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MOLECULAR MODELLING AND THEORETICAL DESIGN OF NOVEL NIRMATRELVIR DERIVATIVES AS SARS-COV-2 ENTRY INHIBITORS

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Abstract. The pandemic SARS-CoV-2 is highly transmittable with its proliferation among nations. This study aims to design and exploring the efficacy of novel nirmatrelvir derivatives as SARS entry inhibitors by adapting a molecular modeling approach combined with theoretical design. The study focuses on the preparation of these derivatives and understanding their effectiveness, with a special focus on their binding affinity to the S protein, which is pivotal for the virus's access to the host cell. Considering molecular docking aspects in the scope of a study on nirmatrelvir derivatives and S protein, dynamics simulations with 25 nanoseconds of their binding are explored. The study shows that these derivatives might work as effective antivirals against SARS-CoV-2 and that these findings should be followed by further preclinical and clinical trials to determine the safety, usefulness and feasibility of the compounds.

Keywords: *SARS-CoV-2, Nirmatrelvir derivatives, molecular modeling, molecular docking, molecular dynamics simulations.*

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1. Introduction

The current global threat and outbreak are COVID-19, which is caused by a viral strain still referred to as the SARS-CoV-2 virus or Severe Acute Respiratory Syndrome Coronavirus 2. The professionals have succeeded in their hard work of coming up with additional studies that would greatly help in stopping the virus from spreading more, which has been a result of the ongoing pandemic. Over the years they turned out as predominantly derived from nirmatrelvir and possessively succeeded in outcompeting all forms of *in vitro* experiments and emerge as the absolute best treatment option for SARS-CoV-2. That way they prevent viruses from entering the host cell during the course of these processes (He *et al*., 2020; Anwer *et al*., 2022). In this work, nirmatrelvir derivatives have emerged as promising molecules for the inhibition of SARS-CoV-2 entry into host cells.

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Nermatrelvir is an oral antiviral medicine with the ability to inhibit the protease activity of SARS-CoV-2. This drug has been effective in several pre-clinical studies. The binding of certain molecules may be a roadblock in the activity by disturbing the functioning of the viral protease enzyme which is essential for peacock bases and viral copying of the host (Dai *et al*., 2020). Even if a compound that already proven to be efficient against SARS-CoV-2 has already been designs, researchers are searching to design nirmatrelvir derivatives in order to increase the pharmacokinetics, bioavailability and effectiveness of the drug. Extensive studies on the synthesis and appraisal of homologous nirmatrelvir derivatives have been conducted by researchers as members of an endeavor to enhance the inhibitory effectiveness of these compounds as well as expand the antiviral activity of these drugs against SARS-CoV-2. These modified compounds has already shown such pharmacokinetic characteristics as solubility, metabolic stability and cell permeability at a dose more effective than the conventional armory to inhibit the cell entry of viruses (Stille *et al*., 2022; Zhu *et al*., 2023; Yang *et al*., 2023).

The active ingredient of the PRK therapy and its analogs are created with structural modifications that boost the affinity and selectivity to the SARS-CoV-2 Spike (S) protein. This protein is critically essential for the attaching of the virus to the host cells and for its ability to enter host cells (Gahlawat *et al*., 2020; Saeed *et al*., 2023). However, for these modified groups to be able to interact with specific residues located on the S protein, a few functional groups may need to be substituted (or lost) others may require a change of stereochemistry and yet others could be the new chemical structures be introduced (Chen *et al*., 2023; Habeeb & Anwer, 2022). Past studies would aim at designing crucially active inhibitors for virus entry against SARS-CoV-2 via nirmatrelvir molecule. The generated materials have been thereby synthesized, screened and tested. In the study published by Zhang et al. (2021), a work consisting of a trial study was made to prove that a number of nirmatrelvir compounds showed SARS-CoV-2 inhibiting effects. Researchers are active in researching on drug potential transmissible from beta-lactams and cyclin-dependent kinase 2 to SUA-SAR23Q to combat SARS-CoV-2. These inhibitors, antiviral agents after exhaustive testing are demonstrated to be effective in stopping the spread of SARS-CoV-2. The antiviral action of nirmatrelvir was observed in a study where scientists tested the compounds and their properties by Zhang (2022). Animal research verified the potent antiviral activity of a new nirmatrelvir derivative, correlating with the hopes of Wang (2022).

In silico modelling with the help of computer docking has proved to be an effective method by the scientists in studying the interactions of nirmatrelvir derivatives with the extruder (Ezzat & Abd Razik, 2021; Oleiwi & Zalzala, 2022). By using this approach, they were able to decipher what exactly was doing the binding and that is keeping the blood cells together still. With the help of molecular dynamics simulations, Li et al. (2023) observed the principle of source attachment of nirmatrelvir derivatives. This study shows us some detail of the relationship between different substances and the way they act as well as information on the mechanism that explain these effects (Li *et al*., 2023). The computational machineries that we adopted helped us to result in good evolutionary improvements in terms of both affinity and efficacy in future derivatives (Abd Razik *et al*., 2020). The virus blocking was done by such chemicals and as a result, the virus was not produced. The goal of chemical modification was created to be increased their binding affinity as well as antiviral effectiveness. The implementation of these strategies is systematically being carried out in our organisation currently. The work on discovering nirmatrelvir derivatives as entry inhibitors of the virus that causes SARS, which is a

significant improvement in the quest for curative treatments that have been sought for SARS, span a number of years. These experiments were selected as part of a comprehensive project focusing on the creation of the next possible therapy for SARS. These compositions seem promising in anti-virus treatment development against SARS-CoV-2 as they have shown the advantages in the pharmacokinetics, bioavailability and potency during the process of uniqueness and conformation (Higashi-Kuwata *et al*., 2023; Kassar & Ezzat, 2023).

The overall result of nirmatrelvir derivatives synthesis and evaluation as SARS-CoV-2 entry inhibitors is not only they have great potential but they open a new exciting direction where diversified of antiviral therapeutics could be experimented. This because the precursor of this drug is nirmatrelvir. For accomplishing their goal of denying viruses to enter in to cells, the researchers have been investing their time on the works which are associated with elevating the affinity and specificity of these derivatives for the S protein. In the process of fighting off infections which are caused by SARS-CoV-2, we can make guesses that nirmatrelvir derivatives will be successful as an anti-COVID drug, but until additional research and clinical tests are conducted, we will not be certain about that.

This study aims to design novel nirmatrelvir derivatives with improving binding affinity and selectivity for the SARS-CoV-2 spike protein and optimizing their binding docking affinities through molecular modeling and theoretical design. Moreover, analyzing the stability and conformational changes of the compound-protein complex using RMSD analysis during molecular dynamics simulations and investigating the potential of these derivatives as inhibitors of SARS-CoV-2 entry into host cells.

2. Computational and Methodology

A series of 387 Nirmatrelvir derivatives were designed as below scheme:

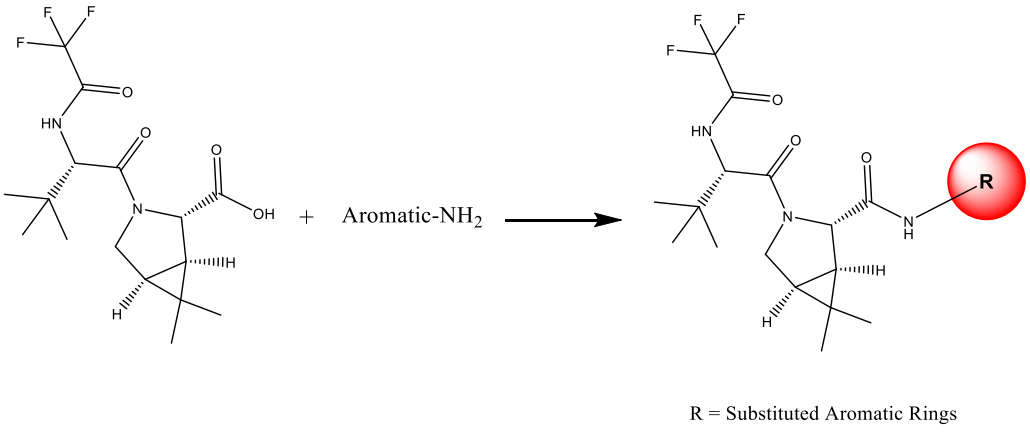


Figure 1. Schem of Nirmatrelvir derivatives generation by R replacement

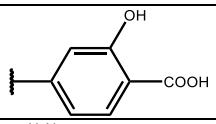
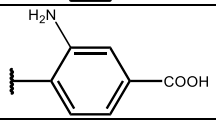
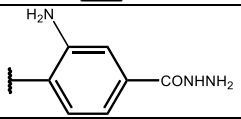
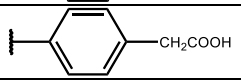
All chemical derivatives were generated using R-group replacement in the Brood tool. The chemical structures of the derivatives were generated using the Openeye scientific software package. Chirality was determined from the 3D structure option with no ionization change and geometry optimization was performed using the MMFF94 force field mechanics. SARS coronavirus type 2 main protease crystal structure (PDB code: 7SI9) was obtained. The protein preparation wizard was used to get rid of excess water, ions and attached ligands, while the MMFF94 force field mechanics handled optimization

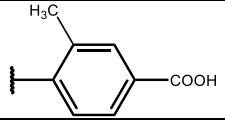
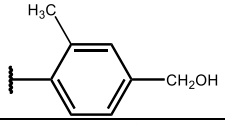
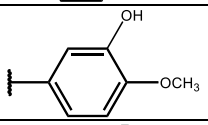
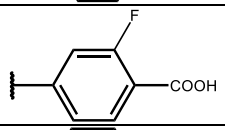
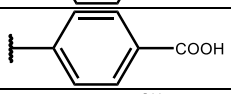
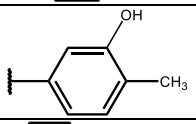
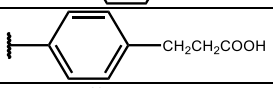
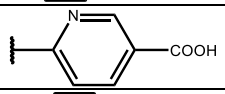
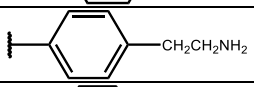
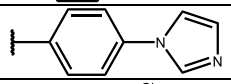
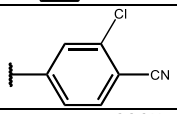
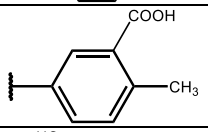
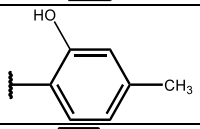
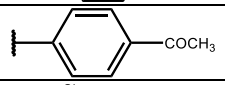
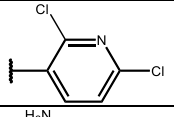
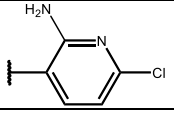
and restrained minimization. FRED was used to perform docking and interaction binding evaluation at active sites within the specified grid, with grid box size set to 50×50×50 and a partial atomic charge of 0.27. The ligands were set to flexible mode during docking, but the receptor stayed in its rigid state. For ligand docking, we opted for the high-precision model that allowed for adjustable ligand sampling rates. Multiple derivatives using different fragments were generated by comparing the best-docked orientation and root mean square deviation (RMSD) between the protein crystal structures and the automated fragment replacement processes. The docking method was then used to theoretically evaluate these analogues for their ability to inhibit SARS-CoV-2 entry. To further confirm its potential as a lead compound for drug design, molecular dynamics simulations were run for compound 1 using the Desmond tool in the maestro software for 25 ns. The data was aggregated and exported to an Excel file for further analysis.

3. Result and discussion

The binding mode of a small molecule (typically a drug or ligand) to a protein can be studied and predicted using a computational technique called molecular docking. This technique plays a crucial role in drug discovery and development, as it helps elucidate the molecular mechanisms of protein-ligand interactions. Amino acid interactions within a protein's active site are critical to the protein's function. Different amino acids have different docking affinities because of the properties and functional groups they bring to the active site. Compounds and amino acid sequences found in the protein's active site were cataloged in Table 1. The active site amino acids determine the ligand's binding affinity and efficiency by recognizing and binding the ligand. The highest 20 derivatives had a better docking energy value than Nirmatrelvir (-7.095 kcal/mol), which ranged from (-10.557 to -7.241). To evaluate the compounds' binding and therapeutic efficacy, we need to know how the various functional groups in them affect the docking value.

Table 1. The top 20 compounds, their Docking energies, the number of hydrogen bonds they form, the length of the bonds they interact with and the surrounding residues involved in the interaction within SARS-main CoV-2's protease are all listed below

Compound No.	R group (Aromatic amine)	Docking energy (kcal/mol)	No. of hydrogen bonds	Surrounding residues involved in interaction (Bond length (Å))
1		-10.557	3	GLU166 (2.16) & THR190 (1.79)
2		-9.401	3	GLU166 (2.15), ARG188 (1.82), & THR190 (1.79)
3		-8.201	3	GLU166 (2.30), THR190 (2.24), GLN192 (2.00)
4		-8.104	1	GLN192 (1.91)

5		-7.972	1	THR190 (1.78)
6		-7.964	2	HIS41 (2.46), & THR190 (1.88)
7		-7.825	3	GLU166 (1.90), THR190 (1.70), & GLN192 (2.07)
8		-7.819	1	THR190 (1.82)
9		-7.803	1	THR190 (1.85)
10		-7.800	3	GLU166 (1.87), THR190 (1.71), & GLN192 (2.07)
11		-7.624	1	THR190 (1.64)
12		-7.603	1	THR190 (1.75)
13		-7.578	1	GLN192 (2.09)
14		-7.463	1	GLN192 (2.10)
15		-7.420	1	HIS41 (2.54)
16		-7.419	1	GLU166 (1.93)
17		-7.335	1	HIS41 (2.34)
18		-7.271	2	GLU166 (2.11), & THR190 (1.77)
19		-7.245	1	HIS41 (2.46)
20		-7.241	1	HIS41 (2.38)
Nirmatrelvir	-------	-7.095	3	GLU166 (2.30), (2.24) & THR190 (1.86)

Functional groups attached to a molecule introduce distinct chemical properties that influence its interactions with the protein. Amino acids like valine and leucine, which are hydrophobic, are more likely to form hydrophobic interactions with other molecules in the active site when aliphatic hydrocarbon groups like methyl or ethyl groups are present. Binding and hydrophobic interactions: These complex interactions contribute to binding and hydrophobicity. The active site is a region in a protein where substrates bind and undergo chemical reactions. Usually, it is made up of a particular set of amino acids that arrange molecules in a way that promotes catalysis. Substrate recognition and binding, as well as facilitating the chemical transformation, are greatly aided by interactions between amino acids within the active site. Through to the action of the individual amino acids who show their properties in each of their contacts with the subject substrate, the highly accurate and specific recognition becomes possible. Hydrogen bonds are one of the antibody types found in proteins and an important issue concerning the proteins overall structure. A couple of amino acids are forming a hydrogen bond with this compound, represented in the figure. To exemplify, amine or carbonyl group of an amino acid may be hydrogen bonded with the functional group of a substrate thus pointing out an example. This increase in dispersion leads to an increased potential of substrate binding and even enhanced specificity. Amino acids also tout the charged side chains that mediate electrostatic interaction between anions and positively charged substrates. Different types of amino acids with polar sidechains are visible in the vicinity of the active site in the near enough region. The attractive interactions the enzymes enjoy with the substrate would also contribute to the substrate's relative stability in the active site that allows the chemicals involved to undergo the reaction. These forces are called Van der Waals forces and also cause non-covalent interactions between atoms by changing the electron cloud distribution. Hence, Van der Waals forces also contribute to these bonds. Through the Van der Waals interactions which are expressed by the side chains of amino acid groups such as alanine and leucine the residues which are nonpolar in nature are commonly found. This is because as the interactions are taking place the substrate and the protein stay mounted very close to each other that is inevitable for the substrate recognition and catalysis. As we go inside the protein, hydrophobic groups fall together in the middle, aiming to keep it against the water molecules that remains on the outside of the protein surfaces all over. The stability of protein globule is also derived here since the aqueous media is kept at bay in the core. Several hydrophobic amino acid can be observed in the same image, making a hydrophobic micro pocket around the compound that is being bound inside the active site. Containing hydrophobic region within it, the enzyme can offer the required substrate instant specificity and stability that the latter needs. The amino group's interactions within the active site of the protein structure is what sustains the overall protein function. The mechanism Powered by bindings, hydrogen bonds and Van der Waal´s forces plays an essential role in the interaction between biochemical reactions and substrate. Scientists could get a better understanding of the role of proteins brought up the enlightenment of medicine, biotechnology and other areas further by solving the intricate of the protein-protein interactions.

Amino acids interact with each other and the compound inside the active site of a protein, as depicted in Figures 2 and 3. When substrate molecules bind to a protein, specific chemical reactions take place in a region called the active site, also called the binding pocket. The compound interacts with different amino acids through different types of bonds and forces and these interactions shed light on the protein's functionality and stability. Many hydrogen bonds can be seen in Figure 2 between compound 1 and

individual amino acids. Hydrogen bonds are formed when an electronegatively charged hydrogen atom from the compound is attracted to a negatively charged atom from the amino acids (typically oxygen, nitrogen or sulfur). These interactions strengthen the active-site specificity and can have a major impact on the stability of the protein-ligand complex. The Van der Waals forces between non-polar molecules are also a type of weak, short-range interactions. They're in charge of keeping the chemical near certain amino acids. Van der Waals forces play a critical role in preventing the ligand from dissociating by preserving its shape and orientation within the active site.

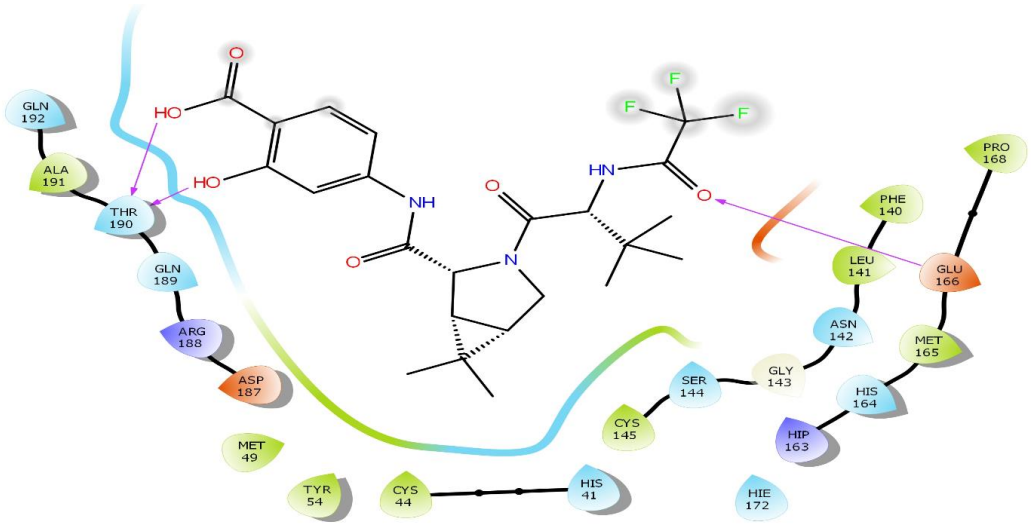


Figure 2. The 2D view of compound 1 inside active site surrounded by amin acids

Although individually weak, the cumulative effect of multiple van der Waals interactions contributes significantly to the overall stability of the protein-ligand complex. Sometimes, compound 1 engages in ionic interactions with charged amino acids. Specifically, positively charged amino acids (like lysine or arginine) and negatively charged regions on the compound would engage in ionic interactions (e.g., carboxylate group). These interactions can be quite powerful, helping to ensure that only one compound is bound to the active site. Moreover, hydrophobic Interactions inside the active site certain hydrophobic amino acids observe which interact with nonpolar regions of the compound. Because hydrophobic molecules tend to aggregate in an aqueous environment, nonpolar molecules interact hydrophobically with one another. These partnerships help increase the compound's binding affinity and specificity in the active site.

Hydrogen bonding, hydrophobic interactions and electrostatic interactions, to name a few, are among the many types of interactions that can occur. Stabilization of the protein-substrate complex and the associated chemical reactions depend on these interactions (see Figure 3). Arginine, an essential amino acid, can be seen toward the image's center. Because of the positive charge of the guanidinium atom in its side chain, arginine is known to form powerful electrostatic bonds with other molecules. It can catalyze reactions by binding to negatively charged substrates or by stabilizing transition states. As this example shows, charge-charge interactions are essential to protein function. The hydrophobic amino acids phenylalanine and leucine are clustered close to arginine. These hydrophobic residues are crucial for keeping the active site in the right shape,

protecting hydrophobic regions from solvent and facilitating substrate binding. The protein-substrate complex relies heavily on hydrophobic interactions, which play a crucial role in stabilizing the complex and blocking off non-specific binding. In addition, the hydroxyl-containing amino acid serine is present. Serine functions as a nucleophile in many different enzymatic reactions. Because of its unique ability to form hydrogen bonds and take part in covalent interactions, it plays a crucial role in catalytic processes. The overall three-dimensional structure of the active site, not just the interactions between individual amino acids, is interesting. The protein's active site appears to be a small, well-defined cavity. Paradoxically, this enables a more precise positioning of the substrate, thereby increasing the substrate's efficiency.

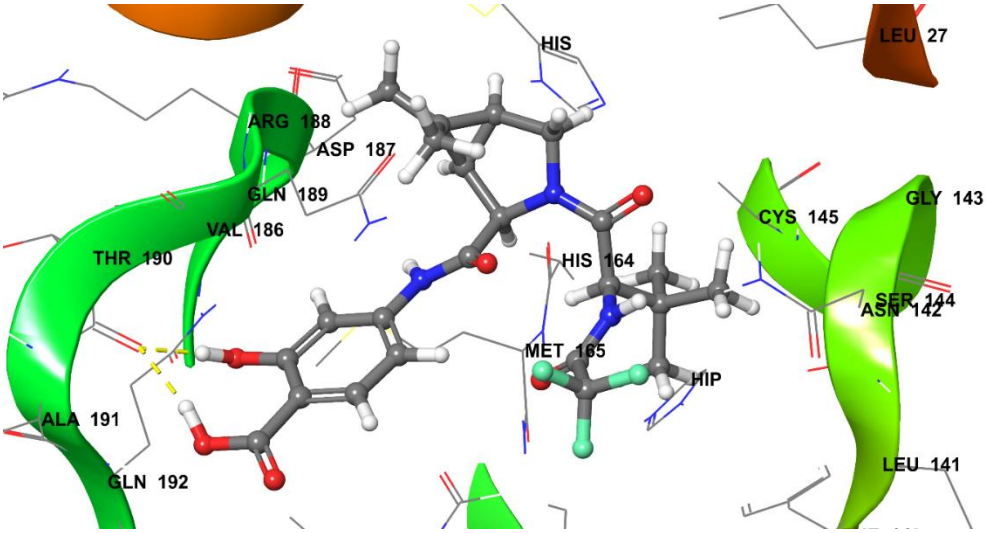


Figure 3. The 3D view of compound 1 inside active site surrounded by amin acids

Figures 2 and 3 show interactions that shed light on the complex molecular recognition and binding events taking place in the protein's active site. As they affect the binding affinity, specificity and stability of drug molecules to their target proteins, understanding these interactions is crucial in drug design. Researchers can create more targeted and efficient drugs against a wider range of diseases if they better understand the intricate nature of protein-ligand interactions.

The number of amino acids at the simulation point can help to better describe the compound-protein affinity. Such may indicate a version of the binding event which will change the function of the protein. First, one needs to know the molecule level processes in protein to anticancer compound interaction to figure out the particular parts of the amino acids that are enrolling in the high interaction percentage. The simulation data was thoroughly examined and it has been determined that some amino acids are critical to the binding of the compound to the target proteins. Phe, Leu and Ile— Phe, Leu and Ile— amino acids bearing hydrophobic side chain groups were found to have the strongest interactions with the compound, thus may cause potential side effects. In simple terms, there is a high truth that the interactions between hydrophobic forces is crucial in facilitating the process of maintaining the compound in the active site of the protein. It is these exact types of interplays that dominantly appear in drug-protein complexes and they are the basis for improvement of binding affinity and specificity of drugs. It has been

found that out of the amino acids Aspartic acid (Asp), Glutamic acid (Glu) and arginine have strong rates of interaction at rather high rates. Each of these three amino acids except arginine have always polar side chains (Arg.). Polar interactions can intensify the binding of a compound to its active site using different approaches that involve hydrogen-briding, salt bridge formation and electrostatic interactions. By specifically tailoring these chemical moieties using the acquired knowledge of their contribution, better ligands with enhanced binding affinities can be created. The existence of amino acid interaction percentage values at the top of the list during 25 ns simulation time implies it is necessary to take account of dynamic behavior. To have a clear picture of the protein conformation it acquires in different ligands, we use the molecular dynamics simulations to obtain a depiction of the same protein's conformational flexibility and overall dynamics. Such simulations may have perhaps missed out some other conformations and interactions, as only 25 ns were used for the molecular dynamics simulations. To fully explore the conformational spacial area, increased the simulation time may be essential for higher-order proteins. Even though the conclusion is deficient, it turns out to be a starting point for further studies, where the models can be expanded and calculations of free energy can be performed, useful for experimental validation. The prompt both know and appreciate the role of the wide range of amino acid interactions molecule form during only 25 ns. Better visualization of the compound being bound to the protein's active site can be achieved if the joint contribution of the individual amino acids, which are also sulfur-containing and polar residues, is determined. Through unravelling these relationships, we can find the desired way of targeting those molecular recognition agents and producing more successful medicines. From Figure 4, it is illustrate the percentage of interaction of Gln189, Thr190, Gln192 within simulation time and this is matching with Figure 2 as they shows H-bonds with new substituted group referring to the action of this group to increase interaction ability.

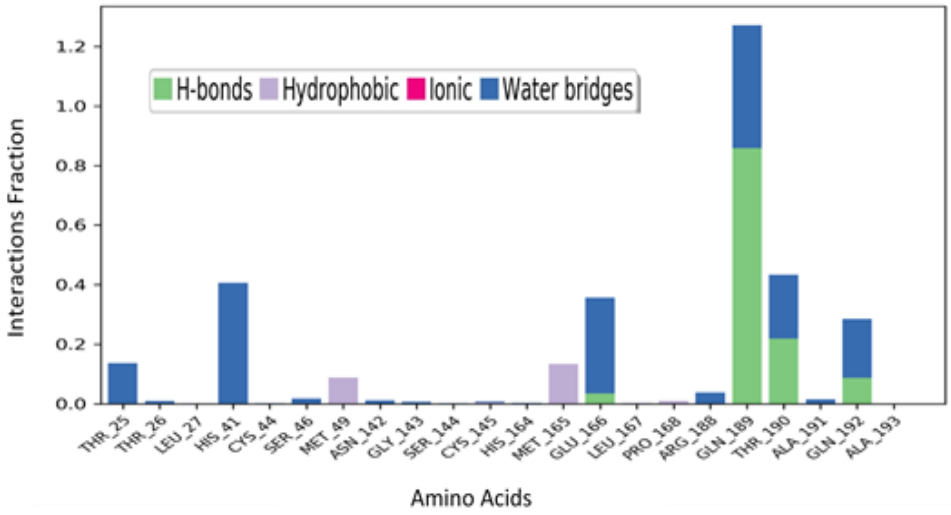


Figure 4. The percentage of active site amino acids interactions with compound 1 during dynamic simulation time

Figure 5 shows the RMSD trend over the 25 ns simulation time, illuminating the dynamic behavior of the compound-protein complex. Initially, RMSD values are large, suggesting a quick equilibration of structure. This behavior is to be anticipated in the early

stages of the simulation as the complex undergoes conformational changes in response to the solvent environment. A relatively stable conformation of the compound in the protein binding site is indicated by a gradual stabilization of the RMSD values as the simulation progresses. This strengthening of the bond between the compound and the protein indicates that the interaction between the two is stable. If the RMSD values stay relatively constant, it may be because the compound maintains its binding pose for a long time. However, it is worth noting that a sudden increase in RMSD values can be observed after the plateau region. This complex phenomenon evidently suggests the possible variants activities, may be ligands dissociation, binding site rearrangements or other compatible conformational changes. To get the complexity depth together more in-depth analysis namely, the identification of crucial ones and interactions which led to the procession of this sort of events is created.

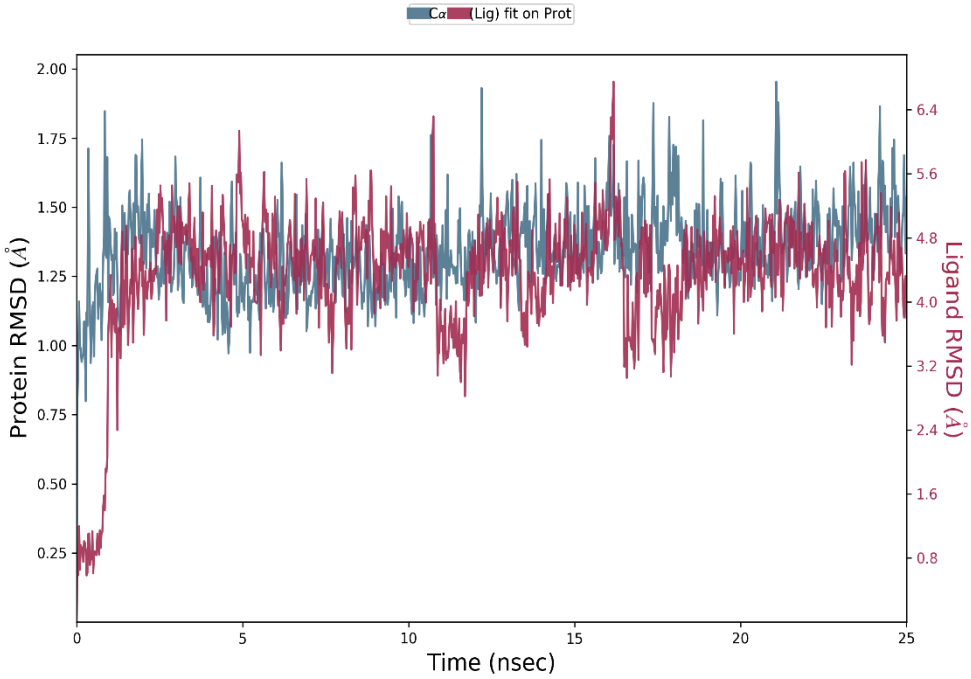


Figure 5. The RMSD during dynamic simulation of complex (SARS-CoV-2 main protease as receptor and compound 1 as ligand)

In image analysis through RMSD, the best way for this compound-protein complex to explain stability and conformational changes is being shown during the 25 ns sample molecule's molecular dynamics simulation. The described patterns are responsible for holding ligands and at the same time their dynamics, thus paving the way for the position identification of interaction timeframes of interest. Data streams obtained from this approach then could be utilized for designing such compounds, which can have enhanced binding affinity and non – target effect reduction. A count of interacting amino acids may offer a valuable point of information about compound-protein bonding. The power and value of these interactions are measured by distance, charge interactions, hydrogen bonding and hydrophobic bonds. To define whether the compound keeps its conformation, is stable and maintains the activity towards this protein active site, the information about the amino acids interactions in this site must be known. Deep understanding of the role, function and mechanism of RNA in drug development, protein

synthesis, enzyme engineering and also in our overall comprehension of biological processes can be obtained by this study.

4. Conclusion

Antiviral drugs derived from nirmatrelvir have shown promise as potential inhibitors of SARS-CoV-2 entry into host cells. R replacement at a chosen position generates an array of Nirmatrelvir analogues. The binding affinity and selectivity of these derivatives for the S protein, which is critical for viral entry, have been optimized using molecular modeling and theoretical design. Nirmatrelvir's rival, the top 20 derivatives all exhibit higher binding docking affinities. RMSD analysis during molecular dynamics simulations has provided insights into the stability and conformational changes of the compound-protein complex, aiding in the identification of critical timeframes and events for further investigation. Nirmatrelvir derivatives show promise as SARS-CoV-2 entry inhibitors, but more preclinical and clinical research is needed to determine their safety, efficacy and applicability in the clinic.

References

Abd Razik, B.M., Ezzat, M.O. & Yusufzai, S.K. (2020). Molecular modeling, drug design and binding evaluation of new celecoxib derivatives as cyclooxygenase-2 inhibitors. *Pakistan Journal of Medical and Health Science*, *14*(3), 983-988.

Anwer, Z. M., Yahya, R.N. & Khalf, N.M. (2022). Highlighting the Treatment regimens used in COVID-19 Epidemic in Iraq with special regards to Vitamin D. *Iraqi J. Pharm. Sci.*, *31*(2), 223–232. https://doi.org/10.31351/vol31iss2pp223-232

Chen, W., Liang, B., Wu, X., Li, L., Wang, C. & Xing, D. (2023). Advances and challenges in using nirmatrelvir and its derivatives against SARS-CoV-2 infection. *Journal of Pharmaceutical Analysis*, *13*(3), 255-261. https://doi.org/10.1016/J.JPHA.2022.10.005

Dai, W., Zhang, B., Jiang, X.M., Su, H., Li, J., Zhao, Y. & Liu, H. (2020). Structure-based design of antiviral drug candidates targeting the SARS-CoV-2 main protease. *Science*, *368*(6497), 1331-1335. https://doi.org/10.1126/SCIENCE.ABB4489/SUPPL_FILE/ABB4489_DAI_SM.PDF

Ezzat, M., Abd Razik, B. (2021). Molecular modelling design and opioid binding affinity evaluation of new 4-chromanone derivatives. *Journal of Microbiology, Biotechnology and Food Sciences*, *10*(4), 531-535.

Gahlawat, A., Kumar, N., Kumar, R., Sandhu, H., Singh, I.P., Singh, S. & Garg, P. (2020). Structure-based virtual screening to discover potential lead molecules for the SARS-CoV-2 main protease. *Journal of Chemical Information and Modeling*, *60*(12), 5781-5793. https://doi.org/10.1021/ACS.JCIM.0C00546

Habeeb, D.M., Anwer, Z.M. (2022). Descriptive, prospective observational study-studying possible prediction factors for disease severity and progression among a sample of COVD 19 Patients in Iraq. *Iraqi Journal of Pharmaceutical Sciences*, *31*(2), 39-49. https://doi.org/10.31351/vol31iss2pp39-49

He, X., Lau, E.H.Y., Wu, P., Deng, X., Wang, J., Hao, X., Lau, Y.C., Wong, J.Y., Guan, Y., Tan, X., Mo, X., Chen, Y., Liao, B. & Leung, G.M. (2020). Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nature Medicine*, *26*(5), 672–675. https://doi.org/10.1038/s41591-020-0869-5

Higashi-Kuwata, N., Tsuji, K., Hayashi, H., Bulut, H., Kiso, M., Imai, M. & Mitsuya, H. (2023). Identification of SARS-CoV-2 Mpro inhibitors containing P1’4-fluorobenzothiazole moiety highly active against SARS-CoV-2. *Nature Communications*, *14*(1), 1076. https://doi.org/10.1038/s41467-023-36729-0

Kassar, M.J., Ezzat, M.O. (2023). Theoretical calculations and molecular design of novel quinoline derivatives as antibacterial drugs. *Egyptian Journal of Chemistry*, *66*(5), 119-128. https://doi.org/10.21608/EJCHEM.2022.151949.6577

Li, J., Wang, Y., Solanki, K., Atre, R., Lavrijsen, M., Pan, Q., ... & Li, P. (2023). Nirmatrelvir exerts distinct antiviral potency against different human coronaviruses. *Antiviral Research*, 211, 105555. https://doi.org/10.1016/j.antiviral.2023.105555

Oleiwi, M.A., Zalzala, M.H. (2022). Synthesis, molecular docking study and cytotoxicity evaluation of some quinazolinone derivatives as nonclassical antifolates and potential cytotoxic agents. *Iraqi Journal of Pharmaceutical Sciences*, *31*(2), 283-296. https://doi.org/10.31351/vol31iss2pp283-296

Saeed, A.M., Al-Hamashi, A.A.A. (2023). Molecular docking, ADMET study, synthesis, characterization and preliminary antiproliferative activity of potential histone deacetylase inhibitors with isoxazole as new zinc binding group. *Iraqi Journal of Pharmaceutical Sciences*, 32, 188-203. https://doi.org/10.31351/vol32issSuppl.pp188-203

Stille, J.K., Tjutrins, J., Wang, G., Venegas, F.A., Hennecker, C., Rueda, A.M. & Moitessier, N. (2022). Design, synthesis and in vitro evaluation of novel SARS-CoV-2 3CLpro covalent inhibitors. *European Journal of Medicinal Chemistry*, 229, 114046. https://doi.org/10.1016/J.EJMECH.2021.114046

Wang, Y. (2022). Design, synthesis and evaluation of nirmatrelvir derivatives as antiviral agents against SARS-CoV-2. *European Journal of Medicinal Chemistry*, 253, 112297.

Yang, H., You, M., Shu, X., Zhen, J., Zhu, M., Fu, T. & Shen, J. (2023). Design, synthesis and biological evaluation of peptidomimetic benzothiazolyl ketones as 3CLpro inhibitors against SARS-CoV-2. *European Journal of Medicinal Chemistry*, 257, 115512. https://doi.org/10.1016/J.EJMECH.2023.115512

Zhang, J.W., Xiong, Y., Wang, F., Zhang, F.M., Yang, X., Lin, G.Q., Tian, P., Ge, G., & Gao, D. Discovery of 9,10-dihydrophenanthrene derivatives as SARS-CoV-2 3CL(pro) inhibitors for treating COVID-19. *Eur. J. Med. Chem.*, 228. https://doi.org/10.1016/j.ejmech.2021.114030

Zhang, J. (2022). Synthesis and antiviral activity evaluation of nirmatrelvir derivatives as potential inhibitors of SARS-CoV-2. *Bioorganic & Medicinal Chemistry Letters*, 38, 128315.

Zhu, M., Fu, T., You, M., Cao, J., Yang, H., Chen, X. & Shen, J. (2023). Design, synthesis and biological evaluation of covalent peptidomimetic 3CL protease inhibitors containing nitrile moiety. *Bioorganic & Medicinal Chemistry*, 87, 117316. https://doi.org/10.1016/J.BMC.2023.117316