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Semi-Empirical Quantum Level Study of the Drug Evogliptin: Structural Characterization,Mesp,Frontier Orbitals and Reactivity Descriptors

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***Abstract*— Diabetes mellitus is one of the most common chronic intransmissible diseases in the world, being the fourth leading cause of death, causing a growing impact on the world and Brazilian health systems, drastically affecting the quality of life of patients, requiring support in the search for drugs more efficient and with less side effects in the control of diabetes.In this context, the present work aimed to electronically and structurally characterize the drug Evoglipitin, as an initial step for future studies to improve this drug. To perform the in silico study at the quantum level, the semi-empirical PM3 algorithm was used to obtain the most stable conformer, as well as to identify reactivity descriptors (HOMO and LUMO) and chemical physical descriptors that will be used to ADME studies. Noting that this study is a fundamental step future studies of structural modification (analogs) and molecular docking studies, aiming at the understanding and promotion of its pharmacological activity.**

***Keywords*— Diabetes mellitus. Drug Design. Frontier orbitals. Theoretical chemistry.**

I.INTRODUCTION

Diabetes mellitus (DM) is a disease characterized by hyperglycemia arising from defects in insulin secretion and / or action. DM is one of the most common chronic intransmissible diseases (NCDs) in the world and is the fourth leading cause of death. Along with chronic kidney disease, it has a growing impact on the global and Brazilian health systems [1].

Evogliptin ((R) -4 - ((R) -3-amino-4- (2,4,5-trifluorophenyl) butanoyl) -3- (tert-butoxymethyl) piperazine-2-one, also known as DA12229 is a bioavailable inhibitor developed by Dong-A ST which received its first approval in South Korea in 2015 for blood glucose control in patients with type 2 diabetes mellitus DPP-4 inhibitors (dipeptidyl peptidase-4) developed by Dong-A ST and its generic name, Evogliptin, comes from the combination of "Evolution-lution" and "Gliptin," which means evolved glyptin with the strengths of existing DPP-4 inhibitors.DPP-4 inhibitors control glucose levels by preventing the breakdown of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) incretin hormones, which stimulate insulin secretion in response to increased blood glucose levels where it occurs after meals [2] [3] using molecular modeling technique For the characterization it will be possible to determine the molecular properties of Evogliptin using Computational Chemistry and the graphic visualization techniques aiming to provide a three-dimensional representation. if the molecule has biological or pharmacological effect [4] [5] [6] In this context, the objective of this study was to characterize the drug molecule Evogliptin as an initial step for future studies of drug design and molecular docking aimed at promoting pharmacological potential and a decrease in side effects.

II.METHODOLOGY

The methodology that was performed in the characterization of the Evogliptin molecule can be performed from a literature review and using the molecular modeling technique where through computational chemistry [7] it was possible to investigate the molecular structures and properties [8]. The study of the Evogliptin molecule was carried out

using MarvinSketch © [9] and ArgusLab® [10] Version 4.0 configured to perform semi-empirical calculations (based on the theory of quantum mechanics with Hamiltonian PM3 [11] (Parametric Method 3) determining Some of its properties through computational calculations were also consulted in the ChemAxon database [12], therefore removing some of its molecular characteristics, the Avogadro [13] program was also used to determine the properties of atoms, properties of bonds, angle properties and torsional properties of atoms.

By removing a molecule in two-dimensional form from the Drugbank virtual repository [14] [15], it had to be geometrically optimized, making it more stable in its energy minimization process (mathematical procedure to locate stable conformations). The optimization was performed using the semi-empirical quantum method (method based on previously calculated approximated solutions of the Schöedinger equation that allow the calculation of some integrals to be eliminated) [16] using the QM_PM3 (Parametric Method 3) parameters, implemented in the Arguslab software. [17].

III.RESULTS AND DISCUSSIONS

Currently the search for new drugs has been increased by the use of new molecules, analogous to traditional drugs, which has its defined drug, which will serve as the basic structure for structural modifications, seeking to enhance the pharmacological effect and / or the reduction of side effects [7] [18]. In this context, it is of fundamental importance to perform the full characterization of the drug to be modified, where we can highlight the characterization of descriptors that have a direct impact on the absorption, distribution, metabolism and excretion pharmacokinetics in the body [19], with lipophilic, where by calculating LogP (octanol / water partition partition coefficient), we can estimate permeability, solubility and bioavailability [20]. Assuming a moderate log P between 0 and 3, which indicates a balanced relationship between permeability and solubility, if log P = 0, then P = 1 and therefore the compound has the same affinity for both phases, if log P <1 and the tendency of the compound is to dissolve preferentially in the aqueous phase, on the other hand, if log P> 0, then P> 1 and the affinity of the compound is higher for the organic phase the lower log p, the more hydrophilic is the compound. The structure of the Evogliptin molecule has an estimated Log P in the order of 0.89, which indicates a greater tendency to be dispersed in polar systems.

The distribution coefficient Log D, which is determined from a compound between two immiscible liquids, being an organic phase (octanol) at a specific pH in this case, is taken as the physiological pH (7,4). When LogD is less than 1, it indicates good solubility, with low absorption due to low permeability, indicating high renal elimination. In the range between 1 and 3, it indicates good intestinal absorption due to a balance between solubility and permeability. Between 3 and 4, they present good permeability, but not significant absorption due to low solubility. When Log D is greater than 5, it indicates that the molecule has low absorption and bioavailability due to low solubility [21]. Evogliptin molecule was estimated to have a Log D in the order of -0.53, indicating high solubility but low intestinal absorption.

Another important parameter for structural characterization is to identify the protonation of the substance in relation to the pH. In the case of Evoglipitin, at physiological pH (7.4) it remains in its protonated form, since its deprotonations occur at pH 8.79 and 13.69, being these parameters fundamental for future molecular docking studies.

Regarding the composition, it was possible to identify a ratio of 56.85% C, 6.53% H, 14.20% F, 10.47% N and 11.96% O, generating a molecular formula C19H26F3N3O3, with an exact molecular weight of 401.192626198 g mol-1, generating an estimated mass spectrum with 3 fragmentation peaks (401.402, 403) with the peak of 401 being the most intense (Fig.1).

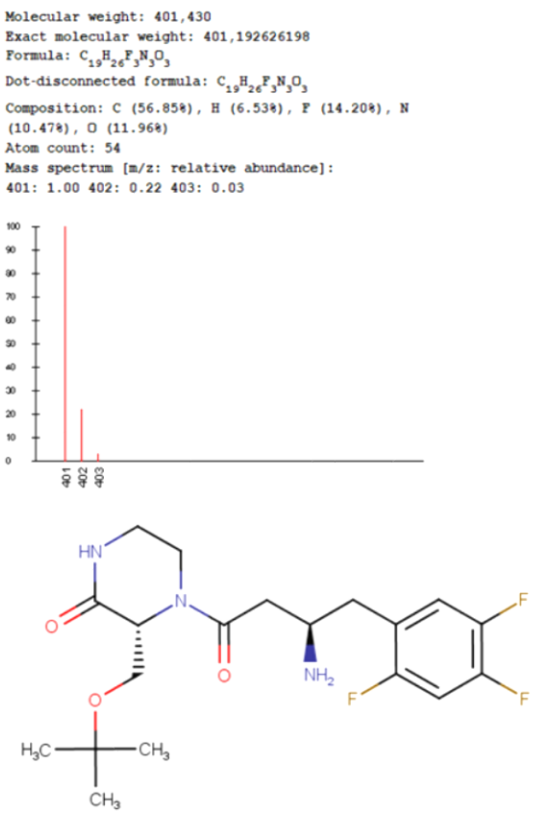

Fig. 1 Elemental analysis (A), two-dimensional structure (B) of the drug Evogliptin

The Hamiltonian quantum mechanical algorithm PM3 (NDDO) was used in the semi-empirical parameter to optimize the structure and obtain the boundary orbitals (HOMO and LUMO) which are orbitals of which reactivity is used [22] [23] [24].HOMO energy measures the electron-donor character of a compound and LUMO energy measures the electron-accepting character [25]. In this case the model in question is the molecule Evogliptin and it was possible to define that the HOMO (fig.2) equals -9.8576 eV which has the contribution mainly of the atoms of (C8, C4, C3), (O15, O7), (N5), (H34) and LUMO (fig.3) -9.8625 eV (C20, C21, C23, C24, C25, C26), other properties necessary for characterization of the molecule as heat of formation were also determined. -241,4179 Kcal mol-1 which can be used to estimate the chemical stability of the molecule, Final SCF Energy -53414959112943,297, Final SCF Energy -123177.9433 kcal mol-1. Electronegativity 9,8600 eV which is a measure of the strength of an atom in attracting to itself electrons involved in a ligant in which that atom also participates. This property can be used to estimate the ability of one molecule to attract electrons from another when an interaction occurs between these two molecules, chemical hardness -0,0024 eV, chemical softness (s) -208,3333, molecules with high potential ionization and high electronegativity have high absolute hardness, and the higher the hardness, the lower the softness of the molecule. Thus, it can be said that hardness represents the resistance of a molecule to deformation and softness represents the ease with which a molecule deforms. The lower the hardness or the greater the softness, the less energy it takes to transition an electron from HOMO to LUMO, Electronic Chemical Potential and Electrophilicity Index [26]. The Gap (HOMO Energy - LUMO Energy) was calculated and can be defined with the energy required for the first quantum leap. This is an important molecular descriptor for future thermodynamic studies related to the reactivity of the molecule.

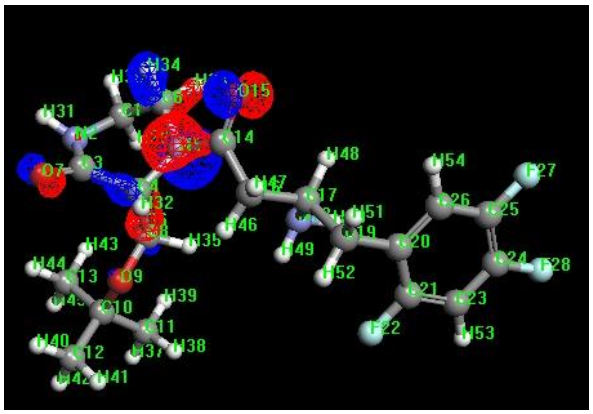

Fig. 2 Frontier Orbital (HOMO)of the drug Evogliptin

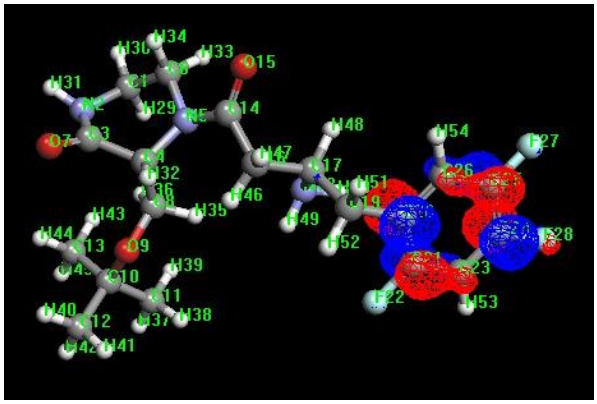

Fig. 3 Frontier Orbital (LUMO) of the drug Evogliptin

TABLE I

Reactivity descriptors of the drug Evogliptin

HOMO	-9,8576 eV
LUMO	-9,8625 eV
Final SCF Energy	-53414959112943,297
Final SCF Energy	-123177.9433 Kcal/mol
Heat of Formation	-241.4179 Kcal/mol
SCF Type	RHF
Atoms	54
Gap	0,0049 eV
Electronicaffinity	9,8625 eV
Vertical ionization potential (I)	9,8576 eV
Electronegativity	9,8600 eV
Chemical hardness	-0,0024 eV
Chemical softness(s)	-208,3333 eV
Eletronic chemical potential	- 9.8600eV
Electrophilicity index	4,9372 eV

From the optimization of the molecule it was possible to plot the MESP (electrostatic potential surface map). MESP is generated after the overlap in the molecule of a positively charged particle that travels over the Van der Waals contact surface and reveals a repulsion region [16] [27]. Together with the dipole moment of the molecule, it can be used to predict the types of intermolecular interaction, as well as the most favorable sites for the formation of interactions between biological molecules and their receptors, as well as being an important tool in the study of breeding and development of new potentially bioactive molecules. MESP is done by calculating the electrostatic potential surface that represents the measure of how positive or negative a particular region of the molecule is by its charge distribution and mapping over the electron density surface (Figure 4). With the analysis of the electrostatic potential map of the Evogliptin molecule, the highlighted white areas of the structure are electron deficient and the regions where the carbon-formed cycles and rings are located as the presence of groups such as amines that remain in neutral zone in dark blue and light blue, the region highlighted in red in the structure has a higher concentration of electrons, nucleophilic region in the areas where oxygen is located (O7, O9, O15).

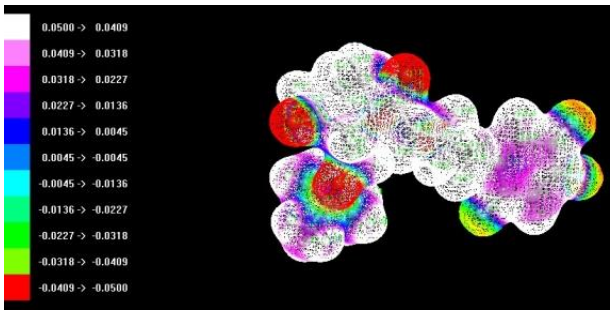

Fig. 4 Electrostatic potential surface map(MESP)of the drug Evogliptin

With respect to charge distribution, the Mulliken Population Analysis, a method for distributing electrons to atoms for the purpose of generating partial atomic charges, was determined. The Mulliken Population Analysis is a method for determining the charge of atoms in the formation of molecules. It has great applicability in the characterization of its biological activity, because the distribution of electrons of the chemical species and the charge density, informs the behavior of the molecule showing its variations between the atoms that compose it, in the studied molecule one can perceive the variations in the atoms of one element such as the carbon with the highest charge was (C14) 0.3104 the least charged (C11) -0.3537, the most charged hydrogen was (H54) 0.2427 and the lowest charged was o (H49) 0.0719, the oxygen with the highest charge was O9 -0.2547 and the lowest oxygen O7 -0.3485, the fluorine atom with the lowest charge was F27 -0.768 and the highest F28 -0 , 0762 and Nitrogen being the highest charge value N5 -0.102 and the lowest charge N2 -0.1192, these being the maximum and minimum values of the charges of atoms. A partition scheme, based on the use of density and sheath matrices, to distribute the electrons of a somewhat fractional molecular entity among its various parts (atoms, bonds, orbitals). As in other

schemes used to distribute electron density in molecules, Mulliken's population analysis is arbitrary and strongly dependent on the base set employed. However, comparing population analyzes for a number of molecules is useful for a quantitative description of intramolecular interactions, chemical reactivity and structural regularities.

TABLE II

Mulliken charges of the drug Evogliptin

ATOMS	CHARGE	ATOMS	CHARGE
1C	-0.2371	28F	-0.0762
2N	-0.1192	29H	0.1397
3C	0.2607	30H	0.1434
4C	-0.1532	31H	0.1453
5N	-0.1026	32H	0.1800
6C	-0.2189	33H	0.1580
7O	-0.3485	34H	0.1384
8C	-0.0900	35H	0.1273
9O	-0.2547	36H	0.1163
10C	0.1114	37H	0.1187
11C	-0.3537	38H	0.1225
12C	-0.3268	39H	0.1112
13C	-0.3534	40H	0.1274
14C	0.3104	41H	0.1190
15C	-0.3830	42H	0.1119
16C	-0.2727	43H	0.1065
17C	0.1489	44H	0.1306
18N	-0.1183	45H	0.1119
19C	-0.2324	46H	0.1413
20C	-0.1117	47H	0.1547
21C	0.0830	48H	0.1713
22F	-0.0924	49H	0.0719
23C	-0.2416	50H	0.0812
24C	0.0720	51H	0.1457
25C	0.0403	52H	0.1475
26C	-0.1732	53H	0.2457
27F	-0.0768	54H	0.2321

TABLE III

Structural descriptors of the drug Evogliptin

atom	Elemento/type		valence	Partial charge
1	C	C3	4	0,027
2	N	NAM	3	-0,312
3	C	C2	3	0,236
4	C	C3	4	0,125
5	N	NAM	3	-0,286
6	C	C3	4	0,031
7	O	O2	1	-0,274
8	C	C3	4	0,075
9	O	O3	2	-0,372
10	C	C3	4	0,061
11	C	C3	4	-0,036
12	C	C3	4	-0,036
13	C	C3	4	-0,036
14	C	C2	3	0,218
15	O	O2	1	-0,276
16	C	C3	4	0,040
17	C	C3	4	0,017
18	N	N3	3	-0,327
19	C	C3	4	-0,009
20	C	CAR	3	-0,008
21	C	CAR	3	0,129
22	F	F	1	-0,205
23	C	CAR	3	0,012
24	C	CAR	3	0,161
25	C	CAR	3	0,159
26	C	CAR	3	-0,018
27	F	F	1	-0,202
28	F	F	1	-0,202

After minimizing molecular energy, each atom of the molecule occupies a steady state of lower energy, achieving a more stable three-dimensional structure. Therefore, it was also calculated as the valence corresponding to each constituent element of Evogliptin, with the most valiant atom. C3 with charge 4, then comes N3 with a valence charge 3, and as the valences of

atoms are O2 and O3 ranging from 1 to 2 respectively and F atoms with valence 1 to 0, characterizing a higher neutral charge structure and higher charge capacity, lower partial power 0.236 of the atom (21 C C2) and lower charge -0.37 a of the atom (9 O O3). Ligand types can be perceived to predominate as covalent as carbon-carbon (C17-C16), (C17-C18), (C16-C15), (C18-C19), (C15-C14) (C7 -C6), carbon-nitrogen (C4-N2), (C1-N1), oxygen-carbon (O3-C10), and as rotary bonds (C12-C13), (C12-C11), (C5-C3), (C5, 02) and (C6-O2).

TABLE IV

Structural descriptors (chemical binding) of the drug Evogliptin

Start storm	**Endst orm**	**Bond order**	**Rotable**	**Lenght(Å)**
F3	C17	1	No	1,34122
C17	C16	2	No	1,39663
C17	C18	1	No	1,412
F2	C18	1	No	1,342
C16	C15	1	No	1,40168
C18	C19	2	No	1,39779
N3	C12	1	No	1,48706
C15	F1	1	No	1,34631
C15	C14	2	No	1,40685
C7	C6	1	No	1,53719
C19	C14	1	No	1,39626
C4	N2	1	No	1,49719
C1	N1	1	No	1,48512
O3	C10	2	No	1,22283
C14	C13	1	No	1,49664
C12	C13	1	Yes	1,54597
C12	C11	1	Yes	1,53803
C9	C6	1	No	1,53669
N2	C10	1	No	1,43198
N2	C3	1	No	1,4995
C5	C3	1	Yes	1,55053
C5	O2	1	Yes	1,41918
C10	C11	1	No	1,52209
C6	O2	1	Yes	1,44409
C6	C8	1	No	1,53608
C3	C2	1	No	1,53365
N1	C2	1	No	1,42901
C2	O1	2	No	1,21835

From the conformational characterization of the compound, it is possible to calculate all angles between the ligand and the torsion angles. Taking as examples of the highest and lowest combination, the angles (C13-C14-C15) and (O2– C5 - C8) with 121.8930 ° and 104.0992. Also, for example, the largest and smallest torsion angles, the systems (C18 - C17 - C16 - H25) and (C17 - C18 - C19 - H26) with 179.9181 ° and -179.9268 °.

IV. Conclusions

Using molecular modeling techniques coupled with quantum theory at the semi-empirical level, it was possible to electronically and structurally characterize the drug Evogliptin, enabling a full understanding of its chemical properties that served as the basis for future structural modification (analog) studies and molecular docking studies, aiming at the understanding and promotion of its pharmacological activity.

V. Acknowledgment

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