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Use of Classic Force Field Mmff94 for Conformational Characterization of Antihypertensive Drug Sacubitril

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Abstract **- Heart failure has become a worldwide problem, affecting the population in a democratic way, leading to high mortality rates, hospitalizations and economic expenditures. Currently we can highlight the drug Sacubitril, which despite its high efficiency, has several adverse effects, which negatively affect the life of patients. In this context, the objective of this study was to use classical molecular modeling techniques to characterize the drug Sacubitril, as an initial step for the development of analogous drugs, with greater therapeutic potential and lower collateral effects. As a first step a virtual screening was performed in repositories (In order to optimize the structure, the classical forcefield MMFF94 was used, where it was possible to characterize its atomic properties, bonds, angles, dihedral angles of the thermodynamically more favorable structure (lower energy The results of this work are summarized in the following table.**

Keywords- **Heart failure, MMFF94, Molecular modeling,Theoretical chemistry.**

I. INTRODUCTION

Heart failure (HF) is recognized as a globally important problem because it is an emerging pathology. In Brazil, for example, it is the cause of greater hospitalization due to cardiovascular diseases. In 2000, its hospitalizations cost about 204 million reais, which represents 4% of total national hospitalization expenses [1]. Its prevalence ranges from 3% to 20% in the population, reaching around 100% in ages over 65 years [2]. Facing some benefits in its treatment is physical training [3] and nutritional therapy [4]. Other methods used continuously are oral drugs, including neprilysin inhibitors [5]. Among these inhibitors find Sacubitril which is commercially sold with the Valsartan inhibitor [5]. Sacubitril is a first-in-class dual angiotensin receptor blocker-neprilysin inhibitor (ARNI) marketed for the treatment of chronic heart failure with reduced ejection fraction [6]. Sacubitril is metabolized by enzymatic conversion of the ethyl ester to the active diacid (LBQ-657, structure not disclosed), which inhibits neprilysin and prevents endogenous natriuretic peptide degradation [5], [7], [8].

In its mechanism of action, the oral drug has as main connections the inhibition of neprilysin, which causes a reduction of the degradation and an increase in the concentration of endogenous natriuretic peptides, besides the levels of vasoconstricting hormones and their combination with the inhibitor Valsartan, which prevents vasoconstricting effects resulting in a vascular resistance in blood pressure [9] [10]. With this drug there was a 2.8% decrease in the overall mortality rate [11]. However, the drug causes several side effects such as: bloating that can cause respiratory difficulties, reduced renal function, dizziness, nausea, gastritis among others [12]. In this context, molecular modeling has been studying the biological actions of several compounds and promoting creations of analogues that maintain their potential already tested, but which have a lower toxicity to users. It has a complete characterization of its structures and the distance of the connections, angles of connections and dihedral angles [13]. In this way the computational chemistry offers a complete characterization giving data such as the heat of formatting, minimum energy, potential, the dipole moment and the specific arrangement of each atom [14-16]. In this context, the present work aimed to use classical molecular modeling techniques to characterize the drug Sacubitril, as an initial step for the development of analogous drugs, with greater therapeutic potential and less side effects.

II. METHODOLOGY

All calculations were performed on personal computers with Intel® processor and Microsoft Windows 10® (version 1709) as the operating system. All force field calculations of the mechanical molecule (MMFF94) [17] were performed using Avogadro® open license software (version 1.2.0) [18] [19].

This work was based on the following methodology: (1) the two-dimensional molecular structure of the Sacubitril compound and its nomenclatures were obtained from the Drugbank® virtual repository (https://www.drugbank.ca) [20]; (2) through ChemSpider® (http://www.chemspider.com) [21] and Drugbank® [20] the physical-chemical properties of the structure as well as pharmacodynamics and their mechanisms were obtained; (3) with the classical force field calculations (MMFF94) [17], performed through Avogadro® freeware, configured for cycles of 500 interactions of the steepest descent algorithm, the geometric optimization was achieved, thus obtaining its conformation of lower potential energy and (4) featuring the bonds, torsion angles and dihedral angles. (5) render the Van der Waals surface map.

III. RESULTS AND DISCUSSIONS

The DrugBank database is a comprehensive, freely accessible, online database containing information on drugs and drug targets. As well as bioinformatics and a cheminformatics resource, DrugBank combines detailed drug (i.e. chemical, pharmacological and pharmaceutical) data with comprehensive drug target (i.e. sequence, structure, and pathway) information [22]. The Drugbank has a complete binder of sacubitril, where we highlight the two-dimensional coordinates of (Figure 1), its characterization, description and identifiers (table I) and its pharmacological properties (table II), noting that Clearance, Affected organisms, Pathways and Pharmacogenomic Effects / ADRs Not Available.

It was not possible to obtain experimental chemical properties but indicates the Predicted Properties (table III) that were essential for the structure studies, highlighting the partition coefficients LogP (3,9) and LogS (-5,6) and (0.000942 mg ml-1) that allowed to define the solvent (polar or non-polar) used in tests of docking or molecular dynamics. Other physical and chemical properties were obtained through the virtual repository, ChemSpider® (http://www.chemspider.com), as the structural composition of the molecule, highlighting its density (1.2 ± 0.1 g cm-3) and its surface tension (45.7 ± 3.0 dyne cm -1). The two-dimensional structure of Sacubitril, obtained through Drugbank®, was then in its ground state, presenting only the molecular formula (C24H29NO5), with a conformation but with potential energy different from its native form (fig.1).

Table I
Molecular identifiers of sacubitril

AccessionNumber	DB09292
Description	sacubitril is a prodrug neprilysin inhibitor used in combination with valsartan to reduce the risk of cardiovascular events in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction. It was approved under the FDA's priority review process for use in heart failure on July 7, 2015.Sacubitril's active metabolite, LBQ657 inhibits neprilysin, a neutral endopeptidase that would typically cleave natiuretic peptides such as atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and c-type natriuretic peptide (CNP). ANP and BNP are released under atrial and ventricle stress, which activate downstream receptors leading to vasodilation, natriuresis and diuresis. Under normal conditions, neprilysin breaks down other vasodilating peptides and also vasoconstrictors such as angiotensin I and II, endothelin-1 and peptide amyloid beta-protein. Inhibition of neprilysin therefore leads to reduced breakdown and increased concentration of endogenous natriuretic peptides in addition to increased levels of vasoconstricting hormones such as angiotensin II.

UNII	17ERJ0MKGI
CAS number	149709-62-6
Weight	Average: 411.498 Monoisotopic: 411.204573038
Chemical Formula	$C_{24}H_{29}NO_5$
InChI Key	PYNXFZCZUAOOQC-UTKZUKDTSA-N
InChI	InChI=1S/C24H29NO5/c1-3-30-24(29)17(2)15-21(25-22(26)13-14-23(27)28)16-18-9-11-20(12-10-18)19-7-5-4-6-8-19/h4-12,17,21H,3,13-16H2,1-2H3,(H,25,26)(H,27,28)/t17-,21+/m1/s1
IUPAC Name	3-{[(2S,4R)-1-{[1,1'-biphenyl]-4-yl}-5-ethoxy-4-methyl-5-oxopentan-2-yl]carbamoyl}propanoic acid
SMILES	[H][C@@](CC1=CC=C(C=C1)C1=CC=CC=C1)(C[C@@]([H])(C)C(=O)OCC)NC(=O)CCC(O)=O

Source*: Virtual Repository Drugbank®* *[https://www.drugbank.ca/drugs/DB09292].*

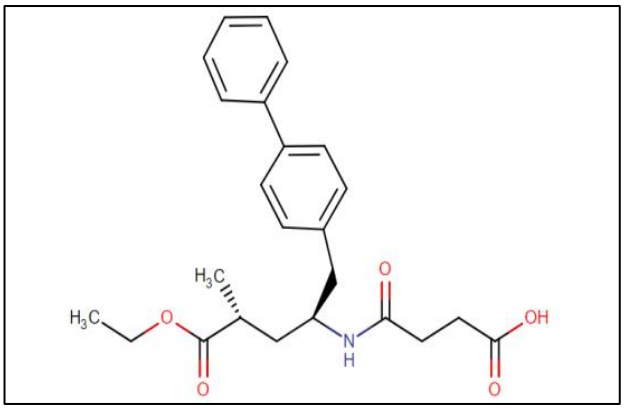

Fig.1 Initial structure of the compound Sacubitril

Source: Repositório virtual Drugbank® *[https://www.drugbank.ca/drugs/DB09292].*

Table II

Pharmacological properties of sacubitril

Indication	Used in combination with valsartan to reduce the risk of cardiovascular events in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction. It is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB.
Associated Conditions	Cardiovascular Events
Pharmacodynamics	n a 7-day valsartan-controlled study in patients with reduced ejection fraction (HFrEF), administration of sacubitril + valsartan (Entresto) resulted in a significant non-sustained increase in natriuresis, increased urine cGMP, and decreased plasma MR-proANP and NT-proBNP compared to valsartan. In a 21-day study in HFrEF patients, it significantly increased urine ANP and cGMP and plasma cGMP, and decreased plasma NT-proBNP, aldosterone and endothelin-1. In clinical studies, this combination had no effect on QTc interval.
Mechanism of action	Sacubitril's active metabolite, LBQ657 inhibits neprilysin, a neutral endopeptidase that would typically cleave natiuretic peptides, which includes: atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and c-type natriuretic peptide (CNP). ANP and BNP are released under atrial and ventricle stress, which activate downstream receptors leading to vasodilation, natriuresis and diuresis. Under normal conditions, neprilysin breaks down other vasodilating peptides and also vasoconstrictors such as angiotensin I and II, endothelin-1 and peptide amyloid beta-protein. Therefore, the inhibition of neprilysin leads to

	reduced breakdown and increased concentration of endogenous natriuretic peptides in addition to increased levels of vasoconstricting hormones such as angiotensin II. (However, when combined with valsartan, would result in blocking of angiotensin II to its receptor, preventing the vasoconstrictive effects and resulting in a decrease in vascular resistance and blood pressure.) Cardiovascular and renal effects of sacubitril is a result of the increased levels of peptides that are normally degraded by neprilysin.
Absorption	Peak plasma concentrations of sacubitril and it's metabolite, LBQ657 are reached in 0.5 hours and 2 hours respectively. Food does not clinically affect the systemic exposure of sacubitril or LBQ657. The oral bioavailability of sacubitril is >60%. It should be noted that the valsartan found in this combination is more bioavailable than other market available valsartan.
Volume ofdistribution	103 L
Proteinbinding	Sacubitril and it's metabolite, LBQ657 are highly bound to plasma protein (94-97%).
Metabolism	acubitril is metabolized to LBQ657 by esterases. A low concentration (<10%) of a hydroxyl metabolite has been identified in plasma.
Route of elimination	52% to 68% of sacubitril (primarily as the active metabolite LBQ657) is excreted in urine. 37% to 48% of sacubitril (primarily as LBQ657) is excreted in feces .
Half life	The half life of sacubitril is 1.1 to 3.6 hours, and the half life of it's metabolite LBQ657 is 9.9 to 11.1 hours.
Toxicity	The most common adverse reactions (≥5%) are hypotension, hyperkalemia, cough, dizziness, and renal failure

Source*: Virtual Repository Drugbank® [https://www.drugbank.ca/drugs/DB09292].*

Table III

Predicted Properties of sacubitril

Property	Value	Source
WaterSolubility	0.000942 mg/mL	ALOGPS
logP	3.9	ALOGPS
logP	3.79	ChemAxon
logS	-5.6	ALOGPS
pKa (StrongestAcidic)	4.18	ChemAxon
pKa (Strongest Basic)	-1.6	ChemAxon
Physiological Charge	-1	ChemAxon
HydrogenAcceptorCount	4	ChemAxon
HydrogenDonorCount	2	ChemAxon
Polar Surface Area	92.7 $Å^2$	ChemAxon
Rotatable Bond Count	12	ChemAxon
Refractivity	114.06 $m^3 \cdot mol^{-1}$	ChemAxon
Polarizability	45.41 $Å^3$	ChemAxon
NumberofRings	2	ChemAxon
Bioavailability	1	ChemAxon
Ruleof Five	Yes	ChemAxon
GhoseFilter	Yes	ChemAxon
Veber'sRule	No	ChemAxon
MDDR-likeRule	No	ChemAxon

In the online repositories the two-dimensional structure is not always in the most stable conformation, being necessary to use computational algorithms to obtain the thermodynamically more stable conformation, that is, the one of smaller energy, being considered the one of smaller energy. This geometric optimization can be performed using several techniques of modeling, where we can highlight the classic methods of force field, such as the Merck Molecular Force Field (MMFF94), developed by Merck Research Laboratories, based on the MM3 force field, parameterized with the Steepest Descent algorithm the MMFF94 optimized the structure of Sacubitril (Figure 2) a, obtaining a structure where the atoms are distributed three-dimensional in a state of least possible potential energy, no longer varying, reaching a stationary point of the energy surface [13].

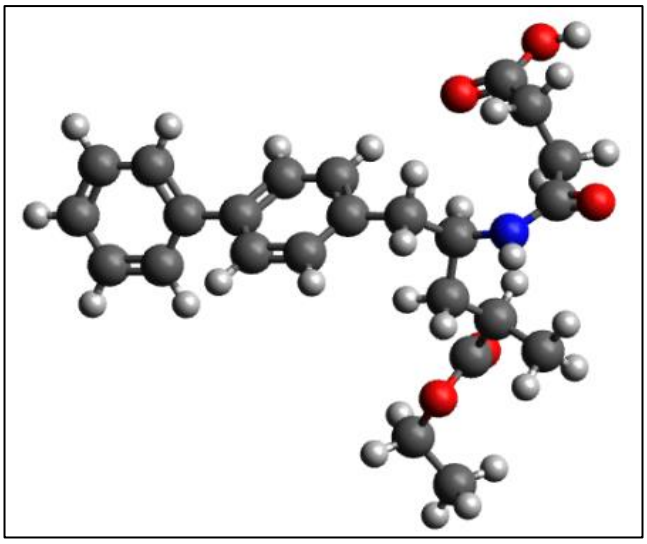

Fig.2 Optimized structure of the compound Sacubitril

After the minimization process, its geometric configuration begins to take its place of lower energy in the structure, so with a theoretically more stable structure, it is possible to calculate the formal and partial charges of each atom. Finally, by rendering the data obtained by the optimization, it was possible to plot the Van der Waals surface (figure 3), and to calculate the formal and partial loads of each atom (Table 4), highlighting the variations observed as in Oxygen atoms (-0.481 to -0.251), Carbon (-0.062 to 0.305), which are due to the differences between electronegativity between atoms, generating a non-uniform partial charge density for each atom distributed in the molecule [24].

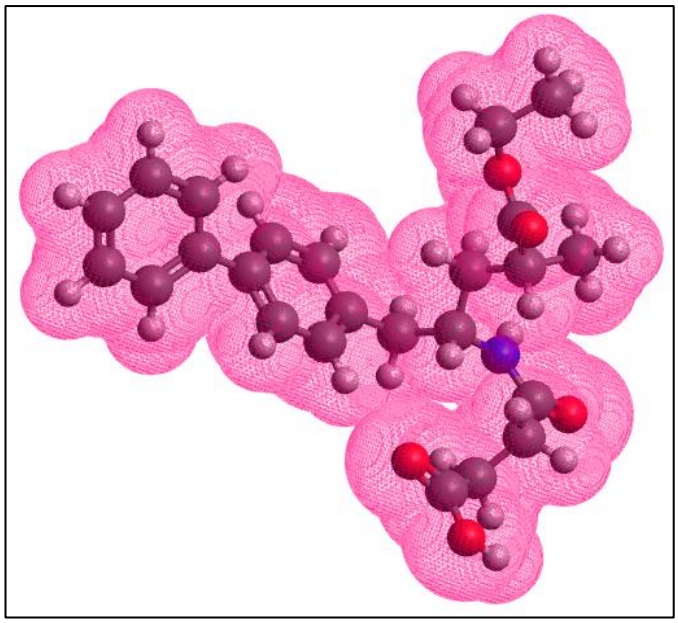

Fig. 3.Van der Waals surface of the Sacubitril

.We can also, by analyzing the connections of the compound Sacubitril, highlight the bonds between carbon-oxygen ((C1-O1), (C4-O5) and (C9-O4) and carbon-carbon ((C13-C14), (C15-C16)) and (C 17 -C 22), (C 18 -C 22), (C 21 -C 22), (C 23 -C 24) groups) as second order or double bonds, and the bond between C 2 -C 3, C6), (C5 - C12), (C6 - C7)) as being the only ones to have a rotatability.

According to the conformational characterization, all the angles between the bonds and the torsion angles, called dihedral, could be calculated. the angles (C4 - N - C5) and (H19 - C12 - H2O) with 130.1933 ° and 105.0844 ° respectively, also, for example, the larger and smaller angles of the dihedral systems, C14-C15-C16) and (C16-C17-C22-C21) with 179.9625 ° and -179.9965 ° respectively.

Table IV

Atomic Properties of Compound Sacubitril

atom	Elementtype		Valence	Formal change	Partialchange	X (Å)	Y (Å)	Z (Å)
1	O	O2	1	0	-0.251	1.44738	-2.31697	-1.37189
2	C	C2	3	0	0.305	2.54673	-2.71022	-1.01242
3	O	O3	2	0	-0.481	2.71490	-3.56249	0.01922
4	C	C3	4	0	0.053	3.83200	-2.24847	-1.63436
5	C	C3	4	0	0.034	4.25206	-0.92214	-1.02705

6	C	C2	3	0	0.214	5.03244	-0.11105	-2.02840
7	N	Nam	3	0	-0.312	4.37877	0.65234	-2.94530
8	C	C3	4	0	0.028	2.94066	0.84773	-3.16256
9	C	C3	4	0	-0.022	2.57769	2.34276	-3.02294
10	C	C3	4	0	0.055	2.85494	2.92464	-1.62170
11	C	C3	4	0	-0.052	4.22220	3.59478	-1.50345
12	C	C2	3	0	0.310	1.78728	3.93278	-1.23474
13	O	O3	2	0	-0.465	1.62867	4.87772	-2.20250
14	C	C3	4	0	0.090	0.64536	5.88758	-1.93322
15	C	C3	4	0	-0.031	1.26892	7.02778	-1.15070
16	O	O2	1	0	-0.251	1.18762	3.90541	-0.16819
17	C	C3	4	0	-0.009	2.57436	0.29573	-4.56156
18	C	Car	3	0	-0.046	1.10676	0.36657	-4.90523
19	C	Car	3	0	-0.058	0.17148	-0.41553	-4.21988
20	C	Car	3	0	-0.054	-1.18947	-0.33277	-4.53210
21	C	Car	3	0	-0.018	-1.65346	0.52895	-5.53749
22	C	Car	3	0	-0.018	-3.08678	0.61745	-5.86227
23	C	Car	3	0	-0.054	-3.83283	-0.53307	-6.16797
24	C	Car	3	0	-0.061	-5.19319	-0.44949	-6.47759
25	C	Car	3	0	-0.062	-5.83184	0.78786	-6.48522
26	C	Car	3	0	-0.061	-5.11175	1.94091	-6.18394
27	C	Car	3	0	-0.054	-3.75117	1.85551	-5.87588
28	C	Car	3	0	-0.054	-0.70632	1.30350	-6.22463
29	C	Car	3	0	-0.058	0.65545	1.22351	-5.91571
30	O	O2	1	0	-0.276	6.26193	-0.15579	-2.05510

IV. CONCLUSIONS

The molecular structure of the Sacubitril compound was geometrically optimized by means of classical force field calculations, using the Avogadro® freeware set up in MMFF94 steepest descent, reaching the theoretically more stable conformation and closer to its native form after the process, it was possible to observe numerous structural properties of the compound, such as the binding distances, their angulations, and some atomic properties. 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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