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ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ietp20

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To cite this article: Markéta Kovalová, Joseph Peter Baraka, Václav Mik, Radek Jorda, Lei Luo, Hao Shao & Vladimír Kryštof (2023) A patent review of cyclin-dependent kinase 7 (CDK7) inhibitors (2018-2022), Expert Opinion on Therapeutic Patents, 33:2, 67-87, DOI: 10.1080/13543776.2023.2195547

To link to this article: https://doi.org/10.1080/13543776.2023.2195547

Published online: 10 Apr 2023.

EXPERT OPINION ON THERAPEUTIC PATENTS
2023, VOL. 33, NO. 2, 67–87
https://doi.org/10.1080/13543776.2023.2195547

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REVIEW

A patent review of cyclin-dependent kinase 7 (CDK7) inhibitors (2018-2022)

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ABSTRACT

Introduction: Cyclin-dependent kinase 7 (CDK7) is a member of the CDK family of serine/threonine protein kinases and participates in the regulation of the cell cycle and mRNA transcription. CDK7 is emerging as a possible drug target in oncology and six exciting drug candidates have already undergone early evaluation in clinical trials.

Areas covered: This review examines CDK7 inhibitors as anticancer drugs reported in patents published in the online databases of the World Intellectual Property Organization and European Patent Office in the 2018–2022 period. This review provides an overview of available inhibitors, including their chemical structures, biochemical profile and stage of development.

Expert opinion: Small-molecule CDK7 inhibitors represent attractive pharmacological modalities for the treatment of various cancer types. Highly potent and selective inhibitors have been discovered and many of them show promising results in several preclinical cancer models. Developed compounds act on the kinase by various mechanisms, including traditional ATP competition, irreversible binding to tractable cysteine 312 outside the active site of CDK7, and induced protein degradation by proteolysis targeting chimeras. Ongoing preclinical research and clinical trials should reveal which strategy will provide the highest benefits.

ARTICLE HISTORY
Received 18 January 2023
Accepted 22 March 2023

KEYWORDS
CAK; cancer; cyclin-dependent kinase 7; kinase inhibitor; PROTAC

1. Introduction

Cyclin dependent kinases (CDKs) constitute a family of serine/threonine protein kinases that form active complexes with corresponding cyclins to regulate cell cycle transitions and transcription [1]. CDK7 associates with cyclin H and MAT1 to form the CDK-activating kinase (CAK) complex, directing cell cycle transitions by phosphorylating the T-loop of cell cycle CDKs, such as CDK1, 2, 4 and 6 [2,3]. CDK7 is also a component of the general transcription factor IIH (TFIIH), facilitating transcription initiation by phosphorylating the C-terminal domain (CTD) heptapeptide repeats of RNA polymerase II (RNAP II) at Ser5 and Ser7 residues [4,5]. In addition, CDK7 phosphorylates CDK9, a component of positive transcription elongation factor b (P-TEFb), which in turn, phosphorylates the Ser2 residue of the RNAP II CTD to allow productive transcription elongation [6].

CDK7 has been intensively pursued as anticancer drug target due to its dysregulated cell cycle control and transcription in cancer cells [2]. The overexpression of CDK7 has been observed in different cancer types, such as mantle cell lymphoma [7], breast cancer [8], multiple myeloma [9], colorectal cancer [10], gastric cancer [11], ovarian cancer [12], oral squamous cell carcinoma [13], glioblastoma [14], and hepatocellular carcinoma [15], and is correlated with tumor aggressiveness and a poor prognosis. CDK7 has also been found to directly phosphorylate or regulate the expression of oncogenic transcription factors, such as c-Myc [16], androgen receptor [17] and estrogen receptor [18]. CDK7 inhibitors have shown efficacy in animal models of most of the abovementioned cancers. In addition, CDK7 inhibition could trigger immune-response signaling [19] by inducing DNA replication stress and genome instability and synergize with anti-PD-1 therapy by inhibiting c-Myc activity to suppress PD-L1 expression [20]. These findings suggest that CDK7 inhibitors, as single agents or combined with other anticancer agents, have the potential to be translated into novel therapeutics.

In addition to cancer, CDK7 is involved in the pathogenesis of autosomal dominant polycystic kidney disease (ADPKD) [21]. Cellular metabolism is altered in ADPKD patients and is driven by super-enhancers (SE)-associated genes. CDK7 is required for the assembly and maintenance of SEs, rendering it a potential target for the treatment of ADPKD. CDK7 is upregulated in ADPKD patients, and its expression is correlated with the disease severity. The inhibition of CDK7 delayed abnormal cyst growth and slowed disease progression in ADPKD mouse models [22]. These results suggest that CDK7 is a promising therapeutic target for ADPKD treatment.

The discovery of highly selective CDK7 inhibitors has been challenging considering that there are 20 members in the CDK

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Article highlights

- CDK7 is a promising therapeutic target for the treatment of cancer.
- Small molecule inhibitors with various mechanisms of action are exploited, including ATP competitors, covalent binders and PROTACs
- Selective CDK7 inhibitors have shown encouraging results in preclinical cancer models.
- Six CDK7 inhibitors have entered phase I/II clinical trials and four of them are still active.
- This review covers CDK7 modulators published in the peer-reviewed literature and patents over the past 5 years

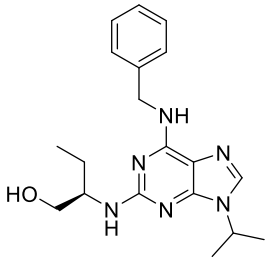
family and that the ATP binding site is highly conserved. Highly selective CDK7 inhibitors have been identified over the past few years, and six of them have entered clinical trials. In this review, we summarize all the efforts in the field, including CDK7 inhibitors reported both in the peer-reviewed literature and patent applications. In addition, we briefly discuss the rationale for and future challenges in developing CDK7 inhibitors as therapeutic agents.

2. Overview of CDK7 inhibitors

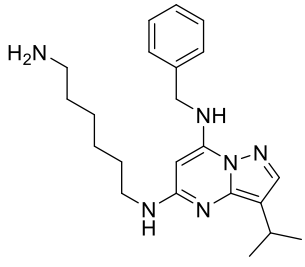
There has been a long-lasting interest in pursuing CDK7 as a therapeutic target, and the selective CDK7 inhibitors reported in the peer-reviewed literature have inspired the discovery of many of these reported in recent patents applications, especially the BS-181 and the THZ1 series. Over the last few years, several reviews covering inhibitors of CDK7 and other transcriptional CDKs have been published [23–25]. In this section, we summarize the CDK7 inhibitors reported in the peer-reviewed literature and provide updates regarding their clinical development (Table 1).

The first identified CDK inhibitors possess relatively low selectivity and interact equipotently with more CDKs, including cell cycle regulating CDK1 and CDK2 and transcriptional CDK7 and CDK9. Suffering from polypharmacology, the anticancer activity of these compounds could not be clearly linked to a single kinase. To identify a potent and selective CDK7 inhibitor, Ali et al. started with roscovitine (**1**), a first-generation pan-CDK inhibitor, using a computational approach [26]. Purine was replaced by pyrazolo[1,5-*a*]pyrimidine based on computational calculations of the free solvation energies of several heterocyclic rings. Molecular docking suggested that there was extra space next to the ethyl substituent, which could be used to improve CDK7 specificity. Removing the hydroxyethyl moiety and replacing the remaining propyl side chain with a 1,6-diaminohexyl substituent resulted in the selective CDK7 inhibitor BS-181 (**2**) with an IC_{50} of 21 nM. BS-181 only inhibited CDK2 with an IC_{50} less than 1 μM when tested against other CDKs and 69 additional kinases, with a 35-fold higher selectivity for CDK7 over CDK2. BS-181 inhibited the growth of different types of cancer cells with IC_{50} values ranging from 11.7 to 37 μM. In MCF-7 cells, BS-181 inhibited RNAP II CTD Ser2/5 phosphorylation, induced cell apoptosis and arrested the cell cycle at the G1 phase [26]. BS-181 inhibited the growth of breast cancer MCF-7 and gastric cancer BGC823 xenografts in mice via intraperitoneal injection [27].

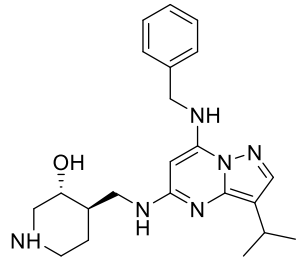
Further optimization of this scaffold led to the orally bioavailable CDK7 inhibitor samuraciclib (**3**, CT7001, ICEC0942) [10]. Samuraciclib inhibited CDK7 with an IC_{50} of 40 nM and was 45-, 15-, 230-, and 30-fold more selective for CDK7 over CDK1, CDK2, CDK5, and CDK9, respectively. When screened against a panel of 117 diverse kinases at 10 μM, an additional five kinases, ERK8, STK33, CHK2, CLK2, and PHK, were inhibited to a similar extent as CDK2. Samuraciclib inhibited the growth of 60 cell lines with a median GI_{50} of 0.25 μM. It also decreased RNAP II CTD Ser2/5/7, CDK1 Thr161 and CDK2 Thr160 phosphorylation in a dose- and time-dependent manner in HCT116 colon cancer cells, resulting in an enrichment of cells in the G2/M phase. Treatment with samuraciclib for 24 hours induced caspase 3/7 and PARP cleavage,



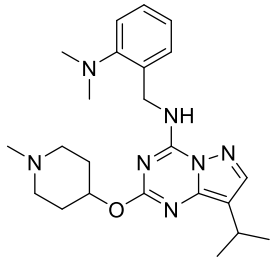
1 (Roscovitine)



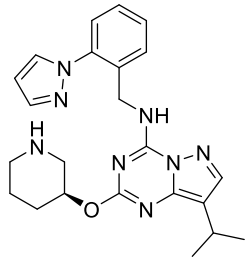
2 (BS-181)



3 (Samuraciclib, CT7001, ICEC0942)



4 (LDC3140)



5 (LDC4297)

Table 1. CDK7 inhibitors in clinical trials.

Compound	Company	Trial Number	Condition/disease	Clinical Phase Status
SY-1365 (Mevociclib)	Syros Pharmaceuticals	NCT03134638	Advanced solid tumor, ovarian and breast cancer.	I; terminated (2021; business reasons)
Samuraciclib (CT7001, ICEC0942)	Carrick Therapeutics	NCT03363893	Advanced solid malignancies, TNBC, CRPC, $HR^+/HER2^-$ BC	I/II; active, not recruiting
LY3405105	Eli Lilly and Company	NCT03770494	Solid tumor, TNBC, ovarian cancer, soft tissue sarcoma, epithelioid sarcoma, bladder cancer	I; terminated (2021; lack of efficacy)
SY-5609	Syros Pharmaceuticals	NCT04247126	Advanced solid tumors, breast cancer, SCLC, pancreatic cancer	I; active not recruiting
		NCT04929223	Metastatic colorectal cancer	I; recruiting
Q901	Qurient Company	NCT05394103	Advanced solid tumors, Advanced or metastatic ovarian cancer, CRPC, endometrial cancer, $HR^+/HER2^-$ BC, colorectal cancer, SCLC, pancreatic cancer	I/II; recruiting
XL102 (AUR102)	Exelixis	NCT04726332	Solid tumors, ovarian cancer, TNBC, HR^+ BC, mCRPC	I; recruiting

Notes: TNBC – triple-negative breast cancer; $HR^+/HER2^-$ BC - hormone receptor positive/HER2 negative breast cancer; CRPC – castration-resistant prostate cancer; SCLC – small cell lung cancer; mCRPC – metastatic castration-resistant prostate cancer.

indicating programmed cell death. In addition, such treatment showed antitumor effects either as a single agent in xenografts of both breast and colorectal cancers or combined with tamoxifen in ER^+ breast cancer xenografts [10].

Recently, a high-resolution cryo-EM structure of human CAK complexed with samuraciclib (PDB ID: 7B5O and 7B5Q) was resolved [28], which explained its selectivity for CDK7 over CDK2 along with the CDK2-samuraciclib crystal structure previously reported (PDB ID: 5JQ5) [29]. The pyrazolopyrimidine core of samuraciclib formed hydrogen bonds with the hinge residue in a similar fashion, Met94 in CDK7 and Leu83 in CDK2 (Figure 1). However, the conformations of both six-ring-bearing substituents of samuraciclib were vastly different. The benzylamine moiety adopted a "ring-up" conformation when bound to CDK7 and a "ring-down" conformation when bound to CDK2. The difference in one residue (Ile10 in CDK2/Leu18 in CDK7) and a slight shift of the protein backbone near the C-terminus of the interdomain linker (around CDK2 Leu83/CDK7 Met94) might account for the distinct benzylamine orientation. The hydroxy group of the 3-hydroxypiperidine ring pointed toward the active site in CDK7 and adopted an OH-in conformation, whereas it pointed toward the solvent and a neighboring β-strand in CDK2 with an OH-out conformation [28].

The phase 1 clinical trial results of samuraciclib in patients with advanced solid tumors were disclosed at the ESMO Congress 2021 [30]. Neutropenia and significant myelosuppression associated with other CDK inhibitors were not observed. Once daily, 240 mg and 360 mg were determined as clinically relevant doses, with 360 mg once per day as the recommended phase II dose. Fifty-seven percent (25/44) of RECIST-evaluable patients exhibited evidence of disease control. In the expansion cohort, 12 of 20 patients with TNBC had stable disease. In another single-arm cohort, 31 patients with advanced $HR^+/HER2^-$ BC who progressed on their prior CDK4/6 received both samuraciclib and fulvestrant, and the RECIST evaluation showed evidence of a reduction in the tumor burden [31]. The treatment was generally well tolerated with mild adverse drug effects. Samuraciclib showed an acceptable pharmacokinetic and safety profile with evidence of antitumor activity [30]. Based on the promising preclinical and clinical results, a phase 2 clinical trial will be jointly sponsored by Carrick and Menarini to evaluate the combination of samuraciclib and Menarini's oral estrogen receptor degrader elacestrant in patients with CDK4/6i-resistant HR^+ BC in 2023.

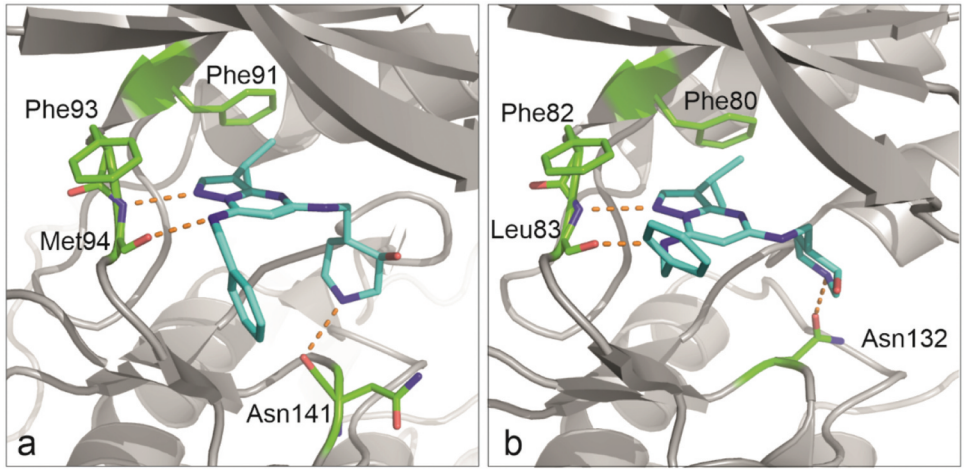


Figure 1. (a) Cryo-EM structure of the CAK-samuraciclib complex (PDB ID: 7B5Q); (b) crystal structure of CDK2-samuraciclib (PDB ID: 5JQ5). The kinases are shown as gray cartoon, the inhibitors are cyan. Nitrogen and oxygen atoms are shown in blue and red, respectively. Hydrogen bonds are denoted by orange dashed lines. Key residues are presented in the stick representation. The images were generated by PyMOL.

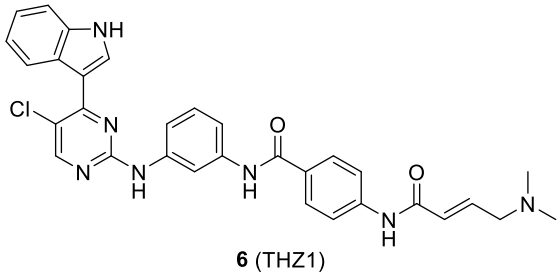
LDC3140 (**4**) and LDC4297 (**5**) were identified from a medicinal chemistry campaign by screening a kinase-biased library centered on BS-181 and other known ATP-competitive kinase inhibitors against CDK7 and a subsequent synthesis of 600 analogs [32]. Both compounds inhibited CDK7 with an IC_{50} less than 5 nM. LDC3140 was over 770-fold selective for CDK7 over the other CDKs tested, including CDK1/2/4/6/9. LDC4297 exhibited a much lower specificity for CDK7 then for the other CDKs, particularly CDK2 (IC_{50} = 6 nM) and CDK1 (IC_{50} = 54 nM). Both compounds decreased RNAP II phosphorylation at Ser5/7 and showed distinct physiological responses at relatively low and high concentrations [32].

THZ1 (**6**) was the first covalent CDK7 inhibitor identified from a cell-based screening and kinase selectivity profiling of an in-house ATP-site-directed kinase inhibitor library by the Gray group [33]. THZ1 inhibited CDK7 by forming a covalent bond with Cys312 located outside the ATP binding site using its acrylamide moiety, which contributed to its activity to a large extent. THZ1 inhibited CDK7 in a time-dependent manner with an IC_{50} of 238 nM at 1 mM ATP and inhibited CDK12/13 (IC_{50} = 893 and 628 nM, respectively) covalently due to a conserved cysteine at a similar position [34]. Molecular docking showed that the aminopyrimidine of THZ1 formed hydrogen bonds with the hinge region residue Met94, and the chlorine atom interacted with the phenylalanine gatekeeper residue (Phe91) [33]. The acrylamide moiety was located in close proximity to Cys312 to form a covalent bond. This model was confirmed by the recently solved cryo-EM structure of the CAK-THZ1 complex (PDB ID: 6XD3, Figure 2a) [35].

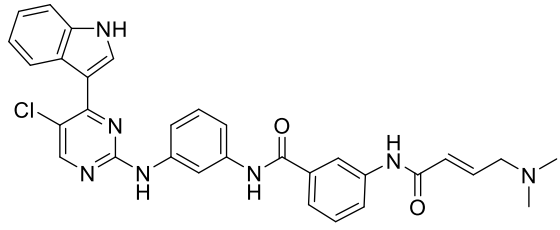
THZ1 was screened against a diverse panel of over 1,000 cancer cell lines and had an IC_{50} less than 200 nM among 53% of these tested. A bioinformatic analysis showed that these sensitive cell lines were characterized by the overexpression of (proto-) oncogenic transcription factors and factors involved in RNAP II-driven transcriptional regulation. THZ1 efficiently killed T-cell acute lymphoblastic leukemia (T-ALL) cell lines with misregulation of T-cell lineage-specific transcription factors at low nM and induced cell apoptosis via the downregulation of the antiapoptotic proteins MCL1 and XIAP. THZ1 also reduced RNAP II Ser2/5/7 phosphorylation and CDK1/2 T-loop phosphorylation and arrested the cell cycle at the G2 phase. THZ1 reduced the global mRNA levels at a high dose, whereas it preferentially decreased only a subset of genes at a low dose, especially *RUNX1*, which contains a large SE domain [33]. THZ1 showed efficacy in cancers addicted to oncogenic transcription factors and SE-associated genes, including T-ALL [33], SCLC [36], melanoma [37], T-cell lymphomas and multiple myeloma xenografted models [38]. However, THZ1 suffered from being a substrate of ABC drug transporters and poor metabolic stability ($T_{1/2}$ of 45 min in mouse plasma, CL = 129 mL/min/kg), limiting its *in vivo* investigations.

Moving the acrylamide of THZ1 from the *para*- to *meta*-position on the benzamide resulted in THZ2 (**7**), which retained selective CDK7 inhibition and improved the half-life 5-fold *in vivo*. In addition, THZ2 blocked tumor growth in a TNBC cell line and patient-derived xenograft (PDX) models [39].

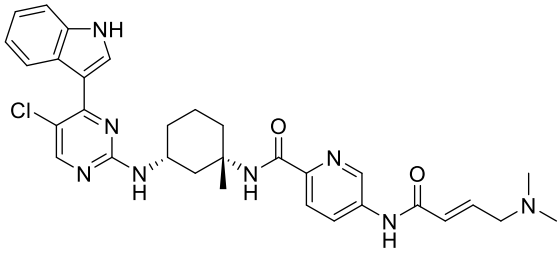
The iterative optimization of the linker between the pyrimidine ring and covalent warhead in THZ1 led to a more metabolically stable analog, SY-1365 (**8**, mevociclib), which had the lowest plasma clearance of 5.6 mL/min/kg and highest k_{inac}/K_i of 0.131 $\mu M^{-1}s^{-1}$ in this series [40]. The docking of SY-1365 to CDK7 demonstrated improved shape complementarity and possible stronger hydrophobic interactions between



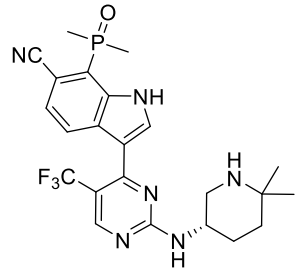
6 (THZ1)



7 (THZ2)



8 (SY-1365, Mevociclib)



9 (SY-5609)
(Patented as 101)

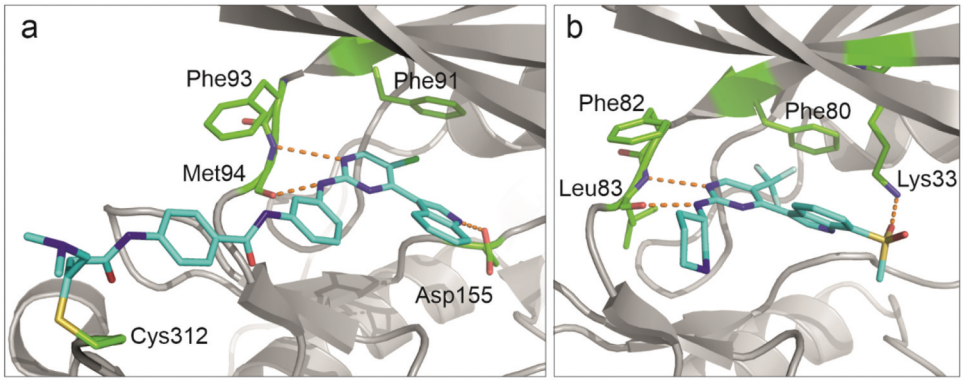


Figure 2. (a) Cryo-EM structure of the CAK-THZ1 complex (PDB ID: 6XD3); (b) crystal structure of SY-5609 analog in CDK2 (PDB ID:7RA5). The kinases are presented as gray cartoon, the inhibitors are cyan. Nitrogen, oxygen and sulfur atoms are shown in blue, red and yellow, respectively. Hydrogen bonds are denoted by orange dashed lines. Key residues are presented in the stick representation. The images were generated by PyMOL.

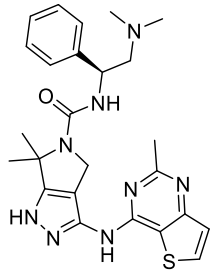
the chiral cyclohexane-1,3-diamine ring and the solvent accessible surface of CDK7, which likely contributed to the increased potency compared with that of THZ1. SY-1365 inhibited CDK7 with an IC_{50} of 369 nM at 2 mM ATP without compound preincubation, whereas the IC_{50} of the other CDKs was 2 mM or greater, including CDK2, CDK9 and CDK12. Seven other kinases (out of 468) were inhibited greater than 90% by SY-1365 at 1 µM in a kinome screen.

The antiproliferative activity of SY-1365 was evaluated in 386 human cell lines representing 26 cancer types. Most of them showed significant growth inhibition and cell killing in the nanomolar range. SY-1365 inhibited RNAP II CTD phosphorylation at Ser2/5/7 and CDK2 Thr160 phosphorylation in a dose- and time-dependent manner in several cell lines. SY-1365 preferentially downregulated SE-related oncogenic transcription factor genes, such as *MYC*, and the most significantly enriched pathways affected by SY-1365 were cell cycle-related and DNA damage repair-related, especially those related to homologous recombination repair and mismatch repair. SY-1365 showed antitumor activities in multiple xenograft models at a dose of 30 or 40 mg/kg once or twice per week, including acute myeloid leukemia (AML; Kasumi-1 and ML-2), ovarian (OVCAR3 and a patient-derived model OV15398), and TNBC PDX models [41–44].

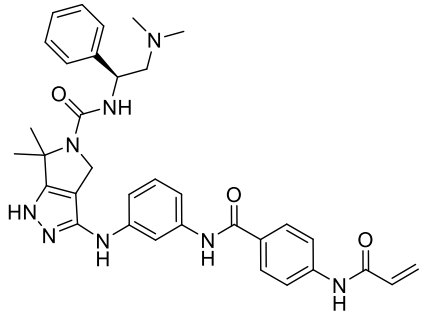
In May 2017, a phase I clinical trial of SY-1365 was initiated with expansions in ovarian and breast cancer [45]. SY-1365 showed linear pharmacokinetics and manageable adverse events in a dose regime ranging from 2–64 mg/m^2, and target engagement was proven by the dose-dependent regulation of gene expression in PBMCs [46]. In the expansion portion, SY-1365 was evaluated as a single agent in patients with high-grade serous ovarian cancer (HGSOC) and relapsed clear cell ovarian cancer and in combination with other anticancer agents in patients with HGSOC and metastatic CDK4/6 inhibitor-resistant HR$^+$ BC. Peri-infusional adverse events were observed due to the IV administration routine, which could be reduced by lowering the doses and extending the infusion times. The best response observed across the expansion cohorts was stable disease in 42% and 64% in the single-agent and combination cohorts, respectively [47]. Based on preclinical and clinical data, Syros believes that higher doses or more frequent dosing will be needed for clinical activity, which could create an overly burdensome dosing schedule for patients. Syros decided to discontinue the clinical development of SY-1365 and prioritize its oral non-covalent CDK7 inhibitor SY-5609 (**9**) [48] patented in 2020 [49]. SY-5609 showed excellent selectivity toward CDK7 (binding of its analog to CDK7 is shown in Figure 2b) and *in vitro* and *in vivo* potency [48]. Based on these promising data, SY-5609 entered a phase I clinical trial (NCT04247126). Since it was patented during the period covered by this paper, SY-5609 is described in detail in the patent section below (chapter 3.2.).

The covalent warhead of THZ1 (**6**) was used in the further development of other CDK7 inhibitors. It was hybridized with a pyrrolidinopyrazole core from the known PAK4 inhibitor PF-3758309 (**10**), which impacts CDK7 as an off-target [50,51]. The hybridization led to YKL-1-116 (**11**) [52], which retained the potent inhibition of CDK7 (IC_{50} = 7.6 nM) but suboptimal antiproliferative activity in cells. Further optimization of the linker length between the aminopyrazole core and covalent warhead resulted in YKL-5-124 (**12**), with similar potency against CDK7 (IC_{50} = 9.7 nM), but higher potency against cancer cells [34]. YKL-5-124 is inactive against CDK12/13 up to 100 µM and more than 130-fold selective for CDK7 over CDK2/9 (IC_{50} of 1.3 and 3.02 µM, respectively). Its high selectivity was proven by KiNativ profiling, and CDK7 was the only target bound by 1 µM YKL-5-124 in Jurkat extracts. Molecular docking studies showed that the 3-aminopyrazolopyrrolidine core formed hydrogen bonds with the hinge region residues Asp92 and Met94, and two additional hydrogen bonds with Lys41 and Asn141 were observed. The acrylamide moiety of YKL-5-124 was positioned in proximity to residue Cys312 to form a covalent bond. The treatment of HAP1 cells with YKL-5-124 inhibited the phosphorylation of CDK1 Thr161 and CDK2 Thr160, caused cell arrest at the G1/S transition, and downregulated the expression of E2F-driven genes. In contrast to THZ1, treatment with YKL-5-124 did not induce cell apoptosis or affect RNAP II CTD phosphorylation [34].

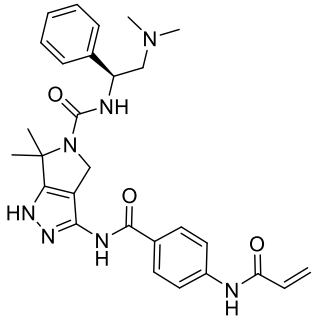
Compound B2 (**13**) was a potent CDK7 inhibitor scaffold-hopped from YKL-5-124 [22]. The aminopyrazole moiety of YKL-5-124 was retained to maintain the hydrogen bonds with the hinge region and the benzoyl motif as the linker to attach the covalent warhead. A pyridine ring was introduced to form a hydrogen bond with Asn142. Molecular docking



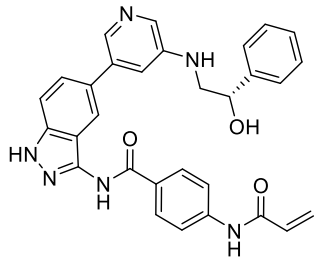
10 (PF-3758309)



11 (YKL-1-116)



12 (YKL-5-124)

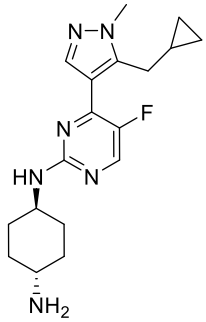


13 (B2)

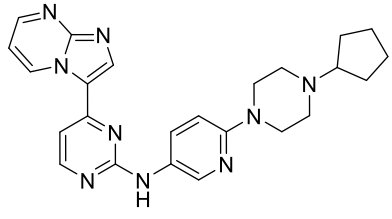
suggested that the modification of pyridine at C5 should be tolerated since there was enough space around this region. The iterative optimization of the substituents at the pyridine C5 position and the addition of the Michael acceptor moiety resulted in the most potent compound B2. It inhibited CDK7 with an IC_{50} value of 4 nM and showed over 100-fold selectivity over the CDKs tested. Compound B2 was further assessed for selectivity using a 51 kinase diversity panel, and nine of them were inhibited by more than 50% at 1 μM, especially GSK3β with 99% inhibition. B2 inhibited GSK3β with an IC_{50} of 148 nM and was 37-fold selective for CDK7 over GSK3β. Compound B2 had acceptable pharmacokinetic properties with a $T_{1/2}$ of 3.44 h and good exposure after subcutaneous administration. B2 showed efficacy in an *in vitro* MDCK cyst model, an *ex vivo* embryonic kidney cyst model and an ADPKD mouse model with minimal toxicity.

Compound A86 (**14**) was discovered in a cell-based screen as a potent CKIα inhibitor, but it also binds to CDK7 and CDK9 with K_D values of 0.34 nM and 5.4 nM, respectively [53]. A86 effectively killed AML cells by stabilizing of p53 and suppressing the transcription of SE-driven oncogenes. A86 showed efficacy in MLL-AF9 and several patient-derived AML xenograft models.

Compound 9q (**15**) is a dual CDK7/9 inhibitor optimized from a pan-selective CDK inhibitor. Compound 9q inhibited CDK7 and CDK9 with IC_{50} values of 55 nM and 38 nm, respectively. However, it also weakly inhibited CDKs 1–6 to a lesser extent [54]. Compound 9q inhibited the growth of a panel of



14 (A86)



15 (9q)

cells with a low micromolar IC_{50}. This compound reduced the phosphorylation of RNAP II Ser2/5 and induced cell apoptosis in MV4–11 cells, arresting the cell cycle at the sub-G1 phase.

Recently, the preclinical data of several other promising CDK7 inhibitors were presented, but their structures have not yet been disclosed. One of them is Q901, a highly selective CDK7 inhibitor developed by the Korean company Qurient. Q901 triggered G1 cell cycle arrest in cells and inhibited tumor growth in an ER^+ BC xenograft model, CDK4/6 inhibitor-resistant PDX model, and many other solid tumors [55,56]. Q901 was evaluated in a broad spectrum of solid tumor cell lines and was found to be more potent in TP53 wild-type cancer cells than in TP53 mutant cells. POLR2A was identified as a potential pharmacodynamic marker due to a dose-response increase in POLR2A expression upon Q901 treatment and a correlation with the tumor growth inhibition rate [57]. Q901 is currently undergoing a phase 1 clinical trial in adult patients with advanced solid tumors via intravenous infusion and selected advanced solid tumors with a cohort expansion at the recommended phase 2 dose (NCT05394103).

XL102, formerly known as AUR102, is a potent, orally bioavailable and highly selective covalent CDK7 inhibitor [58] that was discovered by Aurigene and is currently developed by joint efforts with Exelixis. XL102 induced cell death in various cancer cell lines and caused tumor regression in multiple xenograft models. XL102 under investigation in a phase 1 clinical trial as a single agent and in combination in patients with advanced solid tumors (QUARTZ-10, NCT047263321), including HR^+ BC, TNBC, epithelial ovarian cancer , and mCRPC. The preliminary data from the dose-escalation stage of the trial showed that XL102 reached its T_{max} within 1–3 hours and had a half-life of 5–9 hours. XL102 was well tolerated at the doses evaluated, and treatment-emergent adverse events were observed at high doses but were low grade and reversible. No objective responses were observed at the data cutoff, and patients with stable disease remained in the study. XL102 will be further evaluated in patients in a single-agent dose-escalation cohort, a tumor-specific cohort and a combination cohort [59].

QS1189 is a pyrazolo-triazine-based inhibitor discovered by Qurient, the originator of clinical candidate Q901. QS1189 inhibits CDK7 with an IC_{50} of 15 nM, but it also shows similar inhibition of other CDKs, including CDK16, CDK2 and CDK5 [7]. QS1189 inhibited the growth of mantle cell lymphoma (MCL) cells with IC_{50} values between 50 and 250 nM. Similar to other CDK7 inhibitors, QS1189 decreased RNAP II CTD Ser2/5/7 phosphorylation and downregulated genes involved in transcriptional regulation and the cell cycle in MCL cells. QS1189 induced G2/M cell cycle arrest and cell apoptosis as evidenced by cleaved PARP and Caspase 3.

YPN-005 is highly selective for CDK7 from Yungjin Pharmaceutical with an IC_{50} of 31 nM and inhibited 7 other kinases over 90% at 1 μM in a 468 kinase panel screen, including CDK13, CDK19, CSNK1A1, CSNK1D, CSNK1E, MAPK15, and MAPK10 [60]. YPN-005 showed potent antiproliferative effects in SCLC cells, cisplatin- or etoposide-resistant cells, and organoids derived from SCLC patients. Similar to other CDK7 inhibitors, YPN-005 treatment significantly decreased the phosphorylation of the RNAP II CTD and significantly inhibited tumor growth in xenograft models established from the SCLC cell line H209 and cisplatin- or etoposide-resistant H209 cells. Another study [61] showed its antileukemic potential both *in vitro* and *in vivo*. YPN-005 induced apoptosis and suppressed the expression of c-MYC, FLT3 and STAT5. An *ex vivo* proliferation inhibition assay in primary leukemic cells also showed higher sensitivity in AML cells with FLT3-ITD mutation.

Finally, UD-017 is a potent CDK7 inhibitor with an IC_{50} of 16 nM from Ube Industries that is at least 300-fold more selective for CDK7 over other CDKs [62]. The compound was tested in a panel of 313 kinases, and only 4 other kinases (AMPKα2/β1/γ1, AMPKα1/β1/γ1, haspin, and GSK3β) were inhibited over 90% at 1 μM, but the IC_{50} values were hundreds of nM. UD-017 potently inhibited the growth of a wide range of cancer cells, and c-Myc expression correlated well with its antiproliferative activities [63]. Specifically, UD-017 inhibited the proliferation of the HCT-116 cell line (GI_{50} = 19 nM), and its *in vitro* application led to a decrease in RNAP II CTD, CDK1 and CDK2 phosphorylation, and the induction of apoptosis. It showed *in vivo* efficacy in HCT-116 xenografts alone and in combination with 5-FU [64,65]. UD-017 also strongly inhibited tumor growth in multiple PDX models, including non-small cell lung cancer (LXFL1121), pleura mesothelioma (PXF541), gastric cancer (GXA3067) and sarcoma (SXFS117) [66].

Combinations of several drugs are often used and have been shown to be beneficial in cancer treatment.To date, CDK7 inhibitors have shown *in vitro* and *in vivo* synergistic effect in combination with BH3 mimetics [9,40], BET inhibitors [67], antiestrogens [10,58], p53-activating agents [52] and immunotherapy [19,20]. This strategy has also been tested in the clinical trials particularly for samuraciclib, SY-1365 and SY-5609. Abovementioned treatment strategies have already been reviewed in detail in several papers [5,23,24].

3. New patent literature concerning CDK7 inhibitors

The documents were retrieved from the online databases of the World Intellectual Property Organization (www.wipo.int) and European Patent Office (espacenet.com) and cross-checked in the databases of the American Chemical Society (scifinder.cas.org) and Elsevier (reaxys.com). Duplicate and irrelevant documents not covering small-molecule inhibitors were removed manually, and the remaining patents were sorted according to the chemical similarity of the described compounds. In some cases, the subject compounds have clear similarities to existing agents, and the patents cover only slightly modified analogs that bind CDKs in the same manner. More often, the similarity is less obvious, but at least some structural motifs are conserved.

3.1. THZ1 and THZ2 analogs

The discovery of THZ1 (**6**), the first covalent CDK7 inhibitor, has inspired many researchers, including the team at Chongqing Medical University, who disclosed a series of eight analogs (e.g. example **16**) in which the indole moiety of THZ1 was replaced with various anilines [68]. Further modifications (e.g. addition of the methoxy or methyl group) were introduced on the distal phenyl ring bearing a warhead for covalent attachment to the target protein [68]. All compounds showed similar inhibitory activities on CDK7 at a 200 nM

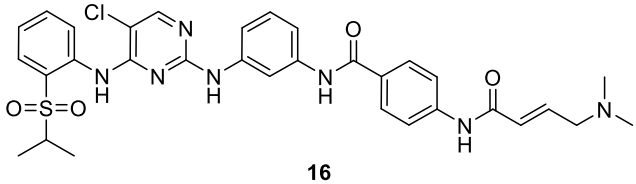
concentration, reaching more than 97%, comparable to THZ1 used as a positive control. The compounds also inhibited the proliferation of the human cancer cell lines MDA-MB-231 and A549 with calculated IC_{50} values below 25 nM.

Encouraged by the striking selectivity of THZ1 and especially THZ2 (**7**), in recent years, several companies have focused on 3-pyrimidin-4-yl-indoles and isosteric 3-pyrimidin-4-yl-pyrrolo[2,3-*b*]pyridines. In this respect, Longtaishen Pharmaceutical Technology Company published a document protecting THZ2 derivatives bearing an additional chain at the benzene ring distal to indole [69]. Compound **17** exhibited interesting inhibitory activity against CDK7 (IC_{50} = 6 nM). In addition, Ancureall Pharmaceuticals Company disclosed THZ2 analogs, in which indole is attached reversely and further modified by carboxamide function [70]. Their set of compounds was tested only to determine the antiproliferative potential in the MOLM-13 cell line. Compound **18** exhibited improved antiproliferative activity (IC_{50} < 1 nM) compared to THZ1 (IC_{50} = 1–10 nM). Information regarding potency or selectivity toward CDK7 was not presented, but the structural similarity to the parental inspiration is obvious.

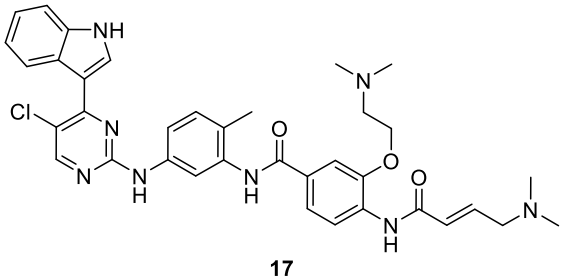
Suzhou Sinovent Pharmaceutical Technology presented set of SY-1365 (**8**) analogs that lacked typical methylsulfonyl or dimethylfosforyl functions [71–73]. Compound **19** displayed CDK7 IC_{50} of 1.06 nM without preincubation, and the IC_{50} decreased below 0.5 nM after 60 minutes. No additional data regarding it selectivity or *in vitro* and *in vivo* potency were shown [73].

One of the most active and successful companies focusing on research investigating pyrimidinylindole derivatives is Syros Pharmaceuticals, the originator of the clinical candidate SY-1365 (**8**) (see Table 1). They published two patents in 2019 describing compounds related to THZ1 and SY-1365, both significantly simplified [74,75]. Most of the presented compounds exhibited great selectivity toward CDK7 with IC_{50} values below 30 nM and IC_{50} values ≥ 500 nM for the other tested kinases, including CDK2, CDK9, and CDK12. All compounds were tested *in vitro* on ovarian and TNBC cell lines; the most potent compounds blocked their proliferation at < 100 nM concentrations. Another large set consisting of 268 compounds was disclosed in 2021 [76]. The compounds showed a wide range of selectivity and potency. For example, **20** effectively inhibited CDK7 (IC_{50} < 20 nM), displayed strong selectivity against CDK2/9/12 (IC_{50} > 5 μM) and exhibited nanomolar inhibition of proliferation of HCC70 and A673 cell lines.

Importantly, Syros Pharmaceuticals presented another clinical candidate, SY-5609 (**9**). The synthesis, preclinical and first clinical data are covered in several patents [49,77–79]. SY-5609 showed excellent selectivity toward CDK7 among the tested kinases. The K_D of SY-5609 was 0.065 nM, and the selectivity was determined as a ratio of $K_i/K_{D\ (CDK7)}$ with values of 40,000, 13,000, and 15,000 for kinases CDK2, CDK9, and CDK12, respectively. SY-5609 was screened against 485 kinases at a 1 μM concentration; the compound inhibited only 9 kinases ≥ 70% (including CDK13, CDK16, CDK17, and CDK18) [48]. The compound was shown to be effective *in vivo* in several PDX, including TNBC, SCLC, and HGSOC. The compound induced at least 50% tumor growth inhibition (TGI) in all models, and in more than half of the models, it led to more than 95% TGI without any evidence of regrowth for 21 days after the last dose. Due to positive outcomes in preclinical *in vivo* studies and its great tolerability, SY-5609 entered phase I clinical trials for advanced solid tumors as a single agent and HR^+ breast



16
(Patented as I-1)



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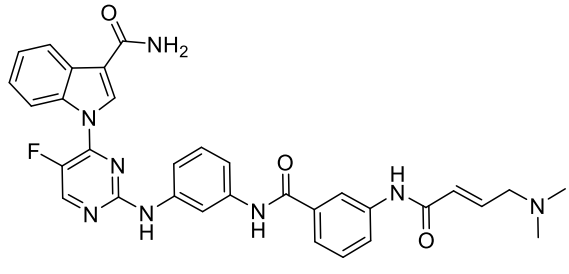
(Patented as 16-31)



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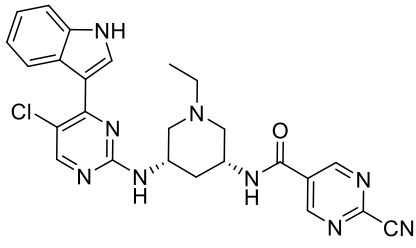
(Patented as 32)



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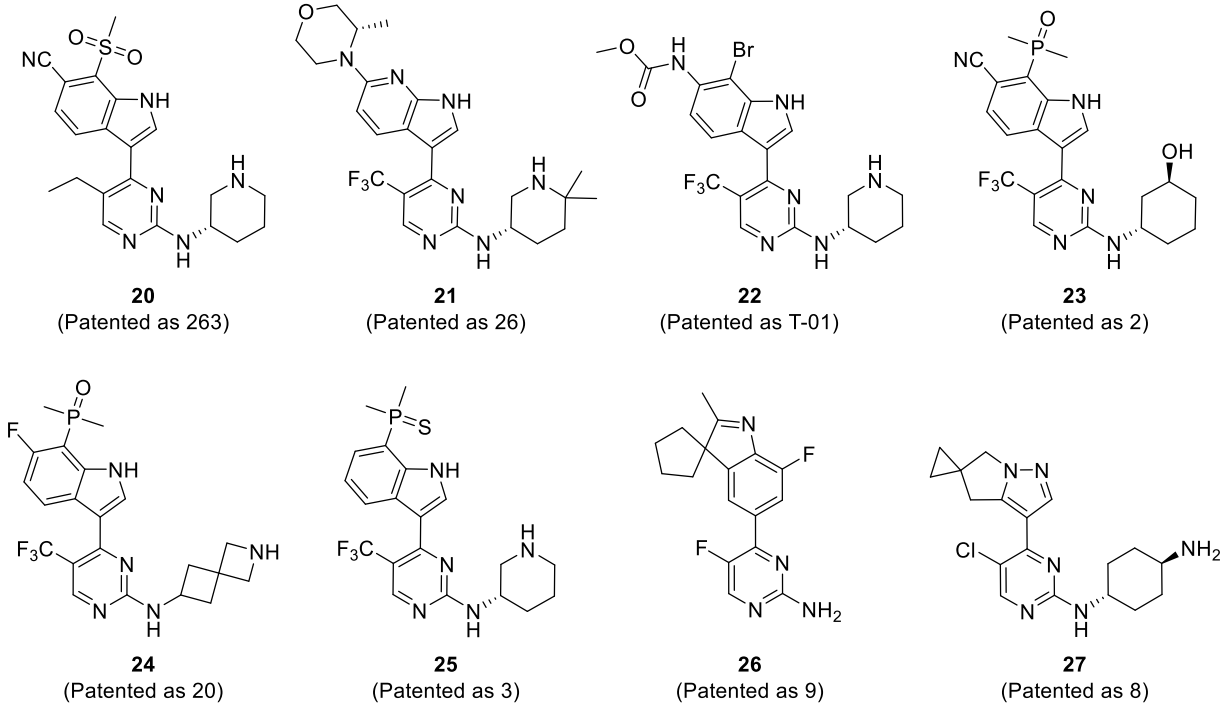
(Patented as SZ-015093)



cancer in combination with fulvestrant (NCT04247126). The first results [79] led to the establishment of the maximum tolerated dose as 3 mg/daily. SY-5609 showed approximately dose-proportional pharmacokinetics and moderate to high interpatient variability. This clinical trial is still ongoing with expansions to several cancer types to study the effect in more homogenous patient populations.

GT Apeiron Therapeutics presented another large group of closely related compounds with a 3-pyrimidin-4-yl-pyrrolo[2,3-*b*]pyridine core with a wide range of selectivity and potency [80–82]. Selectivity was profiled within the group of CDK7, CDK2, CDK9, and CDK12. Compounds potently and selectively inhibited CDK7 with IC_{50} < 20 nM, and the proliferation of the cancer cell lines HCC70 and A2780 was inhibited in the nanomolar range. The compounds also showed enhanced membrane permeability and reflux rate compared to the comparative compound with a similar structure [83]. Compound **21** exhibited great selectivity toward CDK7 (IC_{50} = 9.5 nM) over CDK2/9/12 (IC_{50} > 10 µM) and effectively inhibited the tested cell lines in tens of nM.

Additional compounds inspired by SY-5609 were disclosed by TYC Medicines, who presented compounds based on the pyrimidinylindole core [84]. Similar to previous companies, they tested their first set of compounds in term of kinase selectivity using CDK7, CDK2, CDK9, and CDK12. Example **22** inhibited CDK7 at less than 50 nM, whereas the other kinases were more than 10-fold less sensitive. *In vitro* proliferation assays showed that this compound effectively inhibited the proliferation of breast, ovarian, colorectal, and lung cancer cells. All tested cell lines were inhibited in the nanomolar range, and **22** inhibited proliferation more effectively than SY-5609 in most tested cell lines. The studies also showed that **22** has improved pharmacokinetic parameters compared with SY-5609.

A gap in the chemical space was further filled by Jiangsu Simcere Pharmaceutical Company, who presented a small group of similar pyrimidinylindole derivates related to SY-5609 [85,86]. Compound **23**, which has a cyclohexyl ring instead of piperidine, presented great selectivity toward CDK7 with an IC_{50} of 2.3 nM. The other tested CDKs (i.e. CDK1, CDK2, CDK4, CDK6, CDK9, and CDK12) were inhibited in the micromolar range. Closely related compounds based again on the 3-[(4-trifluoromethyl)pyrimidin-3-yl]indole core with similar potency and selectivity were disclosed by Guangzhou Fermion Technology [87]. The pyrimidine ring was substituted at the C2 position either by an aminocyclohexylamino or piperidin-3-ylamino group or by bicyclic or nitrogen-containing spirocyclic moieties linked to the pyrimidine via an amino or methylamino group (e.g. **24**). In some cases, the hydrogen atom at the C7 position on the indole ring was substituted by a fluorine or cyano group, whereas the C8 position was occupied mostly by dimethylphosphoryl or sulfur-containing functional groups. The most selective compounds inhibited CDK7 at less than 10 nM and additionally tested kinases (CDK2, CDK9, and CDK12) at over 1000 nM. Few related indole derivatives bearing dimethylthiophosphoryl functionality were published in a patent by Newsoara Biopharma [88]. Compound **25** was the most potent, with an IC_{50} of 3.6 nM, but again, no details concerning its selectivity or *in vitro* and *in vivo* activity were provided.

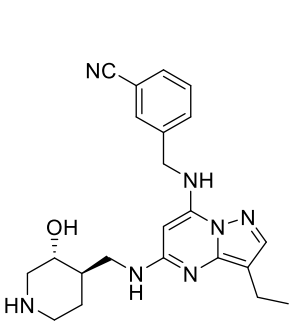
Two additional patents protect compounds resembling THZ1/THZ2 only partly. A group of 38 aminopyrimidines (prepared by Shanghai Lingda Biomedical) are linked to indole or various other fused six- and five-membered nitrogen-containing heterocycles (e.g. indazole, benzo[*d*]imidazole, imidazo[1,2-*a*]pyridine, or tetrahydropyrazolo[4,3-*c*]

pyrimidine) and these are CDK7 inhibitors capable of strongly targeting CDK9 [89]. The first set of inhibitors is represented by 2,4,5-trisubstituted pyrimidines with conserved fluorine atom at the C5 position. The C2 position of pyrimidine was substituted by an amino, aminocyclohexylamino or aminocyclohexanecarboxamido group. The other set of inhibitors consisted of 4,6-disubstituted pyrimidines with the same substituents described above. The CDK7 IC_{50} values of the most active compounds ranged from 20–100 nM; **26** caused a > 80% decrease in CDK7/9 activity tested at 1 and 0.1 μM concentrations.

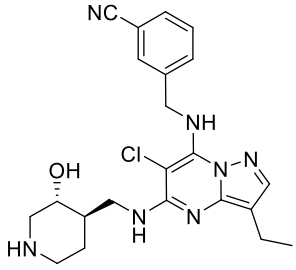
A series of 2-aminopyrimidines substituted with pyrazoles or pyrrolo[1,2-*b*]pyrazoles were disclosed by Beijing Guohong Biomedical Technology [90]. Most compounds showed nanomolar inhibitory activity on both CDK7 and CDK9 and reasonable selectivity over CK1α [90]. The proliferation of the AML cell lines MV-4-11 and MOLM-13 was inhibited by **27** with IC_{50} values of 94 and 32 nM, respectively. Moreover, the synergistic effect of **27** and the p53 activator eprenetapopt in various tumor cell lines and its pharmacokinetic data have been described.

3.2. Pyrazolopyrimidines

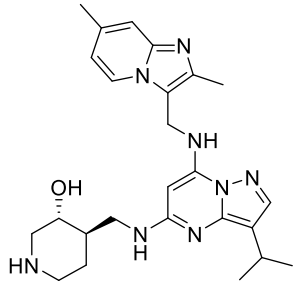
Pyrazolo[1,5-*a*]pyrimidine is a core structure of samuraciclib (CT7001/ICEC0942, **3**), an ATP-competitive, selective inhibitor of CDK7, first-in-class used in clinical trials for the treatment of patients with advanced TNBC, developed by Carrick Therapeutics. In the patent disclosed by the same company, more potent samuraciclib analogs were published [91]. The substitution of ethyl instead of isopropyl at position 3 of the pyrazolo[1,5-*a*]pyrimidine core and introduction of a cyano group to the *meta* position of the benzyl ring in the case of **28** resulted in a 4-fold improvement in CDK7 inhibition in comparison to that of samuraciclib. Furthermore, the presence of a chlorine atom at the pyrazolo[1,5-*a*]pyrimidine C6 position further increased the potency of **29** with a CDK7 IC_{50} value of 4.2 nM and even higher selectivity (CDK2/CDK7 ratio = 571, CDK9/CDK7 ratio = 40). Some derivatives also showed better pharmacokinetic properties in comparison to samuraciclib, such as a lower affinity to human plasma protein and lower efflux ratio, both in two models of multidrug resistant cell lines MDCK-MDR1 and MDCK-BCRP.



28
(Patented as APPAMP-003)



29
(Patented as APPAMP-004)



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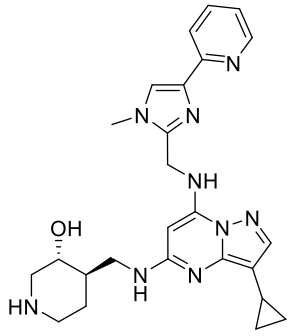
(Patented as H-APPAMP-015)



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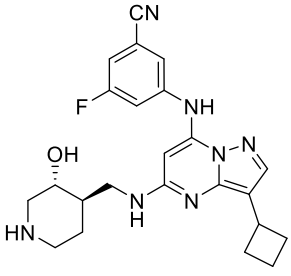
(Patented as PPA-024)



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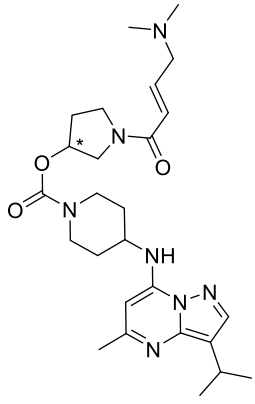
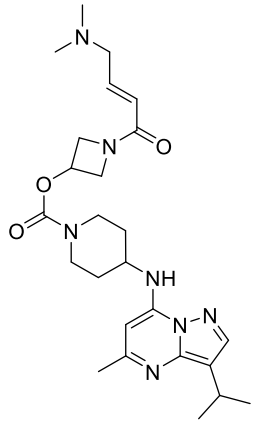
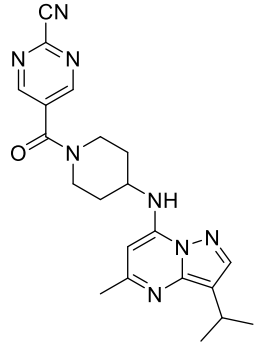


33 (LY3405105)
(Patented as I - mixture of enantiomers)
34
(Patented as II, (*S*)-isomer)
35
(Patented as III, (*R*)-isomer)



36
(Patented as F10)



37
(Patented as SZ-015249)

The same company subsequently presented a series of 45 analogs of samuraciclib, with a benzylamino group at the C7 position substituted with various heterocyclic methylamines [92]. Their inhibitory activity was tested on CDK7 and CDK12, and most compounds showed higher preferences for CDK12. However, compound **30** with a 2,7-dimethylimidazo[1,2-*a*]pyridine-3-methylamino substituent effectively and selectively inhibited CDK7 with an IC_{50} value of 3 nM and a CDK7/CDK12 ratio of 0.01.

Another group of structurally related inhibitors invented by Carrick Therapeutics showed similar activity and selectivity toward CDK7 and CDK12 [93]. The C3 and C5 positions of the pyrazolo[1,5-*a*]pyrimidine core were occupied by substituents similar to those in the previous group, whereas the C7 position was substituted by various heterobiarylmethylamino functionalities. Five compounds showed CDK7 IC_{50} values < 100 nM and CDK7/CDK12 ratios from 1 to 4. The highest CDK7 inhibitory activity was observed in **31** with an IC_{50} value = 17 nM (CDK7/12 = 2.8). Moreover, compound **31** inhibited the viability of A673 cells with IC_{50} = 96.4 nM.

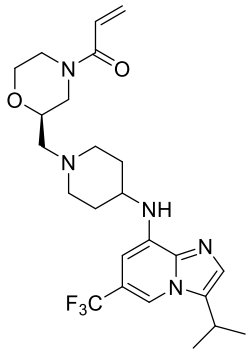
The Translational Genomics Research Institute disclosed another series of potent CDK7 inhibitors structurally related to samuraciclib [94]. The differences from samuraciclib include modifications of all three substituted positions. The hydroxypiperidin-4-ylmethylamine moiety at the C5 position was replaced by piperidin-3-ylamino or piperidin-3-yloxy groups in some compounds, and isopropyl at the C3 position was changed to cyclopropyl or cyclobutyl. Finally, C7 benzylamine was shortened to substituted aniline (e.g. **32**). Several compounds exhibited CDK7 IC_{50} values up to 100 nM. Unfortunately, no information regarding the compound selectivity or activity on cancer cell lines was provided. Much more distinct compounds built on pyrazolo[1,5-*a*]pyrimidine were described in the patent application prepared by Eli Lilly and Company [95]. This document describes the clinical candidate LY3405105 (**33**) and its *S* (**34**) and *R* (**35**) enantiomers. The substitution at the C5 position on the pyrazolo[1,5-*a*]pyrimidine ring was limited to a methyl group, and benzylamine at the C7 position was replaced by a 4-aminopiperidine moiety. This substituent was further equipped with an α,β-unsaturated carbonyl head (intended for covalent attachment to a cysteine residue on CDK7), which was attached via a pyrrolidin-3-yloxycarbonyl bridge. LY3405105 and **35** displayed IC_{50} values of 17.3 nM and 48.7 nM without preincubation with CDK7 and 2.37 nM and 5.06 nM after 3 h preincubation, respectively. The compounds reduced the phosphorylation of Ser5 in the RNAP II CTD and transcription of c-Myc. The selectivity of LY3405105 was tested in a panel of 320 kinases; however, the results were shown only for a set of 11 CDKs. LY3405105 was interestingly selective for CDK7 (IC_{50} = 93 nM), with IC_{50} values equal to 2.83 µM (CDK4), 6.32 µM (CDK9), 7.41 µM (CDK19), 8.08 µM (CDK6), and > 9 µM for the other CDKs. The proliferation inhibition of various cancer cell lines was dose dependent, with IC_{50} values ranging from 14–48 nM. In addition, LY3405105 demonstrated significant activity in several human cancer xenograft models. The results of antiproliferative and growth inhibition studies of more than 150 cancer cell lines indicated that loss-of-function mutations in the *ARIDIA*, *KMT2C* or *RB1* genes represent potential biomarkers for possible patient selection strategies. In 2018, LY3405105 entered a phase I clinical trial for solid tumors (NCT03770494), but the trial was terminated due to a lack of sufficient efficacy.

One highly potent and selective CDK7 inhibitor, **36**, that is structurally closely related to LY3405105 was presented by Longtaishen Medical Technology [96]. The substitution of the pyrrolidine ring by azetidine slightly increased the CDK7 potency compared to both parent molecule enantiomers. The application of compound **36** at 10 and 200 nM concentrations resulted in 41% and 93% decreases in CDK7 activity, respectively. No such strong inhibitory effect was observed in the other CDKs (CDK1/2/4/6/9) even at a 1 µM concentration. In comparison to the *S*-enantiomer of homologous LY3405105 (**34**), compound **36** displayed a higher antiproliferative effect both *in vitro* in MDA-MB-231, MDA-MB-468, A549, and NCI-H1299 cancer cell lines and *in vivo* in nude mouse xenografts.

The last group of CDK7 inhibitors with this core was revealed by Suzhou Sinovent Pharmaceutical Technology [97]. These compounds are structurally related to compounds **33** and **36** from the previous patents with isopropyl, methyl and piperidine-4-ylamino groups at the C3, C5 and C7 positions of the pyrazolo[1,5-*a*]pyrimidine core, respectively. However, different aromatic heterocycles bearing cyano group were attached to the nitrogen atom of the piperidine or aminocyclohexyl moiety via amide bond. The IC_{50} values of CDK7 inhibition were determined after 60 min of incubation of the inhibitor with the enzyme, and the most potent compounds reached single-digit nanomolar activity (e.g. **37**).

3.3. Imidazopyridines

A small group of imidazopyridine derivates, developed as analogs of the mentioned pyrazolo[1,5-a]pyrimidine LY3405105 (33) [95], were described by Eli Lilly and Company [98]. The compounds effectively inhibited CDK7 in the nanomolar range, whereas CDK9 was inhibited in the micromolar range. Moreover, the IC_{50} values of CDK7 decreased approximately 10 times when the enzyme was preincubated with the compounds for 3 hours (66 nM and 6 nM, respectively), indicating the expected irreversible mechanism of inhibition. The selectivity toward CDK7 over CDK9 was also confirmed by a mechanistic analysis of the inhibition of RNAP II CTD phosphorylation at Ser5 over Ser2 as target sites for CDK7 and CDK9, respectively; the data correlated with the biochemical assays. Compound **38** was chosen for screening in a panel of 468 human kinases, revealing great selectivity for CDK7; the only kinase with a residual activity less than 35% was CDK7 (residual activity of 4% at 0.2 µM). The *in vitro* and *in vivo* effect were analyzed with compound **39**. This compound potently inhibited cell proliferation in the low nanomolar range and showed efficacy in breast xenografts.



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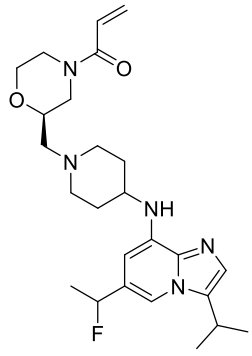
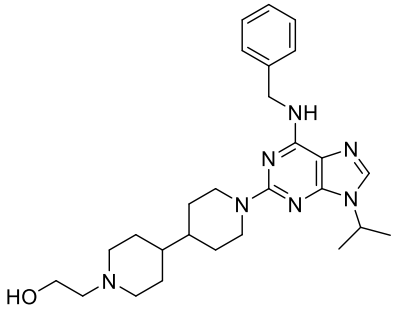
(Patented as 8)



39
(Patented as 1)

3.4. Purines

Some of the first CDK inhibitors, such as roscovitine (**1**), were identified among trisubstituted purines. Although these compounds had relatively low selectivity across CDKs, Tianjin University of Science and Technology developed isoform-specific purine derivatives as CDK7 inhibitors [99]. Trisubstituted derivative **40** was assayed against a broad spectrum of kinases and inhibited CDK7 activity by 88%. The other tested kinases were inhibited by less than 50%, with the exception of CLK2 and CLK4 kinases, which were inhibited by 90 and 92%, respectively. In proliferation assays, this compound was shown to be less effective with IC_{50} values in the micromolar range. Another compound, **41**, was the most effective in *in vitro* tests, with IC_{50} values in the nanomolar range in most tested cell lines. The application of **41** also effectively inhibited angiogenesis (HUVECs, chicken embryo chorioallantoic membrane vascular experiment). However, no information regarding the selectivity of this compound was presented.



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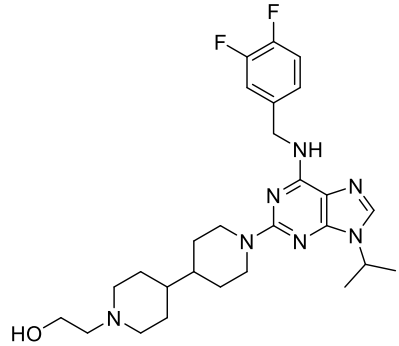

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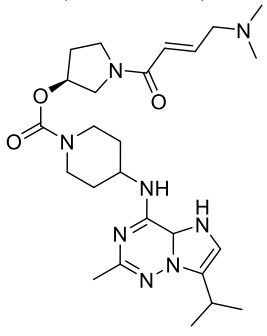

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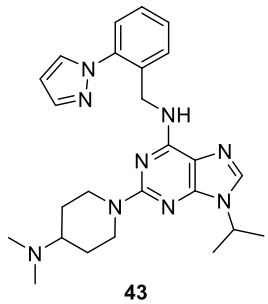
(Patented as SZ-015268)



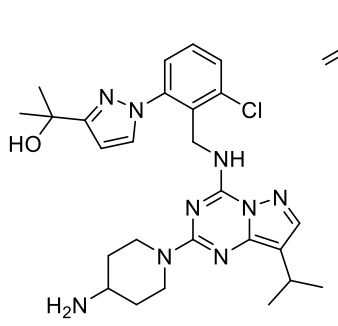
43
(Patented as VII-3)

Suzhou Sinovent Pharmaceuticals presented a group of compounds with purine and various isosteric heterocyclic cores [100]. The tested compounds inhibited CDK7 activity and the proliferation of HCC70 and OVCAR-3 cells in the nanomolar range, but no additional data regarding selectivity were presented. Compound **42** belongs to the purine-isosteric imidazo[2,1-*f*][1,2,4]triazines and was the most potent compound with an $IC_{50} = 23.6$ nM for the inhibition of CDK7. It also inhibited cell proliferation at similar concentrations and was shown to be effective in HCT-116 colon xenograft models.

Additionally, Taizhou EOC Pharma claimed over one hundred potential CDK7 inhibitors based on several heterocyclic motifs, including purines and isosteric heterocycles [101]. The pattern of substitutions clearly corresponds to LDC4297 (**5**). Approximately twenty tested compounds were potent toward CDK7 with IC_{50} values below 100 nM, but the selectivity is unknown. The example purine derivative **43** showed efficacy in breast (MCF7, T47D, and HCC70) and ovarian (OVCAR-3) cancer cell lines with IC_{50} values below 200 nM.

3.5. Pyrazolotriazines

Large and attractive series of pyrazolo[1,5-*a*] [1,3,5] triazine and pyrazolo[1,5-*a*]pyrimidine derivates related to roscovitine



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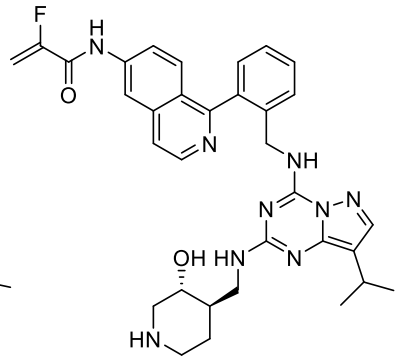
(Patented as 210)



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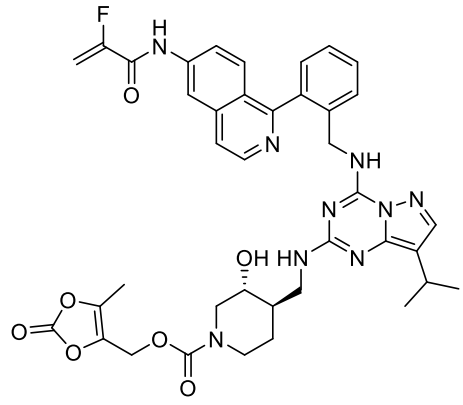
(Patented as 64)



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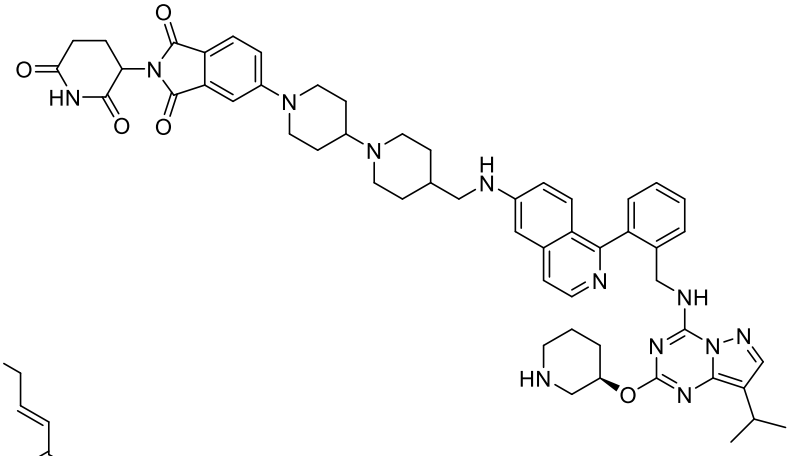
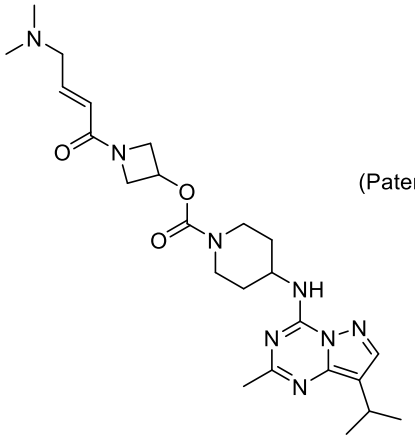
(Patented as 3)



47
(Patented as 31)



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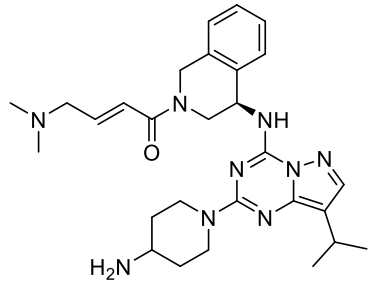
(Patented as D11)



49
(Patented as 82)

(**1**), samuraciclib (**3**) and especially LDC4297 (**5**) were disclosed by Qurient along with the Lead Discovery Center [102,103]. The most interesting reversible compounds inhibit CDK7 with IC_{50} values below 100 nM and simultaneously show at least 200-fold selectivity over CDK1, CDK2, and CDK5 [102]. Compound **44** was further profiled in a panel of 28 different CDK/cyclin complexes, revealing that the IC_{50} of CDK7 was 15 nM, whereas the other CDKs were much less sensitive (IC_{50} > 3 μM). Compound **44** also showed efficacy in several cancer cell lines and an OVCAR-3 xenograft model. Covalent compounds, from the second patent [103], are structurally similar to the above mentioned library but all possess the usual Michael acceptor within the side chain pointing outward the active site of CDK7 supposed to attack its Cys312 (example **45**). It is claimed that these compounds display more than 500-fold selectivity for CDK7 over CDK1/2/5. Their proliferation potency was demonstrated in H460, MV4-11, and A2780 cell lines, which were blocked by sub/micromolar concentrations.

Compound **45** was further optimized by Qurient, who prepared twenty prodrugs of **45** with improved ADME parameters [104]. The described prodrugs of **45** bear various groups modifying the hydroxyl or cyclic amine of the piperidine, such as acyls, carboxylates, valine, etc. The pharmacokinetic parameters after oral administration were substantially improved, and the application of **46** (40 mg/kg qd) displayed the strongest antitumor effect in A2780 xenografts in mice among the five tested prodrugs.

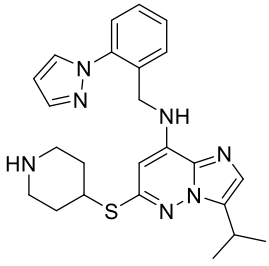
Qurient remained focused on pyrazolotriazine derivates and recently presented a set of CDK7 degraders [105]. The compounds contain either VHL or CRBN ligands attached at various positions to the CDK7 inhibitor via linkers of different lengths and structures. Most presented compounds potently (IC_{50} < 100 nM) and selectively inhibited CDK7 (more than 500-fold selectivity over CDK1, CDK2 and CDK5). The authors claim that the compounds also exhibit high affinity to E3 ubiquitin ligase (K_D typically ≤ 100 nM), although the data were not shown. The application of the compounds to the A2780 cell line resulted in a dose-dependent degradation of CDK, and the most potent compounds exhibited a half-maximal degradation concentration (DC_{50}) < 100 nM. The strongest effect was observed with **47**, which caused a large decrease in the CDK7 levels at 12 nM.

Another set of pyrazolo[1,5-*a*][1,3,5]triazine derivatives was developed by Longtaishen Medical Technology [96,106]. The example compounds bear isopropyl or methyl moieties at the 2 and 8 positions, respectively, and a long chain at the 4-position containing an unsaturated carbonyl moiety, supposedly positioned to bind Cys312 of CDK7. The authors several potent CDK7 inhibitors with selectivity over CDK1, CDK2, CDK4, CDK6, and CDK9. Compound **48** [96] inhibited CDK7 by 95% at 200 nM. The other tested kinases were inhibited by less than 34% when applied at 1000 nM. In addition, **48** showed *in vitro* and *in vivo* anticancer activity. Compounds substituted similarly are claimed by Shanghai Lingda Biomedical, who presented a hundred pyrazolo[1,5-*a*][1,3,5]triazines with low nanomolar potency against CDK7 and some selectivity over CDK9 [107]. Compound **49** belongs to the most potent derivatives with IC_{50} = 2.4 nM, but additional selectivity profiling and *in vitro* or *in vivo* data were not shown.

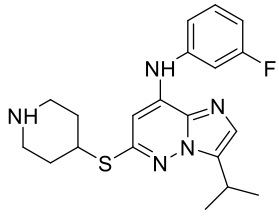
3.6. Imidazopyrazines and imidazopyridazines

Additional isosteres of LDC4297 (**5**) with imidazo[1,2-*a*]pyrazines and imidazo[1,2-*b*]pyridazine skeletons were prepared by the Translation Genomics Research Institute [108]. These compounds share structural similarity to LDC4297, with correspondingly positioned isopropyl and piperidine and pyrazolylphenyl moiety (e.g. **50**), which was even reduced to small function on the phenyl (e.g. **51**). Most compounds are characterized by potency against CDK7 (IC_{50} < 100 nM), but information regarding selectivity was not provided. The antiproliferative activity of selected compounds was determined in a panel of six cell lines with different origins (MiaPaCa2, HPAC, Kasumi1, MDA-MB-231, A2780, and A673); GI_{50} < 1 μM illustrates the effect of the most potent compound **51.**

Completely differently substituted imidazo[1,2-*a*]pyrazines were claimed by Scinnohub Pharmaceutical [109]. Only information regarding the potency to CDK7 is mentioned, and 27 compounds display IC_{50} values below 10 nM. The nanomolar inhibition value (GI_{50} = 10 nM) in the antiproliferative assay of A2780 cells is also presented for the most potent derivative **52**.



50
(Patented as 62)



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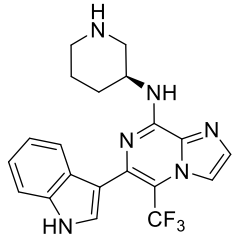
(Patented as 44)



52
(Patented as 43)

3.7. Dihydropyrrolopyrazoles

The Dana Faber Cancer Institute introduced a library of YKL-5-124 (**12**) derivatives containing 33 compounds with covalent binding moiety [110]. Most compounds bear methyl on the pyrazole ring and the phenyl ring, bearing the reactive allyl group is replaced by various other cycles, such as in **53**. The potency of CDK7 is characterized by an IC_{50} value < 100 nM. Another patent [111] showed both covalent and reversible inhibitors, with **54** as the most potent example with IC_{50} = 10.8 nM for CDK7 and > 4.5 µM for both CDK2 and CDK9.

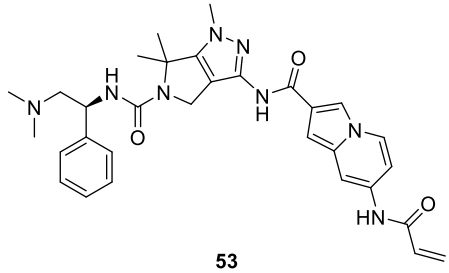
YKL-5-124 also served as a basis for development of several proteolysis targeting chimeras (PROTACs) [112]. These conjugates should represent a set of new chemical tools for CDK7 knockdown and may provide a potential treatment modality for CDK7-associated cancers and autoimmune disorders. In total, 34 pyrrolo[3,4-*c*]pyrazole derivatives were claimed, and their potency at 1 µM in Jurkat cells was screened by a western blot analysis, leading to the identification of lead **55**. Proteasome-dependent CDK7 degradation as an expected mechanism of action was confirmed by additional experiments.

Also Ube Industries reported a series of 11 inhibitors built on the dihydropyrrolopyrazole core that are also structurally related to YKL-5-124 (**56** and **57**) [113]. The authors described not only promising CDK7 inhibitory activities with K_i values ≤ 50 nM and selectivity over PLK1 and CDK2 (K_i ≥ 5 µM or K_i ≥ 300 nM, respectively) but also preliminary *in vivo* data.

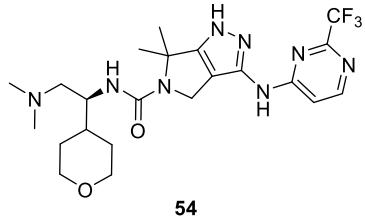
3.8. Phenylpyridines

Phenylpyridine derivatives with a typical reactive enone moiety in the side chain disclosed by the Korean company Yungjin Pharmaceutical (who developed clinical candidate YPN-005) display high CDK7 inhibitory activity with IC_{50} values in the single digit nanomolar range [114–116]. The compounds have low inhibitory activity against CDK2 and CDK5 with supposedly high selectivity based on an assay of a set of 468 kinases. The proliferation of all cancer cell lines is blocked by nanomolar doses; compound **58** exhibited an increased effect on cancer cell lines derived from AML with GI_{50} < 1 nM. These compounds also reduced the phosphorylation level of RNAP II CTD and the expression of c-Myc and Mcl-1 in cancer cells [114].

Similar derivatives, but with limited information regarding their potency and selectivity against CDK7 [117,118], were reported by Aurigene Discovery Technologies, who developed one of the clinically tested CDK7 inhibitors XL102 (mentioned in chapter 2). Example inhibitor **59** [118] inhibited the proliferation



53
(Patented as I-27)



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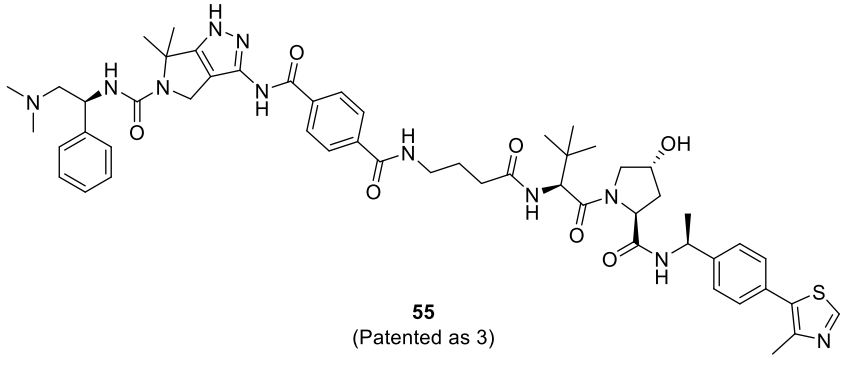
(Patented as 208)



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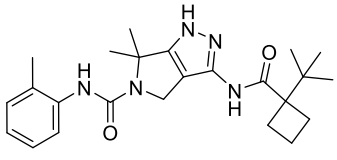
(Patented as 3)



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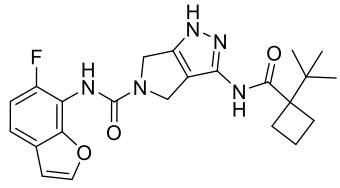
(Patented as 2)



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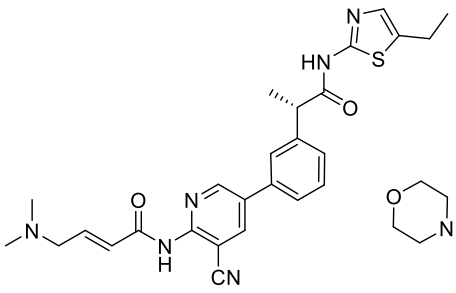
(Patented as 10)



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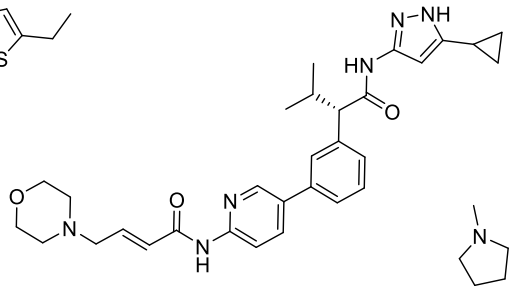
(Patented as 121)



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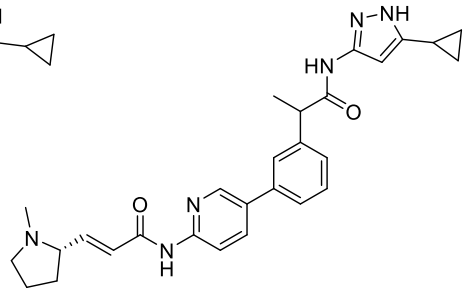
(Patented as 44A)



60
(Patented as 11-3-5)

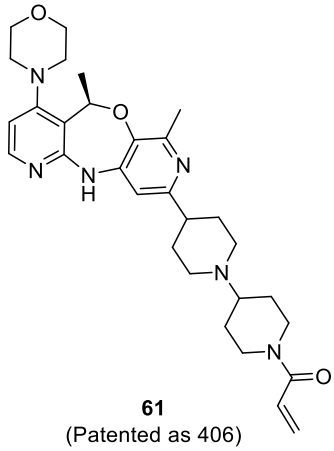
of DU-145 cells and showed a synergistic effect with docetaxel. Finally, Longtaishen Pharmaceutical Technology presented phenylpyridine derivatives, and some of them potently inhibited CKD7; for example, the application of 0.2 μM compound **60** resulted in a 99% decrease in CDK7 activity [119].

3.9. Tricyclic 1,4-oxazepines

Highly original compounds that are structurally distinct from most other CDK inhibitors have been developed by Janssen Pharmaceutica; these compounds were constructed on a tricyclic core containing 1,4-oxazepine [120,121]. The first group of inhibitors contains mostly 4-morpholinylpyridine fused by 7-methyl-1,4-oxazepine to a phenyl or pyridyl ring, which is further substituted by two linked nonaromatic heterocycles terminated with an α,β-unsaturated carbonyl warhead as in compound **61** [120]. In the other group of Janssen inhibitors [121], 4-morpholinylpyridine was replaced by 4-thiomorpholinylpyrimidine as in compound **62**. Both compound series were tested to detect their antiproliferative activity using an isogenic cell line pair expressing wild-type CDK7 or its C312S mutant designed to be insensitive to covalent binders. Whereas the IC_{50} values of the inhibition of wild-type CDK7 were in the single-digit nanomolar range, the mutant was dramatically less sensitive (> 10 μM), confirming the mode of action of the inhibitors.

3.10. Quinazolines and pyridopyrimidines

This chapter summarizes two groups of structurally distinct compounds consisting of two fused six-membered rings. The inhibitors from the first group, disclosed by Kinnate Biopharm, were based on quinazoline, isoquinoline or dihydropyrido[2,3-*d*]pyrimidine scaffolds [122]. The side chains attached to the heterocyclic core and terminated with propionic acid residues or different warheads for covalent modifications (acrylamide, 4-dimethylaminobut-2-enamide, propiolamide or vinylsulfonamide) were formed primarily by 4-aminobenzoylpyrrolidin-3-ylamino or 4-aminobenzoylpiperidin-3-ylamino groups (e.g. **63**). The CDK inhibitory activity was tested in recombinant CDK2, CDK7 and CDK12. The compounds were able to inhibit all these CDK isoforms but with preferences for CDK12. The highest activity was observed in **64**, which had the IC_{50} values below 100 nM



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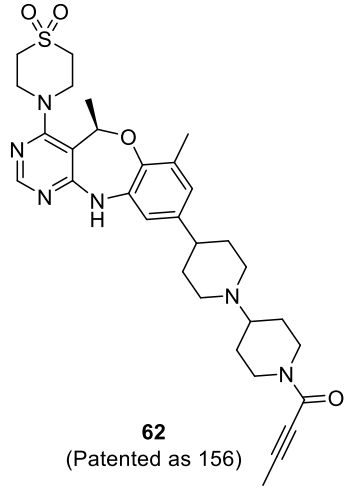
(Patented as 406)



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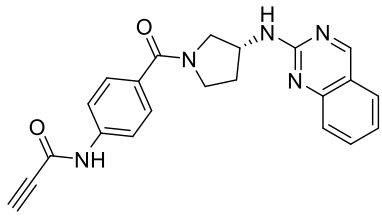
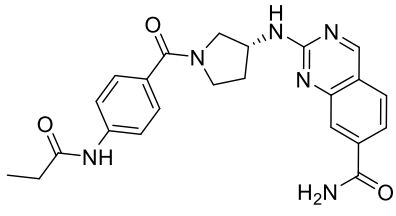
(Patented as 156)



63
(Patented as 70)



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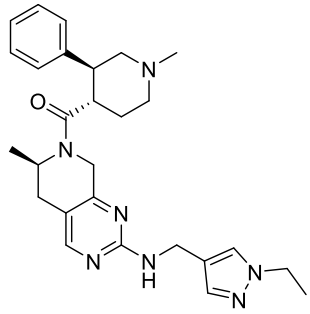
(Patented as 57)



65
(Patented as 58)

for all tested CDKs. Interestingly, in the case of compound **64**, the 4-aminobenzoylpyrrolidin-3-ylamino was modified by a propionic acid residue instead of an α,β-unsaturated carbonyl or vinylsulfonamide reactive group.

The other group of more than 200 potent CDK7 inhibitors structurally based on 1,2,3,4-tetrahydro-2,6-naphthyridine or 5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidine, including for example **65**, was disclosed by Janssen Pharmaceutica [123]. Various *N*-alkyl-3-phenylpiperidin-4-carbonyl functionalities were attached to the nitrogen atom on the saturated ring of the core heterocycle, whereas the pyrimidine ring was substituted by diverse cyclic/heterocyclic amines or heterocyclic methylamines. The compounds displayed high CDK7 inhibitory activity with IC_{50} values in the single-digit nanomolar range. Moreover, the prepared compounds effectively inhibited the phosphorylation of Ser5 in the RNAP II CTD in A549 cells. Nevertheless, no information regarding the compounds' selectivity or anti-proliferative activity was provided.

4. Conclusion

The interest in pursuing CDK7 as a therapeutic target has been ongoing for at least one decade, and significant progress has been achieved in the past few years. The field of CDK7 inhibitors is continuously growing, spanning diverse chemical classes and promising kinase selectivity. In addition, the available compounds possess different mechanisms of inhibition, including conventional competition, irreversible binding and specific induction of CDK7 degradation by heterobifunctional compounds. The new compounds disclosed in 58 patent applications published during the reviewed period, i.e. from 2018 to 2022, span over 15 chemotypes. We classified and summarized the chemical structures and their biochemical and biological properties, providing researchers with a comprehensive update of the field, including exciting clinical candidates.

5. Expert opinion

Cancer cells often display transcriptional addiction, i.e. a state in which they are critically dependent on the continuous production of short life time transcripts, their processing and stability, including those encoding antiapoptotic proteins and oncogenic transcription factors. This, together with the high expression of CDK7 in many cancer types, provides a strong rationale for examining this kinase as a possible target and in parallel stimulates the development of its modulators as drugs for oncology.

In fact, this possibility has been investigated since the discovery that the early generation of pan-selective CDK inhibitors not only block the cell cycle but also potently inhibit transcriptional CDKs (tCDKs). Although early inhibitors usually lacked biochemical selectivity, showed connected toxicities and complicated the understanding of the importance of tCDKs in the antitumor response, they significantly contributed to gaining knowledge regarding the involvement of tCDKs in cancer biology. Intense research has partly solved problems related to potency and selectivity, at least toward some CDKs, such as CDK4-targeting palbociclib or ribociclib, which have been eventually approved as drugs. These stories clearly confirm that selectivity can be obtained even within closely related enzymes of the CDK family.

Luckily, CDK7 also belongs to kinases for which promising inhibitors were developed. At least partly, this has been possible due to the presence of a unique cysteine residue located at the entry to the active site of CDK7, which is tractable by irreversible binders. Although covalent drugs often display significant off-target toxicities related to the presence of reactive function, the first CDK7 irreversible inhibitor, SY-1365 (**8**), has already reached clinical trials, followed by other candidates, such as Q901 and XL102. The high number of patents for irreversible binders published during the reviewed period indicates an unflagging interest in this field.

Selectivity over other CDKs (and other more distinct kinases) could also be obtained with reversible compounds as in the case of samuraciclib (**3**), SY-5609 (**9**), and other clinical candidates. A wealth of patent applications describing similar inhibitors without a reactive group and acting as ATP competitors were also published during the reviewed period. The results of clinical research will hopefully answer the question of whether the toxicity of covalent compounds is manageable and whether reversible drugs provide higher safety. However, a clear answer could be masked by other pharmacological parameters, including selectivity, which usually contributes to target and off-target activity and toxicity.

Nevertheless, the genetic inactivation of CDK7 shows that it is dispensable for global transcription and does not lead to any negative consequences in adult tissues [124]. This finding can have two interesting and partly contradictory implications, indicating that (i) the toxicity of selective CDK7 inhibitors could be low but also that (ii) selective CDK7 inhibition could be compensated by other kinases, and highly selective compounds could not have a sufficient effect. In particular, the second option raises further questions because not all tCDKs, which could have compensatory roles, are tumor-promoting; under some contexts, they could even have opposite functions (for example, CDK8 also has a tumor suppressive role [125]), and their inactivation thus can be counterproductive.

However, another fascinating concept of CDK7 modulation employs induced protein degradation. Developed PROTACs can shed light on possible compensations. In addition, it could help explore other possible functions of CDK7. Some kinases, including partly related CDK6 and CDK9, also play noncatalytic roles and regulate transcription by providing a protein scaffold for interaction with other transcription regulators [126]. It is tempting to speculate that if CDK7 also belongs to this group of multimodal regulators, not only its degradation but also the inactivation of its enzymatic role could eliminate all possible functions, leading to a more pronounced effect.

A deeper understanding of CDK7 biology, eventually allowing the identification of specific genes selectively dependent on CDK7, could translate into better selection of specific cancer types and improvement of such personalized therapeutic strategies. Interest in potent CDK7 inhibitors is continuing, and we expect that further development will reveal the true value of this therapeutic strategy.

Funding

This paper was funded by the European Union - Next Generation EU (National Institute for Cancer Research, programme EXCELES, Project No. LX22NPO5102), Czech Science Foundation (21-06553S) and Palacký University Olomouc (IGA_2022_007).

Declaration of interest

H Shao was supported by the grant from Department of Science & Technology of Hunan Province (2021JJ41015). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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