

In silico Screening of Indonesian Coffee Bioactive Compounds as Potential CDK4-Binding Ligands: An Integrated Molecular Docking and Drug-Likeness Analysis

Fachrurrazie Fachrurrazie^{1,*} , Lilis Sulistiawaty¹ , Joko Untung¹ , Lutfi Anshory² ,
R. Haryo Bimo Setiarto² 

¹ Department of Analytical Chemistry, Politeknik AKA Bogor, Bogor, West Java 16154, Indonesia; fachrurrazie@kemenperin.go.id; (F.F.); lilis-s@kemenperin.go.id; (L.S.); jokountung@kemenperin.go.id; (J.U.);

² Research Center for Applied Microbiology, National Research and Innovation Agency (BRIN), KST Soekarno, Cibinong, Bogor, 16911, Indonesia; lutf012@brin.go.id; (L.A.); rhar002@brin.go.id; (R.H.B.S.);

* Correspondence: fachrurrazie@kemenperin.go.id;

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Abstract: The cyclin-dependent kinase 4 (CDK4)/cyclin D1 signaling axis is a key regulator of G1-to-S phase cell-cycle progression and an established therapeutic target in hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) breast cancer. Although CDK4/6 inhibitors have improved clinical outcomes, acquired resistance and treatment-associated adverse effects highlight the need to explore additional chemical scaffolds with potential CDK4-targeting properties. This study aimed to computationally screen Indonesian coffee-derived bioactive compounds for their potential to interact with human CDK4. A curated library of 133 coffee-associated bioactive compounds was evaluated using molecular docking against the high-resolution crystal structure of human CDK4 in an inactive conformation (PDB ID: 2W9Z; 2.3 Å resolution). Among the screened compounds, 5-O-caffeoylquinic acid showed the most favorable docking score (−6.3 kcal/mol). Two-dimensional interaction analysis indicated that these compounds interacted with residues in the CDK4 binding region, including hydrogen-bond interactions with Asp159, Asn24, and His163, as well as hydrophobic contacts with Val27 and neighboring residues. Drug-likeness assessment showed that the two top-ranked compounds met several criteria of Lipinski's Rule of Five. However, their low lipophilicity (logP = −0.65) and relatively high topological polar surface area (TPSA = 164.75 Å²) may affect membrane permeability and pharmacokinetic behavior. Ramachandran analysis indicated that the CDK4 structure retained acceptable stereochemical quality in the structural model used for the computational analysis. Overall, 5-O-caffeoylquinic acid was prioritized as a potential CDK4-binding scaffold from Indonesian coffee bioactives. These computational findings provide a structural basis for further biochemical and cellular studies to determine their actual CDK4 inhibitory activity, binding affinity, selectivity, and anticancer potential.

Keywords: CDK4; Indonesian coffee bioactives; molecular docking; breast cancer; 5-O-caffeoylquinic acid; 3-caffeoylquinic acid

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1. Introduction

The cyclin-dependent kinase 4 (CDK4)/cyclin D1 signaling pathway is a well-established regulator of cell-cycle progression and an important therapeutic target in hormone receptor-positive (HR+) and human epidermal growth factor receptor 2-negative (HER2-) breast cancer. Activation of the CDK4/cyclin D1 complex promotes phosphorylation of the retinoblastoma (Rb) tumor suppressor protein, facilitating the transition from the G1 to the S phase and thereby supporting tumor-cell proliferation [1,2]. Small-molecule CDK4/6 inhibitors, including palbociclib, ribociclib, and abemaciclib, have substantially improved clinical outcomes in patients with HR+/HER2- breast cancer [3,4]. However, treatment can cause adverse effects, and acquired resistance remains a major clinical challenge. Resistance has been associated with multiple mechanisms, including compensatory activation of alternative cell-cycle regulatory pathways such as the CDK2-cyclin E axis [5]. These clinical considerations have stimulated continued efforts to identify new chemical scaffolds and better understand the structural determinants of CDK4 ligand recognition.

Selectivity within the CDK4/6 family represents an additional challenge because CDK4 and CDK6 share substantial structural similarity, particularly within their ATP-binding regions [5]. Although approved inhibitors are generally described as CDK4/6 inhibitors, differences between the two kinases may offer opportunities to develop compounds with distinct binding profiles. Structural characterization of CDK4 therefore provides an important basis for investigating how small molecules interact with its catalytic region. In this context, the human CDK4/cyclin D1 complex represented by the 2.3 Å crystal structure (PDB ID: 2W9Z) provides a useful structural template for computational ligand-screening studies [2]. The structure represents an inactive CDK4 conformation in which the kinase adopts a distinct arrangement of structural elements surrounding the catalytic cleft [6]. Such conformational features may influence ligand recognition and provide a structural framework for evaluating potential CDK4-binding compounds.

The chemical diversity of Indonesian *Coffea* varieties provides a potentially valuable source of bioactive compounds for computational screening. Coffee contains numerous secondary metabolites, including chlorogenic acids, caffeoylquinic acid (CQA) derivatives, phenolic compounds, and other metabolites whose composition can vary according to cultivar, geographical origin, and processing conditions. Metabolomic profiling using ¹H NMR and chemometric approaches has shown regional differences in Indonesian coffee metabolite profiles, with Lampung Robusta associated with relatively high concentrations of formic acid and quinic acid. In contrast, Gayo and Aceh coffees contain diverse lipid and caffeoylquinic acid signatures [7]. In addition, selected Lampung Robusta fractions have shown cytotoxic activity against MCF-7 breast cancer cells, supporting further investigation of coffee-derived phytochemicals as potential sources of bioactive molecular scaffolds [8]. Among these compounds, 5-O-caffeoylquinic acid and 3-caffeoylquinic acid are of particular interest because of their reported biological activities and structural features that permit multiple hydrogen-bond and polar interactions with protein targets.

Despite this pharmacological potential, the interaction of Indonesian coffee-derived bioactive compounds with the human CDK4 structure remains insufficiently characterized. Previous studies have largely focused on general biological activities, cytotoxicity, or related kinase targets, leaving the structural interaction profiles of these compounds within the CDK4 binding region incompletely explored. Molecular docking can provide an initial assessment of

ligand poses, predicted docking scores, and residue-level interaction patterns, thereby facilitating prioritization of compounds for subsequent experimental investigation. However, docking scores should be interpreted as computational ranking metrics rather than experimentally determined binding free energies, inhibition constants, or direct evidence of biological activity.

Accordingly, the present study performed an *in silico* screening of a curated library of 133 Indonesian coffee-associated bioactive compounds against human CDK4 using the inactive kinase structure represented by PDB ID: 2W9Z. Molecular docking was used to prioritize compounds according to their predicted docking scores and to characterize their interactions with residues within the CDK4 binding region. Additional analyses of drug-likeness and predicted molecular properties were performed to support the prioritization of candidate compounds. The screening identified 5-O-caffeoylquinic acid as the top-ranked compound (docking score: -6.3 kcal/mol), followed by 3-caffeoylquinic acid (-6.1 kcal/mol). Interaction analysis also indicated contacts with Asp159, Asn24, His163, and Val27. These findings provide a computational basis for prioritizing Indonesian coffee-derived compounds as potential CDK4-binding scaffolds and for guiding subsequent biochemical and cellular studies to determine their actual CDK4 inhibitory activity, binding affinity, selectivity, and anticancer effects.

2. Materials and Methods

2.1. Computational resources and software.

All computational analyses were performed on a desktop/laptop workstation equipped with an Intel® Core™ i7-13700H processor, NVIDIA® GeForce RTX™ 4050 GPU (6 GB), 16 GB RAM, and a 1 TB PCIe 4.0 NVMe SSD. Because AutoDock Vina 1.1.2 primarily uses CPU cores for docking calculations, the workstation hardware is reported for computational reproducibility but is not considered a methodological determinant of the docking protocol. AutoDock Vina 1.1.2 was used for molecular docking, while AutoDock Tools (ADT) 1.5.6 was used for preparation of receptor and ligand PDBQT files. Molecular structures were generated or edited using ACD/ChemSketch 12.1 and MarvinSketch. Molecular interaction diagrams and three-dimensional visualization were performed using BIOVIA Discovery Studio Visualizer 2015 and PyMOL. AutoDock Vina 1.1.2 was selected as the docking engine because it implements a stochastic global search procedure and provides predicted docking scores to rank ligand poses. The Vina 1.1.2 manual specifies search-space parameters as Cartesian box centers and dimensions in Å, along with adjustable search exhaustiveness, number of output modes, energy range, CPU usage, and random seed.

2.2. Human CDK4 structure preparation.

The crystal structure of the human cyclin D1–CDK4 complex was obtained from the Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB; PDB ID: 2W9Z). The structure contains cyclin D1 (chain A) and CDK4 (chain B) and was determined by X-ray diffraction. The current RCSB record reports a resolution of 2.45 Å, whereas the original structural publication reports 2.3 Å. For the docking calculations, CDK4 chain B was used as the receptor. Cyclin D1 was excluded from the receptor model if the docking protocol was performed against CDK4 alone. Crystallographic water molecules and non-essential solvent or ion molecules were removed. Because 2W9Z lacks a co-crystallized

small-molecule inhibitor, no crystallographic ligand was available for direct ligand redocking validation. Polar hydrogen atoms were added using AutoDock Tools 1.5.6, followed by assignment of Gasteiger partial atomic charges. The prepared receptor was saved in PDBQT format. Unless otherwise specified, the receptor was treated as rigid during docking. Thus, the present protocol did not include induced-fit receptor flexibility or flexible receptor side chains. AutoDock Vina can accommodate flexible receptor side chains, but this requires a separate flexible-receptor PDBQT representation; such a procedure was not part of the present rigid-receptor workflow.

2.3. Construction and preparation of the coffee bioactive library.

A library of 133 bioactive compounds associated with Indonesian coffee was compiled from previously reported metabolomic, phytochemical, and literature data covering Indonesian *Coffea* varieties, including Robusta from Lampung and Aceh and Arabica from Gayo/Sumatra, Preanger/Java, Bandung, and Bajawa/Flores [10–19]. The library included compounds from several chemical classes, including phenolic acids, caffeoylquinic acid derivatives, alkaloids, volatile compounds, lipids, and diterpenes. Representative compounds included 3-caffeoylquinic acid, 4-caffeoylquinic acid, 5-O-caffeoylquinic acid, caffeine, trigonelline, 2-methylpyrazine, palmitic acid, and 16-O-methylcafestol. Two-dimensional structures were generated or edited using ACD/ChemSketch 12.1 and converted into three-dimensional structures using MarvinSketch. Each ligand was subjected to geometry optimization and energy minimization using the MMFF94 force field. The resulting structures were inspected for chemically reasonable bond geometry and converted to PDBQT format using AutoDock Tools 1.5.6. For ligand preparation, polar hydrogens were retained, Gasteiger partial charges were assigned, non-polar hydrogens were merged according to the AutoDock PDBQT representation, and rotatable bonds were assigned to permit ligand conformational flexibility during docking. The protonation and tautomeric states used for docking were those generated during ligand preparation at the specified preparation stage. No experimental pKa-dependent protonation-state ensemble was evaluated unless otherwise stated in the corresponding ligand preparation files.

2.4. Definition of the CDK4 binding region.

The CDK4 binding region was defined from the ATP-binding/catalytic region of the CDK4 kinase domain and evaluated using the SCFBio Active Site Prediction tool together with structural inspection of PDB 2W9Z. The predicted pocket was inspected in PyMOL to verify that the docking search space encompassed the relevant kinase binding region. The active-site definition was based on the structural location of the kinase ATP-binding cleft rather than on a single predicted residue. Residues identified during pocket analysis were subsequently used to interpret ligand–protein interactions. In particular, the interaction analysis focused on residues directly identified in the final docked poses rather than assuming individual residues were experimentally validated selectivity determinants.

2.5. Molecular docking protocol.

Molecular docking was performed using AutoDock Vina 1.1.2. The receptor was supplied as a rigid PDBQT file, whereas ligand torsional degrees of freedom were retained. The docking search space was defined using the Vina Cartesian box parameters:

Center X : 29.400
Center Y : 26.998
Center Z : 39.322
Size X : 22.5
Size Y : 22.5
Size Z : 22.5

The docking search space was centered over the ATP-binding pocket of human CDK4 (PDB ID: 2W9Z, Chain B) with the following coordinates: Center X = 29.400, Center Y = 26.998, Center Z = 39.322. The search grid box dimensions were defined as Size X = 22.5 Å, Size Y = 22.5 Å, Size Z = 22.5 Å (derived from a 60 × 60 × 60 grid point setting with a standard spacing of 0.375 Å to cover the catalytic region). The following Vina parameters should be reported from the original configuration file or docking logs:

exhaustiveness : low exhaustiveness
num_modes : 9
energy_range : -6.3 to -1.5 kcal/mol
CPU/threads : 20
random seed : Vina default stochastic seeds were used

If no explicit values were specified, the manuscript should state that the Vina defaults were used rather than introducing retrospective values. In Vina 1.1.2, the documented defaults are an exhaustiveness of 8, a maximum of 9 output modes, and an energy range of 3 kcal/mol; the CPU number and random seed can also be explicitly specified. Each ligand was docked independently against the prepared CDK4 receptor. The output poses were ranked according to their Vina docking scores, expressed in kcal/mol. Because these values originate from an empirical docking scoring function, they were interpreted as predicted docking scores and relative ranking metrics, not as experimentally determined binding free energies.

2.6. Docking validation.

Table 1. Statistical RMSD and validation values for re-docked palbociclib conformers (PDB ID: 2W9Z).

Conformer Code	RMSD (Å)	Status
Palbociclib_UL1	0.0000	*) Reference
Palbociclib_UL2	0.6893	
Palbociclib_UL3	0.6900	
Palbociclib_UL4	0.0714	
Palbociclib_UL5	0.2520	
Palbociclib_UL6	0.0484	
Mean ($\bar{x}$)	0.3502	Valid (< 2.0 Å)
Standard Deviation (SD)	0.32	
Standard Error of Mean (SEM)	0.14	
Sample Size (n)	5	

The coordinates reproduced a highly consistent binding mode, with a mean RMSD of 0.3502 ± 0.32 Å (Table 1), demonstrating high precision and reproducible conformer poses within the binding site. As an indirect validation, palbociclib (an FDA-approved drug for HR+/HER2- breast cancer) was prepared using the same ligand-preparation protocol and docked six times into the corresponding CDK4 binding region using the parameters applied to the coffee bioactive library. Because PDB ID 2W9Z does not contain a co-crystallized small-molecule inhibitor, conventional redocking validation based on recovering a native crystallographic ligand pose was not possible. Consequently, the precision and reproducibility of the docking protocol were quantitatively evaluated by re-docking five conformers of the FDA-approved drug palbociclib into the defined binding pocket under identical grid conditions, using the top-ranked docked pose (Palbociclib_UL1) as an internal reference. The

RMSD between the experimentally observed ligand pose and the top-ranked docked pose was calculated as a reference to assess pose-reproduction capability Root Mean Square Deviation (RMSD). The best Vina docking score structure of palbociclib was used as the reference structure. Validation of the molecular docking algorithm was executed by re-docking five conformers of palbociclib into the defined binding pocket under identical grid conditions, as shown (Figure 1). The precision and pose reproducibility of the docking protocol were quantitatively evaluated by calculating the RMSD of the re-docked conformers against the top-ranked docked pose (Palbociclib_UL1) as an internal reference.

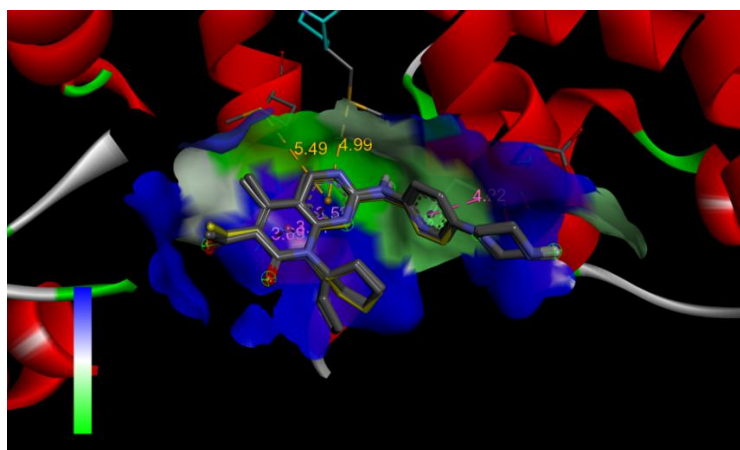


Figure 1. 3D Visualization of the validated active site using Palbociclib (*) reference (yellow-highlighted structure).

2.7. Analysis of docking poses and protein–ligand interactions.

The highest-ranked docking poses were visually inspected using BIOVIA Discovery Studio Visualizer 2015 and PyMOL. The analysis identified hydrogen bonds, hydrophobic contacts, electrostatic interactions, and other non-covalent contacts between the ligands and CDK4 residues (Figure 2).

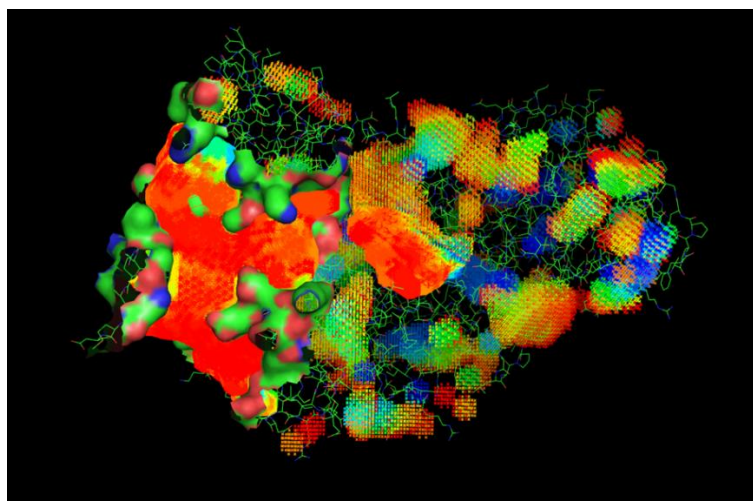


Figure 2. 3D Visualization of the predicted active site in CDK4 (protein 2W9Z).

For each prioritized compound, we recorded the interacting residues directly from the final docking pose and two-dimensional interaction diagram. Particular attention was given to interactions within the ATP-binding region. Residue assignments were verified against the CDK4 chain used for docking to avoid inconsistencies between the docking coordinates and the interaction diagrams. The interaction analysis was used to characterize predicted ligand-

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binding orientations and residue contacts. These interactions were not interpreted as experimental evidence of enzymatic inhibition, persistent binding, conformational stabilization, or competitive inhibition.

2.8. Docking-score ranking and candidate prioritization.

The 133 coffee-derived compounds were ranked according to their predicted Vina docking scores. Compounds with more favorable docking scores were prioritized for subsequent interaction analysis and drug-likeness assessment (Figure 2). The prioritization was based on the relative docking scores and the qualitative compatibility of the predicted poses with the CDK4 binding region (Figure 3). No conversion of Vina docking scores into binding free energies or inhibition constants was performed. In particular, an apparent inhibition constant (K_i) was not calculated from the docking score because such a conversion would require assumptions that are not justified by the present docking protocol.

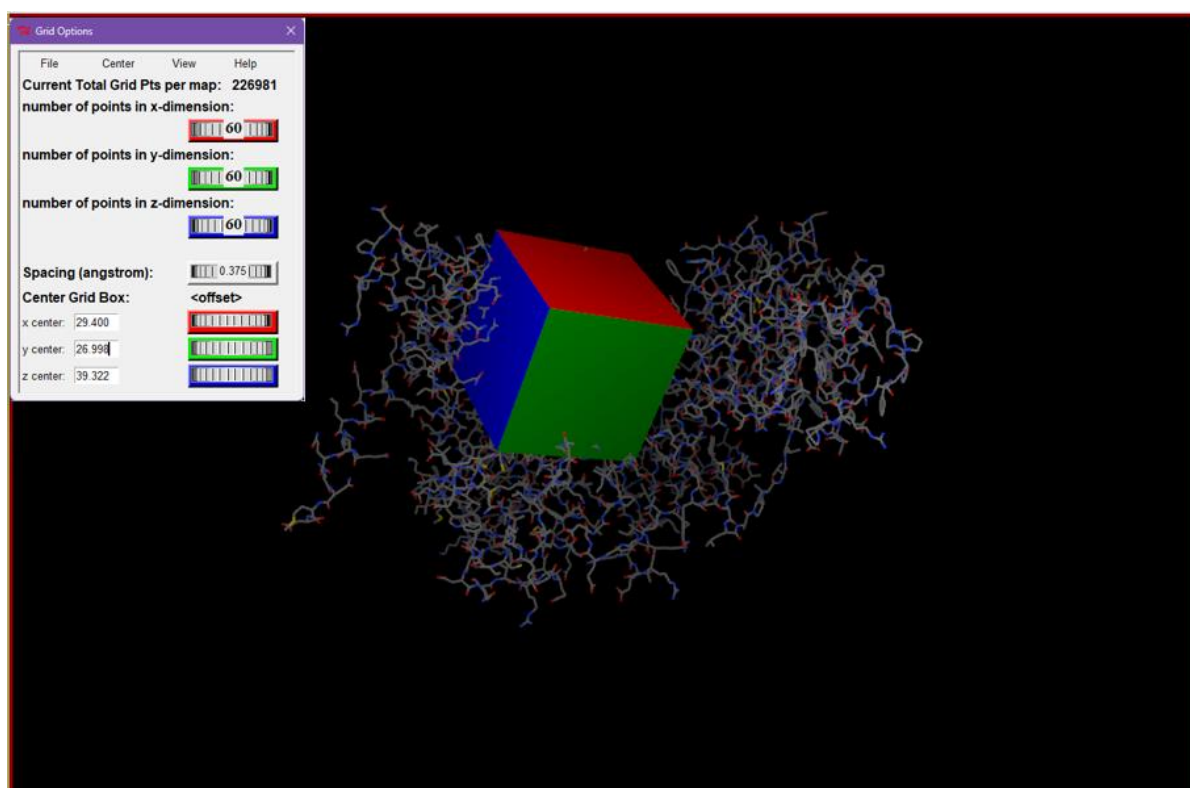


Figure 3. Grid box positioning and parameter configuration for docking analysis of protein 2W9Z.

2.9. Drug-likeness and toxicity prediction.

Drug-likeness properties of the prioritized compounds were evaluated using Lipinski's Rule of Five criteria. The following molecular descriptors were recorded: molecular weight (MW), calculated partition coefficient (logP), hydrogen-bond donor count (HBD), hydrogen-bond acceptor count (HBA), and, where available, topological polar surface area (TPSA). A compound was considered compliant with the conventional Lipinski criteria when MW was ≤ 500 Da, logP was ≤ 5 , HBD was ≤ 5 , and HBA was ≤ 10 . We reported compliance descriptively rather than interpreting it as evidence of pharmacological efficacy or adequate oral bioavailability. The molecular properties were calculated using the specified cheminformatics platform used in the original analysis. If these values were obtained from a web-based platform,

the platform name, version/database release, input structure format, and calculation date should be reported.

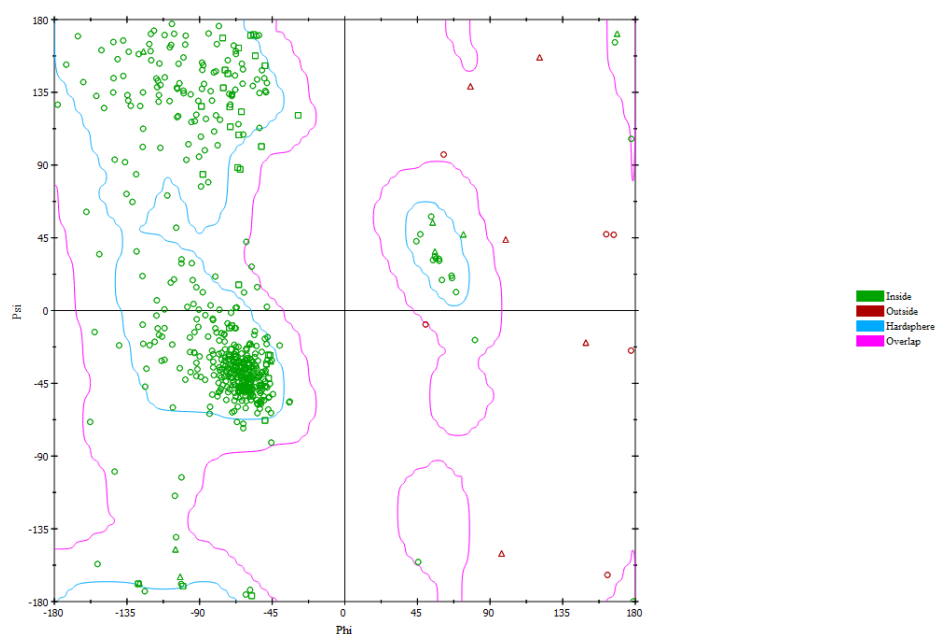
For toxicity prediction, the prioritized compounds were submitted to ProTox 3.0 using their canonical molecular structures in MOL/SMILES format. The predicted toxicity endpoints reported by the platform were recorded together with the corresponding predicted class or probability values. Predictions were interpreted as computational estimates for compound prioritization and not as experimentally established toxicity measurements.

2.10. Statistical and data-reporting considerations.

Because molecular docking produces computational predictions rather than experimental replicate measurements, we did not apply inferential statistical testing to docking scores. Compounds were ranked by docking score generated with AutoDock Vina, and interaction patterns were reported qualitatively based on the corresponding docking poses. Retain all software versions, receptor and ligand structure identifiers, docking configuration files, and output PDBQT files to allow independent reproduction of the calculations. Where stochastic docking was used without a fixed random seed, the stochastic nature of the calculation should be acknowledged when interpreting small differences in docking scores between compounds.

3. Results and Discussion

The stereochemical quality and structural validity of the initial human CDK4 receptor model (PDB ID: 2W9Z) were evaluated via Ramachandran plot analysis (Figure 4). This diagnostic assessment of ϕ (phi) and ψ (psi) backbone dihedral angles provides a critical baseline metric to verify the stereochemical quality and physical realism of the starting macromolecular template before molecular docking. Quantitative analysis of the 2W9Z structural template in Figure 4 indicates that most amino acid residues lie within the most favored and additionally allowed regions, confirming that the receptor structural model is a highly reliable starting configuration. This high initial conformational quality ensures the receptor framework is stereochemically valid for evaluating predicted ligand–residue interactions within the ATP-binding pocket.



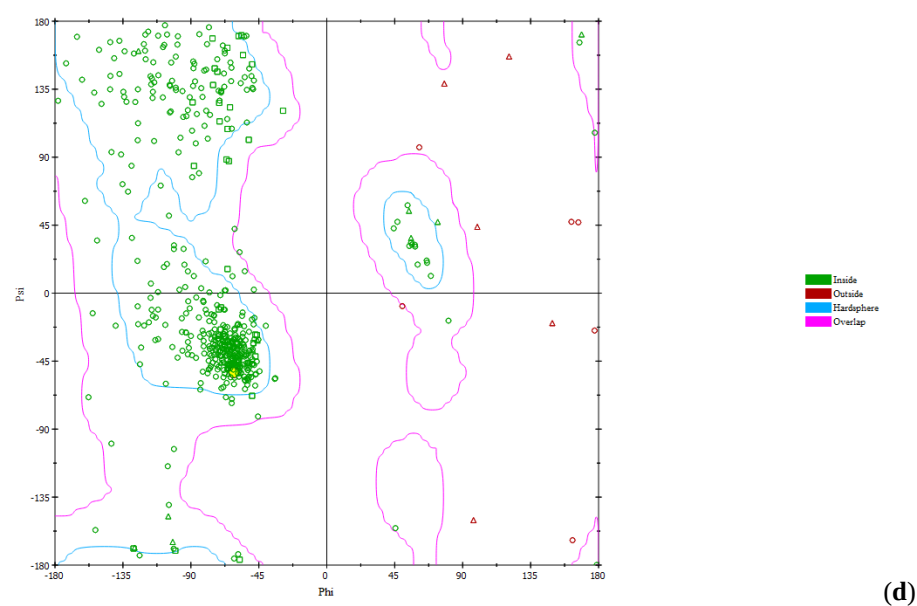
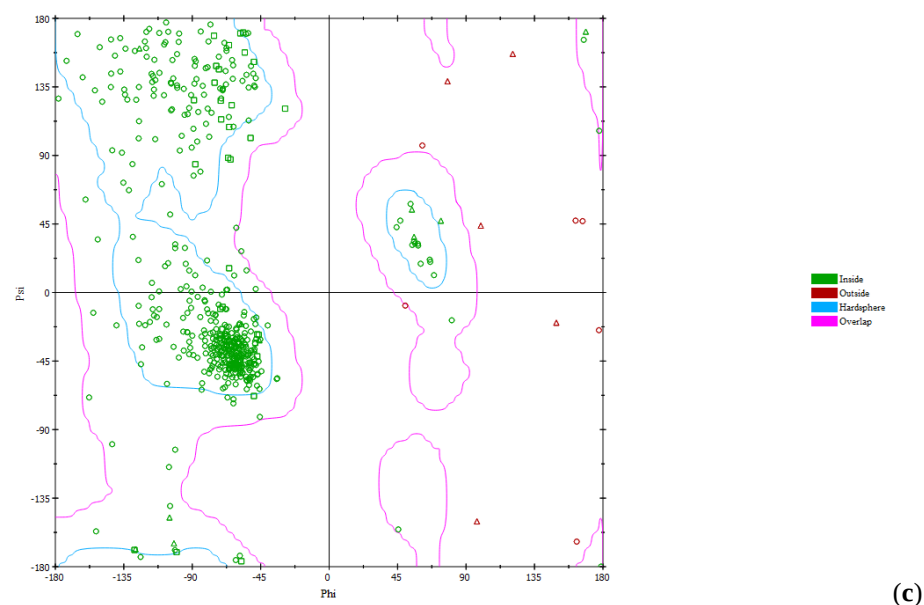
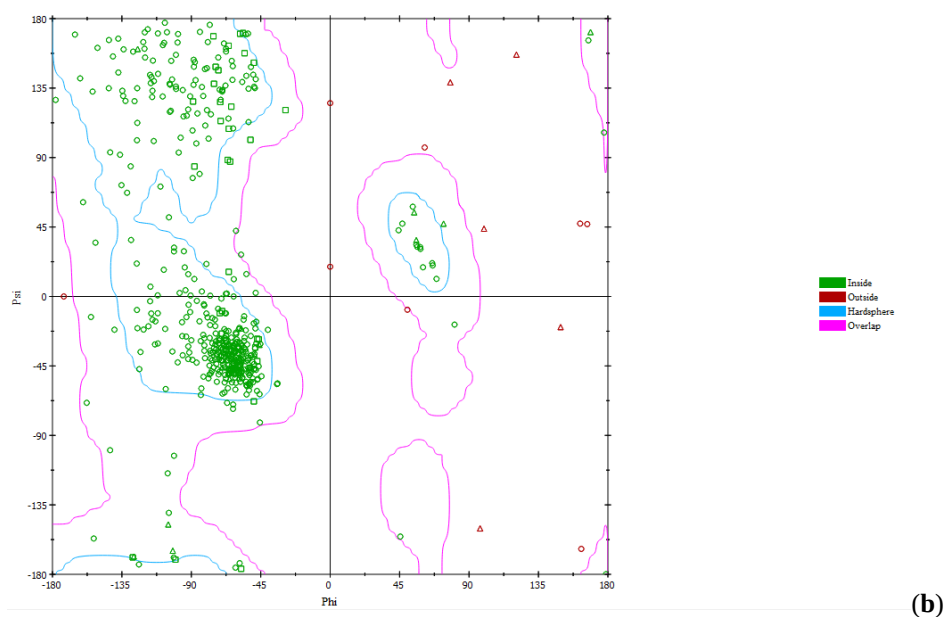


Figure 4. Ramachandran plot of the predicted active site in CDK4 (protein 2W9Z) to docked ligand: (a) 5-O-caffeoylquinic acid; (b) 3-caffeoylquinic acid; (c) chlorogenic acid; and (d) 9-((2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-3,9-dihydro-1H-purine-2,6-dione.

3.1. AutoDock Vina docking score profiling of Indonesian coffee bioactives against CDK4 (PDB ID: 2W9Z).

In this study, we systematically screened a curated library of 133 natural ligands to evaluate their inhibitory potential against the human Cyclin-Dependent Kinase 4 (CDK4) macromolecule [1,20]. Unlike conventional kinase models, this investigation utilized the high-resolution (2.3 Å) crystal structure of the human CDK4/Cyclin D1 complex (PDB ID: 2W9Z), which represents a physiologically stable inactive conformation [6,9]. The preparation protocol involved rigorously removing solvent molecules and adding polar hydrogens, then converting the structure to .pdbqt format for simulation with AutoDock Vina. Using optimized, standardized docking parameters—centered at Cartesian coordinates (x = 29.400, y = 26.998, z = 39.322)—was critical to improve prediction reliability and align with established benchmarks for kinase-targeted CDK4-binding candidate studies. Unlike the observed homolog CDK6, the binding landscape at the CDK4 active site favored specific chlorogenic acid (CGA) isomers. The screening prioritized 5-O-caffeoylquinic acid as the top-ranked compound, with a docking score of −6.3 kcal/mol, followed by 3-caffeoylquinic acid at −6.1 kcal/mol. These values indicate better binding within the ATP-binding pocket of the inactive kinase. While these energies are moderate compared to synthetic third-generation inhibitors, they are significantly more potent than the primary coffee alkaloid, caffeine, which exhibited a markedly lower predicted affinity with an AutoDock Vina docking score of −4.3 kcal/mol in the same catalytic cleft (Table 2). This differentiation underscores the superior pharmacological potential of caffeoylquinic acid scaffolds over methylxanthines for target-specific CDK4 modulation.

Table 2. Docking results of Indonesian coffee bioactives against CDK4.

Ligand Compound Name (IUPAC)	InChI	Docking (AutoDock Vina 2W9Z)
		Vina Score (kcal/mol)
5-O-caffeoylquinic acid	InChI=1S/C16H18O9/c17-9-3-1-8(5-10(9)18)2-4-13(20)25-12-7-16(24,15(22)23)6-11(19)14(12)21/h1-5,11-12,14,17-19,21,24H,6-7H2,(H,22,23)/t11-,12-,14-,16-/m1/s1	-6.3
3-caffeoylquinic acid	InChI=1S/C16H18O9/c17-9-3-1-8(5-10(9)18)2-4-13(20)25-12-7-16(24,15(22)23)6-11(19)14(12)21/h1-5,11-12,14,17-19,21,24H,6-7H2,(H,22,23)/t11-,12-,14+,16-/m0/s1	-6.1
chlorogenic acid	InChI=1S/C16H18O9/c17-9-3-1-8(5-10(9)18)2-4-13(20)25-12-7-16(24,15(22)23)6-11(19)14(12)21/h1-5,11-12,14,17-19,21,24H,6-7H2,(H,22,23)/t11-,12+,14+,16+/m0/s1	-6
9-((2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-3,9-dihydro-1H-purine-2,6-dione	InChI=1S/C10H12N4O6/c15-1-3-5(16)6(17)9(20-3)14-2-11-4-7(14)12-10(19)13-8(4)18/h2-3,5-6,9,15-17H,1H2,(H2,12,13,18,19)/t3-,5-,6-,9-/m1/s1	-6
4-caffeoylquinic acid	InChI=1S/C16H18O9/c17-9-3-1-8(5-10(9)18)2-4-13(21)25-14-11(19)6-16(24,15(22)23)7-12(14)20/h1-5,11-12,14,17-20,24H,6-7H2,(H,22,23)/t11-,12+,14+,16+	-5.9
2-amino-9-((2R,3R,4R,5S)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-1,9-dihydro-6H-purin-6-one	InChI=1S/C10H13N5O5/c11-10-13-7-4(8(19)14-10)12-2-15(7)9-6(18)5(17)3(1-16)20-9/h2-3,5-6,9,16-18H,1H2,(H3,11,13,14,19)/t3-,5-,6+,9+/m0/s1	-5.7
(S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5S)-5-vinylquinuclidin-2-yl)methanol	InChI=1S/C20H24N2O2/c1-3-13-12-22-9-7-14(13)10-19(22)20(23)16-6-8-21-18-5-4-15(24-	-5.5

Ligand Compound Name (IUPAC)	InChI	Docking (AutoDock Vina 2W9Z)
		Vina Score (kcal/mol)
	2)11-17(16)18/h3-6,8,11,13-14,19-20,23H,1,7,9-10,12H2,2H3/t13-,14+,19+,20+/m1/s1	
apocarotenal	InChI=1S/C30H40O/c1-24(13-8-9-14-25(2)16-11-18-27(4)23-31)15-10-17-26(3)20-21-29-28(5)19-12-22-30(29,6)7/h8-11,13-18,20-21,23H,12,19,22H2,1-7H3/b9-8?,15-10+,16-11?,21-20?,24-13-,25-14+,26-17-,27-18-	-5.3
2-n-propylpyrazine	InChI=1S/C7H10N2/c1-2-3-7-6-8-4-5-9-7/h4-6H,2-3H2,1H3	-5.2
(9E,12E,15E)-octadeca-9,12,15-trienoic acid	InChI=1S/C18H30O2/c1-2-3-4-5-6-7-8-9-10-11-12-13-14-15-16-17-18(19)20/h3-4,6-7,9-10H,2,5,8,11-17H2,1H3,(H,19,20)	-5
(R)-furan-2-yl(phenyl)methanol	InChI=1S/C11H10O2/c12-11(10-7-4-8-13-10)9-5-2-1-3-6-9/h1-8,11-12H/t11-/m1/s1	-4.9
2-[(2R,4aR)-4a,8-dimethyl-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-yl]propan-2-ol	InChI=1S/C15H26O/c1-11-6-5-8-15(4)9-7-12(10-13(11)15)14(2,3)16/h12,16H,5-10H2,1-4H3/t12-,15-/m1/s1	-4.9
9,12-octadecadienoic acid (Z,Z)-	InChI=1S/C18H32O2/c1-2-3-4-5-6-7-8-9-10-11-12-13-14-15-16-17-18(19)20/h6-7,9-10H,2-5,8,11-17H2,1H3,(H,19,20)/b7-6?,10-9+	-4.8
2H-2,4a-ethanonaphthalene, 1,3,4,5,6,7-hexahydro-2,5,5-trimethyl	InChI=1S/C15H24/c1-13(2)6-4-5-12-11-14(3)7-9-15(12,13)10-8-14/h5H,4,6-11H2,1-3H3/t14-,15+	-4.7
2-naphthalenemethanol	InChI=1S/C15H26O/c1-11-6-5-8-15(4)9-7-12(10-13(11)15)14(2,3)16/h6,12-13,16H,5,7-10H2,1-4H3/t12-,13-,15-/m1/s1	-4.7
9,12,15-octadecatrien-1-ol, (Z,Z,Z)-	InChI=1S/C18H32O/c1-2-3-4-5-6-7-8-9-10-11-12-13-14-15-16-17-18-19/h3-4,6-7,9-10,19H,2,5,8,11-18H2,1H3	-4.7
butyl (Z,Z)-9,12-octadecadienoate	InChI=1S/C22H40O2/c1-3-5-7-8-9-10-11-12-13-14-15-16-17-18-19-20-22(23)24-21-6-4-2/h9-10,12-13H,3-8,11,14-21H2,1-2H3/b10-9?,13-12-	-4.7
(2R,3S)-3-methyl-2-phenyl-3,6-dihydro-2H-pyran	InChI=1S/C12H14O/c1-10-6-5-9-13-12(10)11-7-3-2-4-8-11/h2-8,10,12H,9H2,1H3/t10-,12+/m0/s1	-4.6
1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione	InChI=1S/C7H8N4O2/c1-10-5-4(8-3-9-5)6(12)11(2)7(10)13/h3H,1-2H3,(H,8,9)	-4.6
3-[(1Z)-buta-1,3-dien-1-yl]-2,4,4-trimethylcyclohex-2-en-1-one	InChI=1S/C13H18O/c1-5-6-7-11-10(2)12(14)8-9-13(11,3)4/h5-7H,1,8-9H2,2-4H3	-4.5
7-methylxanthine	InChI=1S/C6H6N4O2/c1-10-2-7-4-3(10)5(11)9-6(12)8-4/h2H,1H3,(H2,8,9,11,12)	-4.5
3-O-beta-D-galactopyranosyl-D-arabinose	InChI=1S/C11H20O10/c12-1-4(15)10(5(16)2-13)21-11-9(19)8(18)7(17)6(3-14)20-11/h1,4-11,13-19H,2-3H2/t4-,5-,6-,7+,8-,9+,10-,11+/m1/s1	-4.5
(+)-quinic acid	InChI=1S/C7H12O6/c8-3-1-7(13,6(11)12)2-4(9)5(3)10/h3-5,8-10,13H,1-2H2,(H,11,12)/t3-,4+,5+,7+	-4.4
3-methylxanthine	InChI=1S/C6H6N4O2/c1-10-4-3(7-2-8-4)5(11)9-6(10)12/h2H,1H3,(H,7,8)(H,9,11,12)	-4.4
2-[(furan-2-yl)methyl]-1H-pyrrole	InChI=1S/C9H9NO/c1-3-8(10-5-1)7-9-4-2-6-11-9/h1-6,10H,7H2	-4.4
(2Z)-3-(4-hydroxyphenyl)prop-2-enoic acid	InChI=1S/C9H8O3/c10-8-4-1-7(2-5-8)3-6-9(11)12/h1-6,10H,(H,11,12)	-4.4
(1r,3R,4r,5S)-1,3,4,5-tetrahydrocyclohexane-1-carboxylic acid	InChI=1S/C7H12O6/c8-3-1-7(13,6(11)12)2-4(9)5(3)10/h3-5,8-10,13H,1-2H2,(H,11,12)/t3-,4+,5+,7+	-4.4
3,7-dihydro-1H-purine-2,6-dione	InChI=1S/C5H4N4O2/c10-4-2-3(7-1-6-2)8-5(11)9-4/h1H,(H3,6,7,8,9,10,11)	-4.4
5-(nitromethyl)pyrimidine-2,4-diol	InChI=1S/C5H5N3O4/c9-4-3(2-8(11)12)1-6-5(10)7-4/h1H,2H2,(H2,6,7,9,10)	-4.3
9,12,15-octadecatrienoic acid	InChI=1S/C18H30O2/c1-2-3-4-5-6-7-8-9-10-11-12-13-14-15-16-17-18(19)20/h3-4,6-7,9-	-4.3

Ligand Compound Name (IUPAC)	InChI	Docking (AutoDock Vina 2W9Z)
		Vina Score (kcal/mol)
	10H,2,5,8,11-17H2,1H3,(H,19,20)/b4-3+,7-6+,10-9+	
9-octadecenoic acid (Z)-, methyl ester	InChI=1S/C19H36O2/c1-3-4-5-6-7-8-9-10-11-12-13-14-15-16-17-18-19(20)21-2/h10-11H,3-9,12-18H2,1-2H3	-4.3
caffeine	InChI=1S/C8H10N4O2/c1-10-4-9-6-5(10)7(13)12(3)8(14)11(6)2/h4H,1-3H3	-4.3
(2S)-2-amino-3-(1H-imidazol-4-yl)propanoic acid	InChI=1S/C6H9N3O2/c7-5(6(10)11)1-4-2-8-3-9-4/h2-3,5H,1,7H2,(H,8,9)(H,10,11)/t5-/m0/s1	-4.3
(1r,2r,3r,4r,5r,6r)-cyclohexane-1,2,3,4,5,6-hexol	InChI=1S/C6H12O6/c7-1-2(8)4(10)6(12)5(11)3(1)9/h1-12H/t1-,2-,3+,4+,5-,6-	-4.3
(2R,3R,4R,5R,6S)-6-(hydroxymethyl)oxane-2,3,4,5-tetrol	InChI=1S/C6H12O6/c7-1-2-3(8)4(9)5(10)6(11)12-2/h2-11H,1H2/t2-,3-,4+,5+,6+/m0/s1	-4.3
4-vinyl-2-methoxyphenol	InChI=1S/C9H10O2/c1-3-7-4-5-8(10)9(6-7)11-2/h3-6,10H,1H2,2H3	-4.2
7H-purin-6-amine	InChI=1S/C5H5N5/c6-4-3-5(9-1-7-3)10-2-8-4/h1-2H,(H3,6,7,8,9,10)	-4.2
ethyl 3-(pyridin-2-yl)propanoate	InChI=1S/C10H13NO2/c1-2-13-10(12)7-6-9-5-3-4-8-11-9/h3-5,8H,2,6-7H2,1H3	-4.1
4-ethylguaicol	InChI=1S/C9H12O2/c1-3-7-4-5-8(10)9(6-7)11-2/h4-6,10H,3H2,1-2H3	-4.1
5-methyl-6,7-dihydrocyclopentapyrazine	InChI=1S/C8H10N2/c1-6-2-3-7-8(6)10-5-4-9-7/h4-6H,2-3H2,1H3/t6-/m1/s1	-4.1
1,7-dihydro-6H-purin-6-one	InChI=1S/C5H4N4O/c10-5-3-4(7-1-6-3)8-2-9-5/h1-2H,(H2,6,7,8,9,10)	-4.1
(4S)-1-methyl-4-(prop-1-en-2-yl)cyclohex-1-ene	InChI=1S/C10H16/c1-8(2)10-6-4-9(3)5-7-10/h4,10H,1,5-7H2,2-3H3/t10-/m1/s1	-4.1
methyl tetradecanoate	InChI=1S/C15H30O2/c1-3-4-5-6-7-8-9-10-11-12-13-14-15(16)17-2/h3-14H2,1-2H3	-4.1
2-furanpropionic acid	InChI=1S/C7H8O3/c8-7(9)4-3-6-2-1-5-10-6/h1-2,5H,3-4H2,(H,8,9)	-4
pyrazine, 2-methyl-6-(1-propenyl)-, (E)-	InChI=1S/C8H10N2/c1-3-4-8-6-9-5-7(2)10-8/h3-6H,1-2H3/b4-3+	-4
citric acid	InChI=1S/C6H8O7/c7-3(8)1-6(13,5(11)12)2-4(9)10/h13H,1-2H2,(H,7,8)(H,9,10)(H,11,12)	-4
dodecanoic acid	InChI=1S/C13H26O2/c1-3-4-5-6-7-8-9-10-11-12-13(14)15-2/h3-12H2,1-2H3	-4
6-sulfo-galactose	InChI=1S/C6H12O9S/c7-1-2(8)3(9)4(10)5(11)6(12)16(13,14)15/h1-6,8-12H,(H,13,14,15)/t2-,3+,4-,5+,6+/m0/s1	-4
(9E,12E)-octadeca-9,12-dienoic acid	InChI=1S/C18H32O2/c1-2-3-4-5-6-7-8-9-10-11-12-13-14-15-16-17-18(19)20/h6-7,9-10H,2-5,8,11-17H2,1H3,(H,19,20)/b7-6+,10-9+	-4
(Z)-stearohydrazonic acid	InChI=1S/C18H38N2O/c1-2-3-4-5-6-7-8-9-10-11-12-13-14-15-16-17-18(21)20-19/h2-17,19H2,1H3,(H,20,21)	-4
2-acetyl-3-methylpyrazine	InChI=1S/C7H8N2O/c1-5-7(6(2)10)9-4-3-8-5/h3-4H,1-2H3	-3.9
L-(5-3H)-arginine	InChI=1S/C6H14N4O2/c7-4(5(11)12)2-1-3-10-6(8)9/h4H,1-3,7H2,(H,11,12)(H4,8,9,10)/t4-/m0/s1	-3.9
phenylethyl alcohol	InChI=1S/C8H10O/c9-7-6-8-4-2-1-3-5-8/h1-5,9H,6-7H2	-3.9
hexadecanoic acid	InChI=1S/C16H32O2/c1-2-3-4-5-6-7-8-9-10-11-12-13-14-15-16(17)18/h2-15H2,1H3,(H,17,18)	-3.9
pyrazine, 3,5-diethyl-2-methyl-	InChI=1S/C9H14N2/c1-4-8-6-10-7(3)9(5-2)11-8/h6H,4-5H2,1-3H3	-3.8
3-ethyl-2,5-dimethylpyrazine	InChI=1S/C8H12N2/c1-4-8-7(3)9-5-6(2)10-8/h5H,4H2,1-3H3	-3.8
5-hydroxymethylfurfural	InChI=1S/C6H6O3/c7-3-5-1-2-6(4-8)9-5/h1-3,8H,4H2	-3.8
decanoic acid	InChI=1S/C10H20O2/c1-2-3-4-5-6-7-8-9-10(11)12/h2-9H2,1H3,(H,11,12)	-3.8

Ligand Compound Name (IUPAC)	InChI	Docking (AutoDock Vina 2W9Z)
		Vina Score (kcal/mol)
stearic acid	InChI=1S/C18H36O2/c1-2-3-4-5-6-7-8-9-10-11-12-13-14-15-16-17-18(19)20/h2-17H2,1H3,(H,19,20)	-3.8
2,6-diethylpyrazine	InChI=1S/C8H12N2/c1-3-7-5-9-6-8(4-2)10-7/h5-6H,3-4H2,1-2H3	-3.7
1,2-benzenediol	InChI=1S/C6H6O2/c7-5-3-1-2-4-6(5)8/h1-4,7-8H	-3.7
ethanedihydrazide	InChI=1S/C2H6N4O2/c3-5-1(7)2(8)6-4/h3-4H2,(H,5,7)(H,6,8)	-3.7
(2R)-2-aminopentanedioic acid	InChI=1S/C5H9NO4/c6-3(5)10)1-2-4(7)8/h3H,1-2,6H2,(H,7,8)(H,9,10)/t3-/m1/s1	-3.7
pyridine-3-carboxylic acid	InChI=1S/C6H5NO2/c8-6(9)5-2-1-3-7-4-5/h1-4H,(H,8,9)	-3.7
(2S)-pyrrolidine-2-carboxylic acid	InChI=1S/C5H9NO2/c7-5(8)4-2-1-3-6-4/h4,6H,1-3H2,(H,7,8)/t4-/m0/s1	-3.7
methyl (Z)-octadec-13-enoate	InChI=1S/C19H36O2/c1-3-4-5-6-7-8-9-10-11-12-13-14-15-16-17-18-19(20)21-2/h6-7H,3-5,8-18H2,1-2H3	-3.7
1-methylpyridin-1-ium-3-carboxylate	InChI=1S/C7H7NO2/c1-8-4-2-3-6(5-8)7(9)10/h2-5H,1H3	-3.7
pyrazine, (1-methylethenyl)	InChI=1S/C7H8N2/c1-6(2)7-5-8-3-4-9-7/h3-5H,1H2,2H3	-3.6
2-ethyl-3-methylpyrazine	InChI=1S/C7H10N2/c1-3-7-6(2)8-4-5-9-7/h4-5H,3H2,1-2H3	-3.6
(2S,4Z)-2-amino-4-hydroxy-4-iminobutanoic acid	InChI=1S/C4H8N2O3/c5-2(4)8)9)1-3(6)7/h2H,1,5H2,(H,6,7)(H,8,9)/t2-/m0/s1	-3.6
aspartic acid	InChI=1S/C4H7NO4/c5-2(4)8)9)1-3(6)7/h2H,1,5H2,(H,6,7)(H,8,9)/t2-/m1/s1	-3.6
(furan-2-yl)methyl formate	InChI=1S/C6H6O3/c7-5-8-4-6-2-1-3-9-6/h1-3,5H,4H2	-3.6
2-methoxyphenol	InChI=1S/C7H8O2/c1-9-7-5-3-2-4-6(7)8/h2-5,8H,1H3	-3.6
(2R)-2-hydroxybutanedioic acid	InChI=1S/C4H6O5/c5-2(4)8)9)1-3(6)7/h2,5H,1H2,(H,6,7)(H,8,9)/t2-/m1/s1	-3.6
(1Z,3E)-propanedihydrazonic acid	InChI=1S/C3H8N4O2/c4-6-2(8)1-3(9)7-5/h1,4-5H2,(H,6,8)(H,7,9)	-3.6
methyl pyridine-3-carboxylate	InChI=1S/C7H7NO2/c1-10-7(9)6-3-2-4-8-5-6/h2-5H,1H3	-3.6
2-ethyl-5-methylpyrazine	InChI=1S/C7H10N2/c1-3-7-5-8-6(2)4-9-7/h4-5H,3H2,1-2H3	-3.5
2-ethenyl-5-methylfuran	InChI=1S/C7H8O/c1-3-7-5-4-6(2)8-7/h3-5H,1H2,2H3	-3.5
N-methylpyridin-4(1H)-imine	InChI=1S/C6H8N2/c1-7-6-2-4-8-5-3-6/h2-5H,1H3,(H,7,8)	-3.5
1,2-dichlorobenzene	InChI=1S/C6H4Cl2/c7-5-3-1-2-4-6(5)8/h1-4H	-3.4
2-acetylfuran	InChI=1S/C6H6O2/c1-5(7)6-3-2-4-8-6/h2-4H,1H3	-3.4
2-vinylfuran	InChI=1S/C6H6O/c1-2-6-4-3-5-7-6/h2-5H,1H2	-3.4
3-ethylpyridine	InChI=1S/C7H9N/c1-2-7-4-3-5-8-6-7/h3-6H,2H2,1H3	-3.4
5-methylfurfural	InChI=1S/C6H6O2/c1-5-2-3-6(4-7)8-5/h2-4H,1H3	-3.4
2-[(methylsulfanyl)methyl]furan	InChI=1S/C6H8OS/c1-8-5-6-3-2-4-7-6/h2-4H,5H2,1H3	-3.4
(2S,3R,4R,5S)-2,4,5,6-tetrahydroxy-3-[(2H1)methyloxy]hexanal	InChI=1S/C7H14O6/c1-13-7(5(11)3-9)6(12)4(10)2-8/h3-8,10-12H,2H2,1H3/t4-,5+,6+,7-/m0/s1/i1D	-3.4
1-methyl-1H-pyrrole-2-carbaldehyde	InChI=1S/C6H7NO/c1-7-4-2-3-6(7)5-8/h2-5H,1H3	-3.3
(2S)-2,5-dimethylfuran-3-one	InChI=1S/C6H8O2/c1-4-3-6(7)5(2)8-4/h3,5H,1-2H3/t5-/m0/s1	-3.3
2,6-dimethylpyrazine	InChI=1S/C6H8N2/c1-5-3-7-4-6(2)8-5/h3-4H,1-2H3	-3.3

Ligand Compound Name (IUPAC)	InChI	Docking (AutoDock Vina 2W9Z)
		Vina Score (kcal/mol)
2-ethylpyrazine	InChI=1S/C6H8N2/c1-2-6-5-7-3-4-8-6/h3-5H,2H2,1H3	-3.3
2-furfural	InChI=1S/C5H4O2/c6-4-5-2-1-3-7-5/h1-4H	-3.3
2-furanmethanol	InChI=1S/C5H6O2/c6-4-5-2-1-3-7-5/h1-3,6H,4H2	-3.3
2-cyclopenten-1-one, 3-methyl-	InChI=1S/C6H8O/c1-5-2-3-6(7)4-5/h4H,2-3H2,1H3	-3.3
5-deoxy-D-lyxose	InChI=1S/C5H10O4/c1-3(7)5(9)4(8)2-6/h2-5,7-9H,1H3/t3-,4-,5+/m1/s1	-3.3
phenol	InChI=1S/C6H6O/c7-6-4-2-1-3-5-6/h1-5,7H	-3.3
(2S)-2-amino-3-methylbutanoic acid	InChI=1S/C5H11NO2/c1-3(2)4(6)5(7)8/h3-4H,6H2,1-2H3,(H,7,8)/t4-/m0/s1	-3.3
hexane-2,3-dione	InChI=1S/C6H10O2/c1-3-4-6(8)5(2)7/h3-4H2,1-2H3	-3.2
ethyl 3-methylbutanoate	InChI=1S/C7H14O2/c1-4-9-7(8)5-6(2)3/h6H,4-5H2,1-3H3	-3.2
2,3-dimethylpyrazine	InChI=1S/C6H8N2/c1-5-6(2)8-4-3-7-5/h3-4H,1-2H3	-3.1
2,5-dimethylfuran	InChI=1S/C6H8O/c1-5-3-4-6(2)7-5/h3-4H,1-2H3	-3.1
2,5-dimethylpyrazine	InChI=1S/C6H8N2/c1-5-3-8-6(2)4-7-5/h3-4H,1-2H3	-3.1
2-furanmethanethiol	InChI=1S/C5H6OS/c7-4-5-2-1-3-6-5/h1-3,7H,4H2	-3.1
2-methylfuran	InChI=1S/C5H6O/c1-5-3-2-4-6-5/h2-4H,1H3	-3.1
2-Methyl-4,5-dihydro-3(2H)-furanone	InChI=1S/C5H8O2/c1-4-5(6)2-3-7-4/h4H,2-3H2,1H3/t4-/m0/s1	-3.1
(2S)-2-amino-3-hydroxypropanoic acid	InChI=1S/C3H7NO3/c4-2(1-5)3(6)7/h2,5H,1,4H2,(H,6,7)/t2-/m0/s1	-3.1
2-Methylpyrazine	InChI=1S/C5H6N2/c1-5-4-6-2-3-7-5/h2-4H,1H3	-3
3-methylbutanoic Acid	InChI=1S/C5H10O2/c1-4(2)3-5(6)7/h4H,3H2,1-2H3,(H,6,7)	-3
4-aminobutanoic acid	InChI=1S/C4H9NO2/c5-3-1-2-4(6)7/h1-3,5H2,(H,6,7)	-3
hydroxyacetic acid	InChI=1S/C2H4O3/c3-1-2(4)5/h3H,1H2,(H,4,5)	-3
(2R)-2-hydroxypropanoic acid	InChI=1S/C3H6O3/c1-2(4)3(5)6/h2,4H,1H3,(H,5,6)/t2-/m1/s1	-3
1-methylpyridin-1-ium	InChI=1S/C6H8N/c1-7-5-3-2-4-6-7/h2-6H,1H3/q+1	-3
1H-pyrrole	InChI=1S/C4H5N/c1-2-4-5-3-1/h1-5H	-2.9
1-methyl-1H-pyrrole	InChI=1S/C5H7N/c1-6-4-2-3-5-6/h2-5H,1H3	-2.9
pentane-2,3-dione	InChI=1S/C5H8O2/c1-3-5(7)4(2)6/h3H2,1-2H3	-2.9
(2S)-2-aminopropanoic acid	InChI=1S/C3H7NO2/c1-2(4)3(5)6/h2H,4H2,1H3,(H,5,6)/t2-/m0/s1	-2.9
pyridine	InChI=1S/C5H5N/c1-2-4-6-5-3-1/h1-5H	-2.9
1-hydroxybutan-2-one	InChI=1S/C4H8O2/c1-2-4(6)3-5/h5H,2-3H2,1H3	-2.8
2-methylbutanal	InChI=1S/C5H10O/c1-3-5(2)4-6/h4-5H,3H2,1-2H3/t5-/m1/s1	-2.8
acetic acid	InChI=1S/C2H4O2/c1-2(3)4/h1H3,(H,3,4)	-2.8
acetone	InChI=1S/C3H6O/c1-3(2)4/h1-2H3	-2.8
carbamic acid	InChI=1S/CH3NO2/c2-1(3)4/h2H2,(H,3,4)	-2.8
hexanal	InChI=1S/C6H12O/c1-2-3-4-5-6-7/h6H,2-5H2,1H3	-2.8
methyl acetate	InChI=1S/C3H6O2/c1-3(4)5-2/h1-2H3	-2.8
(3R)-3-hydroxy-2-butanone	InChI=1S/C4H8O2/c1-3(5)4(2)6/h3,5H,1-2H3/t3-/m1/s1	-2.7
choline chloride	InChI=1S/C5H14NO/c1-6(2,3)4-5-7/h7H,4-5H2,1-3H3/q+1	-2.7
aminoacetic acid	InChI=1S/C2H5NO2/c3-1-2(4)5/h1,3H2,(H,4,5)	-2.7
butane-2,3-dione	InChI=1S/C4H6O2/c1-3(5)4(2)6/h1-2H3	-2.6
3-methylbutanal	InChI=1S/C5H10O/c1-5(2)3-4-6/h4-5H,3H2,1-2H3	-2.6
pyrazine	InChI=1S/C4H4N2/c1-2-6-4-3-5-1/h1-4H	-2.6

Ligand Compound Name (IUPAC)	InChI	Docking (AutoDock Vina 2W9Z)
		Vina Score (kcal/mol)
1-hydroxypropan-2-one	InChI=1S/C3H6O2/c1-3(5)2-4/h4H,2H2,1H3	-2.5
2-butanone	InChI=1S/C4H8O/c1-3-4(2)5/h3H2,1-2H3	-2.5
acetaldehyde	InChI=1S/C2H4O/c1-2-3/h2H,1H3	-2.2
formic acid	InChI=1S/CH2O2/c2-1-3/h1H,(H,2,3)	-2.1

The docking results reveal a distinct affinity hierarchy: 5-O-CQA (−6.3 kcal/mol) followed by 3-Caffeoylquinic Acid (AutoDock Vina scores = −6.1 kcal/mol). Interestingly, 4-Caffeoylquinic acid, which serves as the primary lead for CDK6, showed reduced affinity for the CDK4 2W9Z template (AutoDock Vina scores = −5.9 kcal/mol), suggesting that the unique topographic features of the CDK4 inactive state—specifically the orientation of the α C-helix—selectively favour the geometry of 5-O-CQA. Among the screened compounds, 5-O-caffeoylquinic acid was among the highest-ranked, exhibiting a Vina docking score of −6.3 kcal/mol. Other caffeoylquinic acid derivatives exhibited scores of approximately −6.1 kcal/mol, whereas caffeine exhibited a docking score of −4.3 kcal/mol (Table 2). These results indicate that the caffeoylquinic acid derivatives produced more favorable predicted docking scores than caffeine under the specific computational conditions used in this study.

The relatively small differences between the top-ranked compounds should, however, be interpreted cautiously. A difference of 0.2–0.4 kcal/mol between docking scores is small relative to the uncertainty associated with docking-scoring functions and does not by itself establish a meaningful difference in experimental binding affinity. Therefore, the ranking of individual caffeoylquinic acid isomers should be considered a computational prioritization rather than evidence that one isomer is intrinsically more potent than another. The present study also does not provide a direct comparison with CDK6 or CDK2. Consequently, the observed ranking cannot be interpreted as evidence of CDK4 isoform selectivity or superiority over CDK6- or CDK2-targeting compounds. Establishing such selectivity would require matched docking and, preferably, experimental biochemical comparisons against the relevant counter-targets, using equivalent protocols.

Overall, the docking analysis identified several caffeoylquinic acid derivatives as computationally prioritized compounds for further investigation against the CDK4 model. These results provide a basis for selecting compounds for experimental testing but do not demonstrate CDK4 inhibition, binding affinity, selectivity, or anticancer activity.

3.2. Analysis of 2D interaction topologies.

High-resolution 2D interaction mapping of the lead complexes (modeled using the 2W9Z template) elucidates the mechanistic basis for these negative AutoDock Vina scores, focusing on the stabilization of the inactive kinase state where the α C-helix remains in the "out" position. The stabilization of these ligands within the catalytic pocket is mediated by a multi-modal interaction profile involving the hinge region and the activation segment:

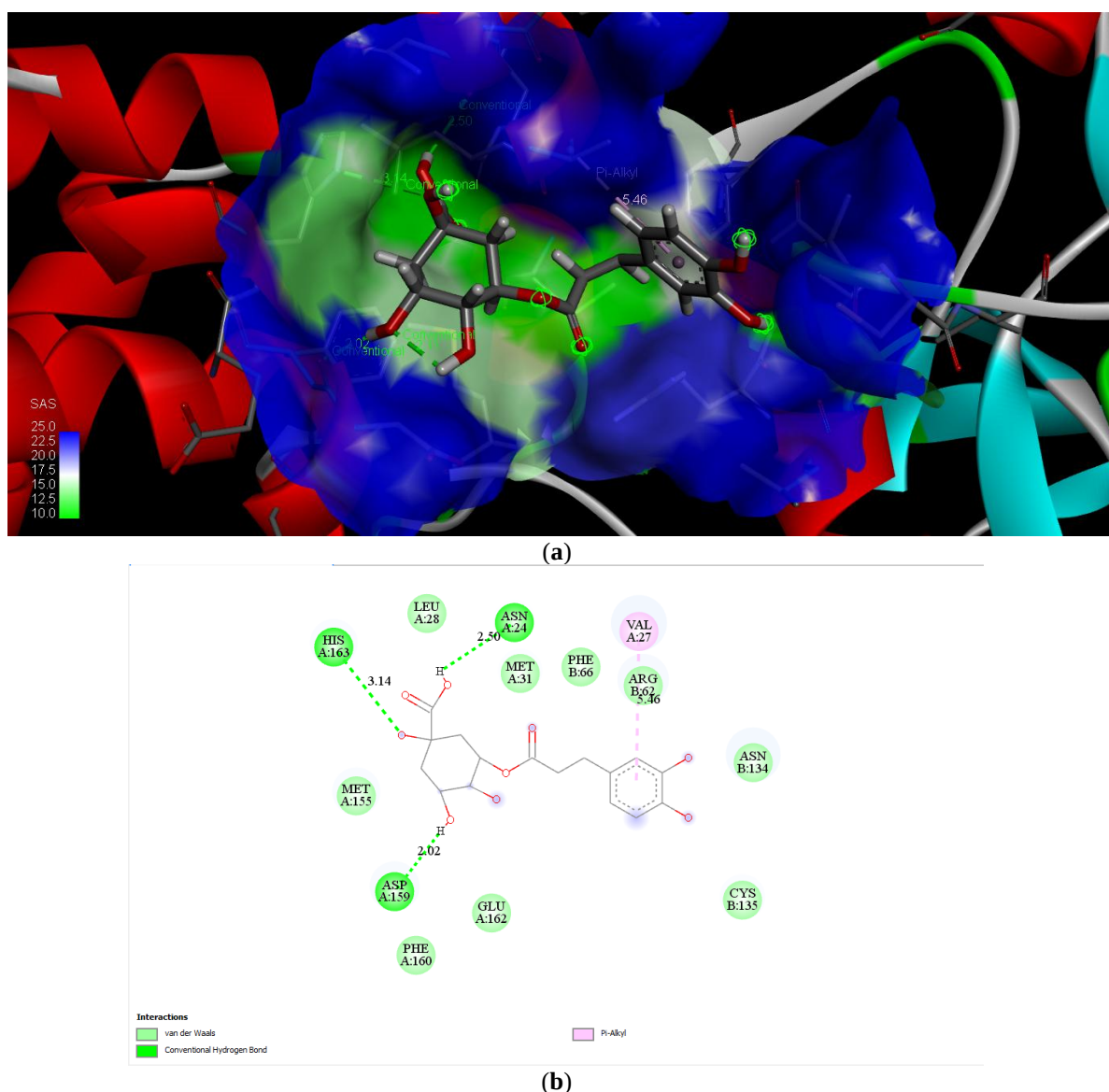
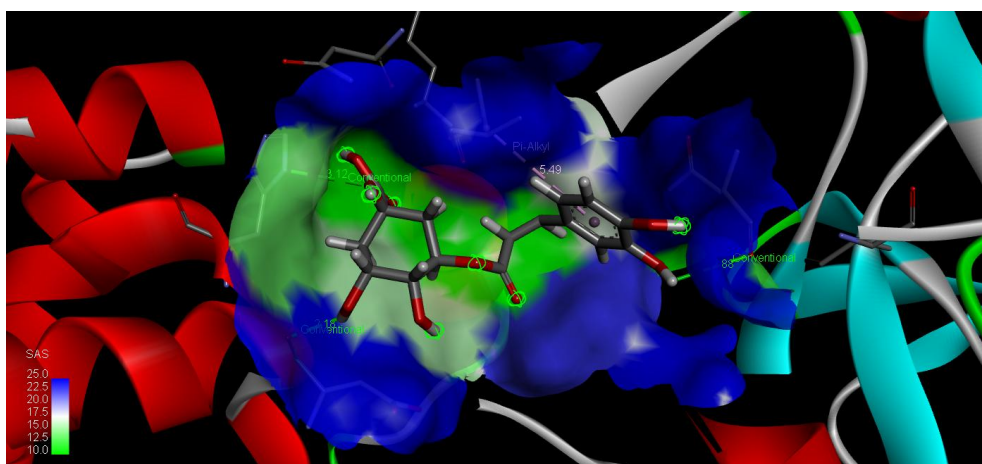


Figure 5. (a) 3D Interaction of 5-O-caffeoylquinic acid against protein 2W9Z and (b) 2D Interaction of 5-O-caffeoylquinic acid against protein 2W9Z.

Conventional Hydrogen Bonding. Three critical hydrogen bonds anchor the interaction. A high-strength interaction is observed with ASP:B:159 at a distance of 2.02 Å, which is vital for targeting the catalytic machinery of the kinase. Further stabilization occurs through ASN:B:24 (2.50 Å) and HIS:B:163 (3.14 Å), effectively tethering the ligand across the lobe interface (Figure 5 and Figure 6).



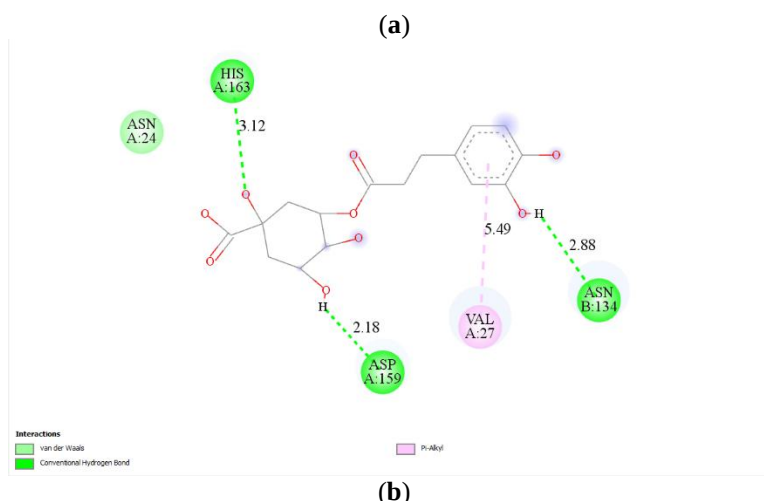


Figure 6. (a) 3D Interaction of 3-caffeoylquinic acid against protein 2W9Z and (b) 2D Interaction of 3-caffeoylquinic acid against protein 2W9Z.

Hydrophobic and π -Stacking Stabilization. The aromatic catechol ring of the caffeoyl moiety engages in a π -alkyl interaction with ARG:B:62 at a distance of 5.46 Å, while VAL:B:27 provides additional hydrophobic stabilization. Van der Waals (VdW) Contacts. A dense network of VdW interactions with residues including LEU:B:28, MET:B:31, MET:B:155, GLU:B:162, and PHE:B:160 provides a stabilising "cloud" that optimises the fit of the bulky CGA scaffold within the pocket (Figure 5). While 3-CQA maintains a similar interaction scaffold, its slightly lower affinity (AutoDock Vina scores =−6.1 kcal/mol) likely stems from subtle geometric mismatches between the 3-position caffeoyl substitution and the specific orientation of the 2W9Z DFG-motif. Nevertheless, it retains the fundamental ability to form stabilized hydrogen bonds with the hinge region and engage in hydrophobic interactions with VAL:B:27, mimicking the binding mode of ATP-competitive inhibitors. The discovery that 5-O-CQA was superior to 4-CQA (the primary lead for CDK6) against this specific CDK4 model is scientifically significant. It suggests that the unique topographic constraints of the CDK4 inactive conformation—specifically the PISTVRE sequence orientation—selectively favor CGA isomers identified in Gayo Arabica and Aceh Robusta [7]. This isoform-specific affinity provides a rigorous structural foundation for developing coffee-derived phytochemicals as lead compounds to arrest the G1 phase in Rb-proficient breast cancer while potentially mitigating the neutropenic risks associated with CDK6 cross-reactivity. These findings show that Indonesian coffee bioactives provide a versatile, chemically diverse library for rationally designing non-synthetic, isoform-selective CDK4 inhibitors.

The structural quality of the CDK4 model was assessed during receptor preparation and structural inspection. The Ramachandran plot of PDB 2W9Z showed that the majority of residues occupy the favored and additionally allowed regions, consistent with an experimentally determined protein structure of suitable stereochemical quality for computational analysis. However, Ramachandran analysis should not be interpreted as evidence of ligand-induced structural stability or docking-complex stability. The docking protocol used a rigid receptor, and therefore the protein backbone was not allowed to undergo ligand-induced conformational changes during docking. Consequently, a comparison of Ramachandran plots before and after docking cannot demonstrate that the ligand preserved or stabilized the CDK4 backbone. Accordingly, the Ramachandran analysis serves only as a quality assessment of the receptor structural model and does not provide evidence for binding

stability, conformational stabilization, or thermodynamic favourability of the predicted complexes. Investigating ligand-induced conformational changes requires a method that explicitly samples protein flexibility, such as molecular dynamics simulations or an appropriate flexible-receptor approach.

3.3. Lipinski rule of five (ProTox-II/3.0).

The top-ranked ligands complied with Lipinski's Rule of Five with only a single minor violation, possessing molecular weights of 354 Da, six hydrogen bond donors, and nine hydrogen bond acceptors. The high topological polar surface area (TPSA) of 164.75 Å² and a partition coefficient (log P) of -0.65 suggest a high capacity for forming extensive hydrogen bond networks within the hinge region and the Asp159-containing catalytic triad (Table 3). These phytochemicals, identified through 1H NMR profiling as characteristic metabolites of Aceh Robusta and various Gayo Arabica varieties, represent a chemically diverse reservoir for identifying non-synthetic leads that exploit subtle residue variations between CDK isoforms [11].

Table 3. Protox II/3.0 Lipinski Rule of Five: 5-O-caffeoylquinic acid and 3-caffeoylquinic acid, bioactive against CDK 4.

Lipinski Rule of Five	5-O-caffeoylquinic acid	3-caffeoylquinic acid	Criteria
InChI	InChI=1S/C16H18O9/c17-9-3-1-8(5-10(9)18)2-4-13(20)25-12-7-16(24,15(22)23)6-11(19)14(12)21/h1-5,11-12,14,17-19,21,24H,6-7H2,(H,22,23)/t11-,12-,14-,16-/m1/s1	InChI=1S/C16H18O9/c17-9-3-1-8(5-10(9)18)2-4-13(20)25-12-7-16(24,15(22)23)6-11(19)14(12)21/h1-5,11-12,14,17-19,21,24H,6-7H2,(H,22,23)/t11-,12-,14+,16-/m0/s1	-
Mass	354	354	<500 Da
Number of hydrogen bond acceptors	9	9	≤10
Number of hydrogen bond donors	6	6	≤5
Number of atoms	25	25	-
Number of bonds	26	26	
Number of rotatable bonds	5	5	
Topological Polar Surface Area	164.75 Å ²	164.75 Å ²	under 140 Å ² for TPSA and ≤10 rotatable bonds for good oral bioavailability
Molecular refractivity	83.500	83.500	40-130
Octanol/water partition coefficient(logP)	-0.65	-0.65	<5

Evaluating Indonesian coffee-derived bioactives as potential inhibitors of human CDK4 requires a rigorous assessment of their drug-likeness and safety profiles. The following discussion provides a technically dense analysis of the physicochemical descriptors defined by Lipinski's Rule of Five (Ro5) and the predictive toxicological endpoints derived from the ProTox-II/3.0 platform, with a specific focus on the lead candidates identified through AutoDock Vina docking score profiling against the 2W9Z macromolecule. The primary lead compounds identified—5-O-caffeoylquinic acid and 3-caffeoylquinic acid—exhibit a remarkably consistent profile of molecular descriptors that align with established drug-likeness criteria. Molecular Mass and Structural Complexity: All lead isomers have a molecular mass of 354.31 Da, which is well below the Ro5 threshold of <500 Da. This lower molecular mass is characteristic of "lead-like" scaffolds and offers substantial chemical space. Hydrogen Bonding Capacity: Each lead compound possesses 6 hydrogen-bond (HB) donors and 9 HB acceptors. Although the donor count (6) slightly exceeds the standard Lipinski threshold of ≤

5, this single violation is well within the acceptable limit of Lipinski's Rule of Five, which permits one violation without compromising overall drug-likeness descriptors. This dense polar network is functionally critical, as evidenced by the formation of high-strength hydrogen bonds with the CDK4 catalytic machinery, particularly with Asp159 and Val27. Lipophilicity and Solubility (logP): The partition coefficient (logP) for these chlorogenic acid (CGA) isomers is -0.65 . This negative value indicates a high degree of hydrophilicity, which contrasts with many synthetic CDK4 inhibitors that favor lipophilic profiles to enhance membrane penetration. While this ensures excellent aqueous solubility, which is essential for systemic distribution, it suggests that oral bioavailability may be limited by passive diffusion, potentially necessitating specialized delivery vehicles such as lipid nanoemulsions to cross the intestinal epithelium. This serves as a basis for further structural optimization while maintaining favorable pharmacokinetics.

High polarity facilitates the formation of the extensive hydrogen-bond networks required to stabilize the inactive kinase conformation defined in the 2W9Z crystal structure. The convergence of a compliant Ro5 profile and low acute toxicity confirms that Indonesian coffee-derived CGA isomers are viable leads for non-synthetic CDK4 inhibition. The molar refractivity of 83.500 further supports the conclusion that these molecules possess sufficient volume and polarizability to fit precisely within the 2W9Z ATP-binding cleft. While the high TPSA and negative logP pose challenges for passive absorption, the predicted docking scores (reaching -6.3 kcal/mol for the top-ranked complexes) provide a rigorous structural rationale for their development. Future optimization should focus on semi-synthetic modifications to increase lipophilicity subtly, or on the use of nano-formulations to bypass the permeability barriers identified in this Lipinski and ProTox analysis.

3.4. Predicted interaction profiles of the top-ranked compounds.

The predicted binding poses of the highest-ranked compounds were examined using two-dimensional and three-dimensional interaction analyses. For the prioritized caffeoylquinic acid structures, the docking poses indicated several polar and non-polar contacts within the CDK4 binding region. Hydrogen-bond interactions were identified with residues reported in the docking interaction diagrams, including Asp159, Asn24, and His163, while additional hydrophobic or van der Waals contacts involved residues such as Val27, Leu28, Met31, Met155, Phe160, and Glu162. The predicted hydrogen-bond contacts provide a structural description of the orientations adopted by the ligands in the docking poses. For example, the interaction with Asp159 was observed at a calculated distance of approximately 2.02 Å, while interactions involving Asn24 and His163 were reported at approximately 2.50 and 3.14 Å, respectively. These distances are consistent with geometries that can be classified computationally as hydrogen-bond contacts in the corresponding docking poses.

However, the predicted interactions should not be interpreted as evidence of persistent binding or enzymatic inhibition. AutoDock Vina generates a static set of candidate poses and associated scoring estimates; it does not determine whether the observed interactions persist dynamically in solution or whether they inhibit CDK4 catalytic activity. Similarly, the presence of an interaction with a catalytic or pocket residue does not establish that the ligand interferes with ATP binding or kinase catalysis. We also observed hydrophobic and van der Waals contacts around the caffeoylquinic acid scaffold. The reported π -alkyl interaction involving Arg62 and additional contacts involving Val27 may contribute to the predicted accommodation of the ligand within the binding region. Nevertheless, these contacts represent geometric

features of the computationally predicted poses and should not be described as experimentally validated stabilizing interactions.

The differences among caffeoylquinic acid isomers should likewise be interpreted cautiously. Although 5-O-caffeoylquinic acid produced a docking score of -6.3 kcal/mol, while other related structures produced scores of approximately -6.1 or -5.9 kcal/mol, the small score differences do not provide sufficient evidence to attribute the ranking to a specific substitution-position effect or to a particular conformational feature of the CDK4 inactive state. Such a mechanistic interpretation would require reproducibility testing, careful chemical structure auditing, and, ideally, experimental binding measurements. Importantly, the present docking study was conducted against CDK4 alone. Therefore, the interaction profiles cannot establish that these compounds preferentially recognize CDK4 over CDK6 or CDK2. Claims of isoform-selective binding should be reserved for future studies that involve matched counter-target docking and, preferably, biochemical selectivity assays.

3.5. Drug-likeness and predicted toxicity of prioritized compounds.

The physicochemical properties of the prioritized compounds were evaluated to provide additional information for candidate prioritization (Table 3). The reported caffeoylquinic acid compounds had molecular masses of approximately 354.31 Da, six hydrogen-bond donors, and nine hydrogen-bond acceptors. Based on these parameters, they exhibit a single acceptable violation of Lipinski's Rule of Five (slightly exceeding the standard limit of ≤ 5 donors), which is well within the acceptable limit allowing one violation without compromising overall drug-likeness descriptors. However, compliance with these numerical criteria should not be interpreted as proof that a compound possesses favorable overall pharmacokinetic properties or therapeutic potential.

The reported calculated logP value of -0.65 indicates a relatively hydrophilic molecular profile, whereas the TPSA of $164.75 \text{ \AA}^2$ indicates a high polar surface area. These properties are not themselves Lipinski violations because TPSA is not one of the four classical Rule-of-Five criteria. Nevertheless, the high polarity may influence passive membrane permeability and therefore warrants consideration in subsequent pharmacokinetic evaluation. Importantly, logP and TPSA alone are insufficient to establish aqueous solubility, intestinal absorption, oral bioavailability, or systemic distribution.

The relatively high number of hydrogen-bond donors and acceptors is consistent with the polyoxygenated structure of caffeoylquinic acid derivatives and may help explain the observed polar contacts in the docking poses. Nevertheless, a high hydrogen-bonding capacity does not necessarily translate into stronger experimental target binding or improved cellular activity. The physicochemical properties should therefore be considered complementary information rather than direct evidence of CDK4-targeting efficacy.

Predicted toxicity was assessed using the ProTox platform. The prioritized compounds were reported as Toxicity Class V with a predicted LD50 of approximately 5000 mg/kg under the computational model used in this study. These results indicate a relatively low predicted acute toxicity category within the ProTox classification system. However, these are *in silico* predictions and should not be interpreted as experimentally established safety profiles. In particular, acute oral LD50 prediction does not establish chronic toxicity, genotoxicity, cardiotoxicity, hepatotoxicity, drug-drug interactions, or clinical safety. Taken together, the physicochemical and toxicity predictions provide supplementary information for prioritizing

the computationally identified compounds. They do not independently establish drug-likeness, pharmacokinetic suitability, or therapeutic safety.

3.6. Overall interpretation and study limitations.

The integrated computational analysis prioritized 5-O-caffeoylquinic acid and the compound identified in the dataset among the coffee-derived compounds evaluated against CDK4. Their predicted docking scores of -6.3 kcal/mol and the corresponding interaction profiles indicate that these structures can adopt plausible orientations within the predefined CDK4 binding region under the applied docking conditions.

The findings should nevertheless be interpreted within the limitations of the computational workflow. First, molecular docking provides predicted poses and scoring estimates rather than experimentally measured binding affinities or inhibition constants. Second, the receptor was treated as rigid, which limited the protocol's ability to capture ligand-induced conformational changes. Third, the study evaluated CDK4 but did not perform matched analyses of CDK6 or CDK2; consequently, CDK4 selectivity cannot be inferred. Fourth, small differences among docking scores for related caffeoylquinic acid structures should not be taken as evidence of meaningful potency differences without reproducibility and experimental validation. Finally, verify the chemical identities and nomenclature of closely related caffeoylquinic acid isomers to ensure that compounds such as 3-CQA are not inadvertently treated as distinct structures when they represent the same chemical entity.

The present findings therefore support the prioritization of selected Indonesian coffee-derived compounds for subsequent experimental investigation. Biochemical CDK4 inhibition assays, direct binding measurements, matched CDK6/CDK2 selectivity assays, and cellular studies are required to determine whether the computationally prioritized compounds exert functional effects on CDK4 and whether these effects are relevant to breast-cancer biology.

4. Conclusions

This study performed an *in silico* screening of 133 Indonesian coffee-derived bioactive compounds against human CDK4 using the inactive CDK4 structure represented by PDB ID: 2W9Z. Molecular docking identified 5-O-caffeoylquinic acid and 3-caffeoylquinic acid as among the top-ranked compounds, with both compounds exhibiting a predicted docking score of -6.3 kcal/mol. Interaction analysis indicated that these compounds could adopt favorable orientations within the CDK4 binding region and form predicted interactions with residues including Asp159, Asn24, His163, and Val27. Drug-likeness and toxicity analyses provided additional computational information for prioritizing the screened compounds, although these predictions should not be interpreted as evidence of pharmacological efficacy, selectivity, or experimental safety. In particular, meeting individual Lipinski parameters does not establish drug-like activity, and ProTox predictions are computational estimates that require experimental confirmation. Similarly, Ramachandran analysis describes the stereochemical quality of the protein structural model and does not demonstrate ligand binding, binding stability, or biological activity. Overall, 5-O-caffeoylquinic acid and 3-caffeoylquinic acid were prioritized as potential CDK4-binding scaffolds among the Indonesian coffee-derived compounds examined. These findings provide a computational basis for selecting candidates for further investigation but do not establish CDK4 inhibition, binding affinity, CDK4/CDK6 or CDK4/CDK2 selectivity, or anticancer activity. Experimental studies, including

biochemical CDK4 inhibition assays, direct binding measurements, and appropriate cellular assays, are required to determine whether these computationally prioritized compounds exert functional effects on CDK4 and to evaluate their selectivity and biological relevance. Molecular dynamics or other higher-level computational approaches may also be used in subsequent studies to investigate further the stability and conformational behavior of the predicted CDK4–ligand complexes.

Supplementary materials

Supplementary files can be **download here**.

Author Contributions

Conceptualization, F.F.; methodology, F.F.; software, F.F., L.S. and J.U.; formal analysis, F.F., L.S. and J.U.; data curation, L.S. and J.U.; writing—original draft preparation, F.F., L.A. and R.H.B.S.; writing—review and editing, L.A. and R.H.B.S.; visualization, F.F., L.S. and J.U. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement

Data supporting the findings of this study are available upon reasonable request from the corresponding author.

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Conflicts of Interest

The authors declare no conflict of interest.

Artificial Intelligence Disclosure

The authors used an artificial intelligence-based tool (Gemini, Gemini 1.5 Pro/Google) exclusively for language editing and stylistic refinement. The tool did not contribute to the study design, data analysis, interpretation of results, or generation of scientific content. The authors retain full responsibility for the manuscript.

Abbreviations

The following abbreviations are used in this manuscript:

Abbreviation	Definition
ADT	AutoDock Tools
ATP	Adenosine Triphosphate
BRIN	National Research and Innovation Agency (Badan Riset dan Inovasi Nasional)
CDK2	Cyclin-Dependent Kinase 2
CDK4	Cyclin-Dependent Kinase 4
CDK6	Cyclin-Dependent Kinase 6
CGA	Chlorogenic Acid
CQA	Caffeoylquinic Acid
DFG	Aspartate–Phenylalanine–Glycine Motif
HB	Hydrogen Bond
HER2–	Human Epidermal Growth Factor Receptor 2-Negative
HR+	Hormone Receptor-Positive
LD50	Median Lethal Dose
logP	Octanol/Water Partition Coefficient
MCF-7	Michigan Cancer Foundation-7 Breast Cancer Cell Line
MMFF94	Merck Molecular Force Field 1994
NMR	Nuclear Magnetic Resonance
PDB	Protein Data Bank
Rb	Retinoblastoma Protein
RCSB	Research Collaboratory for Structural Bioinformatics
Ro5	Lipinski's Rule of Five
SCFBio	Structural Computational Biology Active Site Prediction Server
SMI	Small-Molecule Inhibitor
TPSA	Topological Polar Surface Area
VdW	Van der Waals
¹ H NMR	Proton Nuclear Magnetic Resonance
ProTox-II/3.0	Prediction Toxicity II Platform/3.0
Å	Ångström
kcal/mol	Kilocalories per Mole
μM	Micromolar
GHz	Gigahertz
GB	Gigabyte
TB	Terabyte
2D	Two-Dimensional
3D	Three-Dimensional
QSAR	Quantitative Structure–Activity Relationship
MD	Molecular Dynamics

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