Molecular Interactions and Binding Affinities of Laminarin With Methicillin Resistance Protein (MecR1) and Penicillin-Recognizing Protein (FmtA)

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**Abstract:** Laminarin, a sulfated polysaccharide derived from brown seaweeds, exhibits various biological activities including potential antimicrobial effects. This study investigates the binding interactions and affinities of laminarin with Methicillin Resistance Protein (MecR1) and Penicillin-Recognizing Protein (FmtA) using molecular docking simulations. The binding affinity of laminarin with MecR1 was determined to be -6.3 kcal/mol, revealing three van der Waals interactions and four conventional hydrogen bonds. These interactions suggest a potential disruption of MecR1's role in activating methicillin resistance in Staphylococcus aureus. Additionally, laminarin demonstrated a binding affinity of -5.5 kcal/mol with FmtA, involving three van der Waals interactions, four conventional hydrogen bonds, and two carbon-hydrogen bonds. However, one unfavourable donor-donor interaction with THR391 was observed. These findings indicate that laminarin could impact FmtA’s function in modifying and inactivating penicillin, contributing to its antimicrobial efficacy. The study highlights the potential of laminarin as a novel therapeutic agent against antibiotic-resistant bacteria by disrupting key resistance mechanisms. Further experimental validation is warranted to explore its practical applications in combating antimicrobial resistance.

**Keywords:** Laminarin, Methicillin Resistance Protein (MecR1), Penicillin-Recognizing Protein (FmtA), molecular docking, antimicrobial resistance

# Introduction

Antimicrobial resistance (AMR) represents a major public health challenge, complicating the treatment of bacterial infections and necessitating the development of novel therapeutic strategies [(Ramsundar et al., 2023; Rieshy et al., 2023; S. Singh et al., 2023)](https://paperpile.com/c/QC27nk/rsoAN+QsBX1+0RfMV). Among the growing number of resistant bacterial strains, methicillin-resistant Staphylococcus aureus (MRSA) is particularly concerning due to its resistance to methicillin and other beta-lactam antibiotics [(Nelson et al., 2022)](https://paperpile.com/c/QC27nk/2kcd). This resistance is mediated by specific proteins, including Methicillin Resistance Protein (MecR1) and Penicillin-Recognizing Protein (FmtA), which play crucial roles in the bacterial resistance mechanisms [(Cunha, 2005; Fishovitz et al., 2014)](https://paperpile.com/c/QC27nk/0hFu+zrXH).Laminarin, a natural polysaccharide predominantly derived from brown seaweeds, has demonstrated various biological activities including immunomodulatory, antioxidant, and antibacterial properties [(Karuppusamy et al., 2022)](https://paperpile.com/c/QC27nk/O6fJ). Despite these promising attributes, its potential as an antimicrobial agent against resistant bacterial strains, particularly through interactions with resistance-related proteins, remains underexplored [(Pavithra et al., 2023; Shenoy et al., 2023; Thomas & Jain, 2023)](https://paperpile.com/c/QC27nk/uu7ru+HeFg+ILpZx). Molecular docking provides a computational approach to elucidate these interactions by predicting the binding affinities and interaction profiles between ligands and target proteins [(Morris et al., 2009)](https://paperpile.com/c/QC27nk/Nfon).Methicillin Resistance Protein (MecR1) is a sensor kinase involved in the regulation of beta-lactam resistance in MRSA [(Doshi et al., 2023; Lampl et al., 2023; Pandiyan et al., 2023)](https://paperpile.com/c/QC27nk/5HbST+fONoN+Mniuu). It is part of the two-component regulatory system that activates the transcription of mecA, which encodes the alternative penicillin-binding protein (PBP2a) responsible for methicillin resistance [(Lade et al., 2022; Lade & Kim, 2021)](https://paperpile.com/c/QC27nk/9Kze+VwbO). FmtA, a penicillin-recognizing protein, contributes to bacterial resistance by modifying the structure of penicillin and thereby reducing its efficacy [(Sethuvel et al., 2023)](https://paperpile.com/c/QC27nk/ucS8). Understanding how natural compounds like laminarin interact with these proteins could reveal new therapeutic pathways for combating antibiotic resistance.Recent studies have utilized molecular docking to predict binding interactions and affinities between various ligands and bacterial resistance proteins. This technique allows for the simulation of ligand-protein interactions at the molecular level, providing insights into potential inhibitory effects and mechanisms of action [(Baig et al., 2018)](https://paperpile.com/c/QC27nk/KhoJ). In this context, evaluating the binding affinities of laminarin with MecR1 and FmtA through in silico docking offers a valuable opportunity to identify potential new uses for this polysaccharide.The primary aim of this study is to investigate the molecular interactions and binding affinities of laminarin with Methicillin Resistance Protein (MecR1) and Penicillin-Recognizing Protein (FmtA) using molecular docking simulations [(Janani et al., 2021; Kachhara et al., 2021; Subramanian et al., 2023)](https://paperpile.com/c/QC27nk/xhQvu+NHdEd+0r76z). By elucidating the binding profiles of laminarin with these resistance-related proteins, we aim to assess its potential as a novel antimicrobial agent against resistant bacterial strains.Laminarin is a beta-glucan composed of glucose units linked by beta-1,3 and beta-1,6 glycosidic bonds. Its structural complexity and biological activity have been the subject of various studies, revealing its potential in enhancing immune responses and modulating microbial activities [(Karuppusamy et al., 2022)](https://paperpile.com/c/QC27nk/O6fJ). The polysaccharide’s ability to interfere with bacterial cell walls and its potential for synergistic effects with conventional antibiotics make it a candidate of interest for further investigation [(Shannon & Abu-Ghannam, 2016)](https://paperpile.com/c/QC27nk/MSyW).The interaction between laminarin and MecR1 is hypothesized to involve specific binding sites that may interfere with the protein’s ability to activate the mecA gene, thereby potentially reducing methicillin resistance [(Gandhi et al., 2021; Katyal et al., 2023; Priyadharshini et al., 2023)](https://paperpile.com/c/QC27nk/sbA89+16nbx+YR7j1). Similarly, the binding of laminarin to FmtA could influence the protein’s ability to modify and inactivate penicillin, offering a mechanism to counteract bacterial resistance.By utilizing molecular docking techniques, this study provides a comprehensive analysis of the interaction between laminarin and these resistance proteins. The results are expected to shed light on the polysaccharide’s potential as an adjunct to existing antimicrobial therapies or as a standalone agent against resistant bacterial strains. Such insights are crucial for developing novel strategies to combat AMR and enhance the efficacy of current treatment options.In summary, this study aims to explore the binding affinities and molecular interactions of laminarin with Methicillin Resistance Protein (MecR1) and Penicillin-Recognizing Protein (FmtA) through in silico molecular docking. By leveraging computational tools to predict and analyze these interactions, we seek to uncover new therapeutic potentials for laminarin in addressing antibiotic resistance and improving treatment outcomes for bacterial infections.

# Materials and Methods

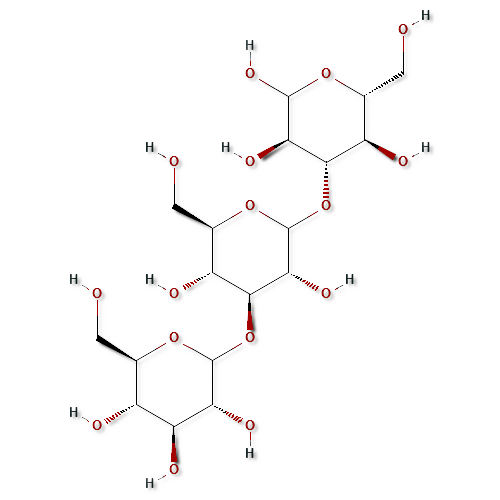
In this study, Laminarin, a non-sulphated polysaccharide with a molecular weight of 504.4 g/mol (PubChem CID: 10724374), was examined as a ligand for its interaction with two biofilm-inducing proteins from Staphylococcus aureus: Methicillin Resistance Protein (MecR1) and Penicillin-Recognizing Protein (PRP) (FmtA) (Saadh et al., 2024). The molecular structures of these proteins were obtained from the RCSB PDB (PDB: 2IWC for MecR1 and PDB: 5ZH8 for PRP) [(Dalal et al., 2022; Marrero et al., 2006)](https://paperpile.com/c/QC27nk/Qsy9+U54D), and were prepared for docking by removing unwanted ligands, chains, and water molecules, and adding polar charges using BIOVIA Discovery Studio Visualizer 2024(Almatrafi et al., 2024). Molecular docking was carried out using PyRx-Python Prescription 0.8 with the Autodoc Vina engine. The docking process included adjusting the grid center and dimensions, with these details recorded and presented in Table 1. The most favorable binding models were identified based on their low binding affinity, and the interactions between Laminarin and the proteins were visualized and analyzed using BIOVIA Discovery Studio Visualizer 2024.

**Table 1.** The grid centre and dimension parameters set for Methicillin Resistance Protein (MecR1) and Penicillin-recognizing protein (PRP) (FmtA)

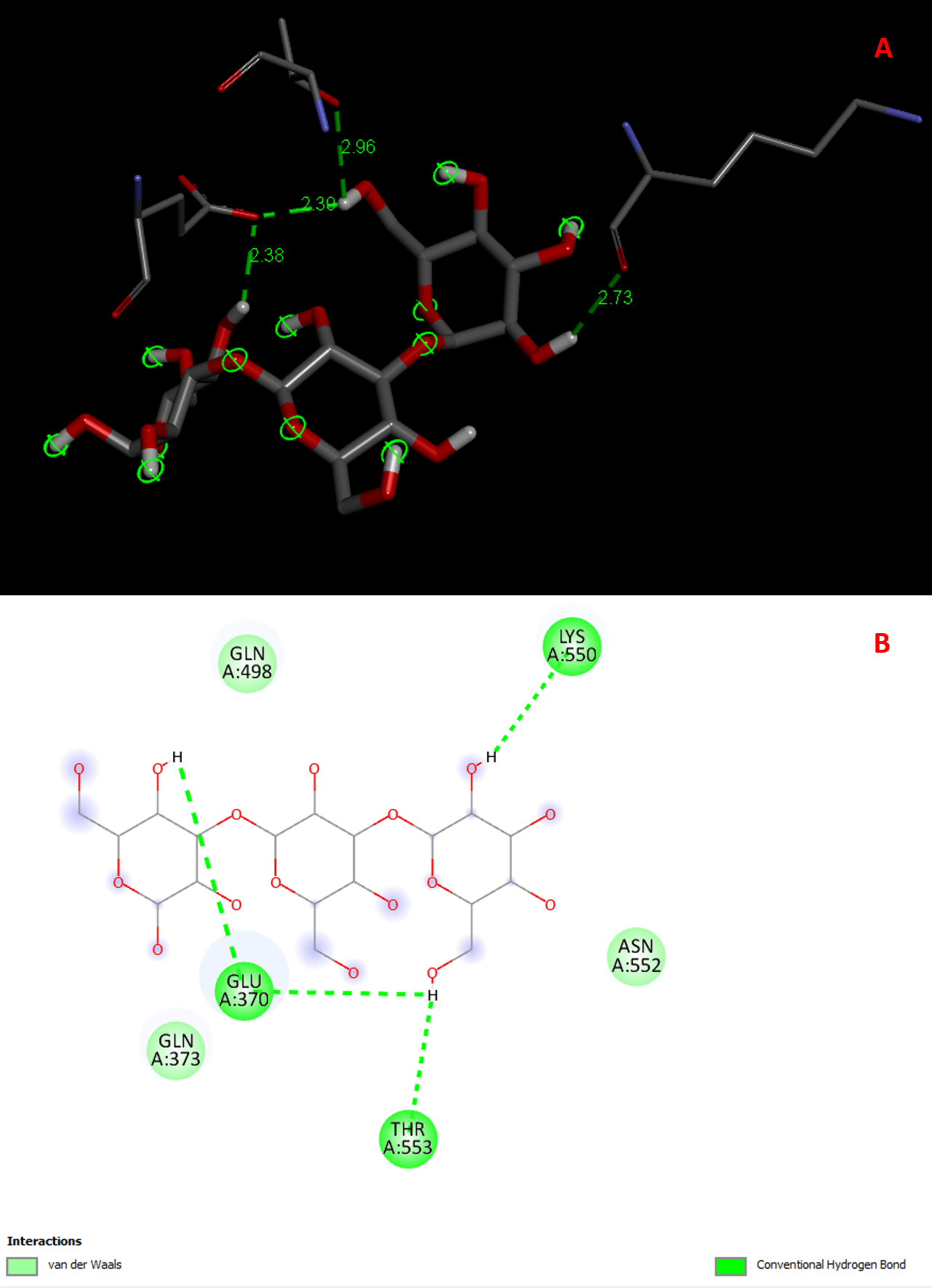
|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Grid Centre | |  | Dimensions (Å) | | |
| Protein | PDB | X | Y | Z | X | Y | Z |
| Methicillin Resistance Protein (MecR1) | 2IWC | 41.85 | 16.65 | 14.37 | 66.47 | 61.84 | 68.55 |
| Penicillin-recognizing protein (PRP) (FmtA) | 5ZH8 | 7.65 | 34.83 | 7.7 | 89.44 | 70.52 | 75.11 |

# Results and Discussion

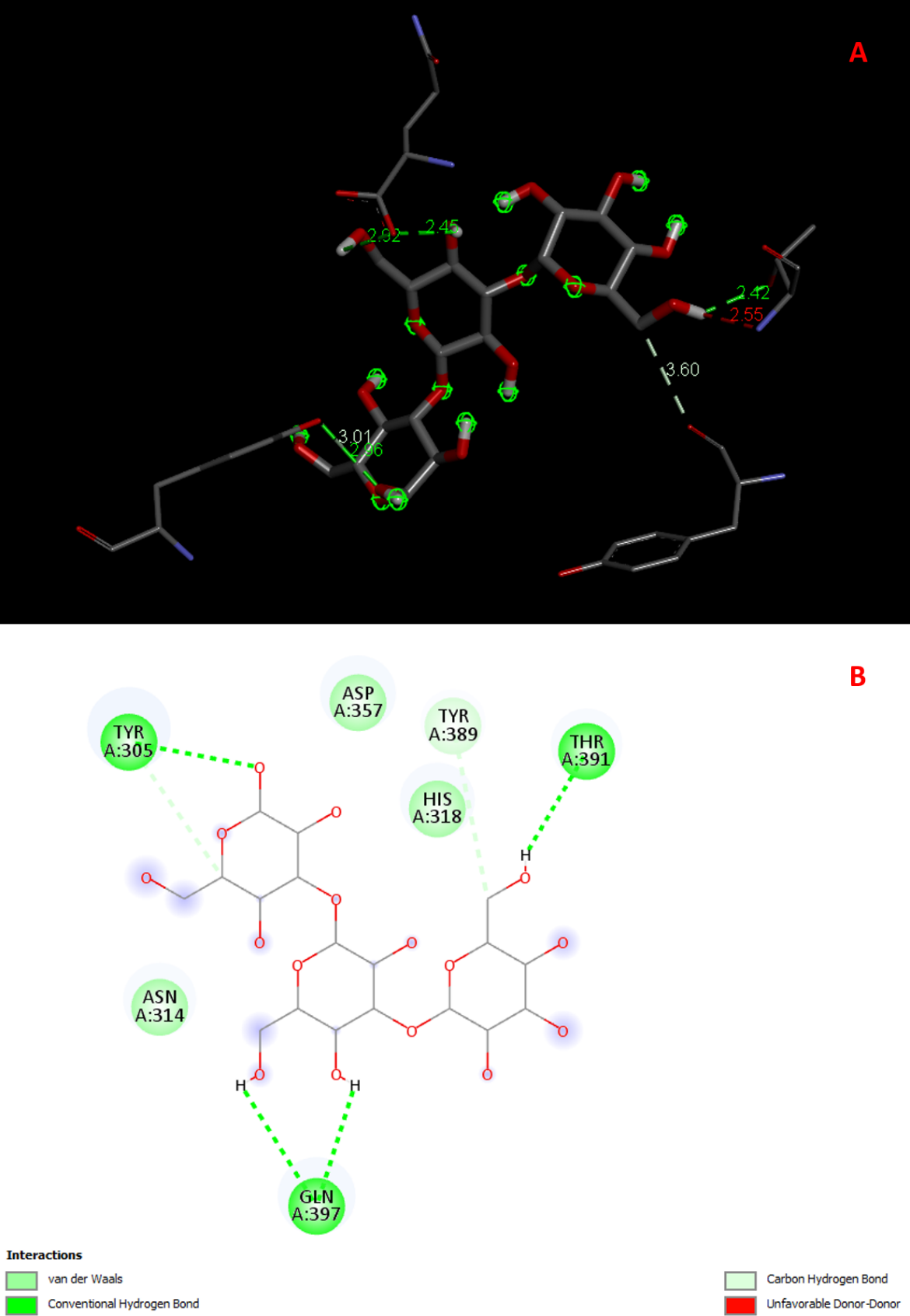
The molecular structure of Laminarin is shown in Figure 1. The lowest binding affinity between Laminarin and Methicillin Resistance Protein (MecR1) was -6.3 kcal/mol, as detailed in Table 2. Docking studies revealed that Laminarin interacts with MecR1 through three van der Waals interactions (with residues GLN498, ASN552, and GLN373) and four conventional hydrogen bonds (with residues GLU370, THR553, and LYS550), as illustrated in Figure 2 and listed in Table 4. For the Penicillin-Recognizing Protein (PRP) (FmtA), the binding affinity of Laminarin was -5.5 kcal/mol (Table 3). Interactions include three van der Waals interactions (with residues ASN314, ASP357, and HIS318), four conventional hydrogen bonds (with residues TYR305, THR391, and two GLN397), two carbon-hydrogen bond interactions (with residues TYR305 and TYR389), and one unfavorable donor-donor interaction (with residue THR391), as depicted in Figure 3 and summarized in Table 5.



**Figure 1.** Molecular structure of a non-sulphated polysaccharide Laminarin



**Figure 2.** Molecular interactions between the ligand Laminarin and Methicillin Resistance Protein (MecR1) showing three van der Waals interactions (GLN498; ASN552; GLN373), and four conventional hydrogen bond interactions (two for GLU370; THR553; LYS550); A) Three-dimensional view, B) Two-dimensional view.



**Figure 3.** Molecular interactions between the ligand Laminarin and Penicillin-recognizing protein (PRP) (FmtA) showing include three van der Waals interactions (ASN314; ASP357; HIS318), four conventional hydrogen bonds (TYR305; THR391; two for GLN397), two carbon-hydrogen bond interactions (TYR305; TYR389), and one unfavourable donor-donor interactions (THR391); A) Three-dimensional view, B) Two-dimensional view.

**Table 2.** The table retrieved after molecular docking between Laminarin and Methicillin Resistance Protein (MecR1) showing binding affinity.

|  |  |  |  |
| --- | --- | --- | --- |
| Ligand | Binding Affinity | rmsd/ub | rmsd/lb |
| 2iwb\_A\_439306\_uff\_E=583.99 | -6.3 | 0 | 0 |
| 2iwb\_A\_439306\_uff\_E=583.99 | -5.9 | 31.663 | 27.714 |
| 2iwb\_A\_439306\_uff\_E=583.99 | -5.9 | 8.857 | 2.51 |
| 2iwb\_A\_439306\_uff\_E=583.99 | -5.8 | 6.129 | 2.923 |
| 2iwb\_A\_439306\_uff\_E=583.99 | -5.7 | 7.514 | 1.82 |
| 2iwb\_A\_439306\_uff\_E=583.99 | -5.7 | 33.089 | 30.99 |
| 2iwb\_A\_439306\_uff\_E=583.99 | -5.6 | 31.822 | 27.95 |
| 2iwb\_A\_439306\_uff\_E=583.99 | -5.6 | 33.137 | 31.137 |
| 2iwb\_A\_439306\_uff\_E=583.99 | -5.5 | 35.081 | 32.598 |

**Table 3.** The table retrieved after molecular docking between Laminarin and Penicillin-recognizing protein (PRP) (FmtA) showing binding affinity.

|  |  |  |  |
| --- | --- | --- | --- |
| **Ligand** | **Binding Affinity** | **rmsd/ub** | **rmsd/lb** |
| 5zh8\_A\_439306\_uff\_E=583.99 | -5.5 | 0 | 0 |
| 5zh8\_A\_439306\_uff\_E=583.99 | -5.5 | 2.053 | 1.472 |
| 5zh8\_A\_439306\_uff\_E=583.99 | -5.4 | 36.454 | 33.152 |
| 5zh8\_A\_439306\_uff\_E=583.99 | -5.4 | 36.469 | 33.991 |
| 5zh8\_A\_439306\_uff\_E=583.99 | -5.4 | 44.429 | 42.637 |
| 5zh8\_A\_439306\_uff\_E=583.99 | -5.3 | 44.664 | 42.212 |
| 5zh8\_A\_439306\_uff\_E=583.99 | -5.2 | 33.917 | 30.721 |
| 5zh8\_A\_439306\_uff\_E=583.99 | -5.2 | 37.039 | 34.499 |
| 5zh8\_A\_439306\_uff\_E=583.99 | -5.2 | 35.268 | 34.07 |

**Table 4.** The table showing bond interactions and its length between Laminarin and Methicillin Resistance Protein (MecR1) showing amino acid residues involves in it

|  |  |  |  |
| --- | --- | --- | --- |
| **Bond Interactions** | **No. of bonds** | **Bond length (Å)** | **Amino acid residue** |
| Van der Waals interactions | 3 |  | GLN498  ASN552  GLN373 |
| Conventional hydrogen bonds | 4 | 2.38 | GLU370 |
| 2.39 | GLU370 |
| 2.96 | THR553 |
| 2.73 | LYS550 |
| Total number of interactions | 7 |  |  |

**Table 5.** The table showing bond interactions and its length between Laminarin and Penicillin-recognizing protein (PRP) (FmtA) showing amino acid residues involves in it

|  |  |  |  |
| --- | --- | --- | --- |
| **Bond Interactions** | **No. of bonds** | **Bond length (Å)** | **Amino acid residue** |
| Van der Waals interactions | 3 |  | ASN314  ASP357  HIS318 |
| Conventional hydrogen bonds | 4 | 2.96 | TYR305 |
| 2.42 | THR391 |
| 2.45 | GLN397 |
| 2.92 | GLN397 |
| Carbon-hydrogen bond | 2 | 3.01 | TYR305 |
| 3.60 | TYR389 |
| Unfavourable donor-donor | 1 | 2.55 | THR391 |
| Total number of interactions | 10 |  |  |

# Discussion

The study of laminarin, a polysaccharide derived from brown seaweeds, reveals promising interactions with key bacterial resistance proteins Methicillin Resistance Protein (MecR1) and Penicillin-Recognizing Protein (FmtA). Through molecular docking simulations, we have elucidated the binding affinities and interaction profiles of laminarin with these proteins, providing insights into its potential as an antimicrobial agent against resistant strains such as methicillin-resistant Staphylococcus aureus (MRSA).Laminarin exhibited a binding affinity of -6.3 kcal/mol with MecR1, as indicated in Table 2. This interaction was characterized by the formation of three van der Waals interactions with residues GLN498, ASN552, and GLN373 (Fig. 2 and Table 4). Van der Waals interactions are crucial for the stabilization of ligand-protein complexes, suggesting that laminarin engages with MecR1 through hydrophobic contacts that may influence the protein’s function. Additionally, laminarin forms four conventional hydrogen bonds with GLU370 (two bonds), THR553, and LYS550. Hydrogen bonds play a critical role in enhancing the specificity and stability of protein-ligand interactions [(Berman et al., 2000)](https://paperpile.com/c/QC27nk/tOm4). The presence of multiple hydrogen bonds indicates a strong binding affinity and suggests that laminarin might effectively interfere with the MecR1 protein’s activity [(Chokkattu et al., 2023; Dharman et al., 2023; Govindaraj & Shanmugam, 2023)](https://paperpile.com/c/QC27nk/qZ1an+R7cGl+ZcM1D).MecR1 is a sensor kinase that regulates the expression of mecA, the gene responsible for methicillin resistance in MRSA. The interaction between laminarin and MecR1 could potentially disrupt this regulatory pathway, offering a novel approach to counteract methicillin resistance. By binding to MecR1, laminarin may interfere with its role in activating mecA, thereby reducing the resistance of MRSA to beta-lactam antibiotics [(Lade et al., 2022; Lade & Kim, 2021)](https://paperpile.com/c/QC27nk/9Kze+VwbO). This mechanism positions laminarin as a potential adjunct therapy to enhance the efficacy of existing antibiotics.Laminarin also showed significant binding with Penicillin-Recognizing Protein (FmtA), with a binding affinity of -5.5 kcal/mol (Table 3). The interaction involves three van der Waals interactions with residues ASN314, ASP357, and HIS318, suggesting a strong hydrophobic component to the binding (Fig. 3 and Table 5). Furthermore, laminarin establishes four conventional hydrogen bonds with TYR305, THR391, and two bonds with GLN397. These interactions are critical for the stabilization and specificity of the ligand-protein complex [(Rajeshkumar & Lakshmi, 2021; Sivakumar et al., 2021)](https://paperpile.com/c/QC27nk/AroK6+RzyVi). Additionally, laminarin forms two carbon-hydrogen bond interactions with TYR305 and TYR389, and one unfavourable donor-donor interaction with THR391.FmtA, a penicillin-recognizing protein, is involved in the modification and inactivation of penicillin, contributing to bacterial resistance [(Merchant et al., 2025; Shenoy et al., 2023; P. Singh et al., 2024)](https://paperpile.com/c/QC27nk/Mz8G+edoZ+HeFg). By interacting with FmtA, laminarin might impact the protein's ability to modify penicillin, potentially reducing the efficiency of this resistance mechanism. The presence of unfavourable donor-donor interactions with THR391 indicates that while laminarin binds effectively, there may be some steric or electrostatic hindrances that could influence the stability of the complex. Despite this, the overall binding profile suggests that laminarin could interfere with FmtA's penicillin-modifying activity, offering another pathway to address antibiotic resistance [(Sethuvel et al., 2023)](https://paperpile.com/c/QC27nk/ucS8).The molecular docking results highlight the potential of laminarin as an antimicrobial agent against resistant bacterial strains. Its interactions with MecR1 and FmtA suggest that it could disrupt the function of these proteins, which are critical to the resistance mechanisms of MRSA. By binding to MecR1, laminarin might impair the activation of mecA, while its interaction with FmtA could affect penicillin inactivation. These interactions support laminarin's potential as a novel adjunct to conventional antibiotics or as a standalone therapeutic agent.The findings of this study provide a basis for further experimental validation of laminarin's antimicrobial properties. In vitro assays and in vivo studies are necessary to confirm its efficacy and to explore the precise mechanisms through which laminarin impacts bacterial resistance. Additionally, understanding the structure-activity relationship of laminarin could help optimize its use in clinical settings and enhance its therapeutic potential.

# Conclusion

In conclusion, molecular docking simulations reveal that laminarin interacts with Methicillin Resistance Protein (MecR1) and Penicillin-Recognizing Protein (FmtA), exhibiting binding affinities that suggest potential antimicrobial activity. The binding profiles indicate that laminarin could disrupt key resistance mechanisms in MRSA, making it a promising candidate for further development as an antimicrobial agent. Continued research is essential to validate these findings and to explore the broader implications of laminarin in combating antibiotic resistance.

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