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Characterization in Silic of Anti-Epiletic Drug (2S)-2-[(4R)-2-Oxo-4-Propylpyrrolidin-1-yl] Butanamide

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***Abstract*- Epilepsy is a chronic neurological disorder characterized by the recurrence of epileptic seizures and affects around 50 million people worldwide. The treatment consists in the consumption of anti-epileptic drugs (AEDs) with the function of providing a better quality of life for the patient. Among the drugs used are (2S)-2-[(4R)-2-oxo-4-propylpyrrolidin-1-yl] butanamide (Brivaracetam) that acts as a ligand for the synaptic vesicle protein 2A (SV2A), is consumed orally and has mild to moderate side effects. Because it is an important drug, the present work aimed to characterize the structure and electronically of the drug (2S)-2-[(4R)-2-oxo-4-propylpyrrolidin-1-yl] butanamide. The molecular structure characterized using the classical force field MMFF94, obtaining the potential energy (-52.310 kJ · mol-1), the dipole moment (2,557), the angles of connection, torsion, the lengths of the connections and the representation of the surface of Van der Waals. The present work consists of an initial stage for future studies of molecular semi-empirical modeling and molecular docking, seeking optimization of the biological potential of this drug and developments of new drugs.**

***Keywords*- Epilepsia, MMFF94, Molecular modeling, theoretical chemistry.**

I. INTRODUCTION

Epilepsy is a chronic neurological disorder that can be caused by genetic, structural, metabolic, immunological and infectious factors [1], characterized by the recurrence of epileptic seizures [2], which may be partial (restricted to a cerebral hemisphere) or generalized (involves the two cerebral hemispheres) [1]. This pathology affects around 50 million people in the world the equivalent of 1% of the world population [2] being children and adolescents most affected [3] and also elderly people over 65 years. The treatment consists of providing a better quality of life for the patient and aims to control the crises minimizing the adverse effects [1]. Antiepileptic drugs (AEDs) are essential in the treatment of epilepsy, but these can cause other diseases and side effects are also common [3]. For this reason, official agencies of the American Academy of Neurology (AAN) and National Institute for Clinical Excellence (NICE) have published official guidelines for recommendations with established drugs (carbamazepine, phenytoin, valproic acid) and encouraging the creation of new anticonvulatory compounds [1].

(2S)-2-[(4R)-2-oxo-4-propylpyrrolidin-1-yl] Butanamide(Brivaracetam,Briviact®), a derivative of levetiracetam and approved in 2016 by the US FDA [4], is a new AED that acts as a ligand for the synaptic vesicle protein 2A (SV2A) [5] which decreases seizure activity in different types of epilepsy [6]. The drug is taken orally and has mild to moderate side effects related to the central nervous system including drowsiness, dizziness and fatigue, apparently disappearing during treatment [7].

Molecular modeling comprises a set of tools with the function of constructing, editing, visualizing, analyzing and storing complex molecular systems [8] providing the complete characterization of a structure [9], allowing the rational planning of drugs using certain parameters that relate structure and activity [10]. Thus, using in silico methods and theoretical calculations, the computational chemistry characterizes the compounds [11], generating indexes relevant for the planning of drugs as: minimum potential energy, formation heat, dipole moment and also structures with high fidelity rate to native structures with stable conformational geometry [12].

Molecular Mechanics or force-field methods use classical type models to predict the energy of a molecule as a function of its conformation. This allows predictions of Equilibrium geometries, transition states and relative energies between conformers or between different molecules. In molecular mechanics, molecules are described as a set of "atoms connected, "rather than nuclei and electrons, as in quantum methods. The model of molecular mechanics is justifiable because the parameters associated with sets of atoms remain fairly constant between different structures, provided that the type and hybridization of the involved atoms are the same. What is done in the molecular mechanics is to develop the so-called force field, a set of energy functions that determine energetic penalties for moving away from the structure of these "normal" values [13-14], seeking to minimize energy, ie, uses an algorithm mathematician seeking to achieve a minimum state of energy, where the attractive forces are maximized and the value of the repulsive forces is reduced (Equation 1) (Fig.1).

$$E = \sum k_b (r - r_0)^2 \quad (1)$$

Express energy due to stretching bonds as a Taylor series about the equilibrium position Re (Equation 2):

$$E(R) = k2(R - Re)2 + k3(R - Re)3 + \cdots (2)$$

Where, R is a bond length. The first term should dominate, k2, k3 are parameters of adjustments, obtained experimentally or by quantum mechanics, Having as main idea the use of the constants for other molecules, since the Most C–H bond lengths are 1.06 to 1.10 °A in, with stretching frequencies between 2900 and 3300 cm−1. This strategy is refined using different “atom types [15] field of force MMFF94 (Merck Molecular Force Field 94), which is a "classical force field", where the atoms and their chemical bonds are treated as spring-mass type systems, reproducing very well the computational data used in their parameterization. In addition, MMFF94 reproduces experimental bond lengths (0.014 Å mean square root [rms]), bonding angles (1.2° rms), vibrational frequencies (61 cm -1 rms), conformational energies (0.38 kcal / mol / rms) and rotating barriers (0.39 kcal / mol rms) almost as well as MM3 for comparable systems [16]. The MMFF94 was parameterized specifically for organic compounds [17]. In this context, the present work aimed to use the field of force MMFF94 to characterize in silico, the drug (2S)-2-[(4R)-2-oxo-4-propylpyrrolidin-1-yl] butanamide as the initial step drug design of new drugs.

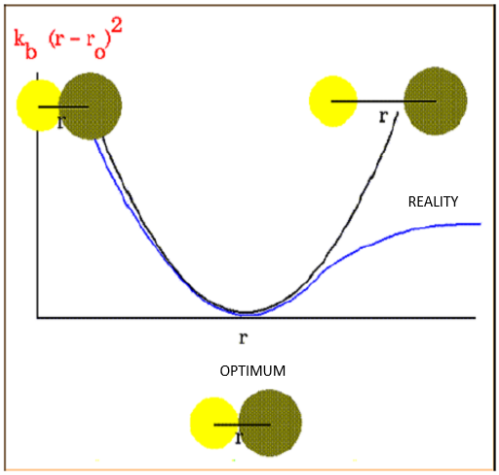

Fig.1. Energy depending on the connection distance described by the model of molecular mechanics
Source: Sant’Anna (2000).

II. METHODOLOGY

Based on the methodology proposed by Dewar et al. [18], the first step of the work was to obtain the following information: the two-dimensional molecular structure of (2S)-2-[(4R)-2-oxo-4-propylpyrrolidin-1-yl] butanamide compound, its nomenclatures, its physicochemical properties, as well as its pharma codynamics and its mechanisms of action. These data were obtained from Drugbank® virtual repositories [www.drugbank.ca] [19] [20] and ChemSpider® [http://www.chemspider.com] [21]. Then, for the geometric optimization of the molecule by means of classical force field calculations (MMFF94), the freeware Avogadro® [17], [22], [23] was configured for cycles of 500 interactions of the steepest descending algorithm. In this way, it was possible to obtain the conformation of the lower potential energy of the molecule, characterizing the connections, the torsion angles and the dihedral

angles, besides visualizing the dipole moment and rendering the surface map of Van der Waals.

All mechanical force field calculations of the molecule (MMFF94) were performed using Avogadro® open license software [17] [22] [23] (version 1.2.0) using computers with AMD V120 processor (2.2 Ghz), 4 GB of RAM and Microsoft Windows 7 Professional® as the operating system.

III. RESULTS AND DISCUSSIONS

The Cartesian coordinates (bi-demensal structure) of (2S)-2-[(4R)-2-oxo-4-propylpyrrolidin-1-yl] butanamide were obtained from the Drugbank® virtual repository [19] [20] to obtain the initial structure and some properties and nomenclatures; some of these important data found were CAS identification number (357336-20-0required to study the structure in molecular modeling, highlighting the partition coefficients LogP (0.86) and LogS (-0.66) and the solubility of (46.8 mg / mL) that allowed to define the solvent (polar or non-polar) used in docking or molecular dynamics tests)(Table I).

Table I

Physicochemical properties of compound (2S)-2-[(4R)-2-oxo-4-propylpyrrolidin-1-yl] butanamide

Property	Value
pKa (Strongest Acidic)	16.29
pKa (Strongest Basic)	-0.57
Solubility in water	46.8 mg/mL
LogP	0.86
LogS	-0.66
Polar Surface Area	63.4 $Å^2$
Refractivity	57.75 $m^3 \cdot mol^{-1}$
polarizability	23.77 $Å^3$

Source*: Virtual Repository Drugbank® [https://www.drugbank.ca/drugs/DB05541].*

Other chemical and physical properties (Table II) could be obtained through the virtual repository ChemSpider® [21], properties related to the structural composition of the molecule, of which we can highlight its density (1.1 ± 0.1 g cm-3) and its surface tension (40.3 ± 3.0 dyne cm-1), and its ability to form hydrogen bonds by determining atoms with the potential to receive or donate electrons in hydrogen bonds.

Table II

Physical-chemical properties of the drug (2S)-2-[(4R)-2-oxo-4-propylpyrrolidin-1-yl] butanamide

Properties	Value
Molecular Formula	$C_{11}H_{20}N_2O_2$
Density	1.1±0.1 g/cm^3
Boiling point	409.3±28.0 °C (760 mmHg)
Steam pressure	0.0±1.0 mmHg (25°C)
Enthalpy of Vaporization	66.1±3.0 kJ/mol
Receptors #H	4
Donors #H	2
Monoisotopic Mass	212.152481 Da
Refractive index	1.494
Molar Refractivity	58.2±0.3 cm^3
Superficial tension	40.3±3.0 dyne/cm
Molar Volume	199.8±3.0 cm^3

Souce: Virtual Repository ChemSpider® [http://www.chemspider.com/Chemical-Structure.8012964.html?rid=74465762-c71d-4684-8aa5-6e4adda43872&page_num=0]

The two-dimensional structure of (2S)-2-[(4R)-2-oxo-4-propylpyrrolidin-1-yl] butanamide (Figure 2), obtained through the Drugbank® [19] [20], was then in its ground state, presenting only the molecular formula (C11H20N2O2) and the connectivity of the atoms, with an initial easy conformation potential energy different from the molecule in its native form.

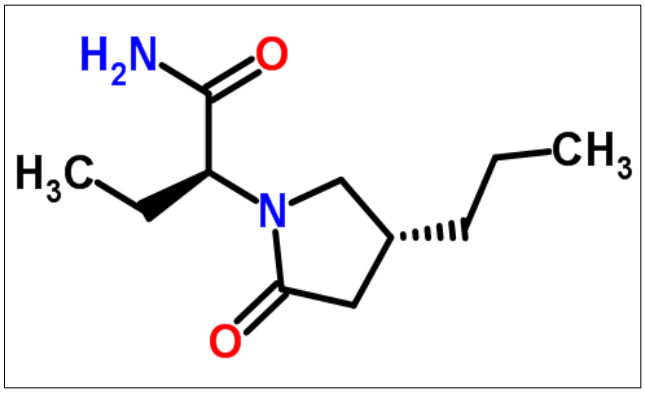

Fig.2The two-dimensional structure of (2S)-2-[(4R)-2-oxo-4-propylpyrrolidin-1-yl] butanamide

Source*: Virtual Repository Drugbank® [https://www.drugbank.ca/drugs/DB05541].*

When drawing a molecule two-dimensionally or withdrawing it from an online repository, it is not in its most stable conformation. In order to obtain more precise calculations about the molecule and its final stable configuration, we need to perform a geometric optimization that uses the energy minimization process [24]. This geometric optimization can be performed through Avogadro® open license software [17], [22] [23], configuring it to perform uninterrupted interaction cycles calculated through the force field MMFF94, parameterized with the Steepest Descent algorithm. The purpose of using molecular mechanics is because it represents the molecules as a set of connected atoms, thus developing energetic functions that maximize the forces of attraction and reduce the forces of repulsion [13-14].

Therefore, the obtained structure [Figure 3], considered theoretically more stable, has a spatial distribution that allows a smaller possible potential energy, making the integral potential energy of the molecule assume a value of (-52,310 kJ · mol-1), no longer varying, reaching a stationary point of the energy surface [8].

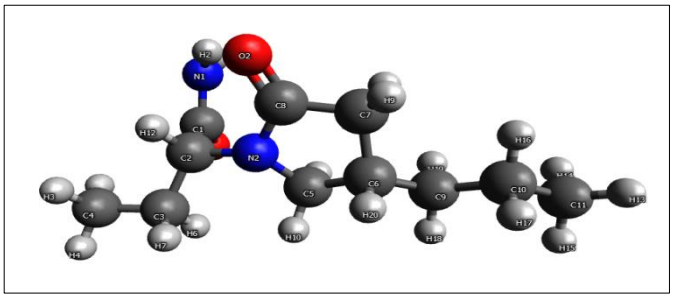

Fig. 3.Optimized structure of the compound (2S)-2-[(4R)-2-oxo-4-propylpyrrolidin-1-yl] butanamide using the force field MMFF94

After geometric optimization, the molecule a theoretically more stable structure, it was possible to calculate the formal and partial charges of all the atoms as well as their valence. All the atoms presented zero formal charge and there were significant variations in their partial loads, such as Hydrogen from 0.023 to 0.145, Carbon from -0.065 to 0.231 and Oxygen from -0.274 to -0.276. These data (Table 3), in particular valence, correspond to the literature, which serves to validate the results obtained.

Despite the neutrality through optimization, it is possible to observe in the results obtained (Table III) the largest and smallest partial (residual) loads. It was noticed that the atoms 1 (N) and 2 (C) presented higher and lower partial charge, respectively, charges coming from the electrons are closer to or farther away from one of the atoms of the bond, carrying load [25].

Table III

Atomic properties of the compound (2S)-2-[(4R)-2-oxo-4-propylpyrrolidin-1-yl] butanamide obtained after optimization using the field of force classic MMFF94

atom	Element type		Valence	Formal change	Partial change	X (Å)	Y (Å)	Z (Å)
1	N	Nam	3	0	-0.328	-6.77886	3.28579	1.33794
2	C	C2	3	0	0.231	-6.47188	3.36929	0.00613
3	H	H	1	0	0.145	-7.64036	2.82492	1.59531
4	H	H	1	0	0.145	-6.37169	3.94893	1.99608

5	O	O2	1	0	-0.274	-7.18386	2.83179	-0.83634
6	C	C3	4	0	0.102	-5.24673	4.25105	-0.31661
7	C	C3	4	0	-0.029	-4.62269	3.90246	-1.67402
8	C	C3	4	0	-0.063	-3.90847	2.55744	-1.65341
9	H	H	1	0	0.023	-3.11332	2.54774	-0.90101
10	H	H	1	0	0.023	-3.45273	2.35873	-2.62871
11	H	H	1	0	0.023	-4.60085	1.73939	-1.43308
12	H	H	1	0	0.029	-5.38357	3.88731	-2.46357
13	H	H	1	0	0.029	-3.8945	4.67514	-1.95076
14	H	Nam	3	0	-0.29	-5.6685	5.65847	-0.24265
15	C	C3	4	0	0.019	-6.4574	6.29892	-1.26914
16	C	C3	4	0	-0.017	-6.53373	7.74538	-0.79247
17	C	C3	4	0	0.028	-6.5537	7.60607	0.73338
18	C	C2	3	0	0.217	-5.82395	6.30767	0.97585
19	H	H	1	0	0.036	-7.5707	7.51217	1.12745
20	H	H	1	0	0.036	-6.03363	8.43416	1.22181
21	H	H	1	0	0.047	-5.96937	6.22251	-2.24431
22	H	H	1	0	0.047	-7.44311	5.82200	-1.30573
23	H	H	1	0	0.060	-4.50185	4.09015	0.47373
24	O	O2	1	0	-0.276	-5.51569	5.85947	2.06975
25	C	C3	4	0	-0.049	-7.73473	8.49336	-1.37185
26	C	C3	4	0	-0.056	-7.76641	9.96193	-0.94460
27	C	C3	4	0	-0.065	-8.94234	10.69674	-1.56859
28	H	H	1	0	0.023	-8.94166	11.74617	-1.25748
29	H	H	1	0	0.023	-9.89261	10.25086	-1.25799
30	H	H	1	0	0.023	-8.88916	10.66680	-2.66159
31	H	H	1	0	0.026	-7.83806	10.03874	0.14607
32	H	H	1	0	0.026	-6.83488	10.45585	-1.24478
33	H	H	1	0	0.027	-7.69490	8.43702	-2.46694
34	H	H	1	0	0.027	-8.66681	8.00245	-1.06469
35	H	H	1	0	0.032	-5.60632	8.25868	-1.08316

In the final geometry of the (2S)-2-[(4R)-2-oxo-4-propylpyrrolidin-1-yl] butanamide compound achieved by the optimization, all the analyzed bonds were characterized with predominance of covalence, where we can highlight the connections between oxygen - carbon ((O1 - C1) and (O2 - C8)) as second - order links, or (C 3 -C 2), (C 5 -C 6), (C 6 -C 7), (C 10 -C 9) and (C 9 -C 6) carbons because they have rotatability [Table IV].

Table IV
Properties of (2S)-2-[(4R)-2-oxo-4-propylpyrrolidin-1-yl] butanamide After Optimization Using Classical Forcefield MMFF94

bond	Type	Initial Atom	Final Atom	Order of Bond	Rotability	Length (Å)
1	C –N	C1	N1	1	NÃO	1.36928
2	N –H	N1	H1	1	NÃO	1.01035
3	N –H	N1	H2	1	NÃO	1.01916
4	O–C	O1	C1	2	NÃO	1.22702
5	C –C	C4	C3	1	NÃO	1.52302
6	C –H	C4	H3	1	NÃO	1.09474
7	C –H	C4	H4	1	NÃO	1.09471
8	C –H	C4	H5	1	NÃO	1.09414
9	C –C	C3	C2	1	SIM	1.53412
10	C –C	C2	C1	1	NÃO	1.54358
11	C –H	C3	H6	1	NÃO	1.09661
12	C –H	C3	H7	1	NÃO	1.09722
13	C –C	C5	C6	1	SIM	1.52488
14	C –C	C6	C7	1	SIM	1.53233
15	C –C	C7	C8	1	NÃO	1.50903
16	C –H	C7	H8	1	NÃO	1.09471
17	C –H	C7	H9	1	NÃO	1.09305
18	C –N	C5	N2	1	NÃO	1.44438
19	C –H	C5	H10	1	NÃO	1.09316
20	C –H	C5	H11	1	NÃO	1.09564
21	C –N	C8	N2	1	NÃO	1.38937
22	N –C	N2	C2	1	NÃO	1.47112
23	C –H	C2	H12	1	NÃO	1.09790
24	O –C	O2	C8	2	NÃO	1.22169
25	C –C	C11	C10	1	NÃO	1.52057
26	C –H	C11	H13	1	NÃO	1.09457
27	C –H	C11	H14	1	NÃO	1.09467
28	C –H	C11	H15	1	NÃO	1.09470
29	C –C	C10	C9	1	SIM	1.52979
30	C –H	C10	H16	1	NÃO	1.09571
31	C –H	C10	H17	1	NÃO	1.09627
32	C –C	C9	C6	1	SIM	1.52891
33	C –H	C9	H18	1	NÃO	1.09726
34	C –H	C9	H19	1	NÃO	1.09732
35	C –H	C6	H20	1	NÃO	1.09912

On the conformational characterization, all the angles between the connections and the torsion angles could be calculated. Taking as examples of higher and lower angulation between bonds, the angles (N2 - C8 - O2) and (C5 - C6 - C7) with 125.8469 ° and 103.0434 ° respectively; (H17 - C10 - C9 - H19) and (H13 - C11 - C10 - C9) with 179.7148 ° and - 179.5155 ° respectively, for example the largest and smallest torsion angles.

In relation to the properties calculated using the Avogadro® software, one can calculate the dipole moment (μ) of the structure that, 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 [25]. 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 [26]. The compound (2S)-2-[(4R)-2-oxo-4-propylpyrrolidin-1-yl] butanamide presented a dipole moment (μ) of estimated value in 2,557 D, characterizing the molecule as polar.

Using the data obtained by the optimization it was possible to render and visualize the Van der Waals surface (fig. 4).

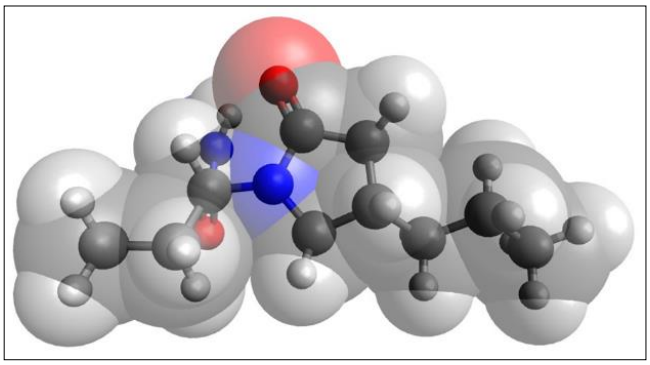

Fig. 4Van der Waals surface of the drug (2S)-2-[(4R)-2-oxo-4-propylpyrrolidin-1-yl] butanamide .

IV. CONCLUSIONS

The molecular structure of the (2S)-2-[(4R)-2-oxo-4-propylpyrrolidin-1-yl] butanamide compound was optimized geometrically by means of classical force field calculations, MMFF94 steepest descent, until reaching the point of least potential energy, reaching the conformation theoretically more stable and closer to its native form, obtaining at the end of this the energy of [-52,310 kJ · mol-1] and dipole moment (2,557 D). The obtained data consist of an initial stage for future studies of molecular semi-empirical modeling and molecular docking, seeking to optimize this compound and its possible analogues in biological potential.

V. ACKNOWLEDGMENT

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