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Review

Recent advances in regulating the cell cycle through inhibiting CDKs for cancer treatment

Weijiao Chen[a,b,Δ], Xujie Zhuang[a,b,Δ], Yuanyuan Chen[a,b,Δ], Huanaoyu Yang[a,b], Linhu Shen[a,b], Sikai Feng[a,b], Wenjian Min[a,b,*], Kai Yuan[a,b,*], Peng Yang[a,b,*]

[a] State Key Laboratory of Natural Medicines and Jiangsu Key Laboratory of Drug Design and Optimization, China Pharmaceutical University, Nanjing 210009, China
[b] Department of Medicinal Chemistry, School of Pharmacy, China Pharmaceutical University, Nanjing 211198, China

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ABSTRACT

The inhibition of cyclin-dependent kinases (CDKs) is considered a promising strategy for cancer treatment due to their role in cell cycle regulation. However, CDK inhibitors with no selectivity among CDK families have not been approved. A CDK inhibitor with high selectivity for CDK4/6 exhibited significant treatment effects on breast cancer and has become a heavy bomb on the market. Subsequently, resistance gradually decreased the efficacy of selective CDK4/6 inhibitors in breast cancer treatment. In this review, we first introduce the development of selective CDK4/6 inhibitors and then explain the role of CDK2 activation in inducing resistance to CDK4/6 inhibitors. Moreover, we focused on the development of CDK2/4/6 inhibitors and selective CDK2 inhibitors, which will aid in the discovery of novel CDK inhibitors targeting the cell cycle in the future.

1. Introduction

Cyclin-dependent kinases (CDKs) play important roles in regulating the cell cycle, and reducing cyclin-dependent kinases (CDK) activity to slow cell cycle progression is considered an effective strategy for inhibiting cell proliferation and treating cancer [1, 2]. However, the early CDK inhibitors that lacked selectivity among CDK families failed to enter the market due to their severe toxicity or poor efficacy [3]. Subsequent research focused on developing selective CDK4/6 inhibitors, resulting in significant success [4, 5].

Palbociclib, the first approved selective CDK4/6 inhibitor, has significantly impacted the treatment landscape of hormone receptor (HR)+/human epidermal growth factor receptor 2 (HER2)–breast cancer treatment. The sales of CDK4/6 inhibitors have increased annually, reaching over $10 billion in 2023 (Fig. 1). However, the efficacy of these agents in breast cancer treatment is gradually diminished by the development of resistance to CDK4/6 inhibitors [6]. Numerous studies have been conducted to elucidate the precise mechanisms underlying this resistance [7–10]. Mechanistic investigations have indicated that CDK2 plays a crucial role in the emergence of CDK4/6 inhibitor resistance, and preclinical trials have demonstrated that targeting CDK2 could help to overcome this resistance [11, 12]. Therefore, in this review, we described the function of CDKs in regulating the cell cycle and the process of identifying selective CDK4/6 inhibitors. Then, we explained the mechanism by which activating CDK2 results in resistance. Furthermore, we summarized the development of the latest CDK inhibitors, including CDK2/4/6 inhibitors and selective CDK2 inhibitors, which might provide guidance for discovering novel CDK inhibitors.

2. Role of CDKs in the Cell Cycle

The cell cycle consists of interphase and the mitotic phase (M). The major function of interphase is to prepare the DNA and proteins that need to be used in the M stage, which are also separated into G_1 (pre-DNA synthesis), S (DNA synthesis) and G_2 (pre-division) [13, 14]. Growing evidence has demonstrated that CDKs, including CDK1, 2, 4, 6, and 7, and their partner cyclins are pivotal regulators of cell cycle progression [15].

CDK4 and CDK6 are similar proteins that can be activated by cyclin D [16]. The CDK4/6-cyclin D complex phosphorylates the retinoblastoma (RB) protein, leading to the release of E2F (Fig. 2) [17–19]. This promotes the formation of the CDK2-cyclin E complex, which further phosphorylates RB and facilitates the transition from G_1 to S phase [20–25]. Subsequently, the CDK2-cyclin A complex continuously phosphorylates RB, driving the progression from S to G_2 transition [26–28]. Finally, the CDK1-cyclin A and CDK1-cyclin B complexes promote the initiation and the smooth progression of mitosis during the M phase (Fig. 2) [29–32]. To prevent premature entry into mitosis, CDK1-related sites are phosphorylated by WEE1 and MYT1 kinases, which inhibit complex formation [33-37]. Additionally, CDK7 regulates the cell cycle by activating CDKs 1, 2, 4, and 6 [38–40].

3. Selective CDK4/6 Inhibitor

Early-stage CDK inhibitors lacked selectivity within the CDK

* Corresponding author.
E-mail addresses: min1218xx@163.com (W. Min); cpuyk1993@163.com (K. Yuan); pengyang@cpu.edu.cn (P. Yang)
Δ These authors contributed equally to this work.

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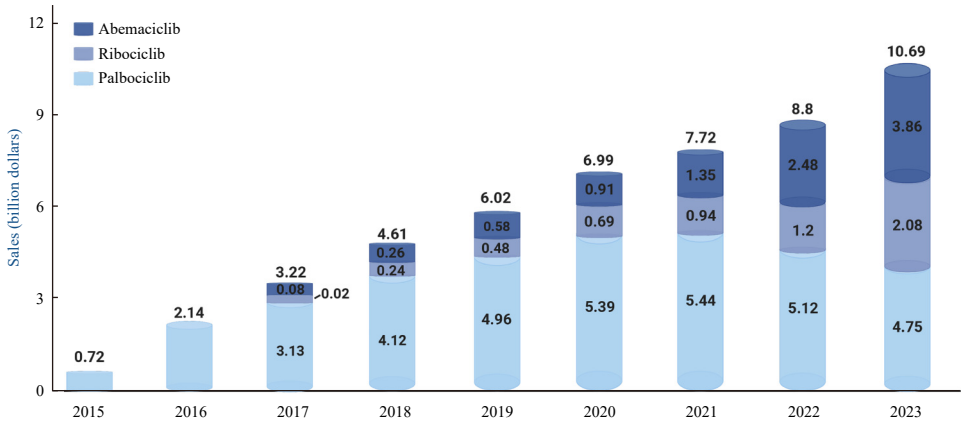


Fig. 1 The sales of selective CDK4/6 inhibitors palbociclib, ribociclib, and abemaciclib in 2015–2023.

family (Fig. 3) [41–49]. An-CDK inhibitors potentially suppress CDK subtypes essential for normal cell growth, leading to severe adverse effects [50–53]. Moreover, the unclear anticancer mechanisms of pan-CDK inhibitors may result in inappropriate patient selection and reduced efficacy in clinical trials [43, 54–56]. Although pan-CDK inhibitors exhibited potent anticancer activity in preclinical trials, many of them exhibited high toxicity or low efficacy in clinical trials [51, 57–60]. Consequently, no pan-CDK inhibitors have successfully passed clinical trials and received market approval [1, 3].

Due to the disappointing outcomes of pan-CDK inhibitors clinical trials, the development of CDK inhibitors has focused on selectively inhibiting CDK4/6. Deletion of CDK4/6 did not affect the growth of normal cells; thus, targeting CDK4/6 might result in relatively low toxicity [4]. Moreover, the selective inhibition of CDK4/6 exerted a single effect on the cell cycle to cause G1 arrest, and this clear anticancer mechanism could allow CDK4/6 inhibitors to find appropriate types of patients in clinical trials and demonstrate potent efficacy for cancer treatment [61]. Currently, the selective CDK4/6 inhibitors palbociclib [5, 62], ribociclib [63], abemaciclib [64], and dalpiciclib [65] (Fig. 4) are approved for the treatment of HR+/HER2– breast cancer, and trilaciclib [66] (Fig. 4) is approved for the treatment of myelosuppression.

In HR+/HER2– breast cancer treatment, combining a CDK4/6 inhibitor with an aromatase inhibitor has demonstrated superior efficacy compared with aromatase inhibitor monotherapy. Consequently, this combination therapy has received regulatory approval for HR+/HER2– breast cancer [67–75]. Furthermore, for patients experiencing disease progression after endocrine therapy, the combination of a CDK4/6 inhibitor with fulvestrant has shown enhanced therapeutic outcomes compared to fulvestrant alone. This selective CDK4/6 inhibitor/fulvestrant combination has subsequently been approved for treating HR+/HER2– breast cancer in patients who have experienced disease progression following endocrine therapy [76–82].

In contrast to palbociclib, ribociclib, and dalpiciclib, which require combination with endocrine therapy for breast cancer

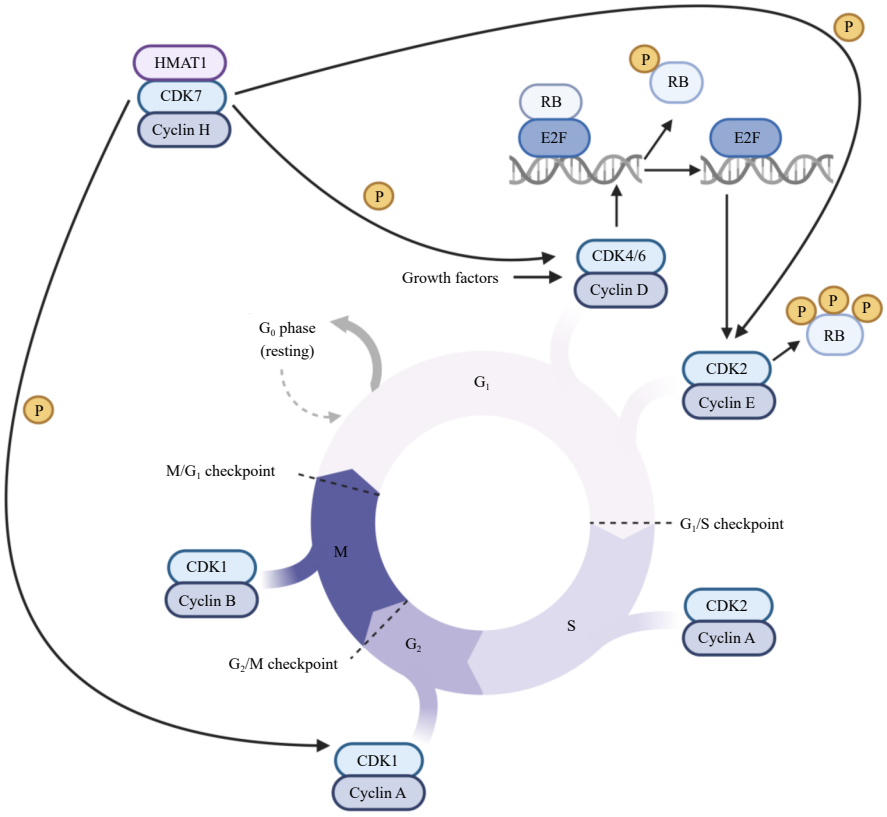


Fig. 2 Role of CDKs in regulating cell cycle progression.

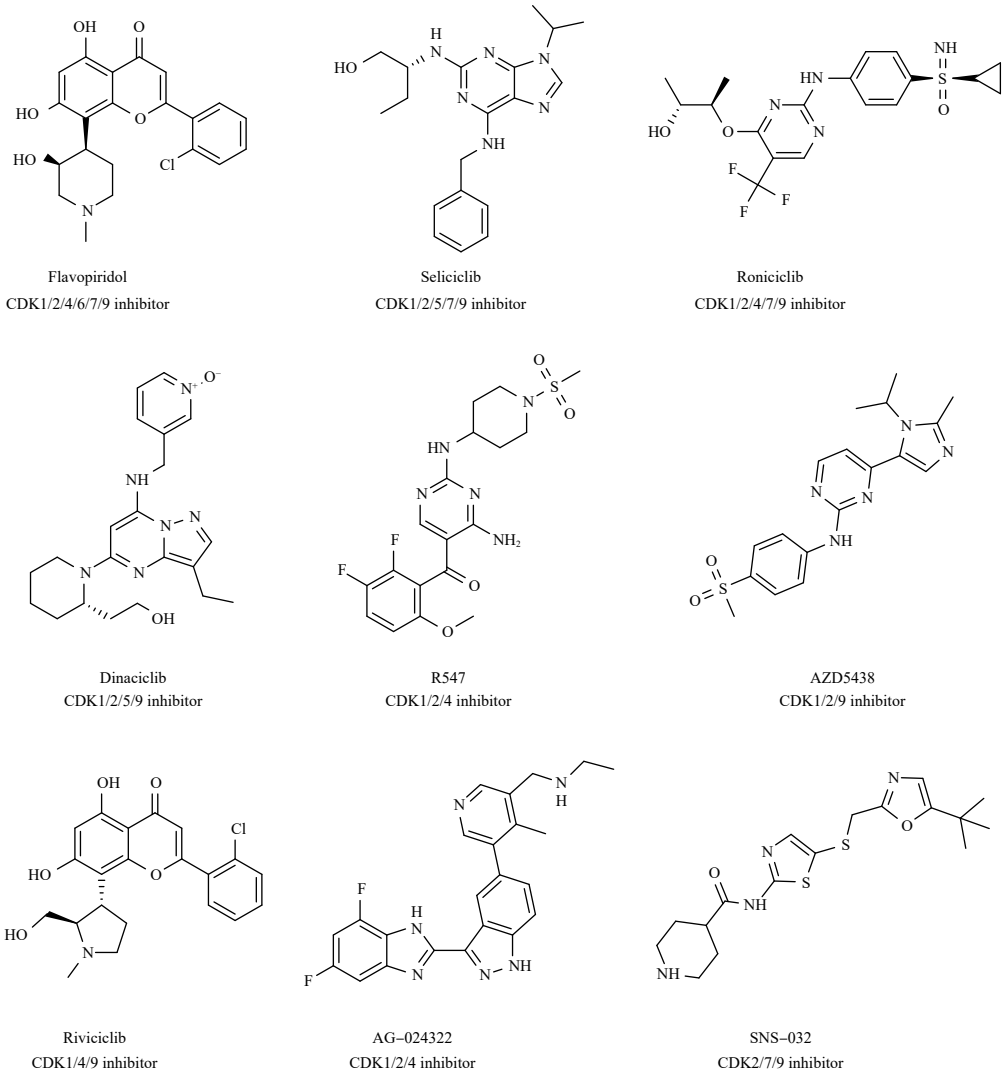


Fig. 3 Representative nonselective CDK inhibitors.

treatment, abemaciclib can also be utilized for treating breast cancer that has progressed following endocrine therapy [83]. Furthermore, the combination of abemaciclib with endocrine therapy post-surgery in early breast cancer patients has demonstrated a significantly reduced recurrence rate compared to endocrine therapy alone. Consequently, in 2023, the Food and Drug Administration (FDA) approved the abemaciclib/endocrine therapy combination as an adjuvant treatment for HR+/HER2–, node-positive, early breast cancer patients at high risk of recurrence [84, 85].

In addition to breast cancer treatment, a selective CDK4/6 inhibitor could also be used to decrease myelosuppression induced by chemotherapy. Trilaciclib (Fig. 4), developed by G1 Therapeutics, received FDA approval in 2021 for the prevention of myelosuppression in patients with extensive-stage small cell lung cancer undergoing platinum/etoposide-containing or topotecan-containing regimens [66]. Unlike palbociclib, ribociclib, abemaciclib, and dalpiciclib, which are administered orally, trilaciclib is delivered via intravenous injection. When administered before chemotherapy, trilaciclib rapidly induces G1 phase arrest in hematopoietic stem cells and progenitor cells, thereby protecting bone marrow cells from chemotherapy-induced damage [86–88].

Due to the extensive dysregulation of the cell cycle in various cancers, selective CDK4/6 inhibitors demonstrate potential for exhibiting potent efficacy across multiple cancer types. Currently, clinical trials of CDK4/6 inhibitors are being conducted to treat a wide range of malignancies, including acute leukemias, liver cancer, prostate cancer, pancreatic adenocarcinoma, liposarcoma, ovarian cancer, atypical neurofibromas, brain tumors and small-cell lung cancer (Table 1).

4. CDK4/6 Inhibitor Resistance Mediated by CDK2

CDK4/6 plays a pivotal role in the transition from the G1 to the S phase by promoting the phosphorylation of RB, which unleashes the activity of the transcription factor E2F. However, when the activity of CDK4/6 is inhibited, various compensatory mechanisms might be employed to bypass the inhibition. Among these mechanisms, one that has been extensively studied is the activation of CDK2. In this scenario, CDK2 is mobilized to continue the phosphorylation of RB, thereby releasing E2F and ensuring the progression of the cell cycle.

The efficacy of selective CDK4/6 inhibitors in breast cancer treatment has been significantly compromised by the development of resistance, prompting numerous studies to investigate the underlying mechanisms [8–10, 89–96]. While various resistance mechanisms have been identified, each accounts for only a portion of the observed resistance. Among these, the activation of CDK2 has emerged as one of the most prominent and extensively studied mechanisms. Multiple investigations have demonstrated that CDK2 plays a crucial role in mediating resistance to CDK4/6 inhibitors in breast cancer (Fig. 5) [12, 95, 97, 98].

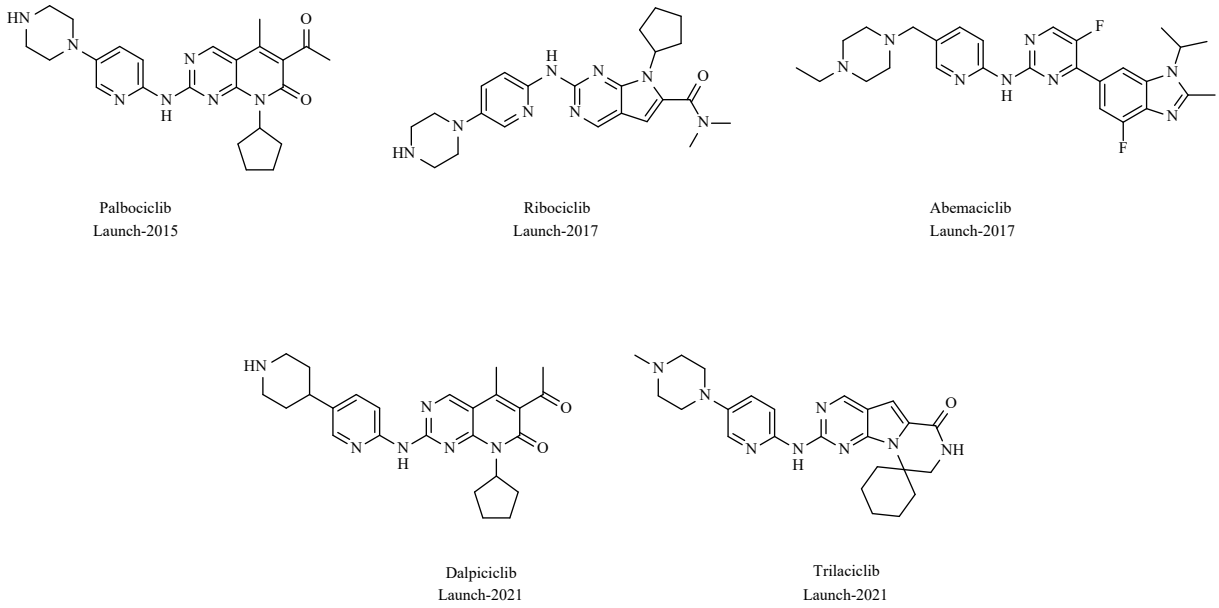


Fig. 4 Selective CDK4/6 inhibitors on the market.

In ER+ breast cancer cells exposed to palbociclib, researchers have noted the regulation of cyclin D levels. Subsequently, cyclin D forms a complex with CDK2, known as the CDK2-cyclin D complex. This interaction leads to the restoration of RB phosphorylation, consequently diminishing palbociclib's efficacy in inducing cell cycle arrest [99].

Phosphatase and tensin homolog (PTEN) is a tumor suppressor gene, which dephosphorylates phosphatidylinositol-3,4,5-trisphosphate (PIP3) and converts it to phosphatidylinositol-4,5-bisphosphate (PIP2), thereby negatively regulating the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway. Inactivation of PTEN leads to an increase in PIP3 levels, which in turn activates the AKT signaling pathway, promoting cell growth and survival and increasing the risk of tumor development. The absence of *PTEN* was observed in ER+ breast cancer patients who were resistant to the ribociclib/letrozole combination. Loss of *PTEN* upregulated AKT activity and promoted resistance to CDK4/6 inhibitors in ER+ breast cancer cells. The combination of an AKT inhibitor with ribociclib displayed antitumor activity against *PTEN*-deficient breast cancer. Further mechanistic studies indicated that the activation of AKT triggers the exocytosis of p27 from the nucleus and subsequently leads to a reduction in p27 activity. Subsequently, the activity of downstream CDK2 and CDK4 increased, which ultimately induced resistance to CDK4/6 inhibitors [92, 100, 101].

Pyruvate dehydrogenase kinase 1 (PDK1) is the pivotal node in the PI3K/AKT pathway, and the activation of PDK1 can activate AKT to promote cell proliferation and inhibit apoptosis. Knockdown of PDK1 increased the antiproliferative activity of ribociclib against ER + breast cancer cells, and the combination of a PDK1 inhibitor with ribociclib also had synergistic effects on ER + breast cancer cells. Elevated levels of PDK1 expression were detected in ribociclib-resistant breast cancer cells, resulting in AKT pathway activation. This upregulated the expression of cyclin A and cyclin E and promoted the activation of CDK2, ultimately contributing to the development of drug resistance. Both PDK1 inhibitors and CDK2 inhibitors can increase the sensitivity of resistant cells to ribociclib [102].

Clinical trials have provided substantial evidence for the critical role of the CDK2-cyclin E complex in the emergence of CDK4/6 inhibitor resistance. Amplification of *CCNE* was observed in ER+ breast cancer patients treated with a CDK4/6 inhibitor [92, 103]. In a cohort of ER+ breast cancer patients treated with palbociclib/letrozole or palbociclib/fulvestrant, PFS significantly decreased when proteolytically cleaved cytoplasmic cyclin E in tumor tissue was detected [104]. Notably, the PALOMA3 trial showed that patients with lower levels of cyclin E exhibited better treatment effects than those with higher levels of cyclin E

Table 1 Representative clinical trials of CDK4/6 inhibitors for different cancers

Drug	NCT number	Stage	Disease
Palbociclib	NCT02310243	I/II	Acute leukemias
Palbociclib	NCT01356628	II	Liver cancer
Palbociclib	NCT02905318	II	Prostate cancer
Ribociclib/Everolimus	NCT02985125	I/II	Pancreatic adenocarcinoma
Ribociclib	NCT03096912	II	Liposarcoma
Ribociclib/Letrozole	NCT03673124	II	Ovarian cancer
Abemaciclib	NCT04750928	I/II	Atypical neurofibromas
Abemaciclib	NCT03220646	II	Brain tumor
Abemaciclib	NCT04967521	III	Dedifferentiated liposarcoma
Abemaciclib	NCT04010357	II	Small-cell lung cancer

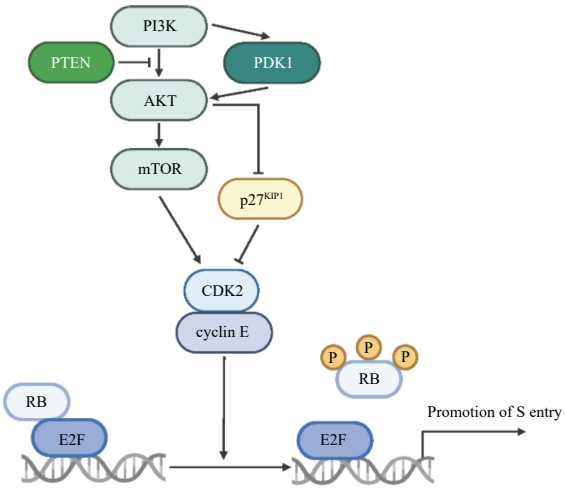


Fig. 5 Main mechanism of CDK4/6 inhibitor resistance mediated by CDK2.

when they received palbociclib/fulvestrant [103].

In summary, these studies demonstrated that CDK2 plays a critical role in maintaining normal cell cycle progression in CDK4/6 inhibitor-resistant breast cancer cells. Furthermore, the combination of CDK2 inhibition, either through knockdown or targeted inhibitors, with CDK4/6 inhibitors significantly impeded the proliferation of resistant cells. Recognizing the pivotal role of CDK2 in CDK4/6 inhibitor resistance, researchers have developed CDK2/4/6 inhibitors and selective CDK2 inhibitors as potential strategies to overcome this resistance.

5. CDK2/4/6 Inhibitor

Several CDK2/4/6 inhibitors, including PF-06873600, NUV-422, RGT-419B, and SCR-8079 (Table 2), have been developed. PF-06873600, developed by Pfizer, was the first CDK2/4/6 inhibitor which come into clinical trials [105]. Through a mobility shift assay, Pfizer discovered palbociclib derivative **1a** (Fig. 6) with CDK2 inhibitory activity (K_i = 5.9 nmol·L^{-1}). The crystal structure of **1a** with CDK2 revealed that the introduced piperidine sulfonamide motif formed hydrogen bond interactions with Asp86 and Lys89. The removal of the methyl group at the *C*'5 position and acetyl group at the *C*'6 position from **1a** afforded **1b** (Fig. 6), which improved the inhibitory activity against CDK2 (K_i = 0.71 nmol·L^{-1}) and selectivity over CDK1 (16.5-fold). The introduction of a methyl group to the cyclopentyl ring at the *N*'8 position generated **1c** (Fig. 6), which exhibited more potent CDK2 inhibitory activity (K_i = 0.09 nmol·L^{-1}) and higher selectivity over CDK1 (26.7-fold). However, human liver microsome (HLM) clearance was also significantly increased (Clint > 482 μL·min^{-1}·mg^{-1}) [106-109]. Further optimization of the cyclopentyl ring provided **1d** (Fig. 6), which retained great CDK2 potency (K_i = 0.2 nmol·L^{-1}), high CDK1 selectivity (22-fold) and increased HLM stability (Clint = 36.4 μL·min^{-1}·mg^{-1}). The addition of the methyl group at the *C*'5 position (**1e**) increased selectivity over CDK1 (45.8-fold) but decreased HLM stability (Clint = 67.4 μL·min^{-1}·mg^{-1}). Finally, the replacement of methyl with difluoromethyl provided PF-06873600, which exhibited obviously improved HLM stability (Clint < 10.8 μL·min^{-1}·mg^{-1}) and retained potent CDK2 inhibitory activity (K_i = 0.13 nmol·L^{-1}) and high CDK1 selectivity (34.6-fold) [105].

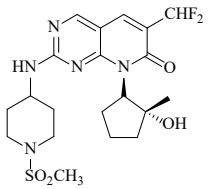
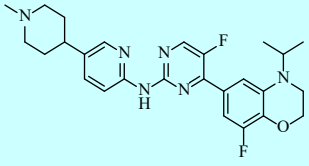
The crystal structure analysis of PF-06873600 bound to CDK2 revealed specific interactions. The methylsulfonyl groups' oxygen atoms formed hydrogen bonds with Asp86 and Lys89 (Fig. 7). the 2-aminopyrimidine moiety of PF-06873600 established two characteristic hydrogen bonds with the hinge region Leu83. At the *N*'8 position, the cyclopentyl group occupied the lipophilic pocket, while the hydroxyl group's oxygen atom formed a hydrogen bond with Gln131. The difluoromethyl group at the *C*'5 position formed van der Waals interactions with the gatekeeper Phe80 (Fig. 7) [105].

Preclinical studies demonstrated that PF-06873600 exhibited inhibitory activity against hormone receptor-positive (HR+) breast cancer and could potentially overcome resistance to cyclin-dependent kinase 4/6 (CDK4/6) inhibitors in HR+ breast cancer [110]. In addition, palbociclib did not significantly affect *CCNE1*-amplified cancers [111], and PF-06873600 potently inhibited these cancers. However, the clinical trial of PF-06873600 was discontinued in November 2022.

CDK2/4/6 inhibitor NUV-422 was granted orphan drug designation by the FDA for malignant glioma treatment in 2021. The indications for NUV-422 in clinical trials included glioma, HR+/HER2− breast cancer, and metastatic castration-resistant prostate cancer. The partial clinical trial of NUV-422 was suspended by the FDA due to the emergence of uveitis in June 2022, and Nuvation Bio discontinued the clinical trial of NUV-422 based on the internal risk-benefit analysis in August 2022.

RGT-419B, developed by Regor Therapeutics, is currently undergoing clinical trials for the treatment of HR+/HER2- breast cancer and other solid tumors in Chinese patients (NCT06299124), as well as HR+/HER2- breast cancer with resistance to CDK4/6 inhibitors (NCT05304962). Furthermore, SCR-8079, a CDK2/4/6 inhibitor developed by Simcere Pharmaceutical, demonstrated potent inhibitory activity against CDK4/6 inhib-

Table 2 Representative CDK2/4/6 inhibitors

Name	Structure	Company	Stage
PF-06873600		Pfizer	Discontinued
NUV-422		Nuvation Bio	Discontinued
RGT-419B	Not available	Regor	Phase I
SCR-8079	Not available	Simcere	Preclinical

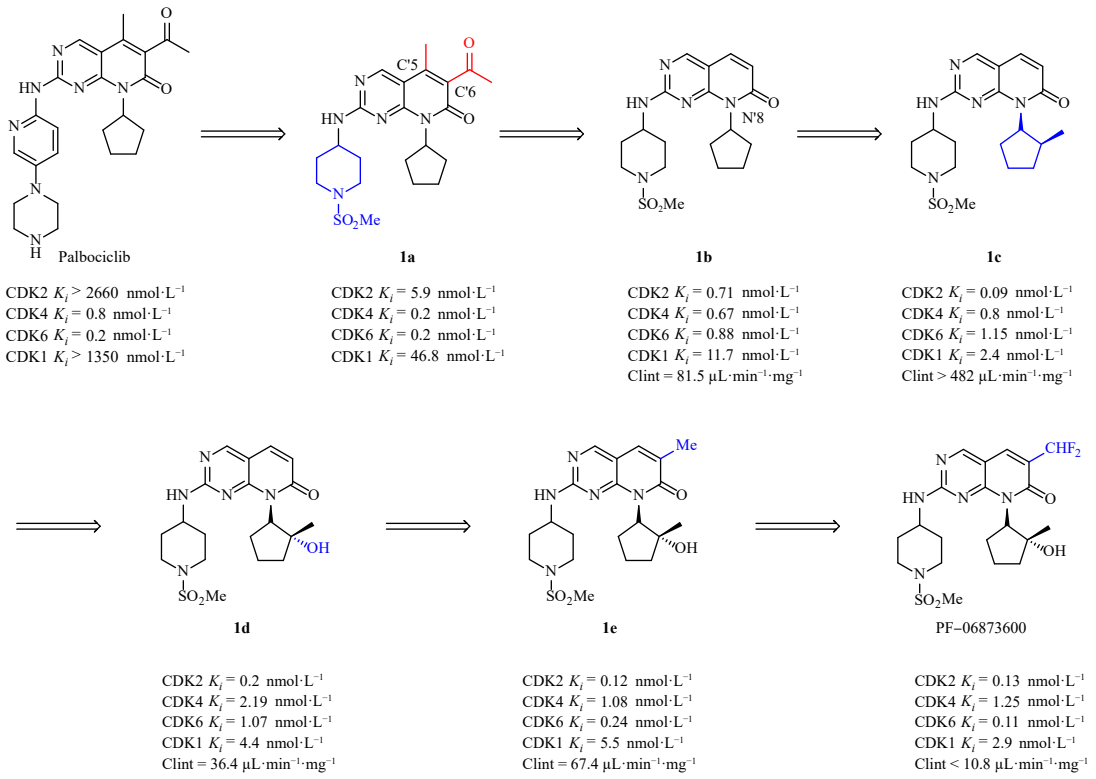


Fig. 6 Identification of the CDK2/4/6 inhibitor PF-06873600.

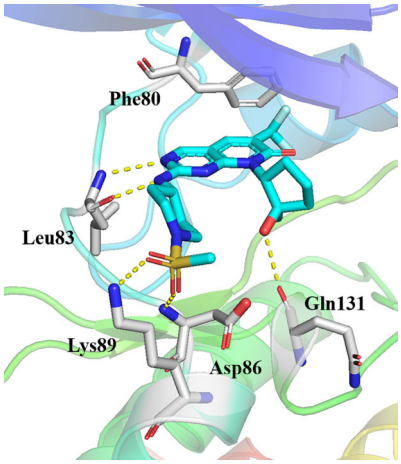


Fig. 7 Crystal structure of PF-06873600 with CDK2 (PDB: 7KJS).

itor-resistant cells in preclinical studies. This compound significantly inhibited the growth of OVCAR3 and MCF-7 xenograft tumors [112-117].

6. Selective CDK2 Inhibitor

Selective CDK2 inhibitors have been a research hotspot in recent years, and a number of selective CDK2 inhibitors, including PF07104091, BLU-222, INCB123667, INX-315, ARTS-021, AZD8421, NKT-3447, and BG-68501, have entered clinical trials (Table 3).

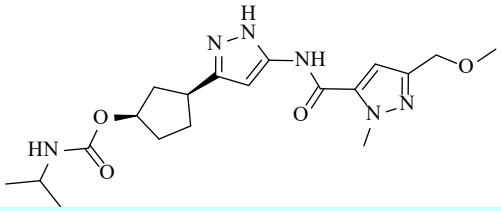
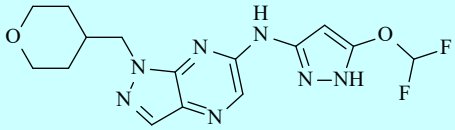
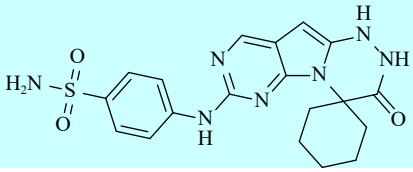
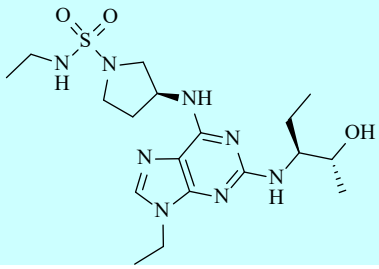
PF07104091 was the first selective CDK2 inhibitor to enter clinical trials. The Phase I trial of PF07104091 (NCT05431153) was completed, demonstrating that PF07104091 as a single agent exhibited tolerability and anticancer activity in breast cancer patients who had developed resistance to CDK4/6 inhibitors [118].

The VELA trial of BLU-222 demonstrated that transient visual adverse events occurred in five patients (19%) by January 2023 [119], and the partial VELA trial was put aside by FDA due to visual adverse events in February 2023. The patients with visual adverse events all recovered when the dose was interrupted or reduced, and further ophthalmologic examinations confirmed that no abnormal findings were observed in the patients after treatment. As a result, this clinical hold on the VELA trial was canceled in March 2023.

INX-315 was developed by Incyclix Bio through structural optimization of trilaciclib (Fig. 8) [120]. The removal of the lactam carbonyl and replacement of the pyridine-piperazine motif with benzyl sulfonamide provided **2a** (Fig. 8), which exhibited significantly improved CDK1 and CDK2 inhibitory activity, but the HLM clearance of **2a** was extremely high, with a half-life of less than 10 min. The optimization of the tricyclic core generated **2b** (Fig. 8), which exhibited reduced inhibition of CDKs 1, 2, 4, 6, and 9 and slightly increased HLM stability. Further modification of the tricyclic core provided INX-315 (Fig. 8), which displayed significantly improved CDK2 potency, selectivity toward CDKs 1, 4, 6, and 9, and metabolic stability [115]. The predicted binding model of INX-315 with CDK2 indicated that the sulfonamide moiety formed two hydrogen bonds with Asp86 and one hydrogen bond with Lys89. In addition, the 2-aminopyrimidine formed hydrogen bonds with Leu83, and the tricyclic core formed one hydrogen bond with Asp145 (Fig. 9) [121].

INX-315 demonstrated the ability to inhibit RB phosphorylation, leading to cell cycle arrest and promotion of therapy-induced senescence (TIS). This mechanism resulted in tumor growth inhibition in *CCNE1*-amplified cancers. In CDK4/6 inhibitor-resistant breast cancer, cell proliferation relied on both CDK4/6 and CDK2. Consequently, combining INX-315 with a CDK4/6 inhibitor exhibited optimal control of proliferation. Additionally, this combination delayed resistance development through enhanced suppression of E2F targets. It is noteworthy that the senescence induced by CDK4/6 or CDK2 inhibitors is re-

Table 3 Representative selective CDK2 inhibitors in clinical trials

Name	Structure	Company	Date[a]
PF07104091		Pfizer	2020-09-16
BLU-222		Blueprint Medicine	2022-04-07
INCB123667	Not available	Incyte	2022-07-05
INX-315		Incyclix Bio	2023-03-28
ARTS-021	Not available	Allorion Therapeutics	2023-08-30
AZD8421		AstraZeneca	2023-12-05
NKT-3447	Not available	NiKang Therapeutics	2024-02-23
BG-68501	Not available	Beigene	2024-02-28

[a]The actual date on which the first participant was enrolled in the clinical study.

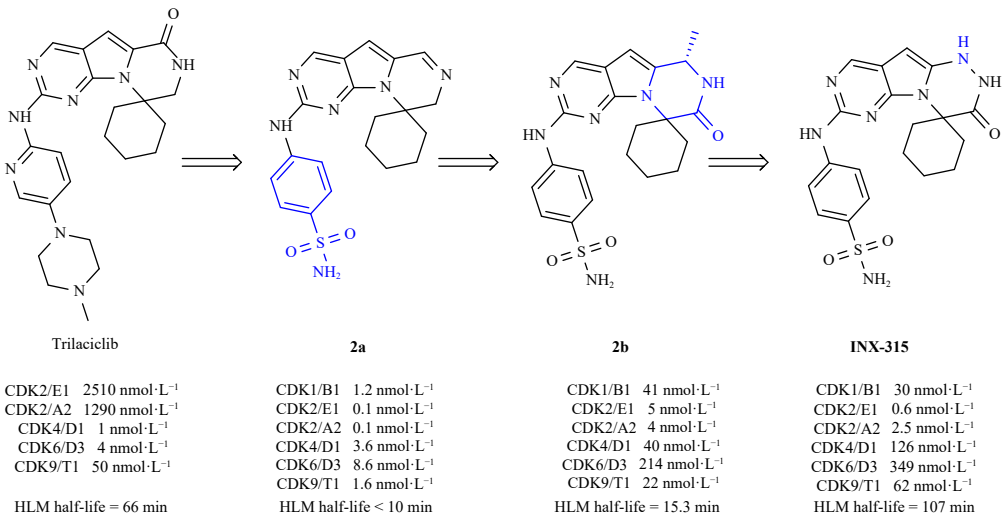


Fig. 8 Identification of the selective CDK2 inhibitor INX-315.

versible and dynamic. CDK4/6 inhibitors remodeled chromatin to induce senescence, and upon resistance development, the chromatin could partially revert to a pre-senescent state. Subsequently, the addition of INX-315 could reverse chromatin to a senescence architecture and reinstate TIS [122].

The structure of INCB123667, developed by Incyte, has not been revealed, but Incyte reported two kinds of selective CDK2 inhibitors, **3** (Fig. 10) and **4** (Fig.11) [123,124]. Hit **3a** (Fig. 10) was identified as a CDK2 inhibitor with an IC_{50} value of 431 nmol·L^{-1} through a high-throughput screen (HTS). Merging pyrimidine and pyrazole scaffolds provided **3b** (Fig. 10), which showed increased CDK2 inhibitory activity, but the potency of **3b** was lost in human whole blood (hWB) [125–127]. The addition of a methyl group to the sulfonamide and the modification of the lactam sub-

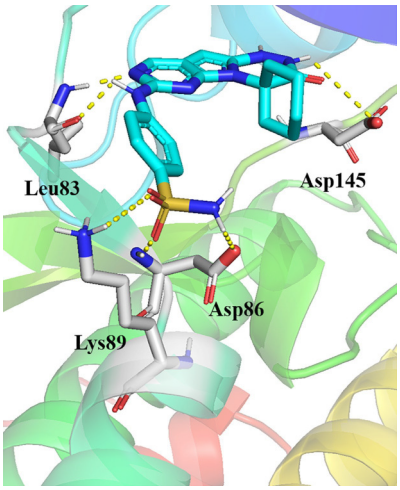


Fig. 9 Predicted binding model of INX-315 with CDK2 (PDB: 7KJS).

stituent (**3c**, Fig. 10) resolved the issues of hWB potency loss and increased selectivity over CDKs 1, 4, and 6. The introduction of polar substituents to the lactam nitrogen generated **3d** (Fig. 10), which exhibited increased HLM stability (hCl = 0.8 $L{\cdot}h^{-1}{\cdot}kg^{-1}$). However, the sulfonamide demethylation of **3d** resulted in high *in vivo* clearance [128, 129]. To resolve this issue, protons were replaced with deuterium to generate **3** (Fig. 10) [130], which displayed obviously decreased sulfonamide demethylation and increased stability in HLM [123].

The hit **4a** (Fig. 11) was also discovered through the HTS of Incyte's in-house compound collection and exhibited medium CDK2 inhibitory activity (IC_{50} = 607 $nmol{\cdot}L^{-1}$) and potent JAK inhibitory activity (IC_{50} < 1 $nmol{\cdot}L^{-1}$) [131-133]. The preliminary structural optimization generated **4b** (Fig. 11), which showed significantly improved inhibitory activity against CDK2 (IC_{50} = 16 $nmol{\cdot}L^{-1}$) and selectivity over JAK2 (IC_{50} > 10000 $nmol{\cdot}L^{-1}$). The replacement of chloro with trifluoromethyl (**4c**, Fig. 11) increased CDK2 potency and CDK1 selectivity. The introduction of the geminal dimethyl alcohol substituent to the pyrazole nitrogen afforded **4d** (Fig. 11), which exhibited more potent CDK2 inhibitory activity, higher CDK1 selectivity, great HLM stability (hCl < 0.5 $L{\cdot}h^{-1}{\cdot}kg^{-1}$), and promising simulated gastric fluid (SGF) solubility (842 $\mu g{\cdot}mL^{-1}$) [134-136]. Replacing methyl with cyclopropyl provided **4** (Fig. 11), which exhibited improved CDK2 inhibitory activity, CDK1 selectivity, and hWB potency and retained high HLM stability (hCl = 0.5 $L{\cdot}h^{-1}{\cdot}kg^{-1}$) and SGF solubility (> 400 $\mu g{\cdot}mL^{-1}$) [124].

The crystal structure of **4** with CDK2 revealed that the two oxygen atoms of cyclopropylsulfonyl formed hydrogen bond interactions with Asp86 and Lys89, and the 2-aminopyrimidine moiety formed two hydrogen bonds with Leu83 (Fig. 12). The triffuoromethyl of pyrimidine was projected toward the gatekeeper Phe80. In addition, the hydroxyl group formed one hydrogen bond with Asp145 (Fig. 12). **4** exhibited great selectivity among more than 50 kinases and no obvious inhibition against multiple cytochrome P450 isoforms or hERG channels, and pharmacokinetic studies in the cyno variety indicated that **4** displayed low clearance, great exposure, and favorable oral bioavailability. Moreover, 4 significantly inhibited RB phosphorylation and tumor growth in the *CCNE1*-amplified OVCAR3 tumors [124].

7. Conclusion and Perspective

The discovery of CDKs' role in cell cycle regulation has prompted extensive research into CDK inhibitors as potential cancer treatments [137-156]. Approved CDK inhibitors, particularly those selectively targeting CDK4/6, have demonstrated significant efficacy and manageable toxicity, becoming the standard first-line therapy for breast cancer [157-163]. However, the development of resistance to CDK4/6 inhibitors poses a substantial challenge to treatment efficacy in breast cancer. Research into this resistance has identified CDK2 activation as a key factor. In response, researchers have developed CDK2/4/6 inhibitors and selective CDK2 inhibitors to combat CDK4/6 inhibitor resistance, offering

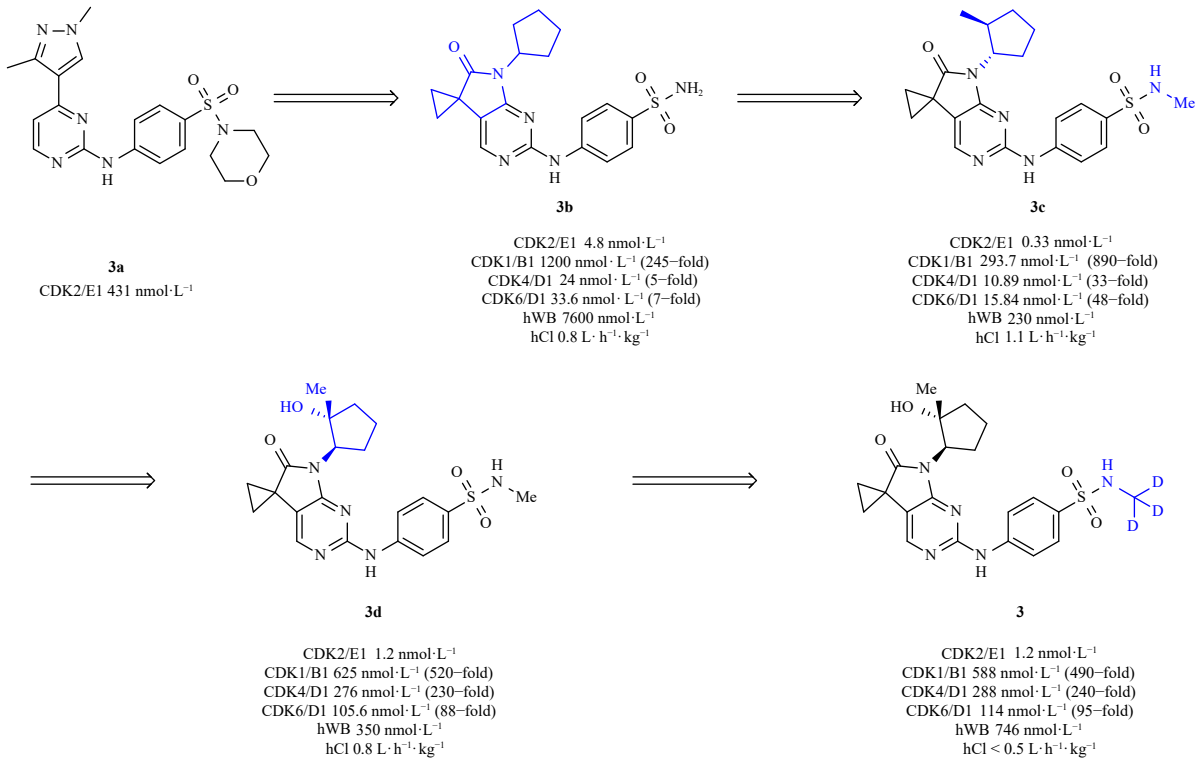


Fig. 10 Identification of Incyte's selective CDK2 inhibitor **3**.

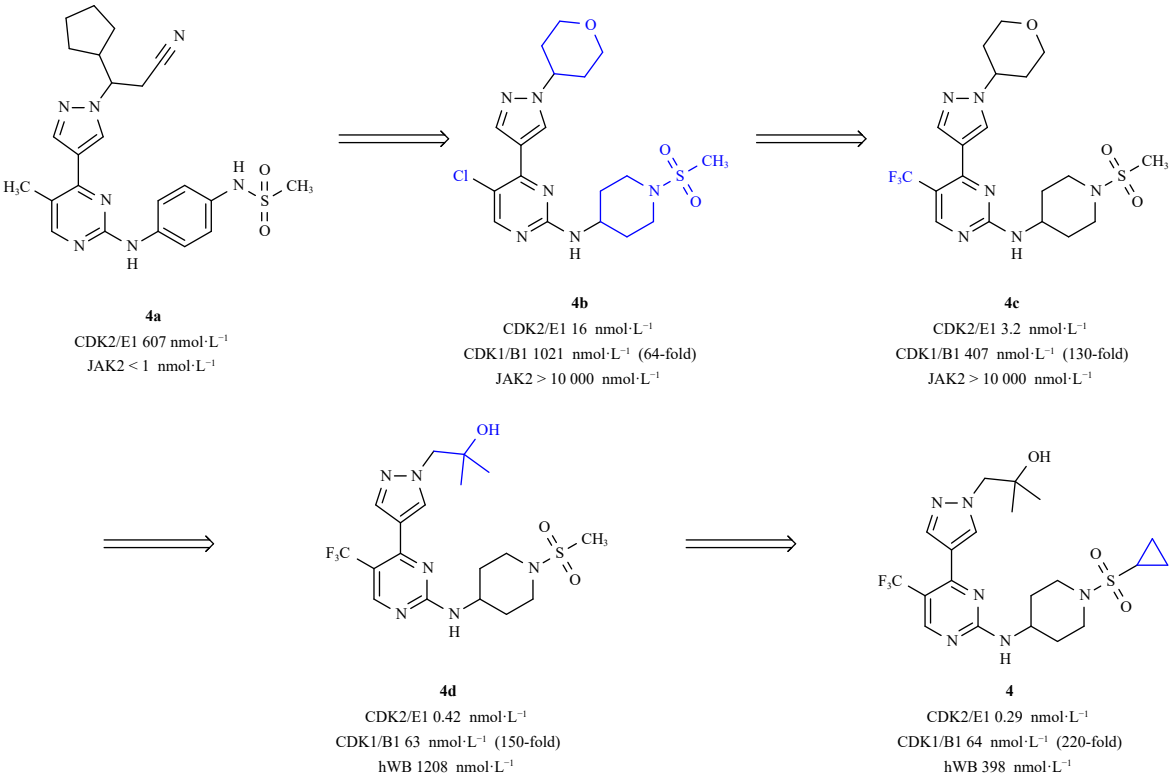


Fig. 11 Identification of Incyte's selective CDK2 inhibitor **4**.

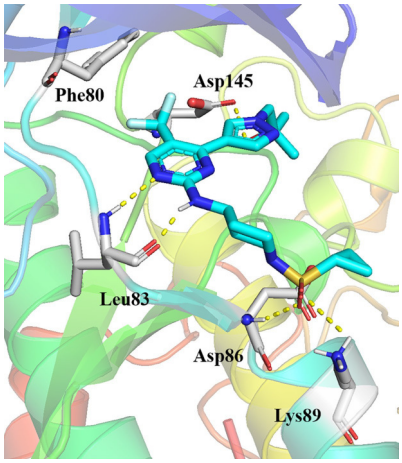


Fig. 12 Crystal structure of selective CDK2 inhibitor **4** with CDK2 (PDB: 8UV0).

a promising approach for treating *CCNE1*-amplified cancers [164-171].

The progression of CDK2/4/6 inhibitors through clinical trials has encountered challenges, with trials for PF-06873600 and NUV-422 being terminated in 2022. In contrast, selective CDK2 inhibitors have garnered increasing interest, with numerous such inhibitors entering clinical trials over the past two years. Compared to CDK2/4/6 inhibitors, selective CDK2 inhibitors potentially offer a safer treatment option for *CCNE1*-amplified cancers by eliminating the toxicity associated with CDK4/6 inhibition. In addition, the combination of a CDK2 inhibitor and a CDK4/6 inhibitor was more flexible than a CDK2/4/6 inhibitor in CDK4/6 inhibitor-resistant breast cancer. By optimizing the dosage of the CDK2 inhibitor and CDK4/6 inhibitor, a treatment schedule with potent efficacy and favorable toxicity was likely to be obtained [172-181].

In addition to targeting CDK2, inhibiting CDK7 also shows promise in overcoming CDK4/6 inhibitor resistance. Clinical trials have demonstrated the efficacy of combining the CDK7 inhibitor samuraciclib with fulvestrant in patients resistant to CDK4/6 inhibitors [182-185]. Notably, resistance mechanisms differ among CDK4/6 inhibitors, such as palbociclib and abemaciclib, with abemaciclib exhibiting significant effects on palbociclib-resistant breast cancer. This underscores the continued necessity for developing novel CDK4/6 inhibitors to address resistance to existing inhibitors. The emerging field of protein degradation in cancer therapy presents another avenue for overcoming resistance, particularly through CDK4/6 degradation, warranting further investigation. While most resistance mechanism studies have focused on CDK4/6 inhibitor monotherapy, patients typically receive combination therapy with endocrine treatments. Future research should emphasize resistance mechanisms in combination therapy to enhance clinical applications. In addition, the most mechanism studies of CDK4/6 inhibitors resistance focused the monotherapy of CDK4/6 inhibitors, but patients often received the combination of CDK4/6 inhibitors and endocrine therapy. Therefore, more mechanism studies should focus on the resistance to combination therapy, which might bring the better clinical application. Furthermore, many CDK inhibitors were derived from natural products, such as flavoalkaloids flavopiridol and riviciclib, indirubin derivatives AG-024322. Meanwhile, many natural products, such as icaritin, pristimerin, asparanin A, licochalcone B, juglone, could regulate activity or expression of CDKs and exhibit potent anticancer activity. Further exploration of natural products may yield novel CDK inhibitors and address limitations of existing inhibitors. In conclusion, the development of CDK inhibitors targeting the cell cycle remains a crucial strategy in cancer treatment [186-212].

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Declaration of competing interest

These authors have no conflict of interest to declare.

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