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Structural Characterization of the Hypoglycemic Drug Glimepiride

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***Abstract*- Diabetes mellitus type 2, associated with other cardiovascular risk factors such as hypertension, obesity and dyslipidemia represent a serious public health problem in Brazil, as well as in most of the world. One of the compounds that has proven effective in combating diabetes is Glimepiride, an oral hypoglycemic agent, which works by increasing the uptake of glucose in the body. The present study aimed to perform the structural and pharmacological characterization of the Glimepiride compound using the MMFF94 force field. Through the Avogadro® program, and based on the literature, it was possible to geometrically optimize the conformational structure of the molecule to a level of energy stability. With the optimized structure, the potential energy of (-932,766 kJ · mol-1) of the structure and its dipole moment (6,523) were calculated, besides the possibility to characterize the atomic bonds, their lengths, angles and torsion angles). The Van der Waals surface and the dipole vector representation of the molecular structure were also rendered and visualized. The obtained data consist of an initial stage for later studies of semi-empirical molecular modeling and, possibly, molecular docking, aiming at the optimization of this compound as to its biological potential.**

***Keywords*- Classical force field.** D**iabetes. Molecular modeling.Theoretical chemistry.**

I.INTRODUCTION

With a global prevalence estimated at 8.8% in 2015, with the prospect of reaching 10.4% of the global population by 2040, Diabetes Mellitus is now considered to be a worldwide epidemic [1], Which can lead to acute and chronic complications that can progress to early disability, cardiovascular, circulatory and neurological changes, as well as the high cost of treatment and frequent hospitalizations [2], with a negative impact on the population's quality of life ,in Brazil, the context is no different, type 2 diabetes is already one of the major causes of morbidity among adults, reaching about 30 to 40% of them and affects 11% of the country's population over 40 , a mass of almost 5 million people[3]. The worrying percentage grows along with urbanization coupled with the absence of physical activities and highly caloric diets [4]. The treatment today goes beyond simple prevention, if it regulates the glycemic control of the diabetic patient, including regular physical activity, new dietary habits and medication, which may be insulin or hypoglycemic compounds [5].

In the treatment of diabetes, as for hypoglycemic agents, there are two classes: biguanides and sulfonylureas. Within the sulfonylurea class, there are three generations of drugs that have been marketed for about 50 years [6]. Glimepiride is an organic compound, classified as sulfonylurea, being the first sulfonylurea of the third generation; which, when compared to other generations of sulfonylurea compounds, is very potent and long acting [7-9]. Sulfonylurea compounds are insulin secretagogues, among them, Glimepiride acts acutely by stimulating GLUT4 translocation, which increases glucose uptake by the body [10], acts by binding to potassium channel receptors sensitive to ATP on the surface of the pancreatic cell, reducing potassium conductance and causing membrane depolarization. The depolarization of the membrane stimulates the influx of calcium ions through voltage-sensitive calcium channels. This increase in the concentration of intracellular calcium ions induces insulin secretion [11-12].

Pharmacological compounds can undergo a process of remodeling, (rational drug planning), coupled with molecular modeling. Drug design can, through computational simulations, minimize the amount of resources involved in a research, accomplishing, with precision, efficiency and considerable speed, tasks that would be very complex and costly when performed experimentally, such as simple and the angles of dihedral angles [13]. Included in this process is molecular modeling, which can be stipulated as a set of tools and computational programs that enable the construction, editing, visualization and analysis of molecular structures. Through in silico methods and theoretical calculations, molecular modeling allows the complete characterization of several molecular structures [14], when determining parameters that correlate structure-activity also allows to study the mechanisms of action of a compound, its biological activity and even its toxicity [15]. Other expressive data for Drug design which can be obtained in silico include the minimum potential energy of the structure and its formation heat, the specific arrangement of each atom in the molecule, its dipole moment, and the HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital) [16]. Obtaining these structures for in silico study is also linked to molecular modeling, either through software's or molecular drawing tools, where the atoms and their bonds, hybridizations, etc. can be gradually built, or through access to virtual repositories of structures, which are virtual databases containing thousands of structures indexed important data about them. In this perspective, the present study aimed to perform the structural characterization and drug Glimepiride, using the MMFF94 force field, as well as perform a virtual screening to obtain its main pharmacological characteristics available in the virtual repositories of molecules, aiming at a future drug study design.

II.METHODOLOGY

For the accomplishment of this work, we used Computer simulation softwares with free license for academic and research purposes. All simulations were performed on a personal computer, based on the Microsoft Windows Seven® Operating System.

Initially, (1) using the descriptor Glimepiride, its two-dimensional molecular structure, its pharmacodynamics and its mechanisms of action were obtained through the Virtual DrugBank® repository (https://www.drugbank.ca) [17]; (2) through the virtual repositories ChemSpider® (http://www.chemspider.com)[18] and PubChem® (https://pubchem.ncbi.nlm.nih.gov) [19], (3) through Avogadro® [20] (version: 1.2.0, library version: 1.2.0, Open Babel) Version: 2.3.90, Qt version: 4.8.6) configured to perform classic Merck molecular force field field calculations (MMFF94) [21], with 500 steepest descent optimization cycles, with convergence 10e-7, where it was possible to obtain the, with the objective of geometric optimization of the molecular structure, generating its conformation. minimum potential energy and, thus, characterizing their gulls and dihedral angles, as well as calculating their dipole moment and Van der Waals surface rendering [21-22].

III. RESULTS AND DISCUSSIONS

Virtual databases such as DrugBank® (https://www.drugbank.ca)[17], ChemSpider® (http://www.chemspider.com)[18] and PubChem® (http://pubchem.ncbi.nlm.nih.gov)[19], it is worth highlighting DrugBank®[17] for combining detailed drug (chemical, pharmacological) data with its specific target data (structure, sequence and pathway), resulting in a relatively comprehensive encyclopedia of pharmacological compounds. We can also observe that the repository contains 11.141 drug structures since its last version: 2.555 approved drugs for small molecules, 965 approved biotechnological drugs (proteins / peptides), 121 nutraceuticals and more than 5.143 experimental drugs; and within this vast catalog, the structure of Glimepiride [23].

Glimepiride is an organic compound, classified as sulfonylurea, being the first sulfonylurea of the third generation; which, when compared to other generations, is very potent and long acting [24].

The two-dimensional structure of the pharmacological compound Glimepiride [Fig. 1] was obtained from the DrugBank® virtual repository (https://www.drugbank.ca)[17], together with its

systematic nomenclature according to IUPAC [3-ethyl-4-methyl -2-oxo-N- (2- {4 - [({[(1S, 4R) -4-methylcyclohexyl] -C-hydroxycarbonimidoyl} amino) sulfonyl] phenyl} ethyl) -2,5-dihydro-1H-pyrrole -1-carboximidic acid] and CAS identification (93479-97-1). Data on various physico-chemical properties (Table I) of the compound were also obtained, which are important for understanding the mechanisms of action and behavior of the molecule, including the solubility of the structure in water (0.0347 mg / mL) and the partition coefficients LogS (-4.2) and LogP (3.03), which indicate the hydrophobicity of the compound and allow to choose which solvent (polar or nonpolar) can be used in future docking tests or as a drug transport route.

Table I
Physico-chemical properties of the compound Glimepiride

Property	Value
Fusion point	207 °C
Solubility in water	0.0347 mgmL-1
LogP	3.03
Logs	-4.2
Polar Surface Area	131.66 Å^2
pKa in acid	2.23
pKa in basic	-0.36
Refractivity	130.85 m3·mol-1
Polarisability	53.31 Å3

Source: DrugBank® Virtual Repository (https://www.drugbank.ca/drugs/DB00222)

In the ChemSpider® repository (http://www.chemspider.com), it was possible to obtain complementary structural information (Table II), however, of high importance to the study of the compound, highlighting the density (1.3 ± 0.1 g / cm3) and its surface tension (58.2 ± 5.0 dyne / cm). In addition to the number of donors and recipients of hydrogen bonds, giving the structure the ability to form 12 bonds of this type.

Table II
Physico-chemical properties of the compound Glimepiride

Property	Value
Molecular Formula	$C_{24}H_{34}N_4O_5S$
Density	1.3±0.1 g/cm^3
Superficial tension	58.2±5.0 dyne/cm
Receptors #H	9
Monoisotopic Mass	490.224976 Da
Refractive index	1.599
Molar Volume	378.8±5.0 cm3
Donors #H	3

Source: ChemSpider® Virtual Repository (www.chemspider.com/Chemical-Structure.16740595.html)

The DrugBank® repository also benefits from data provided by AdmetSAR® (http://lmmd.ecust.edu.cn/admetsar1), a pharmacological database that provides information on the absorption, metabolism, distribution, excretion, and toxicity of various compounds [25]. The data (Table III) collected on the compound Glimepiride show a high intestinal absorption (98.6%) and a relatively high capacity to cross the hematoencephalic barrier (73.22%) in addition to denoting the low toxicity in rats and not -carcinogenicity of the drug.

Table III
Pharmacological properties of the compound Glimepiride (AdmetSAR®)

Property	Value	Probability
Absorption in the Human Intestine	+	0.986
HematoencephalicBarrierPermeability	+	0.7322
Permeability to Caco-2	-	0.6809
Substrate for P-glycoprotein	Substrate	0.7501
Inhibitor I of P-glycoprotein	Does notinhibit	0.6556

Inhibitor II of P-glycoprotein	Inhibitor	0.6124
Renal Transport of OrganicCations	Does notinhibit	0.8241
Substrate CYP450 2C9	Substrate	0.5661
Substrate CYP450 2D6	Non-substrate	0.9116
Substrate CYP450 3A4	Non-substrate	0.5978
Substrate CYP450 1A2	Does notinhibit	0.9045
Inhibitor CYP450 2C9	Inhibitor	0.8949
Inhibitor CYP450 2D6	Does notinhibit	0.9231
Inhibitor CYP450 2C19	Does notinhibit	0.9025
Inhibitor CYP450 3A4	Does notinhibit	0.8309
CYP450 PromiscuousInhibitor	Low Promise CYP Inhibition	0.8599
AMES Test	Non toxic	0.6392
Carcinogenicity	Non-carcinogenic	0.7301
Biodegradation	Notbiodegradableyet	0.68
Rat Toxicity (DL50)	2.4158 LD_{50}, mol/kg	

Source: DrugBank® Virtual Repository (https://www.drugbank.ca/drugs/DB00222).

Based on the DrugBank® drug database, the initial structure of the compound Glimepiride (Fig. 1) presents a two-dimensional arrangement with only the molecular formula (C24H34N4O5S) and the connectivity of the atoms in a spatial plane, providing an easy but structured visualization of the system in a different way from how it is natively (in real disposition).

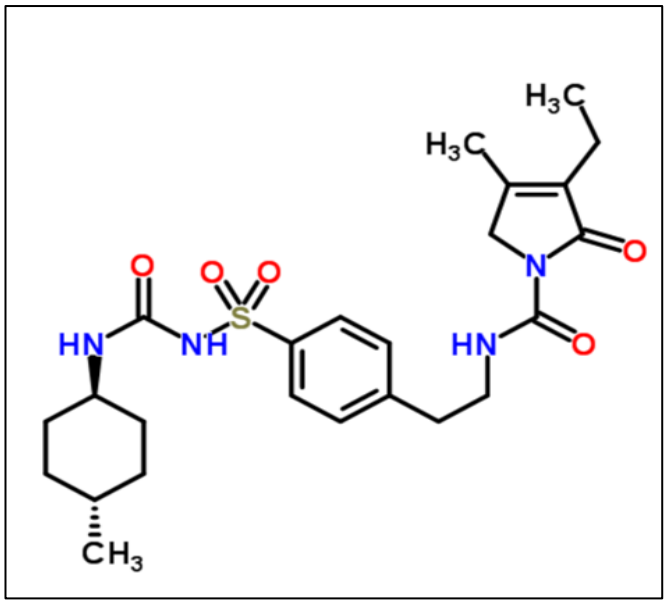

Fig. 1. Initial structure of the compound Glimepiride Source: Chewspider® virtual repository (http://www.chemspider.com/Chemical-Structure.16740595.html?rid=e6eda79b-693d-4e12-b4fa-aabe230f8244).

Like the compound obtained, the database-generated structure or constructed in a molecular design package is not necessarily in its most stable conformation, and therefore any calculation on it does not match the actual properties of the molecule studied. Thus, to perform a precise calculation of the studied structure, it needs to be in its most stable conformation, being necessary to use the energy minimization process to optimize it geometrically [26]. This geometric optimization process was performed in the Glimepiride structure using Avogadro® open license software and configured the program to perform uninterrupted cycles of structure interaction through the classical force field calculations MMFF94,calculations are parameterized on the steepest descent algorithm[21].

Once the geometric optimization process was carried out, each atom then occupied a site of lower potential energy within the structure, making the overall potential energy of the structure as small as possible, generating a structure (Fig. 2) with greater theoretical stability.

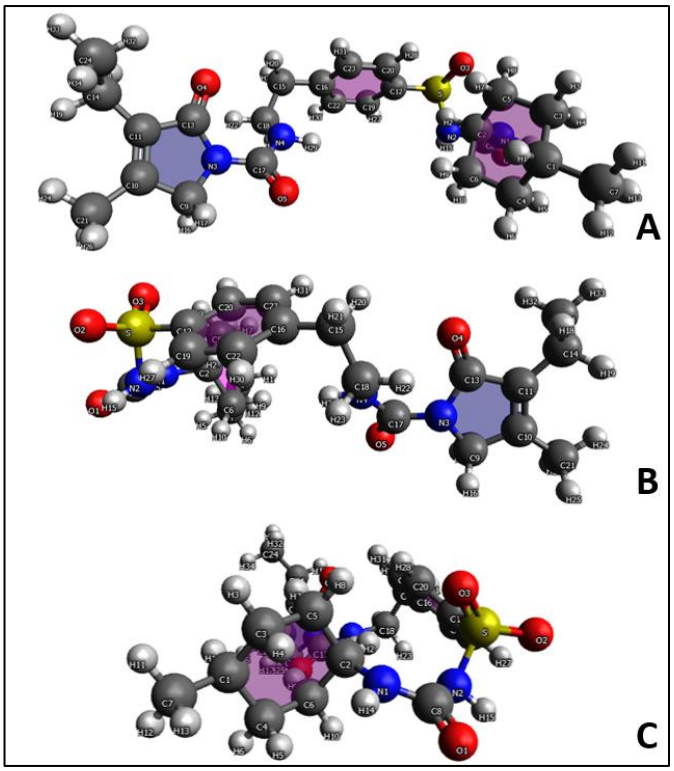

Fig. 2. Optimized structure of Glimepiride compound calculated using MMFF9:(A) Rotation of 0 ° / (B) Rotation of 140 ° / (C) Rotation of 260 °.

When the structure reaches its more stable conformational state and, consequently, each atom takes a specific position no more variable, it becomes possible to observe the valence and the calculation of the formal and partial charges of each atom. These data (Table IV), mainly valence, are congruent to the literature, ratifying the results generated.

The actual charges that each atom, ion or molecule possesses can be predicted with fidelity by their respective formal charge [27]; considering the stability of the structure, the formal charges are of value (0), since the electron pair is equally divided between both the atoms forming the covalent bond, unlike the ionic bonds, that totally transfer electrons from one atom to another [28] . However, there are the residual charges that, contrary to the nullity of the formal charges, have values that represent the electrons (charge) closest to or distant from the atom that make up the bond [29].

Table IV
Atomic properties of the compound Glimepiridecalculated using MMFF94

Atom	Element/ Ttype		Valence	Formal Charge	Partial Change	X (Å)	Y (Å)	Z (Å)
1	S	So2	4	0	0.076	1,15971	-0.54031	-1.00840
2	O	O2	1	0	-0.251	-0.65298	1,95777	0,65370
3	O	O2	1	0	-0,150	0.16104	-0.87121	-2.00200
4	O	O2	1	0	-0,150	1,29400	-1.29292	0.21820
5	O	O2	1	0	-0.270	9.84826	0.16443	-3.15860
6	O	O2	1	0	-0.252	7,92873	3,442,203	-1,60410
7	N	Nam	3	0	-0.295	1,28582	1,46149	1.66580
8	N	Nam	3	0	-0.169	0.96562	1,10143	-0.67160
9	N	Nam	3	0	-0.218	9.42865	2.49343	-3,05900
10	N	Nam	3	0	-0.299	7.25349	1.64290	-2.74800
11	C	C3	4	0	-0.044	3,70131	2.50740	4,27370
12	C	C3	4	0	0.025	2,74056	1,37140	1.68910
13	C	C3	4	0	-0.049	3,03516	1,12750	4,21090
14	C	C3	4	0	-0.049	3,19204	3.41530	3,14700
15	C	C3	4	0	-0.034	3,21107	0,47610	2,83930
16	C	C3	4	0	-0.034	3,37015	2,76800	1,77280
17	C	C3	4	0	-0.062	3,46732	3,15590	5,63700

18	C	C2	3	0	0.319	0,47649	1.49560	0.57510
19	C	C3	4	0	0.046	10.28799	3,64560	-3.00510
20	C	C2	3	0	-0.047	11.62003	3.08570	-3.36870
21	C	C2	3	0	0.015	11.59367	1,74950	-3,45960
22	C	Car	3	0	0.109	2,73477	-0.54130	-1.83320
23	C	C2	3	0	0.250	10.19673	1,33330	-3.118190
24	C	C3	4	0	-0.026	12.65604	0.76470	-3.80060
25	C	C3	4	0	-0.012	6,55135	-0.47730	-3.83340
26	C	Car	3	0	-0.046	5,20339	-0.53160	-3.14620
27	C	C2	3	0	0.309	8,20547	2.56120	-2.44180
28	C	C3	4	0	0.017	7,06828	0,95270	-4.01840
29	C	Car	3	0	-0.035	2,81037	-0.11180	-3.11670
30	C	Car	3	0	-0.035	3,87335	-1,00020	-1.16750
31	C	C3	4	0	-0.042	12.77571	4,00380	-3.55810
32	C	Car	3	0	-0.057	4,04425	-0.10890	-3.81400
33	C	Car	3	0	-0.057	5,10566	-0.98440	-1.82200
34	C	C3	4	0	-0.061	13.22286	0.09570	-2.56060

As for the properties calculated using the Avogadro® software, one can calculate the dipole moment (μ) of the structure which, due to the difference in electronegativity between the atoms, is related to the way the electric charges are distributed by the molecule and to the polarization, separation between positive and negative charges [29]. Some other properties of the structure are directly linked to the dipole moment (μ), as the melting and boiling points and their solubility in water [27]. The compound Glimepiride presented a dipole moment (μ) of estimated value in (6,523), being possible, yet, its vector representation (Fig. 3).

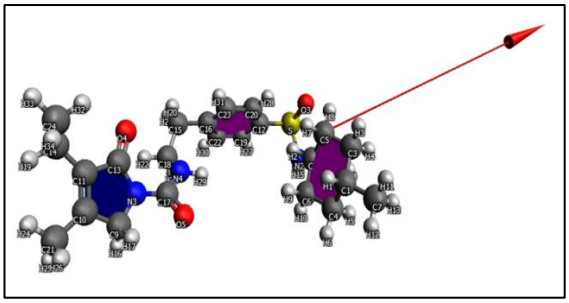

Fig. 3.Vector representation of the dipole moment of the drug Glimepiride calculated using MMFF94.

At the end of the process of energy minimization, it was possible to observe that in all the connections the covalent character prevails, character that can be defined as the congruence between the length of the bond and the average distance between the nuclei of both the ligand atoms when they are at their lowest energy location (their native, more stable form) [29]. (C 2 -C 6), (C 2 -C 6), (C 3 -C 5), (C 3 -C 5), (C 2 -C 5), (C 2 -C 6), (C 2 -C C4 - C6) and (C15 - C18)) as the only ones that allow structure to be rotated.

TABLE V

Properties of Glimepiride drug bonds calculated following the formalism of the classical force field MMFF94

bond	Type	Initialatom	Final Atom	Order of Bond	Rotability	Length(Å)
1	S – O	S	O2	2	No	1.44771
2	S – O	S	O3	2	No	1.44533
3	S – N	S	N2	1	No	1.68709
4	S – C	S	C12	1	No	1.77799
5	O – C	O1	C8	2	No	1.22294
6	O – C	O4	C13	2	No	1.21994
7	O – C	O5	C17	2	No	1.23261
8	N – C	N1	C2	1	No	1.45777
9	N – C	N1	C8	1	No	1.35859
11	N – C	N2	C8	1	No	1.39602
13	N – C	N3	C9	1	No	1.43836
14	N – C	N3	C13	1	No	1.3967
15	N – C	N3	C17	1	No	1.37177
16	N – C	N4	C17	1	No	1.3577
17	N – C	N4	C18	1	No	1.4576
19	C – C	C1	C3	1	Yes	1.53354
20	C – C	C1	C4	1	Yes	1.53399
21	C – C	C1	C7	1	No	1.52771
23	C – C	C2	C5	1	Yes	1.53163
24	C – C	C2	C6	1	Yes	1.5342
26	C – C	C3	C5	1	Yes	1.52858
29	C – C	C4	C6	1	Yes	1.52943
39	C – C	C9	C10	1	No	1.48994
42	C – C	C10	C11	2	No	1.33955
43	C – C	C10	C21	1	No	1.48809
44	C – C	C11	C13	1	No	1.4839
45	C – C	C11	C14	1	No	1.48815
46	C – C	C12	C19	2	No	1.39764
47	C – C	C12	C20	1	No	1.39648
48	C – C	C14	C24	1	No	1.52136
51	C – C	C15	C16	1	No	1.51403
52	C – C	C15	C18	1	Yes	1.53177
55	C – C	C16	C22	2	No	1.40299
56	C – C	C16	C23	1	No	1.40288
59	C – C	C19	C22	1	No	1.39563
61	C – C	C20	C23	2	No	1.39542

Still considering the structural characterization of the compound, a total of 129 angles and 187 dihedral angles (torsion) could be calculated in addition to the 70 connections. The angle (N2 - S - C12) as the lowest angle (101.2493 °) and the angle (C10 - C11 - C14) as the highest angle (131.4252 °) are shown between the angles between the links. (C12 - C19 - C22 - C16) as the lowest angle (0.1204 °) and the dihedral angle (H1 - C1 - C7 - H13) as the highest angle (179.9484 °).

Finally, the software allowed the rendering and visualization of the Van der Waals surface (Fig. 4),

making it possible to distinguish the limits of the volume of each atom.

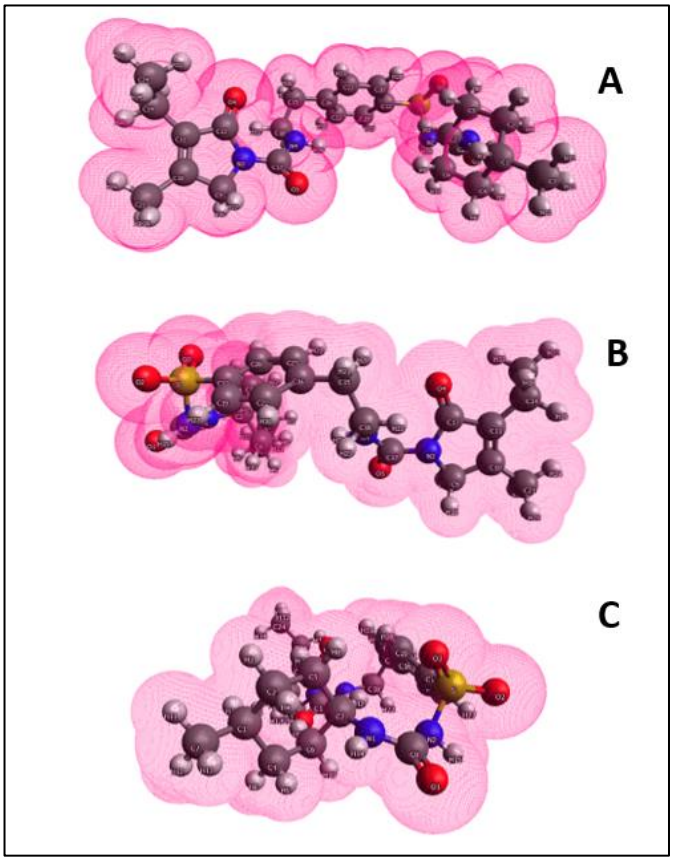

Fig. 4.Van der Waals surface of the drug Glimepiride obtained after geometric optimization using the classical force field MMFF94.
(A) Rotation of 0 ° / (B) Rotation of 140 ° / (C) Rotation of 260 °.

IV. CONCLUSIONS

Modern computational simulation tools, coupled with molecular modeling, have become important in the process of developing new drugs, tools that allow structural characterization of compounds with biological potential; as it was observed in the characterization of the compound Glimepiride, through Avogadro® freeware configured in MMFF94 steepest descent, optimizing its geometry until reaching the most stable conformation, obtaining at the end of this process the energy of [-932,766 kJ · mol-1]. It was also characterized its mass [490,616 g · mol-1] and dipole moment [6,523]. (C2 - C6), (C2 - C6), (C2 - C6), (C1 - C4), (C1 - C4), (C2 - C5), and (C2 - C5) bonds. (C3-C5), (C4-C6) and (C15-C18)) as being the only ones to enable structure rotation. The software together allowed the rendering and visualization of the Van der Waals surface and the vectorial representation of the dipole moment. All the data obtained conceive a preliminary step to the subsequent studies of molecular modeling at semi-empirical quantum level, aiming at the optimization of this compound as to its biological potential.

V. ACKNOWLEDGMENT

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