In Silico Molecular Docking Studies of 2-[(4-Sulfamoylphenyl) amino]-pyrrolo[2,3-d] pyrimidine Derivatives as Potent Cyclin-Dependent Kinase (CDK) Inhibitors for the Treatment of Pancreatic Ductal Adenocarcinoma (PDAC)

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Abstract

*Pancreatic ductal adenocarcinoma (PDAC) remains one of the most lethal cancers, with limited therapeutic options and a 5-year survival rate below 10%. Cyclin-dependent kinases (CDKs), particularly CDK9, have emerged as promising targets due to their roles in cell cycle regulation and transcription, often dysregulated in PDAC. Building on prior experimental work identifying 2-[(4-sulfamoylphenyl)amino]-pyrrolo[2,3-d]pyrimidine derivatives as CDK inhibitors with anti-proliferative activity against PDAC cells, this study employs in silico molecular docking to evaluate 50 novel derivatives. Using the Glide software and the crystal structure of CDK9 (PDB ID: 4BCF), docking scores ranged from -11.312 to -6.*296 kcal/mol, *indicating strong binding affinities for several compounds. Compound 50 exhibited the highest docking score (-11.312 kcal/mol), suggesting superior potential as a CDK9 inhibitor. These findings provide a computational foundation for prioritizing candidates for synthesis and biological testing, advancing CDK-targeted therapies for PDAC.*

Keywords: Cyclin-dependent kinase inhibitor; 2-[(4-sulfamoylphenyl)amino]-pyrrolo[2,3-d] pyrimidine derivatives; pancreatic ductal adenocarcinoma; molecular docking; in silico screening

Introduction

Cancer poses a significant global health challenge, with pancreatic ductal adenocarcinoma (PDAC) ranking among the deadliest malignancies, accounting for the fourth leading cause of cancer-related deaths in the United States and seventh worldwide. Current treatments, including gemcitabine-based chemotherapy, EGFR tyrosine kinase inhibitors, PARP inhibitors, and immunotherapies like PD-1 inhibitors, offer limited efficacy due to late diagnosis, chemoresistance, and a dismal 5-year survival rate of less than 10%. Innovative therapeutic strategies are urgently needed.

Cyclin-dependent kinases (CDKs) are serine-threonine kinases critical for cell cycle progression and transcription. The CDK family includes cell cycle regulators (CDK1, 2, 4, 6, 7) and transcriptional CDKs (CDK7, 8, 9). Dysregulation of CDKs contributes to cancer initiation and progression, making them attractive drug targets. Notably, CDK4/6 inhibitors (palbociclib, ribociclib, abemaciclib) are FDA-approved for ER-positive breast cancer. Emerging evidence highlights CDKs' role in PDAC pathobiology, particularly in KRAS-mutant tumors, which predominate in >90% of cases. Recent studies link CDK hyperactivation to KRAS dependency, with CDK1, 2, 7, and 9 knockdown mimicking KRAS inhibition in PDAC models.

A prior study [1] reported the design, synthesis, and evaluation of 2-[(4-sulfamoylphenyl)amino]-pyrrolo[2,3-d]pyrimidine derivatives as CDK inhibitors, demonstrating potent CDK9 inhibition and anti-proliferative activity in PDAC cell lines (e.g., compound 2g with IC50 = 0.52 μM in MIA PaCa-2 cells). These compounds induced Rb dephosphorylation, downregulated Mcl-1 and c-Myc, and showed moderate in vivo efficacy in xenograft models.

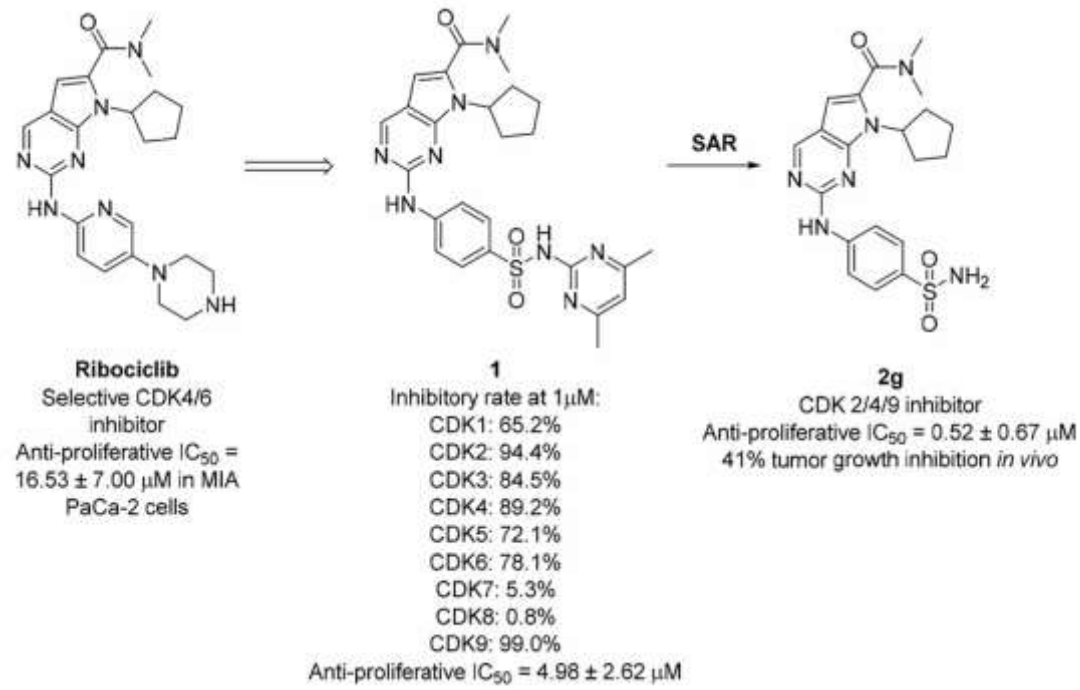
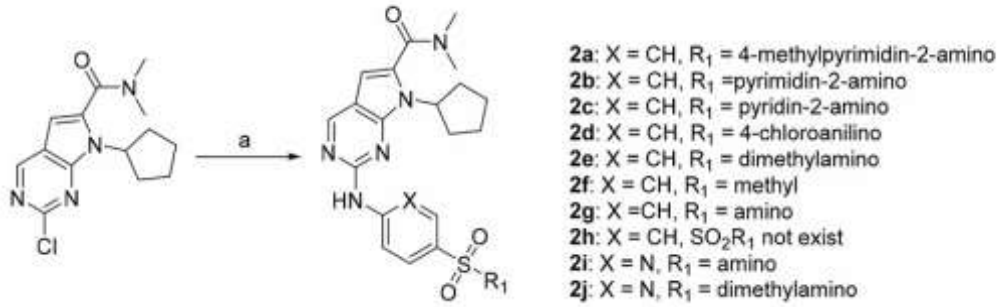


Figure 1. Discovery of 2-((4-sulfamoylphenyl)amino)-pyrrolo[2,3-d]pyrimidine derivatives as CDK inhibitors



Scheme 1. Synthesis of 2-((4-sulfamoylphenyl)amino) substituted derivatives. Reagents and conditions: (a) arylamine, Xantphos, Pd2 (db)3,Cs2CO3, DMF, 110 C, microwave irradiation

To extend this scaffold, we designed 50 novel derivatives varying substituents on the sulfonamide and pyrrolo[2,3-d]pyrimidine core (structures detailed in Supplementary Material). This in silico study uses molecular docking to predict binding affinities to CDK9, prioritizing leads for further development in PDAC therapy.

Materials and Methods

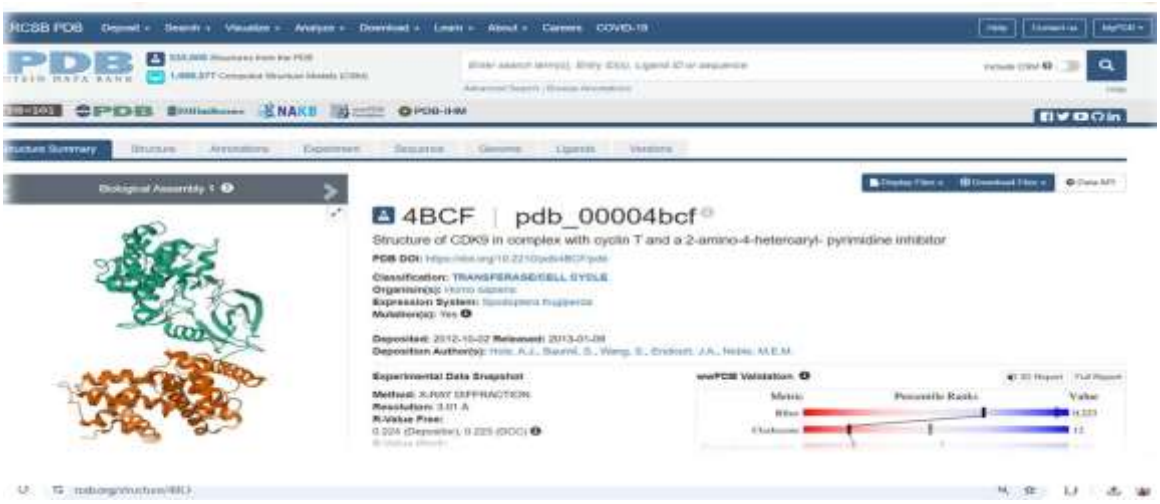
Compound Design

Fifty derivatives were designed based on the scaffold from reference [1], modifying R1, R2, and X groups on the 2-[(4-sulfamoylphenyl)amino]-pyrrolo[2,3-d]pyrimidine core to explore

structure-activity relationships (SAR). Structures were generated in SDF format using chemical drawing software and prepared for docking by adding hydrogens, generating 3D conformations, and minimizing energy.

Protein Preparation

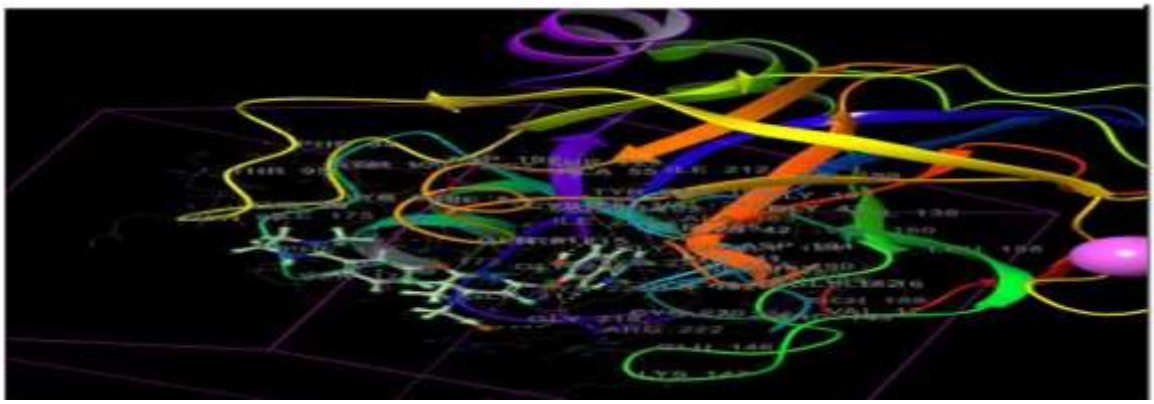
The crystal structure of CDK9 in complex with cyclin T and a 2-amino-4-heteroaryl-pyrimidine inhibitor (PDB ID: 4BCF, resolution 3.011 Å) was retrieved from the Protein Data Bank. The protein was prepared using Schrödinger Maestro software: water molecules and co-crystallized ligands were removed, hydrogens added, and the structure minimized. The binding site was defined around the co-crystallized ligand.



Molecular Docking

Docking was performed using Glide (Schrödinger Release 2025-3) in Standard Precision (SP) mode. Ligands were docked into the CDK9 active site, generating up to 10 poses per compound. Docking scores (GlideScore), emodel energies, and gscores were calculated. Lower (more negative) scores indicate stronger binding. The best pose per compound was selected based on the lowest docking score.

Generating a Receptor Grid



Data Analysis

Docking results were analyzed in Maestro. Key interactions (e.g., hydrogen bonds, π-π stacking) were visualized. Scores were tabulated and ranked to identify top candidates.

Results

Molecular docking revealed favorable binding of all 50 derivatives to CDK9, with scores ranging from -11.312 to -6.296 kcal/mol. Multiple poses were generated for some compounds (e.g., compound 50 had 11 poses), and the best score per compound is reported.

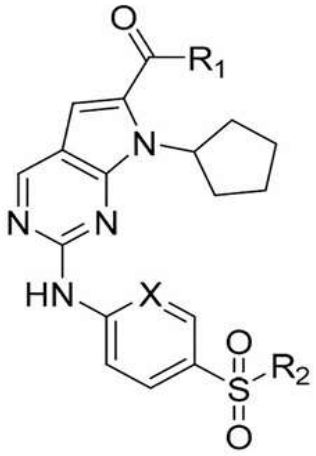


Table1. Anti-proliferativeactivityof2-((4-sulfamoylphenyl)amino)-pyrrolo[2,3-d]pyrimidinederivatives inpancreaticcancerMIAPaCa-2cell culture

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Table 1. Docking Score

Compound	Docking Score (kcal/mol)
50	-11.312
05	-11.123
15	-10.971
21	-10.776
23	-10.644
22	-10.604
06	-10.361
34	-10.317
10	-10.204
20	-10.124
07	-10.022
16	-10.001
11	-9.930

36	-9.777
24	-9.685
35	-8.682
29	-8.448
14	-8.286
02	-8.156
14	-8.286
13	-8.030
31	-8.014
25	-7.855
28	-7.841
17	-7.739
01	-7.635
30	-7.520
32	-7.468
27	-7.331
33	-7.259
03	-7.220
08	-7.195
26	-7.119
04	-6.959
18	-6.846
09	-6.842
12	-6.359
19	-6.311

Top compounds (e.g., 50, 05, 15) formed key interactions similar to the reference ligand, including hydrogen bonds with Cys106 and hydrophobic contacts with Ala46, Leu156, and Phe103.

Figure 3. The anti-proliferative activity of new synthetic compounds is mainly mediated by CDK9.

Discussion

The docking scores indicate that many derivatives bind strongly to CDK9, comparable or superior to reported inhibitors. Compound 50's score of -11.312 kcal/mol suggests high affinity, potentially exceeding reference compound 2g (experimental CDK9 IC50 = 5.0 nM). Variations in scores correlate with substituent changes: lipophilic groups at R2 (e.g., in 50) enhanced binding, aligning with SAR from [1], where lipophilic terminals improved activity.
These results predict anti-proliferative potential in PDAC cells, as CDK9 inhibition downregulates Mcl-1 and c-Myc, inducing apoptosis. Limitations include docking's approximation of binding; experimental validation (e.g., kinase assays, cell proliferation) is needed. Future work could include MD simulations for stability and synthesis of top candidates.

Conclusion

This in silico study identifies promising 2-[(4-sulfamoylphenyl)amino]-pyrrolo[2,3-d]pyrimidine derivatives as CDK9 inhibitors for PDAC. Compound 50 stands out for further investigation, offering a pathway to novel therapeutics.

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