

# Targeting Cyclin-Dependent Kinases (CDKs) for Cancer Therapy: An In-Depth Review of Molecular Candidates, Their Synthesis, Evaluation, and Future Directions

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## Targeting Cyclin-Dependent Kinases (CDKs) for Cancer Therapy: An In-Depth Review of Molecular Candidates, Their Synthesis, Evaluation, and Future Directions

Cyclin-dependent kinases (CDKs) are ser/thr kinases that affect cell cycle progression by phosphorylation of target substrates in a regulated manner. The catalytic mechanisms of these enzymes operate in complex with regulatory cyclin subunits. Their activities are tightly controlled by CKIs and phosphorylation events. The mechanisms of malignant transformation that affect CDK include cyclin overexpression, CKI loss, alteration of upstream signaling pathways, and failure to trigger the compensatory mechanisms necessary to inhibit CDK activity. Ultimately, this results in the disruption of the cell cycle, which leads to dysregulation of cellular proliferation and genomic instability. This comprehensive review focuses on the current status of CDK-targeted cancer therapeutics and the types of principles and mechanisms employed in structure-based drug design. We review how CDK4/6 inhibitors (palbociclib, ribociclib, and abemaciclib) in hormone receptor-positive breast cancer have changed treatment paradigms and the proof of concept for selective CDK targeting as a therapeutic strategy. The acquisition of resistance, however, is not without challenges – alterations to the Rb pathway, upregulation of cyclin E1, and activation of alternative signaling network PI3K/mTOR and RTK/RAS pathways. We present a critical review of recent strategies to overcome resistance, including rational drug combination therapy, new generation inhibitors of alternative isoforms of CDKs (CDK2, CDK7, CDK9, and CDK12), and novel approaches applying PROTACs and molecular glue therapies to lead to degradation of CDK proteins. In addition, biomarker-based patient stratification is examined for harnessing precision medicine in drug delivery outcomes. The development of CDK inhibitors currently faces challenges in achieving selectivity with potency, off-target toxicities, and predictive biomarkers of response. Future research

will examine synthetic lethal interactions, immunological activities following CDK inhibition, and combination with other treatment options including new forms of immunotherapy and epigenetic modulators. This review summarises what we know so far and points out the most promising targets for developing more effective and personalised CDK targeted therapies.

**Keywords:** Cyclin-dependent kinases (CDKs), CDK4/6 inhibitors, Palbociclib, Ribociclib, Abemaciclib, Cancer therapy, Cell cycle regulation, Drug resistance, Targeted therapy, Structure-based drug design, Biomarkers, Precision medicine

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## INTRODUCTION

Cancer is a leading cause of morbidity and mortality worldwide. It is characterized by uncontrolled cell proliferation and a tendency of cells to avoid programmed cell death (apoptosis). Central to these processes is the regulation of the cell cycle, which is mainly run by cyclin-dependent kinases (CDKs) and their cyclin partners. To date, there is a total of 9 types of CDK.

### Cyclin-dependent kinases (CDKs): Structure and Function

CDKs are serine/threonine kinases that control processes ranging from the cell cycle to transcription. Cyclin-dependent kinases function in association with specific cyclins, and their levels

of expression differ during the cell cycle phases. Well-known members of this family include CDK1, CDK2, CDK4, CDK6, and CDK9, with various functions in the cell cycle and in transcription. CDKs become active upon phosphorylation and cyclin binding and their activity is regulated by cyclin-dependent kinase inhibitors (CKIs) as well as by phosphorylation and dephosphorylation [1].

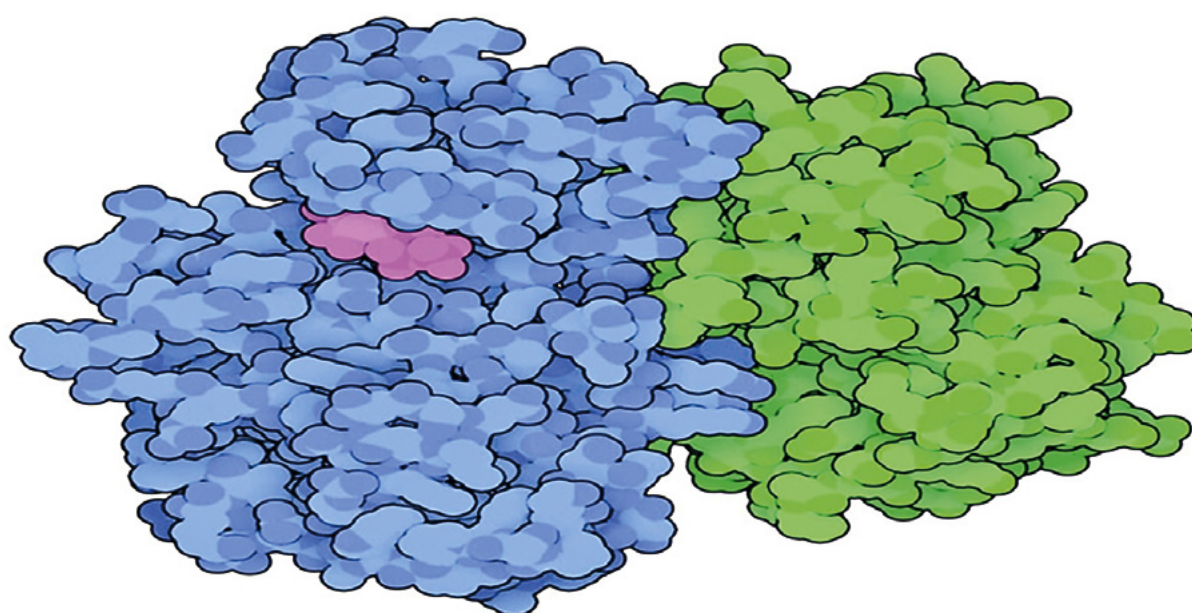
### The Role of CDKs in Oncogenesis

When CDKs or cyclins are improperly activated or highly expressed, they cause uncontrolled proliferation. Expression of CDK 4/6 and cyclin D is common in malignancies. Constitutively active CDKs are mutational drivers of tumorigenesis [2].

### Rationale for CDK Inhibition in Cancer Therapy

The inhibition of CDKs can halt the proliferation of tumor cells, induce them to undergo apoptosis and make cancer cells susceptible to other agents. Multiple inhibitors have shown promising results in clinical trials [3].

Current cancer therapy is based on the notion that the activity of CDK-cyclin complexes is almost universally overactive in human cancers, so these enzymes comprise a prime and clinically validated target for antiproliferative drug development [4]. It is possible to selectively halt the cancer cell cycle by inhibiting these energizing engines, which can then lead to a halt in functioning or death.



**Figure 1.** A 3D model illustrating the interaction between a Cyclin-Dependent Kinase (blue) and its activating Cyclin partner (green). A small molecule inhibitor (magenta) is shown bound within the enzyme's active site, preventing its function.

## Cyclin-dependent kinases (CDKs) and their role in cancer

Cyclin-dependent kinases (CDKs) are serine/threonine kinases that partner with cyclins to facilitate cell cycle phase (G1, S, G2, and M) progression in a timely and coordinated manner. CDK-cyclin complex activity is tightly controlled by an intricate network of activators, inhibitors, and phosphorylation events to regulate cell division and maintain genomic integrity [5].

The cell cycle consists of four main stages: G1, S, G2, and M. A number of CDK-cyclin complexes play an essential role in the process. Such complexes include CDK4/6-cyclin D, CDK2-cyclin E, and CDK1-cyclin A/B (Figure 2). The phosphorylation of Rb by CDK4/6-Cyclin D causes the release of E2F, permitting gene expression necessary for DNA synthesis and S phase entrance. In cancers, this delicacy is frequently disrupted, resulting in baseless expansion, instability, and acquisition of malignant characteristics. Dysregulated CDK activity occurs commonly in a wide representation of human cancers basically due to genetic and epigenetic defect[s] [6]. Enhanced expression of specific cyclins or CDKs, deletion of CDK inhibitors, or variations in upstream signaling pathways can subsequently impact tumor growth due to overactivation of CDK. Abnormal activities of CDKs can lead to the emergence of properties similar to cancer stem cells [6]. The cell cycle consists of four main stages: G1, S, G2, and M. A number of CDK-cyclin complexes play an essential role in the process. Such complexes include CDK4/6-cyclin D, CDK2-cyclin E, and CDK1-cyclin A/B (Figure 2). The phosphorylation of Rb by CDK4/6-Cyclin D causes the release of E2F, permitting gene expression necessary for DNA synthesis and S-phase entrance. In cancers, this delicacy is frequently disrupted, resulting in baseless expansion, instability, and acquisition of malignant characteristics. Dysregulated CDK activity occurs commonly in a wide representation of human cancers basically due to genetic and epigenetic defect[s] [6]. Enhanced expression of specific cyclins or CDKs, deletion of CDK inhibitors, or variations in upstream signaling pathways can subsequently impact tumor growth due to overactivation of CDK. Abnormal activities of CDKs can lead to the emergence of properties similar to cancer stem cells [6].

Figure 3 highlights the various factors that dysregulate CDKs in cancers. The hyperactivity of CDKs resulting from the loss of endogenous CKIs, mutations of IRs-coupled kinases, and the overexpression of cyclins or CDKs lead

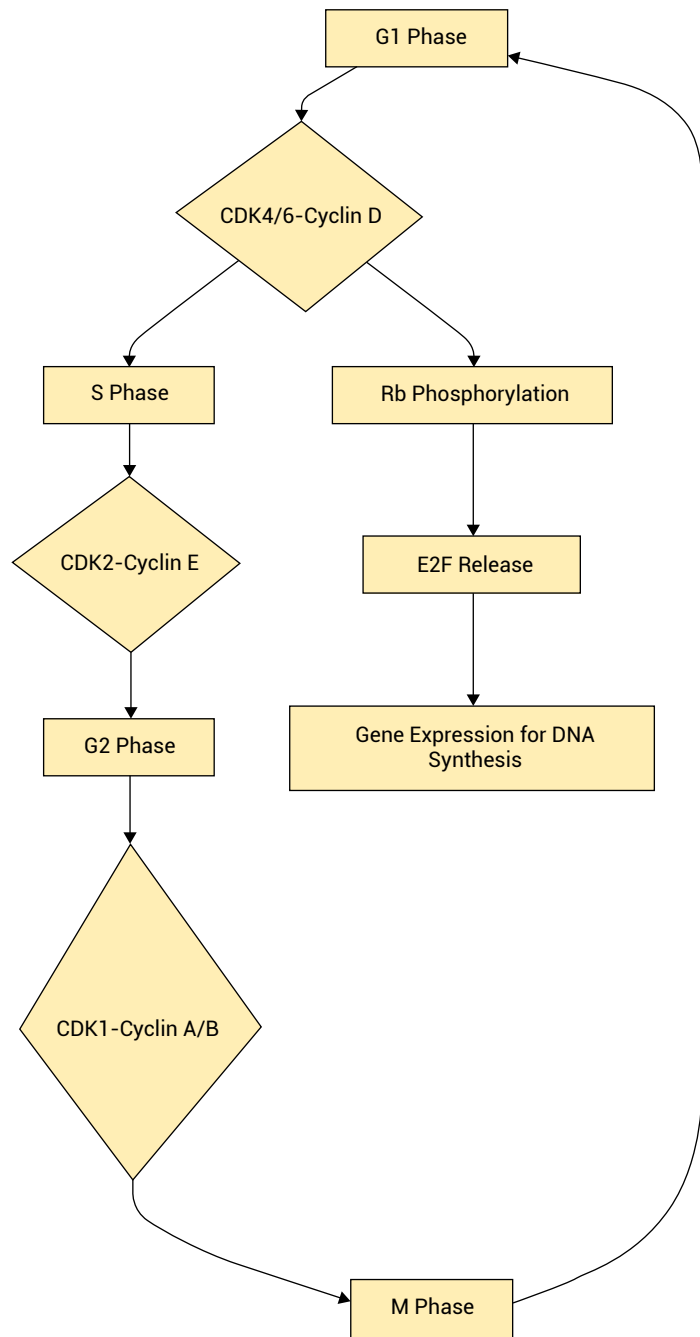
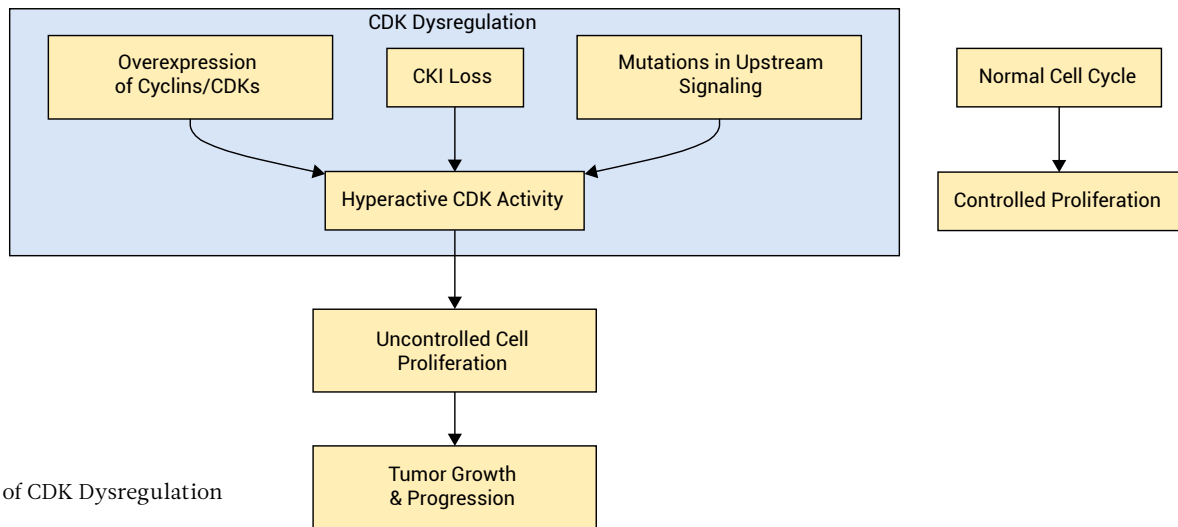


Figure 2. Simplified Cell Cycle Diagram with Key CDKs and Cyclins.

to uncontrolled cell proliferation and eventually, tumour growth.

### Certain CDKs play essential roles in cancer initiation and growth.

- CDK1: The G2/M transition in cell division is initiated by the cyclin B/CDK1 complex. The aberration of this system can cause abnormal cell division and genomic instability which leads to tumor development [7].
- CDK2: Cyclin A-CDK2 complex is mainly involved in the G1/S transition and progression



**Figure 3.** Mechanisms of CDK Dysregulation in Cancer.

through S-phase. While it is not always essential for cell division in all contexts, its dysregulation can lead to uncontrolled cell proliferation and is often associated with resistance to other therapies [8].

- **CDK4/6:** The G1 phase is controlled by cyclin D/CDK4-complex and cyclin D/CDK6-complex by causing Rb phosphorylation, which releases E2F transcription factors from Rb that cause the expression of genes required for DNA synthesis.
- Excessive activity of CDK 4/6 is a common feature in many cancers, rendering these kinases prime targets for therapeutic intervention [6].
- **CDK9:** The transcriptional cyclin-dependent kinase, CDK9, in complex with Cyclin T, regulates gene expression by phosphorylating RNA polymerase II. The abnormal activation of these genes is thought to establish a more favorable environment for tumor proliferation and is

a target in some hematological malignancies and solid tumors [9].

Levels and activity of the specific CDKs can serve as prognostic markers and as indicators of response in cancer treatment. More effective and targeted cancer therapies would depend on a better understanding of the specific roles and regulatory mechanisms of individual CDKs in various tumor types [10].

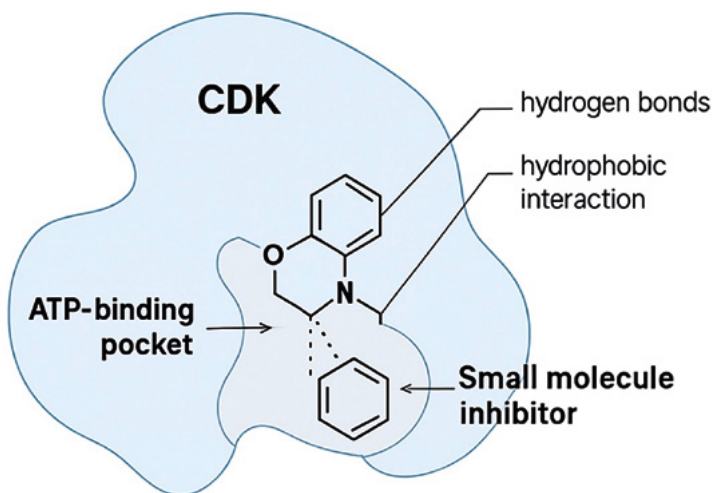
### Evolution and current landscape of CDK inhibitors

The journey from targets to approved drugs of CDK inhibitors has seen many ups and downs with substantial breakthroughs. In the early phases of the project, focus was made upon pan-CDK inhibition. In spite of their potential in causing cancer cell death, first-generation inhibitors nonetheless, had severe toxicities occurring outside of their intended targets at the concentrations needed for the inhibitors to be clinically successful. [11].

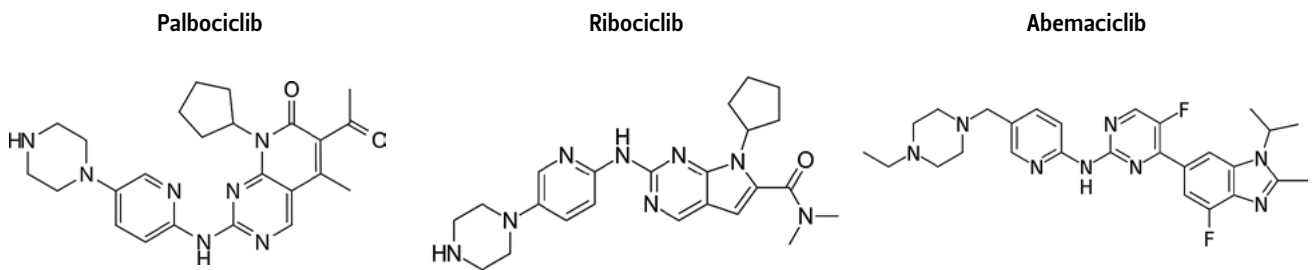
Small molecule inhibitors usually bind in the ATP-binding pocket of a Cyclin-Dependent Kinase (CDK) as illustrated in Figure 4. The affinity and selectivity of the inhibitor are greatly influenced by key interactions, including hydrogen bonds and hydrophobic interactions with key amino acid residues.

The introduction of more selective inhibitors, especially CDK4/6 inhibitors, reinvigorated the field. These second and third generation inhibitors' success has changed the treatment paradigm for some cancers.

- **Palbociclib, Ribociclib, and Abemaciclib.** The selective inhibitors of CDK4/6 have changed the treatment of both HR-positive and HER2-negative advanced breast cancer by blocking the G1-S phase transition of cells, therefore



**Figure 4.** General Binding Mode of CDK Inhibitors.



**Figure 5.** Chemical Structures of Approved CDK4/6 Inhibitors.

stopping cell proliferation. The FDA recognized the success of targeted CDK inhibition in clinical settings, which often involved the combination of endocrine therapy. Inhibitors that act on different targets but that have similar structure and binding modes generally bind to the inactive kinase conformation (in the case of CDK4/6 inhibitors), and they establish fixed hydrogen bond interactions with the appropriate amino acid residues in the CDK4/6 active site [12].

- **Figure 5** shows the chemical structures of the three FDA-approved CDK4/6 inhibitors, Palbociclib, Ribociclib, and Abemaciclib. Research into inhibitors of other CDKs that have different functions in cancer biology continues beyond CDK4/6. Selective CDK4/6 inhibitors have made a big difference in the management of metastatic breast cancer that is hormone receptor positive and HER2 negative.
- **CDK2 Inhibitors:** While CDK2 was initially considered a less critical target due to functional redundancy, its role in resistance to CDK4/6 inhibitors and its involvement in specific oncogene-driven cancers have renewed interest. Efforts are focused on developing selective CDK2 inhibitors to overcome resistance and expand therapeutic options [13].
- **CDK9 Inhibitors:** As a key regulator of transcription, CDK9 has emerged as an attractive target, particularly in hematologic malignancies and some solid tumors where its activity promotes the expression of pro-survival

genes. Novel CDK9 inhibitors like fadraciclib and AZD-4573 have shown promising preclinical antitumor effects [14].

Lower values indicate higher potency. Notably palbociclib, ribociclib, and abemaciclib exhibit high selectivity for CDK4/6 compared to the pan-inhibitor, flavopiridol [15].

### Challenges in CDK Inhibitor Development

Although successes have been achieved, there are several challenges to the use of CDK inhibitors.

**Drug Resistance:** Intrinsic and acquired resistance are both major challenges. Cell cycle component alterations like Rb loss, cyclin E1/other CDK upregulation, or activation of bypass signaling pathways (e.g., PI3K/mTOR, RTK/RAS) resulting in CDK blockade circumvention [16].

As seen in **Figure 6**, cancer cells exhibit diverse mechanisms to overcome sensitivity to CDK inhibitors. Specific changes to cell cycle machinery (Rb loss, cyclin E1 upregulation, CDK overexpression), activation of bypass signaling pathways (PI3K/mTOR, RTK/RAS) and upregulation of drug efflux pumps lead to acquired resistance and diminished response to therapy.

- **Toxicity and Selectivity:** Many kinases possess an ATP binding pocket that is highly conserved. This caused the 1st generation pan-CDK inhibitors to be off-target toxic. There is a challenging effort to design a selective inhibitor with low toxicity to normal cells for CDK other than 4 or 6 [17].

**Table 1.** Comparative Profile of Key CDK Inhibitors.

Inhibitor	Chemical Formula	Main CDK Targets (IC50 nM)	Approved Indication(s)	Key Clinical Side Effects
Flavopiridol	C21H20.CIN05	CDK.1(30), CDK2.(100), CDK4.(20-40), CDK6(60), CDK.9(20)	AML ("orphan drug")	Diarrhea, Nausea, Fatigue, Myelosuppression
Roscovitine	C19H26N6O	CDK2.(700), CDK7.(460), CDK9.(600)	Investigational (e.g., Cushing's)	Nausea, Vomiting, Hypokalemia, Liver enzyme elevation
Palbociclib	C24H29N7O2	CDK.4(11), CDK.6(15)	HR+/.HER2- Breast Cancer	Neutropenia, Leukopenia, Fatigue, Nausea
Ribociclib	C23H3.0N8O	CDK.4(10), CDK.6(39)	HR+/.HER2- Breast Cancer	Neutropenia, Hepatotoxicity (li.ver), QT Prolongation
Abemaciclib	C27H3.2F2N8	CDK.4(2), CDK.6(10)	HR+/.HER2- Breast Cancer	Diarrhea, Neutropenia, Nausea, Fatigue

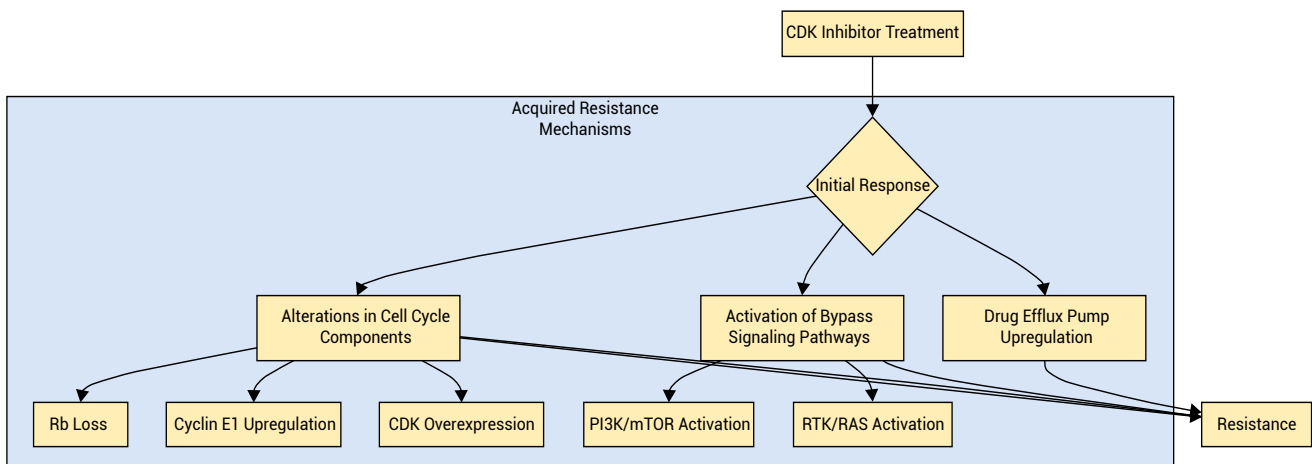


Figure 6. Mechanisms of Resistance to CDK Inhibitors.

- **Biomarkers:** Due to the absence of reliable biomarkers for predicting treatment outcomes and prognosis, the selection of appropriate patients and their monitoring remains challenging. Identifying which patients are likely to respond to CDK inhibitor therapy and which are prone to develop resistance is essential for enabling personalized medicine [18].
- **Limited Efficacy in Certain Cancers:** The effectiveness of CDK4/6 inhibitors is mainly restricted to HR+ breast cancer. With a better understanding of the specific CDK dependencies underlying different cancers, it could be possible to expand their usefulness to other cancer types [19].

**Opportunities in CDK Inhibitor Development**

These challenges also present significant opportunities for future research and development:

**Overcoming Resistance**

- **Combination Therapies:** Researchers are investigating how combinations of CDK inhibitors with other agents, including PI3K inhibitors, mTOR inhibitors, HER2-targeted therapies, chemotherapy, and immunotherapy, may overcome resistance and enhance efficacy [20].
- **Sequential Treatment Strategies:** The creation of ideal series of treatments to slow down or stop the emergence of resistance [21].
- **Next-Generation Inhibitors:** The manufacturing of new inhibitors is possible for the alteration of specific resistance mechanisms or for another selection of CDK isoforms [22].
- **PROTACs (Proteolysis-Targeting Chimeras):** Proteolysis-targeting chimeras (PROTACs) promise a new way to degrade CDK proteins

rather than just inhibiting their enzymatic action, potentially bypassing resistance mechanisms based on protein overexpression [23].

- **Expanding Therapeutic Indications:** A broader range of cancer types, including prostate cancer, lung cancer, and hematologic malignancies, where specific CDK dependencies may exist, will be investigated to assess the efficacy of existing and novel CDK inhibitors [24].
- **Biomarker Discovery and Validation:** Significant research is being done to find solid biomarkers that predict response, monitor resistance, or guide treatment decisions that will lead to personalized oncology [25].
- **Targeting Non-Canonical CDKs:** Exploring the therapeutic potential of other CDKs (e.g., CDK7, and CDK12), which are important for transcription and DNA repair, may offer additional drug discovery opportunities [26].
- **Precision Medicine Approaches:** Using genomic and molecular profiling to identify the right CDK inhibitor or combination treatment based on tumor molecular aberrations [27].

**Current Hurdles**

- **Acquired Resistance:** The most important clinical challenge is that tumors can eventually learn to evade the CDK4/6 barrier. Most commonly, through a complete loss of the Rb protein (which is, after all, the ultimate target of the drug) or through amplification of other cell cycle drivers (like Cyclin E, which activates CDK2, pushing the cell cycle onward without CDK4/6). (Wikipedia, Palbociclib Resistance).
- **Toxicity Management:** CDK4/6 inhibitors are more targeted than cytotoxic agents but do have side effects. On-target toxicities such as

neutropenia (myelosuppression) or off-targets like diarrhea or hepatotoxicity need to be managed for patients to remain on therapy. Future Directions.

- **Combination Therapies:** Smart combinations are the future of CDK inhibition. The combination of agents such as endocrine therapy, apart from CDK inhibitors, can create a better effect. Moreover, it can enhance the efficiency of the inhibitors. Plus, it will delay and also overcome resistance. [3].
- **Targeting Other CDKs:** There is renewed interest in the development of selective inhibitors for additional CDKs. Transcriptional CDKs, specifically CDK7, CDK9, and CDK12, are particularly promising candidates as they regulate the expression of critical oncogenes and help cancer cells survive.
- **Novel Modalities (Targeted Protein Degradation):** Next-generation approach extends beyond simple inhibition. New technologies such as Proteolysis-Targeting Chimeras (PROTACs) are being developed. These molecules do not merely inhibit the active site of the CDK but label the entire CDK protein for destruction by the cell's own waste-disposal machinery. This may offer a more profound and possibly more stable way of removing the target [15].

### Synthesis and *in vitro* evaluation methodologies

The discovery and development of new CDK inhibitors involve chemical synthesis and thorough *in vitro* biological evaluation. These processes are essential to recognize potent and selective compounds that possibly have desirable pharmacological properties.

The steps involved in the discovery and development of CDK inhibitors are shown in **Figure 7**. They start with target identification and lead discovery (it could be high-throughput screening, fragment-based drug discovery, and rational design), lead optimization, preclinical development (*in vitro*, *in vivo*, and ADME/tox studies), clinical development (phases I, II and III), regulatory approval, and post-marketing.

#### Synthesis Methodologies

A combination of rational design and traditional chemical methods is usually utilized for the synthesis of CDK inhibitors.

- **Rational Design:** Using X-ray crystallography of CDK-inhibitor complexes and molecular docking computational methods, it is possible to obtain structural information on the CDK and mediate the design of molecules that can

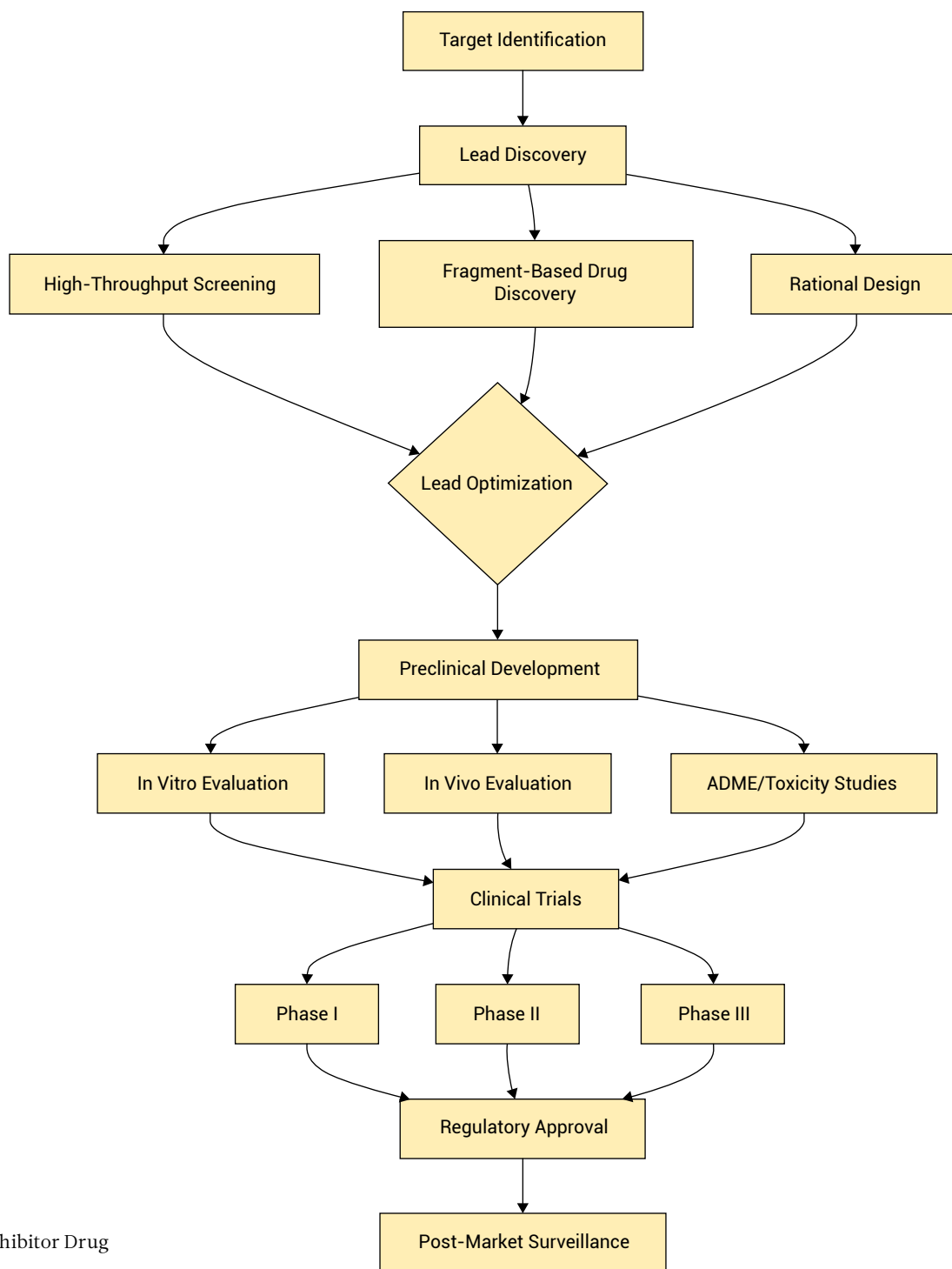
show better binding affinity and selectivity. This usually means changing existing chemical scaffolds or building new ones that will fit into the ATP binding site or allosteric pockets of CDKs [28].

- **Parallel Synthesis and Combinatorial Chemistry:** To hasten the process of drug discovery, parallel synthesis and combinatorial chemistry are often used for generating large libraries of structurally diverse compounds in quick succession. This high-throughput technique advances studies of structure-activity relationships (SAR), enabling researchers to quickly identify structural features that are responsible for biological activity [29].
- **Multi-step Organic Synthesis:** Complex molecules with CDK inhibitory activity are usually synthesized through a series of known reactions. For example, the construction of pyrazole derivatives, oxindole-indole conjugates, and pyrazolo-pyrimidine derivatives as seen in the literature usually requires the use of cyclization, coupling, and other functionalization reactions to complete the synthesis [30, 31].
- **Bioisosteric Replacement:** The concept of bioisosterism involves the substitution of a functional group or atom with a different group or atom that possesses similar chemical or physical properties. This strategy is mainly used for increasing potency, improving pharmacokinetic properties (such as solubility, and metabolic stability), and reducing toxicity. Furthermore, the chief objective behind applying this strategy is to avoid polar or ionic interactions, which can significantly alter biological activity [32].
- **Fragment-Based Drug Discovery (FBDD):** Fragment-based drug design is an increasingly popular approach in which small molecular fragments that bind weakly to the target protein, are first identified. These fragments can subsequently be optimized and grown or linked together to create more potent and selective inhibitors. This approach can work especially well for difficult protein targets such as kinases [33].

When developing compounds during the synthesis phase, it is crucial to ensure selectivity for specific CDK isoforms as well as to optimize drug-likeness properties, including solubility and oral bioavailability. Efficient synthetic routes yielding high-purity compounds should also be developed.

#### *In vitro* evaluation methodologies

The evaluation of CDK inhibitors is multifaceted process, encompassing *in vitro* methodologies



**Figure 7.**  
Overview of CDK Inhibitor Drug  
Discovery Pipeline.

designed to assess their potency, selectivity, and cellular effects. A typical evaluation cascade involves:

- **CDK Kinase Assays:** These are key assays to determine the direct inhibitory effect of compounds on purified recombinant CDK/cyclin complexes. They measure the capacity of one inhibitor to stop a specific substrate from being phosphorylated. Common techniques include:

As illustrated in **Figure 8**, a CDK kinase assay is based on the ability of a CDK-cyclin complex to phosphorylate a substrate in the presence of ATP. Measurement of the level to which a CDK inhibitor inhibits phosphorylation can determine the potency of the compound.

- **Enzymatic Assays (Kinase Assays):** The main processes for ascertaining the inherent inhibitory potency (IC<sub>50</sub>) and selectivity profile of a compound among the purified CDK-cyclin

complexes (e.g., CDK4/Cyclin D1, CDK2/Cyclin E). The test assesses the compound's capacity to prevent a phosphate group from being transferred from ATP to a substrate. Direct measurement of kinase inhibition can be performed to assess compound activity. This represents a key step in distinguishing selective inhibitors, such as palbociclib, from pan-CDK inhibitors [30].

- Cell-based assays measure whether the inhibitor can inhibit the growth of the cancer cells. To discover the GI50 of a compound, one can perform an MTT, MTS, or sulforhodamine B (SRB) assay. To verify engagement within the cellular context, these assays are often performed using cell lines with well-known CDK dysregulation (e.g., Rb-positive breast cancer for CDK4/6 inhibitors) [39].

- Flow analysis is critical for the confirmation of the cell cycle. Mode of Action. We can stain cells using a dye that intercalates with DNA.

The researchers can ascertain the distribution of cells between the G0/G1, S, and G2 and M phases. A successful CDK4/6 inhibitor, for instance, will cause a significant accumulation of cells in the G1 phase. The observed build-up of cells in the G1 phase confirms its intention. Method of cell cycle arrest [40].

## CONCLUSION AND RECOMMENDATIONS

The cyclin-dependent kinase inhibitors (CDKis) field has advanced markedly, with substances that went from hard-to-develop molecules to those that have yielded good clinical benefit, especially in hormone receptor-positive breast cancer. The path has demonstrated the important role of CDKs in cancer pathogenesis and the druggability of targeting these cell cycle regulators.

The prototypes of pan-CDK inhibitors were primarily meant to prove the concept of targeting cyclin-dependent kinases. Nonetheless, off-target toxicities have largely limited their therapeutic utility. As a result, the development of potent and selective CDK4/6 inhibitors has been prioritized. This represents the first drug whose efficacy and toxicity can be managed. The increasing use of compounds that inhibit epidermal growth factor receptor (EGFR) makes FISH and CISH reagent availability essential for prediction of therapeutic effectiveness.

Although the situation concerning CDK inhibitor therapy is not that clear, the emergence of both innate and acquired resistance is a major obstacle to success. Resistance may arise through

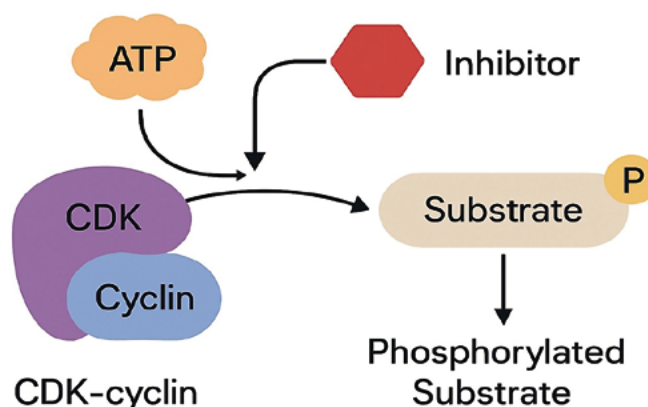


Figure 8. Scheme of a Typical CDK Kinase Assay.

several processes, including alteration of circadian clock elements, activation of bypass signaling pathways, or evolution of specific new genetic aberrations. Furthermore, the selective inhibitors of other CDK isoforms (for instance, CDK2, and CDK9) and the broadening of indications beyond breast cancer remain a hot area of research.

## Recommendations for Future Research and Development

1. Continuing the detailed study of what causes resistance to the current CDK inhibitor will be very useful. Gaining a better understanding will facilitate the development of new agents or rational combination therapies to circumvent or reverse resistance. Further investigations should be carried out in tackling other CDKs such as CDK2, CDK9, and utilizing the PROTAC technology to degrade the proteins of CDK.
2. The development of next-generation, highly selective inhibitors remains a critical objective. Although the CDK4/6 inhibitors have been successful, there is a clear need for other oncogenic CDK (e.g., CDK2, or CDK9) inhibitors with little off-target activity.
3. One of the important strategies to enhance the effectiveness of CDK inhibitors in the treatment of breast cancer is to develop predictive and prognostic robust biomarkers. Such biomarkers can assist in patient selection, and risk stratification, and enable early detection of resistance and therapeutic adjustment for maximal benefit and minimal toxicity.
4. Rationally designed combination therapies, in which CDK inhibitors are paired with other targeted agents (e.g., PI3K/mTOR inhibitors, HER2-targeted agents), endocrine therapy, chemotherapy, and/or immunotherapies, represent an attractive therapeutic strategy. Preclinical and clinical studies should continue

in order to identify synergistic combinations capable of improving efficacy and bypassing resistance.

5. The potential of CDK inhibitors to treat a broader spectrum of cancers beyond breast cancer should be assessed. For instance, future studies may investigate other cancers characterized by CDK malfunctioning. In addition, the integration of CDK inhibitors with other treatments, such as radiotherapy, warrants further exploration.
6. The field of structural biology can be advanced through the development of better tools. The structural biology toolkit is represented by multiple experimental and *in silico* disciplines. Further development of the Art of CryoEM (and other microscopy techniques) will be useful for better understanding of the binding modes of CDK inhibitors.
7. Accordingly, more advanced CDK inhibitors are expected to be developed to maximize their therapeutic potential. Effectively managing challenges and leveraging emerging opportunities will be essential for improving patient outcomes. Therefore, continued research is crucial for the improvement and progress of similar drugs in order to maximize their clinical impact against cancer.

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