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Research Article

Search for SARS-CoV-2 Inhibitors. Is it still needed? Molecular Docking Study of Teicoplanin Derivatives and Vancomycin against SARS-CoV-2 Mpro

Sri Mulyani[1,4*], Nova Dwi Lestari[1], Imam Samodra[2], Fajar Rakhman Wibowo[2], Elfi Susanti VH[1], Tonang Dwi Ardyanto[3]

[1]*Department of Chemistry Education, FTTE, Universitas Sebelas Maret, Surakarta, 57126, Indonesia*
[2]*Department of Chemistry, FMNSe, Universitas Sebelas Maret, Surakarta, 57126, Indonesia*
[3]*Department of Clinical Pathology, FM, Universitas Sebelas Maret, Surakarta, 57126, Indonesia*
[4]*Center for Research and Development of Biotechnology and Biodiversity, Universitas Sebelas Maret, 57126, Indonesia*

[*]*Email: srimulyaniuns@staff.uns.ac.id*

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Abstract
Coronaviruses have been known since 2002 in the case of SARS (Severe Acute Respiratory Syndrome). SARS-CoV-2, the cause of the COVID-19 pandemic, is believed to be an evolution of the SARS-causing coronavirus (SARS-CoV). This evolution shows the complex interaction dynamics between the virus and the host, which have characterized the emergence of new SARS-CoV-2 strain variations until now. Therefore, the search for these antiviral drugs is still critical. MPro is one of the important proteins for the life cycle of pathogenic coronaviruses, so it is an attractive target for developing drugs that inhibit this virus. This study examined the interaction of teicoplanin derivatives and vancomycin as SARS-CoV-2 MPro (6LU7) inhibitors through molecular docking with Autodock Vina. The smallest RMSD value was selected and stored to calculate the energy value. The image of atoms in the ligand and receptor was processed with Autodock Tools, LigPlus, and PyMOL. The study showed that teicoplanin derivatives such as teicoplanin aglycone, teicoplanin-A3-1, and vancomycin had the potential as SARS-CoV-2 Mpro inhibitors. Based on the interaction at the active site and the obtained ΔG values, even the teicoplanin aglycon had a more significant inhibitory potential than other potent inhibitors such as N3.

Keywords: Inhibitors, molecular docking, Mpro COVID-19, 6LU7, teicoplanin

1. INTRODUCTION

Until now, the coronavirus disease (COVID-19), which was declared a global pandemic by the World Health Organization (WHO) in 2020 [1], is still a burden for victims and their families. This disease is caused by SARS-CoV-2, which has the main symptoms of fever, cough, sore throat, runny nose, and difficulty breathing [2]. SARS-CoV-2 is believed to be an evolution of the coronavirus that causes SARS (Severe Acute Respiratory Syndrome), SARS-CoV, and MERS (Middle East Respiratory Syndrome), MERS-CoV. SARS-CoV, which emerged in 2002, MERS-CoV in 2012, and SARS-CoV-2 in 2019, show a relationship [3,4], and a close evolutionary relationship with other coronaviruses. The dynamics of coronavirus evolution influenced by interactions with various host species and the emergence of new variants of SARS-CoV-2, as has happened recently, are very important to understand to prevent future virus outbreaks [4,5]. In addition, the intensive search for antiviral drugs for effective therapy is still critical, and various approaches must be taken, including in silico molecular docking. Docking is a method to predict the preferred orientation of one molecule to a second molecule to bind to each other to form a stable complex [6]. Docking helps predict the strength and type of signal generated. Molecular docking is one of the most frequently used methods in predicting the binding conformation of a small molecule ligand to the appropriate target binding at the atomic level, which supports the behavior of the small molecule in the binding site of the target protein. In drug research,

molecular docking is essential, especially in developing therapies for SARS-CoV-2 infection.

SARS-CoV-2 and SARS-CoV had a sequence similarity of 79%, and their S protein had a similarity of 76.47%. The Mpro protein sequences in SARS-CoV and SARS-CoV-2 are 96% similar [7]. Mpro is the central protease with 306 amino acids and is a key enzyme to mediate the replication and transcription of the coronavirus (CoV) [8], so Mpro has become an attractive target for anti-COVID-19 drugs. A high-resolution crystal structure of Mpro protease and its inhibition are available, facilitating the design of Mpro inhibitors based on specific Mpro structures. Based on this Mpro crystal structure, the search for anti-COVID-19 drugs that can suppress the activity of SARS-CoV-2-Mpro can be carried out using a computational approach [9].

Along with technological developments, the screening process to look for drug candidates is carried out using a computer, commonly known as the virtual screening method or the in-silico method, so that the screening process, which previously required a long time and a reasonably high cost [10], can be streamlined. Molecular modeling or in silico testing has a vital role in the field of medicinal chemistry in order to design, discover, and optimize bioactive compounds in the drug development process. This method provides an evaluation of a drug's potential and toxic risks quickly through molecular computing so that the development of new drugs is more effective and efficient. The in silico test can also reduce the trial-and-error factor because the compound must not be synthesized or available in advance. The search for a virtual protease inhibitor was chosen because it has advantages over other methods; one is the time it takes to speed up the drug discovery process and lower costs [11]. Virtual Screening is a structure-based virtual Screening. The structure-based virtual Screening was chosen because the three-dimensional structure of the target protein, i.e., SARS-CoV-2 Mpro, was available (downloaded from the protein database). With this method, molecular tethering can be carried out to perform Screening based on receptors [12].

A study conducted by Tripathi et al.[13] on the screening and evaluation of drugs approved as significant inhibitors of the SARS-CoV-2 protease showed that teicoplanin is the most effective drug with IC50 ~1.5 μM and is highly compatible with the 3CLPro active site, with a binding energy of -8 kcal/mol. There are hydrogen bonds in the active sites of amino acids, namely His41 and Cys145, hydrophobic bonds in Asp187 and Glu166, and halogen bonds in Leu141 and Ser144 of 3CLPro where the interaction of bonds around and at the active site of amino acids most likely inhibits proton transfer and substrate binding to the active site, leading to impaired protease activity. Azam et al.[14] also showed that teicoplanin interacts hydrophilically and hydrophobically with SARS-CoV-2 MPro through molecular docking studies using AutoDock 4.2. Yu et al.[15] showed that teicoplanin prevents SARS-CoV-2 entry into the cytoplasm of Wuhan-Hu-1 strain cells and the SARS-CoV-2 variant (D614G) with an IC50 of 2.038 μM and 2.116 μM, respectively.

Teicoplanin is a semisynthetic glycopeptide antibiotic with a spectrum of activity similar to vancomycin, with its mechanism of action inhibiting bacterial cell wall synthesis [16]. This antibiotic is for prophylaxis and to treat serious infections caused by Gram-positive bacteria, including *Staphylococcus aureus* and *Enterococcus faecalis* [17]. Teicoplanin has recently shown potential therapeutic efficacy against SARS-CoV-2 in vitro [13,15,18] and in silico molecular docking against SARS-CoV-2 Mpro [14,19]. However, the therapeutic potential of teicoplanin derivatives and glycopeptide antibiotics vancomycin against SARS-CoV-2 has not been much studied. Are teicoplanin derivatives such as teicoplanin aglycon, teicoplanin-A3-1, and vancomycin also potentially active as SARS-CoV-2 Mpro inhibitors? This study aims to explore the therapeutic potential of teicoplanin derivatives and vancomycin as ligands for the main protease enzyme (Mpro) of SARS-CoV-2 through a molecular docking study using Autodock Vina software.

2. RESEARCH METHODS

Ligand structure preparation

The test ligand in the form of the structure of the compound teicoplanin and its relatives was downloaded from PubChem https://pubchem.ncbi.nlm.nih.gov/. PubChem is a collection of chemical substances and biological activities consisting of three parts: substances, compounds, and bioassays. The PubChem CIDs of each of these compounds are in **Table 1**. Each ligand file is downloaded and saved in SDF format, then loaded into Pyrx to minimize its energy and convert the ligand file to .pdbqt format.

Table 1. The pubChem CIDs of ligands used in the molecular docking

CID PubChem	Compounds name	Molecular Formulas
133065662	Teicoplanin	($C_{88}H_{97}C_{l2}N_9O_{33}$)
16154789	Teicoplanin Aglycone	($C_{58}H_{45}C_{l2}N_7O_{18}$)
16152170	Teicoplanin A-3-1	($C_{72}H_{68}C_{l2}N_8O_{28}$)
14969	Vancomycin	($C_{66}H_{75}C_{l2}N_9O_{24}$)

Protein Preparation

The preparation of the Mpro-COVID-19 protein structure with PDB ID: 6LU7 [20] was obtained following the procedure described by Samodra et al.[21]. We accessed the protein through the page https://www.rscb.org/. PDB was a global repository for crystal structures of biological macromolecules. There are two chains in Protein 6LU7, namely A and B. These two chains form homodimers. Based on the analysis, this study used only Chain A to prepare macromolecules. The natural ligand for 6LU7 is compound N3 with PubChem 169452405.

Molecular Docking

In the early stages of the docking process, a validation process was carried out for the target protease by running a docking process for the native N3 inhibitor ligand, and the low RMSD value between docking and conformation indicated a valid performance. In the validation process, grid parameters and docking parameters were used. The pruning is carried out with the grid settings box X: -13.3666524277; Y : 16.149565908; Z : 68.3163713762, which was then further analyzed using the PyrxAutodockVina program thus resulting in an RMSD (Root Mean Square Deviation) < 2 Å. Docking was done by testing four ligand compounds against N3 crystal inhibitors. Docking is done with Autodock Vina, which will produce the best 10 poses for each compound tested. After the docking process is complete, the poses obtained from each studied compound and the best and most acceptable ligand-enzyme interactions are acceptable. The smallest RMSD value is selected and stored to calculate the energy value. The image of atoms in the ligand and receptor was processed with Autodock Tools, LigPlus and PyMOL.

3. RESULTS AND DISCUSSION

This study aimed to analyze the potential of teicoplanin relatives as an alternative drug for COVID-19 through an in-silico molecular docking study that focuses on the interaction of teicoplanin relatives with the SARS-CoV-2 Mpro receptor. The study's results will discuss docking validation and molecular docking of teicoplanin and its relatives.

Docking Validation

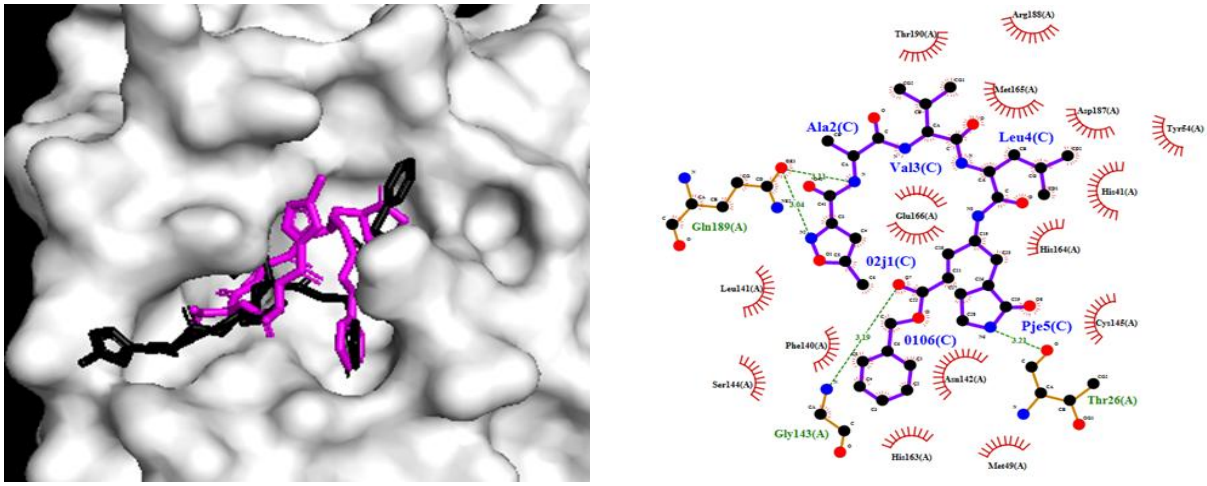
Mpro plays an important role in the coronavirus life cycle by mediating viral replication and transcription, generating attractive drugs for SARS-CoV-2 [20,22]. The active site of Mpro consists of a catalytic dyad consisting of His-41 and Cys 145 residues, which operates the general base catalysis mechanism [9]. The active site of this enzyme contains a site where the inhibitor can bind tightly. The results of the binding validation to the native ligand (N3 inhibitor), the interactions that occur, and the amino acid residues involved around the interactions are shown in **Table 2**.

Based on **Table 2**, the validation test obtained the best Root Mean Square Deviation (RMSD) and Gibbs free energy (ΔG). The RMSD value of the docking results between the N3 Inhibitor and the SARS-CoV-2 Mpro receptor was zero (0), which indicates the stability of the interaction (bond) of the ligand with the receptor and the similarity of the overlapping ligand structure (black ligand and magenta ligand) (**Figure 1**). The smaller the ΔG value, the stronger the bond between the ligand and the receptor, and the more stable the reaction occurs [23]. The validation's Gibs free energy (ΔG) was -7.0 kcal/mol. The interaction obtained by binding the docked N3 ligand (magenta) with the protease Mpro SARS-CoV-2 was hydrogen bonds and hydrophobic interactions.

The hydrogen bonds between the native N3 Inhibitor (magenta ligand) with the Mpro SARS-CoV-2 were at residues Gln189 (3.04 Å), Gly143 (3.19 Å), and Thr26 (3.21 Å) in chain A. In contrast, the hydrophobic interactions were also in chain A, at residues Thr190, Arg188, Met165, Asp187, Tyr54, His41, Glu166, His164, Leu141, Cys145, Phe140, Asn142, Ser144, His163, Met49. These results are similar to the interactions possessed by the original N3 ligand (black colour), which were hydrogen bonds in the A chain found at residues Thr190 (2.85Å), Glu166 (2.83Å), Gln189 (2.93Å), and Phe140 (3.13Å), His163 (2.52 Å), Cys145 (2.98 Å), Gly143 (2.80 Å), and the hydrophobic interactions in the A chain found at residues Leu141, Thr26, Thr24, Asn142, His172, Thr25, His164, His41, Met165, Gln192, Pro168 and Ala191. The N3 inhibitor can be considered valid as a comparison ligand with these results.

Table 2. Results of bonding validation against native ligand (N3 inhibitor)

Ligand Name	RMSD	Gibbs Free Energy (kcal/mol)	Hydrogen Bond	Distance (Å)	Hydrophobic Interactions
Inhibitor N3	0	-7.0	Gln189(A), Gly143(A), Thr26(A)	3.04 3.19 3.21	Thr190(A), Arg188(A), Met165(A), Asp187(A), Tyr54(A), His41(A), Glu166(A), His164(A), Leu141(A), Cys145(A), Phe140(A), Asn142(A), Ser144(A), His163(A), Met49(A)



(A) (B)

Figure 1. (A) The overlapping position between the original N3 ligand (black) and the docked N3 ligand (magenta) to the SARS-CoV-2 Mpro receptor. (B) Interaction of inhibitor N3 with protease Mpro SARS-CoV-2.

Molecular Docking of Teicoplanin and Their Relatives to the SARS-CoV-2 Mpro Receptor

Chemical structure of ligand docking was presented in **Figure 2,** and comparison of the interaction of N3 inhibitor with teicoplanin and relatives against the major protease SARS-CoV-2 in **Table 3** and **Figure 3.**

The results of the molecular docking simulation of the test ligands and N3 inhibitor to the active site of Mpro SARS-CoV-2 showed the stability of the interaction (bond) of the ligand with the receptor and the similarity of the structure of the superimposed ligands. The order of their binding strengths from the largest was as follows: teicoplanin aglycone, N3 inhibitor, teicoplanin A3-1, vancomycin, and teicoplanin. In addition, teicoplanin and its relatives have a conformation close to the original ligand and potentially become an Mpro SARS-CoV-2 protease inhibitor when viewed from the size of these ligands' RMSD and Gibbs-free energy. The results of the energy and interaction differences between the N3 inhibitors and the teicoplanin and its relatives can be seen in **Table 3**. The docking results of the test compounds were analyzed and compared with the N3 inhibitors regarding the binding mode of these compounds.

The top-ranked conformation produced was selected, which has a ΔGbind value with RMSD 0 because it was the best conformation from the completion of each ligand. In addition, the RMSD value is said to be good if it is <2 Å. The greater the deviation, the greater the error in predicting the ligand's interaction with the protein [24]. According to Voet & Voet [25], the complex interaction of protein ligands is characterized by a low binding affinity/Gibbs free energy (ΔG) value and a large amount of hydrogen. A good hydrogen bond distance is generally between 2.5 and 3.5 Å. In the visualization of the results of docking the teicoplanin compound and its relatives, it was found that hydrogen bonds and hydrophobic interactions occurred at several residues (**Table 3**).

The teicoplanin aglycone compound had hydrogen bonds, similar to the N3 inhibitor at two residues, Gln189 at 2.77 Å and Thr26 at 2.96Å. In addition, the same hydrophobic interactions were found in Leu141, Cys145, and Met49 (marked in bold in **Table 3**). Teicoplanin A3-1 had hydrogen bonds, similar to the N3 inhibitor at residue Gln189 (2.96Å) and vancomycin at residue Gly143 (2.99Å). In addition, Teicoplanin A3-1 had the same hydrophobic interactions as the N3 inhibitor, which were found at residues Thr190, Met165, Asn142, and Phe140, and vancomycin at Phe140, Asn142, and Leu141. Teicoplanin also had the same hydrophobic interactions as the N3 inhibitor, found at Leu141, Met165, His164, and Phe140 residues. The residues marked in bold in **Table 3** indicate residues in teicoplanin ligands and their relatives with hydrogen bonds or hydrophobic interactions that are the same as residues in the N3 inhibitor.

The results of the interaction between the test ligands (teicoplanin and their relatives) against the Mpro SARS-CoV-2 receptor showed that teicoplanin and their relatives had similar amino acid residues to N3 inhibitors as the comparison compounds. Judging from the results of the hydrogen bonding and its bond distances in the native ligand, comparison ligand, and the test ligand the requirements have been met.

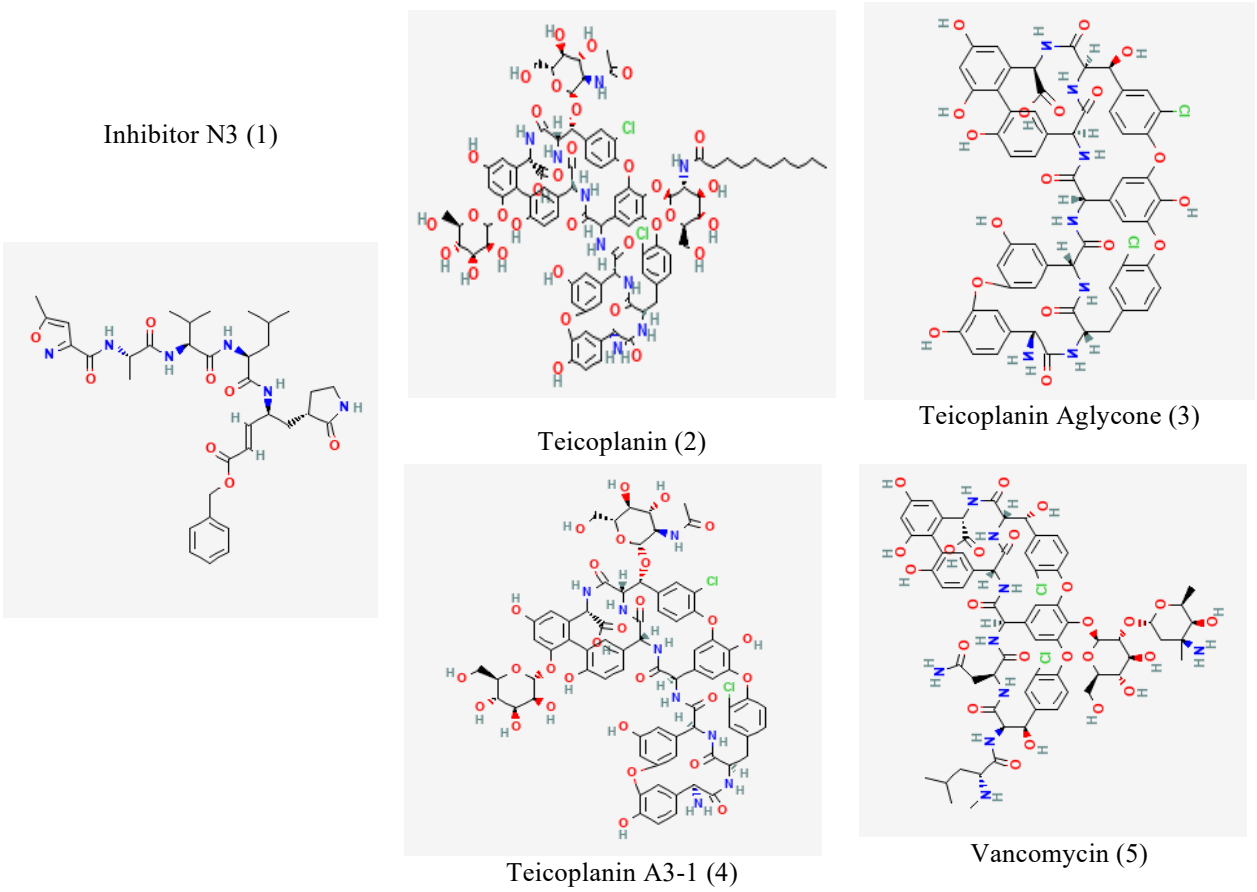
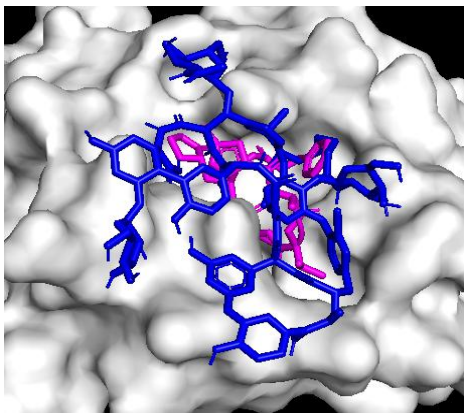


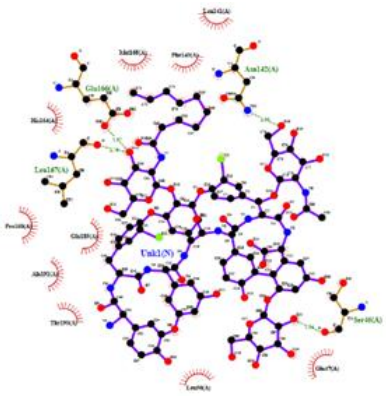
Figure 2. Chemical structure of N3 inhibitor and teicoplanin compounds and their relatives

Table 3. Comparison of the interaction of N3 inhibitors with teicoplanin and relatives against the major protease SARS-CoV-2

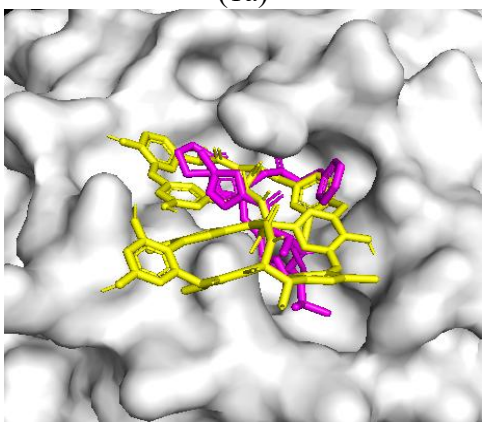
No	Ligand Name	RMSD	Gibbs Free Energy (kcal/mol)	Hydrogen Bond	Distance (Å)	Hydrophobic Interactions
1	N3 inhibitor	0	-7.0	**Gln189(A), Gly143(A), Thr26(A)**	3.04 3.19 3.21	Thr190(A), Arg188(A), Met165(A), Asp187(A), Tyr54(A), His41(A), Glu166(A), His164(A), Leu141(A), Cys145(A), Phe140(A), Asn142(A), Ser144(A), His163(A), Met49(A)
2	Teicoplanin	0	-6.1	Glu166(A), Asn142(A), Leu167(A), Ser46(A),	2.97 3.00 2.67 2.84	**Leu141(A), Met165(A), His164(A)**, Pro168(A), Gln189(A), Ala191(A), Thr190(A), Leu50(A), Glu47(A), **Phe140(A)**
3	Teicoplanin Aglycone	0	-8.7	**Gln189(A)**, Asn142(A), Glu166(A), **Thr26(A)**	2.77 3.23 3.23 2.96	Pro168(A), Ser46(A), **Leu141(A), Cys145(A), Met49(A)**, Gly143(A), Leu27(A), Thr25(A), Thr24(A)
4	Teicoplanin A3-1	0	-6.9	**Gln189(A)**, Arg188(A), His163(A), Ser144(A), Leu141(A)	2.96 3.19 3.15 3.04 2.93	Leu50(A**), Thr190(A), Met165(A), Asn142(A), Phe140(A**)
5	Vancomycin	0	-6.3	Glu166(A), **Gly143(A)**, Leu167(A) Ser46(A)	2.99 2.99 3.02 3.15	Ser139(A), Gly170(A), **Phe140(A), Asn142(A), Leu141(A)**, Pro168(A), Ala191(A), Gln189(A), Leu50(A)



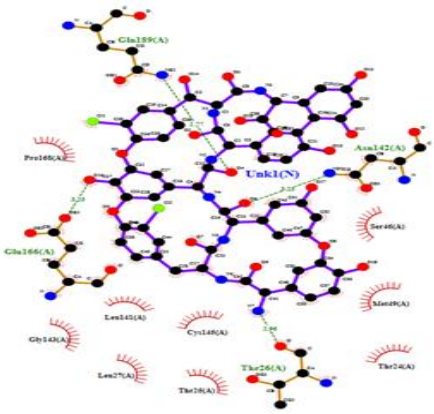
(1a)



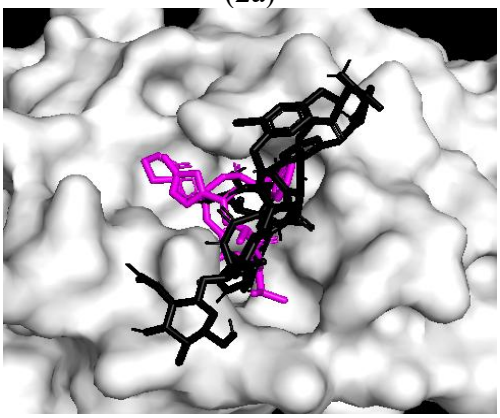
(1b)



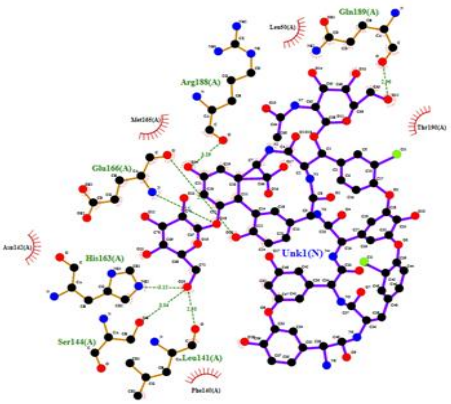
(2a)



(2b)



(3a)



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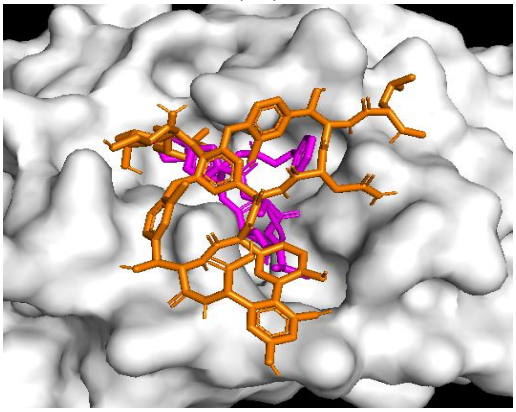
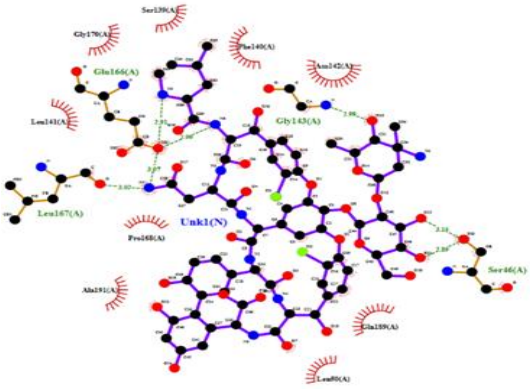


(4a)



(4b)

Figure 3. Comparison of the interaction of N3 inhibitor (magenta) with test ligands (1) Teicoplanin (blue), (2) Teicoplanin aglycone (yellow), (3) Teicoplanin A3-1 (black), and (4) Vancomycin (orange) against the SARS-CoV-2 Mpro receptor. (a) 3D of the overlapping position and (b) 2 D interaction diagrams

Based on the data above, the docked native ligand, test ligand (teicoplanin and its relatives), and reference ligand (N3) interact with Mpro SARS-CoV-2. The engagement of amino acid residues between the ligand and the receptor substantiates this interaction. The nature of the interactions formed includes hydrogen bonds and hydrophobic interactions. These interactions are critical in determining the bond's strength between the drug and the receptor. Typically, the bond formed between the drug and the receptor is reversible, allowing the drug to dissociate from the receptor promptly if the concentration of the drug in the cellular fluid diminishes. The interactions that characterize the drug's and the receptor's relationship must be relatively weak yet sufficiently robust to compete with alternative interactions [26]. Consequently, most docking studies do not identify covalent bonds, as these are irreversible despite their potential to generate strong affinities and stable interactions.

Based on the interaction comparison, the test compound and the reference compound have similar hydrogen bonds, except for the teicoplanin compound. The more hydrogen interactions between the ligand and the receptor amino acid residues, the better the ligand-receptor interaction is predicted. If the test compound binds to the same amino acid residue as the N3 inhibitor, it may have the same activity as the N3 inhibitor. Sardanelli et al.[27] stated that the active site of Mpro SARS-CoV-2 is located at the His41 and Cys145 residues. These residues bind to the natural ligand found in SARS-CoV-2 Mpro, where it is known that the ligand is inhibitory. Based on this information, the N3 inhibitor compound and teicoplanin aglycone bind to the same active site, namely Cys145. Dai et al. (2020) also stated that the cavity of SARS-CoV-2 Mpro active site is located at Cys 145, His41, Met45, Tyr54, Phe140, His163, Met165, Asp166, Phe185, Gly143, and Glu186, which can prevent SARS-CoV-2. Meanwhile, Azam et.al.[28] have proven that teicoplanin interacts by forming hydrogen bonds with SARS-CoV-2 Mpro at the amino acid residues Thr26, His41, Asn142, Ser144, Glu166 and Gln189. From these results, it can be seen that the most important residue that influences the interaction is the Cys145 residue because both the N3 inhibitor compound in the original ligand and the teicoplanin aglycone compound bind to the active site of Cys145.

This description showed that the interactions that occur in the binding of teicoplanin compounds and their relatives to the SARS-CoV-2 Mpro receptor are almost the same as the interactions that occur in binding N3 inhibitors, which are mostly hydrogen bonds and hydrophobic interactions so that teicoplanin compounds and their relatives can inhibit SARS-CoV-2 Mpro activity by inhibiting the replication of the virus.

Figure 3 shows how the ligand interacts in the space of the Mpro receptor macromolecule. Ligands with the appropriate molecular size can fill many parts of the active site of the protein macromolecule and interact better[29]. Many factors affect the affinity between the test ligand and the SARS-CoV-2 Mpro. The final value of the scoring function ΔG_{bind} from the AutodockVina system is ΔG_{gauss}, and $\Delta G_{repulsion}$, ΔG_{Hbond}, $\Delta G_{hydrophobic}$, and ΔG_{tors} [30]. The binding energy ((ΔG_{bind})) in the form of hydrogen bonds (ΔG_{Hbond}) significantly affects the interaction in the docking of molecules. Hydrogen bonds are an electrostatic interaction between a weakly acidic donor group and an atom of a receptor that forms a free electron pair to maintain protein stability.

4. CONCLUSIONS

The interaction of teicoplanin and its relatives with SARS-CoV-2 Mpro is almost similar to the interaction of N3 inhibitors with SARS-CoV-2 Mpro receptors. One of the best test compounds that has the potential to be a candidate for SARS-CoV-2 protease inhibitors, namely teicoplanin aglycone, which interacts best with the SARS-CoV-2 Mpro receptor on the active side of the receptor with a Gibbs free energy value (ΔG) better or smaller than the N3 Inhibitor. These results indicate that Teicoplanin aglycone has the potential to be an alternative drug to treat COVID-19 through inhibition of the SARS-CoV-2 Mpro receptor and requires further evidence through in vitro testing.

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