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Initial Studies of Electronic and Structural Characterization of Anti-Depressive Brexpiprazole

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Abstract - Major Depressive Disorder (MDD) is a clinical disease considered one of the dimensions of schizophrenia. It is currently one of the most difficult mental health problems, with a global reach of approximately 8% male and 15% female. Brexpiprazole acts in the treatment of MDD through the partial agonist activity of dopamine 2D and serotonin 1A inhibitors. The present work aims to conduct initial studies of electronic and structural characterization of the Brexpiprazole through the molecular modeling technique using classical force field calculations (MMFF94). Initially, several physicochemical properties were obtained, such as log P (4.83) and log S (-5.93) and (0.01 mg.ml-1) partition coefficients, which allowed the solvent polarity to be defined. After the geometric optimization, it was possible to obtain the lower energy conformational state (three-dimensional structure) (463,44 KJ.mol-1), resulting in its more stable structure energetically, being this the initial conformation for studies of molecular dynamics. The present work represents the initial stage for a complete study of the electronic and structural characterization of this agonist aiming at future studies of structural modification, docking and molecular dynamics.

Keywords - molecular modeling. MMFF94. Theoretical chemistry.

I. INTRODUCTION

Major depressive disorder (MDD) is a common, chronic and very recurrent disease in the last few years that causes functional disability and affects physical and mental health. Currently, MDD is the fourth disease that most causes disability and social isolation in the world. According to estimates, by 2020 the disease will be the second major anomaly causing functional disabilities. In the Americas, MDD is already the leading cause of disability, surpassing even cardiovascular diseases [1]. Brexpiprazole is a modulator of serotoninergic dopamine activity, acting as a partial agonist on serotonin 5-HT 1A and dopamine D 2 receptors with potent energy and antagonism in 5-HT 2A and norepinephrine. The compound still has a low affinity for these receptors, which results in low levels of sedation compared to other antipsychotic agents. Preclinical tests indicate that Brexpiprazole has antipsychotic therapeutic action as adjuvant treatment for MDD [2].Brexpiprazole belongs to the class of organic compounds called n-aryl piperazines. These are organic compounds formed by a piperazine ring, where the nitrogen ring atom carries an aryl group (Fig. 1) [3].

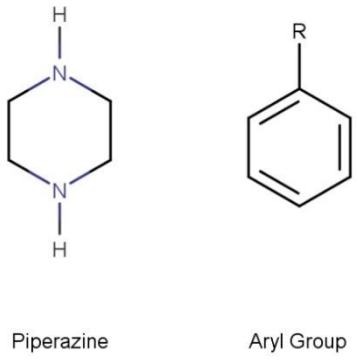

Fig.1.Piperazine and Aryl Group, major ligands of Brexpiprazole.

The reaction mechanism of its synthesis consists in the reaction of 4-chloro-1-benzothiophene with the piperazine linker, forming a free base. The base formed in turn is reacted with 7- (4-chlorobutoxy) -1,2-dihydroquinolin-2-one to give the product Brexpiprazole, IUPAC 7- {4- [4- (1- benzothiophen-4-

yl) piperazin-1-yl] butoxy} -1,2-dihydroquinolin-2-one (Fig. 2) [4].

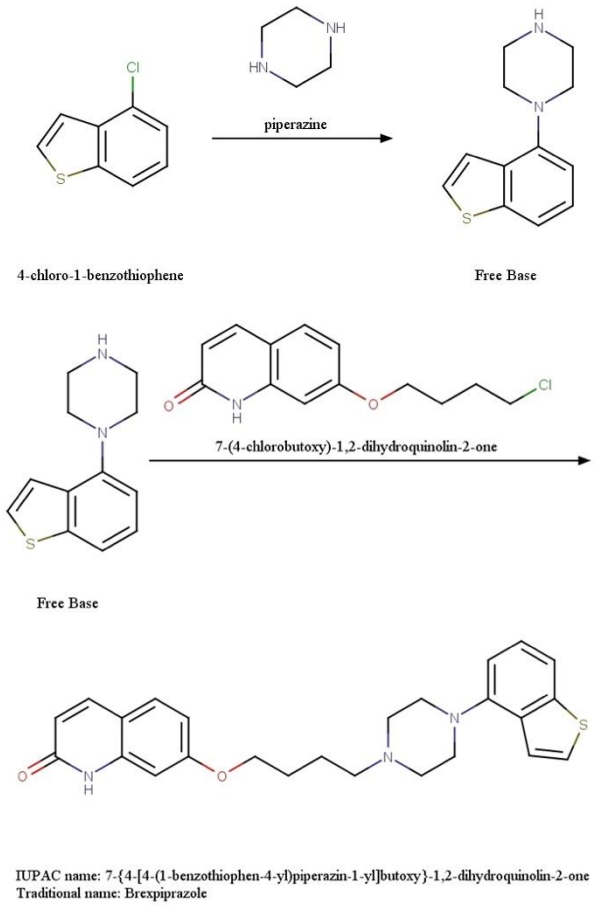

Fig.2 Synthesis reaction of the compound Brexpiprazole. Source: CASTRO, 2015.

Molecular modeling is a set of computational methods that are used as rational planning techniques of biomolecules, as well as the orientation of a hypothesis about their reaction mechanisms and their biochemical action [5]. It has a complete characterization of its structures and the distance of the connections, besides the obtaining of physical-chemical properties, angles of connections and dihedral angles [6].There are several methodologies that use mathematical calculations, parameters and adjustments to characterize a given molecule as to its electronic structure and properties, such as molecular mechanics and molecular dynamics [7].With this perspective, the present work had as objective to carry out initial studies of electronic and structural characterization of the drug Brexpiprazole.

II. METHODOLOGY

Methodology of Study

The physico-chemical properties were obtained by the MarvinSketch © academic license software and the MMFF94 classical force field calculations [5] [8] were made by Avogadro® open license software (version 1.2.0) generating the most stable final conformation of lower energy.The work was carried out based on the following methodology [9]: (1) The two-dimensional structure of the compound Brexpiprazole was obtained in the Drugbank® virtual repository [3]; (2) the two-dimensional structure was delineated in MarvinSketch © academic license software; (3) the physico-chemical properties of the molecule were obtained from the ChemAxon® database [10] contained in MarvinSketch® software; (4) the three-dimensional structure was optimized using classical force field calculations config.d in MMFF94 [7] [8] with the help of Avogadro® open license software, config.d for cycles of 500 interactions of the steepest descending algorithm, generating the smaller structure potential energy; (5) the connections, torsion angles and dihedral angles were presented; (6) the Van der Waals surface map was redone by highlighting the molar volume over the entire length of the molecule; (7) from the molecular properties its biochemical properties were determined.

Calculation Methodology

One of the most important studies of molecular modeling is the Conformational Analysis, whose objective is the analysis of molecular geometric arrangements under optimized conditions of potential energy. The mechanisms of molecular and quantum-chemical mechanics are applied to compute the conformational energies, whereas the methods of molecular dynamics are the exploration of the quantitative relations and the biological characteristics of the studied compound, in order to classify their physicochemical and reactional properties through multiple correlation data [6].

Molecular mechanics, according to IUPAC [15] is described as "calculating the geometries and conformational energies of molecules using a

combination of empirical force fields". In molecular mechanics, molecules are said to be "connected atoms," rather than nuclei and electrons as the quantum method portrays [8].The force field, as defined by IUPAC [7], is described as "a set of functions and parameterization used in calculations of molecular mechanics". It is situated as a set of mathematical equations to cite aspects of molecular behavior such as the formation of angular geometries due to stretching and deformation of interatomic bonds. Within the approach of molecular mechanics, is a set of parameters of potential functions that define the energies of stretching and distortion of the atomic interactions in a molecule, in order to adopt a conformational structure of less stable potential energy [8].

In this model the atomic parameters remain constant, varying only in structural geometry, as long as the hybridization conditions are conserved. The technique involves the use of classical force field calculations that measure the distances and the attractions between the atoms of the molecule through penalties and energetic parameters of stretching and deformation of connections and angulations of geometric conformations. The optimization of energy is introduced in the process where, through a specific mathematical algorithm, it is sought to reduce energy to a minimum value, generating a more stable conformation [8].To express the variation in the position x of a given atom i as a function of time, we need to know the corresponding atomic masses (mi) and the force exerted on each atom in a given position (Fxi). The degree of agitation of the molecules provides energy for the atoms to vary their positions in space [8]. One of the examples of classical force field calculations is the functions that measure the energy term for the stretching of chemical bonds in the region where the energy is minimal, which is of most interest to the molecular modeling study. A simple function as eq. (I) is valid enough to express this aspect (Fig. 3) [5].

$$E = \sum k_b (r - r_0)^2 \qquad \text{(I)}$$

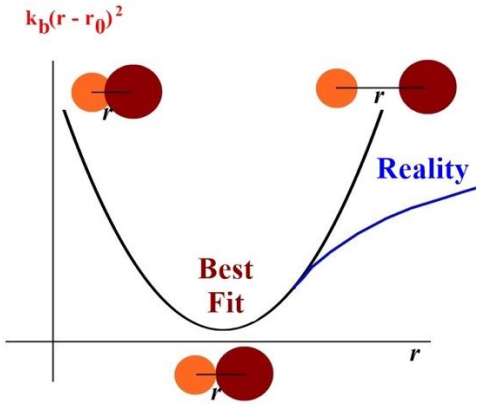

Fig.3 Energy as a function of the bonding distance described by the model of molecular mechanics.
source: SANT`ANNA, 2009.

Where kb is the force constant exerted on a kind of "spring", which represents a chemical bond between two atoms and r - r0 represents the variation of the standard distance between these atoms for that chemical bond; the summation includes all the possible pairs of atoms of a given bond in a molecular system (Fig. 4) [5].

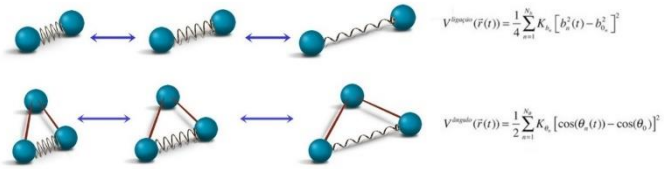

Fig.4 Analogous representation of equations of stretching and deformation of bonds and conformations.
SOUCE: Verli, 2014.

III. RESULTS AND DISCUSSION

In Drugbank® [3] the first information on the compound Brexpiprazole, such as its characterization, description, pharmacological properties, chain classification, its trade name Rexulti®, in addition to other circumscriptions as access number (DB09128), is in the class of organic compounds called n-aryl piperazines, CAS identification number (913611-97-9). The SMILES (Simplified Molecular Input Line System) is a data used to describe the nature of a bioactive compound and the topology of its molecular structure [7] highlighting the functional groups of the

molecule, such as amide (O = C1-N-C2), sulfhydryl (C-S-C4), tertiary amines (C-N3-C) and (C-N- (CC3)) and ether (C-)) (Table I).

The compound Brexpiprazole is indicated for patients with schizophrenia in the treatment of MDD due to its efficacy attributed to the partial agonist activity at the serotonin 1A and dopamine D2 receptors, and the serotonin 2a receptor antagonist activity and its rapid uptake gives within 4 hours after consumption and has 95% oral availability, and can be consumed or not with food. Its route of elimination occurs approximately 25% by urinary routes and 46% fecal [3] (Table II).

Table I
Compounds Identifiers of Compound Brexpiprazole

Drugbank Access Number	DB09128
Description	Brexpiprazole is a new partial agonist of dopamine D2 and serotonin 1A, called serotonin-dopamine activity modulator (SDAM), and a potent antagonist of serotonin 2A receptors, noradrenergic alpha 1B and 2C receptors. Brexpiprazole is approved for the treatment of schizophrenia and as adjunctive treatment for major depressive disorder (MDD). Although failed in Phase II clinical trials for ADHD, it has been developed to provide better efficacy and tolerability (eg, less akathisia, restlessness and / or insomnia) than established adjunctive treatments for major depressive disorder (MDD).
UNII	2J3YBM1K8C
CAS NUMBER	913611-97-9
InChI	ZKIAIYBUSXZPLP-UHFFFAFAYSA-N
InChI	InChI = 1S / C25H27N3O2S / c29-25-9-7-19-6-8-20 (18-22 (19) 26-25) 30-16-2-1-11-27-12-14-28 (15-13-27) 23-4-3-5-24-21 (23) 10-17-31-24 / h3-10,17-18H, 1-2,11-16H2, (H, 26,29)
Smiles	O = C1NC2 = CC (OCCCCN3CCN (CC3) C3 = C4C = CSC4 = CC = C3) = CC = C2C = C1

Source: Drugbank Virtual Repository ® [https://www.drugbank.ca/drugs/DB09128]

Table II
PharmacologicalpropertiesofBrexpiprazole

Indication	As an adjunctive treatment for major depressive disorder (MDD) and for the treatment of schizophrenia.
Conditionsassociated	Major Depressive Disorder (MDD) Schizophrenic Disorders
Mechanismofaction	Although the mechanism of action of brexpiprazole in the treatment of MDD and schizophrenia is unclear, the efficacy of brexpiprazole may be attributed to the partial agonist activity at serotonin 1A and dopamine D2 receptors, and serotonin 2A receptor antagonist activity.
Absorption	Brexpiprazole reaches peak plasma concentration within 4 hours after dosing, and steady state occurs within 10-12 days after dosing. Oral bioavailability is 95% and may be administered with or without food.
Distribution volume	The intravenous volume of distribution is 1.56 l kg-1.
Protein binding	> 99% of plasma-bound protein to serum albumin and α1-acid glycoprotein. Based on in vitro studies, protein binding is not affected by warfarin, diazepam or digitoxin.
Metabolism	Metabolized mainly by enzymes CYP3A4 and CYP2D6 in its main metabolite, DM-3411. DM-3411 isnotconsideredtocontributeanytherapeuticeffect.

Eliminationroute	Approximately 25% urinary excretion and 46% fecal excretion. <1% and ~ 14% of unchanged drug was recovered in urine and faeces, respectively.
Halflife	Brexpiprazole and its main metabolite, DM-3411, have half lives of 91 and 96 hours, respectively.
Release	19,8mL / h / kg
Toxicity	The most commonly observed adverse effects include: weight gain, akathisia, somnolence, tremor, and nasopharyngitis. Neonates are at risk for extrapyramidal and / or withdrawal symptoms if exposed to an antipsychotic during the third trimester of development.

Fonte: Repositório virtual Drugbank® [https://www.drugbank.ca/drugs/DB09128]

The chemical-computational calculations were essential in the study of the physico-chemical properties of Brexpiprazole, properties of the solubility coefficients log P (4.83) and log S (-5.93) and (0.01 mg.ml-1) (Table III) that measures the degree of affinity of a molecule to non-polar environments, defined as lipophilicity, or its degree of solubility in water, which allowed to define the solvent (polar or non-polar) used in docking tests or molecular dynamics [11]. A very important analysis in the technique of molecular modeling is the acidity analysis through the coefficients of hydrogenation potentials such as pKa (13,56) (Table III) which is a quantity inversely proportional to the acidity potential, the value of pKa, the lower its value of acidity [12]. It may be concluded, therefore, that Brexpiprazole has a predominantly basic medium, considering agonist pKalevels. It was possible to determine, through the intramolecular hydrogen bonds of Brexpiprazole, the simultaneous presence of hydrogen proton donors and acceptors. According to Brönsted-Lowry 1923, acid is that donor species of H + protons while the base is defined as an acceptor species of H + protons [12]. Therefore, it was possible to verify that the chemical species Brexpiprazole is predominantly basic because its number of H + proton receptors (4 protons) is greater than the number of proton donors H + (1 proton) (Table III).

Table III
Physical and chemical properties of the compound Brexpiprazole

Property	Value	Property	Value
Molecular Formula	$C_{25}H_{27}N_3O_2S$	HydrogenDonors	1
pKa	13.56	HBL	11.33
(strongeracid)			
pKa (stronger base)	8.40	Polarisability	49.26 Å^3
Isoelectronic Point	10.9 at pH = 7.40	Dipolemoment	3.20 Debye
Solubility in water	0.01 mg / ml	Dipole X	1.30 Debye
log S	-5.93	Dipole Y	-2.58 Debye
log P	4.83	Dipole Z	1.38 Debye
log D	3.79 at pH = 7.40	Polar Surface Area	46,01 Å^2
Physiological Charge	1	Numberofrotating links	7
HydrogenAcceptors	4	Refractivity	129,16 m^3·mol^{-1}

Source:Drugbank® [https://www.drugbank.ca/drugs/DB09128]

The two-dimensional structure of Brexpiprazole (Fig. 5) obtained through Drugbank® [3], was in its ground state, presenting only the molecular formula (C25H29N3O2S) and the connectivity between atoms in the molecule, with an initial, easy- but with potential energy different from its generic conformation.

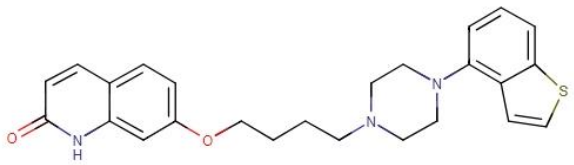

Fig.5 Two-dimensional structure of the compound Brexpiprazole.

Souce:Drugbank®
[https://www.drugbank.ca/drugs/DB00914]

The elementary analysis allowed to determine beginner physical-chemical characteristics, it was possible to make a qualitative or quantitative analysis. Brexpiprazole has a molecular mass of 433.57 g.mol-1, an exact mass of 433,182398295 g.mol-1, with a molecular formula C25H27N3O2S, composed of 69.26% by Carbon, 6.28% by Hydrogen , 9.69% by Nitrogen, 7.38% by Oxygen and 7.39% by Sulfur, having a total of 58 atoms. When submitted to the mass spectrum (relative abundance m / z), it presented four peaks of 433, 434, 435 and 436, with the base peak with relative abundance of 100% being the chemical mass of 433 g.mol-1 (Fig. 6).

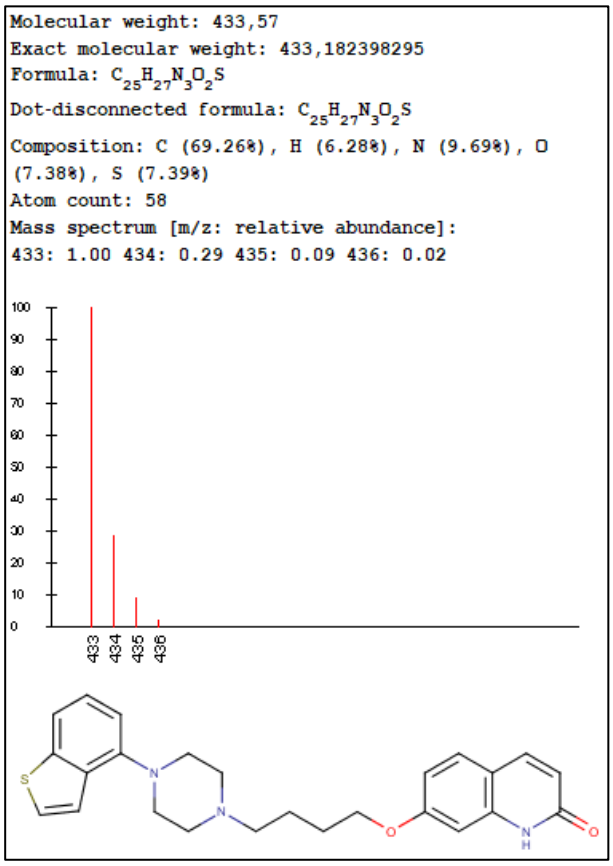

Fig.6 Elemental analysis and basic descriptions of the compound Brexpiprazole.

Not always the two-dimensional structure found in online virtual repositories is in its most stable conformation, making it necessary to use computational algorithms to obtain a molecular geometric optimization of lower potential energy. This geometric optimization can be performed through Avogadro® open license software, configuring it to perform uninterrupted interaction cycles calculated through the force field MMFF94, parameterized with the Steepest Descent algorithm, obtaining a three-dimensional space structure respecting a configuration in which all the atoms of the molecule adopt a stationary point of least potential energy [6]. After the geometric optimization, it was possible to obtain the lower energy conformational state (three-dimensional structure) (463.44 KJ.mol-1) (Fig. 7), resulting in its more stable structure energetically, being this the initial conformation for studies of molecular dynamics.After optimization and, consequently, energy minimization, each atom occupies a steady state of lower energy in the molecule, therefore, with a theoretically more stable three-dimensional structure, it was possible to calculate the valences of each atom, with the C3 atom being highlighted as atom (4 and 1, respectively), the formal charge of the atoms equal to 0, characterizing the structure of neutral load more stable and the partial loads, standing out the greater load partial 0.249 (Atom 27 C Car) and the lowest partial load -0.492 (Atom 20 O O3). (Table IV).

Table IV
Atomic properties of the Brexpiprazole compound obtained after optimization using the classical force field MMFF94

atom	Element / type		Valencia	Formal Charge	Partial Charge	X (Å)	Y (Å)	Z (Å)
1	C	C3	4	0	-0.017	1.55146	0.44651	-0.222158
2	C	C3	4	0	-0.037	1,28893	1.49810	0,85620
3	C	C3	4	0	-0.001	-0.20912	1.81162	0.96793
4	N	N3	3	0	-0.299	-0.50323	2.72988	2.07832
5	C	C3	4	0	0.015	-1.96031	2.75984	2.37378
6	C	C3	4	0	0.025	-2.83110	3.48482	1,31805
7	N	Npl	3	0	-0.327	-2.32347	4.85369	1.09679
8	C	C3	4	0	0.025	-0.88669	4.89622	0,75782
9	C	C3	4	0	0.015	-0.06444	4.12543	1.82075
10	C	Car	3	0	0.038	-3.111668	5.61317	0.21627
11	C	Car	3	0	0.010	-3.75816	6.79925	0,67989
12	C	Car	3	0	0.021	-4.53903	7.54492	-0.20756
13	C	Car	3	0	-0.047	-4.71028	7.15789	-1.54897
14	C	Car	3	0	-0.059	-4.08009	5.99983	-1.99732
15	C	Car	3	0	-0.040	-3.29848	5.24349	-1.13183
16	S	S2	2	0	-0.097	-5.21941	8.93385	0.55699
17	C	Car	3	0	-0.023	-4.49315	8.56157	2.05220
18	C	Car	3	0	-0.045	-3.74754	7.40946	1,98507
19	C	C3	4	0	0.090	3.03731	0,11512	-0.33457
20	O	O3	2	0	-0.492	3,18829	-0.85499	-1.37119
21	C	Car	3	0	0.122	4,45700	-1.28748	-1.64429
22	C	Car	3	0	0.004	5,62214	-0.87899	-0.99364
23	C	Car	3	0	0.053	6,85315	-1.41162	-1.38640
24	C	Car	3	0	-0.001	6.93667	-2.35091	-2.42408
25	C	Car	3	0	-0.048	8,24680	2,88121	-2,80160
26	C	Car	3	0	0.003	9.34713	-2.46858	-2.15846
27	C	Car	3	0	0.249	9.27170	-1.47552	-1,05933
28	O	O2	1	0	-0.268	10.28501	-1.10429	-0.47757
29	N	Nar	3	0	-0.322	8.02770	-1.00459	-0.73688
30	C	Car	3	0	-0.049	5.77047	-2.75748	-3.07113
31	C	Car	3	0	-0.019	4,53877	-2.22554	-2,67936

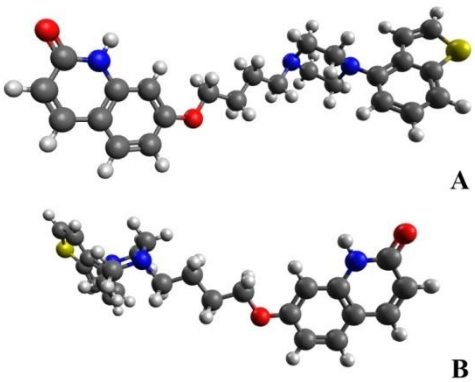

Fig. 7 Structure of the optimized Brexpiprazole compound using the force field MMFF94 (A - Rotation 0 ° / B Rotation 180 °).

As for the properties calculated using the MMFF94 classical force field calculation technique, one can calculate the dipole moment (μ) of the structure that is the distribution of the electric charges along the molecule determining the polarization, given the

difference in electronegativity between the atoms, separation between positive and negative charges [13]. Some other properties of the structure are directly linked to the dipole moment (μ), such as the coefficients of melting and boiling and their solubility in water by the partition coefficients [14]. The compound Brexpiprazole presented a dipole moment (μ) of estimated value in 3.20 Debye, that is to say, it is a polar molecule.In the final structure obtained by the minimization, all the analyzed bonds (Table V) were predominantly covalent in nature, which is defined as having the additional bond length at the mean distance between the atomic nuclei of the ligands in their more stable and lower energy generic form [13].] [14] [15].We can also analyze the carbon-nitrogen (C3-N1), (C5-N2), (C19-N3) and (C23-N3)), carbon-nitrogen ((N1-C4), (N1-C7) (C2 - S), (N2 - C6) and (N2 - C8)), carbon - oxygen (C16 - O1) and (C23 - O2), oxygen - carbon (O1 - C17), carbon - (C 1 -C 4), (C 1 - C 2), (C 1 - C 2), (C 1 - C 2), (C 1 - C 2) (C1-C6), (C2-C3), (C4-C5), (C6-C5), (C2-C3), (C4-C5) C7), (C8-C9), (C3-N1), (N1-C4) and (N1-C7) as rotating linkages.

Table V

Atomic properties of the Brexpiprazole compound obtained after optimization using the classical force field MMFF94

bond	Type	atominitial	AtomFinal	Ligandorder	Rotativity	Connection length(Å)
1	C-C	C1	C2	1	yes	1.52852
2	C-C	C1	C16	1	yes	1.52654
5	C-C	C2	C3	1	yes	1.53459
13	C-C	C4	C5	1	yes	1.54869
21	C-C	C6	C7	1	yes	1.54921
26	C-C	C8	C9	2	yes	1.42592
27	C-C	C8	C13	1	not	1.40964
28	C-C	C9	C10	1	not	1.39762
29	C-C	C9	C15	1	not	1.44082
30	C-C	C10	C11	2	not	1,40659
32	C-C	C11	C12	1	not	1.39258
34	C-C	C12	C13	2	not	1.38997
38	C-C	C14	C15	2	not	1.37398
45	C-C	C17	C18	2	not	1.39562
46	C-C	C17	C25	1	not	1.39929
47	C-C	C18	C19	1	not	1.39761
49	C-C	C19	C20	2	not	1.40215
51	C-C	C20	C21	1	not	1.46294
52	C-C	C20	C24	1	not	1.39427
53	C-C	C21	C22	2	not	1.33963
55	C-C	C22	C23	1	not	1.48323
60	C-C	C24	C25	2	not	1.39768
8	C-N	C3	N1	1	yes	1.4706
16	C-N	C5	N2	1	not	1.47663
50	C-N	C19	N3	1	not	1.40254
58	C-N	C23	N3	1	not	1.36868
41	C-O	C16	O1	1	not	1.42776
57	C-O	C23	O2	2	not	1.22599
31	C-S	C10	S	1	not	1.75528

11	N-C	N1	C4	1	yes	1.48703
12	N-C	N1	C7	1	yes	1.48541
19	N-C	N2	C6	1	not	1.47684
20	N-C	N2	C8	1	not	1.4076
44	O-C	O1	C17	1	not	1.36795
37	S-C	S	C14	1	not	1,70343

Based on the conformational optimization, it was calculated all angles between the connections and the angles of torsion and deformation, called dihedral angles formed by the crossing of two planes, could be calculated. The angles (C8 - C9 - C15) and (C10 - S - C14) with 130,0530 ° and 92,5735 ° respectively and the largest and smallest dihedral angle (C9 - C10) C11 -H15) and (C8-C9-C15-C14) with 179.9972 ° and -179.9953 ° respectively. After the optimization, the molecule began to be config.d in its geometric form of lower energy, theoretically, resulting in its structure more stable, favoring the parameters of molecular dynamics. By rendering the data obtained for the minimization, it was possible to delineate the Van der Waals surface by highlighting the molar volume.

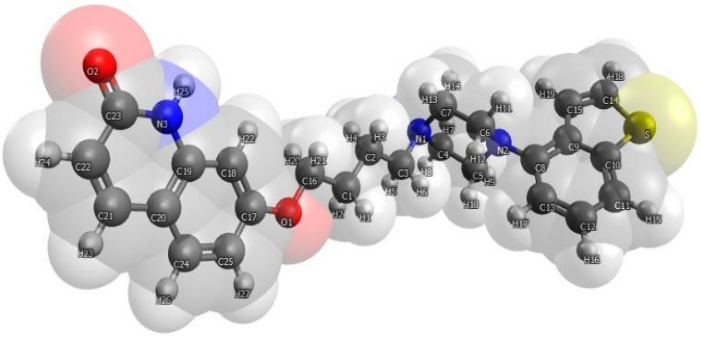

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Fig. 8 Van der Waals surface of the compound Brexpiprazole

IV. CONCLUSION

The obtained physicochemical properties of the Brexpiprazole agonist, commercially sold as Rexulti®, and the electronic and structural minimization of this drug, which was config.d in its most stable conformation of lower potential energy equal to 463.44 KJ.mol -1 by the semi-empirical method (PM3). The calculations also allowed to obtain the geometrically optimized structure of the compound Brexpiprazole by means of the classical force field calculation in MMFF94 until reaching the point of least potential energy, where the derivative of the energy was equal to zero, thus reaching its conformation stable. With the design of the Van der Waals surface it was possible to analyze the molar volume over the entire length of the molecule. The present work represents the initial stage for a complete study of the electronic and structural characterization of this agonist aiming at future studies of structural modification, docking and molecular dynamics.

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VI. REFERENCES

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