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Virtual Screening for Identification of Pyridines and Pyrimidines as Potent CDK9 Inhibitors

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Abstract

Cyclin-dependent kinase 9 (CDK9) has emerged as a promising therapeutic target for various cancers and viral infections due to its crucial role in cell cycle regulation and transcriptional control. In this study, we present a comprehensive virtual screening approach aimed at identifying novel pyridine and pyrimidine derivatives as potent CDK9 inhibitors. Utilizing computational tools and molecular docking simulations, we screened a large chemical library to prioritize compounds with favorable binding affinities and pharmacokinetic properties. Subsequent in silico ADMET (absorption, distribution, metabolism, excretion, and toxicity) analysis was employed to assess the drug-likeness and safety profile of the identified candidates. The top-ranking compounds were further evaluated through molecular dynamics simulations to elucidate their dynamic behavior and stability within the CDK9 binding pocket. Our findings reveal several promising pyridine and pyrimidine derivatives with potential CDK9 inhibitory activity, warranting further experimental validation and optimization for therapeutic development against cancer and other CDK9-associated diseases. This integrative computational approach demonstrates its efficacy in accelerating drug discovery efforts and offers valuable insights into structure-activity relationships for the design of novel CDK9 inhibitors.

Keywords: CDK9 inhibitors, anti cancer drugs, virtual screening, pyridines, pyrimidines.

INTRODUCTION

What are CDK9 inhibitors?

CDK9 inhibitors are a class of drugs that target cyclin-dependent kinase 9 (CDK9), a protein involved in regulating the cell cycle and transcription. CDK9 is a component of the positive transcription elongation factor b (P-TEFb) complex, which is critical for the expression of genes involved in processes like cell growth, differentiation, and apoptosis.

These inhibitors are primarily studied for their potential as anti-cancer agents. By blocking CDK9 activity, they can disrupt the transcription of genes that promote cancer cell proliferation and survival. Additionally, CDK9 inhibitors have shown promise in treating other diseases such as HIV/AIDS, where CDK9 plays a role in viral replication.

Several CDK9 inhibitors have been developed and are in various stages of preclinical and clinical developmet. Some examples include- Flavopiridol, Dinaciclib, Alvocidib (flavopiridol analog), AZD4573 [1-4].

MECHANISM OF ACTION

CDK9 (Cyclin-Dependent Kinase 9) inhibitors are a class of compounds designed to block the activity of CDK9, a protein kinase involved in regulating the cell cycle and transcription. CDK9 forms a complex with cyclin T and is a part of positive transcription elongation factor b (P-TEFb). P-TEFb phosphorylates the C-terminal domain of RNA polymerase II, leading to the release of paused RNA polymerase II into active transcription elongation.

The mechanism of action of CDK9 inhibitors involves blocking the kinase activity of CDK9, which in turn inhibits the phosphorylation of RNA polymerase II. This inhibition leads to the arrest of transcriptional elongation, preventing the production of mRNA for genes involved in cell proliferation, survival, and other essential cellular processes.

By interfering with transcriptional elongation, CDK9 inhibitors can induce cell cycle arrest and promote apoptosis (programmed cell death) in cancer cells that are dependent on continuous transcription for their survival. Therefore, CDK9 inhibitors hold promise as potential anticancer agents, particularly in cancers where dysregulated transcription plays a significant role in disease progression. Additionally, CDK9 inhibitors are being investigated for their potential in treating other diseases where dysregulated transcription contributes to pathology, such as certain viral infections and cardiac hypertrophy[5-9].

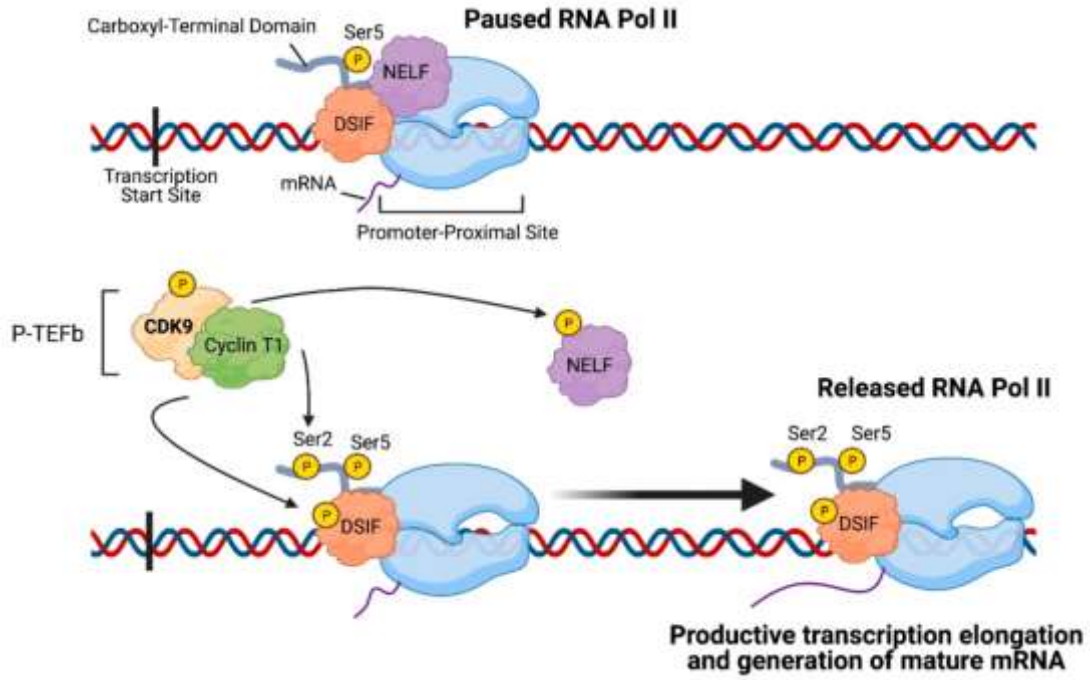


Figure: 1 mechanism of action of CDK9 inhibitors

Pyridine derivatives:

1. Pyridine is a heterocyclic aromatic compound with a six-membered ring containing one nitrogen atom.
2. Various pyridine derivatives have been synthesized and evaluated for their CDK9 inhibitory activity.
3. These compounds often undergo structural modifications to enhance their potency, selectivity, and pharmacokinetic properties.
4. Pyridine derivatives can interact with the ATP-binding site of CDK9, thereby inhibiting its kinase activity[10-15].

Pyrimidine derivatives:

1. Pyrimidine is another heterocyclic aromatic compound that contains two nitrogen atoms in a six-membered ring.
2. Pyrimidine derivatives have also been investigated as CDK9 inhibitors. Similar to pyridine derivatives, these compounds are designed to interact with the ATP-binding site of CDK9, thereby inhibiting its kinase activity and downstream signaling pathways involved in cell proliferation and survival.
3. Structural modifications of pyrimidine scaffolds aim to enhance potency, selectivity, and other pharmacological properties of the inhibitors[10-15].

VIRTUAL SCREENING

Virtual screening is a computational technique used in drug discovery to identify potential drug candidates from large libraries of compounds. Instead of physically testing each compound in a laboratory setting, virtual screening uses computer algorithms and molecular modeling to predict the likelihood that a compound will bind to a target molecule of interest, such as a protein associated with a disease[table 1-2].

- •Protein id: 8K5R [figure-2]
- •Protein Name: CDK9/cyclin T1 in complex with KB-0742
- •Classification: TRANSCRIPTION
- •Organism(s): Homo sapiens
- •Resolution: 3.37 Å
- •Chain:A-330 and B-259 amino acids

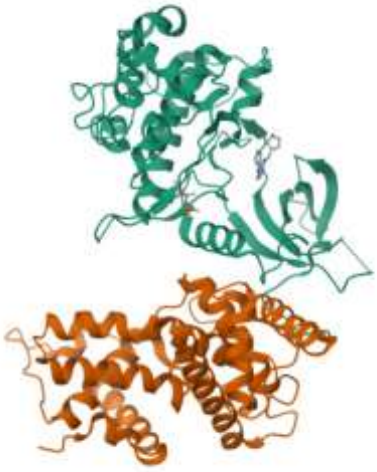


Figure: 2 protein 8K5R

LIGANDS

- Ligands was downloaded from pubchem database.
- Ligand selection done by using lipinski rule and activity of particular ligand.

S.no	PUBCHEM ID	Binding energy kcal/mol
1	89594	-5.5
2	16004	-4.7
3	10371	-4.8
4	1049	-4.5
5	641266	-5.4
6	1727	-4.1
7	8635	-5.2
8	79222	-4.6
9	1094883	-4.9
10	76258	-5.3
11	205586	-5.6
12	938	-5.2
13	936	-5.2
14	7522	-5.7
15	2181	-5.5
16	767	-5.2
17	79	-5.0
18	7675	-5.0
19	7521	-4.9
20	10439	-4.6

21	8817	-5.2
22	7963	-4.6
23	7502	-4.7
24	1474	-5.8
25	7728	-5.2
26	7953	-5.0
27	7937	-4.8
28	7970	-4.5
29	16584	-5.2
30	7047	-6.0
31	16990	-4.7
32	2761171	-5.0
33	7526	-4.5
34	135408742	-6.8
35	129011822	-8.5
36	135419024	-6.3
37	135400471	-7.0
38	135459491	-6.3
39	135770216	-6.1
40	135599726	-7.5
41	135415580	-6.7

42	135527764	-6.6
43	135541675	-6.4
44	135415581	-6.5
45	135408736	-7.2
46	135481940	-7.0
47	139596941	-5.8
48	135398752	-6.4
49	135446206	-6.5
50	90688312	-7.3
51	135409957	-7.0
52	135418580	-6.5
53	91749128	-7.1
54	91749129	-7.1
55	91749131	-7.4
56	91749133	-7.4
57	91749137	-7.3
58	91749144	-6.6
59	135401907	-6.7
60	135444498	-6.4
61	135420611	-6.6
62	135408763	-6.2

63	135399235	-6.5
64	135403646	-6.2
65	135445058	-6.7
66	136057764	-6.1
67	135413525	-6.7
68	135408766	-6.5
69	136041714	-6.3
70	135402055	-6.3
71	135470126	-6.6
72	135408640	-6.6
73	135493710	-6.5
74	135439714	-6.9
75	135401776	-7.5
76	135418928	-6.5
77	135398708	-6.3
78	91749679	-7.7
79	135448147	-7.2
80	135487866	-6.5
81	135424353	-7.1
82	135406869	-6.2
83	135410720	-6.0

84	135431249	-6.2
85	135431330	-6.3
86	135476780	-6.5
87	135402388	-6.4
88	135416732	-6.2
89	100318	-5.9
90	151174	-8.4
91	610950	-6.6
92	3042423	-6.8
93	3811929	-6.9
94	90408860	-8.3
95	5329462	-8.0
96	5329467	-6.9
97	9965429	-7.3
98	11098241	-7.2
99	24798742	-6.8
100	24971381	-6.7
101	71543359	-8.0
102	73755149	-8.0
103	90408860	-7-7
104	135472985	-6.2

Table: 1 binding affinity of pyridine and pyrimidine derivatives

S.NO	PUBCHEM ID	Binding energy kcal/mol
1	129011822	-8.5
2	91749679	-7.7
3	151174	-8.4
4	90408860	-8.3
5	71543359	-8.3
6	73755149	-8.0

Tables: 2 HIT molecules with highest binding interactions

SwissADME

SwissADME will process the input and provide a comprehensive report detailing various molecular properties. These properties include drug-likeness (assessed through filters like Lipinski's Rule of Five), pharmacokinetics (such as absorption, distribution, metabolism, and excretion profiles), physicochemical properties (like molecular weight, logP, and solubility), and potential bioavailability. The results are presented in a user-friendly format, including visual representations and detailed numerical data, which can be used to assess the drug-like potential and other relevant characteristics of the molecule. Using SwissADME we predicted the following properties of the hit molecules:

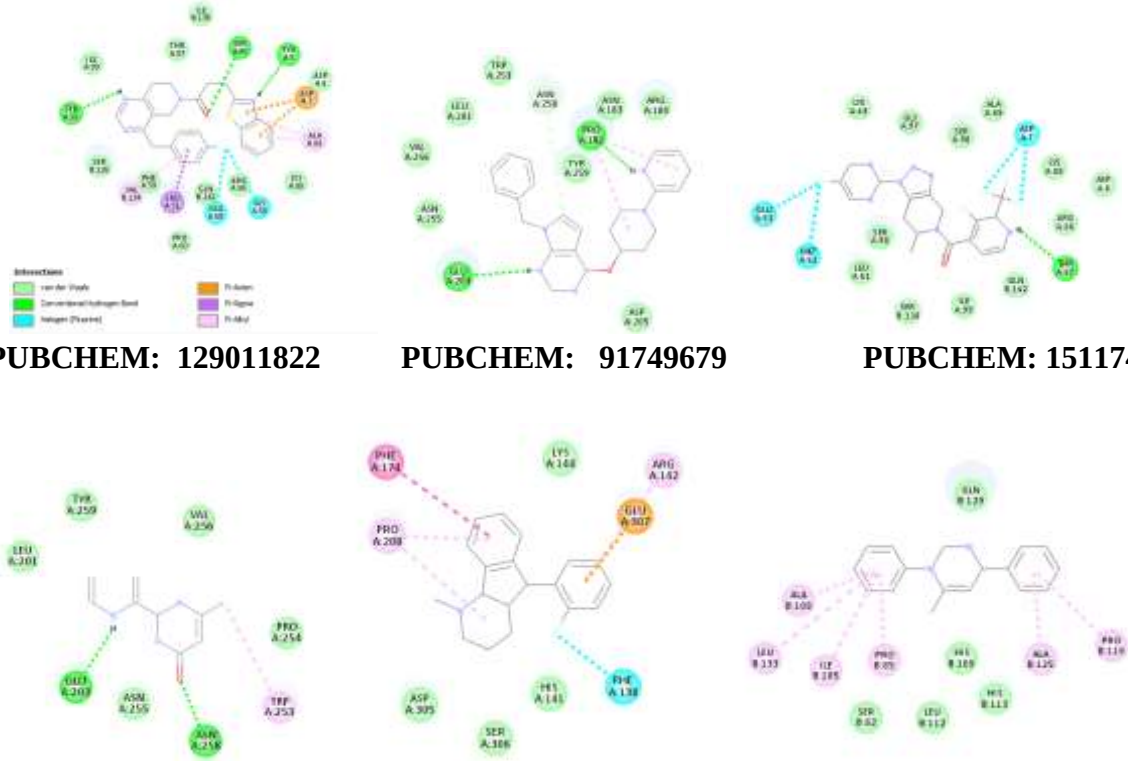
Name	**ilogp**	**Logs(esol)**	**Gi-Absorption**	**Lipinski**	**Bioavailability**	**Logk_p**
129011822	3.23	-4.54	high	yes	0.55	-5.08
91749679	3.00	-3.88	high	yes	0.55	-5.37
151174	2.93	-4.82	low	yes	0.11	-8.28
90408860	2.51	-3.86	high	yes	0.55	-6.22
71543359	3.44	-5.15	high	yes	0.55	-6.09
73755149	3.39	-5.05	high	yes	0.55	-5.70

Table: 3 ADME properties of active molecules using SWISSADME:

BIOVIA Discovery Studio

BIOVIA Discovery Studio is a comprehensive software suite designed for molecular modeling, simulation, and visualization. It is primarily used in the fields of life sciences, particularly in drug discovery and materials science. Developed by Dassault Systèmes, Discovery Studio provides a range of tools for researchers to explore the structure and behavior of biological molecules, facilitating the design and optimization of new compounds.

The platform offers high-quality 3D visualization tools, allowing researchers to explore molecular interactions, study the results of simulations, and communicate their findings effectively. The molecular interactions of the hit molecules have been vistualized by this method and they are:



PUBCHEM: 129011822 **PUBCHEM: 91749679** **PUBCHEM: 151174**

PUBCHEM: 90408 **PUBCHEM: 71543359** **PUBCHEM: 73755149**

Figure: 3 visualization of the HIT molecules using biovia

CONCLUSION

virtual screening of pyridines and pyrimidines has demonstrated their potential as potent inhibitors of CDK9, offering a computational approach to drug discovery. By leveraging molecular docking and other computational techniques, we can efficiently identify and prioritize compounds with favorable binding affinities to the ATP-binding pocket of CDK9. Pyridine and pyrimidine derivatives have shown promising results in inhibiting CDK9 activity, offering a foundation for the development of novel therapeutics targeting cancer and other diseases characterized by dysregulated cell proliferation and transcription[figure-3].

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