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DOCKING FUNDAMENTALS FOR SIMULATION IN NANOSCIENCE

FUNDAMENTOS DE DOCKING PARA SIMULAÇÃO EM NANOCIÊNCIAS[1]

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ABSTRACT

This work reviews the literature on the molecular docking process, presenting the simulation methodology, the construction parameters and how the results are interpreted. In this context, a study of molecular docking is carried out using the binding protein of the COVID-19 virus with the human cell, called spike, and an antiviral molecule called heparin. As a result, the parameters reached, distances, energies and three-dimensional positioning of the ligand-receptor system are shown. This type of work is currently done in the area of discovering new drugs, or drugs discovered with the aid of the computer. As a final discussion, it concludes the importance of computational knowledge as a way to support various chemical, physical and biological activities in the multidisciplinary field of nanoscience and nanotechnology.

Keywords: physicochemical simulation, drug design, bioinformatics.

RESUMO

Este trabalho faz uma revisão da literatura sobre o processo de docking molecular, apresentando a metodologia de simulação, a parâmetros de construção e como os resultados são interpretados. Neste contexto, um estudo de docking molecular é realizada utilizando a proteína de ligação do vírus COVID-19 com a célula humana, denominada spike, e um antiviral molécula chamada heparina. Como resultado, são apresentados os parâmetros alcançados, distâncias, energias e posicionamento tridimensional do sistema ligante-receptor. Este tipo de trabalho é feito atualmente na área de descoberta novas drogas ou drogas descobertas com a ajuda do computador. Como uma discussão final, conclui a importância de conhecimento computacional como forma de apoiar diversas atividades químicas, físicas e biológicas no campo multidisciplinar da nanociência e nanotecnologia.

Palavras-chave: *simulação físico-química, design de drogas, bioinformática*

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INTRODUCTION

Docking is a class of computer simulation to verify the most adequate molecular modeling to provide a link between a target molecule - usually a protein - and a study molecule, the so-called ligand forming a stable complex (LENGAUER & RAREY, 1996). Molecular Docking techniques aim to predict the best way of binding a ligand to a macromolecule, in this case a protein. Docking consists of the generation of several possible conformations of the ligand in three-dimensional positions of the protein called binding sites (SALMASO & STEFANO, 2018).

Molecular docking is recognized as an effective resource to predict substrate binding with its receptor, some commonly used approaches comprise drug design based on ligand and receptor structure (SINGH *et al.*, 2013). Because the drug discovery and development process is so expensive, molecular docking can reduce the time and resources used in experimental testing.

There are several examples of molecular docking in the literature with biological applications, for example, in (TAVASSOLY *et al.*, 2020), they investigated the compatibility of antiviral drugs in the treatment and blocking of cell entry for COVID-19. According to (SURYWANSHI *et al.*, 2021), they presented a study on the blocking of viral entry into cells, investigating important points of peptides related to the binding of the Spike protein of SARS-CoV-2 with ACE2 (Angiotensin-Converting Enzyme 2).

In the study by (ACHARYA *et al.*, 2019), they performed molecular docking simulations to evaluate some phytochemicals that have actions on proteins belonging to breast cancer (ERα - Estrogen receptor, PR - Progesteron receptor, EGFR - Epidermal growth receptor and mTOR - Mammalian target of Rapamycin), good results were proven for the chosen furanocumarias and the molecular docking tests were validated through *in vitro* tests.

This work presents the fundamentals involved in molecular modeling and simulation called Docking and how its results can qualify theoretical and experimental work in the field of nanoscience.

In December 2019, Coronavirus disease (COVID-19) was first recognized as a disease caused by severe acute respiratory syndrome (SARS-CoV-2), with the main site of infection in Wuhan, China. COVID-19 has been a serious threat to global public health with limited treatment. In this context, several researches are being carried out to find an effective treatment against the disease, one of the fastest alternatives being the reuse of existing medicines.

Several drugs are under evaluation to determine the suitability and treat COVID-19, one of these promising compounds being heparin, which is widely used in thrombotic events associated with disease-induced pathology.

The approach chosen to perform molecular docking as an example in this work was the evaluation of heparin (ligand) with the Spike protein of SARS-CoV-2 (receptor), analyzing the points of interaction between the involved parties.

According to (YUE *et al*., 2021; WEST *et al*., 2020), free circulating heparin has an antiviral effect and can block the entry of the virus into host cells, as the cellular heparan sulfate binds to the SARS protein -CoV-2 and cooperates with the cell surface receptor angiotensin-2 converting enzyme (ACE2) mediating infection.

METHODOLOGY

Docking basically involves a macromolecule (usually a protein, peptides or a stretch of DNA), called a target and a second structure which is called a ligand. The process of predicting the binding between the target and the ligand is done through the three-dimensional location of the sites that can house the volume of the ligand. This location is done by algorithms that identify the empty space and its probability of biological compatibility.

In a first step, the ligand must be treated, analyzing in its structure places of possible torsion (allowing it to adapt to different spatial conformations, making angular movements in its three-dimensional structure), calculating its electronic charges.

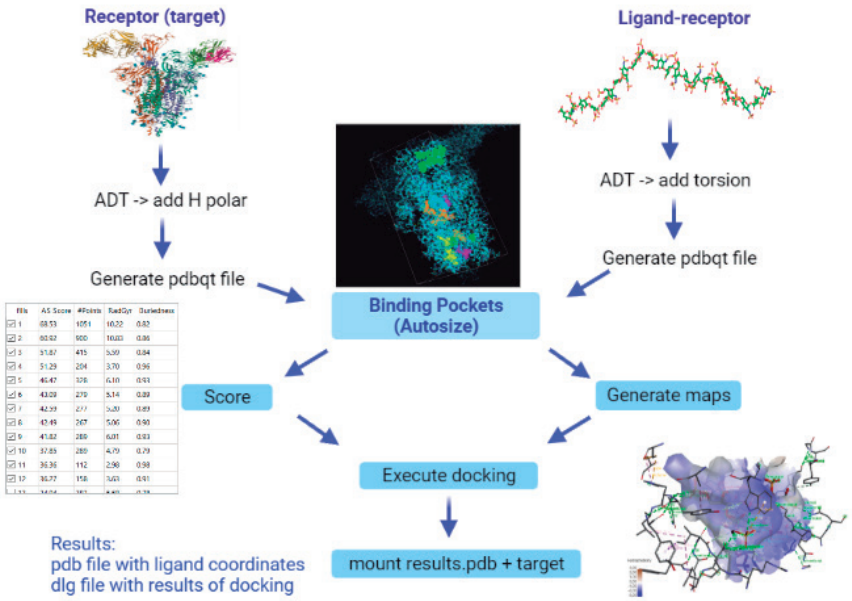
In the next step, the target molecule (receptor) must be treated with the identification of charges, correction of unbound atoms (stabilizing the structure) and solvating the medium with water molecules.

One of the software evaluated is AutoDock Vina (Vina) (EBERHARDT, MARTINS, *et al*., 2021) is one of the Docking programs in the AutoDock Suite, along with AutoDock4 (AD4), AutoDock-GPU, AutoDockFR, and AutoDock- CrankPep.

Vina is arguably among the most used programs, probably due to its ease of use and speed when compared to other plug-in programs in the suite and elsewhere, as well as being open source.

In Figure 1 we present the molecular docking methodology used.

Figure 1 - Flowchart with the molecular docking methodology used.



Source: Author construction.

Research groups around the world have modified and built on Vina's source code, improved the search algorithm (QuickVina), made the interface more user-friendly by allowing modification of punctuation terms through the user interface (Smina), and improved the scoring function for docking carbohydrates (Vina-Carb) and halogen bonds (VinaXB), as well as ranking and scoring (Vinardo).

The docking (binding) process at the molecular level that control the coupling ligands to proteins, at the basic level can be described by the laws of quantum chemistry, where the time evolution of molecular systems are expressed in terms of the wave functions of atoms. In practical calculations, however, approximations are used, where the dynamics of the system is defined using atoms represented by point masses that move in the molecular force fields. Molecular forces are determined by electrostatics and chemical bonding interactions between atoms (STAROSOLSKI and POLAńSKI, 2007).

Docking consists of the positioning of the ligand in relation to the target molecule and the binding score based on some metrics, such as scoring functions and the RMSD (Root-Mean-Square Deviation), which is a measure of the average distance - in Ångstroms - between the atoms of the two ligands (target molecule and binding molecule) and is used to measure the quality of the Docking process.

As a metric, the RMSD between the ligand and the receptor must be less than 2 Ångstroms while the affinity value must be as negative as possible (TROTT and OLSON, 2010).

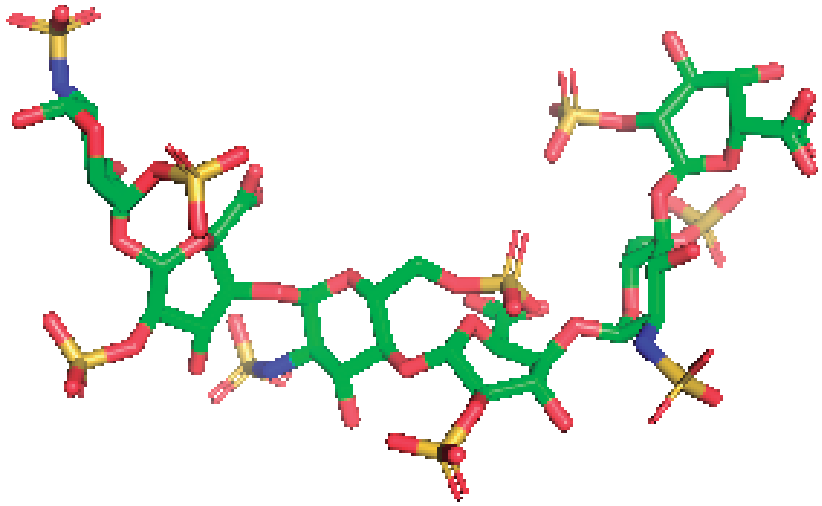
RESULTS AND DISCUSSIONS

In this study, heparin was evaluated, demonstrating that it interacts with the Spike protein of SARS-CoV-2, which is dependent on the cell surface receptor, the angiotensin-converting enzyme 2 (ACE2-angiotensin-converting enzyme 2).

The results of in-silico analysis indicated that heparin interacts with COVID-19 coronavirus Spike protein 6VYB (WALLS *et al.*,2020), confirming studies of TAVASSOLY (2020) carried out with similar objectives to this study. The receiver with PDBid 6VYB was prepared by adding hydrogens to the ADT.

The binder used with PDBid 3IRJ was prepared in the ADT software, adjusting its torsion, but its degree of polymerization was changed from 24 to 6 by the author's choice (Figure 2), to solve some compatibility problems of dimension with the Spike protein 6VYB used (Figure 3). In future works we will use different degrees of polymerization to compare the results.

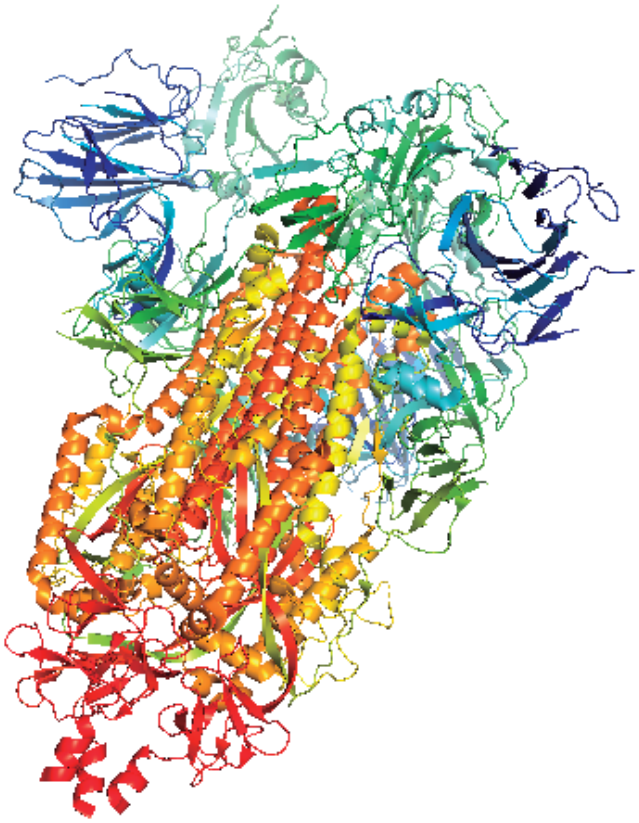
Figure 2 - Heparin (3IRJ edited to six units).



Source: Author

Afterwards, the Autosize Software was used to verify the possible points of affinity between the ligand and the receptor, presenting the following scoring results in Table 1. The first 3 results were presented, but only the first one was used to perform molecular docking. The affinity value for an optimal score (or first place) is the one with the smallest negative value (in kcal/mol) while the RMSD must be less than 2 (Angstroms).

Figure 3 - Coronavirus SARS-CoV-2 Spike Protein (6VYB).



Source: Author.

In this table, mode 1 is the one calculated with the best disposition in the fit of heparin in the site defined by the docksite with the best possibility of better energy interaction and three-dimensional position.

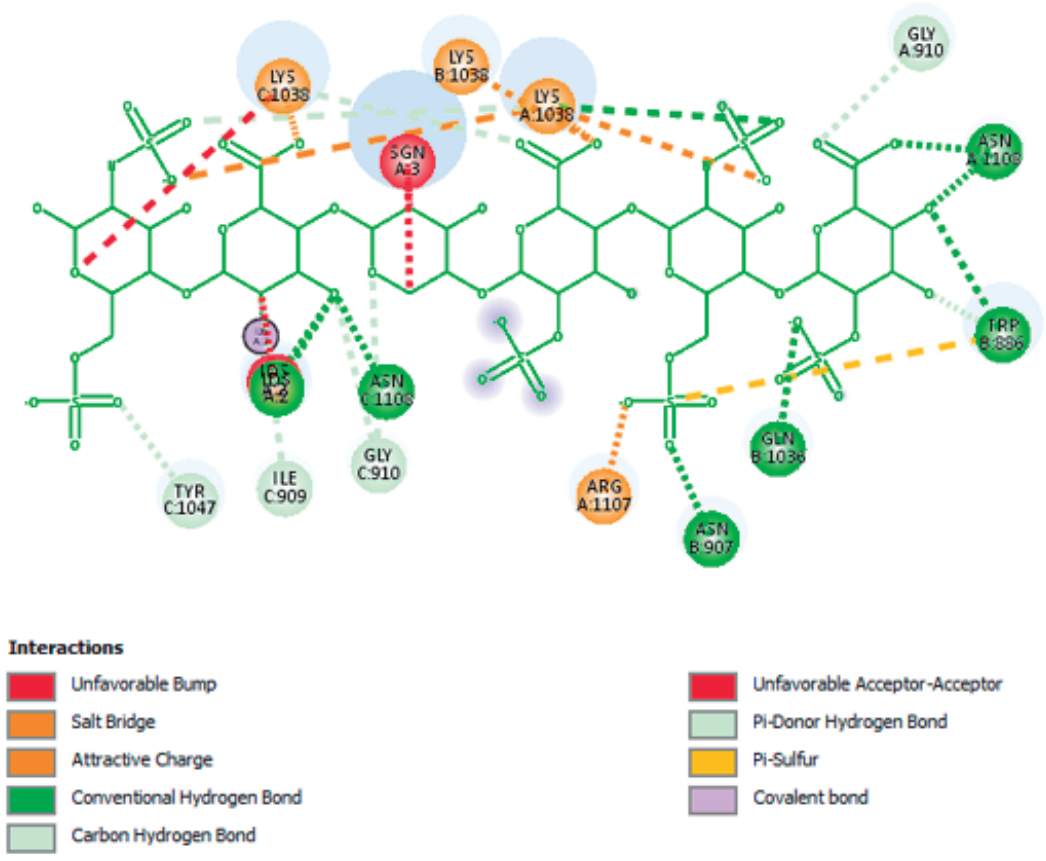
Table 1 - Score Obtained.

mode	Affinity (kcal/mol)	clust. rmsd	ref. rmsd	clust. size	Rmsd stdv	Energy stdv	Best run
1	-23.6	0.0	-1.0	1	NA	NA	047
2	-23.2	5.9	-1.0	1	NA	NA	038
3	-22.6	7.4	-1.0	1	NA	NA	009

Source: Author construction.

Finally, molecular docking was performed, which presented the following results, described in the sequence through the images of the interaction.

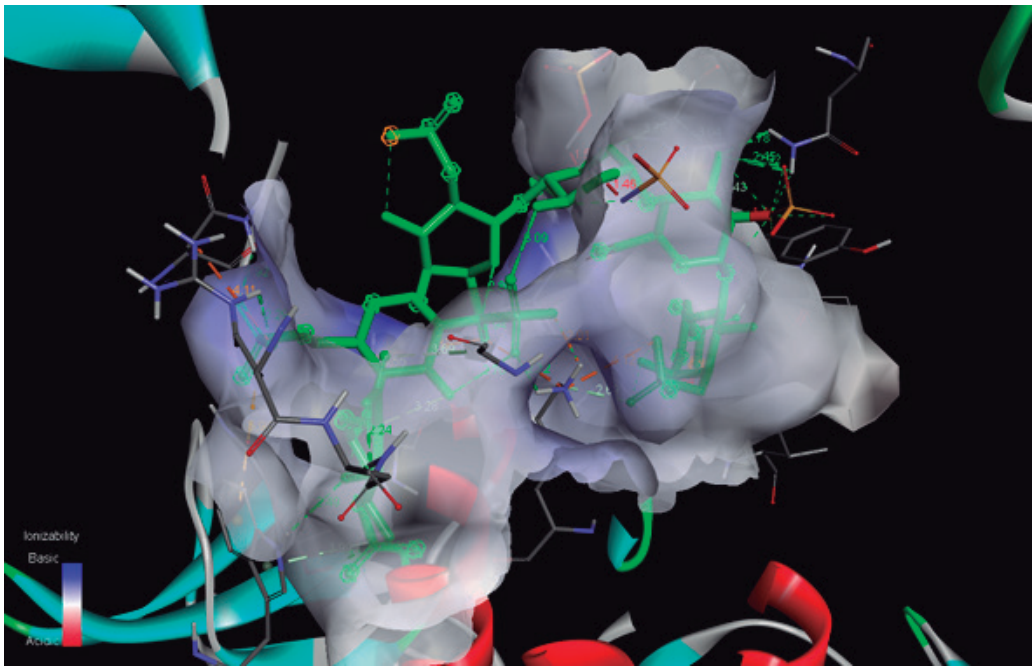
Figure 4 - Two dimensional view of ligand results of docking 6VYB and 3IRJedit



Source: Author

In Figure 4, it is possible to observe the types of bonds that occur in the six units of Heparin edited from 3IRJ and with which fragments of the 6VYB protein. There are three attractive charges between lysines and heparin. Yet another attractive filler with an arginine. Another seven conventional hydrogen bonds are shown.

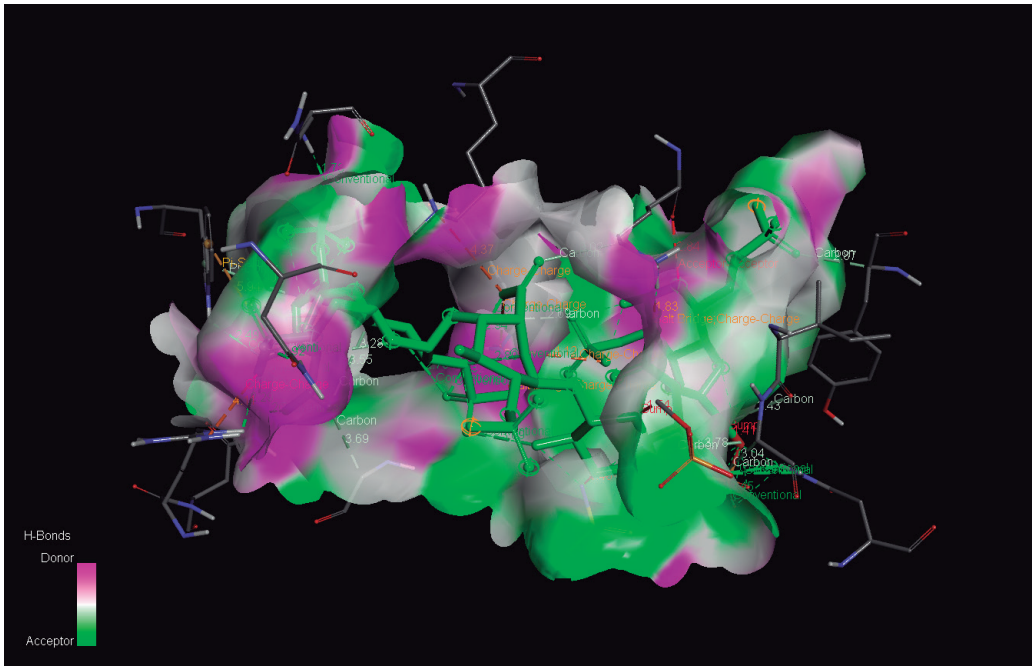
Figure 5 - Three dimensional view of interaction between 6VYB and 3IRJedit



Source: Author

In Figure 5, it is possible to observe in three dimensions the interactions of heparin with the spike protein of the SARS-Cov-2 coronavirus in the position shown in Figure 4, in addition to showing the distances of the bonds and showing an ionizability tending to basic values - seen in blue, as per the diagram.

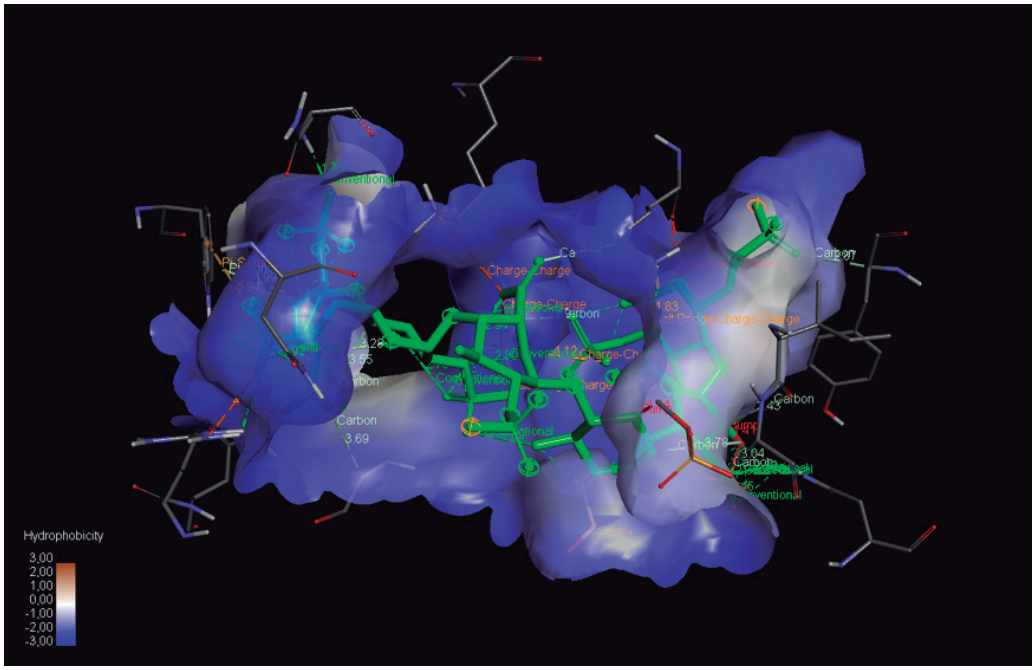
Figure 6 - Three-dimensional diagram showing hydrogen bond interactions, showing the docking area with markings where charge-donating (purple) and charge-accepting (green) interactions occur in 6VYB protein.



Source: Author

In Figure 6, the hydrogen bond interactions are shown, showing the docking area with markings where charge-donating and charge-accepting interactions occur in the 6VYB protein. Distances are also shown and you can see which atoms are interacting (marked with a green circle).

Figure 7 - Hydrophobicity in the docking region



Source: Author

Figure 7 shows the binding region with hydrophobicity values (ranging from -3 to 3), when it is possible to observe the upper part with a greater interaction with hydrogen atoms (blue region) while the lower part is more hydrophobic .

CONCLUSION

The use of computing to study the interactions between different chemical compounds, at the molecular level, with proteins, peptides and stretches of DNA has been a very important strategy in the discovery of new drugs, in the design of new drugs, in the study of the interaction of biomolecules and also in the interaction of nanostructures with complex biological systems.

Using a lot of software with different approaches and after studying the tools, it is possible to achieve different results that serve as a starting point for in vitro and perhaps even in vivo investigations, enabling the optimization of resources to complete the validation of simulation outputs of docking.

The computational use showed an interesting interaction between an antiviral with the spike protein of the SARS-Cov-2 coronavirus, providing a starting point for evaluations with different chemical configurations of heparin, varying in its size, molecular weight and evaluating different configurations to obtain a compound possible to synthesize in the laboratory.

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