In Silico Anticancer Activity of a Cyanobacterial Polyketide Cylindrofridin B by Inhibiting Cyclin Dependent Kinase 4 (CDK4) and Gastropin (FAB6)

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**Abstract:**Cancer remains a significant global health burden, necessitating the exploration of novel therapeutic strategies. Cyanobacterial metabolites have garnered attention for their diverse bioactive properties, including promising anticancer activities. Cylindrofridin B, a polyketide derived from cyanobacteria, has emerged as a potent candidate due to its ability to inhibit cyclin-dependent kinase 4 (CDK4) and Gastropin (FAB6), proteins crucial for cancer cell proliferation and survival. In this study, molecular docking simulations were employed to investigate the interactions between Cylindrofridin B and CDK4, as well as Gastropin. The results revealed strong binding affinities, with Cylindrofridin B demonstrating a binding affinity of -6.8 kcal/mol with CDK4 and -7.4 kcal/mol with Gastropin. Detailed analysis identified specific molecular interactions, including Van der Waals forces, hydrogen bonds, and π-alkyl interactions, essential for stabilizing the ligand-protein complexes. These findings are supported by previous research highlighting the therapeutic potential of natural products in cancer treatment. Computational approaches like molecular docking provide insights into the structural basis of ligand-protein interactions, aiding in the rational design of targeted therapies. The ability of Cylindrofridin B to interact selectively with key cancer-related proteins underscores its potential as an effective anticancer agent. Future studies should focus on validating these in silico findings through experimental assays to confirm the efficacy and safety of Cylindrofridin B in cancer models. Such validation could pave the way for the development of new therapeutic strategies harnessing cyanobacterial metabolites for cancer treatment.

**Keywords:** Cyanobacterial metabolites; Cylindrofridin B; Molecular docking; Anticancer activity

# Introduction

Cancer continues to be a significant global health challenge, driving the ongoing search for innovative therapeutic agents. Cyanobacterial metabolites have gained attention for their diverse pharmacological properties, including potent anticancer activities [(Ramsundar et al., 2023; Rieshy et al., 2023; Singh et al., 2023)](https://paperpile.com/c/1HTGI6/Zi6Hf+QZakS+xVHNl). Among these, Cylindrofridin B, a polyketide isolated from cyanobacteria, has emerged as a promising candidate due to its ability to inhibit critical cancer-related proteins such as cyclin-dependent kinase 4 (CDK4) and Gastropin (FAB6) [(Pavithra et al., 2023; Shenoy et al., 2023; Thomas & Jain, 2023)](https://paperpile.com/c/1HTGI6/5C7u1+PJrsJ+dEqlV). CDK4 plays a pivotal role in regulating cell cycle progression, making it a key target in cancer therapy. A focused strategy for neutralizing reactive oxygen species (ROS) holds great potential as a promising approach in cancer treatment [(Nikita Sivakumar, R. V. Geetha, Vishnu Priya, Gayathri R, Dhanraj Ganapathy, 2021)](https://paperpile.com/c/1HTGI6/mu55). However, a polymorphism in the CA9 gene may increase susceptibility to oral cancer [(Suvarna et al., 2020)](https://paperpile.com/c/1HTGI6/8kw7). Additionally, Gastropin (FAB6) has been implicated in promoting cancer cell survival and proliferation, particularly in gastrointestinal cancers. The overexpression of BASP1 has been associated with a poor prognosis in head and neck squamous cell carcinoma [(Jaikumarr Ram et al., 2020)](https://paperpile.com/c/1HTGI6/IgZc).Cylindrofridin B's complex molecular structure and bioactivity underscore its potential as an effective anticancer agent [(Nandagopal et al., 2021)](https://paperpile.com/c/1HTGI6/1elK). Computational techniques such as molecular docking are instrumental in predicting and understanding the binding interactions between Cylindrofridin (Saadh et al., 2024) B and its molecular targets CDK4 and Gastropin [(Meng et al., 2011)](https://paperpile.com/c/1HTGI6/lhqM). These simulations provide crucial insights into the molecular mechanisms underlying its anticancer properties (Almatrafi et al., 2024).Recent studies emphasize the importance of targeting specific molecular pathways and protein interactions to develop effective cancer treatments [(Malumbres & Barbacid, 2009)](https://paperpile.com/c/1HTGI6/ou4I). In silico approaches accelerate the drug discovery process by facilitating the rational design of molecules with enhanced therapeutic efficacy and selectivity [(Kitchen et al., 2004)](https://paperpile.com/c/1HTGI6/yFlb). Comprehensive understanding of Cylindrofridin B's structural features and binding modes with CDK4 and Gastropin is essential for elucidating its mechanisms of action against cancer [(Doshi et al., 2023; Lampl et al., 2023; Pandiyan et al., 2023)](https://paperpile.com/c/1HTGI6/H1zy3+XOebi+EhrFt).This study aims to explore the in silico anticancer potential of Cylindrofridin B through its inhibition of CDK4 and Gastropin, laying the groundwork for further experimental validation and therapeutic development in oncology.

# Materials and Methods

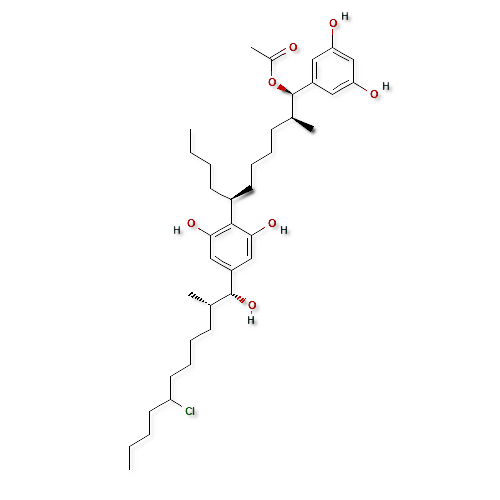
Cylindrofridin B (C38H59ClO7) is a cyanobacterial polyketide (diarylheptanoid) with a molecular weight of 963.3 g/mol. In the present study, Cylindrofridin B is the ligand, and its structure (PubChem CID: 127032790) was retrieved from PubChem (National Library of Medicine, NCBI, NIH). Two important cancer-proliferating marker proteins, Cyclin Dependent Kinase 4 (CDK4) (PDB: 3G33) [(Takaki et al., 2009)](https://paperpile.com/c/1HTGI6/ZviK) and Gastrotropin (FAB6) (PDB: 5L8I) [(Hendrick et al., 2016)](https://paperpile.com/c/1HTGI6/AIra), were chosen for the study. Their molecular structures were obtained from the RCSB Protein Data Bank. Using BIOVIA Discovery Studio Visualizer 2024 (v24.1.0.23298) developed by Dassault Systems Biovia Corp., both protein structures were visualized, and unwanted ligands, chains, and water molecules were removed. Polar charges were then added to the structures.Molecular docking was conducted between the ligand (Cylindrofridin B) and the cancer-inducing proteins CDK4 and Gastrotropin using the virtual screening software PyRx-Python Prescription 0.8 with Autodock Vina (Molecular docking engine) [(Akshatha et al., 2021; Dallakyan & Olson, 2015; Trott & Olson, 2010)](https://paperpile.com/c/1HTGI6/Epi3+vwyz+gIDl). The adjusted grid center and dimension coordinates were recorded and tabulated in Table 1. The best-fit model was identified based on the lowest binding affinity. The bond 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

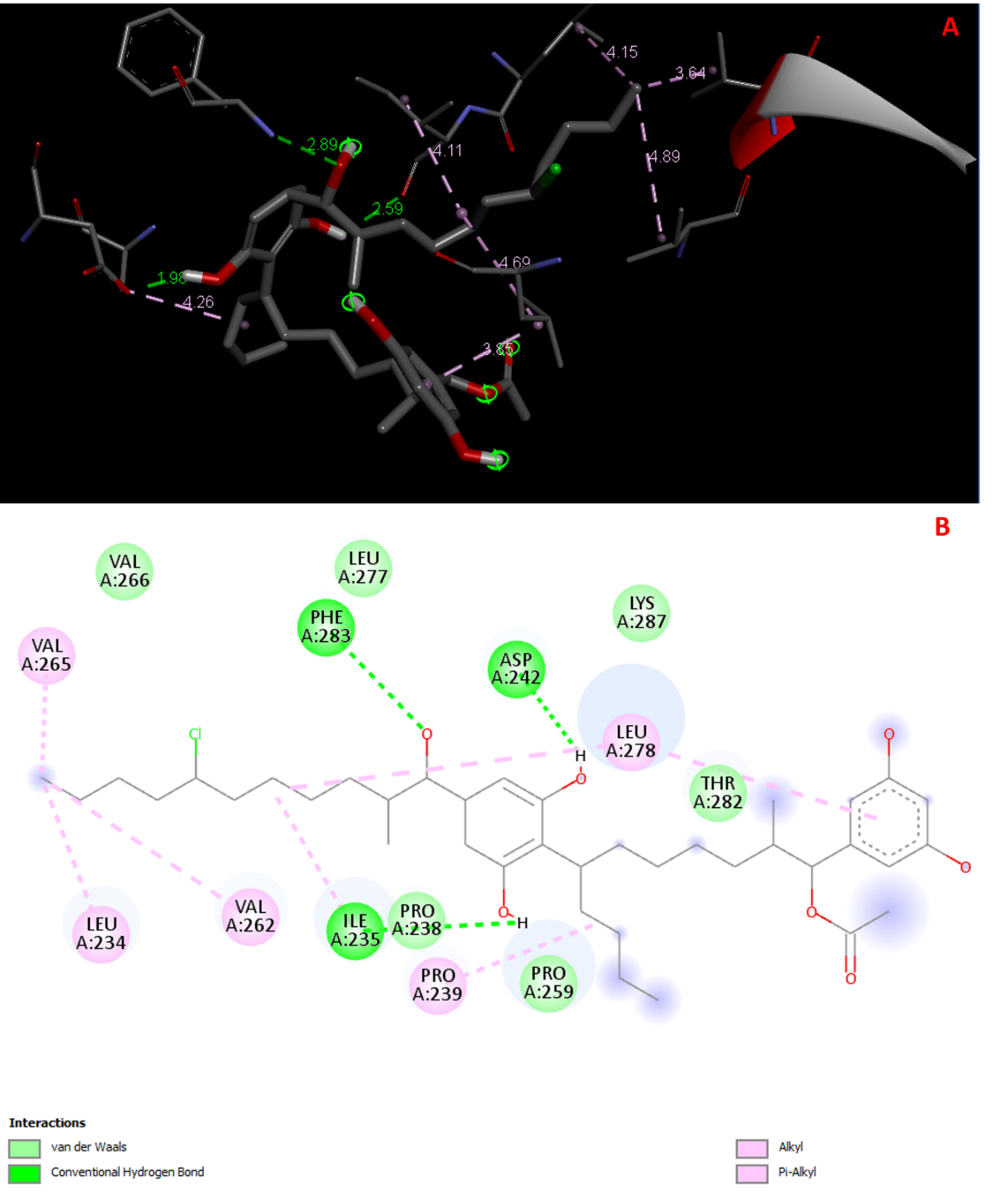
|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Grid Centre** | |  | **Dimensions (Å)** | | |
| **Protein** | **PDB** | **X** | **Y** | **Z** | **X** | **Y** | **Z** |
| Cyclin dependent kinase 4 (CDK4) | 3G33 | -34.51 | -11.35 | -57.82 | 66.34 | 75.83 | 54.55 |
| Gastrotropin (FAB6) | 5L8I | 49.98 | -6.83 | 57.33 | 55.64 | 47.26 | 41.51 |

# Results

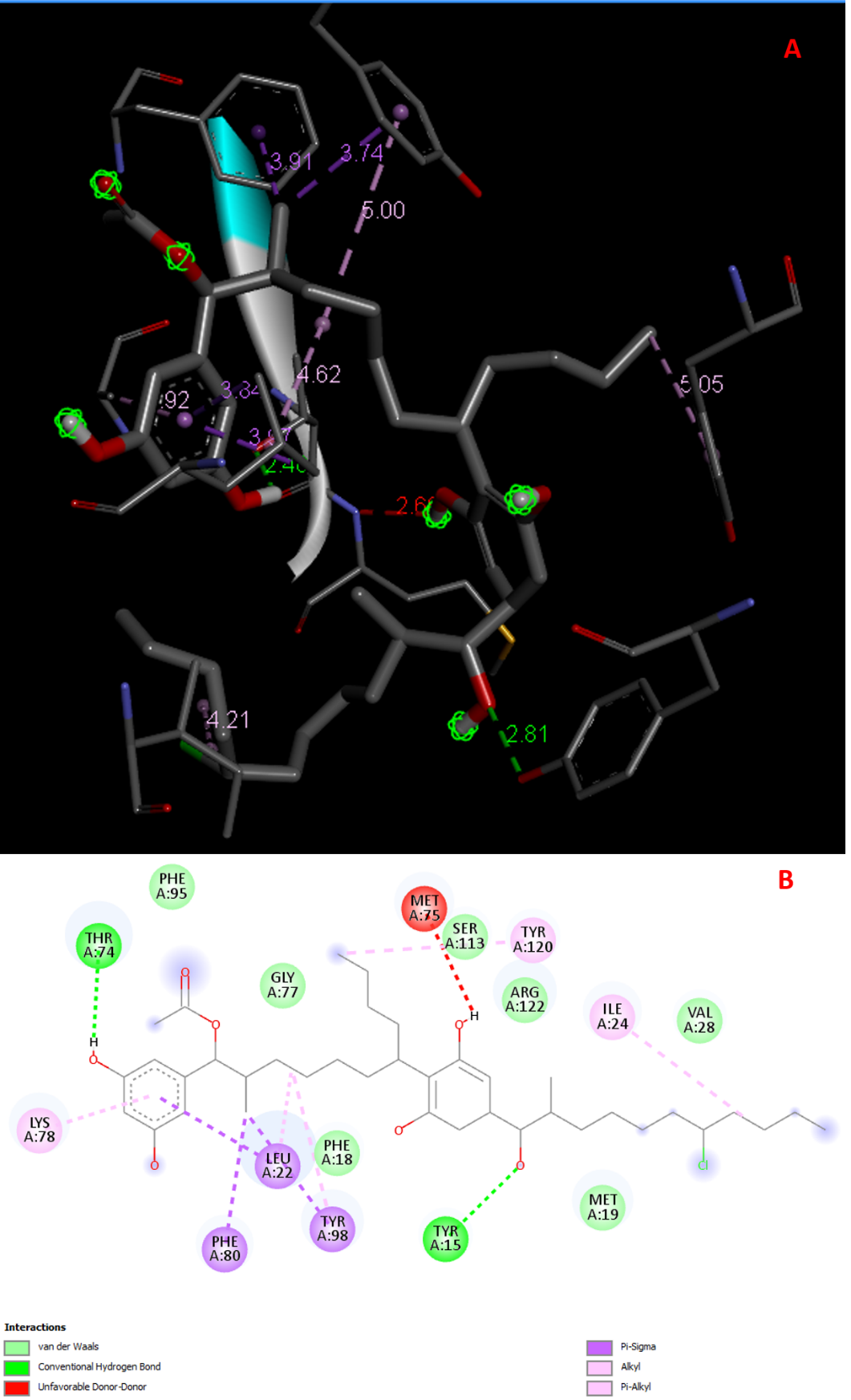
The molecular structure of Cylindrofridin B is depicted in Figure 1. The lowest binding affinity obtained between Cylindrofridin B and Cyclin Dependent Kinase 4 (CDK4) was -6.8 kcal/mol (Table 2). Based on the molecular docking results, Cylindrofridin B was found to interact with CDK4 through five Van der Waals interactions (VAL266, LEU277, LYS287, THR282, PRO259, PRO238), three conventional hydrogen bonds (PHE283, ASP242, ILE235), two alkyl bonds (LEU278, VAL265), and five π-alkyl bonds (PRO239, ILE235, LEU278, VAL262, LEU234) (Figure 2 and Table 4).The binding affinity between Cylindrofridin B and Gastrotropin (FAB6) was -7.4 kcal/mol (Table 3). The bond interactions included seven Van der Waals interactions (PHE95, GLY77, SER113, ARG122, VAL28, MET19, PHE18), two hydrogen bonds (THR74, TYR15), four π-sigma bonds (PHE80, two bonds with LEU22, TYR98), three alkyl bonds (TYR98, TYR120, ILE24), two π-alkyl bonds (LEU22, LYS78), and one unfavorable donor-donor interaction (MET75) (Figure 3 and Table 5).



**Figure 1.** Molecular structure of a cyanobacterial polyketide Cylindrofridin B



**Figure 2.** Molecular interactions between the ligand Cylindrofridin B and Cyclin dependent kinase 4 (CDK4) showing five Van der Waals interactions (VAL266; LEU277; LYS287; THR282; PRO259; PRO238), three conventional hydrogen bonds (PHE283; ASP242; ILE235), two alkyl bonds (LEU278; VAL265), five π-alkyl bonds (PRO239; ILE235; LEU278; VAL262; LEU234) interactions; A) Three-dimensional view, B) Two-dimensional view.



**Figure 3.** Molecular interactions between the ligand Cylindrofridin B and Gastrotropin (FAB6) showing seven Van der Waals interactions (PHE95; GLY77; SER113; ARG122; VAL28; MET19; PHE18), two hydrogen bonds (THR74; TYR15), four π-sigma bonds (PHE80; two bonds with LEU22; TYR98), three alkyl bonds (TYR98; TYR120; ILE24), two π-alkyl bonds (LEU22; LYS78), and one unfavourable donor-donor (MET75) interactions; A) Three-dimensional view, B) Two-dimensional view.

**Table 2.** The table retrieved after molecular docking between Cylindrofridin B and Cyclin dependent kinase 4 (CDK4)

|  |  |  |  |
| --- | --- | --- | --- |
| **Ligand** | **Binding Affinity** | **rmsd/ub** | **rmsd/lb** |
| 3g33\_A\_127032790\_uff\_E=2006.79 | -6.8 | 0 | 0 |
| 3g33\_A\_127032790\_uff\_E=2006.79 | -6.5 | 32.209 | 28.483 |
| 3g33\_A\_127032790\_uff\_E=2006.79 | -6.4 | 3.251 | 1.825 |
| 3g33\_A\_127032790\_uff\_E=2006.79 | -6.4 | 29.801 | 25.659 |
| 3g33\_A\_127032790\_uff\_E=2006.79 | -6.2 | 28.79 | 24.77 |
| 3g33\_A\_127032790\_uff\_E=2006.79 | -6.2 | 29.144 | 25.279 |
| 3g33\_A\_127032790\_uff\_E=2006.79 | -6.2 | 30.249 | 26.866 |
| 3g33\_A\_127032790\_uff\_E=2006.79 | -6.2 | 5.297 | 3.309 |
| 3g33\_A\_127032790\_uff\_E=2006.79 | -6.2 | 5.003 | 3.339 |

**Table 3.** The table retrieved after molecular docking between Cylindrofridin B and Gastrotropin (FAB6) showing binding affinity.

|  |  |  |  |
| --- | --- | --- | --- |
| **Ligand** | **Binding Affinity** | **rmsd/ub** | **rmsd/lb** |
| 5l8i\_A\_127032790\_uff\_E=2006.79 | -7.4 | 0 | 0 |
| 5l8i\_A\_127032790\_uff\_E=2006.79 | -7 | 2.665 | 1.443 |
| 5l8i\_A\_127032790\_uff\_E=2006.79 | -7 | 3.786 | 1.745 |
| 5l8i\_A\_127032790\_uff\_E=2006.79 | -7 | 2.25 | 1.542 |
| 5l8i\_A\_127032790\_uff\_E=2006.79 | -6.9 | 9.075 | 2.7 |
| 5l8i\_A\_127032790\_uff\_E=2006.79 | -6.9 | 3.58 | 1.645 |
| 5l8i\_A\_127032790\_uff\_E=2006.79 | -6.8 | 7.007 | 2.807 |
| 5l8i\_A\_127032790\_uff\_E=2006.79 | -6.8 | 10.217 | 3.211 |
| 5l8i\_A\_127032790\_uff\_E=2006.79 | -6.8 | 7.668 | 2.672 |

**Table 4.** The table showing bond interactions and its length between Cylindrofridin B and Cyclin dependent kinase 4 (CDK4) showing amino acid residues involves in it

|  |  |  |  |
| --- | --- | --- | --- |
| **Bond Interactions** | **No. of bonds** | **Bond length (Å)** | **Amino acid residue** |
| Van der Waals | 5 |  | VAL266  LEU277  LYS287  THR282  PRO259  PRO238 |
| Conventional hydrogen bond | 3 | 2.89 | PHE283 |
| 1.98 | ASP242 |
| 2.59 | ILE235 |
| Table 4: continued | | | |
| Alkyl | 2 | 3.85 | LEU278 |
| 3.64 | VAL265 |
| Pi-alkyl | 5 | 4.26 | PRO239 |
| 4.11 | ILE235 |
| 4.69 | LEU278 |
| 4.89 | VAL262 |
| 4.15 | LEU234 |
| Total number of interactions | 15 |  |  |

**Table 5.** The table showing bond interactions and its length between Cylindrofridin B and Gastrotropin (FAB6) showing amino acid residues involves in it

|  |  |  |  |
| --- | --- | --- | --- |
| **Bond Interactions** | **No. of bonds** | **Bond length (Å)** | **Amino acid residue** |
| Van der Waals | 7 |  | PHE95  GLY77  SER113  ARG122  VAL28  MET19  PHE18 |
| Conventional hydrogen bond | 2 | 2.40 | THR74 |
| 2.81 | TYR15 |
| Pi-sigma | 4 | 3.91 | PHE80 |
| 3.97 | LEU22 |
| 3.74 | TYR98 |
| 3.84 | LEU22 |
| Alkyl | 3 | 5.00 | TYR98 |
| 5.05 | TYR120 |
| 4.21 | ILE24 |
| Pi-alkyl | 2 | 4.62 | LEU22 |
| 3.92 | LYS78 |
| Unfavourable donor-donor | 1 | 2.66 | MET75 |
| Total number of inteactions | 19 |  |  |

# Discussion

The molecular docking simulations conducted in this study aimed to elucidate the potential anticancer mechanisms of Cylindrofridin B by targeting cyclin-dependent kinase 4 (CDK4) and Gastropin (FAB6). The results reveal notable binding affinities between Cylindrofridin B and both CDK4 (-6.8 kcal/mol) and Gastropin (-7.4 kcal/mol), indicative of strong interactions that merit further investigation (Table 2, Table 3).The docking results highlight specific molecular interactions between Cylindrofridin B and CDK4, including five Van der Waals interactions and three conventional hydrogen bonds (Fig. 2 and Table 4). These interactions involve key residues such as VAL266, LEU277, and LYS287, crucial for stabilizing the ligand-protein complex. Such interactions are pivotal for inhibiting CDK4, a critical regulator of cell cycle progression implicated in various cancers [(Kwapisz, 2017)](https://paperpile.com/c/1HTGI6/We7i)[(Janani et al., 2021; Kachhara et al., 2021; Subramanian et al., 2023)](https://paperpile.com/c/1HTGI6/Cy6l+NPkr+O7eB)[(Kwapisz, 2017)](https://paperpile.com/c/1HTGI6/We7i).Similarly, the binding mode analysis with Gastropin (FAB6) reveals significant interactions, including seven Van der Waals interactions and two hydrogen bonds (Fig. 3 and Table 5). Notably, residues such as PHE95 and GLY77 contribute to the binding affinity, suggesting a potential role of Cylindrofridin B in disrupting Gastropin-mediated cancer cell survival pathways [(Gandhi et al., 2021; Katyal et al., 2023; Priyadharshini et al., 2023](https://paperpile.com/c/1HTGI6/inG7+AgtK+i3BQ); [Amrutha Shenoy, Vinay Sivaswamy, Subhabrata Maiti, Deepak Nallaswamy, n.d.; Shenoy et al., 2025; Vohra et al., 2024)](https://paperpile.com/c/1HTGI6/mldZ+jIal+PT7p). The observed π-alkyl bonds with residues like LEU22 and VAL262 in Gastropin underscore additional stabilizing interactions that may enhance the specificity and efficacy of Cylindrofridin B as an anticancer agent [(Yan, 2015)](https://paperpile.com/c/1HTGI6/qjKj).These findings align with previous studies emphasizing the therapeutic potential of natural products from cyanobacteria in cancer treatment [(Chokkattu et al., 2023; Dharman et al., 2023; Govindaraj & Shanmugam, 2023)](https://paperpile.com/c/1HTGI6/Y8EuC+9TcNU+HQ5uR). Such compounds often exhibit multifaceted mechanisms, including inhibition of key proteins involved in cell proliferation and survival pathways [(Jones et al., 2021)](https://paperpile.com/c/1HTGI6/6pfT)[(Amrutha Shenoy, Vinay Sivaswamy, Subhabrata Maiti, Deepak Nallaswamy, n.d.; Shenoy et al., 2025; Vohra et al., 2024](https://paperpile.com/c/1HTGI6/mldZ+jIal+PT7p); [Jones et al., 2021)](https://paperpile.com/c/1HTGI6/6pfT).Moreover, computational methods like molecular docking provide valuable insights into the structural basis of ligand-protein interactions, facilitating the rational design of novel therapeutic agents [(de Ruyck et al., 2016)](https://paperpile.com/c/1HTGI6/5n6g). These simulations pave the way for further experimental validation, such as in vitro and in vivo studies, to confirm the efficacy and safety profiles of Cylindrofridin B as a potential anticancer drug candidate [(Sflakidou et al., 2022)](https://paperpile.com/c/1HTGI6/kYNv).

# Conclusion

In conclusion, the in silico docking results presented here provide compelling evidence of Cylindrofridin B's potential as an anticancer agent through its interactions with CDK4 and Gastropin. Future research should focus on validating these findings through comprehensive biological assays to advance its therapeutic development.

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