A DFT study of synthetic drug topiroxostat: MEP, HOMO, LUMO

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Abstract— Disorders metabolic with hyperuricemia, blood state in which is uric acid above the normal plasma levels are becoming a public health problem worldwide because uric acid levels show be an important marker of other risk factors cardiovascular diseases such as hypertension, obesity, dyslipidemia, hyperinsulinemia and sedentary lifestyle. Topiroxostat is an, non-purine, selective xanthine oxidase inhibitor, orally-administered developed for the treatment of hyperuricemia .This study utilized the density functional theory (DFT-B3LYP/6-31G) to characterize the electronic and structurally Topiroxostat drug, getting SCF (-22529.63117 eV), Potential Energy (-44946.54945 eV), Kinetic Energy (22416.91828 eV), Dipole moment (8.07717 Debye) e identifying its electrophilic (H20,N3) and nucleophilic sites(N1, N2, N4, N5 and N6), and calculating descriptors that assist in the compression of the possible reaction mechanisms will this drug, these being fundamental data for future studies of molecular coupling, to elucidate the reaction mechanism of this drug, targeting a further increase of its pharmacological action.

Keywords: Disorders metabolic. DFT. HOMO. LUMO. MEP.

1 INTRODUCTION

Hyperuricemia is a metabolic disorder characterized by excessive urate blood product from a disorder in metabolism of purines, which have been observed over several decades is becoming a public health problem worldwide [1], [2] [3]. Major clinical problems associated with hyperuricemia are gouty arthritis, tophi and uric acid kidney stones [4]. Besides being related to the development of arthropathy, hyperuricemia is an independent predictor of mortality in patients at high cardiovascular risk [5]. Although it is not an independent risk factor for the development of ischemic heart disease and overall mortality, uric acid levels have been shown to be an important marker for other risk factors of cardiovascular diseases such as, hypertension, obesity, dyslipidemia, hyperinsulinemia and sedentary lifestyle [6]. Hyperuricemia is an increase in serum monosodium urate (uric acid) concentrations. Gout is secondary to the inflammatory response that provokes MSU deposits in the tissue. Gout is the most common inflammatory arthropathy in the general population [7]. For decades, these medical problems were the main indications for the maintenance of blood uric acid levels in the normal range. However, in recent years, results derived from epidemiological and animal studies have shown the importance of hyperuricemia in the occurrence of chronic kidney disease (CKD), coronary heart disease and high blood pressure [5][8][9]. Purines are nitrogenous organic bases formed the nucleoprotein degradation, especially those of animal origin. Urea is the major end product of protein metabolism, and only small part Human nitrogen is eliminated in the form of acid uric [6] [10]. Xanthine oxidoreductase (XOR) in humans is the rate-limiting enzyme in charge of the conversion of hypoxanthine to xanthine and of xanthine to uric acid (UA) in purine metabolism, and it produces reactive oxygen species (ROS) in vivo. In rodents, UA was metabolized to allantoin by uricase, which was absent in higher primates [11].

Topiroxostat is an, non-purine, selective xanthine oxidase (XO) inhibitor, orally-administered developed for the treatment of hyperuricemia, discovered and developed by Fuji Yakuhin [12] [13], differential with the conventional inhibitors such as XO febuxostat, for interacting with the essential amino acid residues of the solvent channel [13].

Molecular modeling, consists of a set of features and visualization software, construction, editing and analysis of molecules serving as the basis of pharmacological planning; characterization of such a structure, such as the calculation of their bond angles, their bond distances and their angles dihedral is not so simple to perform on a trial basis [14], if necessary, then use methods in silico for the characterization may, by theoretical calculations based on quantum physics that optimize the geometric structure, until it reaches its most stable conformation, but also can indicate some very important indexes for the design of new drugs such as energies of HOMO orbital border (Highest Occupied Molecular orbital) and LUMO (Lowest Unoccupied

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Molecular orbital), minimum potential energy, dipole moment and the specific layout of each atom in the molecule.

This present study aimed to use the theory of functional density (DFT- B3LYP/6-31G) to characterize electronic and structurally the topiroxostat drug, which is the initial step for future studies of molecular docking, to elucidate the reaction mechanism of this drug, targeting a future increase in its action pharmacological.

2 METHODOLOGY

All the computations were performed on Dell Inspiron personal computer with intel® Core ™ i7-4510U processor, 16 GB RAM, 2GB AMD Radeon® video card and Microsoft Windows 8.1® as operating system. All density functional theory (DFT) calculations were performed by using the ORCA (ab initio, DFT, and semi-empirical SCF-MO package) program package [15].

All calculations were performed in the framework of DFT with spin unrestricted setting at becke's three parameter hybrids function combined with the Lee-Yang-Parr correlation functional (B3LYP) computational level, using the 6-31G (d) basis set for the ground state optimization [16] [17]. All calculations were made using as a solvent dimethyl sulfoxide (DMSO). Since the electron correlation effects have been extensively considered in DFT method, a precisely predicted structure of the molecule can be evolved. The frontier molecular orbital's and the HOMO e LUMO energy gap has been computed.

This research was conducted in four stages: at first, it performed a search of the molecular structure repository ChemSpider® (chemspider.com) (using the descriptor Topiroxostat), which was obtained by the two-dimensional coordinates of the molecule and the basic descriptors of the molecule (name identifiers, molecular formula, mass monoisótopo and solubility). The second stage to obtain the molecular modeling calculations and potential energy (SCF) which was acquired by applying ab initio method of density functional theory (DFT) was used Orca software [15]. The third stage, using the data generated by modeling, it was possible to obtain the population distribution of Mulliken, plot the potential map electrostatic surface (MESP) and the frontier orbitals (HOMO-Highest Occupied Molecular Orbital), (LUMO-Lowest Unoccupied Molecular Orbital). The fourth stage we used the values of the frontier orbitals for the descriptors: Gap, eléctron affinity (A), electronegativity (χ), vertical ionization potential (i), chemical hardness (η), chemical softness (s), eletronic chemical potential (μ), electrophilicity index (ω) [18] [19] [20].

3 RESULTS AND DISCUSSIONS

The computational chemistry is a series of techniques used in chemical research problems in a computer, using mathematical methods for the calculation of molecular properties and the molecular simulation behavior [21]. According to the repository ChemSpider® Topiroxostat the drug molecule (ChemSpider ID28637853) has official IUPAC name for 4- [3- (4-Pyridinyl) -1H-1,2,4-triazol-5-yl] -2- pyridinecarbonitrile, $C_{13}H_8N_6$ molecular formula, molecular weight equal to 248,243 Da, monoisotopo mass 248.081039 Da, with solubility in dimethylsulfoxide (DMSO) to 10mM. When using a molecular design software to build the two-dimensional structure of a molecule or obtain the same a virtual database received only the initial coordinates of the molecule into a form that can easily see all the atoms in a same plane, so it does not it is in its most stable form. For effective study, we need more precise calculations on the molecule and its conformation (more stable) with minimum potential energy as possible, then we need to carry out the process of geometric optimization, where we use the energy minimization process [22].

Using the ORCA software (ab initio, DFT and semi-empirical SCF-MO package) program package [M1] we can optimize the molecular structure by calculation functional theory density (DFT), based on quantum mechanics theory [21], checked stationary point where the potential energy of the molecule Topiroxostat (Self Consistent Field- SCF) assuming a value of -22529.63117 eV Components (Nuclear Repulsion: 32449.00115 eV Electronic energy: -54978.63232 eV One Electron energy : -94850.83398 eV, Two Electron Energy: 39872.20166 eV), Virial components (Potential Energy: -44946.54945 eV, Kinetic Energy: 22416.91828 eV, Virial Ratio: 2.00502803), with DFT components (N (Alpha): 63.999982232235 electrons, N (Beta): 63.999982232235 electrons, N (Total): 127.999964464471 electrons, E (X): -87.279603363829 Eh, and (c): -5.179924171937 Eh, and (XC): -92.459527535765 Eh), Dipole moment (8.07717 Debye), obtaining the molecular structure more stable conformation and optimized (Fig.1).

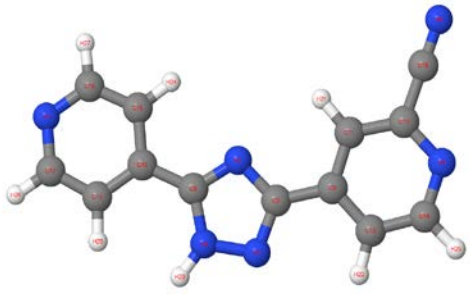

Fig.1: optimized structure of the drug Topiroxostat

Analysis of the population is the charge distribution in molecules study seeking to accurately model the magnitude and location of the partial load of atoms in a molecule as a rigorous version of assigning partial charges on the atoms [23] . Population analysis of Mulliken, is based on molecular orbital theory associated with coefficients determined by the Hartree-Fock method, population analysis based on the division of the electrons of a molecule in a population loop on the basis of function, and the population of covering, where N is the total number of system electrons. Partial atomic charges are unobservable characteristics of molecules and, therefore, the whole idea of the population of modeling electron is not unique. To assign charges to atoms, we must define the spatial region of atoms, then add up all the charge in the region [24]. Mulliken's populations can be considered soundly defined from the quantum mechanical point of view, even if they remain not observable molecular properties. It is based on the linear combination of atomic orbitals and therefore the wave function of the molecule. The electrons are partitioned to the atoms based on the nature of the atomic orbitals contribution the molecular wave function. Generally, the total number of electrons in the molecule N can be expressed by the equation (1) [23] [25].

$$N = \sum_j^{electrons} \int \psi_j(r_j)\psi_j(r_j)dr_j$$
$$= \sum_j^{electrons} \sum_{r,s} \int c_{jr}\varphi_r(r_j)c_{js}\varphi_s(r_s)dr_j \quad (1)$$
$$= \sum_j^{electrons} \left(\sum_r c_{jr}^2 + \sum_{r \neq s} c_{jr}c_{js}S_{rs} \right)$$

Where r and s index the atomic orbital basis functions φ, c jr are coefficients of the basis function r in the Atomic orbital j , and S is the matrix pre-defined overlap. Mulliken atomic population can be considered as the summation of Atomic orbitais population contributions, because, Mulliken equally divide the charge density of the atoms and atom associated with a k (2) [23] [25].

$$N_k = \sum_j^{electrons} \left(\sum_{r \in k} c_{jr}^2 + \sum_{r,s \in k, r \neq s} c_{jr}c_{js}S_{rs} + \sum_{r \in k, s \in k} c_{jr}c_{js}S_{rs} \right) \quad (2)$$

Where the first two terms come from the basis functions on the kth atom and the last term is the part shared with all other atoms. The partial charge on atom k can be expressed according to the equation (3) [22] [24].

$$q_k = Z_k - N_k \quad (3)$$

where Zk is its atomic number.

Mulliken's populations can be considered soundly defined from the quantum mechanical point of view, even if they remain not observable molecular properties. Currently, the population analysis Mulliken is the traditional method most used between the chemical used to determine loads atoms in formation of molecules, their popularity is due to intensive applications that are used in molecular orbital theory can be calculated easily, directly getting all the variables needed to make the population analysis, no computational cost is not necessary [25]. By subjecting the molecule to Pomalidomide Mulliken population analysis (Table 1), it was observed that the carbon atoms of the -0.009266 0.427486 (0.436752 variation and) were who suffered greater variation, followed by nitrogen atoms ranging from - 0.191069 -0.582650 the (range of 0.391581) and the hydrogen atoms of 0.359650 to 0.130451 (range 0.229194).

TABLE 1

Population analysis de Mulliken of drug Topiroxostat

ATOM	CHANGE	ATOM	CHANGE
0 N	-0.435306	14 C	-0.110872
1 N	-0.191069	15 C	0.010813
2 N	-0.582650	16 C	-0.006084
3 N	-0.362040	17 C	-0.009266
4 N	-0.351959	18 C	0.030324
5 N	-0.234381	19 H	0.359650
6 C	0.176362	20 H	0.193838
7 C	0.427486	21 H	0.176166
8 C	0.137096	22 H	0.130451
9 C	0.130713	23 H	0.183657
10 C	-0.080095	24 H	0.158888
11 C	-0.126682	25 H	0.153933
12 C	0.183385	26 H	0.161480
13 C	-0.123839		

Using the output file generated by optimizing the structure of the frontier orbitals were generated HOMO and LUMO, and the potential of the electrostatic surface map (MESP) that can be expressed according to equation (4).

$$V(r) = \sum_{A} \frac{Z_A}{|\vec{R}_A - \vec{r}|} - \int \frac{\rho(\vec{r})}{|\vec{r}' - \vec{r}|} dr' \quad (4)$$

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 as a function of the cores [26].The potential surface map electrostatic (MESP), provides a visual method that helps to identify the relative polarity of the compounds [27], identifying the nucleophilic and electrophilic sites which, together with the dipole moment of the molecule can be used to predict types of intermolecular interaction as well as the most favorable sites for the formation of interactions between biological molecules and [28] receptors [29], but also is an important tool in the study of new drugs [30]. The hottest shades (tending to red) indicate negative values of electrostatic potential - regions rich in electrons. In Fig.2 we can observe the regions of higher nucleophilicity of the nitrogen atoms (N1, N2, N4, N5 and N6) and more electrophilic region in Hydrogen(H20) e nitrogen (N3).

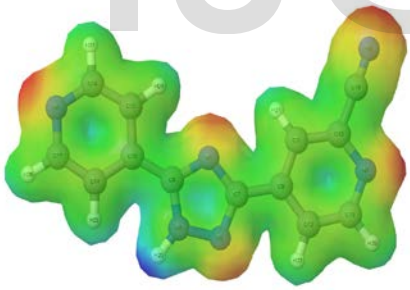

Fig.2. Potential Map Electrostatic (MEP). of drug Topiroxostat

The theory of frontier orbitals, based on the principle that when the molecular orbitals of two reactants begin to interact and overlap, leads to the formation of two new molecular orbitals, a binder, less power, and another antibonding, higher energy [31]. We exemplify it in a reaction utilizing the nucleophilic substitution second order mechanism where the reaction begins by occupied orbital interaction higher energy (HOMO - Highest Occupied Molecular Orbital), which contains the electron pair that will be donated the acceptor, the substrate with the molecular orbital unoccupied lower energy (LUMO – Lowest Unoccupied Molecular Orbital), so we can relate the energy of the HOMO (εHOMO) and LUMO (εLUMO) with a pair of attractive force of electrons that can be donated (high energy HOMO), but also, we can relate this energy change with the ability to receive electrons (low energy LUMO). The HOMO in ground state and LUMO distribution for the structure are shown in Fig.3 Fig.4 respectively. Red and green color distributions represent positive and negative phase in molecular orbital wave function, respectively. observing the Fig.3 it is noted that the orbitals of atoms N1, C8, C14, C15, C17, C18, C17 and N5 contributed in forming the orbital HOMO, still observing an asymmetric distribution of positive and negative phase mainly in the atoms N1, N2 and C8. In forming the LUMO (Fig. 2-b) we observe the contribution of all nitrogen atoms of carbon atoms (C11, C16). observing the LUMO can observe a symmetrical distribution of positive and negative phase.

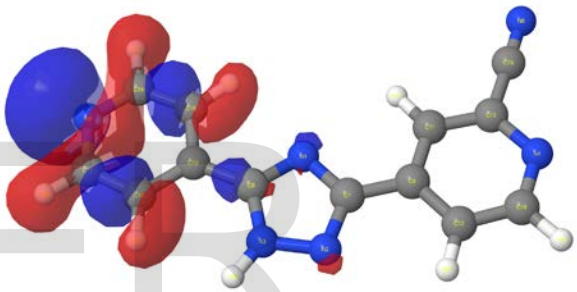

Fig. 3.- Orbital frontier HOMO of drug Topiroxostat

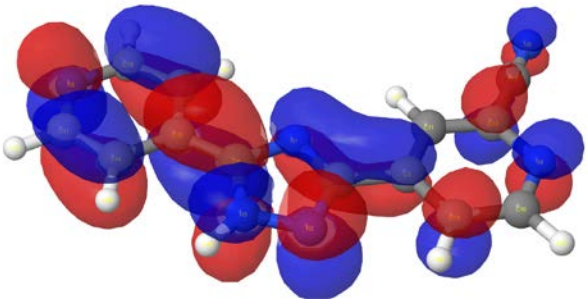

Fig. 4.- Orbital Border LUMO of drug Topiroxostat

The HOMO and LUMO energies are used as chemical reactivity ratios and are usually associated with other indexes such as the electron affinity and ionization potential [31]. Global reactivity descriptors act as a bridge between stability of the structures and global chemical reactivity [18][19]. To relate the structure and reactivity of molecules was used the values of the frontier orbitals to calculate the GAP (5) [19][20][31][32].The molecules have the large band

gaps, which are usually stable and unreactive. Those which have smaller band gaps are reactive as they can easily interact with the reactants

$$GAP = (\varepsilon_{HOMO} - \varepsilon_{LUMO}) \quad (5)$$

Ionization potential(I) is the minimum energy required to remove an electron from an atom or molecule [18][19], electron affinity (A) is described as the change in energy when an electron added to a neutral atom in the gaseous phase[18], chemical softness (S) , electronic chemical potential (μ) as characteristic of electronegativity of compounds [18][19], Electronegativity (c) and chemical hardness (h) help to predict about the formation of chemical bonds and the physical, chemical properties of the compound [18],. The values of the frontier orbitals for the descriptors [18][19][31]: Gap, eléctron affinity (A), electronegativity (χ), vertical ionization potential(I), chemical hardness (η)[19], chemical softness(s), eletronic chemical potential (μ), electrophilicity index (ω) showed table 2.

TABLE 2

Some global reactivity properties of drug Topiroxostat

PARAMETERS	VALUE
ε_{HOMO}	-7.201411 eV
ε_{LUMO}	-2.252368 eV
GAP	4.949043 eV
Eléctron affinity (A)	2.252368 eV
Eletronegativity (χ)	4.726890 eV
Vertical Ionization potential (I)	7.201411 eV
Chemical hardness (η)	2.47452 eV
Chemical softness (S)	0.20206 eV^{-1}
Eletronic chemical potential (μ)	-4.72689 eV
Electrophilicity index (Ω)	4.51471 eV

4 CONCLUSION

The application of computational chemistry has been increasingly frequent in the scientific universe, since its use, and its various tools, brought to this medium, many changes and innovations in the way of conducting research and producing knowledge. Thus, its use has allowed to carry out studies and research, and thus enabling to reach accurate results with a minimization of time and costs. Therefore, using the density functional theory it possible to characterize electron and structurally synthetic drug Topiroxostat, getting SCF (-22529.63117 eV), Potential Energy (-44946.54945 eV), Kinetic Energy (22416.91828 eV), Dipole moment (8.07717 Debye) e identifying its electrophilic (H20, N3) and nucleophilic sites (N1, N2, N4, N5 and N6), and calculating descriptors that assist in the compression of the possible reaction mechanisms will this drug.

This work is an initial step toward improving drug, as from the complete understanding of the characteristics that influence the reactivity of the compound, we can start designing new compounds by structural modifications (Drug Information).

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