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In Silico Study of Antidepressant Drug Vortioxetine: A Description of their Physical Chemistry Properties using Classical Molecular Mechanics Methods MMFF94

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Abstract **- Currently, depression is a common disease worldwide, with an estimated 350 million people affected, in the pathological sense. In this context, Vortioxetine, which acts in an innovative way, stands out because it has a differentiated action on serotonin receptors acting as inhibitor, antagonist, agonist or partial agonist in different receptor subtypes. The present work aimed to characterize insilic, the drug Vortioxetine, we obtained the four conformers of lower energy (thermodynamically more stable), calculated byclassic molecular mechanicsMMFF94(Merck Molecular Force Field), then was selected from among the four comformers, the most stable. Then, molecular modeling calculations were carried out to bring about a refinement of the drug structures, obtaining properties of the molecule(logP, logD, polar surface, isoelectric point, pKa with and without resonance, Huckel analysis, charge, density of charge and electronics), being this work fundamental for future studies of drug design and molecular docking.**

Keywords **- MMFF94, Physical chemistry properties of Vortioxetine.**

I. INTRODUCTION

Depression is the affective alteration most studied and spoken today. Classified as a mood disorder, it governs the attitudes of the subjects modifying the perception of them, starting to see their problems as major catastrophes [1]. According to data from the World Health Organization (WHO), depression represents today the fourth most diagnosed "disease" in the world and it is estimated that 1/6 of the population presented or will present some depressive manifestation [2]. Among the antidepressants used, Vortioxetine appears to be prominent because it acts on different receptors for serotonin in the brain, blocking the action of some receptors and has some stimulating action. In addition, Vortioxetine blocks the action of the serotonin transporter, responsible for the elimination of serotonin from its sites of activity in the brain, thus increasing Serumtonin activity. It is used for the treatment of major (highest) pressure depression in adults. Major depression is a condition in which patients have mood disorders that interfere with their daily lives [3].

Vortioxetine is a multimodal compound thought to work through a combination of two pharmacological modes of action: inhibition and receptor of the serotonin receptor (5-HT) activity. It functions as a 5-HT3, 5-HT7 and 5-HT1D receptor antagonists, 5-HT1A receptor agonist, 5-HT1B receptor agonist and 5-HT transporter inhibitor. With the advent of computational chemistry, molecular modeling techniques are widely used in order to obtain a complete characterization of the compound, thus benefiting not only in the theoretical study but also in the practical study of the drug [4]. Molecular modeling is one of the area of Pharmaceutical Sciences studying the molecular origins of the biological activity of drugs, determining the parameters that relate structure and activity and applying these fundamentals in the rational planning of drugs [5]. This area consists of a set of tools for the construction, editing and visualization, analysis and storage of complex molecular systems. These tools can be applied in strategies of direct and indirect modeling of new drugs [6]. There are many options as to the calculation method to be applied in a particular molecular modeling strategy. In this work we will be based

on the optimized molecule in MMFF94 (Merck Molecular Force Field) [7].

II. MATERIALS AND METHODS

In this work, we had the use of free software with licenses registered on its official websites, based on the Windows 10 operating system. To obtain the molecule and its information in the literature, a search was made in the ChemSpider® database and PubChem©. After obtaining the drug, a structural optimization was done through the Marvin software. The optimization was performed by MMFF94 (Molecular Mechanic Force Field 94) with optimization limit very strict, diversity limit of 0.1 in Hyperfine. After the software brought the 4 molecules of lower energy, the molecule of lower energy (547.52 Kj / mol) was selected. Using the software, calculations were made to obtain the general and physical chemistry properties of the molecule. Data, image and graphs were obtained on the most diverse properties, such as: logP, polar surface, isoelectric point, pKa, charge density, eletorn density, order electrophilic and nucleophilic.

III. RESULTS AND DISCUSSIONS

In the ChemSpider repository, it is a bioinformatics resource for free access to research, it also provides technical data on the molecule for guidance in laboratoryresearch as well as data:two-dimensional formula[8], where we can observe the connectivity of atoms (Fig.1) Molecular Formula (C18H22N2S), Average Mass (298,446 IUPAC name (1- {2 - [(2,4-dimethylphenyl) sulfanyl] phenyl} piperazine), CAS identification number (508233-74-7), Molecular weight (298.45),Exact molecular weight(298.150369890),Composition: (C (72.44%), H (7.43%), N (9.39%), S (10.74%)),Mass spectrum (m / z: relative abundance(298: 1.00 299: 0.21 300: 0.07 301: 0.01)) . The physical chemical properties, In the results obtained through the Marvin software [9]. The software provided us with pKa data showing the basal acid balance of the Vortioxetine molecule which underwent a sharp change near pH 7.5. Since its neutral molecule (basic concentration) tends to rise aggressively from the pH mentioned. It is known that the neutral molecule has 1 pair of free electron for each nitrogen, thus assuming the molecule with basic properties(table 1). However, the molecule only stabilized with the attack of a nitrogen to H +. The hydrogenation of the second non-nitrogen obtained stability for the molecule (fig. 2).

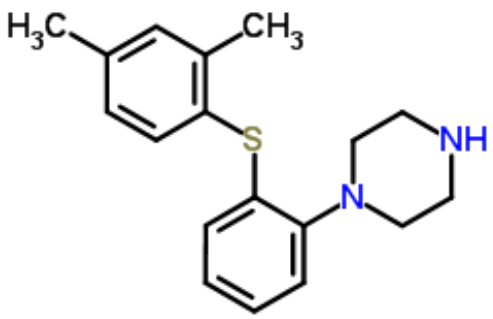

Fig. 1. Vortioxetine chemical structure available from the ChemSpider® Repository. (Chemspider ID:8141643)

Table 1
Percentage of drug concentrations with pH variation. %-1. Molecule neutral. %-2. NH +. % -3. 2 NH +

pH	%-1	%-2	%-3
0.00	0.00	99.07	0.93
0.50	0.00	99.70	0.30
1.00	0.00	99.91	0.09
1.50	0.00	99.97	0.03
2.00	0.00	99.99	0.01
2.50	0.00	100.00	0.00
3.00	0.00	100.00	0.00
3.50	0.00	100.00	0.00
4.00	0.00	100.00	0.00
4.50	0.00	100.00	0.00
5.00	0.01	99.99	0.00
5.50	0.05	99.95	0.00
6.00	0.14	99.86	0.00
6.50	0.45	99.55	0.00
7.00	1.40	98.60	0.00
7.50	4,31	95.69	0.00
8.00	12.47	87.53	0.00
8.50	31.06	68.94	0.00
9.00	58.76	41.24	0.00
9.50	81.83	18.17	0.00
10.00	93.44	6.56	0.00

10.50	97.83	2.17	0.00
11.00	99.30	0.70	0.00
11.50	99.78	0.22	0.00
12.00	99.93	0.07	0.00
12.50	99.98	0.02	0.00
13.00	99.99	0.01	0.00
13.50	100.00	0.00	0.00
14.00	100.00	0.00	0.00

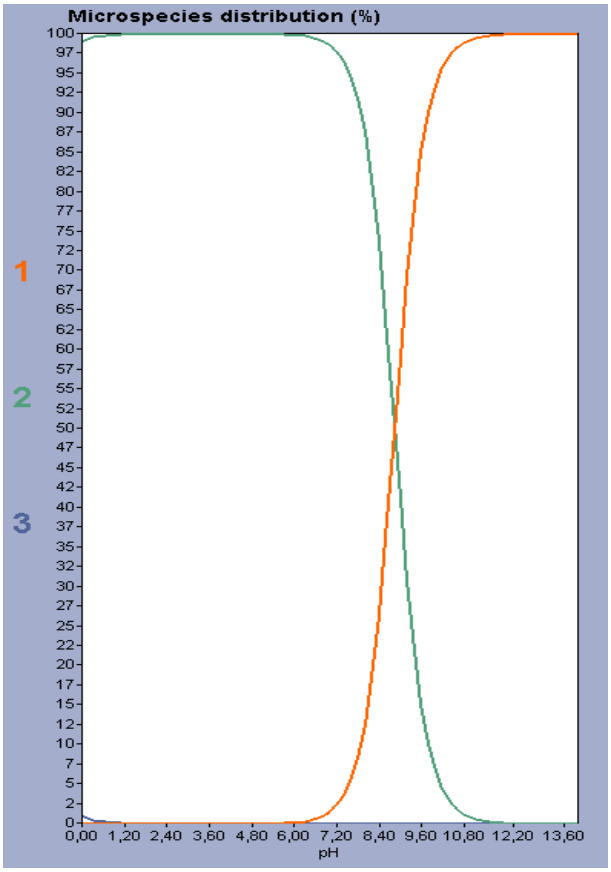

Fig. 2. Distribution of micro species in% as a function of pH (1. Neutral molecule. 2. NH+.3. 2 NH+)

The partition coefficient (LogP)is the ratio of the concentration of the compound in octanol to its concentration in water[10]. The distribution coefficient is the ratio of the sum of the concentrations of all species of the compound in Î ± -ethanol to the sum of the concentrations of all species of the compound in water [11]. Based on acid / basic dissociation reactions, we can introduce the concept of a partition coefficient for cationic and anionic species and for neutral species [12], [13]. As it can be observed in fig. 3, the Vortioxetine molecule has a predominant lipophilic character (LogP = 4.76), and in the regions where we find the atoms of Nitrogen, we can observe a hydrophilic region.

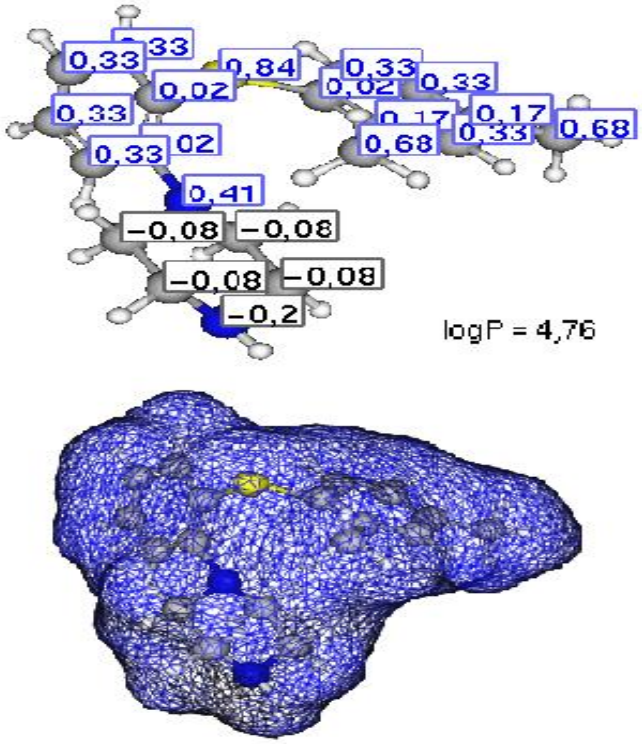

Fig 3. The partition coefficient (LogP)calculated for the Vortioxetine molecule.

However, most known drugs contain ionizable groups, this shows the drug distribution of small molecules with DrugBank and is likely to be charged at physiological pH and LogP only correctly describes the molecular partition coefficient neutral (not charge). LogD the distribution constant is a better descriptor of the lipophilicity of a molecule. This can be determined in a manner similar to LogP, but instead of using water, the aqueous phase is adjusted to a specific pH using a buffer. Log D is therefore pH-dependent, therefore, one must specify the pH at which log D was measured. Of particular interest is log D at pH = 7.4 (the physiological pH of the blood serum) [14].When we compute the partition coefficient in relation to the pH change for the Vortioxetine molecule, we can see an increase in lipidicity with an increase in pH (fig. 4).

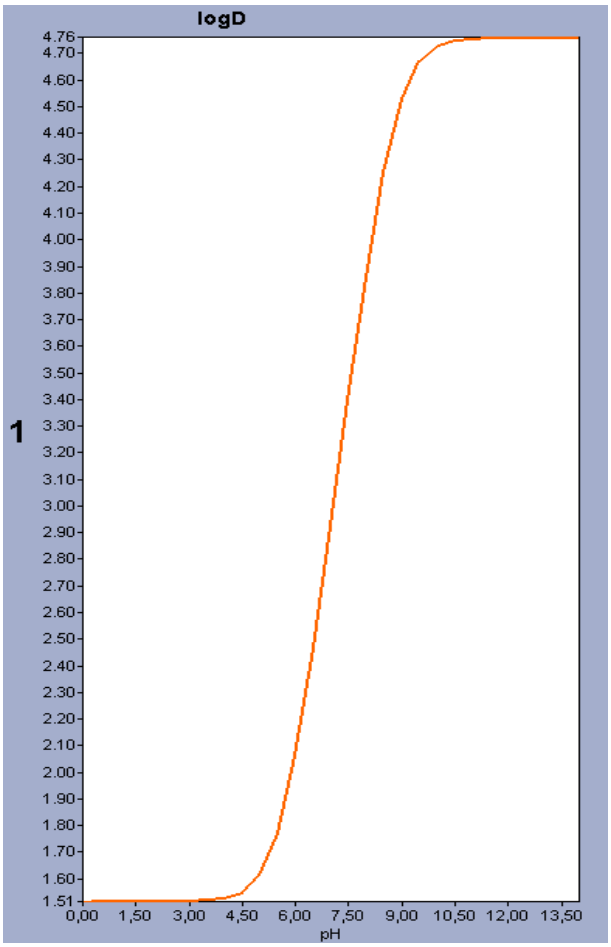

Fig. 4. Variation of LogD as a function of pHcalculated for the Vortioxetine molecule.

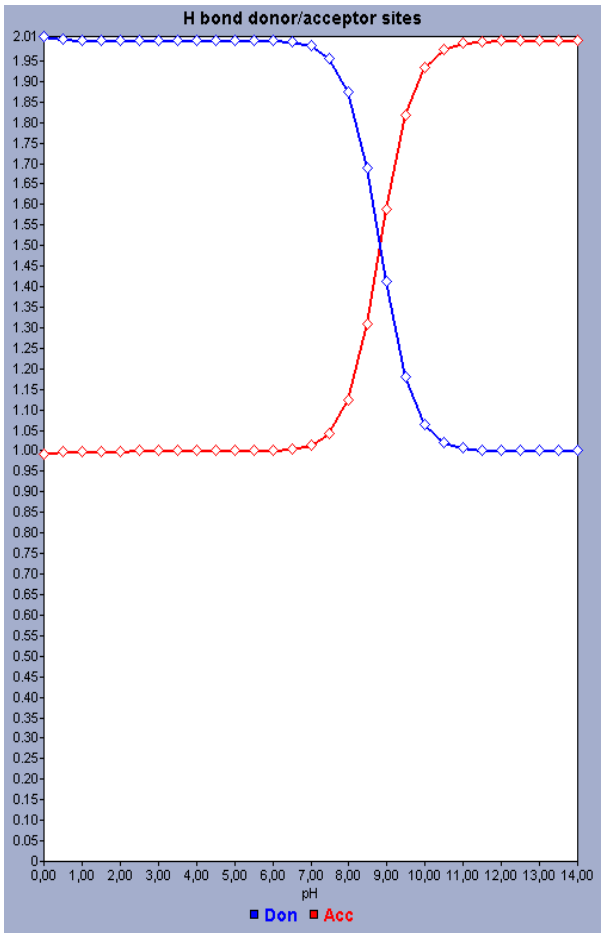

Fig. 5. H bond donor/acceptor as a function of pHcalculated for the Vortioxetine molecule.

The Hydrogen Bond Donor-Acceptor Plugin calculates atomic hydrogen bond donor and acceptor inclination. Atomic data and overall hydrogen bond donor and acceptor multiplicity are displayed for the input molecule (or its microspecies at a given pH). The weighted average hydrogen bond donor and acceptor multiplicities taken over the microspecies and the distribution of their occurrences are computed for different pHs and displayed in a chart [15]. In fig. 5 we can observe the acceptor donor relationship of H dependent on the pH of the Vortioxetine molecule

The isoelectric point (pI) of a molecule is the pH at which the molecule has no liquid charge. Knowing the pI may be important in predicting, the solubility of a molecule at a given pH; Predicting the pI for molecules can used in the processes of separation and purification. Fig. 6 shows the charge variation of the vortioxetine molecule in relation to the charge variation in relation to pH.

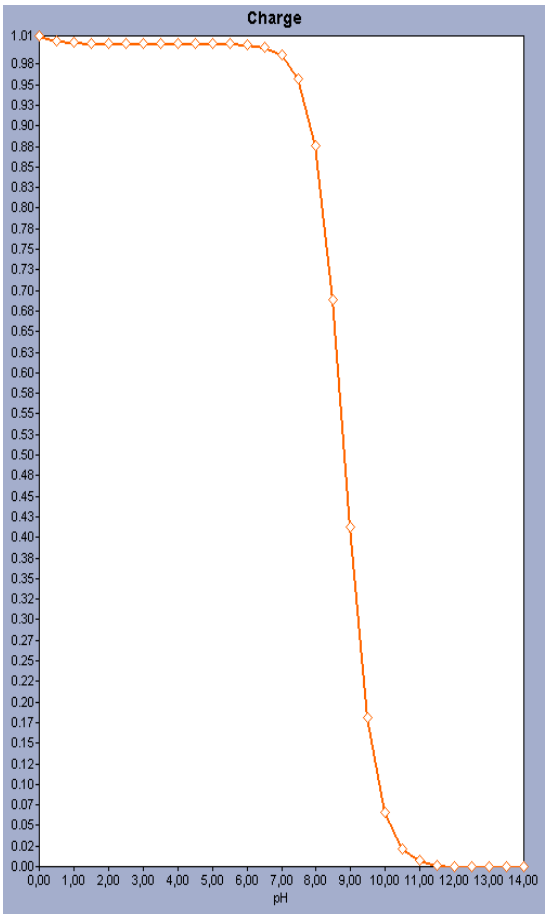

Fig. 6. Change in charge as a function of pHcalculated for the Vortioxetine molecule.

The polar surface area (PSA) is formed by polarized atoms of a molecule. It is a descriptor that shows good correlation with the molecular transport passive through the membranes and allows the estimation of the transport properties of drugs [16],the vortioxetine molecule has a calculated polar surface area (PSA) ofwith a radius 1.4 Å 15.27Å and 19 molecular surface area of 19.85 Å (at pH 7.4), Van der Waals surface area (3D) (469,38 Å), and Van der Waals surface area (3D) (472.39 Å) at pH 7.4.The Hückel Analysis Plugin is able to calculate different structural descriptors for aromatic atoms. The L (+) and L (-) location energies for electrophilic and nucleophilic etching at an aromatic center are calculated by the Hückel method. A smaller L (+) or L (-) value means a more reactive atomic location. The order of the atoms in E (+) or in the Nu (-) attack is adjusted according to their locational energies. The total π energy, the electron density π and the total electric density are also calculated by the Hückel method. According to the chemical environment, the following parameters have ideal Coulomb parameters and integral resonance: B, C, N, O, S, F, Cl, Br, I. [17-19].using the analysis method of huckel analysis was calculated to the HMO E (+) / Nu (-) order (fig. 7), Electron density (fig. 8), Charge density (fig. 9) of the molecule of vortioxetine.

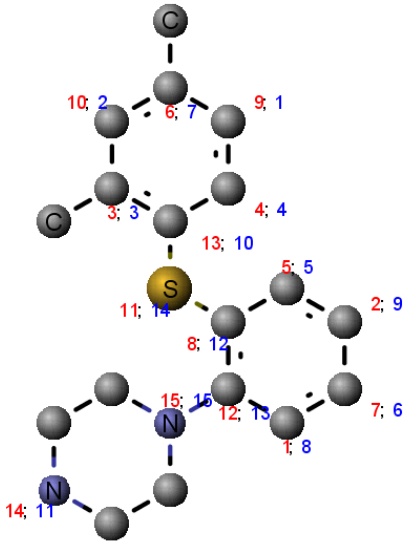

Fig. 7. HMO E (+) / Nu (-) order calculated using the Huckel analysis method for the vortioxetine molecule

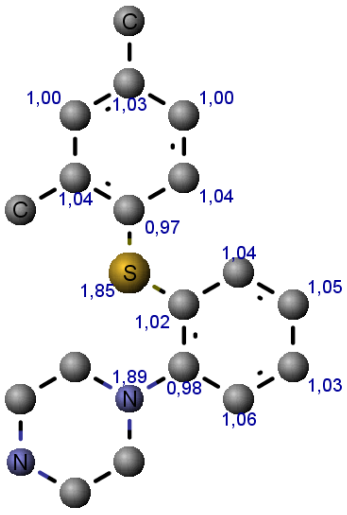

Fig. 8. Electron density calculated using the Huckel analysis method for the vortioxetine molecule

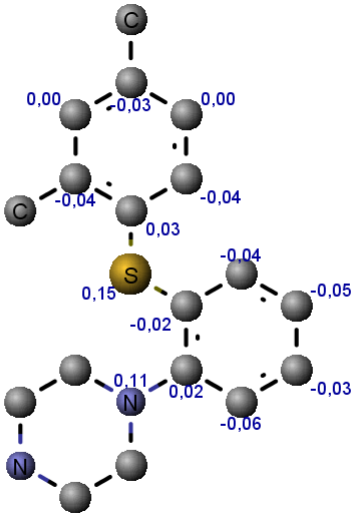

Fig. 9. Charge densitycalculated using the Huckel analysis method for the vortioxetine molecule

IV CONCLUSIONS

The in silico study of the drug Vortioxetine, using its optimized molecule among the 4 obtained, using MMFF94, was possible to obtain chemical physical properties in which it fits for the electronic, structural and biological description. With the generated data, it was possible to identify its basicity with the pH graph, along with properties such as LogP, LogD, PI, Polar surface, Molecular surface as a function of pH.Thus, this research may serve as a basis for future drug design studies, as well as in the aid of molecular docking research and molecular bioactivities.

V ACKNOWLEDGMENT

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