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Original Article

In Silico Design of New Monoglyceride Vanillate as Anti-Methicillin Resistant *Staphylococcus aureus* with Molecular Docking and Molecular Dynamic Approach

Febri Odel Nitbani[a], Putra Jiwamurwa Pama Tjitda[b*], Pius Dore Ola[a], Mayavira Veronica Hahuly[c]

[a]*Depatment of Chemistry, Faculty of Science and Engineering, University of Nusa Cendana, Kupang, Indonesia,* [b]*Department of Pharmacy, Health Polytechnic of Kupang, Kupang, Indonesia,* [c]*Agrotechnology Study Program, Faculty of Agriculture, University of Nusa Cendana, Indonesia.*

Abstract

New medicines for *Staphylococcus aureus* strain resistance are being developed using an *in silico* approach, modifying monoglyceride with vanillic acid to balance hydrophilic and hydrophobic properties. Furthermore, the structure of the design compounds (M1-M9) was optimized using the AM1 method and docked to *Staphylococcus aureus* penicillin-binding protein 2a (SauPBP2a) (PDB ID: 1mwt) as a receptor. The binding energy and molecular interaction were evaluated and compared to Penicillin G as a standard. The best dock score of a designed compound is used to evaluate its complex stability using molecular dynamics simulation. The docking results revealed that the monoglyceride containing vanillic acid improved the interaction with the receptor. Increasing the number of methylene chains (-CH_2-) in the acyl group on the saturated product reduced binding energy. The outcomes also demonstrated that monorisinoleylvanillate (Compound M9), an unsaturated monoglycerylvanillate, exhibited the best binding energy of -7.1 kcal/mol. Ser462 and Asn464 are two important amino acids for catalytic domains that interact well with the product, having binding distances of 2.64 and 2.01, respectively. The M9 compound was the most stable SauPBP2a complex among design compounds, as confirmed by molecular dynamics simulation using CABS-Flex and the iMODS server. This compound will be synthesized using vanillic acid and methyl ricinoleate, and its activity against MRSA will be validated through in vitro assays in subsequent research.

Keywords: Drug discovery, Monoglycerylvanillate, MRSA, SauPBP2a, Molecular Docking, Molecular dynamics.

Corresponding Author: Putra Jiwamurwa Pama Tjitda, Department of Pharmacy, Health Polytechnic of Kupang, Kupang, Indonesia. E-mail: putrachemist_jc@yahoo.com

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1. Introduction

One of the most challenging problems in 21st-century medicine is the resistance of several bacterial pathogens to known antibiotics [1]. The multidrug-resistant bacteria from *Staphylococcus aureus* Strain is Methicillin-Resistant *Staphylococcus aureus* (MRSA).

Infectious diseases caused by MRSA have shown an increase in morbidity and mortality rates [2]. Its persistence and quick invasive infection has become a severe threat to humanity. MRSA has shown serious resistance to beta-lactam antibiotics and has also continued to develop resistance mechanisms to daptomycin and macrolides [3]. Consequently, the number and types of antibiotics to treat infectious diseases caused by MRSA are minimal. This indicates an urgent need to discover and develop new types of antibiotics as anti-MRSA agents.

The search for novel antibiotics continues today, and antibiotic compounds have also been developed from lipid compounds. Monoglyceride compounds from vegetable oils are well-known as antimicrobial lipids [4]. Monolaurin, monocaprin, and monomyristin are monoglycerides of medium-chain fatty acids, and they have great potential as broad-spectrum antimicrobial lipids that can inhibit the growth of Gram-positive bacteria, such as *S. aureus* and MRSA [5]. These monoglycerides have less balanced lipophilic and hydrophilic groups. Hence, they are ineffective in penetrating the cell membrane when transported in the body and require the addition of polar groups, such as phenolic compounds [6]. Therefore, monoglycerides as antimicrobial lipid agents must be combined with other natural ingredients rich in hydrophilic groups, such as vanillin [6].

Combining one material with others is based on a rational chemical reaction. Based on the chemical structure, one of the vanillin derivatives, namely vanillic acid with a carboxylic group (-COOH), can be combined with α-monoglycerides, which have a hydroxyl group (-OH) through an esterification reaction using an acid catalyst or lipase enzyme. This combination produces a phenolic lipid compound, monoglycerylvanillate, which has the potential as an antimicrobial agent and has balanced lipophilic and hydrophilic groups. Rationally, the combination of vanillic acid and alpha-monoacylglyceride was accomplished through laboratory synthesis through an esterification reaction.

Antibiotic discovery through classical synthesis methods often requires a long period with higher costs, but this does not guarantee the effectiveness of their biological activities. Pure and high-yield antibiotic compounds are sometimes successfully synthesized, but the antibiotic activity is low or vice versa. Consequently, the approach to discovering compounds with potential as antibiotics in silico is a promising breakthrough. Molecular docking is an in silico alternative method appropriate for optimizing compounds with potential as anti-MRSA agents based on the drug design structural principles.

This research aims to discover new inhibitors of *S. aureus* penicillin-binding protein 2a (SauPBP2a) by optimizing drug discovery. Based on many studies, it appears that resistance has been associated with a reduction in a drug's activity and effectiveness. In addition, many drugs on the market are proven to be toxic. This project focuses on developing new Monoglyceride Vanillate derivatives in silico using several saturated and unsaturated fatty acids. Molecular docking studies and molecular dynamic simulations confirmed the activity. Penicillin Binding

Protein 2a (PBP2a) is a transpeptidase enzyme that plays a role in the biosynthesis of peptide crosslinking [7]. PBP2a inhibition often triggers cell wall weakness, which can lead to cell death [8]. Therefore, the enzyme becomes a potential target in developing novel drugs for anti-MRSA candidates. This compound is further suggested for laboratory biological activity studies in vitro.

2. Materials and Methods

2.1. Materials

Several software applications are needed to execute this study. These include ChemDraw Professional 16 for creating the compounds, Chem 3D 16 for converting 2D to 3D structures, AutoDock Vina, and AutoDock Tools 1.5.6 for performing molecular docking. In addition, visualization of chemical interactions using Discovery Studio Client 2021.

2.2. Molecular Docking of Monoglyceride Vanillate Derivatives

In silico studies of Monoglyceride Vanillate derivatives on SauPBP2a were studied with molecular docking using Auto Dock Vina and MGL tools [9]. The three-dimensional structure of SauPBP2a (PDB ID: 1mwt) was taken from the RSCB website with a resolution of 2.45 Å. Furthermore, protein preparation was carried out by separating Penicillin G as a native ligand and adding polar hydrogen and Kollman charge. Protocol docking validation was done by redocking the native ligand on SauPBP2a with X, Y, and Z box sizes of 20 × 20 × 20 Å spacing. The docking protocol was accepted when the RMSD value obtained was < 2Å [10].

The 2D structures of the design compounds were sketched using Chemdraw Professional 16 and then converted to 3D structures using Chem 3D. All design compound geometry optimization was carried out using Gaussian 09 software. The Austin Model 1 (AM1) method is applied to geometry optimization, followed by storage in pdb format. Each of them was docked against SauPBP2a using a validated docking protocol. Subsequently, their chemical interaction binding energy value was evaluated and studied to determine candidate compounds for anti-MRSA.

2.3. Molecular Dynamic

The lowest binding energy of compounds obtained through molecular docking is studied to determine their stability when bound to their complex ligands and proteins. Molecular dynamics servers, such as the CABS Flex 2.0 server (http://biocomp.chem.uw.edu.pl/CABSflex2/index) and iMODS (https://imods.iqfr.csic.es/), are used to evaluate complex stability. An RMSF plot illustrates the stability of interactions between ligand and acid amino residue. CABS-Flex server was used to generate the RMSF plot. Simulation is carried out in the default setting. Additionally, the iMODS server also determines protein stability. Deformability, B-graph, eigenvalues, and covariance graph demonstrate the stability.

3. Results and Discussion

3.1. Molecular Docking

Activity evaluation of the Monoglyceride Vanillate derivatives as anti-methicillin-resistant *S. aureus* was carried out against the

SauPBP2a receptor using molecular docking. In the first stage, the docking protocol was validated by the native ligand (penicillin G) re-docking against SauPBP2a. **Figure 1** shows a superimposition of a native ligand over a re-docked variant. The validation results of the RMSD value was 1.148.

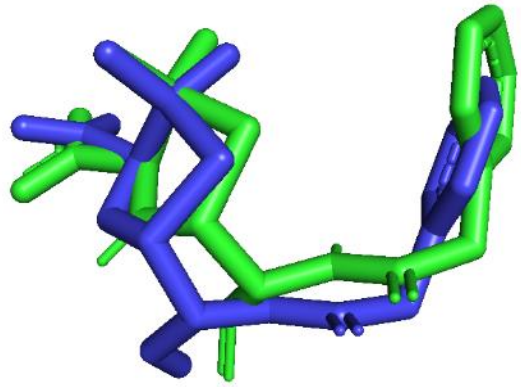


Figure 1. Superimpose native ligand (blue) into redocking native ligand (green) (RMSD: 1.148 Å).

Molecular docking results showed that the penicillin G chemical interactions were in the SauPBP2a binding pocket, as shown in **Figure 2a** and **2b** shows several important amino acids, which serve as this protein's catalytic domain and interact with penicillin G. Furthermore, amino acids, such as Ser462, Asn464, Ser598, and Thr600, interacted using hydrogen bonding [11]. The beta-lactam ring opening occurred due to the interaction with Ser403. Hydrophobic reactions, including alkyl and pi-alkyl, were also observed between methyl groups substituted in the thiazolidine ring with Tyr446 and Met641. Previous studies also revealed that ionic interactions between the O atom of the carboxylic group and Lys406 stabilized the penicillin G complex with SauPBP2a.

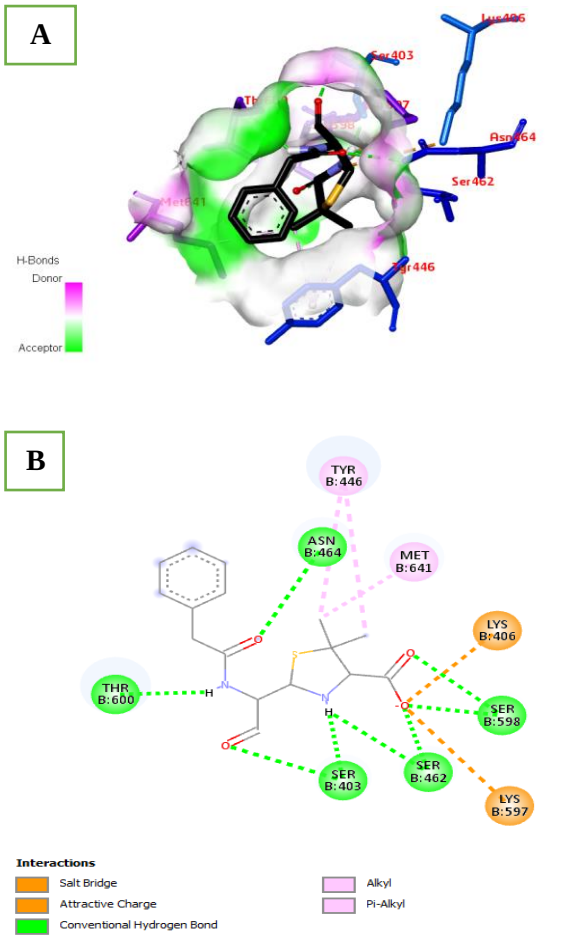


Figure 2. Chemical interactions of penicillin G as a native ligand in the binding pocket of SauPBP2a: (A) 3D and (B) 2D.

In this study, new designs of Monoglyceride Vanillate compounds were produced, as shown in **Figure 3**. The glycerol backbone structure was maintained during the production process. Vanillin bonded to the hydroxyl group attached to the alpha carbon of the glycerol backbone through an esterification reaction to increase its polarity.

The presence of phenolic groups is expected to facilitate hydrogen bonding interactions on the active site of the SauPB2a binding pocket. Meanwhile, the primary alcohol group on the glycerol backbone was modified with various antimicrobial lipid compounds, such as monoglycerides, to produce the Monoglyceride Vanillate derivatives.

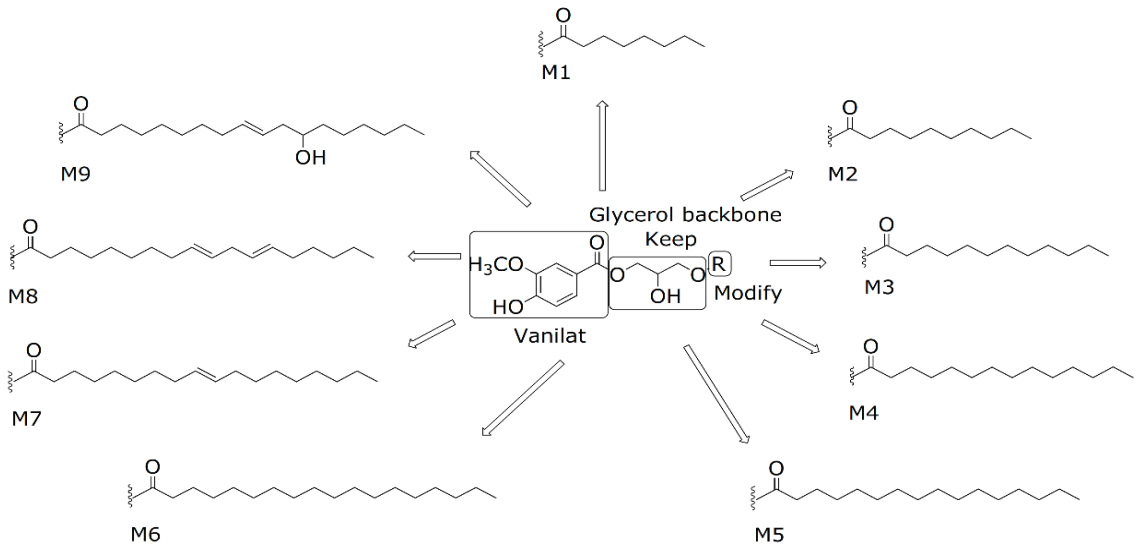


Figure 3. Chemical interactions of penicillin G as a native ligand in the binding pocket of SauPBP2a: (A) 3D and (B) 2D.

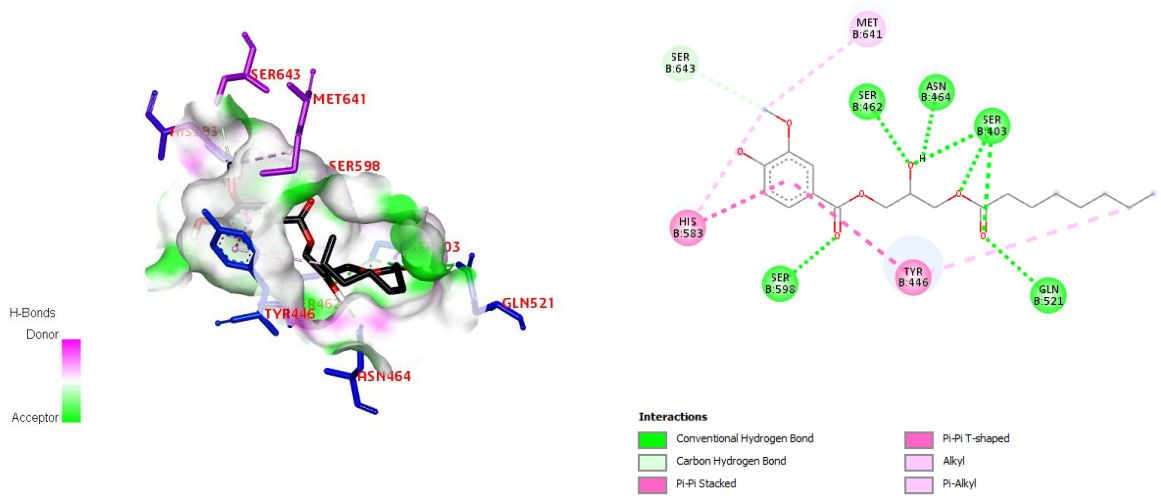
Nine design compounds were assessed for their inhibitory activity against the SauPBP2a receptor using molecular docking. The binding energies of the molecules obtained from the process are presented in **Table 1**. Compound M1 has a satisfactory binding energy of -7.0 kcal/mol.

Table 1. The binding energy of all Monoglyceride Vanillate derivatives to the SauPBP2a receptor**.**

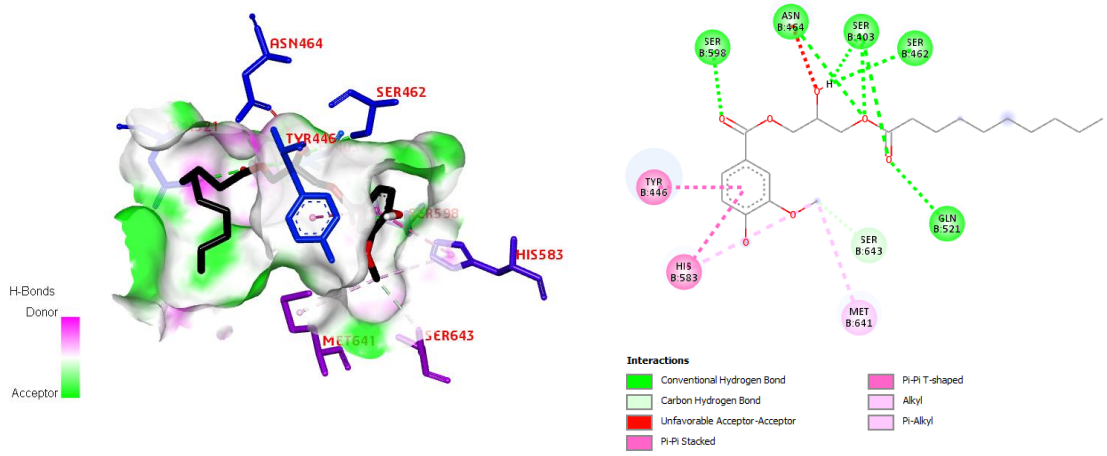
Id Compound	Name Compound	Binding Energy (Kcal/mol)
Native ligand	Penicillin-G	-7.6
M 1	Monocapryl Vanillate	-7.0
M 2	Monocarpic Vanillate	-7.1
M 3	Monolaurin Vanillate	-6.9
M 4	Monomyristil Vanillate	-6.8
M 5	Monopalmityl Vanillate	-6.7
M 6	Monostearyl Vanillate	-6.4
M 7	Monoolein Vanillate	-6.7
M 8	Monolinolein Vanillate	-7.1
M 9	Monorisinoleyl Vanillate	-7.1

Furthermore, the acyl group of caprylic acid (C7) also contributed to the interaction with the SauPBP2a binding pocket through hydrophobic association against Tyr446, as shown in **Figure 4a**. The results also showed that the benzene ring of vanillate stabilized the interaction with Tyr446. Other associations with the catalytic domain were found in the amino acids Ser462, Asn464, and Ser598 through hydrogen bonding.

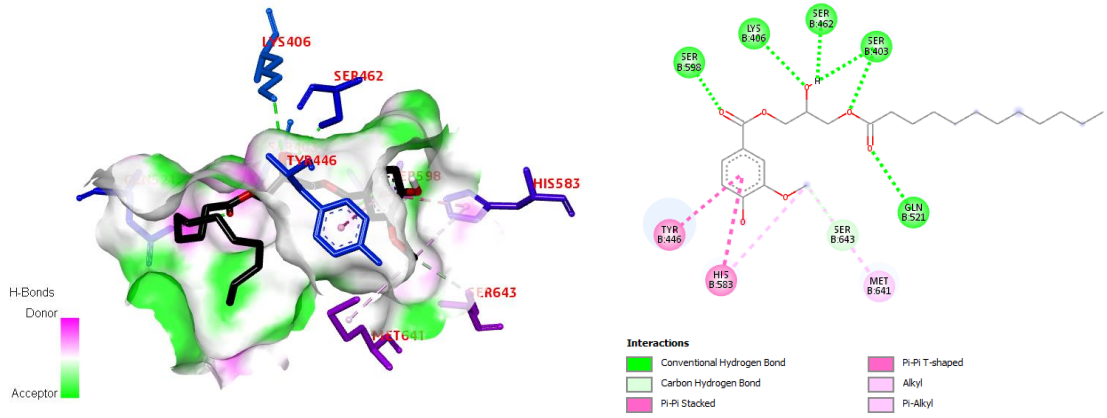
Several efforts were made to increase the carbon chain of the acyl group in monoglycerides to improve their inhibitory activity. The acyl chain was increased to 9 carbon atoms to form a monocaprine compound. This treatment led to a slight increase in the binding energy value of -7.1 kcal/mol. **Figure 4b** shows two important types of amino acids in the catalytic domain, namely Ser462, and Ser598, which interacted through hydrogen bonds with lengths of 2.60 Å and 2.99 Å, respectively.


SER643
MET641
SER598
GLN521
TYR446
ASN464
H-Bonds
Donor
Acceptor
MET B:641
SER B:643
ASN B:464
SER B:462
SER B:403
HIS B:583
SER B:598
TYR B:446
GLN B:521
Interactions
Conventional Hydrogen Bond
Carbon Hydrogen Bond
Pi-Pi Stacked
Pi-Pi T-shaped
Alkyl
Pi-Alkyl

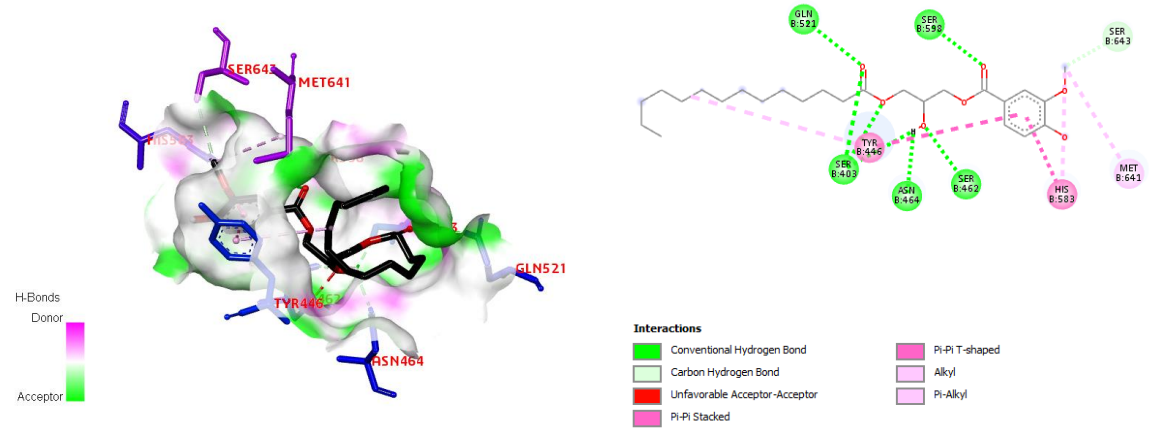
(A)


ASN464
SER462
TYR446
HIS583
MET641
SER643
H-Bonds
Donor
Acceptor
ASN B:464
SER B:403
SER B:462
SER B:598
TYR B:446
GLN B:521
SER B:643
HIS B:583
MET B:641
Interactions
Conventional Hydrogen Bond
Carbon Hydrogen Bond
Unfavorable Acceptor-Acceptor
Pi-Pi Stacked
Pi-Pi T-shaped
Alkyl
Pi-Alkyl

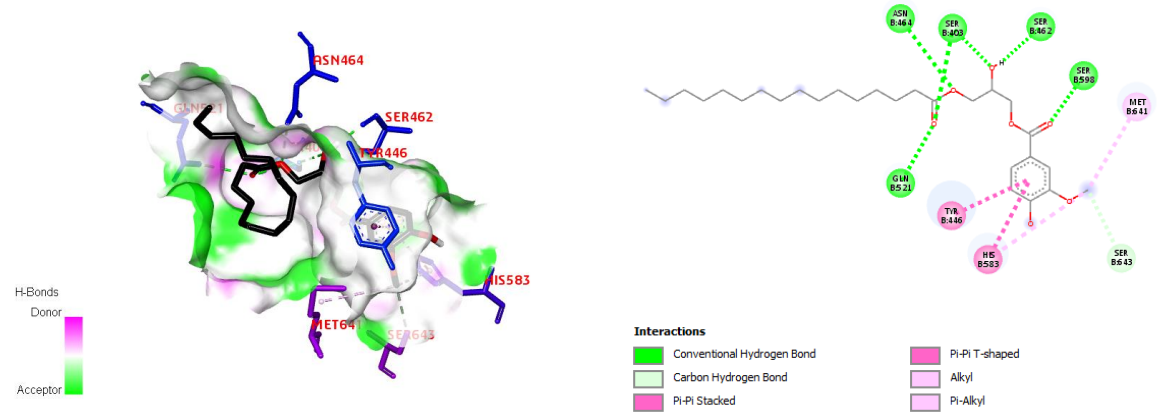
(B)


LYS406
SER462
TYR446
HIS583
H-Bonds
Donor
Acceptor
SER462
LYS B:406
SER B:403
SER B:598
GLN B:521
TYR B:446
SER B:643
HIS B:583
MET B:641
Interactions
Conventional Hydrogen Bond
Carbon Hydrogen Bond
Pi-Pi Stacked
Pi-Pi T-shaped
Alkyl
Pi-Alkyl

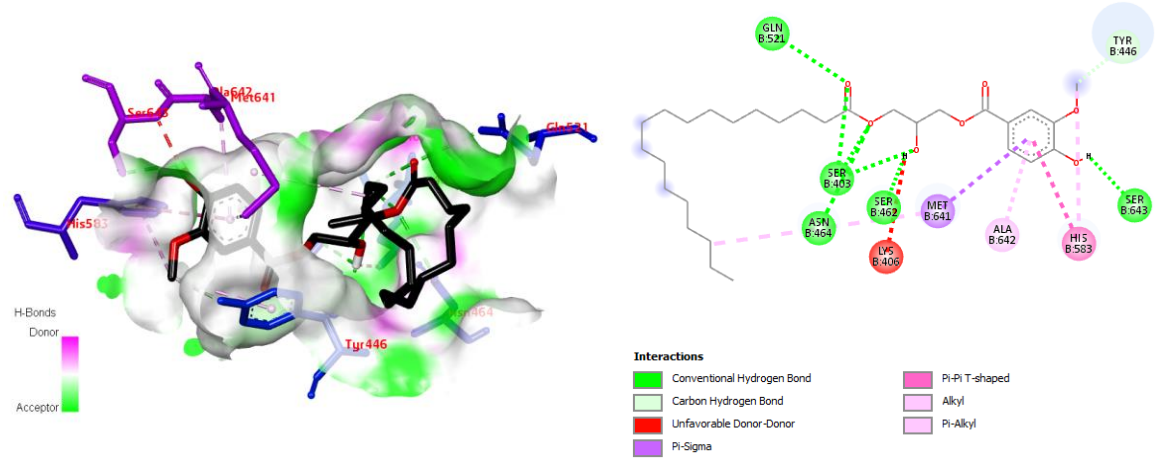
(C)



(D)



(E)



(F)

Figure 4. 3D and 2D chemical interactions from the series of saturated Monoglyceride Vanillate compounds: (A) M1, (B) M2, (C) M3, (D) M4, (E) M5, and (F) M6.

The distance produced was slightly closer than the interaction in the M1 compound. Furthermore, the increase in the complex stability of compounds M2 and SauPBP2a was also affected by the hydrophobic interactions with Tyr446 and Met641 (**Table S1**).

The trends in compounds M1 and M2 provided clues to continuously increase the carbon number of acyl groups from monolaurin (M3, C11), monomyristin (M4, C13), monopalmitin (M5, C15), and monostearin (M6, C17).

Molecular docking results showed a decrease in the binding energy of M3-M4 compounds to -6.9, -6.8, -6.7, and -6.4 kcal/mol, respectively, as shown in **Table 1**. This was due to the loss of interaction between the M3 compound and the catalytic domain in Asn464. Increasing the number of acyl chain carbons in compound M4 increased the bond distance in the amino acids Ser403 and Asn464, namely 2.31 to 2.77 Å and 2.17 to 2.24 Å compared to M3, respectively.

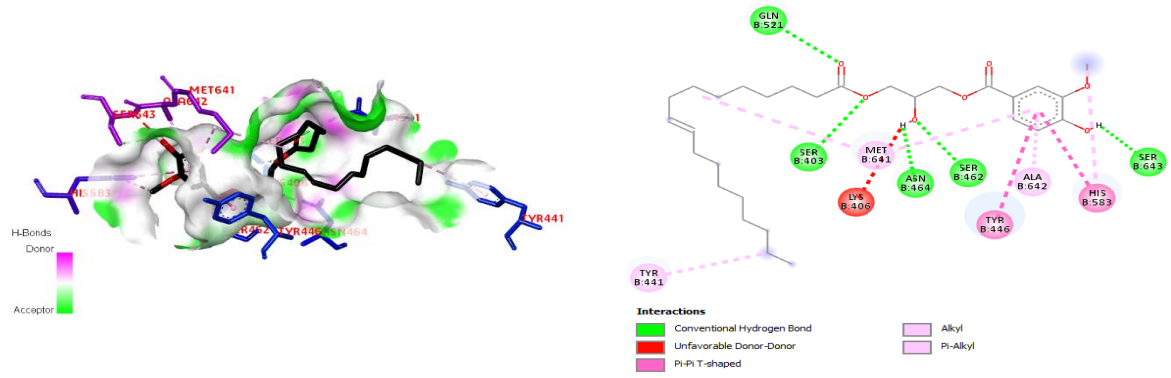
For compound M5, the data showed an increase in bond distance in Ser403 and Asn464, namely 2.96 and 3.17 Å, respectively, with the same trend as compound M4. The lowest binding energy was found in M6 due to the increasing number of acyl chain carbons from the monoglyceride. However, the interaction between the O atoms of M6 has a slightly lower bond distance than M5. The results also showed that M6 interactions in the catalytic domain (Asn464) experienced an increase in bond distance, namely 3.17 Å, as shown in **Figure 4f**. The decrease in the binding energy value was due to the increase in the length and saturated properties of the acyl chain. Therefore, studies concerning the unsaturated nature of the acyl chain in Monoglyceride Vanillate are continuously being developed.

The saturated acyl groups in monoglycerides were replaced with unsaturated acyl groups, as observed in compound M7, and they produced good results in improving the design compound activity. Furthermore, M7 experienced an increase in binding energy with a value of -6.7 kcal/mol. **Figure 5a** shows the improved bond distance in the hydrogen bonding interaction of the C-bonded hydroxyl group to Asn464, namely 2.83 Å. The bent shape due to the pi bond in the side chain was assumed responsible for directing the O atom to interact with the SauPBP2a catalytic domain. The complex stability was enhanced by the interaction of the amino acid Met641 with the benzene ring and the alkene group of the side chain (C9) through pi-sigma and pi-alkyl associations, respectively.

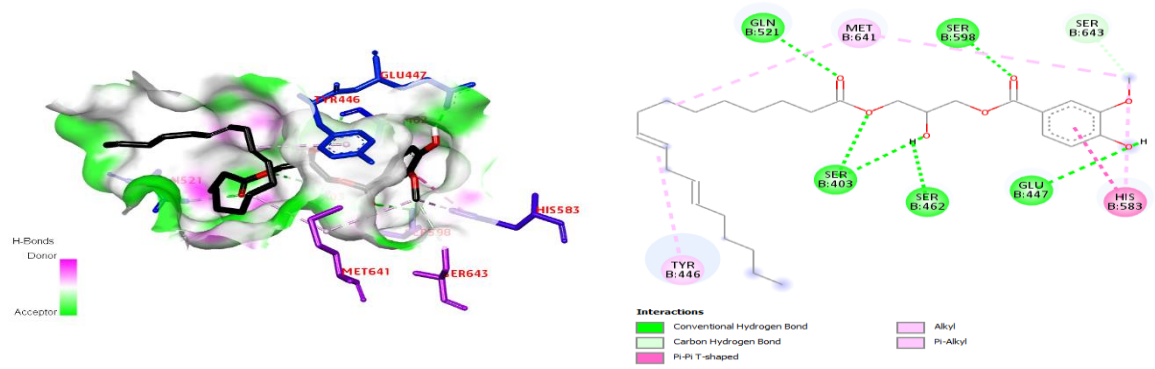
The subsequent modification involves monoglycerides from monolinolein with an acyl chain called C17:2 to obtain compound M8. Adding the saturation degree of the acyl chain caused a perfect change in the binding energy value of -7.1 kcal/mol. The docking results showed a decrease in the bond distance in the interaction with Ser462 of 2.28 Å compared to compound M7, as shown in **Figure 5b**. The presence of H-methoxy and alkene groups stabilized the hydrophobic interaction on Met641.

Interesting data were also found on replacing the Monoglyceride Vanillate side chain with the acyl group of ricinoleic acid (compound M9). The docking data for the monorisinoleyl vanillic compound showed that

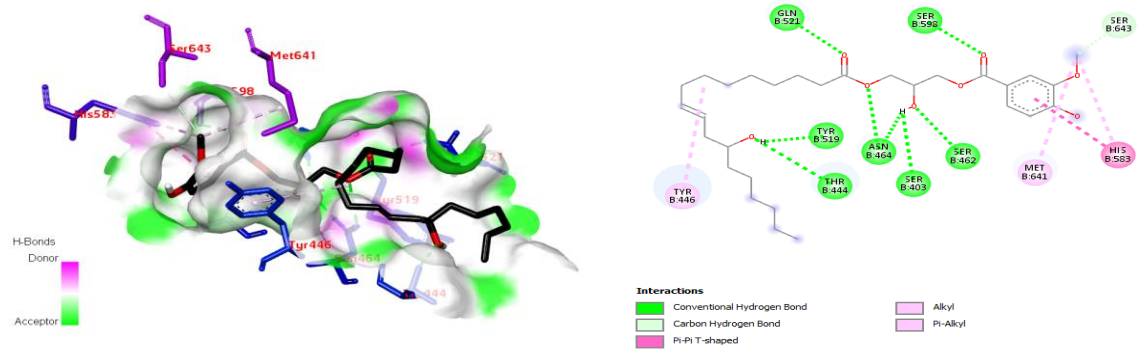
the interaction with Ser403 and Asn464 can be improved, while this interaction was not found in compound M8, as shown in **Figure 5c**. Although the hydrophobic interaction with Met641 is only stabilized through pi-alkyl interactions with methoxy groups, there were still improvements in the bond spacing of Ser403 and Asn464, namely 2.64 Å and 2.01 Å, respectively. Meanwhile, compared with the standard, the interaction using the amino acids in the catalytic domain, namely Ser462 and Asn464, shows a lower bond distance of 2.86 Å and 2.01 Å.



(A)



(B)



(C)

Figure 5. 3D and 2D chemical interactions of the unsaturated Monoglyceride Vanillate compound series: (A) M7, (B) M8, and (C) M9.

3.2. Molecular Dynamic

The molecular docking results showed that the three compounds with the lowest binding energy are M2, M8, and M9. The stability complex SauPBP2a on M2, M8, and M9 compounds was evaluated by CABS-Flex 2.0 server. This evaluation gives an RMSF plot, as shown in **Figure 6**. The highest fluctuation on the RMSF plot indicates the flexibility of amino acid residues. While the flexibility of amino acid residues is low, it indicates that complex SauPBP2a-tested compound is stable with an RMSF value of 1-3 Å [12,13].

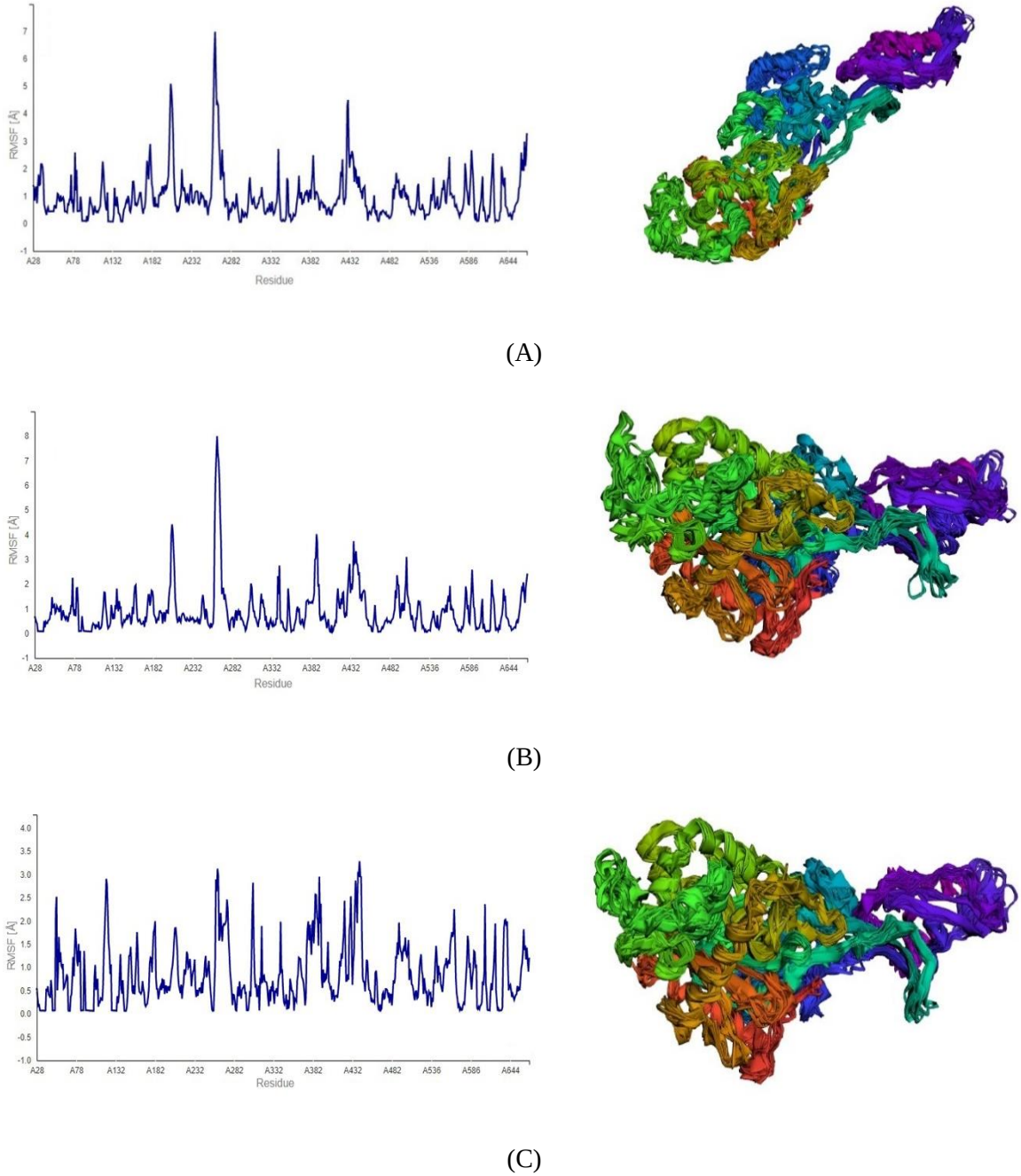


Figure 6. RMSF plot and 3D structure of complex SauPBP2a with: (A) compound M2, (B) compound M8, and (C) compound M9.

The flexibility of complex M9-SauPBP2a showed that the RMSF value is lower than the two compounds' other. Additionally, compound M9 formed stable interactions with amino acid residues 403-600. Even though complex M9-SauPBP2a has a low RMSF value, less than 3 Å. It means that compound M9 is more stable than compounds M2 and M8. Moreover, the stability interaction of the three compounds was also determined using the iMODs server. The analysis was based on Normal Mode Analysis (NMA). **Figures 7a, 8a,** and **9a** illustrate receptor flexibility.

The highest deformability indicates that a molecule is easily deformed on its residues. Three complexes show low deformability (<1) [14,15]. As shown in **Figures 7b, 8b, and 9b**, the B-factor graph shows the arrangement of each atom in a crystal. The receptor is mobile and flexible when the B-factor value is high [16]. From all three complexes, their B-factor appears similar. Furthermore, eigenvalues show the receptor stiffness (**Figure 7c, 8c, and 9c**). The lowest eigenvalue is that the protein receptor tends to be stiff [17]. **Table 2** provides eigenvalues for three complexes.

The three complexes' eigenvalue is low and similar for all complexes. This means compounds M2, M8, and M9 can form stable interactions with SauPBP2a. **Figures 7d, 8d, and 9d** display a covariance matrix between residues for three compounds. The red color indicates that each residue is correlated with its others, the white color describes uncorrelated residues, and the blue color shows anticorrelation between each residue [18]. This data shows that compounds M2, M8, and M9 have good correlations with less non-correlation (white) and anticorrelation (blue).

The in silico study of Monoglyceride Vanillate provides new insights, indicating that this compound has significant potential for development as an antimicrobial lipid. Compound M9 has been identified as the most effective anti-MRSA agent. Ricinoleic and vanillic acids can be used as starting materials for synthesizing Compound M9.

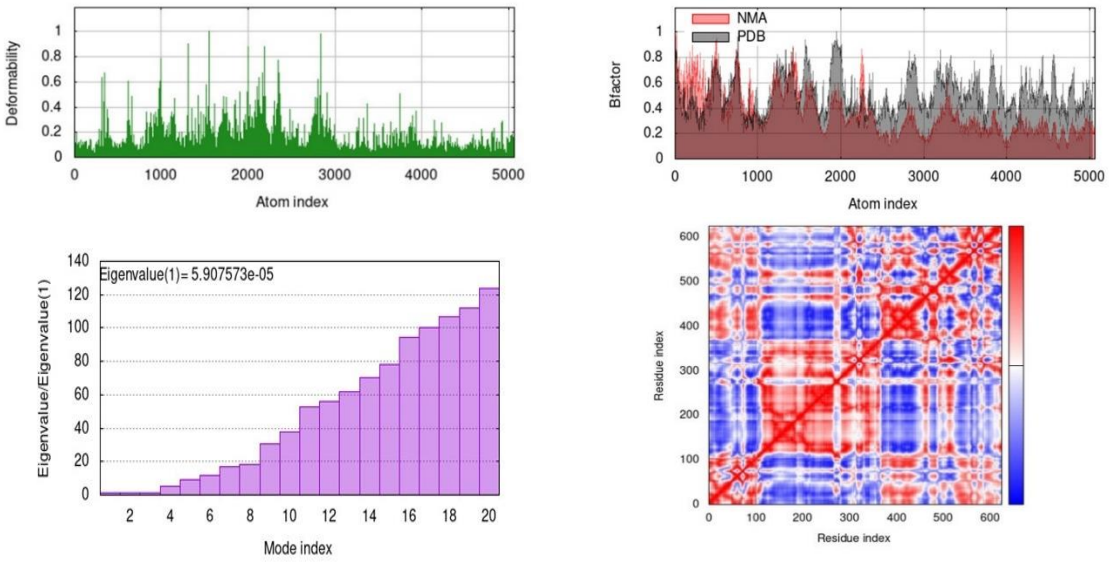


Figure 7. NMA results using the iMODS server for compound M2: (A) deformability graph (top left), (B) B-factor graph (top right), (C) eigenvalue (below left), and (D) variance plot (below right).

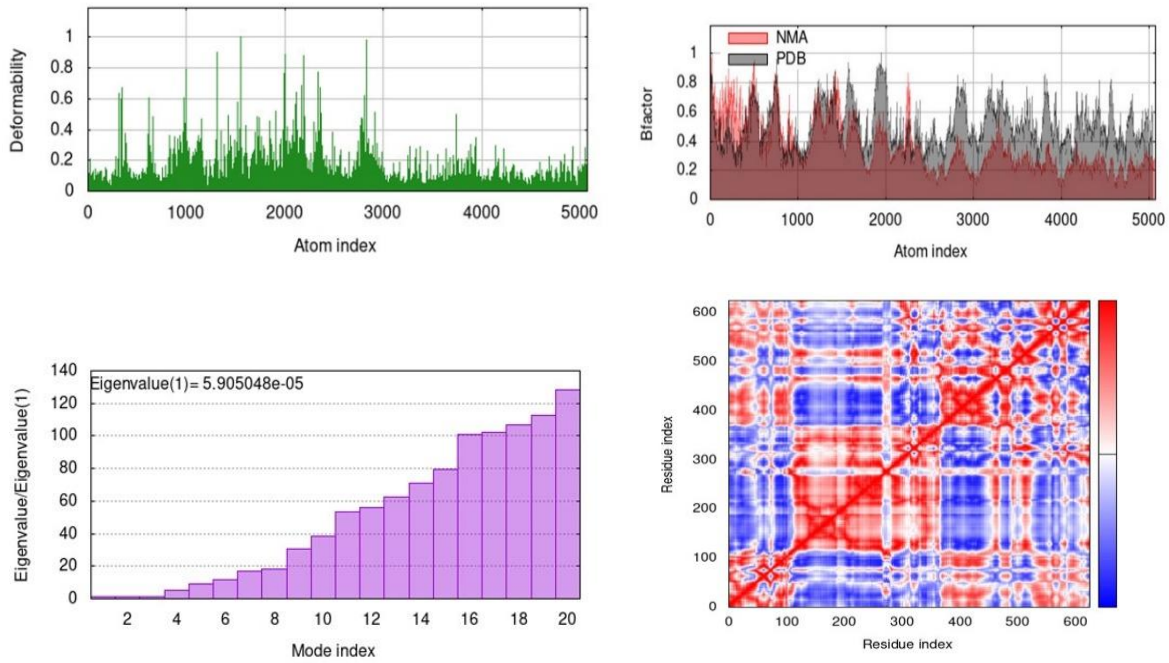


Figure 8. NMA results using the iMODS server for compound M8: (A) deformability graph (top left), (B) B-factor graph (top right), (C) eigenvalue (below left), and (D) variance plot (below right).

Table 2. Eigen value from iMODS server calculation

Complex	Eigen value
M2-SauPBP2a	5.91×10^{-5}
M8-SauPBP2a	5.91×10^{-5}
M9-SauPBP2a	5.90×10^{-5}

In addition to their abundant availability, research shows that both compounds exhibit significant antimicrobial activity. Ricinoleic acid has been shown to inhibit *Staphylococcus aureus* by 8.1 mm ± 0.2 at a concentration of 200 µg/mL [19]. Consistent with these findings, ricinoleic acid isolated from castor oil inhibits *Staphylococcus aureus* up to 16.35 mm at a 2% concentration [20].

Meanwhile, vanillic acid can inhibit *Staphylococcus aureus* with a MIC value of 600 µg/mL [21]. Although both compounds exhibit good antibacterial activity, combining these materials for synthesizing Monoglyceride Vanillate offers enhanced inhibitory effects. The balance of lipophilic and hydrophilic properties is expected to increase its effectiveness as an anti-MRSA agent. Furthermore, Compound M9 has demonstrated stable interactions with the catalytic domain of the SauPBP2a protein, particularly with residues Ser403 and Asn464, according to in silico data.

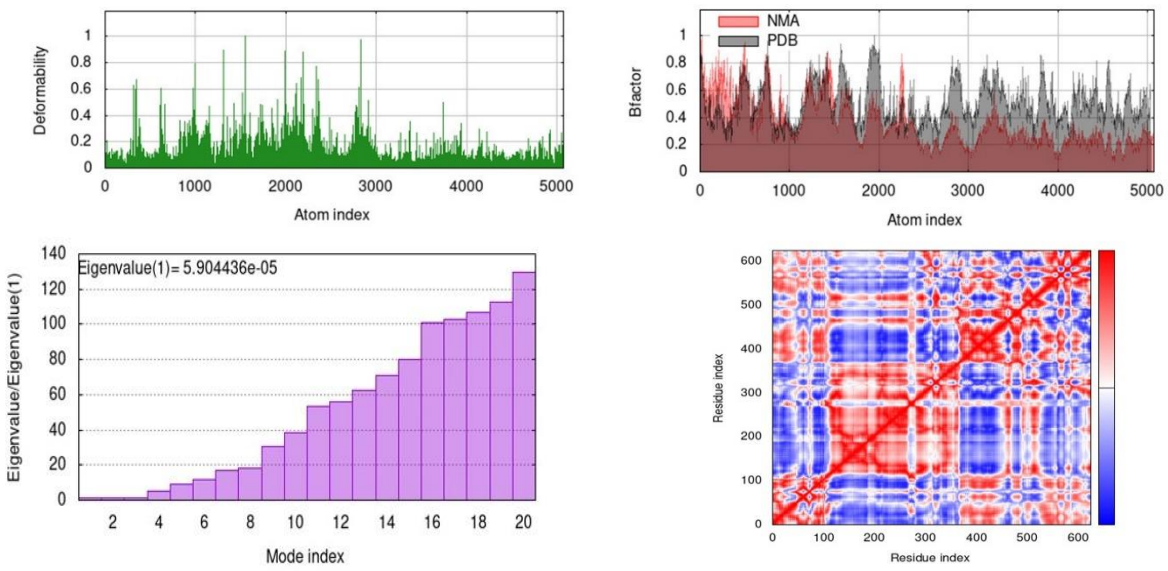


Figure 9. NMA results using the iMODS server for compound M9: (A) deformability graph (top left), (B) B-factor graph (top right), (C) eigenvalue (below left), and (D) variance plot (below right).

4. Conclusion

The design of monoglyceride derivative compounds, namely Monoglyceride Vanillate, using saturated and unsaturated monoglycerides with vanillic acid increased the interactions with the active site of SauPBP2a. The presence of the benzene and H-methoxy rings contributed to the hydrophobic interaction. Modifying the side chain, namely acyl groups in Monoglyceride Vanillate, influences binding energy and chemical associations. Increasing the number of acyl carbon decreased the binding energy in saturated Monoglyceride Vanillate. Replacement of the chain from saturated to unsaturated in Monoglyceride Vanillate can increase binding energy. Furthermore, some interactions with the important amino acids of SauPBP2a produced lower bond lengths. A stable complex with SauPBP2a was formed using unsaturated Monoglyceride Vanillate. Molecular dynamic simulation showed the M9 compound forms a more stable interaction with the SauPBP2a receptor based on RMSF values. On the other hand, the iMODS server results demonstrated that compounds M2, M8, and M9 have stable complexes with the SauPBP2a receptor. Notably, we concluded that compound M9 is the best candidate as an anti-MRSA agent. This compound can be synthesized from a variety of naturally occurring starting materials, including vanillic acid and methyl ricinoleate. Additionally, its activity against MRSA will be confirmed through in vitro assays.

Conflict of interest

The authors declare to have no conflict of interest.

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Table S1. The chemical interaction of complex between designed compound and receptor

Id compound	Name compound	Interaction		
		Hydrogen bonding	**Hydrophobic**	**Other**
Native ligand	Penicillin-G	Ser403 (1.76 Å), Ser462 (2.92 Å), Asn464 (3.04 Å), Ser598 (3.02 Å), Thr600 (2.73 Å)	Tyr 446, Met641	Lys406 (attractive charge) Lys597 (Salt bridge)
M1	Monocapryl Vanillate	Ser403 (2.85 Å), Ser462 (2.87 Å), Asn464 (1.79Å), Gln521 (3.10 Å), Ser598 (3.02 Å), Ser643 (3.57 Å)	Tyr446, His583, Met641	-
M2	Monocarpic Vanillate	Ser403 (2.01 Å), Ser462 (2.60 Å), Asn464 (3.28 Å), Gln521 (3.14 Å), Ser598 (2.99 Å), Ser643 (3.55 Å)	Tyr446, His583, Met641	-
M3	Monolaurin Vanillate	Ser403 (2.31 Å), Ser462 (3.03 Å), Asn464 (2.17 Å), Gln521 (3.14 Å), Ser598 (3.04 Å), Ser643 (3.66 Å)	Tyr446, His583, Met641	-
M4	Monomyristil Vanillate	Ser403 (2.77 Å), Ser462 (2.76 Å), Asn464 (2.24 Å), Gln521 (3.27 Å), Ser598 (3.07 Å), Ser643 (3.66 Å)	Tyr446, His583, Met641	-
M5	Monopalmityl Vanillate	Ser403 (2.96 Å), Ser462 (1.91 Å), Asn464 (3.17 Å), Gln521 (3.25 Å), Ser598 (2.99 Å), Ser643 (3.59 Å)	Tyr446, His583, Met641	-
M6	Monostearyl Vanillate	Ser403 (2.71 Å), Ser462 (2.05 Å), Tyr446 (3.72 Å, Asn464 (3.25 Å), Gln521 (3.38 Å), Ser643 (2.23 Å)	His583, Met641, Ala642	-
M7	Monoolein Vanillate	Ser403 (2.71 Å), Ser462 (2.83 Å), Asn464 (1.83 Å), Gln521 (3.29 Å), Ser643 (2.92 Å)	Tyr441, Tyr446, His583, Met641, Ala642	-
M8	Monolinolein Vanillate	Ser403 (2.97 Å), Ser462 (2.28 Å), Gln521 (2.98 Å), Ser598 (3.02 Å), Ser643 (3.65 Å)	Tyr446, His583, Met641	-
M9	Monorisinoleyl Vanillate	Ser403 (2.64 Å), Ser462 (2.86 Å), Thr444 (3.05 Å), Gln521 (3.13 Å), Tyr519 (2.25 Å), Ser598 (3.02 Å), Ser643 (3.78 Å)	Tyr446, His583, Met641	-