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Semi-Empirical Quantum Characterization of the Drug Selexipag: HOMO and LUMO and Reactivity Descriptors

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***Abstract*— With the increase in the world population, the number of new diseases has increased, and one of these diseases is Pulmonary Arterial Hypertension (HAP), which causes an increase in the circulatory system in the lungs region, which can result in hospitalizations or in more severe cases resulting in death of the patient. The drug selexipag has been used because of its agonist effect on prostacyclin IP receptors, how-ever it has several side effects. In this context, the present work aimed to characterize the drug molecule, using quantum methods at the semi-empirical level, it was possible to optimize the drug structure, obtaining its conformation of lower energy, it was also made the identification and characterization of the border orbitals, as well as to obtain the reactivity descriptors and to identify their possible reactive sites. In this context, the present work represented an initial stage for future studies of drug design and molecular docking aiming at the promotion of pharmacological potential and a decrease in side effects.**

***Keywords*— LUMO. HOMO. Theoretical chemistry.**

I. INTRODUCTION

Pulmonary arterial hypertension (PAH) is characterized by its circulatory abnormality that aggravates Pulmonary Vascular Resistance (PVR), through the intermediary of mixed mechanisms involving vasoconstriction, arterial wall remodeling and thrombosis. Being that this ends up causing a worsening, due to the increase of the pulmonary vascular resistance, being able to result in premature death. [1]. One of the mechanisms studied in PAH and the imbalance in the production of prostacyclin, an arachidonic acid metabolite produced by endothelial cells, has several effects (antiproliferative, antithrombotic, anti-inflammatory and antimitogenic) and stimulates adenosine monophosphate (cyclic AMP). In this context, the drug Selexipag, which acts as a selective agonist of prostacyclin IP receptors, ie acts on a relevant effect in the treatment of (PAH), is highlighted, however it has several side effects where headache, diarrhea and nausea are prominent, which negatively impact patients' quality of life [2-4]. In his context, the objective of this study was to characterize the drug molecule selexipag as an initial step for future studies of drug desing and molecular docking aimed at promoting pharmacological potential and a decrease in side effects.

II. METHODOLOGY

With the advancement in processing power, computational chemistry has fostered molecular modeling, allowing the use of increasingly efficient computation methods to simulate physical and chemical structures such as solids, molecules, atoms, among others. In this context we can highlight the semi-empirical methods, which uses the experimental data to optimize the theoretical calculations [5] [6] [7] [8].

The fundamental step for the initial simulation process of the selexipag was to obtain the two-dimensional structure of the molecule, which provided the connection sequence between the atoms. Currently we find several virtual repositories of molecules where we can highlight the DrugBank (https://www.drugbank.ca/), which provides besides the two-dimensional structure diverse Physical-chemical properties [9]. For the design of the structure and obtaining the values of PKa, the code MarvinSketch© [10-13]. For the preparation of inputs and realization of structural optimization simulations

at the quantum level, the ArgusLab® code (Version 4.0.1) [14-15] was used to perform semi-empirical simulations using the Parametric Method 3 (QM_PM3), performing the structural optimization of the molecule and obtaining data that made it possible to plot the electrostatic potential map [16-17], the frontier orbitals [18] (HOMO and LUMO) and perform the population analysis of Mulliken [19]

III. RESULTS AND DISCUSSIONS

Selexipag is part of the class of organic compounds known as dialkylarylamines. This class has aliphatic aromatic amines where in the amino group is linked directly with two aliphatic chains and one aromatic group [figure 1], Weight Average 496.63, Monoisotopic mass 496.2144267, Chemical Formula

C26H32N4O4S, UNII 5EXC0E384L, CAS number 475086-01-2,

, InChI Key QXWZQTURMXZVHJ-UHFFFAOYSA-N, I nChI. 1S / C26H32N4O4S / c1-20 (2) 30 (16-10-11-17-34-19-24 (31) 29-35 (3,32) 33) 23-18-27-25 (21-12- 6-4-7-13-21) 26 (28-23) 22-14-8-5-9-15-22 / h4-9,12-15,18,20H, 10-11,16-17, 19H2.1-3H3, (H, 29.31), IUPAC Name

2- {4 - [(5,6-diphenylpyrazin-2-yl) (propan-2-yl) amino] butoxy} -N-methanesulfonylacetamide

(C 2 = CC = C 2) = C (N = C 1) Cl = CC = CC = C , has a polarisability of 54.98 Å3, Log P 3.76, which shows the affinity in a polar or apolar medium, (octanol / water) are the parameters to determine the affinity, the lower its hydrophilic value will be the molecule, according to the Log P result, the selexipag molecule has a higher affinity for hydrophobic environments (Table I) [20]. The value of PKa equivalent to 3.77, this value explains the type of protein that comes in contact with the same substance and even in an environment with pH> 3.77 the hydrogen that is bound with the nitrogen will ionize and form H +, leaving the compound with physiological load -1 (Figure 1), also obtaining the fundamental factors for the implantation of the Molecular Docking study [20-21].

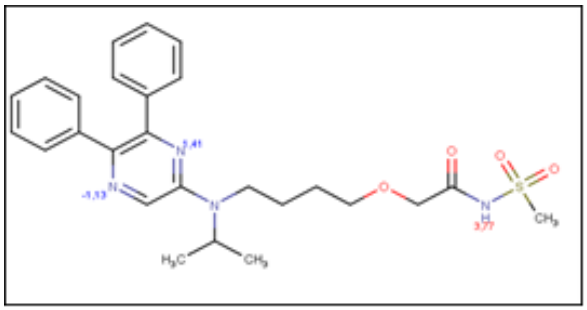

Fig.1 Two-dimensional structure and PKa of the selexipag
Source: DrugBank repository

TABLE I

Physical-chemical properties of the selexipag molecule

PROPERTY	VALUE
WaterSolubility	0.00434 mg mL-1
logP	4.4
logP	3.76
logS	-5.1
pKa (StrongestAcidic)	3.77
pKa (Strongest Basic)	1.41
Physiological Charge	-1
HydrogenAcceptorCount	7
HydrogenDonorCount	1
Polar Surface Area	101.49 Å2
Rotatable Bond Count	11
Refractivity	136.81 m3·mol-1
Polarizability	54.98 Å3
Number of Rings	3
Bioavailability	1
Rule of Five	Yes

By getting the two-dimensional repository structure online (DrugBank) or even drawing in the program, the molecule of interest does not have adequate stability, and to arrive at a stable point it should first make an optimization of its structure, so that the calculations made in the program have a greater accuracy [22]. Using the semi-empirical quantum method PM3, we

use experimental values in order to avoid certain calculations of some integrals, with the presence of already defined values (parameterized values) [5] and thus obtaining results a structure (Figure 2) and with geometric optimization calculations we acquired the lowest potential energy state of the selexipag (-128735.6491 kcal mol-1), formation heat -74.6158 kcal / mol, the value of the dipole moment 2.87376570 D.

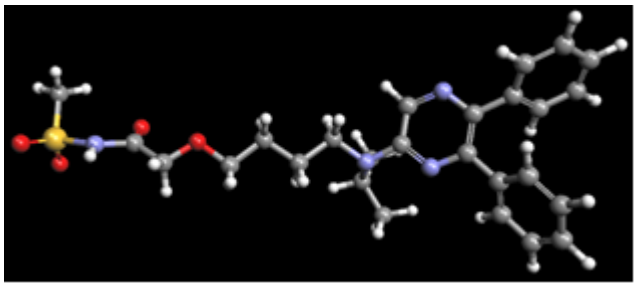

Fig.2 Optimized three-dimensional structure of selexipag.

After the geometric optimization, it was possible to identify and render the HOMO (High Occupied Molecular Orbital) orbitals, and the LUMO orbitail (Lowest Unoccupied Molecular Orbital), characterizing the orbitals 93 (figure 3) and 94 (figure 4). the representation of HOMO and LUMO has values (-9.04917 eV), (-0.71653 eV), respectively. We can highlight that the LUMO orbital and its phases are represented by the positive (Blue), and negative (Red), in the HOMO orbital we perceive that there is an asymmetry between the positive and negative phases, and the LUMO orbital has its symmetrical phases.

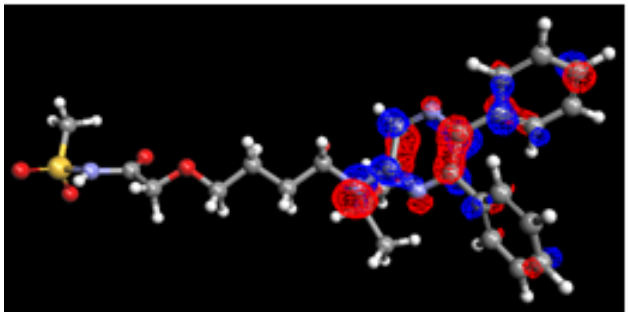

Fig. 3 Representation of the HOMO orbital in the selexipag compound

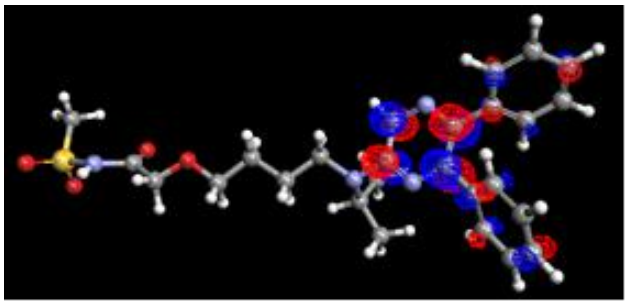

Fig. 4 Representation of the HOMO orbital in the selexipag compound

The HOMO orbital represents (molecular orbital of greater energy), already the LUMO is (molecular orbital of smaller energy), being that the HOMO has a direct relation with the character of electro spraying of the molecule, and the LUMO that due to its energetic characteristic, it has an electron-receptor character of the compound [xxx]

The GAP is the difference between the values of the edge orbitals, and this is a very important parameter for its stability. Compounds having the larger band ranges tend to be more stable, and when the band ranges are smaller, the compound becomes more reactive to an interaction with reactants. The parameter GAP obtained a value of (8.33264 eV), being the parameter used to calculate the reactivity descriptors (electronegativity, ionization potential, electron affinity, chemical hardness, electronic potential) (Table II). Emphasized that electronegativity and hardness are responsible for characterizing how certain chemical and physical properties will behave. The term hardness is basically the ability of a given material to withstand a certain pressure when in contact with a deforming machine [23-28].

TABLE II
Reactivation descriptors of selexipag

Parameters	Values
HOMO	-9.04917 eV
LUMO	-0.71653 eV
Electronicaffinity	0.71653 eV
Vertical ionizationpotential	9.04917 eV
Electronegativity	4.88285 eV
Chemicalhardness	4.16632 eV
Chemicalsoftness	0.12000 eV
Electronicchemicalpotential	-4.88285 eV
Electrophilicity index	2,86130 eV

Each atom in a compound has its own charge, and this charge is very important because they can demonstrate how its molecular structure is formed and also how to give its biological activity. Its charge density is responsible for describing its distribution of electrons that is related to the chemical behavior of each species. To perform the calculations, we used the atomic charges of Mulliken (Table III) [28]. With this method we have the possibility of dividing the density of the charges between two uniform atoms, and this occurs without the interference of electronegativity. Table 3 shows all variations of the charges of the atoms of the same elements, since the carbon with the highest charge is C29 with 0.3437, and the lowest is C33 with -0.8525. Already the oxygen its greatest charge is O27 with -0.2699 and the lowest is O34 with -0.8391. Hydrogen has the highest charge H46 with 0.2288 and the lowest is H60 with 0.0947. The nitrogen has the highest load N19 with -0.0128 and the lowest is the N30 with -0.6508. And there is only one sulfur in the selexipag molecule and it is the S32 with 2.3372.

TABLE III
Population analysis of Mulliken'sselexipag molecule

Atoms	Charge	Atoms	Charge
C1	-0.1677	O35	-0.8278
C2	-0.1927	H36	0.2012
C3	-0.1835	H37	0.1946
C4	-0.1963	H38	0.1926
C5	-0.1597	H39	0.1942
C6	-0.0427	H40	0.2026
C7	-0.0430	H41	0.2036
C8	-0.0099	H42	0.1941
C9	-0.0511	H43	0.1923
C10	-0.1532	H44	0.1949
C11	-0.1988	H45	0.2044
C12	-0.1808	H46	0.2288
C13	-0.1946	H47	0.1357
C14	-0.1660	H48	0.1286
N15	-0.0426	H49	0.1188
N16	-0.0359	H50	0.1036
C17	-0.2252	H51	0.1203
C18	-0.0548	H52	0.1169
N19	-0.0128	H53	0.1086
C20	-0.1081	H54	0.1071
C21	-0.3140	H55	0.1332
C22	-0.3461	H56	0.1398
C23	-0.2088	H57	0.1217
C24	-0.2460	H58	0.1353
C25	0.2594	H59	0.1403
C26	-0.0627	H60	0.0947
O27	-0.2469	H61	0.1009
C28	-0.0914	H62	0.1284
C29	0.3437	H63	0.1156
N30	-0.6508	H64	0.1975
O31	-0.3533	H65	0.1869
S32	2.3372	H66	0.1882
C33	-0.8525	H67	0.2116
O34	-0.8391	-	-

After obtaining the results of the atomic charges of Mulliken we began to calculate the potential electrostatic map of the molecule of selexipag we can identify the nucleophilic and electrophilic areas, being nucleophilic are structures rich in electrons that have a high charge and that are donated to the empty orbitals of electrophiles, because in order to have an effective interaction the orbitals must have a similar energy, thus passing from the filled orbital to an empty orbital [13], and thus calculating the surface of the electrostatic potential and the surface of electronic density. After the detailed analysis of the potential electrostatic map (Figure 5), we conclude that in the red nucleophilic region there was a higher concentration of electrons and are located in the (N15, N16, N19, N30, O27, O31, O34, O35) white electrolytes represent the lack of electrons, but the

region in which the rings formed by carbons have a violet color representing neutrality [29].

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Graphics may be full color. Graphics must not use stipple fill patterns because they may not be reproduced properly. Please use only *SOLID FILL* colors which contrast well both on screen and on a black-and-white hardcopy, as shown in Fig. 1.

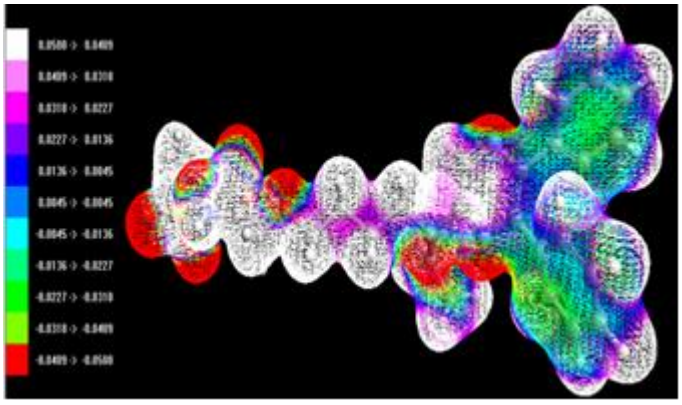

Fig. 5 Potential map representation of selexipag

IV. CONCLUSIONS

Using semi-empirical quantum methods, it was possible to optimize the structure of the drug selexipag, obtaining its lower energy conformation, to identify and characterize the border orbitals, as well as to obtain the reactivity descriptors and to identify their possible reactive sites. In this context the present work represented an initial stage for future studies of drug design and molecular docking.

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