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In silico screening of brazilian semiarid compounds to identify potential drugs with glucocorticoid receptor interaction

Triagem in sílico de compostos do semiárido brasileiro para identificação de potenciais fármacos com interação ao receptor glicocorticoide

En proyección de silico de compuestos de brasileño semiárido para la identificación de posibles drogas con interacción del receptor de glucocorticoides

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Abstract

The glucocorticoid receptor regulates the anti-inflammatory response, and prevents transcription of anti-inflammatory substances such as nuclear factor kB and lipocortin-1, IL-2, IL-6, TNF and prostaglandins. Thus, a search for new molecules with potential interaction with the glucocorticoid receptor is an interesting strategy for the treatment of inflammatory diseases. Virtual screening has proven to be a viable tool for discovering new products at lower cost and practicality. Thus, the aim of this study is to identify and evaluate brazilian semiarid compounds with anti-inflammatory potential with glucocorticoid receptor action through molecular coupling. Protein selection was performed by searching the 3D structure database, Protein Data Bank. A total of 382 semi-arid molecules available in the ZINC database of State University of Feira de Santana (UEFS) were used. Molecular docking was performed using Autodock Vina and as interaction clouds analyzed by the Discovery Studio Visualizer program. Mometasone furoate shows a binding energy of -12.7 Kcal.mol-1. A ZINC 69481862 molecule fits Lipinski and Veber rules, however, the best interaction was the ZINC 69482012 molecule, evidenced by the binding energy -11.2 Kcal.mol-1. Analyses of intermolecular interactions have shown that Van der Waals interactions and electrostatic bonds are crucial for the binding of the molecule at the receptor's active site. It is necessary to test in vitro to verify the viability and toxicity of the potential drug.

Keywords: Virtual Screening; Molecular Docking; Anti-inflammatory Potential; Glucocorticoid Receptor.

Resumo

O receptor glicocorticoide regula a resposta anti-inflamatória ao impedir a transcrição de proteínas pró-inflamatórias, como o fator nuclear kB e lipocortina-1, IL-2, IL-6, TNF e prostaglandinas. Dessa forma, a busca de novas moléculas com potencial interação com o receptor glicocorticoide é uma estratégia interessante para o tratamento de doenças inflamatórias. A triagem virtual tem se demostrado uma ferramenta viável para a descoberta de novos fármacos, pelo baixo custo e praticidade. Assim, o objetivo deste estudo é identificar e avaliar os compostos do semiárido brasileiro com potencial anti-inflamatório com ação no receptor glicocorticoide, através do acoplamento molecular. A seleção da proteína se deu através da busca no banco de dados de estruturas 3D, Protein Data Bank. Foram utilizadas um total de 382 moléculas do semiárido disponíveis no banco de dados ZINC, pela Universidade Estadual de Feira de Santana (UEFS). O docking molecular foi realizado utilizando o Autodock Vina e as nuvens de interações foram analisadas pelo programa Discovery Studio Visualizer. O Furoato de Mometasona apresentou energia de ligação de -12,7 Kcal.mol-1. A molécula ZINC 69481862 se enquadrou nas regras de Lipinski e Veber, entretanto, a melhor interação foi da molécula ZINC 69482012, evidenciada pela energia de ligação -11,2 Kcal.mol-1. Análises das interações intermoleculares demonstraram que as interações de Van der Waals e ligações eletrostáticas são cruciais para a ligação da molécula no sitio ativo do receptor. Faz-se necessário testes in vitro para averiguar a viabilidade e toxicidade do potencial fármaco.

Palavras-chave: Triagem Virtual; Acoplamento Molecular; Potencial Anti-inflamatório; Receptor Glicocorticoide.

Resumen

El receptor de glucocorticoides regula la respuesta antiinflamatoria al prevenir la transcripción de proteínas proinflamatorias como el factor nuclear kB y lipocortin-1, IL-2, IL-6, TNF y prostaglandinas. Por lo tanto, la búsqueda de nuevas moléculas con interacción potencial con el receptor de glucocorticoides es una estrategia interesante para el tratamiento de enfermedades inflamatorias. La evaluación virtual ha demostrado ser una herramienta viable para el descubrimiento de nuevos medicamentos, debido a su bajo costo y practicidad. Por lo tanto, el objetivo de este estudio es identificar y evaluar los compuestos del semiárido brasileño con potencial antiinflamatorio que actúa sobre el receptor de glucocorticoides a través del acoplamiento molecular. La selección de proteínas se realizó buscando en la base de datos de estructura 3D, Protein Data Bank. Se utilizaron un total de 382 moléculas

semiáridas disponibles en la base de datos ZINC de la Universidad Estatal de Feira de Santana (UEFS). El acoplamiento molecular se realizó utilizando Autodock Vina y las nubes de interacción fueron analizadas por el programa Discovery Studio Visualizer. El Furoato de Mometasona muestra una energía de unión de -12.7 Kcal.mol-1. La molécula ZINC 69481862 se ajusta a las reglas de Lipinski y Veber, sin embargo, la mejor interacción fue la molécula ZINC 69482012, evidenciada por la energía de unión -11.2 Kcal.mol-1. Los análisis de las interacciones intermoleculares han demostrado que las interacciones de Van der Waals y los enlaces electrostáticos son cruciales para la unión de la molécula en el sitio activo del receptor. Son necesarias pruebas in vitro para verificar la viabilidad y la toxicidad del fármaco potencial.

Palabras clave: Cribado virtual; Acoplamiento molecular; Potencial anti-inflamatório; Receptor de glucocorticoides.

1. Introduction

Inflammation is a local or systemic physiological process, responsible for eliminating stimuli that cause injury, repair tissue and promote immune memory (Fullerton & Gilroy, 2016). Inflammatory criticisms are complex and mediated by the immune system, through macrophages and dendritic cells, with a production of soluble mediators, such as system complement, cytokines and chemokines, which cause the influx of neutrophils and monocytes in the information site. However, acute and systemic inflammation can result in organ failure and tissue death, and if it persists for a long period of time, it can cause chronic inflammatory diseases, including autoimmunity and câncer (Fullerton & Gilroy, 2016; Kumar, 2019).

Among the receptors involved in the inflammatory process, are the nuclear receptors of the glucocorticoid type. Glucocoirticoid receptors are a product of the NR3C1 gene located on chromosome 5q31-32, and are present throughout the body with different sensitivities. These factors act of transcription in response to a hormone, modulating the expression of target genes (Faria & Longui, 2006; Kadmiel & Cidlowski, 2013).

The formation of the glucocorticoid receptor complex regulates the anti-inflammatory response by two engines: genetic transrepression, which is the recruitment of the histone deacetylase enzyme induces DNA condensation, thus preventing the transcription of pro-inflammatory substances, such as the factor nuclear kB and lipocortin-1; and genetic transaction, in which there is an increase in acetylation of genes encoding anti-inflammatory proteins, such as IL-2, IL-6, TNF and prostaglandins (Torres, Insuela & Carvalho, 2012).

No drug development process, a virtual study or screening in silicone, is demonstrated as a viable strategy due to its lower cost and practicality (Shityakov & Foerster, 2014; Martins et al., 2014). In view of high cost of drug development, computational approaches are used to screen a large number of compounds and then select a restricted number of drug uses (Kazmi et al., 2019). Virtual screening uses molecular documentation, which identifies compounds with chemical characteristics and the different ligand distances used to determine the molecular target. Thus, it allows the selection of molecules that present a set of favorable intermolecular interactions (Rodrigues et al., 2012).

The virtual screening process depends on a database with a wide molecular diversity, which provides the compounds for the tests to be carried out. Among the virtual libraries, the ZINC database has a rich collection with more than 20 million compounds, available for free (Irwin & Shoichet, 2005). The Feira de Santana State University provides a collection of hundreds of cataloged molecules from the Brazilian semiarid region.

According to Ministry of the Environment (2020), the brazilian semiarid region occupies approximately 11.5% of the national territory; and is an estimated eight thousand plant species, of which 318 species are endemic to the caatinga. In these plant species, there is great potential for pharmacological use (Barreiro & Bolzani 2009). Studies by Costa et al., 2008; Costa et al., 2010 demonstrated that the Brazilian semiarid region has plants with immunomodulatory and antibacterial activities.

The glucocorticoid receptor is a potential pharmacological target in the treatment of inflammatory and autoimmune disorders (Kadmiel & Cidlowski, 2013). Thus, the search for new molecules that interact with the glucocorticoid receptor is important to aggregate the therapeutic collection of inflammatory diseases. There is a lack of related studies, so the objective is to identify and evaluate compounds from the Brazilian semiarid region with anti-inflammatory potential with action on the glucocorticoid receptor, through molecular coupling.

2. Materials and Methods

2.1 Protein selection

Protein selection was carried out by searching the 3D structure database, Protein Data Bank - PDB (Berman et al., 2000). The selection filters were the experimental X-ray diffraction method, with a resolution and R value greater than 2.0 Å and 0.2, respectively. The

presence of a ligand, mometasone bore and a nuclear activator in the receptor structure is considered.

2.2 Preparation of the protein

The AutodockTools 1.5.6.rc3 (Sanner 1999) program was used to prepare a three-dimensional structure of the molecular target, or the glucocorticoid receptor. Through the preparation of the molecular target it is possible to carry out fitting studies. In this process, the binders and solvents present in the structure are removed. They are hydrogen gases and fillers to adapt the chemical structure. The spatial determination of the target site of the receptor was made through the position of the ligand and interaction with the receptor, with the determination of the active site being made. For this purpose, the AutodockTools 1.5.6.rc3 (Sanner 1999) program was also used to determine how to coordinate the search space of the active location of the receiver. Through the grid box, the coordinates of the research space were applied in the space of 1 Å.

2.3 Selection of semiarid molecules

A total of 382 semiarid molecules are available in the ZINC (Irwin & Shoichet, 2005) database provided by the State University of Feira de Santana. As molecules present in the .mol2 format, the databases were converted to the .pdbqt format using the Autodock Tools 1.5.6.rc3 (Sanner, 1999) program.

2.4 Docking and identification of interactions with the glucocorticoid receptor

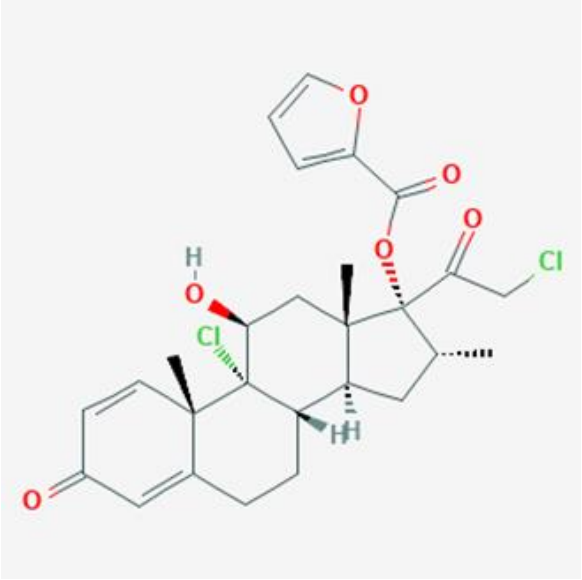
The coupling or molecular coupling was performed using Autodock Vina (Trott & Olson, 2010) which is responsible for calculating the binding energy of the ligand interaction with the receptor. The results were observed from the computer's command prompt. Together with the identified binding energies, such as clouds of interactions and the present amino acid residues analyzed by the Discovery Studio Visualizer (BIOVIA, 2016) program. The parameters of Lipinski (Lipinski et al., 2001) and Veber (Veber et. al., 2002) for oral bioavailability were considered in the analysis of the molecules.

3. Results and Discussion

The protected protein in the PDB database - Protein Data Bank (Berman et al., 2000) for the - glucocorticoid receptor - code PDB 4P6W. The anchor box for selecting a spatial position of the connection site has 27,336, -51,637 and -36,965 X, Y and Z coordinates, respectively, and 10 x 14 x 14 Â dimensions.

The mometasone furoate ligand (Figure 1) was used as a prototype to relate to the results. The binding energy resulting from the interaction between a crystallized structure of the NR3C1 glucocorticoid receptor and mometanosa furoate was equal to -12.7 Kcal.mol^{-1}. According to Derendorf and Meltzer (Derendorf & Meltzer, 2008) mometasone furoate is a potent corticosteroid that inhibits pro-inflammatory mediators by a downregulation mechanism, acting on the glucocorticoid receptor. In vitro assays, mometasone furoate stimulated the gene transactivation of the glucocorticoid receptor more potently (Smith & Kreutner, 1998). This molecule inhibited the production of TNF-α, interferon-y, leukotrienes and histamine (Kim et al., 2019).

Figure1. 2D structure of the Mometasone Furoate molecule.



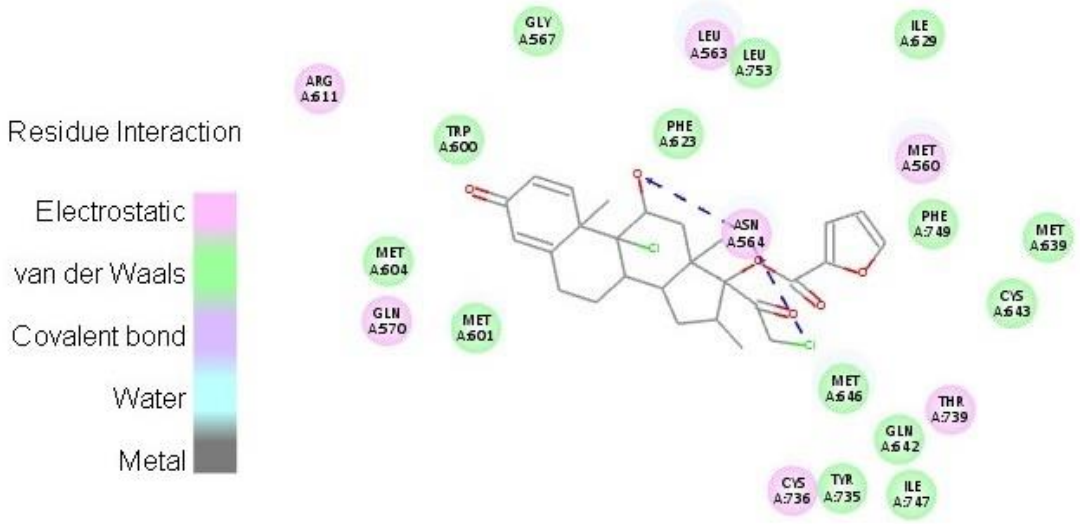
Source: PubChem Database Kim et al., (2019)

Dey & Bishayi (2019) demonstrated that the interaction of this receptor with the corticoid dexamethasone reduced the microglial inflammation caused by S.aureus, by inhibiting the expression of nitric oxide. Through a docking method with induced docking (IDF - Induced-fit Docking), mometasone furoate, a potent anti-inflammatory glucocorticoid,

was used as a ligand to attach to the glucocorticoid receptor. There is a high affinity between the ligand and the 17α position of the receptor, facilitated by hydrophobic interactions (Wang, Aslanian & Madison, 2008; Chen et al., 2005).

Thus, the molecule ZINC 69482012 may have an affinity for the glucocorticoid receptor NR3C1, when comparing the proximity of values with the binding energy of mometasone furoate with the receptor. The analysis of the interactions between amino acid residues and the mometasone furoate ligand takes place through the 2D diagram shown in Figure 2.

Figure 2. Amino acid residues from the RG active site that interact with mometasone furoate.



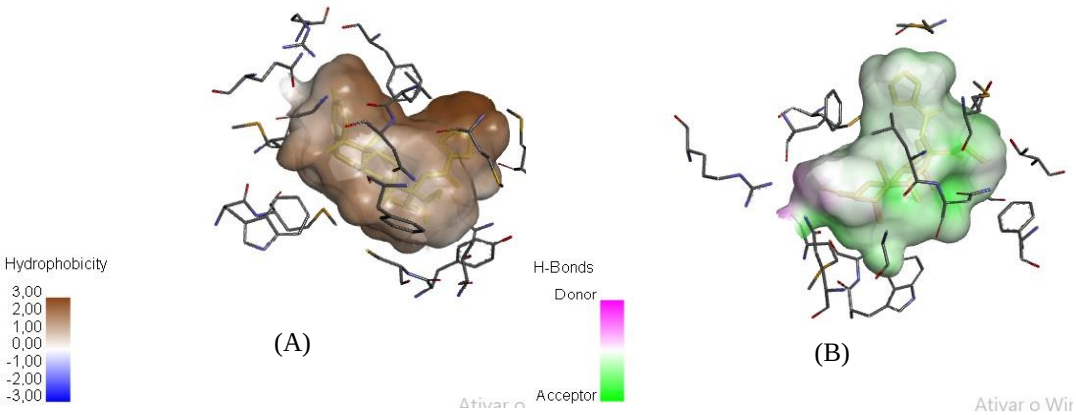
Source: Prepared by the Authors, (2019).

Intermolecular bonds between protein and ligand occur mainly by Van der Walls forces, electrostatics and hydrogen bonds (Silva et al., 2020). Notably the greater predominance of interactions is of the Van der Waals type, fundamental for the interaction of the ligand with the active site of the protein, and this interaction occurs with the amino acid residues: LEU566, MET604, GLY567, TRP600, MET601, LEU753, PHE623, ALA605, LEU608, PHE749, LEU732, ILE629, MET646, MET639, CYS643, GLN642, TYR735 and ILE747. To a lesser extent, there are also electrostatic interactions between the active site and the ligand, verified by the ARG611, LEU563, GLN570, ASN564, MET560, CYS736 and THR739 residues.

In Figure 3A, it can be seen that most of the interactions between the active site of the glycocoirticoid receptor and mometasone furoate are of the Van der Waals type, through the visualization of the hydrophobicity cloud, represented by the brownish color. Figure 3B

shows the hydrogen acceptor and donor regions represented by the greenish and pink colors, respectively.

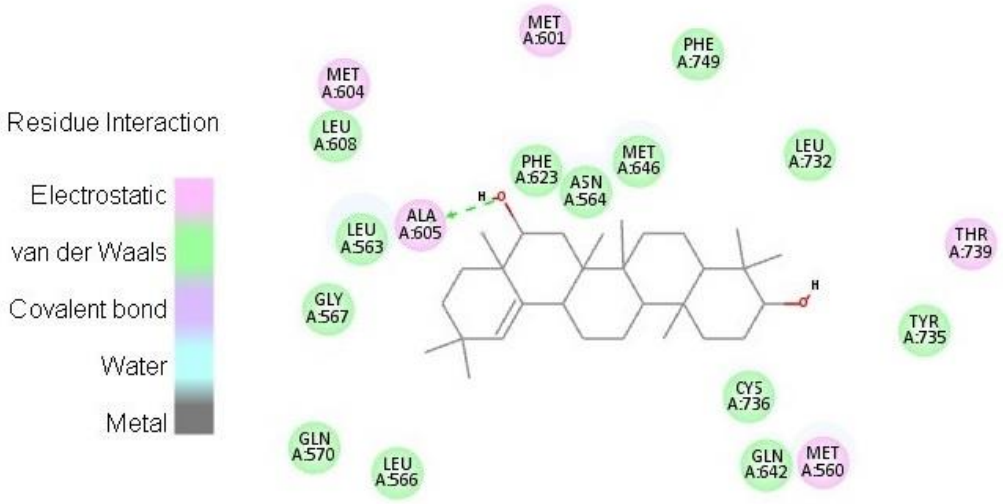
Figure 3. Electronic cloud in the RG active site and its interaction with Mometanosa Furoate. (A) Hydrophobic interactions (B) Hydrogen bond.



Source: Prepared by the Authors, (2019).

The ZINC 69482012 molecule has similarities to mometasone furoate in its interaction with amino acid residues. There is a predominance of Van der Waals interactions, in addition to electrostatic interactions. Both molecules have at least one interaction with the amino acid residues: GLY567, PHE623, MET646, GLN642, ASN564, TYR735, GLN570, THR739, CYS736, MET601 and PHE749. This correspondence between the molecules may be one of the reasons for the interaction with the glucocorticoid receptor active site (Figure 4).

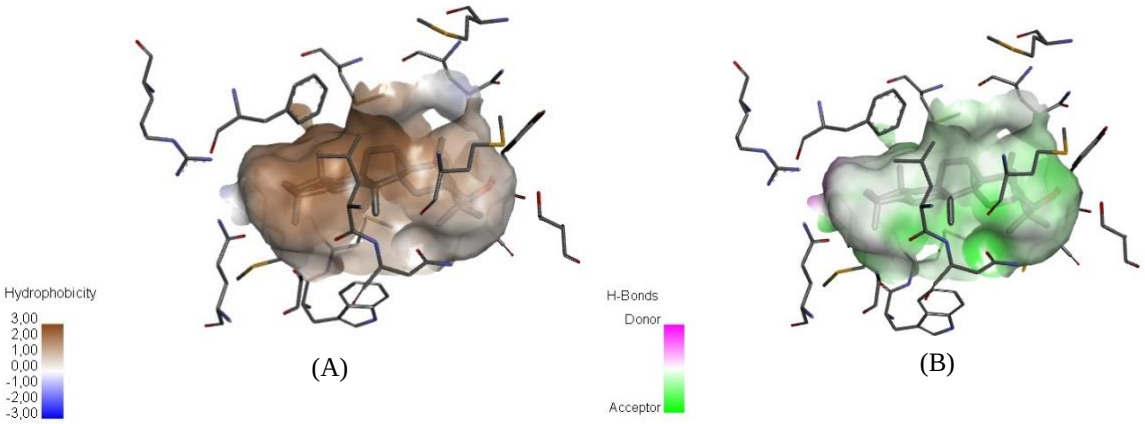
Figure 4. Amino acid residues from the RG active site that interact with ZINC 69482012.



Source: Prepared by the Authors, (2019).

In the analysis of the hydrophobicity clouds and hydrogen bonds (Figure 5) of the ZINC 69482012 molecule, it is noted that it is composed of hydrophobic groups and hydrogen acceptors, represented by the brownish and greenish colors, respectively. In accordance with the structure and chemical groups of mometasone furoate.

Figure 5. Electronic cloud at the active site of the RG and its interaction with ZINC 69482012. (A) Hydrophobic interactions (B) Hydrogen bond.

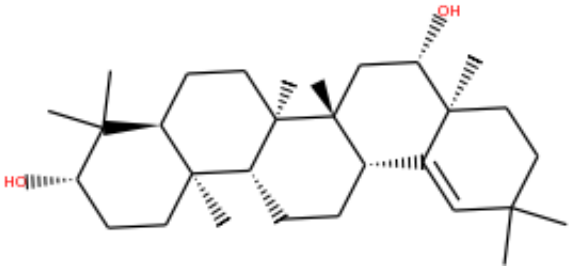


Source: Prepared by the Authors, 2019. Source: Prepared by the Authors, (2019).

Among the 382 molecules tested in the Bahian semiarid region with the glucocorticoid receptor NR3C1, the most favorable interaction showed a binding energy equivalent to -11.2 Kcal.mol^{-1}, while the least favorable interaction was equal to +21.1 Kcal.mol^{-1}.

The molecular coupling was performed with a total of 382 cataloged molecules from the Bahian semiarid available in the ZINC database of the State University of Feira de Santana. The code molecule ZINC 69482012, chemically named (3S, 6R, 8S, 11R, 12S,15S,16R,19S,21R)3,7,7,11,16,20,20heptamethylpentacyclo[13.8.0.03,12.06,11.01,21]tricos-1(23)-ene-8,19-diol (Figure 6), obtained the best binding energy with the active site of the glucocorticoid receptor (-11.2 Kcal.mol-1). The ZINC 69482012 molecule does not fit the rules of Lipinski (Lipinski et al., 2001) and Veber (Veber et. al., 2002), therefore, its pharmaceutical presentation should be non-oral.

Figure 6. 2D structure of the ZINC 69482012 molecule.



Source: ZINC Database Irwin & Shoichet, (2005)

The parameters established by Lipinski (Lipinski et al., 2001) and Veber (Veber et. al., 2002) are observed for the development of a possible oral drug. The oral bioavailability of the molecules is predicted by descriptors, analyze that parameters: Log P, number of electron donor groups, number of electron acceptor groups, molecular weight, number of rotatable bonds and polar surface area to determine the solubility and permeability of drugs before the membrane.

Thus, although the ZINC 69481862 molecule does not have the best binding energy among the analyzed molecules, it has the best potential as an oral drug (Table 1).

Table 1. Parameters for assessing the oral bioavailability of the ZINC molecule 69481862.

Parameters	ZINC 69481862*	Reference Values**
Number of electron donos	0	< 5
Number of electron acceptors	3	< 10
Molecular weight (g.mol^{-1})	468.546	< 500
LogP	4.338	< 5
Number of rotational connections	4	≤ 10
Polar surface area (Å^2)	95	≤ 140

Source: ZINC Database (Irwin & Shoichet, 2005), (Lipinski et al., 2001; Veber et. al., 2002)
* Values made available by ZINC Database (Irwin & Shoichet, 2005)
** Reference values according to (Lipinski et al., 2001; Veber et. al., 2002)

The modeling studies show that the lower the resulting binding energy between the ligand and the target site, the better the interaction affinity. This anchorage uses the

connection energy generated in the process, to validate and capture intermolecular interactions (Sivakumar, Sajeevan & Bright Singh, 2016; Ozawa et al., 2019).

Molecular coupling and the study of the chemical structure of molecules are successful strategies to obtain a configuration of new drugs (Ferreira et al., 2005). Zianna et. al (2019) demonstrated an agreement between in vitro and silica studies, when evaluating the bacterial activity of the complex formed by the compound Paladium (II) and the Schiff base. These models are used both in industry and academia, and from them it is possible to predict the conformation of the ligand at the target site and its viability (Drwal & Griffith et al., 2013).

The molecule discussed in this study, ZINC 69482012, has the potential to interact with the glucocorticoid receptor NR3C1, and may have anti-inflammatory activity, however, evaluation of toxicological and pharmacokinetic parameters is necessary to determine the safety and viability of the drug as an anti-inflammatory medicine.

In silico studies have been shown to be an efficient strategy for the discovery of new drugs, however it is important to note that the results may or may not be confirmed in vivo (Zheng et al., 2013).

4. Conclusion and Suggestions

The ligand ZINC 69481862 fit the rules of Lipinski and Veber, however, the best interaction was of the molecule ZINC 69482012, evidenced by the binding energy -11.2 Kcal.mol-1. Although it does not fit the parameters of oral bioavailability, the potential drug can be proposed by other routes of non-oral administration.

The analysis of the interactions involved in the ligand-receptor complex demonstrated that hydrophobic bonds and electrostatic interactions are essential for the coupling of the molecule to the target site. Such characteristics were also verified in the molecule with the best interaction, ZINC 69482012. The clouds of interaction corroborated the forces at work in the system, Van der Waals connections.

From the results obtained, in vitro tests are necessary to ascertain the feasibility and further investigation in relation to the ZINC 69482012 molecule, to determine the toxicity and safety of the potential drug.

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