Evaluation of the Anticancer Potential of Cyanobacterin Through Inhibition of Heat Shock 70 Kda Protein (HSPA6) and Cyclin-Dependent Kinase 4 (CDK4) - an In-Silico Approach

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**Abstract:** A documented secondary metabolite of cyanobacteria is called cyanobacterin; nonetheless, there is a significant lack of information regarding their biological tests. Therefore, a molecular docking effort was conducted to interpret its anticancer activity. The study's findings indicate that the ligand cyanobacterin binds to heat shock 70 kDa protein (HSPA6) and cyclin-dependent kinase 4 (CDK4) with a stronger affinity of -7.4 kcal/mol and -7.9 kcal/mol, respectively. Cyanobacterin's chlorine interacts with CDK4's tyrosine (TYR:127) and HSPA6's arginine (ARG:38) through alkyl bond interactions. Increased CDK4 activity is linked to uncontrolled cell division, which is a defining feature of cancer. CDK4 aids in the growth and survival of tumors by encouraging cell cycle progression. In a similar vein, HSP70 promotes tumor growth by stabilizing and facilitating the activity of signaling molecules and oncoproteins that control cell survival and proliferation. According to the study, cyanobacterin binds highly to heat shock 70 kDa protein (HSP70) and cyclin-dependent kinase 4 (CDK4), two indicators linked to the development of cancer.

**Keywords:** Cyanobacterin; CDK4; HSP70; Molecular docking.

# Introduction

It is well established that cyanobacterial metabolites have cytotoxic effects on cancer cells via a variety of ways. By causing cell cycle arrest and encouraging apoptosis (programmed cell death) in cancer cells, it has been shown to prevent cell proliferation [(Nandagopal et al., 2021)](https://paperpile.com/c/CrHAsT/YpE16). The main way that cyanobacterin operates as an algicide is by interfering with essential physiological functions in algae. It obstructs the processes necessary for algae growth and reproduction through metabolic pathways, breaks down cellular membranes, or hinders photosynthesis[(Ramsundar et al., 2023; Rieshy et al., 2023; Singh et al., 2023)](https://paperpile.com/c/CrHAsT/qa0TI+YRUDw+1z855). Cyanobacterin is frequently seen as being more environmentally benign than typical chemical algicides because it comes from natural sources and, when applied properly, may have lesser toxicity to non-target organisms [[(Ishibashi et al., 2005; Zanchett & Oliveira-Filho, 2013)](https://paperpile.com/c/CrHAsT/sK0oF+jbZAu). A study evaluated the onset and progression of oral complications in 40 head and neck cancer patients undergoing chemoradiotherapy [(Pavithra et al., 2023; Shenoy et al., 2023; Thomas & Jain, 2023)](https://paperpile.com/c/CrHAsT/tTwxf+R4Zzl+20EIX). Most complications emerged by the second week, with severity peaking in the sixth week [(Chokkattu et al., 2023; Dharman et al., 2023; Govindaraj & Shanmugam, 2023)](https://paperpile.com/c/CrHAsT/egMek+Un8EU+jMs8A). Awareness of these issues can help clinicians develop better management strategies to improve patients' quality of life [(Keziah et al., 2022)](https://paperpile.com/c/CrHAsT/svpha).Cyclin-Dependent Kinase 4 (CDK4) phosphorylates important proteins involved in the G1 to S phase transition, which plays a critical role in controlling cell cycle progression [(Gandhi et al., 2021; Katyal et al., 2023; Priyadharshini et al., 2023)](https://paperpile.com/c/CrHAsT/L4kDv+iS3L9+do67A). Regarding the prognosis of cancer, CDK4 has been linked to a number of cancer forms, where dysregulation or overexpression of the protein can cause unchecked cell proliferation, a characteristic of cancer [(Janani et al., 2021; Kachhara et al., 2021; Subramanian et al., 2023)](https://paperpile.com/c/CrHAsT/pEVT8+w3v41+pSSoN). The significance of CDK4 in cancer biology and treatment approaches is highlighted by its dual position as a therapeutic target and a possible prognostic indicator, as demonstrated by its participation in cancer prognosis [(Fassl et al., 2022; Kollmann et al., 2013; Spring et al., 2019)](https://paperpile.com/c/CrHAsT/P2ORi+wrjwV+Ca3Ti).As a molecular chaperone, Heat Shock Protein 70 (HSP70) is a member of the heat shock protein family [(Doshi et al., 2023; Lampl et al., 2023; Pandiyan et al., 2023)](https://paperpile.com/c/CrHAsT/4ufAx+XwGHS+miBmA). HSP70 has a variety of functions in cancer that may affect the prognosis. HSP70 aids in the survival of cancer cells under harsh circumstances, such as those brought on by radiation, chemotherapy, and the environment surrounding the tumor [(Rajeshkumar & Lakshmi, 2021; Sivakumar et al., 2021)](https://paperpile.com/c/CrHAsT/2od8L+Oz9fu). Because it promotes cell survival in harsh environments, its overexpression in cancer cells has been linked to treatment resistance and a worse prognosis. Higher HSP70 levels have been associated with worse outcomes in a number of malignancies. This is frequently because of its function in encouraging metastasis, survival of cancer cells, and resistance to apoptosis (programmed cell death), all of which are essential components of cancer growth and resistance to treatment. The multidimensional significance of HSP70 in tumor growth, treatment resistance, and immune system interaction is highlighted by its association with cancer prognosis. Gaining insight into these areas may result in new treatment strategies and improved prognostic evaluations for cancer patients [(Calderwood & Gong, 2016; Chatterjee & Burns, 2017; Das et al., 2019)](https://paperpile.com/c/CrHAsT/Ia06J+KRYIp+HsJ9M). More focused research is necessary to fully comprehend the precise mechanisms by which cyanobacterin exerts its anticancer effects, particularly any interactions with the CDK4 and HSP70 pathways. Consequently, the current work aimed to interpret the in silico molecular docking and molecular interactions of cyanobacterin that impede HSPA6 (HSP70) and CDK4.

# Materials and Methods

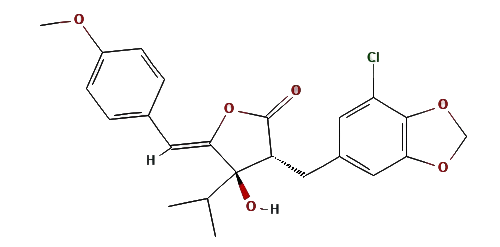
A naturally occurring substance with a molecular weight of 430.9 g/mol, cyanobacterin (C23H23ClO6) is produced by several cyanobacteria, particularly the freshwater cyanobacterium *Scytonema hofmanii*, which is well-known for its beneficial qualities [(Mason et al., 1982)](https://paperpile.com/c/CrHAsT/DiorT). Its potential as an antibacterial and anti-inflammatory agent has attracted interest. Studies indicate that it might find use in agriculture and pharmacology, especially in the creation of novel medications and eco-friendly insecticides. However, further studies are needed to fully understand its mechanisms and potential risks before widespread application. The ligand structure of cyanobacterin (PubChem CID: 6437843) was retrieved from PubChem (National Library of Medicine, NCBI, NIH). The two important cancer biomarker proteins such as Cyclin-dependent kinase 4 (CDK4) (PDB: 6P8E) [(Guiley et al., 2019)](https://paperpile.com/c/CrHAsT/VOwA8) and Heat shock 70 kDa protein 6 (HSPA6) (PDB: 3FE1) [(Wisniewska et al., 2010)](https://paperpile.com/c/CrHAsT/5yHyZ) were selected for the investigation, and the RCSB PDB protein data library was used to obtain their molecular structure. Using BIOVIA Discovery Studio Studio Visualizer 2024 (v24.1.0.23298) (Dassault Systems Biovia Corp.), the protein structures were both visualized and undesired ligands, chains, and water molecules were eliminated and added with polar charges.PyRx-Python Prescription 0.8, a virtual screening program, was used to perform molecular docking between the ligand and proteins using Autodoc Vina (Molecular docking engine) [(Akshatha et al., 2021; Dallakyan & Olson, 2015; Trott & Olson, 2010)](https://paperpile.com/c/CrHAsT/nrkvX+VvuhA+LYdhq). The coordinates for the altered grid centre and size were noted and tallied in **Table 1.** The low binding affinity led to the derivation of the best-fit model. The BIOVIA Discovery Studio Visualizer 2024 was used to record, analyse, and evaluate the bond interactions between the ligand and the protein.

**Table 1:** The grid centre and dimension parameters set for cyclin dependent kinase 4 (CDK4) and heat shock 70kDa protein (HSP6).

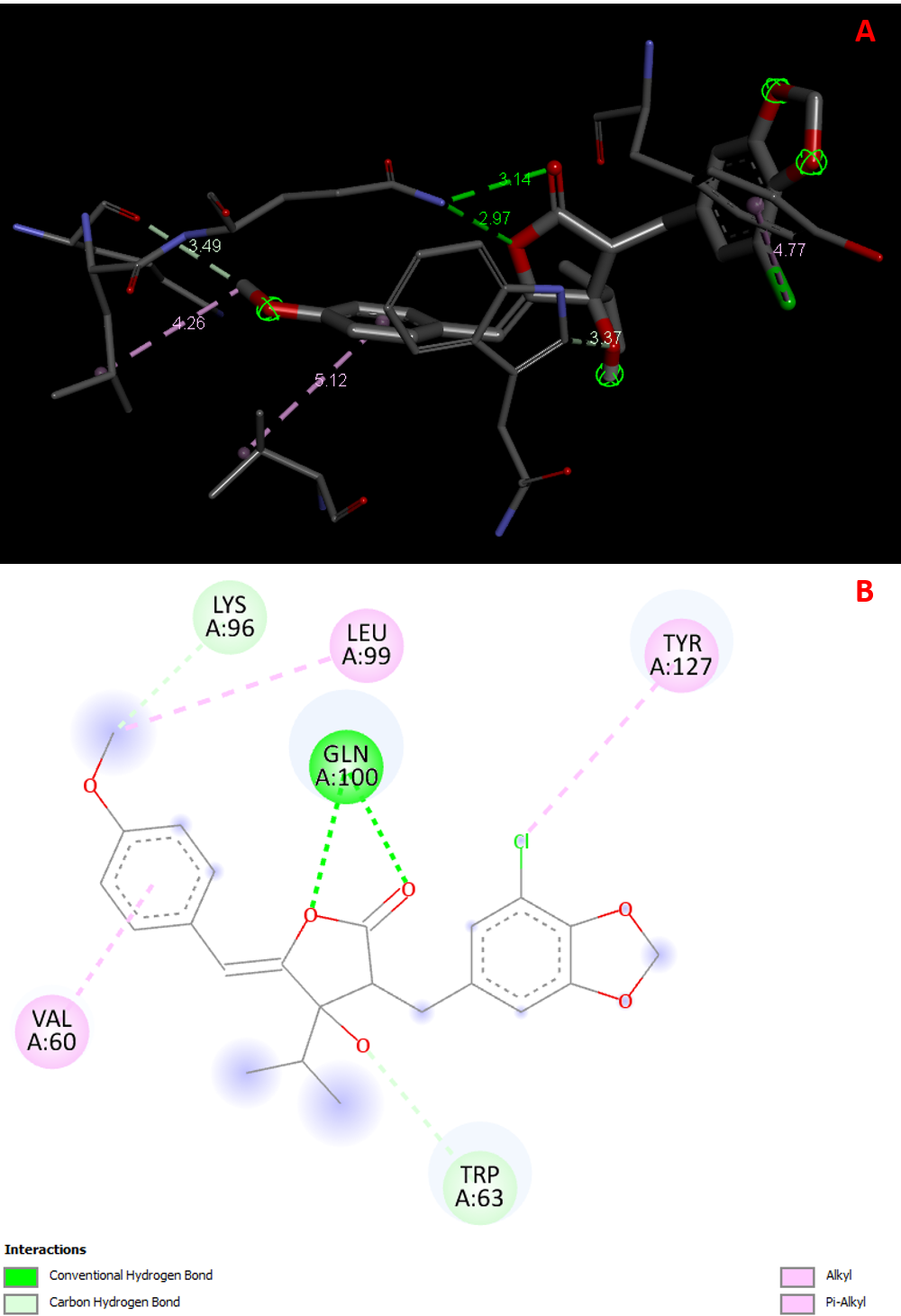
|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Grid Centre | |  | Dimensions (Å) | | |
| Protein | PDB | X | Y | Z | X | Y | Z |
| Cyclin-dependent kinase 4 (CDK4) | 6P8E | 36.08 | 13.84 | 43.61 | 67.95 | 69.56 | 63.43 |
| Heat shock 70 kDa protein (HSPA6) | 3FE1 | 73.7 | -27.74 | 0.04 | 69.46 | 71.81 | 72.99 |

# Results and Discussion

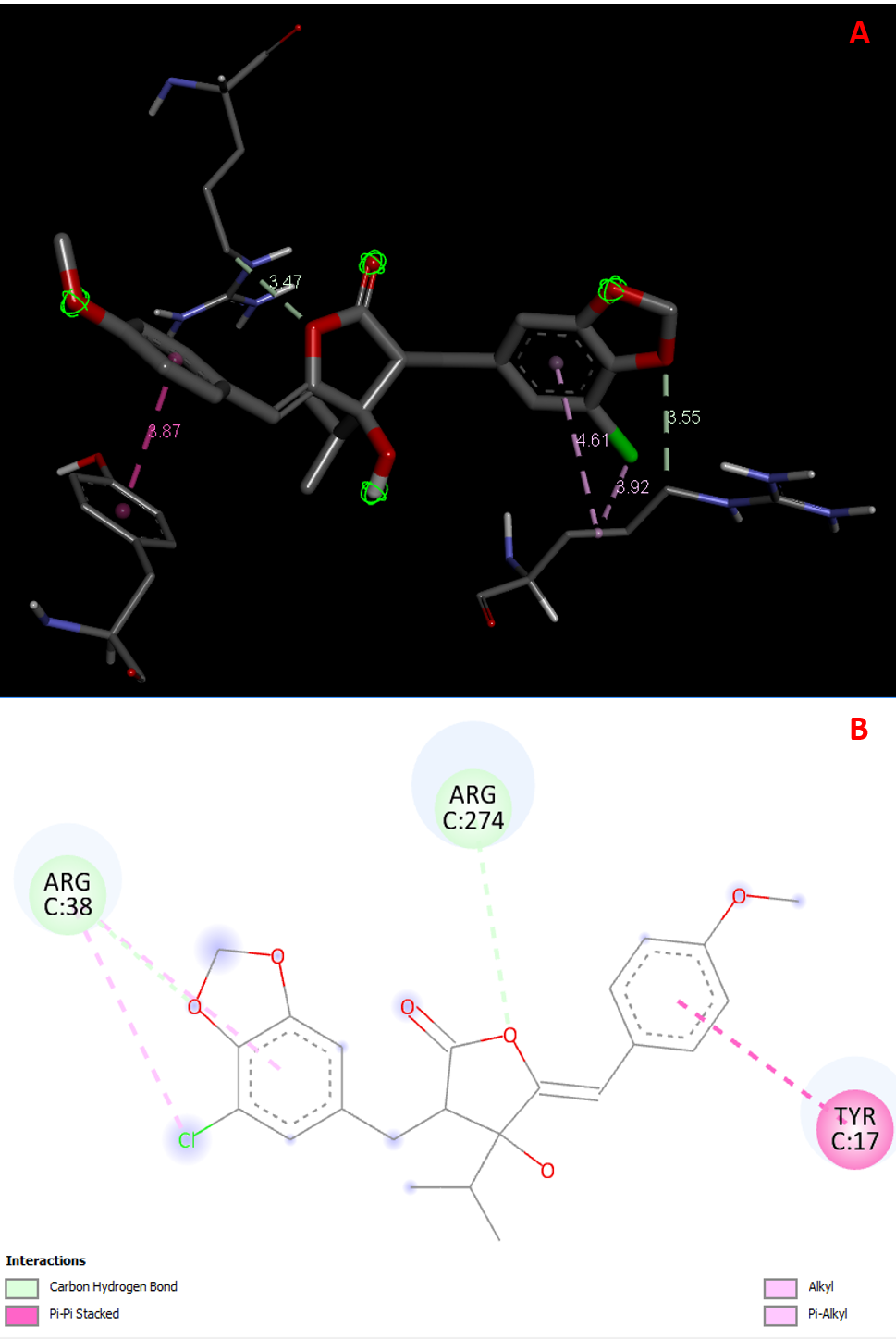
The capacity of cyanobacterin, a substance generated from cyanobacteria, to inhibit or kill algae has been investigated. The prospective applications of this feature in other disciplines, including bioactive tests like anticancer activity, make it interesting. By focusing on photosynthesis, respiration, enzyme activity, and the creation of oxidative stress, cyanobacterins have the ability to restrict the growth of algae. Therefore, it was examined for anticancer efficacy against two anticancer biomarkers, CDK4 and HSPA6, in the current study. The binding affinities of the ligand cyanobacterin (Fig. 1) with heat shock 70 kDa protein (HSPA6) (3FE1) and cyclin-dependent kinase 4 (CDK4) (6P8E) were determined to be -7.9 kcal/mol and -7.4 kcal/mol, respectively (Table 2 & 3) (Almatrafi et al., 2024). According to Figure 2 and Table 4, the molecule cyanobacterin has two hydrogen bonds, two carbon-hydrogen bonds, two alkyl bond interactions, and one π-alkyl bond with CDK4 (6P8E). With one alkyl, π- π Stacked, and π- alkyl bond interactions, the cyanobacterin in HSPA6 (3FE1) only creates two carbon-hydrogen bonds (Fig. 3 & Table 5).Cyanobacterin has the lowest binding energy of -7.9 kcal/mol with HSPA6, despite having more bond contacts with CDK4 (binding free energy -7.4 kcal/mol), including two more hydrogen bond interactions (Saadh et al., 2024). Thus, cyanobacterin has a higher binding affinity for both HSPA6 and CDK4, with the affinity for HSPA6 being considerably higher. Furthermore, cyanobacterin's chlorine interacts via alkyl bonds with CDK4's arginine (ARG:38) and tyrosine (TYR:127), respectively. Induction of dopamine significantly reduced Bcl-2, PI3K, and Akt expression, enhancing cell death in a dose-dependent manner. Exercise-induced dopamine shows potential as an anticancer agent against lung cancer [(Sanjay et al., 2022)](https://paperpile.com/c/CrHAsT/OvM64). It has been found that desacetylmicrocolin B from Lyngbya cf. polychroa and gallinamide A from Schizothrix sp. are anti-neuroblastoma cyanobacterial peptides. These peptides exhibit potency against human (IMR-32, NB7, and SH-SY5Y) and mouse (Neuro-2a, N-18) cell lines [(Jones et al., 2021; Linington et al., 2009)](https://paperpile.com/c/CrHAsT/Gq30q+0g6cV). Another study assesses the quality of life among 225 treated head and neck cancer patients using the EORTC QLQ C-30 and QLQ-HN35 instruments and showed severe oral health issues, particularly in patients receiving combined treatments. Quality of life assessments should inform treatment planning and postoperative care strategies [(Deb Barma et al., 2021)](https://paperpile.com/c/CrHAsT/7SDtn). In SH-SY5Y lines, cyclolaxaphycins B and B3 elevate caspase 3 with IC50 values of 1.8 and 0.8 µM, respectively [(Alvariño et al., 2020)](https://paperpile.com/c/CrHAsT/p3epR). One of the essential components in the onset of apoptosis is caspase-8. Its suppression promotes and amplifies NB carcinogenesis [(Stupack et al., 2006; Tummers & Green, 2017)](https://paperpile.com/c/CrHAsT/hLmA6+MzW6X). Somocystinamide A stimulates caspase-8 activation in Neuro-2a and NB7 cells [(Wrasidlo et al., 2008)](https://paperpile.com/c/CrHAsT/rv5Ko). In the present study, cyanobacterin, a metabolite of cyanobacteria that has been shown to have anti-algal action, concurrently demonstrated anticancer activity through its association with HSP70 and CDK4.



**Figure 1.** Molecular structure of Cyanobacterin with a single chlorine



**Figure 2.** Molecular interactions between the ligand Cyanobacterin and cyclin dependent kinase 4 (CDK4) showing two hydrogen bonds, one carbon-hydrogen bond and an alkyl bond interaction with chlorine, A) Three-dimensional view, B) Two-dimensional view.



**Figure 3.** Molecular interactions between the ligand Cyanobacterin and heat shock 70kDa protein 6 (hsp70) showing two carbon-hydrogen bond interaction and an alkyl bond interaction with chlorine, A) Three-dimensional view, B) Two-dimensional view.

**Table 2.** The table retrieved after molecular docking between cyanobacterin and CDK4 showing binding affinity.

|  |  |  |  |
| --- | --- | --- | --- |
| **Ligand** | **Binding Affinity** | **rmsd/ub** | **rmsd/lb** |
| 6p8e-1\_6437843\_uff\_E=741.23 | -7.4 | 0 | 0 |
| 6p8e-1\_6437843\_uff\_E=741.23 | -7 | 38.237 | 36.118 |
| 6p8e-1\_6437843\_uff\_E=741.23 | -6.6 | 16.674 | 14.043 |
| 6p8e-1\_6437843\_uff\_E=741.23 | -6.5 | 16.281 | 14.051 |
| 6p8e-1\_6437843\_uff\_E=741.23 | -6.4 | 2.026 | 1.652 |
| 6p8e-1\_6437843\_uff\_E=741.23 | -6.4 | 22.141 | 18.419 |
| 6p8e-1\_6437843\_uff\_E=741.23 | -6.4 | 36.784 | 34.658 |
| 6p8e-1\_6437843\_uff\_E=741.23 | -6.3 | 29.632 | 26.824 |
| 6p8e-1\_6437843\_uff\_E=741.23 | -6.3 | 19.967 | 17.804 |

**Table 3.** The table retrieved after molecular docking between Cyanobacterin and HSPA6 showing binding affinity.

|  |  |  |  |
| --- | --- | --- | --- |
| Ligand | Binding Affinity | rmsd/ub | rmsd/lb |
| 3fe1-3\_6437843\_uff\_E=741.23 | -7.9 | 0 | 0 |
| 3fe1-3\_6437843\_uff\_E=741.23 | -7.8 | 1.998 | 1.287 |
| 3fe1-3\_6437843\_uff\_E=741.23 | -7.5 | 22.848 | 17.13 |
| 3fe1-3\_6437843\_uff\_E=741.23 | -7.4 | 3.372 | 2.591 |
| 3fe1-3\_6437843\_uff\_E=741.23 | -7.3 | 21.827 | 18.673 |
| 3fe1-3\_6437843\_uff\_E=741.23 | -7.3 | 22.232 | 18.027 |
| 3fe1-3\_6437843\_uff\_E=741.23 | -7.1 | 28.039 | 26.501 |
| 3fe1-3\_6437843\_uff\_E=741.23 | -7 | 8.112 | 4.4 |
| 3fe1-3\_6437843\_uff\_E=741.23 | -7 | 8.462 | 6.741 |

**Table 4.** The table showing bond interactions and its length between cyanobacterin and CDK4 showing amino acid residues involves in it

|  |  |  |  |
| --- | --- | --- | --- |
| **Bond Interactions** | **No. of bonds** | **Bond length (Å)** | **Amino acid residue** |
| Conventional Hydrogen Bond | 2 | 3.14 | GLN100 |
| 2.97 | GLN100 |
| Carbon Hydrogen Bond | 2 | 3.37 | TRP63 |
| 3.49 | LYS96 |
| Alkyl | 2 | 4.26 | LEU99 |
| 4.77 | TYR127 |
| Pi-Alkyl | 1 | 5.12 | VAL60 |
| Total interactions | 7 |  | |

**Table 5.** The table showing bond interactions and its length between cyanobacterin and HSPA6 showing amino acid residues involves in it

|  |  |  |  |
| --- | --- | --- | --- |
| **Bond Interactions** | **No. of bonds** | **Bond length (Å)** | **Amino acid residue** |
| Carbon Hydrogen Bond | 2 | 3.55 | ARG98 |
| 3.47 | ARG274 |
| Alkyl | 1 | 3.92 | ARG98 |
| Pi-Pi Stacked | 1 | 3.87 | TYR17 |
| Pi-Alkyl | 1 | 4.61 | ARG38 |
| Total interactions | 5 |  | |

# Conclusion

Cyanobacterin is a secondary metabolite derived from cyanobacteria. However, there is a significant lack of biological assays exploring its potential. Therefore, efforts were made to investigate its anticancer activity using molecular docking. The study revealed that cyanobacterin binds with high affinity to cyclin-dependent kinase 4 (CDK4) and heat shock 70 kDa protein (HSP70), both of which are biomarkers associated with cancer development.

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