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In silico screening of compounds from the Bahia semiarid region for identification of potential inhibitors of the p38 MAPK protein

Triagem in silico de compostos oriundos do semiárido baiano para identificação de potenciais inibidores da proteína p38 MAPK

Selección in silico de compuestos semiáridos de Bahía para identificar inhibidores potenciales de la proteína MAPK p38

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Abstract

The P38 MAPK protein is mainly involved in the synthesis of the proinflammatory cytokines IL1 and TNF-alpha and is important in the maintenance and amplification of the inflammatory process. Therefore, this protein presents high potential as a pharmacological target in the search for new treatments for inflammatory diseases. In silico approach has been of great importance to develop quick and inexpensive target identification and way to discover new bioactive molecules. This study used a computer ligand-docking method to screen the compounds from the Bahia semiarid region *in silico* for their ability to inhibit p38 MAPK activity. The protein crystallographic structure of the p38 MAPK was obtained from the Macromolecular Protein Data Bank. Northeast semiarid molecules were obtained from the ZINC database. The database was screened and a set of 233 molecules were selected as candidates using filtering based on parameters of the rule of Lipinski and Verber. The docking was carried out using the program Autodock Vina in its default configuration. The compound with ZINC databank code: 91596862 was found the most promising compound acoording to their binding free energy value obtained in the docking experiments (11,1 Kcal.mol-1) Intermolecular interactions analysis suggested that Van der Waals interactions are crucial to the ZINC molecule 69481892 in the active site of the p38 MAPK protein. Data resulting from all dockings are significant, although it has low accuracy. Thus, the hypothetical results of these *in silico* studies should be confirmed by *in vitro* and/or *in vivo* tests.

Keywords: Molecular docking simulation; Inflammation; p38 mitogen-activated protein kinases.

Resumo

A proteína p38 está envolvida na síntese de citocinas proinflamatórias, principalmente IL1 e TNFα, sendo importante na manutenção e amplificação dos processos inflamatórios. Assim, esta proteína apresenta elevado potencial como alvo farmacológico na busca por novos tratamentos de doenças inflamatórias. Uma forma rápida e de baixo custo para a descoberta de novas moléculas bioativas é através da realização estudos *in silico*. Com isso, o objetivo deste estudo é a identificação de compostos oriundos do semiárido baiano com potencial atividade inibitória da proteína p38 MAPK, através de estudos de acoplamento molecular. A estrutura cristalográfica da proteína foi obtida no banco de estruturas de macromoléculas Protein Data Bank. As moléculas do semiárido nordestino foram obtidas através do banco de dados ZINC. Dentre as moléculas disponíveis, apenas 233 foram selecionadas para os estudos de acoplamento molecular, uma vez que enquadraram-se nos parâmetros das regras de Lipinski e Verber. O docking foi realizado utilizando o programa Autodock Vina em sua configuração padrão. A molécula de código ZINC 69481892 foi a única selecionada como promissora no que diz respeito à inibição da proteína p38 MAPK, já que a energia de ligação com a p38 foi -11,1 Kcal.mol^{-1}. Analises das interações intermoleculares demonstraram que as interações de Van der Waals são cruciais para a ligação da molécula ZINC 69481892 no sitio ativo da proteína. Estes dados resultantes da realização de dockings são significativos, entretanto de baixa acurácia. Assim, os resultados hipotéticos dos estudos *in sílico* devem ser confirmados por estudos *in vitro* e/ou *in vivo*.

Palavras-chave: Simulação de acoplamento molecular; Inflamação; Proteínas quinases p38 ativadas por mitógeno.

Resumen

La proteína p38 participa en la síntesis de citocinas proinflamatorias IL1 y TNF-alfa, principalmente, siendo importante en el mantenimiento y la amplificación del proceso inflamatorio. Por lo tanto, esta proteína presenta alto potencial como diana farmacológica en la búsqueda de nuevos tratamientos para las enfermedades inflamatorias. Una forma rápida y barata las nuevas moléculas bioactivas de descubrimiento es mediante la realización de estudios *in silico*. El objetivo de este estudio es la identificación de compuestos de moléculas semiáridos noreste con potencial actividad inhibidora de la proteína p38 MAPK, a través de acoplamiento molecular. La estructura cristalográfica de la proteína se obtuvo sobre la base de datos de macromoléculas Protein Data Bank. Las moléculas semiáridas del noreste se obtuvieron de la base de datos de ZINC. Entre las moléculas disponibles en la base de datos,

se seleccionaron sólo 233 estudios de acoplamiento molecular, una vez que encajan en los parámetros de la regla de Lipinski y Verber. El acoplamiento se llevó a cabo utilizando el programa Autodock Vina en su configuración predeterminada. El código de la molécula ZINC 69481892 fue seleccionado como prometedor con respecto a la inhibición de la proteína p38 MAPK, puesto que la energía de enlace con la p38 fue -11.1 Kcal.mol^{-1}. El análisis de las interacciones intermoleculares demostró que las interacciones de Van der Waals son cruciales para la molécula ZINC 69481892 en el sitio activo de la proteína. Datos resultantes de los atraques son importantes, aunque tiene baja precisión. Así, los hipotéticos resultados de estos estudios *in silico* deben confirmarse por pruebas *in vitro* o *in vivo*.

Palabras clave: Simulación del acoplamiento molecular; Inflamación; Proteínas quinasas p38 activadas por mitógenos.

1. Introduction

Inflammation is a positive reaction of the organism in response to chemical, physical or microbiological injury, and when uncontrolled, it contributes to the development of several pathologies (Alessandri et al., 2016). Cells of the innate immune system, such as macrophages and dendritic cells mediate inflammatory reactions initially, which have antigen-recognizing receptors that activate various signaling cascades and initiate the development of the inflammatory process by chemical mediators. Because of this activation, a series of chemical mediators (cytokines, chemokines, etc.) are released, amplifying the immune response. Acute inflammation can result in tissue death (Medzhitov, 2008; Kumar, 2019).

Among the antigen-recognizing receptors, standard recognition receptors (TLRs), RIG-type receptors and nucleotide oligomerization domains (NODs)are capable of recognizing the molecular patterns associated with pathogens (PAMPS) (Medzhitov, 2008; Kawai & Akira, 2016). These receptors activate signaling cascades that culminate in cell differentiation and proliferation, apoptosis and synthesis of proinflammatory cytokines (Kawai & Akira, 2016; Caruso et al., 2014). Recognizing pathogen receptors mediate the activation of mitogen-activated protein kinases (MAPK) (Kawai & Akira, 2016). This family of serine/threonine protein kinases is subdivided into 3 subfamilies, ERK, p38 and JNK. These proteins are responsible for several biological functions related to mitosis, apoptosis, metabolism, motility and cell differentiation (Cargnello & Roux, 2011).

The protein kinase activated by mitogen p38 has 4 isoforms, p38α, p38β, p38γ and p38δ, p38α being the most correlated to the development of stress and inflammation. The synthesis of p38 protein can also be stimulated by oxidative stress, ischemia, hypoxia, ultraviolet radiation and proinflammatory cytokines. The main activity of p38 is the induction of cytokine synthesis, mainly IL1 and TNFα, causing amplification of inflammation (Cargnello & Roux, 2011; Ravindra, Achaiah & Sastry, 2008).

The p38 protein has high potential as a pharmacological target in the search for new treatments for inflammatory diseases mainly due to its participation in the development and maintenance of the inflammatory process. Inhibition of this protein has been widely reported in the literature as a treatment for inflammation. Lee et al., 2013 demonstrated that the p38 signaling cascade activated by reactive nitrogen species induces apoptosis in embryonic cellsand amplifies the production of free radicals. This protein is also directly associated with inflammation in the lung tissue. P38 inhibitory substances were able to control acute pulmonary inflammation in mice, with a significant reduction in cytokines and inflammatory cells (Lima et al., 2011).

However, even with several studies on p38 inhibition, the effective substances available for this purpose are very scarce (Song et al., 2017; Choi, Beitz & Lee, 2019; Firgany & Sarhan, 2020). Drugs such as skepinone, a selective inhibitor of p38, are still being tested (Storch et al., 2014). Another example is losmapimod, which is in phase III studies but has not shown promising results (O'Donoghue et al., 2016). Given the above, there is a need to search for new molecules that inhibit the p38 protein, especially in an attempt to insert these substances into the therapeutic arsenal of inflammatory diseases.

In the pharmaceutical industry, computer technologies have been increasingly used to reduce time and costs in the process of discovering new drugs, such as selecting a restricted number of compounds to be analyzed (Kazmi et al., 2019). The progress of molecular biology and the techniques of X-ray crystallography and nuclear magnetic resonance have allowed structural studies of pharmacological targets to increase the success rate in the search for bioactive substances (Ferreira et al., 2015; Rodrigues et al., 2012). With the diversity of information available in the databases, virtual screening techniques have played a fundamental role in the discovery of new drugs (Ferreira, Oliva & Andricopulo, 2011).

The main purpose of virtual screening is to identify compounds from a database that are more likely to bind to a particular molecular target, that is, that are biologically active (Rodrigues et al., 2012). The greatest benefits of this technique are its high performance, low cost and simple operation, advantages that determine the preference of its use (Ferreira, Oliva

& Andricopulo, 2011). These strategies have been increasingly explored as they are productive, cost-effective and quick to implement (Ferreira et al., 2015). These characteristics are interesting mainly to reduce the time for the discovery of new drugs. For the success of virtual screening, it is essential to select substances that are more likely to have pharmacological activity. In this scenario, the Northeastern semi-arid appears as an important source of prospecting for new compounds.

The northeastern semi-arid region is a region of vast biodiversity; thus, it is an area that has a high potential for presenting biologically active molecules, especially with regard to endemic vegetation (Gonçalves, 2015). The Brazilian semiarid region is concentrated in the northeast region and corresponds to one of the great Brazilian biomes, the caatinga, which has plants that are potential sources of new drug prototypes (Ministério da Ciência e Tecnologia do Brasil, 2006; Trentin et al., 2011). Specific climatic and environmental conditions, such as the scarcity of water and heat for most of the year, give this environment the ability to develop a high number of unique endemic species, which differs in semiarid biodiversity from other Brazilian regions (Ministério da Ciência e Tecnologia do Brasil, 2006). Brazil has a wide variety of plant species, in which there is a high use of medicinal plants by the population, however, there are few studies on the phytochemical and pharmacological profile of substances in this area (Santana et al., 2020; Albuquerque et al., 2007).

Thus, the object of this study is to identify compounds from the Bahia semiarid with potential inhibitory activity of the MAP38 p38 protein through molecular coupling studies.

2. Materials and Methods

2.1 Protein selection

A search in the 3D structure bank of macromolecules Protein Data Bank (PDB) (Berman et al., 2000) was carried out to select the crystallographic structure of the p38 protein, code PDB 3QUE. As selection filters, the presence of a binding inhibitor and the experimental X-ray diffraction method were considered, with resolution and r value greater than 2.0 Å and 0.2, respectively.

2.2 Preparation of the protein

Through the AutodockTools 1.5.6.rc3 (Sanner, 1999) program, the three-dimensional structure of the molecular target was prepared for docking studies. In processing the protein, all the ligands and solvent molecules were removed. In addition, hydrogen atoms and charges for adapting the chemical structure of the protein were added. The active site was determined based on the position of the cocrystallized inhibitor next to the protein. The grid box was centered on the active site of the molecule using the program AutodockTools 1.5.6.rc3 (Sanner, 1999), and the coordinates of the search space were established in a space of 1 Å. The anchor box presented X, Y and Z coordinates of 2,617, 2,217 and 22,968, respectively, and dimensions of 9 x 10 x 18 Å.

2.3 Selection of Bahia semiarid molecules

A total of 503 molecules from the Bahia semiarid region were obtained through the ZINC database (Irwin & Shoichet, 2005) provided by the State University of Feira de Santana. Of these, only 233 fit the parameters of the rule by Lipinski et al. (Lipinski et al., 2001) and Verber et al. (Veber et. al., 2002) and were therefore selected for molecular coupling studies. The molecules were obtained in the .mol format and were converted to the .pdbqt format using the Autodock Tools 1.5.6.rc3 program (Sanner, 1999).

2.4 Docking and identification of potential anti-inflammatory drugs

Docking was performed using Autodock Vina (Trott & Olson, 2010) in its standard configuration. The preparation of the input files with the extension .pdbqt was performed using the program Autodock Tools 1.5.6.rc3 (Sanner, 1999). The binding energies were analyzed together with the linker-receptor interactions using the Discovery Studio Visualizer program (BIOVIA, 2016).

3. Results and Discussion

The molecules coupled to the active site of the p38 MAP kinase protein were selected according to the rule of Lipinski et al (Lipinski et al., 2001) and Verber et al (Veber et al., 2002). These descriptors predict the oral bioavailability of the molecules, since through the

analysis of the physicochemical characteristics of the substances, it is possible to predict the solubility and permeability of drugs across membranes (Lipinski et al., 2001; Veber et al., 2002). Thus, the substance ZINC 69481892 can present satisfactory oral bioavailability, since it is within the parameters for good permeability between membranes and solubility (Table 1).

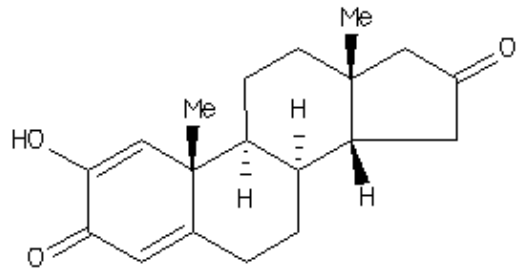
Table 1. Parameters for assessing the probable oral bioavailability of the ZINC molecule 69481892.

Parameters	ZINC 69481892*	Reference Values**
Number of electron donos	1	< 5
Number of electron acceptors	3	< 10
Molecular weight (g.mol^{-1})	300,398	< 500
LogP	2,70	< 5
Number of rotational connections	0	≤ 10
Polar surface area (Å^2)	54	≤ 140

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

Molecular anchoring was performed with a total of 233 molecules from the Bahian semiarid region. Among the tested molecules, the ZINC code molecule 69481892, named (8R,9S,10S,13R,14R)-2-hydroxy-10,13-dimethyl-7,8,9,11,12,14,15,17-octahidro-6H-ciclopenta[a]phenanth (Figure 1), was selected as promising with regard to the inhibition of p38.

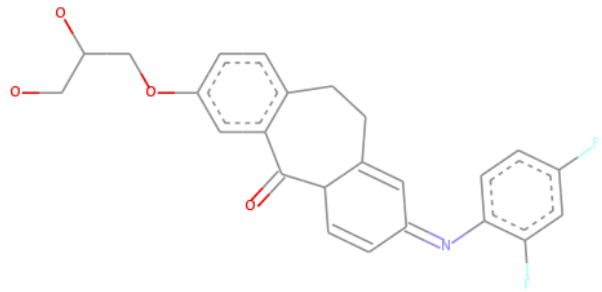
Figure 1. Two-dimensional structure of the ZINC molecule 69481892.



Source: ZINC Database (Irwin & Shoichet, 2005).

The inhibitor used as a prototype to compare the results was skepinone (Figure 2), the cocrystallized inhibitor of the PDB structure of the p38 MAPK protein. The binding energy resulting from the interaction between p38 and skepinone is -11.5 Kcal.mol^{-1}. According to Koeberle et al 2012, skepinone is a potent selective inhibitor of the p38 MAPK protein. In *in vitro* assays, this molecule inhibited the production of inflammatory cytokines regulated by p38, such as TNF-α, interleukin 1β and interleukin-10 (Koeberle et al., 2012).

Figure 2. Two-dimensional structure of the skepinone.



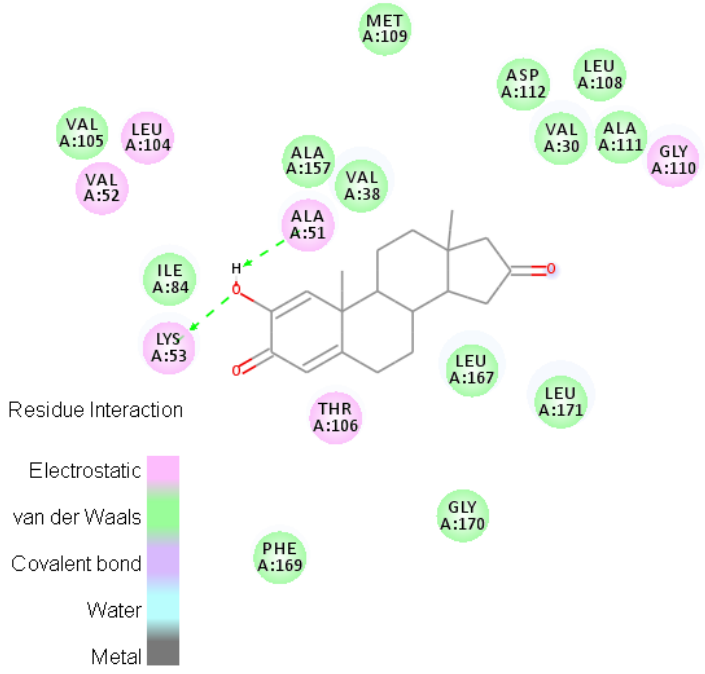
Source: Koeberle et al. (2012).

Among the tested semiarid molecules, the most favorable interaction showed a binding energy of -11.1 Kcal.mol^{-1} and the least favorable 0.5 Kcal.mol^{-1}. In molecular coupling studies, compounds with lower binding energy with the target are those with the greatest affinity in the interaction (Shityakov &Foerster, 2014). The ZINC 69481892 molecule showed a -11.1 Kcal.mol^{-1} binding energy, while the skepitone presented a -11.5 Kcal.mol^{-1}. Thus, it can be said that the compound ZINC 69481892 has an affinity with p38 comparable

to the affinity of the skepione / p38 bond. Thus, it appears that the molecule ZINC 69481892 is a probable inhibitor of p38 MAPK.

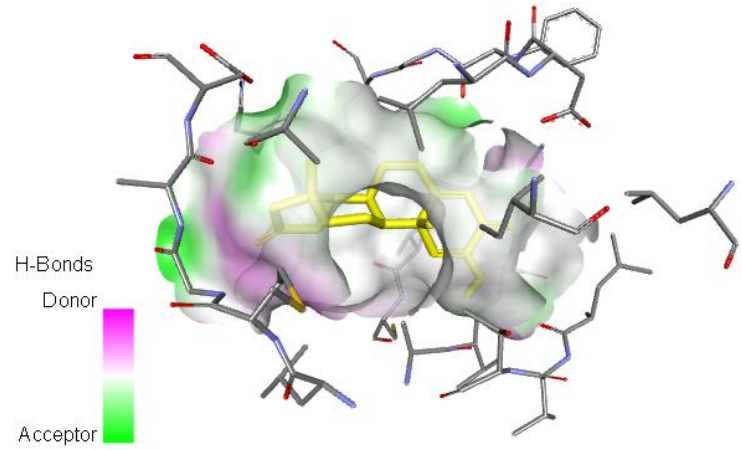
The interactions between the amino acid residues and the ZINC 69481892 ligand are of the Van der Waals type; however, hydrogen bonds also occur (Figure 3). It is possible to verify that the compound in question interacts with residues LYS53, ALA51, THR106, GLY110, VAL52, and LEU104 through electrostatic interactions. The hydrogen acceptor and donor regions can be seen in Figure 4 in the greenish and pink colors, respectively. With the residues VAL105, ILE84, ALA157, VAL38, MET109, ASP112, LEU108, VAL30, ALA111, LEU167, LEU171, GLY170 and PHE169, the interactions are from Van der Waals, and these interactions are crucial for binding at the active site of the protein. Most of the interactions between the ZINC 69481892 molecule and p38 are hydrophobic, with this type of interaction highlighted in Figure 5 in brownish tones.

Figure 3. Amino acid residues from the p38 active site that interact with ZINC 69481892.



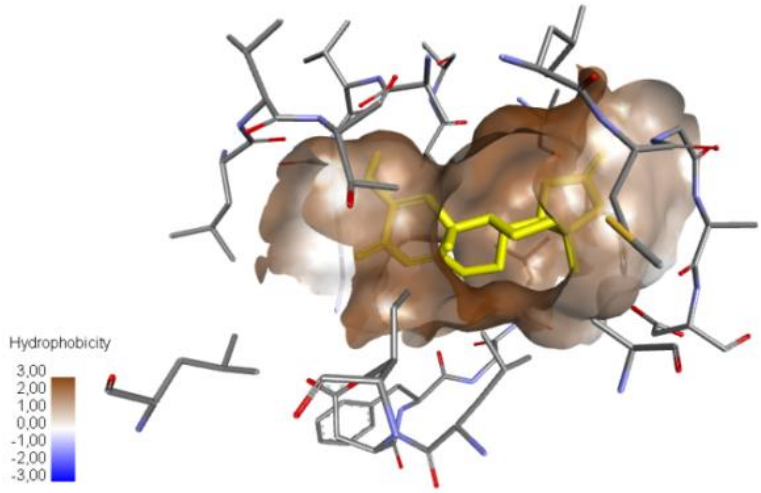
Source: Prepared by the Authors (2019).

Figure 4. Hydrogen bonds between p38 protein and ZINC 69481892.



Source: Prepared by the Authors (2019).

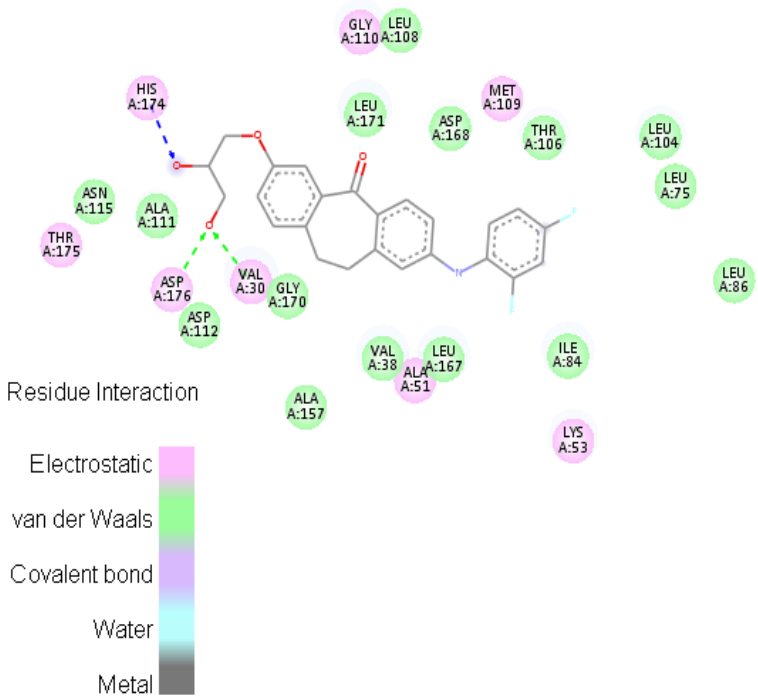
Figure 5. Hydrophobic interactions between p38 protein and ZINC 69481892.



Source: Prepared by the Authors (2019).

Both skepinone and the ZINC 69481892 molecule interact with the target site of the receptor through hydrogen bonds and Van der Waals bonds (Figures 3 and 6). Both molecules exhibit at least one interaction with the amino acid residues ALA51, LYS53, MET109, GLY110, VAL30, ALA111, ASP112, GLY170, VAL38, LEU167, ILE84, LEU104, THR106, LEU171, and LEU108. The similar structure of these two molecules may be one of the reasons for the similar affinity to the active site of the p38 MAPK protein. As seen in Figures 1 and 2, both the ZINC 69481892 molecule and skepinone are present in their structure rich in hydrophobic groups and aromatic rings.

Figure 6. Amino acid residues from the active site of p38 that interact with skepinone.



Source: Prepared by the Authors (2019).

Molecular coupling studies, even though not showing high accuracy, generate significant results since they predict the forms of connection between receptor and ligand, the conformations assumed by the ligand and the probable binding energy of the complex (Ferreira et al., 2015). The evaluation of the inhibitory activity of acetylcholinesterase carried out by Bahadori and collaborators (2016) demonstrated the reliability of the molecular coupling studies, since the *in vitro* and *in silico* results obtained corroborated each other. Similarly, Papaneophytou et al 2015 associated in silico and in vitro studies to propose TNF-α inhibitors, as well as proposing better conformational changes to obtain more potent inhibitors.

It is important to note that in silico studies present hypothetical results that may or may not be confirmed by *in vitro*and/or *in vivo* studies (Zheng et al., 2013). Thus, the molecule (8R, 9S, 10S, 13R, 14R)-2-hydroxy-10,13-dimethyl-7,8,9,11,12,14,15,17-octahidro-6H-ciclopenta [a] phenanth potentially blocks the MAP38 p38 protein; however, for confirmation, it is necessary to carry out experimental investigations. Among the experiments that can be performed are pharmacological activity tests, as well as the evaluation of pharmacokinetic and toxicological parameters (Guido, Andricopulo & Glaucius, 2010).

4. Conclusion

Performing a virtual screening using molecular anchorage studies is very valid in the search for drugs with potential anti-inflammatory activity. Even with hypothetical results, *in silico* techniques help to reduce cost and time, as well as being useful in directing tests that are more specific. An important factor in carrying out this type of study is the availability of protein crystallographic structures in databases, as well as the structures of small molecules of unknown pharmacological potential. This quality information is crucial for obtaining results closer to the real and for the success of docking.

Inhibition of MAPK p38 protein is a promising alternative for the treatment of inflammatory diseases, since this protein is directly associated with the development and maintenance of inflammation. Only the binding molecule ZINC 69481892 from the Bahia semiarid proved to be a potential inhibitor of p38 MAPK, since the molecule ZINC 69481892 showed a binding energy of -11.1 Kcal.mol^{-1}, while the prototype inhibitor presented -11.5 Kcal.mol^{-1}. The use of computational tools to analyze the protein/probable inhibitor complex is of unparalleled importance for understanding the interactions involved in binding. Hydrophobic bonds are essential for binding the compound to the active site of the enzyme. The main interactions involved in the complex are hydrogen bonds and Van der Waals interactions.

With these promising results, further studies on the toxicity of the ZINC 69481892 ligand are necessary when considering this molecule as a possible drug. In addition, *in vitro* and *in vivo* studies are essential to confirm the results obtained.

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