of a positively charged particle that under the van contact surface der molecule Waals reveals a repulsion region, representing the positive potential of blueness and the region in the negative potential of the molecule, represented by the red color [14]. The properties demonstrates by electrostatic potentials Molecular - SEM (Fig. 2) based on the charge density defined from the molecular wave function map of electrostatic potential Median interaction of a positively charged point with nuclei and electrons of a molecule [15].

The hottest shades (tending to red) indicate negative values of electrostatic potential - regions rich in electrons, in the case of Rilpivirine molecule area more electronegative is composed of nitrogen atoms, as the cooler tones (tending to blue) representing electron deficiency were especially marked in rings benzene compounds exclusively of carbon and hydrogen atoms (focusing on areas of carbon), establishing this area as more electropositive.

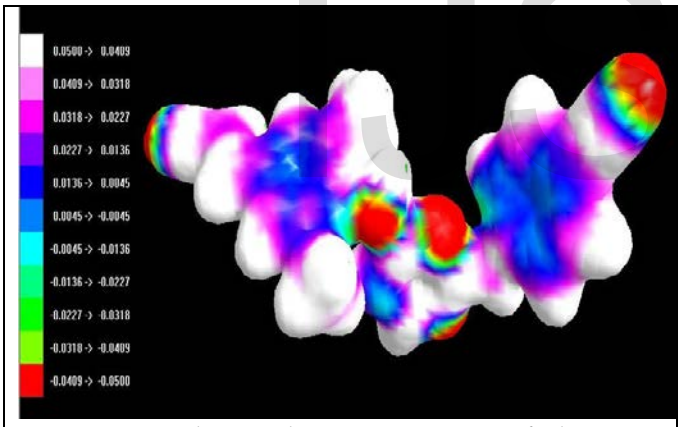

Fig. 2. Potential Map Electrostatic (MEP). of rilpivirine

According to Xavier [16], are said frontier molecular orbitals those where the chemical reactions actually occur. The orbital HOMO (High Occupied Molecular Orbital) measures the electron-donor character of a compound and the LUMO (Low Unoccupied Molecular Orbital) measures the electron-acceptor character. From these definitions, it is observed that 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. The energies of the HOMO and LUMO are used as chemical reactivity indices and are commonly correlated with other indices, such as electron affinity and ionization potential [18]. The frontier orbitals of Rilpivirine® are shown below (Fig. 3).

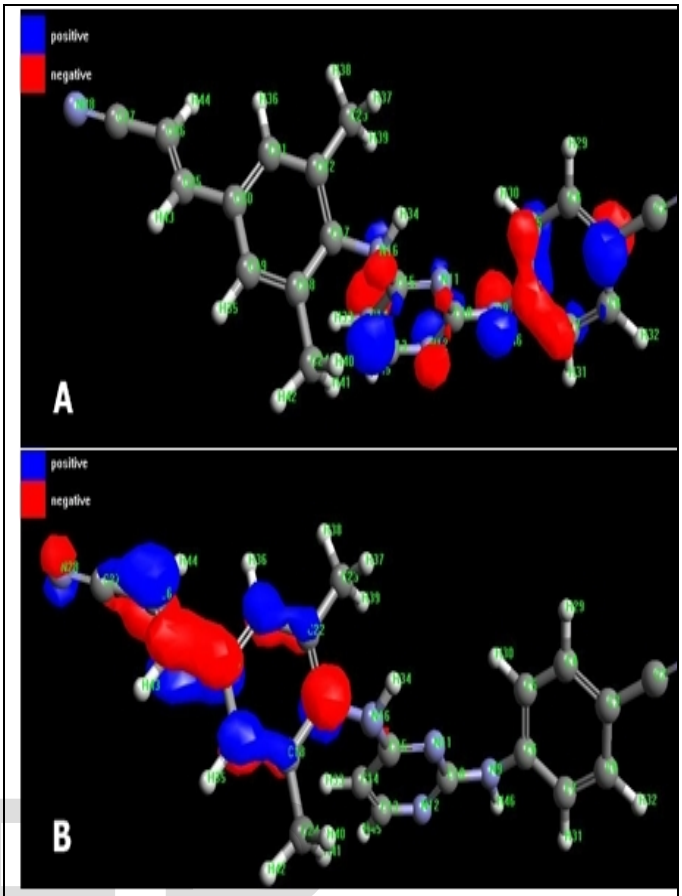

Fig. 3.- Orbital Border [A] HOMO orbital and [B] the LUMO.of rilpivirine

Fig. 3 shows the spatial orientation of the frontier orbitals HOMO and LUMO, obtained by the semi-empirical method AM1, to analyze the positioning of the orbitals is revealed that the degree of HOMO density is located in the initial part of rilpivirine molecule covering the first atoms nitrogen and significant parts of the first rings in relation to the LUMO this concentration stops from the third aromatic ring, not including the methyl groups, and extends to the end of the molecule in the last nitrogen atom, these data are chemical- descriptors quantum play an important role in chemical reactions and the formation of several charge transfer complex [14].

3 CONCLUSÕES

From this work, it can be concluded that modeling and optimization of rilpivirine showed that the molecule has stable conformation, has potential energy -99219.0042 Kcal mol $^{-1}$ and heat of formation 184.4424 kcal mol^{-1}. The Mulliken population analysis is noted that the carbon atom has a higher energy variation, with

a value of 0.6338 KJ Mol $^{-1}$ and the H atom has the smallest variation, which is 0.1843 KJ Mol $^{-1}$.

The modeling of the drug contributed effectively in the study of their structural properties, as well as in anticipation of possible sites most likely to occur interaction with their receptors, and these studies of fundamental importance for future studies employing correlations between structure three-dimensional and biological activity of rilpivirina®.

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