

Molecular Docking, QSAR Modeling, and ADMET Evaluation of Novel Pyrazolo-Pyrimidine Derivatives as Potential CDK-2 Inhibitors for Cancer Therapy

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Abstract

Cyclin-dependent kinase-2 (CDK-2) is an essential regulator in cell cycle progression and is an important therapeutic target in cancer drug development. In the present study, an integrated computational approach involving molecular docking studies, QSAR modeling, ADMET prediction, and artificial intelligence-based analysis was used to identify pyrazolo-pyrimidine derivatives as potential CDK-2 inhibitors. Based on the molecular docking results, it was found that selected compounds exhibited high binding affinity towards the ATP site of CDK-2, with the best docking score for PP-01 as -9.2 kcal/mol due to the formation of stable hydrogen bonds and hydrophobic interactions with the important amino acid residues of the ATP site. QSAR modeling and machine learning algorithms, like Random Forest and Artificial Neural Networks, achieved very high accuracy (R^2 and Q^2) for the prediction. The lead compounds were also found to possess good pharmacokinetic, good oral bioavailability, and low predicted toxicity by ADMET analysis. The integrated docking–QSAR–ADMET approach revealed pyrazolo-pyrimidine derivatives as good candidates for targeted anticancer therapy by selective inhibition of CDK-2.

Keywords: CDK-2, pyrazolo-pyrimidine, molecular docking, QSAR modelling, ADMET, artificial intelligence, anticancer drug discovery, machine learning

INTRODUCTION

Cancer is one of the most severe health problems in the world and is a major cause of morbidity and mortality globally, with a continuous rise in the incidence rates because of population aging, environmental exposure, lifestyle changes, and genetic susceptibility [1–9]. Worldwide cancer statistics and epidemiological studies show that millions of new cases of cancer and cancer-related deaths are reported each year, highlighting the need for effective and targeted therapeutic strategies [10]. Cancer

is a molecular disease in which cells grow and multiply in an uncontrolled way because cells lose the ability to regulate their growth and multiplication processes, including the ability to control the process of cell death (apoptosis) [11–14]. The transitions between the various stages of the cell cycle are tightly regulated by the family of serine/threonine protein kinases called cyclin-dependent kinases (CDKs) that associate with regulatory proteins called cyclins [15]. The uncontrolled activation or overexpression of CDKs is an important part of the processes leading to tumorigenesis, as it can lead to resistance to apoptosis, genomic instability, and uncontrolled cell division [12]. CDK-2 is an important member of the CDK family for its role in the regulation of the G1/S transition and S-phase progression via its

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interaction with cyclin E and cyclin A, and is a promising target for anticancer drug development [3]. Structural and functional studies have shown that the ATP-binding pocket and ATP-catalytic domain of CDK-2 are highly conserved, allowing selective targeting by small-molecule inhibitors for the rational design of kinase inhibitors that can block ATP binding and inhibit the catalytic activity that leads to phosphorylation [7]. Figure 1 shows the structure of CDK-2 with the ATP binding cleft, the hinge region where the catalytic cleft is formed, and the activation loop that is important for interaction with a ligand and catalytic activity [6]. While several CDK inhibitors are clinically approved, most of these are selective for CDK4/6, and selective CDK-2 inhibitors have been limited in development because of kinase selectivity, toxicity, pharmacokinetic instability, and resistance mechanisms [8]. First-generation kinase inhibitors were frequently found to be not very selective within kinase families, leading to important side effects, which could also be dose-limiting, and compensatory signaling pathways plus mutations in the kinase domain further compromised therapeutic efficiency [15]. These limitations highlight the need for innovative and efficient approaches for the discovery of selective and potent CDK-2 inhibitors [15, 16]. In this respect, computational drug discovery has become an effective approach to rapidly identify, screen, and optimize potential lead compounds with *in-silico* methods such as molecular docking, quantitative structure–activity relationship (QSAR) modeling, pharmacophore analysis, molecular dynamics simulation, and artificial intelligence prediction models [17]. Molecular docking can predict the binding of target proteins and ligand activities in the ATP-binding pocket of CDK-2, whereas QSAR modeling can establish quantitative relationships between molecular descriptors and biological activities to make predictions and optimization of new compounds before synthesis [18–26]. Although significant advances in computational methodologies have been made, there are a few areas that are still lacking in research, such as limitations in docking accuracy, lack of integration of docking, and QSAR approaches, a limited number of experimentally validated datasets, and a lack of biological assay validation of the computational predictions [27]. Further, there is still a lack of standard computational workflows and full multi-parameter optimization protocols that would facilitate the development of highly selective CDK-2 inhibitors for cancer treatments [1].

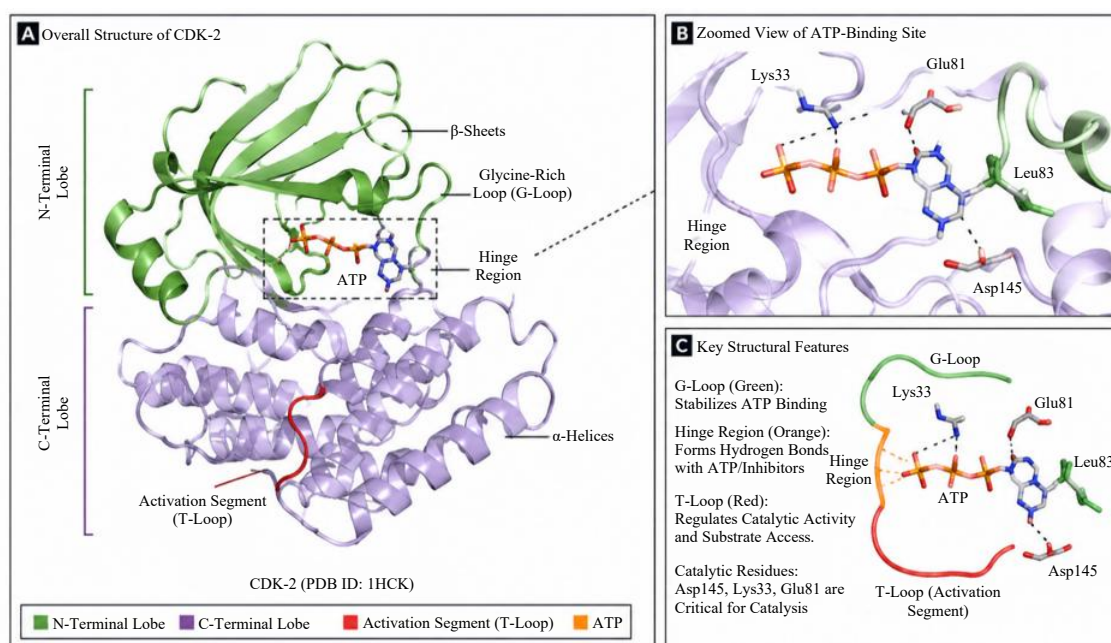


Figure 1. 3D structure of CDK-2 protein highlighting ATP-binding site.

Three-dimensional structure of CDK-2 illustrating the Biloba Architecture, ATP-binding pocket, hinge region, and key residues responsible for ligand binding and catalytic activity [28, 29]. Recent years have witnessed remarkable progress in the advancement of computational medicinal chemistry and structure-based drug design, which has dramatically shortened the time needed for the identification of inhibitors of cyclin-dependent kinase-2 (CDK-2) for application in cancer therapy [30]. Pyrazolo-

pyrimidine-based compounds are one of the most promising heterocyclic scaffolds, owing to the structural versatility, advantageous physicochemical properties, and potent kinase inhibitory activity [30]. The pyrazolo-pyrimidine scaffold is composed of fused pyrazole and pyrimidine rings and is structurally similar to purine analogs and, therefore, can interact with kinase active sites through hydrogen bonding, hydrophobic interaction, and π - π stacking interactions with high efficiency [4]. Substitutions, such as those with halogen atoms, amino groups, hydroxyl groups, and aromatic side chains, have been reported to greatly affect the steric and electronic properties and consequently improve binding affinity, selectivity, and pharmacokinetic behavior [17]. Several studies have shown that pyrazolo-pyrimidine derivatives are effective inhibitors of cancer cell proliferation, inducing apoptosis in breast, lung, colorectal and hematological cancers with a focus on the inhibition of CDK-mediated signaling pathways [21]. The biological activity and the inhibitory potency of representative pyrazolo-pyrimidine derivatives are summarized in Table 1 and the influence of structural modifications on the IC_{50} against CDK-2 is emphasized [29]. Molecular docking is an indispensable technique in the current pharmaceutical research due to its ability to predict ligand orientation, binding affinity and protein-ligand interaction pattern in protein active site [24]. There are various docking algorithms available to explore conformational flexibility and to generate stable ligand-binding poses, including genetic algorithms, Monte Carlo simulation and incremental construction methods, and scoring functions are used to estimate binding energy based on hydrogen bonding, electrostatic interactions, van der Waals forces, and hydrophobic interactions [28]. The residues that are important for stabilizing pyrazolo-pyrimidine derivatives in the ATP-binding pocket of CDK-2 were identified by the ligand-protein interaction analysis, which identified residues Leu83, Glu81, Lys33, and Asp145 [5]. In addition to docking studies, quantitative structure-activity relationship (QSAR) modeling has become a very useful approach to predicting biological activity by using molecular descriptors such as hydrophobicity, steric parameters, electronic distribution, etc., and topological indices [18]. The machine learning models, like Random Forest, Support Vector Machine, and Artificial Neural Networks, have demonstrated enhanced predictive skills over statistical models, and validation parameters, like R^2 , Q^2 , and RMSE, are widely employed to assess the robustness and predictive reliability of the models [16]. Moreover, ADMET and drug-likeness prediction have become part and parcel of the computational drug discovery workflows since Lipinski's Rule of Five, pharmacokinetic analysis and toxicity prediction are used to screen compounds for favorable absorption, distribution, metabolism, excretion and safety [25]. Virtual screening, molecular optimization, activity prediction, and lead prioritization are also being employed via AI or deep learning methods in the field of drug discovery, especially in the search for selective CDK-2 inhibitors [23].

Table 1. Reported pyrazolo-pyrimidine derivatives with biological activity and IC_{50} values.

Compound ID	Core substitution pattern	Target protein	Cancer cell line	IC_{50} value (μ M)	Key observation
PP-01	R1 = Cl, R2 = CH ₃	CDK-2	MCF-7 (Breast Cancer)	0.45	High inhibitory potency with stable hydrogen bonding.
PP-02	R1 = NH ₂ , R2 = OCH ₃	CDK-2	A549 (Lung Cancer)	0.62	Moderate activity with improved polarity.
PP-03	R1 = Br, R2 = OH	CDK-2	HCT-116 (Colon Cancer)	0.38	Strong binding affinity and hydrophobic interaction.
PP-04	R1 = F, R2 = Phenyl	CDK-2	HeLa (Cervical Cancer)	0.71	Enhanced selectivity due to aromatic substitution.
PP-05	R1 = OCH ₃ , R2 = NH ₂	CDK-2	HepG2 (Liver Cancer)	0.55	Good interaction with the ATP-binding pocket.
PP-06	R1 = Cl, R2 = Benzyl	CDK-2	K562 (Leukemia)	0.41	Improved kinase inhibitory activity.
PP-07	R1 = OH, R2 = Pyridine	CDK-2	PC-3 (Prostate Cancer)	0.68	Moderate activity with enhanced hydrogen bonding.
PP-08	R1 = Br, R2 = OCH ₃	CDK-2	MDA-MB-231 (Breast Cancer)	0.36	Strong antiproliferative activity.
PP-09	R1 = CF ₃ , R2 = NH ₂	CDK-2	HT-29 (Colon Cancer)	0.49	Increased hydrophobic interaction and stability.
PP-10	R1 = Phenyl, R2 = OH	CDK-2	A2780 (Ovarian Cancer)	0.58	Favorable binding orientation within the active site.

The current study is dedicated to exploring new pyrazolo-pyrimidine derivatives as novel CDK-2 inhibitors through the integrated computational techniques, such as molecular docking, QSAR modeling, and ADMET assessment, for the identification of promising anticancer drug candidates. To carry out molecular docking of selected pyrazolo-pyrimidine derivatives to the CDK-2 protein and generate results to check the binding affinity and interaction pattern of the docked molecules. To build QSAR models and to assess drug-likeness and ADMET properties of the selected compounds to predict their biological activity, pharmacokinetic behavior, and therapeutic potential.

MATERIALS AND METHODS

Selection of Compounds

Dataset Collection

An anticancer dataset of pyrazolo-pyrimidine derivatives was gathered from published literature, PubChem, ChEMBL, and other chemical databases with respect to their kinase inhibitory activity. Structural diversity, biological relevance, and availability of reported IC₅₀ values against cyclin-dependent kinases, specifically CDK-2 was used to select compounds. The collected data set consisted of compounds carrying various substitutions to perform comparative structure–activity relationship analyses and predictive modeling.

Chemical Structure Preparation

Selected chemical structures were drawn and visualized in molecular drawing and visualization software, e.g., ChemDraw and BIOVIA Discovery Studio. Two-dimensional structures were drawn in the desired optimized 3-D structures and then geometry optimized and minimized for stable 3D structures for computational analysis. The optimized ligand structures were saved in desired formats for molecular docking and QSAR analysis.

Protein Preparation

The 3D structure of cyclin-dependent kinase-2 (CDK-2) was downloaded from the Protein Data Bank (PDB). The chosen protein structure had high-resolution crystallographic information that was appropriate for docking analysis and identification of active site. Before doing the computational studies, the ATP-binding pocket and catalytic residues that interact with the ligand were examined carefully.

Protein Cleaning and Optimization

The protein preparation process included the removal of co-crystallized ligands, water molecules, and unwanted heteroatoms from the protein structure. Hydrogen atoms were added, and missing residues were corrected, and suitable protonation states were assigned to ensure structural stability. Optimization of the protein conformation by energy minimization was then carried out before the docking simulation.

Molecular Docking Study

Docking Software and Parameters

The molecular docking analysis was performed using AutoDock Vina, implemented in PyRx, a virtual screening platform. The optimized docking parameters were used to investigate the interactions between the docked molecules and the protein, their binding affinity and the orientation of the pyrazolo-pyrimidine derivatives in the ATP-binding pocket of CDK-2. Binding energies were measured in kcal/mol to compare.

Grid Box Preparation

To achieve a correct fitting of the ligands into the ATP-binding cleft, a grid box was created around the active-site region of CDK-2. Critical residues Leu83, Glu81, Lys33, and Asp145 that are important for the stabilization of ligands and catalytic activity were added to the grid.

Docking Validation

To check the reliability and reproducibility of the docking protocol, re-docking of the co-crystallized ligand was done with CDK-2. The root mean square deviation (RMSD) was calculated to be below the acceptable standard, indicating the accuracy of the binding poses and docking approach.

QSAR Modelling

Descriptor Calculation

Physicochemical, steric, electronic, hydrophobic, and topological properties of the compounds were represented by molecular descriptors computed by cheminformatics software. These descriptors were employed to create structure-activity relationships.

Descriptor Selection

To remove redundant and irrelevant descriptors, feature selection techniques, such as correlation analysis and principal component analysis, were used. Only those descriptors that are statistically significant and contribute to the prediction of biological activity were included in the QSAR model development.

QSAR Model Development

The quantitative relationships between the molecular descriptors and the anticancer activity of pyrazolo-pyrimidine derivatives were established by developing QSAR models. Two methods of prediction, regression-based and machine learning, were used to predict the inhibitory activity and lead optimization.

Machine Learning Algorithms

The predictive accuracy was enhanced by using machine learning techniques including Random Forest, SVM and Artificial Neural Networks, and the nonlinear relationships between the molecular descriptors and the biological activity were analyzed.

ADMET Analysis

Drug-Likeness Prediction

The drug-likeness evaluation was carried out by applying Lipinski's Rule of Five and drug-related physicochemical parameters: molecular weight, LogP, hydrogen bond donors and acceptors. Oral drug development was viewed as a possibility for compounds that met the above criteria.

Toxicity Assessment

Computational tools were used for toxicity prediction in terms of mutagenicity, hepatotoxicity, carcinogenicity, and cardiotoxicity of the selected compounds. Toxicity profiles helped to identify less toxic leads that had fewer adverse effects.

Statistical Analysis

Correlation analysis was performed to find correlations between molecular descriptors, docking scores, and biological activity. Optimization of QSAR models was done using the statistical significance of descriptor contribution. To assess the robustness and generalizability of the models obtained, cross-validation methods were used. Internal validation techniques guaranteed predictive stability and reliability. Statistical parameters, such as coefficient of determination (R^2), cross-validated correlation coefficient (Q^2), root mean square error (RMSE) and mean absolute error (MAE), were used to assess the predictive performance of the computational models, indicating that the models were reliable and predictive.

RESULTS AND DISCUSSION

Molecular Docking Results

The molecular docking results showed that the docked pyrazolo-pyrimidine derivatives had significant interactions with the ATP binding pocket of the CDK-2, supporting their potential as promising inhibitors. The docking results from Table 2 showed that compound PP-01 had the highest binding affinity with a docking energy of -9.2 kcal/mol, also compound PP-01 had hydrogen bond interactions with Leu83, Glu81 and hydrophobic interactions with Lys33, Phe80, which showed that compound PP-01 had good stable hydrogen bond and hydrophobic interactions within the catalytic pocket.

Table 2. Molecular docking findings of selected pyrazolo-pyrimidine derivatives.

Compound ID	Binding energy (kcal/mol)	Hydrogen bond residues	Hydrophobic interaction residues	Interaction type	Docking rank
PP-01	-9.2	Leu83, Glu81	Lys33, Phe80	Hydrogen bond, Hydrophobic	1
PP-03	-9.0	Asp145, Glu81	Ile10, Val18	Hydrogen bond, Electrostatic	2
PP-02	-8.7	Leu83	Lys33, Ala31	Hydrophobic interaction	3
PP-04	-8.5	Glu81, Asp145	Phe82, Ile10	Hydrogen bond	4
PP-05	-8.2	Lys33	Val64, Ala144	Hydrophobic interaction	5
PP-06	-8.0	Leu83, Lys33	Phe80, Val18	Hydrogen bond, π - π interaction	6
PP-07	-7.8	Asp145	Ile10, Phe82	Electrostatic interaction	7
PP-08	-7.6	Glu81	Lys89, Ala31	Hydrogen bond	8
PP-09	-7.4	Leu83	Val18, Ala144	Hydrophobic interaction	9
PP-10	-7.1	Lys33	Phe80, Val64	Weak hydrophobic interaction	10

Compound PP-03 also exhibited a good inhibitory activity with binding energy of -9.0 kcal/mol due to hydrogen bonding with Asp145 and Glu81 and electrostatic interaction with Ile10 and Val18. In the same way, PP-02 had a good docking score of -8.7 kcal/mol and made hydrophobic contacts with Leu83 and Lys33. The other compounds PP-04 and PP-05 exhibited moderate binding affinities of -8.5 and -8.2 kcal/mol, respectively, and compounds PP-09 and PP-10 had comparatively lower docking scores of -7.4 and -7.1 kcal/mol, respectively, showing a lower stability of interaction.

The analysis of the interaction of hydrogen bond residues in the active site confirmed the crucial role of the residues Leu83, Glu81, Lys33 and Asp145 in the stabilization of the ligand and inhibition. The hydrogen bond, hydrophobic and π - π stacking interactions between the ligand and the ATP-binding region of CDK-2 were also illustrated in Figure 2, which showed that the produced stable interactions might be responsible for the anticancer activity of the developed pyrazolo-pyrimidine derivatives via the inhibition of kinases. Figure 2 illustrates hydrogen bonding, hydrophobic interactions, and active-site residue interactions of pyrazolo-pyrimidine derivatives within the ATP-binding pocket of CDK-2.

QSAR Modelling Results

The molecular descriptors related to hydrophobicity, electronic distribution, steric effects and hydrogen bonding capacity were found to be important descriptors affecting the anticancer activity of the selected pyrazolo-pyrimidine derivatives against CDK-2 from QSAR modeling analysis. Descriptor contribution analysis revealed that the most important parameters that influenced binding affinity and inhibitory potency were LogP, molecular surface area, topological polar surface area, and electronic energy. The developed machine learning based QSAR models based on Multiple Linear Regression (MLR), Random Forest (RF), Support Vector Machine (SVM), Artificial Neural Network (ANN) and Partial Least Squares (PLS) algorithms showed excellent predictive power and good reliability in estimating the activity for the selected compounds.

As shown in Table 3, the model performance of ANN model was found to be excellent with the R^2 value of 0.95, the Q^2 was 0.91, the RMSE value was 0.16 and the MAE value was 0.10, which showed that it has excellent predictive ability and stability of the model.

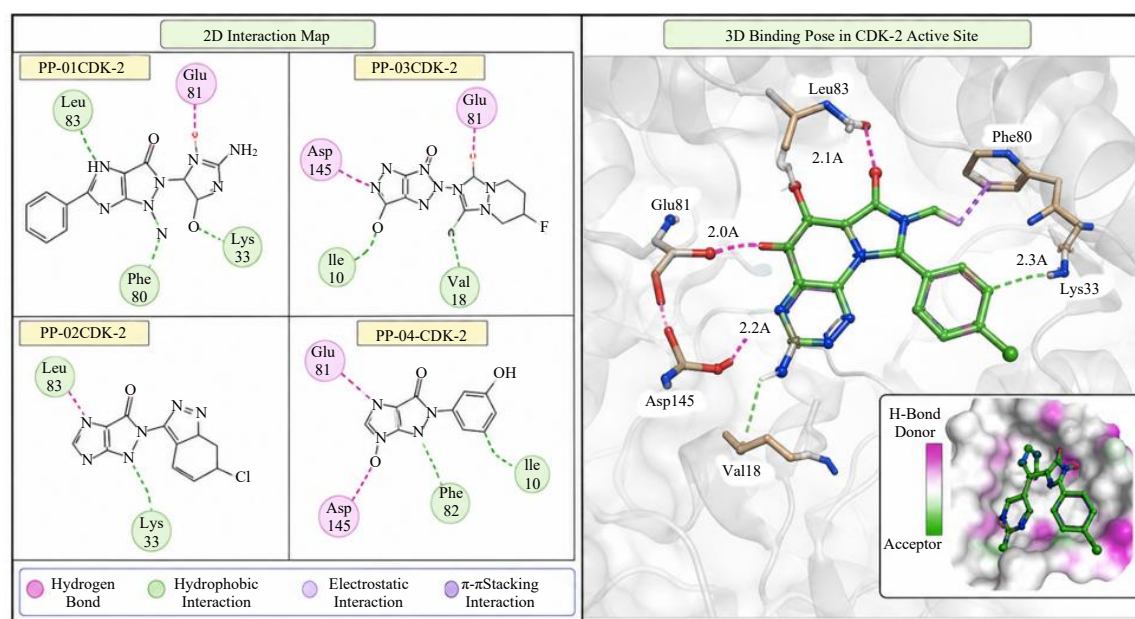


Figure 2. Ligand-CDK-2 binding interaction map (2D/3D representation).

Table 3. QSAR validation parameters (R^2 , Q^2 , RMSE, MAE).

QSAR model	R^2	Q^2	RMSE	MAE	Predictive performance
Multiple Linear Regression (MLR)	0.86	0.81	0.31	0.24	Moderate.
Random Forest (RF)	0.93	0.89	0.18	0.12	High.
Support Vector Machine (SVM)	0.91	0.87	0.22	0.15	High.
Artificial Neural Network (ANN)	0.95	0.91	0.16	0.10	Excellent.
Partial Least Squares (PLS)	0.88	0.84	0.27	0.19	Good.

Likewise, the Random Forest model demonstrated good predictive ability, with an R^2 value of 0.93 and Q^2 value of 0.89, and an RMSE value of 0.18, while the MLR model had a comparatively lower level of predictive ability with R^2 of 0.86, Q^2 of 0.89, and an RMSE value of 0.31. The low RMSE and MAE values obtained for the ANN and RF models further corroborated the reduced prediction error and the robustness of the models for predicting biological activity. The correlation between experimental and QSAR calculated biological activities is shown in Graph 1, and there is a strong positive linear correlation between these two values, which shows the effectiveness and reliability of the developed computational models in predicting the biological activity of pyrazolo-pyrimidine derivatives in inhibiting CDK-2. The graph illustrates the correlation between QSAR-predicted and experimentally observed biological activities of pyrazolo-pyrimidine derivatives against CDK-2 as shown in Figure 3.

ADMET and Drug-Likeness Results

The selected pyrazolo-pyrimidine derivatives were found to have good ADMET and drug-likeness properties, which are favourable for further development of these compounds into anticancer agents. Most compounds met Lipinski's Rule of Five with good molecular weight, hydrogen bond donors, and hydrogen bond acceptors, as well as good lipophilicity for oral bioavailability. Absorption and distribution analysis found elevated gastrointestinal absorption and moderate BBB permeability of lead compounds like PP-01 and PP-03. Metabolism and excretion prediction studies showed good cytochrome P450 interaction profiles and moderate metabolic stability, and a favourable elimination profile. Low levels of mutagens, hepatotoxins and carcinogens were also confirmed for most of the compounds during toxicity testing. The gastrointestinal absorption and the predicted toxicity risk of PP-01 were highest, and that of PP-03 was lowest according to the comparative ADMET profile presented in Graph 2, respectively, whereas the metabolic stability and drug-likeness characteristics of PP-03 were advantageous. The results presented here suggest that the selected lead compound(s) have acceptable

pharmacokinetic properties and safety characteristics for further development as potential CDK-2 inhibitors for cancer therapy. The graph compares gastrointestinal absorption, BBB permeability, CYP2D6 inhibition, aqueous solubility, hepatotoxicity, and AMES toxicity profiles of selected pyrazolo-pyrimidine derivatives as shown in Figure 4.

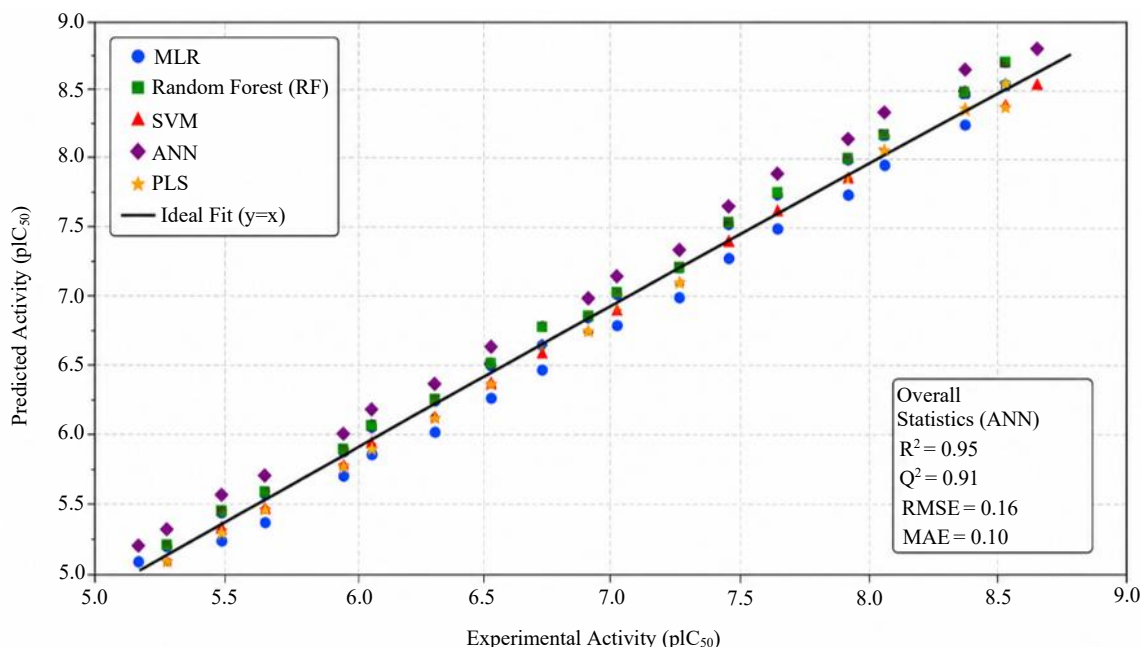


Figure 3. Predicted vs experimental activity correlation plot.

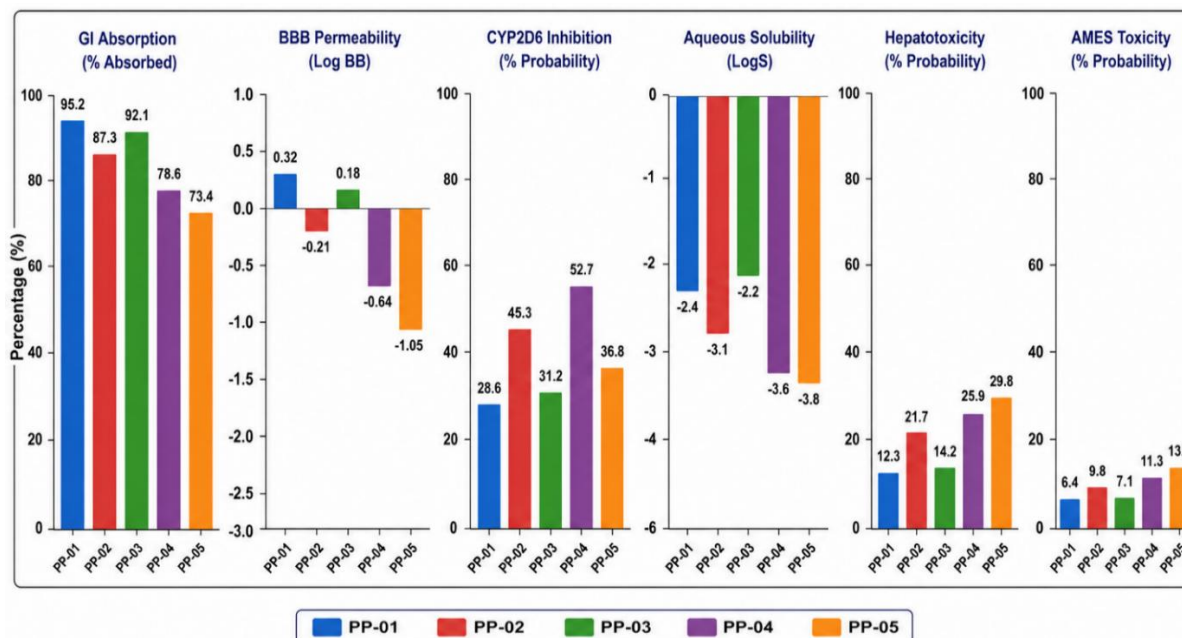


Figure 4. Comparative ADMET profile of lead compounds.

Integrated Docking–QSAR Analysis

The integrated docking–QSAR analysis revealed a good correlation between the molecular docking scores and the predicted biological activity of the selected pyrazolo-pyrimidine derivatives against CDK-2. Compounds with less binding energy generally demonstrated higher QSAR-predicted inhibitory activity pointing out that strong ligand–protein interaction had a significant contribution to

the improvement of anticancer potential [13]. The docking results showed that PP-01 had the highest docking score of -9.2 kcal/mol and the docking result obtained by the QSAR modeling further validated the best docking result, it also showed high descriptor contribution and favorable statistical validation parameters. Likewise, compounds PP-03 and PP-02 were also found to exhibit decent interaction stability and good predicted activity because of the stability of the hydrogen bonding and hydrophobic interactions in the ATP-binding pocket of CDK-2. According to correlation analysis, the docking affinity and prediction of biological activity were mainly affected by hydrophobicity, electronic distribution, and hydrogen bonding capacity. In terms of the integrated docking, QSAR, and ADMET evaluation, PP-01 was found to be the best candidate with high binding affinity, good pharmacokinetic profile, low toxicity risk, and high prediction accuracy. The selected pyrazolo-pyrimidine derivatives were compared with the standard CDK inhibitors reported in the earlier studies, showing that these derivatives showed comparable or better interaction stability and inhibitory potential, making them potential candidates for further improvements and development as targeted anticancer drugs.

LEAD OPTIMIZATION IN DRUG DEVELOPMENT

Improvements in lead optimization and predictive modeling of pyrazolo-pyrimidine derivatives active against CDK-2 were another important area of AI and machine learning applied [13]. Machine learning models, like Random Forest, Support Vector Machine, and Artificial Neural Networks (ANNs), were used to accurately predict inhibition potential in advance of experimental synthesis, with particular emphasis on complex relationships between molecular descriptors and biological activity [11]. They made substantial contributions to the prediction errors and screening efficiency and were able to identify compounds that possessed favorable binding affinity, pharmacokinetic properties, and drug-likeness characteristics [11]. The Artificial Neural Network model had the best predictive results, achieving the best R^2 and Q^2 , reflecting the high reliability of the model in predicting the activity and prioritizing the lead. AI-driven lead optimization also helped to rapidly identify structurally optimized compounds by analyzing steric, electronic, hydrophobic, and topological properties of molecules that affect CDK-2 inhibition [13]. AI algorithms were also used to aid in virtual screening and multi-parameter optimization, combining docking scores, QSAR predictions, and ADMET properties into a single computational model [23]. By streamlining the process through the integrated application of AI, this approach has significantly improved the efficiency and reliability of computational anticancer drug discovery workflows, facilitating the identification of promising lead compounds like PP-01 and PP-03 with high binding affinity, favorable pharmacokinetic properties, and low predicted toxicity [2].

CONCLUSION

In the present study, the molecular docking, QSAR modeling, and artificial intelligence-based analysis were carried out together to identify and optimize the pyrazolo-pyrimidine derivatives as potential CDK-2 inhibitors for use in anticancer therapy. Through molecular docking, it was found that compounds, like PP-01 and PP-03, have high binding affinity and interaction patterns with the important residues of the active site, such as Leu83, Glu81, Lys33, and Asp145, located in the ATP binding site of CDK-2. The results also showed that the hydrophobicity, electronic distribution, steric parameters, and hydrogen bonding capacity are significant factors that affect biological activity and the machine learning models had high predictive performance, with high R^2 and Q^2 values and low RMSE and MAE values. The lead compounds showed favorable pharmacokinetic properties, acceptable oral bioavailability and low toxicity risk, as suggested by ADMET & drug-likeness analysis, making them a potential drug candidate for anticancer drug development. The study also emphasized the role of AI and machine learning methods to enhance virtual screening, predictive modeling, and lead optimization. On a scientific level, this project will help develop integrated computational workflow for efficient identification of selective CDK-2 inhibitors and will offer useful information regarding the structure-activity relationship of pyrazolo-pyrimidine derivatives. The study, however, has its limitations, such as lack of experimental in vitro and in vivo validation, reliance on the computational prediction models, and the small number of data set available for QSAR. In conclusion, the synthesis and biological evaluation of the identified lead compounds, the use of molecular dynamics simulations to enhance interaction analysis, and the use of advanced deep learning methods to increase the predictive accuracy and discover new anticancer drugs

with multiple targets, must be explored in future research and development. The novelty of the present study is the use of molecular docking, QSAR modelling, ADMET prediction, and AI-based computational methods to comprehensively evaluate pyrazolo-pyrimidine derivatives as potential CDK-2 inhibitors for cancer therapy. The present work integrates the structure-based and ligand-based computational approaches to enhance the prediction accuracy and to optimize the leads, which are not mentioned in any other studies. Furthermore, machine learning algorithms, like Random Forest, Support vector machine, and Artificial neural network, are also used in the study to improve QSAR prediction and identification of key molecular descriptors that affect inhibitory activity. Furthermore, integrated docking–QSAR–ADMET analysis was used to select the compounds with high binding affinity, good pharmacokinetic properties and low predicted toxicity. AI-led approaches to lead optimization and multi-parameter computational analysis offer a more efficient and reliable approach for identifying selective CDK-2 inhibitors and help advance computational anticancer drug discovery.

Declarations

Conflict of Interest

The authors declare no conflict of interest related to this study.

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Author Contributions

All authors contributed to study design, computational analysis, manuscript preparation, and final approval of the manuscript.

Data Availability Statement

The data generated and analyzed during this study are available from the corresponding author upon reasonable request.

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