Assessment on the Antibiofilm Activity of a Polyketide Lyngbyastatin 4 on Inhibiting the Biofilm Inducing Proteins Glucosyltransferase-I (Gtfb) and Vicr-Like Protein (Covr) of Streptococcus Mutans

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**Abstract:** Dental caries, primarily caused by Streptococcus mutans biofilms, remains a significant global health concern. This study investigates the antibiofilm activity of Lyngbyastatin 4, a marine-derived polyketide, against S. mutans, focusing on its interactions with two key biofilm-inducing proteins: Glucosyltransferase-I (GtfB) and VicR-like protein (CovR). Molecular docking analyses were performed to elucidate the binding affinities and interaction patterns between Lyngbyastatin 4 and these target proteins. The results revealed a strong interaction between Lyngbyastatin 4 and GtfB, with a binding affinity of -8.9 kcal/mol. This interaction was characterized by an extensive network of bonds, including five Van der Waals interactions, five conventional hydrogen bonds, four carbon-hydrogen bonds, and various π-interactions. In contrast, the interaction with CovR was weaker, showing a binding affinity of -5.1 kcal/mol and fewer bond interactions. These findings suggest that Lyngbyastatin 4 may exert its antibiofilm effects primarily through the inhibition of GtfB, potentially disrupting glucan synthesis crucial for biofilm formation. The weaker interaction with CovR implies a possible secondary effect on biofilm-related gene expression regulation. This differential binding pattern provides insights into the mechanism of action of Lyngbyastatin 4 and highlights its potential as a novel antibiofilm agent against S. mutans. This study contributes to our understanding of natural product-based strategies for combating dental caries and emphasizes the potential of marine-derived compounds in oral health applications. Further experimental validation is needed to confirm these computational findings and fully elucidate the antibiofilm properties of Lyngbyastatin 4.

**Keywords:** Lyngbyastatin 4; Streptococcus mutans; Antibiofilm activity; Glucosyltransferase-I (GtfB); Molecular docking

# Introduction

Dental caries, commonly known as tooth decay, remains a significant global health concern affecting individuals across all age groups [(Ramsundar et al., 2023; Rieshy et al., 2023; S. Singh et al., 2023)](https://paperpile.com/c/dhmMGS/8lMq7+kHWAl+gw4xx). Tooth loss from dental caries affects quality of life, including mastication and speech(Saadh et al., 2024) (Almatrafi et al., 2024). A study at found that extractions were most common in males (53.98%) and in the 31-40 age group (22.31%) [(Pratha et al., 2020)](https://paperpile.com/c/dhmMGS/pL5e). Genetic polymorphisms and mutations in Streptococcus mutans differ between children with and without early childhood caries [(Pavithra et al., 2023; Shenoy, Maiti, et al., 2023; Thomas & Jain, 2023)](https://paperpile.com/c/dhmMGS/OYvtb+kS5W8+mt7Op). The number of S. mutans genotypes also varies between caries-active and caries-free children. More studies are needed to fully understand these gene mutations and their diversity for definitive conclusions [(Ravikumar et al., 2021)](https://paperpile.com/c/dhmMGS/llGV). The primary etiological agent responsible for this widespread oral disease is Streptococcus mutans, a gram-positive bacterium renowned for its ability to form tenacious biofilms on tooth surfaces [(Loesche, 1986)](https://paperpile.com/c/dhmMGS/Xghb). These biofilms, composed of bacterial cells embedded in an extracellular polymeric substance (EPS), serve as a protective barrier against antimicrobial agents and host immune responses, contributing to the persistence and progression of dental caries [(Flemming & Wingender, 2010)](https://paperpile.com/c/dhmMGS/Lo6K). The formation of S. mutans biofilms is a complex process regulated by various genetic and environmental factors. Two key proteins play crucial roles in this process: Glucosyltransferase-I (GtfB) and the VicR-like protein CovR [(Maheshwaran et al., 2024; Merchant et al., 2025; Shenoy, Rohinikumar, et al., 2023)](https://paperpile.com/c/dhmMGS/s4aFM+4Wcon+NFBF0). GtfB is responsible for synthesizing water-insoluble glucans, which form the structural scaffold of the biofilm matrix, while CovR acts as a global regulator of virulence gene expression, including those involved in biofilm formation [(Bowen & Koo, 2011; Stipp et al., 2013)](https://paperpile.com/c/dhmMGS/jxVZ+Onub).Given the increasing prevalence of antibiotic resistance and the limitations of conventional antimicrobial approaches, there is a growing interest in developing novel strategies to combat S. mutans biofilms [(Doshi et al., 2023; Lampl et al., 2023; Pandiyan et al., 2023)](https://paperpile.com/c/dhmMGS/I2guU+vXuLo+Bk7af). One promising avenue of research involves the exploration of natural products, particularly marine-derived compounds, for their potential antibiofilm properties [(Mayer et al., 2013)](https://paperpile.com/c/dhmMGS/KlY0). Among these, polyketides have emerged as a class of secondary metabolites with diverse biological activities, including antimicrobial and anti-biofilm effects [(Hertweck, 2009)](https://paperpile.com/c/dhmMGS/wQ4G).Lyngbyastatin 4, a cyclic depsipeptide belonging to the polyketide family, was initially isolated from the marine cyanobacterium Lyngbya confervoides [(Matthew et al., 2007)](https://paperpile.com/c/dhmMGS/SMnC). This compound has garnered attention for its potent inhibitory effects against various proteases and its potential therapeutic applications in cancer and inflammation [(Kwan et al., 2009)](https://paperpile.com/c/dhmMGS/14Be). However, its antibiofilm activity against oral pathogens, particularly S. mutans, remains largely unexplored [(Amrutha Shenoy, Vinay Sivaswamy, Subhabrata Maiti, Deepak Nallaswamy, n.d.; Shenoy et al., 2025; Vohra et al., 2024)](https://paperpile.com/c/dhmMGS/Lkcw6+8S4S0+JI7He)The present study aims to assess the antibiofilm activity of Lyngbyastatin 4 against S. mutans, with a specific focus on its potential to inhibit the biofilm-inducing proteins GtfB and CovR. This investigation is driven by the hypothesis that Lyngbyastatin 4 may interfere with the expression or function of these key proteins, thereby disrupting the biofilm formation process and potentially offering a novel approach to combating dental caries.

# Materials and Methods

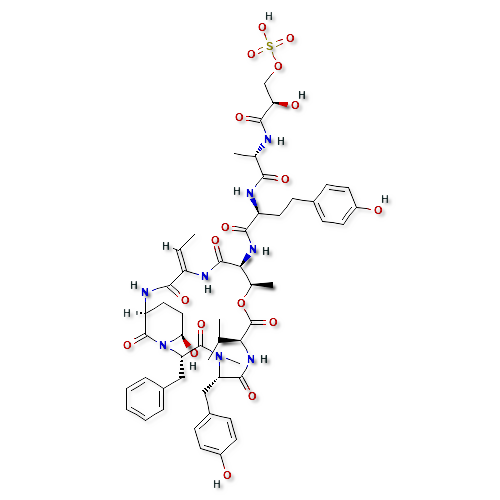
Lyngbyastatin 4 (C53H68N8O18S) is a cyanobacterial polyketide with a molecular weight of 1137.2 g/mol. In this study, Lyngbyastatin 4 serves as the ligand, with its structure retrieved from PubChem (CID: 16104920) at the National Library of Medicine, NCBI, NIH.The research focused on two key biofilm-inducing marker proteins: Glucosyltransferase-I (GtfB) (PDB: 8FJC) [(Schormann et al., 2023)](https://paperpile.com/c/dhmMGS/XHz6) and VicR-like Protein (CovR) (PDB: 8FK2) [(Liu et al., 2023)](https://paperpile.com/c/dhmMGS/sLnB) from Streptococcus mutans. Their molecular structures were obtained from the RCSB Protein Data Bank. The protein structures were visualized using BIOVIA Discovery Studio Visualizer 2024 (v24.1.0.23298) by Dassault Systems Biovia Corp., where unnecessary ligands, chains, and water molecules were removed, and polar charges were added.Molecular docking studies were conducted using the ligand Lyngbyastatin 4 and the biofilm-inducing proteins Glucosyltransferase-I (GtfB) and VicR-like Protein (CovR) with the PyRx-Python Prescription 0.8 virtual screening software, employing Autodoc Vina as the docking engine [(Akshatha et al., 2021; Dallakyan & Olson, 2015; Trott & Olson, 2010)](https://paperpile.com/c/dhmMGS/i0h1+R7me+5Djl). The adjusted grid center and dimension coordinates were documented in Table 1. The best-fit model was selected based on the lowest binding affinity, and the interactions between the ligand and the proteins were visualized, interpreted, and recorded using BIOVIA Discovery Studio Visualizer 2024.

**Table 1.** The grid centre and dimension parameters set for MCP-1 and NFκB

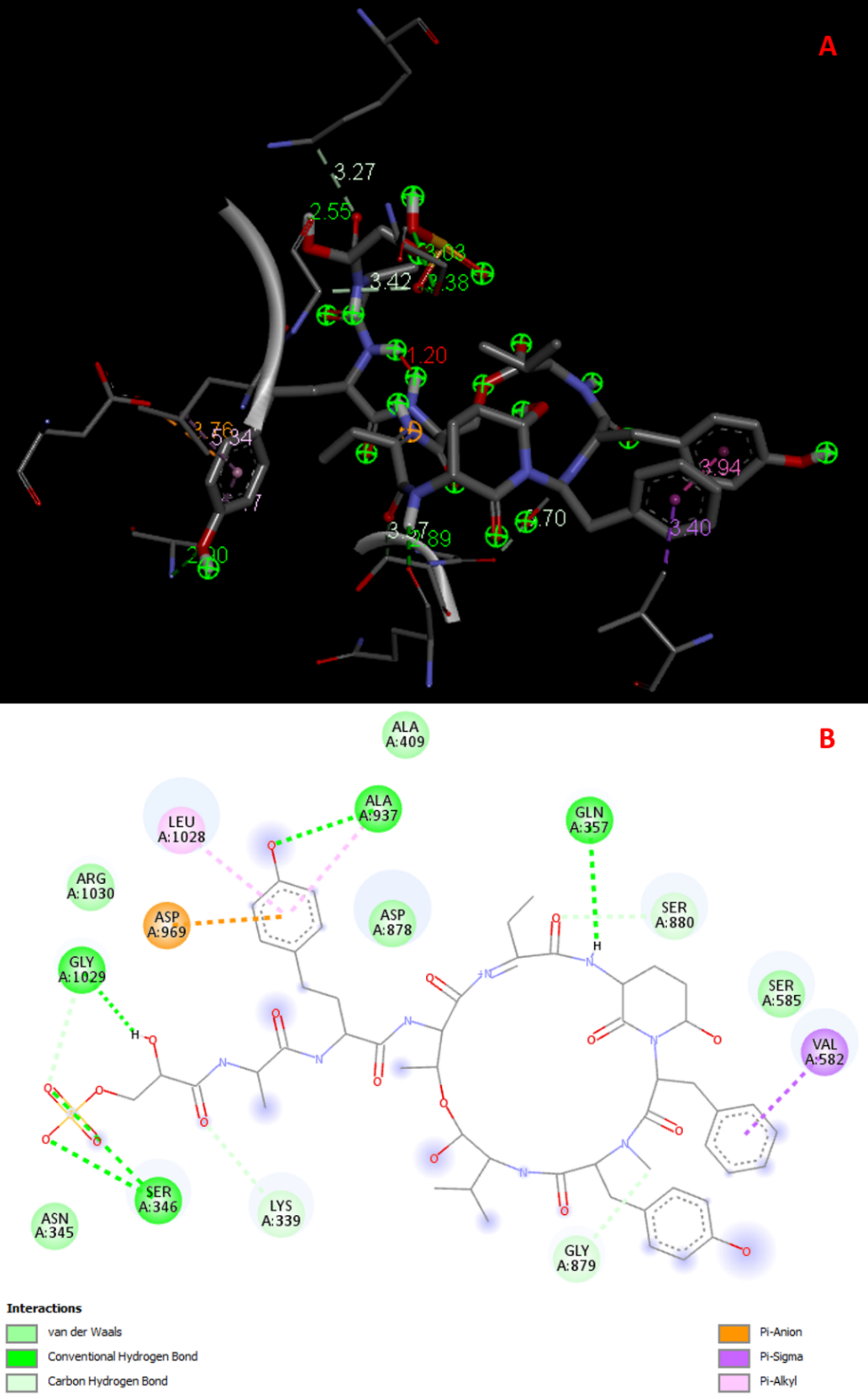
|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Grid Centre** | |  | **Dimensions (Å)** | | |
| Protein | PDB | X | Y | Z | X | Y | Z |
| Glucosyltransferase-I (GtfB) | 8FJC | -9.58 | 26.14 | 9.96 | 97.09 | 120.61 | 103.05 |
| VicR-like protein (CovR) | 8FK2 | 27.92 | 58.91 | -13.51 | 50.63 | 50.28 | 51.12 |

# Results

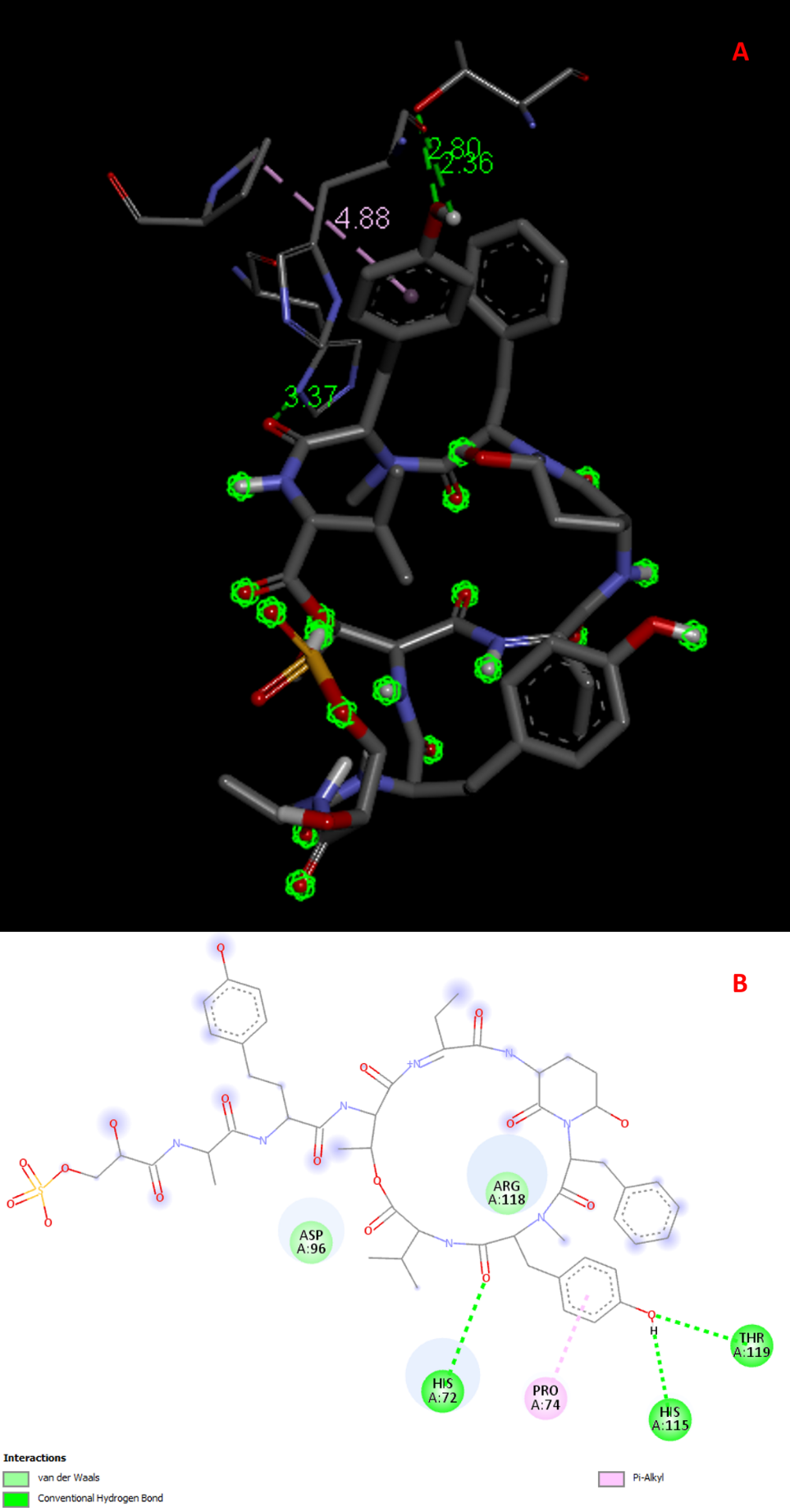
The molecular structure of Lyngbyastatin 4 is illustrated in Figure 1. The lowest binding affinity observed between Lyngbyastatin 4 and Glucosyltransferase-I (GtfB) was -8.9 kcal/mol (Table 2). Molecular docking analysis revealed that Lyngbyastatin 4 interacts with GtfB through five Van der Waals interactions involving ARG1030, ASN345, SER585, ASP878, and ALA409. Additionally, it forms five conventional hydrogen bonds with GLN357, ALA937, GLY1029, and two bonds with SER346. The ligand also engages in four carbon-hydrogen bonds with SER880, GLY879, LYS339, and GLY1029. Furthermore, interactions include one π-anion bond with ASP969, one π-sigma bond with VAL582, and two π-alkyl interactions with ALA937 and LEU1028 (Fig. 2 and Table 4). For the VicR-like protein (CovR), the binding affinity with Lyngbyastatin 4 was -5.1 kcal/mol (Table 3). This interaction comprises two Van der Waals contacts with ASP96 and ARG118, three conventional hydrogen bonds with HIS72, THR119, and HIS115, and one π-alkyl interaction with PRO74 (Fig. 3 and Table 5).



**Figure 1.** Molecular structure of a cyanobacterial polyketide Lyngbyastatin 4



**Figure 2.** Molecular interactions between the ligand Lyngbyastatin 4 and Glucosyltransferase-I (GtfB) showing five Van der Waals interactions (ARG1030; ASN345; SER585; ASP878; ALA409), five conventional hydrogen bonds (GLN357; ALA937; GLY1029; two bonds with SER346), four carbon-hydrogen bonds (SER880; GLY879; LYS339; GLY1029), one π-anion (ASP969); one π-sigma (VAL582), and two π-alkyl (ALA937; LEU1028) interactions; A) Three-dimensional view, B) Two-dimensional view.



**Figure 3**. Molecular interactions between the ligand Lyngbyastatin 4 and VicR-like protein (CovR) showing two Van der Waals interactions (ASP96; ARG118), three conventional hydrogen bonds (HIS72; THR119; HIS115), and one π-alkyl (PRO74) interactions; A) Three-dimensional view, B) Two-dimensional view.

**Table 2.** The table retrieved after molecular docking between Lyngbyastatin 4 and Glucosyltransferase-I (GtfB)

|  |  |  |  |
| --- | --- | --- | --- |
| **Ligand** | **Binding Affinity** | **rmsd/ub** | **rmsd/lb** |
| 8fjc\_A\_16104920\_uff\_E=3976.03 | -8.9 | 0 | 0 |
| 8fjc\_A\_16104920\_uff\_E=3976.03 | -8.5 | 4.808 | 2.589 |
| 8fjc\_A\_16104920\_uff\_E=3976.03 | -8.2 | 2.711 | 1.809 |
| 8fjc\_A\_16104920\_uff\_E=3976.03 | -7.9 | 25.965 | 20.226 |
| 8fjc\_A\_16104920\_uff\_E=3976.03 | -7.8 | 25.767 | 21.058 |
| 8fjc\_A\_16104920\_uff\_E=3976.03 | -7.8 | 5.321 | 2.626 |
| 8fjc\_A\_16104920\_uff\_E=3976.03 | -7.8 | 22.988 | 19.135 |
| 8fjc\_A\_16104920\_uff\_E=3976.03 | -7.8 | 16.869 | 9.495 |
| 8fjc\_A\_16104920\_uff\_E=3976.03 | -7.7 | 10.667 | 3.424 |

**Table 3.** The table retrieved after molecular docking between Lyngbyastatin 4 and VicR-like protein (CovR) showing binding affinity.

|  |  |  |  |
| --- | --- | --- | --- |
| **Ligand** | **Binding Affinity** | **rmsd/ub** | **rmsd/lb** |
| 8fk2\_A\_16104920\_uff\_E=3976.03 | -5.1 | 0 | 0 |
| 8fk2\_A\_16104920\_uff\_E=3976.03 | -5.1 | 33.072 | 28.047 |
| 8fk2\_A\_16104920\_uff\_E=3976.03 | -5 | 15.947 | 8.918 |
| 8fk2\_A\_16104920\_uff\_E=3976.03 | -5 | 15.091 | 8.151 |
| 8fk2\_A\_16104920\_uff\_E=3976.03 | -5 | 33.213 | 28.065 |
| 8fk2\_A\_16104920\_uff\_E=3976.03 | -4.8 | 34.049 | 30.442 |
| 8fk2\_A\_16104920\_uff\_E=3976.03 | -4.6 | 32.699 | 29.308 |
| 8fk2\_A\_16104920\_uff\_E=3976.03 | -4.6 | 33.847 | 28.579 |
| 8fk2\_A\_16104920\_uff\_E=3976.03 | -4.6 | 17.003 | 10.148 |

**Table 4.** The table showing bond interactions and its length between Lyngbyastatin 4 and Glucosyltransferase-I (GtfB) showing amino acid residues involves in it

|  |  |  |  |
| --- | --- | --- | --- |
| **Bond Interactions** | **No. of bonds** | **Bond length (Å)** | **Amino acid residue** |
| Van der Waals interactions | 5 |  | ARG1030  ASN345  SER585  ALA409  ASP878 |
| Conventional hydrogen bonds | 5 | 2.89 | GLN357 |
| 2.90 | ALA937 |
| 2.55 | GLY1029 |
| 3.03 | SER346 |
| 3.38 | SER346 |
| Carbon-hydrogen bonds | 4 | 3.37 | SER880 |
| 3.70 | GLY879 |
| 3.27 | LYS339 |
| 3.42 | GLY1029 |
| Pi-anion | 1 | 3.76 | ASP969 |
| Table 4: continued | | | |
| Pi-sigma | 1 | 3.40 | VAL582 |
| Pi-alkyl | 2 | 5.17 | ALA937 |
| 5.34 | LEU1028 |
| Total number of interactions | 18 |  |  |

**Table 5.** The table showing bond interactions and its length between Lyngbyastatin 4 and VicR-like protein (CovR) showing amino acid residues involves in it

|  |  |  |  |
| --- | --- | --- | --- |
| **Bond Interactions** | **No. of bonds** | **Bond length (Å)** | **Amino acid residue** |
| Van der Waals interactions | 2 |  | ASP96  ARG118 |
| Conventional hydrogen bond | 3 | 3.37 | HIS72 |
| 2.80 | THR119 |
| 2.36 | HIS115 |
| Pi-alkyl | 1 | 4.88 | PRO74 |
| Total number of interactions | 6 |  |  |

# Discussion

The molecular docking analysis of Lyngbyastatin 4 with Glucosyltransferase-I (GtfB) and VicR-like protein (CovR) of Streptococcus mutans provides valuable insights into the potential antibiofilm activity of this marine-derived polyketide. The results reveal significant differences in binding affinities and interaction patterns between Lyngbyastatin 4 and the two target proteins, suggesting a preferential inhibitory effect on GtfB over CovR. Lyngbyastatin 4, as depicted in Figure 1, is a complex cyclic depsipeptide with a unique structural framework [(Pavithra et al., 2023; Shenoy, Maiti, et al., 2023; Thomas & Jain, 2023)](https://paperpile.com/c/dhmMGS/OYvtb+kS5W8+mt7Op). This molecular architecture appears to play a crucial role in its binding capabilities, particularly with respect to GtfB [(Doshi et al., 2023; Lampl et al., 2023; Pandiyan et al., 2023)](https://paperpile.com/c/dhmMGS/I2guU+vXuLo+Bk7af). The lowest binding affinity of -8.9 kcal/mol between Lyngbyastatin 4 and GtfB (Table 2) indicates a strong and energetically favorable interaction. This binding affinity is substantially lower than typical thresholds for biologically relevant protein-ligand interactions, which are often considered significant at -6.0 kcal/mol or lower [(Du et al., 2016)](https://paperpile.com/c/dhmMGS/R8GI). The strength of this interaction suggests that Lyngbyastatin 4 could effectively inhibit GtfB function, potentially disrupting the synthesis of water-insoluble glucans that are critical for S. mutans biofilm formation [(Janani et al., 2021; Kachhara et al., 2021; Subramanian et al., 2023)](https://paperpile.com/c/dhmMGS/esgsB+bNRnO+FsTGh). A study evaluated the antibacterial effects of chlorhexidine and pomegranate peel extract (PPE) oral rinses on S. mutans, Lactobacilli, and Veillonella in patients with advanced dental caries. Although PPE showed some antimicrobial activity, chlorhexidine was significantly more effective in reducing S. mutans after four weeks (p = 0.043) [(Jacob et al., 2021)](https://paperpile.com/c/dhmMGS/KRkA).The extensive network of interactions between Lyngbyastatin 4 and GtfB, as illustrated in Figure 2 and detailed in Table 4, further supports the likelihood of effective inhibition [(Gandhi et al., 2021; Katyal et al., 2023; Priyadharshini et al., 2023)](https://paperpile.com/c/dhmMGS/zsJJS+WzQzZ+oYNjS). The presence of five Van der Waals interactions, five conventional hydrogen bonds, four carbon-hydrogen bonds, and various π-interactions indicates a multifaceted binding mode that could stabilize the ligand-protein complex [(Chokkattu et al., 2023; Dharman et al., 2023; Govindaraj & Shanmugam, 2023)](https://paperpile.com/c/dhmMGS/QPrEd+xL74b+aX22r). Of particular interest are the conventional hydrogen bonds formed with GLN357, ALA937, GLY1029, and SER346 (two bonds). These hydrogen bonds are known to play a crucial role in determining the specificity and strength of protein-ligand interactions [(Patil et al., 2010)](https://paperpile.com/c/dhmMGS/A0Tg). The diversity of interactions, including π-anion, π-sigma, and π-alkyl interactions, suggests that Lyngbyastatin 4 may be able to adapt to and exploit various binding pockets within the GtfB structure [(Rajeshkumar & Lakshmi, 2021; Sivakumar et al., 2021)](https://paperpile.com/c/dhmMGS/LX2Oh+CHhL4).The involvement of residues such as ARG1030, ASN345, and SER585 in these interactions is noteworthy, as these amino acids are often conserved in glucosyltransferases and may be integral to the catalytic function of GtfB [(Ren et al., 2016)](https://paperpile.com/c/dhmMGS/bV2J). By interacting with these residues, Lyngbyastatin 4 could potentially interfere with the enzyme's active site or induce conformational changes that impair its ability to synthesize glucans. This mechanism of action would be consistent with the observed antibiofilm effects of other natural products that target glucosyltransferases in S. mutans [(Jeon et al., 2011)](https://paperpile.com/c/dhmMGS/sHcG).In contrast to the strong interaction with GtfB, the binding of Lyngbyastatin 4 to the VicR-like protein CovR appears to be considerably weaker, with a binding affinity of -5.1 kcal/mol (Table 3). This affinity, while still indicating a favorable interaction, is significantly higher (less negative) than that observed for GtfB. The interaction profile between Lyngbyastatin 4 and CovR is also less extensive, comprising only two Van der Waals interactions, three conventional hydrogen bonds, and one π-alkyl interaction (Figure 3 and Table 5). This limited interaction network suggests that Lyngbyastatin 4 may have a less pronounced effect on CovR function compared to its impact on GtfB.The observed differences in binding affinities and interaction patterns between Lyngbyastatin 4 and the two target proteins (GtfB and CovR) may have important implications for the compound's overall antibiofilm activity against S. mutans. The stronger interaction with GtfB suggests that Lyngbyastatin 4 could primarily exert its antibiofilm effects through the inhibition of glucan synthesis rather than through modulation of CovR-regulated gene expression. This preferential targeting of GtfB aligns with the critical role of glucans in the structural integrity and virulence of S. mutans biofilms [(Bowen & Koo, 2011)](https://paperpile.com/c/dhmMGS/jxVZ).However, it is important to note that even the weaker interaction with CovR could still contribute to the overall antibiofilm activity of Lyngbyastatin 4. CovR, as a global regulator of virulence gene expression in S. mutans, influences various aspects of biofilm formation and bacterial pathogenicity (6). Even a modest modulation of CovR activity could potentially lead to downstream effects on biofilm-related gene expression, complementing the more direct inhibition of glucan synthesis through GtfB targeting.The differential binding affinities and interaction patterns observed in this study also provide valuable insights for future drug design efforts. The strong and specific interaction between Lyngbyastatin 4 and GtfB could serve as a starting point for the development of more potent and selective GtfB inhibitors. Structure-activity relationship studies could focus on enhancing the interactions identified in this analysis, particularly the hydrogen bonding network and π-interactions, to further improve binding affinity and specificity [(Shenoy, Rohinikumar, et al., 2023; P. Singh, Maiti, et al., 2024; P. Singh, Shenoy, et al., 2024)](https://paperpile.com/c/dhmMGS/f4Yjv+kuVmb+NFBF0).While the molecular docking results are promising, it is crucial to acknowledge the limitations of in silico approaches. The static nature of docking simulations may not fully capture the dynamic aspects of protein-ligand interactions in physiological conditions. Additionally, factors such as solvent effects, protein flexibility, and potential allosteric interactions are not always adequately represented in docking studies. Therefore, these computational findings should be validated and complemented by experimental studies, including in vitro enzyme inhibition assays, biofilm formation assays, and structural biology techniques such as X-ray crystallography or NMR spectroscopy.

# Conclusion

In conclusion, the molecular docking analysis of Lyngbyastatin 4 with GtfB and CovR provides compelling evidence for its potential as an antibiofilm agent against S. mutans. The strong and specific interaction with GtfB suggests a primary mechanism of action through inhibition of glucan synthesis, while the weaker interaction with CovR may contribute to a multi-faceted antibiofilm effect. These findings not only support the further investigation of Lyngbyastatin 4 as a promising lead compound for dental caries prevention but also highlight the potential of marine-derived natural products in the development of novel antibiofilm strategies.

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