Review article

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Selective Cyclin-Dependent Kinase Inhibitors for Cancer Therapy: A Narrative Review of Molecular Docking Insights from Natural, Synthetic, and Hybrid Scaffolds

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Abstract: Cyclin-dependent kinases (CDKs) regulate cell-cycle progression, transcription, and genomic stability. Their dysregulation contributes to cancer development and therapeutic resistance, but the conserved ATP-binding architecture of CDKs complicates the development of isoform-selective inhibitors. This review aimed to compare molecular docking-guided design strategies across natural, synthetic, semi-synthetic, and hybrid scaffolds, identify determinants of CDK selectivity, and evaluate the progression of computational candidates toward experimental and clinical validation. A narrative review was conducted from 1 November 2025 to 31 January 2026. PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar were searched for relevant publications issued from January 2020 to January 2026. Evidence was synthesised thematically according to scaffold class, docking methodology, structural selectivity, and biochemical, cellular, *in vivo*, or clinical validation. Synthetic scaffolds provided the clearest basis for iterative structure–activity optimisation and experimental validation. Natural products expanded chemical diversity but were frequently supported only by computational or cytotoxicity evidence, while semi-synthetic and hybrid scaffolds offered opportunities for pharmacological optimisation. Potency was mainly associated with conserved hinge binding, whereas selectivity appeared to depend on peripheral or allosteric interactions and conformational differences. Docking scores alone did not establish affinity, target engagement, or isoform selectivity. Molecular docking should be integrated with comparative enzyme assays, kinome profiling, cellular target-engagement studies, and pharmacokinetic and *in vivo* evaluation to guide the development of clinically relevant, resistance-aware CDK inhibitors.

Keywords*:* Cyclin-dependent kinases, Molecular docking, Isoform selectivity, Cancer therapy, Kinase inhibitors

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INTRODUCTION

Cyclin-dependent kinases (CDKs) regulate cell-cycle progression, transcription, DNA repair, and genomic stability. CDK1, CDK2, CDK4, and CDK6 primarily control cell-cycle transitions, whereas CDK7, CDK8, CDK9, and CDK12 regulate transcription and DNA-damage responses. Their dysregulation promotes uncontrolled proliferation, genomic instability, and treatment resistance, making CDKs important anticancer targets [1,2].

The clinical success of palbociclib, ribociclib, and abemaciclib has validated selective CDK4/6 inhibition in hormone receptor–positive breast cancer. However, toxicity and resistance, including compensatory cyclin E–CDK2 signalling, may limit durable responses and support investigation of CDK2 and transcription-associated CDKs [3-5].

Molecular docking facilitates virtual screening, binding-pose prediction, and scaffold optimisation but cannot independently demonstrate affinity, target engagement, or isoform selectivity [6,7]. Synthetic scaffolds permit systematic structure–activity optimisation, whereas natural products expand chemical diversity and may provide templates for semi-synthetic or hybrid development [8,9]. Nevertheless, comparison across studies is restricted by inconsistent docking protocols and limited biochemical, cellular, kinome-wide, and *in vivo* validation.

OBJECTIVE OF THE STUDY

This narrative review compares molecular-docking-guided design strategies across synthetic, natural, semi-synthetic, and hybrid CDK-inhibitor scaffolds. It evaluates structural determinants of isoform selectivity, distinguishes computational predictions from experimentally validated activity, and identifies design and validation priorities for developing clinically translatable CDK inhibitors.

MATERIAL AND METHODS

Design

This study was conducted as a narrative review between 1 November 2025 and 31 January 2026. It examined the rational design of selective cyclin-dependent kinase inhibitors for cancer therapy, focusing on molecular-docking evidence for synthetic, natural, semi-synthetic, hybrid, and natural-product-inspired scaffolds. The review considered cancer-relevant CDK isoforms, structural determinants of selectivity, docking methodology, structure–activity relationships, and progression from computational prediction to biochemical, cellular, *in vivo*, and clinical evidence. Reporting was informed by the Scale for the Assessment of Narrative Review Articles [10].

Literature search strategy

PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar were searched for English-language publications issued between 1 January 2020 and 31 January 2026. ClinicalTrials.gov and regulatory sources were consulted to verify clinical-development status, and reference lists of relevant articles were examined for additional publications. Earlier seminal studies were included only when necessary to explain CDK biology, clinical development, or computational methodology. Search concepts included “cyclin-dependent kinase,” “CDK inhibitor,” individual CDK isoforms, “cancer,” “molecular docking,” “virtual screening,” “structure-based drug design,” “molecular dynamics,” “selectivity,” “natural product,” “synthetic,” “semi-synthetic,” and “hybrid scaffold.” Boolean operators and database-specific syntax were adapted for each database.

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Study eligibility and selection

Studies were eligible when they investigated small-molecule CDK inhibitors relevant to cancer and provided sufficient computational, structural, biochemical, cellular, animal, or clinical information for interpretation. Studies focusing exclusively on non-cancer conditions, macromolecular therapeutics, or non-CDK targets were excluded, as were duplicate publications, non-English articles, conference abstracts without adequate methodological information, and studies in which docking procedures or biological outcomes could not be evaluated. The search yielded 642 records; after 154 duplicates were removed, 488 records were screened, 45 full-text publications were assessed, and 18 studies were included in the core evidence synthesis.

Data extraction and synthesis

Data were extracted on publication characteristics, CDK target, scaffold classification, protein structure or Protein Data Bank identifier, ligand and receptor preparation, docking software, protocol validation, predicted binding interactions, molecular-dynamics conditions, biochemical potency, comparator-CDK testing, cellular activity, target engagement, *in vivo* efficacy, pharmacokinetics, toxicity, and clinical status. Evidence was classified as docking-only, computationally supported, biochemically validated, cellularly validated, *in vivo* validated, or clinically evaluated. Findings were synthesised thematically using a scaffold–selectivity–translation framework that compared scaffold-dependent design strategies, structural determinants of selectivity, methodological limitations, and advancement across the translational evidence hierarchy.

Methodological quality was appraised narratively using predefined domains: suitability of the protein structure, transparency of ligand and receptor preparation, docking validation, treatment of receptor flexibility and structural water, reporting of scoring methods, comparator-CDK or kinome testing, experimental confirmation, and consistency between evidence and conclusions. Joanna Briggs Institute critical-appraisal tools were consulted for applicable experimental and clinical designs [11]. Appraisal findings should be presented in the evidence-profile table rather than combined into a numerical quality score. Because this was a narrative review, formal PRISMA screening, protocol registration, statistical pooling, meta-analysis, and systematic risk-of-bias assessment were not performed.

CDK Structure, Function, and Therapeutic Classes

Cyclin-dependent kinases (CDKs) are serine/threonine kinases activated through association with cyclins and regulated by phosphorylation and endogenous CDK inhibitors. CDK1, CDK2, CDK4, and CDK6 principally coordinate cell-cycle progression, whereas CDK7, CDK8, CDK9, and CDK12/13 regulate transcription, RNA processing, and DNA-damage responses [1,2,12]. Their dysregulation promotes sustained proliferation, genomic instability, and treatment resistance. Therapeutic agents may therefore be classified as cell-cycle CDK inhibitors, transcriptional CDK inhibitors, multi-CDK inhibitors, allosteric inhibitors, covalent inhibitors, or targeted degraders. The clinical success of palbociclib, ribociclib, and abemaciclib established CDK4/6 inhibition as an effective strategy in hormone receptor-positive breast cancer, although efficacy remains dependent on tumor context and functional retinoblastoma signaling [4,5]. The functional diversity, therapeutic rationale, representative inhibitors, and evidential maturity of major cancer-relevant CDK classes are summarised in Table 1.

Table 1 illustrates the uneven clinical maturity of CDK-directed therapy. CDK4/6 inhibition is supported by randomised clinical evidence, whereas CDK1, CDK2, CDK7, CDK8/19, CDK9, and CDK12/13 strategies remain predominantly investigational. Importantly, evidence of biochemical inhibition should not be interpreted as evidence of isoform selectivity or clinical efficacy. The limited activity of LY3405105 despite measurable CDK7 target occupancy exemplifies the translational gap between molecular engagement and therapeutic benefit [16].

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Table 1. Biological functions, cancer relevance, and therapeutic evidence for major CDK classes

CDK class	Principal biological function	Cancer relevance and therapeutic rationale	Representative inhibitors	Selectivity and translational considerations	Current evidence level
CDK1	Controls G2/M transition, chromosome segregation, and mitotic fidelity	CDK1 inhibition may suppress rapidly proliferating tumours and enhance sensitivity to DNA-damaging agents. However, CDK1 is essential for division in many normal cells, potentially narrowing the therapeutic window	Dinaciclib and other multi-CDK inhibitors	Most reported compounds inhibit additional CDKs. Potency against CDK1 does not establish CDK1-specific biological activity, and systemic inhibition may produce haematological toxicity	Predominantly mechanistic and preclinical evidence; limited evidence for clinically effective CDK1-selective therapy [1,13]
CDK2	Regulates G1/S progression, DNA replication, centrosome duplication, and replication-fork stability	Cyclin E–CDK2 activation is associated with uncontrolled proliferation and may provide a bypass mechanism in tumours resistant to CDK4/6 inhibition	Roscovitine, dinaciclib, and experimental pyrazolopyrimidine derivatives	The ATP-binding site is highly conserved. Credible CDK2 selectivity requires comparison with CDK1, CDK4/6, CDK7, CDK9, and the broader kinome. Cellular cytotoxicity alone does not establish CDK2 engagement	Substantial biochemical and cellular evidence, with emerging clinical development but no established CDK2-selective standard therapy [3,14]
CDK4/6	Phosphorylates retinoblastoma protein and promotes cyclin D–dependent G1/S transition	CDK4/6 dependency is clinically established in hormone receptor–positive breast cancer. Inhibition restores retinoblastoma-mediated cell-cycle control when the pathway remains functional	Palbociclib, ribociclib, and abemaciclib	These agents demonstrate pharmacological CDK4/6 selectivity, although their kinase profiles, toxicity, pharmacokinetics, and clinical activity differ. Resistance may involve retinoblastoma loss, cyclin E–CDK2 activation, or compensatory signalling	Strongest evidence among CDK classes, including randomised and longitudinal clinical trials [4,5,15]

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Table 1. Biological functions, cancer relevance, and therapeutic evidence for major CDK classes (Continued)

CDK class	Principal biological function	Cancer relevance and therapeutic rationale	Representative inhibitors	Selectivity and translational considerations	Current evidence level
CDK7	Functions as a CDK-activating kinase and regulates RNA polymerase II transcription initiation through TFIIH	CDK7 inhibition may simultaneously suppress cell-cycle activation and oncogenic transcription, particularly in transcriptionally dependent tumours	SY-1365 and LY3405105	Covalent engagement can prolong target occupancy and improve biochemical discrimination. Nevertheless, suppression of transcription in normal tissues may limit tolerability. The limited clinical activity of LY3405105 indicates that target occupancy alone is insufficient for therapeutic efficacy	Biochemical, cellular, animal, and early-phase clinical evidence; clinical efficacy remains unestablished [16,17]
CDK8/19	Regulates stimulus-dependent transcription as part of the Mediator kinase module	Context-dependent alteration of CDK8/19 signalling may support oncogenic transcription, tumour progression, or treatment resistance	Senexin-class and other experimental CDK8/19 inhibitors	Biological effects are highly context dependent and may differ according to tumour type and transcriptional state. Selectivity between CDK8 and CDK19 remains challenging	Primarily mechanistic and preclinical evidence; clinical utility remains uncertain [2,12]
CDK9	Promotes transcriptional elongation through P-TEFb-mediated phosphorylation of RNA polymerase II at Ser2	CDK9 inhibition reduces transcription of short-lived oncogenic and anti-apoptotic proteins, including MYC and MCL1, providing a rationale for targeting transcription-dependent malignancies	AZ5576, alvocidib, and related investigational CDK9 inhibitors	Selective inhibition must be distinguished from broad transcriptional suppression. MYC or MCL1 dependence may influence sensitivity, but these biomarkers require prospective clinical validation. Systemic transcriptional toxicity may constrain exposure	Strong mechanistic and preclinical evidence, but limited clinical validation of selective CDK9 inhibition [2,18]

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Table 1. Biological functions, cancer relevance, and therapeutic evidence for major CDK classes (Continued)

CDK class	Principal biological function	Cancer relevance and therapeutic rationale	Representative inhibitors	Selectivity and translational considerations	Current evidence level
CDK12/13	Regulates transcriptional elongation, RNA processing, alternative splicing, and expression of DNA-damage-response genes	CDK12 alteration may impair homologous-recombination repair and create sensitivity to DNA-damaging or DNA-repair-directed therapies. Pharmacological inhibition may increase genomic stress in selected tumours	Experimental CDK12/13 inhibitors and degraders	CDK12 and CDK13 have substantial structural and functional overlap. ATP-site inhibitors may also affect other transcriptional CDKs. Biomarker selection and direct confirmation of DNA-repair disruption are required	Mechanistic and emerging preclinical evidence; therapeutic index and clinical efficacy remain uncertain [1,2]

Note. CDK = cyclin-dependent kinase; MCL1 = myeloid cell leukaemia 1; MYC = MYC proto-oncogene; P-TEFb = positive transcription elongation factor b; TFIIH = transcription factor IIH. Inclusion of an inhibitor does not indicate regulatory approval or demonstrated clinical efficacy. Evidence levels reflect the highest stage represented in the cited literature, not equivalent support for every agent within a CDK class.

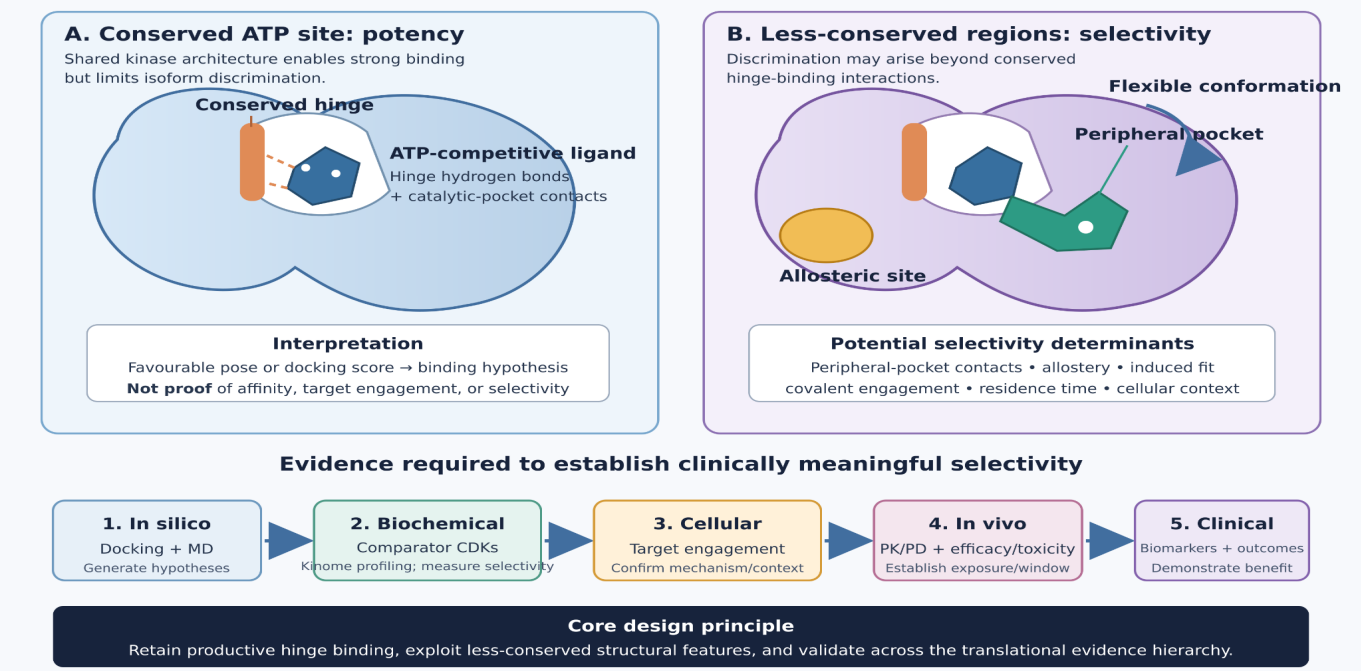


Figure 1. Structural basis of potency and selectivity in cyclin-dependent kinase inhibitor design. (A) ATP-competitive inhibitors commonly form hydrogen bonds with conserved hinge-region residues and occupy the catalytic ATP pocket. These interactions can support potency but provide limited evidence of CDK isoform discrimination because the ATP-binding architecture is highly conserved across the kinase family. (B) Selectivity may be improved by extending ligands into less-conserved peripheral or hydrophobic pockets, stabilising isoform-preferred conformations, engaging allosteric sites, or exploiting covalent interactions and differences in residence time. Docking and molecular-dynamics simulations can generate and refine these structural hypotheses, but clinically meaningful selectivity requires sequential confirmation through comparative CDK enzyme assays, broader kinome profiling, cellular target-engagement studies, and pharmacokinetic, *in vivo*, and clinical evaluation. Adapted conceptually from Lim and Kaldis [1], Łukasik et al. [12], Pantsar and Poso [6], and Salmaso and Moro [7]. Figure created by the authors.

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Definitions and Determinants of CDK Selectivity

CDK selectivity should not be treated as a single property. Isoform selectivity denotes preferential activity against one CDK relative to closely related CDKs; kinome selectivity concerns activity across the broader kinase family; biological-context selectivity reflects dependence on a particular molecular alteration; and tumor–normal selectivity describes preferential effects on malignant rather than non-malignant cells. Potency against one CDK, without testing comparator kinases, does not demonstrate selectivity.

Most ATP-competitive inhibitors bind conserved hinge-region residues; therefore, hinge binding largely determines potency rather than isoform discrimination. Selectivity more often arises from interactions with less-conserved hydrophobic pockets, gatekeeper-adjacent regions, solvent-exposed residues, conformationally flexible loops, or allosteric sites. Residence time, cellular ATP concentration, cyclin-associated conformations, intracellular distribution, and target abundance may further modify functional selectivity. Credible claims consequently require comparative enzymatic assays, kinome profiling, target-engagement studies, or genetic confirmation rather than docking scores alone. As illustrated in Figure 1, conserved hinge interactions primarily support binding potency, whereas isoform selectivity may require exploitation of less-conserved peripheral or allosteric regions and confirmation across successive experimental levels.

Computational Approaches and Limitations

Molecular docking is valuable for virtual screening, pose generation, interaction mapping, and rational prioritisation of analogues. Its interpretive value increases when combined with pharmacophore modelling, ADMET prediction, molecular dynamics, consensus scoring, and free-energy calculations. Molecular dynamics can examine the persistence of predicted contacts and receptor flexibility, while MM/PBSA and MM/GBSA provide approximate energetic comparisons across related complexes [7,19].

Nevertheless, docking scores are algorithm-dependent estimates and should not be interpreted as measured binding affinities. Results are affected by protein-structure quality, protonation and tautomeric states, conserved water molecules, receptor flexibility, grid definition, ligand preparation, and scoring-function bias [6]. Cross-study comparison is particularly problematic when different protein structures and protocols are used. Redocking of a co-crystallised ligand, reporting of root-mean-square deviation, use of appropriate comparators, and experimental validation are therefore essential. Predicted binding should be described as a mechanistic hypothesis rather than confirmation of inhibition or selectivity. The principal methodological limitations affecting the interpretation and reproducibility of CDK molecular-docking studies, together with recommended mitigation strategies, are summarised in Table 2.

These limitations indicate that docking scores should not be interpreted as direct measures of affinity, selectivity, or therapeutic efficacy. The scaffold-specific evidence discussed below was therefore evaluated according to docking validation, complementary computational analyses, comparator-CDK testing, and the availability of biochemical, cellular, *in vivo*, or clinical confirmation.

Synthetic CDK-Inhibitor Scaffolds

Synthetic scaffolds provide the strongest basis for iterative structure activity optimisation because their hinge-binding cores, substituent orientation, physicochemical properties, and peripheral-pocket interactions can be modified systematically. Frequently investigated classes include pyrazolopyrimidines, triazolopyrimidines, quinazolines, aminopyrimidines, indoles, and related fused heterocycles. Across these classes, a productive design strategy is to retain a well-oriented hinge-binding motif while modifying solvent-facing or hydrophobic substituents to improve selectivity and pharmacokinetic behaviour.

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Table 2. Principal limitations of CDK molecular docking and recommended mitigation

Methodological issue	Effect on interpretation	Recommended mitigation
Rigid receptor structure	May miss induced-fit or isoform-specific conformations	Ensemble docking, alternative crystal structures and molecular dynamics [7]
Uncertain protonation or tautomeric state	Alters electrostatic interactions and predicted pose	Report pH assumptions and enumerate plausible protonation and tautomeric states
Treatment of conserved water molecules	Water removal or retention may change hinge and pocket interactions	Test alternative water states and justify retained structural waters
Scoring-function limitations	Docking score may not correlate with affinity or selectivity	Redocking, comparator ligands, consensus scoring and experimental binding assays [6]
Inadequate docking validation	Increases the risk of unreliable poses	Redock the co-crystallised ligand and report RMSD, grid definition and pose-selection criteria
Limited receptor sampling	Underrepresents protein flexibility and allosteric states	Molecular dynamics or enhanced conformational sampling
Approximate free-energy estimation	MM/PBSA and MM/GBSA results depend on sampling and model assumptions	Use consistent protocols, report uncertainty and avoid treating estimates as measured affinity [19]
Absence of comparator kinases	Prevents valid claims of CDK isoform selectivity	Test closely related CDKs and perform broader kinome profiling
Cytotoxicity without target engagement	Cannot establish that CDK inhibition caused cellular effects	Add cellular target-engagement, pathway-modulation and genetic-rescue experiments
Predicted ADMET only	Cannot establish exposure, safety or therapeutic index	Measure solubility, permeability, metabolic stability, pharmacokinetics and *in vivo* toxicity

Nassar et al. [14], for example, integrated synthesis, docking, enzyme inhibition, and cellular testing in the development of pyrazolopyrimidine and triazolopyrimidine CDK2 inhibitors. Compound 15 inhibited CDK2/cyclin A2 with an IC_{50} of 0.119 ± 0.007 μM and demonstrated nanomolar antiproliferative activity in HCT-116, MCF-7, and HepG2 cells. These results support biological activity, but CDK2 selectivity cannot be concluded without comparative testing against related CDKs and broader kinome profiling. This distinction illustrates why synthetic optimisation should be guided by both potency and experimentally measured off-target activity.

Representative CDK7 and CDK9 inhibitors

Selective inhibition of transcription-associated CDKs extends CDK-directed therapy beyond cell-cycle arrest. CDK7 regulates both CDK activation and RNA polymerase II–dependent transcription; consequently, its inhibition may simultaneously disrupt cell-cycle progression and oncogenic transcription. SY-1365 is a covalent CDK7 inhibitor that was designed to engage a non-conserved cysteine residue outside the canonical hinge-binding interaction. Preclinical studies demonstrated sustained target engagement, suppression of RNA polymerase II phosphorylation, reduction of short-lived survival proteins such as MCL1, and antitumour activity across selected solid-tumour and haematological models [17]. Although SY-1365 entered a phase I study in advanced solid tumours, its clinical efficacy has not been established; it should therefore be described as a clinically evaluated investigational compound rather than a clinically validated therapy [20].

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LY3405105 provides an important example of the gap between biochemical target engagement and clinical benefit. This orally administered covalent CDK7 inhibitor produced dose-dependent target occupancy in a phase I study involving 54 patients with advanced solid tumours. The maximum tolerated dose was 20 mg once daily, but no complete or partial responses were observed; stable disease was the best response in a subset of participants, and further development was not planned. These findings demonstrate that target occupancy and pharmacokinetic exposure do not necessarily translate into meaningful antitumour activity, reinforcing the need for biomarker-guided patient selection and validated tumour dependence on CDK7 [16].

CDK9 controls transcriptional elongation through P-TEFb-mediated phosphorylation of RNA polymerase II. AZ5576 selectively inhibited CDK9 in preclinical models of diffuse large B-cell lymphoma, reducing RNA polymerase II phosphorylation and the expression of short-lived survival proteins, including MCL1 and MYC. Its activity was greater in MYC-expressing models, and antitumour effects were observed in both cellular and animal experiments [18]. Nevertheless, this evidence remains preclinical and does not establish clinical safety or efficacy. Collectively, these agents illustrate that transcriptional CDK selectivity may be achieved through covalent or structurally optimised inhibition, but therapeutic translation remains limited by systemic transcriptional toxicity, tumour heterogeneity, pharmacokinetics, and the absence of validated predictive biomarkers.

Natural-Product Scaffolds

Natural products expand the accessible chemical space through stereochemical complexity, rigid ring systems, and functional-group arrangements that may be underrepresented in conventional synthetic libraries [8,9]. Flavonoids, polyphenols, alkaloids, terpenoids, and marine metabolites have consequently been screened against several CDKs. These compounds can provide useful starting structures and may reveal unconventional binding features.

However, natural-product studies are commonly limited to docking, short molecular-dynamics simulations, and general cytotoxicity assays. Polyphenols may also produce non-specific effects through aggregation, redox activity, membrane interactions, or modulation of multiple signaling pathways. Cellular growth inhibition therefore cannot automatically be attributed to CDK inhibition. Natural candidates should be regarded as screening leads until direct binding, enzyme inhibition, target engagement, selectivity, and exposure are demonstrated. Their principal contribution is chemical diversity rather than immediate evidence of clinical suitability.

Semi-Synthetic, Hybrid, and Natural-Product-Inspired Scaffolds

These categories should be distinguished carefully. A semi-synthetic compound is produced through chemical modification of an isolated natural parent molecule. A molecular hybrid combines two pharmacophores or structural motifs in one molecule, while a natural-product-inspired scaffold is synthetically constructed using structural features derived from a natural compound. A hybrid is not necessarily semi-synthetic.

These approaches seek to preserve biologically valuable natural-product features while improving potency, solubility, metabolic stability, and synthetic tractability. Semi-synthesis can modify functional groups associated with poor exposure or non-specific activity, whereas hybridisation may combine a CDK-binding motif with a second pharmacophore. Nevertheless, increased molecular size and lipophilicity may reduce permeability and increase metabolic liability. Docking-supported optimisation should therefore be accompanied by comparative enzyme assays, physicochemical measurements, metabolic-stability testing, and confirmation that hybridisation produces a genuine advantage over the parent components.

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Comparative Evidence Synthesis

The three scaffold classes support different discovery strategies. Synthetic compounds are generally analogue-driven, allowing systematic optimisation of potency, selectivity, and drug-like properties. Natural products are predominantly selection-driven, with virtual screening used to identify candidates from chemically diverse libraries. Semi-synthetic and hybrid compounds are feature-driven, combining selected natural and synthetic characteristics to address specific limitations.

Overall, synthetic scaffolds possess the strongest evidence because they are more frequently supported by enzyme assays, structure–activity series, cellular studies, and pharmacological optimisation. Natural scaffolds offer broader chemical diversity but are commonly supported only by computational screening. Semi-synthetic and hybrid scaffolds occupy an intermediate position: they provide rational opportunities for optimisation, but their reported advantages are often based on predicted rather than experimentally demonstrated improvements. Scaffold origin alone does not determine quality; the strength of evidence depends on comparative selectivity testing and progression beyond computational prediction. Representative compounds and scaffold classes are compared in Table 3 according to docking methodology, quantitative potency, selectivity evidence, and level of experimental validation.

Table 3 demonstrates a marked imbalance in evidential maturity. Synthetic CDK2 inhibitors are supported by quantitative biochemical and cellular data, although their isoform selectivity remains insufficiently characterised. Natural-product candidates largely remain computational leads, while reliable translational evidence for semi-synthetic scaffolds is particularly limited. Among transcriptional CDK inhibitors, SY-1365 and AZ5576 showed mechanistically coherent preclinical activity, whereas the phase I experience with LY3405105 demonstrated that target occupancy may not translate into clinical response. Clinically established CDK4/6 inhibitors therefore remain the most appropriate benchmark because their selectivity, pharmacology, toxicity, and therapeutic benefit have been evaluated across the complete translational pathway.

Table 3. Representative CDK inhibitors classified by scaffold, selectivity strategy, and level of translational evidence

Representative agent	Scaffold and target	Structural or computational evidence	Quantitative experimental findings	Selectivity evidence	Evidence level and critical interpretation
Compound 14	Synthetic thioglycoside–triazolopyrimidine; CDK2/cyclin A2	Docked to CDK2 (PDB: 2A4L) using CDOCKER; redocking RMSD of 0.5 Å; predicted hinge interaction with Leu83	Enzyme IC_{50}: 0.057 ± 0.003 μM; cellular IC_{50}: 45 nM in MCF-7, 6 nM in HCT-116, and 48 nM in HepG2 cells	Potency was demonstrated, but comparative CDK or kinome profiling was not reported	Biochemical and cellular evidence. Cytotoxicity supports activity but does not independently establish CDK2-mediated effects or isoform selectivity [14]
Compound 15	Synthetic thioglycoside–triazolopyrimidine; CDK2/cyclin A2	Docked to CDK2 (PDB: 2A4L); predicted hinge interaction with Leu83	Enzyme IC_{50}: 0.119 ± 0.007 μM; cellular IC_{50}: 46 nM in MCF-7, 7 nM in HCT-116, and 48 nM in HepG2 cells	Comparator-CDK and kinome data were not reported	Biochemical and cellular evidence. Demonstrates potency rather than confirmed CDK2 selectivity [14]

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Table 3. Representative CDK inhibitors classified by scaffold, selectivity strategy, and level of translational evidence (Continued)

Representative agent	Scaffold and target	Structural or computational evidence	Quantitative experimental findings	Selectivity evidence	Evidence level and critical interpretation
Marine compounds 41369 and 50843	Natural-product database leads; CDK4/6	Pharmacophore screening, LibDock, ADMET prediction, and 100-ns molecular dynamics using CDK4 (PDB: 2W96) and CDK6 (PDB: 5L2S)	Direct enzyme inhibition, cellular target engagement, and *in vivo* activity were not reported	Dual CDK4/6 binding was predicted; broader kinome selectivity remains unknown	Computational evidence only. These compounds should be presented as prioritised leads requiring experimental confirmation [21]
Semi-synthetic CDK candidates	Chemically modified natural products; various proposed CDK targets	Docking frequently predicts improved hinge or hydrophobic-pocket interactions relative to parent compounds	Reliable comparative enzyme, cellular, and pharmacokinetic data remain limited in the reviewed literature	Improved selectivity is generally predicted rather than experimentally demonstrated	Evidence gap. No semi-synthetic candidate in the verified evidence set supports a robust quantitative comparison with established synthetic inhibitors
SY-1365	Synthetic covalent inhibitor; CDK7	Designed to achieve sustained CDK7 engagement through covalent binding; reduced RNA polymerase II phosphorylation and expression of short-lived survival proteins	Demonstrated low-nanomolar biochemical activity, cellular growth inhibition, and antitumour activity in selected xenograft models	Preferential CDK7 engagement was supported preclinically, but therapeutic selectivity over normal transcription-dependent tissues remains uncertain	Biochemical, cellular, *in vivo*, and phase I evaluation. Clinical efficacy was not established; the compound should be described as investigational [17]
LY3405105	Oral synthetic covalent inhibitor; CDK7	Covalent target engagement produced dose-dependent CDK7 occupancy in peripheral blood and skin	In 54 phase I participants, target occupancy approached 75% at doses ≥15 mg once daily; MTD was 20 mg once daily. Stable disease was the best response in 17 patients, with no complete or partial responses	Target occupancy confirmed pharmacological engagement but did not demonstrate tumour-selective inhibition	Phase I clinical evidence. Limited antitumour activity demonstrates that target engagement does not necessarily translate into clinical efficacy [16]

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Table 3. Representative CDK inhibitors classified by scaffold, selectivity strategy, and level of translational evidence (Continued)

Representative agent	Scaffold and target	Structural or computational evidence	Quantitative experimental findings	Selectivity evidence	Evidence level and critical interpretation
AZ5576	Synthetic ATP-competitive inhibitor; CDK9/cyclin T	Inhibited CDK9-dependent RNA polymerase II Ser2 phosphorylation and transcriptional elongation	Reduced MCL1 and MYC transcripts and proteins and inhibited diffuse large B-cell lymphoma models *in vitro* and *in vivo*	Preferential CDK9 activity was supported preclinically; systemic transcriptional effects and clinical therapeutic index remain unresolved	Biochemical, cellular, and animal evidence. MYC expression was associated with greater susceptibility, but this remains a candidate predictive relationship rather than a clinically validated biomarker [18]
Palbociclib, ribociclib, and abemaciclib	Synthetic ATP-competitive inhibitors; CDK4/6	Structural and pharmacological optimisation supports CDK4/6 inhibition, although agent-specific kinome profiles differ	Randomised trials demonstrated improved outcomes when these agents were combined with endocrine therapy in HR-positive/HER2-negative breast cancer	Pharmacological CDK4/6 selectivity is supported, but functional efficacy depends on intact retinoblastoma signalling and tumour context	Clinical evidence. These agents provide the strongest translational benchmark for evaluating emerging CDK inhibitors [4,5,15]

Note. ADMET = absorption, distribution, metabolism, excretion, and toxicity; CDK = cyclin-dependent kinase; HR = hormone receptor; IC_{50} = half-maximal inhibitory concentration; MTD = maximum tolerated dose; NR = not reported; PDB = Protein Data Bank; RMSD = root-mean-square deviation. Docking scores produced using different software, protein structures, and preparation procedures should not be compared directly. Cellular cytotoxicity does not independently establish CDK target engagement, while biochemical potency against one CDK does not demonstrate isoform or kinome selectivity.

Translation From Docking to Biochemical, Cellular, In Vivo, and Clinical Evidence

Docking occupies the earliest stage of a translational evidence hierarchy. A predicted pose establishes binding plausibility; biochemical assays establish direct inhibition; cellular target-engagement and pathway studies determine whether inhibition occurs in a biological environment; animal studies assess exposure, efficacy, and toxicity; and clinical trials evaluate safety and therapeutic benefit in humans. Evidence at one level should not be presented as proof of the next.

Enzyme potency may not translate into cellular activity because of permeability, efflux, protein binding, metabolism, or intracellular ATP competition. Similarly, cytotoxicity does not identify the responsible target without target-engagement or genetic-rescue experiments. The strongest preclinical evidence therefore combines biochemical potency, comparator-CDK testing, kinome profiling, cellular target engagement, pharmacokinetic exposure, pharmacodynamic modulation, and *in vivo* efficacy. The clinical validation of CDK4/6 inhibitors demonstrates that successful translation depends not only on kinase affinity but also on tumor biology, patient selection, tolerability, and combination strategy [5,15].

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Resistance, Toxicity, Pharmacokinetics, and Combination Strategies

Resistance to CDK inhibition may arise through target alteration, cyclin amplification, compensatory CDK activation, loss of retinoblastoma function, or reactivation of downstream proliferative signaling. In CDK4/6-treated breast cancer, increased cyclin E–CDK2 activity can bypass G1 arrest, providing a rationale for CDK2-directed or rational combination strategies [3]. Resistance should therefore be investigated through longitudinal molecular profiling rather than docking against the original target alone.

Toxicity reflects both on-target effects in proliferating normal tissues and off-target kinase inhibition. Neutropenia, gastrointestinal toxicity, fatigue, and hepatotoxicity illustrate the need to balance pathway suppression with therapeutic index [5]. Pharmacokinetic optimisation should address solubility, permeability, metabolic stability, protein binding, oral exposure, and tissue distribution; favourable in silico ADMET predictions cannot replace measured data. Clinically successful combination strategies should be mechanism-based, as illustrated by combining CDK4/6 inhibitors with endocrine therapy. Other combinations involving DNA-damage-response inhibitors, transcriptional inhibitors, or targeted therapies require evidence that enhanced efficacy outweighs overlapping toxicity.

Design Principles and Future Directions

Future design should begin with a clearly defined therapeutic context and type of selectivity. Potent hinge binding should be combined with occupation of less-conserved pockets, exploitation of isoform-specific conformations, or allosteric and covalent strategies where appropriate. Representative structures of both the intended target and major off-targets should be incorporated early, followed by biochemical selectivity panels and cellular target-engagement assays.

Computational workflows should report protein structures, preparation procedures, protonation states, conserved waters, docking-validation results, scoring methods, and simulation conditions. Ensemble docking and molecular dynamics may improve treatment of protein flexibility, but prospective experimental testing remains necessary. Natural and hybrid candidates require particular attention to assay interference, aggregation, solubility, metabolism, and attribution of cellular effects. Integration of structural biology, chemoproteomics, kinome profiling, pharmacokinetics, patient-derived models, and biomarker-guided clinical development offers the clearest route toward clinically meaningful selectivity.

DISCUSSION

This review aimed to compare molecular docking-guided design strategies across natural, synthetic, and semi-synthetic or hybrid CDK-inhibitor scaffolds, identify determinants of CDK selectivity, and evaluate their translational evidence. The findings suggest three complementary strategies: analogue-driven optimisation of synthetic compounds, selection-driven screening of natural products, and feature-driven modification of hybrid or semi-synthetic scaffolds. Scaffold origin alone, however, does not determine therapeutic value; the strength of evidence depends on comparative selectivity testing and progression from computational prediction to experimental validation.

CDK selectivity remains challenging because family members share conserved ATP-binding and hinge regions [1,12]. Hinge interactions may support potency, whereas isoform discrimination appears to depend more on less-conserved peripheral pockets, solvent-exposed residues, allosteric sites, and protein conformational states. Consequently, activity against one CDK cannot establish isoform or kinome selectivity without testing related CDKs or conducting broader kinase profiling.

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Docking is useful for screening, pose prediction, and scaffold optimisation, but docking scores are not direct measurements of affinity, target engagement, or biological selectivity [6]. Molecular dynamics and MM/PBSA or MM/GBSA analyses may improve interpretation by considering receptor flexibility and binding energetics, although their conclusions remain dependent on protein preparation, force fields, sampling, and scoring assumptions [7,19]. Computational findings should therefore be treated as mechanistic hypotheses requiring experimental confirmation.

Synthetic scaffolds showed the strongest translational support because they were more frequently evaluated through structure–activity series, enzyme assays, and cellular studies. For example, compound 15 reported by Nassar et al. [14] inhibited CDK2/cyclin A2 with an IC_{50} of 0.119 ± 0.007 μM and showed nanomolar antiproliferative activity. Nevertheless, these findings demonstrate potency rather than CDK2 selectivity because comparative kinase testing was not reported. Natural products broaden chemical diversity but are commonly supported by docking and cytotoxicity data alone [8,9]. Their cellular effects may reflect polypharmacology, aggregation, redox activity, or other off-target mechanisms. Semi-synthetic and hybrid approaches may improve natural-product properties, but predicted improvements in ADMET or affinity require direct physicochemical and pharmacokinetic confirmation.

The evidence hierarchy was highly uneven. Human evidence was concentrated in randomised and longitudinal trials of CDK4/6 inhibitors in hormone receptor-positive breast cancer, where combination with endocrine therapy improved clinically relevant outcomes [5,15]. Most other CDK inhibitors were supported by computational, biochemical, cellular, or animal evidence. Cell and animal studies can support mechanistic or causal inference under controlled conditions but cannot fully reproduce tumor heterogeneity, systemic exposure, toxicity, or human resistance. In particular, cytotoxicity alone does not confirm CDK target engagement.

Resistance may arise through retinoblastoma-pathway loss, cyclin E–CDK2 activation, target alteration, or compensatory signaling [3,4]. These mechanisms indicate that biochemical selectivity does not necessarily ensure durable efficacy. Biomarker-guided combinations may therefore be required, although potential benefits must be balanced against overlapping toxicity and reduced therapeutic index.

Interpretation is limited by heterogeneous protein structures, docking protocols, enzyme conditions, cell lines, and validation methods. Cellular potency may also be confounded by permeability, metabolism, efflux, protein binding, and off-target activity. The narrative design of this review, absence of formal PRISMA screening, and lack of quantitative pooling may have introduced selection bias and limit direct comparison among scaffolds.

Future studies should report reproducible docking protocols and validate candidates through comparator-CDK assays, kinome profiling, cellular target engagement, genetic confirmation, pharmacokinetic studies, and resistant tumor models. Overall, molecular docking is most valuable within an integrated workflow. Synthetic scaffolds currently provide the most mature evidence, natural products expand chemical diversity, and hybrid approaches offer rational opportunities for optimisation; however, clinically meaningful selectivity requires experimental and translational confirmation.

CONCLUSION

This review compared molecular docking-guided strategies across natural, synthetic, semi-synthetic, and hybrid CDK-inhibitor scaffolds and evaluated the determinants and evidence supporting CDK selectivity. Synthetic scaffolds currently provide the strongest basis for systematic optimisation and experimental validation, whereas natural products broaden chemical diversity and semi-synthetic or hybrid approaches offer opportunities to improve selected pharmacological properties. However, favourable docking poses and scores indicate

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binding plausibility rather than isoform selectivity or therapeutic efficacy. Selectivity depends principally on exploiting less-conserved peripheral or allosteric regions and must be confirmed through comparative biochemical assays, kinome profiling, cellular target engagement, and pharmacokinetic and *in vivo* evaluation. Molecular docking is therefore most valuable as part of an integrated, experimentally validated workflow for developing clinically relevant, resistance-aware CDK inhibitors.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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AUTHOR CONTRIBUTIONS

All authors contributed to the conceptualisation, literature search, evidence evaluation, interpretation, manuscript drafting, critical revision, and approval of the final manuscript. All authors have read and agreed to the published version of the manuscript and accept responsibility for its content.

DECLARATION OF ARTIFICIAL INTELLIGENCE USE

Artificial intelligence-assisted tools were used solely for language editing and improving the clarity, grammar, and readability of the manuscript. The authors independently reviewed and verified the scientific content, interpretations, citations, and final text and accept full responsibility for the manuscript.

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